NCCN Guidelines: Highlights of Recent Management Updates

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I have no disclosures

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Objectives

Discuss	Discuss updates to 2022/23 NCCN guidelines for Detection, Prevention, & Risk Reduction
Identify	Identify patient population changes to high-risk cancer screening management
Review	Review case studies implementing guideline changes into practice

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What's new?

- Breast, Ovarian, Pancreas (BOP) - Moderate Risk Genes
- Colorectal High-Risk assessment
- Tyrer Cuzick Risk Calculator / Equity Data
- New Clinical Trials / Vaccines

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BOP Gene table updates

- NBN removed, added insufficient evidence footnote (NEJM, 2021 – No Br Risk)
- Male & Prostate cancer risks added for BRCA ½
  - Consider annual mmg men >50, esp BRCA2
- Breast - Removed mention of specific histology (ER+, lobular) except BRCA1 (TNBC)

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NCCN Guidelines Version 1.2023
Gene Summary: Risks and Management

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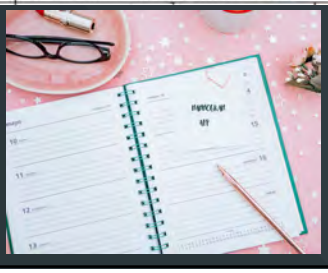
CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
ATM	• **Absolute risk:** 20%–40%[3,4,5,6] • **Management:**[b] ▸ Screening: Annual mammogram at age 40 y and consider breast MRI with contrast starting at age 30–35 y[c,d,e] ▸ Risk reduction: Evidence insufficient for risk-reducing mastectomy (RRM); manage based on family history • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 2%–3%[10-12] • **Management:**[f] ▸ Risk reduction: Evidence insufficient for risk-reducing salpingo oophorectomy (RRSO); manage based on family history • **Strength of evidence of association with cancer:** Strong	**Pancreatic cancer** • **Absolute risk:** ~5%–10%[9,23] • **Management:** Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A • **Strength of evidence of association with cancer:** Strong **Prostate cancer** • Emerging evidence for association with increased risk[24]
	Comments: Heterozygous *ATM* P/LP variants should not lead to a recommendation to avoid radiation therapy at this time. See Discussion for information regarding the c.7271T>G variant. See GENE-B for reproductive implications/ recessive disease.		



Br MRI - From age 40

Anticipate Colorectal cancer screening recommendations within a year

c.7271T>G – Br Ca Risk may be >50%

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

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Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
BRIP1	• **Absolute risk:** Insufficient data to define • **Management:** Insufficient data; managed based on family history • **Strength of evidence of association with cancer:** Limited, potential increase in female breast cancer[8]	• **Absolute risk:** 5%–15%[10-12,39] • **Management:** ▸ Risk reduction: Recommend RRSO at age 45–50 y[11] • **Strength of evidence of association with cancer:** Strong	**Other cancers** • Unknown or insufficient evidence
	Comments: See GENE-B for reproductive implications/ recessive disease. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of P/LP variants in *BRIP1* appears to be sufficient to justify RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset of ovarian cancer.		

Absolute Risk – From >10%

From Consider

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

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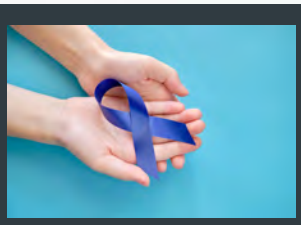
Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
CHEK2	• **Absolute risk:** 20%–40%[5,6,42,43] • **Management:**[b] ▸ Screening: Annual mammogram at age 40 y and consider breast MRI with contrast starting at age 30–35 y[c,d,e] ▸ Risk reduction: Evidence insufficient for RRM; manage based on family history • **Strength of evidence of association with cancer:** Strong[44]	**Evidence of increased risk:** No established association	**Colorectal cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (GENE-1)
	Comments: Risk data are based only on frameshift P/LP variants. The risks for most missense variants are unclear but for some P/LP variants, such as Ile157Thr, the risk for breast cancer appears to be lower and does not reach the threshold for management change. Management should be based on best estimates of cancer risk for the specific P/LP variant.		



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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
NF1	• **Absolute risk:** 20%–40%[52,53] • **Management:**[b] ▸ Screening: Annual mammogram starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[c,d] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • **Strength of evidence of association with cancer:** Strong	**Evidence of increased risk:** No established association (removed "only apply to individuals with a clinical diagnosis of NF ")	**Malignant peripheral nerve sheath tumors, GIST, others** • Recommend referral to *NF1* specialist for evaluation and management
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		
PALB2	• **Absolute risk:** 41%–60%[5,8,22,54] • **Management:**[b] ▸ Screening: Annual mammogram and breast MRI with contrast at 30 y[c,d] ▸ Risk reduction: Discuss option of RRM • **Strength of evidence of association with cancer:** Strong **Male breast cancer** • **Absolute risk:** 0.9% by age 70 y[22] • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 3%–5%[10-12,22,61,62] • **Management:**[i] ▸ Risk reduction: Consider RRSO at age >45 y[h] • **Strength of evidence of association with cancer:** Strong	**Pancreatic cancer** • **Absolute risk:** 5%–10% • **Management:** Screen P/LP variant carriers with a family history of pancreatic cancer, see PANC-A • **Strength of evidence of association with cancer:** Limited **Other cancers** • Unknown or insufficient evidence
	Comments: See GENE-B for reproductive implications/ recessive disease.		

From evidence insufficient, Absolute Risk is the same

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Gene Summary: Risks and Management

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
RAD51C	• **Absolute risk:** 20%–40%[5,7,44] • **Management:** Annual mammogram and consider breast MRI with contrast starting at age 40 y • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 10%–15%[10-12,63,64] • **Management:** ▸ Risk reduction: Recommend RRSO at 45–50 y[h] • **Strength of evidence of association with cancer:** Strong	**Other cancers** • Unknown or insufficient evidence
	Comments: See GENE-B for reproductive implications/ recessive disease. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of P/LP variants in RAD51C appears to be sufficient to justify RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	• **Absolute risk:** 20%–40%[5,7,44] • **Management:** Annual mammogram and consider breast MRI with contrast starting at age 40 y • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 10%–20%[10-12,63,64] • **Management:** ▸ Risk reduction: Recommend RRSO at 45–50 y[h] • **Strength of evidence of association with cancer:** Strong	**Other cancers** • Unknown or insufficient evidence
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of P/LP variants in RAD51D appears to be sufficient to justify RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		

From insufficient data

From consider & >10%

From consider & >10%

Footnotes on GENE-A 8 of 10 References on GENE-

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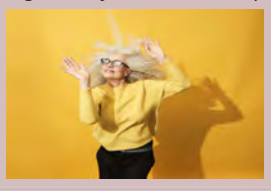
HRT (BRCA) s/p RRSO

(Sx induced menopause)

HRT Commentary Expanded	Removed
• "HRT recommendations should be tailored depending on each patient's personal hx of breast cancer and/or br ca risk reduction strategies. HRT is a consideration for premenopausal patients *(until age 45-50)* who do not carry a dx of breast cancer or have other contraindications for HRT." • "Consider preop menopause management consult if patient is still premenopausal at time of RRSO" (Chlebowski R,et al. JAMA Oncol 2015)	• "For those who have not elected RRSO, transvaginal US combined with CA-125 for ov ca screening, although of uncertain benefit, may be considered at the clinicians discretion starting at age 30-35." (UK Familial Ov Ca Screening Study, JCO, 2013) 

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Breast Cancer Risk Reduction

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Breast Cancer Risk Reduction

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ELEMENTS OF RISK[k]

Individual does not meet any of the familial risk criteria or tests negative for a genetic predisposition →

Elements that increase risk[l]
- Family history
- Increasing age
- Ethnicity/race[m]
- Lifestyle factors
  - Increased body mass index (BMI)
  - Alcohol consumption
  - Current or prior estrogen and progesterone hormone agent[n]
- Reproductive history
  - Younger age at menarche
  - Nulliparity/Lower parity
  - Older age at first live birth
  - Older age at menopause
- Other
  - History of lobular carcinoma in situ (LCIS); Atypical hyperplasia (ductal and/or lobular)
  - Number of prior breast biopsies
    - ◊ Procedure done with the intent to diagnose cancer; multiple biopsies (needle/excision) of the same lesion are scored as one biopsy.
  - Mammographic breast density (heterogeneously and/or extremely dense breasts)
  - Prior thoracic radiation therapy (RT) <30 y of age

Elements that decrease risk
- Menopause before age 45 y
- Prior risk-reducing agent
- Exercise
- Breastfeeding

→ For breast cancer risk assessment and management, see BRISK-4

E.g. Progesterone IUD + Implants (LARC)

[k] The management of DCIS and invasive breast cancer is available in the NCCN Guidelines for Breast Cancer.
[l] See Table 2, Nattinger AB, et al. Ann Intern Med 2016;164:ITC81-ITC96.
[m] There are differences in risk associated with race and ethnicity. Further studies are needed for social determinants of health and existing health care disparities to better understand this relationship.
[n] Based on the available data, hormonal IUDs have very low systemic absorption and associated breast cancer risk.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Breast Cancer Risk Reduction

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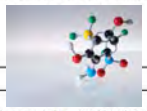
BREAST CANCER RISK-REDUCING AGENTS

Tamoxifen[a,b,c]	Raloxifene[a,b]	Aromatase Inhibitors (exemestane and anastrozole)[e]
• Data regarding tamoxifen risk reduction are limited to pre- and postmenopausal individuals ≥35 years of age with a Gail Model 5-year breast cancer risk of ≥1.7% or a 10-year risk by IBIS/Tyrer-Cuzick of ≥5% or a history of LCIS. • Tamoxifen: 20 mg per day for 5 years was shown to reduce risk of breast cancer by 49%. Among individuals with a history of atypical hyperplasia, this dose and duration of tamoxifen was associated with an 86% reduction in breast cancer risk. Low-dose tamoxifen (5 mg per day for 3 years)[d] is an option only if patient is symptomatic on the 20-mg dose or if patient is unwilling or unable to take standard-dose tamoxifen.[1] • The efficacy of tamoxifen risk reduction in individuals who are carriers of *BRCA1/2* and other pathogenic mutations is less well studied than in other risk groups. Limited data suggest there may be a benefit, likely a larger benefit, for *BRCA2* carriers. • For healthy, high-risk, premenopausal individuals, data regarding the risk/benefit ratio for tamoxifen appear relatively favorable (category 1). • For high-risk postmenopausal individuals, data regarding the risk/benefit ratio for tamoxifen are influenced by age, presence of uterus, or comorbid conditions (category 1). There are insufficient data on ethnicity and race.	• Data regarding raloxifene risk reduction are limited to postmenopausal individuals ≥35 years of age with a Gail Model 5-year breast cancer risk ≥1.7% or a 10-year risk by IBIS/Tyrer-Cuzick of ≥5% or a history of LCIS. • Raloxifene: 60 mg per day was found to be equivalent to tamoxifen for breast cancer risk reduction in the initial comparison. While raloxifene in long-term follow-up appears to be less efficacious in risk reduction than tamoxifen, consideration of toxicity may still lead to the choice of raloxifene over tamoxifen in individuals with an intact uterus. • There are no data regarding the use of raloxifene in individuals who are carriers of *BRCA1/2* and other pathogenic mutations or who have had prior thoracic radiation. • For high-risk postmenopausal individuals, data regarding the risk/benefit ratio for raloxifene are influenced by age or comorbid conditions (category 1). There are insufficient data on ethnicity and race. • Use of raloxifene for breast cancer risk reduction in premenopausal individuals is inappropriate unless part of a clinical trial.	• Data regarding exemestane are from a single large randomized study limited to postmenopausal individuals ≥35 years of age with a Gail Model 5-year breast cancer risk ≥1.7% or a 10-year risk by IBIS/Tyrer-Cuzick of ≥5% or a history of LCIS. • Data regarding anastrozole are from a single large randomized study limited to postmenopausal individuals 40 to 70 years of age with the following risk compared with the general population: ▸ Aged 40 to 44 years - 4 times higher ▸ Aged 45 to 60 years - ≥2 times higher ▸ Aged 60 to 70 years - ≥1.5 times higher Individuals who did not meet these criteria but had a Tyrer-Cuzick model 10-year breast cancer risk >5% were also included. • Exemestane: 25 mg per day was found to reduce the relative incidence of invasive breast cancer by 65% from 0.55% to 0.19% with a median follow-up of 3 years. • Anastrozole: 1 mg per day was found to reduce the relative incidence of breast cancer by 53% with a median follow-up of 5 years. • There are retrospective data that aromatase inhibitors can reduce the risk of contralateral breast cancer in *BRCA1/2* patients with ER-positive breast cancer who take aromatase inhibitors as adjuvant agents. • For high-risk postmenopausal individuals, data regarding the risk/benefit ratio for aromatase inhibitor agents are influenced by age and comorbid conditions such as osteoporosis (category 1). There are insufficient data on ethnicity and race. • Use of aromatase inhibitors for breast cancer risk reduction in premenopausal individuals is inappropriate unless part of a clinical trial. See next page for footnotes and references



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BRISK-B
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Colorectal

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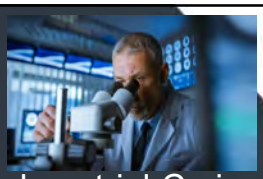
Lynch Syndrome Eval (footnotes!)



- Universal screening of all CRC/Endometrial Ca is recommended ID pts with LS (Pros/Cons)
- Tumor screening for MMR defic is recommended for all CRC & endometrial ca regardless of age
- **Tumor screening of CRCs for MMR deficiency for purposes of screening for LS is not required if MGPT is chosen as the strategy for screening for LS, but MMR testing may still be required for CRC therapy selection (BRAF/other)**
- Consider tumor screening for MMR deficiency for sebaceous neoplasms + the following adenocarcinomas: small bowel, Ovarian, gastric, pancreas, biliary tract, brain, bladder, urothelial, and adrenocortical cancers regardless of age (Latham et. al 2019, JCO)

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Lynch Syndrome Tables
(MLH1, MSH2/6, PMS2)

Gastric & small bowel ca screening now recommended for all genes:

- **Upper GI surveillance with EGD (w random bx to assess H.Pylori) starting at 30-40 yrs & repeat Q 2-4 yrs, with colonoscopy**
- Initiation <30 yrs and/or surveillance interval <2 y may be considered based on FH of upper GI Ca or Barrett esophagus w dysplasia
- The value of eradication (H. Pylori) for prevention of Ga Ca in LS is unkn

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Lynch Syndrome Tables

New study cited for all genes (no changes to age to start; MSH6 & PMS2 colonoscopy frequency now every 1-3 yrs.)

- "One study has modeled the cost effectiveness of various strategies for age on initiation and frequency of colonoscopy for reducing incidence and mortality among individuals with LS. They reported that the optimal age to initiate and follow up screening was age 25, repeating every 1 year for MLH1 LS, age 25 repeating every 2 years for MSH2 LS, age 35 repeating every 3 years for MSH6 LS, and age 40 repeating every 3 years for PMS2 LS
- (Kastrinos F, et al. Gastroenterology 2021)"

Colonoscopy	MLH1	MSH2/EPCAM	MSH6	PMS2
Age to start (years)	20-25	20-25	30-35	30-35
Frequency (years)	1-2	1-2	1-3	1-3

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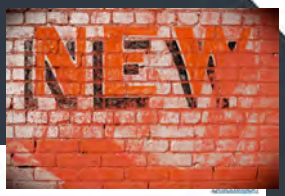
(Classic) FAP (Table - 9 Ca Risks)



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Familial Adenomatous Polyposis

FAP: CANCER RISKS

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y[a]	Cumulative Risk for Diagnosis Through Lifetime for General Population[a]	References
Colon cancer (without colectomy)	39 years (median)	Approaches 100%	4.1%	Reference: 1
Colon cancer (post-colectomy)	• Rectal (s/p IRA): 46–48 years • Pouch and ATZ/rectal cuff (s/p IPAA): Not available	• Rectal (s/p IRA): 10%–30%[b] • Pouch and ATZ/rectal cuff (s/p IPAA): <1%–3%	4.1%	References: 2–10
Duodenal or periampullary cancer	50–52 years	<1%–10%	__%[f]	References: 11–19
Gastric cancer	52–57 years	0.1%–7.1%[c]	0.8%	References: 19–27
Small bowel cancer (distal to duodenum)	43 years	<1%	0.3%	Reference: 19
Intra-abdominal desmoid tumors	31–33 years	10%–24%[d] Mutations in the 3' end of the APC gene have a higher risk[e]	__%[g]	References: 28–33
Thyroid cancer (predominantly papillary thyroid carcinoma)	26–44 years	1.2%–12%	1.2%	References: 34–44
Hepatoblastoma	18–33 months	0.4%–2.5%	__%[g]	References: 45–49
Pancreatic cancer	52 years	1%–2%	1.7%	Reference: 37
CNS cancer (predominantly medulloblastoma)	18 years	1%	0.6%	References: 50–51

Footnotes on FAP-A 2 of 3
References on FAP-A 2 of 3 and FAP-A 3 of 3

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FAP-A 1 OF 3

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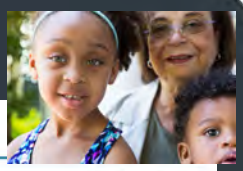
PJS (STK11)



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Peutz-Jeghers Syndrome

Peutz-Jeghers Syndrome: Adult Surveillance

Site	% Lifetime Risk[d]	Screening Procedure and Interval	Initiation Age (y)
Breast (women)	32%–54%	• Mammogram and breast MRI annually[f] • Clinical breast exam every 6 mo	Discuss option RRM ~ 30 y (25)
Colon	39%	• High-quality colonoscopy every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology.	~ 18 y
Stomach	29%	• Upper endoscopy every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology.	~ 18 y
Small intestine	13%	• Small bowel visualization (video capsule endoscopy or CT/MRI enterography) every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology.	~ 18 y
Pancreas	11%–36%	• Annual imaging of the pancreas with either EUS or MRI/MRCP (both ideally performed at center of expertise). Also see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic	~ 30–35 y[g]
Cervix (typically minimal deviation adenocarcinoma[e])	At least 10%	• Annual pelvic examination and Pap smear • Consider total hysterectomy (including uterus and cervix) once completed with childbearing	~ 18–20 y
Uterus	9%	• Annual pelvic examination with endometrial biopsy if abnormal bleeding	~ 18–20 y
Ovary (SCTAT)	At least 20%	• Annual pelvic examination with annual pelvic ultrasound	~ 18–20 y
Lung	7%–17%	• Provide education about symptoms and smoking cessation. See NCCN Guidelines for Smoking Cessation. No other specific recommendations have been made.	
Testes (Sertoli cell tumors)	9%	• Annual testicular exam and observation for feminizing changes	Continued from pediatric screening

[d] Hearle N, et al. Clin Cancer Res 2006;12:3209–3215; Giardiello FM, et al. Gastroenterology 2000;119:1447–1453; Ishida H, et al. Surg Today 2016;46:1231–1242.
[e] Formerly known as cervical adenoma malignum.
[f] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (BRCA-A) for further breast screening recommendations regarding mammogram and breast MRI screening. High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably days 7–15 of menstrual cycle for premenopausal women. The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, et al. Cancer 2012;118:2021–2030.
[g] Based on clinical judgment, early initiation age may be considered, such as 10 y younger than the earliest age of onset in the family.

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PJS-3

Sex Cord Tumor w Annual Tubules

Consider start testicular screening Exam - Age 1

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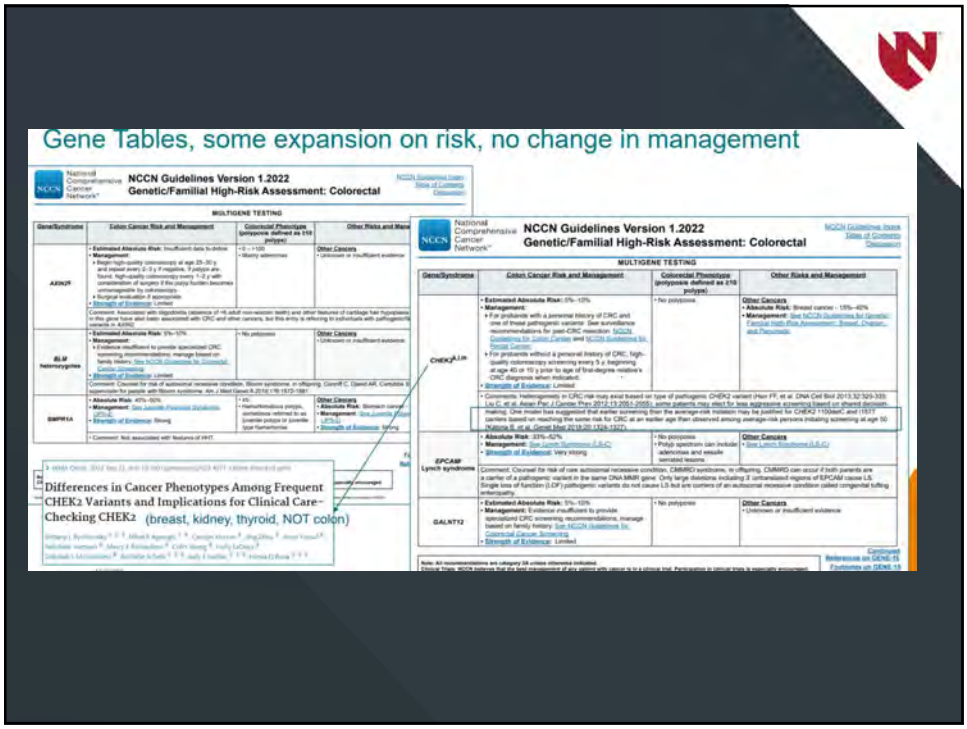
Gene Tables, some expansion on risk, no change in management
NCCN Guidelines Version 1.2022
Genetic/Familial High-Risk Assessment: Colorectal
MULTIGENE TESTING
Differences in Cancer Phenotypes Among Frequent CHEK2 Variants and Implications for Clinical Care–Checking CHEK2 (breast, kidney, thyroid, NOT colon)

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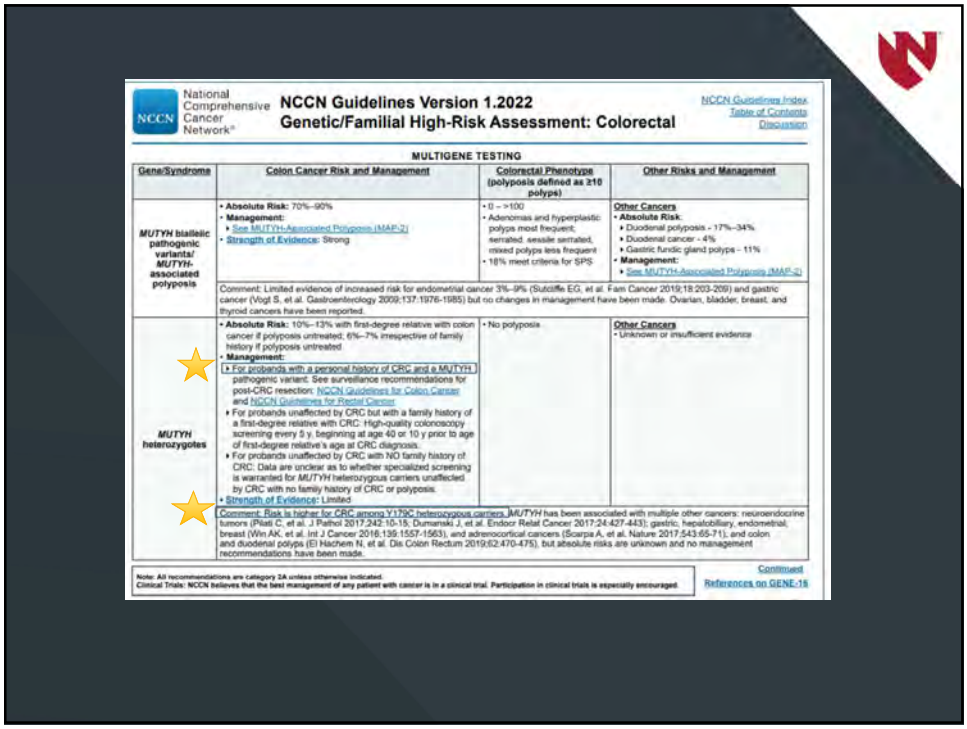
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Genetic/Familial High-Risk Assessment: Colorectal
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Gene/Syndrome
Colon Cancer Risk and Management
Colorectal Phenotype (polyposis defined as ≥10 polyps)
Other Risks and Management
MUTYH biallelic pathogenic variants/ MUTYH-associated polyposis
• Absolute Risk: 70%–90%
• Management:
See MUTYH-Associated Polyposis (MAP-2)
• Strength of Evidence: Strong
• 0 – >100
• Adenomas and hyperplastic polyps most frequent; serrated, sessile serrated, mixed polyps less frequent
• 18% meet criteria for SPS
Other Cancers
• Absolute Risk:
Duodenal polyposis - 17%–34%
Duodenal cancer - 4%
Gastric fundic gland polyps – 11%
• Management:
See MUTYH-Associated Polyposis (MAP-2)
Comment: Limited evidence of increased risk for endometrial cancer 3%–9% (Sutcliffe EG, et al. Fam Cancer 2019;18:203-209) and gastric cancer (Vogt S, et al. Gastroenterology 2009;137:1976-1985) but no changes in management have been made. Ovarian, bladder, breast, and thyroid cancers have been reported.
MUTYH heterozygotes
• Absolute Risk: 10%–13% with first-degree relative with colon cancer if polyposis untreated; 6%–7% irrespective of family history if polyposis untreated
• Management:
For probands with a personal history of CRC and a MUTYH pathogenic variant: See surveillance recommendations for post-CRC resection: NCCN Guidelines for Colon Cancer and NCCN Guidelines for Rectal Cancer
For probands unaffected by CRC but with a family history of a first-degree relative with CRC: High-quality colonoscopy screening every 5 y, beginning at age 40 or 10 y prior to age of first-degree relative's age at CRC diagnosis.
For probands unaffected by CRC with NO family history of CRC: Data are unclear as to whether specialized screening is warranted for MUTYH heterozygous carriers unaffected by CRC with no family history of CRC or polyposis.
• Strength of Evidence: Limited
• No polyposis
Other Cancers
• Unknown or insufficient evidence
Comment: Risk is higher for CRC among Y179C heterozygous carriers. MUTYH has been associated with multiple other cancers: neuroendocrine tumors (Pilati C, et al. J Pathol 2017;242:10-15; Dumanski J, et al. Endocr Relat Cancer 2017;24:427-443); gastric, hepatobiliary, endometrial, breast (Win AK, et al. Int J Cancer 2016;139:1557-1563), and adrenocortical cancers (Scarpa A, et al. Nature 2017;543:65-71), and colon and duodenal polyps (El Hachem N, et al. Dis Colon Rectum 2019;62:470-475), but absolute risks are unknown and no management recommendations have been made.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Continued
References on GENE-15

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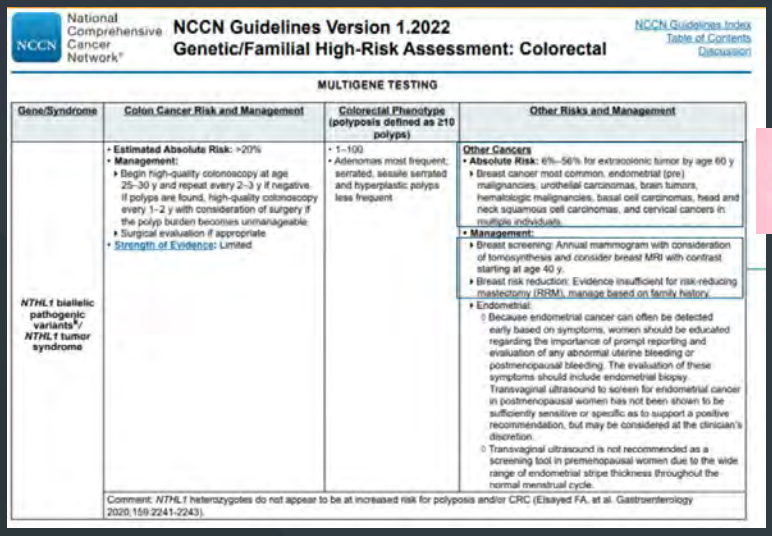

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Genetic/Familial High-Risk Assessment: Colorectal

NCCN Guidelines Index
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Discussion

MULTIGENE TESTING

Gene/Syndrome	Colon Cancer Risk and Management	Colorectal Phenotype (polyposis defined as ≥10 polyps)	Other Risks and Management
NTHL1 biallelic pathogenic variants[f]/ *NTHL1* tumor syndrome	• **Estimated Absolute Risk:** >20% • **Management:** ▸ Begin high-quality colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, high-quality colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable. ▸ Surgical evaluation if appropriate • Strength of Evidence: Limited	• 1–100 • Adenomas most frequent; serrated, sessile serrated and hyperplastic polyps less frequent	**Other Cancers** • **Absolute Risk:** 6%–56% for extracolonic tumor by age 60 y ▸ Breast cancer most common, endometrial (pre) malignancies, urothelial carcinomas, brain tumors, hematologic malignancies, basal cell carcinomas, head and neck squamous cell carcinomas, and cervical cancers in multiple individuals • **Management:** ▸ Breast screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y. ▸ Breast risk reduction: Evidence insufficient for risk-reducing mastectomy (RRM); manage based on family history ▸ Endometrial: ◊ Because endometrial cancer can often be detected early based on symptoms, women should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy. Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. ◊ Transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.
	Comment: *NTHL1* heterozygotes do not appear to be at increased risk for polyposis and/or CRC (Elsayed FA, et al. Gastroenterology 2020;159:2241-2243).		

No NCCN BOP Recs

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Longitudinal Study for Early Detection of Pancreas Cancer

IRB 335-18 – Prospective, Non-Interventional Study

Goal: Identify/Validate biomarkers of preclinical disease.

Eligibility

1) New Onset Diabetes Cohort
2) Pancreatic cystic neoplasm/Chronic pancreatitis
3) Inherited Risk Cohort (APC, ATM, BRCA ½, CDKN2A, Lynch, Palb2, STK11, TP53)

Funding: NCI (PI: Hollingsworth), Pilot Grant UNMC CCTR, Project Purple

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Early detection study acknowledgements

Not limited to…

If you think your patient is eligible for the early detection study:

- **Email kelsey.klute@unmc.edu**
- **Clinicaltrials.gov: Blood Markers of Early Pancreas Cancer**
- **NCT03568630**

With the patient's permission, our study team can reach out to the patient to discuss the study.

NIH NATIONAL CANCER INSTITUTE
Division of Cancer Prevention
Pancreatic Cancer Detection Consortium (PCDC)
project purple
CCTR Pilot Grant Program
University of Nebraska Medical Center

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Current US studies with possible germline eligibility

Study Number	Study Name	phase	committee	status	Network PI	Sponsor	Biomarker
20156	PH3 Alpe BYL719 Olap BRCA OC	III	GYN Oncology	OPEN	Tenerielio, Michael G.	NOVARTIS	BRCA
20248	STAR PH3 Nirap Abira HRR mCSPC	III	GU Malignancy	OPEN	Ravilla, Rahul	JANSSEN	BRIP1/CDK12/CHEK2/FANCA/PALB2/RAD51B/RAD54L/BRCA1/BRCA2
20418	Ph3 Nira Her2- triple- BC ctDNA (ZEST)	III	Breast Cancer	OPEN	Aponte, Emmalind	GlaxoSmithKline	BRCA/HRD/HER2-
21253	PH3 Pac-Carbo-Oreg EO FT or PC	III	GYN Oncology	OPEN	Cloven, Noelle G.	GOG Foundation /OncoQuest Pharmaceuticals Inc.	BRCA1/BRCA2
21309	Ph1 XMT-1536 in Combo HGSOC (UPGRADE-A)	I	Early Development Program	Call Proj Mgr	Anderson, Charles K.	IQVIA /Mersana Therapeutics, Inc	BRCA2/BRCA1
21400	Ph2 TJ004309 + Atezo OC/ST	II	GYN Oncology	Call Proj Mgr	Lee, Christine M.	I-MAB BioPharma /THERADEX	BRCA1/BRCA/BRCA2/PD-1/PD-L1

PARP Inhibitors & Immunotherapy

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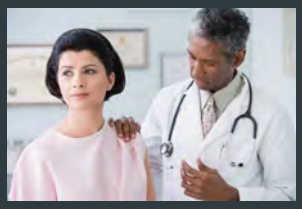
BRCA-PTEN Vaccine Trial

Vaccine for **High Risk BRCA1, BRCA2, or PTEN** Mutation Positive Patients (Cleveland Clinic-IRB 16-520 – Recruiting)



Goal: design & develop a targeted immunotherapeutic breast ca vaccine for patients with germline mutations conferring a high risk of breast (& other) cancers.

Inclusion Criteria

-Adult women 18 years of age

-BRCA1, BRCA2 _or *PTEN* mutation

-Planning standard of care treatment mastectomy, a treatment mastectomy w contralateral RR mastectomy, or a bilateral RR mastectomy

-OR-

Planning standard of care reduction mammoplasty (control group)

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Prostate Screening for Men with Inherited Risk of Developing Aggressive Prostate Ca (PATROL)

- BRCA2, BRCA1, ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, PMS2, TP53, HOXB13
- **Goal:** Investigate ways to detect prostate ca earlier in men at increased genetic risk
- Study samples of blood, urine, and/or tissue
  - Further understand the genetics of prostate ca
  - ID ways to detect ca earlier
  - Improve treatment & methods of early detection.
- (**ClinicalTrials.gov ID :** NCT04472338)

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PRS – Ready for Prime Time?

Can we use this number as a threshold for High Risk breast screening or surgery?

Barriers

- Calibration
- Risk Discrimination
- PRS not equitable – Majority of data in European descent
  - Need more African, Latin, Asian individuals in studies
- Which threshold? If use 20% (like TC) Only 5% of PRS scores higher than 20%, AA scores even less
- Construction of clinically valid assays, Interpretation for indiv. Pts, Development of workflows to support their use in clinic (Hao et al. 2022 Nature Medicine)

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Actionable PRS score data for management guidance in clinic?

1) Confluence Project – NCI – **Results 2024**
   - a large research resource of over 300,000 cases and 300,000 controls of different ancestries—doubling current sample sizes to study the genetic architecture of breast cancer.

2) WISDOM Study – Risk based mammography study
   - Annual mmg vs.
   - Personalized approach (Family History, Genetic testing result, lifestyle, health history, breast density)
   - BCSC + 96 SNP PRS – Large validation study
   - **Results 2024/2025**

3) My PeBS (Personalising Br Screening – Randomised risk-based screening trial
   - 85,000 women in 6 Countries
   - **Results 2024**

4) CanRisk / Boadicea – 313 SNP PRS
5) My Risk – TC + 86 SNP PRS

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PRS Takeaway

- Tyrer Cuzick V.8 – Best Breast cancer risk predictor today
- NCCN – PRS not to be used for mgmt
  - May change in 2-5 years!

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NCCN: Transgender Ca Screening Recommendations

Transgender Females (male to female)	Recommendation	Transgender Males (female to male)	Recommendation
Mammogram	Yes, 5 years after starting estrogen & 10 yrs before youngest breast cancer in family	**Mammogram Breast MRI**	Without top surgery-yes s/p top surgery-yes, if breast cancer gene& enough breast tissue
Colon	Yes	**Colon**	Yes
Prostate	Yes & followed by Urology if BRCA2	**Ovary**	No

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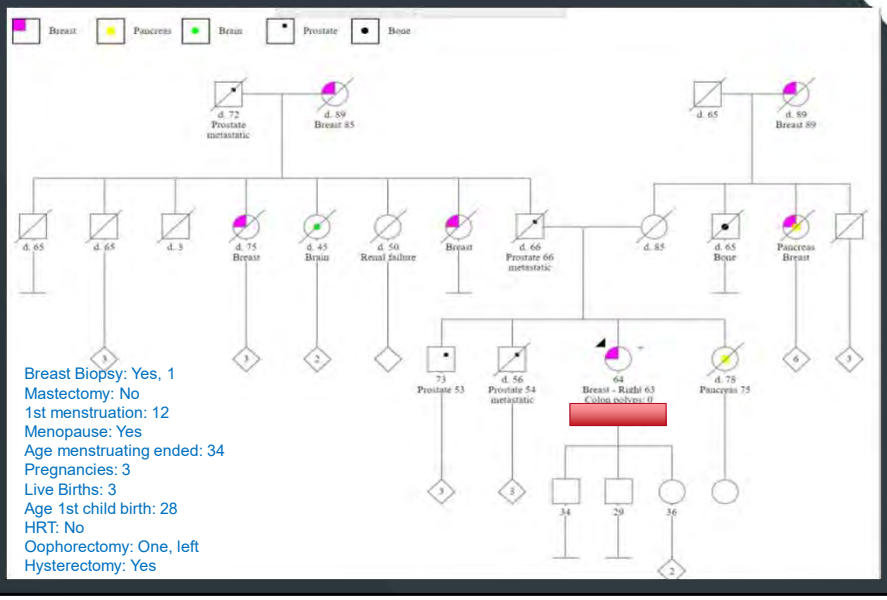
Case 1 : Moira



Breast Biopsy: Yes, 1
Mastectomy: No
1st menstruation: 12
Menopause: Yes
Age menstruating ended: 34
Pregnancies: 3
Live Births: 3
Age 1st child birth: 28
HRT: No
Oophorectomy: One, left
Hysterectomy: Yes

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Palb2

RESULTS

PALB2 **Pathogenic Mutation: c.2167_2168delAT**

SUMMARY

POSITIVE: Pathogenic Mutation Detected

Cancer Type	Risk for General Population	Risk for *PALB2*
Breast cancer (assigned female at birth)	13%	**41-60%**
Breast cancer (assigned male at birth)	0.1%	**0.9%**
Pancreatic cancer	1-2%	**5-10%**
Ovarian cancer	1-2%	**3-5%**
Prostate cancer	12%	Possibly increased based on limited evidence

*Other possible cancer risks related to *PALB2* pathogenic/likely pathogenic variants have not been specified

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Management Recs: Moira

- Mmg/Breast MRI – surveillance second breast ca, Consider RRM
- MRCP/EUS Annually (FDR PDAC)
- New! Consider RRSO (Gyn Onc Referral)
- Clinical Trial – Early Markers Pancreas Ca
- Diet, Physical Activity, Alcohol, Facingourrisk.org

NCCN (2023); Googan et al. (2020) CAPS

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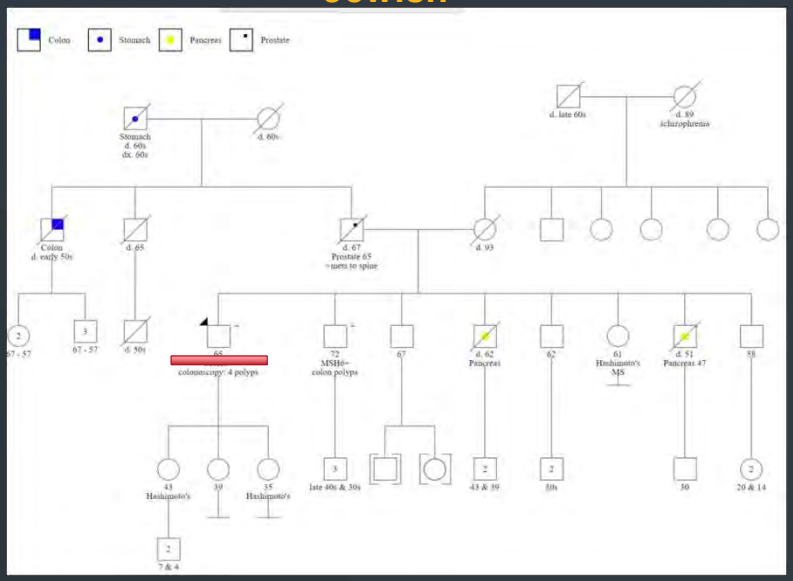
Case 2: Henry - Paternal Ancestry: Ashkenazi Jewish



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MSH6 – Lynch Syndrome

(NCCN 2.2022)

GENE	MUTATION	INTERPRETATION
MSH6	c.171del (p.Arg58Glyfs*23) Heterozygous	High Cancer Risk This patient has Lynch syndrome/Hereditary Non-Polyposis Colorectal Cancer (HNPCC).

	MLH1	MSH2/ EPCAM	MSH6	PMS2
Colon	46-61%	33-52%	10-44%	8.7-20%
Endometrial/ Ovarian	34-54% 4-20%	21-57% 8-38%	16-49%, 1-13%	3.1% 1.3%
Gastric/ Pancreas	5-7% No data	0.2-9% 0.5-1.6%	1-7.9% 1.4-1.6%	0.9% 1.6%
Bladder/ Biliary/ Urothelial	0.2-5% 1.5-3.7%	4.4-12.8%	1-8.2% 0.2-1% 0.7-5.5%	2.4% 0.2%
Small Bowl	0.4-11%	1.1-10%	1-4%	0.1-0.3%
Prostate	4.4-13.8%	3.9-23.8%	2.5-11%	11.6%
Brain	No data	2.5-7.7%	0.8-1.8%	0.6%

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MSH6 Management Recs: Henry

(NCCN 2.2022)

Cancer Risk	Management
Colon	1-3 years (NEW!)
Gastric, Duodenal, Small Bowel	EGD (w random bx-assess H.Pylori) -starting age 30-40 yrs & Repeat Q 2-4 yrs, with colonoscopy
Urothelial	Annual UA with microscopy starting at 30-35
Prostate	Consider Annual PSA
Nervous System	Consider annual Neuro exam at age 25-30

- Lynch Syndrome Int
- Hereditary Colon Cancer Takes Guts
- Great Plains Colon Ca Task Force

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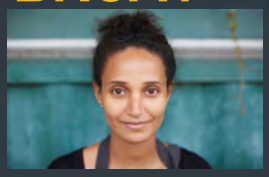
Case 3: Rihanna 35F - BRCA1+

- 35F
- BRCA1 +
- s/p RRSO/TAH 1 month ago, non-smoker, no clotting hx
- Hot flashes Q1 hr, no longer enjoying her job/role as a mother/wife, bloated, insomnia
- She is asking you for Estrogen alone HRT
- Do you consider prescribing?

Yes!



- NCCN – HRT is a consideration
- premenopausal
- No Hx Br Ca
- No other CI
- Consider preop menopause mgmt referral

(Chlebowski et al. (2015) JAMA Onc)

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Case 4: Nicole (NCCN 2.2022)

29 yo Transgender female
BRCA2+

- FH: Breast Ca – Mother (39), Father - Colon Ca (55)
  Mat Aunt – Melanoma (49)
- Started Estrogen (feminizing hormone therapy) (24)
  - Dr. Jean Amoura – NE Med
- She asks if you recommend a mammogram, colonoscopy?
- Anything else? (Derm – FBSE – Melanoma Risk)

Transgender Female (assigned male at birth)	Ca Screening Rec
Mammogram	Yes, 5 yrs after starting estrogen & 10 yrs before youngest breast cancer in the family
Colon	Yes, age 45
Prostate	Yes, followed by Urology or CRPC

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Questions?

Thank you!
Enjoy the Symposium!

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