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MOLECULAR SUBTYPING OF OBSTRUCTIVE VS. NON-OBSTRUCTIVE AZOOSPERMIA: DIAGNOSTIC PRECISION FOR SURGICAL OUTCOMES

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ABSTRACT

The most serious type of male infertility is azoospermia, which is mostly divided into obstructive and non-obstructive varieties with specific pathophysiological and prognostic implications. Conventional diagnostic methods are based on clinical, hormonal, and histologic evaluation but the techniques are not very precise in estimating the outcome of sperm retrieval in surgery. This narrative review summarizes recent developments in molecular subtyping of azoospermia with an emphasis on genetic, epigenetic, transcriptomic, proteomic, and multi-omics biomarker panels, which can be effectively used to increase diagnostic discrimination and prognostic validity. Etiological stratification with genetic markers like CFTR mutations and Y-chromosome microdeletions and next-generation sequencing has further enriched the spermatogenesis-related variants. New non-invasive overepigenetic and transcriptomic signatures -such as microRNAs, long non-coding RNAs and cell-free DNA fragmentomics- have potential to provide subtype differentiation and prediction of residual spermatogenesis. Proteomic biomarkers as TEX101 and LDHC, especially combined with the hormonal parameters and multi-omics models, enhance the stratification of risk in pre-operative. Predictive algorithms based on machine learning that uses both molecular and clinical data show improved prediction of the success of testicular sperm extraction (TESE). Together, molecular subtyping is a radical move toward accurate andrology, wherein individualized surgical advice, unnecessary interventions, and maximized assisted reproduction results are attained. To translate these advances into clinical practice, further validation and clinical integration of multi-omics panels is needed.

INTRODUCTION

Overview of Azoospermia

The most severe form of male infertility is azoospermia that is characterized by the lack of spermatozoa in at least two equally examined, centrifuged semen samples. It has an epidemiological prevalence rate of about 1% in the general male population and about 10-15% in men who have undergone infertility testing across the world (1). There are two main types of azoospermia, which are clinically characterized by obstruction (obstructive azoospermia - OA) and lack of obstruction (non-obstructive azoospermia - NOA) (2). OA is typified by intact testicular spermatogenesis which has functional obstruction

of sperm transport by ductal blockage (such as developmental bilateral absence of the vas deferens, obstruction of ejaculatory ducts or epididymal ducts), making it subject to surgical or micro-surgical therapy. Conversely, NOA is caused by inherent testicular pathology, often severe spermatogenic failure due to primary testicular failure, or hypothalamic-pituitary-gonadal axis malfunction, and is the most common type of azoospermia (3). A clear OA/NOA distinction is necessary to prognosticate and to plan therapy and determine the likelihood of successful sperm recovery to assisted reproductive methods like testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI) (4).

Obstructive vs. Non-Obstructive Mechanisms

The boundary between obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) has its clinical basis in the differences in the pathophysiological roots of the two conditions. OA is caused by a physical blockage of the male reproductive tract which prevents the expression of spermatozoa into the ejaculate despite normal intratesticular spermatogenesis. Etiologies include: congenital bilateral naivete of the vas deferens - often associated with cystic fibrosis transmembrane conductance regulator (CFTR) mutations - fibrotic scarring due to infection or prior surgery, and blockage of the ejaculatory ducts. OA has a lower relative prevalence compared to NOA, but accurate diagnosis is of great importance, since the spermatogenesis process is generally intact, and sperm may be successfully retrieved surgically out of the epididymis or testis to be used in assisted reproduction (4). On the other hand, NOA indicates an inherent testicular dysfunction which is the impaired sperm production that can be ascribed to the primary testicular failure or abnormal regulatory signaling through hypothalamic-pituitary-gonadal axis. NOA constitutes most cases of azoospermic, and is linked to Sertoli-cell-only syndrome, maturation arrest, or hypospermatogenesis. The difference between these entities conventionally depends on a full-fledged clinical examination involving endocrine testing (such as high levels in follicle-stimulating hormone), testicular volume, radiographic examination, and, in some cases, diagnostic biopsy, as a stress of the need to properly classify patients so that they can be managed optimally (5).

At the molecular level, new evidence suggests that there are differences in gene expression and regulation between OA and NOA beyond the macroscopic and hormonal differences between their anatomy and physiology. Recent studies have elucidated divergent genetic and transcriptomic sexual dysfunctions that characterize spermatogenic failure in NOA, including the aberrant expression of genes implicated in germ-cell development and spermatogenesis, including cytoskeleton protein and related regulatory networks as revealed by microarray and computational analysis (6). Moreover, non-coding RNA species, such as long non-coding (lncRNAs) and microRNAs, show different patterns of expression in patient with NOA as compared to fertile controls, which points to the role of epigenetic processes in the arrest of spermatogenesis (7). Despite these differences in the systemic inflammatory gene expression, the clinical utility of these molecular differentials as routine diagnostic translation is still in research. With the development of more precise diagnostics, molecular biomarkers alongside traditional clinical parameters have the potential to provide a new avenue of subtype classification and the development of personalized therapeutic approaches (8).

Table 1: Key Differences Between Obstructive and Non-Obstructive Azoospermia

Feature	Obstructive Azoospermia (OA)	Non-Obstructive Azoospermia (NOA)
Spermatogenesis	Typically normal	Impaired or absent
Testicular volume	Normal or near normal	Reduced in many cases
FSH levels	Usually normal or mildly elevated	Often significantly elevated
Cause	Physical blockage of the ducts or vas deferens	Testicular failure or intrinsic spermatogenic defect
Genetic associations	CFTR mutations (in some cases)	Wide range of gene mutations and regulatory changes
Sperm retrieval potential	High from epididymis/testis	Variable, often lower success rates
Molecular signatures	Limited specific changes	Distinct transcriptomic and epigenetic dysregulation
Clinical management	Possible surgical correction	Focus on sperm retrieval (TESE) and fertility support

Molecular Subtyping of Azoospermia

Molecular subtyping of obstructive azoospermia (OA) is mainly aimed at the identification of gene-expression and regulatory signatures which distinguish between true ductal obstruction and retained intratesticular spermatogenesis. In OA, seminiferous tube spermatogenesis is generally intact, and the molecular changes that happen are associated rather with allogenic or acquired ductal malformations than with an underlying testicular pathology. A case in point is a congenital bilateral vas deferens (CBAVD) absence, often associated with pathogenic mutations in the CFTR gene and a definite genetic determinant of obstruction that is independent of testicular defects, therefore determining a definite genetic basis of obstruction. Also, in-depth transcriptomic profiling of ejaculated or epididymal samples can distinguish between patients with a functional spermatogenesis and those with total obstruction to provide molecular information to guide clinical decision-making. The most current metabolomic studies of seminal plasma have revealed some unique metabolic signatures that can differentiate NOA and OA and differentiate between certain histological subtypes in azoospermia, thus showing the promise of non-invasive subtyping methods (9).

In comparison, non-obstructive azoospermia (NOA) is a heterogeneous group of molecular subtypes, which express different pathways of spermatogenic impairment. In contrast to OA, NOA subtypes are characterized by the disturbances in the germ-cell proliferation, meiotic development, chromatin restructuring and Sertoli-germ cell interaction. Genomics studies with whole-exome sequencing and transcriptomic profiling have demonstrated that NOA patients harbor a continuum of genetic variants spread throughout a range of biological pathways and some of the genes show correlated patterns of expression depending on specific spermatogenesis stages (10). Epigenetic dysregulation, such as modifications to microRNAs, long non-coding RNAs (lncRNAs), piRNAs and circular RNAs, has become a key factor in the stratification of NOA subtypes as these regulatory molecules determine key features of germ-cell development and can define discrete phenotypes of NOA (11). Recent transcriptomic analyses using machine-learning algorithms have found that there are specific clusters of cases of NOA each one with their own unique set of gene-expression signatures that can be used to form multi-gene biomarker panels that may predict subtype and, perhaps, the likelihood of successful sperm retrieval (12).

Table 2: Molecular Subtyping Features in Obstructive vs. Non-Obstructive Azoospermia

Aspect	Obstructive Azoospermia (OA)	Non-Obstructive Azoospermia (NOA)
Primary Process	Physical blockage of ducts	Intrinsic spermatogenic failure
Underlying Genetic Etiology	*CFTR* mutations (e.g., CBAVD) and ductal development genes	Multiple genes involved in germ cell development, meiosis, and DNA repair
Transcriptomic Profile	Reflects intact spermatogenesis	Reflects disrupted spermatogenesis and cell cycle regulation
Non-coding RNA Signatures	Limited characterization	Dysregulated miRNAs, lncRNAs, piRNAs, circRNAs
Metabolomic Signatures	Distinct from NOA enabling stratification	Varies with histological subtype
Biomarker Panels	Focused on confirming obstruction while preserving spermatogenesis	Panels differentiate NOA subtypes and correlate with sperm retrieval success
Clinical Application	Determining presence of obstruction (surgical correction feasible)	Personalized risk prediction for sperm retrieval outcomes
Predictive Value for TESE	High (spermatogenesis intact)	Variable, depends on subtype and molecular signature

Genetic Biomarkers in Azoospermia

Genetic biomarkers are essential means of differentiating the etiological subtypes of azoospermia and are increasingly being included in the pre-surgical evaluation to increase the diagnostic accuracy and predict the likelihood of successful sperm recovery. Of these markers, the most widely recognized are mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which are highly recognized to be strongly associated with congenital bilateral absence of the vas deferens (CBAVD), a type of obstructive azoospermia, which spares spermatogenesis (13). The identification of CFTR pathogenic variants in azoospermic patients allows developing an obstructive aetiology, which subsequently helps guide clinicians to perform epididymal or testicular sperm retrieval procedures that often result in high proportions of viable sperm that can be used in intracytoplasmic sperm injection (ICSI). Genetic confirmation of obstruction is also helpful in providing prognostic assurance to couples since in such patients, the spermatogenic functions would be relatively intact (14).

Non-obstructive azoospermia (NOA), however, is a heterogenous cluster of testicular dysfunctions, which is based on the disturbed spermatogenesis. Y chromosome azoospermia factor (AZF) deletions (AZFa, AZFb, and AZFc) that are variably involved in germ-cell depletion are the most clinically relevant genetic markers in NOA. Removals of the AZFa or AZFb domains as a whole are very predictive of the absence of any spermatogenesis and are linked to an insignificant chance of any sperm recovery through testicular sperm extraction (TESE). On the other hand, deletions of the AZFc region have been detected partly to result in residual spermatogenic foci and in rare cases, permits sperm retrieval, thus allowing clinically viable stratification of NOA cases (15).

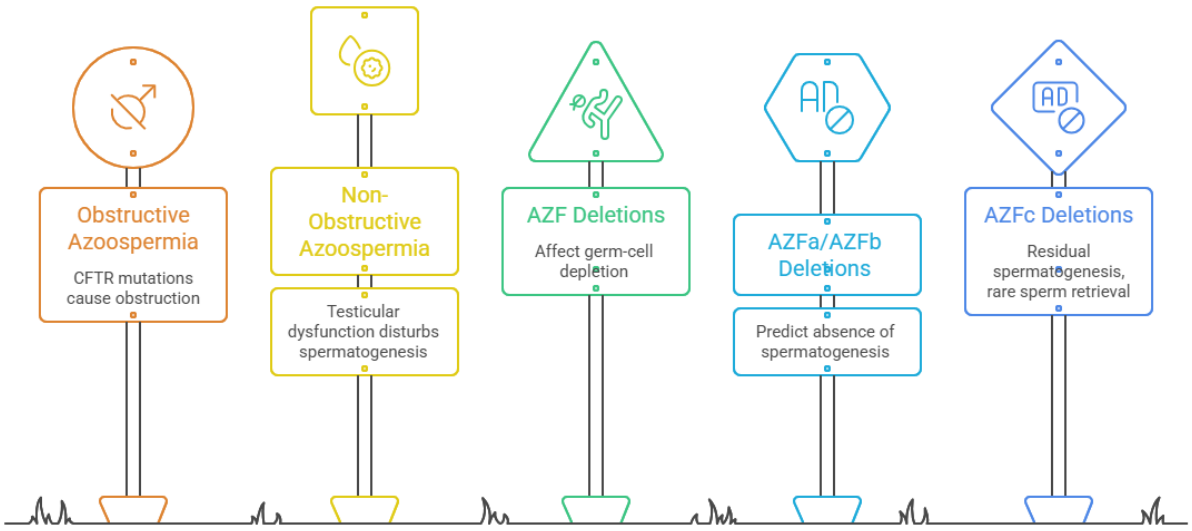

Figure 1: Genetic Determinants and Molecular Pathways in Azoospermia Subtyping

In addition to these conventional indicators, recent advances in next-generation sequencing (NGS) and whole-exome sequencing (WES) have enabled the identification of other forms of the gene that narrow the molecular profile of NOA. Spermatogenesis arrest at specific stages has been suggested to have been caused by pathogenic mutations in genes including TEX11, M1AP, TDRD9 and SYCP3. As an example, the mutation of TEX11 has often been related to meiotic arrest, which is characterized by a severe deficiency of post-meiotic germ cells, and therefore a low probability of sperm recovery. Conversely, mutations in genes implicated in hypospermatogenesis can continue to show foci of active spermatogenesis, which provides a slight but clinically significant chance of effective sperm harvesting through TESE (16).

Specialized NGS arrays incorporating known and novel genes related to azoospermia have demonstrated higher diagnostic accuracy compared with standard cytogenetics, and as such have enabled clinicians to cluster NOA patients into molecular subsets with different risk profiles to surgery. This molecular stratification leads to improved patient counseling on the one hand but on the other hand it helps reduce unnecessary surgeries and makes therapeutic decision-making process consistent with the personalized risk assessment and resource utilization in the context of fertility care (17).

Epigenetic and Transcriptomic Panels

Biomarkers Epigenetic and transcriptomic: Non-invasive approaches to subtype discrimination in azoospermia, outside of traditional genetic analysis, now attracted interest through non-coding RNAs. Of these organelles, microRNAs (miRNAs) are the most well-studied group of small non-coding transcripts, due to their key regulatory roles in spermatogenesis and their reported stability in seminal plasma and sperm tissue. Recent studies indicate that a repertoire of miRNAs is differentially expressed between azoospermic and fertile controls; miRNAs which are repeatedly down-regulated in non-obstructive azoospermia (NOA) include hsaelliated mir-34c-5p, hsaelliated mir-34b-3p and hsaelliated mir-202-3p, thus indicative of disruption of germ-cell development and of dysregulation of pathways involved in cellular metabolism and inflammation (18). Importantly, miRNA profiling has already shown to be a promising non-invasive modality of differentiating azoospermic subtypes and assessing spermatogenic activity. Associations between seminal plasma changed miRNA expression and particular histopathological phenotype such as Sertoli-cell-only syndrome versus spermatogenic

arrest indicate that miRNAs do not only define disease biology, but also predict the availability of spermatozoa in testicular tissue prior to surgical excision. By way of example, seminal hsa -mir -34c -5p has better discriminative efficiency between normal and azoospermic profiles with an area under an receiver operating characteristic (AUC) of about 0.98 (19).

In addition to miRNAs, lncRNAs and other transcriptomic components provide a complete epigenetic substrate in regard to spermatogenic competence. LncRNA panels and extracellular-vesicle-associated lncRNA panels assayed in seminal plasma have been developed to predict the occurrence of testicular spermatozoa with great accuracy; a canonical nine- lncRNA signature, e.g. its AUC of 0.986 during initial training and 0.960 during external validation at predicting sperm retrieval, outperforms traditional hormonal indices (20). Similarly, certain seminal lncRNAs, such as TUG1, CDKN2B-AS1, and H19, possess strong diagnostic and prognostic performance, and some of them are related to the outcome after TESE and highlight their potential use in pre-operative decisions (7).

In addition to RNA-based biomarkers, epigenetic signatures, including the presence of altered DNA methylation and cell-free DNA (cfDNA) fragmentomic profiles are becoming key indicators of spermatogenic impairment. The dissective analysis of seminal plasma has provided the discrete infertility phenotypes, suggesting that the pattern of the cfDNA could reflect the underlying testicular pathology and provide additional prognostic information regarding the outcomes of the surgical intervention in combination with RNA biomarkers (21). Together, epigenetic and transcriptomic panels (miRNAs, lncRNAs and cfDNA signatures) represent a complex molecular architecture that further classifies azoospermia and enhances pre-operative prediction of sperm recovery success, thus pointing the clinical practice towards a precision diagnostics in male infertility.

Table 3: Epigenetic and Transcriptomic Biomarkers in Azoospermia

Biomarker Type	Specific Markers / Panels	Biological Significance	Predictive Value for Sperm Retrieval	Ref.
miRNAs	hsa-miR-34c-5p, hsa-miR-34b-3p, hsa-miR-202-3p	Regulate germ cell proliferation, meiosis, and apoptosis	Differentiates NOA subtypes; correlates with presence of sperm in TESE	(18, 19)
lncRNAs	TUG1, CDKN2B-AS1, H19; 9-lncRNA panel	Modulate gene expression in spermatogenesis; influence Sertoli–germ cell communication	High accuracy in predicting sperm retrieval (AUC 0.96–0.986)	(7, 20)
piRNAs / circRNAs	PIWIL2-related piRNAs, circRNA panels	Involved in germ cell differentiation and genome stability	Associated with spermatogenic arrest; potential non-invasive predictors	(22)
Cell-free DNA (cfDNA) / Fragmentomics	cfDNA methylation patterns	Reflects testicular cell turnover and epigenetic dysregulation	Distinguishes azoospermia subtypes; aids TESE outcome prediction	(21)

Proteomic and Hormonal Biomarkers

In addition to RNA-based biomarkers, epigenetic signatures, including the presence of altered DNA methylation and cell-free DNA (cfDNA) fragmentomic profiles are becoming key indicators of spermatogenic impairment. The dissective analysis of seminal plasma has provided the

discrete infertility phenotypes, suggesting that the pattern of the cfDNA could reflect the underlying testicular pathology and provide additional prognostic information regarding the outcomes of the surgical intervention in combination with RNA biomarkers (23). Together, epigenetic and transcriptomic panels (miRNAs, lncRNAs and cfDNA signatures) represent a complex molecular architecture that further classifies azoospermia and enhances pre-operative prediction of sperm recovery success, thus pointing the clinical practice towards a precision diagnostics in male infertility (24).

Proteomic profiles are still complemented by the hormonal biomarkers but their single prediction strength is weak. Classical hormones like follicle stimulating hormone (FSH) and inhibin B have moderate associations with spermatogenic status and do not always predict success in sperm retrieval. New evidence suggests that proteomic signature data combined with hormonal measurements and seminal biomarkers like TEX101 increases prediction success in successful sperm extraction in non-obstructive azoospermia (25). On the whole, the incorporation of proteomic and hormonal markers into multivariate panels proves to have a potential in enhancing the non-invasive diagnosis and optimization of surgical decisions in azoospermia.

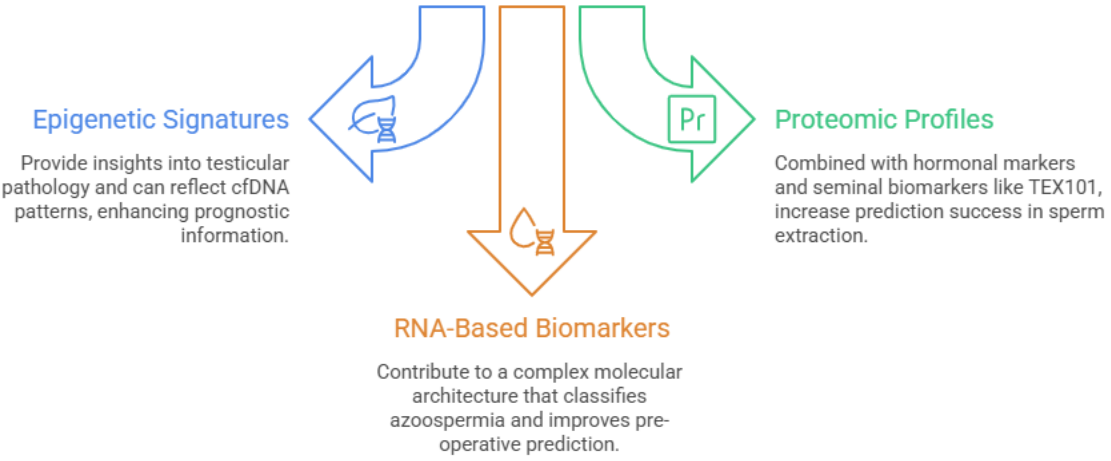

Figure 2: Multi-Omics Integration Model for Predicting Sperm Retrieval Success in Azoospermia Integrated Non-Invasive Diagnostic Models

More recent technologies in multiomics technique have made it possible to create combination non invasive diagnostic models of azoospermia, integrating genetic, epigenetic, transcriptomic, proteomic and hormonal biomarkers. The objectives of these models include the differentiation of subtypes and the modeling of the success rate of sperm retrieval without the use of invasive testicular biopsies. As an example, the seminal plasma miRNA and long-noncoding RNA (lncRNA) profiles combined with proteomic biomarkers like TEX101 and LDHC are much better in distinguishing between obstructive and non-obstructive azoospermia (high diagnostic accuracy of 0.95) compared to seminal plasma miRNA and long-noncoding RNA (lncRNA) on their own (12, 19, 26).

Multivariate datasets have also increased predictive ability because machine learning algorithms are applied to them. The combination of genetic variants, Y chromosome microdeletions, concentrations of hormones, and epigenetic signatures can categorize patients into molecular subtypes and have the highest likelihood of predicting the success of testicular sperm extraction (TESE) with high accuracy (17, 27). Through these non-invasive models, clinicians can maximize patient education, minimize unneeded surgery procedures and tailor fertility treatment. Existing studies are still upgrading

these tools to clinically deployable panels that combine multi-omics data into easy-to-use predictive systems, which is a significant advance towards precision andrology in azoospermia management (28, 29).

Molecular Predictors of Sperm Retrieval Success

The precise prognosis of sperm retrieval is a significant clinical issue in non-obstructive azoospermia (NOA), and the application of molecular biomarkers has become a key tool that can be used to inform surgical decision-making. Genetic markers, such as Y -chromosome microdeletions (AZFa, AZFb, AZFc) are the strongest predictors: complete deletions of either AZFa or AZFb essentially exclude sperm retrieval, but incomplete deletions of AZFc retain a modifiable but clinically significant chance of success (15). Spermatogenesis-related pathogenic variants of genes (TEX11, M1AP, and TDRD9) have been linked to certain histological subtypes, including maturation arrest and Sertoli-cell-only syndrome, which is linked to low TESE success rates (16).

When genetic profiling is coupled with epigenetic markers, this improves the predictive accuracy. miRNAs (e.g., hsa 34c 5p of miR) and lncRNA panels (e.g. TUG1, H19) of seminal plasma have been implicated in residual spermatogenesis, allowing stratification of patients into high- or low-probability groups of sperm retrieval. None of the invasive indicators of germ-cell presence alone is an adequate readout to determine the presence of germ cells, and proteomic indicators like TEX101, LDHC and HSPA2 are also a useful functional readout to predict surgical outcomes (30-32).

Multi-omics models that combine genetic, epigenetic, transcriptomic, and proteomic biomarkers with classic clinical variables (e.g., testicular volume, FSH) have been shown to be better predictors. The use of machine-learning algorithms on these data sets can produce personalized probability of successful TESE, and thus, minimizing unnecessary surgical operations and maximizing patient counseling. All in all, molecular predictors have become the foundation of precision reproductive medicine and are changing how azoospermic men are handled, as they are no longer administered through empirically motivated decisions but one that is evidence-based and tailored to the specific patient (26, 27).

Conclusion and Future Directions

Molecular sub-typing and panel biomarkers have revolutionized the diagnosis of azoospermia, by facilitating the accurate distinction between obstructive and non-obstructive azoospermia and by enhancing the success rate of prognosing sperm retrieval. The innovation of genetic, epigenetic, transcriptomic and proteomic profiling and machine-learning pushes the personalization of surgical and fertility processes. The future is characterized by creation of non-invasive multi-omics assays and widened prediction algorithms, as well as wider clinical application of biomarker-based approaches to maximize assisted reproduction success and reduce the unnecessary interventions. Increasing perfection of these molecular tools is likely to make precision andrology normal practice in the treatment of azoospermia.

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