Cancer Genetics – Testing and Management of Hereditary Risk

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Objectives

- Describe current genetic testing practices for personal diagnoses and family history of cancer
- Apply appropriate screening/management recommendations for patients with hereditary breast, ovarian, prostate, pancreatic, and colon cancer predisposition syndromes
- Recognize essential process elements related to genetic testing outside of genetics clinics

Germline (hereditary) genetic testing in oncology

One result with many areas of impact

- Comprehensive risk assessment
- Anticipatory guidance for future cancer risk
  - Cancer risk management options
- Familial impact

At/after cancer diagnosis

- Understanding of cancer etiology
- Possible impact on therapeutics

Approach to testing – no longer just BRCA!

Multigene panel testing is the norm – testing many genes at once

- Disease-centric multigene panel (eg. Breast ca genes only)
- Pan-cancer multigene panel
  - Genes associated with broad spectrum of cancer risk
- Variation among options (guidelines-based vs. those with minimal/emerging evidence)
- Very uncommon to test for single gene/syndrome
  - Exception: when familial variant is already known…but still consider a panel

Genetic testing for patients with breast cancer

***BRCA1, BRCA2**, CDH1, PALB2, PTEN, STK11, TP53*

8-9% unselected patients test positive

American Society of Breast Surgeons (ASBS)

- All patients with breast cancer

National Comprehensive Cancer Network (NCCN)

- All triple negative (ER/PR/HER2)
- All patients making decisions about treatment
- All males
- Age 50 or younger for other breast cancer types
- Any age with significant family history

Genetic testing for unaffected patients – family history of breast cancer

National Comprehensive Cancer Network (NCCN)

- 1st or 2nd degree relative with one of the "qualifying cancers" (previous slide) except for those who are testing for treatment decisions only
- Those with greater than 5% chance of mutation using risk models

Breast: Different genes bring different risks

Gene	Absolute breast cancer risk	Age to initiate screening (NCCN)
BRCA1	60-72%	MRI age 25; Mammo age 30
BRCA2	55-69%	MRI age 25; Mammo age 30
TP53	>60%	MRI age 20; Mammo age 30
CDH1	37-55%	MRI and mammo age 30
PALB2	32-53%	MRI and mammo age 30
PTEN	40-60%	MRI and mammo age 30
STK11	32-54%	MRI and mammo age 30
ATM	21-24%	Consider MRI age 30-35; Mammo age 40
BARD1	17-30%	Mammo and consider MRI age 40
CHEK2	23-27%	Consider MRI age 30-35; Mammo age 40
NF1	20-40%	MRI and mammo age 30
RAD51C/RAD51D	~20%	Mammo and consider MRI age 40

Breast risk reduction

- Risk-reducing agents (e.g. tamoxifen)
- Risk-reducing mastectomies (RRM)
  - Up to 90% reduction in risk
  - Discussion of timing, psychological impact, reconstruction options, possible complications
  - Contralateral RRM often considered at time of unilateral breast cancer diagnosis
    - Need timely test results

Genetic testing for patients with ovarian cancer

ATM, ***BRCA1, BRCA2****, BRIP1, PALB2, RAD51C, RAD51D,* Lynch Syndrome genes

NCCN, Society of Gynecologic Oncology (SGO), others

- All patients with epithelial ovarian cancer (and 1st/2nd degree relatives) - includes fallopian tube and peritoneal primaries

Patients with NON-epithelial ovarian cancers should sometimes also receive genetic testing but the associated genes are different

- Example: SMARCA4 variants associated with small cell carcinoma, hypercalcemic type

Standard of ovarian cancer risk management

- Risk reducing bilateral Salpingo oophorectomy (RRBSO)
  - +/- hysterectomy
  - Specialized pathology protocol – serial sectioning
  - Reduces ovarian cancer risk by ~ 80%
  - May increase risk for cardiovascular disease, osteoporosis, cognitive impairment, all-cause mortality
- Emerging considerations for salpingectomy with delayed BSO

Ovarian cancer risk genes

Gene	Lifetime Risk	Recommend/Consider RRSO @ Age
BRCA1	39-58%	Recommend @ 35-40
BRCA2	13-29%	Recommend @ 40-45
BRIP1	5-15%	Recommend @ 45-50
RAD51D	10-20%	Recommend @ 45-50
RAD51C	10-15%	Recommend @ 45-50
PALB2	3-5%	Consider @ 45-50
Lynch Syndrome genes	1-38%	Individualized option
ATM	2-3%	Insufficient evidence to recommend – manage based on fam hx

Genetic testing for patients with prostate cancer

ATM, BRCA1, BRCA2, CHEK2, HOXB13, TP53

NCCN -

- All patients with metastatic disease (Stage IVB) or node-positive (Stage IVA) cancer
- Very high- or high-risk disease
- All Ashkenazi Jewish patients
- All patients who also have significant family history (including breast, ovarian, pancreas)

All 1st degree relatives of above

Prostate cancer genes

Gene	Absolute prostate cancer risk	Age to have/consider prostate screening
BRCA2	19-61%	Recommend age 40
BRCA1	7-26%	Consider age 40
CHEK2	Emerging evidence	Consider age 40
ATM	Emerging evidence	Consider age 40

- Prostate cancer screening interval dependent on results and risk level
  Baseline PSA
  Baseline digital rectal examination

Genetic testing for patients with pancreatic cancer

ATM, BRCA1, BRCA2, CDKN2A, PALB2, STK11, TP53, Lynch Syndrome genes

NCCN

- All patients with exocrine pancreatic cancer
- All 1st degree relatives with exocrine pancreatic cancer

Pancreatic cancer genes

Gene	Absolute pancreatic cancer risk	Age to have/consider pancreatic screening (or 10 years younger than youngest familial dx
STK11	>15%	Age 30-35
CDKN2A	>15%	Age 40
BRCA2	5-10%	Age 50
ATM	5-10%	Age 50
BRCA1	Up to 5%	Age 50 only for those with family history in 1st/2nd degree relative
PALB2	2-5%	Age 50 only for those with family history in 1st/2nd degree relative
TP53	~5%	Age 50 only for those with family history in 1st/2nd degree relative

Pancreatic cancer screening

- Screening should take place in high-volume center after discussion about limitation, possible costs, uncertainties
- Annual contrast-enhanced MRI/MRCP and/or endoscopic ultrasound
  - Shorter intervals based on clinical judgement

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Genetic testing for patients with colon cancer

Such as: *APC, ATM, AXIN2, BMPR1A, GALNT12, GREM1,* Lynch syndrome *(MLH1, MSH2, MSH6, PMS2, EPCAM), POLE, POLD1, PTEN, SMAD4, STK11, TP53.*

National Comprehensive Cancer Network (NCCN):

- CRC diagnosed <50 y
- CRC and another LS-related cancer, any age
- CRC and a 1st or 2nd degree relative with a LS-related cancer <50 y
- CRC and ≥2 1st or 2nd degree relatives with a LS-related cancer, any age

*LS-related cancers: colon, endometrial, gastric, ovarian, pancreatic, urothelial, brain, sebaceous adenomas/carcinoma, keratoacanthomas

Lynch syndrome screening outcomes

Tumor Screening Outcome	Possible Cause	Likelihood of Lynch Syndrome	Perform LS Genetic Testing
All proteins present	N/A	Reduced	No
MLH1/PMS2 absent	*BRAF* mutation or *MLH1* hypermethylation	Reduced	No
	MLH1 germline variant	Increased	Yes
MSH2/MSH6 absent	*MSH2* or *EPCAM* germline variant (Rarely – *MSH6* mutation)	Increased	Yes
MSH6 absent	*MSH6* germline variant	Increased	Yes
PMS2 absent	*PMS2* germline variant (Rarely – *MLH1* mutation)	Increased	Yes
MSI – unstable	*BRAF* mutation or *MLH1* hypermethylation	Reduced	No
	Germline variant	Increased	Yes

Lynch Syndrome: different genes bring different risks

NCCN

Cancer Type	General Population	*MLH1*	*MSH2, EPCAM*	*MSH6*	*PMS2*
Colorectal	4.2%	46-61%	33-52%	10-44%	8.7-20%
Endometrial	3.1%	34-54%	21-57%	16-49%	13-26%
Ovarian	1.3%	4-20%	8-38%	≤1-13%	1.3-3%
Hepatobiliary Tract	0.2%	1.9-3.7%	0.02-1.7%	0.2-≤1%	0.2-≤1%
Urinary Tract/Bladder	2.4%	0.5-7%	2.2-28%	0.7-8.2%	≤1-3.7%
Small Bowel	0.3%	0.4-11%	1.1-10%	≤1-4%	0.1-0.3%
Brain/CNS	0.6%	0.7-1.7%	2.5-7.7%	0.8-1.8%	0.6-≤1%
Gastric	0.9%	5-7%	0.2-9.0%	≤1-7.9%	Inadequate data
Pancreas	1.6%	6.2%	0.5-1.6%	1.4-1.6%	≤1-1.6%
Sebaceous Neoplasm	Unspecified	Increased	Increased	Increased	Increased
Prostate	11.6%	4.4-13.8%	3.9-23.8%	2.5-11.6%	4.6-11.6%

Lynch Syndrome Surveillance Options

NCCN

Cancer Type	Recommendations
Colorectal Cancer	• *MLH1, MSH2, EPCAM:* Colonoscopy every 1-2 y beginning at age 20-25 (or 2-5 years younger than earliest diagnosis if <25 • *MSH6, PMS2:* Colonoscopy every 1-3 y beginning at age 30-35 (or 2-5 years younger than earliest diagnosis if <25 • Consideration of taking daily aspirin (discretion of physician)
Endometrial and Ovarian Cancer	• Education regarding symptoms • Consideration of complete hysterectomy with bilateral salpingo-oophorectomy after childbearing ages • Consideration of endometrial biopsy every 1-2y beginning at age 30-35 • TVUS and CA-125 surveillance could be considered but no evidence of efficacy
Gastric and Small Bowel Cancer	• Endoscopy every 2-4y beginning at age 30-40y - consider random biopsy when known risk factors are present
Pancreatic Cancer	• Based on family history – with ≥1 FDR/SDR with pancreatic cancer • Beginning at age 50 (or 10y younger than earliest family diagnosis) • Annual magnetic resonance cholangiopancreatography (MCRP) and/or endoscopic ultrasound (EUS)
Urothelial Cancer	• Consider annual urinalysis beginning at age 30-35
Brain/CNS Cancer	• Consider annual physical/neurological exam beginning at age 25-30
Skin Manifestations	• Consider dermatology full body exam every 1-2y; age to begin is individualized
Prostate Cancer[21]	• Manage based on gene and family history • Consider annual screens at age 40

Genetic testing for patients with polyposis

Such as: *APC, AXIN2, BMPR1A, GREM1, MBD4*, MSH3*, MUTYH*, NTHL1*, POLD1, POLE, PTEN, RNF43, SMAD4, STK11.*

National Comprehensive Cancer Network (NCCN):

- ≥10 cumulative adenomas
- ≥2 Peutz-Jeghers-type hamartomatous polyps of the GI tract plus mucocutaneous hyperpigmentation
- ≥5 serrated polyps proximal to the rectum

*Biallelic variants only (i.e., autosomal recessive conditions)

Genetic testing for patients with endometrial cancer

Such as: Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM), NTHL1* (biallelic), *POLD1, POLE, PTEN, TP53*

National Comprehensive Cancer Network (NCCN):

- EC diagnosed <50 y
- EC and another LS-related cancer, any age
- EC and a 1st or 2nd degree relative with a LS-related cancer <50 y
- EC and ≥2 1st or 2nd degree relatives with a LS-related cancer, any age

*LS-related cancers: colon, endometrial, gastric, ovarian, pancreatic, urothelial, brain, sebaceous adenomas/carcinoma, keratoacanthomas

Genetic testing for unaffected patients – family history of CRC, EC, etc.

National Comprehensive Cancer Network (NCCN):

- ≥1 1st degree relative with CRC or EC <50y
- ≥1 1st degree relative with CRC or EC plus another LS-related cancer, any age
- ≥2 1st or 2nd degree relatives with LS-related cancer, including one <50y
- ≥3 1st or 2nd degree relatives with LS-related cancer, any age
- Those with ≥5% chance of mutation using risk models

Standard of CRC & EC cancer risk management

- Colon cancer
  - Earlier, more frequent colonoscopies
  - Other polyposis – endoscopies
- Endometrial cancer
  - Symptom awareness
  - TVUS screening not sufficiently sensitive or specific, but may be considered in post-menopausal women

Principles of Cancer Risk Assessment

- Pre-test counseling
- Testing considerations
- Testing approach
- Risk to relatives
- Reproductive options
- Tumor genomic testing
- Post-test counseling

Principles of Cancer Risk Assessment

- Pre-test counseling
  - Assessing patient's needs, level of concern, goals
  - Collecting family history
  - Preparing the patient for possible outcomes
    - Positive, negative, VUS
  - Discussing possible management changes
  - Discuss plan for result disclosure
  - Informed consent, including GINA if applicable

Principles of Cancer Risk Assessment

- Testing considerations
  - Multi-gene panels, including for people with previously limited testing
  - Full sequencing and testing for large genomic rearrangements
  - Commercial or academic labs, CAP and CLIA certified
  - Appropriate sample type
  - Testing of minors only if medical management differs <18

Principles of Cancer Risk Assessment

- Testing approach
  - Test affected individual(s) first
  - Unaffected individuals can be uninformative negatives
  - Cascade testing of a VUS is not advised

Principles of Cancer Risk Assessment

- Risk to relatives
  - Depending on result and inheritance pattern
  - Cascade testing
  - Changes to management in at-risk relatives
- Reproductive options
  - IVF and PGT

Principles of Cancer Risk Assessment

- Tumor genomic testing
  - “Somatic” testing may provide information suggesting a potential germline finding

Principles of Cancer Risk Assessment

- Post-test counseling
  - Discuss results and associated risks
  - Recommend medical management options
    - Specialist referrals
  - Importance of notifying family members
  - Other resources