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ACMG PRACTICE GUIDELINE

Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)

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ABSTRACT

Purpose: This workgroup aimed to develop an evidence-based clinical practice guideline for the use of noninvasive prenatal screening (NIPS) for pregnant individuals at general risk for fetal trisomy 21, trisomy 18, or trisomy 13 and to evaluate the utility of NIPS for other chromosomal disorders.

Methods: The NIPS Evidence-Based Guideline Work Group ($n = 7$) relied on the results from the recent American College of Medical Genetics and Genomics (ACMG) systematic review to form the evidentiary basis of this guideline. Workgroup members used the Grading of Recommendations Assessment, Development, and Evaluation Evidence to Decision framework to draft recommendations. The guideline underwent extensive internal and external peer review with a public comment period before approval by the ACMG Board of Directors.

Results: Evidence consistently demonstrated improved accuracy of NIPS compared with traditional screening methods for trisomies 21, 18, and 13 in singleton and twin gestations. Identification of rare autosomal trisomies and other microdeletion syndromes with NIPS is an emerging area of interest.

Conclusion: ACMG strongly recommends NIPS over traditional screening methods for all pregnant patients with singleton and twin gestations for fetal trisomies 21, 18, and 13 and strongly recommends NIPS be offered to patients to screen for fetal sex chromosome aneuploidy.

Note: After publication of this Guideline, ACMG decided to change the name for this screening from "non-invasive prenatal screening", and its corresponding acronym, to "prenatal cell-free DNA screening". Future ACMG publications about this topic will now include the revised terminology.

The Board of Directors of the American College of Medical Genetics and Genomics approved this evidence-based guideline on October 24, 2022.

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Introduction

The American College of Medical Genetics and Genomics (ACMG) published a position statement on noninvasive prenatal screening (NIPS) using cell-free DNA for fetal aneuploidy in 2016,[1] which recommended that all pregnant patients be made aware of the availability of NIPS and its superior sensitivity for detecting common trisomies (13, 18, and 21). In addition, NIPS and the attendant pre- and post-test counseling should be accessible to all pregnant patients. It has become increasingly apparent that inequities exist across health systems, with many patients not being offered or made aware of this technology for screening.[2] In an effort to address these disparities, this guideline makes recommendations based on the results from a recent systematic evidence review (SER) undertaken by the ACMG[3] and addresses the use of NIPS for chromosome disorders for all pregnant patients. This evidence-based guideline (EBG) replaces the 2016 position statement.

Before the introduction of NIPS, traditional screening for fetal trisomy 21 (T21) and/or trisomy 18 (T18) comprised multiple algorithms implemented in either the first trimester, the second trimester, or both. Table 1 lists the most common variations of screening along with reported detection rates of T21. Descriptions of the various protocols and their relative screening characteristics can be found in a number of publications.[5,6] The largest prospective study that examined these methods of screening in the United States was called the First- and Second-Trimester Evaluation of Risk (FASTER) trial, with results published in 2005.[7] For the purpose of comparing traditional screening with NIPS in the absence of direct comparisons, we chose to use results from FASTER as representative of generally accepted performance of traditional screening. The highest performance of traditional screening is obtained with some combination of first and second trimester analysis, whether biochemical and/or sonographic, as was done in the FASTER trial. Table 2 compares many of the key features of NIPS vs traditional screening.

NIPS was introduced into clinical practice in late 2011. As with the introduction of traditional serum screening in the late 1980s, the primary focus of NIPS was to identify pregnancies with trisomy 21. NIPS has continued to evolve with an ongoing expansion of applications that go well beyond common trisomies covered by traditional screening, because the technology can interrogate the entire fetal genome. These additional findings have the potential for greater variability in analytical validity and clinical utility. More notably, the use of NIPS by general-risk patients has led to its widespread use across all ages and risk groups and has been adopted by some national health care systems.[8,9] Despite substantial agreement across professional societies, access to NIPS remains uneven in the United States.

Recognizing that NIPS continues to expand beyond the detection of trisomy 21 and other trisomies detected through traditional screening, the SER also evaluated currently available evidence examining screening for sex chromosome aneuploidies (SCAs), rare autosomal trisomies (RATs), and copy number variants (CNVs) for which comparisons with traditional methodologies are not possible.

This guideline addresses the utility of NIPS across pregnant individuals with singleton or twin pregnancies. After review of published studies, it was apparent that many reports did not consistently provide specifics about what proportion of the cohort examined was high-risk vs otherwise. In the United States, the proportion of pregnancies occurring in individuals aged 35 years or older at estimated

Table 1 Traditional methods/protocols used for T21 screening in pregnancy

Methods/Protocols	Detection Rate (%)
First trimester	
NT sonogram	64-70
NT + serum analytes (alone or in combination: PAPP-A, free or total β-hCG)	82-87
Second trimester	
Maternal serum AFP, unconjugated estriol, hCG (triple screen)	69
Maternal serum AFP, unconjugated estriol, hCG + inhibin A (quad screen)	81
First and second trimester combinations	
Integrated: NT + PAPP-A + quad	94-96
Stepwise sequential: NT + serum analytes (testing offered if positive) + quad (if first trimester screen negative)	95

ACOG, American College of Obstetricians and Gynecologists; *AFP*, alpha-fetoprotein; *hCG*, human chorionic gonadotropin; *NT*, nuchal translucency; *PAPP-A*, pregnancy-associated plasma protein A; *T21*, trisomy 21.
Adapted from ACOG Committee on Practice Bulletins.[4]

Table 2 Comparison of NIPS with traditional screening

Traditional screening	NIPS
First and/or second trimester	Any time during gestation ≥10 wk
Best performance when both trimesters combined	One time laboratory test
US is component of most algorithms	No US required
Includes NTD screening (second trimester)	No NTD screening
No SCA screening	SCA screening unless declined
Not FDA approved	Not FDA approved
Rare for "no-call"	No-call about 1%
Near 100% coverage by third party	Inconsistent insurance coverage
Diminished screening performance in twin pregnancies	Screening performance in twin pregnancies equivalent to singletons
No specific screening for CNV	Targeted or genome-wide CNV screening available

CNV, copy number variant; *FDA*, U.S. Food and Drug Administration; *NIPS*, noninvasive prenatal screening; *NTD*, neural tube defect; *SCA*, sex chromosome aneuploidy; *US*, ultrasound.

due date is about 19% (692,000 of the 3.6 million in 2020).[10] Therefore, a general-risk population for purposes of the guideline will be comprised mostly of individuals younger than 35 years at estimated due date.

Methods

Workgroup composition

In 2019, ACMG's Board of Directors approved a proposal to develop an EBG pertaining to the use of NIPS in a general-risk population that would update the 2016 position statement.[1] The ACMG Professional Practice and Guidelines Committee convened 2 separate workgroups to support this endeavor: an SER group and an EBG panel. ACMG's Board of Directors approved the appointment of an individual who is a clinical geneticist to serve as the chair of the EBG panel. Additional panelists were identified/selected from ACMG members representing experts in laboratory genetics (Y.M.N.A., R.G.B., K.G.M.), genetic counseling (S.D.), clinical genetics (A.E., J.S.D., S.K.), and obstetrics (J.S.D., S.K.). Consistent with ACMG policy, workgroup members were free from financial conflicts of interest, which was affirmed after independent review by the ACMG Conflicts, Composition, and Procedure Review Committee. Panel discussions included a lay individual who had familiarity with prenatal aneuploidy screening. Further guidance was provided by ACMG methodologists (M.M., J.M.).

SER

The EBG panel and methodologist (M.M.) developed key research questions to guide the SER process. Full methodological details and results of the SER can be found in Rose et al.[3] In brief, the SER sought to compare the performance characteristics of NIPS as a screening method with traditional prenatal screening methods (eg, quad screen) for select chromosomal anomalies in both general-risk singleton and twin pregnancies. Specific genetic abnormalities included common chromosomal trisomies as well as chromosomal imbalances that are not amenable to traditional screening. In addition, information was sought on the potential for maternal findings and the psychosocial impact of NIPS. Finally, the SER considered the cost-effectiveness of NIPS as a screening method in a general-risk population.

Evidence to decision framework

The EBG panel used the Grading of Recommendations, Assessment, Development, and Evaluation Evidence to Decision framework to create recommendations. Details about the Grading of Recommendations, Assessment, Development, and Evaluation Evidence to Decision framework and its components have been published elsewhere (see, eg, Alonso-Coello et al).[11] The EBG panel ranked each outcome on a scale from 1 to 9, with 9 representing an outcome of critical importance to the decision-making process and 1 representing an outcome not important to the process. Results from the SER were compiled into an evidence table that included an overall assessment including risk of bias, inconsistency, indirectness of the evidence, imprecision of the results, and concern for publication bias. Results of the primary random-effects meta-analyses from the SER and key findings from any sensitivity analyses were included in the evidence table and an overall certainty in the results (high, moderate, low, very low) was determined.

Recommendations were made based on quality and certainty of evidence.[12] A "strong recommendation" is given when there is clear evidence to support one alternative over another (or over the current standard practice). A "conditional recommendation" is made when the evidence for and against an intervention are closely balanced, there is uncertainty about the effects of the intervention, there is questionable cost-effectiveness, or there is significant variability in patients' values and preferences for the intervention. A conditional recommendation in the context of clinical care requires careful examination of the relevant evidence and a shared decision-making process. If there is insufficient evidence to support either a positive or negative position on the specific topic/key question, no recommendation is given.

In addition to the results of the SER, the EBG panel further considered emerging peer-reviewed evidence accepted/published after the final search was performed by the SER, relevant information from conference presentations, and other gray literature. Because of the scarcity of head-to-head comparisons of the performance characteristics of NIPS and traditional prenatal screening methods, the EBG panel incorporated data from existing reviews and clinical experiences with traditional prenatal methods.

Prioritization of outcomes was considered at multiple timepoints in the EBG process: while structuring the SER, after receipt of the results from the SER, and before finalizing the recommendations. These decisions required ≥80% agreement of the panelists, with any dissent documented. After receipt of the SER results, panelists used the PanelVoice component of GRADEpro software to independently decide on 12 domains: the priority of the issue, how substantial the desirable effects (benefits) and undesirable effects (harms) were, the certainty of the evidence, the overall balance of effects, resource requirements to enact NIPS and the certainty of those resource requirements, the cost-effectiveness of NIPS compared with existing prenatal screening methods, patient values and preferences, potential impact of NIPS on health equity, feasibility of implementing NIPS, and stakeholder acceptability of NIPS. Results from the PanelVoice voting were compiled in GRADEpro and the workgroup achieved consensus for final determinations and draft recommendation statements (direction and strength) on a conference call. All authors contributed to the writing and editing of the manuscript,

which was approved by the ACMG Board of Directors following extensive internal and external peer review and a public comment period.

Recommendation: ACMG RECOMMENDS NIPS OVER TRADITIONAL SCREENING METHODS FOR ALL PREGNANT PATIENTS WITH SINGLETON GESTATION FOR FETAL TRISOMIES 21, 18, AND 13 (STRONG RECOMMENDATION BASED ON HIGH CERTAINTY OF EVIDENCE)

The SER demonstrated consistently superior performance of NIPS, which outperformed traditional screening in all parameters and across all studies in general-risk populations of individuals with a singleton pregnancy.[3] Specifically, the detection rate for fetal trisomy 21 (T21) was 98.8% (95% CI = 97.8%-99.3%) with a corresponding false-positive rate (FPR) of 0.04% (95% CI = 0.02%-0.08%). This is contrasted with the detection rates obtained with traditional methods in the FASTER trial, which incorporated first and/or second trimester testing.[7] Detection rates in that trial across the entire cohort in the first trimester was 77% to 82%, with a corresponding 3% to 5% screen-positive rate depending on the risk cutoff. It should be noted, however, that detection rates for fetal T21 using traditional first-trimester screening methods were confirmed in the FASTER trial to be lower in younger patients (75%, with 5% FPR), which had also been reported by others.[13,14]

The sensitivities and specificities for the detection of the common trisomies using NIPS in general-risk populations are essentially the same as that demonstrated in high-risk cohorts (eg, aged 35 years or older). Because of the lower prevalence of these trisomies in pregnancies of younger patients, the positive predictive value (PPV) of NIPS for that cohort will be reduced compared with that of individuals at higher a priori risk. Nonetheless, when examining PPV across the various cohorts studied over the past 5 years, PPV is reported at 91.8% for T21 (95% CI = 88.4%-94.23%) (see Table 1 in Rose et al).[3]

With the use of NIPS, the empirical detection rate of fetal T18 is 98.83% (95% CI = 95.45%-99.71%) and of trisomy 13 (T13) is 92.85% (95% CI = 81.15%-97.5%). Corresponding FPR for those trisomies are 0.07% (95% CI = 0.03%-0.17%) and 0.04% (95% CI = 0.02%-0.08%), respectively (Table 1 in Rose et al).[3] The PPVs for T18 and T13 are lower than for T21, largely because of the corresponding lower prevalence of those conditions. The PPV for T18 in the SER was 65.8% (95% CI = 45.3%-81.7%) and for T13 was 37.2% (95% CI = 26.1%-50.0%).

Screening performance for T18 and T13 were also reported in the FASTER trial and resulted in detection rates of up to 100% for T18 and 44% for T13.[15] It should be noted that the T13 cases detected were from pregnancies that had screened positive for T21 or T18, because there was no specific algorithm for T13 screening. No studies on traditional screening report PPVs for T18 or T13, but given their lower prevalence, the PPVs are likely to be lower than with screening for T21, which is generally reported to be about 3%.

There are certain pregnancy factors that can interfere with performance/interpretation of NIPS. A common example is a vanishing twin gestation. Given the high incidence of aneuploidy in early embryonic demise, such an event in one twin may affect the correct interpretation of the status of the living twin. There was no evidence identified by the SER to support altering the option of NIPS in a pregnancy with a known vanishing twin, although the patient should be counseled that accuracy may be impacted. The American College of Obstetricians and Gynecologists states that NIPS should not be performed in such circumstances.[16] Known maternal malignancy is also a relative contraindication of offering NIPS given the somatic genomic aberrations that are present in the cancerous cells. Such aberrations may be detected with NIPS but cannot generally be ascribed to fetal or maternal origin without additional evaluation.

In summary, NIPS has consistently higher screening performance in the detection of fetal T21/18/13 in singleton pregnancies than any of the traditional screening approaches.

Recommendation: ACMG RECOMMENDS NIPS OVER TRADITIONAL METHODS FOR TRISOMY SCREENING IN TWIN GESTATIONS (STRONG RECOMMENDATION, BASED ON HIGH CERTAINTY OF EVIDENCE)

The SER concluded that NIPS for T21 in twin pregnancies demonstrates equivalent screening characteristics to that of singleton pregnancies, with a sensitivity of 98.2% (95% CI = 88.2%-99.7%) and specificity of 99.9% (95% CI = 99.8%-100%),[3] although fewer published studies exist than the number of studies in singleton gestations.

The number of reports on twin pregnancies screened for T18 and T13 is smaller than that for T21. Despite this, results are generally consistent across studies and approximate the performance in single gestations; this was also confirmed in the SER. For the reports on NIPS for T18 and T13, the SER reported sensitivities of 90% (95% CI = 67.6%-97.5%) and 80% (95% CI = 30.9%-97.3%), respectively, in twin pregnancies, with corresponding specificities of 99.95% (95% CI = 99.8%-100%) and 99.93% (95% CI = 99.4%-100%).[3]

The FASTER trial did not include twin pregnancies, and there are limited data with respect to performance of traditional screening in twin pregnancies. One large report from France demonstrated detection rates of T21 of around 63%[17] using second trimester biochemistry (with an FPR of 10.8%) and a smaller series of patients from the United Kingdom using first-trimester nuchal translucency (NT) screening with

biochemistry reported 75% detection with 9% FPR.[18] There are no studies that have specifically focused on screening for T18 in twin pregnancies. Traditional screening methods were generally not available to screen for T13 in twins.

Recommendation: ACMG RECOMMENDS THAT NIPS BE OFFERED TO PATIENTS WITH A SINGLETON GESTATION TO SCREEN FOR FETAL SCA (STRONG RECOMMENDATION, BASED ON HIGH CERTAINTY OF EVIDENCE)

The option of screening for fetal SCA is unique to NIPS and has not been available through traditional screening. Therefore, direct comparisons of screening performance between these 2 modalities cannot be done.

The screening performance of NIPS for SCA was shown to be high in the SER across all 4 common types: monosomy X, XXX, XXY, and XYY. Overall detection rate for any SCA was 99.6% (95% CI = 94.8%-100%) and specificity was 99.8% (95% CI = 99.7%-99.9%). However, there appear to be differences in PPVs across the different SCAs. For example, the PPVs for NIPS were 29.5% (95% CI = 22.7%-37.4%) for results indicating increased risk for 45,X, 54% (95% CI = 40.6%-66.8%) for XXX, 74% (95% CI = 59.5%-84.7%) for XXY, and 74.5% (95% CI = 58.4%-85.8%) for XYY. There are biological reasons why the PPV for 45,X may be lower, eg, higher rates of placental mosaicism for monosomy X[19] or maternal mosaicism for 45,X that by definition would not be identified through amniocentesis. The studies did not uniformly specify the type of diagnostic testing performed to confirm the SCA. The possibility of placental mosaicism for SCA should be included in pre- and post-test counseling.

Incorporation of SCAs into prenatal screening protocols is likely to be a new experience for most providers. Pretest counseling for SCA screening may be challenging for clinicians who are not familiar with them. Unlike the autosomal aneuploidies, most individuals with SCA are not ascertained at birth because of the lack of distinctive phenotypic features. In addition, if a pregnancy is screen-positive for SCA, and it is confirmed through diagnostic testing, the ability to provide accurate prognostic information prenatally may be impacted by a reliance on historically biased reports of postnatally ascertained cases. When counseling about SCAs, the source of information should be based on prospective follow-up of children born following a prenatal diagnosis of the specific SCA.[20]

Patients receiving confirmatory results should be referred to professionals who can provide an accurate depiction of the phenotype. The potential for neurobehavioral differences related to some of these conditions should be provided, along with the most recent evidence of medical interventions that may mitigate some of those outcomes.[21]

NIPS also carries the potential for identifying a SCA in the pregnant individual. For example, there is a well-recognized age-related increase in 45,X mosaicism in lymphocytes of 46,XX patients that is not associated with Turner syndrome.[22] However, this should not be assumed to be the explanation of a positive screen for 45,X, and these individuals should be offered diagnostic fetal evaluation. In addition, suspicion for pre-existing maternal mosaic Turner syndrome should lead to further evaluation, ideally by a medical geneticist, that includes maternal karyotyping. Individuals with confirmed mosaic maternal Turner syndrome should be referred to a maternal-fetal medicine specialist and a cardiologist because of increased risks for various perinatal morbidities.

Clinical experience has demonstrated that not all pregnant individuals will pursue screening for SCA, and clinical laboratories offering NIPS generally provide an opt-out option. Furthermore, SCA screening is limited or unavailable in twins, depending on technology and chorionicity.

Recommendation: ACMG SUGGESTS THAT NIPS FOR 22q11.2 DELETION SYNDROME BE OFFERED TO ALL PATIENTS (CONDITIONAL RECOMMENDATION, BASED ON MODERATE CERTAINTY OF THE EVIDENCE)

A conditional recommendation should be interpreted as follows: most patients would request this and most clinicians would offer NIPS for this purpose, after a discussion about the benefits and limitations of screening and in the context of shared decision-making.

The term CNV is used herein to indicate segmental genomic imbalances, microdeletions, or microduplications but not numerical chromosome imbalances. The prevalence of clinically relevant CNVs in karyotypically normal fetuses is approximately 2% as demonstrated via diagnostic studies and is higher in fetuses with known anatomical anomalies.[23,24] Individually, any given CNV is rare; however, the 22q11.2 deletion syndrome (22q11.2DS), the most common pathogenic CNV identified prenatally, has been estimated to have a prevalence range of 1 in 990[25] to 1 in 2148.[26] There is no known maternal age impact on the incidence of fetal CNVs.[27]

Two main approaches to CNV screening have been reported: (1) targeting of specific well-recognized microdeletion/duplication syndromes and (2) a broader genome-wide approach. For the analysis of screening performance, it is probably more appropriate to address CNV screening characteristics for an individual entity (eg, 22q11.2DS) rather than as a collective group. The SER demonstrates that sensitivity and specificity of CNV screening in general is below that of the common trisomies and SCAs.

A recent study[28] that was not included in the SER prospectively assessed the performance of SNP-based NIPS for the most commonly known microdeletion syndrome, 22q11.2DS. In a cohort of 18,289 pregnancies with complete genetic follow-up, those investigators reported a detection of 10 in 12 cases of 22q11.2DS (using an updated algorithm that was developed during data analysis after enrollment was completed). Using a risk cutoff of 1 in 100, there were 19

screen-positive cases for a FPR of 0.05%. The PPV with this approach was 52.6%. Eleven of the 12 subjects had their blood drawn in the first trimester.[28] It should be noted that this cohort included pregnancies that were later identified to have structural fetal anomalies, therefore the incidence of 22q11.2DS was likely higher than in the general pregnancy population.

Further support for NIPS for 22q11.2DS was observed in a cost-effectiveness study from the United States, which modeled 4 million pregnant individuals undergoing prenatal genetic screening.[29] Compared to NIPS for the most common trisomies alone, the additional screening of 5 microdeletion syndromes, including 22q11.2DS, improved effectiveness by 977 quality-adjusted life years, reduced costs by $90.9 million, and was the dominant screening strategy in >92% of trials.

Recommendation: AT THIS TIME, THERE IS INSUFFICIENT EVIDENCE TO RECOMMEND ROUTINE SCREENING FOR CNVs OTHER THAN 22q11.2 DELETIONS (NO RECOMMENDATION, OWING TO LACK OF CLINICALLY RELEVANT EVIDENCE AND VALIDATION)

At this time, genome-wide CNV screening in the United States is designed for detection of CNVs of ≥7 megabases. However, a prospective study of diagnostic genome arrays in a series of pregnancies, some of which were complicated with fetal anomalies, reported that the large majority of clinically relevant CNVs were <7 megabases.[30] Limitations such as these should be included in pretest counseling.

There are few studies with complete follow-up of pregnancies screened for CNVs, and sensitivity and specificity data are limited. Most reports include information only about positivity rates, and therefore PPVs have been calculated from those cohorts. The cohorts in these studies are heterogeneous and many contain fetuses with ultrasound anomalies, suggesting that estimates are likely to be impacted by ascertainment bias. The SER reported PPVs ranging from 0%[31] to 80.56%.[32]

Clinical validation of NIPS for substantially rarer disorders is challenging. Small CNV-driven syndromes often escape detection even at birth, making an accurate determination of birth prevalence, PPV and negative predictive value (NPV) difficult. Additional studies that include follow-up genomic testing of newborns are needed to correctly define the PPV and NPV.

Although there is insufficient evidence and undetermined clinical utility to recommend its routine use at the population level, there will be families for whom NIPS for CNVs could be offered based on the pregnancy or family history. Pretest counseling is critical in allowing individuals to make well-informed decisions about pursuing this option. Consultation with a genetics health care professional would be prudent in any case when NIPS is being considered as an alternative to diagnostic testing. Finally, this workgroup recognizes that advancements in technology will likely improve the screening performance for these rarer conditions.

The 2016 position statement did not recommend NIPS for genome-wide CNV screening. Our current position reaffirms this, primarily because of the limited clinical utility and uncertainties regarding PPV and NPV and the lack of clinical validation of routine use.

Recommendation: AT THIS TIME, THERE IS INSUFFICIENT EVIDENCE TO RECOMMEND OR NOT RECOMMEND NIPS FOR THE IDENTIFICATION OF RATs (NO RECOMMENDATION, OWING TO LACK OF CLINICALLY RELEVANT EVIDENCE)

RATs are any trisomy other than those involving chromosomes 13, 18, 21, X, or Y. Liveborn infants with RATs are exceptionally rare, at least in a nonmosaic state, and RATs identified during the prenatal period are generally present in a mosaic state.[33] Nearly all RATs that occur in nonmosaic states result in an early miscarriage. Mosaicism identified at the time of chorionic villi sampling (CVS) occurs in 1% to 2% of pregnancies.[34] Of these, the large majority represent confined placental mosaicism (CPM). Follow-up amniocentesis is generally recommended to clarify the status of the fetus with respect to the mosaicism detected on CVS. The incidence of mosaic RATs identified at the time of CVS is 0.6%.[19] In this series of 52,673 CVS cases, only 8 of 316 (2.53%) mosaic RATs identified at CVS were confirmed through amniocentesis. The rare cases of mosaicism confirmed by amniocentesis, however, are associated with a wide range of phenotypic consequences.[35]

It is technically possible to use NIPS to detect aneuploidies involving all chromosomes, but clinical implementation of detecting RATs has not been demonstrated. CPM may be associated with growth restriction in the fetus, along with other adverse perinatal events, but there are currently no methods to predict which specific cases will result in adverse outcome. Identification of CPM for a RAT before potential manifestations, such as intrauterine growth restriction is also of questionable clinical utility. Surveillance interventions for pregnancies with CPM are likely to create anxiety and stress for the patient. Although NIPS may demonstrate analytical validity for RATs, there is low clinical utility.

Our conclusion is that there is insufficient evidence to support the routine use of NIPS for screening for RATs, with potential for harms outweighing the benefits at this time.

Clinical Utility of NIPS

There are several aspects of implementing NIPS that could be considered evidence of utility, including uptake of screening, decisions surrounding diagnostic testing,

incorporation of NIPS results with fetal ultrasound findings later in pregnancy, and others. One example of clinical utility is to determine how the availability of NIPS impacts the uptake of diagnostic testing.

Historically, advanced maternal age was the single largest indication for diagnostic testing. Several reports have documented that after the introduction of NIPS, there was a substantial decline in the number of diagnostic procedures.[8,36]

The SER identified several studies including patients with mixed indications that uniformly demonstrated reductions in diagnostic testing both when NIPS was used as a primary screen or as a secondary screen (following abnormal traditional screening). Overall, reports included in the SER demonstrated a 31% to 79% reduction in diagnostic procedures depending on the population and indications.[3]

The impact of NIPS on diagnostic testing rates in a historically low-risk population is not likely to be as dramatic given fewer of these individuals would seek out primary diagnostic testing. The primary indications for diagnostic testing in this cohort have most often been abnormal traditional screening and/or detection of "soft markers" at the time of midtrimester anatomical survey. Many professional societies state that diagnostic testing is the preferred method of evaluation after positive traditional screening, but they also state that NIPS is an acceptable alternative with appropriate counseling about limitations.[16] Many patients use NIPS as a secondary screen (instead of diagnostic testing) if traditional screening has returned positive results.[37-39]

Prenatal sonography performed in the midtrimester has historically been used to adjust risk for fetal T21 or T18 by assessing for the presence of "soft markers." Patients with the presence of a soft marker on fetal ultrasound who would have routinely been offered amniocentesis now may be offered NIPS in the absence of previous screening. If NIPS indicates reduced risk, further testing is usually not recommended.[40] This is because the presence of a soft marker is not associated with an absolute risk but rather a likelihood ratio, none of which are large enough to negate the degree of risk reduction associated with negative NIPS results.

Another possible measure of utility is the reduction in the number of diagnostic procedures required to establish a diagnosis in cases of abnormal screening. The number of diagnostic tests needed to confirm a suspected trisomy is 1 per PPV. Therefore, applying the reported PPVs (Table 3) for the 2 screening modalities for fetal T21 yields the following:

The PPV for NIPS for T21 is 50% to 95%, which means 1.1 to 2 amniocentesis procedures to confirm trisomy in an affected pregnancy. Traditional screening PPV for T21 is about 2.2% to 3.6%, which translates as needing to perform between 28 to 45 diagnostic procedures to confirm a single case, depending on the specific traditional screening algorithm.

Table 3 Calculations of PPVs of traditional screening for trisomy 21

First trimester combined screening (using 1:300 cutoff) $N = 36{,}120$[a]				
		DS		
		+	–	Row Total
Screen result	+	75	2018	2093
	–	17	34,010	34,027
Column total		92	36,028	

Second trimester quadruple screen (using 1:300 cutoff) $N = 35{,}236$[b]				
		DS		
		+	–	Row Total
Screen result	+	74	2988	3062
	–	13	32,161	32,174
Column total		87	35,149	

Sequential screening, both trimesters (using 1:150 first trimester, 1:300 second) $N = 33{,}546$[c]				
		DS		
		+	–	Row Total
Screen result	+	82	3680	3762
	–	5	29,779	29,784
Column total		87	33,459	

DS, Down syndrome; *FPR*, false-positive rate; *PPV*, positive predictive value.

Adapted from Malone et al.[7]

[a]FPR = 5.6%; PPV = 75/2093 = 3.6%.

[b]FPR = 8.5%; PPV = 74/3062 = 2.4%.

[c]FPR = 11%; PPV = 82/3762 = 2.2%.

"No-Call" Results

The SER found that approximately 1% of initial patient samples submitted for NIPS are not provided a result and are termed "no-call". Optimal management of such pregnancies remains unclear and depends to some degree on the potential reason for the no-call result. The most frequent explanation for no-call results is insufficient fetal fraction, ie, the proportion of circulating DNA that is from the placenta and, not maternal. Repeat testing (which inherently is at a later gestational age) provides a result approximately 75% to 80% of the time.[41]

Some studies have demonstrated a higher than expected rate of fetal chromosome disorders in pregnancies that have no-call results.[42] Others have not confirmed that association.[43] The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend offering diagnostic testing to individuals with a no-call result.[16] There are a number of maternal conditions that have been associated with higher no-call rates. These include the use of certain anticoagulants,[44] autoimmune disorders,[45] and obesity.[41] There are some technological interventions that may mitigate the impact of low fetal fraction.[46] There are no current studies that have determined the optimal approach for individuals with these concurrent

morbidities who receive a no-call result. Low fetal fraction has been associated with a number of adverse outcomes, but definitive rates of pregnancy complications and surveillance protocols have not been established.[47]

It should be noted that failure to obtain all elements of a traditional screening protocol can also occur. In the FASTER trial, failure to obtain the NT measurement occurred in 4.5% of pregnancies analyzed. Furthermore, 2.6% of the NT sonograms submitted as part of quality control were deemed unacceptable.[7]

There are reports of higher rates of no-call with NIPS in twin pregnancies than in singleton pregnancies that should be communicated as part of pretest counseling.[48] Different laboratories use proprietary algorithms to assess the sufficiency of fetal fraction and tend to use the lower of the 2 fetal fractions to determine the adequacy of the specimen to make a call. This is believed to be because of the placental mass differences between the 2 gestations, which may also be associated with aneuploidy in one of the twins.

Pretest and Post-test Counseling

As with all prenatal screening and diagnostic testing, appropriate pre- and post-test counseling is an integral aspect of informed decision-making. Multiple professional society statements addressing NIPS emphasize the importance of accurate and thorough pre- and post-test genetic counseling. We affirm the principles of counseling for NIPS that were highlighted in the 2016 position statement, including providing up-to-date, balanced, and accurate information and personalized, patient-centered counseling.

Other groups have similarly listed critical points to cover during pretest counseling.[49] Pretest counseling should include a discussion of the optional and screening nature of NIPS, the types of conditions that can and cannot be screened for, the types of test results (including no-call results and incidental findings) that can be received, information about positive and negative predictive values, and the recommendation for confirmation of any abnormal results. Previously unknown parental chromosome abnormalities may be uncovered in mosaic or complete states, eg, 22q11.2DS.

Post-test counseling for negative results should emphasize the reduction, but not elimination, of risk, and the fact that NIPS only screens for select conditions and does not reduce the risk for other genetic disorders. Recommendations for neural tube defect screening should be included in counseling as NIPS is not designed to detect fetal structural abnormalities. Post-test counseling for positive results should include a discussion of the PPV of the result, a balanced description of the condition for which the screen was positive, including information about the spectrum of outcomes associated with the particular condition, and the recommendation for prenatal or postnatal confirmation of the NIPS results. There should be particular emphasis on prenatal diagnostic confirmation before any decisions with respect to pregnancy termination are made. In addition, patients should be provided with access to educational materials that have been developed from collaborations between health care professional groups and advocacy organizations.

Benefits vs Harms

Timing of results from aneuploidy screening is a major consideration in assessing the benefits of the various options. Obtaining screening results during the first trimester provides the pregnant individual with either early reassurance, or in the event of a positive screen, the ability to pursue testing with ample time to consider reproductive options as warranted. Changes to delivery planning or transfer of care may be considerations. If pregnancy termination is elected, undertaking that earlier in pregnancy is associated with greater safety and lower costs.

Earlier screening in twin pregnancies is also beneficial. The diagnostic confirmation of aneuploidy in a twin gestation is more complex than in singletons and is impacted by the chorionicity and gestational age of the pregnancy. Most dizygotic twins will be discordant for a trisomy, with 1 affected fetus and 1 euploid fetus. Patients should be counseled about the availability of selective reduction if that is a consideration. Most studies indicate that this is safer when performed in the first trimester;[50] another clear advantage of earlier screening and diagnosis.

The SER found insufficient evidence to make conclusions about the psychosocial impact of NIPS. There is a potential for iatrogenic psychological harm such as anxiety and stress associated with a number of pregnancy-related screens, tests, or interventions, particularly with respect to fetal evaluation. Some of the anxiety and concern surrounding prenatal screening can be mitigated with appropriate pretest counseling.[51] The SER found no evidence that NIPS is more likely to result in those types of harms than other forms of screening. The noted potential harms are applicable to any type of prenatal screening for chromosome abnormalities. No studies have compared potential harms associated with NIPS in a head-to-head comparison with traditional screening methods.

A number of benefits and concerns have been raised in reviews of patient perspectives on pregnancy screening and NIPS in particular. The Ontario Health Technology Assessment[52] delineates several of them as listed in Table 4.

Screening pregnant individuals for fetal aneuploidy has been an established option for more than 5 decades.[54] The potential for stigmatization of individuals with chromosome disorders that can be detected via prenatal screening is not a new concern. There is no evidence that NIPS impacts that potential differently than traditional screening. Patient autonomy is deeply rooted within the professional medical genetics community. Providers should emphasize the informed and shared decision-making that surrounds screening and/or testing in a supportive environment.

Table 4 Patient perspectives on NIPS: Benefits and concerns as reported by Health Quality Ontario

Benefits	Concerns
Better accuracy	Too widely available
Less physical risk than diagnostic testing	Simplicity may undermine informed decision-making
Earlier availability of results	Inequities of cost/access
	Pressure to have test and/or to terminate pregnancy if affected
	Insufficient pretest information

NIPS, noninvasive prenatal screening.
Adapted from Vanstone et al.[53]

Insufficient pre- and post-test counseling, rather than NIPS itself, represents potential and avoidable harms. Health care professionals offering NIPS should be well-versed in the limitations of screening for low prevalence conditions. Patients must receive thorough pretest counseling that details the benefits, limitations, and risks of NIPS, particularly highlighting the screening nature of the test, the possibility for false-positive results and the appropriate follow-up of results. Similarly, post-test counseling is essential to thoroughly discuss the meaning and implications of screen-positive results.[49]

Advances in NIPS technology continue to overcome aspects of its use that could negatively impact subgroups of pregnant individuals. The previously mentioned increased incidence of no-call results occurring more frequently in patients with high body mass index (BMI) is one example. Although most labs report being able to obtain a valid screen result upon retesting of a maternal sample at a later gestational age, this is not always the case. Technologies that improve the likelihood of obtaining valid screening results in individuals with high BMI should be pursued, because this provides another opportunity to improve health equity, given the unequal distribution of high BMI across subpopulations in the United States.[46]

Because of the methodology of NIPS, there is the potential to incidentally identify certain maternal conditions. This includes the identification of maternal chromosome imbalances and unsuspected maternal malignancies.

It is estimated that 25 to 27 in 100,000 pregnant individuals experience a malignancy during pregnancy, most commonly breast cancer.[55] The genomic aberrations that occur in malignant cells may be detected when performing NIPS. The likelihood of maternal malignancy is the highest when the NIPS result demonstrates multiple aneuploidies or an autosomal monosomy[56] that is not confirmed with fetal diagnostic testing.

There are no data regarding sensitivity or specificity of NIPS in identifying maternal neoplasms. In addition, there are no validated clinical approaches to the evaluation of individuals found to have a NIPS result suggestive of neoplastic disease, although some centers have suggested protocols.[57,58] The SER did not identify studies that allowed for the determination of best evaluation methods for patients with such results.

Identification of maternal genomic aberrations may occur as a result of NIPS. When NIPS raises suspicion for chromosomal variants that are not confirmed in the fetus, parental chromosome analysis should be considered as guided by laboratory interpretation. Whether identification of maternal genomic variants is associated with clinical benefit or harm has not been systematically evaluated. There are no known associations between abnormal traditional serum screening patterns and maternal genomic variants.

The current body of scientific evidence is insufficient to answer the question of whether NIPS can identify more maternal conditions than traditional screening. There is also insufficient evidence addressing the relative risks/benefits of identifying these maternal conditions during pregnancy. Ongoing studies, such as the IDENTIFY study (https://clinicaltrials.gov/ct2/show/NCT04049604?term=NCT04049604), that specifically address detection of maternal malignancies following select NIPS results will likely provide guidance as to the optimal evaluation of such patients.

Economic Considerations

The SER identified 10 studies that addressed the economic impact of implementing NIPS in a general-risk population. Some studies investigated first-line screening, whereas others explored secondary screening (as a follow-up to abnormal traditional screening). The EBG group focused on the use of NIPS as a primary screen because of its superior clinical utility and availability of use across the full range of gestational ages.

Economic impact depends on multiple considerations, including the patient population, health care system, governmental or third-party payers, and retail or discounted pricing of the test, as well as downstream costs of evaluation of positive NIPS. Most studies in the SER looked at costs of screening and testing but did not include extended time horizons (eg, costs associated with raising a child with a chromosome disorder).

The definition of cost-effectiveness varies depending on which stakeholder's perspective is used. For patients, obtaining a reliable result in early pregnancy is a major advantage of NIPS compared with traditional methods. Cost to detect a single case of trisomy 21 is frequently used for economic analysis but may not reflect the value of an assay as experienced by patients who have early and reliable screening results.

The SER determined that most existing literature takes the perspective of a public payer, and not the pregnant individual. Nonetheless, it concluded that primary screening with NIPS may be cost-effective in certain screening strategies.[29,59]

Given the significant reduction in diagnostic procedures performed in pregnancies screened with NIPS, much of the cost savings is highly dependent on the consistency of

pricing of diagnostic testing across centers and insurance plans. Laboratories performing NIPS price the test differently depending on the payer involved. Substantial cost differences are likely present across different countries and their respective health care systems. Even within the United States, the out-of-pocket costs vs amount paid by insurance plans is highly variable and generally undisclosed and thus not amenable to systematic study.

The utility and value of NIPS to pregnant individuals extends beyond the price of the test. No studies quantified the patient perspective utility when examining economic impact.

Conclusion

The key outcome of this EBG is that ACMG recommends NIPS for all pregnant individuals over traditional screening for common trisomies (in singleton and twin pregnancies) and SCAs (singleton pregnancies). This recommendation is driven primarily by the overall superior screening characteristics of NIPS. In addition, the convenience of obtaining results from a single first trimester blood draw is advantageous for patients.

Introduction of NIPS into clinical practice has resulted in a dramatic reduction of invasive (diagnostic) testing. Patients view the ability to have a reliable and accurate screen that may preclude the need for such testing as a large benefit.[52]

To provide the highest level of care and meaningful recommendations, careful and thorough counseling is imperative. Further investigation of the variety of information delivery formats for this counseling is warranted.

Further study is needed to address several aspects of NIPS implementation. Screening for CNV merits further validation. Education and training of providers that offer NIPS should be standardized and updated as new developments are introduced. Informative education materials that are free of marketing interests and provide well-founded benefits and limitations of screening should be developed and validated. The impact of potential harms remains understudied and should be specific to the variety of conditions included in the different NIPS assays.

NIPS has been a practice-changing advance in prenatal care. Its expansion into use for a general-risk population should be applied with the diligence and attentiveness it deserves.

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Conflict of Interest

J.S.D. is on the clinical advisory board of InformedDNA. K.G.M. is a director/employee of a clinical laboratory that performs several genetic and genomic analyses on a fee-for-service basis. All other authors declare no conflicts of interest.

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CORRECTION

Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)

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In the article "Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)" by Dungan JS et al (*Genet Med* 2023;25:100336), the following updates were made. After publication of this Guideline, ACMG decided to change the term for this screening from "non-invasive prenatal screening", and its corresponding acronym, to "prenatal cell-free DNA screening". Future ACMG publications about this topic will now include the revised terminology. On page 4 (left-hand column), the sentence "Corresponding FPR for those trisomies are 0.07% (95% CI = 0.03%-0.17%) and 0.04% (95% CI = 0.02%-0.08%), respectively (Table 3 in Rose et al).[3]" was updated to "Corresponding FPR for those trisomies are 0.07% (95% CI = 0.03%-0.17%) and 0.04% (95% CI = 0.02%-0.08%), respectively (Table 1 in Rose et al).[3]" On page 12, reference 43 was updated to "43. Rousseau F, Langlois S, Johnson J, et al. Prospective head-to-head comparison of accuracy of two sequencing platforms for screening for fetal aneuploidy by cell-free DNA: the PEGASUS study. *Eur J Hum Genet*. 2019;27(11):1701-1715. http://doi.org/10.1038/s41431-019-0443-0". The authors would like to apologize for any inconvenience this may have caused. The article has been corrected online and can be accessed at https://doi.org/10.1016/j.gim.2022.11.004.

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