

The Impact of High and Moderate Penetrance Breast Cancer Gene Alterations on Familial Cascade Testing in Multi-Gene Panel Positive Probands

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BACKGROUND

- Single site testing has been the standard of care for familial cascade testing when a proband tests positive for a pathogenic/likely pathogenic (P/LP) variant in a high penetrance breast cancer gene.
- We examined the types of tests ordered for family members of probands that tested positive on a breast cancer multigene panel test (MGPT), and explored the differences in the type of familial testing ordered by healthcare providers.
- Analysis also included observing the differences in familial tests ordered between probands that were found to carry an alteration in a high penetrance gene verses a moderate penetrance gene.

Figure 1: Proband's Alteration Penetrance Type

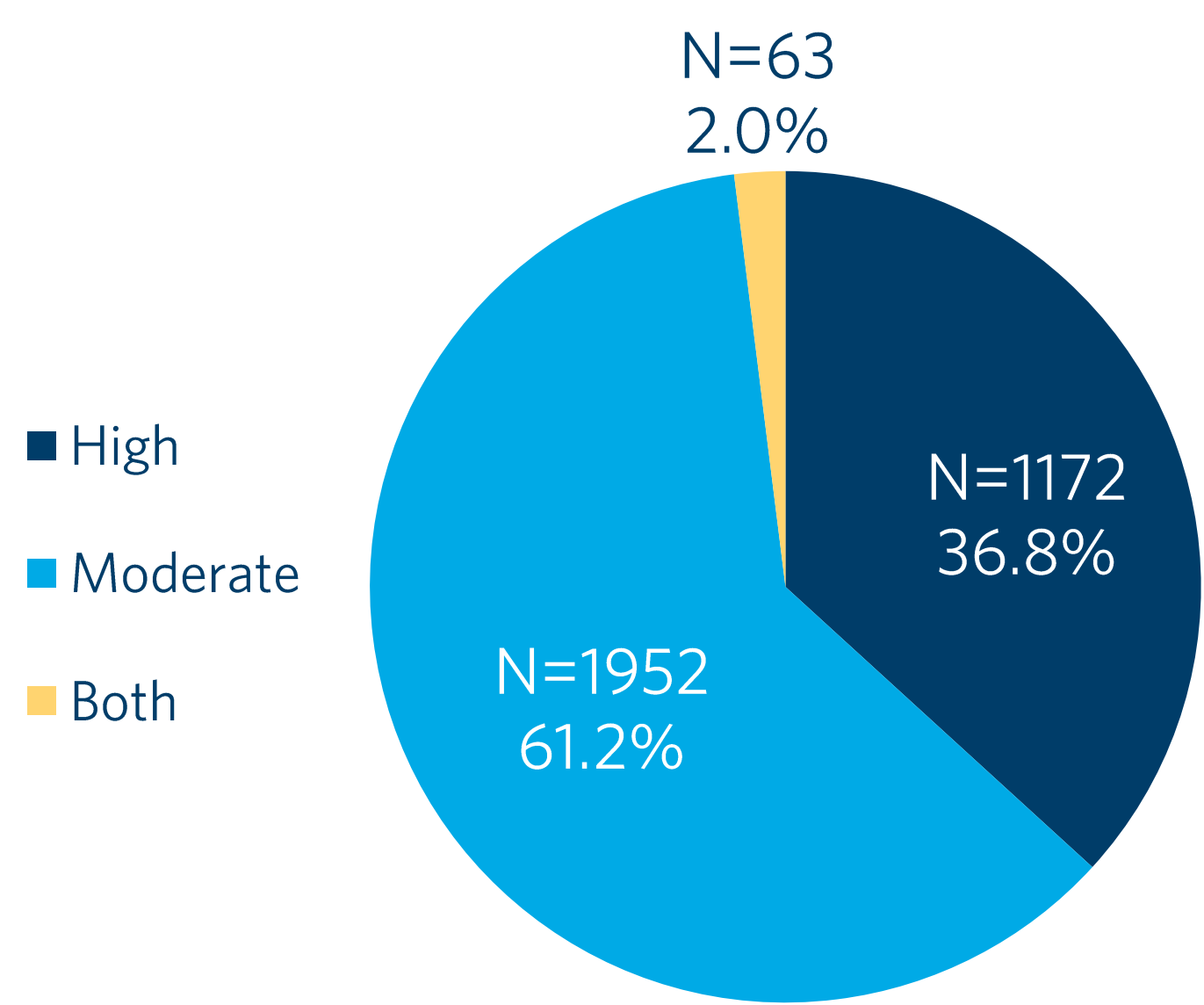
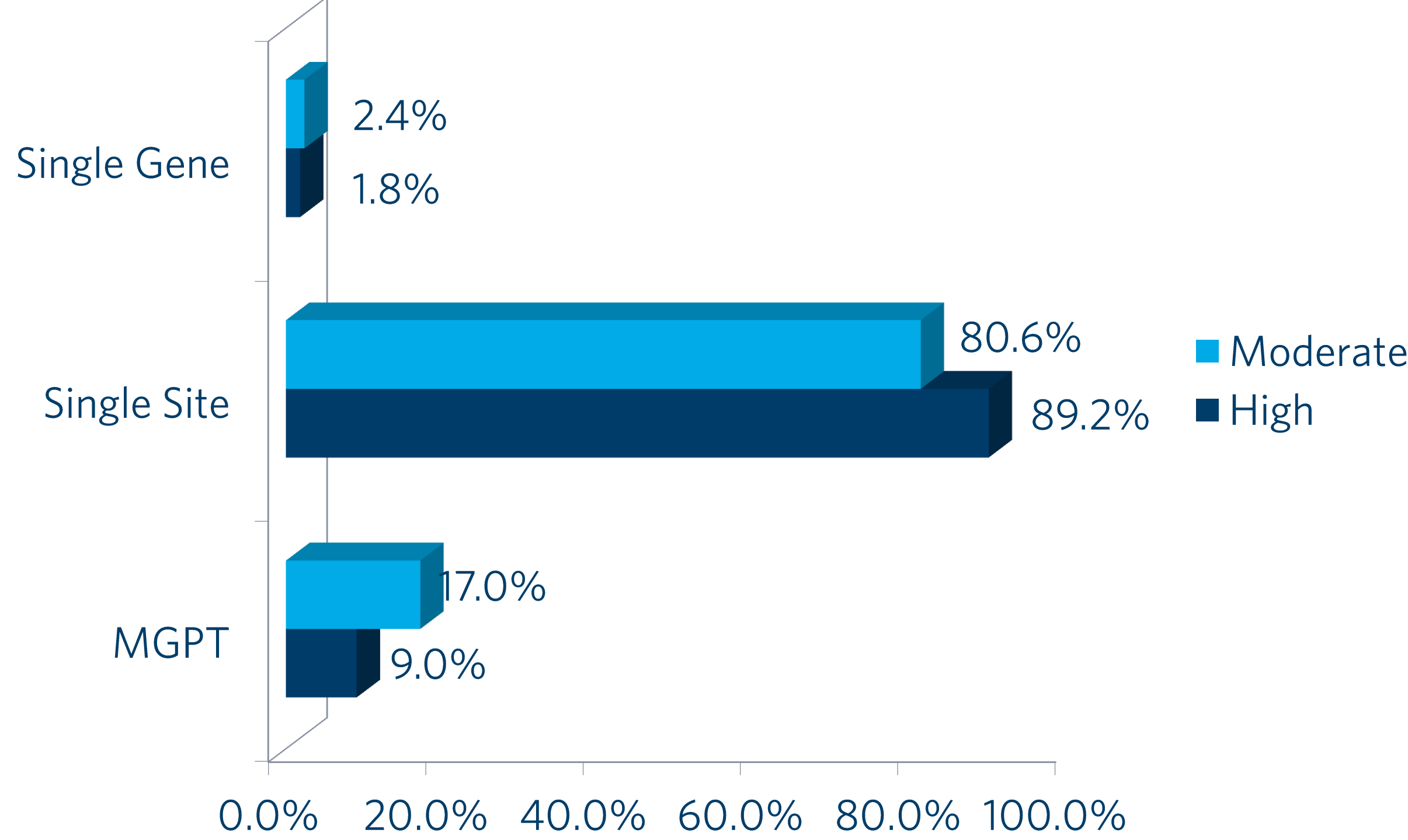


Figure 2: Familial Testing Ordered Based on Proband's Penetrance Type



METHODS

- Data from probands who tested positive for a P/LP variant on a 17-gene hereditary breast cancer MGPT between August 2012 and December of 2016 were retrospectively reviewed.
- The ordering trends and results of all subsequent family members tested at a commercial laboratory were assessed.
- The genes we considered to be high penetrance were *BRCA1*, *BRCA2*, *CDH1*, *NF1*, *PTEN*, and *TP53*.
- The genes we considered to be moderate penetrance were *ATM*, *BARD1*, *BRIP1*, *CHEK2*, *MRE11A*, *MUTYH*, *NBN*, *PALB2*, *RAD50*, *RAD51C*, and *RAD51D*.

Figure 3: Total Family Members Tested Per Proband

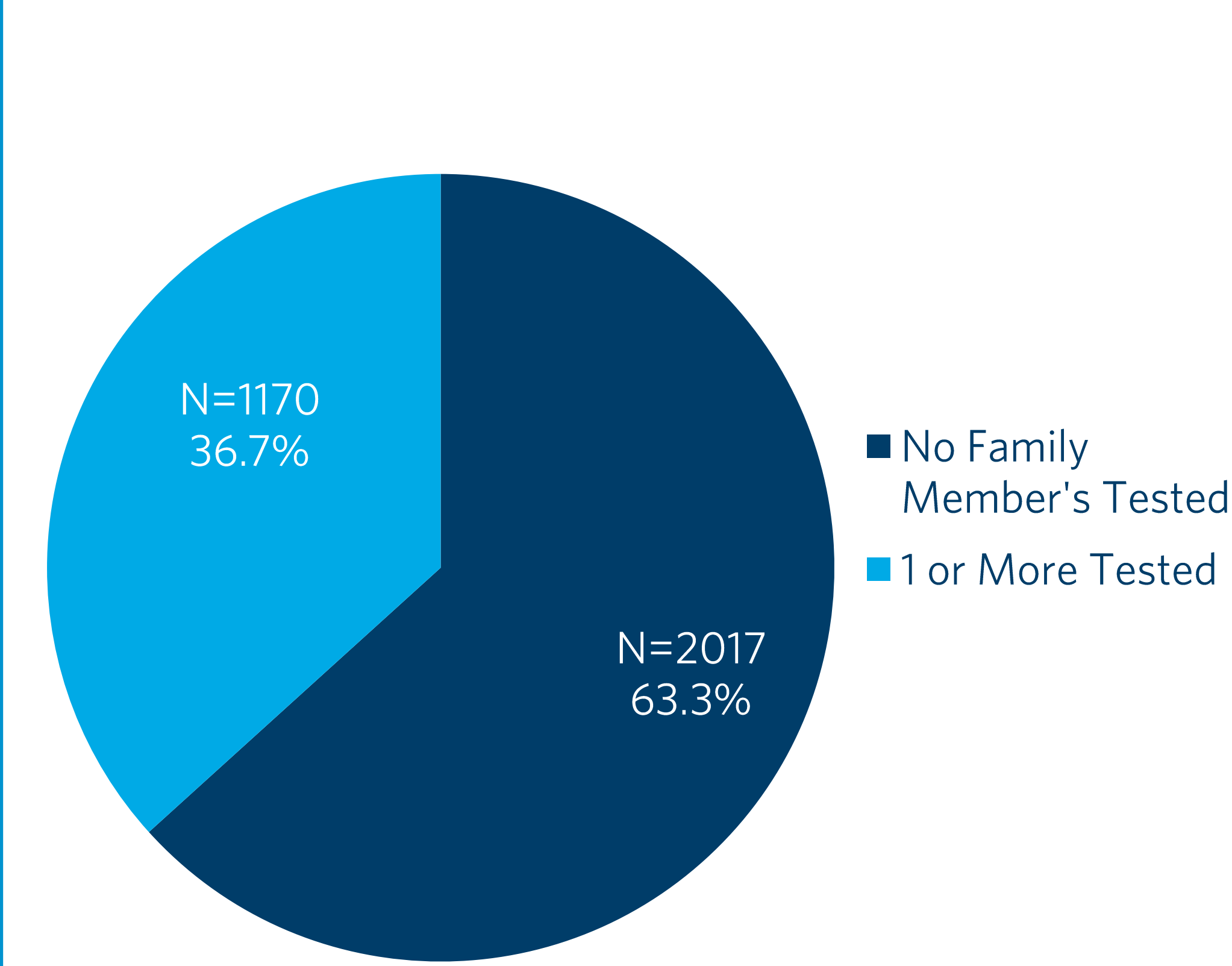


Figure 4: Number of Family Members Tested Per Proband

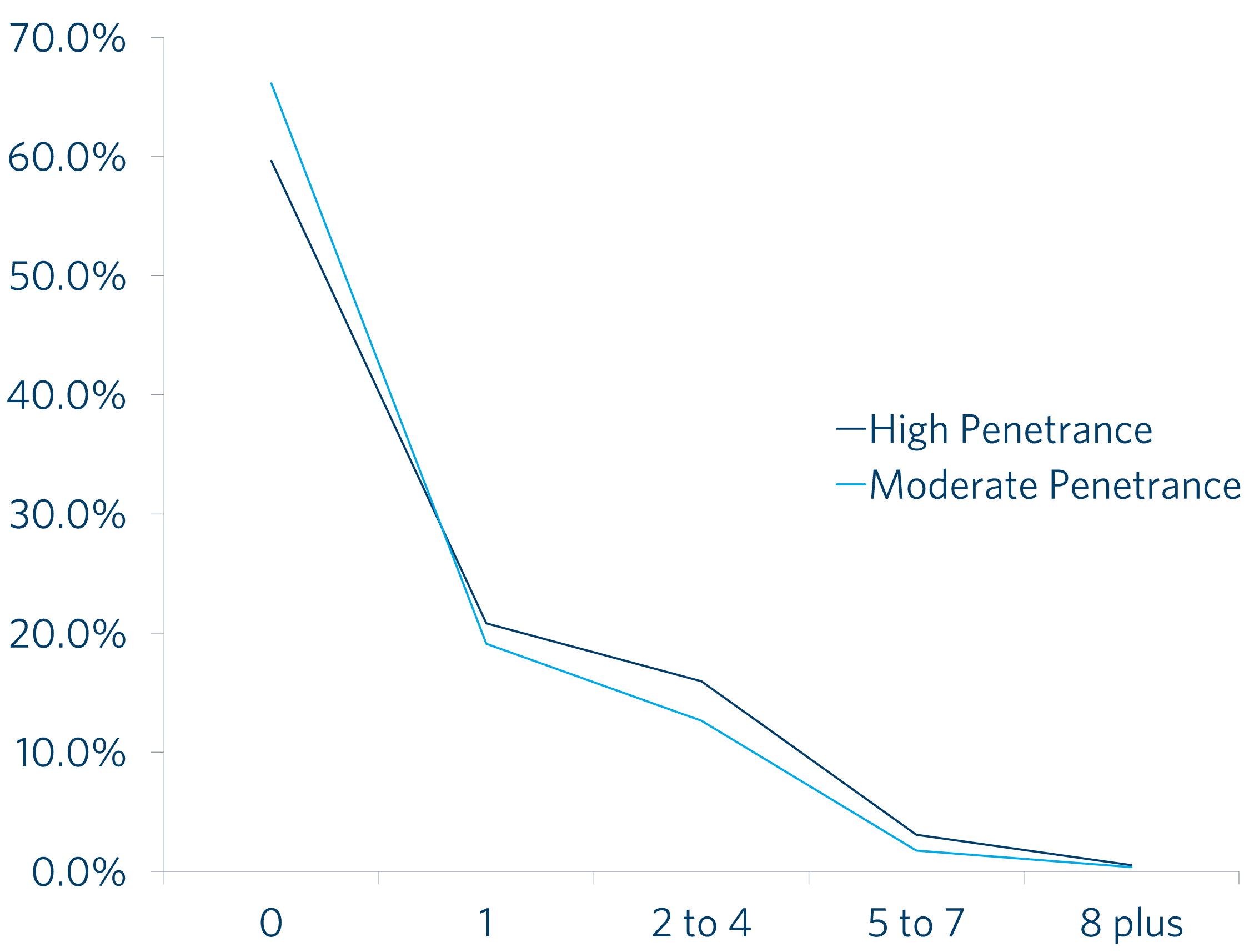
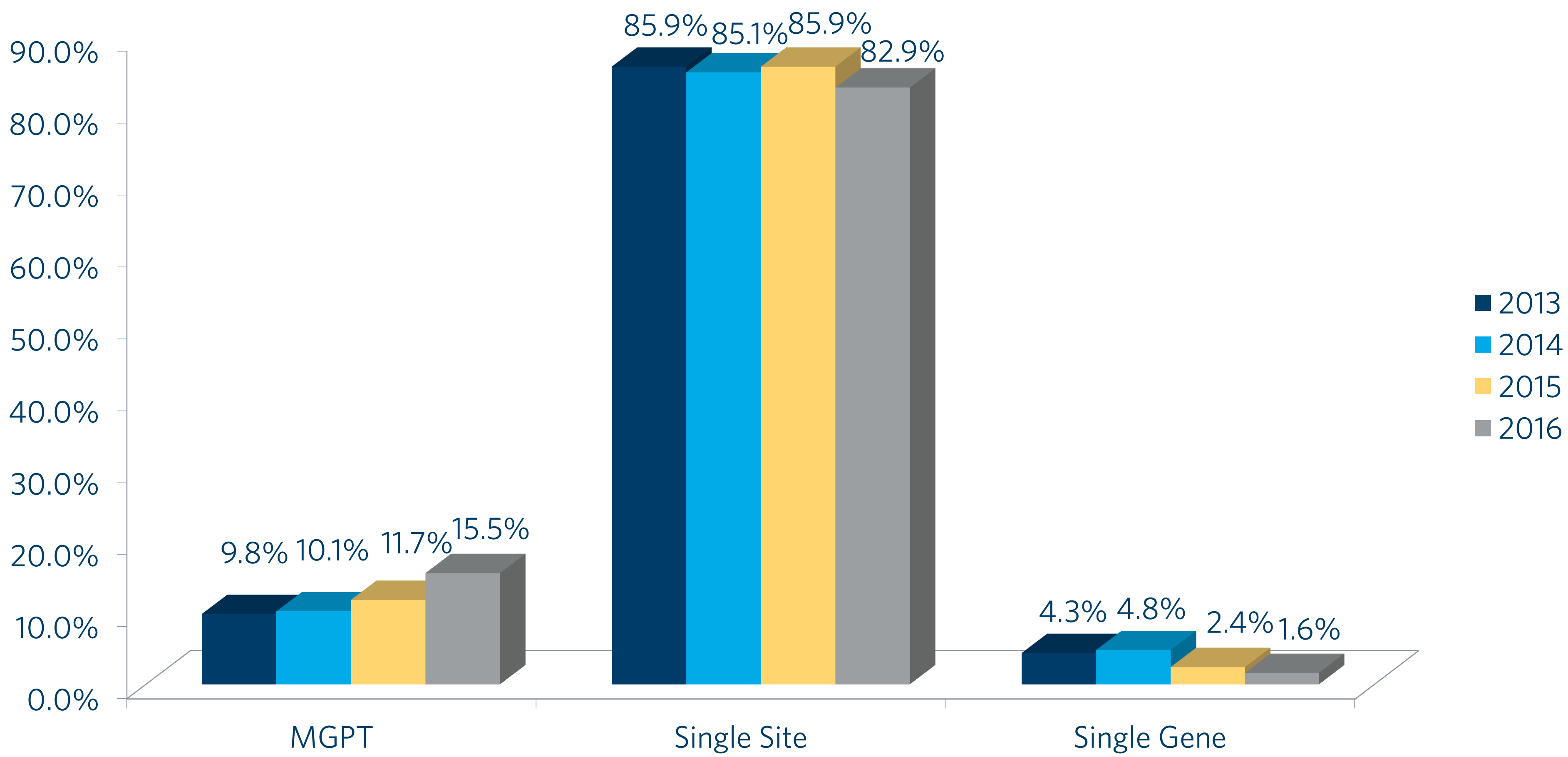


Figure 5: Familial Ordering Trends by Year



RESULTS

- The familial ordering patterns were assessed for families that had at least one or more family member tested after receiving their positive result (Figure1).
- The family members who sent in samples for cascade testing were categorized based on the type of test ordered (Figure 2).
 - When a proband was found to carry a P/LP variant, single site testing as follow up for other family members was most common (84.4%); however, some clients chose to order MGPT (13.5%) or single gene testing (2.1%) for family members while referencing the familial alteration in the requisition form.
- Of all probands that received a positive result, regardless of penetrance, 36.7% had 1 or more family members tested where as, 63.3% had no family members tested (Figure 3).
 - The percentage of probands with moderate penetrance gene alterations that had no family members tested was slightly higher (66.1%) than probands that had high penetrance gene alterations (59.6%) (Figure 4).
 - In addition, probands with high penetrance gene alterations tended to have a higher percentage of family members tested than did probands with moderate penetrance gene alterations (Figure 4).
- We examined trends in the types of cascade testing subsequently ordered from 2013 to 2016. (Figure 5)
 - There was a steady increase in MGPT ordered for family members of positive probands between 2013 (9.8%) and 2016 (15.5%).
 - There was a slight corresponding decrease in single site orders between 2013 (85.9%) and 2016 (82.9%).

TAKE-HOME POINTS

- Cascade testing continues to be a crucial part of clinical care for families at an increased risk for disease. However, for the majority of probands with a P/LP variant, cascade testing was not performed and suggests that many family members are unaware of the potential for increased cancer risk.
- We show evidence of a slow shift in cascade testing ordering trends with more providers choosing MGPT for family members instead of single site testing to perhaps detect other P/LP variants that could provide a better understanding of the clinical phenotypes seen in a family.
- The data also suggest that ordering providers may be more likely to order MGPT for family members when the proband receives a moderate penetrance result.
- We demonstrate that probands with a higher penetrance alteration have a higher percentage of family members tested than do moderate penetrance probands.