The time dimension and the future of infertility treatments

David F. Albertini¹

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Among the increasingly fashionable additions to the spectrum of human ARTs are those aimed at bringing the element of time into the equation of prognosis and treatment strategies for infertility [1]. Distancing from the everyday goings on in the embryology laboratory having to do with scheduling and the bewildering array of “time-sensitive” duties has been the arrival of time-lapse morphokinetics—the real-time analysis of events that have enhanced what we can observe. The confluence of technologies involving advances in embryo culture, imaging, and algorithms designed to extract and objectify behaviors of human embryos from fertilization to the blastocyst stage is allowing practitioners to make educated guesses that influence treatment outcomes. Indeed, a series of papers this month take a close and hard look at some of the promising insights gained from morphokinetic analyses buttressing its ever-expanding utility as ONE metric with which to gauge embryo quality. Of these papers, one stands out—at least in sending a clear message to the ART community.

Barash and colleagues deliver the goods to our readership in their multiparametric assessment of ART efficiency recognizing in principle something we have been all too remiss in admitting—no single measure of embryo quality is likely to have true prognostic value (*Association between growth dynamics, morphological parameters, the chromosomal status of the blastocysts, and clinical outcomes in IVF PGS cycles with single embryo transfer* [10.1007/s10815-017-0944](https://doi.org/10.1007/s10815-017-0944)). With concerns raised a year ago at ESHRE regarding inter-clinic

variability in PGS technique and readout, this single-center study brought all the available embryo quality assessment tools together in an evaluation of ongoing pregnancy rates following SET. Of course, we await the LBR results but in the meantime, there is yet another sense of optimism given the association their work identifies between “good-old” morphology and euploidy. That wide variation exists within similar age groups with respect to ploidy and morphology only reinforces the fact that whether it be morphokinetics, morphology, PGS, proteomics, or cast-off DNA analysis, that multicenter double-blind prospective study we are waiting for will require amalgamation of as many assays as bear credible outcomes—hence the *multiparametricity* of it all!

In defocusing and returning to the subject of time, it is well known (but not-so-often mentioned) that the temporal dimension as related to human reproduction casts a much broader net on the principles, practices, and prerogatives governing many aspects of reproductive medicine. Among the most obvious is the fact that aging of the human organism plays directly into the socio-economic nature of reproductive medicine—and is hardly tangential to the ongoing needs of patients who may have waited too long! And in the more targeted of timing factors comes the element of genetics; without a doubt, patients now have an array of genetic tests available for the detection of monogenic disorders that allow them to evade passing along potentially harmful conditions to offspring as a result of embryo PGD [2]. But what about testing in the era of precision medicine? What lies ahead with respect to acquiring a genetic predisposition readout for your personalized fecundity index?

This is exactly the subject tackled in this issue in our Fellows Forum series (*Precision reproductive medicine: multigene panel testing for infertility-risk assessment* [10.1007/s10815-017-0938](https://doi.org/10.1007/s10815-017-0938)). Stephen Collins from Yale

✉ David F. Albertini
dalbertini@thechr.com

¹ The Center for Human Reproduction, New York, NY, USA

University School of Medicine offers an insightful, and yet critical, review of what is fast becoming a trademark for the future of genetic testing embodying an evolving technology not yet broached by the ethical, financial, and societal scrutiny that will come in due course. This prospectus anticipates for our readership many the questions being raised when test results come to the crossroads of patient and genetic counselor interactions not unlike those becoming more familiar in ART clinics with the ongoing conversations regarding mosaicism levels following PGS testing.

A positive step forward has recently been made by two well-known clinics that have accepted the challenge to define and validate various PGS platforms and most importantly keyed in on the critical question of specificity and sensitivity with regard to what appears to be mixtures of whole or segmented chromosome collections found not uncommonly mosaic human embryos.

The first of these investigations comes from the group of Nathan Treff and colleagues at the Foundation for Embryonic Competence (*Evaluation of comprehensive chromosome screening platforms for the detection of mosaic segmental aneuploidy* [10.1007/s10815-017-0924](https://doi.org/10.1007/s10815-017-0924)). Basing their study on a six-cell trophectoderm biopsy, admixtures of cells from euploid or aneuploid lines (obtained commercially) were modeled in totals of six cells per sample before assaying comparable mixtures with three comprehensive chromosome screening (CCS) methods currently in use. The authors draw attention to the promise of NGS-based detection methods but also openly recognize that detection of segmental aneuploidy requires further development to obtain a level sensitivity and specificity before establishing utility in a clinical setting.

The second study comes from Fragouli and colleagues at Oxford University and draws upon a similar strategy for validation, again using combinatorial ratios of cells with known levels of ploidy [3]. What distinguishes this paper is the extension of validation criteria based on NGS detection to mosaicism levels in trophectoderm biopsies that had been cataloged from patients who underwent embryo transfer and for which there was outcome data (mostly of the ongoing pregnancy or not varieties). While poorer outcomes were observed from the transfer of mosaic embryos ($N = 44$), compared to euploid embryos ($N = 51$), indicating that levels of aneuploidy (mostly due to whole chromosome aneuploidy) negatively impacted developmental competence, a “minority” of mosaic

embryos were successful in establishing apparently normal pregnancies. Once again, the need for LBR outcome data is obvious as is the need for more complete studies of this kind that take full advantage of the rigorous validation standards so often neglected in PGS studies reported from other groups.

These papers stand out as cautionary notes on the evolving nature of testing technologies and the awareness that limits of detection and sensitivity remain “works-in-progress” as far as satisfying their suitability as a screen for gross (whole) chromosomal abnormalities but not those of a more subtle character. That inherent limitations remain essential to resolve is obvious with respect to various steps along the pathway from sample preparation methods like whole genome amplification [4] through to harnessing detection strategies for copy number variations in single cells or the small collectives typically obtained during trophectoderm biopsy [5].

As a community deeply invested in the care and management of human infertility, we would be well advised to not lose sight of the growing non-Mendelian nature of diagnostics being confronted by many medical disciplines. Cases in point deserving of our attention include the recent discovery of both germline and acquired mutations [6] that have been traced back to the earliest events in human development [7].

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