original reports

Pediatric Somatic Tumor Sequencing Identifies Underlying Cancer Predisposition

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abstract

PURPOSE The diagnosis of cancer predisposition in pediatric patients with cancer is vital for treatment decisions, surveillance, and management of at-risk family members. Somatic tumor testing can identify potential underlying constitutional variants that confer increased cancer risk. Here, we report the characteristics of constitutional variants identified through tumor testing.

MATERIALS AND METHODS Data were abstracted from medical record review of 1,023 patients who received in-house somatic tumor testing over a 28-month period. Patients were identified for testing using referral criteria developed as a collaboration between genomic diagnostics, pathology, and oncology. Characteristics of patients who underwent constitutional testing, including family history and variant loss of heterozygosity, were tracked.

RESULTS From 1,023 patients who underwent somatic tumor sequencing in a 28-month period, 210 variants were identified in 141 patients (13.8%) that were concerning for cancer predisposition syndromes requiring intervention. A total of 73 variants in 41 patients have undergone clinical confirmatory testing thus far. Of these, 26 variants were confirmed to be constitutionally present (35.6%). Among patients tested, 23 (56.1%) of 41 total patients were diagnosed with a cancer predisposition syndrome.

CONCLUSION Our data demonstrate that more than one third of variants in tumor somatic sequencing that were concerning for underlying cancer predisposition were constitutionally confirmed. Overall, somatic tumor testing identified potential cancer predisposition syndromes in pediatric patients, and some would not have been identified on the basis of clinical history alone.

INTRODUCTION

The incidence of constitutional genetic aberrations leading to cancer predisposition in pediatric patients with cancer is estimated at 8% to 12%.[1-4] Results from large somatic sequencing studies confirm that this rate of constitutional aberrations can be inferred from somatic sequencing results.[5,6] The timely diagnosis of a cancer predisposition syndrome can have significant implications not only for the patient, but also for affected and unaffected family members. Follow-up of any features of a cancer predisposition syndrome is essential for appropriate management, surveillance, and family planning for these individuals.

Clinical and historical features that suggest a pediatric patient with cancer may have a predisposition syndrome include a family history of the same cancer or related cancers, clinical features of a predisposition syndrome, bilateral/multifocal primary cancer or multiple cancers, certain types of cancer that rarely occur except in a predisposed patient, and a much earlier than expected age at diagnosis. Indeed, certain tumors should lead to referral for constitutional testing in all cases,[7] and referral criteria that are based on family history of cancer in first- and second-degree relatives have been established.[1,8,9] Specific recommendations to test for a constitutional mutation in certain cancer types and/or predisposition syndromes, such as retinoblastoma, neuroblastoma, and Li-Fraumeni syndrome (LFS), also exist.[10-12] Studies have shown, however, that clinical features and family history alone are not reliable predictors of underlying constitutional mutations leading to cancer predisposition syndromes.[2,3] Furthermore, suspicion of cancer predisposition on the basis of genomic findings within the tumor has been shown to be a more powerful tool in uncovering potential constitutional change than tumor type and clinical history, and pediatric patients with cancer may have constitutional mutations in cancer predisposition genes in the absence of known risk factors.[3]

Somatic genetic testing of tumor tissue is used increasingly in the evaluation of children and adolescents with cancer for diagnosis, risk stratification, and

ASSOCIATED CONTENT

Appendix

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

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CONTEXT

Key Objective

When a child is diagnosed with cancer, most families are uncertain why their child developed a rare and devastating disease. For an important minority, an underlying cancer predisposition syndrome as a result of a constitutional pathogenic variant may underlie malignancy; however, these can be difficult to identify in patients who lack syndromic features and/or a family history of cancer.

Knowledge Generated

This study demonstrates that pathogenic variants identified through somatic next-generation sequencing can indicate the presence of a constitutional cancer-predisposing variant. In a cohort of more than 1,000 pediatric patients with cancer who underwent somatic panel sequencing, nearly 14% had findings requiring referral for constitutional testing. Of those who underwent testing, more than one half were diagnosed with a cancer predisposition syndrome, some of whom would not have been identified on the basis of clinical history alone.

Relevance

In conducting somatic tumor sequencing, it is necessary to carefully evaluate for indicators of constitutional cancer predisposition syndromes.

treatment decisions.[13] Results of tumor sequencing can suggest the presence of an underlying cancer predisposition syndrome through a variety of indicators, including a variant allele fraction (VAF) of 0.4 to 1.0 or identification of pathogenic or founder mutations in known cancer predisposition genes. As tumor sequencing becomes more common and comprehensive, it is important for both patients and family members that appropriate measures are in place for genetic counseling and subsequent constitutional testing. In this report, we describe our experience in conducting cancer predisposition evaluation on the basis of somatic sequencing findings in cancer samples identified using in-house next-generation sequencing testing panels. Appropriate referral is vital not only for conducting constitutional genetic testing, but also for identifying other at-risk family members.

MATERIALS AND METHODS

Data were abstracted from the medical records of all patients who underwent in-house somatic tumor genetic testing using multigene panels over a 28-month period. Potential constitutional likely pathogenic and pathogenic variants were identified during clinical analysis of somatic panels offered through the Children's Hospital of Philadelphia Genomic Diagnostics Laboratory. These targeted panels provided comprehensive analysis of hematologic and solid tumors for fusion genes, single-nucleotide variants, insertion/deletion variants, and copy number variants for 117 to 238 genes[13,14] (Appendix Table A1). These panels are performed on the majority of diagnostic samples obtained from Children's Hospital of Philadelphia pediatric patients with cancer at initial diagnosis or relapse. Of note, retinoblastoma tumors are not routinely tested via this mechanism.

Variants were identified for potential follow-up constitutional testing if they met any of the following criteria: pathogenic or likely pathogenic variants in genes known to be associated with cancer predisposition[15] with VAF between 0.4 and 1.0; large indels or exonic deletions/duplications in genes known to be associated with cancer predisposition regardless of VAF; and/or suspected constitutional pathogenic variants regardless of VAF if the variant was a known founder mutation, or if clinical features, such as tumor type, suggested constitutional predisposition related to the involved variant. These reasons for referral were divided into the following categories: VAF, Clinical Concern/Tumor Type, and Known Founder. The panels also provided copy number variation and loss of heterozygosity information that aided in the interpretation of the VAF for a given variant. Once identified in tumor tissue, the potential for suspicious variants to be of constitutional origin was described in the somatic tumor report issued to the ordering physician, usually an oncologist.

These suspected constitutional variants were tagged by the Genomic Diagnostics Laboratory for referral to the Cancer Predisposition Program (CPP). The CPP and ordering physician then discussed the need for cancer predisposition consultation, and pretest genetic counseling was arranged via the CPP as appropriate. If patients chose to pursue constitutional testing, targeted Sanger sequencing analysis or other appropriate genomic testing was performed using a constitutional—nontumor—sample, either blood or skin fibroblasts. Results were reported back to the CPP, which then contacted the patient or parents, and post-test genetic counseling was offered. Constitutional results were also reported to and reviewed with the oncologist. Somatic panel testing was not used as a substitute for clinical judgment, and a patient with concerning features of cancer predisposition would always be referred to the CPP regardless of somatic panel results. Clinical features and family history were abstracted from charts when

available, but a complete family history review was not conducted by an oncologist, geneticist, or genetic counselor for patients not seen by the CPP. Factors included in the analysis of patients seen by the CPP included family history of cancer, presence of multifocal or bilateral disease, loss of heterozygosity in the tumor, and clinical features of diagnosis, such as clinical diagnostic criteria for neurofibromatosis type 1 (NF1) or tuberous sclerosis, in addition to the aforementioned referral criteria. Tumor type association with the presence of a constitutional variant—for example, rhabdoid tumor and *SMARCB1* pathogenic variant—was also tracked.[7] Data also included age at diagnosis and turnaround time of constitutional testing (days between the result report of somatic testing and the date of constitutional testing). As detailed in Results, some variants had been previously constitutionally confirmed, and some were confirmed on the basis of clinical features alone and did not have testing completed. Neither were included in the statistical analysis. Constitutional testing was listed as incomplete in all cases in which the CPP did not meet with the family to discuss the variant, even if testing may not ultimately have been suggested. Finally, results were deemed conclusive when the genetic testing was interpretable and inconclusive when additional sample would be required to make a definitive diagnosis.

Data were analyzed using STATA and R statistical programming languages, and statistical significance was determined using Wilcoxon rank-sum test and χ^2 test, when appropriate. Visualizations were generated using the ggplot2 package.[16]

The human investigations performed in this study were completed after approval by the Children's Hospital of Philadelphia Institutional Review Board and in accordance with the requirements of the Department of Health and Human Services, where appropriate.

RESULTS

Population Demographics

Records were reviewed for 1,023 patients who underwent somatic panel testing between February 2016 and June 2018. A total of 210 somatic variants in 141 patients were suspected to be constitutional pathogenic or likely pathogenic variants, which is 13.8% of patients who underwent somatic panel testing during this time period. Of 141 patients, 51 had CNS tumors, 63 had non-CNS solid tumors, and 27 had leukemia or lymphoma. Demographic features of these patients are listed in Table 1. VAF met criteria for referral (≥ 0.4) in 78% of cases (n = 164), including those with copy number variant in a potential cancer predisposition gene. The remainder of variants were referred for the presence of a founder mutation (2.9%; n = 6) or a tumor type–specific variant concerning for cancer predisposition (55.2%; n = 116), and some patients were referred for multiple reasons. VAF in all cases ranged from 0.05 to 0.98 (Table 2).

TABLE 1. Demographics

Demographic	CNS (n = 51)	Solid (n = 63)	Hematologic (n = 27)	Total (N = 141)
Age, years, mean	8	10	9	
Sex				
Female	25	40	15	80
Male	26	23	12	61
Race/ethnicity				
White	32	42	9	83
Black	5	5	2	12
Hispanic/Latino	5	4	3	12
Other	9	12	13	34
Primary *v* relapse				
Primary	44	57	14	115
Relapse/recurrent	7	6	13	26

Somatic Findings in Predisposition Genes

A total of 210 variants were identified in a total of 66 genes. A heatmap of genes with a suspected constitutional variant identified in 2 or more individuals is shown in Figure 1 (full variant list, including tumor type, in Appendix Table A2). As expected, potential constitutional variants were most frequently identified in the *TP53* gene, occurring in 35% of individuals referred (n = 46). The second most frequent gene with potential constitutional variants was *NF1* (17%; n = 27, including 6 individuals with an identified *TP53* variant), followed by *SMARCB1, MUTYH, APC, ATM, MSH6, WT1,* and *DICER1.* Founder mutations were identified in 6 patients—for example, 4 of the 7 variants identified in *APC* were I1307K, a known founder risk allele in the Ashkenazi Jewish population that does not lead to familial adenomatous polyposis, but confers increased cancer risk in adulthood.[17] Some variants identified had implications for immediate treatment decisions, such as *TP53* variants that were identified in patients with anticipated radiation therapy, and an attempt was made to prioritize these patients for testing and counseling. Other individuals required the initiation of childhood screening for other tumors—for example,

TABLE 2. Variant Allele Frequency Distribution

VAF	Frequency, No.	%
0.05-0.19	14	6.6
0.2-0.39	33	15.6
0.4-0.59	118	55.9
0.6-0.79	12	5.7
0.79-0.98	34	16.1

NOTE. All percentages calculated out of total variants identified (n = 210).

Abbreviation: VAF, variant allele frequency.

FIG 1. Somatic findings. Frequency of concerning somatic variants identified, as described by frequency, tumor type (liquid, non-CNS solid, and CNS), primary versus relapsed/refractory specimen, and specific cancer diagnosis. Not included are variants occurring in fewer than 2 individuals (Appendix Table A1). AML, acute myeloblastic leukemia; AT/RT, atypical teratoid/rhabdoid tumor; B-ALL, B-acute lymphoblastic leukemia; DNET, dysembryoplastic neuroepithelial tumor; GIST, GI stromal tumor; JMML, juvenile myelomonocytic leukemia; MPNST, malignant peripheral nerve sheath tumor; T-ALL, T-acute lymphoblastic leukemia.

DICER1, WT1, 11p loss/aberrations, and non-I1307K *APC* variants—and in these cases screening was initiated during ongoing cancer treatment after a constitutional diagnosis was made.

Of note, several heterozygous variants identified had implications for adult cancer risk, but did not change management in the pediatric age range (*MSH6, MUTYH, ATM, BRCA1,* and *BRCA2*). These were still referred for genetic counseling, as they could have implications for family members and for the individual patient later in life. Testing decisions on these variants were made on a case-by-case basis, in discussion with the family and the oncologist, and in most cases, it was recommended that constitutional testing of the proband be deferred until age 18 years or older. Occasionally in adolescent patients, the patient preferred to complete testing.

Constitutional Testing

A total of 210 variants were determined to warrant follow-up for potential constitutional alterations on the basis of initial somatic panel review (Fig 2; Appendix Table A2). At the time of this study, no individuals were found to have a constitutional variant that was not indicated on panel testing.

Previously tested. A total of 10 patients with 11 variants had undergone testing previously on the basis of clinical suggestion of a cancer predisposition syndrome before somatic sequencing. Of the variants previously tested, eight were

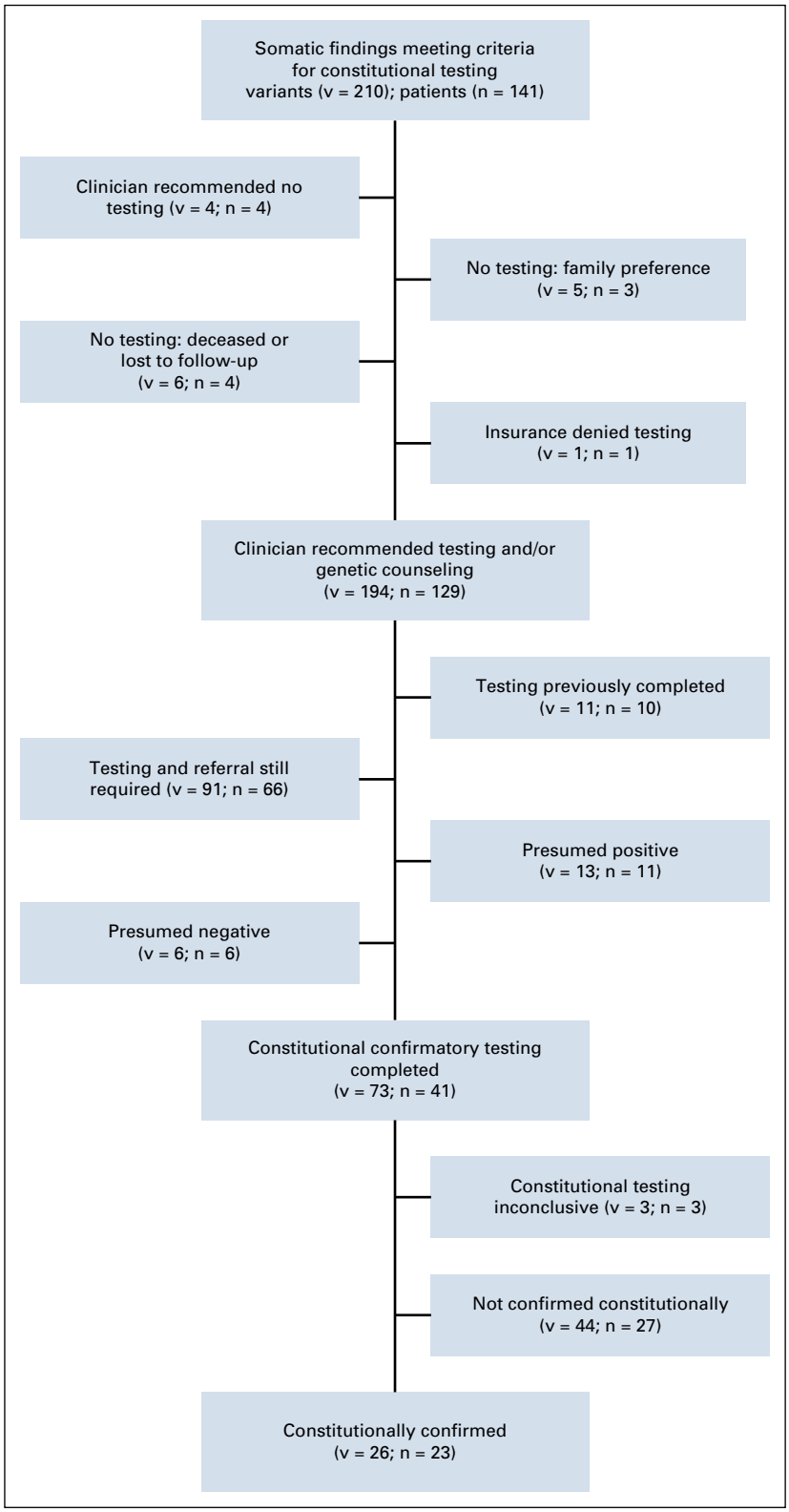

FIG 2. Schematic representation of patients referred for constitutional testing. Includes patients who did not have testing performed for clinical reasons, patients who still require referral and genetic testing, and results of testing for the patients for whom testing was conducted. Patients were presumed positive if they met clinical criteria for a diagnosis without the need for genetic testing, and were presumed negative when they did not meet clinical criteria for a diagnosis. In all cases, the individual was evaluated clinically.

constitutionally present and three were somatic only. These were not included in the analysis of characteristics of tested patients done below, as these patients had already been seen and/or were being observed by the CPP and thus were identified before somatic testing.

Constitutional testing completed. Of 38 patients with constitutional testing that led to conclusive results, at least one potentially predisposing variant identified in tumor tissue was confirmed to be constitutional in 23 patients (60.5%) and in 26 total variants of 73 variants tested (35.6%; Fig 2).

TP53 was the most frequently identified mutated gene by the laboratory referral pipeline. Of 21 cases in which constitutional *TP53* testing was performed, the variant was constitutionally identified in 6 cases (28.6%). Of these individuals, three would not have otherwise been referred for LFS testing. Of the total number of patients with a somatic *TP53* variant (n = 46), 19.6% were constitutionally affected (n = 9; includes those patients who previously tested positive). A full list of variants tested is included in Appendix Table A2.

A total of 3 variants in 3 individuals had inconclusive testing. In these cases, the sample was either contaminated with leukemia cells or the constitutional material obtained was insufficient. In all three cases, the patient died before the completion of additional testing.

In some cases, the finding was presumed positive without genetic testing. In 13 variants in 11 individuals, the finding was presumed positive. This was based on known familial mutations in *APC* I1307L (n = 2), *BRCA1* (n = 1), and *BRCA2* (n = 1), or on the basis of an existing clinical diagnosis in seven NF1 patients already being observed by the neurofibromatosis clinic. In six variants in five individuals, testing was presumed negative, as individuals did not meet criteria for a syndrome that was not present clinically. This included NF1 (n = 4), tuberous sclerosis (n = 1), and Kabuki syndrome (n = 1). These patients were clinically evaluated before this determination and the variant was discussed with the family. In these cases, variants were not included in the tested category in subsequent analyses; however, it is important to note that constitutional testing is not always required to confirm or rule out a diagnosis. In all cases, somatic mosaicism was considered and discussed with family when appropriate.

Testing not completed. In some cases, constitutional testing was not performed after discussion with the family, per family preference and/or clinician recommendation. Constitutional testing was deferred in a total of 4 variants associated with adult-onset cancer risk until adulthood after discussion with family and review of family history (*APC* I1307L [n = 2], *BLM* [n = 1], *MUTYH* [n = 1]). This would likely be the recommendation for other somatic variants in adult-onset predisposition syndromes included in the genetic testing not done category; however, genetic counseling and family history review need to take place before constitutional testing is deferred completely. A total of 8 families—8 patients and 12 variants—preferred not to pursue constitutional testing, in one case because of a lack of insurance approval for testing.

Referral Still Required

Finally, a large number of patients—66 patients and 91 variants—still require referral to the CPP before constitutional testing can be completed. Our program is actively working to ensure that all families with a concerning somatic variant receive appropriate genetic counseling.

Characteristics of Tested Patients

Historically, the suspicion for constitutional cancer predisposition is based on clinical characteristics, including family history, physical features of a predisposition syndrome, presence of bilateral/multifocal disease, and/or a specific tumor type strongly associated with a predisposition syndrome. Characteristics of patients who were either confirmed or not confirmed constitutionally are included in Table 3. Using a cutoff of $\alpha = .05$, patients who were identified to have an underlying tumor predisposition were younger (mean age, 6.15 years *v* 10.77 years; $P = .0062$). Testing turnaround time was not significantly faster in patients with an underlying predisposition (83 days *v* 108 days; $P = .488$). Patients with a concerning family history or bilateral or multifocal disease were more likely to have the variant confirmed constitutionally ($P = .048$ and .017, respectively; bilateral disease was present in three individuals with atypical teratoid/rhabdoid tumor and a *SMARCB1* deletion and in one patient with a *BARD1* mutation and a composite pheochromocytoma and neuroblastoma). Tumor type and variant association, such as rhabdoid tumor and *SMARCB1* variant, was not predictive, with a near even frequency of being constitutional or not ($P = .964$). There was no significant difference between those confirmed and not confirmed in VAF ≥ 0.4 or in tumor loss of heterozygosity.

DISCUSSION

Somatic Findings Concerning for Cancer Predisposition

Of the more than 1,000 children, adolescents, and young adults who underwent somatic tumor testing in the 28 months included within this study period, 13.9% had somatic results that were concerning for a constitutional cancer predisposition. Of note, this does not include tumor types that routinely do not undergo somatic testing at our institution—retinoblastoma or Hodgkin lymphoma—or for

TABLE 3. Characteristics of All Patients Who Underwent Clinical Testing

Characteristic	Confirmed (n = 26)	Not Confirmed (n = 44)	*P*
Mean age at diagnosis, years	6.15	10.77	.0062
Mean turnaround time, days	83.03	107.55	.488
Positive family history, No. (%)	7 (26.92)	4 (9.09)	.048
Bilateral disease, No. (%)	4 (15.38)	0 (0.00)	.017
Tumor type concerning for predisposition, No. (%)	17 (65.38)	29 (65.91)	.964
VAF ≥ 0.4, No. (%)	21 (80.77)	34 (77.27)	.73
Loss of heterozygosity in tumor, No. (%)	16 (61.54)	31 (70.45)	.443

Abbreviation: VAF, variant allele frequency.

which tissue was not available and thus is not a comprehensive evaluation of all patients with cancer at our institution. Referrals were made in most cases for variants with VAF $>$ 0.4, although in 22.2% of variants VAF was lower than this threshold, and clinical suspicion based on the specific variant prompted CPP referral.

As expected, given the frequency of both constitutional and somatic mutations,[2,18] *TP53* was the most frequently mutated gene that prompted referral to the CPP. Of the 21 patients with a *TP53* mutation in tumor tissue who were referred for testing, 6 (28.6%) were diagnosed with LFS on the basis of a constitutional finding of a known *TP53* pathogenic/likely pathogenic variant, three of whom would not have been referred based on accepted LFS testing guidelines.[15,19] Even including all somatic variants, at least 19.6% of patients with somatic LFS variants are constitutionally affected, a proportion higher than that observed in the adult population. All of these patients are now being observed by the CPP and are receiving recommended surveillance.[20] The next most frequent mutation found was in *NF1*, but decisions about constitutional testing were sometimes made on the basis of the presence or absence of characteristic clinical features of NF1. These patients were all referred to our multidisciplinary neurofibromatosis clinic and observed there if clinical features of NF1 were present, and constitutional testing was not conducted routinely. For other variants, patients were tested and recommendations were made in accordance with accepted practices, when available (Appendix Table A2). Of note, for some variants clinical guidelines are not yet established, and in these cases families received genetic counseling regarding the lack of accepted tumor surveillance practices and/or additional study needed regarding the constitutional presence of a variant. In cases in which constitutional testing would not affect clinical management—for example, no additional childhood surveillance would be required—families were informed of the result and adult relatives were counseled that they could consider testing for themselves, but testing was usually not sent for the child. Finally, a discussion of somatic mosaicism occurred in the setting of inconclusive or negative results, or in cases in which families decided not to pursue genetic testing because of lack of clinical features of a disorder.

Additional study is required to analyze the power of somatic panel testing to identify pediatric patients with constitutional cancer predisposition, with and without the incorporation of clinical data, such as multifocality, tumor type, syndromic features, and family history. In addition, many patients have not yet been referred to the CPP to discuss constitutional testing, and qualitative review would suggest a variety of reasons for this, including emotional stress on the family at the time of cancer diagnosis and the additional stress of predisposition evaluation during treatment, although this has not been systematically studied at our institution. We plan to continue offering genetic testing and counseling to patients not yet referred to ensure an eventual 100% referral rate.

Interpretation of Somatic Results Concerning for Cancer Predisposition

The most significant differences in those constitutionally confirmed were known clinical risk factors, namely, a significant/concerning family history of cancer and bilateral or multifocal disease. In fact, all bilateral/multifocal tumors were associated with underlying cancer predisposition. Of interest, tumor type, VAF, and loss of heterozygosity (LOH) were not significant indicators of the constitutional presence of a variant. This suggests that VAF and LOH alone are not sufficient to rule out a cancer predisposition syndrome. Although it may seem surprising that tumor type was not predictive, this is consistent with the known prevalence of a cancer predisposition syndrome in these tumor types. Thus, clinical predictors of cancer predisposition remain important in the interpretation of somatic results.

More than one half of patients who received constitutional testing were found to have an underlying cancer predisposition syndrome, often requiring changes in treatment plan, ongoing surveillance, and familial testing. Some of these patients could have been referred for testing on the basis of patient age, type of cancer, and/or family history of cancer; however, others would not have been suspected as a result of a lack of these features. Thus, the incorporation of somatic testing results proves to be an important supplement to clinical judgment in identifying cancer predisposition syndromes.

In conclusion, somatic tumor sequencing is a powerful tool in pediatric cancer to risk-stratify patients and identify appropriate therapy, and its use is becoming increasingly widespread. This testing can also lead to the identification of variants that raise concern for an underlying constitutional cancer predisposition. Identification of these variants is vital for the treatment and ongoing tumor surveillance for both patients and family members. Collaboration between the genomic diagnostics laboratory, pathology, and oncology can assist in identifying and coordinating appropriate testing for cancer predisposition.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Somatic Cancer Panels

Comprehensive Hematologic Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
ABL1	ABL proto-oncogene 1, nonreceptor tyrosine kinase	HGNC:76
ASXL1	Additional sex combs-like 1, transcriptional regulator	HGNC:18318
ASXL2	Additional sex combs-like 2, transcriptional regulator	HGNC:23805
ATRX	ATRX, chromatin remodeler	HGNC:886
BCL11B	B-cell CLL/lymphoma 11B	HGNC:13222
BCL6	B-cell CLL/lymphoma 6	HGNC:1001
BCOR	BCL6 corepressor	HGNC:20893
BCORL1	BCL6 corepressor like 1	HGNC:25657
BRAF	B-Raf proto-oncogene, serine/threonine kinase	HGNC:1097
BRINP3	BMP/retinoic acid inducible neural specific 3	HGNC:22393
CALR	Calreticulin	HGNC:1455
CBL	Cbl proto-oncogene	HGNC:1541
CCND3	Cyclin D3	HGNC:1585
CD79A	CD79a molecule	HGNC:1698
CD79B	CD79b molecule	HGNC:1699
CDC25C	Cell division cycle 25C	HGNC:1727
CDKN2A	Cyclin-dependent kinase inhibitor 2A	HGNC:1787
CDKN2B	Cyclin-dependent kinase inhibitor 2B	HGNC:1788
CEBPA	CCAAT/enhancer binding protein alpha	HGNC:1833
CREBBP	CREB binding protein	HGNC:2348
CRLF2	Cytokine receptor-like factor 2	HGNC:14281
CSF1R	Colony-stimulating factor 1 receptor	HGNC:2433
CSF3R	Colony-stimulating factor 3 receptor	HGNC:2439
CTCF	CCCTC-binding factor	HGNC:13723
DDX41	DEAD-box helicase 41	HGNC:18674
DNM2	Dynamin 2	HGNC:2974
DNMT1	DNA methyltransferase 1	HGNC:2976
DNMT3A	DNA methyltransferase 3 alpha	HGNC:2978
DOT1L	DOT1-like histone lysine methyltransferase	HGNC:24948
EBF1	Early B-cell factor 1	HGNC:3126
EED	Embryonic ectoderm development	HGNC:3188
ELANE	Elastase, neutrophil expressed	HGNC:3309
EP300	E1A binding protein p300	HGNC:3373
EPOR	Erythropoietin receptor	HGNC:3416
ERG	ERG, ETS transcription factor	HGNC:3446
ESR1	Estrogen receptor 1	HGNC:3467
ETNK1	Ethanolamine kinase 1	HGNC:24649
ETS1	ETS proto-oncogene 1, transcription factor	HGNC:3488
ETV6	ETS variant 6	HGNC:3495
EZH2	Enhancer of zeste 2 polycomb repressive complex 2 subunit	HGNC:3527

(Continued on following page)

TABLE A1. Somatic Cancer Panels (Continued)

Comprehensive Hematologic Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
FBXW7	F-box and WD repeat domain containing 7	HGNC:16712
FLT3	Fms related tyrosine kinase 3	HGNC:3765
GATA1	GATA binding protein 1	HGNC:4170
GATA2	GATA binding protein 2	HGNC:4171
GATA3	GATA binding protein 3	HGNC:4172
HNRNPK	Heterogeneous nuclear ribonucleoprotein K	HGNC:5044
HRAS	HRas proto-oncogene, GTPase	HGNC:5173
IDH1	Isocitrate dehydrogenase [NADP(+)]) 1, cytosolic	HGNC:5382
IDH2	Isocitrate dehydrogenase [NADP(+)] 2, mitochondrial	HGNC:5383
IKZF1	IKAROS family zinc finger 1	HGNC:13176
IKZF3	IKAROS family zinc finger 3	HGNC:13178
IL7R	Interleukin 7 receptor	HGNC:6024
JAK1	Janus kinase 1	HGNC:6190
JAK2	Janus kinase 2	HGNC:6192
JAK3	Janus kinase 3	HGNC:6193
KDM6A	Lysine demethylase 6A	HGNC:12637
KIT	KIT proto-oncogene receptor tyrosine kinase	HGNC:6342
KMT2A	Lysine methyltransferase 2A	HGNC:7132
KMT2C	Lysine methyltransferase 2C	HGNC:13726
KMT2D	Lysine methyltransferase 2D	HGNC:7133
KRAS	KRAS proto-oncogene, GTPase	HGNC:6407
LEF1	Lymphoid enhancer binding factor 1	HGNC:6551
LYL1	LYL1, basic helix-loop-helix family member	HGNC:6734
MAP2K1	Mitogen-activated protein kinase kinase 1	HGNC:6840
MPL	MPL proto-oncogene, thrombopoietin receptor	HGNC:7217
MSH2	MutS homolog 2	HGNC:7325
MSH6	MutS homolog 6	HGNC:7329
MYB	MYB proto-oncogene, transcription factor	HGNC:7545
MYD88	Myeloid differentiation primary response 88	HGNC:7562
NF1	Neurofibromin 1	HGNC:7765
NOTCH1	Notch 1	HGNC:7881
NPM1	Nucleophosmin 1	HGNC:7910
NRAS	NRAS proto-oncogene, GTPase	HGNC:7989
NSD1	Nuclear receptor binding SET domain protein 1	HGNC:14234
NSD2	Nuclear receptor binding SET domain protein 2	HGNC:12766
NT5C2	5′-nucleotidase, cytosolic II	HGNC:8022
PAX5	Paired box 5	HGNC:8619
PDGFRA	Platelet-derived growth factor receptor alpha	HGNC:8803
PHF6	PHD finger protein 6	HGNC:18145
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1	HGNC:8979
PRPF40B	PremRNA processing factor 40 homolog B	HGNC:25031
PRPF8	PremRNA processing factor 8	HGNC:17340
PTEN	Phosphatase and tensin homolog	HGNC:9588

(Continued on following page)

TABLE A1. Somatic Cancer Panels (Continued)

Comprehensive Hematologic Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
PTPN11	Protein tyrosine phosphatase, nonreceptor type 11	HGNC:9644
RAD21	RAD21 cohesin complex component	HGNC:9811
RB1	RB transcriptional corepressor 1	HGNC:9884
RELN	Reelin	HGNC:9957
RPL10	Ribosomal protein L10	HGNC:10298
RTEL1	Regulator of telomere elongation helicase 1	HGNC:15888
RUNX1	Runt-related transcription factor 1	HGNC:10471
SETBP1	SET binding protein 1	HGNC:15573
SETD2	SET domain containing 2	HGNC:18420
SF1	Splicing factor 1	HGNC:12950
SF3A1	Splicing factor 3a subunit 1	HGNC:10765
SF3B1	Splicing factor 3b subunit 1	HGNC:10768
SH2B3	SH2B adaptor protein 3	HGNC:29605
SMC1A	Structural maintenance of chromosomes 1A	HGNC:11111
SMC3	Structural maintenance of chromosomes 3	HGNC:2468
SRSF2	Serine and arginine rich splicing factor 2	HGNC:10783
STAG2	Stromal antigen 2	HGNC:11355
STAT3	Signal transducer and activator of transcription 3	HGNC:11364
SUZ12	SUZ12 polycomb repressive complex 2 subunit	HGNC:17101
TAL1	TAL bHLH transcription factor 1, erythroid differentiation factor	HGNC:11556
TCF3	Transcription factor 3	HGNC:11633
TERT	Telomerase reverse transcription	HGNC:11730
TET2	Tet methylcytosine dioxygenase 2	HGNC:25941
TINF2	TERF1 interacting nuclear factor 2	HGNC:11824
TLX1	T-cell leukemia homeobox 1	HGNC:5056
TLX3	T-cell leukemia homeobox 3	HGNC:13532
TP53	Tumor protein p53	HGNC:11998
U2AF1	U2 small nuclear RNA auxiliary factor 1	HGNC:12453
U2AF2	U2 small nuclear RNA auxiliary factor 2	HGNC:23156
UBA2	Ubiquitin-like modifier activating enzyme 2	HGNC:30661
USH2A	Usherin	HGNC:12601
USP7	Ubiquitin-specific peptidase 7	HGNC:12630
WT1	Wilms tumor 1	HGNC:12796
ZRSR2	Cinc finger CCCH-type, RNA binding motif and serine/arginine rich 2	HGNC:23019

Comprehensive Solid Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
ABL1	ABL proto-oncogene 1, nonreceptor tyrosine kinase	HGNC:76
ACVR1	Activin A receptor type 1	HGNC:171
AKT1	AKT serine/threonine kinase 1	HGNC:391
AKT2	AKT serine/threonine kinase 2	HGNC:392
AKT3	AKT serine/threonine kinase 3	HGNC:393
ALK	ALK receptor tyrosine kinase	HGNC:427
AMER1	APC membrane recruitment protein 1	HGNC:26837

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TABLE A1. Somatic Cancer Panels (Continued)

Comprehensive Hematologic Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
APC	APC, WNT signaling pathway regulator	HGNC:583
AR	Androgen receptor	HGNC:644
ARAF	A-Raf proto-oncogene, serine/threonine kinase	HGNC:646
ARID1A	AT-rich interaction domain 1A	HGNC:11110
ARID1B	AT-rich interaction domain 1B	HGNC:18040
ARID2	AT-rich interaction domain 2	HGNC:18037
ASXL1	Additional sex combs-like 1, transcriptional regulator	HGNC:18318
ATM	ATM serine/threonine kinase	HGNC:795
ATR	ATR serine/threonine kinase	HGNC:882
ATRX	ATRX, chromatin remodeler	HGNC:886
AURKA	Aurora kinase A	HGNC:11393
AURKB	Aurora kinase B	HGNC:11390
AXIN1	Axin 1	HGNC:903
AXL	AXL receptor tyrosine kinase	HGNC:905
B2M	Beta-2-microglobulin	HGNC:914
BAP1	BRCA1 associated protein 1	HGNC:950
BARD1	BRCA1 associated RING domain 1	HGNC:952
BCL2	BCL2, apoptosis regulator	HGNC:990
BCL6	B-cell CLL/lymphoma 6	HGNC:1001
BCOR	BCL6 corepressor	HGNC:20893
BCORL1	BCL6 corepressor-like 1	HGNC:25657
BLM	Bloom syndrome RecQ like helicase	HGNC:1058
BRAF	B-Raf proto-oncogene, serine/threonine kinase	HGNC:1097
BRCA1	BRCA1, DNA repair associated	HGNC:1100
BRCA2	BRCA2, DNA repair associated	HGNC:1101
BRD4	Bromodomain containing 4	HGNC:13575
BRIP1	BRCA1-interacting protein C-terminal helicase 1	HGNC:20473
CARD11	Caspase recruitment domain family member 11	HGNC:16393
CBFB	Core-binding factor beta subunit	HGNC:1539
CBL	Cbl proto-oncogene	HGNC:1541
CCND1	Cyclin D1	HGNC:1582
CCND2	Cyclin D2	HGNC:1583
CCND3	Cyclin D3	HGNC:1585
CCNE1	Cyclin E1	HGNC:1589
CD274	CD274 molecule	HGNC:17635
CD79B	CD79b molecule	HGNC:1699
CDC73	Cell division cycle 73	HGNC:16783
CDH1	Cadherin 1	HGNC:1748
CDK12	Cyclin-dependent kinase 12	HGNC:24224
CDK4	Cyclin-dependent kinase 4	HGNC:1773
CDK6	Cyclin-dependent kinase 6	HGNC:1777
CDK8	Cyclin-dependent kinase 8	HGNC:1779
CDKN1B	Cyclin-dependent kinase inhibitor 1B	HGNC:1785

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TABLE A1. Somatic Cancer Panels (Continued)

Comprehensive Hematologic Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
CDKN2A	Cyclin-dependent kinase inhibitor 2A	HGNC:1787
CDKN2B	Cyclin-dependent kinase inhibitor 2B	HGNC:1788
CDKN2C	Cyclin-dependent kinase inhibitor 2C	HGNC:1789
CHEK1	Checkpoint kinase 1	HGNC:1925
CHEK2	Checkpoint kinase 2	HGNC:16627
CIC	Capicua transcriptional repressor	HGNC:14214
CREBBP	CREB-binding protein	HGNC:2348
CRKL	CRK-like proto-oncogene, adaptor protein	HGNC:2363
CRLF2	Cytokine receptor-like factor 2	HGNC:14281
CSF1R	Colony-stimulating factor 1 receptor	HGNC:2433
CTCF	CCCTC-binding factor	HGNC:13723
CTNNB1	Catenin beta 1	HGNC:2514
DAXX	Death domain-associated protein	HGNC:2681
DDR2	Discoidin domain receptor tyrosine kinase 2	HGNC:2731
DICER1	Dicer 1, ribonuclease III	HGNC:17098
DNMT3A	DNA methyltransferase 3 alpha	HGNC:2978
DOT1L	DOT1-like histone lysine methyltransferase	HGNC:24948
EED	Embryonic ectoderm development	HGNC:3188
EGFR	Epidermal growth factor receptor	HGNC:3236
EP300	E1A-binding protein p300	HGNC:3373
EPHA3	EPH receptor A3	HGNC:3387
EPHA5	EPH receptor A5	HGNC:3389
EPHB1	EPH receptor B1	HGNC:3392
ERBB2	Erb-b2 receptor tyrosine kinase 2	HGNC:3430
ERBB3	Erb-b2 receptor tyrosine kinase 3	HGNC:3431
ERBB4	Erb-b2 receptor tyrosine kinase 4	HGNC:3432
ERG	ERG, ETS transcription factor	HGNC:3446
ESR1	Estrogen receptor 1	HGNC:3467
ETV6	ETS variant 6	HGNC:3495
EZH2	Enhancer of zeste 2 polycomb repressive complex 2 subunit	HGNC:3527
FANCA	Fanconi anemia complementation group A	HGNC:3582
FANCC	Fanconi anemia complementation group C	HGNC:3584
FBXW7	F-box and WD repeat domain containing 7	HGNC:16712
FGF19	Fibroblast growth factor 19	HGNC:3675
FGF3	Fibroblast growth factor 3	HGNC:3681
FGF4	Fibroblast growth factor 4	HGNC:3682
FGFR1	Fibroblast growth factor receptor 1	HGNC:3688
FGFR2	Fibroblast growth factor receptor 2	HGNC:3689
FGFR3	Fibroblast growth factor receptor 3	HGNC:3690
FGFR4	Fibroblast growth factor receptor 4	HGNC:3691
FLCN	Folliculin	HGNC:27310
FLT1	Fms-related tyrosine kinase 1	HGNC:3763
FLT3	Fms-related tyrosine kinase 3	HGNC:3765

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TABLE A1. Somatic Cancer Panels (Continued)

Comprehensive Hematologic Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
FLT4	Fms-related tyrosine kinase 4	HGNC:3767
FOXL2	Forkhead box L2	HGNC:1092
FOXP1	Forkhead box P1	HGNC:3823
FUBP1	Far upstream element-binding protein 1	HGNC:4004
GATA1	GATA-binding protein 1	HGNC:4170
GATA2	GATA-binding protein 2	HGNC:4171
GATA3	GATA-binding protein 3	HGNC:4172
GNA11	G protein subunit alpha 11	HGNC:4379
GNAQ	G protein subunit alpha q	HGNC:4390
GNAS	GNAS complex locus	HGNC:4392
GRIN2A	Glutamate ionotropic receptor NMDA type subunit 2A	HGNC:4585
GSK3B	Glycogen synthase kinase 3 beta	HGNC:4617
H3F3A	H3 histone family member 3A	HGNC:4764
HGF	Hepatocyte growth factor	HGNC:4893
HIST1H1C	Histone cluster 1 ^{1}H family member c	HGNC:4716
HIST1H3B	Histone cluster 1 H3 family member b	HGNC:4776
HNF1A	HNF1 homeobox A	HGNC:11621
HRAS	HRas proto-oncogene, GTPase	HGNC:5173
IDH1	Isocitrate dehydrogenase [NADP(+)] 1, cytosolic	HGNC:5382
IDH2	Isocitrate dehydrogenase [NADP(+)] 2, mitochondrial	HGNC:5383
IGF1R	Insulin-like growth factor 1 receptor	HGNC:5465
IKBKE	Inhibitor of nuclear factor kappa B kinase subunit epsilon	HGNC:14552
IKZF1	IKAROS family zinc finger 1	HGNC:13176
IL7R	Interleukin 7 receptor	HGNC:6024
INPP4B	Inositol polyphosphate-4-phosphatase type II B	HGNC:6075
IRF4	Interferon regulatory factor 4	HGNC:6119
IRS2	Insulin receptor substrate 2	HGNC:6126
JAK1	Janus kinase 1	HGNC:6190
JAK2	Janus kinase 2	HGNC:6192
JAK3	Janus kinase 3	HGNC:6193
JMJD1C	Jumonji domain containing 1C	HGNC:12313
JUN	Jun proto-oncogene, AP-1 transcription factor subunit	HGNC:6204
KDM5A	Lysine demethylase 5A	HGNC:9886
KDM5C	Lysine demethylase 5C	HGNC:11114
KDM6A	Lysine demethylase 6A	HGNC:12637
KDR	Kinase insert domain receptor	HGNC:6307
KEAP1	Kelch-like ECH-associated protein 1	HGNC:23177
KIT	KIT proto-oncogene receptor tyrosine kinase	HGNC:6342
KMT2A	Lysine methyltransferase 2A	HGNC:7132
KMT2C	Lysine methyltransferase 2C	HGNC:13726
KRAS	KRAS proto-oncogene, GTPase	HGNC:6407
MAP2K1	Mitogen-activated protein kinase kinase 1	HGNC:6840
MAP2K2	Mitogen-activated protein kinase kinase 2	HGNC:6842

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TABLE A1. Somatic Cancer Panels (Continued)

Comprehensive Hematologic Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
MAP2K4	Mitogen-activated protein kinase kinase 4	HGNC:6844
MAP3K1	Mitogen-activated protein kinase kinase kinase 1	HGNC:6848
MAPK1	Mitogen-activated protein kinase 1	HGNC:6871
MCL1	MCL1, BCL2 family apoptosis regulator	HGNC:6943
MDM2	MDM2 proto-oncogene	HGNC:6973
MDM4	MDM4, p53 regulator	HGNC:6974
MED12	Mediator complex subunit 12	HGNC:11957
MEF2B	Myocyte enhancer factor 2B	HGNC:6995
MEN1	Menin 1	HGNC:7010
MET	MET proto-oncogene, receptor tyrosine kinase	HGNC:7029
MITF	Melanogenesis-associated transcription factor	HGNC:7105
MLH1	MutL homolog 1	HGNC:7127
MPL	MPL proto-oncogene, thrombopoietin receptor	HGNC:7217
MRE11	MRE11 homolog, double-strand break repair nuclease	HGNC:7230
MSH2	MutS homolog 2	HGNC:7325
MSH6	MutS homolog 6	HGNC:7329
MTOR	Mechanistic target of rapamycin kinase	HGNC:3942
MUTYH	MutY DNA glycosylase	HGNC:7527
MYB	MYB proto-oncogene, transcription factor	HGNC:7545
MYC	MYC proto-oncogene, bHLH transcription factor	HGNC:7553
MYCN	MYCN proto-oncogene, bHLH transcription factor	HGNC:7559
MYD88	Myeloid differentiation primary response 88	HGNC:7562
MYOD1	Myogenic differentiation 1	HGNC:7611
NF1	Neurofibromin 1	HGNC:7765
NF2	Neurofibromin 2	HGNC:7773
NFE2L2	Nuclear factor, erythroid 2-like 2	HGNC:7782
NKX2-1	NK2 homeobox 1	HGNC:11825
NOTCH1	Notch 1	HGNC:7881
NOTCH2	Notch 2	HGNC:7882
NPM1	Nucleophosmin 1	HGNC:7910
NRAS	NRAS proto-oncogene, GTPase	HGNC:7989
NSD2	Nuclear receptor- binding SET domain protein 2	HGNC:12766
NTRK1	Neurotrophic receptor tyrosine kinase 1	HGNC:8031
NTRK2	Neurotrophic receptor tyrosine kinase 2	HGNC:8032
NTRK3	Neurotrophic receptor tyrosine kinase 3	HGNC:8033
PALB2	Partner and localizer of BRCA2	HGNC:26144
PAX5	Paired box 5	HGNC:8619
PBRM1	Polybromo 1	HGNC:30064
PDCD1	Programmed cell death 1	HGNC:8760
PDGFRA	Platelet-derived growth factor receptor alpha	HGNC:8803
PDGFRB	Platelet-derived growth factor receptor beta	HGNC:8804
PHOX2B	Paired-like homeobox 2b	HGNC:9143
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	HGNC:8975

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TABLE A1. Somatic Cancer Panels (Continued)

Comprehensive Hematologic Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
PIK3CG	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma	HGNC:8978
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1	HGNC:8979
PIK3R2	Phosphoinositide-3-kinase regulatory subunit 2	HGNC:8980
PIM1	Pim-1 proto-oncogene, serine/threonine kinase	HGNC:8986
PPM1D	Protein phosphatase, Mg^{2+}/Mn^{2+}-dependent 1D	HGNC:9277
PPP2R1A	Protein phosphatase 2 scaffold subunit Aalpha	HGNC:9302
PRDM1	PR/SET domain 1	HGNC:9346
PRKAR1A	Protein kinase cAMP-dependent type I regulatory subunit alpha	HGNC:9388
PTCH1	Patched 1	HGNC:9585
PTEN	Phosphatase and tensin homolog	HGNC:9588
PTPN11	Protein tyrosine phosphatase, nonreceptor type 11	HGNC:9644
RAD50	RAD50 double-strand break repair protein	HGNC:9816
RAD51	RAD51 recombinase	HGNC:9817
RAF1	Raf-1 proto-oncogene, serine/threonine kinase	HGNC:9829
RARA	Retinoic acid receptor alpha	HGNC:9864
RB1	RB transcriptional corepressor 1	HGNC:9884
RET	Ret proto-oncogene	HGNC:9967
RHOA	Ras homolog family member A	HGNC:667
RICTOR	RPTOR independent companion of MTOR complex 2	HGNC:28611
RNF43	Ring finger protein 43	HGNC:18505
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase	HGNC:10261
RPTOR	Regulatory-associated protein of MTOR complex 1	HGNC:30287
RUNX1	Runt-related transcription factor 1	HGNC:10471
SDHA	Succinate dehydrogenase complex flavoprotein subunit A	HGNC:10680
SDHB	Succinate dehydrogenase complex iron sulfur subunit B	HGNC:10681
SDHC	Succinate dehydrogenase complex subunit C	HGNC:10682
SDHD	Succinate dehydrogenase complex subunit D	HGNC:10683
SETD2	SET domain containing 2	HGNC:18420
SF3B1	Splicing factor 3b subunit 1	HGNC:10768
SMAD2	SMAD family member 2	HGNC:6768
SMAD4	SMAD family member 4	HGNC:6770
SMARCA4	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4	HGNC:11100
SMARCB1	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1	HGNC:11103
SMO	Smoothened, frizzled class receptor	HGNC:11119
SOCS1	Suppressor of cytokine signaling 1	HGNC:19383
SOX2	SRY-box 2	HGNC:11195
SPEN	Spen family transcriptional repressor	HGNC:17575
SPOP	Speckle type BTB/POZ protein	HGNC:11254
SRC	SRC proto-oncogene, nonreceptor tyrosine kinase	HGNC:11283
STAG2	Stromal antigen 2	HGNC:11355
STK11	Serine/threonine kinase 11	HGNC:11389

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TABLE A1. Somatic Cancer Panels (Continued)

Comprehensive Hematologic Malignancies Panel

HGNC-Approved Symbol	Approved Name	HGNC ID
SUFU	SUFU negative regulator of hedgehog signaling	HGNC:16466
SUZ12	SUZ12 polycomb repressive complex 2 subunit	HGNC:17101
TENT5C	Family with sequence similarity 46 member C	HGNC:24712
TERT	Telomerase reverse transcription	HGNC:11730
TET2	Tet methylcytosine dioxygenase 2	HGNC:25941
TGFBR2	Transforming growth factor beta receptor 2	HGNC:11773
TNFAIP3	TNF alpha-induced protein 3	HGNC:11896
TNFRSF14	TNF receptor superfamily member 14	HGNC:11912
TOP1	DNA topoisomerase I	HGNC:11986
TP53	Tumor protein p53	HGNC:11998
TP63	Tumor protein p63	HGNC:15979
TSC1	TSC complex subunit 1	HGNC:12362
TSC2	TSC complex subunit 2	HGNC:12363
TSHR	Thyroid-stimulating hormone receptor	HGNC:12373
U2AF1	U2 small nuclear RNA auxiliary factor 1	HGNC:12453
VHL	Von Hippel-Lindau tumor suppressor	HGNC:12687
WT1	Wilms tumor 1	HGNC:12796
XPO1	Exportin 1	HGNC:12825

NOTE. All genes included in each of the panels. Comprehensive hematologic panel was sent on leukemia/lymphoma cases, and solid tumor panel was sent on CNS and non-CNS solid tumors.

TABLE A2. All Identified Variants

Somatic Finding (gene)	Somatic Finding (cDNA)	Somatic Finding (protein)	Diagnosis	Group
11p15 cnLOH	NA	NA	Wilms tumor	Genetic testing not done (referral pending)
ALK	c.3824G>A	p.Arg1275Gln	Neuroblastoma	S>G not confirmed
	c.3824G>A	p.R1275Q	Neuroblastoma	S>G not confirmed
APC	c.1744-2A>G	NA	Osteosarcoma	Genetic testing not done (family, prefer to follow clinically)
	c.3920T>A	p.Ile1307Lys	Papillary thyroid carcinoma	Genetic testing not done (provider, deferred to adulthood)
	c.3920T>A	p.Ile1307Lys	Pilocytic astrocytoma	Genetic testing not done (provider, presumed positive)
	c.3920T>A	p.Ile1307Lys	Colon adenocarcinoma	Genetic testing not done (provider, presumed positive)
	c.4364delA	p.Asn1455fs*18	Papillary thyroid carcinoma	Genetic testing not done (family deferred)
	c.646C>T	p.Arg216*	Astrocytoma	Genetic testing not done (family, prefer to follow clinically)
	c.3920T>A	p.Ile1307Lys	Neuroblastoma	Genetic testing not done (provider, deferred to adulthood)
ARID1A	c.4993+1G>C	NA	Rhabdomyosarcoma	Genetic testing not done (referral pending)
ASXL1	c.1822_1830delinsGGGGTTGGACT	p.Trp608Glyfs*96	Wilms tumor	S>G not confirmed
	c.1934dupG	p.Gly646fs	AML	S>G not confirmed
ATM	c.1124delG	p.Arg375fs	Congenital mesoblastic nephroma, cellular type	Genetic testing not done (referral pending)
	c.2921+1G>A	NA	Low grade glioma	Genetic testing not done (referral pending)
	c.3802delG	p.Val1268*	DNET	S>G confirmed
	c.3980T>G	p.Leu1327*	Medulloblastoma	Genetic testing not done (referral pending)
	c.5932G>T	p.Glu1978*	Pilocytic astrocytoma	Genetic testing not done (referral pending)
	c.8786+1G>A	p.?	Papillary thyroid carcinoma	Genetic testing not done (referral pending)
BAP1	c.601G>T	p.Glu201*	Medulloblastoma	Genetic testing not done (referral pending)
BARD1	c.448C>T	p.Arg150*	Composite neuroblastoma/ pheochromocytoma	S>G confirmed
BCOR	c.4285_4295del	p.Gly1429Serfs*10	Rhabdomyosarcoma	Genetic testing not done (referral pending)
	c.4537C>T	p.Arg1513*	Wilms tumor	Genetic testing not done (referral pending)
BLM	c.772_773delCT	p.Leu258Glufs*7	Pilomyxoid astrocytoma	Genetic testing not done (provider, deferred to adulthood)
BRAF	c.1790T>A	p.Leu597Gln	T-ALL	Genetic testing not done (referral pending)
BRCA1	c.5266dupC	p.Gln1756Profs*74	Ewing sarcoma	Genetic testing not done (provider, presumed positive)

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TABLE A2. All Identified Variants (Continued)

Somatic Finding (gene)	Somatic Finding (cDNA)	Somatic Finding (protein)	Diagnosis	Group
BRCA2	c.1294G>T	p.E432*	Urothelial carcinoma	Genetic testing not done (referral pending)
	c.5946delT	p.Ser1982fs	Congenital mesoblastic nephroma	Genetic testing not done (provider, presumed positive)
	c.5946delT	p.Ser1982fs	Adrenocoritcal tumor	S>G confirmed
BRIP1	c.2108delAinsTCC	p.Lys703Ilefs*3	Ependymoma	Genetic testing not done (deceased, family preferred not to pursue)
	c.2392C>T	p.Arg798*	Congenital mesoblastic nephroma	Genetic testing not done (referral pending)
CBL	c.1111T>C	p.Tyr371His	Dysgerminoma	Genetic testing not done (referral pending)
	c.1141T>C	p.Cys381Arg	JMML	S>G confirmed
CDKN1B	c.25G>A	p.Gly9Arg	Glioblastoma	Genetic testing not done (deceased, family preferred not to pursue)
CDKN2A	c.203_207delCGGAG	p.Glu69Glnfs*49	Rhabdomyosarcoma	Genetic testing not done (referral pending)
CHEK2	c.1100delC	p.Thr367Metfs*15	Pituitary adenoma	Genetic testing not done (referral pending)
	c.433C>T	p.Arg145Trp	Pilocytic astrocytoma	S>G confirmed
CIC	c.2787dupT	p.Ser930fs*1	Neuroblastoma	Genetic testing not done (referral pending)
CREBBP	c.1568_1571delCCCT	p.Pro523fs	B-ALL	S>G not confirmed
	c.4021C>T	p.Arg1341*	T-ALL	Genetic testing not done (referral pending)
CSF3R	c.2221C>T	p.Gln741*	AML	S>G not confirmed
	c.2326C>T	p.Q776*	B-ALL	Genetic testing not done (referral pending)
	c.799delG	p.Glu267fs	AML	Genetic testing not done (referral pending)
CTCF	c.544delG	p.Glu182Asnfs*40	T-ALL	Genetic testing not done (referral pending)
	c.700dupG	p.Glu234fs	Meningioangiomatosis	Genetic testing not done (referral pending)
CTNNB1	c.133_135delTCT	p.Ser45del	Wilms tumor	Genetic testing not done (referral pending)
	c.133_135delTCT	p.Ser45del	Wilms tumor	Genetic testing not done (referral pending)
	c.134C>A	p.Ser45Tyr	Wilms tumor	Genetic testing not done (referral pending)
DICER1	c.2328dupT	p.Leu777fs	Papillary thyroid carcinoma	S>G not confirmed
	c.2830C>T	p.Arg944*	Papillary thyroid carcinoma	S>G not confirmed
	c.5113G>A	p.Glu1705Lys	Sex-cord stromal tumor	S>G not confirmed
	c.5315_5316del	p.Phe1772Cysfs*6	Pineoblastoma	Genetic testing not done (referral pending)
	c.5425G>A	p.Gly1809Arg	Sex-cord stromal tumor	S>G not confirmed
	Partial 14q loss	Partial 14q loss	Pleuropulmonary blastoma	S>G confirmed
DNMT3A	c.2645G>A	p.Arg882His	Ganglioneuroblastoma	S>G confirmed
EPOR	c.1299_1305dup	p.L436Pfs*11	AML	S>G not confirmed

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TABLE A2. All Identified Variants (Continued)

Somatic Finding (gene)	Somatic Finding (cDNA)	Somatic Finding (protein)	Diagnosis	Group
ETV6	c.1075C>T	p.Arg359*	B-ALL	Genetic testing not done (referral pending)
	c.1129G>T	p.Ala337Ser	T-ALL	Genetic testing not done (referral pending)
FANCA	c.3349A>G	p.Arg1117Gly	Papillary thyroid carcinoma	Genetic testing not done (referral pending)
GATA1	c.38_39delAG	p.E13Afs*26	AML	S>G not confirmed
GATA2	Deletion 3q21.3	p.Q776*	AML	Genetic testing not done (referral pending)
IKZF1	c.1095_1096dupCC	p.Gln366Profs*50	B-ALL	Genetic testing not done (referral pending)
	c.484C>T	p.Arg162Trp	B-ALL	Genetic testing not done (referral pending)
IL7R	c.353G>A	p.Cys118Tyr	AML	Genetic testing not done (referral pending)
JAK1	c.1972G>T	p.V658F	AML	Inconclusive germline
	c.2171G>A	p.Arg724His	T-ALL	Genetic testing not done (referral pending)
JAK2	c.3188G>A	p.Arg1063His	B-ALL	Genetic testing not done (referral pending)
	c.3188G>A	p.Arg1063His	Neuroblastoma	Genetic testing not done (referral pending)
JAK3	c.1970G>A	p.Arg657Gln	T-ALL	Genetic testing not done (referral pending)
KEAP1	c.1519C>T	p.Arg507*	Papillary thyroid carcinoma	Genetic testing not done (referral pending)
KMT2D	c.4163G>T	p.Arg1388Leu	B-ALL	Genetic testing not done (provider, presumed negative)
KRAS	c.35G>A	p.Gly12Asp	Plexiform neurofibroma	S>G confirmed
MITF	c.1255G>A	p.Glu419Lys	Colon adenocarcinoma	Genetic testing not done (family deferred)
	c.1255G>A	p.Glu419Lys	Teratoma	Genetic testing not done (referral pending)
MPL	c.1069C>T	p.Arg357*	Low-grade glioma	Genetic testing not done (referral pending)
	c.391+5G>C	p.?	Papillary thyroid carcinoma	Genetic testing not done (referral pending)
MSH2	c.1906G>C	p.Ala636Pro	Diffuse midline glioma	S>G confirmed
MSH6	c.1489A>T	p.Arg497*	Diffuse high-grade glioma	S>G confirmed
	c.3261dupC	p.F1088Lfs*5	B-ALL	S>G not confirmed
	c.3261dupC	p.Ser1153*	Diffuse high-grade glioma	S>G not confirmed
	c.3863_3865dupAAT	p.Phe1289*	Anaplastic astrocytoma	S>G confirmed
	c.3964G>T	p.Glu1322*	Diffuse midline glioma	Genetic testing not done (referral pending)
	del	NA	Medulloblastoma	S>G not confirmed

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TABLE A2. All Identified Variants (Continued)

Somatic Finding (gene)	Somatic Finding (cDNA)	Somatic Finding (protein)	Diagnosis	Group
MUTYH	c.1178G>A	p.Gly393Asp	Neuroblastoma	Genetic testing not done (deceased, family preferred not to pursue)
	c.1178G>A	p.Gly393Asp	Alveolar rhabdomyosarcoma	S>G confirmed
	c.1178G>A	p.Gly393Asp	Ependymoma	Genetic testing not done (referral pending)
	c.1187-2A>G	p.?	Papillary thyroid carcinoma	Genetic testing not done (provider, deferred to adulthood)
	c.527A>G	p.Tyr176Cys	Astrocytoma	Genetic testing not done (referral pending)
	c.536A>G	p.Y179C	Wilms tumor	Genetic testing not done (referral pending)
	c.725G>A	p.Arg242His	MPNST	Genetic testing not done (referral pending)
	c.924+3A>C	NA	Langerhans cell histiocytosis	S>G confirmed
NF1	c.1756_1759delACTA	p.Thr586fs	AML	S>G confirmed
	c.1840_1841dupAA	p.Asn614Lysfs*18	AML	Genetic testing not done (provider, presumed negative)
	c.1885G>A	p.Gly629Arg	Gliosarcoma	S>G confirmed
	c.2173G>T	p.Glu725*	Pilocytic astrocytoma	S>G confirmed
	c.2446C>T	p.Arg816*	Diffuse astrocytoma	Genetic testing not done (discussed, but family lost to follow-up)
	c.2709G>A	p.Val903Val	Pilocytic xanthoastrocytoma	Genetic testing not done (referral pending)
	c.3299_3309delinsGA	p.Ser1100Cysfs*9	Pilocytic astrocytoma	Genetic testing not done (referral pending)
	c.3628_3638delGAACTGGTCAC	p.Glu1210Asnfs*4	Neurofibroma	Genetic testing not done (referral pending)
	c.3827G>A	p.Arg1276Gln	Pilocytic astrocytoma	S>G not confirmed
	c.4084C>T	p.Arg1362*	Embryonal rhabdomyosarcoma	Genetic testing not done (provider, presumed positive)
	c.4372G>A	p.Glu1458Lys	Pilocytic astrocytoma	S>G confirmed
	c.4600C>T	p.Arg1534*	Pleomorphic xanthoastrocytoma	S>G not confirmed
	c.480-1G>A	NA	Anaplastic astrocytoma	S>G confirmed
	c.4966delA	p.Thr1656Glnfs*42	Neurofibroma	Genetic testing not done (provider, presumed positive)
	c.5158G>T	p.E1720*	MPNST	Genetic testing not done (referral pending)
	c.5647_5664delACCTTTAATTTAAAAATCinsT	p.Thr1883*	Embryonal rhabdomyosarcoma	Genetic testing not done (provider, presumed positive)
	c.574C>T	p.Arg192*	B-ALL	Genetic testing not done (provider, presumed positive)
	c.5902C>T	p.Arg1968*	Diffuse astrocytoma	S>G not confirmed
	c.6147+1G>A	p.?	Anaplastic astrocytoma	Genetic testing not done (provider, presumed negative)

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TABLE A2. All Identified Variants (Continued)

Somatic Finding (gene)	Somatic Finding (cDNA)	Somatic Finding (protein)	Diagnosis	Group
	c.6653_6704+69del	p.R2218Nfs*30	Anaplastic astrocytoma	Genetic testing not done (referral pending)
	c.7045dup	p.Arg2349Profs*5	ALL	Genetic testing not done (provider, presumed negative)
	c.7926C>G	p.Tyr2642*	Neurofibroma	Genetic testing not done (provider, presumed negative)
	c.8160+1G>C	NA	Embryonal rhabdomyosarcoma	Genetic testing not done (provider, presumed positive)
	c.818delT	p.Leu273fs	Myoepithelial carcinoma	Genetic testing not done (provider, presumed positive)
	c.910C>T	p.Arg304*	Low-grade glioma	S>G not confirmed
	Del	NA	Pilocytic astrocytoma	Genetic testing not done (referral pending)
	Del exon 37-58	NA	AML	Genetic testing not done (provider, presumed positive)
	Loss partial 17q	NA	Low-grade glioma	Genetic testing not done (discussed, but family lost to follow-up)
NF2	c.1021C>T	p.Arg341*	Schwannoma	S>G confirmed
	c.169C>T	p.Arg57*	Meningioangiomatosis	Genetic testing not done (referral pending)
NOTCH1	c.4754T>A	p.Leu1585Gln	T-ALL	Genetic testing not done (referral pending)
	c.7572dupC	p.His2526fs	T-ALL	Genetic testing not done (referral pending)
PALB2	c.2167_2168delAT	p.Met723fs	Synovial sarcoma	Genetic testing not done (referral pending)
Partial 11p loss including WT1	Partial 11p loss	Partial 11p loss	Wilms tumor	S>G confirmed
PAX5	c.910+1G>A	NA	B-ALL	Genetic testing not done (referral pending)
PDGFRA	c.1977C>A	p.Asn659Lys	Glioblastoma	S>G not confirmed
PHF6	c.585+1G>A	p.?	T-ALL	Genetic testing not done (referral pending)
PRKAR1A	c.629_630insT	p.Arg211Glufs*22	Sertoli cell	Genetic testing not done (referral pending)
PTEN	c.425_437delins13	p.Arg142_Leu146delinsGlnGlyLysPhe*	Papillary thyroid carcinoma	S>G confirmed
PTPN11	c.1510A>G	p.Met504Val	JMML	Genetic testing not done (referral pending)
	c.181G>T	p.Asp61Tyr	B-ALL	Inconclusive constitutional testing
	c.923A>G	p.Asn308Ser	Glioblastoma	Genetic testing not done (referral pending)
RB1	c.1848dupA	p.G617Rfs*36	Alveolar soft part sarcoma	Genetic testing not done (referral pending)
RUNX1	c.484A>G	p.Arg162Gly	MDS/AML	S>G not confirmed
SDHA	c.91C>T	p.Arg31*	Pilocytic astrocytoma	Genetic testing not done (family deferred)
	c.91C>T	p.Arg31*	GIST	S>G confirmed

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TABLE A2. All Identified Variants (Continued)

Somatic Finding (gene)	Somatic Finding (cDNA)	Somatic Finding (protein)	Diagnosis	Group
SH2B3	c.1038dupG	p.Leu347fs	AML	S>G not confirmed
	c.1203delinsGA	p.Tyr401*	B-ALL	Genetic testing not done (referral pending)
	c.622G>C	p.Glu208Gln	AML	S>G confirmed
SMARCA4	c.3475G>A	p.G1159R	Neuroblastoma	S>G not confirmed
SMARCB1	c.157C>T	p.Arg53*	AT/RT	S>G not confirmed
	c.740_741insATCTG	p.Tyr248Serfs*21	Malignant rhabdoid tumor	S>G not confirmed
	c.742_743del	p.Tyr248Profs*32	AT/RT	S>G confirmed
	del	NA	AT/RT	Genetic testing not done (referral pending)
	del	NA	AT/RT	S>G confirmed
	del exon 2-4	NA	AT/RT	S>G confirmed
	del exon 6-8	NA	AT/RT	Inconclusive constitutional testing
	Homozygous deletion	Homozygous deletion	AT/RT	Genetic testing not done (referral pending)
	Loss partial chr 22q inc SMARCB1 (hmz)	NA	AT/RT	S>G not confirmed
	Loss partial chr 22q inc SMARCB1 (hmz)		AT/RT	S>G not confirmed
	Partial 22q loss	Del	AT/RT	S>G confirmed
TERT	c.-124C>A	NA	Medulloblastoma	Genetic testing not done (referral pending)
TP53	c.524G>A	p.Arg175His	GBM	Genetic testing not done (referral pending)
	c.1000G>C	p.Gly334Arg	Neuroblastoma	S>G confirmed
	c.1009C>G	p.Arg337Gly	Adrenocoritcal tumor	S>G confirmed
	c.1021_1025del	p.Phe341Argfs*4	Gliosarcoma	Genetic testing not done (referral pending)
	c.1024C>T	p.R342*	Wilms tumor	Genetic testing not done (referral pending)
	c.1129G>T	p.Ala337Ser	Anaplastic astrocytoma	Genetic testing not done (referral pending)
	c.329G>T	p.Arg110Leu	T-ALL	S>G confirmed
	c.358A>G	p.Lys120Glu	Colon adenocarcinoma	S>G not confirmed
	c.375G>T	p.Thr125Thr	Ependymoma	S>G confirmed
	c.384_387del	p.Ala129Serfs*40	GBM	S>G not confirmed
	c.404G>T	p.C135F	Ependymoma	S>G not confirmed
	c.479T>A	p.Met160Lys	Metastatic neuroendocrine carcinoma of colon	Genetic testing not done (referral pending)
	c.517G>A	p.V173M	AT/RT	S>G not confirmed
	c.524G>A	p.Arg175His	Anaplastic astrocytoma	S>G not confirmed
	c.524G>A	p.Arg175His	Embryonal rhabdomyosarcoma	S>G not confirmed
	c.524G>A	p.R175H	Undifferentiated sarcoma	Genetic testing not done (referral pending)

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TABLE A2. All Identified Variants (Continued)

Somatic Finding (gene)	Somatic Finding (cDNA)	Somatic Finding (protein)	Diagnosis	Group
	c.527G>A	p.Cys176Tyr	Osteosarcoma	Genetic testing not done (referral pending)
	c.527G>A	p.Cys176Tyr	Diffuse midline glioma	Genetic testing not done (referral pending)
	c.536A>C	p.His179Pro	Burkitt leukemia	S>G not confirmed
	c.536A>G	p.His179Arg	Diffuse high-grade glioma	Genetic testing not done (referral pending)
	c.586C>T	p.Arg196*	Diffuse midline glioma	Genetic testing not done (referral pending)
	c.643A>G	p.Ser215Gly	Diffuse midline glioma	S>G confirmed
	c.646G>A	p.V216M	B-ALL	S>G not confirmed
	c.658T>A	p.Y220N	Embryonal rhabdomyosarcoma	Genetic testing not done (referral pending)
	c.676G>A	p.Gly226Ser	Anaplastic astrocytoma	S>G confirmed
	c.703A>G	p.Asn235Asp	GBM	S>G not confirmed
	c.711G>A	p.Met237Ile	Osteosarcoma	Genetic testing not done (referral pending)
	c.733G>A	p.Gly245Ser	Diffuse high-grade glioma	Genetic testing not done (referral pending)
	c.733G>A	p.Gly245Ser	Rhabdomyosarcoma	S>G not confirmed
	c.742C>T	p.Arg248Trp	Osteosarcoma	Genetic testing not done (referral pending)
	c.742C>T	p.Arg248Trp	Pleomorphic xanthoastrocytoma	S>G not confirmed
	c.743G>A	p.Arg248Gln	Myoepithelial carcinoma	S>G confirmed
	c.743G>A	p.Arg248Gln	Osteosarcoma	S>G not confirmed
	c.743G>A	p.Arg248Gln	T-ALL	S>G not confirmed
	c.743G>A	p.Arg248Gln	Ewing sarcoma	S>G not confirmed
	c.743G>A	p.Arg248Gln	GBM	S>G not confirmed
	c.789_833delinsCCCT	p.L264Pfs*28	Diffuse astrocytoma	Genetic testing not done (referral pending)
	c.796delG	p.Gly266fs	GBM	Genetic testing not done (referral pending)
	c.817C>T	p.Arg273Cys	Diffuse midline glioma	Genetic testing not done (deceased, family preferred not to pursue)
	c.817C>T	p.Arg273Cys	B-ALL	S>G not confirmed
	c.817C>T	p.Arg273Cys	Osteosarcoma	Genetic testing not done (referral pending)
	c.817C>T	p.Arg273Cys	Anaplastic astrocytoma	Genetic testing not done (referral pending)
	c.818G>A	p.R273H	AML	Genetic testing not done (referral pending)
	c.845G>C	p.Arg282Pro	B-ALL	S>G not confirmed
	c.847C>T	p.Arg283Cys	B-ALL turned to AML	S>G confirmed
	c.853G>A	p.Glu285Lys	Diffuse midline glioma	S>G confirmed
	Del	NA	Alveolar soft part sarcoma	Genetic testing not done (pending insurance approval)

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TABLE A2. All Identified Variants (Continued)

Somatic Finding (gene)	Somatic Finding (cDNA)	Somatic Finding (protein)	Diagnosis	Group
TSC1	c.2672dup	p.Asn891Lysfs*13	Osteosarcoma	Genetic testing not done (provider, presumed negative)
TSC2	c.225+2T>C	NA	Diffuse high-grade glioma	S>G not confirmed
VHL	Partial deletion exon 2	Partial deletion exon 3	CNS hemangioblastoma	S>G confirmed
WT1	c.1104_1105insAG	p.Arg369fs	T-ALL	Genetic testing not done (referral pending)
	c.1109_1110insC	p.Val371fs	T-ALL	Genetic testing not done (referral pending)
	c.1129_1130insCCGTA	p.Leu378fs	Wilms tumor	Genetic testing not done (referral pending)
	c.1129_1139dup p.Ser381Leufs*72	p.Ser381Leufs*72	Wilms tumor	S>G not confirmed
	c.1140dup	p.Ser381Valfs*4	Wilms tumor	Genetic testing not done (referral pending)
	c.1390G>A	p.D464N	Wilms tumor	Genetic testing not done (referral pending)
	c.778C>T	p.Gln260*	Wilms tumor	Genetic testing not done (referral pending)

NOTE. All identified variants as sorted by affected gene, including the variant identified in somatic panel testing, and results of constitutional testing, if available. If not tested, reason listed in parentheses.

Abbreviations: AML, acute myeloid leukemia; AT/RT, atypical teratoid/rhabdoid tumor; B-ALL, B-acute lymphoblastic leukemia; DNET, dysembryplastic neuroendocrine tumor; GBM, glioblastoma multiforme; GIST, GI stromal tumor; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPNST, malignant peripheral nerve sheath tumor; NA, not applicable; T-ALL, T-acute lymphoblastic leukemia.