THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Screening, Prevention, Early Detection, & Genetic Risk

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October 10, 2024

OBJECTIVES

- **Become familiar with current cancer screening, prevention, & early detection recommendations.**
- **Recognize the genetic basis of cancer, genetic assessment & testing, as well as common genetic predisposition syndromes**
- **Identify screening & prevention guidelines for individuals with hereditary risk**
- **Address the role of the APRN in cancer risk assessment, primary & secondary prevention, including risk reduction and cancer screening**

Chapter 1: Cancer Prevention, Screening, and Early Detection

Primary Prevention

“consists of interventions aimed at keeping the carcinogenic process from beginning”

AOCN, pg. 3

Secondary Prevention

“is the discovery of cancerous or precancerous conditions while still in their earliest stage, when the disease is most likely to be treated successfully.”

AOCN, pg. 3

Tertiary Prevention

“is applied to those individuals who have already been diagnosed with a malignancy with the intent of keeping the original disease in remission as long as possible.”

AOCN, pg. 3

Primary Prevention

Tobacco Use

- Considered a contributing or causative agent in multiple malignancies
- Thought to cause up to 90% of lung cancers
- Leading cause of preventable cancer related & non-cancer related deaths
- Over 4,000 chemicals identified of which 55 identified as carcinogens

AOCN, pg. 3

Tobacco Related Cancers

- Lung
- Nasal cavity
- Larynx
- Pharynx
- Esophagus
- Stomach
- Colon
- Rectum
- Liver
- Pancreas
- Kidney
- Bladder
- Uterine cervix
- Mucinous ovarian
- Myeloid leukemia

AOCN, pg. 3

Smoking Cessation

Time Elapsed After Smoking Cessation

- 2 weeks- 3 months
- 1- 9 months
- 12 months
- 5- 15 years
- 10 years
- 15 years

Health Benefits

- Improvements in circulation, oral hygiene, pulmonary function, and skin tone
- Ciliary function restored in lungs
- Coronary artery disease risk reduced 50% compared to current smokers
- Stroke risk reduced to that of nonsmokers
- Risk of death from lung cancer reduced by 50% compared to current smokers
- Coronary heart disease risk reduced to that of nonsmokers

AOCN, pg. 5

Smoking Cessation Counseling

5 A's

- ASK
- ADVISE
- ASSESS
- ASSIST
- ARRANGE

AOCN, pg. 5

5 R's

- RELEVANCE
- RISKS
- REWARDS
- ROADBLOCKS
- REPETITION

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Table 1-4. First-Line Therapy for Treating Tobacco Abuse

Drug	Dose	Common Side Effects	Precautions/ Contraindications	Cost
Bupropion SR	Start 1–2 weeks before quit date at a dose of 150 mg daily for 3 days, then BID for up to 7–12 weeks (can consider up to 6 months after quitting)	Insomnia, dry mouth	Contraindicated in patients with history of seizure or eating disorder Pregnancy class C	Prescription; ~$3.33/day
Nicotine gum	2 mg (< 25 cig/day); 4 mg (≥ 25 cig/day) Use at least one piece every 1–2 hours for first 6 weeks; use up to 12 weeks; do not exceed 24 pieces/day.	Dyspepsia, mouth soreness, hiccups, jaw ache	Caution is advised among patients immediately post–myocardial infarction (MI) (2 weeks) or with serious arrhythmias or unstable chest pain. Dentures may prohibit proper use; patients should avoid eating or drinking 15 minutes prior to and during use. Pregnancy class D	Over the counter; 2 mg: ~$48/box of 100–170 pieces; 4 mg: ~$63/box of 100–110 pieces
Nicotine inhaler	6–16 cartridges/day for 6 months, tapering over last 3 months	Mouth or throat irritation, cough, rhinitis	Caution is advised among patients immediately post-MI (2 weeks) or with serious arrhythmias or unstable chest pain. Patients should avoid eating or drinking 15 minutes prior to and during use. Pregnancy class D	Prescription; ~$196/box of 168 cartridges
Nicotine lozenges	2 mg (patients smoking first cigarette > 30 minutes after waking); 4 mg (patients smoking < 30 minutes after waking) Use at least 9 lozenges/day for first 6 weeks and continue up to 12 weeks; do not exceed 20 lozenges/day.	Mouth irritation, hiccups, nausea, dyspepsia	Patients should not chew or swallow lozenges. Caution is advised among patients immediately post-MI (2 weeks), with serious arrhythmias or unstable chest pain Patients should avoid eating or drinking 15 minutes prior to and during use.	Over the counter; 2 mg: ~$34/box of 72 lozenges; 4 mg: ~$39/box of 72 lozenges

Table 1-4. First-Line Therapy for Treating Tobacco Abuse *(Continued)*

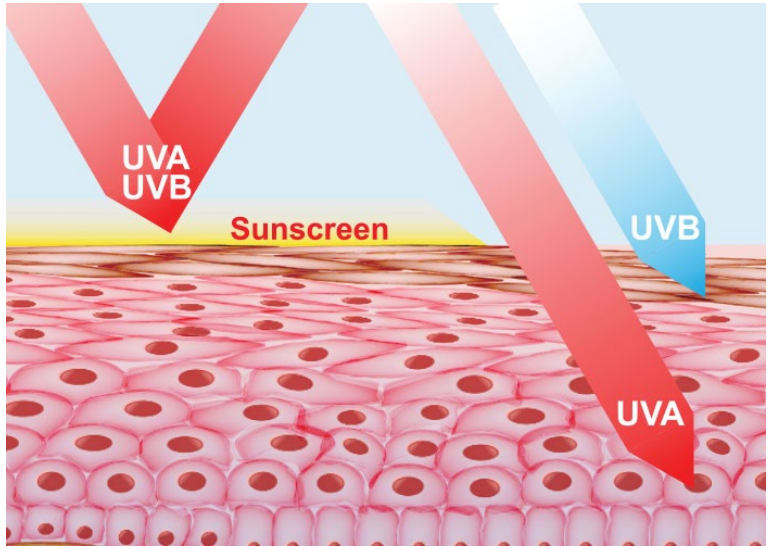
Drug	Dose	Common Side Effects	Precautions/ Contraindications	Cost
Nicotine nasal spray	Initially 1–2 doses/hour and minimum of 8 doses/day; no more than 40 doses/day for 3–6 months	Nasal irritation	Caution is advised among patients immediately post-MI (2 weeks) or with serious arrhythmias or unstable chest pain. Pregnancy class D	Prescription; ~$49/bottle
Nicotine patch	Step-down dosing: 21 mg/24 hours for 4 weeks, then 14 mg/24 hours for 2 weeks, then 7 mg/24 hours for 2 weeks Single-patch dosing: 22 mg/24 hours (heavy smokers); 11 mg/24 hours (light smokers)	Local skin irritation	Caution is advised among patients immediately post-MI (2 weeks) or with serious arrhythmias or unstable chest pain. Pregnancy class D	Prescription or over the counter; 1 box of any dose ranges from $37–$48
Varenicline	0.5 mg once a day for 3 days, then BID for 4 days, then 1 mg BID for total of 12 weeks	Insomnia, nausea	Caution is advised in patients with creatinine clearance < 30 ml/min. Monitor for changes in mood or behavior in all patients, and consider psychiatric history before use. Pregnancy class D	Prescription; ~$130 for a 30-day supply

Note. Based on information from Chaney & Sheriff, 2012; Fiore et al., 2008.

AOCN, pg. 7-8

Sun Exposure

- **Ultraviolet light is a known carcinogen**
  - UVA rays: Penetration of deeper skin layers; responsible for premature aging
  - UVB rays: Vary depending on time and season
- **Avoid exposure to sunlight from 10am to 4pm**
- **Avoid artificial exposure**
  - E.g., tanning booths



- **Skin protection**
  - Wide brim hat
  - Long sleeve shirts, pants
  - Sunglasses
  - Sunscreen (SPF or 15 or higher)
    - Apply 30min prior to sun exposure
    - Reapply after two hours, after swimming, sweating, or toweling off
    - Water resistance sunscreens maintain SPF for 40min
    - Very water resistant maintain SPF for 80min

Diet & Exercise

- **Obesity, physical inactivity, and poor nutrition are the 2nd major risk factor for cancer behind tobacco use**

- **Obesity is linked to higher risk of:**
  - Esophagus, pancreas, colon and rectum, postmenopausal breast cancer, endometrium, kidney, thyroid, gallbladder, liver, cervix, and ovarian cancer.

- **Recommendations:**
  - Smaller portion sizes
  - Limit consumption of processed and/or red meats and alcohol
  - 2.5 cups of vegetables and fruits/day
  - Whole grains over refined grains
  - Adults: at least 150min of moderate-intensity activity or 75min of vigorous activity per week
  - Children/Adolescents: at least 60min of moderate-intensity every day or vigorous activity 3 days/week
  - Limit sedentary activities

Chemoprevention

“Chemoprevention is defined as the use of natural, synthetic, or biologic agents to reverse, suppress, or prevent carcinogenic progression” (NCI, 2014a).

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Tamoxifen/Raloxifene

Tamoxifen- Premenopausal Women

- Selective Estrogen Receptor Modulator (SERM)
- FDA approved in 1998
- Approved for prevention of invasive breast cancer in women with hx of non-invasive breast cancer (DCIS, LCIS, Atypical Ductal Hyperplasia)
- Should be individualized
  - Higher incidence of thromboembolic events and endometrial cancer

Raloxifene- Postmenopausal Women

- 2nd generation SERM
- Reduces invasive breast cancer in high risk postmenopausal
- Fewer cases of uterine cancer, thrombotic events, and cataracts

Celecoxib

- **COX-2**
  - Catalytic enzyme in prostaglandin synthesis induced in inflammatory conditions, including tumor proliferation
  - COX-2 is overexpressed in majority of adenocarcinomas

- **Celecoxib**
  - COX-2 inhibitor
  - FDA approval for 400mg PO BID for prevention of adenomatous polyps in patients with familial adenomatous polyposis (FAP)- Hereditary Colon Cancer Syndrome
  - Not approved for use in general public

AOCN, pg. 12

Human Papillomavirus Vaccines (HPV)

- Three FDA approved vaccines available for prevention of cervical cancer, precancerous or dysplastic cervical and vaginal lesions, and genital warts associated with HPV.

- Gardasil approved 2006 (HPV types 6,11, 16, & 18)- almost 100% effective in women not yet infected

- Cervarix approved 2009 (HPV 16 & 18 only)

- Gardasil 9 approved 2014 (5 additional subtypes)

Secondary Prevention & Screening

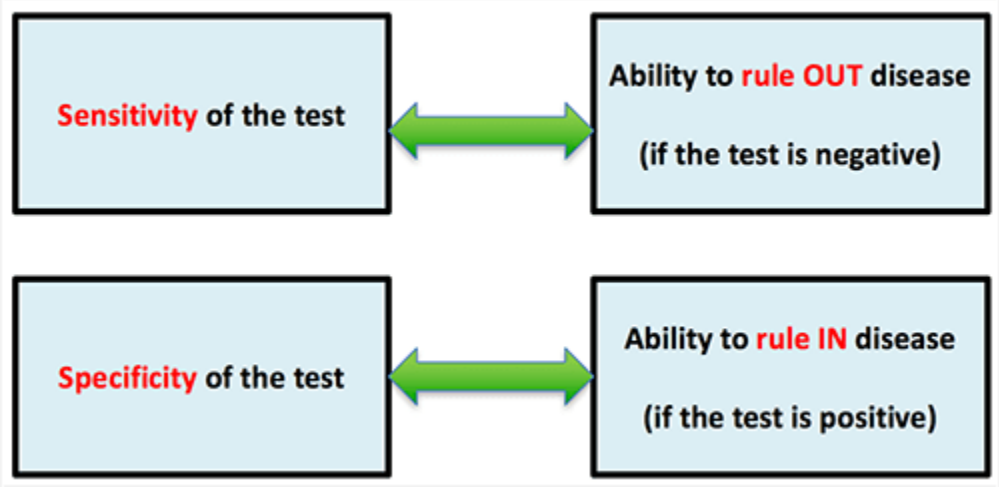
Sensitivity vs. Specificity

Sensitivity

- The proportion of people with cancer that are found to have a positive test
- Higher sensitivity means fewer false-negative results

Specificity

- The proportion of people without cancer that have negative results
- Higher specificity, the fewer false-positive results



Breast Cancer Screening

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NCCN Guidelines Version 1.2021
Breast Cancer Screening and Diagnosis

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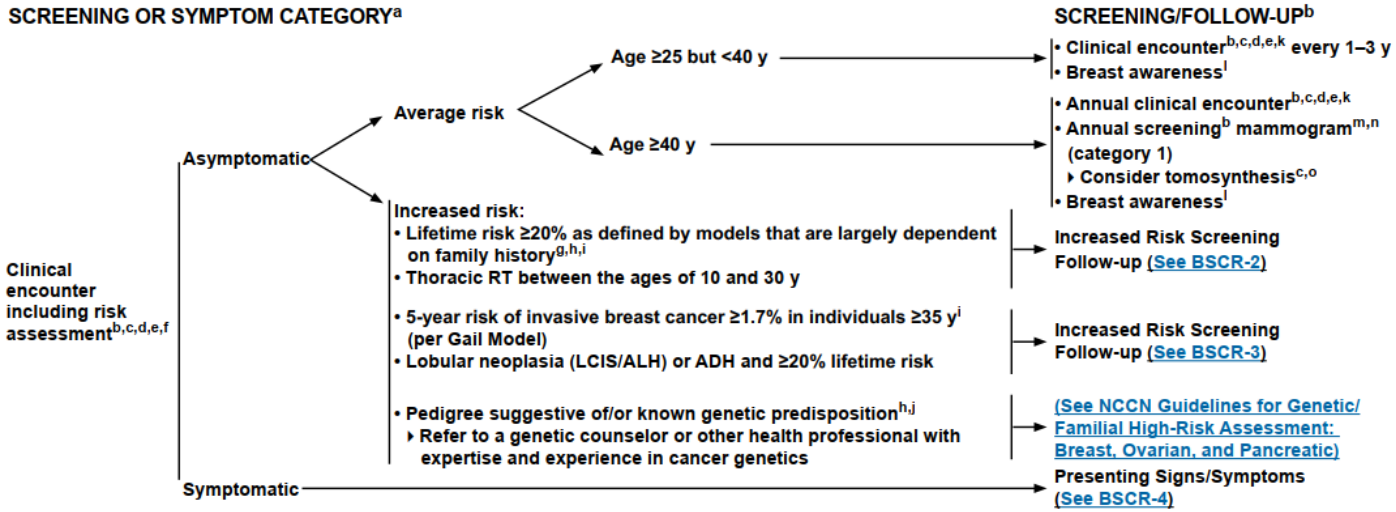

[a]For individuals with a prior history of breast cancer, please refer to the NCCN Guidelines for Breast Cancer - Surveillance Section.
[b]See Breast Screening Considerations (BSCR-A).
[c]Medicare and insurers allow the individual direct access to scheduling for screening mammography.
[d]At minimum, medical and family history should be obtained and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, and preferably a clinical breast exam even in asymptomatic individuals when feasible.
[e]Refer to the NCCN Guidelines for Breast Cancer Risk Reduction for a detailed qualitative and quantitative risk assessment.
[f]For pregnant and lactating individuals, see BSCR-C.
[g]Individuals with a lifetime risk of 15%–20% may be considered for supplemental screening on an individual basis, depending on risk factors.
[h]Risk models that are largely dependent on family history (eg, Claus, BRCAPRO, Tyrer-Cuzick). See NCCN Guidelines for Breast Cancer Risk Reduction.
[i]See Comparison of predictive models for risk assessment (NCCN Guidelines for Breast Cancer Risk Reduction).
[j]There is variation in recommendations for initiation of screening for different genetic syndromes. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[k]Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers and assure ongoing risk assessment.
[l]Individuals should be familiar with their breasts and promptly report changes to their health care provider.
[m]See Mammographic Evaluation (BSCR-20).
[n]Shared decision-making is encouraged based on individuals' values and preferences.
[o]Tomosynthesis can decrease call back rates and improve cancer detection but has not been sufficiently studied to determine if it improves disease-specific mortality.

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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SCREENING OR SYMPTOM CATEGORY[a] | **SCREENING/FOLLOW-UP**

Increased Risk:

Lifetime risk ≥20% as defined by models that are largely dependent on family history[g,h,i]

- Clinical encounter[b,c,d,e,k] every 6–12 mo
  - To begin when identified as being at increased risk, but not prior to age 21 y
  - Consider referral to a genetic counselor or other health professional with expertise and experience in cancer genetics, if not already done
  - Consider referral to a breast specialist as appropriate
- Annual screening[b] mammogram,[m] consider tomosynthesis[o]
  - To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, not prior to age 30 y or age 40 y (whichever comes first)
- Recommend annual breast MRI[p]
  - To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, not prior to age 25 y[q] or age 40 y (whichever comes first)
  - Consider contrast-enhanced mammography[b] or whole breast ultrasound[b] for those who qualify for but cannot undergo MRI
- Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness[l]

OR

Thoracic RT between the ages of 10 and 30 y

Current age <25 y

- Annual clinical encounter[b,c,d,e,k]
  - Beginning 8 y after RT
- Breast awareness[l]

Current age ≥25 y

- Clinical encounter[b,c,d,e,k] every 6–12 mo
  - Begin 8 y after RT
- Annual screening[b] mammogram,[m] consider tomosynthesis[o]
  - Begin 8 y after RT but not prior to age 30 y
- Recommend annual breast MRI[p]
  - Begin 8 y after RT but not prior to age 25 y
  - Consider contrast-enhanced mammography[b] or whole breast ultrasound[b] for those who qualify for but cannot undergo MRI
- Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction)
- Breast awareness[l]

Note: All recommendations are category 2A unless otherwise indicated.
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Breast Cancer Screening

MRI screening

- **Not been found to reduce mortality in any group of women**
- **ACS and NCCN recommend annual breast screening with MRI as adjunct to MMG in high-risk women**
  - Women 20-25% or greater lifetime risk
  - BRCA1/BRCA2 carriers
  - Women with first degree relative with BRCA1/BRCA2
  - Li-Fraumeni
  - PTEN mutation
  - Significant family hx of breast or ovarian
  - Hx of mantle radiation therapy associate with tx for Hodgkin lymphoma

Cervical Cancer Screening

Population	Recommendation	Grade
Women aged 21 to 65 years	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women aged 21 to 29 years. For women aged 30 to 65 years, the USPSTF recommends screening every 3 years with cervical cytology alone, every 5 years with high-risk human papillomavirus (hrHPV) testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting). See the Clinical Considerations section for the relative benefits and harms of alternative screening strategies for women 21 years or older.	A
Women younger than 21 years	The USPSTF recommends against screening for cervical cancer in women younger than 21 years.	D
Women who have had a hysterectomy	The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (ie, cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.	D
Women older than 65 years	The USPSTF recommends against screening for cervical cancer in women older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. See the Clinical Considerations section for discussion of adequate prior screening and risk factors that support screening after age 65 years.	D

Colorectal Cancer Screening

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RISK ASSESSMENT FOR COLORECTAL CANCER

Average risk:

- Age ≥45 years[a]
  - The data supporting lowering the age to initiate screening are largely from modeling studies.
  - Between 1992 and 2015 there was a relative increase of 30% in the incidence of CRC in 40 year olds. However, this translates into an absolute difference in incidence of 8.2 cases per 100,000.[b]
  - We currently lack empirical data to support screening in those <50 years, as screening studies in average-risk individuals have been limited to those aged ≥50 years.
  - Considerations for the age to initiate CRC screening may be dependent on race/ethnicity, patient preference, and resources available. Because there are multiple options for screening, the choice of a particular screening modality should include a conversation with the patient concerning their preference and availability.
- No history of adenoma or sessile serrated polyp (SSP)[c] or CRC
- No history of inflammatory bowel disease (IBD)
- Negative family history for CRC or confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) or an advanced SSP[d] (≥1 cm, any dysplasia)

→ See Average-Risk Screening and Evaluation (CSCR-3)

Increased risk:

- Personal history
  - Adenoma or SSP[c] → See Follow-up of Clinical Findings: Polyp Found at Colonoscopy (CSCR-5)
  - CRC → See Increased Risk Based on Personal History of Colorectal Cancer (CSCR-7)
  - IBD (ulcerative colitis, Crohn's disease) → See Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease (CSCR-8)
- Positive family history → See Increased Risk Based on Positive Family History (CSCR-11)

Colorectal Cancer Screening

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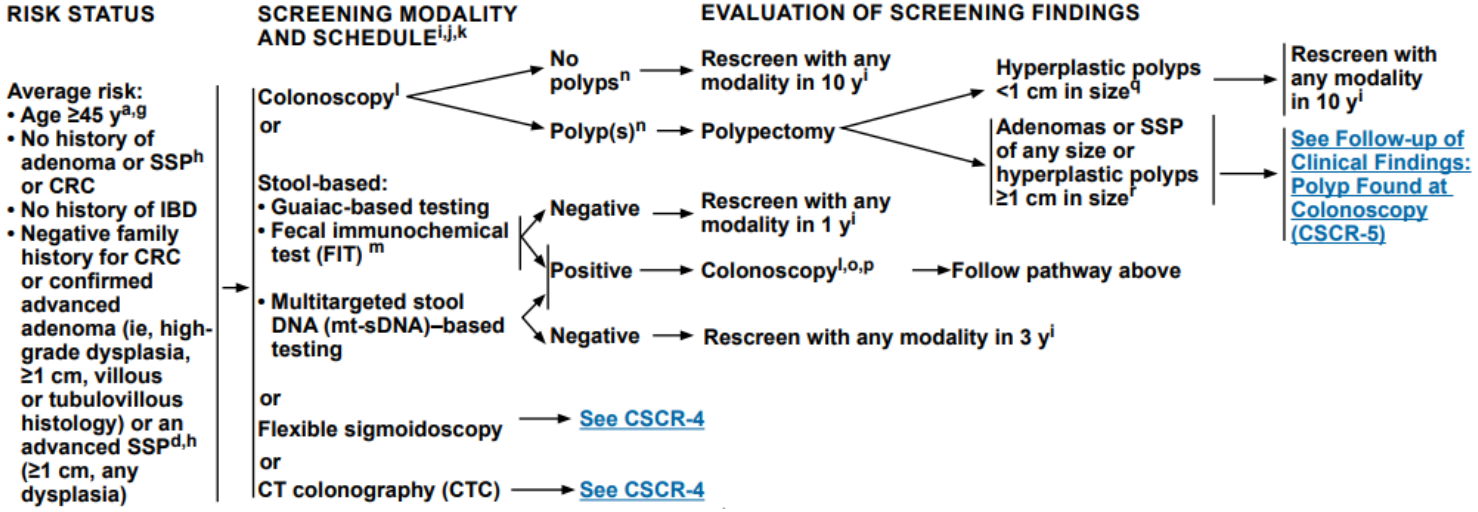

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RISK ASSESSMENT FOR COLORECTAL CANCER (CONT.)

Evaluation of alarm symptoms in patients <45 years:
Signs and symptoms of CRC such as iron deficiency anemia, rectal bleeding, or a change in bowel habits presenting in individuals <45 years warrant prompt evaluation with a colonoscopy or at least with flexible sigmoidoscopy.

- Half of the patients who present with early-onset CRC are <45 years of age.[b,e] The incidence of CRC in individuals <50 years has increased 22% between 2003 and 2013.[f]
- The majority of CRCs in these younger individuals appear to be sporadic but an inherited cancer syndrome should be ruled out given the higher incidence of inherited CRC syndromes in younger patients when compared to older patients.[f]

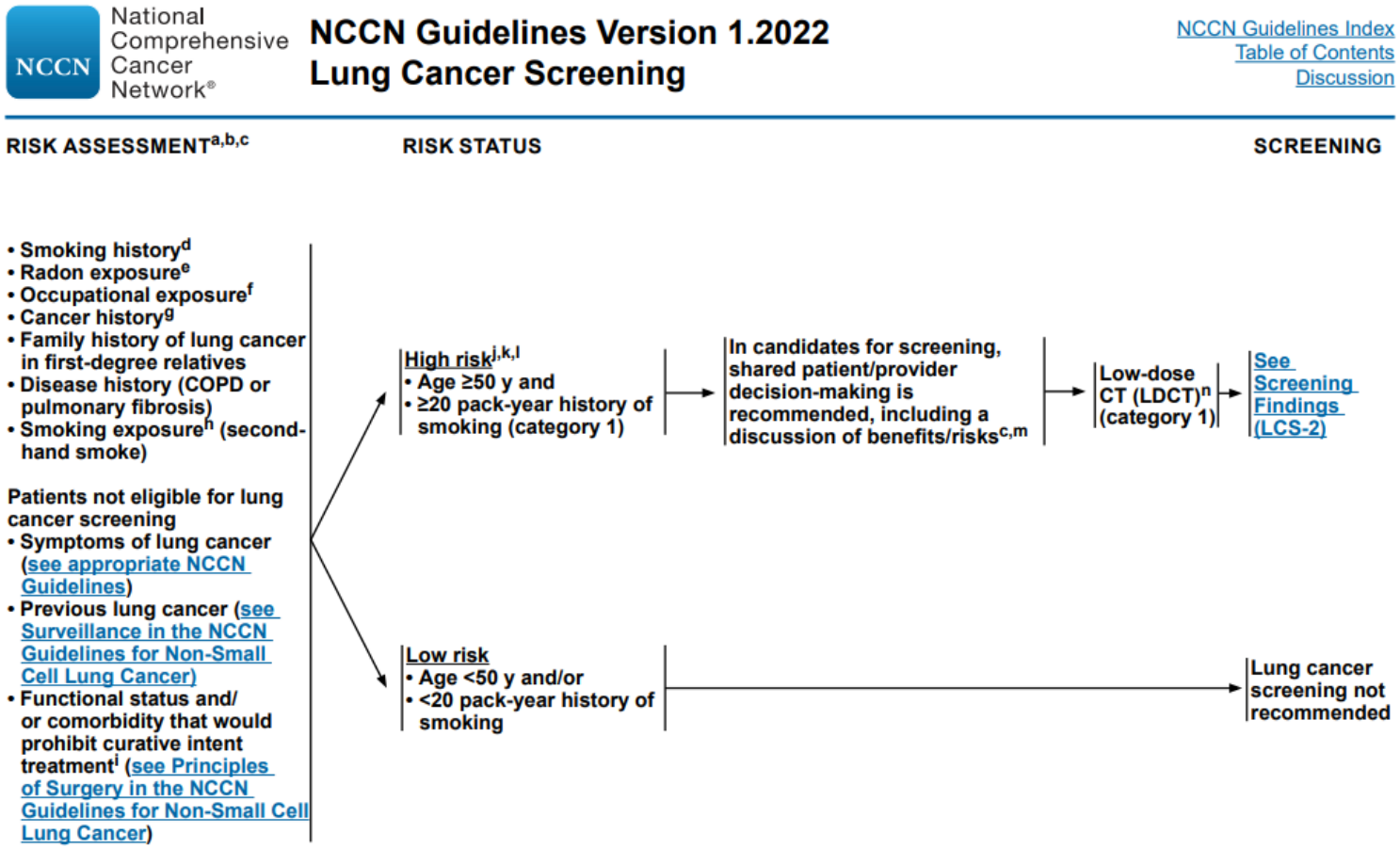
High-risk syndromes:

- Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC])
- Polyposis syndromes
  - Classical familial adenomatous polyposis
  - Attenuated familial adenomatous polyposis
  - *MUTYH*-associated polyposis
  - Peutz-Jeghers syndrome
  - Juvenile polyposis syndrome
  - Serrated polyposis syndrome (rarely inherited)
  - Colonic adenomatous polyposis of unknown etiology
- Cowden syndrome/PTEN hamartoma tumor syndrome
- Li-Fraumeni syndrome

→ See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal

→ See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Lung Cancer Screening



Prostate Cancer Screening

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Prostate Cancer Early Detection

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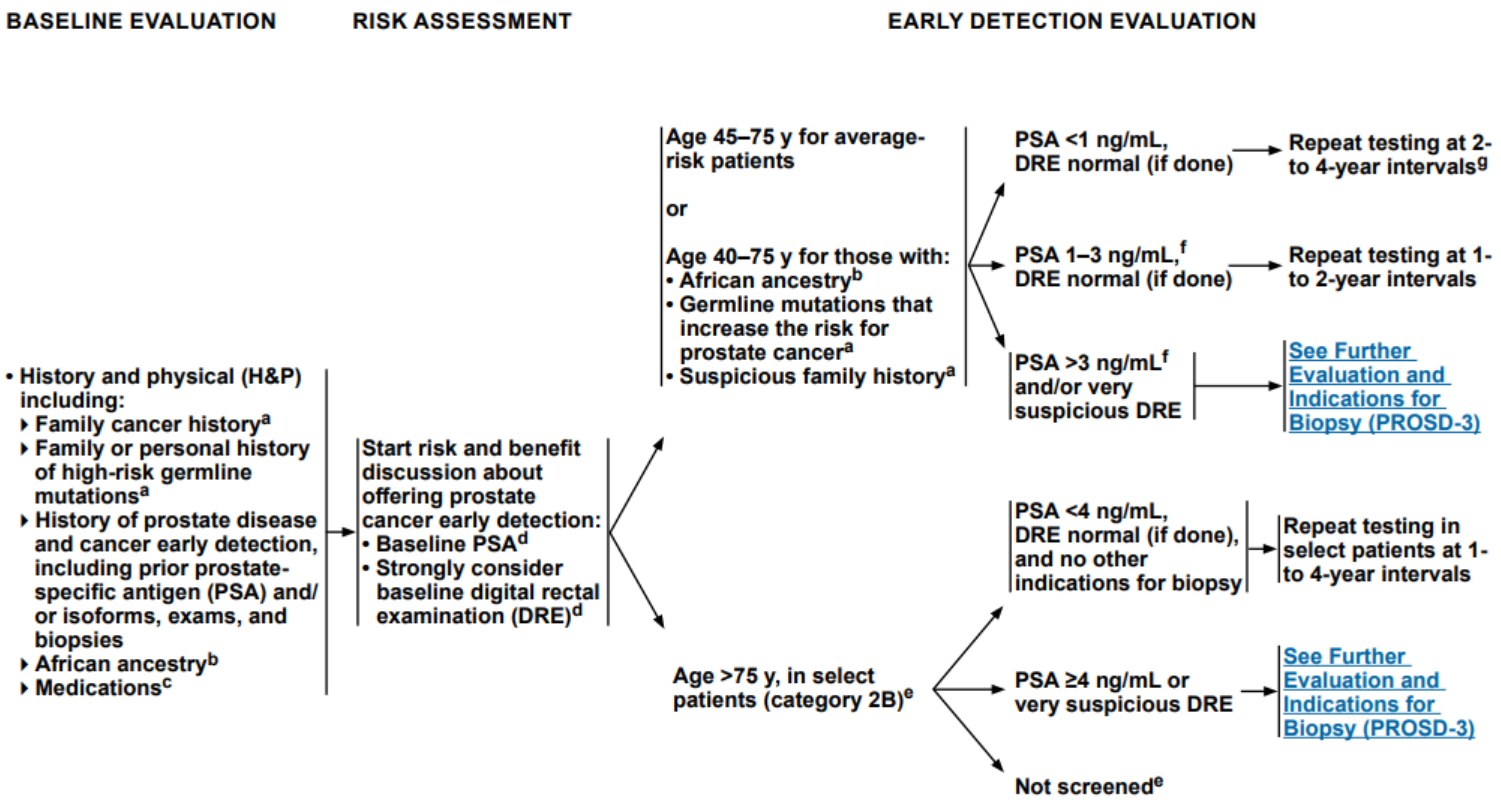
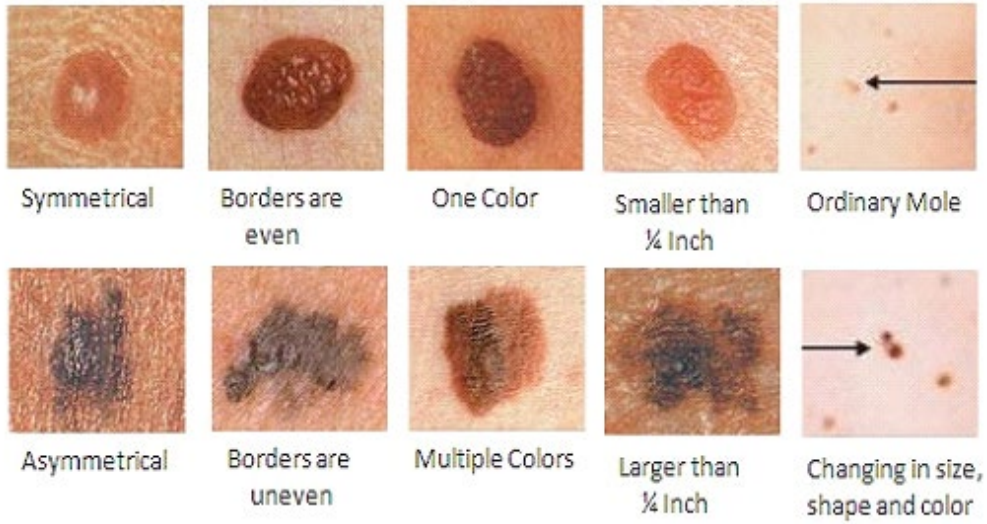


Skin Cancer Screening



- **A= Asymmetry:** ½ of the mole does not match the other half
- **B= Border irregularity:** The edges of the mole are irregular, blurred, jagged, or notched
- **C= Color:** The color of the mole is not uniform, with varying degrees of tan, brown, or black
- **D= Diameter:** The diameter of the mole is greaser than 6 mm, or the size of a pencil eraser
- **E= Evolving:** any change of the mole. E.g., bleeding, itching, crusting

Chapter 2: Genetic Risk

Genetic Risk

- Human Genome Project
- 5-10% Hereditary Cancers
- Recognition of high-risk population
- Legal & Ethical implications
- New Population:
  - **“Pre-Vivors”**

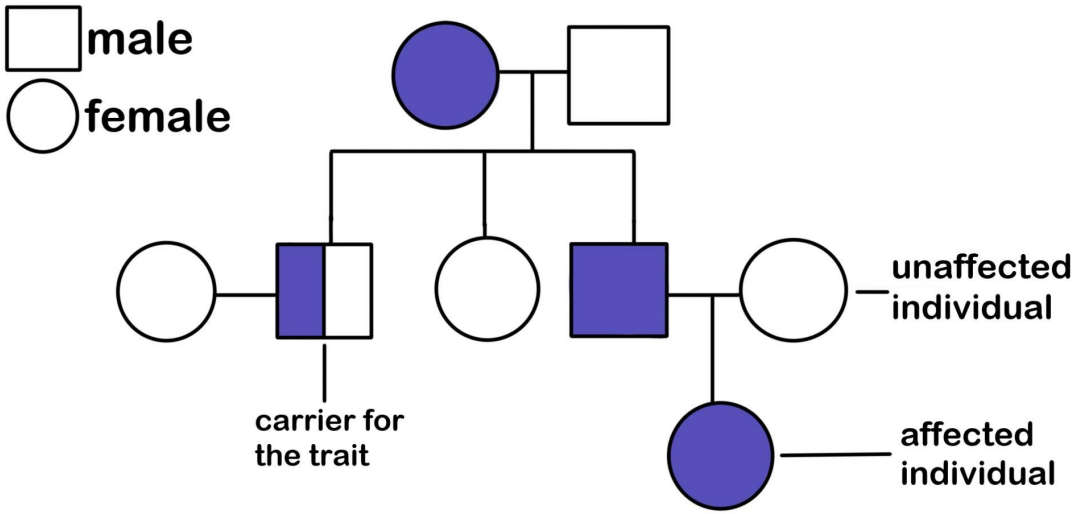
APRN Basic Competencies

- Risk Assessment & Interpretation
- Genetic Education, Counseling, Testing, & Results Interpretation
- Clinical management
- Ethical, Legal & Social Implications
- Professional Roles
- Leadership
- Research

APRN Competencies

- DETAILED EVALUATION
- EXPANDED HISTORY
- RISK ASSESSMENTS
- FAMILY HISTORY
- PEDIGREE ANALYSIS

- APPROPRIATE PHYSICAL ASSESSMENTS
- SCREENING TESTING
- FAMILY ASSESSMENTS & REFERRALS



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Genetic Professionals

- **Geneticists-** physicians with board certification in genetics from American Board of Medical Genetics
- **Credentialed genetic nurses-** credentialed nurses by the ANCC
  - Masters' degree to obtain American Nurses Credentialing Center (AGN-BC)
  - 1,500 hours of Genetic Practice
  - 30 hours CE in genetics
  - Peer & Supervisor evaluations
- **Licensed genetic counselor-** health care professionals with specialized graduate degrees in medical genetics and counseling
  - Certified by the American Board of Genetic Counseling

Current Commercial Testing

Genetic Terminology

- ALLELE
- AUTOSOMAL DOMINANT
- AUTOSOME
- BIALLELIC
- CHROMOSOME
- GENE
- GENOME
- GENOTYPE
- GERM-LINE
- HETEROZYGOUS
- HOMOZYGOUS
- MUTATION
- ONCOGENE
- PENETRANCE
- PHENOTYPE
- PROBAND
- PROMOTER
- RECESSIVE
- SOMATIC CELLS
- TUMOR SUPPRESSOR GENE

AOCN, pg. 32-33

Epidemiology- Types of Risk

- ABSOLUTE
- ATTRIBUTABLE
- INCIDENCE
- POPULATION
- PREVALENCE
- RELATIVE
- RISK FACTOR

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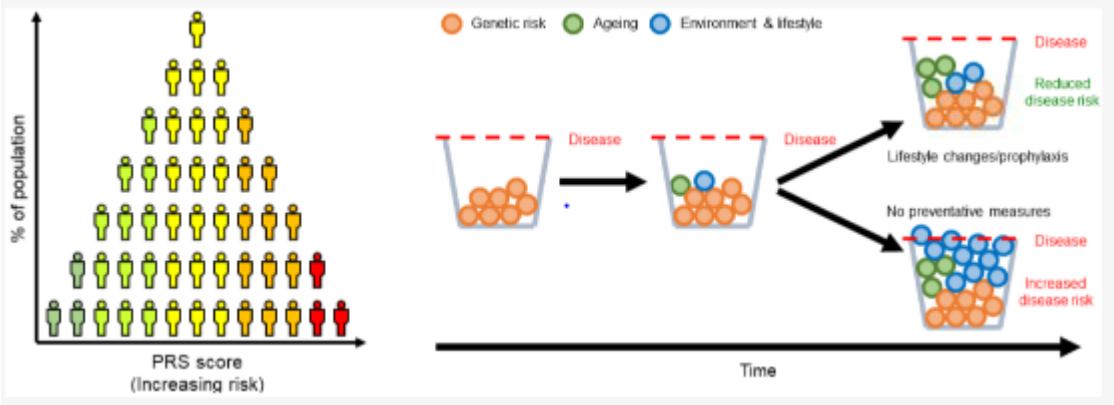

Genetic Basis of Cancer

- **Somatic:** occurs during growth & development of a tissue or organ

  Vs.

- **Germ-line:** occurs at conception in the ova or sperm

- **Proto-oncogenes**
  - Regulate normal cell growth
- **Oncogenes**
  - Associated with abnormal cell growth- leading to increased cellular proliferation and uncontrolled growth
- **Mismatch repair (MMR)**
  - Repair mistakes that occur during DNA replication
- **Tumor suppressor genes**
  - Caretaker genes: maintain integrity of genetic material
  - Gatekeeper genes: regulate proliferation and cell life

Hereditary Cancers- Germline

- BRCA1
- BRCA2
- MSH 2
- MLH 1
- P16
- PTEN
- FAP

- Estimated 10-15% of all cancer have a hereditary basis

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Somatic Mutations

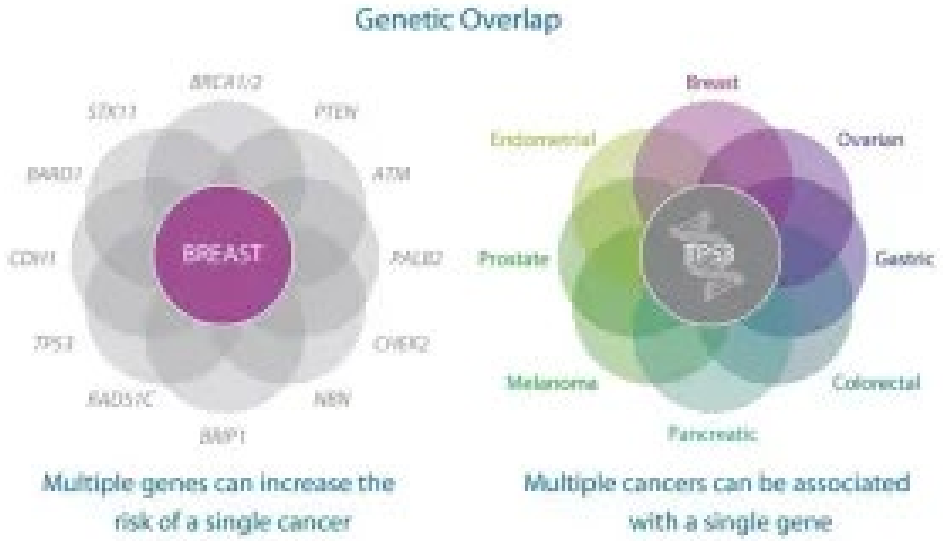
- E.g., HER2/neu amplification in breast cancer, Philadelphia chromosome in chronic leukemia

- Estimated that 85% of cancer are from somatic mutations
- Sporadic cancer
- Timing occurs after conception
- Cannot be passed to subsequent generations

Common Genetic Cancer Predisposition Syndromes

Common Genetic Cancer Predisposition Syndromes

- **Hereditary Breast Cancer Syndrome**
- **Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC)**
- **Familial Adenomatous Polyposis Syndrome (FAP)**
- **Hereditary Melanoma**
- **Hereditary Pancreatic Cancer**



Hereditary Breast Cancer Syndromes

- **BRCA1/2**
  - Caretaker genes by maintaining genomic stability
  - Recognize and repair damaged DNA
  - Cell cycle checkpoint control
- **5-10% breast cancer caused by BRCA1/2 mutations**
- **Risk of breast cancer development between 33-50% by age 50**
- **Cumulative risk by age 70 is 87%**
- **BRCA1/2 mutations**
  - Associated with melanoma and prostate
  - Gastric, pancreatic, male breast cancers
- **BRCA1 related tumors**
  - Medullary histopathology
  - Higher histologic grade
  - More likely to be triple negative
- **High risk Populations**
  - Ashkenazi Jewish
  - Dutch
  - Icelandic descent
- **NCCN updates**
  - Identify individuals who have not had comprehensive testing
  - Likely before 2013
- **Other hereditary syndromes a/w BRCA1/2**
  - Li-Fraumeni
  - Cowden
  - Peutz-Jeghers
  - Diffuse hereditary gastric syndromes

AOCN, pg. 37 & 42

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Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53*. See GENE-A)[a,d,e,f]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - By Age at Diagnosis and Family History
    - ≤45 y
    - 46–50 y with ANY:
      - Unknown or limited family history[g]
      - Multiple primary breast cancers (synchronous or metachronous)
      - ≥1 close blood relative[h] with breast, ovarian, pancreatic, or prostate cancer at any age
    - ≥51 y
      - ≥1 close blood relative[h] with ANY:
        - breast cancer at age ≤50 y or male breast cancer at any age
        - ovarian cancer any age
        - pancreatic cancer any age
        - metastatic,[i] intraductal/cribriform histology, or high- or very-high risk group (see NCCN Guidelines for Prostate Cancer) prostate cancer any age
      - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
      - ≥2 close blood relatives[h] with either breast or prostate cancer (any grade) at any age
    - Any Age
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (See NCCN Guidelines for Breast Cancer)
      - To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER-2 negative breast cancer[j]
      - Triple-negative breast cancer
      - Lobular breast cancer with personal or family history of diffuse gastric cancer. See NCCN Guidelines for Gastric Cancer
      - Male breast cancer
      - ≥1 close blood relative[g] with male breast cancer
  - By Ancestry
    - Ashkenazi Jewish ancestry
- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[m]
    - If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[n]

Criteria met → See GENE-1

If testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Continued on CRIT-3

Footnotes on CRIT-2A

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

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Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR OVARIAN CANCER SUSCEPTIBILITY GENES[a] (See GENE-A)

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of epithelial ovarian cancer[p] (including fallopian tube cancer or peritoneal cancer) at any age
- Family history of cancer only
  - An unaffected individual with a first- or second-degree blood relative with epithelial ovarian cancer[i] (including fallopian tube cancer or peritoneal cancer) at any age[m]
  - An unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[n]

Criteria met → See GENE-1

If testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Hereditary Nonpolyposis Colorectal Cancer Syndrome- Lynch Syndrome MSH2, MLH1, PMS2, MSH6, EPCAM

- **3-5% of colorectal cancers**
  - Associated with endometrial, ovarian, gastric, bile duct, small bowel, renal pelvis, and ureter cancers
- **80% lifetime risk of colorectal cancer**
- **60% lifetime risk of endometrial cancer in women and 12% lifetime risk of ovarian cancer**
- **1-12% lifetime risk of stomach cancer as compared to 1% in general population**
- **Right sided colon cancer**
- **Poorly differentiated tumors**
  - Mucoid and signet cell features
- **Bethesda Criteria**
  - Method to determine further MSI or IHC testing

Presence of one or more of these factors is suggestive of HNPCC and warrants evaluation:

- **Personal hx of colorectal and/or endometrial CA dx < age 50**
- **1st degree relative with colorectal CA dx < age 50**
- **Two or more relatives with colorectal CA or an HNPCC-associated cancer**
  - Endometrial, ovarian, gastric, hepatobiliary, small bowel, renal pelvis, sebaceous adenomas, or ureter cancers; at least one relative must be a 1st degree relative of another
- **Colorectal CA occurring in two or more generations on same side of family**
- **Personal hx of colorectal CA and 1st degree relative with adenomas diagnosed < age 40**
- **Affected relative with known HNPCC mutation**

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Lynch Syndrome

CRITERIA FOR THE EVALUATION OF LYNCH SYNDROME

- Known LS pathogenic variant in the family
- Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age[a] (See LS-A)
- An individual with colorectal or endometrial cancer and any of the following:
  - Diagnosed <50 y
  - A synchronous or metachronous LS-related cancer[b] regardless of age
  - 1 first-degree or second-degree relative with an LS-related cancer[b] diagnosed <50 y
  - ≥2 first-degree or second-degree relatives with an LS-related cancer[b] regardless of age
- Family history[c] of any of the following:
  - ≥1 first-degree relative with a colorectal or endometrial cancer diagnosed <50 y
  - ≥1 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer[b] regardless of age
  - ≥2 first-degree or second-degree relatives with LS-related cancers,[b] including ≥1 diagnosed <50 y
  - ≥3 first-degree or second-degree relatives with LS-related cancers[b] regardless of age
- Increased model-predicted risk for Lynch syndrome
  - An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (ie, $PREMM_5$, MMRpro, MMRpredict)
    - ◊ Individuals with a personal history of colorectal and/or endometrial cancer with a $PREMM_5$ score of ≥2.5% should be considered for multi-gene panel testing.
    - ◊ For individuals without a personal history of colorectal and/or endometrial cancer, some data have suggested using a $PREMM_5$ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.

→ See Strategies For Evaluating LS (LS-2)

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Lynch Syndrome

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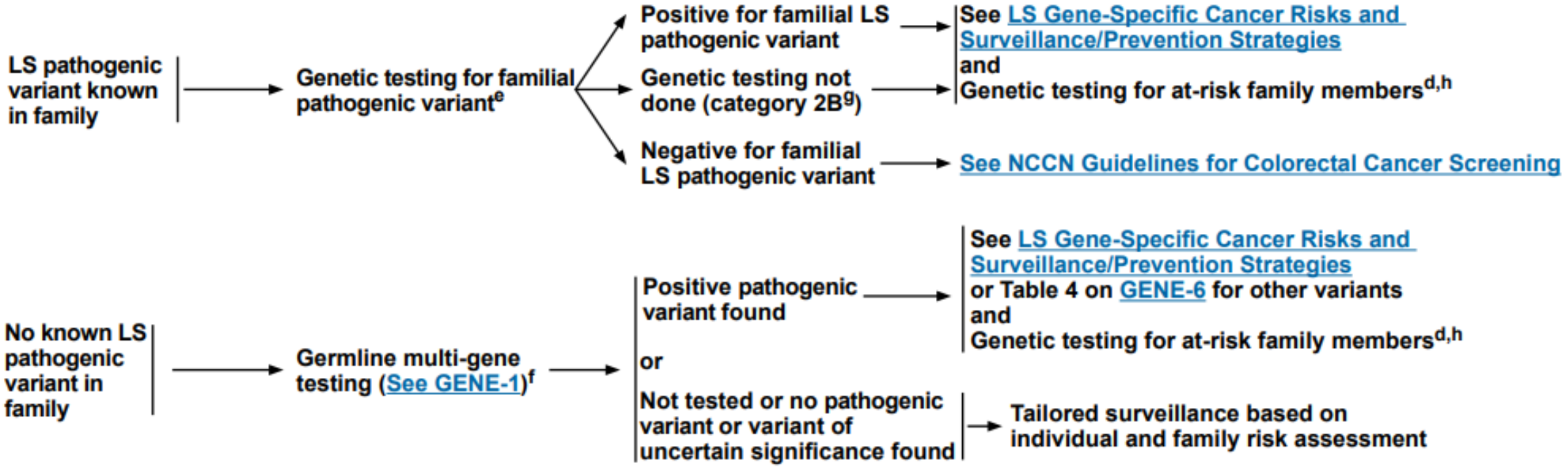
STRATEGIES FOR EVALUATING FOR LS IN INDIVIDUALS MEETING CRITERIA FOR THE EVALUATION OF LS



Familial Adenomatous Polyposis Syndromes
APC, MUTYH (MYH)

- **Typically characterized by 100+ adenomatous colonic polyps**
- **1% colorectal cases**
- **Mean age: 39**
- **75% may develop adenomas by age 20**
- **Less severe form: attenuated familial adenomatous polyposis (AFAP)**
- **800 mutations in APC gene**
- **MYH- biallelic mutations of MUTYH gene**
  - Recessive
  - 22-29% north Europeans with more than 10 adenomatous polyps
- **MUTYH-associated polyposis (MAP)**
  - Autosomal recessive
    - 0.5%-1% of all colorectal cancer
    - Risk of colon CA 19% by age 50 and 43% by age 60

Presence of one or more of these factors is suggestive of hereditary FAP/AFAP and warrants evaluation:

- **Patient with clinical dx of FAP (100+ polyps)**
- **Suspected FAP or AFAP (15-99 polyps)**
- **1st degree relative with known FAP or MYH mutation**
- **Patient with any # of adenomas in family with FAP**

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Familial Adenomatous Polyposis/AFAP

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PHENOTYPE

Classical FAP:[a]
- Germline *APC* pathogenic variant
- Presence of ≥100 cumulative adenomas[b] (sufficient for clinical suspicion of FAP) or fewer polyps at younger ages, especially in a family known to have FAP
- Autosomal dominant inheritance[c]
- Possible associated additional findings
  - CHRPE
  - Osteomas, supernumerary teeth, odontomas
  - Desmoids, epidermoid cysts
  - Duodenal and other small bowel adenomas
  - Gastric fundic gland polyps
- Increased risk for medulloblastoma, papillary carcinoma of the thyroid (<2%), and hepatoblastoma (1%–2%, usually age ≤5 y)
- Pancreatic cancer (<1%)
- Gastric cancer (0.5%–1.3%)
- Duodenal cancer (4%–12%)

RISK STATUS

- Personal history of classical FAP → See Treatment and Surveillance (FAP-1)
- Family history of classical FAP, at-risk family member, family pathogenic variant known → See Genetic Testing and Surveillance (FAP-2)

Attenuated FAP:[d]
- Germline *APC* pathogenic variant
- Presence of 10–<100 cumulative adenomas (average of 30 polyps)
- Frequent right-sided distribution of polyps
- Adenomas and cancers at age older than classical FAP (mean age of cancer diagnosis >50 y)
- Upper GI findings, thyroid and duodenal cancer risks are similar to classical FAP
- Other extraintestinal manifestations such as CHRPE are unusual
- Desmoid tumors are associated with 3' mutations in the APC gene

RISK STATUS

- Personal history of AFAP → See Treatment and Surveillance (AFAP-1)
- Family history of AFAP, at-risk family member, family pathogenic variant known → See Genetic Testing and Surveillance (AFAP-2)

[a] A clinical diagnosis of classical FAP is suspected when >100 polyps are present at a young age; however, genetic testing with multi-gene panel testing is recommended to differentiate FAP, MAP, polyposis due to a mutation in a rare gene for which testing is available, and colonic polyposis of unknown etiology. Identification of a germline APC pathogenic variant confirms the diagnosis of FAP.

[b] Individuals with >100 polyps occurring at older ages (35–40 years or older) may be found to have AFAP.

[c] There is a 30% spontaneous new pathogenic variant rate; thus, family history may be negative. This is especially noteworthy if onset age <50 y.

[d] There is currently no consensus on what constitutes a clinical diagnosis of AFAP. AFAP is considered when >10–<100 adenomas are present and is confirmed when an APC pathogenic variant is identified. Genetic testing with multi-gene panel testing is recommended to differentiate FAP/AFAP, MAP, polyposis due to a mutation in a rare gene for which testing is available, and colonic polyposis of unknown etiology.

Hereditary Melanoma
p16 & CDK4 Mutations

- **Autosomal dominant disease**
- **10% of all melanomas**
- **CDK4 gene**
- **Germ-line mutations in tumor suppressor p16 (CDKN2A) account for 25-40%**
  - Lifetime risk up to 60% of developing melanoma
  - Lifetime risk up to 17% of pancreatic cancer

Presence of one or more of these factors in an individual or family hx is suggestive of hereditary melanoma and warrants evaluation:

- **3 or more primary melanomas in one individual**
- **Patient with melanoma with 3 or more melanomas in the family**
- **Melanoma and pancreatic cancer in an individual and/or family**
- **1st degree relative of p16 mutation carrier**

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Hereditary Pancreatic Cancer
PALB2 & BRCA2

- **Patients with at least one close relative with pancreatic CA**
- **Individual with two or more close relatives with pancreatic CA**
- **Individual with Ashkenazi Jewish descent with personal hx of pancreatic cancer or 1st degree relative with pancreatic cancer**
- **PALB2 mutation in family**

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- **Other genes associated**
  - BRCA1/2, CDKN2A, and Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2, and EPCAM)

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Hereditary Cancer Testing Criteria

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TESTING CRITERIA FOR PANCREATIC CANCER SUSCEPTIBILITY GENES (See GENE-A)[a]

Testing is clinically indicated in the following scenarios:
• See General Testing Criteria on CRIT-1.
• Exocrine pancreatic cancers[q] ▸ All individuals diagnosed with exocrine pancreatic cancer[r] ▸ First-degree relatives of individuals diagnosed with exocrine pancreatic cancer[s] • Neuroendocrine pancreatic tumors - See NCCN Guidelines for Neuroendocrine and Adrenal Tumors

Criteria met → See GENE-1

If testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Prevention and Screening Strategies for Those With Hereditary Risk

Hereditary Breast & Ovarian Screening

Signs & Symptoms: Breast CA

- Presence of lump
- Skin thickening
- Change in skin or color
- Change in nipple direction
- Nipple discharge

Signs & Symptoms: Ovarian CA

- Vague abdominal pain/Gastrointestinal symptoms
- Weight loss
- Bloating

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Hereditary Breast & Ovarian Screening: Known BRCA1/2 Mutation

Screening

- **BREAST**
  - Monthly self breast exam starting age 18
  - CBE Q6 months starting age 20
  - Annual mammogram (Limitations in younger d/t dense breast tissue) with MRI starting age 25
- **OVARY**
  - Pelvic exam Q6 months starting age 25
  - TVUS starting age 25 Q6-12 months
  - Serum CA 125 Q6-12 months starting age 25

Prevention

- **BREAST**
  - Consider prophylactic mastectomy (95% risk reduction)
  - Consider chemoprevention (5-10 yrs before earliest age family member diagnosis)
    - Tamoxifen Premenopausal
    - Raloxifene Postmenopausal
  - Consider prophylactic oophorectomy (risk reduction 50%)
- **OVARY**
  - Consider prophylactic bilateral salpingo-oophorectomy between ages 35-40 (risk reduction 85-96%)
  - 2-18% will have occult ovarian cancers at time of surgery

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BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

GENERAL

- Education regarding signs and symptoms of cancer(s), especially those associated with *BRCA* gene pathogenic/likely pathogenic variants.

BREAST CANCER

- Female
  - Breast awareness[a] starting at age 18 years.
  - Clinical breast exam, every 6–12 months,[b] starting at age 25 years.
  - Breast screening[c,d]
    - Age 25–29 years, annual breast MRI[e] screening with contrast[f] (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
    - Age 30–75 years, annual mammogram with consideration of tomosynthesis and breast MRI[e] screening with contrast.
    - Age >75 years, management should be considered on an individual basis.
    - For individuals with a *BRCA* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram with consideration of tomosynthesis and breast MRI should continue as described above.
  - Discuss option of risk-reducing mastectomy
    - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
  - Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy.
- Consider risk reduction agents as options for breast cancer, including discussion of risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).
- Male
  - Breast self-exam training and education starting at age 35 years.
  - Clinical breast exam, every 12 months, starting at age 35 years.
  - Consider annual mammogram screening in men with gynecomastia starting at age 50 or 10 years before the earliest known male breast cancer in the family (whichever comes first).[g]

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

[a] Females should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self exam (BSE) may facilitate breast self awareness. Premenopausal individuals may find BSE most informative when performed at the end of menses.

[b] Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical breast exam every 6–12 mo is the concern for interval breast cancers.

[c] The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, Lee JM, Kong CY, et al. Cancer 2012;118:2021-2030.

[d] Lehman CD, et al. J Natl Cancer Inst 2016;108.

[e] The criteria for high-quality breast MRI include a dedicated breast coil, the ability to perform biopsy under MRI guidance, radiologists experienced in breast MRI, and regional availability. Breast MRI is preferably performed on days 7–15 of a menstrual cycle for premenopausal patients. FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue.

[f] Breast MRI is preferred due to the theoretical risk of radiation exposure in pathogenic/likely pathogenic variant carriers.

[g] There are only limited data to support screening for male breast cancer. Gao Y, et al Radiology 2019;293:282-291.

BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

OVARIAN/UTERINE CANCER

- Recommend risk-reducing salpingo-oophorectomy (RRSO),[h] typically between 35 and 40 years, and upon completion of childbearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 years in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. See 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, hormone replacement therapy, and related 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 individuals are still at risk for developing ovarian cancer. In addition, in premenopausal individuals, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.
- Limited data suggest that there may be a slightly increased risk of serous uterine cancer among individuals with a *BRCA1* pathogenic/likely pathogenic variant. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the *BRCA* population needs to be undertaken. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for individuals with a *BRCA1* pathogenic/likely pathogenic variant prior to surgery.
- Individuals who undergo hysterectomy at the time of RRSO are candidates for estrogen-alone hormone replacement therapy, which is associated with a decreased risk of breast cancer compared to combined estrogen and progesterone, which is required when the uterus is left in situ (Chlebowski R, et al. JAMA Oncol 2015;1:296-305).
- Address psychosocial and quality-of-life aspects of undergoing RRSO.
- For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, although of uncertain benefit, may be considered at the clinician's discretion starting at age 30–35 y.
- Consider risk reduction agents as options for ovarian cancer, including discussion of risks and benefits (See Discussion for details).

Hereditary Nonpolyposis Colorectal Cancer- Lynch Syndrome Known MLH1, MSH2, MSH6, PMS2, EPCAM Mutations

Screening

- **COLON**
  - Annual colonoscopy beginning age 20-25
  - Consider gastroscopy and upper endoscopy
- **UTERUS/OVARIES**
  - Biannual pelvic exam beginning age 25
  - TVUS + CA 125 beginning age 30-35 Q6-12 months
- **UROGENITAL**
  - Consider annual urinalysis with cytology and renal imaging

Prevention

- **COLON**
  - Consider chemoprevention with aspirin
  - Consider colectomy
    - In patients who cannot or will not undergo regular colonoscopy
- **UTERUS/OVARIES**
  - Consider chemoprevention with OCPs
  - Consider prophylactic hysterectomy with BSO between ages 35-40 or when childbearing complete

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Familial Adenomatous Polyposis Syndromes

Screening

- **Risk of colorectal cancer is near 100% and can occur before age 20**
- **Colonoscopy + Upper endoscopy at puberty**

Prevention

- **Proctocolectomy + ileal pouch anal anastomosis**
  - Permanent stoma not necessary
  - Small risk bladder/sexual dysfunction
- **Total abdominal colectomy + ileorectal anastomosis**
  - Requires regular endoscopy of rectum post procedure
  - Not recommended if many rectal polyps prior to surgery
- **Total proctocolectomy with ileostomy**
  - Permanent stoma
  - Removes all risk of colorectal cancer
  - Bladder/sexual dysfunction possible
- **Celecoxib**
- **Aspirin**

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Hereditary Melanoma

Early Detection

- **Monthly self fully body exams with full length mirrors/handheld mirrors**
- **Full body photos Q6 months**
- **Clinical skin check Q6 months starting age 10**
  - May increase frequency during puberty/pregnancy
- **Prompt biopsy/removal of suspicious lesions**

Prevention

- **Limit UV light, mostly hrs 10am and 3pm**
- **Protective clothing**
- **Broad spectrum sunscreen with UV A/B protection**
  - At least SPF 30

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Hereditary Pancreatic Cancer
BRCA2, PALB2, CDKN2A, & Lynch Genes

Population

- **When to screen**
  - Some say to start age 35-45 or 10-15 years prior to earliest dx in family
  - Guidelines vary based on organization
- **High Risk**
  - Two or more cases in family
  - Patients with BRCA2 who have family hx of pancreatic, PALB2, and CDKN2A mutations
  - Carriers of CDKN2A or STK11
  - Hx of diabetes, pancreatitis, increased alcohol consumption and smoking increases risk of cancer development

Screening

- **Serum CA19-9 and CEA**
- **MRI/CT**
- **Endoscopic US**
- **ERCP**
- **MRCP**

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PANCREATIC CANCER SCREENING

- Emerging data have examined the efficacy of pancreatic cancer screening in select individuals at increased risk for exocrine pancreatic cancer. To date, most such studies have restricted pancreatic cancer screening to individuals with:
  1. A known pathogenic/likely pathogenic germline variant in a pancreatic cancer susceptibility gene (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53*; see GENE-A) and a family history of pancreatic cancer (first-degree or second-degree relative) from the same side of the family as the germline pathogenic/likely pathogenic variant; or
  2. A family history of exocrine pancreatic cancer in ≥2 first-degree relatives from the same side of the family, even in the absence of a known pathogenic/likely pathogenic germline variant (many centers would enroll individuals with one affected first-degree relative and one second-degree relative); or
  3. A family history of exocrine pancreatic cancer in ≥3 first- and/or second-degree relatives from the same side of the family, even in the absence of a known pathogenic/likely pathogenic germline variant.
- These studies have typically started screening with contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS) in such high-risk individuals.

- Potential benefits of pancreatic cancer screening include a suggestion of downstaging, compared to historical data, in that 75%–90% of screen-detected pancreatic cancer has been surgically resectable at diagnosis (which is markedly higher than historical rates of resectability with pancreatic cancers detected due to symptoms).[a,b] There has also been a suggestion of improved mortality compared to historical data, with one study demonstrating an 85% 3-year overall survival rate after screen-detected pancreatic cancer in high-risk individuals,[a] and another study demonstrating a 24% 5-year overall survival rate following screen-detected pancreatic cancer in individuals with germline c.67G>C CDKN2A variants.[b] One study[a] also demonstrated 100% overall survival among 10 individuals with screen-detected precursor lesions (intraductal papillary mucinous neoplasms [IPMN] with high-grade dysplasia and/or high-grade pancreatic intraepithelial neoplasia [PanIN]) treated with surgical resection.

- Although evidence for downstaging has emerged in recent studies, longer-term studies are needed to determine if this downstaging translates to improved survival. Evidence from patients with sporadic forms of pancreatic ductal adenocarcinoma suggest that long-term survival is common for patients who present with stage I disease. Since many patients who undergo pancreatic surveillance have pancreatic abnormalities, mostly subcentimeter pancreatic cysts (42% of high-risk individuals in one study[c] had at least one pancreatic mass/cyst and/or duct abnormality), there is potential for unnecessary interventions (such as fine-needle aspiration [FNA] and in some cases surgery). Although there is much more experience with evaluating and managing pancreatic cysts and other pancreatic imaging abnormalities, determination of the overall risk/benefits of pancreatic surveillance requires further study. Results of surveillance of high-risk individuals performed in tertiary care/high-volume centers under clinical trial settings may not be the same as those performed in routine clinical practice. Data are beginning to better define which screen-detected lesions in high-risk individuals should be considered to be at particularly high risk for neoplastic progression (eg, those with a solid pancreatic mass, those with pancreatic duct abnormalities, those with growing pancreatic cysts[a]), but further data are needed to better define the threshold for surgical intervention in high-risk individuals undergoing pancreatic cancer screening.

PANCREATIC CANCER SCREENING

- For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers. The panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening.
- Consider screening using annual contrast-enhanced MRI/MRCP and/or EUS, with consideration of shorter screening intervals, based on clinical judgment, for individuals found to have potentially concerning abnormalities on screening. The panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.

- For all individuals with pathogenic/likely pathogenic germline variants in *STK11*
  - Consider pancreatic cancer screening beginning at age 30–35 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).

- For all individuals with pathogenic/likely pathogenic germline variants in *CDKN2A*
  - Consider pancreatic cancer screening beginning at age 40 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).

- For individuals with pathogenic/likely pathogenic germline variants in one of the other pancreatic cancer susceptibility genes (A*TM, BRCA1, BRCA2, MLH1, MSH2, MSH6, EPCAM, PALB2, TP53*), see GENE-A.
  - Consider pancreatic cancer screening beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified pathogenic/likely pathogenic germline variant.[d]
  - The panel does not currently recommend pancreatic cancer screening for carriers of mutations in genes other than *STK11* and *CDKN2A* in the absence of a close family history of exocrine pancreatic cancer.

Hereditary Pancreatitis Genes

- For individuals with pathogenic/likely pathogenic variants in *PRSS1* or other hereditary pancreatitis genes AND a clinical phenotype consistent with hereditary pancreatitis[e]
  - Consider pancreatic cancer screening 20 years after onset of pancreatitis, or at age 40 years, whichever is earlier.

Indications for Genetic Assessment, Models, and Process

Indications for Genetic Testing

- **EARLY AGE OF CANCER(S)**
- **MULTIPLE FAMILY MEMBERS WITH SAME CANCER(S)**
- **KNOWN GENETIC MUTATION(S) IN FAMILY**
- **ASHKENAZI JEWISH ANCESTRY**
- **MULTIPLE CANCERS IN AN INDIVIDUAL(S)**
- **CLOSE DEGREE OF AFFECTED INDIVIDUAL(S)**
- **CLUSTER OF AFFECTED INDIVIDUALS ON SAME SIDE OF FAMILY**
- **BILATERAL CANCER IN SAME ORGAN**
- **EVIDENCE OF AUTOSOMAL DOMINANT INHERITANCE:**
- Two or more generations affected with both males & females

Risk Assessment Models

- GAIL
- CLAUS
- TYRER-CUZICK
- WIJNEN
- PREMM
- MMRpro

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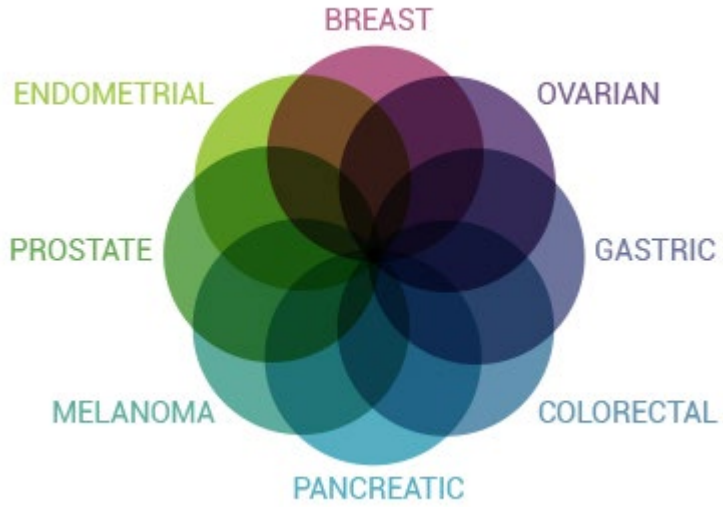

Genetic Testing Process

- **Consultation with a qualified health professional with expertise in genetics**
- **Sign consent**
- **Preauthorization is desirable with letter of medical necessity**
- **Buccal (Saliva) or blood sample sent**
- **Results 2-4 wks or 6-8 weeks with NGS**
- **Results discussed in person or telephone**
- **Discuss implications for other family members**
- **Counseling by credentialed genetic professional may be indicated with children/adolescents which will take place with the parental guardian**
  - Known mutations associated with FAP, MEN, VHL syndrome

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Potential Risks, Benefits, and Limitations of Testing

- **Risk**
  - Loss of privacy and psychosocial distress
  - Failure of genetic condition disclosure could result in cancellation of a life or disability insurance policy
    - Genetic Information Nondiscrimination Act of 2008 (GINA) protects patient's genetic information
    - Group health insurance plans cannot use genetic information to deny or limit eligibility for coverage or increase premiums and genetic information cannot be considered a preexisting condition
      - Does not apply for individual or self-insured plans

- **Benefits**
  - Identification can provide proper cancer prevention and early detection measures

- **Outcomes of Testing**
  - Positive Results
  - True Negative Results
  - Negative Results- No mutation Identified in Family
  - Variant of Indeterminate Significance

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Implications for Oncology APRNs

Implications for Oncology APRNs

- CERTIFICATION
- CONTINUING EDUCATION
- DISSEMINATION OF KNOWLEDGE
- PARTICIPATION IN RESEARCH
- CLINICAL TRIAL PARTICIPATION
- ACTIVELY PRACTICE IN GENETICS
- ASSIST IN EDUCATION OF PATIENTS AND PUBLIC
- ACTIVE INVOLVEMENT IN PROFESSIONAL ORGANIZATIONS

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Questions?