Dear EAA Members,

This edition of publication news contains a lot of excellent ground-breaking work for your attention, including articles in *Nature* and *Science*! There are also two new issues of *Andrology*, including the latest special thematic issue on male contraception. Some exciting topics in this issue: immune modulation by gender-affirming testosterone treatment, ovarian germ cell ageing and cancer susceptibility, defective DNA repair and testis ageing, FSH and blood vessels, AMH/Sertoli cell function in inherited bone marrow failure syndromes, RNA-binding proteins in mammalian spermatogenesis, single cell transcriptome of cryptorchid testes, pathogenic variants in *RXFP2* and *HENMT1*, value of WES in infertility diagnostics, piRNA clusters in various species, PNLDC1 as a contraception target, CCDC188 and acephalic spermatozoa, immunosuppressive neutrophils in prostate cancer, and more.

The latest issues of *Andrology*

The biggest EAA event of 2024 was the European Congress of Andrology (ECA2024), held 4-6 September in Stockholm. Whether or not you attended the ECA, you can catch up with the work presented there by browsing through the abstracts:

Andrology, September 2024, pp 1-156
Volume 12, Issue S2
Special Issue: 13th European Congress of Andrology, September 4–6, 2024, Stockholm, Sweden

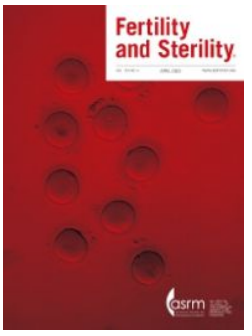
Do not miss the latest thematic issue of *Andrology*! It is focused on male contraception, and was edited by experts Christina Wang, Maria Cristina Meriggiola & Dimitrios G. Goulis. The issue contains the previously announced and published online *Guidelines for practice and development of male contraception*, which were jointly endorsed by the EAA and the ASA. There are also several interesting articles discussing various approaches to male or couple contraception, including a review on clinical guidelines on vasectomy.

Andrology, October 2024, pp 1463-1609

Clinical andrology and epidemiology

This excellent longitudinal study performed systems-level analyses in 23 individuals undergoing gender-affirming testosterone therapy (trans men). Their immune response shifted from 'female-like' (virus-fighting) to increased monocyte responses and potentiated interferon-γ responses, primarily in natural killer cells. These findings illustrate the dynamic and sex-divergent regulation of human immunity by sex hormones, with implications for the health of individuals undergoing hormone therapy.

Lakshmikanth T, Consiglio C, Sardh F, Forlin R, Wang J, Tan Z, Barcenilla H, Rodriguez L, Sugrue J, Noori P, Ivanchenko M, Piñero Páez L, Gonzalez L, Habimana Mugabo C, Johnsson A, Ryberg H, Hallgren Å, Pou C, Chen Y, Mikeš J, James A, Dahlqvist P, Wahlberg J, Hagelin A, Holmberg M, Degerblad M, Isaksson M, Duffy D, Kämpe O, Landegren N, Brodin P. Immune system adaptation during gender-affirming testosterone treatment. ***Nature***. 2024 Sep;633(8028):155-164. https://doi.org/10.1038/s41586-024-07789-z
Commentaries in *Nature*: McCarthy MM: https://doi.org/10.1038/d41586-024-02432-3
Sidik S: https://doi.org/10.1038/d41586-024-02869-6



In transgender girls, semen parameters, investigated in the context of fertility preservation, were variable, with only around 40% normospermic. In a subset of young patients, surgical sperm retrieval by electroejaculation was needed.

Ralph P, Mahoud M, Schlager D, Lee WG, Wafa R, Williamson E, Butler G, Ralph D, Sangster P. UK Data Collection of Semen Quality in Transgender Adolescent Females Seeking Fertility Preservation. ***Fertil Steril***. 2024 Sep 6:S0015-0282(24)02218-0. https://doi.org/10.1016/j.fertnstert.2024.09.006

How to treat gynecomastia in adolescent males with partial androgen insensitivity syndrome (PAIS)? This retrospective study found that gynecomastia is very frequent (91%) in PAIS and resolves spontaneously in only a small subset of patients. Surgical management may be more effective than medical therapy.

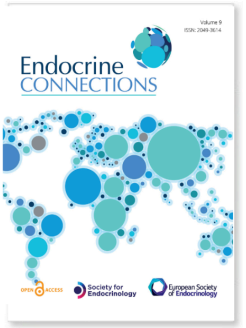
Patjamontri S, Lucas-Herald AK, Bryce J, van den Akker E, Cools M, Globa E, Guerra-Junior G, Hiort O, Hofman P, Holterhus PM, Hughes IA, Juul A, Nordenstrom A, Russo G, Stancampiano MR, Seneviratne SN, Tadokoro-Cuccaro R, Thankamony A, Weintrob N, Zelinska N, Ahmed SF. Gynecomastia and Its Management In Boys With Partial Androgen Insensitivity Syndrome. ***J Clin Endocrinol Metab***. 2024 Aug 30:dgae562. https://doi.org/10.1210/clinem/dgae562

The assessment of the efficacy of oral testosterone undecanoate (TLANDO 225 mg twice daily) in comparison to topical testosterone gel (AndroGel) in male patients with hypogonadism was performed in this trial.
The oral T treatment improved libido and sexual frequency. Serum T was within the reference range in 87% of patients without dose titration.

Miner M, Wang C, Kaminetsky J, Khera M, Goldstein I, Carson C 3rd, Chidambaram N, King S, Dobs A. Safety, efficacy, and pharmacokinetics of oral testosterone undecanoate in males with hypogonadism. ***Andrology***. 2024 Sep 10. https://doi.org/10.1111/andr.13747

This study investigated the association between reproductive hormones and brachial-ankle pulse wave velocity (as a proxy for arterial stiffness) in obese male and female subjects. The authors identified FSH as a potential risk factor for arteriosclerosis in obese male subjects.

Lin Y, Song E, Jin H, Jin Y. Reproductive hormones and sex differences in relation to brachial-ankle pulse wave velocity in obese subjects: a retrospective case-control study. ***Endocr Connect.*** 2024 Aug 19;13(9):e240190. https://doi.org/10.1530/ec-24-0190

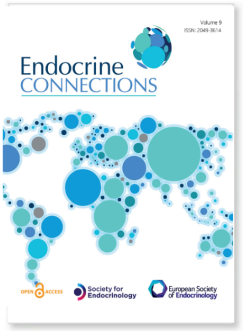


FSH receptor (FSHR) has been described also in extra-gonadal tissues. This study investigated FSH role in endothelium using human umbilical vein endothelial cells (HUVECs), and the findings suggest that FSH at high concentrations could compromise the endothelial membrane, partially explaining the increased risk of cardiovascular diseases in menopausal women and men with hypogonadism.

Rocca MS, Pannella M, Bayraktar E, Marino S, Bortolozzi M, Di Nisio A, Foresta C, Ferlin A. Extragonadal function of follicle-stimulating hormone: evidence for a role in endothelial physiology and dysfunction. ***Mol Cell Endocrinol.*** 2024 Sep 25:112378. https://doi.org/10.1016/j.mce.2024.112378

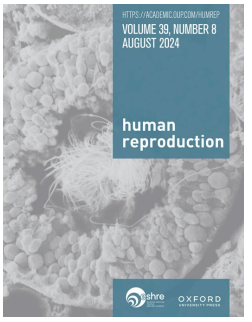
Fanconi anaemia (FA), Diamond–Blackfan anemia (DBA) and dyskeratosis-related disorders are inherited bone marrow failure syndromes (IBMFS). Individuals with FA have reduced fertility. In this study, serum AMH levels were assessed in pubertal and adult males with these disorders, and found significantly lower than in controls, suggesting a defect in the Sertoli cell function.

Stratton P, Giri N, Bhala S, Sklavos MM, Alter BP, Savage SA, Pinto LA. Reduced anti-Müllerian hormone levels in males with inherited bone marrow failure syndromes. ***Endocr Connect.*** 2024 Aug 7;13(9):e230510. https://doi.org/10.1530/ec-23-0510



Isolated Sertoli cells (SCs) from frozen testis samples of azoospermic adult Klinefelter men (47,XXY) are capable of proliferating in vitro and maintaining their karyotype, and main phenotypical and functional characteristics at least for 60 days, similarly to Sertoli cells isolated from 46,XY samples.

Giudice MG, Kanbar M, Poels J, Duquenne A, Wyns C. Long-term culture of human Sertoli cells from adult Klinefelter patients as a first step to develop new tools for unravelling the testicular physiopathology. ***Hum Reprod.*** 2024 Sep 5:deae201. https://doi.org/10.1093/humrep/deae201

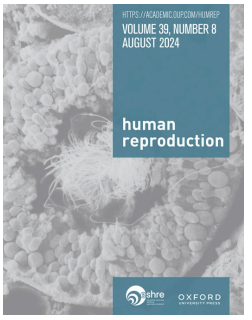


Androgenetics

Studies focussing on genetic integrity of ovarian germ cells can be relevant for male germ cells. This study found a link between ovarian ageing and cancer susceptibility, with damaging germline variants being associated with all-cause cancer risk in both men and women. Common genetic variants associated with earlier ovarian ageing associated with an increased rate of maternally derived de novo mutations.

Stankovic S, Shekari S, Huang QQ, Gardner EJ, Ivarsdottir EV, Owens NDL, Mavaddat N, Azad A, Hawkes G, Kentistou KA, Beaumont RN, Day FR, Zhao Y, Jonsson H, Rafnar T, Tragante V, Sveinbjornsson G, Oddsson A, Styrkarsdottir U, Gudmundsson J, Stacey SN, Gudbjartsson DF; Breast Cancer Association Consortium; Kennedy K, Wood AR, Weedon MN, Ong KK, Wright CF, Hoffmann ER, Sulem P, Hurles ME, Ruth KS, Martin HC, Stefansson K, Perry JRB, Murray A. Genetic links between ovarian ageing, cancer risk and de novo mutation rates. ***Nature***. 2024 Sep;633(8030):608-614. https://doi.org/10.1038/s41586-024-07931-x

Commentary by Anne Goriely in ***Nature***: Menopause age shaped by genes that influence mutation risk. https://doi.org/10.1038/d41586-024-02665-2



Biallelic variants in *RXFP2* were identified in two related patients with cryptorchidism and male infertility due to spermatogenic arrest at the spermatid stage. This study corroborates *RXFP2* as gene implicated in autosomal recessive congenital bilateral cryptorchidism, and possibly also in germ cell maturation.

Syryn H, Van de Velde J, De Clercq G, Verdin H, Dheedene A, Peelman F, Sinclair A, Ayers KL, Bathgate RAD, Cools M, De Baere E. Biallelic RXFP2 variants lead to congenital bilateral cryptorchidism and male infertility, supporting a role of RXFP2 in spermatogenesis. ***Hum Reprod.*** 2024 Sep 2:deae195. https://doi.org/10.1093/humrep/deae195

ANDROLOGY

HENMT1 encodes an RNA methyltransferase involved in the methylation of PIWI-interacting RNAs.
A homozygous nonsense variant in *HENMT1* was identified by WES in a patient with spermiogenesis arrest. Similar phenotype was observed in mutant mice, which had significantly derepressed retrotransposon LINE1.

Li M, Abbas T, Wang Y, Zhi A, Zhou J, Ma A, Murtaza G, Wu Y, Shah W, Zubair M, Khan MA, Iqbal F, Jiang X, Zhang H, Shi Q. A homozygous nonsense variant in HENMT1 causes male infertility in humans and mice. Andrology. 2024 Sep 25.
https://doi.org/10.1111/andr.13767

ANDROLOGY

The authors showed that exome sequencing (ES) with combined copy number variant (CNV) and single nucleotide variant (SNV) analysis is a reliable first-tier method to detect the most common genetic causes of male infertility.

In addition, new variants can be detected, almost doubling the diagnostic yield of this approach.

Oud MS, de Leeuw N, Smeets DFCM, Ramos L, van der Heijden GW, Timmermans RGJ, van de Vorst M, Hofste T, Kempers MJE, Stokman MF, D'Hauwers KWM, Faas BHW, Westra D. Innovative all-in-one exome sequencing strategy for diagnostic genetic testing in male infertility: Validation and 10-month experience. ***Andrology***. 2024 Aug 24.
https://doi.org/10.1111/andr.13742

BMC Medical Genomics

167 patients with male infertility and 210 fertile controls were screened using whole exome sequencing (WES).

Novel variants of 17 known causative and 12 candidate genes (many X-linked) were identified in 23 patients, again proving that WES is effective in the genetic diagnosis of primary male infertility.

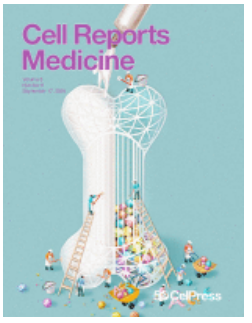
Zhou H, Yin Z, Ni B, Lin J, Luo S, Xie W. Whole exome sequencing analysis of 167 men with primary infertility. ***BMC Med Genomics*.** 2024 Sep 12;17(1):230.
https://doi.org/10.1186/s12920-024-02005-3

Translational and basic andrology

A marked improvement in the knowledge on the role of RNA-binding proteins (RBP) in mammalian spermatogenesis! This excellent study performed proteome-wide mapping of endogenous RBPs in mouse male germ cells and built an RBP atlas of mouse spermatogenesis. They discovered glutamic acid-arginine (ER) patch, which promotes RNA-binding activity and demonstrated consequences of disturbing the RBP system. The authors also performed WES of >1000 infertile men, uncovering enrichment of homozygous LOF and DNS variants in infertile patients.

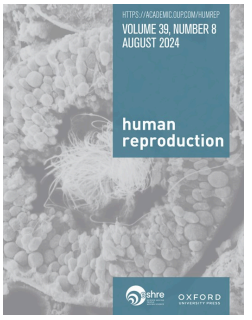
Li Y, Wang Y, Tan YQ, et al et Guo X, Lin M, Zheng K. The landscape of RNA-binding proteins in mammalian spermatogenesis. ***Science***. 2024 Aug 29:eadj8172.
https://doi.org/10.1126/science.adj8172

Single-cell transcriptomes were obtained from >45 K individual testicular cells obtained from adult men with cryptorchidism and healthy controls. In addition to problems with germ cells, the study found involvement of somatic cells. A novel mechanism is the activation and degranulation of mast cells, causing interstitial fibrosis via TGF-β1 and cathepsin G secretion.



Wang X, Liu Q, et al et, Guo J, Zhang Z. Decoding the pathogenesis of spermatogenic failure in cryptorchidism through single-cell transcriptomic profiling. ***Cell Rep Med.*** 2024 Sep 17;5(9):101709.
https://doi.org/10.1016/j.xcrm.2024.101709

This study constructed a single-cell transcriptomic atlas of testes from 3 young and 3 old men (validated in 10 biopsies from both age groups). The atlas offers insights into the molecular mechanisms of human testicular ageing, including suggestion that defective DNA repair in spermatogonial stem cells may be a potential driver for increased *de novo* germline mutations with age.

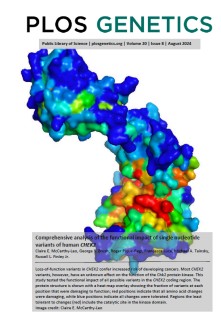


Xia K, Luo P, et al et Sun X, Deng C, Xiang AP. Single-cell RNA sequencing reveals transcriptomic landscape and potential targets for human testicular ageing. ***Hum Reprod.*** 2024 Sep 6:deae199.
https://doi.org/10.1093/humrep/deae199

PIWI-interacting RNAs (piRNAs) safeguard genome integrity by silencing mobile genetic elements. This elegant study generated a roadmap of piRNA clusters across seven species, and identified a class of dynamic piRNA clusters in humans.

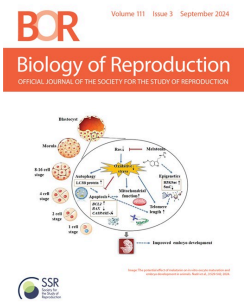
Konstantinidou P, Loubalova Z, Ahrend F, Friman A, Almeida MV, Poulet A, Horvat F, Wang Y, Losert W, Lorenzi H, Svoboda P, Miska EA, van Wolfswinkel JC, Haase AD. A comparative roadmap of PIWI-interacting RNAs across seven species reveals insights into de novo piRNA-precursor formation in mammals. ***Cell Reports.*** 2024 Sep 19;43(10):114777.

PNLDC1 is required for piRNA trimming and loss-of-function mutations in human *PNLDC1* cause azoospermia. In this study, the trimmer activity of PNLDC1 in mice was inactivated in postnatal germ cells causing transposon activation and male infertility. Ablating the catalytic activity of PNLDC1 in adult males is a promising novel strategy for non-hormonal male contraception.



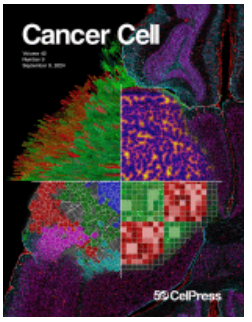
Wei C, Yan X, Mann JM, Geng R, Wang Q, Xie H, Demireva EY, Sun L, Ding D, Chen C. PNLDC1 catalysis and postnatal germline function are required for piRNA trimming, LINE1 silencing, and spermatogenesis in mice. ***PLoS Genet***. 2024 Sep 23;20(9):e1011429. https://doi.org/10.1371/journal.pgen.1011429

A knockout (KO) mouse model explored the role of coiled-coil domain containing 188 (Ccdc188), which shows testis-enriched expression. Ccdc188 KO male mice were sterile, most of spermatozoa were acephalic, and the spermatozoa in the cauda epididymis lacked a mitochondrial sheath.



Qiu Y, Shimada K, Yamamoto K, Ikawa M. Loss of CCDC188 causes male infertility with defects in the sperm head-neck connection in mice. ***Biol Reprod***. 2024 Sep 18:ioae137. https://doi.org/10.1093/biolre/ioae137

A remarkable study shedding light on hypercoagulability commonly associated with prostate cancer. Using single-cell RNA sequencing (scRNA-seq) of the prostate tumor microenvironment (TME) in a mouse model, the study found that immunosuppressive neutrophils (PMN-MDSCs) are a key source of coagulation factor X (FX). FX activation within the TME enhances androgen-independent tumor growth, and is associated with worse survival in patients with castrate-resistant prostate cancer.



Calì B, Troiani M, Bressan S, Attanasio G, et al et, Ruf W, de Bono J, Alimonti A. Coagulation factor X promotes resistance to androgen-deprivation therapy in prostate cancer. ***Cancer Cell.*** 2024 Sep 16:S1535-6108(24)00317-9. https://doi.org/10.1016/j.ccell.2024.08.018