Cancer Genetics: Common Hereditary Cancer Syndromes

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Learning Goals

- Understanding sporadic v. familial v. hereditary cancers
- Patterns of inheritance of hereditary cancer risk
- Characteristics of inherited cancer syndromes
- Goals of genetic counseling and testing for hereditary cancer
- Diagnosis and management of cancer syndromes
  - Hereditary Breast (Ovarian) Cancer
  - HNPCC – Lynch syndrome/ FAP- Familial Polyposis
  - Gene Panels
- Cancer Genomics – profiling tumors; personalized oncology
HEREDITARY CANCER GENETICS

- Identification of germline and familial genetic alterations that increase risk of cancer
- Development of targeted screening and early detection techniques prevent development of advanced cancers
- Incorporation of moderate and low-penetrant, common genetic variants in risk prediction and modification
- Germline mutations may direct targeted treatments
Precision Medicine in Cancer: Tumor Profiling and Therapeutics

- **TUMOR CANCER GENOMICS**
  - Identification of tumor *genetic* alterations that drive carcinogenesis
  - Development of *drugs* that can effectively inhibit the function of these genetic alterations
  - Molecularly [*targeted*] therapies to be used consistently and effectively in patients with cancer
  - Assessment and prediction of drug *response* and *resistance* mechanisms
  - *Germline* genetic testing and risk assessment based on tumor genomic profiles
Incidence of Hereditary Breast and Ovarian Cancer

- Breast Cancer:
  - Sporadic: 90%
  - Hereditary: 10%

- Ovarian Cancer:
  - Sporadic: 75%
  - Hereditary: 25%
BRCA1-Associated Cancers
Lifetime Risks

Breast cancer ~65% by age 70 (51-75%)
Second primary breast cancer ~50-60%
Ovarian cancer: ~39% (22 – 51%)
Smaller increased risk of other cancers (i.e. prostate, pancreas)
BRCA2-Associated Cancers
Lifetime Risks

Breast cancer: 45%
40% 2nd – primary

Male breast cancer: 6%
Prostate cancer: 25%

Ovarian cancer: 11-20%

Increased risk of prostate, laryngeal, bile duct, stomach, melanoma and pancreatic cancers (~1.5 – 3 fold risk)
Age-Specific Cancer Risks

**Figure 3**  Cumulative risk of breast (♦) and ovarian (■) cancer in BRCA1-mutation carriers.

**Figure 4**  Cumulative risk of breast (♦) and ovarian (■) cancer in BRCA2-mutation carriers.
How common are hereditary BRCA mutations?

- 1/400 in the general population
  - (Early population studies suggesting 1/200)

- 1/40 in the Ashkenazi (Eastern European) Jewish population

- 5% of breast cancer diagnoses
How much does testing cost?

- $4000 BRCA1 and BRCA2 gene testing due to patent until Supreme Court overturned 6/2013
- 6/2013: Multigene NGS panels (now up to 100 genes)
- Now $900-$4000 insurance contracts
- $250 (out of pocket at 2 labs)
U.S. Supreme Court Strikes Down Human Gene Patents

13 June 2013
2019 Breast CA Genetic Testing Guidelines

- National Comprehensive Cancer Network (NCCN) Expert consensus revised yearly; http://www.nccn.org
- Family member with known BRCA1/2 mutation
- Personal history of breast cancer, with:
  - Onset age \( \leq 45 \) (7% prevalence)
  - Onset < 50 and one close relative with breast, ovarian
  - Two primary breast cancers; first <50
  - Onset any age, if \( \geq 2 \) close relatives with breast /ovarian/ pancreatic/ prostate (Gleason >7)
  - Triple negative (ER/ PR/ Her2 neu negative) \(<60\) (5-10%)
  - High-risk ethnicity, such as Ashkenazi (20-25% prevalence) with any above cancer history
- Personal history of ovarian cancer (10% prevalence)
- Male breast cancer (12-16% prevalence)
- Stage IV prostate or Gleason > 7 (10-12% prevalence)
- Pancreatic cancer (10% prevalence)
- Close family member meeting above criteria (if most informative unavailable)
High Breast Cancer Risk Syndromes

- **P53 (Li-Fraumeni Syndrome)**
  - Mutation prevalence 1/5,000-20,000; 7-20% de novo
  - Sarcoma, brain, leukemia, colon, childhood cancers
  - 30-50% breast cancer, age [31]: prevalence 7% in breast cancers <35

- **PTEN (Cowden’s Syndrome)**
  - Mutation prevalence 1/200,000; >75% de novo
  - Uterine cancers, thyroid dysfunction, mucosal lesions, OFC>98%
  - 40-50% lifetime breast cancer risk; 10% thyroid, increased uterine & colon

- **STK11 (Peutz Jeghers Syndrome)**
  - Mutation prevalence 1/60,000 - 300,000; 50% de novo
  - High risk for breast (50%), colon (40%), ovarian (20%) and other cancers
  - Lip freckles in childhood

- **CDH1 (Hereditary Diffuse Gastric Cancer Syndrome)**
  - Mutation prevalence 1/100,000-300,000? De novo?
  - 60-80% develop gastric cancer
  - 40-50% lifetime risk of lobular breast cancer

Moderate Breast Cancer Risk Syndromes

- **ATM**
  - Mutation prevalence 1/100
  - OR =2-4 for breast cancer risk; OR =2 for colon cancer
  - Possible pancreatic risk

- **CHEK2**
  - Mutation prevalence up to 1/66 (Dutch); others 1/200-1/500
  - Breast (OR=2.6-4.8), colon (OR=2) cancer risks
  - Possible prostate and thyroid cancer risk

- **PALB2**
  - Mutation prevalence ~1/1000
  - OR =3-5 for breast cancer risk
  - Suggestion of increased ovarian and pancreatic cancer risks

Low Breast Cancer Risk Syndromes

- **BRIP1, BARD1, RAD51C, RAD51D**
  - Prevalence uncertain
  - OR= 2-3 for breast cancer
  - OR 3-6 for ovarian cancer with BRIP1, RAD51D

- **RAD 50, MRE11A, NBN**
  - Prevalence uncertain
  - 1.5-2.0 OR breast cancer risk
  - Possibly ovarian cancer risk

- **NF1, Lynch, MUTYH**
  - Traditionally not breast cancer genes; other defining symptoms
  - Prevalence much more common; 1/3000, 1/300, 1/50
  - Breast cancer risk varies (OR= 2 fold; 5 fold <50 for NF1)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Race/Ethnicity</th>
<th>Testing Panel</th>
<th>Deleterious Mutations</th>
<th>Variants of Uncertain Significance</th>
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<tbody>
<tr>
<td>Walsh et al, <em>Proc Natl Acad Sci</em> 2011</td>
<td>360</td>
<td>Ovarian cancers, unselected</td>
<td>Not reported</td>
<td>BROCA (University of Washington, WA; 21 genes)</td>
<td>6.1% (non-BRCA1/2)</td>
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<td>Harrell et al, American Society of Human Genetics Annual Meeting, 2013</td>
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<td>Ovarian cancers, unselected (extension of above study)</td>
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<td>BROCA (University of WA; 41 genes)</td>
<td>5.5% (non-BRCA1/2)</td>
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<td>Walsh et al, American Society of Human Genetics Annual Meeting, 2013</td>
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<td><em>BRCA1</em>/<em>2</em>-negative, personal or family history of ≥8 breast or ovarian cancers</td>
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<td>BROCA (University of WA; 41 genes)</td>
<td>15.8% (non-BRCA1/2)</td>
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<td>Olopade et al, <em>American Society of Human Genetics Annual Meeting, 2013</em></td>
<td>395</td>
<td>Cancer genetics clinic testing sample</td>
<td>100% African American</td>
<td>BROCA (University of WA; 41 genes)</td>
<td>4.1% (non-BRCA1/2)</td>
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<tr>
<td>Tung et al, <em>Cancer</em> 2014</td>
<td>2158</td>
<td>Testing laboratory database (Myriad Genetics, for <em>BRCA1</em>/<em>2</em>)</td>
<td>Mostly Non-Hispanic (NH) White</td>
<td>MyRisk (Myriad, 25 genes)</td>
<td>4.3% (non-BRCA1/2)</td>
<td>42%</td>
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<td>Castara et al, <em>Eur J Hum Genet</em> 2014</td>
<td>708</td>
<td>Met practice guidelines criteria for <em>Hereditary Breast / Ovarian Cancer Syndrome</em></td>
<td>Not reported</td>
<td>Custom designed (16 genes)</td>
<td>5.6% (non-BRCA1/2)</td>
<td>Not reported</td>
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<tr>
<td>Kurian et al, <em>J Clin Oncol</em> 2014</td>
<td>198</td>
<td>Met practice guidelines criteria for <em>BRCA1</em>/<em>2</em> testing (most <em>BRCA1</em>/<em>2</em>-negative)</td>
<td>70% NH White, 20% Asian American</td>
<td>Custom designed (42 genes)</td>
<td>11.4% (non-BRCA1/2)</td>
<td>88%</td>
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<td>Ford et al, Montreal Hereditary Breast and Ovarian Cancer Symposium, 2014</td>
<td>380</td>
<td>Testing laboratory database (Ambry)</td>
<td>70% NH White, 20% Asian American, 2% Hispanic</td>
<td>Hereditary Cancer Panel (Invitae, 29 genes)</td>
<td>9% (non-BRCA1/2)</td>
<td>35%</td>
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<tr>
<td>LaDuca et al, <em>Genet Med</em> 2014</td>
<td>2079</td>
<td>Breast cancer at age &lt;40, <em>BRCA1</em>/<em>2</em>-negative</td>
<td>69% NH White, 24% African American</td>
<td>BreastNext, CancerNext, ColoNext, OvaNext (Ambry, 13-24 genes)</td>
<td>7-10% (non-BRCA1/2)</td>
<td>15-25%</td>
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<td>Maxwell et al, American Society of Clinical Oncology Annual Meeting, 2014</td>
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<td>Ovarian cancer patients in laboratory database</td>
<td>Not reported</td>
<td>Custom designed (22 genes)</td>
<td>11% (non-BRCA1/2)</td>
<td>19%</td>
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<td>Langer et al, American Society of Clinical Oncology</td>
<td>648</td>
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<td>MyRisk (Myriad, 25 genes)</td>
<td>6.2% (non-BRCA1/2)</td>
<td>40.6%</td>
</tr>
</tbody>
</table>
Panel Identified Hereditary Mutations

**OVARIAN CANCER MUTATIONS**

- BRCA1: 40%
- BRCA2: 23%
- TP53: 3%
- RAD51C: 2%
- RAD50: 2%
- PALB2: 2%
- MRE11: 2%
- CHEK2: 2%
- BRIP1: 1%
- NBN: 1%
- MSH6: 1%

Ovarian: 10-18%; BRCA1/2 10-18%; 5-9% other genes

**BREAST CANCER MUTATIONS**

- BRCA1: 28%
- BRCA2: 24%
- TP53: 9%
- PALB2: 10%
- BARD1: 1%
- BRIP1: 3%
- RAD51C: 1%
- RAD51D: 1%
- PMS2: 1%
- MSH6: 4%
- CDKN2A: 1%
- CDH1: 3%
- NF1: 1%
- ATM: 1%
- CHEK2: 1%

Breast: 5% BRCA1/2; 5% other genes

Walsh et al, *PNAS* 2011
IBIS: Tyrer-Cuzick Future Breast Risk

- Woman's age is 35 years.
- Age at menarche was 12 years.
- Person is nulliparous.
- Person is premenopausal.
- Height is 1.6 m.
- Weight is 70 kg.
- Woman has never used HRT.

Risk after 10 years is 2.463%.
10 year population risk is 0.988%.
Lifetime risk is 24.4%.
Lifetime population risk is 10.06%.
Probability of a BRCA1 gene is 0%.
Probability of a BRCA2 gene is 0%.

![Risk Graph](http://www.ems-trials.org/riskevaluator/)
Case 1

- 49 yo female NED after pancreas cancer at 43
- Striking family hx; many cancers on both sides
- Relatives refused GT
- Which is parent of origin?
- What about the other parent?
- Remember GT was single gene and costly

[Genealogy diagram showing family history with various cancer types and ages at diagnosis]
2002 PAT: Italy  MAT: Italy

24-1

- 42: d. Gastric Ca@ 40
- 70s: d. CvDz
- 40s: d. CHF
- 70s: d. "old"

- 80: d.? CRC@ 68
  - 60s: d. Bladder Ca
  - 8: d. BrCa@ 69
  - 72: Gall Bladder@ 72
- 78: BrCa@ 40s
  - 50: CRC@ 50
  - 72: Gastric Ca@ 72
- 42: d. BrCa@ 39
- 52: d. BrCa@ 45
- 60: d. CRC@ 58

- 75: Pan CA@ 43
  - BRCA2 +
- 49: BRCA2 +

- 23: 21: 16
- 12: 10: 8
- 45: BrCa@ 36
  - Melanoma@ 38
12 year later-late 2013

Niece turns 24; sister comes in for genetic testing
Case 1: Cascade Testing

- Patient returned and tested positive for the ATM
- Her daughter who had positive BRCA2 test did NOT have ATM
- Her daughter who had tested negative for BRCA2 was positive for ATM
- Paternal aunt finally had GT and was positive for ATM
Case 2

- 60 yo male referred to evaluate newly found colon oligopolyposis
- History of IVDA/ ETOH and liver cancer; s/p transplant
- History of aggressive prostate cancer at 59
- Family history of breast cancer in 3 close relatives including Dad, 1/2 sister and Daughter at age 22
- Daughter then died of Glio at 26
Differential Diagnosis

• BRCA1/2 and other breast cancer syndromes
• Polyposis cancer syndromes
• Li Fraumeni/multiple cancer syndrome
• Other undefined cancer syndrome
Case 2: Results

10/25/18

PAT: English
MAT: Danish
Consanguinity: Denied
A. Jewish: Denied

Breast Ca 59
Liver Ca 52
Prostate Ca 59
TP53 pos.

60
61
~ 85
~ 85
~ 85

51
d.MI

22
26
2
2

Brain (GBM)

20

33

68
Breast Ca 48

1

20/30/18

PAT: English
MAT: Danish
Consanguinity: Denied
A. Jewish: Denied

61
Breast Ca 59
Liver Ca 52
Prostate Ca 59
TP53 pos.

33
LP 53 neg.

22
26

20

2

TP53 pos.
Tumor Sites in Families with TP53 Germline Mutations

- Breast: 24%
- Bone: 12.6%
- Brain: 12%
- Soft tissue: 11.6%
- GI: 7%
- Gynecol: 5.3%
- Hematol: 4.2%
- Adrenal: 3.6%
- Other: 14.1%

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>All</th>
<th>Population</th>
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<tbody>
<tr>
<td>20</td>
<td>10%</td>
<td>18%</td>
<td>12%</td>
<td>0.7%</td>
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<tr>
<td>30</td>
<td>21%</td>
<td>49%</td>
<td>35%</td>
<td>1.0%</td>
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<tr>
<td>40</td>
<td>33%</td>
<td>77%</td>
<td>52%</td>
<td>2.2%</td>
</tr>
<tr>
<td>50</td>
<td>68%</td>
<td>93%</td>
<td>80%</td>
<td>5.1%</td>
</tr>
</tbody>
</table>


2019 NCCN Guidelines

Li Fraumeni Testing Criteria

- Individual from a family with known P53 mutation
- Classic Li-Fraumei Syndrome (LFS) (70%+):
  - Proband with sarcoma <45 AND
  - First-degree relative with cancer <45 AND
  - 1st or 2nd relatives with cancer <45 or sarcoma at any age; same side of family
- Chompret criteria (25-35%+):
  - Proband with LFS tumor <46 (sarcoma, brain, breast, ACC, leukemia, lung) AND 1st or 2nd degree relative with LFS tumor <56 OR multiple primary tumor at any age
  - OR proband with multiple tumors; 1st <46 AND 2 in LFS spectrum
  - OR Adrenal Cortical Carcinoma or Choroid Plexus Carcinoma, rhabdosarcoma or embryonal anaplastic at any age
- Proband with breast cancer <35 AND BRCA ½ negative (7%+)
Managing Hereditary Risk
High Risk Breast/ Ovarian CA Carriers

- **Female Breast Risk**
  - Monthly SBE starting at 18
  - CBE q 6-12 months start at 20-25 (or 5 yr < 1\textsuperscript{st} dx)
  - Annual breast MRI starting at 25 (tailor to fm)
  - Annual MRI and mammogram starting at 30-75
  - Discuss prophylactic bilateral mastectomies

- **Ovarian Risk**
  - Risk reducing salpingo-oophrectomy (RRSO)
    - 35-40 in BRCA1 carriers
    - 40-45 in BRCA2 carriers

- **Males**
  - Monthly self breast exams and annual CBE start at 35
  - Prostate screening starting at 40
NCCN LFS Screening Guidelines

- Breast Risk
  - Monthly SBE starting at 18
  - CBE q 6-12 months start at 20-25 (or 5 yr < 1st dx)
  - Annual breast MRI starting at 20-29 (tailor to fm)
  - Annual MRI and mammogram starting at 30-75
  - Discuss prophylactic bilateral mastectomies
Other Cancer Risks
- Discuss limits of screening options
- Annual physical exam with skin and neuro exam
- Use XRT for treatment with caution
- Colonoscopy q 2-5 years starting at 25
- Investigate options for novel technologies
  - Whole body MRI, ultrasounds, brain MRI
- Target screenings based on family history
- Educate patient on early symptoms
Psychological Issues

- Proband proceeded with total colectomy despite our recommendations against it
- Recent contact with his wife; she reports he never recovered from surgery and died within 2 years
- Son has been episodically MIA; has completed 1 cycles of screening in 3 years
- Son did attend LFS meeting in 2010/ connected with peer support at that time
Psychological Interventions

- Specialized mental health professionals
- On-line support groups
- Genetic counselor network/ assistance with family communication and referrals
- Peer referrals
- LFS Consortium/ Family Network
Causes of Hereditary Susceptibility to Colorectal Cancer

- Familial Lynch Syndrome
- Hereditary
  - AC-1 without MMR (Familial CRC of type "X")
  - FAP; AFAP
  - Mixed polyposis syndrome
  - Ashkenazi I1307K
  - CHEK2 (HBCC)
  - MYH
  - TGFB1
  - PJS
  - FJP
  - CD
  - Hamartomatous polyposis

Sporadic
Clinical Features of HNPCC (Lynch Syndrome)

- Early but variable age at CRC diagnosis (~45 years)
- Tumor site in proximal colon predominates (2/3rds)
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors
- Autosomal pattern of inheritance
- 1/400 (recent population studies suggest 1/250)
Cancer Risks in Lynch Syndrome

- Colorectal: 78%
- Endometrial: 43%
- Stomach: 10%
- Urinary tract: 10%
- Biliary tract: 15%
- Ovarian: 9%
## NCCN Guidelines Version 1.2018

### Lynch Syndrome

#### Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>MLH1 or MSH2</th>
<th>Mean Age of Onset</th>
<th>MSH6</th>
<th>Mean Age of Onset</th>
<th>Risk</th>
<th>Mean Age of Onset</th>
<th>Risk</th>
<th>Mean Age of Onset</th>
<th>Risk</th>
<th>Mean Age of Onset</th>
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</thead>
<tbody>
<tr>
<td>Colon</td>
<td>4.5%</td>
<td>52%–82%</td>
<td>44–61 years</td>
<td>10%–22%</td>
<td>54 years</td>
<td>15%–20%</td>
<td>61–66 years</td>
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<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%–60%</td>
<td>48–62 years</td>
<td>16%–26%</td>
<td>55 years</td>
<td>15%</td>
<td>49 years</td>
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<tr>
<td>Prostate</td>
<td>11.6%</td>
<td>~30%</td>
<td>59–69 years</td>
<td>~30%</td>
<td>69–69 years</td>
<td>Not reported</td>
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<tr>
<td>Ovary</td>
<td>1.3%</td>
<td>MLH1 - 11%–20% by age 70 y, MSH2 - 15%–24% by age 70 y</td>
<td>56 years</td>
<td>~3%</td>
<td>63 years</td>
<td>†</td>
<td>70–78 years</td>
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<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>1%–4%</td>
<td>50–57 years</td>
<td>Not reported</td>
<td>Not reported</td>
<td>†</td>
<td>Not reported</td>
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<tr>
<td>Uterine tract</td>
<td>&lt;1%</td>
<td>1%–7%</td>
<td>54–60 years</td>
<td>&lt;1%</td>
<td>65 years</td>
<td>†</td>
<td>Not reported</td>
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<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%–6%</td>
<td>47–49 years</td>
<td>Not reported</td>
<td>54 years</td>
<td>†</td>
<td>59 years</td>
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<td>Brain/CNS</td>
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<td>1%–3%</td>
<td>~50 years</td>
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<td>45 years</td>
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<td>Sebaceous neoplasms</td>
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<td>1%–9%</td>
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<tr>
<td>Pancreas</td>
<td>&lt;1%</td>
<td>1%–6%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
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</tbody>
</table>

†The combined risk for renal pelvic, stomach, ovary, small bowel, ureter, and brain is 6% to age 70 (Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008;135:419-428).

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.
Universal Tumor Screening

• All colon, uterine, ovarian tumors screened for Lynch protein loss
  • Occurs in 15% of colon tumors
  • If loss of MSH2, MSH6 or PMS2- germline test
  • If loss of MLH1, check for methylation or BRAF mutation first
  • Refer positive screen cases for tumor/germline testing
  • Half of Lynch IHC loss is due to double somatic tumor/ not hereditary mutations so parallel testing is needed

• Recently started Lynch IHC screening for all solid tumors
  • Based on PD1 blockade therapy

• This is likely to be replaced by direct germline testing as the costs continue to drop and tumor screening becomes more common
Clinical Features of FAP

- Estimated penetrance for adenomas >90%
- Risk of extracolonic tumors (upper GI, desmoid, osteoma, thyroid, brain, other)
- CHRPE may be present
- Untreated polyposis leads to 100% risk of cancer
Genetics of FAP

- Autosomal dominant inheritance; 1/10,000
- Caused by mutations in APC tumor suppressor gene on chromosome 5q
- Up to 30% of patients have de novo germline mutations
- Attenuated FAP associated with terminal mutations
- 1-2% risk of childhood hepatoblastoma (10% cases); slight increased thyroid risk
Indications for **APC/MUTYH** Gene Testing

- polyposis (>100 adenomas)
- attenuated FAP (10 or 20-99 adenomas)
- Bilateral CHRPE
- Childhood hepatoblastoma
- Childhood desmoids

MAP syndrome/MUTYH gene

- **Multiple adenomatous polyposis (MAP) syndrome**
  - Autosomal recessive; mutations in the MYH gene
  - Median number of polyps = 55
  - Mean age of polyp diagnosis = 30-50 years
  - Polyps mainly small, mildly dysplastic tubular adenomas. Some tubulovillous, hyperplastic, serrated adenomas, microadenomas

- 30% of individuals with 15-100 polyps have homozygous mutations in the MYH gene

- Genetic testing should be offered if >10-20 polyps (and APC gene testing negative)

- High single mutation carrier rate = 1/50
<table>
<thead>
<tr>
<th>Additional Colon Cancer Gene Polyposis</th>
<th>Non-Polyposis</th>
</tr>
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<tbody>
<tr>
<td>POLE</td>
<td>CHEK2</td>
</tr>
<tr>
<td>POLD1</td>
<td>ATM</td>
</tr>
<tr>
<td>GREM1</td>
<td>NBN</td>
</tr>
<tr>
<td>STK11</td>
<td>TP53</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>CDH1</td>
</tr>
<tr>
<td>SMAD4</td>
<td>PTEN</td>
</tr>
<tr>
<td>NTHL1</td>
<td></td>
</tr>
</tbody>
</table>
Reverse Engineering Genetics

Tumors are now being sequenced for many cancer related mutations hoping to detect actionable driver mutations (targets)

Perhaps 10% of driver mutations may be germline. We are beginning to test for tumor identified mutations that could be heritable.
Tumor Heterogeneity

Intratumoral heterogeneity within a primary tumor

Intermetastatic heterogeneity between two metastases

Intrametastatic heterogeneity within metastatic lesions

Interpatient heterogeneity
Liquid Biopsies

Plasma sample before treatment

Exome sequencing

Plasma sample at progression

Analysis of mutations in plasma DNA

Identification of mutations selected by treatment
N=1566
16% had a presumed pathogenic germline variant; **12.6%** in known CA
59% of these were not concordant with the patient’s cancer type
100% had at least one VUS
5% have actionable therapies (expanding)
3.5% “incidental” mutations; need to pre-consent to disclose
N=1040 patients, median age was 58 years
81.3% had stage IV prostate, renal, pancreatic, breast or colon cancer

182 (17.5%) had germline cancer risk mutations
149 (14.3%) with moderate- to high-penetrance mutations;
101 patients tested (9.7%; CI: 8.1-11.7) did not meet clinical guidelines,
including 65 (6.25%) with moderate- to high-penetrance mutations.

Germline findings led to discussion or initiation of change to targeted therapy
in 38 patients (4%)
Some Mutations do not “Stay in Their Lane”

Larger panels reveal some surprising overlap between syndromes
Targeting the Hallmarks of Cancer

Summary (Genetics):

- Next Gen Sequencing has revolutionized hereditary testing; cost and spectrum. This creates a need for complex pre- and post test counseling.
- Always try to test the most informative relative first: youngest, most affected, living.
- Clinical overlap may require you consider more than one syndrome.
- None of these genetic tests are comprehensive.
- Empiric risk counseling is the default if no mutation is found.
- Genetic counseling is time consuming but critical to predicting most likely syndrome, understanding the limits of tests, contextualizing the outcomes and options.
- Balancing the individual and family needs is an art.
Summary (Genomics):

- Next Gen Sequencing opened doors to massive tumor profiling to identify driver mutations
- Actionable mutations expand as pathways are defined and targeted therapies developed
- DNA maintenance genes may increase cancer risks beyond traditional associations (change lanes)
- Tumors are ever changing and can still outrun targeted treatments
- Tumor biology is complex; we can only treat a fraction of what we can test
- We can still only test a portion of cancer genes
- Liquid biopsy – currently insufficient sensitivity
- **We are moving toward an era of broad, tumor/germline paired genetic testing; a marriage of hereditary genetics and tumor genomics**
# Program Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>James Ford, MD</td>
<td>Director, Tumor Genomics, Upper GI and other Syn.</td>
</tr>
<tr>
<td>Allison Kurian, MD, MSc</td>
<td>Associate Director, Breast/Ovarian Syn.</td>
</tr>
<tr>
<td>Uri Ladabaum, MD</td>
<td>Lower GI Syn.</td>
</tr>
<tr>
<td>Rochelle Reyes, PA</td>
<td>Cancer Genomics</td>
</tr>
</tbody>
</table>

### Genetic Counselors
- Nicki Chun, MS, CGC
- Kerry Kingham MS, CGC
- Rachel Koff, MS, CGC
- Madeline Graf, MS, CGC
- Courtney Rowe-Teeter, MS, CGC
- Karlene Lara-Otaro, MS, CGC
- Meredith Gerhart, MS, CGC
## BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS\(^a,b\)

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Increased risk of BC&lt;br&gt;• Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y,c,d&lt;br&gt;• RRM: Evidence insufficient, manage based on family history.</td>
<td>No increased risk of OC</td>
<td>Unknown or insufficient evidence for pancreas or prostate cancer</td>
</tr>
<tr>
<td></td>
<td><strong>Comments:</strong> Insufficient evidence to recommend against radiation therapy. Counsel for risk of autosomal recessive condition in offspring.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>Increased risk of BC&lt;br&gt;• See BRCA Mutation-Positive Management</td>
<td>Increased risk of OC&lt;br&gt;• See BRCA Mutation-Positive Management</td>
<td>Prostate cancer&lt;br&gt;• See BRCA Mutation-Positive Management</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Increased risk of BC&lt;br&gt;• See BRCA Mutation-Positive Management</td>
<td>Increased risk of OC&lt;br&gt;• See BRCA Mutation-Positive Management</td>
<td>Pancreas, Prostate, Melanoma&lt;br&gt;• See BRCA Mutation-Positive Management</td>
</tr>
<tr>
<td>BRIP1</td>
<td>No increased risk of BC</td>
<td>Increased risk of OC&lt;br&gt;• Consider RRSo at 45–50 y</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td><strong>Comments:</strong> Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in <strong>BRIP1</strong> appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td>Increased risk of lobular BC&lt;br&gt;• Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y,c,d&lt;br&gt;• RRM: Evidence insufficient, manage based on family history.</td>
<td>No increased risk of OC</td>
<td>Diffuse gastric cancer&lt;br&gt;• See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer</td>
</tr>
<tr>
<td></td>
<td><strong>Continued</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


\(^b\)The following genes and others are found on some of the panels, but there is insufficient evidence to make any recommendations for breast MRI, RRSo, RRM: BARD1, FANCC, MRE11A, MUTYH heterozygotes, RECQL4, RAD50, RINT1, SLX4, SMARCA4, or XRCC2.

\(^c\)May be modified based on family history (typically beginning screening 5–10 years earlier than the youngest diagnosis in the family but not later than stated in the table) or specific gene mutation.

\(^d\)For women with mutations who are treated for breast cancer and have not had bilateral mastectomy, screening should continue as described.
### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

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.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td>Increased risk of breast cancer</td>
<td>No increased risk of ovarian cancer</td>
<td>Colon</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram with</td>
<td></td>
<td>• See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td></td>
<td>consideration of tomosynthesis and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>consider breast MRI with contrast</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>age 40 y&lt;sup&gt;0&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2,</td>
<td>Unknown or insufficient evidence for</td>
<td>Increased risk of ovarian cancer</td>
<td>Colon, Uterine, Others</td>
</tr>
<tr>
<td>MLH1,</td>
<td>breast cancer risk&lt;sup&gt;0&lt;/sup&gt;</td>
<td>• See NCCN Guidelines for Genetic/Familial</td>
<td>• See NCCN Guidelines for Genetic/Familial</td>
</tr>
<tr>
<td>MSH6,</td>
<td>• Manage based on family history</td>
<td>High-Risk Assessment: Colorectal</td>
<td>High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td>PMS2,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPCAM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>Increased risk of breast cancer</td>
<td>Unknown or insufficient evidence for ovarian cancer risk</td>
<td>Unknown or insufficient evidence</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>consideration of tomosynthesis and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>consider breast MRI with contrast</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>age 30–50 y&lt;sup&gt;0&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF1</td>
<td>Increased risk of breast cancer</td>
<td>No increased risk of ovarian cancer</td>
<td>Malignant peripheral nerve sheath tumors, GIST, others</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram with</td>
<td></td>
<td>• Recommend referral to NF1 specialist for evaluation and</td>
</tr>
<tr>
<td></td>
<td>consideration of tomosynthesis starting</td>
<td></td>
<td>management</td>
</tr>
<tr>
<td></td>
<td>at age 30 y and consider breast MRI with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>contrast from ages 30–50 y&lt;sup&gt;0&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>family history</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments: Risk data are based only on frameshift pathogenic/likely pathogenic variants. The risks for most missense/pathogenic variants are unclear but for some pathogenic/likely pathogenic variants, such as MSH6, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.

Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating pathogenic/likely pathogenic variant. Although risks for other pathogenic/likely pathogenic variants have not been established it is prudent to manage patients with other truncating pathogenic/likely pathogenic variants similarly to those with 657del5. Counsel for risk of autosomal recessive condition in children.

Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Screening recommendations only apply to individuals with a clinical diagnosis of NF. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.

**RRM: Risk-reducing mastectomy**

**Footnotes on GENE-5**

**Continued**
## BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

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<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALB2</td>
<td>Increased risk of breast cancer</td>
<td>Unknown or insufficient evidence for ovarian cancer risk</td>
<td>Unknown or insufficient evidence</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comments: Counsel for risk of autosomal recessive condition in offspring.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>Increased risk of breast cancer</td>
<td>No increased risk of ovarian cancer</td>
<td>See Cowden Syndrome Management</td>
</tr>
<tr>
<td></td>
<td>• See Cowden Syndrome Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td>Unknown or insufficient evidence for breast cancer risk</td>
<td>Increased risk of ovarian cancer</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>• Consider RRSO at 45-50 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in RAD51C appears to be sufficient to justify consideration of 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51D</td>
<td>Unknown or insufficient evidence for breast cancer risk</td>
<td>Increased risk of ovarian cancer</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>• Consider RRSO at 45-50 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in RAD51D appears to be sufficient to justify consideration of 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>Increased risk of breast cancer</td>
<td>Increased risk of non-epithelial ovarian cancer</td>
<td>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td></td>
<td>• Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
<td>• See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Evidence insufficient, manage based on family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td>Increased risk of breast cancer</td>
<td>No increased risk of ovarian cancer</td>
<td>See Li-Fraumeni Syndrome Management</td>
</tr>
<tr>
<td></td>
<td>• See Li-Fraumeni Syndrome Management</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RRM:** Risk-reducing mastectomy  
**RRSO:** Risk-reducing salpingo-oophorectomy

---

**Footnotes on GENE-5**

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.
<table>
<thead>
<tr>
<th>GENE</th>
<th>STRENGTH OF EVIDENCE</th>
<th>RISK LEVEL</th>
<th>ASSOCIATION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Well-established</td>
<td>High</td>
<td>FAP &amp; AFAP</td>
<td>See APC and MUTYH Genetic Testing Criteria (APC/MUTYH-1)</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>Well-established</td>
<td>High</td>
<td>JPS</td>
<td>See Juvenile Polyposis Syndrome Guidelines (JPS-1)</td>
</tr>
<tr>
<td>EPCAM</td>
<td>Well-established</td>
<td>High</td>
<td>LS</td>
<td>See Lynch Syndrome Guidelines (LS-1)</td>
</tr>
</tbody>
</table>

*RPS20 is an emerging gene that is potentially linked to CRC, and there are not enough data at present to include RPS20 on this list.

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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.
### Table 4: Evaluation of CRC Genes Commonly Included on Multi-Gene Panels

<table>
<thead>
<tr>
<th>GENE</th>
<th>STRENGTH OF EVIDENCE</th>
<th>RISK STATUS</th>
<th>ASSOCIATION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GREM1</td>
<td>Not well-established</td>
<td>Uncertain – presumed high risk from limited case reports</td>
<td>Hereditary mixed polyposis syndrome due to a 40kb duplication upstream of GREM1 in Ashkenazi Jewish ancestry only</td>
<td>Jaeger E, et al. Nat Genet 2012; 44:699-703.</td>
</tr>
<tr>
<td>MLH1</td>
<td>Well-established</td>
<td>High</td>
<td>LS</td>
<td>See Lynch Syndrome Guidelines (LS-1)</td>
</tr>
<tr>
<td>MSH2</td>
<td>Well-established</td>
<td>High</td>
<td>LS</td>
<td>See Lynch Syndrome Guidelines (LS-1)</td>
</tr>
<tr>
<td>MSH6</td>
<td>Well-established</td>
<td>High</td>
<td>LS</td>
<td>See Lynch Syndrome Guidelines (LS-1)</td>
</tr>
<tr>
<td>MUTYH biallelic mutations</td>
<td>Well-established</td>
<td>High</td>
<td>MAP</td>
<td>See APC and MUTYH Genetic Testing Criteria (APC/MUTYH-1)</td>
</tr>
<tr>
<td>MUTYH heterozygotes</td>
<td>Not well-established</td>
<td>Uncertain – moderate at most</td>
<td>Possible increased risk for CRC</td>
<td>Win AK, et al. Gastroenterology 2014;146:1208-1211.</td>
</tr>
</tbody>
</table>
### Table 4: Evaluation of CRC Genes Commonly Included on Multi-Gene Panels

<table>
<thead>
<tr>
<th>GENE</th>
<th>STRENGTH OF EVIDENCE</th>
<th>RISK STATUS</th>
<th>ASSOCIATION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMS2</td>
<td>Well-established</td>
<td>High</td>
<td>LS</td>
<td>See Lynch Syndrome Guidelines (LS-1)</td>
</tr>
<tr>
<td>PTEN</td>
<td>Well-established</td>
<td>Moderate-High</td>
<td>Cowden syndrome/PTEN hamartoma syndrome</td>
<td>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian</td>
</tr>
<tr>
<td>SMAD4</td>
<td>Well-established</td>
<td>High</td>
<td>Juvenile polyposis syndrome</td>
<td>See Juvenile Polyposis Syndrome Guidelines (JPS-1)</td>
</tr>
<tr>
<td>STK11</td>
<td>Well-established</td>
<td>High</td>
<td>PJS</td>
<td>See Peutz-Jeghers Syndrome Guidelines (PJS-1)</td>
</tr>
<tr>
<td>TP53</td>
<td>Well-established</td>
<td>High</td>
<td>Li-Fraumeni syndrome</td>
<td>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian</td>
</tr>
</tbody>
</table>

*RPS20 is an emerging gene that is potentially linked to CRC, and there are not enough data at present to include RPS20 on this list.*

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