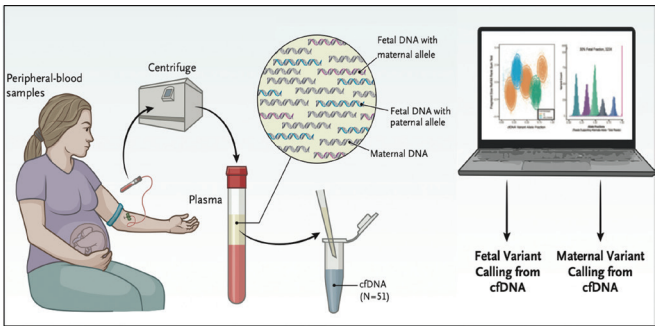

Figure 1: Workflow of Noninvasive Fetal Exome Sequencing (NIFS). Figure adapted from Brand et al., NEJM (2023)

Noninvasive Fetal Sequencing: A Simple Maternal Blood Test that Enables Comprehensive Prenatal Genetic Screening

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Non-invasive prenatal testing (NIPT) has enabled the detection of fetal chromosomal aneuploidies, such as trisomy 21 (Down syndrome), by providing a fetal screening method that requires only a maternal blood sample. The uptake of NIPT has been staggering, now approaching ~50% of all pregnancies in the US and most developed countries. In parallel, the landscape of genetic testing has dramatically shifted with technologies that now survey all human genes and mutations using complete genome and/or exome sequencing (GS/ES). Standard NIPT is blind to all these sequence variants and submicroscopic copy number variants (CNVs) of clinical relevance to fetal and/or maternal health. Consequently, the diagnostic gold standard for high-resolution genetic testing still requires an invasive medical procedure on the mother, such as amniocentesis, despite high cost, infrastructure demands, and procedural risks to both fetus and mother. A comprehensive noninvasive fetal screen would thus represent a paradigm-shifting advance for maternal-fetal medicine and could provide access to all expectant mothers worldwide.

To address this unmet need, our team at MGH has developed a noninvasive fetal sequencing (NIFS) platform capable of sequencing and interpreting ~23,000 protein-coding genes directly from a maternal plasma sample. After demonstrating technical feasibility on 51 samples in a proof-of-principle study (Brand et al., NEJM) and have now completed a large-scale validation against prospective invasive fetal sequencing. In an analysis of 577 maternal plasma samples (9-38 weeks of gestation), NIFS achieved over 96% sensitivity and 97% precision compared to ES/GS following an invasive procedure. Compared to this gold standard, NIFS confidently detected 95.3% of all diagnostic variants, including 100% of clinically relevant CNVs all of which were missed by NIPT. NIFS also identified unexpected and clinically important pregnancy situations, such as a maternal bone marrow transplant, molar pregnancy, and fetal twin demise. Moreover, NIFS provided a maternal carrier screen with a reportable finding in 58.3% of mothers.

Overall, NIFS offers a scalable, noninvasive platform for comprehensive prenatal genetic screening. By removing the need for invasive procedures, this technology has the potential to open access to complete fetal and maternal genetic screening to all pregnant persons. Our approach sets the stage for the utility of genetic screening as a tool for longitudinal precision healthcare and, together with commercial partners and the clinical expertise of our team, offers re-interpretation services of a 'genome for life'. NIFS is thus positioned to redefine clinical practice in maternal-fetal medicine, with significant commercial and healthcare system implications.