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Application of Diagnostic Indicators for Biological Test Validation in Assisted Reproductive Technology

Nicolas Nafati1*, Ounissa Ait-Ahmed1 and Samir Hamamah1,2

1Nicolas Nafati. Unité 1203-INSERM, Hôpital Saint Eloi, 80Av Augustin Fliche, 34000 Montpellier, France 2CHU Arnaud de Villeneuve, 371 Av, Doyen Gaston Giraud, 34295 Montpellier Cedex 05, France, Email: debyee1965@yahoo.co.uk

ABSTRACT

In the field of medical reproductive research, the selection of embryos with the best potential for implantation is the main challenge for biologists. Several studies suggest that genes involved in the Oocyte-Cumulus Cell crosstalk could represent candidate genebiomarkers for selecting embryos with the highest implantation potential.Therefore, the principle objective of this study is to verify the transcriptomic experimental data from 21 biomarker genes by RT-qPCR (Real-Time quantitative Polymerase Chain Reaction) of 102 embryonic/cumulus cell samples from patients undergoing in vitro fertilization. Since variability (noises) from various sources (biological, technical, etc.) was observed,there is a reasonable doubt about the capability of these transcriptomic data to provide a reliable and robust pregnancy predictive model. So, our goal is to verify if the genomic signature could be used as biomarker. If so, one can stipulate that the transcriptome is predictable and could generate a reliable mathematical model. Stochastic modelling is based on the Multiple Logistic Regression (MLR) which is bimodal and therefore binary, seems adequate to give a conclusion regarding this genomic signature capacity to predict the absence or presence of Pregnancy (Pr) event. In this work, the observed event will be represented by a dependent random vector Y that takes the value 1 if pregnancy occurs and 0 if not. The prediction value of this vector also depends on the noise (ε) induced by the variabilities mentioned above. Bio-stochastic tools such as the ROC (Receiver Operating Characteristic measure) curve and its AUC (Area Under the ROC Curve), the probabilistic likelihood indicators, the Odds Ratio (OR), and finally the Youden Index (YI), appear as a simple and an effective biological decision tools to verify the validity of this genomic signature as biomarker to predict pregnancy (Pr). The analysis of the bio-statistical indicator results indicate that the obtained predictive model is non-discriminant, suggesting a bias in the transcriptomic data.

A biomarker can be used for early diagnosis of a disease, identification of individuals for disease prevention, as a potential drug target, or as a potential marker for a drug response. A biomarker may also limit the use of drug (and therefore costs) to the population of patients where the drug will be safe and efficacious. A biomarker in reproduction could be used to improve assessment of exposure, identify subgroups susceptible to treatment, predict outcome and/or differentiate subgroups with potentially different etiologies of disease. Despite many potential uses there is low participation in reproductive biology to develop molecular biomarkers which may be directly related to the low number of new molecular entities entering clinical trials. As the number of candidate markers

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in reproductive medicine is increasing, it is important to understand the pathway of development from discovery to clinical utility and recognize that the vast majority of potential markers will not be clinically useful due to a variety of pitfalls. Extensive testing, validation and modification needs to be performed before a biomarker is demonstrated to have clinical utility. New opportunities and partnerships exist and should hasten the development of biomarkers in reproduction. As more biomarkers are moved into practice, a better educated biomarker consumer will enhance the possibility that biomarker(s) will realize their great potential.

Concomitant with the increase in discovery of biomarker, there must be education on how markers will be used in clinical medicine. Unfortunately, there is no paradigm that applies to the clinical use of a biomarker in general. The use of each biomarker needs to be individualized. The link of a biomarker to the underlying biological process is not a requisite for the marker to have clinical utility. However, connecting the mechanistic dots of a marker to a condition will likely increase clinical uptake. Alternatively, a biomarker developed along a putative etiologic line also has drawbacks. A false assumption that there is a universal mechanism of disease etiology, or progression, will invariably lead to poor utility in complex diseases (such as sub-fertility) or in diverse populations. A biomarker may be of great utility for a subgroup, but not for all. For example, the detection of a chlamydia antibody is not a good biomarker for all forms of tubal disease. Egg quality is not solely a function of the paracrine and endocrine function of the granulosa cell; it is possible that a woman can have "decreased ovarian reserve" and still have a normal AMH.

A common reason for a biomarker to fail is that it may be associated with one aspect of a disease, but not the aspect of clinical importance. A biomarker for endometriosis based on inflammation may be of limited value if pain is not associated with generalized inflammation (but instead some other process). Another example is that of putative biomarkers of in vitro embryonic development. The pace of cell division, or metabolism of an embryo in vitro, does predate implantation and thus may be informative as a biomarker. However, implantation and the development of an early pregnancy are also strongly associated with maternal factors which are still not completely understood. Thus, the association between cell division and implantation may be strong, but insufficient to incorporate myriad clinical factors that influence conception after embryo transfer. At the very least the limitations of prediction (the intended use) of any biomarker must be clearly established and understood by potential users.

Keywords: Reproduction; Oocyte-Cumulus Cell; Gene-Biomarkers; qPCR; Variabilities; Pregnancy; Predictive Model; Bio-stochastic; Nondiscriminant; Non-informative