Cushing's syndrome

- **Rare (2-3 / Mio / Year), but possible much more frequent**
- **Female sex preponderance (3−4:1)**
- **Age 20−50 yrs**

- Case XLV Minnie G. at the time of her first consultation with Cushing in 1910. Cushing H: The Pituitary Body and its Disorders. Philadelphia: JB Lippincott, 1912.

1910. 23-year-old *"young woman of extraordinary appearance with reduced height of 4 foot 9 inches (ie, 1·45 m), round face, hypertrichosis, thin skin, increased adipose tissue, and linea atophica over the abdomen, deep brownish-purple in colour" - "A somewhat bizarre polyglandular syndrome"*

1958: Death due to arteriosclerotic heart disease (no mentioning of Cushing's syndrome)

Case Report: 17 year old female

- Passionate soccer player
- Youth national team player
- Stops growing (compared to twin sister, who grows additional 6 cm)
- Gains weigth despite regular high intensity soccer training
- Falls more and more back with her max. sprinting speed

14 yrs

Case Report: 17 year old female

- Passionate soccer player
- Youth national team player
- Stops growing (compared to twin sister, who grows additional 6 cm)
- Gains weigth despite regular high intensity soccer training
- Falls more and more back with her max. sprinting speed

14 yrs

15.5 yrs

Case Report

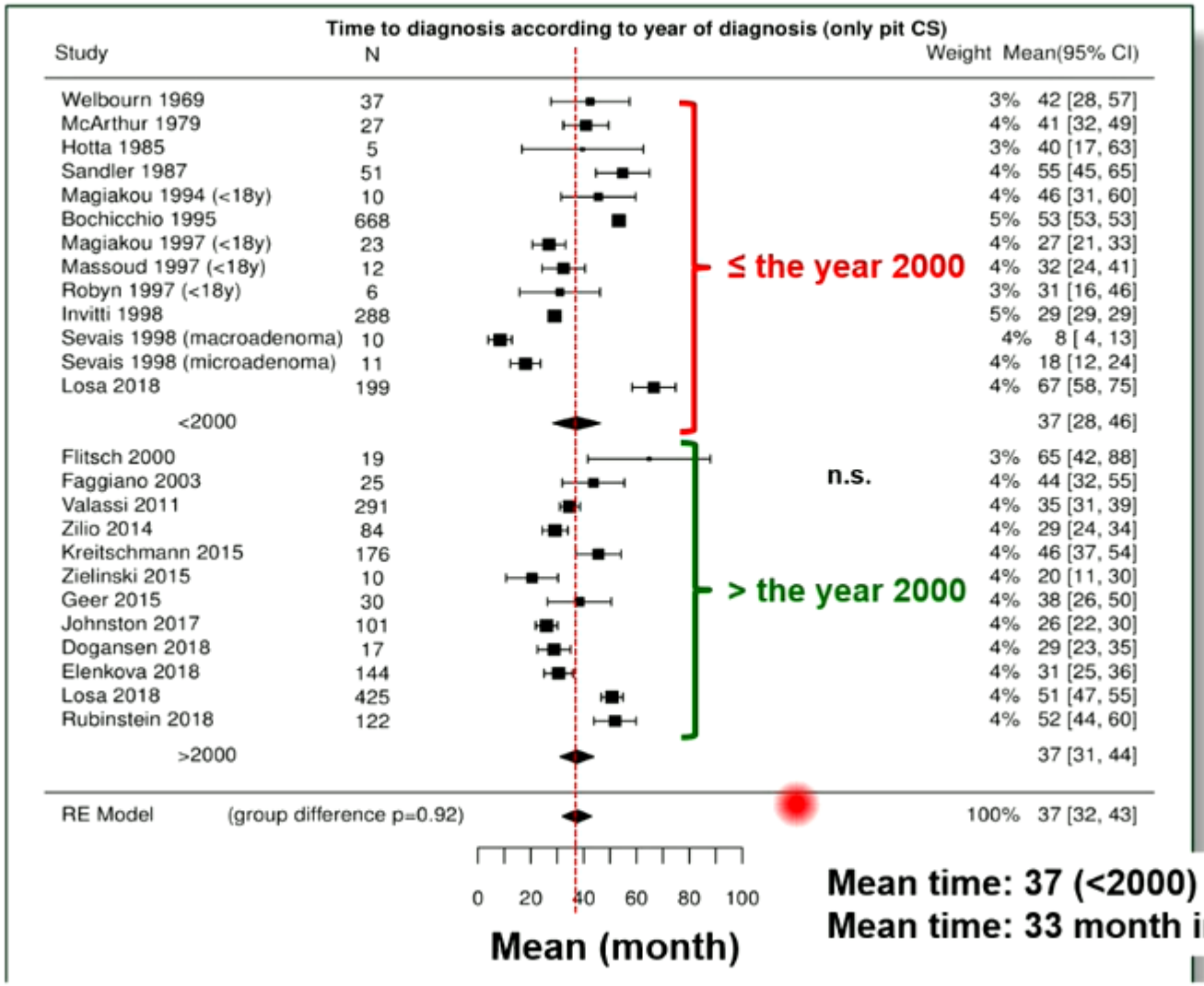
- Progressive symptoms over 2 years (now at age 17)
- New: secondary amenorrhea and easy bruising
- Multiple consultions with Pediatrician => Endocrinologist

14 yrs

15.5 yrs

17 yrs

Mean time to diagnosis remains constant over 7 decades: 37 month in 5.367 patients

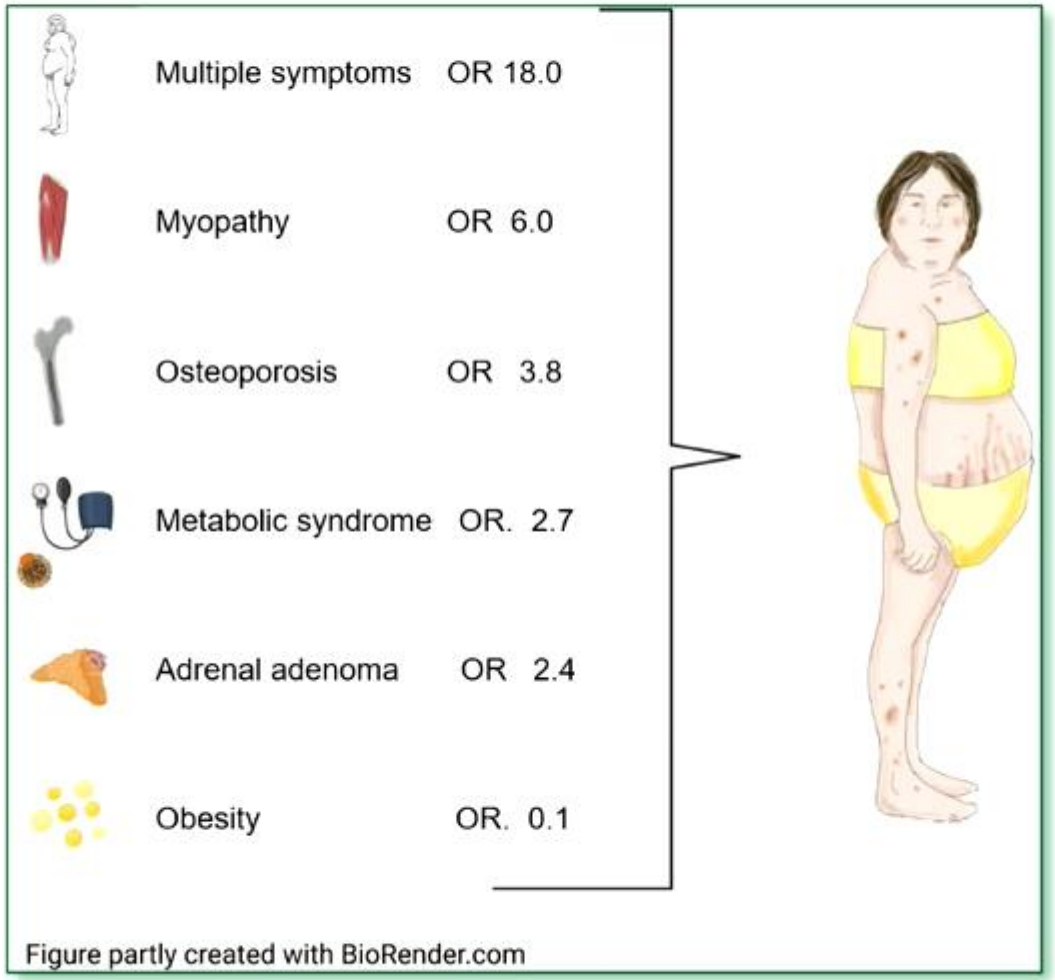


Mean time: 37 (<2000) and 37 (>2000) month in adults
Mean time: 33 month in pediatric patients

Rubinstein **G** et al., JCEM 2020:105 dgz136

Stick to Recommendations of ES Guidelines 2008!

Lead symptoms of 377 consecutive patients evaluated for Cushing's syndrome in LMU Pituitary Center of Excellence since 2012



Braun et al. Journal of Clinical Endocrinology & Metabolism, 2022, Vol. 107, No. 9

Symptoms in patients with Cushing's syndrome can be mild!

Prospective data of LMU Pituitary Center; n=129; 2012-2020

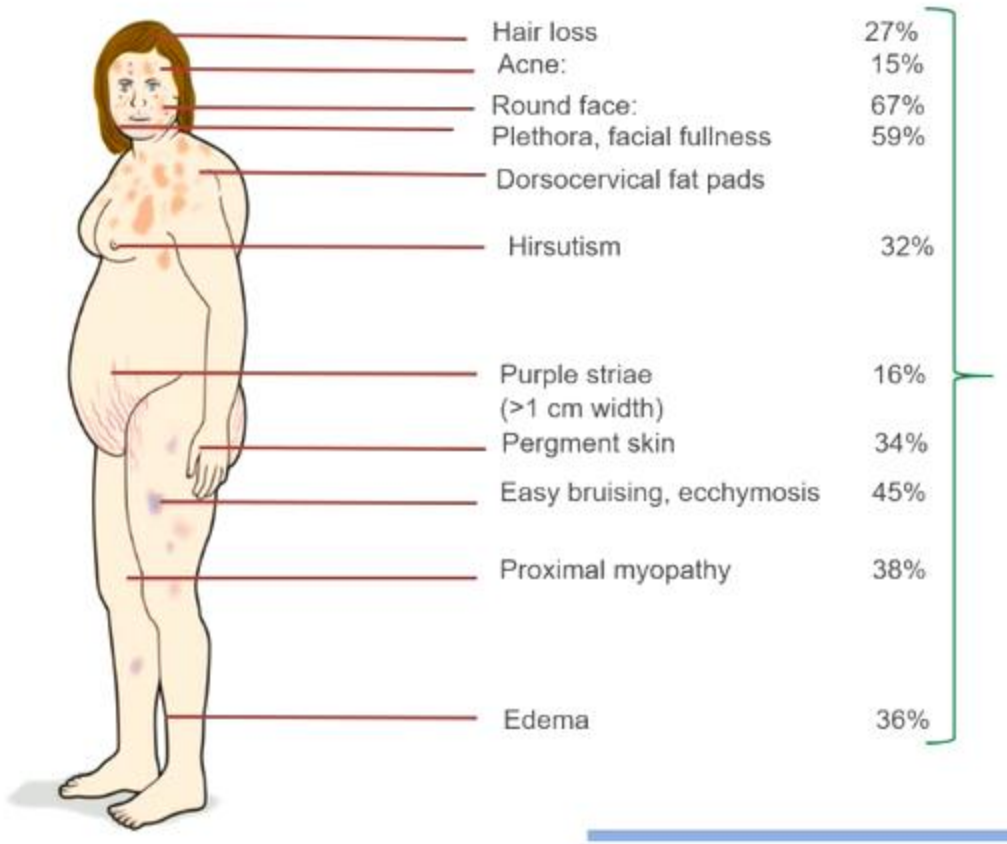


Table: Number of clinical signs

	Pituitary CS (N = 83)	Adrenal CS (N = 31)	Ectopic CS (N = 11)	All patients (N = 125)	Sum-mary
0	2%	0%	0%	2%	28%
1	1%	3%	0%	2%	
2	5%	7%	9%	6%	
3	16%	16%	18%	16%	
4	5%	10%	0%	6%	50%
5	16%	16%	0%	14%	
6	12%	19%	9%	14%	
7	13%	10%	9%	12%	
8	15%	16%	27%	16%	22%
9	10%	3%	27%	10%	
10	5%	0%	0%	3%	
11	1%	0%	0%	1%	
Median and ranges	6 (4 – 8)	5 (3 – 7)	8 (3 – 9)	6 (4 – 8)	

Braun et al. European Journal of Endocrinology Oktober 2024

Comorbidities of patients with Cushing's syndroms lead to increased mortality: *Timely diagnosis is key!*

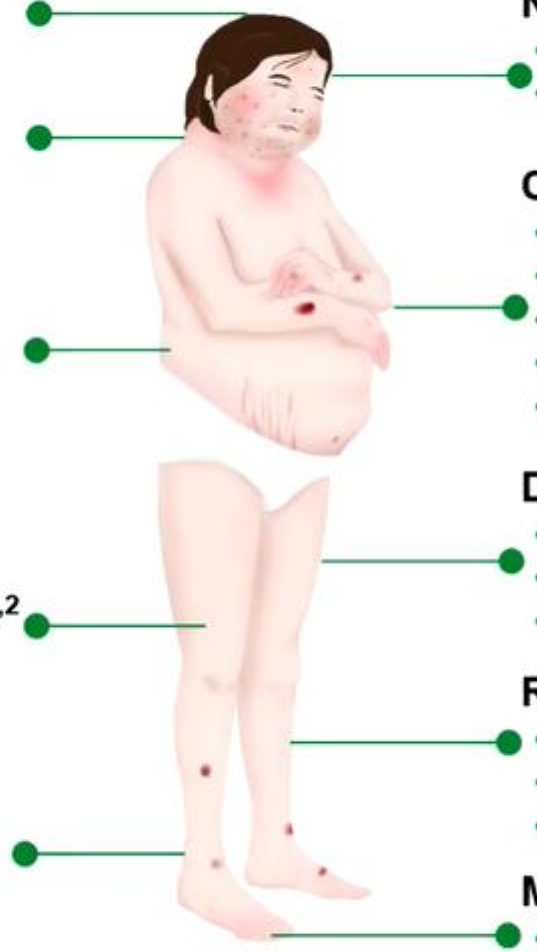
Cognitive impairment[1]

Immunodeficiency[1,2]
- Opportunistic infections

Metabolic disorders[1,2]
- Obesity
- Elevated fasting glucose
- Diabetes
- Dyslipidaemia
- Hepatic steatosis

Hypercoagulopathy/ haemostatic abnormalities[1,2]
- Venous thromboembolism
- Easy bruising

Autoimmune disorders[3]
- Thyroiditis
- Sjögren's syndrome



Neuropsychiatric dysfunction[1]
- Depression
- Anxiety
- Psychosis
- Insomnia

Cardiovascular disease[1,2]
- Hypertension
- Myocardial infarction
- Stroke
- Peripheral artery disease
- Hypokalaemia

Dermatological manifestations[1,2]
- Acne
- Hirsutism
- Poor wound healing
- Purple striae
- Skin thinning

Reproductive manifestations[1]
- Infertility
- Sexual dysfunction
- Menstrual dysfunction

Musculoskeletal disorders[1,2]
- Myopathy
- Osteoporosis

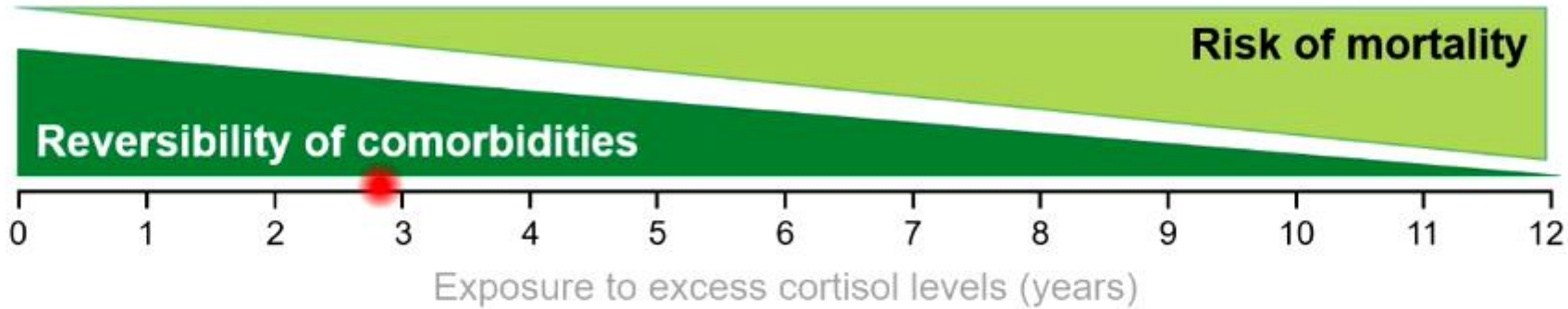
Impaired HRQoL[1]

Increased mortality and morbidity[1,2,4]
- **Standardised mortality ratio of 3.0 (95% CI: 2.3–3.9)**[4]

CI, confidence interval; HRQoL, health-related quality of life

1. **Fleseriu M** *et al. Nat Rev Endocrinol* 2023;19:581–99; 2. **Gadelha M** *et al. Lancet* 2023;402:2237–52;

Hypercortisolism is associated with increased morbidity and mortality

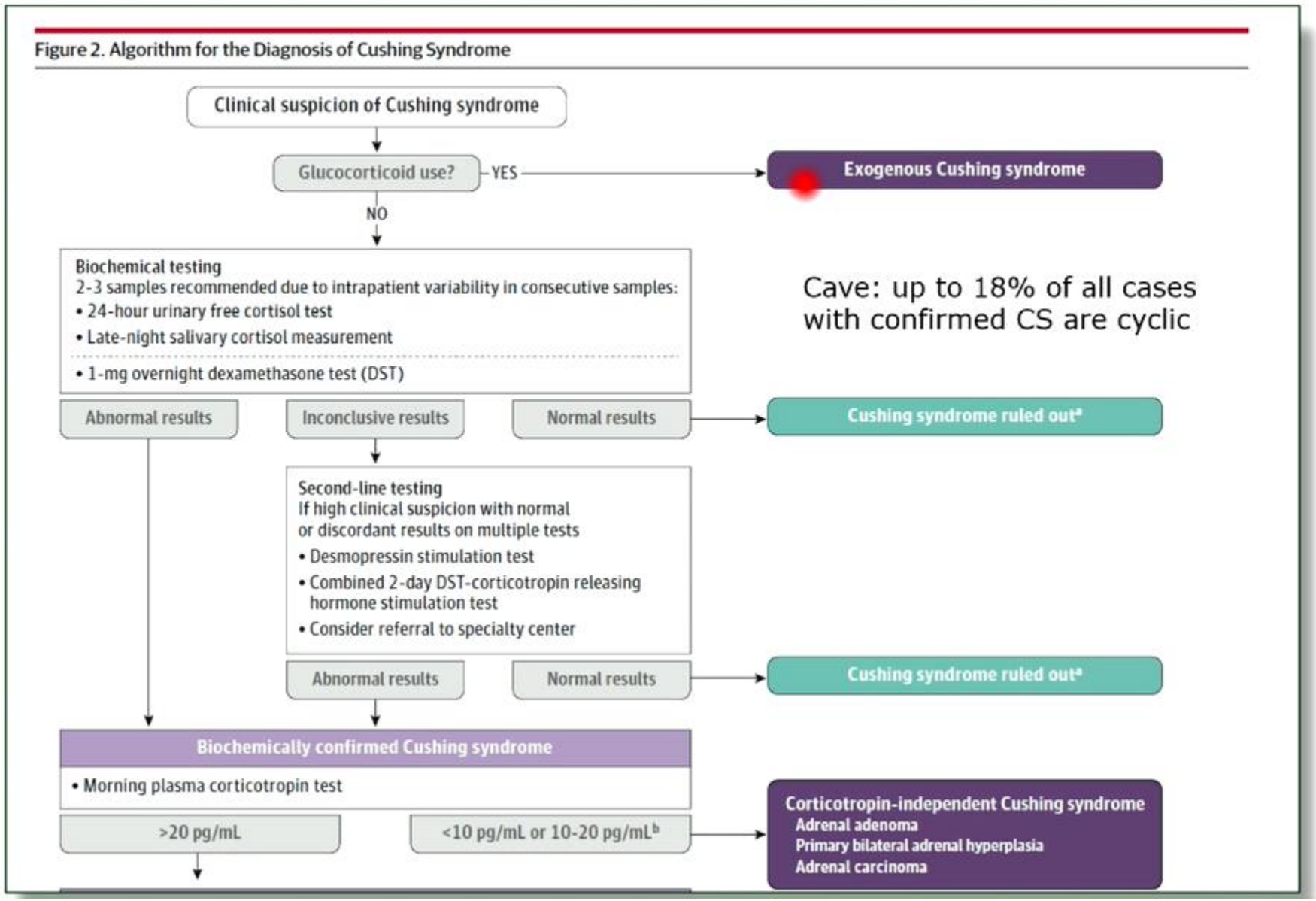


Increased risk of mortality is related to the **persistence** of **comorbidities** such as **hypertension** and **diabetes**[1,2]

Comorbidities should be **actively treated** to **alleviate clinical burden**[2,3]

1. **Braun L** *et al. J Neuroendocrinol* 2022;e13113; 2. **Pivonello R** *et al. Lancet Diabetes Endocrinol* 2016;4:611–29;
3. **Fleseriu M** *et al. Lancet Diabetes Endocrinol* 2021;9:847–75

Cushing's syndrome: Evaluation

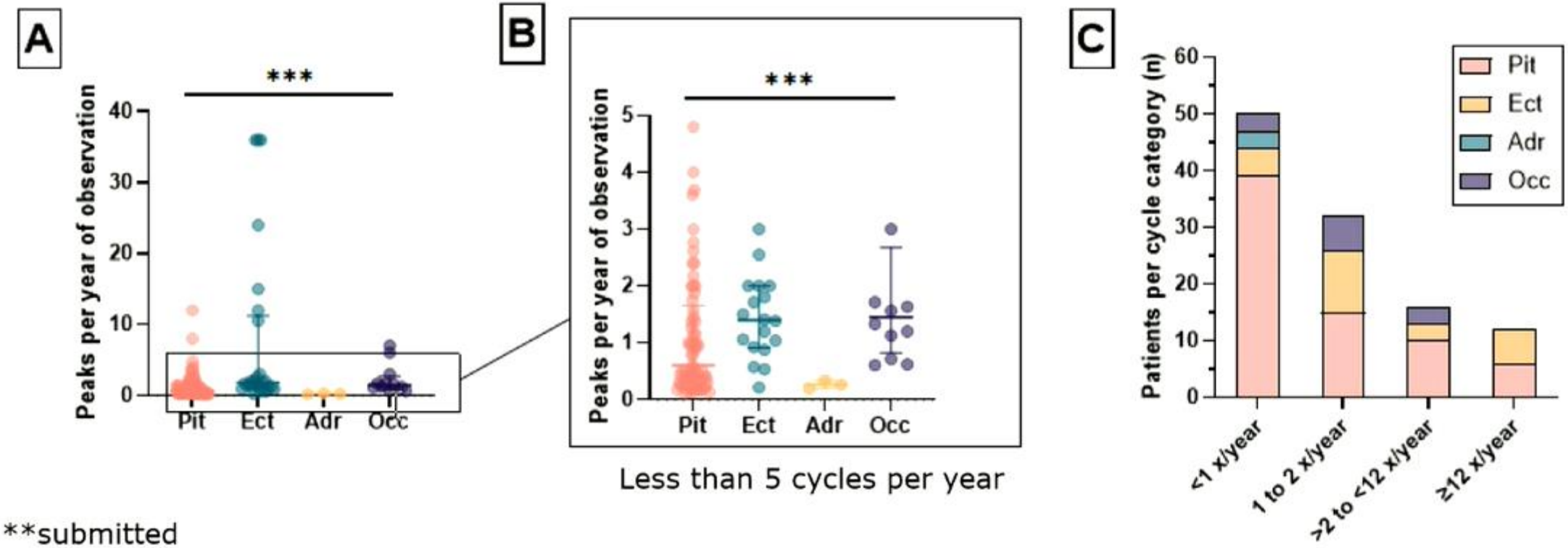


Cave: up to 18% of all cases with confirmed CS are cyclic

Reincke&Fleseriu, JAMA 2023

Cyclic Cushing's syndrome: Number of peaks and peak frequencies

Cyclic Cushing's syndrome appears with 14-18 % more frequent than thougth*



**submitted

*Elisabeth. Nowak, et al. Lancet D&§ 2023; **Elisabeth Nowak et al, submitted

Case Report

- Progressive symptoms over 2 years (now at age 18)
- New: secondary amenorrhea and easy bruising
- Pediatrician => Endocrinologist => Neurosurgeon
- 1 mg Dexamethason-Test: Cortisol 9.0 µg/dl (ULN < 1.8)
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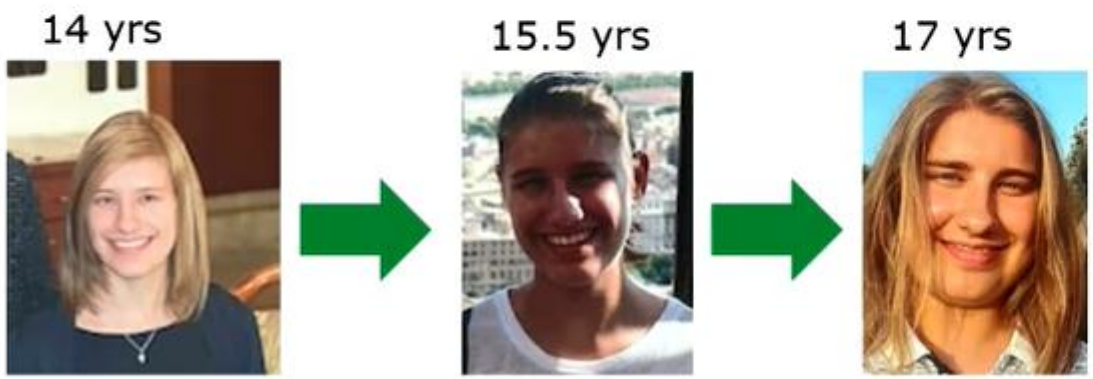
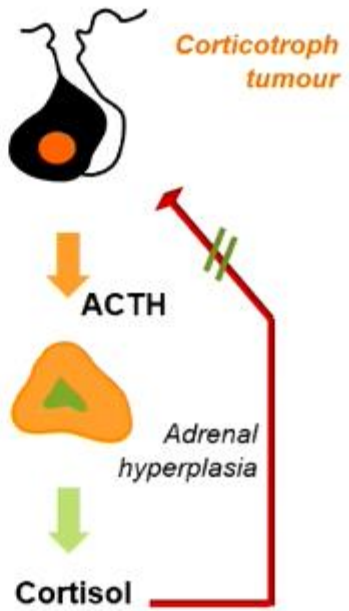
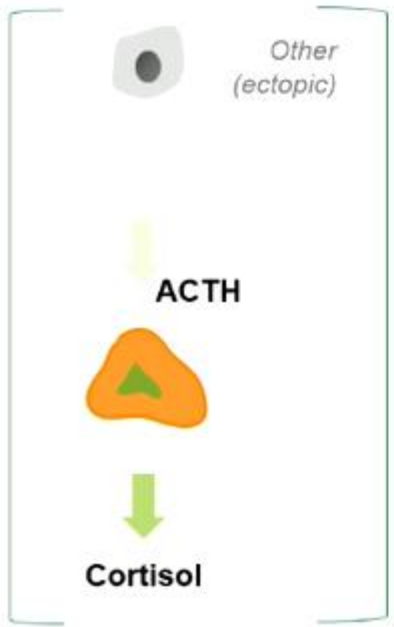
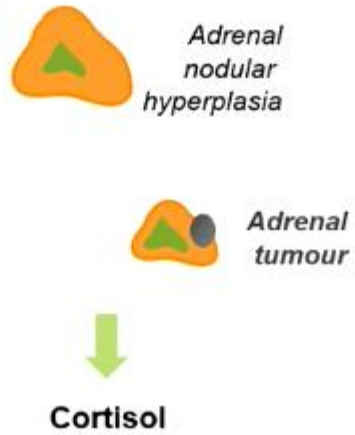


Endogenous hypercortisolism

Cushing's disease (60-70%)	Ectopic Cushing's syndrome (6-10%)	Adrenal Cushing's syndrome (20-30%)

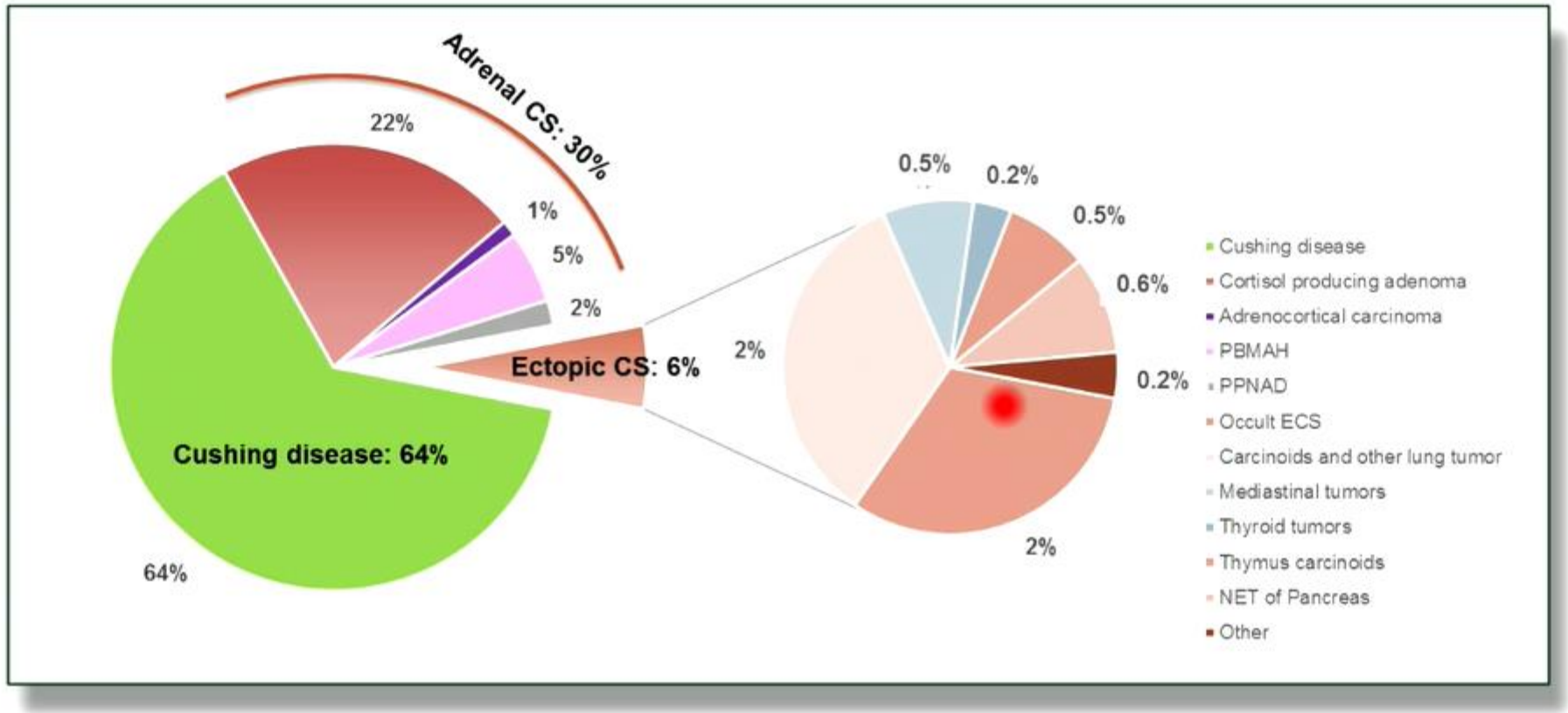






Plasma ACTH:	HIGH	VERY HIGH	SUPPRESSED

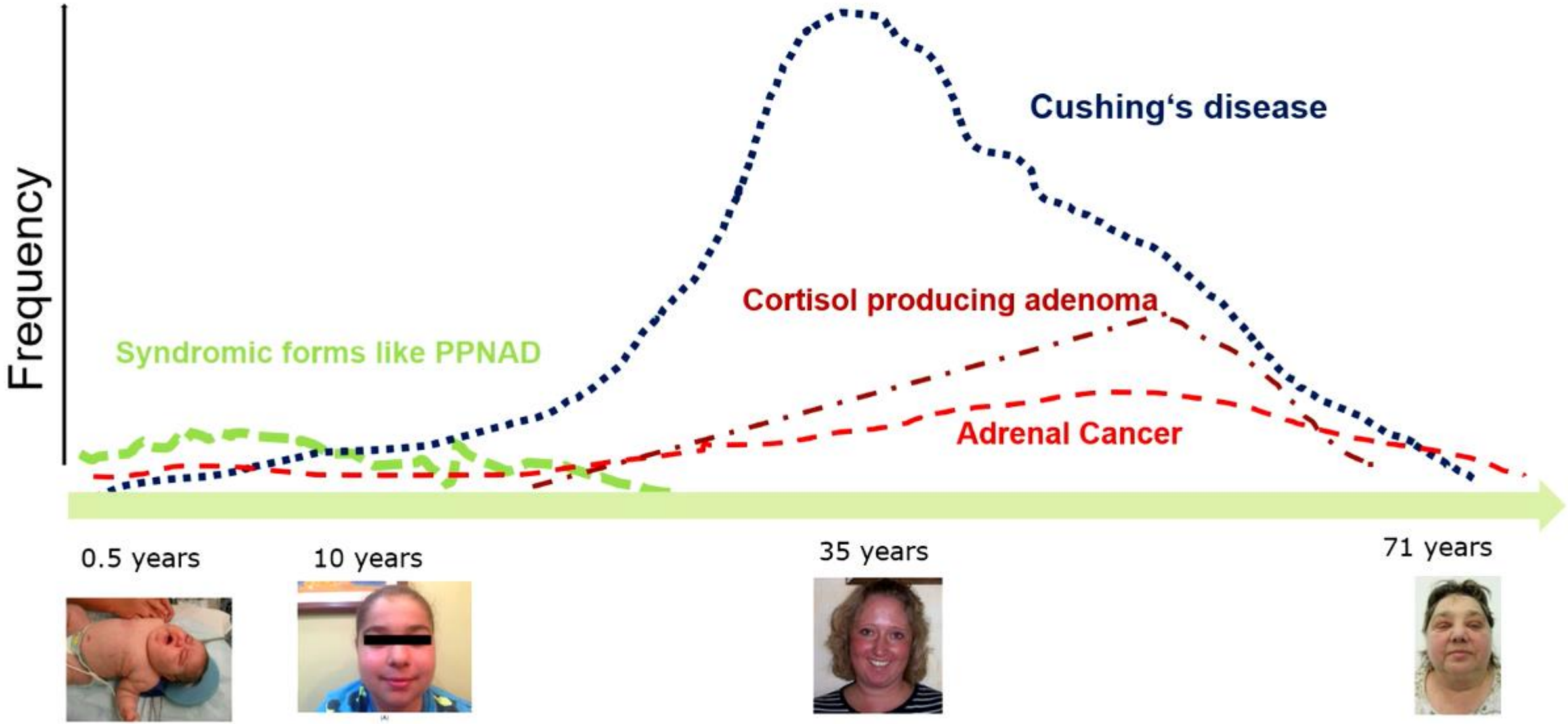
Cushing's syndrome: Causes and Prevalences



Reincke M &Fleseriu M, JAMA 2023

Combined data on 2264 patients in the prospective ERCUSYN registry in Europe (n=480; 2000-2010),[5] a retrospective series in Beijing, China (n=1636, 2008-2017), and the prospective Munich Cushing Registry (n=148; 2012-2019) (personal data).

Cushing's syndrome: Subtypes over life-time



Case Report

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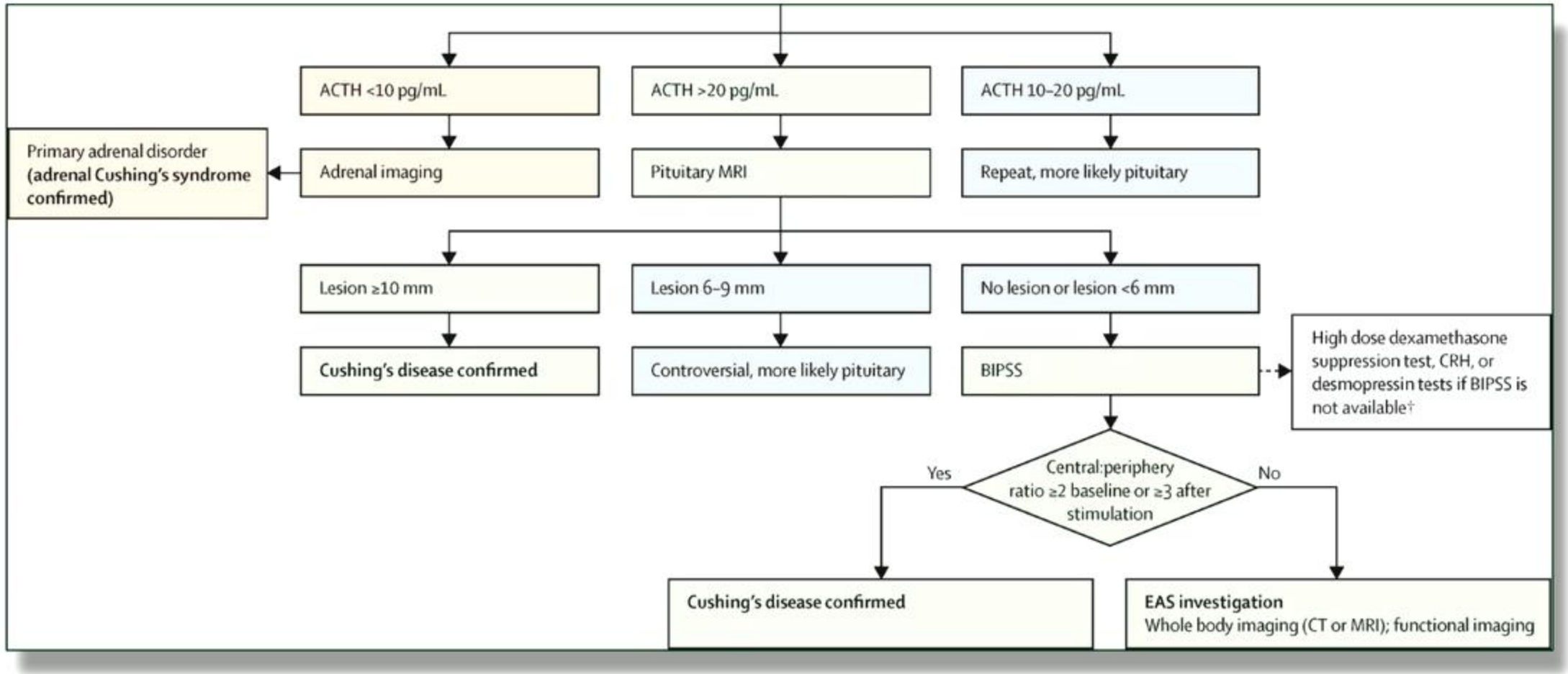
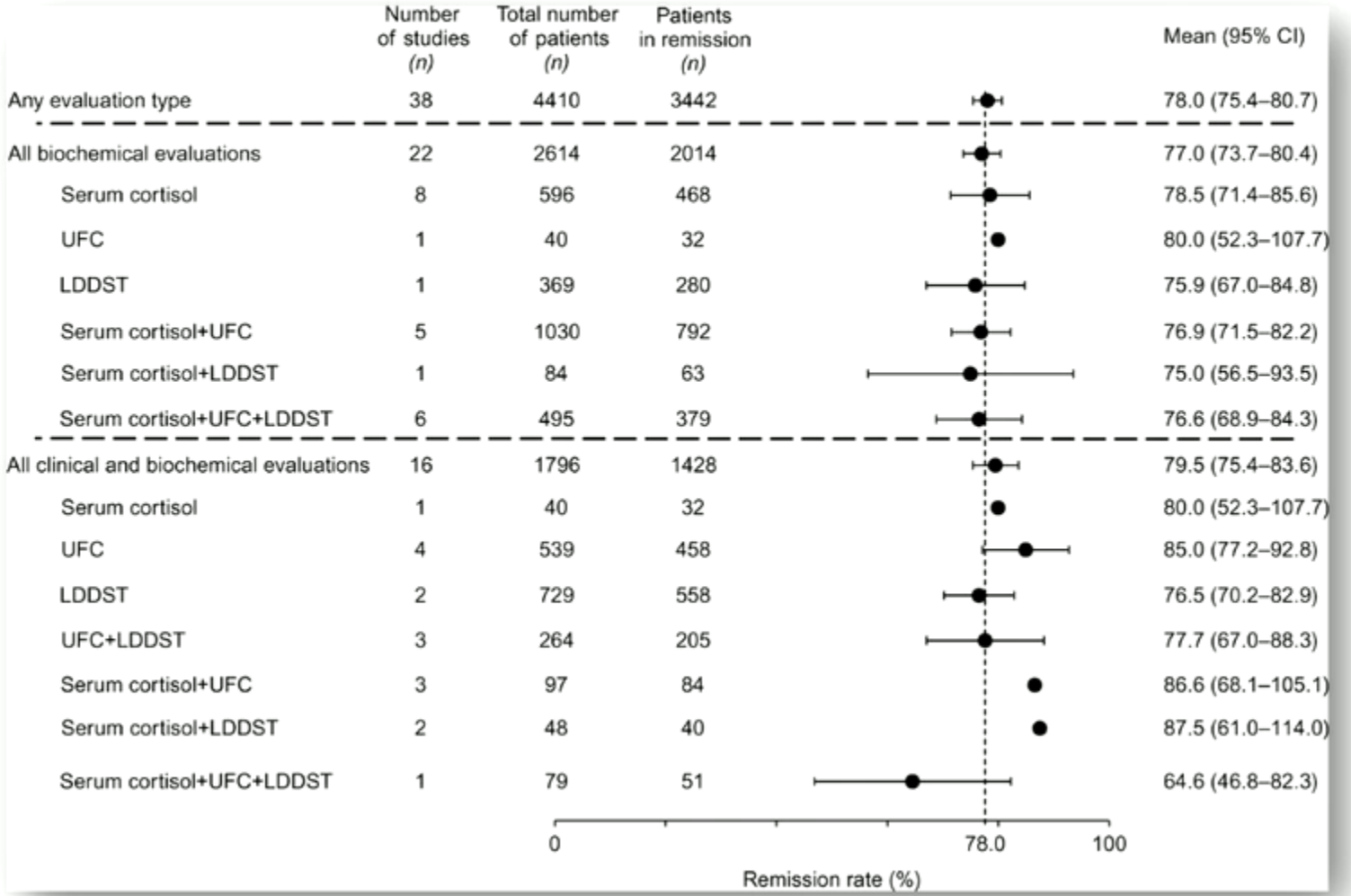
- Plasma ACTH 77 pg/ml (10-50)
- Pituitary MRI : 4 mm lesion

Algorithm for diagnosis of Cushing's syndrome aetiologies



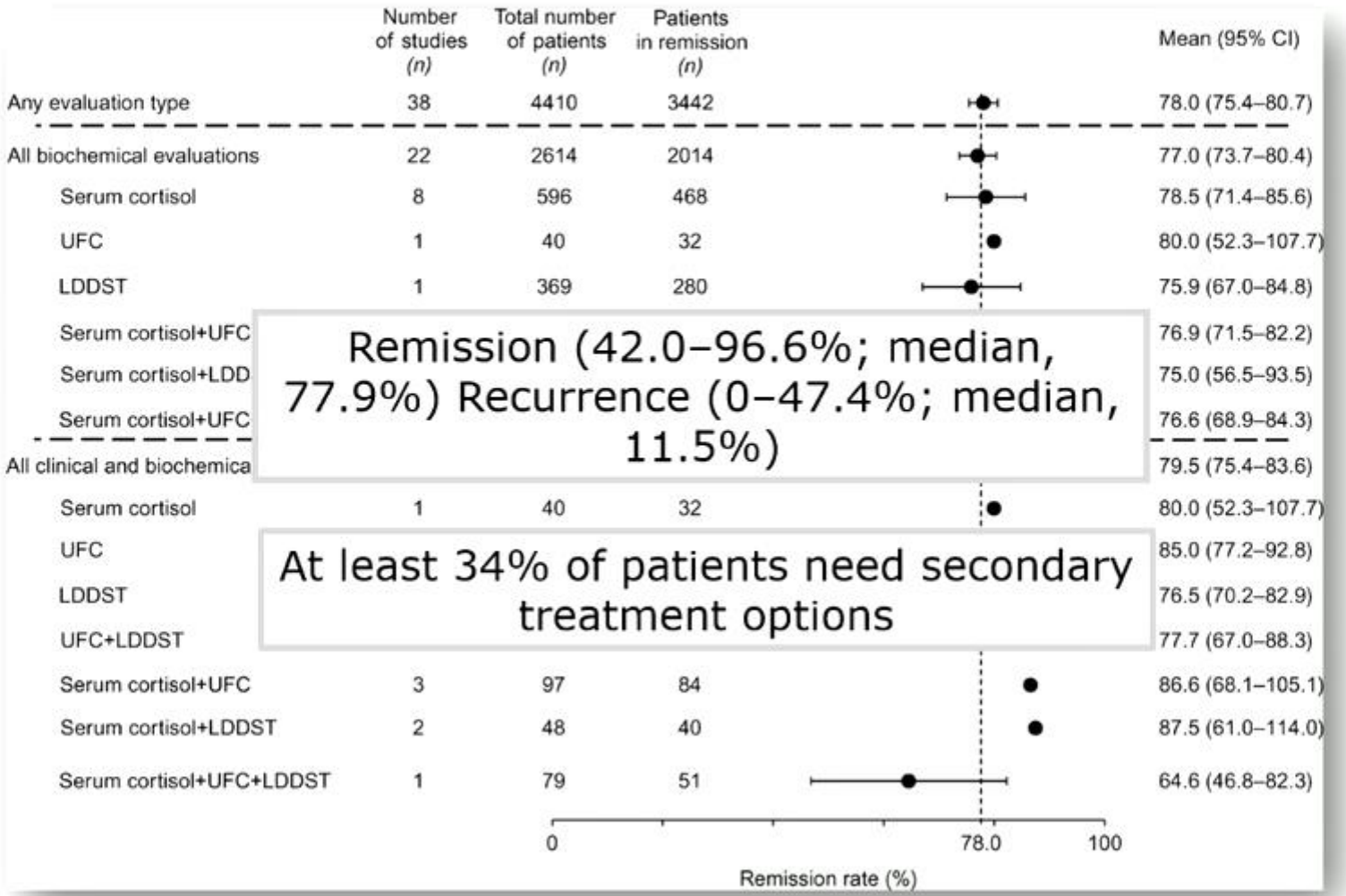
Moniica Gadelha et al., Lancet 2023, 402, 2237

Transsphenoidal Pituitary Surgery: Outcomes



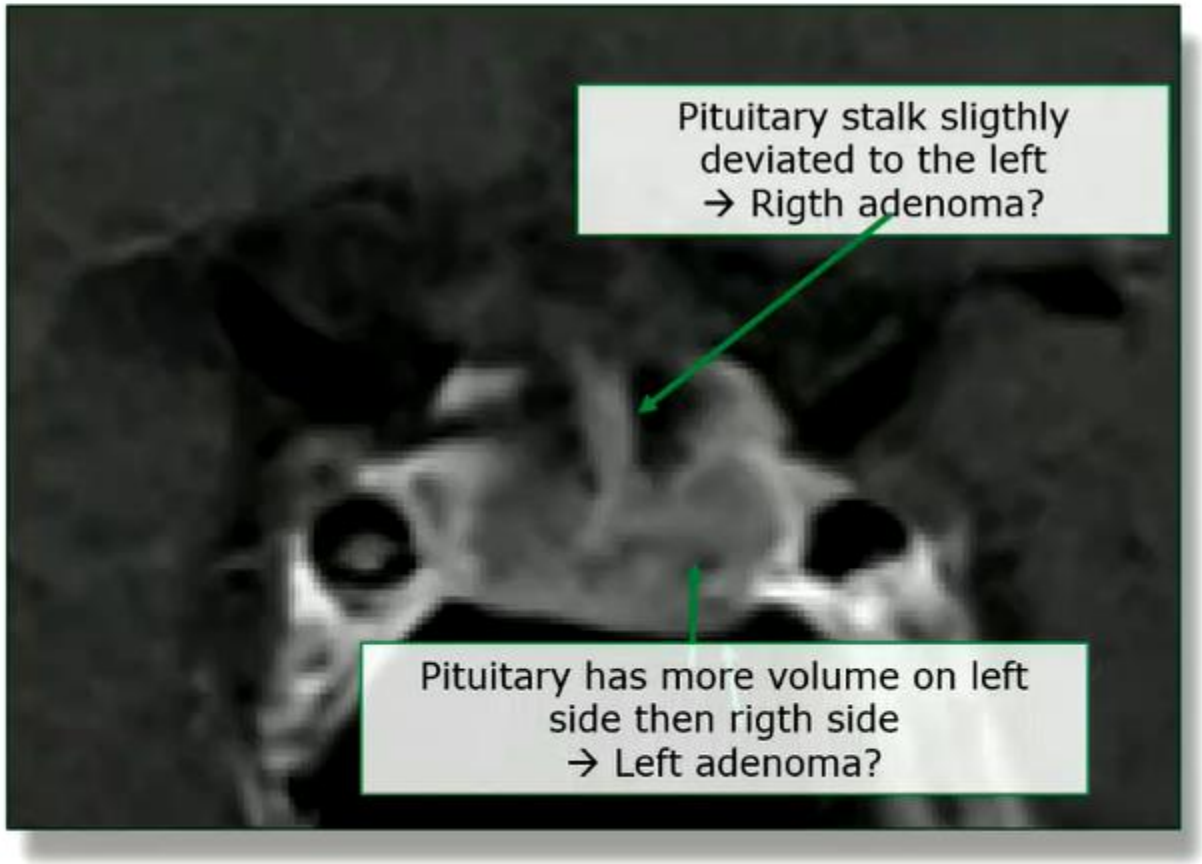
Stephan Petersenn, et al. Eur J Endocrinol 2015;172:R227-R239

Transsphenoidal Pituitary Surgery: Outcomes



Stephan Petersenn, et al. Eur J Endocrinol 2015;172:R227-R239

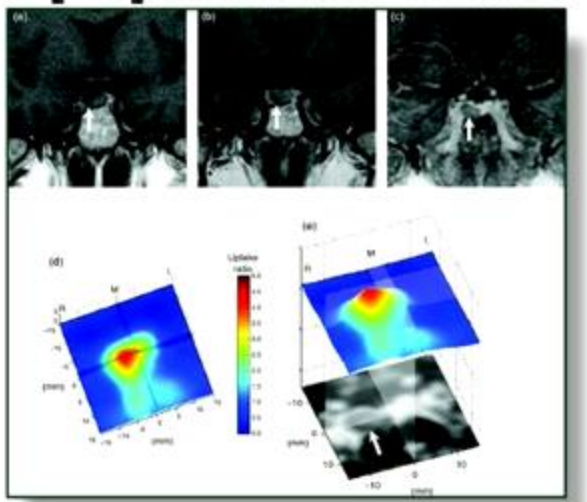
Typical problems of MRI interpretation in Cushing‘s disease



Molecular Imaging in ACTH-dependent Cushing's syndrome:

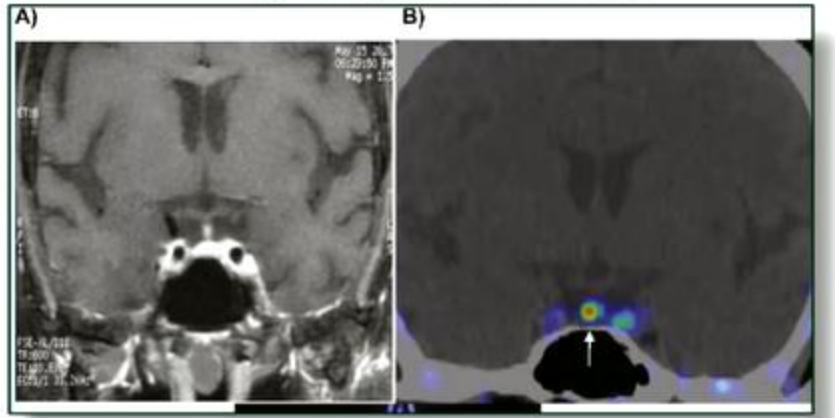
NIKUM

[^{11}C]methionine-PET/CT



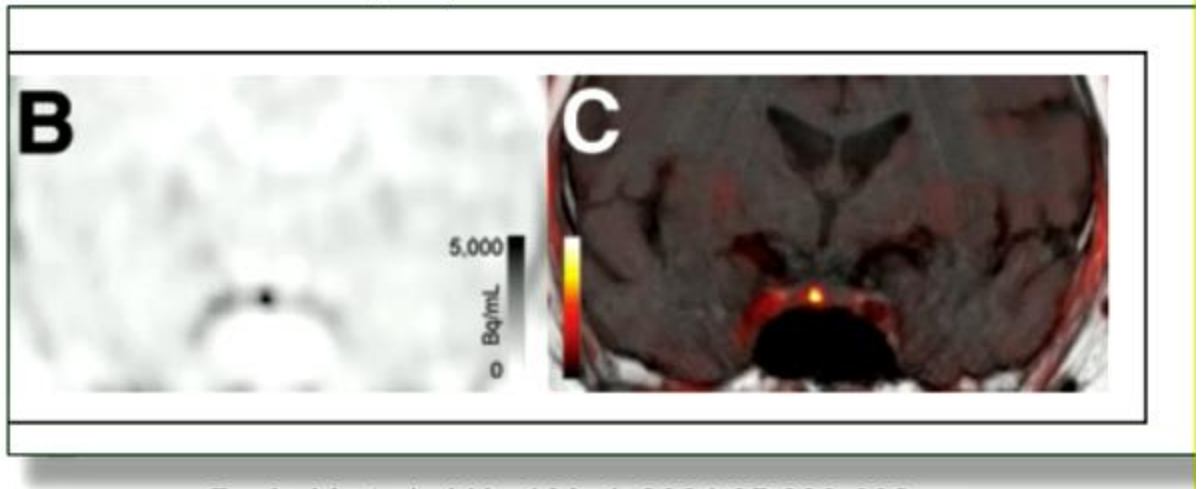
Koulouri O, …, **Gurnell M**. Eur J Endocrinol. 2015 Oct;173:M107-20.

[^{68}Ga]CRH PETCT



Rama W, et al. J Clin Endocrinol Metab. 2021 Mar 25;106

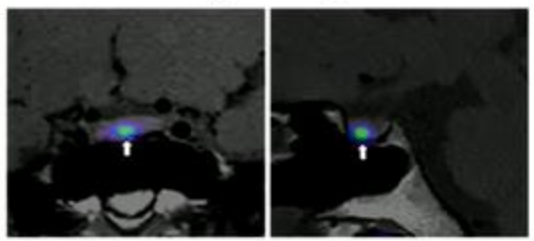
[^{18}F]FET-PET/MRI



Pruis IJ et al. J Nucl Med. 2024;65:688-692

Accuracy and Value of CXCR4-targeted PET/MRI Using ^{68}Ga-Pentixafor for Tumor Localization in Cushing Disease

[^{68}Ga]Pentixafor-PETCT



- Prospective study of 43 participants with Cushing disease.
- ^{68}Ga-pentixafor PET/MRI had 93% sensitivity in localizing 38 of 41 ACTH-secreting pituitary tumors.
- The SUV_{max} was higher in ACTH-secreting pituitary tumor than in normal pituitary tissue (3.9 vs 1.3).

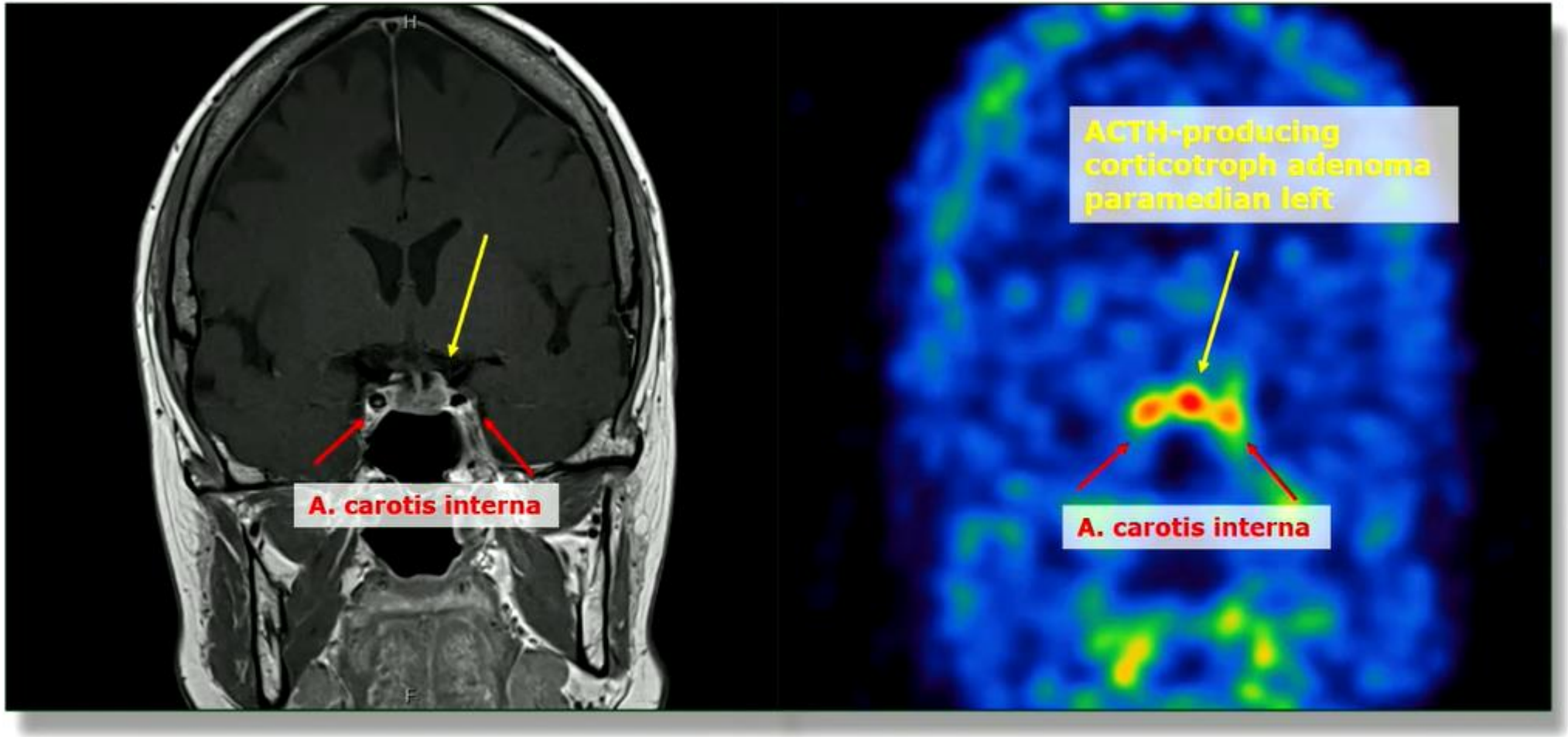
Wu Yue and Wu Yanfei et al. Published: December 17, 2024
https://doi.org/10.1148/radiol.233469

Radiology

Our own LMU expierence June 2024 to January 2025 in 10 consecutive patient

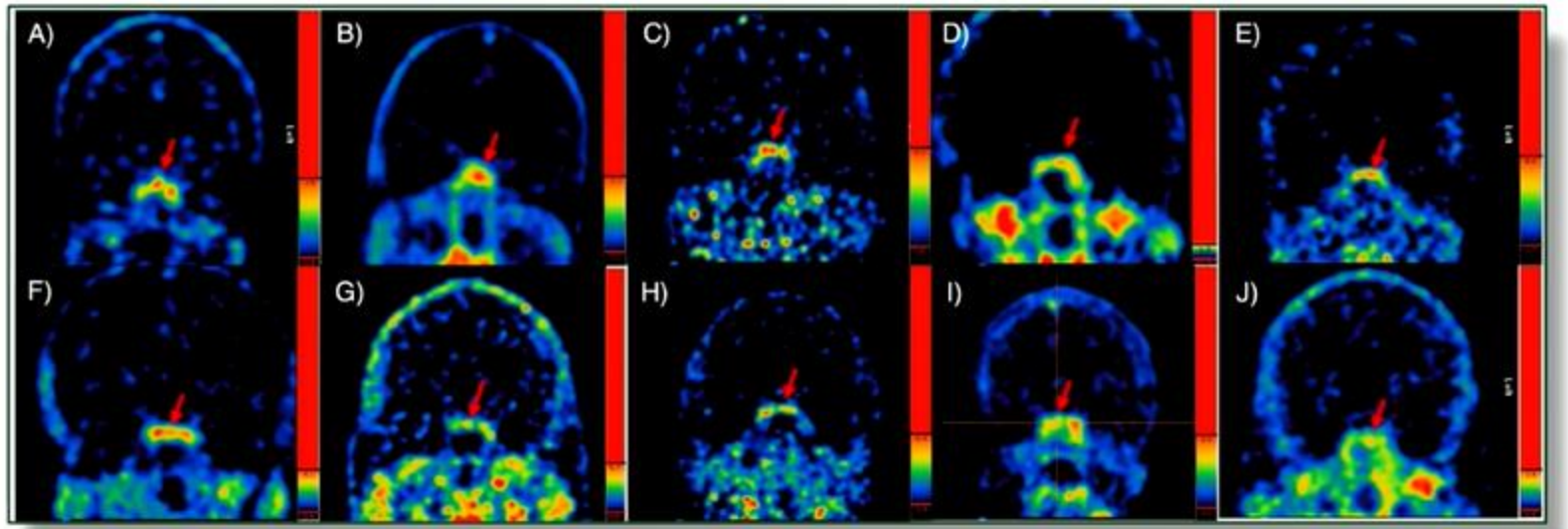
MRI ± IPSS ± [^{18}F]FET-PET in 10 de novo patients with Cushing‘s disease

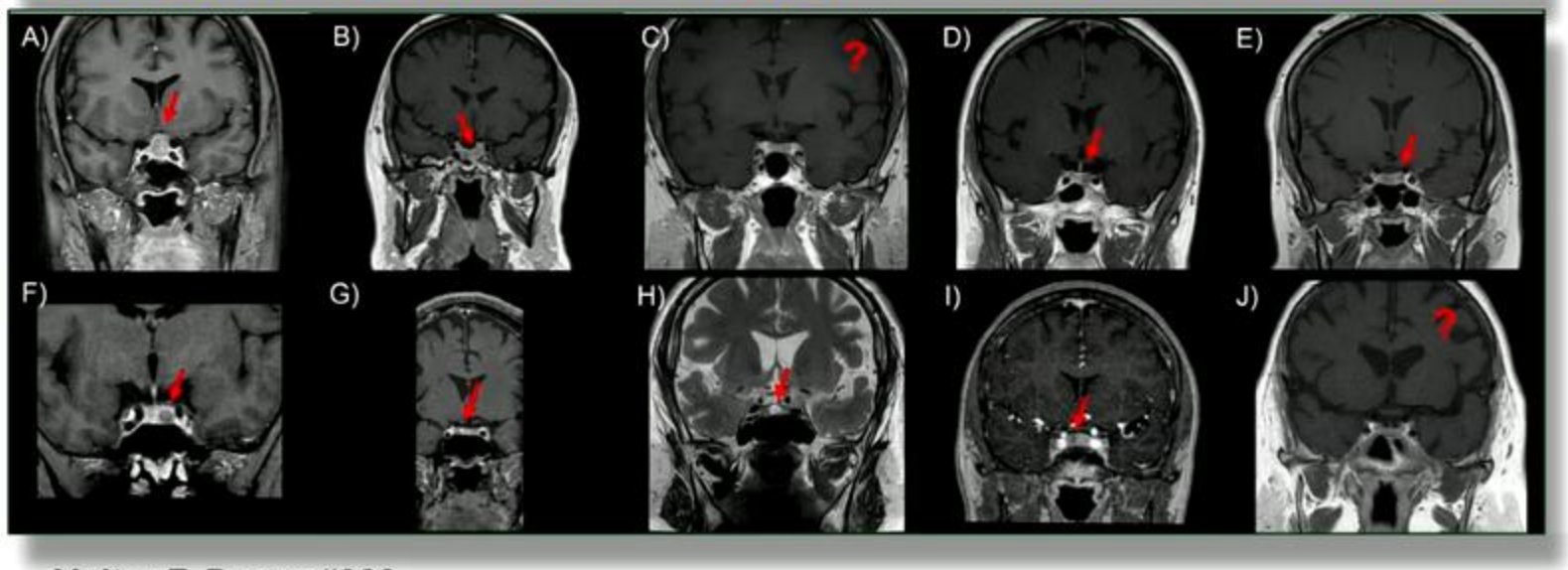
[^{18}F]Fluorethyltyrosin-PET:



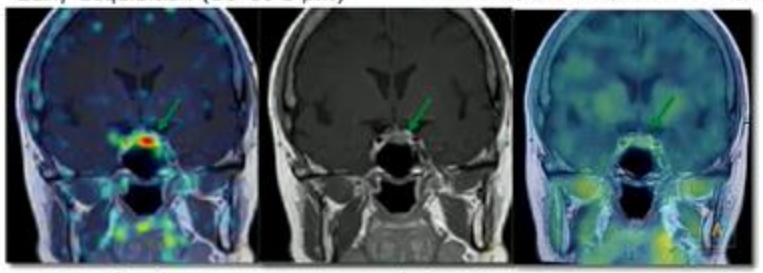
LMU KLINIKUM

[^{18}F]FET-PET shows Hotspots in all 10 consecutive Patients



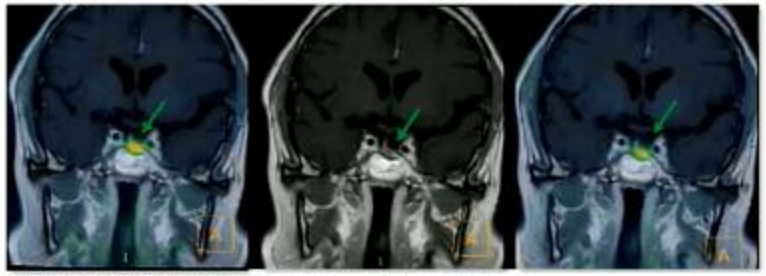


Early acquisition (30-60 s p.i.) Late acquisition (20-40 min p.i.)



Dynamic [^{18}F]FET-PET in patient with first diagnosis

Early acquisition (5-10 min p.i.) Late acquisition (20-40 min p.i.)



Dynamic [^{18}F]FET-PET in patient with recurrence

Völter F, Poster #828

Pilot study: [^{18}F]FET-PET for preoperative localisation in 10 patients with suspected Cushing's disease

Results:

- 10 Patients (5 microadenomas, 2 macroadenomas, 3 MRI negativ)
- Focal intrasellar hot spots **in all patients**
- 9/10 Patienten underwent transsphenoidal surgery
  - PET localization was in all cases confirmed intraoperatively and histologically (100% sensitivity und specificity)
- Postoperative evaluation:
  - Remission in **100% of cases** (Median cortisol 1.8 µg/dl (0.6–3.3)

Breakthrough 1: Molecular Imaging is rapidly advancing and will guide neurosurgery in the future

Völter F, Poster #828

Case Report

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- New: Secondary amenorrhea and easy bruising
- Pediatrician => Endocrinologist
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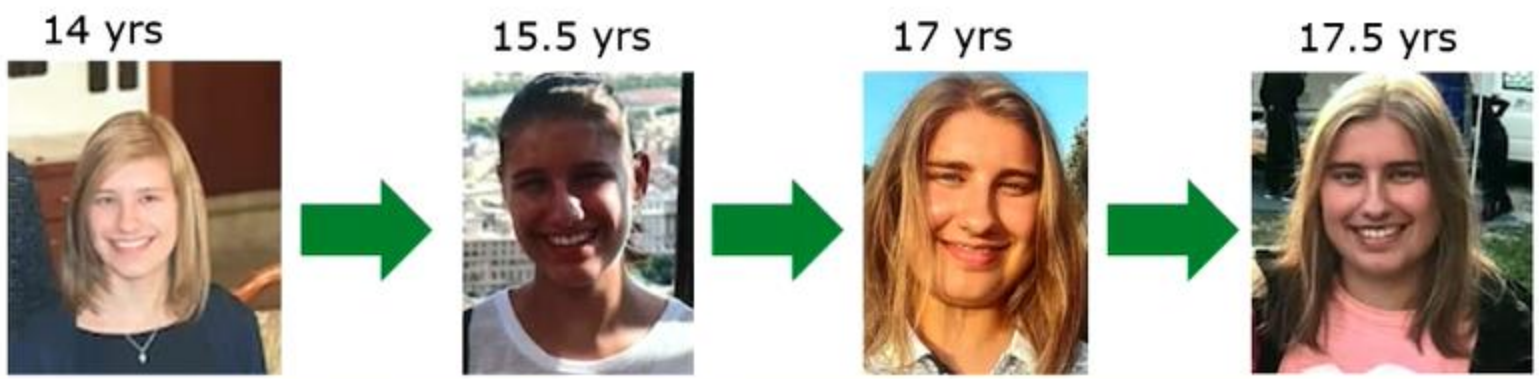
- Late-nigth salivary cortisol 7.3 ng/ml (ULN < 1.7)
- Plasma ACTH 77 pg/ml (10-50)
- Pituitary MRI : 4 mm lesion
- Transsphenoidal surgery => Remission; Histology: Corticotroph tumor, USP mut+



Molecular Pathophysiology of Cushing's disease

1912 1932 1934 1950 1990 2015

Bishop PMF, Close HG. A Case of Basophil Adenoma of the Anterior Lobe of the Pituitary: **Cushing's Syndrome**. Guy's Hosp Rep 1932;82:143-5

Cushing's disease association with **pituitary basophilism** (Bauer, ActaMedScan 1950)

Clonal Origin of Pituitary Adenomas*

VIVIEN HERMAN, JAMES FAGIN, RIVKAH GONSKY, KALMAN KOVACS, AND SHLOMO MELMED

Journal of Clinical Endocrinology and Metabolism Vol. 73, No. 4

Clonal Composition of Pituitary Adenomas in Patients with Cushing's Disease: Determination by X-Chromosome Inactivation Analysis*

HEINRICH M. SCHULTE‡, EDWARD H. OLDFIELD, BRUNO ALLOLIO‡, DAVID A. KATZ‡, RICHARD A. BERKMAN, AND IQBAL UNNISA ALI

Journal of Clinical Endocrinology and Metabolism Vol. 73, No. 2

Monoclonality of Corticotroph Macroadenomas in Cushing's Disease*

CHRISTINE GICQUEL, YVES LE BOUC, JEAN-PIERRE LUTON, FRANÇOIS GIRARD, AND XAVIER BERTAGNA

nature genetics

Mutations in the deubiquitinase gene *USP8* cause Cushing's disease

Martin Reincke[1,13], Silviu Sbiera[1,2,13], Akira Hayakawa[3,13], Marily Theodoropoulou[4,13], Andrea Osswald[1], Felix Beuschlein[1], Thomas Meitinger[5–7], Emi Mizuno-Yamasaki[3], Kohei Kawaguchi[3], Yasushi Saeki[8], Keiji Tanaka[8], Thomas Wieland[5], Elisabeth Graf[5], Wolfgang Saeger[9], Cristina L Ronchi[10], Bruno Allolio[2,11], Michael Buchfelder[12,13], Tim M Strom[5,6,13], Martin Fassnacht[1,2,10,13] & Masayuki Komada[3,13]

Open ORIGINAL ARTICLE

Cell Research (2015) 25:306-317

www.nature.com/cr

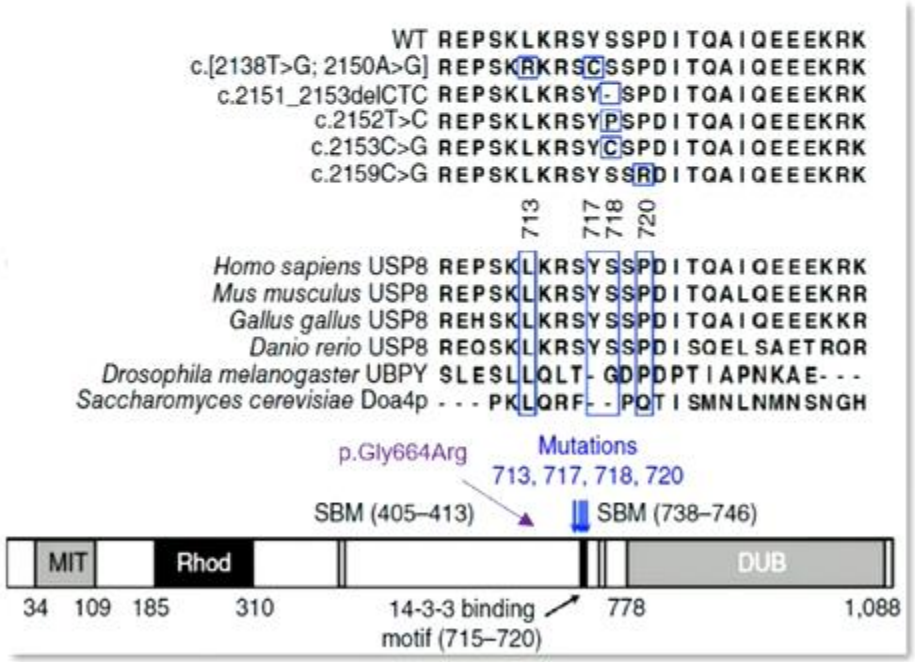
Recurrent gain-of-function *USP8* mutations in Cushing's disease

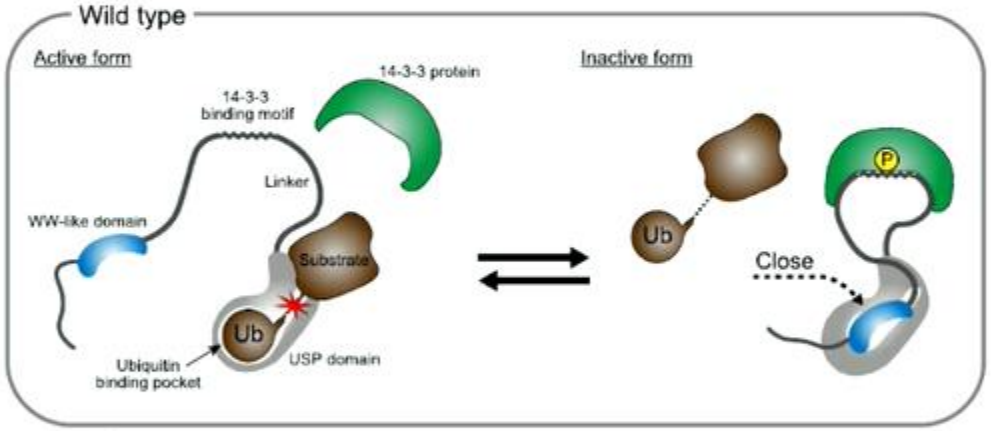
Zeng-Yi Ma[1, *], Zhi-Jian Song[2, *], Jian-Hua Chen[2, 3, *], Yong-Fei Wang[1, *], Shi-Qi Li[2, *], Liang-Fu Zhou[1], Ying Mao[1], Yi-Ming Li[4], Rong-Gui Hu[1], Zhao-Yun Zhang[4], Hong-Ying Ye[4], Ming Shen[1], Xue-Fei Shou[1], Zhi-Qiang Li[2], Hong Peng[5], Qing-Zhong Wang[1], Dai-Zhan Zhou[1], Xiao-Lan Qin[1], Jue Ji[1], Jie Zheng[2], Hong Chen[6], Yin Wang[6], Dao-Ying Geng[7], Wei-Jun Tang[1], Chao-Wei Fu[8], Zhi-Feng Shi[1], Yi-Chao Zhang[1], Zhao Ye[1], Wen-Qiang He[1], Qi-Lin Zhang[1], Qi-Sheng Tang[1], Rong Xie[1], Jia-Wei Shen[2], Zu-Jia Wen[2], Juan Zhou[2], Tao Wang[9], Shan Huang[9], Hui-Jia Qiu[1], Ni-Dan Qiao[1], Yi Zhang[1], Li Pan[1], Wei-Min Bao[1], Ying-Chao Liu[10], Chuan-Xin Huang[11], Yong-Yong Shi[2, 12], Yao Zhao[1]

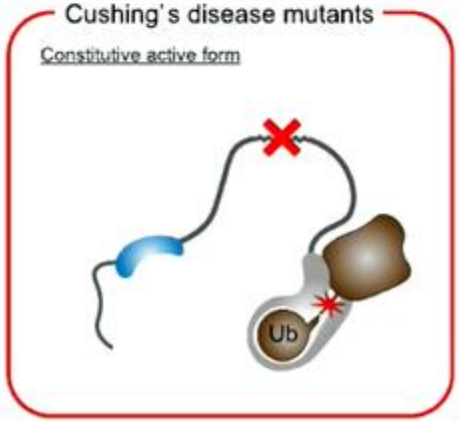
Harvey Cushing, *The Pituitary Body and Its Disorders: Clinical States Produced By Disorders of the Hypophysis Cerebri*. 1912

The USP8 mutational hotspot

- Ubiquitin specific peptidase 8: de-ubiquitinase
- Somatic mutational **hotspot**: p.Ser718/p.Pro720 (plus one outside the hotspot: p.Gly664Arg)
- (First) Detected in 40%/60% of corticotroph tumours
- Disrupt 14-3-3 binding → abolish autoinhibitory function







2015 to 2025: 10 years of USP8 research

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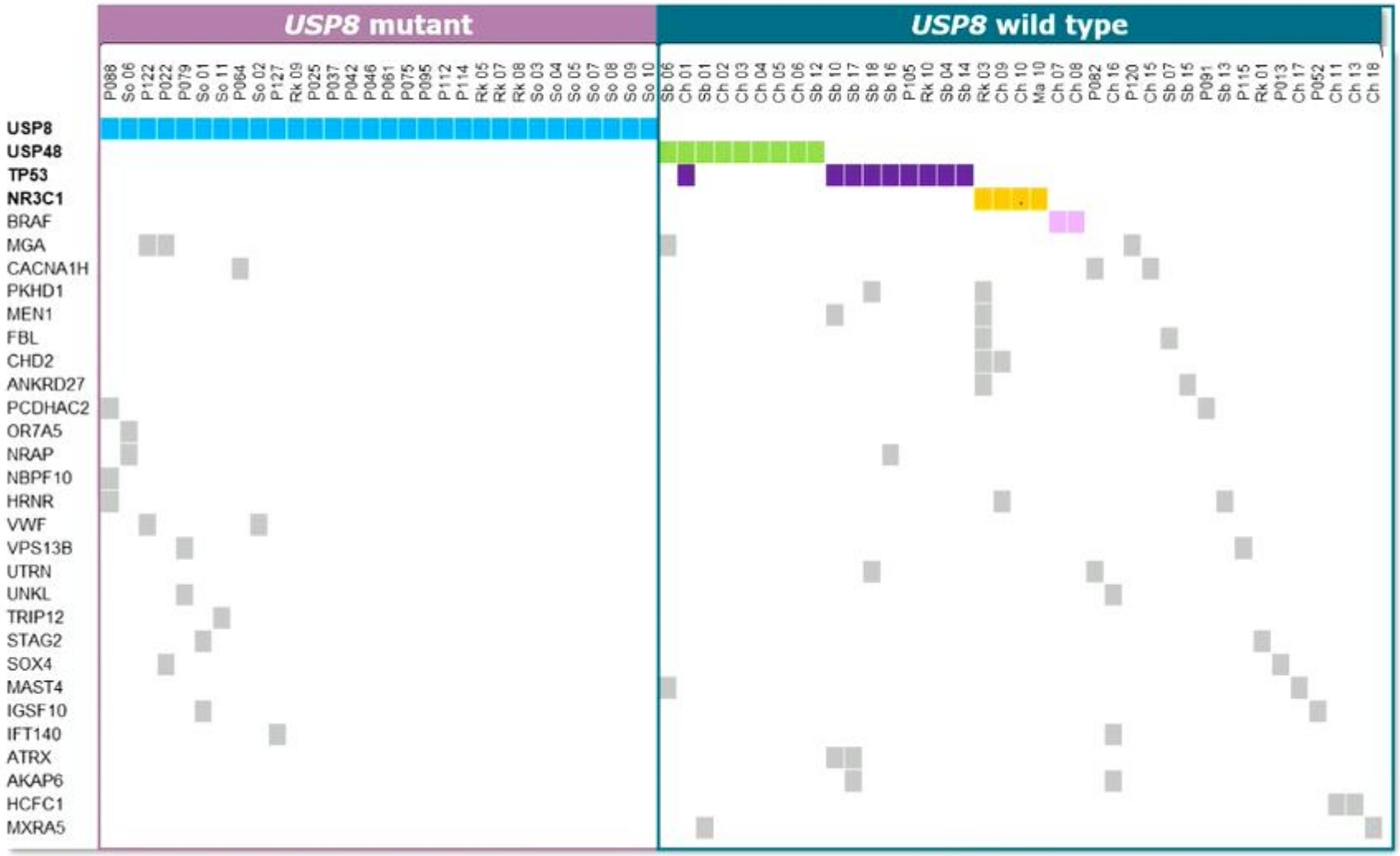
Luis Gustavo Perez-Rivas



n=85 functional corticotorph tumours

NGS data from:

- *Reincke et al., Nat Gen 2015*
- *Ma et al., Cell Res 2015*
- *Song et al., Cell Res 2016*
- *Chen et al., Nat Comm 2018*
- *Sbiera et al., Neurooncol 2019*
- *Neou et al., Cancer Cell 2020*

~68% samples with recurrent mutated genes

Somatic variants present in more than 2 corticotroph tumors.

n=85 functional corticotroph tumors

Compiled by Luis Gustavo Perez-Rivas (n=85 functional corticotroph tumours; somatic variants >2 cases)

Reincke et al., Nat Gen 2015; Ma et al., Cell Res 2015; Song et al., Cell Res 2016; Chen et al., Nat Comm 2018; Sbiera et al., Neurooncol 2019; Neou et al., Cancer Cell 2020

Systematic Review and Meta-analysis

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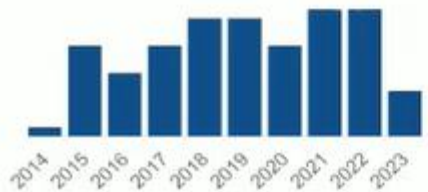
Luis Gustavo
Perez-Rivas

Embase

PubMed

WEB OF SCIENCE

Scopus



3009 extracted records

567 duplicated records

1875 after duplicated records removed

1594 records excluded by title/abstract

281 full-text assessed for eligibility

37 case reports (<3 patients)
15 reviews
43 not related to Cushing's disease
114 without *USP8* status
35 without clinical information

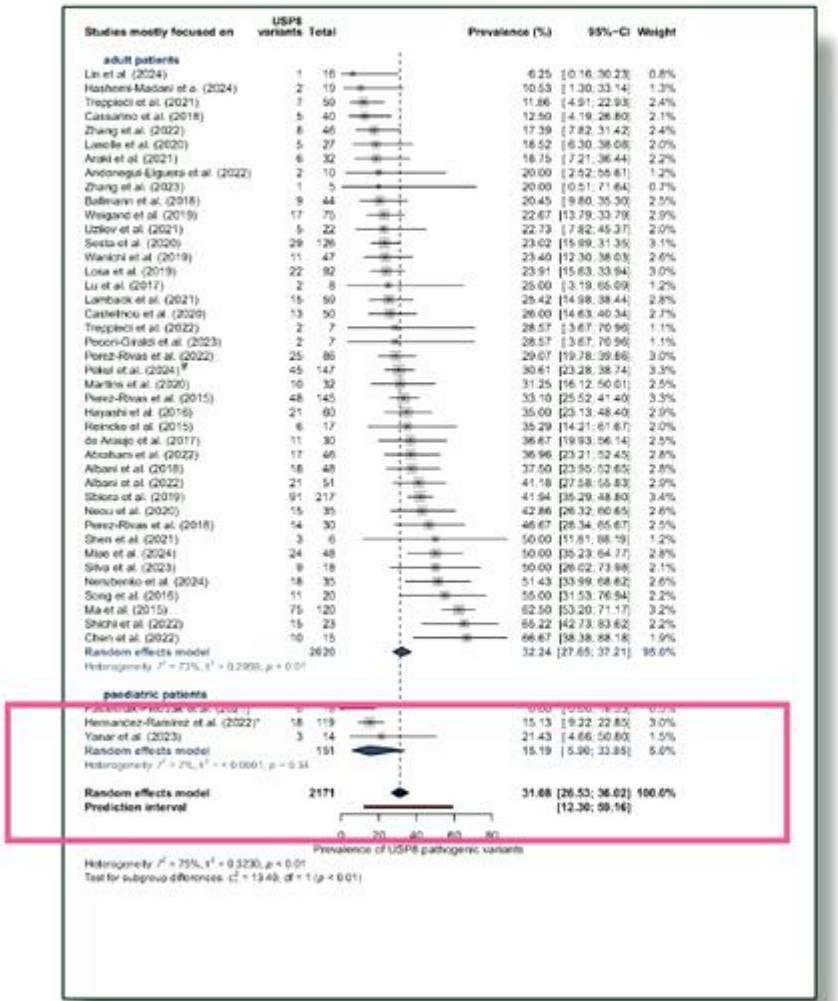
51 publications with *USP8* status

3 articles with same cohort of patients

44 studies reported in the meta-analysis (2.171 tumors)

Statistical analysis

Prevalence and association of somatic USP8 variants



Pooled prevalence in adults: 32.2%

Pooled prevalence in children: 15.1%

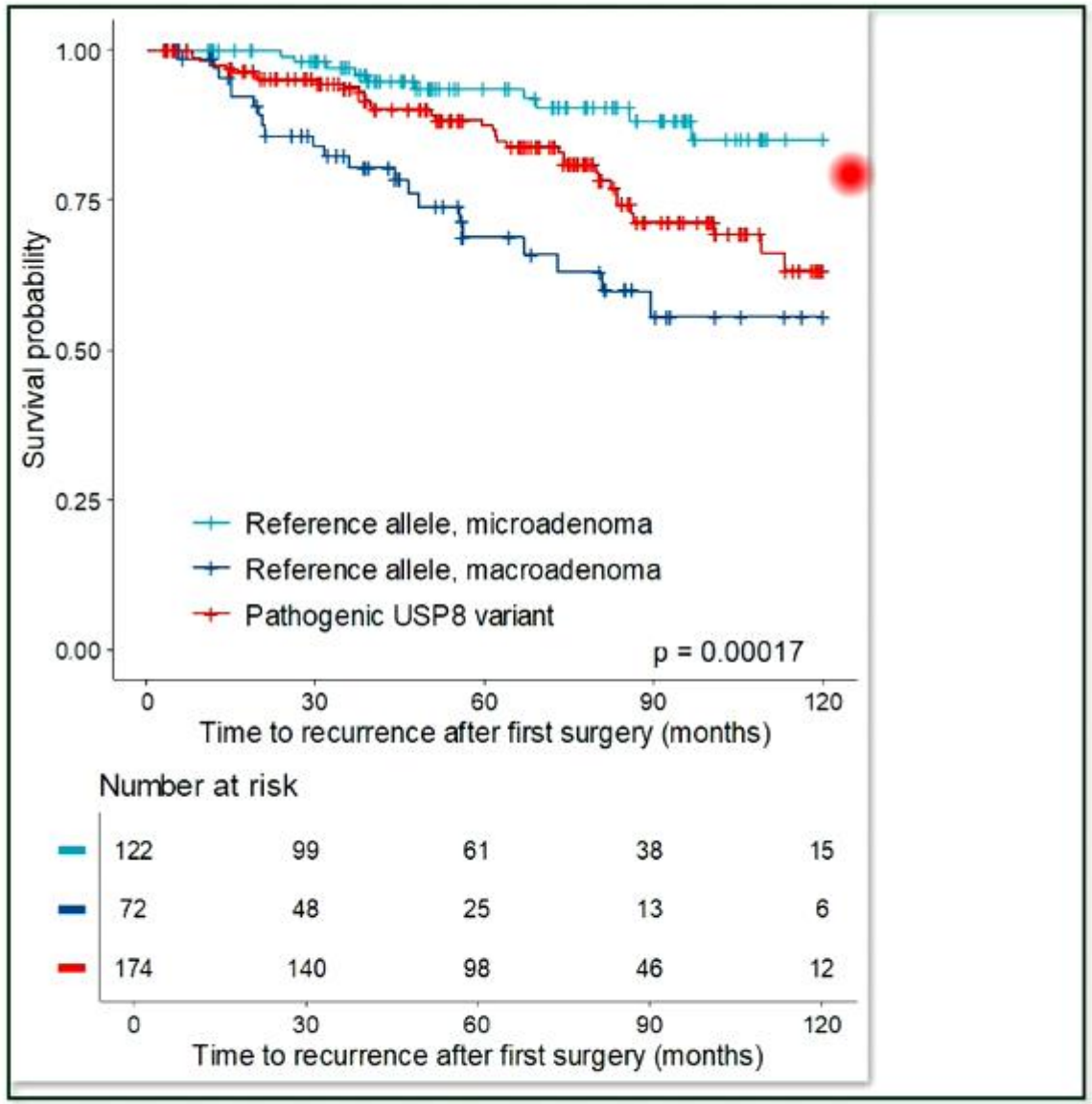
Variables	Effect size*,#,§ [95% CI]	*P-value*	*k*
Age at diagnosis* (years)	-5.1 [-7.8, -2.3]	<0.001	28
Sex§ (female)	3.9 [2.8, 5.5]	<0.001	30
BMI* (kg/m²)	1.5 [-0.2, 2.7]	0.092	8
Preoperative plasma ACTH# (pg/dl)	-0.7 [-9.8, 8.4]	0.887	23
Preoperative serum cortisol# (pg/dl)	0.8 [-0.2, 1.9]	0.123	18
Preoperative 24h UFC# (pg/dl)	-21.5 [-200, 157]	0.806	13
Max. tumour diameter# (mm)	-0.8 [-2.5, 0.8]	0.344	23
Tumour size§ (macroadenoma)	0.9 [0.5, 1.6]	0.654	23
Invasion§	0.6 [0.3, 1.4]	0.256	17
Knosp grade§ (≥3)	0.4 [0.2, 1.0]	0.071	7
Ki67 index§ (≥3)	1.12 [0.6, 2.1]	0.677	8
Postoperative remission§	1.8 [1.1, 2.9]	0.001	18
Recurrence§	2.38 [1.0, 4.3]	0.043	10

** difference of means*

 # difference of medians

§ odds ratio

Luis Perez-Rivas et al. Eur J Endocrinol 2025, accepted



371 tumor samples

HUASHAN HOSPITAL

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ESPE Henning Andersen Award 2025
for the most highly rated abstracts

Seven participating centres

Germany

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Uniklinikum Erlangen

Universitätsklinikum Tübingen

UKE Universitätsklinikum Hamburg-Eppendorf

China

華山醫院 HUASHAN HOSPITAL

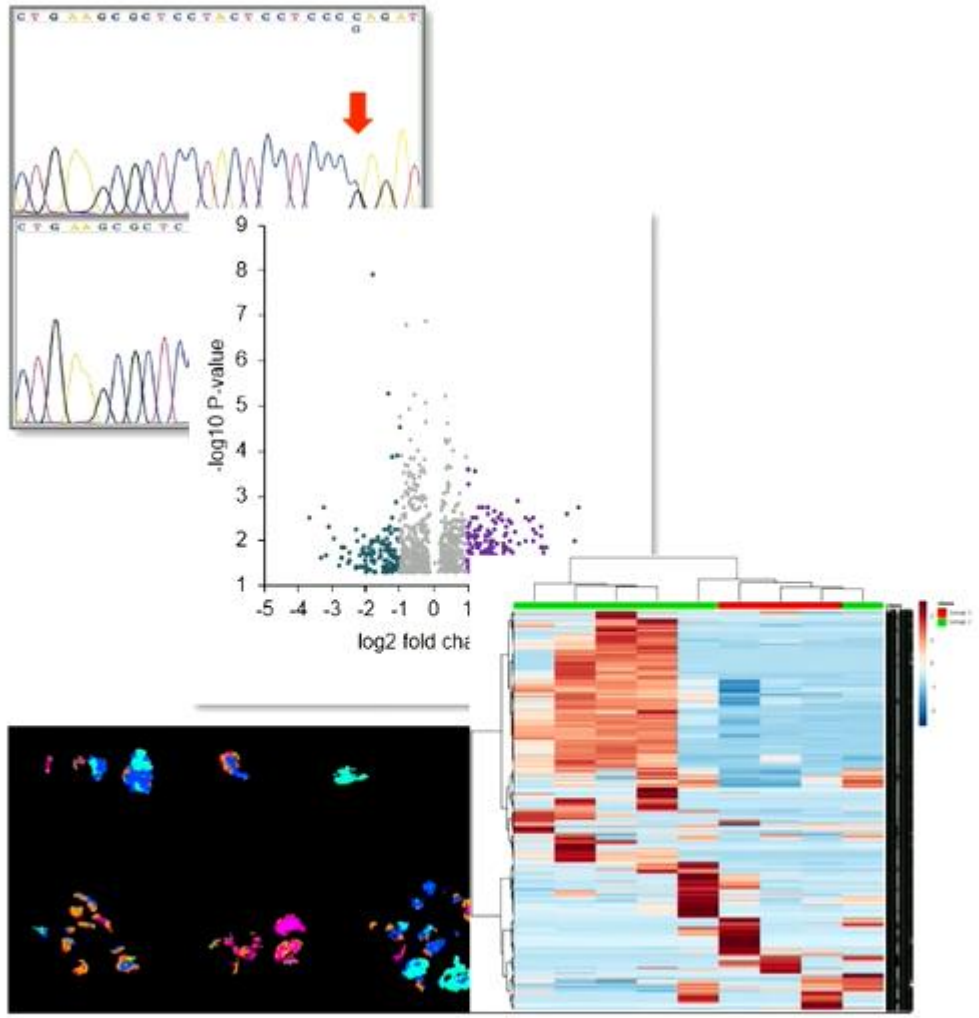
Spain

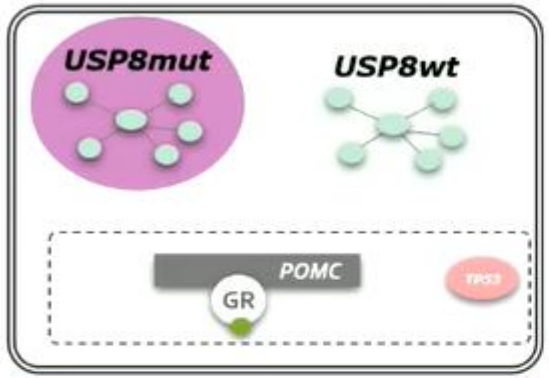
Clínic Barcelona

USA

Brigham and Women's Hospital
Founding Member, Mass General Brigham

Zhang Q, …. Perez-Rivas LG. ESE-ESPE 2025





Surgery

Pharmaceuticals

Disease progression

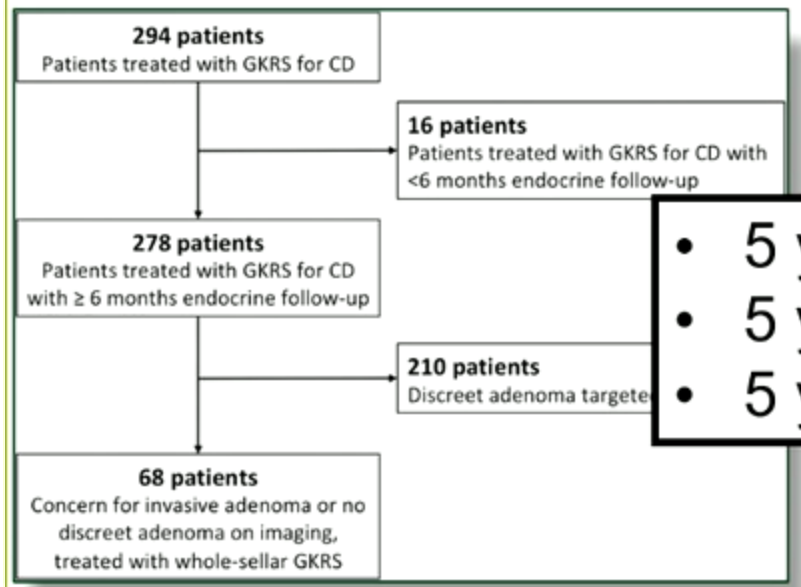
Breakthrough 2: The biomarker USP8 will advance precision medicine in Cushing‘s disease

Case Report

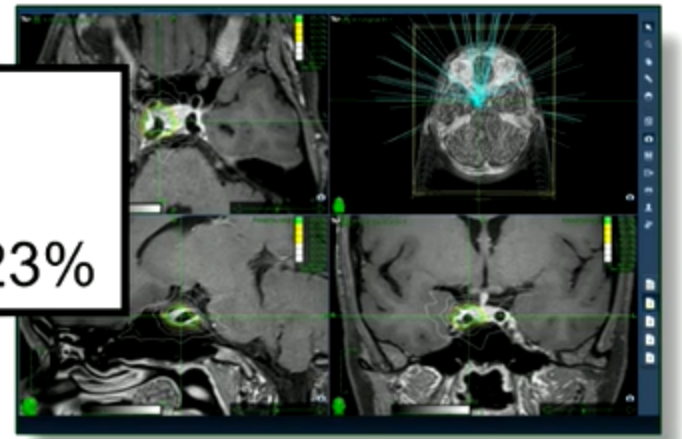
- Progressive symptoms over 2 years (now at age 18)
- New: Secondary amenorrhea and easy bruising
- Pediatrician => Endocrinologist
- 1 mg Dexamethason-Test: Cortisol 9.0 µg/dl (ULN < 1.8)
- UFC: 444 µg/day (ULN <83); Late-nigth salivary cortisol 7.3 ng/ml (ULN < 1.7)
- Plasma ACTH 77 pg/ml (10-50); Pituitary MRI : 4 mm lesion
- Transsphenoidal surgery => Remission (USP8 mut+)
- One year after TSS: Recurrence => GRACE Study (Relacorilant)
- Cyberknife radiosurgery 2023

Gamma Knife Radiosurgery (GKRS)

Retrospective, multicentric, n=68, whole sellar radiation
Shepard MJ, et al. World Neurosurg. 2018 May 18



- 5 year remission rate 76%
- 5 year recurrence rate 13%
- 5 year new pituitary deficiency rate: 23%



Shepard MJ, et al. Technique of Whole-Sellar Stereotactic Radiosurgery for Cushing Disease: Results from a Multicenter, International Cohort Study. World Neurosurg. 2018 May 18. pii: S1878-8750(18)31020-9.

Therapy in Cushing's syndrome, when surgery have failed

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First-line treatment:[1–3]

Surgery to remove primary lesion(s)

Failed surgery or poor candidate

Recurring disease, bridging therapy

Further options:[1,3,4]

Radiation, adrenalectomy

Second-line treatment:[1–5]

Medical therapy

Glucocorticoid receptor blocker[3–5]

- ✓ Mifepristone (for patients with hyperglycaemia)*

Adrenal steroidogenesis inhibitors[2,3]

- ⊖ Etomidate
- ✓ Ketoconazole
- ✓ Levoketoconazole
- ✓ Metyrapone
- ✓ Mitotane†
- ✓ Osilodrostat

Pituitary directed[3,4]

- ⊖ Cabergoline‡
- ✓ Pasireotide sc

✓ Licensed in the **USA and/or EU** for CS or CD ⊖ Used off label

*Approved in the USA to treat hyperglycaemia in patients with CS and type 2 diabetes mellitus; †Approved in the USA/EU to treat advanced adrenocortical carcinoma; ‡Used off label to treat CD; CD, Cushing's disease; CS, Cushing's syndrome; sc, subcutaneous

1. **Nieman LK** *et al. J Clin Endocrinol Metab* 2015;100:2807–31; 2. **Fleseriu M, Biller BMK**. *Pituitary* 2022;25:795–809; 3. **Fleseriu M** *et al. Lancet Diabetes Endocrinol* 2021:9:847–75; 4. **Pivonello R** *et al. Front Endocrinol (Lausanne)* 2020:11:648; 5. **Fleseriu M** *et al. J Clin Endocrinol Metab* 2012:97:2039–49

Medical therapy of Cushing‘s syndrome

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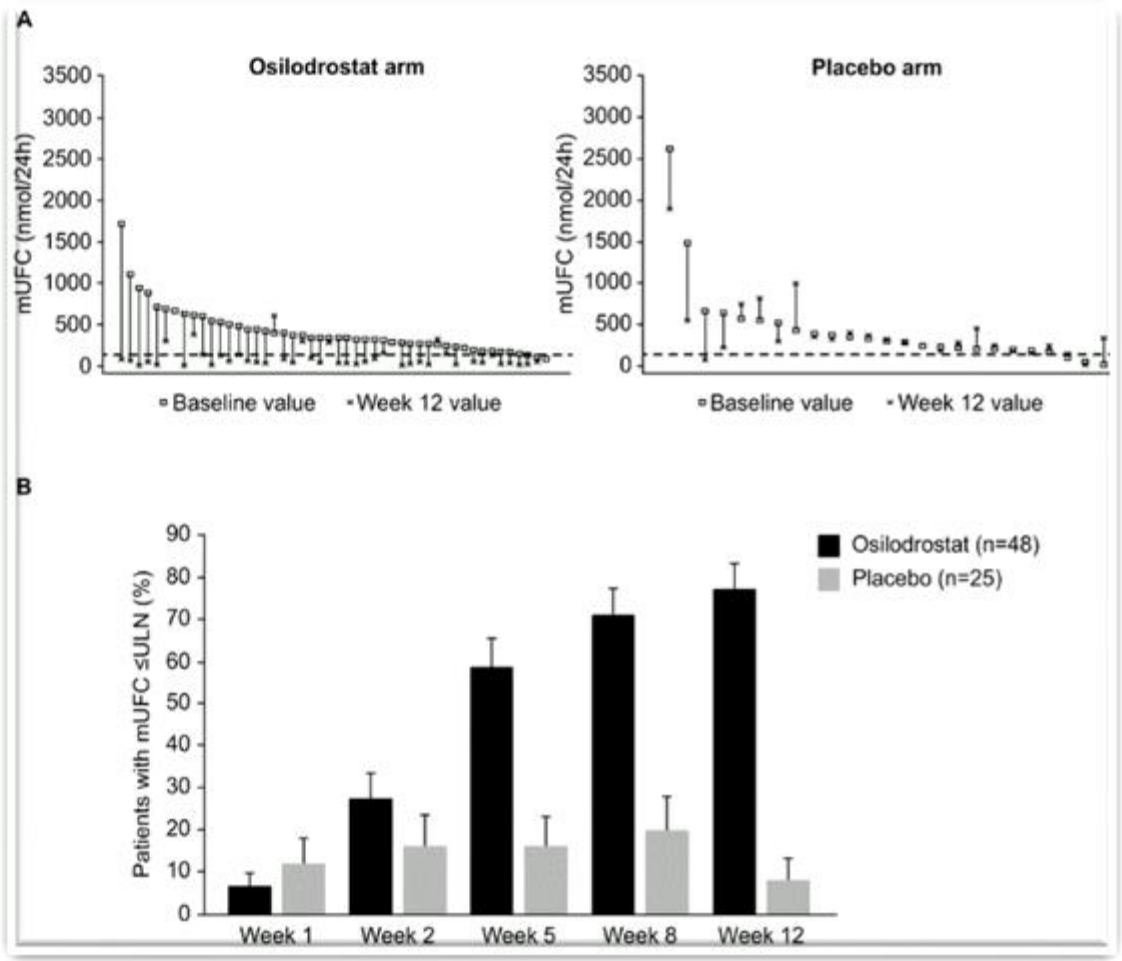
Approved drugs for therapy of Cushing‘s syndrome

- Pasireotide: 2012 (USA + EU): Cushing‘s disease
- Metyrapon und Ketoconazol 2014: (EU): Cushing‘s syndrome
- Mifepristone 2016 (USA): Cushing‘s syndrome
- Osilodrostat 2021 (USA and EU): Cushing‘s syndrome
- Levoketokonazol 2022+2024 (USA and EU): Cushing‘s syndrome

- Relacorilant (CORT125134) in Phase III (Q4 2025?)
- Roscovitine / Seliciclib in Phase III
- Clofutriben in Phase II (ACSpire)
- Atumelnant in Phase Ib/IIa

Phase III Study of Osilodrostat in Cushing‘s Disease



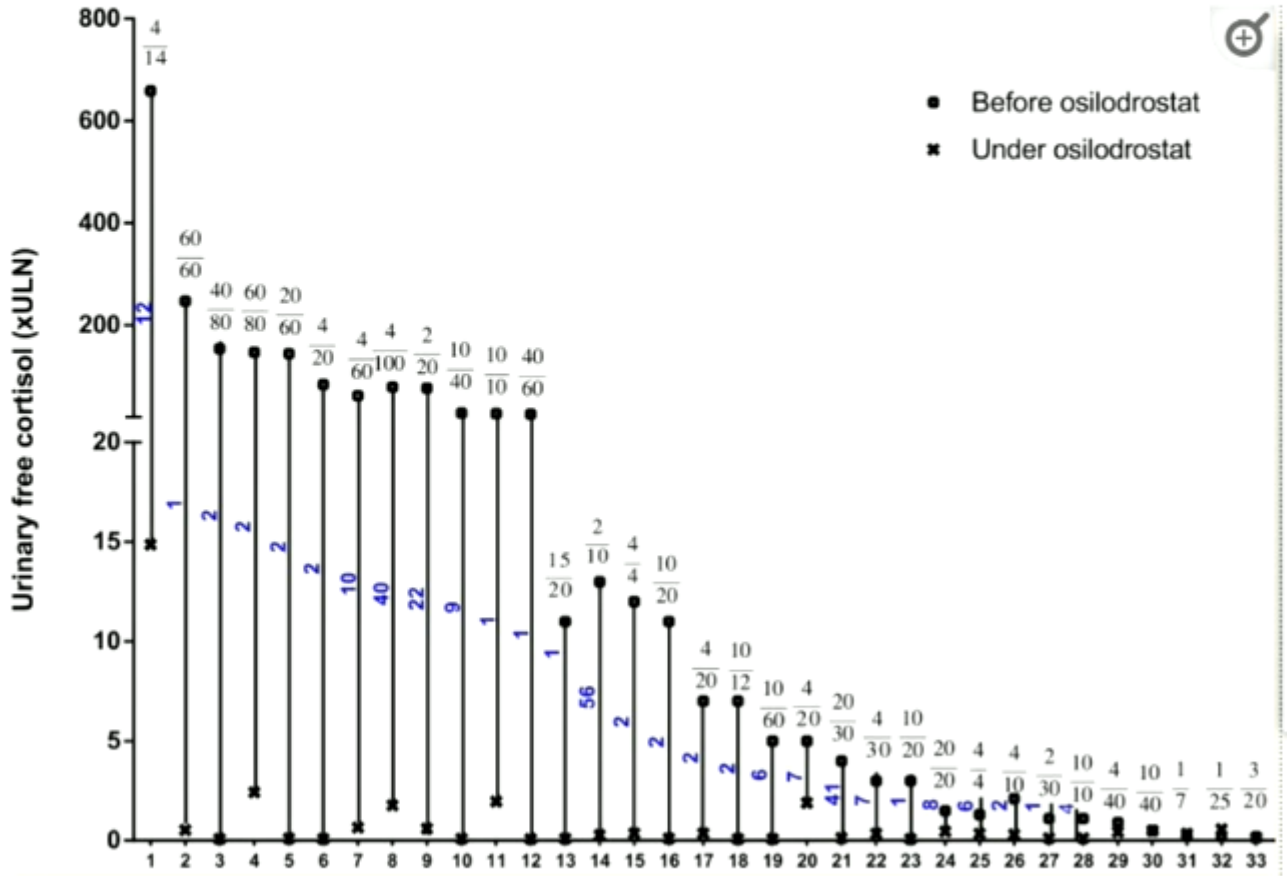
Primary endpoint UFC<ULN
Osilodrostat: 77%
Placebo: 8%

Improved:
- Blood pressure
- HbA1C
- HDL-Cholesterin
- Weigth
- Waist circumference

Side effects
- 37% Loss of appetite
- 35% arthralgia
- 33% Nausea
- 15-25% Adrenal crisis
- Increase in hirsutism 4/33

Mônica Gadelha et al. J Clin Endocrinol Metab. 2022;107:e2882-e2895.

Is Osilodrostat Effective in Paraneoplastic (Ectopic) Cushing's syndrome?



Efficacy (UFC < ULN):
-De novo monotherapy: 9/11 (82%)
-Second line monotherapy: 13/13 (100%)
- therapy: 6/9 (67%)
-Dose: 2-100 mg osilodrostat
-Titration n=6; block and replace n=27

Side effects: 8/33 (24%) of patients had at least one episode of adrenal insufficiency grade 3 and 4; one patient died due to adrenal crisis

Dormoy A, et al. J Clin Endocrinol Metab. 2023 May 17;108:1475-1487.

Longterm remission and recurrens rates in Cushing's syndrome: Results of 296 patients in Munich

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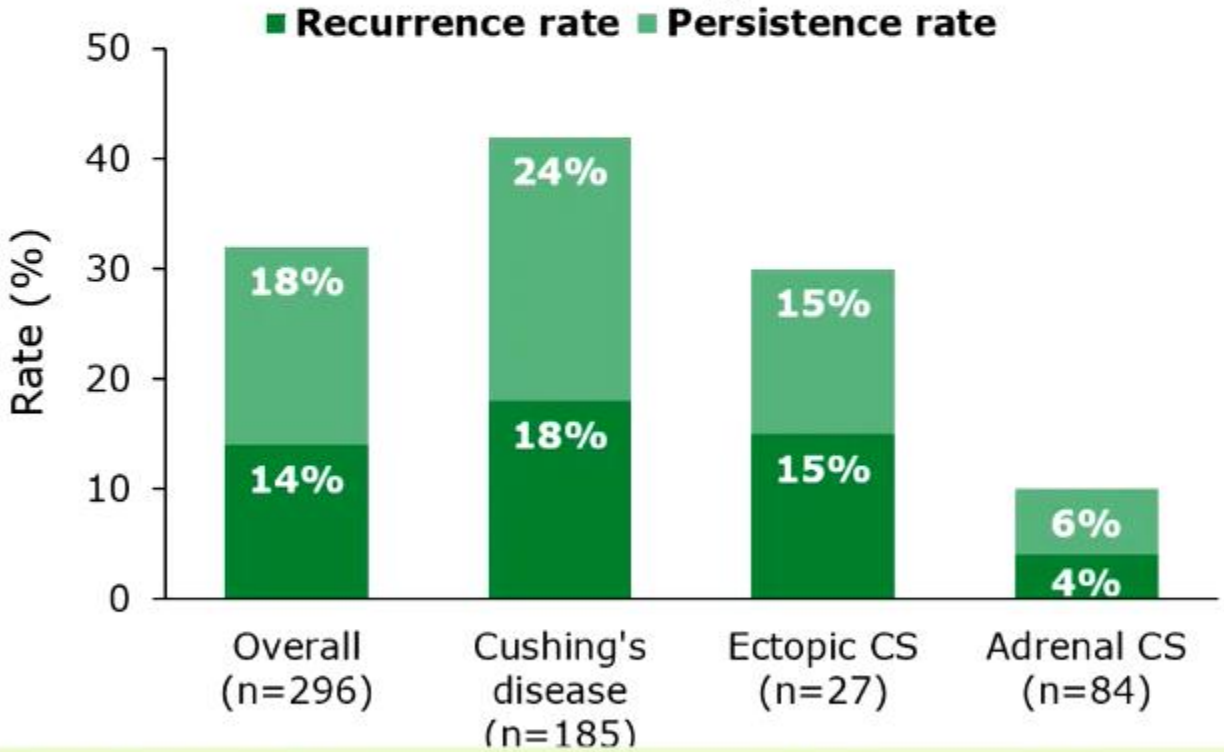
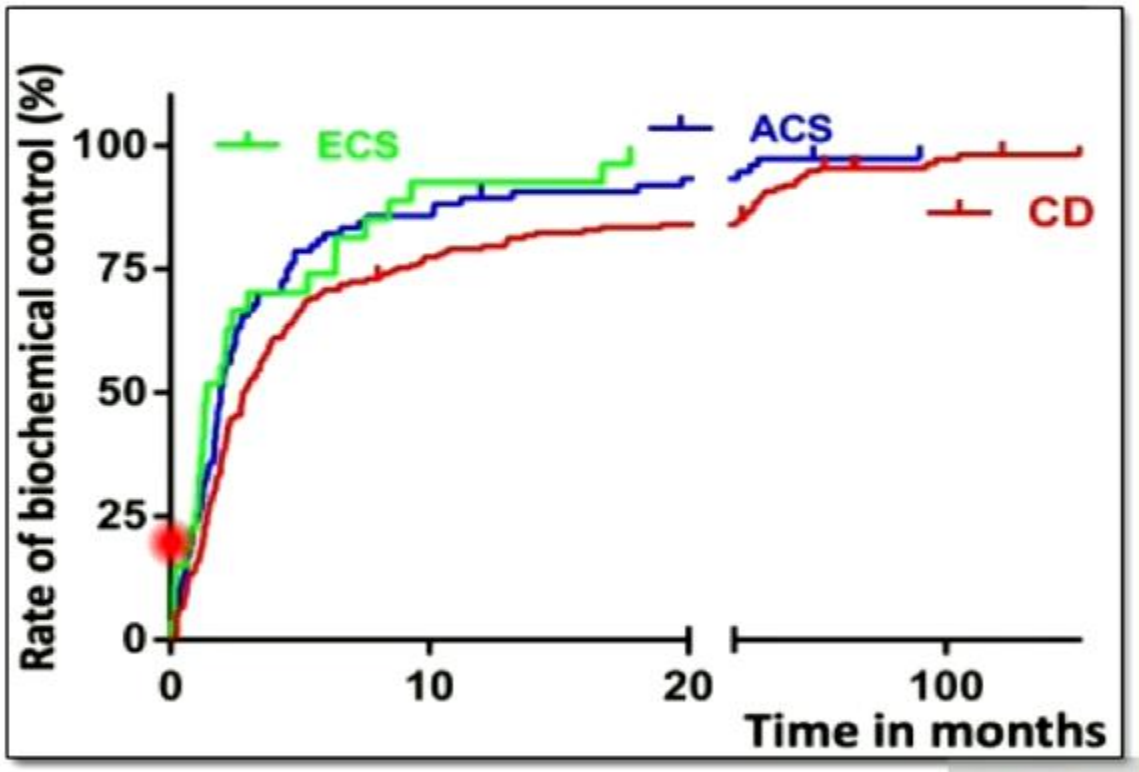
Recurrence/persistence rates following first-line therapy* for Cushing's syndrome overall and by aetiology[1]



Final Control Rate:	**92%.**	**100%**	**94%**



*First-line therapy was surgery (96%) or medical therapy (4%). Median time from biochemical control to recurrence of hypercortisolism was 49.5 months

1. **Ritzel K** *et al. J Clin Endocrinol Metab* 2024;dgae337

Case Report

- Progressive symptoms over 2 years (now at age 18)
- New: Secondary amenorrhea and easy bruising
- Pediatrician => Endocrinologist
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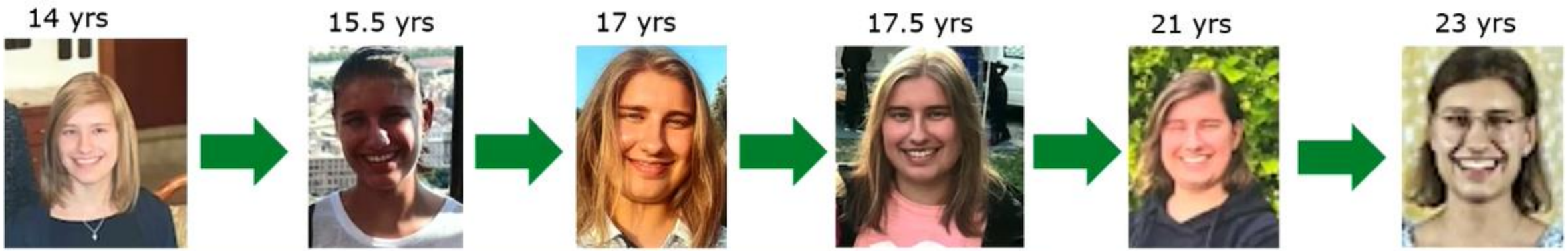
- Cyberknife radiosurgery 2023 => Metyrapone + Ketokonazol + 15 mg Hydrocortisone (UFC < 10 µg/d)



This remarkable young women now aged 24

- -played soccer at high amateur level until recently
- -made her Abitur (A level)
- -Crossed the Alpes while on block & replace in 2023
- -finished her education and became sivil servant (Beamte)
- -moved into a shared apartment and has a boyfriend

She has a normal weigth and no evidence of

- -Osteoporosis
- -Myopathy
- -Psychiatric comorbidities
- -Metabolic disease, etc

Summary: Crosstalk between Pituitary and Adrenal Gland over Lifetime in Cushing‘s syndrome 100 years after Minnie G

- Optimized treatment of patients with Cushing‘s syndrome has improved, but remains a major challenge
- During the last ten years, three major breakthroughs have emerged:
  - *Molecular Imaging* guiding transsphenoidal surgery
  - *USP8 as a molecular predictor* of disease recurrence for future personalized medicine approach
  - *Medical therapy* to control Cushing‘s syndrome if surgery failed

Acknowledging the work of the following groups

Clinician Scientists

- Adriana Albani
- Christina Behr
- Leah Braun
- Julia Fazel
- Markus Kroiss
- Lisa Müller
- Elisabeth Nowak
- Hanna Nowotny
- Matthias Öttle

CRC-TRR

- **Felix Beuschlein**
- **Mario Detomas**
- **Martin Fassnacht**
- **Christina Pamporaki**

- Andrea Oßwald-Kopp
- Katrin Ritzel
- Anna Riester
- German Rubinstein
- Junia Schweizer
- Isabel Stüfchen
- Friedericke Völter
- Frederick Vogel

Neuroendocrinology

Marily Theodoropoulou
Luis Gustavo Perez-Rivas
Vivian von Selzam
Julia Simon
Adriana Albani
Sicheng Tang
Xin Feng
Elisabeth Ruoff
Prajina Sharma

KUM - ENDO

Nicole Reisch.
Jochen Schopohl
Stephanie Zopp
& the Cushing ambulance
Dunja Reiß

Endokrinologisches Labor

Martin Bidlingmaier
Katharina Schilbach

Medicover

Günter Stalla

Neurosurgery

Jun Thorsteindottir (Klinikum Großhadern)
Jürgen Honegger (Tübingen)
Jörg Flitsch (UKE)
Michael Buchfelder, Yining Zhang (Erlangen)

Neuropathology

Jochen Herms, Sigrun Roeber, Patrick Harter (Großhadern)
Wolfgang Saeger (UKE)

DFG SFB 205
The Adrenal: Central Relay in Health and Disease