Les phéochromocytomes

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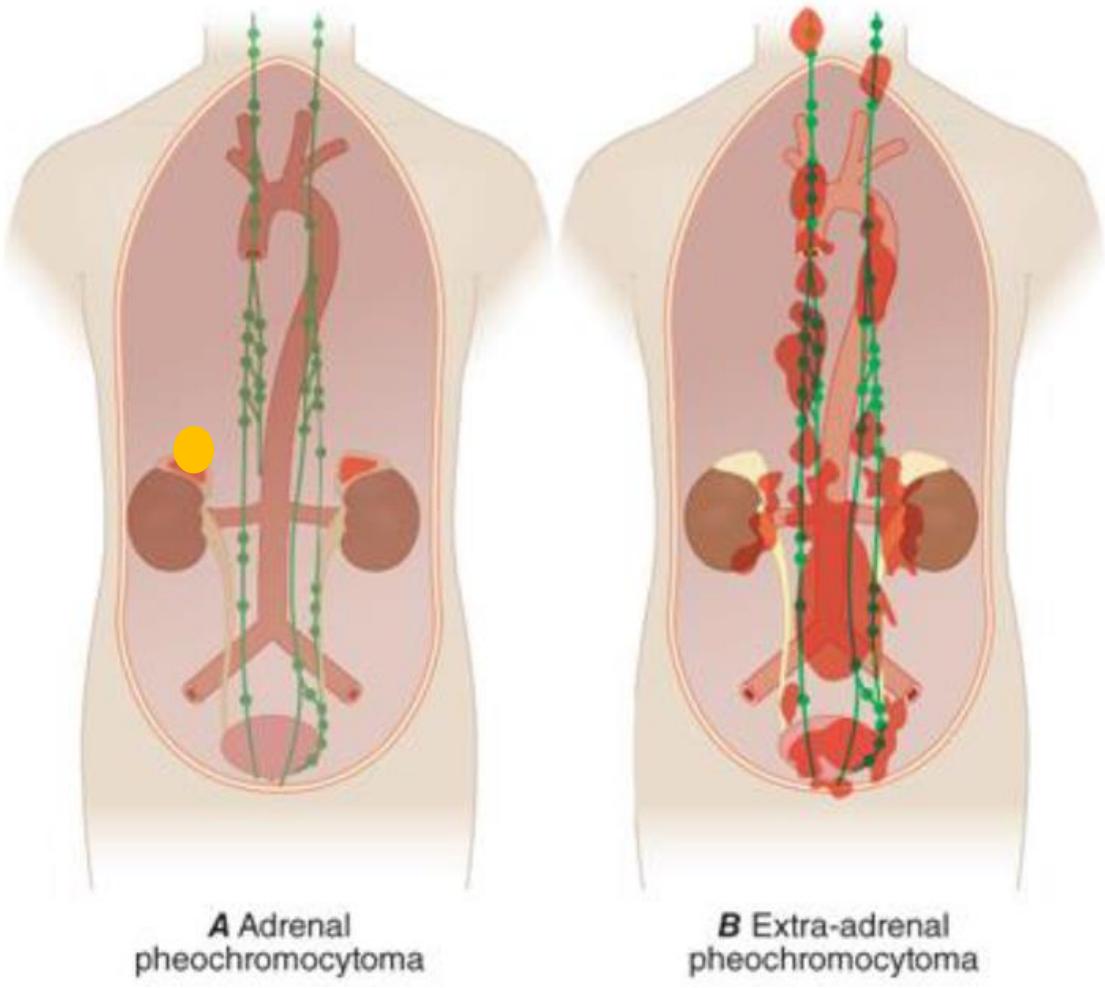
Phéochromocytomes et paragangliomes

Épidémiologie

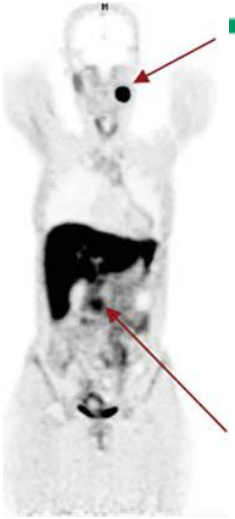
- **Incidence rare: 2-8/million/an**
- **Âge:**
  - **Pic: 30-60 ans moyenne:40 ans**
  - **10%: enfance**
- **Cause héréditaire:**
  - **10% avant 1990**
  - **35-40% actuel**
- **Localisation:**
  - **Surrénale: 85%**
    - **Maligne: 10%**
  - **Extra-surrénale: 15%**
    - **Maligne: 35%**



Paragangliomes

© *de Harrison's Principles in Internal Medicine*

The common embryogenesis of chromaffin cells and sympathetic ganglion cells from primitive cells of the neural crest



Neural crest origin cells

Preaortic paravertebral sympathetic plexus (paraganglia, primarily secrete norepinephrine)

Chromaffin cells → Paraganglioma

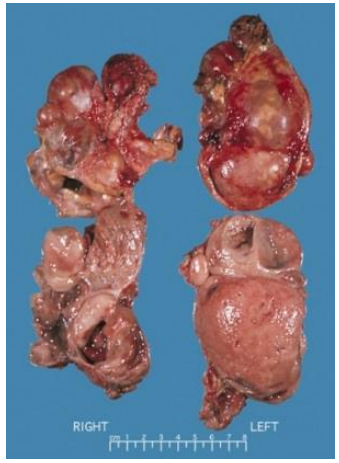
Adrenal medulla

Neuroblasts → Neuroblastoma

Neuroblasts → Sympathetic ganglion cells

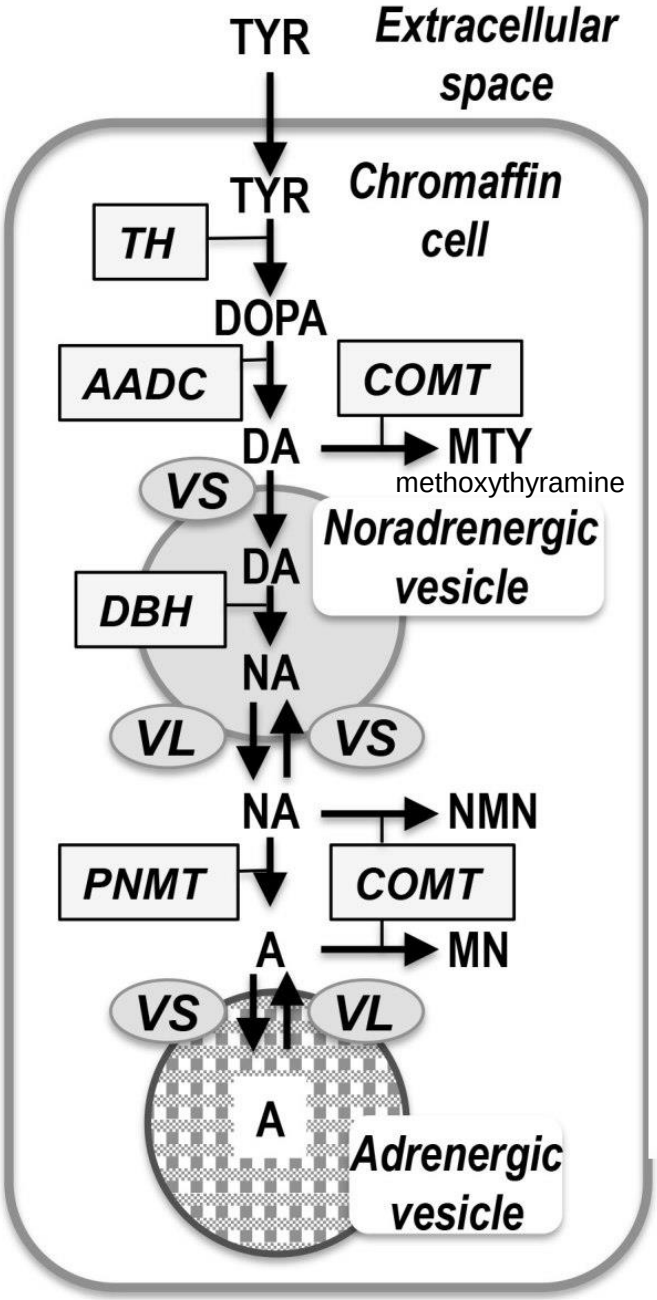
Pheochromoblasts → Pheochromocytoma

Pheochromoblasts → Mature chromaffin cells (primarily secreting epinephrine)



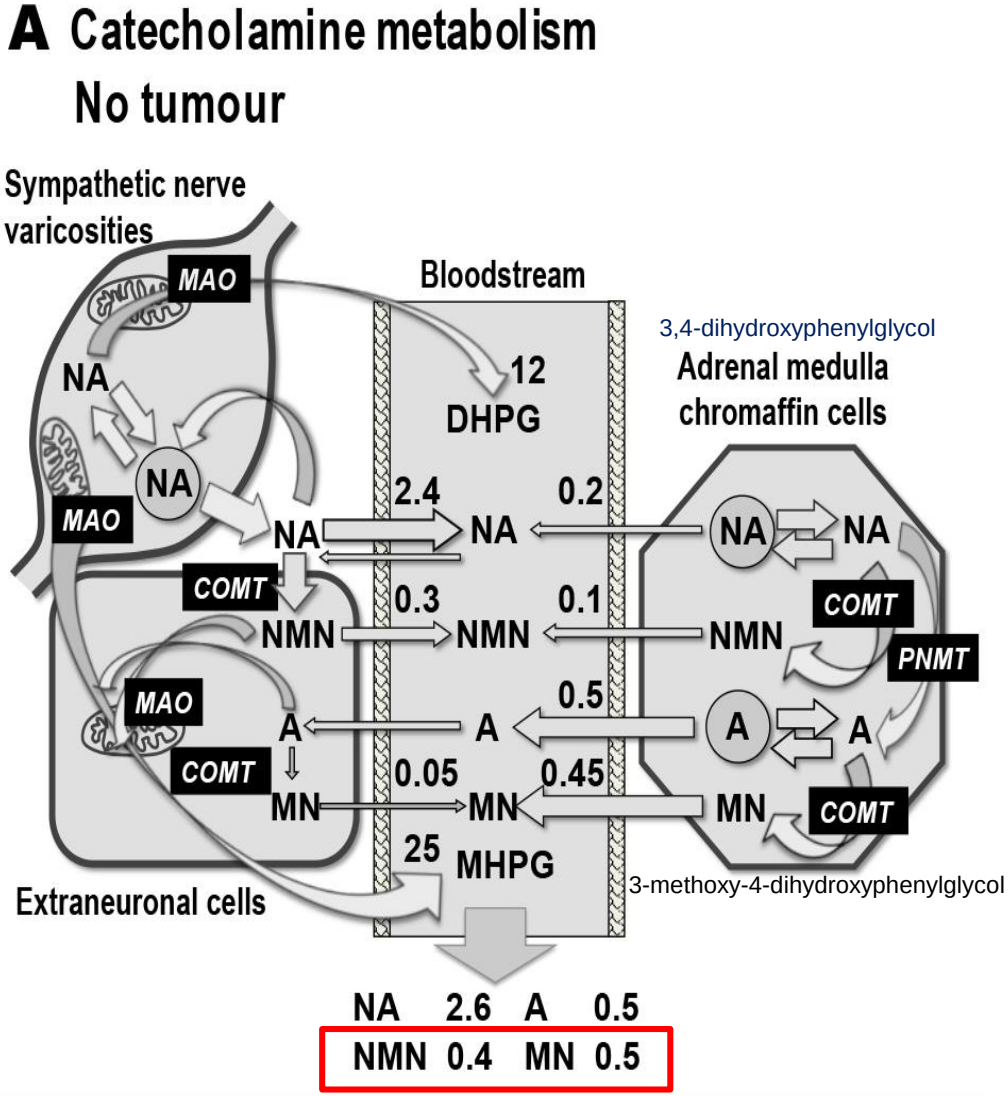
Carty SA, Young WF et al UpToDate 2018

Cathecholamine synthesis and metabolism



Vesicular sequestration

Vesicular leakage



Eisenhofer et al Clin Biochem Rev 38, 69, 2017

TABLE 2
Classic clinical presentation in patients with pheochromocytoma, present in approximately 40% of patients.

Episodic or paroxysmal hypertension
Headache
Diaphoresis
Flushing

Table 2
Frequency of signs and symptoms in patients with PHEO/PGL.

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

Frequency: highest (++++) to lowest (+). Adapted with permission from Pacak.[106]

Martucci VL and Pacak K, Curr Prob Cancer, 38: 7-14, 2014

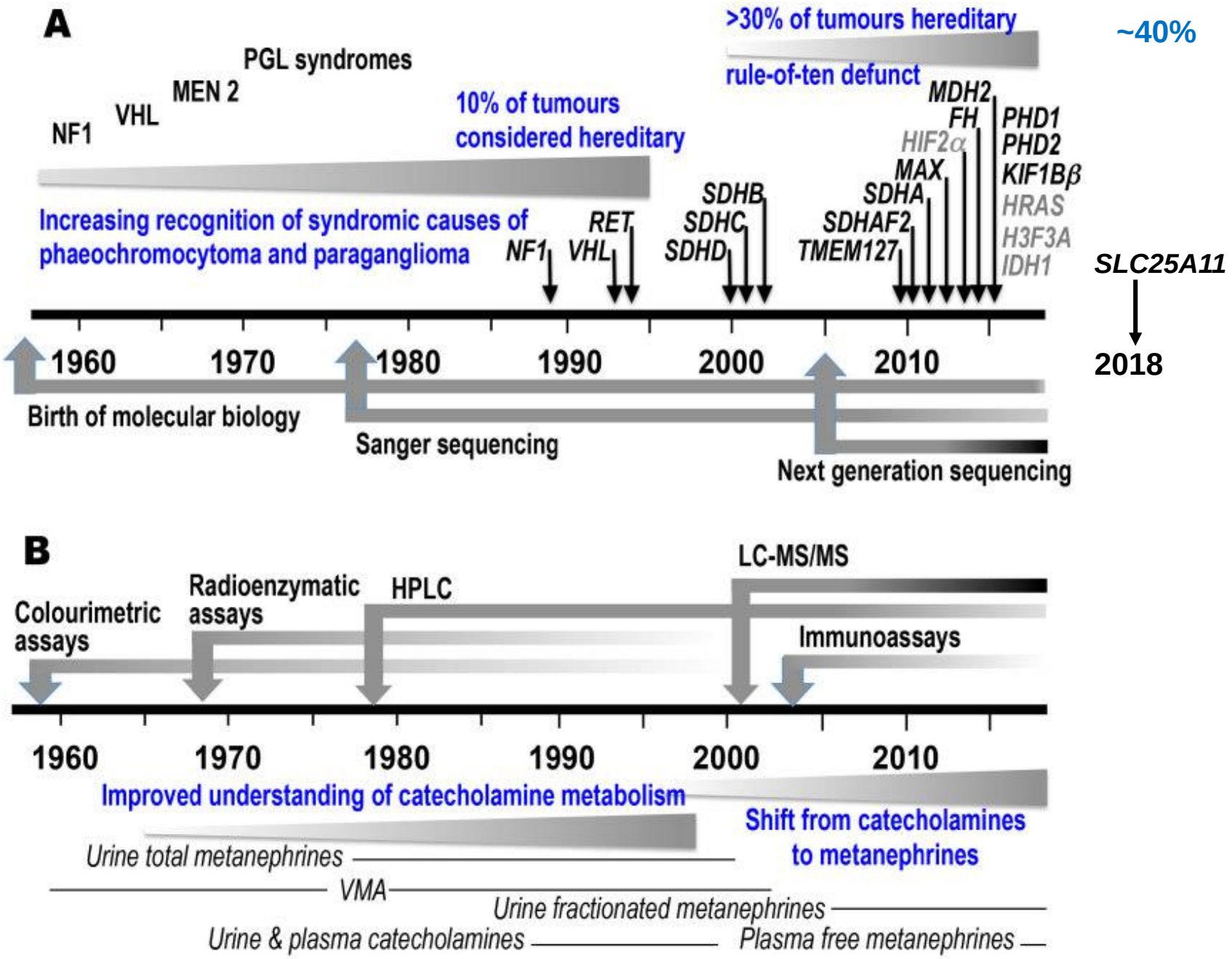
Until 1995 90% of pheos were believed sporadic, 10%: genetic, bilateral, malignant

Table 4. Hereditary syndromes and subtypes of pheochromocytoma

Syndrome	Susceptibility gene	Tumor location
MEN type 2A, 2B	RET	Adrenal (bilateral)
VHL type 2A, 2B, 2C	VHL	Adrenal (bilateral)
Neurofibromatosis type 1	NF1	Adrenal
Familial paraganglioma syndrome type 1, 3, 4	SDHA, SDHB, SDHC	Head and neck, adrenal, extra-adrenal (i.e., gastrointestinal stromal tumor)
Familial pheochromocytoma	Chr 2, 16	Adrenal, extra-adrenal

MEN: Multiple Endocrine Neoplasia
VHL: Von Hilpel- Lindau syndrome

Varshney N et al, Journal of Kidney Cancer and VHL; 4: 20–29, 2017



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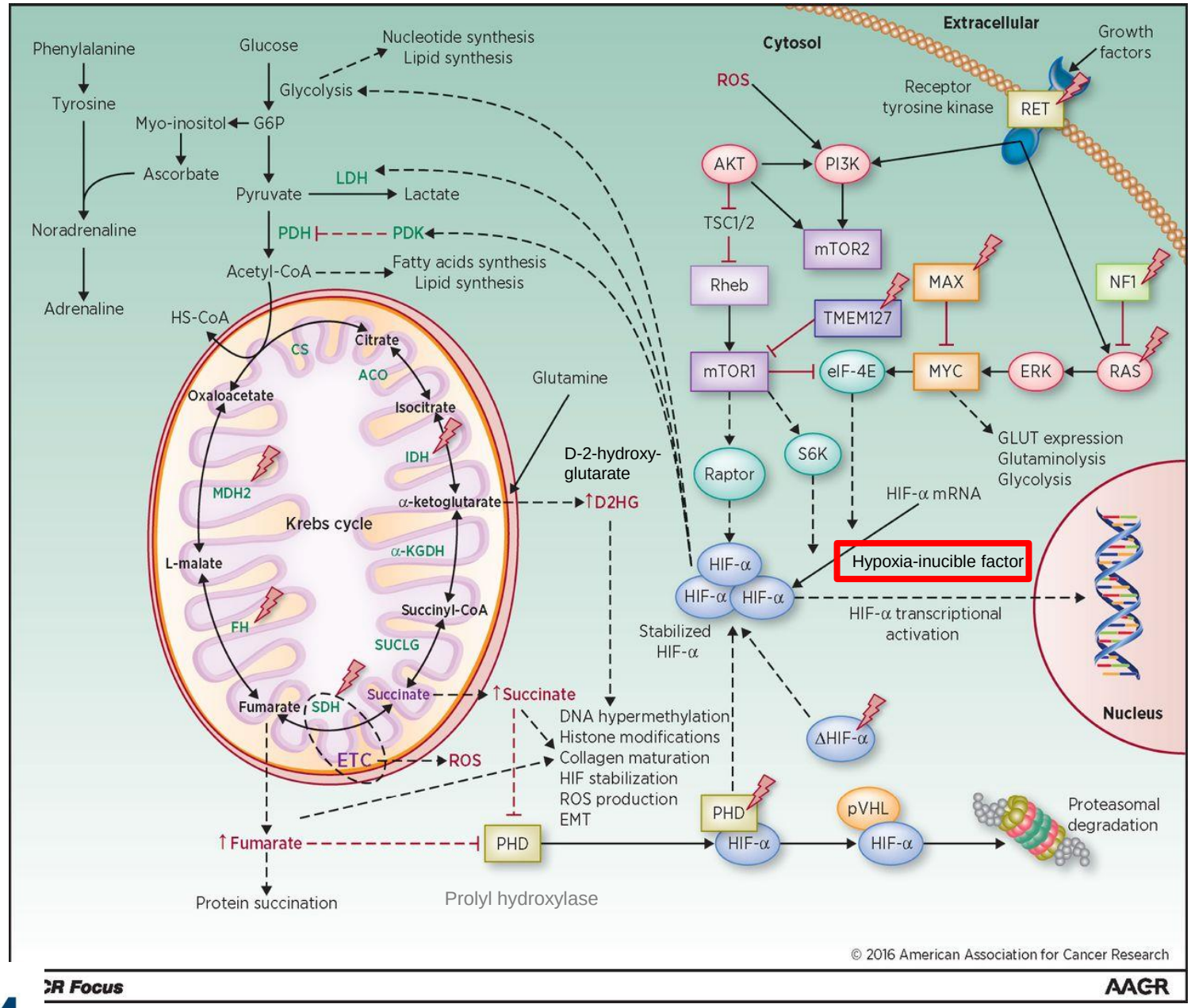
Eisenhofer et al Clin Biochem Rev 38, 69, 2017

Table 1. PPGL Clusters and Driver Genes

Molecular Clusters	Proportion Hereditary	Official Symbol	Official Full Name	Type	Germline/Somatic
Pseudohypoxia TCA cycle–related (10%–15% of PPGLs)	~100%	*SDHA*	Succinate dehydrogenase complex flavoprotein subunit A	TS	Germline
		SDHB	Succinate dehydrogenase complex iron sulfur subunit B	TS	Germline
		SDHC	Succinate dehydrogenase complex subunit C	TS	Germline (genetic/ epigenomic)
		SDHD	Succinate dehydrogenase complex subunit D	TS	Germline
		SDHAF2	Succinate dehydrogenase complex assembly factor 2	TS	Germline
		FH	Fumarate hydratase	TS	Germline
Pseudohypoxia, *VHL/EPAS1*-related (15%–20% of PPGLs)	25%	*VHL*	Von Hippel–Lindau tumor suppressor	TS	Germline/somatic
		EPAS1	Endothelial PAS domain protein 1	OG	Postzygotic/somatic
Wnt signaling (5%–10% of PPGLs)[a]	0%	*CSDE1*	Cold shock domain containing E1	TS	Somatic
		MAML3	Mastermind like transcriptional coactivator 3	OG, fusion	Somatic
Kinase signaling (50%–60% of PPGLs)	20%	*RET*	Ret proto-oncogene	OG	Germline/somatic
		NF1	Neurofibromin 1	TS	Germline/somatic
		MAX	MYC-associated factor X	TS	Germline/somatic
		TMEM127	Transmembrane protein 127	TS	Germline
		HRAS	HRas proto-oncogene, GTPase	OG	Somatic

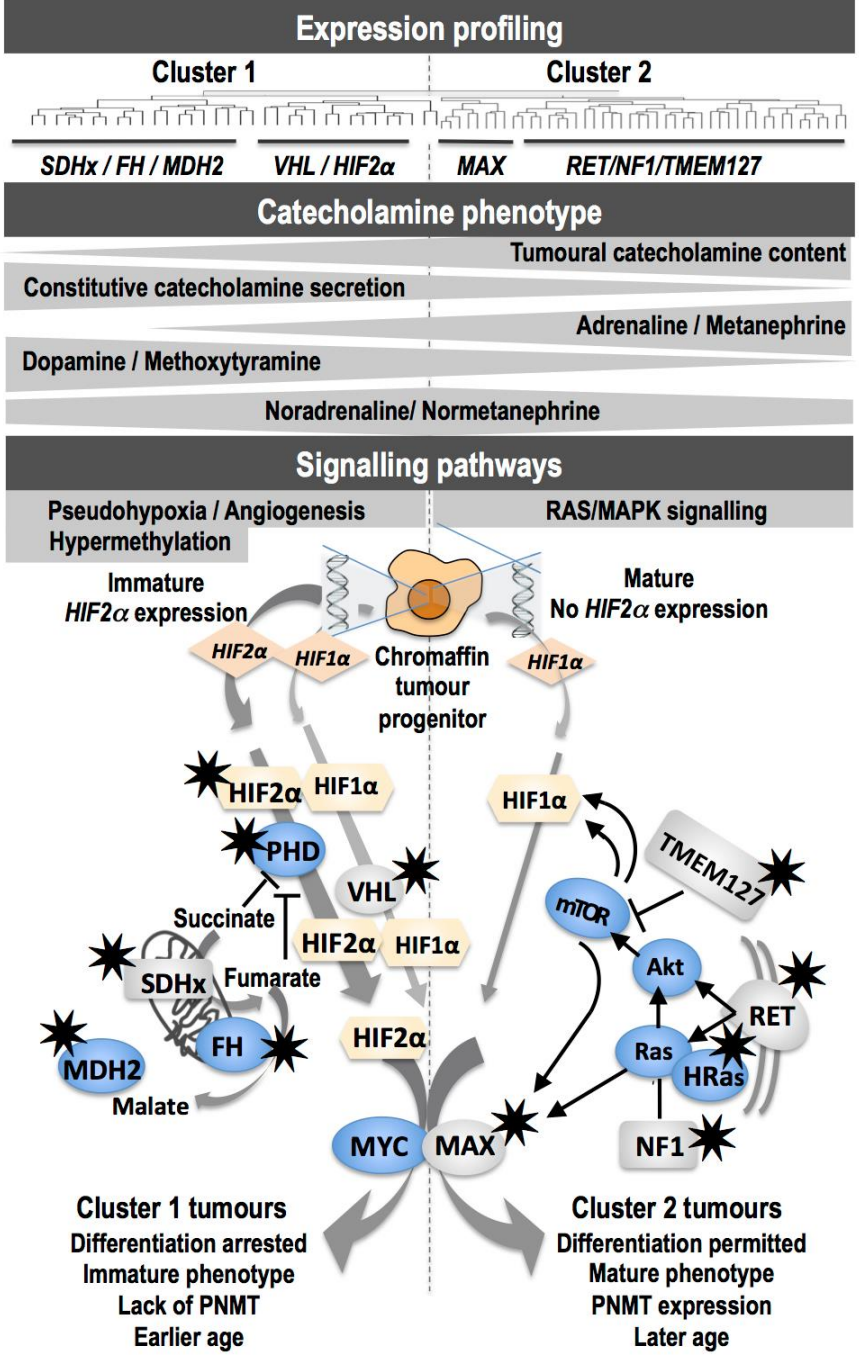
Crona J, Taieb D and Pacak K Endocrine Reviews 38: 489, 2017

Metabolic changes in PHEO/PGL.



Ivana Jochmanova and Karel Pacak Clin Cancer Res;22:5001-5011, 2016

Microarray Transcriptome de PPGL



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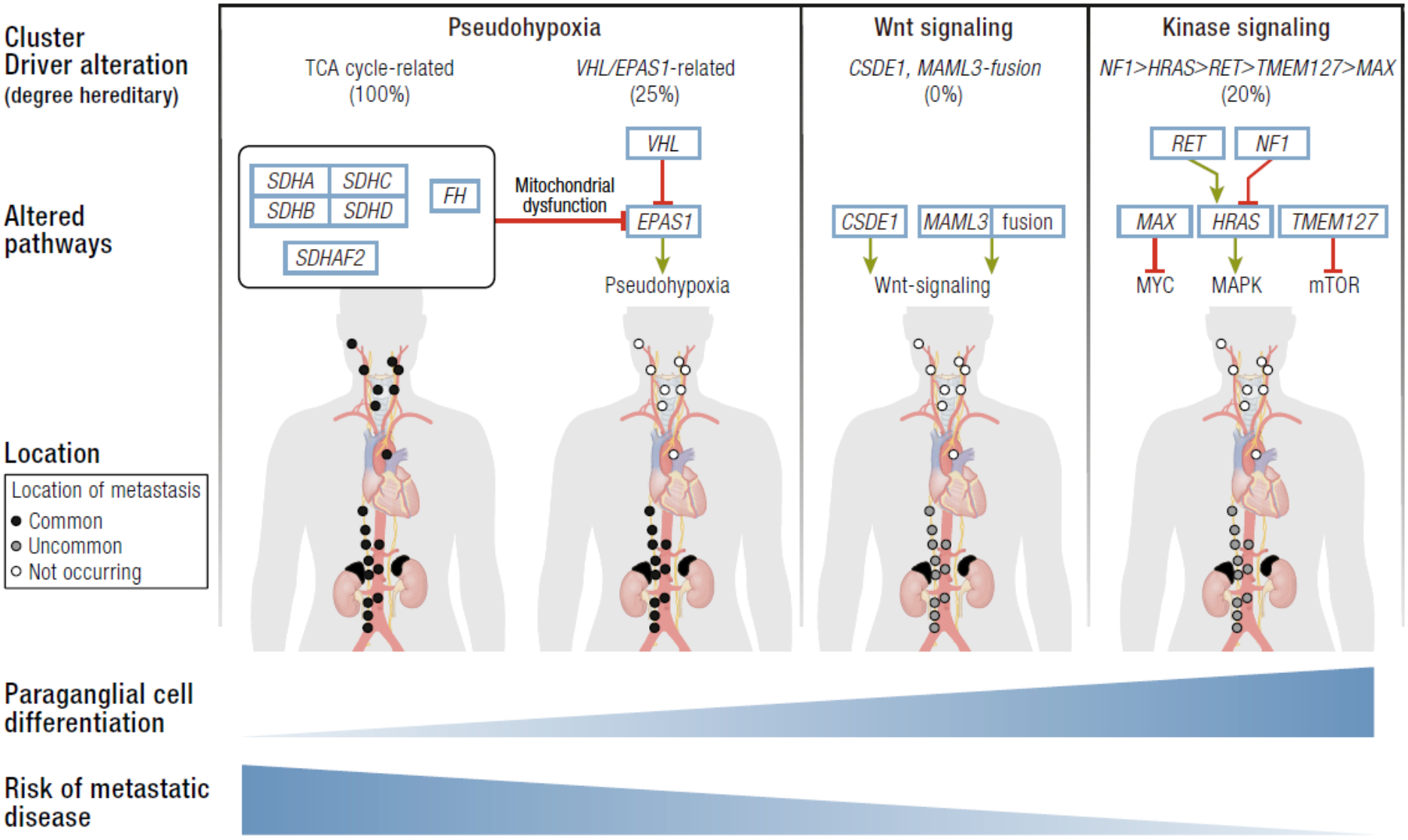
Eisenhofer et al Clin Biochem Rev 38, 69, 2017



Crona J, Taieb D and Pacak K Endocrine Reviews 38: 489, 2017

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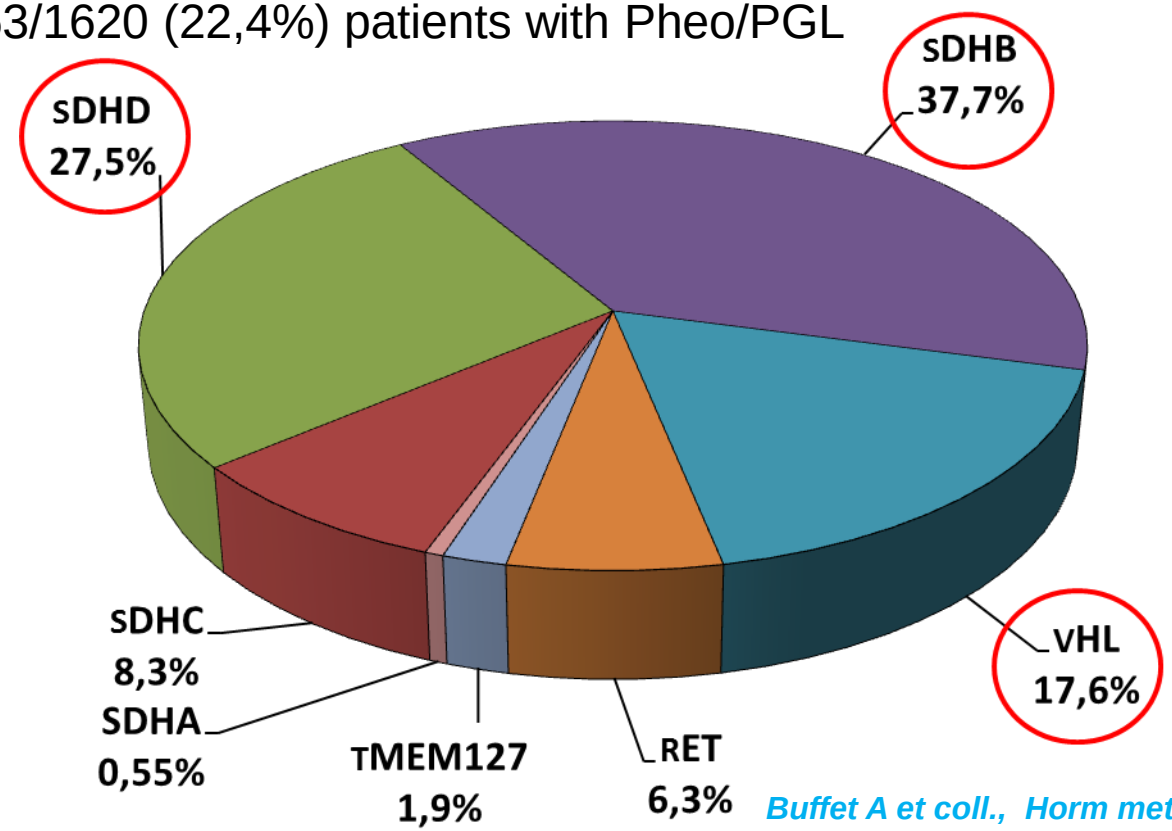
Table 8. Detected Germline Mutations in All PPGL Patients

First Author, Year (Ref.)	No. of Cases	Mutations											
		SDHB	*SDHD*	*SDHC*	*VHL*	*RET*	*NF1*	*SDHA*	*SDHAF2*	*TMEM127*	MAX	n	%
Lefebvre, 2012 (170)	269	21	12	6	ND	ND	ND	ND	0	5	ND	44	16.3
Amar, 2005 (165); Burnichon, 2009 (166)	721	99	131	16	25	16	13	ND	ND	ND	ND	300	41.6
Mannelli, 2009 (162)	501	24	47	4	48	27	11	ND	ND	ND	ND	161	32.1
Cascón, 2009 (163)	237	25	11	1	20	36	ND	ND	ND	ND	ND	93	39.2
Jafri, 2012 (167)	501	121	44	ND	19	ND	ND	ND	ND	ND	ND	184	36.7
Erlic, 2009 (168)	1149	73	28	2	120	80	43	ND	ND	ND	ND	346	30.1
Korpershoek, 2011 (169)	316	16	26	2	19	26	21	5	5	2	ND	122	38.6
Total n	3694	379	299	31	251	185	88	5	5	7		1250	33.8
Mutation rate		10.3	8.9	1.0 (31/3193)	7.3 (251/3425)	6.3 (185/2924)	3.3 (88/2687)						

ND, not determined.

Lenders JWM et al.J Clin Endocrinol Metab 99: 1915–1942, 2014

Mutations in 363/1620 (22,4%) patients with Pheo/PGL



Buffet A et coll., Horm metab Res, 44: 359, 2012

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Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline

Jacques W. M. Lenders, Quan-Yang Duh, Graeme Eisenhofer, Anne-Paule Gimenez-Roqueplo, Stefan K. G. Grebe, Mohammad Hassan Murad, Mitsuhide Naruse, Karel Pacak, and William F. Young, Jr

TABLE 3
When to suspect a pheochromocytoma.

Biochemical evaluation clearly indicated
Resistant hypertension requiring multiple antihypertensive medications
Hyperadrenergic episodes (anxiety or palpitations or flushing diaphoresis)
Incidental adrenal tumor in an asymptomatic patient
Family history of pheochromocytoma or familial predisposing syndrome
Biochemical evaluation should be strongly considered
Paroxysmal or new-onset hypertension
Unexplained anxiety attacks
Idiopathic cardiomyopathy
Hypertension or cardiomyopathy in a young patient (< 25 y)
Severe hypertension or pressor response during anesthesia or sedation (ie, for colonoscopy)

Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline

Table 2. Medications That Are Implicated in Adverse Reactions in Patients with Pheochromocytoma and That Can Precipitate a Crisis

Class of Drugs	Examples
Dopamine D2 receptor antagonists (including some antiemetic agents and antipsychotics)	Metoclopramide, sulpiride, amisulpride, tiapride, chlorpromazine, prochlorperazine, droperidol
β-Adrenergic receptor blockers[a]	Propranolol, sotalol, timolol, nadolol, labetalol
Sympathomimetics	Ephedrine, pseudoephedrine, fenfluramine, methylphenidate, phentermine, dexamfetamine
Opioid analgesics	Morphine, pethidine, tramadol
Norepinephrine reuptake inhibitors (including tricyclic antidepressants)	Amitriptyline, imipramine,
Serotonin reuptake inhibitors (rarely reported)	Paroxetine, fluoxetine
Monoamine oxidase inhibitors	Tranylcypromine, moclobemide, phenelzine
Corticosteroids	Dexamethasone, prednisone, hydrocortisone, betamethasone
Peptides	ACTH, glucagon
Neuromuscular blocking agents	Succinylcholine, tubocurarine, atracurium

[a] Although most case reports on β-adrenergic receptor blockers pertain to nonselective blockers, selective β_1-blockers may also precipitate a crisis because at higher doses they may lose β_1-selectivity.

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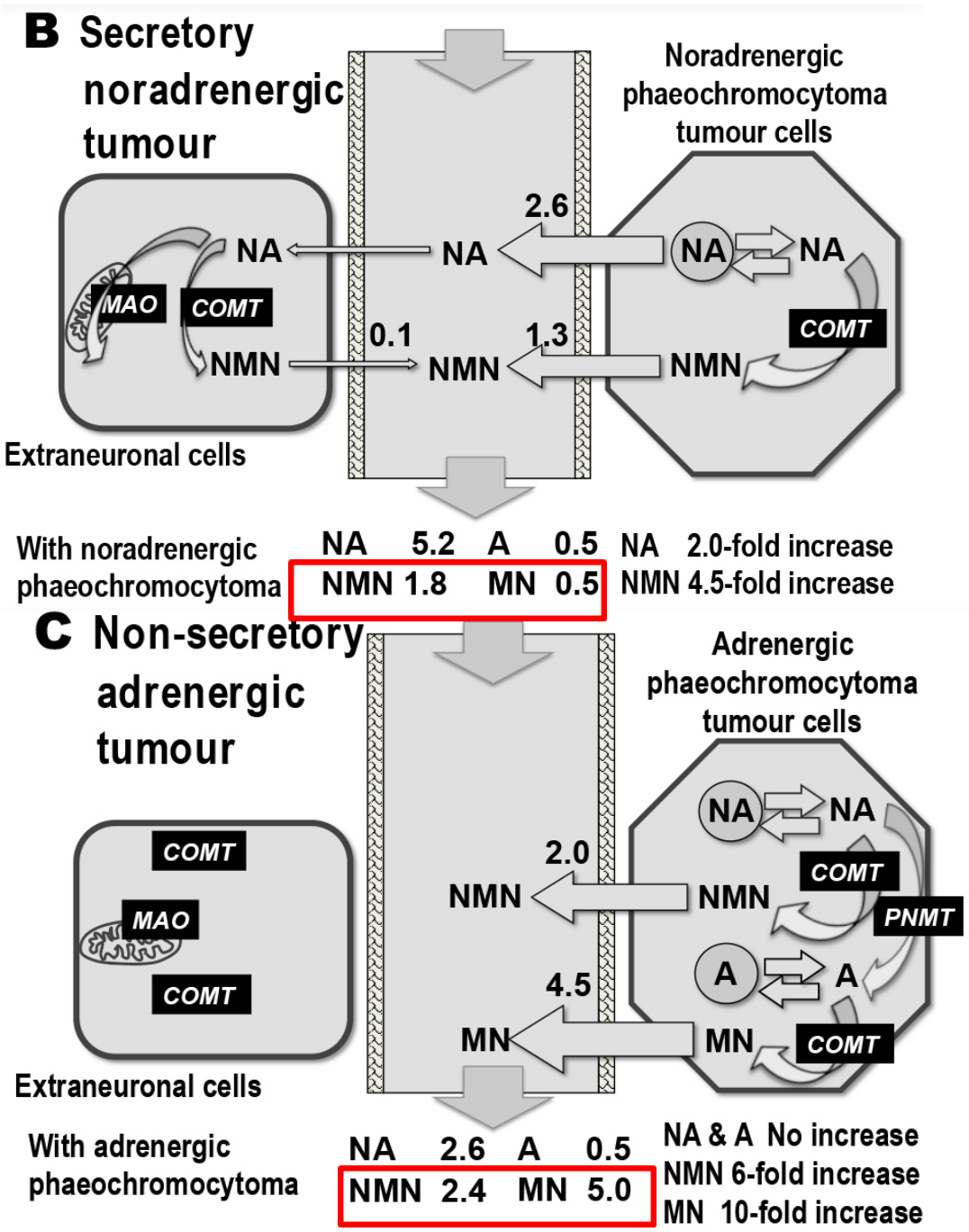
Lenders JWM et al.J Clin Endocrinol Metab 99: 1915–1942, 2014



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Eisenhofer et al Clin Biochem Rev 38, 69, 2017

Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline

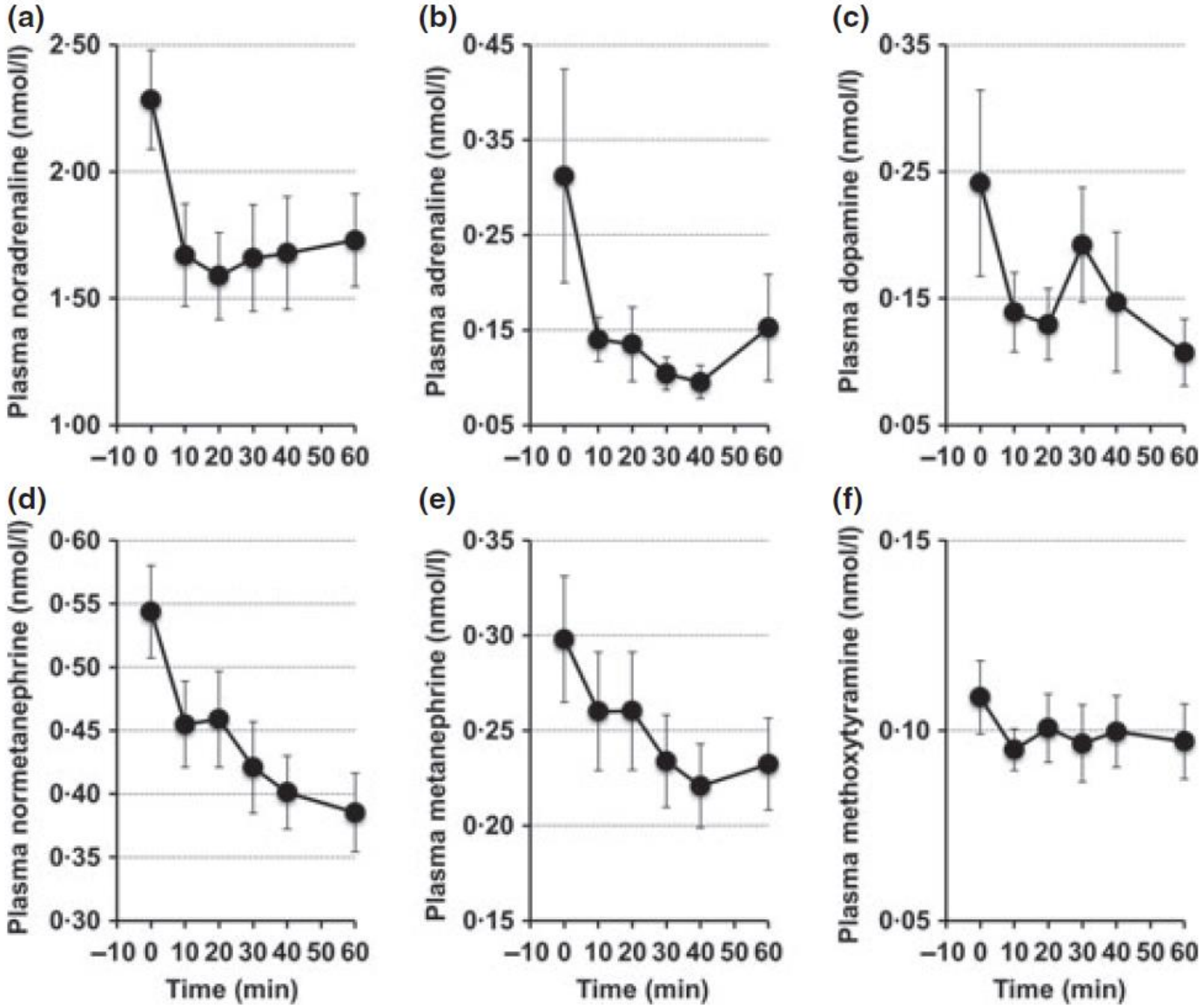
Table 5. Comparison of Diagnostic Performance of Plasma Free Versus Urinary Fractionated Metanephrines from 5 Available Studies

	Sensitivity		Specificity	
First Author, Year (Ref.)	**Plasma**	**Urine**	**Plasma**	**Urine**
Lenders, 2002 (39)	98.6% (211/214)	97.1% (102/105)	89.3% (575/644)	68.6% (310/452)
Unger, 2006 (42)	95.8% (23/24)	93.3% (14/15)	79.4% (54/68)	75.0% (39/52)
Hickman, 2009 (46)[a]	100.0% (14/14)	85.7% (12/14)	97.6% (40/41)	95.1% (39/41)
Grouzmann, 2010 (48)	95.7% (44/46)	95.0% (38/40)	89.5% (102/114)	86.4% (121/140)
Unger, 2012 (53)	89.5% (17/19)	92.9% (13/14)	90.0% (54/60)	77.6% (38/49)

[a] Data restricted to that available from Table 4 of those studies where all measurements were made.

Lenders JWM et al.J Clin Endocrinol Metab 99: 1915–1942, 2014

Plasma catecholamine after transition from seated to supine posture



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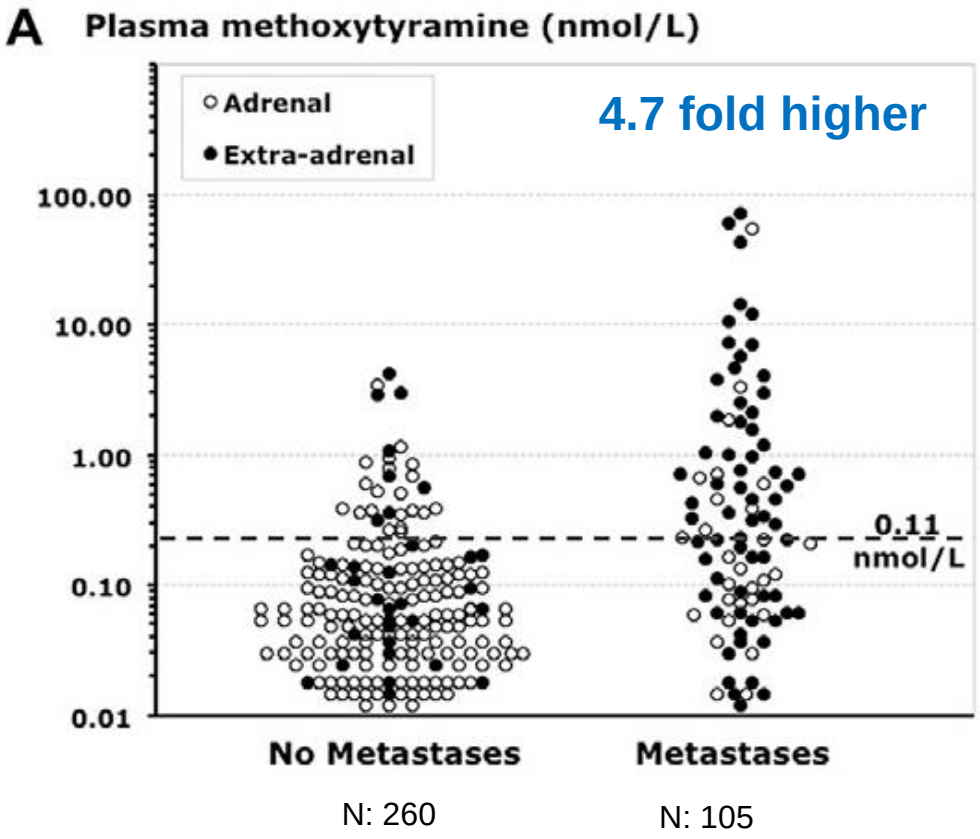
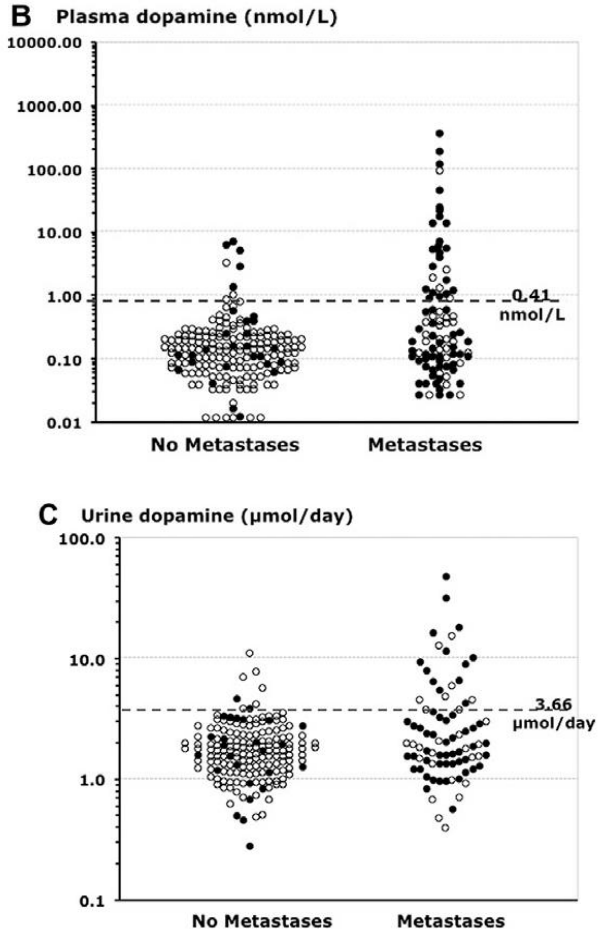
Därr D,...Eisenhofer G. Clin Endocrinoly 80: 478, 2014

Plasma methoxytyramine: A novel biomarker of metastatic pheochromocytoma and paraganglioma in relation to established risk factors of tumour size, location and *SDHB* mutation status ☆

Graeme Eisenhofer [a,b,*], *Jacques W.M. Lenders* [b,c], *Gabriele Siegert* [a], *Stefan R. Bornstein* [b], *Peter Friberg* [d], *Dragana Milosevic* [e], *Massimo Mannelli* [f], *W. Marston Linehan* [g], *Karen Adams* [h], *Henri J. Timmers* [c,h], *Karel Pacak* [h]





Eur J Cancer 48:1739-49, 2012

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Table 2. Age-Related Upper Cut-off Values for Plasma Metanephrines and 3-Methoxytyramine

Age, yr	Normetanephrine, nmol/L	Metanephrine, nmol/L	3-Methoxytyramine, nmol/L
5–17	0.47	0.45	0.10
18–29	0.58	0.45	0.10
30–39	0.70	0.45	0.10
40–49	0.79	0.45	0.10
50–59	0.87	0.45	0.10
>60	1.05	0.45	0.10

Lenders JWM and Eisenhofer G. Endocrinol Metab 32: 152-161, 2017

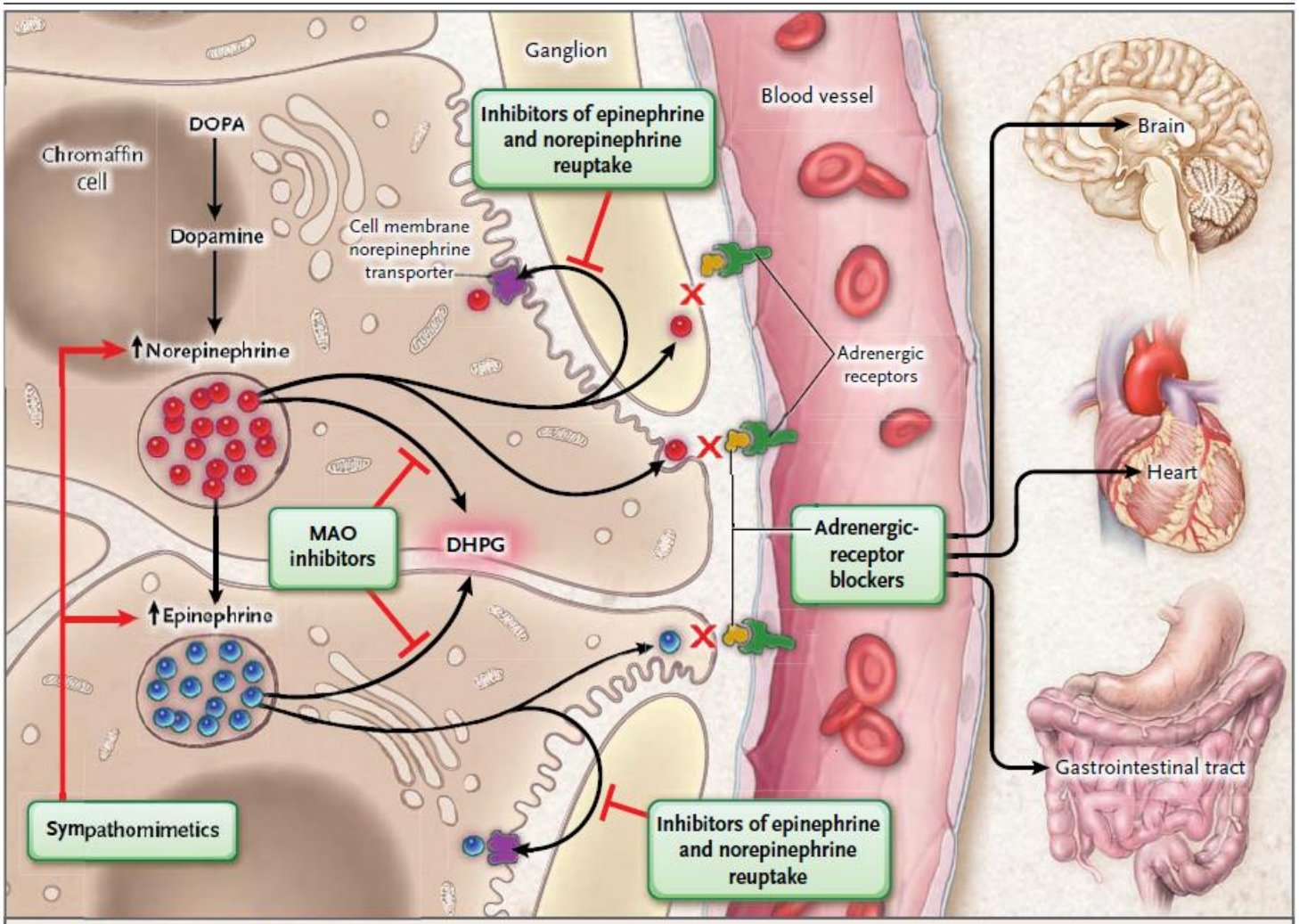

Figure 1. Mechanisms of Pharmacologic Interference with Catecholamines and Metanephrines.

Sympathomimetic agents such as ephedrine, amphetamine, caffeine, and nicotine increase the release of norepinephrine and epinephrine. Monoamine oxidase (MAO) inhibitors block the conversion of norepinephrine and epinephrine to dihydroxyphenylglycol (DHPG), leading to increased concentrations and availability of these two catecholamines. Drugs that inhibit norepinephrine and epinephrine reuptake, such as serotonin–norepinephrine reuptake inhibitors (e.g., venlafaxine), "selective" serotonin-reuptake inhibitors, and tricyclic antidepressants, lead to increased concentrations of norepinephrine and epinephrine in the synaptic clefts. The α-adrenergic-receptor blockers and β-adrenergic-receptor blockers reduce the effects of catecholamines on end organs such as the brain, heart, gastrointestinal tract, and others. DOPA denotes dihydroxyphenylalanine.

Neary NM et al N Engl J Med 2011; 364:2268-2270

Table 7. Major Medications That May Cause Falsely Elevated Test Results for Plasma and Urinary Metanephrines

	Plasma		Urine	
	NMN	MN	NMN	MN
Acetaminophen[a]	++	−	++	−
Labetalol[a]	−	−	++	++
Sotalol[a]	−	−	++	++
α-Methyldopa[a]	++	−	++	−
Tricyclic antidepressants[b]	++	−	++	−
Buspirone[a]	−	++	−	++
Phenoxybenzamine[b]	++	−	++	−
MAO-inhibitors[b]	++	++	++	++
Sympathomimetics[b]	+	+	+	+
Cocaine[b]	++	+	++	+
Sulphasalazine[a]	++	−	++	−
Levodopa[c]	+	+	++	+

Abbreviations: MAO, monoamine oxidase; MN, metanephrine; NMN, normetanephrine; ++, clear increase; +, mild increase; −, no increase.

[a] Analytical interference for some but not all methods employing LC-ECD.

[b] Pharmacodynamic interference leading to increased levels affecting all analytical methods.

[c] Analytical interference with some LC-ECD assays, and also pharmacodynamic interference increase the dopamine metabolite 3-methoxytyramine affecting all analytical methods.

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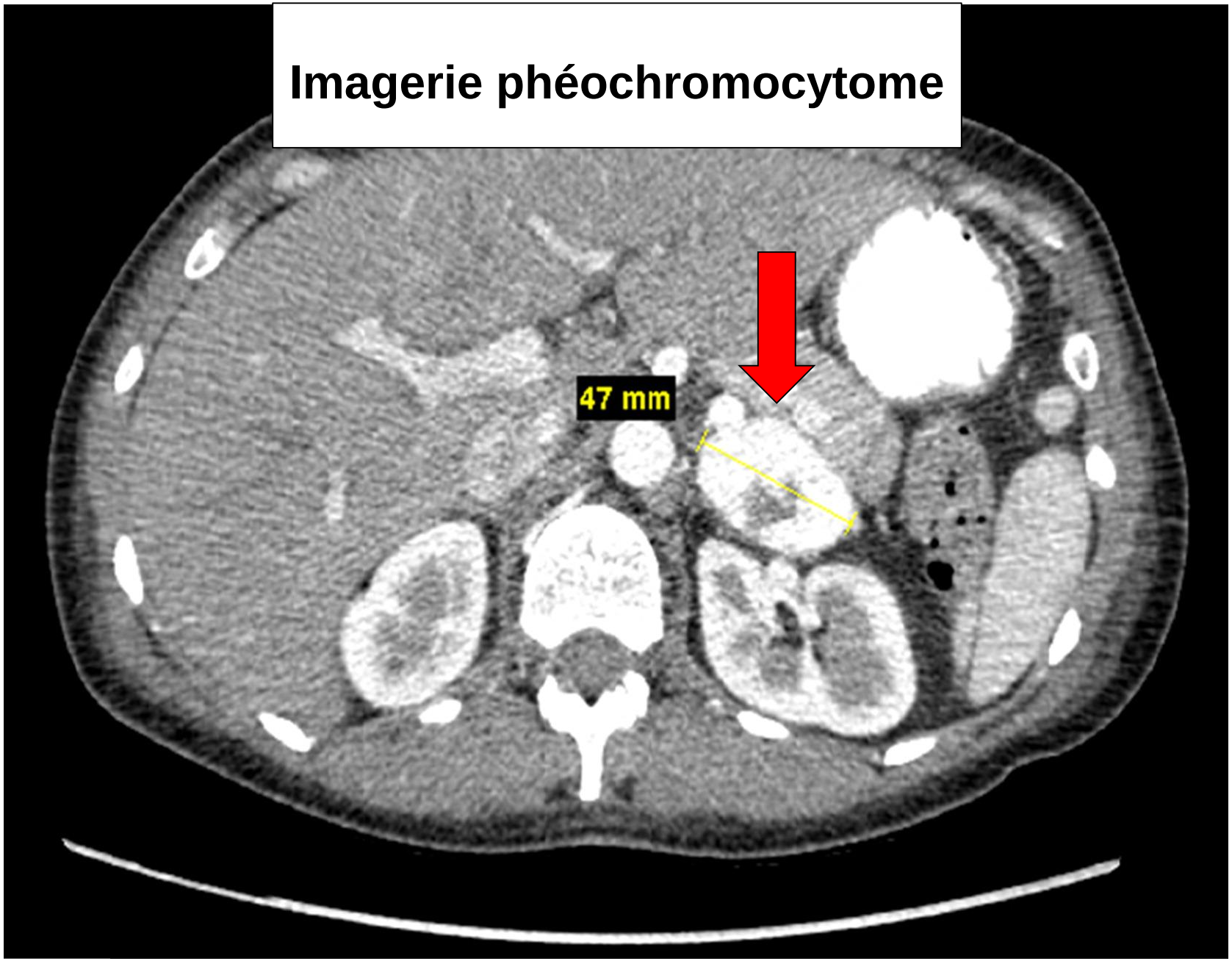
Lenders JWM et al.J Clin Endocrinol Metab 99: 1915–1942, 2014

TABLE 5
Foods to avoid for patients with pheochromocytoma.

Chocolate
Beer and wine
Cured or smoked meats
Aged cheeses (including yogurt and sour cream)
Fermented soy bean or fish products (tofu, soy sauce, fish sauce, and shrimp paste)
Nuts (peanuts, coconuts, and Brazil nuts)
Certain fruits (raspberries, red plums, pineapples, bananas, and figs)
Certain vegetables (avocados, eggplants, fava beans, snow peas, green beans, and sauerkraut)

Hodin R et al. Current Problems in Surgery 51: 151-87, 2014

Imagerie phéochromocytome



Tomographie axiale

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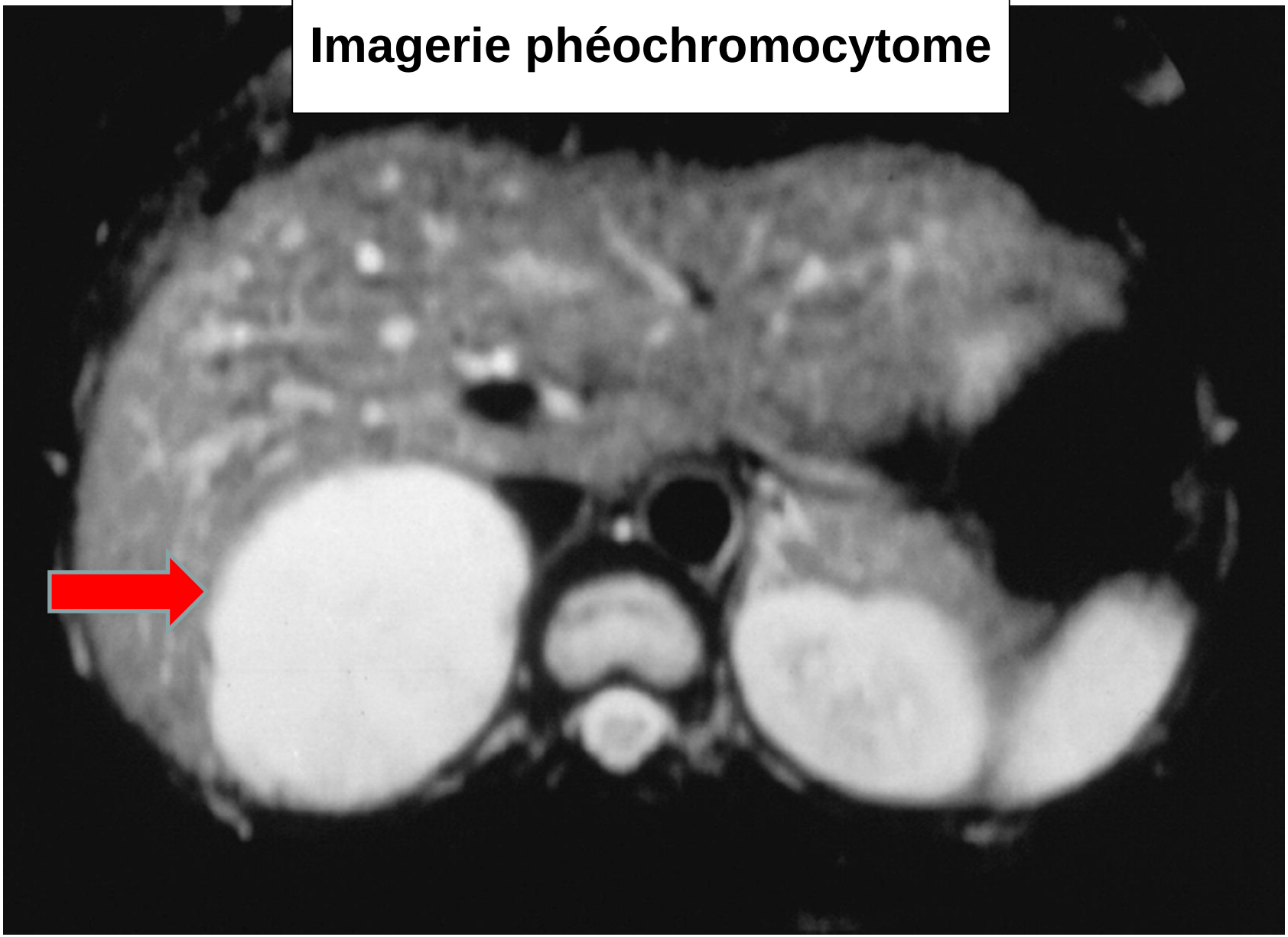
Imagerie phéochromocytome



IRM gadolinium

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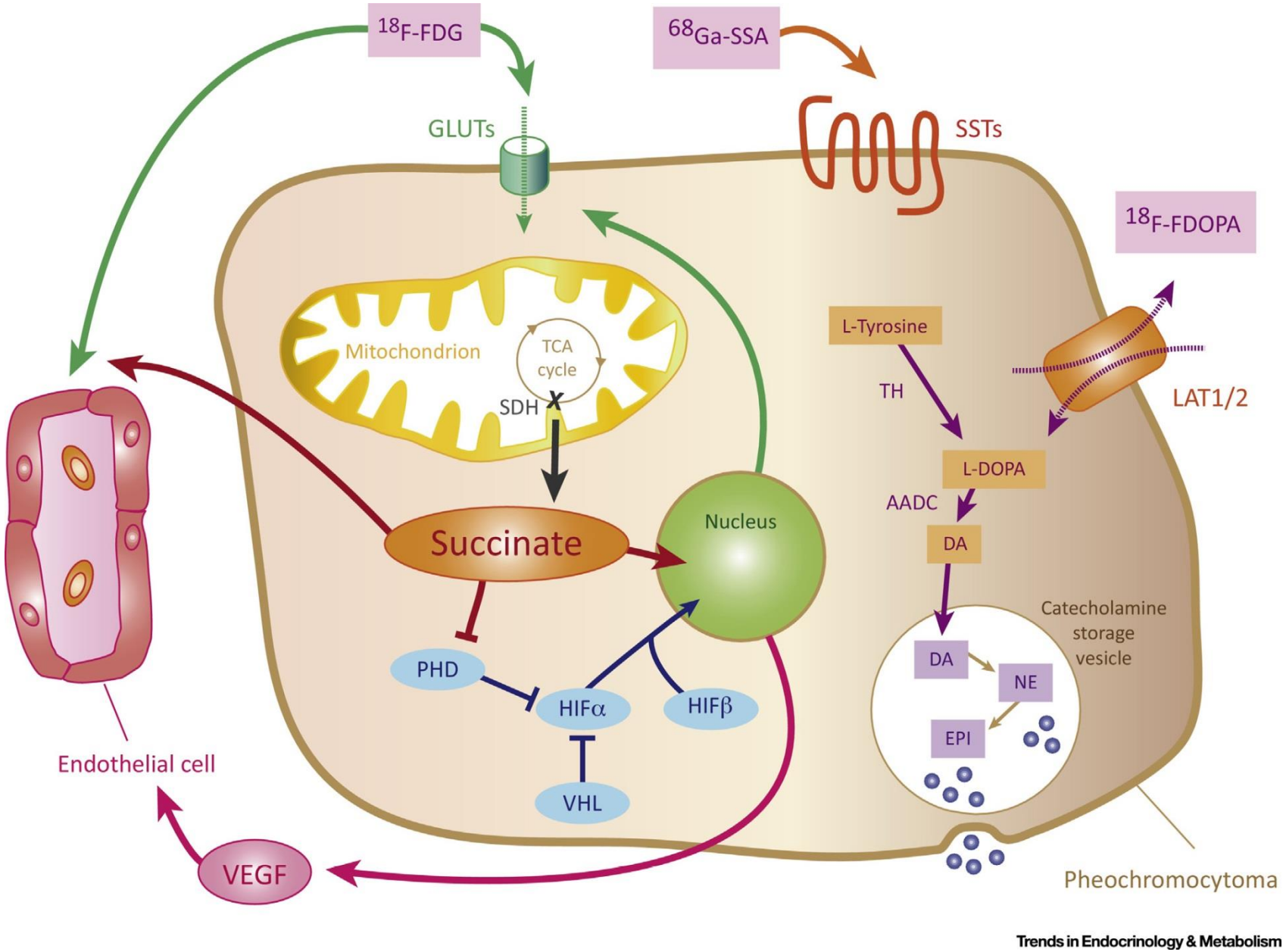
Table 2
Diagnostic imaging modalities: strengths and weaknesses

	Strengths	Weakness
CT with and without IV contrast	• Localizes Pheo/PGL with 88%–100% sensitivity • Easiest for surgeon to interpret • Often the only imaging modality necessary to localize and plan for resection	• Lacks specificity • Lower sensitivity (64%) for extra-adrenal or bilateral tumors • Requires IV contrast
MRI	• Localizes Pheo/PGL with 88%–100% sensitivity • Localizes extra-adrenal and familial adrenal Pheo/PGL with near 100% sensitivity • Avoids radiation exposure of CT	• Difficult to interpret for surgical planning • Less tolerated by some patients (claustrophobia)
123 I-MIBG-SPECT with or without CT	• Can confirm biochemical diagnosis of Pheo/PGL with 95%–100% specificity	• Lower sensitivity than CT/MRI • 50% of normal adrenal glands demonstrate uptake (false positives) • Sensitivity reduced in familial PGL, malignant disease and extra-adrenal Pheo/PGL
Octreotide scan	• High sensitivity for metastatic disease • Can be positive in tumors that have no MIBG uptake	• Variable uptake in tumors • Less sensitive than 123 I-MIBG for primary disease

Kiernan CM and Solorzano C. Surg Oncol Clin N Am 25: 119-38, 2016



Trends in Endocrinology & Metabolism

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Taieb D and Pacak K TEM 28 :807-817, 2017

18 F-FDG PET/CT	• Superior to 123 I-MIBG, 18 F-FDA in visualization of malignant Pheo/PGL and metastasis; especially in patients with *SDHB* mutations	• Cannot be differentiated between benign and malignant lesions • Expensive
18 F-FDA PET/CT	• Good imaging agent for Pheo/PGL • Superior to 123 or 131 I-MIBG in detection of Pheo/PGL especially for malignant tumors (testing only in VHL)	• Difficult to produce and limited availability • Normal adrenal uptake (false positives) • Expensive
18 F-FDOPA PET/CT	• Superior to 123 I-MIBG in detection of Pheo/PGL • Does not concentrate within normal adrenal tissue	• Low sensitivity for metastatic Pheo/PGL • Limited availability • Expensive
68 Ga-DOTATATE PET/CT	• High sensitivity in patients with high risk of PGL and metastatic disease • Superior to 123-MIBG in detecting lesions in all locations, particularly bone	• Available only in clinical trials • Expensive

Abbreviations: 68-Ga-DOTATATE, 68-gallium 1,4,7,10-teraazacyclododecane-1,4,5,10-teraacetic acid-octreotate; CT, computed tomography; FDA, fluorodopamine; FDG, fluorodeoxyglucose; FDOPA, fluorodihydroxy-phenylalanine; IV, intravenous; MIBG, I-metaiodobenzylguanidine; PGL, paraganglioma; Pheo, pheochromocytoma; SPECT, single-photon emission CT.

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Kiernan CM and Solorzano C. Surg Oncol Clin N Am 25: 119-38, 2016

SDHB mutated patient

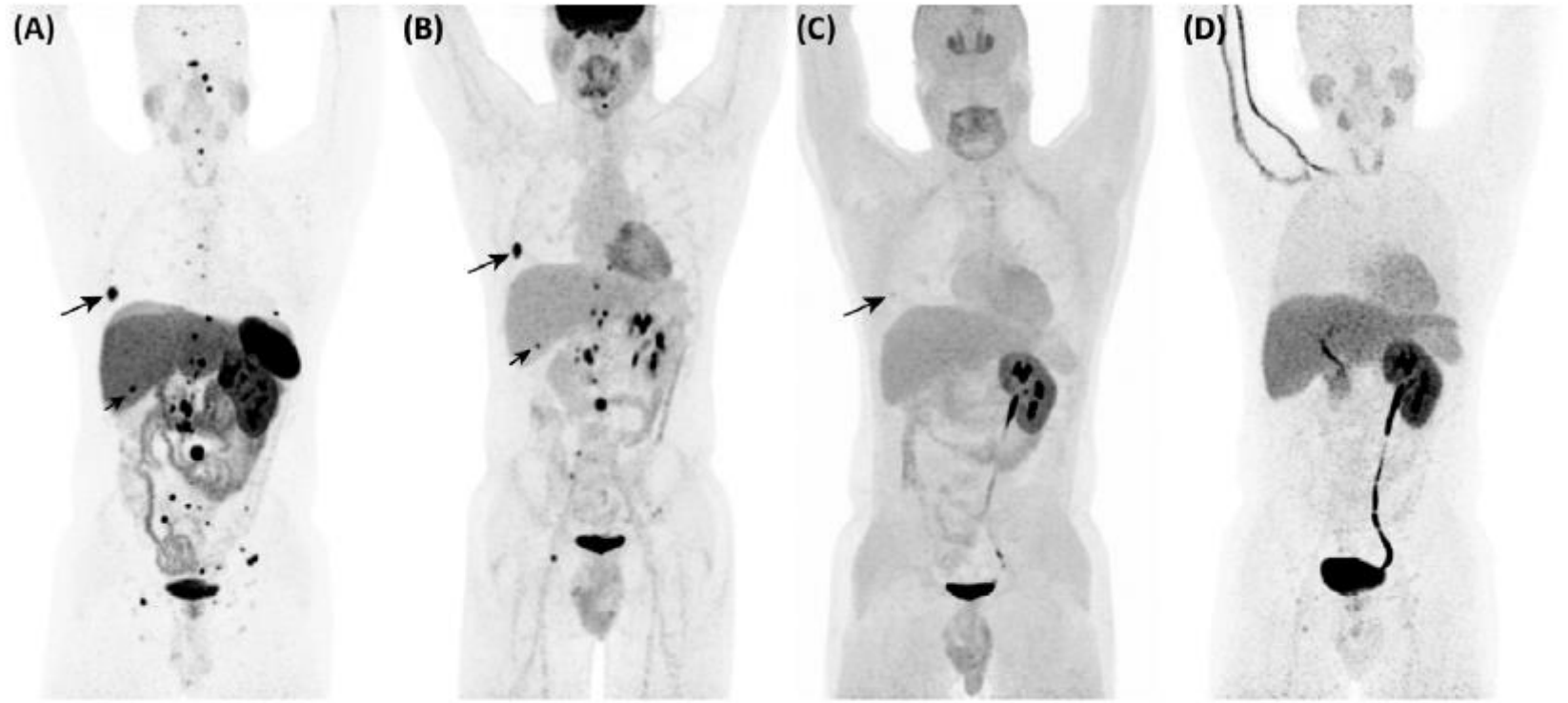

Figure 2. PET-Based Imaging Phenotyping in a Patient with Metastatic Pheochromocytoma. A 23-year-old *SDHB* patient who was first diagnosed with right adrenal pheochromocytoma at the age of 10 years presents to us with metastases (hotspots) in the lung (long arrow), liver (short arrow), retroperitoneum, and skeleton. PET images using four different radiopharmaceuticals are presented: ^{68}Ga-DOTATATE (A), ^{18}F-FDG (B), ^{18}F-FDOPA (C), and ^{18}F-FDA (D). ^{68}Ga-DOTATATE identifies more metastatic lesions than ^{18}F-FDG (B), whereas ^{18}F-FDOPA (C) shows a doubtful uptake focus in the right lower lung nodule, marked by a long arrow, while ^{18}F-FDA (D) is essentially negative. This imaging feature is typical of *SDHB*-related metastatic pheochromocytoma. Abbreviations: DOTATATE, Tyr3-octreotate; FDG, 2-fluoro-2-deoxy-D-glucose; FDOPA, fluorodopa; PET, positron emission tomography.

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Taieb D and Pacak K TEM 28 :807-817, 2017

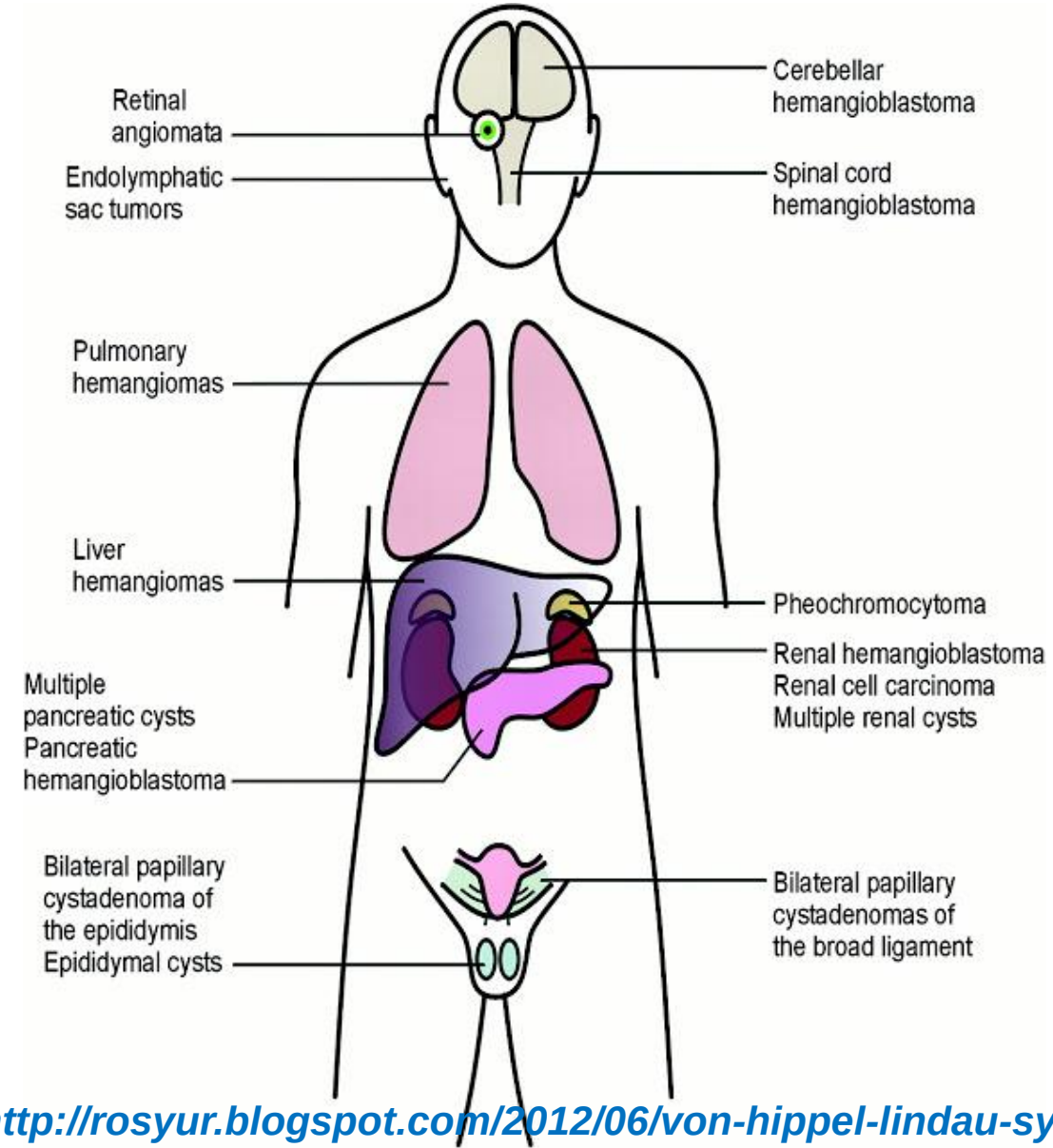
Table 1. Current Proposed PET Radiopharmaceuticals for PPGL Imaging According to Genetic Background

	Location	Other related tumor conditions	First-choice radiopharmaceutical	Second-choice radiopharmaceutical
SDHB	Adrenal/extradrenal	GISTs, RCCs, and pituitary adenomas	^{68}Ga-DOTA-SSAs	^{18}F-FDG
SDHD	Adrenal/extradrenal	GISTs, RCCs, and pituitary adenomas	^{68}Ga-DOTA-SSAs	^{18}F-FDG
SDHC	Adrenal/extradrenal	GISTs, RCCs	^{68}Ga-DOTA-SSAs	^{18}F-FDG
FH	Adrenal/extradrenal	Skin and uterine leiomyomas, RCCs, uterine leiomyosarcomas and ovarian mucinous cystadenomas	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
VHL	Adrenal/extradrenal	RCCs, CNS hemangioblastomas, pancreatic and testicular tumors	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
EPAS1/HIF2A	Adrenal/extradrenal	Somatostatinomas	^{18}F-FDOPA	^{18}F-FDG
MEN2	Adrenal	MTC, parathyroid adenomas, or hyperplasia	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
NF1	Adrenal	Neurofibromas, peripheral nerve sheath tumors, and gliomas	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
TMEM127	Adrenal	RCCs	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
MAX	Adrenal/extradrenal	Renal oncocytomas	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs

CRCHUM RESEARCH CENTRE

Taieb D and Pacak K TEM 28 :807-817, 2017

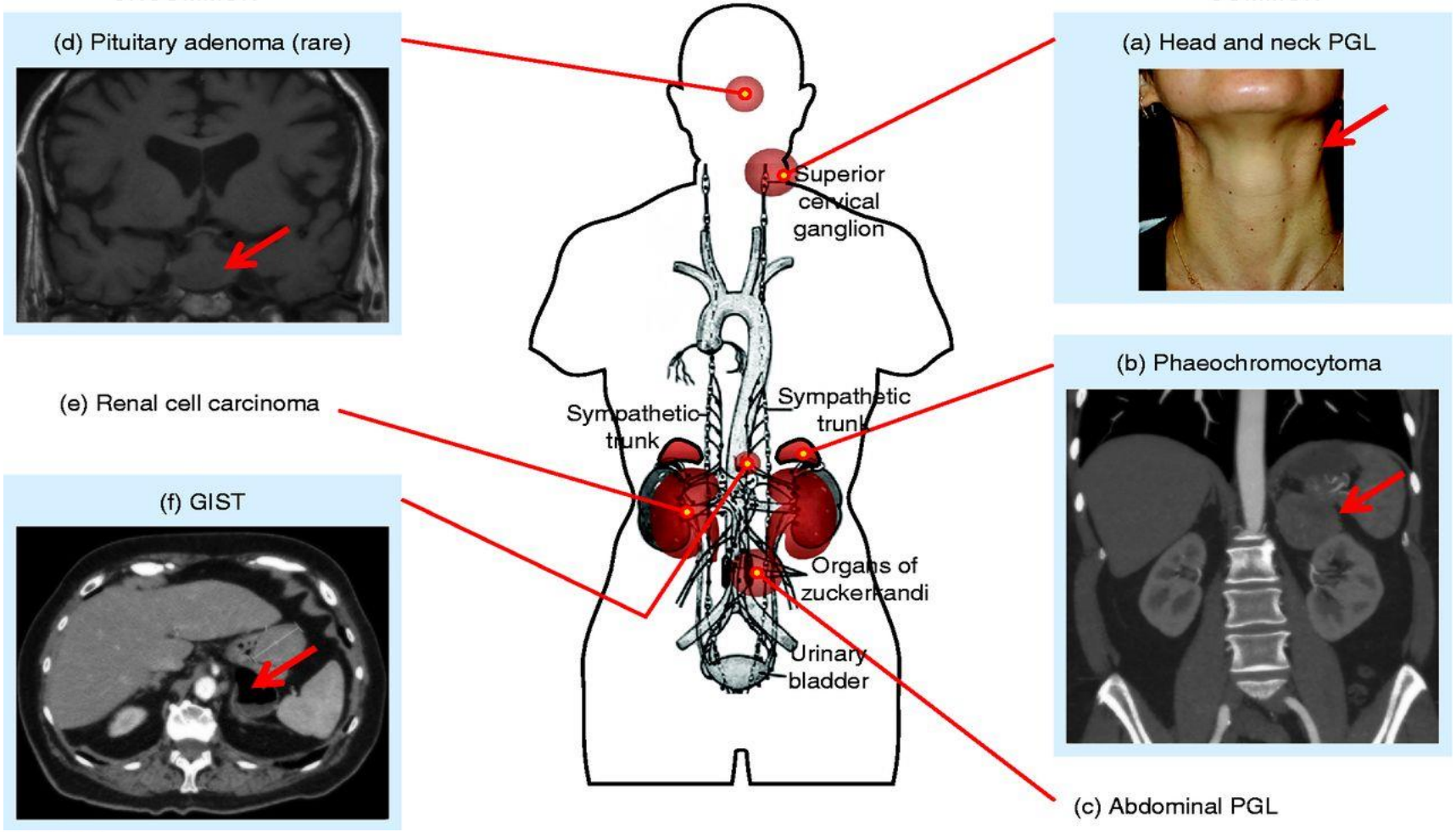
von Hippel-Lindau disease *VHL (3p25-26)*



http://rosyur.blogspot.com/2012/06/von-hippel-lindau-syndrome.html

Table 1 Clinical features (penetrance) of PGL syndromes 1–5

Syndrome	Gene	PC	TAPGL	HNPGL	Multifocal	Malignant	RCC	Other
PGL1	*SDHD*[a]	~10–25%	20–25%	85%	55–60%	~4%	~8%	GIST and PA
PGL2	*SDHAF2*[a]	0	0	100%	0	0	0	–
PGL3	*SDHC*	0	Rare	?[b]	15–20%	0%	Rare	GIST
PGL4	*SDHB*	20–25%	50%	20–30%	20–25%	~30%	~14%	GIST and PA
PGL5	*SDHA*	Rare	Rare	Rare	Rare	Rare	0	GIST and PA



CRCHUM RESEARCH CENTRE

Benn D, Robinson BG, Clifton-Bligh RJ. Endocrine-Related Cancer, 22, T91, 2015

Table 1 Main characteristics of cluster 2 hereditary pheochromocytomas.

Disease	Multiple endocrine neoplasia type 2		Neurofibromatosis type 1	Familial PPGL with *TMEM127* gene mutation	Familial PPGL with *MAX* gene mutation
Gene	*RET*		*NF1*	*TMEM127*	*MAX*
Chromosomal locus	10q11.21		17q11.2	2q11.2	14q23.3
Gene function	proto-oncogene		tumor suppressor gene	tumor suppressor gene	tumor suppressor gene
Genetic Mechanism	activating mutation		inactivating mutation	inactivating mutation	inactivating mutation
Inheritance	AD		AD	AD	AD
Phenotype	Multiple Endocrine Neoplasia type 2A MTC (100%), PHEO (50%), primary HPTH (25%), notalgia	Multiple Endocrine Neoplasia type 2B MTC (100%), PHEO (50%), marfanoid habitus, mucosal neuromas	Neurofibromas (95%), café au lait spots (90%), iris hamartomas (90%), bony lesion, skinfold freckling (80%), optic pathway tumor (15%). PHEO (0, 1–10%)	Single or bilateral PHEO (30–50%); PGL (0–4%), renal cell carcinoma, C cell hyperplasia	Bilateral PHEO, thoraco-abdominal PGL, renal oncocytoma **Prolactinoma/ acromegaly***
Secretion profile	Both metanephrins and normetanephrins		Both metanephrins and normetanephrins	Mainly metanephrins secretion	Mainly normetanephrins secretion
PHEO malignancy	Rare		<10%	Rare	<25%

AD, autosomal dominant; HPTH, hyperparathyroidism; MTC, medullary thyroid carcinoma; PHEO, pheochromocytoma; PGL, paraganglioma; PPGL, pheochromocytoma and paraganglioma.

Transmembrane Protein 127

MYC Associated Factor X

**Roszko KL e al J Endo Soc1:1401-1407, 2017*
Daly AF et al Endocr Relat Cancer 25:L37 2018

Guerin C, Romanet P, Taieb D, Brue T, Lacroix A, Sebag F, Barlier J, Castinetti F Endocr Relat Cancer. 25, T15-T28, 2018

CRCHUM RESEARCH CENTRE

Earn 2.0 CME Credits

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- ✓ Genetic councillor
- ✓ Medical geneticist
- ✓ Imaging specialist
- ✓ Biochemist
- ✓ Endocrine surgeon
- ✓ Pathologist
- ✓ Medical Oncologist
- ✓ Radio-oncologist

3.0 Genetic Testing

3.1 We recommend that all patients with PPGLs should be engaged in shared decision making for genetic testing. (1|⊕⊕⊕◯)

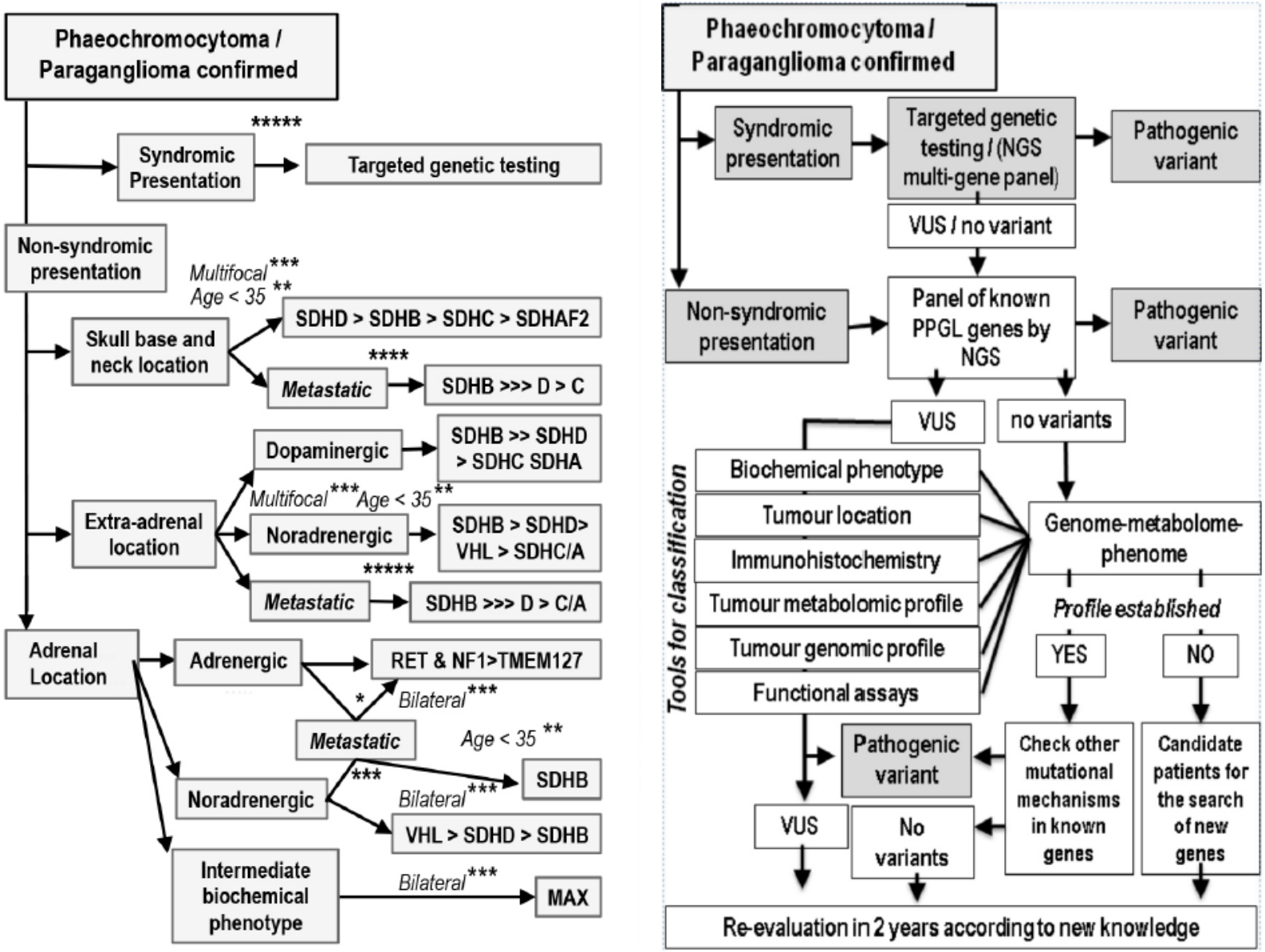
3.2 We recommend the use of a clinical feature-driven diagnostic algorithm to establish the priorities for specific genetic testing in PPGL patients with suspected germline mutations. (1|⊕⊕⊕◯)

3.3 We suggest that patients with paraganglioma undergo testing of succinate dehydrogenase (SDH) mutations and that patients with metastatic disease undergo testing for *SDHB* mutations. (2|⊕⊕⊕◯)

3.4 We recommend that genetic testing for PPGL be delivered within the framework of health care. Specifically, pretest and post-test counseling should be available. All tests for PPGL genetic testing should be performed by accredited laboratories. (Ungraded recommendation)

CRCHUM RESEARCH CENTRE

Lenders JWM et al.J Clin Endocrinol Metab 99: 1915–1942, 2014



CRCHUM RESEARCH CENTRE

Eisenhofer et al Clin Biochem Rev 38, 69, 2017

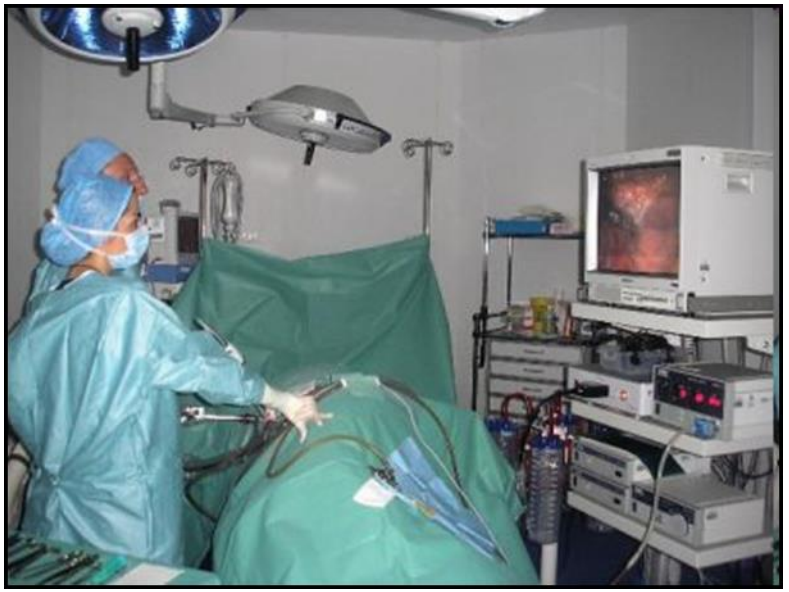
Thérapie Phéos et PPGL

	Scenario	Intervention
Staging and blockade	Elevated plasma or urine normetanephrine and/or metanephrine	a. alpha-adrenoceptor blocker, eg, doxazosin 1–2 mg, increase 2–4 mg weekly to maximum tolerated dosage for ≤30 mg/d.
		b. Localization studies CT, MRI, or PET/CT.
Localized stage	Thoracic or abdominal/pelvic	Curative resection, if safe.
	HN	Surgery, external beam radiation, locoregional therapy, or watchful waiting. If not possible, follow algorithm for malignant disease 5.3.1.

CRCHUM RESEARCH CENTRE

Crona J, Taieb D and Pacak K Endocrine Reviews 38: 489, 2017

Medical therapy of catecholamine excess



CRCHUM RESEARCH CENTRE

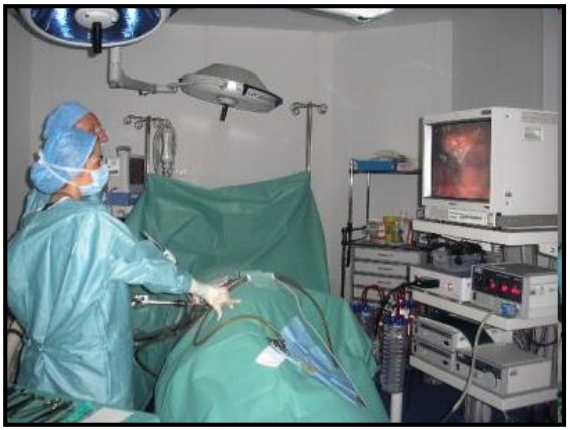
Naranjo J et al J Cardiothorac Vasc Anesth, 31, 1427, 2017

Table 3
Perioperative blockade regimens to begin 10 to 14 days before surgery

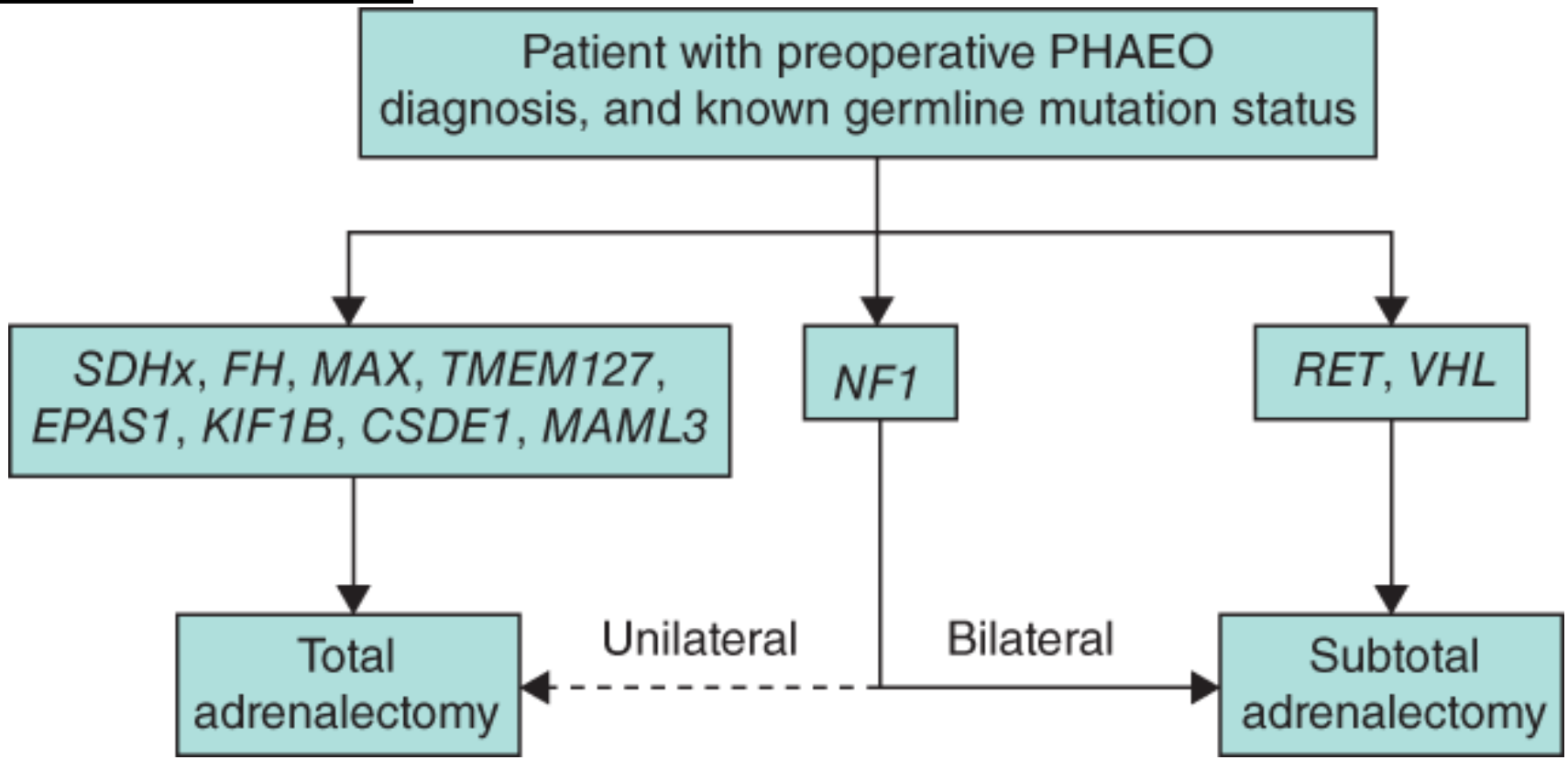
Category	Drug	Dosing	Common Side Effects
Nonselective alpha-blocker	Phenoxybenzamine	10 mg given 2–3 times per day (up to 60 mg daily)	Orthostatic hypotension, nasal congestion, tachycardia
	Phentolamine	Intravenous 2.5–5 mg boluses	
Selective alpha-1 blockers	Doxazosin	2–4 mg given 2–3 times per day	Orthostatic hypotension, dizziness, tachycardia
	Prazosin	1–2 mg given 2 times per day	
	Terazosin	1–4 mg given once daily	
Dihydropyridine calcium channel blockers	Nicardipine	30 mg 2 times per day	Headache, edema
	Amlodipine	5–10 mg once daily	
Tyrosine hydroxylase inhibitor	Metyrosine	250–500 mg titrated up to 4 times per day	Severe fatigue, extrapyramidal neurologic side effects, nausea
Selective beta-1 blocker only after full alpha-blockade	Metoprolol	25–100 mg given 2 times per day	Fatigue, dizziness, asthma exacerbation
Nonselective beta-blocker only after full alpha-blockade	Propranolol	20–40 mg given 2–3 times per day	Fatigue, dizziness, asthma exacerbation

CRCHUM RESEARCH CENTRE

Fishbein L. Hematol Oncol Clin N AM 30: 135-50, 2016



Extent of surgery for phaeochromocytomas in the genomic era



CRCHUM RESEARCH CENTRE

Rossitti HM, Söderkvist P, Gimm O. Br J Surg. 2018 Jan;105(2):e84-e98.

Table 2. TNM classification of pheochromocytoma and paraganglioma

Primary tumor size			
TX	Primary tumor cannot be assessed		
T1	Tumor <5 cm in greatest dimension, no extra-adrenal invasion		
T2	Tumor ≥5 cm or sympathetic paraganglioma of any size, no extra-adrenal invasion		
T3	Tumor of any size with invasion into surrounding tissues (e.g., liver, pancreas, spleen, and kidneys)		
Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
NO	No lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
	M1a: distant metastasis to only bone		
	M1b: distant metastasis to only distant lymph nodes/liver or lung		
	M1c: distant metastasis to bone and multiple other sites		
Stage grouping			
Stage 1	T1	N0	M0
Stage 2	T2	N0	M0
Stage 3	T1	N1	M0
	T2	N1	M0
	T3	Any N	M0
Stage 4	Any T	Any N	M1

CRCHUM RESEARCH CENTRE

Jimenez C et al AJCC cancer staging manuel. 8th ed. NewYork: Spinger pp919-27

Table 4
Comparison of features in the PASS and GAPP pathologic scoring systems for predicting malignancy in PCC/PGL

PASS Features (Points)	GAPP Features (Points)
Histologic pattern • Large nests or diffuse growth (2)	Histologic pattern • Zellballen (0) • Large or irregular nests (1) • Pseudorosettes (1)
Cellularity • High (2)	Cellularity • Low <150 cells/U (0) • Moderate 15–200 cells/U (1) • High >250 cells/U (2)
Necrosis • Present (2)	Necrosis • Absent (1) • Present (2)
Invasion • Vascular invasion (1) • Capsular invasion (1)	Invasion (vascular or capsular) • Absent (0) • Present (1)
Mitosis • Mitotic figures (more than 3/10 high-powered fields) (2) • Atypical mitoses (2)	Ki67 proliferation index • <1% (0) • 1%–3% (1) • >3% (2)
Other features • Extension to adipose tissue (2) • Cell spindling (2) • Cellular monotony (2) • Nuclear pleomorphism (1) • Nuclear hyperchromasia (1)	Catecholamine type • Epinephrine elevated with or without norepinephrine (0) • Norepinephrine and/or dopamine but without epinephrine (1) • Nonsecreting (0)
Maximum Score = 20	Maximum Score = 10

CRCHUM RESEARCH CENTRE

Fishbein L Hematol Oncol Clin N AM 30: 135-50, 2016

European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated for a phaeo or a paraganglioma

1.1. Diagnosis of malignancy

R 1.1. Definition: presence of metastasis in lymph node / distant sites.

R 1.2. FDG PET/CT preoperatively in patients with:

- paragangliomas;
- pheos and elevated 3-methoxytyramine
- *SDHB* germline mutations

1.2. Perioperative workup

R 2.1. All patients with PPGL should be considered for genetic testing.

R 2.2. Chromogranin A pre-op: patients with normal MN, NMN or 3 MT

R 2.3. MN and 3MT 2–6 weeks after surgery if elevated pre-op

R 2.4. CGA 2–6 weeks post surgery (N pre-op MN and 3MT with + CGA)

R 2.5. Imaging 3 months post-op if elevated MN or 3MT or non secreting

1.3. Duration of follow-up

R 3.1. At least 10 years in all, life-time in young, genetic, large tumors, PGL

1.4. Monitoring methods

R 4.1. plasma or urinary MN and 3MT every year

R 4.2. annual CGA if MN/3MT-negative and CGA + pre-op,

R 4.3. imaging tests every 1–2 years if non secreting PPGL

CRCHUM RESEARCH CENTRE

Plouin PF et al European Journal of Endocrinology 174, G1–G10, 2016

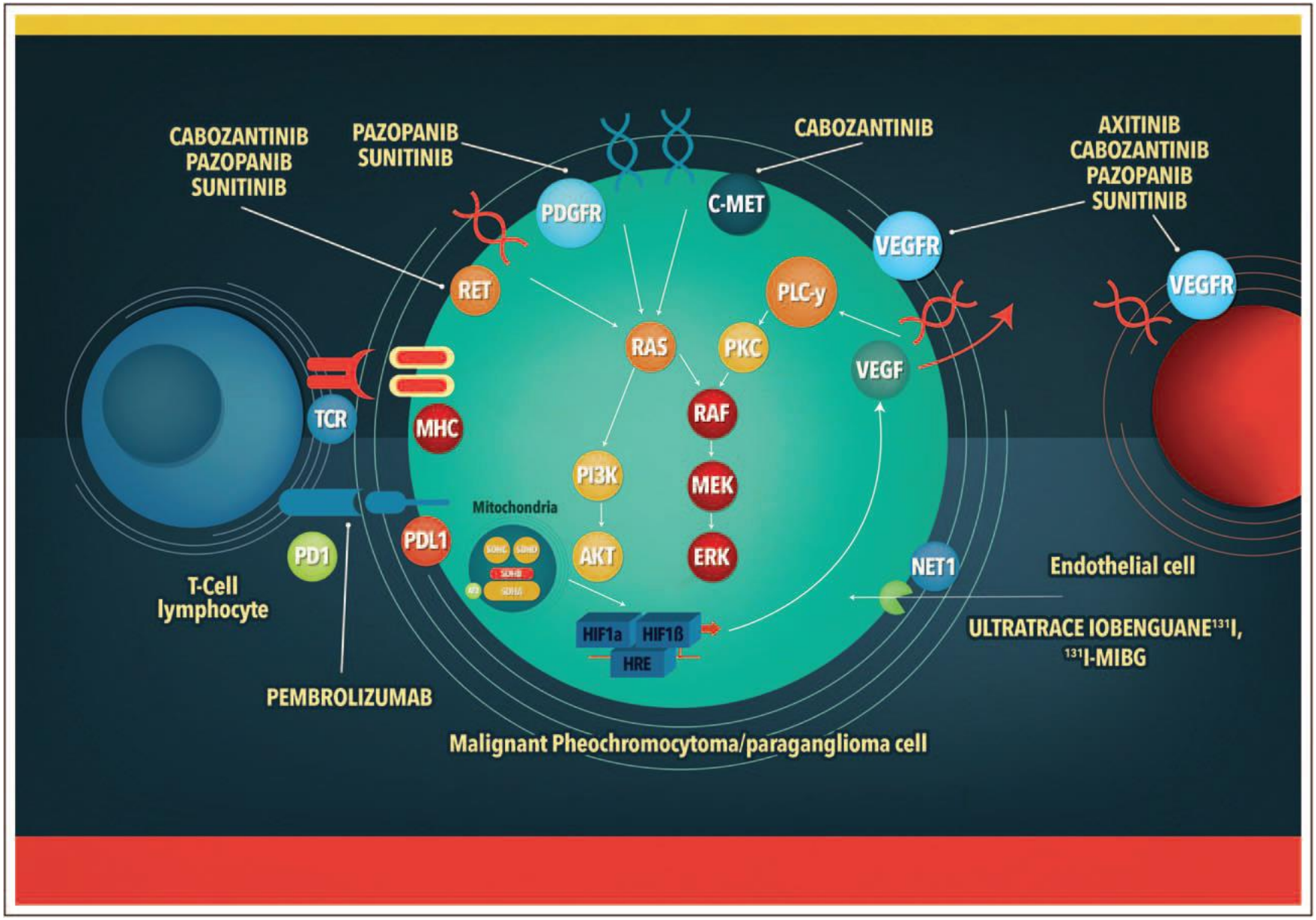
Table 5. Treatment Manual for PPGL

	Scenario	Intervention	Ref	#
Metastatic stage	Elevated plasma or urine normetanephrine and/or metanephrine	a. Palliative doxazosin 1–2 mg, increase 2–4 mg weekly. Balance maximum tolerated dosage to quality of life.	(191)	3.1.1
		b. Before start of any treatment, doxazosin according to 1.1.		3.1.2
	Confined disease	Surgery, external radiation, or locoregional therapy if safe and with acceptable morbidity. If not, proceed to 3.3.1.		3.2
	Disseminated disease	Medical treatment to alleviate hormone or mass effect alternatively at disease progression. Perform ^{123}I-MIBG scintigraphy and ^{68}Ga-DOTATATE PET/CT.		3.3
	First-line ^{131}I-MIBG or ^{68}Ga-DOTATATE positive[a]	^{123}I-MIBG = ^{68}Ga-DOTATATE, choose ^{131}I-MIBG.		3.4.1
		^{123}I-MIBG > ^{68}Ga-DOTATATE, choose ^{131}I-MIBG.		3.4.2
		^{123}I-MIGB < ^{68}Ga-DOTATATE, choose ^{177}Lu-DOTATATE.		3.4.3
	Second-line or first-line ^{123}I-MIBG/^{68}Ga-DOTATATE negative	Priority I. Rechallenge ^{123}I-MIBG or ^{68}Ga-DOTATATE		3.5.1
		Priority II. CVD,[a] if WHO performance status >1 or wish for nonhospitalization, proceed to 3.5.3.		3.5.2
		Priority III. Temozolomide, Tyrosine kinase inhibitor or experimental therapy.	(213, 214)	3.5.3

CRCHUM RESEARCH CENTRE

Crona J, Taieb D and Pacak K Endocrine Reviews 38: 489, 2017

Potential medical therapies for malignant pheochromocytomas

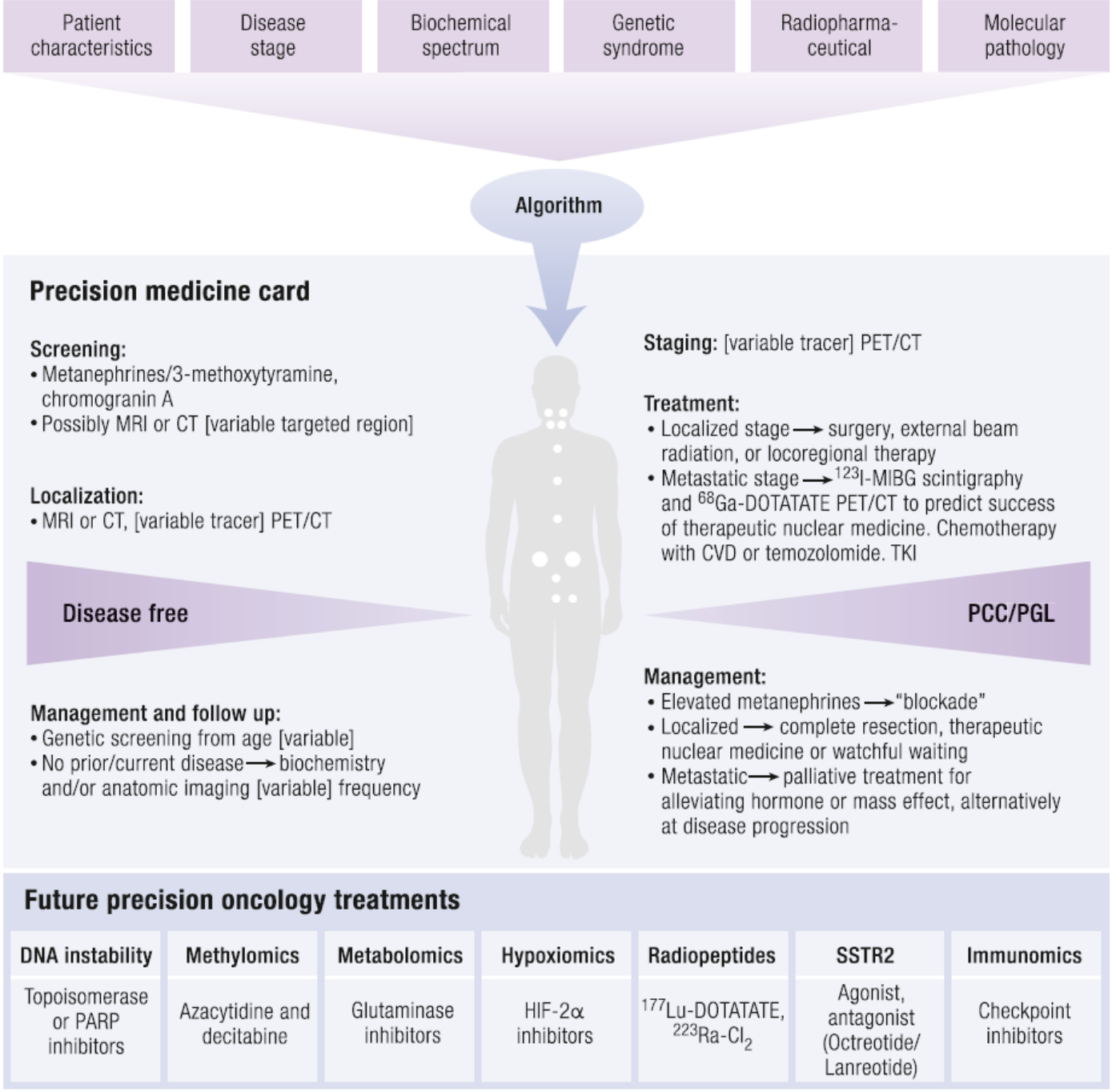


CRCHUM RESEARCH CENTRE

Roman-Gonzalez A and Jimenez C Curr Opin Endocrinol Diabetes Obes. 24 :174-183, 2017

Medication	Clinical trial name	NCI Clinical Trial Registration no.	Intervention	Primary endpoint	Status
Ultratrace iobenguane I-131	Pivotal Phase 2 Study of Ultratrace Iobenguane I-131 (AZEDRA) in Patients with Malignant Relapsed/Refractory Pheochromocytoma/ Paraganglioma	NCT00874614	Two doses of 500 mCi or 8 mCi/kg in patients with weight ≤62.5 kg	Blood pressure control	Active, not recruiting
Ultratrace iobenguane I-131	Expanded Access Program of Ultratrace Iobenguane I131 for Malignant Relapsed/Refractory Pheochromocytoma/ Paraganglioma	NCT02961491	Two doses of 500 mCi or 8 mCi/kg in patients with weight ≤62.5 kg	Safety	Actively recruiting
Sunitinib	Sunitinib in Patients with Recurrent Paraganglioma/ Pheochromocytoma (SNIPP)	NCT00843037	50 mg orally daily for 4 weeks; 2-week rest period (repeating 6-week cycles)	Best ORR (RECIST 1.1)	Actively recruiting
Sunitinib	The First International Randomized Study in Malignant Progressive Pheochromocytoma and Paraganglioma (FIRSTMAPPP)	NCT01371201	37.5 mg daily vs. placebo	PFS at 12 months	Actively recruiting
Pazopanib	Pazopanib Hydrochloride in Treating Patients With Advanced or Progressive Malignant Pheochromocytoma or Paraganglioma	NCT01340794	400 mg daily for 2 weeks followed by 800 mg daily	Best ORR RECIST 1.1	Terminated
Axitinib	Phase II Study of Axitinib (AG-013736) With Evaluation of the VEGF-pathway in Metastatic, Recurrent or Primary Unresectable Pheochromocytoma/ Paraganglioma	NCT01967576	5 mg every 12 h (28-day cycle). Dose escalation beginning at weeks 4–7 to 10 mg every 12 h	PFS	Closed for recruitment
Cabozantinib	Cabozantinib in Patients with Unresectable Metastatic Pheochromocytomas and Paragangliomas	NCT02302833	60 mg orally daily, with titration to 40–20 mg depending on side effects	Best ORR (RECIST 1.1)	Actively recruiting
Everolimus	RAD001 in Pheochromocytoma or Nonfunctioning Carcinoid	(NCT01152827)	10 mg orally daily	PFS at 4 months	Completed
Pembrolizumab	Evaluation of Efficacy of Pembrolizumab in Patients with Rare Tumors	NCT02721732	200 mg intravenously every 3 weeks with restaging after 3 cycles	Nonprogression rate	Actively recruiting

Roman-Gonzalez A and Jimenez C Curr Opin Endocrinol Diabetes Obes. 24 :174-183, 2017

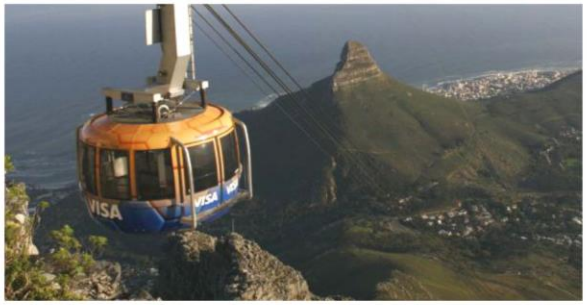


Future precision oncology treatments

DNA instability	Methylomics	Metabolomics	Hypoxiomics	Radiopeptides	SSTR2	Immunomics
Topoisomerase or PARP inhibitors	Azacytidine and decitabine	Glutaminase inhibitors	HIF-2α inhibitors	^{177}Lu-DOTATATE, ^{223}Ra-Cl_2	Agonist, antagonist (Octreotide/ Lanreotide)	Checkpoint inhibitors

CRCHUM RESEARCH CENTRE

Crona J, Taieb D and Pacak K Endocrine Reviews 38: 489, 2017



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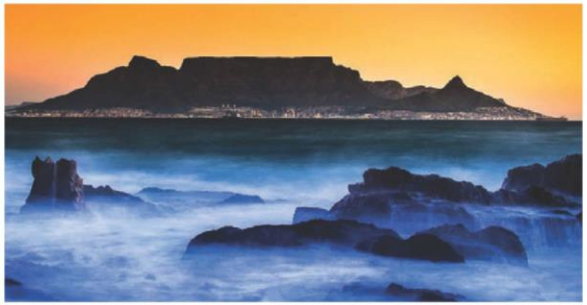
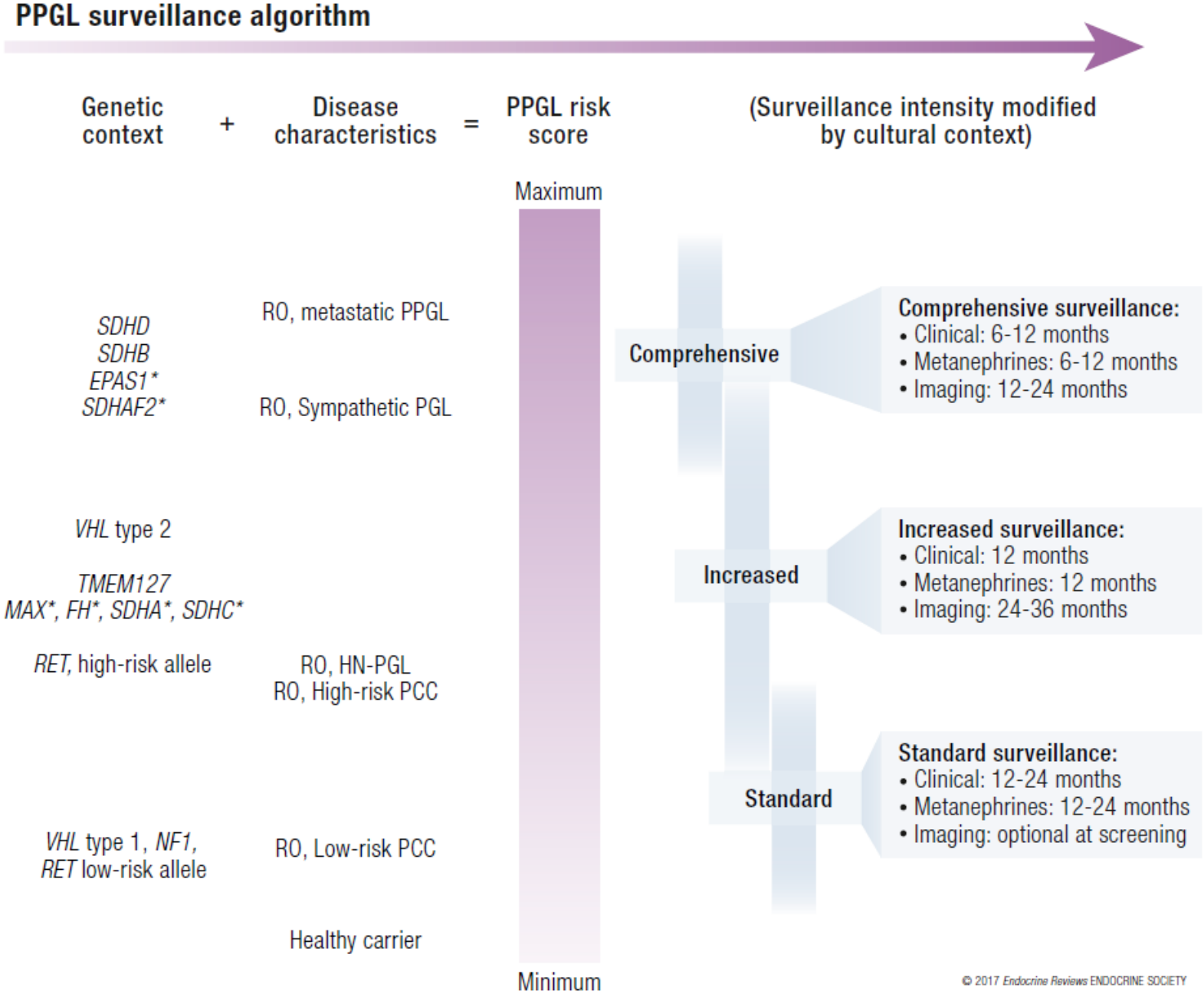


Les phéochromocytomes

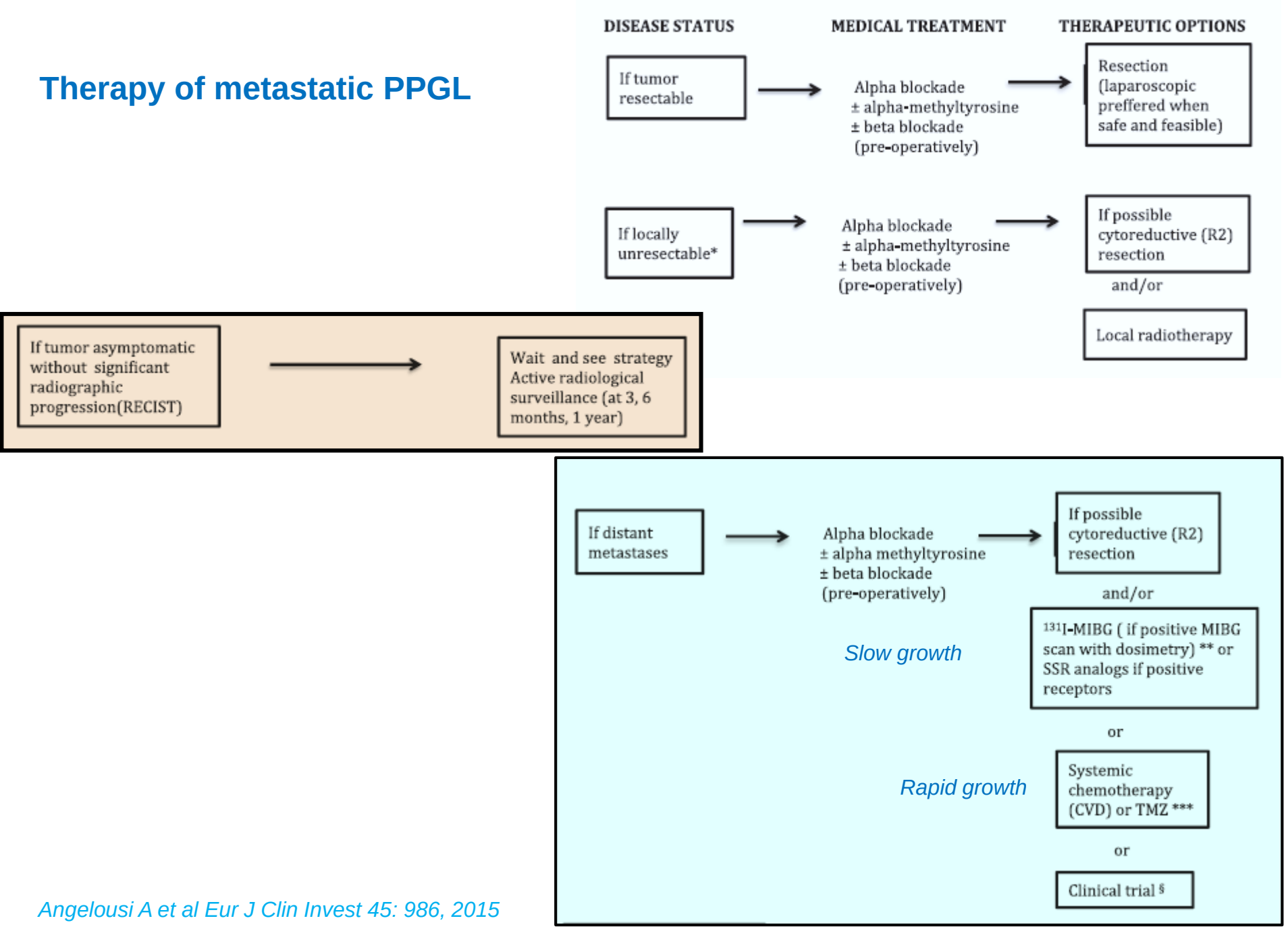
Période de Questions



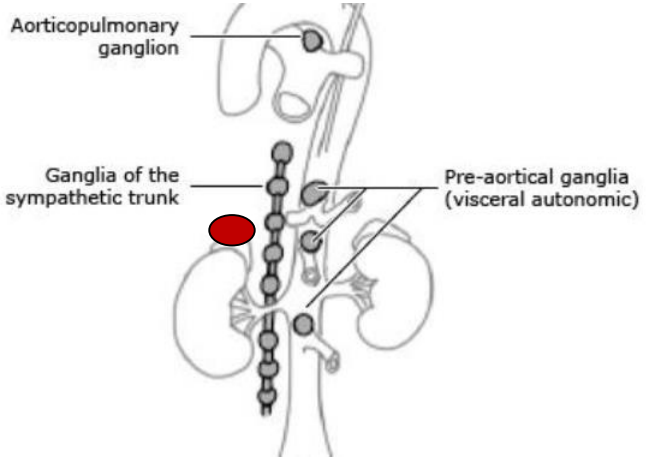
CRCHUM RESEARCH CENTRE

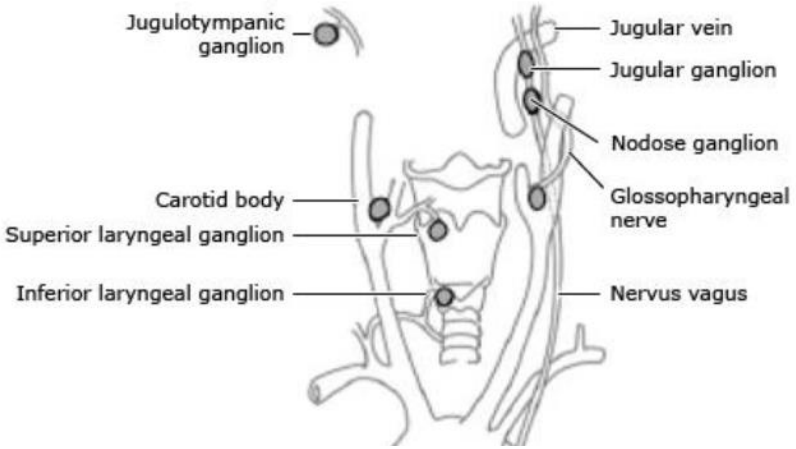
Crona J, Taieb D and Pacak K Endocrine Reviews 38: 489, 2017

Therapy of metastatic PPGL



Angelousi A et al Eur J Clin Invest 45: 986, 2015





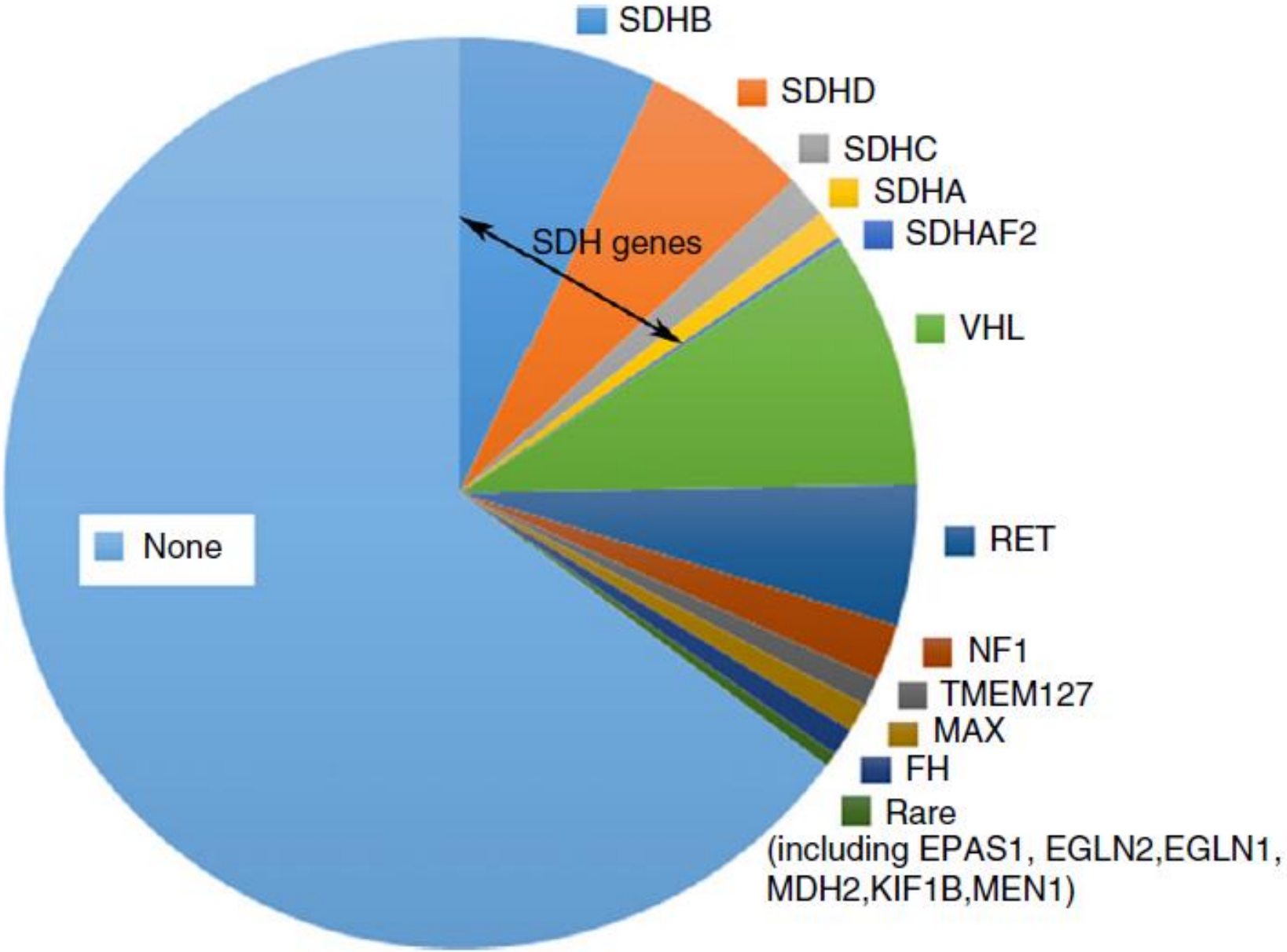
Carty SA, Young WF et al UpToDate 2018

Characteristics of the two broad categories of paragangliomas (World Health Organization classification)

Characteristic	*Sympathoadrenal*	*Parasympathetic*
Chromaffin status	Chromaffin paragangliomas	Non-chromaffin paragangliomas, often called chemodectomas or glomus tumours
Location	Adrenal medulla (most common)	Head and neck, also upper mediastinum
Distribution	Also symmetrically distributed along the prevertebral and paravertebral axis (thoracoabdominal and pelvic paraganglia)	Found in 20 distinct anatomic locations: carotid body (major paraganglion, the most common tumour location), jugular foramen, Jacobsen tympanic plexus, and vagal and aortic paraganglia (upper mediastinum)
Hormonal activity	Usually, but not always, hormonally active (catecholamine producing: noradrenalin, adrenalin, dopamine, L-DOPA)	Hormonally inactive in 95% of cases (only rarely associated with catecholamine production)

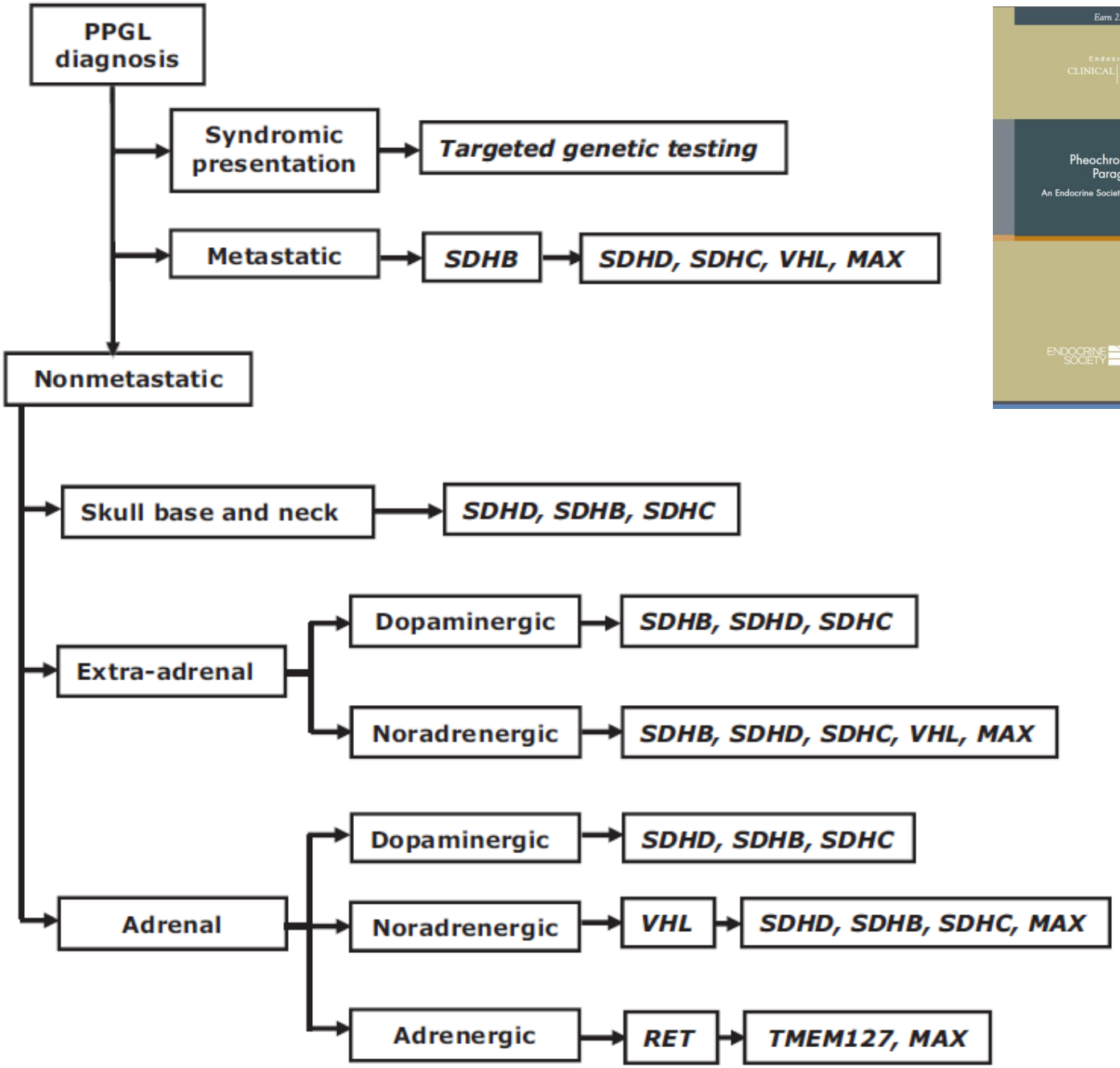
CRCHUM RESEARCH CENTRE

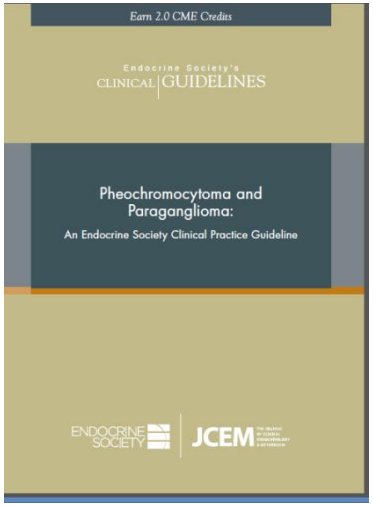
Lefebvre and Foulkes, Current Oncology, 21, 8-17, 2014



CRCHUM RESEARCH CENTRE

Turchini J et al. Histopathology 72: 97-105, 2018



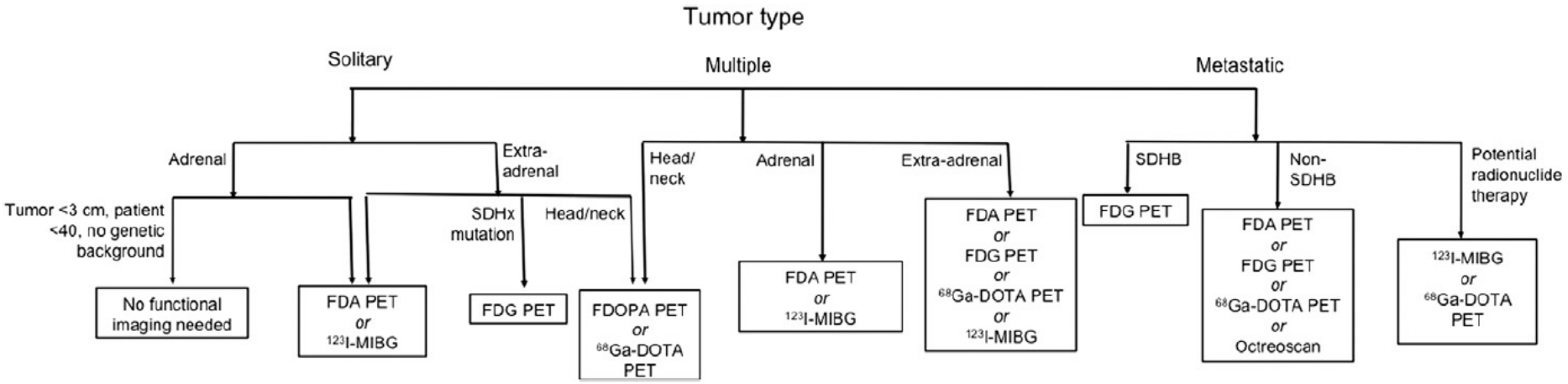


CRCHUM RESEARCH CENTRE

Lenders JWM et al.J Clin Endocrinol Metab 99: 1915–1942, 2014

Table 4
Sensitivities and specificities of imaging modalities.

Imaging modality	Primary (nonmetastatic)		Adrenal PHEO (%)	Extra-adrenal PGL (%)	Head and neck PGL (%)	SDHx carriers (%)	Meta-static (%)	SDHB metastatic (%)	Non-SDHB metastatic (%)	Bone metastases (%)
	Sensitivity (%)	Specificity (%)								
CT/MRI	66-100	40-90	–	–	80-92	85.7-87.5	45-100	78-96	71	37.8-96
FDA PET	77-88	90	–	–	40-46	–	76-97	76-88	76	79-100
FDG-PET	58-88	90	–	–	69-80	–	74-91.4	74-100	62-67.3	76-93.7
FDOPA PET	67-93	95-100	93.9	47.1-90	96.5-100	–	45-100	20-45	93	–
MIBG	52-87	75-100	85-87	58-67	18-50	42.70	38-92.4	44-80	59-66	20.75-76
Octreoscan	25-54	75	–	–	64-100	69.50	68.5-88.9	59-81	–	–
^{68}Ga-DOTA peptides	80-100	85.7	–	–	100	60	91.70	–	–	100



CRCHUM RESEARCH CENTRE

Martucci VL and Pacak K, Curr Prob Cancer, 38: 7-14, 2014

Mutation type and contribution to disease

Gene	Chromosomal Location	Inheritance	Germline*	Somatic*	Mosaic	Gross deletions	Tumour Locations
RET	10q11.21	AD	5-10%	10%	NR	NR	A (bilat 50-80%) >>> EA
VHL	3p25.3	AD	7-10%	10%	Yes	Yes†	A (bilat 50%) > EA, >>> H&N PGL
NF1	17q11.2	AD	3-5%	20-40%	Yes	Yes	A (bilat 16%) >>>> EA
SDHD	11q23.1	AD, PT	9-10%	<1%	NR	Yes	H&N > EA > A
SDHB	1p36.13	AD	10%	<1%	NR	Yes	EA > H&N > A
SDHC	1q23.3	AD	<5%	0%	Yes	NR	H&N > EA > A
SDHA	5p15.33	AD	3%	<1%	NR	NR	EA >> A
SDHAF2	11q12.2	AD, PT	<1%	0%	NR	NR	H&N >>> A
TMEM127	2q11.2	AD	<2%	0%	NR	NR	A (bilat 35%) >> EA
MAX	14q23.3	AD, PT	<2%	<2%	NR	Yes	A (bilat 68%) >> EA
FH	1q42.1	AD	<2%	0%	NR	Yes	A + EA > H&N
MDH2	7q11.23	AD	<1%	0%	NR	NR	EA >> A
KIF1Bβ	1p36.22	AD	<1%	?	NR	NR	A
EGLN1/ PHD2	1q42.1	?	<1%	NR	NR	NR	EA > A
EGLN2/ PHD1	19q13.2	?	<1 %	NR	NR	NR	EA > A
HIF2α/ EPAS1	2p21	?	<0.1%	5-7%	Yes	NR	EA > A
H3F3A	1q42.12	?	NR	NR	Yes	NR	A + EA
HRAS	11p15.5	?	NR	10%	NR	NR	A > EA
IDH1	2q24	?	NR	<1%	NR	NR	H&N
SLC25A11	17	?	~1%	NR			EA, metastasis+++

Mitochondrial 2-oxoglutarate/malate carrier

Buffet et al Cancer Res on line Feb 5 2018

CRCHUM RESEARCH CENTRE

Eisenhofer et al Clin Biochem Rev 38, 69, 2017

Figure 1 A representative scheme of RET receptor tyrosine kinase structure is depicted.

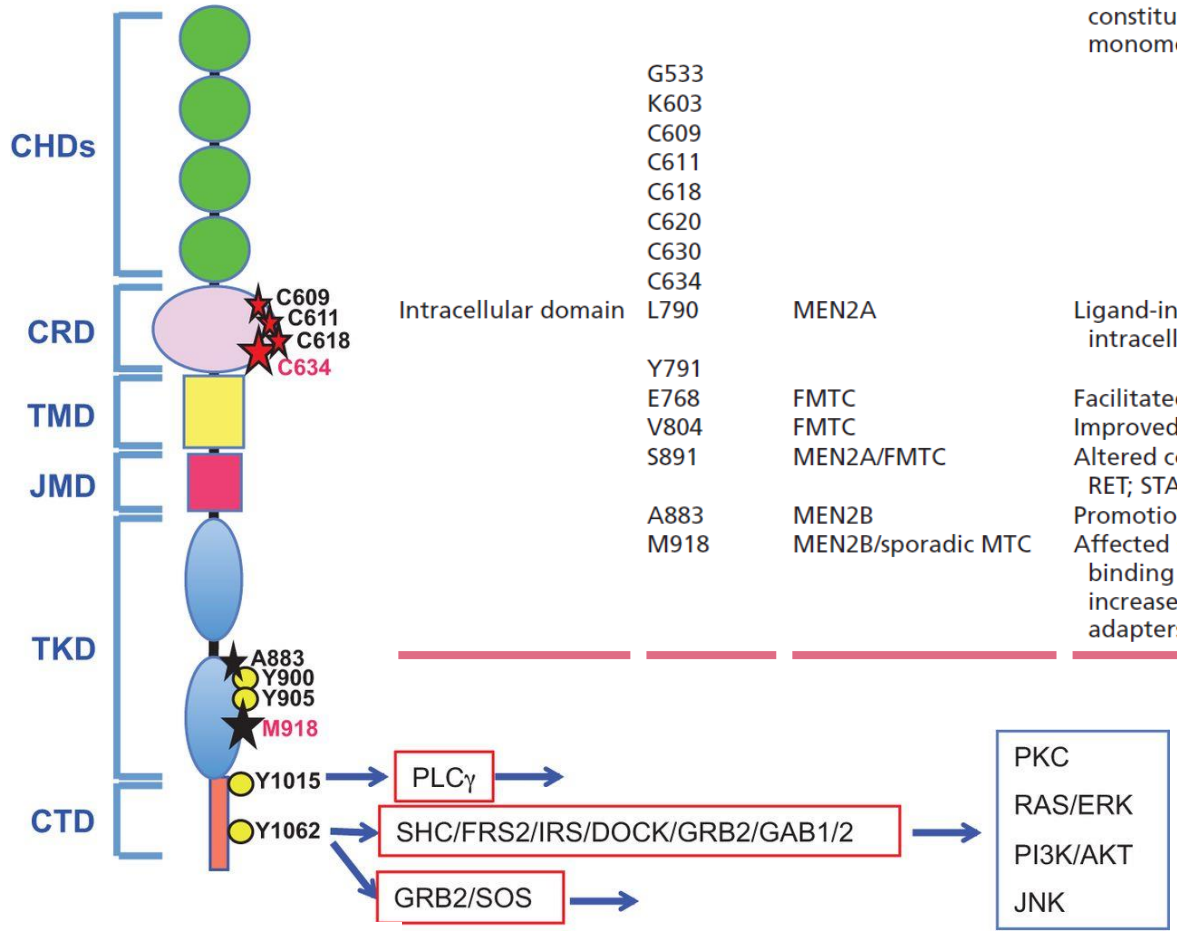


Table 2 The principal RET mutations in MTC are reported.

RET domain	Codons	Phenotype	Effects
Extracellular domain	G321	MEN2A/FMTC	Altered folding and protein maturation; ligand-independent constitutive dimerization; formation of disulfide bridges between monomers; activation of the kinase
	G533		
	K603		
	C609		
	C611		
	C618		
	C620		
	C630		
	C634		
Intracellular domain	L790	MEN2A	Ligand-independent dimerization; enhanced phosphorylation of intracellular substrates; increased STAT3 phosphorylation
	Y791		
	E768	FMTC	Facilitated transition to active conformation
	V804	FMTC	Improved access to ATP binding site
	S891	MEN2A/FMTC	Altered conformation of activation loop; activation of monomeric RET; STAT3 phosphorylation
	A883	MEN2B	Promotion of protein active form
	M918	MEN2B/sporadic MTC	Affected stability of RET inactive dimer conformation, increasing ATP binding affinity; altered affinity of RET for downstream substrates; increased Y1062 phosphorylation; more efficient recruitment of adapters and activation of downstream signaling

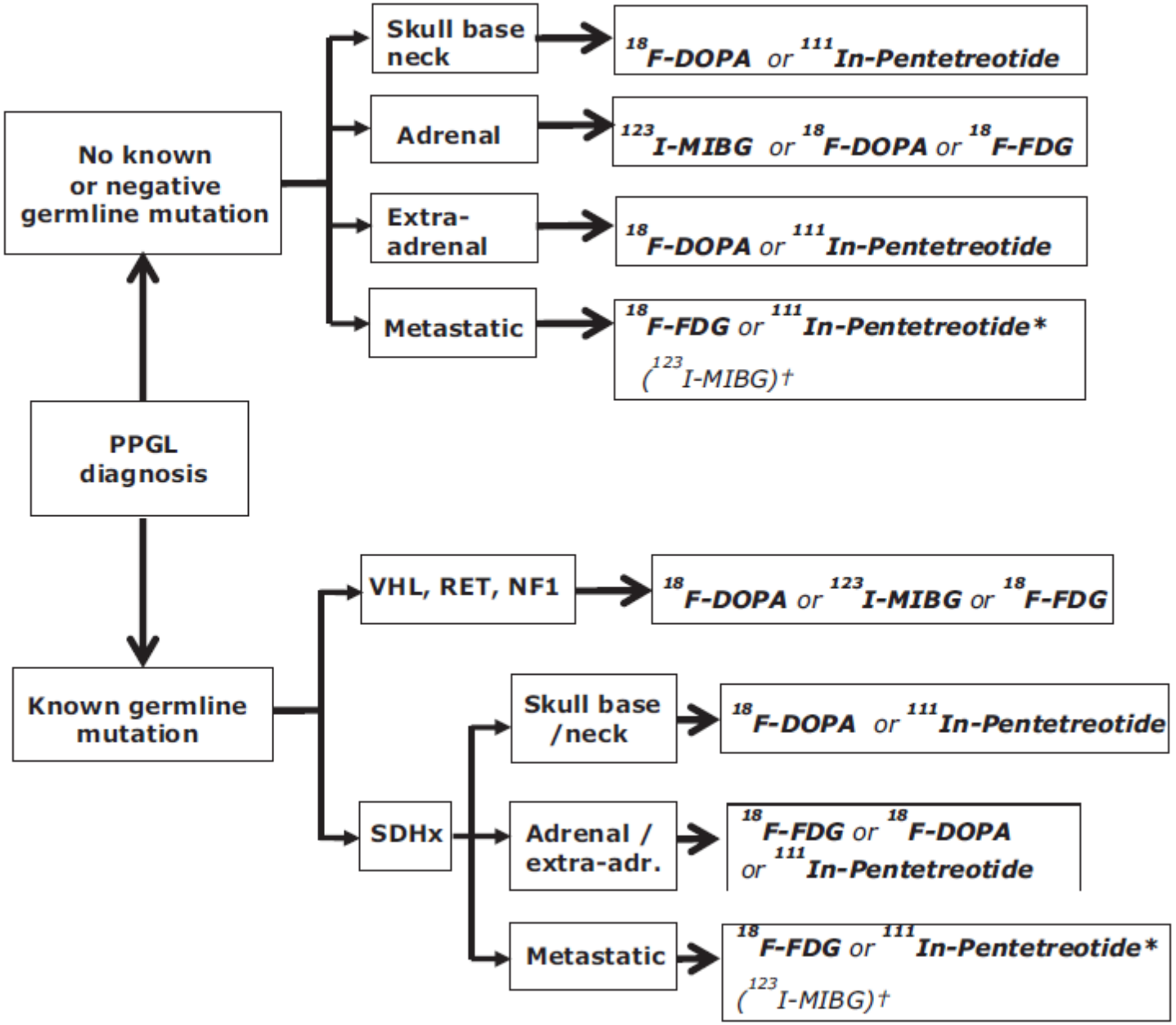
CRCHUM
RESEARCH CENTRE

Castellone MC, Melillo RM. Endocr Relat Cancer 2018;25:T105-T119

Risk for Aggressive MTC Based on Genotype and Recommended Interventions

ATA [1] Risk Level	Pathogenic Variants [2, 3]	Age of Prophylactic Surgery	Age to Begin Screening	
			For PHEO	For HPT [4]
Level D (highest risk)	p.Ala883Phe p.Met918Thr p.Val804Met+p.Glu805Lys [5] p.Val804Met+p.Tyr806Cys [5] p.Val804Met+p.Ser904Cys [5]	As soon as possible in 1st year of life	8 yrs	NA
Level C	p.Cys634Arg/Gly/Phe/Ser/Trp/Tyr	<5 yrs	8 yrs	8 yrs
Level B	p.Cys609Phe/Arg/Gly/Ser/Tyr p.Cys611Arg/Gly/Phe/Ser/Trp/Tyr p.Cys618Arg/Gly/Phe/Ser/Tyr p.Cys620Arg/Gly/Phe/Ser/Trp/Tyr p.Cys630Arg/Phe/Ser/Tyr p.Asp631Tyr p.633/9 bp dup p.634/12 bp dup p.Val804Met+p.Val778Ile [5]	Consider <5 yrs; may delay if criteria met [5]	Codon 630 pathogenic variant: 8 yrs All others: 20 yrs	Codon 630 pathogenic variant: 8 yrs All others: 20 yrs
Level A	p.Arg321Gly p.531/9 bp dup p.532 dup p.Cys515Ser p.Gly533Cys p.Arg600Gln p.Lys603Glu p.Tyr606Cys p.635/insert ELCR;p.Thr636Pro p.Lys666Glu p.Glu768Asp p.Asn777Ser p.Leu790Phe p.Val804Leu/Met p.Gly819Lys p.Arg833Cys p.Arg844Gln p.Arg866Trp p.Ser891Ala p.Arg912Pro	May delay beyond age 5 yrs if criteria met [6]	20 yrs	20 yrs

Marquard J, Eng C, Gene Reviews 2015



CRCHUM RESEARCH CENTRE

Lenders JWM et al.J Clin Endocrinol Metab 99: 1915–1942, 2014

Table 1. Classification of Von Hippel-Lindau Syndrome

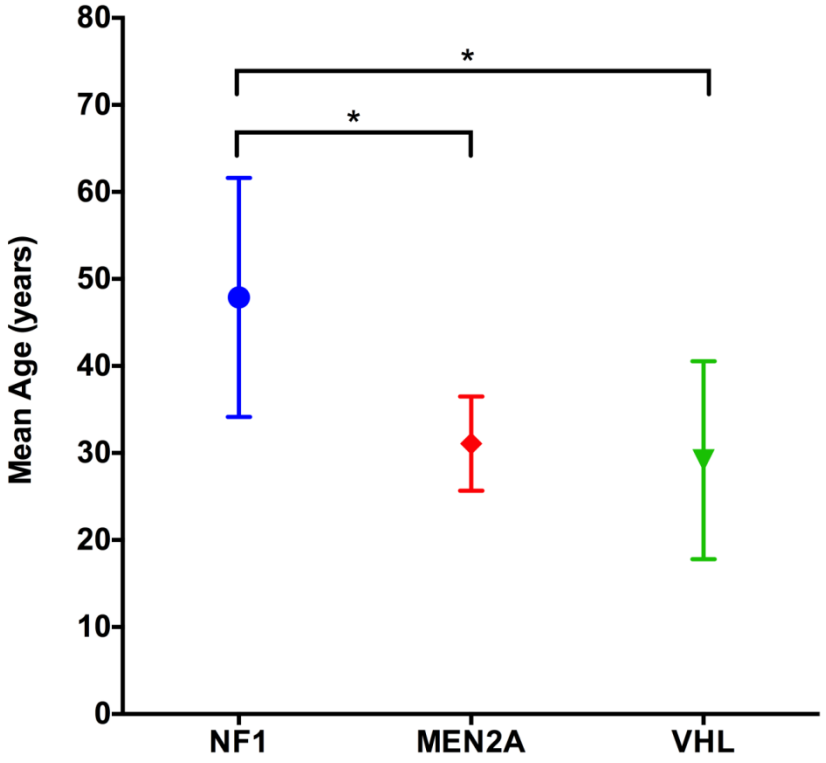
Type	Clinical findings	Mutations
Type 1 (decreased risk for PCC)	Retinal and CNS HB, RCC, pancreatic cysts, and neuroendocrine tumors	Truncating or missense mutations
Type 2 (increased risk for PCC)		
Type 2A (low risk of RCC)	PCC, retinal HB, CNS HB	Missense mutation
Type 2B (high risk of RCC)	PCC, RCC, Retinal HB, CNS HB, pancreatic cyst, and neuroendocrine tumors	
Type 2C	PCC only	

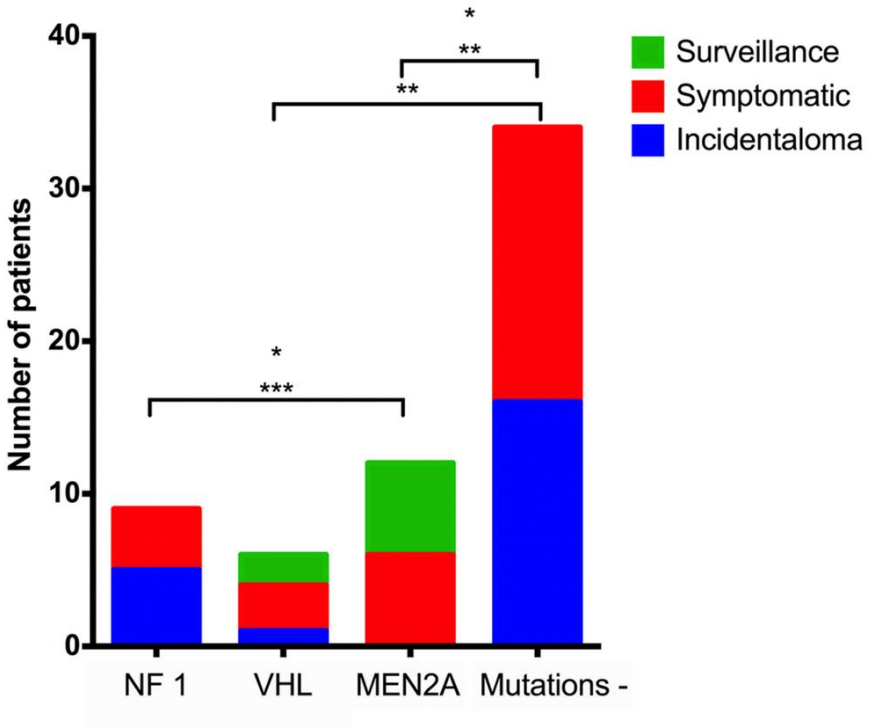
Table 3. Frequency of lesions and average age range of presentation in VHL patients

Clinical Feature	Average (range) of presentation (years)	Frequency (%)	Reference
CNS hemangioblastoma	30 (9–78)	60–80%	1
Retinal hemangioblastoma	25 (1–67)	49–62%	4, 6
Endolymphatic sac tumors	31 (12–50)	6–15%	7, 15
Renal cell carcinoma or cysts	39 (16–67)	30–70%	6
Pheochromocytoma	30 (5–58)	10–20%	6
Pancreatic neuroendocrine tumors or cysts	36 (1–70)	35–70%	8, 15
Epididymal cystadenomas	Unknown (16–40)	25–60%	6, 15
Broad ligament cystadenomas	Unknown (16–46)	Unknown	8

Varshney et al, Journal of Kidney Cancer and VHL 4: 20, 2017

NF1 and pheochromocytoma at CHUM





CRCHUM RESEARCH CENTRE

Moramarco J et al Clin Endocrinol (Oxf). 86, 332, 2017

Renal tumors and PPGL association syndromes (RAPTAS)

Table 3. Clinical and Molecular Genetic Features of Non-VHL RAPTAS Cases Identified in the Literature

Gene	Mutation	Group A/B	(PC/PGL/HNPGL) Location (Age)	RCC Tumor Type (Age in Years)	Sex	Tumor of Relative (Age in Years)	Reference
SDHB	c.3G>A (p.Met1Ile)	A+B	PGL (25)	Bilateral RCC (25)	M	RCC, brother (23)	13
SDHB	c.3G>A (p.Met1Ile)	B	No	Unilateral RCC (23)	M	RCC, PGL, brother (25)	13
SDHB	Exon 3 deletion	A	HNPGL (30)	Unilateral RCC (36)	M		13, 33
SDHB	c.166-170 del CCTCA (p.Pro56TryfsX5)	A	PGL (28)	Unilateral RCC (28)	M		33
SDHB	C.423+1G>A	B	No	Unilateral RCC		PC, brother (44)	7, 33
SDHB	Exon 1 deletion	B	No	Unilateral RCC[a] (36)	M	RCC, brother (25)[a]	39
SDHB	Exon 1 deletion	A+B	PC	Unilateral RCC (42)	F	PGL, sister	39
SDHB	268C>T (p.Arg90X)	A+B	PGL	Unilateral RCC (61)	M	PGL, son	33
SDHB	c.286G>A (p.Gly96Ser)	B	No	Unilateral RCC (52)[a]	F	RCC, daughter	39
SDHB	c.541-2A>G	B	No	Unilateral RCC (19)	F	PGL, mother	39
SDHB	c.689G>A (p.Arg230His)	B	No	Unilateral RCC (52)	F	PGL, daughter	39
SDHB	c.541-2A>G	B	No	Unilateral RCC (50)	M	RCC, brother[a]	39
SDHB	Del exon 1	A	PGL (17)	Unilateral renal oncocytoma	F		39
SDHB	c.170A>G (p.His57Arg)	B		Unilateral RCC[a] (28)	M	PGL, mother[a]	20
SDHB	c.847-50delTCTC	A+B	Unilateral RCC (26)	PGL	M	RCC, PGL, brother (24)	20
SDHC	c.397C>T (p.Arg133X)	B	No	Unilateral RCC (53)[a]	F	RCC, son (40)	39
SDHC	c.3G>A (p.Met1I)	B	HNPGL (46)	Bilateral RCC (48,60)	M	Bilateral RCC, mother (48,60)	40
SDHD	c.239G>T (p.Leu80Arg)	A+B	Bilateral HNPGL (17), PGL(28)	Unilateral RCC (45)[a]	M	HNPGL, father, PC brother	39
TMEM127	c.308delG (p.Gly103Alafs)	A	PC (47)	Unilateral RCC (47)	F		6
MAX	Deletion exon 1+2	A+B	Bilateral PC (45)	Unilateral oncocytoma (45)	M	Bilateral PC, brother (28)	8

Abbreviations: F, female; M, male.

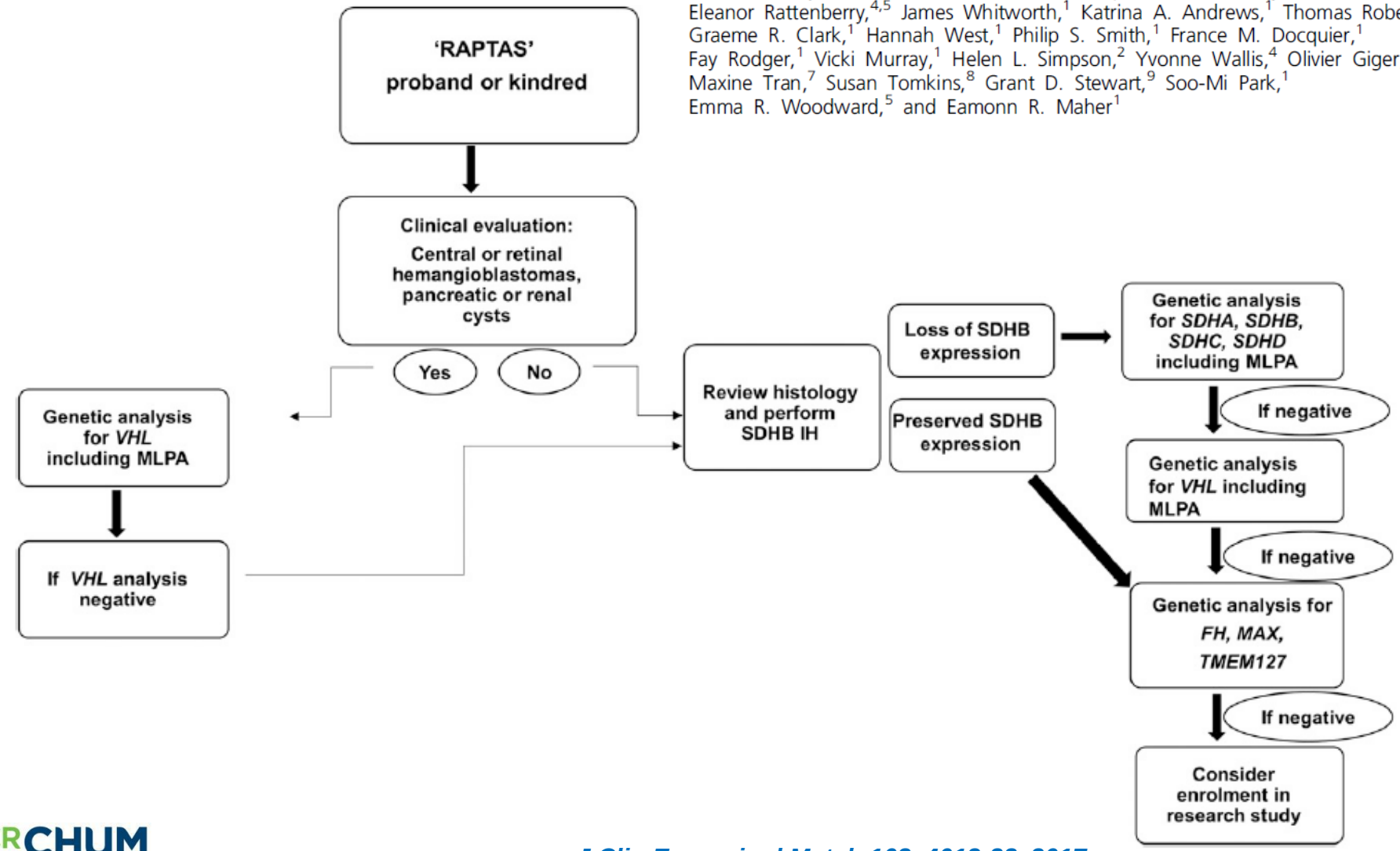
[a]Metastatic disease.

Casey RT et al J Clin Encocrinol Metab 102, 4013-22, 2017

CRCHUM RESEARCH CENTRE

Clinical and Molecular Features of Renal and Pheochromocytoma/Paraganglioma Tumor Association Syndrome (RAPTAS): Case Series and Literature Review

Ruth T. Casey,[1,2] Anne Y. Warren,[3] Jose Ezequiel Martin,[1] Benjamin G. Challis,[2] Eleanor Rattenberry,[4,5] James Whitworth,[1] Katrina A. Andrews,[1] Thomas Roberts,[6] Graeme R. Clark,[1] Hannah West,[1] Philip S. Smith,[1] France M. Docquier,[1] Fay Rodger,[1] Vicki Murray,[1] Helen L. Simpson,[2] Yvonne Wallis,[4] Olivier Giger,[3] Maxine Tran,[7] Susan Tomkins,[8] Grant D. Stewart,[9] Soo-Mi Park,[1] Emma R. Woodward,[5] and Eamonn R. Maher[1]

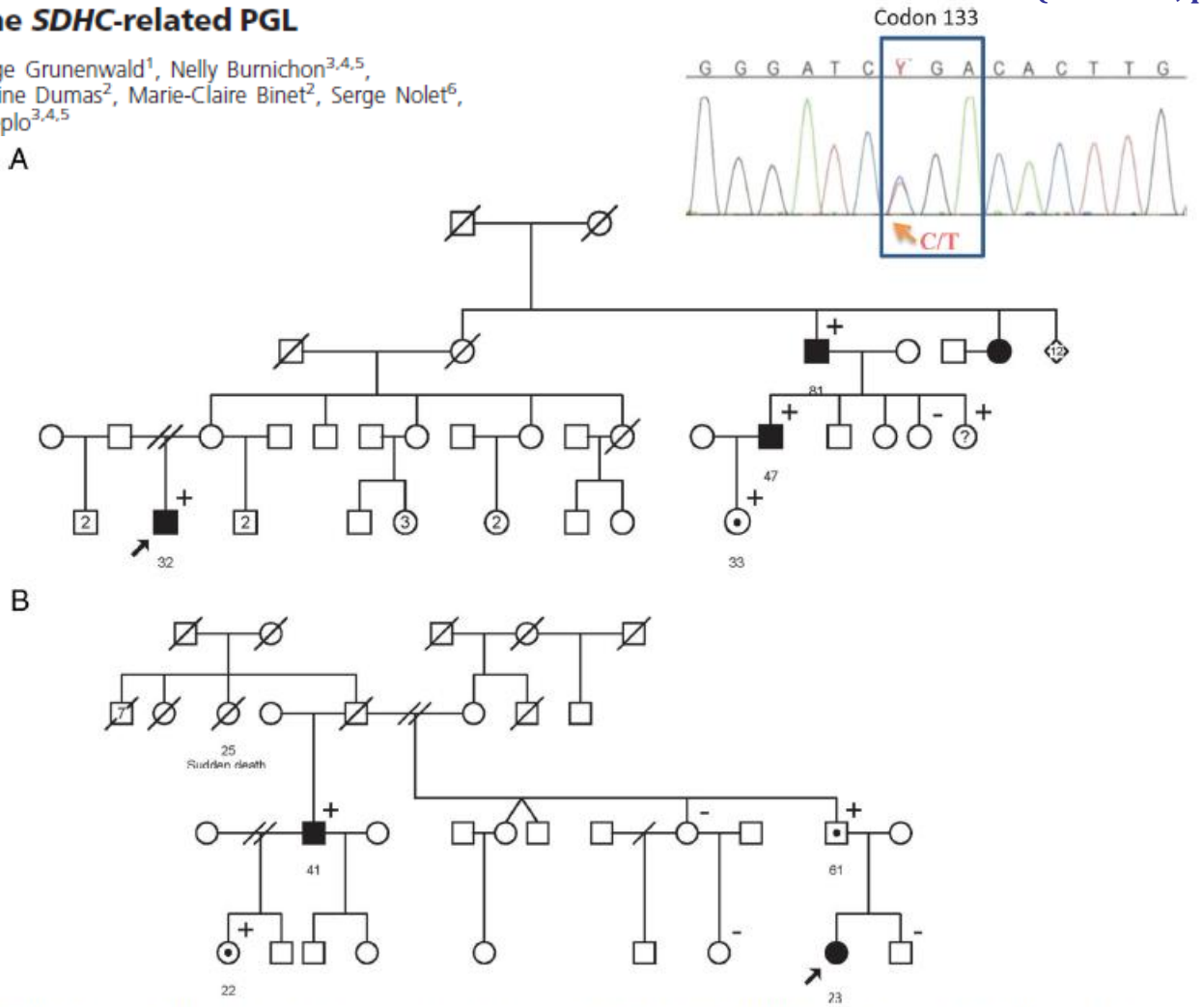


J Clin Encocrinol Metab 102, 4013-22, 2017

A *SDHC* FOUNDER MUTATION CAUSES PARAGANGLIOMAS (PGL) IN THE FRENCH CANADIANS: new insights on the *SDHC*-related PGL

Isabelle Bourdeau[1,2], Solange Grunenwald[1], Nelly Burnichon[3,4,5], Emmanuel Khalifa[3,4,5], Nadine Dumas[2], Marie-Claire Binet[2], Serge Nolet[6], Anne-Paule Gimenez-Roqueplo[3,4,5]

(c.397C>T, p.Arg133X)

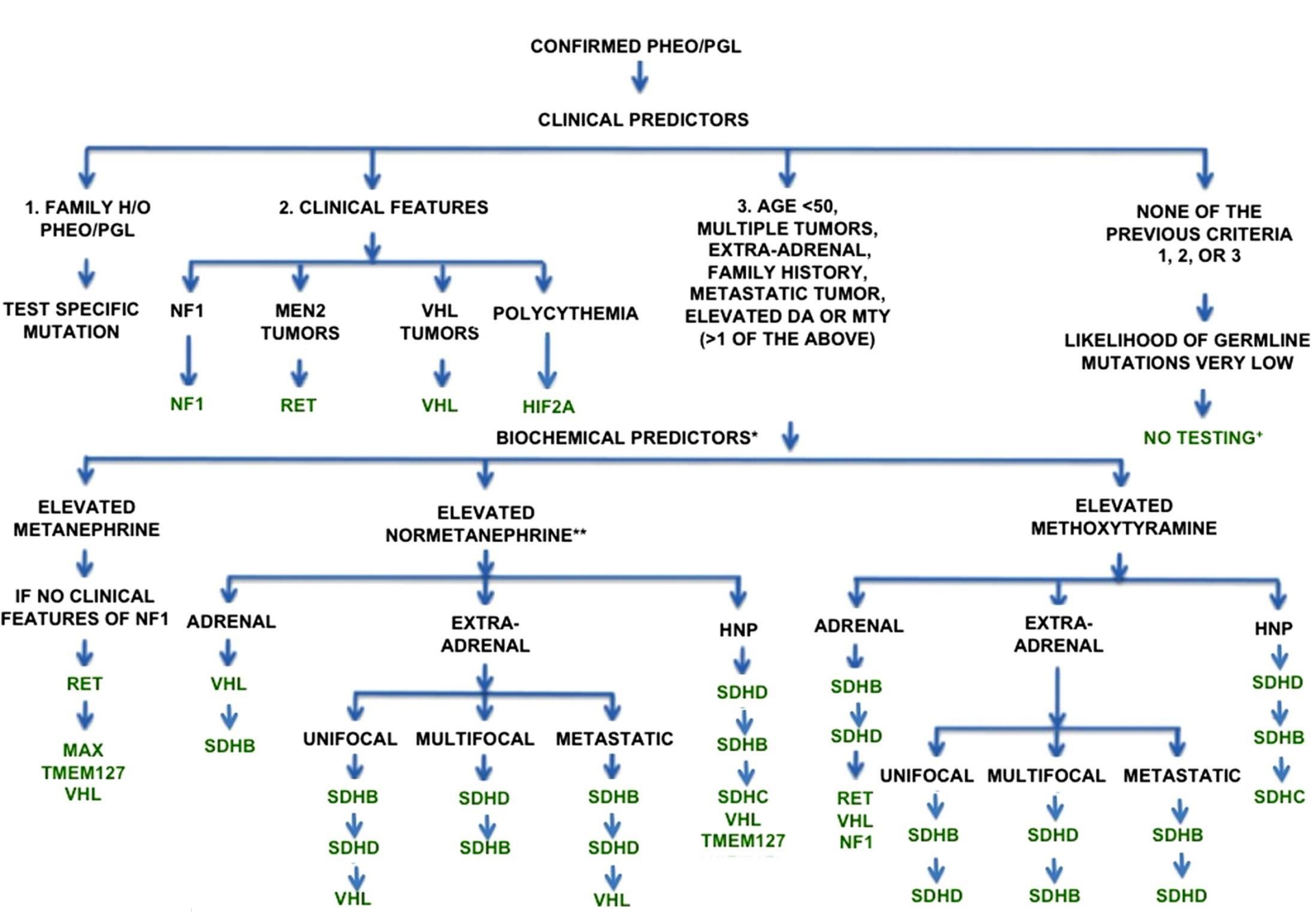


13/29 French-Canadian patients with PGLs (44.8%) carried a germline mutation

9/13 had a *SDHC* gene mutation (c.397C>T, p.[Arg133Ter])

CRCHUM RESEARCH CENTRE

J Clin Endocrinol Metab. 101: 4710-18, 2016



CRCHUM RESEARCH CENTRE

V.L. Martucci, K. Pacak / Curr Probl Cancer 38 (2014) 7–41

Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline

Table 9. Presurgical Medical Preparation

Drug	Starting Time	Starting Dose	Final Dose[b]
Preparation 1			
Phenoxybenzamine	10–14 d before surgery	10 mg b.i.d.	1 mg/kg/d
or Doxazosine	10–14 d before surgery	2 mg/d	32 mg/d
Preparation 2			
Nifedipine[a]	As add-on to preparation 1 when needed	30 mg/d	60 mg/d
or Amlodipine[a]	As add-on to preparation 1 when needed	5 mg/d	10 mg/d
Preparation 3			
Propranolol	After at least 3–4 d of preparation 1	20 mg t.i.d.	40 mg t.i.d.
or Atenolol	After at least 3–4 d of preparation 1	25 mg/d	50 mg/d

Abbreviations: b.i.d., twice daily; t.i.d., three times daily.

[a] Add when blood pressure cannot be controlled by α-adrenoceptor blockade (preparation 1).

[b] Higher doses usually unnecessary.

CRCHUM RESEARCH CENTRE

Lenders JWM et al.J Clin Endocrinol Metab 99: 1915–1942, 2014

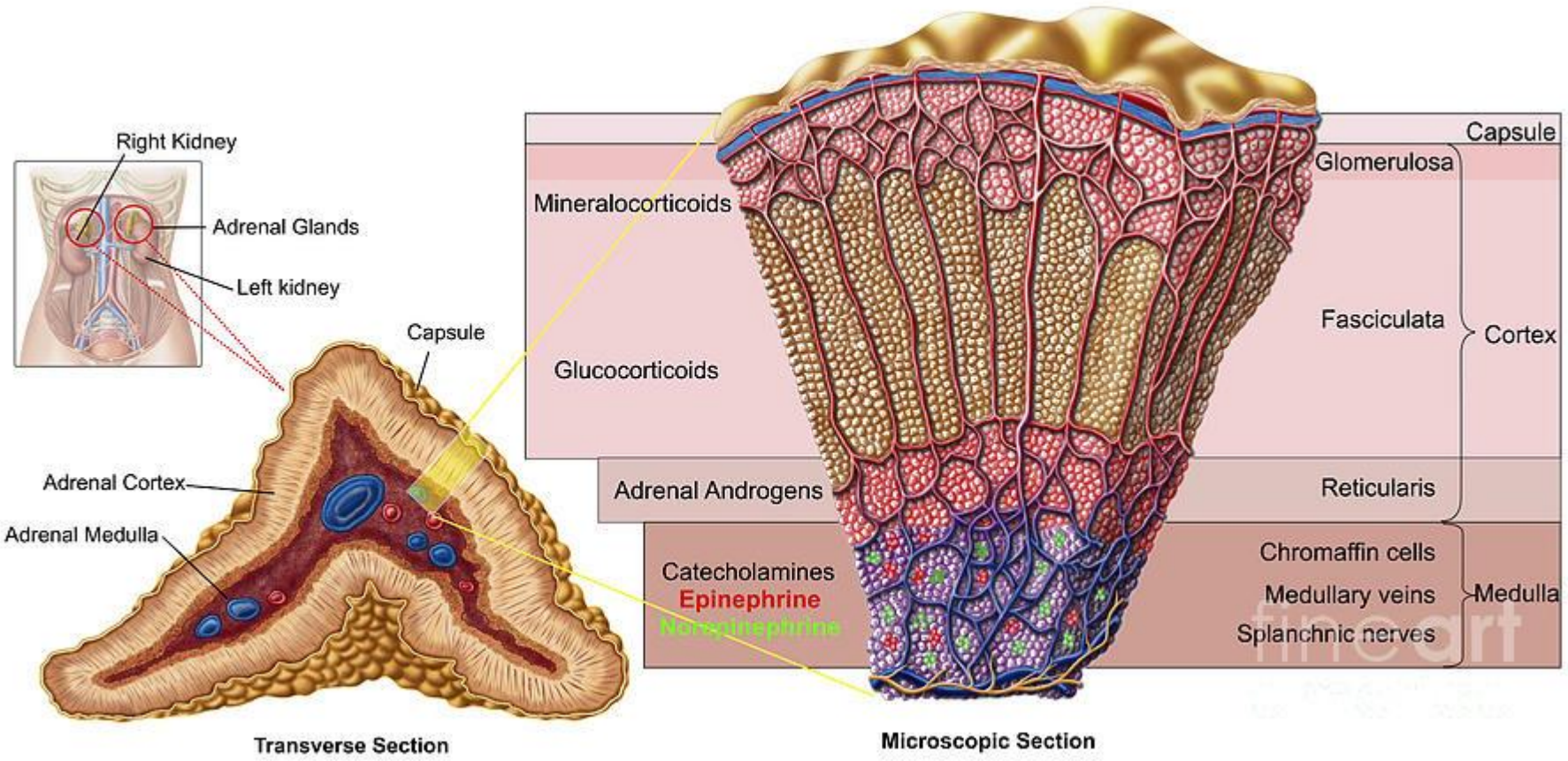
TABLE IV Screening and follow-up recommendations for risk of pheochromocytoma or paraganglioma in mutation carriers

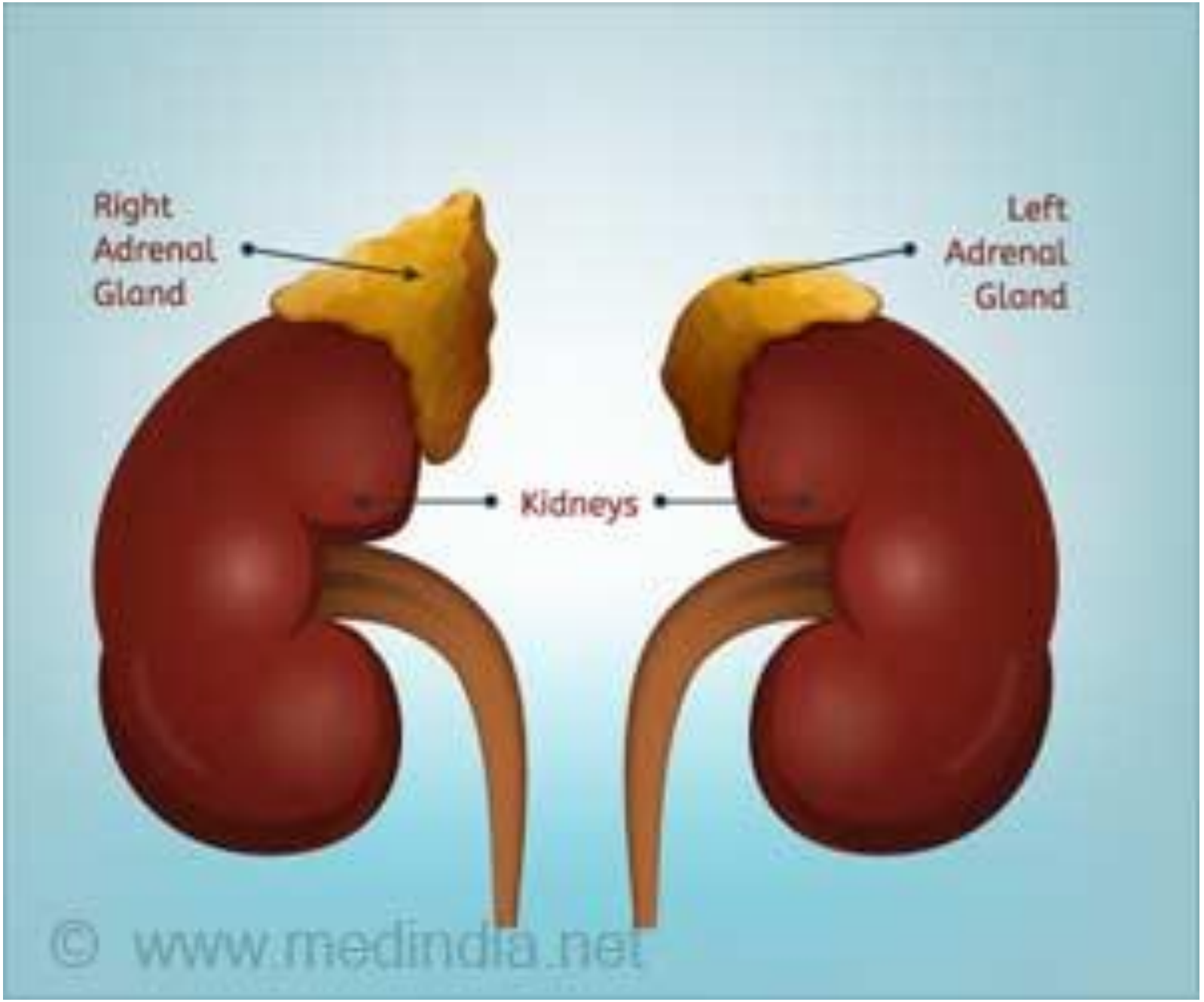
Recommendation	*Susceptibility gene*			*Syndrome*		
	SDHB	SDHC	SDHD	VHL	MEN2	NF1
Age to begin screening (years)	5–10	5–10	5–10	5	8–20	5
Physical exam and BP	Every 6–12 months	Every 6–12 months	Every 6–12 months	Annually	Annually	Annually
Urinary excretion of fractionated metanephrines and catecholamines in 24 hours	Annually	Annually	Annually	Annually after age 11	Annually	If abnormal BP
MRI–CT of abdomen, thorax, and pelvis	Every 6–24 months	Every 1–4 years	Every 1–4 years	If abnormal biochemistry	If abnormal biochemistry	If abnormal biochemistry
MRI–CT of skull base and neck	Every 2–4 years	Every 6–36 months	Every 6–36 months	—	—	—
Periodic MIBG scintigraphy	Every 2–4 years	Every 1–4 years	Every 1–4 years	—	—	—
Screening for renal cell carcinoma	Consider	—	—	Abdominal US or MRI annually after age 16	—	—

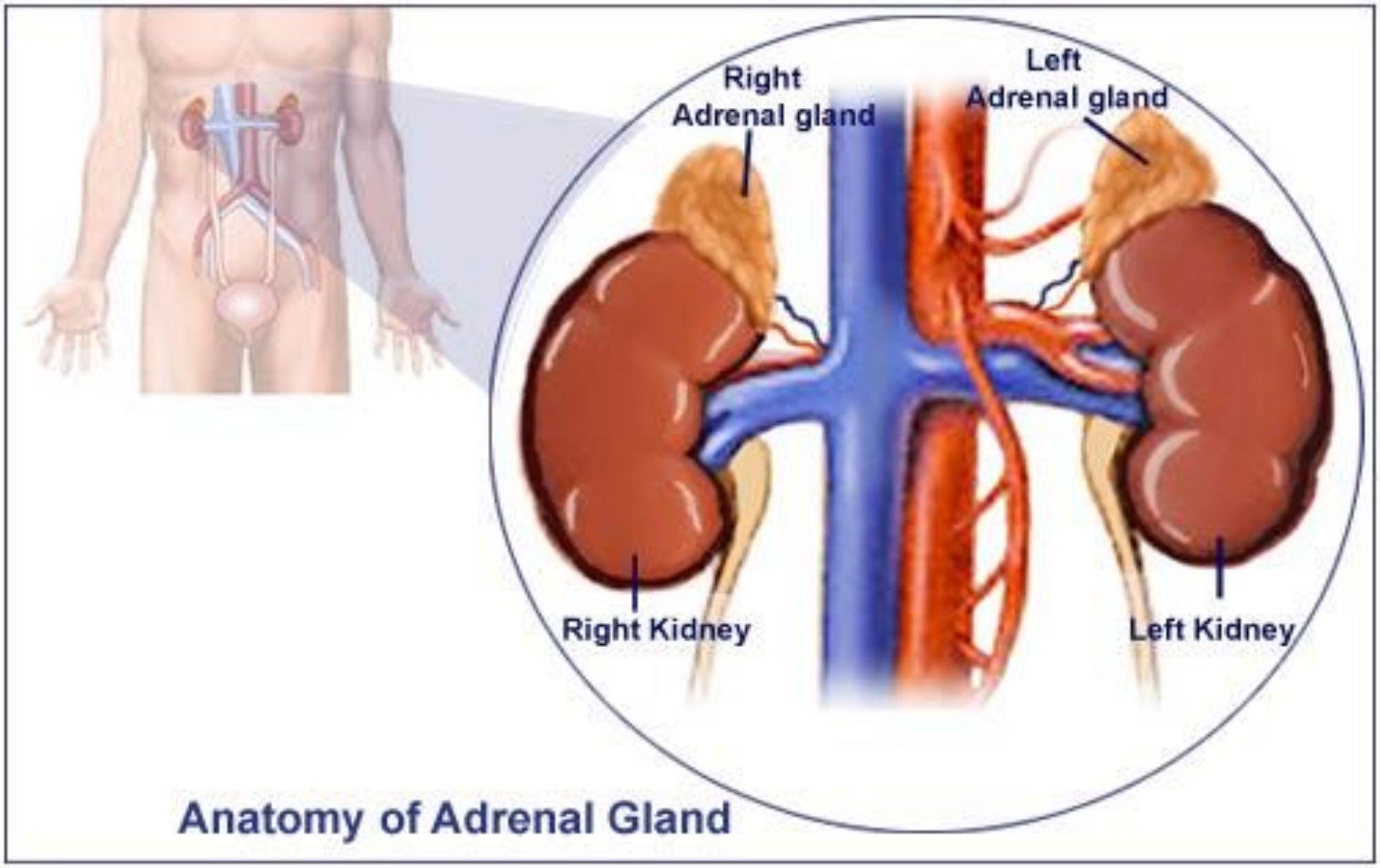
BP = blood pressure; MRI = magnetic resonance imaging; CT = computed tomography; MIBG = metaiodobenzylguanidine; US = ultrasonography.

CRCHUM RESEARCH CENTRE

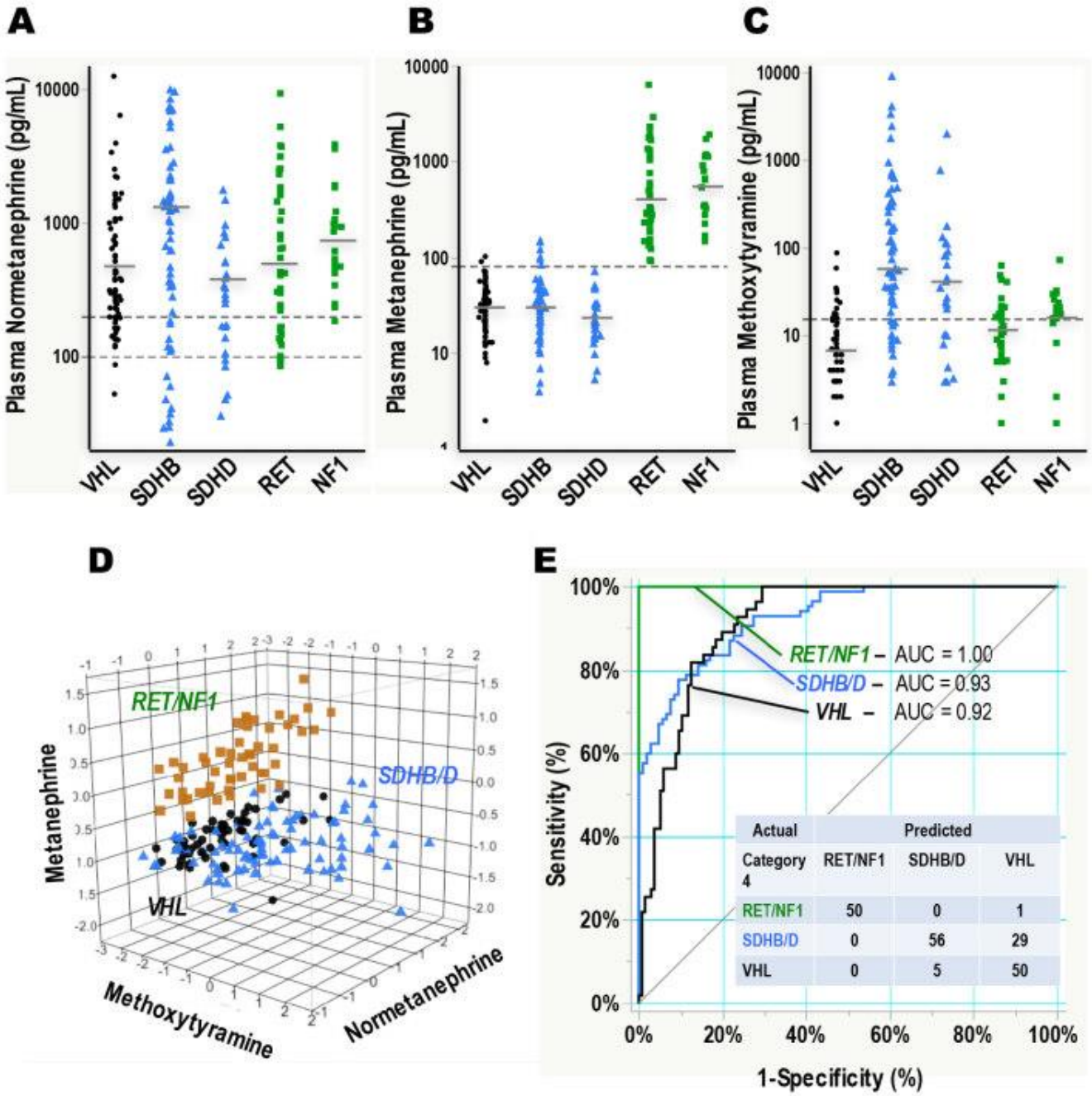
Lefebvre and Foulkes, Current Oncology, 21, 8-17, 2014


Right Kidney
Adrenal Glands
Left kidney
Capsule
Adrenal Cortex
Adrenal Medulla
Transverse Section
Capsule
Glomerulosa
Mineralocorticoids
Fasciculata
Cortex
Glucocorticoids
Adrenal Androgens
Reticularis
Chromaffin cells
Catecholamines
Medullary veins
Medulla
Epinephrine
Splanchnic nerves
Norepinephrine
Microscopic Section


Right
Adrenal
Gland
Left
Adrenal
Gland
Kidneys
© www.medindia.net



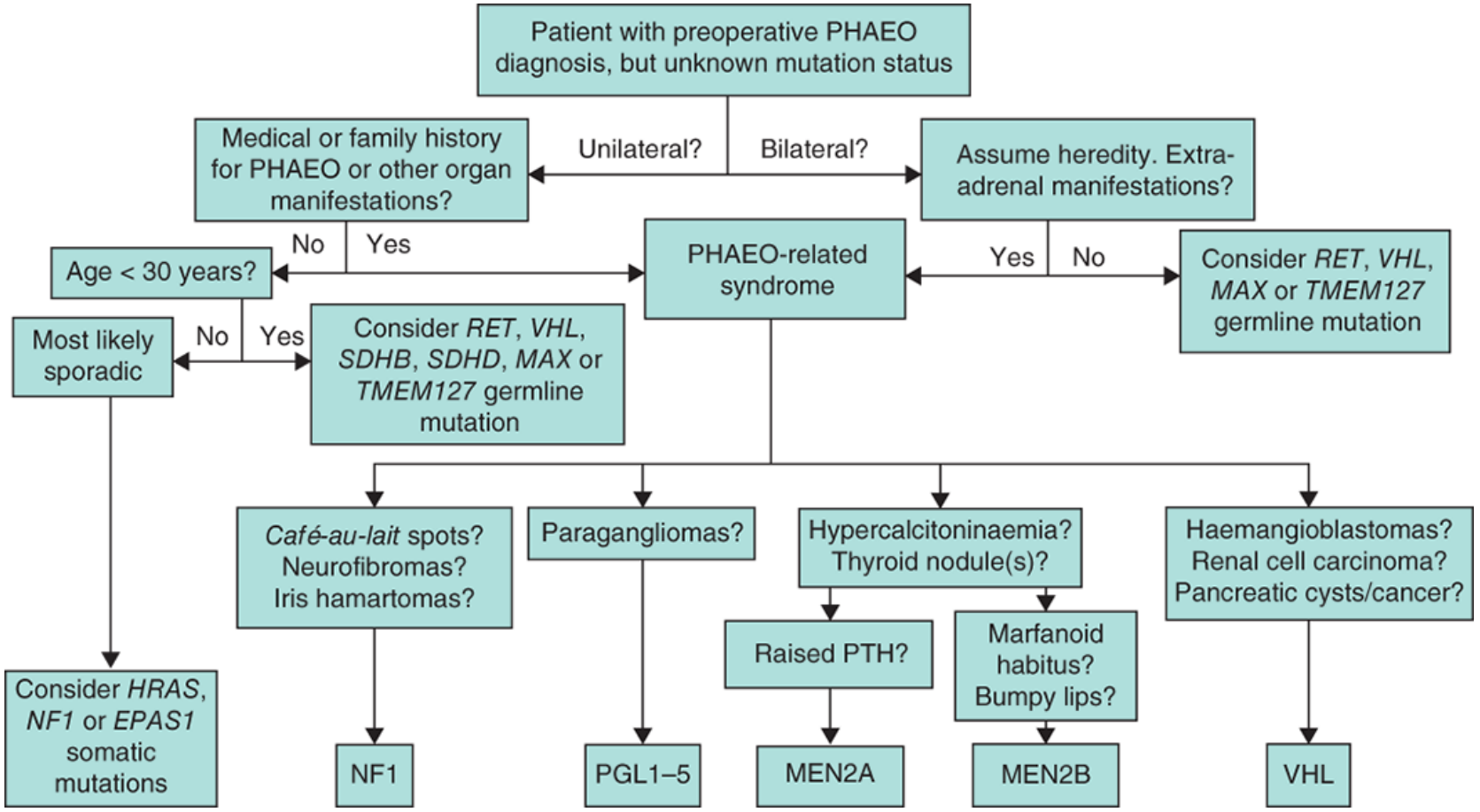
Anatomy of Adrenal Gland



CRCHUM RESEARCH CENTRE

Eisenhofer et al Clin Biochem Rev 38, 69, 2017

Extent of surgery for phaeochromocytomas in the genomic era



CRCHUM RESEARCH CENTRE

Rossitti HM, Söderkvist P, Gimm O. Br J Surg. 2018 Jan;105(2):e84-e98.

Table 4. Biochemical and Imaging Approach to PPGL

Cluster	Gene	Biochemistry	Functional Imaging	Near Future Developments
Pseudohypoxic, TCA cycle–related	*SDHA* *SDHB* *SDHC* *SDHD* *SDHAF2*	Norepinephrine/normetanephrine, 3-methoxytyramine chromogranin A	^{68}Ga-DOTATATE PET/CT	Metabolite profiling, MR spectroscopy
	FH			
Pseudohypoxic *VHL/EPAS1*-related	*VHL*-related	Norepinephrine/normetanephrine	VHL-related should have similar imaging as EPAS 1 related = 18F-DOPA PET/CT	Hypoxia imaging
	EPAS1-related		^{18}F-DOPA PET/CT (*EPAS1*)	
Wnt signaling	*CSDE1*	Norepinephrine/normetanephrine, epinephrine/metanephrine	Optimal tracer unknown	
	MAML3			
Kinase signaling	*RET* *NF1* *MAX*	Norepinephrine/normetanephrine, epinephrine/metanephrine	^{18}F-DOPA PET/CT	
	TMEM127			
	HRAS			

Abbreviations: DOPA, dihydroxyphenylalanine; FDG, fluorodeoxyglucose.

CRCHUM RESEARCH CENTRE

Crona J, Taieb D and Pacak K Endocrine Reviews 38: 489, 2017

Adrenal neuroendocrine tumors TNM staging AJCC UICC 2017

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T1	PH <5 cm in greatest dimension, no extra-adrenal invasion
T2	PH ≥5 cm or PG-sympathetic of any size, no extra-adrenal invasion
T3	Tumor of any size with invasion into surrounding tissues (eg, liver, pancreas, spleen, kidneys)
NOTE: Parasympathetic paragaglioma are not staged because they are largely benign.	

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Regional lymph node metastasis

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis to only bone
M1b	Distant metastasis to only distant lymph nodes/liver or lung
M1c	Distant metastasis to bone plus multiple other sites

Prognostic stage groups

Pheochromocytoma/sympathetic paraganglioma

When T is...	And N is...	And M is...	Then the stage group is...
T1	N0	M0	I
T2	N0	M0	II
T1	N1	M0	III
T2	N1	M0	III
T3	Any N	M0	III
Any T	Any N	M1	IV

PH: pheochromocytoma; PG: paraganglioma.

PH: within adrenal gland; PG-sympathetic: functional; PG-parasympathetic: nonfunctional, usually in the head and neck region.

Classifications of tumor severity and extent for head and neck neck paragangliomas

Fisch classification [1,2]	
Class A	Tumors that arise along the tympanic plexus on the cochlear promontory
Class B	Tumors with invasion of hypotympanon; cortical bone over jugular bulb intact
Class C_1	Tumors with encroachment of the carotid foramen, but no invasion of the carotid artery
Class C_2	Tumors with destruction of the vertical carotid canal
Class C_3	Tumors that invade the horizontal portion of the carotid canal, but do not reach the foramen lacerum
Class C_4	Tumors with growth to foramen lacerum and along the carotid artery and the cavernous sinus
Class $De_{1/2}$	Tumors with intracranial but only extradural extension; $De_{1/2}$ according to displacement of dura (De_1 = less than 2 cm, De_2 = more than 2 cm)
Class $Di_{1/2/3}$	Tumors with intracranial and intradural extension; $Di_{1/2/3}$ according to depth of invasion into posterior cranial fossa (Di_1 = less than 2 cm, Di_2 = between 2 and 4 cm, Di_3 = more than 4 cm
Jackson/Glasscock classification [3]	
Type 1	Small tumor involving the jugular bulb, middle ear, and mastoid process
Type 2	Extending under internal auditory canal; may have intracranial extension
Type 3	Extending into petrous apex; may have intracranial extension
Type 4	Extending beyond petrous apex into clivus or infratemporal fossa; may have intracranial extension

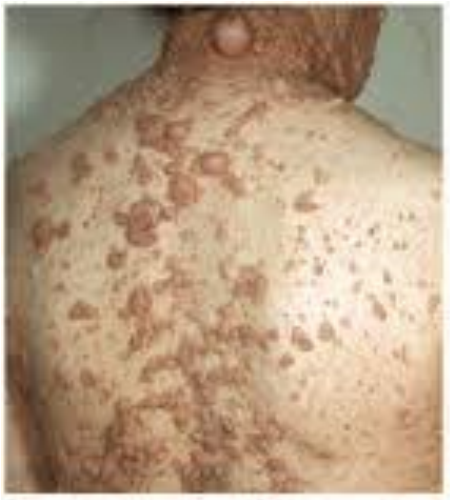
References:

1. *Fisch U, Mattox D. Microsurgery of the skull base. Thieme, Stuttgart-New York, 1988, page 149.*
2. *Boedeker CC. Paragangliomas and paraganglioma syndromes. GMS Curr Top Otorhinolaryngol Head Neck Surg 2011; 10:Doc03.*
3. *Jackson CG, Glasscock ME 3rd, Harris PF. Glomus Tumors. Diagnosis, classification, and management of large lesions. Arch Otolaryngol 1982; 108:401.*

Neurofibromatosis type 1: *NF1* (von Recklinghausen disease)

TABLE III Clinical diagnostic criteria for neurofibromatosis type 1 (NF1) (note that pheochromocytoma is not listed)

Criterion (must fulfil at least 2)	*Proportion of NF1 patients (%)*
Six or more café-au-lait spots 1.5 cm or larger in postpubertal individual 0.5 cm or larger in prepubertal individual	86.7
Two or more neurofibromata of any type or one or more plexiform neurofibromata	89
Freckling in the axilla, neck, or groin	83
Optic glioma	—
Two or more Lisch nodules	63
Distinctive bony lesion (dysplasia of sphenoid bone or long-bone cortex)	—
A first-degree relative with NF1	71



CRCHUM RESEARCH CENTRE

Lefebvre and Foulkes, Current Oncology, 21: 2014