Received: 15 March 2023 | Revised: 4 December 2024 | Accepted: 30 December 2024

DOI: 10.1002/jgc4.2025

ORIGINAL ARTICLE

National Society of Genetic Counselors WILEY

Uptake rates for non-invasive prenatal screening for single-gene disorders associated with advanced paternal age

Kylie Katz[1] | Justin S. Brandt[2] | Gary Heiman[3] | Laurie Simone[4] | Shama Khan[2] | Pranali Shingala[5] | Elena Ashkinadze[2]

[1]Division of Medical Genetics, Department of Pediatrics, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA

[2]Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA

[3]Department of Genetics and the Human Genetics Institute of New Jersey, Rutgers, The State University of New Jersey, Piscataway, New Jersey, USA

[4]Hackensack University Medical Center, Hackensack, New Jersey, USA

[5]Department of Medical Genetics and Genomics, Icahn School of Medicine at Mount Sinai, New York City, New York, USA

Correspondence
Kylie Katz, Division of Medical Genetics, Department of Pediatrics, Rutgers Robert Wood Johnson Medical School, 89 French St, 2nd Floor, New Brunswick, NJ 08901, USA.
Email: kylie.katz@rutgers.edu

Abstract

This study sought to quantify uptake rates of non-invasive prenatal screening for de novo single-gene disorders (NIPS-SGD) in pregnant subjects whose reproductive partner is of advanced paternal age (APA) and to determine individual parameters associated with higher test uptake rates. A cross-sectional study was performed of pregnant subjects who received prenatal genetic counseling at a mid-size tertiary care center and were offered NIPS-SGD for APA (defined as 45 or older at delivery) between June 1, 2017 and April 13, 2021. We included non-anomalous, singleton gestations who conceived without donor egg/sperm. The outcome was measured as subjects who elected to do NIPS-SGD versus subjects who declined. Multivariable logistic regression was used to develop a model to discriminate between those who opted for testing and those who did not. 186 subjects were offered NIPS-SGD and met inclusion criteria. 70 had testing and 116 declined. Overall uptake rate was 38%. Several individual parameters were associated with higher test uptake including utilization of other screenings such as NIPS for aneuploidy (OR 3.4), carrier screening (OR 7.0) and invasive diagnostic testing (OR 8.4), presence of reproductive partner (OR 4.3), medicaid insurance (OR 2.6), and counseling at an offsite location (OR 2.0). AUC for the final regression model predicting NIPS-SGD uptake was 0.79. Based on this study, subjects who are information seekers and who opt for other prenatal screenings are more likely to pursue NIPS-SGD for de novo conditions associated with APA.

KEYWORDS
advanced paternal age, genetic counseling, genetic testing, non-invasive prenatal screening for single-gene disorders, prenatal diagnosis

1 | INTRODUCTION

Non-invasive prenatal screening (NIPS) is a methodology that utilizes placental cell-free DNA (cfDNA) within the maternal plasma to screen for fetal aneuploidy. This screen is sensitive for the detection of common trisomies, including trisomy 21, 18, and 13, and has been expanded to detect sex chromosome aneuploidies and some microdeletions (Benn, 2014). Recent advances in cfDNA technology have allowed for the screening of some single-gene disorders (SGD) (Allen et al., 2017).

In 2017, Baylor Genetics and Natera Lab released a non-invasive prenatal screening panel for single-gene disorders (NIPS-SGD), which screens for 25 de novo X-linked or dominant single-gene conditions associated with 30 different genes (Table 1). Some of the conditions on this panel have a known paternal age effect, meaning

that changes in these genes show a higher rate in offspring of older fathers and have a known gain of function pathogenic effect (Brandt et al., 2019). There is no consensus for what is considered "advanced paternal age" (APA), although many professional societies consider APA to be 40 years or older at delivery (Toriello & Meck, 2008). The combined incidence of these conditions is approximately 1 in 600 (Zhang et al., 2019). Many of these conditions occur de novo and have no or limited discriminating ultrasound findings. Two studies regarding the efficacy of NIPS-SGD found it has >99% sensitivity and specificity (Mohan et al., 2022; Zhang et al., 2019). This screen can be performed on any pregnancy after 9 weeks gestation, and requires a maternal serum sample, similar to NIPS for aneuploidy (NIPS-A). Initial iterations of this NIPS-SGD panel also required a paternal sample, although this is no longer required as of August 2021.

NIPS-SGD is commercially available and may be offered to pregnant people, but the uptake of this test and the factors influencing these decisions are unknown. Understanding barriers to NIPS-SGD uptake is important to address potential disparities. Therefore, we performed a cross-sectional study of pregnant subjects who presented for genetic counseling and whose reproductive partner was 45 years old or older at delivery. We sought to assess screen uptake rates and evaluate patient characteristics that may be associated with a higher or lower interest in this technology. We hypothesized that there would be high rates of NIPS-SGD utilization and that financial barriers/payer status would impact utilization.

What is known about this topic

- Studies have explored uptake rates and the associated factors for NIPS-Aneuploidy, but these parameters have not been evaluated for NIPS-SGD.

What this paper adds to the topic

- There is high uptake rate (38%) when subjects are offered NIPS-SGD for advanced paternal age and proper pre-test counseling is provided.
- A potential barrier to testing identified was the reproductive partner being available, but recent changes in testing requirements have eliminated this barrier.

2 | MATERIALS AND METHODS

We performed a retrospective, cross-sectional study of pregnant subjects who were seen for genetic counseling at a mid-size tertiary care center in central New Jersey. The study period was June 1, 2017 to April 13, 2021. Subjects whose reproductive male partners were 45 years or older at delivery were counseled regarding the potential reproductive impact of advanced paternal age (APA) and offered NIPS-SGD. The Rutgers University New Brunswick Health Sciences Institutional Review Board (IRB) approved this study under a waiver of informed consent.

Subjects were included if they had non-anomalous, singleton gestations, and had a male partner who was 45 or older at time of delivery. Subjects were excluded if they were offered NIPS-SGD for other indications (e.g., ultrasound findings) and if they had multiple gestation pregnancies. Subjects were also excluded if pregnancies were conceived with assisted reproduction that used donor egg or sperm per the requirement of the genetic laboratory during the study period. If subjects had more than one pregnancy during the study period, only the first pregnancy was included in the study. The outcome was measured by determining which subjects elected to have the NIPS-SGD testing.

All subjects who had genetic counseling at the tertiary care center (and 3 satellite offices) are logged in a centralized tracking system, and genetic counseling reports and associated documentation are recorded in an electronic medical record. Pregnant subjects meeting the inclusion criteria were identified in this system. We abstracted the following data: subject's age at delivery, male reproductive partner's age at delivery, ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and Asian), insurance type (Medicaid, commercial), indication for referral (advanced maternal age [AMA], abnormal ultrasound, aneuploidy screening, carrier results/family history, multiple indications, or other), whether the subject accepted or declined NIPS-SGD, whether the subject had other prenatal screening or testing (conventional aneuploidy screening, cfDNA screening for aneuploidy, carrier screening, diagnostic testing through chorionic villus sampling or amniocentesis), the gestational age and gravida status at the time of visit, and whether the male reproductive partner was present at the session. For those who pursued NIPS-SGD testing, the screening results and the turnaround time were obtained, as well as whether a redraw was necessary.

For subjects who declined screening, the reason for declining was also determined from the consultation notes, if provided. The reported reasons for declining that we ascertained were categorized into the following groups: reproductive partner unavailable for testing, testing overload/anxiety, test characteristics (too new, too low yield), financial concerns, and faith that their fetus was healthy and testing unnecessary.

The outcome variable was defined as the uptake rate of NIPS-SGD. Fifteen independent variables were considered as predictors of the outcome. Of these independent variables, 11 were binary: did the subject have expanded carrier screening, experience fertility problems, was the reproductive partner present, did the subject pursue invasive testing, did the subject pursue NIPS-A, subject's age (<35 and ≥35), gestational age (1st trimester and 2nd/3rd trimester), gravida (1st pregnancy and not 1st pregnancy), location (RWJ or other), and insurance status (Medicaid vs. commercial). Paternal age was included as a continuous variable. The remaining 2 variables were categorical: indication for seeking genetic counseling and ethnicity.

2.1 | Statistical analysis

We performed descriptive analysis to compare the subjects that had opted for testing versus those that had opted out of testing. We also

TABLE 1 Genes included on non-invasive prenatal screening for single-gene disorders and their associated disorders.

Gene	Disorder
FGFR3	Achondroplasia
	CATSHL syndrome
	Crouzon syndrome
	Hypochondroplasia
	Muenke syndrome
	Thanatophoric dysplasia types I, II
FGFR2	Antley Bixler syndrome
	Apert syndrome
	Crouzon syndrome
	Jackson Weiss syndrome
	Pfeiffer syndrome type 1, 2, 3
JAG1	Alagille syndrome
MAP2K2	Cardiofaciocutaneous syndrome type 4
BRAF	Cardiofaciocutaneous syndrome type 1
	Noonan syndrome
MAP2K1	Cardiofaciocutaneous syndrome type 3
	Noonan syndrome
SOS1	Noonan syndrome
RIT1	Noonan syndrome
KRAS	Noonan syndrome
NRAS	Noonan syndrome
SOS2	Noonan syndrome
SHOC2	Noonan syndrome
CBL	Noonan syndrome
PTPN11	Juvenile myelomonocytic leukemia (JMML)
	LEOPARD syndrome (Noonan syndrome with multiple lentigines)
	Noonan syndrome
RAF1	LEOPARD syndrome (Noonan syndrome with multiple lentigines)
	Noonan syndrome
HRAS	Costello syndrome
	Noonan syndrome
TSC1	Tuberous sclerosis type 1
TSC2	Tuberous sclerosis type 2
NSD1	Sotos syndrome 1
MECP2	Rett syndrome
SYNGAP1	Intellectual disability
CDKL5	Epileptic encephalopathy, early infantile, 2
CHD7	CHARGE syndrome
NIPBL	Cornelia de Lange syndrome 1
SMC1A	Cornelia de Lange syndrome 2
SMC3	Cornelia de Lange syndrome 3
RAD21	Cornelia de Lange syndrome 4
HDAC8	Cornelia de Lange syndrome 5
COL1A1	Osteogenesis imperfecta type I, II, III, IV
	Ehlers Danlos syndrome classic, type VIIA
COL1A2	Osteogenesis imperfecta type II, III, IV
	Ehlers Danlos syndrome cardiac valvular form, type VIIB

calculated the proportion of subjects who agreed to have the test each year it was offered (2017 to 2021). Categorical data were compared using the percentages. For continuous data, the means and standard deviations (SD) were calculated.

Using multivariable logistic regression, we developed a model for NIPS-SGD uptake. Backward elimination was performed to determine a parsimonious final model using the Akaike information criterion (AIC) as the stopping rule (Chowdhury & Turin, 2020; Dziak et al., 2020). The predictive probability of the final model was calculated by the area under the receiver-operating characteristic (AUC), where an AUC value of 0.5 represents a model with no predictive ability and an AUC of 1.0 represents a model with perfect predictive ability (Steyerberg et al., 2010; Zweig & Campbell, 1993). All data analysis was conducted using Stata statistical software version 17 (StataCorp, 2021).

3 | RESULTS

A total of 186 pregnant subjects were offered NIPS-SGD testing due to APA during the study period and met inclusion criteria. Of these subjects, 70 opted to have NIPS-SGD testing, making the overall uptake rate 37.6% (Figure 1). There were 116 subjects who opted not to have testing.

Clinical characteristics of study subjects are displayed in Table 2. The mean age of subjects was 37.5 years and the mean reported paternal age was 48.6 (SD 4.3) years. Subjects who had NIPS-SGD were numerically more likely to have counseling with reproductive partners present and to be primigravida. These subjects were also more likely to have invasive testing and carrier screening compared to subjects who did not have NIPS-SGD.

While the overall uptake rate of the screen is 37.6% ($n=70$), we looked at the uptake per year the test was offered in this study (2017 to 2021) to observe if there were any changes in uptake rates over time. While 2017 had a high uptake rate of 44%, the proportion of subjects who agreed to have NIPS-SGD increased from 26% in 2018 to 50% in 2021 (Figure 2).

Of the 70 subjects that received NIPS-SGD testing, all came back negative for PAE mutations. There were no unexpected results. The mean turnaround time for results was 20.0 days (SD 5.3 days).

Multivariate analyses of clinical characteristics and NIPS-SGD uptake were performed to determine which combination of factors were associated with NIPS-SGD uptake. The final parsimonious model for NIPS-SGD uptake included whether the reproductive partner was present, whether they had Medicaid insurance, whether they were counseled at an offsite location, whether the subject had invasive testing, whether the subject had NIPS-A and whether they had carrier screening (Table 3). Whether the subject had invasive testing had the greatest association with NIPS-SGD uptake (OR=8.4). The AUC for the final regression model for NIPS-SGD uptake was 0.79.

Of the 116 subjects who declined NIPS-SGD testing, we were able to ascertain the reported reason for declining for 50 (43.1%) subjects. 18 (36%) subjects reported they were declining due to their reproductive partner being unavailable, 12 (24%) reported it

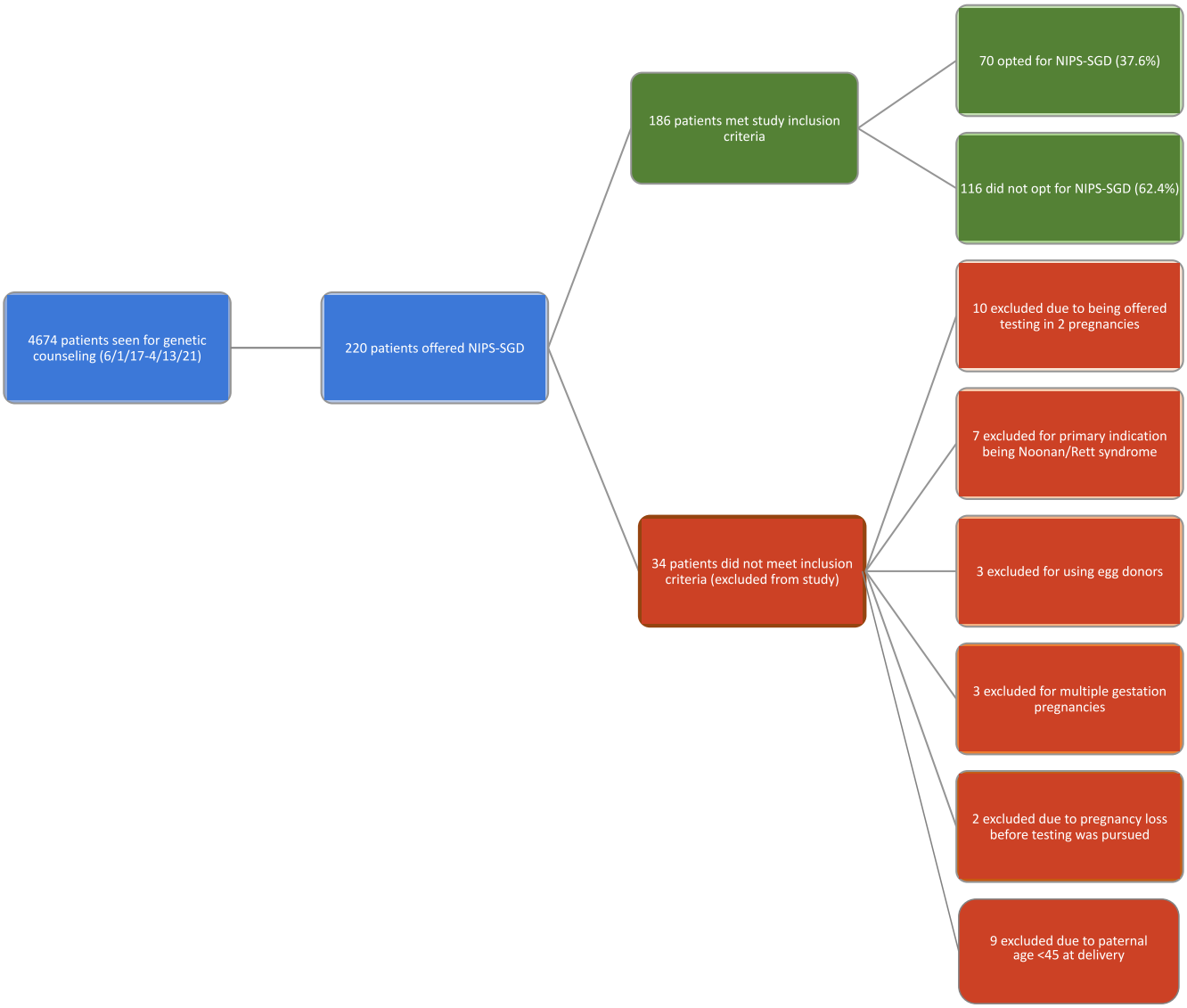

FIGURE 1 Study flow diagram.

was due to testing overload/anxiety about further testing, 10 (20%) reported it was due to the test being too new or having a low yield, 8 (16%) reported it was due to financial concerns or the cost of testing, and 2 (4%) reported it was due to their faith.

4 | DISCUSSION

4.1 | Principal findings

In this cross-sectional study of pregnant subjects who had genetic counseling for APA and who were offered NIPS-SGD, we evaluated the uptake rates of the screen and examined the clinical factors associated with screen uptake to determine what barriers may exist in the pursuit of this testing. The main findings of our study were that the following six factors were significantly associated with NIPS-SGD uptake: if subjects had additional prenatal testing through NIPS-A, carrier screening, or invasive diagnostic testing, if the reproductive partner was present, if the patient had Medicaid insurance, and if the initial counseling took place at an offsite location.

4.2 | Results in context

The overall NIPS-SGD uptake for APA was 37.6%. Compared to uptake of NIPS-A, a 2021 study from the Netherlands found uptake was 46% (van der Meij et al., 2021). Other studies have estimated the uptake of NIPS-A in the United States to be anywhere from 25% to 78% (Gadsbøll et al., 2020; Kostenko et al., 2019). Based on these estimates, uptake of NIPS-SGD was similar with studies evaluating uptake for NIPS-A.

While there have been no previous studies looking at factors affecting NIPS-SGD uptake, there have been many studies describing the factors associated with uptake of other prenatal screening methodologies including NIPS-A. These studies have found that higher educational level, higher socioeconomic status, advanced maternal age, and an increased risk for a genetic anomaly are significantly

TABLE 2 Clinical characteristics of subjects offered non-invasive prenatal screening for single-gene disorders.

		NIPS-SGD	
	All subjects, *N* = 186	No exposure, *N* = 116	Exposure, *N* = 70
Location			
Main site	98 (52.7)	68 (58.6)	30 (42.9)
Satellite	88 (47.3)	48 (41.4)	40 (57.1)
Reproductive partner present	64 (34.4)	29 (25.0)	35 (50.0)
Race/ethnicity			
NH White	76 (40.9)	45 (38.8)	31 (44.3)
NH Black	35 (18.8)	24 (20.7)	11 (15.7)
Hispanic	41 (22.0)	27 (23.3)	14 (20.0)
Asian	34 (18.3)	20 (17.2)	14 (20.0)
Indication for counseling			
AMA	110 (59.1)	72 (62.1)	38 (54.3)
Abnormal U/S or screen	10 (5.4)	5 (4.3)	5 (7.1)
Family history	11 (5.9)	8 (6.9)	3 (4.3)
Multiple indications	37 (19.9)	18 (15.5)	19 (27.1)
Other (IVF, APA)	18 (9.7)	13 (11.2)	5 (7.1)
Maternal age			
<35 years old	37 (19.9)	24 (20.7)	13 (18.6)
>35 years old	149 (80.1)	92 (79.3)	57 (81.4)
Gestational age			
1st trimester	111 (59.7)	65 (56.0)	46 (65.7)
2nd/3rd trimester	75 (40.3)	51 (44.0)	24 (34.3)
Gravida			
1st pregnancy	35 (18.8)	17 (14.7)	18 (25.7)
Not 1st pregnancy	151 (81.2)	99 (85.3)	52 (74.3)
Payment type			
Medicaid	33 (17.7)	21 (18.1)	12 (17.1)
Private insurance	153 (82.3)	95 (81.9)	58 (82.9)
Fertility issues	40 (21.5)	22 (19.0)	18 (25.7)
NIPS testing	149 (80.1)	94 (81.0)	55 (78.6)
Expanded carrier screening	142 (76.3)	76 (65.5)	66 (94.3)
Invasive Testing	29 (15.6)	9 (7.8)	20 (28.6)
Paternal Age, years[a]		48.4 (4.5)	48.6 (4.3)

Note: Data is *n* (percent).

Abbreviations: AA, African–American; AMA, advanced maternal age; APA, advanced paternal age; IVF, in vitro fertilization; NH, non-Hispanic; U/S, ultrasound.

[a]Data is mean (standard deviation).

associated with prenatal test uptake (Di Mattei et al., 2021; van der Meij et al., 2021).

Our study was unable to obtain and analyze the education level for our subjects. We were also unable to directly ascertain the socio-economic status of our subjects, although we did include insurance type in our analysis as a surrogate. We found there was a significant association between insurance type and test uptake in our final analytical model, with patients who had Medicaid insurance being 2.6 times more likely to pursue testing than those with Private insurance. Additionally, 16% of the subjects who reported their reason for declining testing said it was due to financial concerns. Patients who had Medicaid insurance would not be billed for the testing, so those who were concerned about costs were those with commercial insurance, as some commercial insurance plans were out of network with the lab performing this testing and would thus be associated with an out-of-pocket cost.

We analyzed maternal age and found there was no significant association with NIPS-SGD uptake, but there was also not a significant association with increasing paternal age and NIPS-SGD uptake.

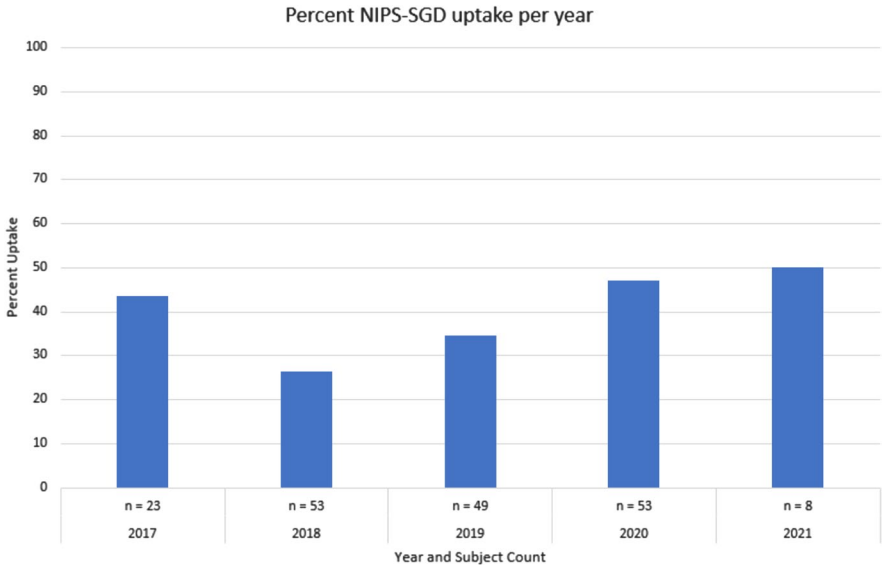

FIGURE 2 Percent NIPS-SGD uptake per year.

TABLE 3 Multivariable logistic regression analysis assessing factors associated with non-invasive prenatal screening for single-gene disorders uptake.

Predictor variable	Odds ratio	95% confidence interval
Reproductive partner present		
No	1.0 (reference)	
Yes	4.3	2.0–9.1
Invasive testing		
No	1.0 (reference)	
Yes	8.4	2.1–32.9
Non-invasive prenatal screening for aneuploidy		
No	1.0 (reference)	
Yes	3.4	0.9–12.5
Carrier screening		
No	1.0 (reference)	
Yes	7.0	2.2–22.3
Location		
Main site	1.0 (reference)	
Satellite	2.0	1.0–4.3
Payment type		
Medicaid	1.00 (reference)	
Private	0.39	0.1–1.2

4.3 | Clinical implications

Our study has several clinical implications. Individuals who opt for any prenatal screening/testing may be more likely to pursue novel fetal screening options. We found that the factor most strongly associated with test uptake was whether the subject had also undergone invasive diagnostic testing for prenatal diagnosis. We also found that subjects who had invasive testing during their pregnancy were eight times more likely to opt for NIPS-SGD, those who had carrier screening were seven times more likely, and those who had NIPS-A were three times more likely. Information seekers are more likely to pursue broad testing and screening when given the options.

The uptake rates for NIPS-SGD increased over time, with the highest uptake rates being in 2020 and 2021. Although 2017 also had a very high uptake rate of 44%, this may be due to the much smaller sample size that year. This follows a similar trend that was seen for the uptake of NIPS-A, which found an annual increase in uptake after the test was released (van der Meij et al., 2021) These trends reflect increasing comfort with novel screening tests as subjects and providers accept these screening methodologies as routine.

Subjects whose male reproductive partner was present during their genetic counseling session were four times more likely to pursue NIPS-SGD than those whose partner was not present in the session. Additionally, the reproductive partner being unavailable for testing was the highest reported reason for declining, with 36% of subjects citing this reason. Although this could be the result of laboratory policy requiring a paternal blood sample for duo testing (a requirement that changed in August 2021), these results suggest that the presence of the reproductive partner influences whether patients elect to have NIPS-SGD. This finding is consistent with prior studies that have shown that relationship factors influence subjects' decision-making regarding prenatal testing (Laberge et al., 2019; Nazare et al., 2011). While this NIPS-SGD test no longer requires a paternal sample, it is important for future prenatal technology to consider that requirement of a paternal sample may affect uptake and accessibility of testing.

Subjects who received counseling at an offsite location were twice as likely to pursue NIPS-SGD than those who received counseling at the main site. One possible explanation for this that we considered was that subjects at the offsite locations were more likely to have medicaid insurance than subjects at the main site. However, looking into this further we found that of the subjects seen at the

main site, 71% had private insurance while 29% had medicaid insurance, and of the subjects seen at the offsites, 94% had private insurance and only 6% had medicaid. Each of the offsite locations may have had different primary genetic counselors working there, different doctors present who may have also provided opinions on patient testing, as well as different patient populations in regards to factors such as socioeconomic class and education levels, so it is difficult to isolate which factor or factors may be the reason for this association with test uptake.

4.4 | Strengths and limitations

Our study has several strengths. This study was conducted at a large urban tertiary care center and its satellites with multiple ABGC board-certified genetic counselors who were trained to discuss reproductive impact of APA and the potential benefits of NIPS-SGD to screen for associated de novo X-linked or dominant conditions. This increases the generalizability of our study.

A limitation of our study is its retrospective design. We relied on data that was abstracted from the clinical charts and provider logs which may be subject to provider bias. For some variables, such as reasons for declining NIPS-SGD, there was incomplete information that may have biased our results. We also did not have information about subject and partner's education level, which has been associated with prenatal testing uptake rates in some studies (Dicke et al., 2014; Gil et al., 2015). Additionally, our sample size was relatively limited ($n=186$) and additional research into this subject on a larger sample size would be needed to further validate the results described in this paper. Despite these limitations, the study provides novel insight into the factors that drive uptake of NIPS-SGD for APA.

5 | CONCLUSIONS

In this cross-sectional study of pregnant subjects having genetic counseling through a large tertiary care center in central New Jersey, we found that just over one-third of subjects who were offered NIPS-SGD for APA opted to have this screen. Several factors correlated with higher screen uptake rates including if the subject had additional prenatal testing, if the reproductive partner was present, and if the patient had Medicaid insurance and thus were not expected to incur an out-of-pocket cost. As NIPS-SGD screening becomes more readily available and male partner samples are no longer required, we anticipate that screen uptake rates may continue to increase.

AUTHOR CONTRIBUTIONS

All the authors made substantial contributions to the conception and design of this work, as well as data acquisition, analysis, and interpretation. Kylie Katz drafted the work, and all authors were involved in revising it critically for important intellectual content. All authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

This work was completed while the first author was in training for genetic counseling, and this work was a portion of the first author's degree requirement.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Deidentified data and datasets can be made available upon request to the authors.

ETHICS STATEMENT

Human Studies and Informed Consent: This study was approved by the Rutgers University Institutional Review Board (IRB). Informed consent was waived, as the research involves no more than minimal risk to the subject, and the waiver did not adversely affect the rights and welfare of the subjects.

Animal Studies: No non-human animal studies were carried out by the authors for this article.

ORCID

Kylie Katz https://orcid.org/0000-0002-1187-8535

REFERENCES

Allen, S., Young, E., & Bowns, B. (2017). Noninvasive prenatal diagnosis for single gene disorders. *Current Opinion in Obstetrics and Gynecology*, *29*(2), 73–79. https://doi.org/10.1097/GCO.0000000000000347

Benn, P. (2014). Non-invasive prenatal testing using cell free DNA in maternal plasma: Recent developments and future prospects. *Journal of Clinical Medicine*, *3*(2), 537–565. https://doi.org/10.3390/jcm3020537

Brandt, J. S., Cruz Ithier, M. A., Rosen, T., & Ashinadze, E. (2019). Advanced paternal age, infertility, and reproductive risks: A review of the literature. *Prenatal Diagnosis*, *39*(2), 81–87. https://doi.org/10.1002/pd.5402

Chowdhury, M. Z. I., & Turin, T. C. (2020). Variable selection strategies and its importance in clinical prediction modelling. *Family Medicine and Community Health*, *8*(1), e000262. https://doi.org/10.1136/fmch-2019-000262

Di Mattei, V., Ferrari, F., Perego, G., Tobia, V., Mauro, F., & Candiani, M. (2021). Decision-making factors in prenatal testing: A systematic review. *Health Psychology Open*, *8*(1), 2055102920987455. https://doi.org/10.1177/2055102920987455

Dicke, J. M., Van Duyne, L., & Bradshaw, R. (2014). The utilization and choices of aneuploidy screening in a midwestern population. *Journal of Genetic Counseling*, *23*(5), 874–880. https://doi.org/10.1007/s10897-014-9711-x

Dziak, J. J., Coffman, D. L., Lanza, S. T., Li, R., & Jermiin, L. S. (2020). Sensitivity and specificity of information criteria. *Briefings in Bioinformatics*, *21*(2), 553–565. https://doi.org/10.1093/bib/bbz016

Gadsbøll, K., Petersen, O. B., Gatinois, V., Strange, H., Jacobsson, B., Wapner, R., Wapner, R., Vermeesch, J. R., NIPT-Map Study Group, & Vogel, I. (2020). Current use of noninvasive prenatal testing in

Europe, Australia and the USA: A graphical presentation. *Acta Obstetricia et Gynecologica Scandinavica*, *99*(6), 722–730. https://doi.org/10.1111/aogs.13841

Gil, M. M., Giunta, G., Macalli, E. A., Poon, L. C., & Nicolaides, K. H. (2015). UK NHS pilot study on cell-free DNA testing in screening for fetal trisomies: Factors affecting uptake. *Ultrasound in Obstetrics and Gynecology*, *45*(1), 67–73. https://doi.org/10.1002/uog.14683

Kostenko, E., Chantraine, F., Vandeweyer, K., Schmid, M., Lefevre, A., Hertz, D., Zelle, L., Bartha, J. L., & Di Renzo, G. C. (2019). Clinical and economic impact of adopting noninvasive prenatal testing as a primary screening method for fetal aneuploidies in the general pregnancy population. *Fetal Diagnosis and Therapy*, *45*(6), 413–423. https://doi.org/10.1159/000491750

Laberge, A. M., Birko, S., Lemoine, M. È., Le Clerc-Blain, J., Haidar, H., Affdal, A. O., Dupras, C., & Ravitsky, V. (2019). Canadian pregnant Women's preferences regarding NIPT for down syndrome: The information they want, how they want to get it, and with whom they want to discuss it. *Journal of Obstetrics and Gynaecology Canada*, *41*(6), 782–791. https://doi.org/10.1016/j.jogc.2018.11.003

Mohan, P., Lemoine, J., Trotter, C., Rakova, I., Billings, P., Peacock, S., Kao, C. Y., Wang, Y., Xia, F., Eng, C. M., & Benn, P. (2022). Clinical experience with non-invasive prenatal screening for single-gene disorders. *Ultrasound in Obstetrics & Gynecology*, *59*(1), 33–39. https://doi.org/10.1002/uog.23756

Nazare, B., Fonseca, A., Gameiro, S., & Canavarro, M. C. (2011). Amniocentesis due to advanced maternal age: The role of marital intimacy in couples' decision-making process. *Contemporary Family Therapy*, *33*(2), 128–142. https://doi.org/10.1007/s10591-011-9151-9

StataCorp. (2021). *Stata statistical software: Release 17*. StataCorp LLC.

Steyerberg, E. W., Vickers, A. J., Cook, N. R., Gerds, T., Gonen, M., Obuchowski, N., Pencina, M. J., & Kattan, M. W. (2010). Assessing the performance of prediction models: A framework for traditional and novel measures. *Epidemiology (Cambridge, Mass.)*, *21*(1), 128–138. https://doi.org/10.1097/EDE.0b013e3181c30fb2

Toriello, H. V., Meck, J. M., & Professional Practice and Guidelines Committee. (2008). Statement on guidance for genetic counseling in advanced paternal age. *Genetics in Medicine*, *10*(6), 457–460. https://doi.org/10.1097/GIM.0b013e318176fabb

van der Meij, K. R. M., de Groot-van Mooren, M., Carbo, E. W. S., Pieters, M. J., Rodenburg, W., Sistermans, E. A., Cornel, M. C., Henneman, L., & Dutch NIPT Consortium. (2021). Uptake of fetal aneuploidy screening after the introduction of the non-invasive prenatal test: A national population-based register study. *Acta Obstetricia et Gynecologica Scandinavica*, *100*(7), 1265–1272. https://doi.org/10.1111/aogs.14091

van der Meij, K. R. M., Kooij, C., Bekker, M. N., Galjaard, R. H., Henneman, L., & Dutch NIPT Consortium. (2021). Non-invasive prenatal test uptake in socioeconomically disadvantaged neighborhoods. *Prenatal Diagnosis*, *41*(11), 1395–1400. https://doi.org/10.1002/pd.6043

Zhang, J., Li, J., Saucier, J. B., Feng, Y., Jiang, Y., Sinson, J., McCombs, A. K., Schmitt, E. S., Peacock, S., Chen, S., Dai, H., Ge, X., Wang, G., Shaw, C. A., Mei, H., Breman, A., Xia, F., Yang, Y., Purgason, A., … Eng, C. M. (2019). Non-invasice prenatal sequencing for multiple Mendelian monogenic disorders using circulating cell-free fetal DNA. *Nature Medicine*, *25*(3), 439–447. https://doi.org/10.1038/s41591-018-0334-x

Zweig, M. H., & Campbell, G. (1993). Receiver-operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine. *Clinical Chemistry*, *39*(4), 561–577.

How to cite this article: Katz, K., Brandt, J. S., Heiman, G., Simone, L., Khan, S., Shingala, P., & Ashkinadze, E. (2025). Uptake rates for non-invasive prenatal screening for single-gene disorders associated with advanced paternal age. *Journal of Genetic Counseling*, *34*, e2025. https://doi.org/10.1002/jgc4.2025