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Pheochomocytoma & Paraganglioma

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Target Audience: Patients and Care Givers

Disclosures: No biases other than I'm an endocrinologist

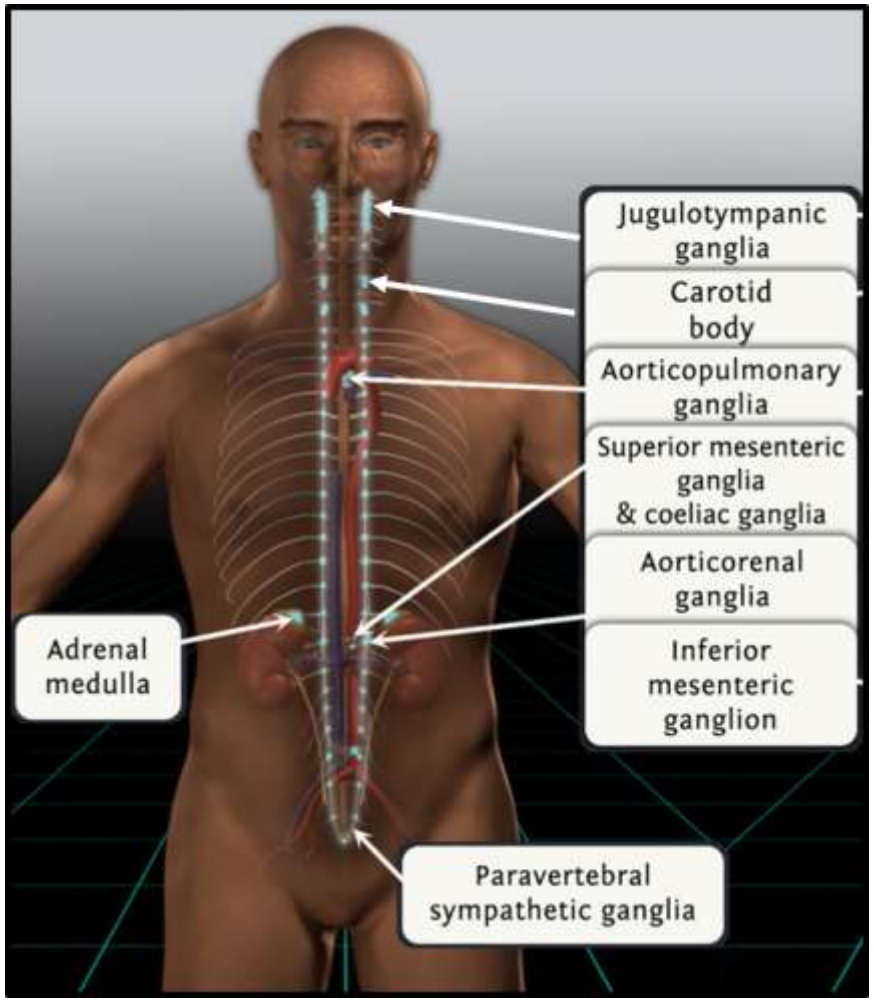
ABCs of Pheochromocytomas&Paragangliomas =PPGL

PPGL are rare neuroendocrine tumors of chromaffin cells

2-8 cases/1 mil./year

Pheochomocytomas arise from the inner portion of adrenal gland

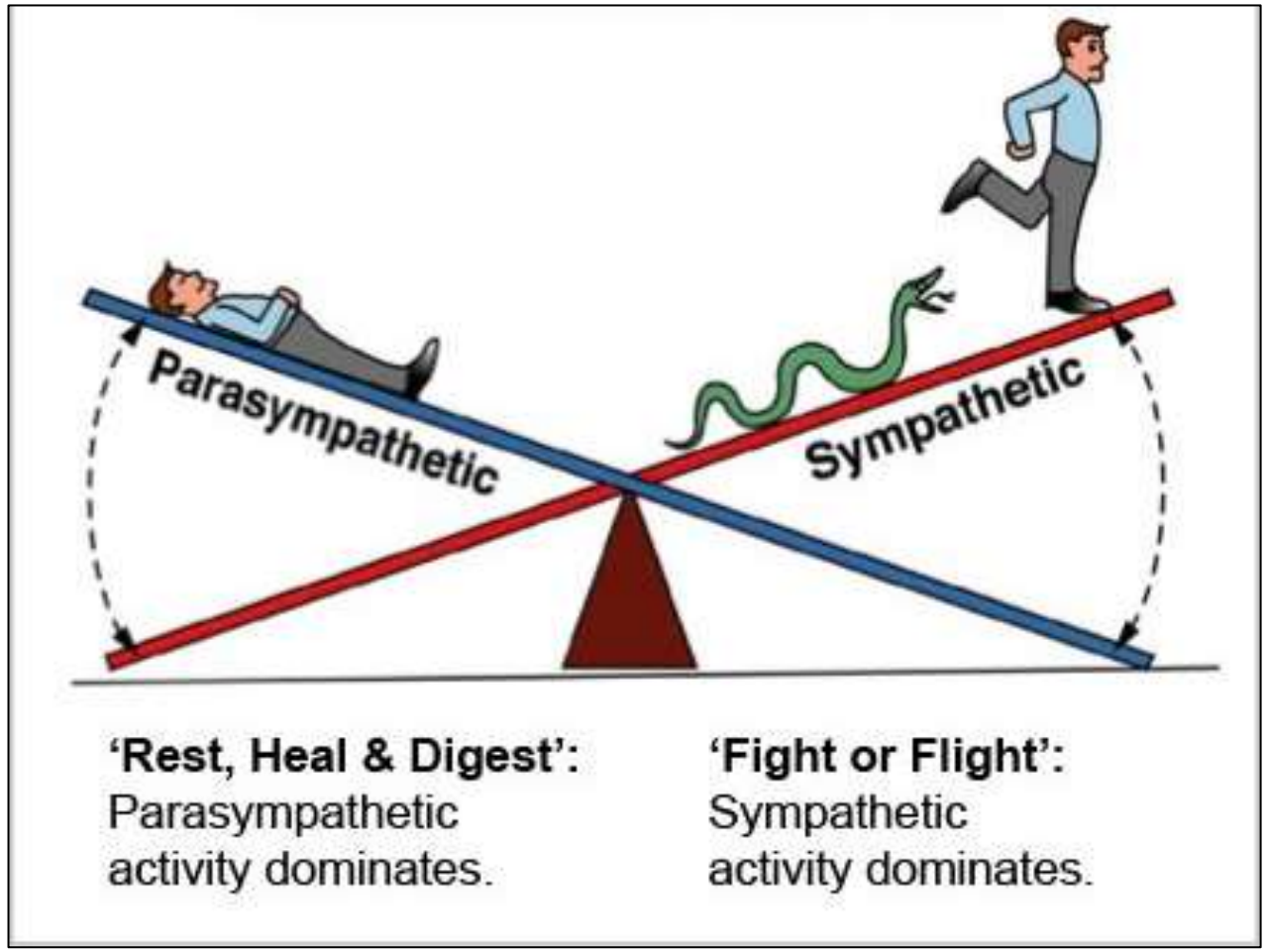
Paragangliomas arise from the special structures called ganglia.

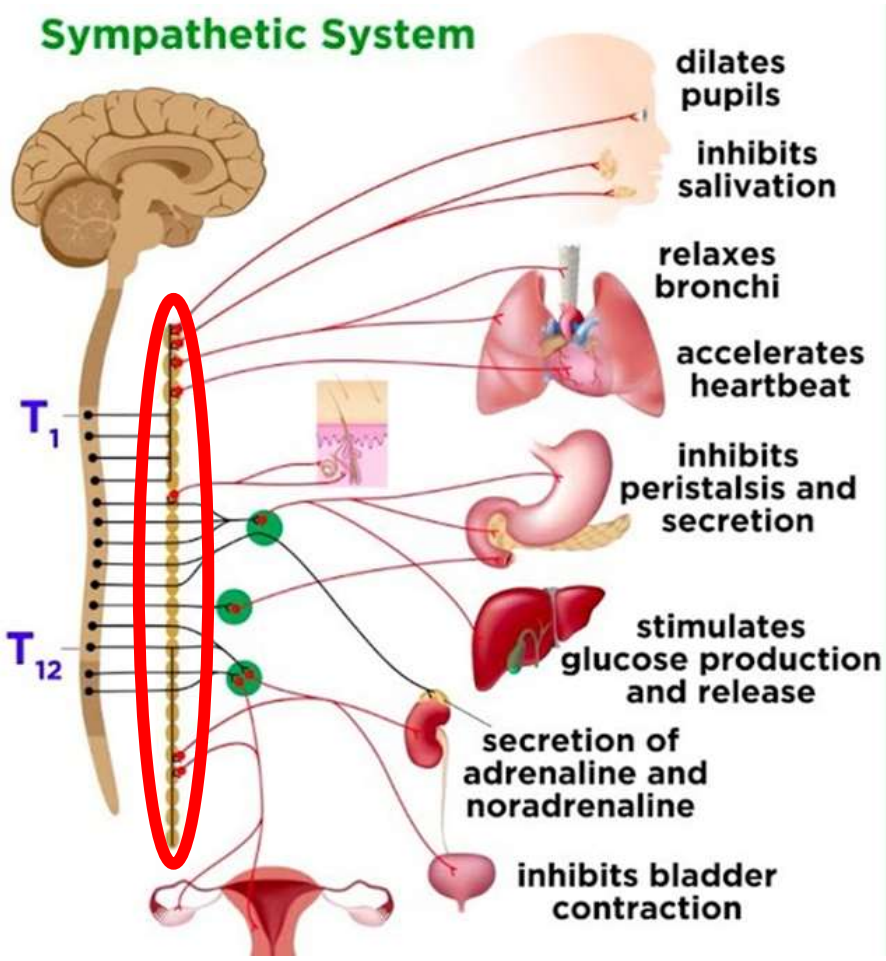


Autonomic Nervous System

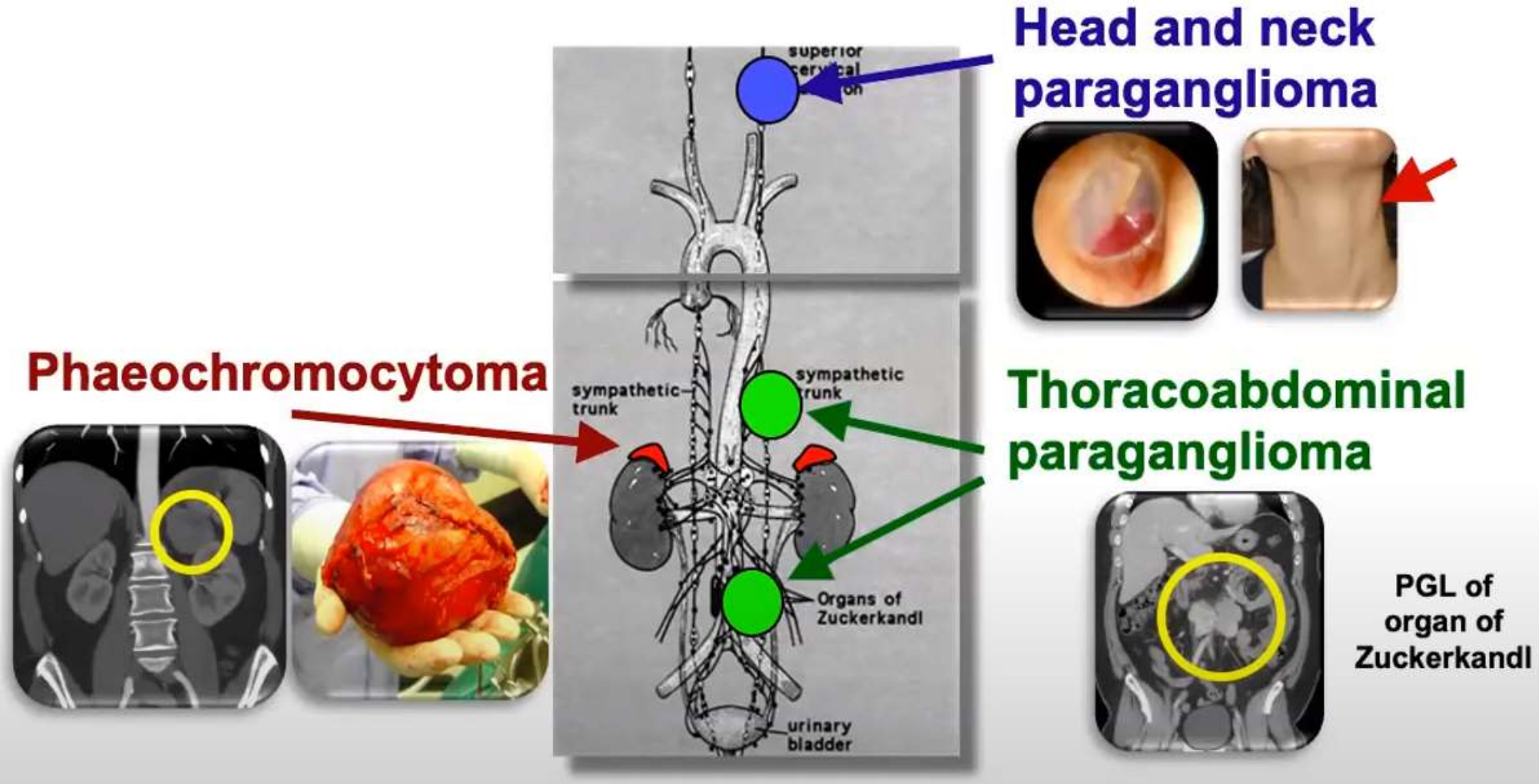
Autonomic Nervous System

= **involuntary** part of neuron network that coordinates internal body organs function.

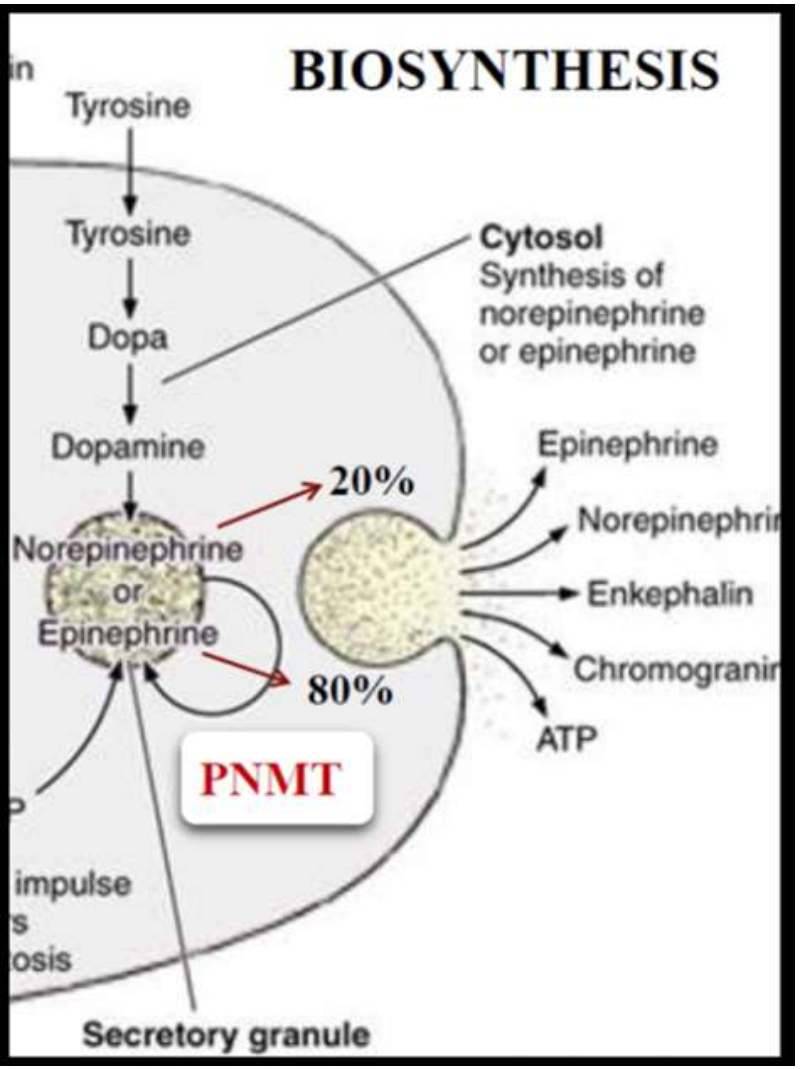


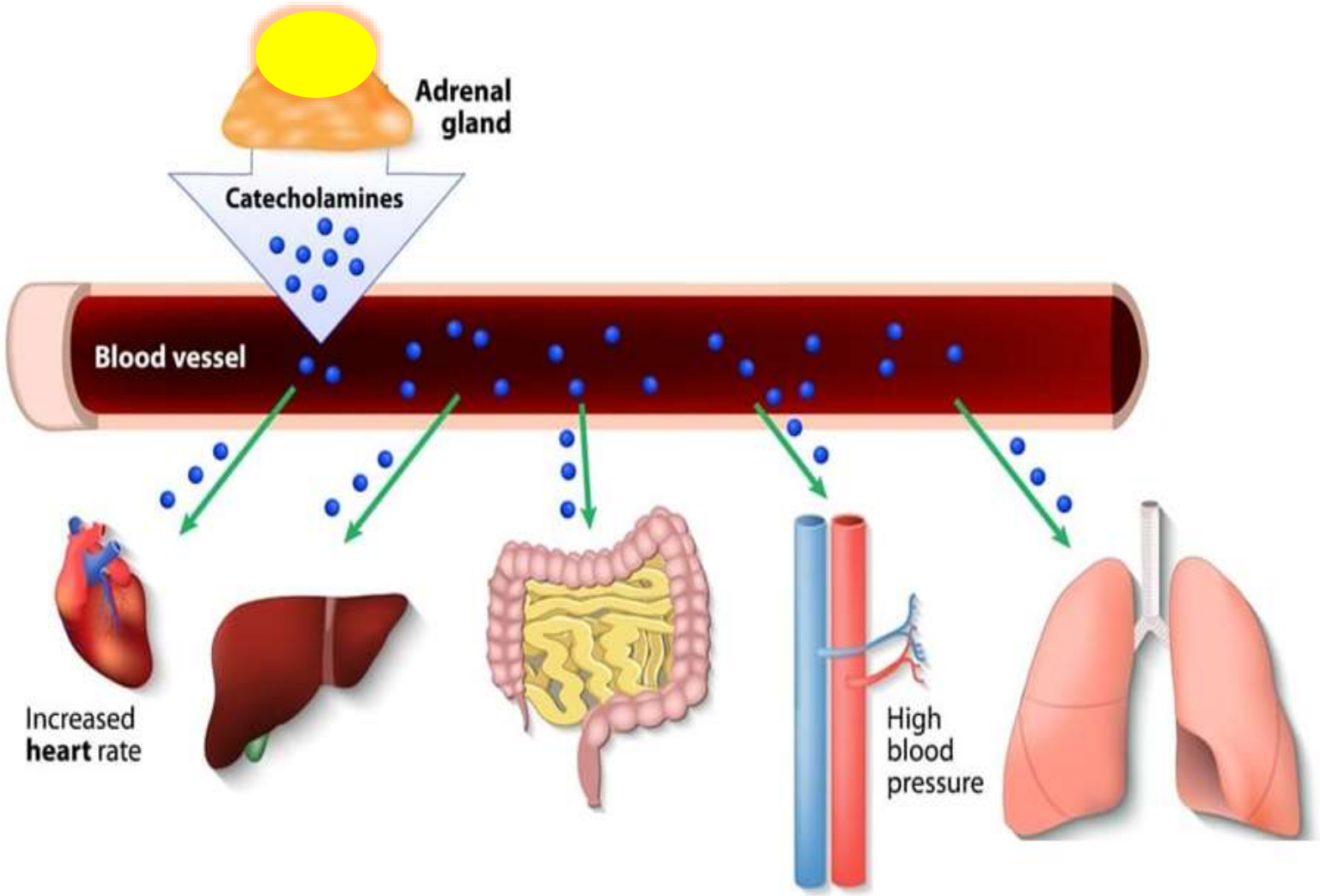


Pheochromocytomas versus Paragangliomas



PPGL produce cathecholamines





PPGL manifestations = hormonal excess

Weight loss

PANIC ATTACK-TYPE SYMPTOMS

Abdominal discomfort

Tremors

NERVOUSNESS

Constipation

Nausea

Chest pain

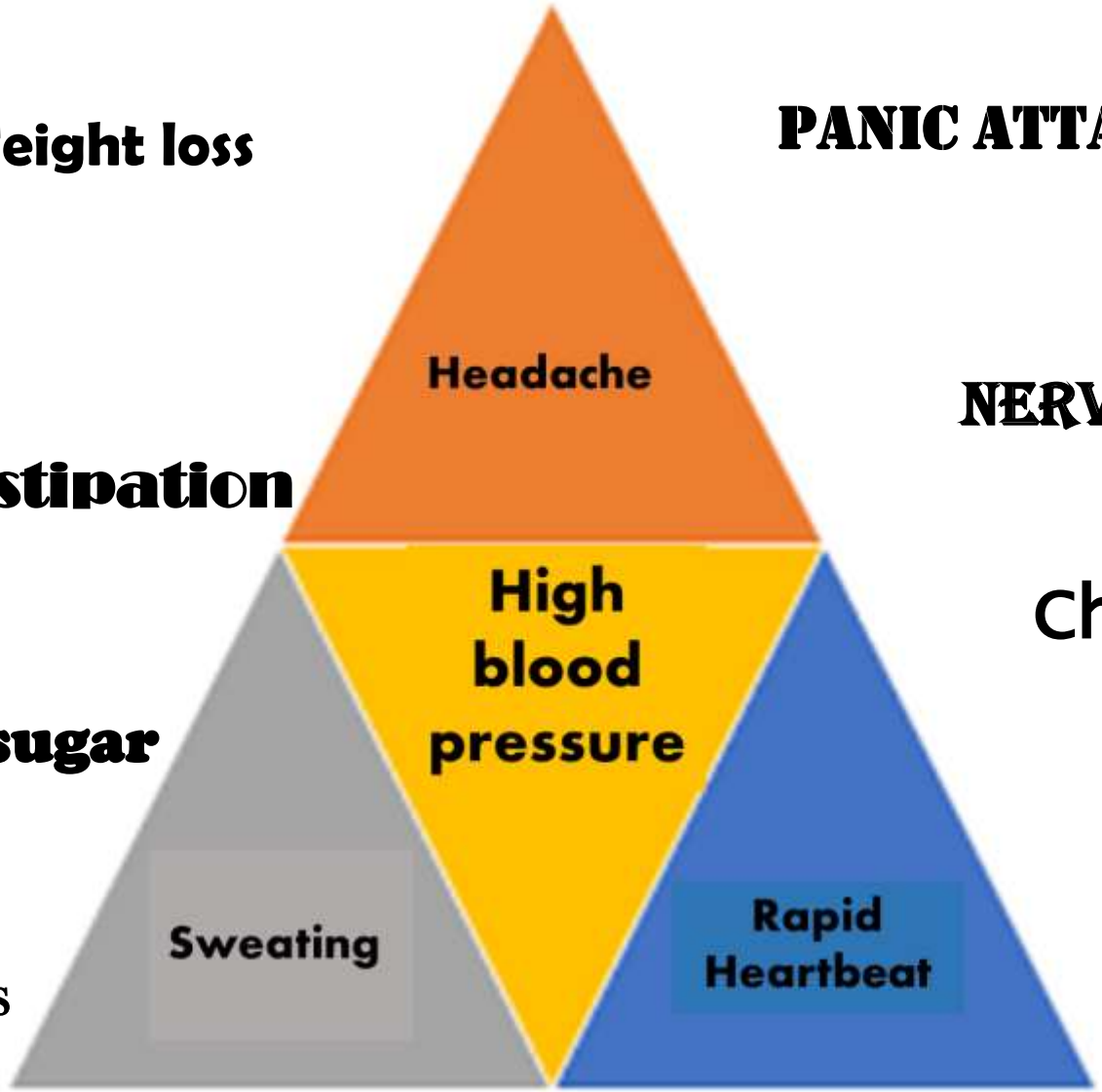
Pallor

High blood sugar

Weakness

Abnormal response to certain medications

Heat intolerance



Pheo “spells”

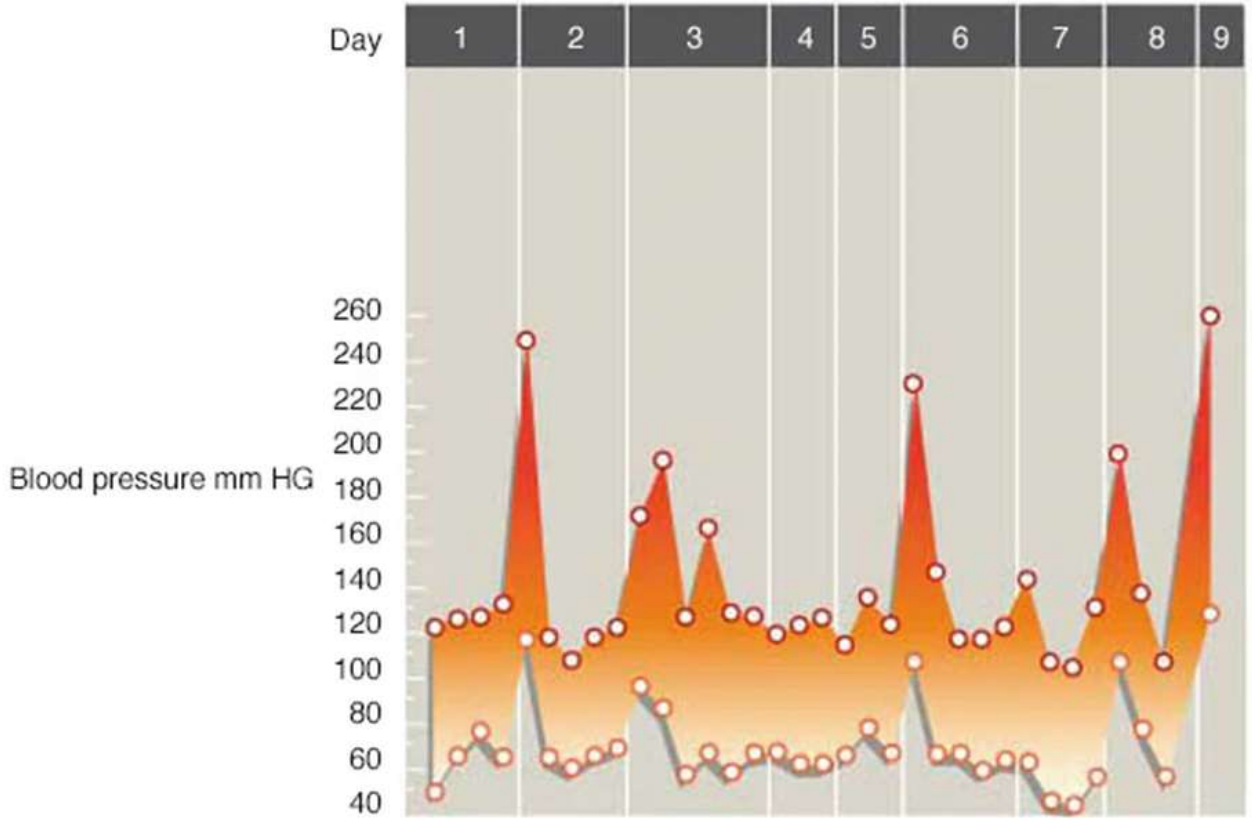
“Pheo attacks” or “spells” – episodes of sudden symptoms caused by rapid influx of cathecholamines into the blood system

Attack duration: 20-30 min

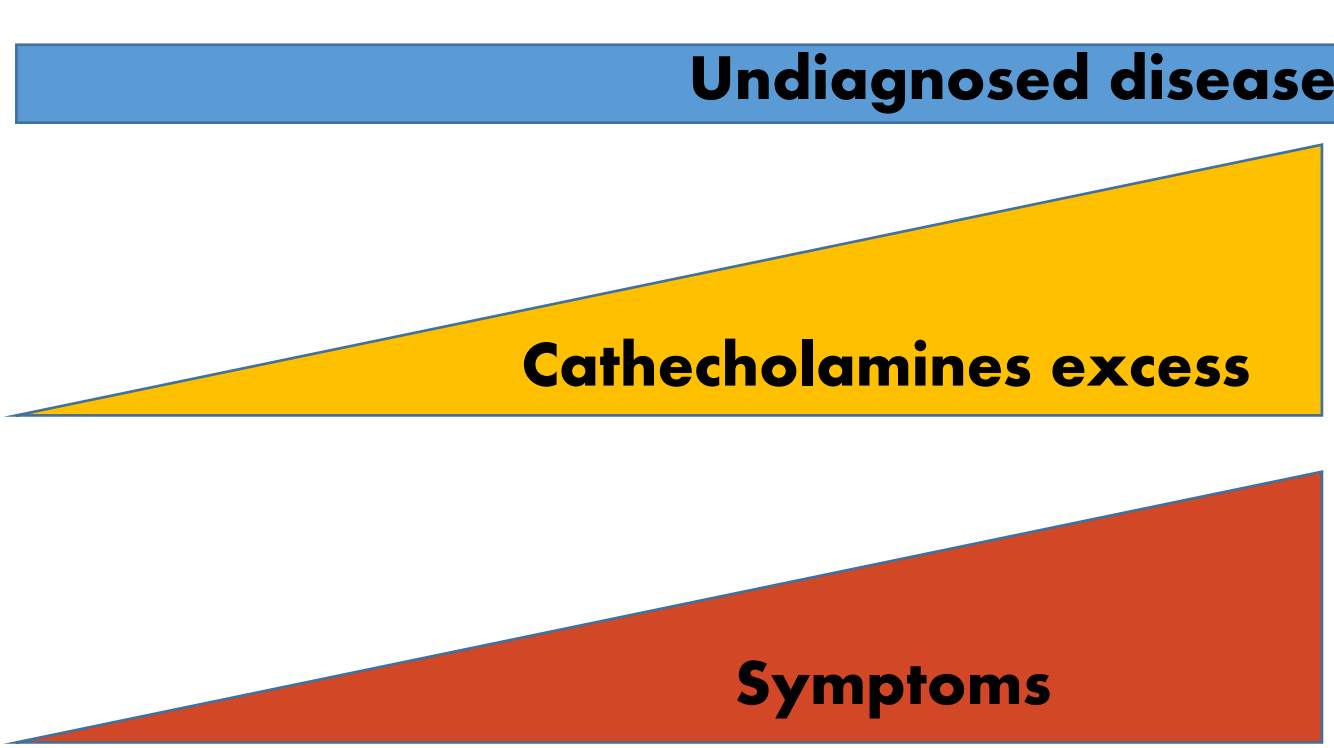
Frequency: daily to once every few month

Spontaneously or may be triggered by:

- **stress**
- **exercise (lifting, straining)**
- **a variety of medications**
- **food**
- **surgery etc.**



Importance of early diagnosis



If untreated PPGL can be fatal!

- Heart attack
- Stroke
- Arrhythmia
- Malignant hypertension (Pheo crisis)

*Tumor metastasis

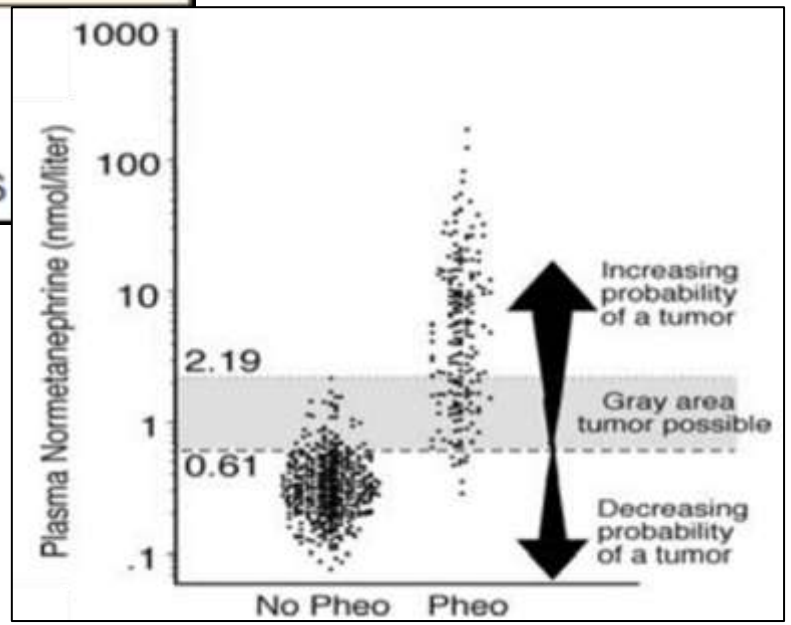
When to suspect PPGL

- Paroxysmal symptoms “Pheo spells”
- Resistant hypertension
- Hypertension onset at a young age
- Abnormal blood pressure response to drugs, anesthesia, surgery
- A family history of PPGL
- A syndrome that predisposes to PPGL (MEN2, VHL, NF1)
- An incidentally discovered adrenal mass (25% of PPGL diagnosis)

PPGL diagnosis and imaging

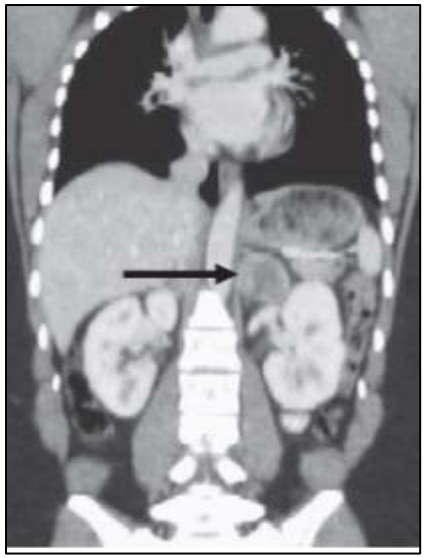
1. Biochemical diagnosis

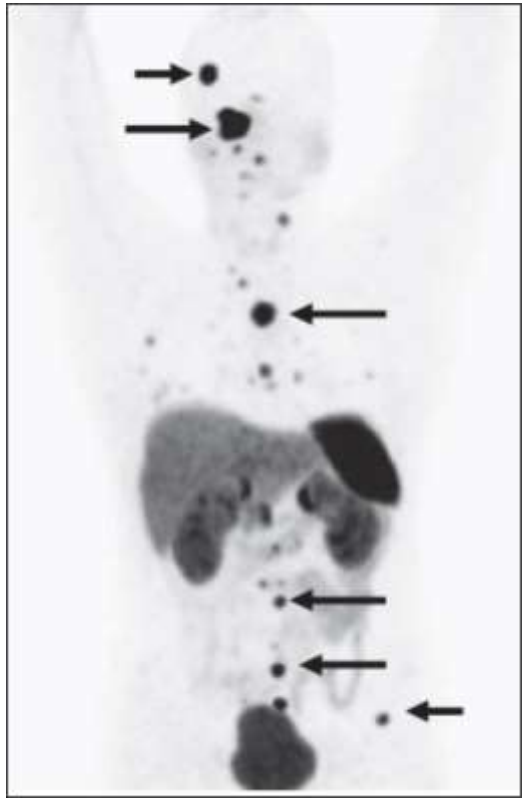
DIAGNOSTIC METHOD
24-h urinary tests
Catecholamines
Fractionated metanephrines
Total metanephrines
Plasma tests
Catecholamines
Free metanephrines



2. Tumor localization

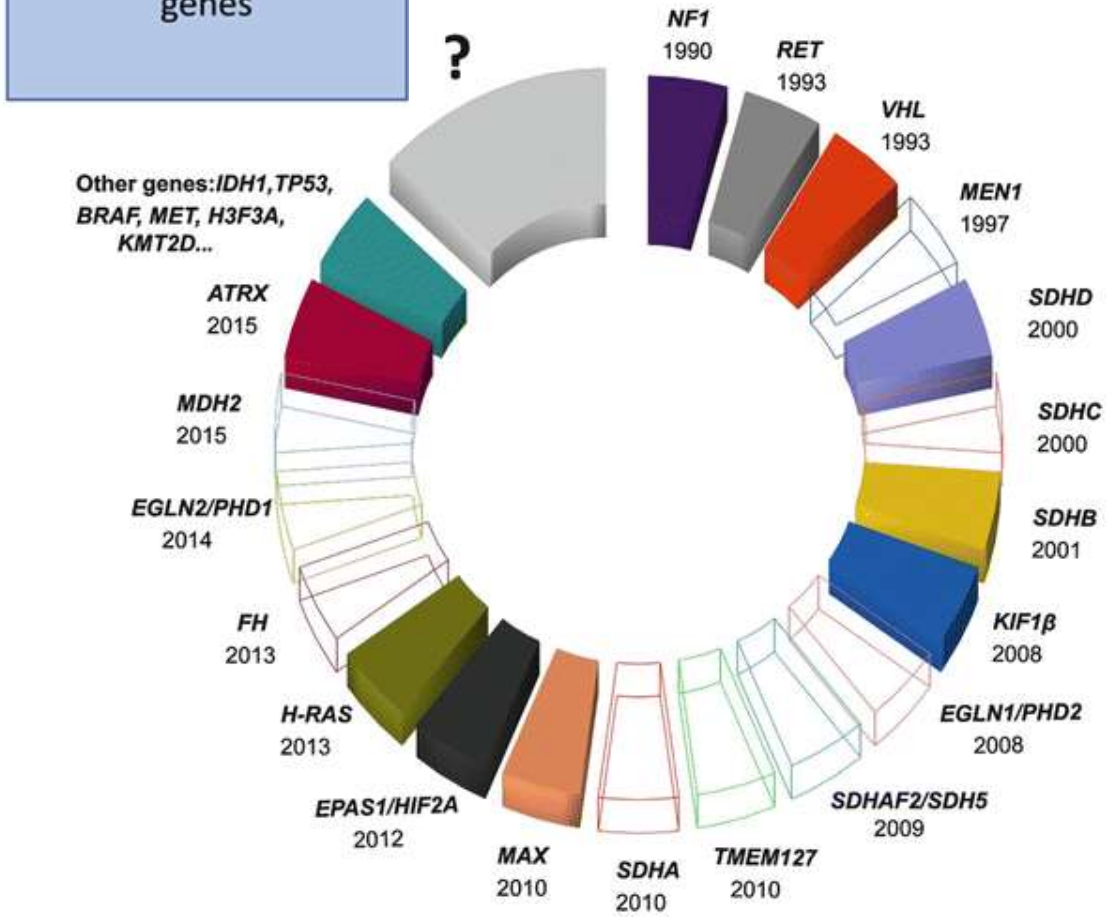
- CT/MRI
- Ga68 DOTATATE PET/CT
- F DOPA PET/CT
- FDG PET/CT



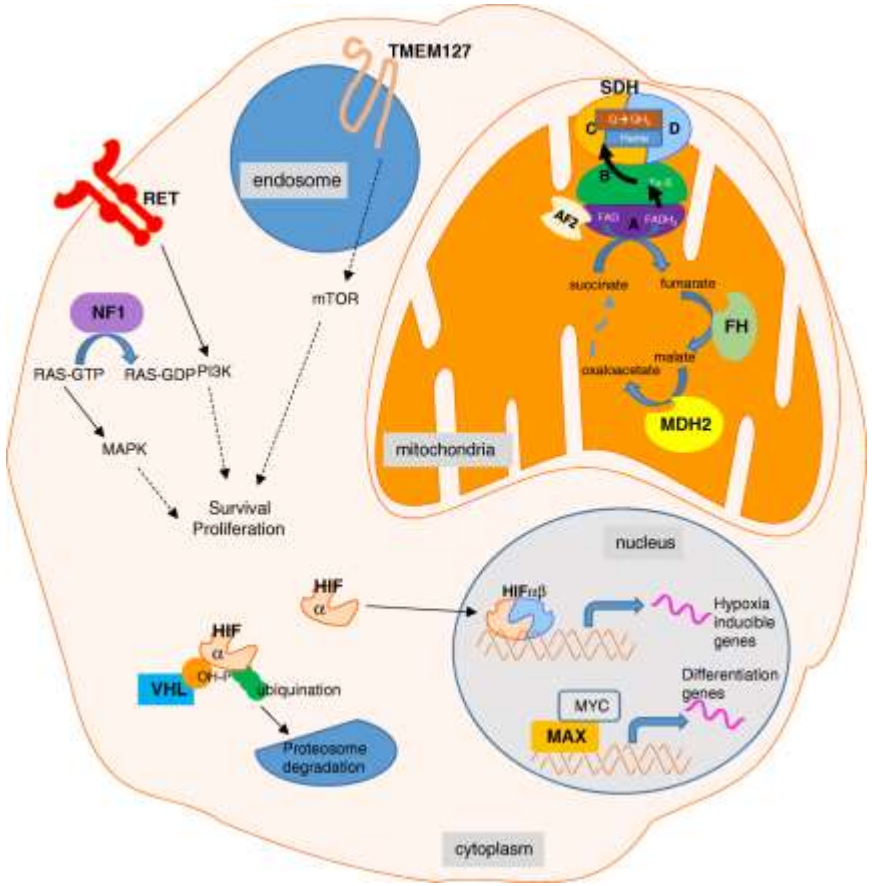


Genetics role in PPGL development

Disease-modifying genes



Chromaffin cell



3 Clusters

- Pseudohypoxia
- Wnt signaling
- Kinase signaling

Fishbein et al. Hypertension 2019

Genetics role in PPGL development

Cluster 1 "pseudo-hypoxia"	Cluster 2 "kinase"	Cluster 3 (or 2B) "Wnt altered"
VHL	RET	MAML3
EPAS1	NF1	CSDE1
PHD1	TMEM127	TP53
IRP	MAX	
SDHD	KIF1B	
SDHB	HRAS	
SDHC	MET	
SDHA	MERTK	
SDHAF2	DNMT3A	
FH	FGFR1	
MDH2	BRAF	
SLC25A11		
GOT2		
IDH1, 2		

1. **Oncogenes**
2. **Tumor suppressors**

RET is a driver in MEN2 syndrome

SDHB accounts for ~40% of metastatic PPGL

Fishbein et al. Hypertension 2019

PPGL have the highest degree of heritability of any other endocrine tumor type

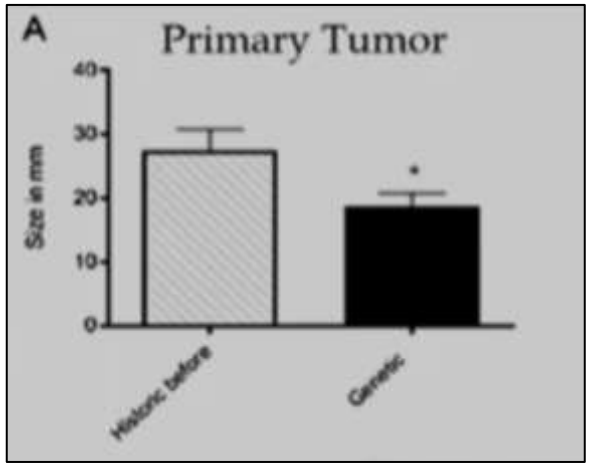
- Germline mutations occur in ~40% of PPGL

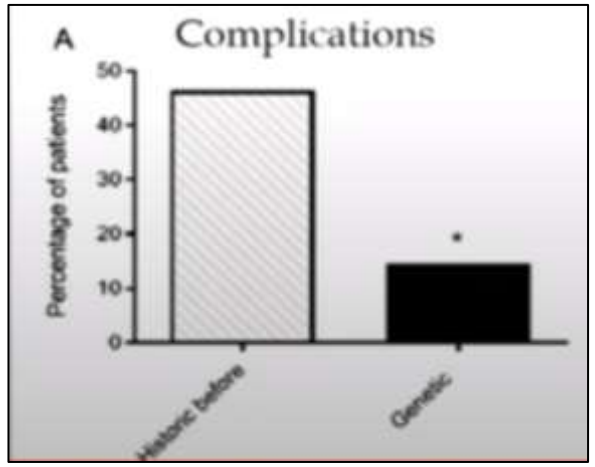
Why genetic testing is important?

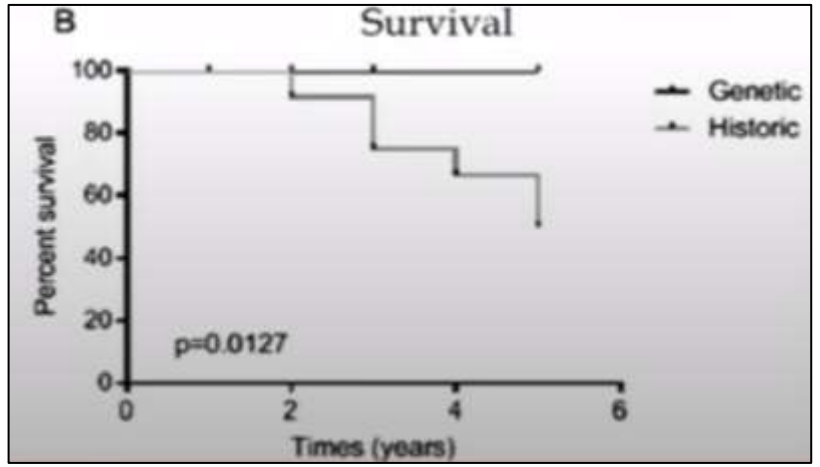
- Risk to develop additional PPGL further in life (~10%) – young age, extra-adrenal locations, germline mutation
- Risk to develop metastatic disease → SDHB, FH, MDH2
- Direct implications for family members

Positive impact of genetic testing (Buffet et al. JCEM 2019)

- Historic group (96 pts) vs. Genetic group (125 pts)

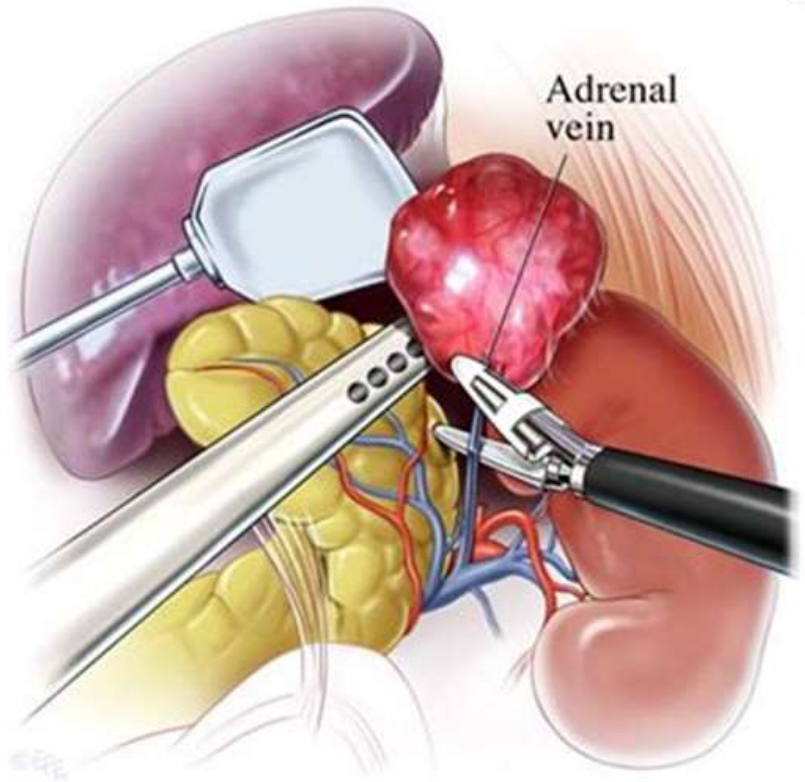




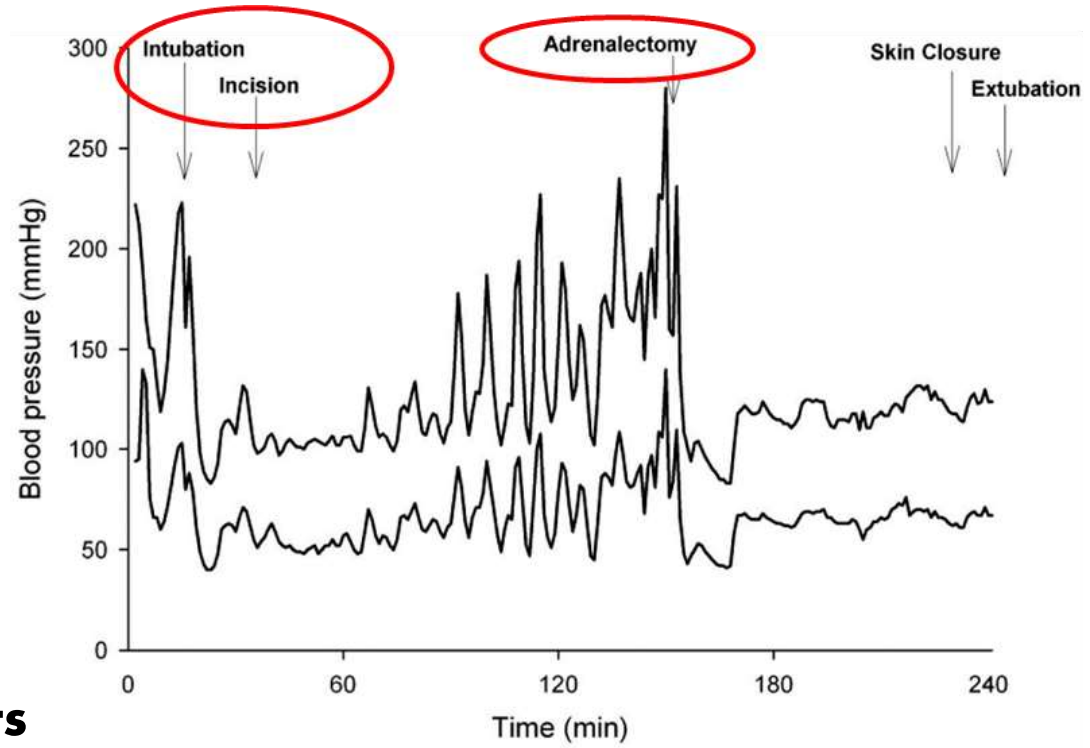


PPGL SURGERY

Complete tumor removal → usually laparoscopic surgery total adrenalectomy (in some familial cases cortical sparing adrenal surgery).



Pre-operative medications: alpha-blockade



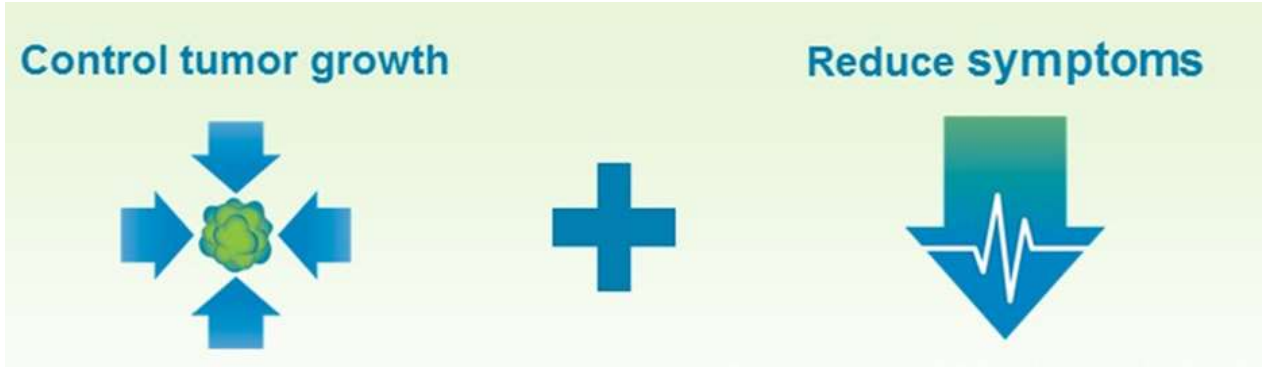
Experienced OR team: surgeons and anesthesiologists

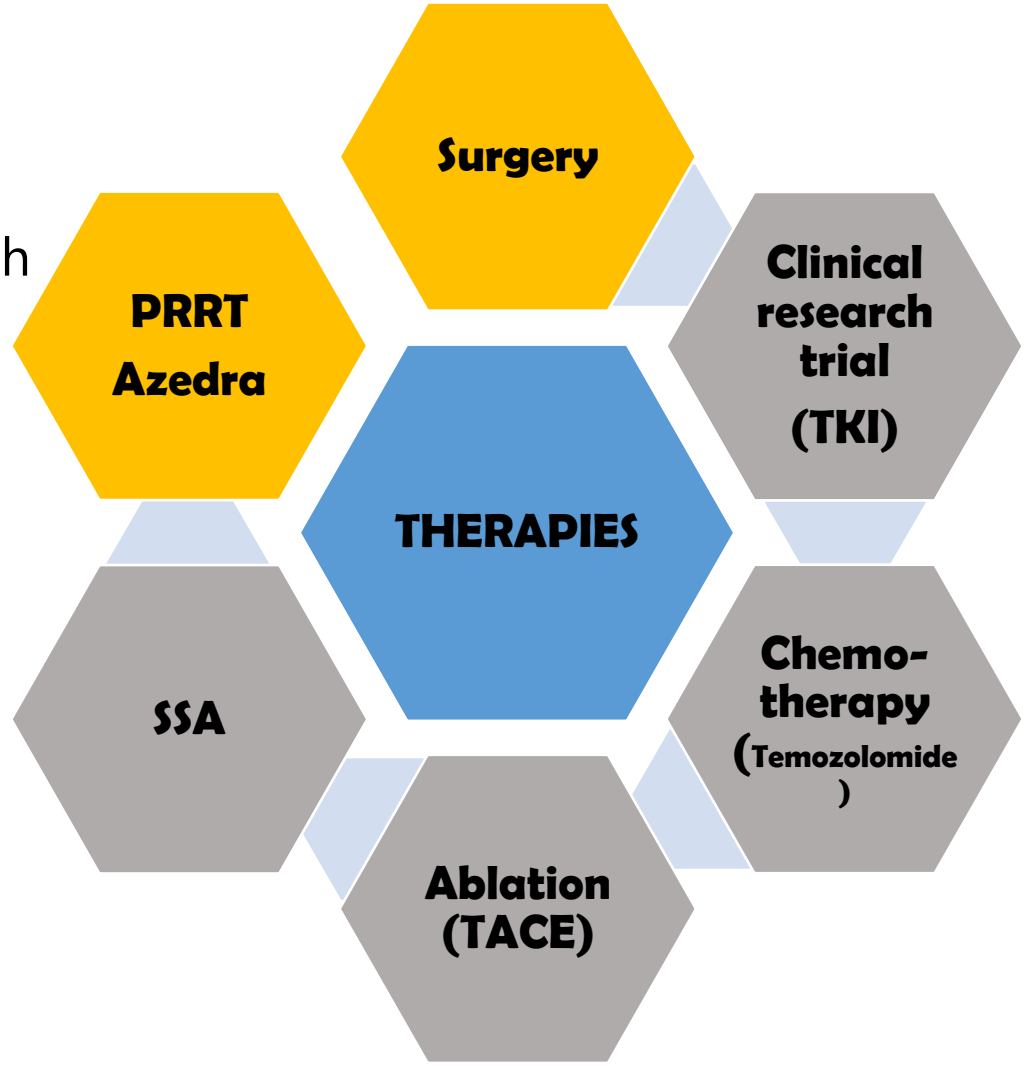
Dijkhuizen et. al Int J Endocrinol Metab (2013)

Metastatic PPGL

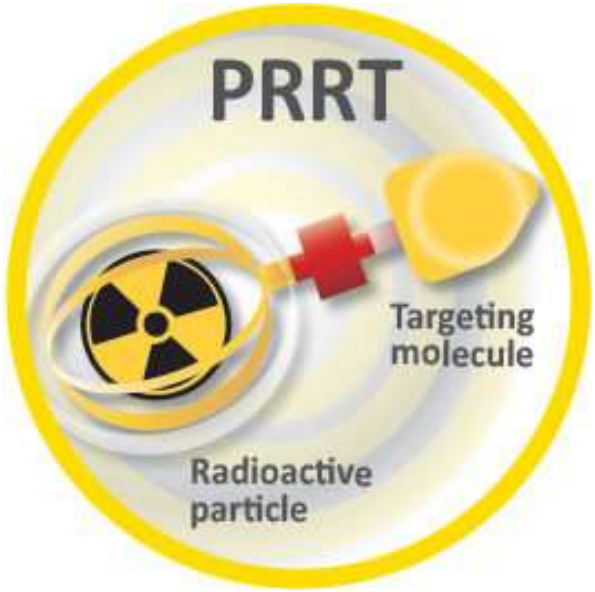
- ~10-15% of PPGL are metastatic at diagnosis
- Tumor progression is the most common cause of death
- Symptoms related to hormonal excess

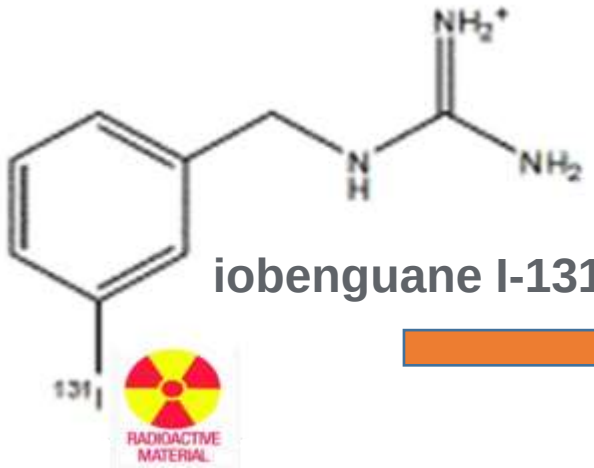
cause up to 30% of malignant PPGL deaths





Targeted radiotherapy for metastatic PPGL





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Study	n	Radiographic response, % of patients		
		PD	SD	MR/PR
Pinato, 2016	5	20	60	20
Forrer, 2008	28	28	46	25
Kong 2017	20	14	50	36
van Essen, 2006	12	25	50	17
Imhof, 2011	39	NS	NS	47
Zovato, 2012	4	0	50	50
Puranik, 2015	9	0	100	0
Nastos, 2017	9	0	100	
Prasad, 2008	20	NS	NS	30
PRRT Compiled Data	146	**12**	**65**	**28**
AZEDRA®	64	4.7	68.8	23.4

Pryma et al. J Nucl Med 2019
Mak et al. Neuroendocrinology 2019

Take away message

- **PPGL are rare tumors, but *not so rare in specialized centers***
- **High *mortality rate with delayed diagnosis* / inappropriate treatment**
- **Most *PPGL can be cured***
- **Experienced OR team is critical for *safe surgery***
- ***Genetic testing* strongly recommended in all cases**
- **Life *long follow-up***
- ***Individualized approach* for patients with metastatic PPGL**

Nothing about rare disease is

simple – not the diagnosis

not the management

not the long term care

Thank you for your attention