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

Holoprosencephaly Panel, Sequencing and Deletion/Duplication, Fetal

ARUP test code 2008863

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
Holoprosencephaly Panel Specimen, Fetal	Cultured Amnio
Holoprosencephaly Panel Interp, Fetal	Positive

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

INDICATION FOR TESTING
Fetal ultrasound findings of semilobar holoprosencephaly, microcephaly, transposition of great vessels, cleft lip and palate

RESULT
One pathogenic variant was detected in the ZIC2 gene.

PATHOGENIC VARIANT
Gene: ZIC2 (NM_007129.3)
Nucleic Acid Change: c.1277del; heterozygous
Amino Acid Alteration: p.Pro426ArgfsTer129
Inheritance Pattern: Autosomal dominant

INTERPRETATION
One copy of a pathogenic variant, c.1277del; p.Pro426ArgfsTer129, was detected in the ZIC2 gene by massively parallel sequencing and confirmed by Sanger sequencing in this prenatal sample. Pathogenic ZIC2 variants are associated with holoprosencephaly 5 (MIM: 609637). This molecular result is consistent with a diagnosis of holoprosencephaly.

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 ZIC2 c.1277del; p.Pro426ArgfsTer129 variant has been previously identified in a cohort of holoprosencephaly (HPE) patients (Roessler, 2009), and is reported in an additional female patient described as having semi-lobar HPE (Solomon, 2010). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant results in a premature termination codon in the last exon of the ZIC2 gene. While this may not lead to nonsense-mediated decay, it is expected to create a truncated ZIC2, and frameshift variants occurring after this variant have also been identified in HPE patients (Roessler, 2009). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation, including a discussion of medical screening and management, is recommended. At-risk family members, beginning with parents, should be offered testing for the identified pathogenic ZIC2 variant. Additionally, even if neither parent is found to carry the variant, prenatal diagnosis should be offered in future pregnancies because parental somatic or germline mosaicism for the identified ZIC2 pathogenic variant cannot be excluded (Familial Mutation, Targeted Sequencing, Fetal; ARUP test code 2001980).

COMMENTS
Benign and likely 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
Roessler E, et al. The full spectrum of holoprosencephaly-associated mutations within the ZIC2 gene in humans predicts loss-of-function as the predominant disease mechanism. Hum Mutat. 2009;30(4):E541-54.

Solomon BD, et al. Mutations in ZIC2 in human holoprosencephaly: description of a novel ZIC2 specific phenotype and comprehensive analysis of 157 individuals. J Med Genet. 2010;47(8): 513-24.

This result has been reviewed and approved by [redacted]

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Maternal Contamination Study Fetal Spec	24-212-111520	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Maternal Contam Study, Maternal Spec	24-212-111520	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Holoprosencephaly Panel Specimen, Fetal	24-212-111520	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Holoprosencephaly Panel Interp, Fetal	24-212-111520	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