PERFORMANCE OF NCCN GUIDELINES IN IDENTIFYING HEREDITARY BREAST AND OVARIAN CANCER SYNDROME AND LYNCH SYNDROME: RESULTS FROM A LARGE COHORT STUDY

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Background

- Genetic testing for hereditary breast and ovarian cancer syndrome (HBOC) and Lynch syndrome (LS) in lower risk populations has been proposed by some experts, but has not yet been broadly tested or implemented.
- Multi-gene cancer panels, ordered for a variety of indications, often include testing for HBOC and LS.
- Due to other cancer genetic indications, many patients who may be at low risk for HBOC are now obtaining genetic testing for *BRCA1* and *BRCA2*.
- Similarly, many patients who may be at low risk for LS obtain genetic testing for the mismatch repair genes.
- Analysis of panel testing results allows for insight into patients who test positive for HBOC and LS but did not meet criteria for testing for these syndromes.

Methods

- We conducted a multi-center, prospective cohort study of 2000 patients undergoing genetic counseling and hereditary cancer panel testing between August 2014 and November 2016.
- Patients were enrolled if they met standard testing criteria or had a ≥2.5% probability of a mutation when using a standard mutation probability model (BRCAPRO, MMRPRO, PENN2, BOADICEA, PREMM, or Tyrer-Cuzick).
- Genes included on the panel: *APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11*, and *TP53*. In July 2016, *GREM1*, *POLD1*, *POLE* were added to the panel.
- Prior to testing, a cancer genetics specialist (GC, NP, MD) determined which syndromes were in the differential diagnosis.
- Providers specified which genes would have been tested outside a panel test using clinical judgment.
- For patients who tested positive for HBOC or LS, a pedigree analysis was performed to determine if the patient met 2017 NCCN testing criteria for HBOC or LS.

Results

- The median age was 51 years, 81% were female, 73% had a cancer diagnosis, 39% were Hispanic (Table 1).
- 242 (12.1%) patients tested positive for ≥1 mutation.

Table 1. Patient Demographics and Test Results

Category	Total	Mutation Positive
All Patients	2,000	242 (12.1%)
Female, N (%)	1,613 (80.7%)	189 (78.1%)
Age, Median (Range)	51 (16-92)	53 (22-89)
Personal History of Cancer, N (%)	1,451 (72.6%)	189 (78.1%)
Race/Ethnicity, N (%)		
Non-Hispanic White	807 (40.4%)	101 (41.7%)
Hispanic	781 (39.1%)	97 (40.1%)
Asian	234 (11.7%)	27 (11.2%)
Non-Hispanic Black	75 (3.8%)	10 (4.1%)
Other/Multiple	103 (5.2%)	7 (2.9%)

Results

Analysis of HBOC Positive Cases

- 76 patients were positive for a mutation in *BRCA1* and/or *BRCA2*.
  - 40 *BRCA1*, 35 *BRCA2*, 1 both.
- 91% (69/76) met 2017 NCCN guidelines for HBOC testing.
  - The 7 cases missed by the NCCN guidelines included 3 patients with breast cancer diagnosed at age 46 or 47 with no additional testing indications and 4 patients tested for a primary indication of LS or *CDH1* (Examples in Figure 1).
- HBOC was in the pre-test differential diagnosis in 93% (71/76) of cases and the counselor indicated that they would have tested for *BRCA1* and *BRCA2* even in a gene-by-gene approach.
  - Counselors consistently indicated they would test for single cases of breast cancer diagnosed between 45 and 50.
  - Counselors missed the cases with LS and *CDH1* indications.

Analysis of Lynch Syndrome Positive Cases

- 38 patients were positive for a LS mutation.
  - 8 *MLH1*, 10 *MSH2*, 8 *MSH6*, 10 *PMS2*, 1 *EPCAM, 1* both *MLH1* and *PMS2*.
- 8% (3/38) met Amsterdam I criteria, 11% (4/38) met Amsterdam II criteria, 47% (18/38) met Revised Bethesda Guidelines, and 89% (34/38) met the NCCN guidelines.
  - The four cases missed by NCCN included two PMS2+ cases, (Figure 2) and two cases of patients with sebaceous adenomas, including one MSH6+ and MSH2+ case.
- Genetics providers considered LS in the pre-test differential diagnosis in 95% (36/38) of cases and would have ordered LS genetic testing outside of a panel in 89% (34/38) of cases.
  - *PMS2* mutations were detected in the four cases that would have been missed, all of which had HBOC as the primary indication for testing.

Figure 1. Examples of HBOC Positive Patients Missed by NCCN guidelines or Pre-Test Differential Diagnosis

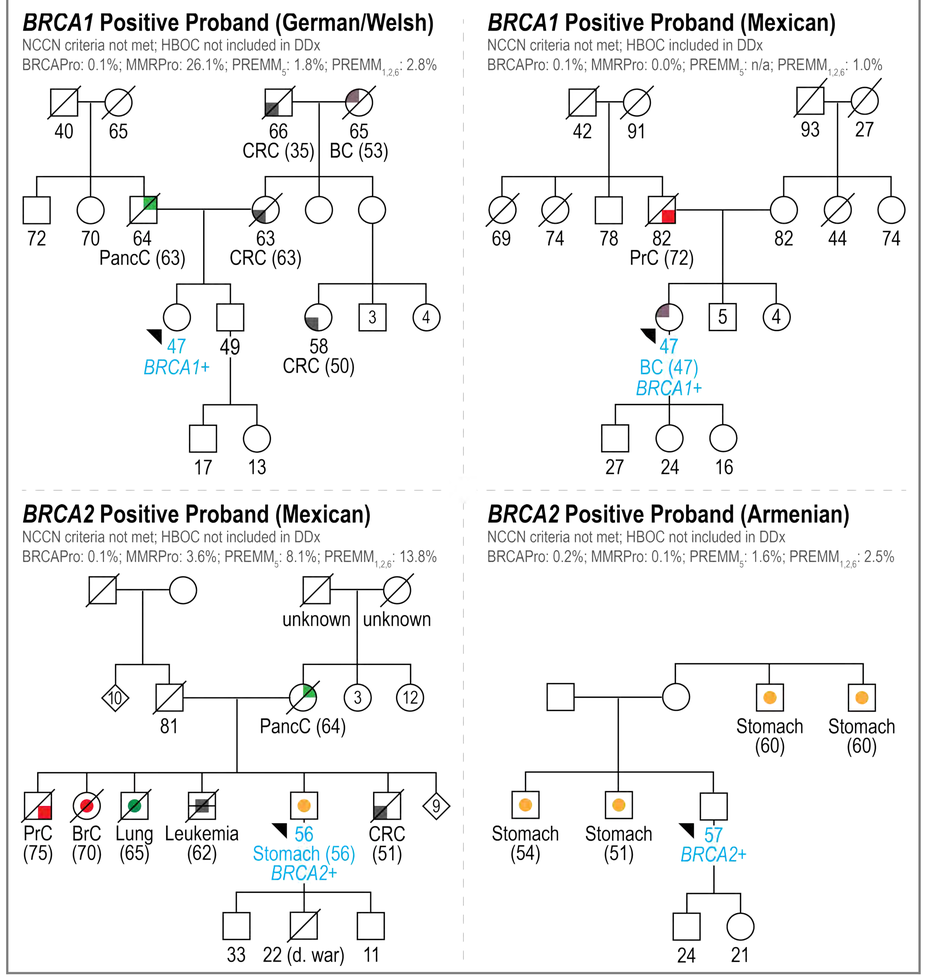
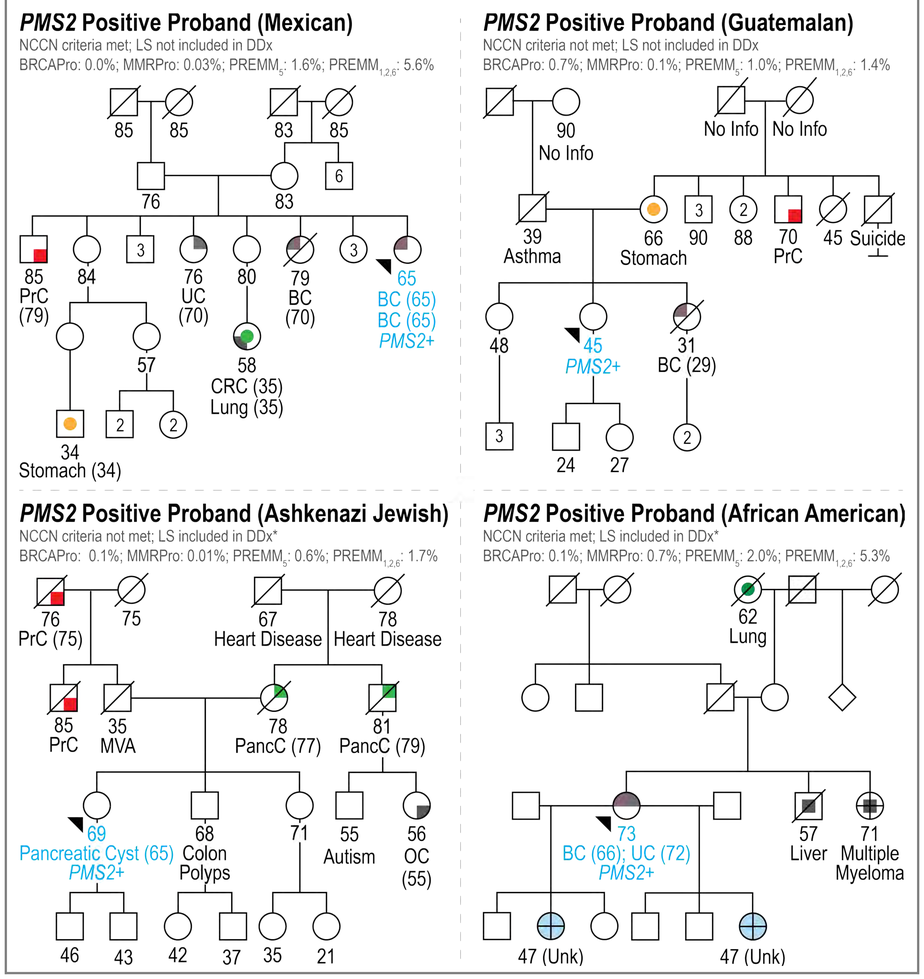


Figure 2. Examples of LS Positive Patients Missed by NCCN guidelines or Pre-Test Differential Diagnosis



*LS would not have been tested outside of a panel

Abbreviations: BC, breast cancer; BrC, brain cancer; CRC, colon/rectal cancer; OC, ovarian cancer; PancC, pancreatic cancer; PrC, prostate cancer; UC, uterine cancer; Unk, unknown

Conclusions

- In summary, the HBOC NCCN guidelines missed 9% of cases, including some single cases of breast cancer diagnosed under age 50.
- Some *BRCA2* families presented with history of gastric cancer.
- Amsterdam, Amsterdam II, and Bethesda guidelines performed poorly, Lynch Syndrome NCCN guidelines would have missed 11% of cases.
- The Lynch cases that would have been missed on counselors pre-test differential diagnosis were *PMS2*+.
- The phenotype of PMS2+ individuals warrants further study.

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