Clinical presentation and management considerations for 77 breast cancer patients with germline PALB2 mutations

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Background

PALB2 is considered to be a moderate- to- high-penetrance breast cancer predisposition gene, and recently revised National Comprehensive Cancer Network (NCCN) 1.2016 Guidelines recommend that PALB2 mutation carriers undergo an annual breast MRI and consider surgical prophylaxis. Growing implementation of multigene hereditary breast cancer panels is expected to discover more patients with moderate-to-high penetrance gene findings. Our study describes the clinical presentation of 77 PALB2 mutation carriers and reviews risk-management considerations for the purpose of helping clinicians prepare themselves and their patients to deal with actionable results.

Methods

Seventy-seven (77) sequential patients who had been referred for genetic testing were selected based on the identification of a Pathogenic or Likely Pathogenic (P/LP) variant in PALB2 and on a personal history of cancer. De-identified personal and family histories that had been provided by ordering clinicians were examined.

Results

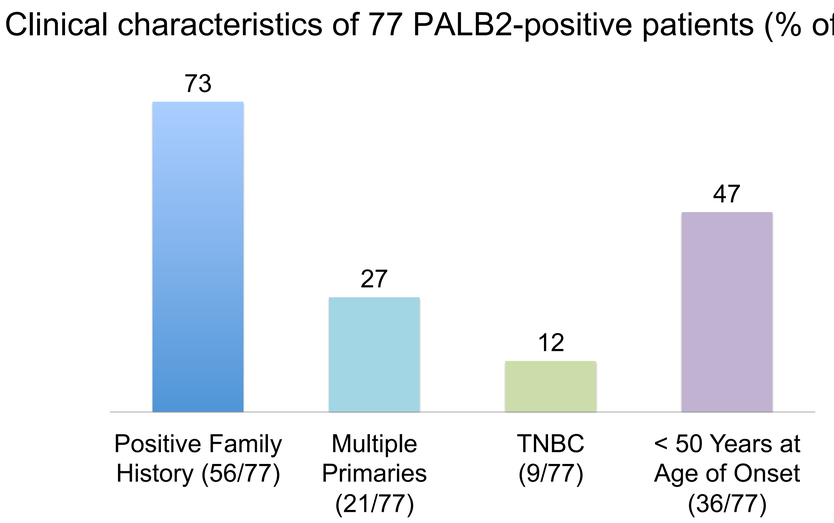
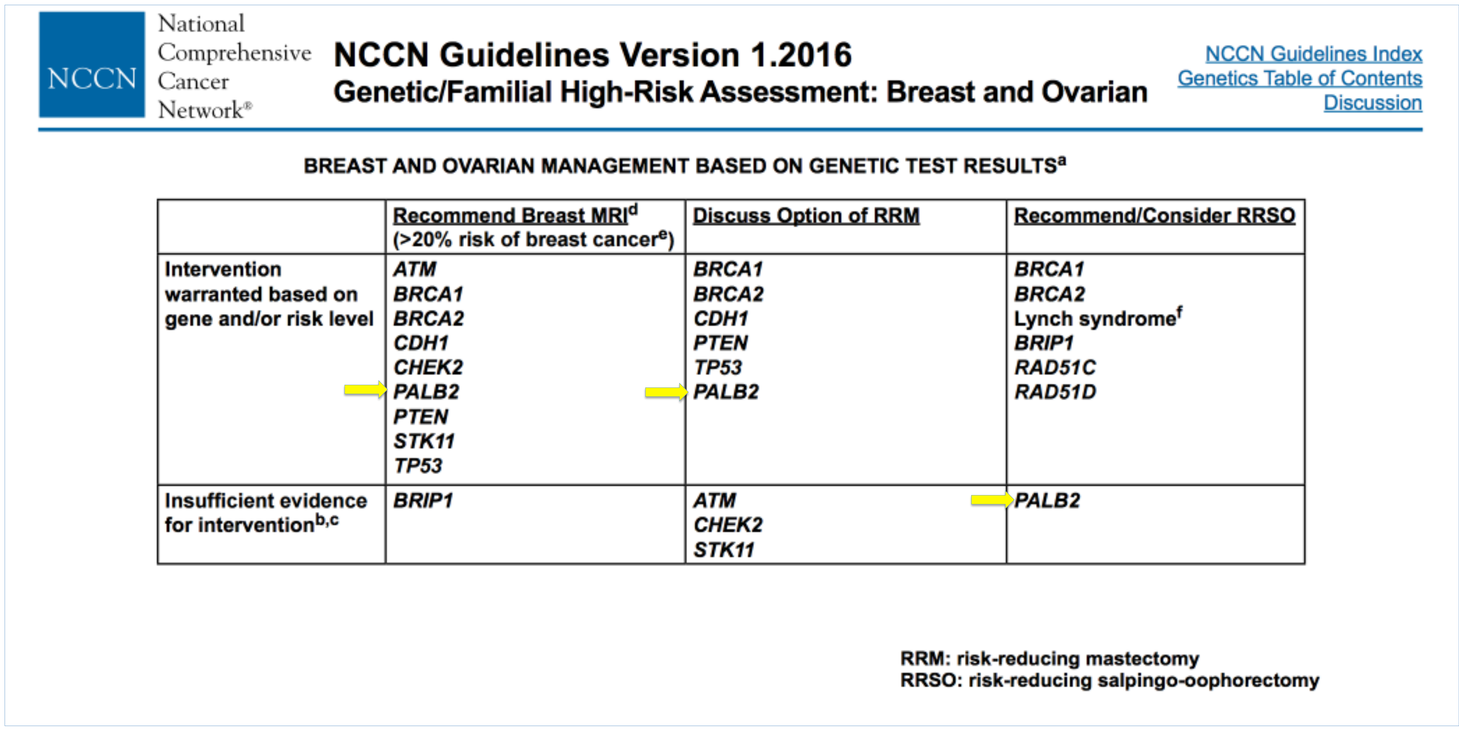


Figure 1. Frequency of clinical characteristics reported by clinician as the indication for testing. "Positive family history" includes patients with 2 or more first-degree relatives with breast cancer or any type of cancer <55 years of age. "Multiple primaries" includes patients with bilateral breast cancer or breast and any other type of cancer.



National Comprehensive Cancer Network®

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

NCCN Guidelines Index
Genetics Table of Contents
Discussion

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	*ATM* *BRCA1* *BRCA2* *CDH1* *CHEK2* *PALB2* *PTEN* *STK11* *TP53*	*BRCA1* *BRCA2* *CDH1* *PTEN* *TP53* *PALB2*	*BRCA1* *BRCA2* Lynch syndrome[f] *BRIP1* *RAD51C* *RAD51D*
Insufficient evidence for intervention[b,c]	*BRIP1*	*ATM* *CHEK2* *STK11*	*PALB2*

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

Figure 2. Screen shot of recently revised NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2016

Conclusions

- Based on recent revisions to NCCN Guidelines, management of PALB2-positive patients includes breast MRI and consideration of risk-reducing mastectomy.
- This patient series highlights clinical aspects of PALB2-related breast cancer suggestive of a high-penetrance gene, including presentation of early-onset and multiple primary cancers.
- PALB2 is mutated in the germline of roughly 1% of appropriately tested patients. It confers lifetime breast cancer risks from 30% to 60% based on family history (Antoniou, AC, et al. NEJM. 2014; 371(6):497-506), which, at the high end, is comparable to risk from BRCA2.
- More research is needed to understand the relationship between PALB2 and other cancers.

Limitations of study: ascertainment bias, limited information on tumor pathology/hormone receptor status, and an unconfirmed family history