זרקור על חידושים מכנס ENEA אחרון

פרופ' יונה גרינמן
מרכז רפואי תל אביב-סוראסקי

Agenda

חידושים או חשיבות קלינית

- **Neurohypophysis** (Symposium)
  - Central DI from a patient's perspective
  - Oxytocin
- **Acromegaly** (Symposium and oral presentations)
  - Paradoxical increase of GH in Acromegaly- clinical implications
  - Oral treatment
- **Cushing** (oral presentations and posters, meet the expert)
  - Osilodrostat
  - Nonpeptide ACTH (MC2) receptor antagonist
  - Clinical highlights
- **Prolactinoma genetics** (oral presentation)
  - Germline
- **Medical treatment of craniopharyngioma** (symposium and poster)

Central diabetes insipidus from a patient's perspective: management, psychological co-morbidities, and renaming of the condition: results from an international web-based survey

Cihan Atila, Paul Benjamin Loughrey, Aoife Garrahy, Bettina Winzeler, Julie Refardt, Patricia Gildroy, Malak Hamza, Aparna Pal, Joseph G Verbalis, Christopher J Thompson, Lars G Hemkens, Steven J Hunter, Mark Sherlock, Miles J Levy, Niki Karavitaki, John Newell-Price, John A H Wass, Mirjam Christ-Crain

מדגיש נקודות חשובות לשיפור הטיפול

- Central diabetes insipidus is a rare neuroendocrine condition
- Data on treatment-associated **side-effects, psychological comorbidities, and incorrect management are scarce.**
- Cross-sectional, anonymous web-based survey using a customized questionnaire designed by endocrinologists and patients
- Between Aug 2021, and Feb 2022, **1034** patients with central DI participated in the survey.
- 91% were adults (80% women); median age 44 years [34–54]).

Lancet Diabetes Endocrinol 2022; 10: 700–09

Etiology

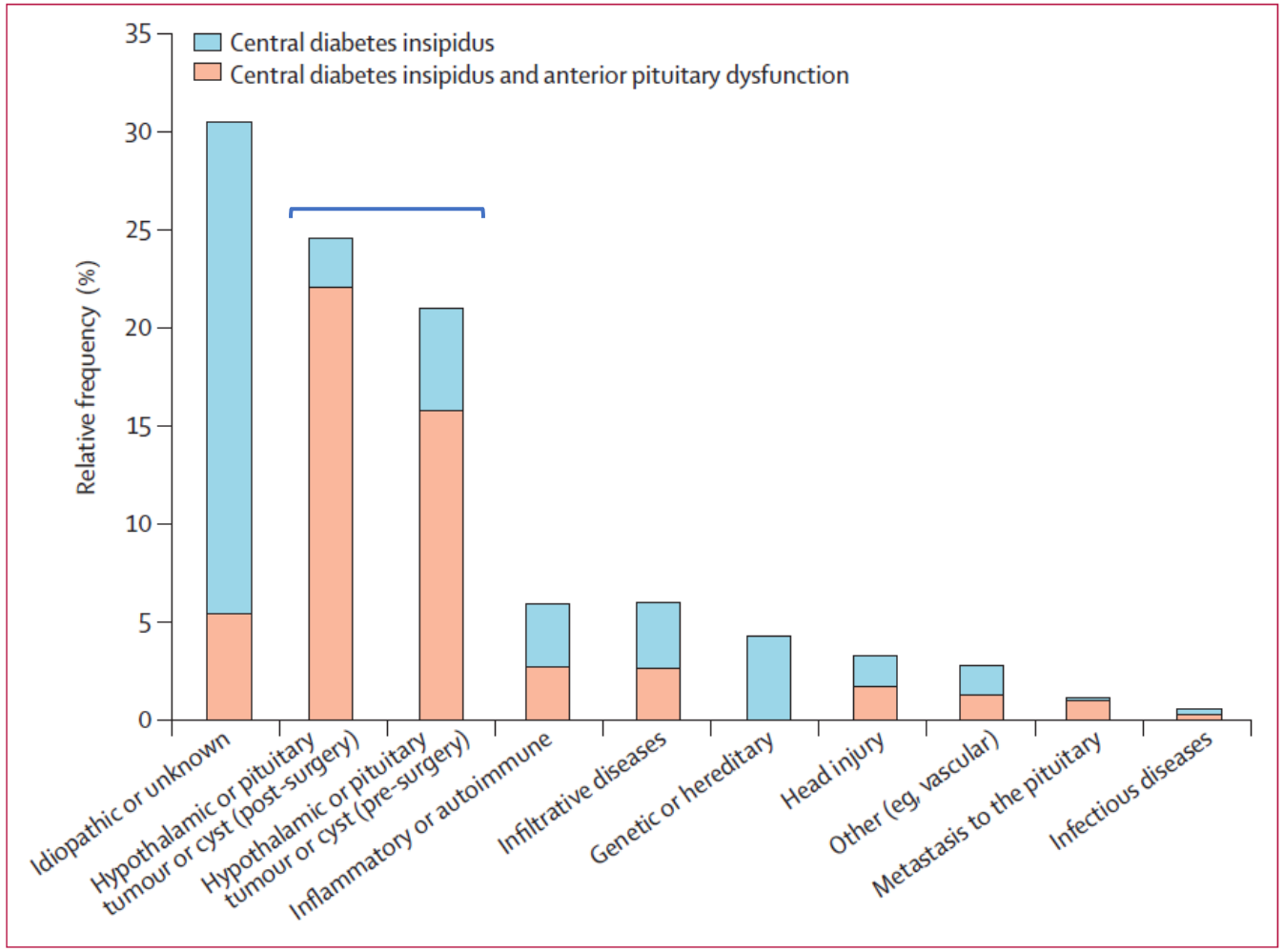


Figure 1: Causes of central diabetes insipidus

Idiopathic -30%
Tumors and cysts (46%)
(pre-surgical 21%;
Postsurgical 25%)

53% of the cohort had combined posterior and anterior pituitary dysfunction

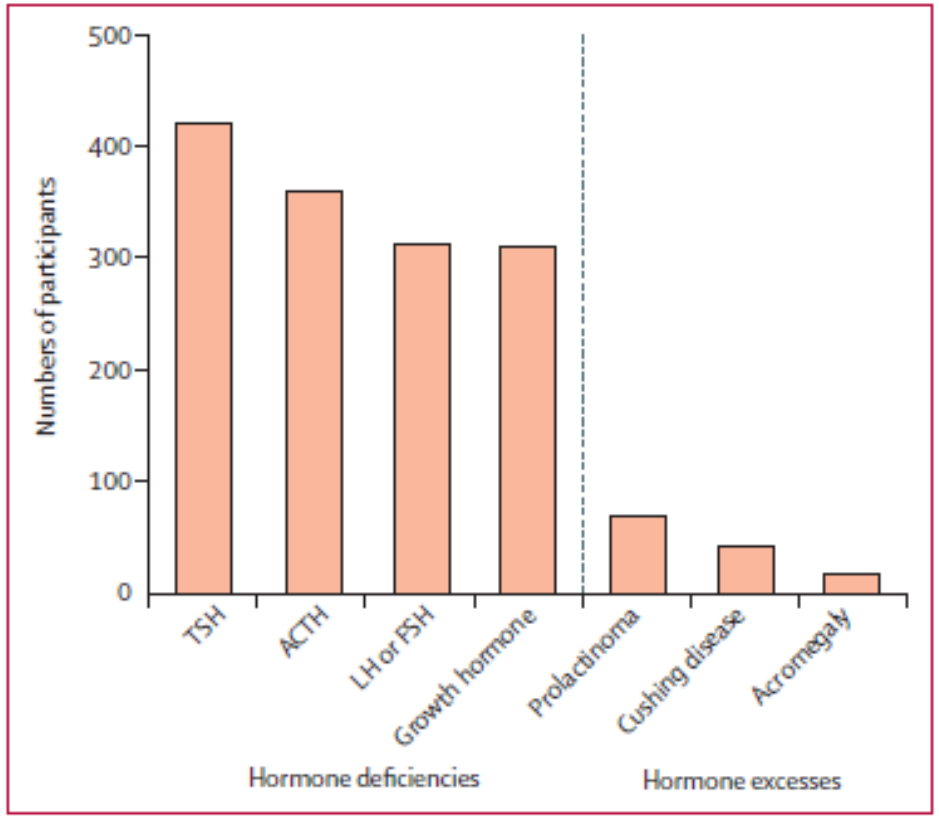


Figure 2: **Anterior pituitary dysfunction**

56% received oral tablets

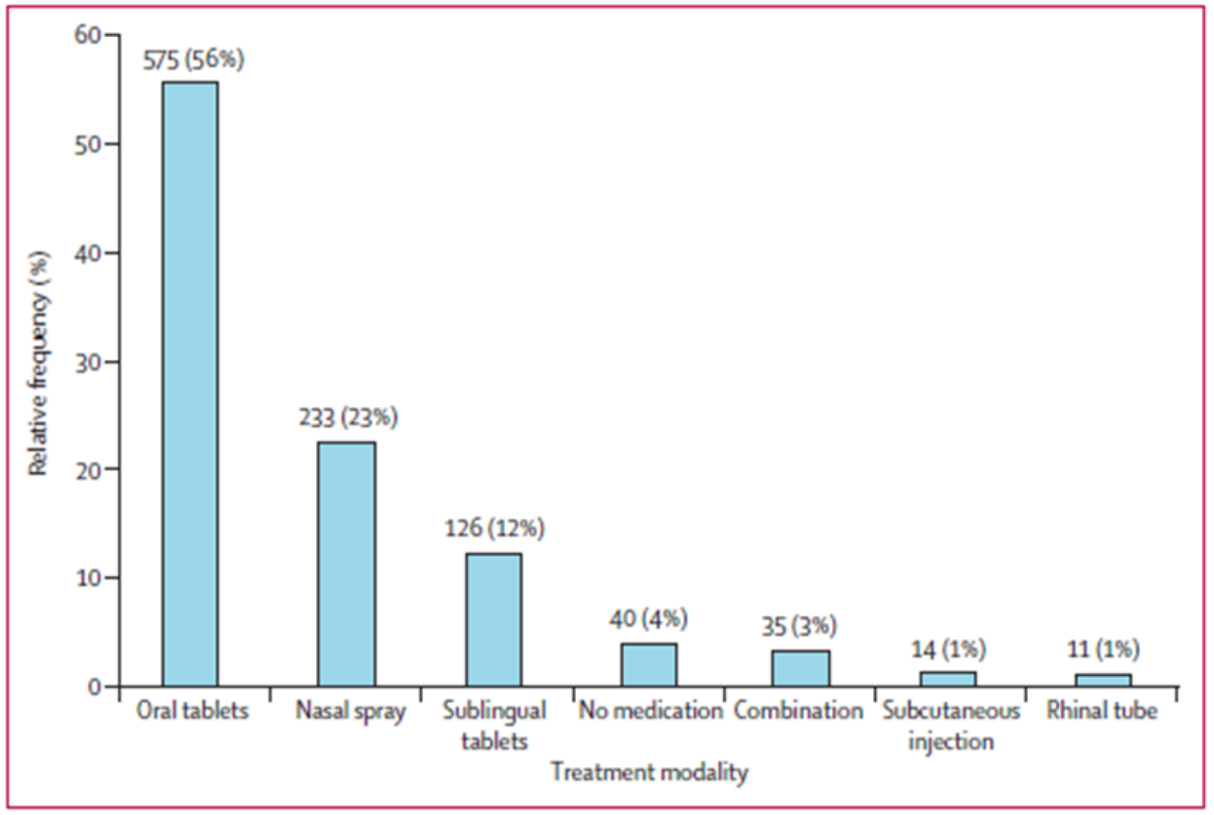


Figure 3: **Type of desmopressin preparation**

Main findings

- **26%** of 994 patients on desmopressin therapy had **hyponatremia** and **15%** had **hypernatremia leading to hospitalization**.
- Patients who routinely **omitted or delayed desmopressin** to allow intermittent aquaresis (67%) had a significantly lower prevalence of hyponatremia (17%) compared with those not aware (32%) of this approach (odds ratio 0·44).
- Of patients who had to be hospitalized for any medical reason, 13%) of patients **did not receive desmopressin while in a fasting state** (nil by mouth) while **without IV fluid** replacement and reported symptoms of dehydration
- **24%** had **problems receiving desmopressin** during hospitalization (56% non-availability, 41% provision only on a scheduled time)
- Call for a campaign to **increase awareness and education of medical personnel**, and the request to **include desmopressin as a high-alert medication with 24 h access in hospitals**

Main findings (cont.)

- 660 (64%) participants reported lower quality of life (decreased social and recreational activities)
- 369 (36%) had psychological changes (anxiety, decreased mood, sleep disturbances) subjectively associated with their central diabetes insipidus (**irrespective of additional anterior pituitary deficiencies**)
- **Potential role for oxytocin deficiency in the increased psychopathology** (oxytocin has antidepressant, anxiolytic, and socioemotional functioning properties)
- 823 (80%) participants encountered a situation where central diabetes insipidus was confused with diabetes mellitus by health-care professionals
- 884 (85%) participants supported **renaming the disease**

The Journal of Clinical Endocrinology & Metabolism, 2022, **00**, 1–3
https://doi.org/10.1210/clinem/dgac547

Position Statement

Changing the Name of Diabetes Insipidus: A Position Statement of the Working Group for Renaming Diabetes Insipidus

Hiroshi Arima,[1] Timothy Cheetham,[2,3] Mirjam Christ-Crain,[4] Deborah Cooper,[5] Juliana Drummond,[6] Mark Gurnell,[7] Miles Levy,[8] Ann McCormack,[9,10,11] John Newell-Price,[12] Joseph G. Verbalis,[13] and John Wass,[14] on behalf of The Working Group for Renaming Diabetes Insipidus

- Proposed name change:
- Central DI- arginine vasopressin deficiency (AVP-D)
- Nephrogenic DI- arginine vasopressin resistance (AVP-R)

(Oral) New provocation test using MDMA (‘Ecstasy’) demonstrates Oxytocin (OT) deficiency in patients with central diabetes insipidus.

Atila*, R. Murugesua , F. Holzea , N. Varghesea , A. Eckerta , M. Liechtia , M. Christ-Crain- University of Basel, Switzerland

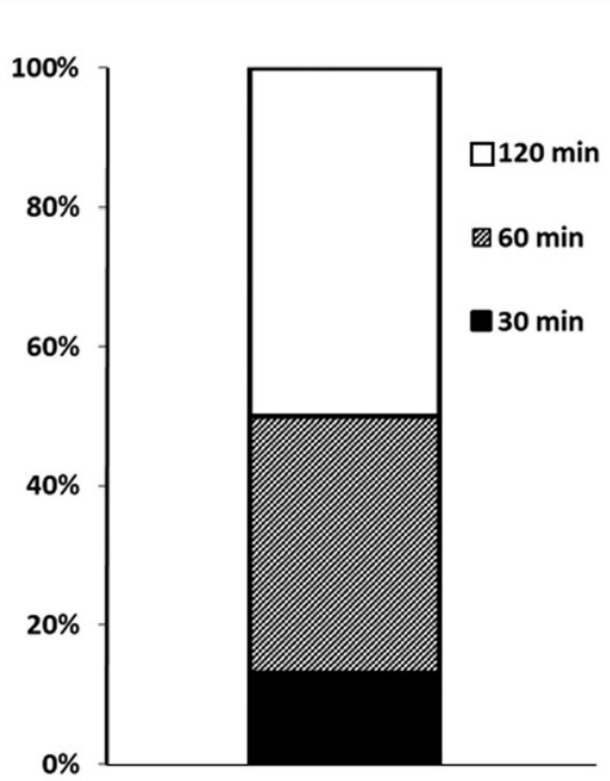
- Do patients with DI have OT deficiency?
- Basal measurements of OT are not reliable
- Methylenedioxymethamphetamine (MDMA, ‘ecstasy’) leads to a marked increase in circulating OT levels in healthy adults.
- Randomized, double-blind, placebo-controlled, cross-over study in patients with DI (N=15) and healthy controls (n=15) .
- Single oral dose of MDMA (100mg) oxytocin measurements at baseline and after 90, 120, 150, 180, 300 minutes

Results

- Healthy controls, median [IQR] OT level at baseline was **77** [59-94] pmol/ml and increased by **603** [335-914] pmol/ml
- Patients with DI, median OT level at baseline was **60** pmol/ml [51-74] and **remained stable** (increased by 66 [14-94] pmol/ml). Group difference of 538 pmol/l (95%CI [359-716]; $p<0.01$).
- **Psychological evaluation**: higher median scores for **anxiety and alexithymia** (difficulty identifying and expressing emotions), and **lower rates of correct emotion recognition** in 'angry' and 'fearful' faces in patients compared to healthy controls
- **This is the first proof of OT deficiency in patients with central DI correlating with psychopathological findings**

Paradoxical GH increase during OGTT: implications in managing acromegaly Dominique MAITER

- About one-third of acromegaly patients have a paradoxical GH increase during OGTT (first described in 1966)
- The mechanisms of this paradoxical GH rise in are not completely understood, but a role of GIP has been strongly suggested based on:
  - IV injection of GIP induced paradoxical GH response
  - Ectopic expression of GIPR in some somatotroph adenomas, all of which had paradoxical response to OGTT
- A PR was defined as an **increase greater than 25%** at any time point of the test, compared to the basal fasting GH concentration
- 30/110 patients **(27%)** had a PR to OGTT



Time of GH peak during OGTT

Eur J Endocrinol (2021) 185, 313–321

PR+ are older, have diabetes more often, have smaller and less invasive tumors with relatively high GH secretion, and are mostly hypointense in T2

	PR - (n=80)	PR + (n=30)	P-value
Age	44.3± 15.6	52±15.6	0.013
Diabetes Mellitus	6%	30%	0.005
Macro/micro	65/15	18/12	0.022
Cavernous sinus invasion	35%	17%	0.048
Tumor surface (cm2)	1.92 (0.18-8.25)	1.1 (0.16-5.91)	0.036
IGF1/tumor surface	1.08 (0.17-7.87)	2.35 (0.28-9.06)	0.011
Hypointense in T2	48%	92%	<0.001

No differences in basal GH and IGF1, MF ratio, KI 67 index

Better response to SRL treatment

The mechanisms increasing SSA responsiveness in PR+ patients may involve in part an additional inhibitory effect of SSA on GIP, which likely mediates post-glucose GH secretion in these patients

Characterization of sporadic somatotropinomas with high GIP receptor expression

Olivia Faria[1,5,6] · Renan Lyra Miranda[2,5,6] · Carlos Henrique de Azeredo Lima[2,5,6] · Alexandro Guterres[2,5,6] · Nina Ventura[3,4,5,6] · Monique Alvares Barbosa[3,5,6] · Aline Helen da Silva Camacho[2,5,6] · Elisa Baranski Lamback[1] Felipe Andreiuolo[2,5,6] · Leila Chimelli[2,5,6] · Leandro Kasuki[1,5,6,7,8] · Mônica R. Gadelha[1,2,5,6,7]

- 74 patients categorized by GIPR+ (upper quartile) or GIPR- by RT-PCR

	GIPR+ (n=18)	GIPR- (N=56)	
Sparsely granulated	**17%**	53%	p=0.028
Gsp mutation	11%	**50%**	p=0.005

Pituitary (2022) 25:903–910

(oral) Long-term treatment with oral paltusotine for acromegaly: Results from the ACROBAT Advance study

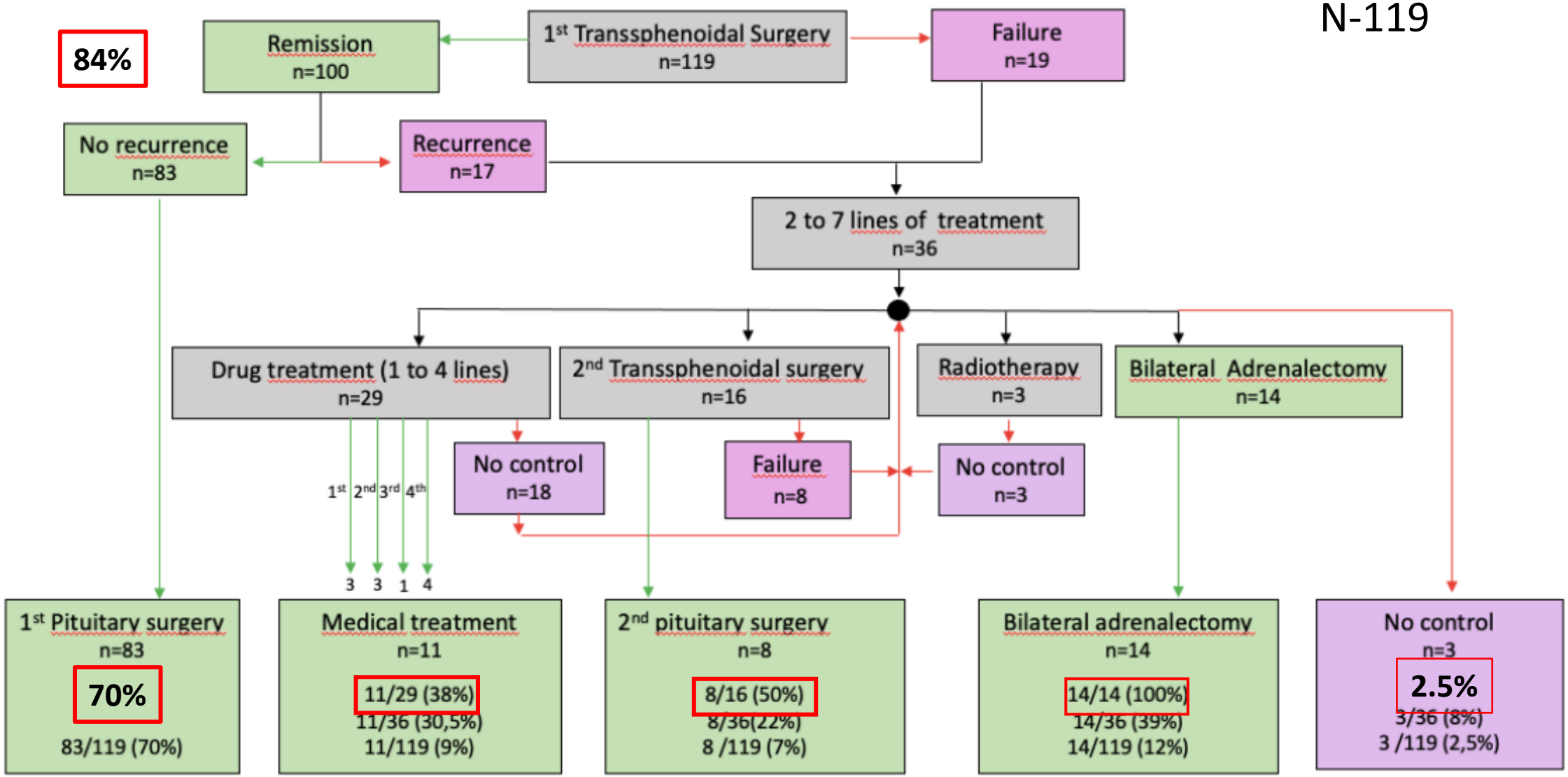
H. Randeva , M. Gadelha , M. Gordon , E. Mezosi, M. Doknic, M. Toth, C. Boguszewski, R. Luo, A. Krasner, A. Casagrande, S. Struthers

- **Paltusotine is a once daily, oral, nonpeptide, somatostatin receptor agonist highly selective for subtype 2 receptor**
- ACROBAT Advance - **ongoing, phase 2**, non-randomized, multicenter, open-label, extension study.
- **41** patients (23 F, median age 52, 85% previous pituitary surgery, no patient had RT)
- Pre-trial **all subjects were on the somatostatin receptor ligands (SRLs), as monotherapy or in combination therapy with cabergoline or pegvisomant.**
- Most subjects were on the maximum approved dose of SRL prior to study entry.
- **At the time of this data cut, IGF-1 levels were equivalent to study entry, either as paltusotine monotherapy (n=29) or in combination with cabergoline (n=112)**:
- IGF-1 (median (IQR)x ULN)) Study entry (n=41) 1.15 (0.84, 1.4) Week 51 (n=23) 1.13 (0.86, 1.39)
- Adverse events reported were consistent with symptoms of acromegaly (headache 29.3%, arthralgia 22%, and fatigue 14.6%) or the known GI side effects of SRLs.
- **In conclusion, once-daily, oral paltusotine lowered and maintained IGF-1 at levels comparable to prior injected SRL therapy for up to 51 weeks.**

(poster) Treatment of Cushing's disease (CD) after primary failure of pituitary surgery or recurrence: evaluation of long-term control by medical treatment o.

Chabre Grenoble

N-119



Medical treatment

Treatment N= 29	Exposed	Controlled
Ketoconazole	**27**	**6**
Metyrapone	**15**	**1**
Cabergoline	11	0
Osilodrostat	**8**	**6**
Mitotane	3	0
Pasireotide	3	0

- Drug treatment-long-term control of 11/36 (30%) patients, who were all treated by adrenal cortisol synthesis inhibitors.
- Drug treatment also allowed to delay surgery in 13/16 patients treated by a 2nd transsphenoidal surgery and in 11/14 patients treated by bilateral adrenalectomy

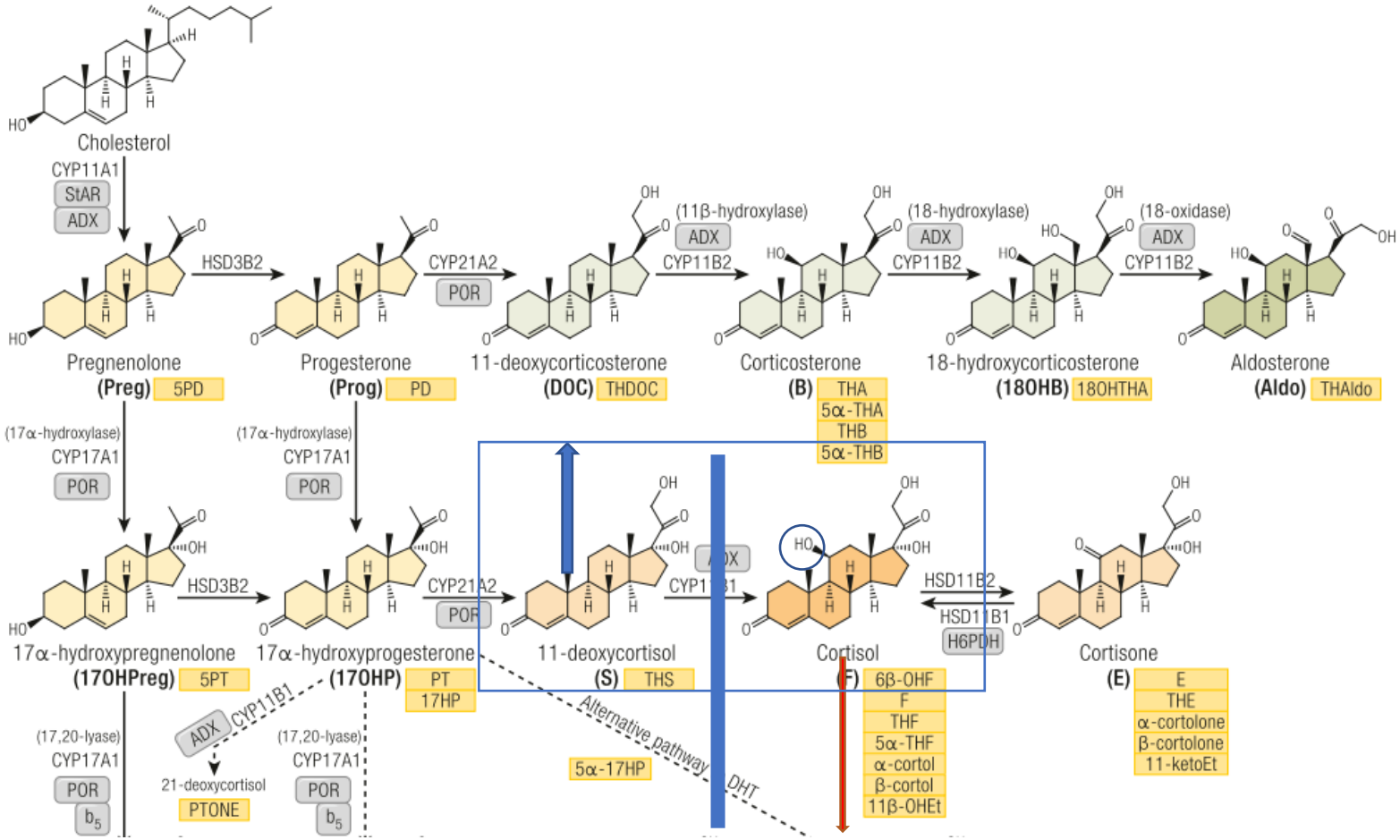
(oral) Improvements in hypertension and diabetes mellitus with osilodrostat in Cushing's disease patients: Exploratory analyses from the Phase III LINC 3 study.

Pivonello, M. Fleseriu, J. Newell-Price), A. Shimatsu, A. Lacroix, RJ. Auchus, A. Piacentini, AM. Pedroncelli , BMK. Biller

- At baseline, 119/137 patients **(87%) had hypertension**; osilodrostat for 48 weeks;
- SBP >130 mmHg (n=79) decreased to <=130 mmHg at weeks 12 and 48 in **58%, and 49%**
- Baseline DBP >90 mmHg (n=50) decreased to <=90 mmHg at weeks 12 and 48 in **72%, and 66%**
- SBP/DBP did not increase in patients without baseline hypertension.
- **Of 85 patients receiving antihypertensives at baseline, 40% stopped/reduced the dose and 40% increased the dose/number of antihypertensives during the study**

- At baseline, 61/137 patients **(45%) had diabetes mellitus.**
- FPG decreased from >=100 mg/dL at baseline (n=36) to <100 mg/dL by weeks 12 and 48 in **58%,** and **44%**
- **49% taking antihyperglycemics at baseline stopped/reduced the dose and 23% increased the dose/number of antihyperglycemics during the study**
- **Neither changes in blood pressure nor in blood glucose parameters correlated with changes in UFC from baseline**.

(MTP) New biochemical tools in the diagnosis and follow up of Cushing's disease- Martin Bidlingmeier

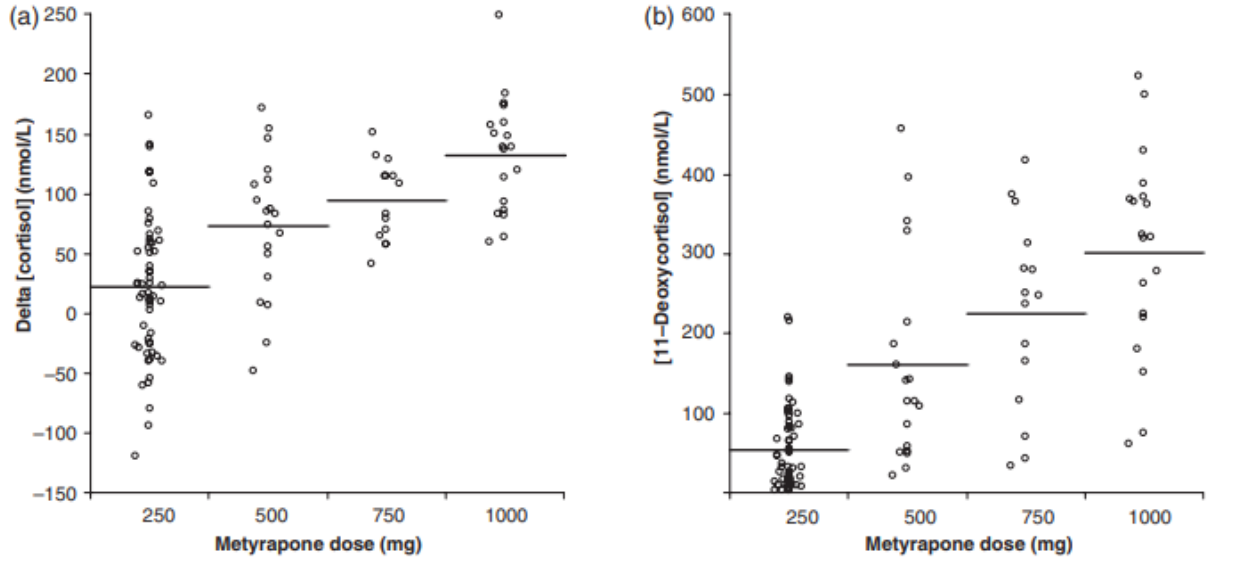


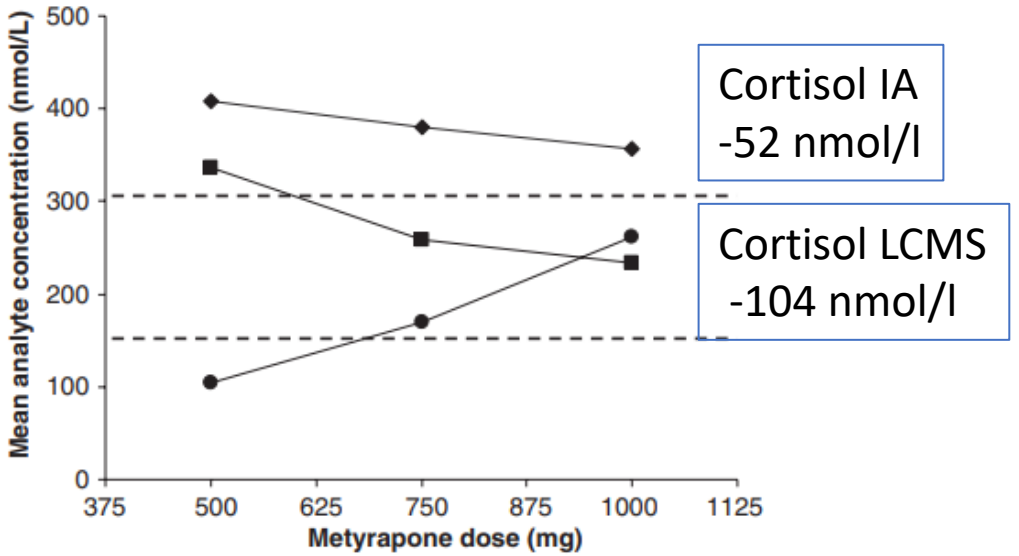
Endocrine Reviews 40: 1605 – 1625, 2019)

Metyrapone- >10 fold increase in 11-deoxycortisol
Osilodrostat ?

Cortisol assay problems- metyrapone

LCMS/MS vs Siemens ADVIA Centaur XP analyser





Mean difference in serum cortisol results between LC-MS/MS vs immunoassay (delta cortisol) positively correlated with metyrapone dose.

If 11-deoxycortisol cross-reacts with the assay:

- overestimation of cortisol
- inappropriate dose escalation
- failure to diagnose hypoadrenalism

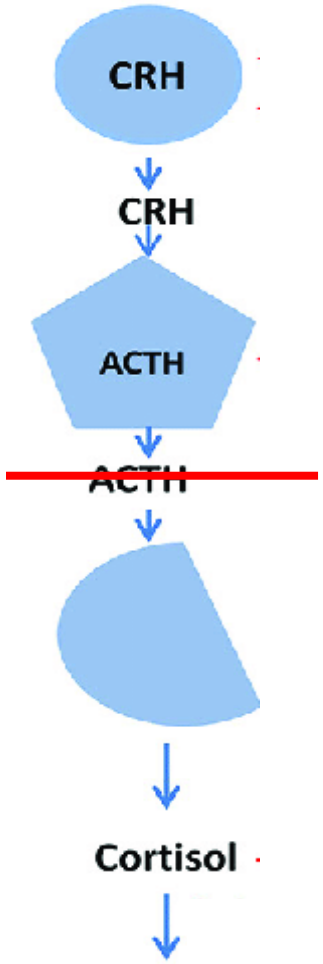
Annals of Clinical Biochemistry Volume 48 September 2011

Other immunoassays?

- Variable cross-reactivity in different assays (serum and urine)
- Diasorin- 3% cross-reactivity
- IDS-ISYS

(oral) CRN04894: an oral, nonpeptide ACTH (MC2) receptor antagonist decreased basal and stimulated cortisol secretion in healthy volunteers

P. Trainer, C. Ferrara-Cook, A. Ayala, R. Luo, S. Miller, Y. Wang, M. Hernandez-Illas), S. Sturthers, S. Betz, A. Krasner



- CRN04894 is a potent, orally bioavailable, nonpeptide **Melanocortin type 2 Receptor (MC2R) antagonist** that is >1000-fold selective for MC2R (exclusively expressed in the adrenal cortex) over other MCR subtypes.
- Randomized, double-blinded, placebo-controlled, multiple ascending dose study in healthy volunteers
- Oral, once-daily CRN04894 administered at 22:00 for **10 days**.
- **Serum cortisol was measured daily at 08:00** and circadian rhythm studies were undertaken
- An IV **1 mcg ACTH (1-24) test**

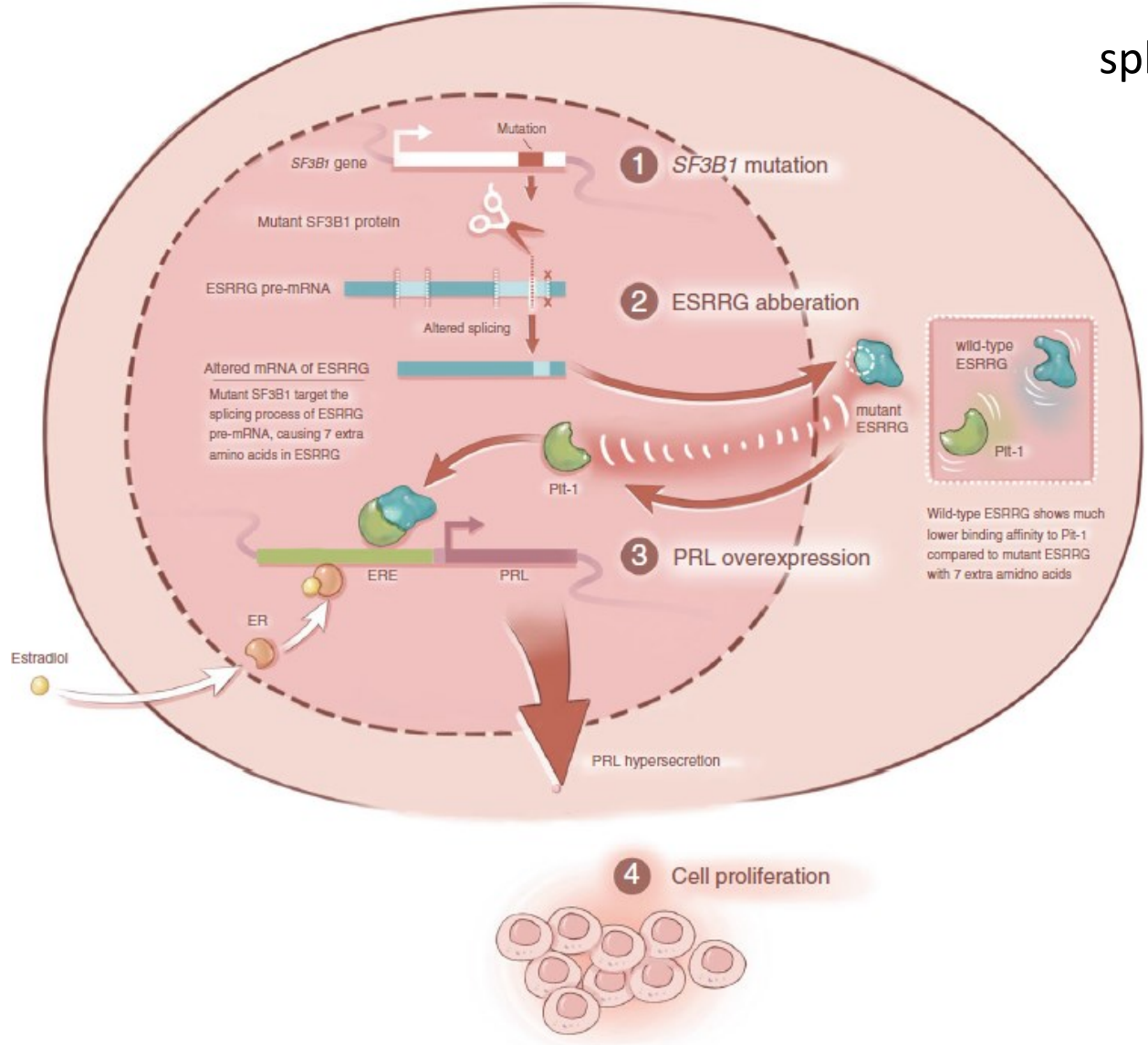
ARTICLE

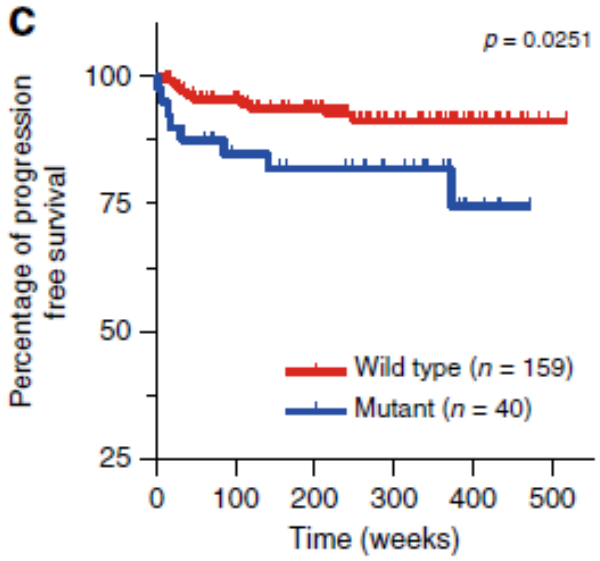
https://doi.org/10.1038/s41467-020-16052-8 OPEN

Somatic *SF3B1* hotspot mutation in prolactinomas

spliceasome

SF3B1 R625H mutation causes **aberrant splicing of estrogen related receptor gamma (ESRRG)**, which results in stronger binding of Pit-1, leading to excessive PRL secretion.



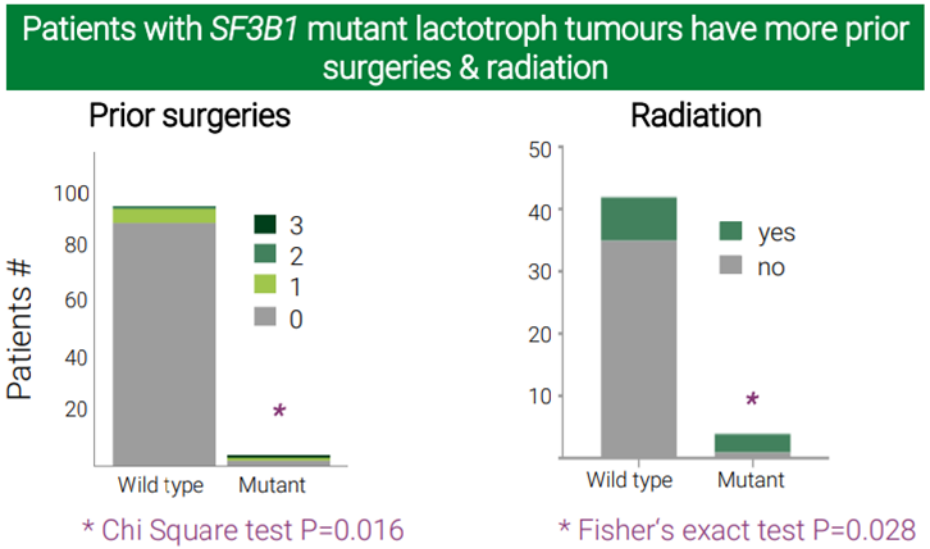


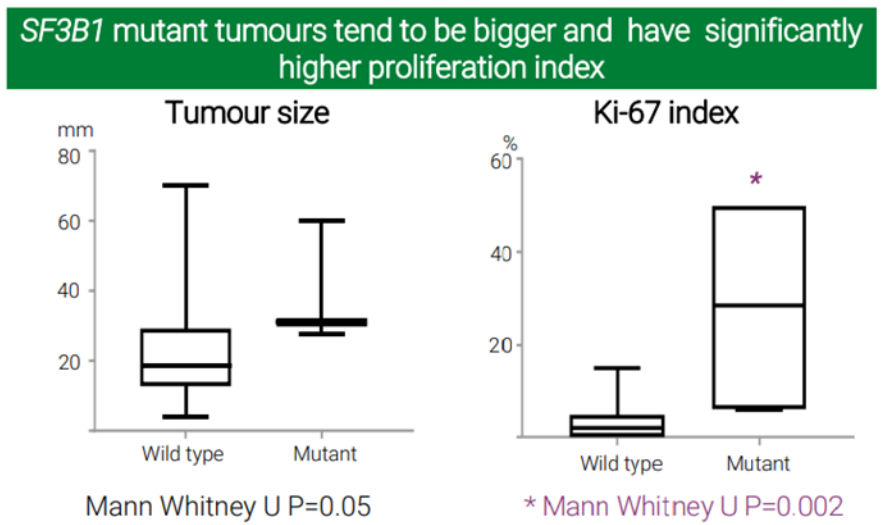
Prevalence of somatic SF3B1 mutations in lactotroph tumours.

Simon, LG. Perez-Rivas, J. Flitsch, M. Buchfelder, J. Thorsteinsdottir, H. Lasolle, C. Cortet, F. Chasseloup, D. Maiter, P. Chanson, G. Raverot, M. Theodoropoulou

- Caucasian cohort of patients with lactotroph tumors.
- **101** patients: 98 patients with lactotroph tumours (54 male) and **3 lactotroph carcinomas** (3 male
- SF3B **%):** 2 carc omas, 3 not

SF3B1 c.1874G>A (p.Arg625His) variant is uncommon (<4%) in lactotroph tumors but is strongly linked to aggressive lactotroph tumors and carcinomas



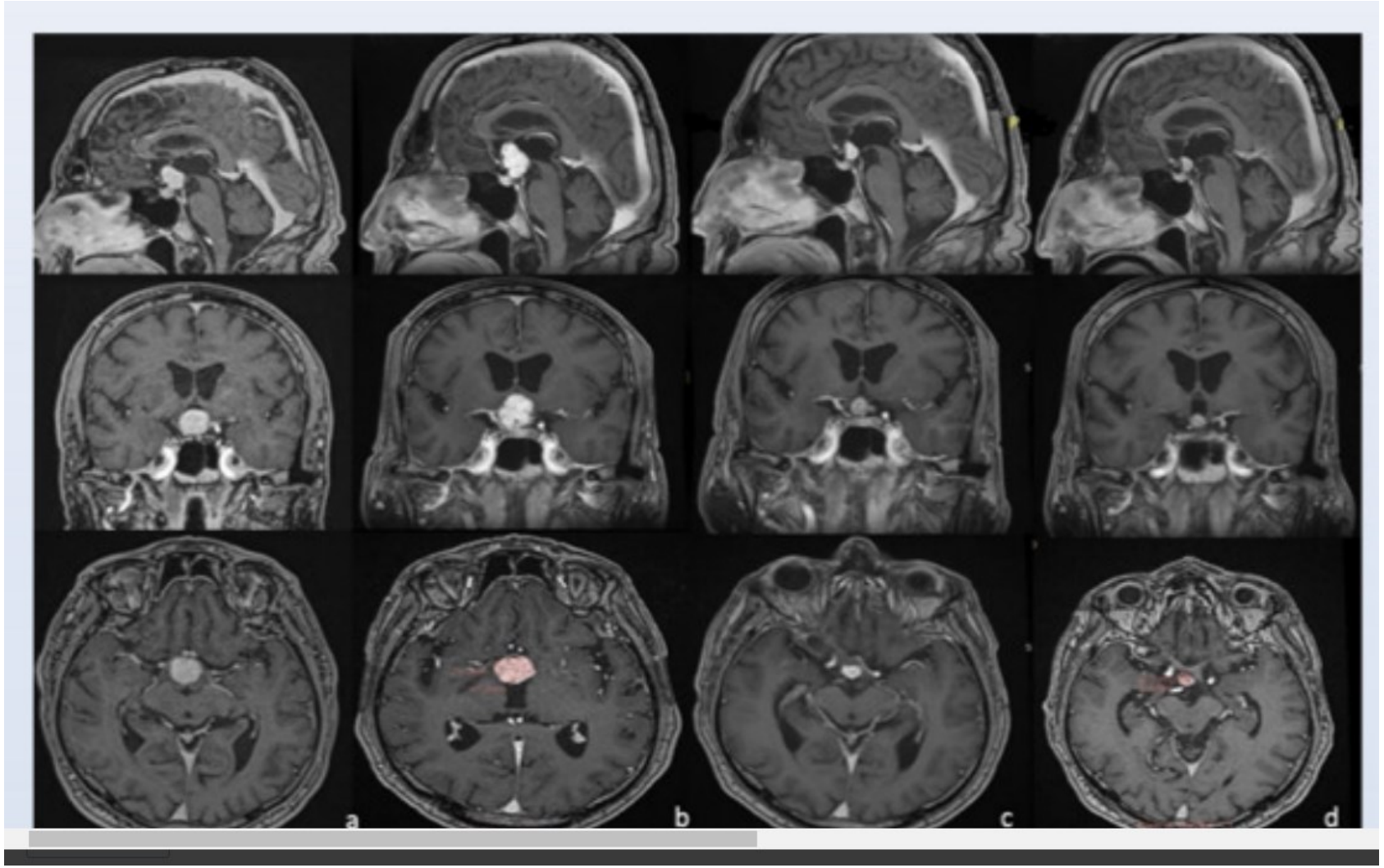


Neoadjuvant B-RAF and MEK inhibitor targeted therapy for Adult Papillary Craniopharyngiomas: A new treatment paradigm

Calvanese et al- Raverot- Lyon

- BRAF V600E- over 90% of papillary craniopharyngioma
- In **three recurrent** cases target therapy was administered as adjuvant treatment (i.e **after surgery and/or radiotherapy**).
- In one solid tumor, only a tumor biopsy was performed and the combined BRAF/MEK inhibition therapy was administered as **pure neo-adjuvant treatment (i.e. before surgery or/and radiotherapy).**
- A drastic and rapid tumor volume reduction was reported in case of **solid** papillary craniopharyngiomas (i.e. 60% after 2 and 90% after 5 months of treatment)
- In **cystic** form, the rate and magnitude of response is much slower and more modest

In the neo-adjuvant case, a near total response was obtained which dramatically minimized the target of the radiotherapy.



Diagnosis

Post-biopsy

Neoadjuvant Rx 2 months

4 months

Change in the current Craniopharyngioma treatment paradigm

- To avoid high-risk procedures.
- In cases of giant or invasive tumors-a tumor biopsy to identify patients with Papillary craniopharyngiomas harboring BRAF V600E mutation.
- In such tumors, neoadjuvant combined therapy should be applied to shrink the tumor before considering a curative approach
- Smaller target - hoping for a reduction in long-term morbidity and a better tumoral control.


THANK
YOU