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Review Article

DNA Repair Dysfunction in Male Infertility: Mechanisms, Biomarkers, and Clinical Applications

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Emerging evidence implicates DNA repair dysfunction as a central contributor to male infertility, driving spermatogenic failure, genomic instability, and compromised sperm function. During spermatogenesis, germ cells rely on coordinated activity of homologous recombination, non-homologous end joining, base excision repair, and mismatch repair pathways to maintain genomic integrity under oxidative and replicative stress. Disruption of these systems leads to defective meiotic recombination, aberrant chromatin remodeling, and increased sperm DNA fragmentation, manifesting as oligozoospermia, azoospermia, or reduced fertilization potential. Recent advances in molecular diagnostics, such as phosphorylated H2A histone family member X immunostaining, DNA fragmentation assays, comet and terminal deoxynucleotidyl transferase dUTP nick end labeling tests, and next-generation sequencing of DNA repair genes, offer mechanistically anchored biomarkers for patient stratification. Integration of DNA repair profiling with oxidative stress and chromatin packaging assessments enhances diagnostic resolution and supports personalized therapeutic strategies. Translating these molecular insights into clinical practice provides a novel framework for precision reproductive medicine, informing assisted reproductive technology selection, therapeutic targeting, and genetic counseling to improve outcomes in male infertility.

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Introduction

Male infertility is a major global health concern, affecting an estimated 50 million men and contributing to nearly half of all cases of couple infertility. Despite significant advances in reproductive medicine, the molecular mechanisms underlying male reproductive failure remain incompletely defined, limiting the development of precise diagnostic and therapeutic strategies [1-3].

Among emerging molecular determinants, DNA repair dysfunction has gained increasing attention as a central contributor to spermatogenic disruption and compromised sperm function [4, 5]. During spermatogenesis, germ cells undergo extensive chromatin remodeling and are exposed to diverse sources of DNA damage, including oxidative stress, replication errors, and programmed meiotic double-strand breaks. The integrity of germ cell DNA is maintained by tightly regulated repair systems, homologous recombination (HR), non-homologous end joining (NHEJ), base excision repair (BER), and mismatch repair (MMR), which collectively preserve genomic stability and ensure the production of functional spermatozoa [5-7]. Dysregulation of these pathways has been associated with infertility phenotypes such as oligozoospermia, asthenozoospermia, azoospermia, and elevated sperm DNA fragmentation [8-10].

Recent advances in molecular and cellular diagnostics, including Phosphorylated H2A histone family member X (γH2AX) immunostaining, comet and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assays, and next-generation sequencing (NGS), have provided new insights into DNA repair deficiencies and their diagnostic potential. These technologies enable precise evaluation of DNA repair capacity and genomic integrity in sperm, facilitating the discovery of mechanistically anchored biomarkers and improved patient stratification [11-13]. Understanding the molecular architecture and clinical relevance of DNA repair pathways in male germ cells not only enhances diagnostic accuracy but also holds translational promise for guiding assisted reproductive technologies (ART), predicting treatment outcomes, and informing personalized therapeutic interventions.

DNA repair pathways in spermatogenesis: Molecular architecture and infertility links

Spermatogenesis is a dynamic, tightly regulated process that involves mitotic proliferation, meiotic recombination, and extensive chromatin remodeling. Germ cells are particularly vulnerable to DNA damage due to high transcriptional activity, oxidative stress, and programmed double-strand breaks (DSBs) essential for meiotic crossover formation [1, 3, 14]. Chromatin remodeling events -such as histone-to-protamine transition and repair-associated histone modifications- play a critical role in regulating DNA accessibility and repair fidelity during germ cell maturation [14, 15]. To preserve genomic integrity, male germ cells deploy a suite of DNA repair pathways, each tailored to lesion

type and developmental stage, including HR, NHEJ, BER, and MMR (Table 1) [4, 6, 16].

Homologous recombination

HR is a high-fidelity DNA repair pathway essential during meiosis, particularly for resolving programmed DSBs that facilitate crossover formation and chromosomal synapsis. Key mediators include RAD51, DMC1, BRCA1/2, and the MRN complex, which orchestrate strand invasion and template-guided repair. Disruption of HR impairs homolog pairing and recombination, leading to meiotic arrest, germ cell apoptosis, and non-obstructive azoospermia [6, 7].

Recent studies have identified RAD51C and BRCA2 mutations in infertile men, confirming their role in HR failure and testicular histopathology [6, 7]. Diagnostic tools such as γH2AX immunostaining provide mechanistic insight into unresolved DSBs and defective HR kinetics [16, 17]. Persistent γH2AX foci in spermatocytes correlate with meiotic arrest and Sertoli cell-only syndrome. Additionally, next-generation sequencing panels targeting HR-related genes (e.g. RAD51C, BRCA2) support genetic counseling and stratification in idiopathic azoospermia [4, 5].

NHEJ

NHEJ is a rapid but error-prone repair mechanism active in mitotic spermatogonia and post-meiotic spermatids, where speed of repair is prioritized over sequence fidelity. Core components include Ku70/Ku80, DNA-PKcs, XRCC4, and Ligase IV, which mediate direct ligation of broken DNA ends. Defective NHEJ has been implicated in sperm aneuploidy, failure of chromatin condensation, and genomic instability [8, 9]. Transcriptomic profiling has revealed downregulation of NHEJ components in idiopathic infertile men, suggesting pathway exhaustion or epigenetic silencing. Diagnostic assays, such as the Comet assay under neutral conditions, can detect DSBs that are typically repaired by NHEJ [18, 15]. Furthermore, chromatin packaging defects, including abnormal protamine ratios and histone retention, may reflect impaired NHEJ-mediated chromatin remodeling [21, 22].

Base excision repair

BER is the primary defense against oxidative base lesions and single-strand breaks, which are abundant in the testicular microenvironment due to elevated reactive oxygen species (ROS). Key enzymes include 8-oxoguanine DNA glycosylase (OGG1), APE1, and XRCC1, which sequentially recognize, excise, and replace damaged bases. Polymorphisms in OGG1 and XRCC1 have been associated with high sperm DNA fragmentation index (DFI) and reduced motility [10, 11]. Diagnostic evaluation of BER dysfunction includes: a TUNEL assay that detects unrepaired 3′-OH ends, reflecting BER failure [14]; oxidative stress markers that show elevated 8-hydroxy-2′-deoxyguanosine (8-OHdG), ROS, and reduced total antioxidant capacity (TAC), and correlate with BER exhaustion [19, 20]. Also, a proteomic profiling 2024 study confirmed reduced expression of BER proteins in spermatozoa from men with high DFI, reinforcing their role as mechanistic biomarkers [11].

MMR

MMR safeguards replication fidelity by correcting base mismatches and insertion-deletion loops that arise during DNA synthesis. Core regulators include MutL Homolog 1 (MLH1), MutS Homolog 2 (MSH2), and Post-meiotic Segregation Increased 2 (PMS2), which coordinate lesion recognition and excision. In the context of male infertility, MMR dysfunction has been implicated in spermatogenic arrest and genomic instability. Immunohistochemical analyses of testicular biopsies from infertile men have demonstrated depletion of MMR proteins, particularly in cases of maturation arrest and Sertoli cell-only syndrome, suggesting a mechanistic link between MMR failure and impaired germ cell development [12].

Chromatin remodeling and repair accessibility

Chromatin dynamics intricately regulate DNA repair during spermatogenesis. The histone-to-protamine transition, essential for sperm nuclear condensation, is modulated by repair-associated histone modifications such as γH2AX, H3K9me3, and H2A.Z, which influence DNA accessibility and repair enzyme recruitment [13, 14]. Disruption of this transition compromises chromatin compaction and impairs the accessibility of repair machinery, exacerbating genomic instability [16]. In addition, chromatin packaging defects, including abnormal protamine 1/2 ratios, persistent histone retention, and epigenetic alterations such as promoter methylation of repair genes, further restrict repair enzyme access to DNA lesions. These structural and epigenetic barriers contribute to persistent DNA damage, elevated sperm DNA fragmentation, and reduced fertilization potential, underscoring the critical role of chromatin remodeling in determining repair efficiency and reproductive competence [21, 22].

Diagnostic biomarkers of DNA repair dysfunction in male infertility

Contemporary evaluation of male infertility has shifted from descriptive semen parameters toward mechanistic interrogation of DNA repair fidelity. Spermatogenic cells are uniquely vulnerable to genomic insults due to high transcriptional activity, programmed meiotic DSBs, and oxidative stress [1, 3, 19]. Consequently, the integrity of DNA repair systems, particularly HR, NHEJ, and BER, is central to sperm quality, chromatin integrity, and reproductive potential (Table 2) [4, 6].

Diagnostic tools that interrogate dysfunction in these pathways offer unprecedented resolution in stratifying infertile phenotypes and guiding personalized interventions. Techniques such as γH2AX immunostaining, Comet and TUNEL assays, and next-generation sequencing of repair genes have enabled molecular characterization of repair deficiencies, linking them to clinical outcomes and ART success rates (Table 2) [1,4].

Sperm DNA fragmentation assays: Functional readouts of repair failure

DFI reflects the cumulative failure of DNA repair systems to resolve strand breaks and maintain chromatin integrity. Elevated DFI has been associated with reduced fertilization

potential, poor embryo quality, and adverse ART outcomes [20, 23]. The TUNEL assay detects unrepaired 3'-OH DNA ends, implicating defective BER and apoptotic signaling [14]. The Comet assay, particularly under alkaline conditions, reveals single-strand breaks and alkali-labile sites—hallmarks of oxidative overload and BER exhaustion [15, 19]. The sperm chromatin structure assay (SCSA) quantifies chromatin susceptibility to acid-induced denaturation, indirectly reflecting protamine deficiency, histone retention, and impaired chromatin compaction, all of which restrict repair enzyme access [10, 21, 22]. These assays provide functional insights into sperm DNA integrity and repair efficiency, and their integration into clinical workflows has improved diagnostic resolution and patient stratification in idiopathic infertility [9, 24].

Table 1. DNA repair pathways, key molecules involved, and associated dysfunction outcomes

Repair pathway	Key molecules	Dysfunction outcome
Homologous recombination	RAD51, BRCA2, DMC1	Meiotic arrest, non-obstructive azoospermia
Non-homologous end joining	Ku70/Ku80, XRCC4	Aneuploidy, chromatin condensation failure
Base excision repair	OGG1, XRCC1, APE1	High sperm DNA fragmentation, oxidative base lesions
Mismatch repair	MLH1, MSH2, PMS2	Replication errors, maturation arrest

BRCA1/2= Breast cancer type 1/2 susceptibility proteins; RAD51= RAD51 recombinase; DMC1= DNA Meiotic recombinase 1; KU70/KU80= Ku autoantigen 70/80 complex; XRCC1= X-ray repair cross complementing protein 1; XRCC4= X-ray repair cross complementing protein 4; APE1= Apurinic/ apyrimidinic endonuclease 1; OGG1= 8-oxoguanine DNA glycosylase; MLH1= MutL homolog 1; MSH2= MutS homolog 2; PMS2 = Post-meiotic segregation increased 2
Note: All listed pathways and dysfunction outcomes are supported by clinical and mechanistic evidence [6–12].

Table 2. Diagnostic biomarkers and detection tools for dna repair dysfunction in male infertility

Biomarker Category	Representative Markers / Tools	Diagnostic Target
DNA damage response	γH2AX immunostaining	DSB detection and checkpoint activation [16, 17]
DNA fragmentation	TUNEL assay, Comet assay, SCSA	Single- and double-strand breaks; chromatin integrity [14, 15]
Genetic profiling	NGS panels targeting RAD51C, BRCA2, OGG1, MLH1	HR, BER, MMR gene variants linked to infertility [5,6,11,12,25]
Oxidative stress	8-OHdG, ROS levels, TAC	Oxidative DNA lesions and repair exhaustion [19, 20]
Chromatin packaging	Protamine 1/2 ratios, histone retention	Repair accessibility and nuclear condensation defects [21, 22]

γH2AX = Phosphorylated H2A histone family member X; DSB= Double-strand break; TUNEL= Terminal deoxynucleotidyl transferase dUTP Nick end labeling; SCSA= Sperm chromatin structure Assay; HR= homologous recombination; BER = Base excision repair; MMR= Mismatch repair; OGG1 = 8-Oxoguanine DNA glycosylase; MLH1= MutL homolog 1; 8-OHdG= 8-hydroxy-2′-deoxyguanosine; ROS= Reactive oxygen species; TAC = Total antioxidant capacity

γH2AX immunostaining: A direct marker of double-strand breaks

γH2AX is rapidly deposited at sites of DSBs and serves as a sentinel of HR activation [16]. In infertile men, persistent γH2AX foci in spermatocytes and spermatozoa indicate unresolved DSBs and defective HR kinetics, often correlating with meiotic arrest and Sertoli cell-only syndrome [17]. Immunohistochemical detection of γH2AX in testicular biopsies provides a mechanistically anchored diagnostic readout, linking molecular damage to histopathological outcomes [12, 13]. Emerging evidence also suggests that γH2AX expression may be modulated by chromatin accessibility and epigenetic context, reinforcing its role as a dynamic biomarker of repair failure [14, 16].

Next-generation sequencing: Genomic dissection of repair pathways

NGS platforms enable targeted interrogation of DNA repair genes implicated in male infertility. Mutations in RAD51C, BRCA2, XRCC1, and MLH1 have been identified in men with non-obstructive azoospermia, maturation arrest, and elevated DFI [5-7, 11, 12]. Transcriptomic profiling has revealed downregulation of HR and NHEJ components in idiopathic infertile men, suggesting pathway exhaustion or regulatory silencing [8,18]. In parallel, epigenetic studies have demonstrated promoter methylation and reduced expression of BER genes such as OGG1 and APE1, linking oxidative stress to repair failure and spermatogenic disruption [2, 19, 22].

NGS-based diagnostics not only facilitate molecular classification of infertility phenotypes but also inform genetic counseling, ART planning, and therapeutic targeting in precision reproductive medicine [4, 25].

Oxidative stress biomarkers coupled to BER dysfunction

Oxidative stress plays a pivotal role in male infertility, particularly through its impact on BER pathways. Biomarkers such as 8-OHdG, ROS levels, and TAC are frequently elevated in infertile men, reflecting redox imbalance and oxidative DNA damage. These markers correlate with reduced activity of key BER enzymes, including OGG1 and XRCC1, indicating functional collapse of repair mechanisms under oxidative overload [18-20]. Proteomic analyses have confirmed depletion of BER proteins in spermatozoa from men with high DFI, reinforcing the mechanistic link between oxidative stress and impaired DNA repair capacity. The integration of oxidative biomarkers with fragmentation assays enhances diagnostic resolution and supports targeted antioxidant therapy in select infertility phenotypes [11, 18, 20].

Chromatin packaging defects as biomarkers of genomic instability

Chromatin remodeling is essential for DNA repair accessibility during spermatogenesis. Disruption of repair-associated histone modifications including γH2AX, H3K9me3, and H2A.Z, impairs the histone-to-protamine transition, compromising nuclear condensation and exposing sperm DNA to damage. These

modifications serve as markers of genomic instability and repair inefficiency [13, 14].

Additional chromatin packaging defects such as abnormal protamine 1/2 ratios, persistent histone retention, and epigenetic alterations (e.g., promoter methylation of DNA repair genes) further restrict the access of repair enzymes to DNA lesions. These structural and epigenetic markers are increasingly recognized as diagnostic modalities for assessing sperm chromatin integrity, DNA repair accessibility, and reproductive competence [21, 22].

Clinical implications of DNA repair markers in reproductive technology

The identification of defective DNA repair pathways in male infertility has profound implications for clinical practice, reproductive decision-making, and therapeutic innovation. As mechanistic insights into spermatogenic DNA repair deepen, the integration of repair profiling into diagnostic and therapeutic frameworks is rapidly advancing [23].

Precision stratification in ART

Men with elevated sperm DNA fragmentation, persistent γH2AX foci, or mutations in HR and BER genes exhibit poorer outcomes in conventional *in vitro* fertilization and intracytoplasmic sperm injection. Stratification based on DNA repair dysfunction enables tailored ART strategies. Stratifying patients by repair pathway dysfunction enables tailored ART strategies, such as testicular sperm extraction to bypass post-testicular damage, or antioxidant preconditioning to mitigate oxidative overload. Recent meta-analyses confirm that DNA repair-informed selection improves fertilization rates and embryo quality [20, 23, 24].

Genetic counseling and carrier screening: reproductive and oncologic relevance

Pathogenic variants in DNA repair genes (e.g., *BRCA2*, *RAD51C*, and *XRCC1*) not only impair spermatogenesis but may also confer heritable cancer risk, particularly in the context of germline instability. Incorporating repair gene panels into infertility evaluations supports dual-purpose counseling, addressing both reproductive outcomes and oncologic surveillance. This is especially critical in consanguineous populations, familial cancer syndromes, and idiopathic azoospermia, where early identification of carriers informs long-term health planning [4, 6, 7].

Therapeutic modulation of DNA repair pathways

Recent therapies are focusing on modulating DNA repair capacity. Small molecules that enhance BER enzyme activity (e.g., OGG1 activators), epigenetic modulators that restore chromatin accessibility, and ROS scavengers targeting mitochondrial dysfunction are under investigation. Preclinical and early-phase clinical trials are evaluating whether repair-enhancing interventions can rescue spermatogenic output, reduce DNA fragmentation, and improve ART success rates [11, 19].

Integration of DNA repair biomarkers into predictive clinical algorithms

DNA repair biomarkers such as DFI thresholds, γH2AX intensity, and repair gene expression are being incorporated into predictive models for ART outcomes. Machine learning approaches trained on molecular and clinical features can forecast fertilization potential, embryo viability, and miscarriage risk, enabling personalized

reproductive planning. Such tools enable personalized reproductive planning, optimize resource allocation, and support evidence-based counseling in fertility clinics [23-25].

Conclusion

The central findings of this review, which establish DNA repair dysfunction as a key driver of male infertility through defective meiotic recombination, aberrant chromatin remodeling, and elevated sperm DNA fragmentation - manifesting as oligozoospermia, azoospermia, or poor fertilization outcomes- are schematically integrated in Figure 1. This model further delineates how disruptions in homologous recombination, non-homologous end joining, base excision repair, and mismatch repair pathways underpin the development of mechanistically informed biomarkers (e.g. γH2AX, TUNEL, comet assays) and their translation into clinical practice for precision diagnostics, patient stratification, and tailored therapeutic interventions.

Recent advances in male infertility research have shifted the diagnostic paradigm from descriptive semen parameters toward mechanism-based stratification. The characterization of DNA repair pathways, particularly HR, NHEJ, BER, and MMR, has enabled the development of molecularly anchored diagnostic tools, including γH2AX immunostaining, sperm DNA fragmentation assays, oxidative stress profiling, and next-generation sequencing of repair genes. These modalities support precision reproductive planning, genetic counseling, and targeted therapeutic interventions, marking a significant progression in reproductive medicine. Despite promising developments, several limitations constrain the clinical translation of DNA repair biomarkers:

- Validation gaps: Many biomarkers lack robust validation across diverse populations and infertility phenotypes.
- Limited accessibility: Advanced assays (e.g., NGS, proteomics) remain cost-prohibitive and are not widely available in routine clinical settings.
- Incomplete integration: Repair profiling is rarely incorporated into standardized ART decision algorithms or longitudinal outcome tracking.
- Contextual ambiguity: Repair dysfunction signatures may overlap with other etiologies (e.g., epigenetic defects, metabolic stress), complicating interpretation without multi-omic support. These limitations underscore the need for standardized protocols, cross-cohort validation, and cost-effective platforms to ensure equitable clinical adoption.

To fully realize the potential of DNA repair profiling in male infertility, future efforts should prioritize the following:

- Longitudinal studies are needed to link DNA repair biomarkers with ART outcomes, miscarriage risk, and offspring health, thereby establishing their prognostic and clinical relevance.
- Integration of multi-omic data -including genomic, epigenetic, proteomic, and metabolic layers- is essential to contextualize repair dysfunction within broader cellular networks and uncover synergistic mechanisms of infertility.

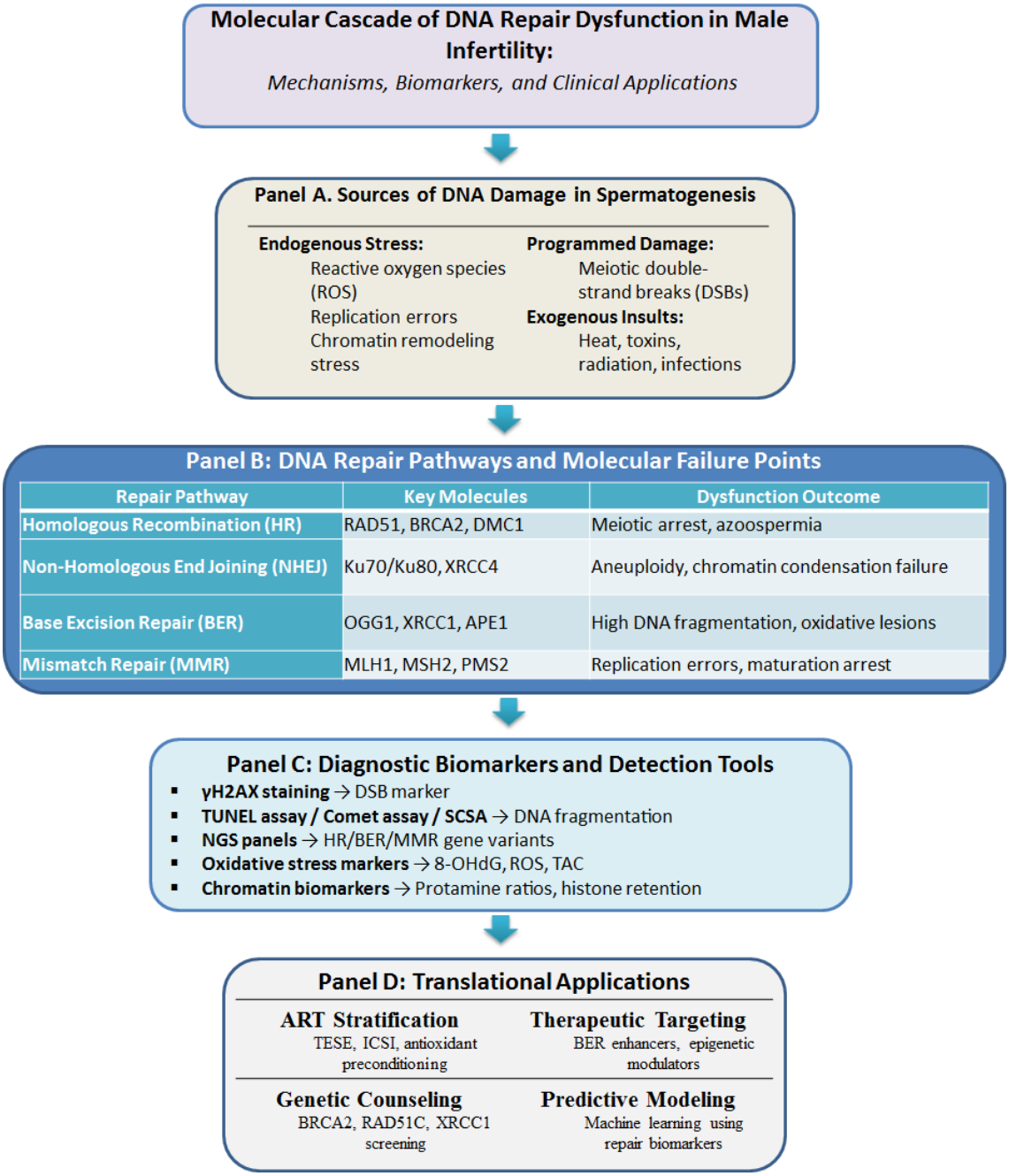

Fig. 1. Mechanisms, biomarkers, and clinical applications of DNA repair dysfunction in male infertility

BRCA2= Breast cancer type 2 susceptibility proteins; RAD51= RAD51 recombinase; DMC1= DNA Meiotic recombinase 1; KU70/KU80= Ku autoantigen 70/80 complex; XRCC4= X-Ray Repair Cross complementing protein 4; OGG1= 8-oxoguanine DNA glycosylase; XRCC1= X-Ray repair cross complementing protein 1; APE1= Apurinic/ apyrimidinic endonuclease 1; MLH1= MutL homolog 1; MSH2= MutS homolog 2; PMS2 = Post-meiotic segregation increased 2; DSB= Double-strand break; 8-OHdG= 8-hydroxy-2′-deoxyguanosine; ROS= Reactive oxygen species; TAC = Total antioxidant capacity; TESE= Testicular sperm extraction; ICSI= Intracytoplasmic sperm injection

- Development of predictive algorithms using machine learning can forecast reproductive success based on repair signatures, building on prior advancements in phenotype-to-mechanism stratification.
- Therapeutic innovation is underway, with promising approaches including small-molecule activators of repair enzymes, antioxidant regimens to mitigate oxidative stress, and chromatin accessibility enhancers to restore repair efficiency.
- Global standardization of biomarker panels and reporting metrics is critical to ensure cross-center reproducibility, facilitate clinical benchmarking, and support equitable implementation across diverse populations.

Together, these strategies will accelerate the transition from phenotype-based classification to mechanism-informed reproductive care, bridging molecular diagnostics with personalized therapeutic pathways and advancing the field of precision andrology.

Ethical Considerations

The Ethics Committee of Shahid Sadouqhi University of Medical Sciences (IR.SSU.SRH.REC.1401.011) approved the study.

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Conflict of Interest

The authors declared no conflict of interest.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contribution

Conceptualization: F.P, M.A; Investigation: F.P; Writing original draft: F.P; Writing review & editing: M.A.

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