



EAA Literature Alert Edition July 2022

If you are one of the new EAA members – this monthly service informs our members about noteworthy publications of relevance for andrologists, with special emphasis on studies performed in the EAA accredited training centres. Keywords for this edition: X-chromosome genes, hypogonadotropic hypogonadism, circular RNAs in Klinefelter syndrome, hypospadias, testosterone treatment of older men, weight loss and sperm, microfluidic sperm preparation, diagnosis of Leydig cell tumours, ultrasound therapy for prostate cancer, testis-sparing surgery, acrosome proteins, semen microbiota.

Androgenetics



A landmark multicentre study from IMIGC and GEMINI Consortia, led by the EAA President and involving several EAA centres. The study provided novel evidence for the involvement of numerous X chromosome genes in the pathogenesis of male infertility, based on a comprehensive analysis performed in >2300 men with azoospermia/cryptozoospermia. 21 genes were recurrently mutated in infertile men (e.g. *RBBP7*) and 34 genes were moderately linked to male infertility.

Riera-Escamilla A, Vockel M, Nagirnaja L, Xavier MJ, Carbonell A, Moreno-Mendoza D, Pybus M, Farnetani G, Rosta V, Cioppi F, Friedrich C, Oud MS, van der Heijden GW, Soave A, Diemer T, Ars E, Sánchez-Curbelo J, Kliesch S, O'Bryan MK, Ruiz-Castañe E; GEMINI Consortium, Azorín F, Veltman JA, Aston KI, Conrad DF, Tüttelmann F, Krausz C. Large-scale analyses of the X chromosome in 2,354 infertile men discover recurrently affected genes associated with spermatogenic failure. *Am J Hum Genet.* 2022 Jul 4:S0002-9297(22)00260-9. Epub ahead of print. PMID: 35809576.

<https://doi.org/10.1016/j.ajhg.2022.06.007>

Free Share Link: <https://authors.elsevier.com/a/1fNY5qeX2Won>

Commentary and interview with C. Krausz in *New Scientist*:

<https://www.newscientist.com/article/2327863-infertility-in-some-men-may-be-caused-by-x-chromosome-mutations/>



Exome sequencing (ES) data in a large cohort of patients with isolated hypogonadotropic hypogonadism (IHH), incl. Kallmann syndrome and their family members, identified 29 CNVs in 13 genes. Syndromic phenotypes resulting from single gene CNVs validated pleiotropy of some IHH genes.

Stamou MI, Brand H, Wang M, Wong I, Lippincott MF, Plummer L, Crowley WF, Talkowski M, Seminara S, Balasubramanian R. Prevalence and Phenotypic Effects of Copy Number Variants in Isolated Hypogonadotropic Hypogonadism. *J Clin Endocrinol Metab.* 2022 Jul 14;107(8):2228-2242.

<https://doi.org/10.1210/clinem/dgac300>

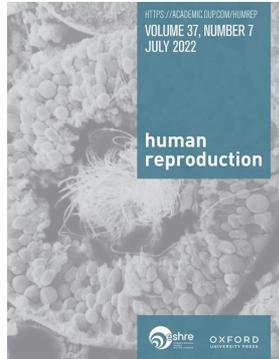
Comment by J. Young in JCEM:

<https://doi.org/10.1210/clinem/dgac377>

Profiling of circular RNAs (circRNAs) in patients with Klinefelter and Turner syndrome showed

differential expression of circRNAs throughout the genome in several tissues. The host-genes from which several of these circRNAs were derived were associated with known phenotypic traits.

Johannsen EB, Just J, Viuff MH, Okholm TLH, Pedersen SB, Lauritsen KM, Trolle C, Bülow Pedersen MG, Chang S, Fedder J, Skakkebaek A, Gravholt CH. Sex chromosome aneuploidies give rise to changes in the circular RNA profile: A circular transcriptome-wide study of Turner and Klinefelter syndrome across different tissues. *Front. Genet.*, 22 July 2022
<https://doi.org/10.3389/fgene.2022.928874>



This Chinese study of men with asthenozoospermia identified pathogenic variants in *KCNU1* (encoding a sperm-specific potassium channel) causing impaired acrosome reaction in humans and mouse.

Liu R, et al et, Kuang Y. Bi-allelic variants in *KCNU1* cause impaired acrosome reactions and male infertility. *Hum Reprod.* 2022 Jun 30;37(7):1394-1405. PMID: 35551387.
<https://doi.org/10.1093/humrep/deac102>

Clinical andrology and epidemiology

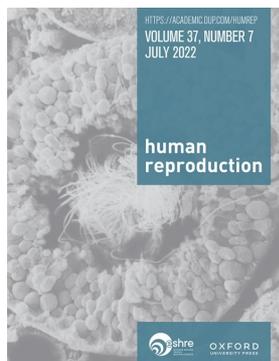
THE LANCET
Healthy Longevity



This international meta-analysis of randomised controlled trials concluded that testosterone therapy in men with hypogonadism (mean age 65 years) does not increase their short-term to medium-term risk of cardiovascular complications. However, hormone therapy should still be used selectively, paying attention to individual risk profiles in individuals (e.g. atherosclerosis).

Hudson J, Cruickshank M, Quinton R, Aucott L, Aceves-Martins M, Gillies K, Bhasin S, Snyder PJ, Ellenberg SS, Grossmann M, Travison TG, Gianatti EJ, van der Schouw YT, Emmelot-Vonk MH, Giltay EJ, Hackett G, Ramachandran S, Svartberg J, Hildreth KL, Groti Antonic K, Brock GB, Tenover JL, Tan HM, Kong CHC, Tan WS, Marks LS, Ross RJ, Schwartz RS, Manson P, Roberts S, Andersen MS, Magnussen LV, Hernández R, Oliver N, Wu F, Dhillon WS, Bhattacharya S, Brazzelli M, Jayasena CN. Adverse cardiovascular events and mortality in men during testosterone treatment: an individual patient and aggregate data meta-analysis. *Lancet Healthy Longevity* 2022; 3(6):e381-e393. PMID: 35711614.
[https://doi.org/10.1016/s2666-7568\(22\)00096-4](https://doi.org/10.1016/s2666-7568(22)00096-4)

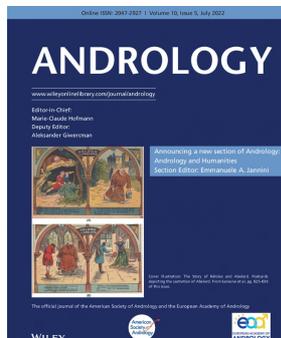
Commentary by E. Michos & M. Budoff: [https://doi.org/10.1016/S2666-7568\(22\)00115-5](https://doi.org/10.1016/S2666-7568(22)00115-5)



A randomized, controlled trial assessed the effect of weight loss on sperm concentration in obese men. The participants had 8-week low-calorie diet followed by 1 year of either: placebo, exercise training, or GLP-1 analogue liraglutide, alone or in combination. Sperm counts improved after the weight loss and all weight maintenance strategies.

Andersen E, Juhl CR, Kjølner ET, Lundgren JR, Janus C, Dehestani Y, Saupstad M, Ingerslev LR, Duun OM, Jensen SBK, Holst JJ, Stallknecht BM, Madsbad S, Tørekov SS, Barrès R. Sperm count is increased by diet-induced weight loss and maintained by exercise or GLP-1 analogue treatment: a randomized controlled trial. *Hum Reprod.* 2022; 37(7):1414-1422. PMID: 35580859.
<https://doi.org/10.1093/humrep/deac096>

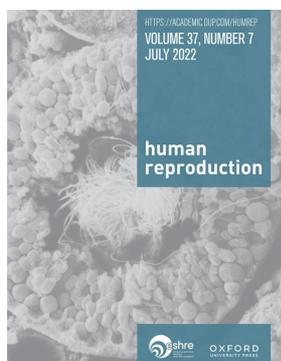
The latest publication from the European Male Aging Study (EMAS), which characterized INSL3 as a biomarker to assess gonadal status in aging



men. The study found that INSL3 declines at approximately 15% per decade from 40 years of age, and is affected by BMI. INSL3 is not affected by short-time gonadotrophin and testosterone level changes.

Anand-Ivell R, Heng K, Severn K, Antonio L, Bartfai G, Casanueva FF, Huhtaniemi IT, Giwercman A, Maggi M, O'Neill TW, Punab M, Rastrelli G, Slowikowska-Hilczer J, Tournoy J, Vanderschueren D, Wu FCW, Ivell R. Association of age, hormonal, and lifestyle factors with the Leydig cell biomarker INSL3 in aging men from the European Male Aging Study cohort. **Andrology**. 2022 Jun 30. doi: 10.1111/andr.13220. Epub ahead of print. PMID: 35770372.

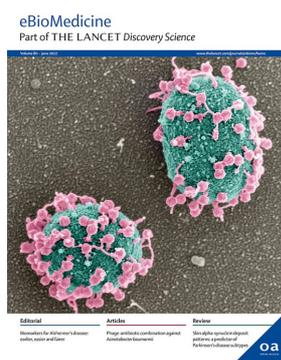
<https://doi.org/10.1111/andr.13220>



This large cohort study from Australia showed that children born with the aid of IVF/ICSI whose mothers were treated with adjuvant corticosteroids during the first trimester had an increased risk of cryptorchidism, hypospadias and talipes. Physicians should be careful in using corticosteroids in the critical first trimester and should counsel patients regarding the potential risks of this treatment.

Thalluri V, Woodman RJ, Vollenhoven B, Tremellen K, Zander-Fox D. Exposure to corticosteroids in the first trimester is associated with an increased risk of urogenital congenital anomalies. **Hum Reprod**. 2022 Jun 23:deac142. Epub ahead of print. PMID: 35734908.

<https://doi.org/10.1093/humrep/deac142>



This study from Ghent, Vienna and Copenhagen assessed the endocrine and seminal parameters, and performed exome-based analysis of a panel of selected genes in 193 young adult men born with non-syndromic hypospadias. Growth and spermatogenesis were significantly compromised, especially in men born small for gestational age. Long-term andrological follow-up is recommended.

Tack LJW, Spinoit AF, Hoebeke P, Riedl S, Springer A, Tonnhofer U, Hiess M, Weninger J, Mahmoud A, Tilleman K, Van Laecke E, Juul A, Albrethsen J, De Baere E, Van De Velde J, Verdin H, Cools M. Endocrine outcome and seminal parameters in young adult men born with hypospadias: A cross-sectional cohort study. **eBioMedicine**. 2022 Jun 24;81:104119. Epub ahead of print. PMID: 35759917.

<https://doi.org/10.1016/j.ebiom.2022.104119>



This Swedish study found that men born with hypospadias have an increased risk of impacted growth and androgen-related comorbidities in adolescence and adulthood, including hypogonadism, and metabolic and cardiovascular disease, increasing with severity of phenotype.

Phillips L, Lundholm C, Kvist U, Almqvist C, Nordenskjöld A, Nordenvall AS. Increased androgen-related comorbidity in adolescents and adults born with hypospadias: a population-based study. **Andrology**. 2022 Jul 18. doi: 10.1111/andr.13229. Epub ahead of print. PMID: 35848332.

<https://doi.org/10.1111/andr.13229>

Contrast-enhanced ultrasound (CEUS) demonstrated high diagnostic accuracy in identifying benign Leydig cell tumours, the most common non-palpable tumours detected in infertile men, who may benefit from enucleation.

Corcioni B, Brandi N, Marasco G, Gaudiano C, De Cinque A, Ciccarese F, Ercolino A, Schiavina R, Brunocilla E, Renzulli M, Golfieri R. Multiparametric Ultrasound for the diagnosis of Leydig cell tumours in non-palpable testicular lesions. **Andrology**. 2022 Jul 17. Epub ahead of print. PMID: 35842907.

<https://doi.org/10.1111/andr.13233>

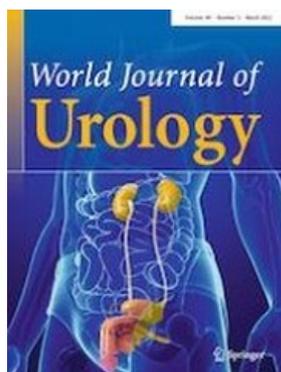


THE LANCET Oncology



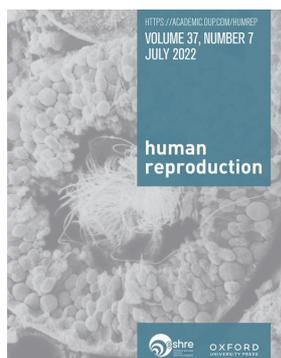
Attention urologists treating patients with prostate cancer. This study found that MRI-guided focused ultrasound focal therapy can effectively and safely reduce treatment burden for patients with localised grade group 2 or 3 intermediate-risk prostate cancer, who can be spared radical whole-gland treatment.

Ehdaie B, Tempany CM, Holland F, Sjoberg DD, Kibel AS, Trinh QD, Durack JC, Akin O, Vickers AJ, Scardino PT, Sperling D, Wong JYC, Yuh B, Woodrum DA, Mynderse LA, Raman SS, Pantuck AJ, Schiffman MH, McClure TD, Sonn GA, Ghanouni P. MRI-guided focused ultrasound focal therapy for patients with intermediate-risk prostate cancer: a phase 2b, multicentre study. *Lancet Oncol.* 2022 Jul;23(7):910-918. doi: 10.1016/S1470-2045(22)00251-0. Epub 2022 Jun 14. PMID: 35714666. [https://doi.org/10.1016/s1470-2045\(22\)00251-0](https://doi.org/10.1016/s1470-2045(22)00251-0)



This systematic review and meta-analysis confirmed that testis-sparing surgery (TSS) in patients with testicular germ cell tumours (TGCT), which requires adjuvant testicular radiotherapy to eradicate GCNIS, has no real benefits (except very rare exceptions), and radical orchiectomy remains the standard of care.

Grogg JB, Dursun ZH, Beyer J, Eberli D, Poyet C, Hermanns T, Fankhauser CD. Oncological and functional outcomes after testis-sparing surgery in patients with germ cell tumours: a systematic review of 285 cases. *World J Urol.* 2022 Jul 12. Epub ahead of print. PMID: 35821265. <https://link.springer.com/article/10.1007/s00345-022-04048-6>



Patients randomized to microfluidic sperm preparation had similar cleavage- and blastocyst-stage embryo quality and clinical and ongoing pregnancy rates to those who underwent standard sperm processing for IVF with ICSI.

Quinn MM, Ribeiro S, Juarez-Hernandez F, Simbulan RK, Jalalian L, Cedars MI, Rosen MP. Microfluidic preparation of spermatozoa for ICSI produces similar embryo quality to density-gradient centrifugation: a pragmatic, randomized controlled trial. *Hum Reprod.* 2022; 37(7):1406-1413. PMID: 35522187. <https://doi.org/10.1093/humrep/deac099>

Translational and basic andrology

A comprehensive and dynamic cell map of first-



and second-trimester human (and mouse) gonads, published by an international team led from Wellcome Sanger Institute, Cambridge, UK.

Among exciting findings concerning the development of the testis: identification of a new gonadal cell lineage on the interface with mesonephros (PAX8+), two different populations of fetal testicular macrophages, evidence for microglia- and osteoclast-like molecular signatures, and more.

Garcia-Alonso L, Lorenzi V, Mazzeo CI, Alves-Lopes JP, Roberts K, Sancho-Serra C, Engelbert J, Marečková M, Gruhn WH, Botting RA, Li T, Crespo B, van Dongen S, Kiselev VY, Prigmore E, Herbert M, Moffett A, Chédotal A, Bayraktar OA, Surani A, Haniffa M, Vento-Tormo R. Single-cell roadmap of human gonadal development. *Nature* 2022 Jul 6. Epub ahead of print. PMID: 35794482.

<https://doi.org/10.1038/s41586-022-04918-4>.



In vitro culture of human fetal testicular tissues was used to investigate the effects of chemotherapy-exposure on germ cell sub-populations. Numbers of germ cells were significantly reduced in tissues from fetuses exposed to cisplatin at mid- and late-second trimester, but not earlier.

Matilionyte G, Rimmer MP, Spears N, Anderson RA, Mitchell RT. Cisplatin Effects on the Human Fetal Testis – Establishing the Sensitive Period for (Pre)Spermatogonial Loss and Relevance for Fertility Preservation in Pre-Pubertal Boys. *Frontiers Endocrinol* 14 July 2022.

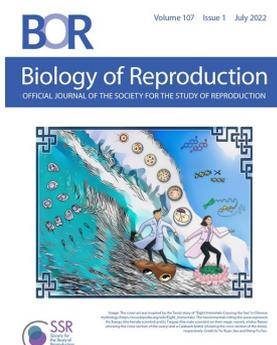
<https://doi.org/10.3389/fendo.2022.914443>



Bone marrow derived mesenchymal stem cells (BM-MSC) resemble Sertoli cells. In this mouse model study BM-MSC were co-cultured with spermatogonial stem cells (SSC) *in vitro*. The authors reported that the system supported the survival and expansion of the SSPC pool and differentiation of spermatogonia to round spermatids.

Önen S, Köse S, Yersal N, Korkusuz P. Mesenchymal stem cells promote spermatogonial stem/progenitor cell pool and spermatogenesis in neonatal mice *in vitro*. *Sci Rep*. 2022 Jul 7;12(1):11494. doi: 10.1038/s41598-022-15358-5. PMID: 35798781.

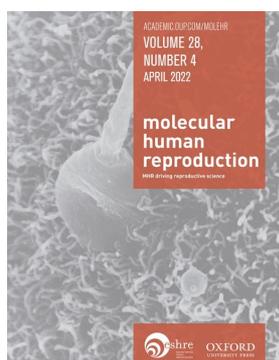
<https://doi.org/10.1038/s41598-022-15358-5>



PRSS54 is a testis-specific serine protease in mouse and human. This study demonstrated that it is present in sperm, and loss of PRSS54 in mice resulted in abnormalities of spermatids, acrosome deformation and defective sperm-zona penetration. The data indicate that PRSS54 plays an important role in regulating acrosome biogenesis, sperm function and male fertility.

Shen C, Xiong W, Li C, Ge H, Shen Y, Tang L, Zhang H, Lu S, Fei J, Wang Z. Testis-specific serine protease PRSS54 regulates acrosomal granule localization and sperm head morphogenesis in mice. *Biol Reprod*. 2022 Jul 21:ioac146. Epub ahead of print. PMID: 35863763.

<https://doi.org/10.1093/biolre/ioac146>



The authors determined the role of sulfhydryl oxidase (SOX), secreted by seminal vesicle, in epididymal sperm maturation in the mouse model. The SOX protein binds to spermatozoa and increases their progressive motility while inhibiting the acrosome reaction *in vitro*. The SOX binding to the sperm acrosome may prevent premature capacitation.

Balu R, Ramachandran SS, Mathimaran A, Jeyaraman J, Paramasivam SG. Functional significance of mouse seminal vesicle sulfhydryl oxidase on sperm capacitation *in vitro*. *Mol Hum Reprod*. 2022 Jul 9:gaac025. Epub ahead of print. PMID: 35809071.

<https://doi.org/10.1093/molehr/gaac025>

This study characterized the seminal microbiota in fertile controls and infertile men using full-length *16S rRNA* gene sequencing, and compared to classic sperm quality parameters and oxidative stress levels. Significant differences between fertile and infertile men were found in the relative presence of several microbial genera.

Garcia-Segura S, Del Rey J, Closa L, Garcia-Martínez I, Hobeich C, Castel AB, Vidal F, Benet J, Ribas-Maynou J, Oliver-Bonet M. Seminal Microbiota of Idiopathic Infertile Patients and Its Relationship With Sperm DNA Integrity. *Front Cell Dev Biol.* 2022 Jun 28;10:937157. doi: 10.3389/fcell.2022.937157. PMID: 35837328; PMCID: PMC9275566.
<https://doi.org/10.3389/fcell.2022.937157>

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