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Discovery Life Sciences
800 Hudson Way, Suite 1700
Huntsville AL 35806

Test Performed: HAD QGEN MultiModal

Report Date
Status -

Patient		Specimen	
DLS Patient ID	F00113096	Date of Procedure	Feb 10, 2020
Date of Birth	Mar 20, 1965	Primary Harvest Site	Urinary Bladder
Age	54		
Sex	Male		
Ethnicity	Non-Hispanic		
Race	White		
Diagnosis	Bladder Cancer, Transitional Cell Carcinoma (Papillary)		

Result: Positive

14
Clinically Significant Variants

4
Therapies with Potential Clinical Benefit

Actionable Variants With Associated Therapies

		Approved Therapies			
Gene / Variant	**Allelic Fraction**	**Bladder Cancer, Transitional Cell Carcinoma (papillary)**	**Other Indications**	**Associated With Resistance**	**Clinical Trials**
FGFR3 c.746C>G p.S249C g.1801841C>G **Tier 1A** Pathogenic	60.0% (of 126 reads)	erdafitinib	-	-	10
FBXW7 c.1244_1245delGA p.R415fs*21 g.152328381_152328382delTC **Tier 2C** Likely Pathogenic	1.46% (of 137 reads)	-	-	-	1
TP53 c.1140delT p.H380fs*? g.7669651delA **Tier 2C** Likely Pathogenic	1.95% (of 410 reads)	-	bortezomib /rituximab lenalidomide /rituximab rituximab	-	3
TSC1 † c.2509_2510dupAA p.N837fs*13 g.132900829_132900830insTT	62.0% (of 196 reads)	-	-	-	2

		Approved Therapies			
Gene / Variant	**Allelic Fraction**	**Bladder Cancer, Transitional Cell Carcinoma (papillary)**	**Other Indications**	**Associated With Resistance**	**Clinical Trials**
Tier 2C **Likely Pathogenic**					

† Allele Fraction (AF) >40%. AF suggests that it may be germline and pathogenic or likely pathogenic. Recommend obtaining confirmatory germline testing.

Variants Without Associated Therapies

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
FGFR3 c.1587_1595delGAAGATGAT p.M529_M531del g.1805604_1805612delAGATGATGA	1.11% (of 451 reads)	loss	**Tier 2C**	**Likely Pathogenic**
FGFR3 c.1593_1595delGAT p.M531del g.1805614_1805616delGAT	1.14% (of 438 reads)	loss	**Tier 2C**	**Likely Pathogenic**
APC c.53delC p.P18fs*62 g.112707769delC	1.89% (of 318 reads)	loss	**Tier 3**	**Likely Pathogenic**
CDH1 c.376_382delCCGCCCC p.P126fs*87 g.68801875_68801881delCCGCCCC	1.48% (of 135 reads)	loss	**Tier 3**	**Likely Pathogenic**
CDH1 c.449delG p.R150fs*65 g.68808485delG	3.34% (of 299 reads)	loss	**Tier 3**	**Likely Pathogenic**
CDH1 c.452delGinsAAAAA p.R151fs*18 g.68808488delGinsAAAAA	3.24% (of 309 reads)	loss	**Tier 3**	**Likely Pathogenic**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
CDH1 c.463_464delGA p.D155fs*12 g.68808494_68808495delAG	1.76% (of 284 reads)	loss	**Tier 3**	Likely Pathogenic
CDH1 c.619_621delATT p.I207del g.68808775_68808777delTTA	1.67% (of 359 reads)	loss	**Tier 3**	Likely Pathogenic
CDH1 c.622delGinsAA p.E208fs*15 g.68808783delGinsAA	2.29% (of 350 reads)	loss	**Tier 3**	Likely Pathogenic
CDH1 c.1382+1G>A g.68815760G>A	5.05% (of 99 reads)	loss	**Tier 3**	Pathogenic

Variants of Unknown Clinical Significance

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
AKT1 c.1363+1G>A g.104770744C>T	12.0% (of 175 reads)	loss	**Tier 3**	**Uncertain Significance**
AKT1 c.828+1G>C g.104773454C>G	14.0% (of 152 reads)	loss	**Tier 3**	**Uncertain Significance**
AKT1 c.46+2_46+3delTTinsGG g.104792595_104792596delAAinsCC	11.0% (of 132 reads)	loss	**Tier 3**	**Uncertain Significance**
AKT1 c.39C>A p.H13Q g.104792605G>T	2.38% (of 168 reads)	normal	**Tier 3**	**Uncertain Significance**
ALK c.511A>C	7.14% (of 42 reads)	normal	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
p.S171R g.29920149T>G				
CDH1 c.543C>A p.N181K g.68808704C>A	2.59% (of 193 reads)	loss	**Tier 3**	**Uncertain Significance**
CDH1 c.547G>A p.D183N g.68808708G>A	3.5% (of 200 reads)	loss	**Tier 3**	**Uncertain Significance**
CDH1 c.626G>A p.R209K g.68808787G>A	3.41% (of 352 reads)	normal	**Tier 3**	**Uncertain Significance**
CDH1 c.1652T>A p.I551K g.68822124T>A	2.56% (of 312 reads)	loss	**Tier 3**	**Uncertain Significance**
CTNNB1 c.365T>G p.V122G g.41225077T>G	1.26% (of 159 reads)	loss	**Tier 3**	**Uncertain Significance**
CTNNB1 c.1416_1423delCAGCCGAC p.S473fs*21 g.41233756_41233763delGACCAGCC	2.0% (of 350 reads)	loss	**Tier 3**	**Uncertain Significance**
CTNNB1 c.1424delA p.H475fs*32 g.41233767delA	1.25% (of 320 reads)	loss	**Tier 3**	**Uncertain Significance**
CTNNB1 c.1429G>A p.E477K g.41233772G>A	5.16% (of 310 reads)	normal	**Tier 3**	**Uncertain Significance**
CTNNB1 c.1755C>A p.H585Q g.41235795C>A	5.12% (of 488 reads)	normal	**Tier 3**	**Uncertain Significance**
CTNNB1 c.2285T>C	1.76% (of 510 reads)	normal	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
p.L762P g.41239281T>C				
DDR2 c.2003_2005delGCC p.R668del g.162775796_162775798delCCG	1.2% (of 166 reads)	loss	**Tier 3**	**Uncertain Significance**
DNMT3A c.69T>A p.D23E g.25249660A>T	2.52% (of 119 reads)	normal	**Tier 3**	**Uncertain Significance**
ERBB2 c.2205C>A p.Y735* g.39723657C>A	1.92% (of 312 reads)	loss	**Tier 3**	**Uncertain Significance**
ERBB2 c.2208+2T>G g.39723662T>G	10.0% (of 296 reads)	loss	**Tier 3**	**Uncertain Significance**
EZH2 c.965A>G p.N322S g.148819630T>C	59.0% (of 196 reads)	normal	**Tier 3**	**Uncertain Significance**
FGFR3 c.599_600delGC p.R200fs*80 g.1801519_1801520delCG	1.64% (of 183 reads)	loss	**Tier 3**	**Uncertain Significance**
FGFR3 c.1413-2A>C g.1805353A>C	3.24% (of 185 reads)	loss	**Tier 3**	**Uncertain Significance**
FGFR3 c.1534+5G>A g.1805481G>A	1.43% (of 140 reads)	loss	**Tier 3**	**Uncertain Significance**
FGFR3 c.1603C>A p.H535N g.1805627C>A	4.49% (of 401 reads)	loss	**Tier 3**	**Uncertain Significance**
FGFR3 c.1604_1605delACin	1.73% (of 404 reads)	loss	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
sTA p.H535L g.1805628_1805629 delACinsTA				
FGFR3 c.1605C>A p.H535Q g.1805629C>A	4.09% (of 391 reads)	gain	**Tier 3**	**Uncertain Significance**
FGFR3 c.1944C>A p.Y648* g.1806158C>A	3.91% (of 230 reads)	loss	**Tier 3**	**Uncertain Significance**
FOXL2 c.675G>T p.A225A g.138946048C>A	3.75% (of 160 reads)	normal	**Tier 3**	**Uncertain Significance**
FOXL2 c.663G>T p.A221A g.138946060C>A	2.29% (of 175 reads)	normal	**Tier 3**	**Uncertain Significance**
GNA11 c.476+1G>C g.3113485G>C	3.85% (of 104 reads)	loss	**Tier 3**	**Uncertain Significance**
GNA11 c.606-2A>C g.3118922A>C	2.34% (of 128 reads)	loss	**Tier 3**	**Uncertain Significance**
GNAS c.759C>A p.Y253* g.58909724C>A	1.91% (of 524 reads)	loss	**Tier 3**	**Uncertain Significance**
IDH1 c.342C>A p.C114* g.208248441G>T	1.3% (of 307 reads)	loss	**Tier 3**	**Uncertain Significance**
IDH1 c.335_342delTTATC TGC p.I112fs*29 g.208248441_20824 8448delGCAGATAA	1.47% (of 340 reads)	loss	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
IDH1 c.268C>A p.Q90K g.208248515G>T	8.13% (of 320 reads)	gain	**Tier 3**	**Uncertain Significance**
IDH1 c. 261_266delGTTGAA p.L88_K89del g.208248517_20824 8522delTTCAAC	4.01% (of 349 reads)	loss	**Tier 3**	**Uncertain Significance**
IDH2 c.1272-5T>A g.90084358A>T	2.7% (of 259 reads)	loss	**Tier 3**	**Uncertain Significance**
IDH2 c.115+1G>A g.90102275C>T	3.26% (of 337 reads)	loss	**Tier 3**	**Uncertain Significance**
JAK2 c. 658_659delGAinsTT p.D220F g.5054606_505460 7delGAinsTT	1.13% (of 177 reads)	loss	**Tier 3**	**Uncertain Significance**
KIT c.2791_2792delAGin sGA p.S931D g.54737269_547372 70delAGinsGA	3.45% (of 58 reads)	loss	**Tier 3**	**Uncertain Significance**
MPL c.816delG p.W272fs*5 g.43340088delG	2.06% (of 243 reads)	loss	**Tier 3**	**Uncertain Significance**
NOTCH1 c.7244_7246delCAC p.P2415del g.136496493_13649 6495delGTG	3.41% (of 88 reads)	loss	**Tier 3**	**Uncertain Significance**
NOTCH1 c.6366_6367delGC p.Q2123fs*144 g.136497372_136497 373delGC	1.5% (of 133 reads)	loss	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
NOTCH1 c.4934T>C p.L1645P g.136504757A>G	1.61% (of 124 reads)	loss	**Tier 3**	**Uncertain Significance**
NOTCH1 c.4040dupA p.N1347fs*2 g.136505855_136505856insT	2.8% (of 107 reads)	loss	**Tier 3**	**Uncertain Significance**
NOTCH1 c.3720C>A p.N1240K g.136506897G>T	4.59% (of 109 reads)	loss	**Tier 3**	**Uncertain Significance**
NOTCH1 c.1256-3_1256-2delCAinsTG g.136517939_136517940delTGinsCA	6.25% (of 32 reads)	loss	**Tier 3**	**Uncertain Significance**
NPM1 c.541_549delTTTGATGAT p.F181_D183del g.171400162_171400170delTGATGATTT	1.43% (of 140 reads)	loss	**Tier 3**	**Uncertain Significance**
PMS2 c.24-3T>G g.6006034A>C	1.38% (of 217 reads)	loss	**Tier 3**	**Uncertain Significance**
PTEN c.692C>A p.P231H g.87957910C>A	1.17% (of 256 reads)	normal	**Tier 3**	**Uncertain Significance**
PTPN11 c.14+1G>A g.112419126G>A	4.24% (of 425 reads)	loss	**Tier 3**	**Uncertain Significance**
RET c.2225_2226delCGinsTA p.T742I g.43116672_43116673delCGinsTA	2.08% (of 96 reads)	gain	**Tier 3**	**Uncertain Significance**

Gene / Variant	Allelic Fraction	Function	Classification	Assessment
SRC c.144_145delCG p.G49fs*45 g.37384295_37384296delCG	1.11% (of 719 reads)	loss	**Tier 3**	**Uncertain Significance**
SRC c.345C>A p.N115K g.37386169C>A	2.99% (of 167 reads)	normal	**Tier 3**	**Uncertain Significance**
VHL c.464-5T>G g.10149782T>G	2.36% (of 127 reads)	loss	**Tier 3**	**Uncertain Significance**

Therapeutic Implications for Bladder Cancer, Transitional Cell Carcinoma (Papillary)

Therapies	Gene / Variant	Response	Therapies Description
erdafitinib	***FGFR3*** p.S249C g.1801841C>G **Tier 1A** Pathogenic	Sensitive	Erdafitinib, a kinase inhibitor, is FDA-approved for treating adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations as detected by an FDA-approved companion diagnostic and progressed during or following at least one line of prior platinum-containing chemotherapy including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Therapeutic Implications for Other Indications

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
bortezomib/ rituximab	***TP53*** p.H380fs*? g.7669651delA **Tier 2C** Likely Pathogenic	Sensitive	Bortezomib, a proteasome inhibitor, in combination with rituximab, a CD20-directed cytolytic antibody, and cyclophosphamide, an alkylating drug, and doxorubicin, an anthracycline topoisomerase inhibitor, and prednisone, a corticosteroid, is EMA-approved for treating adult patients with previously untreated mantle cell lymphoma, who are unsuitable for haematopoietic stem cell transplantation.
lenalidomide/ rituximab	***TP53*** p.H380fs*? g.7669651delA	Sensitive	Lenalidomide, a thalidomide analogue, in combination with rituximab, a CD20-directed cytolytic antibody, is FDA- and EMA-approved for treating patients with previously treated follicular

Therapies for Other Indications	Gene / Variant	Response	Therapies Description
	Tier 2C **Likely Pathogenic**		lymphoma (FL); lenalidomide, in combination with rituximab, is FDA-approved for treating patients with previously treated marginal zone lymphoma (MZL).
rituximab	***TP53*** p.H380fs*? g.7669651delA **Tier 2C** **Likely Pathogenic**	Sensitive	Rituximab, a CD20-directed cytolytic antibody, is FDA-approved for treating adult patients with relapsed or refractory, low grade or follicular, CD20-positive B cell Non-Hodgkin's Lymphoma (NHL) as a single agent; previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy; non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens; previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide; rituximab is EMA-approved for treating adult patients with previously untreated stage III-IV follicular lymphoma in combination with chemotherapy; follicular lymphoma (maintenance therapy) responding to induction therapy; stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy; CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy; for treating paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL), in combination with chemotherapy; and for treating patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia in combination with chemotherapy.

Available Clinical Trials

Gene / Variant	Trial Title Trial ID	Treatments	Trial Phase	Location / Contact
FGFR3 p.S249C g.1801841C>G **Tier 1A** **Pathogenic**	A Randomized Phase 2 Study of Erdafitinib Versus Investigator Choice of Intravesical Chemotherapy in Subjects Who Received Bacillus Calmette-Guérin (BCG) and Recurred With High Risk Non-Muscle-Invasive Bladder Cancer (NMIBC) and FGFR Mutations or Fusions NCT04172675	mitomycin C erdafitinib gemcitabine	Phase 2	United States: AZ, CO, NY, PA, TN Study Contact; JNJ. CT@sylogent.com; 844-434-4210;
FGFR3 p.S249C g.1801841C>G **Tier 1A** **Pathogenic**	A Phase 2 Study of Erdafitinib in Subjects With Advanced Solid Tumors and FGFR Gene Alterations NCT04083976	erdafitinib	Phase 2	United States: AZ, CO, FL, GA, MA, ME, MI, NC, NJ, NY, OH, PA, TN, TX, WI Study Contact; JNJ. CT@sylogent.com; 844-434-4210;
FGFR3 p.S249C g.1801841C>G **Tier 1A** **Pathogenic** ***TSC1*** p.N837fs*13 g.132900829_132900830insTT **Tier 2C** **Likely Pathogenic**	Targeted Agent and Profiling Utilization Registry (TAPUR) Study NCT02693535	sunitinib	Phase 2	United States: AL, AZ, CA, FL, GA, HI, IL, IN, ME, MI, NC, ND, NE, NH, OK, OR, PA, SD, TX, UT, VA, WA Pam Mangat, MS; pam.mangat@asco.org;
FGFR3 p.S249C g.1801841C>G **Tier 1A** **Pathogenic** ***TSC1*** p.N837fs*13 g.132900829_132900830insTT **Tier 2C** **Likely Pathogenic**	Molecular Analysis for Therapy Choice (MATCH) NCT02465060	AZD4547 erdafitinib	Phase 2	United States: AK, AL, AR, AZ, CA, CO, CT, DC, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, ME, MI, MN, MO, MS, MT, NC, ND, NE, NH, NJ, NV, NY, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY See clinicaltrials.gov for contact information.
FGFR3 p.S249C g.1801841C>G	Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Infigratinib for the Adjuvant Treatment of Subjects With Invasive	infigratinib	Phase 3	United States: AZ, CA, FL, OH, TN, TX QED Therapeutics;

Gene / Variant	Trial Title Trial ID	Treatments	Trial Phase	Location / Contact
Tier 1A **Pathogenic**	Urothelial Carcinoma With Susceptible FGFR3 Genetic Alterations (PROOF 302) NCT04197986			Proof302.ct@qedtx.com ; 1-877-280-5655;
FGFR3 p.S249C g.1801841C>G **Tier 1A** **Pathogenic**	A Phase 3 Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Subjects With Advanced Urothelial Cancer and Selected FGFR Gene Aberrations NCT03390504	pembrolizumab erdafitinib docetaxel vinflunine	Phase 3	United States: AK, CA, DC, FL, IL, KY, MD, NC, NH, NV, NY, OH, TX, VA, WA Study Contact; JNJ.CT@sylogent.com; 844-434-4210;
FGFR3 p.S249C g.1801841C>G **Tier 1A** **Pathogenic**	A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumors Harboring Activating FGFR Mutations or Translocations (FIGHT-208) NCT04003623	pemigatinib	Phase 2	United States: CA, FL, HI, IL, MD, NJ, OH, SD, TX, UT Incyte Corporation Call Center (US); medinfo@incyte.com; 1.855.463.3463;
FGFR3 p.S249C g.1801841C>G **Tier 1A** **Pathogenic**	A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumor Malignancies Harboring Activating FGFR Mutations or Translocations NCT03822117	pemigatinib	Phase 2	United States: AZ, CA, FL, IA, IL, IN, KS, LA, MA, ME, MN, NC, NH, NJ, NV, NY, OK, SC, TN, TX, VA, WA, WI, WV Incyte Corporation Call Center(U.S); medinfo@incyte.com; 1.855.463.3463;
FGFR3 p.S249C g.1801841C>G **Tier 1A** **Pathogenic**	Phase II Study of Ponatinib for Advanced Cancers With Genomic Alterations in Fibroblastic Growth Factor Receptor (FGFR) and Other Genomic Targets (KIT, PDGFRá, RET FLT3, ABL1) NCT02272998	ponatinib	Phase 2	United States: OH The Ohio State University Comprehensive Cancer Center; Jamesline@osumc.edu; 1-800-293-5066;
FGFR3 p.S249C g.1801841C>G **Tier 1A** **Pathogenic**	A Phase 2, Open-Label, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Plus Pembrolizumab Versus Pemigatinib Alone Versus Standard of Care as First-Line Treatment for Metastatic or Unresectable Urothelial Carcinoma in Cisplatin-Ineligible Participants Whose Tumors Express FGFR3 Mutation or	carboplatin pembrolizumab gemcitabine pemigatinib	Phase 2	United States: CA, DE, GA, IL, ME, NJ, NY, OR, SC, TN, TX Incyte Corporation Call Center (US); medinfo@incyte.com; 1.855.463.3463;

Gene / Variant	Trial Title Trial ID	Treatments	Trial Phase	Location / Contact
	Rearrangement (FIGHT-205) NCT04003610			
FBXW7 p.R415fs*21 g.152328381_152328382delTC **Tier 2C** **Likely Pathogenic**	A Phase II Study of M6620 (VX-970) in Selected Solid Tumors NCT03718091	berzosertib	Phase 2	United States: MA Gregory M Cote, MD, PhD; gcote@mgh.harvard.edu ; 617-724-4000;
TP53 p.H380fs*? g.7669651delA **Tier 2C** **Likely Pathogenic**	A Phase 1, Multicenter, Open-label, Dose-Exploration and Dose-Expansion Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 650 in Subjects With Advanced Solid Tumors NCT04293094	AMG 650	Phase 1	United States: CA, IN, MO, NY, TN, TX Amgen Call Center; medinfo@amgen.com; 866-572-6436;
TP53 p.H380fs*? g.7669651delA **Tier 2C** **Likely Pathogenic**	A Phase Ia/Ib, Open Label, Dose-escalation Study of the Combination of BI 907828 With BI 754091 and BI 754111, Followed by Expansion Cohorts, in Patients With Advanced Solid Tumors NCT03964233	bi754111 BI 907828 BI 754091	Phase 1	United States: CT, NY, TX Boehringer Ingelheim; clintriage.rdg@boehringer-ingelheim.com; 1-800-243-0127;
TP53 p.H380fs*? g.7669651delA **Tier 2C** **Likely Pathogenic**	Study of APR-246 in Combination With Pembrolizumab in Subjects With Solid Tumor Malignancies NCT04383938	pembrolizumab eprenetapopt	Phase 1 /Phase 2	United States: MO, TX Eyal Attar, MD; info@aprea.com; +1 617 804 6947;

Individual Variant Interpretations

Gene ***FGFR3***
Exon 7
Nucleotide NM_000142.5: g.1801841C>G c.746C>G
Amino Acid p.S249C
Function gain
Allelic Fraction 60.0% (of 126 reads)
Classification **Tier 1A**
Assessment **Pathogenic**

Interpretation
FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene ***FBXW7***
Exon 9
Nucleotide NM_033632.3: g.152328381_152328382delTC

Interpretation
FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which is responsible for recruitment of substrates for targeted degradation by the proteasome [177]. Fbxw7 targets include several known proto-oncogenes, including Cyclin E1, Notch1, Myc, Aurora-A, and

	c.1244_1245delGA
Amino Acid	p.R415fs*21
Function	loss
Allelic Fraction	1.46% (of 137 reads)
Classification	**Tier 2C**
Assessment	**Likely Pathogenic**

Jun [1, 177, 25]. FBXW7 inactivating mutations have been reported in a large variety of tumors and, combined with the oncogenic potential of several FBXW7 substrates, leads to the conclusion that FBXW7 is a general tumor suppressor [1].

Gene	***FGFR3***
Exon	12
Nucleotide	NM_000142.5: g.1805604_1805612delAGATGATGA c.1587_1595delGAAGATGAT
Amino Acid	p.M529_M531del
Function	loss
Allelic Fraction	1.11% (of 451 reads)
Classification	**Tier 2C**
Assessment	**Likely Pathogenic**

Interpretation
FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene	***FGFR3***
Exon	12
Nucleotide	NM_000142.5: g.1805614_1805616delGAT c.1593_1595delGAT
Amino Acid	p.M531del
Function	loss
Allelic Fraction	1.14% (of 438 reads)
Classification	**Tier 2C**
Assessment	**Likely Pathogenic**

Interpretation
FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene	***TP53***
Exon	11
Nucleotide	NM_000546.6: g.7669651delA c.1140delT
Amino Acid	p.H380fs*?
Function	loss
Allelic Fraction	1.95% (of 410 reads)
Classification	**Tier 2C**
Assessment	**Likely Pathogenic**

Interpretation
The TP53 gene encodes the tumor suppressor p53, a protein that is involved in the DNA damage cell cycle checkpoint and causes cell cycle arrest when it senses DNA damage. p53 can also activate DNA repair genes, or induce apoptosis in the presence of DNA damage. It has been called the cellular gatekeeper [105]. Loss of p53 is common in aggressive advanced cancers [22]. Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias [140, 112, 153]. Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects [92, 84, 174, 123, 67].

Gene	***TSC1***
Exon	20
Nucleotide	NM_000368.5: g.132900829_132900830insTT c.2509_2510dupAA
Amino Acid	p.N837fs*13

Interpretation
TSC1 encodes Hamartin, which forms a heterodimer with Tuberin to act as a GTPase activating protein (GAP) for Rheb, a potent activator of the mammalian target of rapamycin (mTOR). By converting Rheb from a GTP- to GDP-bound state, the TSC1/2 heterodimer inactivates Rheb and suppresses mTOR activity [72, 160]. Germline mutations in TSC1 or TSC2 are associated with the rare autosomal dominant syndrome, tuberous

Function loss Allelic Fraction 62.0% (of 196 reads) Classification **Tier 2C** Assessment **Likely Pathogenic**	sclerosis complex. Patients with this disorder develop nonmalignant tumors in many organs including the brain, kidney, lung, heart, and liver [18].
Gene ***AKT1*** Exon 13 Nucleotide NM_005163.2: g.104770744C>T c.1363+1G>A Amino Acid Function loss Allelic Fraction 12.0% (of 175 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** AKT1 encodes Akt1, an intracellular serine/threonine kinase. Akt is recruited to the cell membrane via its pleckstrin homology domain (PHD), where it may be phosphorylated and activated [170]. Although Akt activation has been shown to be insufficient to induce tumor formation on its own, it has been shown to accelerate tumor formation and increase metastasis in animal models of cancer [69, 70, 37].
Gene ***AKT1*** Exon 9 Nucleotide NM_005163.2: g.104773454C>G c.828+1G>C Amino Acid Function loss Allelic Fraction 14.0% (of 152 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** AKT1 encodes Akt1, an intracellular serine/threonine kinase. Akt is recruited to the cell membrane via its pleckstrin homology domain (PHD), where it may be phosphorylated and activated [170]. Although Akt activation has been shown to be insufficient to induce tumor formation on its own, it has been shown to accelerate tumor formation and increase metastasis in animal models of cancer [69, 70, 37].
Gene ***AKT1*** Exon 2 Nucleotide NM_005163.2: g.104792595_104792596delAAinsCC c.46+2_46+3delTTinsGG Amino Acid Function loss Allelic Fraction 11.0% (of 132 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** AKT1 encodes Akt1, an intracellular serine/threonine kinase. Akt is recruited to the cell membrane via its pleckstrin homology domain (PHD), where it may be phosphorylated and activated [170]. Although Akt activation has been shown to be insufficient to induce tumor formation on its own, it has been shown to accelerate tumor formation and increase metastasis in animal models of cancer [69, 70, 37].
Gene ***AKT1*** Exon 2 Nucleotide NM_005163.2: g.104792605G>T c.39C>A Amino Acid p.H13Q Function normal Allelic Fraction 2.38% (of 168 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** AKT1 encodes Akt1, an intracellular serine/threonine kinase. Akt is recruited to the cell membrane via its pleckstrin homology domain (PHD), where it may be phosphorylated and activated [170]. Although Akt activation has been shown to be insufficient to induce tumor formation on its own, it has been shown to accelerate tumor formation and increase metastasis in animal models of cancer [69, 70, 37].
Gene ***ALK*** Exon 1 Nucleotide NM_004304.5:	**Interpretation** ALK encodes Anaplastic lymphoma kinase (Alk), a receptor tyrosine kinase that is part of the insulin receptor superfamily and induces

g.29920149T>G c.511A>C Amino Acid p.S171R Function normal Allelic Fraction 7.14% (of 42 reads) Classification **Tier 3** Assessment **Uncertain Significance**	downstream activation of pathways associated with cell survival, angiogenesis, and proliferation [53]. ALK was originally identified in anaplastic lymphoma as a fusion partner with the gene product of NPM1; ALK has subsequently been identified as a fusion partner with numerous other genes, including EML4 in lung cancer [135, 151, 53, 5]. The ALK gene can become oncogenic by a gene rearrangement, copy number gain, or genetic mutation [53, 5].
Gene ***APC*** Exon 1 Nucleotide NM_001127511.3: g.112707769delC c.53delC Amino Acid p.P18fs*62 Function loss Allelic Fraction 1.89% (of 318 reads) Classification **Tier 3** Assessment **Likely Pathogenic**	**Interpretation** APC (adenomatous polyposis coli) encodes the protein Apc, which plays critical roles in regulating cell division and adhesion. Apc interacts with beta-catenin and controls signaling in the Wnt pathway, which helps regulate embryonic development and cell differentiation [110]. APC is a tumor suppressor gene that was originally characterized based on the prominent role that inactivation of Apc plays in colorectal carcinogenesis; however, APC mutation and Wnt/beta-catenin pathway activation have subsequently been implicated in other tumor types as well [50, 134, 47]. In the absence of functional Apc, beta-catenin accumulates and is translocated to the nucleus, where it promotes the transcription of genes promoting cellular proliferation [63]. In addition, Apc has been reported to play a role in microtubule spindle formation and chromosomal segregation [82, 46, 54].
Gene ***CDH1*** Exon 3 Nucleotide NM_001317184.2: g.68801875_68801881delCCGCCCC c.376_382delCCGCCCC Amino Acid p.P126fs*87 Function loss Allelic Fraction 1.48% (of 135 reads) Classification **Tier 3** Assessment **Likely Pathogenic**	**Interpretation** CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].
Gene ***CDH1*** Exon 4 Nucleotide NM_001317184.2: g.68808485delG c.449delG Amino Acid p.R150fs*65 Function loss Allelic Fraction 3.34% (of 299 reads) Classification **Tier 3** Assessment **Likely Pathogenic**	**Interpretation** CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].
Gene ***CDH1*** Exon 4 Nucleotide NM_001317184.2: g.68808488delGinsAAAAA c.452delGinsAAAAA Amino Acid p.R151fs*18	**Interpretation** CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].

Function	loss
Allelic Fraction	3.24% (of 309 reads)
Classification	**Tier 3**
Assessment	**Likely Pathogenic**

Gene	***CDH1***
Exon	4
Nucleotide	NM_001317184.2: g.68808494_68808495delAG c.463_464delGA
Amino Acid	p.D155fs*12
Function	loss
Allelic Fraction	1.76% (of 284 reads)
Classification	**Tier 3**
Assessment	**Likely Pathogenic**

Interpretation
CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].

Gene	***CDH1***
Exon	5
Nucleotide	NM_001317184.2: g.68808704C>A c.543C>A
Amino Acid	p.N181K
Function	loss
Allelic Fraction	2.59% (of 193 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].

Gene	***CDH1***
Exon	5
Nucleotide	NM_001317184.2: g.68808708G>A c.547G>A
Amino Acid	p.D183N
Function	loss
Allelic Fraction	3.5% (of 200 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].

Gene	***CDH1***
Exon	5
Nucleotide	NM_001317184.2: g.68808775_68808777delTTA c.619_621delATT
Amino Acid	p.I207del
Function	loss
Allelic Fraction	1.67% (of 359 reads)
Classification	**Tier 3**
Assessment	**Likely Pathogenic**

Interpretation
CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].

Gene	***CDH1***
Exon	5
Nucleotide	NM_001317184.2:

Interpretation
CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity

g.68808783delGinsA A c.622delGinsAA Amino Acid p.E208fs*15 Function loss Allelic Fraction 2.29% (of 350 reads) Classification **Tier 3** Assessment **Likely Pathogenic**	via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].
Gene ***CDH1*** Exon 5 Nucleotide NM_001317184.2: g.68808787G>A c.626G>A Amino Acid p.R209K Function normal Allelic Fraction 3.41% (of 352 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].
Gene ***CDH1*** Exon 9 Nucleotide NM_001317184.2: g.68815760G>A c.1382+1G>A Amino Acid Function loss Allelic Fraction 5.05% (of 99 reads) Classification **Tier 3** Assessment **Pathogenic**	**Interpretation** CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].
Gene ***CDH1*** Exon 11 Nucleotide NM_001317184.2: g.68822124T>A c.1652T>A Amino Acid p.I551K Function loss Allelic Fraction 2.56% (of 312 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** CDH1 encodes E-cadherin, a cellular adhesion protein that binds beta-catenin. E-cadherin plays a vital role in tissue architecture and integrity via cell-cell interactions [124]. Loss of E-cadherin expression leads to decreased cellular adhesion, and in some experimental contexts results in cell migration and metastasis [183, 111].
Gene ***CTNNB1*** Exon 4 Nucleotide NM_001098209.2: g.41225077T>G c.365T>G Amino Acid p.V122G Function loss Allelic Fraction 1.26% (of 159 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** CTNNB1 encodes beta-catenin, a key downstream component of the Wnt signaling pathway. Beta-catenin interacts with E-cadherin to regulate cell-cell adhesion, and as a component of the Wnt pathway, plays a role in development and cell proliferation and differentiation [85]. CTNNB1 can act as an oncogene and altered expression of beta-catenin can lead to abnormal signaling in various diseases, including modulation of gene transcription to drive cancer initiation, progression, survival, and relapse [161].
Gene ***CTNNB1***	**Interpretation**

Exon	9
Nucleotide	NM_001098209.2: g.41233756_41233763delGACCAGCC c.1416_1423delCAGCCGAC
Amino Acid	p.S473fs*21
Function	loss
Allelic Fraction	2.0% (of 350 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

CTNNB1 encodes beta-catenin, a key downstream component of the Wnt signaling pathway. Beta-catenin interacts with E-cadherin to regulate cell-cell adhesion, and as a component of the Wnt pathway, plays a role in development and cell proliferation and differentiation [85]. CTNNB1 can act as an oncogene and altered expression of beta-catenin can lead to abnormal signaling in various diseases, including modulation of gene transcription to drive cancer initiation, progression, survival, and relapse [161].

Gene	***CTNNB1***
Exon	9
Nucleotide	NM_001098209.2: g.41233767delA c.1424delA
Amino Acid	p.H475fs*32
Function	loss
Allelic Fraction	1.25% (of 320 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
CTNNB1 encodes beta-catenin, a key downstream component of the Wnt signaling pathway. Beta-catenin interacts with E-cadherin to regulate cell-cell adhesion, and as a component of the Wnt pathway, plays a role in development and cell proliferation and differentiation [85]. CTNNB1 can act as an oncogene and altered expression of beta-catenin can lead to abnormal signaling in various diseases, including modulation of gene transcription to drive cancer initiation, progression, survival, and relapse [161].

Gene	***CTNNB1***
Exon	9
Nucleotide	NM_001098209.2: g.41233772G>A c.1429G>A
Amino Acid	p.E477K
Function	normal
Allelic Fraction	5.16% (of 310 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
CTNNB1 encodes beta-catenin, a key downstream component of the Wnt signaling pathway. Beta-catenin interacts with E-cadherin to regulate cell-cell adhesion, and as a component of the Wnt pathway, plays a role in development and cell proliferation and differentiation [85]. CTNNB1 can act as an oncogene and altered expression of beta-catenin can lead to abnormal signaling in various diseases, including modulation of gene transcription to drive cancer initiation, progression, survival, and relapse [161].

Gene	***CTNNB1***
Exon	11
Nucleotide	NM_001098209.2: g.41235795C>A c.1755C>A
Amino Acid	p.H585Q
Function	normal
Allelic Fraction	5.12% (of 488 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
CTNNB1 encodes beta-catenin, a key downstream component of the Wnt signaling pathway. Beta-catenin interacts with E-cadherin to regulate cell-cell adhesion, and as a component of the Wnt pathway, plays a role in development and cell proliferation and differentiation [85]. CTNNB1 can act as an oncogene and altered expression of beta-catenin can lead to abnormal signaling in various diseases, including modulation of gene transcription to drive cancer initiation, progression, survival, and relapse [161].

Gene	***CTNNB1***
Exon	15
Nucleotide	NM_001098209.2: g.41239281T>C c.2285T>C
Amino Acid	p.L762P
Function	normal
Allelic Fraction	1.76% (of 510 reads)
Classification	**Tier 3**

Interpretation
CTNNB1 encodes beta-catenin, a key downstream component of the Wnt signaling pathway. Beta-catenin interacts with E-cadherin to regulate cell-cell adhesion, and as a component of the Wnt pathway, plays a role in development and cell proliferation and differentiation [85]. CTNNB1 can act as an oncogene and altered expression of beta-catenin can lead to abnormal signaling in various diseases, including modulation of gene transcription to drive cancer initiation, progression, survival, and relapse [161].

Assessment	**Uncertain Significance**

Gene	***DDR2***
Exon	16
Nucleotide	NM_001014796.3: g.162775796_162775798delCCG c.2003_2005delGCC
Amino Acid	p.R668del
Function	loss
Allelic Fraction	1.2% (of 166 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
DDR2 encodes Discoidin Domain-containing Receptor 2 (Ddr2), a tyrosine kinase involved in normal bone development [172, 108, 171]. Ddr2 functions as a receptor for fibrillar collagen at the cell surface and regulates cell differentiation, migration, and proliferation, and is involved in remodeling of the extracellular matrix [172, 108]. Germline homozygous DDR2 mutation has been reported to cause spondylo-meta-epiphyseal dysplasia with short limbs and abnormal calcifications (SMED-SL) [9]. Ddr2 has been reported to be overexpressed in several types of carcinoma and to be involved in cell proliferation and invasion, likely via activation of MMP2 [122, 86].

Gene	***DNMT3A***
Exon	2
Nucleotide	NM_153759.3: g.25249660A>T c.69T>A
Amino Acid	p.D23E
Function	normal
Allelic Fraction	2.52% (of 119 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
DNMT3A encodes the protein DNA (cytosine 5)-methyltransferase 3A, or Dnmt3a, a methyltransferase that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation [30, 164]. The role of DNMT3A in cancer is unclear, with both an oncogenic and tumor suppressor role reported [166, 42, 35, 181, 48, 89]. In addition, DNMT3A mutations often result in altered DNA methylation patterns as opposed to globally increased or decreased methylation [71, 115, 120].

Gene	***ERBB2***
Exon	18
Nucleotide	NM_004448.3: g.39723657C>A c.2205C>A
Amino Acid	p.Y735*
Function	loss
Allelic Fraction	1.92% (of 312 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
ERBB2 (also known as HER2/neu) encodes the receptor tyrosine kinase Her2, which functions as an oncogene, and belongs to the same family as Egfr. Amplification, mutation, and overexpression of ERBB2 can lead to excessive proliferation and tumor formation, and has been reported to play a role in several types of cancer [62, 61]. Activating alterations in the ERBB2 gene or Her2 overexpression may predict sensitivity to Her2 inhibitors [116, 163, 26, 7]. ERBB2 alterations are reported to be mutually exclusive with EGFR and KRAS mutations in non-small cell lung cancer [24, 147]. Exon 20 insertions in ERBB2, resulting in ERBB2 activation, are more common in never smokers in non-small cell lung cancer compared to smokers [147, 24, 4].

Gene	***ERBB2***
Exon	18
Nucleotide	NM_004448.3: g.39723662T>G c.2208+2T>G
Amino Acid	
Function	loss
Allelic Fraction	10.0% (of 296 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
ERBB2 (also known as HER2/neu) encodes the receptor tyrosine kinase Her2, which functions as an oncogene, and belongs to the same family as Egfr. Amplification, mutation, and overexpression of ERBB2 can lead to excessive proliferation and tumor formation, and has been reported to play a role in several types of cancer [62, 61]. Activating alterations in the ERBB2 gene or Her2 overexpression may predict sensitivity to Her2 inhibitors [116, 163, 26, 7]. ERBB2 alterations are reported to be mutually exclusive with EGFR and KRAS mutations in non-small cell lung cancer [24, 147]. Exon 20 insertions in ERBB2, resulting in ERBB2 activation, are more common in never smokers in non-small cell lung cancer compared to smokers [147, 24, 4].

Gene	***EZH2***
Exon	9
Nucleotide	NM_004456.5:

Interpretation
EZH2 encodes the protein Enhancer of zeste homolog 2 (Ezh2), a histone lysine methyltransferase that is the catalytic subunit of Polycomb

g.148819630T>C c.965A>G	repressive complexes (PRC2/3), which methylate lysine 9 and 27 of histone H3 and lysine 26 of histone H1 and cause transcriptional repression of target genes [98, 90, 125]. Target genes repressed by this complex include HOXC8, HOXA9, MYT1, CDKN2A and retinoic acid target genes [114, 21, 95]. In cancer cells, an Ezh2-containing complex has been suggested to result in de novo DNA methylation to target genes for repression [141]. The role of EZH2 in cancer is complex: it is overexpressed and may function as an oncogene in some cancers, but in other cancers poor prognosis has been associated with EZH2 inactivating mutations, suggesting it may have a tumor suppressor role as well [29, 180].
Amino Acid p.N322S Function normal Allelic Fraction 59.0% (of 196 reads) Classification **Tier 3** Assessment **Uncertain Significance**	

Gene ***FGFR3*** Exon 5 Nucleotide NM_000142.5: g.1801519_1801520delCG c.599_600delGC Amino Acid p.R200fs*80 Function loss Allelic Fraction 1.64% (of 183 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene ***FGFR3*** Exon 11 Nucleotide NM_000142.5: g.1805353A>C c.1413-2A>C Amino Acid Function loss Allelic Fraction 3.24% (of 185 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene ***FGFR3*** Exon 11 Nucleotide NM_000142.5: g.1805481G>A c.1534+5G>A Amino Acid Function loss Allelic Fraction 1.43% (of 140 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene ***FGFR3*** Exon 12 Nucleotide NM_000142.5: g.1805627C>A c.1603C>A Amino Acid p.H535N Function loss Allelic Fraction 4.49% (of 401 reads) Classification **Tier 3**	**Interpretation** FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several

Assessment **Uncertain Significance**	cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene ***FGFR3*** Exon 12 Nucleotide NM_000142.5: g.1805628_1805629delACinsTA c.1604_1605delACinsTA Amino Acid p.H535L Function loss Allelic Fraction 1.73% (of 404 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene ***FGFR3*** Exon 12 Nucleotide NM_000142.5: g.1805629C>A c.1605C>A Amino Acid p.H535Q Function gain Allelic Fraction 4.09% (of 391 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene ***FGFR3*** Exon 14 Nucleotide NM_000142.5: g.1806158C>A c.1944C>A Amino Acid p.Y648* Function loss Allelic Fraction 3.91% (of 230 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** FGFR3 encodes Fibroblast growth factor receptor 3 (Fgfr3), a tyrosine kinase cell surface receptor that is a member of the fibroblast growth factor receptor (Fgfr) family. The Fgfr family plays an important role in cell differentiation, growth, and angiogenesis, via binding of twenty Fgf family member ligands and subsequent activation of signaling pathways [133, 41]. Gain of function mutations in FGFRs have been reported in several cancer types [41, 178]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis [130, 107, 165].

Gene ***FOXL2*** Exon 1 Nucleotide NM_023067.4: g.138946048C>A c.675G>T Amino Acid p.A225A Function normal Allelic Fraction 3.75% (of 160 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** FOXL2 encodes Forkhead box protein L2, or FOXL2, which is a transcription regulator involved in ovarian differentiation and maintenance [15, 103, 101, 97]. FOXL2 has been reported to positively or negatively regulate a number of target genes, including genes involved in steroidogenesis, inflammation, apoptosis, and detoxification [128, 10, 40]. FOXL2 has also been proposed to be involved in stress response [11]. The FOXL2 C134W mutation has been suggested to be a driver in adult-type ovarian granulosa cell tumors [145, 142, 88]. FOXL2 mutations have also been reported to be associated with blepharophimosis/ ptosis/ epicanthus inversus syndrome (BPES) and non-syndromic premature ovarian failure [33, 14, 101].

Gene ***FOXL2*** Exon 1	**Interpretation** FOXL2 encodes Forkhead box protein L2, or FOXL2, which is a

Nucleotide	NM_023067.4: g.138946060C>A c.663G>T
Amino Acid	p.A221A
Function	normal
Allelic Fraction	2.29% (of 175 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

transcription regulator involved in ovarian differentiation and maintenance [15, 103, 101, 97]. FOXL2 has been reported to positively or negatively regulate a number of target genes, including genes involved in steroidogenesis, inflammation, apoptosis, and detoxification [128, 10, 40]. FOXL2 has also been proposed to be involved in stress response [11]. The FOXL2 C134W mutation has been suggested to be a driver in adult-type ovarian granulosa cell tumors [145, 142, 88]. FOXL2 mutations have also been reported to be associated with blepharophimosis/ ptosis/ epicanthus inversus syndrome (BPES) and non-syndromic premature ovarian failure [33, 14, 101].

Gene	***GNA11***
Exon	3
Nucleotide	NM_002067.5: g.3113485G>C c.476+1G>C
Amino Acid	
Function	loss
Allelic Fraction	3.85% (of 104 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
GNA11 encodes the protein Guanine nucleotide-binding protein subunit alpha-11 (G alpha-11), one of a family of 16 genes that encodes G protein alpha subunits; GNA11 encodes one of four proteins in the Gq class of subunits, along with GNAQ, GNA14, and GNA15 [77, 36]. Gq proteins activate phospholipase C and act as modulators of transmembrane signaling. G alpha-11 is ubiquitously expressed. Activating mutations in GNA11 are frequent in uveal melanoma and lead to activation of the MAPK pathway and oncogenic transformation [167].

Gene	***GNA11***
Exon	5
Nucleotide	NM_002067.5: g.3118922A>C c.606-2A>C
Amino Acid	
Function	loss
Allelic Fraction	2.34% (of 128 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
GNA11 encodes the protein Guanine nucleotide-binding protein subunit alpha-11 (G alpha-11), one of a family of 16 genes that encodes G protein alpha subunits; GNA11 encodes one of four proteins in the Gq class of subunits, along with GNAQ, GNA14, and GNA15 [77, 36]. Gq proteins activate phospholipase C and act as modulators of transmembrane signaling. G alpha-11 is ubiquitously expressed. Activating mutations in GNA11 are frequent in uveal melanoma and lead to activation of the MAPK pathway and oncogenic transformation [167].

Gene	***GNAS***
Exon	10
Nucleotide	NM_000516.6: g.58909724C>A c.759C>A
Amino Acid	p.Y253*
Function	loss
Allelic Fraction	1.91% (of 524 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
The GNAS gene locus produces several distinct transcripts, due to transcription from multiple promoters and alternative splicing. GNAS encodes the alpha subunit of the stimulatory G protein (Gs-alpha) variants Gnas-1, Gnas-2, and the extra-large variants (XL-alphas), XLas-1, XLas-2, XLas-3. The GNAS locus also encodes the proteins Nesp55 and Alex [59]. The Gnas and XLas proteins are guanine-nucleotide binding proteins (G proteins) that are involved in hormonal regulation of adenylate cyclase. Activating mutations in GNAS may lead to increased cAMP levels and increased cellular signaling, which has been associated with excessive proliferation and tumor development [81, 179, 113]. Activating mutations in GNAS occur predominantly at R201. GNAS R201H and R201C are mutations commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with activating GNAS mutations [31, 176, 119].

Gene	***IDH1***
Exon	4
Nucleotide	NM_005896.4: g.208248441G>T c.342C>A

Interpretation
IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis; Idh1 is localized to the cytoplasm and peroxisome and Idh2 is

Amino Acid	p.C114*
Function	loss
Allelic Fraction	1.3% (of 307 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

localized to the mitochondria [139]. Mutations in these enzymes result in downstream effects that are associated with tumorigenesis [3]. Certain IDH1 mutations, such as those at R132, result in downstream effects that are associated with tumorigenesis [56, 3]. IDH1 R132 mutations promote the reduction of alpha-ketoglutarate to 2-hydroxyglutarate, which is considered a potential onco-metabolite, with the coincident conversion of NADPH to NADP+ [56, 175, 104].

Gene	***IDH1***
Exon	4
Nucleotide	NM_005896.4: g.208248441_208248448delGCAGATAA c.335_342delTTATCTGC
Amino Acid	p.I112fs*29
Function	loss
Allelic Fraction	1.47% (of 340 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis; Idh1 is localized to the cytoplasm and peroxisome and Idh2 is localized to the mitochondria [139]. Mutations in these enzymes result in downstream effects that are associated with tumorigenesis [3]. Certain IDH1 mutations, such as those at R132, result in downstream effects that are associated with tumorigenesis [56, 3]. IDH1 R132 mutations promote the reduction of alpha-ketoglutarate to 2-hydroxyglutarate, which is considered a potential onco-metabolite, with the coincident conversion of NADPH to NADP+ [56, 175, 104].

Gene	***IDH1***
Exon	4
Nucleotide	NM_005896.4: g.208248515G>T c.268C>A
Amino Acid	p.Q90K
Function	gain
Allelic Fraction	8.13% (of 320 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis; Idh1 is localized to the cytoplasm and peroxisome and Idh2 is localized to the mitochondria [139]. Mutations in these enzymes result in downstream effects that are associated with tumorigenesis [3]. Certain IDH1 mutations, such as those at R132, result in downstream effects that are associated with tumorigenesis [56, 3]. IDH1 R132 mutations promote the reduction of alpha-ketoglutarate to 2-hydroxyglutarate, which is considered a potential onco-metabolite, with the coincident conversion of NADPH to NADP+ [56, 175, 104].

Gene	***IDH1***
Exon	4
Nucleotide	NM_005896.4: g.208248517_208248522delTTCAAC c.261_266delGTTGAA
Amino Acid	p.L88_K89del
Function	loss
Allelic Fraction	4.01% (of 349 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis; Idh1 is localized to the cytoplasm and peroxisome and Idh2 is localized to the mitochondria [139]. Mutations in these enzymes result in downstream effects that are associated with tumorigenesis [3]. Certain IDH1 mutations, such as those at R132, result in downstream effects that are associated with tumorigenesis [56, 3]. IDH1 R132 mutations promote the reduction of alpha-ketoglutarate to 2-hydroxyglutarate, which is considered a potential onco-metabolite, with the coincident conversion of NADPH to NADP+ [56, 175, 104].

Gene	***IDH2***
Exon	10
Nucleotide	NM_002168.4: g.90084358A>T c.1272-5T>A
Amino Acid	
Function	loss

Interpretation
The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis. Idh1 is localized to the cytoplasm and peroxisome and Idh2 is localized to the mitochondria [139]. Mutations in these enzymes result in downstream effects that are

Allelic Fraction 2.7% (of 259 reads) Classification **Tier 3** Assessment **Uncertain Significance**	associated with tumorigenesis [3]. IDH2 alterations, most notably at codons R140 and R172, alter the normal catalytic activity of the enzyme to promote the conversion of 2-ketoglutarate to d-2-hydroxyglutarate, a potential oncometabolite [56, 175, 139, 34, 96]. IDH mutations also result in oxidative cellular conditions and increased methylation, suggesting that these could be early stage events in specific cancers [3, 27].
Gene ***IDH2*** Exon 1 Nucleotide NM_002168.4: g.90102275C>T c.115+1G>A Amino Acid Function loss Allelic Fraction 3.26% (of 337 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis. Idh1 is localized to the cytoplasm and peroxisome and Idh2 is localized to the mitochondria [139]. Mutations in these enzymes result in downstream effects that are associated with tumorigenesis [3]. IDH2 alterations, most notably at codons R140 and R172, alter the normal catalytic activity of the enzyme to promote the conversion of 2-ketoglutarate to d-2-hydroxyglutarate, a potential oncometabolite [56, 175, 139, 34, 96]. IDH mutations also result in oxidative cellular conditions and increased methylation, suggesting that these could be early stage events in specific cancers [3, 27].
Gene ***JAK2*** Exon 7 Nucleotide NM_004972.4: g.5054606_5054607delGAinsTT c.658_659delGAinsTT Amino Acid p.D220F Function loss Allelic Fraction 1.13% (of 177 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** The JAK2 (Janus kinase 2) gene encodes the Jak2 protein, a tyrosine kinase that regulates signals triggered by cytokines and growth factors, such as erythropoietin, interleukins, and GM-CSF [74]. Mutations in the JAK2 gene play a significant role in the pathogenesis of hematological malignancies, and aberrant Jak2 signaling has also been found in some types of solid tumors [102, 143, 58, 137]. In addition, JAK2 mutations have been implicated in clonal hematopoiesis and detection of JAK2 mutations, and V617F in particular, in the circulating tumor DNA of solid tumor patients requires further investigation to exclude the presence of those alterations in peripheral blood cells [68, 138].
Gene ***KIT*** Exon 20 Nucleotide NM_000222.3: g.54737269_54737270delAGinsGA c.2791_2792delAGinsGA Amino Acid p.S931D Function loss Allelic Fraction 3.45% (of 58 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** The KIT gene encodes the tyrosine kinase receptor Kit (also known as c-Kit or CD117), which is expressed on the cell surface of a variety of cell types, including hematopoietic stem cells and melanocytes. Binding of the Kit ligand stem cell factor (SCF, or steel factor) leads to Kit dimerization and activation of the PI3K/Akt and Ras/MAPK signaling pathways that regulate cellular proliferation and survival [109]. KIT is considered to be a proto-oncogene, and activating mutations of the KIT gene can lead to tumorigenesis [45].
Gene ***MPL*** Exon 5 Nucleotide NM_005373.3: g.43340088delG c.816delG Amino Acid p.W272fs*5 Function loss	**Interpretation** MPL (Myeloproliferative Leukemia Virus Oncogene) encodes the thrombopoietin receptor (TPO-R) protein, a cytokine receptor that promotes megakaryocyte differentiation through the Jak/Stat and MAPK /ERK signaling pathways [6, 39, 117].

Allelic Fraction	2.06% (of 243 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Gene	***NOTCH1***
Exon	34
Nucleotide	NM_017617.5: g.136496493_136496495delGTG c.7244_7246delCAC
Amino Acid	p.P2415del
Function	loss
Allelic Fraction	3.41% (of 88 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
NOTCH1 encodes Notch1, a member of the Notch family of receptors, which contain an extracellular domain with several EGF-like repeats. Upon binding of membrane bound ligands, the Notch1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex regulating genes involved in cell fate determination, proliferation, and apoptosis [93]. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or oncogene [91, 173].

Gene	***NOTCH1***
Exon	34
Nucleotide	NM_017617.5: g.136497372_136497373delGC c.6366_6367delGC
Amino Acid	p.Q2123fs*144
Function	loss
Allelic Fraction	1.5% (of 133 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
NOTCH1 encodes Notch1, a member of the Notch family of receptors, which contain an extracellular domain with several EGF-like repeats. Upon binding of membrane bound ligands, the Notch1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex regulating genes involved in cell fate determination, proliferation, and apoptosis [93]. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or oncogene [91, 173].

Gene	***NOTCH1***
Exon	26
Nucleotide	NM_017617.5: g.136504757A>G c.4934T>C
Amino Acid	p.L1645P
Function	loss
Allelic Fraction	1.61% (of 124 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
NOTCH1 encodes Notch1, a member of the Notch family of receptors, which contain an extracellular domain with several EGF-like repeats. Upon binding of membrane bound ligands, the Notch1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex regulating genes involved in cell fate determination, proliferation, and apoptosis [93]. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or oncogene [91, 173].

Gene	***NOTCH1***
Exon	25
Nucleotide	NM_017617.5: g.136505855_136505856insT c.4040dupA
Amino Acid	p.N1347fs*2
Function	loss
Allelic Fraction	2.8% (of 107 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
NOTCH1 encodes Notch1, a member of the Notch family of receptors, which contain an extracellular domain with several EGF-like repeats. Upon binding of membrane bound ligands, the Notch1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex regulating genes involved in cell fate determination, proliferation, and apoptosis [93]. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or oncogene [91, 173].

Gene	***NOTCH1***
Exon	23
Nucleotide	NM_017617.5:

Interpretation
NOTCH1 encodes Notch1, a member of the Notch family of receptors, which contain an extracellular domain with several EGF-like repeats.

	g.136506897G>T c.3720C>A
Amino Acid	p.N1240K
Function	loss
Allelic Fraction	4.59% (of 109 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Upon binding of membrane bound ligands, the Notch1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex regulating genes involved in cell fate determination, proliferation, and apoptosis [93]. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or oncogene [91, 173].

Gene	***NOTCH1***
Exon	7
Nucleotide	NM_017617.5: g.136517939_136517940delTGinsCA c.1256-3_1256-2delCAinsTG
Amino Acid	
Function	loss
Allelic Fraction	6.25% (of 32 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
NOTCH1 encodes Notch1, a member of the Notch family of receptors, which contain an extracellular domain with several EGF-like repeats. Upon binding of membrane bound ligands, the Notch1 intracellular domain (NICD) is cleaved and forms part of a transcription factor complex regulating genes involved in cell fate determination, proliferation, and apoptosis [93]. Depending on cellular context, NOTCH1 can act as either a tumor suppressor or oncogene [91, 173].

Gene	***NPM1***
Exon	7
Nucleotide	NM_199185.3: g.171400162_171400170delTGATGATTT c.541_549delTTTGATGAT
Amino Acid	p.F181_D183del
Function	loss
Allelic Fraction	1.43% (of 140 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
NPM1 encodes nucleophosmin (Npm1), a nuclear phosphoprotein involved in numerous critical cellular processes including ribosome biogenesis and export, centrosome duplication, chromatin remodeling, and DNA repair [121, 44, 28]. Npm1 regulates the ARF/p53 pathway and enhances the oncogenic activities of Myc [20]. NPM1 mutations, particularly C-terminal truncations, have been reported frequently in myeloid malignancies, and although mutation has not been commonly found in solid tumors, overexpression of the Npm1 protein has been reported [162, 43, 76, 127, 83, 44]. Alterations in NPM1 and changes in Npm1 expression have been reported to affect the ARF/p53 pathway, and Npm1 has also been reported to function as a histone chaperone protein [94, 152, 66, 65].

Gene	***PMS2***
Exon	1
Nucleotide	NM_000535.7: g.6006034A>C c.24-3T>G
Amino Acid	
Function	loss
Allelic Fraction	1.38% (of 217 reads)
Classification	**Tier 3**
Assessment	**Uncertain Significance**

Interpretation
PMS2 encodes a member of the mismatch repair (MMR) gene family. MMR proteins are responsible for correcting DNA errors introduced either during replication, or as a result of DNA damage or chemical modification [148, 131]. Specifically, Pms2 and Mlh1 heterodimerize to form the MutL-alpha complex, which has an essential role as an ATPase that supports the functions of the MutS complex in DNA mismatch repair [148, 131]. MMR proteins, including the MutL-alpha complex, have also been implicated in the meiotic and mitotic cell cycle [131]. Germline mutations in PMS2 contribute to development of Hereditary Non-Polyposis Colorectal Cancer (HNPCC; Lynch syndrome), although PMS2 mutations have been shown to have a smaller role than MLH1/MSH2 alterations; PMS2 alterations have been reported to account for 6% of Lynch syndrome cases, as compared with 40-50% cited for MLH1/MSH2 alterations [126, 60, 19]. Carriers of germline PMS2 mutations have an increased risk of various cancers, including a reported cumulative risk of developing cancer by age 70 of 15-20% for colorectal cancer, 15% for endometrial cancer, and 25-32% for any Lynch syndrome-associated cancer [144, 75].

Gene ***PTEN*** Exon 7 Nucleotide NM_000314.8: g.87957910C>A c.692C>A Amino Acid p.P231H Function normal Allelic Fraction 1.17% (of 256 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** PTEN (Phosphatase and Tensin homolog) is a phosphatase that removes phosphate groups primarily from inositide (rather than protein) substrates. It functions as a tumor suppressor by negatively regulating the PI3K/Akt/mTOR pathway [149]. Loss of PTEN (through mutation or deletion) can lead to uncontrolled cell growth and suppression of apoptosis [154]. PTEN haploinsufficiency has been associated with tumorigenesis in some tumor types, including astrocytoma and prostate cancer [99, 168, 100, 32]. PTEN germline mutations are found in several cancer-predisposition syndromes, such as Cowden syndrome and Proteus syndrome [64].
Gene ***PTPN11*** Exon 1 Nucleotide NM_002834.5: g.112419126G>A c.14+1G>A Amino Acid Function loss Allelic Fraction 4.24% (of 425 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** PTPN11 encodes Tyrosine-protein phosphatase non-receptor type 11, also known as Shp-2, which plays a critical role in both embryonic development and in cancer [57]. Activating mutations in PTPN11 have been found in a variety of cancers, most notably hematological malignancies such as juvenile leukemia [159, 13]. The precise role of these mutations remains to be determined, as there is evidence that the gene can act as both a tumor suppressor and oncogene depending on the context [159, 8, 155]. Germline mutations in PTPN11 (which encodes the protein Shp-2) are associated with Noonan syndrome, a developmental disorder reported to confer predisposition towards several cancers [159, 78].
Gene ***RET*** Exon 12 Nucleotide NM_020975.6: g.43116672_43116673delCGinsTA c.2225_2226delCGinsTA Amino Acid p.T742I Function gain Allelic Fraction 2.08% (of 96 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** RET (Rearranged during Transfection) encodes Ret, a receptor tyrosine kinase primarily expressed in cells of the nervous system. It has been identified as a proto-oncogene that results in transformation of cells upon recombination with a partner gene [157]. RET gene fusions have been shown to be tumorigenic in various mouse models in preclinical studies [23, 158, 55, 132]. Sporadic RET mutations have been associated with multiple neuroendocrine and epithelial cancers and are especially prevalent in medullary thyroid carcinoma [129]. RET germline mutations have been reported to be involved in a hereditary tumor syndrome that, depending on nature and position of the mutation, as well as the tissue involved, results in familial medullary thyroid carcinoma, Multiple endocrine neoplasia type 2A (MEN 2A) and MEN 2B [51, 118].
Gene ***SRC*** Exon 4 Nucleotide NM_198291.3: g.37384295_37384296delCG c.144_145delCG Amino Acid p.G49fs*45 Function loss Allelic Fraction 1.11% (of 719 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** SRC encodes the protein Src, which belongs to a family of related non-receptor tyrosine kinases, and is involved in cell proliferation and migration [182, 136]. Src interacts with a number of downstream substrates important for tumor growth, survival, and invasion, including focal adhesion kinase (FAK) and receptor tyrosine kinases such as Egfr and Her2 [87, 136, 38, 169]. High expression and activity of Src have been observed in several cancer types and Src activity has been implicated in tumor progression and metastasis [73, 2, 156, 150, 49].
Gene ***SRC*** Exon 5 Nucleotide NM_198291.3:	**Interpretation** SRC encodes the protein Src, which belongs to a family of related non-receptor tyrosine kinases, and is involved in cell proliferation and

g.37386169C>A c.345C>A Amino Acid p.N115K Function normal Allelic Fraction 2.99% (of 167 reads) Classification **Tier 3** Assessment **Uncertain Significance**	migration [182, 136]. Src interacts with a number of downstream substrates important for tumor growth, survival, and invasion, including focal adhesion kinase (FAK) and receptor tyrosine kinases such as Egfr and Her2 [87, 136, 38, 169]. High expression and activity of Src have been observed in several cancer types and Src activity has been implicated in tumor progression and metastasis [73, 2, 156, 150, 49].
Gene ***VHL*** Exon 2 Nucleotide NM_000551.4: g.10149782T>G c.464-5T>G Amino Acid Function loss Allelic Fraction 2.36% (of 127 reads) Classification **Tier 3** Assessment **Uncertain Significance**	**Interpretation** VHL is the gene encoding the protein pVHL, or the von Hippel-Lindau tumor suppressor. Germline mutations in VHL have been associated with von Hippel-Lindau (vHL) disease, an autosomal dominant syndrome associated with tumors in multiple organs [12, 16, 17]. pVHL normally plays a role in the degradation of hypoxia-inducible factors (HIFs); inactivation of pVHL may therefore lead to an upregulation of HIF proteins and concomitant upregulation of VEGF pathway members that promote tumor growth and angiogenesis [79, 80, 146, 52]. Somatic inactivation of VHL, either via mutation or hypermethylation, is seen in the vast majority of clear cell renal carcinomas (ccRCC) and is central to its pathogenesis [106].

Genes Tested

QIAGEN Multimodal Panel - *ABL1, AKT1, ALK, APC, ATM, BCL6, BRAF, CDH1, CDKN2A, CSF1R, CTLA4, CTNNB1, DDR2, DNMT3A, EGFR, ERBB2, ERBB4, EREG, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, FOXL2, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, IRF4, JAK2, JAK3, KDR, KIT, KRAS, MAP2K1, MET, MLH1, MME, MPL, MSH2, MSH6, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PMS2, PRH2, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, TSC1, VHL*

Methods and Limitations

Nucleic acid processing, library construction, and sequencing methods for the custom QIAGEN MultiModal QIAseq assay are available upon request. Sequencing data was processed using the CLC Genomics Server bioinformatics platform, the Biomedical Genomics Analysis Server Plugin, and QIAGEN Clinical Insight Interpret.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (7.1.20201218), Ingenuity Knowledge Base (B-release), CADD (v1.6), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2020-04-06), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2020-11-17 10:02:34.0), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (B-release), MITOMAP: A Human Mitochondrial Genome Database. http://www.mitomap.org, 2019 (2020-06-19), PolyPhen-2 (v2. 2.2), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Nov 20 02:39), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 33), CentoMD (5.3), OMIM (July 06, 2020), gnomAD (2.1.1), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2020-09-15), DGV (2016-05-15), COSMIC (v92), HGMD (2020.3), OncoTree (oncotree_2019_03_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 153, GRCh38 153), SIFT4G (2016-02-23)

Disclaimer

The results provided in this report are for Research Use Only (RUO) and informational in nature. The information contained in this report cannot be used for paient treatment and/or prognostic decisions. No interpretations of genomic variants have been made by Discovery Life Sciences.

Clinical Significance of Variants Based on AMP / ASCO / CAP Guidelines*

Strong Significance	**Tier 1A**	• Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis • Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	• Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies • Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential Significance	**Tier 2C**	• Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis • Biomarker is an inclusion criterion for an active clinical trial • Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	• Biomarker shows plausible response or resistance based on case or preclinical studies • Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain Significance	**Tier 3**	• Biomarker has uncertain clinical significance and not known to be likely benign or benign

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