Update on Pheochromocytoma and Paraganglioma: Focusing on Advanced/Metastatic Disease.

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NIH NATIONAL CANCER INSTITUTE

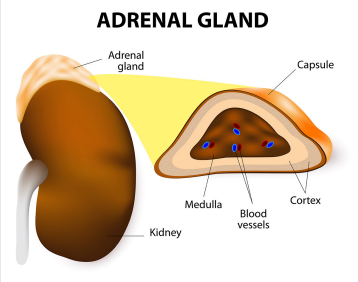
February 17, 2022

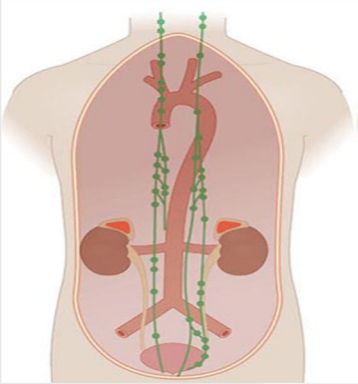
Outline

- Definition of Pheochromocytomas and Paragangliomas (PHEO/PARA)
- Clinical features
- Genetics of PHEO/PARA
- Biochemical diagnosis and localization studies
- Management of metastatic PHEO/PARA
- Clinical trials currently available

Pheochromocytoma and Paraganglioma (PHEO/PARA)

Pheochromocytoma and paraganglioma are rare neuroendocrine tumors and these tumors produce an excess amount of catecholamine hormone.





Pheochromocytoma: Forms in the adrenal medulla (the center of the adrenal gland)

Paragangliomas: Originates in the parasympathetic or sympathetic nervous system (nerves outside of the adrenal gland)

Parasympathetic paragangliomas:
Most often found in the head and neck
95% casos: non-functional/non-secreting

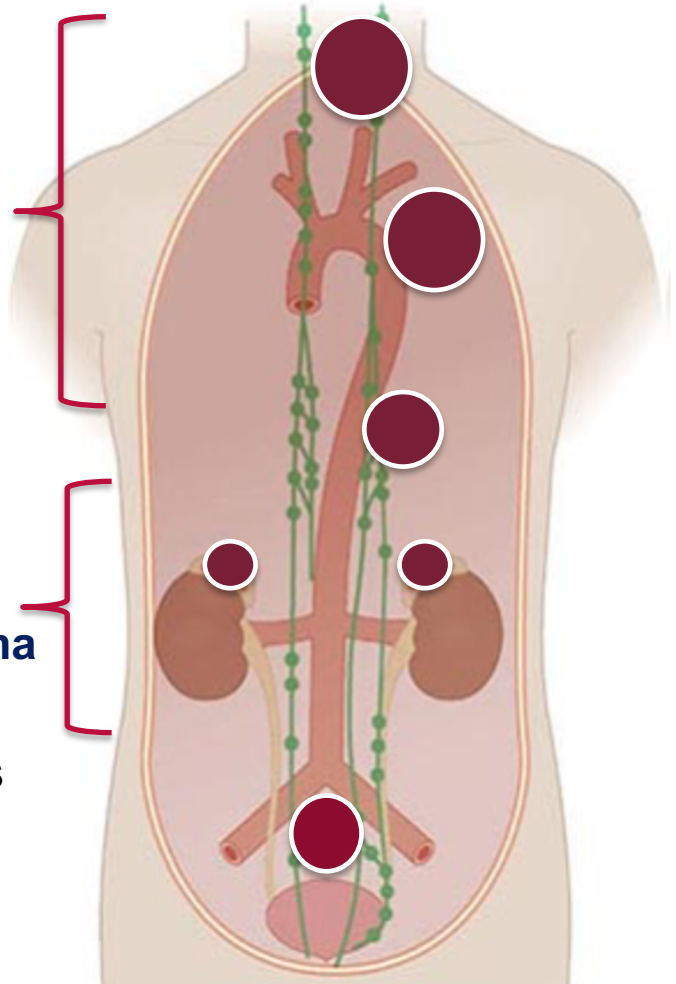
Sympathetic paragangliomas:
Located in the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis
Functional/secreting

Pheochormocytomas
Adrenal medulla

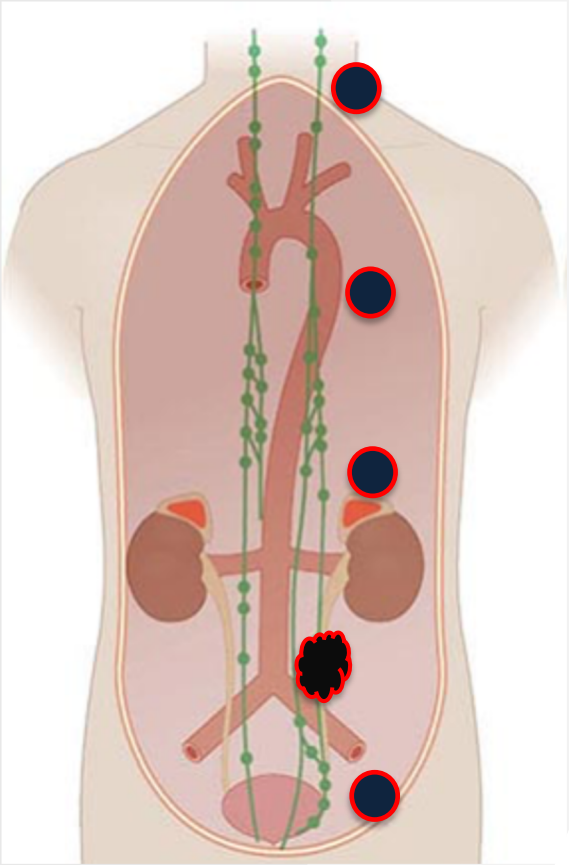
Functional/secreting

Paraganglioma
Extra-adrenal
15-20% of cases

Pheochromocytoma
Adrenal
80-85% of cases



Paragangliomas



3% Head and neck

Head and Neck
Parasympathetic ganglia
Not associated with catecholamine secretion

12% Thorax

80-85% Abdomen

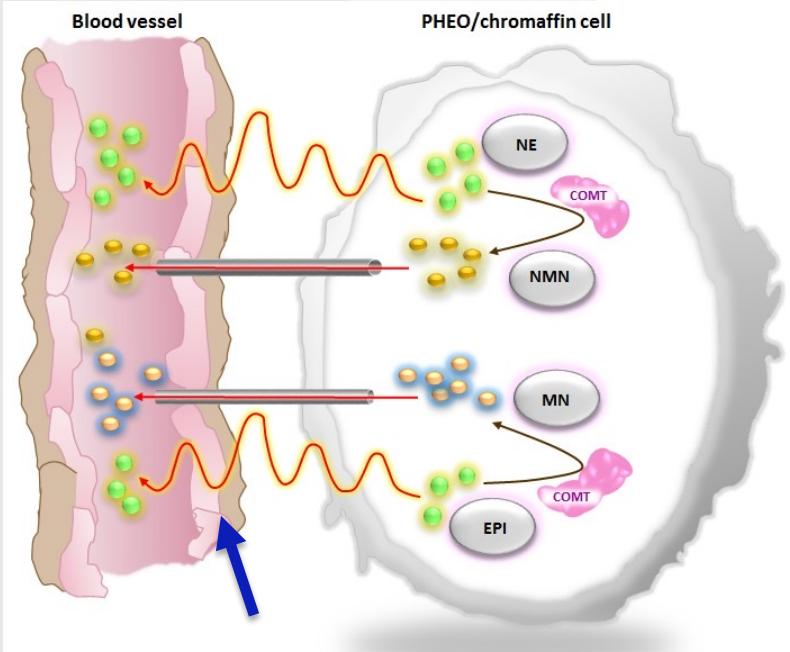
<5% Pelvis
(bladder, prostate)

Thorax y abdomen:
Sympathetic chain
Catecholamine secretion

Paragangliomas occur most commonly → Abdomen

Harrison's endocrinology. 3rd ed. New York, NY: McGraw-Hill.
Lee.World J Surg. 2008 May;32(5):683-7

Clinical Features



α blockers: doxazosin, phenoxybenzamine
prazosin, terazosin

*α blockers is recommended before any procedure, ablative or systemic therapies

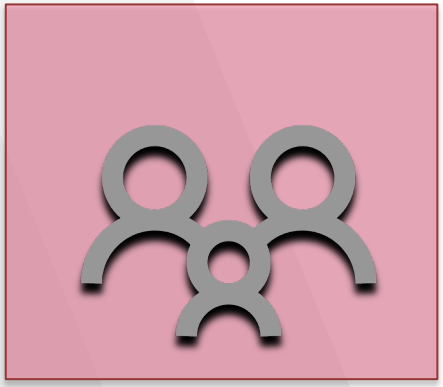
Symptoms	Incidence	Signs	Incidence
Headaches	++	Hypertension	++++
Palpitations	+++	Tachycardia or reflex bradycardia	+++
Sweating	+++	Postural hypotension	++
Anxiety/nervousness	++	Hypertension, paroxysmal	++
Tremulousness	++		
Nausea/emesis	++	Weight loss	++
Pain in chest/abdomen	++	Pallor	++
		Hypermetabolism	++
Weakness/fatigue	+++	Fasting hyperglycemia	++
Dizziness	+	Tremor	++
Heat intolerance	+	Increased respiratory rate	++
Paresthesias	+	Decreased gastrointestinal motility	++
Constipation	++	Psychosis (rare)	very rare
Dyspnea	+	Flushing, paroxysmal (rare)	+
Visual disturbances	+		
Seizures, grand mal	very rare		

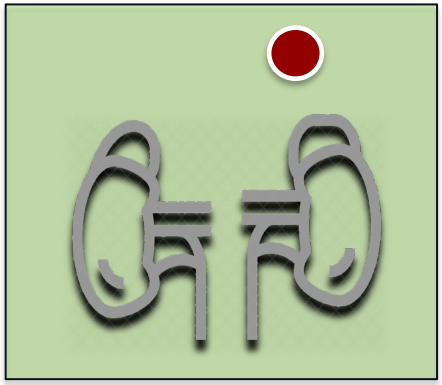
Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021
Pacak et al. DeGroot Endocrinology Textbook, 2021
Lenders et al. J. Hypertens. 2020; 38:1443
Eisenhofer et al. Eur. J. Cancer 2012; 48:1739

Factors That Can Precipitate the Crisis

- Physical exertion
- Postural changes (changes in body position)
- Stress, trauma, pain
- Ingestion of food or drinks (cheeses, bananas, caffeine, beers and wines, soy sauce, fermented and smoked foods)
- Drugs (decongestants, amphetamine, cocaine, corticosteroids)
- Surgery and anesthesia
- Chemotherapy, endoscopy, catheterization
- Urination or bladder distention (bladder tumors)

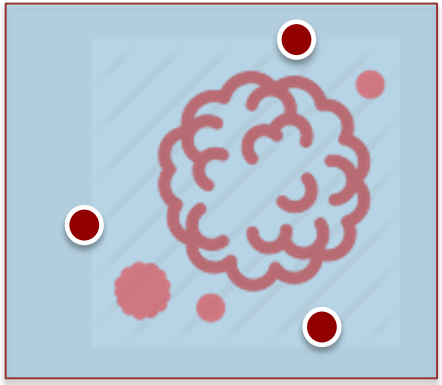
30-40%
Hereditary
(germline mutations)





25%
Paragangliomas

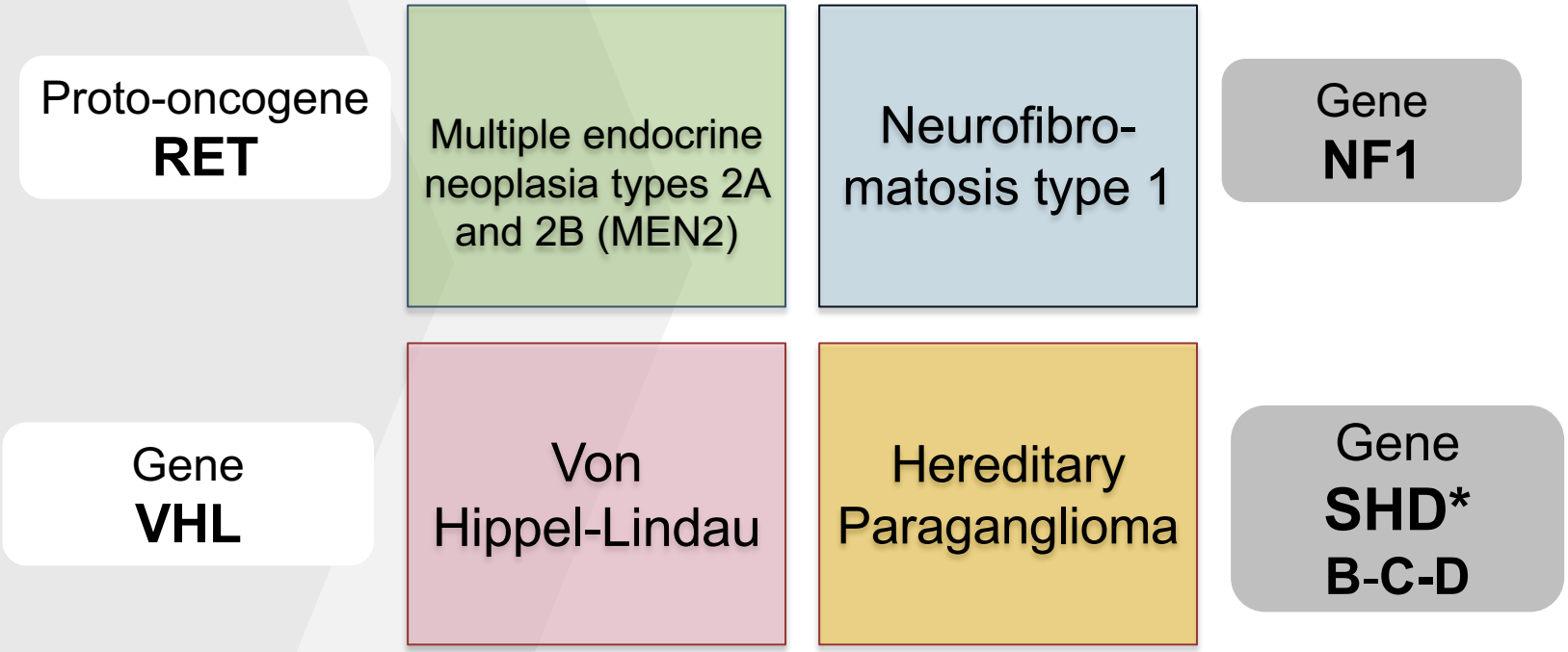
10%
Bilateral



15-25%
Malignant

Nat Rev Endocrinol. 2015;11:101–11

Hereditary Syndromes



SDH: Succinate dehydrogenase

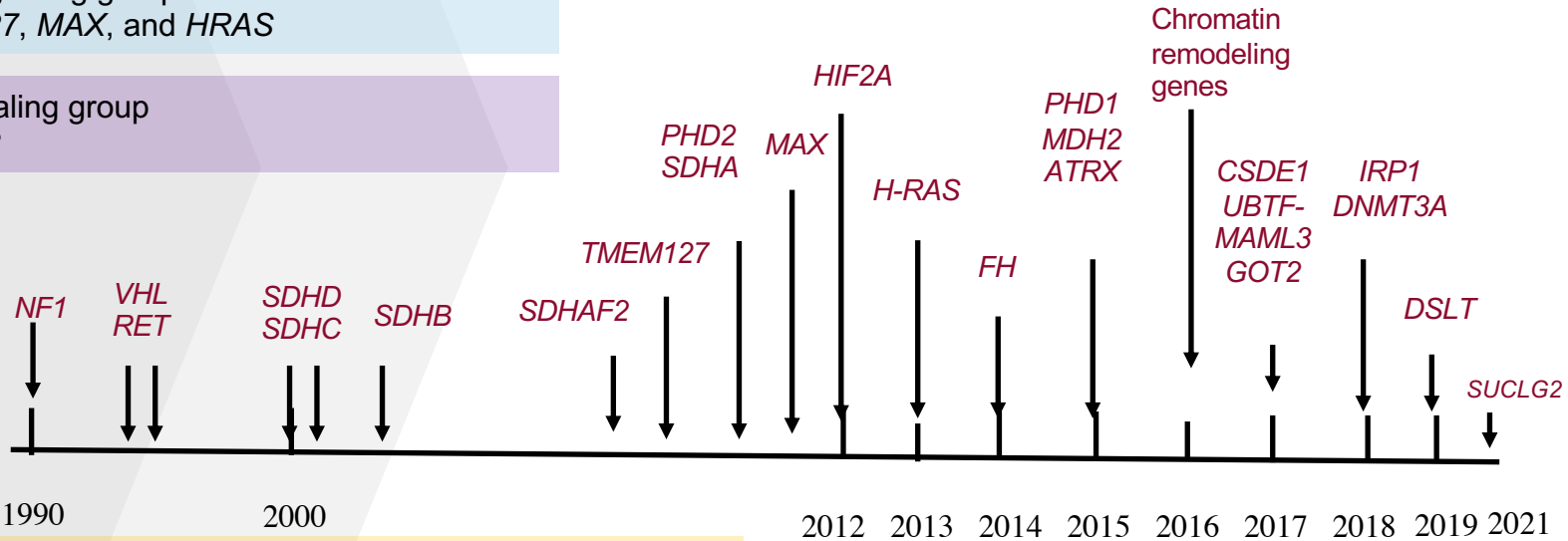
Nat Rev Endocrinol. 2015;11:101–11

Genetics PHEO/PARA

Cluster I: Pseudohypoxia group
DHA, SDHB, SDHC, SDHD, SDHAF2, FH, VHL
IDH1/2, MHD2, PHD1/2, and *HIF2/EPAS1*

Cluster II: Kinase signaling group
RET, *NF1*, *TMEM127*, *MAX*, and *HRAS*

Cluster III: Wnt signaling group
CSDE1 and *MAML3*



- 30%-45% PPGL → germline pathogenic variant
- > 40% SDHB for metastatic PHEO/PARA

Adapted. Courtesy of K. Pacak

Fishbein et al. Cancer Cell 2017; 31:181
Crona et al. Endocr. Rev. 2017; 38:489
Dahia et al. Nat. Rev. Cancer 2014; 14:108
Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021

Genetic Counseling

- All patients diagnosed with pheochromocytoma and paraganglioma should be referred to genetic counseling
- 30-40% are hereditary
- Helps guide surveillance in patients and their families
- Establish risk for
  - Develop another pheochromocytoma or paraganglioma
  - Recurrence/metastasis
  - Other associated tumors

When to Suspect PHEO/PARA?

- Signs and symptoms of catecholamine excess
- Increased blood pressure caused by drugs, anesthesia, or surgery
- Unexplained blood pressure variability
- Adrenal Incidentaloma
- Difficulty controlling the blood pressure
- Personal or family history: pheochromocytoma/paraganglioma
- Cancer predisposition syndromes to Pheochromocytoma (VHL, MEN 2, NF1)

Berkel. Eur J Endocrinol. 2014 Feb 4;170(3):R109-19
Lenders.J Clin Endocrinol Metab, June 2014, 99(6):1915–1942

Biochemical Diagnosis

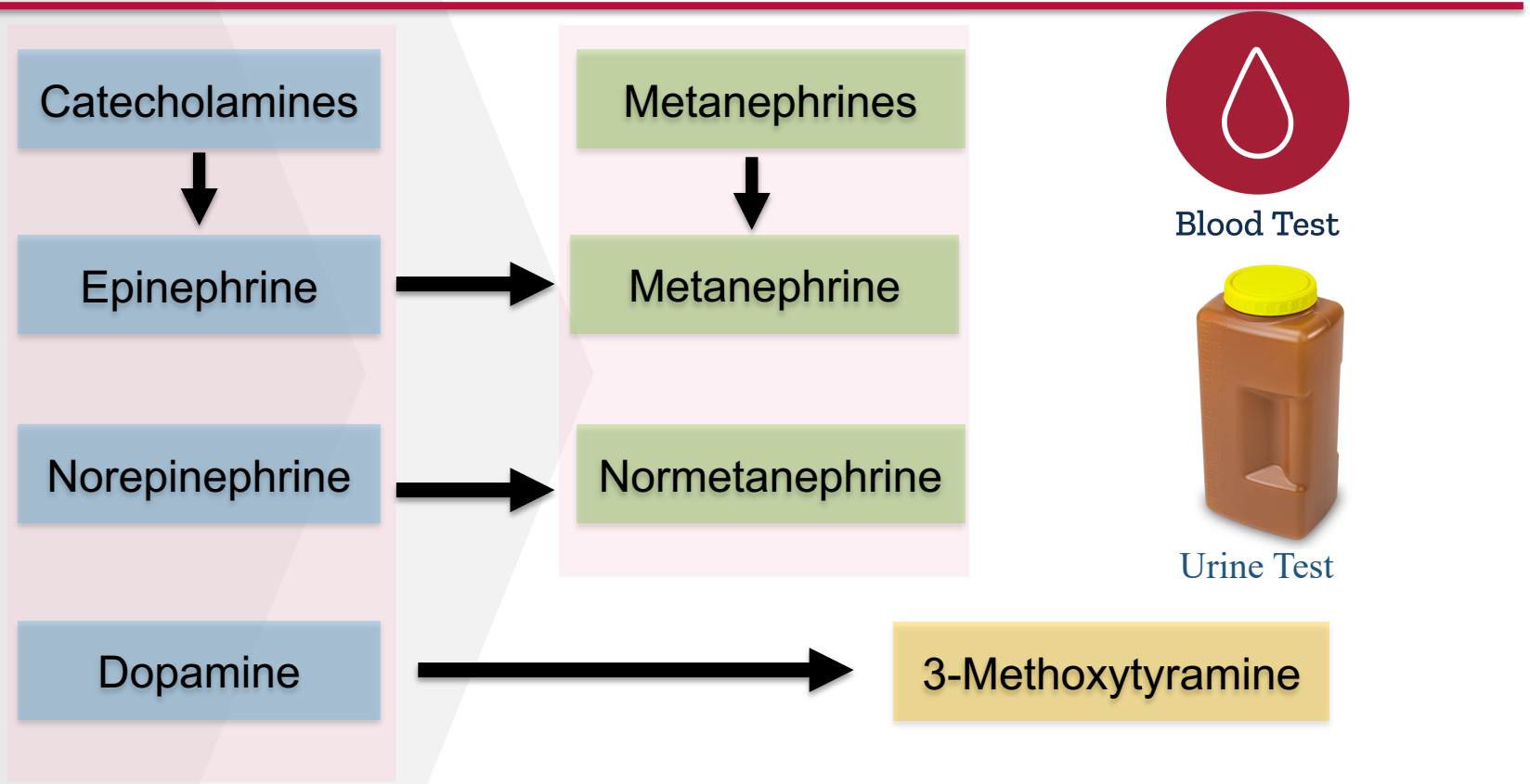
- Blood test (plasma free metanephrines): Higher than normal amounts of certain catecholamines may be a sign of a pheochromocytoma

- 24-hour urine analysis: A higher than normal amount of certain catecholamines can be a sign of a pheochromocytoma

Stop medication, if possible
• Tricyclic antidepressants (Amitriptyline, Imipramine) • Anxiolytics (Xanax, Valium, Trazodone, Ativan) • Sleep aids (Ambien, Lunesta) • Norepinephrine and serotonin reuptake inhibitors (venlafaxine, duloxetine) • Some nonselective alpha blockers (phenoxybenzamine) • Cocaine, marijuana, other illicit drugs • Caffeine, alcohol

Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline. JCME2014

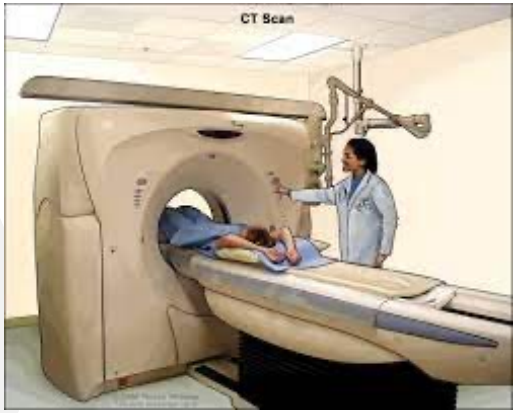
Plasma and Urine Test

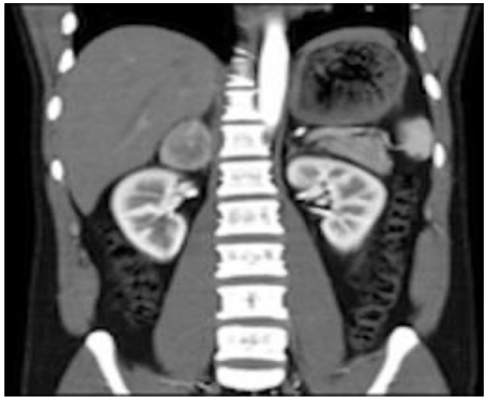


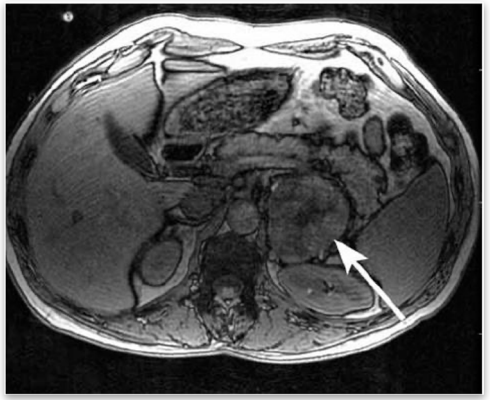
Localization by Images

- **Computed tomography (CT)**
- **Magnetic resonance imaging (MRI)**

A procedure that makes a series of detailed pictures inside of the body, such as the neck, chest, abdomen, and pelvis



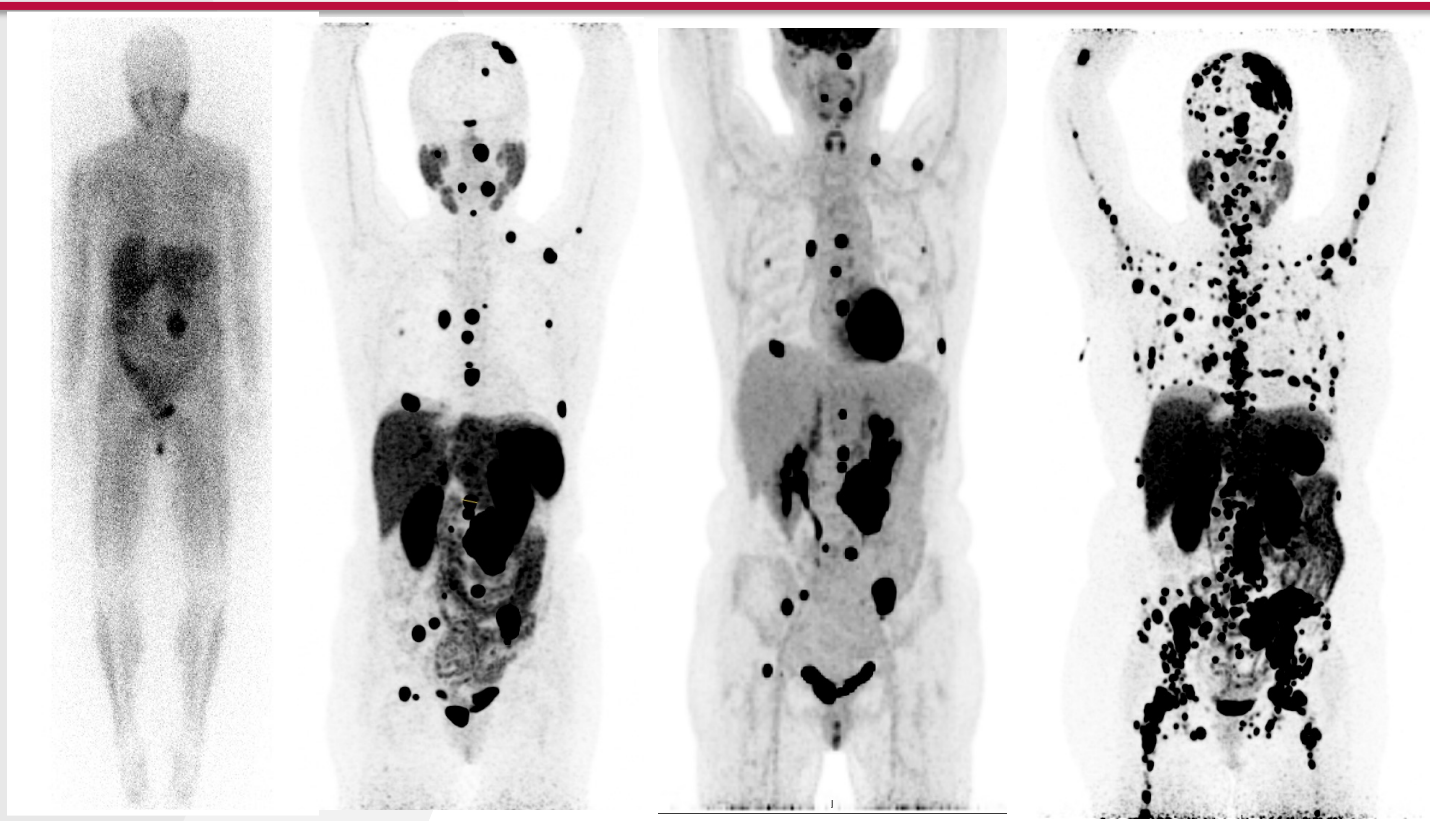




Indication of Functional Imaging

- All paragangliomas
- Pheochromocytomas > 5 cm (risk of metastasis)
- Recurrent and metastatic disease
- Suspected pheochromocytoma or paraganglioma with no symptoms/evaluation of retroperitoneal mass
- Evaluation of ^{131}MIBG/^{177}Lu-DOTATATE therapy in metastatic disease

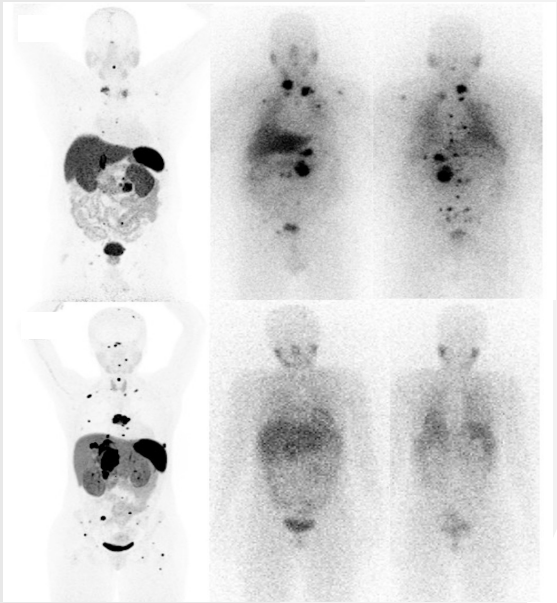
Functional Imaging for PHEO/PARA



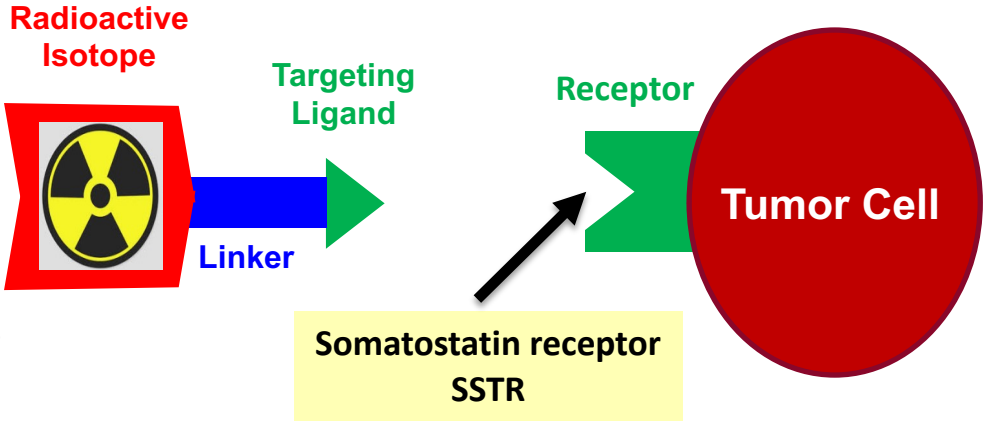
^{123}I-MIBG F-DOPA PET FDG PET ^{68}Ga-DOTATATE PET

Molecular Imaging PHEO/PARA → Theranostics

- Diagnosis, staging, follow up of PPGL
- Selection for targeted molecular radiotherapy



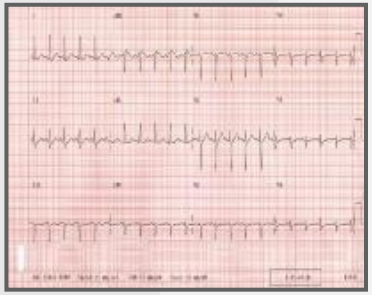
^{68}Ga-Dotatate ^{123}I-MIBG



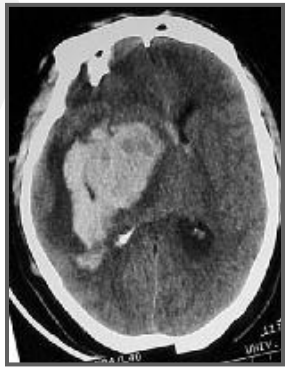
Sensitivities metastatic PHEO/PARA	
^{123}I-MIBG	50-60%
^{68}Ga-Dotatate	98-99%
^{18}F-FDG	68-92%

PHEO/PARA as a Volcano

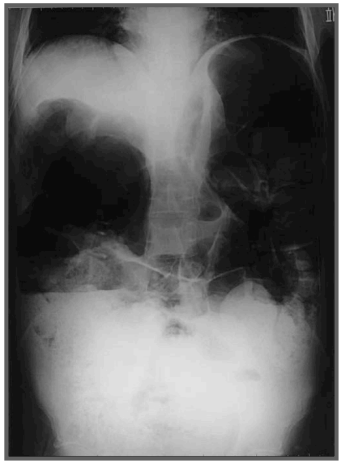
The concentrations of catecholamines in PHEO tissue are enormous (more than a billion times higher than in plasma), creating a volcano that can erupt at any time (episodes are called storms, attacks, or spells).



Sinus tachycardia



Large intracerebral hemorrhage



Ileus

All patients with PHEO must receive α (β) adrenoceptor blockade

Medications Commonly Used for Hemodynamic Control in Patients With PHEO/PARA

Class of Drug	Drug Name	Common Adverse Effects
α-Blockers*	Doxazosin, phenoxybenzamine, prazosin, terazosin	Orthostatic hypotension, dizziness, tachycardia
β-Blockers	Metoprolol, atenolol, propranolol *Labetalol	Fatigue, dizziness, asthma exacerbation
Calcium channel blockers	Amlodipine , Nifedipine	Edema, headache
Tyrosine hydroxylase inhibitor	Metyrosine	Severe fatigue, neurologic adverse effects, nausea, diarrhea, anxiety

*α blockers is recommended before any procedure, surgery, ablative or systemic therapies

Pacak and Del Rivero. Endotext, 2013
Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021

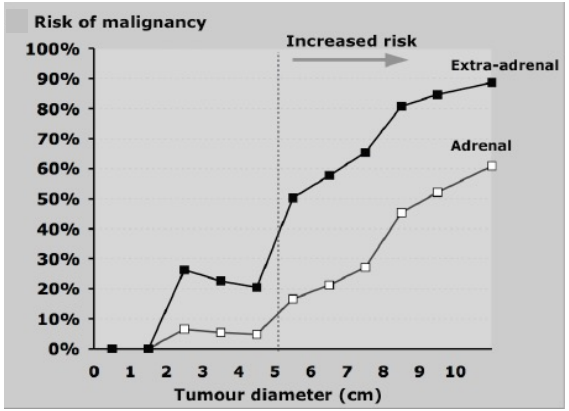
Surveillance after PHEO/PARA Removal

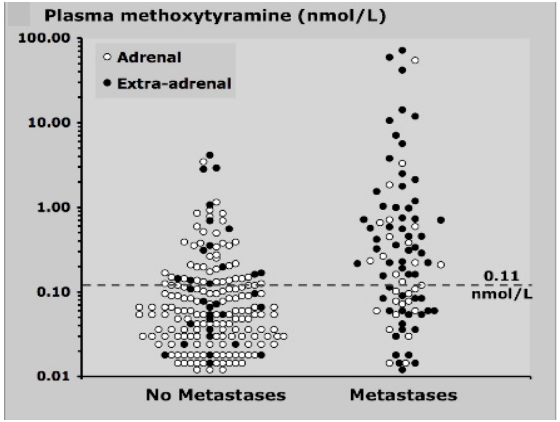
For all patients, check biochemistries 4-8 weeks post-op

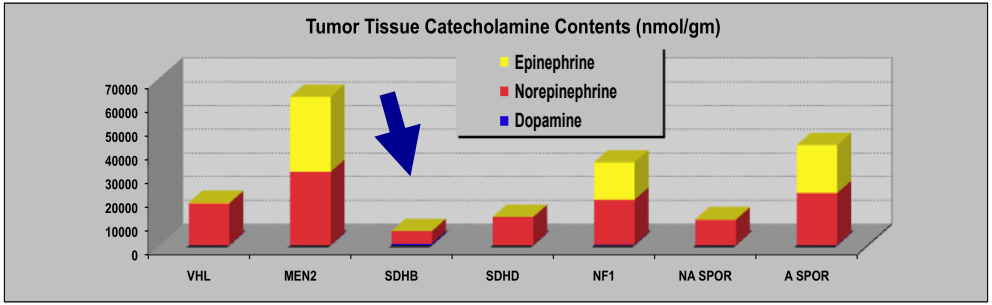
PHEO/PGL sporadic	• Lifetime annual biochemistry • Consider imaging if >4-5 cm in size, extra-adrenal or young age
PHEO/PGL VHL, NF1, RET	• Lifetime annual biochemistry • Imaging per syndrome guidelines
PHEO/PGL SDHx	• Biochemistries at 6 months and then lifetime at least annual biochemistries • Full body CT/MRI at mutation diagnosis and then at least every 2 years

Clinical Predictors of Malignancy

- Tumor size (>5 cm PHEO, >4 cm PARA)
- Extra-adrenal location
- SDHB-related PGL has the highest metastatic potential
- Methoxytyramine levels







Eisenhofer et al. Endocr. Relat. Cancer 2011; 18:97
Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021

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

Management of Advanced/Metastatic PHEO/PARA

Alpha-blockade
Doxazosin, phenoxybenzamine

Beta blocker
Calcium channel blocker
Metyrosine

Locally advanced/unresectable

- Observation
- Cytoreductive surgery
- TKI (sunitinib, cabozantinib, axitinib)
- ^{131}I-MIBG
- PRRT with ^{177}Lu-dotatate**

Distant metastasis

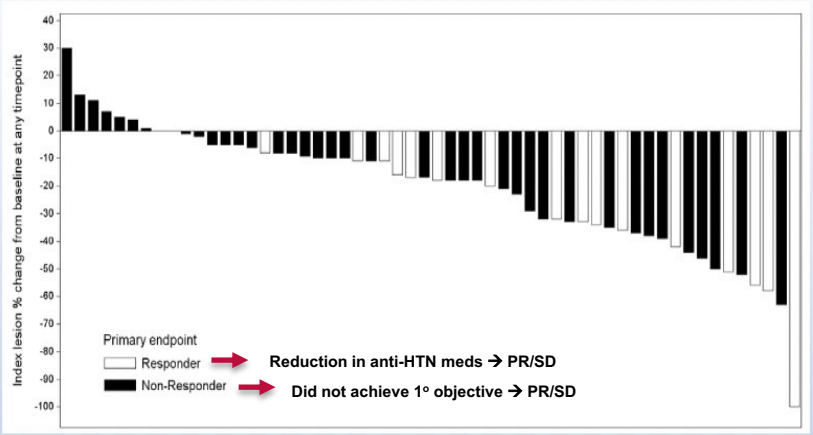
- Observation
- Cytoreductive surgery
- Systemic chemotherapy(CVD/TMZ)
- TKI (sunitinib, cabozantinib, axitinib)
- ^{131}I-MIBG
- PRRT with ^{177}Lu-dotatate
- Clinical trial

FDA approves iobenguane I 131 for rare adrenal gland tumors

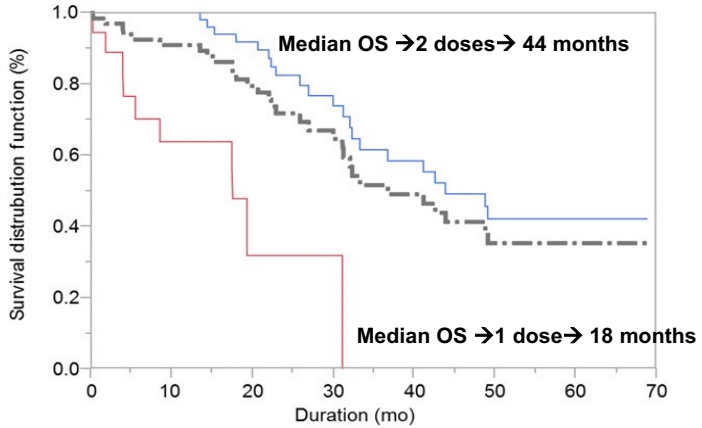
On July 30, 2018, the Food and Drug Administration approved iobenguane I 131 (AZEDRA, Progenics Pharmaceuticals, Inc.) for adult and pediatric patients (12 years and older) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who require systemic anticancer therapy.

Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021
NCCN Guidelines 2021

HSA-^{131}MIBG Therapy



92% had a partial response or stable disease



Median overall survival: 36.7 mo (95% CI: 29.9-49.1mo)

Recommendation

High specific activity ^{131}I-MIBG should be considered for patients requiring systemic therapy and who have MIBG-avid disease

Pryma et al. J Nucl Med. 2019;60:625-30

Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021

Chemotherapy

Recommendation

Cytotoxic chemotherapy should be considered first line when patients have bulky disease (defined as many large metastases) (significant majority) or symptomatic or rapidly progressive disease

Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021

CVD (cyclophosphamide, vincristine and dacarbazine)

	Study Type	No. Of Patients	Tumor Response
Averbuch et al.	Non-randomized, single-arm trial	14	55%
Huang et al.	Retrospective	18	11%
Tanabe et al.	Retrospective	17	47.1%

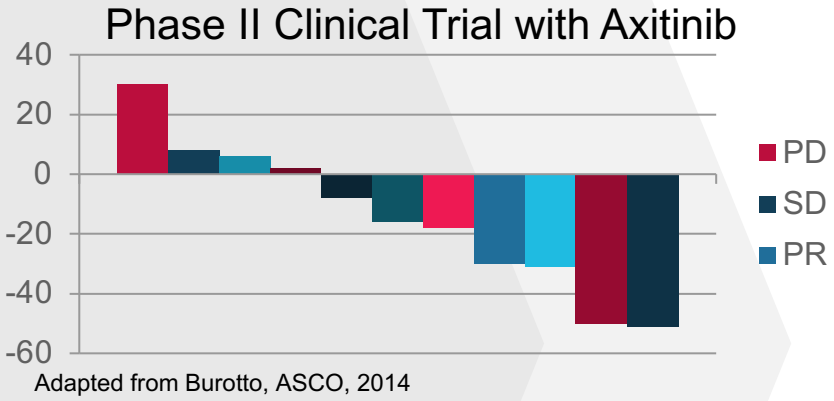
Temozolomide

	Study Type	No. of Participants	Partial Response Rate
Hadoux et al	Retrospective	15	30% (5:15)
DFCI	Retrospective	8	37.5% (3:8)

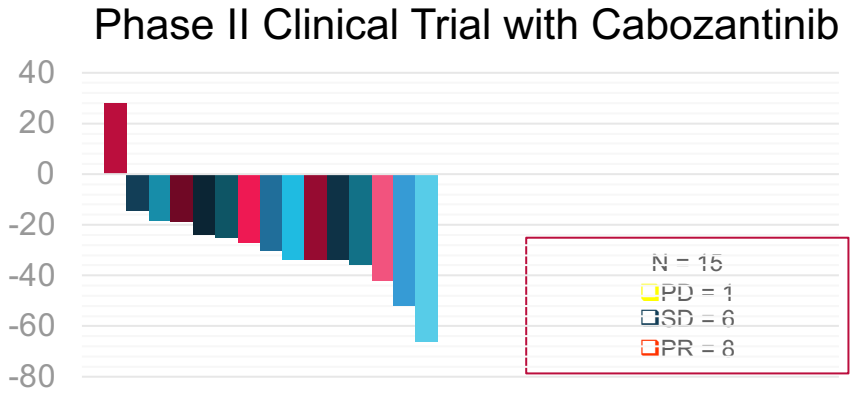
Averbuch S. Annals of Internal Medicine 1988; 109: 267-73.
Huang H. Cancer 2008;113:2020-8.
Tanabe. Hormones & Cancer. 2013; 4: 103-10.

Cancer. 2014; 135: 2711-2720.
Journal of Clinical Oncology .2014.32.15_suppl.e15157

Tyrosine Kinase Inhibitor (TKI) Therapy



Adapted from Burotto, ASCO, 2014



Recommendation

The TKIs could be a therapeutic option for patients with metastatic PHEO/PARA, especially for those with tumors non-avid on MIBG, mixed tumors, and patients with contraindications for MIBG therapy (ie, bone marrow suppression due to bone metastases) or for any patients with rapid progression.

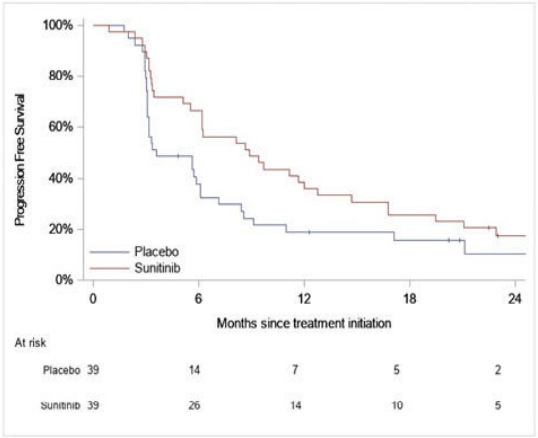
First International Randomized Study in Malignant Progressive Pheochromocytoma and Paraganglioma (FIRSTMAPPP)

Sunitinib
Treatment Improved Survival for Malignant Pheochromocytoma and Paraganglioma

FIRSTMAPPP: MEDIAN PFS

Median PFS in both arms

Median PFS is
- 8.9 months in Sunitinib arm (95% CI: [5.5; 12.7])
- 3.6 months in Placebo arm (95% CI: [3.1; 6.1]).

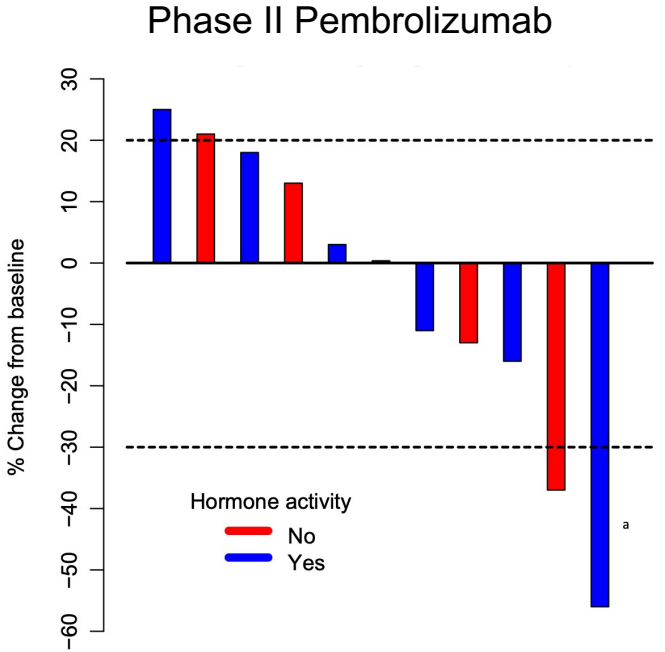


ESMO 2021

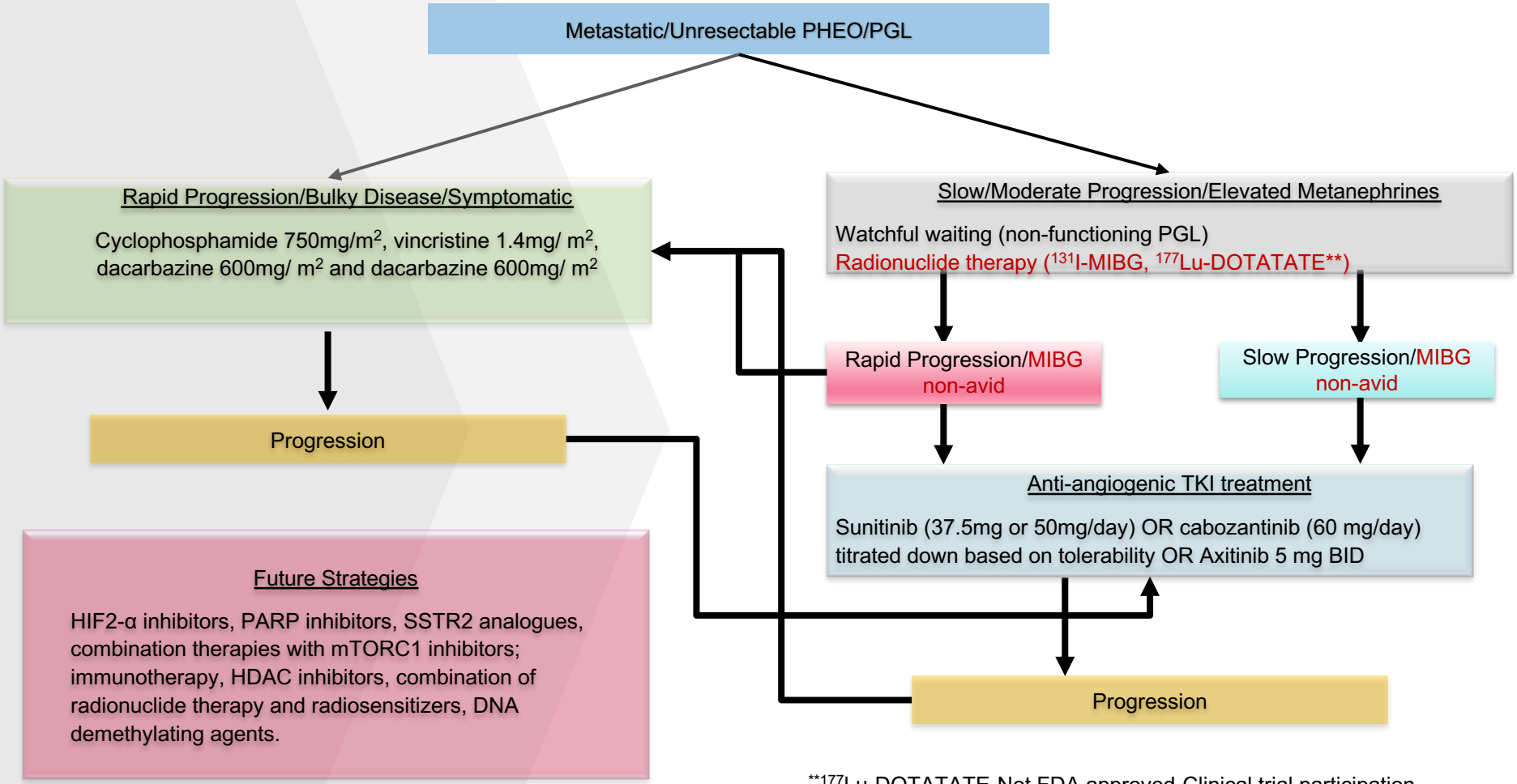
Immunotherapy

Recommendation

Immunotherapy may bring benefits to subgroups of patients with progressive metastatic PHEO/PARA. Given the very limited data and that the mechanisms that determine a positive response are unknown, we recommend immunotherapy be limited to clinical trials at this time



Jimenez et al. Cancers (Basel). 2020;12:2307.



**177Lu-DOTATATE-Not FDA approved-Clinical trial participation

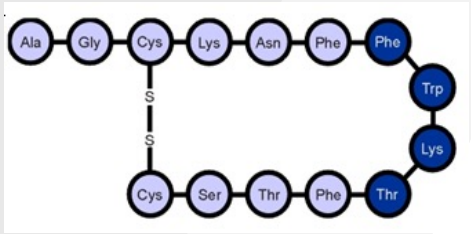
Ilanchezhian M, Del Rivero. Curr Treat Options Oncol. 2020 Aug 29;21(11):85
Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021

Clinical Trials for Advanced/Metastatic Pheochromocytoma and Paraganglioma

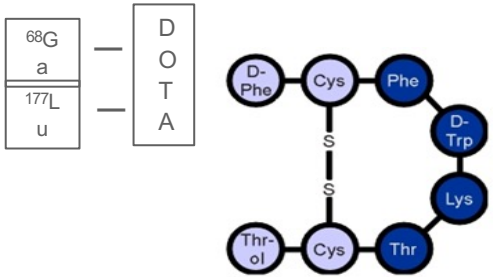
INSERT DATE

Diagnosis, Pathophysiology, and Molecular Biology of Pheochromocytoma and Paraganglioma (NCT00004847)

- Pheochromocytoma(PHEO) and paraganglioma (PGL): catecholamine-producing tumors
- Orphan disease: 0.8 per 100,000 (NIH: ~200 patients per year)
- Limited treatment options when metastatic
- Over-express somatostatin receptor (>90%)



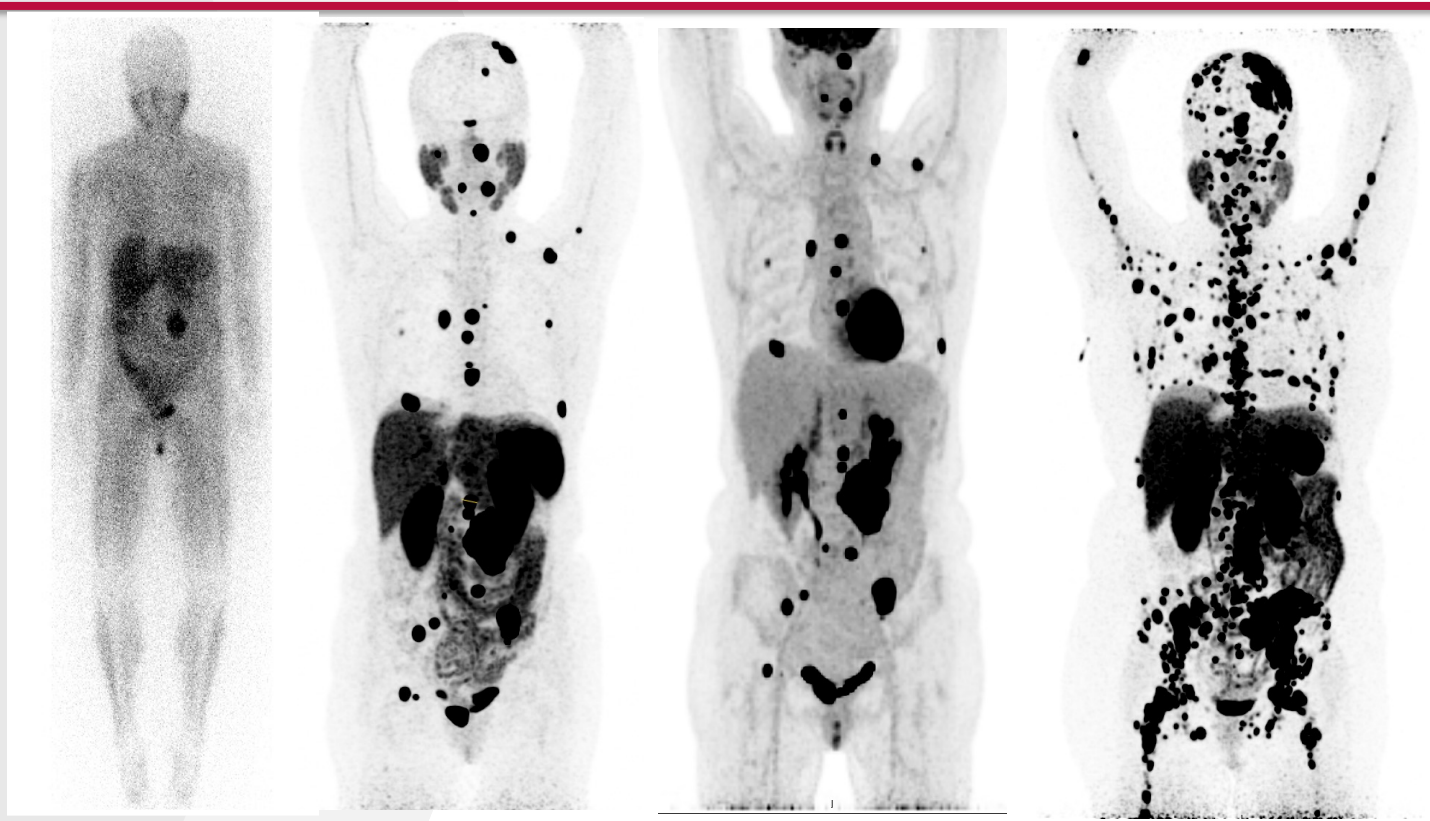
Natural ligand: Somatostatin



Small molecule analog: ^{68}Ga/^{177}Lu-DOTA-Octreotate

Dr. Karel Pacak

^{68}Ga-DOTATATE Scan



^{123}I-MIBG | PET F-DOPA | PET FDG | ^{68}Ga-DOTATATE PET

Lu-177-DOTATATE (Lutathera) in Therapy of Inoperable Pheochromocytoma/Paraganglioma (NCT03206060)

Phase II study

- **Patients >18 years-old**
- Patients with metastatic or inoperable Pheochromocytoma/ Paraganglioma
- SSTR+ disease as documented by positive Ga-68-DOTATATE PET scan

Dr. Frank Lin

NIH NATIONAL CANCER INSTITUTE

4 cycles of ^{177}Lu-Dotatate every 2 months

Dose 1	Dose 2	Dose 3	Dose 4

Secondary Objectives:

- Overall Survival (OS): The amount of time the patient is alive after start of this treatment
- Objective response rate (ORR): The percentage of patients whose cancer shrinks or disappears after treatment
- Determine changes in plasma biochemical markers
- Evaluate Quality of Life (QoL)
- Determine ability to decrease anti-hypertensive medication

Primary Objective
Progression-free survival (PFS)
The percentage of people who did not have new tumor growth or cancer spread during or after treatment.
This means the cancer is still there but not growing or spreading.

Phase II to Evaluate the Efficacy and Dosimetry of Lutathera in Adolescent Patients With SSTR positive GEP-NETs, PPGL: NETTER-P (NCT04711135)

Patients

- Age **12 to <18** years a the time of enrolment
- Metastatic or locally advanced, G1 or G2 (Ki67% >20%)
- SSRT+ GEP-NETs, PPGLs

4 cycles of ^{177}Lu-Dotatate every 2 months

Dose 1	Dose 2	Dose 3	Dose 4

Multicenter International Study

University of Iowa
University of Kentucky
Cincinnati Children's Hospital
Children's Hospital of Philadelphia
Texas's Children Hospital

Objectives:

- Evaluate organ radiation doses
- Evaluate safety and tolerability of Lutetium ^{177}Lu-Dotatate
- Evaluate cumulative safety of Lutetium Lu-177 Dotatate
- Evaluate long-term safety

A021804: Randomized phase II trial: Temozolomide vs. Temozolomide + Olaparib in PHEO/PARA (NCT04394858)

Dr. Kim Perez

Primary Objective

- Compare the progression-free survival (PFS) of patients with advanced PHEO/PARA receiving temozolomide and olaparib to that of patients receiving temozolomide alone

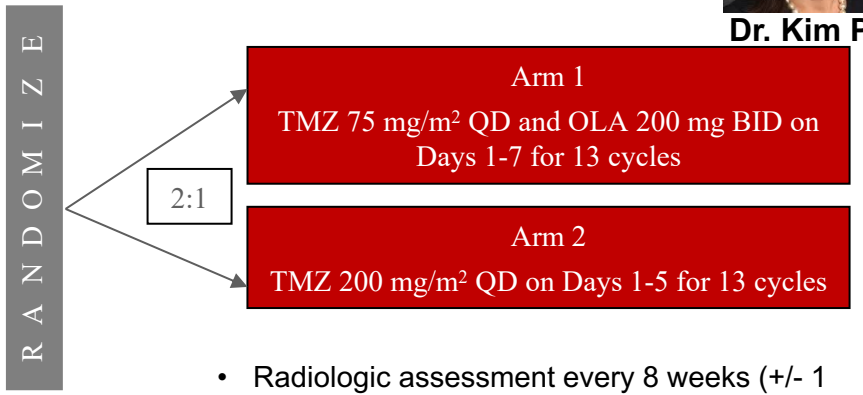
Secondary Objective

- To compare the overall survival (OS) of patients with PHEO/PARA receiving temozolomide and olaparib vs. temozolomide alone.
- To compare the objective response rate (ORR) associated with temozolomide and olaparib vs. temozolomide alone
- To evaluate and compare the toxicity profile of temozolomide-based combinations and olaparib vs. temozolomide

Schema

For Arm 1: One Cycle = 21 Days

For Arm 2: One Cycle = 28 Days



- Radiologic assessment every 8 weeks (+/- 1 week)
- Treatment is to continue for 13 cycles or until disease progression, unacceptable adverse event, or withdrawal of consent

Cabozantinib S-malate in Treating Patients With Metastatic Pheochromocytomas or Paragangliomas (NCT02302833)

Phase II Study

- Patients with advaced or metastatic Pheochromcoytoma/Paraganglioma

→

Cabozantinib once a daily

Courses repeat every 4 weeks in the absence of disease progression or unacceptable toxicity.

→

Primary Objective:
Objective response rate (OS): The percentage of patients whose cancer shrinks or disappears after treatment, determined by computed tomography (CT) or magnetic resonance imaging (MRI).

Secondary Objectives:

- To estimate progression-free survival at 1-year.
- To correlate blood pressure control and change/discontinuation of antihypertensive medications with tumor responses
- To correlate plasma metanephrines and chromogranin A with tumor responses.

Dr. Camilo Jimenez

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

NIH NATIONAL CANCER INSTITUTE

Study of Axitinib (AG-013736) With Evaluation of the VEGF-pathway in Pheochromocytoma/Paraganglioma (NCT03839498)

Phase II Study

- Patients with advaced or metastatic Pheochromcoytoma/ paraganglioma

→ **Axitinib** orally twice a day every 12 hours →

Primary Objective
Objective response rate (OS): The percentage of patients whose cancer shrinks or disappears after treatment,

Secondary Objectives
Progression-free survival (PFS): The percentage of people who did not have new tumor growth or cancer spread during or after treatment.

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Dr. Antonio (Tito) Fojo

LAnreotide in Metastatic Pheochromocytoma / PARAganglioma (LAMPARA) (NCT03946527)

Phase II Study

- Patients with advaced or metastatic Pheochromcoytoma/ paraganglioma

→ Lanreotide 120 mg deep subcutaneous injection every 4 weeks (±7 days) for 52 weeks, followed by an extension phase →

Primary Objective
Rate of tumor growth: Tumor growth measured by a CT or MRI scan in pre-treatment, and minimum of three scans (prior to every 3rd visit, or every 12 weeks) in post-treatment.

Secondary Objective:
- Overall survival (OS)
- Overall Response Rate (ORR)
- Progression-free survival (PFS)

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Dr. Antonio (Tito) Fojo

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Belzutifan/MK-6482 for the Treatment of Advanced Pheochromocytoma/Paraganglioma (PPGL) or Pancreatic Neuroendocrine Tumor (pNET) (NCT04924075)

Phase II Study

12 years and older
Patients with advaced or metastatic Pheochromcoytoma/ Paraganglioma and Pancreatic Neuroendocrine Tumors

Pheochromcoytoma/ Paraganglioma

Belzutifan 120 mg daily

Pancreatic Neuroendocrine Tumors

Belzutifan 120 mg al día

Primary Objective:

Objective Response Rate (ORR)

Secondary Objectives:

Duration of Response (DOR)

Time to Response (TTR)

Disease Control Rate (DCR)

Progressive Free Survival (PFS)

Overall Survival (OS)

Multicenter International Study
Cedars-Sinai Medical Center
University of Iowa
Johns Hopkins Hospital
Icahn School of Medicine at Mount Sinai
Vanderbilt University Medical Center
MD Anderson

A Novel Therapeutic Vaccine (EO2401) in Metastatic Adrenocortical Carcinoma or Malignant Pheochromocytoma/Paraganglioma (NCT04187404)

Phase I/II Study

- Patients with advaced or metastatic Pheochromcoytoma/ Paraganglioma and
- Adrenocortical cancers

Cohort 1: Phase I: Safety
patients with adrenal carcinoma or progressive malignant pheochromocytoma/paraganglioma
EO2401 in combination with nivolumab

Cohort 2: Phase II
Patients with adrenocortical cancer previously treated or untreated patients
EO2401 in combination with nivolumab

Cohort 2: Phase II
Patients with pheochromocytoma and paraganglioma previously treated or untreated patients
EO2401 in combination with nivolumab

Primary Objective:
Adverse events assessment

Multicenter International Study
MD Anderson

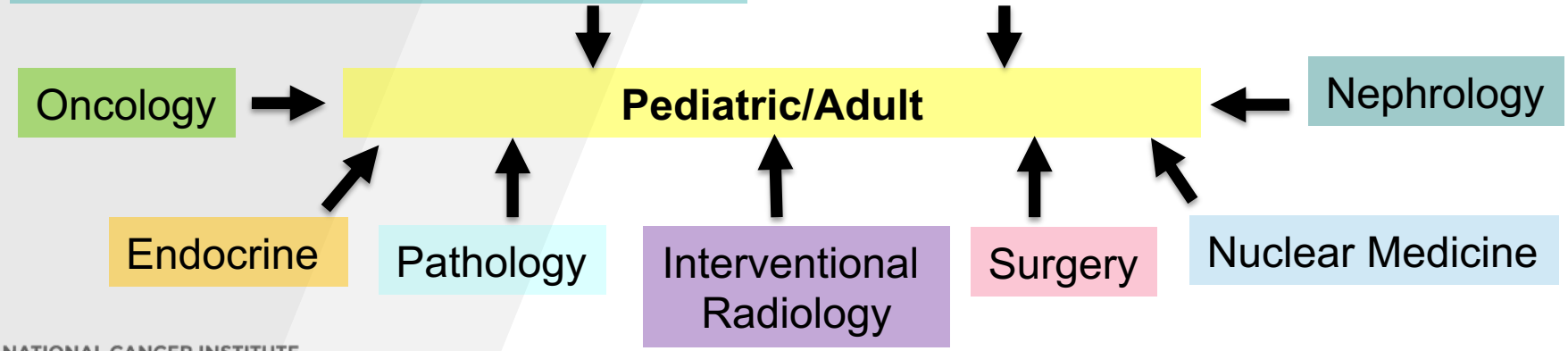
PPGL Therapeutics Program (PPTP)

Natural History Studies

- Diagnosis, Pathophysiology, and Molecular Biology of Pheochromocytoma and Paraganglioma
- Tissue Procurement and Natural History Study of Neuroendocrine Neoplasms (NENs) including Adrenocortical Carcinoma (ACC)

Clinical Trials

- Lu-177-DOTATATE (Lutathera) in Therapy of Inoperable PPGL
- Randomized phase II trial: TMZ vs. TMZ + Olaparib in PHEO/PGL
- Belzutifan/MK-6482 for the Treatment of Advanced PPGL or pNET
- LAnreotide in Metastatic PPGL(LAMPARA)



Take Home Points

- Pheochromocytoma / Paraganglioma are rare tumors with severe or life-threatening damage to other body systems, especially the cardiovascular system
- Genetic counseling is recommended on all patients : 40% hereditary cause
- 24-hour urine/plasma fractionated metanephrines have high sensitivity.
- CT and MRI localize the primary tumor
- Functional images allow to characterize the tumor, detect metastases and evaluate possible systemic treatments
- First line medical treatment is alpha blockers
- When the pheochromocytoma or paraganglioma is localized, surgical resection is the treatment of choice.
- Systemic treatment in malignant pheochromocytoma/paraganglioma depends on disease progression
- A multidisciplinary team is needed to guide patient management

Giovanna J. Imbesi

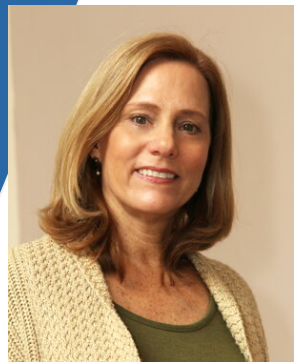
“Individually, we are one drop. Together, we are an ocean”

Lisa Yen

Lindsey Jeu De Vine

Mary Donlevy

LACNETS



Donna Gavin

Kavya Velagapudi

Thank you!

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