Re-accreditation report of the EAA training Centre of the Dutch-speaking Brussels Free-University for the period 2012 - 2015

Full name and address of the centre

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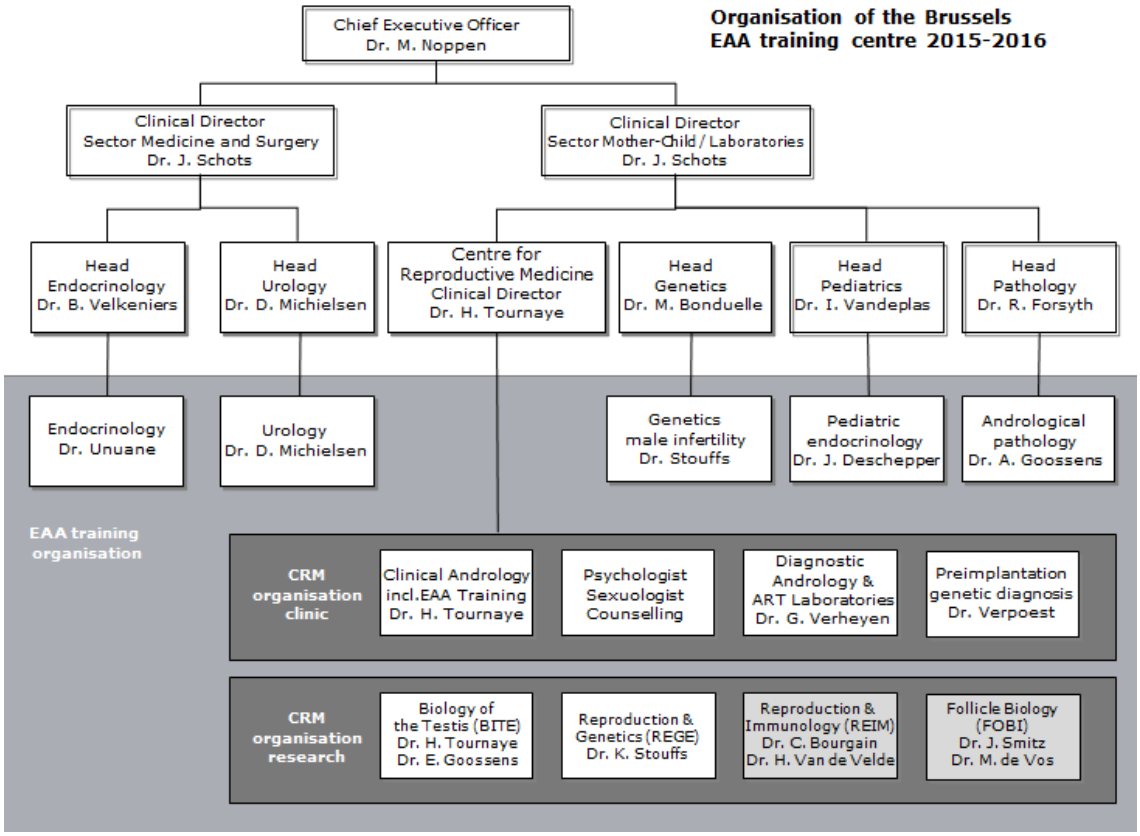
History of the Centre

The EAA training Centre of the Dutch-speaking Brussels Free-University was started as an initiative of the Centre for Reproductive Medicine (CRM). This Centre, established as an interdepartmental institute by the University Hospital in 1983, pioneered several innovative techniques in assisted reproduction with a focus on male infertility. In 1992 our Centre introduced intracytoplasmic sperm injection (ICSI) through the research laboratory headed by Dr. Van Steirteghem. In 1989 Dr. H. Tournaye joined the CRM and became in charge for the reproductive andrology clinic. Because more andrological patients were treated, internal collaborations were initiated with other departments within our University Hospital. This catalyzed the application for becoming an EAA training centre in 1997. The Centre was visited and approved as an EAA training centre on October 6, 1997 (see report in International Journal of Andrology 1999, vol 22 Supplement 1, 59-63). On March 25, 2005 and on May 24, 2012 the Brussels EAA training centre was re-visited and re-approved.

Organisation of the EAA Training Centre

The EAA training centre has a cross-departmental organisation similar to the EAA training centres in Leuven and Ghent (see figure).
The training is coordinated by Prof. Dr. H. Tournaye, head of the Centre for Reproductive Medicine since 2011. He is in charge for the reproductive andrology clinic and the clinical andrology training at the University Hospital of Brussels. Besides his clinical work, he is appointed full professor in developmental and reproductive biology at the Brussels Free University. He is currently member of the Infertility Guidelines Group of the European Association of Urology (EAU). He is past chairman of the Special Interest group in Andrology of the European Society of Human Reproduction and Embryology (ESHRE) (1999-2004), the Dutch-Flemish Society for the study of Fertility (Vereniging Fertiliteitsstudie) (2001-2006) and the Belgian Society for Reproductive Medicine (BSRM).
The core activity resides within the CRM. As per January 1, 2016, the centre has currently 170 staff members. The CRM has a close formal collaboration for research and treatment with the Centre for Medical Genetics (head Prof. Dr. M. Bonduelle). Close collaborations have also been developed with the department of Endocrinology (head Prof. Dr. B. Velkeniers), the department of Urology (head Prof. Dr. D. Michielsen) and the department of Pathology (head Prof. Dr. R. Forsyth). The visiting hours for the outpatient clinics at the Centre

for Reproductive Medicine, the Centre for Medical Genetics, the department of Endocrinology and the department of Urology are concurrent. This facilitates the circulation of both patients and trainees within the EAA conglomerate. There are occasional collaborations with the department of Radiology (head Prof. Dr. J. De Mey) for varicocele embolisations and with the department of pediatrics (head Prof. Dr. Y. Vandeplas) for pediatric endocrinology (liaison Prof. Dr. J. De Schepper).



Organisational chart of the Brussels EAA training centre (white boxes in grey area are part of the training set-up).

Management of andrological patients

Patients either are primary (by GP), secondary (by OB/Gyn, urologist or endocrinologist) or tertiary (only from other IVF-centres) referrals. Patients can contact either section of the EAA conglomerate but will be looked after by the appropriate expert. Patients with erectile dysfunction and specific urological disorders are referred to and worked-up by the urologist. Patients with endocrine disorders are referred to and worked-up by the endocrinologist. The majority of andrological patients have reproductive failure, although often in combination with other andrological problems. They are referred to the CRM

where they will be looked after by Dr. H. Tournaye or Dr. Vloeberghs. Together with the other departments in the EAA conglomerate, the CRM provides a broad spectrum of both diagnostic tools and treatments within the field of andrology (see appendix 1).

In 2013, together with Prof. J. De Schepper a 'Klinefelter Clinic' was founded within the UZ Brussels. This dedicated clinic has a multidisciplinary approach, and includes endocrinologists (adult and pediatric), urologists, reproductive andrologists, geneticists, psychologists and psychiatrists (adult and pediatric).

The clinical management of patients with andrological disease is evidence-based whenever possible. When for patients with reproductive failure no such treatment is available, a non-specific approach is used, i.e. assisted reproductive techniques. A detailed activity report is produced on a yearly basis for patients with reproductive failure. Enclosed in appendix 2 is the clinical activity report for the core activities in 2015. The clinical information has been re-organized into a paper-less computer-based system (informatization of patient files). In the future search and query tools will be added to this system. Recent clinical developments include the set-up of an infectious clinical pathway in agreement with the European and Belgian tissue directive to help viral-infected patients who want to reproduce and an oncofertility clinical pathway. Our oncofertility platform offers all potential preventive strategies to patients of all ages, including prepubertal boys facing germ-cell loss.
In 2015 the clinic has been re-accredited for the European Board & College of Obstetrics and Gynaecology certified training centre for both subspecialty training in reproductive medicine and basic training in OBGYN. The subspecialty includes theoretical and practical training in andrology.

Since 2005 the andrology laboratory and the ART laboratory have an ISO 15189 accreditation including both Quality Management Requirements and Technical Requirements.
In both the andrology and ART laboratory, an IVF-witness quality control system has been introduced.
For its inter- and intra observer quality control for basic semen analysis, the andrology laboratory is also participating in the external quality control program of ESHRE and the national external quality control for andrology laboratory techniques provided through the federal ministry of health of Belgium.

The andrology and all ART laboratories are being rebuilt according to the prerequisites of the European and Belgian tissue directives. These laboratories are audited by the Belgian Federal Agency for Medicines and Health Products (FAMHP).
A separate infectious lab to process viral-infected gametes from patients undergoing ART is available.
In 2015 the clinic obtained the highest accreditation possible, i.e. ISO 15224.

Andrological education

In Belgium, as in almost all European countries, andrology is not recognised as a specialty. However, a law of February 15, 1999 specifies that any clinic officially recognised for IVF treatment must include a "medical doctor with a special expertise in andrology", however, without stating how this expertise must be obtained. Patients with andrological disease will be looked after either by an Ob/Gyn, either by an urologist or by an endocrinologist. The Brussels EAA training can provide andrological training to Ob/Gyns, endocrinologists and urologists. Trainees can circulate between the different departments involved in the EAA conglomerate and get a training in a full range of diagnostic and therapeutic facilities as listed in appendix 1 .
Dr. V. Vernaeve was the first EAA-certified andrologist who graduated from the Brussels EAA training centre (currently working in Barcelona, Spain). In 2008 Dr. Ashraf Zeidan became an EAA-certified andrologist (currently working in Cairo, Egypt) and Dr. Biljana Popovic-Todorovic obtained the EAA-certification in 2009 (currently working in Belgrade, Serbia).
In 2007 a joint EAA-ESHRE course on reproductive andrology was organized at our institution. This was a 3-day course attended by 120 participants. In the future a joint course with the EAA centres of Leuven and Manchester will be organized (target 2017).

Research activities

There are extensive research activities in the field of andrology which are undertaken in either a clinical setting or in the research unit. Projects running in 2010 include:

- Research on testicular stem cell cryopreservation, transplantation and grafting in prepubertal boys facing gonadotoxic cancer treatment
- Research on testicular stem cell loss and preservation in 47, XXY Klinefelter patients, including prepubertal boys
- Research on the molecular mechanisms causing male infertility by gene array and next generation sequencing approaches,
- Research on imprinting in human gametes and embryos,
- Research on preimplantation genetic diagnosis on human embryos
- Research on expression of markers of totipotency and differentiation in human gametes and embryos
- Research on in-vitro culture and differentiation of human embryonic stem cells
- Follow-up studies of children born after in-vitro fertilisation and intracytoplasmic sperm injection

The ongoing research work has been published in many peer-reviewed journals (see appendix 3).

Appendix 1. Diagnostic and therapeutic facilities for andrological patients

(CRM= Centre for Reproductive Medicine)

Diagnosis	**Provider in EAA conglomerate**
routine semen analysis (WHO 2010)	CRM
biochemical seminal markers	CRM
immunologic tests, incl. SCMC	CRM
computer-assisted motility analysis	CRM
endocrine testing	CRM- Dep. of Endocrinology
cytogenetic testing	Centre for Medical Genetics
CFTR-gene mutation testing	Centre for Medical Genetics
Y-microdeletion testing	Centre for Medical Genetics
androgen receptor gene mutation testing	Centre for Medical Genetics
preimplantation genetic diagnosis (PGD)	Centre for Medical Genetics
transrectal ultrasound	Department of Urology
scrotal ultrasound	Department of Radiology
phlebography	Department of Radiology
vasography	CRM-Department of Radiology
electron microscopy	Department of Histopathology
testis biopsy	CRM-Dep. of Histopathology

Treatment	Provider in EAA conglomerate
endocrine therapy	CRM and Dep. of Endocrinology
puberty and growth	Department of Pediatrics
intersex	Dept. of Urology & Endocrinology
erectile dysfunction	Department of Urology
sexual dysfunction	CRM
infectious disease	CRM and Dept. of Urology
vasectomy	CRM and Dept. of Urology
vaso-vasostomy	CRM
vaso-epididymostomy	CRM
epididymolysis	CRM
electroejaculation	CRM
MESA and PESA	CRM
testis biopsy and TESE	CRM
testicular fine-needle aspiration	CRM
IUI	CRM
IUI with donor semen	CRM
IVF	CRM
ICSI	CRM
PGD-ICSI	CRM and genetics
semen banking	CRM
testicular tissue banking	CRM
testicular stem cell banking	CRM - BITE
transurethral resection (deroofing)	Department of Urology
varicocele correction	Dept. of Urology and Radiology

Appendix 2. Profile of core activities during 2012-2015

	2012	2013	2014	2015
Patients with erectile dysfunction	*	*	*	*
Ultrasounds (scrotal and transrectal)	791	823	1060	999
Patients with secondary hypogonadism (high FSH)	414	336	270	302
Patients with primary hypogonadism (low FSH)	9	7	6	10
Patients with delayed puberty	**	**	**	**
All patients with male infertility	2164	2083	1891	1865
New patients with male infertility	692	665	561	569
Diagnostic semen analyses	1727	1670	1612	1590
Tray agglutination test (immunologic test)	24	0	0	0
Biochemical markers (fructose and alpha-glucosidase)	89	94	74	78
Semen cryopreservation				
Heterologous (donor)	465	536	549	561
Homologous (auto conservation)	529	495	505	510
Intrauterine insemination				
Husband semen	1285	1311	1283	1197
Donor semen	1869	1666	1492	1300
In-vitro fertilization	202	166	156	158
Intracytoplasmic sperm injection	3959	3965	4047	4473
Embryo aneuploidy screening and PGD	616	607	630	724
Embryo cryopreservation freezing cycles	2317	2267	2374	2900
MESA, PESA, TESE and FNA	230	273	237	226
Electroejaculation	2	8	2	6
Male microsurgery (vasovasostomy and vasoepididymostomy)	21	10	8	7
Vasectomy	110	131	131	138

*exact figures not received in time, however, last 4 years ± 60 patients/year at diabetes clinic and ± 380 patients/year at urology clinic
** exact figures not received in time, however, last 4 years ± 40-50 patients/year

Appendix 3. List of peer-reviewed international publications in the field of andrology from the Brussels EAA since last report
(with 10 last 3-years representative publications in bold)

1. **Gies I, Oates R, De Schepper J, Tournaye H. Testicular biopsy and cryopreservation for fertility preservation of prepubertal boys with Klinefelter syndrome: a pro/con debate. Fertil Steril. 2016 Feb;105(2):249-55. doi:10.1016/j.fertnstert.2015.12.011. Epub 2015 Dec 31. Review. PubMed PMID:26748226.**

2. Gies I, Tournaye H, De Schepper J. Attitudes of parents of Klinefelter boys and pediatricians towards neonatal screening and fertility preservation techniques in Klinefelter syndrome. Eur J Pediatr. 2016 Mar;175(3):399-404. doi: 10.1007/s00431-015-2657-7. Epub 2015 Oct 22. PubMed PMID: 26494133.

3. Van Saen D, Pino Sánchez J, Ferster A, van der Werff ten Bosch J, Tournaye H, Goossens E. Is the protein expression window during testicular development affected in patients at risk for stem cell loss? Hum Reprod. 2015 Dec;30(12):2859-70. doi: 10.1093/humrep/dev238. Epub 2015 Sep 23. PubMed PMID: 26405262.

4. Den Hond E, Tournaye H, De Sutter P, Ombelet W, Baeyens W, Covaci A, Cox B, Nawrot TS, Van Larebeke N, D'Hooghe T. Human exposure to endocrine disrupting chemicals and fertility: A case-control study in male subfertility patients. Environ Int. 2015 Nov;84:154-60. doi: 10.1016/j.envint.2015.07.017. Epub 2015 Aug 24. Review. PubMed PMID: 26292060.

5. **Picton HM, Wyns C, Anderson RA, Goossens E, Jahnukainen K, Kliesch S, Mitchell RT, Pennings G, Rives N, Tournaye H, van Pelt AM, Eichenlaub-Ritter U, Schlatt S; ESHRE Task Force On Fertility Preservation In Severe Diseases. A European perspective on testicular tissue cryopreservation for fertility preservation in prepubertal and adolescent boys. Hum Reprod. 2015 Nov;30(11):2463-75. doi: 10.1093/humrep/dev190. Epub 2015 Sep 10. PubMed PMID: 26358785**.

6. **Vloeberghs V, Verheyen G, Haentjens P, Goossens A, Polyzos NP, Tournaye H. How successful is TESE-ICSI in couples with non-obstructive azoospermia? Hum Reprod. 2015 Aug;30(8):1790-6. doi: 10.1093/humrep/dev139. Epub 2015 Jun 16. PubMed PMID:26082482**

7. De Vos A, Abraham M, Franceus N, Haentjens P, Tournaye H, Verheyen G, Van de Velde H. Deposition of the spermatozoon in the human oocyte at ICSI: impact on oocyte survival, fertilization and blastocyst formation. J Assist Reprod Genet. 2015 Jun;32(6):865-71. doi: 10.1007/s10815-015-0482-6. Epub 2015 May 1. PubMed PMID: 25925348; PubMed Central PMCID: PMC4491076.

8. Gies I, De Schepper J, Tournaye H. Progress and prospects for fertility preservation in prepubertal boys with cancer. Curr Opin Endocrinol

Diabetes Obes. 2015 Jun;22(3):203-8. doi: 10.1097/MED.0000000000000162. Review. PubMed PMID: 25871958.

9. Tournaye H, Dohle GR, Barratt CL. Fertility preservation in men with cancer. Lancet. 2014 Oct 4;384(9950):1295-301. doi: 10.1016/S0140-6736(14)60495-5. Review. PubMed PMID: 25283570.

10. Goossens E, Tournaye H. Male fertility preservation, where are we in 2014? Ann Endocrinol (Paris). 2014 May;75(2):115-7. doi: 10.1016/j.ando.2014.03.011. Epub 2014 Apr 29. Review. PubMed PMID: 24793992.

11. De Brucker M, Camus M, Haentjens P, Francotte J, Verheyen G, Tournaye H. Cumulative delivery rates after ICSI with donor spermatozoa in different age groups. Reprod Biomed Online. 2014 May;28(5):599-605. doi: 10.1016/j.rbmo.2014.01.010. Epub 2014 Jan 31. PubMed PMID: 24631165.

12. Blockeel C, Knez J, Polyzos NP, De Vos M, Camus M, Tournaye H. Should an intrauterine insemination with donor semen be performed 1 or 2 days after the spontaneous LH rise? A prospective RCT. Hum Reprod. 2014 Apr;29(4):697-703. doi: 10.1093/humrep/deu022. Epub 2014 Feb 18. PubMed PMID: 24549212.

13. Belva F, Painter RC, Schiettecatte J, Bonduelle M, Roelants M, Roseboom TJ, Tournaye H, De Schepper J. Gender-specific alterations in salivary cortisol levels in pubertal intracytoplasmic sperm injection offspring. Horm Res Paediatr. 2013;80(5):350-5. doi: 10.1159/000355515. Epub 2013 Nov 7. PubMed PMID: 24217344.

14. Goossens E, Tournaye H. [Fertility preservation in boys: spermatogonial stem cell transplantation and testicular grafting]. Gynecol Obstet Fertil. 2013 Sep;41(9):529-31. doi: 10.1016/j.gyobfe.2013.07.013. Epub 2013 Aug 21. French. PubMed PMID: 23972916.

15. Faes K, Tournaye H, Goethals L, Lahoutte T, Hoorens A, Goossens E. Testicular cell transplantation into the human testes. Fertil Steril. 2013 Oct;100(4):981-8. doi: 10.1016/j.fertnstert.2013.06.016. Epub 2013 Jul 11. PubMed PMID: 23850302.

16. Baert Y, Van Saen D, Haentjens P, In't Veld P, Tournaye H, Goossens E. What is the best cryopreservation protocol for human testicular tissue banking? Hum Reprod. 2013 Jul;28(7):1816-26. doi: 10.1093/humrep/det100. Epub 2013 Apr 7. PubMed PMID: 23569082.

17. Vloeberghs V, Verheyen G, Tournaye H. Intracytoplasmic spermatid injection and in vitro maturation: fact or fiction? Clinics (Sao Paulo). 2013;68 Suppl 1:151-6. Review. PubMed PMID: 23503965; PubMed Central PMCID: PMC3583157.

18. De Brucker M, Camus M, Haentjens P, Verheyen G, Collins J, Tournaye H. Assisted reproduction using donor spermatozoa in

women aged 40 and above: the high road or the low road? Reprod Biomed Online. 2013 Jun;26(6):577-85. doi:10.1016/j.rbmo.2013.02.008. Epub 2013 Feb 24. PubMed PMID: 23523377.

19. Goossens E, Van Saen D, Tournaye H. Spermatogonial stem cell preservation and transplantation: from research to clinic. Hum Reprod. 2013 Apr;28(4):897-907. doi: 10.1093/humrep/det039. Epub 2013 Feb 20. Review. PubMed PMID: 23427228.

20. Van Saen D, Goossens E, Haentjens P, Baert Y, Tournaye H. Exogenous administration of recombinant human FSH does not improve germ cell survival in human prepubertal xenografts. Reprod Biomed Online. 2013 Mar;26(3):286-98. doi: 10.1016/j.rbmo.2012.11.013. Epub 2012 Dec 1. PubMed PMID: 23352099.

21. Goossens E, Tournaye H. Adult stem cells in the human testis. Semin Reprod Med. 2013 Jan;31(1):39-48. doi: 10.1055/s-0032-1331796. Epub 2013 Jan 17. Review. PubMed PMID: 23329635.

22. Goossens E, Tournaye H. Functional sperm produced after spermatogonial stem cell transplantation into rhesus. Asian J Androl. 2013 Mar;15(2):216-7. doi:10.1038/aja.2012.155. Epub 2013 Jan 14. PubMed PMID: 23314659; PubMed Central PMCID: PMC3739158.

23. Van Saen D, Goossens E, Aerts JL, Haentjens P, Tournaye H. Does early cell death cause germ cell loss after intratesticular tissue grafting? Fertil Steril. 2013 Apr;99(5):1264-1272.e1. doi: 10.1016/j.fertnstert.2012.12.019. Epub 2013 Jan 10. PubMed PMID: 23312508.

24. De Vos A, Van de Velde H, Bocken G, Eylenbosch G, Franceus N, Meersdom G, Tistaert S, Vankelecom A, Tournaye H, Verheyen G. Does intracytoplasmic morphologically selected sperm injection improve embryo development? A randomized sibling-oocyte study. Hum Reprod. 2013 Mar;28(3):617-26. doi: 10.1093/humrep/des435. Epub 2013 Jan 4. PubMed PMID: 23293218.

25. De Vos A, Polyzos NP, Verheyen G, Tournaye H. Intracytoplasmic morphologically selected sperm injection (IMSI): a critical and evidence-based review. Basic Clin Androl. 2013 Nov 8;23:10. doi: 10.1186/2051-4190-23-10. eCollection 2013. PubMed PMID: 25780572; PubMed Central PMCID: PMC4349780.

26. Ning L, Meng J, Goossens E, Lahoutte T, Marichal M, Tournaye H. In search of an efficient injection technique for future clinical application of spermatogonial stem cell transplantation: infusion of contrast dyes in isolated cadaveric human testes. Fertil Steril. 2012 Dec;98(6):1443-8.e1. doi:10.1016/j.fertnstert.2012.08.023. Epub 2012 Sep 14. PubMed PMID: 22981175.

27. Kyrou D, Kolibianakis EM, Fatemi HM, Grimbizis GF, Theodoridis TD,

Camus M,Tournaye H, Tarlatzis BC, Devroey P. Spontaneous triggering of ovulation versus HCG administration in patients undergoing IUI: a prospective randomized study. Reprod Biomed Online. 2012 Sep;25(3):278-83. doi: 10.1016/j.rbmo.2012.05.005. Epub 2012 May 23. PubMed PMID: 22796236.

28. Tournaye HJ, Cohlen BJ. Management of male-factor infertility. Best Pract Res Clin Obstet Gynaecol. 2012 Dec;26(6):769-75. doi: 10.1016/j.bpobgyn.2012.05.005. Epub 2012 Jun 16. PubMed PMID: 22704953.

29. Gies I, De Schepper J, Goossens E, Van Saen D, Pennings G, Tournaye H. Spermatogonial stem cell preservation in boys with Klinefelter syndrome: to bank or not to bank, that's the question. Fertil Steril. 2012 Aug;98(2):284-9. doi:10.1016/j.fertnstert.2012.04.023. Epub 2012 May 17. Review. PubMed PMID:22608314.

30. Jungwirth A, Giwercman A, Tournaye H, Diemer T, Kopa Z, Dohle G, Krausz C; European Association of Urology Working Group on Male Infertility. European Association of Urology guidelines on Male Infertility: the 2012 update. Eur Urol. 2012 Aug;62(2):324-32. doi: 10.1016/j.eururo.2012.04.048. Epub 2012 May 3. PubMed PMID: 22591628.

31. Baert Y, Goossens E, van Saen D, Ning L, in't Veld P, Tournaye H. Orthotopic grafting of cryopreserved prepubertal testicular tissue: in search of a simple yet effective cryopreservation protocol. Fertil Steril. 2012 May;97(5):1152-7.e1-2. doi: 10.1016/j.fertnstert.2012.02.010. Epub 2012 Feb 25. PubMed PMID: 22369773.

32. Gies I, De Schepper J, Van Saen D, Anckaert E, Goossens E, Tournaye H. Failure of a combined clinical- and hormonal-based strategy to detect early spermatogenesis and retrieve spermatogonial stem cells in 47,XXY boys by single testicular biopsy. Hum Reprod. 2012 Apr;27(4):998-1004. doi:10.1093/humrep/des002. Epub 2012 Feb 7. PubMed PMID: 22313866.

33. Stouffs K, Vandermaelen D, Massart A, Menten B, Vergult S, Tournaye H, Lissens W. Array comparative genomic hybridization in male infertility. Hum Reprod. 2012 Mar;27(3):921-9. doi: 10.1093/humrep/der440. Epub 2012 Jan 11. PubMed PMID: 22238114.

34. Tournaye H. Is there any reproductive future left for men? Facts Views Vis Obgyn. 2012;4(4):255-8. PubMed PMID: 24753917; PubMed Central PMCID: PMC3987484.

35. Ortega-Hrepich C, Vanderlinden E, Bourgain C, Devroey P, Tournaye H. Paratesticular leiomyoma in an azoospermic patient and -successful testicular sperm extraction (TESE) for intracytoplasmic sperm injection (ICSI) with an ongoing pregnancy. Facts Views Vis Obgyn. 2012;4(3):213-5. PubMed PMID: 24753910; PubMed Central PMCID: PMC3991402.

36. Tournaye H. Male factor infertility and ART. Asian J Androl. 2012 Jan;14(1):103-8. doi: 10.1038/aja.2011.65. Epub 2011 Dec 19. Review. PubMed PMID: 22179511; PubMed Central PMCID: PMC3735146.

37. Van Saen D, Gies I, De Schepper J, Tournaye H, Goossens E. Can pubertal boys with Klinefelter syndrome benefit from spermatogonial stem cell banking? Hum Reprod. 2012 Feb;27(2):323-30. doi: 10.1093/humrep/der425. Epub 2011 Dec 12. PubMed PMID: 22166807.

38. Massart A, Lissens W, Tournaye H, Stouffs K. Genetic causes of spermatogenic failure. Asian J Androl. 2012 Jan;14(1):40-8. doi: 10.1038/aja.2011.67. Epub 2011 Dec 5. Review. PubMed PMID: 22138898; PubMed Central PMCID: PMC3735159.

39. Van Saen D, Tournaye H, Goossens E. Presence of spermatogonia in 47,XXY men with no spermatozoa recovered after testicular sperm extraction. Fertil Steril. 2012 Feb;97(2):319-23. doi: 10.1016/j.fertnstert.2011.11.009. Epub 2011 Dec 2. PubMed PMID: 22137495.