Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication

ARUP test code 2011156

Primary Antibody Deficiency Specimen	Whole Blood

Primary Antibody Deficiency Panel Interp

Positive

RESULT
Two copies of a likely pathogenic variant was detected in the RAG2 gene.

LIKELY PATHOGENIC VARIANT
Gene: RAG2 (NM_000536.4)
Nucleic Acid Change: c.1352G>C, Homozygous
Amino Acid Alteration: p.Gly451Ala
Inheritance: Autosomal recessive

INTERPRETATION
Two copies of a likely pathogenic variant, c.1352G>C, p.Gly451Ala, was detected in the RAG2 gene by massively parallel sequencing. Pathogenic RAG2 variants are associated with autosomal recessive severe combined immunodeficiency, B cell-negative (MIM: 601457) and Omenn syndrome (MIM: 603554). This result is consistent with a diagnosis of a RAG2-related disorder.

Please refer to the background information included in this report for a list of the genes analyzed, methodology and limitations of this test.

Evidence for variant classification:
The RAG2 c.1352G>C, p.Gly451Ala variant (rs121918575) is reported in the literature as a compound heterozygote in multiple individuals affected with combined immunodeficiency syndrome and Omenn syndrome (Schuetz 2008, Schuetz 2014 Sharapova 2020, Tirosh 2019, Walter 2015, Wu 2019). Functional analyses of the variant protein show reduced V(D)J recombination activity (Schuetz 2014, Tirosh 2019). This variant is reported in ClinVar (Variation ID: 13138) and is found in the non-Finnish European population with an overall allele frequency of 0.007% (9/129174 alleles) in the Genome Aggregation Database. The glycine at codon 451 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.913). Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified likely pathogenic RAG2 variant (Familial Targeted Sequencing, ARUP test code 3005867).

H=High, L=Low, *=Abnormal, C=Critical

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Schuetz C et al. An immunodeficiency disease with RAG mutations and granulomas. N Engl J Med. 2008 May 8;358(19):2030-8. PMID: 18463379
Schuetz C et a. Lesson from hypomorphic recombination-activating gene (RAG) mutations: Why asymptomatic siblings should also be tested. J Allergy Clin Immunol. 2014 Apr;133(4):1211-5. PMID: 24331380
Sharapova SO et al. The Clinical and Genetic Spectrum of 82 Patients With RAG Deficiency Including a c.256_257delAA Founder Variant in Slavic Countries. Front Immunol. 2020 Jun 10;11:900. PMID: 32655540
Tirosh I et al. Recombination activity of human recombination-activating gene 2 (RAG2) mutations and correlation with clinical phenotype. J Allergy Clin Immunol. 2019 Feb;143(2):726-735. PMID: 29772310
Walter JE et al. Broad-spectrum antibodies against self-antigens and cytokines in RAG deficiency. J Clin Invest. 2015 Nov 2;125(11):4135-48. PMID: 26457731
Wu KY et al. Arthritis in Two Patients With Partial Recombination Activating Gene Deficiency. Front Pediatr. 2019 Jul 5;7:235. PMID: 31334206

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Primary Antibody Deficiency Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Primary antibody deficiencies are a group of genetic disorders affecting antibody production. Three categories of primary antibody deficiencies include common variable immunodeficiency disorders (CVID), agammaglobulinemia, and hyper-IgM syndrome.

EPIDEMIOLOGY: Incidence is estimated at 1 in 10,000.

INHERITANCE: X-linked, autosomal dominant, or autosomal recessive; dependent on the causative gene

CLINICAL SENSITIVITY: Approximately 20 percent for CVID; 75-80 percent for hyper-IgM syndrome; 90 percent for agammaglobulinemia; unknown for other syndromes

GENES TESTED: ADA; ADA2; AICDA; ATM; ATP6AP1; BLNK; BTK; CARD11; CD19; CD27; CD40; CD40LG; CD70; CD79A; CD79B; CDCA7; CR2; CTLA4; CXCR4*; DCLRE1C*; DNMT3B; GATA2; HELLS; ICOS; IGHM; IGLL1; IKZF1; IL21R; KDM6A; KMT2D; LRBA; MOGS; MS4A1; NBN; NFKB1; NFKB2; NFKBIA**; PIK3CD; PIK3R1; PLCG2; PRKCD*; RAC2; RAG1; RAG2; RNF168; SH2D1A; STAT3; TCF3**; TNFRSF13B; TRNT1; TTC37; UNG; XIAP*; ZBTB24
*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
**Deletion/duplication analysis is not available for this gene.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a primary antibody deficiency. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
CXCR4 (NM_001348056, NM_001348059) exon(s) 2
DCLRE1C (NM_001350965) exon(s) 15
DCLRE1C (NM_001350966) exon(s) 13
DCLRE1C (NM_001350967) exon(s) 16
PRKCD (NM_001354676, NM_001354678) exon(s) 1
XIAP (NM_001167, NM_001204401, NM_001378590, NM_001378591, NM_001378592) exon(s) 4

Single exon deletions/duplications will not be called for the following exons:
ADA (NM_000022, NM_001322051) 1; CXCR4 (NM_001348056) 2; CXCR4 (NM_001348059) 2; DCLRE1C (NM_001033855) 4-9; DCLRE1C (NM_001033857, NM_001289077) 6-10; DCLRE1C (NM_001033858, NM_001289079) 7-11; DCLRE1C (NM_001289076, NM_001289078) 3-7; DCLRE1C (NM_001350965) 4-9,15; DCLRE1C (NM_001350966) 3-7,13; DCLRE1C (NM_001350967) 6-10,16; DCLRE1C (NM_022487) 4-8; HELLS (NM_018063, NM_001289067, NM_001289068, NM_001289069, NM_001289070, NM_001289072) 7; HELLS (NM_001289071) 8; HELLS (NM_001289073) 6; IGLL (NM_152855) 2; IKZF1 (NM_001291846, NM_001291847) 4; MOGS (NM_001146158) 2; PRKCD (NM_001354676, NM_001354678) 1; XIAP (NM_001167, NM_001204401, NM_001378590, NM_001378592) 4; XIAP (NM_001378591) 5

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

H=High, L=Low, *=Abnormal, C=Critical

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Primary Antibody Deficiency Specimen	22-311-110773	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Primary Antibody Deficiency Panel Interp	22-311-110773	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical