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What advances may the future bring to the diagnosis, treatment, and care of male sexual and reproductive health?

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Over the past 40 years, since the publication of the original *WHO Laboratory Manual for the Examination and Processing of Human Semen*, the laboratory methods used to evaluate semen markedly changed and benefited from improved precision and accuracy, as well as the development of new tests and improved, standardized methodologies. Herein, we present the impact of the changes put forth in the sixth edition together with our views of evolving technologies that may change the methods used for the routine semen analysis, up-and-coming areas for the development of new procedures, and diagnostic approaches that will help to extend the often-descriptive interpretations of several commonly performed semen tests that promise to provide etiologies for the abnormal semen parameters observed. As we look toward the publication of the seventh edition of the manual in approximately 10 years, we describe potential advances that could markedly impact the field of andrology in the future. (Fertil Steril® 2022;117:258–67. ©2021 by American Society for Reproductive Medicine.)

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With the publication of the 6th edition of the *WHO Laboratory Manual for the Examination and Processing of Human Semen*, the advances in the field of andrology to date are evident and reflect over 40 years of technical refinement of the routine semen analysis that improved the precision and accuracy of the procedure as well as the addition of new tests to evaluate semen characteristics or sperm function together with the removal of tests that are no longer widely employed (e.g., the postcoital cervical mucus penetration test). In this article, we look toward the future and discuss some of the impacts of this work to date, the emerging areas for the development of new procedures, as well as a glimpse of the future and thoughts about where the field will be headed over the next 10 years of the publication of this manual and its new editions to come.

DIAGNOSTIC APPROACHES WILL BE IMPROVED: BASIC SEMEN ANALYSIS WILL BE STANDARDIZED AND THUS THE RESULTS COMPARABLE THROUGHOUT THE WORLD

A plethora of data, including that from well-established Andrology External Quality Assurance schemes, independent of country of origin, demonstrate that there is considerable variability in the results of the basic semen analysis (1–3). There are several reasons for this, for example, lack of adherence to established methods, poor training, and/or the use of a variety of methods to perform the analysis (3). This variability has significant clinical ramifications because a semen analysis result in 1 laboratory may not be comparable to that in another. Moreover, it can make comparisons between data sets difficult. Although these issues are well documented and have been a continual source of concern, these challenges remain (4).

A focus of the 6th edition is to provide clear and standardized methods that focus among others on the basic analysis (Chapter 2 of the *WHO Laboratory Manual for the Examination and Processing of Human Semen* [5]). Providing simplified methods obviates a primary difficulty in performing high-quality semen analysis and helps address the reproducibility crisis that has beset semen analysis for a number of years. Moreover, because the basic techniques described are robust and easy to follow, it is anticipated that this will facilitate higher-quality training. However, on their own, simplified methods will not be sufficient. If, in the next 5–10 years, we are to achieve comparable results from semen analysis from different laboratories, complementary tactics need to be actioned.

There is an absolute need to have a renewed and reinvigorated approach to training andrology laboratorians in these methodologies. One challenge in improving regional, national, and global comparability in semen analysis has been the roadblock in training laboratory personnel in robust methods. This is slightly surprising because several well-proven methods for training staff are published (6) and many courses are available, for example, the European Society of Human Reproduction and Embryology (7, 8) and various courses put forth by the American Association of Bioanalysts, American Society of Andrology, and other societies worldwide.

Therefore, we understand how to train staff; however, in general, these methods can be expensive and are not widely used. Hands-on wet laboratory training is optimal. However, currently, with the travel restrictions in force for many working in healthcare institutions, this is not an option. Thus, a key limitation with in-person training courses is limited access. Therefore, we need to develop flexible training systems (on the basis of well-proven principles) that can be widely implemented. In this context, the coronavirus disease 2019 pandemic has opened a new world of learning and opportunity with the development of teaching methods that can be delivered in the virtual world using webinars and live, interactive presentations with video microscopy. There are now a whole host of sophisticated, proven tools to assist learning. Moreover, as both students and teachers, we are more familiar with these online approaches and, thus, more willing to adopt these educational modalities. Embracing, adapting, and employing these new methods, we can deliver flexible education and training programs in andrology to suit all manner of scenarios and requirements. We can be confident that we will be able to develop sophisticated and effective training systems for all staff. We envision the rapid development of a standardized training strategy and pre- and in-service training curricula in the near future on the basis of the current protocols published in the World Health Organization (WHO) 6th edition (5). This will be a major achievement in andrology and radically improve our ability to standardize basic semen analysis throughout the world.

Another aspect to improving standards in basic semen analysis is the very recent development of a formal International Organization for Standardization (ISO) standard (23162:2021) for Basic Semen Examination (9). This is the first time that this has been achieved. The ISO standards are based on the same principles as the sixth edition of the manual and specify the minimum requirements for equipment and critical aspects of methods for best practice. Adoption of these standards will support laboratories seeking accreditation. Moreover, because ISO is applicable through the world, adherence to this standard is likely to be manifested in an overall improvement in quality of semen assessment globally.

The reproducibility of scientific data is, of course, not a unique problem for andrology (10–12). Several tools suggested to address these challenges include the provision of robust materials and methods and checklist for publication in journals, for example, STAR methods in Cell Press journals (13). In andrology, we now have clear robust methods, and with new educational methods to use for staff training, we can look forward to a world where a robust semen analysis is the norm.

PARADIGM SHIFT IN THE PATHWAY FOR INVESTIGATIONS AND DIAGNOSIS OF MALE FACTOR INFERTILITY

Semen analysis, along with physical examination and history, is the cornerstone in the diagnosis of male factor

infertility (14–17). Currently, the analysis needs to be performed in a laboratory. However, in the 6th edition, there is a discussion on emerging technologies (Chapter 4.6 of the *WHO Laboratory Manual for the Examination and Processing of Human Semen* [5]), which may widen the availability of semen analysis into the community. One aspect identified was the potential use of home assays for the assessment of sperm motility. With the recent implementation of widespread telemedicine for several types of clinical office visits, it is not surprising that home assays for a variety of clinical diagnostic tests would be created. At-home testing in andrology has a long history (18, 19), and several new tests that assess sperm motility and/or concentration were recently launched (20). A number of kits commercially available today have yet to be rigorously evaluated in large-scale trials, including comprehensive comparisons with standardized laboratory methods, so their current clinical value in diagnosis is limited. However, technology is rapidly evolving, and as the assays improve, it is very likely that men assessing their own samples (providing robust and acceptable diagnostic information) will be a reality in the next 5 years. Therefore, patients will have a pivotal role to play in their own health management as witnessed in several other arenas, for example, blood glucose levels for diabetes and retinal imaging (21, 22). Once the technologies are demonstrated to be accurate and precise, there is a need to determine the role these assays play in the patient diagnostic pathway, for example, are they additional, complementary, or replacement tests, and can they be used to triage patients (23)? *The tests may be cheaper and easier to use than traveling to andrology laboratories for semen analysis. They can be used in large-population–based studies of lifestyle changes or potential environmental exposures and may help to identify infertility in men.* Certainly, these at-home or mail-in test kits could be particularly important for those living in rural or underdeveloped areas lacking sufficient healthcare, and at the very least, they may provide the patient with some data on their semen parameters pointing to the need for a clinical evaluation and diagnostic semen analysis if abnormalities are present. If positive answers are forthcoming, this will significantly increase effectiveness and patient satisfaction. The coronavirus disease 2019 pandemic has indicted that we can do more at-home testing to manage our healthcare than previously recognized.

TRANSFORMATIVE CHANGES IN QUALITY AND SPEED OF OBTAINING DATA FOR THE DIAGNOSIS AND PROGNOSIS OF MALE FACTOR INFERTILITY

The recent American Society for Reproductive Medicine/American Urological Association joint publication on the male factor infertility practice guidelines identified significant evidence gaps in both the diagnosis and treatment of male factor infertility (14–17). Yet, there are a relatively few clinical trials in the area implying that unless some things change, these gaps will remain (24, 25) (e.g., https://clinicaltrials.gov/; https://www.nihr.ac.uk/). However, this scenario is unlikely because real progress in this space will be made in the next 5 years. This optimism is formatted on the following 4 themes: first, our knowledge of the production, formation, and workings of a human spermatozoon is rapidly expanding. The burgeoning pipeline of knowledge will significantly facilitate the development of new diagnostic tools and encourage individuals to seek clinical evaluation and potential treatment regimes.

Second, we have new ways of collaborating together. Global initiatives to link colleagues in our discipline to transform the way we work, formulate, and address key questions are in place, for example, the Male Reproductive Health Initiative (https://www.eshre.eu/Specialty-groups/Special-Interest-Groups/Andrology/MRHI) and International Male Infertility Genomics Consortia (http://www.imigc.org/) (26). Moreover, several countries, such as Australia, developed a coordinated nationwide strategy for male reproductive health (Healthy Male: https://www.healthymale.org.au/). Male factor infertility is a substantial global health issue that necessitates a comprehensive and coordinated approach—we are now at the precipice of achieving this reality.

Third, concomitant with the aforementioned, our paradigm of how we organize and execute experiments is changing. This coupled with a global approach to male reproductive health makes it easier and more efficient to rapidly attain critical information. For example, Nichols et al. (27) outline "a more strategic approach to research focused on the accumulation of evidence via designed sequence of studies." In essence, they suggest an integrated approach to the design of studies to address key hypotheses to enable a more rapid synthesis of evidence than currently feasible.

Finally, there are a number of novel "artificial-intelligence" methods under development aimed at using machine-learning–based analysis of sperm. The application of these deep-learning classification methods to sperm was applied to routinely measured semen parameters, such as morphology (28–30) and motility (31). Other approaches used the measurement of sperm parameters critical to key sperm functions to predict fertilization potential of sperm, such as intracellular pH to assess capacitation to predict conventional fertilization success in normozoospermic patients (32), sperm videos to assess sperm motility (31), sperm selection for intracytoplasmic sperm injection (ICSI) in in vitro fertilization (IVF) on the basis of the classification of the sperm head, and sperm motility and/or DNA integrity (33). The application of powerful technology examining single cell heterogeneity and function in other disciplines is likely to be a fruitful line of investigation, for example, Cell Painting, which allows the assessment of several thousand features of each individual cell (34). These examples described are predicted to provide improved sperm selection, rather than using the somewhat subjective interpretation of the WHO criteria for morphology assessment that varies markedly between laboratories and even technologists. It is noteworthy to remember that in the embryology laboratory, strict morphology as described cannot be used on the sperm to be selected for ICSI on the basis of the WHO laboratory methods for assessing sperm

morphology, and these diagnostic methods were not designed for that purpose. There are likely to be several emerging technologies that will substantially affect the future diagnosis of male factor infertility.

Hence, the identification of other novel criteria of classification of live, functional sperm will be a powerful advance in the field. Again, the utilization of these computer-based technologies will revolutionize the approach to performing a semen analysis and andrology laboratory procedures. Adopting such methods, we are likely to rapidly enhance our understanding of the diagnosis and treatment of male reproductive failure as well as improve patient outcomes.

ADVANCES IN "-OMIC" TECHNOLOGIES AND SPERM BIOLOGY WILL PROVIDE SEVERAL NEW ADVANCED AND EXTENDED ASSAYS ASSESSING THE FUNCTIONAL COMPETENCE OF THE SPERMATOZOON

With the advent of various next-generation sequencing (whole exome and whole genome sequencing) and other "-omic" technologies (array comparative genomic hybridization)—transcriptomic, proteomic, metabolomic, lipidomic, glycomic, epigenomic, and other advanced technologies—we have witnessed an exponential increase in research reports on the molecular/cellular/system defects present in a wide variety of male reproductive deficiencies. As the mechanisms of action of these genetic, genomic, epigenetic, transcriptomic, proteomic, and metabolomic defects are defined, we will further define the etiologies of most causes of male reproductive deficiencies. For example, it is clear that damaging mutations and copy number variants (microdeletions and microduplications) causing changes in the expression levels of dosage-sensitive genes may affect reproductive system development (35–39) and function (40–42), as well as fetal, childhood, adolescent, and/or adult development and/or function of other organ systems in the body. Indeed, a search of the website, GeneCards (43), reveals that >3,600 genes have been reported to be associated with human male factor infertility when defective. Another >3,200 gene defects impacting male reproductive development and function (including encoding some of the proteins involved in sperm chromatin structure, such as the protamines and histones, and genes encoding protein ion channel, exchangers, and transporters, such as CATSPR and Slo3 K+ channels, discussed in Chapter 4 of the 6th edition of the *WHO Laboratory Manual for the Examination and Processing of Human Semen* [5]) are mentioned. Although the biochemical measurement of these later proteins in sperm is performed in some andrology laboratories throughout the world using biochemically based assays (5), the knowledge of the genes encoding these chromatin structure, ion channel, exchanger, and transporter proteins allows translation to the medical genetics diagnostic laboratories (44, 45). The identification of the specific genetic defects underlying sperm dysfunction will then allow not only a diagnosis of the defect but also an etiology.

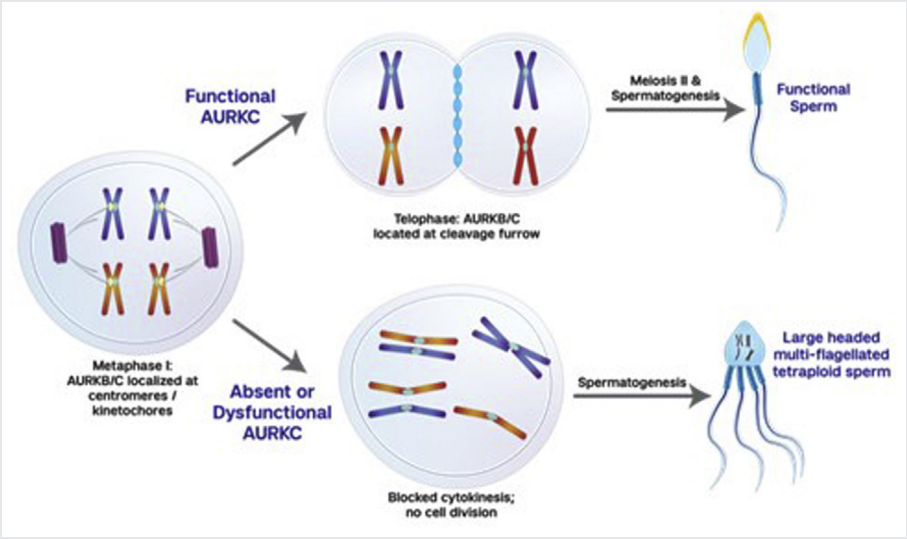
Other gene defects are associated with genitourinary birth defects (as reviewed by Punjani and Lamb [46]). While some but not all of approximately 6,000 genes have undergone rigorous testing to prove causation beyond an association and their mechanism of action (needed for a clearer understanding of the patient phenotype and, in some instances, drug discovery for new medical therapies), there is no doubt that this knowledge will prove to be informative in the future, as additional studies are performed to allow eventual translation for use in the evaluation of the male reproductive health. Thus, there will be improved clinical diagnosis and a personalized medicine-based approach to patient treatment.

THE ADVENT OF GENETIC AND GENOMIC TESTING MAY PARTIALLY REPLACE THE ROUTINE SEMEN ANALYSIS AND PROVIDE MORE DEFINED ETIOLOGIES FOR TERATOZOOSPERMIA, ASTHENOZOOSPERMIA, AND SPERMATOGENIC FAILURE

An impressive area of success showing the potential of these precision medicine-based genetic findings (but by no means the only one) is in the study of teratozoospermia (predominantly globozoospermia and macrozoospermia and/or asthenozoospermia [multiple abnormalities of the sperm flagella and primary ciliary dyskinesia]—sperm defects seen in the andrology laboratory during a routine semen analysis). Herein, the identification of defective genes encoding proteins involved in cytokinesis during meiosis (resulting in macrozoospermia [Fig. 1]), sperm flagella formation and function (Fig. 2) (resulting in a variety of anomalies seen in a routine semen analysis including absent, short, bent/misaligned, coiled, and irregularly shaped flagella and severe motility defects with occasional head anomalies) (47, 48), and globozoospermia (Fig. 3) is used clinically to counsel patients about their chances for successful ICSI-IVF outcomes or about other reproductive decisions regarding alternative paths to parenthood (as reviewed by Coutton et al. [47] and Wang et al. [48]). Future studies of these genes and the other >6,000 genes mentioned earlier are expected to have a powerful impact on improving the diagnosis and perhaps even medical treatment of some forms of male reproductive failure as well as providing some useful information about the probability of successful ICSI-IVF outcome for these and other male reproductive health concerns. Because many of these "male reproductive health"-related genes are expressed in select other tissues or even broadly throughout the body, it is likely that they are associated with additional health risks for men with reproductive failure (as reviewed by Punjani and Lamb [49], Brubaker et al. [50], Eisenberg et al. [51], Eisenberg et al. [52], Eisenberg et al. [53], Eisenberg et al. [54], Eisenberg et al. [55], Eisenberg et al. [56], Glazer et al. [57], and Hanson et al. [58]), the causes of which are currently largely unknown.

Regarding the area of medical comorbidities associated with male reproductive failure, current research focuses on whether infertility is the "canary in the coal mine" that foretells an increased likelihood of other diseases (49). Given the wide range of genes required for fertility (59–61), it is not

FIGURE 1



Macrozoospermia results from damaging mutations in aurora kinase C (AURKC). When AURKC is mutated, there is premature chromosome segregation, and cytokinesis is blocked during meiosis, resulting in large, headed multitailed, polyploid sperm formation. The c.144delC mutation is common in men of European and North African origin with macrozoospermia. For these men, intracytoplasmic sperm injection-in vitro fertilization is not recommended because the chances of a normal pregnancy are slim. AURKB/C = aurora kinase B/C.

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surprising to learn that male reproductive failure is associated with several other conditions. For disorders, such as low testosterone level or male hypogonadism (62, 63), it may be difficult to discern whether some associated conditions, such as malignancies and mortality, are a cause of decreased androgen action either through its cognate steroid receptor or signaling via a nongenomic pathway or whether the associated disease resulted in hypogonadism. Male hypogonadism is a risk for a number of conditions including diabetes, metabolic syndrome, cardiovascular disease, hypertension, and Alzheimer disease, but the reasons for this may be multifactorial. For some men, low testosterone levels may reflect poor health, sedentary lifestyles, obesity, or cardiovascular disease, whereas for others, it may represent their natural course of aging. The associations of male factor infertility with mortality (54, 63, 64), malignancies (not only testis cancer) (51, 58, 65–73) in infertile men and their family members (58, 64, 74), immune dysfunction (50, 57, 75), and other nonreproductive disorders (56, 76) remain to be clearly defined by additional research.

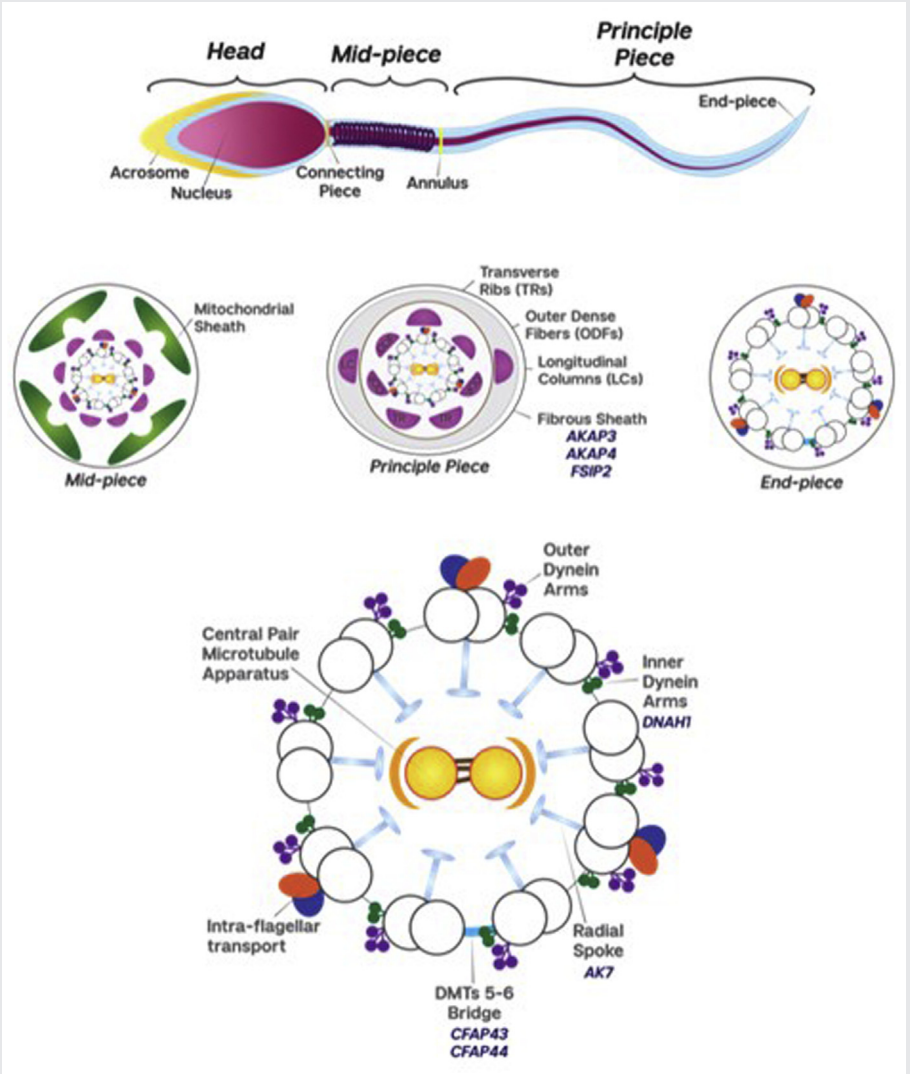
In other areas of medicine, such as nephrology or oncology, there is an increasing awareness that conditions thought to be isolated genetic defects (congenital birth defects and malignancies) are actually syndromic with an array of associated other anomalies that are present or may arise throughout the lifespan. There is an increased need for strong basic and translational research studies to define the molecular basis of male reproductive failure and identify new druggable targets to bypass or ameliorate deficiencies or impact protein overexpression that may underlie not only the reproductive failure but also the comorbidities.

THE PROMISE OF NOVEL THERAPEUTIC DEVELOPMENT IN AREAS SUCH AS STEM CELL REJUVENATION AFTER SPERMATOGENIC FAILURE OF TOXIC INSULT OR IN VITRO SPERMATOGENESIS MAY BE REALIZED

Over the past 70 years, the treatments available for male reproductive failure (with the exception of surgical approaches for obstructive and nonobstructive azoospermia/testicular microdissection with ICSI) remained relatively stagnant. Nevertheless, there are novel methods under development to effectively use spermatogonial stem cells to rejuvenate spermatogenesis after gonadotoxin exposures (e.g., chemotherapy) (77). The initial studies were predominantly performed in rodent models. A challenge with these studies in mouse models was that only a small fraction of transplanted spermatogonial stem cells could repopulate the tubules. However, Nakamura et al. (78) developed a strategy to rejuvenate the host mouse fertility using transient treatment with a chemical inhibitor of retinoic acid synthesis. If this therapy works well in humans, it will greatly enhance the likelihood of successful treatment of patients with secondary infertility after chemotherapy or radiation therapy by direct treatment of either the host or the cells in vitro. This advance using mouse models (78), together with the in vitro reconstitution of male germ cell development from mouse pluripotent stem cells (79), should result in a paradigm changes in not only our understanding of spermatogenesis but the ability to translate these in vivo and in vitro findings to the human.

Studies on human spermatogonial stem cells such as those mentioned earlier have been performed, although

FIGURE 2



Multiple morphological anomalies of the sperm flagella (MMAF) refer to sperm morphology anomalies usually associated with asthenoteratozoospermia. In men with asthenoteratozoospermia, there is a relatively high frequency of mutations in dynein axonemal heavy chain 1 (*DNAH1*), cilia and flagella associated protein 44 (*CFAP44*), and cilia and flagella associated protein (*CFAP43*) (these 3 protein defects account for approximately one-third 3 of MMAF cases) with mutations involving adenylate kinase 7 (*AK7*), cilia and flagella associated protein 69 (*CFAP69*), centrosomal protein 135 (*CEP135*), A-kinase anchoring protein 3 (AKAP3), or A-kinase anchoring protein 4 (AKAP4). As a result, structural defects of the centriole assembly, peri-axenome structure, and the axenome can be present, affecting the proximal centriole, 9 + 2 central pairs of microtubules, fibrous sheath and outer dense fibers, mitochondrial sheath, outer and inner dynein arms, radial spokes, and nexin-dynein regulation complex.

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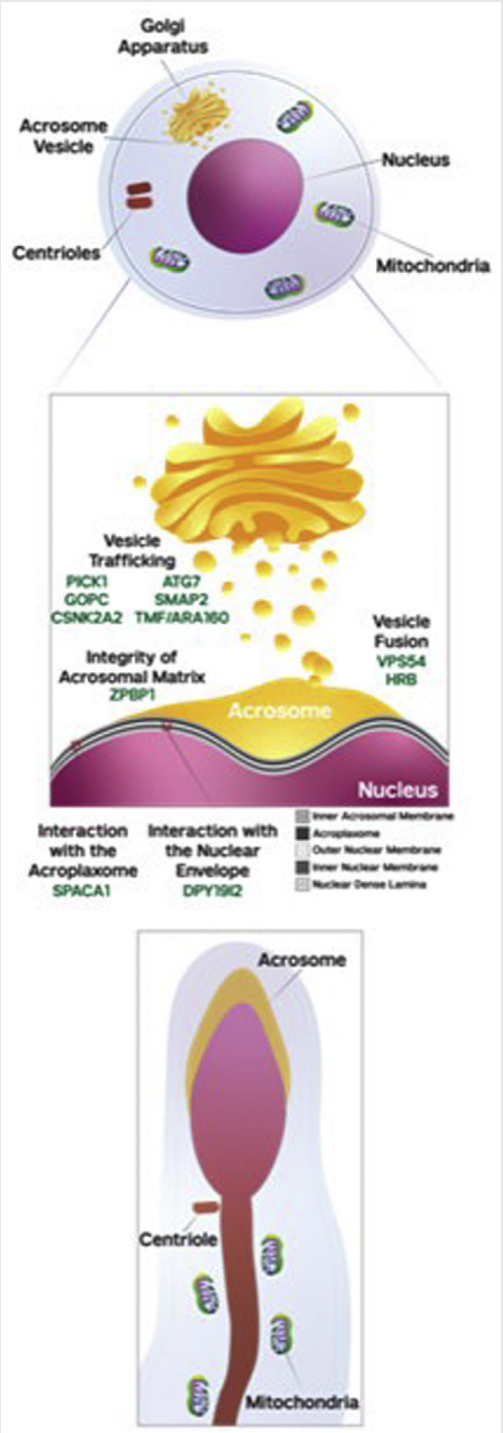
some results are controversial (because of the lack of a functional assay system). Important advances for this field are the molecular signatures identified in a human testis transcriptional atlas that defined 5 developmental spermatogonial states (as well as numerous other cell types and lineages in the testis), including a novel spermatogonial stem cell state (infant spermatogonial stem cell state 0) with several similarities to adult spermatogonial stem cell state (80, 81).

These human spermatogonial stem cells were also used to generate embryonic stem cell-like cells thought to have the potential to differentiate into the 3 developmental cell lineages and eventually functional tissues, which generated great interest in the lay press. However, reports of continuous culture of these pluripotent cells remain controversial, in large part because of methodological issues (81). In addition, even if the therapeutic use of human spermatogonial stem cell autotransplantation in cancer survivors becomes a possibility, there must be a high bar of safety because concerns remain regarding the potential for contamination of the spermatogonial stem cells with malignant cells. These cells must be

FIGURE 3



Genes encoding the critical proteins required for the acrosome biosynthesis. Globozoospermia is a sperm morphology anomaly that is readily identified in a routine semen analysis when the sperm appear round-headed with an absent, atrophied, or misplaced acrosome. There are 2 main defective genes commonly present in globozoospermic men. Spermatogenesis associated protein 16 (*SPATA16*) is highly expressed in human testis, and damaging mutations are identified in a significant percentage of globozoospermic men. A second gene, *DPY19L2*, exhibits either copy number variations (gene dosage changes) or damaging mutations that are more common in men in some different geographic and ethnic regions who show mainly type I globozoospermia with a high percentage of abnormal sperm. For men with complete globozoospermia, intracytoplasmic sperm injection with oocyte activation can be attempted, but the likelihood of achieving successful fertilization and live birth is significantly reduced compared with men with sperm with a normal acrosome.

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eliminated before autotransplantation to restore spermatogenesis after recovery in cancer survivors. Other possible approaches include employing iPS cells where adult somatic cells are programmed to differentiate into spermatogonial stem cells and reprograming of somatic cells to become spermatogonial stem cells. A method for the in vitro differentiation of human primordial germ cell-like cells from human-induced pluripotent stem cells and subsequently into M-prospermatogonia-like cells and T1 prospermatogonia-like cells using long-term cultured xenogeneic reconstituted testes was recently reported (82). These findings came about because of the rapidly expanding knowledge on the basis of the mechanisms of human germ cell development. There is no doubt that any technical issues that remain can be resolved in the future to allow eventual translation from the bench to the bedside to restore spermatogenesis in cancer survivors.

Alternative approaches using organ cultures, organoids, and other approaches to develop in vitro systems for completion and maintenance of spermatogenesis in vitro offer additional promise for the treatment of both secondary infertility and perhaps some forms of spermatogenic failure. In fact, researchers have tried for approximately 100 years to achieve complete spermatogenesis in vitro, and despite the recent marked advances beginning in the 1960s (83), the limited successes in recent years using mouse models have not been successfully directly applied for humans (84). In the past 20 years, qualitative but not quantitative spermatogenesis has been achieved in vitro culminating in live offspring, and various improvements have been employed including several microfluidic devices and 3-dimensional culture systems. Importantly, achieving complete spermiogenesis may no longer be required in vitro. There were significant concerns regarding the safety of round spermatid or nucleus injection after the case report from Zech et al. (85) after 4 pregnancies after round spermatid injection, with 2 cases resulting in major malformations. On the other hand, studies in animal models were encouraging. More recently, Tanaka et al. (86) reported the successful birth of 90 babies born after round spermatid injection into oocytes and their normal physical and cognitive development up to 2 years of age. A clinical trial is ongoing to further substantiate this earlier observation. Thus, the need for completion of spermiogenesis in vitro may not be necessary for the subsequent use of the spermatids with intracytoplasmic injection. With increasing knowledge of the delicate and species-specific microenvironments needed for the completion of spermatogenesis, researchers are moving closer to achieving this goal while still maintaining the genetic, genomic, and epigenomic integrity of the sperm (84). Despite the steady research advances realized in this field, additional studies will be required before this is achieved with human samples given the biologic complexity of spermatogenesis and testis function.

THE IMPACT OF THESE CURRENT AND FUTURE ADVANCES

In closing, the continued improvement of procedures for the laboratory evaluation and processing of human semen over the past >40 years has expanded the knowledge of male reproductive function and diagnosis of specific forms of dysfunction and set the stage for large multinational studies of semen parameters and characteristics worldwide. The improved rigor, precision, and accuracy that the current standardized protocols describe will now set the stage for advanced clinical trials aimed at filling the significant evidence gaps in both the diagnosis and treatment of male factor infertility needed to improve clinical care (14–17). In addition, the genomic revolution now allows the clinical diagnostic laboratories to realize quantum leaps in improved patient diagnosis in several areas of medicine. In andrology, we are on the forefront of vastly improving our diagnostic abilities to define precise etiologies and comorbidities and eventually (perhaps) develop medically based treatments for men with reproductive failure to improve not only their fertility potential but also their overall health. Translation of the new technologies described earlier (spermatogonial stem cell transplantation and spermatogenesis in vitro) to serve the clinical needs will require additional research. In the future, these methods should move from the laboratory to the clinical arena to provide therapeutic options for men with reproductive health-related conditions. However, because of the complexity of the systems involved and the substantial risks that otherwise healthy individual may be subjected to, there must be a high bar to ensure safety and a positive outcome. Despite these caveats, certainly, the future looks promising for improving the health and fertility of the male with reproductive failure through precision medicine and the application of advanced technologies for advanced diagnosis and treatment.

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