What a patient should know about paraganglioma (PGL): For our children, for our future

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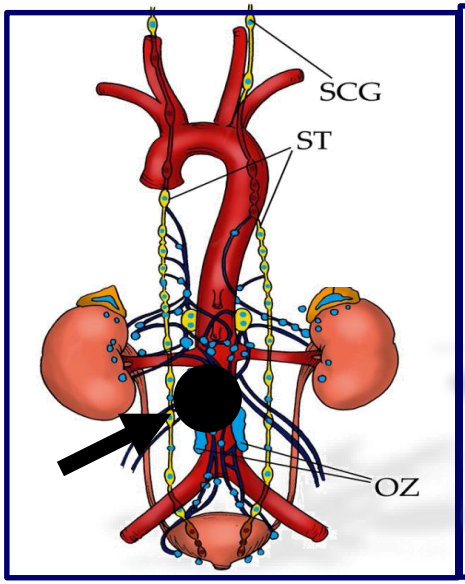
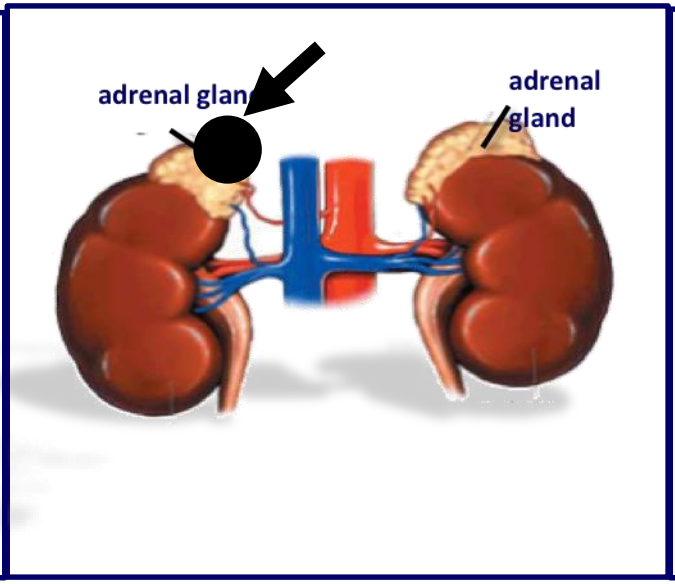
PHEO/PGL: definition/location

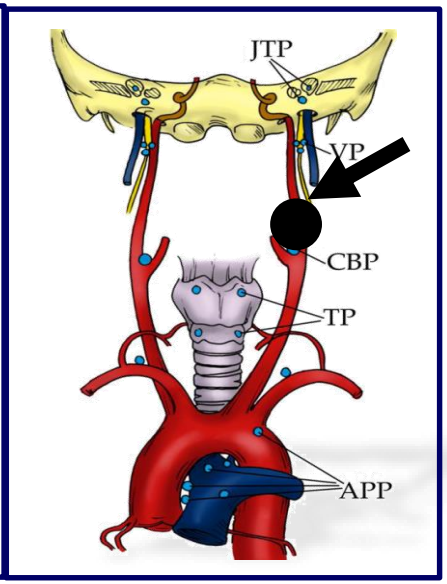
PHEOs/PGLs are *neuroendocrine tumors* characterized by production of catecholamine and their metabolites (metanephrines/methoxytyramine).



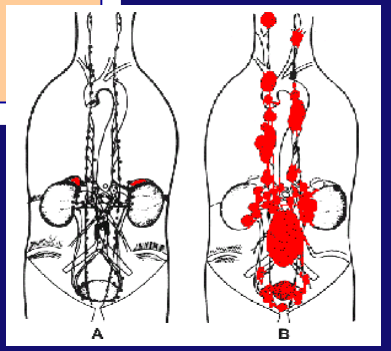
PGL (abdomen & mediastinum, 20%)



PHEO (adrenal gland PGL, 75%)



HNPGL (head & neck, 5%)



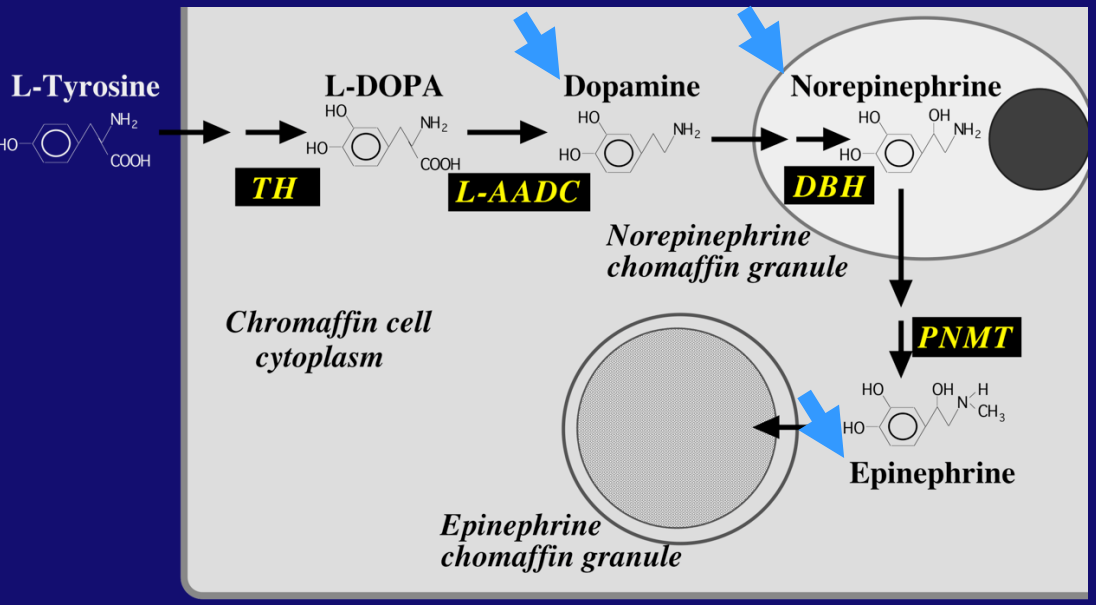
PHEO: pheochromocytoma; OZ: the organ of Zuckerkandl; CBP: carotid body PGL

PHEO/PGL: A clinical chameleon

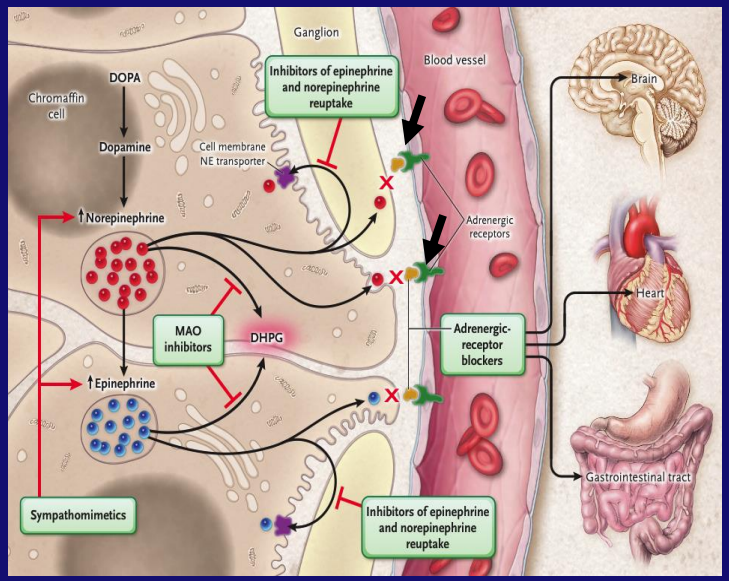
Signs		Symptoms	
Hypertension	++++	Headaches	++++
Sustained hypertension	++	Palpitations	++++
Paroxysmal hypertension	++	Anxiety/nervousness	+++
Postural hypotension	+	Tremulousness	++
Tachycardia or reflex bradycardia	+++	Weakness, fatigue	++
Excessive sweating	++++	Nausea/vomiting	+
Pallor	++	Pain in chest/abdomen	+
Flushing	+	Dizziness or faintness	+
Weight loss	+	Paresthesias	+
Fasting hyperglycemia	++	Constipation (rarely diarrhea)	+
Decreased gastrointestinal motility	+	Visual disturbances	+
Increased respiratory rate	+		

Lenders…Pacak et al. Lancet 2005; 366:665
Pacak JCEM 2007; 92:4069

PHEO/PGL synthesize 3 catecholamines



Catecholamines are released and act through adrenoceptors



All catecholamines are metabolized to yield metanephrines:

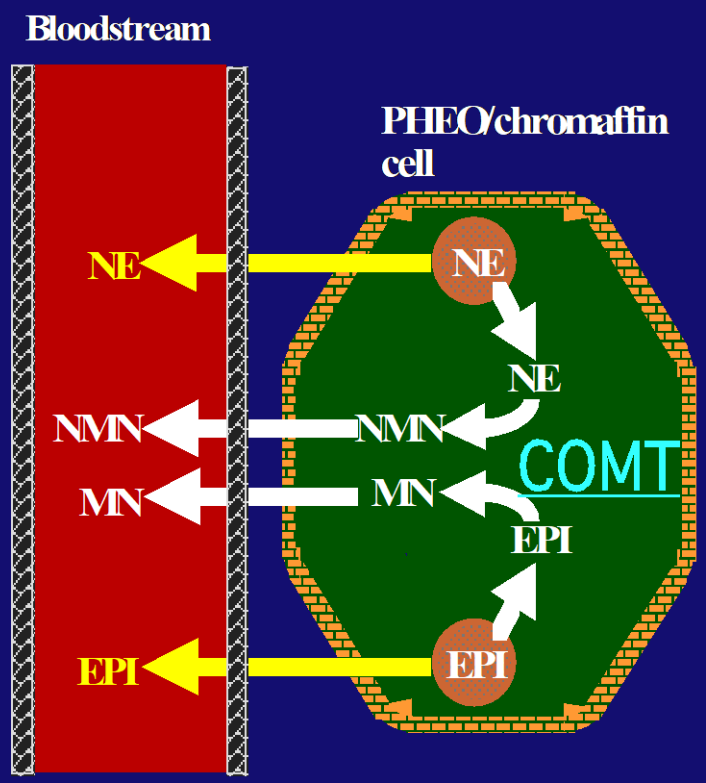
Norepinephrine (NE) → Normetanephrine (NMN)

Epinephrine (EPI) → Metanephrine (MN)

Dopamine (DA) → Methoxytyramine (MTX)

Pacak & Neary NEJM 2011; 364:2268

Biochemical diagnosis of PHEO/PGL: Metanephrines as O-methylated catecholamine metabolites



Metanephrines are produced *continuously* and *independently* of catecholamine secretion.

214 patients with, and 600 patients without PHEO/PGL were included

Biochemical test	Sensitivity (%)		Specificity (%)	
	Children	Adults	Children	Adults
Plasma normetanephrine and metanephrine	100	99	94	89
Plasma norepinephrine and epinephrine	92	84	91	81
Urinary normetanephrine and metanephrine	100	97	95	69
Urinary norepinephrine and epinephrine	100	86	83	88
Urinary vanillylmandelic acid	-	64	-	95

Lenders et al. JAMA 2002; 287:1427
Lenders et al. Lancet 2005; 366:665
Sawka et al. JCEM 2004; 89:2859

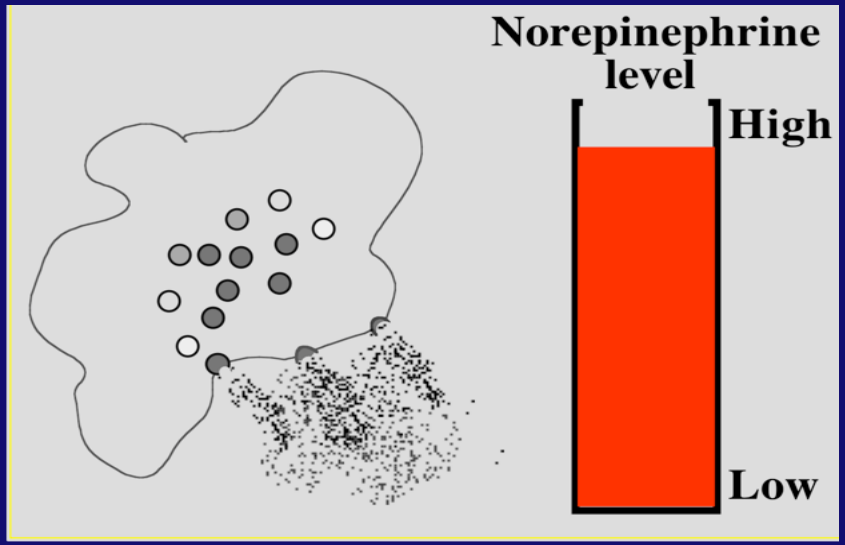
Distinguishing sympathetic activation (false-positives) from pheochromocytoma (true-positives)

Grey zone: Results between the URL and 3-4x above the URL

The Clonidine Suppression Test

Basis of the Test

- **Acts on alpha$_2$ adrenoceptors in the brain and on sympathetic nerve endings**
- **Decreases norepinephrine release from sympathetic nerves**
- **Has no effect on catecholamine release from pheochromocytomas**



Biochemical diagnosis of PHEO: Influence of posture and age

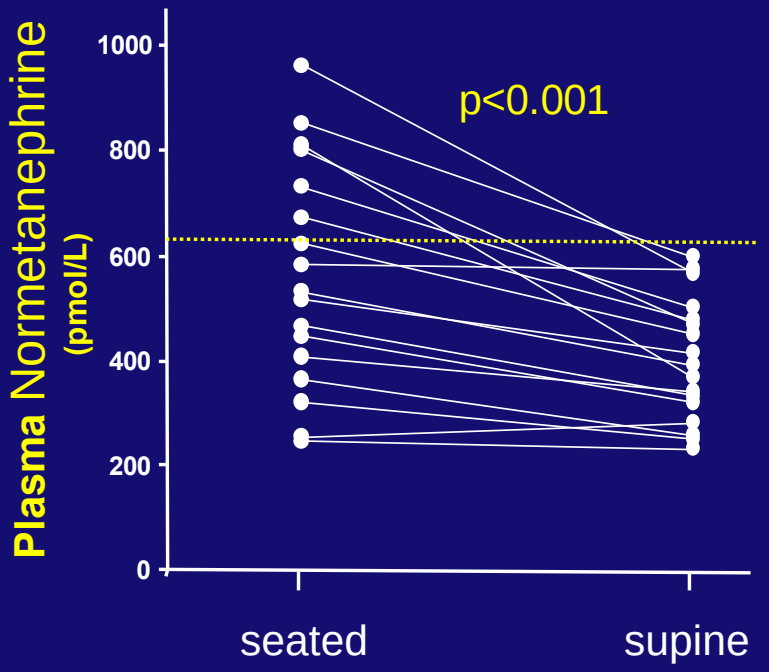


Table 2 Diagnostic accuracy of biochemical tests in the diagnosis of P/PGL

	Studies [number]	SE [%]	SP [%]	AUC [partial][a]	TA [%]	NPV [0.5%][b]	[5%][c]	PPV [0.5%][b]	[5%][c]
HPLC	15	94	93	0.947	93–94	n.a.		n.a.	
IA	11	91	93	0.911	91–93	n.a.		n.a.	
Supine	10	95*	95**	0.942	95–95	0.9997	0.9972	0.0872	0.5000
Seated	10	89*	94	0.913	89–94	0.9994	0.9939	0.0694	0.4384
Urine	11	93	90**	0.932	90–93	0.9996	0.9959	0.0446	0.3286

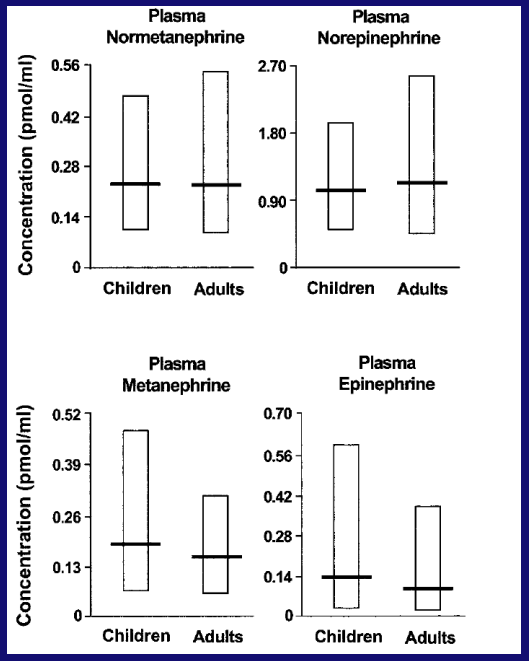
SE sensitivity, *SP* specificity, *TA* test accuracy range (for prevalence ranges between 0.0 and 1.0), *NPV* negative predictive value, *PPV* positive predictive value, *n.a.* not assessed

*Supine vs. seated $p < 0.02$; **supine vs. 24-h urine $p < 0.03$

[a] For details, see Methods

[b] Prevalence of P/PGL among hypertensive subjects (0.2–0.6%)

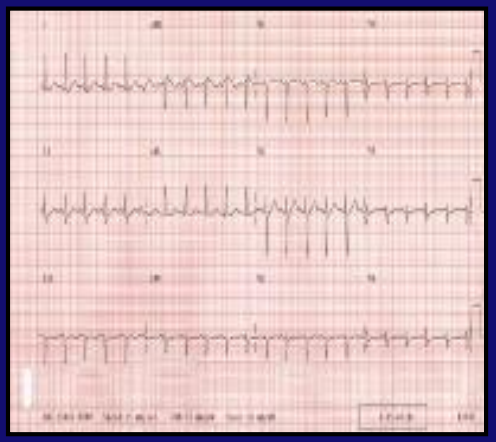
[c] Prevalence of P/PGL in subjects with incidentaloma



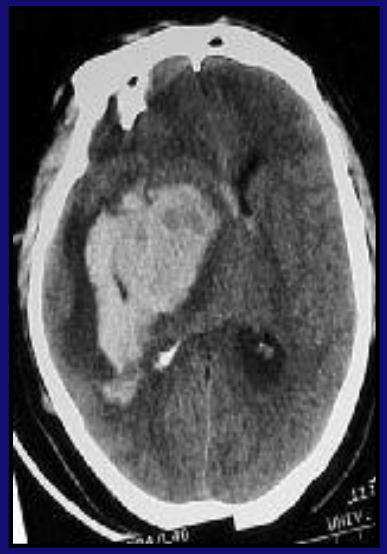
Darr et al. Endocrine 2017; 56:495
Weise et al. JCEM 2002; 87:1955

PHEO as a volcano

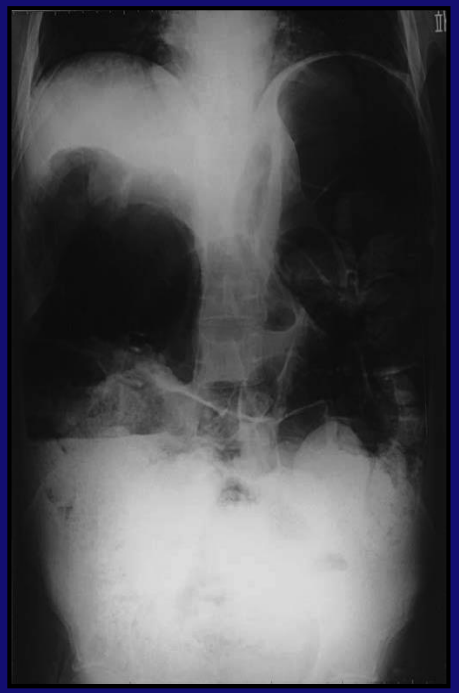
Concentrations of catecholamines in PHEO/PGL tissue are enormous (more than a thousand times higher than in plasma), creating a volcano that can erupt at any time (episodes are called storms, attacks, or spells).



Sinus tachycardia



Large intracerebral hemorrhage



Ileus

All patients with PHEO/PGL must receive α/β adrenoceptor blockade

PHEO/PGL: pharmacological treatment

Pharmacological blockade

Alpha blockers: the first choice

Beta blockers: (only if tachycardia is present)

Ca channel blockers: 2nd choice (on those with mild hypertension)

Blockade of catecholamine synthesis: Metyrosine (Demser)

PHEO/PGL: Alpha adrenoceptor blockade

Non-selective α blocker (e.g. phenoxybenzamine)

- Usual dose: 10 mg TID; up to 200 mg as a total dose
- Very potent and very effective
- Effective for very active tumors and metastatic disease
- Nicely maintains BP intraoperatively

PHEO/PGL: Alpha adrenoceptor blockade

Selective $\alpha 1$ blockers (e.g. Doxazosin)

- Very well tolerated, hypotension less common
- Usually maintain a stable BP intraoperatively
- Do not cause severe tachycardia
- The first dose should be given at night; can be given in the morning before surgery (have a shorter half-life)
- Cheaper

PHEO/PGL: Beta adrenoceptor blockade

- Used in patients with tachycardia
- Should never be used before alpha blockers
- Atenolol (Tenormin) 12.5-25 mg QD or BID preferred at NIH
- Metoprolol (Lopressor): 25-50 mg TID or QID
- Propranolol (Inderal): 20-80 mg QD-TID
- Avoid Labetalol as the initial drug (α:β is about 1:4-7)

PHEO/PGL: Demser

- Catecholamine synthesis blocker (tyrosine hydroxylase)
- Very effective and good for preoperative blockade
- Metyrosine (Demser): 250 mg QD-TID or a higher dose; can cause severe depression, also some anxiety, excellent for the improvement of bowel movement

Main drugs contraindicated in PHEO/PGL

TABLE 3. Main classes of drugs with contraindications in patients with pheochromocytoma

Drug class	Relevant clinical uses
β-Adrenergic blockers[a]	May be used to treat conditions that result from catecholamine excess (*e.g.* hypertension, cardiomyopathy, heart failure, panic attacks, migraine, tachycardia and cardiac dysrhythmias)
Dopamine D2 receptor antagonists	Control of nausea, vomiting, psychosis, hot flashes and for tranquilizing effect
Tricyclic antidepressants	Treatment of insomnia, neuropathic pain, nocturnal enuresis in children, headaches, depression (rarely)
Other antidepressants (serotonin and NE reuptake inhibitors)	Depression, anxiety, panic attacks, antiobesity agents
Monoamine oxidase inhibitors	Non-selective agents rarely used as antidepressants (due to "cheese effect").
Sympathomimetics[a]	Control of low blood pressure during surgical anesthesia; decongestants; antiobesity agents
Chemotherapeutic agents[a]	Antineoplastic actions; treatment of malignant pheochromocytoma
Opiate analgesics[a]	Induction of surgical anesthesia
Neuromuscular blocking agents[a]	Induction of surgical anesthesia
Peptide and steroid hormones[a]	Diagnostic testing

Adapted from Eisenhofer *et al.* (76).

[a] These drugs have therapeutic or diagnostic use in pheochromocytoma, but usually only after pretreatment with appropriate antihypertensives (*e.g.* α-adrenoceptor blockers).

Reglan

Pacak JCEM 2007; 92:4069

PHEO/PGL: Rule of surgical divergence

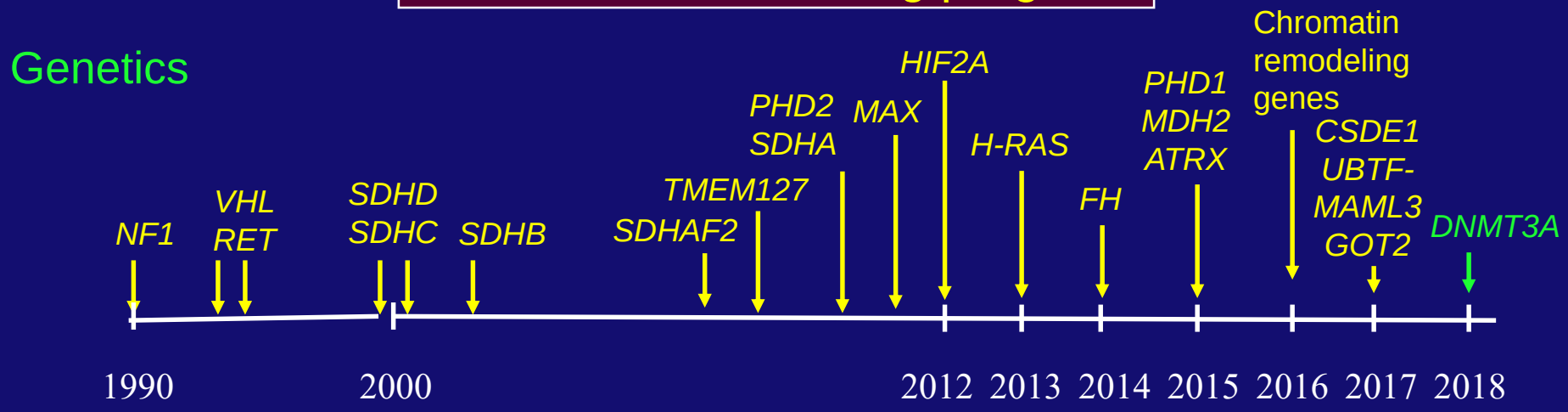
Acute events (e.g. myocardial infarction, trauma, intestinal perforation)

The rule of surgical divergence applies

- First, fix the acute problem and second, remove PHEO/PGL
- Pregnancy: 3rd trimester: delivery before PHEO/PGL removal

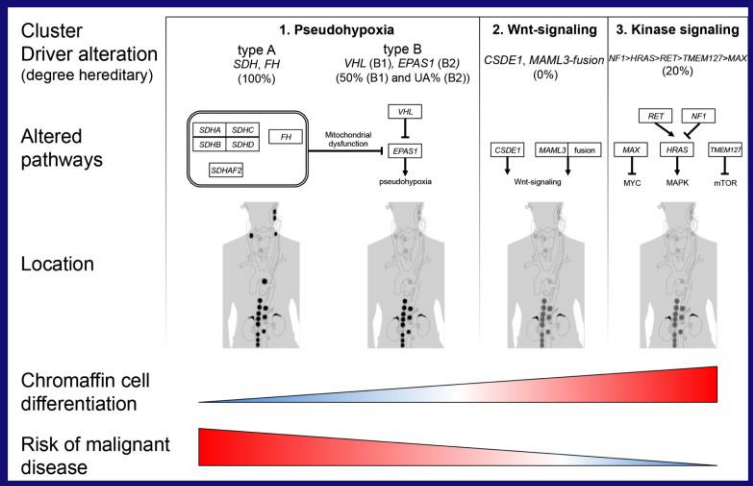
Pacak, AACE Clinical Case Reports 2016; 2:e78

PHEO/PGL: continuing progress



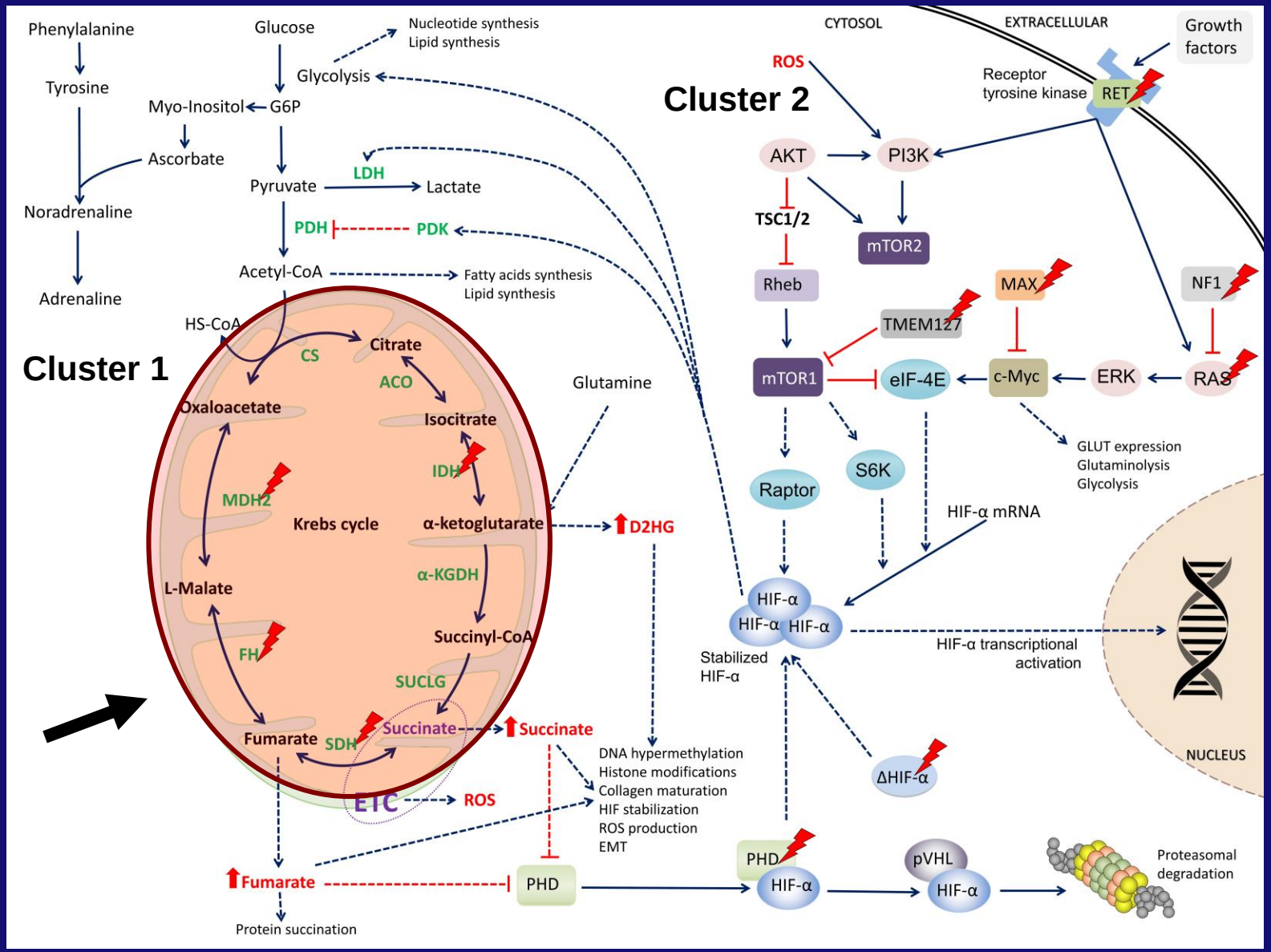
- 23 genes involved in the pathogenesis of PHEO
- 27-35% are inherited (germline mutations)
- 30-39% have somatic mutations
- 7% have fusion genes

ISP 2017:
Exome sequencing recommended



ISP: International Symposium on Pheochromocytoma; Sydney, Australia, 2017
The Cancer Genome Atlas, Co-chairs: Pacak, Nathanson, Wilkerson, Cancer Cell, 2017; 31:181
Crona… Pacak; Endocr. Rev. 2017; 38:489
Remacha et al. Genet. Med. 2018; in press

PHEO: Cluster 1 & 2



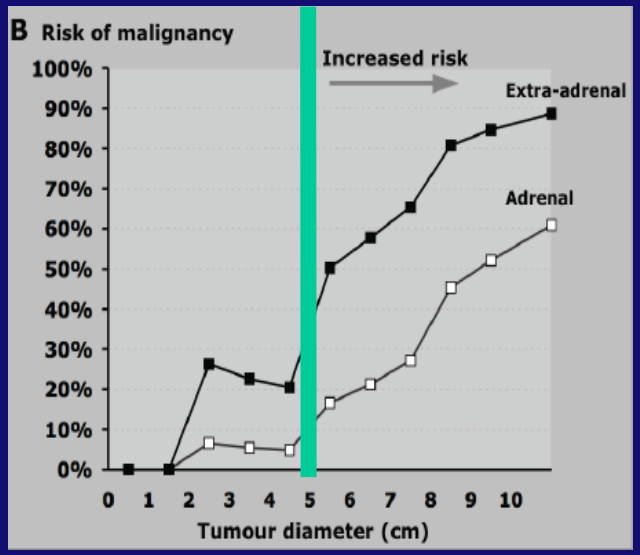
SDH: succinate dehydrogenase

Jochmanova & Pacak, Clin. Cancer Res.; 2016; 22:5001

Tumor size and extra-adrenal location as predictors of metastatic PHEO/PGL

365 patients with PHEO/PGL, including 105 with metastases

SIZE & LOCATION

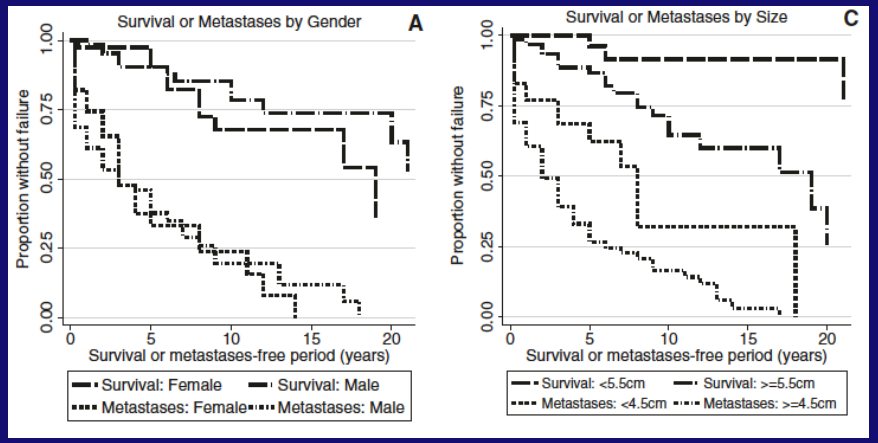


Zelinka et al. Eur.J. Clin. Invest.; 2011; 41:1121
Eisenhofer et al. Eur. J. Cancer; 2012; 48:1739

106 patients with metastatic SDHB PHEO/PGL were included

- Survival did not differ between PHEO and PGL pts
- 26% metastatic disease at the initial dg. or within 6 months
- Overall 50% developed metastatic disease during the first 5 years

Tumor size and years to metastases (median)
<= 4 cm: 8
4-6 cm: 4
6-9 cm: 3
> 9 cm: 1



Schovanek et al. BMC Cancer 2014; 14:523

Pediatric PPGL: An overview and pertinent facts

- 5-10% of all PPGLs
- The mean age of onset: 10 to 13 with male predominance

Table 1. Demographic and Tumor Characteristics of Pediatric and Adult Patients With PPGLs

Characteristics	Pediatric	Adult	*P* Value
N	95	653	
Age at initial diagnosis[a]	13.3 ± 3.5	44.7 ± 14.4	
Male	55.8% (53/95)	48.1% (314/653)	0.0980
Primary tumor locations			
Solitary adrenal	22.1% (21/95)	56.2% (367/653)	<0.0001
Solitary extra-adrenal	33.7% (32/95)	21.6% (141/653)	<0.0001
Bilateral adrenal	11.6% (11/95)	8.7% (57/653)	0.2020
Multifocal[b]	32.6% (31/95)	13.5% (88/653)	<0.0001
Hereditary cases[c]	80.4% (74/92)	52.6% (273/519)	<0.0001
Recurrent primary tumors[d]	29.5% (28/95)	14.2% (93/653)	<0.0001
Metastatic disease	49.5% (47/95)	29.1% (190/653)	<0.0001
No. N/D phenotype	93.2% (68/73)	57.3% (337/588)	<0.0001

Pamporaki et al. JCEM 2017; 102:1122
Baush et al. Endocr. Relat. Cancer 2014; 21:17

Guidelines for diagnosis and prevention of familial/hereditary PHEO

	Starting age	Endocrine consultation (H&P)	ENT consultation (H&P)	Metanephrines	Imaging
***SDHD, SDHAF2, MAX* (when paternally inherited)**	18 (or 5-10 depending on earliestmanifestation in family)	yearly + before surgery	yearly	yearly	Head+neck MRI at least every 3y. Abdomen/chest imaging when indicated (metanephrines)
SDHB	10	yearly + before surgery	yearly	yearly	Head+neck MRI at least every 3y. Abdomen+chest imaging (MRI) at least every 3y
SDHA, SDHC, TMEM127	18 (or 5-10 depending on earlies manifestation in family)	yearly + before surgery	yearly	yearly	Abdomen/chest imaging when indicated (metanephrines)

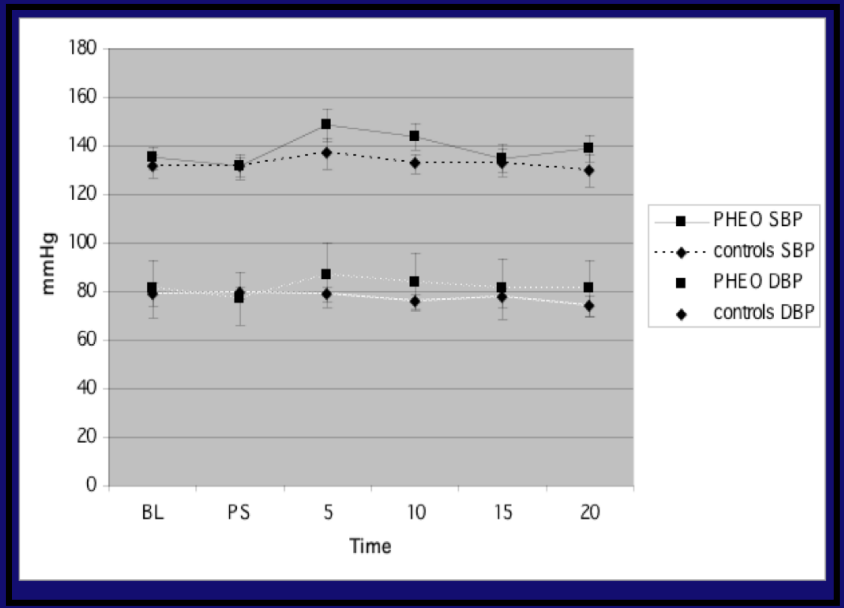
Personal recommendations for *SDHB* carriers:

plasma metanephrines/methoxytyramine for age 5 (yearly)
whole body MRI at age 10, if negative start with CT/MRI (alternate every 3 years from age 13-15

Dutch Association for Clinical Genetics, 2017

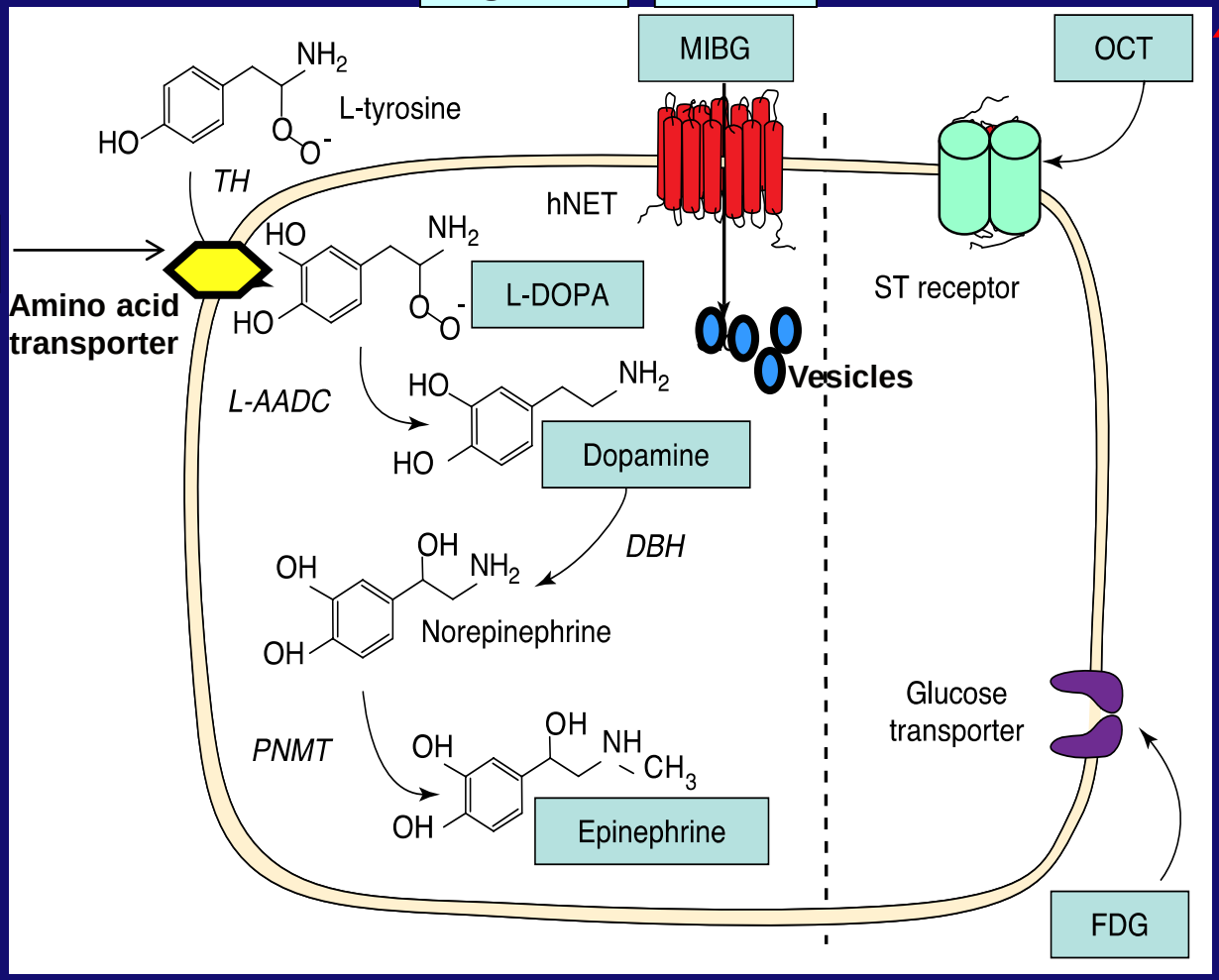
CT contrast: No harm to patients with PHEO/PGL

CT non-ionic contrast (22 patients



Baid et al. Ann. Intern. Med. 2009; 150:27

PHEO localization: ^{68}Ga-DOTA analogs



SSTR2: somatostatin receptor type 2

Adapted from Ilias et al. Trends Endocrinol. Metab. 2005; 16:66
& Pacak et al. Endocr. Rev. 2004; 25:568

Why functional imaging in localization of PHEO/PGL?

- Although very sensitive, anatomical imaging has a limited specificity.
- With anatomical imaging, postoperative changes may impair PHEO/PGL visualization.
- An anatomical whole body scan is not routinely performed unless requested.

PHEO/PGL and somatostatin receptors (SSTRs) imaging

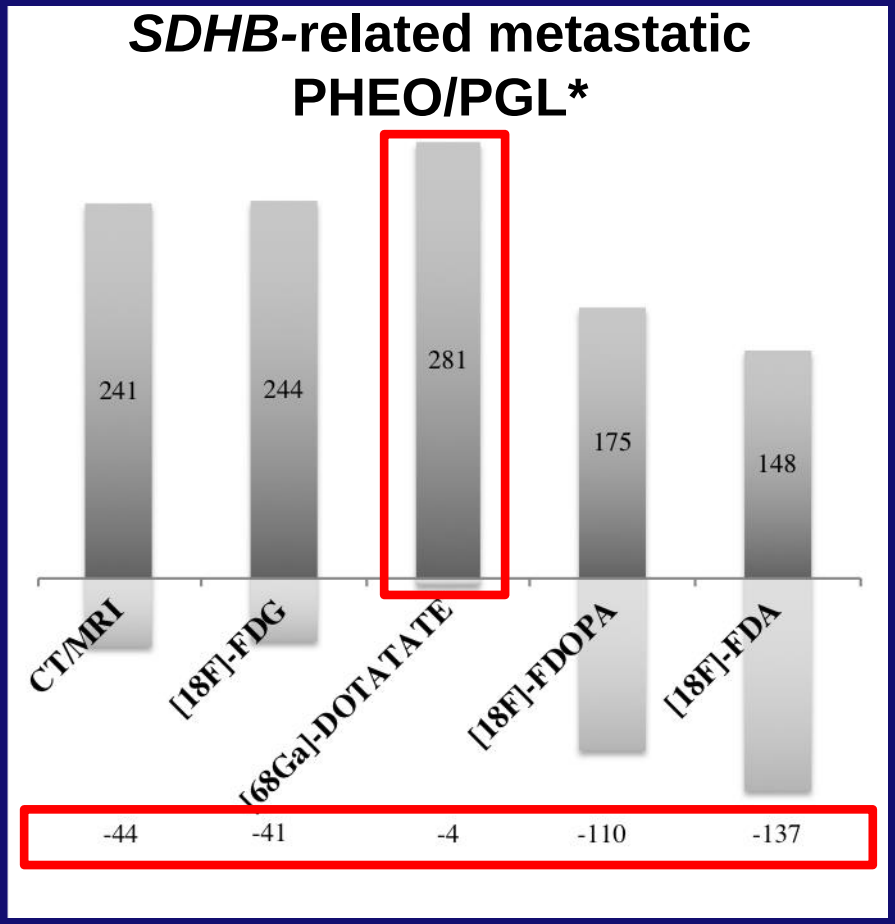
- PHEOs/PGLs express SSTRs (mainly type 2) allowing for the use of *Octreoscan scintigraphy* (relatively poor spatial resolution)

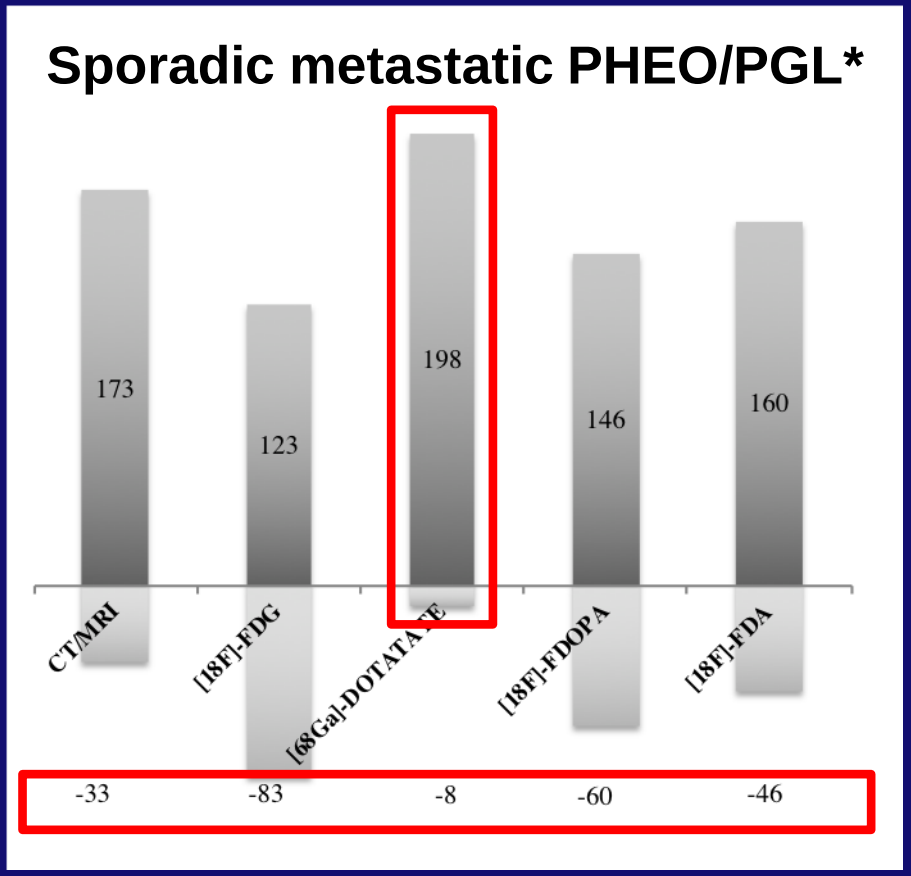
	SST1	SST2	SST3	SST4	SST5
PHEO	++/+++ (15-20%)	++/+++ (75-80%)	-	-	+ (5%)
PGL	+++ (20%)	+++ (80%)	-	-	-

+-+++: level of expression, %: proportion of SSTRs-expressing PHEO/PGL

- SSTR imaging can be performed with PET/CT to improve spatial resolution and sensitivity; PET/CT also provides more rapid whole-body tomographic imaging for precise anatomic localization

^{68}Ga-DOTATATE PET/CT performance in patients with metastatic PHEO/PGL compared to other imaging modalities





* Only patients in whom all imaging modalities were performed

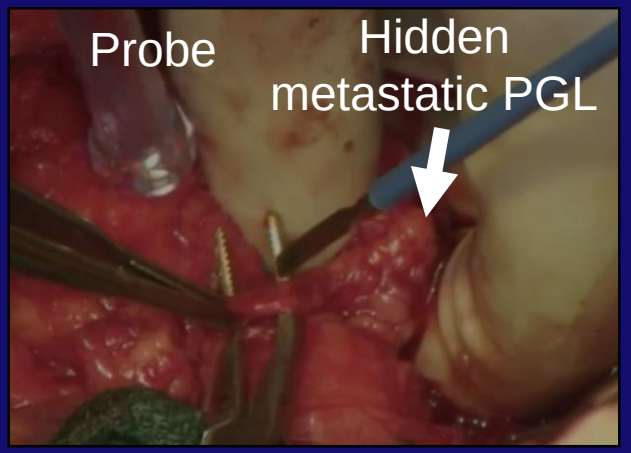
Janssen et al., Eur. J. Nucl. Med. Mol. Imaging 2016; i43:1784
Janssen et al. Clin. Cancer Res. 2015; 21:3888

Overall performance of ^{68}Ga-DOTATATE PET/CT compared to other imaging modalities and clinical outcomes

Detection rate	[^{68}Ga]-DOTATATE	[^{18}F]-FDG	[^{18}F]-FDOPA	[^{18}F]-FDA	CT/MRI
Total lesions %	513/525 98%	392/525 75%	325/525 68%	318/525 61%	435/525 83%

These results suggest the immediate clinical outcomes:

- Modifications in imaging guidelines for these tumors
- Use of ^{177}Lu-DOTA analogs for radiotherapy of metastatic PHEO/PGL
- Use of a gamma probe to discover hidden metastatic tumors



Take home message

Seemingly non-specific problems (headache, sweating, heart beating fast) can be first signs of PHEO/PGL.

All patients with PHEO/PGL secreting catecholamines must be on adrenoceptor blockade. Beta blockade cannot be used prior to before alpha blockade being initiated.

Tumor size matters, along with location and genetic background.

Reglan is detrimental for patients with PHEO/PGL.

Biochemical diagnosis of PHEO/PGL is based on the measurement of plasma/urine metanephrines (be aware of pediatric reference limits).

CT/MRI should be done only if there is a biochemical proof of that PHEO/PGL is present.

Acknowledgements

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Many thanks to outside NIH co-investigators: D. Taieb, G. Eisenhofer, A. Tischler, J. Widimsky, Z. Frysak, A. Grossman, H. Ghayee, and many others.

To the world you may be just one person,
but to one person you may be the world.

Pheochromocytoma/Paraganglioma:
An Endocrine Society Clinical Practice Guideline

Task force chair: Jacques W.M. Lenders, MD, PhD

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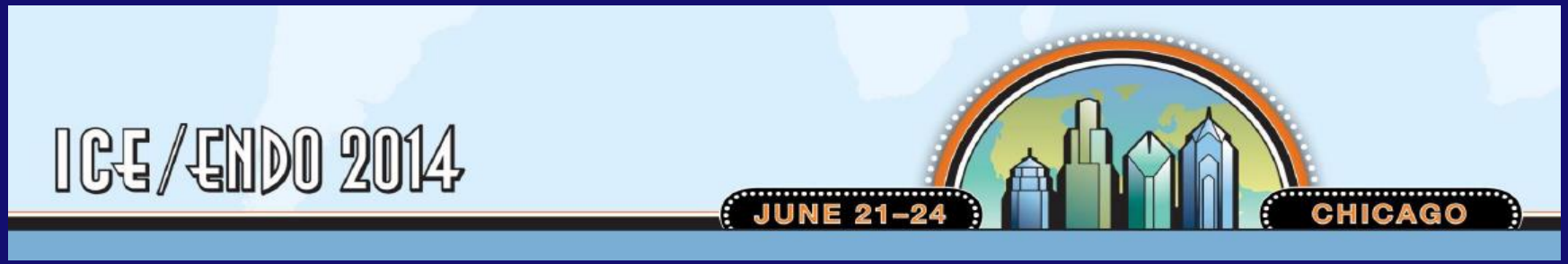

JCEM 2014; 99:1915