Classificació dels tumors hipofisiaris: novetats i implicacions

Betina Biagetti

Vall d'Hebron

No tinc conflicte d’interessos

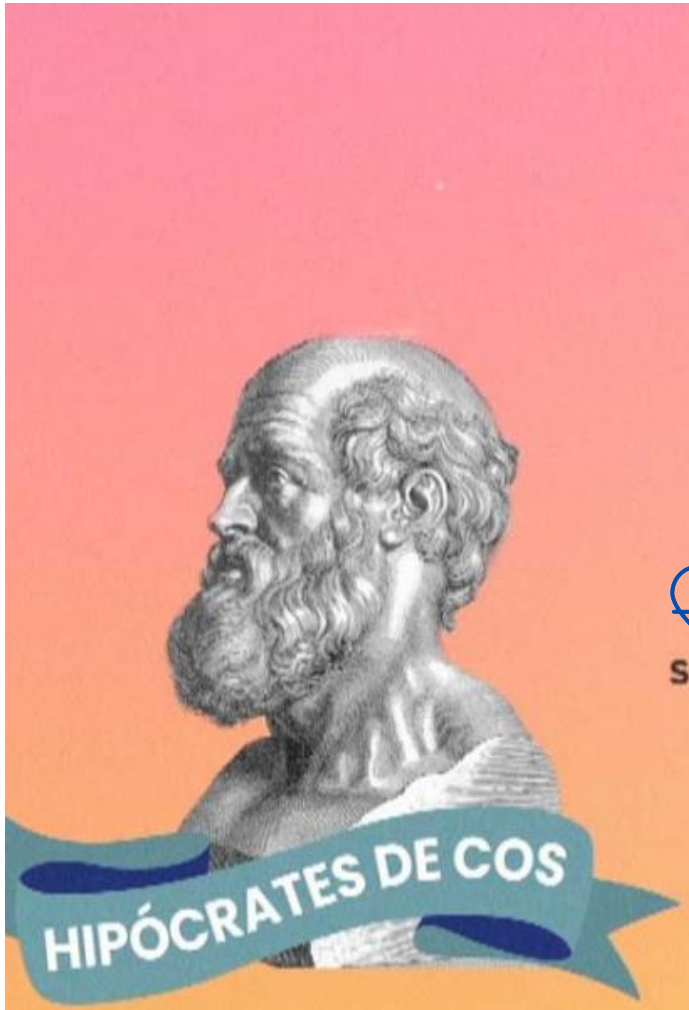
Índex

1. Antecedents històrics
2. Objectius de la classificació del les lesions hipofisiàries implicacions
3. A propòsit d'un cas
4. Conclusions

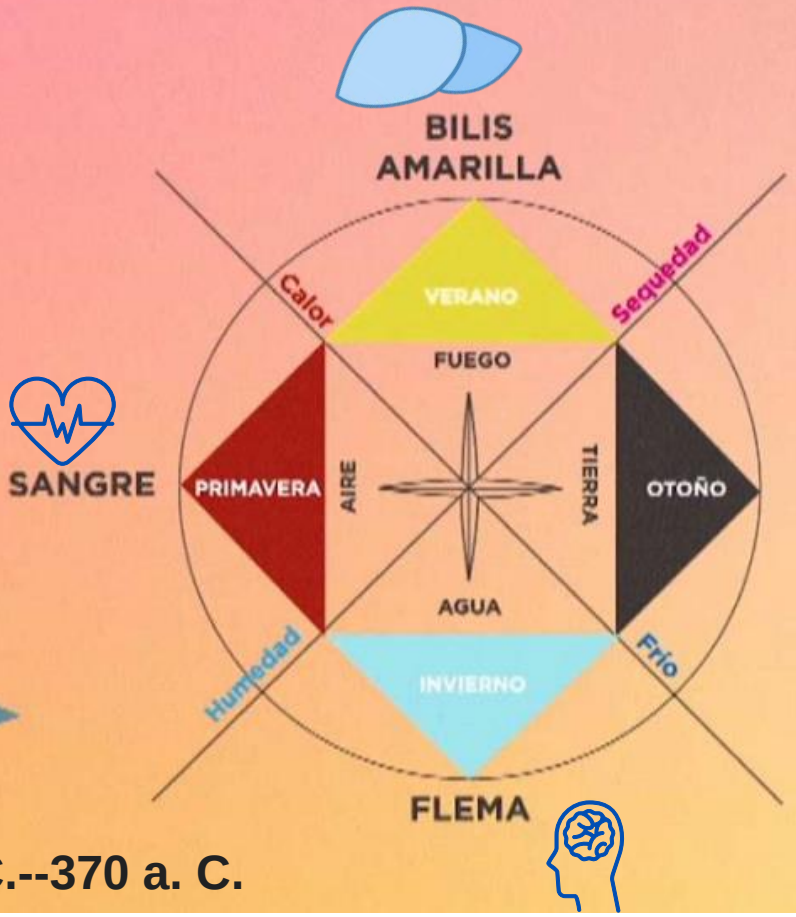
1. Antecedents històrics

National Museum of American History

1. Antecedents històrics: Teoria dels humors

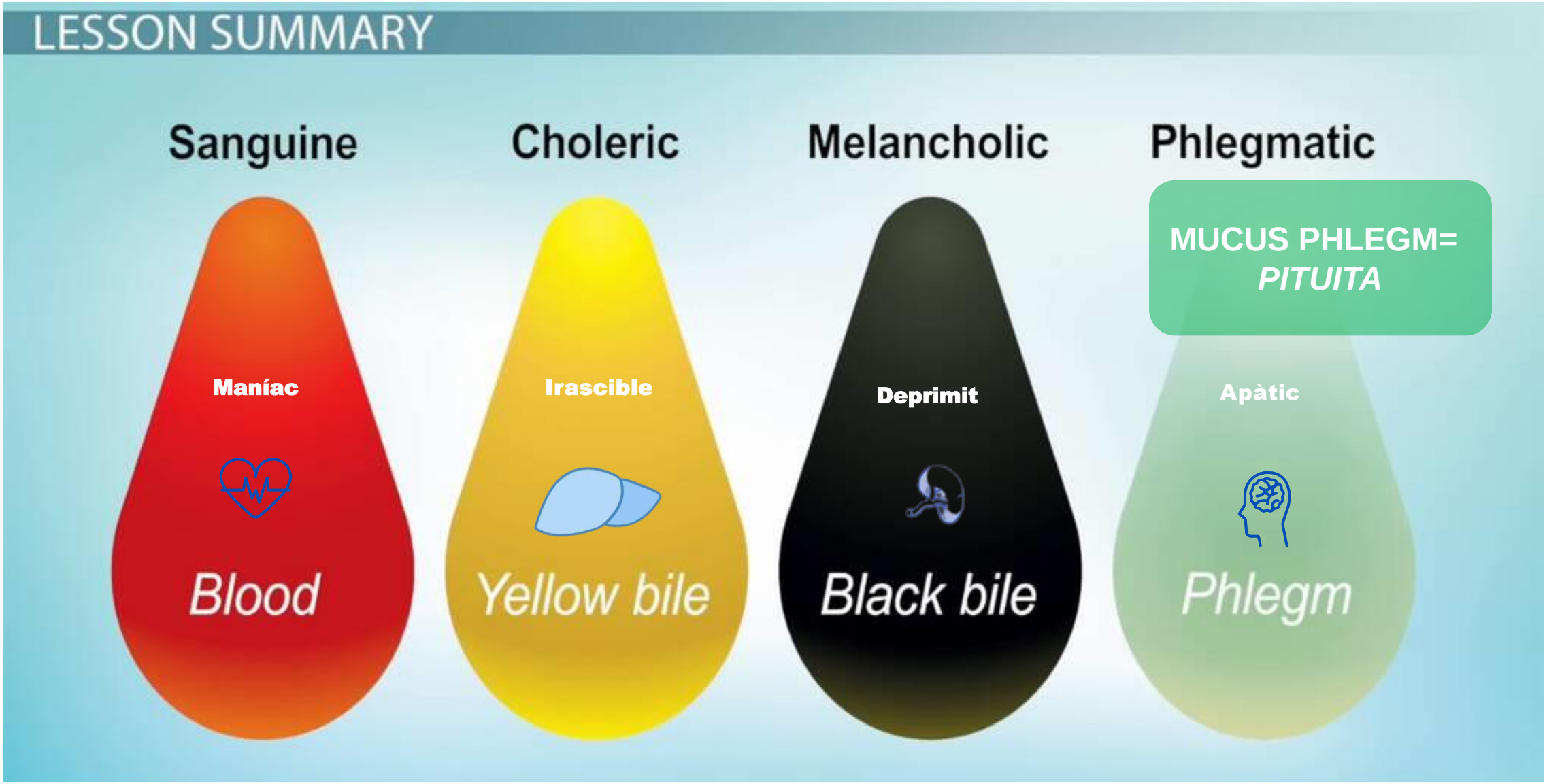


Grecia Siglo V a. C., 460 a. C.--370 a. C.



BILIS NEGRA

LESSON SUMMARY



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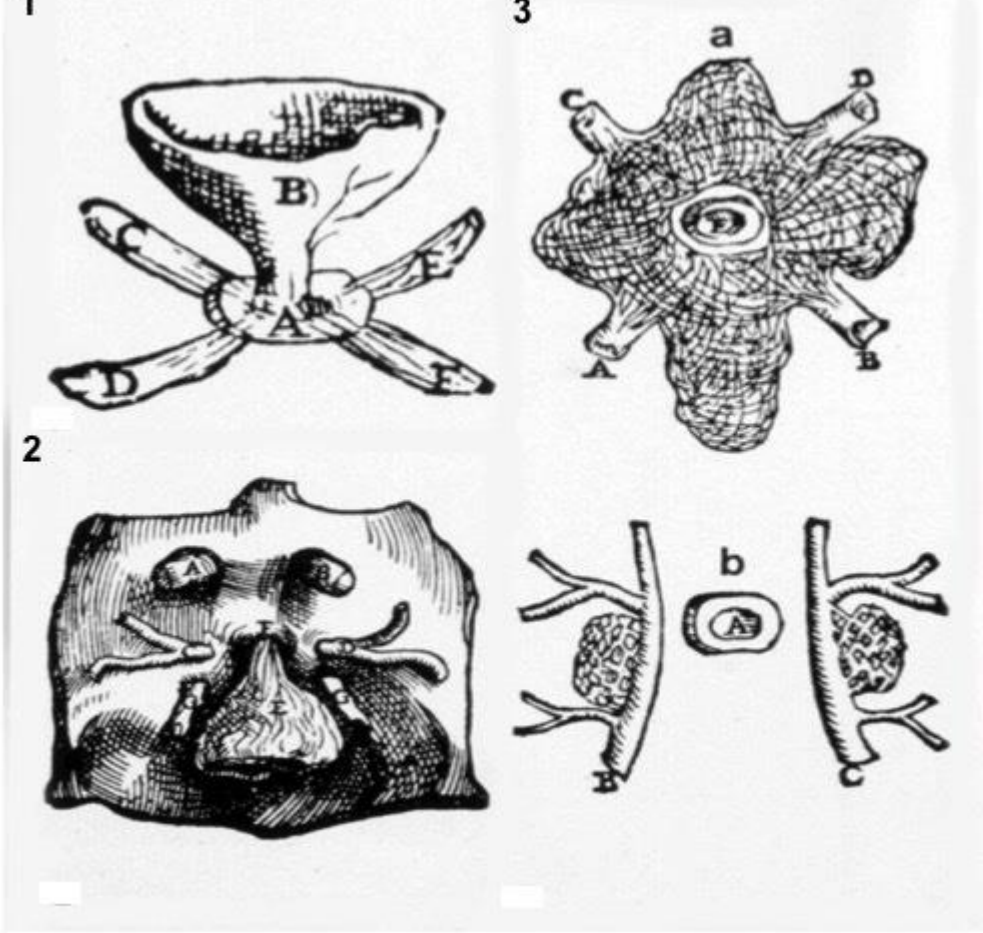
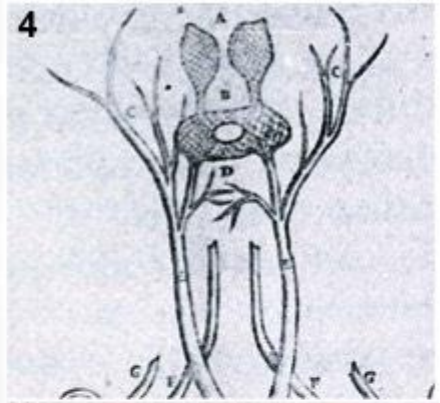
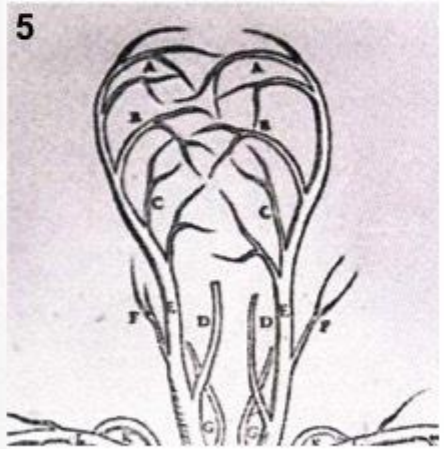
Andrés Vesalio







(A) hypothalamic infundibulum B) ducts comprising the foramen lacerum and superior orbital fissure believed to drain brain **mucus or phlegm (in Latin pituita)** from the pituitary gland to the nasopharynx;

Pituitary gland, showing drainage channels of phlegm, page 64 of *De Humani Corporis Fabrica* 1543

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Pituitary tumors were first described over 100 years ago

Pierre Marie,
father of acromegaly

1886 → 1912

Harvey Cushing,
father of Cushing's
Disease

Marie P. *Rev Med Paris* 1886;6:297–302;
Cushing H. *Bull Johns Hopkins Hosp* 1932;50:137–195

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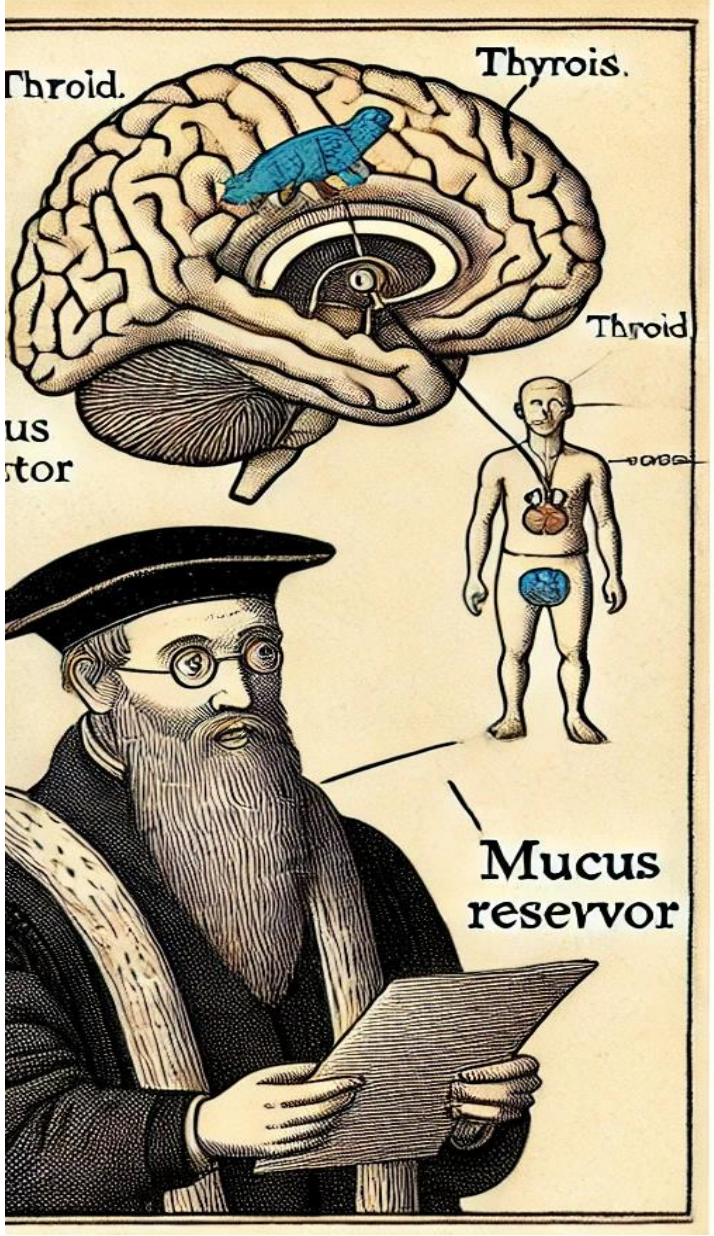
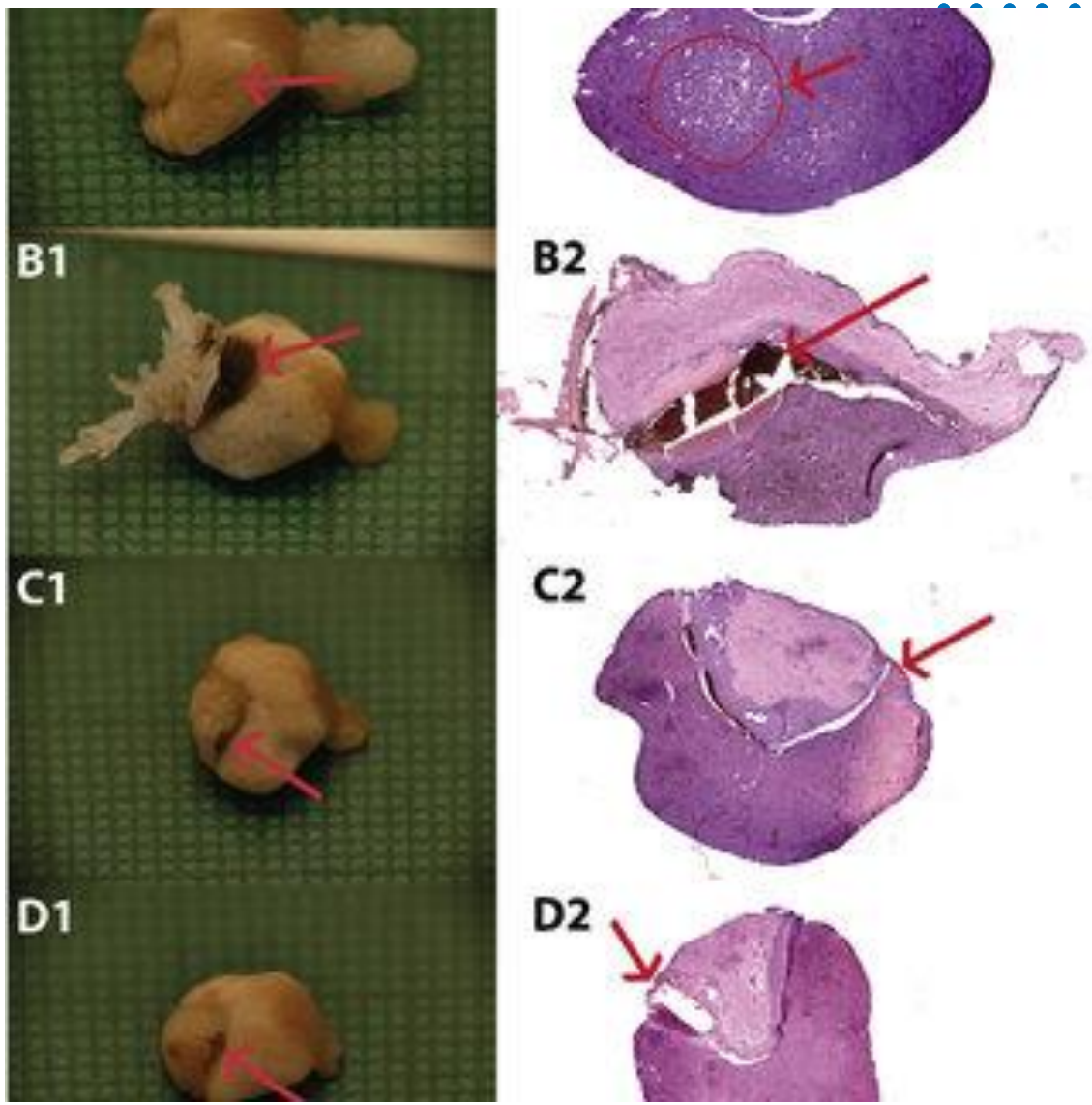


Exocrine gland

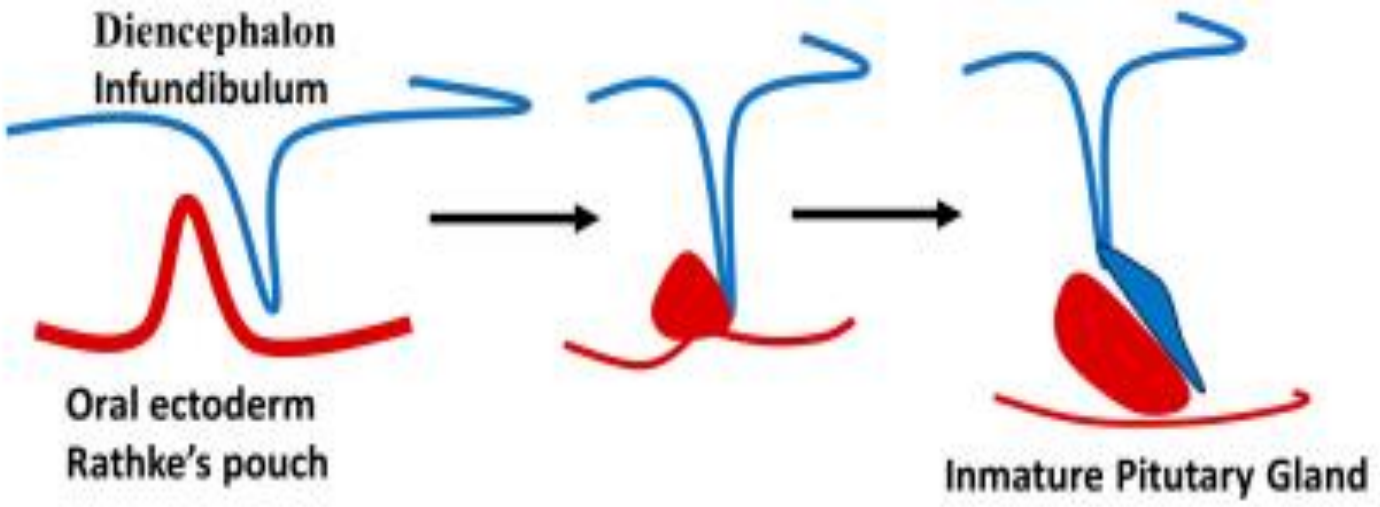
Master gland

2. Classificació



2. Classificació

1. Normal pituïtari gland

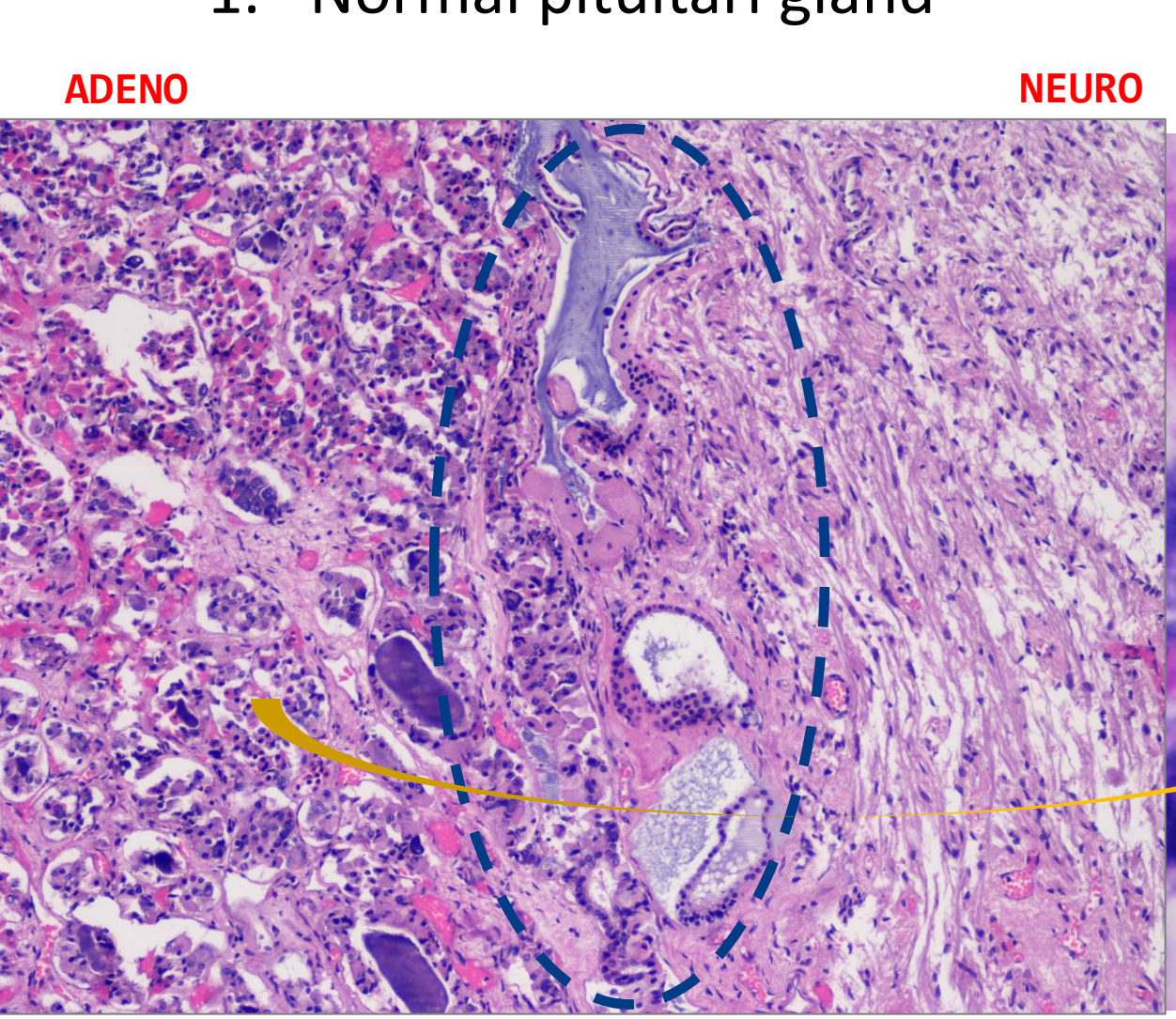


Setmana 4 del desenvolupament fetal

Biagetti B et al IJMS 2022

2. Classificació

1. Normal pituïtari gland



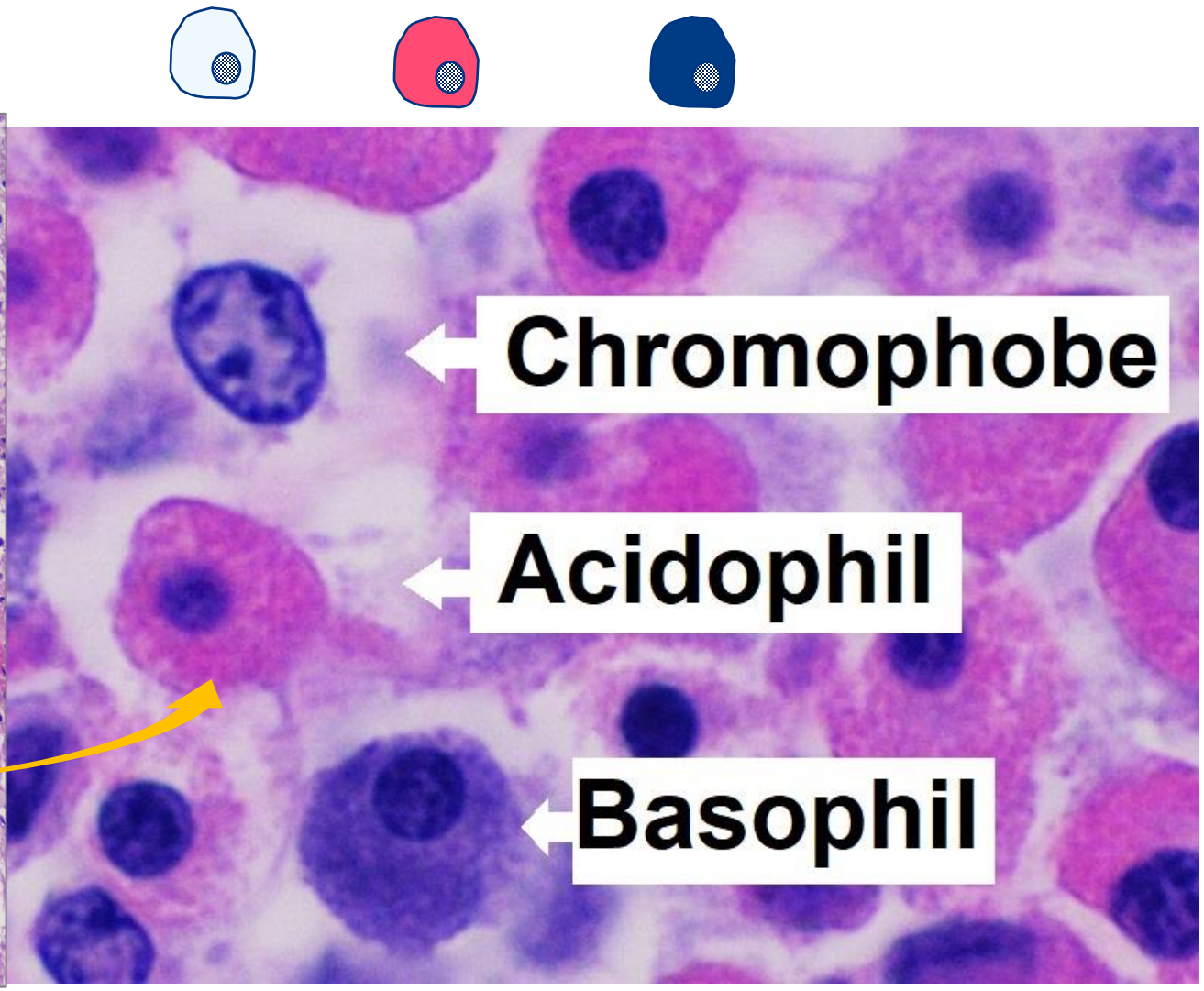
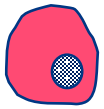


Imagen facilitada por Elena Martinez-Saez

Version 1: Tinctorial (1912-1934)

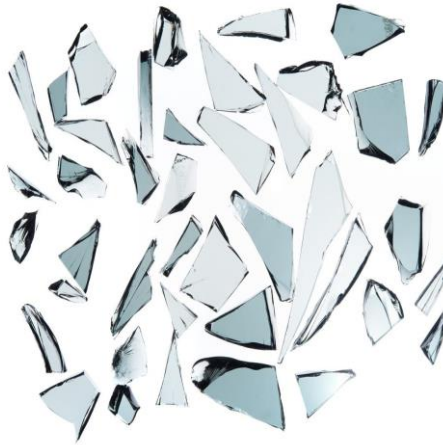
Acidophilic cells Acromegaly	Basophilic cells Cushing's Disease	**Chromophobic cells** **NFPA**



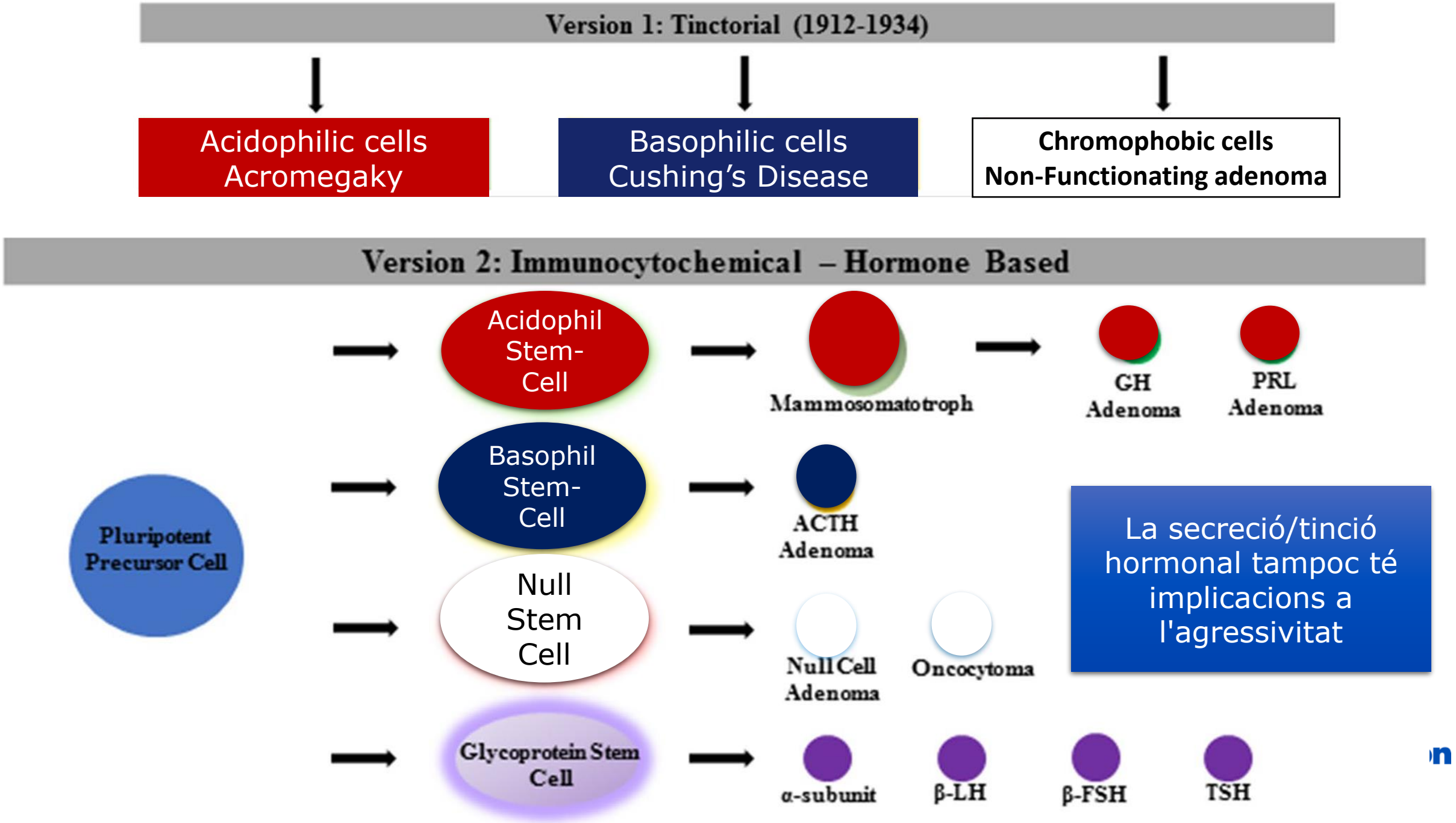
RED BUT…

BLUE BUT…

COLORLESS BUT…



Vall d'Hebron


Version 1: Tinctorial (1912-1934)
Acidophilic cells
Acromegaky
Basophilic cells
Cushing's Disease
Chromophobic cells
Non-Functionating adenoma
Version 2: Immunocytochemical – Hormone Based
Pluripotent Precursor Cell
Acidophil Stem-Cell
Mammosomatotroph
GH Adenoma
PRL Adenoma
Basophil Stem-Cell
ACTH Adenoma
Null Stem Cell
Null Cell Adenoma
Oncocytoma
Glycoprotein Stem Cell
α-subunit
β-LH
β-FSH
TSH
La secreció/tinció hormonal tampoc té implicacions a l'agressivitat

Version 3: Transcription Factors (2017 – Present)

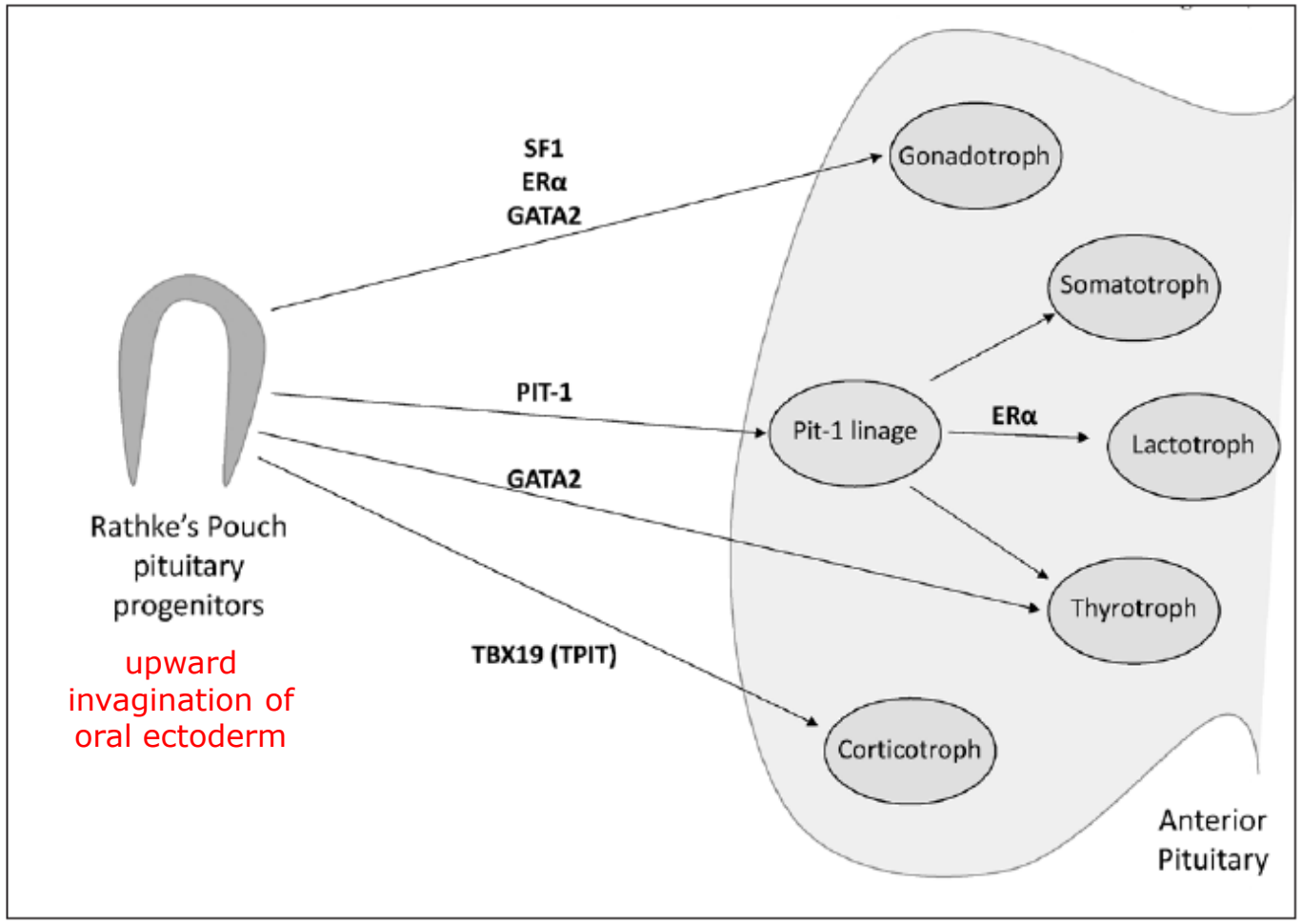
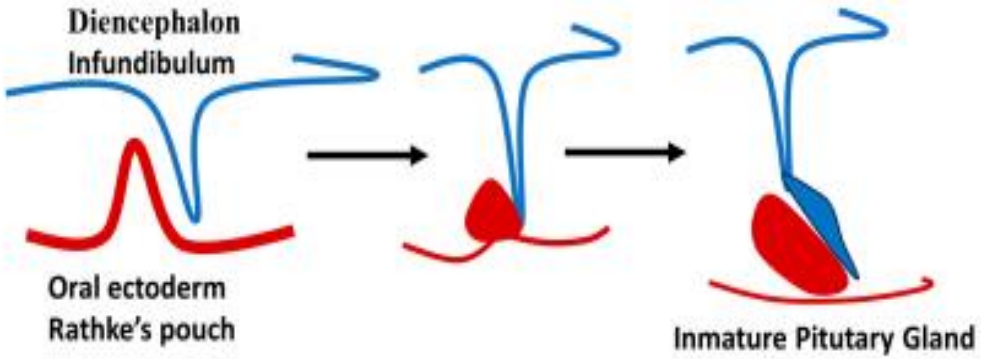


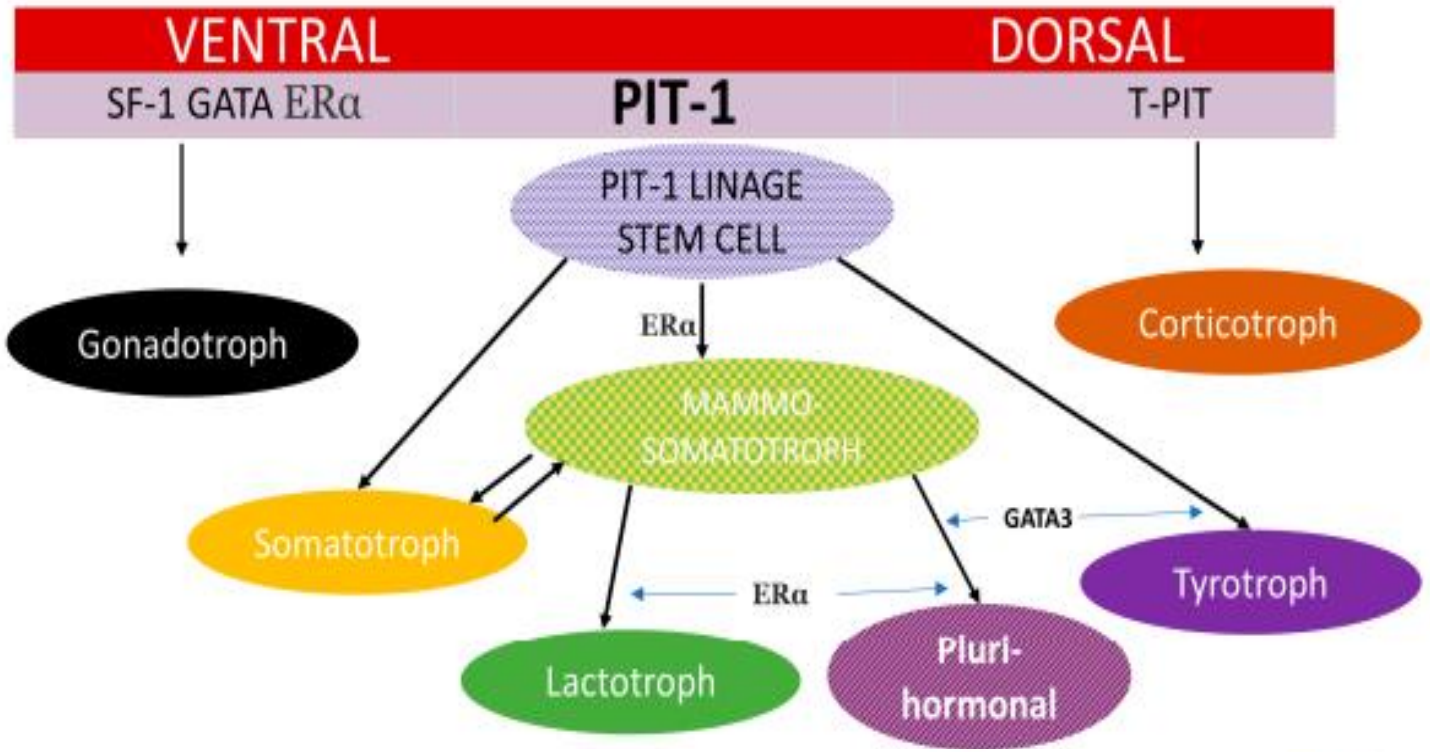
Fig. 1. Simplified figure on pituitary development highlighting the transcription factors now commended by the new World Health Organization guidelines (18) to characterize pituitary adenomas if necessary. *ERα* = estrogen receptor-alpha; *SF1* = splicing factor 1.

Els FT promouen la diferenciació cel·lular

Chung Thong Lim; Márta Korbonits. **Clinicopathology of Pituitary Adenoma, *Endocr Pract.* 2018**



Horizontal section o Pituitary



International Journal of *Molecular Sciences*

Review

Prolactin and Growth Hormone Signaling and Interlink Focused on the Mammosomatotroph Paradigm: A Comprehensive Review of the Literature

Marta Araujo-Castro [1,2,*], Mónica Marazuela [3,4], Manel Puig-Domingo [5,6] and Betina Biagetti [7,8,*]

International Journal of *Molecular Sciences*

Review

Molecular Pathways in Prolactinomas: Translational and Therapeutic Implications

Betina Biagetti * and Rafael Simò *

Endo-ERN European Reference Network on Rare Endocrine Conditions

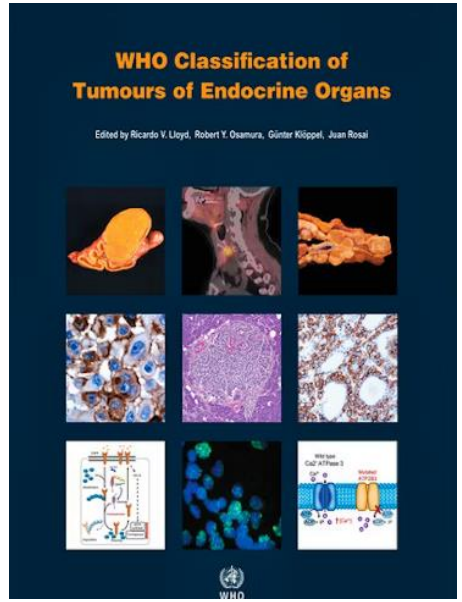
Designació CSUR Patologia Hipotàlem Hipofisiària

European Reference Network

ciberer Centro de Investigación Biomédica en Red Enfermedades Raras

Vall d'Hebron

2. Classificació



La classificació de l'OMS s'ha revisat 3 cops en 20 anys:

- 2004 Classificació de tumors endocrins (3a edició)
- 2017 Classificació de tumors endocrins (4a edició)
- 2022 Classificació de tumors endocrins (5a edició)

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Version 3: Transcription Factors (2017 – Present)

	IHQ	IHQ+ FT	FT + IHQ
	OMS, 2004		
Nomenclature	Typical Adenoma Atipical Adenoma Carcinoma		
Terminology	Hormone secretion		
Staging	Non staging		
Proliferation markers	Ki67<3% P53 diffuse Mitosis (<2)		
Risk	Atypical adenoma		

Invasive tumo
proliferative (
mitosis), rapid
- Crooke's cell
- Silent corticot
- Lactotroph in
- Plurihormona
- Sparsely gran
- Null Cell

Only accurate histological subtyping
- Crooke's cell
- Silent corticotroph
- Acidophil Stem Cell
- Inmature PIT1-linage
- Sparsely granulated GH
- Null Cell

M. Beatriz S. Lopes Acta Neuropathol (2017)
Ozgur Mete Head and Neck Pathology (2022)

Endocr Pathol (2017) 28:228–243
DOI 10.1007/s12022-017-9498-z

Overview of the 2017 WHO Classification of Pituitary Tumors

Ozgur Mete[1,2,3] · M. Beatriz Lopes[4]

Table 2 The 2017 WHO pathological classification of pituitary adenomas

Adenoma types	Morphological variants	Pituitary hormones by immunohistochemistry	Transcription factors and other co-factors
Somatotroph adenomas			
	Densely granulated somatotroph adenoma	GH	Pit-1, ERα
	Sparsely granulated somatotroph adenoma	GH	Pit-1, ERα
	Mammosomatotroph adenoma	GH, PRL (in different cells) ± α-subunit	Pit-1, ERα
	Mixed somatotroph-lactotroph adenoma	GH, PRL (in different cells) ± α-subunit	Pit-1, ERα
Lactotroph adenomas			
	Sparsely granulated lactotroph adenoma	PRL	Pit-1, ERα
	Densely granulated lactotroph adenoma	PRL	Pit-1, ERα
	Acidophil stem cell adenoma	PRL, GH	Pit-1, ERα
Thyrotroph adenoma		TSH ± α-subunit	Pit-1
Corticotroph adenomas			
	Densely granulated corticotroph adenoma	ACTH	Tpit
	Sparsely granulated corticotroph adenoma	ACTH	Tpit
	Crooke's cell adenoma	ACTH	Tpit
Gonadotroph adenoma		β-FSH, β-LH, α-subunit (various combinations)	SF-1, GATA2, ERα
Null cell adenoma		None	None
Plurihormonal adenomas			
	Pit-1-positive plurihormonal adenoma (previously termed Silent subtype 3 adenoma)	GH, PRL, β-TSH ± α-subunit	Pit-1
	Adenomas with unusual immunohistochemical combinations	Various combinations	

Endocrine Pathology (2022) 33:6–26
https://doi.org/10.1007/s12022-022-09703-7

Overview of the 2022 WHO Classification of Pituitary Tumors

Sylvia L. Asa[1] · Ozgur Mete[2] · Arie Perry[3] · Robert Y. Osamura[4]

The 2022 WHO classification of pituitary neuroendocrine tumors (PitNETs)

PitNET Type	Subtype	Transcription factors	Hormones	LMWK
PIT1-lineage PitNETs				
Somatotroph tumors	Densely granulated somatotroph tumor	PIT1	GH, α-subunit	Perinuclear
	Sparsely granulated somatotroph tumor	PIT1	GH	Fibrous bodies (> 70%)
Lactotroph tumors	Sparsely granulated lactotroph tumor	PIT1, ERα	PRL (paranuclear dot-like)	Weak or negative
	Densely granulated lactotroph tumor		PRL (diffuse cytoplasmic)	Weak or negative
			(predominant), PRL, -subunit	Perinuclear
			ubunit, βTSH	Weak or negative
			nomorphic tumor cells with redominant GH expression nd variable PRL, βTSH, and α-subunit	Perinuclear
Immature PIT1-lineage tumor		PIT1 (ERα, GATA3)	Monomorphic tumor cells with focal/variable staining for no hormones, or one or more of GH, PRL, βTSH, and/or unit	Focal/variable
			horphic tumor cells with (predominant) and GH l/variable)	Scattered fibrous bodies
			troph tumor component: α-subunit depending on tumor subtype; lactotroph tumor component: PRL (diffuse or paranuclear depending on the subtype)	Tumor subtype characteristics
TPIT-lineage PitNETs				
Corticotroph tumors	Densely granulated corticotroph tumor	TPIT	ACTH and other POMC derivates	Strong, always diffuse
	Sparsely granulated corticotroph tumor			Variable (often diffuse)
	Crooke cell tumor			Perinuclear ring–like cytoplasmic
SF1-lineage PitNETs				
Gonadotroph tumor		SF1, ERα, GATA3	α-subunit, βFSH, βLH, or none	Variable or negative
PitNETs with no distinct cell lineage				
Plurihormonal tumor		Multiple combinations	Multiple combinations in a monomorphous tumor population	Variable
Null cell tumor		None	None	Variable

De 3 colores a 7 tipos de adenoma-----12 tipos de PitNET

El término PitNET genera controversias

Asa et al. Endocrine Pathology (2022) 33:6–26

Table 1 The 2022 WHO classification of pituitary neuroendocrine tumors (PitNETs)

PitNET Type	Subtype	Transcription factors	Hormones	LMWK
PIT1-lineage PitNETs				
Somatotroph tumors	Densely granulated somatotroph tumor	PIT1	GH, α-subunit	Perinuclear
	Sparsely granulated somatotroph tumor	PIT1	GH	Fibrous bodies (> 70%)
Lactotroph tumors	Sparsely granulated lactotroph tumor	PIT1, ERα	PRL (paranuclear dot-like)	Weak or negative
	Densely granulated lactotroph tumor		PRL (diffuse cytoplasmic)	Weak or negative
Mammosomatotroph tumor		PIT1, ERα	GH (predominant), PRL, α-subunit	Perinuclear
Thyrotroph tumor		PIT1, GATA3	α-subunit, βTSH	Weak or negative
Mature plurihormonal PIT1-lineage tumor		PIT1, ERα, GATA3	Monomorphic tumor cells with predominant GH expression and variable PRL, βTSH, and α-subunit	Perinuclear
Immature PIT1-lineage tumor		PIT1 (ERα, GATA3)	Monomorphic tumor cells with focal/variable staining for no hormones, or one or more of GH, PRL, βTSH, and/or α-subunit	Focal/variable
Acidophil stem cell tumor		PIT1, ERα	Monomorphic tumor cells with PRL (predominant) and GH (focal/variable)	Scattered fibrous bodies
Mixed somatotroph and lactotroph tumor*		PIT1, ERα**	Somatotroph tumor component: GH ± α-subunit depending on tumor subtype; lactotroph tumor component: PRL (diffuse or paranuclear depending on the subtype)	Tumor subtype characteristics
TPIT-lineage PitNETs				
Corticotroph tumors	Densely granulated corticotroph tumor	TPIT	ACTH and other POMC derivates	Strong, always diffuse
	Sparsely granulated corticotroph tumor			Variable (often diffuse)
	Crooke cell tumor			Perinuclear ring-like cytoplasmic
SF1-lineage PitNETs				
Gonadotroph tumor		SF1, ERα, GATA3	α-subunit, βFSH, βLH, or none	Variable or negative
PitNETs with no distinct cell lineage				
Plurihormonal tumor		Multiple combinations	Multiple combinations in a monomorphous or plurimorphous population	Variable
Null cell tumor		None	None	Variable

PitNET-Pit1

PitNET-TPIT

PitNET-SF1

PitNET-sin linaje celular distintivo

1. Somatotropo (DG/
2. Lactotropo /EG)
3. Mamosomatotropo
4. Mixto somato-lactotropo
5. Tirotropo
6. Plurihormonal maduro de linaje PIT1
7. Plurihormonal Inmaduro de linaje PI
8. Stem cell acidófilo

1. Corticotropo (DG/EG/Cr)

1. Gonadotropo

1. Plurihormonal
2. Null cell

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2. Classificació

1. Diagnòstics
2. Comunicació
3. Terapèutics
4. Pronòstics

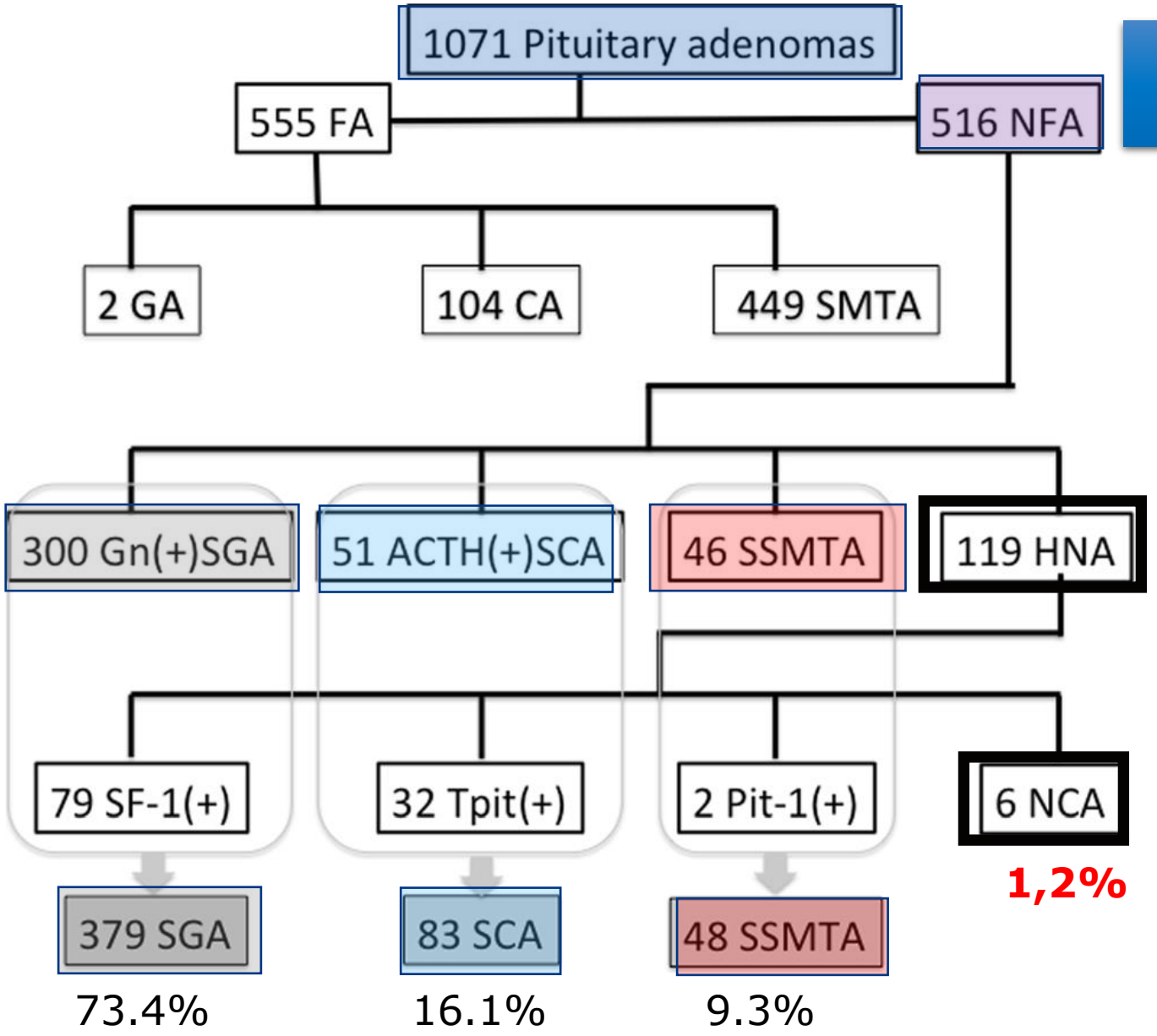
2. Classificació

1. Diagnòstics ✅
2. Comunicació
3. Terapèutics
4. Pronòstics

2. Classificació

1. Diagnòstics ✅
2. Comunicació ✅
3. Terapèutics
4. Pronòstics

Vall d'Hebron



Primera lliçó
NFA ≠ a Gonadotropo o SF1

Hormone-Negative Adenomas

Segona lliçó
FT milloren la tipificació

Hiroshi Nishioka et al. Endocr Pathol (2015)

Vall d'Hebron

2. Classificació

1. Diagnòstics 
2. Comunicació 
3. Terapèutics 

4. Pronòstics

2. Classificació

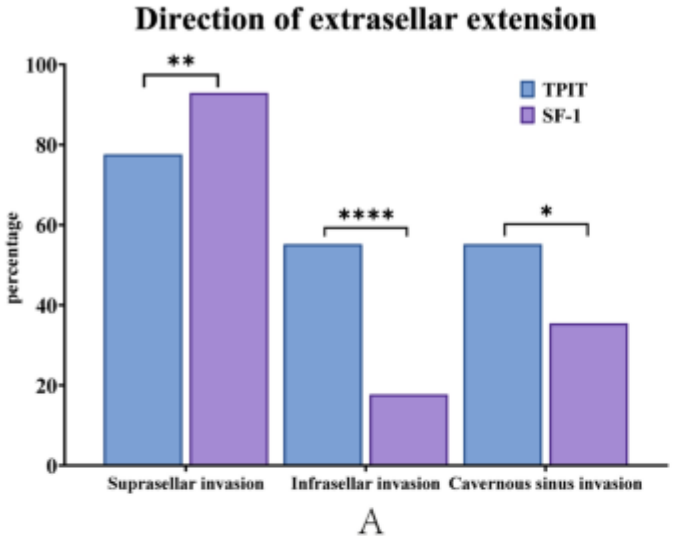
1. Diagnòstics 
2. Comunicació 
3. Terapèutics 

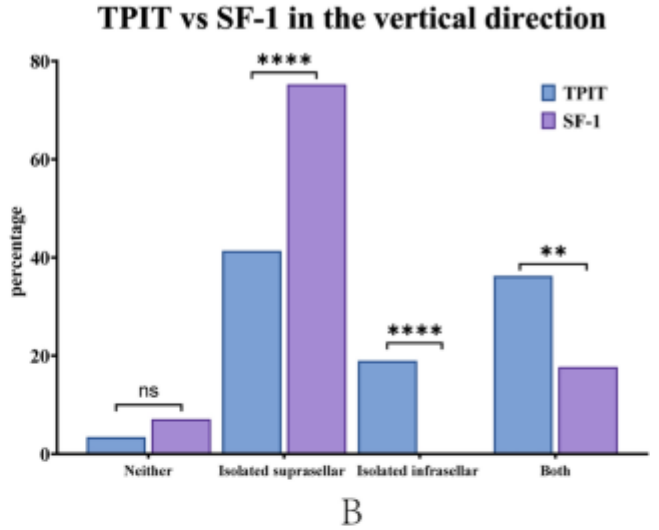
4. Pronòstics 

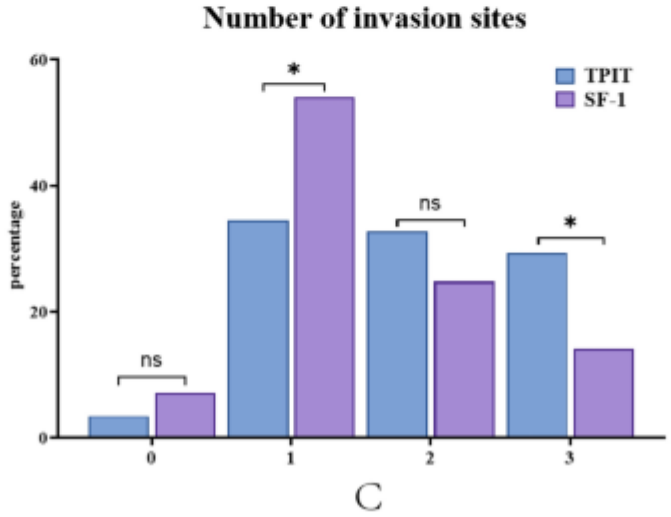
CAP SISTEMA DE QUALIFICACIÓ O ESTRATIFICACIÓ PRONÒSTICA

Vall d'Hebron

Variable	TPIT	SF-1	*p* value
Number of patients	58	113	
Female	47(81.03)	31(27.43)	< 0.0001
Age(year)	48.67 ± 12.31	53.90 ± 12.96	0.0120
Mean tumor diameter(mm)	28	26	ns
Extrasellar extension	56(96.55)	105(92.92)	ns
Suprasellar extension			
Any	45(77.59)	105(92.92)	0.0061
Isolated	24(41.38)	85(75.22)	< 0.0001
Infrasellar extension			
Any	32(55.17)	20(17.70)	< 0.0001
Isolated	11(18.97)	0(0)	< 0.0001
Cavernous sinus invasion			
Any	32(55.17)	40(35.40)	0.0148
Isolated	0(0)	0(0)	ns
Multiple regions of extension	36(62.07)	44(38.94)	0.0058







The expression of TFs affects the extrasellar growth pattern of NFPAs.

- **TPIT tumors exhibit a higher propensity for bone invasion**
- **SF-1 suprasellar**

Jiakun Xu et al. Scientific Reports January 2025

3. A propòsit d'un cas

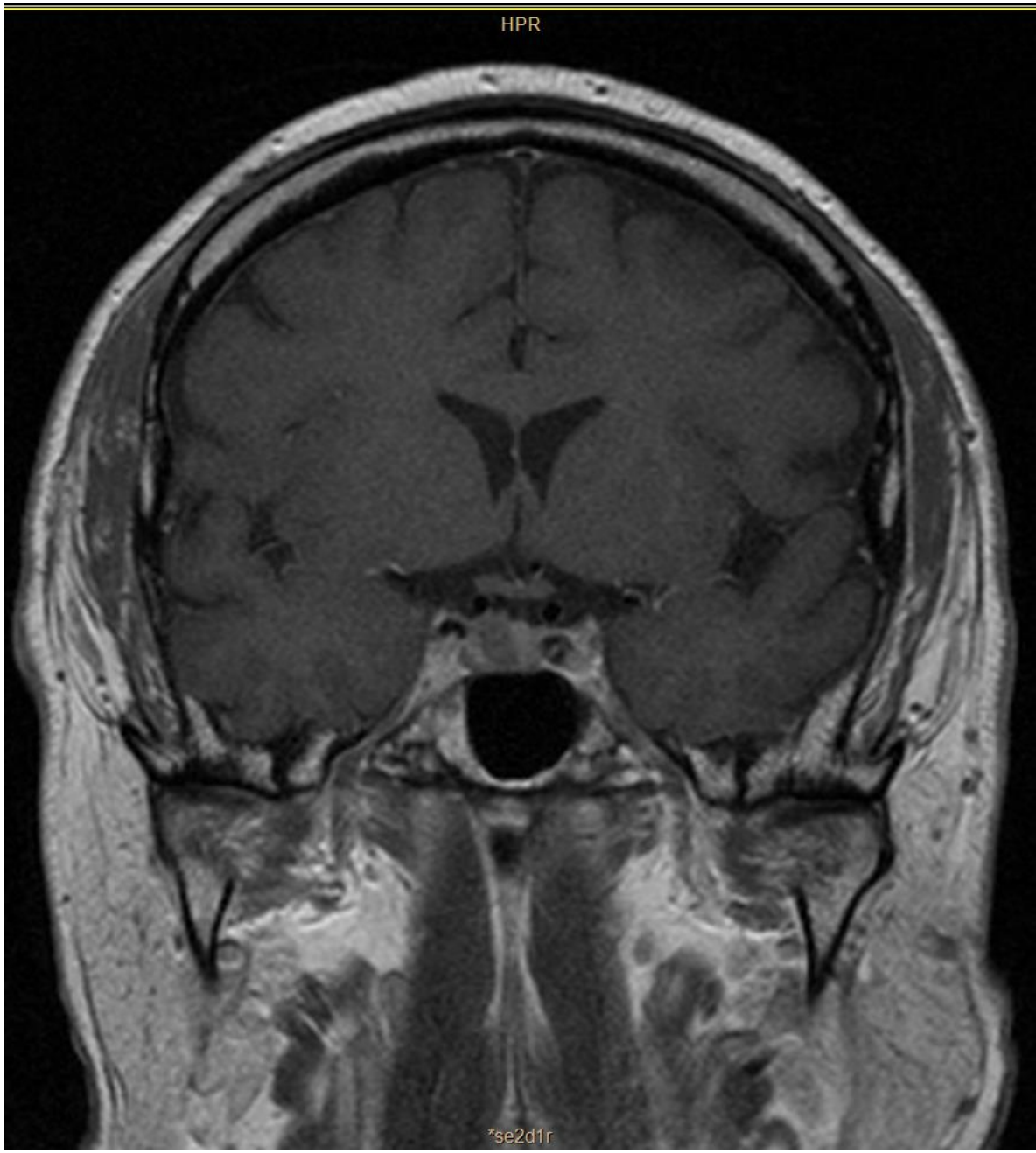
♂ 61 anys

- Dx incidental arran de PTNC 2014
- Lesió de 9-10mm
- PRL 406ng/dL N< 17ng/mL
- **Que li diem?**

- **Tractament CBG fins a 7mg/sem**

→sense normalitzar PRL

→Sense reducció de tamany



CABERGOLINE RESITANCE
Failure to achieve normal PRL levels
Failure to achieve tumor size reduction of at least 50 % with maximal conventional doses of medication (2.5 mg/week of cabergoline)

Mark E. Molitch J Neurooncol (2014)

Long-term Follow-up of 84 Patients With Giant Prolactinomas—A Swedish Nationwide Study

Christos Himonakos,[1,2] Pia Burman,[3] Henrik Borg,[4] Per Dahlqvist,[5] Britt Edén Engst
Bertil Ekman,[7] Louise Emilsson,[8,9,10] Daniel S. Olsson,[11,12,13] Oskar Ragnarsson,[11,12]
Jeanette Wahlberg,[14,15] Anna-Karin Åkerman,[1,14] Charlotte Höybye,[1,16]
and Katarina Berinder[1,16]

Table 3. Multivariate analysis of the variables associated with combined biochemical and tumor response at the last follow-up in patients with primary dopamine agonist treatment (n = 79)

	OR (95% CI)	*P*-value
Initial serum PRL	1.00 (1.00-1.00)	.66
Initial max tumor diameter	0.98 (0.89-1.1)	.62
Multimodal treatment	0.21 (0.02-1.9)	.16
PRL <2xULN at year 1	30.5 (4.9-189.8)	<.001
Reduction of max tumor diameter ≥20% at year 1	14.8 (1.8-122.9)	.012

Abbreviations: CI, confidence interval; OR, odds ratio; PRL, prolactin; ULN, upper level of normal.

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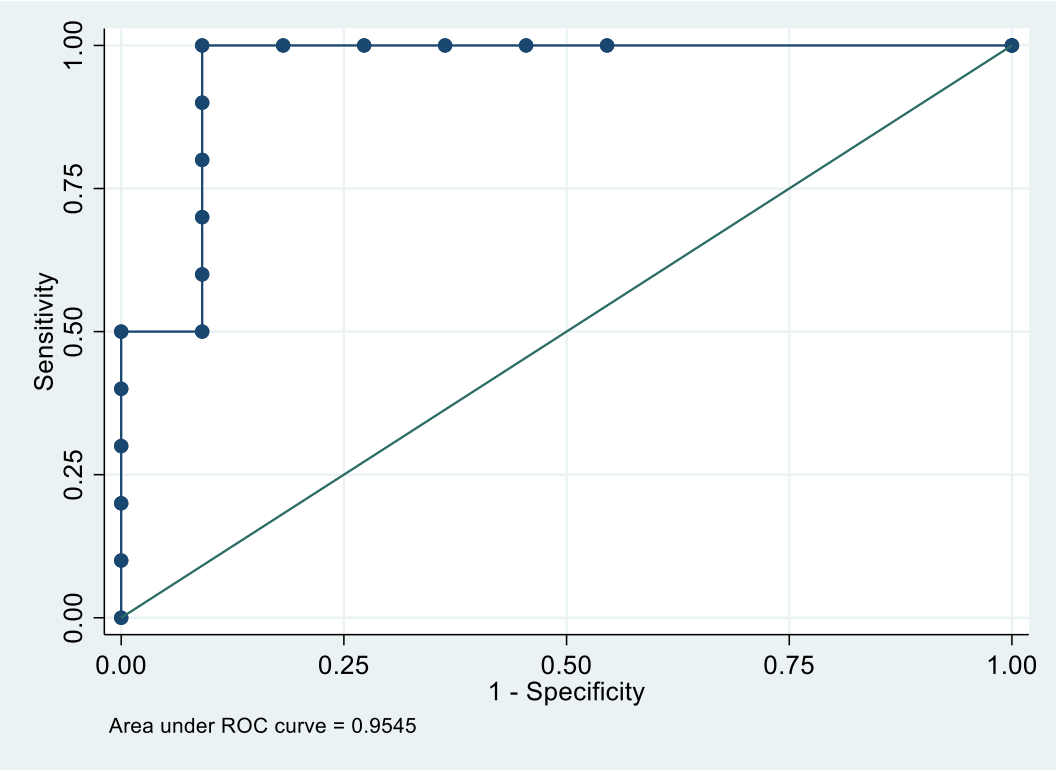

Shrinkage by the third month predicts long-term response of macroprolactinoma after cabergoline

Betina Biagetti[1], Silvana Sarria-Estrada[2,5], Yiken Karelys Ng-Wong[2], Elena Martinez-Saez[3], Anna Casteràs[1], Esteban Cordero Asanza[4], Irene Hernandez[1], Marina Giralt-Arnaiz[6] and **Rafael Simò[1]**

[1]Diabetes and Metabolism Research Unit, Vall d'Hebron University Hospital and Vall d'Hebron Research Institute (VHIR), Universidad Autónoma de Barcelona, Barcelona, Spain, [2]Neuroradiology Section, Radiology Department, [3]Pathology Department, [4]Neurosurgery and Neurotraumatology, Vall d'Hebron University Hospital, Barcelona, Spain, [5]Department of Autonomous, University of Barcelona (UAB), Barcelona, Spain, and [6]Department of Biochemistry, Vall d'Hebron University Hospital, Barcelona, Spain

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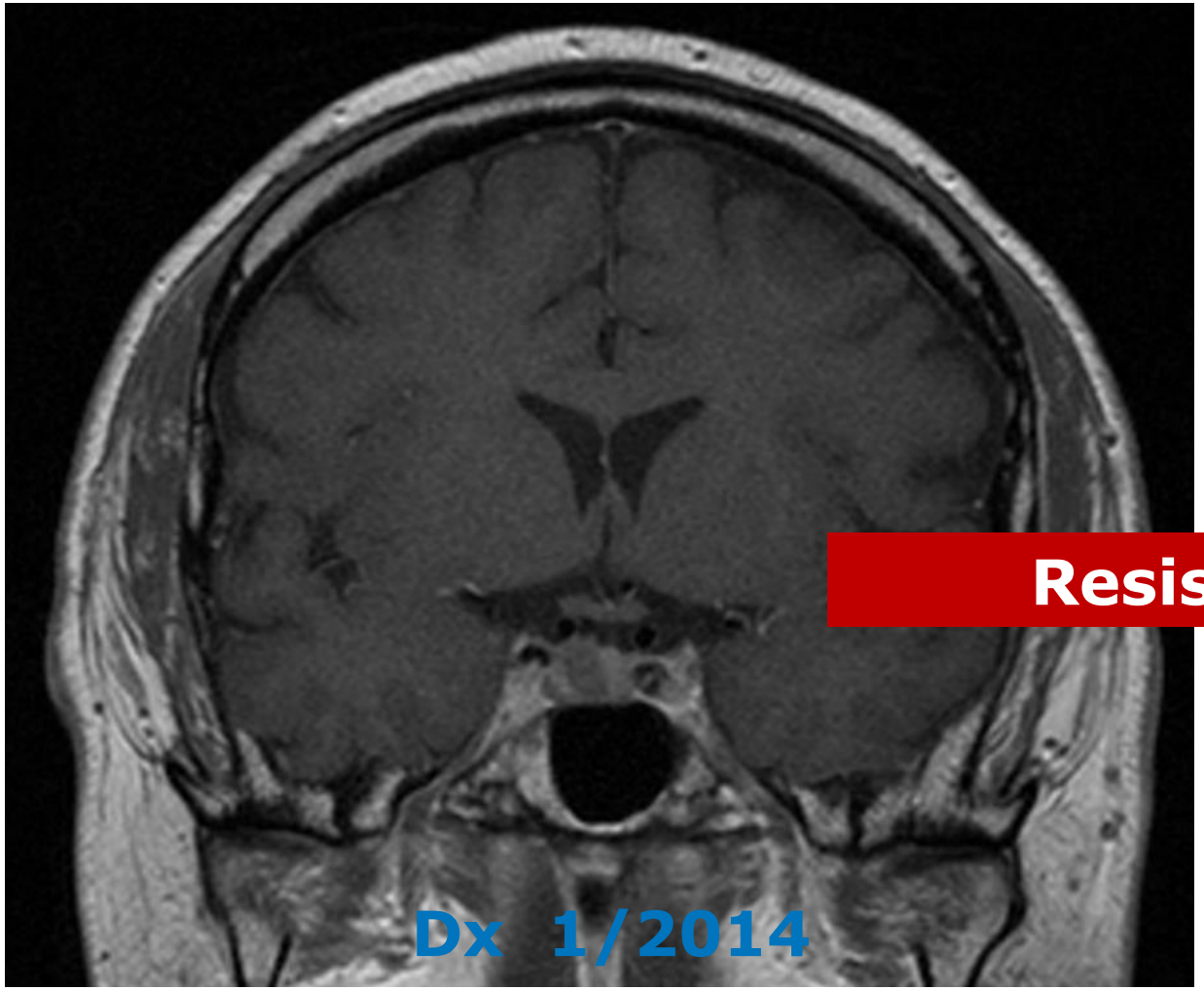
European Journal of Endocrinology **(2021) 185, 1–9**

PUNTO DE CORTE OPTIMO
30% de reducción de volume al 3er mes

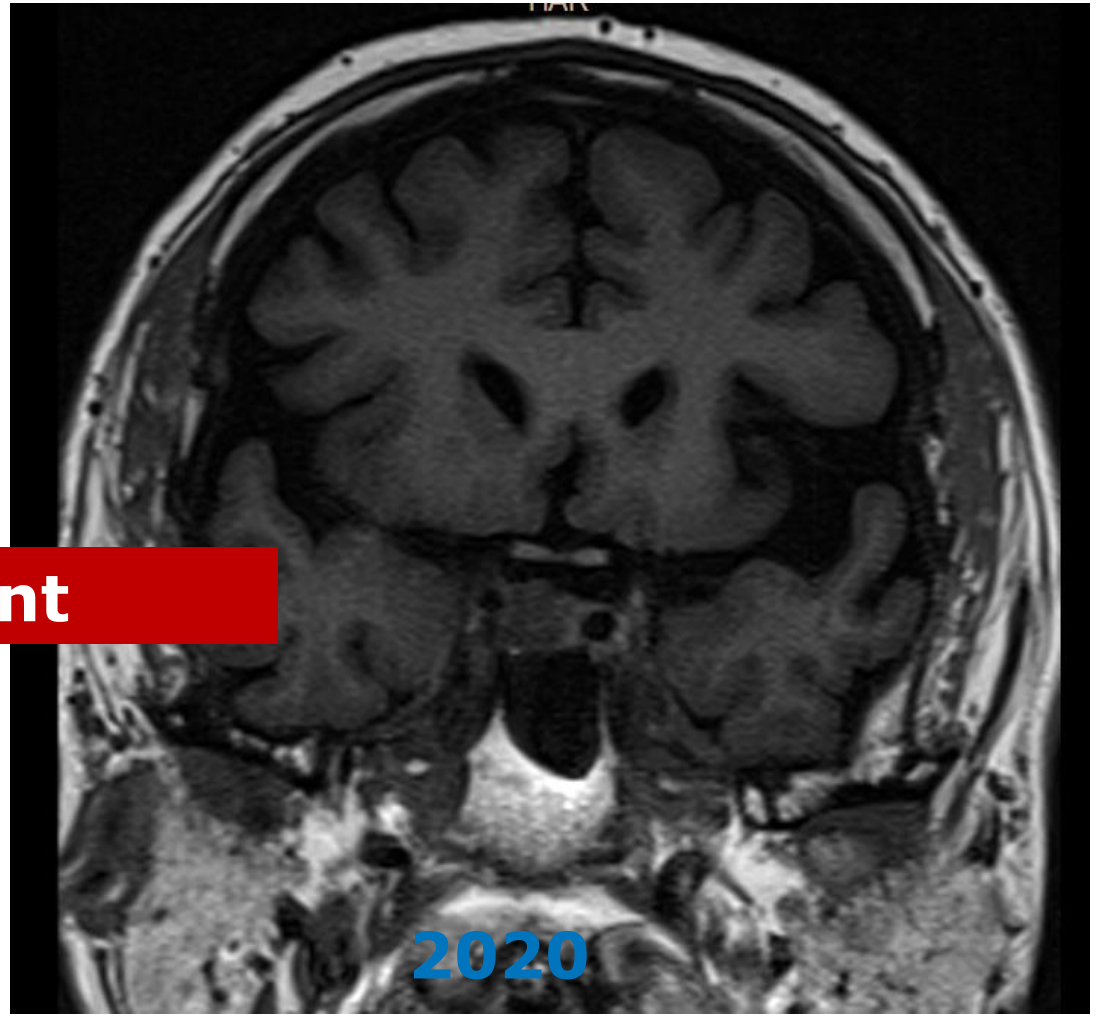
ROC	-- Binomial Exact --			
Obs	Area	Std. Err.	[95% Conf.	Interval]
30	0.9545	0.0479	0.76184	0.99880

REG LOG edad, sexo, invasión de los senos nasales, volumen tumoral basal, dosis de CBG, niveles de prolactina y porcentaje de reducción del volumen tumoral a los 3-4 meses de tratamiento.

Vall d'Hebron



Resistent



PRL 406ng/mL N< 17ng/mL

Vall d'Hebron

INFORME ANATOMIA PATOLÒGICA (VH - 20 - B - 021386)

Mostres remeses
A Biòpsia d'hipòfisi

P:26.08.2020 09:22:52 **R:**26.08.2020 15:11:55

DESCRIPCIÓ MACROSCÒPICA

A) "Lesión hipofisaria, resección":
Se remiten varios fragmentos irregulares de tejido de coloración marronácea y consistencia elástica que en conjunto miden 2 x 0,8 x 0,3 cm. IT/1.

DESCRIPCIÓ MICROSCÒPICA

Fragmentos de tejido hipofisario con alteración difusa de la arquitectura, con rotura de la trama reticulínica y proliferación en sábana de células con núcleos redondos, de mediano tamaño, nucleolo prominente y citoplasmas claros eosinófilos pálidos. Ausencia de actividad mitósica relevante, atipias o necrosis.
Se observa expresión difusa de prolactina (intensa), y en menor medida GH y ACTH (parcheadas). Ausencia de expresión de LH, FSH y TSH. Se observa una pequeña banda de glándulas de arquitectura preservada que expresa las seis hormonas estudiadas, T-Pit y SF1. Ausencia de sobreexpresión de p53. El índice de proliferación celular (Ki67) es elevado, alcanzado el 20% en algunas áreas. Ausencia de expresión de citoqueratina CAM5.2 en la lesión, en el tejido preservado sigue un patrón densamente granular. Expresión intensa y difusa de Pit1 en la lesión.

DIAGNÒSTIC

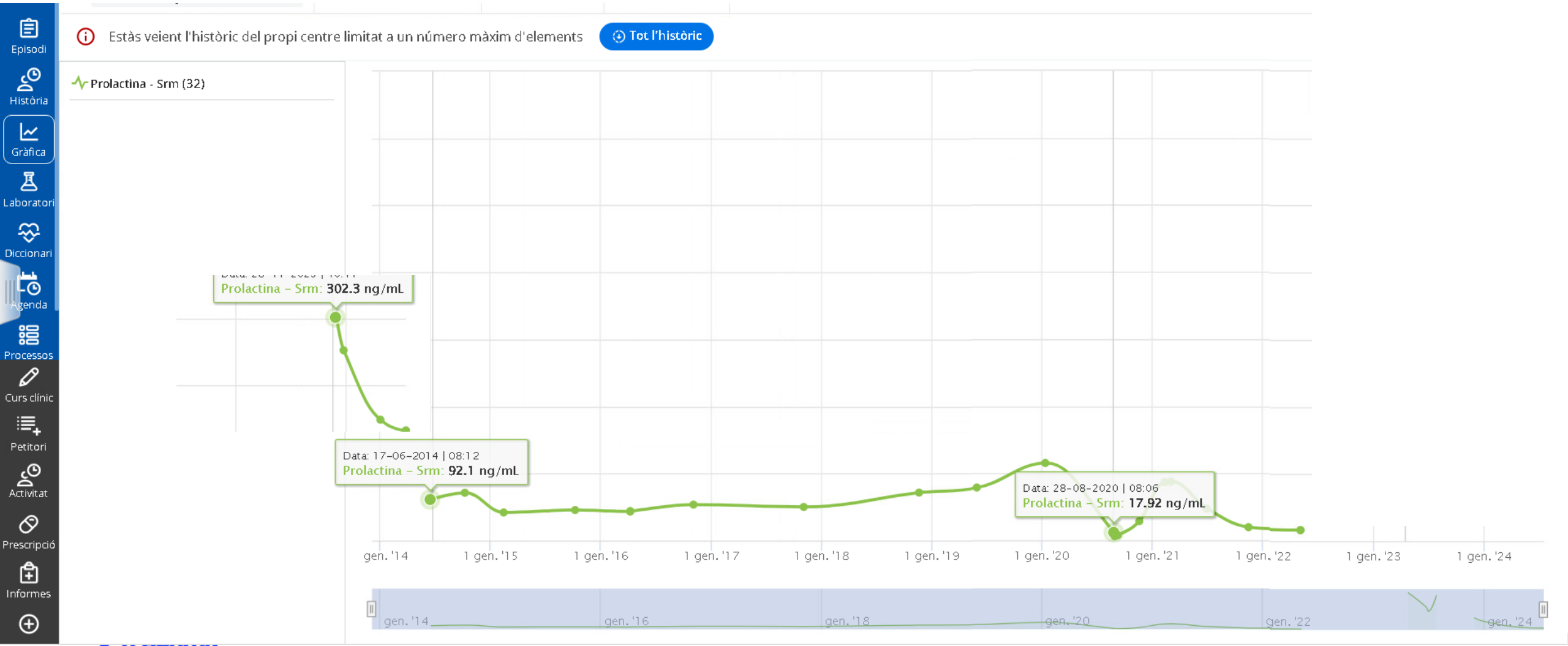
"Lesión hipofisaria, resección":

Adenoma lactotropo con elevado índice de proliferación celular (expresión difusa de prolactina, parcheada de GH y ACTH, expresión difusa de Pit1).

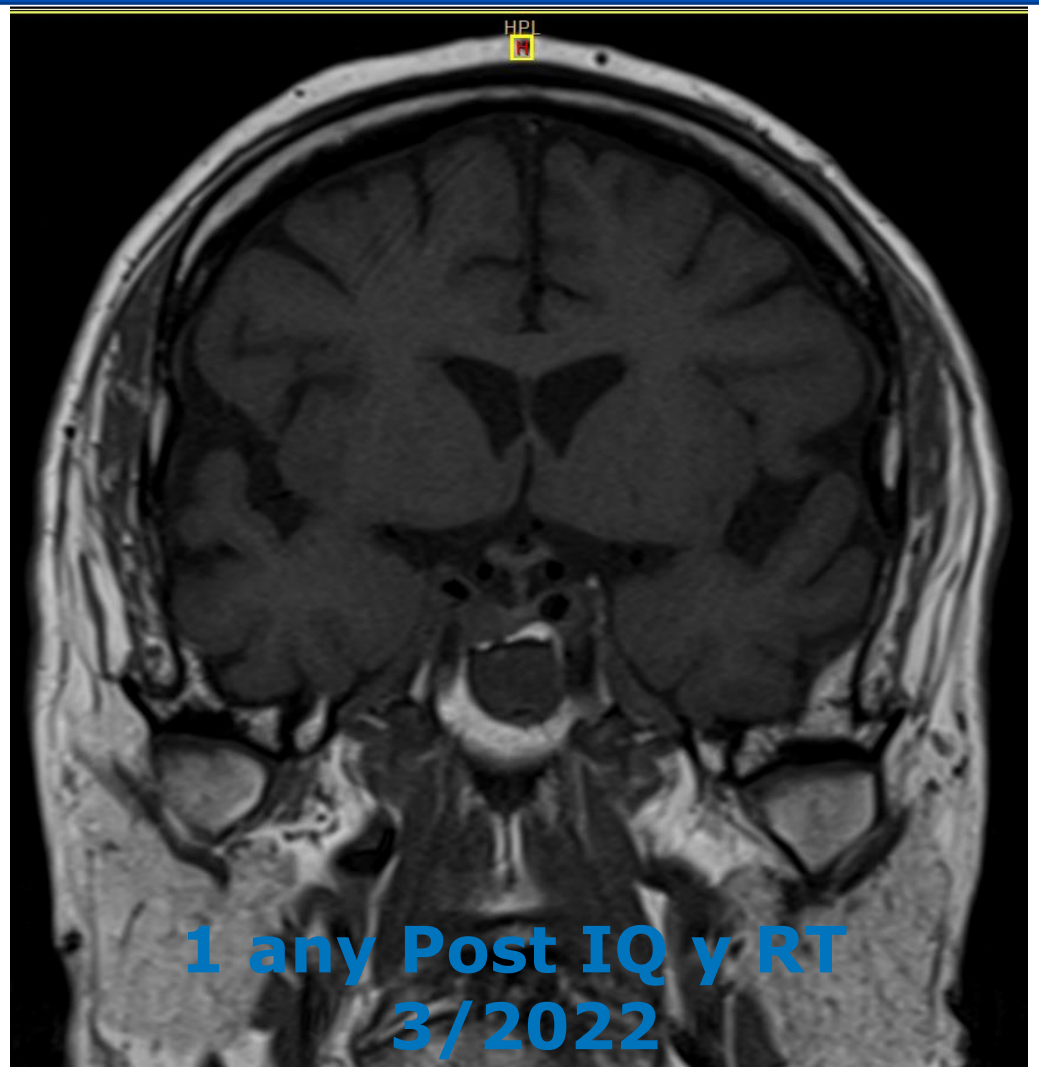
EQUIP DIAGNÒSTIC

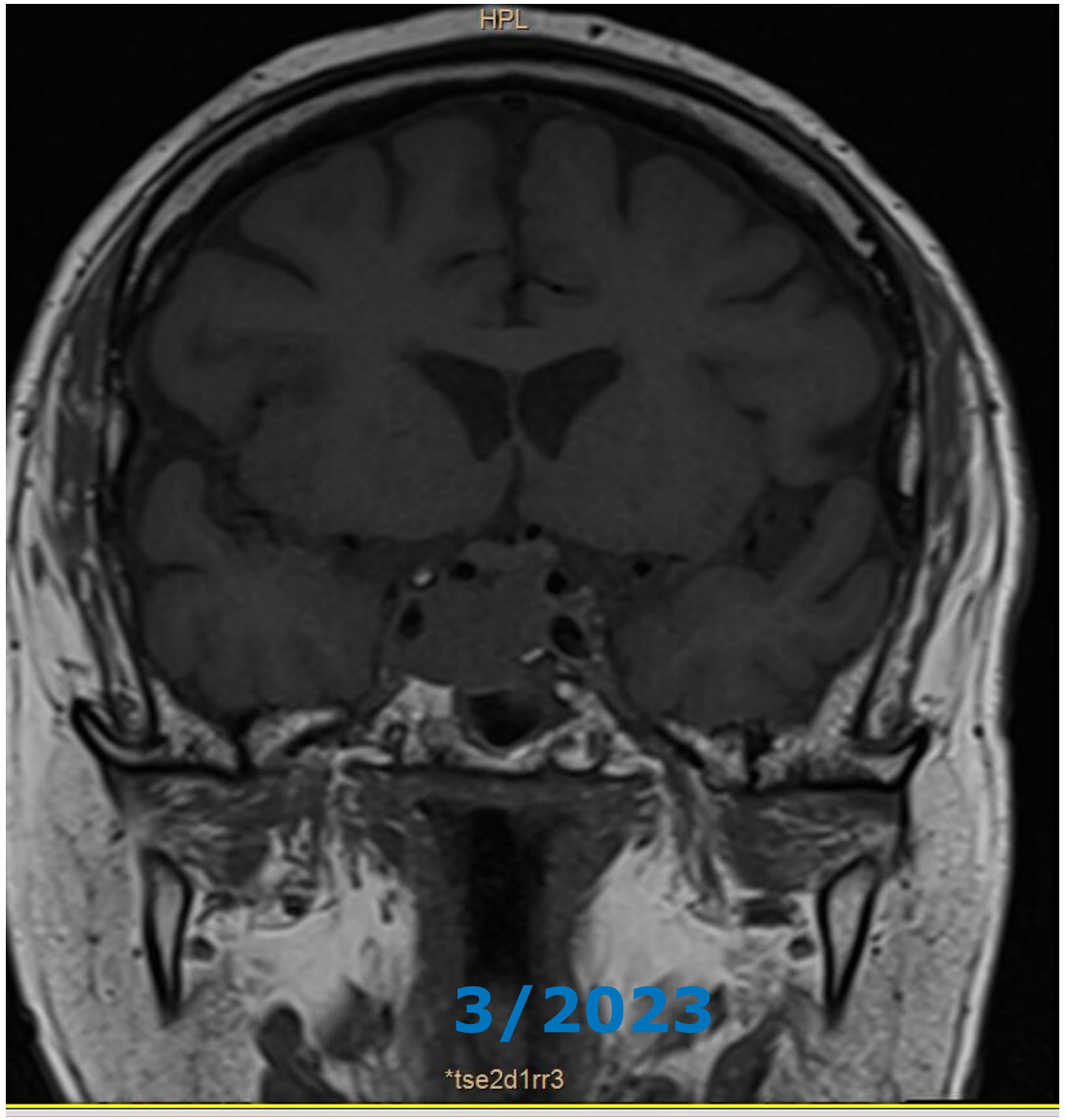
Patòleg : MARTINEZ SAEZ, ELENA ANTIMA
Resident : MELGAR RIVERA, DORIS SOFIA

IQ 01/2021 +
Radioteràpia 4/2021


Episodi
Història
Gràfica
Laboratori
Diccionari
Agenda
Processos
Curs clínic
Petitori
Activitat
Prescripció
Informes
Estàs veient l'històric del propi centre limitat a un número màxim d'elements
Tot l'històric
Prolactina - Srm (32)
Prolactina – Srm: 302.3 ng/mL
Data: 17-06-2014 | 08:12
Prolactina – Srm: 92.1 ng/mL
Data: 28-08-2020 | 08:06
Prolactina – Srm: 17.92 ng/mL
gen. '14
1 gen. '15
1 gen. '16
1 gen. '17
1 gen. '18
1 gen. '19
1 gen. '20
1 gen. '21
1 gen. '22
1 gen. '23
1 gen. '24

IQ 01/2021
Radioteràpia 4/2021





Prolactina 38-50ng/mL N< 17ng/mL

Prolactina 580-950 ng/mL N< 17ng/mL

MICROSCÒPIA

A) Pequeños fragmentos de tejido hipofisario que muestra, la mayoría de ellos, una alteración de la arquitectura, con rotura de la trama reticulínica y proliferación en sábana de células con núcleos redondos, de mediano tamaño, cromatina granular fina y citoplasmas basófilos o cromófobos. No se observa actividad mitótica relevante, atipias nucleares ni áreas de necrosis.

Se observa expresión nuclear difusa de Pit1 en las áreas de lesión, sin expresión de T-Pit ni SF1. Expresión de GATA3 y de receptores de estrógenos en ocasionales células. Expresión difusa de prolactina. Se encuentran focos de GH, FSH y ACTH en áreas que conservan el patrón de reticulina y podrían corresponder a áreas de hipófisis preservada. Ausencia de expresión de LH y TSH. Ausencia de sobreexpresión de p53 (inferior al 1%). El índice de proliferación celular (Ki67) alcanza el 30% en las áreas de mayor actividad. La expresión de citoqueratina CAM5.2 es prácticamente nula en las áreas de lesión.

DIAGNÒSTIC

A) **"Hipófisis, biopsia":**

Adenoma hipofisario/tumor neuroendocrino pituitario (PitNET) de linaje Pit1 con expresión predominante de prolactina y elevado índice de proliferación celular.

- Ausencia de hipermetilación del promotor del gen MGMT.

Noa: la lesión parece corresponder a un adenoma lactotropo densamente granular por el perfil de expresión de factores de transcripción y hormonas hipofisarias, sin embargo presenta un índice de proliferación celular inusualmente alto para un adenoma hipofisario.

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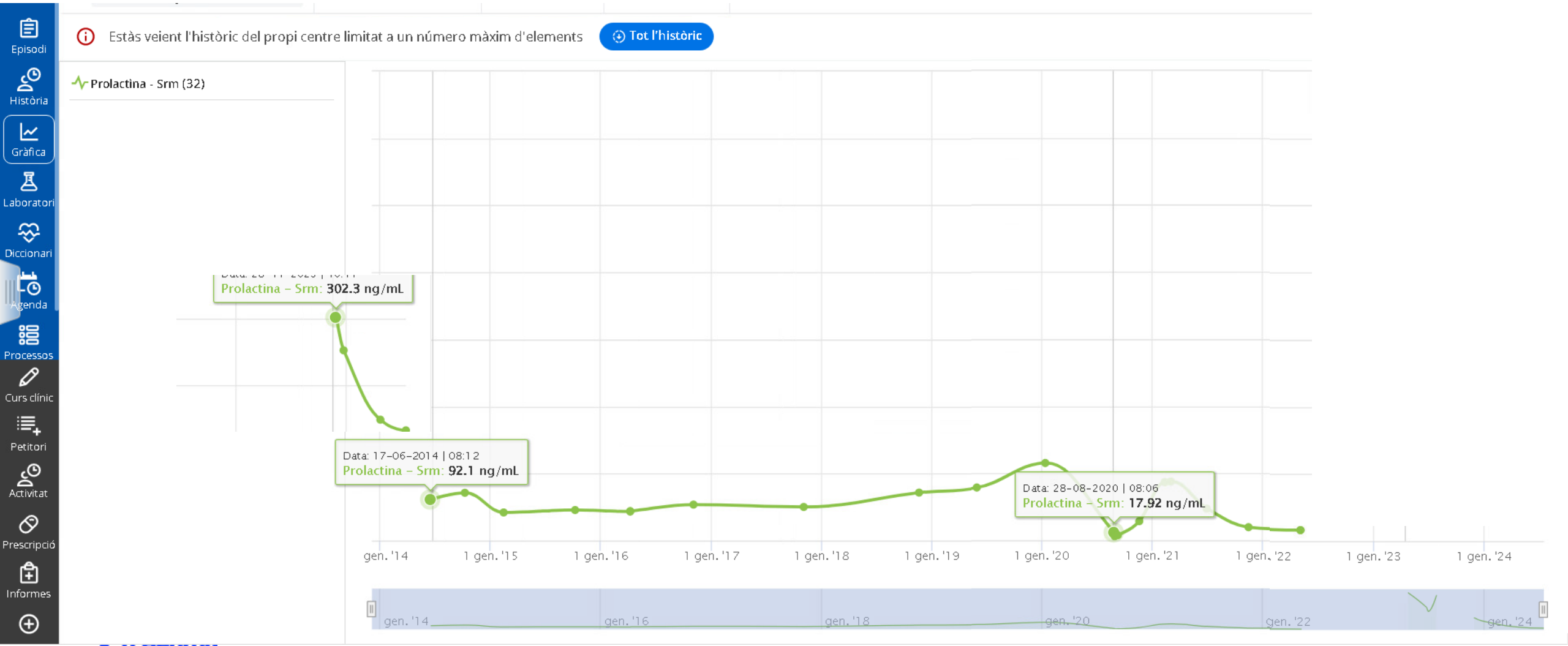
- **Pasireotide 3 mesos** sense resposta ni PRL ni mida
- MGMT va ser no metilat però igualment es va iniciar protocol de quimioteràpia amb **capecitabina i temozolamida**
- Després de 3 cicles, la RMN va mostrar reducció de la lesió juntament amb reducció de les concentracions de prolactina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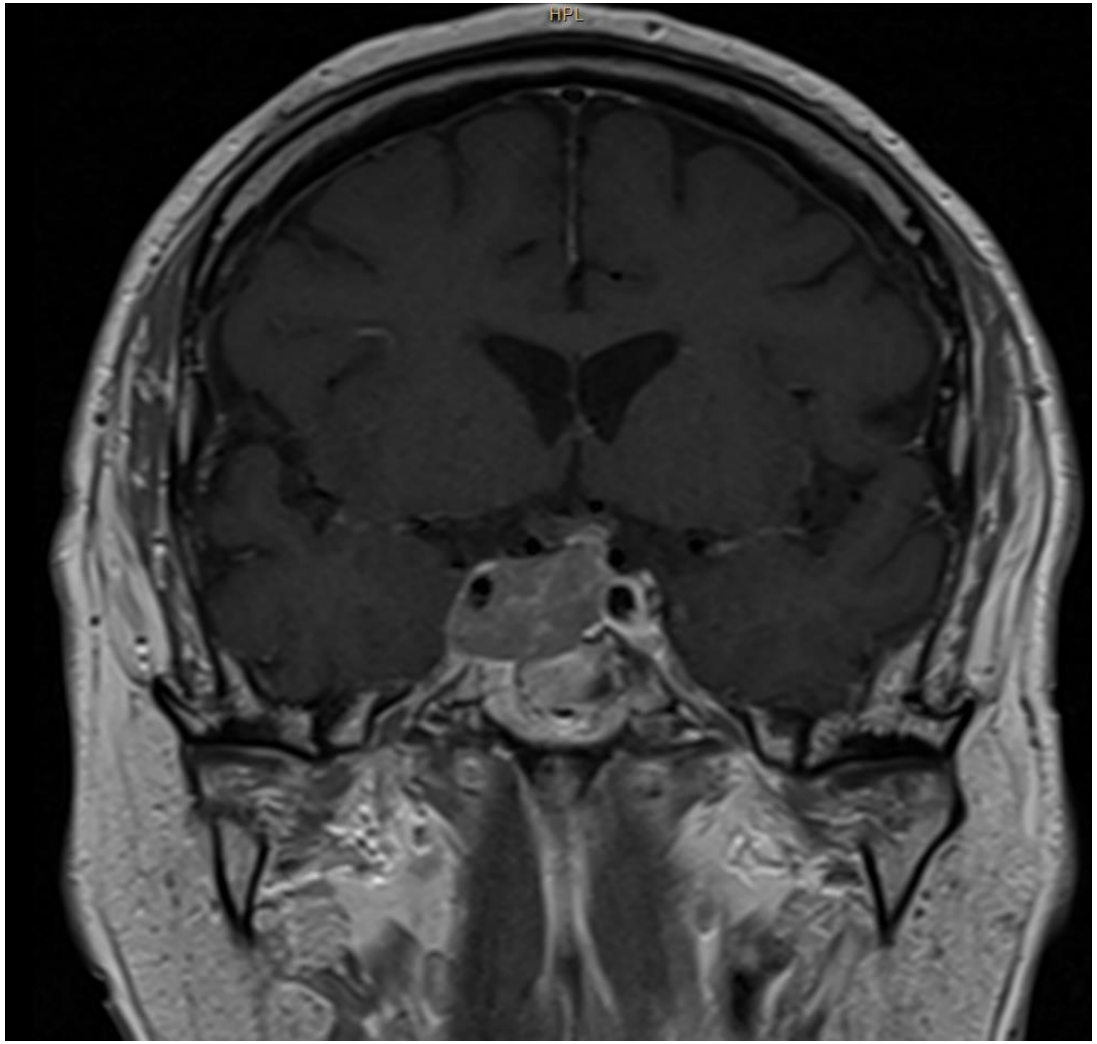
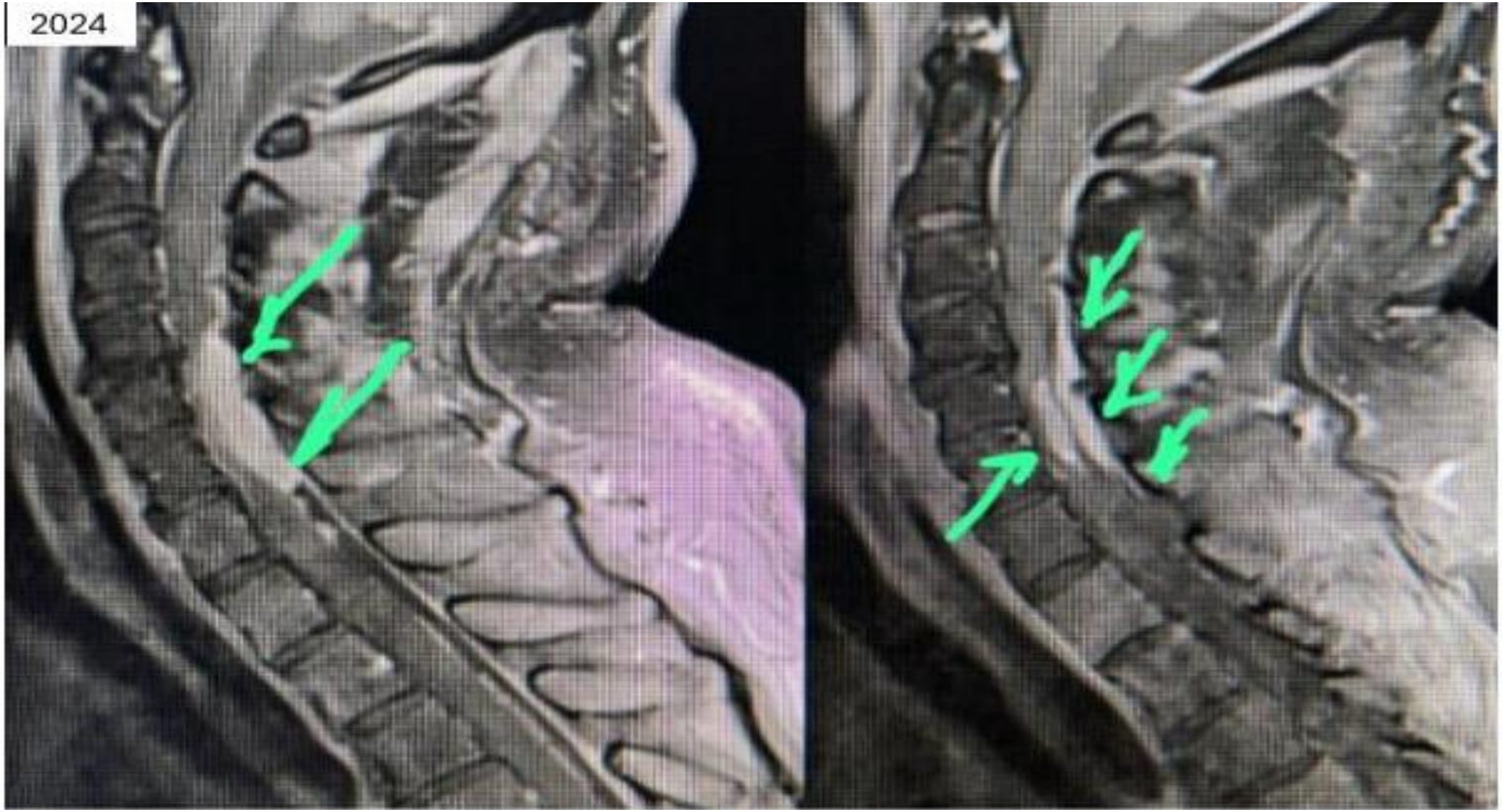
1 gen. '20
1 gen. '21
1 gen. '22
1 gen. '23
1 gen. '24

2na IQ 4/2023



2na IQ 10/2023 + QT

- **El maig del 2024, el pacient inicia amb cervicàlgia associat a tetraparèsia progressiva fins al punt de no poder caminar**



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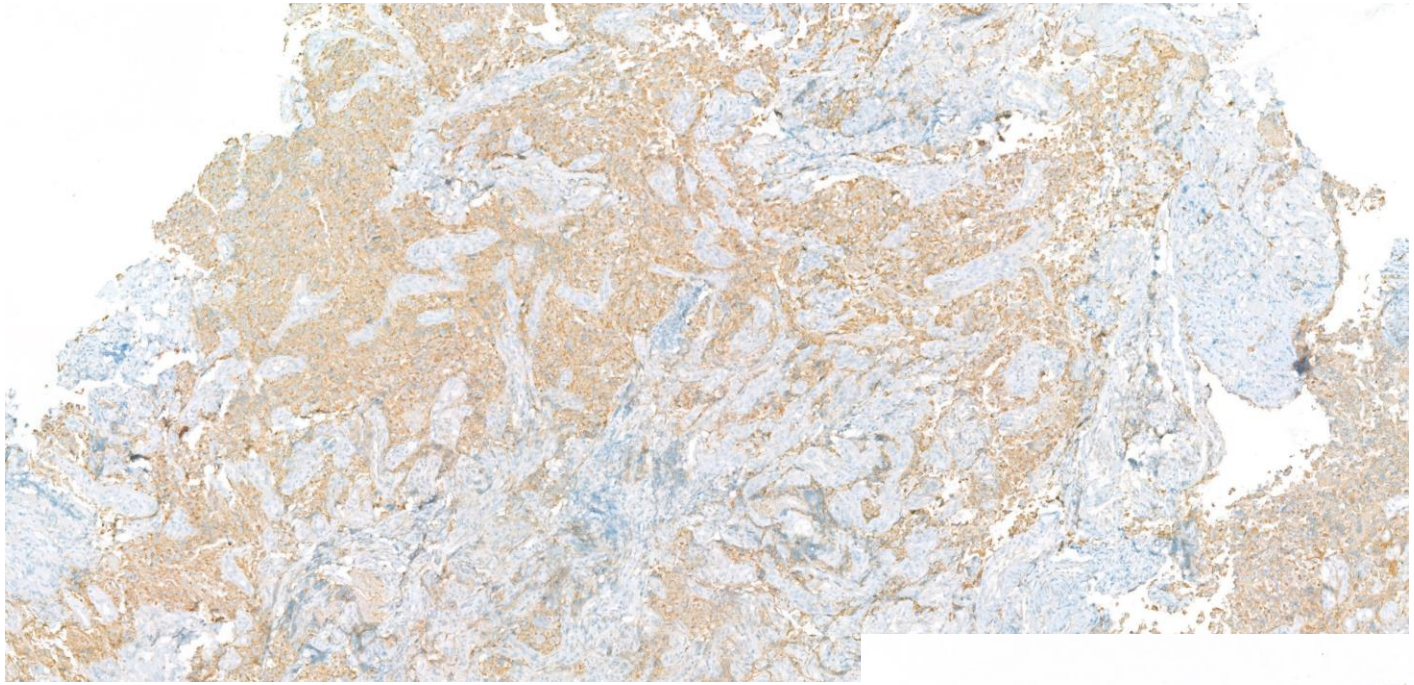
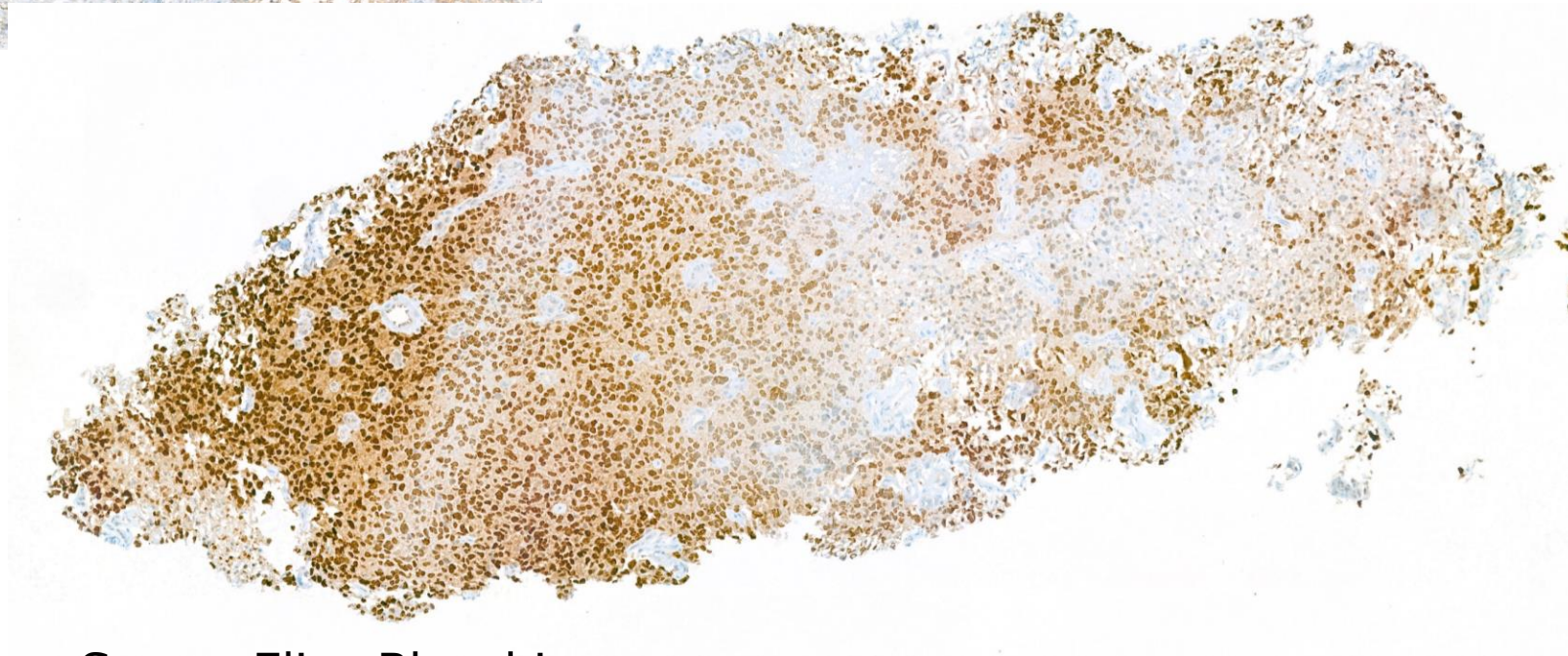


Prolactina



Pit1

Imagen facilitada por Elena Martinez-Saez y Elisa Blanchi

Alertes

1. Home
2. **Edat NO**
3. Resistent a CAB
4. **Mida NO**
5. **La actual classificació no va ajudar a esbrinar el pronòstic**
6. **Ki-67 - DG**

Classificació

1. Diagnòstics 
2. Comunicació 
3. Terapèutics 

4. Pronòstics 

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3. Conclusions

1. El coneixement de les **lesions hipofisiàries** s'ha incrementat de manera exponencial durant els darrers anys.
2. Els factors de transcripció (FT) hipofisiaris **permeten tipificar actualment de forma correcta** més del 95% de les lesions.
3. La actual classificació no te implicacions pronòstiques evidents
4. Necessitem urgentment **millorar marcadors pronòstics**

Vall d'Hebron

Moltes gracies

CONTACTE:

betinaloys.biagetti@vallhebron.cat

BetinaBiagetti

Vall d'Hebron