

# Expanding our understanding of clinical laboratory testing in male infertility patients

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*Response to:* Marmar JL. Is testing of sperm DNA fragmentation (SDF) ready for the basic work-up of male infertility? *Transl Androl Urol* 2017;6:S437-9.

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Dr. Marmar in his commentary contextualizing the article by Agarwal *et al.* (1) has provided constructive suggestions regarding the clinical use of SDF testing (2). First, Dr. Marmar illustrates the importance of the standardization process by calculating precision, accuracy, and coefficient of variation associated with the testing, and provides references for readers interested in deepening their understanding about clinical laboratory testing on male patients. Second, the author revisited the importance of varicocele in the modern ICSI era given the newest Cochrane systematic review and meta-analysis conclusion that “treatment of infertile men with a clinically manifest varicocele and poor semen quality may be of benefit” (3). Third, Dr. Marmar provoke readers with two intriguing questions: (I) should ROS testing be considered for the infertility work-up, as well? and (II) will additional testing add significant costs to the patients? In our response, we aim to provide insights on his remarks.

Indeed, both accuracy, the degree to which the measurement reflects the real value, and precision, the reproducibility of the results, are critical for clinicians relying on the results provided by laboratory testing to guide counseling, further workup, and management of infertile couples (4,5). Notwithstanding, even semen analysis suffers from standardization issues despite the efforts of the World Health Organization to elaborate and update guidelines for the laboratory examination of human semen (6). Not surprising, the situation with SDF testing is not much different despite

the genuine efforts to standardize the assays (7-11). Owing to the complex nature of semen, basic and advanced semen analysis, including SDF testing, should be carried out in laboratories equipped with proper instrumentation and skilled technicians. Moreover, internal and external quality control programs, including proficiency testing, should be an integral element of the services provided. Lastly, validation of test systems, quality assurance during all testing processes, and proper communication with clinicians and patients as regards the pre- and post-analytical assay elements are of utmost importance (5,12).

As far as the importance of varicocele in the ICSI era is concerned, Dr. Marmar himself contributed remarkably to the refinements of varicocele surgery. In 1985, the first microsurgical varicocele with an operating microscope and microsurgical instruments was reported by the author (13). Nowadays, the “Marmar technique” for varicocele repair has become the method of choice for the majority of urologists subspecialized in male infertility (14,15).

Lastly, in this section, we attempt to answer Dr. Marmar’s questions mentioned above. Indeed, an increasing body of evidence indicates that oxidative stress represents a central element [reviewed by Cho *et al.* (15)]. In varicocele patients, reactive oxygen species (ROS) are released by the principal cells in the epididymis, endothelial cells of the dilated pampiniform plexus, and testicular cells (germ cells, Leydig cells, macrophages, and peritubular cells).

Excessive ROS has been associated with SDF; the latter is postulated to be one of the mediators of poor sperm quality and resulting infertility in affected men (15). However, not all men with varicocele exhibit high SDF results. In one study involving 55 patients with clinical varicocele and infertility, increased DNA damage (defined as the mean of the control group plus 2SD) was noted in 49% patients with normal semen profile and 58% of patients with abnormal semen parameters (16). Added to this, intrinsic mechanisms may counteract the actions of ROS that might explain why many men retain their fertility in the presence of a varicocele. Measuring ROS in infertile men, including those with varicocele, may offer additional information, particularly for those with normal SDF results (17). In this scenario, protective antioxidant mechanisms may still be active providing a dynamic equilibrium. However, a deviation from homeostasis might lead to impairment in sperm function and consequent infertility. Also, ROS testing could be useful not only to monitor the results of interventions and to guide couples in the decision of pursuing ART but also suggest options for prevention (17). Although SDF testing, and also ROS testing, add costs that are not currently covered by many insurance companies, their significance should be weighed as a function of the likely better reproductive outcomes on an individual basis.

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### Footnote

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