Title: Single gene (SGT) vs. Multi-gene panel testing (MGPT) for *TP53* germline mutations in Li Fraumeni syndrome (LFS)

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Background: LFS is a rare highly penetrant hereditary cancer syndrome associated with pathogenic germline mutations in the *TP53* gene. Traditionally, testing of *TP53* has been limited to individuals and families who meet well-established criteria. With the advent of MGPT, *TP53* analysis is expanded beyond these selected groups.

Methods: *TP53* testing by Ambry Genetics for 25,182 patients were collected. Retrospective review of personal and family cancer histories of those with a pathogenic or likely pathogenic *TP53* alteration (*TP53+*) was conducted, with solicitation of more complete family cancer histories ongoing. Cancer histories were examined to identify specific patterns and to determine whether any NCCN testing criteria were met including Classic criteria, Chompret criteria, and breast cancer (BC) diagnosis <age 36 yrs. All p values are from two-sided Fisher exact tests.

Results: Of 25,182 individuals, 187 (0.74%) were *TP53+*; these results came from SGT (118 of 2956, 3.99%) and from 8 MGPT panels (69 of 22,226, 0.31%). Of all those tested with adequate data, 95% having SGT had a personal cancer history v. 82% of those having MGPT.
Among 102 *TP53+* by SGT providing family history data, 73% (95% CI 63%-81%) met Classic or Chompret criteria for LFS, compared to 30% (95% CI 19%-47%) of 66 *TP53+* by MGPT (p=0.0000001); adding in the cases meeting the BC<age 36 criterion means 85% of those *TP53+* from SGT and 53% of those *TP53+* on MGPT had one of the 3 NCCN testing criteria. The personal BC<age 36 criteria was the only 1 of the 3 criteria met for 29% of 48 *TP53+* on 4 MGPT related to women's cancers v. 6% of 18 *TP53+* on the other 4 MGPT (p=0.05).

Conclusion: This is the largest cohort of *TP53* mutation carriers reported from one testing laboratory to date. MPGT enables the identification of *TP53* mutations in individuals who would not otherwise have been tested by established LFS testing criteria. Further study is needed to determine whether patients and kindreds ascertained by SGT v. MGPT have truly different or similar LFS manifestations. Efforts to compile more complete family history are ongoing. Ultimately, these findings may alter counseling of those with a molecular diagnosis of LFS.

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