Identification of the TP53 p.R337H Variant in Tumor Genomic Profiling Should Prompt Consideration of Germline Testing for Li-Fraumeni Syndrome

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PURPOSE Li-Fraumeni syndrome (LFS) is rare in the worldwide population, but it is highly prevalent in the Brazilian population because of a founder mutation, TP53 p.R337H, accounting for 0.3% of south and southeastern population. Clinical criteria for LFS may not identify all individuals at risk of carrying the Brazilian founder mutation because of its lower penetrance and variable expressivity. This variant is rarely described in databases of somatic mutations. Somatic findings in tumor molecular profiling may give insight to identify individuals who might be carriers of LFS and allow the adoption of risk reduction strategies for cancer.

MATERIALS AND METHODS We determined the frequency of the TP53 p.R337H variant in tumor genomic profiling from 755 consecutive Brazilian patients with pan-cancer. This is a retrospective cohort from January 2013 to March 2020 at a tertiary care center in Brazil.

RESULTS The TP53 p.R337H variant was found in 2% (15 of 755) of the samples. The mutation allele frequency ranged from 30% to 91.7%. A total of seven patients were referred for genetic counseling and germline testing after tumor genomic profiling results were disclosed. All the patients who proceeded with germline testing (6 of 6) confirmed the diagnosis of LFS. Family history was available in 12 cases. Nine patients (9 of 12) did not meet LFS clinical criteria.

CONCLUSION The identification of the TP53 p.R337H variant in tumor genomic profiling should be a predictive finding of LFS in the Brazilian population and should prompt testing for germline status confirmation.

INTRODUCTION Approximately 5%-10% of all cancers occur in the context of an inherited cancer predisposition syndrome.1 Germline genetic testing is offered according to clinical criteria. Inherited pathogenic variants in cancer susceptibility genes are found in 26%-56% of individuals who do not fulfill any clinical criteria.2 This may be due to incomplete penetrance, late-onset cancer diagnosis, or lack of knowledge about family history.

Tumor genomic profiling has been used to detect potential actionable somatic alterations in advanced refractory, or relapsed cancer.3,4 In cohorts of adult patients, not stratified by the risk of hereditary cancer, the frequency of incidental germline findings associated with cancer predisposition syndromes ranges from 3% to 19.7%.6,9,12 In pediatric cancer cohorts, the frequency is up to 10%.5,13 Patients should be educated about this possibility before undergoing somatic mutation analysis.1 Providers should communicate the limitations, risks, and benefits of receiving germline findings.

Mandelker et al.6 assessed the effectiveness of hereditary cancer syndrome diagnosis through paired tumor and normal tissue genetic sequencing in comparison with germline testing guided only by clinical guidelines. Among 1,040 tested patients, 17.5% (182 of 1,040) had pathogenic variants associated with cancer predisposition syndromes. However, only 45.5% (81 of 182) of these patients fulfilled clinical criteria for germline testing.
Because of the elevated prevalence of Li-Fraumeni Syndrome (LFS) in the Brazilian population, mainly caused by the founder germline mutation TP53 p.R337H, and its rare occurrence as a somatic finding, we sought to evaluate the frequency of the TP53 p.R337H variant in Brazilian patients with pan-cancer undergoing routine tumor genomic profiling.

**Knowledge Generated**

The TP53 p.R337H variant was detected in 2% (15 of 755) of all tumors. None of the cases had received a diagnosis of LFS before somatic profiling.

**Relevance**

Oncology health care professionals should be aware that patients with Brazilian ancestry and identification of TP53 p.R337H variant in somatic tumor testing should be referred for genetic counseling and germline testing for LFS, even for patients who do not meet clinical criteria for the syndrome.

The identification of tumor genetic abnormalities, such as microsatellite instability (MSI), mutations in cancer susceptibility genes, or recognized founder mutations, may optimize the identification of individuals at risk for inherited cancer syndromes. This strategy may improve referral for germline testing.

In Brazil, a founder mutation in TP53, c.1010G>A p.Arg337His (NM000546.6), known as p.R337H, is associated with a higher prevalence of Li-Fraumeni syndrome (LFS). It is estimated that 0.3% of south and southeastern Brazilian populations carry this variant. Despite the fact that classical LFS core cancers are young-onset breast cancer, adrenocortical cancer, CNS cancer, and sarcomas, a wider spectrum of tumors has been described in this high-risk population. More recently, a higher incidence of lung and thyroid cancer has been described in p.R337H carriers.

Somatic mutations in the TP53 gene are one of the most frequent alterations in human cancer. Nevertheless, the TP53 Database from the International Agency for Research on Cancer (IARC) indicates that p.R337H is extremely rare as a somatic event in tumors. The TP53 p.R337H variant is reported in very low frequency in somatic mutation databases, such as the Precision Oncology Knowledge Base (OncoKB) and the Catalogue of Somatic Mutations in Cancer (COSMIC v91).

A total of 549 different TP53 pathogenic variants are listed in the germline TP53 IARC database (1,512 families and 3,433 individuals). The TP53 p.R337H variant is reported in 117 families and 292 individuals. In the Genome Aggregation Database (gnomAD v2.1.1), considering all the whole-exome sequencing samples included (N = 125,423), three heterozygous individuals are observed, two of them with Latino (admixed American) ancestry.

Because of the elevated prevalence of this pathogenic germline variant in the Brazilian population and its rare occurrence as a somatic finding, we sought to evaluate the frequency of the TP53 p.R337H variant in patients with pan-cancer undergoing routine tumor genomic profiling.

**MATERIALS AND METHODS**

A retrospective analysis of tumor tissue-based genomic data reports was performed between January 2013 and March 2020. Consecutive samples received by the Pathology Department of Hospital Sírio-Libanês (SP, Brazil) were included. Tumor tissue from archival formalin-fixed paraffin-embedded blocks or imprinted specimens was submitted to either commercially targeted next-generation sequencing assays FoundationOne (F1) or Trusight Tumor 170 (TST 170) panels (Illumina Inc, San Diego, CA). Both panels included the analysis of TP53 gene. Reports with the finding of the variant p.R337H were selected for further analysis. This project was approved by the Institutional Research Ethics Committee (approval number 3.830.276). A waiver of informed consent of study participants was granted. Patients were not contacted because there was no previous consent for the disclosure of possible incidental germline findings.

Clinical data (tumor site, sex, age at somatic test, and stage of disease) were extracted from provider information present in genomic profiling reports. Reports containing the p.R337H variant were selected, and medical records from these patients were analyzed retrospectively. Data collection included histology subtype, age at cancer diagnosis, tobacco exposure, somatic molecular findings during tumor genomic profiling, family history, presence of close relatives (first- to third-degree relatives) affected by cancer before age 50 years, previous primary cancers, GC consultation, and germline testing result.

**RESULTS**

**Cohort Characteristics**

Tumor genomic profiling reports from 755 unique patients were reviewed. Tumor genomic profiling assays (F1) were performed in 551 samples, and the TST170 assay was performed in 204. The cohort characteristics are shown in.
Table 1. Male patients represented 52% of the sample. The most frequently tested malignancies according to the primary site were lung (29%, 220 of 755), CNS (7.8%, 59 of 755), colorectal (8.6%, 65 of 755), and bone or soft tissue sarcomas (8.7%, 66 of 755). Carcinomas represented 79% (591 of 755) of all samples. Nonpneothelial tumors corresponded to 21% (155 of 755) of the samples. The majority of samples were from patients with metastatic, refractory, or relapsed cancer. Cases of primary CNS tumors included all disease stages.

Detection of the **TP53** p.R337H Variant

The **TP53** p.R337H variant was detected in 2% (15 of 755) of all tumors. Clinical data from these patients are shown in Appendix Table A1. Tumor spectrum included eight cases of lung cancer, four soft tissue sarcomas (three leiomyosarcomas and one sarcoma not otherwise specified), one hepatocellular carcinoma, one papillary thyroid carcinoma, and one glioblastoma. The mutant allele frequency (MAF) ranged from 30% to 91.7%. Tumor mutational burden (TMB) and MSI data were available for eight cases. All of them had TMB < 10 mutations/Mb and lack of MSI.

The median age at cancer diagnosis in the p.R337H carriers was 47 years (range 29-68 years). Two patients had more than one primary cancer. Patient 7 had a breast cancer diagnosis at age 57 years and a second primary lung cancer at age 68 years (Appendix Table A1). Patient 11 had a gastric cancer at age 57 years and a second primary lung cancer at age 59 years (Appendix Table A1). Genomic tumor profiling was performed only in the lung cancer samples in both cases.

All lung cancer cases were adenocarcinomas. Seven tumors (7 of 8) occurred in nonsmokers. The median age at diagnosis was 57 years (range 33-68 years). Three patients were affected before age 50. Age at time of diagnosis was not available in one case. Five cases (62.5%, 5 of 8) were positive for epidermal growth factor receptor (EGFR) mutations (one mutation in exon 18 G719A+I706T, one mutation in exon 20 p.Ala767.Val769dup, one mutation in exon 20 D770+N771insY, and two mutations in exon 21 L858R). Only one case (1 of 5) showed programmed death ligand-1–positive expression by immunohistochemistry (tumor proportion score of 5%), and programmed death ligand-1 testing information was lacking in three cases.

None of the cases with the p.R337H variant had a diagnosis of LFS before somatic profiling. Family history of cancer was present in the medical records of 12 patients (12 of 15). Fifty percent (6 of 12) had a family member affected by cancer before age 50 years. Retrospective analysis revealed that three of 12 patients met clinical criteria for **TP53** germline testing (Table 2).

A total of seven patients (7 of 15) were referred for GC and germline testing after tumor genomic profiling results were disclosed according to medical records. Only one patient (1 of 7) diagnosed with lung cancer at age 33 years refused to undergo germline testing. LFS was confirmed in all six patients tested. In eight cases (8 of 15), there was no information about GC referral and/or germline testing.

**DISCUSSION**

The American College of Medical Genetics and Genomics recommends, since 2015, that all patients undergoing tumor genomic profiling should receive pretest GC and be allowed to opt for receiving secondary germline findings. Nevertheless, GC is not routinely offered in somatic tests for treatment selection. In the current study, one in 50 tumor genomic profiling reports (2%, 15 of 755) was able to identify the **TP53** p.R337H variant. Detailed data on family history were available in the medical records of 12 individuals whose tumor carried the founder mutation. Three individuals (3 of 12, 25%) met Chompret clinical criteria, but none had received an LFS diagnosis before the somatic test. Nine of 12 patients (75%) did not meet clinical Chompret criteria for germline testing.

GC referral is advisable for patients with a somatic pathogenic variant in a known cancer susceptibility gene. Among seven patients with documented referral for GC, one refused to perform germline testing. All the patients who proceeded with a germline test (6 of 6) were found to carry the p.R337H variant. This finding confirms the need for GC and germline testing for known founder mutations identified during tumor genomic profiling.

In the context of somatic genomic data, the MAF represents the fraction of sequencing reads that reports the mutant allele at a given locus. Since the majority of hereditary syndromes are autosomal dominant, pathogenic somatic variants may be suspected of germline origin when MAF is between 30% and 50%, which means a heterozygous state. However, elevated MAFs may also reflect an acquired mutation in a high percentage of tumor cells or ploidy. In the present study, the MAFs of p.R337H in the somatic tests varied from 30.0% to 91.7%.

**TP53** variants are not usually suspicious for hereditary cancer since they are a very common somatic finding associated with carcinogenesis. Somatic **TP53** pathogenic variants are present in approximately 96% of small-cell lung cancers, 45% of non–small-cell lung carcinomas, 12%–48% of hepatocellular carcinomas, 3.9%–58.5% of sarcomas, 28%–90% of glioblastomas, and 40% of papillary thyroid carcinomas. Interestingly, p.R337H is not frequently reported in somatic mutation databases. Among 4,942 mutations in **TP53**, 29 mutations have been reported in codon 337 by OncoKB, a database of somatic mutations screened through the cancer gene panel MSK-IMPACT (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets). However, none of the 29 mutations reported included p.R337H. In COSMIC, 82 samples have the p.R337H, but 66 of 82 (80%) were reported in adenocortical tumors from Brazilian cohorts. The other 16 cases were distributed in...
head and neck cancers (including thyroid), breast, renal, hepatocellular carcinoma, neuroblastoma, and meningioma. TP53 somatic hotspots occur mainly within the DNA-binding domain. Codon 337 is not a hotspot for somatic mutations, but it is a well-defined hotspot for germline alterations related to LFS in the Brazilian population. The p.R337H variant is localized in the oligomerization domain and affects the formation of p53 tetramers and transactivation activity of the protein, resulting in a dominant negative effect over the wild-type allele. According to the p53 mutation database of the IARC, the single most frequent germline mutation is TP53 p.R337H. This high representation of p.R337H in the IARC database is due to the Brazilian cohort of p.R337H carriers described in 2007.

Bone and soft tissue sarcomas account for approximately 25% of cancers in LFS families, and the majority (67%) occur before age 20 years. Osteosarcoma, leiomyosarcoma, and rhabdomyosarcoma represent the most frequently diagnosed subtypes. In the present series of patients with TP53 p.R337H detected in tumor profiling, 26.6% (4 of 15) had been diagnosed with soft tissue sarcomas (three leiomyosarcomas and one sarcoma not otherwise specified). All leiomyosarcomas were diagnosed before the age of 45 years. In a recent Brazilian publication, 8% of unselected sarcomas (n = 502, 68.1% with stage III or IV) harbored the TP53 p.R337H variant, and the majority was diagnosed after age 40 years.

In addition to sarcomas, CNS tumors are one of the most prevalent cancers in LFS. Approximately 40% of LFS families have at least one member with a brain tumor. There are two known age peaks for brain tumor manifestations in LFS; the first is in early childhood (age 0-5 years), and the second is in young adults (age 30-40 years). The case identified in this cohort with somatic detection of the TP53 p.R337H variant and germline confirmation had a multiforme glioblastoma IDH wild type at age 29 years, without methylation of MGMT or mutations in ATRX and TERT. IDH mutations arising in the setting of germline TP53 mutations are associated with TERT promoter mutations, neither of which were detected in this case.

Among our sample of detected p.R337H, there was one case of hepatocellular carcinoma and one case of papillary thyroid carcinoma. The incidence of thyroid cancer reported in patients with LFS with classic DNA-binding domain mutations is 0.9% (3 of 415). However, Formiga

### TABLE 1. Baseline Cohort Characteristics

| Cohort Characteristic | No. of Patients, N = 755, No. (%) |
|-----------------------|-----------------------------------|
| Median age at NGS somatic testing, years, median (range) | 60 (2-92) |
| Sex | |
| Male | 393 (52.0) |
| Female | 362 (48.0) |
| Primary cancer site or histology | |
| Lung | 220 (29.1) |
| Soft tissue sarcoma | 66 (8.7) |
| Colorectal | 65 (8.6) |
| CNS—gliomas only | 59 (7.8) |
| Pancreas | 49 (6.5) |
| Gynecologic | 43 (5.7) |
| Breast | 36 (4.8) |
| Gastroesophageal | 31 (4.1) |
| Unknown primary | 31 (4.1) |
| Liver and biliary tract | 25 (3.3) |
| Prostate | 21 (2.8) |
| Head and neck | 18 (2.4) |
| Renal and urothelial | 18 (2.4) |
| Hematologic | 12 (1.6) |
| Salivary glands | 12 (1.6) |
| Pediatric sarcomas | 11 (1.4) |
| Adrenal | 7 (1.0) |
| Not available | 1 (0.1) |
| Other tumors | 30 (4.0) |

Abbreviation: NGS, next-generation sequencing.

*Gynecologic included fallopian tube, ovarian, and uterine tumors.

*Gastroesophageal carcinomas included stomach, esophagus, and gastroesophageal carcinomas.

*Other tumors included thyroid, melanoma, meningioma, malignant mesothelioma, and testicular.

### TABLE 2. TP53 Gene-Specific Germline Testing Criteria

| Criteria | Description |
|----------|-------------|
| Chompret | Proband with a cancer in the LFS spectrum before age 46 years AND at least one first- or second-degree relative with an LFS tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors; OR Proband with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum* and the first of which occurred before age 46 years; OR Proband with adrenocortical carcinoma, choroid plexus tumor, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history; OR Female proband with breast cancer before age 31 years |

Abbreviation: LFS, Li-Fraumeni syndrome.

*LFS spectrum cancers include soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, and lung bronchoalveolar cancer.

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Some publications have suggested an association between EGFR-mutated lung cancer and LFS.\textsuperscript{19,45} The co-occurrence of TP53 and EGFR pathogenic variants is reported in 19\% of lung adenocarcinomas.\textsuperscript{49} Barbosa et al\textsuperscript{19} reported nine cases of lung cancer in an LFS cohort of 164 patients with p.R337H; eight of them (89\%, 8 of 9) had EGFR mutations. In our sample, five cases (62.5\%, 5 of 8) had EGFR mutations. A recently published study found an association with somatic mutations in EGFR and ERBB2, as well as low TMB in the tumor lung samples carrying the TP53 p.R337H variant.\textsuperscript{47} Two of eight lung tumor samples, from the present study, had TMB information, and both cases showed a low TMB (< 10 mutations/Mb). Only one case showed ERBB2 somatic mutation, and it was not associated with the presence of EGFR mutation.

The present study has several limitations: (1) it is a retrospective analysis on the basis of test reports from a single tertiary private institution; (2) the cohort is based mostly on patients with metastatic, refractory, or relapsed cancer; (3) the TP53 p.R337H variant was an incidental finding during tumor genomic profiling; and (4) complete clinical information, including age at cancer onset and family history, was only obtained through medical records in the case of TP53 p.R337H variant identification. Nevertheless, to our knowledge, this is the first study to describe the frequency of the Brazilian LFS founder mutation in somatic tumor profiles of a pan-cancer population unselected by age, cancer subtype, or family history.

In conclusion, these results should make oncology health care professionals aware that patients with Brazilian ancestry and identification of TP53 p.R337H variant in somatic tumor testing should be referred for GC and germline testing for LFS, even for patients who do not meet LFS criteria.

**DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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## APPENDIX

### TABLE A1. Characteristics of Patients With Somatic Detection of TP53 p.R337H Variant

| ID | Sex | Life Status | Primary Cancer Site | Histology | Age at Cancer Diagnosis (years) | Tobacco Exposure | Clinically Relevant Data From Tumor Profile | MAF R337H in the Somatic Test (%) | Genetic Counseling | Family History of Cancer | Germline Genetic Test | Previous Primary Cancers |
|----|-----|-------------|---------------------|-----------|---------------------------------|-----------------|-------------------------------------------|---------------------------------|-------------------|---------------------|---------------------|---------------------|
| 1  | M   | D           | Lung                | Adenocarcinoma   | 47                 | N                             | VHHL P81S, TP53 R337H, KEI splice site 924+1G>T, MUTYH G382D, and RB1 G3095A, M5 not informed TMB not informed EGFR-negative ALK-negative PD-L1 not informed | 30.0                             | N                  | Father—prostate cancer (71 years) and paternal aunt—colorectal cancer (75 years) | N               | None               |
| 2  | F   | NA          | STS                 | NOS               | 56                 | NA                            | R61I R366fs*45 and TP53 R337H, M5 not informed TMB not informed | 89.0                             | NA                  | NA                  | NA                  | NA                  |
| 3  | M   | D           | Lung                | Adenocarcinoma   | 33                 | N                             | ERBB2 P780S, Y781insGSP, NF1 rearrangement intron 2A, BCL2L2 amplification, KMT2C (MLL9) C310*, NTRK1 amplification, and TP53 R337H, M5 stable TMB low EGFR-negative ALK-negative PD-L1-negative | 85.8                             | Y                  | Maternal aunt—breast cancer (59 years), maternal grandmother—breast cancer (< 50 years), maternal grand aunt—breast cancer (> 50 years), and maternal great uncle—lung cancer (> 50 years) | N               | None               |
| 4  | M   | NA          | Thyroid             | Papillary carcinoma | NA                 | NA                            | BRAF V600E and TP53 R337H, M5 stable TMB low | 57.8                             | NA                  | NA                  | NA                  | NA                  |
| 5  | M   | NA          | STS                 | Leiomyosarcoma    | 34                 | N                             | AXL amplification, ATR R2089*, ATRX loss exons 17-25, and TP53 R337H, M5 stable TMB low | 91.7                             | NA                  | Father—glioblastoma (59 years), maternal cousin—lung cancer, and mother—breast cancer (60 years) | NA               | NA                  |
| 6  | M   | A           | CNS                 | Glioblastoma multiforme | 29                 | N                             | CDK4 amplification, ERBB3 amplification, TP53 R337H, JH4-WT, and no ATRX or TERT mutations, M5 stable TMB low | 59.5                             | Y                  | Father—prostate cancer (64 years) | Y                | None               |
| 7  | F   | NA          | Lung                | Adenocarcinoma   | 68                 | N                             | EGFR L858R, HGF amplification, CDKN2A/B loss, FANCD2 loss exons 14-16, KDM5A amplification, and TP53 R337H, M5 stable TMB low EGFR-positive ALK-negative PD-L1 not informed | 56.3                             | N                  | Mother—breast cancer (65 years) and maternal aunt—lung cancer (80 years) | NA               | Breast cancer (57 years) |

(Continued on following page)
| ID | Sex | Life Status | Primary Cancer Site | Primary Cancer Site | Histology | Age at Cancer Diagnosis (years) | Tobacco Exposure | Clinically Relevant Data From Tumor Profile | MAF R337H in the Somatic Test (%) | Genetic Counseling | Family History of Cancer | Germline Genetic Test | Previous Primary Cancers |
|----|-----|------------|---------------------|---------------------|-----------|-------------------------------|----------------|------------------------------------------|----------------------------------|-------------------|----------------------|-------------------|-----------------------|
| 8  | M   | A          | STS                 | Leiomysarcoma       | 42        | N                             |                | C17orf39 amplification, RB1 splice site 138-1G>C, and TP53 R337H MS stable TMB low | 67.0                             | NA                | Father—Hodgkin lymphoma, maternal cousin–breast cancer (45 years), maternal cousin–melanoma (45 years), maternal cousin–breast cancer (40 years), and maternal uncle–unknown cancer (60 years) | Y                  | None                |
| 9  | M   | NA         | Liver               | Hepatocellular carcinoma | 55        | N                             |                | CCND1 amplification, CDK4 amplification, FGF19 amplification, KRAS amplification, FGFR3 amplification, FGFR4 amplification, TERT promoter-124C>T, and TP53 R337H MS stable TMB low | 85.8                             | Y                 | No                                  | NA                | None                |
| 10 | M   | A          | STS                 | Leiomysarcoma       | 43        | Y                             |                | Kit amplification, PDGFRA amplification, RET amplification, JUN amplification, LRP1B S1645*, and TP53 R337H MS stable TMB low | 82.4                             | Y                 | Maternal aunt–breast cancer (56 years), maternal aunt–multiple myeloma (62 years), brother–rectal sarcoma (45 years), paternal cousin–breast cancer (50 years), paternal aunt–multiple myeloma (65 years), paternal aunt–gastrintestinal cancer (55 years), paternal cousin–breast cancer (40 years), paternal aunt–gastrintestinal cancer (80 years), and paternal cousin–gastrintestinal cancer (60 years) | Y                  | None                |
| 11 | M   | NA         | Lung                | Adenocarcinoma      | 59        | N                             |                | KRAS c.34G>T, p.Gly12Cys, STK11 c.580G>C, and p.Asp194His MS not informed TMB not informed EGFR-negative ALK-negative PD-L1-negative | 83.8                             | Y                 | Maternal grandfather–lung cancer (77 years), father–lung cancer (45 years), maternal uncle–unknown cancer, paternal uncle–gastrintestinal cancer (55 years), paternal aunt–lung cancer (70 years), paternal aunt–breast cancer (65 years), paternal aunt–breast cancer (44 years), maternal cousin–multiple myeloma (61 years), and paternal grandfather–renal cancer (70 years) | Y                  | Gastric cancer (57 years) |
| 12 | F   | A          | Lung                | Adenocarcinoma      | 60        | N                             |                | CKDN2A c.247C>T, p.His83Tyr, EGFR c.2156G>T, and TP53 R337H MS not informed TMB not informed EGFR-positive ALK-negative PD-L1-negative | 62.8                             | Y                 | Sister–breast and esophagial cancer (>50 years), grandnephew–adenocortical carcinoma (8 months), maternal aunt–colorectal cancer (>50 years), maternal grandfather–head and neck cancer (>50 years), and father–liver cancer (53 years) | Y                  | None                |
| 13 | F   | NA         | Lung                | Adenocarcinoma      | 57        | N                             |                | EGFR c.2300_2308dup (p.Ala767_Val769dup) and TP53 R337H MS not informed TMB not informed EGFR-positive ALK-negative PD-L1-positive | 62.4                             | N                 | Mother–multiple myeloma (82 years) | N                  | None                | (Continued on following page)
TABLE A1. Characteristics of Patients With Somatic Detection of TP53 p.R337H Variant (Continued)

| ID | Sex | Life Status | Primary Cancer Site | Histology | Age at Cancer Diagnosis (years) | Tobacco Exposure | Clinically Relevant Data From Tumor Profile | MAF R337H in the Somatic Test (%) | Genetic Counseling | Family History of Cancer | Germline Genetic Test | Previous Primary Cancers |
|----|-----|-------------|---------------------|-----------|---------------------------------|------------------|----------------------------------|--------------------------------|------------------|------------------------|----------------------|--------------------------|
|    |     |             |                     |           |                                 |                  |                                   |                                |                  |                        |                      |                          |
| 14 | F   | NA          | Lung               | NA        | NA                              | NA               | EGFR c.2573T>G, p.(Leu858Arg), and TP53 R337H MS not informed TMB not informed EGFR-positive ALK-negative PD-L1-negative | 78.5               | NA               | NA                     | NA                   | NA                       |
| 15 | M   | A           | Lung               | Adenocarcinoma | 36                             | N                | EGFR ins20 (p.Asp770_Asn771insTyr/Asp770-N771insY) and CDKN2A/B loss MS not informed TMB not informed EGFR-positive ALK-negative PD-L1-negative | 51.3               | Y                | Mother-breast cancer (45 years), maternal uncle-prostate cancer (45 years), and maternal grandfather-prostate cancer (61 years) | Y                     | None                     |

Abbreviations: A, alive; D, deceased; EGFR, epidermal growth factor receptor; F, female; M, male; MAF, mutant allele frequency; MS, microsatellite; N, no; NA, not available; NOS, not otherwise specified; PD-L1, programmed death ligand-1; STS, soft tissue sarcoma; TMB, tumor mutational burden; Y, yes.