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Provider Information

Physician	Dr. Leonard McCoy
Institution	Enterprise Health
Case Id	SD123

Patient Information

Name	RD-NGSPROGENITYCANCER-SAMPLE13
Gender	Male
Date of Birth	10/11/2016
Id	1234

Sample Information

Sample Site	Blood	**Avg. Read Depth**	542x
Sample Type	Blood	**Collection Date**	10/3/2016
Collection Met…	Blood	**Receipt Date**	10/10/2016
Panel Coverage	99.73%	**Report Date**	10/11/2016

Results

Positive: Mutations with an establish somatic link detected.

Affected Genes

APC (0)	*ATM* (0)	*BARD1* (0)	*BMPR1A* (0)	*BRCA1* (0)	***BRCA2* (1)**	*BRIP1* (0)	*CDH1* (0)	*CDK4* (0)	*CDKN2A* (0)	*CHEK2* (0)
EPCAM (0)	*KLLN* (0)	*MEN1* (0)	*MLH1* (0)	*MSH2* (0)	***MSH6* (1)**	*MUTYH* (0)	*NBN* (0)	*NF1* (0)	*PALB2* (0)	*PMS2* (0)
POLD1 (0)	*POLE* (0)	***PTEN* (1)**	*RAD51C* (0)	*RAD51D* (0)	***RET* (1)**	*STK11* (0)	*TP53* (0)	*VHL* (0)		

Primary Findings

Gene	Type	Variant	Exon	Pathogenicity
BRCA2	CNV	4 exon duplication spanning 8,812bp	8-12	Pathogenic
MSH6	Heterozygous	NM_000179.2:c.2633T>C(NP_000170.1:p.Val878Ala)	4	Pathogenic
RET	Heterozygous	NM_020975.4:c.2996C>T(NP_066124.1:p.Ala999Val)	18	Pathogenic

Interpretation Summary

CNV and mutations found in BRCA2 as well as RET

Recommendations

Recommended for Sorafenib trial

OncoMD Drug Summary

OncoMD Trial Summary

RET

Cancer Type	Country	Drugs	Inclusion Criterion	Status	Trial Number
Neoplasms	Australia	Sorafenib (Nexavar, BAY43-9006)	RET MUTATION	Recruiting	NCT00625378
Soft Tissue Sarcoma	Australia	Sunitinib malate	RET MUTATION	Recruiting	NCT00753727
Neoplasms	Belgium	Sorafenib (Nexavar, BAY43-9006)	RET MUTATION	Recruiting	NCT00625378
Neoplasms	Brazil	Sorafenib (Nexavar, BAY43-9006)	RET MUTATION	Recruiting	NCT00625378
Hepatocellular Carcinoma	Brunei Darussalam	Sorafenib tosylate	RET MUTATION	Recruiting	NCT01135056
Neoplasms	Canada	Sorafenib (Nexavar, BAY43-9006)	RET MUTATION	Recruiting	NCT00625378
Paraganglioma	Canada	Sunitinib	RET MUTATION	Recruiting	NCT00843037
Kidney Cancer	Canada	sunitinib malate	RET MUTATION	Recruiting	NCT01099423
Hepatocellular Carcinoma	China	Sorafenib tosylate	RET MUTATION	Recruiting	NCT01135056
Hepatectomy	China	sorafenib	RET MUTATION	Recruiting	NCT01409499

Individual Variant Interpretations

NP_000170.1:p.Val878Ala in Exon 4 of *MSH6* (NM_000179.2:c.2633T>C) Pathogenic

This is a Missense Variant located in the MSH6 gene.

In 2 patients with hereditary nonpolyposis colorectal cancer (see HNPCC5, 614350) who had the same mutation in the MLH3 gene (E1451K; {604395.0005}), Wu et al. (2001) also found a heterozygous mutation in the MSH6 gene. One was a val878-to-ala mutation (V878A), and the other was an insertion of a T at nucleotide position 650 (650insT; {600678.0007}).

This gene has been observed to exhibit Autosomal dominant and Autosomal recessive inheritance pattern.

It has been associated with Colorectal cancer hereditary nonpolyposis type 5, Endometrial cancer familial, and Mismatch repair cancer syndrome.

Hereditary nonpolyposis colorectal cancer type 5 is a cancer predisposition syndrome characterized by onset of colorectal cancer and/or extracolonic cancers, particularly endometrial cancer, usually in mid-adulthood. The disorder shows autosomal dominant inheritance with incomplete penetrance (summary by Castellsague et al., 2015).

For a phenotypic description and a discussion of genetic heterogeneity of hereditary nonpolyposis colorectal cancer (HNPCC), see HNPCC1 (120435).

Molecular basis is known for 614350 because hereditary nonpolyposis colorectal cancer-5 (HNPCC5) is caused by heterozygous mutation in the MSH6 gene (600678) on chromosome 2p16.

NP_066124.1:p.Ala999Val in Exon 18 of *RET* (NM_020975.4:c.2996C>T) Pathogenic

This is a Missense Variant located in the RET gene.

The RET protooncogene is one of the receptor tyrosine kinases, cell-surface molecules that transduce signals for cell growth and differentiation. The RET gene was defined as an oncogene by a classical transfection assay. RET can undergo oncogenic activation in vivo and in vitro by cytogenetic rearrangement (Grieco et al., 1990). Mutations in the RET gene are associated with multiple endocrine neoplasia, type IIA (MEN2A; 171400), multiple endocrine neoplasia, type IIB (MEN2B; 162300), Hirschsprung disease (HSCR; aganglionic megacolon; 142623), and medullary thyroid carcinoma (MTC; 155240).

{121:Plaza-Menacho et al. (2006)} reviewed the genetics and molecular mechanisms underlying the different inherited neural crest-related disorders involving RET dysfunction.

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Central hypoventilation syndrome congenital, Medullary thyroid carcinoma, Multiple endocrine neoplasia IIA, Multiple endocrine neoplasia IIB, Pheochromocytoma, and Hirschsprung disease susceptibility to 1.

The disorder described by Hirschsprung (1888) and known as Hirschsprung disease or aganglionic megacolon is characterized by congenital absence of intrinsic ganglion cells in the myenteric (Auerbach) and submucosal (Meissner) plexuses of the gastrointestinal tract. Patients are diagnosed with the short-segment form (S-HSCR, approximately 80% of cases) when the aganglionic segment does not extend beyond the upper sigmoid, and with the long-segment form (L-HSCR) when aganglionosis extends proximal to the sigmoid (Amiel et al., 2008). Total colonic aganglionosis and total intestinal HSCR also occur.

Genetic Heterogeneity of Hirschsprung Disease

Several additional loci for isolated Hirschsprung disease have been mapped. HSCR2 (600155) is associated with variation in the EDNRB gene (131244) on 13q22; HSCR3 (613711) is associated with variation in the GDNF gene (600837) on 5p13; HSCR4 (613712) is associated with variation in the EDN3 gene (131242) on 20q13; HSCR5 (600156) maps to 9q31; HSCR6 (606874) maps to 3p21; HSCR7 (606875) maps to 19q12; HSCR8 (608462) maps to 16q23; and HSCR9 (611644) maps to 4q31-q32.

HSCR also occurs as a feature of several syndromes including the Waardenburg-Shah syndrome (277580), Mowat-Wilson syndrome (235730), Goldberg-Shprintzen syndrome (609460), and congenital central hypoventilation syndrome (CCHS; 209880).

Whereas mendelian modes of inheritance have been described for syndromic HSCR, isolated HSCR stands as a model for genetic disorders with complex patterns of inheritance. Isolated HSCR appears to be of complex nonmendelian inheritance with low sex-dependent penetrance and variable expression according to the length of the aganglionic segment, suggestive of the involvement of one or more genes with low penetrance. The development of surgical procedures decreased mortality and morbidity, which allowed the emergence of familial cases. HSCR occurs as an isolated trait in 70% of patients, is associated with chromosomal anomaly in 12% of cases, and occurs with additional congenital anomalies in 18% of cases (summary by Amiel et al., 2008).

Molecular basis is known for 142623 because of evidence that susceptibility to Hirschsprung disease-1 (HSCR1) is associated with variation in the RET gene (164761) on chromosome 10q11.

Multiple endocrine neoplasia type IIB (MEN2B) is an autosomal dominant hamartoneoplastic syndrome characterized by aggressive medullary thyroid carcinoma (MTC), pheochromocytoma, mucosal neuromas, and thickened corneal nerves. Most affected individuals have characteristic physical features, including full lips, thickened eyelids, high-arched palate, and marfanoid habitus. Other more variable features include skeletal anomalies and gastrointestinal problems (review by Morrison and Nevin, 1996).

For a discussion of genetic heterogeneity of multiple endocrine neoplasia (MEN), see MEN1 (131100).

Molecular basis is known for 162300 because of evidence that multiple endocrine neoplasia type IIB (MEN2B) is caused by heterozygous mutation in the RET gene (164761) on chromosome 10q11. Most patients (95%) carry a specific M918T mutation ({164761.0013}) in exon 16 of the RET gene.

Multiple endocrine neoplasia type IIA is an autosomal dominant syndrome of multiple endocrine neoplasms, including medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid adenomas. MEN2B (162300), characterized by MTC with or without pheochromocytoma and with characteristic clinical abnormalities such as ganglioneuromas of the lips, tongue and colon, but without hyperparathyroidism, is also caused by mutation in the RET gene (summary by Lore et al., 2001).

For a discussion of genetic heterogeneity of multiple endocrine neoplasia, see MEN1 (131100).

Molecular basis is known for 171400 because multiple endocrine neoplasia type IIA (MEN2A) is caused by heterozygous mutation in the RET oncogene (164761) on chromosome 10q11.

Incidental Findings

NP_000305.3:p.Asp268Glu in Exon 8 of *PTEN* (NM_000314.4:c.804C>A)

This is a Missense Variant located in the PTEN gene.

The PTEN gene encodes a ubiquitously expressed tumor suppressor dual-specificity phosphatase that antagonizes the PI3K signaling pathway through its lipid phosphatase activity and negatively regulates the MAPK pathway through its protein phosphatase activity (summary by Pezzolesi et al., 2007).

This gene has been observed to exhibit Autosomal dominant and Autosomal recessive inheritance pattern.

It has been associated with Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome 1, Endometrial carcinoma somatic, Lhermitte-Duclos syndrome, Macrocephaly/autism syndrome, Malignant melanoma somatic, PTEN hamartoma tumor syndrome, Squamous cell carcinoma head and neck somatic, VATER association with macrocephaly and ventriculomegaly, Glioma susceptibility 2, Meningioma, and Prostate cancer somatic.

Blumenthal and Dennis (2008) provided a detailed review of PTEN-related tumor syndromes.

Molecular basis is known for 153480 because of evidence that this disorder results from mutations in the PTEN gene (601728).

Cowden syndrome-1 (CWS1; 158350) and macrocephaly/autism syndrome (605309) are allelic disorders with overlapping clinical features. Approximately 60% of BRRS patients have PTEN mutations (Blumenthal and Dennis, 2008).

VACTERL describes a constellation of congenital anomalies, including vertebral anomalies, anal atresia, congenital cardiac disease, tracheoesophageal fistula, renal anomalies, radial dysplasia, and other limb defects; see 192350. Cases of familial VACTERL with hydrocephalus (H) have been reported with suggestion of autosomal recessive or X-linked inheritance (see 314390).

Other patients thought to have VACTERL-H, including 2 unrelated infants reported by Porteous et al. (1992), had been found to have Fanconi anemia (see 227650). Porteous et al. (1992) suggested that chromosomal breakage studies should be performed in all cases of VACTERL/VACTERL-H to rule out Fanconi anemia. Alter et al. (2007) noted that a VATER phenotype had been reported in Fanconi anemia of complementation groups A (227650), C (227645), D1 (605724), E (600901), F (603467), and G (614082). X-linked VACTERL-H is also associated with mutations in the FANCB gene (300515).

Molecular basis is known for 276950 because a mutation in the PTEN gene ({601728.0030}) was identified in 1 patient with VATER association with macrocephaly and ventriculomegaly.

Molecular basis is known for 605309 because of evidence that macrocephaly/autism syndrome is caused by heterozygous mutation in the PTEN gene (601728) on chromosome 10q23.

Molecular basis is known for 613028 because glioma may present as part of a tumor predisposition syndrome caused by mutation in the PTEN gene (601728) on chromosome 10q23.

For a general phenotypic description and a discussion of genetic heterogeneity of glioma, see GLM1 (137800).

NP_000050.2:p.Ile2944Phe in Exon 22 of *BRCA2* (NM_000059.3:c.8830A>T)

This is a Missense Variant located in the BRCA2 gene.

This gene has been observed to exhibit Autosomal recessive, Somatic mutation, and Autosomal dominant inheritance pattern.

It has been associated with Fanconi anemia complementation group D1, Wilms tumor, Breast cancer male susceptibility to, Breast-ovarian cancer familial 2, Glioblastoma 3, Medulloblastoma, Pancreatic cancer 2, and Prostate cancer.

Fanconi anemia (FA) is a clinically and genetically heterogeneous disorder that causes genomic instability. Characteristic clinical features include developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark of FA is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair (summary by Deakyne and Mazin, 2011).

For additional general information and a discussion of genetic heterogeneity of Fanconi anemia, see 227650.

Molecular basis is known for 605724 because Fanconi anemia complementation group D1 can be caused by homozygous or compound heterozygous mutation in the BRCA2 gene (600185) on chromosome 13q13.

Molecular basis is known for 612555 because susceptibility to familial breast-ovarian cancer-2 (BROVCA2) results from heterozygous germline mutations in the BRCA2 gene (600185) on chromosome 13q13.

For a discussion of genetic heterogeneity of breast-ovarian cancer susceptibility, see BROVCA1 (604370).

For general discussions of breast cancer and ovarian cancer, see 114480 and 167000, respectively.

Molecular basis is known for 613029 because glioma can present as part of a tumor predisposition syndrome caused by germline mutation in the BRCA2 gene (600185) on chromosome 13q13.

For a general phenotypic description and a discussion of genetic heterogeneity of glioma, see GLM1 (137800).

Molecular basis is known for 613347 because susceptibility to pancreatic cancer is conferred by heterozygous mutation in the BRCA2 gene (600185) on chromosome 13q13.

For background, phenotypic description, and a discussion of genetic heterogeneity of pancreatic carcinoma, see 260350.

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Additional Information

Test

Illumina TruSight Myeloid Sequencing Panel

Indication

The panel targets 54 tumor suppressor genes and oncogenetic hotspots for somatic mutations in hematological malignancies.

Background

The TruSight Myeloid Sequencing Panel uses next-generation sequencing (NGS) technology to provide a comprehensive assessment of 54 genes (tumor suppressor genes and oncogenetic hotspots) in one test. The panel targets mutations with known involvement in acute myeloid leukemia (AML). Myelodsyplastic syndrome (MDS), myelopriliferative neoplasms (MPN), chronic myelogenous leukemia (CML), and juvenile myelomocylic leukemia (JMML). The result is a single assay for accurate, economical, and rapid profiling of liquid tumors for disease status and prognosis, in multiple samples.

Method

TruSight Myeloid features a highly optimized oligo pool specific for investigating genomic changes associated with hematological malignancies. The panel focuses on ~ 141 kb of genomic content consisting of 568 amplicons of ~ 250 bp in length designed against the human NCB37/mg19 reference genome. The oligo pool targets 15 full genes (exons only) plus exonic hotspots of an additional 39 genes, providing nearly 100% coverages of all targeted regions.

This optimized oligo pool provides uniform coverage of the target regions, enabling > 500x coverage for 95% of amplicons at > 5,000x mean coverage.

Sequence data generated from TruSight Myeloid libraries are analyzed using the on-instrument MiSeq Reporter software. After demultiplexing and FASTQ file generation, the software uses a custom banded Smith-Waterman aligner to align the reads against the human hg10 reference genome to create BAM files. The Somatic Variant Caller then performs variant analysis for the specified regions. The outputs are VCF or gVCR files, which are text files that contain SNPs and small indels.

Limitations

This test may not detect all variants in non-coding regions that could affect gene expression or copy number changes encompassing all or a large portion of the gene.

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