

Unraveling the utility and limitations of clinical practice guidelines

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Dr. Glina in his commentary (1) responding to the practice recommendations for sperm DNA fragmentation (SDF) testing based on clinical scenarios by Agarwal *et al.* (2) discussed the challenges of elaborating male infertility guidelines and the limitations of SDF methods.

In this reply, our objective is threefold. First, we contextualize the utility of clinical guidelines as a useful tool to help clinicians enhance the quality of healthcare deliverable to patients. Secondly, we provide additional information about studies comparing different methods SDF. Lastly, we discuss in more detail the information provided by the guidelines issued by the European Association of Urology (EAU) and the American Society for Reproductive Medicine (ASRM) regarding the utility of SDF testing.

The role for and utility of clinical practice guidelines (CPG) have received increasing attention. The reasons stem from the continuous growth of medical knowledge and the need to improve efficiency in the diagnosis and treatment of medical conditions. As far as male infertility is concerned, various clinical guidelines have been developed by different societies. Such documents can be useful instruments aiming to help urologists and other healthcare practitioners to enhance the quality of healthcare deliverable to patients. Equally important, CPGs in our field may discourage potentially harmful or ineffective interventions during the evaluation and management of men with fertility problems (3).

To date, at least seven guidelines have been developed by expert panels from various societies for the evaluation of the infertile male and varicocele [reviewed by Esteves and Chan (3), Shridharani *et al.* (4), and Roque and Esteves (5)].

While all guidelines include recommendations, they differ in scientific rigor, stakeholder representation (e.g., inclusion of patient representatives) and implementation applicability. For instance, the guidelines issued by EAU grade some recommendations and relate that to levels of evidence (6). The guidelines from the American Urological Association (AUA) and ASRM, which concur with each other, differ from the EAU guidelines concerning methods of collection, extraction, and interpretation of data (7).

A possible explanation for the discrepancies seen among these guidelines is the limited evidence available to synthesize recommendations, as pointed out by Dr. Glina. Half of the recommendations made by the EAU guidelines are grades B or C, thus indicating that most evidence originates from non-randomized clinical trials and retrospective studies (6). These figures are not much different than our proposed guidelines for SDF testing based on clinical scenarios (2), which is the subject of scrutiny in this issue of *Translational Andrology and Urology*. Furthermore, the AUA Practice Guidelines Committee found insufficient outcome data to support a formal evidence-based guideline, thus highlighting that the evidence used to provide recommendations was generally of a low-quality level, being derived overwhelmingly from non-randomized studies.

Interestingly, specific limitations of conventional semen analysis were neglected by most guidelines, and not all of them have updated their reference ranges to the values proposed by the 2010 WHO manual. We concur with Dr. Glina that the recent changes in the reference values issued by the WHO is more scientific-based as controlled studies

involving couples with a known time to pregnancy were used to establish the new limits. However, other reasons than a decline in male fertility may explain why the new reference values for human semen characteristics are lower in 2010 WHO manual than those previously reported. These include the characteristics of included studies concerning the population analyzed and the methods used for semen evaluation (8,9). As a matter of fact, a recent systematic review examining the temporal decline in concluded that there is not enough evidence to confirm a worldwide decline in sperm counts (10). And there is no reason to believe that the changes in the 2010 WHO reference values were associated with this arguable phenomenon, as discussed elsewhere (8-10).

As far the methods to measure SDF are concerned, the literature is rich in studies comparing the various [reviewed by Esteves *et al.* (11)]. Overall, these are not interchangeable as they measure different aspects of SDF—though they are interrelated to a greater or lesser extent via properties of the DNA (12).

Lastly, the recommendations provided by CPGs regarding SDF should be analyzed from a holistic viewpoint. The Practice Committee of the ASRM in its opinion about the diagnostic evaluation of the infertile male, states that “*existing data relating to the relationship between abnormal DNA integrity and reproductive outcomes are too limited to routinely recommend any of these tests for the male partner in an infertile couple...*” (7). Apparently, this statement fully satisfies the critics of the clinical utility of SDF testing. However, the sentence continues as “*...but the effect of abnormal sperm DNA fragmentation on the value of IUI or IVF and ICSI results may be clinically informative*”. Not surprising, the statement above, if read in full, is entirely aligned with our proposed guidelines, which advocate the use of SDF in specific clinical scenarios, including ART failures (2). The importance of SDF to reproductive outcomes is also acknowledged by the latest EAU guidelines on male infertility, which states that “*the increase in SDF is associated with reduced chances of natural conception and an increased chance of early pregnancy loss*” (6). It is therefore suggested that SDF testing reflects the quality of the entire semen specimen, not just the damaged sperm detected in the test result.

In summary, delivering outstanding medical care requires providing care that is effective, safe, and based on the best possible evidence. Important principles to achieve a real evidence-based medicine include: (I) individualized evidence in a format that clinicians and patients can understand; (II)

delivery of care characterized by expert judgment rather than mechanical rule following; (III) decisions shared with patients through meaningful conversations; and (IV) a strong clinician-patient relationship built in all the aspects of care (13). The primary objective of our proposed CPG is to translate the best evidence into practice and provide a framework of standardized care while maintaining clinical autonomy and physician judgment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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