Disclosures

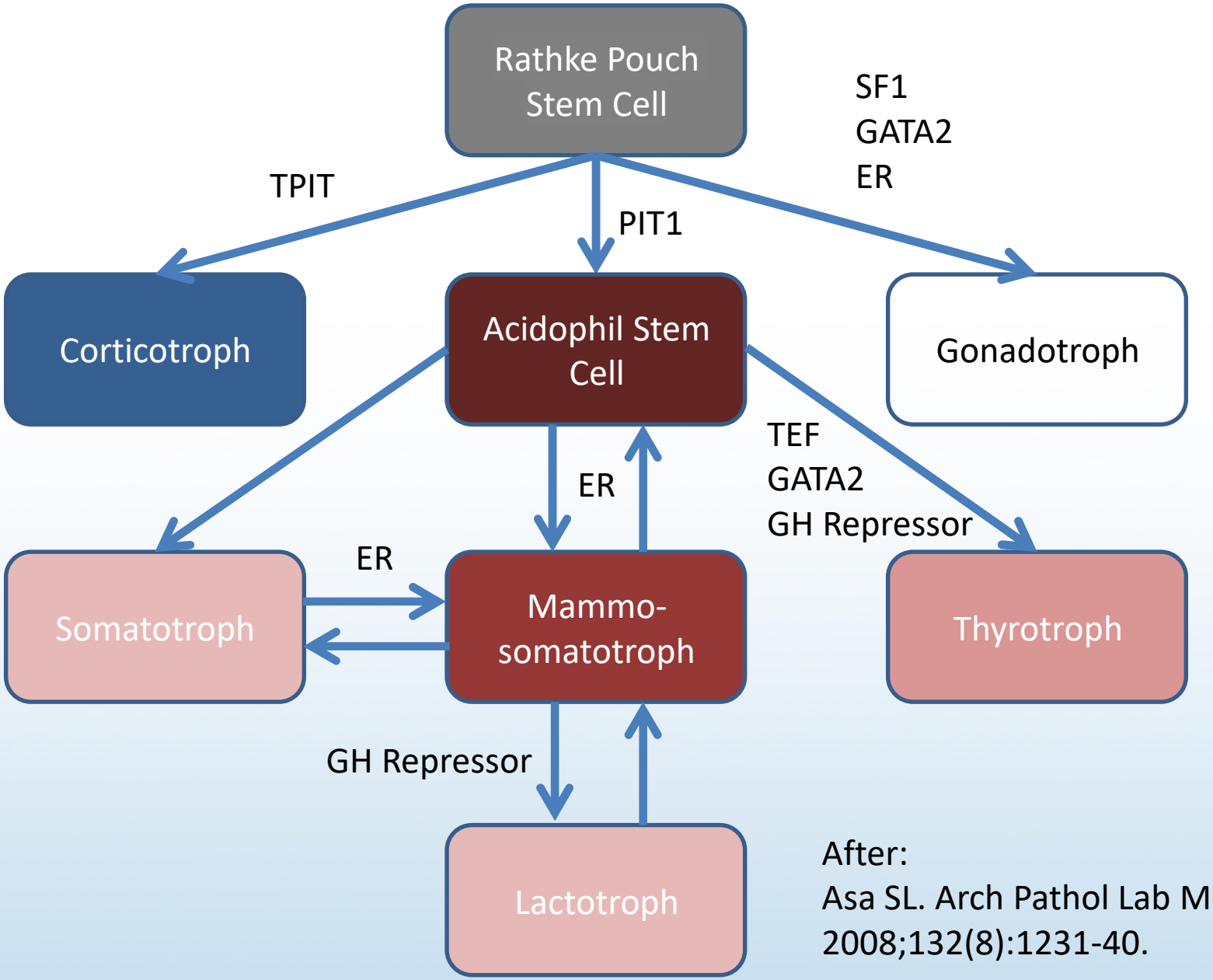
- I have no relevant financial relationships to disclose

Learning Objectives

- Explain the general structure of the WHO PitNET/pituitary adenoma classification and the special considerations needed in defining a classification with overlapping groups.
- Outline the most important limitations to the current WHO classification of PitNET/pituitary adenoma.
- Describe the relationship between falsifiability and classification, and list 3-4 common sources of ambiguity in our current tumor classifications.

Properties of PitNET/Pituitary Adenoma

- Neuroendocrine tumor with variable differentiation in the fashion of anterior pituitary cells
- Three families: SF1, TPIT, PIT1
- Overlap within and between families is a feature, not a bug
  - See especially Dottermusch (PMID: 38228887) for SF1+/PIT1+ tumors
  - See especially Asa (PMID: 39579326) for SF1+/TPIT+ tumors



After:
Asa SL. Arch Pathol Lab Med 2008;132(8):1231-40.

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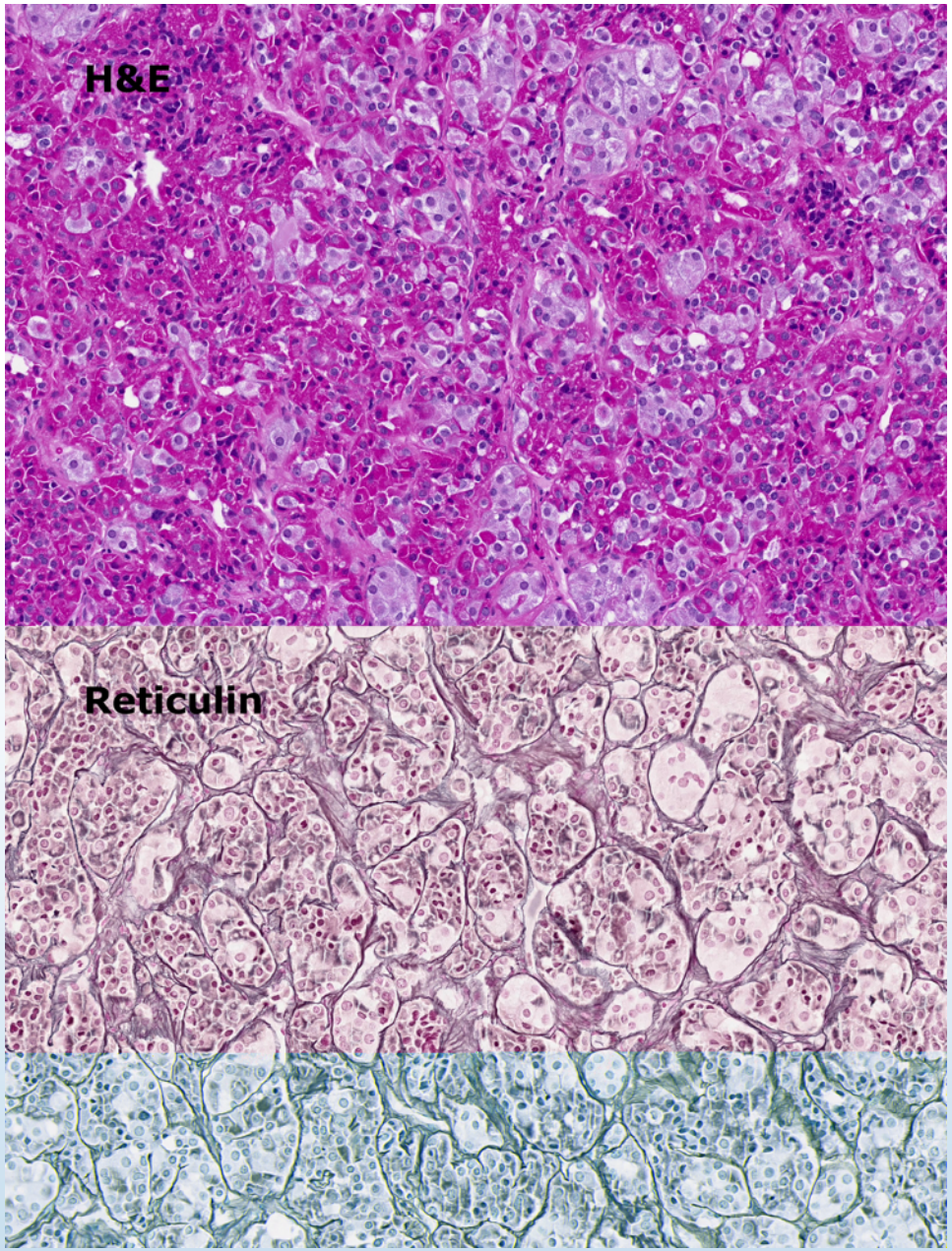
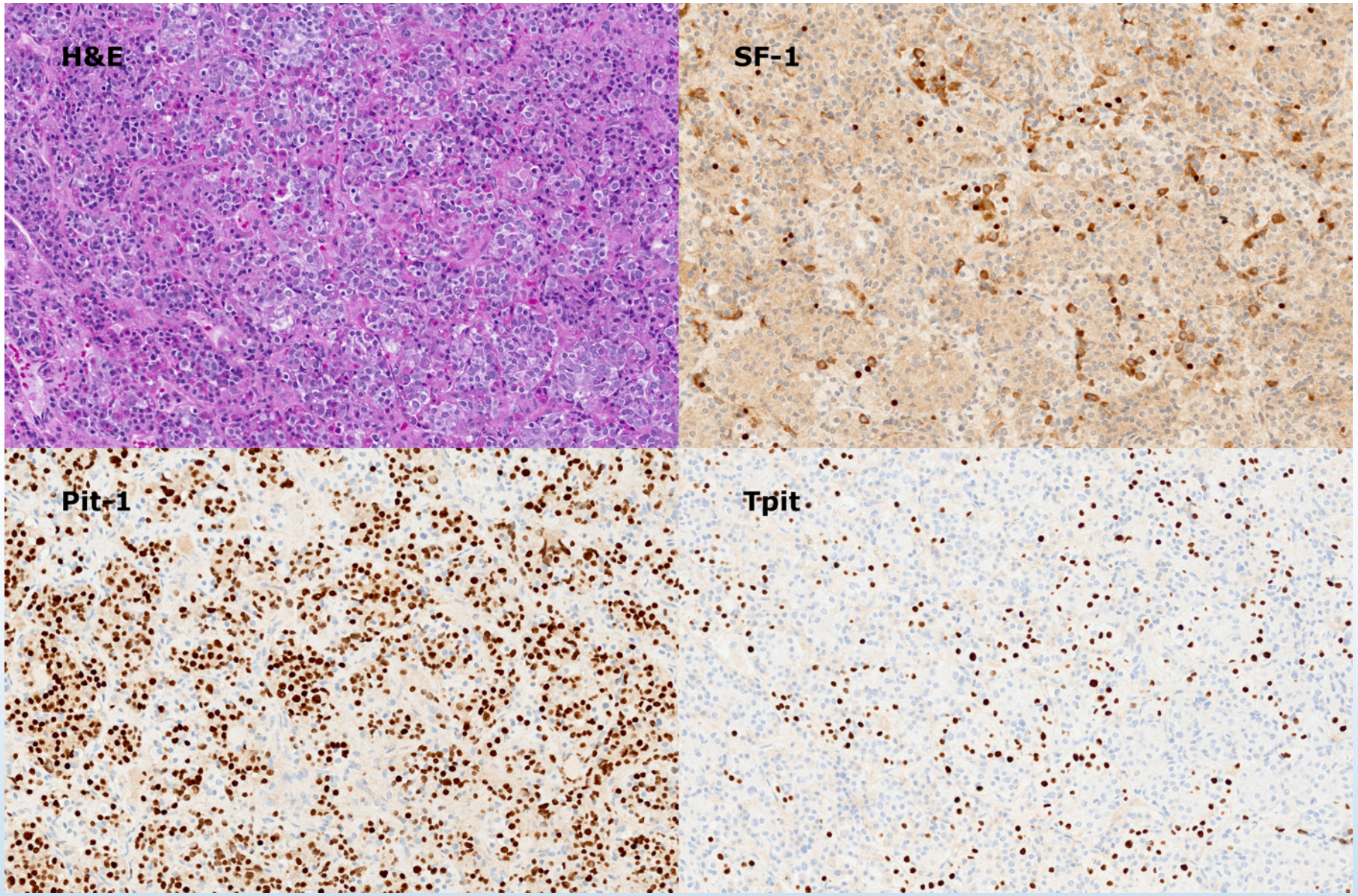


Normal anterior pituitary



Normal anterior pituitary

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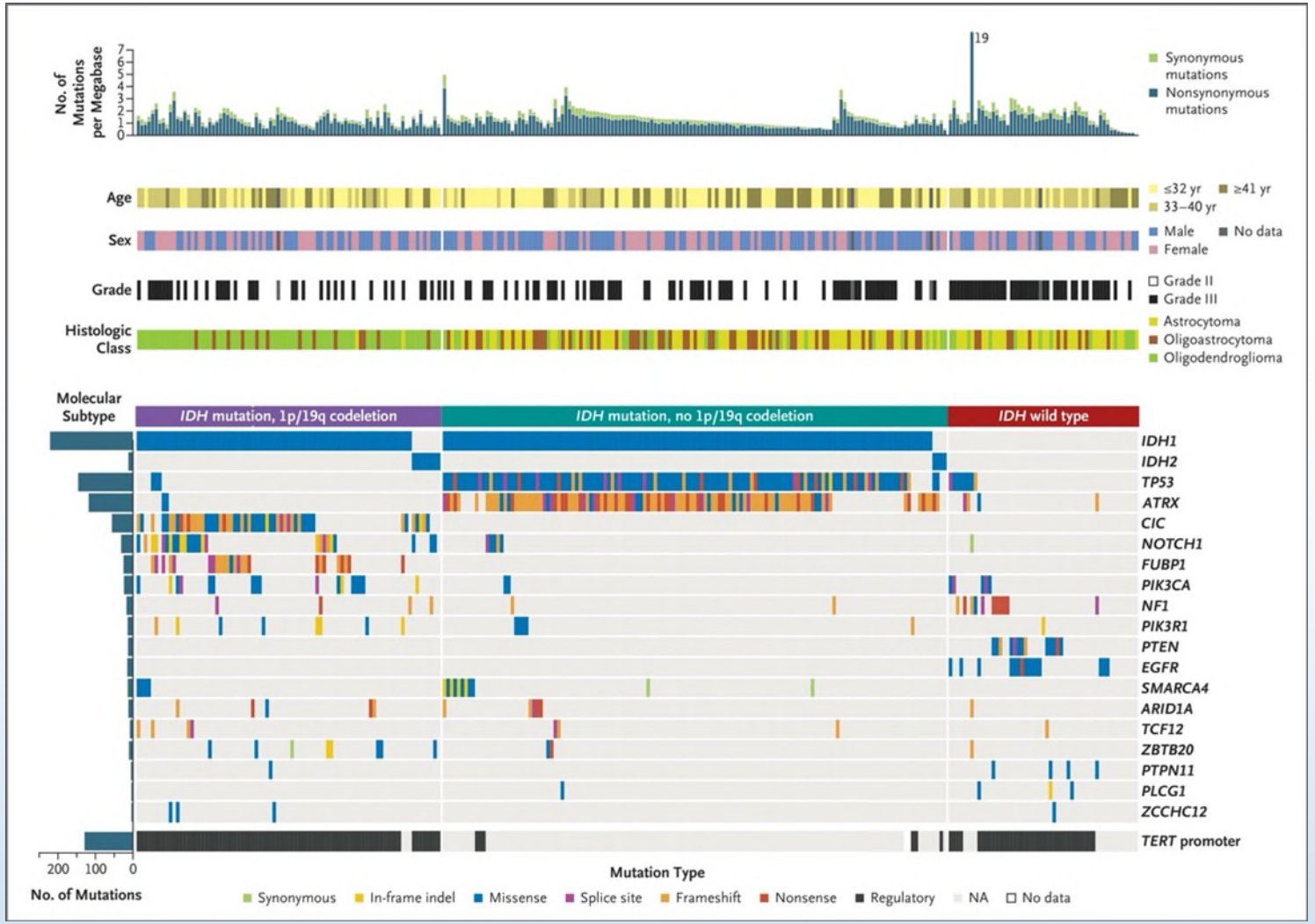
Mutational Landscape of Somatic Alterations in Lower-Grade Glioma.



The NEW ENGLAND JOURNAL of MEDICINE

Well displayed data can change the world…

Oligoastrocytoma was arguably shown to be a collective delusion by Brat et al. 2015.

The Cancer Genome Atlas Research Network. N Engl J Med 2015;372:2481-2498

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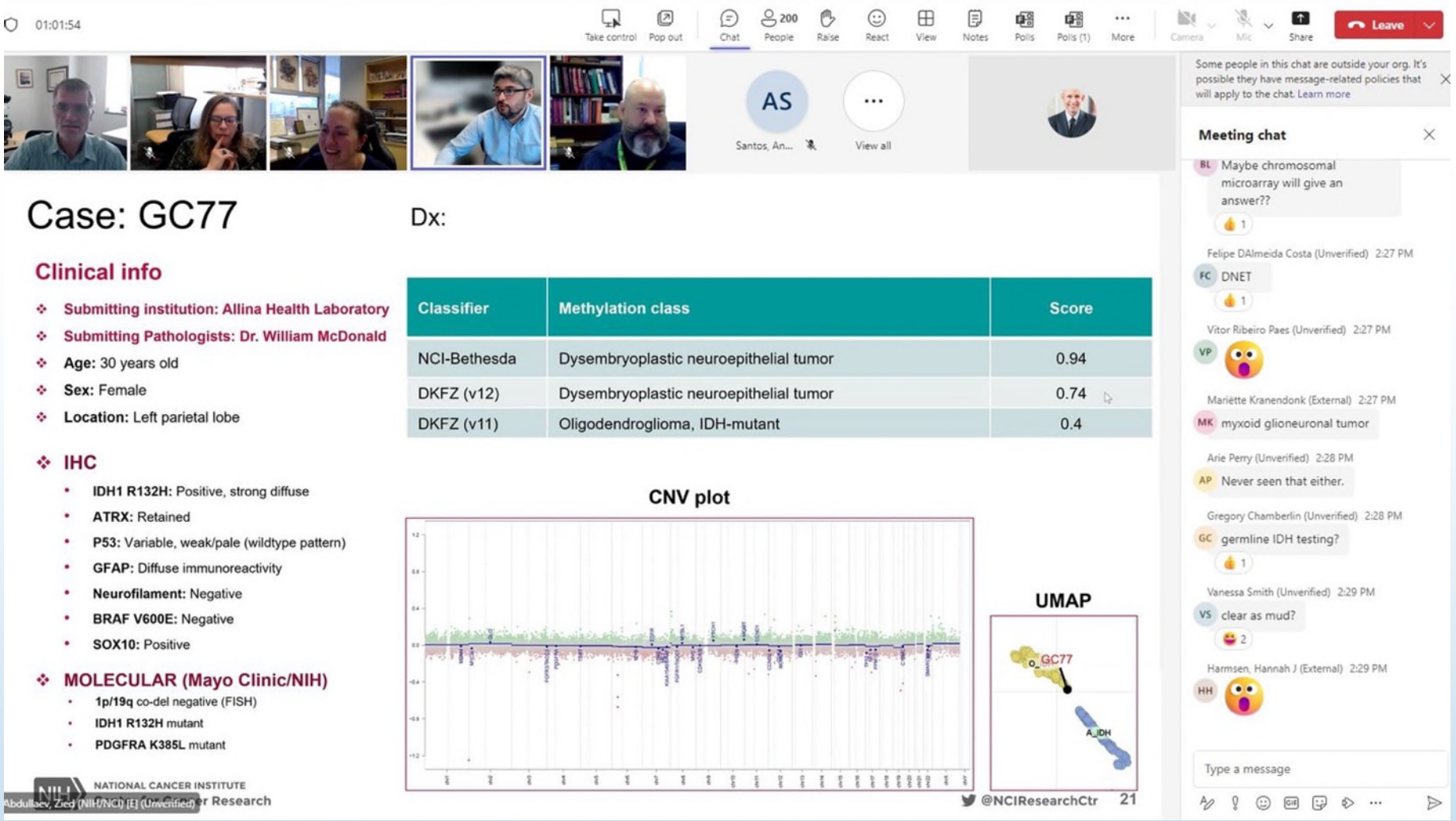
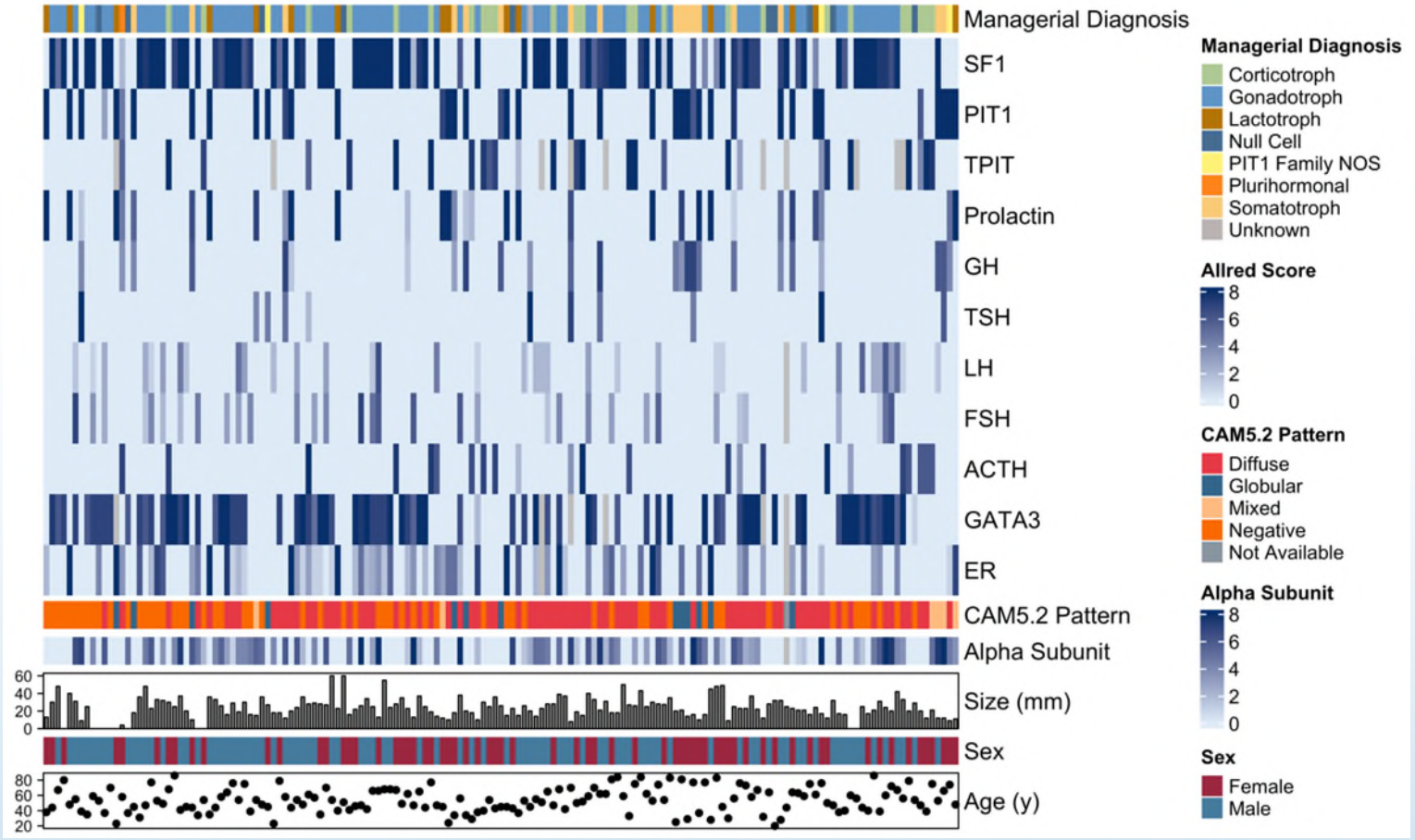
NIH/NCI Neuro-Oncology Tumor Methylation Conference: Machine Learning's Role in the Classification Problem



Unsorted Data from 157 Adenomas



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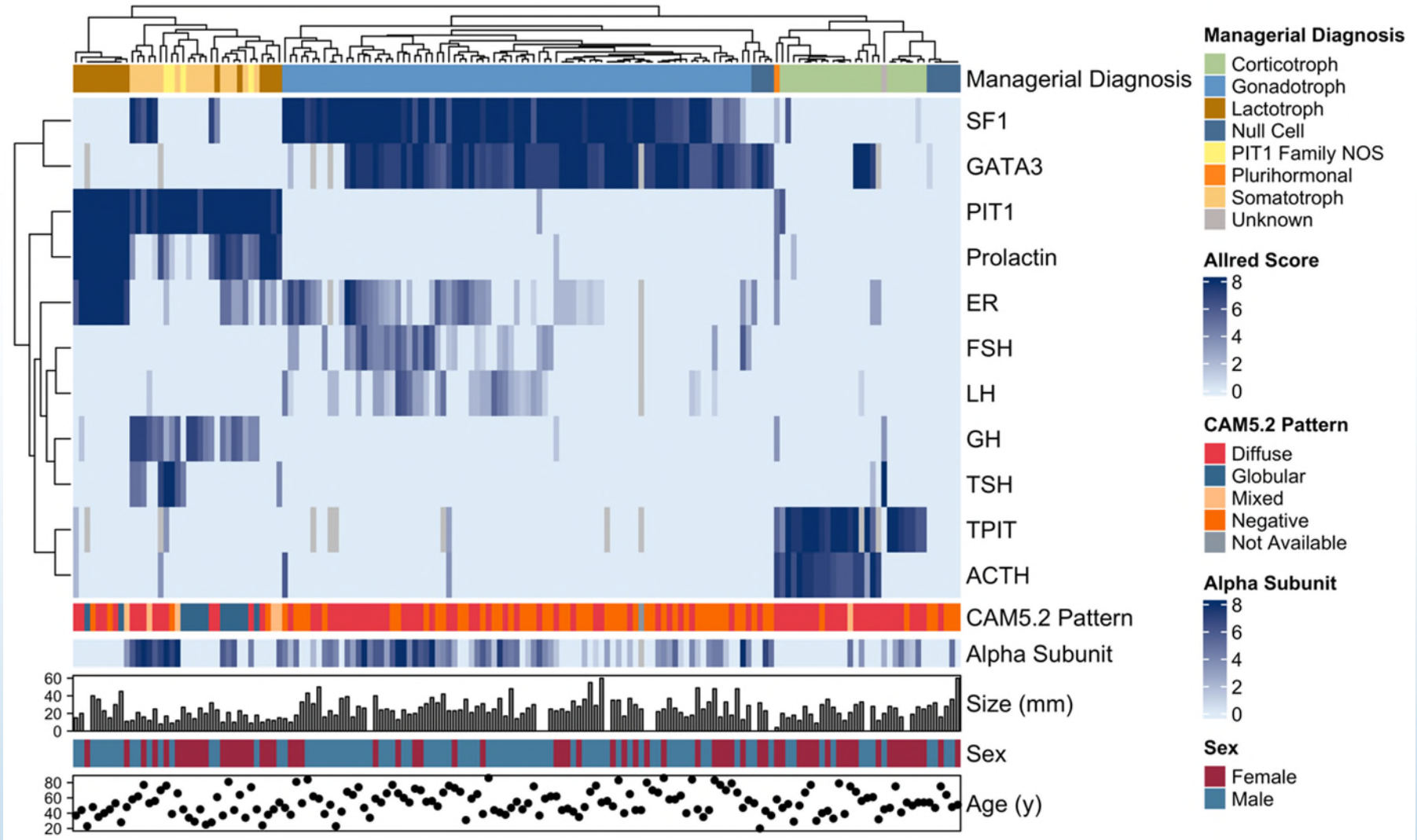
157 Adenomas: Organized with ML



McDonald,
Free Neuropathol 2024,
PMID: **38213550**

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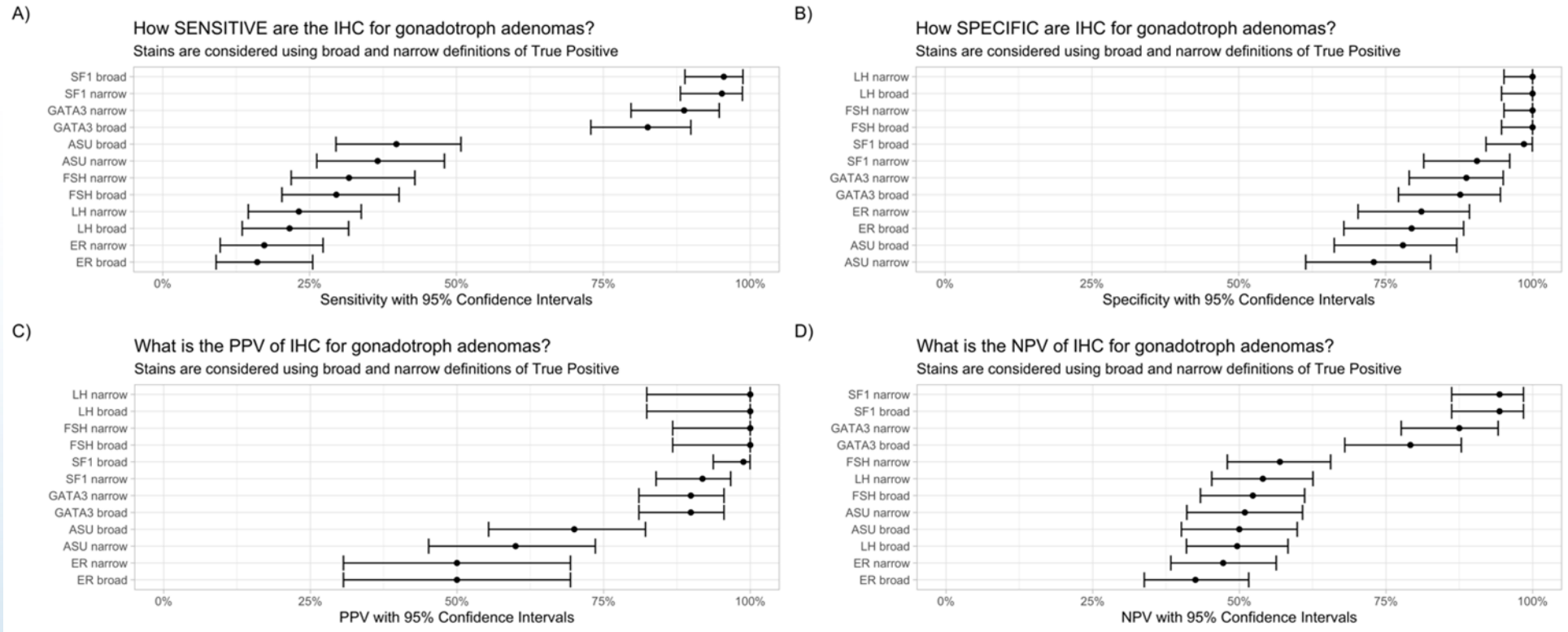
Gonadotroph

- PitNET/adenoma with variable immunoreactivity for gonadotropins (βFSH, βLH, α-subunit) and/or SF1; absence of PIT1 and TPIT expression
- The most common tumor in our cohort
- Typically nonfunctioning, macroadenoma

PathPresenter.net example of gonadotroph tumor

Gonadotrophs



McDonald,
Free Neuropathol 2024,
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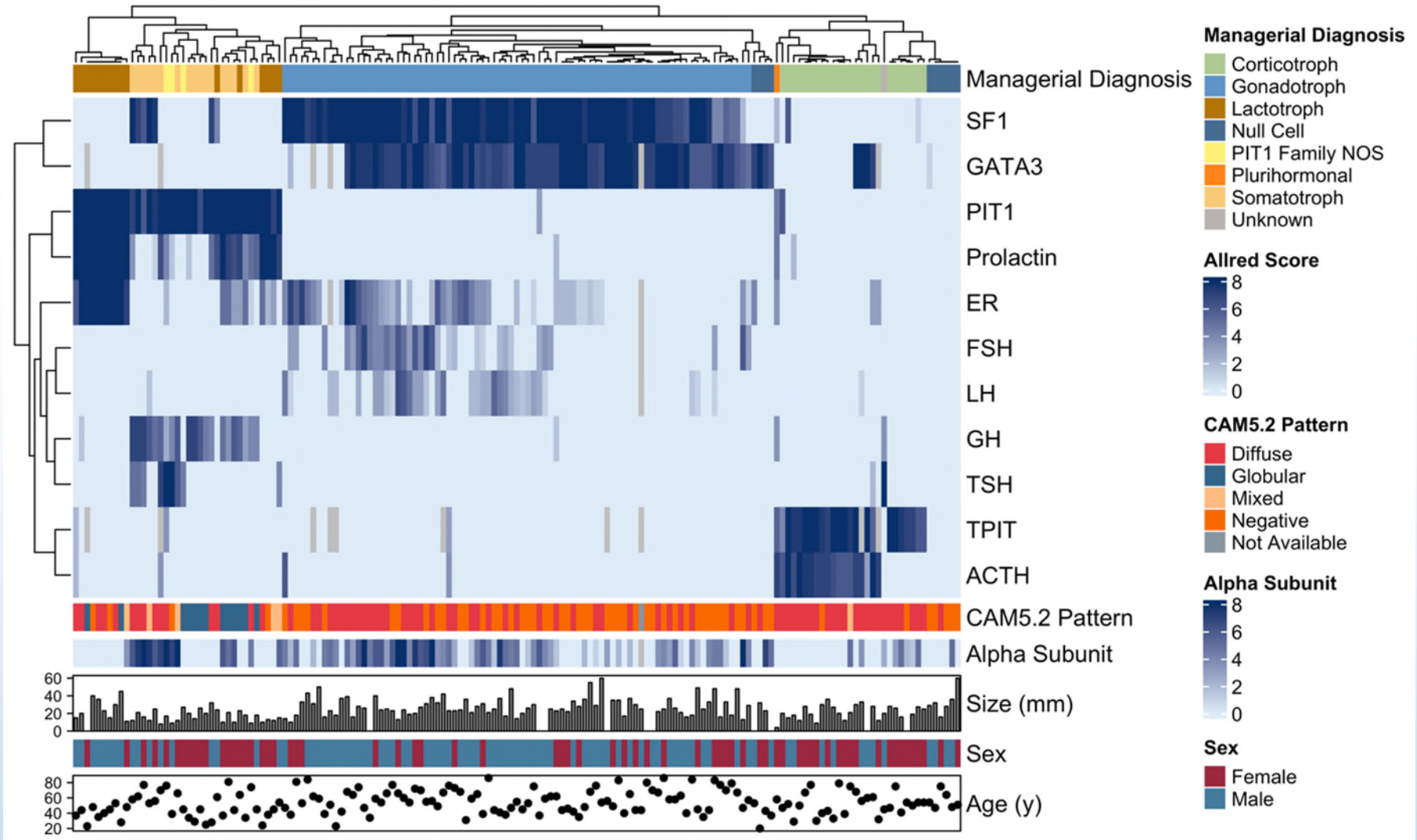
157 Adenomas: Organized with ML



McDonald,
Free Neuropathol 2024,
PMID: **38213550**

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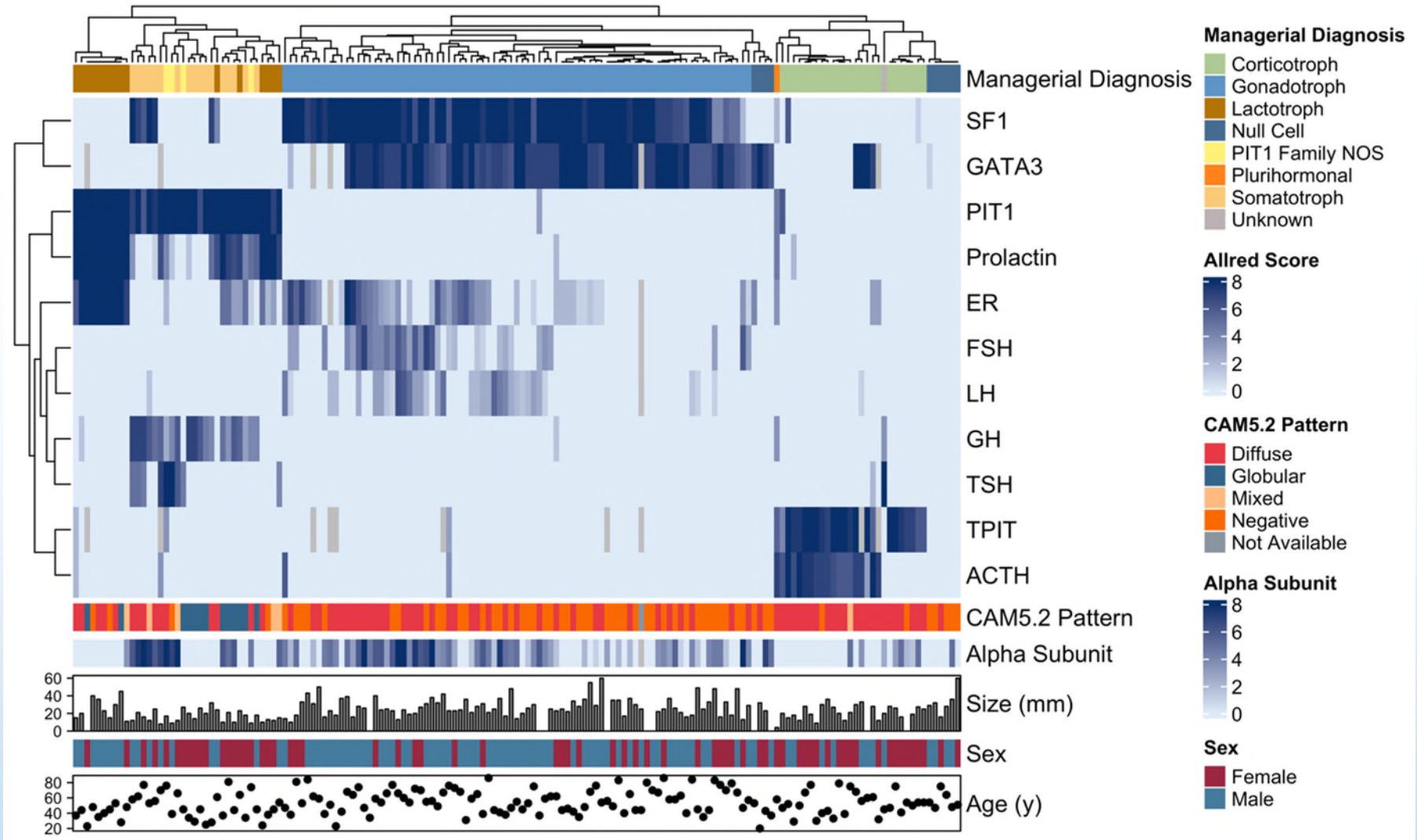
Corticotroph

- **Densely granulated** corticotroph tumors: TPIT positivity, diffuse ACTH or PAS reactivity, negativity for PIT1 and SF1, often diffuse keratin, and basophilic cytoplasm
- **Sparsely granulated** corticotroph tumors: TPIT positivity, variable to absent/scarce ACTH or PAS expression, negativity for PIT1 and SF1, often diffuse keratin, faintly basophilic or amphophilic cytoplasm
- **Crooke cell tumors**: TPIT positivity, relocation of ACTH and PAS positive granules to the cell periphery and perinuclear, ring-like keratin

PathPresenter.net example of corticotroph tumor

157 Adenomas: Organized with ML



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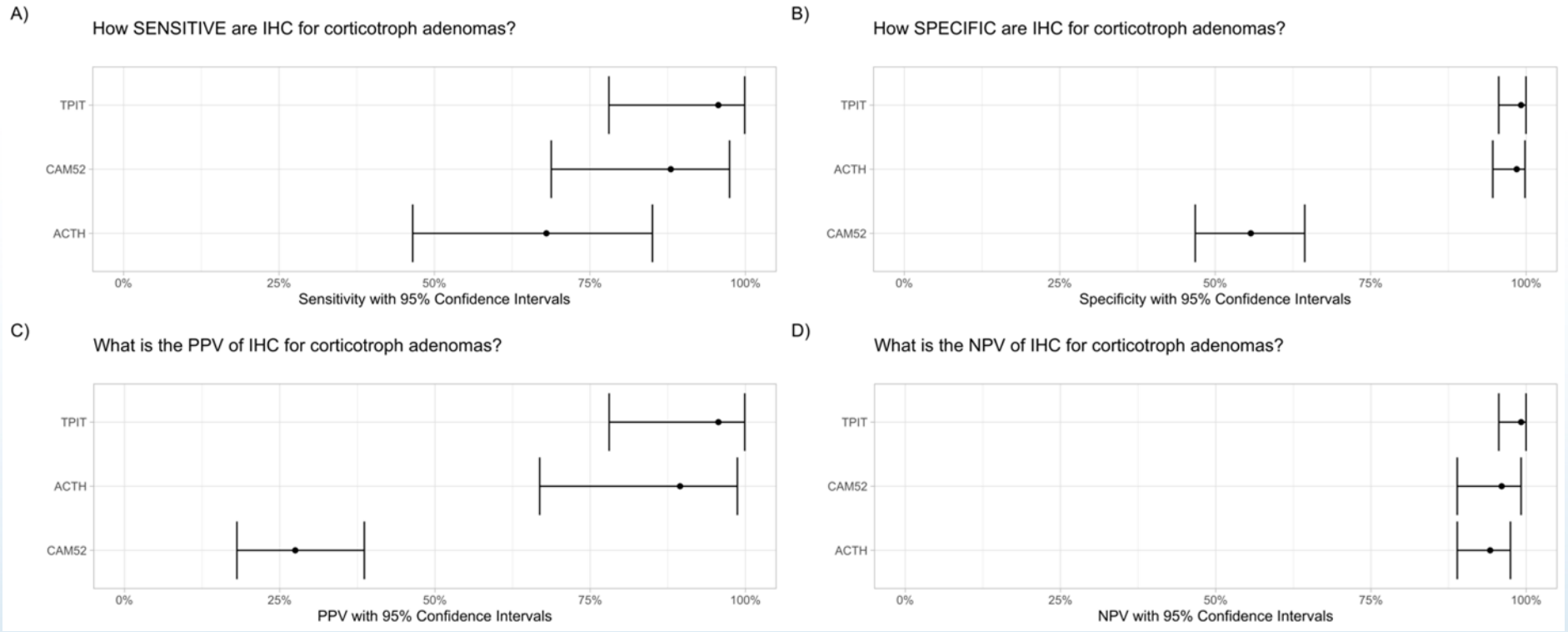
Corticotrophs



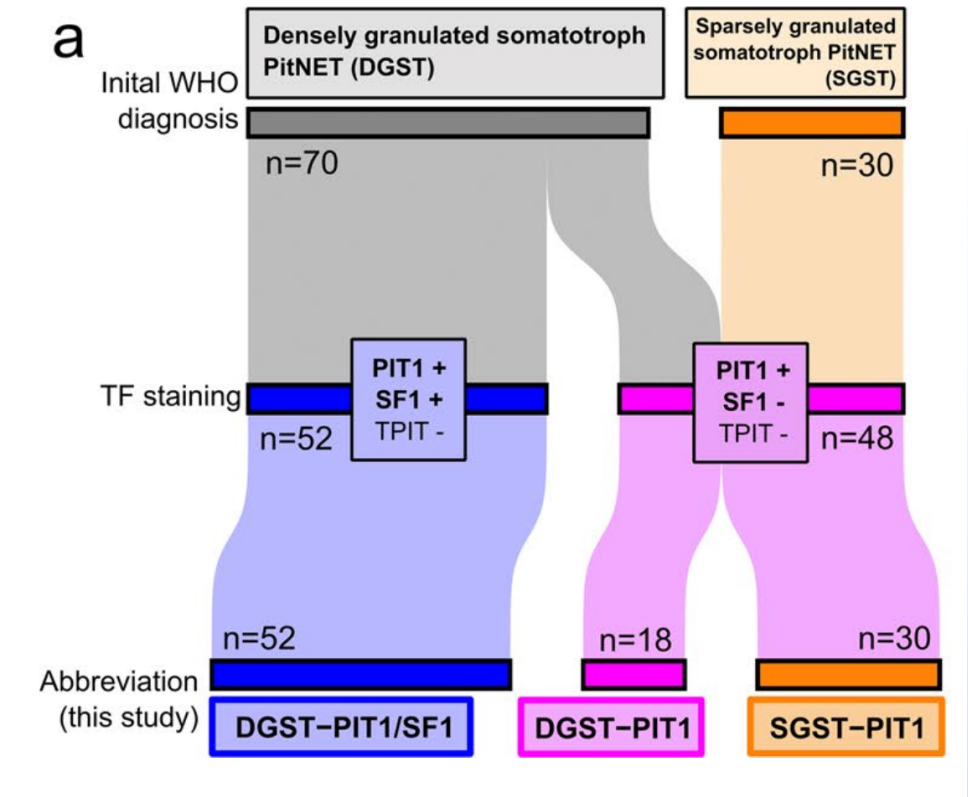
McDonald,
Free Neuropathol 2024,
PMID: **38213550**

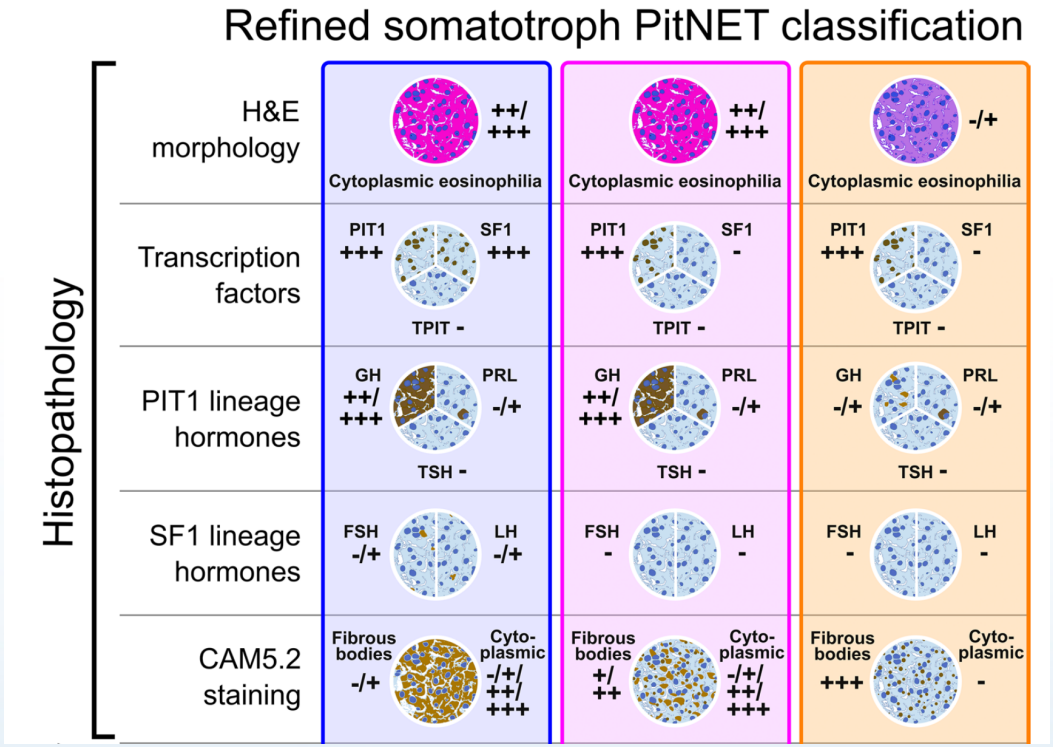
PIT1 Family, “Simple” Classes

- Lactotroph
- Somatotroph, sparsely granulated*
- Somatotroph, densely granulated
- Thyrotroph

*I make this distinction, but note that Swanson et al. Pituitary 2021 (PMID: 33074402) found that sparse or dense granularity did not distinguish between remission rates in 131 acromegaly-associated tumors.

PIT1/SF1 Co-expression





Dottermusch 2024

PMID: 38228887

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PIT1 Family, Complex Classes

- Mammosomatotroph
- Mixed somatotroph and lactotroph
- Mature plurihormonal PIT1-lineage
- Immature PIT1-lineage
- Acidophil stem cell

PIT1 Family Tumors: Abstracting the WHO Classification

Adenoma Type	PRL	GH	TSH	ASU	GATA3	ER
Somatotroph	-	+ (DG: strong, SG:weak/var)	-	- (SG), +(DG)	-	-
Mammosomatotroph	+ (usu < GH)	+	-	+	-	+
Lactotroph	+	-	-	-		+
Thyrotroph			+	var	var	
Mature Plurihormonal PIT1	var	+	var	+	+	+
Immature PIT1	lim	lim	lim		var	var
Acidophil Stem Cell	var	-/min			-	var
Mixed Somatotroph-Lactotroph	+	+		-(lact), var(som)		+(lact)
Plurihormonal adenoma	IHC expression of adenohypophyseal hormones and transcription factors belonging to at least 2 different pituitary cell lineages					

https://www.pathologyoutlines.com/topic/stainsPIT1.html

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PIT1 Family, Challenges of the Current Classification

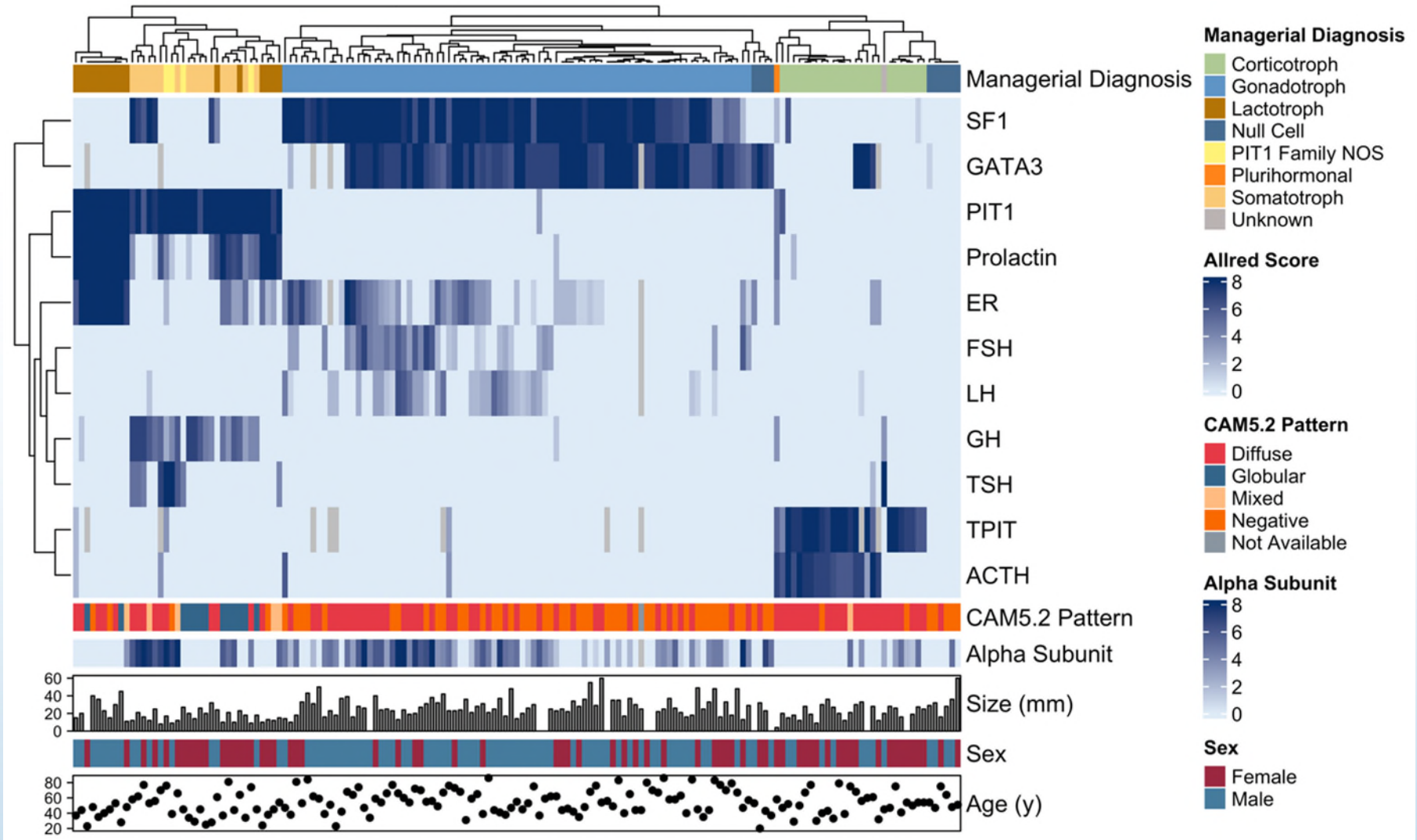
- Underscore the importance of distinguishing between **classification features** and **other variables**
- **Overlapping features** in PIT1 family classes
- On what scale do we measure **maturity**, or **acidophilia**, or **granularity**? Are these reliably bimodal?
- **Karl Popper**: falsifiability is central to the scientific method
  - **Not even wrong**: “Das ist nicht nur nicht richtig; es ist nicht einmal falsch.”
    - Wolfgang Pauli, as recorded by Rudolf Peierls

Pit-1 Family: Example Case

- Lactotroph
  - Pituitary neuroendocrine tumor with immunoreactivity for PIT1, extensive prolactin immunoreactivity, and absence of other pituitary hormone staining

PathPresenter.net example: recurrent lactotroph tumor?

157 Adenomas: Organized with ML



McDonald,
Free Neuropathol 2024,
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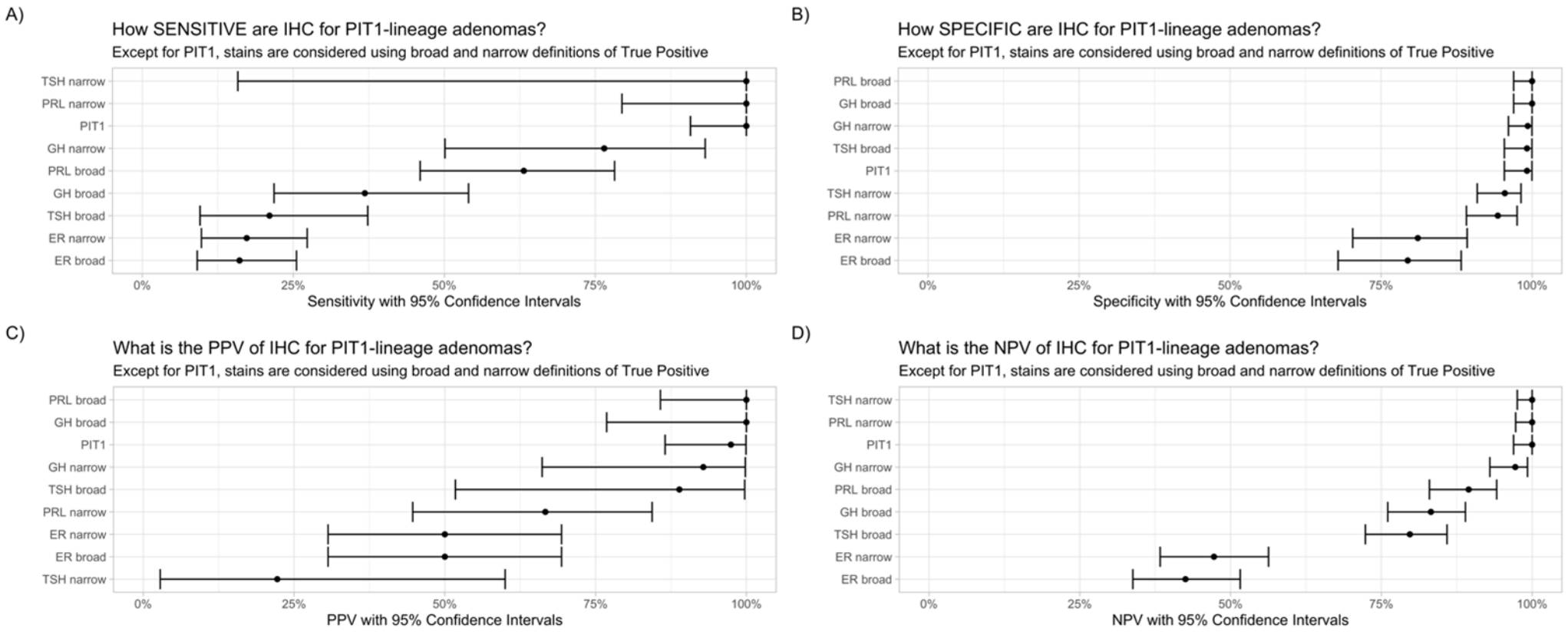
PIT1 Family



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DKFZ Classifier v 12.8

3 of 7 classes are somatotropin-producing

Heidelberg Epignostix CNS Tumor Classifier (v12.8)

149 MC Pituitary adenoma, subtype ACTH-producing (novel)
The "mc Pituitary adenoma, ACTH-producing" represents corticotroph pituitary tumours, arising as a clonal neoplastic proliferation of anterior pituitary hormone-producing cells. Recurrent somatic mutations of USP48 or USP8 have been reported in these tumours, and chromosomal imbalances at the copy number level can also be observed. Median age of onset is around 45-50 years.

150 MC Pituitary adenoma, subtype gonadotrophin-producing (novel)
The "mc Pituitary adenoma, gonadotrophin-producing" represents gonadotroph pituitary tumours, arising as a clonal neoplastic proliferation of anterior pituitary hormone-producing cells. No recurrent somatic mutations have been reported in these tumours as yet, and chromosomal imbalances at the copy number level are rare. Median age of onset is around 60-65 years.

151 MC Pituitary adenoma, subtype prolactin-producing (novel)
The "mc Pituitary adenoma, prolactin-producing" represents lactotroph pituitary tumours, arising as a clonal neoplastic proliferation of anterior pituitary hormone-producing cells. No recurrent somatic mutations have been reported in these tumours as yet, but chromosomal imbalances at the copy number level are frequently observed. Median age of onset is around 55-60 years.

152 MC Pituitary adenoma, subtype STH-producing, subclass densely granulated A (novel)
The "mf Pituitary adenoma, STH producing" includes the currently provisional methytlation classes "mc Pituitary adenoma, subtype STH-producing, subclass densely granulated A", "mc Pituitary adenoma, subtype STH-producing, subclass densely granulated B", and "mc Pituitary adenoma, subtype STH-producing, subclass sparsely granulated". This mf represents somatotroph pituitary tumours, arising as a clonal neoplastic proliferation of anterior pituitary hormone-producing cells. Recurrent somatic mutations of GNAS have been reported in these tumours, and copy number alterations affecting whole chromosomes are also often observed. Median age of onset is around 45-50 years.

153 MC Pituitary adenoma, subtype STH-producing, subclass densely granulated B (novel)
The "mf Pituitary adenoma, STH producing" includes the currently provisional methytlation classes "mc Pituitary adenoma, subtype STH-producing, subclass densely granulated A", "mc Pituitary adenoma, subtype STH-producing, subclass densely granulated B", and "mc Pituitary adenoma, subtype STH-producing, subclass sparsely granulated". This mf represents somatotroph pituitary tumours, arising as a clonal neoplastic proliferation of anterior pituitary hormone-producing cells. Recurrent somatic mutations of GNAS have been reported in these tumours, and copy number alterations affecting whole chromosomes are also often observed. Median age of onset is around 45-50 years.

154 MC Pituitary adenoma, subtype STH-producing, subclass sparsely granulated (novel)
The "mf Pituitary adenoma, STH producing" includes the currently provisional methytlation classes "mc Pituitary adenoma, subtype STH-producing, subclass densely granulated A", "mc Pituitary adenoma, subtype STH-producing, subclass densely granulated B", and "mc Pituitary adenoma, subtype STH-producing, subclass sparsely granulated". This mf represents somatotroph pituitary tumours, arising as a clonal neoplastic proliferation of anterior pituitary hormone-producing cells. Recurrent somatic mutations of GNAS have been reported in these tumours, and copy number alterations affecting whole chromosomes are also often observed. Median age of onset is around 45-50 years.

155 MC Pituitary adenoma, subtype TSH-producing (novel)
The "mc Pituitary adenoma, TSH-producing" represents thyrotroph pituitary tumours, arising as a clonal neoplastic proliferation of anterior pituitary hormone-producing cells. No recurrent somatic mutations have been reported in these tumours as yet, but chromosomal imbalances at the copy number level are frequently observed. Median age of onset is around 45 years.

https://app.epignostix.com/#/classifiers

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Null

- *Essential*: PitNET/adenoma with lack of immunoreactivity for pituitary-lineage transcription factors and pituitary hormones
- *Desirable*: additional immunostains to rule out sellar paraganglioma and other neuroendocrine neoplasms

- Possibly a final common pathway for typically longstanding tumors

tSNE plot from McDonald et al. 2021

Provocative Ideas

- PitNET is a cumbersome term
- Photomicrographs are illustrations, not evidence
- Current WHO classification of pituitary tumors is still based upon poorly supported ultrastructural observations
- Classification variables (features) must be distinguished from other variables *in advance*; a classification must be falsifiable in order to be useful
- Statistical learning/machine learning methods needed to repair the current classification
- Practice location and clubs determine current practices in PitNET classification
- Greater attention to the classification problem is needed; beware “stealth features” or untested claims about feature distribution

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Kelsey McDonald, PhD

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- Allina Health Center for Healthcare Innovation (Minneapolis, MN)
- Abbott Northwestern Hospital Foundation (Minneapolis, MN)
- John H. Ripley Grant for Laboratory Quality Assurance (CAP Foundation, 2015)

Steroidogenic Factor 1, Pit-1, and Adrenocorticotropic Hormone

A Rational Starting Place for the Immunohistochemical Characterization of Pituitary Adenoma

William C. McDonald, MD; Nilanjana Banerji, PhD; Kelsey N. McDonald, PhD; Bridget Ho, CCRC; Virgilia Macias, MD; Andre Kajdacsy-Balla, MD, PhD

The Role of T-box Transcription Factor in a Pituitary Adenoma Diagnostic Algorithm

William C. McDonald, MD; Kelsey N. McDonald, PhD; Jordan A. Helmer, BS; Bridget Ho, CCRC; Amber Wang, MD; Nilanjana Banerji, PhD

-Zeynep Temerit Kumm, MD, pathology resident
-Marie Meyer, Manager of Clinical Research, Neuro Research Admin, Allina Health

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