Genetics and Stillbirth

Tsegaselassie Workalemahu, MS, PhD[a,*],
Monica H. Wojcik, MD, MPH[b]

KEYWORDS

• Stillbirth • Exome sequencing • Chromosomal microarray • Genome sequencing
• Autopsy • Inherited

KEY POINTS

- Chromosomal abnormalities contribute to stillbirths, particularly in early gestation.
- Chromosomal microarray detects ~6-13% of stillbirths, while exome sequencing identified submicroscopic and single-gene causes in an additional ~5-10% of previously unexplained stillbirths.
- Parent-offspring whole genome sequencing has the potential to reveal inherited and de novo pathogenic variants in known and novel genes.
- Family-based studies integrating genomics with autopsy and placental pathology may enhance diagnostic clarity, improve recurrence risk counseling and guide precision approaches to reduce stillbirth incidence.

INTRODUCTION

Stillbirth remains one of the most common adverse pregnancy outcomes, and affects over 3 million pregnancies per year worldwide,[1,2] disproportionately affecting low-income and middle-income countries. In the United States, stillbirth is defined as death of a fetus prior to or during birth at 20 weeks' or greater gestation and occurs in 5.48 per 1000 births, exceeding rates in most high-resource countries.[1,3] In contrast to other high-resource countries, stillbirth rates in the United States have not decreased in the past decade.[1,4] The burden of stillbirth is profound, with lasting psychological and emotional consequences for families.[5] Additionally, women experiencing stillbirth are at an increased risk of its recurrence[6,7] and other obstetric complications in subsequent pregnancies.[8]

Stillbirth is a complex obstetric outcome that occurs due to known and suspected causes that include maternal medical or reproductive abnormalities, for example, placental disorders, aneuploidy, infection, and maternal immunologic, endocrine

[a] Department of Obstetrics and Gynecology, University of Utah Health, Salt Lake City, UT, USA;
[b] Divisions of Newborn Medicine & Genetics and Genomics, Boston Children's Hospital, Boston, MA, USA
* Corresponding author.
E-mail address: u6026132@umail.utah.edu

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Abbreviations	
CMA	chromosomal microarray
CNVs	copy number variants
ES	exome sequencing
FF	fresh frozen
FFPE	formalin-fixed paraffin-embedded
GS	genome sequencing
SNPs	single nucleotide polymorphisms
SNVs	single nucleotide variants
SVs	structural variants
VUS	variant of unknown significance
WGS	whole-genome sequencing

disorders, and Mendelian syndromes.[9] These factors vary by gestation.[10] Stillbirths in early gestation (20–27 weeks' gestation) may be caused by chromosomal abnormalities, including aneuploidy.[11] In late stillbirths (28 weeks' gestation to the onset of labor), fetal growth restriction, often secondary to placental insufficiency, is more common,[12] while among term stillbirths (≥37 weeks' gestation), cord accidents account for a substantial proportion of stillbirths. However, systematic evaluation of stillbirth is lacking, and while the majority of cases in the United States has incomplete evaluations, approximately 50% of stillbirth cases remain unexplained.[13]

GENETIC TESTING MODALITIES

Genetic evaluation following stillbirth in the United States typically involves chromosomal assessment of the placenta and fetus with the use of karyotype or chromosomal microarray (CMA) technologies.[14] Karyotype detects chromosomal aberrations, as aneuploidies in the form of monosomy or trisomy, but is limited by tissue requirements (eg, viable cells) and misses submicroscopic genetic abnormalities. Due to the ability to obtain a result with nonviable cells and to evaluate submicroscopic gains or losses of chromosomal material, CMA offers a higher diagnostic yield (~6%–13%) compared to karyotyping.[15] CMA may detect copy number variants (CNVs) occurring as deletion or duplication of genomic material at hundreds of base pairs in length. An additional benefit of the CMA testing over karyotype is that it may be performed on extracted DNA rather than cultured cells, which can be more easily accessible following stillbirth (eg, in cases where unexpected stillbirths occur and may require time to arrange for the sample collection required for cell culture). Additionally, given the relatively lower cost of this test and the prevalence of aneuploidy and CNV syndromes in stillbirth, CMA is a reasonable first-line approach following anomalous or nonanomalous stillbirth. However, the relevance of other types of genetic aberrations in stillbirths is not well characterized, and the mechanism by which they contribute to stillbirth is not understood.

Emerging technologies such as exome sequencing (ES) in stillbirth cases with normal karyotype have identified single nucleotide variants (SNVs) in single genes among approximately 5% to 10% of previously unexplained stillbirths. These smaller genetic abnormalities cannot be detected via CMA.[16–18] ES selectively targets protein-coding regions, comprising roughly 1% to 2% of the human genome, but captures approximately 85% of pathogenic variants causing Mendelian disorders, making it a highly efficient and clinically robust tool for diagnosing single-gene diseases. However, not all stillbirths are caused by single-gene mutations.

Advanced molecular technologies including whole genome sequencing (GS) have expanded discovery of previously unrecognized broader range of variant types, for

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example, coding and noncoding SNVs and structural variants (SVs) for several complex neonatal diseases. However, whole GS is currently underutilized but shown as promising for improving stillbirth diagnosis in research settings.[19] Genetic testing of stillbirth may also include postmortem placental histopathology, fetal autopsy, and maternal testing for thrombophilia or infection, which vary widely by institution.[20] Consistent with American College of Obstetricians and Gynecologists (ACOG)/Society for Maternal-Fetal Medicine (SMFM) guideline and Perinatal Society of Australia & New Zealand (PSANZ) Care Around Stillbirth and Neonatal Death Guideline,[21,22] we propose an algorithm to recommend a tiered genetic evaluation (**Fig. 1**). We propose evaluation of unexplained stillbirth beginning with fetal and placental examination, followed by first-line cytogenetic testing and proceeding to ES/GS incorporating parental samples when feasible.

However, there are financial barriers to genetic testing for stillbirth in many countries including the United States. Thus, broader application of ES/GS for stillbirth is not yet routine due to challenges related to sample acquisition in addition to cost and insurance coverage (as well as sample acquisition). Moreover, pretest counseling, variant interpretation, and posttest counseling for return of results remain substantial barriers to clinical implementation—particularly in light of genetics and genomics workforce challenges.[23] The present diagnostic limitations in stillbirth hinder effective counseling and risk assessment in future pregnancies and underscores the need for advanced approaches, including genomics to investigate the cause of death in stillbirth. Consequently, families are often left frustrated and without answers. Despite the emotional and medical impact of stillbirth, there is limited current effort in studying genetic etiologies of stillbirth using population-based data,[24] although additional research in this area is forthcoming.

CURRENT EVIDENCE

Aneuploidy

Abnormalities with aneuploidy are among the most common genetic causes of stillbirth.[25] These include trisomy 16, the most common autosomal trisomy in early gestation stillbirths and Monosomy X (45,X). In late gestation stillbirths, chromosomes 21, 18, and 13 trisomy are recurrently observed.[26,27]

Copy Number Variants

A genome-wide analysis using high-resolution Illumina SNP arrays has identified 24 putative novel CNVs in placental and fetal samples of stillbirths without anomalies (n = 54).[28] Using a larger study with similar methodology, Reddy and colleagues[29] identified CNVs classified as pathogenic, benign, and variants of unknown significance in 396 (74.4%) samples from stillbirths (including stillbirths with fetal structural abnormalities). Furthermore, genome-wide CNV analysis of formalin-fixed paraffin-embedded umbilical cord samples identified deletions and duplications in 44% of stillbirths 23 weeks' or greater gestation (n = 86), including recurrent chromosomes 1p and 11q alterations linked to placental underperfusion.[30] Approximately 5% to 10% of previously unexplained stillbirths had karyotype abnormalities or CNVs.[20,29]

Mendelian Genetic Disorders and Single-gene Mutations

Mendelian genetic disorders contribute to stillbirth, although the exact figure is difficult to quantify due to lack of a systematic approach to genetic evaluation of stillbirth. Both isolated structural anomalies[31] and certain prenatal conditions such as hydrops, as well as genetic syndromes that may present with anomalies, hydrops, or even isolated

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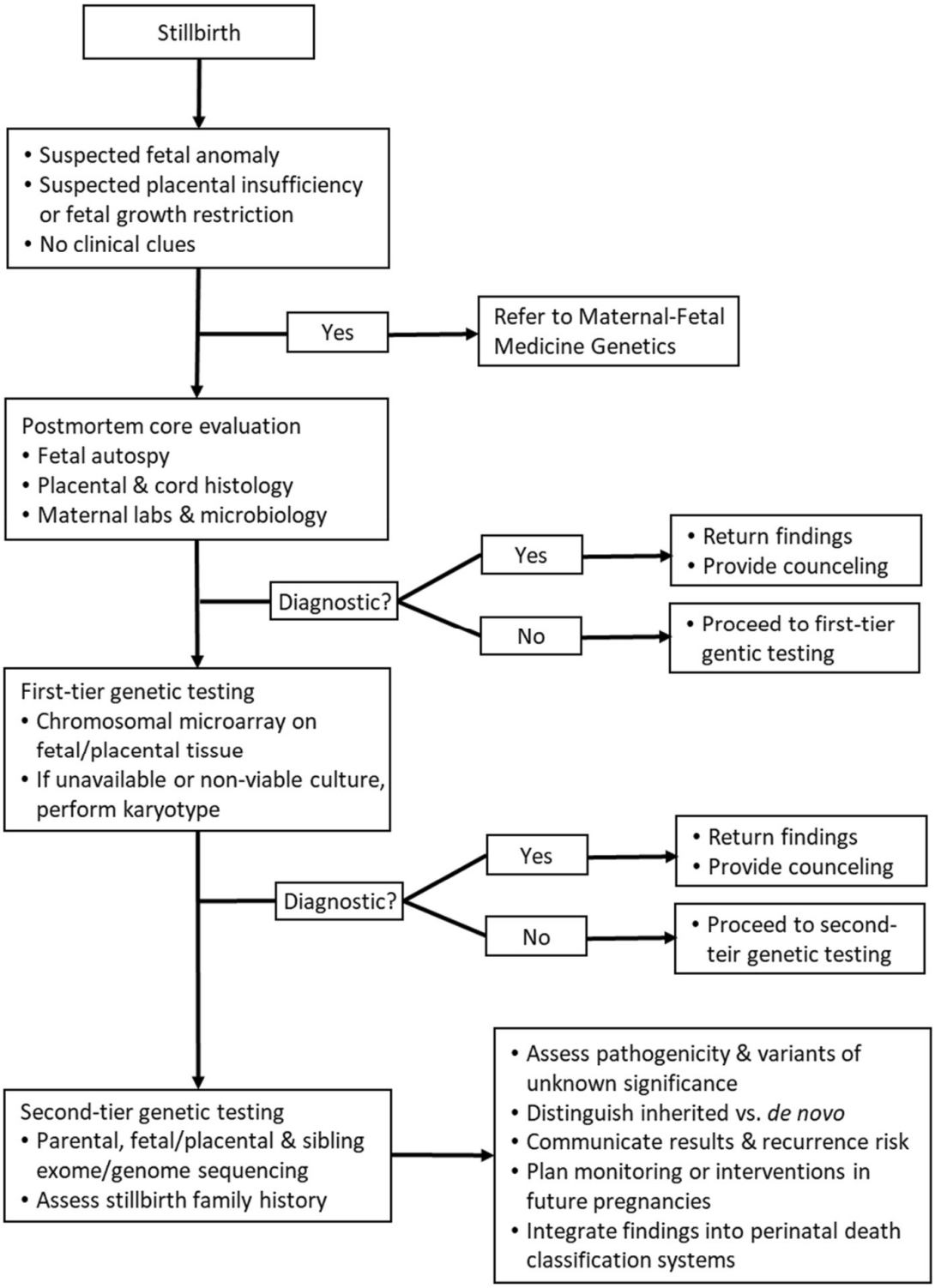

Fig. 1. Algorithm for clinical genetic evaluation of stillbirth.

growth restriction are known to confer a higher risk of stillbirth.[32,33] Genetic syndromes implicated in stillbirth risk include commonly recognized aneuploidy syndromes such as Down syndrome in addition to ultrarare monogenic conditions, such as cardiac channelopathies.[34] For example, long QT syndrome-associated genes (eg, *KCNQ1*, *KCNH2*, and *SCN5A*) encode voltage-gated cardiac ion channels, and pathogenic variants in these 3 genes have been identified in chromosomally normal stillbirths (n = 91).[35]

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For stillbirths observed in the setting of fetal structural abnormalities, the diagnostic yield of genetic testing modalities is higher[36,37]; this is expected given the association of genetic syndromes with congenital anomalies and stillbirth.[38]

Other single-gene and Mendelian disorders, such as X-linked conditions that are particularly lethal for male fetuses may contribute to stillbirth.[39] Cardiac conduction system immaturity may also contribute to stillbirth. For example, targeted (candidate gene) sequencing of 70 cardiac-associated genes (eg, *KCNJ2*) in 290 stillbirths in a Swedish cohort identified pathogenic ion channelopathy variants more frequently in cases compared to matched population-based controls,[40] suggesting that genes relevant to cardiac arrythmias may cause fetal death, in the absence of structural abnormalities.[41] These limited findings highlight the importance of including monogenic conditions in the differential diagnosis of stillbirth but require further investigation in larger cohorts.

Single Nucleotide Polymorphisms and Heritable Risk Factors

Beyond monogenic disorders, non-Mendelian genetic factors, which include common variants (single nucleotide polymorphisms [SNPs] with small effects) and rare variants (SNVs with large effects) may contribute to stillbirth.[40] Emerging genome-wide association studies have identified SNPs associated with conditions that are closely tied to stillbirth, including fetal growth restriction,[42] placental function, and pre-eclampsia.[43] This underscores the relevance of polygenic factors to these complex adverse outcomes including stillbirth. However, genome-wide SNP analyses of stillbirth to date are very limited in scope and sample size in providing evidence for putative markers for validation.

Furthermore, limited studies have investigated heritable risk factors for stillbirth. One intergenerational study that evaluated mother–daughter pairs did not find statistically significant association between mothers with history of stillbirth and stillbirth risk in daughters.[44] Given that there are both maternal and paternal contributions to the fetal genotype, a recent study evaluated inherited risk using broader pedigrees to understand the extent to which genes may affect stillbirth risk.[45] The study evaluated multiple generations of Utah families (n = 390 pedigrees) and showed significant familial aggregation of stillbirth (familial standardized incidence ratio $\geq$2.00, $P < .05$). Additionally, the study conducted a matched case–control analysis of stillbirth cases (n = 9404) and controls (pregnancies without prior history of stillbirth or pregnancy loss; n = 18,808) and showed that relatives of cases had increased stillbirth risk compared with relatives of controls. Stillbirth risk was stronger in the male relatives of cases, compared with male relatives of controls, indicating paternally inherited risk that was not detectable in the prior mother–daughter pair study. Increased stillbirth risk in distant relatives (eg, third-degree relatives) may indicate that genes rather than shared environment may contribute to stillbirth risk. Understanding the inheritance of stillbirth may allow appropriate counseling and pregnancy management to prevent stillbirth based on family history, with a tiered approach to pregnancy monitoring and intervention informed by family-based risk assessment.

By leveraging family-based designs that potentially reduce phenotypic heterogeneity and provide control for shared environment, some efforts were made to identify putative markers. These markers may include compound heterozygous, de novo and missense SNVs and SVs that can be detected by whole GS. Spontaneously occurring mutations (de novo) and inherited mutations, which require parental genotype, can enhance interpretation of genomic findings to support genetic counseling and clinical management. For example, utilizing parent–offspring genotypes, a candidate-gene whole ES analysis of structurally normal second-to-third trimester losses identified

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de novo and recessive mutations in cardiac sodium-channel genes (eg, *SCN2A*),[46] confirming lethal ion-channelopathies as plausible mechanisms. Additionally, a recent pilot study conducted whole GS in a prospective cohort study of reproductive-age parents and their conceptuses (embryonic losses, fetal deaths, stillbirths, and live births).[47] The study identified 122 SNVs across 122 genes, with only 1 recurring variant in stillbirth.[48] Of these, 7 de novo and 1 autosomal dominant SNVs were pathogenic (loss-of-function intolerance >0.9), impacting genes (eg, fibrillin 2 [*FBN2*], dicer 1, ribonuclease III [*DICER1*], and TAO kinase 1 [*TAOK1*]) that are known to be associated with placental and fetal development.[49,50] The findings from the study demonstrate that larger whole GS studies using families may help identify inherited and de novo variants that cause stillbirth or contribute to increased stillbirth risk.

Epigenetic Contributors

Limited studies investigated epigenetic modifications, which include DNA methylation, histone modifications and gene expression, that may mediate the effects of parental exposures (eg, smoking, stress, nutrition, or environmental exposures) on fetal and placental development and contribute to stillbirth. A tissue methylation analysis showed that 18% of chromosomally normal stillbirths (10 out of 57) exhibited hypermethylation at multiple imprinted genes including H19 imprinted maternally expressed transcript (*H19*), maternally expressed 3 (*MEG3*), and paternally expressed 3 (*PEG3*).[51] Among male individuals with hypermethylation patterns in *H19* gene, biallelic insulin growth factor 2 (*IGF2*) expression that was absent from spontaneous pregnancy loss cases was demonstrated.[51] Additionally, analysis of second-trimester fetal-placental tissues showed upregulated *TET2/3* expression and abnormal methylation/expression of *IGF2*, cyclin dependent kinase inhibitor 1C (*CDKN1C*), mesoderm specific transcript (*MEST*) key regulators of placental growth in idiopathic pregnancy loss.[52] Dysregulation of placental gene expression related to angiogenesis, inflammation, and oxidative stress may also contribute to stillbirth, and studies that enable our understanding of the placenta as a key mediator of genetic and environmental interactions in fetal outcomes are critical.[53] Therefore, epigenetic dysregulation alone can critically impair development even in the absence of chromosomal abnormalities, underscoring the potential of integrating methylation profiling into clinical evaluations for unexplained stillbirth.

CURRENT CLINICAL CHALLENGES

Given the current evidence to support a wide variety of Mendelian contributions to stillbirth, a comprehensive genomic approach to the postmortem evaluation is warranted. However, multifactorial barriers limit broad access to genomic investigation, particularly in communities with limited access to health care. Additional resources are, therefore, needed to implement and evaluate a comprehensive system for postmortem genomic evaluation. Here, we provide the present genetic testing modalities in clinical and research setting, their strengths and limitations, and recommended clinical roles in **Table 1**.

FUTURE CLINICAL DIRECTIONS

To improve the diagnostic yield and clinical utility of genetic testing in stillbirth, several strategies are needed. Trio-based whole-ES/GS in unexplained cases is critical to improve diagnosis of stillbirth. For example, in the largest stillbirth cohort in the United States, analysis of maternal–fetal ES data from stillbirth cases (n = 241)[54] allowed identification of genetic variants with characteristics designed to enrich for pathogenicity in

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Table 1
Genetic testing modalities in stillbirth

Genetic Testing Modality	Tissue/Sample(s)	Potential Diagnostic Abnormalities	Strengths	Limitations	Recommended Clinical Role

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Table 1
(continued)

Genetic Testing Modality	Tissue/Sample(s)	Potential Diagnostic Abnormalities	Strengths	Limitations	Recommended Clinical Role
WGS (short-read)	Fetal/placental DNA ± parents	SNVs, indels, SVs, short tandem repeats, noncoding variants	Comprehensive variant detection; improved SV detection vs ES	Higher cost; complex analysis; clinical interpretation of noncoding variants still maturing	Research/diagnostic in specialized centers; ideal for comprehensive unresolved cases
Genome-wide SNP arrays on FFPE/ umbilical cord (CNV profiling)	FFPE umbilical cord, placental tissue	CNVs from archived tissue	Enables retrospective studies where fresh tissue unavailable	Need validation (eg, quantitative polymerase chain reaction); interpretation of small CNVs may be challenging	Valuable for archived samples and for expanding sample size in research
Epigenetic assays (methylation arrays, imprinting panels)	Placental/fetal tissue	Imprinting defects, methylation abnormalities	Detects imprinting/ epimutation etiologies not seen on DNA sequencing	Research stage; clinical laboratories limited; interpretation standards evolving	Consider in research or when clinical suspicion of imprinting disorders
Integrative pathology + genomics (autopsy + placental histology + genetics)	Multimodal	Correlates molecular findings with histopathology to increase diagnostic yield	Highest clinical yield when combined	Requires coordinated resources and consent	Standard of care: perform autopsy and placental examination with targeted genomic testing

Abbreviations: CMA, chromosomal microarray; CNV, copy-number variant; ES, exome sequencing; FFPE, formalin-fixed paraffin-embedded; FF, fresh frozen; SNV, single-nucleotide variant; VUS, variant of unknown significance; WGS, whole-genome sequencing.

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Mendelian disease genes from the Online Mendelian Inheritance in Man database. Specifically, stillbirth cases showed enrichment of loss-of-function variants, that is, variants that are predicted to disrupt protein function in genes that are intolerant to such variation in human populations (loss-of-function observed/expected upper bound fraction $\leq$0.24; odds ratio = 2.15: 95% confidence interval: 1.46–3.06). The variants were also enriched in genes that have not been associated with human diseases (odds ratio = 2.22; 95% confidence interval: 1.41–3.34). Notably, loss-of-function variants accounted for almost 10% of previously unexplained cases, suggesting that unexplained stillbirths were attributable to known Mendelian disorders. This suggested that single-gene variants may be lethal. Without paternal genotypes, inherited variants could not be distinguished from de novo variants, posing challenges including incomplete penetrance and difficulty with directly identifying the pathogenic variants affecting diverse set of genes in regulatory regions. Even with known (candidate) genes, the estimated bounds of stillbirth diagnostic rate were approximately 6% to 13%. With parental genotype, diagnostic yield of stillbirth could be up to 3 fold higher, consistent with other studies that report a similar increase in the diagnostic yield of complex phenotypes by using parent–offspring trios compared with maternal–fetal dyads or singletons.[55,56] By including paternal genotypes, the true diagnostic yield of stillbirth may be higher than the cumulative estimated diagnostic yield of stillbirth. The added benefit of GS using a full trio (stillborn child, live born sibling, and both parents) would allow for more comprehensive evaluation of both inherited and de novo variants, and those with loss-of-function variants that are enriched in cases compared with controls could be determined to increase the diagnostic yield of stillbirth[56] (with observed odds ratios greater than those in ES study of maternal–fetal dyads).

Finally, broader incorporation of placental genomics, including methylation and transcriptomic profiling, may offer additional insights into fetal-placental pathophysiology.[57] Future research may prioritize genes contributing to placental insufficiency, which can cause stillbirth and regulate angiogenesis, trophoblast invasion, and nutrient transport. For example, weighted gene coexpression and differential expression analyses in human placentas with intrauterine growth restriction (a proxy for placental insufficiency) have nominated genes (eg, fms related receptor tyrosine kinase 1 [*FLT1*], GATA binding protein 3 [*GATA3*], and signal transducer and activator of transcription 5A [*STAT5A*]) associated with placental dysfunction.[58] In addition, preclinical models are already exploring placenta-targeted gene therapy (eg, adenoviral/viral delivery of insulin-like growth factor 1 [*IGF-1*] or vascular endothelial growth factor A [*VEGF*]) and nanoparticle-mediated placental drug delivery systems to rescue fetal growth and placental health.[59,60] Bridging those mechanistic candidates with translational delivery technology could pave the way toward first-in-human interventions for pregnancies at high risk of stillbirth from placental insufficiency.

Furthermore, development of integrated risk models combining clinical, genetic, and environmental data using machine learning may enable personalized risk prediction.[61,62] Risk models may require development of robust polygenic risk scores, leveraging SNPs identified in well-powered stillbirth genome-wide association study (GWAS) to enable early risk stratification in pregnancies at elevated risk for stillbirth. Increased investment in research and infrastructure is needed to support widespread adoption of genomic technologies in stillbirth evaluation.

SUMMARY

Stillbirth remains a pressing global health challenge, with approximately half of cases lacking an identifiable cause despite comprehensive evaluations. Genetic

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actors play critical but underrecogni edroles in many stillbirthcases. Failure to identi ya cause or stillbirthis challenging or amilies and encumbers e orts to prevent additional stillbirths. Advances in genomic technology have revealed both Mendelianand comple genetic contributionsto etaldemise particularlyin une plainedstillbirth.Incorporatinggenomic testing into clinical practice through parent o springtrio se uencing and placental assessments has the potentialto trans orm our understandingo stillbirthand improve care or a ected amilies. Futuree ortsmust ocus on e pandingaccess to genetic testing enhancinginter pretationo genomic indings and translatingresearch indingsintoactionableclin ical insights.

Best Practices

What is the current practice for stillbirth?

The ACOG/SMFM and PSANZ/Stillbirth CRE strongly recommend a standardized evaluation after stillbirth, including fetal autopsy, placental and membrane histology, and genetic testing (karyotype or CMA as first-tier).[1,2] Genetic testing identifies chromosomal abnormalities in up to 6% to 13% of stillbirths.[3,4] However, genetic diagnosis in many stillbirths would not be identified via karyotype and CMA alone and require genome-wide sequencing (ES or genome sequencing).[5,6]

Best Practice/Guideline/Care Path Objective(s):

The objective is to increase diagnostic yield following stillbirth to provide answers to families, guide future pregnancy counseling, and inform targeted clinical interventions.

What changes in current practice are likely to improve outcomes?

With recent evidence supporting an improved diagnostic yield using ES,[4] future changes to clinical practice may integrate parent–offspring trio exome/genome protocols when available.

Is there a clinical algorithm? If so, please include

We provide an algorithmic protocol following ACOG OC-10[1] and PSANZ[2] in . Genetic evaluation flowchart includes

1. Autopsy and placental examination
2. Karyotype or CMA
3. Further molecular testing (eg, exome, gene panel) if results are negative and family history is positive.

Pearls/Pitfalls at the point-of-care:

Pearls:

Collect fresh fetal/placental tissue and cord blood as soon as possible to obtain quality DNA material.

Consider CMA over karyotype unless a viable culture can be assured.

Identify resources to obtain further exome/genome sequencing

Pitfalls:

Decline in autopsy limits tissue availability for diagnosis.

Overreliance on karyotype misses submicroscopic CNVs.

Certain diagnoses could only be found by exome or genome sequencing

Cost and access barriers for exome and genome sequencing technologies delay integration

Major Recommendations:

1. Perform full fetal and placental examinations including pathology and genetics in all stillbirths.
2. Prioritize CMA as first-line genetic test and offer exome or genome sequencing if CMA is nondiagnostic.
3. Collect parental and live born sibling samples to boost interpretation accuracy.
4. Adopt structured genetic testing algorithms (see).
5. Provide genetic counseling postresult to support families and management of subsequent pregnancies.

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