original reports abstract

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

Renata Lazari Sandoval, MD[1]; Cibele Masotti, PhD[2]; Mariana Petaccia de Macedo, PhD[3]; Maurício Fernando Silva Almeida Ribeiro, MD[4]; Ana Carolina Rathsam Leite, MD[1]; Sibele Inacio Meireles, PhD[3]; Rodrigo Medeiros Bovolin, MD[1]; Fernando Costa Santini, MD[4]; Rodrigo Ramella Munhoz, MD[4]; Denis Leonardo Fontes Jardim, PhD[4]; Artur Katz, MD[4]; Anamaria Aranha Camargo, PhD[2]; Gustavo dos Santos Fernandes, MD[1]; and Maria Isabel Achatz, PhD[4]

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.

JCO Global Oncol 7:1141-1150. © 2021 by American Society of Clinical Oncology

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 and refractory or relapsed cancers. Germline information is not usually disclosed in tumor-only sequencing. In addition, pretest genetic counseling (GC) is not routinely offered to obtain consent regarding the disclosure of possible unexpected findings associated with germline data. Nevertheless, a high frequency of germline pathogenic variants has been revealed by tumor genomic profiling in patients with metastatic, refractory, or relapsed cancer.[3-8] 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.

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on May 25, 2021 and published at ascopubs.org/journal/go on July 16, 2021: DOI https://doi.org/10.1200/GO.21.00097

CONTEXT

Key Objective

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.[14] 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.[15-17] 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.[18-20]

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)[21] indicates that p.R337H is extremely rare as a somatic event in tumors.[22] The *TP53* p.R337H variant is reported in very low frequency in somatic mutation databases, such as the Precision Oncology Knowledge Base (OncoKB)[23] and the Catalogue of Somatic Mutations in Cancer (COSMIC v91).[24]

A total of 549 different *TP53* pathogenic variants are listed in the germline *TP53* IARC database (1,512 families and 3,433 individuals).[22] The *TP53* p.R337H variant is reported in 117 families and 292 individuals. In the Genome Aggregation Database (gnomAD v2.1.1),[25] 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. Nonepithelial 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 received 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.[27] 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.[14] 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.[14]

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.[28] However, elevated MAFs may also only reflect an acquired mutation in a high percentage of tumor cells or ploidies. 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.[29] Somatic *TP53* pathogenic variants are present in approximately 96% of small-cell lung cancers,[30] 45% of non–small-cell lung carcinomas,[31] 12%–48% of hepatocellular carcinomas,[32] 3.9%-58.5% of sarcomas,[33] 28%-90% of glioblastomas,[34] and 40% of papillary thyroid carcinomas.[35] 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).[36] 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 adrenocortical tumors from Brazilian cohorts.[37] The other 16 cases were distributed in

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[a]	43 (5.7)
Breast	36 (4.8)
Gastroesophageal[b]	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[c]	30 (4.0)

Abbreviation: NGS, next-generation sequencing.

[a]Gynecologic included fallopian tube, ovarian, and uterine tumors.

[b]Gastroesophageal carcinomas included stomach, esophagus, and gastroesophageal carcinomas.

[c]Other tumors included thyroid, melanoma, meningioma, malignant mesothelioma, and testicular.

head and neck cancers (including thyroid), breast, renal, hepatocellular carcinoma, neuroblastoma, and meningioma.

TP53 somatic hotspots occur mainly within the DNA-binding domain.[38] Codon 337 is not a hotspot for somatic mutations,[38] but it is a well-defined hotspot for germline alterations related to LFS in the Brazilian population.[15-17] 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.[39] According to the p53 mutation database of the IARC, the single most frequent germline mutation is *TP53* p.R337H.[21] This high representation of p.R337H in the IARC database is due to the Brazilian cohort of p.R337H carriers described in 2007.[15]

Bone and soft tissue sarcomas account for approximately 25% of cancers in LFS families, and the majority (67%) occur before age 20 years.[40] 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.[20]

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.[41] 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).[42] 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.[41,42]

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).[43] However, Formiga

TABLE 2. TP53 Gene-Specific Germline Testing Criteria[26]

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[a] 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.

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

et al[44] described a higher incidence in a Brazilian p.R337H cohort, and 10.9% of carriers had a personal history of papillary thyroid carcinoma.

An increased risk of lung cancer has been described in LFS,[18,45,46] but the magnitude of this risk is still unknown. The majority of cases are represented by adenocarcinomas, female patients, and diagnosis before age 50 years.[45] Lung cancer represented 29% (220 of 755) of our samples, and 3.6% (8 of 220) of the tumor lung samples carried the *TP53* p.R337H variant. Mascarenhas et al[47] analyzed 513 non–small-cell lung cancer tumor genomic profiles from a Brazilian lung cancer cohort and found the *TP53* p.R337H variant in the 4.3% of the samples.

All lung cancer samples carrying the *TP53* p.R337H variant were adenocarcinomas, from five male and three female patients. Most of the patients were affected after the age of 56 years (4 of 7). According to the first revision of Chompret criteria in 2009,[48] a proband with lung cancer < 46 years and at least one family member (first- or second-degree relatives) with a core LFS cancer is eligible for *TP53* germline testing. Only two patients of lung cancer (28.5%, 2 of 7) fulfilled the Chompret criteria.

Some publications have suggested an association between *EGFR*-mutated lung cancer and LFS.[19,45] The co-occurrence of *TP53* and *EGFR* pathogenic variants is reported in 19% of lung adenocarcinomas.[49] Barbosa et al[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.[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.

AFFILIATIONS

[1]Department of Oncology, Hospital Sírio-Libanês, Distrito Federal, Brazil
[2]Department of Molecular Oncology, Hospital Sírio-Libanês, São Paulo, Brazil
[3]Department of Pathology, Hospital Sírio-Libanês, São Paulo, Brazil
[4]Department of Oncology, Hospital Sírio-Libanês, São Paulo, Brazil

CORRESPONDING AUTHOR

Renata Lazari Sandoval, MD, Hospital Sírio-Libanês, Centro de Oncologia, Brasília, SGAS 613/614 Conjunto E Lote 95, Distrito Federal 70200-730, Brazil; e-mail: rsandoval.med@gmail.com.

AUTHOR CONTRIBUTIONS

Conception and design: Renata Lazari Sandoval, Cibele Masotti, Maurício Fernando Silva Almeida Ribeiro, Ana Carolina Rathsam Leite, Rodrigo Medeiros Bovolin, Rodrigo Ramella Munhoz, Denis Leonardo Fontes Jardim, Gustavo dos Santos Fernandes, Maria Isabel Achatz
Financial support: Anamaria Aranha Camargo
Administrative support: Rodrigo Medeiros Bovolin, Anamaria Aranha Camargo
Provision of study materials or patients: Rodrigo Medeiros Bovolin, Maria Isabel Achatz
Collection and assembly of data: Renata Lazari Sandoval, Cibele Masotti, Mariana Petaccia de Macedo, Maurício Fernando Silva Almeida Ribeiro, Ana Carolina Rathsam Leite, Sibele Inacio Meireles, Rodrigo Medeiros Bovolin, Rodrigo Ramella Munhoz, Gustavo dos Santos Fernandes
Data analysis and interpretation: Renata Lazari Sandoval, Cibele Masotti, Maurício Fernando Silva Almeida Ribeiro, Rodrigo Medeiros Bovolin, Fernando Costa Santini, Rodrigo Ramella Munhoz, Denis Leonardo Fontes Jardim, Artur Katz, Anamaria Aranha Camargo, Gustavo dos Santos Fernandes, Maria Isabel Achatz
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I =Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

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

Maurício Fernando Silva Almeida Ribeiro
Travel, Accommodations, Expenses: Foundation Medicine

Rodrigo Medeiros Bovolin
Stock and Other Ownership Interests : Abbott Laboratories (ABT), Johnson & Johnson (JNJ), Novo Nordisk A/S (NVO), Edwards Lifesciences (EW), Zoetis Inc (ZTS), Gilead Sciences (GILD), Varian Medical Systems Inc. (VAR), Varex Imaging Corporation (VREX)

Fernando Costa Santini
Honoraria: Merck Sharp & Dohme, Roche, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, Wyeth, Amgen
Consulting or Advisory Role: Merck Sharp & Dohme, Bristol Myers Squibb, AstraZeneca, Roche, Bayer, Lilly, Amgen
Speakers' Bureau: Roche, Merck Sharp & Dohme, AstraZeneca, Bayer
Travel, Accommodations, Expenses: Bayer, Merck Sharp & Dohme, Bristol Myers Squibb

Rodrigo Ramella Munhoz
Honoraria: Bristol Myers Squibb, MSD, Roche, Novartis, Sanofi, Merck Serono
Consulting or Advisory Role: Roche, Merck Serono, Sanofi, Bristol Myers Squibb
Speakers' Bureau: Bristol Myers Squibb, MSD, Novartis, Roche
Research Funding: Lilly, Roche, Bristol Myers Squibb, Novartis, MSD
Travel, Accommodations, Expenses: Bristol Myers Squibb, MSD, Roche, Sanofi

Denis Leonardo Fontes Jardim
Honoraria: Janssen-Cilag, Roche/Genentech, Astellas Pharma, MSD Oncology, BMS Brazil, Pfizer, Libbs, Merck
Consulting or Advisory Role: Janssen-Cilag, Pfizer, MSD
Travel, Accommodations, Expenses: MSD, BMS Brazil, Janssen-Cilag

Gustavo dos Santos Fernandes
Honoraria: Roche, MSD Oncology, Bayer
Research Funding: Roche, Memorial Sloan-Kettering Cancer Center, BMS Brazil
Travel, Accommodations, Expenses: Roche

Maria Isabel Achatz
Consulting or Advisory Role: Roche
Speakers' Bureau: AstraZeneca, MSD Oncology, Merck Sharpe & Dohme

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

We thank Dr Renata de Almeida Coudry for initiating the genomic profiling data at the Pathology Department of Hospital Sírio Libanês.

REFERENCES

1. Robson ME, Bradbury AR, Arun B, et al: American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol 33:3660-3667, 2015
2. Offit K, Tkachuk KA, Stadler ZK, et al: Cascading after peridiagnostic cancer genetic testing: An alternative to population-based screening. J Clin Oncol 38:1398-1408, 2020
3. Catenacci DV, Amico AL, Nielsen SM, et al: Tumor genome analysis includes germline genome: Are we ready for surprises? Int J Cancer 136:1559-1567, 2015
4. Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443-453, 2016
5. Meric-Bernstam F, Brusco L, Daniels M, et al: Incidental germline variants in 1000 advanced cancers on a prospective somatic genomic profiling protocol. Ann Oncol 27:795-800, 2016
6. Mandelker D, Zhang L, Kemel Y, et al: Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA 318:825-835, 2017 [Erratum: JAMA 320:2381, 2018]
7. Clark DF, Maxwell KN, Powers J, et al: Identification and confirmation of potentially actionable germline mutations in tumor-only genomic sequencing. JCO Precis Oncol 3:1-11, 2019
8. You YN, Borras E, Chang K, et al: Detection of pathogenic germline variants among patients with advanced colorectal cancer undergoing tumor genomic profiling for precision medicine. Dis Colon Rectum 62:429-437, 2019
9. Schrader KA, Cheng DT, Joseph V, et al: Germline variants in targeted tumor sequencing using matched normal DNA. JAMA Oncol 2:104-111, 2016 [Erratum JAMA Oncol 2:279, 2016]
10. Seifert BA, O'Daniel JM, Amin K, et al: Germline analysis from tumor-germline sequencing dyads to identify clinically actionable secondary findings. Clin Cancer Res 22:4087-4094, 2016
11. Jones S, Anagnostou V, Lytle K, et al: Personalized genomic analyses for cancer mutation discovery and interpretation. Sci Transl Med 7:283ra53, 2015
12. Parsons DW, Roy A, Yang Y, et al: Diagnostic yield of clinical tumor and germline whole-exome sequencing for children with solid tumors. JAMA Oncol 2:616-624, 2016
13. Mody RJ, Wu YM, Lonigro RJ, et al: Integrative clinical sequencing in the management of refractory or relapsed cancer in youth. JAMA 314:913-925, 2015
14. DeLeonardis K, Hogan L, Cannistra SA, et al: When should tumor genomic profiling prompt consideration of germline testing? JCO Oncol Pract 15:465-473, 2019
15. Achatz MI, Olivier M, Le Calvez F, et al: The TP53 mutation, R337H, is associated with Li-Fraumeni and Li-Fraumeni-like syndromes in Brazilian families. Cancer Lett 245:96-102, 2007
16. Garritano S, Gemignani F, Palmero EI, et al: Detailed haplotype analysis at the TP53 locus in p.R337H mutation carriers in the population of Southern Brazil: Evidence for a founder effect. Hum Mutat 31:143-150, 2010
17. Custódio G, Parise GA, Kiesel Filho N, et al: Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors. J Clin Oncol 31:2619-2626, 2013
18. Couto PP, Bastos-Rodrigues L, Schayek H, et al: Spectrum of germline mutations in smokers and non-smokers in Brazilian non-small-cell lung cancer (NSCLC) patients. Carcinogenesis 38:1112-1118, 2017
19. Barbosa MVR, Cordeiro de Lima VC, Formiga MN, et al: High prevalence of EGFR mutations in lung adenocarcinomas from Brazilian patients harboring the TP53 p.R337H variant. Clin Lung Cancer 21:e37-e44, 2020
20. Volc SM, Ramos CRN, Galvão HCR, et al: The Brazilian TP53 mutation (R337H) and sarcomas. PLoS One 15:e0227260, 2020
21. International Agency for Research on Cancer: http://www-p53.iarc.fr/germline.html
22. Bouaoun L, Sonkin D, Ardin M, et al: TP53 variations in human cancers: New lessons from the IARC TP53 database and genomics data. Hum Mutat 37:865-876, 2016
23. Precision Oncology Knowledge Base (OncoKB): https://oncokb.org/
24. Catalogue Of Somatic Mutations In Cancer: COSMIC v91. https://cancer.sanger.ac.uk/cosmic
25. Genome Aggregation Database: http://gnomad.broadinstitute.org/

26. Slavin TP, Banks KC, Chudova D, et al: Identification of incidental germline mutations in patients with advanced solid tumors who underwent cell-free circulating tumor DNA sequencing. J Clin Oncol 36:3459-3465, 2018
27. ACMG Board of Directors: ACMG policy statement: Updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. Genet Med 17:68-69, 2015
28. Raymond VM, Gray SW, Roychowdhury S, et al: Germline findings in tumor-only sequencing: Points to consider for clinicians and laboratories. J Natl Cancer Inst 108:djv351, 2015
29. Zhou R, Xu A, Gingold J, et al: Li-Fraumeni syndrome disease model: A platform to develop precision cancer therapy targeting Oncogenic p53. Trends Pharmacol Sci 38:908-927, 2017
30. Sameshima Y, Matsuno Y, Hirohashi S, et al: Alterations of the p53 gene are common and critical events for the maintenance of malignant phenotypes in small-cell lung carcinoma. Oncogene 7:451-457, 1992
31. Chiba I, Takahashi T, Nau MM, et al: Mutations in the p53 gene are frequent in primary, resected non-small cell lung cancer. Lung Cancer Study Group. Oncogene 5:1603-1610, 1990
32. Dhanasekaran R, Nault JC, Roberts LR, et al: Genomic medicine and implications for hepatocellular carcinoma prevention and therapy. Gastroenterology 156:492-509, 2019
33. Taubert H, Meye A, Würl P: Soft tissue sarcomas and p53 mutations. Mol Med 4:365-372, 1998
34. Zhang Y, Dube C, Gibert M Jr, et al: The p53 pathway in glioblastoma. Cancers (Basel) 10:297, 2018
35. Cancer Genome Atlas Research Network: Integrated genomic characterization of papillary thyroid carcinoma. Cell 159:676-690, 2014
36. Zehir A, Benayed R, Shah RH, et al: Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 23:703-713, 2017 [Erratum: Nat Med 23:1004, 2017]
37. Mermejo LM, Leal LF, Colli LM, et al: Altered expression of noncanonical Wnt pathway genes in paediatric and adult adrenocortical tumours. Clin Endocrinol (Oxf) 81:503-510, 2014
38. Hainaut P, Pfeifer GP: Somatic TP53 mutations in the era of genome sequencing. Cold Spring Harb Perspect Med 6:a026179, 2016
39. Petitjean A, Achatz MI, Borresen-Dale AL, et al: TP53 mutations in human cancers: Functional selection and impact on cancer prognosis and outcomes. Oncogene 26:2157-2165, 2007
40. Ognjanovic S, Olivier M, Bergemann TL, et al: Sarcomas in TP53 germline mutation carriers: A review of the IARC TP53 database. Cancer 118:1387-1396, 2012
41. Orr BA, Clay MR, Pinto EM, et al: An update on the central nervous system manifestations of Li-Fraumeni syndrome. Acta Neuropathol 139:669-687, 2020
42. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RG, et al: Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med 372:2481-2498, 2015
43. Bougeard G, Renaux-Petel M, Flaman JM, et al: Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 33:2345-2352, 2015
44. Formiga MNDC, de Andrade KC, Kowalski LP, et al: Frequency of thyroid carcinoma in Brazilian TP53 p.R337H carriers with Li Fraumeni syndrome. JAMA Oncol 3:1400-1402, 2017
45. Ricordel C, Labalette-Tiercin M, Lespagnol A, et al: EFGR-mutant lung adenocarcinoma and Li-Fraumeni syndrome: Report of two cases and review of the literature. Lung Cancer 87:80-84, 2015
46. Caron O, Frebourg T, Benusiglio PR, et al: Lung adenocarcinoma as part of the Li-fraumeni syndrome spectrum: Preliminary data of the LIFSCREEN randomized clinical trial. JAMA Oncol 3:1736-1737, 2017
47. Mascarenhas E, Gelatti AC, Araújo LH, et al: Comprehensive genomic profiling of Brazilian non-small cell lung cancer patients (GBOT 0118/LACOG0418). Thorac Cancer 12:580-587, 2021 Mar
48. Tinat J, Bougeard G, Baert-Desurmont S, et al: 2009 version of the Chompret criteria for Li Fraumeni syndrome. J Clin Oncol 27:e108-e110, 2009
49. Kosaka T, Yatabe Y, Endoh H, et al: Mutations of the epidermal growth factor receptor gene in lung cancer: Biological and clinical implications. Cancer Res 64:8919-8923, 2004

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	*VHL* P81S, *TP53* R337H, *KEL* splice site 924+1G>T, *MUTYH* G382D, and *RB1* Q395* MS 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	*RB1* D566fs*45 and *TP53* R337H MS not informed TMB not informed	89.0	NA	NA	NA	NA
3	M	D	Lung	Adenocarcinoma	33	N	*ERBB2* P780_Y781insGSP, *NF1* rearrangement intron 24, *BCL2L2* amplification, *KMT2C* (*MLL3*) C310*, *NKX2-1* amplification, and *TP53* R337H MS 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 great 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 MS 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 MS 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, *IDH*-WT, and no *ATRX* or *TERT* mutations MS 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 MS 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)

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
8	M	A	STS	Leiomyosarcoma	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, *FGF3* amplification, *FGF4* amplification, *TERT* promoter-124C>T, and *TP53* R337H MS stable TMB low	85.8	Y	No	NA	None
10	M	A	STS	Leiomyosarcoma	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–breast cancer (65 years), paternal aunt–gastrointestinal cancer (80 years), paternal aunt–gastrointestinal cancer (55 years), paternal cousin–breast cancer (40 years), paternal aunt–gastrointestinal cancer (80 years), and paternal cousin–gastrointestinal 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), paternal uncle–unknown cancer, paternal uncle–gastrointestinal cancer (55 years), paternal aunt–liver cancer (70 years), paternal aunt–breast cancer (65 years), paternal aunt–breast cancer (44 years), paternal cousin–multiple myeloma (51 years), and paternal grandfather–renal cancer (70 years)	Y	Gastric cancer (57 years)
12	F	A	Lung	Adenocarcinoma	60	N	*CDKN2A* c.247C>T p.His83Tyr, *EGFR* c.2156G>C p.Gly719Ala, and *TP53* R337H MS not informed TMB not informed *EGFR*-positive *ALK*-negative PD-L1–negative	62.8	Y	Sister–breast and esophageal cancer (>50 years), grandnephew–adrenocortical 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/D770_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.

