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Non-invasive prenatal testing in mitigating concerns from invasive prenatal diagnostic testing: retrospective assessment of utility in an academic healthcare system in the US

Kibum Kim [1,2] Linda Kaitlyn Craft [3]

¹Department of Pharmacy Systems, Outcomes and Policy, University of Illinois at Chicago, Chicago, Illinois, USA
²Department of Pharmacotherapy, The University of Utah, Salt Lake City, Utah, USA
³University of Utah, Salt Lake City, Utah, USA

Correspondence to
Dr Kibum Kim;
kkim204@uic.edu

ABSTRACT

Objective Non-invasive prenatal testing (NIPT) is a front-line screening for fatal chromosomal aneuploidy. In pregnant women with a risk of having fetal congenital disorders, NIPT is anticipated to reduce the needs of invasive prenatal diagnostic test (IPD). The objective of this study was to understand the acceptance of NIPT and the utility of NIPT to mitigate concerns about IPD in the US high-risk pregnancy management.

Design and setting This was a retrospective observational research using healthcare records obtained from an academic healthcare system in the US. The study consisted of site-level longitudinal analysis and patient-level cross-sectional analysis.

Participant A total of 5660 new high-risk pregnancies with age ≥35 years were identified for the longitudinal trend analysis. Cross-sectional utility assessment included 2057 pregnant women.

Exposure and outcome measures Longitudinal trends of NIPT order, IPD procedure and the number of patients diagnosed with high-risk pregnancy were descriptively summarised. In the cross-sectional assessment, we tested the association between the use of NIPT and IPD using multivariable regression.

Results The rate of increase in the NIPT use exceeded the changes in the number of high-risk pregnancies with age ≥35 years, while the number of annual IPD procedures has fluctuated without specific trends. There was no significant association between the numbers of NIPT and IPD with the adjusted ORs between 0.90 and 1.14 (p>0.1). The order of NIPT was not selected as an independent variable predicting the use of IPD. Clinical characteristics indicating low socioeconomic status and limited healthcare coverage are associated with less use of NIPT and lower clinical utility.

Conclusion Although prenatal care accepted NIPT over the last decade, the utility of NIPT in mitigating concerns on IPD is unclear and needs further investigation. Limited clinical utility should be addressed in the context of disparity in prenatal care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study includes both healthcare system level and patient-level assessments on the utility of non-invasive prenatal testing (NIPT) in the US healthcare setting.
⇒ Summary statistics segmented by calendar year specifically demonstrated the acceptance of NIPT in a US academic medical centre driven by the expansion of insurance coverage.
⇒ Factors other than the clinical motivations are descriptively and inferentially tested in the assessment of NIPT utility and access.
⇒ Although this study provides viable insight into the use and utility of the advanced prenatal care strategy, general limitations of single-site observational research warrant a multisite health outcomes study.

familier life trajectory, both emotionally and financially.[1–8] People living with congenital disability and their caregivers suffer from impaired quality of life.[1 2] Despite major improvements in medical management and social support, long-term morbidities, particularly neurodevelopmental and mental health issues, remain a cause for concern.[9 10] In the era of patient-centric medical care, the early detection of FCA enhances reproductive autonomy and helps expectant parents to contemplate before making an irrevocable conclusion.[11 12]

There have been advances in prenatal care that enable expectant parents to learn of congenital disorders, allowing them to have the power to control pregnancy and child-bearing earlier and make informed medical decisions. Maternal serum screening (MSS) was a minimally invasive traditional approach to determine the risk of fetal congenital disorders.[13–15] However, the risk of FCA based on MSS does not well predict the actual chromosomal anomalies, as it has a positive predictive

INTRODUCTION

Fetal chromosomal anomalies (FCA) has a significant influence on the personal and

value inferior to the predictive accuracy of a combination of other non-invasive measures, including maternal age, fetal nuchal translucency and fetal heart rate.[13–17] A better prediction of congenital disorders has been achieved via diagnostic invasive prenatal testing (IPD), which includes amniocentesis, chorionic villus sampling (CVS) and fetal blood sampling. Although providing patients with clinically valid data with a 99% positive prediction of certain FCAs, IPD is associated with a minor but sizeable increase in the rate of miscarriage and infection.[3] Complications after IPD has been a concern to both providers and expectant mothers.[3]

Non-invasive prenatal testing (NIPT), or cell-free DNA (cfDNA) testing, is a screening to help identify potential genetic concerns.[14] NIPT relies on the presence of free-floating cfDNAs which arise when cells die and release the DNA into the bloodstream from the placenta. If the percentage of cfDNA fragments for a particular chromosome is higher than expected, it indicates that the fetus has an increased likelihood of having a disorder associated with that chromosome, and is generally followed by further testing. NIPT has been shown to have a sensitivity and specificity above 99% for detecting trisomy 21, as well as a 98% positive predictive value for fetal trisomy 18, and a 99% positive predictive value for fetal trisomy 13 with a combined false-positive rate of 0.13%.[7 14]

NIPT showed promise in reducing unnecessary invasive medical procedures but is associated with a high upfront cost to healthcare plans in the US healthcare setting.[4] When it is covered, NIPT can cost payers upwards of US$3000 and patients with insurance are left with an out-of-pocket cost.[6] In addition, many state Medicaid plans and some health plans are not on board to pay for NIPT.[4 6] While NIPT has upfront costs, implementation of this procedure has the potential to reduce unnecessary medical costs and potential maternal or fetal harm. A previous model-based study demonstrated that NIPT can reduce the number of unnecessary invasive tests by 94.8% and decrease IPD-related miscarriages by 90%.[18] Out of 1 000 000 simulated scenarios, replacing MSS with NIPT would result in an increase in 893 detections of FCA and would be followed by a cost savings of approximately US$170 million.[8]

A screening test has clinical utility, beyond analytical validity and clinical validity, in a practice when it potentially influences and improves clinical decisions.[19–21] Thus, potential cost savings to payers would be achieved when analytically valid test is translated into a clinical utility: NIPT significantly influences clinical decision and outcomes as hypothesised. Nevertheless, NIPT results may be a small addition to a previous standard of care, rather than become the most critical component, to determine the needs of further actions. Clinical practice can still be directed by ultrasound assessment, patient preference, and provider's previous training, which may not result in the cost-effective use of the NIPT as simulated. A study performed in early 2010s showed a decline in the number of amniocenteses coincided with the use of NIPT.[22] Similarly, a recent

time-series assessment on the use of invasive diagnostic test in Australilian healthcare system demonstrated that the decrease in IPD since 2000 continued after NIPT started being covered by the public sector since 2013.[23] Nevertheless, the lack of assessment on the patient-level association on the NIPT and IPD left the downstream effect of NIPT from the clinical utility standpoint unanswered.

The objectives of this study were to assess the acceptance of NIPT in clinical practice setting, to evaluate the role of NIPT in alleviating the need for IPD, and to explore the patient-level characteristics that lead to the order of NIPT and IPD. We hypothesised that there would be a negative association between the order of NIPT and the frequency of IPD performed, which is a strong signal of the clinical utility of NIPT in high-risk pregnancy management.

METHODS
Study design and setting
This is a retrospective observational research consisting of two sections: (1) a healthcare system-level longitudinal change analysis and (2) patient-level cross-sectional analysis using data from the University of Utah enterprise data warehouse from which comprehensive clinical records and healthcare resource utilization at the University of Utah Health are available.

Patient and public involvement
Patients were not involved in this study.

NIPT acceptance
We compared the number of NIPT to the total number of high-risk pregnancies with age ≥35 years (advanced maternal age) and the number of IPD performed at a site level to visualise the acceptance of NIPT into the healthcare setting. We looked at the longitudinal variation to see if the numbers of NIPT and IPD over time align with or exceeds the changes in the number of new high-risk pregnancies with advanced maternal age. Analytic cohort included pregnant women with one or more records of high-risk pregnancy (ICD-10-CM O09.x or ICD-9-CM V23.x) between January 2012 and December 2018.[24–30] Eligible subjects were 35 years old or older at the first date of the high-risk pregnancy diagnosis. The NIPTs ordered during the study period within the healthcare network were identified using terminology available from institutional treatment records including "NON-INVASIVE PRENATAL", "NIPT FETAL ANEUPLOIDY", "NIPT FETAL MICRODELETION", "CELL-FREE DNA" as well as available brand names of NIPT tests. To be labled as the IPD of interest, the procedure happened within the healthcare system was defined using texts "chorionic villus" and "amniocenteses" from pathology, laboratory and procedure records. Descriptive statistics include the number of patients ordering NIPT, receiving IPD procedures, and seeing providers for a new high-risk pregnancy.

Patient-level analysis
Study cohort identification
The analytic cohort for the patient-level analysis was a subset of patients from the longitudinal cohort: subjects

with a diagnosis of high-risk pregnancy (ICD-10-CM O09.x) at any point between October 2015 and December 2018 with the patient aged 35 years or older.[24–30] NIPT can generally be considered once the gestational age is past 9 weeks, which can be followed by additional CVS before the gestational weeks 11 and 14 of pregnancy.[14] Amniocentesis is usually performed between 15 and 18 weeks of gestational age although more amniocentesis procedures are now being performed at 11–14 weeks' gestation.[31] The first prenatal visit for a new pregnancy usually happens around the gestational age of 8 weeks.[32] All things considered, eligible subjects had a record of prenatal care from the first-trimester (ICD-10-CM O09.x1, O09.5x1, O09.6x1, O09.8x1) and must be followed by the University of Utah Health for longer than 90-day period from that first-trimester visit, which allowed for a sufficient window to cover both NIPT and IPD. The accuracy of NIPT results is debatable in patients having more than one fetus. Thus, any expectant mothers with one or more records of multiple gestation (ICD-10-CM O30.x) were excluded from this study.[24] All the selected subjects were 35 years old or older at the first encounter with the first-trimester prenatal care visit. Clinical characteristics, demographic characteristics and records of NIPT and IPD were collected over the 90-day follow-up period. Patient characteristics were identified from the review of diagnosis codes, enrolment information and demographic tables. Patient characteristics as underlying conditions for the high-risk pregnancy included maternal age (ICD-9 659.63, ICD-10 O09.51x, O09.52x), insufficient prenatal care (ICD-9 V23.7, ICD-10 O09.3), genitourinary tract infection during pregnancy (ICD-9 646.0x, ICD-10 O23.x), grand multiparity (ICD-9 659.4, ICD-10 O09.40), type 1 or type 2 diabetes (ICD-9 250, ICD-10 O24.01, O24.11), history of hypothyroidism (ICD-9 243, ICD-10 E00,E01,E02), hypertension (ICD-9 642.3x, 642.9x, ICD-10 O13.9), social problems (ICD-10 O09.3, O09.70, O09.71, O09.72, O09.73), drug/alcohol use during pregnancy (ICD-9 649, ICD-10 O99.33), type of health plan and obesity (ICD-10 O99.21).[24–30]

Exposure and outcomes

The exposure for the patient-level analysis is the order of NIPT. We used the same text-search algorithm used for the site-level NIPT acceptance to determine the NIPT order. The date of NIPT order was matched with the date of medical encounter for pregnancy to confirm the order was not misplaced and was part of prenatal care. The outcome of this study is the administration of IPD, either CVS or Amniocentesis. The procedure performed within the institutional healthcare network was defined using texts "chorionic villus" and "amniocentesis, laboratory and procedure records." We also used applicable Current Procedural Terminology codes including 59000, 59105, 76945 and 76946 to confirm that the IPD was performed. To be classified as an exposure or outcome, the procedure or order record had to fall within the 90-day follow-up period.

Statistical analysis

For the site-level analysis, the number of patients receiving NIPT order, the number of IPD performed, and the number of new high-risk pregnancies within the healthcare system for each calendar year were longitudinally described. The number of patients with NIPT, IPD and high-risk pregnancy with advanced maternal age was presented by the calendar year.

Maternal age at the first prenatal visit with a diagnosis of first trimester check-up record was summarised using mean and SD and compared between the NIPT and no-NIPT groups using Student t-test. Categorical variables including type of health plan, grouped age (35–39, 40–44 and 45+), and specific risk factors including insufficient prenatal care, social problems, genitourinary infection, gestational diabetes, grand multiparity, hypothyroidism, substance/alcohol abuse, overweight/obese and hypertension in pregnant women were compared between the NIPT and no-NIPT groups and were summarised using frequency and percentage. Type of health plan was regrouped into two, commercial insurance versus all the others to address the small number of patients in each non-commercially insured or uninsured subgroups. Age was also categorised into two groups, 35–39 versus 40 or older. To address the influence of the clinical factors on the decision to perform IPD, patient characteristics at the date of the first prenatal visit were also compared between IPD and no-IPD groups. Using χ^2 test, or Fisher's exact test for the small patient counts (<5 count), categorical variables as a clinical characteristic were compared between the NIPT and no-NIPT groups, and between IPD and no-IPD groups.

We compared the rate of IPD between the patients who received NIPT and those who did not receive NIPT. Proportion of patients receiving IPD during the 90-day assessment period between the NIPT and no-NIPT groups were statistically compared using χ^2 test. The OR and 95% CI estimate from a logistic regression model presented the direction and precision of the association measure. In a multivariable approach, baseline characteristics that were marginally different (p<0.1) between the NIPT and no-NIPT were included as regression covariates. Due to the small number of subjects and outcomes relative to the number of covariates that need to be adjusted for (ie, dimensionality in a regression model), the multivariable approach may not address all the differences in the baseline characteristics simultaneously.[33] Thus, in addition to running an inclusive multivariable regression model, we calculated the ORs of IPD for NIPT in a series of logistic regression models where each regression included each single covariate.

A further assessment tested the significance of NIPT as a predictor out of the clinical factors using a multivariable regression model selection process. Variable selection in the logistic regression was performed using a stepwise forward selection approach with significance levels for entering and removing effects of 0.5 and 0.35. The final model including NIPT as a predictor was supposed to
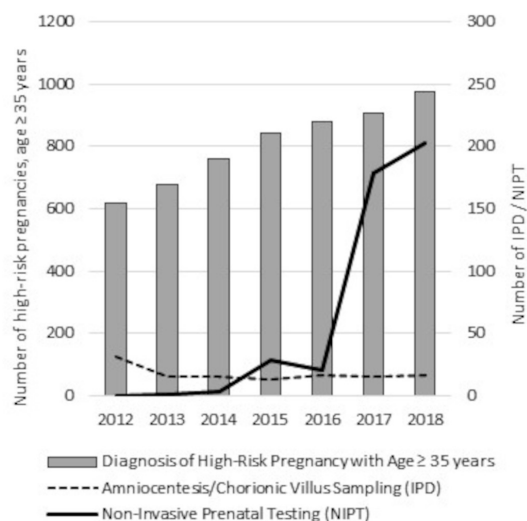
Figure 1 Longitudinal trends in the number of high-risk pregnancies with advanced maternal age (age ≥35 years), invasive prenatal testing (IPD), and NIPT.

indicate that NIPT is a critical factor, to assist providers in determining the need for IPD. Statistical analysis was performed using SAS software V.9.4 (SAS Institute).

RESULTS

Site-level NIPT acceptance

A total of 5660 new high-risk pregnancies with advanced maternal age were identified between 2012 and 2018. The number of high-risk pregnancies with advanced maternal age in 2018 was 977 which is 158% of the 2012 (n=616) and 116% of the 2015 (n=841) count. The numbers of NIPT and IPD performed within the selected pregnant women were 436 and 126, respectively. There were no specific trends in the number of annual IPD (figure 1). The annual NIPT order in 2018 was 203 which was 7 times 29 cases in 2015. Overall the rate of increase in NIPT use exceeded the change in the number of high-risk pregnancy with advanced maternal age (figure 1).

Patient-level analysis

The study cohort consists of 2057 pregnant women at or older than 35 years with a diagnosis of high-risk pregnancy. We identified a total of 551 NIPT orders for the patients included in the study cohort. The difference in the age distribution between the NIPT and no-NIPT group was not statistically nor clinically significant with the respective proportions of subjects younger than 40 of 84.94% versus 82.07. The NIPT cohort was more dominated by commercially insured patients (99.27%) compared with the no-NIPT cohort (79.42%). Based on the analysis of clinical characteristics, patients who received NIPT generally carried less risk factors than the no-NIPT patients with the respective proportions of gestational diabetes (11.62% vs 18.86%, p<0.01), substance or alcohol abuse (1.27% vs 6.24%, p<0.01), overweight or obese (28.31% vs 36.06%, p<0.01) and hypertension (13.25% vs 17.80%, p=0.01). Social problem was the only risk factor more

prevalent among the NIPT than the no-NIPT groups (2.9% vs 1.00%, p<0.01), but the difference in the proportion was nominal from the clinical standpoint. (table 1).

When the analysis grouped high-risk pregnancy into patients who received IPD (n=56) and patients who did not (n=2001), the proportion of patients younger than 40 years out of the IPD recipients was significantly less than the proportion among the no-IPD (66.07% vs 83.31%, p<0.01). The difference in the mean±SD age was marginally significant (p=0.09) between the IPD and no-IPD groups (37.89±2.61 vs 37.35±2.37). There was a significant difference in the proportion of commercially insured pregnancy (94.64% vs 84.46, p=0.04, regrouped health plan type) with the larger proportion of commercially insured patients among those who received IPD. The prevalence of clinical risk factors was generally lower among the IPD versus no-IPD, including genitourinary infection (7.14% vs 11.69%), gestational diabetes (10.71% vs 17.09%) and hypertension (10.71% vs 16.74%), but the differences were not statistically significant. The lack of statistical significance was likely attributed to the small number of IPD procedures (table 2).

From the tabulate analysis, the proportion of patients who received IPD among the NIPT patients during the 90-day assessment period was 2.90% which was slightly larger than the rate of IPD performed without NIPT record (2.66%, table 1). The results were not statistically nor clinically significant (p=0.76, tables 1 and 2). The logistic regression model, without any adjustment for the baseline characteristics, resulted in the OR (95% CI) of 1.10 (0.61 to 1.97). Patient demographics and clinical risk factors had only a nominal impact on the adjusted OR calculation. When the association was adjusted for all patient characteristics with p<0.1, the OR (95% CI) was 0.90 (0.49 to 1.65). The stepwise model selection process chose age (35–39 vs 45≤), type of health plan (commercial vs all non-commercial), social problem, gestational diabetes and hypertension as independent variables in the logistic regression model. Of the selected variables, 40 years or older (OR=2.74 (95% CI 1.54 to 4.81), p<0.01) and commercial insurance (OR=3.19 (95% CI 0.10 to 1.04), p=0.06) showed a significant or marginally significant association with IPD (table 3). NIPT was not considered to be an independent variable that predicts IPD use while the selection process finalised the multivariable regression model.

DISCUSSION

Our assessment confirms that a rapid and gradual increase in the use of NIPT outpaced the increase in the need for a maternity care for the high-risk pregnancy with advanced age. Although the acceptance of NIPT was partially explained by the longitudinal changes in the characteristics of pregnancy, such as becoming older and increasing prevalence of pre-existing conditions, it is mainly attributable to coverage expansion, particularly among the patients enrolled in a commercial health plan.[24–31] Our

Table 1 Clinical characteristics and demographics of non-invasive prenatal testing (NIPT) versus no NIPT groups

	NIPT (n=551)	No-NIPT (n=1506)	P value*
Demographic information			
Age, mean (SD)	37.23 (2.25)	37.41 (2.42)	0.11†
Grouped age (three groups)			0.17
35–39	468 (84.94)	1236 (82.07)	
40–44	80 (14.52)	251 (16.67)	
45 ≤	3 (1.26)	19 (0.54)	
Grouped age (two groups)			0.13
35–39	468 (84.94)	1236 (82.07)	
40 ≤	83 (15.06)	270 (17.93)	
Health plan			<0.01
Commercial insurance	547 (99.27)	1196 (79.42)	
Government	0 (0)	3 (0.20)	
Medicaid	2 (0.36)	270 (17.93)	
Medicare	2 (0.36)	20 (1.33)	
Other Insurance/unknown	0 (0)	17 (1.13)	
Health plan—two grouped			<0.01
Commercial	547 (99.27)	1196 (79.42)	
All non-commercial	4 (0.73)	310 (20.58)	
Clinical characteristics and risk factors			
Insufficient prenatal care	4 (0.73)	22 (1.46)	0.18
Social problem	16 (2.9)	15 (1.00)	<0.01
Genitourinary infection	58 (10.53)	180 (11.95)	0.37
Gestational diabetes	64 (11.62)	284 (18.86)	<0.01
Grand multiparity	0	0	n/a
Hypothyroidism	90 (16.33)	216 (14.34)	0.26
Substance abuse/alcohol abuse	7 (1.27)	94 (6.24)	<0.01
Overweight/obese	156 (28.31)	543 (36.06)	<0.01
Hypertension	73 (13.25)	268 (17.80)	0.01
IPD during the 90-day follow-up	16 (2.90)	40 (2.66)	0.76

*P value from χ^2 test or Fisher's exact test if an expected count of patient is less than five from a tabulate analysis.
†P value from Student's t-test.
IPD, invasive prenatal diagnostic testing including amniocentesis and chorionic villus sampling.

results are comparable to the outcomes of a recent time-series analysis comparing the orders of NIPT and number of IPD in that there has been a significant increase in the order of NIPT with a subtle decrease in the number of IPD, with the adjusted incidence rate ratio of 0.97.[34]

To the best of our knowledge, our study includes the first patient-level assessment to analyse the clinical utility of NIPT in the US healthcare setting. Because IPD is followed by the likelihood of complications, one of the expected benefits of NIPT is to diminish the need for diagnostic IPD. To achieve the expected cost saving or cost-effectiveness, NIPT needs to achieve an anticipated decrease in the IPD by 66%–93%.[35] Not being aligned with the anticipated clinical scenario, our study did not find a strong signal of the negative association between the order of NIPT and the frequency of IPD. We tentatively concluded that the utility

NIPT in alleviating IPD-related concerns would be, at best, nominal in managing high-risk pregnancy with advanced maternal age based on the OR of 0.90 from our multivariable logistic regression model.

A decision assisted by multiple risk factors, imaging and confirmatory diagnostic procedure partially explains the reason for the subtle influence of NIPT on the following diagnostic tests. A recent chart review showed that the first-trimester ultrasonography still provides valuable clinical information about fetal anatomy.[36] Typically, the first-trimester ultrasonography determines the presence of trisomy 18 with a sensitivity of 70%, while a previous multiple marker test detected 43% of cases.[37 38] In combination with invasive diagnostic testing, the standard screening process without NIPT already achieved 100% sensitivity and negative predictive value.[39] This likely

Table 2 Clinical characteristics and demographics of IPD versus no IPD groups

	IPD (n=56)	No-IPD (n=2001)	P value*
Demographic information			
Age, mean (SD)	37.89 (2.61)	37.35 (2.37)	0.09†
Grouped age (three groups)			<0.01
35–39	37 (66.07)	1667 (83.31)	
40–44	19 (33.93)	312 (15.59)	
45 ≤	0 (0)	22 (1.10)	
Grouped age (two groups)			<0.01
35–39	37 (66.07)	1667 (83.31)	
40 ≤	19 (33.93)	334 (16.69)	
Health plan			0.34
Commercial insurance	53 (94.64)	1690 (84.46)	
Government	0 (0)	3 (0.15)	
Medicaid	3 (5.36)	269 (13.44)	
Medicare	0 (0)	22 (1.10)	
Other insurance/unknown	0 (0)	17 (1.0.85)	
Health plan—regrouped			0.04
Commercial	53 (94.64)	1690 (84.46)	
All non-commercial	3 (5.36)	311 (15.54)	
Clinical characteristics and risk factors			
Insufficient prenatal care	0 (0)	26 (1.30)	0.39
Social problem	2 (3.57)	29 (1.45)	0.19
Genitourinary infection	4 (7.14)	234 (11.69)	0.29
Gestational diabetes	6 (10.71)	342 (17.09)	0.21
Grand multiparity	0	0	n/a
Hypothyroidism	8 (14.29)	298 (14.89)	0.90
Substance abuse/alcohol abuse	3 (5.36)	98 (4.90)	0.88
Overweight/obese	21 (37.50)	678 (33.88)	0.57
Hypertension	6 (10.71)	335 (16.74)	0.23
NIPT during the 90-day follow-up	16 (28.57)	535 (26.74)	0.76

*P value from χ^2 test or Fisher's exact test if an expected count of patient is less than 5 from a tabulate analysis.
†P value from Student's t-test.
IPD, invasive prenatal diagnostic testing including amniocentesis and chorionic villus sampling; NIPT, non-invasive prenatal testing.

involves clinical scenarios that providers and patients confirm the presence or absence of a congenital malformation by standard combination screenings witnout NIPT in many cases.[40–43] Thus, a substantial proportion of prenatal care would not be altered by the use of NIPT.

Congenital malformation is a subject of environmental and socioeconomic factors. For example, being placed in a lower quartile of social deprivation is associated with a 30% increase in the rate of live-born congenital disease.[44] Therefore, the ultimate goal of prenatal screening, to achieve the reproductive autonomy mediated by reducing complications and herediatary malformation with a properly informed decision, will not be accomplished until underprivileged pregnancies have access to advanced prenatal care strategies. However, Medicaid enrollees still have limited prenatal care as indicated by 20% of the

US states that do not cover the cost of NIPT[45–47] whereas the majority of commercial health plans have expanded NIPT coverage to all pregnancies.[45–47] Not being enrolled in a commercial health plan was also a negative indicator for further IPD to confirm the presence of genetic disorder. Considring the significant changes in the pranal care strategy coincided with the beginning of a nationwide coverage for advanced prenatal screenings,[48] any coverage gap in access to prenatal care and the potential influence of the disparity has to be addressed to achieve the equity in reproductive autonomy, specifically in the US healthcare setting. Our data obtained from the real-world assessments warrant future research in and revision of the current policy to improve the utility of clinically advanced strategies in prenatal care, particularly in a disadvantaged population.

Table 3 OR of invasive prenatal testing (IPD) for non-invasive prenatal testing (NIPT) from logistic regression with single and multiple covariate adjustments

Covariates	OR (95% CI)
No covariate adjustment	1.10 (0.61 to 1.97)
Grouped age (35–39 vs 40≤)	1.14 (0.63 to 2.05)
Insufficient prenatal care	1.09 (0.60 to 1.96)
Social problem	1.07 (0.59 to 1.93)
Genitourinary infection	1.09 (0.60 to 1.96)
Gestational diabetes	1.06 (0.59 to 1.91)
Hypothyroidism	1.10 (0.61 to 1.98)
Substance or alcohol abuse	1.10 (0.61 to 1.99)
Overweight or obese	1.11 (0.62 to 2.00)
Hypertension	1.07 (0.60 to 1.94)
Health plan (commercial vs all non-commercial)	0.94 (0.52 to 1.71)
All variables with p<0.1*	0.90 (0.49 to 1.65)

*Regression model includes type of health plan (commercial vs all non-commercial), social problem, gestational diabetes, hypothyroidism, substance/alcohol abuse, and overweight/obese as covariates for the NIPT-IPD association.

There are a couple of factors that may be associated with the decision to perform IPD based on our administrative data, such as having commercial insurance and being aged between 35 and 39 years. This may be due to patients with commercial insurance having greater access to healthcare, which is consistent with results from a previous studies.[42 44] Insufficient prenatal care, social problems, and substance/alcohol abuse may be associated with less likelihood to receive NIPT and/or IPD. These associations may be related to Medicaid and underserved populations that do not have as great of access to healthcare resources, as well as types of providers that patient will see.[34 49 50] It is important that doctors and midwives provide adequate information on the benefits and limitations associated with NIPT, specifically for the minorities and underprivileged population.

The interpretation of our data should be considered in light of several limitations. First, the identification of both exposure and outcomes are limited by the procedures and orders defined by the administrative records. Although the quality of the study using the institutional data was confirmed by multiple observational studies, the likelihood of misclassification could not be ruled out. The study findings need to be confirmed by a detailed medical note review and warrant a confirmatory randomised controlled study. Second, our research was limited to a single healthcare system in the US healthcare setting. Future research may include multisite observational databases to establish the generalizability of study findings. Also, the use of both NIPT and IPD in the US healthcare setting would be significantly influenced by the patient socioeconomic status that were not fully controlled in this study. Any future attempts have to further investigate the

disparity in achieving informed decisions and its influence on the overall utility of the advanced prenatal care technologies. Lastly, the size of the study cohort was associated with wide CIs, limiting statistical inference. Although the point estimates confirm the no-to-nominal influence of NIPT on IPD, a further assessment using a larger cohort is warranted. Despite the limitations, our study provides valuable insight into the use of NIPT.

In conclusion, our study delineates the acceptance of NIPT in prenatal care. However, the utility of NIPT in mitigating concerns on IPD use has not been established. Future study needs to address inequal access to advanced prenatal care strategies, including NIPT and IPD.

ORCID iD
Kibum Kim http://orcid.org/0000-0002-8676-7434

REFERENCES
1 Barros ALO, Barros AO, Barros GLdeM, *et al*. Burden of caregivers of children and adolescents with Down syndrome. *Cien Saude Colet* 2017;22:3625–34.
2 Geelhoed EA, Bebbington A, Bower C, *et al*. Direct health care costs of children and adolescents with Down syndrome. *J Pediatr* 2011;159:541–5.
3 Ghi T, Sotiriadis A, Calda P, *et al*. ISUOG practice guidelines: invasive procedures for prenatal diagnosis. *Ultrasound Obstet Gynecol* 2016;48:256–68.
4 BabyCenter. Panorama testing BILL $4000, doctor said it would cost $200. Available: https://community.babycenter.com/post/a62696863/panorama-testing-bill-4000-doctor-said-it-would-cost-200 [Accessed 18 Mar 2021].
5 Minear MA, Lewis C, Pradhan S, *et al*. Global perspectives on clinical adoption of NIPT. *Prenat Diagn* 2015;35:959–67.
6 Perinatal Services BC. Non-Invasive prenatal testing (NIPT). Available: http://www.perinatalservicesbc.ca/health-professionals/professional-resources/screening/prenatal-genetic/non-invasive-prenatal-testing-nipt [Accessed 18 Mar 2021].
7 Petersen AK, Cheung SW, Smith JL, *et al*. Positive predictive value estimates for cell-free noninvasive prenatal screening from data of a large referral genetic diagnostic laboratory. *Am J Obstet Gynecol* 2017;217:691.e1–691.e6.

8   Walker BS, Nelson RE, Jackson BR, *et al*. A cost-effectiveness analysis of first trimester non-invasive prenatal screening for fetal trisomies in the United States. *PLoS One* 2015;10:e0131402.

9   Derridj N, Bonnet D, Calderon J, *et al*. Quality of life of children born with a congenital heart defect. *J Pediatr* 2022;244:148–53.

10 Mebius MJ, Kooi EMW, Bilardo CM, *et al*. Brain injury and neurodevelopmental outcome in congenital heart disease: a systematic review. *Pediatrics* 2017;140. doi:10.1542/peds.2016-4055. [Epub ahead of print: 13 06 2017].

11 Robertson JA. *Children of choice: freedom and the new reproductive technologies*. Princeton, UK: Princeton University Press, 1996.

12 Mackenzie C, Stoljar N. *Relational autonomy: feminist perspectives on autonomy, agency, and the social self*. Oxford, UK: Oxford University Press, 2000.

13 labcorp. Maternal serum screening, second trimester. Available: https://www.labcorp.com/help/patient-test-info/maternal-serum-screening-second-trimester#:~:text=Maternal%20serum%20screening%20is%20a,or%20a%20condition%20called%20anencephaly [Accessed 16 Mar 2021].

14 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics, Committee on Genetics, Society for Maternal-Fetal Medicine. Screening for fetal chromosomal abnormalities: ACOG practice Bulletin, number 226. *Obstet Gynecol* 2020;136:e48–69.

15 LeFevre NM, Sundermeyer RL. Fetal aneuploidy: screening and diagnostic testing. *Am Fam Physician* 2020;101:481–8.

16 ACOG Committee on Practice Bulletins. ACOG practice Bulletin No. 77: screening for fetal chromosomal abnormalities. *Obstet Gynecol* 2007;109:217–28.

17 Santorum M, Wright D, Syngelaki A, *et al*. Accuracy of first-trimester combined test in screening for trisomies 21, 18 and 13. *Ultrasound Obstet Gynecol* 2017;49:714–20.

18 Kostenko E, Chantraine F, Vandeweyer K, *et al*. Clinical and economic impact of adopting noninvasive prenatal testing as a primary screening method for fetal aneuploidies in the general pregnancy population. *Fetal Diagn Ther* 2019;45:413–23.

19 Kim K, Magness JW, Nelson R, *et al*. Clinical utility of pharmacogenetic testing and a clinical decision support tool to enhance the identification of drug therapy problems through medication therapy management in polypharmacy patients. *J Manag Care Spec Pharm* 2018;24:1250–9.

20 Lesko LJ, Zineh I, Huang S-M. What is clinical utility and why should we care? *Clin Pharmacol Ther* 2010;88:729–33.

21 Quinn B. Payers and the assessment of clinical utility for companion diagnostics. *Clin Pharmacol Ther* 2010;88:751–4.

22 Beamon CJ, Hardisty EE, Harris SC, *et al*. A single center's experience with noninvasive prenatal testing. *Genet Med* 2014;16:681–7.

23 Hui L, Hutchinson B, Poulton A, *et al*. Population-Based impact of noninvasive prenatal screening on screening and diagnostic testing for fetal aneuploidy. *Genet Med* 2017;19:1338–45.

24 The Web's Free 2021 ICD-10-CM/PCS Medical Coding Reference, 2021. Available: https://www.icd10data.com/

25 The Web's Free ICD-9-CM Medical Coding Reference, 2021. Available: http://www.icd9data.com/2014/Volume1/240-279/240-246/244/244.9.htm

26 Raskind-Hood C, Saraf A, Riehle-Colarusso T, *et al*. Assessing pregnancy, gestational complications, and co-morbidities in women with congenital heart defects (data from ICD-9-CM codes in 3 us surveillance sites). *Am J Cardiol* 2020;125:812–9.

27 Persson M, Pasupathy D, Hanson U, *et al*. Pre-pregnancy body mass index and the risk of adverse outcome in type 1 diabetic pregnancies: a population-based cohort study. *BMJ Open* 2012;2:e000601.

28 Persson M, Winkvist A, Mogren I. Lifestyle and health status in a sample of Swedish women four years after pregnancy: a comparison of women with a history of normal pregnancy and women with a history of gestational diabetes mellitus. *BMC Pregnancy Childbirth* 2015;15:57.

29 Kuhle S, Muir A, Woolcott CG, *et al*. Maternal pre-pregnancy obesity and health care utilization and costs in the offspring. *Int J Obes* 2019;43:735–43.

30 Quinley KE, Falck A, Kallan MJ, *et al*. Validation of ICD-9 codes for stable miscarriage in the emergency department. *West J Emerg Med* 2015;16:551–6.

31 Olney RS, Moore CA, Khoury MJ. Chorionic villus sampling and amniocentesis: recommendations for prenatal counseling. Atlanta, GA Centers for Disease Control and Prevention; 2021. https://www.cdc.gov/mmwr/preview/mmwrhtml/00038393.htm#:~:text=Amniocentesis%20is%20usually%20performed%20at,11%2D14%20weeks'%20gestation

32 Your first prenatal visit. Available: https://americanpregnancy.org/healthy-pregnancy/planning/first-prenatal-visit-71023/ [Accessed 18 Mar 2021].

33 Cepeda MS, Boston R, Farrar JT, *et al*. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol* 2003;158:280–7.

34 Quinlan TAG, Schroeder B, Kwon S, *et al*. Economic impact of coverage expansion for non-invasive prenatal testing through a performance-based risk-sharing agreement. *Pharmacoecon Open* 2021;5:449–58.

35 Garfield SS, Armstrong SO. Clinical and cost consequences of incorporating a novel non-invasive prenatal test into the diagnostic pathway for fetal trisomies. *Journal of Managed Care Medicin* 2021;15:34–41.

36 Rao R, Han C, Silverman N, *et al*. 378: utility of first trimester ultrasound in the setting of NIPT incorporation into practice: a retrospective pilot review. *Am J Obstet Gynecol* 2015;212:S198.

37 Brumfield CG, Wenstrom KD, Owen J, *et al*. Ultrasound findings and multiple marker screening in trisomy 18. *Obstet Gynecol* 2000;95:51–4.

38 Yeo L, Guzman ER, Day-Salvatore D, *et al*. Prenatal detection of fetal trisomy 18 through abnormal sonographic features. *J Ultrasound Med* 2003;22:581–90.

39 Park SY, Jang IA, Lee MA, *et al*. Screening for chromosomal abnormalities using combined test in the first trimester of pregnancy. *Obstet Gynecol Sci* 2016;59:357–66.

40 Benn P, Borell A, Chiu R, *et al*. Position statement from the aneuploidy screening Committee on behalf of the Board of the International Society for prenatal diagnosis. *Prenat Diagn* 2013;33:622–9.

41 Raised maternal age in pregnancy. Available: https://www.rdehospital.nhs.uk/media/hrxj1nho/patient-information-leaflet-raised-maternal-age-in-pregnancy-rde-19-089-001.pdf [Accessed 18 Mar 2021].

42 What are some factors that make a pregnancy high risk? Available: https://www.nichd.nih.gov/health/topics/high-risk/conditioninfo/factors [Accessed 18 Mar 2021].

43 Mackie FL, Allen S, Morris RK, *et al*. Cell-free fetal DNA-based noninvasive prenatal testing of aneuploidy. *Obstet Gynecol* 2017;19:211–8.

44 Peyvandi S, Baer RJ, Chambers CD, *et al*. Environmental and socioeconomic factors influence the Live-Born incidence of congenital heart disease: a population-based study in California. *J Am Heart Assoc* 2020;9:e015255.

45 Gadsbøll K, Petersen OB, Gatinois V, *et al*. Current use of noninvasive prenatal testing in Europe, Australia and the USA: a graphical presentation. *Acta Obstet Gynecol Scand* 2020;99:722–30.

46 Benoy ME, Iruretagoyena JI, Birkeland LE, *et al*. The impact of insurance on equitable access to non-invasive prenatal screening (NIPT): private insurance may not pay. *J Community Genet* 2021;12:185–97.

47 Löwy I. Non-Invasive prenatal testing: a diagnostic innovation shaped by commercial interests and the regulation conundrum. *Soc Sci Med* 2020;113064:113064.

48 Vinante V, Keller B, Huhn EA, *et al*. Impact of nationwide health insurance coverage for non-invasive prenatal testing. *Int J Gynaecol Obstet* 2018;141:189–93.

49 Goudie A, Martin B, Li C, *et al*. Higher Rates of Preventive Health Care With Commercial Insurance Compared With Medicaid: Findings From the Arkansas Health Care Independence "Private Option" Program. *Med Care* 2020;58:120–7.

50 van der Steen SL, Houtman D, Bakkeren IM, *et al*. Offering a choice between NIPT and invasive PND in prenatal genetic counseling: the impact of clinician characteristics on patients' test uptake. *Eur J Hum Genet* 2019;27:235–43.