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MALE SEXUAL DYSFUNCTION AND DISORDERS (A PASTUSZAK AND N THIRUMAVALAVAN, SECTION EDITORS)

Recent Advances and Future Opportunities to Diagnose Male Infertility

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Abstract

Purpose of Review Infertility affects 10–15% of couples, making it one of the most frequent health disorders for individuals of reproductive age. The state of childlessness and efforts to restore fertility cause substantial emotional, social, and financial stress on couples. Male factors contribute to about half of all infertility cases, and yet are understudied relative to female factors. The result is that the majority of men with infertility lack specific causal diagnoses, which serves as a missed opportunity to inform therapies for these couples.

Recent Findings In this review, we describe current standards for diagnosing male infertility and the various interventions offered to men in response to differential diagnoses. We then discuss recent advances in the field of genetics to identify novel etiologies for formerly unexplained infertility.

Summary With a specific genetic diagnosis, male factors can be addressed with appropriate reproductive counseling and with potential access to assisted reproductive technologies to improve chances of a healthy pregnancy.

Keywords Male infertility · Unexplained infertility · Diagnosis · Azoospermia · Monogenic disorder

Introduction

According to the American Society for Reproductive Medicine, infertility is a disorder "defined by the failure to achieve a successful pregnancy after 12 months or more of appropriate, timed, unprotected intercourse or therapeutic donor insemination [1]." It affects 10–15% of couples, making it one of the most common disorders for individuals between the ages of 20 and 45 years [2].

Infertility can cause substantial emotional, social, and financial stress on couples. The majority of young Americans view parenthood as a future desired state [3]. The inability to meet this expectation leads to a variety of reactions including negative identity, a sense of inadequacy, a feeling of lack of personal control, grief and sense of loss, anger and resentment, anxiety and stress, low life satisfaction, depression, isolation, and shame [4–7].

These negative consequences extend beyond the individual. Within a couple, infertility-related stress can lead to marital distress and dissatisfaction [8]. Infertility in heterosexual couples affects each partner differently: more women have concerns about a loss of emotional intimacy in their relationship, while men more frequently experience a lack of sexual satisfaction due to pressure to perform for conception over pleasure [9]. Infertility may also cause challenges to the couple within the context of their society. In some pronatalist cultures including those from Israel, Pakistan, and Southern Africa, adult status is obtained by bearing children [6]. Childlessness leads to ostracism from the community, including grounds for divorce in some Bangladeshi settlements [6].

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There is also a tremendous financial burden to accessing fertility care and assisted reproductive technologies (ART), such as intrauterine insemination (IUI) and in vitro fertilization (IVF). In the USA, most patients pay out-of-pocket for treatments, as only six states mandate insurance coverage for infertility treatments [10]. The median out-of-pocket price for infertility treatments including couples receiving either non-cycle-based treatment, medication only, IUI, or IVF is $5338 [11]. The most expensive intervention is IVF, which has an average expense of $12,513 for one cycle, representing about half of an individual's annual disposable income (as calculated by average labor costs after taxes) [12]. In addition to treatment costs, time spent on office visits adds up to an average of two work weeks a year [13]. The problem worsens when considering that ART interventions may take a long time to be successful; at least six cycles with timed intercourse are necessary to cover the period in which 90% of conceptions will occur [14]. IUI and IVF are also used for couples with unexplained infertility, where the likelihood of achieving pregnancy is lower [15].

The high cost for treatment serves as a barrier for access to care. In the USA, couples earning a cumulative income of less than $100,000 are more likely to be dissuaded from choosing IVF intervention [11]. This leads to the ethical concern that the high out-of-pocket costs for infertility treatment discriminate against groups of lower socioeconomic status [10]. Moreover, disparities exist between the outcomes of infertility treatment; women of African American, Asian, and Hispanic backgrounds experience longer time to conception, lower implantation and clinical pregnancy rates, and higher miscarriage from ART than their Caucasian counterparts [16–18].

Men comprise the largest understudied group in infertility research and treatment, even though 40–50% of infertile couples have male factor infertility [19, 20]. While intracytoplasmic sperm injection (ICSI) and IVF now provide a more direct role for men in infertility treatment, women's bodies have been the focus of most medical interventions. The clinical file is sometimes linked with the woman's medical record and not her partner's, and men are not always a part of an infertility consultation [20, 21]. The disproportionate focus on the role of the woman in fertility is hypothesized to result from male-dominant cultures which blame women for fertility challenges as a way of deflecting a threat to male masculinity, potency, and virility [21–23]. Like most women, the majority of men desire parenthood and expect to be fathers [24, 25]. Facing an infertility diagnosis results in profound grief, loss of control, a sense of inadequacy, and isolation [26]. The exclusion of men from most scientific and psychosocial literature in the context of infertility means that less is known about the mechanisms underlying and consequences of male infertility [20]. This highlights an unmet need to understand male infertility.

An Overview of the Adult Male Reproductive System

Male fertility relies on the successful production of healthy gametes called spermatozoa. The male reproductive system can be broken into three distinct modules responsible for sperm development: pre-testicular, testicular, and post-testicular [2]. Pre-testicular contributions to gametogenesis rely on a properly functioning hypothalamic-pituitary-gonadal (HPG) axis, which uses hormones to signal initiation of gametogenesis in the testes [27]. The HPG axis begins with the hypothalamic secretion of gonadotropin-releasing hormone (GnRH), which promotes production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. LH stimulates Leydig cells in the testes to release testosterone, which together with FSH communicate with Sertoli cells in the testes to support sperm production [28]. Testosterone, along with inhibin B, facilitates negative feedback of the HPG axis by controlling activity from the hypothalamus and pituitary [27–29].

Spermatogenesis occurs in the seminiferous tubules of the testes. Germ cells develop in a spatially organized fashion from the basal membrane to the lumen [30]. Spermatogenesis involves the differentiation of primordial germ cells (spermatogonia) to mature sperm (spermatozoa) in a process that takes approximately 70 days [28]. Spermatogonia undergo several rounds of mitosis to renew the germ cell population while creating cells capable of differentiating. Some of these daughter cells develop into diploid primary spermatocytes, which become haploid secondary spermatocytes after the first meiotic division. Secondary spermatocytes differentiate into spermatids after a second meiotic division, which then mature into spermatozoa through a process called spermiogenesis [30]. Finally, mature sperm are released from the seminiferous epithelium through a process called spermiation [31].

The post-testicular phase involves final processing of semen for export out of the body through ejaculation. First, sperm in the seminiferous tubules are transported to the epididymis to undergo functional development through a process called epididymal maturation [31]. Next, semen enters the vas deferens and travels to the ejaculatory ducts, where it is combined with secretory products of male accessory glands including the seminal vesicle and the prostate [27]. The final ejaculate, which is composed of 10% sperm by volume, exits through the urethra [27, 28]. Sperm undergo a final maturation step called capacitation, which occurs in the female reproductive tract and enables sperm to develop a hyperactivated form of forward progressive motility, acrosome reaction, and the ability to penetrate and fertilize the egg [31].

Diagnostic Work-up for Male Infertility

A systematic diagnostic work-up is necessary to identify the best treatment options for infertile couples with male factor infertility. The World Health Organization's (WHO) current recommendation involves an initial evaluation including medical history, physical exam, and semen analysis followed by referral to a urologist, an andrologist, or another male reproduction specialist in cases of abnormal findings [32••]. The medical history in the initial evaluation first collects information about the reproductive history such as coital frequency, previous fertility, information about the partner's fertility, and sexual history including sexually transmitted infections [32••]. Patients are then asked about lifestyle factors, including BMI, smoking, and exposure to heat, which have been shown to influence semen parameters although diagnosing infertility by these factors is still controversial [32••, 33]. An understanding of medications taken can also inform a diagnosis as different drugs can reduce fertility by cytotoxicity from radiation with chemotherapy or inhibition of the HPG axis through exogenous testosterone [2]. Finally, questions are asked relating to anatomical dysfunction including proximal trauma, surgeries including vasectomies, torsion, cryptorchidism, erectile and ejaculatory dysfunction, and genitourinary infections [34].

After obtaining a medical history, signs of endocrine-related disorders, scrotal pathologies, and penile pathologies are investigated by physical exam [2]. A look at secondary sexual characteristics including musculature, hair distribution, and breast tissue can suggest a pre-testicular etiology including testosterone deficiency or hormonal imbalance [34]. A genital exam explores scrotal pathologies including varicoceles, abnormal testicular location, and small testicular size, which when atrophied below 12 ml may indicate primary testicular failure [2, 34]. Palpation of other structures can indicate forms of post-testicular obstruction including absence of the vas deferens [2, 34, 35••]. Finally, examination of the penis may reveal pathologies such as hypospadias that may indicate potential challenges with sperm placement into the vagina [34].

The final part of an initial evaluation is a semen analysis, as multiple semen parameters can be predictive of testicular production, function, and maturation [32••, 36, 37]. The work-up includes a single collection of ejaculate after 2 to 7 days of abstinence and assesses parameters including volume, pH, and sperm concentration, count, motility, morphology, and vitality [38]. A deviation from normal parameters can provide insight into a diagnosis (Table 1). Normozoospermia is described when the routine spermatozoa evaluation shows values above the lower reference value limits. Alternatively, results below the lower reference values for sperm volume, concentration, motility, and morphology describe hypospermia, oligozoospermia, asthenozoospermia, and teratozoospermia, respectively. Low sperm counts can further be delineated further based upon sperm concentrations less than five million/ml ejaculate (severe oligozoospermia),

Table 1 Lower reference limits of semen parameters

Parameter	Lower reference limit values
Macroscopic appearance	
Semen volume	≥ 1.5 ml
pH	≥ 7.2
Routine spermatozoa evaluation	
Total sperm count	≥ 39 million/ejaculate
Sperm concentration	≥ 15 million/ml
Total motility	≥ 40% progressive and non-progressive
Progressive motility	≥ 32% fast and slow
Sperm morphology	≥ 4% normal
Follow-up testing	
White blood cells (used if round cells are found on initial microscopic evaluation)	< 1 million/ml peroxidase-positive leukocytes
Mixed agglutination reaction (MAR) test or immunobead test (used if agglutination is found on initial microscopic evaluation)	< 50%
Vitality (used if total motility is < 40%)	≥ 58% live spermatozoa
Biochemical analysis of seminal fluids	
Zinc	≥ 2.4 μmol/ejaculate
Fructose	≥ 13 μmol/ejaculate
α-glucosidase	≥ 20 mU/ejaculate

Semen parameter reference limits are adapted from [2, 38, 39]

spermatozoa absent from fresh semen but visible in a pellet after centrifugation (cryptozoospermia), and the complete absence of sperm in the ejaculate (azoospermia) [39].

Parameters can also help explain the etiology of infertility. For example, after ruling out collection error, a low ejaculate volume may suggest potential retrograde ejaculation, ejaculatory duct obstruction, prostatitis, inflammation of the seminal vesicles, or androgen deficiency [35••, 40, 41]. A high concentration of white blood cells and very basic pH measurements can indicate infections [2]. Alternatively, agglutination of motile spermatozoa and confirmation of anti-sperm antibodies by mixed agglutination reaction (MAR) or immunobead testing support immunologic infertility [39]. Finally, low concentrations of seminal fluid markers including α-glucosidase, fructose, and zinc reflect potential obstruction in the epididymis, seminal vesicles, and prostate, respectively [2].

If an abnormality in sperm count or concentration is detected by initial evaluation and confirmed by a second semen analysis, then hormone analysis may be warranted to pinpoint further the etiology [32••]. The measurement of total testosterone concentration and serum FSH can help distinguish pretesticular from testicular and post-testicular etiologies [42, 43]. Low levels of testosterone (reference range > 12 nmol/l) and associated low serum FSH levels (reference range 1–7 IU/l) suggest hypogonadotropic hypogonadism, which can be treated with human chorionic gonadotropin (hCG) or FSH [2, 34, 44]. Testosterone can also be abnormally high in pretesticular etiologies if the patient uses exogenous testosterone or illicit anabolic androgenic steroids, in which case cessation of use can sometimes restore sperm production [35••, 44, 45]. Alternatively, high FSH often indicates primary testicular failure, with more severe defects including Sertoli cell-only syndrome (SCOS) correlating with more elevated FSH [2, 35••]. However, FSH may also be normal with testicular pathologies that occur later in spermatogenesis such as meiotic arrest [2, 43]. This may be hard to distinguish from post-testicular etiologies, which often show normal hormone levels [2, 35••]. To distinguish further the etiologies as a way of identifying proper treatments for a patient, a genetic work-up is then recommended [43].

Diagnostic Genetic Testing for Male Infertility

Currently, the most common genetic testing for male infertility involves sequencing of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, assessing Y chromosome microdeletions (YCMD), and karyotype analysis [2, 32••, 34, 35••, 46••, 47–50].

Variants in *CFTR* are found in 80–90% of cases of congenital bilateral absence of the vas deferens (CBAVD), a condition that occurs in 1–2% of infertile males and 25% of men with obstructive azoospermia (OA) [46••, 51]. While men harboring two variant *CFTR* alleles with severe functional defects have symptomatic cystic fibrosis, compound heterozygotes with less severe functional defects in *CFTR* or men with a single pathogenic allele may have only the CBAVD phenotype [51]. Absence of the vas deferens may be detected by physical exam, but a genetic understanding of the etiology is critical for proper treatment of a male with *CFTR* variants. While males with CBAVD resulting from *CTFR* pathogenic variants can have children with the assistance of ART such as testicular sperm extraction (TESE) followed by ICSI and IVF, genetic testing of *CFTR* is recommended for the biological mother. Carrier screening resulting in positive findings for the couple offers the subsequent option of pre-implantation genetic diagnosis (PGD) to eliminate the risk of transmitting cystic fibrosis to offspring [32••, 46••, 51]. While *ADGRG2* (encoding the epididymal- and efferent duct-specific adhesion G protein-coupled receptor G2) was identified recently as a second gene with variants causal for CBAVD when mutated, testing for this gene is not yet a routine part of diagnostic genetic testing for OA [52].

Males with non-obstructive azoospermia (NOA) or severe oligozoospermia should be tested for 0.8–7.7 Mb deletions in the azoospermia factor (AZF) region of the Y chromosome (or YCMD), which are found in 5–15% of these patients [32••, 49, 53]. The AZF region resides in Yq11 and is subdivided into AZFa (0.8 Mb), AZFb (6.2 Mb), and AZFc (3.5 Mb) [47, 49, 54]. The AZF region is critical for fertility because several genes responsible for spermatogenesis map therein including DEAD box polypeptide 3 (*DDX3Y*) in AZFa, lysine-specific demethylase 5D (*KDM5D*) in AZFb, and deleted in azoospermia (*DAZ*) in AZFc [55, 56]. These genes play a variety of roles in sperm development including RNA metabolism in pre-meiotic germ cells, chromatin remodeling in meiosis, and translation regulation, respectively [55, 56]. To identify which if any YCMDs are present, polymerase chain reaction (PCR) assays are performed for markers inside the region and flanking the borders of each AZF subregion [49, 57]. The diagnosis is critical because treatment options vary based upon the deletion. No spermatozoa will be found from TESE performed on men with complete AZFa, AZFb, or AZFb/c microdeletions, so treatment alternatives including donor sperm and adoption might be considered [32••, 49, 58]. Alternatively, males with complete AZFc deletions may have some residual spermatogenesis, with a 50% success rate from TESE [46••, 59]. Sperm cryopreservation is also warranted as sperm production decreases with age in men with AZFc deletions [59]. This knowledge is also important for genetic counseling, as any male offspring conceived from a male with an AZFc deletion will inherit the same Y chromosome. Thinking ahead, sperm cryopreservation in young adulthood for male offspring might be recommended in anticipation of decreasing spermatogenesis with age [32••].

Finally, karyotyping, which assesses the number and structure of chromosomes, is also recommended for all men with NOA or severe oligozoospermia, as 15% of men with NOA and 4% of men with moderate to severe oligozoospermia have chromosomal abnormalities [32••, 42, 49]. The most common finding for men with NOA is Klinefelter syndrome (47,XXY and variants such as 48,XXXY and 46,XY/47,XXY), which is found in 14% of their karyotypes [49, 60, 61]. This diagnosis is helpful for predicting the prognosis of TESE, as sperm retrieval has been successful in 40–50% of men with Klinefelter syndrome [62, 63]. Another sex chromosome abnormality that may be found is 46,XX testicular disorder of sex development (DSD), or de la Chapelle syndrome, which has a rarer frequency of 1 in 20,000 [49, 64, 65]. In most cases, the male phenotype results from a paternal translocation of the gene *SRY* (sex-determining region on the Y chromosome) from the short arm of the Y chromosome to the short arm of the X chromosome [64]. 46,XX testicular DSD males lack germinal cells, so TESE is not advisable [49, 64, 65].

Balanced chromosomal aberrations (BCAs), which have an abnormal order of the chromosomes without any cytologically detectable gain or loss of genetic material, are found five to ten times more frequently in infertile men than in the general population [57, 66]. BCAs can be categorized into Robertsonian translocations, reciprocal translocations involving a sex chromosome, reciprocal translocations with autosomes, insertions, and inversions [66]. Of these types of BCAs, reciprocal translocations involving sex chromosomes often result in more severe phenotypes with a higher incidence in azoospermic men than in oligozoospermic men [66]. Y;autosome (Y;A) translocations identified in azoospermic men often involve a breakpoint in Yq11, which disrupts the AZF region critical for spermatogenesis [66]. X;autosome (X;A) translocations are thought to impact fertility severely because they may lead to X-reactivation during meiotic prophase, disrupting critical meiotic sex chromosome inactivation (MSCI) [47, 67, 68].

The mechanism is less clear for other classes of BCAs, which have extremely variable outcomes ranging from azoospermia to normal semen parameters [46••]. There is a general assumption that individuals with BCAs produce unbalanced gametes as a product of meiosis, which are selected against during spermatogenesis resulting in a lower sperm count and subsequent infertility [47, 57]. However, this is not wholly true. While carriers of BCAs are more likely to have low sperm counts than karyotypically normal men, there is no significant relationship between fertility and sperm counts above 20 million/ml, so slight decreases in sperm count above that level do not imply a decrease in fertility [37]. In one cohort from the Czech Republic, the average sperm count of men with reciprocal translocations was 66.5 million/ml compared to 72.7 million/ml in controls, and less than 3% of reciprocal translocation carriers had a sperm count of < 5 million/ml [69]. In a Japanese cohort that used a cutoff of < 5 million/ml, there was no significant enrichment of BCA carriers in the NOA or severe oligozoospermia groups compared to controls [70]. It is also true that men with BCAs have more signs of spermatocyte apoptosis, such as externalized phosphatidylserine and DNA fragmentation [71], but this is not necessarily due to selection against unbalanced gametes. In male BCA carriers, the distributions of meiotic segregation products at different spermatogenic stages show concordance, suggesting that there is no cellular selection based on chromosomal imbalances from post-meiotic spermatocytes to mature spermatozoa [72].

Despite the common misinterpretation that carriers of BCAs have reduced fertility due to unbalanced gametes decreasing sperm count, it is true that unbalanced gametes double the risk of miscarriages [61, 73]. In 3–5% of couples with recurrent miscarriages, at least one partner is found by karyotype analysis to have a balanced reciprocal translocation [73]. In addition, unbalanced gametes can lead to congenital malformations in surviving offspring [61]. As a result, identification of a BCA can alter treatment options, as PGD with IVF provides identification of balanced or normal embryos prior to transfer [32••, 49].

Unexplained Infertility: Challenges and Opportunities

While many factors contribute to infertility, at least 20% of infertility cases are unexplained [47]. For male infertility, it is estimated that 40–72% of men lack a specific causal diagnosis beyond a descriptive category of male factor infertility [19, 46•, 50•]. Genetic defects may be responsible for many of these idiopathic cases, as mutations in over 600 genes have been shown to decrease fertility in animal models [74, 75•]. Most of these genes have not yet been linked to male infertility in humans, likely because of the decreased reproductive fitness of infertile individuals that reduces the number of large families available for human genetic analysis as well as the genetic heterogeneity of the disorder [50•, 76]. As a result, identifying genes involved in unexplained infertility could be a rich area of study [46••, 50•].

While not currently a routine diagnostic for male infertility, the application of array-based comparative genomic hybridization (aCGH) to investigate copy number variants (CNVs) in subjects with male infertility has revealed novel variants on both sex chromosomes and autosomes that are risk factors or causative for spermatogenic failure [77, 78]. Analysis of sperm DNA fragmentation, by methods such as DNA breakage detection fluorescence in situ hybridization (DBD-FISH) and in situ nick translation (ISNT), may also help predict a male infertility diagnosis [79, 80]. In addition, with the development of large-scale sequencing approaches through next-generation sequencing (NGS) and subsequent genome-wide

approaches in both small case studies and large consortia including the Genetics of Male Infertility Initiative (GEMINI) and the International Male Infertility Genomics Consortium (IMIGC), progress has been made in identifying monogenic forms of male infertility (Table 2) [49, 50•, 57, 76, 118–122].

Table 2 Monogenic causes of non-syndromic male infertility in humans

- Non-obstructive azoospermia (NOA) or severe oligozoospermia
  - *CCDC155* (618125) [76]
  - *DBY* (400010) [81]
  - *DNAH6* (603336) [82]
  - *FANCM* (609644) [83]
  - *HIWI* (605571) [84]
  - *KLHL10* (608778) [85]
  - *MCM8* (608187) [86]
  - *MEIOB* (617670) [82]
  - *NANOS2* (608228) [76]
  - *PLK4* (605031) [87]
  - *SPINK2* (605753) [88]
  - *SPO11* (605114) [76]
  - *SYCE1* (611486) [89]
  - *SYCP2* (604105) [90]
  - *SYCP3* (604759) [91]
  - *TAF4B* (601689) [92]
  - *TDRD7* (611258) [93]
  - *TDRD9* (617963) [94]
  - *TEX11* (300311) [95, 96]
  - *TEX14* (605792) [76, 82]
  - *TEX15* (605795) [97]
  - *WNK3* (300358) [76]
  - *XRCC2* (600375) [98, 99]
  - *ZMYND15* (614312) [92]
- Morphological and/or functional anomalies
  - Acephalic spermatozoa
    - *PMFBP1* (618085) [100]
    - *SUN5* (613942) [101]
  - Asthenozoospermia
    - *CATSPER1* (606389) [102]
    - *SLC26A8* (608480) [103]
  - Globozoospermia
    - *DPY19L2* (613893) [104, 105]
    - *SPATA16* (609856) [106]
  - Macrozoospermia
    - *AURKC* (603495) [107]
- Multiple morphological abnormalities of the sperm flagella (MMAF)
  - *ARMC2* (618424) [108]
  - *CFAP43* (617558) [109]
  - *CFAP44* (617559) [109]
  - *CFAP69* (617949) [110]
  - *DNAH1* (603332) [111, 112]
  - Oligoasthenoteratozoospermia (OAT)
    - *CDC14A* (603504) [113]
    - *SEPT12* (611562) [114, 115]
  - Oocyte activation failure
    - *PLCZ1* (608075) [116]

This list of genes has been self-curated for evidence of gene-disease association according to the Clinical Genome Resource (ClinGen) framework [117]. OMIM numbers are written in parentheses next to the gene symbol. A review of genes implicated in other forms of male infertility, including syndromic and endocrine disorder-based infertility, may be found in Oud et al. [75•]

Additionally, recent research from the Developmental Genome Anatomy Project (DGAP) has revealed another explanation for how BCAs reduce fertility. DGAP is an NIH-funded research study that identifies genes disrupted or dysregulated by chromosomal rearrangements in subjects with a BCA and a clinical finding presumed to have a genetic etiology. Genes disrupted or dysregulated by such rearrangements are a well-recognized paradigm in human genetics for underlying abnormal phenotypes [123–132]. By using this well-established DGAP infrastructure to investigate the phenotype of male infertility, our group recently uncovered dysregulation of *SYCP2* in a male with severe oligozoospermia and karyotype with a balanced translocation, 46,XY,t(20;22)(q13.3;q11.2) [90•]. Further exploration has demonstrated that dysregulation of *SYCP2*, which encodes a component of the lateral element substructure of the synaptonemal complex, is etiologic in the subject's phenotype. This suggests that genes disrupted or potentially dysregulated by rearrangement breakpoints should be evaluated for causality in infertile males with BCAs.

While mostly confined to the research realm, these discoveries will hopefully be employed clinically as they may be informative for predicting therapeutic outcomes in patients [46••, 133]. For example, men with *AURKC* mutations have sperm that are often polyploid [107]. Due to the high risk of aneuploidies from even normal-appearing spermatozoa, ICSI is not recommended for these patients [133]. Alternatively, men with *DPY19L2* or *SPATA16* pathogenic variants have globozoospermia characterized by acrosome-deficient sperm [104, 106]. Because of their inability to activate oocytes, artificial oocyte activation can improve outcomes for fertilization rate, embryo formation, and clinical pregnancy with ICSI and IVF [134, 135]. This is in contrast to men who have multiple morphological abnormalities of the sperm flagella (MMAF) with mutations from *ARMC2*, *CFAP43*, *CFAP44*, *CFAP69*, or *DNAH1*, where ICSI without any additional activation procedure is expected to have a high rate of success [46••, 109–111].

Conclusions

Infertility is a common disorder with widespread emotional, social, and financial consequences. To identify the best treatment for male infertility, a systematic diagnostic work-up is used to pinpoint the etiology. However, many infertile males still lack a specific causal diagnosis after this evaluation. Advances in genetic testing show promise in identifying new etiologies for male infertility. Future use of aCGH, NGS, gene panels, or investigation of rearrangement breakpoints in the case of BCA carriers may establish a definitive causal diagnosis, offer prognostic value for TESE and clinical pregnancy, and assess risks for potential offspring.

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Compliance With Ethical Standards

Conflict of Interest The author declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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