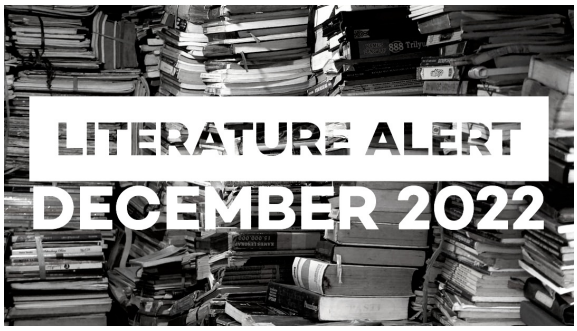


EUROPEAN ACADEMY OF ANDROLOGY

Dear EAA Members,

A very strong end to the current year in the field of andrology, culminating with excellent translational work! In this edition we are spoilt with high impact publications in *Nature, Nature Communications, eLife, PNAS, Development* and others. A stringent selection was needed to cut down the list of noteworthy publications to a manageable number. For a popular book for clinicians treating couple infertility, please scroll to the end. Enjoy the reading!

Clinical andrology and epidemiology



This study from the Copenhagen Centre found that in young men from the general population, higher LH was associated with adverse cardiovascular risk factors, and conversely, higher testosterone and total sperm count were associated with more favourable cardiometabolic indices. Reproductive hormones and semen quality may be early biomarkers of cardiovascular health.

Hansen LS, Priskorn L, Holmboe SA, Jensen TK, Hansen AH, Andersson AM, Jørgensen N. Testicular function is associated with cardiometabolic health markers; a cross-sectional study of 2,289 young men. ***Andrology*** 2022 Dec 15. Epub ahead of print. PMID: 36520458.
https://doi.org/10.1111/andr.13365



Tamsulosin, an alpha1-adrenergic blocker commonly prescribed for benign prostatic hyperplasia (BPH) can cause ejaculatory disorders, especially in younger patients. Using a new ex vivo model system, this study found that tamsulosin disturbed the obligatory noradrenaline-induced contractions in prostate ducts, seminal vesicles and epididymis.

Seidensticker M, Tasch S, Mietens A, Exintaris B, Middendorff R. Treatment of benign prostatic hyperplasia and abnormal ejaculation: live imaging reveals tamsulosin - but not tadalafil - induced dysfunction of prostate, seminal vesicles and epididymis. ***Reproduction***. 2022 Nov 7;164(6):291-301. PMID: 36173812.
https://doi.org/10.1530/rep-22-0197

frontiers in Endocrinology

A large study of patients with congenital hypogonadotropic hypogonadism (CHH) confirmed the male predominance (2.6:1) of CHH. The prevalence of non-reproductive phenotypic features was significantly higher in males than in females, with kidney abnormalities affecting only male patients.

Federici S, Cangiano B, Goggi G, Messetti D, Munari EV, Amer M, Giovanelli L, Hrvat F, Vezzoli V, Persani L, Bonomi M. Genetic and phenotypic differences between sexes in congenital hypogonadotropic hypogonadism (CHH): Large cohort analysis from a single tertiary centre. ***Front Endocrinol*** (Lausanne). 2022 Dec 2;13:965074. PMID: 36531499.
https://doi.org/10.3389/fendo.2022.965074

frontiers in Endocrinology

This prospective, Danish population-based birth cohort study, revealed that high in utero exposure to endocrine disrupters BPA and BP-3 was associated with a compensated reduced Leydig cell function in males at 18-20 years of age.

Holmboe SA, Henriksen LS, Frederiksen H, Andersson AM, Priskorn L, Jørgensen N, Juul A, Toppari J, Skakkebæk NE, Main KM. Prenatal exposure to phenols and benzophenones in relation to markers of male reproductive

function in adulthood. ***Front Endocrinol*** 2022 Dec 9;13:1071761, PMID: 36568115.
https://doi.org/10.3389/fendo.2022.1071761

COVID-19



The recently released January 2023 issue of Andrology contains the 5th batch of articles on the impact of COVID-19 on male reproductive health:

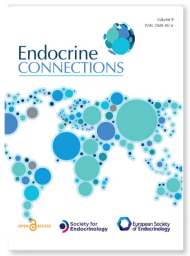
Salar et al. Effect of COVID-19 infection on the erectile function. ***Andrology***. 2023; 11(1):10-16.

Salonia A, et al. Testosterone in males with COVID-19: a 12-month cohort study. ***Andrology***. 2023; 11(1):17-23.
López-Rodríguez R, et al. Androgen receptor polyQ alleles and COVID-19 severity in men: A replication study. ***Andrology***. 2023; 11(1):24-31.

Amodio G, et al. Combined plasma levels of IL-10 and testosterone, but not soluble HLA-G5, predict the risk of death in COVID-19 patients. ***Andrology***. 2023; 11(1):32-44.

In addition, there is an interesting correspondence concerning the previously published claim that Covid-19 vaccination BNT162b2 might temporarily impair sperm concentration and motility:

Gat et al. ***Andrology*** 2022; 10(6):1016-22.
https://onlinelibrary.wiley.com/toc/20472927/2023/11/1



This Danish study showed that low testosterone and LH concentrations were predictive of severe respiratory failure in men with COVID-19, whereas low LH and FSH were predictive of severe respiratory failure in women.

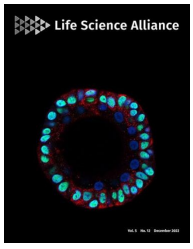
Clausen CL, Holm Johannsen T, Erik Skakkebæk N, Frederiksen H, Ryrsø CK, Dungu AM, Hegelund MH, Faurholt-Jepsen D, Krogh-Madsen R, Lindegaard B, Linneberg A, Kårhus LL, Juul A, Benfield T. Pituitary-gonadal hormones associated with respiratory failure in men and women hospitalized with COVID-19: an observational cohort study. ***Endocr Connect***. 2022; 12(1):e220444. PMID: 36472925.
https://doi.org/10.1530/ec-22-0444

Androgenetics

nature COMMUNICATIONS

Two international consortia GEMINI and IMIGC, connecting androgenetics enthusiasts around the world, incl. several members of the EAA, performed exome-sequencing in over 1000 NOA cases, and identified a plausible recessive Mendelian cause in 20%. Integration with sc-RNA sequencing data showed that azoospermia genes can be grouped into molecular subforms with synchronized expression patterns, which may provide a rational basis for disease classification.

Nagirnaja L, Lopes AM, Charng W, Miller B, Stakaitis R, Golubickaite I, Stendahl A, Luan T, Friedrich C, Mahyari E, Fadial E, Kasak L, Vigh-Conrad K, Oud MS, Xavier MJ, Cheers SR, James ER, Guo J, Jenkins TG, Riera-Escamilla A, Barros A, Carvalho F, Fernandes S, Gonçalves J, Gurnett CA, Jørgensen N, Jezek D, Jungheim ES, Kliesch S, McLachlan RI, Omurtag KR, Pilatz A, Sandlow J, Smith J, Eisenberg ML, Hotaling JM, Jarvi KA, Punab M, Rajpert-De Meyts E, Carrell DT, Krausz C, Laan M, O'Bryan MK, Schlegel PN, Tüttelmann F, Veltman JA, Almstrup K, Aston KI, Conrad DF. Diverse Monogenic Subforms of Human Spermatogenic Failure. ***Nature Commun*** 2022, 13, 7953 (2022).
https://doi.org/10.1038/s41467-022-35661-z

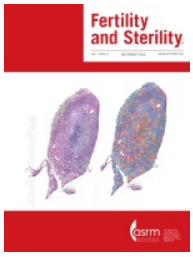


The authors from the Münster Center generated whole transcriptome profiles of germ cells using tissues from patients with arrest at successive steps of germ cell differentiation. They found novel germ cell–specific markers, some misregulated genes in male infertility and thousands of genes showing germ cell–specific isoforms.

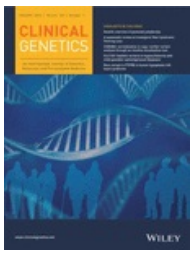
Siebert-Kuss LM, Krenz H, Tekath T, Wöste M, Di Persio S, Terwort N, Wyrwoll MJ, Cremers JF, Wistuba J, Dugas M, Kliesch S, Schlatt S, Tüttelmann F, Gromoll J, Neuhaus N, Laurentino S. Transcriptome analyses in infertile men reveal germ cell-specific expression and splicing patterns. ***Life Sci Alliance***. 2022; 6(2):e202201633. PMID: 36446526
10.26508/lsa.202201633

This study established a novel luciferase assay allowing to functionally assess *DMRT1* missense variants, and identified such variants in 11 infertile men with crypto- or azoospermia within the MARGE cohort in Germany.

Emich J, Gaikwad AS, Stallmeyer B, Fietz D, Schuppe HC, Oud MS, Kliesch S, Gromoll J, Friedrich C, Tüttelmann F. Functional assessment of DMRT1 variants and their pathogenicity for isolated male infertility. ***Fertil Steril***. 2022 Dec 24:S0015-

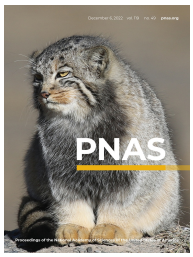


0282(22)01982-3. Epub ahead of print. PMID: 36572623.
https://doi.org/10.1016/j.fertnstert.2022.10.032



This study reported a sex-reversed 46,XY DSD patient with a FGF9 variant D195N, which disrupts FGF9 protein homodimerisation and reduces Sertoli cell proliferation and Wnt4 repression in mice.

Croft B, Bird AD, Ono M, Eggers S, Bagheri-Fam S, Ryan JM, Reyes AP, van den Bergen J, Baxendale A, Thompson EM, Kueh AJ, Stanton P, Thomas T, Sinclair AH, Harley VR. FGF9 variant in 46,XY DSD patient suggests a role for dimerization in sex determination. ***Clin Genet***. 2022 Nov 9. Epub ahead of print. PMID: 36349847.
https://doi.org/10.1111/cge.14261



A fascinating study showing that a small male-specific duplication upstream of *Sox9* on an autosome can substitute for a Y chromosome in an exceptional rodent species that lacks a Y chromosome and *Sry* (both sexes have a single X chromosome).

Terao M, Ogawa Y, et al et Kuroiwa A. Turnover of mammal sex chromosomes in the *Sry*-deficient Amami spiny rat is due to male-specific upregulation of *Sox9*. ***Proc Natl Acad Sci U S A***. 2022 Dec 6;119(49):e2211574119. Epub 2022 Nov 28. PMID: 36442104.
https://doi.org/10.1073/pnas.2211574119

Translational and basic andrology



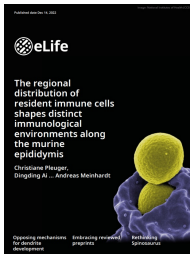
A remarkable *tour-de-force*! This important study analysed single-nucleus transcriptome data for testes from 11 species, including 7 primates. The authors found that testis is rapidly evolving and identified temporal expression changes of genes across species and conserved expression programs controlling ancestral spermatogenic processes. Genes predominantly expressed in spermatogonia and Sertoli cells accumulated on X chromosomes during evolution. They also uncovered that meiotic sex-chromosome inactivation (MSCI) is an ancestral mammalian feature.

Murat F, Mbengue N, Winge SB, Trefzer T, Leushkin E, Sepp M, Cardoso-Moreira M, Schmidt J, Schneider C, Mößinger K, Brüning T, Lamanna F, Belles MR, Conrad C, Kondova I, Bontrop R, Behr R, Khaitovich P, Pääbo S, Marques-Bonet T, Grützner F, Almstrup K, Schierup MH, Kaessmann H. The molecular evolution of spermatogenesis across mammals. ***Nature***. 2022 Dec 21. Epub ahead of print. PMID: 36544022.
https://www.nature.com/articles/s41586-022-05547-7
The summary of the paper: https://www.nature.com/articles/d41586-022-04221-2



An important riddle solved! Why 80% of radiation-induced mutations in humans are transferred by the male germline? The authors addressed this in nematode C. elegans. The ‘culprit’ is linker histone H1, which after radiation triggers heterochromatin formation that shields the paternally inherited genome damage from proper repair by homologous recombination, so maternal error-prone polymerase theta-mediated end joining is used instead.

Wang, S., Meyer, D.H. & Schumacher, B. Inheritance of paternal DNA damage by histone-mediated repair restriction. ***Nature*** (Dec 21, 2022). Epub ahead of print.
https://lnkd.in/gfCjc58s



This elegant Giessen-Melbourne study investigated region-specific immunity along the epididymal duct in the mouse model of bacterial epididymitis. The authors uncovered striking differences in immunological landscapes of the proximal and distal regions. They propose that resident immune cells are strategically positioned along the epididymal duct to properly respond to specific immunological challenges.

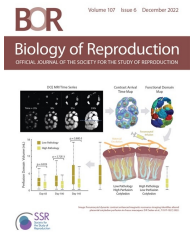
Pleuger C, Ai D, Hoppe ML, Winter LT, Bohnert D, Karl D, Guenther S, Epelman S, Kantores C, Fijak M, Ravens S, Middendorff R, Mayer JU, Loveland KL, Hedger M, Bhushan S, Meinhardt A. The regional distribution of resident immune cells shapes distinct immunological environments along the murine epididymis. ***Elife***. 2022 Dec

14;11:e82193. PMID: 36515584.
https://doi.org/10.7554/elife.82193



The authors generated a novel model of unilateral undescended testis UDT in gubernaculum-specific *Wnt4* knockout mice (*Wnt4*-cKO) and carefully characterised the consequences. The findings highlight the crucial role of *WNT4* in testicular development.

Seth A, Bournat JC, Medina-Martinez O, Rivera A, Moore J, Flores H, Rosenfeld JA, Hu L, Jorgez CJ. Loss of WNT4 in the gubernaculum causes unilateral cryptorchidism and fertility defects. ***Development***. 2022 Dec 1;149(23):dev201093. doi: 10.1242/dev.201093. Epub 2022 Nov 30. PMID: 36448532.
https://doi.org/10.1242/dev.201093



The primary cilium was identified as a key factor in the Hedghog signalling, together acting as a master regulator of genes involved in the development of Wolffian duct (embryonic precursor of the epididymis).

Alves MBR, Girardet L, Augière C, Moon KH, Lavoie-Ouellet C, Bernet A, Soulet D, Calvo E, Teves ME, Beauparlant CJ, Droit A, Bastien A, Robert C, Bok J, Hinton BT, Belleannée C. Hedgehog signaling regulates Wolffian duct development through the primary cilium. ***Biol Reprod***. 2022 Dec 15:ioac210. Epub ahead of print. PMID: 36525341.
https://doi.org/10.1093/biolre/ioac210



Insulin-like growth factor 2 (IGF2) was found in human spermatozoa, and the signalling investigated in vitro using porcine sperm. Sperm IGF2 seems to downregulate the expression of mitogens released by the Sertoli cells (e.g. GDNF), possibly influencing their sensitivity to FSH and contributing to paracrine regulation of spermatogenesis.

Cannarella R, Mancuso F, Arato I, Lilli C, Bellucci C, Gargaro M, Curto R, Aglietti MC, La Vignera S, Condorelli RA, Luca G, Calogero AE. Sperm-carried IGF2 downregulated the expression of mitogens produced by Sertoli cells: A paracrine mechanism for regulating spermatogenesis? ***Front Endocrinol*** (Lausanne). 2022 Nov 29;13:1010796. PMID: 36523595.
https://doi.org/10.3389/fendo.2022.1010796



Investigators at the Brussels Centre analysed the transcriptome of fibrotic and non-fibrotic testicular tissue from individuals with Klinefelter syndrome or testis atrophy. The most informative DEGs included *VCAM1*, and X-linked fibrotic genes *MXRA5*, *CX* and *VCX3B*.

Willems M, Olsen C, Caljon B, Vloeberghs V, De Schepper J, Tournaye H, Van Saen D, Goossens E. Transcriptomic differences between fibrotic and non-fibrotic testicular tissue reveal possible key players in Klinefelter syndrome-related testicular fibrosis. ***Sci Rep***. 2022 Dec 13;12(1):21518. PMID: 36513788.
https://doi.org/10.1038/s41598-022-26011-6



This study looked at endogenous glucocorticoid receptor (GR) signalling in Leydig cells using inducible transgene mouse models. Adult depletion of GR in Leydig cells reduced expression of LH receptor (*Lhcgr*) and of steroidogenic enzymes required for normal androgen production.

Gannon AL, Darbey AL, Chensee G, Lawrence BM, O'Donnell L, Kelso J, Reed N, Parameswaran S, Smith S, Smith LB, Rebourcet D. A Novel Model Using AAV9-Cre to Knockout Adult Leydig Cell Gene Expression Reveals a Physiological Role of Glucocorticoid Receptor Signalling in Leydig Cell Function. ***Int J Mol Sci***. 2022 Nov 30;23(23):15015. PMID: 36499341.
https://www.mdpi.com/1422-0067/23/23/15015

Methodology

A facile *in vitro* differentiation and meiotic initiation system was developed for manipulation by chemical agents that cannot be safely administered



to live animals. In addition, the authors present a transgenic mouse model enabling fluorescence-activated cell sorting-based isolation of spermatogonia at specific developmental stages as well as meiotic spermatocytes.

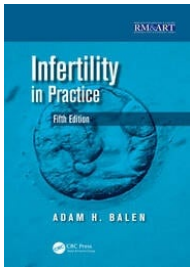
Kirsanov O, Johnson T, Malachowski T, Niedenberger BA, Gilbert EA, Bhowmick D, Ozdinler PH, Gray DA, Fisher-Wellman K, Hermann BP, Geyer CB. Modeling mammalian spermatogonial differentiation and meiotic initiation in vitro. ***Development***. 2022 Nov 15;149(22):dev200713. PMID: 36250451.
https://doi.org/10.1242/dev.200713



The experienced team from Turku (Finland) further improved the method of stage recognition in histological analysis of the mouse testis. “STAGETOOL” is a fluorescent labelling-based automated method that enables simultaneous stage and cell-type analysis of spermatogenesis, with 99.1% accuracy.

Meikar O, Majoral D, Heikkinen O, Valkama E, Leskinen S, Rebane A, Ruusuvuori P, Toppari J, Mäkelä JA, Kotaja N. STAGETOOL, a Novel Automated Approach for Mouse Testis Histological Analysis. ***Endocrinology***. 2022 Dec 19;164(2):bqac202. PMID: 36461763.
https://doi.org/10.1210/endocr/bqac202

Book of the Month



Infertility in Practice

By Adam Balen

A thoroughly updated practical guide for clinicians managing infertile couples, mainly addressed to gynaecologists and fertility clinics, but covering also the “male factor”.

5th Edition
eBook Published 21 December 2022
Imprint CRC Press, London
Pages: 442
eBook ISBN9781003094951
https://doi.org/10.1201/9781003094951

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