A Significant Proportion of *TP53* Pathogenic Variants Detected with a Hereditary Pan-Cancer NGS Panel Are Somatically Acquired

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BACKGROUND

- Individuals with germline pathogenic variants (PVs) in *TP53* have Li-Fraumeni Syndrome (LFS), which is associated with a high cancer risk and early (<45) age of diagnosis.
- NCCN guidelines recommend that individuals with LFS receive aggressive cancer screening and possibly risk-reducing mastectomy.
- We have previously demonstrated that ~40% of *TP53* PVs are detected at allele frequencies consistent with somatically acquired variants (10–30%) and are associated with increasing age (>60).
- Anecdotal evidence indicates that somatic variants are not restricted to the 10–30% range, but can rise to a level that overlaps with the NGS allele frequency expected for a germline variant (30–70%).
- Given the significant clinical management differences, it is critical to determine if a *TP53* PV is somatically acquired or is present in the germline.
- We present findings from a commercial testing laboratory program offered to all individuals with an apparent germline PV in *TP53* to determine whether the PV is germline or somatic in origin.

METHODS

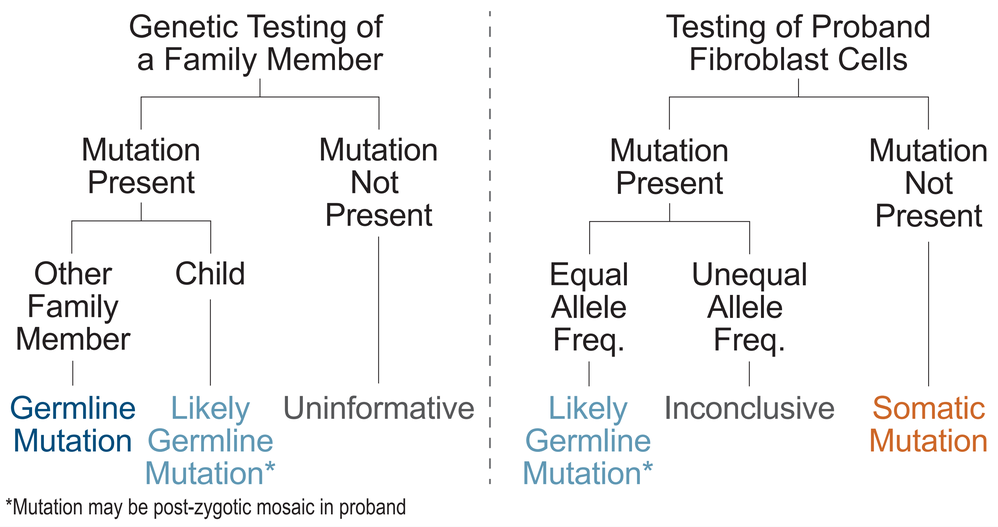
COHORT AND GENETIC TESTING

- We evaluated individuals who were tested with a multi-gene hereditary cancer panel between September 2013 and February 2017 and were found to have an apparent germline PV in *TP53* (NGS allele frequency of 30–70%; N=191).
- PVs are those variants that receive a laboratory classification of Deleterious or Suspected Deleterious.

CONFIRMATORY TESTING

- Individuals with an apparent germline *TP53* PV were offered confirmatory single-site Sanger sequencing on a fibroblast sample or single-site testing of a blood or saliva sample from a family member.

Figure 1. Possible Outcomes of Confirmatory Testing



*Mutation may be post-zygotic mosaic in proband

RESULTS

Figure 2. Summary

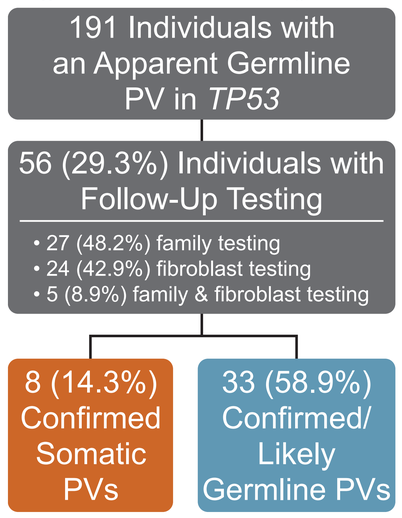
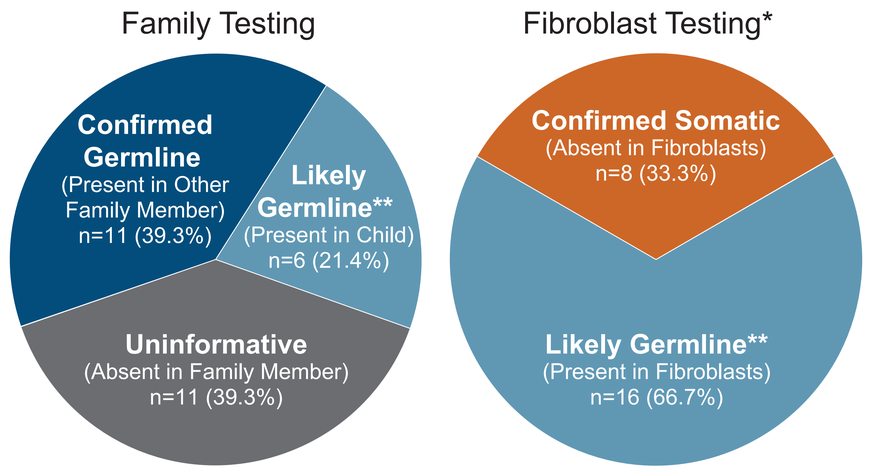


Figure 3. Results of Confirmatory Testing



*Excludes 4 individuals with inclonclusive results **Mutations may be post-zygotic mosaic

- Follow-up testing confirmed that 8/56 individuals (14.3%) carry somatic PVs in *TP53* (Figures 2 and 3), with NGS allele frequencies ranging from 34–57% (Figure 4).
- 33/56 individuals (58.9%) were found to carry confirmed/likely germline PVs in *TP53* (Figures 2 and 3), with NGS allele frequencies distributed around 50% (range 36–54%; Figure 4).
- Individuals with confirmed/likely germline PVs in *TP53* had younger ages at testing and first cancer diagnosis compared to those with confirmed somatic PVs in *TP53* (Figure 5).

Figure 4. NGS Allele Frequency

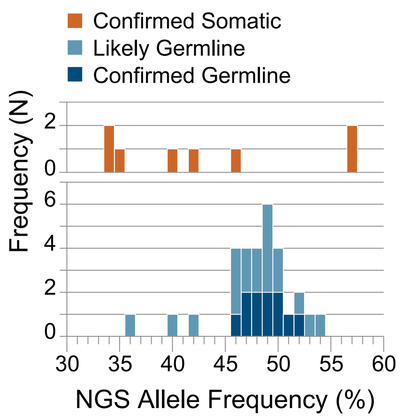
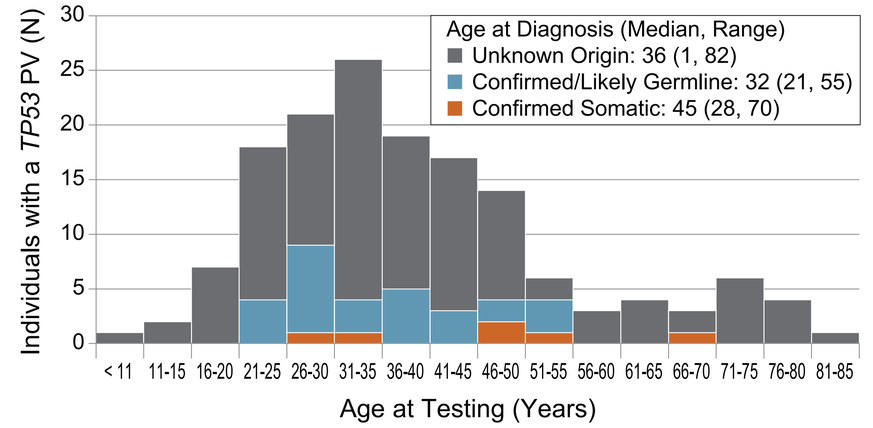


Figure 5. Age at Testing Among Individuals with Apparent Germline PVs in TP53



CONCLUSIONS

- This ongoing program demonstrates that *TP53* PVs detected with NGS read frequencies consistent with an inherited, germline PV can be either germline or somatic in origin.
- The confirmation of germline *TP53* PVs has a significant impact on medical management decisions, especially for those who may have an atypical LFS clinical presentation.
- Conversely, confirmation of a somatic PV will prevent inappropriate patient care and unnecessary family testing.
- Overall, this supports a conservative approach to the interpretation of *TP53* positive findings and the need for follow-up testing in individuals with apparent germline *TP53* PVs.

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