DSD team
Ghent

man, vrouw en kind
Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

GONADECTOMY IN AIS :

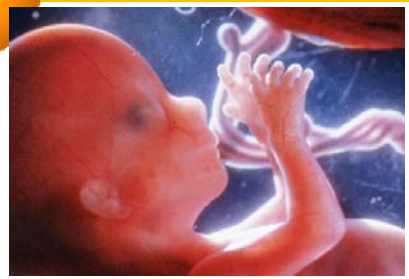
WHERE DO WE COME FROM, WHERE DO WE GO TO?

Martine Cools

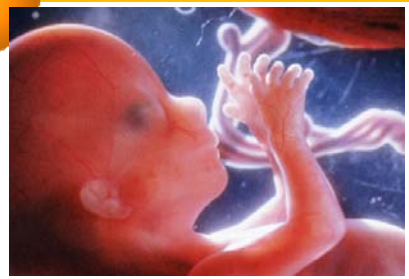
Pediatric Endocrinologist

Ghent, Belgium

Typical sexual development



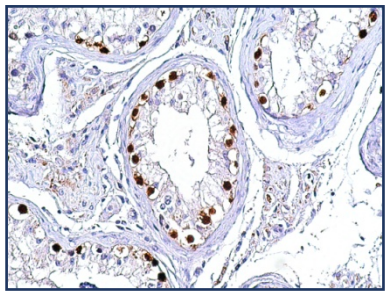
Sexual development in complete AIS



Tumors in DSD patients

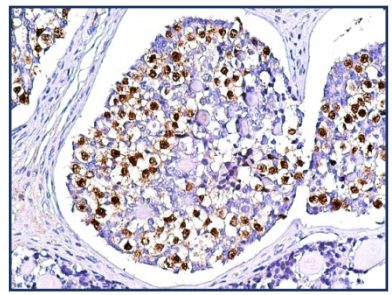
Carcinoma in situ

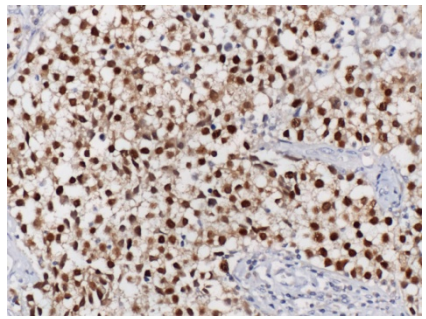
- Local (not invasive)
- Gonadectomy



Gonadoblastoma

- Local (not invasive)
- Gonadectomy

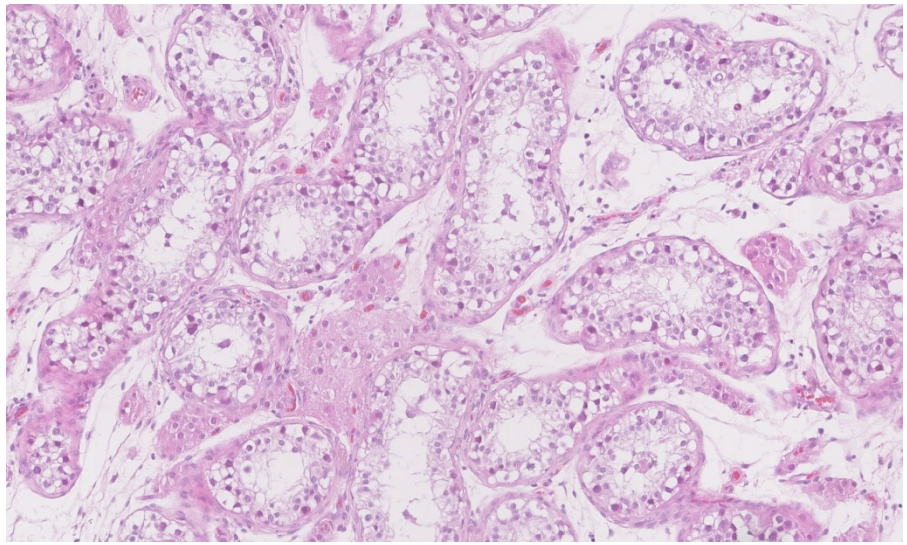




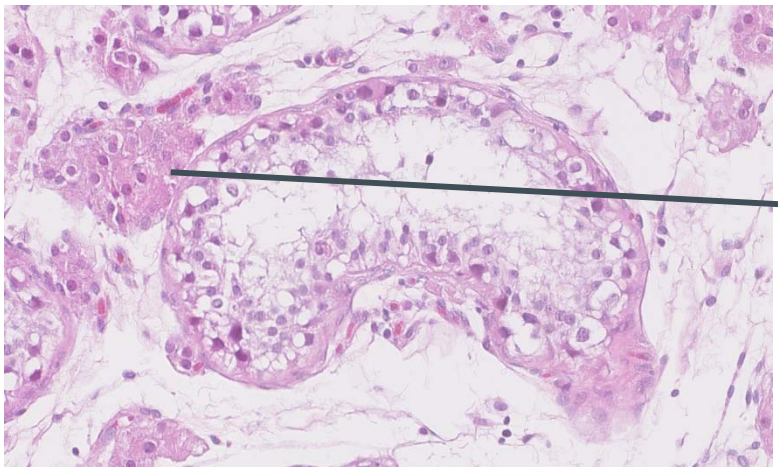
Seminoma / Dysgerminoma / Non-seminoma

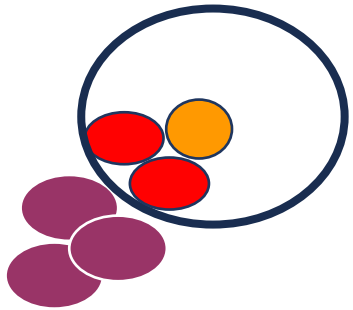
- Invasive
- Gonadectomy + chemotherapy

The gonads in AIS

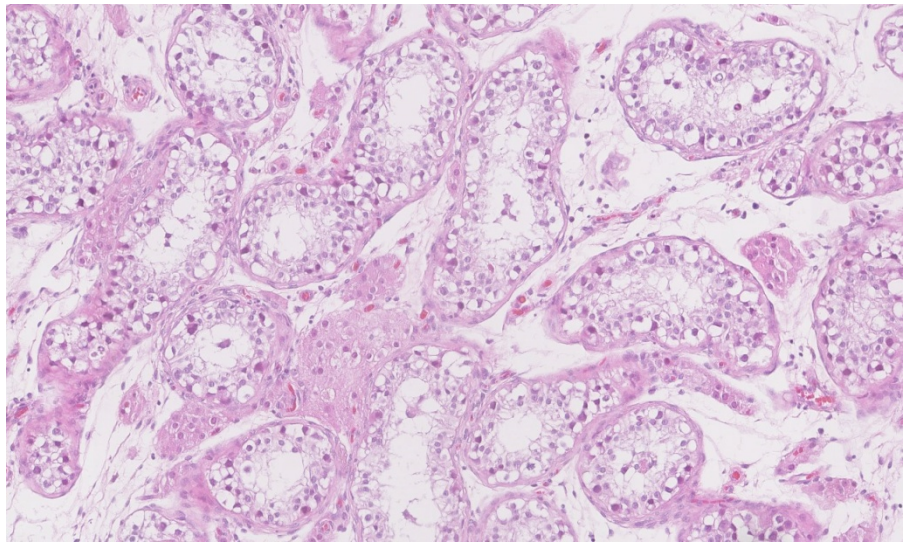


Leydig cell: T

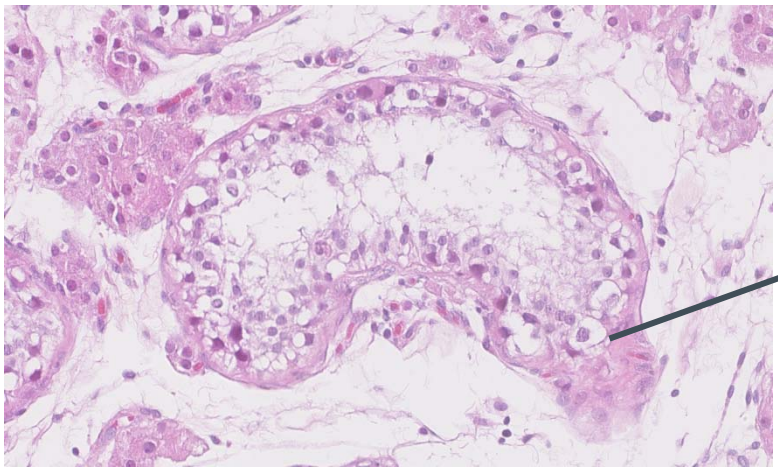




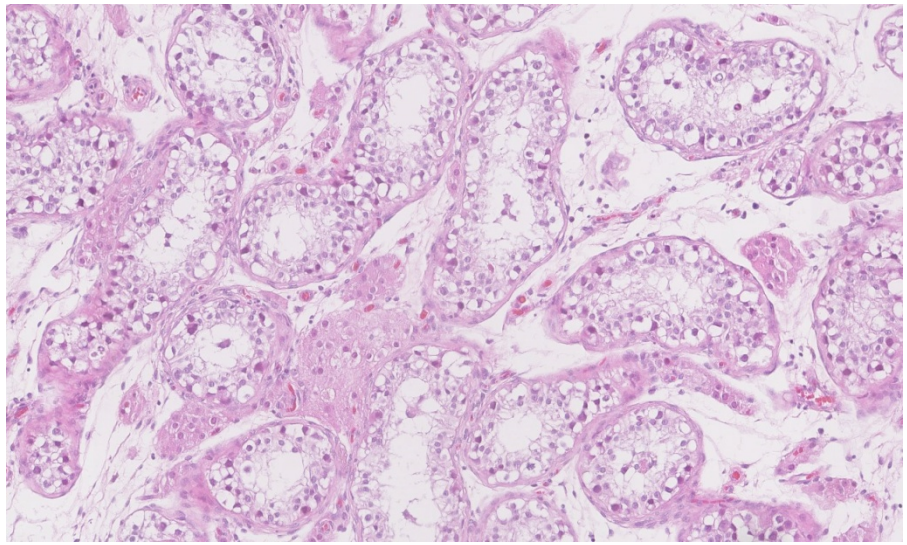
The gonads in AIS



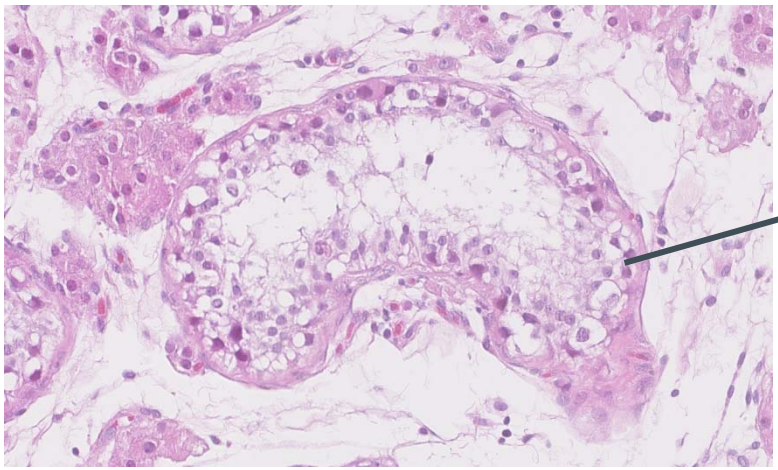
Germ cell

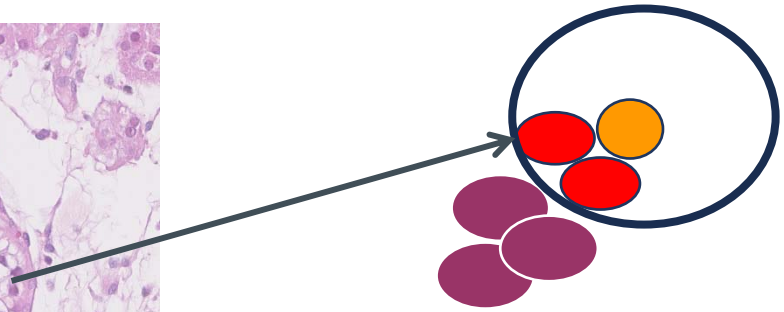


The gonads in AIS



Sertoli cell: AMH +
support for germ cells



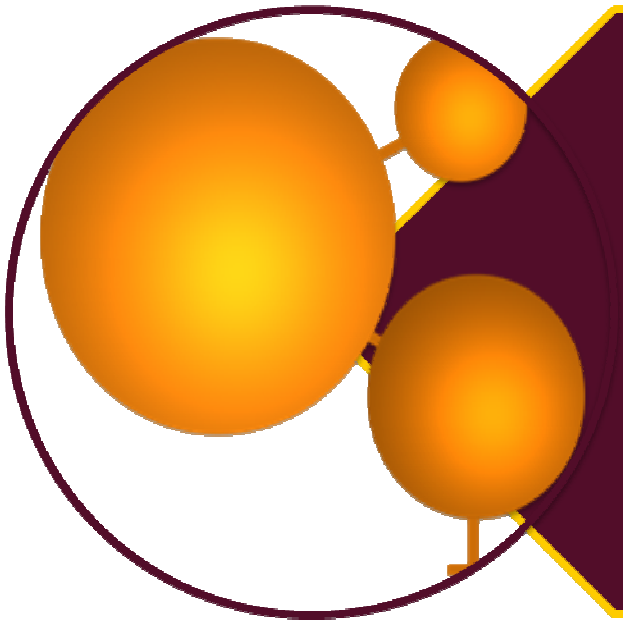


Gonadectomy in AIS

WHERE DO WE COME FROM?

In 2004

In 2004

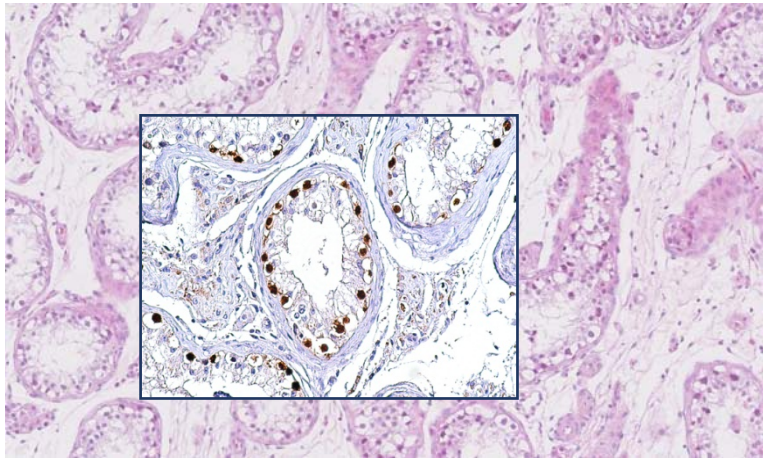


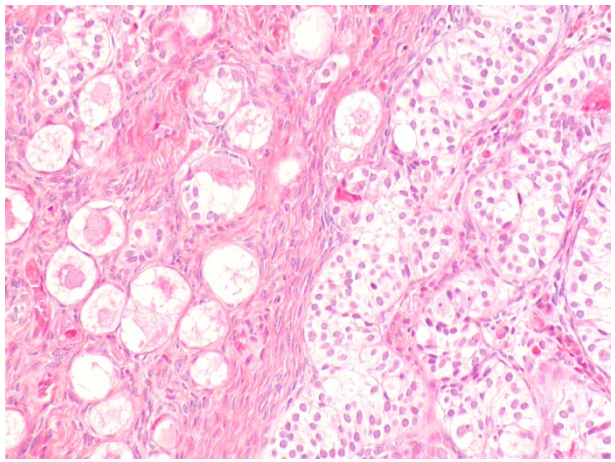
Difficulties in research

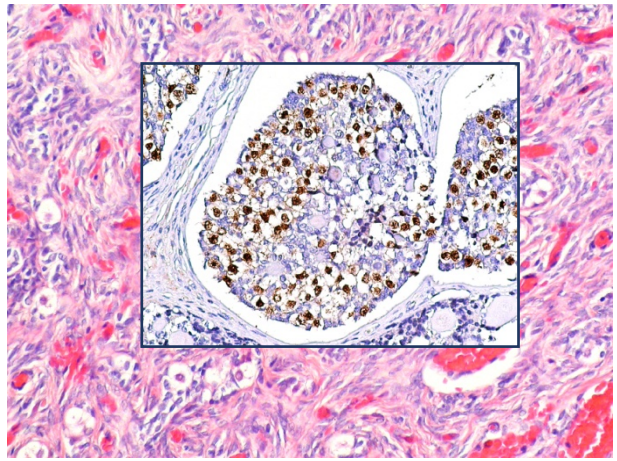
- Confusing terminology and classification
- Lack of good criteria to detect tumors in young children
- Prophylactic gonadectomy: Not many tumors

In 2004

Confusing terminology and classification







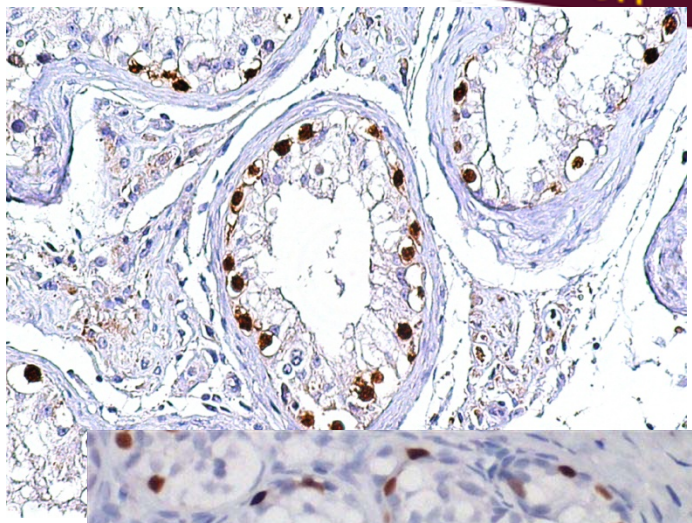
In 2004

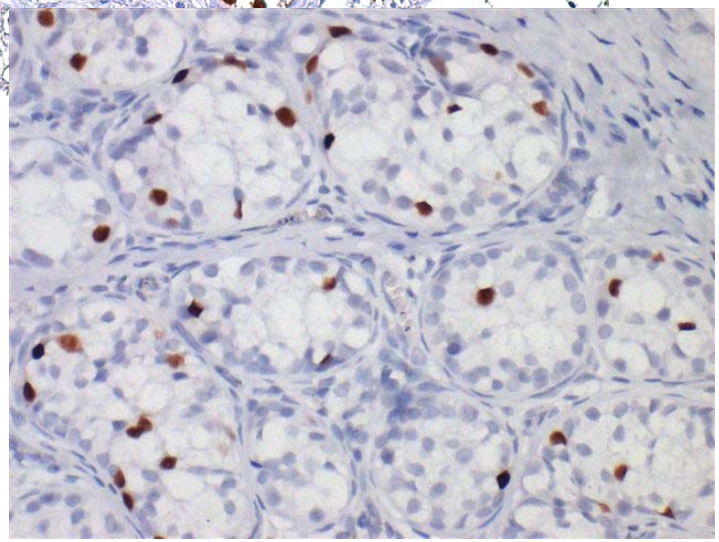
Confusing terminology and classification

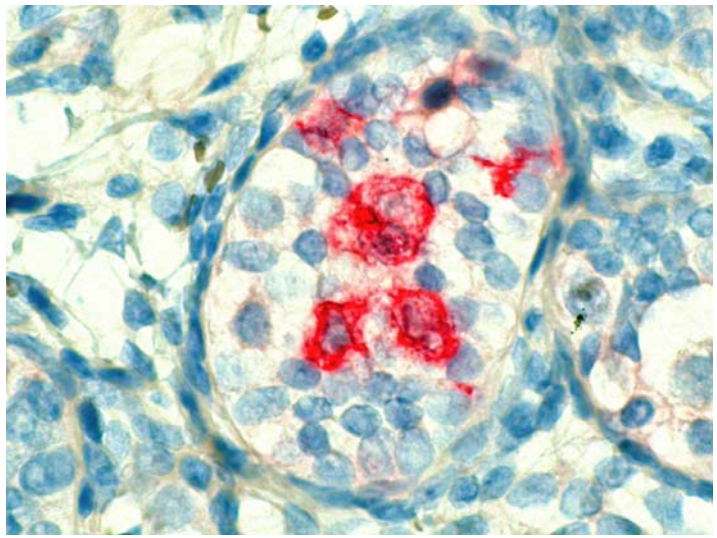
Sex Chromosome DSD	46,XY DSD	46,XX DSD
45,X (Turner syndrome and variants) **47,XXY (Klinefelter syndrome and variants)** **45,X/46,XY (MGD, ovotesticular DSD)** **46,XX/46,XY (chimeric, ovotesticular DSD)**	**Disorders of gonadal (testicular) development:** (1) complete gonadal dysgenesis (2) partial gonadal dysgenesis (3) gonadal regression (4) ovotesticular DSD	**Disorders of gonadal (ovarian) development:** (1) ovotesticular DSD; (2) testicular DSD (eg, SRY^+, duplicate SOX9); (3) gonadal dysgenesis
	Disorders in androgen synthesis or action: (1) androgen biosynthesis defect (2) defect in androgen action (eg, CAIS, PAIS); (3) luteinizing hormone receptor defects (eg, Leydig cell hypoplasia, aplasia); and (4) disorders of anti-Müllerian hormone and anti-Müllerian hormone receptor (persistent Müllerian duct syndrome)	**Androgen excess:** (1) fetal (eg, 21-hydroxylase deficiency, 11-hydroxylase deficiency); (2) fetoplacental (aromatase deficiency, POR [P450 oxidoreductase]); (3) maternal (luteoma, exogenous, etc)
	Other (eg, severe hypospadias, cloacal extrophy)	**Other** (eg, cloacal exstrophy, vaginal atresia, MURCS [Müllerian, renal, cervicothoracic somite abnormalities], other syndromes)

In 2004

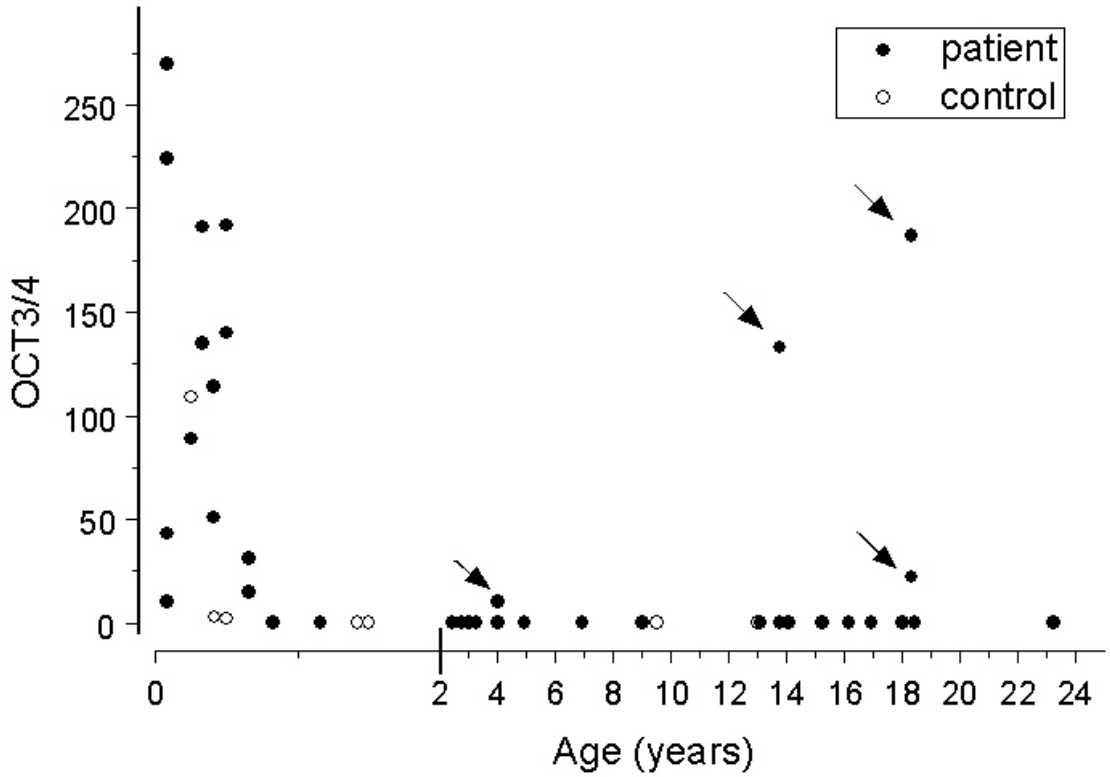
Lack of good criteria for tumors in children







Additional criteria for correct diagnosis



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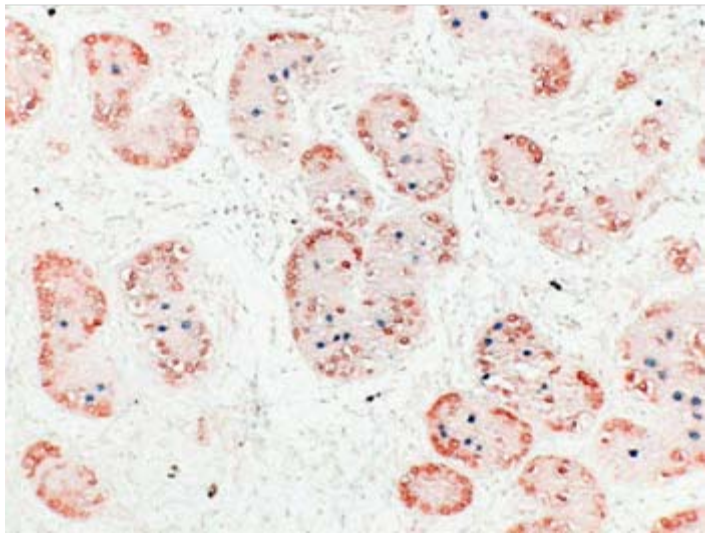

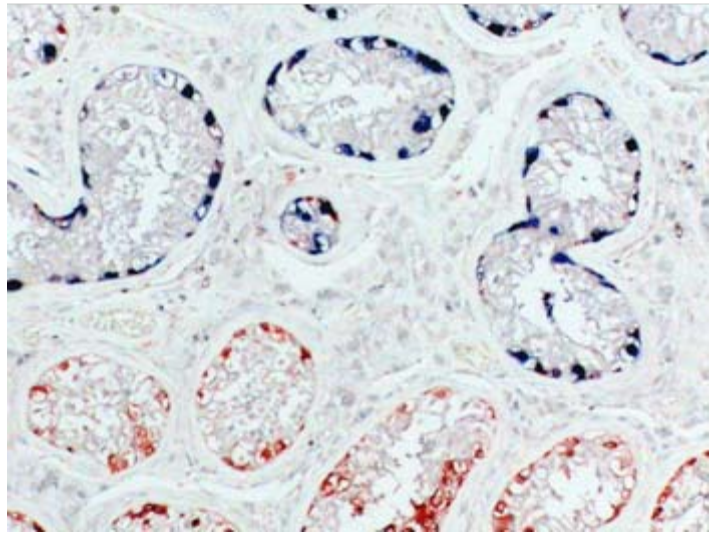

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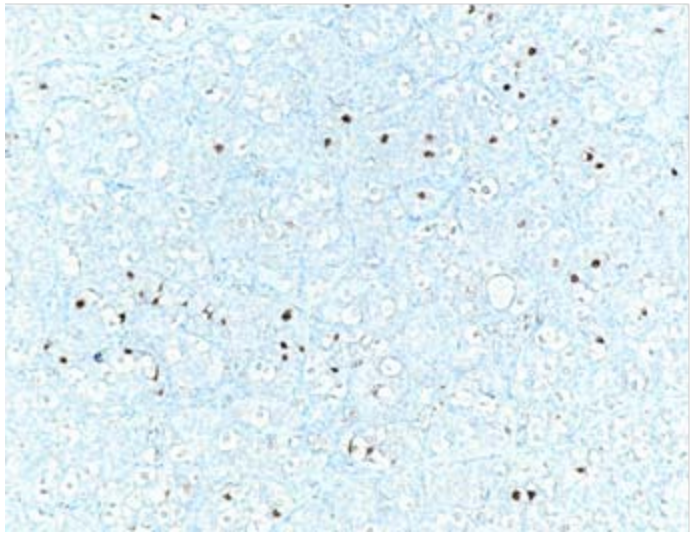

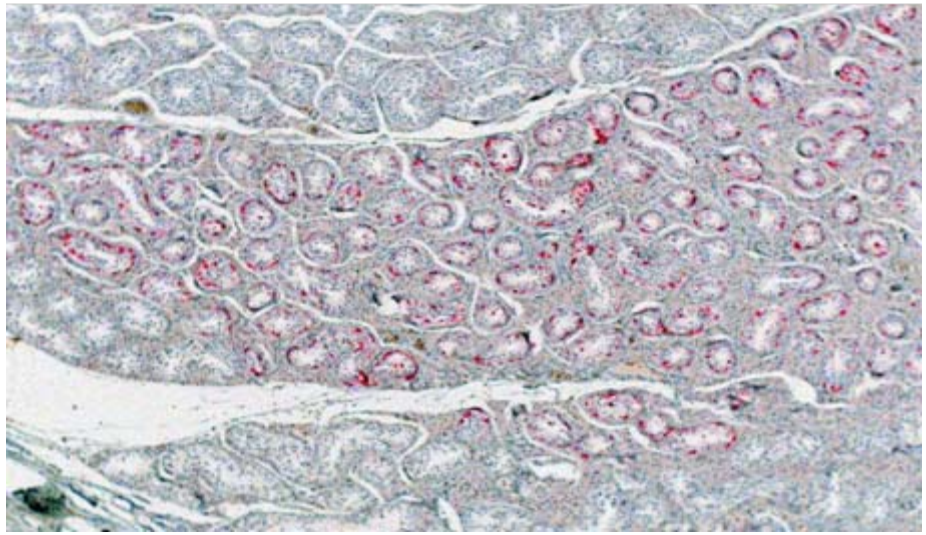

Tumor risk in DSD: new insights

	Estimated tumor prevalence	Type of precursor lesion	
		CIS	GB
Undervirilization	2.3% (probably higher if untreated)	~100%	~0%
AIS	5.5% (20–30% if untreated)		
CAIS	0.8%		
PAIS	15%		
GD	12% (probably >30% if untreated and/or selected for the presence of the Y chromosome)	8%	92%
45,X/46,XY and variants	15–40%		
46,XY GD	30%		
Mixed GD/asymmetrical gonadal differentiation	15% (>30% if untreated and/or selected for the presence of the Y chromosome)		
True hermaphroditism	2.6%		
Frasier syndrome	60% (limited data)		
Denys-Drash syndrome with 46,XY karyotype	40% (limited data)		

Cools et al, Endocrine Reviews 2006

Tumor risk in DSD: new insights

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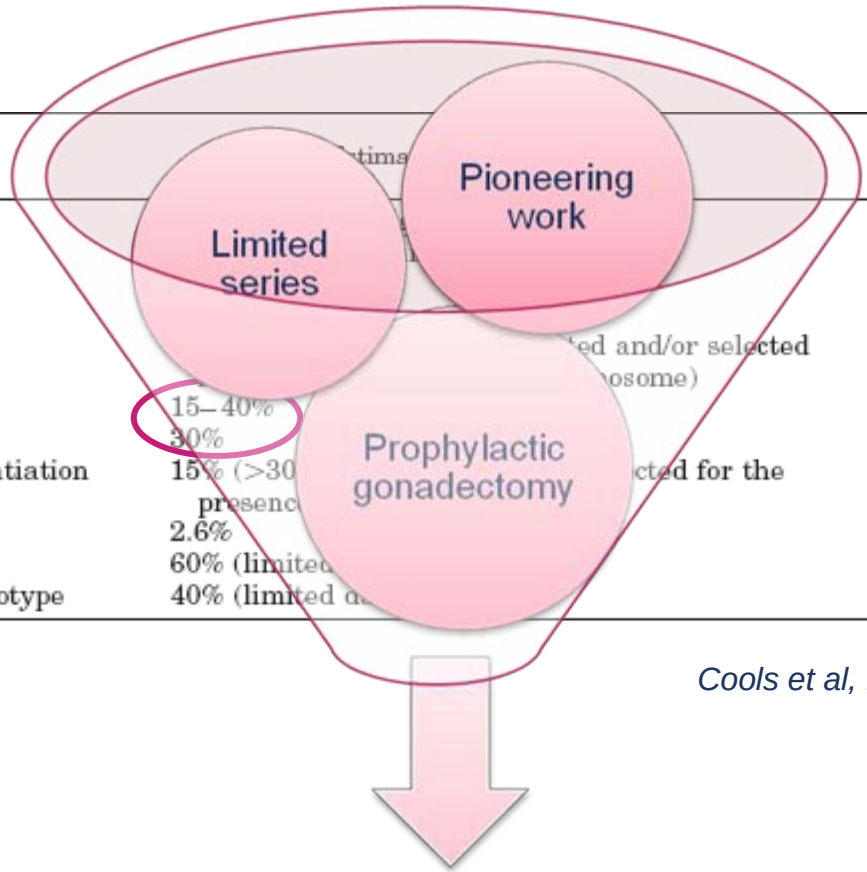
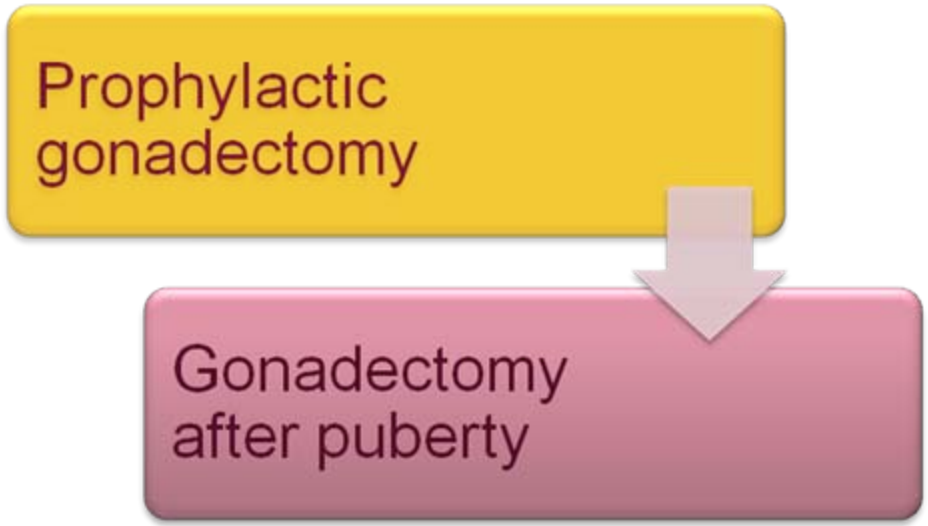


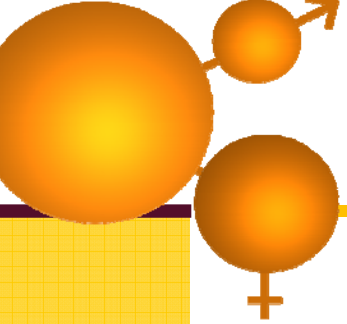
Cools et al, Endocrine Reviews 2006

Modified approach in (C)AIS

Modified approach

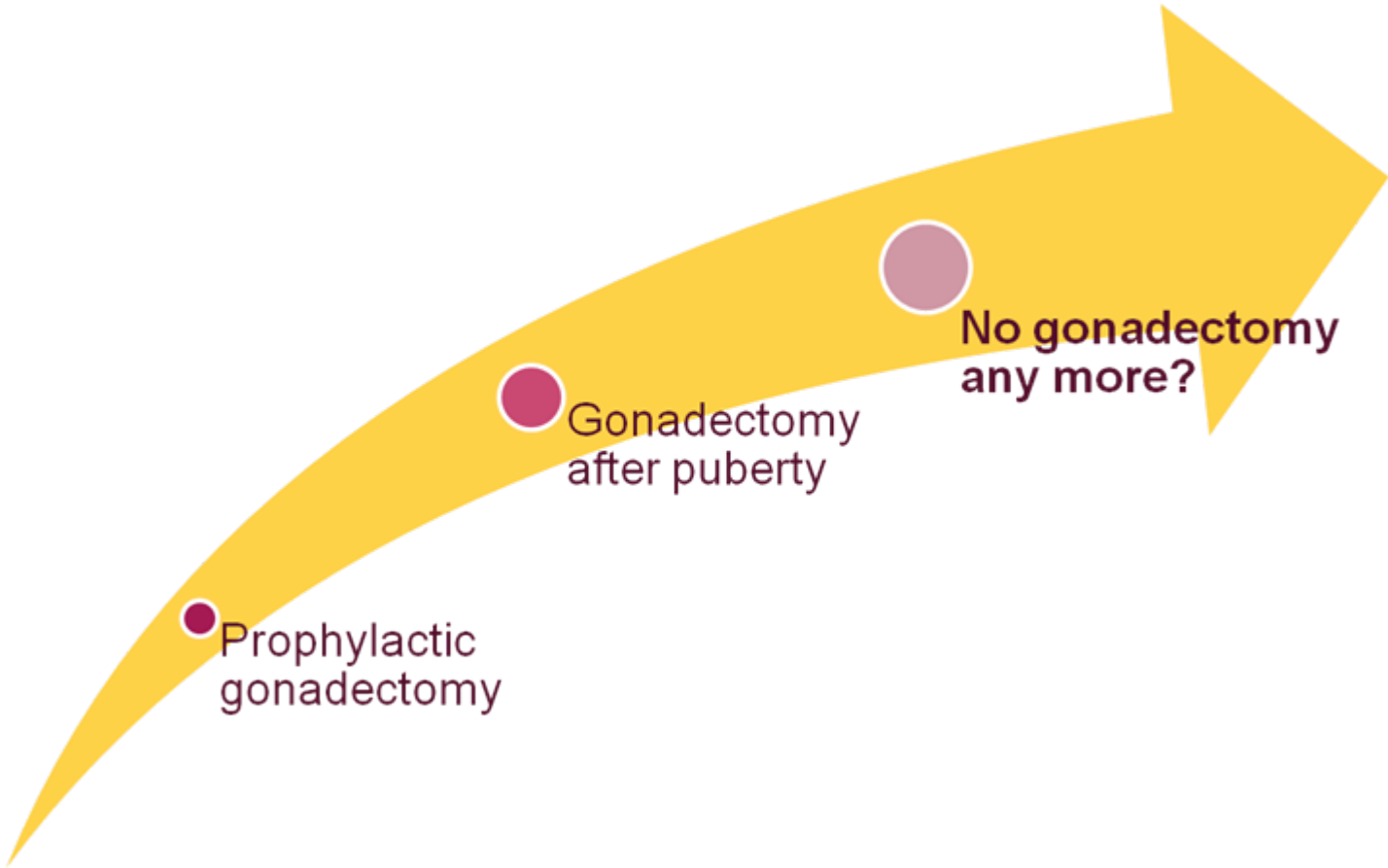


- Spontaneous breast development
- Decision by patient, not by parents
- Only for CAIS, not for PAIS



Gonadectomy in AIS

WHERE DO WE GO TO?


No gonadectomy any more?
Gonadectomy after puberty
Prophylactic gonadectomy

Benefits and risks of leaving gonads *in situ*

+	??	-
• Decision by patients • No need for HRT • Allows development of Gender identity (PAIS) • Avoid operation (laparascopy) • Contribute to self esteem	• Fertility?? • Bone mass, ?? • Tumor risk low on theoretical grounds but largely unknown • Other???	• T production during puberty, virilisation (PAIS) • Psychological burden

Tumor risk postpuberty?

Own series (n=46):

PAIS + CAIS > 14y

- 22 gonadectomy
- 1/22 CIS, CAIS

Cheikhelard et al, J Urol 2008, 1496-1501 (n=29):

Postpubertal CAIS

- 16 gonadectomy
- 1/16 CIS

?

•132 prepubertal: No CIS (0%)

• CIS in 2 / 58 postpubertal CAIS (3.4%)

• No CIS in 20 PAIS

Modalities for FU?

Audi et al, JCEM 2010, 1876-88, **(n=57):**

CAIS + PAIS postpubertal

- 22 gonadectomy (20 CAIS, 2 PAIS)
- 6 no gonadectomy
- No tumors

Our approach for gonads in AIS

PAIS and T biosynthesis disorders, raised female

Prepubertal gonadectomy

In case of unclear gender indentity: Intensive psychological counselling and follow-up, diagnosis and decision ideally in the prepubertal period

PAIS and T biosynthesis disorders, raised male

Orchidopexy, intensive follow-up with physical examination, self-examination, ultrasound from puberty onwards

Postpubertal bilateral extensive biopsy (x2), gonadectomy or irradiation in case of CIS

Repeat bilateral biopsy (x2) after 10 years?

Gonadectomy to avoid breast development? Gonadectomy in case of T suppletion?

CAIS

Discuss with patient: Postpubertal gonadectomy vs follow-up with MRI (modalities?)

In case of inguinal gonads: Place intra-abdominally or labial or leave in place or remove

Examples : Personalized care

Case 1

- Diagnosis in 2005, at 17y
- Deletion of AR : CAIS
- Bilateral inguinal gonads
- R/ Bilateral gonadectomy + HRT
- Vaginal replacement: Bowel interposition

Case 1

- Diagnosis in 2011, at 17y
- Option: Bilateral gonadectomy + HRT OR gonads *in situ* with MRI FU and informed consent
- Vaginal replacement: Vaginal dilation

Case 2

- Cousin of case 1
- Diagnosis in 2007, at 4y
- Bilateral inguinal gonads
- R/ Bilateral biopsy: no germ cells ► gonads at the internal inguinal ring
- Psychological counseling just started

Examples : Personalized care

- ° 1997: Inguinal hernia right ► Biopsy : Testis
- Diagnosis : AIS
- 2001 : Gonadectomy left / right side: no gonad found
- 2008: Is there still a gonad on the right side?
  - HCG test: T rise : yes!
- Material from 1997 revised:
  - GC +++, epididymis +++,

CAIS or PAIS?

Gonadectomy right

- Start HRT
- Vaginal dilation