In Silico Enrichment of Fetal Fraction to Improve Fetal Aneuploidy Detection in Non-invasive Prenatal Testing

Socioeconomic and Racial Disparities in Non-invasive Prenatal Testing Access

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

Over the last decade, non-invasive prenatal testing (NIPT) has become more prevalent as a way of screening for possible fetal aneuploidies during pregnancy. NIPT works by using bioinformatics techniques to sequence and then analyze the fetal DNA circulating in the maternal bloodstream, and therefore requires only a maternal blood draw in order to collect the genetic material, compared with the invasive procedures required by other prenatal testing techniques (van der Meij et al., 2022). The noninvasive nature of NIPT, as well as its ability to be conducted as early as the first trimester of a pregnancy, has led to its use in an estimated 25-50% of pregnancies in the United States (Ravitsky et al., 2021).

However, despite its increasing use, there remain gaps in the efficacy of NIPT. Its Positive Predictive Value, a measure of how likely a fetus is to have an aneuploidy given a positive NIPT result, ranges only between 45% and 80%, and patients with low fetal fraction, or low amounts of fetal DNA circulating in the maternal bloodstream, remain incredibly likely to receive an inconclusive result (Samura & Okamoto, 2020). The development of a technique to better classify DNA as fetal or maternal could help provide a mechanism of *in silico* fetal fraction (FF) enrichment, allowing more patients to receive more accurate NIPT results. This provides the basis for the technical component of the project, which aims to analyze existing NIPT data to assign every genomic location a fetal probability score (FPS), which would indicate the likelihod that a genomic fragment from that site is fetal in origin. This FPS can then be used to digitally enrich fetal fraction in order to more accurately call aneuploidy even with low FF.

Along with NIPT's potential technical shortcomings, clinicians increasingly prescribing NIPT has also begun to raise questions about its accessibility, especially among racial minorities and socioeconomically disadvantaged populations historically underserved by the medical field

(Chetty et al., 2013). Better understanding the challenges that exist in the accessibility and reliability of NIPTs for these communities is a key first step in the process of addressing and one day eliminating those disparities. Therefore, the STS component of this project will focus on using the Social Construction of Technology model to highlight the social groups involved in NIPT and elucidate how their differing goals result in barriers to equitable NIPT access.

Technical Topic

Multiple peer-reviewed studies have shown that low fetal fraction (FF) remains the most common reason for a no-call result, which occurs when the NIPT algorithms are unable to make a decision on whether a fetal chromosomal abnormality exists, with an FF less than 4% able to account for up to 50% of all test failures (Samura & Okamoto, 2020; Yaron, 2016). Patients who receive a no-call result typically have to either repeat the NIPT process, opt for an invasive testing procedure, which carries a 1 in 300 risk of fetal harm, or proceed with no prenatal testing at all (Warsof, 2015; Yaron, 2016). These findings provide a rationale for why improving fetal fraction *in silico*, meaning via better computational analysis techniques, can lead to expanded NIPT access: currently, the largest barrier to more successful NIPT outcomes is test failure due to low FF. Ashoor et al. (2013) further found that women of Afro-Caribbean origin, or with higher BMI, tend to have lower FF on average, indicating that already-vulnerable groups may be the most likely to experience NIPT failure. Therefore, improving the ability of NIPT to make accurate calls even when analyzing minimal fetal DNA will help more patients of all backgrounds receive prenatal testing information without suffering additional costs or possible harm to their pregnancy.

While Yaron (2016) provides a clinical justification for the technical project, studies by Chan et al. (2016) and Sun et al. (2018) provide the scientific foundation. Both of these peer-

reviewed studies showed that DNA from certain genomic sites is more likely to be fetal DNA than maternal DNA (Chan et al., 2016; Sun et al., 2018). This suggests that a DNA fragment from the maternal bloodstream can be classified as more likely to be fetal or non-fetal based entirely on its genomic origin location. Before this work by Chan et al. (2016) and Sun et al. (2018), it was thought to be impossible to computationally determine whether fragments were fetal in origin after the maternal blood draw and sequencing steps were already completed, so their work is a cornerstone upon which this technical research rests.

The aim of this technical research project is therefore to work with computational biologists, bioinformaticians, and computer scientists to assign every genomic site a fetal probability score (FPS), using a combination of computational, statistical, and metagenomic analysis techniques on existing NIPT data. This site-specific FPS, which would indicate the likelihood of DNA from a given site being fetal DNA, could then be incorporated into NIPT pipelines to artificially enrich FF by giving greater weight to DNA with a higher FPS when predicting fetal aneuploidy. The goal is that this enhanced NIPT algorithm will be able to better predict aneuploidy even in cases of low FF, resulting in fewer no-call results.

STS Topic

A study conducted in 2021 showed that NIPT uptake was two times lower in socioeconomically disadvantaged communities compared to other neighborhoods, citing an economic barrier due to insufficient insurance coverage as the primary cause (Meij et al., 2021). Even though this study was based on data in the Netherlands, the conclusions reached by Meij et al. (2021) can also be applied here, where medical insurance is a topic of huge importance in the discussion around health care access. In the United States, private insurance companies generally cover the cost of NIPT for patients defined as high-risk, but there is no standardized regulation

enforcing this (Gadsbøll et al., 2020). This leaves insurance companies at their own discretion as to whether they cover NIPT, and for whom. Further, Medicaid, whose customer base primarily consists of low-income families, provides no coverage at all for NIPT in nine states, and covers patients defined as average-risk in only six states (Gadsbøll et al., 2020). With out-of-pocket costs for NIPT ranging from several hundred to a thousand dollars, many socioeconomically disadvantaged families may be unable to afford NIPT if they lack insurance or their insurance does not cover the test (Meij et al., 2021). Therefore, it is clear that insurance coverage, or lack thereof, functions as one socioeconomic barrier to equitable NIPT access. One of the goals of this STS project will be to further explore how insurance coverage affects NIPT access and understand what other socioeconomic barriers may also exist.

Intertwined with the economic barriers, several studies in the peer-reviewed prenatal care research journal Prenatal Diagnosis suggest there also exists a racial disparity in NIPT uptake. In 2013, just after NIPT became available, Caucasian women were found to be more likely to decline an invasive procedure at the studied testing center compared with Hispanic women (Chetty et al.). Similarly, Yarrington et al. conducted a retrospective study in 2021 which showed that Black and Hispanic women were less likely to use NIPT compared with white women, at 19%, 15%, and 33% use respectively. These studies suggest a race-based difference in NIPT uptake that hints at underlying issues in how NIPT is presented, explained, or made available to women of color compared to Caucasian women.

A recent paper by van der Meij et al. (2022) presented inadequate prenatal counseling as one reason behind this, discussing how barriers to access are not only physical or financial, but also perpetuated by a systemic knowledge gap. Van der Meij et al. made the compelling argument that patients who don't have sufficient knowledge of NIPT's purpose, strengths, and

limitations cannot be said to have equal access to it, and may additionally be less likely to choose NIPT or benefit from its results if they do (2022). This suggests that adequate genetic counseling during the prenatal care process is an important component of establishing equitable NIPT access. Research by Christopher et al. (2022) further found that women from underprivileged racial and socioeconomic backgrounds were less likely to receive adequate aneuploidy counseling during their first prenatal care visit, reaffirming this as a possible barrier and an important avenue for further investigation.

Further understanding these socioeconomic and racial barriers to NIPT success can provide important insight. Therefore, the goal of this STS research would be to use Social Construction of Technology (SCOT) to describe and connect the different social groups contributing to the NIPT process, in order to understand how to improve equity in prenatal care among all pregnant people. SCOT was chosen as the primary framework due to its ability to incorporate inherent power imbalances, such as that which exists between a physician and a pregnant patient. Various relevant groups, including healthcare providers, pregnant people, insurance companies, and NIPT companies, will be included in the SCOT analysis. Primary research, such as case studies on the use of NIPT in diverse communities, statistical analysis of NIPT uptake among various socioeconomic and racial groups, and clinical sources describing the NIPT prescription process, will be used to flesh out the motivations of each social group and understand this topic.

Conclusion

The goal of this research is two-fold. From a technical perspective, the objective is to analyze existing NIPT patient data to generate a data table containing a fetal probability score for every genomic site, which can then be used to improve the accuracy of the NIPT bioinformatics

pipeline and help more pregnant people receive more accurate prenatal testing results. The second aim is to better understand the economic and cultural barriers that have led to decreased NIPT use among underserved socioeconomic and racial groups in the United States. The combined focus of both of these goals is ultimately to pave the way for increased access to accurate NIPT testing among all pregnant people who wish to learn about the genomic health of their developing baby.

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