



Dear EAA Members,

The April edition highlights several interesting publications in all areas of andrology. As ever we recommend the latest issue of *Andrology*, packed with interesting basic and clinical science. Other topics: exploding burden of prostate cancer, distinct classes of hypogonadotropic hypogonadism, progesterone use in IVF, infertility and cancer risk, hypogonadism and headache, bone density in transgenders, orchiopexy, RAS-opathies in infertile men, exomes in diagnostics of infertility, onco-immunology sex bias, shared origin of genital and hindlimb structures, ATRX syndrome, CatSper activation, PFAS effect on sperm, RUNX in epididymal development, human infertility single-cell testis atlas, and more.

Clinical andrology and epidemiology

The fourth issue of *Andrology* in 2024 has been released, with several interesting articles (*a few previously highlighted in the EAA alerts*), including: two meta-analyses - on vasovasostomy techniques and influence of chronic alcohol consumption on gonads, two studies on risk factors for erectile dysfunction, three articles on Peyronie's disease /penile fractures /penile carcinoma, inflammatory markers, sperm cryopreservation, sperm DNA fragmentation, testis function after immunotherapy, cyclooxygenases and murine spermatogonia, and more.

<https://onlinelibrary.wiley.com/toc/20472927/current>



Prostate cancer is the most common cancer in men and accounts for 15% of cancers, and even higher proportion in men of African heritage. The expert group projects that new cases will rise from 1.4 million in 2020 to 2.9 million by 2040. Ageing and improving life expectancy are behind the big increase, so it cannot be prevented by lifestyle changes. The rise in prostate cancer is likely to be mirrored by rises in diabetes and heart disease, so early diagnosis programmes should focus on men's health more broadly.

James ND, Tannock I, et al et Tunariu N, Villanti P, Xie LP. The Lancet Commission on prostate cancer: planning for the surge in cases. *Lancet*. 2024 Apr 4:S0140-6736(24)00651-2.

[https://doi.org/10.1016/s0140-6736\(24\)00651-2](https://doi.org/10.1016/s0140-6736(24)00651-2)



This multicentre study identified predictors of reversal following treatment in two distinct classes of males with congenital hypogonadotropic hypogonadism (CHH). Patients with reversal (14%) had larger testis volume, no micropenis, and higher serum FSH, consistent with the Pasqualini syndrome (fertile eunuch). Patients without reversal were more likely to have anosmia, cryptorchidism, absence of puberty and two or more rare genetic variants.

Dwyer AA, McDonald IR, Cangiano B, Giovanelli L, Maione L, Silveira LFG, Raivio T, Latronico AC, Young J, Quinton R, Bonomi M, Persani L, Seminara SB, Lee CS. Classes and predictors of reversal in male patients with congenital hypogonadotropic hypogonadism: a cross-sectional study of six international referral centres. *Lancet Diabetes Endocrinol.* 2024 Apr;12(4):257-266.

[https://doi.org/10.1016/s2213-8587\(24\)00028-7](https://doi.org/10.1016/s2213-8587(24)00028-7)

Commentary by B. Anawalt:

[www.thelancet.com/journals/landia/article/PIIS2213-8587\(24\)00065-2/fulltext](http://www.thelancet.com/journals/landia/article/PIIS2213-8587(24)00065-2/fulltext)

This randomized placebo-controlled study investigated acute effects of testosterone (T) on whole-body protein metabolism in hypogonadal and eugonadal conditions. The application of transdermal T did not counteract the negative effects of hypogonadism with no effects on protein metabolism within five hours of administration.

Ornstrup MJ, Høst C, Rittig N, Gravholt CH. Acute Effects of Testosterone on Whole-Body Protein Metabolism in Hypogonadal and Eugonadal Conditions: A Randomized, Placebo-Controlled, Crossover Study. *J Appl Physiol* (1985). 2024 Apr 18.

<https://doi.org/10.1152/jappphysiol.00078.2024>

Can the addition of progesterone and neurotensin, molecular agents found in the female reproductive tract, increase the fertilization potential of human spermatozoa? Progesterone 10 μ M increased sperm binding to hyaluronan and hyperactive motility, while neurotensin had no effect.

McPherson NO, Nottle M, McIlpatrick S, Saini A, Hamilton H, Bowman E, Tully CA, Pacella-Ince L, Zander-Fox D, Bakos HW. Clinical use of progesterone in human sperm preparation media for increasing IVF success. *Reprod Biomed Online* (RBMO) 2024 Apr;48(4):103625.

<https://doi.org/10.1016/j.rbmo.2023.103625>

This analysis analysed large family datasets and found distinct overall cancer risk and familial multicancer patterns in the azoospermia and severe oligozoospermia cohorts, suggesting heterogeneity in cancer risk by type of subfertility and within subfertility type.

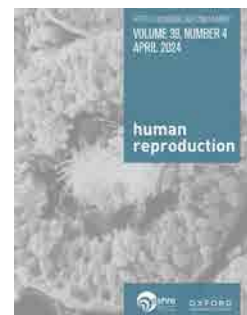
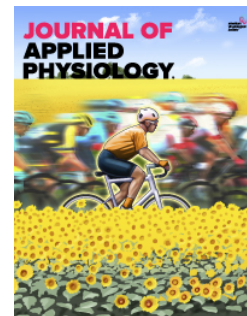
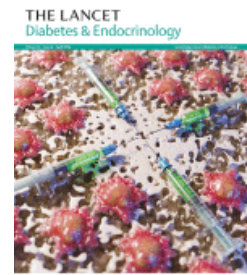
Ramsay JM, Madsen MJ, Horns JJ, Hanson HA, Camp NJ, Emery BR, Aston KI, Ferlic E, Hotaling JM. Describing patterns of familial cancer risk in subfertile men using population pedigree data. *Hum Reprod.* 2024 Apr 3;39(4):822-833.

<https://doi.org/10.1093/humrep/dead270>

Androgens have been hypothesized to be involved in the pathophysiology of cluster headache due to the male predominance. This study showed that the male endocrine system is altered in patients with cluster headache to a state of compensated hypogonadism.

Petersen AS, Kristensen DM, Westgate CSJ, Folkmann-Hansen T, Lund N, Barloese M, Søborg MK, Snoer A, Johannsen TH, Frederiksen H, Juul A, Jensen RH. Compensated Hypogonadism Identified in Males with Cluster Headache: A Prospective Case-Controlled Study. *Ann Neurol.* 2024 Apr 1.

<https://doi.org/10.1002/ana26906>



Transgenderers can be treated with gonadotropin-releasing hormone agonists (GnRHa) followed by testosterone or estradiol, which may impact bone mineral density (BMD). This study of transgender youth (n = 56) found that BMD Z-score was negatively correlated with GnRHa duration and positively correlated with BMI.

Roy MK, Bothwell S, Kelsey MM, Ma NS, Moreau KL, Nadeau KJ, Rothman MS, Nokoff NJ. Bone Density in Transgender Youth on Gender-Affirming Hormone Therapy. *J Endocr Soc (JES)*. 2024 Mar 12 bvae045, <https://doi.org/10.1210/jendso/bvae045>



This retrospective study examined the link between pediatric orchiopexy for undescended testicles (UDT) and testicular torsion in childhood and adult fertility. UDT, especially bilateral UDT was a risk factor for low sperm concentration (OR: 6.3).

Newman NH, Farber I, Lunenfeld E, Zeadna A, Vardi IH, Assi Z. Orchiopexy: one procedure, two diagnoses - different male infertility outcomes. *Asian J Androl*. 2024 Apr 19. <https://doi.org/10.4103/aja202410>



The authors investigated the association between body composition and dynamic responses of the pituitary-testis axis in men. A higher BMI was associated with lower basal serum LH and testosterone, but hormone responses following pituitary-testis axis stimulation were less dependent on BMI.

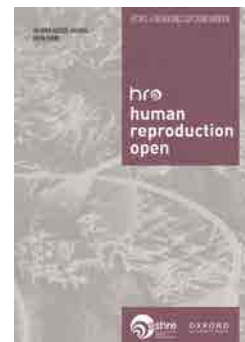
Abildgaard J, Bang AK, Nordkap L, Priskorn L, Jørgensen N. The influence of body composition on the response to dynamic stimulation of the endocrine pituitary-testis axis. *Int J Obes (Lond)*. 2024 Apr 12. Epub ahead of print. <https://doi.org/10.1038/s41366-024-01518-2>



Debate

This article summarised the joint ESHRE and Male Reproductive Health Initiative (MRHI) Campus workshop held in 2022 in Budapest. Male reproductive health is a serious global issue, and a plethora of gaps in knowledge necessitates international collaboration and multidisciplinary research and high-quality clinical trials. There is also an urgent need to educate young people and the general public.

De Jonge CJ, Barratt CRJ, Aitken RJ, Anderson RA, Baker P, Chan DYL, Connolly MP, Eisenberg ML, Garrido N, Jørgensen N, Kimmins S, Krausz C, McLachlan RI, Niederberger C, O'Bryan M, Pacey A, Priskorn L, Rautakallio-Hokkanen S, Serour G, Veltman JA, Vogel DL, Vazquez-Levin MH. Current global status of male reproductive health. *Hum Reprod Open*, 2024; hoae017, <https://doi.org/10.1093/hropen/hoae017>



Androgenetics

RASopathies are syndromes caused by congenital defects in the Ras/mitogen-activated protein kinase (MAPK) pathway genes.



Variants in 22 RASopathy-linked genes were screened in ESTonian ANDrology (ESTAND) cohort and validated by GEMINI cohort. Undiagnosed RASopathies were especially enriched among patients with a history of cryptorchidism.

Juchnewitsch AG, Pomm K, Dutta A, Tamp E, Valkna A, Lillepea K, Mahyari E, Tjagur S, Belova G, Kübarsepp V, Castillo-Madeen H, Riera-Escamilla A, Põlluuaas L, Nagirnaja L, Poolamets O, Vihljajev V, Sütt M, Versbraegen N, Papadimitriou S, McLachlan RI, Jarvi KA, Schlegel PN, Tennisberg S, Korrovits P, Vigh-Conrad K, O'Bryan MK, Aston KI, Lenaerts T, Conrad DF, Kasak L,

Punab M, Laan M. Undiagnosed RASopathies in infertile men. *Front Endocrinol.* 2024 Apr 9;15:1312357. <https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2024.1312357/full>

Likely pathogenic and pathogenic (LP/P) variants in 638 candidate genes for male infertility were screened in the ESTAND cohort of 521 men with idiopathic spermatogenic failure (SPGF) and 323 normozoospermic men. Molecular diagnosis was reached in 12% men with SPGF, with findings in 39 genes; including *BNC1* and *NR5A1*.

Lillepea K, Juchnewitsch AG, Kasak L, Valkna A, Dutta A, Pomm K, Poolamets O, Nagirnaja L, Tamp E, Mahyari E, Vihljajev V, Tjagur S, Papadimitriou S, Riera-Escamilla A, Versbraegen N, Farnetani G, Castillo-Madeen H, Sütt M, Kübarsepp V, Tennisberg S, Korrovits P, Krausz C, Aston KI, Lenaerts T, Conrad DF, Punab M, Laan M. Toward clinical exomes in diagnostics and management of male infertility. *Am J Hum Genet.* 2024 Apr 12:S0002-9297(24)00086-7. <https://authors.elsevier.com/a/1ivySgeXA8fZ>



Sex-based differences outside reproduction

Sex differences are present across multiple non-reproductive organ cancers, with male individuals generally experiencing higher incidence of cancer with poorer outcomes. This review summarizes the biological hallmarks of this sex bias, with focus on signalling from sex hormones and chromosome-encoded gene products, along with epigenetic mechanisms in tumour and immune cells such as myeloid cells and T cells.

Xiao T, Lee J, Gauntner TD, Velegraki M, Lathia JD, Li Z. Hallmarks of sex bias in immuno-oncology: mechanisms and therapeutic implications. *Nature Rev Cancer.* 2024 Apr 8. <https://doi.org/10.1038/s41568-024-00680-z>



Translational and basic andrology

The hindlimb and external genitalia of tetrapods are thought to derive from an ancestral common primordium.



This excellent study found one of the mechanisms: inactivation of *Tgfb1* resulted in an extra pair of hindlimbs growing from the pericloacal mesoderm instead of the external genitalia. *Tgfb1* modulates the accessibility status of regulatory elements that control the gene networks leading to the formation of genital or hindlimb structures.

Lozovska A, Korovesi AG, Dias A, Lopes A, Fowler DA, Martins GG, Nóvoa A, Mallo M. *Tgfb1* controls developmental plasticity between the hindlimb and external genitalia by remodeling their regulatory landscape. *Nature Commun* 15, Mar 20;15(1):2509 (2024). <https://doi.org/10.1038/s41467-024-46870-z>

ATR-X (alpha thalassemia, mental retardation, X-linked) syndrome features atypical genitalia and small testes with few seminiferous tubules, which was also shown in the KO mouse model (*ScAtxKO*). This study investigated the mechanisms, and the data suggest that *ATR-X* protects a *Yp* region from DNA damage, thereby preventing Sertoli cell death and testicular failure.

León NY, Le TNU, Garvie A, Wong LH, Bagheri-Fam S, Harley VR. Y chromosome damage underlies testicular abnormalities in ATR-X syndrome. *iScience.* 2024 Mar 28;27(5):109629. <https://doi.org/10.1016/j.isci.2024.109629>



A potential new regulator of the sperm transition zone was identified in this study. *CEP76* was identified previously as a candidate fertility gene in men. The mutant mice were sterile and their spermatozoa were immotile, with severe abnormalities of annulus, and fibrous sheath, and with abnormal protein distribution. CEP76 dictates annulus positioning and structure, suggesting that annulus is a part of the spermatid transition zone.

Houston BJ, Merriner DJ, Stathatos GG, Nguyen JH, O'Connor AE, Lopes AM, Conrad DF, Baker M, Dunleavy JE, O'Bryan MK. Genetic mutation of *Cep76* results in male infertility due to abnormal sperm tail composition. *Life Sci Alliance*. 2024 Apr 3;7(6):e202302452.

<https://doi.org/10.26508/lsa.202302452>



Two studies from the same group examined the human sperm function, with focus on CatSper activation. They found that extracellular vesicles (EVs) increase the intracellular Ca^{2+} concentrations $[Ca^{2+}]_i$ via activating CatSper channels, and modulate sperm hypermotility. EV from asthenozoospermic semen caused a lower increase of $[Ca^{2+}]_i$. The second study revealed that Na^+/H^+ exchangers are regulators of human CatSper and KSper.

1. Zhang X, *et al et* Zeng X. Both protein and non-protein components in extracellular vesicles of human seminal plasma improve human sperm function via CatSper-mediated calcium signaling. *Hum Reprod*. 2024 Apr 3;39(4):658-673. <https://doi.org/10.1093/humrep/deae018>

2. Liang M, *et al et* Zeng X. Flagellar pH homeostasis mediated by Na^+/H^+ exchangers regulates human sperm functions through coupling with CatSper and KSper activation. *Hum Reprod*. 2024 Apr 3;39(4):674-688.

<https://doi.org/10.1093/humrep/deae020>



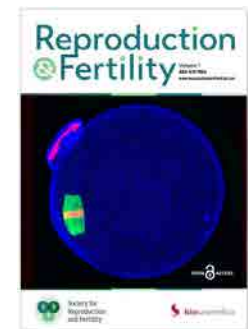
Two independent studies in mice examined effects of endocrine disruptors poly- and perfluoroalkyl substances (PFAS) on male reproduction. The first study raises the prospect that sperm exposed to PFAS potentially harbor an alternate stress signal that is delivered to the embryo upon fertilization. The second study investigated the effects of the PFOS and the newer “clean energy” PFAS lithium on the tumorigenicity and found that both chemicals promoted the growth of TGCT cells in mouse xenografts, and PFOS also altered steroid biosynthesis and fatty acid metabolism in TGCT cells.

1. Calvert L, Martin JH, *et al et*, Nixon B. Assessment of the impact of direct in vitro PFAS treatment on mouse spermatozoa. *Reprod Fertil*. 2024 Mar 8;5(1):e230087.

<https://doi.org/10.1530/raf-23-0087>

2. Boyd RI, Shokry D, *et al et*, Spinella MJ. Perfluorooctanesulfonic Acid Alters Pro-Cancer Phenotypes and Metabolic and Transcriptional Signatures in Testicular Germ Cell Tumors. *Toxics*. 2024 Mar 22;12(4):232.

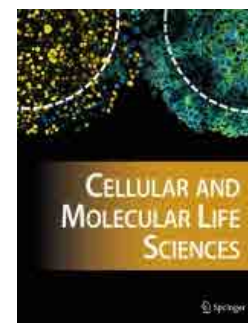
<http://dx.doi.org/10.3390/toxics12040232>



Transcription factors families expressed in the developing mouse epididymides were identified in this study, including RUNXs. Mechanistic characterisation suggested that RUNXs are master regulators of several essential signalling pathways necessary for the maintenance of differentiation of the epididymal epithelium.

Toriseva M, Björkgren I, Junnila A, Mehmood A, Mattsson J, Raimoranta I, Kim B, Laiho A, Nees M, Elo L, Poutanen M, Breton S, Sipilä P. RUNX transcription factors are essential in maintaining epididymal epithelial differentiation. *Cell Mol Life Sci*. 2024 Apr 17;81(1):183.

<https://doi.org/10.1007/s00018-024-05211-5>



The authors generated the human infertility single-cell testis atlas (HISTA), an interactive web tool for understanding human spermatogenesis through scRNA-Seq analysis. HISTA has already contributed to published research and can be updated with input from the research community or downloaded and modified for individual needs.

Mahyari E, Vigh-Conrad KA, Daube C, Lima AC, Guo J, Carrell DT, Hotaling JM, Aston KI, Conrad DF. The human infertility single-cell testis atlas (HISTA): an interactive molecular scRNA-Seq reference of the human testis *Andrology*. 2024

Apr 5. Epub ahead of print. <https://doi.org/10.1111/andr.13637>



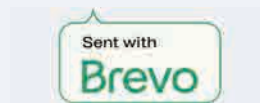
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Office: Szent István Krt. 7., 1055, Budapest, Hungary

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