



Literature alert

March 2026

After a one-year pause, the literature alerts are back due to popular demand. This edition highlights fertility preservation in pre-pubertal patients, translational work in testicular and prostate cancer, a couple of excellent clinical trials, an attempt to catalogue comorbidities of monogenic forms of infertility, as well as several ground-breaking basic studies, including building the testis from pluripotent stem cells *in vitro*, germ cell development profiling, microglia signalling to the gonads, 'selfish' small RNAs, epigenetic inheritance, and programming of spermiogenesis. For advances in sperm analysis scroll all the way to the end.

For new EAA members, a brief explanation: These monthly alerts highlight recent noteworthy publications in all areas of andrology. We prioritise original studies and contributions from EAA centres. We also promote our official journal *Andrology*. Original studies are increasingly published first as preprints, so we present also these, with a general warning that the peer-review has not yet been completed. Review articles are generally excluded, except when they present important clinical guidelines, or high-quality meta-analyses. We encourage you to share these alerts with colleagues. If you wish to suggest a publication for inclusion – please contact the EAA Librarian (RajpertDeMeyts.EAA@gmail.com).

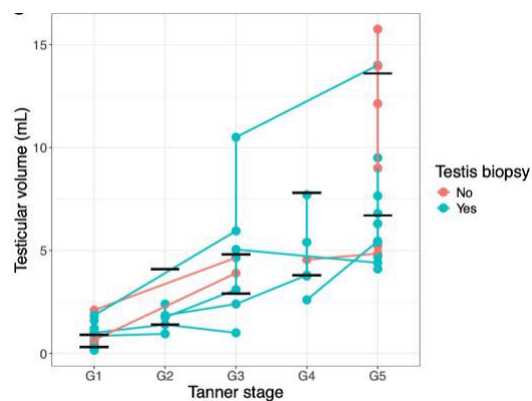
The latest issue of *Andrology*



The March 2026 issue of *Andrology* has been released. It contains articles published online during the second half of 2025, so you might have read some of the articles before. The **Editor's pick** of the month is a very impressive original study of penis innervation, emphasizing the frenular delta as a specialized centre of sexual sensation (*Cepeda-Emiliani et al.* from Spain) but the issue contains several interesting articles. Do not miss the interview with a distinguished andrologist, Dr. Giovanni Colpi, and an entertaining biblical story of infertility (or rather late-onset fertility) in Abraham's family.

<https://onlinelibrary.wiley.com/toc/20472927/2026/14/3>

Clinical andrology and epidemiology



Banking of testicular tissue has been an experimental option for fertility preservation in boys subjected to gonadotoxic treatment. The EAA Centre in Ghent (Belgium) is one of the leaders in the field. The team followed systematically the boys who underwent testicular biopsies, with reassuring results (*Delgouffe et al.*). All patients had preserved testis function, and experienced spontaneous puberty.

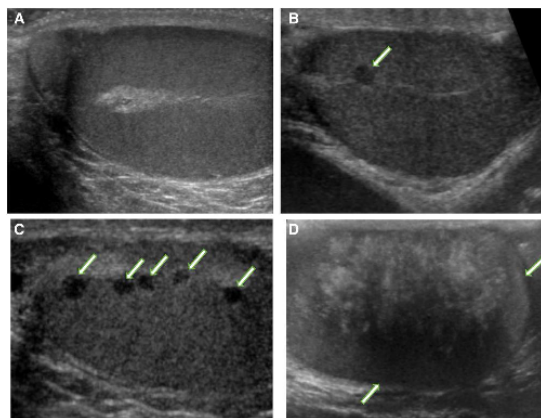
The quality of the stored biopsies was subsequently confirmed by the first ever successful autologous transplantation of the cryopreserved immature testicular tissue to a now adult survivor. The tissue grafts revascularized and initiated spermatogenesis, giving hope for fertility restoration.

Delgouffe E, Regin M, Vloeberghs V, Ernst C, Tournaye H, Gies I, Goossens E. Pubertal development following pediatric gonadotoxic treatment and immature testicular tissue banking. *Int J Mol Sci.* 2026 Feb 25;27(5):2139.

<https://doi.org/10.3390/ijms27052139>

Goossens E, Vloeberghs V, De Beer E, Delgouffe E, Mateizel, I, Ernst C, Waelput W, Gies I, Tournaye H. First successful transplant of human immature testicular tissue after gonadotoxic therapy during childhood: complete spermatogenesis in intra-testicular grafts. *medRxiv PREPRINT*

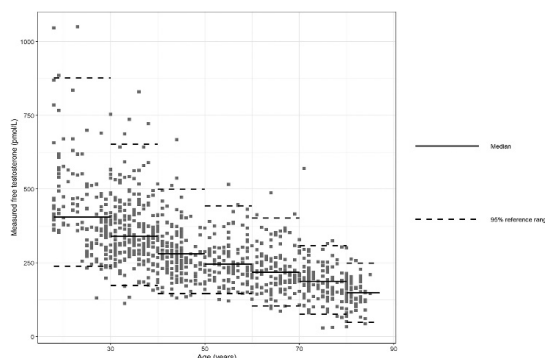
<https://doi.org/10.64898/2026.03.04.26347483>;



To characterize the natural history of TART in males with classic CAH, this longitudinal study analysed clinical data and serial scrotal ultrasounds during childhood and in adulthood. TART formation was frequently found in prepubertal boys, with a characteristic pattern of development from a single hypoechoic nodule to multiple nodules to a mass near the mediastinum testis. The authors proposed a radiologic staging.

Vaid S, Kulkarni S, Marko J, Sinaii N, Sukin C, Burkardt D, Eustace Q, Mallappa A, Merke DP. Longitudinal Characterization and Sonographic Staging of Testicular Adrenal Rest Tumors. *J Clin Endocrinol Metab.* 2026 Feb 20;111(3):698-706.

<https://doi.org/10.1210/clinem/dgaf498>



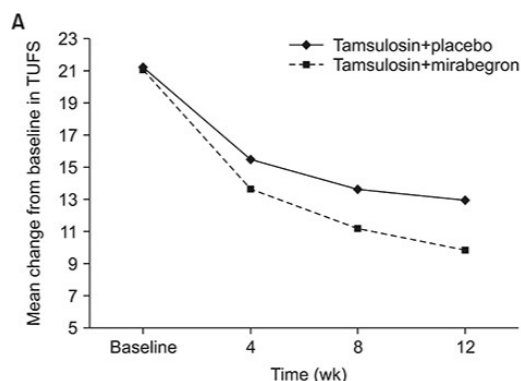
If you have missed this important reference study from the EAA Centre in Leuven (Belgium) – it has appeared in JCEM in its final form. The study reported LC-MS/MS-measured serum concentrations of free testosterone in a large cohort of healthy males. The authors highlighted the influence of age and BMI.

Walravens J, Snaterse G, Narinx N, Reyns T, Van Uytvanghe K, Vanderschueren D, Wu FCW, Kaufman JM, Antonio L, Fiers T, Lapauw B. Age-Stratified Reference Ranges for Directly Measured Serum Free Testosterone in Community-Dwelling and Healthy Men. *J Clin Endocrinol Metab.* 2026 Feb 20; 111(3): e787-e793.

<https://doi.org/10.1210/clinem/dgaf507>

The largest ever retrospective cohort study addressed the possible aggravation of prostatic disorders by testosterone replacement therapy (TRT) in older men (≥ 65 y.) with hypogonadism, using data from Medicare (USA). TRT use was associated with significant reduction in prostate cancer hazard (16%) but a modest increase (13%) in benign prostatic hyperplasia hazard. These associations varied by treatment duration, route, and AI coadministration.

Baik SH, Baye F, Fung KW, Xian H, McDonald CJ. Association Between Testosterone Replacement Therapy and Prostatic Disorders in Elderly Hypogonadal Men. *J Clin Endocrinol Metab*. 2026 Feb 20;111(3):e794-e810. <https://doi.org/10.1210/clinem/dgaf504>



This multicentre placebo-controlled trial from Korea evaluated the efficacy and safety of mirabegron and tamsulosin combination therapy compared to tamsulosin monotherapy in patients with benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS). The combination therapy was more effective than monotherapy in improving LUTS, particularly storage symptoms, with a comparable safety profile.

Kam SC, Shin YS, *et al.* et Kim TH. Efficacy and Safety of Mirabegron and Tamsulosin Combination Therapy Compared to Tamsulosin Monotherapy for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: Results of a Multicenter, Randomized, Double-Blind, Phase III Clinical Trial. *World J Mens Health*. 2026 Apr 44(2): 427-437. <https://doi.org/10.5534/wjmh.250085>

A special issue of *Andrology* devoted to **testicular cancer** is currently being compiled and will appear in print soon. We highlight here three recent studies:



In the collaborative study from two EAA Centres (Florence and Barcelona), the overall and site-specific cancer risk was assessed among relatives of patients with testicular germ cell tumours (TGCT). Interestingly, familial clustering of cancers comprised several other malignancies, incl. those in the Lynch syndrome spectrum.

Krausz C, Abrardo C, Rosta V, Moreno-Mendoza D, Bressan L, Vannucci M, Passerotti R, Meacci A, Farnetani G, Bonini V, Corona G, Fino MG, Ruiz-Castañé E, Riera-Escamilla A. Broader familial cancer risk in relatives of testicular cancer patients: Insights from two Mediterranean populations. *Andrology*. 2026 Mar 10: e70211. <https://doi.org/10.1111/andr.70211>

Semen samples from TGCT patients were comprehensively analysed before and after chemotherapy. Patients with non-seminoma had better baseline sperm parameters than those with seminoma but the opposite was observed after chemotherapy. Notably, sperm quality correlated positively with abundance of a critical epigenetic mark histone H4K12ac.

Sanovec O, Simonik O, *et al.* et Komrskova K. Impact of chemotherapy on sperm functional characteristics in patients with testicular germ cell tumours. *Andrology*. 2026 Mar 6:e70203. <https://doi.org/10.1111/andr.70203>

The EAA centre in Copenhagen has a long-standing experience in diagnosis of testicular cancer. In this study, the expression of currently most sensitive serum TGCT markers; miR-371a-3p and miR-373-3p, was explored in TGCT tissues and demonstrated a good correlation with the levels in serum.

Mørup N, Tatli M, Wagner T, Albrechtsen HM, Saritas G, Daugaard G, Winge SB, Almstrup K. In situ expression of miR-371a-3p and miR-373-3p in testicular germ cell tumours and detection in serum. *Andrology*. 2026 Mar 11: e70207. <https://doi.org/10.1111/andr.70207>

Androgenetics

Polygenic scores predicting complex diseases ought to include in males the loss of Y chromosome (LOY), as was demonstrated in this study from Japan. LOY in pancreatic β cells observed in ageing men can potentially impair glucose metabolism and augment the risk of diabetes.

Sato, G., Yamamoto, Y., *et al.* et Kadowaki T, Okada Y. Genetic regulation across germline and somatic variation on the Y chromosome contributes to type 2 diabetes. **Nature Med** 32, 894–905 (2026).
<https://doi.org/10.1038/s41591-026-04213-z>



To better counsel patients with genetic forms of infertility, a framework was developed that allows the generation of gene-specific phenotyping protocols. The first attempt dealt with comorbidities associated with infertility caused by mutations in *MEI1* and *DNAH17* and was based on deep phenotyping and available *in silico* resources. The authors call for international collaboration to develop similar protocols for other genes associated with male and female infertility.



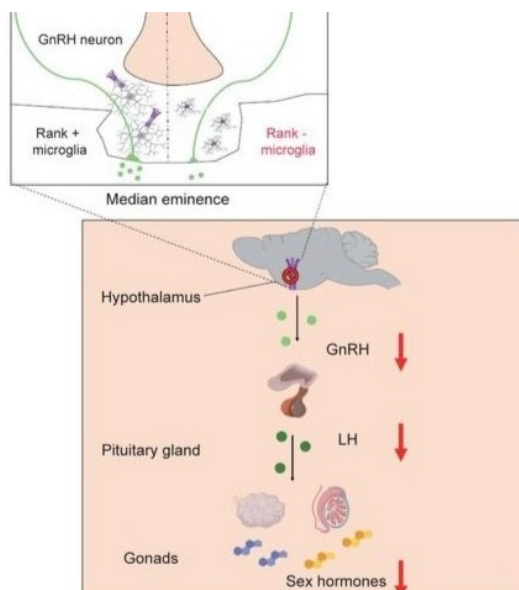
G W van der Heijden, D Westra, M C S van Olden, W Hobo, M S Oud, R M Smits, Ö Baysal, H Bogers, K D'Hauwers, M J E Kempers, J F M Jacobs, J A Veltman, M F Stokman, L Ramos, A clinical protocol for the detection of comorbidities associated with monogenic causes of male infertility, **Hum Reprod**, 2026; deag038.
<https://doi.org/10.1093/humrep/deag038>

The team at the EAA Center in Münster performed exome sequencing in a family with several brothers affected by infertility and variably impaired spermatogenesis. They identified a potentially pathogenic variant in *HIPK4*, which is a novel candidate gene associated with teratozoospermia with sperm head defects.



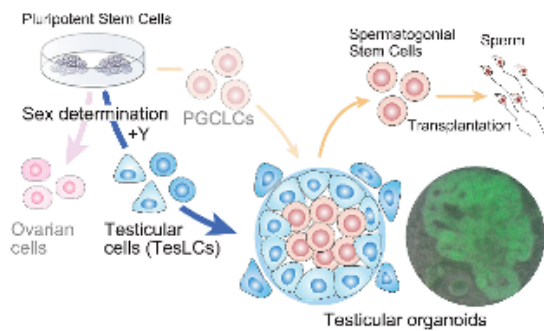
Koser SA, Rieck C, Aprea I, Krallmann C, Gaikwad SA, Wallmeier J, Tenardi-Wenge R, Di Persio S, Neuhaus N, Raidt J, Omran H, Laurentino S, Kliesch S, Stallmeyer B, Friedrich C, Tüttelmann F. *HIPK4* is a novel gene 1 associated with teratozoospermia and male infertility. **medRxiv PREPRINT** March 4, 2026.
<https://doi.org/10.64898/2026.03.04.26346694>

Translational and basic andrology



A new neuroimmune mechanism potentially regulating fertility was identified by researchers from Spain. The studies showed that microglia (primary immune cells of the central nervous system, similar to macrophages) modulate GnRH neuronal activity within the hypothalamic–pituitary–gonadal axis via RANK signalling. Disruption of this pathway in animal models led to hypogonadotropic hypogonadism (HH), delayed puberty and infertility in both sexes. Male mice had small testes and low testosterone. In addition, the researchers identified rare gene variants of *RANK* in patients with HH.

Collado-Sole A, Borjini N *et al.* et Tena-Sempere M, Pitteloud N, Gonzalez-Suarez E. Microglia Rank signaling regulates GnRH neuronal function and the hypothalamic-pituitary-gonadal axis. **Science**. 2026 Mar 12:eae66999.
<https://doi.org/10.1126/science.aeb66999>



The world is getting closer to producing a functional testis and bionic gametes *in vitro*. Breakthrough studies from Japan reconstituted testicular somatic cells from mouse pluripotent stem cells, recapitulating the sex-determination process. The reconstituted somatic niche supported differentiation of pluripotent stem cell-derived primordial germ cells into spermatogonial stem cells. These spermatogonia differentiated into functional spermatozoa upon transplantation into testis.

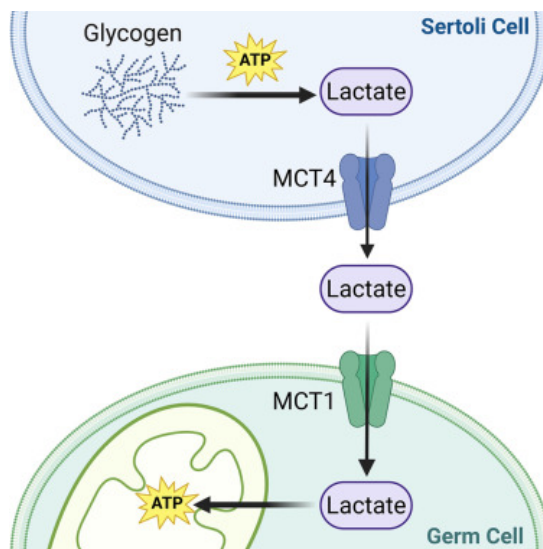
Sato T, Yoshino T, *et al.* et Hayashi K, Ogawa T. Generation of functionally competent testicular somatic cells from pluripotent stem cells. **Sci Adv.** 2026 Feb 27;12(9):eadz0269.

<https://doi.org/10.1126/sciadv.adz0269>

Yoshino T, Sasada H, *et al.* et Saitou M, Ogawa T, Hayashi K. Reconstitution of sex determination and the testicular niche using mouse pluripotent stem cells. **Science.** 2026 Feb 26;391(6788):eaea0296.

<https://doi.org/10.1126/science.aea0296>

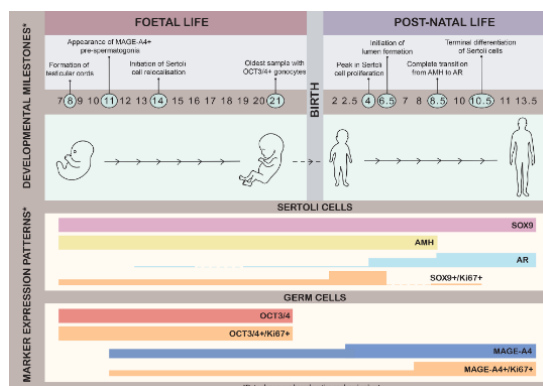
Comment by Mitchell RT: [How to build a testis, cell by cell.](#)



At the onset of sex differentiation glycogen is accumulated only in male gonads. This study showed that glycogen is dispensable for Sertoli cell differentiation but it is required to produce lactate, which is then transported via the lactate shuttle to germ cells, attracting them to the forming cords and supporting their development.

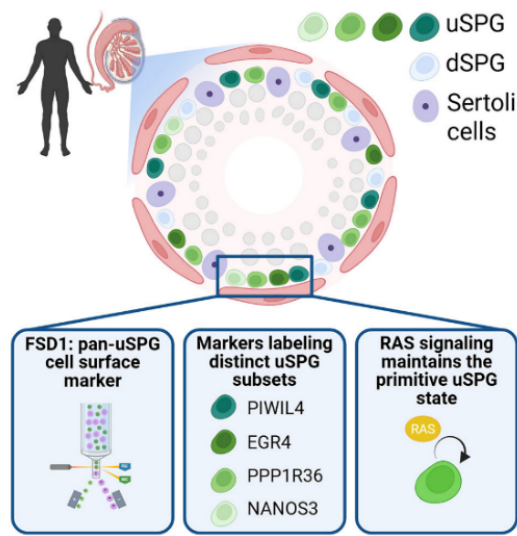
Estermann MA, Sheheen J, Grimm SA, Tezak B, Chen YY, Morita T, H-C Yao H, Capel B. Glycogen and lactate metabolism in mouse fetal Sertoli cells sustain the germ line. **Cell Rep.** 2026 Mar 10;45(3):117069.

<https://doi.org/10.1016/j.celrep.2026.117069>



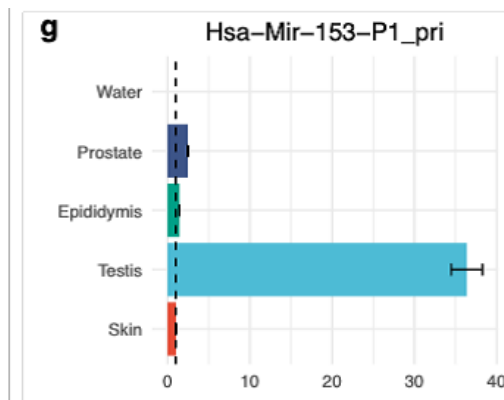
A large series of human foetal and prepubertal testicular samples were comprehensively examined using established markers (OCT3/4, AMGEA4, AMH, AR) allowing temporal mapping of Sertoli- and germ cell maturation. The data suggest that Sertoli cell maturation precedes the initiation of spermatogenesis well before the start of puberty.

Sanou I, Lakshmipathi M, Schönhage LK, van Daalen SKM, de Winter-Korver CM, Meißner A, Hamer G, de Rooij DG, Mitchell RT, Mulder CL. Temporal dynamics of Sertoli and germ cell development in human foetal and prepubertal testis. **Biol Open.** 2026 Feb 15;15(2):bio062319. <https://doi.org/10.1242/bio.062319>



In an attempt to characterise heterogeneous subsets of human spermatogonia (SPG), this study screened single-cell RNA-seq datasets for possible protein markers for classically defined SPG populations. The cell populations were sorted using these markers, and then subjected to transcriptomic profiling. The RAS signalling pathway was identified as essential to maintain the primitive SPG identity.

Capponi C, Smith C, Medica A, Hsieh TC, Orwig KE, Tan K. Decoding the heterogeneity of human undifferentiated spermatogonia reveals RAS-dependent regulation of stem cell fate. *Cell Rep*. 2026 Feb 24; 45(2):116868. <https://doi.org/10.1016/j.celrep.2025.116868>



Researchers from the EAA Centre in Copenhagen analysed circulating small non-coding RNAs (sncRNAs) in patients with prostate cancer before and after castration. In total, 16 sncRNAs were consistently altered, the majority were testicular piRNAs, but also miRNAs, some not previously reported. However, it was not possible to establish whether these circulating sncRNA carry endocrine signals.

Main AM, Sørensen LH, Winge SB, Fode M, Sønksen J, Juul A, Østergren PB, Mørup N, Almstrup K. Changes in circulating small non-coding RNAs after castration in a cohort of prostate cancer patients. *Sci Rep*. 2026 Feb 3;16(1):7060. <https://doi.org/10.1038/s41598-026-38334-9>



The role of piRNAs in pachytene spermatocytes has been debated, because these RNAs are rapidly diverging. This fascinating study reported that most mouse pachytene piRNAs have no biological function but instead 'selfishly' promote their own production. The small minority of pachytene piRNAs that reduce target mRNA abundance enhance sperm fitness and fertility, thereby ensuring production of the entire pachytene piRNA repertoire.

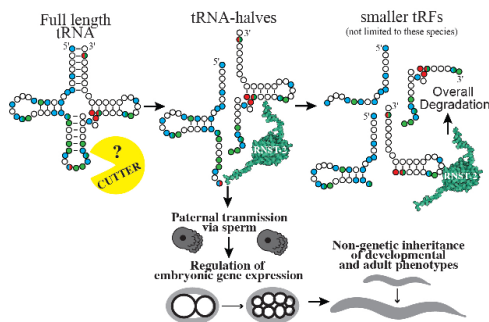
Cecchini K, Zamani M, Ajaykumar N, Vega-Badillo J, Bagci A, Bailey S, Zamore PD, Gainetdinov I. Cleavage of mRNAs by a minority of pachytene piRNAs improves sperm fitness. *Nature*. 2026 Feb 4. <https://doi.org/10.1038/s41586-026-10102-9>



The generational stability and transmission of epigenetic alterations across twenty generations of rats, after ancestral exposure to vinclozolin was investigated in this study.

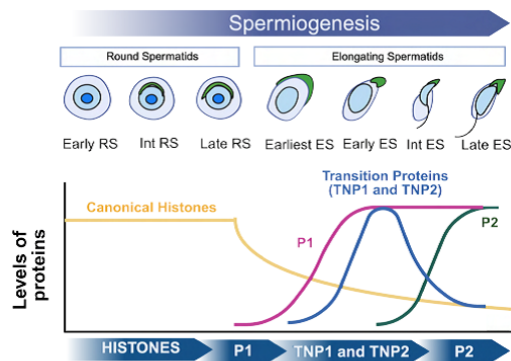
An increase in differential DNA methylated regions was observed across multiple generations, and new problems (e.g. parturition problems in females) appeared. Male rats exhibited elevated levels of germline apoptosis suggesting epigenetic dysregulation in spermatogenesis. The observations may have implications for human health after exposure to environmental toxicants.

Korolenko AA, Nilsson EE, De Santos S, Skinner MK. Stability of epigenetic transgenerational inheritance of adult-onset disease and parturition abnormalities. *Proc Natl Acad Sci U S A*. 2026 Feb 24;123(8):e2523071123. <https://doi.org/10.1073/pnas.2523071123>



The environment can modulate epigenetic information in gametes. The diet of male rodents was shown to regulate specific miRNAs and tRNA-derived RNAs (tDRs), the latter especially in sperm. This study found that the tDR mechanism is conserved in worms (*C. elegans*), and identified the RNaseT2 enzyme, *rnst-2*, as a regulator of tDR accumulation. The study positions the worm as a model for paternal non-genetic inheritance.

Galambos NS, Crocker OJ, Schneider BK, *et al.* et Conine CC. tRNA-derived RNA processing in sperm transmits non-genetically inherited phenotypes to offspring in *C. elegans*. **Nat Commun.** 2026 Mar 15. <https://doi.org/10.1038/s41467-026-70029-7>



Two elegant studies in mouse models revisited the process of spermiogenesis, which requires replacing chromatin's nucleosomes by transition proteins (TNPs) followed by protamines (PRM1, PRM2). The first study revised the order and revealed a direct histone-to-PRM1 exchange, followed by TNPs and PRM2. The second study delineated the spatio-temporal sequence in which transient chromatin loosening precedes and enables region-selective protamine-driven compaction.

Rabbani M, Apell Z, *et al.* et, Wilson TE, Hammoud SS. 3D chromatin compartment of round spermatids encodes the spatiotemporal program of histone-to-protamine exchange in spermiogenesis. **bioRxiv PREPRINT** 12 March 2026. <https://doi.org/10.64898/2026.03.10.710708>

Hada M, Zhong C, *et al.* et Ikawa M, Baek SH, Okada Y. Genome compartments guide protamine replacement and genome stability during spermiogenesis. **bioRxiv PREPRINT** 10 March 2026. <https://doi.org/10.64898/2026.03.08.710361>

Andrology lab

For specialists in semen analysis and sperm selection for ART, two recent suggestions of methodological improvements, with self-explanatory titles:



Shahali S, Mortimer ST, McLachlan R, O'Bryan MK, Zander-Fox D, Mortimer D, Ackermann K, Neild A, Nosrati R. Refined trajectory smoothing and deep learning classification of human sperm motility. **Hum Reprod.** 2026 Mar 1;41(3):332-342. <https://doi.org/10.1093/humrep/deag005>



Meitei HY, Predheepan D, Uppangala S, R VL, Kalthur G, Schlatt S, Adiga SK. Bicarbonate buffer enhances functional sperm selection compared to Zwitterionic buffers in sperm preparation. **Sci Rep.** 2026 Mar 18;16(1):9332. <https://doi.org/10.1038/s41598-026-44733-9>

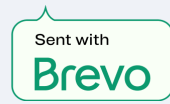
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