

PERCORSI DECISIONALI PER LA GESTIONE
DEL BAMBINO E DELL'ADOLESCENTE

GINECOMASTIA

S. BERNASCONI

CLINICA PEDIATRICA

UNIVERSITA' DI PARMA



16 - 21 LUGLIO 2011

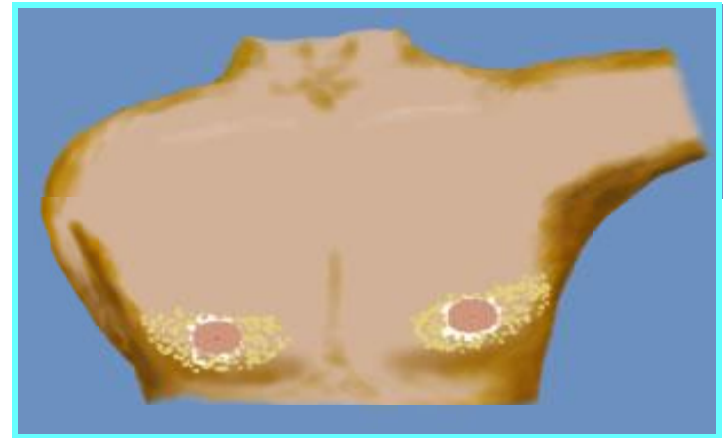
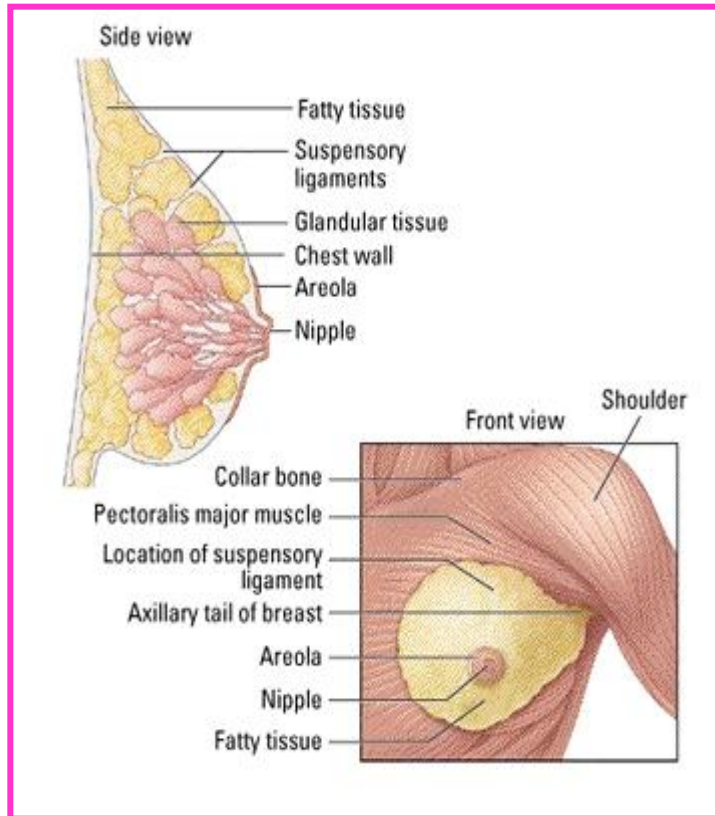
Centro Congressi Kaya Artemis
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Ginecomastia : definizione

Ingrandimento concentrico della ghiandola mammaria in soggetti di sesso maschile, dovuto alla proliferazione del tessuto ghiandolare mammario

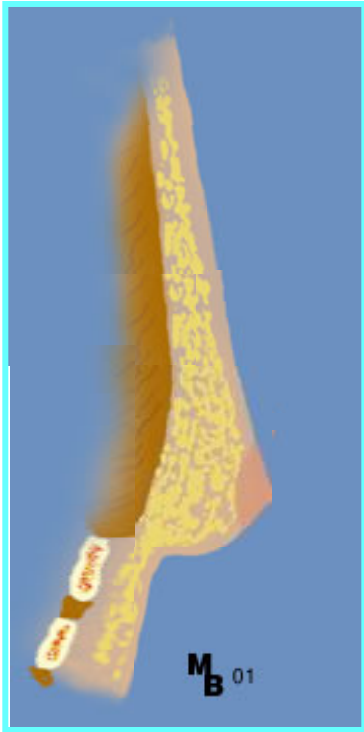


Ginecomastia vs Pseudoginecomastia

- **Adipomastia:** presenza di tessuto adiposo senza un vero e proprio aumento del tessuto ghiandolare sottostante



Ginecomastia vs Pseudoginecomastia



Adipomastia

Vari gradi di ginecomastia

Ginecomastia vs Pseudoginecomastia

E' possibile riconoscere **ecograficamente**

5 diversi strati:

a) cutaneo

b) adipe sottocutaneo (< 8 mm)

c) **struttura ghiandolare (< 8 mm), a forma triangolare con base alla parete toracica ed apice alla areola**

d) adipe prepettorale , molto sottile

e) muscoli pettorali

Ginecomastia vs Pseudoginecomastia

- **Adipomastia:** presenza di tessuto adiposo senza un vero e proprio aumento del tessuto ghiandolare sottostante
- **Mastite:** dolorabilità, segni di flogosi



Ginecomastia vs Pseudoginecomastia

- **Adipomastia:** presenza di tessuto adiposo senza un vero e proprio aumento del tessuto ghiandolare sottostante
- **Mastite:** dolorabilità, segni di flogosi
- **Tumori:** secrezione ematica, consistenza dura e/o irregolare



Ginecomastia vs Pseudoginecomastia

Breast Cancer Incidence in Adolescent Males Undergoing Subcutaneous Mastectomy for Gynecomastia: Is Pathologic Examination Justified? A Retrospective and Literature Review

John C. Koshy, *Plast. Reconstr. Surg.* 127: 1, 2011

...In our current study, we only found one case of **atypical ductal hyperplasia** in 81 patients treated for gynecomastia with subcutaneous mastectomy at three major academic institutions within the Texas Medical Center over the past 10 years....

.....the incidence rate for adolescent gynecomastia associated with malignancy **would be** 0.012 percent....



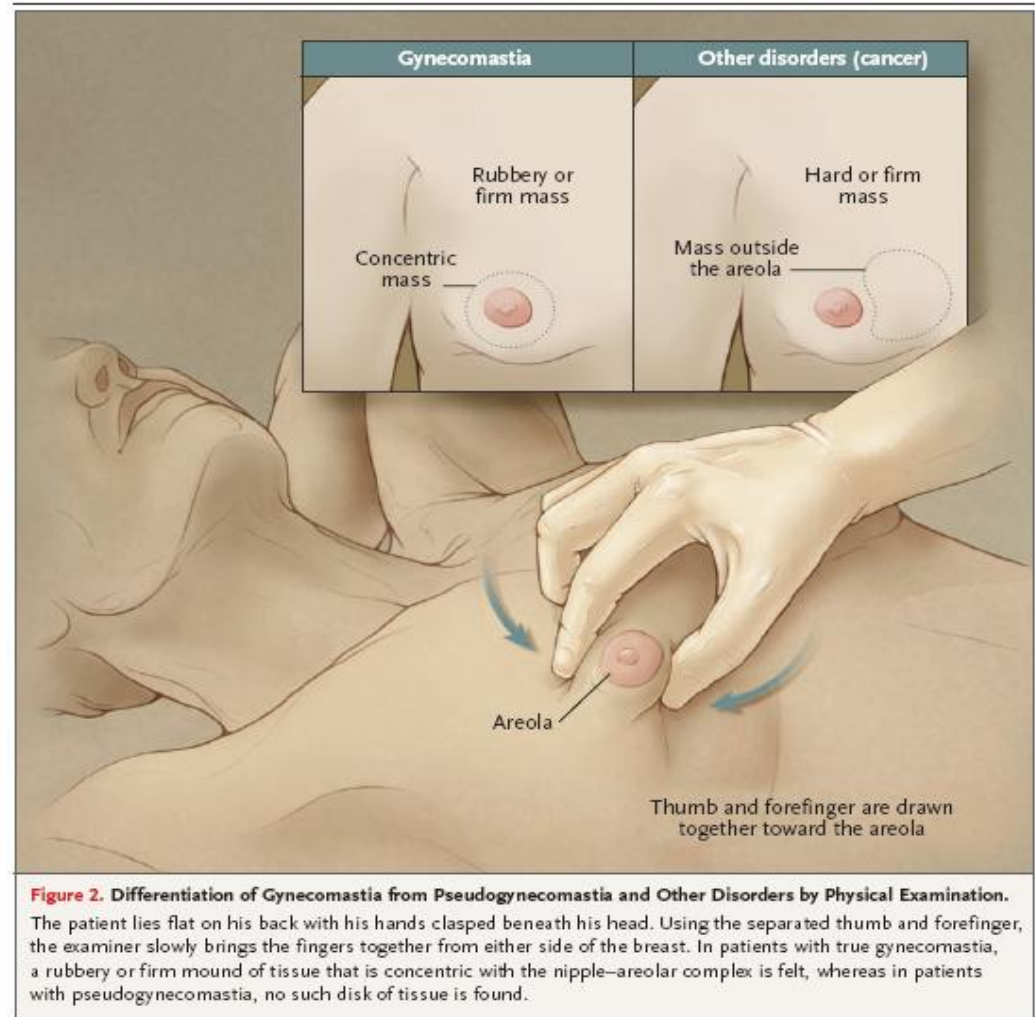
Gynecomastia vs Pseudogynecomastia

Gynecomastia

Glenn D. Braunstein, M.D.

Worrisome signs which may indicate more serious disease include; hard or firm breast tissue, unilateral growth, location outside the nipple–areolar complex, and overlying skin changes, such as dimpling or nipple retraction

N Engl J Med 2007;357:1229-37.



Ginecomastia

- ***1) - quale la forma più frequente nella comune esperienza clinica?***



Ginecomastia

Ginecomastia puberale “fisiologica”

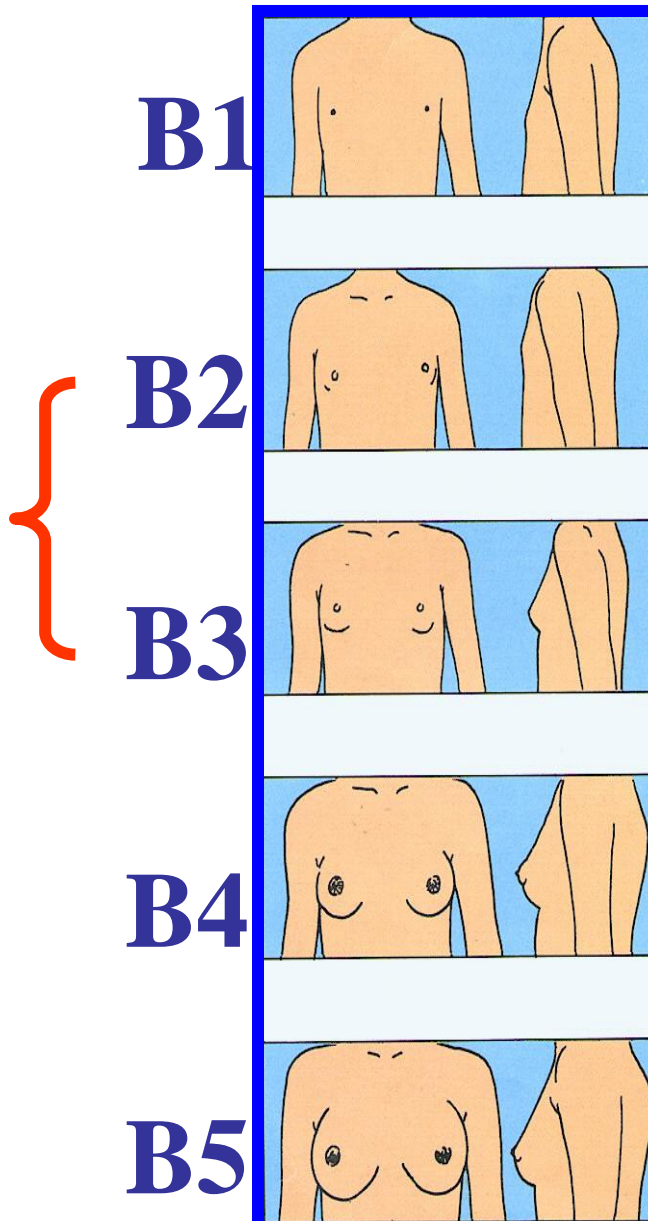


Ginecomastia puberale “fisiologica”

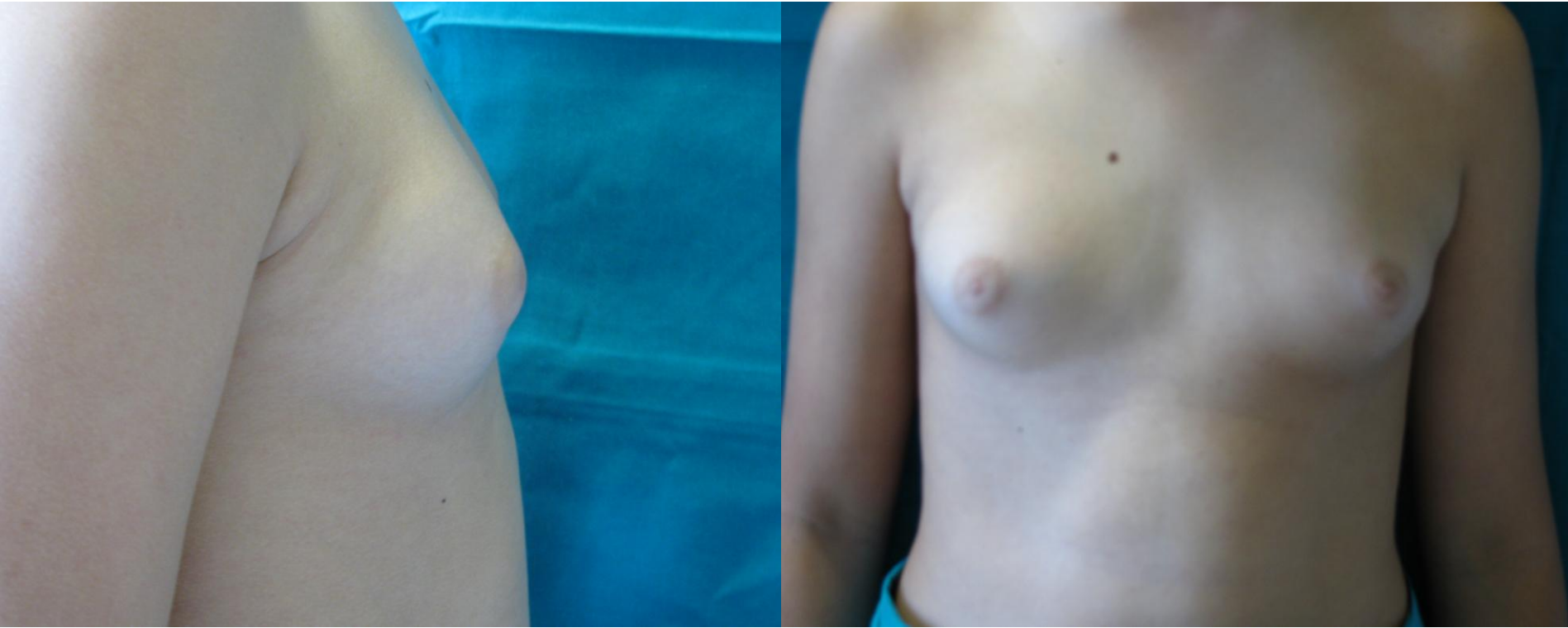


Vari gradi di ginecomastia

Ginecomastia puberale “fisiologica”



Ginecomastia puberale “fisiologica”



Ragazzo di 13 anni Casistica personale



Ginecomastia puberale “fisiologica”



Ginecomastia puberale “fisiologica”

- ***a) – frequenza di presentazione ?***



Ginecomastia puberale “fisiologica”

GYNECOMASTIA

N Engl J Med 1993

GLENN D. BRAUNSTEIN, M.D.

Table 1. Prevalence of Gynecomastia.

STUDY	GROUP STUDIED	CRITERIA USED*	AGE OF SUBJECTS (YR)	No. STUDIED	No. (%) WITH GYNECOMASTIA
Pubertal gynecomastia					
Nydick et al. ³	Boy Scouts	≥0.5 cm	10–16	1865	722 (39)
Neyzi et al. ⁴	Turkish schoolboys	Firm subareolar tissue	9–17	993	70 (7)
Lee ⁵	U.S. schoolboys	Firm subareolar disk	Pubertal boys	29	20 (69) ←
Fara et al. ⁶	Italian schoolboys	≥0.5 cm	11–14	681	228 (33)
Harlan et al. ⁷	U.S. youths	≥1 cm	12–17	3522	147 (4)
Moore et al. ⁸	Normal Swiss volunteers	≥0.5 cm	8.5–17.5	135	30 (22)
Biro et al. ⁹	U.S. schoolboys	Palpable glandular tissue	10–15	377	183 (49)

Ginecomastia puberale “fisiologica”

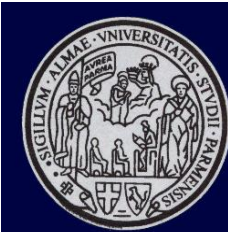
Gynecomastia in adolescents

Christina A. Nordt^a and Amy D. DiVasta^{a,b}

Curr Opin Pediatr 20:375–382

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1040-8703

The reported prevalence of pubertal gynecomastia ranges from 3.9 to 64.6% [4^{••},5]. This large variance is likely in part due to the lack of uniform breast size criteria to define gynecomastia. Investigators have used measurements ranging from 0.5 to 2 cm to make the diagnosis [2].

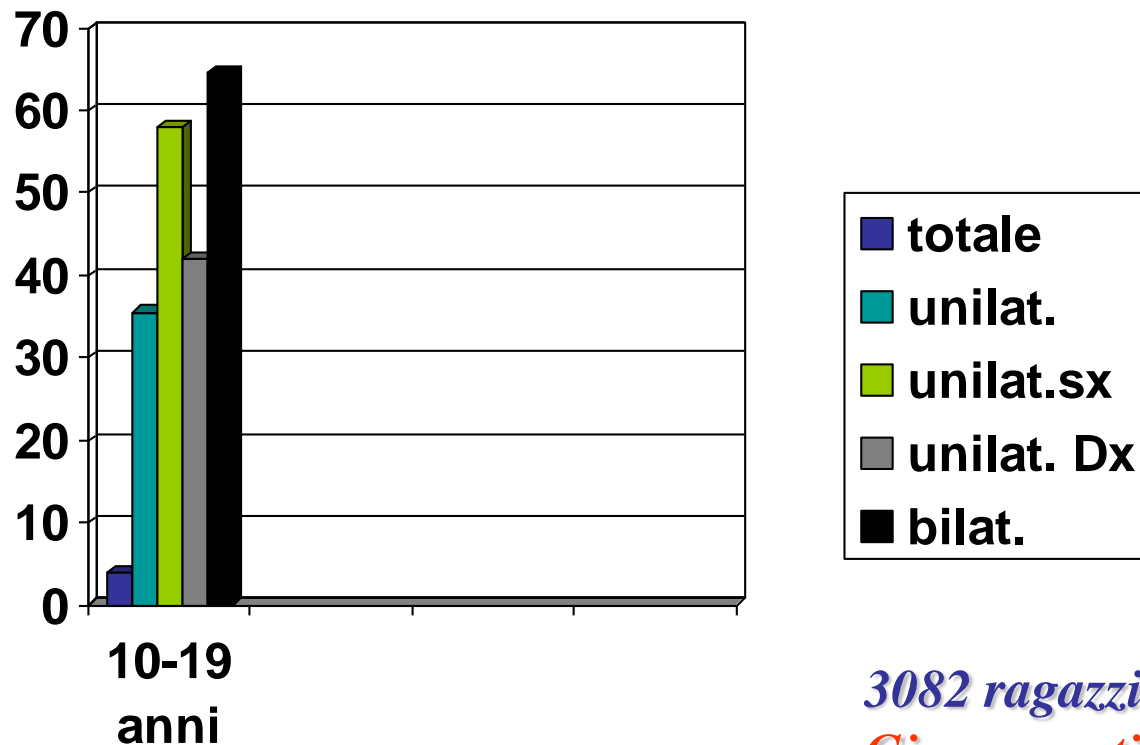


Ginecomastia puberale “fisiologica”

Relationship of Adolescent Gynecomastia with Varicocele and Somatometric Parameters: A Cross-Sectional Study in 6200 Healthy Boys

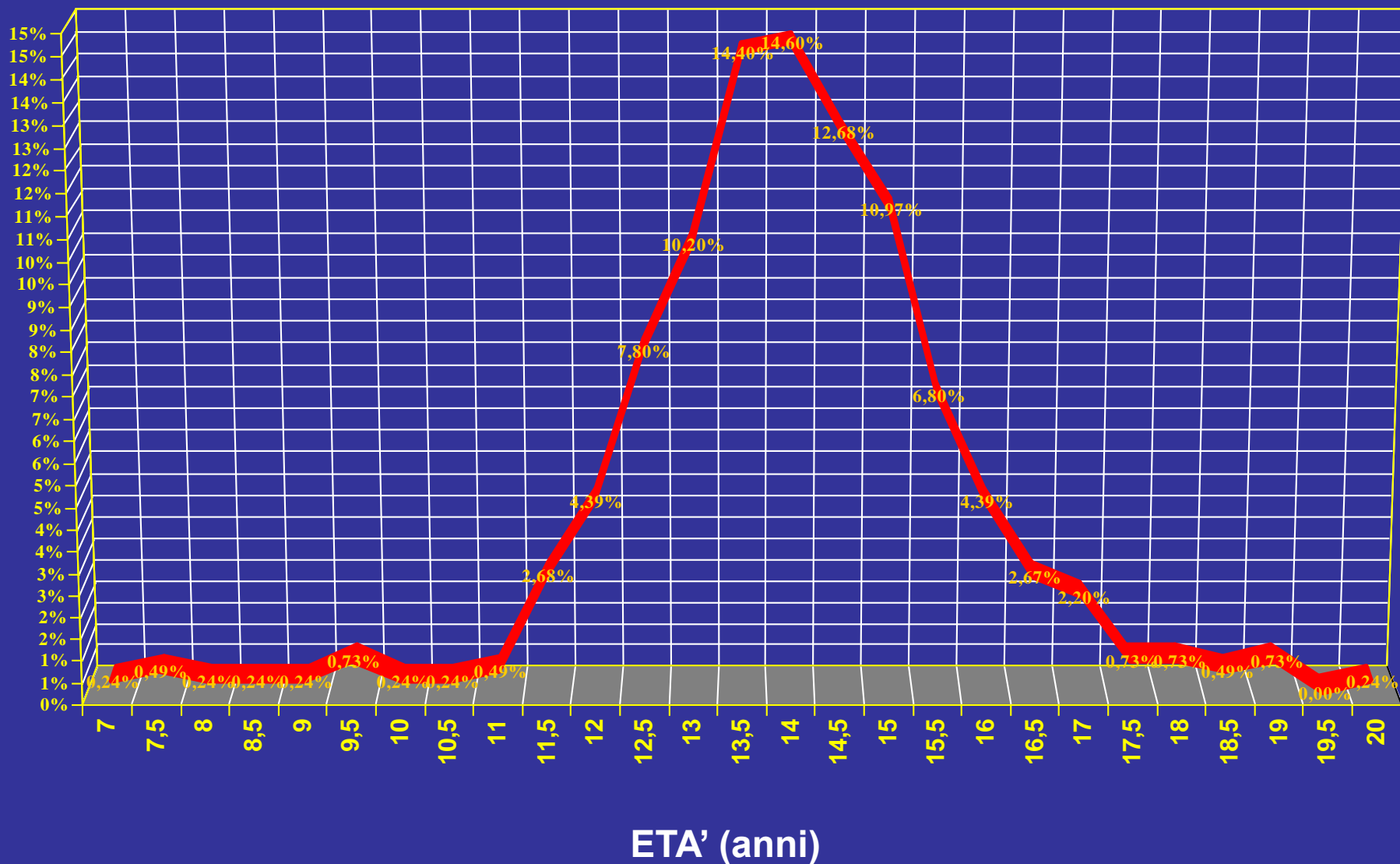
Journal of Adolescent Health 41 (2007) 126–131

Philip Kumanov, M.D., Ph.D.^a, Fnu Deepinder, M.D.^b, Ralitsa Robeva, M.D.^a,
Analia Tomova, M.D., Ph.D.^a, Jianbo Li, Ph.D.^c, Ashok Agarwal, Ph.D.^{b,*}

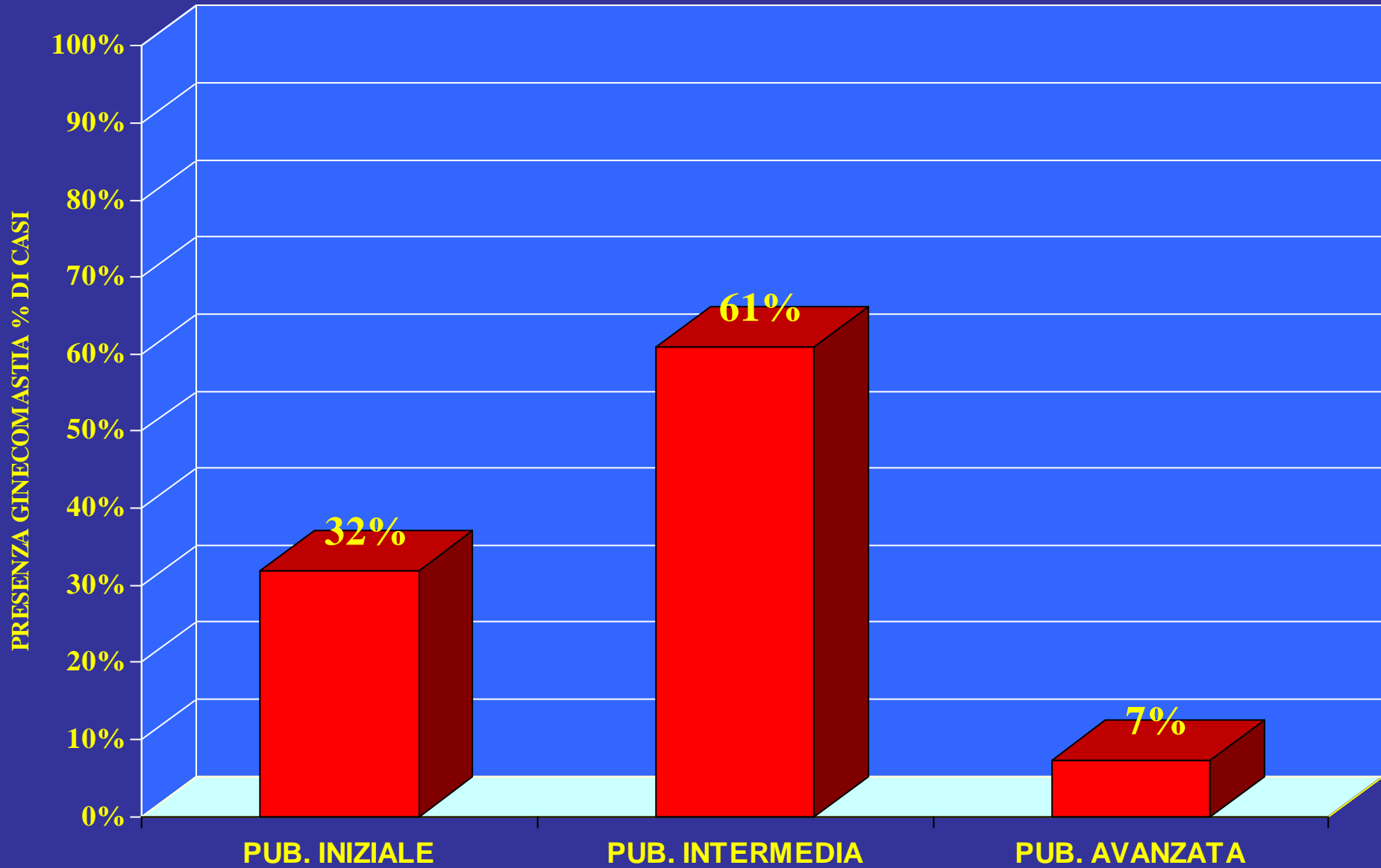


3082 ragazzi sani tra 10 e 19 anni
Ginecomastia = 1 cm di diametro

DISTRIBUZIONE DELLA GINECOMASTIA IN RAPPORTO ALL'ETA' DI COMPARSA



U.O. PEDIATRIA - FERRARA



Ginecomastia puberale “fisiologica”

Relationship of Adolescent Gynecomastia with Varicocele and Somatometric Parameters: A Cross-Sectional Study in 6200 Healthy Boys

Journal of Adolescent Health 41 (2007) 126–131

Philip Kumanov, M.D., Ph.D.^a, Fnu Deepinder, M.D.^b, Ralitsa Robeva, M.D.^a, Analia Tomova, M.D., Ph.D.^a, Jianbo Li, Ph.D.^c, Ashok Agarwal, Ph.D.^{b,*}

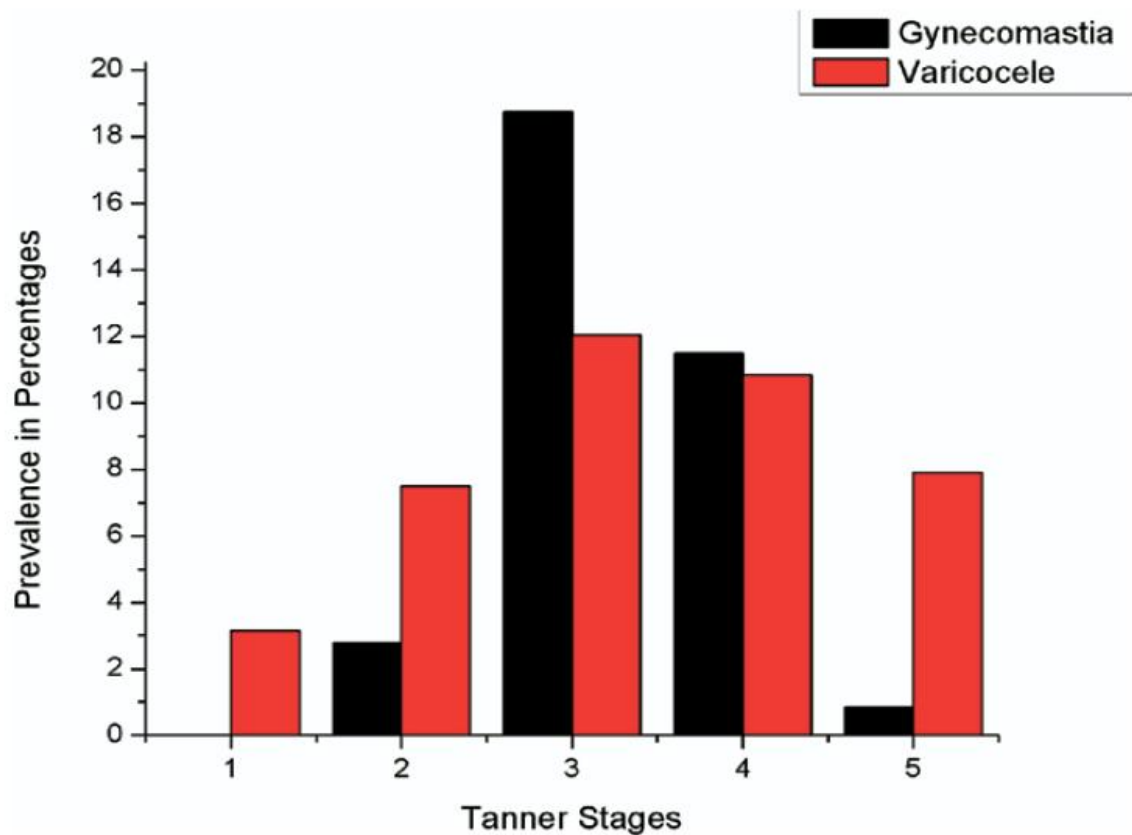


Figure 2. Prevalence of gynecomastia (n = 121) and varicocele (n = 245) according to pubic hair Tanner stages in boys of age 10–19 years (n = 3082). Data are expressed as percentages.



Ginecomastia puberale “fisiologica”

- ***a) - frequenza di presentazione ?***
- ***b) – storia naturale ?***



Ginecomastia puberale “fisiologica”

...The breast tissue enlargement ***usually*** regresses within ***1–2 years*** ; persistence beyond age 17 years is uncommon... (Nordt 2008)

...The adolescent should be reassured that the gynecomastia is a normal variation of puberty and ***should*** regress spontaneously within ***18 to 24 months***... (Cakan 2007)

...Within ***1–3 years***, up to ***90%*** of boys have regression of their breast enlargement...(Ma 2008)

Ginecomastia puberale “fisiologica”

- ***a) - frequenza di presentazione ?***
- ***b) - storia naturale ?***
- ***c) – eziopatogenesi ?***



Ginecomastia puberale “fisiologica”

EZIOPATOGENESI

- 1) NON DEFINITA***
- 2) SQUILIBRIO TRANSITORIO RAPPORTO T/E2***
- 3) MAGGIORE SENSIBILITA' RECETTORIALE***
- 4) LEPTINA***



Ginecomastia puberale “fisiologica”

LEPTINA

LIVELLI EMATICI PIU' ELEVATI IN CASI DI GINECOMASTIA

:

- 1) STIMOLAZIONE RECETTORI MAMMARI**
- 2) “ ATTIVITA' AROMATASICA**
- 3) ATTIVAZIONE RECETTORI ESTROGENICI**



Ginecomastia

- **1) - quale la forma più frequente nella comune esperienza clinica?**
- **2) - cosa pensate della ginecomastia prepuberale?**



Ginecomastia Prepuberale

Prepubertal gynaecomastia: aetiology, course and outcome

Clinical Endocrinology (2004) 61, 55–60

Table 1 Prepubertal gynaecomastia in 29 boys: pertinent data at diagnosis, changes in breasts size, and pubertal onset

Patient no.	At diagnosis					Course					
	CA (years)	BA SDS	Ht SDS	BMI SDS	TV (ml)	Breast diameter (cm)		Follow-up (years)	Regression (years)	Increase (years)	Pub. onset (years)
						Right	Left				
1	4.0	1.9	0.9	0.0	2.0	1.5	1.5	5.0			PP
2	4.6	-0.7	0.6	2.5	2.0	6.5	6.5	4.7			PP
3*	5.6	7.6	1.7	2.3	3.0	8.5	7.0	6.0			9.8
4	5.9	-1.2	0.5	0.9	1.5	1.5	1.5	6.5			12.8
5	7.0	0.9	0.4	3.0	1.5	1.5	1.5	2.0			PP
6	7.2	-1.1	0.1	-0.5	2.0	1.5	NP	3.5	1.7		NA
7	7.5	-1.4	1.3	0.9	1.5	NP	3.0	8.0		0.8	14.1
8*	7.6	6.6	1.7	0.1	3.0	4.0	4.0	2.5			PP
9	7.6	1.6	1.4	2.6	2.5	2.4	2.3	2.7			NA
10	7.8	-0.6	0.8	1.0	2.5	2.5	2.5	2.1	1.4		NA
11	8.0	-3.2	-1.4	1.8	2.0	13.0	12.0	3.3			NA
12	8.0	-1.9	0.5	1.6	1.5	NP	1.5	2.0		0.6	PP
13	8.2	1.3	0.3	1.5	2.0	1.5	NP	2.3	2.0		NA
14	8.4	-0.6	-0.1	-0.6	1.5	NP	7.5	3.5		1.0	11.0
15	8.9	0.7	1.0	0.6	1.0	1.5	1.5	1.6		0.5	NA
16	9.0	2.0	1.1	0.0	2.0	1.5	1.5	1.5			PP
17	9.1	-2.0	-0.3	0.1	1.5	1.5	1.5	1.8	1.5		NA
18	9.2	-2.0	-0.6	0.3	2.0	1.5	NP	2.0		0.7	NA
19	10.0	3.1	1.2	2.6	3.0	1.5	1.5	1.4			10.7
20	10.3	3.7	1.4	2.2	1.5	11.0	12.0	1.3			13.5
21	10.5	1.8	1.0	1.3	2.0	14.0	14.0	1.5			NA
22	10.5	1.8	1.5	2.1	3.0	22.0	22.0	2.3	0.8		12.0
23	10.6	0.6	1.0	2.4	3.0	6.0	5.0	3.3			12.0
24	11.0	0.1	-0.1	0.7	2.0	NP	1.5	1.8		1.0	12.5
25	11.0	0.7	0.6	2.9	2.0	2.2	2.3	1.5			11.5
26	11.5	1.3	0.6	1.0	3.0	8.0	8.0	6.0			12.3
27	11.5	-1.6	-0.2	1.8	2.0	18.0	17.0	1.2			NA
28	12.2	0.7	0.6	2.2	2.0	13.0	13.5	2.1			13.1
29	12.4	-2.8	0.2	0.7	2.0	9.0	9.0	1.7			13.0

CA, chronological age; BA, bone age; SDS, standard deviation score; Ht, height; BMI, body mass index; Pub, pubertal; TV, testicular volume; NP, nonpalpable; PP, prepubertal; NA, not available. *Patient with hyperaromatase syndrome.

Of the 29 boys with prepubertal gynaecomastia, only two were found to have an underlying pathology, namely, hyperaromatase syndrome. The other 27 were considered to have idiopathic gynaecomastia.



Ginecomastia Prepuberale

Prepubertal Gynecomastia in Two Monozygotic Twins with Peutz-Jeghers Syndrome: Two Years' Treatment with Anastrozole and Genetic Study

Horm Res Paediatr 2011;75:374–379

Anna Grandone Emanuele Miraglia del Giudice Grazia Cirillo
Michele Santaripa Filomena Coppola Laura Perrone



Fig. 1. Patient I at first evaluation.
Fig. 2. Patient II at first evaluation.



Ginecomastia Prepuberale

Prepubertal Gynecomastia Linked to Lavender and Tea Tree Oils

N Engl J Med 2007;356:479-85.

Derek V. Henley, Ph.D., Natasha Lipson, M.D., Kenneth S. Korach, Ph.D.,

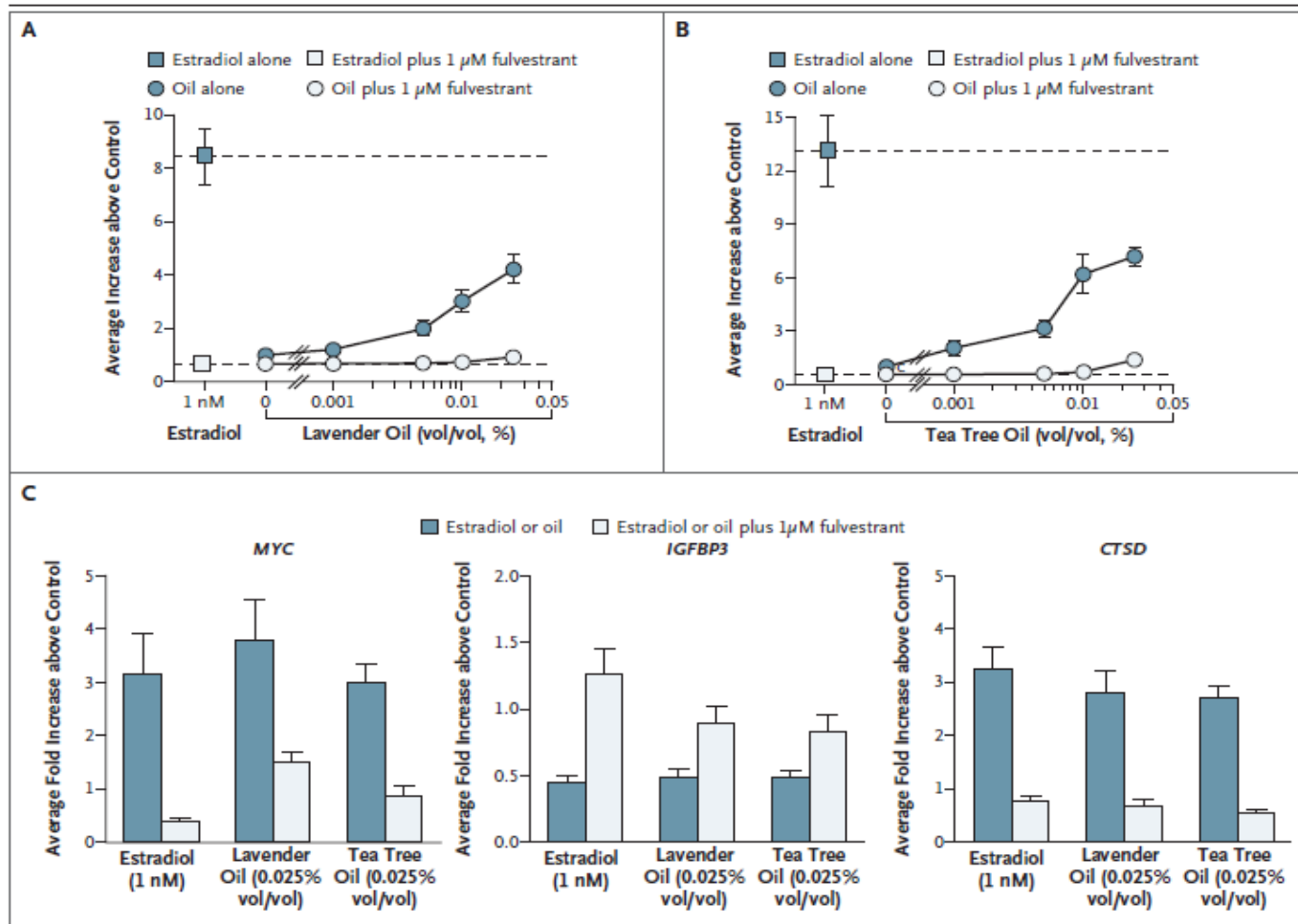
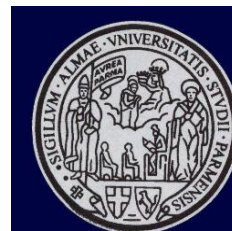


Figure 1. Estrogenic Activity of Lavender and Tea Tree Oils in Human Breast-Cancer (MCF-7) Cells.

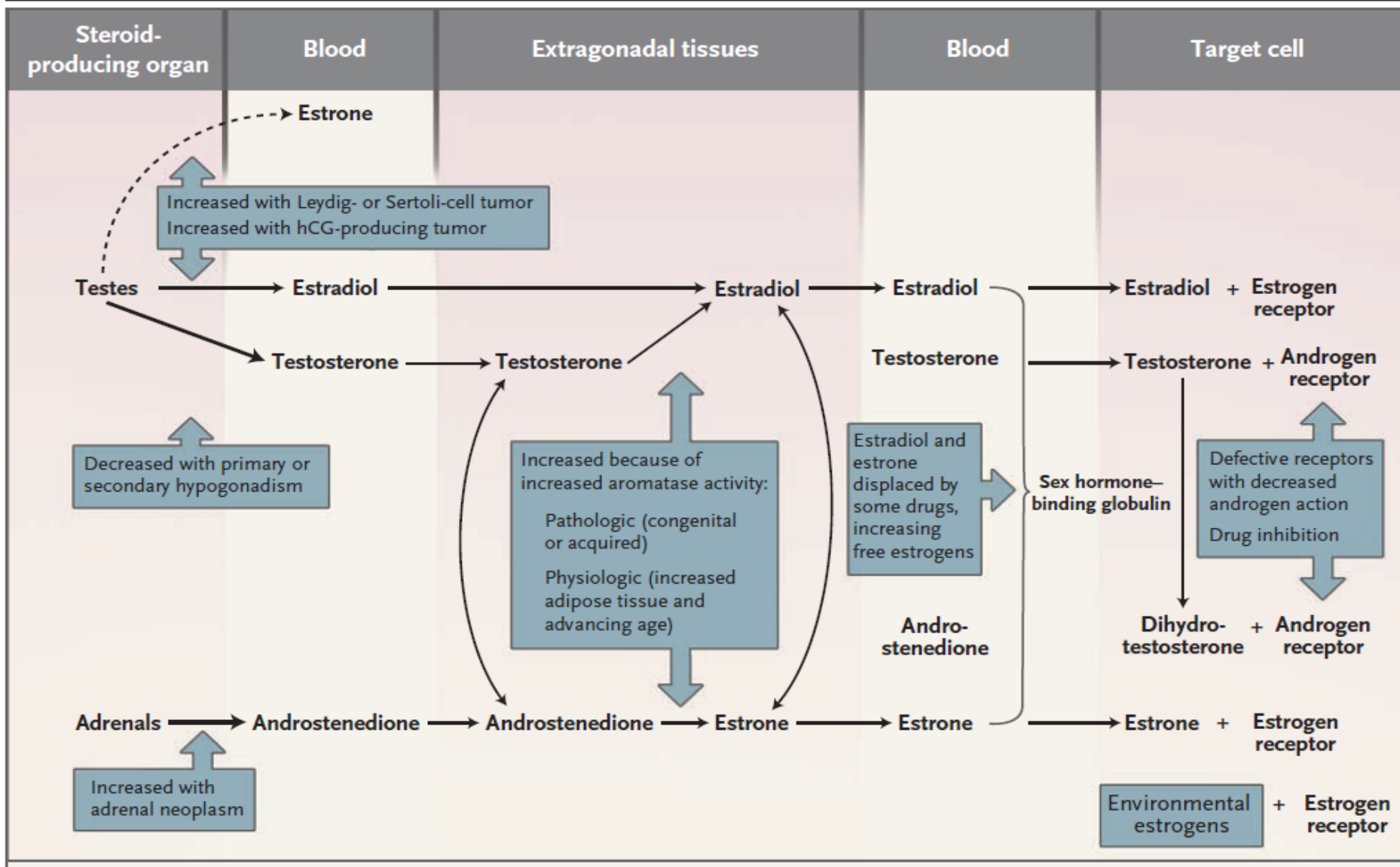


Ginecomastia

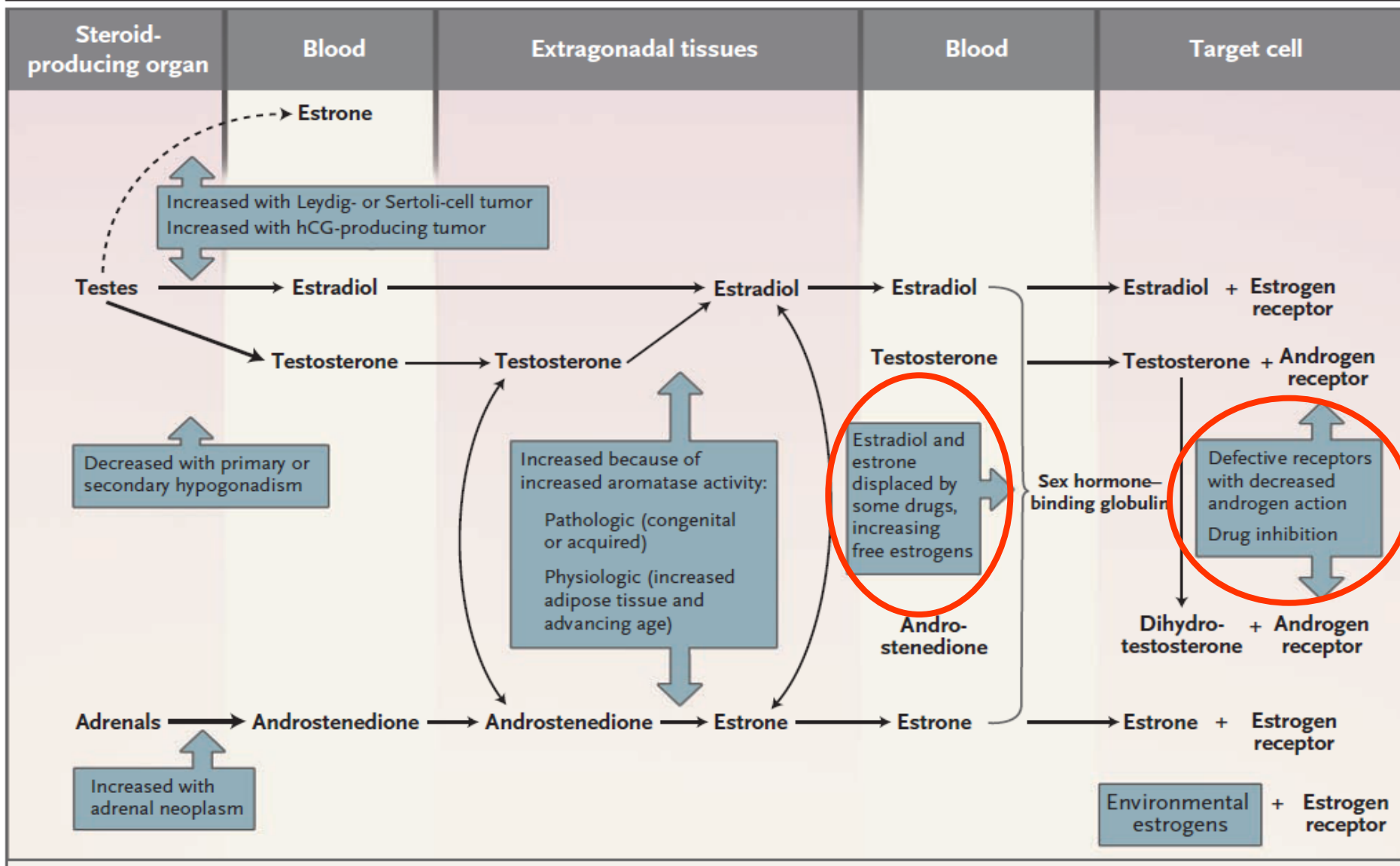
- 1) - quale la forma più frequente nella comune esperienza clinica?**
- 2) - cosa pensate della ginecomastia prepuberale ?**
- 3) - quali le forme secondarie o patologiche?**



Ginecomastia



Ginecomastia



Ginecomastia

Gynecomastia in adolescents

Christina A. Nordt^a and Amy D. DiVasta^{a,b}

Current Opinion in Pediatrics 2008

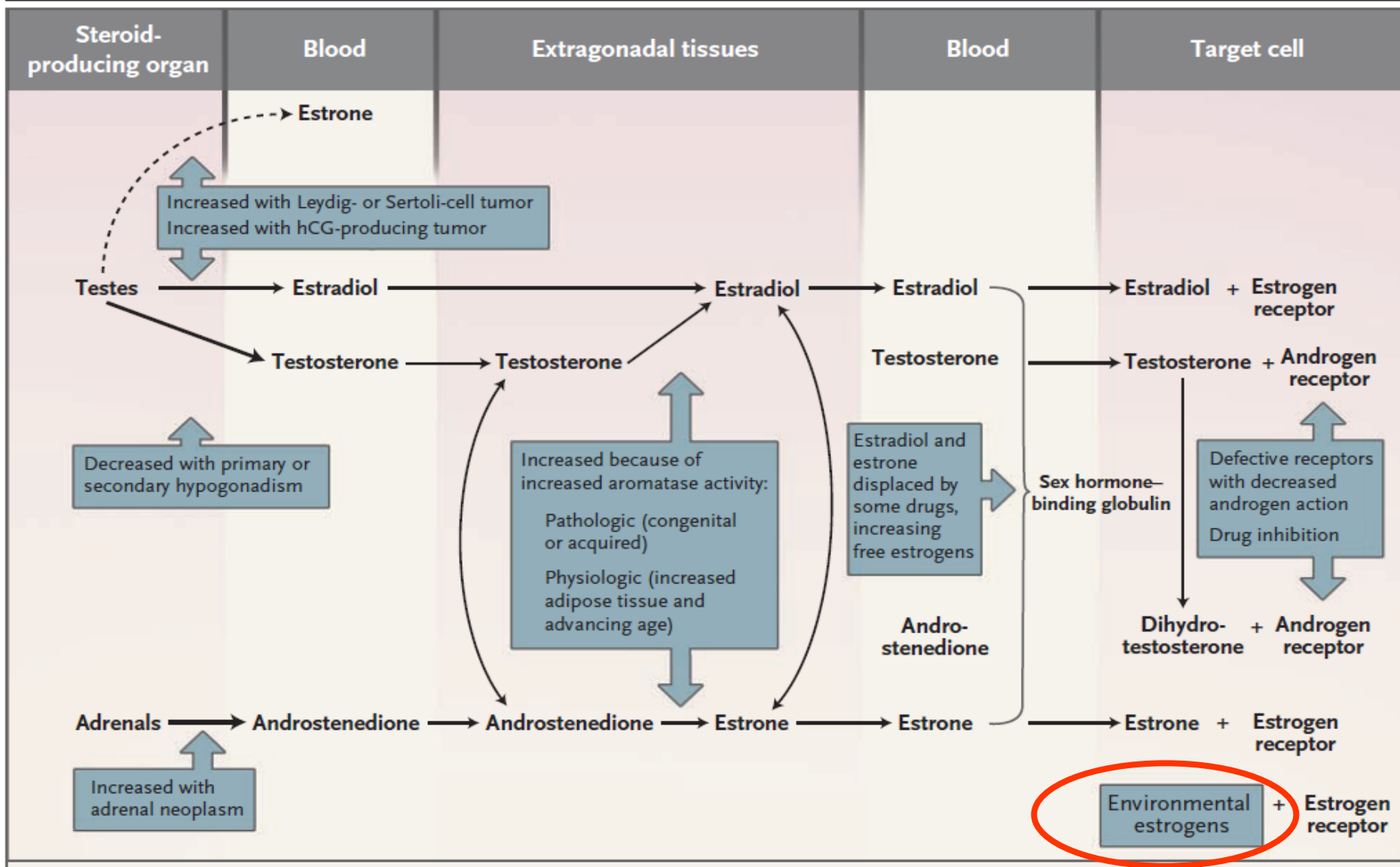
Table 1 Drugs implicated in development of gynecomastia

Hormones	Cancer chemotherapeutics
Estrogens ^a	Medications
Testosterone ^a	Alkylating agents ^a
Anabolic-androgenic steroids ^a	Antibiotics
Chorionic gonadotropin ^a	Isoniazid
Psychoactive agents	Metronidazole
Phenothiazines	Ketoconazole ^a
Atypical antipsychotic agents	Antiulcer medications
Diazepam	Cimetidine ^a
Haloperidol	Ranitidine
Tricyclic antidepressants	Omeprazole
Cardiovascular drugs	Drugs of abuse
Digoxin ^a	Marijuana
Verapamil	Alcohol
Captopril	Heroin
Methyldopa	Methadone
Nifedipine	Amphetamines
Enalapril	Other medications
Reserpine	Phenytoin
Minoxidil	Penicillamine
Antiandrogens or inhibitors of androgen synthesis	Theophylline
Cyproterone ^a	Metoclopramide
Spirolactone ^a	Antiretrovirals
Flutamide ^a	

^a Strong relationship considered to exist between these drugs and gynecomastia [12,15^{••}]. Adapted from Joffe [15^{••}].



Ginecomastia



Ginecomastia

Plasma Phthalate Levels in Pubertal Gynecomastia

Erdem Durmaz, Elif N. Özmert, Pinar Erkekoglu, Belma Giray, Orhan Derman, Filiz Hincal and Kadriye Yurdakök
Pediatrics 2010;125:e122; originally published online December 14, 2009;

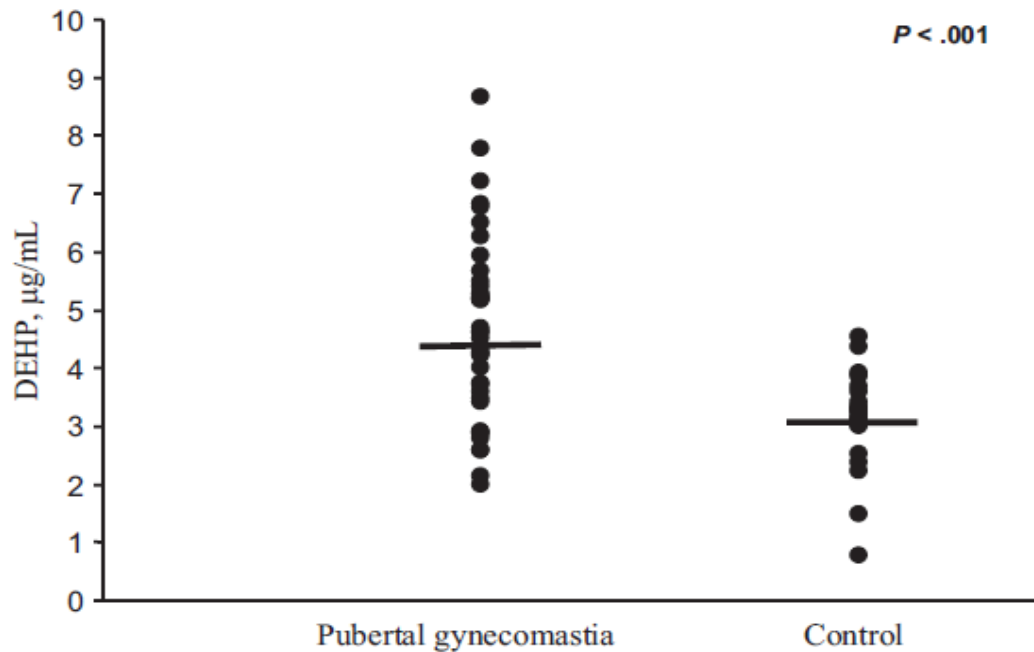


FIGURE 2

The distribution of DEHP levels in patients with pubertal gynecomastia and control patients.



Ginecomastia

Plasma Phthalate Levels in Pubertal Gynecomastia

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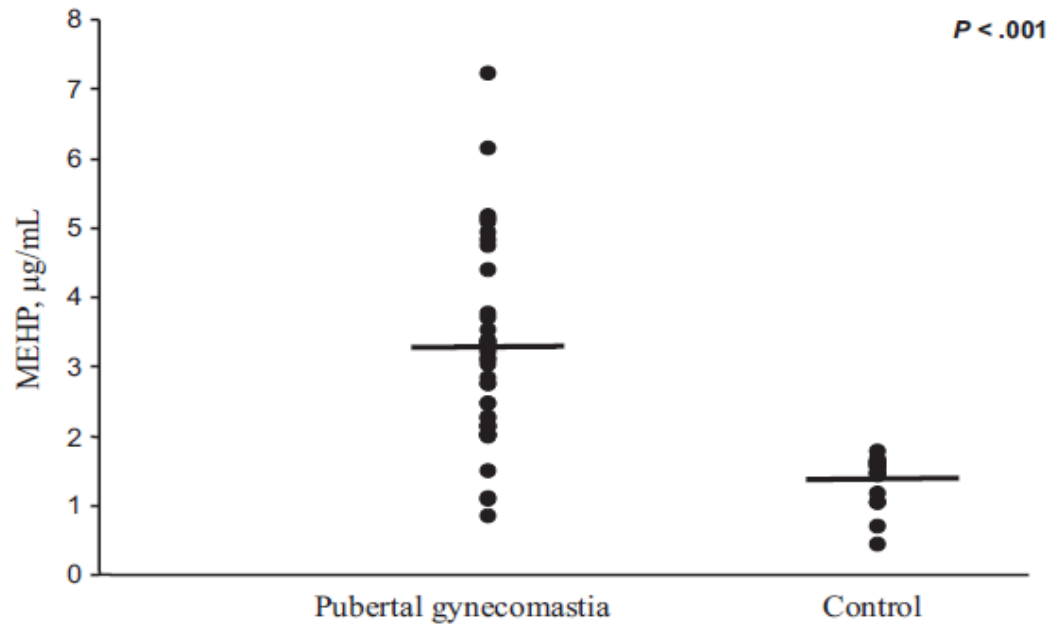


FIGURE 3

The distribution of MEHP levels in patients with pubertal gynecomastia and control patients.



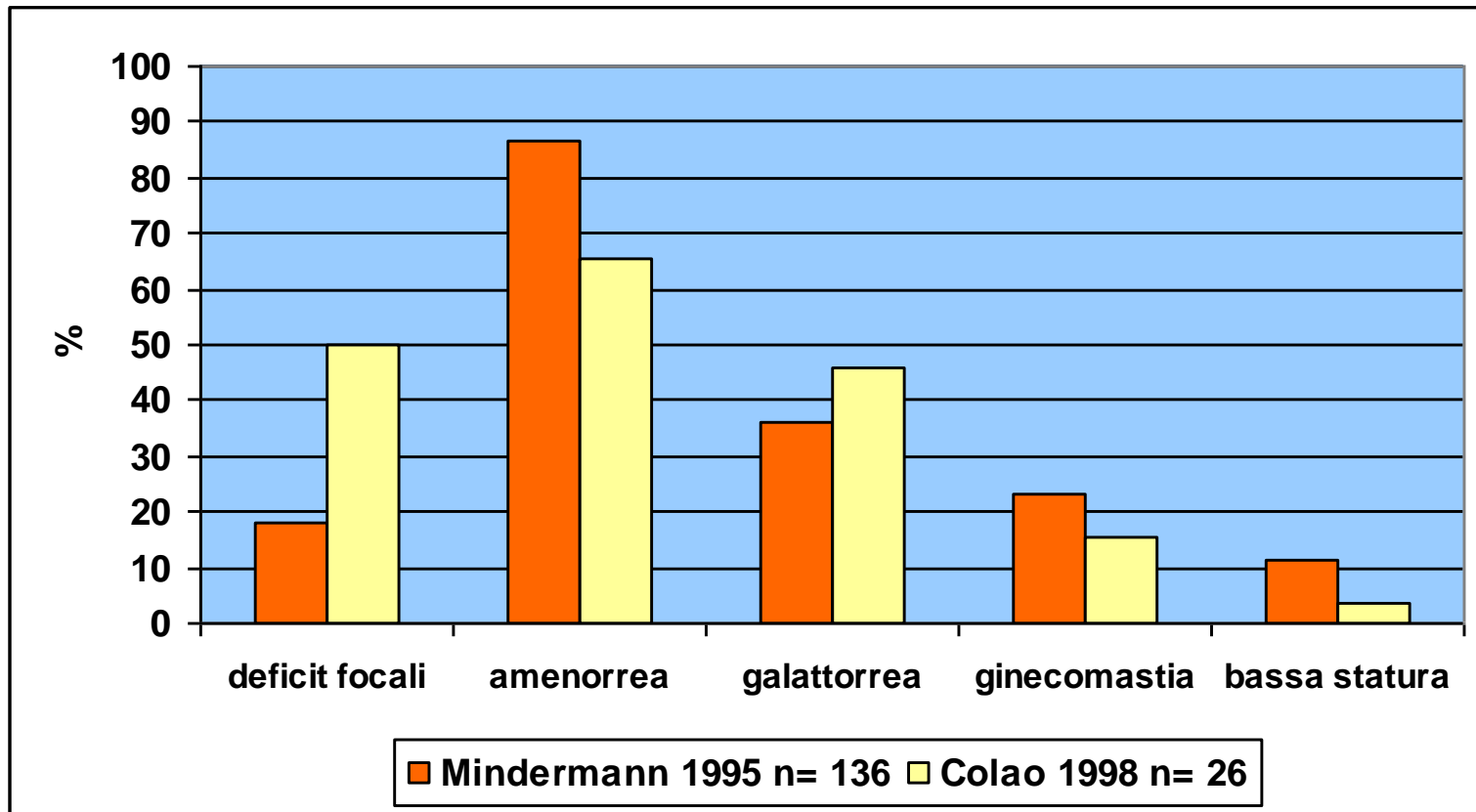
Ginecomastia

- 1) - quale la forma più frequente nella comune esperienza clinica?**
- 2) - cosa pensate della ginecomastia prepuberale ?**
- 3) - quali le forme secondarie o patologiche?**
- 4) – altri ormoni ?**



Ginecomastia

SINTOMI D'ESORDIO



Ginecomastia

Condition	Symptoms	Signs
Tumor		
Testicular		
Leydig-cell or Sertoli-cell	Testicular pain, enlargement, or both; decreased libido	Testicular mass or enlargement, contralateral testis with some atrophy, signs of feminization
Germ-cell	Testicular pain, enlargement, or both; symptoms of metastases (e.g., back pain, hemoptysis)	Testicular mass
Adrenocortical	Weight loss, decreased libido, possible symptoms of coexisting Cushing's syndrome or mineralocorticoid excess	Abdominal mass, signs of Cushing's syndrome or mineralocorticoid excess (hypertension)
Ectopic hCG-secreting	Weight loss; respiratory symptoms with lung carcinoma; abdominal symptoms with hepatocellular, gastric, or renal-cell carcinoma	Dependent on location of primary tumor and presence or absence of metastases
Hypogonadism		
Primary		
	Decreased libido, erectile dysfunction, vasomotor symptoms	Decreased testicular size, hard texture with Klinefelter's syndrome, soft texture if acquired; incomplete development of secondary sexual characteristics with pre-pubertal onset; possible findings of a systemic disorder (e.g., hemochromatosis)
Secondary		
	Decreased libido, erectile dysfunction, symptoms of other pituitary hormone deficiency, headache, visual symptoms	Decreased testicular size; possible visual-field cuts from a pituitary or parasellar tumor; signs of hypothyroidism, excess or deficiency of growth hormone; galactorrhea (rare)



Ginecomastia

Liver disease	Anorexia, nausea, vomiting, weight loss (or weight gain with ascites), edema, jaundice, pruritus	Jaundice, enlarged or shrunken liver, ascites, edema
Renal disease	Anorexia, fatigue, nausea, vomiting, oliguria or polyuria, pruritus, yellowish skin	Lethargy, asterixis, uremic hue, hypertension
Androgen insensitivity	Decreased libido, infertility	Possible hypospadias or ambiguity of genitalia, possible neurologic findings (e.g., proximal muscle weakness with fasciculations and tremor in X-linked spinal and bulbar muscular atrophy)
Familial or sporadic aromatase excess syndrome	None	Prepubertal onset of ginecomastia; accelerated increase in height in childhood, reduced final height; incomplete virilization



Ginecomastia

Sindrome da eccesso di aromatasi:
caratteristiche cliniche

Ginecomastia familiare prepuberale nei maschi

Macromastia familiare e pubertà precoce
isosessuale nelle femmine

Ginecomastia

Primo paziente, un bambino con ginecomastia ed aumentata aromatizzazione extra-ghiandolare, descritto da Hemsell *et al.* (J.Clin. Invest. 1977; 60:455)

Una famiglia descritta da Berkowitz *et al.* in cui la ginecomastia era presente in 5 maschi di 2 generazioni successive; suggerita una trasmissione X-linked (J.Clin. Invest. 1985; 75:1763)

Ginecomastia

Una famiglia con 4 soggetti affetti descritta da Vottero *et al.* in cui i maschi presentavano ginecomastia e pubertà precoce eterosessuale e le femmine macromastia e/o pubertà precoce isosessuale

(JCEM 1998; 83:1348)

Recentemente Shozu *et al.* hanno descritto padre e figlio, entrambi con una storia di ginecomastia prepuberale ed accelerata velocità di crescita dall'età di 5 anni

(N ENGL J MED 2003; 348(19):1855)

Età: 9 anni

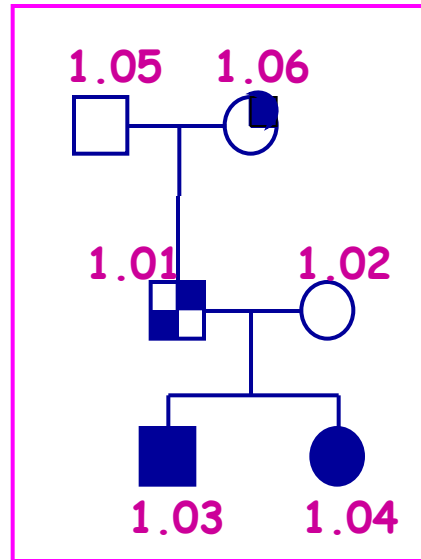


Probando

Età: 8 anni

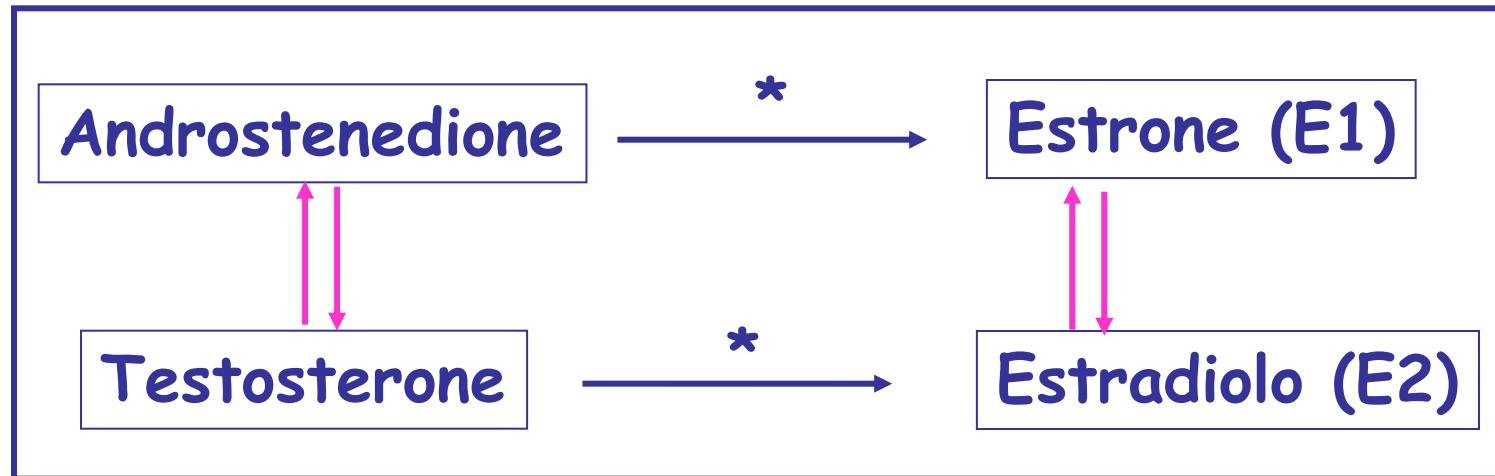


Sorella



Ginecomastia

Aromatasi (P450arom): enzima chiave nella biosintesi degli estrogeni

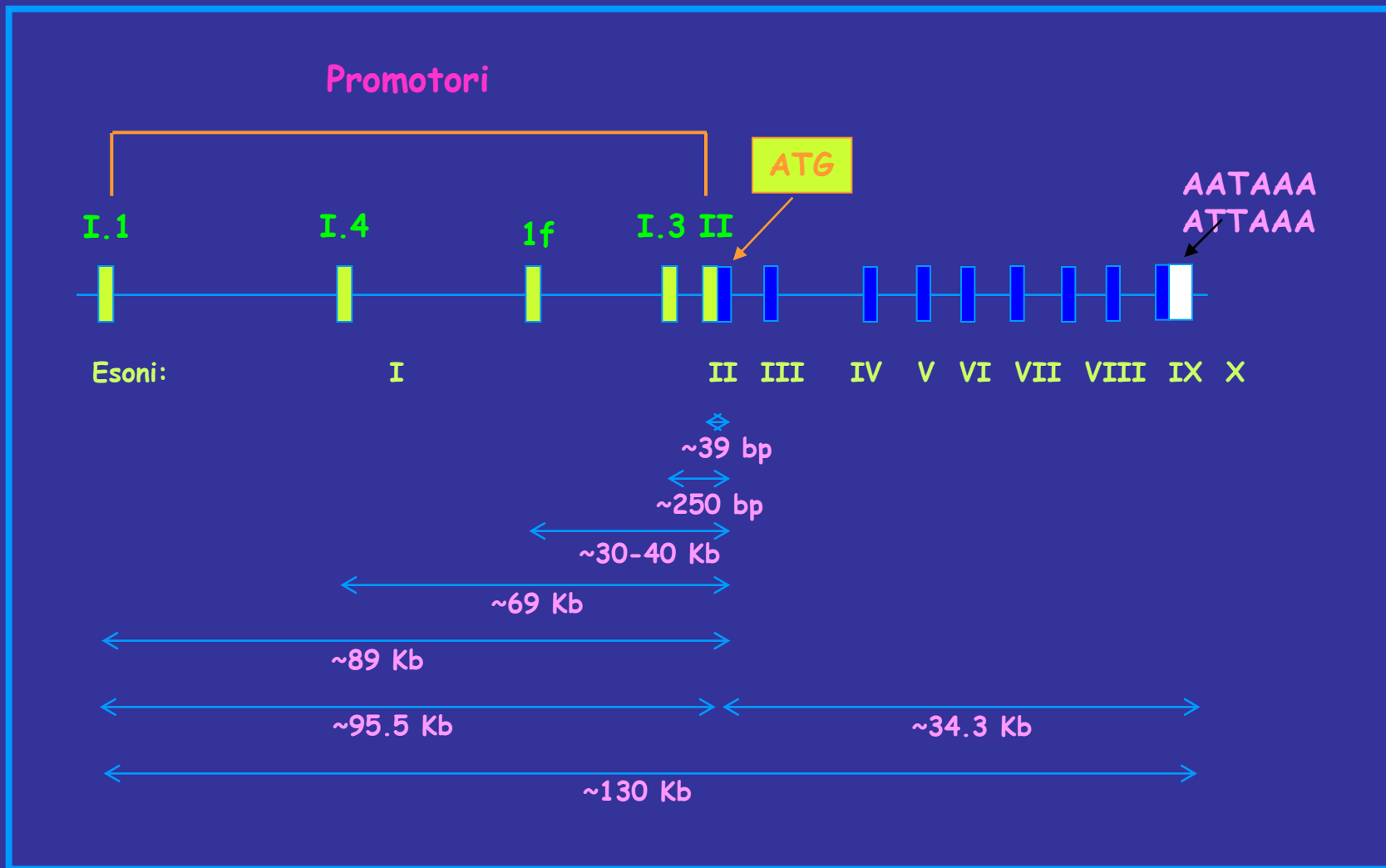


Complesso enzimatico: citocromo P450

+

flavoproteina NADPH-P450 reduttasi

Diagramma del gene dell'aromatasi



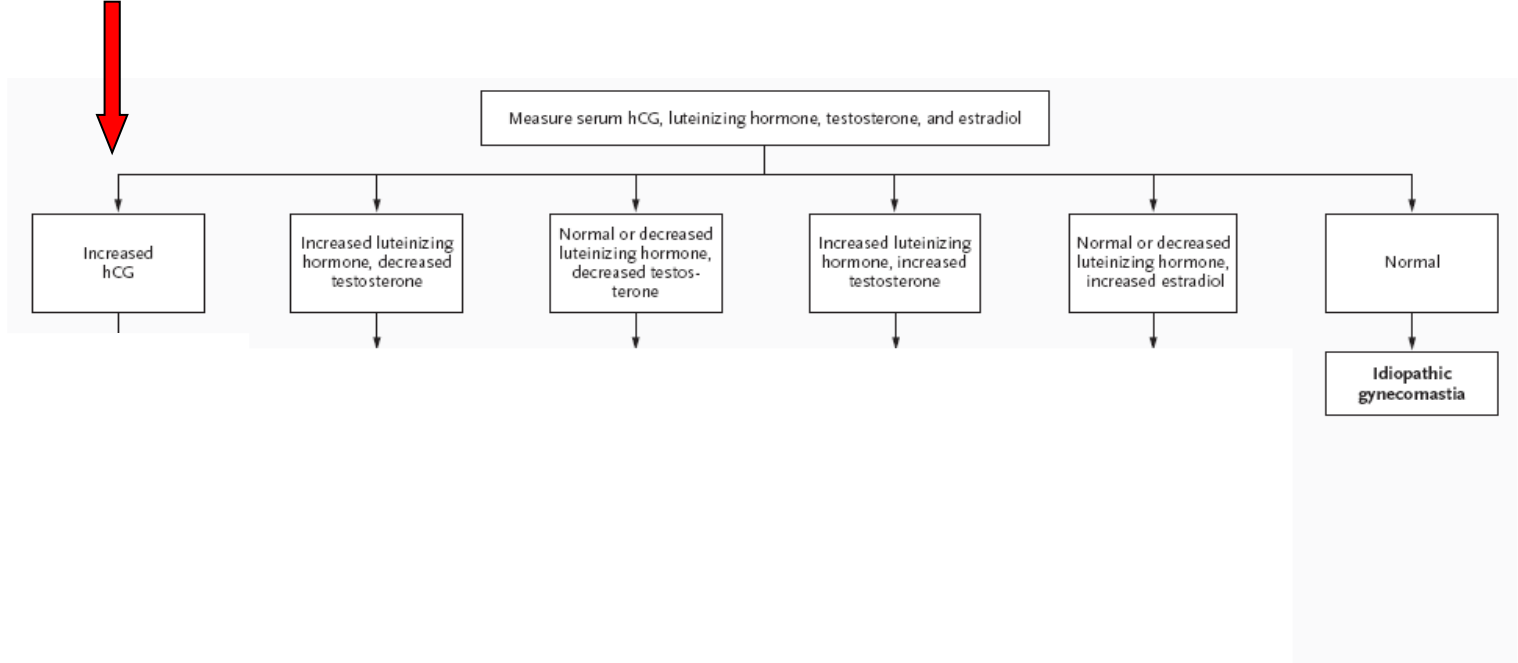
Laboratorio

	Probando	Sorella	Padre
• Sintomi	ginecomastia prepuberale	pubertà precoce	ginecomastia prepuberale
• EC (anni)	10	7.5	35
• EO (anni)	14	11	-
• T (ng/dl)	23	<20	234
• D ₄ (ng/dl)	9.1	<6.8	26.8
• E ₂ (pg/ml)	8.6	8.9	60*
• E ₁ (pg/ml)	43.7**	62.2**	82**

Gynecomastia

Glenn D. Braunstein, M.D.

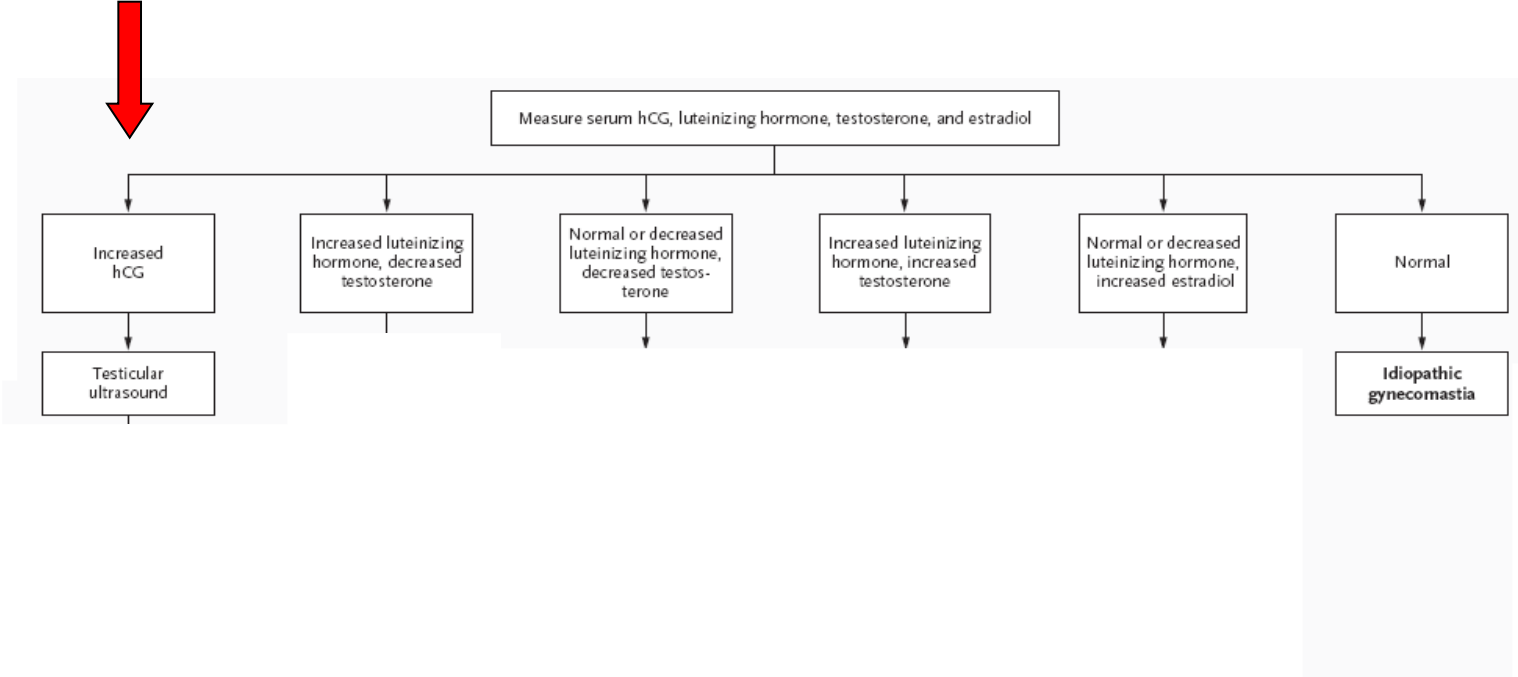
N Engl J Med 2007;357:1229-37.



Gynecomastia

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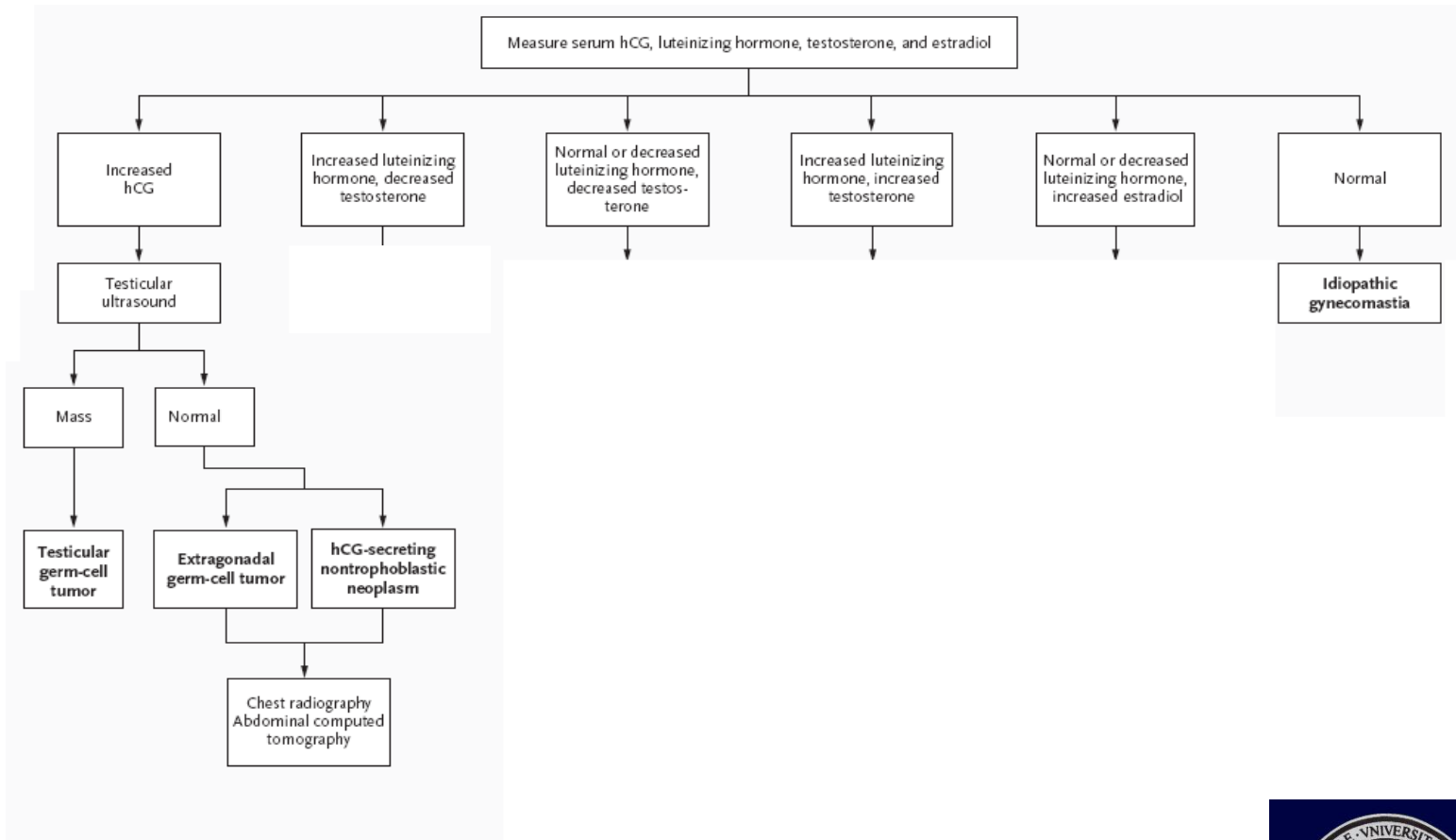
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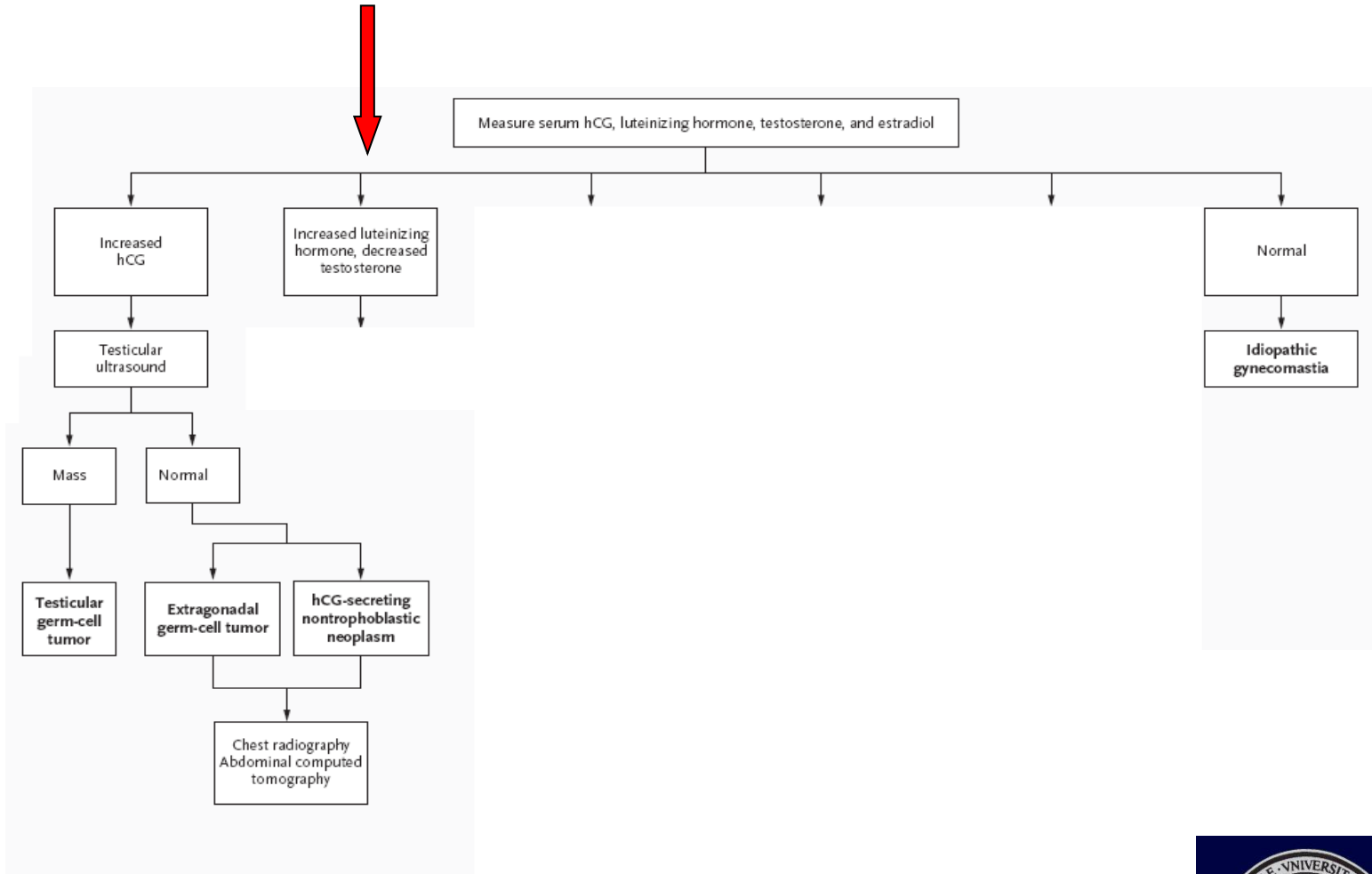
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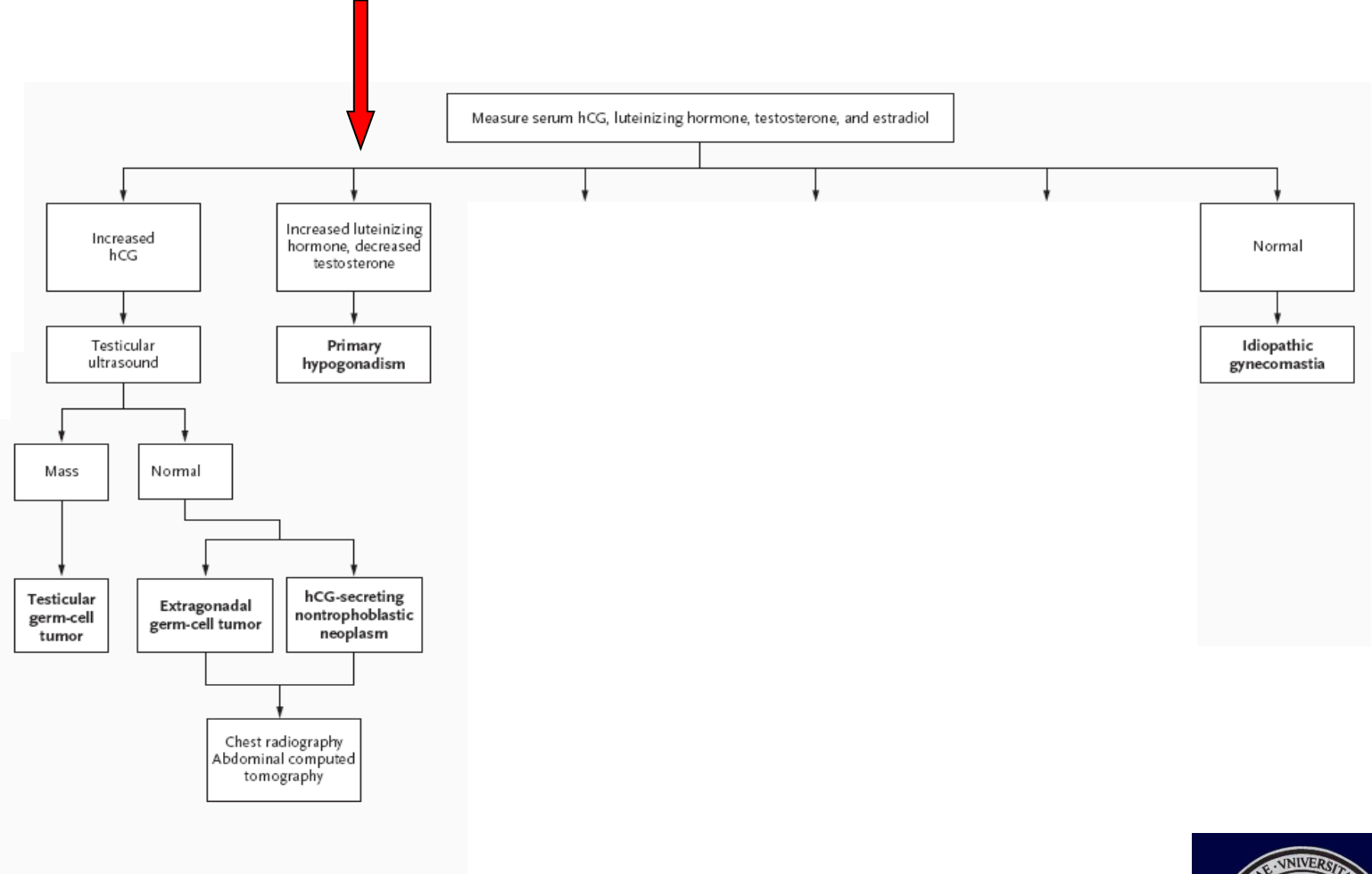
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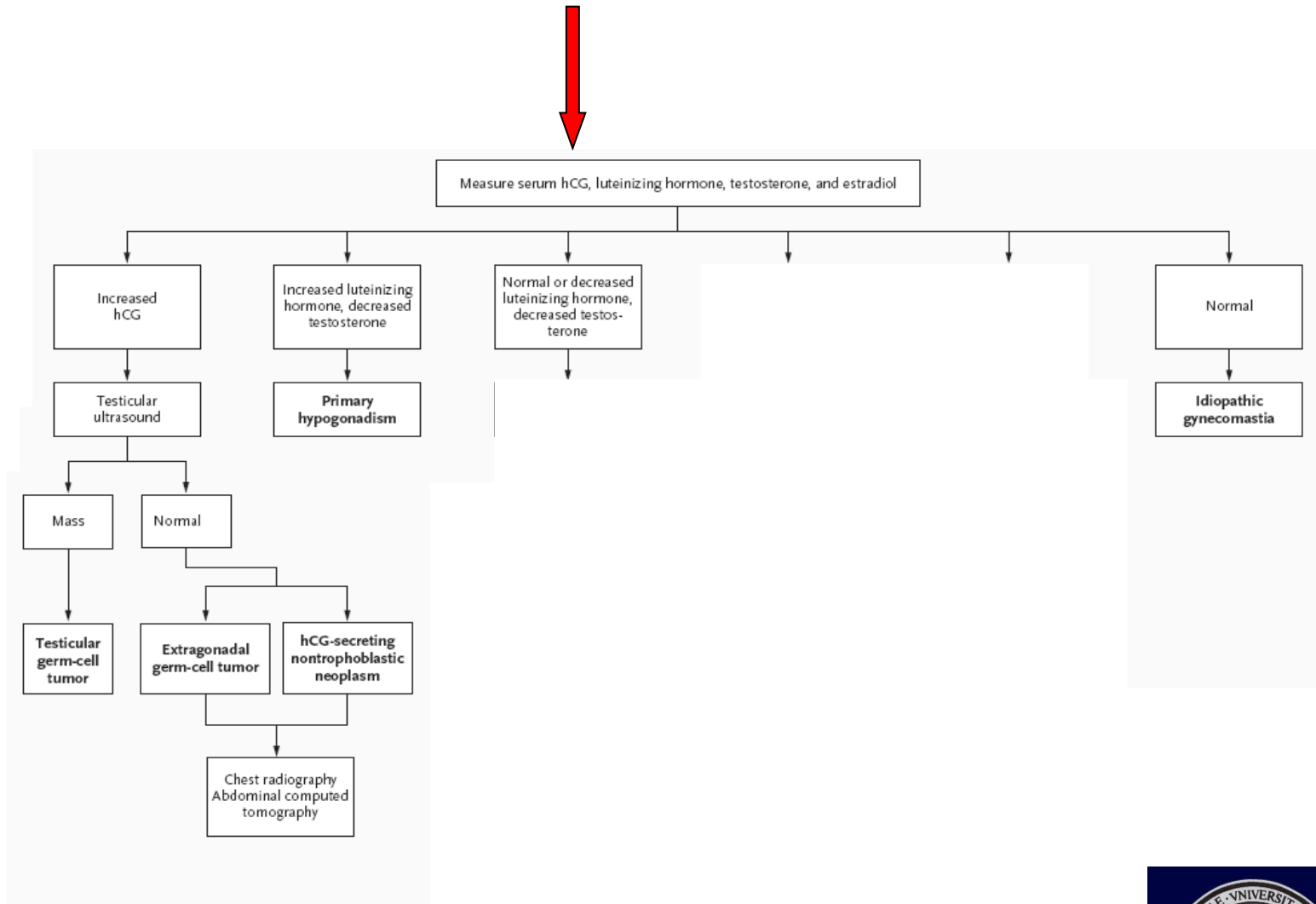
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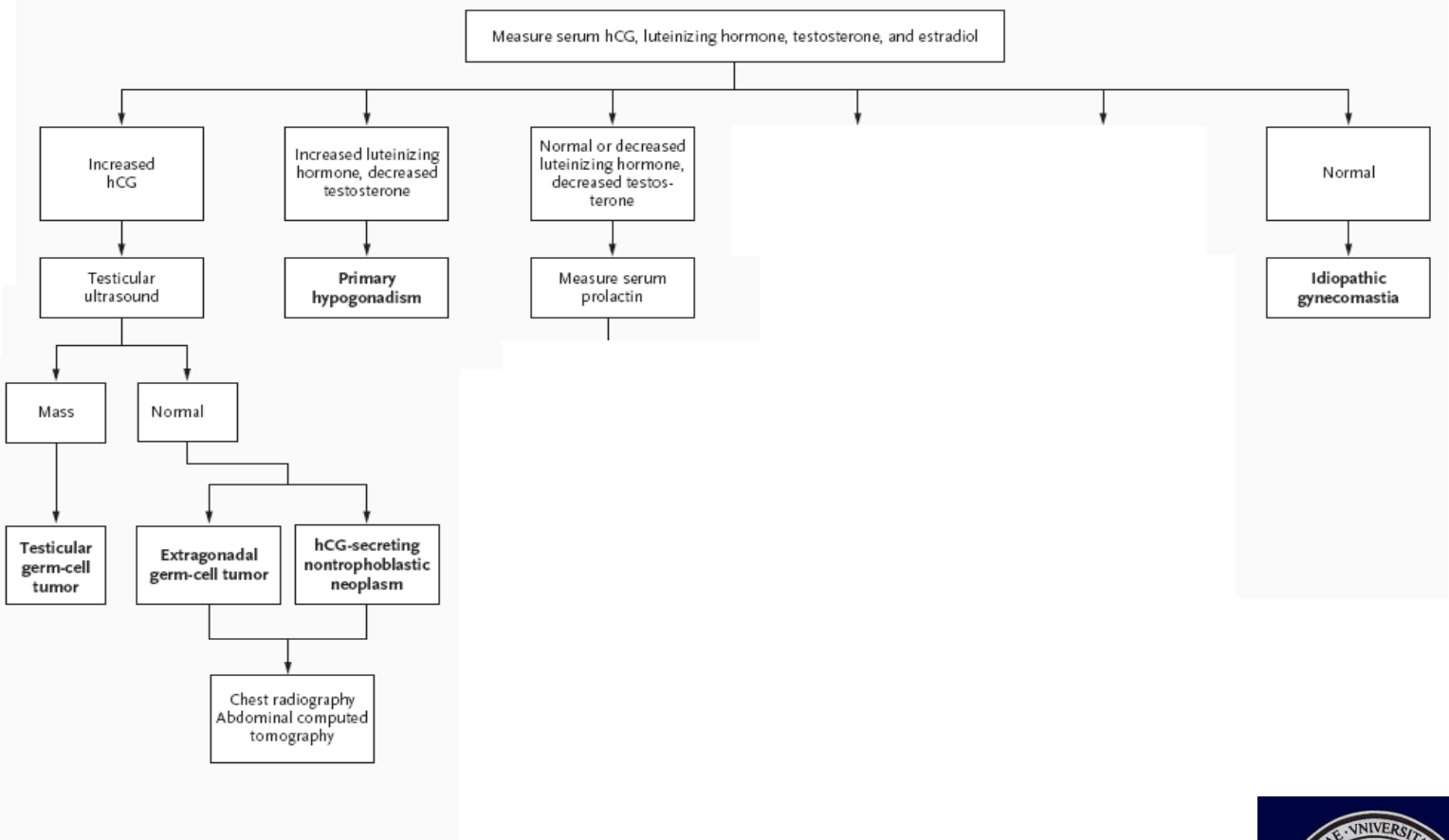
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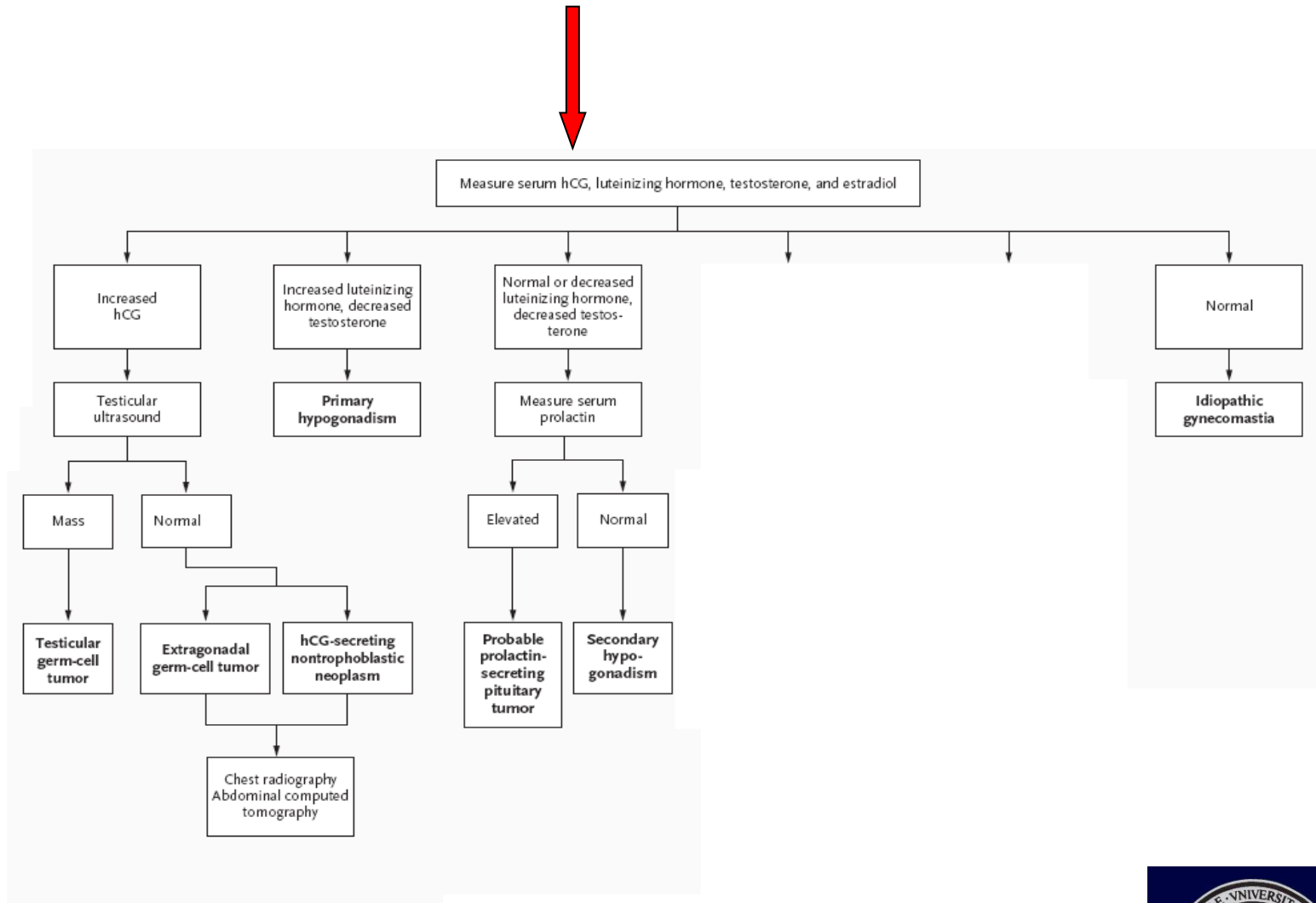
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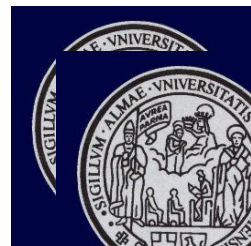
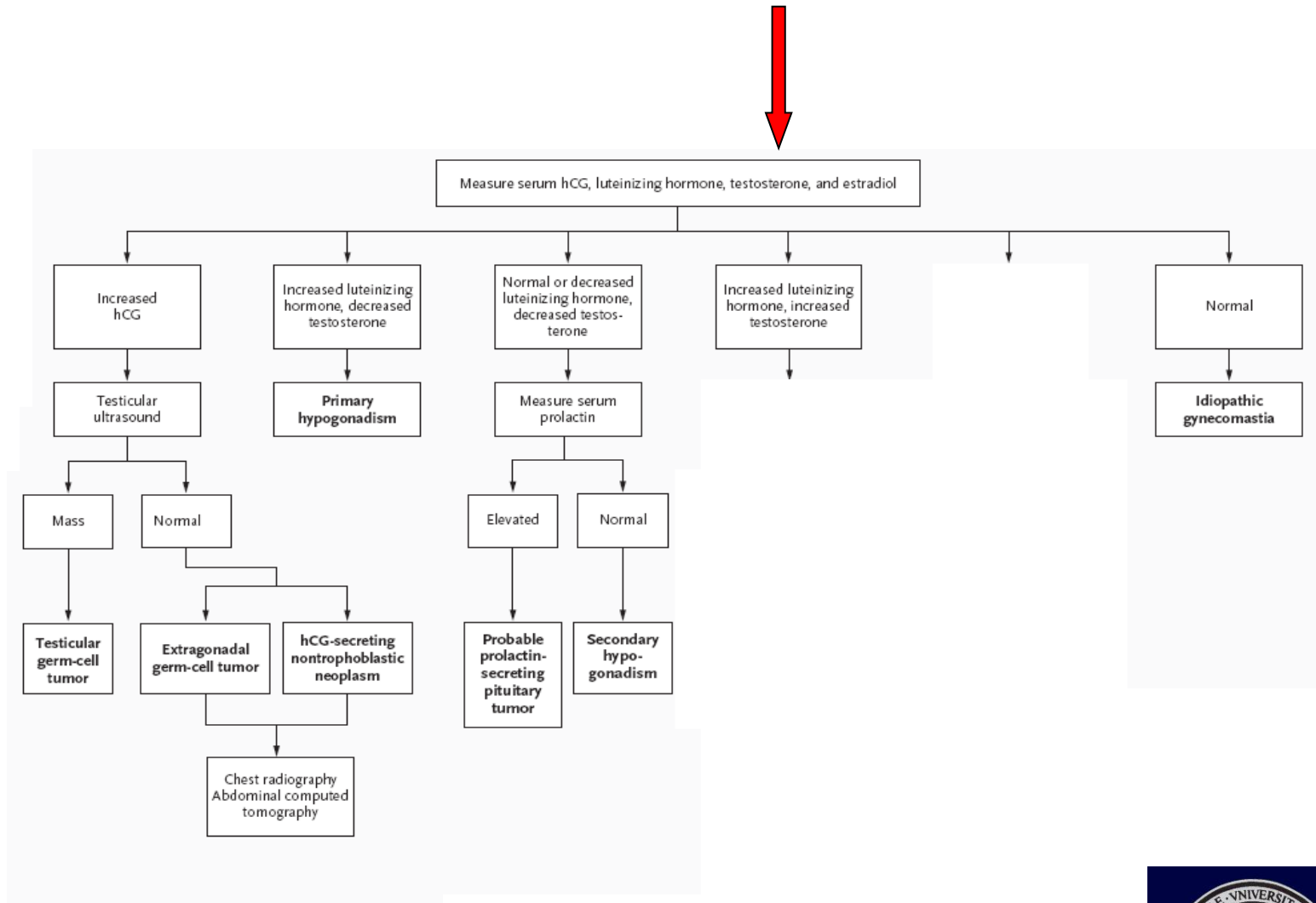
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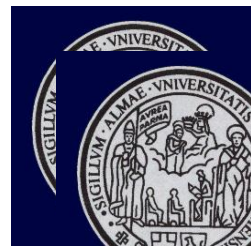
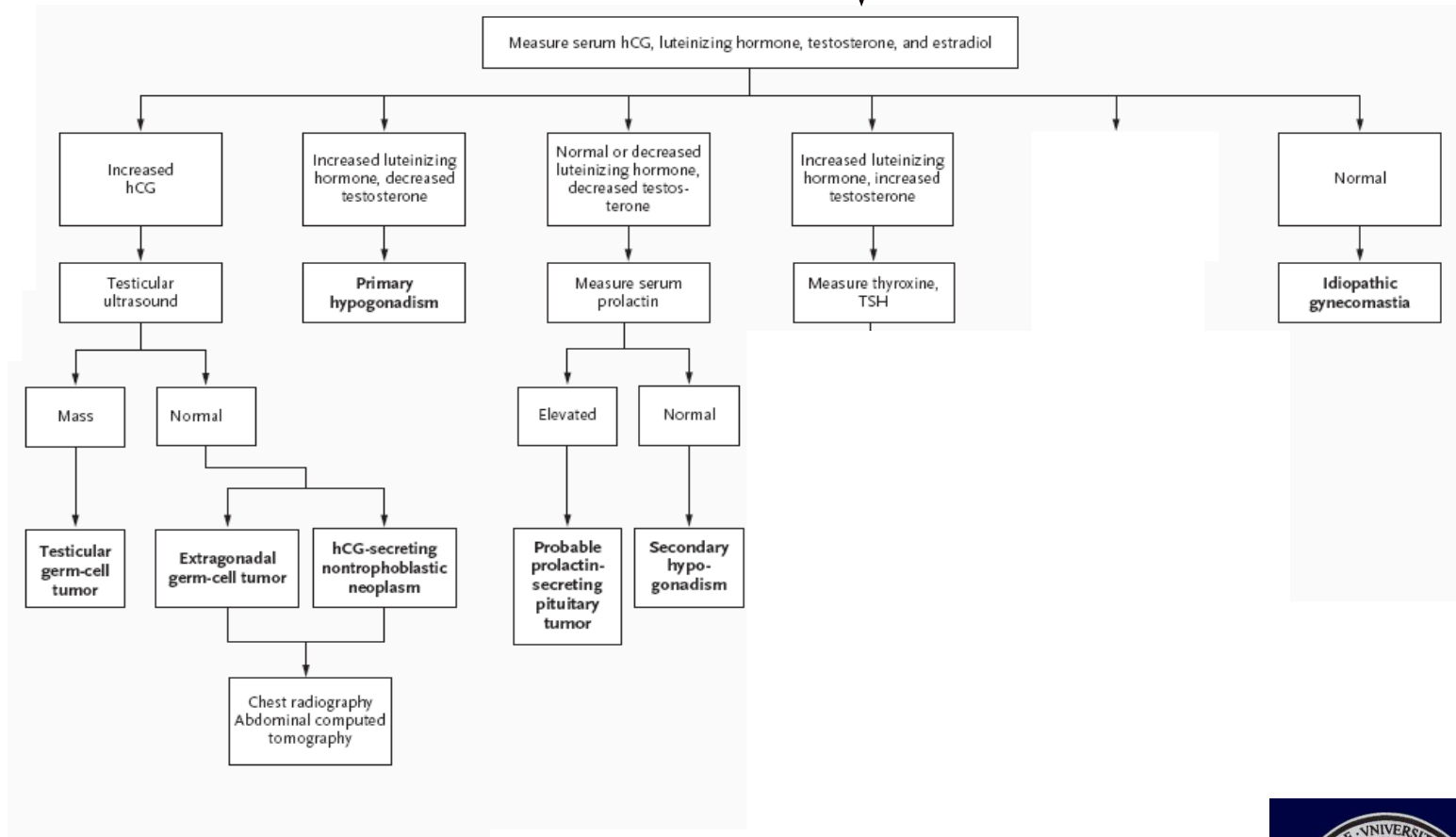
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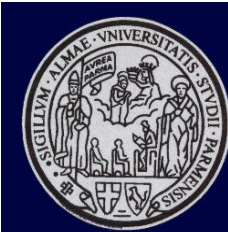
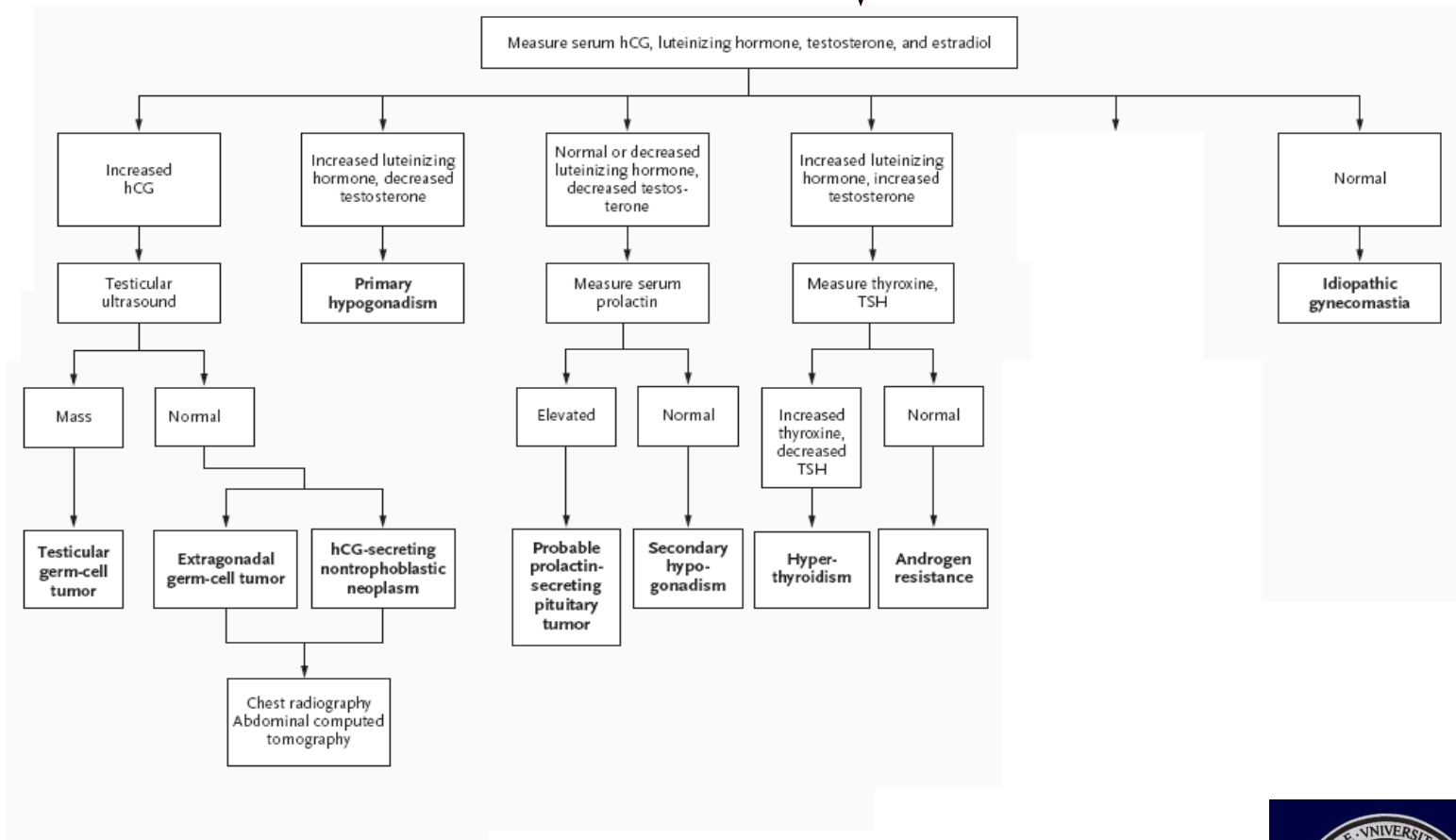
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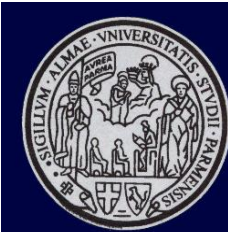
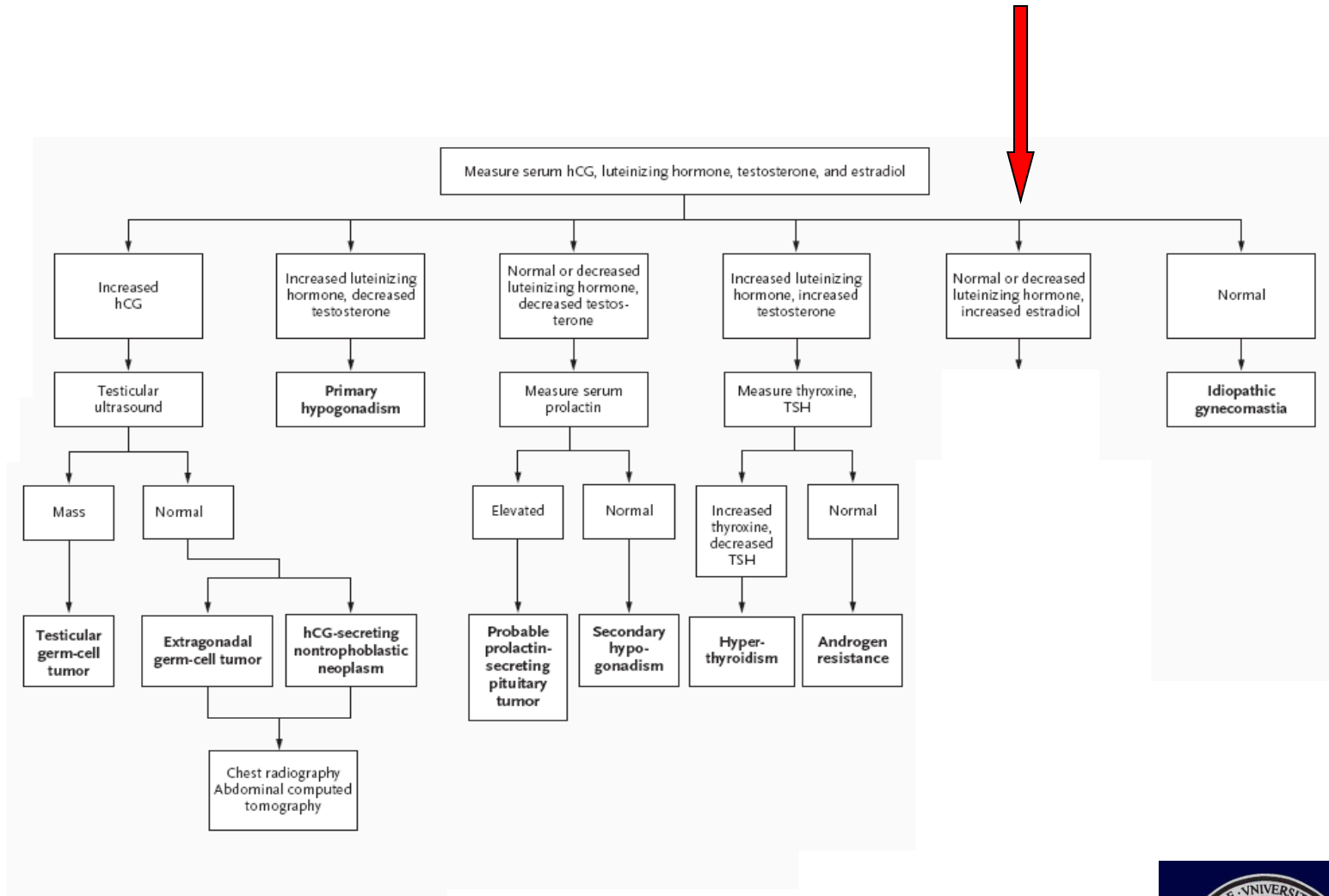
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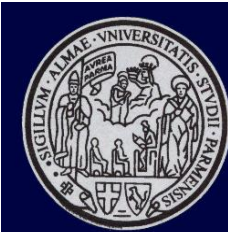
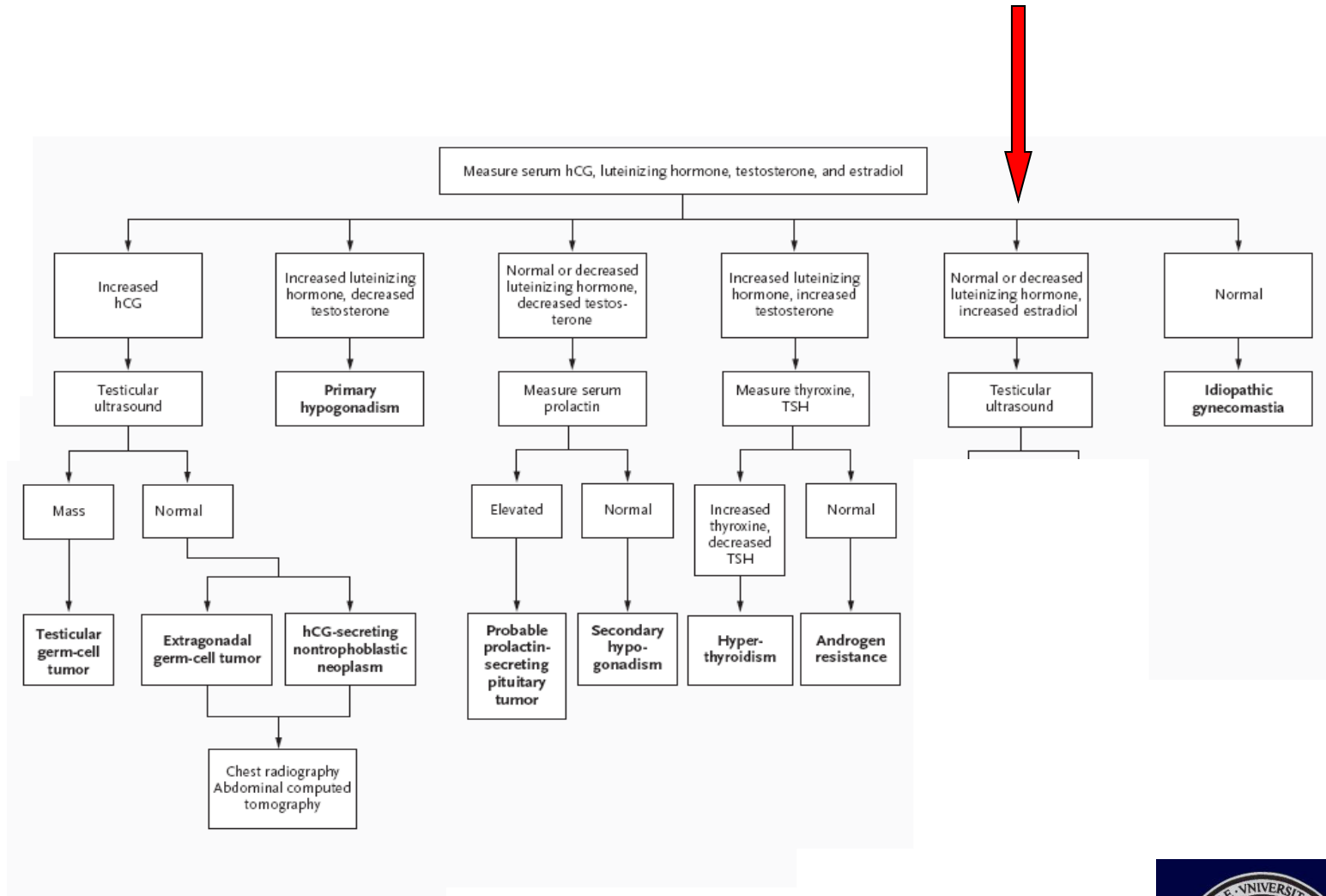
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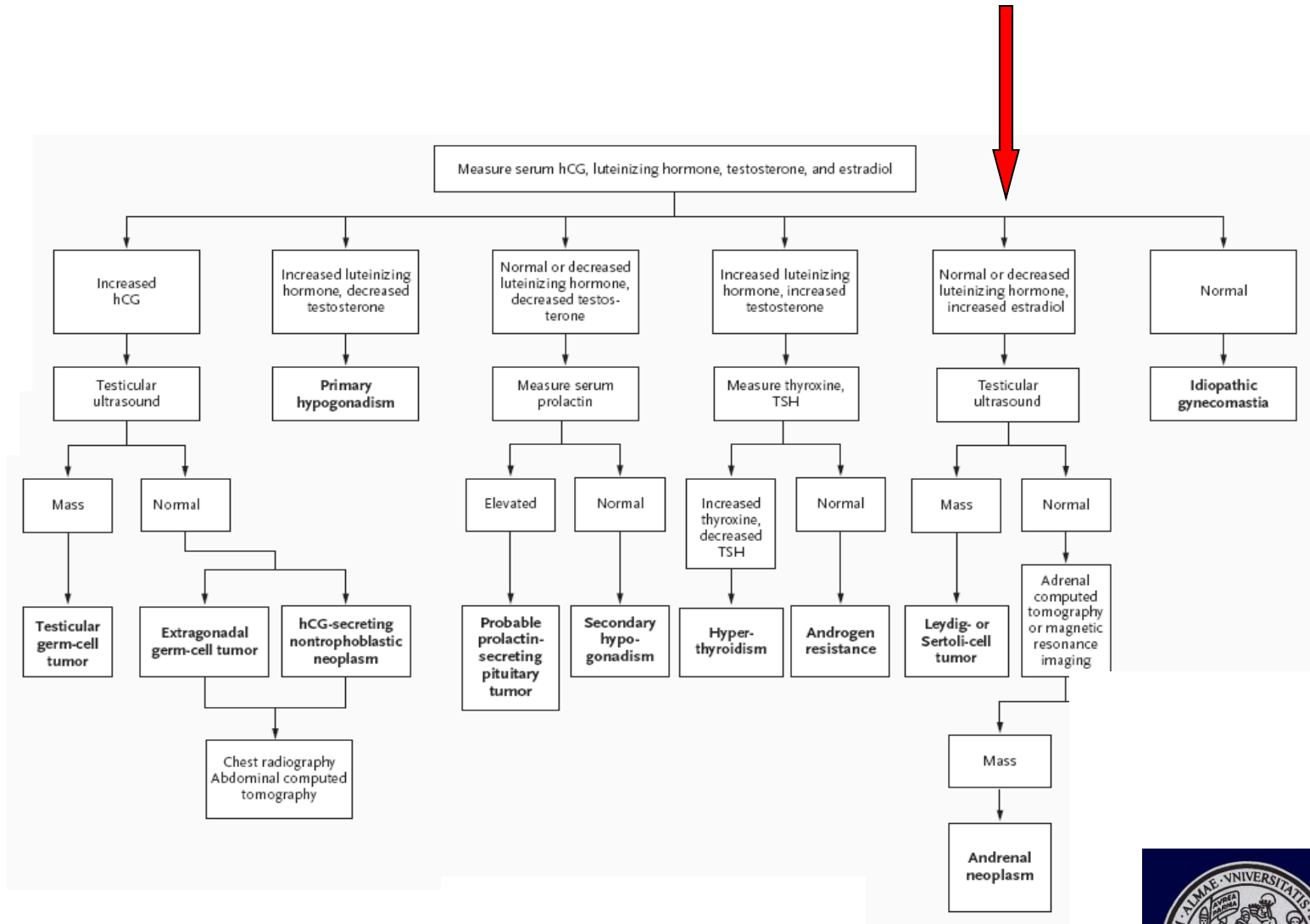
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Ginecomastia

- 1) - quale la forma più frequente nella comune esperienza clinica?**
- 2) - cosa pensate della ginecomastia prepuberale ?**
- 3) - quali le forme secondarie o patologiche?**
- 4) – quale terapia nella forma “ fisiologica” ?**



Ginecomastia puberale “fisiologica”

WHICH MEDICATIONS EFFECTIVELY REDUCE PUBERTAL GYNAECOMASTIA?

Arch Dis Child March 2010 Vol 95 No 3

1. *Reassurance* is widely regarded as the safest and most reasonable form of “treatment”, as the condition is usually asymptomatic and self-limiting.
2. *Surgery* may be considered in boys who are not obese when there is significant breast tenderness or psychosocial morbidity. However, surgery is associated with complications such as scarring, skin retraction and hypesthesia.⁸ Also, the condition may recur postoperatively.



Ginecomastia puberale “fisiologica”

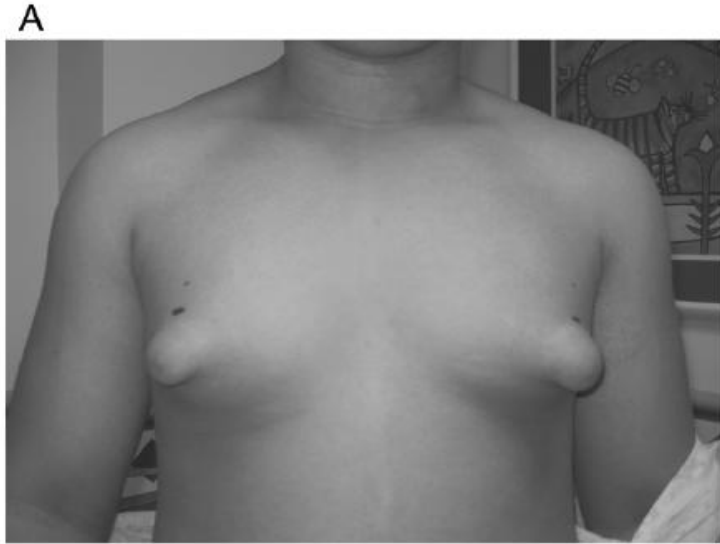


Fig. 1 A, Bilateral gynecomastia primarily contained to the subareolar area. Simple SQM via a partial circumareolar incision was performed. B, The postresection appearance after SQM.



Fig. 6 A and B, Before and after pictures in a young man who underwent RM for gynecomastia. Note the ptotic breasts with displaced NAC preoperatively. The postoperative picture shows some excoriation from eschar at the margins of the NAC, but this resolved completely, with an excellent cosmetic outcome.

Ginecomastia puberale “fisiologica”

WHICH MEDICATIONS EFFECTIVELY
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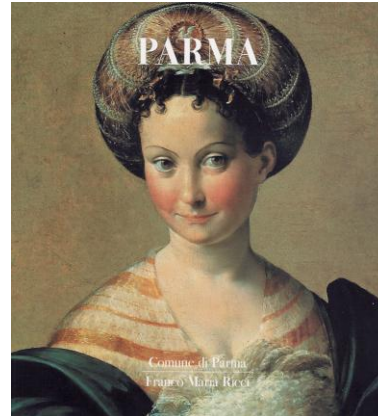
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3. *Pharmacological treatment* aims to correct the imbalance of oestrogens and androgens that is thought to cause proliferation of breast tissue. Several drugs are reported in the literature. Tamoxifen, raloxifene and clomiphene block the effects of oestrogen on the breast, while anastrozole and testolactone inhibit its production. Danazol (an androgen) acts to counterbalance the stimulatory effects of oestrogens.

Clinical bottom line

- ▶ Tamoxifen appears to be safe and possibly effective in reducing the size of glandular tissue in persistent pubertal gynaecomastia, but may be ineffective in reducing breast tissue completely and eliminating the need for future surgery. (Grade B)
- ▶ Anastrozole may not be more effective than placebo in decreasing the size or volume of breast tissue in persistent pubertal gynaecomastia and its long-term effects and safety are still unknown. (Grade D)
- ▶ Pharmacological management of gynaecomastia has not been formally assessed from a psychological perspective. (Grade D)

Grazie per l'attenzione



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