2015 Annual conference in reproductive medicine
“Decoding the genomics of infertility and ART”
22-23 May 2015 - Madrid, Spain
General information

Venue
Melià Castilla Hotel
Calle del Capitán Haya, 43
28020 Madrid, Spain

Language
The official language of this live educational conference will be English

Format
Using a highly innovative format and tools, this educational initiative will allow the audience to express their own views and opinions through debates, real-time surveys, discussion, voting system, question wall, questions cards, dedicated website and mobile application.

Dedicated website
Access http://www.2015rmannualconference.org to:
1. View the scientific programme
2. Get your certificate of attendance
3. Get your EACCME certificate
4. Fill in the Post-event surveys

Mobile Application
Download the conference application “EXCEMEDRM” and enjoy easy access to the:
1. Scientific programme
2. Faculty list
3. Meeting rooms map
4. Question wall
5. Tweets from the conference

Any question?
You can post your questions on:
1. Question card
2. Question wall on the mobile application
EXCEMED live educational conference on:

2015 Annual conference in reproductive medicine:
Decoding the genomics of infertility and ART
22-23 May, 2015 - Madrid, Spain

Aim

Genetics plays a key role in human reproduction. Knowledge of the genetics of reproduction is useful to comprehend the successes and failures of human conception and fertility treatments. Embryologists and biologists have introduced genetics into assisted reproductive treatment (ART) with the aim of enhancing success in conception. Genetic application has certainly played a vital role in alleviating inherited disorders through pre-implantation genetic diagnosis (PGD). However, it is debated whether the application of pre-implantation genetic screening and pharmacogenomics is beyond the theory. Since the early application of genetics into ART there have been advances in the techniques and applications. The ultimate aim is to “decode the genomics of infertility and ART” and inform clinicians, biologists and scientists about strategies which will translate to patient success. This live educational conference, supported through working groups and lively discussion, will introduce approaches and technologies that can be used to improve patient outcomes.

Learning objectives

By attending this live educational conference, attendees will:

• Acquire knowledge of the key genetic aspects of human reproduction
• Apply an understanding of human genetics to improve IVF success
• Be able to apply current evidence-based recommendations to achieve the best outcomes from ART

Target audience

This programme is targeted at clinicians, embryologists, biologists and scientists working in ART who wish to update their knowledge of advanced techniques and scientific innovation.
Accreditation

EXCEMED (www.excemed.org) is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide the following CME activity for medical specialists. The EACCME is an institution of the European Union of Medical Specialists (UEMS), www.uems.net.

The CME activity “Decoding the genomics of infertility and ART” is designated for a maximum of 9 (nine) hours of European external CME credits. Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME credits to an equivalent number of AMA PRA Category 1 Credits™. Information on the process to convert EACCME credit to AMA credit can be found at www.ama-assn.org/go/internationalcme.

Live educational activities, occurring outside of Canada, recognized by the UEMS-EACCME for ECMEC credits are deemed to be Accredited Group Learning Activities [Section 1] as defined by the Maintenance of Certification Program of The Royal College of Physicians and Surgeons of Canada.

EXCEMED adheres to the principles of the Good CME Practice group (gCMEp)

Share your opinion with us

We are always looking for ways to bring our educational activities to the next level and meet your needs as a healthcare practitioner.
You will be asked to answer a real-time survey during this event, followed by a post-event online survey on the dedicated website to find out if the experience met your educational expectations. Your views also help us tailor future initiatives.

Thank you for taking the time to participate.

Register to EXCEMED website:
www.reproductive-medicine.excemed.org

follow us on
http://twitter.com/EXCEMED_Repro

EXCEMED_Repro
Scientific committee

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Falmer, UK

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Congress Coordinator: Titty Alvino
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Scientific Programme
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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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<tr>
<td>8.45</td>
<td><strong>EXCEMED Opening</strong></td>
<td>R. Fischer (Germany)</td>
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<tr>
<td>8.55</td>
<td>Welcome and introduction</td>
<td>F.M. Ubaldi (Italy)</td>
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<td>Real-time survey</td>
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<tr>
<td>9.00</td>
<td><strong>Session I: Genetics and infertility</strong></td>
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<td></td>
<td>Chairmen: G.P. Schatten (USA) - A. Murdoch (UK)</td>
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<tr>
<td>9.00</td>
<td>L1: Genetic aspects of folliculogenesis</td>
<td>K. Liu (Sweden)</td>
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<td>9.25</td>
<td>L2: Genetics of male infertility: clinical implications</td>
<td>A. Ferlin (Italy)</td>
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<td>9.50</td>
<td>L3: Genetics of ageing gametes – What is the mechanism?</td>
<td>E. Hoffmann (UK)</td>
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<td>10.15</td>
<td>Let’s talk</td>
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<td>10.35</td>
<td>Coffee break</td>
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<td></td>
<td>Experts meet-up</td>
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<td>11.00</td>
<td><strong>Session II: Clinical genetics</strong></td>
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<td>Chairmen: A. Capalbo (Italy) - S.K. Sunkara (UK)</td>
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<td>11.00</td>
<td>L4: PGD for monogenic disease: where are we and where can we go?</td>
<td>N. Treff (USA)</td>
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<tr>
<td>11.25</td>
<td>L5: PGS for aneuploidy screening in ART: who will benefit and what is the evidence?</td>
<td>R.T. Scott Jr. (USA)</td>
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<td>11.50</td>
<td>L6: Non invasive techniques for aneuploidy screening</td>
<td>S. Hamamah (France)</td>
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<tr>
<td>12.15</td>
<td>Let’s talk</td>
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<tr>
<td>12.35</td>
<td>Lunch</td>
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<td>Experts meet-up</td>
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Session III: iCOS
Chairmen: F.M. Ubaldi (Italy) - R. Fischer (Germany)

13.30  L7: Pharmacogenomics and iCOS  
M. Simoni (Italy)

13.55  L8: Genetic ethiology of poor and hyper responders  
S.K. Sunkara (UK)

14.15  L9: Can we improve clinical results in poor responders?  
H. Yarali (Turkey)

14.35  L10: Hyper responders: safety while maximizing the results  
R. Orvieto (Israel)

Revisiting real-time survey

15.00  Let’s talk

15.20  Coffee Break

Experts meet-up

15.45  Breakout Session
Attendees will be divided into 4 groups and will attend 2 workshops: one on clinical genetics and a second on poor responders.

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<th>Group A</th>
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<th>Group D</th>
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<tr>
<td>15.45-16.45</td>
<td>Q&amp;A: clinical genetics</td>
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<td>Q&amp;A: poor responders</td>
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<td>R.T. Scott Jr. (USA)</td>
<td>N. Treff (USA)</td>
<td>F.M. Ubaldi (Italy)</td>
<td>H. Yarali (Turkey)</td>
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16.45-17.45 | Q&A: poor responders | Q&A: poor responders | Q&A: clinical genetics | Q&A: clinical genetics |
| F.M. Ubaldi (Italy) | H. Yarali (Turkey) | R.T. Scott Jr. (USA) | N. Treff (USA) |

17.45  End of the day

Legend: L: Lecture; KNL: Keynote lecture;
Session IV: Lab technology
Chairmen: L. Rienzi (Italy) - S. Hamamah (France)

8.00  Highlights and summary from the first day
R. Fischer (Germany)
Real-time survey

8.10  L11: Can time lapse technology predict embryo euploidy? Where are we today?
N. Basile (Spain)

8.35  L12: Optimizing embryo biopsy (techniques and timing)
A. Capalbo (Italy)

9.00  L13: Genetic technologies for PGS
N. Treff (USA)

9.25  Let’s talk

9.40  Coffee break
Experts meet up

10.00 L14: The genetic role of mitochondria, clinical applications and prospective
A. Murdoch (UK)

10.25 KNL: The role of epigenetic and imprinting in extended embryo culture: would it affect the health
of the child?
G.P. Schatten (USA)

11.00  Let’s talk

11.10  Breakout session
Attendees will be divided into 4 groups and will attend 2 workshops: one on normal & hyper
responders and a second on lab technology

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<td>R. Fischer (Germany)</td>
<td>R. Orvieto (Israel)</td>
<td>L. Rienzi (Italy)</td>
<td>N. Basile (Spain)</td>
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Q&A: lab technology - cryopreservation - media - biopsy - time lapse
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Q&A: normal & hyper responders
Q&A: normal & hyper responders

L. Rienzi (Italy)  N. Basile (Spain)  R. Fischer (Germany)  R. Orvieto (Israel)

13.10  Back to plenary room
Session V: Scientific summary

Chairmen: F.M. Ubaldi (Italy) - R. Fischer (Germany)

Revisiting real-time survey

13.15 Scientific summary of the conference
J.L.H. Evers (The Netherlands)

13.35 Closing remarks
R. Fischer (Germany)

13.40 End of the conference

Closing lunch
Biographies
Antonio Capalbo received his Bachelor of Science degree in Biotechnology from University of Rome ‘La Sapienza’ and Ph.D. magna cum laude in Human Genetics at the Catholic University of Sacred Heart of Rome in 2011. In 2011 he obtained II level Master Degree in Epidemiology and statistical data analysis at the Eastern Virginia Medical School and the Jones Institute for Reproductive Medicine, Virginia, USA. Dr. Basile is a certified Senior Clinical Embryologist by ESHRE and recently finished her PhD at the Universidad Rey Juan Carlos, Madrid, Spain. She has a keen interest in clinical research, and has been involved in many research projects, especially in the area of morphokinetics, at her current institution and at her previous appointment at Reproductive Medicine Associates of New York, USA. Dr. Basile has co-authored numerous book chapters and papers for peer review journals.

Antonio Capalbo
G.EN.E.R.A. Centre for Reproductive Medicine
Rome, Italy

Natalia Basile is a Senior Embryologist at the Instituto Valenciano de Infertilidad, Madrid, Spain, a position she has held since 2008. She obtained her degree in Biochemistry from the Universidad Argentina John F. Kennedy, Buenos Aires, Argentina and her Master of Science degree in Clinical Embryology and Andrology from the Eastern Virginia Medical School and the Jones Institute for Reproductive Medicine, Virginia, USA. Dr. Basile is a certified Senior Clinical Embryologist by ESHRE and recently finished her PhD at the Universidad Rey Juan Carlos, Madrid, Spain. She has a keen interest in clinical research, and has been involved in many research projects, especially in the area of morphokinetics, at her current institution and at her previous appointment at Reproductive Medicine Associates of New York, USA. Dr. Basile has co-authored numerous book chapters and papers for peer review journals.
Johannes L.H. Evers is Professor emeritus of Obstetrics and Gynaecology at Maastricht University, Maastricht, The Netherlands and Director of the Centre for Reproductive Medicine and Biology at the Maastricht University Medical Centre. He is Programme Leader of the research programme Fertility & Early Embryo Development in the Division of Developmental Biology, GROW, School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands and Editor-in-Chief of Human Reproduction. Professor Evers has been Past-Chairman of the European Society of Human Reproduction and Embryology (ESHRE), of the Dutch National Committee on Research in Human Subjects, and of the World Endometriosis Society. He has (co)authored well over 250 original articles in peer-review journals. Professor Evers has received the following honours and awards: fellowship ad eundem of the British Royal College of Obstetricians and Gynaecologists; Established Clinician Award of ESHRE; World Infertility Award of the American Infertility Association; honorary member of scientific societies in the Middle East, Argentina, Australia, India, Argentina, Russia and the UK.
Alberto Ferlin

Department of Medicine DIMED
University of Padua
Padua, Italy

Alberto Ferlin is Associate Professor of Clinical Pathology at the University of Padova, Department of Medicine, Unit of Andrology and Reproductive Medicine and Head of the Regional Centre for Klinefelter syndrome, the Molecular Biology Lab, and the PGD Program of the University Hospital of Padova. He obtained his Medical Degree in Medicine at the University of Padua, Italy in 1995 and the Specialization in Endocrinology and Metabolism at the same University in 2000 and a PhD in Endocrinological and Haematological Sciences in 2005. His principal research fields include molecular biology and genetics of spermatogenesis and male infertility, cryptorchidism and testicular cancer; role of FSH in the regulation of spermatogenesis and therapy of male infertility; pharmacogenetics of male infertility; testicular expression profiles in male infertility; functional analysis of androgen receptor gene, INSL3 and Y chromosome genes; pre-implantation genetic diagnosis; sperm genetics; molecular and clinical aspects of Klinefelter syndrome; testis-bone cross-talk; systemic effect of INSL3; male hypogonadism and male osteoporosis. Dr. Ferlin participated to research programs of the University of Padova, Telethon, Italian Ministry of University, Veneto Region, Italian Health Ministry. Cooperation with European and non-European research projects. Dr. Ferlin is member of several scientific societies including the Endocrine Society, American Society of Human Genetics, European Society of Human Genetics, European Society of Human Embryology and Reproduction, Italian Society of Endocrinology, Italian Society of Andrology and Medical Sexology, Italian Society of Human Genetics and Italian Society of Pathophysiology of Reproduction. He is also President-Elect of the Italian Society of Andrology and Medical Sexology (2016-2018). He has been invited speaker to more than 50 international congresses and 100 national congresses and is winner of 12 scientific awards in national and international congresses. Dr. Ferlin is also Associate Editor of Human Reproduction, Andrology, and Frontiers in Endocrinology, and referee for many international scientific journals as well as author of more than 300 publications.
Robert Fischer
Fertility Centre Hamburg
Hamburg, Germany

Robert Fischer is founder and medical director of the IVF unit at the Fertility Center Hamburg - one of Germany’s largest and leading IVF centres. In July 1998 the Fertility Center Hamburg was one of the first centres in Germany and worldwide to introduce certified quality management according to the ISO 9001. In 2002 the IVF laboratory became ISO 17025 certified. Prior to these developments, he pioneered in 1983 and was medical director of the first outpatient IVF unit in Hamburg. Author of numerous publications in national and international scientific journals and books, as well as lectures at conferences worldwide, he is also an active member of the American Society of Reproductive Medicine, founding member of the European Society of Human Reproduction and past member of its advisory committee as well as founding member of the German reproductive organisations, “AG Gynäkologische Endokrinologie und Fortpflanzungsmedizin” and “Berufsverband Reproduktionsmedizinischer Zentren”.

Juan Antonio García-Velasco
IVI Madrid
Rey Juan Carlos University
Madrid, Spain

Juan Antonio García-Velasco is Director of IVI Madrid as well as Director of the Masters Degree in Human Reproduction, Director of the Postgraduate course in Nursingin Human Reproduction, and Associate Professor of Obstetrics and Gynecology, Rey Juan Carlos University in Madrid. He is the author of more than 100 scientific articles as well as 22 book chapters and abstracts on human reproduction, especially on endometriosis and both hyper- and hypo- ovarian stimulation response. He has been a Principal Investigator for the Spanish Ministries of Health and Education. Dr Velasco has served on the editorial board of Fertility and Sterility and has been a member of ESHRE’s Advisory Committee.
Samir Hamamah
Service of Reproductive Biology and IVF
CHU Montpellier - Hôpital Arnauld de Villeneuve
Montpellier, France

Samir Hamamah is Professor in Reproductive Medicine at the Medical school and University-hospital of Montpellier, France, Chair of the Reproductive Biology department as well as the ART/PGD Division at Arnaud de Villeneuve hospital, Montpellier and Director of the INSERM U 1203 ‘Early embryo development and pluripotency’. His research field is gene expression profiles of human cumulus–oocyte complexes, early embryo and endometrial cells, RNA profiles on the genomic scale, and identifying specific transcripts using DNA chips, Embryo stem cells and hiPS and nucleic acids circulating cf DNA and MicroRNAs in serum, HFF and culture medium used for in vitro embryo culture. Professor Hamamah has published more than 150 articles in refereed journals, 50 books chapters and 10 books. He has been invited speaker to 300 national and international scientific meetings and received numerous awards such as the Prix de la Société d’Andrologie de Langue Française in 1991, the Prix de l’International Society of Andrology in 1993 and the Prix de la Société Française pour l’Etude de la Fertilité in 1993.

Eva Hoffmann
MRC Genome Damage and Stability Centre
University of Sussex
Falmer, UK

Eva Hoffmann carried out her B.A. in Biological Sciences and Ph.D. in Biochemistry at the University of Oxford, UK. She conducted postdoctoral research in the Department of Genetics, University of Leicester, UK, and as an EMBO Fellow at HHMI, Yale University, US. In 2005, she was awarded a Royal Society Dorothy Hodgkin Fellowship and shortly thereafter started her lab at the MRC Genome Damage and Stability Centre, University of Sussex, UK. She is currently a MRC Senior Fellow and Professor of Chromosome Stability. Her lab is interested in genomic and chromosome changes in the germline of sexually reproducing organisms and their association with infertility and human congenital disorders. Her lab uses human embryos, oocytes, mouse models, and budding yeast to understand chromosome recombination and segregation in meiosis. Dr Hoffmann is an EMBO Young Investigator and co-chair of the Human MeioMap Consortium together with Alan Handyside. She is a member of the MRC Training and Careers Group, sits the advisory Committees for the SUSTAIN trial and EU7 ‘COMREC’ study, and is a member of the Mammalian Meiosis Network Committee.
Kui Liu
Department of Chemistry & Molecular Biology
University of Gothenburg
Gothenburg, Sweden

Kui Liu is a professor at the Department of Chemistry and Molecular Biology, the University of Gothenburg. The research of his laboratory focuses on the molecular mechanisms of ovarian follicular development. Dr. Liu obtained his Ph.D. from Umeå University, Sweden in 1999, and after his postdoc period at Harvard Medical School, USA, he became an assistant professor in 2003 in Umeå University. He became a professor in 2009 and moved to the University of Gothenburg in 2011.

Alison Murdoch
International Centre for Life
Institute of Genetic Medicine
Newcastle University
Newcastle upon Tyne, UK

Alison Murdoch established The Newcastle Fertility Centre at Life which is now recognised as one of the leading NHS fertility centres in the UK. The clinic provides a full range of treatments for subfertility including IVF, sperm and egg donation. The principal research interests in the Department relate to the molecular processes which control cell division in the earliest stages of human development (oocyte meiosis and early embryo cell division). Recent successful research to reduce the risk of transmission of mitochondrial disease to the baby has led to UK legislation to enable the translation of the techniques to clinical practice. Her principal role in the team is the ethical and regulatory issues related to embryo research and to the donation of embryos and eggs for research. Professor Murdoch is past Chair of the British Fertility Society. She has been closely involved with the Department of Health and the regulators in the setting of clinical and laboratory standards in this field. She is a member of the Advisory Committee on the Safety of Blood, Tissues and Organs and a past member of the Nuffield Council of Bioethics.
Raoul Orvieto

Infertility and IVF Unit
Department of Obstetrics and Gynaecology
The Chaim Sheba Medical Center
Tel Hashomer, Israel

Raoul Orvieto is a full professor at the Sackler Faculty of Medicine, Tel Aviv University and the Director of the Infertility and IVF unit, at the Sheba [Tel-Hashomer] Medical Center, Israel. He has been author and co-author of more than 200 publications in national and international journals. His scientific interests include various aspects of controlled ovarian hyperstimulation (COH). The role of GnRH-analogues, and specifically GnRH agonist versus antagonist in COH for IVF and several aspects of ovarian hyperstimulation syndrome (OHSS): pathophysiology, prediction, prevention and its relation to the inflammatory response.

Laura Rienzi

G.EN.E.R.A.
Centre for Reproductive Medicine
Rome, Italy

Laura Rienzi, Senior Clinical Embryologist, is Laboratory Director at the GENERA Centres for Reproductive Medicine. With academic degrees in Biology and Reproductive Medicine, she has an intense activity including educational, editorial, practitioner and author of more than 110 articles, reviews and book chapters. Internationally recognized for her expertise in human clinical embryology and research as evidenced by numerous invitations to speak at national and international scientific meetings. She is member of the editorial board for the 1st edition of the "WHO Infertility Guidelines". In 2008, she founded together with Dr. Filippo Maria Ubaldi the GENERA Centres for Reproductive Medicine where she is Laboratory Director of the 4 Centres in Italy [Rome, Marostica, Umbertide, Naples]. Her current areas of interest include in vitro fertilization, ICSI, human embryo culture, studies of gamete, zygote and embryo morphology in relation to their developmental ability and chromosomal constitution (PGD, PGS), as well as cryopreservation of embryos and oocytes. In 2014 she has been nominated as President of the Italian Society of Embryology, Reproduction and Research [SIERR].
Gerald Phillip Schatten is Director of the Pittsburgh Development Center, Deputy Director of the Magee-Womens Research Institute (MWRI), serves as the Vice Chair of the Department of Obstetrics, Gynecology and Reproductive Sciences and Director of the Division of Developmental and Regenerative Medicine, as well as Professor of Cell Biology and Physiology at the University of Pittsburgh School of Medicine in Pennsylvania. Prior to founding the PDC at Magee-Womens and the University of Pittsburgh, Dr. Schatten was Research Director of the Center for Women’s Health and Professor of Obstetrics and Gynecology and Cell and Developmental Biology at the Oregon Health and Science University in Portland, Oregon. He was also a senior scientist and ART Director at the Oregon National Primate Research Center. Dr. Schatten is the recipient of a MERIT award, was honored by the Czech Academy of Sciences with their Purkinje Medal of Science, elected as a Delegate of the American Association for the Advancement of Sciences, among other honors. His 300+ papers on stem cells, regeneration, fertilization, cell biology, development, infertility, and assisted reproductive technologies have appeared in premier journals including Nature and Science. Dr. Schatten is also an eloquent advocate for research in reproduction, development, regeneration and stem cells.
Richard T. Scott Jr. is a board certified Reproductive Endocrinologist and founding partner of Reproductive Medicine Associates of New Jersey where he functions as scientific director, clinical director, and embryology lab director. Dr. Scott is Professor and Director, Division of Reproductive Endocrinology, Department of Obstetrics, Gynecology, and Reproductive Science, Robert Wood Johnson Medical School of Rutgers University. Additionally Dr. Scott is the Director, Reproductive Endocrine Fellowship, Robert Wood Johnson Medical School. He is also Chairman of the Board for FAAEC which supports research into embryonic reproductive competence. He received his medical degree from the University of Virginia Medical School and then completed his fellowship in Reproductive Endocrinology at the Jones Institute for Reproductive Medicine in Norfolk, Virginia. Dr. Scott’s work has been published in over 350 peer reviewed articles, book chapters, and abstracts. Dr. Scott’s contribution to the field of reproductive endocrinology has been recognized and honored by both academic institutions and patient advocacy groups. He’s been awarded the ASRM Prize Paper Award three times, SART Prize Paper Award three times, STAR Achievement Award from the American Society of Reproductive Medicine, and Professor of The Year, American College of Obstetricians and Gynecologists.
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Abstracts
In humans and other mammalian species, follicular development is a complicated process. The pool of resting primordial follicles serves as the source of developing follicles and fertilizable ova for the entire length of female reproductive life. In recent years, molecular mechanisms underlying follicular activation and development have become more evident, mainly through the use of genetically modified mouse models. Recently reported mutant mouse models have shown that a synergistic and coordinated suppression of follicular activation provided by multiple inhibitory molecules is necessary to preserve the dormant follicular pool. Several molecules and pathways operating in both the somatic primordial follicle granulosa cells (pfGCs) and oocytes have been shown to be important for primordial follicle activation and development. In this presentation, we will summarize both historical and recent studies on mammalian primordial follicular activation and focus on the up-to-date knowledge of molecular networks controlling this important physiological event. These advances may provide a better understanding of human ovarian physiology and pathophysiology for future clinical applications.

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Large body of evidence clearly shows the high prevalence (10–15%) of genetic causes of male infertility. Although a relatively small number of genetic tests are recommended in clinical practice, new development in this field will probably suggest in the near future the possible translation of new genetic markers into the diagnostic workup of an infertile male. Genetic tests should routinely be included in the diagnostic workup of infertile men but they should be selected in the context of a comprehensive clinical evaluation. Genetic tests allow appropriate assistance of infertile couples, as they explore the cause of the infertility and assess the risk of the couple to transmit its genetic characteristics. It is presumed that some new genetic and epigenetic tests will be introduced in clinical practice in the near future. Another extremely interesting area is related to the identification of genetic markers of FSH action and for a pharmacogenetic approach to FSH treatment of normogonadotrophic oligozoospermia. Polymorphisms in FSH receptor (FSHR) and FSHβ-chain (FSHB) genes have been demonstrated to influence serum FSH levels and spermatogenesis, and preliminary reports showed a role for these polymorphisms in selecting patients for and in predicting the response to FSH treatment.
Inherited genome changes occur in the germline of humans, especially during meiosis, the specialized cell division that halves the number of chromosome sets in the gametes. Human females and males differ tremendously in their recombination programmes, as well as in the errors in chromosome segregation. 10-30% of natural human conceptions are aneuploid (missing or extra chromosomes) and 70-90% of these originate from the egg. Maternal age is the major factor predisposing to an increased risk of aneuploidy, as well as altered recombination patterns in the offspring. Despite their importance for human health, our understanding of recombination and chromosome segregation in female meiosis remains rudimentary. Two major reasons for this are the difficulties in accessing the human female germline directly and the challenge of single cell genomics.

We, and others, are overcoming these challenges and are exploiting the access to the human germline in ART to understand genome changes and age-related effects on human gametes directly using sperm, eggs, and embryos. Recently, we developed novel methods to recover the genetic information from all three products of single meioses, termed ‘MeioMapping’. As part of the Human MeioMap Project, we are using these maps to understand the origins of maternally-derived aneuploidies in human conceptions.
Since the first reported cases of PGD for single gene disorders over 20 years ago, many advances in technology have emerged. Recent focus has been placed on the ability to simultaneously evaluate aneuploidy of all 24 chromosomes. Approaches include whole genome amplification (WGA) with next generation sequencing, array CGH, or SNP array analysis for chromosome screening and either a second PCR for SGD loci or karyomapping from the SNP genotyping data. This lecture will review these methods along with the development of qPCR for chromosome screening and SGD testing without WGA. With the growing use of carrier screening and the improvements in clinical success rates with trophectoderm biopsy and CCS, the future of PGD for monogenic disorders may become a more mainstream solution in the management of reproductive health.
Validated screening paradigms for embryonic aneuploidy screening are now available for routine clinical application and have been shown to enhance selection of reproductively competent embryos. Key to the development of these protocols has been enhanced amplification strategies and the availability of reliable 24 chromosome testing platforms. It is now possible to attain reliable analysis of the genetic complement at several stages during embryonic development.

In addition to chromosome screening platform validation studies, there are data from several randomized controlled trials demonstrating that embryonic aneuploidy screening enhances implantation and delivery rates in couples undergoing ART. These technologies add a powerful new tool to aid embryologists when selecting the embryos with the highest reproductive potential for transfer. However, integrating aneuploidy screening into clinical practice impacts more than embryo selection in the embryology laboratory. To safely perform trophectoderm biopsy extended culture is required and in programs without an on-site molecular genetics laboratory, it mandates vitrification of the embryos for transfer in a future cycle. Perhaps the most important part of the enhanced implantation rates associated with chromosome screening is the impact it has on decisions regarding the number of embryos to transfer. A recent randomized controlled trial has demonstrated that a single embryo transfer of a screened embryo attains the same delivery rate as the transfer of two unscreened embryos. The multiple pregnancy rate decreased from 48% to 0% in that study. Subsequent evaluations have demonstrated dramatic reductions in preterm labor, low birth weight, and neonatal intensive care unit admissions. In fact, the risk for these adverse obstetrical outcomes returned to a level equivalent to the general obstetrical population. There is also an impact on health care costs. While embryonic aneuploidy screening increases the costs of any given ART treatment cycle, the enhanced outcomes result in an overall reduction in the number of treatment required to attain a delivery. The near elimination of multiple gestations and the dramatic decrease in preterm delivery and neonatal intensive care unit utilization also dramatically reduces expenditures for health care system providing their care.

While important studies remain to be done to evaluate some subsets of the infertile population, the majority of the infertile population may benefit from embryonic aneuploidy screening. Excellent delivery rates with safer obstetrical and neonatal outcomes greatly reduce the burden of treatment in optimizing the pathway to building a healthy family.
Pre-implantation genetic diagnosis (PGD) is a powerful clinical tool to identify aneuploidy embryos with or at risk of specific genetic diseases before implantation in utero after in vitro fertilization (IVF). PGD is performed on embryo biopsies that are obtained by aspiration of one or two cells from pre-implantation embryos at day 3 or day 5/6 of culture. However this is a very traumatic method, but it cannot be avoided because non-invasive procedures to assess the genetic status of pre-implantation embryos are not available yet. We hypothesize, that cell-free nucleic acids, which are released by embryos in the culture medium during the IVF procedure, could be used for genetic screening.

Cell-free DNA (cfDNA) molecules, which are released mostly by apoptotic or necrotic cells, are also found in body fluids and can be used as biomarkers of pathological conditions. Indeed, circulating cfDNA in the bloodstream is also being used to detect gynecological abnormalities, whereas fetal cfDNA in maternal blood constitutes a non-invasive biomarker for fetal aneuploidy.

Similarly, miRNAs are involved in the regulation of mammalian embryo development. Global miRNA expression profiling suggests that miRNA synthesis and degradation dynamically coexist during preimplantation embryo development. Many miRNAs are expressed in developing mammalian embryos and hESCs, including miR-320, miR-92a, let-7a and miR-146b. Recent reports indicate that deregulated miRNA expression in the embryo is associated with human infertility and the embryo miRNA expression profile varies according to its chromosomal make-up and sex. As miRNAs have been detected in the culture medium following release by cells grown in culture, it would be possible to quantify the embryonic miRNAs released in the medium in order to monitor embryo health during preimplantation in vitro culture. The cfDNA as well as miRNAs offers a promising opportunity, by a non-invasive method, to evaluate ovarian failure and pregnancy outcome.
FSH is fundamental for gonadal function and reproduction in both men and women. FSH act via binding to its specific receptors, the FSHR. The receptor gene is characterised by a large number of SNPs (more than 2100 listed in the NCBI SNP database), most of them located in intronic regions and of unknown heterozygosity rate. Some SNPs, especially those which are nonsynonymous and located in exons have been studied in association with gonadal function.

The FSHR SNPs at nucleotide position 919 and 2039 in exon 10 are very common (heterozygosity: 0.469) and result in the aminoacid transition Thr/Ala at codon 307 and Asn/Ser at codon 680, respectively. In the Caucasian population the two SNPs are mostly in linkage disequilibrium with the Thr307-Asn680 variant covering 55% and the Ala307-Ser680 variant 45% of the alleles. The other two possible combinations represent < 1% of all alleles in Caucasians, while they are more frequent in the far East. In addition, there is a G/A SNP in the promoter region at position –29, with the G allele covering 75% and the A allele 25% of the alleles in Caucasians, while the distribution is equal (50%) in Indonesians [3, 4]. Finally, a -211G>T in FSHB, encoding the beta subunit of FSH, has been demonstrated to be a major determinant of FSH serum levels. We recently demonstrated that all these SNPs appear first in Homo, result in reduced FSH action and are present with variable frequencies and combinations worldwide. Stringent clinical studies demonstrate that the FSHR genotype influences serum FSH levels and gonadal response in both sexes.

Serum FSH levels depend on the -211G>T SNP, influencing transcriptional activity of the FSHB promoter. Genotypes reducing FSH action are overrepresented in infertile subjects. While the clinical relevance of the FSHR polymorphisms alone is limited, the combination of FSHR and FSHB genotypes has a much stronger impact than either one alone in both sexes. About 20% of people are carrier of the alleles associated with lower serum FSH levels/reduced FSH expression or activity, possibly less favorable for reproduction. Prospective studies need to investigate whether stratification of infertile patients according to their FSHR-FSHB genotypes improves clinical efficacy of FSH treatment compared to the current, naive approach. A relative enrichment of less favorable FSHR-FSHB genotypes may be related to changes in human reproductive strategies and be a marker of some health-related advantage at the costs of reduced fertility.

Overall, the current literature is rather consistent in showing the association of the FSHR Asn680Ser polymorphism with menstrual cycle features. To date, the Asn680Ser FSHR polymorphism can be considered as a clear, absolute genetic marker of reproductive features or dysfunctions, since it modulates ovarian response to FSH, both in women and in men. Indeed, women with homozygous FSHR Ser680 genotype requires a higher number of FSH ampoules in ovarian hyperstimulation, compared to the homozygous Asn680 carriers. These data suggests that the FSHR Ser680 genotype is less sensitive to the FSH action in vivo, compared to the FSHR Asn680 genotype, and we recently demonstrated in vitro the molecular mechanism thereof.
Poor ovarian response (POR) and PCOS pose a challenge to controlled ovarian stimulation (COS). Whilst POR is associated with cycle cancellation and poor prognosis following IVF, PCOS is associated with an unsolicited hyper response and risk of OHSS. Although advanced female age is one of the pertinent causes of POR, genetic and acquired conditions also have an aetiological role. Chromosomal aberrations and mutations or variability in specific genes involved in reproductive ageing are implicated in reduced ovarian reserve and resultant POR. Structural and numerical abnormalities of the X chromosome are linked to accelerated oocyte apoptosis and depletion resulting in early ovarian ageing. The common genetic causes of ovarian insufficiency which is the extreme eventuality for poor responders are Turner’s syndrome and FMR1 premutation. Follicle stimulating hormone receptor (FSH) and leuteinising hormone receptor (LHR) mutations are amongst other genetic disorders implicated in POR.

PCOS is a complex disorder of uncertain aetiopathogenesis. It is inherited as a complex polygenic trait and several genes in the multiple biochemical pathways implicated in PCOS have been evaluated. In addition to the underlying genetic basis environmental factors have been shown play an important role in the aetiology of PCOS and environmental influences are thought to unmask the underlying genetic predisposition to PCOS. This presentation will discuss the various genetic factors that have been implicated in the aetiology of POR and PCOS and speculate on the clinical implications of such association.
Despite publication of large number of articles on poor ovarian response (POR) in the last two decades, it has not been possible to identify any efficient treatment to improve ovarian response and pregnancy rates. Most studies are single-center based and underpowered (“miniature”). The main objective of this presentation is to review the literature, from an evidence-based medicine perspective, on the effectiveness of the various available treatment modalities in patients with POR undergoing in-vitro fertilization (IVF). Bologna criteria for defining POR, while being a step forward, may not be perfect since various subgroup of patients fulfilling Bologna criteria may not be homogenous and associated with different live birth rates following IVF. Regarding the various controlled ovarian stimulation (COS) protocols, neither the use of different GnRH-agonist protocols nor the use GnRH-antagonist protocols improve pregnancy outcome. However, GnRH-antagonist protocols may reduce treatment burden. Increasing FSH dose does not overcome POR. In theory, estrogen or combined oral contraceptive pill priming in the preceding luteal phase may contribute to follicular synchronization and hence increased number of mature follicles in women at risk of POR. However, there is insufficient evidence to comment on improved outcome with such priming. Addition of recombinant human luteinizing hormone (r-hLH) to recombinant human follicle-stimulating hormone (r-hFSH) in COS may be beneficial for women with POR. In a recent meta-analysis enrolling 40 randomized controlled trials (RCTs) (6443 patients), significantly more oocytes (+0.75 oocytes) were retrieved and significantly higher clinical pregnancy rate (risk ratio=1.30) was attained with r-hFSH plus r-hLH versus r-hFSH alone. There may be a positive effect with the use of growth hormone (GH) supplementation in patients with POR; however, studies have been small-scaled, weak and heterogeneous, and larger trials are needed. Pre-treatment with transdermal testosterone prior to IVF has been reported to improve the clinical outcomes for patients with POR undergoing IVF in 3 RCTs. However, the results should be interpreted with caution due to the small sample size of the available 3 trials and the heterogeneities. The available evidence does not support the routine use of dehydroepiandrosterone (DHEA) as an adjuvant in patients with POR undergoing IVF. Furthermore, potential side effects of long-term androgen supplementation in women seeking fertility have not been widely addressed. Reduced treatment burden should be one of the main objectives in patients with POR. In this context, natural cycle IVF with/without minimal stimulation in women seeking fertility have not been widely addressed. Reduced treatment burden should be one of the main objectives in patients with POR. In this context, natural cycle IVF with/without minimal stimulation in women seeking fertility have not been widely addressed. Reduced treatment burden should be one of the main objectives in patients with POR. In this context, natural cycle IVF with/without minimal stimulation in women seeking fertility have not been widely addressed. Reduced treatment burden should be one of the main objectives in patients with POR. In this context, natural cycle IVF with/without minimal stimulation in women seeking fertility have not been widely addressed. Reduced treatment burden should be one of the main objectives in patients with POR. In this context, natural cycle IVF with/without minimal stimulation in women seeking fertility have not been widely addressed. Reduced treatment burden should be one of the main objectives in patients with POR. 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Controlled ovarian hyperstimulation (COH) is an important variable for the success of in vitro fertilization–embryo transfer (IVF-ET). The two most common protocols for COH incorporate GnRH-agonists and antagonists co-treatment, mainly to prevent a premature rise in luteinizing hormone. While the hitherto published information on pregnancy rate is still debatable, the utilization of GnRH antagonists in COH protocols is increasing, as a result of its clear advantage in reducing the incidence of severe ovarian hyperstimulation syndrome (OHSS).

COH which combines GnRH antagonist co-treatment and GnRH agonist trigger has become a common tool aiming to eliminate severe early OHSS. However, the observed decrease in implantation and pregnancy rates following this approach has encouraged different modifications of luteal support aiming to improve outcome. One of the suggest approach is the 1500 IU hCG luteal rescue, which appears to be a promising protocol, aiming to reduce (rather than eliminating) severe early OHSS, without compromising outcome.

In this presentation we discuss the different suggested strategies and offer a strict triage, aimed at eliminating the occurrence of severe OHSS based on several clinical observations, including the role of GnRH-antagonist in COH protocols, the use of different luteal rescue protocols and the ability to transfer embryos in the blastocyst stage.
The recent introduction of time-lapse systems in the IVF laboratory has solved the problem of applying static and subjective scoring systems to the evaluation of dynamic processes such as embryo development. Semi or completely automatic time-lapse systems allow uninterrupted surveillance of the embryos and the detection and quantification of various events (e.g. pronuclear formation, syngamy, embryo cleavages, compaction and blastocyst formation). Since that initial step, new kinetic markers associated with higher implantation potential have been proposed, the safety of these systems has been validated, and the effects of different intrinsic and extrinsic factors on kinetic markers has been analyzed.

On the other hand, it is very well known that chromosomal abnormalities are one of the most common causes of abnormal embryos in IVF. The correlation between chromosomal content and embryo morphology and development has been studied based on static observations, however very little is known from a dynamic point of view. A handful of studies have addressed this issue utilizing time-lapse technology to analyze and compare the morphokinetic behavior of chromosomally normal and abnormal embryos. Specific markers related to early and late stages of development have been found to differ between chromosomally normal and abnormal embryos giving rise to algorithms that may increase the probability of selecting chromosomally normal embryos in a non-invasive way. However, results can be contradictory and some authors suggest that morphokinetic characteristics cannot be used to select euploid blastocysts in poor-prognosis patients regarded as candidates for pre-implantation genetic screening. Therefore we should be cautious: the selection of embryos through time-lapse technology should not be considered as a replacement to PGS and large multicentre studies are needed in order to clarify the possible relation between morphokinetics and embryo euploidy. However, and specially considering it’s non-invasive nature, there is no harm in utilizing this approach as a selection tool for good prognosis patients that are not indicated for PGS or for patients that are indicated for PGS (history of implantation failure or early pregnancy loss) but that for any legal, social or economic reasons do not wish or can not have PGS performed. In these situations, a clear benefit is gained with morphokinetic screening and selection using a defined algorithm.
Usually, embryo selection criteria are still limited to morphology and/or morphokinetic assessment of preimplantation development, but they are insufficient by themselves to improve significantly IVF transfer outcomes. Considering the high impact of chromosome aneuploidies in human reproduction, Preimplantation Genetic Screening (PGS), a diagnostic technique aiming at the selection of euploid embryos to be transferred within a cohort of embryos produced by a couple during an IVF cycle, is currently exploited as the main genetic testing method for embryo selection. In this presentation, a comprehensive overview of the different biopsy approaches for preimplantation genetic screening based embryo selection will be provided. Blastomere biopsy at day 3 of embryo development failed to show enhanced embryo selection as largely demonstrated by several Randomized Control Trials (RCTs) and meta-analyses in the last years when used together with FISH based aneuploidy screening. Other than the use of a low coverage aneuploidy screening methods as FISH, the removal of one blastomere at the cleavage stage has been shown to affect embryonic reproductive competence. Furthermore, all current genetic technologies do not perform at best when used on a single cell. Looking backward in preimplantation window, polar bodies (PBs) approach has been evaluated also as not appropriate since paternal and post-zygotic errors are not detectable and low accuracy in prediction of female derived aneuploidies was also claimed in recent publications. Looking forward in preimplantation development, instead, blastocyst stage trophectoderm (TE) biopsy is bringing solid evidences and encouraging clinical outcomes. This stage, in fact, guarantees a more robust genetic analysis, no impact of biopsy and a low impact of chromosomal mosaicism on genetic testing. In this presentation, an overview of pros and cons of different timings for biopsy and aneuploidy screening will be provided. We will focus on their strengths, their validation status, their weaknesses and the challenges for implementing them in an IVF laboratory.
Aneuploidy is the most common genetic abnormality in humans. Preimplantation genetic screening (PGS) now routinely involves the analysis of all 24 chromosomes and is commonly referred to as comprehensive chromosome screening (CCS). Technologies have included metaphase comparative genomic hybridization (CGH), array CGH, single nucleotide polymorphism (SNP) arrays with quantitative or qualitative approaches, quantitative real time PCR (qPCR), and next generation sequencing (NGS). Many differences exist amongst methodologies including the amplification strategies used and level of evidence for accuracy and clinical predictive value. This lecture will compare and contrast current methods of CCS and review the evidence supporting clinical application to improve the success of IVF.
Mitochondria are the structures within the cytoplasm of every cell that provide vital energy for normal function. There are numerous copies in each cell and if some of these are abnormal, disability and early death may follow. The physiology of mitochondria is complex and the inheritance of disease is often difficult to predict.

Mitochondria are passed through the female line only via the cytoplasm in the eggs. Thus it is theoretically possible to prevent transmission of abnormal mitochondria to a child by replacing them with normal mitochondria before implantation. Our early research in the mouse and then with abnormally fertilised human embryos has proved that this may be technically possible. Further research is ongoing using donated eggs from healthy women.

After debate, the UK Parliament passed regulations in February 2015 that will permit these techniques to be translated into clinical treatment. In this presentation the scientific, ethical and regulation hurdles will be discussed.
‘Decoding the genomics of infertility and ART’ is already an impressive, worthy and timely objective. Yet, beyond genomics, epigenetic modifications add complexities for reproductive medical clinicians as well as scientists in several fields. This lecture will synthesize much of the presentations and discussions during the meeting. Additionally, it will present a primer on the state of knowledge regarding epigenetics and imprinting so vital for patient counseling and clinical understandings of the fuller ramifications of innovative treatments. The lecture also will consider some of the latest reports which have implications on: ‘The role of epigenetic and imprinting in extended embryo culture’ and whether they ‘would affect the health of the child’.

The emerging fields of epigenetics and genomic imprinting are providing stunning, totally unanticipated, discoveries regarding the contributions of our parents, grandparents and earlier ancestors on every aspect of our health and behavior. These discoveries fundamentally alter our ideas that inheritance is primarily, almost exclusively, the result of DNA transmission – Nuclear and Mitochondrial DNA alike. This Keynote Lecture will first consider the basic aspects of epigenetic inheritance, genomic imprinting and non-nuclear transmission of essential components for the zygote and embryo. It will highlight some of the latest finding regarding ART and epigenetic analyses, and the frontiers of the state of knowledge. As with all aspects of medicine, clinicians need to have both basic information as well as evidence-based clinical findings, in order to properly evaluate the benefits of any procedure versus any safety or other risks. We will consider the current state of knowledge regarding epimutation profiling and its relations to ART offspring. Also, we will evaluate whether impaired gametes themselves are at the root cause of the epimutation or other epigenomic concern. There are many other implications of epigenetic inheritance, especially in neuropsychiatry and pharmacogenomics.

Overall, this lecture will both consider the state of knowledge and areas of concern regarding ‘The role of epigenetic and imprinting in extended embryo culture: Would it affect the health of the child?’ This is envisioned as particularly appropriate and timely in light of our Conference’s objectives to “decode the genomics of infertility and ART.”

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The following faculty provided information regarding significant commercial relationships and/or discussions of investigational or non-EMEA/FDA approved (off-label) uses of drugs:

Natalia Basile  
Declared no potential conflict of interest

Antonio Capalbo  
Declared receipt of the 2013 Grant for Fertility Innovation

Johannes L.H. Evers  
Declared no potential conflict of interest

Alberto Ferlin  
Declared no potential conflict of interest

Robert Fischer  
Declared no potential conflict of interest

Juan Antonio García-Velasco  
Declared receipt of grants from Merck, MSD and Ferring

Samir Hamamah  
Declared receipt of grants and contracts from Ferring in 2013, 2014 and 2015

Eva Hoffmann  
Declared receipt of the Medical Research Council (MRC), UK SNRF fellowship and the MRC funded project grant and that her presentation will include labelled use of the Illumina SNP array [Human CytoSNPv12]

Kiu Liu  
Declared no potential conflict of interest

Alison Murdoch  
Declared no potential conflict of interest

Raoul Orvieto  
Declared receipt of honoraria from Ferring

Laura Rienzi  
Declared no potential conflict of interest

Gerald Phillip Schatten  
Declared receipt of grants and contracts from the National Institute of Health

Richard T. Scott Jr.  
Declared to be member of Ferring Pharmaceutical advisory board and to be board member of the Foundation for the Assessment and Enhancement of Embryonic Competence, Inc.

Manuela Simoni  
Declared receipt of grants and contracts from Merck Serono

Sesh Kamal Sunkara  
Declared no potential conflict of interest

Nathan Treff  
Declared receipt of the 2015 Grant for Fertility Innovation

Filippo Maria Ubaldi  
Declared no potential conflict of interest

Hakan Yarali  
Declared receipt of honoraria and consultation fees from Merck Serono and that during his presentation off-labeled use of Letrozole/Testosterone gel/Growth Hormone will be mentioned.
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