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University Hospital
Schleswig-Holstein

ESHRE Campus 2009

Reproductive Andrology:
Linking laboratory to clinical practice
Thessaloniki 1. – 3. October 2009

Minimal diagnostic clinical and laboratory procedures in men with reduced semen quality

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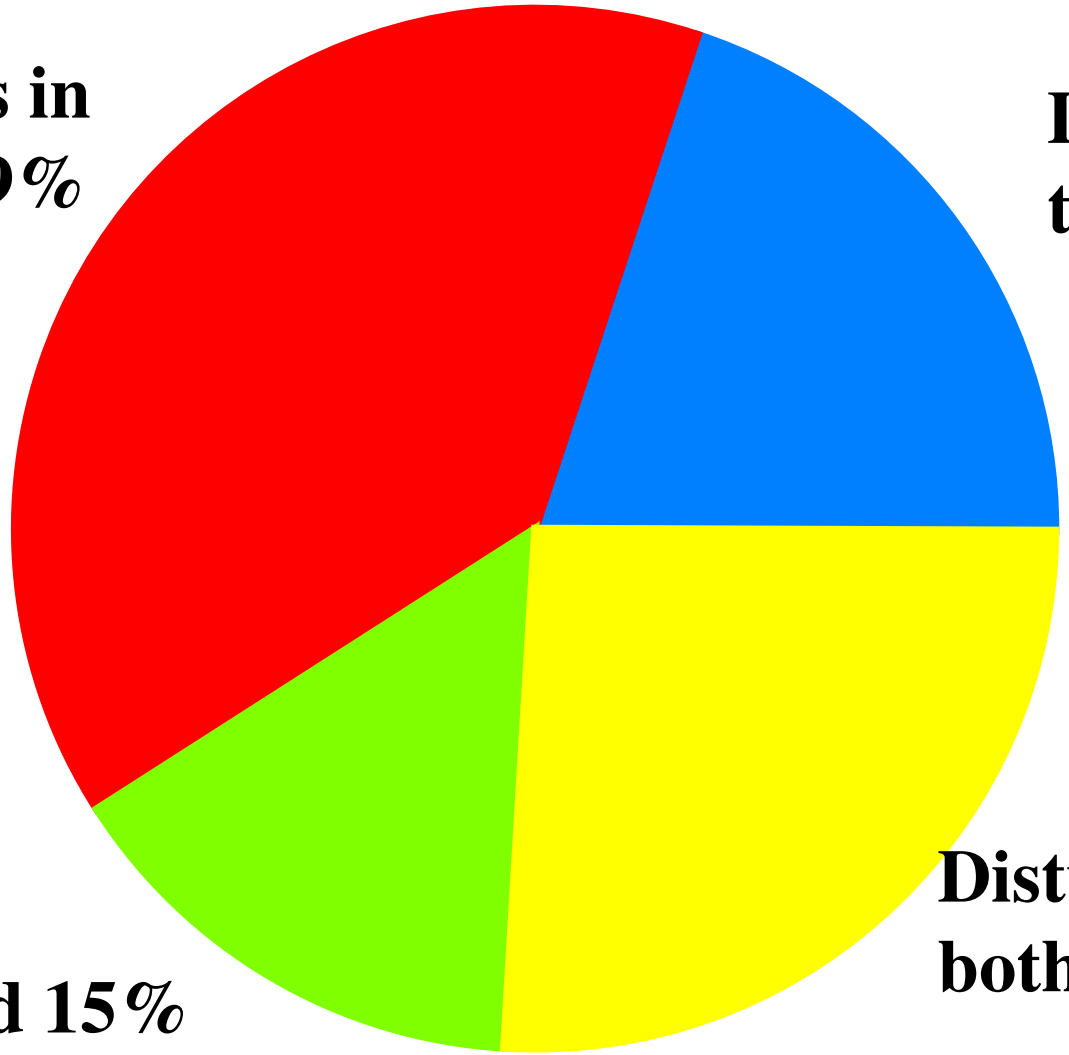
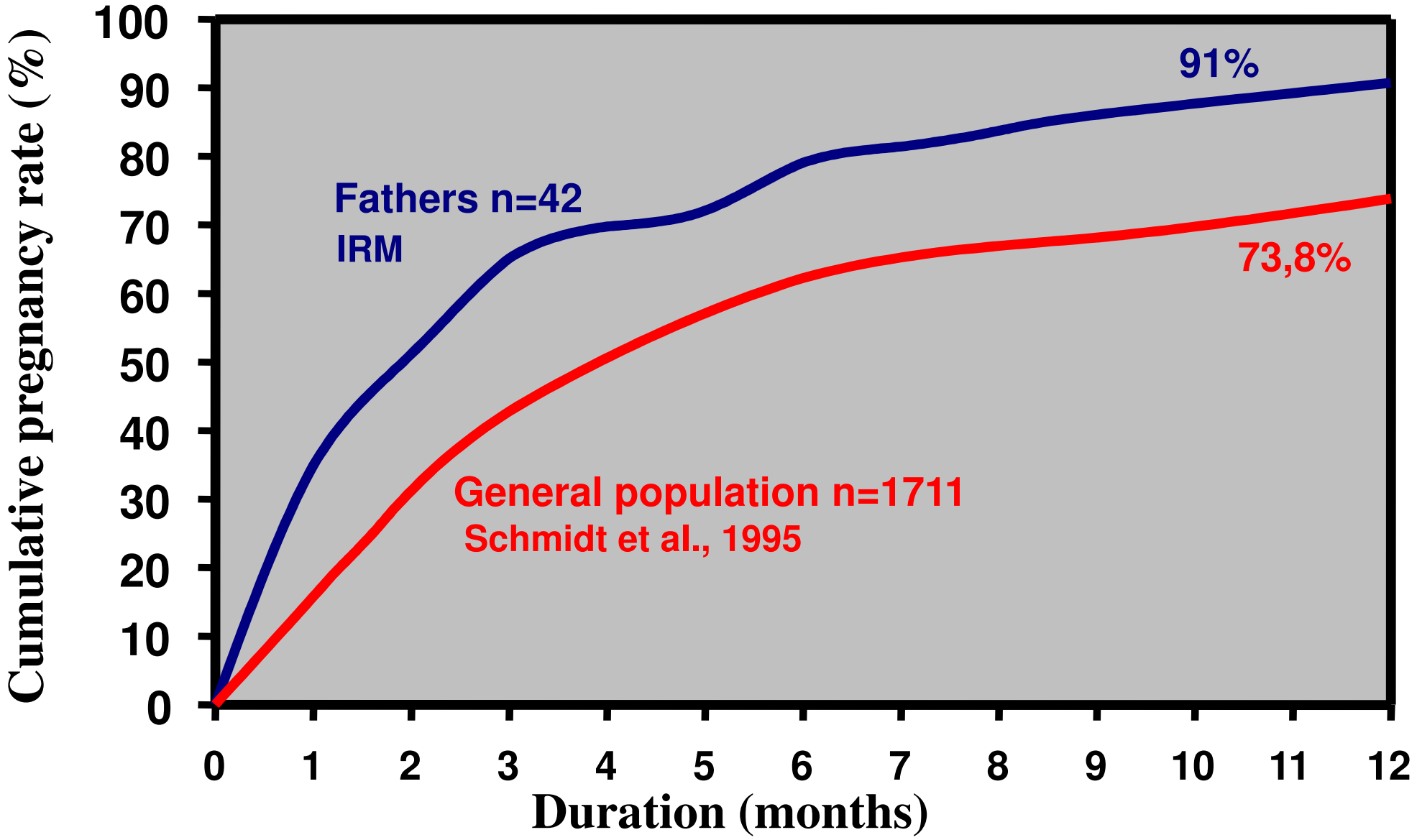
Distribution of causes of involuntary childlessness between men and women (WHO 1987)

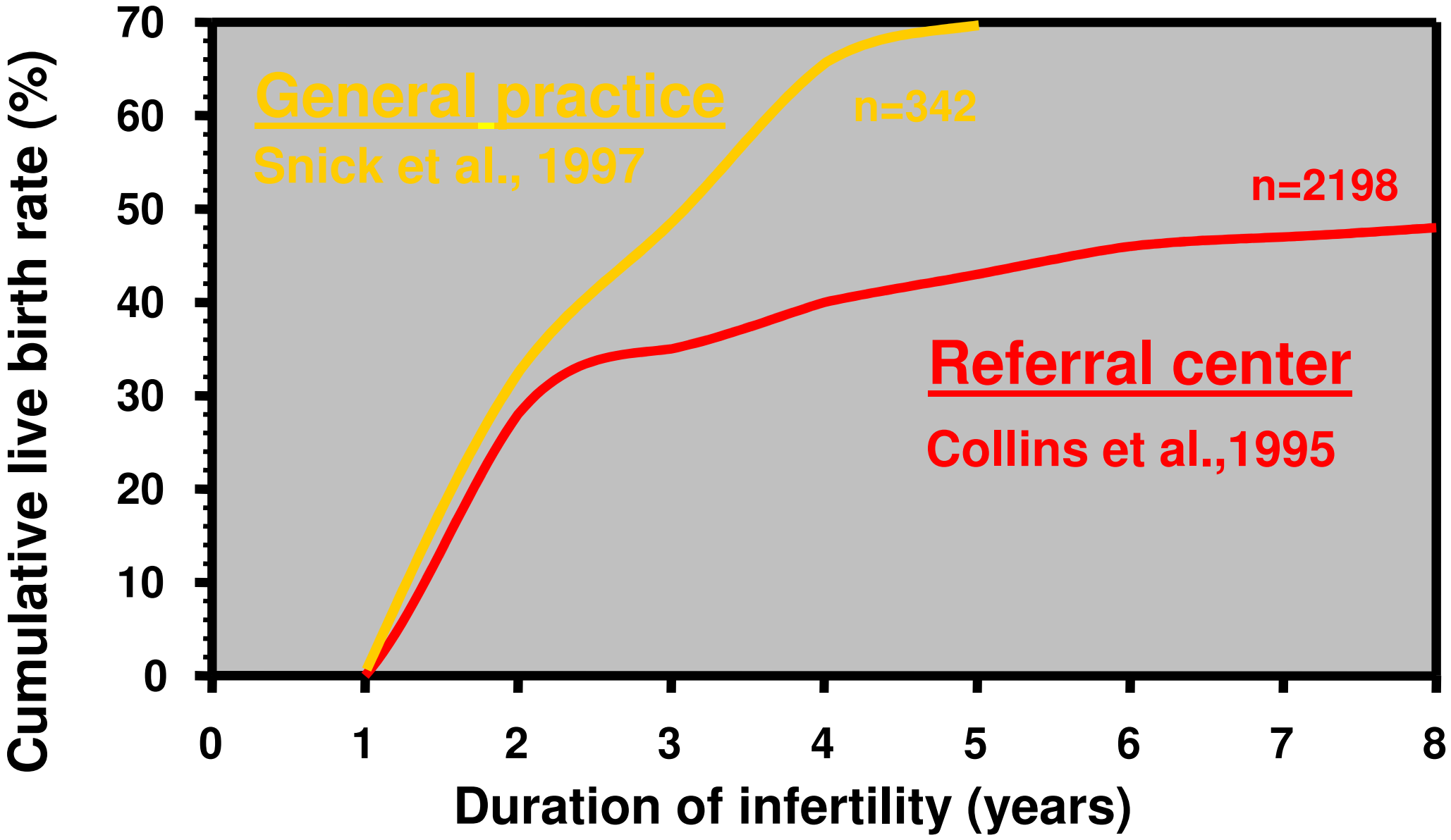


Cumulative pregnancy rate in untreated couples




born to be Wild

Cumulative live birth rate in untreated infertile couples



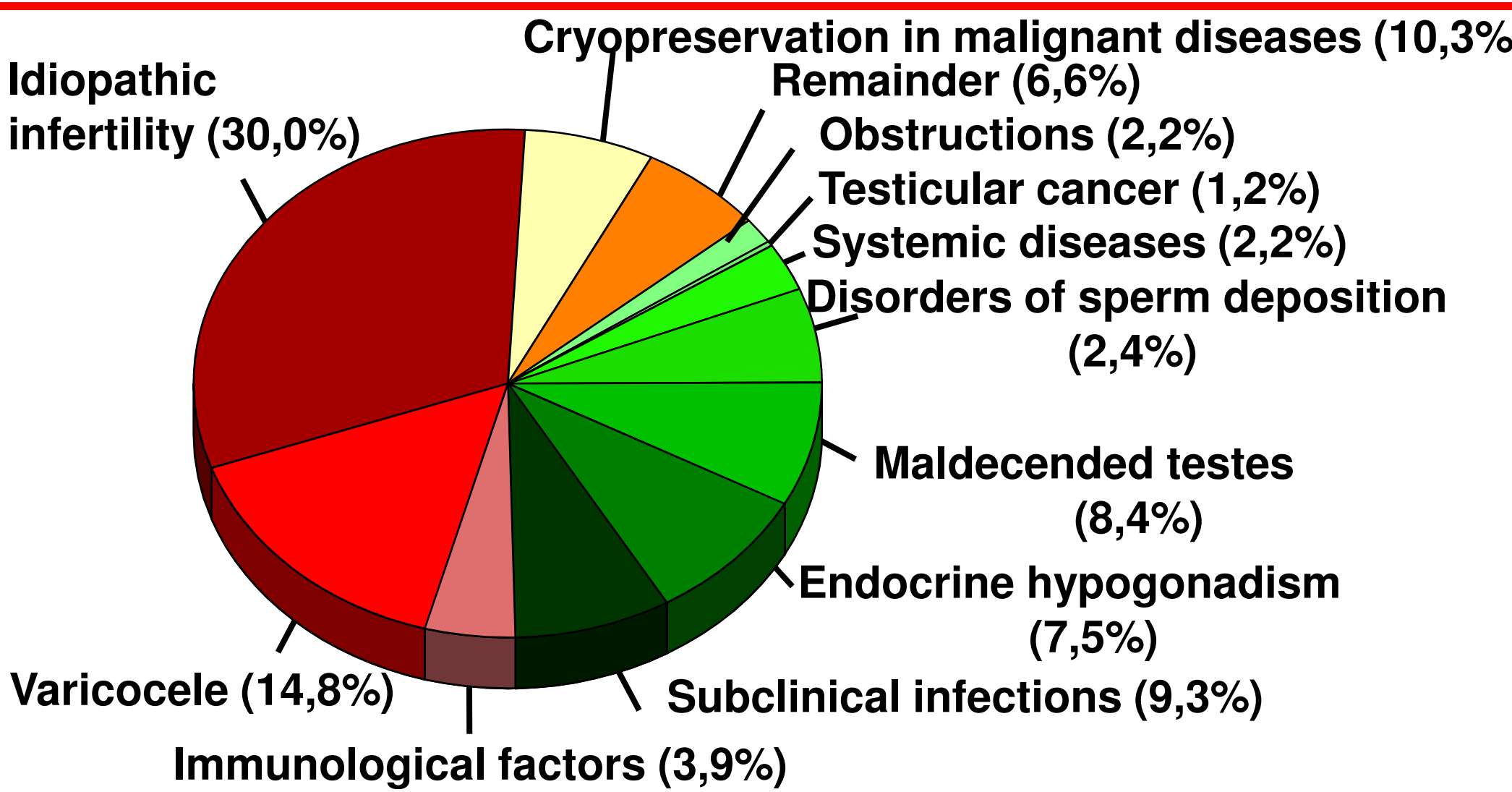
Effectiveness of treatment

"Treatment effectiveness can be judged fairly only in randomized clinical trials, because conception without therapy can occur in most infertile couples over time."

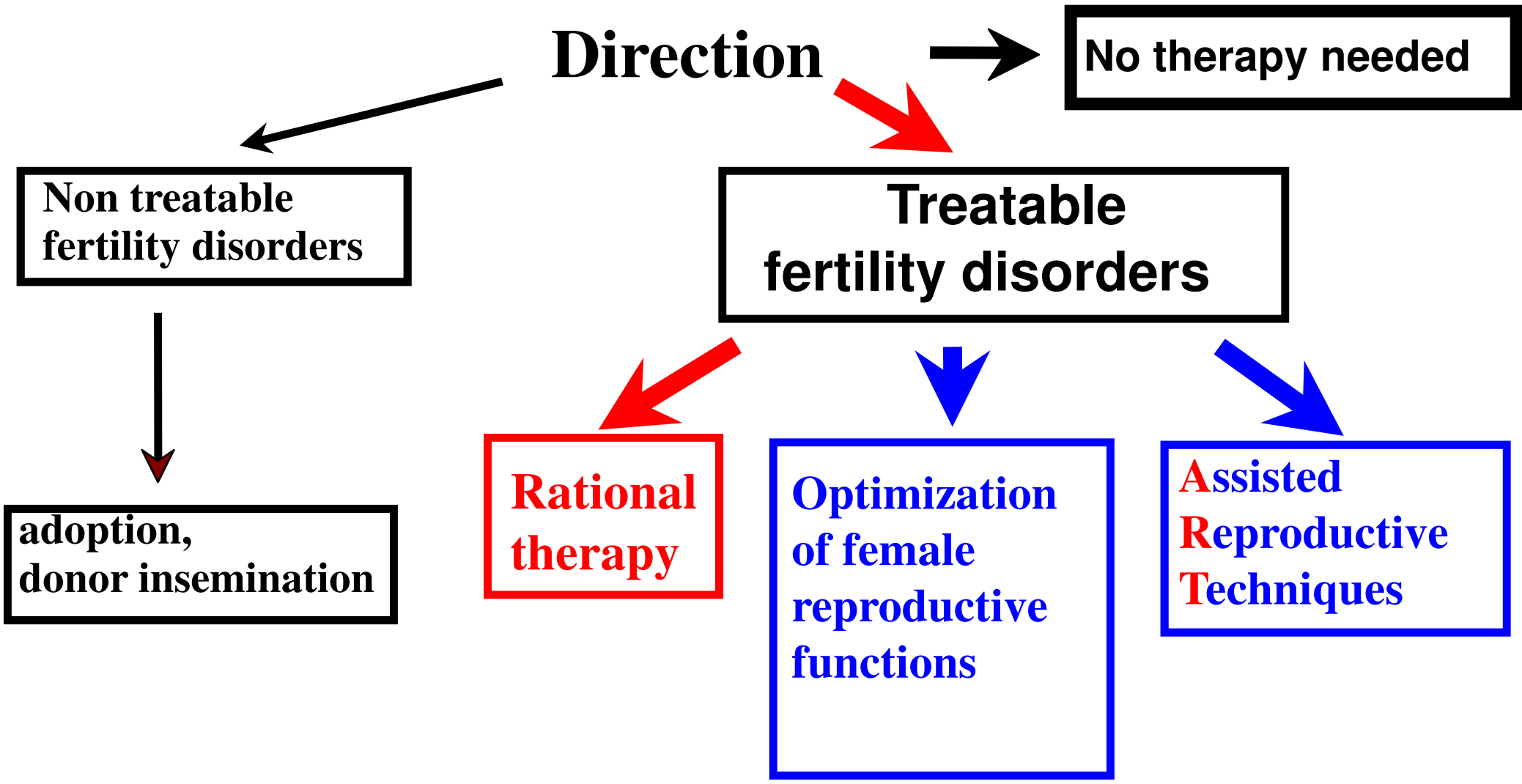
The ESHRE Capri workshop 1996. Guidelines to the prevalence, diagnosis, treatment and management of infertility. Hum. Reprod. 11: 1775 - 1807, 1996

Percentage distribution of diagnoses of 12945 consecutive patients attending the Institute of Reproductive Medicine of the University of Münster

Nieschlag & Behre, Andrology, Male reproductive health and dysfunction, Springer, 2009



Tasks of the andrological diagnostic evaluation



Relevant international and national recommendations/ guidelines

- **The male infertilty best practice policy committee of the American Urological Association (AUA) and the practice committee of the American Society for Reproductive Medicine (ASRM)**
  Fertil. Steril., 86 Supl. 4: S202-09, 2006

- **The Institute for Clinical System Improvement (ICSI)**
  http://www.icsi.org/infertility/diagnosis_and_management_of_infertility_2301.html, 2004

- **National Institute for Clinical Excellence (NICE) of the NHS.**
  http://www.nice.org.uk/pdf/CG011niceguideline.pdf, 2004

- **The ESHRE Capri Workshop**
  Hum. Reprod. 11: 1779-807, 1996

- **European Association of Urology (EAU) Guidelines on male infertility**
  http//www.uroweb.org/fileadmin/tx_eauguidelines/Male%20Infertility.pdf, 2008.

When to do an evaluation for male infertility?

The male infertilty best practice policy committee of the AUA and ASRM,
The Institute for Clinical System Improvement (ICSI)
National Institute for Clinical Excellence (NICE)

- **No pregnancy within one year of regular unprotected intercourse**

before one year if

- **Known/supected male infertilty risk factors (e.g. bilateral cryptorchidism)**
- **Known/supected female infertility risk factors (e.g. age over 35 years)**
- **Couple questions the male partner´s fertility potential**

Minimal andrological diagnosis

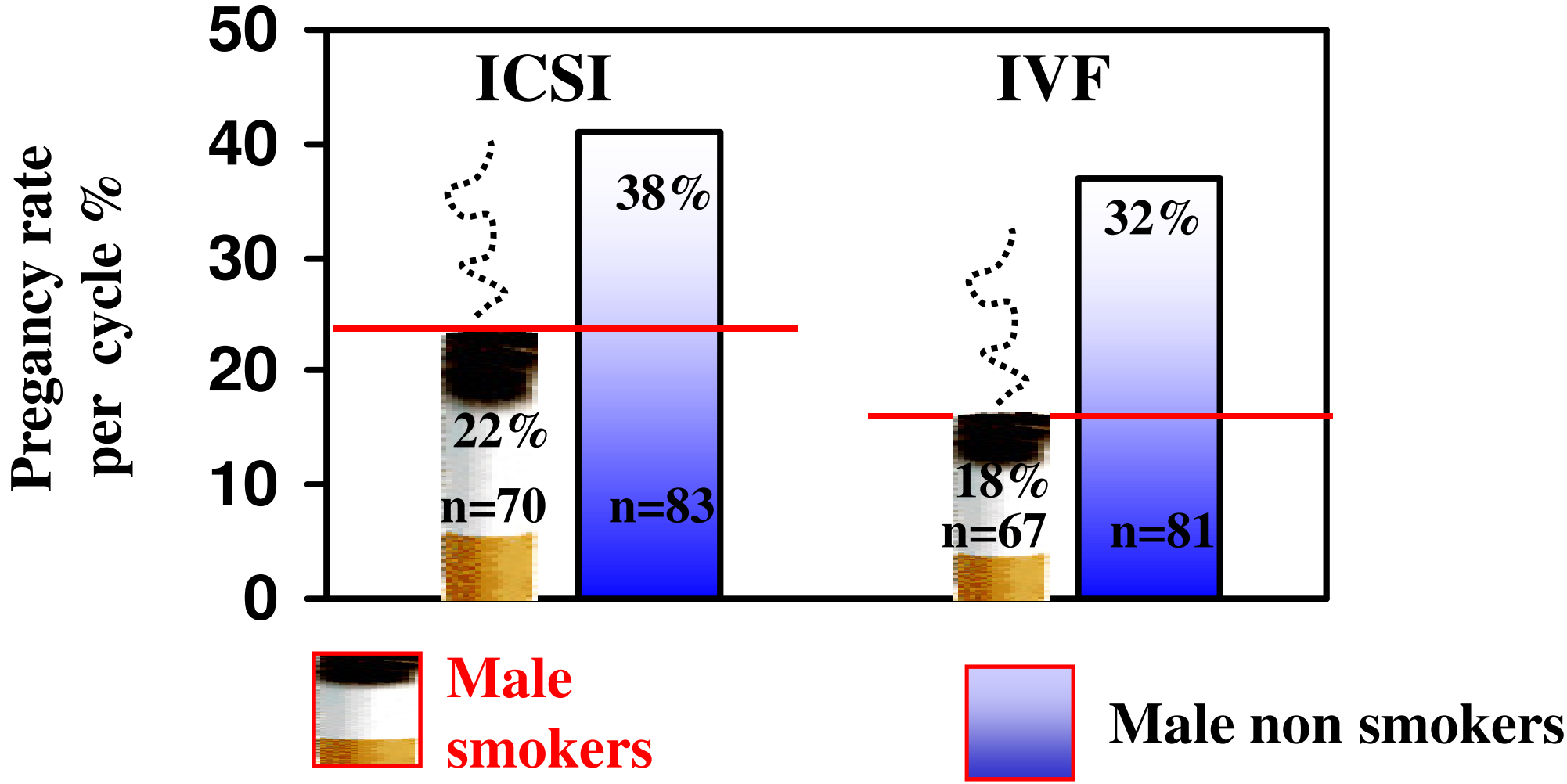
The male infertilty best practice policy committee of the AUA and ASRM 2006, The ESHRE Capri Workshop 1996; National Institute for Clinical Excellence (NICE) 2004, The Institute for Clinical System Improvement (ICSI) 2004 European Association of Urology (EAU) 2008

- **Semen Analysis (AUA-ASRM / ESHRE, NICE, ICSI, EAU)**
  - **After 2-3 days of sexual abstinence**
  - **Twice seperated by at least one month (if abnormal)**
  - **WHO; 4. edition 1999**
  - **(Quality control)**

- **Medical History/ Couple medical history (AUA-ASRM, NICE, ICSI)**
  - **Coital frequency and timing**
  - **Duration of infertility and prior fertility**
  - **Childhood illnesses and developmental history**
  - **Systemic medical illnesses**
  - **Prior surgeries**
  - **Sexual history including sexually transmitted diseases**
  - **Gonadal toxin exposure including heat**

Success rate for IVF and ICSI in male smokers

Zitzmann et al., Fertil. Steril. 79: 1550, 2003



Complete andrological diagnosis

The male infertilty best practice policy committee of the AUA and ASRM, 2006; The Institute for Clinical System Improvement (ICSI), 2004; National Institute for Clinical Excellence (NICE) 2004; European Association of Urology (EAU) 2008

- Semen Analysis
- Medical History/ Couple medical history
- **Physical Examination (Minimal in ICSI)**
  - **Recommended in cases of :**
    - **Abnormal male medical history**
    - **Abnormal semen analysis**
    - **Couples with unexplained infertility**
    - **Treated female factor and persistent infertility**
- **(Ultrasound)**

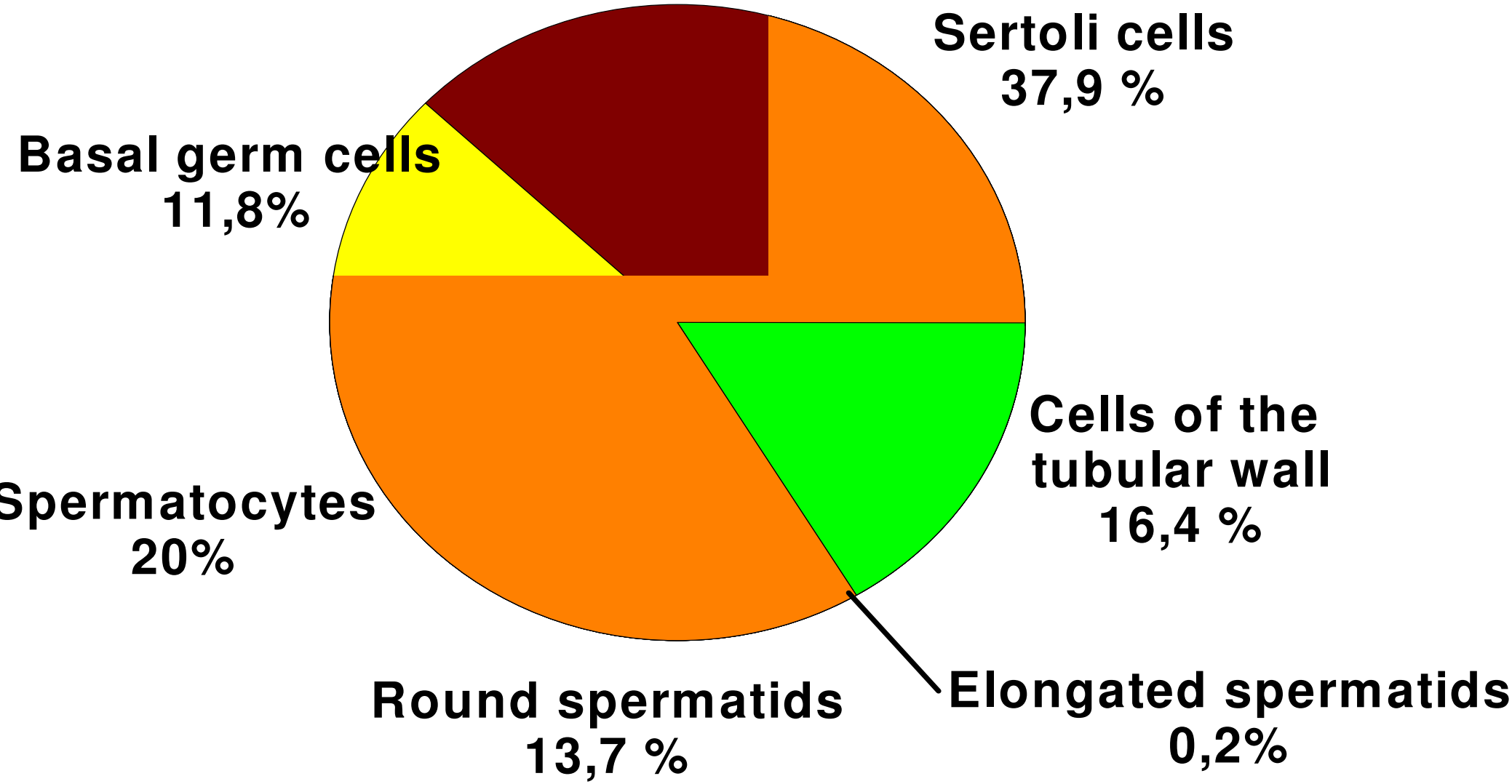
Genital examination

The male infertilty best practice policy committee of the AUA and ASRM, 2006; The Institute for Clinical System Improvement (ICSI), 2004;

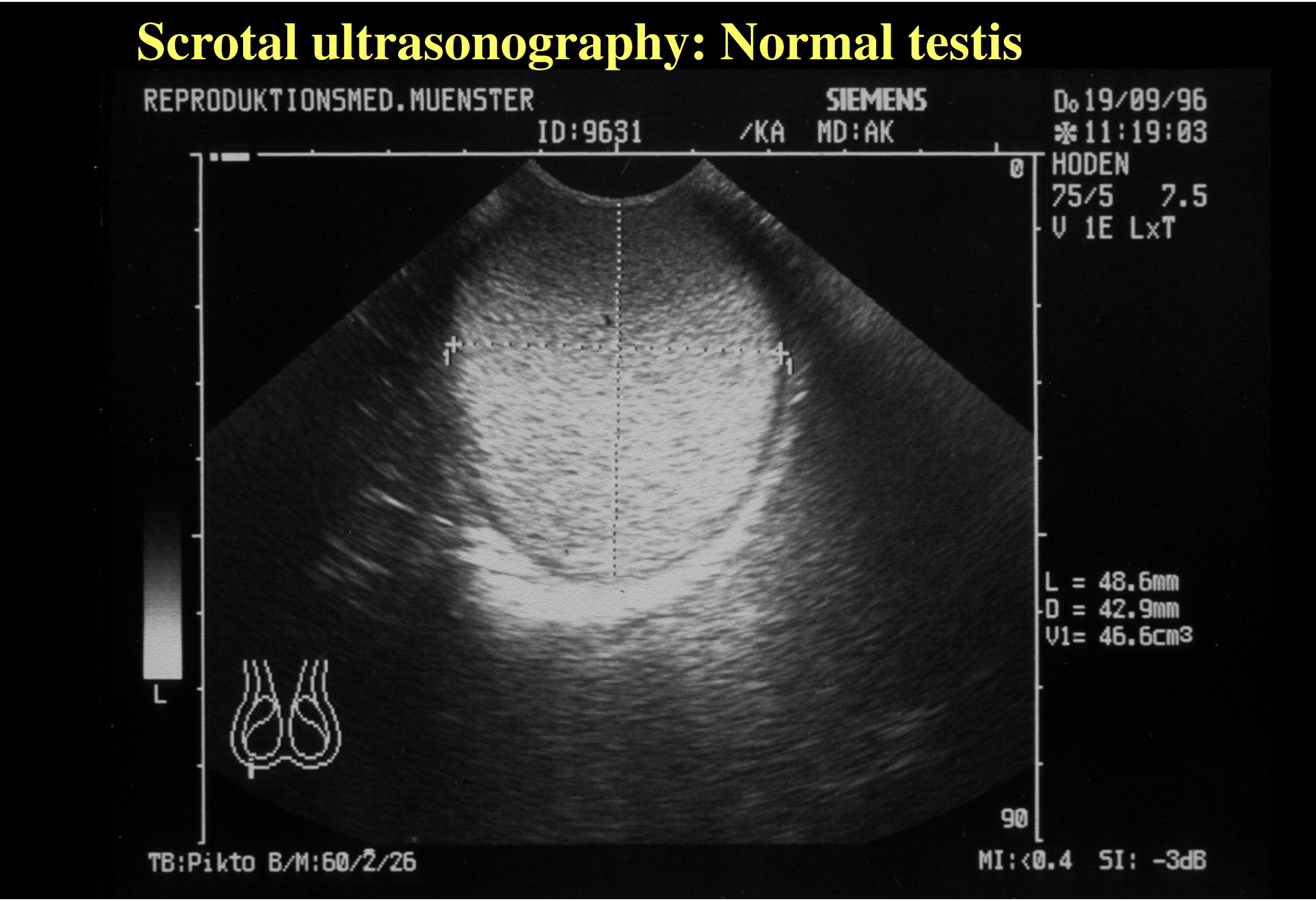
- **Examination of the Penis**
- **Palpation of the testis and measurement of the size**
- **Presence and consitency of both vasa and epididymides**
- **Evaluation of the plexus pampiniformis**
- **Secondary sex characteristics**
- **Digital rectal examination**

Volumetric composition of human testes

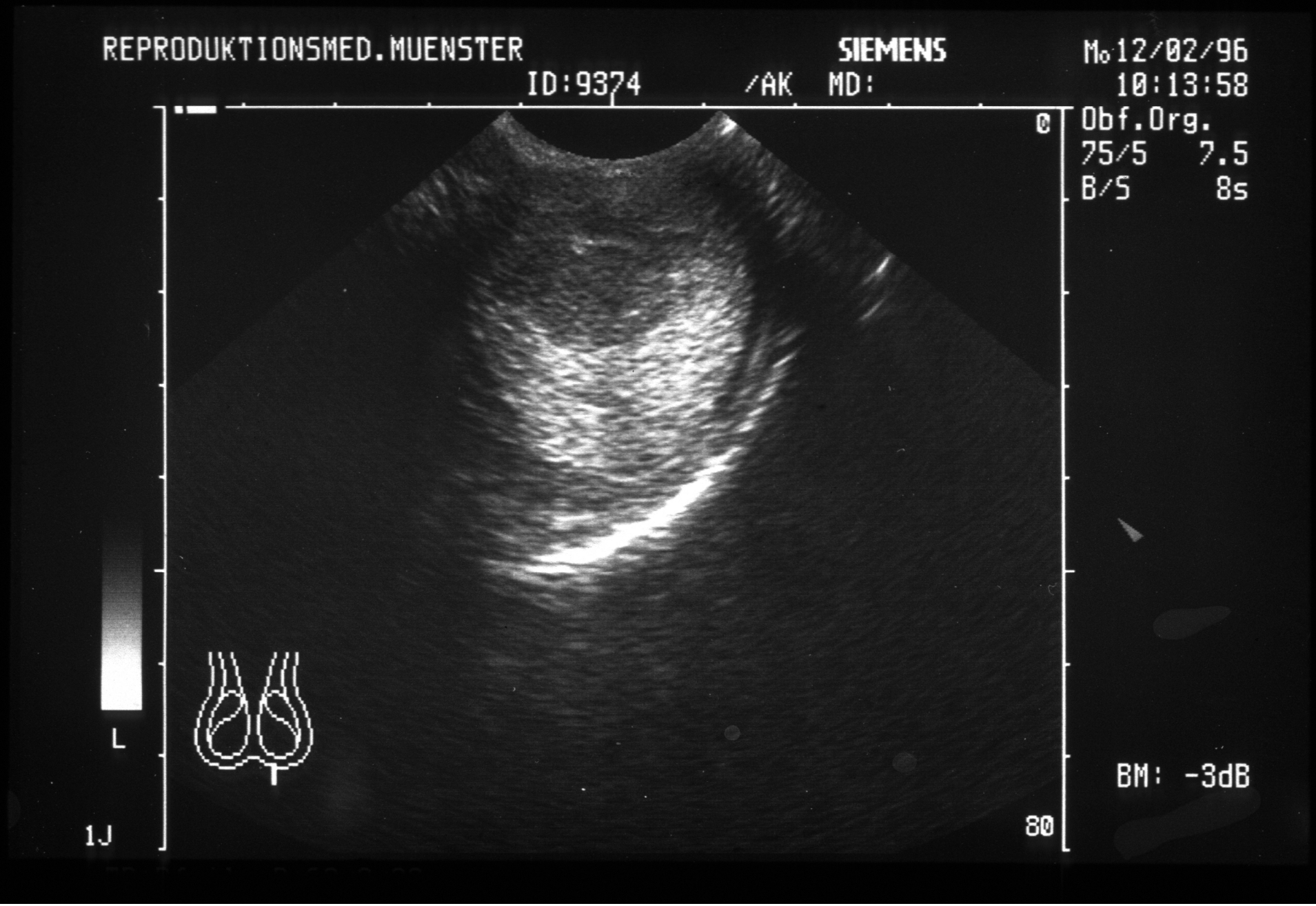
(Russell et al. 1990)



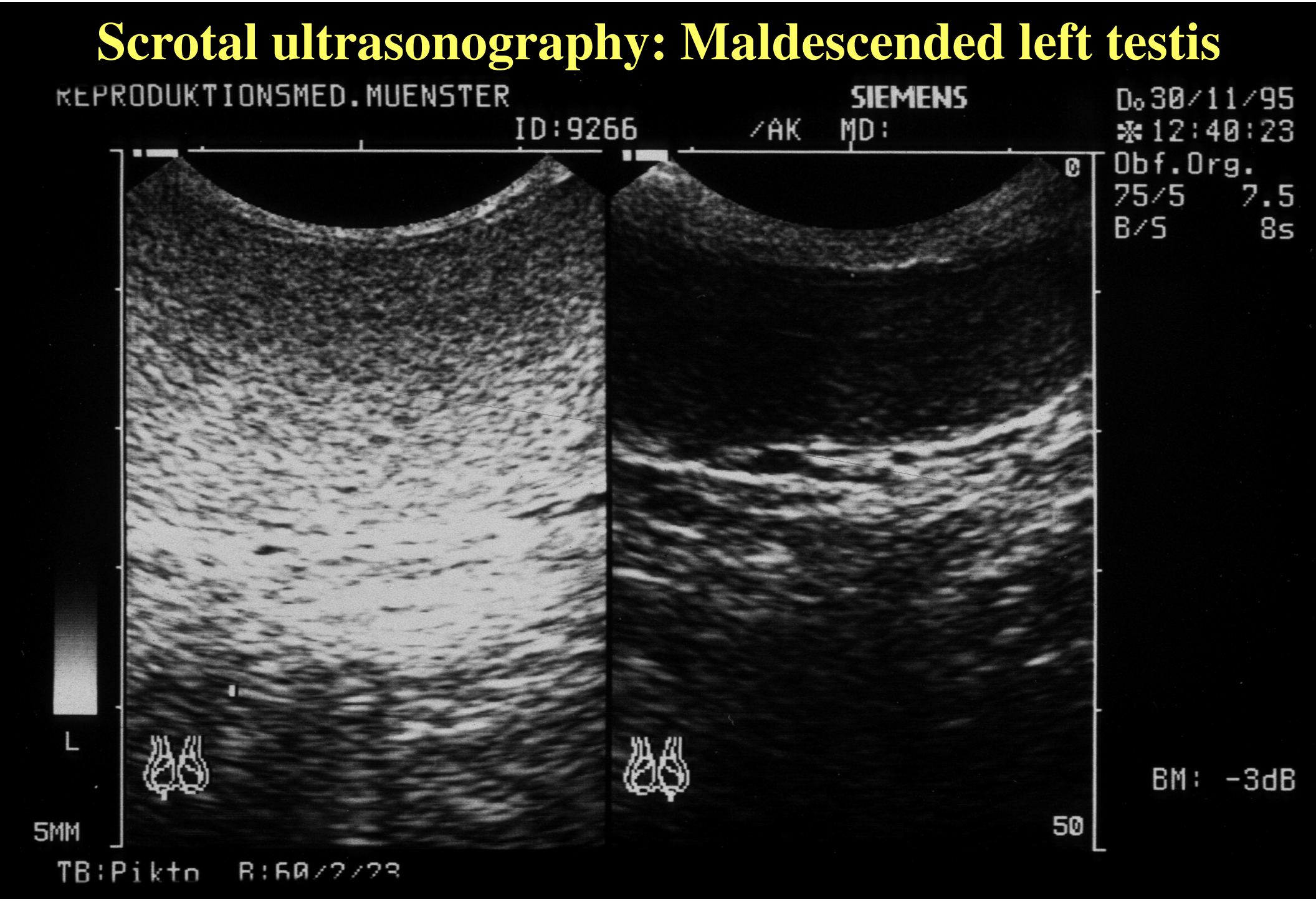
Scrotal ultrasonography: Normal testis



Scrotal ultrasonography: Seminoma



Scrotal ultrasonography: Maldescended left testis



Classification of varicoceles

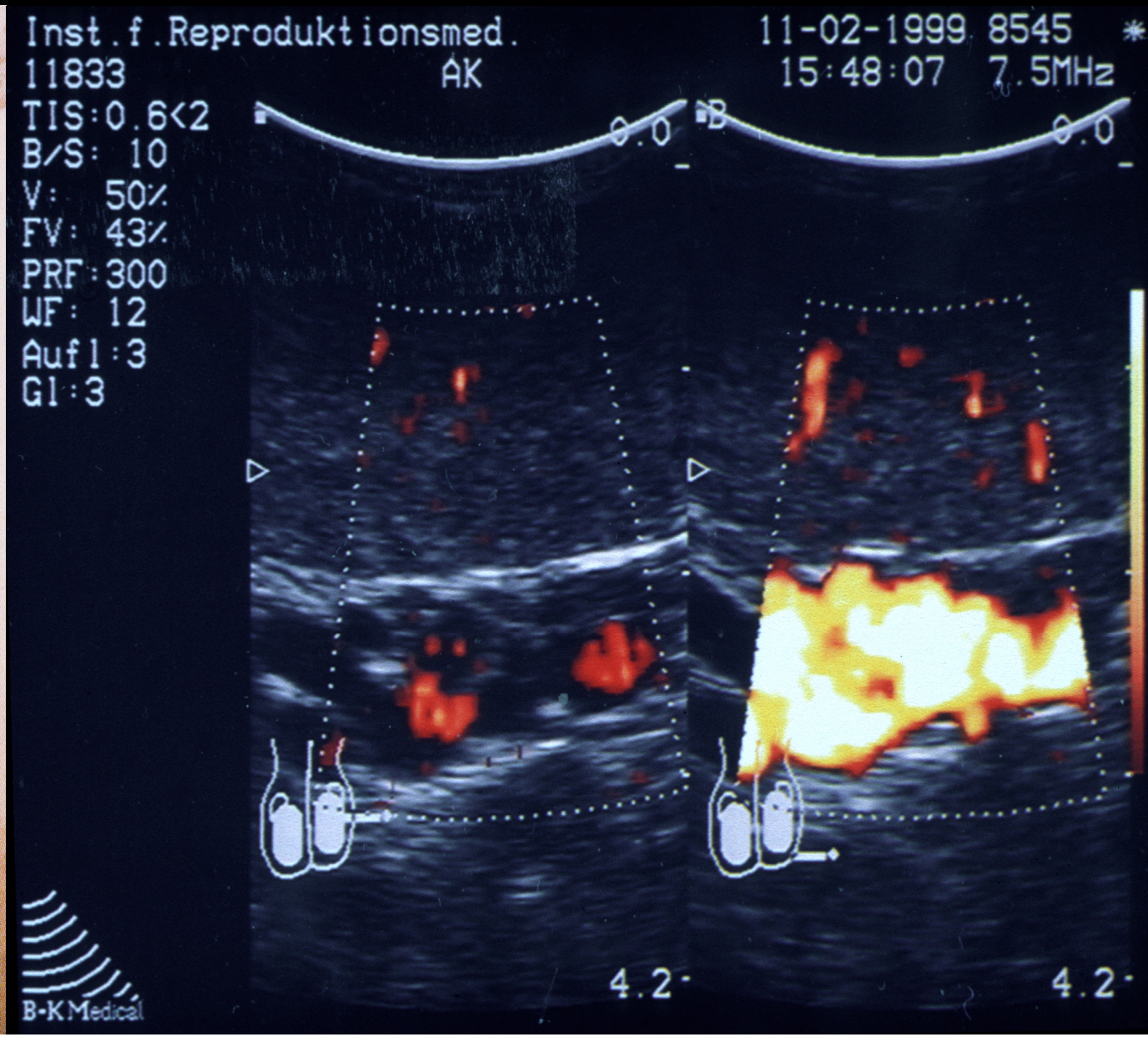
Dubin L., Amelar RD. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil.Steril. 21: 606-9, 1970

Grade I Enlargement of the pampiniform plexus, only palpable during Valsalva maneuver.

Grade II Clearly palpable enlargement of pampiniform plexus.

Grade III Visible enlargement of the pampiniform plexus.

Varicocele: Genital and sonographic diagnosis



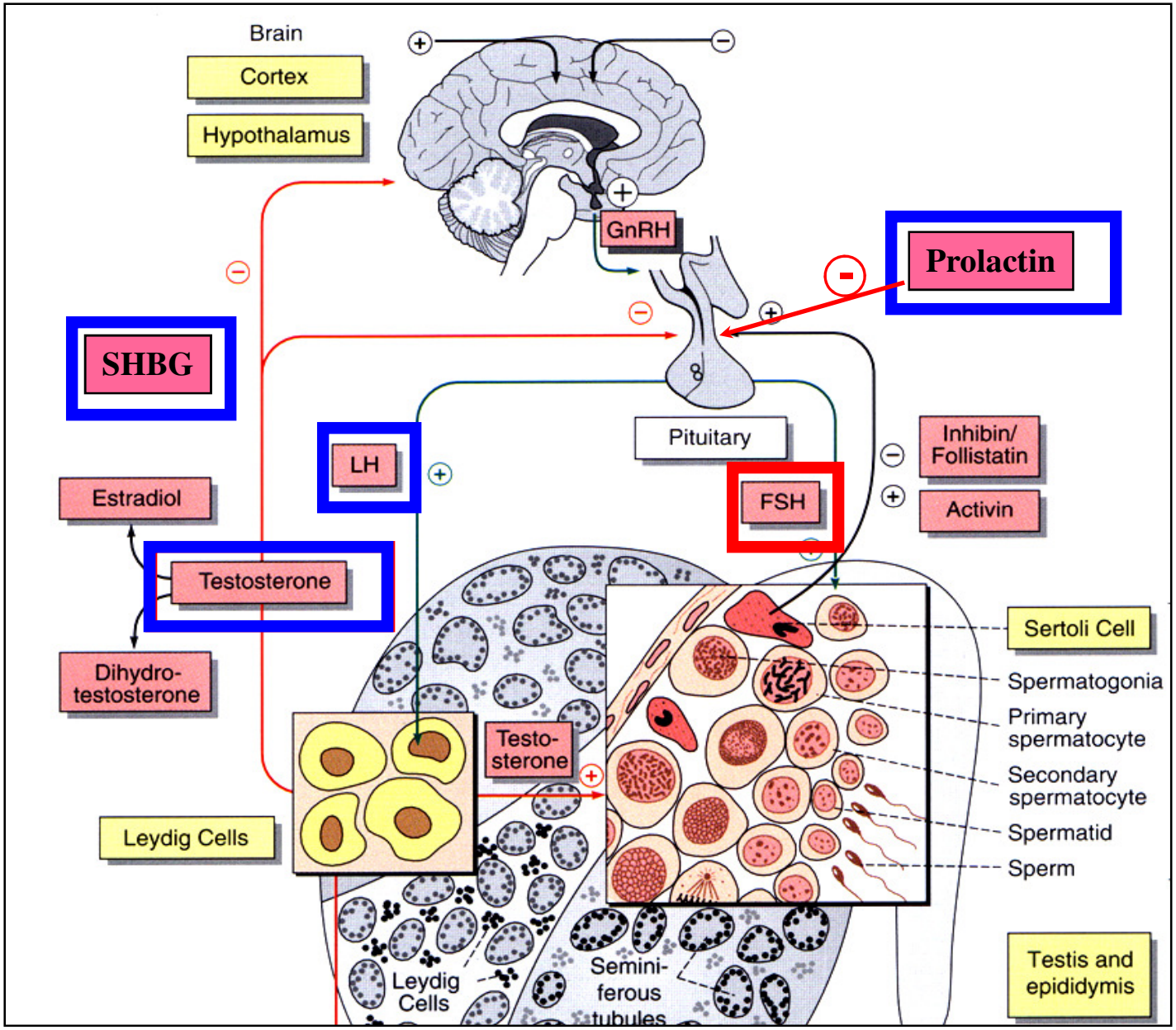
Complete andrological diagnosis

The male infertilty best practice policy committee of the AUA and ASRM, The Institute for Clinical System Improvement (ICSI), 2004; European Association of Urology (EAU) 2008

- Semen Analysis
- Medical History/ Couple medical history
- Physical Examination
- **Endocrine laboratory diagnosis**
  - **Initial recommended in cases of :**
    - **Low sperm count especially if less 10 mill/ml**
    - **Impaired sexual function**
    - **Clinical findings suggestive of a endocrinopathy**

Minimal:
FSH, testosterone

Additional in cases of low testosterone:
Repeat testosterone
SHBG
LH
Prolactin

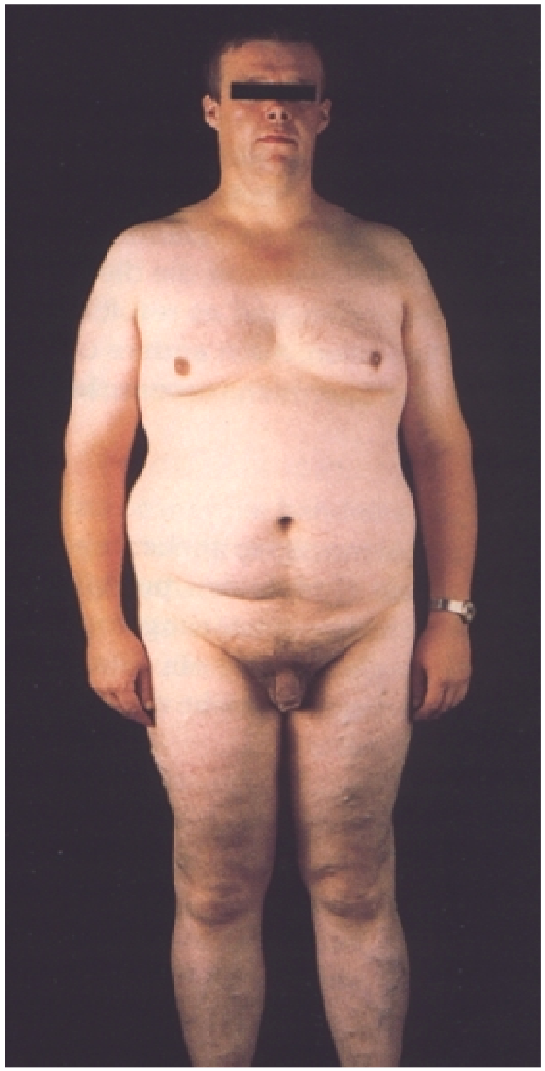


Nieschlag & Behre, Andrology, Male reproductive health and dysfunction, Springer, 2000

Various diagnoses for male hypogonadism

PRIMARY HYPOGONADISM (LH/FSH↑, T↓)

- Klinefelter syndrome, XX male syndrome
- Testicular damage (tumor, trauma)
- Disturbances of testosterone synthesis
- Inactivation of the LH receptor



LATE ONSET HYPOGONADISM (LH/FSH↑← , T↓)

SECONDARY HYPOGONADISM (LH/FSH ↓, T↓)

- Hypothalamic disorders (e.g. Kallmann syndrome, idiopathic hypogonadotropic hypogonadism)
- Pituitary disorders (inherited, tumor, ischemia/ bleeding, chronic diseases, radiation)

Nieschlag & Behre, Andrology, Male reproductive health and dysfunction, Springer, 2009

Symptoms characteristic for androgen deficiency and Late Onset hypogonadism

Category A

ABC Reduced libido, erectile frequency and quality particularly nocturnal erections

ABC Depressed mood and decreased cognitive, intellectual activity and spatial ability

ABC Decreases in lean body mass, muscle volume and strength, Loss of vigor

ABC Increase in visceral fat

ABC Decreased bone mineral density with osteoporosis and increased fracture risk

Category B

AB Sleep disturbances

AB Decrease in body hair and skin alterations

AC Breast discomfort, gynaecomastia

AC Testicular atrophy and very small or shrinking testis (especially < 5 ml)

Category C

A Hot flushes, sweats

A Infertility with low to zero sperm counts

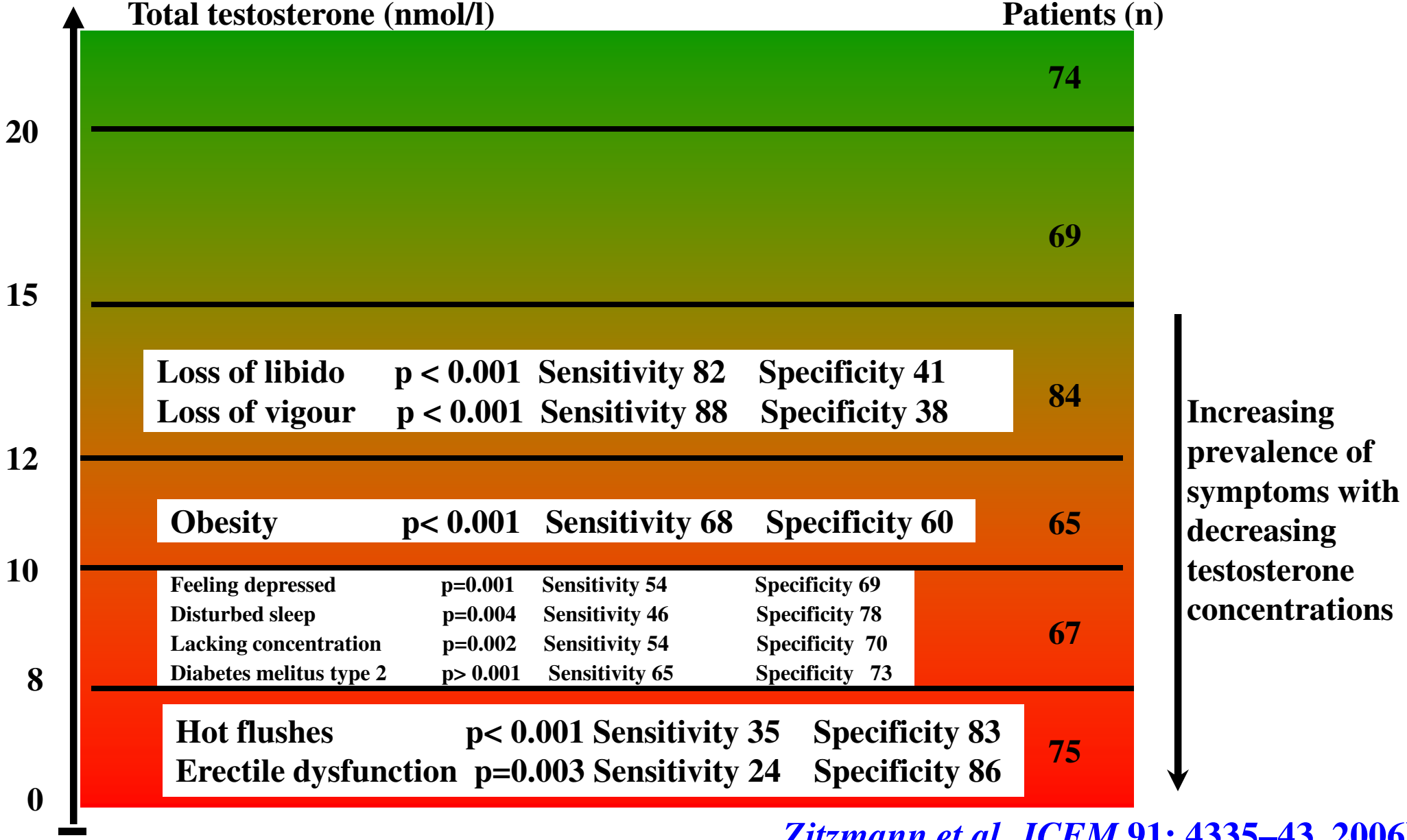
A Incomplete sexual development, eunuchoidsm, aspermia

A Bhasin et al. An Endocrine Society Clinical Practice Guideline, JCEM 91: 1995-2010, 2006

B Wang et al. ISA, ISSAM, EAU and ASA recommendations, J. Androl. 30: 1-9, 2009

C The best practice committee of the American Society for Reproductive Medicine , Fertil. Steril 86: S236-40, 2006

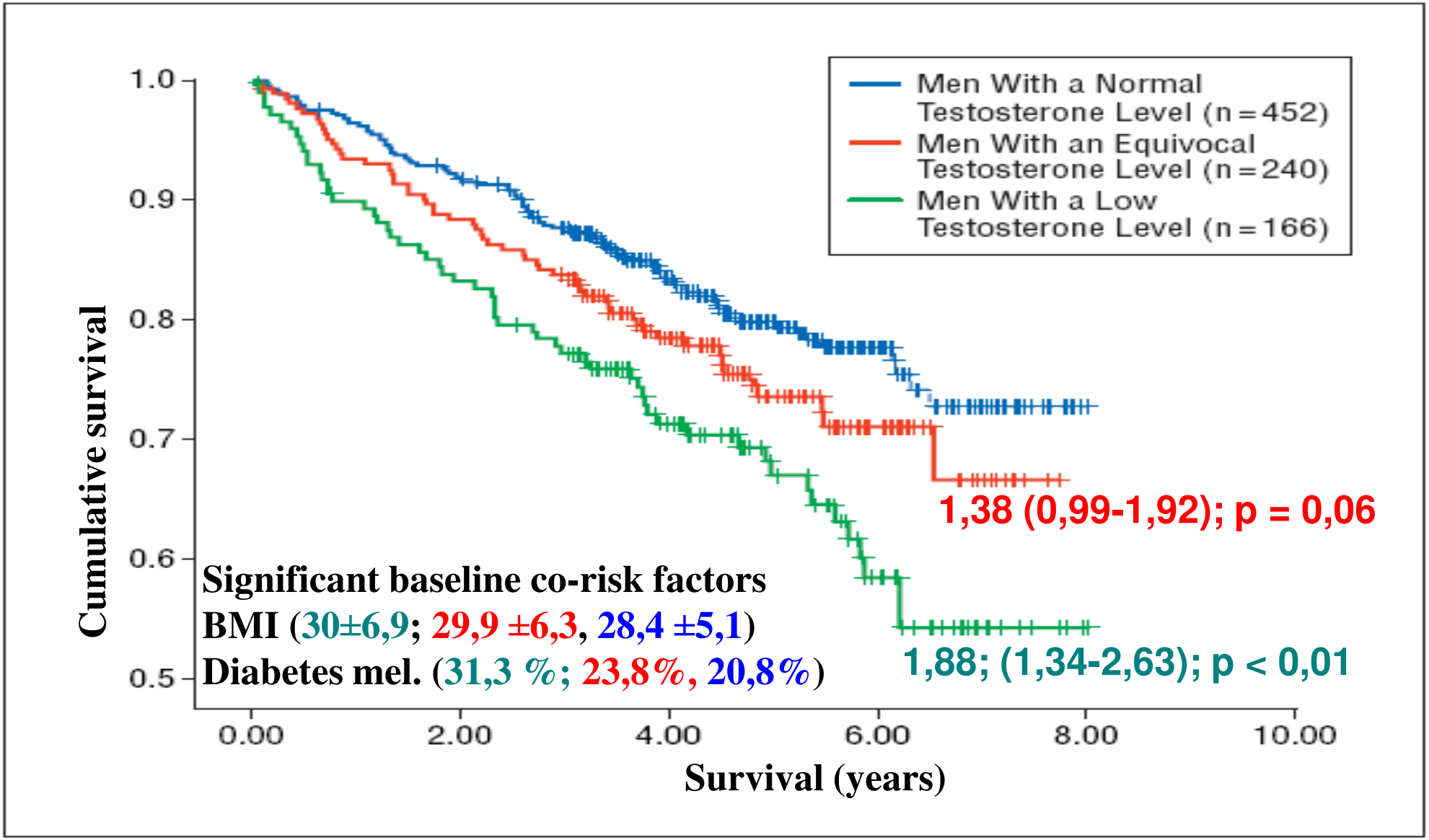
Accumulation of psychosomatic symptoms and metabolic risk factors with decreasing testosterone levels



Zitzmann et al. JCEM 91: 4335–43, 2006)

Kaplan-Meier survival curves in 858 men (> 40 ys) with normal, low-normal und decreased serum testosterone levels

Shores et al., *Arch Intern Med 166: 1660, 2006*



Additional procedures for andrological diagnosis

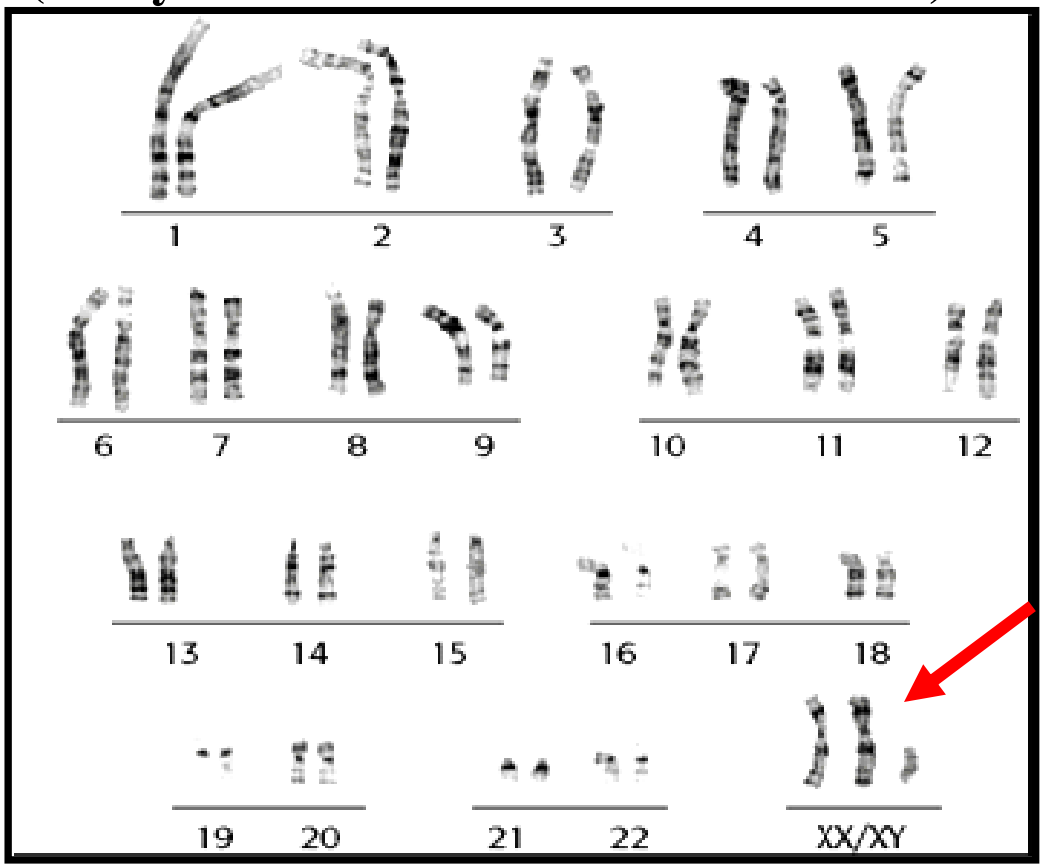
Genetic Laboratory Diagnosis

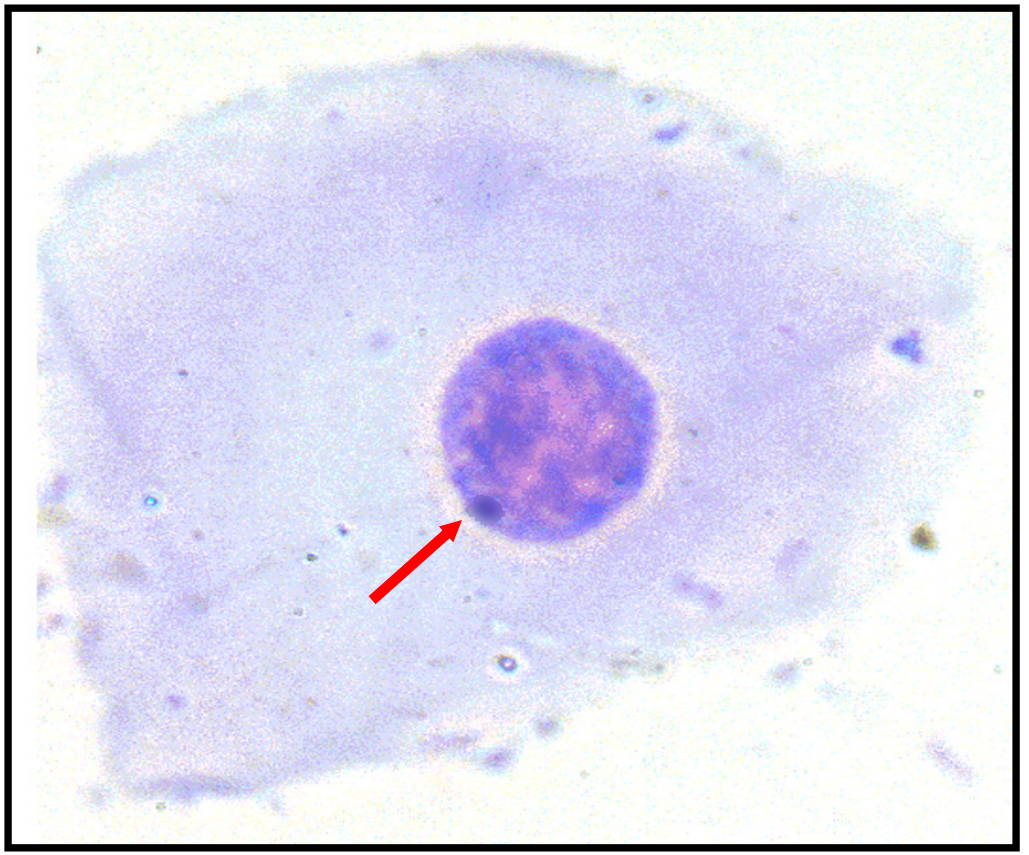
The male infertilty best practice policy committee of the AUA and ASRM, 2006;
European Association of Urology (EAU); 2008

- Karyotyping
- Molecular genetics
  - Y-chromosome microdeletions
  - Cystic Fibrosis Gene Mutations

Diagnostic work up in case of suspected Klinefelter Syndrom (Kamischke et al., J. Androl. 24: 41- 48, 2003)

Indication: Every patient with a hypergonadotropic azoospermia and firm, small testes (usally below < 5 ml bitesticular volume)





Gold standard: karyotype analysis in GTP banded metaphase lymphocytes

Screening: Barr bodies in buccal smear
Specificity: 95 % Sensitivity: 82 %

Additional procedures for andrological diagnosis

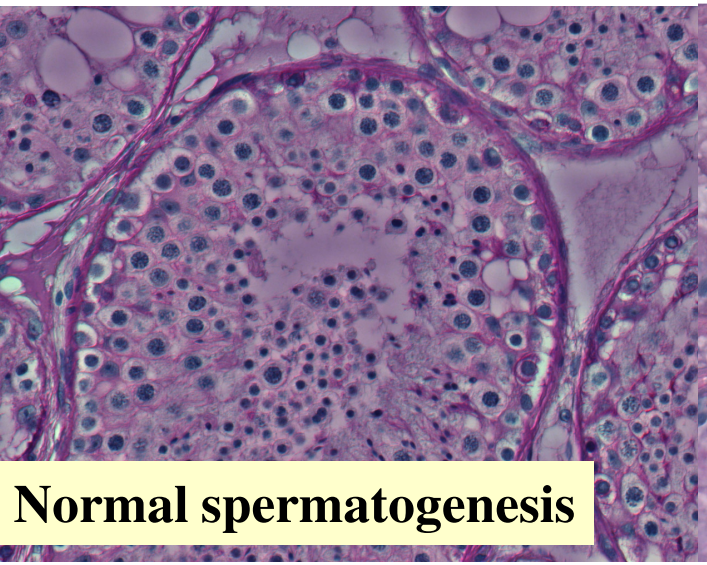
Testicular Biopsy

The male infertilty best practice policy committee of the AUA and ASRM, 2006;European Association of Urology (EAU), 2008

- Diagnostic / therapeutic testicular biopsy for ultimate differentiation between

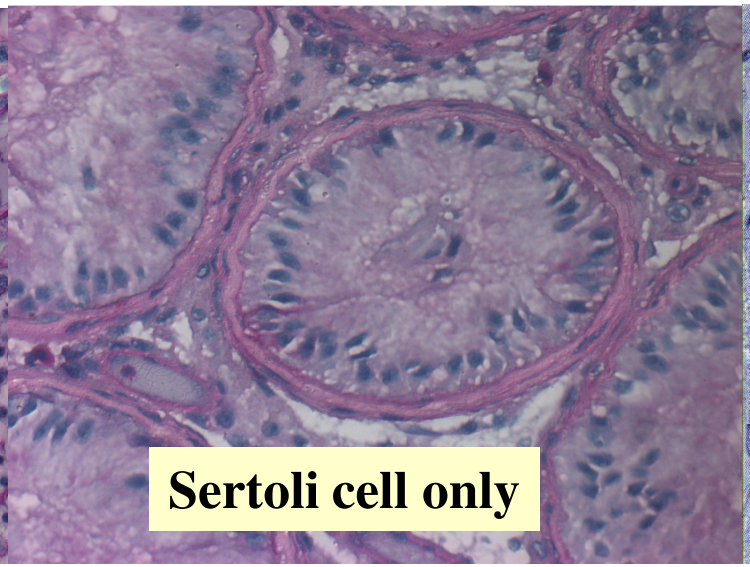
- Diagnostic testicular biopsy for diagnosis of malignancy

Obstructive azoospermia



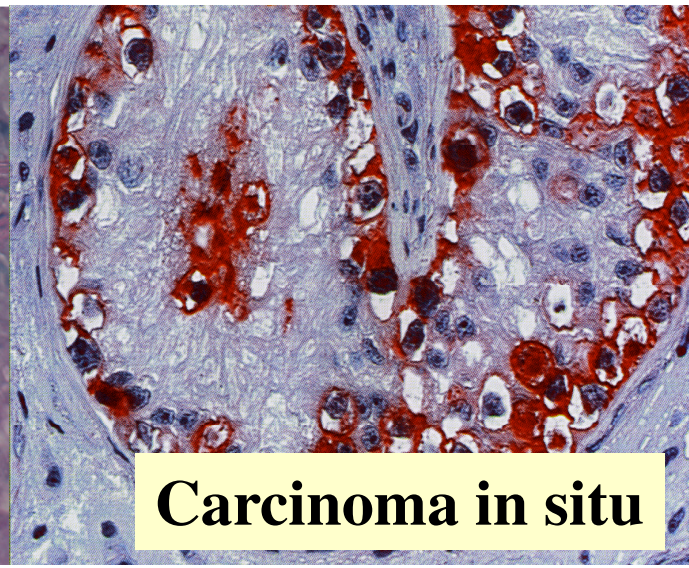
Normal spermatogenesis

Testicular azoospermia



Sertoli cell only

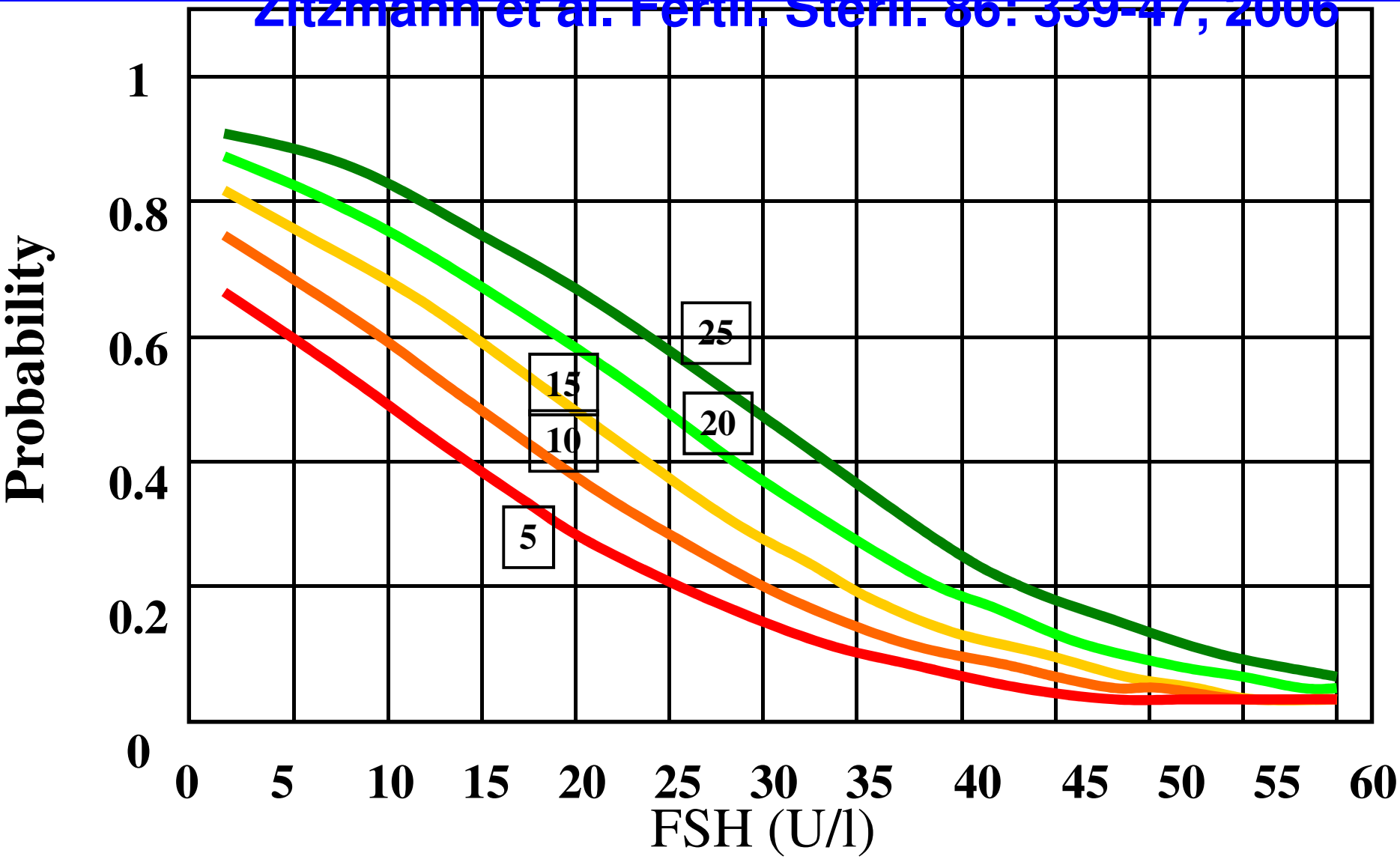
Malignancy



Carcinoma in situ

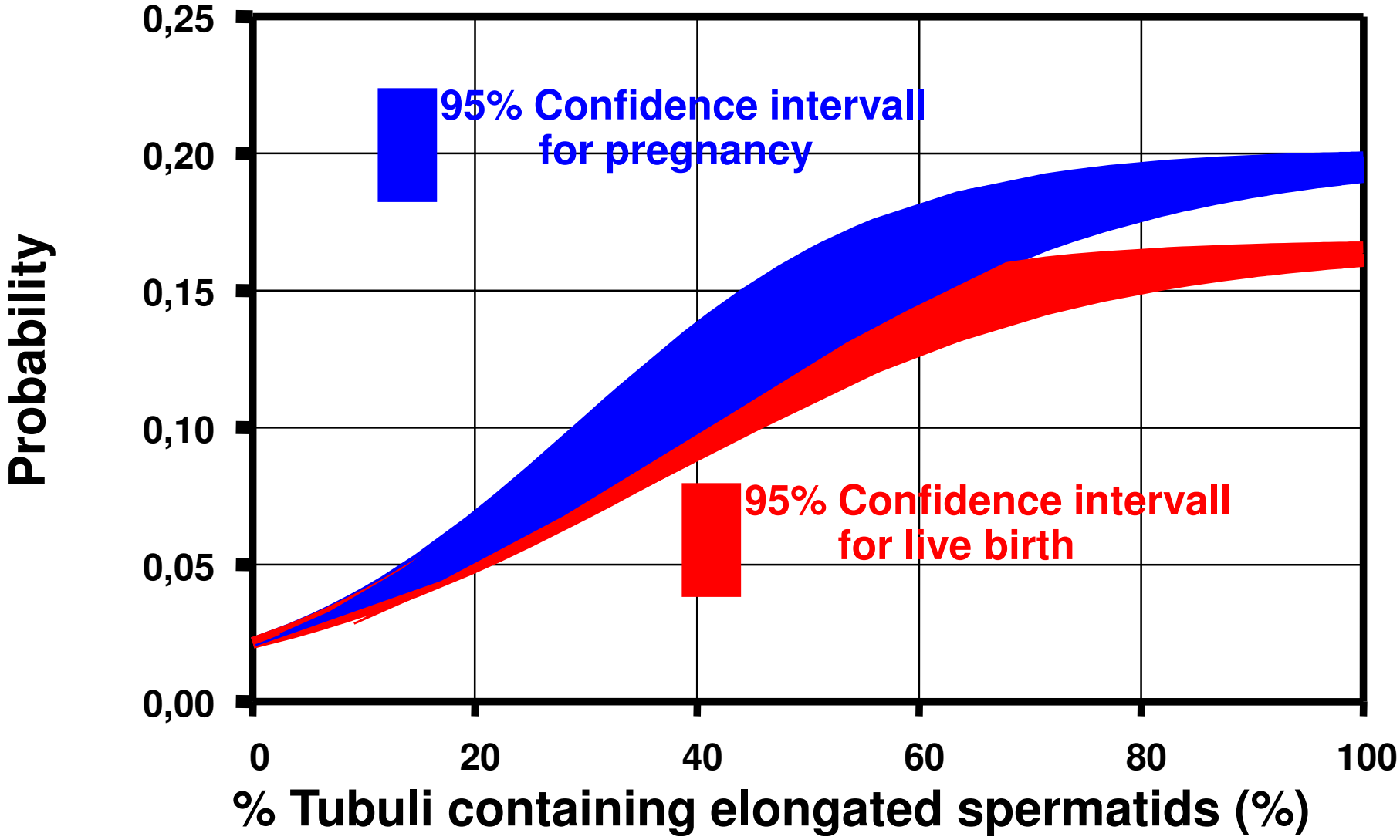
Probability curves to predict chances of obtaining elongated spermatids from testicular biopsies using noninvasive parameters

Zitzmann et al. Fertil. Steril. 86: 339-47, 2006



Probability curves for the prediction of clinical pregnancies and live births after ICSI with testicular sperms depending on the percentage of testicular tubuli containing elongated spermatids

Zitzmann et al. Fertil. Steril. 86: 339-47, 2006



Additional procedures for andrological diagnosis

Post-ejaculatory urinanalysis

The male infertilty best practice policy committee of the AUA and ASRM, 2006;
European Association of Urology (EAU), 2008

Retrograde ejaculation (Substantial emission of ejaculate into the bladder):

Complete (no antegrade fraction) or incomplete (only minimal antegrade fraction) permanent or intermittent absence of an antegrade ejaculation (< 1 ml) with presence of spermatozoa and/or fructose in postorgasmic urine analysis.

Anejaculation (Failure of seminal emission into the posterior urethra):

Permanent or intermittent complete absence of an antegrade ejaculation combined with a non-viscous, fructose-negative and spermatozoa negative postorgasmic urine analysis.

Murphy and Lipshulz, Anomalies of ejaculation.Urol.Clin.North.Am. 14: 596, 1987

Summary

- An evaluation for male infertility should be done if no pregnancy occured within one year of regular unprotected intercourse or if there are known/supected male or female infertilty risk factors.
- A minimal andrological diagnosis consists of a semen analysis according to actual WHO standards and a medical history with special emphasis to the sexual history.
- A complete andrological diagnosis should be done in all couples with major abnormalities in the minimal andrological diagnosis and should include in addition a complete genital (sonographically) and (physical) examination.
- An endocrine evaluation of FSH and testosterone (LH, Prolactin, SHBG) should be done in all patients with major impairments of spermatogenesis (< 10 Mill/ml) or suspicion of endocrine abnormalities.
- Decreases of libido, bone density, erectile quality and quantity as well as changes in behavioural pattern, body composition and hair pattern are key symptoms for the diagnosis of androgen deficiency.
- Additional procedures for male infertility work-up include genetic laboratory testings, the conductance of a diagnostic / therapeutic testicular biopsy and an evaluation for anejaculation/ retrograde ejaculation if indicated by results of the previous examinations.