

Objectives

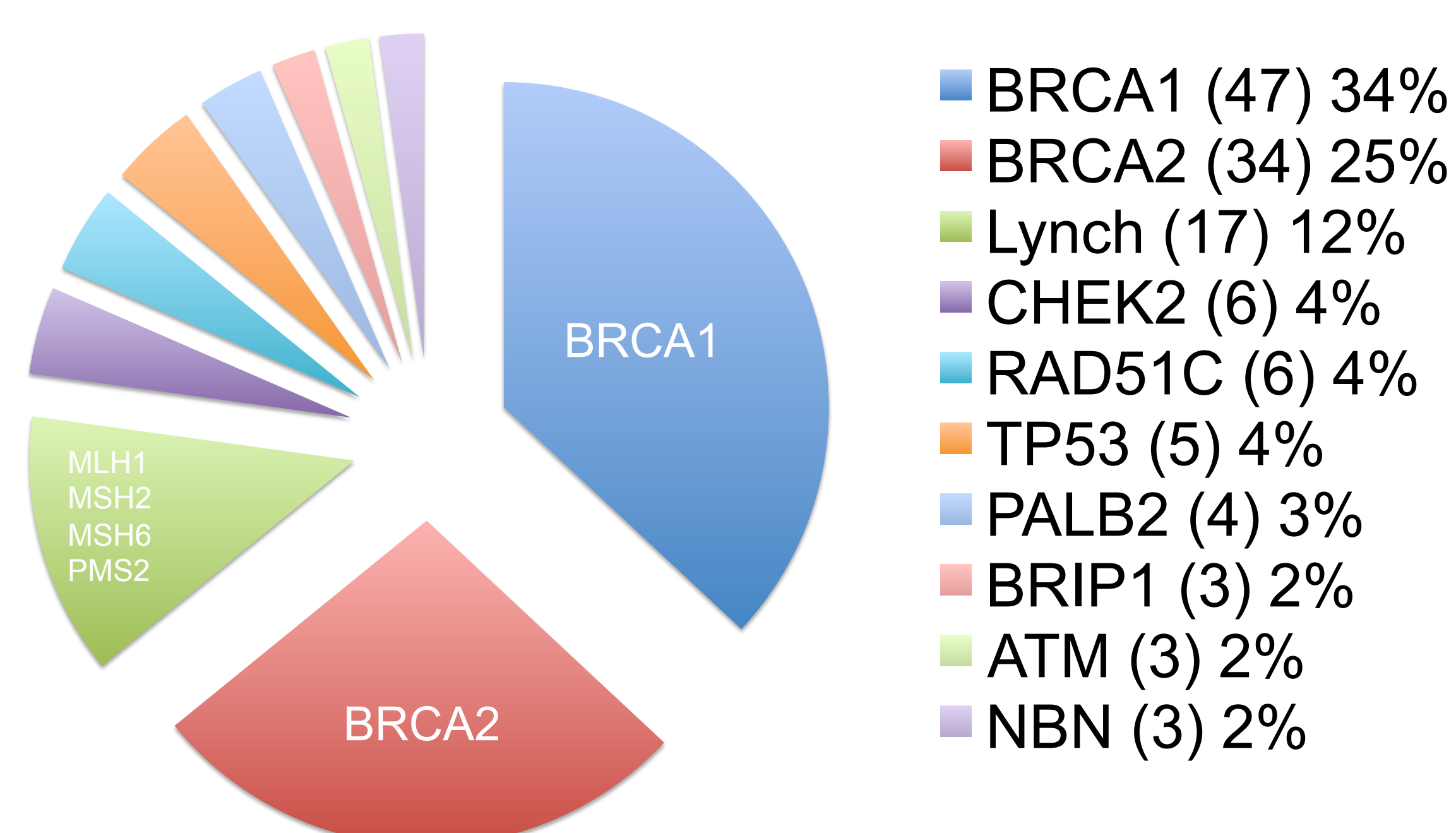
A new paradigm in genetic testing for ovarian cancer is emerging. With next-generation sequencing (NGS), clinicians can choose to test only high-penetrance genes, or they can test a more comprehensive panel of 30+ cancer genes for roughly the same cost. The clinical utility of high-penetrance genes such as BRCA1, BRCA2, and the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2, and EPCAM) is established. New NCCN Guidelines provide additional guidance for non-canonical genes such as ATM, BRIP1, CHEK2, PALB2, RAD51C, and RAD51D. We report data on the prevalence of pathogenic variants in ovarian cancer patients and highlight management changes for non-canonical genes.

Methods

One hundred twenty eight (128) of 1,034 sequential ovarian cancer patients who had been referred for germline genetic testing were selected based on the identification of a Pathogenic or Likely Pathogenic (P/LP) variant in a cancer susceptibility gene. De-identified personal and family histories, which had been provided by ordering clinicians, were examined.

Results

Proportion of genes contributing to the 128 mutations identified



Results (continued)

Twelve percent (12%) of the 1,034 ovarian cancer patients tested positive (128/1,034). As expected, mutations in BRCA1, BRCA2, and the Lynch genes were the most common findings. ATM, BRIP1, CHEK2, PALB2, and RAD51C accounted for an additional 17% (22/128) of positive cases.

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Genetic/Familial High-Risk Assessment: Breast and Ovarian

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BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS^a

	Recommend Breast MRI ^d (>20% risk of breast cancer ^e)	Discuss Option of RRM	Recommend/Consider RRSO
Intervention warranted based on gene and/or risk level	<ul style="list-style-type: none"> ATM BRCA1 BRCA2 CDH1 CHEK2 PALB2 PTEN STK11 TP53 	<ul style="list-style-type: none"> BRCA1 BRCA2 CDH1 PTEN TP53 PALB2 	<ul style="list-style-type: none"> BRCA1 BRCA2 Lynch syndrome^f BRIP1 RAD51C RAD51D
Insufficient evidence for intervention ^{b,c}	<ul style="list-style-type: none"> BRIP1 	<ul style="list-style-type: none"> ATM CHEK2 STK11 	<ul style="list-style-type: none"> PALB2

RRM: risk-reducing mastectomy
RRSO: risk-reducing salpingo-oophorectomy

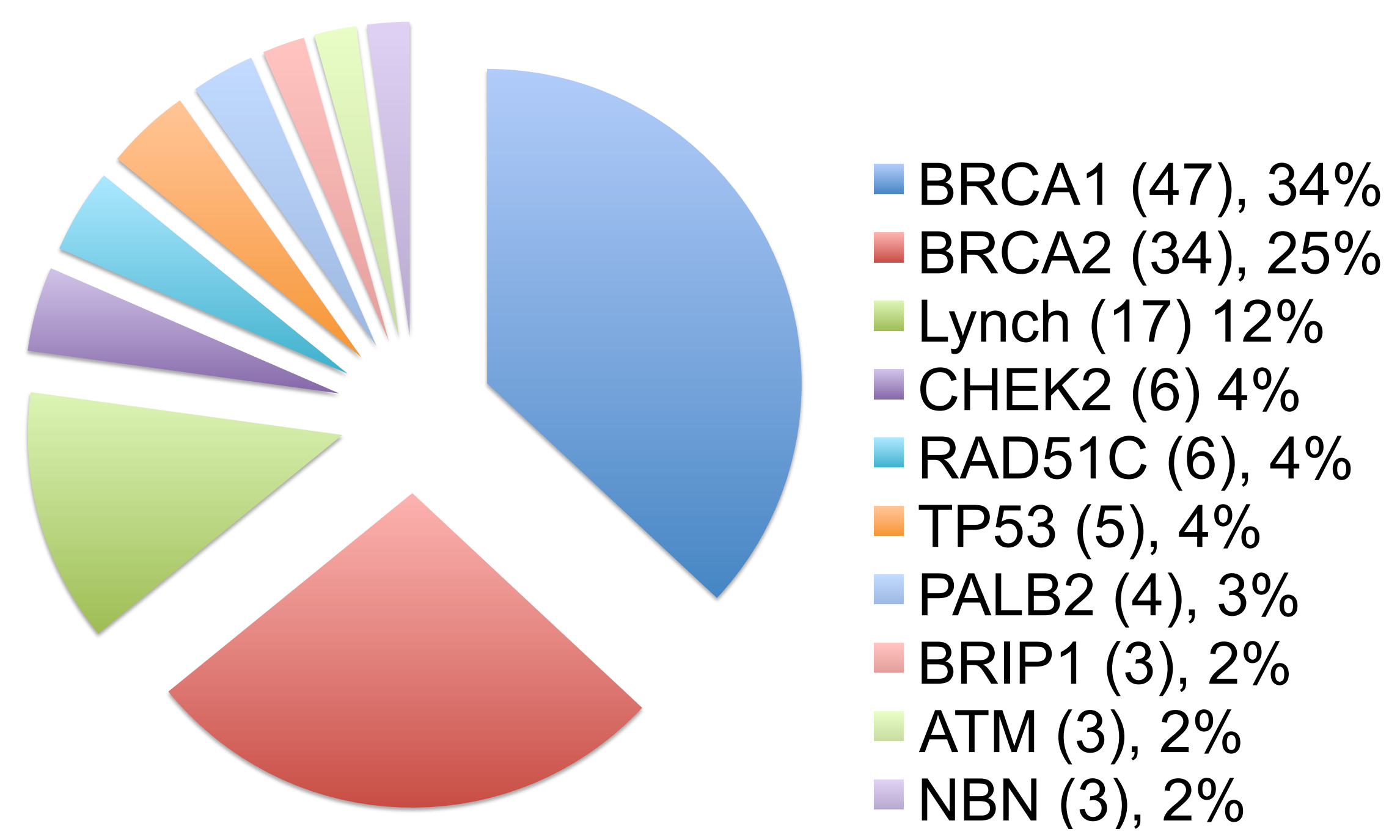
Figure 1. Screen shot of recently revised NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2016

Conclusions

- These data highlight the benefit of expanded gene panels for the evaluation of hereditary cancer. Also highlighted is the impact that these results can have on cancer surveillance protocols beyond HBOC and Lynch syndrome genes.
- Positive findings in ATM, CHEK2, and PALB2 impact breast surveillance protocols. PALB2 patients with a strong family history may warrant special consideration, including risk-reducing mastectomy.
- Ovarian cancer patients with mutations in BRIP1, PALB2, RAD51C, and RAD51D may consider risk-reducing salpingo-oophorectomy.
- More research is needed to understand the relationship between newer genes and other cancers.

Limitations of study: ascertainment bias, variation of panel size leading to underrepresentation of some genes and lower detection rate, and unconfirmed medical histories

Proportion of genes contributing to the 128 mutations identified



BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS^a

	Recommend Breast MRI^d (>20% risk of breast cancer ^e)	Discuss Option of RRM	Recommend/Consider RRSO
Intervention warranted based on gene and/or risk level	<ul style="list-style-type: none"> → <i>ATM</i> <i>BRCA1</i> <i>BRCA2</i> <i>CDH1</i> → <i>CHEK2</i> → <i>PALB2</i> <i>PTEN</i> <i>STK11</i> <i>TP53</i> 	<ul style="list-style-type: none"> <i>BRCA1</i> <i>BRCA2</i> <i>CDH1</i> <i>PTEN</i> <i>TP53</i> → <i>PALB2</i> 	<ul style="list-style-type: none"> <i>BRCA1</i> <i>BRCA2</i> Lynch syndrome^f → <i>BRIP1</i> → <i>RAD51C</i> → <i>RAD51D</i>
Insufficient evidence for intervention^{b,c}	<ul style="list-style-type: none"> → <i>BRIP1</i> 	<ul style="list-style-type: none"> → <i>ATM</i> → <i>CHEK2</i> <i>STK11</i> 	<ul style="list-style-type: none"> → <i>PALB2</i>

RRM: risk-reducing mastectomy
RRSO: risk-reducing salpingo-oophorectomy