I. Introduction and Purpose

Discordant cell-free fetal DNA screening and follow-up fetal diagnostic test results continue to challenge genetic counselors and other health care providers. Currently, limited information is available to aid providers in appropriately counseling patients about residual risks or additional testing in these circumstances. The purpose of this abstract is to provide an example of apparently discordant cell-free DNA test results and the subsequent findings following genetic counseling and additional testing. In this case, fetal chromosomal microarray identified the cause of the discrepancy between the cell-free DNA test result and the fetal karyotype. This approach may be useful for other patients with apparently discordant cell-free DNA test results.

II. Findings

A 38-year-old, G3P2 Caucasian female was referred for prenatal genetic counseling for a cell-free DNA test that was screen positive for trisomy 21. The patient had a first trimester anatomy ultrasound which identified no abnormalities. Nuchal translucency measurement was performed and measured 2.5mm. A three generation pedigree was obtained and family history was deemed noncontributory. The patient was counseled that given her maternal age and the sensitivity/specificity of the testing for chromosome 21, the positive predictive value was estimated to be 91%. Of note, fetal fraction on NIPT was 8.7%. The patient elected chorionic villus sampling and karyotype was normal female (46, XX). Microarray testing was run concurrently and revealed a 9.7 MB interstitial duplication on chromosome 21 at the following linear position: arr[hg19] 21q21.1q21.3(21,714,362-31,454,692)x3. Parental studies performed by qPCR analysis revealed the fetal duplication was de novo. FISH probe analysis was then performed, which revealed two normal hybridization signals in this region of chromosome 21 in each parent. The size of the alteration and the de novo origin indicate the possibility of clinical significance; however, no cases with the same breakpoints were found in the literature. One case of a much larger overlapping duplication was identified and was reported to be associated with hypotonia, joint hyperlaxity, developmental delay with speech delay, and brachycephaly. No other dysmorphic features besides brachycephaly were noted in the individual in the case report. Our patient was counseled about variable expressivity of copy number variants as well as the uncertain clinical impact of the result. The patient was also counseled that recurrence risk for future pregnancies is low but the possibility of gonadal mosaicism could not be excluded. The patient elected pregnancy termination at 14 weeks gestation.

III. Discussion and Conclusion

This case report confirms the importance of follow-up fetal diagnostic testing after positive cfDNA results. Furthermore, because this finding was not detected by traditional cytogenetic analysis, prenatal chromosomal microarray should be considered in cases of apparently discordant cfDNA and karyotype results. It is considered the preferred testing methodology by The American Congress of Obstetrics and Gynecology (ACOG Committee Opinion 581). Alternatively, the use of genome-wide cfDNA tests may also identify these at-risk cases and allow the clinician to order the appropriate analysis on diagnostic testing. As illustrated by this case, microarray analysis provided an explanation for the cfDNA result and relevant clinical information regarding the fetal prognosis for the patient.

IV. References