Genetic Testing in Patients with Breast Cancer: Who Should Get Tested?

Nadine M. Tung, MD
Beth Israel Deaconess Medical Center
• Yes: BRCA1/2, PALB2, ATM, CHEK2
• Rare (syndrome-related): TP53, CDH1, PTEN, STK11
• Growing evidence (RR 1.7-2.1): BARD1, RAD51C, RAD51D (esp ER-); + NF1
• Less clear: MSH6
• No evidence: NBN (incl 675del5), BRIP1, RAD50
<table>
<thead>
<tr>
<th>Gene</th>
<th>CARRIERS Study</th>
<th>BCAC (truncating PV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1</strong></td>
<td>7.62 (5.33-11.27)</td>
<td>10.57 (8.02-13.93)</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>5.23 (4.09-6.77)</td>
<td>5.85 (4.85-7.06)</td>
</tr>
<tr>
<td><strong>PALB2</strong></td>
<td>3.83 (2.68-5.63)</td>
<td>5.02 (3.73-6.76)</td>
</tr>
<tr>
<td><strong>CDH1</strong></td>
<td>2.5 (1.01-7.07)</td>
<td>0.86 (0.37-1.98)</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>NA</td>
<td>3.06 (0.63-14.91)</td>
</tr>
<tr>
<td><strong>STK11</strong></td>
<td>NA</td>
<td>1.6 (0.48-5.28)</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>NA</td>
<td>2.25 (0.85-6.0) (sig when family studies included)</td>
</tr>
<tr>
<td><strong>ATM</strong></td>
<td>1.82 (1.46-2.27)</td>
<td>2.1 (1.71-2.57)</td>
</tr>
<tr>
<td><strong>CHEK2</strong> (truncating)</td>
<td>2.47 (2.02-3.05)</td>
<td>2.54 (2.21-2.91)</td>
</tr>
<tr>
<td><strong>BARD1</strong></td>
<td>1.37 (0.87-2.16)</td>
<td>2.09 (1.35-3.23)</td>
</tr>
<tr>
<td><strong>RAD51C</strong></td>
<td>1.2 (0.75-1.93)</td>
<td>1.93 (1.20-3.11)</td>
</tr>
<tr>
<td><strong>RAD51D</strong></td>
<td>1.72 (0.88-3.51)</td>
<td>1.80 (1.11-2.93)</td>
</tr>
<tr>
<td><strong>MSH6</strong></td>
<td>1.22 (0.77-1.96)</td>
<td>1.96 (1.15-3.33) false-discovery probability not &lt; 0.05</td>
</tr>
</tbody>
</table>

High risk
Syndrome-related
Mod risk
Mod risk?

Hu et al. NEJM 2021; Dorling et al. NEJM 2021
# Breast Cancer Susceptibility Genes

(risk for breast cancer overall)

<table>
<thead>
<tr>
<th>Genes with High Risk (RR &gt; 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2</td>
</tr>
<tr>
<td>PALB2</td>
</tr>
<tr>
<td>TP53</td>
</tr>
<tr>
<td>CDH1</td>
</tr>
<tr>
<td>STK11</td>
</tr>
<tr>
<td>PTEN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genes with Mod Risk (RR 2 - 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
</tr>
<tr>
<td>CHEK2 (truncating)</td>
</tr>
<tr>
<td>BARD1?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genes with More Mod Risk (~ 1.7 - 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAD51C ?</td>
</tr>
<tr>
<td>RAD51D ?</td>
</tr>
<tr>
<td>NF1 ? (individuals w/o clinical NF)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genes with Less Certain Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSH6 ?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
</tr>
</thead>
</table>

Hu et al. NEJM 2021
Dorling et al. NEJM 2021
Outline

- Existing guidelines for germline testing for hereditary breast and ovarian cancer (HBOC).
- Should all breast cancer pts be offered germline genetic testing?
- When should tumor genomic profiling trigger germline testing?
- Should all Ashkenazi Jewish individuals be offered gBRCA testing?
- Pros and cons of offering population genetic testing to all women: BRCA? Multi-gene-panel?
ACMG Variant Classification

- Variant Classification:
  - Pathogenic (deleterious)
  - Likely pathogenic
  - Variant Unknown Significance (VUS)
  - Likely benign
  - Benign

"mutation"
Guidelines for germline *BRCA* testing

- NCCN
- NICE (UK) – use ≥ 10% probability of *BRCA* mutation
- NBCG (Norway)
- ASCO – 2016 breast cancer survivorship guidelines
- USPSTF- primarily for unaffected women
**NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (V2.2021)**

**Universal HBOC testing: patient with non-breast cancer**

- Ovarian Cancer: EOC/FT/PPC
- Pancreatic Cancer (exocrine)
- Prostate Cancer
  - Metastatic/advanced
  - Ashkenazi Jewish
  - Intraductal/cribriform histology
  - High or very high risk group
  - Appropriate family hx: breast cancer (dx ≤ age 50), ovarian, met prostate, pancreatic
- Familial mutation in a cancer susceptibility gene
- Mutation in cancer risk gene identified through tumor profiling
- Anyone with > 5% probability of *BRCA1/2* mutation based on prior probability model
NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (V2.2021)

**HBOC testing: patient with breast cancer**

- **Age < 45**
- **Age 46-50**
  - Limited family hx
  - 2nd breast cancer (any age)
  - ≥ 1 relative with breast, ovarian, pancreatic or prostate cancer (any age)
- **Age < 60: TNBC**
- **Any Age:**
  - Ashkenazi Jewish
  - Male
  - Family hx:
    - ≥ 1 relative with breast (dx ≤ age 50), ovarian, pancreatic or prostate cancer (metastatic, intraductal/cribriform histology; high or very high risk)
    - 2 or more breast cancer diagnoses in relatives (any age)
    - To aid with systemic Rx (e.g. HER2-neg metastatic Br Ca/ PARPi)

fam hx = up to 3rd degree relative (same side family)
NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (V2.2021)

- **Affected or unaffected:**
  - 1<sup>st</sup> or 2<sup>nd</sup> degree relative of someone who meets criteria (last 2 slides)
    - Only FDR if the only indication is a relative with pancreatic or prostate cancer

- **Consider testing for HBOC genes**
  - Two or more breast cancers – 1<sup>st</sup> breast cancer dx age 50-65 years
  - 2.5% - 5% probability of BRCA mutation by any model (e.g. BRCAPro)
  - Any Ashkenazi Jewish individual
    - Testing should not be offered outside of a medical framework or clinical trial
## Sensitivity of guidelines for gBRCA mutations (among patients with breast cancer)

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE (UK)</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>NBCG (Norway)</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>NCCN/ ASCO</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>Dx &lt;40 yo</td>
<td>32%</td>
<td>94%</td>
</tr>
<tr>
<td>Dx &lt;50 yo</td>
<td>74%</td>
<td>75%</td>
</tr>
<tr>
<td>Dx &lt;60 yo</td>
<td>89%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Grindedal et al. BMC Cancer 2017
NCCN Guidelines are very sensitive for identifying \textit{BRCA} mutation carriers

- 488 unselected newly diagnosed, early stage breast cancer patients at DFCI
  - Submitted blood for research

- 30/30 germline \textit{BRCA1}/\textit{BRCA2} mutation carriers identified met NCCN testing criteria

\cite{Tung, Garber et al. JCO 2016}
Don’t forget about other high-risk Breast Cancer genes…

- **TP53** (Li-Fraumeni syndrome)
  - Sarcoma, breast, brain, leukemia, adrenal cortex (SB²LA)
- **CDH1** (Lobular-diffuse gastric)
  - Lobular breast cancer; diffuse gastric cancer
- **PTEN** (Cowden syndrome)
  - Colon, endometrial, thyroid & kidney cancer; skin manifest, macrocephaly; GI hamartomatous polyps
- **STK11** (Peutz-Jeghers syndrome)
  - Breast & GI (incl pancreas) cancers, hamartomatous polyps, ovarian sex cord, testicular sertoli, lip & oral mucosal freckling
Germline *TP53* testing recommendation

<table>
<thead>
<tr>
<th>Age of Breast Tumour Onset</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When TP53 testing should systematically be performed</strong></td>
<td></td>
</tr>
<tr>
<td>Before 31</td>
<td>Invasive breast carcinoma <em>or ductal carcinoma in situ</em> (DCIS)</td>
</tr>
</tbody>
</table>
| Before 36 | - *Bilateral* invasive breast carcinoma or DCIS  
| | - *Multifocal* invasive breast carcinoma or DCIS  
| | - *HER2+* invasive breast carcinoma or DCIS  
| | - Phyllode tumour |
| Before 46 | - Invasive breast carcinoma *and a second* TP53 core tumour in the patient *or* invasive breast carcinoma *and one first- or second-degree relative with a TP53 core tumour before 56 years* ab |
| **When TP53 testing may be offered** | |
| Before 46 | - *Bilateral* invasive breast carcinoma  
| | - *HER2+* invasive breast carcinoma *and a familial history of HER2+ breast cancer* |
| **When TP53 testing should not be performed** | |
| After 46 | **No previous TP53 core tumour before 46 and no familial history fulfilling Chompret criteria** |

*Chompret criteria* (14), b **TP53 core tumour**: breast cancer, soft-tissue sarcoma, osteosarcoma, central nervous system tumour, adrenocortical carcinoma. DCIS: **ductal carcinoma in situ**.
Retest appropriate patients

- Retake family history regularly
- Moving target: continuous changes...
  - Criteria for genetic testing
  - Personal & family history
  - Sensitivity of mutation detection
  - Genes included in panels
- Large rearrangement analysis of $BRCA1/2 : 2006$
- Multigene panels – first available 2013
Outline

- Existing guidelines for germline testing for HBOC.
- Should all breast cancer pts be offered germline genetic testing?
- When should tumor genomic profiling trigger germline testing?
- Should all Ashkenazi Jewish individuals be offered gBRCA testing?
- Pros and cons of offering population genetic testing to all women: BRCA? Multi-gene-panel?
How many mutations are missed by NCCN criteria for patients with breast cancer?

- Study (Beitsch et al)
  - ~1000 breast ca pts - no previous genetic testing
  - 20 community and academic sites
  - 50% did not meet 2017 NCCN criteria for HBOC testing

- 80 gene panel; 11 breast cancer-related genes

Beitsch et al. JCO 2018
How many mutations are missed with NCCN criteria? (Beitsch study)

- Mutations found: 480 pts who did not meet NCCN criteria for HBOC:
  - 0.6% of pts had a BRCA mutation
  - 0.8%: high-risk breast cancer gene (3 BRCA, 1 PALB2)
  - 2.7% moderate-risk breast cancer gene: ATM (5), CHEK2 (7), NBN (1)
  - 4.2%: non-breast cancer risk gene [MSH6 (1), RAD51C/D (3), MUTYH (8), genes without recs (8)]
  - Total: 7.9% had any mutation

Beitsch et al. JCO 2018
How many mutations are missed by NCCN criteria for patients with breast cancer?

- Study (Yadav et al)
  - ~3900 breast ca pts from Mayo clinic tumor registry, dx 2000-2016
  - ~ 50% did not meet 2020 NCCN criteria for HBOC testing

- Tested for 9 breast cancer susceptibility genes:
  - BRCA1/2, CDH1, PTEN, TP53, PALB2
  - ATM, CHEK2, NF1

Yadav et al. JCO 2020
How many mutations are missed with NCCN criteria? (Yadav study)

- Mutations found: 2,035 pts who did not meet NCCN criteria for HBOC:
  - 0.7% of pts had a BRCA mutation
  - 1.4%: high-risk breast cancer gene: BRCA + 8 PALB2, 4 CDH1, 3 TP53
  - 2.2% moderate-risk breast cancer gene: ATM (15), CHEK2 (28), NF1(1)

Yadav et al. JCO 2020
## Mutations missed with NCCN criteria

<table>
<thead>
<tr>
<th>Gene</th>
<th>Yadav (Mayo) % pts with missed mutat</th>
<th>Beitsch % pt with missed mutat</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2</td>
<td>0.7%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Hi risk Br Ca gene (inc PALB2)</td>
<td>1.4%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Mod risk Br Ca gene (only ATM, CHEK2, NF-1 tested)</td>
<td>2.2%</td>
<td>2.8% (only ATM, CHEK2, NBN found)</td>
</tr>
</tbody>
</table>

Beitsch et al. JCO 2018
Yadav et al. JCO 2020
Genetic testing should be made available to all patients with a personal history of breast cancer. …include *BRCA1/BRCA2* and *PALB2*, with other genes as appropriate for the clinical scenario and family history.


Should all early stage breast cancer patients have genetic testing? Yes

- < 50% who qualify (by NCCN criteria) are being offered testing
  - Underutilization is greatest in minority and underserved populations
  - Criteria are too complicated to remember

- For those who do NOT qualify for BRCA1/2 testing:
  - ~1% have mutation in hi risk Br Ca gene (Beitsch; Yadav)
  - ~ 3% have mutations in moderate risk Br Ca gene

- Mutations in high risk non-breast ca genes are occasionally identified (Lynch)

Kurian JAMA 2017; Kurian JCO 2018; Childers JCO 2017; McCarthy JCO 2016; Knerr JNCI 2019
Benefits of identifying mutations in high-risk Br Ca genes in patients with breast cancer

- Prevention and surveillance
  - Prophylactic mastectomy
  - Breast MRI
  - BSO (BRCA1/2)

- Treatment: metastatic breast cancer
  - PARPi:
    - gBRCA1/2: OlympiAD and EMBRACA
    - gPALB2: Olaparib Expanded (TBCRC 048)

- Cascade testing for relatives

But most of the mutations in breast cancer risk genes missed without universal germline testing are in moderate risk genes (e.g., ATM, CHEK2)

What is the value of identifying these mutations in our patients with breast cancer?
Mutations in moderate-risk Br Ca genes in patients with breast cancer: management implications?

- **Risk for contralateral breast cancer (CBC)**
  - Some data for CHEK2 1100delC
  - CBC RR 2.8 (10-12% 10 yr risk); RR 3.5 if 1st breast cancer ER+

- **Radiation**
  - No data to withhold RT (including ATM, though more data needed)

- **Systemic Therapy**
  - Olaparib Expanded (TBCRC 048)- ATM, CHEK2: no response to PARPi

- **Relatives**
  - Autosomal dominant- cancer risks
  - Autosomal recessive - reproductive: ATM, NBN, PALB2, BRIP1, RAD51C

Weischer et al JCO 2012; Reiner et al JNCI 2020
ASCO guidelines for management of hereditary breast cancer (BRCA1/2, PALB2, ATM, CHEK2)

- For patients with breast cancer with germline CHEK2 or ATM mutations, local therapy decisions should NOT be based on mutation alone
  - XRT should not be avoided
  - Other factors (age at dx, fam hx) should be used in deciding bilateral mastectomy
  - If no mastectomy- annual breast MRI (+ mammogram) recommended

Tung, Robson, Zakalik et al. JCO 2020
Should all early stage patients with breast cancer have genetic testing? No

- For those who do NOT meet criteria:
  - < 1% will have mutation in BRCA/high-risk breast ca genes (Beitsch)
  - Most mutations are in
    - moderate-risk breast cancer genes or
    - non-breast cancer genes (population testing)

- Better use of resources: identify more patients who DO meet criteria
Should all early stage patients with breast cancer have genetic testing? No

- Limited resources
  - 700 cancer genetic counselors in USA
  - Some insurance still require genetic counselor involvement

- $400 million/yr to test all breast cancer pts (w/o counseling)

- Insurance may not always pay if don’t meet NCCN criteria
  - ….exacerbate disparities in testing

- Until there is guaranteed insurance coverage and better genetic testing delivery models- stick to NCCN criteria

Milliron & Griggs JCO 2018
Potential harms of identifying moderate risk mutations or VUS in breast cancer genes

- Misinterpretation of clinical significance
  - Unnecessary mastectomies
  - Avoidance of radiation
  - Unnecessary bilateral salpingo-oophorectomy (BSO)
Increased bilateral mastectomy with VUS in BRCA1/2

- Br Ca pts in SEER database (Georgia and LA) who underwent genetic testing
  - 57% met NCCN criteria, “higher risk”
  - 42% did not, “avg risk”

- Pts with VUS in BRCA1/2: 40-50% had bilateral mastectomy
420 pts with unilateral Br Ca who underwent multi-gene panel testing at MD Anderson

- Likelihood of CRRM
  - OR 20.2 if BRCA1/2 mutation
  - OR 3.9 for non-BRCA1/2 mutation (p < 0.001): 2/3 ATM & CHEK2
  - OR 1.8 for VUS in any gene (p< 0.001)
Did breast cancer treatment differ for patients with mutation or VUS in non-\textit{BRCA} gene?

- Br Ca pts dx 2014-2016 (SEER database Georgia and California)
- Rx for non-\textit{BRCA}1/2 mutations* c/w no mutation
  - ↑ bilateral mastectomy: OR 2.4
  - ↓ XRT (e.g. after lumpectomy) OR 0.71, but NS
- Rx did not differ for VUS in non-\textit{BRCA} gene

* 2/3 mutations = \textit{ATM} & \textit{CHEK2}, though also include \textit{TP53, PALB2, CDH1, PTEN}

Kurian et al. JAMA Oncol 2020
PROMPT: Unnecessary oophorectomy

- Prospective Registry of MultiPlex Testing (PROMPT)
- Examine frequency of RRSO in individuals with genetic alterations without ovarian cancer (OC) risk >5%

Results:
- ↑ RRSO in those with VUS in OC gene (BRCA1/2, Lynch, BRIP1, RAD51C/D)
- 10-19% with P/LP variant in CHEK2, ATM, PALB2 reported RRSO
- Sometimes RRSO were < age 50

Study limitations
- Some RRSO may have been for treatment (confounder)
- RRSO may be appropriate for some patients (e.g. PALB2 mutation & FHx of OC)

Domchek et al. ASCO 2020
Summary: Universal genetic testing for patients with breast cancer?

- Universal genetic testing in patients with breast cancer misses no mutations and overcomes complicated testing criteria that may be hard to remember

- But:
  - Cost
  - Mutations missed using NCCN criteria are rare, and high risk mutations even rarer
  - Potential harm from inappropriate recommendations for patients with mutations in moderate risk genes, genes of unclear significance, VUS
So we must ask: What is the goal?

- 100% sensitivity for identification of mutations in cancer risk genes?
- Which genes?
  - Breast cancer genes:
    - High Risk
    - Moderate Risk
  - Non-breast cancer genes: population testing
    - High risk (e.g. Lynch)
    - Moderate/low risk (e.g. MUTYH)
- At what cost?
Hybrid approach: universal testing for breast cancer dx before age X, criteria testing after age X

- Easier to remember
- Takes advantage of the fact that most mutations (high risk genes) occur in those diagnosed at younger age
- Spares (automatic) testing in older patients, less likely to have clinically meaningful mutation and more likely to have CHIP (e.g. \textit{TP53})
- Less costly than universal testing for all patients with breast cancer
How many mutations are missed if universal genetic testing is done for all patients with breast cancer diagnosed by age 65, with NCCN criteria used for those diagnosed > age 65?

Yadav et al. JCO 2020
Argument for universal testing for patients with breast cancer dx by age 65

- % of pts who do not meet NCCN criteria, yet have a mutation

<table>
<thead>
<tr>
<th>Breast Cancer dx by age:</th>
<th>BRCA1/2</th>
<th>Hi risk BC genes</th>
<th>Hi &amp; mod risk BC genes (incl ATM, CHEK2, NF1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 65 yo</td>
<td>1%</td>
<td>1.7%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

Desai et al. Cancer 2020; Yadav et al. JCO 2020
Argument for universal testing for patients with breast cancer dx by age 60-65

- What % of pts who do not meet NCCN criteria have a mutation

<table>
<thead>
<tr>
<th>Breast Cancer dx by age:</th>
<th>BRCA1/2</th>
<th>Hi risk BC genes</th>
<th>Hi &amp; mod risk BC genes (incl ATM, CHEK2, NF1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 65 yo</td>
<td>1%</td>
<td>1.7%</td>
<td>4.4%</td>
</tr>
<tr>
<td>≤ 60 yo</td>
<td>1%</td>
<td>1.9%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

- This ~ 2% frequency of missed mutations is comparable to 2.5% of BRCA mutations among unselected individuals of Ashkenazi Jewish ancestry. Should 2-2.5% be the threshold to recommend universal testing in a population?

Desai et al. Cancer 2020; Yadav et al. JCO 2020
## Hybrid approach to genetic testing?

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity of detecting an existing mutation</th>
<th>% BC pts spared genetic testing</th>
<th>% of BC pts with mutation missed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA1/2</td>
<td>Hi Risk BC genes</td>
<td>Hi &amp; mod risk BC genes</td>
</tr>
<tr>
<td>ASBrS</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>&lt; 65 yo</td>
<td>98%</td>
<td>98%</td>
<td>92%</td>
</tr>
<tr>
<td>NCCN v1.2020</td>
<td>87%</td>
<td>79%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Yadav et al. JCO 2020
Hybrid approach to genetic testing?

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity of detecting an existing mutation</th>
<th>% BC pts spared genetic testing</th>
<th>% of BC pts with mutation missed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA1/2</td>
<td>Hi Risk BC genes</td>
<td>Hi &amp; mod risk BC genes</td>
</tr>
<tr>
<td>ASBrS</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>NCCN + all dx by age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65 yo</td>
<td>98%</td>
<td>95%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCCN v1.2020</td>
<td>87%</td>
<td>79%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Yadav et al. JCO 2020
### Hybrid approach to genetic testing?

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity of detecting an existing mutation</th>
<th>% BC pts spared genetic testing</th>
<th>% of BC pts with mutation missed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>BRCA1/2</strong></td>
<td>Hi Risk BC genes</td>
<td>Hi &amp; mod risk BC genes</td>
</tr>
<tr>
<td>ASBrS</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>NCCN + all dx by age:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| ≤ 65 yo  | 98%         | 95%              | 92%                      | 21%                            | 0.4% **BRCA1/2**  
0.8% hi risk BC gene  
2.3% any BC gene |
| ≤ 60 yo  | 95%         | 91%              | 87%                      | 31%                            | 0.4% **BRCA1/2**  
1% hi risk BC gene  
2.1% any BC gene |
| NCCN v1.2020 | 87%         | 79%              | 70%                      | 52%                            | 0.7% **BRCA1/2**  
1.4% hi risk BC gene  
3.6% any BC gene |

Yadav et al. JCO 2020
## Hybrid approach to genetic testing?

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity of detecting an existing mutation</th>
<th>% BC pts spared genetic testing</th>
<th>% of BC pts with mutation missed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA1/2</td>
<td>Hi Risk BC genes</td>
<td>Hi &amp; mod risk BC genes</td>
</tr>
<tr>
<td>ASBrS</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>NCCN + all dx by age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65 yo</td>
<td>98%</td>
<td>95%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60 yo</td>
<td>95%</td>
<td>91%</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCCN v1.2020</td>
<td>87%</td>
<td>79%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Yadav et al. JCO 2020
Desai et al. Cancer 2020
Outline

- Existing guidelines for germline testing for HBOC.
- Should all breast cancer pts be offered germline genetic testing?
- When should tumor genomic profiling trigger germline testing?
- Should all Ashkenazi Jewish individuals be offered gBRCA testing?
- Pros and cons of offering population genetic testing to all women: BRCA? Multi-gene-panel?
Which pathogenic variants (PV) in tumor genomic profiling should prompt germline testing?

1: Does the pt meet criteria for germline genetic testing regardless of tumor profiling? If yes: germline testing
   - 8% germline PV not identified by tumor testing

Schrader et al. JAMA Oncol 2016; Lincoln et al. JAMA Network Open 2020
Which pathogenic variants (PV) in tumor genomic profiling should prompt germline testing?

1: Does the pt meet criteria for germline genetic testing regardless of tumor profiling? If yes: germline testing

2: Is the pathogenic variant (PV) in a cancer susceptibility gene that you would test for?

DeLeonardis et al. J Oncol Pract 2019
ACMG reportable secondary findings, and cancer risk genes with published management recommendations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>CDKN2A</td>
<td>PTEN</td>
</tr>
<tr>
<td>BRCA1</td>
<td>DICER1</td>
<td>RAD51C</td>
</tr>
<tr>
<td>BRCA2</td>
<td>FH</td>
<td>RAD51D</td>
</tr>
<tr>
<td>BRIP1</td>
<td>FLCN</td>
<td>RB1</td>
</tr>
<tr>
<td>CHEK2</td>
<td>HOXB13</td>
<td>RET</td>
</tr>
<tr>
<td>EGFR</td>
<td>MEN1</td>
<td>SDHA/SDHB/SDHC/S</td>
</tr>
<tr>
<td>TP53</td>
<td>MLH1</td>
<td>DHD</td>
</tr>
<tr>
<td>APC</td>
<td>MSH2, MSH6, PMS2, EPCAM</td>
<td>SMAD4</td>
</tr>
<tr>
<td>BAP1</td>
<td>NBN</td>
<td>SMARCA4</td>
</tr>
<tr>
<td>CDH1</td>
<td>NF1</td>
<td>STK11</td>
</tr>
<tr>
<td>CDK4</td>
<td>NF2</td>
<td>TSC1, TSC2</td>
</tr>
<tr>
<td></td>
<td>PALB2</td>
<td>VHL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WT1</td>
</tr>
</tbody>
</table>

DeLeonardis et al. J Oncol Pract 2019
**ESMO endorsed genes for tumor → germline analysis**

**Box 1. Recommendations for genes to be included for germline focussed analysis and triggering of germline sample laboratory confirmation**

<table>
<thead>
<tr>
<th>Any tumour type</th>
<th>Associated tumour type only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour arising any age</strong></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>RAD51C</td>
</tr>
<tr>
<td>BRCA2</td>
<td>RAD51D</td>
</tr>
<tr>
<td>BRIP1</td>
<td>RET</td>
</tr>
<tr>
<td>MLH1</td>
<td>SDHA</td>
</tr>
<tr>
<td>MSH2</td>
<td>SDHAF2</td>
</tr>
<tr>
<td>MSH6</td>
<td>SDHB</td>
</tr>
<tr>
<td>PALB2</td>
<td>SDHC</td>
</tr>
<tr>
<td>PMS2</td>
<td>SDHD</td>
</tr>
<tr>
<td>VHL</td>
<td>TSC2</td>
</tr>
<tr>
<td></td>
<td>MUTYH</td>
</tr>
<tr>
<td><strong>Tumour arising age &lt;30 only</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RB1</td>
</tr>
<tr>
<td></td>
<td>APC</td>
</tr>
</tbody>
</table>

*Renal tumours to be excluded.*

*MUTYH should be included for germline focussed tumour analysis but reporting and germline follow-up testing should only be performed on detection of two pathogenic variants.*

*Brain tumours to be excluded.*
Which genes/PV from tumor profiling should trigger germline testing

- **Always**
  - BRCA1/2, Lynch genes, PALB2, BRIP1, RAD51C/D
  - Founder mutations (e.g., BRCA1 c.185delAG; CHEK2 c.1100delC)

- **Needs review**
  - PV in gene commonly mutated in a cancer type
    - TP53 in TNBC; CDH1 in lobular breast cancer

- **When in doubt- refer** for germline testing
Which pathogenic variants (PV) in tumor genomic profiling should prompt germline testing?

1: Does the pt meet criteria for germline genetic testing regardless of tumor profiling? If yes: germline testing

2: Is the pathogenic variant (PV) in a cancer susceptibility gene that you would test for?

3: Confirm pathogenicity of the variant (ClinVar)
   - Only PV/LPV merit referral for germline testing

DeLeonardis et al. J Oncol Pract 2019
Outline

- Existing guidelines for germline testing for HBOC.
- Should all breast cancer pts be offered germline genetic testing?
- When should tumor genomic profiling trigger germline testing?
- Should all Ashkenazi Jewish individuals be offered gBRCA testing?
  - “Ashkenazi”: Eastern and Central European ancestry
- Pros and cons of offering population genetic testing to all women: BRCA? Multi-gene-panel?
Universal 3-site BRCA1/2 testing for all Ashkenazi Jewish (AJ) individuals?

- 1/40 unselected AJ individuals have a gBRCA mutation (10x more common)
- > 90-95% of BRCA mutations are in one of the 3 founder mutations
- Up to 56% of AJ BRCA mutation carriers are missed using current criteria
- Penetrance for breast & ovarian cancer in unselected AJ BRCA mutation carriers is similar to that in carriers who meet testing criteria
  - Study in AJ men (Israel); evaluating cancers in female relatives
- Cost effective: 3 site BRCA testing in AJ women > age 30

D’Andrea GIM 2016
Manchanda JNCI 2015
Gabai-Kapara PNAS 2014
Universal 3-site BRCA1/2 testing for AJ: existing concerns

- False negatives – for those who need more testing
- Availability of appropriate medical and surgical management for carriers identified
- Liability
- Feasibility: service delivery model to handle population testing

D’Andrea GIM 2016
Manchanda JNCI 2015
Gabai-Kapara PNAS 2014
Bfor study: 3 site *BRCA* testing to AJ indivs at no cost

How to Participate in the *BfOR* Study

- Register
- Give consent
- Get tested
- Get results
- Follow-up

Computer algorithm determines who needs more than 3-site *BRCA* testing

Morgan et al. JCO 2019
Universal 3-site BRCA1/2 testing for all Ashkenazi Jewish (AJ) individuals?

- Seems reasonable to offer testing (3 site BRCA):
  - If post-test counseling available from knowledgeable provider

- NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (V2.2021) say to “consider” testing
  - Will insurance cover?
Outline

- Existing guidelines for germline testing for HBOC
- Should all breast cancer pts have germline genetic testing?
- When should tumor genomic profiling trigger germline testing?
- Should all Ashkenazi Jewish individuals have BRCA testing?
- Population genetic testing for all women: BRCA1/2 ? Panel?
Universal *BRCA1/2* genetic testing (non-Ashkenazi)?

- Advocating *BRCA1/2* testing women ≥ age 30 (King 2014)
  - Don’t disclose VUS

- *BRCA1/2* universal testing NOT cost effective in general population (Long 2015)

- Population testing *BRCA1/2, PALB2, BRIP1, RAD51C/D* is cost effective for women ≥ age 30 vs ≥ 10% threshold (Manchanda 2018)

- Population *BRCA1/2* testing offered in Canada (Internet/saliva)- $165

King et al JAMA 2014; Long et al JAMA Oncol 2015; Manchanda et al JNCI 2018; Narod JCO 2018
## Population BRCA testing: AJ vs non-Ashkenazi

<table>
<thead>
<tr>
<th></th>
<th>AJ</th>
<th>General pop testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mutation prevalence</strong></td>
<td>1/40</td>
<td>~ 1/400</td>
</tr>
<tr>
<td><strong>% of cancer due to mutats</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>~10 % (11%)</td>
<td>2-3 (&lt; 5) %</td>
</tr>
<tr>
<td>Ovarian</td>
<td>40%</td>
<td>10-15%</td>
</tr>
<tr>
<td><strong>Test</strong></td>
<td>3 site AJ founder test</td>
<td>Full sequencing</td>
</tr>
<tr>
<td>(less expensive)</td>
<td></td>
<td>(more costly)</td>
</tr>
<tr>
<td><strong>Penetrance</strong></td>
<td>Same for carriers</td>
<td>Unknown if</td>
</tr>
<tr>
<td>identified thru clinical criteria or pop</td>
<td>testing</td>
<td>penetrance differs</td>
</tr>
<tr>
<td><strong>VUS</strong></td>
<td>No VUS</td>
<td>4% VUS; more in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>less tested pops</td>
</tr>
</tbody>
</table>
Population testing in general population?
Panel testing

<table>
<thead>
<tr>
<th></th>
<th>AJ</th>
<th>General Pop testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation prevalence</td>
<td>1/40</td>
<td>1/400</td>
</tr>
<tr>
<td>% of cancer accounted for by mutations</td>
<td>11%</td>
<td>40%</td>
</tr>
<tr>
<td>Penetrance</td>
<td>Same for carriers identified thru clinical criteria or pop testing</td>
<td>Unknown if penetrance differs</td>
</tr>
<tr>
<td>Tests</td>
<td>3 site AJ founder test</td>
<td>Full seq; thousands of mutations</td>
</tr>
</tbody>
</table>

Panels would yield far more VUS; more genes- more VUS
Potential harms of population germline testing (non-Ashkenazi)

- Those who test positive:
  - Unnecessary screening, prevention surgeries and anxiety especially for:
    - Lower penetrant “high risk” mutations (no fam hx)
    - Moderate risk mutations for which clinical utility is not established (ATM)
    - Mutations in genes with unclear clinical validity (RAD50)
- Those who test negative:
  - False reassurance
- VUS
VUS and lower penetrant mutations increase the potential for harms

- The burden of VUS:
  - Misinterpretation and overtreatment
  - Convey reclassifications
  - Anxiety
  - Cost of counseling

- The higher the % VUS and the lower the penetrance of mutations identified, the more potential for harm and the less cost-effective.
Conclusion

- NCCN criteria are sensitive for BRCA mutations - not 100%
  - Most mutations missed are in moderate risk breast cancer genes or non-breast cancer genes; need technology EMR; consider hybrid approach
- PV in cancer susceptibility genes on tumor profiling should be recognized and trigger referral for germline testing
- Offering population BRCA testing for Ashkenazi Jewish individuals - seems justified if logistics can be worked out
- Population testing for non-Ashkenazi, not as clear/more complicated
- As we move towards broader genetic testing - need new delivery service models (e.g oncology-led testing for cancer patients).
NCCN Member Institutions

- **Who We Are**
  An alliance of leading cancer centers devoted to patient care, research, and education

- **Our Mission**
  To improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives

- **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally

NCCN.org – For Clinicians | NCCN.org/patients – For Patients

© National Comprehensive Cancer Network, Inc. 2021, All Rights Reserved. No part of this publication may be reproduced or transmitted in any other form or by any means, electronic or mechanical, without first obtaining written permission from NCCN®.