ARUP LABORATORIES
800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Jonathan R. Genzen, MD, PhD, Chief Medical Officer

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

Pancreatitis Panel (CFTR, CTRC, PRSS1, SPINK1), Sequencing

ARUP test code 3004788

PANC Specimen	Whole Blood

PANC Interp

Positive

RESULT
One pathogenic variant was detected in the PRSS1 gene.

PATHOGENIC VARIANT
Gene: PRSS1 (NM_002769.5)
Nucleic Acid Change: c.86A>T; Heterozygous
Amino Acid Alteration: p.Asn29Ile
Inheritance: Autosomal dominant

INTERPRETATION
One copy of a pathogenic variant, c.86A>T; p.Asn29Ile, was detected in the PRSS1 gene by massively parallel sequencing. PRSS1 gene variants are primarily dominant gain-of-function variants that cause pancreatitis by promoting premature trypsinogen activation in the pancreas. Thus, this individual is at-risk for autosomal dominant hereditary pancreatitis. Clinical manifestations of hereditary pancreatitis are variable and age dependent. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

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 PRSS1 c.86A>T; p.Asn29Ile variant (rs111033566), also known as Asn21Ile, has been reported as a common PRSS1 pathogenic variant in hereditary pancreatitis (Rebours 2009, Rosendahl 2013), and co-segregates with affected individuals in multiple unrelated families (Ferec 1999, Gorry 1997, Teich 1998). Functional analyses reveal that the variant protein has enhanced auto-activation activity in acidic environments, which is predicted to be the pathogenic mechanism (Sahin-Toth 2000a, Sahin-Toth 2000b). This variant is also reported in ClinVar (Variation ID: 11877). The asparagine at codon 29 is weakly conserved, and computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.269). Based on available information, this variant is considered to be 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 pathogenic PRSS1 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
Ferec C et al. Mutations in the cationic trypsinogen gene and evidence for genetic heterogeneity in hereditary pancreatitis. J Med Genet. 1999 Mar;36(3):228-32. PMID: 10204851.
Gorry MC et al. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology. 1997 Oct;113(4):1063-8. PMID: 9322498.
Rebours V et al. The natural history of hereditary pancreatitis: a national series. Gut. 2009 Jan;58(1):97-103. PMID: 18755888.
Rosendahl J et al. CFTR, SPINK1, CTRC and PRSS1 variants in chronic pancreatitis: is the role of mutated CFTR overestimated? Gut. 2013 Apr;62(4):582-92. PMID: 22427236.
Sahin-Toth M et al. Gain-of-function mutations associated with hereditary pancreatitis enhance autoactivation of human cationic trypsinogen. Biochem Biophys Res Commun. 2000a Nov 19;278(2):286-9. PMID: 11097832.
Sahin-Toth M. Human cationic trypsinogen. Role of Asn-21 in zymogen activation and implications in hereditary pancreatitis. J Biol Chem. 2000b Jul 28;275(30):22750-5. PMID: 10801865.
Teich N et al. Mutations of the cationic trypsinogen in hereditary pancreatitis. Hum Mutat. 1998;12(1):39-43. PMID: 9633818.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Pancreatitis Panel (CFTR, CTRC, PRSS1, SPINK1), Sequencing

CHARACTERISTICS: Pancreatitis is a relatively common disorder with multiple etiologies that causes inflammation in the pancreas. Acute pancreatitis (AP) is a result of sudden inflammation, and patients may present with increased pancreatic enzyme concentrations. Chronic pancreatitis (CP) is a syndrome of progressive inflammation that may lead to permanent damage to pancreatic structure and function. Genetic testing can be utilized to determine a genetic cause of idiopathic or hereditary AP or CP and/or to assess risk of disease in family members.

EPIDEMIOLOGY: CP affects approximately 4-12 per 100,000 individuals per year.

CAUSE: Pathogenic germline variants in genes associated with idiopathic pancreatitis.

INHERITANCE: Autosomal dominant for PRSS1; autosomal recessive/digenic for CFTR, CTRC, and SPINK1.

CLINICAL SENSITIVITY: Approximately 48 percent of idiopathic pancreatitis.

GENES TESTED: CFTR (NM_000492), CTRC (NM_007272), PRSS1 (NM_002769), SPINK1 (NM_003122)
Deletion/duplication analysis is not available for these genes.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, including intronic variants 5T (IVS8), c.1680-886A>G (c.1679+1.6kbA>G), and c.3718-2477C>T of the CFTR gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage or known low quality, and to confirm reported variants that do not meet acceptable quality metrics.

ANALYTICAL SENSITIVITY/SPECIFICITY: 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.

LIMITATIONS: A negative result does not exclude a heritable form of pancreatitis. 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, deep intronic variants, and large deletions/duplications will not be identified. 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.

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
PANC Specimen	22-311-110799	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
PANC Interp	22-311-110799	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