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Original Research

A Prospective, Multi-Site Study of Performance of Cell-Free DNA Testing for Recessive Conditions in a Large, General-Risk Pregnancy Population

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OBJECTIVE: To evaluate the clinical performance of cell-free DNA (cfDNA) screening as a primary screening tool for autosomal recessive conditions in a large, prospective, general-risk population.

METHODS: We conducted a prospective analysis of pregnant individuals who underwent carrier screening with a reflex cfDNA fetal risk assessment at nine participating U.S. institutions. The conditions evaluated included cystic fibrosis, spinal muscular atrophy, and beta and alpha hemoglobinopathies. The cfDNA results were categorized as high risk (at least 1-in-4 predicted fetal risk) or low risk. Test performance metrics were calculated using Wilson Score 95% CIs.

RESULTS: There were 2,403 cfDNA results among 2,212 pregnant carriers with singleton pregnancies at a gestational age of at least 10 weeks at participating sites (188 individuals were carriers for more than one condition). The neonatal or fetal outcome was known for 2,369 (98.6%) cfDNA results. A cfDNA fetal risk of at least 1 in 4 was returned for 1.3%, and the cfDNA fetal risk test had a specificity of 99.5%, a negative predictive value of 99.9%, a sensitivity of 94.4%, and a positive predictive value (PPV) of 58.6%.

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All participant institutions received research funding to conduct the study at their institutions from BillionToOne Inc.

The authors gratefully acknowledge the contributions of the clinical and research staff who assisted with data extraction and coordination across participating sites. At Hackensack Meridian Health, the authors thank Nathalie Pena, Karen Valdes, Aksa Saju, and Rose Williams. At the Medical University of South Carolina, the authors thank Alexis Tomlin. The authors also acknowledge Lindsey Hendry and Arghal Ahmad at Shannon Medical Center. At Summa Health, the authors thank Melissa Maddie, Gregg Shreve, Megan Kasperczyk, Jeremy Kick, Tom Callihan, and Emily Kurtz. At the University of Alabama at Birmingham, the authors thank Angela R Seasley, Kaylyn Kirksey, Mickey Parks, Nancy Saxon, and Amy Leath. At the University of North Carolina School of Medicine, the authors thank Karen Dorman and Amber Ivins. The authors thank the clinical team at Birth & Women's Care. Finally, at the University of Texas Health Science Center, the authors acknowledge Luana Goulet and Brenna Albracht. The authors sincerely appreciate the time and effort of all contributors whose work made this study possible.

Akila Subramaniam, Associate Editor of O&G Open, *was not involved in the review or decision to publish this article.*

Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure

Julia Wynn, Shannon Rego, Andrew Haddad, Rachel Levan, and Jennifer Hoskovec are employees of and have equity in BillionToOne Inc. Andrew S. Haddad and Kelly Helton are paid advisors for BillionToOne Inc. Akila Subramaniam receives research funding from Johnson & Johnson, Natera, and the National Institutes of Health. Emily E. Hardisty is a paid advisor for Natera. The other authors did not report any potential conflicts of interest.

ISSN: 0029-7844/26

CONCLUSION: In this large, racially and ethnically diverse general-risk pregnant carrier sample, cfDNA fetal risk assessment accurately distinguished high-risk and low-risk pregnancies with greater PPV than traditional carrier screening, without requiring a partner sample. Combined with prior peer-reviewed studies that assessed cfDNA fetal risk screens, these findings support the possibility of cfDNA fetal risk assessment as a primary screen to identify pregnancies at high risk for autosomal recessive conditions.

(Obstet Gynecol 2026;00:1–7)
DOI: 10.1097/AOG.0000000000006403

Cell-free DNA (cfDNA) analysis for determining the fetal risk of autosomal recessive conditions has become increasingly accessible, with multiple labs offering it and increasing adoption by payers.[1–5] Cell-free DNA screening directly analyzes circulating placenta trophoblast in the pregnant person's bloodstream to assess the pregnancy-specific risk for the fetus to be affected, without the need for a partner sample.

An important clinical advantage of cfDNA screening for autosomal recessive conditions is its ability to provide meaningful fetal risk assessment in general-risk pregnancies at an early gestational age, even when partner carrier testing is unavailable. In routine prenatal care, partner testing is frequently incomplete or delayed due to factors such as insurance limitations, geographic separation, limited access to health care services, or patient-specific circumstances.[6–9]

Previous studies of cfDNA fetal risk assessment for autosomal recessive conditions have demonstrated high sensitivity and positive predictive value (PPV) in cohorts enriched for high-risk cases. These studies established the assay's ability to identify affected fetuses at high risk across diverse populations.[2,4] However, because such designs do not fully reflect clinical practice, there remains a need for evidence generated in more representative populations. The objective of the current study is to provide a more clinically representative assessment of cfDNA fetal risk assessment by conducting a prospective study of a cohort of identified carriers (the target population). This study enables more accurate and generalizable estimates of test performance, particularly specificity and negative predictive value (NPV), which are essential for evaluating the utility of a population-based screening test in practice.

METHODS

This was a prospective study of pregnant individuals who underwent clinical carrier screening at one of nine institutions and delivered before December 5, 2025. All patients had UNITY carrier screening with a reflex to cfDNA fetal risk analysis as part of their routine clinical care and met the clinical testing requirements, including having a singleton pregnancy with a gestational age of at least 10 weeks (the gestational age cutoff for the assay has since been validated for 9 weeks). The study was approved by the WCG IRB, which served as the central IRB for this study; local IRB approval to cede to the WCG IRB was obtained from participating institutions when necessary.

The study sample included pregnant patients who were found to be heterozygous carriers of a pathogenic or likely pathogenic variant for one or more conditions included on the carrier screen during the study period–which included cystic fibrosis (CF), spinal muscular atrophy, beta and alpha hemoglobinopathies–and met the clinical eligibility for fetal risk assessment via reflex cfDNA. Clinical criteria for reflex to cfDNA included a gestational age of at least 10 weeks at the time of draw, a singleton non–egg donor pregnancy, and a sample that passed sample quality control (ie, correct tube and label). This analysis focused on a general-risk population–patients with unknown partner carrier status at the time of testing–reflecting both the intended use of the assay and current practice at the participating institutions. Cases in which the partner was a known carrier of the same condition as the pregnant person at the time of testing (ie, a high-risk couple) were excluded from the main analysis. The high-risk couples were analyzed separately (Appendix 1, available online at https://links.lww.com/AOG/E945) because differences in disease prevalence between these two populations would render the NPV and PPV in both populations uninformative if combined. Patients with incomplete cfDNA results were excluded for the following reasons: 1) failure to meet sample quality control, 2) cfDNA analysis did not provide a fetal risk, 3) no results, or 4) the patient had a pregnancy loss or transferred care from the participating institution before diagnostic testing for the condition of concern.

Samples from the pregnant individuals were processed according to an established clinical protocol. Carrier screening is first performed using genomic DNA from the pregnant person; the methodology has been previously described in detail and is described in Appendix 2 (available online at https://links.lww.com/AOG/E945).[2] The screen reflexes to cfDNA analysis for fetal risk assessment when the pregnant person has one or more pathogenic or likely pathogenic variants via genomic DNA carrier screening. The technology of cfDNA screening for autosomal recessive conditions previously has been described in detail.[1–4] Briefly, a personalized

numerical risk is computed for the fetus to have the condition that the pregnant person carries. This risk is derived from: 1) fetal fraction (lower limit, 1%), which is calculated by amplifying known polymorphic alleles, identifying paternal alleles where the maternal genotype is homozygous, and doubling the allele fraction of the paternal alleles; 2) molecular counts of cfDNA using Quantitative Counting Templates; 3) variants that are distinct from the maternal genotype (ie, inherited variants from the nonpregnant person), which are detected by amplification and next generation sequencing of the relevant gene; 4) maternal variant fraction, which is calculated by performing dosage analysis on *HBB* exon 1, *CFTR* variants,[4] and *SMN1* one-copy variants; and 5) the a priori risk of the fetus to be affected, which is the general U.S. population carrier frequency when the partner carrier status is unknown. Although partner carrier screening is not required, it is offered through the laboratory if the partner is available and provides a sample. The a priori fetal risk is adjusted based on the partner's carrier status, increasing to 1 in 4 if the partner is a carrier. Of note, separate risks are reported if the condition of interest is known to disproportionately affect certain populations. For example, the prior risk of hemoglobin H disease in *HBA1/HBA2* single-deletion carriers increases from 1 in 2,280 to 1 in 372 when the partner is of Southeast Asian ancestry. Additional details of the cfDNA screening methodology are in the Appendix 2 (https://links.lww.com/AOG/E945).

The primary outcome of this study is the fetal or neonatal diagnosis of the condition for which the pregnant person was a carrier, ascertained by medical record review by the ordering institution. Data collected included newborn screening (NBS) and follow-up diagnostic testing for hemoglobinopathies, CF, and spinal muscular atrophy for the neonate resulting from the patient's included pregnancy. Additional records relevant to the conditions were collected, including molecular genetic test results (prenatal or postnatal) and laboratory test results (ie, hemoglobin electrophoresis, sweat test).

Newborn screening is a state-run program designed to achieve high sensitivity, at the expense of specificity, to identify neonates at risk of being affected by the conditions screened.[10–12] The institutions in this study were located across eight states and all perform NBS for the conditions included on the UNITY carrier screening panel. Details of NBS and state-specific NBS programs are summarized in Appendices 2 and 3 (available online at https://links.lww.com/AOG/E945). All patients included in the study had completed clinical follow-up if they screened positive by NBS to confirm or rule out the diagnosis.

Data extraction was completed by research coordinators at the participating sites who were not involved in the clinical care of the patients at least 4 weeks and up to 5 years after the estimated pregnancy due date. Data were entered into secure network databases unique to each site. Records were reviewed for completeness by a central coordinator, and follow-up questions were resolved through secure communications. In all cases, the fetal or neonatal affected status was confirmed through established clinical diagnostic testing and molecular or other laboratory testing for the indicated condition, resulting in a definitive diagnosis. Unaffected neonate status was confirmed by a normal NBS result, the absence of neonatal symptoms, or the absence of two pathogenic variants for the condition of concern on molecular testing.

The cfDNA screening results were considered concordant with the outcome if the cfDNA screening result was less than 1 in 4 (decreased-risk or low-risk) and the fetus or neonate was unaffected or if the cfDNA screening result was at least 1 in 4 (high-risk) and the fetus or neonate was affected. The cfDNA screening results were considered discordant if the fetus or neonate was unaffected and the cfDNA screening result was at least 1 in 4 or if the fetus or neonate was affected and the cfDNA screening result was less than 1 in 4 (Appendix 4, available online at https://links.lww.com/AOG/E945).

Cell-free DNA fetal risk assessment returns a pregnancy-specific quantitative risk of up to 9 in 10 and as low as 100 times below the a priori. For data analysis, the results were converted to binary categories. Pregnancies were designated high-risk among individuals who were carriers and whose cfDNA analysis calculated a risk of an affected pregnancy at least 1 in 4. All other pregnancies among carriers were designated low risk. A high-risk threshold of at least 1 in 4 was used in this analysis, because this is the maximum risk reported in traditional carrier screening when both the pregnant individual and the reproductive partner are identified as carriers (Appendix 4, https://links.lww.com/AOG/E945).

Summary data were compiled from all cases. Pregnancy and assay characteristics of patients with and without cfDNA results and those and with and without fetal and neonatal outcomes were evaluated using *t* tests, Mann-Whitney *U* tests, Wilcoxon rank-sum tests, analysis of variance, and Fisher exact tests to assess potential bias in cfDNA assay performance

and outcome collection. Clinical analytics of the cfDNA screen were computed, and included sensitivity, specificity, PPV, and NPV; Wilson Score 95% CIs were computed separately for the general-risk and high-risk couple samples (Appendix 1, https://links.lww.com/AOG/E945). A Brier[13] score was calculated by taking the mean squared difference between the predicted risk and the observed outcome to assess the performance of the cfDNA individual numerical fetal risk results. A Brier score more accurately measures performance of a continuous risk score than sensitivity and specificity, which require binary categories. The score ranges from 0 to 1, with 0 indicating perfect prediction. Statistical analyses were completed in RStudio 2026.01, and $P=.05$ was considered significant.

RESULTS

A total of 14,263 unique orders for carrier screening of pregnant individuals were received from the collaborating institutions during the study period. The individuals were diverse in race and ethnicity and representative of regions of the United States where they received care, including states with larger Hispanic and Black populations than the general U.S. population (Table 1). There were 2,767 general-risk carriers, yielding a carrier frequency of 19%, consistent with published U.S. carrier frequencies (Table 1).

Among the 2,767 general-risk carriers, there were 3,056 cfDNA tests; 284 individuals were carriers of more than one condition. Eighty tests were not completed because the sample did not pass quality control: The sample did not meet clinical testing requirements due to multiple gestation, a gestational age of less than 10 weeks, insufficient sample volume, or a mislabeled or unlabeled tube. Sixty-four tests had an initial no result after the cfDNA assay was attempted due to a fetal fraction of less than 1.0% or insufficient predicted molecular count, and a second sample was requested but not received. There were 14 final no-result cases in which the cfDNA analysis could not provide an informative fetal risk estimate (0.46% of cfDNA tests). Cases in which the sample did not pass quality control or the cfDNA test did not return a result had no differences in maternal age, gestational age, or race and ethnicity, but had a lower fetal fraction compared with cases in which the cfDNA assay was able to return a result (Appendices 1 and 5, available online at https://links.lww.com/AOG/E945).

For the 2,898 cfDNA tests with results, there were 495 for which the outcome was not available because the pregnancy ended without a live birth (n=68) or the patient transferred care and no prenatal diagnostic testing was performed (n=427; Fig. 1). Neonatal or fetal outcomes were known for 2,369 of 2,403 (98.6%) cfDNA test results from 2,212 pregnant individuals (n=188 carriers of more than one condition) who met the inclusion criteria: either prenatal diagnostic testing was complete or the pregnancy resulted in a live birth at the study institution (Fig. 1). There were no differences in pregnant person race or ethnicity, fetal fraction, turnaround time, maternal age, or gestational age at the time of testing among those with known, unavailable, or unknown outcomes (Appendices 1, 6, and 7, available online at https://links.lww.com/AOG/E945).

The median turnaround time for carrier screening was 9 days (IQR 4–11 days) when the test did not reflex to cfDNA and 14 days (IQR 11–18 days) for patients identified as carriers and with tests that reflexed to cfDNA (Appendix 8, https://links.lww.com/AOG/E945). The median gestational age at the time the results were received was 14 weeks for the carrier screening-only sample and 15 weeks for the carrier with the cfDNA sample (IQR 12–16 weeks). The median fetal fraction, measured only in individuals with cfDNA testing, was 6.6% (IQR 4.3–9.6%; Appendix 8, https://links.lww.com/AOG/E945).

Table 1. Proportion of the Full Sample of Patients of a Specific Race or Ethnicity and Carrier Frequency of the Sample by Race and Ethnicity

Race and Ethnicity	% of Total Sample	Carrier Sample (n)	Carrier Frequency (%)
Asian	3.16	87	19.29
Black	25.99	1,593	42.97
Hispanic	15.75	345	15.35
White, non-Hispanic	20.42	377	12.95
None of the above*	6.64	158	16.68
Unknown	28.04	207	NA
Total		2,767	19.39

NA, not available.
* Includes individuals who identified as more than one race or listed a specific country or region rather than a race or ethnicity (eg, India or Dominican Republic).

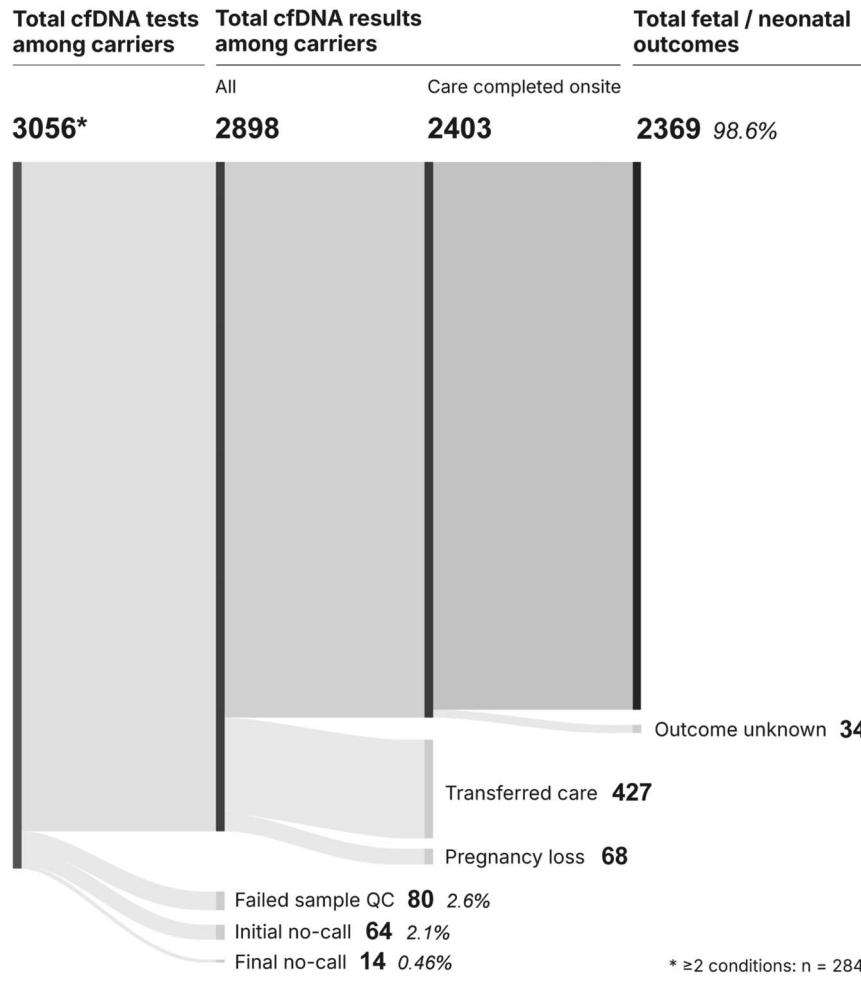

Fig. 1. Study sample assembly. *Patients who were carriers of two or more conditions (n=284). QC, quality control.

McElwee. A Study of cfDNA Testing for Recessive Conditions. Obstet Gynecol 2026.

Among the 2,898 cfDNA tests, 1.3% received a cfDNA fetal risk estimate of at least 1 in 4 for the fetus to be affected. There were 18 affected cases in the full sample of 2,369 cfDNA tests with outcomes known across the four conditions (Table 2). The proportions of tests for each condition were consistent with the carrier frequencies in the sample population (Appendix 9, available online at https://links.lww.com/AOG/E945). There was a single case in which a pregnancy received a low-risk cfDNA result, but the neonate was diagnosed postnatally with sickle cell disease; this case had a fetal fraction of 8.2%. Two of the 29 patients with high-risk cfDNA results pursued prenatal diagnostic testing, and the remaining 27 had postnatal diagnostic testing

Table 2. Cell-Free DNA Fetal Risk and Fetus and Neonate Affected Status and Calculated Assay Performance Analytics Based on Outcomes Collected for the General-Risk Cases

	Affected (n)	Unaffected (n)	% (95% CI)
Less than 1 in 4	1	2,339	
At least 1 in 4	17	12	
Sensitivity			94.44 (74.24–99.01)
Specificity			99.49 (99.11–99.71)
PPV			58.62 (40.74–74.49)
NPV			99.96 (99.76–99.99)
Prevalence of disease			0.76 (0.48–1.20)

PPV, positive predictive value; NPV, negative predictive value.

through the NBS process. In the sample of general risk carriers, the cfDNA screening had a specificity of 99.5% (95% CI, 99.1–99.7%), an NPV of 99.9% (95% CI, 99.8–99.9%), a sensitivity of 94.4% (95% CI, 74.2–99.0%), and PPV of 58.6% (95% CI, 40.74–74.49%; Table 2). There were no cases with an intermediate risk (less than 1 in 4 and at least a priori for the condition of concern) with an affected fetus or neonate.

Because the 1-in-4 threshold is somewhat arbitrary and the assay produces a continuous fetal risk assessment, the Brier score was calculated to assess the agreement between the patient-specific cfDNA fetal risk estimate and fetal and neonatal outcomes. The Brier score was 0.0033 (95% CI, 0.002–0.005), indicating a strong correlation between the cfDNA fetal risk estimate and fetal outcome, as demonstrated by prior studies.[2–4] A range of quantitative cfDNA fetal risks was distributed across the fetal fraction (Appendix 10, available online at https://links.lww.com/AOG/E945), and concordance was not associated with fetal fraction (Appendix 1, https://links.lww.com/AOG/E945).

There were 43 pregnant patients with 32 known neonatal outcomes for which both the patient and the partner were known carriers (a high-risk couple). These cases were excluded from the primary analysis to avoid bias in assessing assay performance in a general-risk sample, given significant differences in a priori risk. An analysis of assay performance in high-risk couples, along with additional supporting performance information, is provided in Appendix 1 (https://links.lww.com/AOG/E945).

DISCUSSION

This large prospective multi-site study, with near-complete outcome collection for patients who completed care at a participating study site, demonstrated excellent clinical performance of carrier screening with cfDNA analysis of fetal risk as a primary screen for autosomal recessive conditions such as CF, spinal muscular atrophy, and beta and alpha hemoglobinopathies (*HBB*, *HBA*) in a general-risk population.

Traditional autosomal recessive carrier screening workflows require reproductive partner testing, introducing logistical, financial, and social barriers that can delay or prevent complete fetal risk assessment. Multiple U.S.-based studies have shown that partner screening occurs in less than 50% of indicated cases, even when cost and blood draw barriers are removed.[6–9] In a real-world traditional workflow, all carriers (19% of the full sample of 14,263 pregnancies sent for carrier screening) would have been referred for partner testing. However, fewer than half of the pregnancies with an affected fetus (eight cases) would have completed follow-up and been identified as high risk in this workflow.[6,9] In contrast, the carrier screening with reflex to a cfDNA-based workflow evaluated here required follow-up in less than 1% of the full sample; due to high-risk or uninformative results.

The importance of early and equitable diagnosis of affected fetuses has grown substantially with the emergence of highly effective prenatal and neonatal therapies for genetic conditions. Prenatal *CFTR* modulator therapy for CF has shown potential to dramatically change the natural history of CF when initiated early in gestation.[14] Early diagnosis enables life-saving in utero transfusions for alpha-thalassemia major,[15] and there are reports of prenatal treatment for spinal muscular atrophy and early-term delivery of affected fetuses to facilitate initiation of postnatal treatment, and extensive data showing that even a brief delay in therapy can result in irreversible motor neuron loss.[16–20] These advancements highlight the need for screening approaches that identify high-risk fetuses early in general-risk populations.[14,15,19,20] A cfDNA-based screening workflow enables partner-independent, personalized fetal risk assessment, helping ensure access to all reproductive options, including these therapies.[2–4]

The study was conducted in eight states in the United States, including some states with larger proportions of Black and Hispanic individuals than the national average. However, carriers from all major U.S. racial and ethnic groups were represented, and observed carrier frequencies matched published population estimates.[21] The study focused on screening the general-risk pregnancy population; the sample size for high-risk couples was too small to provide an informative analysis of the assay's performance in this population. Fetal or neonatal outcomes were available for 98% of cfDNA tests, with no differences in demographics or test characteristics between those with and without known outcomes (Appendix 1, https://links.lww.com/AOG/E945), indicating an unbiased assessment of assay performance. There was no difference in assay concordance with neonatal outcome across fetal fractions; however, a recognized limitation of cfDNA assays is a higher rate of no results at low fetal fraction, as observed in this sample. The cfDNA assay measures fetal fraction and expected molecular count to ensure there is sufficient cfDNA present in the sample from the gene of interest, regardless of the total fetal fraction of cfDNA. This second measurement allows for a fetal fraction threshold of 1.0%.

The study sample was predominantly non-White (78%). These groups can face greater barriers to partner

testing, increasing the risk of delayed or incomplete fetal risk assessment under traditional screening models.[22–24] The cfDNA assay showed equivalent analytic performance among White carriers, non-Hispanic carriers, and carriers of other races (Appendix 1, https://links.lww.com/AOG/E945). These results demonstrate that sequencing-based, partner-independent screening can deliver equitable and reliable fetal risk assessments.

Together with prior publications, this study provides strong evidence that carrier screening with cfDNA-based fetal risk is a robust, reliable, and equitable method for refining autosomal recessive reproductive risk in the diverse, general-risk pregnant populations in the United States.

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PEER REVIEW HISTORY

Received March 24, 2026. Received in revised form June 8, 2026. Accepted June 11, 2026. Peer reviews and author correspondence are available at https://links.lww.com/AOG/E946.