# Single gene (SG) vs. Multi-Gene Panel (MGP) testing for *TP53* germline mutations in Li-Fraumeni syndrome (LFS)

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## Background

LFS is a highly penetrant, rare (1 in 20,000 prevalence), autosomal dominant, hereditary cancer syndrome associated with pathogenic germline mutations in the *TP53* gene.

Core component cancers of LFS include bone and soft tissue sarcomas, brain tumors, leukemias, ACC, CPC, and breast cancer. The frequency of *TP53* mutations in women with breast cancer diagnosed at <30 years has been reported at <1% to 7%.

Traditionally, testing of *TP53* has been limited to individuals and families who meet well-established criteria. With the advent of MGP tests, *TP53* analysis has expanded beyond these selected groups.

### Table 1: NCCN LFS Testing Criteria

| Criteria | Description |
|---|---|
| Classic | • Proband diagnosed with sarcoma age < 45 years<br>• AND a first-degree relative with cancer age < 45 years<br>• AND another first-degree or second-degree relative in the lineage with any cancer before this age or sarcoma at any age. |
| Chompret (2009) | • Proband with LFS tumor before age 46 AND<br>• At least 1 FDR or SDR with early cancer (age<56 years) or multiple primaries<br>• OR multiple tumors, 2 of which are LFS component tumors; 1 <age 46 years<br>• OR Proband with ACC or CPC |
| Early-age-onset BC | • Individual with breast cancer ≤ age 35 |

## Methods

*TP53* testing was performed via SG and 8 different MGP by Ambry Genetics for 25,182 patients. Personal and family history data was obtained from test requisitions forms for all probands. Additional personal and family history data was collected on *TP53*+ individuals (defined here as those with Class 4 & 5 variants).

Cancer and family histories were examined to determine whether any National Comprehensive Cancer Network (NCCN) testing criteria were met including Classic criteria, Chompret criteria (2009), and breast cancer (BC) diagnosis ≤ age 35 years. All p values are from two-sided Fisher exact tests.

## Results

### Table 2: Overall Results

| Test Result | Single Gene Test (n=2,956) | | All Multi-gene Panels (n=22,226) | |
|---|---|---|---|---|
| | n | % | n | % |
| *TP53*+ | 118 | 4.0* | 69 | 0.31* |
| *TP53* VUS | 39 | 1.3 | 101 | 0.45 |
| *TP53*- | 2,802 | 94.7 | 22,055 | 99.2 |

*p=1x10$^{-9}$

### Table 3: Cancer Histories of *TP53*+ and *TP53* VUS Probands*

| | | SG, *TP53*+ (n=119) | MGP, *TP53*+ (n=81) | SG, VUS (n=42) | MGP, VUS (n=95) |
|---|---|---|---|---|---|
| **Cancer Diagnosis** | | 99%† | 94%† | 98%‡ | 82%‡ |
| **Cancer Dx ≤ age 18** | | 29%† | 1%† | 21%‡ | 3%‡ |
| **Core Component Cancers (non-BC)** | Sarcoma | 39% | 12% | 29% | 5% |
| | Brain | 11% | 4% | 12% | 1% |
| | Leukemia | 4% | 1% | 5% | 3% |
| | ACC | 3% | 1% | 2% | 0% |
| | CPC | 0% | 0% | 0% | 0% |
| | **Total** | 55%† | 17%† | 43%‡ | 9%‡ |
| **Breast cancer ≤ age 35** | | 31% | 32% | 24% | 9% |
| **Breast Cancer** | | 54% | 67% | 50%‡‡ | 76%‡‡ |

*additional *TP53*+ probands were included in this analysis

•†There were significantly more cancer diagnoses, pediatric cancers, and total core component cancer diagnoses in SG vs. MGP *TP53*+ probands.

• ‡The same findings were true for SG vs. MGP *TP53* VUS probands.

• ‡‡There were significantly more breast cancer diagnoses in the MGP*TP53* VUS group than in the SG *TP53* VUS group.

### Table 4: Clinical Characteristics of *TP53*+ Kindreds by Test Type

| Criteria Met | Single Gene (n=102) | Multi-Gene Panel (n=66) |
|---|---|---|
| Classic or Chompret | 73% (95% CI 63%-81%) | 30% (95% CI 19%-47%) |
| NCCN Testing Criteria (Table 1: above plus Proband Dx of Breast cancer age ≤ 35 | 85% (95% CI 77% - 92%) | 53% (95% CI 40% - 65%) |

*analysis was limited to probands with sufficient phenotypic and FHx data available

## Conclusions

- MGP testing enables the identification of *TP53* gene mutations in individuals who would not otherwise have been suspected based on established LFS testing criteria.
- *TP53* mutation carriers ascertained through MGPs are less likely to have had a cancer diagnosis, pediatric cancers, core component tumors, and fulfill Classic or Chompret testing schema.
- Breast cancers were more common in *TP53*+ and *TP53* VUS probands identified through MGP testing. This likely reflects referral bias for the test ordered.
- Prospective cohorts are needed to evaluate whether a *TP53*+ result through MGP testing in non-classic LFS families is predictive of future LFS cancers in the kindred.
- Although *TP53* VUS rates are low, increasing use of MGPs will likely generate additional VUS that will require classification.
- Current guidelines for *TP53* testing bias our results on prior FHx of these probands.
- These data raise questions about the penetrance of *TP53* mutations and LFS syndrome definition. Family history data will be critical to their resolution.

Abbreviations: ACC: adrenocortical carcinoma; BC: breast cancer. CPC: choroid plexus carcinoma, Dx: Diagnosis; FHx: Family history ; FDR: first -degree relative; MGP: Multi-Gene Panel; NCCN: National Comprehensive Cancer Network SDR: second-degree relative; SG: Single-Gene; VUS: Variant of Uncertain Significance (Class 3 for this poster).