BILATERAL PHAEOCHROMOCYTOMA & PARAGANGLIOMA

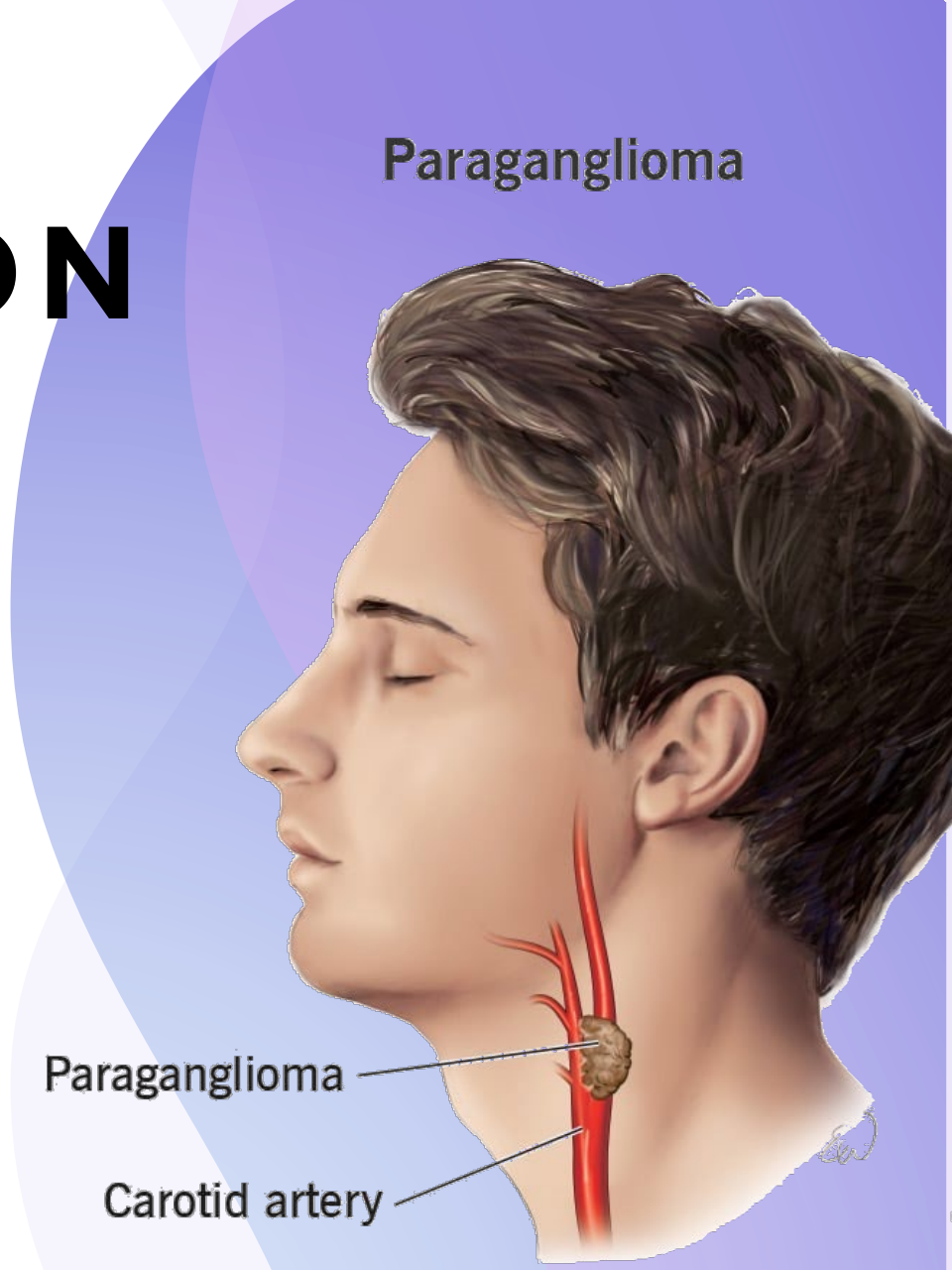
Carol Lai

NTEC Endocrine Surgery

CASE PRESENTATION

75/M

- PMH
  - Bilateral carotid body tumors with excision done in 1998 and 2000, Pathology: benign paraganglioma (2.8 and 3.2cm)
  - Gastric GIST with endoscopic resection done in 1/2019
  - Chronic subdural hemorrhage with burr hole operation in 2/2022

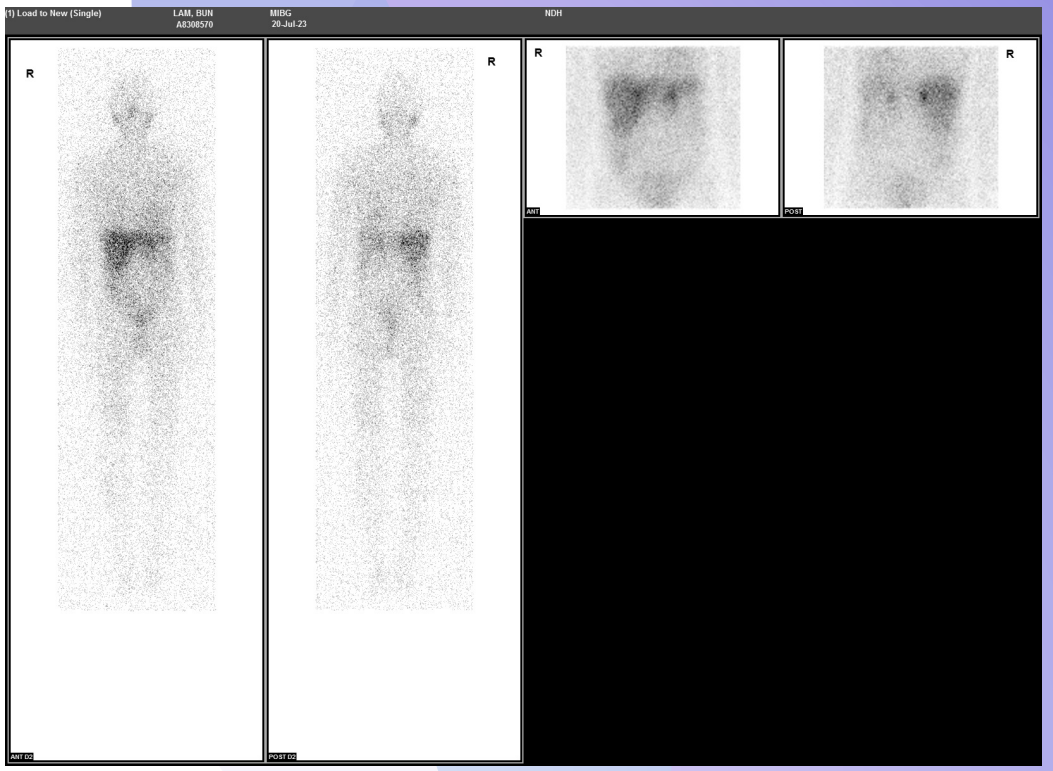


HPI

- FU in Medical for 1cm left adrenal incidentaloma since 2012
  - Repeated 24hour urine catecholamines showed borderline noradrenaline levels
  - Serial CT showing static in size of left adrenal nodule, CC since 2015
- Presented again with incidental findings of frequent PVC on ECG
  - Found elevated plasma free metanephrine and normetanephrine in private workup
  - 24hr urine normetanephrine is elevated to 1094

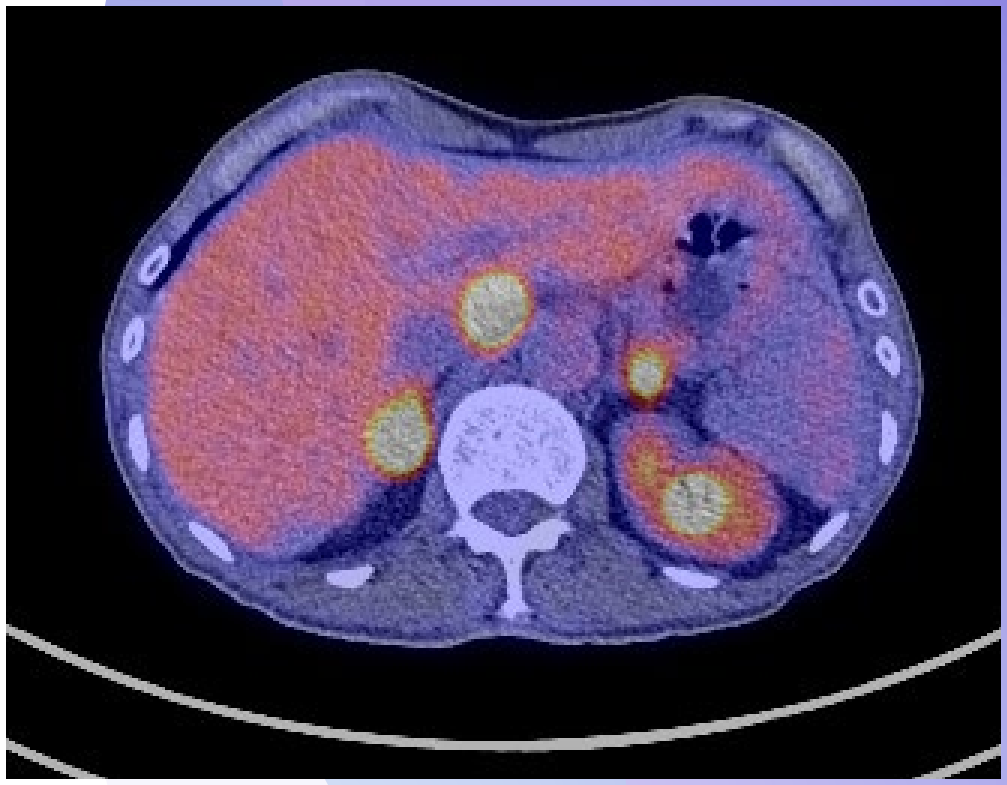
IMAGING

- CT 24/4/2023:
  - 2.1 x1.8x2.0cm right adrenal nodule
    1.1 x0.9x1.1cm left adrenal nodule
    Both with non-contrast HU >30; post-contrast HU >200; delayed absolute and relative washout
  - 1.9x1.8x1.8cm aortocaval heterogenously enhancing lesion
- MIBG 18/7/2023:
  - Bilateral adrenal lesions show mild MIBG uptake suggestive of phaeochromocytoma
  - The aortocaval lesion abutting the caudate lobe appears photopenic with no abnormal uptake



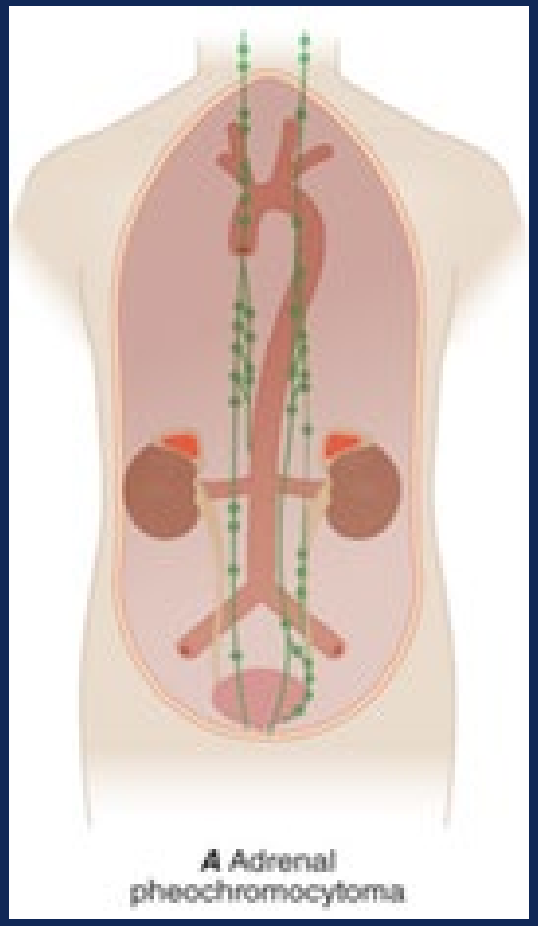
IMAGING

- ^{18}F-FDG & ^{68}Ga DOTATATE PET/CT
  - Bilateral adrenal glands are enlarged with increased ^{18}F-FDG (~10 SUVmax)& ^{68}Ga DOTATATE metabolism (~18 SUVmax), suggestive of phaeochromocytoma
  - A 2.3x1.7cm soft tissue lesion in upper aorto-caval region showed more ^{18}F-FDG avid (26.3 SUVmax) than ^{68}Ga DOTATATE (8.1 SUVmax), suggestive of paraganglioma
- Pending OT for laparoscopic bilateral adrenalectomy + paraganglioma excision

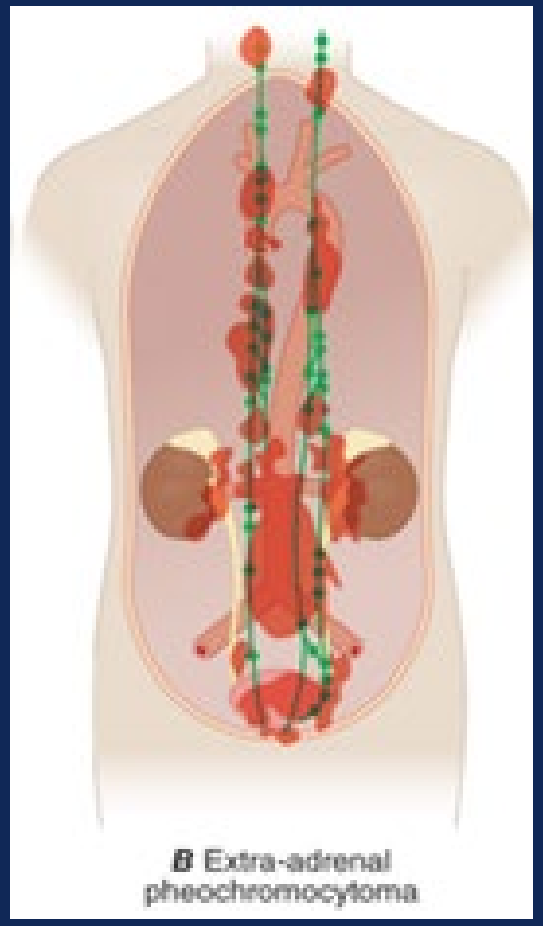


WHAT IS THE MOST APPROPRIATE IMAGING MODALITY FOR PPGLs?

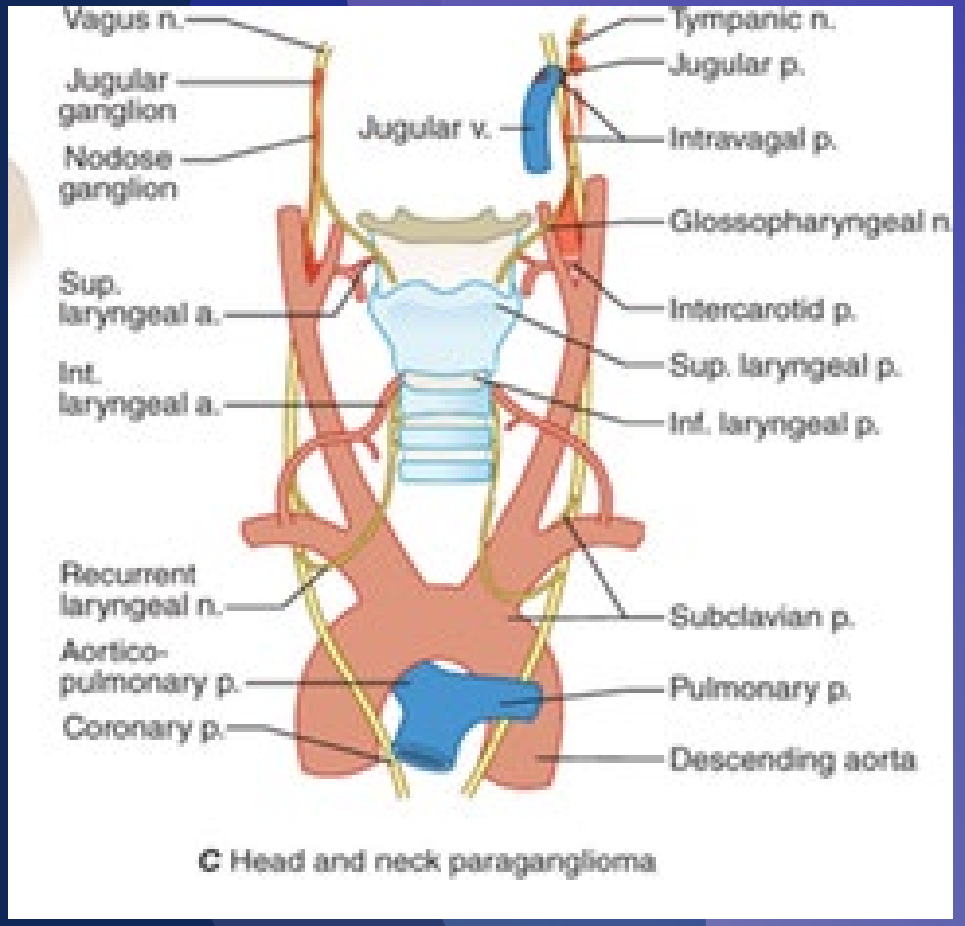
BACKGROUND



A Adrenal pheochromocytoma



B Extra-adrenal pheochromocytoma



C Head and neck paraganglioma

GENETIC ASSOCIATION

- ~~10% familial rule~~ → 40-45% PPGLs have a germline/somatic mutation
- ~15 well-known PPGL driver genes ; >12 genetic syndromes
- Classified into 3 clusters of genetic mutations

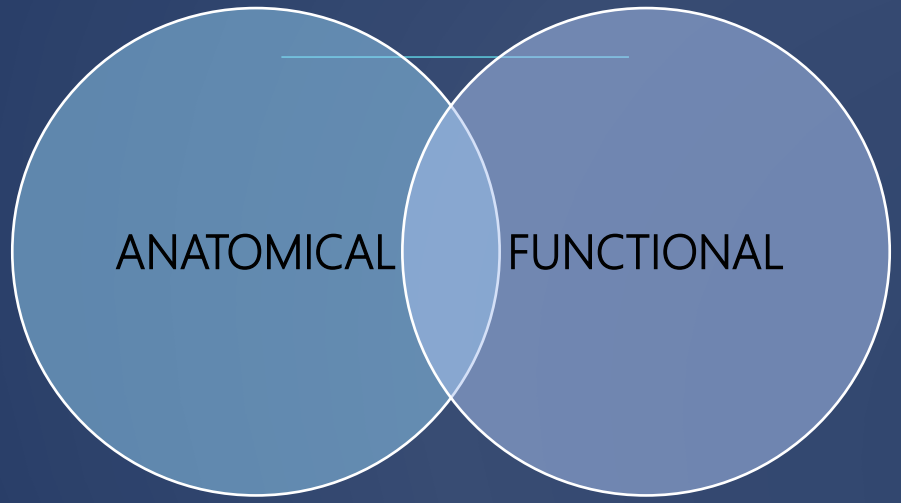
PPLG driver genes	Genetic syndromes
Succinate Dehydrogenase (*SDHA*, *SDHB*, *SDHC*, *SDHD* & *SDHAF2*)	Hereditary paragangliomas syndromes (PGL syndromes) PGL1 and PGL4 syndromes are the most common
von Hippel–Lindau (*VHL*)	VHL syndrome
RET	Multiple endocrine neoplasia type 2 syndrome
NF1	Neurofibromatosis type 1 syndrome
MAX	Familial PPGLs *MAX*-related
TMEM127	Familial PPGLs *TMEM127*-related
Fumarate Hydratase (*FH*)	Hereditary leiomyomatosis and renal cell cancer
EPAS1	Pacak–Zhuang syndrome
HRAS, *CSDE1*, and *MAML3*	Sporadic PPGLs

Clustering of inherited pheochromocytoma and paraganglioma syndromes

Cluster 1: pseudohypoxia	Cluster 2: kinase signaling
VHL	*RET*
SDHA, SDHB, SDHC, SDHD	*NF1*
SDHAF2	*TMEM127*
FH	*MAX*
EGLN1/2 (PHD1)	
MDH2	
Generally, more aggressive	Generally, more pheochromocytomas with an adrenergic phenotype

Cluster 3 (Wnt signaling) represents only genes with nonfamilial associations

IMAGING MODALITIES



ANATOMICAL IMAGING

- CT Adrenal protocol
  - Sensitivity >95% (for lesions 5-10mm)
  - non-contrast phase > venous phase > delayed phase (7-15min)
  - HU >10 on non-contrast phase > contrast enhancement > delayed washout
- MRI
  - intermediate to high intensity on T2 images; light bulb appearance on T2
  - not a 1st line imaging modality
  - mainly for HNPGL

FUNCTIONAL IMAGING

- Aim:
  - ✓ Diagnostic for indeterminate biochemical/imaging findings
  - ✓ Identify multifocal tumors/ metastasis
  - ✓ Evaluate the aggressiveness of tumor behavior
  - ✓ Detection of therapeutic molecular targets
- Based on catecholamine metabolism and secretion/ glucose metabolism/ somatostatin receptor status

^{123}I-MIBG SCINTIGRAPHY

- Radioactive iodine-labelled ^{123}I metaiodobenzylguanidine
- Analogue of guanidine - structurally resembling norepinephrine → Accumulates in noradrenergic secreting sympathetic ganglia & chromaffin cells
- SN 85-88% for phaeochromocytoma; 56-75% for PGL (even lower for HNPGL)
- ☹ Takes 24hour from administration of ^{123}I to imaging

  ☹ Lugol's iodine solution is prescribed to prevent ^{123}I uptake by thyroid

  ☹ some antiHTs/ antidepressants/ sympathomimetics may interfere with MIBG uptake and should be discontinued

^{18}F-FDG PET/CT

- Based on glucose uptake and metabolism
- ☺ SN 80-100%
- Radiographic genotype-phenotype correlation:
  - Higher uptake in SDH and VHL related tumors (Pseudohypoxia clusters)
    VS Lower uptake in MEN2/NF1 related tumors (Kinase-signaling clusters)
  - Possible explanation is the altered oxygen metabolism causing increased glycolysis and intracellular glucose requirement

^{18}F-DOPA PETCT

- Radiolabeled amino acid as a marker of dopamine synthesis
- Higher sensitivity for MEN2 and NF1 (kinase signaling cluster 2)
- ☺ Limited uptake in normal adrenal glands – improving detection rate of small phaeochromocytomas

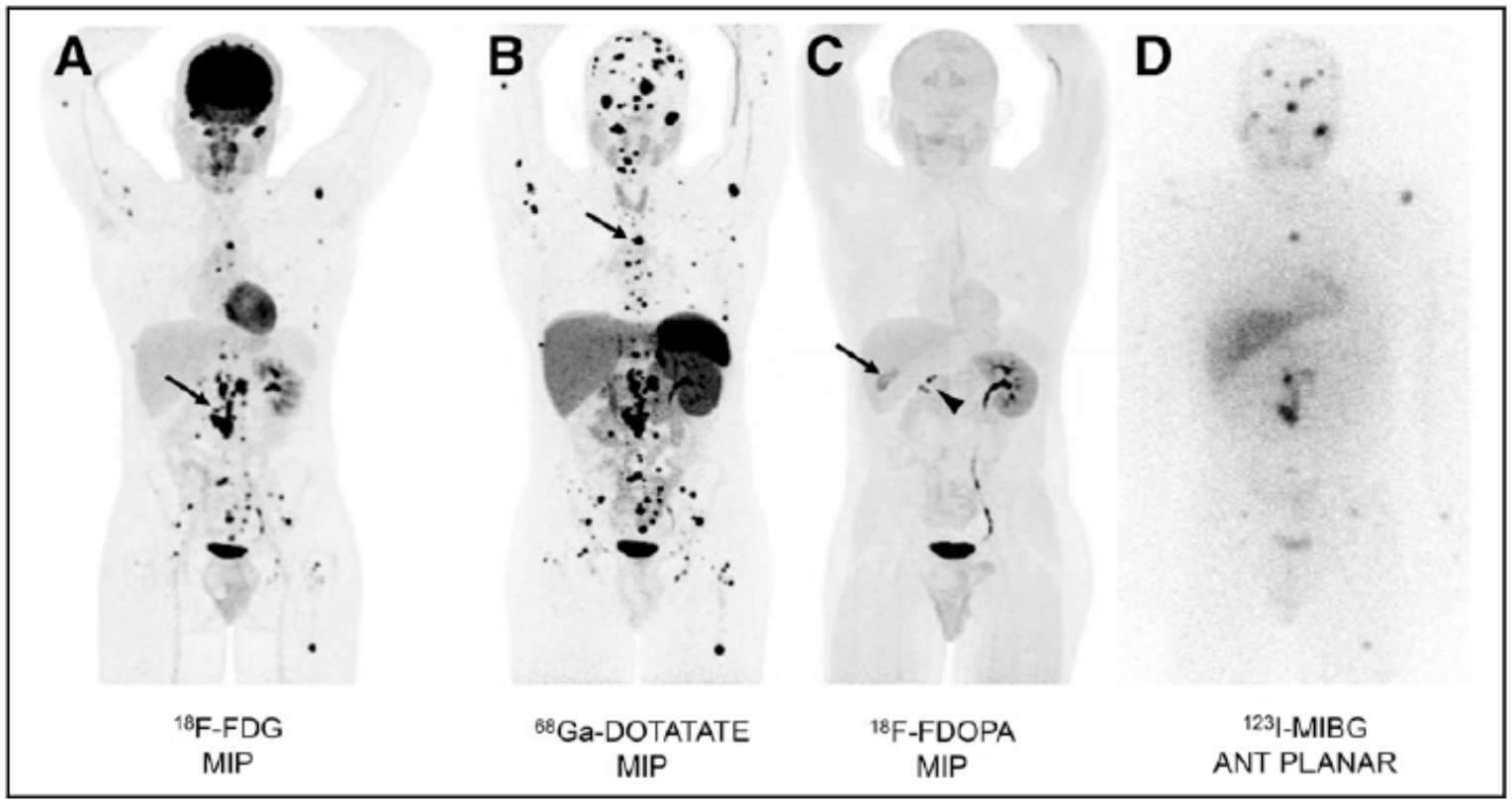
^{68}Ga-DOTA-SSA (DOTATE/DOTATOC/DOTANOC PETCT)

- Somatostatin binds to somatostatin receptors (SSTRs 1,2,3,4,5)
- SSTR2 is the most common over-expressed receptor in PPGLs
- Using different ^{68}Ga labelled somatostatin analogs:
  - DOTATATE: DOTA-Tyr3-octreotate (oxodotreotide) binds to SSTR 2
  - DOTATOC: DOTA-Tyr3-octreotide (edotreotide) binds to SSTRs 2 and 5
  - DOTANOC: DOTA-Nal3-octreotide binds to SSTRs 2, 3 and 5
- SN >92% and high detection rate across wide range of mutations
- ☺ Time from administration to imaging is ~90mins

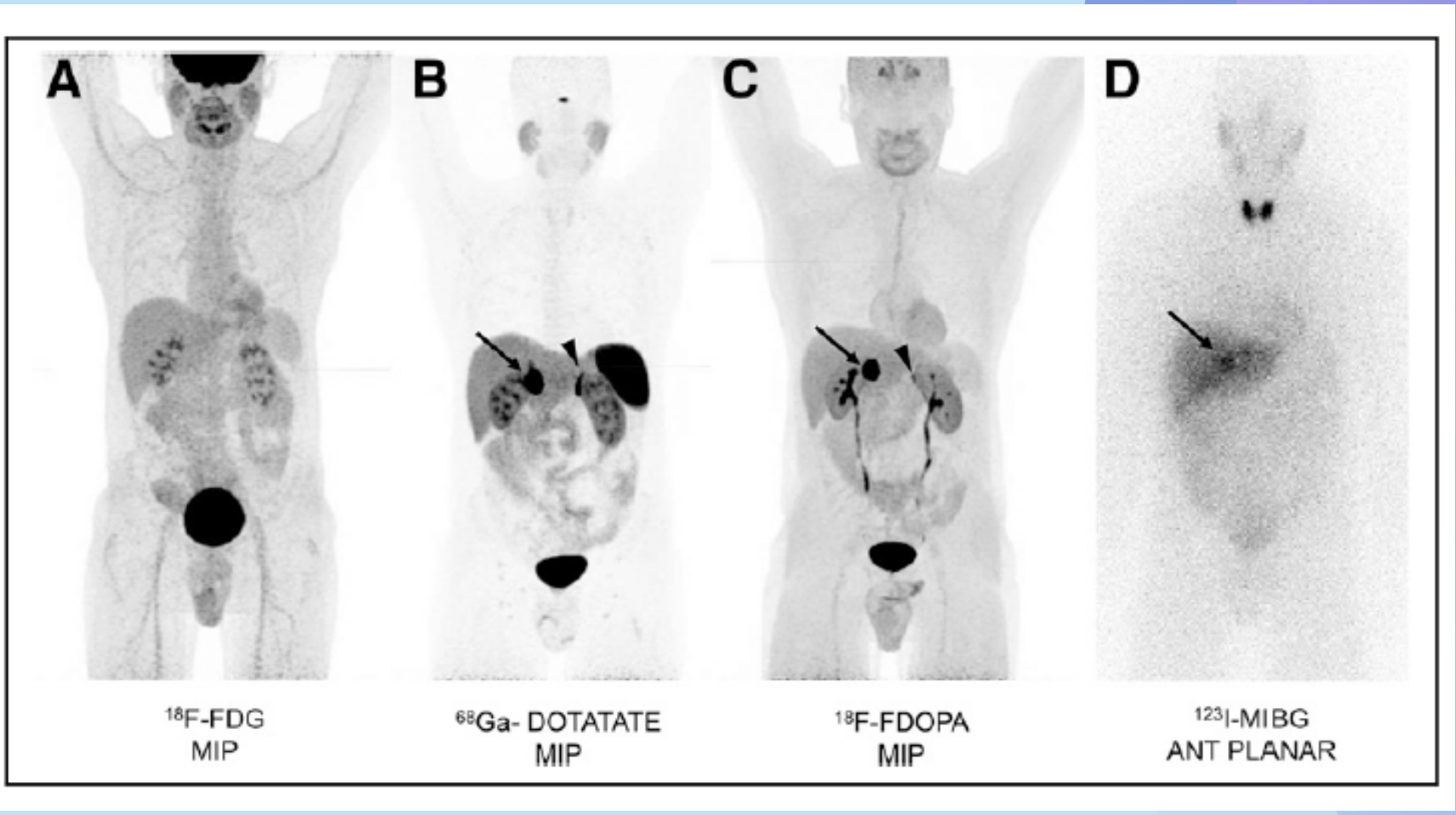
GENOTYPE & RADIOLOGICAL PHENOTYPE

- Cluster 1A
  - SDHx-related PPGLs (mostly PGLs) strongly express the SSTR2
  - → highest sensitivity in ^{68}GA-DOTA-SSA PET/CT
- Cluster 1B
  - VHL/EPAS1-related PPGLs (specifically PCCs) show stronger expression of the L-type amino-acid transporter and less SSTR2 expression
  - → ^{18}F-FDOPA is more sensitive than ^{68}GA-DOTA-SSA PET/CT
- Cluster 2
  - kinase signaling–related tumors (MEN2/NF1)
  - exhibit high ^{18}F-FDOPA uptake with low uptake of the remaining adrenal gland
- Cluster 3
  - Wnt signaling related tumors
  - lack of data

A 20-Y-OLD MAN WITH SDHB-ASSOCIATED METASTATIC PARAGANGLIOMA



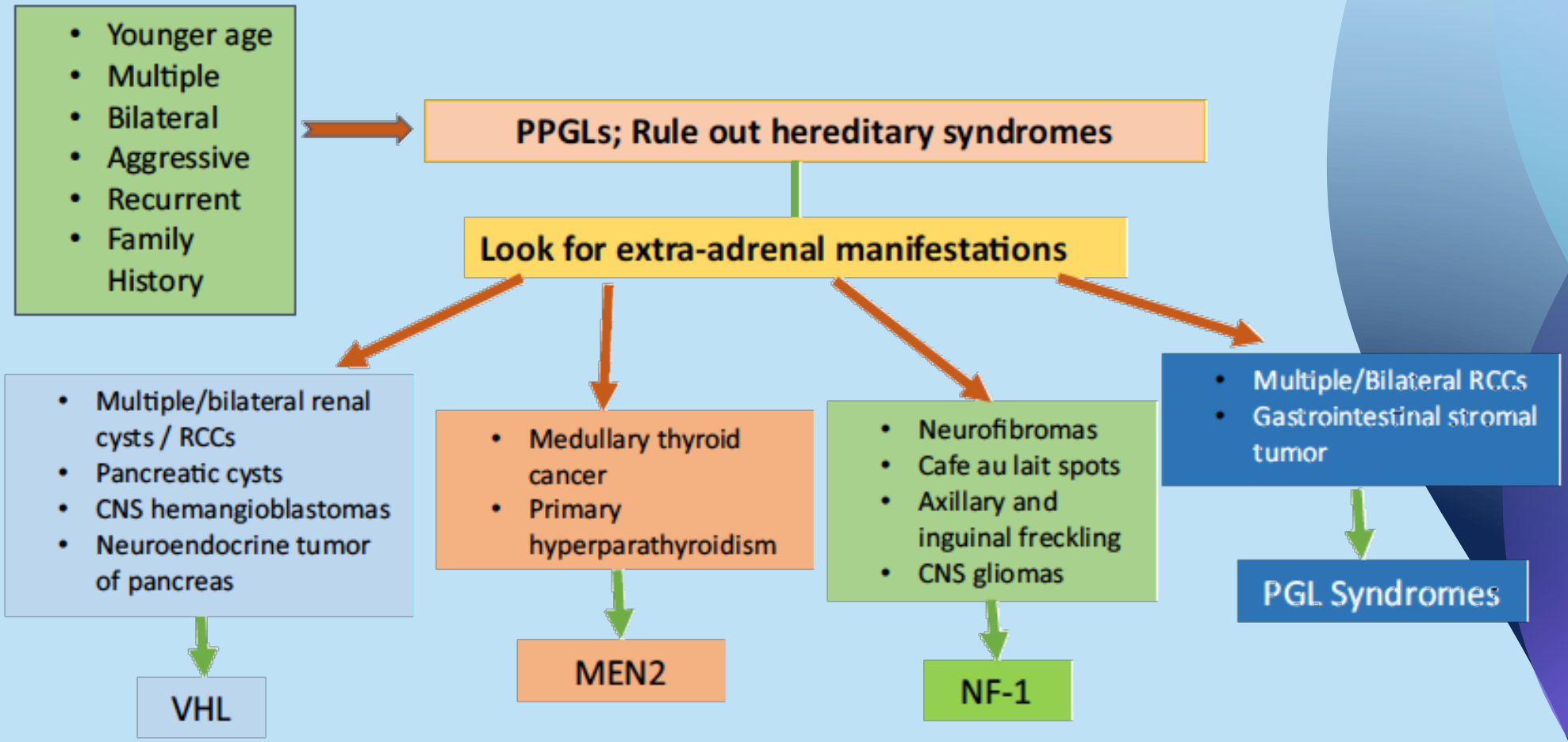
A 54-Y-OLD MAN WITH BENIGN SPORADIC RIGHT ADRENAL PHEOCHROMOCYTOMA

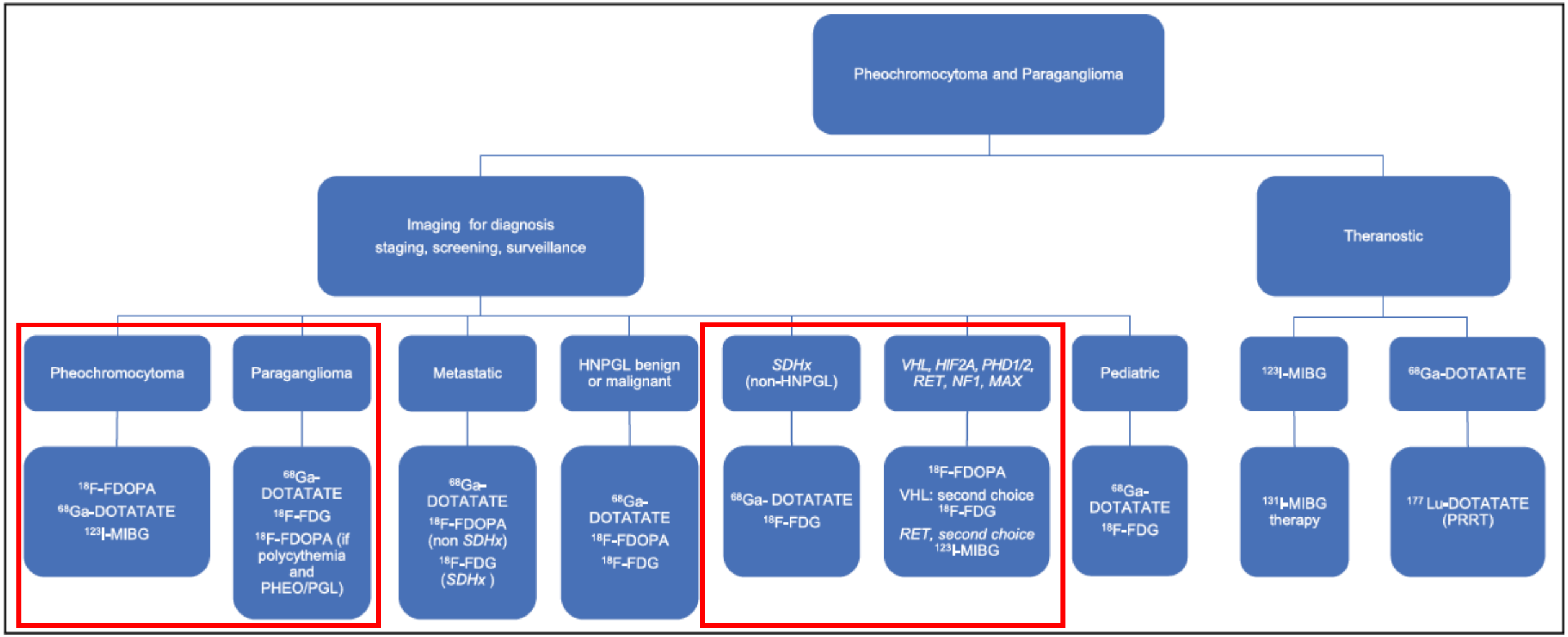


FUTURE DIRECTION

NEXT GENERATION SEQUENCING

BEFORE THE FUTURE COMES…




Pheochromocytoma and Paraganglioma
Imaging for diagnosis staging, screening, surveillance
Theranostic
Pheochromocytoma
Paraganglioma
Metastatic
HNPGL benign or malignant
SDHx (non-HNPGL)
VHL, HIF2A, PHD1/2, RET, NF1, MAX
Pediatric
123I-MIBG
68Ga-DOTATATE
18F-FDOPA 68Ga-DOTATATE 123I-MIBG
68Ga-DOTATATE 18F-FDG 18F-FDOPA (if polycythemia and PHEO/PGL)
68Ga-DOTATATE 18F-FDOPA (non SDHx) 18F-FDG (SDHx)
68Ga-DOTATATE 18F-FDOPA 18F-FDG
68Ga- DOTATATE 18F-FDG
18F-FDOPA VHL: second choice 18F-FDG RET, second choice 123I-MIBG
68Ga-DOTATATE 18F-FDG
131I-MIBG therapy
177 Lu-DOTATATE (PRRT)

BACK TO OUR CASE

Clinical:	• History of bilateral HNPGL
Biochemical:	• Elevated urine normetanephrine
Anatomical imaging	• Bilateral phaeochromocytoma +paraganglioma

SDHx-associated PPGL is suspected → ^{68}Ga DOTA-SSA PET/CT should be the first choice

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