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INVITED COMMENTARY

Male Fertility

Are genetic biomarkers the future of male fertility testing?

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Men with infertility are subjected to numerous diagnostic tests in attempts to determine the nature of their condition. Initially, medical, surgical, and birth histories are elicited with investigations including semen analyses, hormonal panels, and imaging studies such as scrotal or trans-rectal ultrasounds. In cases of men with nonobstructive azoospermia (NOA), these inquiries may all return normal results. More specific testing involving karyotyping and Y-chromosome microdeletion analysis are then performed. When all of these results are normal, a definitive diagnosis must be pursued in the form of a testicular biopsy to determine the physiological ability of the testicle to conduct spermatogenesis.[1]

Novel biomarkers are constantly being explored to more accurately diagnose male fertility. Song *et al*.[2] present a manuscript that eloquently illustrates the multiple approaches being taken to discover noninvasive, highly specific and sensitive genetic biomarkers for the diagnosis of testicular failure. The perfect biomarker would be all of these previously mentioned factors along with being able to diagnose the condition at an early stage, being both cost-effective and accurate, while exposing the patient to minimal risk.[1]

Genetic abnormalities are theorized to contribute to ~15%–30% of male factor infertility. Indeed, at present, large structural aberrations (as detected by karyotype analysis) and smaller genomic deletions (Y-microdeletion studies for the AZF/azoospermia factor, and the CFTR test for cystic fibrosis) are currently the best tests available to diagnose and explain certain etiologies in the infertile male. A serum genetic approach currently appears to be the most promising, given that semen for proteomic analysis is complicated by the components of both sperm and seminal plasma. The latter of which contains excretions from the prostate, seminal vesicles, and bulbouretheral glands.

Karyotype studies have found ~2% of infertile men have karyotype abnormalities, a rate 5 times greater than the general population[3] hinting at the possibilities for genetic screening. The holy grail of biomarker research is the creation of a genetic panel that would screen a wide number of known genes to accurately diagnose infertility and/or predict success at *in vitro* fertilization without the need for a surgical biopsy. Parallels can be derived from the realm of prostate cancer where the utilization of PSA has been enhanced with the use of biomarkers such as PCA3 and TMPRSS2-ERG.[4] Companies such as Myriad Genetics Inc., have taken these concepts a step further offering the Prolaris prognostic screening test to measure tumor growth characteristics to help determine disease progression. Applying such a concept to male fertility makes an attractive proposition and could serve to eliminate the need for surgical intervention in males with infertility in general, and NOA in particular.

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