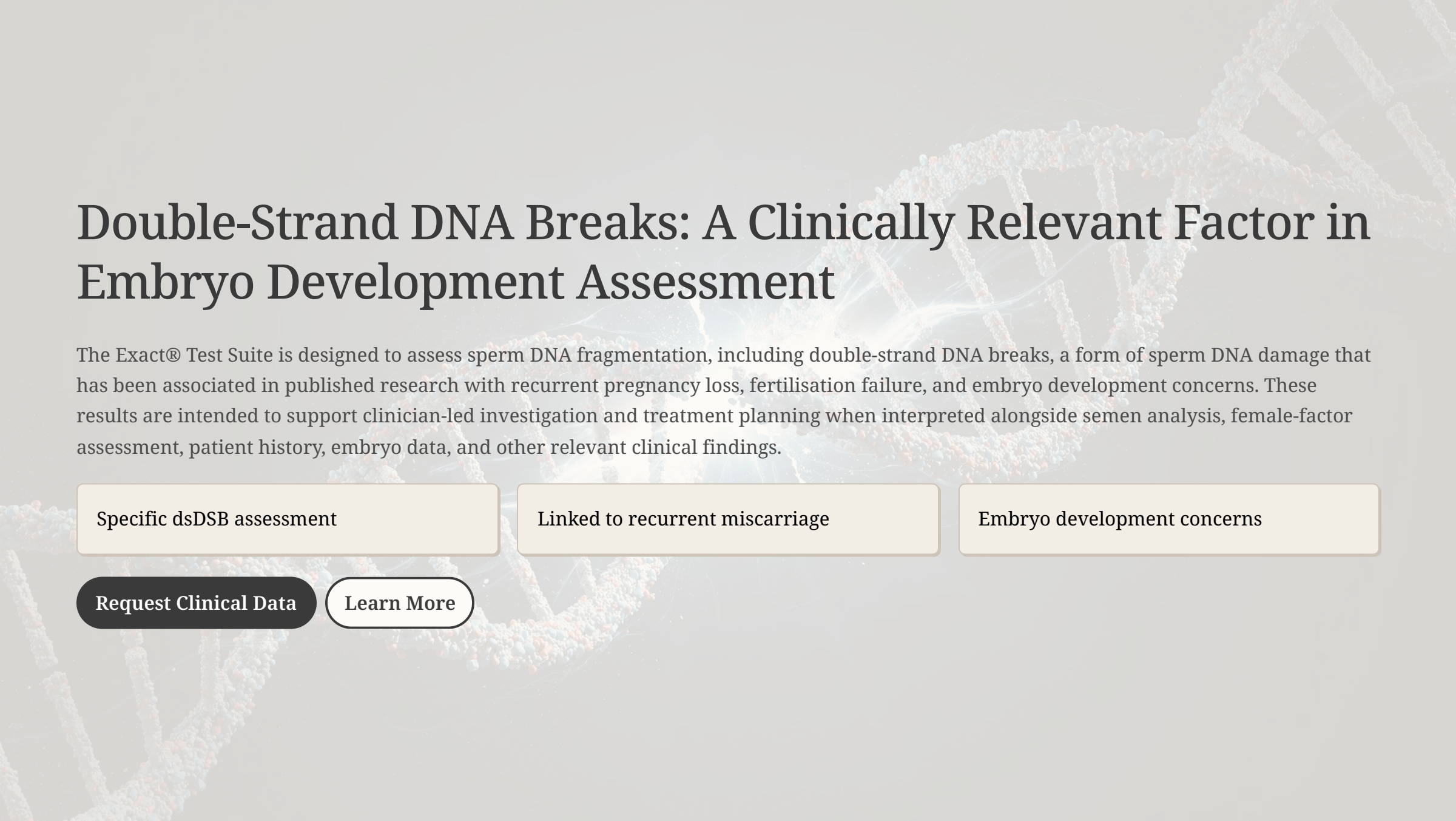




Double-Strand DNA Breaks: A Clinically Relevant Factor in Embryo Development Assessment

The Exact® Test Suite is designed to assess sperm DNA fragmentation, including double-strand DNA breaks, a form of sperm DNA damage that has been associated in published research with recurrent pregnancy loss, fertilisation failure, and embryo development concerns. These results are intended to support clinician-led investigation and treatment planning when interpreted alongside semen analysis, female-factor assessment, patient history, embryo data, and other relevant clinical findings.

Specific dsDSB assessment

Linked to recurrent miscarriage

Embryo development concerns

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What Are Double-Strand DNA Breaks?

Sperm DNA fragmentation (SDF) is not a single, uniform entity. It encompasses structurally distinct lesions that differ profoundly in their clinical consequences. Among these, double-strand DNA breaks (dsDSB) represent one of the more clinically significant forms of sperm DNA damage that can be introduced into an embryo at the moment of fertilisation.

⚠️ dsDSBs may be more difficult for the oocyte to repair after fertilisation.

A double-strand break occurs when both phosphodiester backbone strands of the DNA helix are severed at or near the same locus. Unlike single-strand nicks—which exist along the same double helix but leave one intact strand as a template—double-strand breaks sever the molecule entirely. There is no intact complementary strand remaining to guide accurate repair. In somatic cells, sophisticated repair mechanisms such as homologous recombination (HR) and non-homologous end joining (NHEJ) can resolve these breaks, albeit imperfectly. In the early embryo, these pathways are not yet active. The oocyte's repair machinery, while capable of addressing certain single-strand lesions, is functionally unable to execute the high-fidelity repair of dsDSBs.

Key Structural Distinction

Single-Strand Nick — One intact template strand remains. The oocyte can attempt repair.

Double-Strand Break — Both strands severed simultaneously. No template remains. Accurate repair may be limited after fertilisation and depends on oocyte repair capacity.

This structural distinction—single strand versus double strand—is not a matter of degree. It is a categorical difference in damage type, mechanism of origin, and downstream embryological consequence. Yet until the introduction of the Exact® Test Suite, few routine clinical SDF platforms are designed to distinguish between these two lesion classes within a clinical sperm DNA fragmentation assessment.

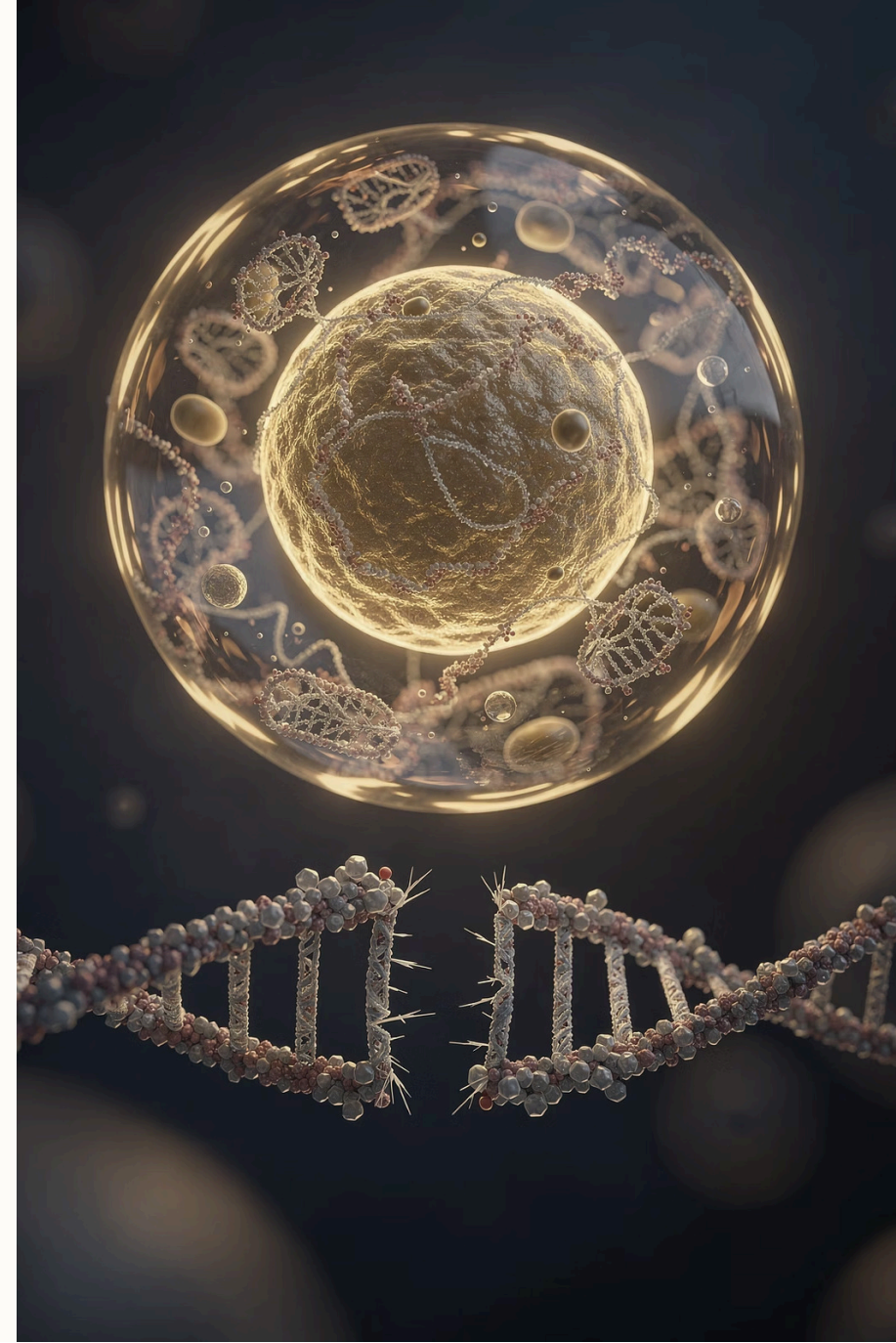
Why Double-Strand Breaks May Be Clinically Significant

The embryological context in which sperm DNA damage must be assessed is fundamentally different from any somatic tissue environment. Following fertilisation, the newly formed zygote enters a period of developmental transition during which paternal genome activation is delayed. The oocyte cytoplasm assumes primary responsibility for surveillance and correction of sperm-derived DNA damage, but its repair capacity is specifically limited.

Base-Excision Repair — Requires an intact complementary strand as template. Effective for single-strand lesions.

Double-Strand Break — No template strand present. Repair machinery may have limited capacity for accurate reconstruction.

Oocyte-mediated repair of sperm DNA is largely restricted to base-excision repair and single-strand break ligation — mechanisms that require an intact complementary strand as a template. When dsDSBs are present, this template is absent. The repair machinery encounters a severed molecule with limited informational basis for accurate reconstruction. In some cases, imperfect repair processes may contribute to genomic instability at the affected loci.



Potential Pathways Associated with Embryo Development Failure

Embryos formed from dsDSB-damaged sperm do not follow a single failure pathway. Depending on the severity and locus of damage, as well as the oocyte's residual repair capacity, four potential clinical patterns have been described in the literature. Each represents a different stage at which dsDSB-driven genomic instability manifests — and each contributes to the spectrum of reproductive failure seen in clinical IVF and natural conception cycles.



Fertilisation Failure

Sperm carrying extensive dsDSBs may fail to activate the oocyte appropriately or may trigger immediate apoptotic responses within the zygote. This may contribute to fertilisation failure in selected cases — an outcome that is sometimes misattributed to oocyte quality or laboratory conditions.



Early Arrest (Day 1–2)

Where fertilisation does occur, the resulting zygote may initiate cleavage but arrest at the 2–4 cell stage. This early developmental block is a hallmark of severe paternal genomic instability and is strongly associated with elevated dsDSB indices. The embryo may be less likely to progress through the critical early cell divisions required for blastocyst formation.



Implantation Failure

Some dsDSB-damaged embryos reach the blastocyst stage but harbour sufficient genomic errors to preclude endometrial attachment and invasion. Some embryos may fail to implant despite transfer, contributing to repeated implantation failure — a clinically frustrating outcome that is rarely investigated at the level of sperm DNA integrity.

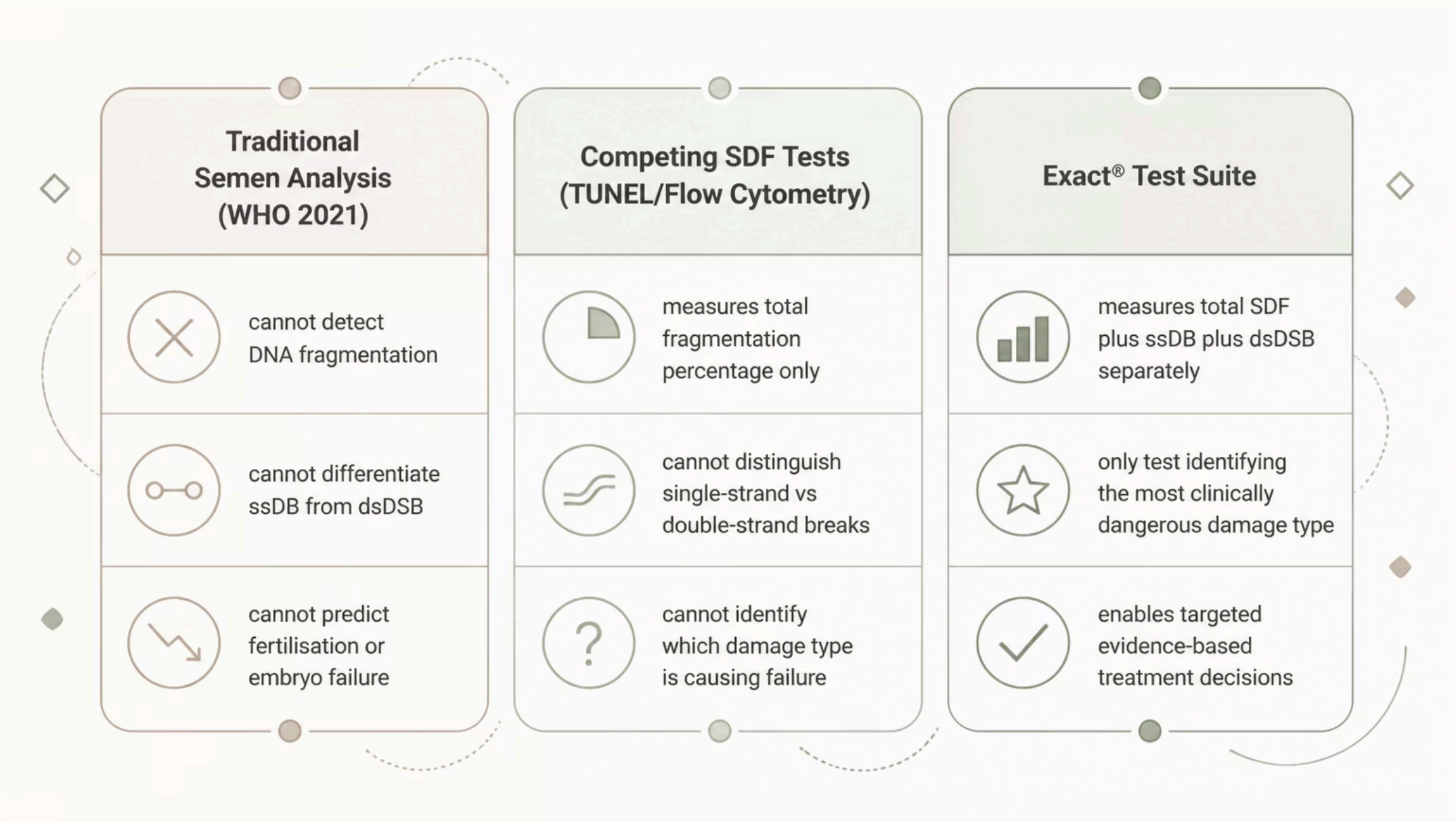


Miscarriage

The most clinically visible consequence: an embryo implants and initiates a pregnancy, but unrepaired DNA damage may be one contributory factor in pregnancy loss. This outcome encompasses chemical pregnancies, early clinical miscarriages, and — in severe cases — recurrent pregnancy loss across multiple treatment cycles.

The Diagnostic Gap: What Standard Testing May Not Assess

The limitations of conventional semen analysis in the context of sperm DNA integrity are well-established in the reproductive medicine literature. However, the diagnostic gap extends significantly beyond the obvious absence of DNA fragmentation assessment in WHO 2021-standard semen analysis. Even among laboratories that have adopted SDF testing, the prevailing methodologies leave an important diagnostic gap: the specific identification and quantification of double-strand breaks.



Traditional semen analysis parameters — concentration, motility, morphology — provide information about the structural and kinetic properties of the sperm population. They do not directly assess the integrity of the genetic payload being delivered to the oocyte. A semen sample can present with entirely normal WHO parameters and yet carry a dsDSB burden that may contribute to recurrent IVF failure in some cases. This diagnostic gap has historically resulted in clinical investigations that overlook the male factor entirely, directing costly and emotionally burdensome further investigation toward the female partner.



How Different SDF Testing Methods Report DNA Damage

The adoption of sperm DNA fragmentation testing has grown substantially in recent years, driven by an expanding evidence base linking elevated SDF to impaired IVF outcomes. TUNEL assay and flow cytometry-based platforms are now offered by a number of reference laboratories and are increasingly requested by reproductive endocrinologists managing patients with unexplained infertility or recurrent pregnancy loss.

18% Fragmentation — Predominantly Single-Strand Nicks

Reparable lesions. Oocyte repair mechanisms may compensate. Lower prognostic risk.

18% Fragmentation — Significant dsDSB Component

Double-strand breaks that may be less readily repaired. No template for reconstruction. Potentially different clinical implications.

However, these methodologies share a fundamental and clinically consequential limitation: they report a single aggregate fragmentation index representing the total proportion of sperm with any detectable DNA damage, without discriminating between single-strand nicks and double-strand breaks. A TUNEL result of, for example, 18% fragmentation provides no information about the structural character of that damage. It could represent a population in which the predominant lesion type is reparable single-strand nicks — or one in which a clinically significant proportion of the fragmented molecules carry double-strand breaks that may be less readily repaired. These two scenarios may carry potentially different clinical implications for fertilisation, embryo development, and pregnancy outcome, yet they are reported identically by current standard SDF platforms.

i This diagnostic equivalence — treating fundamentally different lesion types as a single metric — represents an important limitation between available testing and the granular clinical intelligence that may be required for evidence-based male factor management in ART.

The Exact® Test Suite: A Three-Dimensional Assessment

The Exact® Test Suite was developed to address precisely the diagnostic shortfall that characterises both conventional semen analysis and standard SDF methodologies. Rather than reporting a single fragmentation index, the Exact® platform generates a three-component profile that characterises the sperm DNA damage landscape with highly detailed clinical resolution.

Total SDF Index

The aggregate proportion of sperm carrying any form of detectable DNA damage, providing compatibility with existing clinical reference ranges and historical patient data. This component allows direct comparison with results obtained from prior TUNEL or flow cytometry assessments.

Single-Strand Break (ssDSB) Quantification

Isolated measurement of single-strand nicks and gaps within the sperm DNA. While still clinically significant at high levels, single-strand breaks are at least theoretically addressable by oocyte repair mechanisms, and their identification enables appropriate clinical stratification of the overall fragmentation burden.

Double-Strand Break (dsDSB) Quantification

A clinically relevant component. Specific, isolated quantification of double-strand breaks — a specialist service designed to provide this measurement. It is this parameter that carries reported associations with recurrent pregnancy loss, fertilisation failure, and embryo development arrest.

Supporting Evidence-Informed Treatment Decisions

The availability of dsDSB-specific quantification changes the clinical conversation around male factor infertility. Rather than managing SDF as a binary elevated/non-elevated finding, the Exact® Test Suite enables clinicians to stratify patients by the character of their DNA damage — a distinction that may have implications for laboratory technique selection, cycle planning, and patient counselling around prognosis and expectations.

⚠ Without dsDSB Differentiation

- Empirical antioxidant protocols without mechanistic rationale
- Repeated IVF cycles without addressing underlying sperm DNA pathology
- Unexplained recurrent miscarriage attributed incorrectly to female factors
- Delayed identification of severe male-factor contributors to failure
- No basis for differentiating between sperm preparation strategies

✅ With Exact® dsDSB Data

- May help identify patients for whom surgical sperm retrieval (testicular vs. ejaculate) could be considered by the clinical team to access DNA-intact populations
- Evidence-based selection of sperm preparation protocols, including density gradient or MACS selection
- May support discussion of ICSI with physiological selection (PICSI) in selected high-dsDSB cases
- Targeted investigation of aetiological drivers: varicocele, oxidative stress, infection, or chemotherapy-related damage
- May support monitoring of changes over time when serial testing is clinically appropriate

Clinical Relevance: Recurrent Miscarriage and Embryo Failure

The association between elevated sperm DNA fragmentation and adverse reproductive outcomes is well-supported in the peer-reviewed literature. Meta-analyses have demonstrated consistent relationships between high SDF and reduced fertilisation rates, impaired blastocyst development, lower clinical pregnancy rates, and elevated miscarriage rates in both natural and assisted conception. However, the majority of this evidence has been generated using total SDF indices — blunt instruments that aggregate all DNA damage types into a single figure.

Total SDF Index — Aggregates all DNA damage types. Much may be repairable. Explains heterogeneity in outcome studies.

dsDSB Fraction — Damage that may be less readily repaired after fertilisation. Reported mechanistic association with embryo development failure. A clinically relevant variable.

The emerging mechanistic literature on dsDSBs specifically points to a potentially more specific mechanistic association with embryo development failure pathways than total SDF alone can explain. Where total SDF reflects the overall burden of DNA damage — much of which may be repairable — the dsDSB fraction represents the proportion of that damage that may be potentially less repairable in the post-fertilisation environment. This distinction may explain the substantial heterogeneity observed in SDF outcome studies, where patients with similar total SDF indices demonstrate markedly different clinical outcomes.

Recurrent implantation failure and recurrent miscarriage in couples with seemingly adequate embryo quality may represent the clinical signature of an elevated paternal dsDSB burden — a pathology that is not routinely differentiated by many standard SDF platforms.

For reproductive endocrinologists managing patients with unexplained recurrent pregnancy loss, repeated implantation failure following euploid embryo transfer, or consistent early embryo arrest despite optimised laboratory conditions, the dsDSB index provides a specialist diagnostic variable that may provide mechanistic insight into observed clinical outcomes. It may help clinicians investigate patterns of unexplained failure using a measurable sperm DNA parameter.





CLINICAL PRECISION

MALE FERTILITY DIAGNOSTICS

The Exact® Test Suite: Advanced Diagnostic Resolution

The Exact® Test Suite occupies a specialist position within the landscape of male fertility diagnostics. Designed to specifically isolate and quantify double-strand DNA breaks, it provides reproductive medicine practitioners with a level of diagnostic resolution not routinely available through many standard semen analysis or SDF testing approaches — whether standard semen analysis, TUNEL assay, flow cytometry-based SDF testing, or other established methodologies.



Designed to Specifically Assess dsDSBs

Designed to specifically isolate and quantify double-strand DNA breaks in clinical sperm samples.



Associated with Recurrent Failure Patterns

dsDSB quantification identifies the damage type reported to be associated with fertilisation failure, embryo arrest, implantation failure, and recurrent miscarriage.



Enables Targeted Intervention

Three-component profiling provides the clinical granularity that may support evidence-informed, mechanism-directed treatment decisions in selected ART treatment planning contexts.

For fertility clinic directors and laboratory directors evaluating the male factor diagnostic pathway, the integration of Exact® Test Suite reporting into the clinical work-up of patients presenting with recurrent failure, unexplained infertility, or persistent poor embryo quality represents a meaningful and evidence-informed step toward more individualised and evidence-informed reproductive care.

⚠ This information is intended for healthcare professionals and educational purposes only. Examen test results should be interpreted by a qualified clinician in the context of the patient's full medical history, semen analysis, female-factor assessment, embryo development data, and other relevant investigations. The test does not diagnose infertility on its own and does not guarantee fertilisation, pregnancy, live birth, miscarriage reduction, or ART treatment success.