Pediatric Pheochromocytoma/ Paraganglioma (PPGL)

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pheopara
ALLIANCE

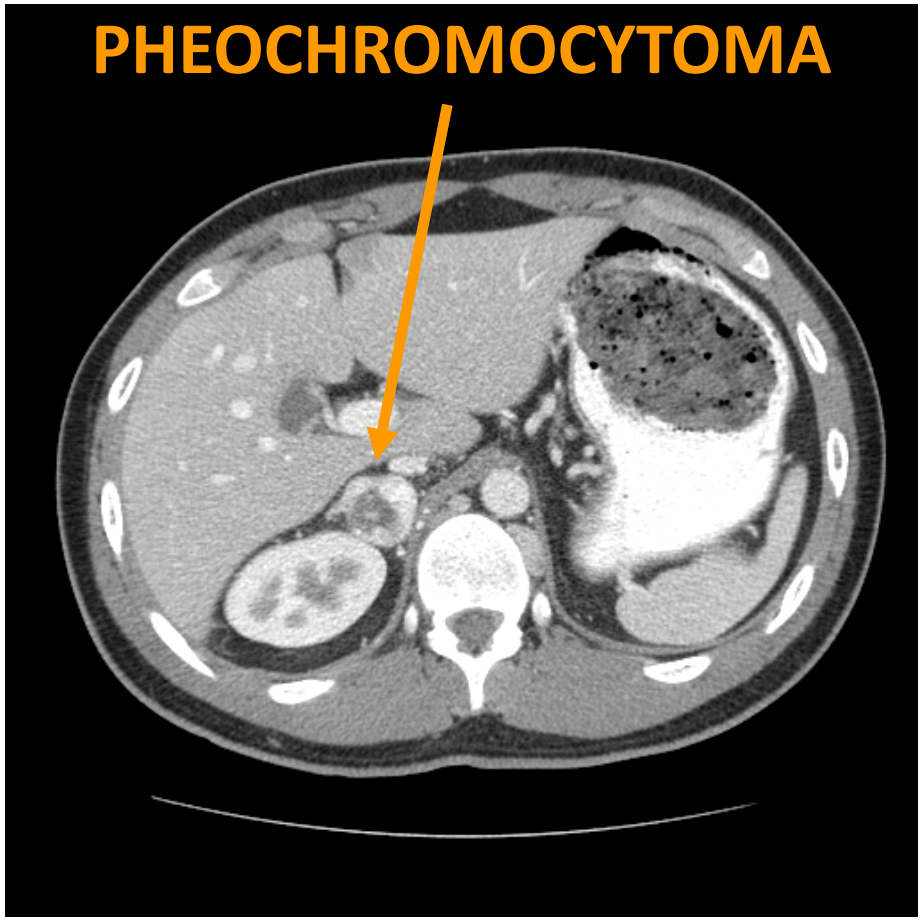
Disclosures:

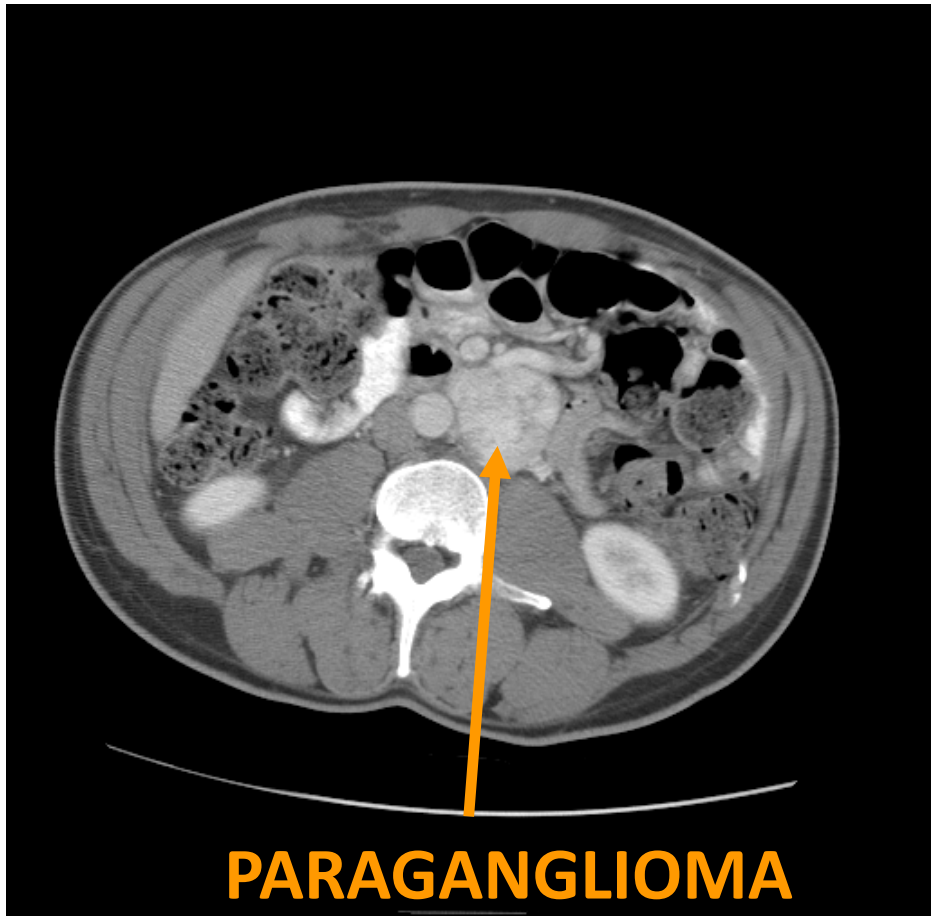
None

Objectives

- Discuss the clinical presentation of PPGL in children, including the most common hereditary syndromes
- Highlight differences between children and adults with PPGL
- Discuss the diagnosis and treatment of pediatric PPGL, including metastatic disease

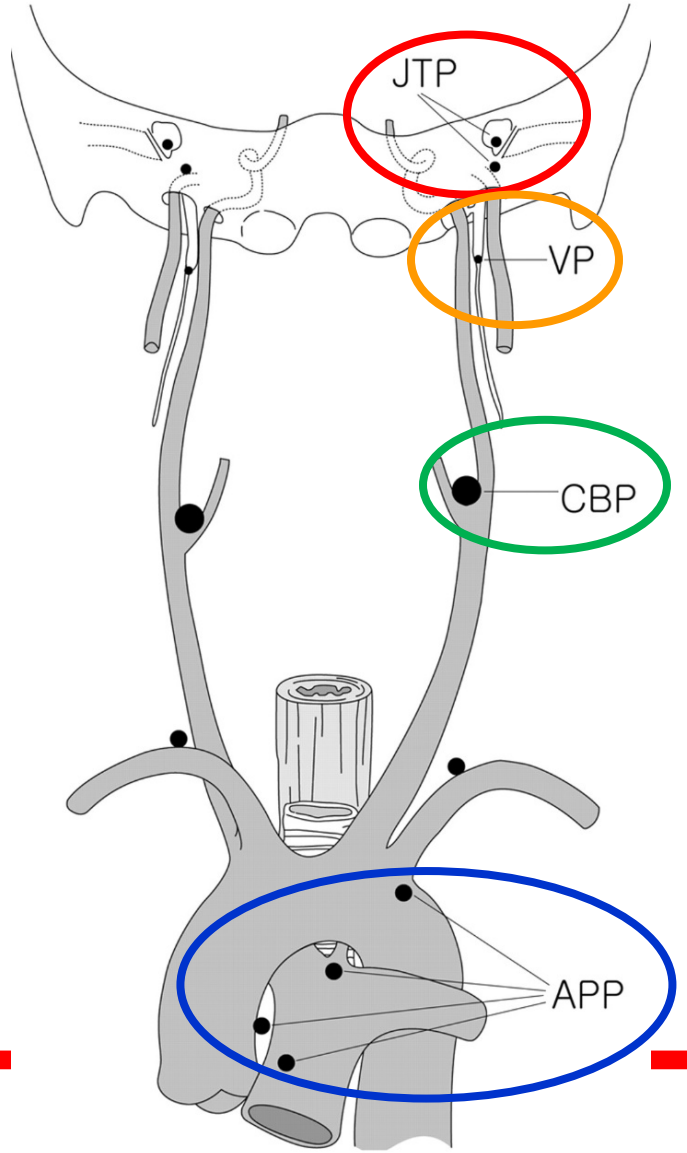
Chromaffin Cell Tumors*





***PHEO and sympathetic/functional PGL arise from chromaffin cells; parasympathetic or non-functional PGL are known as non-chromaffin paragangliomas**

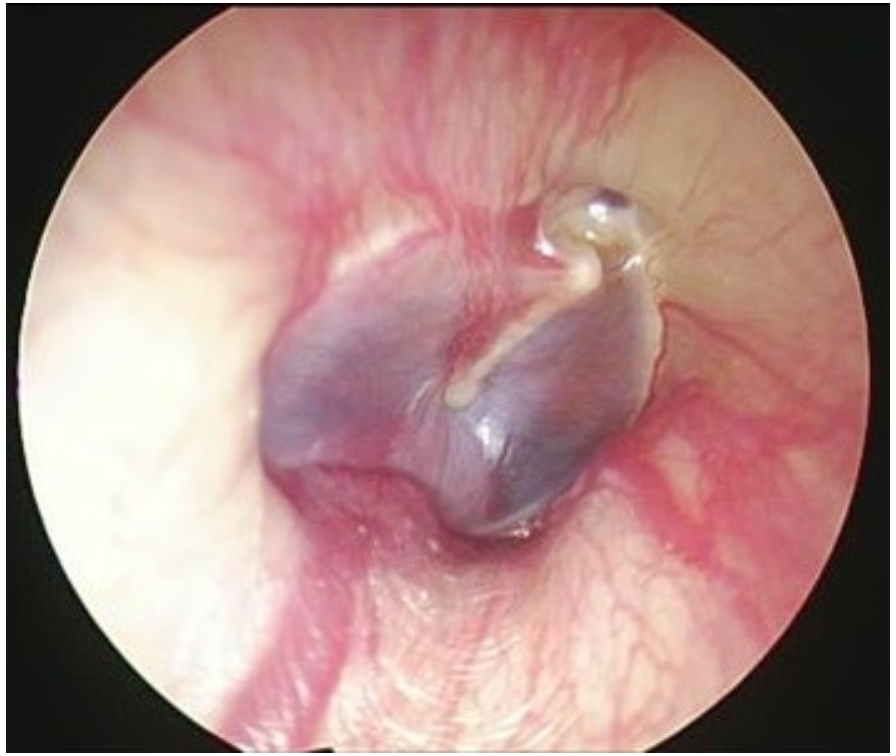
Parasympathetic PGLs



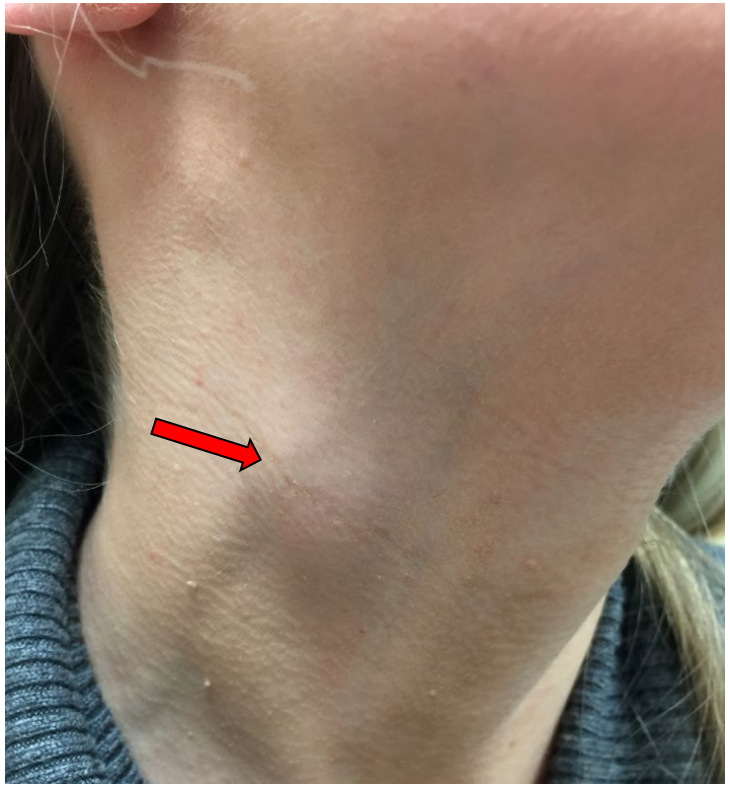
- Historically called “glomus tumors” or “chemodectomas”
- 1-3% functional
- Anatomic tumor locations
  - Glomus tympanicum/jugulare or jugulotympanic
    - middle ear mass, tinnitus, hearing loss
  - Vagal
    - neck mass, dysphagia, hoarseness
  - Carotid body
    - neck mass, cranial nerve palsy
  - Aortopulmonary body
    - none, unless large enough to cause pain or shortness of breath

Parasympathetic PGLs

Glomus tympanicum (middle ear PGL)

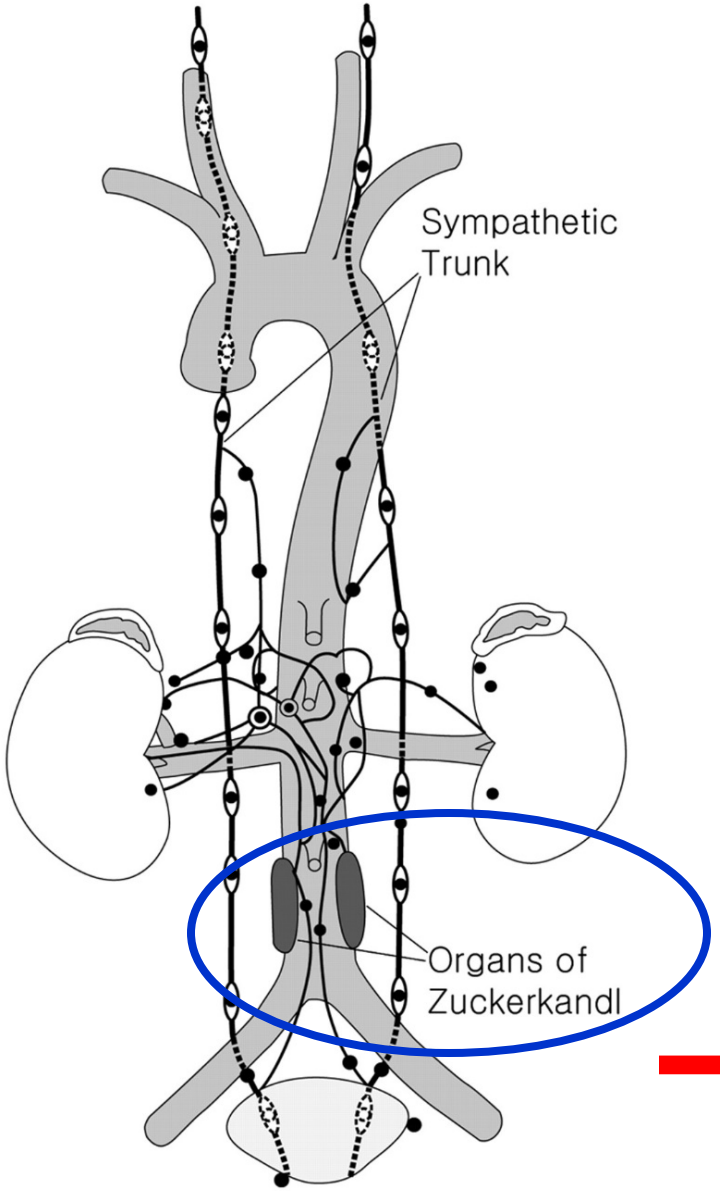


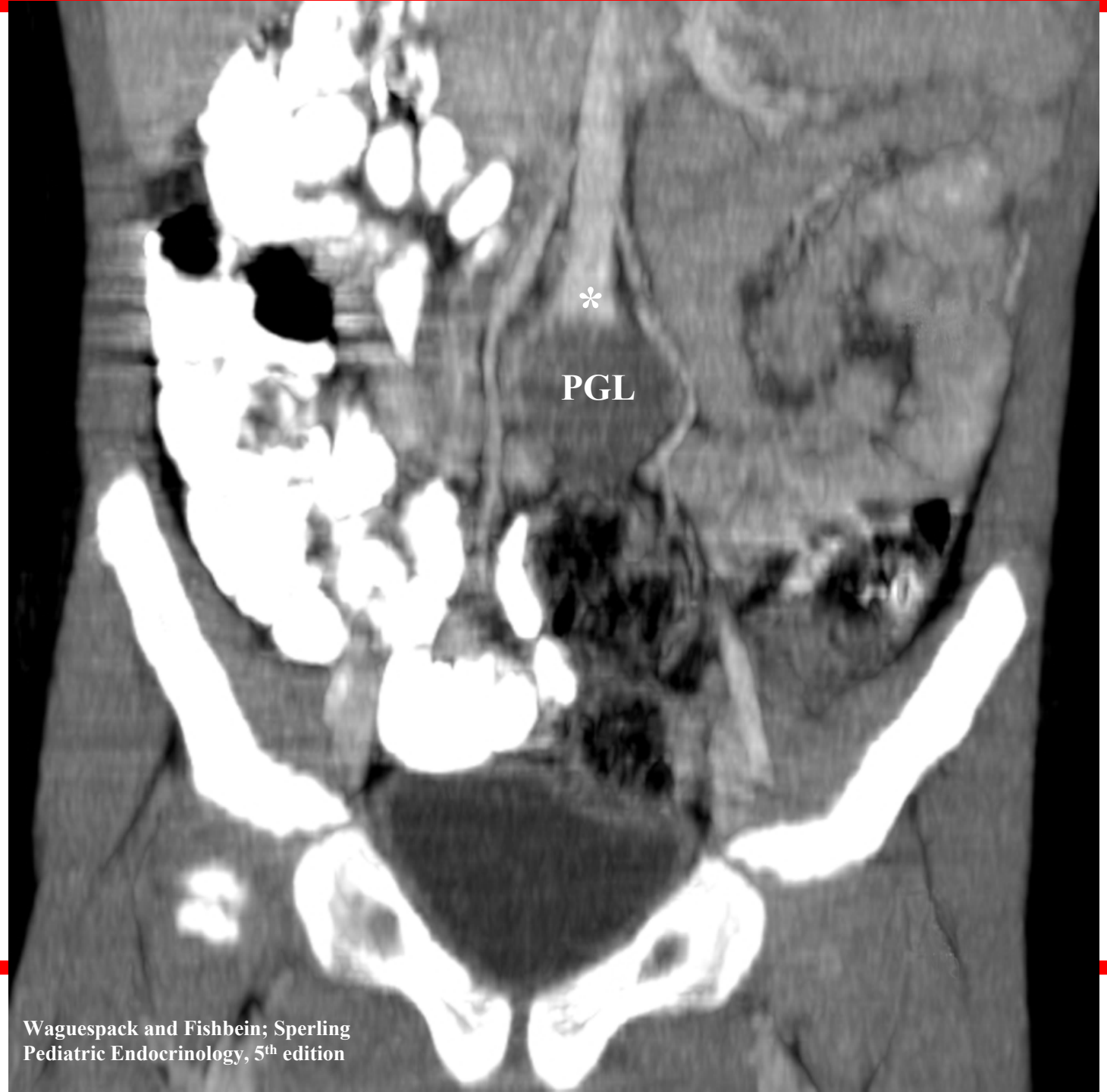
Glomus caroticum (carotid body PGL)



Sympathetic PGLs

- Most hypersecrete catecholamines
- Posterior mediastinum and abdomen/pelvis
  - Organs of Zuckerkandl





Waguespack and Fishbein; Sperling Pediatric Endocrinology, 5th edition

PPGL in Children

- Very rare--Incidence of 2/million/year
- 0.8-1.7% of hypertensive children
- 13% of all PPGL with childhood presentation
- Average age of diagnosis 13 years
- Extra-adrenal (up to 60%) & bilateral (10-25%)
- Up to 80% hereditary
- More likely to be metastatic (esp. PGL)

Pamporaki et al. *J Clin Endocrinol Metab*, April 2017, 102(4):1122–1132

PPGL: Children vs Adults

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

Abbreviations: N/D, noradrenergic/dopaminergic.

[a]Age is shown as mean ± standard deviation.

[b]Multifocal locations indicate multiple extra-adrenal tumors or extra-adrenal and adrenal tumors but exclude bilateral adrenal tumors unless accompanied by one or more extra-adrenal tumors.

[c]Results were retrieved from 611 patients who underwent genetic testing.

[d]Recurrent primary tumors are defined as recurrences at an original site of tumor resection as well as new primary tumors at other locations a year or more after diagnosis of the first primary tumor.

Pamporaki et al. J Clin Endocrinol Metab, April 2017, 102(4):1122–1132

PPGL in Children—Clinical Presentation

- 70-90% present with HTN, usually sustained (up to 2% of hypertensive children)
- Sweating, visual problems, weight loss, nausea/vomiting, and polyuria/polydipsia
- Decreased school performance & behavioral problems
- Classic triad (paroxsymal sweating, HA, palpitations) uncommon
- Symptoms less common in inherited tumors

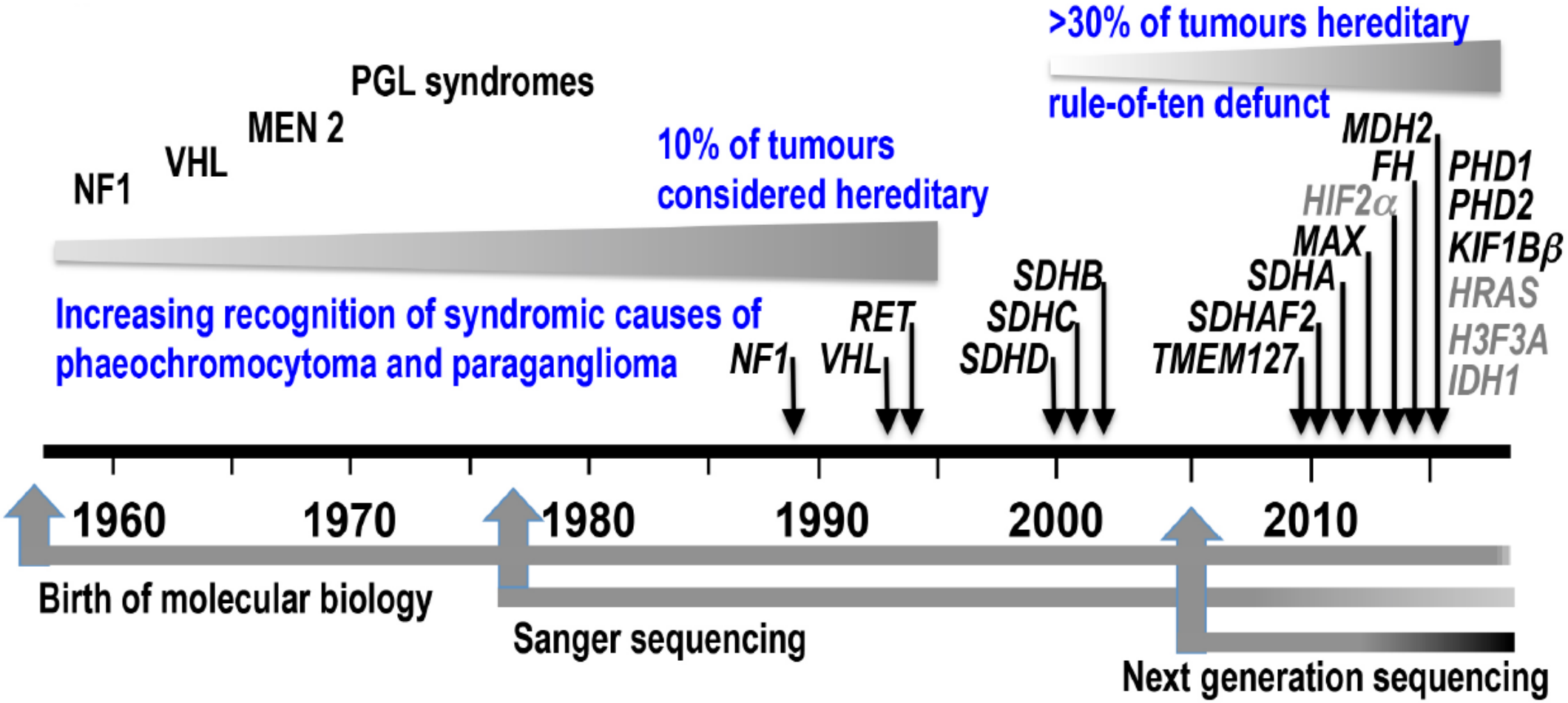
PHEO/PGL—Signs & Symptoms

TABLE 1. Pheochromocytoma: Clinical findings according to age

	<20	>20
Hypertension		
Sustained	93%	68%
Without paroxysms	63%	58%
With paroxysms	37%	42%
Paroxysmal	7%	26%
Normotension	0	5%
Other symptoms		
Headache	95%	90%
Sweating	90%	92%
Visual disturbances	80%	47%
Neurologic signs	65%	57%
Tachycardia, dysrhythmias	35%	72%
Weight loss	15%	72%

Barontini et al. Ann. N.Y. Acad. Sci. 1073: 30–37 (2006).

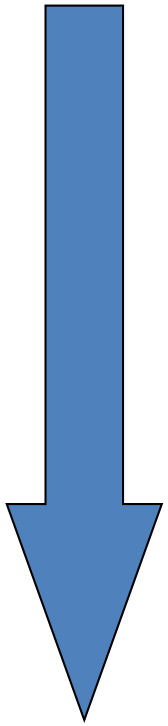
The Genetics of PHEO/PGL



Eisenhofer G *et al. Clin Biochem Rev* 2017

Pediatric PPGL

Most Common



Least Common

VHL -PHEO

SDHB -PGL

SDHD[1]

RET

NF1

TMEM127

MAX

SDHC, SDHA, SDHAF2[1]

*Others**

Germline mutations found in 80% of children

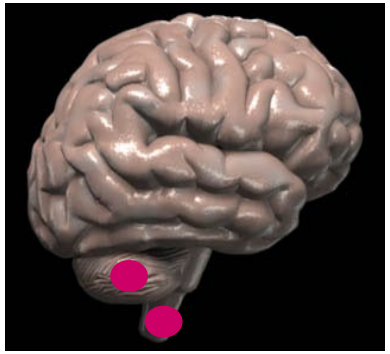
[1]Parent of origin effects; clinical disease not present in children of females

**FH, IDH1, HIF2A/EPAS1, PHD1 and PHD2, MDH2, KIF1β, MEN1*

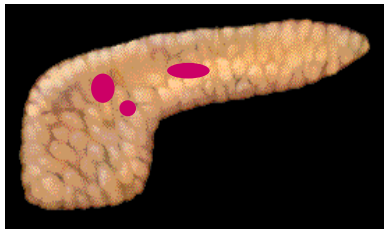
Dahia P *Nature Reviews Cancer* 2014; Neumann HP *NEJM* 2002; Neumann HP *Endo Rel Cancer* 2017, Pamporaki *JCEM* 2017

Von Hippel-Lindau Disease

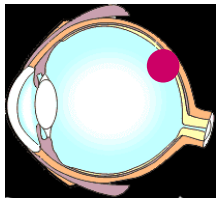
CNS Hemangioblastoma
80%



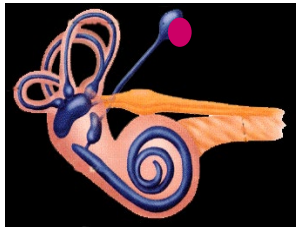
Pancreatic NET
11-17%



Retinal
Hemangioblastoma
85%

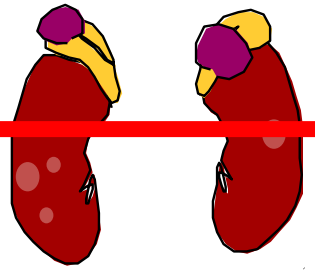


Endolymphatic
Sac Tumors
4%



Pheochromocytoma
20-30%

Renal Carcinoma
40+%



Epididymal
Cystadenoma
60% of males

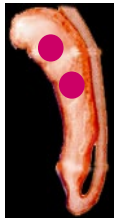
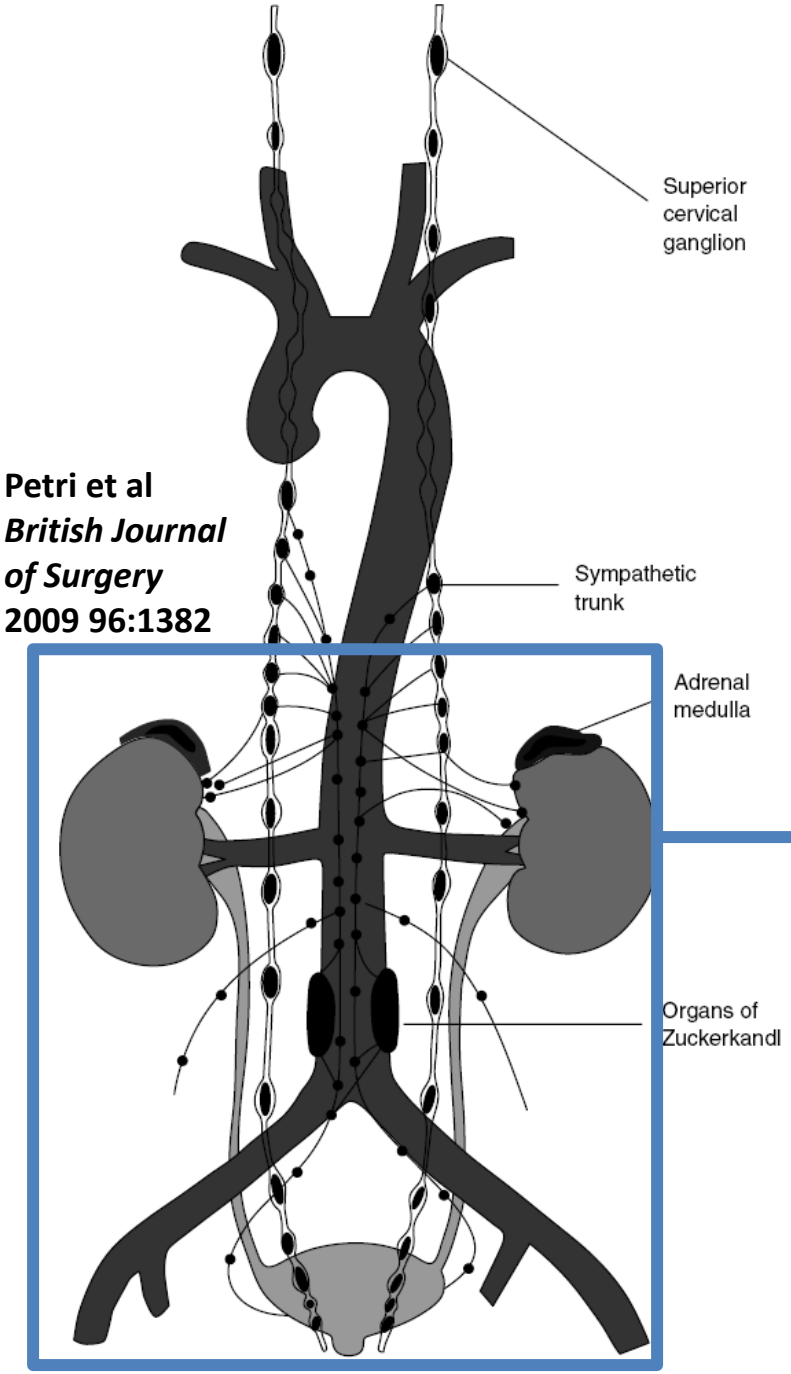


Figure Courtesy of Gilbert J. Cote, PhD

Hereditary Paraganglioma Syndromes:



Petri et al
British Journal of Surgery
2009 96:1382

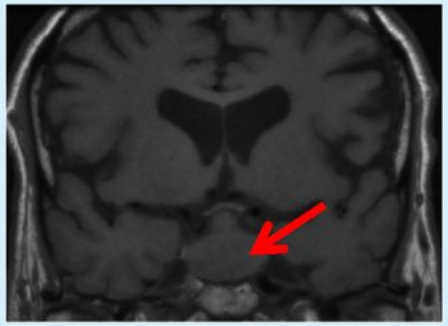
- PGL1 (*SDHD*)
- PGL2 (*SDHAF2*)
- PGL3 (*SDHC*)
- PGL4 (*SDHB*) — Higher rate of malignancy
- PGL5 (*SDHA*)

Inactivating mutations in *SDHx*, leading to dysfunction of complex II in the electron transport chain

SDHx-associated Tumors

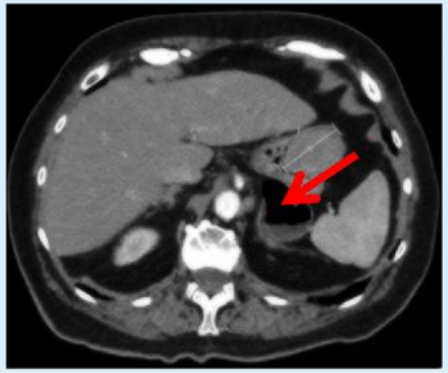
UNCOMMON

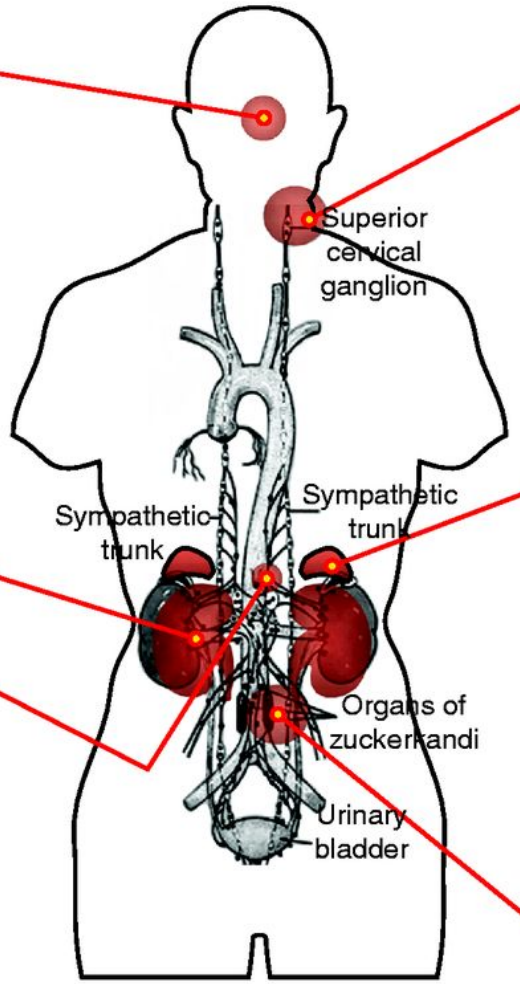
(d) Pituitary adenoma (rare)



(e) Renal cell carcinoma

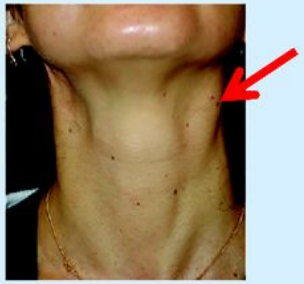
(f) GIST



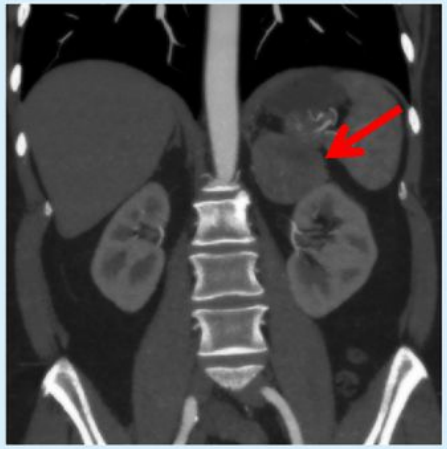


COMMON

(a) Head and neck PGL



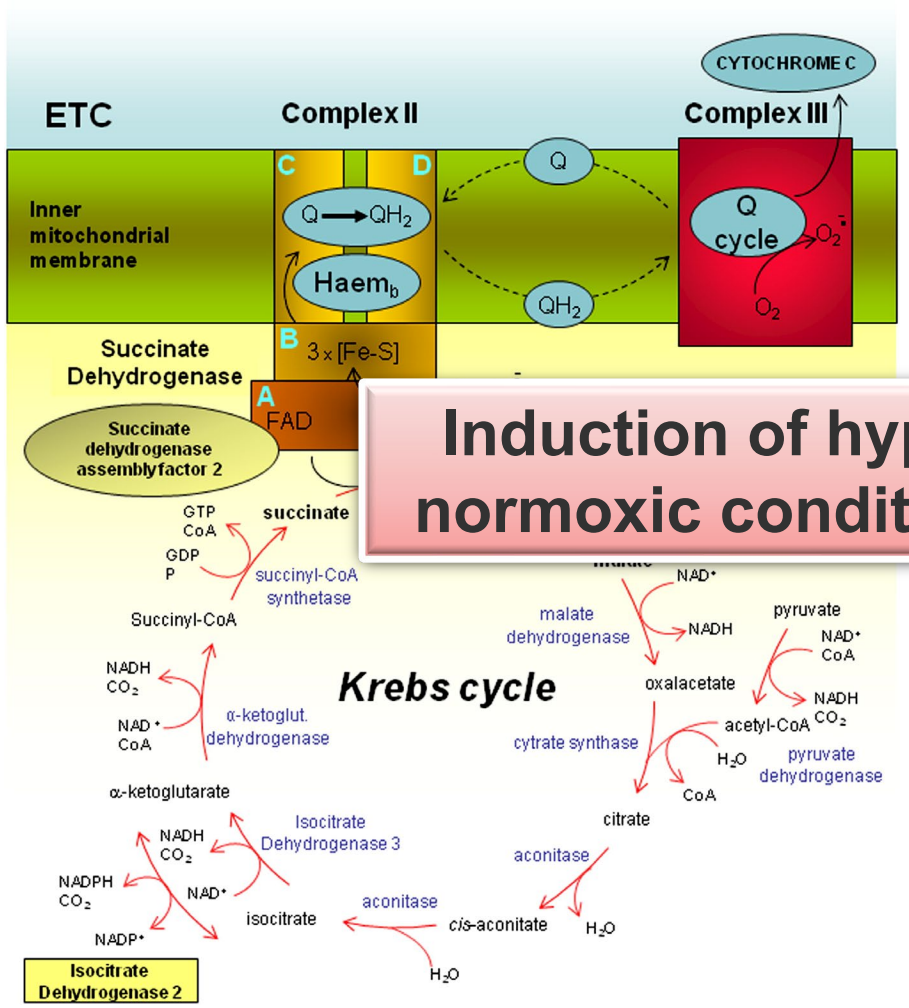
(b) Phaeochromocytoma



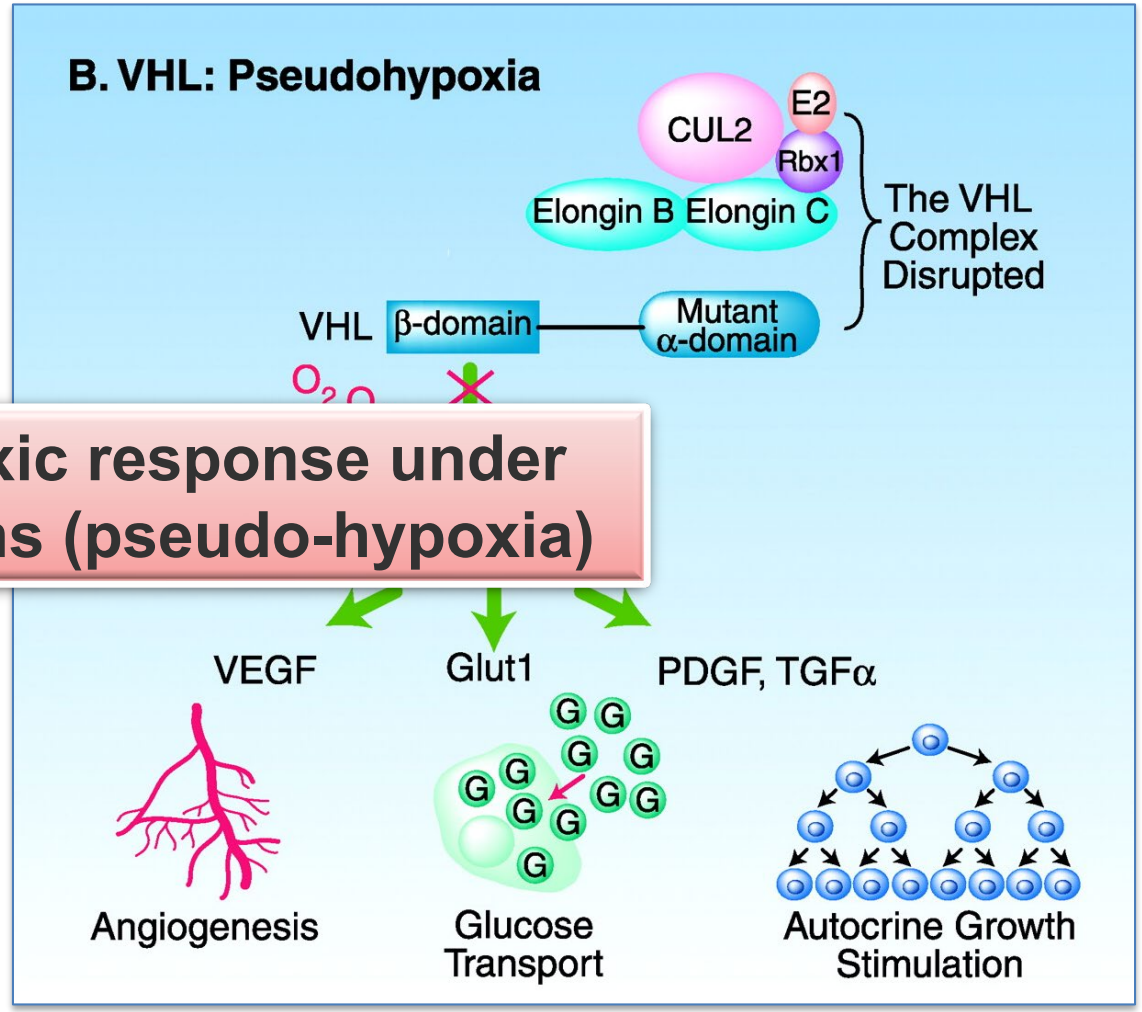
(c) Abdominal PGL

Benn DE *et al.*, *Endocr Relat Cancer*. 2015

SDHx and VHL



Induction of hypoxic response under normoxic conditions (pseudo-hypoxia)

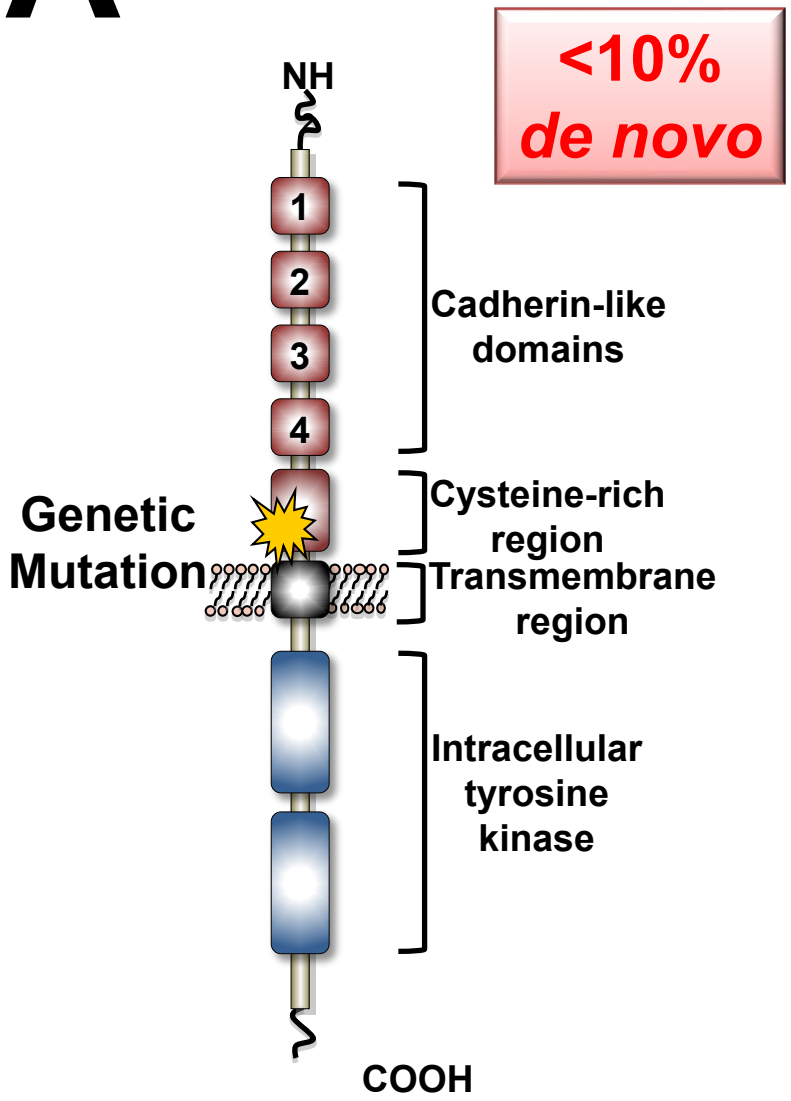


Bardella *et al. Biochimica et Biophysica Acta* 1807 (2011) 1432–1443

Bratslavsky *et al.* Clin Cancer Res 2007;4667 13(16)

MEN2A

- **Medullary Thyroid Carcinoma** (MTC) (> 90%)
- **Parathyroid Neoplasia** (0-20%)
- **Pheochromocytoma** (0-50%)

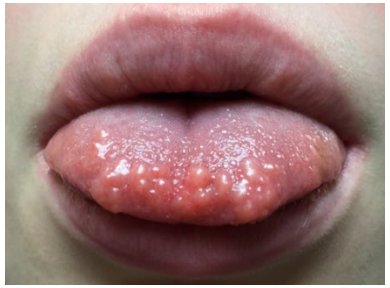


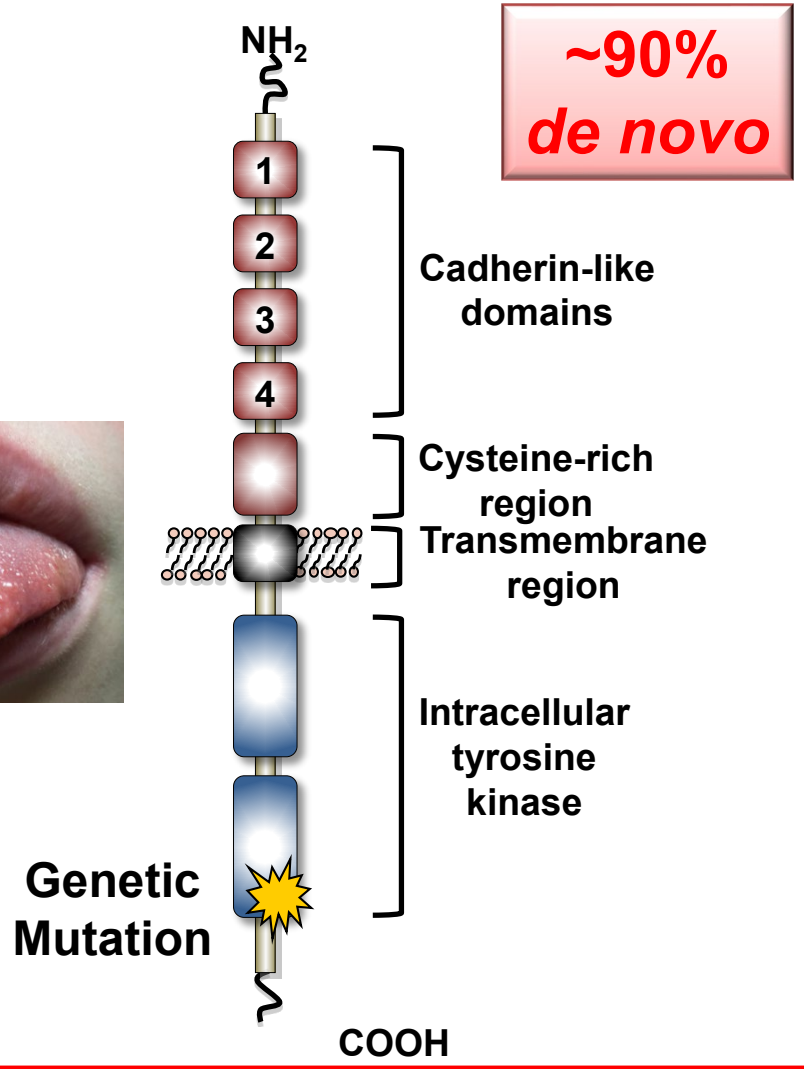
RET Figure adapted from Waguespack *et al. Nat Rev Endocrinol.* 2011 Aug 23;7(10):596-607

RET tyrosine kinase receptor

MEN2B

- **Medullary Thyroid Carcinoma (MTC) (100%)**
- **MEN2B Phenotype (100%)**
- **Pheochromocytoma (~50%)**

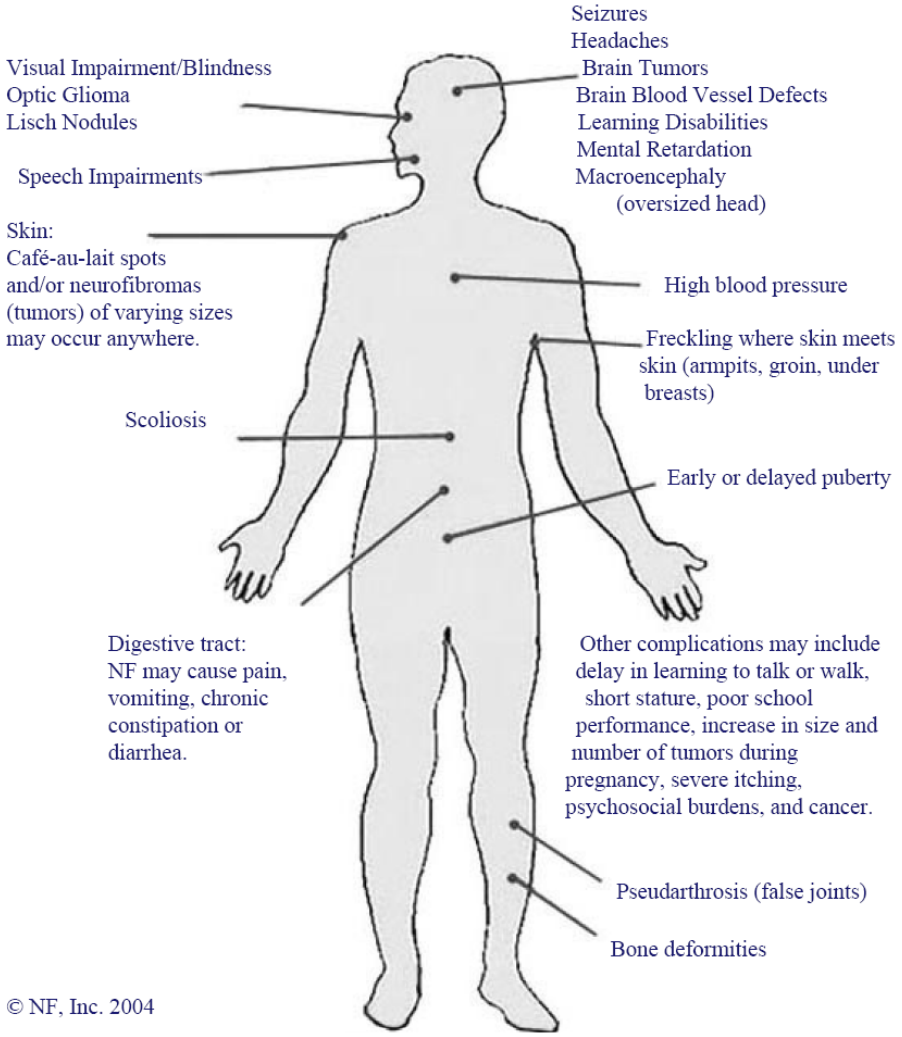




RET Figure adapted from Waguespack *et al. Nat Rev Endocrinol.* 2011 Aug 23;7(10):596-607

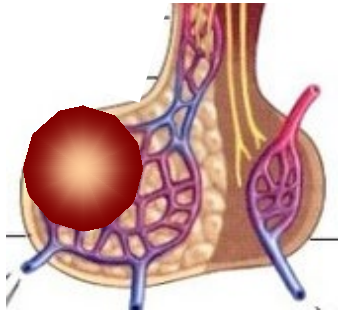
RET tyrosine kinase receptor

NF1

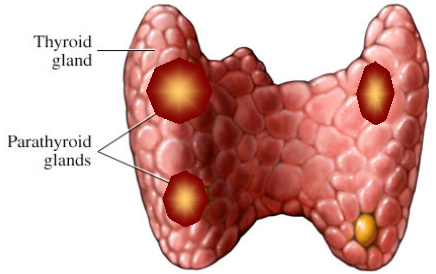


PHEO 2-6%; adult onset
Screen pts with HTN

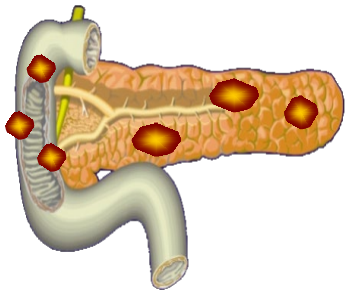
MEN1



Anterior Pituitary Adenomas 30-40%



Parathyroid Hyperplasia > 97%



Duodenopancreatic Neuroendocrine Tumors 75%

Very rare; adult onset
Screen pts with HTN, adrenal mass

Other Genes Implicated in Hereditary PPGL

- *TMEM127*
- *MAX*
- *FH*
- *HIF2A (aka EPAS1)*[1]
- *PHD1 and PHD2 (aka EGLN2 and EGLN1)*[2]
- *BAP1*
- *KIF1β*
- *MDH2*

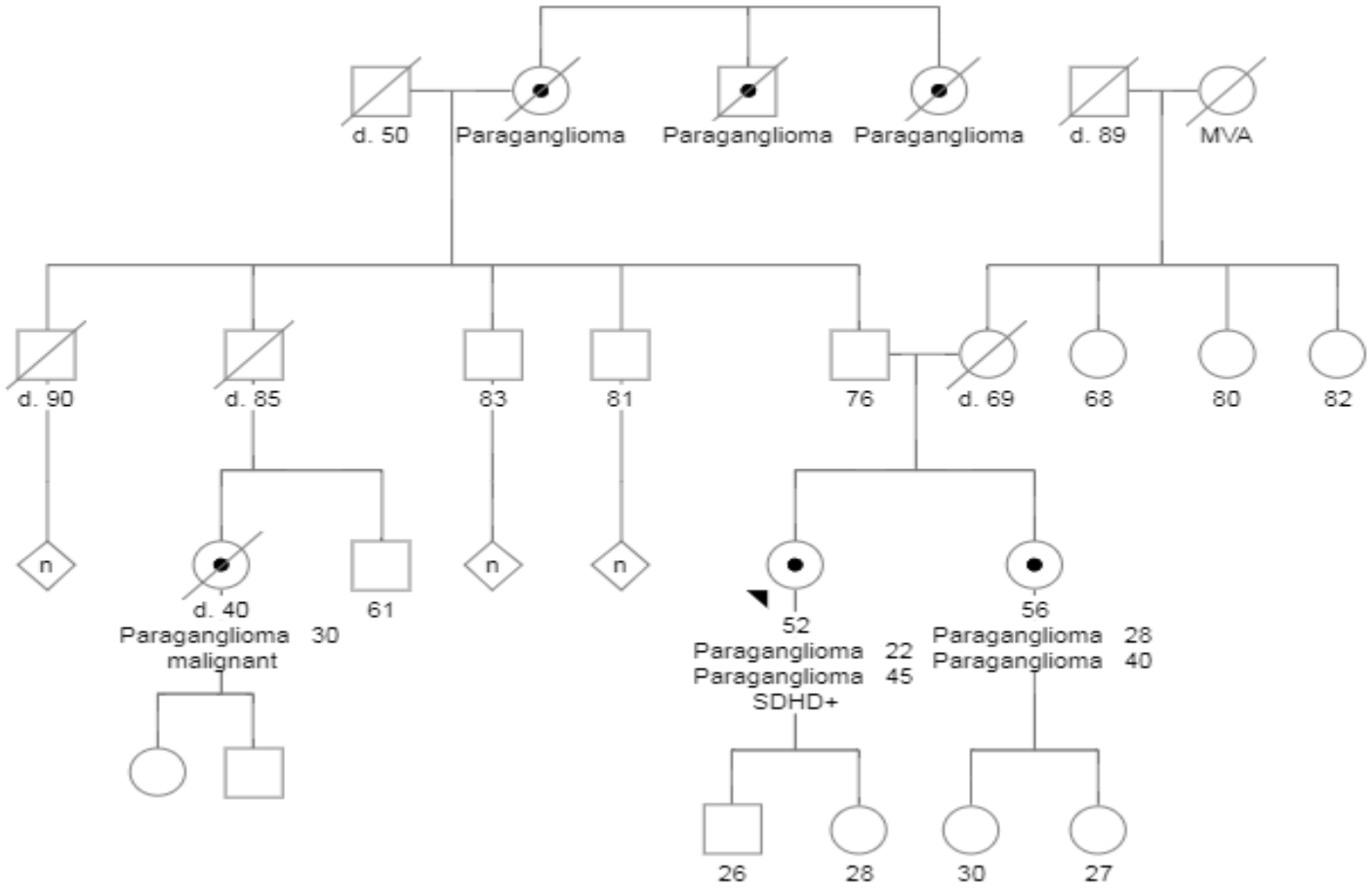
- Incomplete penetrance of PPGL
  - Typically adult onset
  - Few cases published
- Screening guidelines not well established

[1]Somatic mutations in cyanotic congenital heart disease

[2]Associated with polycythemia

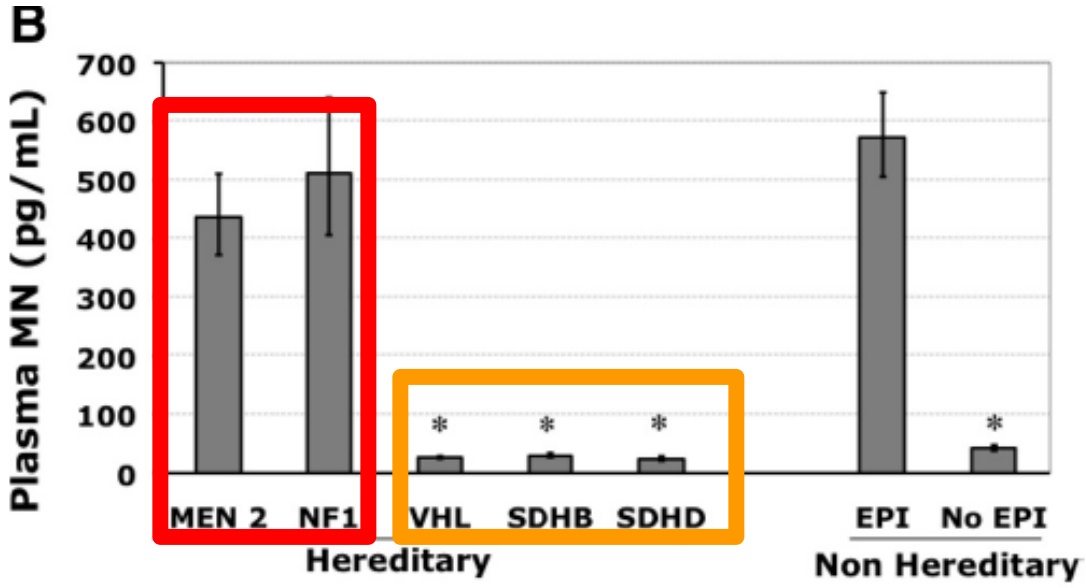
Muth *J Intern Med* 2019; Neumann *Endocrine Related Cancer* 2018; Eisenhofer *Clin Biochem Rev* 2017

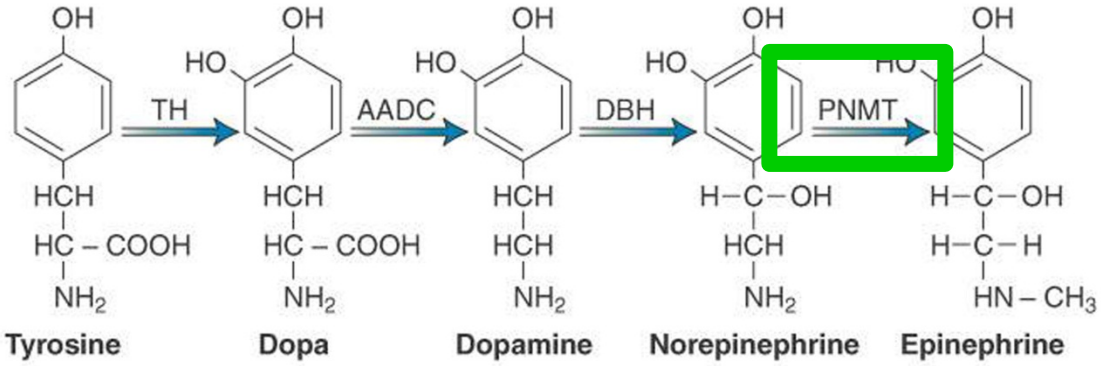
Parent-of-Origin Effects in *SDHD* and *SDHAF2* (and possibly *MAX*)



Pedigree courtesy of Samuel Hyde, MMSc, CGC

Mutation & Tumor Phenotype





- VHL and *SDHx* tumors are *noradrenergic (Cluster 1; pseudohypoxia)*
- MEN, NF1, and sporadic tumors are *adrenergic (Cluster 2; tyrosine kinase signaling)*
- Difference in expression of PNMT

Eisenhofer G *et al.* *J Clin Endocrinol Metab.* 96, Feb 2011; Williams Textbook of Endocrinology 11th ed.

Hereditary PPGL Screening

Gene	Typical Age to Start	Testing
RET	11-16[1]	Annual Metanephrines[2]
SDHB	5	Annual Metanephrines[2] Annual Catecholamines[3] Annual Chromogranin A Periodic Imaging[4,5]
VHL	5	Annual Metanephrines[2] Periodic Imaging[4,6]

[1] Depends on the specific *RET* mutation; age 11 years for 634, 883 and 918, and age 16 years for others
[2] Plasma free metanephrines or urinary fractionated metanephrines
[3] Consider 3-methoxytyramine if a dopamine secreting tumor is suspected
[4] Avoid ionizing radiation for screening purposes
[5] Abdominal/pelvis US in very young patients; Whole body MRI every 2 years in older patients
[6] Abdominal US or MRI done in conjunction with imaging for other tumors

Lenders *et al.* *J Clin Endocrinol Metab.* 2014; Wells *et al.* *Thyroid.* 2015; Rednam *et al.* *Clin Cancer Res.* 2017; Tufton *et al.* *J Endo Soc.* 2017; Else *et al.* GeneReviews® 2018; van Leeuwaarde *et al.* GeneReviews® 2018; Waguespack and Fishbein 2019

PHEOs Identified by Screening are Smaller and Less Symptomatic

Pheochromocytomas in the sporadic group were significantly larger compared with the hereditary group (7.3±0.7 vs 3.7±0.5 cm, $P<0.01$).

Table 3 Perioperative findings. Data are shown as mean (S.E.M.), unless otherwise mentioned.

	Pheochromocytomas		
Intraoperative events	Sporadic	Screening	***P* value**
Operation time *m* (min) ±S.E.M.	175±20	167±18	0.78
SAP>160 mmHg	21 (75%)	16 (50%)	0.03*
Episodes *m*±S.E.M.	4.1±0.8	3.7±0.7	0.68
Duration *m*±S.E.M.	50.3±10.7	40.7±10.3	0.54
MAP<60 mmHg	16 (49%)	11 (34.4%)	0.08
Episodes *m*±S.E.M.	2.3±0.7	2.6±0.7	0.71
Duration *m*±S.E.M.	20.4±8.6	29.2±11.1	0.54
Blood loss			
Median *m* (cc)	500	300	

SAP, systolic arterial pressure; MAP, mean arterial pressure; *Statistically significant.

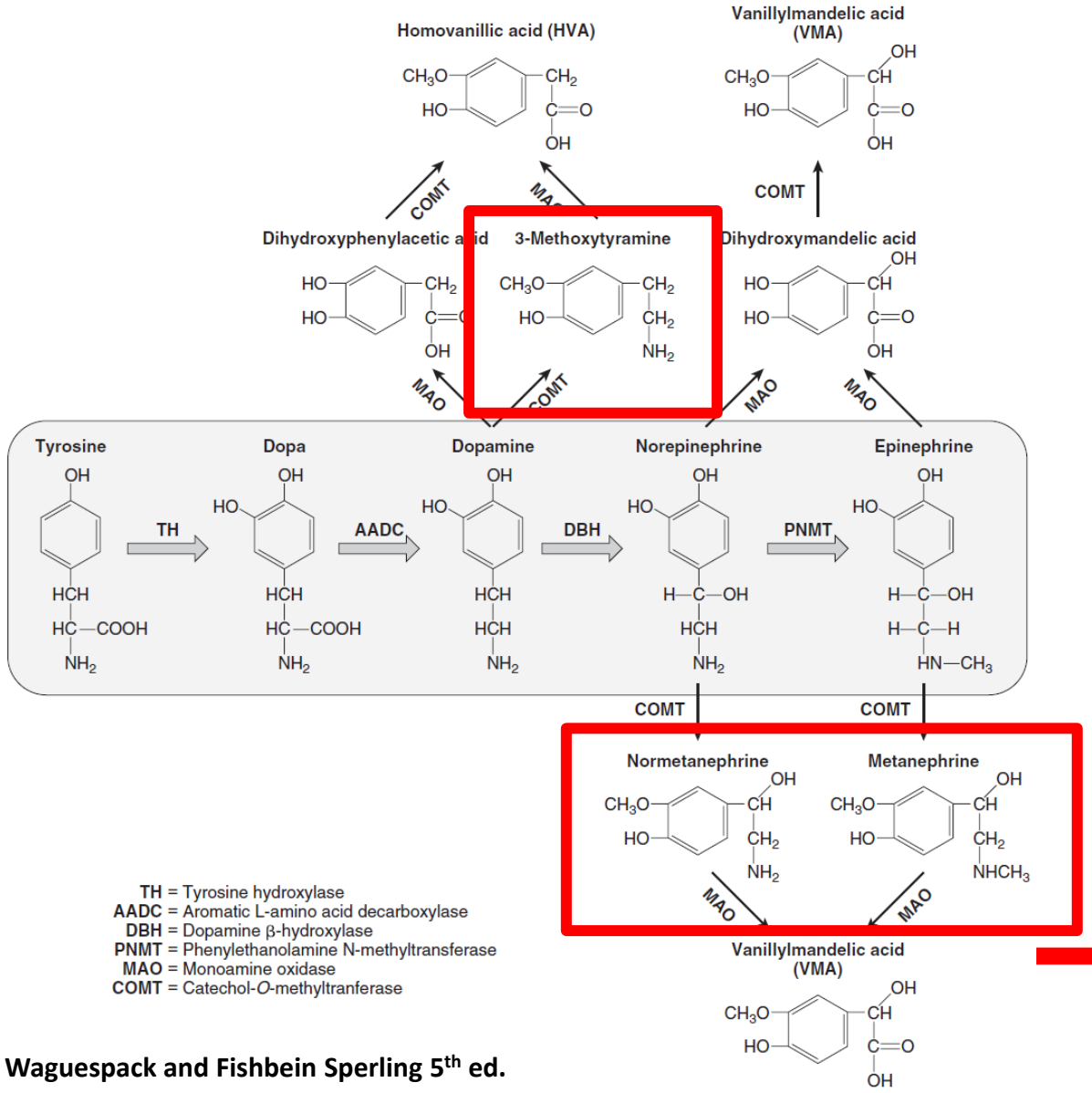
Table 1 Clinical characteristics at the time of diagnosis of patients with sporadic pheochromocytomas versus patients with pheochromocytomas detected by screening. Data are shown as mean (S.E.M.), unless otherwise mentioned.

	Pheochromocytomas		
Characteristics	Sporadic	Screening	***P* value**
Number of patients	28	32	
Gender (*n* (%))			
Males	14 (50%)	21 (66%)	0.22
Body mass index (kg/m^2)	24.5±0.7	25.3±0.7	0.44
Age (at diagnosis (years))	47±3	41±2	0.07
Symptoms (*n* (%))			
Diaphoresis	21 (75%)	11 (34%)	<0.01*
Palpitations	18 (64%)	9 (28%)	0.01*
Headache	16 (57%)	12 (38%)	0.13
Diap.+palp.+head.	11 (39%)	5 (16%)	0.04*
Dizziness	9 (32%)	9 (28%)	0.74
Pallor	12 (43%)	4 (13%)	0.01*
Nausea	12 (43%)	1 (3%)	<0.01*
Vomiting	6 (21%)	0	<0.01*
Flushes	2 (7%)	5 (16%)	0.43
Hypertension (>140/90 mmHg)	15 (54%)	11 (34%)	0.13
Type 2 diabetes mellitus (*n* (%))	5 (18%)	1 (3%)	0.01*
Systolic blood pressure (mmHg)	156.4±4.7	143.1±2.8	0.02*
Mean arterial pressure (mmHg)	116.0±3.5	106.8±2.0	0.03*
Diastolic blood pressure (mmHg)	95.7±3.4	88.6±1.9	0.07
Antihypertensive medication (*n* (%))	13 (46%)	4 (13%)	<0.01*

Diap., diaphoresis; Palp., palpitations; head, headache; *Statistically significant.

van Duinen et al. Screening and Pheochromocytomas *Eur J Endocrinol.* Vol 163, 121-27. Apr 2010.

PHEO/PGL- Diagnosis

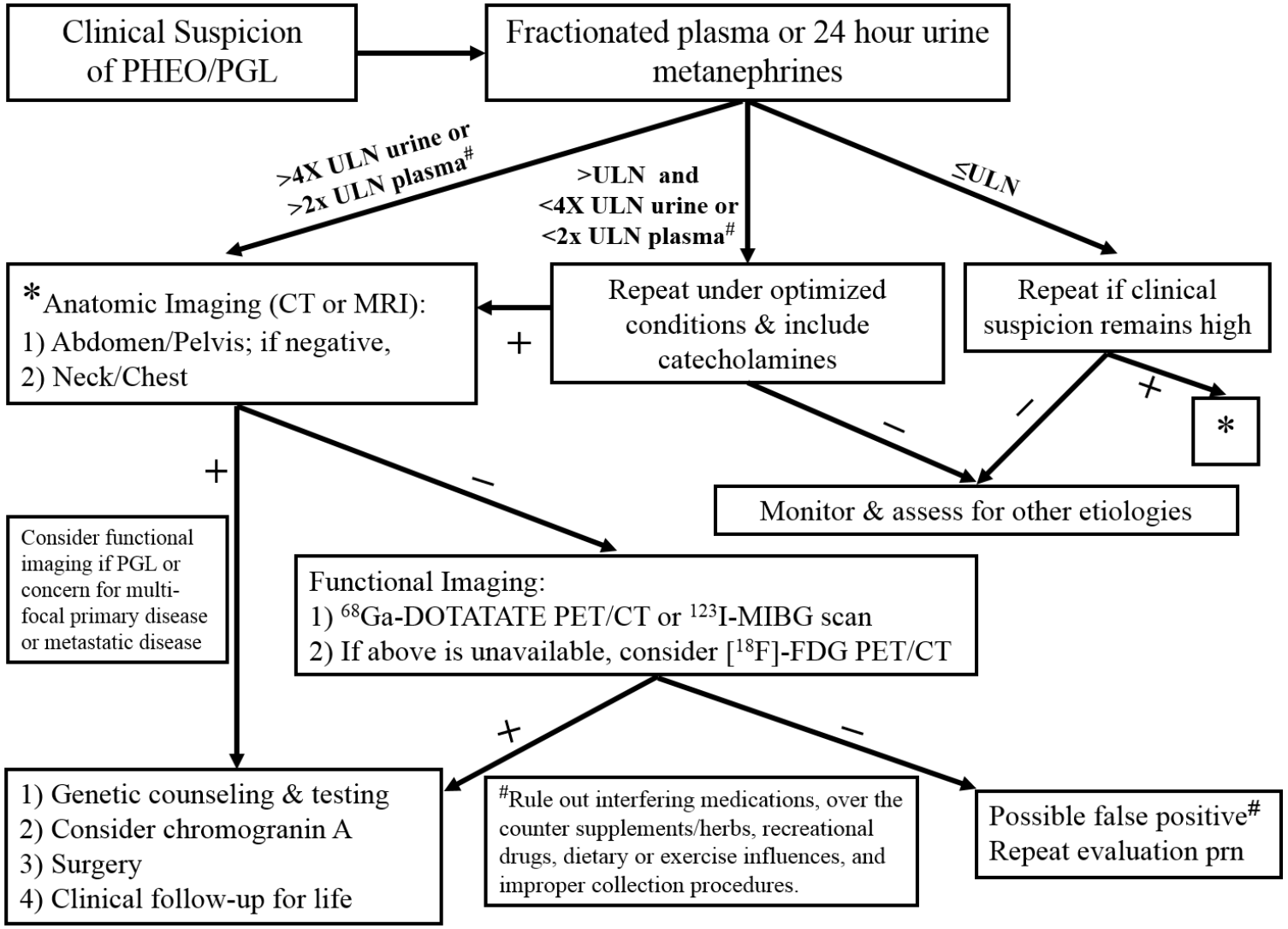


Measurement of plasma and/or 24 urine fractionated metanephrines (metanephrines + normetanephrines)

Waguespack and Fishbein Sperling 5th ed.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

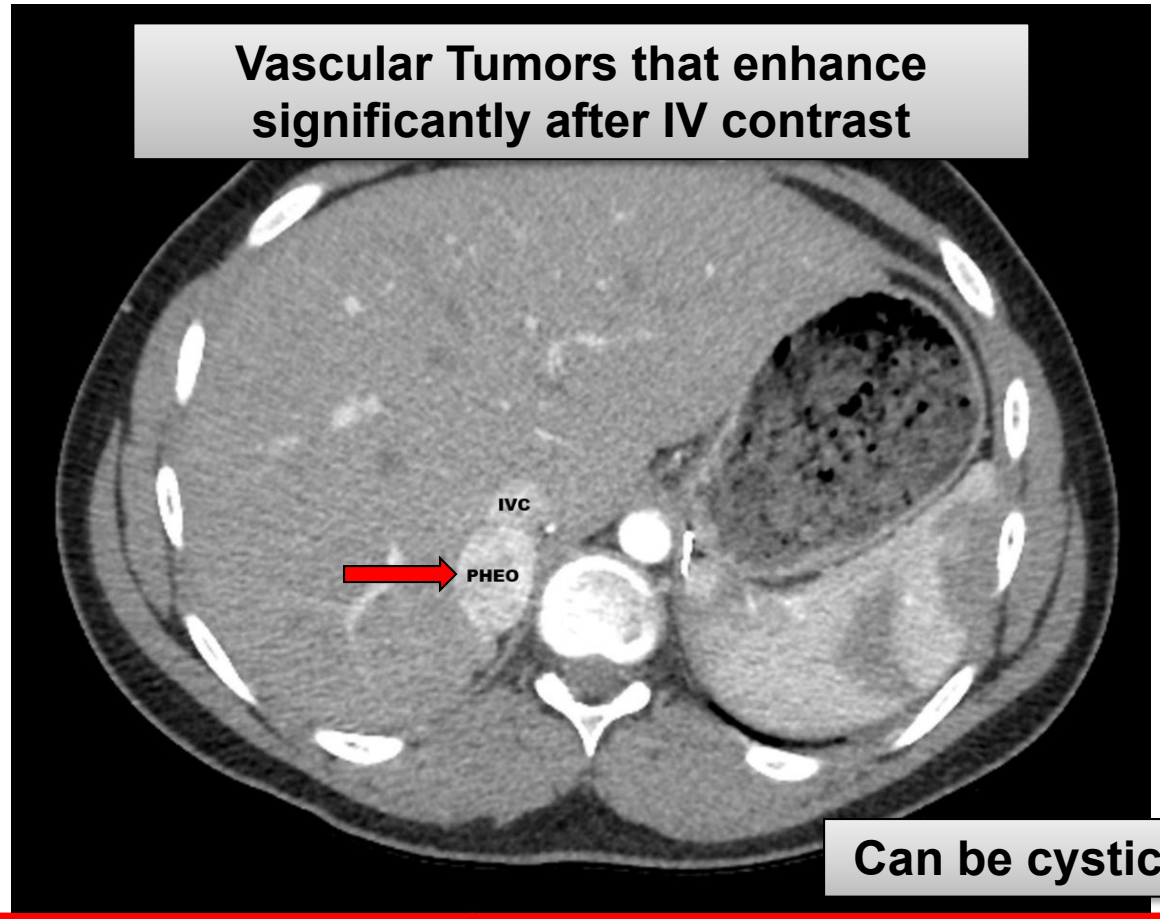
PPGL- Diagnosis



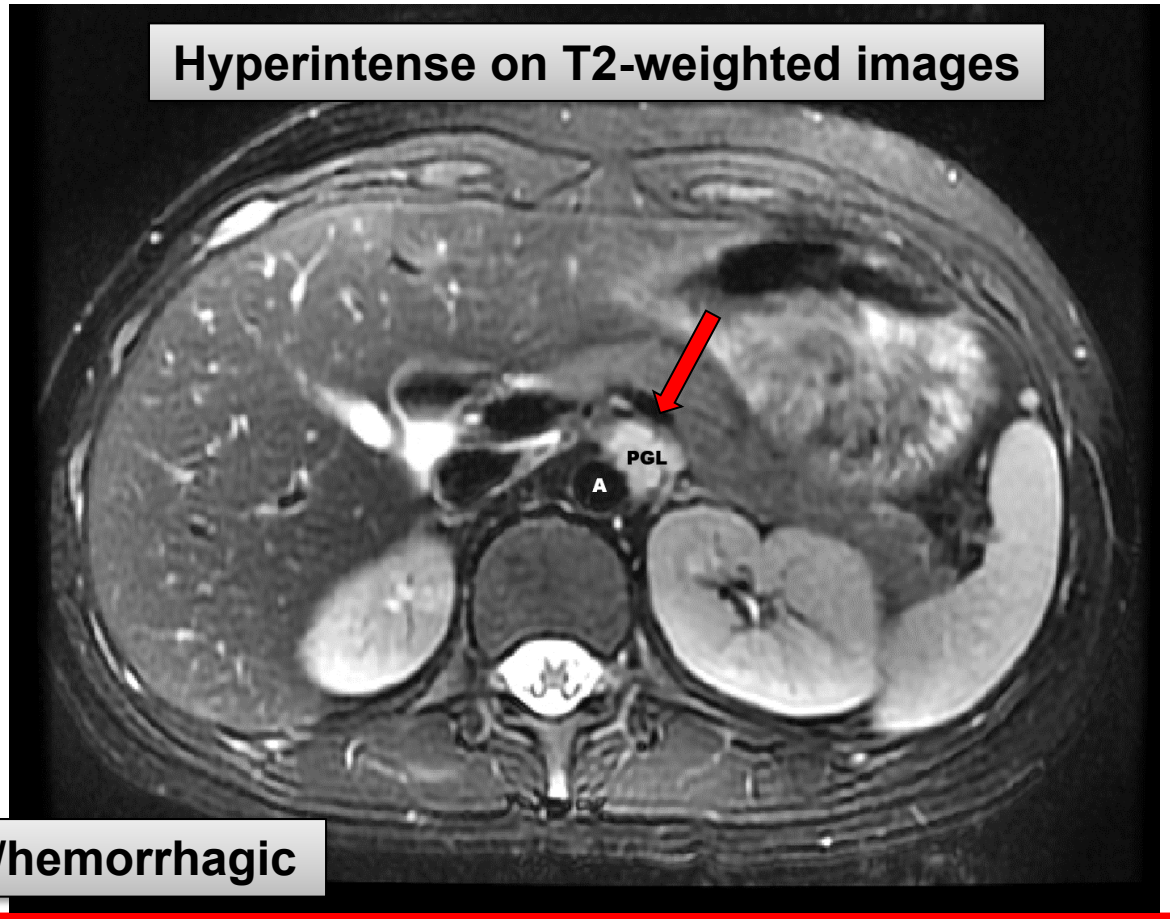
Waguespack and Fishbein, Sperling 5th ed.

Anatomic Imaging for PHEO/PGL

CT



MRI

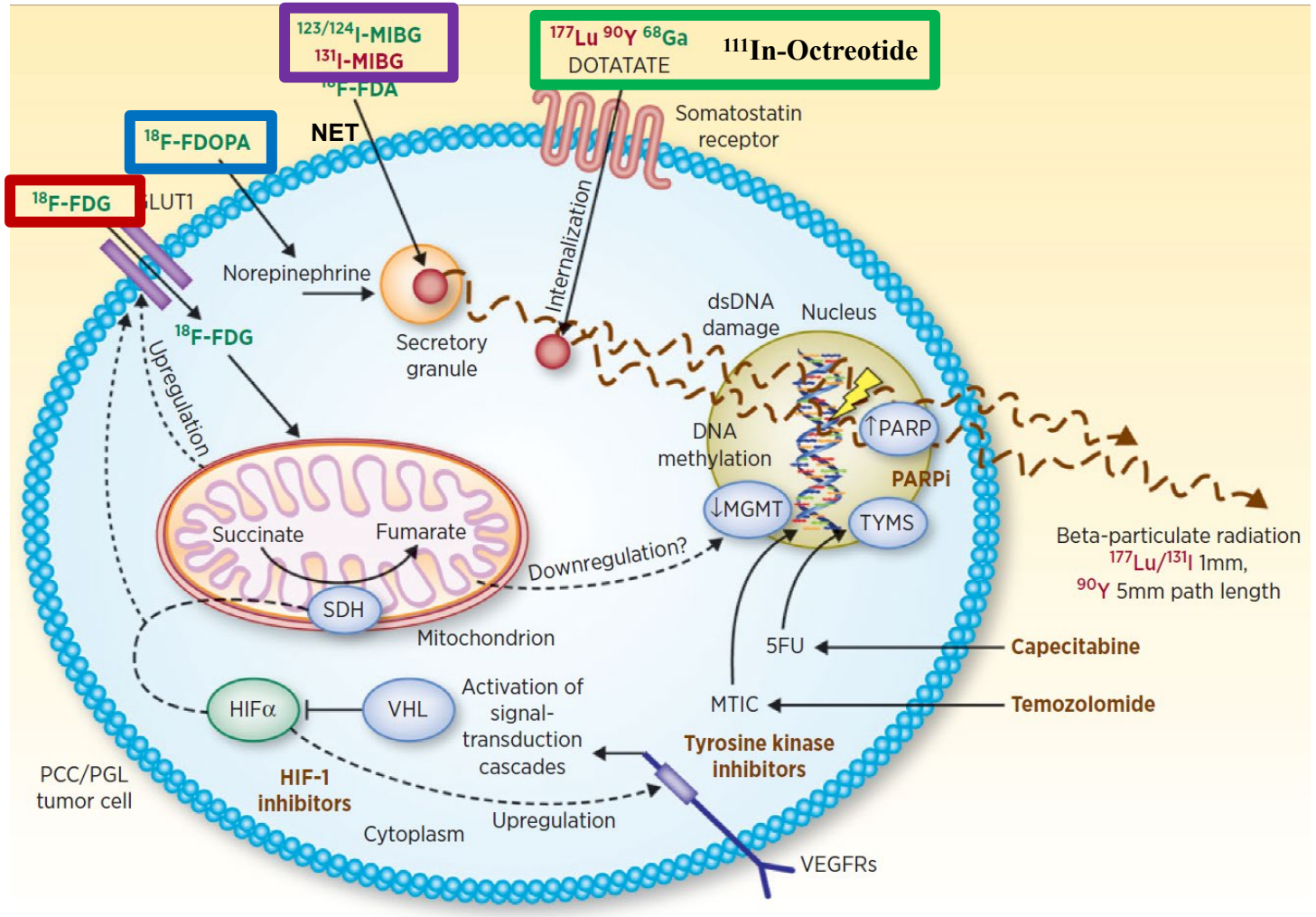


Can be cystic/hemorrhagic

Waguespack and Fishbein, Sperling 5th ed

Functional Imaging for PPGL

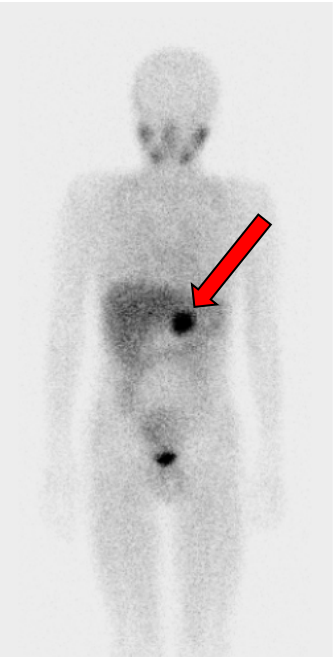
- **Scintigraphy**
  - ^{123}I-MIBG
  - ^{111}In-Octreotide
- **PET**
  - ^{18}F-FDG
  - ^{68}Ga-DOTATATE
  - ^{18}F-DOPA

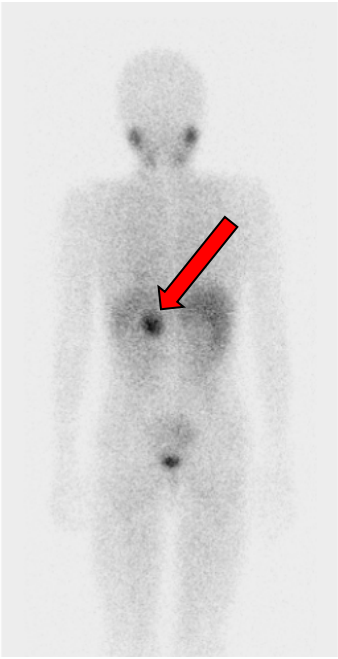


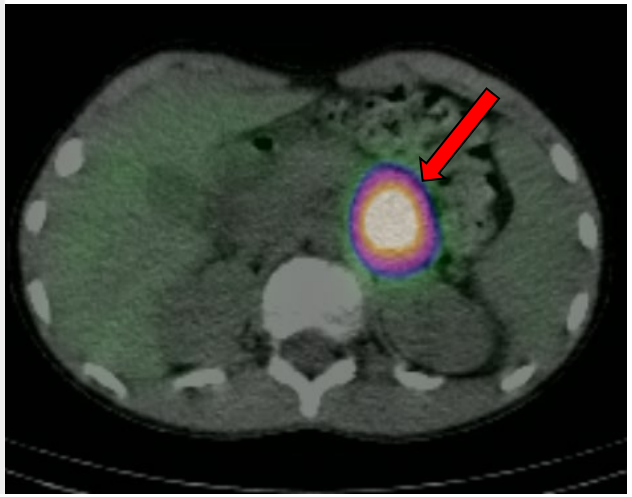
Hofman and Hicks *Clin Cancer Res* 2015

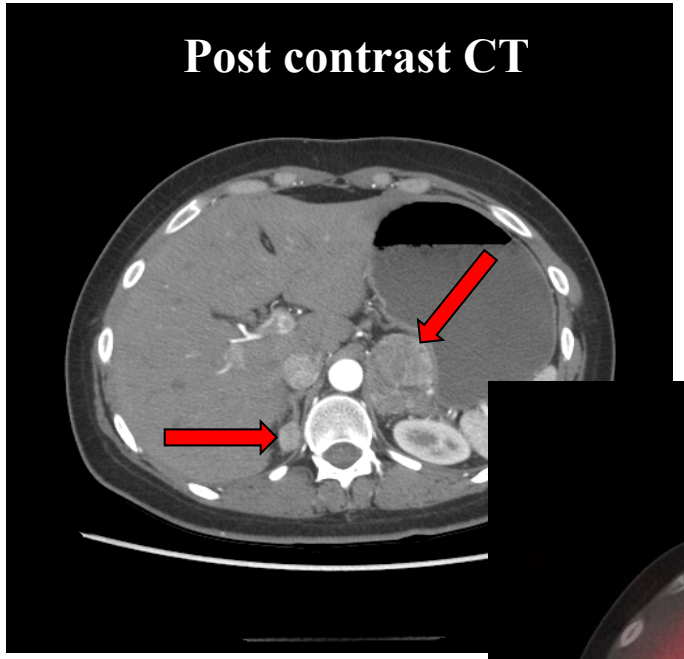
Functional Imaging for PHEO/PGL

- ^{123}MIBG scan

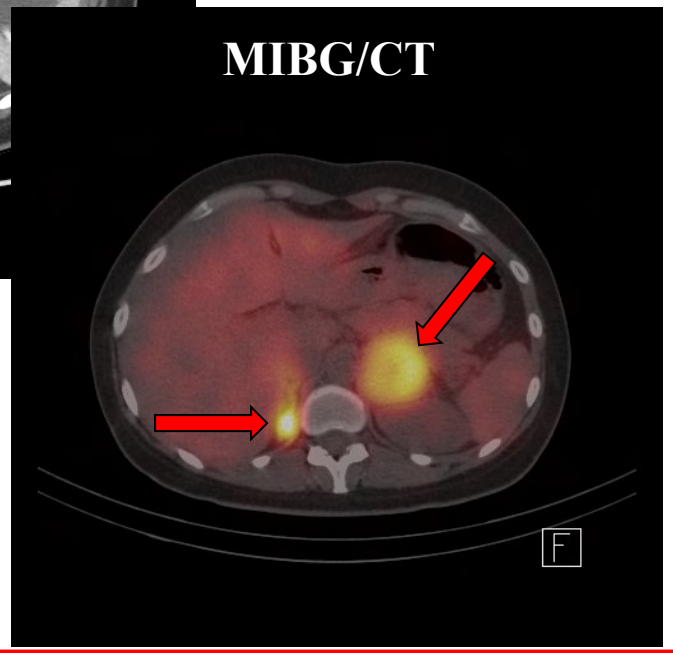






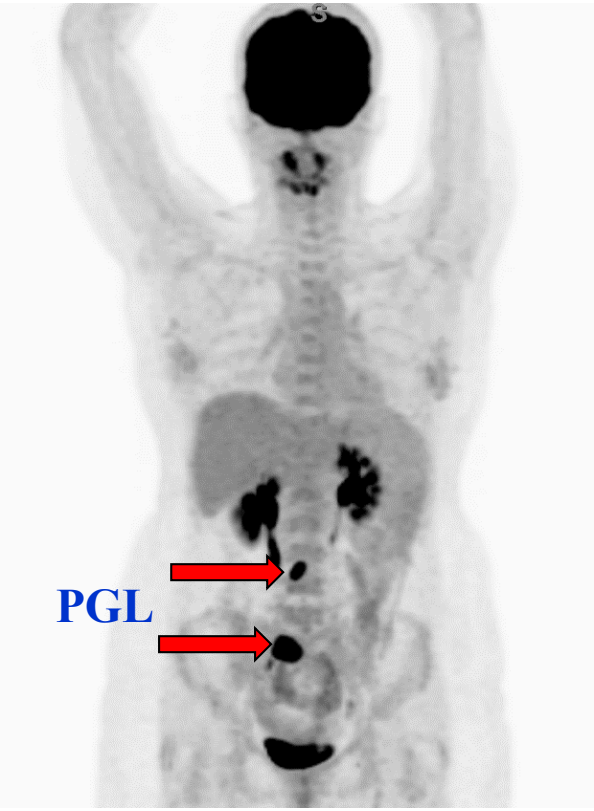


MEN2a and Bilateral PHEOS

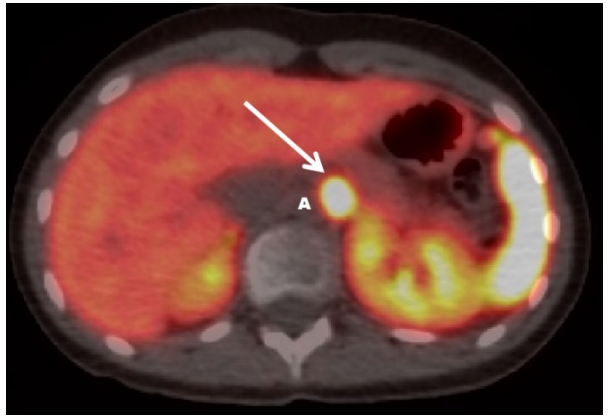


Functional Imaging for PHEO/PGL

- ^{18}FDG PET/CT



- ^{68}Gallium Dotatate PET/CT



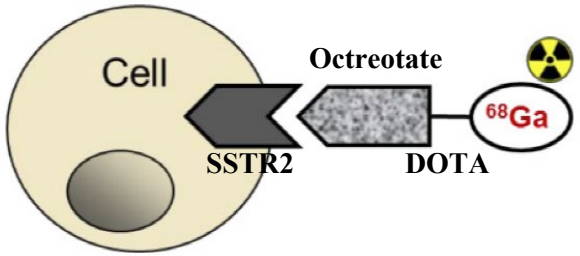
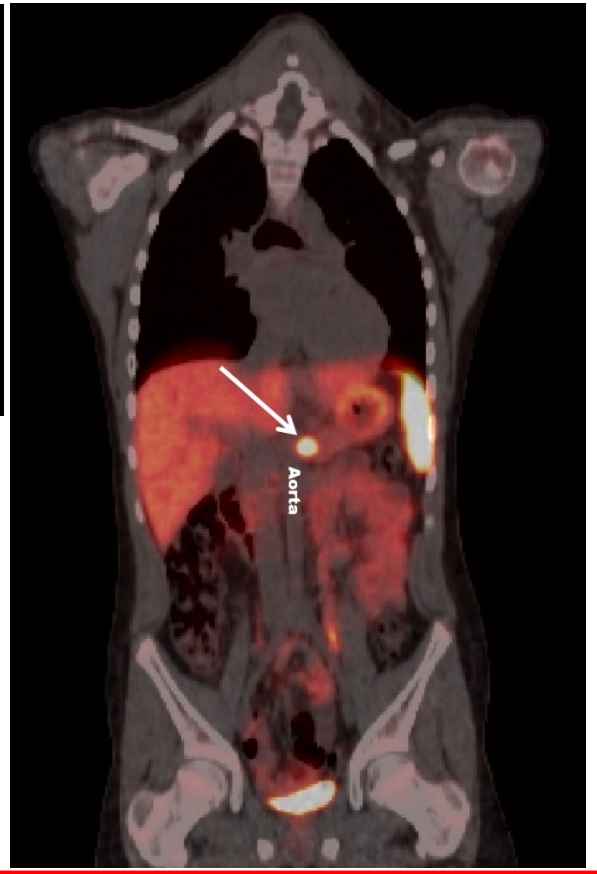


Figure Adapted from Velikyan *Theranostics* 2014



Waguespack and Fishbein, Sperling 5th ed., In press

PHEO/PGL- Pre-op Medical Management

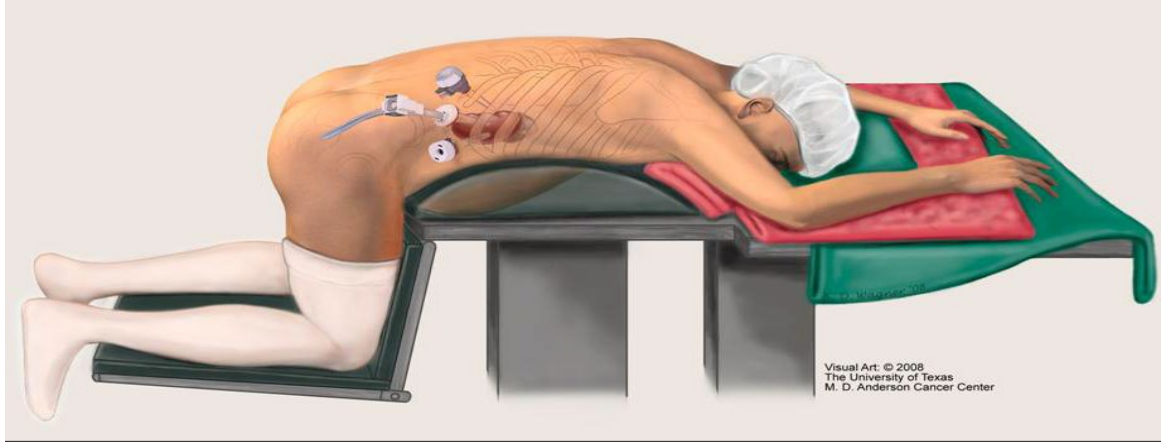
TABLE 14-3 **Preoperative Medical Management of Pheochromocytoma/Sympathetic Paraganglioma**

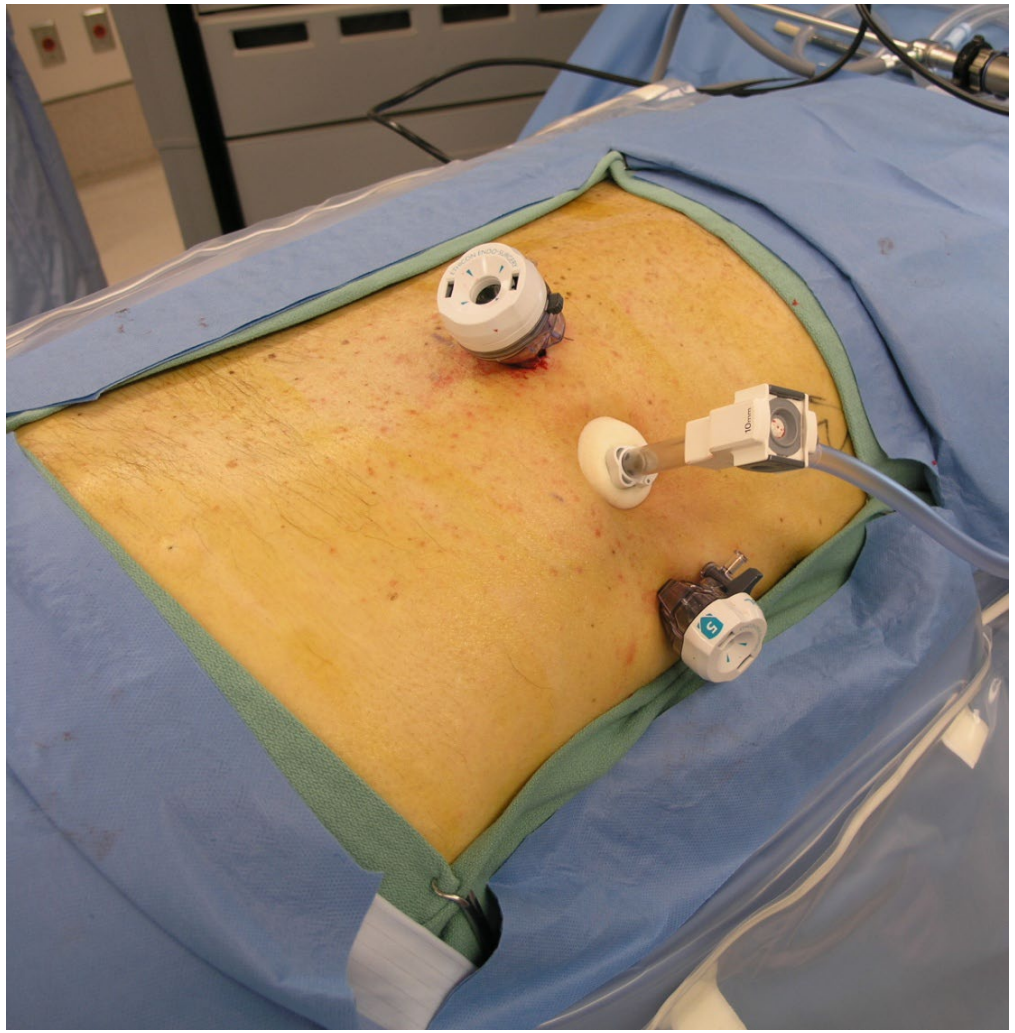
Drug Class	Drug	Mechanism of Action	Initial Pediatric Dose
α-adrenergic receptor blockers	Doxazosin	α_1-antagonist	0.5-1 mg daily
	Phenoxybenzamine	α_1- and α_2-antagonist	0.2-0.5 mg/kg/day divided BID (max 10 mg BID)
	Prazosin	α_1-antagonist	0.05-0.1 mg/kg/day divided TID (max 1 mg TID)
β-adrenergic receptor blockers	Atenolol	β_1- antagonist	0.5-1 mg/kg/dose daily (max 50 mg daily)
	Metoprolol	β_1- antagonist	1-2 mg/kg/day divided BID (max 50 mg BID)
	Propranolol	β_1- and β_2-antagonist	0.5-1 mg/kg/day divided BID (max 40 mg BID)
Calcium channel blockers	Nifedipine (sustained release)	Calcium channel blocker	0.25-0.5 mg/kg/day daily or BID (max 60 mg total daily dose)
Inhibitors of catecholamine synthesis	Metyrosine	Tyrosine hydroxylase inhibitor	125-250 mg divided BID-TID

Waguespack and Ying Sperling 4th ed.

Surgery

- Open Adrenalectomy
  - Large PHEOs
- Laparoscopic Adrenalectomy
  - Anterior transperitoneal
  - Posterior retroperitoneal

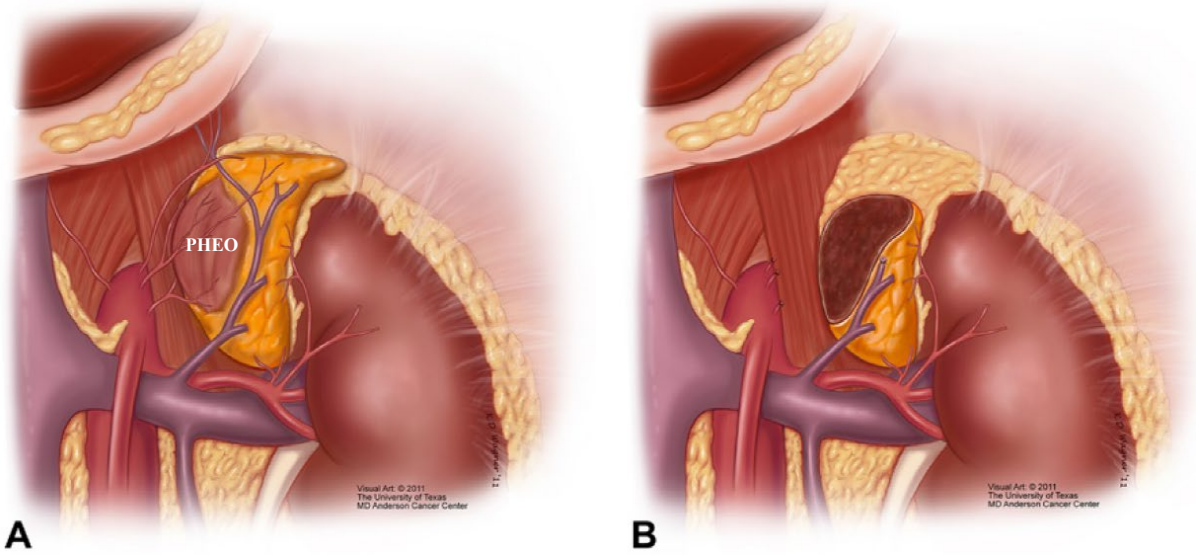




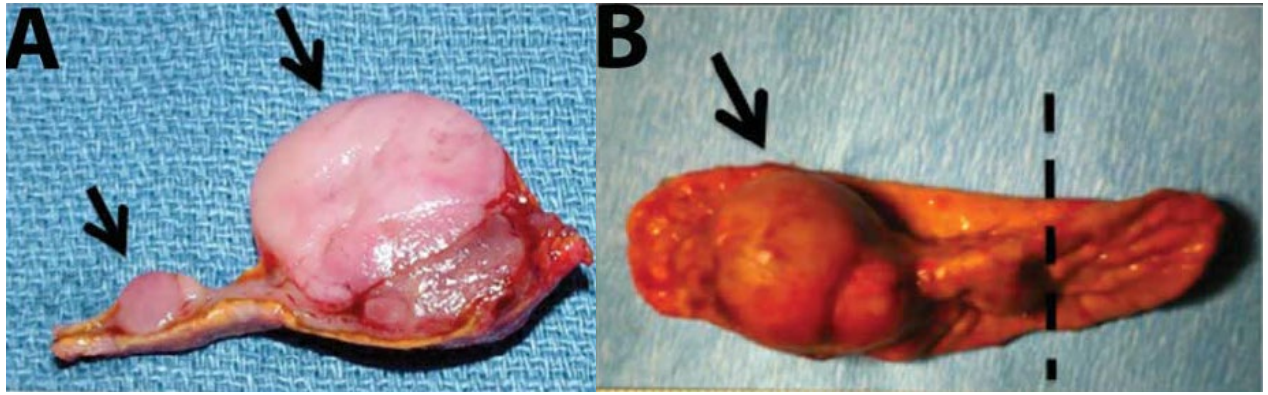
Calendar et al. *Adv Surg* 2009; Perrier et al. *Ann Surg* 2008;Schreinemakers et al. *Br J Surg* 2010; Benhammou et al. *J Urol* 2010

Cortical-Sparing Adrenalectomy

- In MEN1, MEN2, and VHL[1]:
  - 7% recurrence in cortical-spared remnants
  - steroid independence in 78% at 3 years
- In MEN2A[2]:
  - 3% recurrence
  - 57% steroid independence
- In MEN2B[3]:
  - 10% recurrence
  - 62% steroid independence



Grubbs *et al. J Am Coll Surg* 2013

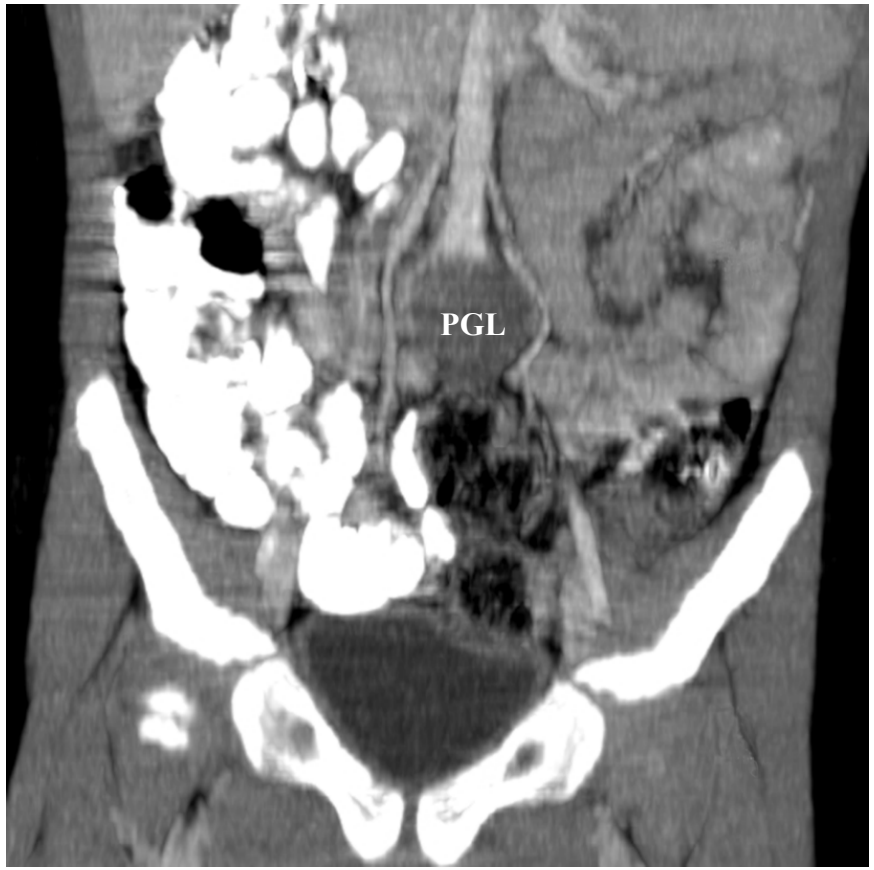


Castinetti *et al. Eur J Endocrinol 2016*

[1]Grubbs *et al. J Am Coll Surg* 2013; [2]Castinetti et al. *Lancet Oncol* 2014; [3]Castinetti et al. *Lancet Diabetes Endocrinology 2019*

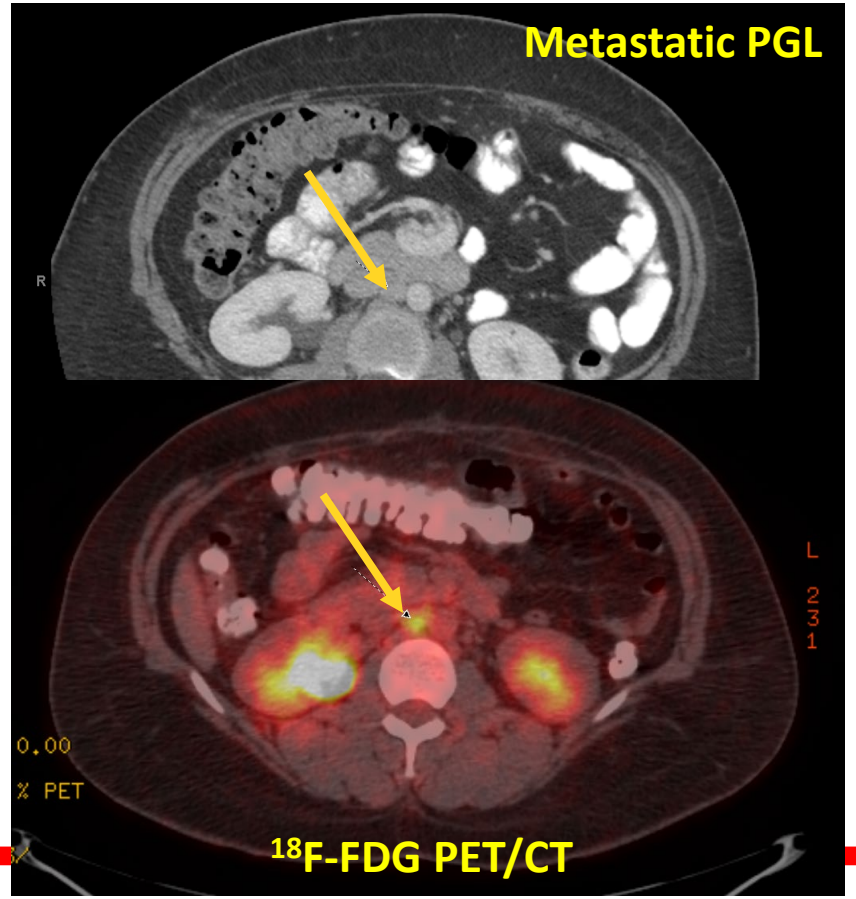
Lifelong Follow Up Required

- **September 1996, age 15**



- **August 2012, age 31**

Refractory HTN during pregnancy



Metastatic PPGL

- No histological, biochemical, molecular, or genetic characteristics that predict malignant potential
- PGL>PHEO
- Sympathetic>Parasympathetic
- PPGL > 5cm; sympathetic PGL regardless of size
- SDHB+

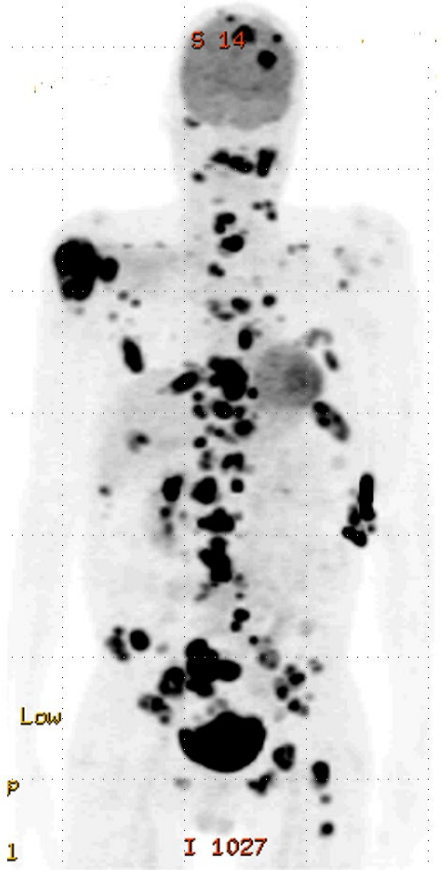
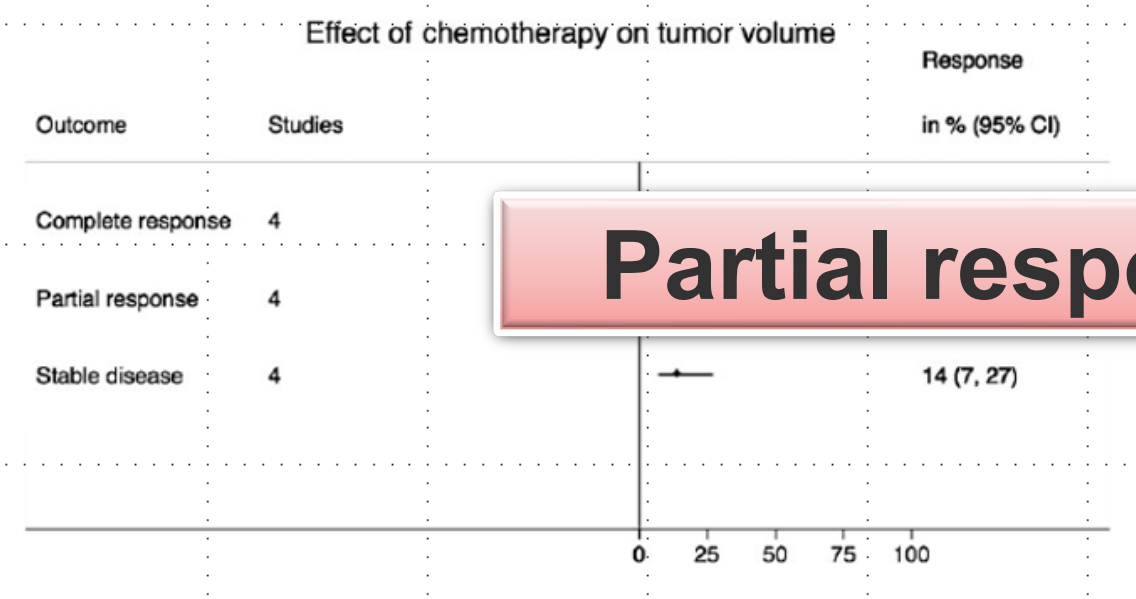


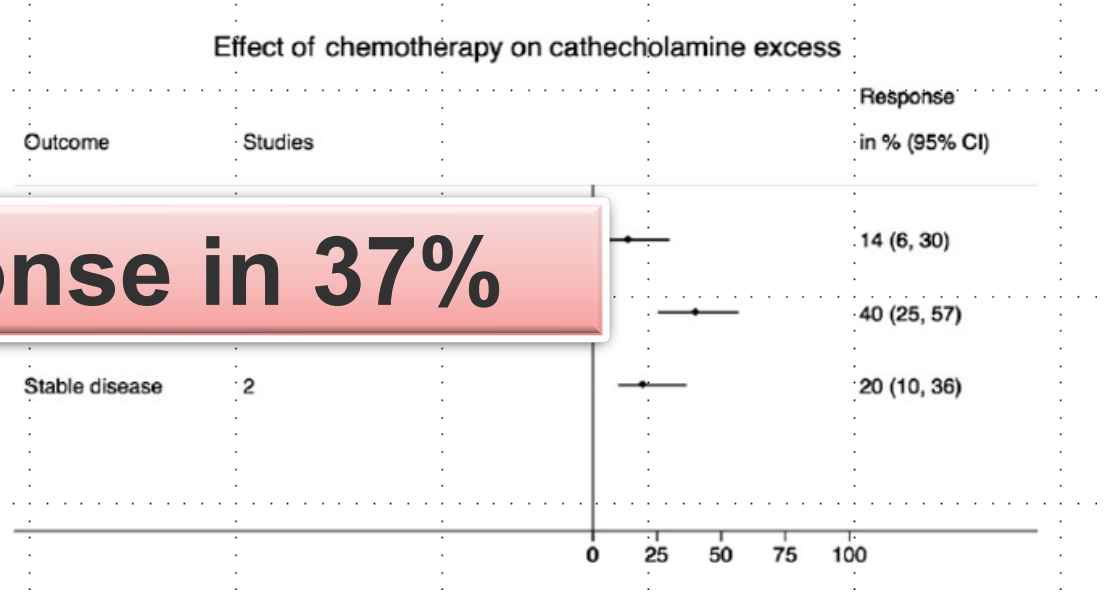
Image courtesy of Dr. C. Jimenez

Dahia *et al.* Endocr Relat Cancer. 2020 Aug;27(8)

Chemotherapy

- **Cyclophosphamide, vincristine, and dacarbazine (CVD)**

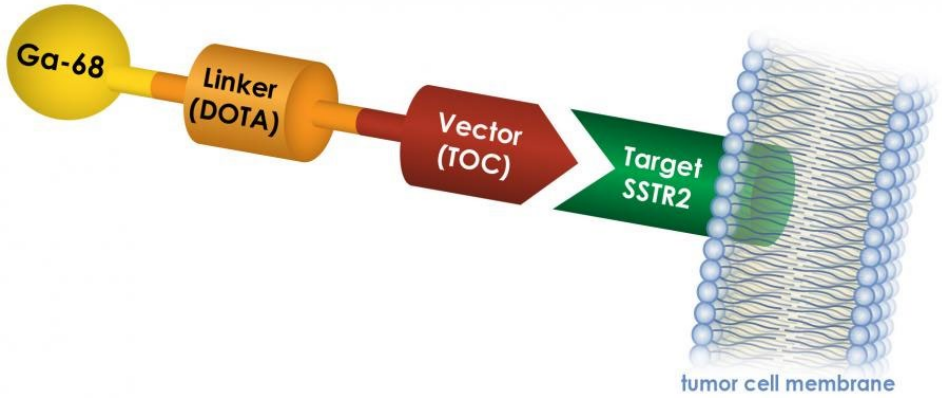


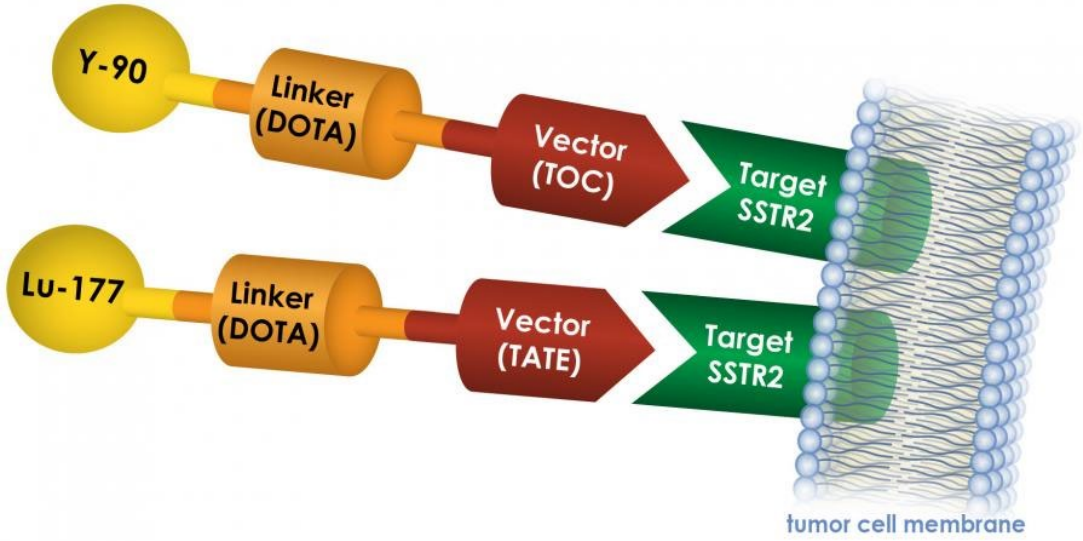


Partial response in 37%

Niemeijer *et al. Clin Endocrinol* 2014 Nov;81(5):642-51.

Theranostics





https://uihc.org/health-topics/what-theranostics

Radiopharmaceutical Options

- **I-131 MIBG (Azedra®)**

INDICATIONS AND USAGE

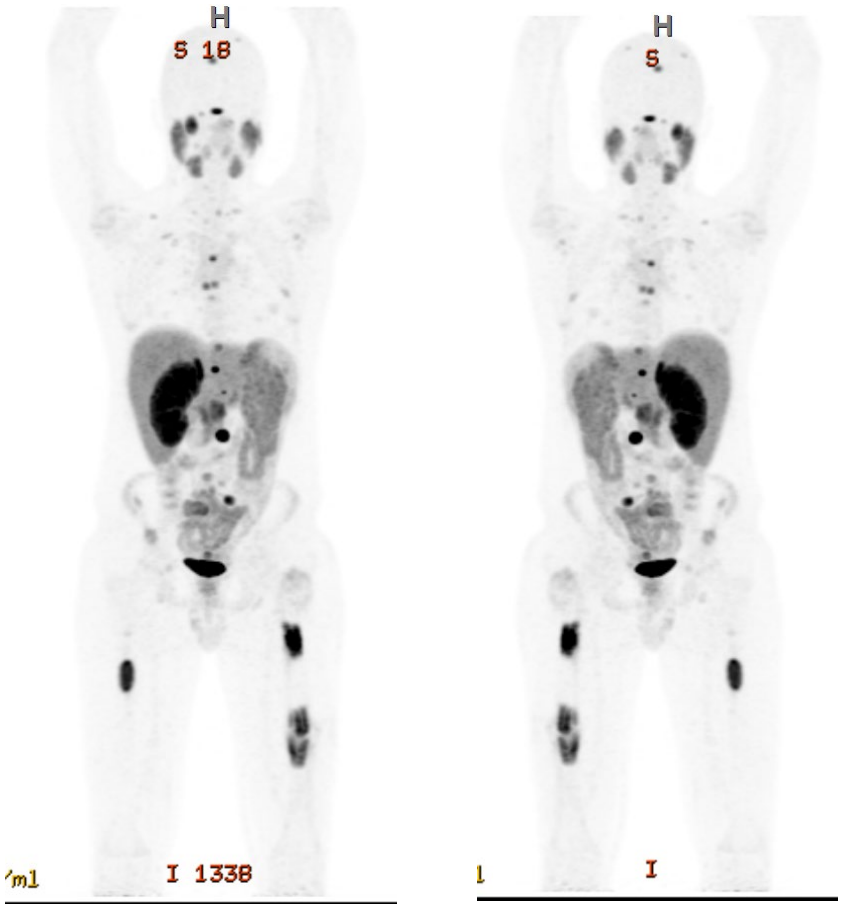
AZEDRA is a radioactive therapeutic agent indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. (1)

- **Lu-177 DOTATATE (Lutathera®)**

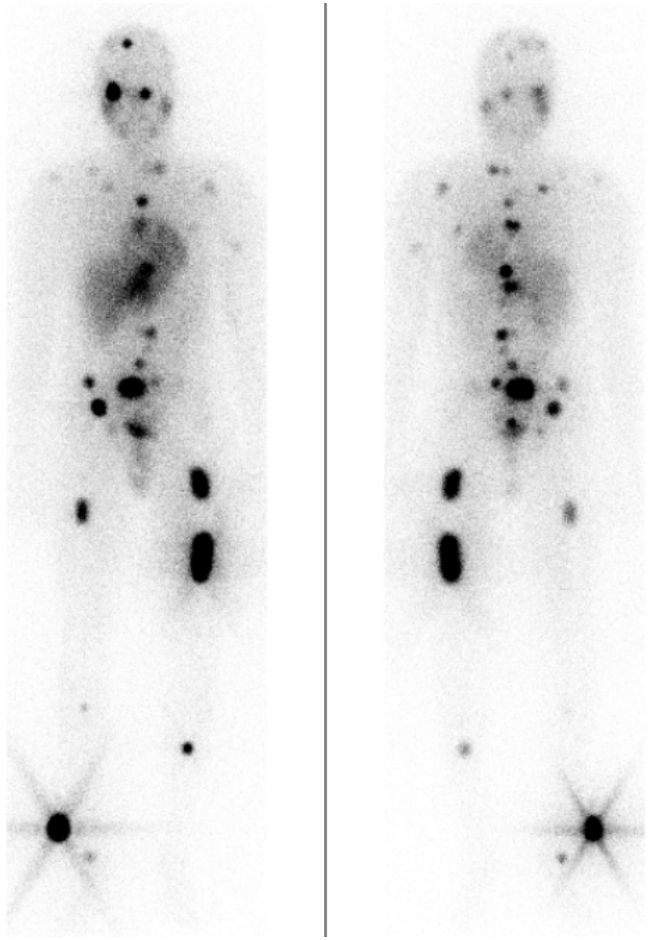
INDICATIONS AND USAGE

LUTATHERA is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. (1)

Ga 68 dotatate scan



Iobenguane I131 scan



High-Specific-Activity ^{131}I-MIBG

AZEDRA was proven to reduce the need for antihypertensive medication

Primary endpoint[1]

Reduction or discontinuation of antihypertensive medication by at least 50% for at least six months

25% of patients treated with AZEDRA achieved the primary endpoint (n=17/68, 95% CI: 16–37%)

AZEDRA was shown to reduce the size of tumors

Secondary endpoint[1]

Overall tumor response, assessed radiographically per RECIST 1.0

22% of patients treated with AZEDRA achieved a partial response (n=15/68, 95% CI: 14–33%)

53% of responders experienced durable tumor responses lasting 6 months or longer

www.Azedra.com

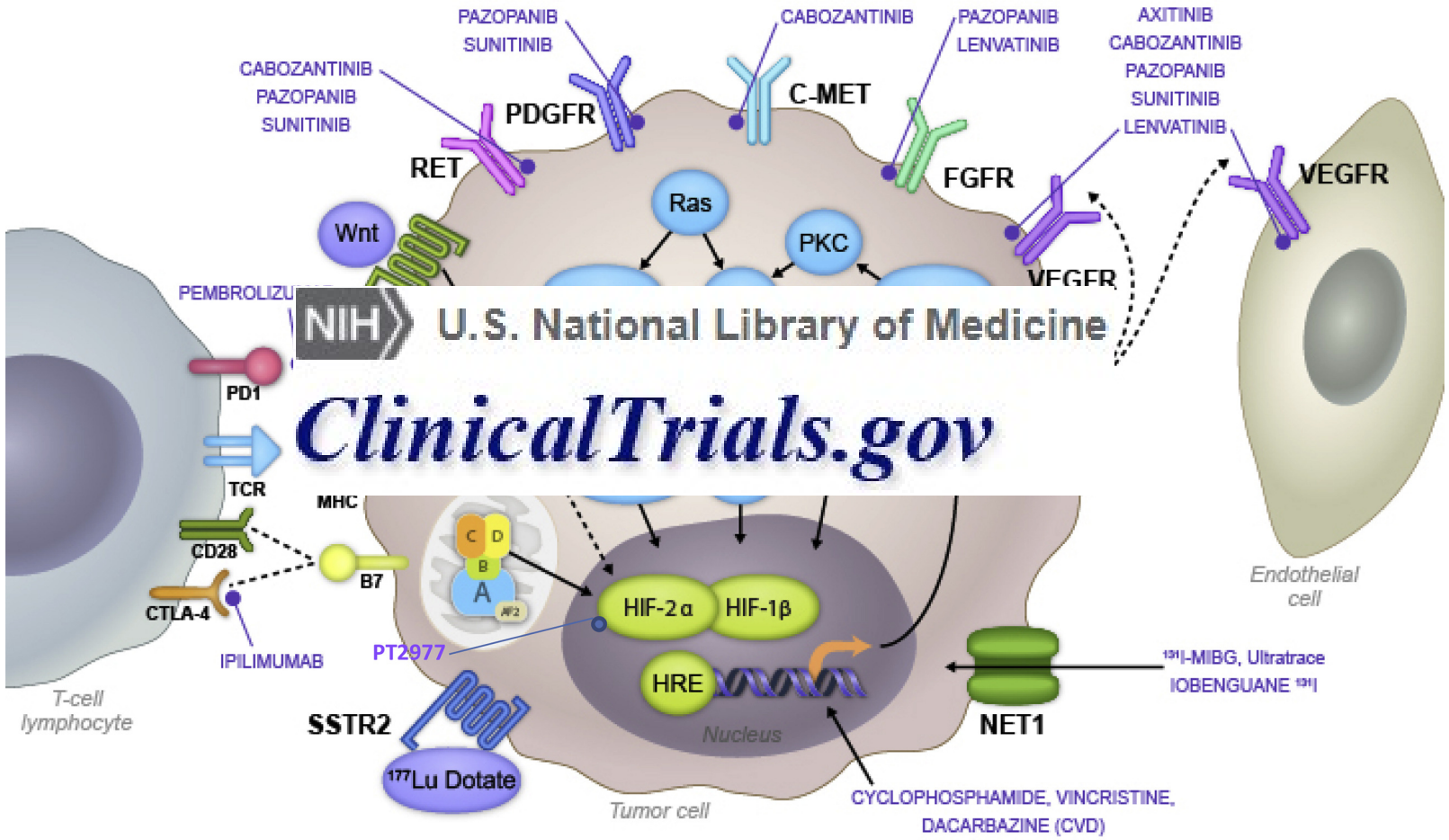
N=68; median age 55 yr (16-76; 1<age 18)

AE by preferred term	Treatment-related AE, all grades	Treatment-related AE, grades 3–5	Any AE, all grades
Nausea	52 (76)	1 (1)	53 (78)
Thrombocytopenia	49 (72)	28 (41)	49 (72)
Anemia	40 (59)	14 (21)	43 (63)
Leukopenia	41 (60)	28 (41)	41 (60)
Fatigue	32 (47)	7 (10)	41 (60)
Neutropenia	39 (57)	26 (38)	39 (57)
Vomiting	33 (49)	1 (1)	36 (53)
Dry mouth	27 (40)	0	28 (41)
Dizziness	16 (24)	1 (1)	27 (40)
Headache	15 (22)	0	21 (31)
Hypotension	8 (12)	1 (1)	18 (26)
Decreased appetite	14 (21)	1 (1)	17 (25)
Diarrhea	11 (16)	2 (3)	16 (24)
Constipation	4 (6)	1 (1)	16 (24)

Data are numbers followed by percentages in parentheses.
Grade 1 = mild AE; grade 2 = moderate AE; grade 3 = severe AE; grade 4 = life-threatening or disabling AE; grade 5 = death related to AE.

Pryma *et al. J Nucl Med.* 2019 May;60(5):623-630

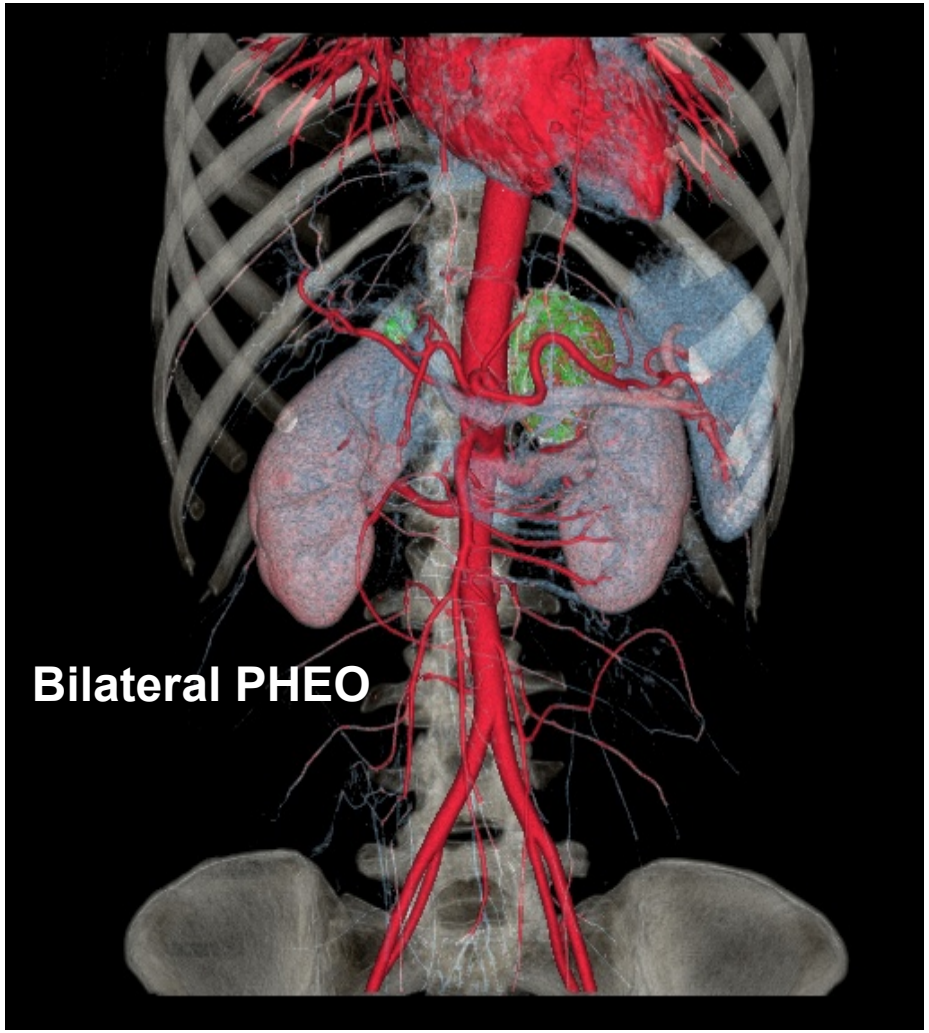
Systemic approaches to metastatic PPGL



Jasim and Jimenez *Best Practice & Research Clinical Endocrinology & Metabolism* 34 (2020)

Summary

- Pediatric PPGL are rare tumors that account for up to 2% of children with hypertension
- PPGL of childhood onset are more likely to be hereditary (cluster 1), noradrenergic, and multifocal/bilateral
- The major genetic syndromes in childhood are VHL and the familial paraganglioma syndromes (*SDHx* mutations)
- Malignancy risk is high (primarily due to *SDHB* mutations) and lifelong FU required for metachronous and metastatic disease
- Prospective screening typically incorporates labs and imaging (MRI); recommendations are primarily based on expert opinion



Thank You!

I am...

PHEO
PARA
PHEAR
LESS

pheopara.org