To fibroblast or not to fibroblast: Outcomes and clinical features of patients pursuing confirmatory germline testing following *TP53*-positive results

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BACKGROUND

- Due to the nature of NGS read depth and frequency of somatic variants in genetic testing specimens, a realized limitation is the identification of genetic variants of unknown origin, often in *TP53*.
- Confirmatory testing with an alternative specimen, such as cultured fibroblasts, is often utilized to rule-in a germline origin to help diagnose Li-Fraumeni syndrome (LFS).
- Most confirmatory cultured fibroblast testing (CCFT) results are non-informative, and it is a burdensome process for patients, providers, and the testing laboratory.

Aim: Assess if specific clinical characteristics are associated with informative CCFT.

METHODS

Retrospective review of patients with a *TP53* pathogenic variant (PV) identified on hereditary cancer multigene panel testing (MPT) from 1/1/2018 – 8/15/2024

Clinical history reviewed for those who pursued CCFT

Demographics and cancer history compared between those with informative (positive) CCFT and non-informative (negative) CCFT

RESULTS

Cancer Type	Informative (Positive) CCFT N (%)	Non-informative (Negative) CCFT N (%)
Bladder	1 (3.0%)	1 (0.6%)
Blood	0 (0%)	7 (4.5%)*
Breast (all)	23 (71.9%)	102 (65.4%)
Triple positive breast	1 (4.4%^)	5 (4.9%^)
Triple negative breast	1 (4.4%^)	13 (12.8%^)
Cervical	0 (0%)	2 (1.3%)
Cholangiocarcinoma	0 (0%)	1 (0.6%)
Colorectal	1 (3.1%)	9 (5.8%)
GIST	0 (0%)	1 (0.6%)
Kidney	0 (0%)	2 (1.3%)
Laryngeal	0 (0%)	1 (0.6%)
Liver	1 (3.1%)	0 (0%)
Lung	0 (0%)	2 (1.3%)
Melanoma	1 (3.1%)	3 (1.9%)
Neuroendocrine tumor	1 (3.%)	1 (0.6%)
Ovarian	0 (0%)	4 (2.6%)
Pancreatic	0 (0%)	2 (1.3%)
Prostate	0 (0%)	8 (5.1%)
Sarcoma	3 (9.4%)***	2 (1.3%)**
Thyroid	0 (0%)	5 (3.2%)
Uterine	1 (3.1%)	3 (1.9%)
All cancers	32	156

^Percentage represents proportion of all breast cancers that were triple positive or triple negative

*Blood cancers: 3 multiple myeloma, 3 lymphoma, and 1 chronic lymphocytic leukemia

**Sarcomas in non-informative CCFT cohort: 1 Kaposi sarcoma and 1 uterine leiomyosarcoma

***Sarcomas in the informative CCFT cohort: 1 osteosarcoma, 1 soft tissue sarcoma, and 1 leiomyosarcoma (not otherwise specified)

1,665 patients with *TP53* PV on MPT

10% Known in Family or met Chompret

152 pursued CCFT

1,348 no known CCFT

26 (17%) informative CCFT

126 (83%) non-informative CCFT

Average age at germline testing (years)

41.9 (range: 12-71) | 61.5 (range: 20-90)

p<0.0001

Average age at first cancer diagnosis, excluding non-melanoma skin (years)

39.5 (range: 12-71) | 55.8 (range: 26-86)

p<0.0001

Number of cancer diagnoses per patient, excluding non-melanoma skin (patient count)

0: 1 (3.8%)	0: 14 (11.1%)
1: 19 (73.1%)	1: 76 (60.3%)
2+: 6 (23.1%)	2+: 36 (28.6%)
Average diagnoses per patient: 1.23	Average diagnoses per patient : 1.25

p=0.38

TAKE HOME POINTS

Patients most likely to benefit from CCFT with informative results, leading to a diagnosis of LFS:

- Those with a younger age at germline testing (statistically significant).
- Those with a younger age at initial cancer diagnosis (statistically significant).
- Those with a LFS-associated sarcoma (observational trend).

A higher number of total cancer diagnoses did **not** indicate a benefit to CCFT.

Age at diagnosis and/or sarcoma history should be considered when determining the utility of CCFT following identification of a *TP53* PV on MPT.