Personalized Medicine in Infertile Men

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KEYWORDS

• Male infertility • Personalized medicine • Sperm • Molecular biomarkers • OMICS

KEY POINTS

- Male infertility is a heterogeneous disorder that is responsible for 30% of cases of infertility in the couple. Occasionally, its diagnose remain incomplete or unknown.
- Personalized medicine is a new approach in clinical assistance, providing a prevention, diagnose and treatment tailored for each patient.
- The omics technologies enhance the knowledge in the human reproduction field, permitting a deeper insight of male gamete and the molecular origin of infertility.
- The identification of novel molecules involved in sperm function and used them as biomarkers may provide a new diagnostic tool and the improvement of sperm selection techniques.
- Personalized medicine promises to be a both diagnostic and therapeutic tool in the clinic management of male infertility, providing a new medical approach toward individualization of infertility treatment.

WHAT IS PERSONALIZED MEDICINE?

Personalized medicine can be defined as the application of specific medical techniques, drugs and/or processes to individual patients to prevent, diagnose, or cure disease, in contrast with the old approach of treating them all similarly, based on the detailed knowledge of unique and explicit characteristics of the individual's and the disease, at either the genotype, physiology, environmental exposure, or lifestyle, among other factors, levels in a precise and tailor-made form. It is a revolutionary approach for disease prevention and treatment that considers individual variability into all areas of health care.[1] To this end, knowing the exact causes of the disease, and the underlying physiology, is key when trying to develop tools to treat, and from this approach, more effectively, efficiently, and with fewer side effects, are expected thus resulting in a benefit for all patients.

Similarly, this term is often also designated as precision medicine, aiming, for instance, to stratify diseases, patients, or responses to drugs in taxonomic groups, and to predict more accurately which treatment and prevention strategies for particular disorders will be efficient in homogeneous groups of people.[2,3] It is a change compared with the traditional one-size-fits-all approach, in which both the disease prevention and treatment are designed for the average person or population. This new strategy makes medicine personalized, preventive, predictive, and participatory for each patient.[3]

These concepts were born at the beginning of the 21st century, just after the publication of the Human Genome Project in 2003.[4] Thanks to this revolutionary milestone, the way of understanding the diagnosis and treatment of human diseases has evolved from generality to individuality, and such transformation has been possible owing, among other factors, to the development in

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Urol Clin N Am 47 (2020) 245–255
https://doi.org/10.1016/j.ucl.2019.12.011

parallel of high-output molecular analyses techniques and computational tools based on big data and large-scale data management, for instance, from the different -omic sciences.[5,6] All these developments permitted imagining a new approach, unthinkable just decades before.

This change in health management includes a deeper comprehension about individual's information to determine predisposition to specific diseases and to predict the efficacy or safety of treatments, as well as opening the possibility to develop patient-specific treating approaches. The aim is to provide personalized assistance in[7]:

- Prevention: analysis of (among other factors) genomic information to know the individual susceptibility to develop a disease, allowing its early detection rather than their observing later clinical manifestations, and also, to improve the ability to predict which treatment will work best in each case, to increase efficiency.[6,8]
- Diagnosis: understanding of the origin, underlying risk factors, molecular mechanisms involved, and genetic variants responsible of the occurrence of the disease to develop and use specific biomarkers to detect, classify, and monitor the course of disease.[2,9,10]
- Treatment: establish a specific therapy based on the disease's intrinsic and specific features[5] and tailored to the patient, considering the genetic, biochemical, physiologic and environmental patient's traits.[1,2]

To date, as an example, there are approaches to personalized medicine at different levels, in medical specialties such as oncology and immunology, where the approach to the problem goes from the study of the genetic profile of the patient and the disease (as in the case of tumors), to some cases where a personalized medical treatment can be established and adjusted to increase the effectiveness and possibilities of recovery, against what the historical method to solve the health problem has been.[1,11]

The wider application of such methods in other medicine fields is expected to be introduced sooner than later, and the current trend from general to more specific, and even personalized approaches, in preventing, diagnosing, and treating are now, to some extent, often present when dealing with infertile patients, including infertile males.

WHAT IS KNOWN ABOUT MALE INFERTILITY, WHAT REMAINS TO BE DEFINED, AND HOW CLOSE ARE WE TO THE PERSONALIZED MEDICINE IN MALE INFERTILITY

The social impact of infertility can be considered high, because nearly 15% of couples at their reproductive ages are unable to conceive after 1 year of unprotected intercourse.[12] According to the American Society for Reproductive Medicine, male factor infertility is responsible for 30% of cases of infertility in the couple and roughly speaking 40% can be attributed to female causes. The remaining 30% is usually classified as caused by the combination of both female and male factors, or simply remains unexplained so far (the so-called idiopathic infertility).[13,14]

Male infertility, considered as the inability of a male to satisfy his reproductive aims through sexual intercourse, can be considered as a multifactorial disorder, in some cases caused by known and specific causes such as chromosomal abnormalities, infections, gene mutations, varicocele, hormonal disruption, or reproductive tract obstructions, among others,[15] that result in the impossibility or reduction of the conceiving likelihood. These causes can be temporary or permanent, and can also be divided between men able to produce low numbers and/or physiologically incompetent spermatozoa, or those unable to complete spermatogenesis.

From this variety of possibilities, it seems obvious that there is a need to approach each case individually.

Currently, the routine evaluation of male infertility is mainly based on semen analysis. This technique evaluates semen quality by means of measuring the ejaculate macro and microscopic parameters as sperm cell density, motility, morphology and viability, according to World Health Organization's manual criteria.[16]

However, it does not provide predictive information on the fertile potential in males, nor for fertilization or the assisted reproduction treatment success.[17] A normal result of semen analysis does not guarantee fertility and none of the semen parameters indicate a proper sperm physiologic function. In fact, 30% of normozoospermic men are unable to achieve pregnancy.[18] This limitation as a predictive test does not imply that basic semen analysis results are not a cost-effective way to estimate fertility potential, decide which are the most convenient therapeutic approaches and assisted reproduction techniques to be used, and also detect cases where additional tests may be required to better discern the causes of infertility and/or avoid reproductive risks to the offspring.

Facing that situation, a more detailed physical and clinical examination should be performed.[19] For instance, the absence of spermatozoa or the presence of abnormal sperm in the ejaculate may reflect chromosomic disorders. Nowadays, to investigate the genetic origin of a disrupted

spermatogenesis, the clinically relevant test are karyotype and Y-linked microdeletions assays.[15]

The karyotype is one of the genetic tests used to complement male infertility evaluation where the sperm counts are low and permits the chromosome structure to be examined. The karyotype anomalies are related to chromosomic deletions or translocations, that, ultimately, affect sperm production,[20,21] showing reduction in sperm concentration.

In contrast, the study of the microdeletions of the Y-chromosome is performed to inspect the chromosome integrity. These microdeletions affect azoospermia factor genes and it is associated with severe oligospermic and azoospermic men. Clinical evaluation of Y-chromosome microdeletions may the opportunity to find sperm in a testicular biopsy,[15,22] and also the possibility to transmit this condition to the progeny. Genetic counseling is needed in these cases.[22]

This clinical evaluation of male infertility is to some extent superficial and limited, and does not examine the concomitant sperm physiology related to fertility. Spermatozoa can be considered as the most specialized cells within the human body. The male gamete is more than the carrier of genetic information from the progenitor, because it provides, among other things, proteins and RNA-rich cytoplasm to the future embryo,[23,24] that are well-related with reproductive success.

The spermatogenesis is a complex and highly specific process that requires an exact coordination of the molecular pathways involved.[25] A failure in these processes involves the formation of immature and/or dysfunctional sperm cells. If the sperm's competence to trigger a correct embryonic development is compromised, it will be reflected in poor results in assisted reproduction cycles.

The molecular factors related to fertilization failures, poor embryonic quality, or poor clinical outcomes cannot be completely explained with conventional semen analyses so far. Besides, there are other sperm intrinsic characteristics impossible to be assessed only by means of spermiogram requiring other specific tests.[26] Within such characteristics, one may find DNA fragmentation, chromatin compaction, membrane integrity, and maturity or apoptosis level,[23,26] and also a significant number of investigational tests not translated yet to the clinical practice, but pretending to satisfy a personalized medicine approach. This fact clearly denotes the need to develop new male infertility tests. The improvements required are closely link with the need to find and to select the best quality sperm before attempting in vitro fertilization or intracytoplasmic sperm injection (ICSI)[27] to achieve an ongoing pregnancy and a healthy infant, or enabling the selection of one specific sperm sample among several ejaculates from the same male because of their specific probabilities of success. Sperm selection techniques based on molecular traits are going to be one of the strategies designed with this purpose. The objective of these methods is to isolate sperm with the best characteristics from the seminal sample to fertilize the oocytes,[28] mimicking the natural selection process realized by the female reproductive tract.[23]

Broadly, these techniques select or deselect sperm based on their molecular characteristics, such as apoptosis markers (like in magnetic activated cell sorting), sperm surface charge, or its ability to bind to hyaluronic acid (physiologic intracytoplasmic sperm injection). In contrast, other selection techniques assess the male gamete morphology at higher magnification (intracytoplasmic morphologically selected sperm injection) or its birefringence.[23,27,28]

With these techniques, the sperm cell is not damaged, nor is integrity endangered, and after isolating them, the spermatozoa can be used for reproduction purposes coupled with assisted reproduction techniques afterward. Currently, some of the molecules linked to fertility in sperm, where a specific sperm selection methodology has been developed and are currently available to select sperm are phosphatidyl serine (apoptosis marker), ubiquitin (defective sperm marker), and phospholipase A2 (sperm capacitation).[23] Conversely, negative selection isolates a sperm pool with inadequate molecular characteristics, discarding them, and enriching in physiologically better spermatozoa, ultimately obtaining a seminal sample enriched with the most competent cells is obtained, aiming to improve the success of assisted reproduction treatments.[29]

Nevertheless, despite the theoretic benefit of these selection methods, the latest reviews noted that clinical outcomes (implantation, pregnancy, and live birth rates) cannot be enhanced by means of current sperm selection techniques,[27,28] or in other cases, clinical information is still lacking. At present, regardless of an active effort to identify the causes of male infertility, a lot of men are undiagnosed and other are unable to have offspring without a justified reason.

New diagnostic techniques are necessary to ascertain the cause of infertility and to recognize both semen and sperm quality, and to design appropriate strategies for fertility treatment or sperm selection, optimizing clinical outcomes.[23] In this respect, personalized medicine is a new approach in the diagnosis of male infertility and its clinical treatment.

PERSONALIZED REPRODUCTIVE MEDICINE

Personalized medicine approaches have a great potential as diagnostic and therapeutic tool in the field of human reproduction and infertility treatment. Knowing the different molecular and pathophysiologic mechanisms that result in infertility is one of the focal points from which to establish an appropriate diagnosis and treatment for each couple.

Individual differences in disease development and in response to medication as a result of genetic and environment differences are evident. Therefore, the classical one-size-fits-all approach in infertility treatments does no benefit everyone and should be abandoned. The focus of assisted reproduction techniques should to evolve toward individualization of infertility treatment, tailoring the treatment according to the patient's conditions and requirements, with the aim to increase the chance of achieving a live birth. In this sense, personalized reproductive medicine is a good opportunity to improve the efficiency of assisted reproduction treatments and their cost effectiveness, decreasing both the number of cycles needed and the cost of treatment, as well as diminishing the patient's emotional burden.[30]

This approach has already been applied in the management of female infertility. Treatment individualization is carried out in ovarian stimulation protocols, tailored to their own prediction of ovarian response. For instance, the anti-Mullerian hormone value and the antral follicle count determine the dosses necessary for ovarian stimulation, avoiding both a poor or hyper response.[31] Another example is embryo transfer according to the receptivity stage of endometrium (window of implantation), which differs between patients.[32] This strategy maximizes the chances of implantation in cases where the patient shows a displacement on the receptive period, and consequently, pregnancy likelihood.

Nonetheless, male infertility remains partly unexplored, and greater effort is needed to optimize diagnosis and treatment. Owing to the limitations presented by semen analysis as a diagnostic (and predictive) tool, new effective methods should be created for the establishment of the infertility etiology, identification of fertilization potential, and prediction of the most efficacy therapy.

Personalized medicine can largely benefit male's reproductive health by helping to prevent, diagnose and treat diseases related to the male reproductive system.[33] For example, understanding how genes are associated with certain disease onset has been helpful in, for example, prostate cancer and benign prostatic hyperplasia.

Patients who carry a mutation may know the susceptibility to develop a specific disease; being a BRCA1/2 or HOXB13 gene mutation carrier increases prostate cancer risk, but also allows for the planning of an appropriate prevention program. In patients with benign prostatic hyperplasia, different single nucleotide polymorphism variants are associated with different degrees of disease aggressiveness. In both cases, its understanding led to the development of targeted pharmacogenomic therapies that improve healing.[34]

Personalized medicine in male infertility management seems promising. Technological advances have unraveled a myriad of molecular factors involved in reproduction function and, thus, sperm physiology.

The emergence of *omic* sciences is currently permitting to enhance the knowledge in this field, thereby getting a deeper insight of the male gamete, with the intention of finding pivotal molecules of the biological processes and to determine the genetic and/or molecular cause of male infertility.[35–37] They also aim to discover certain molecules that can be used as sperm novel biomarkers and/or therapeutic targets.[1,24,31,32]

NEW APPROACHES: OMICS TECHNOLOGY AS A DIAGNOSTIC TOOL AND INFERTILITY BIOMARKERS

To be able to personalize medical treatments, the physiologic function of the involved cells is mandatory. Knowing the exact causes of disease may lead to define the exact way of treating it. To this end, in recent years, the development of high-output technologies permitted a detailed examination of infertility-related causes, moving forward and advancing this path.

The omics sciences study molecules and their interactions, and the processes that occur from DNA to biological function. This technology provides a large-scale information about genes, proteins, and metabolites, at a relatively low cost and effort. The identification of novel molecules involved in sperm function and the development of sperm selection techniques are essential to improve existing diagnosis and treatment of male infertility in a personalized manner. To this end, several approaches have been attempted.

Genomics

Genomics studies the set of genes of an individual. In the last years, there has been an exponential growth in knowledge of genes related to human fertility. More than a thousand genes have been correlated with human male fertility,[38] so far. Spermatogenesis is a complex biological process in

which several genes are implicated. An impairment or alteration on their expression is reflected by producing defective sperm germ cells that are unable to fulfill their tasks.

Genomic and GWAS studies have concluded definitely that male infertility is frequently a heterogeneous disorder,[38–40] which makes its diagnose and management extremely complicated. Defects in these genes decreased the male reproductive potential, as exposed by Matzuk's study. Gene mutations or single nucleotide polymorphisms[41] are linked to spermatogenesis failures, which are shown as an abnormal male gamete's production, different degrees of oligospermia, azoospermia, or sperm morphologic defects.[25]

Last-generation technology such as arrays comparative genomic hybridization allowed for the analysis of a large set of genes, to identify in infertile individuals which genes are mutated and which are not. These genes and their genetic variants are likely to be diagnostic biomarkers of male infertility.

A review of the items published to date shows a large number of genes involved, but none definitively causing infertility by themselves. For example, USPD8 and UBD are related to decreased sperm quality, H[39] whereas ATM, AURKC, and BRCA2 are associated with defects in sperm production, morphology, and motility.[25] Some polymorphisms in the hormone-sensitive lipase modify the sperm lipid's metabolism and conferred a greater risk for infertility in carrier individuals.[42]

The difficulty of genomic studies resides in the huge number of genes that are analyzed, and which of these might be used as biomarkers, to define therapies related to each specific alteration. An understanding of the number of genes involved and their interaction with others to increase the risk of infertility should be one of the subsequent objectives of reproductive male genetics. Pinpointing these risk genes or their variants could be used to create a multigene panel testing for male infertility. With this analysis, it would ne possible to screen a hundred or more risk alleles simultaneously.[11]

Nowadays, similar multigene panel tests are used to assess breast cancer risk.[43] Recently, as an example, an American company has created Fertilome (Celmatix Inc., New York, NY), a multigene panel testing for evaluating the woman infertility.[44] Fertilome technology examines a set of risk genes (49 specific single nucleotide variants in 32 genes) implicated in various adverse reproductive conditions in women.[43,44]

Likewise, if the male infertility risk alleles were identified, a multigene panel testing could be created. That offers the possibility of a more efficient and comprehensive clinical evaluation of men who attend an assisted reproduction clinic. On balance, multigene panel testing will be able to used like a personalized medicine tool in the male infertility diagnose. Further studies into the clinical benefit and cost effectiveness of these genetic test are needed. In addition, research to validate all the risk alleles and to identify their action's mechanism will make the multigene panel testing more reliable.

Transcriptomics

The term transcriptomics refers to the science that evaluates the total content of RNAs, which reflects gene expression profiles within cells or tissues. It is well-known that sperm RNAs play a pivotal role in fertilization and early embryonic development,[45,46] hence the importance of their evaluation.

Examination of the messenger RNA profiles of sperm samples can be used as a diagnostic tool in fertility.[47,48] Transcriptomics assays provide a more detailed understanding of spermatozoon-related gene expression among fertile and infertile men. The transcriptomic profile may be used in seminal plasma or in sperm. In the latter, as an invasive method, the analyzed sperm cannot be used in the subsequent assisted reproduction technique.[35]

Numerous studies found differentially expressed genes in infertile men. Profound discrepancies in messenger RNA sperm expression profiles between fertile and infertile men (with normal semen parameters) was found.[49] Indeed, PRM1/2, SPZ-1, and CREM transcripts were identified to be potential biomarkers.[24] The review carried out by Jodar and colleagues[45] summarizes several upregulated or downregulated sperm transcripts in different male's pathologic conditions. Furthermore, it exposes the essential role of small noncoding RNAs in sperm competence and in early embryonic development.[45]

Likewise, different messenger RNAs expression pattern was found in patients with Sertoli cell-only syndrome, obstructive and nonobstructive azoospermia (NOA), asthenozoospermia, and in those patients with fertilization failures and idiopathic infertility.[47] Moreover, the transcriptomic sperm profile after ICSI was different among who obtained a viable pregnancy and those that did not. In the pregnancy group, 44 sperm transcripts exhibited increased expression levels.[50]

The sperm RNA expression profile could be a tool to assess seminal quality and to predict the reproductive success. This technology could complement basic semen analysis and evaluate the

individual molecular pattern associated with patient's fertile potential.[51] Despite the previous studies revealed that the individual's transcriptomic profile may be a potential diagnostic method, further investigation, and clinical validation are required.

Proteomics

Another approach is provided by the Proteomics, which evaluates both the structure and function of cell and tissue's proteins. This new science has been used in the study of human reproduction, giving rise to a deeper insight in all involved the physiologic processes and molecules. In addition, it leads to the discovery of numerous proteins susceptible to be biomarkers or therapeutic targets.

The purpose of proteomics in precision medicine is to make a noninvasive differential diagnosis among fertile or infertile patients and identified the molecular origin of male's infertility.[35] The semen analysis by proteomic technology reveals proteins that may be engaged in the infertility condition.[52] Because the semen contains the sperm fraction and seminal plasma,[53] together with the fact that proteins may belong to seminal plasma, sperm, or both,[54] the analysis by proteomics technology becomes complex.

The seminal plasma is the result of the secretion of the prostate, seminal vesicles, and bulbourethral glands. It is a protein-rich fluid and creates an ideal environment for spermatozoon survival.[54] Within seminal plasma, there are only tissue-specific proteins owing to the blood–testis barrier, thus generating specific male biomarkers.[4]

Historically, the study of unique seminal plasma proteins showed which are the most abundant (lactoferrin, semenogelin 1/2, transferrin, laminin),[39] whereas others are used nowadays as biomarkers to screen the men's health status (prostate-specific antigen, prostatic acid phosphatase, and semenogelin).[55,56]

Several reviews expose which potential infertility biomarkers were found in the seminal plasma proteome. Eventually, there are differently expressed proteins in those men with a pathologic condition: abnormal seminal parameters (as oligospermia, asthenospermia, or teratospermia), azoospermia, varicocele, and idiopathic infertility.[33,50,53,57,58] A review by Kovac and associates[39] review highlights some of the proteins likely to be biomarkers of male infertility, such as prolactin-inducible protein, HAS, SPAG11B, and TEXT101.

Going into detail, the proteins TEXT101 and ECM1 are 2 effective biomarkers for the noninvasive diagnosis of azoospermia type.[59] Testicular biopsy is the only method to discern between obstructive azoospermia (OA) and NOA, a highly invasive procedure. ECM1 protein is able to differentiate an obstructive azoospermia from NOA (or a normal spermatogenesis), with high sensitivity and specificity.[59]

In contrast, TEXT101 distinguishes an OA from an NOA and discriminate the NOA subtypes.[59,60] Differential expression of TEXT101 diagnoses a hypospermatogenesis or maturation arrest, in which it is possible to find few foci of spermatogenesis, from Sertoli cell-only syndrome, in which there is no sperm production.

The clinical value of TEXT101 is that it would be able to assess vasectomy success, distinguish the NOA subtype, and predict the outcome of sperm retrieval procedures, or avoid testicular biopsy.[60] Clinical assays of these 2 proteins offer a noninvasive and differential diagnosis, establishing the clinical action strategy.

Although in this case the analysis can be considered as invasive, because each analyzed sperm will be destroyed, the specific spermatozoa proteome has also been evaluated, providing a further understanding of protein localization (head, midpiece, or tail)[53] and function. Sperm proteins have a key role in the sperm morphology and motility, and in all physiologic events which sperm performs to achieve oocyte fertilization.[53] Furthermore, its proteins undergo significant posttranslational modifications (like ubiquitination, acetylation, phosphorylation, methylation),[40,57] increasing male gamete complexity.

The aim is unveiling the molecular factors involved in correct sperm function, to then evaluate how this information can be used clinically to improve reproductive results in a personalized way.

The proteome study provided numerous novel biomarkers that promise to be a male infertility diagnostic tool associated with a pathologic condition.[39] These proteins can be used as a sperm-selective tool, using the magnetic activated cell sorting technique or flow cytometry, to isolate sperm with a specific characteristic of the seminal sample.[28,29] A protein must be in the external sperm membrane to act as a selection device and to be a proven fertility biomarker.

The proteome assessment of asthenozoospermic men and normozoospermic donors concluded that there are 17 differentially expressed proteins. In fact, 14 of these 17 proteins belong to 3 functional domains: structure and movement, cell energy production, and cell signaling.[61] The analysis of the spermatic proteome of normozoospermic but infertile men revealed the 3 impaired metabolic pathways involved: motility, training, acrosomic reaction, and in oocyte–sperm communication.[62]

Additionally, differences in sperm proteins expression patterns in men with infertility (both primary and secondary) where found when compared with the proteome of proven fertility men. Validation analyzes showed that the BAG6 (underexpressed) and HIST1H2BA (overexpressed) proteins are also important candidates to be infertility biomarkers.[57]

The sperm proteome analysis of men with idiopathic infertility but normozoospermic identified 3 proteins (Annexin A2, Sp17, and SERPINAS) as potential noninvasive biomarkers of infertility.[18] ANXA 1 and 2 expression was related with DNA integrity, suggesting their use as new biomarkers in combination with transcriptomic analyses.[63]

In summary, proteomics techniques allow comparing protein profiles in 2 different biological conditions. The ultimate purpose is to design new and noninvasive diagnostic tools and to enhance sperm selection techniques, presuming an improvement in the success rates in assisted reproduction techniques. Nevertheless, it is required the clinical validation of the proteins recognized as potential infertility biomarkers and to confirm that these proteins can diagnose male infertility with high sensitivity and specificity.

Metabolomics

Metabolomics studies the biochemical compounds that cell generates and/or uses owing to its metabolism. Metabolomic study complements the information provided by the analyses performed in genomics and proteomics, giving a complete overview of all the involved molecules and their accurate cell functioning.[64]

Because metabolomic technology analyzes thousands of different types of metabolites (carbohydrates, lipids, amino acids, nucleic acids, cofactors, etc), multiple analytical platforms to maximize the metabolome analysis are required.[35] In addition, a vast amount of complex data is generated, which needs to be evaluated and understood in the biochemical cell's context.

In this sense, the metabolic profile has already become a new tool for clinical diagnosis and treatment.[64] This technique can be designed also a noninvasive diagnostic method in semen and the results can be obtained rapidly. Owing to the complexity and recent development and affordability of the metabolomic assays, their application in the study of male infertility is recent.

In the search for novel biomarker metabolites, studies published to date focus on discovering the distinct metabolic compounds in different pathologic situations, as reproductive impairments or in an oxidative environment. Differences in seminal plasma oxidative stress biomarkers concentration (-CH, -NH, -OH, and ROH) were different between men with proven fertility and idiopathic infertility, vasectomy, and varicocele. There were also discrepancies in the compounds citrate, lactate, glycerylphosphorylethanolamine, among donors and infertile man.[65]

In another study, the analysis of seminal fluid from infertile men showed that, among 10 metabolites, citrate, tyrosine, alanine, glycerophosphocholine, and phenylalanine can be used as male infertility biomarkers.[66] Similarly, differences in biomarker profiles have been established between diverse forms of male infertility. The upregulation and downregulation of several metabolites, like arginine, citrate, proline, fructose, and lysine, was found in the idiopathic infertility group. In addition, lysine concentration may be used as a male infertility biomarker.[67]

One of the latest analyses compares the sperm sample lipid profile that led to a pregnancy with those that did not after using the ICSI technique; 10 different lipids were significantly higher in the group that did not achieve a pregnancy. Among them, the ceramides may be a potential diagnostic and predictive clinical tool.[68]

The metabolomic science examines the end products of gene expression and their translation in cell metabolites. The analysis of seminal plasma provides several potential biomarkers of male infertility, with the aim of being used both as noninvasive diagnostic and predictive tool of the assisted reproduction treatment success. Future investigations will reveal whether these metabolic analyses can be included in the clinical routine.

NEW DIRECTIONS

It seems that those direct causes of infertility in men, namely, genetic alterations at a karyotype level, hormonal alterations, obstructions, and infections, among others, can now be easily identified and in many cases corrected, but the challenge lies in those cases where sperm counts and microscopic characteristics seem normal but still fail to achieve their purpose.

There is no doubt that the application of -omic sciences in the study of human fertility, and specifically in male infertility, generates and will bring vast amounts of data. These should be analyzed with caution and properly evaluated before applied clinically, to separate nonpathologic biological variations from physiologically relevant traits. Particularly, once a potential biomarker has been identified and shows to be relevant, it must be taken into clinical realm. This requires the validation of its effectiveness and performance in a clinical environment.

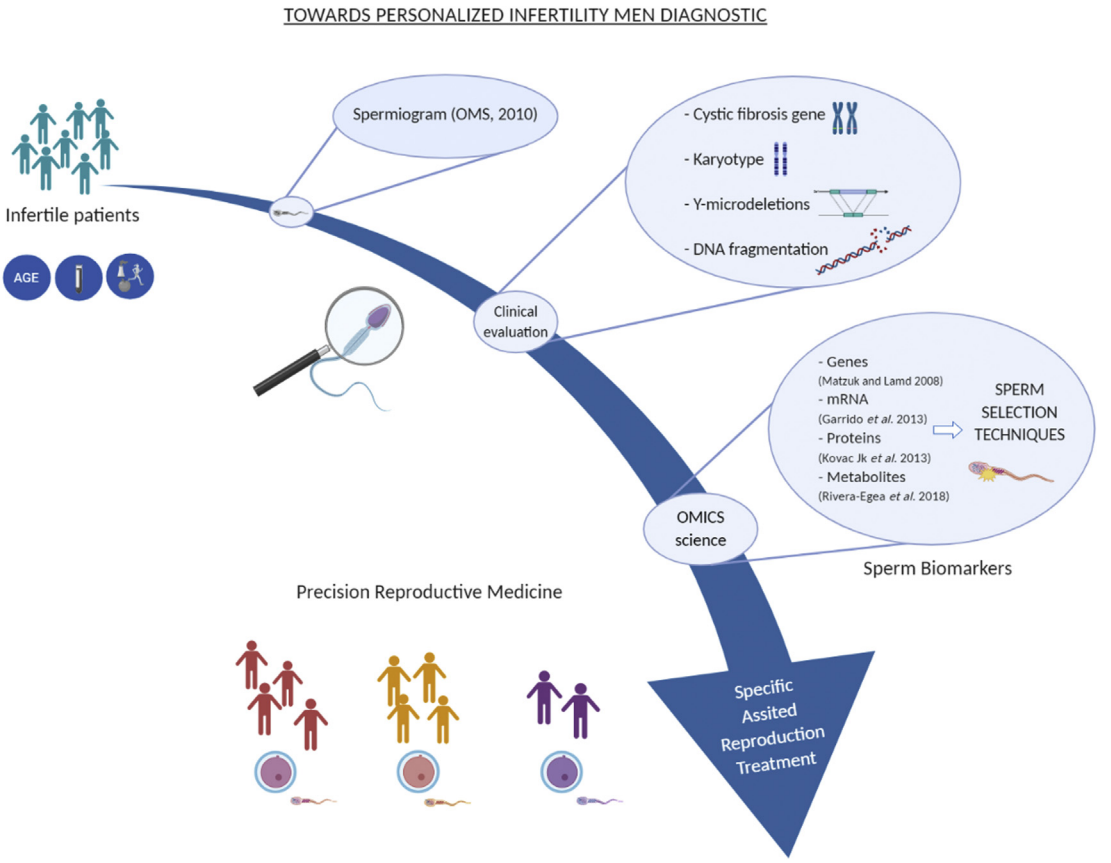

Fig. 1. Personalized medicine is a new approach in male infertility diagnosis and clinical specific treatment according to the intrinsic characteristics of each patient. This new strategy integrates all relevant clinical information to design the most optimal reproductive treatment and increase the likelihood of success. Beginning with the basic semen analysis, this is complemented by a more comprehensive clinical evaluation. Finally, sperm analysis with omics science technologies, would provide a much deeper knowledge of semen quality, being a source of potential biomarkers to be used in sperm selection techniques.

All the articles in this field published to date are only biomedical assays undertaken on a small and specific population. For these results to be scientifically valid and extrapolated to a general population, and in the case of the development of therapeutic tools from this knowledge, in some cases it is necessary to conduct randomized controlled trials with the aim to demonstrate their safety and efficacy before introducing them into clinical practice.[69,70]

Nowadays, the clinics offer to the patients additional interventions or supplements for their in vitro fertilization treatment, with the intention of increasing their chances of pregnancy. These add-on treatments are frequently being criticized,[69,71,72] owing to the lack of evidences supporting their use. As an example, the Human Fertilisation and Embryology Authority published a list of techniques and treatments with doubtful effectiveness and safety in assisted reproduction treatments.

In many cases, the best way to be certain that a technique is effective enough to be used in routine clinical practice is to carry out a randomized controlled trial.[73] The search for new diagnostic markers and therapeutic targets should be based on these premises, before offering in the future a personalized and effective treatment for infertile men. In the near future, there will be multiparametric assays able to measure a set of sperm biomarkers useful in the personalized diagnosis of male infertility, and a number of specific, evidence-based, personalized sperm selection or therapeutic techniques will improve the reproductive results of infertile males.

SUMMARY

The values on which personalized medicine are grounded and the potential benefits for our patients have led scientists to implement them in

the human reproduction discipline. Precision medicine gathers the most relevant data involved in human health, from the genetic code to social behaviors to specifically design medical solutions for specific populations or cases. This new insight will allow huge advances in the diagnosis and treatment of reproductive diseases, which will be reflected in personalized health care for patients who comes to an assisted reproduction center.

Currently, the diagnosis of male infertility is limited to spermiogram, which does not provide prognostic information on male fertility potential. In some cases, this basic sperm analysis yields results leading to more specific tests to complement the results, and identify some infertile patients subpopulations, candidates to be treated in a specific way, but the majority remain idiopathic. New diagnostic methods of sperm are required to assess the chances of achieving pregnancy. In this sense, the personalized medicine promises to permit both diagnostic and therapeutic tools in the clinical management of male infertility (**Fig. 1**).

Recent studies hold the promise that these biomarkers will allow a noninvasive infertility diagnosis and the improvement of the sperm selection techniques. More studies are needed to confirm the effectiveness of these diagnostic methods and to use these novel biomarkers in clinical practice. However, there is no doubt that personalized medicine is a new approach in male infertility diagnosis and clinical treatment that is very promising.

DISCLOSURE

The authors have nothing to disclose.

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