BMJ 2017;356:j752 doi: 10.1136/bmj.j752 (Published 2017 February 14)

LETTERS

INTERVENTIONS IN UK FERTILITY CENTRES

Continuing to deliver: the evidence base for pre-implantation genetic screening

Darren K Griffin *professor of genetics*[1], Simon Fishel *president and head of research and development*[2], Tony Gordon *managing director and laboratory director*[3], Yuval Yaron *director*[4], Jamie Grifo *program director*[5], Ariel Hourvitz *director*[6], Svetlana Rechitsky *laboratory director*[7], Janine Elson *consultant gynaecologist*[2], Joshua Blazek *senior scientist*[3], Francesco Fiorentino *founder and chief executive officer*[8], Nathan Treff *director of molecular biology*[9], Santiago Munne *founder and director*[10], Milton Leong *adjunct professor*[11], Andreas Schmutzler *co-director*[12], Attila Vereczkey *medical director*[13], Tarek Ghobara *consultant obstetrician*[14], László Nánássy *laboratory director*[13], Michael Large *laboratory director*[15], Samir Hamamah *medical head*[16], Robert Anderson *founder*[17], Luca Gianaroli *director*[18], Dagan Wells *director*[19]

[1]School of Biosciences, University of Kent, Canterbury, UK; [2]CARE Fertility Group UK, Nottingham, UK; [3]Genesis Genetics US, Plymouth, MI, USA; [4]Unit for Prenatal Genetic Diagnosis, Genetic Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [5]New York University (NYU) Langone Fertility Center, New York, NY, USA; [6]Reproduction Laboratory, Sackler School of Medicine, Tel Aviv, Israel; [7]Reproductive Genetic Innovations, Northbrook, IL, USA; [8]Genoma Group, Molecular Genetics Laboratories, Rome, Italy; [9]Reproductive Medicine Associates of New Jersey, USA; [10]Reprogenetics, Livingston, NJ, USA; [11]McGill University, Montreal, Canada; [12]gyn-medicum IVF Center, Goettingen, Germany; [13]Versys Clinics Human Reproduction Institute, Budapest, Hungary; [14]University Hospitals Coventry and Warwickshire, Coventry, UK; [15]Cooper Genomics, Houston, TX, USA; [16]ART/PGD department, INSERM, Montpellier, France; [17]Southern California Center for Reproductive Medicine, Newport Beach, CA, USA; [18]SISMeR Reproductive Medicine Unit, Bologna, Italy; [19]Preimplantation Genetic Diagnosis Laboratory, University of Oxford, NIHR Biomedical Research Centre, Oxford, UK

We respond to the comments made in the BBC commissioned article by Heneghan and colleagues and the *Panorama* programme by Deborah Cohen about pre-implantation genetic screening (PGS), which was among the three "add on" treatments highlighted in the programme and the 41 listed in the article.[1 2] Currently an extensive evidence base supports the efficacy of PGS: more than 20 retrospective studies and four randomised controlled trials suggest that, if performed to a high standard, PGS can, and does, improve IVF success for some patient groups.[3-7] We accept, however, that all studies are open to criticism and thus support further investigations, randomised and retrospective. However, the programme, in our view misleadingly, gives the impression of viewing PGS as unsupported by published evidence. We also question the wisdom of highlighting the opinion of only one laboratory, known opponents of PGS, without providing balance by presenting the evidence base in favour of PGS.

We are strong advocates of evidence based medicine and agree that medical practice should be supported by "well designed and conducted studies." We emphasise, however, that the quality of study design is comparatively easy to assess by reading an article: whether the study has been well conducted is more difficult to judge. The study by Mastenbroek et al (the only one cited in the programme) is a clear example[8]: mining the evidence indicates that the authors' specific practice of cleavage stage embryo biopsy, not screening for chromosome abnormalities in itself, led to reduced IVF success/pregnancy rates. In any case, PGS has now moved on to trophectoderm biopsy and whole karyotype screening (both improved procedures) and higher quality embryological practice.

We thus offer the hand of collaboration to the Oxford group in the hope of working together to consider the evidence base that supports IVF innovations in general (and PGS in particular) in its unique setting. In a discipline in which the outcome measure is the likelihood of achieving a healthy live birth, countless individual components can have a profound effect on the success of IVF. To assess each individually in randomised controlled trials would be prohibitive and far too late for many: indeed

d.k.griffin@kent.ac.uk

patients may be denied the opportunity of the highest quality treatment until the trial was published (and no doubt criticised further). The hitherto unpublished ESTEEM trial is a good example, to date criticised for its recruitment strategy, mixed skill variance, and now out of date technology.[9]

Together we can consider the comparative value of single centre and retrospective studies and the possible pitfalls surrounding relying on randomised controlled trials alone. We should also consider the implications of not implementing PGS—for example, the harm that could be caused to patients who have an adverse outcome assuming that they could, and would, have chosen to avoid it had PGS been offered.

We all want every patient receiving IVF to be given the highest possible chances of success. With an open minded, pragmatic approach to evidence based medicine, we can increase success rates further.

Competing interests: The corresponding author (DKG) does not have competing interests (as he is an academic researcher) other than being treasurer of the Pre-implantation Genetic Diagnosis International Society (PGDIS) and a collaborator with clinics that perform PGS. The other authors are clinicians and PGS practitioners as well as members of laboratories whose business is to process PGS samples.

Full response at: http://www.bmj.com/content/355/bmj.i6295/rr-1.

1 Heneghan C, Spencer EA, Bobrovitz N, et al. Lack of evidence for interventions offered in UK fertility centres. *BMJ* 2016;356:i6295. doi:10.1136/bmj.i6295 pmid:27890864.
2 Panorama. Inside Britain's fertility business. BBC. Last on BBC2, 2 Dec 2016. Available till December 2017 at http://www.bbc.co.uk/programmes/b084ngkd.
3 Lee E, Illingworth P, Wilton L, Chambers GM. The clinical effectiveness of preimplantation genetic diagnosis for aneuploidy in all 24 chromosomes (PGD-A): systematic review. *Hum Reprod* 2015;356:473-83. doi:10.1093/humrep/deu303 pmid:25432917.
4 Dahdouh EM, Balayla J, García-Velasco JA. Comprehensive chromosome screening improves embryo selection: a meta-analysis. *Fertil Steril* 2015;356:1503-12. doi:10.1016/j.fertnstert.2015.08.038 pmid:26385405.
5 Chen M, Wei S, Hu J, Quan S. Can comprehensive chromosome screening technology improve IVF/ICSI outcomes? A meta-analysis. *PLoS One* 2015;356:e0140779. doi:10.1371/journal.pone.0140779. pmid:26470028.
6 Chang J, Boulet SL, Jeng G, Flowers L, Kissin DM. Outcomes of in vitro fertilization with preimplantation genetic diagnosis: an analysis of the United States Assisted Reproductive Technology Surveillance Data, 2011-2012. *Fertil Steril* 2016;356:394-400. doi:10.1016/j.fertnstert.2015.10.018 pmid:26551441.
7 Virtual Academy of Genetics. A statement on the use of preimplantation genetic screening (PGS) of chromosomes for IVF patients. 2015. http://www.ivf-worldwide.com/cogen/general/cogen-statement.html
8 Mastenbroek S, Twisk M, van Echten-Arends J, et al. In vitro fertilization with preimplantation genetic screening. *N Engl J Med* 2007;356:9-17. doi:10.1056/NEJMoa067744 pmid:17611204.
9 European Society of Human Reproduction and Embryology. About ESTEEM. https://www.eshre.eu/Data-collection-and-research/ESTEEM/About-ESTEEM.aspx