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Decisions Regarding Prenatal Diagnosis Following Abnormal Cell-Free DNA Results

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I. Objective

In their 2016 Practice Bulletin on Screening for Prenatal Aneuploidy, ACOG stresses the importance of diagnostic testing for all women with a positive cell-free DNA (cfDNA) test result, stating that a diagnostic procedure should be performed before any irreversible action is taken. The purpose of the study was to assess the uptake of prenatal diagnosis by women referred for genetic counseling due to a positive cfDNA result.

II. Methods

A total of 4,225 patients seen over a 5 year time period (2012-2017) were included. All patients in the study were offered the option of prenatal diagnosis as appropriate for gestational age. In order to determine if the disorder influenced the decision, positive cfDNA results were subdivided by categories: Down syndrome (DS), trisomy 13, trisomy 18, sex chromosome aneuploidy (SCA), structural chromosome abnormalities, other trisomies, triploidy, uninterpretable DNA pattern, and test failed (see detail **Figure 1**). The structural chromosome abnormality subcategory consisted predominantly of known microdeletion syndromes while the sex chromosome abnormalities and other trisomies included various chromosome abnormalities (see **Table 1**).

Figure 1. Distribution of positive cfDNA results

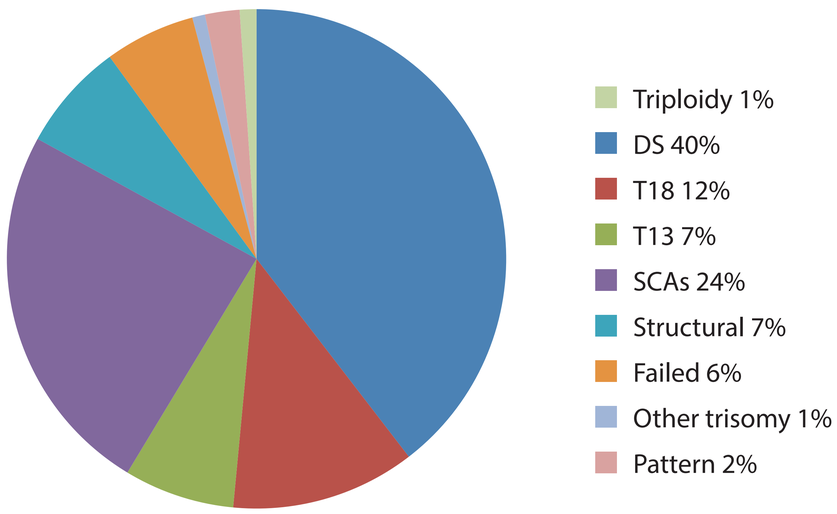


Table 1. Distribution of results in other categories

Other Trisomies		Structural Chromosome Abnormalities		Sex Chromosome Abnormalities	
Result	**n**	**Result**	**n**	**Result**	**n**
Trisomy 3	1	22q (DiGeorge)	179	XXX	247
Trisomy 7	6	5p (Cri-du-chat)	33	XXY	243
Trisomy 8	3	1p36	18	XYY	107
Trisomy 16	19	15q (AS/PWS)	58	X	433
Trisomy 20	1	4p (Wolf-Hirschhorn)	2	XXYY	3
Trisomy 22	5	Other Del / Dup > 7 MB	8		

III. Results

Overall, 55.7% of patients chose to proceed with prenatal diagnosis, 36.8% declined and 7.5% were undecided (**Figure 2**). Patients were most likely to proceed with prenatal diagnosis when their cfDNA result was positive for trisomy 18 followed closely by trisomy 13 and DS. Just over 50% of patients chose to proceed when results were positive for other trisomies and structural abnormalities. Roughly 40% of patients chose to proceed with positive results for SCAs, triploidy, and uninterpretable DNA pattern. The lowest uptake was in women with failed tests (**Figure 3**).

Figure 2. Overall patient decisions regarding prenatal diagnosis

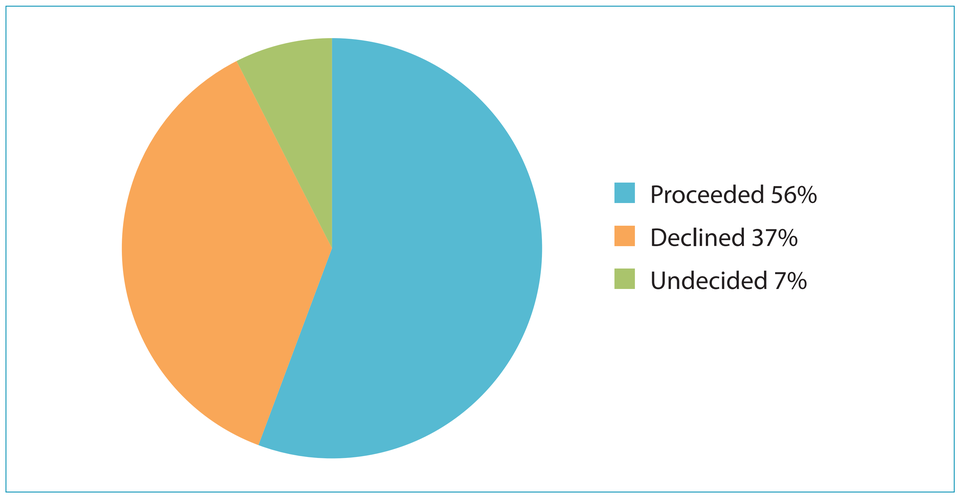
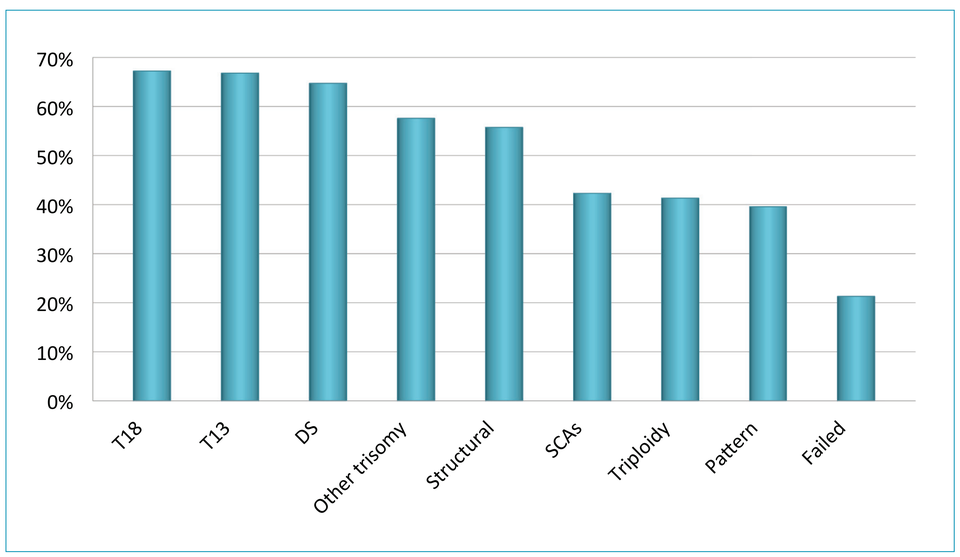


Figure 3. Percentage of patients proceeding with prenatal diagnosis distributed by cfDNA result



IV. Conclusions

This study illustrates that patients are more likely to undergo prenatal diagnosis when their results are positive for a severe trisomy as compared to less severe conditions such as SCAs or less clear results such as failed tests. Though cfDNA has a high sensitivity and specificity, positive predictive values can be low depending on patient age and chromosome abnormality. The clinical utility of prenatal diagnosis is clear regardless of the disorder and includes confirmation of the predicted abnormality for appropriate management of the pregnancy and delivery. It is equally important to identify pregnancies with an abnormal but discordant chromosome finding. Finally, confirmation is essential for counseling regarding recurrence risks in future pregnancies.

Although this study does not allow for analysis of factors influencing decision-making, anecdotal information suggests that patients often decline prenatal testing when they do not intend to consider pregnancy termination. However, diagnostic testing may reveal a normal fetal karyotype, alleviating anxiety and forestalling unnecessary planning for a nonexistent diagnosis. Alternatively, confirmation of the predicted abnormality affords patients and care providers the opportunity to properly prepare for the birth of an affected baby. Some women may also forego prenatal testing in favor of ultrasound, assuming that a normal study excludes the condition, while abnormal findings confirm. Some patients with abnormal ultrasound findings may choose to terminate their pregnancy without diagnostic confirmation. In these cases, testing on products of conception is recommended.

Given the breadth of disorders that patients may be faced with as well as the potential for aneuploidy with cfDNA test failures, appropriate pre-test education is essential for informed decision making. When abnormal results are obtained, genetic counseling is critical for patient understanding of the risk(s) identified by cfDNA testing, the positive predictive value of these results, limitations of ultrasound, and benefits of prenatal diagnosis. As this study shows, a significant percentage of patients will choose not to pursue prenatal diagnosis therefore follow-up later in pregnancy and post-delivery will need to be considered. Future studies evaluating diagnostic testing decisions based on positive predictive values may also be informative.

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