Please note, these are the actual video-recorded proceedings from the live CME event and may include the use of trade names and other raw, unedited content.

Genetic Testing in the Age of PARP: Who and How to Test?

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Disclosures

Honoraria	AstraZeneca Pharmaceuticals LP, Clovis Oncology

Case presentation: Dr Robson

47-year-old woman with BRCA1 c.68_69delAG germline mutation

- Stage II TNBC → bilateral MRM and adjuvant AC → paclitaxel
- Metastatic disease: weekly paclitaxel, capecitabine and vinorelbine followed by wedge resection of RUL nodule
- November 2007: Enrolled on an ICEBERG trial and began olaparib capsules 400 mg po BID – ongoing CR

Case presentation: Dr Domchek

69-year-old woman with BRCA1 germline mutation

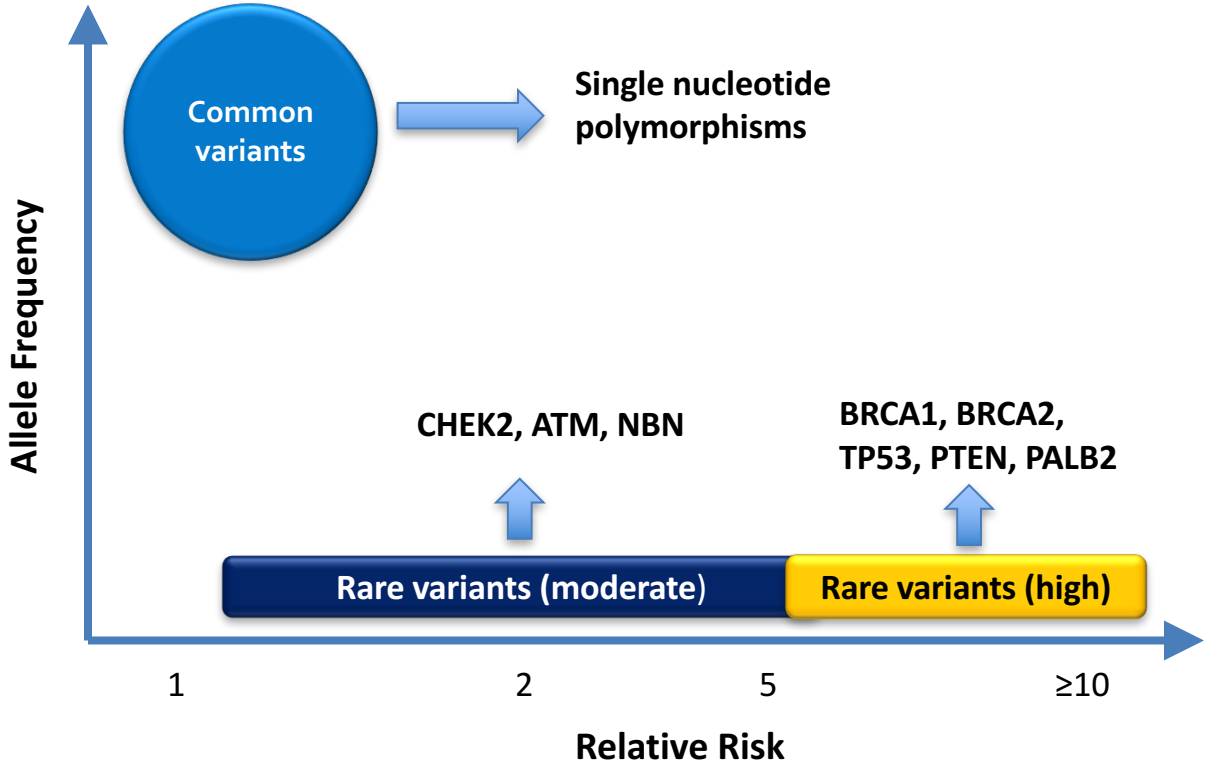
- 1982: Stage I T1N0M0 ER/PR-negative breast cancer: MRM
- 2007: Stage I T1N0M0 TNBC: MRM → adjuvant CMF
- 2008: Metastatic TNBC to the lung treated with docetaxel/bevacizumab on study → PD
- June 2008: Olaparib clinical trial – ongoing CR

Who should be considered for germline testing for BRCA1/2 ?

- Continuously evolving with new assessment of risk/benefit
  - Benefits: Risk assessment, options for prevention, change in systemic therapy including targeted therapeutics
  - Risks: VUS, costs, complex information with psychological burden
  - Different considerations in different stages of care

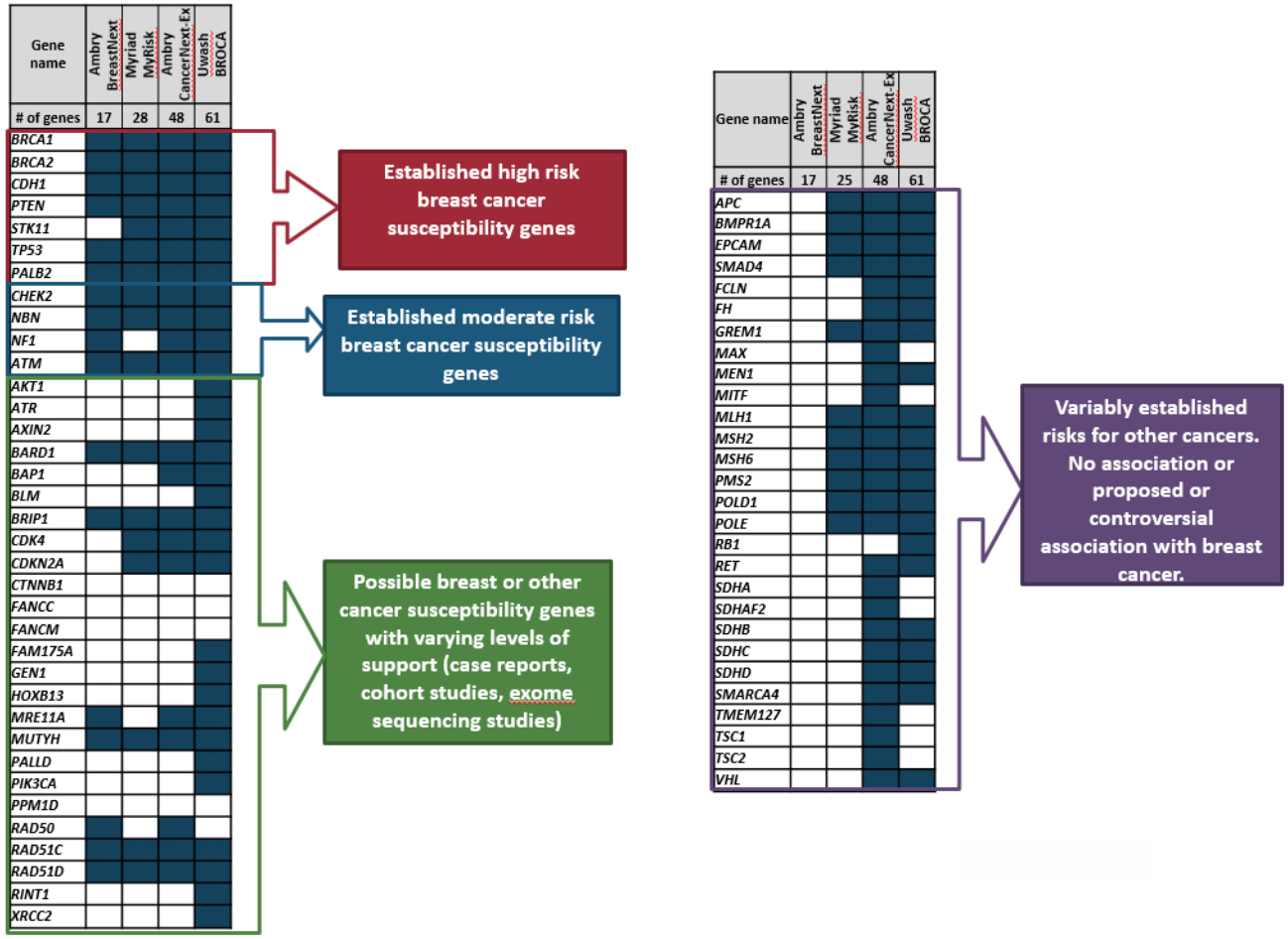
- Debate about where the threshold should lie
  - Fact: certain patients have much higher chance of having a *BRCA1/2* mutation than others
  - Let's be sure not to miss them as we debate the rest

Cancer Risk Variants



Lots of options….

Multiplex panel testing for analysis of germline cancer susceptibility



Prevalence of *BRCA1/2* mutation in unselected patients with breast cancer?

	Total	*gBRCA1*	*gBRCA2*	*sBRCA1*	*sBRCA2*
TCGA (n)	858	17	18	9	14
		1.98%	2.1%	1.0%	1.6%

Courtesy of Kara Maxwell

Multiple other studies of unselected patients with breast cancer

- Unselected germline mutations prevalence 2-3% (Syrhakoski et al JNCI 2000, Malone et al Cancer Research 2006)
- Unselected <50, 5.4% (van der Broek et al 2015)
- TNBC: 11.2% (Couch et al JCO 2015)
- Ashkenazi Jewish: 11.7% (Warner et al JNCI 1999)

NCCN guidelines: Early-stage breast cancer

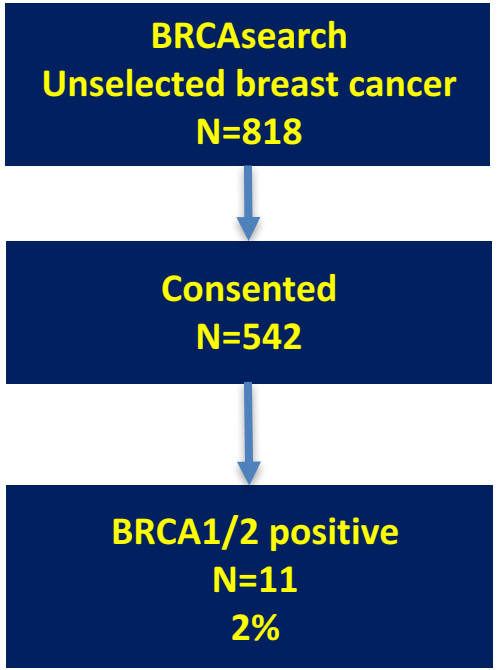
- Breast cancer <45
- Breast cancer <50
  - Bilateral breast cancer
  - ≥1 relative with breast cancer, pancreatic cancer or high-grade or metastatic prostate cancer
  - Unknown or limited family history
- Breast cancer <60 with TNBC
- Breast cancer any age
  - >1 relative with BC <50 or ovarian cancer or male breast cancer
  - >2 relatives with breast, pancreatic or high-grade/met prostate
- Ovarian cancer
- Male breast cancer
- Ashkenazi Jewish with breast cancer
- **BRCA1/2 mutation found on somatic testing**

How do NCCN guidelines perform?

- Review of 1,123 patients at MD Anderson
- Individuals with breast cancer who underwent genetic testing
- If only criteria was breast cancer <45: 1.6%
- If an individual only met 1 criteria: 3.2%
- If >1 criteria: 12%

Cropper et al, JNCCN 2017

How do NCCN guidelines perform?



- 9 of 11 BRCA1/2 mutation carriers met NCCN criteria
- 0.3% of patients with unselected breast cancer
- NCCN criteria detected 82% of mutation carriers

Nilsson et al, BCRT 2017

What about patients with metastatic breast cancer?

- Will there be more mutations?
- Metastatic prostate cancers have more *BRCA1/2* mutations than early stage
- Pritchard et al, NEJM 2016

- Will there be fewer mutations?
- Data from the POSH study suggests that patients with *BRCA1/2* early-stage breast cancer do better
- Eccles, SABCS 2016

NCCN Breast Cancer Guidelines

- Olaparib
- “Option for HER2-negative BRCA1/2 positive tumors”
- “Patients with HER2-negative disease eligible for single-agent therapy are eligible for germline BRCA1/2 testing”

Version 3.2017
November 10, 2017

We want all possible options for our patients

- Approach #1:
  - **Germline testing of patients with early-stage disease:**
  - Most women present with early-stage breast cancer first
  - Currently NCCN guidelines for germline testing will identify most (but not all) of those with BRCA1.2 mutations
  - Make sure to identify those individuals then!
  - **Somatic sequencing of metastatic disease:**
    - As part of clinical care – biopsy of first metastatic site
    - Repeat ER, PR, HER2
    - MSI for agnostic pembrolizumab indication
    - Somatic sequencing: AKT, HER2 mutations, PI3Kinase, BRCA1/2, etc
    - Reflex to germline on those with somatic mutations identified

We want all possible options for our patients

- Approach #2:
- **Germline testing of all patients with metastatic breast cancer**
  - Particularly if somatic sequencing is not done
- Cost? Efficiency? Yield?
- To be continued….

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