

Dear EAA Members,

For your special attention: two best practice guideline papers have been published in *Andrology* in September (on the "early view" page): the updated EAA-EMQN guidelines for the analysis of the Y-chromosome microdeletions, and the EAA-ASA guidelines on male contraception. The latter is the first ever instance of clinical guidelines prepared jointly by the EAA and the ASA. We also recommend - as always - the latest issue of *Andrology* (vol. 11, nr. 7), with several interesting articles (some previously announced) including the important call for improving standards of reporting the semen analysis results, with an editorial comment. Other interesting topics: sex hormones, influence of obesity, alcohol consumption on male health, risk factors for sexual dysfunction in middle-aged men, diagnostic biopsy and sperm retrieval in mTESE, sperm DNA methylation and ART outcomes, organ culture of immature human testis tissue, DMRT1 and germline commitment, gene-editing correction of Leydig cell insufficiency, and more.

## Clinical andrology and epidemiology



An expert panel of EAA and ASA experts reviewed the current state of the art in male contraception, and generated a consensus guideline comprising sixty evidence-based and graded recommendations, with focus on couple-centered communication, barrier methods, semen analysis and contraceptive efficacy, physical agents, and surgical methods. The authors underlined that efficient and safe, preferably reversible, male-directed methods must be evaluated and introduced into clinical practice.

Wang C, Meriggiola MC, Amory JK, Barratt CLR, Behre HM, Bremner WJ, Ferlin A, Honig S, Kopa Z, Lo K, Nieschlag E, Page ST, Sandlow J, Sitruk-Ware R, Swerdloff RS, Wu FCW, Goulis DG. Practice and development of male contraception: European Academy of Andrology and American Society of Andrology guidelines. *Andrology*. 2023 Sep 20. Epub ahead of print. <https://doi.org/10.1111/andr.13525>

### Annals of Internal Medicine®

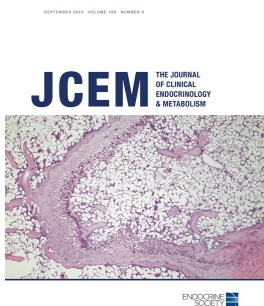
A meta-analysis of prospective cohort studies (>25000 men) revealed multiple factors associated with variations in sex hormone concentration.

Reduced testosterone and increased LH concentrations may indicate impaired testicular function in older age. Interpretation of individual testosterone measurements should account particularly for age (>70 y.), obesity, diabetes, and cancer.

Marriott RJ, Murray K, Adams RJ, Antonio L, Ballantyne CM, Bauer DC, Bhasin S, Biggs ML, Cawthon PM, Couper DJ, Dobs AS, Flicker L, Handelsman DJ, Hankey GJ, Hannemann A, Haring R, Hsu B, Karlsson M, Martin SA, Matsumoto AM, Mellström D, Ohlsson C, O'Neill TW, Orwoll ES, Quartagno M, Shores MM, Steveling A, Tivesten A, Travison TG, Vanderschueren D, Wittert GA, Wu FCW, Yeap BB. Factors Associated With Circulating Sex Hormones in Men : Individual Participant Data Meta-analyses. *Ann Intern Med*. 2023 Aug 29. Epub ahead of print. <https://doi.org/10.7326/m23-0342>

Men with obesity (18-60 y.) with normal sperm concentration or oligozoospermia were randomised to either a low energy diet (800Kcal/day) for 16-weeks, or a brief dietary intervention. Both treatments may be sufficient to improve sperm motility in men with obesity but larger controlled trials are needed.

Sharma A, Papanikolaou N, Abou Sherif S, Dimakopoulou A, Thaventhiran T, Go C, Holtermann Entwistle O, Brown A, Luo R, Jha R, Prakash A, Khalifa D, Lewis H, Ramaraju S, Leeds AR, Chahal H, Purkayastha S, Henkel R, Minhas S, Frost G,



Dhillon WS, Jayasena CN. Improvements in sperm motility following low or high intensity dietary interventions in men with obesity. *J Clin Endocrinol Metab.* 2023 Sep 1:dgad523. Epub ahead of print. <https://doi.org/10.1210/clinem/dgad523>



Two articles in the latest issue of Andrology looked at the impact of life-style factors on male reproductive function. The Herkommer et al. study, showed that one-third of 50-year-old men experienced some form of sexual dysfunction. Several risk factors (e.g. obesity) are modifiable, underlying the role of men's education. The meta-analysis by Santi et al. showed that the alcohol consumption reduced circulating concentrations of total and free testosterone, and SHBG, but increased the levels of estradiol.

Herkommer K, Meissner VH, Dinkel A, Jahnen M, Schiele S, Kron M, Ankerst DP, Gschwend JE. Prevalence, lifestyle, and risk factors of erectile dysfunction, premature ejaculation, and low libido in middle-aged men: first results of the Bavarian Men's Health-Study. *Andrology.* 2023 Sep 7. Epub ahead of print. <https://doi.org/10.1111/andr.13524>  
Santi D, Cignarelli A, Baldi M, Sansone A, Spaggiari G, Simoni M, Corona G. The chronic alcohol consumption influences the gonadal axis in men: Results from a meta-analysis. *Andrology.* 2023 Sep 14. Epub ahead of print. <https://doi.org/10.1111/andr.13526>



A retrospective analysis of 50 NOA males who underwent mTESE found that initial diagnostic biopsy did not detect spermatozoa in half of the patients who later showed positive sperm retrieval. Preoperative variables were not consistently predictive of sperm retrieval success, except that increased inflammation biomarkers reduced the chance of sperm retrieval during mTESE.

Kaltsas A, Markou E, Zachariou A, Dimitriadis F, Symeonidis EN, Zikopoulos A, Mamoulakis C, Tien DMB, Takenaka A, Sofikitis N. Evaluating the Predictive Value of Diagnostic Testicular Biopsy for Sperm Retrieval Outcomes in Men with Non-Obstructive Azoospermia. *Journal of Personalized Medicine.* 2023; 13(9):1362. <https://doi.org/10.3390/jpm13091362>



The Utah team analysed sperm DNA methylation data from 1344 men seeking fertility assessment or treatment in comparison with data from sperm donors. Methylation variability in gene promoters could augment the predictive ability of the semen analysis and be a reliable biomarker for assessing ART outcomes.

Miller RH, DeVilbiss EA, Brogaard KR, Norton CR, Pollard CA, Emery BR, Aston KI, Hotaling JM, Jenkins TG. Epigenetic determinants of reproductive potential augment the predictive ability of the semen analysis. *F S Sci.* 2023 Sep 13:S2666-335X(23)00049-6. Epub ahead of print. <https://doi.org/10.1016/j.xfss.2023.09.001>



Mild Leydig cell insufficiency affects a substantial proportion of testicular cancer survivors. This trial examined the effect of transdermal testosterone (T) replacement therapy vs placebo in correlation with pre-treatment hormone profiles, and found that the patients with low INSL3 and hCG-stimulated T concentrations had decreased fat mass after the T therapy.

Medici C, Jørgensen N, Juul A, Albrethsen J, Kreiberg M, Lauritsen J, Wagner T, Rosenvilde J, Daugaard G, Bandak M. Insulin-like Factor 3, Basal and Human Chorionic Gonadotropin-Stimulated Testosterone as Biomarkers to Predict the Effect of Testosterone Replacement in Testicular Cancer Survivors with Mild Leydig Cell Insufficiency. *Clin Genitourin Cancer.* 2023 Aug 16:S1558-7673(23)00188-X. Epub ahead of print. <https://doi.org/10.1016/j.clgc.2023.08.005>

The feasibility of inducing in vitro spermatogenesis from human immature testicular tissue (ITT) cryopreserved prior to initiation of gonadotoxic therapy was investigated. Thawed ITT from pre- and peri-pubertal patients were maintained in organotypic culture for up to 32 days. Spermatogonia differentiated to primary spermatocytes but complete spermatogenesis was not observed.

Younis N, Caldeira-Brant AL, Chu T, Abdalla S, Orwig KE. Human immature testicular tissue organ culture: a step towards fertility preservation and restoration. *Front Endocrinol* (Lausanne). 2023 Aug 28;14:1242263. <https://doi.org/10.3389/fendo.2023.1242263>

## Debate



The background behind a checklist that declares the laboratory methods used in a scientific study was explained by internationally recognised andrologists. They stressed that valid andrological diagnoses and treatments cannot rely solely on semen examination results. Therefore, scientific journals should require a checklist helping assessment of submitted manuscripts to improve the quality of their publications.

Björndahl L, Esteves SC, Ferlin A, Jørgensen N, O'Flaherty C. Improving standard practices in studies using results from basic human semen examination. *Andrology*. 2023 Oct;11(7):1225-1231. <https://doi.org/10.1111/andr.13504>  
**Editorial comment:** <https://doi.org/10.1111/andr.13518>

## Methods



A previously developed procedure of sperm cryopreservation with a tip-microVapour Fast Freezing, was tested in this pilot study. The procedure produced lower levels of sperm DNA fragmentation than straws, and appears to be promising to cryopreserve semen samples from severe oligozoospermic patients.

Dabizzi S, Calamai C, Degl'Innocenti S, Boni L, Vignozzi L, Maggi M, Baldi E, Muratori M. Tip-microVapour Fast Freezing: A novel easy method for cryopreserving severe oligozoospermic samples. *Andrology*. 2023 Sep 14. Epub ahead of print. <https://doi.org/10.1111/andr.13531>

## Androgenetics



A thorough update of the 2013 EAA-EMQN (the European Molecular Genetics Quality Network) laboratory guidelines has been published. The Guidelines summarize recent clinically relevant advances and provide an update on the results of the external quality assessment program. A must for all diagnostic labs in the field of androgenetics.

Krausz C, Navarro-Costa P, Wilke M, Tüttelmann F. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions: State of the art 2023. *Andrology*. 2023 Sep 6. Epub ahead of print. <https://doi.org/10.1111/andr.13514>



This study from the EAA Centre in Riga investigated by WES the association of azoospermia (NOA) with genetic variant burden. Bioinformatic analysis identified increased burden of alterations in genes involved in DNA binding/condensation and repair, and in ribosome biosynthesis and gene expression processes, including sumoylation.

Alkšere B, Puzuka A, Lazovska M, Vainselbaum NM, Vasiļonoks JK, Penka E, Fodina V, Ērenpreiss J. Exploring the Potential of Exome Sequencing in Idiopathic Azoospermia: A Genetic Burden and Network Analysis Study. *Andrologia*, Article ID 3107568, 2023, in press. <https://doi.org/10.1155/2023/3107568>

## Translational and basic andrology



Primordial germ cell (PGC) specification establishes an epigenetic programme for gametogenesis. This study followed the progression of PGC-like cells derived from human embryonic stem cells in vitro and concluded that DMRT1 as an essential factor regulating the transition from nascent PGCs to gametogenesis-competent cells, involving locus-specific epigenetic resetting.

Irie N, Lee SM, Lorenzi V, Xu H, Chen J, Inoue M, Kobayashi T, Sancho-Serra C, Drousioti E, Dietmann S, Vento-Tormo R, Song CX, Surani MA. DMRT1 regulates human germline commitment. *Nature Cell Biol.* 2023 Sep 14. doi: 10.1038/s41556-023-01224-7. Epub ahead of print. <https://doi.org/10.1038/s41556-023-01224-7>



Hereditary primary hypogonadism (HPH) can be caused by aberrations in testosterone synthesis in Leydig cells. This study reports correcting HPH by transplantation of gene-edited stem Leydig cells using a novel Lhcgr nonsense-point-mutation mouse model. Ex vivo gene-editing approach is a promising strategy for HPH therapy in men.

Xia K, Wang F, Tan Z, et al et, Xiang AP. Precise Correction of Lhcgr Mutation in Stem Leydig Cells by Prime Editing Rescues Hereditary Primary Hypogonadism in Mice. *Adv Sci.* 2023 Sep 11:e2300993. Epub ahead of print. <https://doi.org/10.1002/adv.202300993>



This experimental study shows the potential for elevated activin A signalling to replicate some aspects of fetal phthalate exposure prior to the masculinization programming window, influencing fetal testis growth and increasing the risk of testicular dysgenesis.

Whiley PAF, Luu MCM, O'Donnell L, Handelsman DJ, Loveland KL. Testis exposure to unopposed/elevated activin A *in utero* affects somatic and germ cells and alters steroid levels mimicking phthalate exposure. *Front Endocrinol (Lausanne).* 2023 Sep 1;14:1234712. <https://doi.org/10.3389/fendo.2023.1234712>

### Case of the month



The first report of the overlap between White-Sutton syndrome and Kallmann syndrome caused by a *POGZ* mutation in a patient with congenital hypogonadotropic hypogonadism. The defect did not impair GnRH neurogenesis but disrupted growth of neural progenitors and branching of axons. Puberty was induced successfully but the testis function remained insufficient.

Eskici N, Madhusudan S, Vaaralahti K, Yellapragada V, Gomez-Sanchez C, Kärkinen J, Almusa H, Brandstack N, Miettinen PJ, Wang Y, Raivio T. Congenital hypogonadotropic hypogonadism in a patient with a de novo *POGZ* mutation. *Eur J Endocrinol.* 2023 Aug 2;189(2):271-280. <https://doi.org/10.1093/ejendo/lvad111>

### European Academy of Andrology

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

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