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

Noonan Spectrum Disorders Panel, Sequencing, Fetal

ARUP test code 2010769

Maternal Contamination Study Fetal Spec	Fetal Cells Single fetal genotype present; no maternal cells present. Fetal and maternal samples were tested using STR markers to rule out maternal cell contamination.
Maternal Contam Study, Maternal Spec	Whole Blood For quality assurance purposes, ARUP Laboratories will confirm the above result at no charge following delivery. Order Confirmation of Fetal Testing and include a copy of the original fetal report (or the mother's name and date of birth) with the test submission. Please contact an ARUP genetic counselor at (800) 242-2787 extension 2141 prior to specimen submission.
Noonan Disorders Seq. Specimen, Fetal	Cultured Amnio
Noonan Disorders Seq. Interp, Fetal	Positive RESULT One pathogenic variant was detected in the PTPN11 gene. PATHOGENIC VARIANT Gene: PTPN11 (NM_002834.5) Nucleic Acid Change: c.781C>T; Heterozygous Amino Acid Alteration: p.Leu261Phe Inheritance: Autosomal Dominant INTERPRETATION One pathogenic variant, c.781C>T; p.Leu261Phe, was detected in the PTPN11 gene by massively parallel sequencing in this prenatal sample. Pathogenic PTPN11 variants are inherited in an autosomal dominant manner, and are associated with LEOPARD syndrome 1 (MIM: 151100) and Noonan syndrome 1 (MIM: 163950). This result is consistent with a diagnosis of a PTPN11-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 PTPN11 c.781C>T; p.Leu261Phe variant (rs397507525) is reported in the literature in several individuals affected with

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Noonan syndrome including multiple de novo and familial occurrences (Ezquieta 2012, Binder 2012, Pannone 2017, Bessis 2019, Monies 2019, Lorca 2021). This variant occurs within the highly conserved active site domain and in vitro functional analyses demonstrate a significant increase in basal level phosphatase activity consistent with the gain-of-function disease mechanisms of Noonan syndrome (Pannone 2017). This variant is also reported in ClinVar (Variation ID: 40520). This variant is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. Additionally, variants in this (p.Leu261His) and nearby (p.Leu262Arg) codons have been identified in affected individuals (Pannone 2017 and Ferrero 2012). Based on available information, the p.Leu261Phe 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 PTPN11 variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics.
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
Bessis D et al. Dermatological manifestations in Noonan syndrome: a prospective multicentric study of 129 patients positive for mutation. Br J Dermatol. 2019 Jun;180(6):1438-1448. PMID: 30417923.
Binder G et al. Health and quality of life in adults with Noonan syndrome. J Pediatr. 2012 Sep;161(3):501-505.e1. PMID: 22494877.
Ezquieta B et al. Alterations in RAS-MAPK genes in 200 Spanish patients with Noonan and other neuro-cardio-facio-cutaneous syndromes. Genotype and cardiopathy. Rev Esp Cardiol (Engl Ed). 2012 May;65(5):447-55. English, Spanish. PMID: 22465605.
Ferrero GB et al. Transcriptional hallmarks of Noonan syndrome and Noonan-like syndrome with loose anagen hair. Hum Mutat. 2012 Apr;33(4):703-9PMID: 22253195
Monies D et al. Lessons Learned from Large-Scale, First-Tier Clinical Exome Sequencing in a Highly Consanguineous Population. Am J Hum Genet. 2019 Jun 6;104(6):1182-1201. PMID: 31130284
Lorca R et al. Compound heterozygosity for PTPN11 variants in a subject with Noonan syndrome provides insights into the mechanism of SHP2-related disorders. Clin Genet. 2021 Mar;99(3):457-461. PMID: 33354767.
Pannone L et al. Structural, Functional, and Clinical Characterization of a Novel PTPN11 Mutation Cluster Underlying Noonan Syndrome. Hum Mutat. 2017 Apr;38(4):451-459. PMID: 28074573.

This result has been reviewed and approved by [redacted]

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BACKGROUND INFORMATION: Noonan Spectrum Disorders Panel, Sequencing, Fetal

CHARACTERISTICS: Group of disorders caused by variants in genes involved in the Ras/mitogen activated protein kinase (MAPK) pathway. Common symptoms include short stature, heart defect, developmental delay, coagulation defects, lymphatic dysplasia and undescended testes. Disorders tested include Noonan syndrome (NS), cardiofaciocutaneous (CFC) syndrome, Costello syndrome (CS), LEOPARD syndrome, Legius syndrome, and Noonan-like syndrome with loose anagen hair.

EPIDEMIOLOGY: Prevalence is 1 in 1,000 to 1 in 2,500 for NS.

CAUSE: Pathogenic germline variants in genes involved in the MAPK pathway.

INHERITANCE: Autosomal dominant for all analyzed genes.

CLINICAL SENSITIVITY: Approximately 99 percent for CFC, 80-90 percent for CS, 95 percent for LEOPARD syndrome and 75 percent for NS.

GENES TESTED: BRAF, CBL, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RASA2, RIT1, SHOC2, SOS1, SOS2, SPRED1

METHODOLOGY: Targeted 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 confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of a MAPK pathway disorder. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding 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 US 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.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Maternal Contamination Study Fetal Spec	22-307-112132	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Maternal Contam Study, Maternal Spec	22-307-112132	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Noonan Disorders Seq. Specimen, Fetal	22-307-112132	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Noonan Disorders Seq. Interp, Fetal	22-307-112132	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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