Update on Pheochromocytoma (PHEO) and Paraganglioma (PGL): Implications for Clinical Practice

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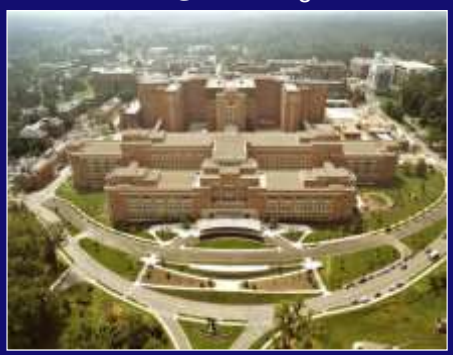


National Institutes of Health

Disclosure

Nothing to disclose

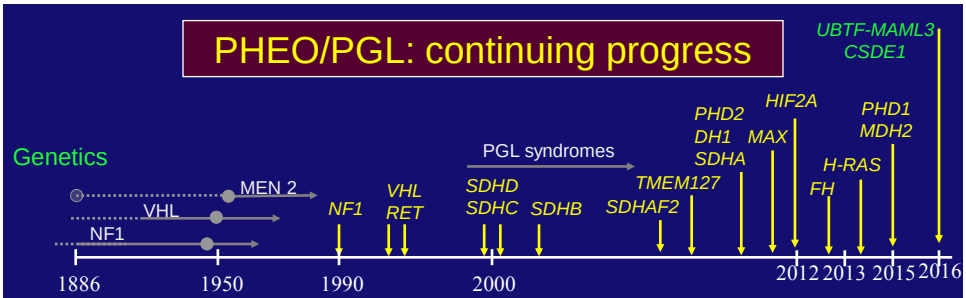
PHEO/PGL: Updated Facts

Current important facts:

- In about 70% of PHEOs/PGLs, a genetic defect is known (30% have germline and 40% have somatic mutations); 22 PHEO/PGL susceptibility genes are currently known
- Biochemical dg. and localization is highly successful
- Clinical practice guidelines launched in 2014 & 2016
- New treatments using ^{177}Lu-DOTATATE (Lutathera®) and ^{223}Radium dichloride (Xofigo®) are on the horizon

Chairs: Pacak, Nathanson, Wilkerson, The Cancer Genome Atlas data, 2016
NIH protocols in preparation

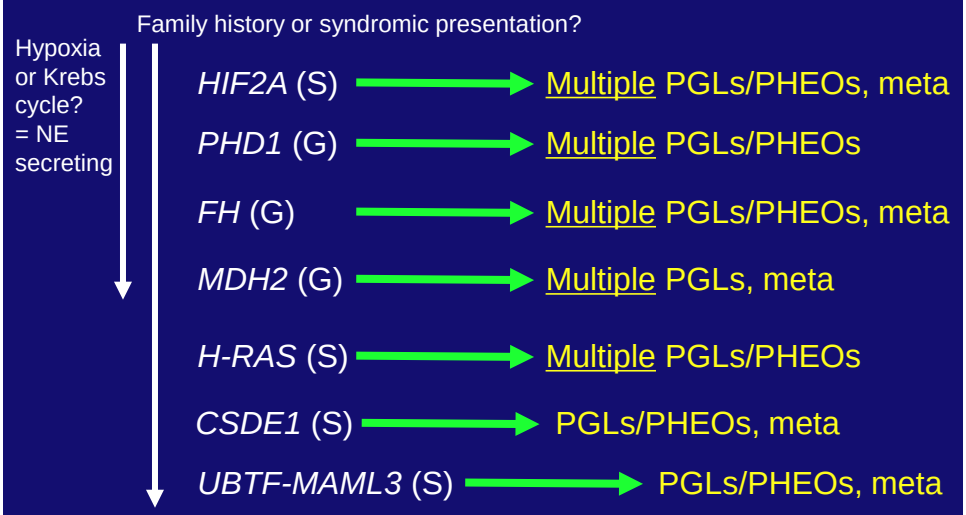
PHEO/PGL: continuing progress



UBTF-MAML3: upstream binding transcription factor-mastermind like transcriptional coactivator 3

CSDE1: cold shock domain-containing E1

New PHEO/PGL susceptibility genes



S: somatic; G: germline; meta: metastatic

Zhuang et al. NEJM 2012; 6:922
Crona et al. JCEM 2013; 98:E1266
Letouze et al. Cancer Cell 2013; 23:739
Oudijk et al. JCEM 2014; E1376
Cascon, JNCI 2015JNCI, in press
TCGA, 2016, in preparation

Current characteristics of *SDHB/D*-related PHEOs/PGLs

- Mostly extra-adrenal abdominal, some HNPGLs (SDHD), aggressive, multiple, metastatic (if from an abdominal PGL, 40% chance of *SDHB* mutation)
- Most mediastinal, organ of Zuckerkandl, cardiac (78%), and urinary bladder (50%) PGLs
- Kidney cancer (14%)
- Gastrointestinal stromal tumors & pituitary adenomas (PRL, GH) “3P syndrome?”
- Pancreatic neuroendocrine tumors

Auchus et al. Endocr. Relat. Cancer 2009; 16:291
Martucci et al. Urol. Oncol. 2015; 33:167
Martucci et al. Am. J. Cardiol. 2015; 115:1753
Xekouki et al. JCEM 2015; 100:E710
Niemeijer et al. JCEM 2015; i100:1386

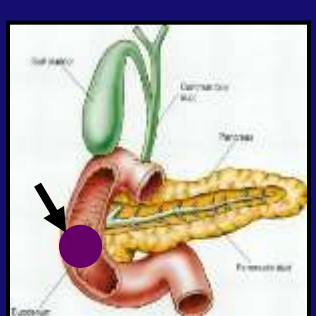
Update on metastatic SDHB and sporadic PHEO/PGL

- 132 patients were included (27 children, 105 adults), 73 had SDHB, 59 were sporadic metastatic PHEO/PGL
- Only 16% of all primary tumors were smaller than 4.5 cm
- In children, metastatic PHEO/PGL was mainly due to SDHB. In adults, tumors were equally distributed between SDHB and sporadic
- 23% of SDHB and 16% of sporadic PHEO/PGL had metastatic disease at initial diagnosis
- Survival: 5 & 10 years: SDHB: 92%/76%; sporadic: 95%/86%

Turkova et al. Endocr. Pract. 2016; 22:302

HIF2A-related new neuroendocrine tumor syndrome

- In all patients, polycythemia presents at birth or early childhood; EPO levels are always elevated
- PGLs: Mostly extra-adrenal multiple abdominal, less commonly PHEOs, median age: 17 years, 29% metastatic, ALL NE-producing
- Somatostatinoma: always in the 2nd portion of the duodenum, median age: 29 years, 40% multiple, 60% metastatic,
- Cholelithiasis in almost all patients
- Cysts in kidney, breast, lung, pancreas in 57% of patients
- Various retinal changes

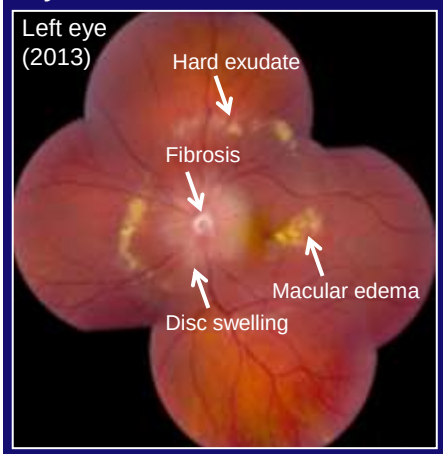


HIF2A: hypoxia-inducible factor 2α gene (also called *EPAS1*)

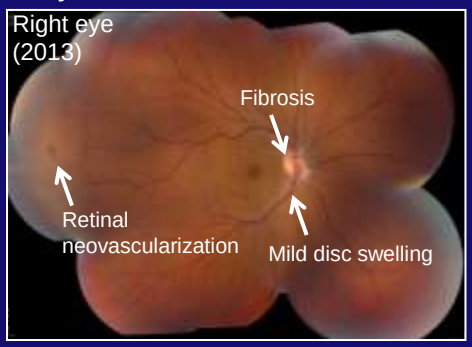
Zhuang et al. NEJM 2012; 367:922-930
Pacak et al. JCO 2013;
Garbrecht et al. Endocr. Relat. Cancer 2008; 15:229
Därr et al., in preparation

HIF2A-related syndrome: Ocular findings

9 y. o.



32 y. o.

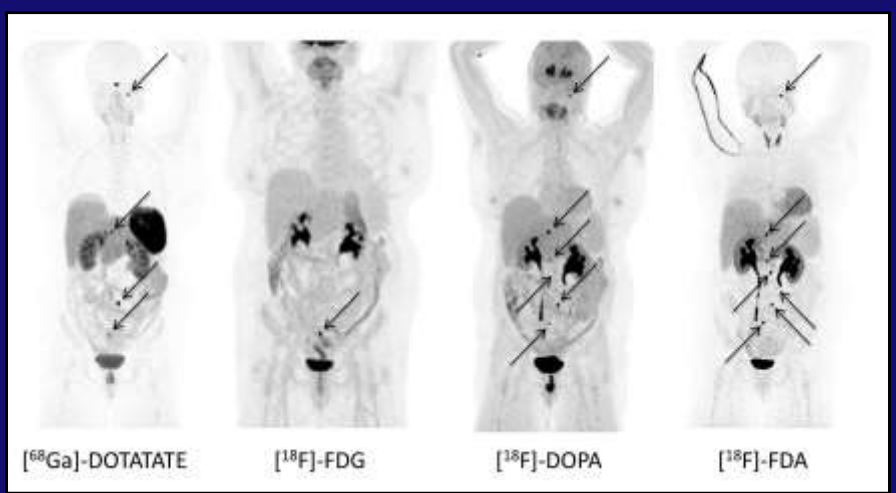


70% of patients were found to have ocular abnormalities.

First successful laser surgery was performed in May 2016 at the NIH.

Pacak et al. Ophthalmology; 2014; 12:2291
& unpublished observations

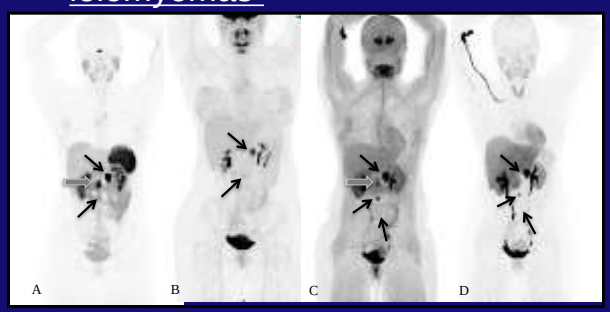
Functional imaging in the localization of PGL/PHEO-related to *HIF2A* mutations



Därr et al., in preparation

Germline fumarate hydratase (*FH*) mutations

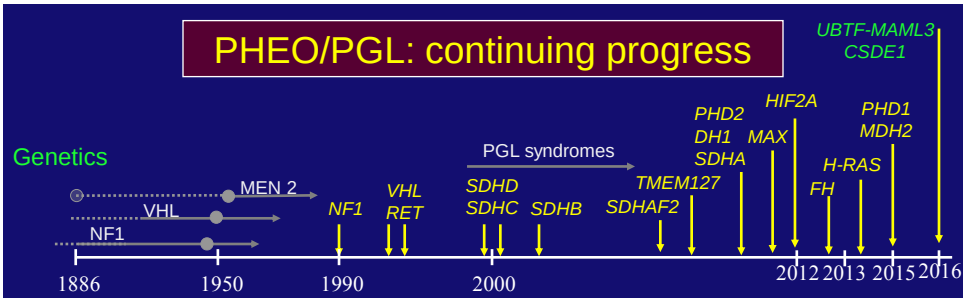
- PHEO/PGL: multiple, also head and neck
- Moderate rate of malignancy (2nd to *SDHB*)
- NE producing tumors
- Papillary renal cell carcinoma, uterine fibroids, leiomyomas

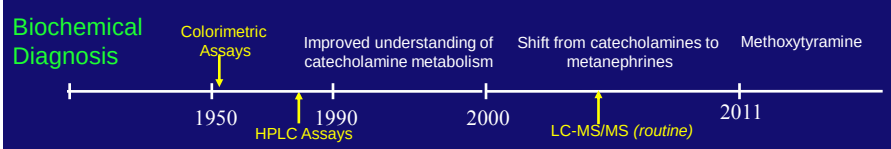


^{68}Ga-DOTATATE ^{18}F-FDG ^{18}F-FDOPA ^{18}F-FDopamine

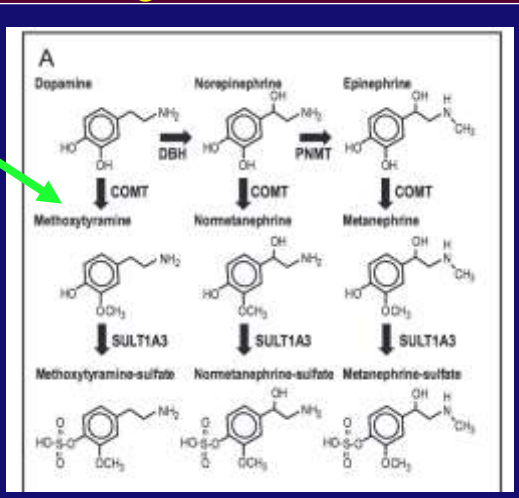
Letouze et al. Cancer Cell 2013; 23:739
Castro-Vega et al. Hum. Mol. Genet. 2014; 23:2440
Clark et al. JCEM 2014; 99:E2406
Nambuba et al. Endocr. Pract.; in press

PHEO/PGL: continuing progress



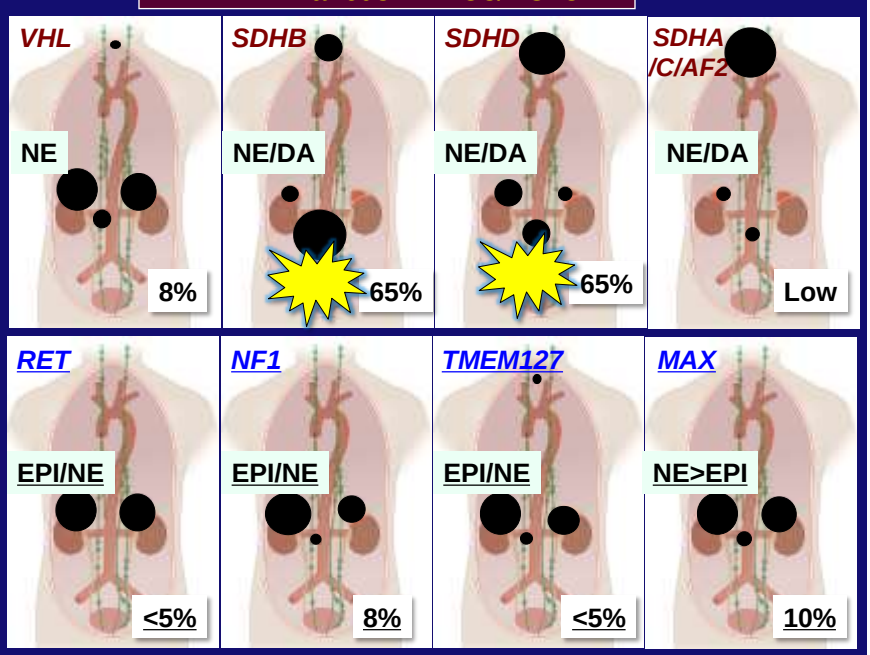


Methoxytyramine (MTY) as a new biomarker in the diagnosis of PHEO/PGL



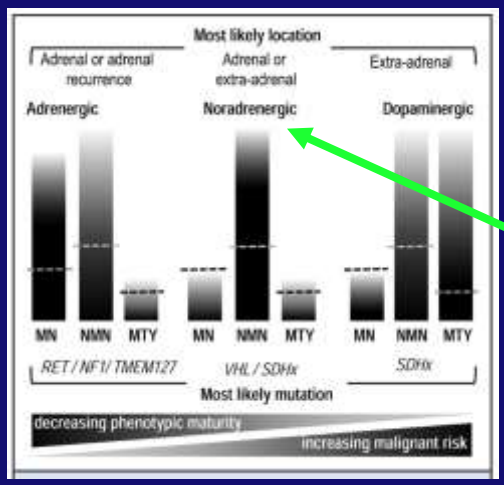
Eisenhofer et al. Clin. Chem. 2014; 60:12

MTY in various PHEOs/PGLs



Adapted from G. Eisenhofer & Neumann et al. Harrison's Principles of Internal Medicine

Biochemical-genetic phenotype



Krebs cycle (*FH*, *MDH2*) and hypoxia (*HIF2A*, *PHD1/2*) genes

Eisenhofer et al. Clin. Chem. 2014; 60:12

Are patients with functional PHEO/PGL initially receiving a proper adrenoceptor blockade?

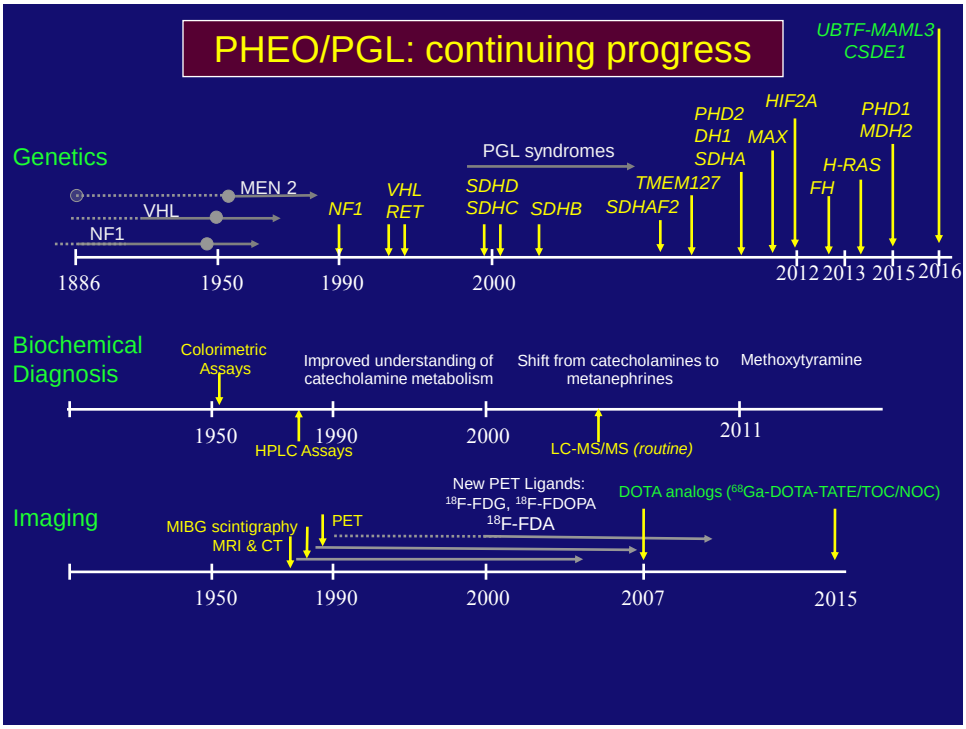
- 381 patients were included
- 69.3% were treated properly (93% received α-adrenoceptor blockade - phenoxybenzamine)

Table 5. Rate of prescription of a proper pharmacological treatment by each subspecialty. Those that managed less than or equal to 10 patients were not included

Subspecialty	Patients, *n*	Appropriate treatment, *n* (%)
Endocrinology	226	183 (81)
Surgery	35	19 (54·3)
Internal medicine	24	14 (58·3)
Cardiology	21	9 (42·9)
Family medicine	18	2 (11·1)
Nephrology	18	16 (88·9)
Oncology	15	7 (46·7)
Paediatrics	14	11 (78·6)

- Of those not treated properly, 53% did not receive any form of medication

Vara Luiz et al. Clin. Endocrinol. 2016; in press



PHEO/PGL and somatostatin receptors (SSTRs) imaging

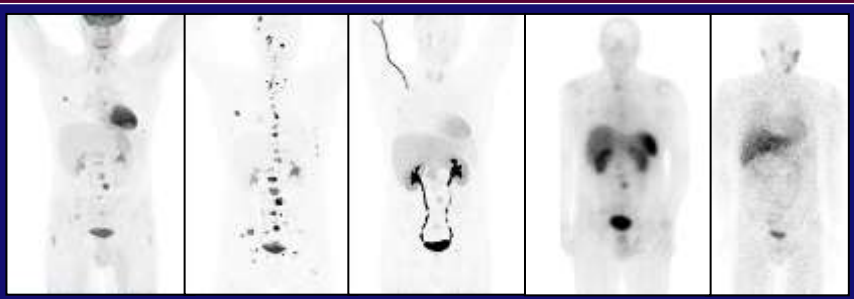
- PHEOs/PGLs express SSTRs (mainly type 2) allowing for the use of Octreoscan scintigraphy (relatively poor spatial resolution)

	SSTR1	SSTR2	SSTR 3	SSTR4	SSTR5
PHEO	++/+++ (15-20%)	++/+++ (75-80%)	-	-	+ (5%)
PGL	+++ (20%)	+++ (80%)	-	-	-

+: level of expression; %: proportion of SSTRs-expressing PHEO/PGL

- SSTR imaging can be performed with PET/CT to improve spatial resolution and sensitivity; PET/CT also provides a more rapid whole-body tomographic imaging, therefore, obtaining a precise anatomic localization

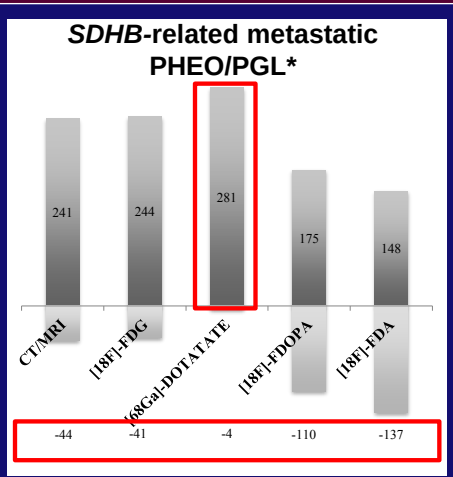
^{68}Ga-DOTATATE PET/CT in *SDHB*-related metastatic PGL



[^{18}F]-FDG | [^{18}F]-FDOPA | [^{18}F]-FDA | Octreoscan | [^{123}I]-MIBG

[^{68}Ga]-DOTATATE

^{68}Ga-DOTATATE PET/CT performance in patients with *SDHB*-related metastatic PHEO/PGL compared to other imaging modalities



* Only patients in whom all imaging modalities were performed

17 patients with *SDHB*-related metastatic PHEO/PGL were included (imaging comparator: composite of functional and anatomical imaging)

Janssen et al. Clin. Cancer Res. 2015; 21:3888

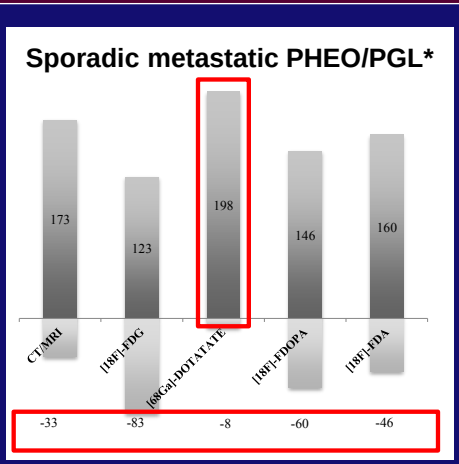
^{68}Ga-DOTATATE PET/CT performance in patients with *SDHB*-related metastatic PHEO/PGL compared to other imaging modalities

Detection rate	[^{68}Ga]-DOTATATE	[^{18}F]-FDG	[^{18}F]-FDOPA	[^{18}F]-FDA	CT/MRI
All compartments	285/289 98.6%	248/289 85.8%	175/285 61.4%	148/285 51.9%	245/289 84.8%
Mediastinum	65/65 100%	57/65 87.7%	39/65 60.0%	39/65 60.0%	55/65 84.6%
Lungs	62/63 98.4%	45/63 71.4%	45/63 71.4%	18/63 28.6%	62/63 98.4%
Abdomen	43/43 100%	40/43 93.0%	31/43 72.1%	19/43 44.2%	33/43 76.7%
Liver	5/5 100%	3/5 60.0%	4/5 80.0%	0/5 0.0%	5/5 100%
Bone	95/98 96.9%	91/98 92.9 %	41/94 43.6%	57/94 60.6%	82/98 83.7%

Number of identified lesions and detection rate (%) in 17 patients with *SDHB*-related PHEOs/PGLs
(imaging comparator: composite of functional and anatomical imaging)

Janssen et al. Clin. Cancer Res. 2015; 21:3888

^{68}Ga-DOTATATE PET/CT in sporadic metastatic PHEO/PGL compared to other imaging modalities



* Only patients in whom all imaging modalities were performed

22 patients with sporadic metastatic PHEO/PGL were included
(imaging comparator: composite of functional and anatomical imaging)

Janssen et al., Eur. J. Nucl. Med. Mol. Imaging 2016; in press

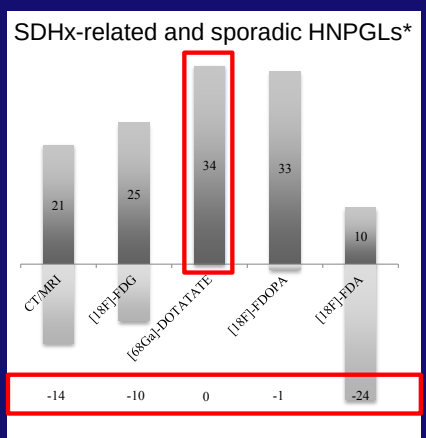
^{68}Ga-DOTATATE PET/CT performance in sporadic metastatic PHEO/PGL compared to other imaging studies

Detection rate	[^{68}Ga]-DOTATATE	[^{18}F]-FDG	[^{18}F]-FDOPA	[^{18}F]-FDA	CT/MRI
All compartments	450/461 97.6%	226/461 49.2%	181/242 74.8%	160/206 77.7%	276/461 81.6%
Mediastinum	46/46 100%	26/46 56.5%	17/24 70.8%	21/21 100%	27/46 58.7%
Lungs	89/94 94.7%	52/94 55.3%	52/53 98.1%	26/38 68.4%	89/94 94.7%
Abdomen	74/74 100%	42/74 56.8%	30/41 73.2%	35/38 92.1%	57/74 77.0%
Liver	42/48 100%	6/48 12.5%	11/13 84.5%	9/13 69.2%	45/48 93.8%
Bone	199/199 100%	100/199 50.3 %	71/111 64.0%	69/96 71.2%	158/199 79.4%

Number of identified lesions and detection rate (%) in 22 patients with sporadic metastatic PHEOs/PGLs
(imaging comparator: composite of functional and anatomical imaging)

Janssen et al., Eur. J. Nucl. Med. Mol. Imaging 2016; in press

^{68}Ga-DOTATATE performance in patients with HNPGLs compared to other imaging modalities



* Only patients in whom all imaging modalities were performed

20 patients with *SDHx*-related or sporadic HNPGLs were included
(imaging comparator: composite of functional and anatomical imaging)

Janssen et al. J. Nucl. Med. 2016; 57:186

^{68}Ga-DOTATATE performance in patients with HNPGLs compared to other imaging modalities

Detection rate	[^{68}Ga]-DOTATATE	[^{18}F]-FDOPA	[^{18}F]-FDG	[^{18}F]-FDA	CT/MRI
Total	38/38 100%	37/38 97.4%	27/38 71.1%	10/34 29.4%	23/38 60.5%
Jugulotympanic	12/12 100%	11/12 91.7%	8/12 66.7%	4/10 40.0%	5/12 41.7%
Glomus vagale	10/10 100%	10/10 100%	9/10 90.0%	0/10 0.0%	8/10 80.0%
Carotid body	8/8 100%	8/8 100%	6/8 75.0%	3/7 42.9%	7/8 87.5%
Lymph nodes	8/8 100%	8/8 100%	4/8 50.0%	3/7 42.9%	3/8 37.5%

Number of identified head and neck lesions and detection rate (%) in 20 patients with HNPGLs
(imaging comparator: composite of functional and anatomical imaging)

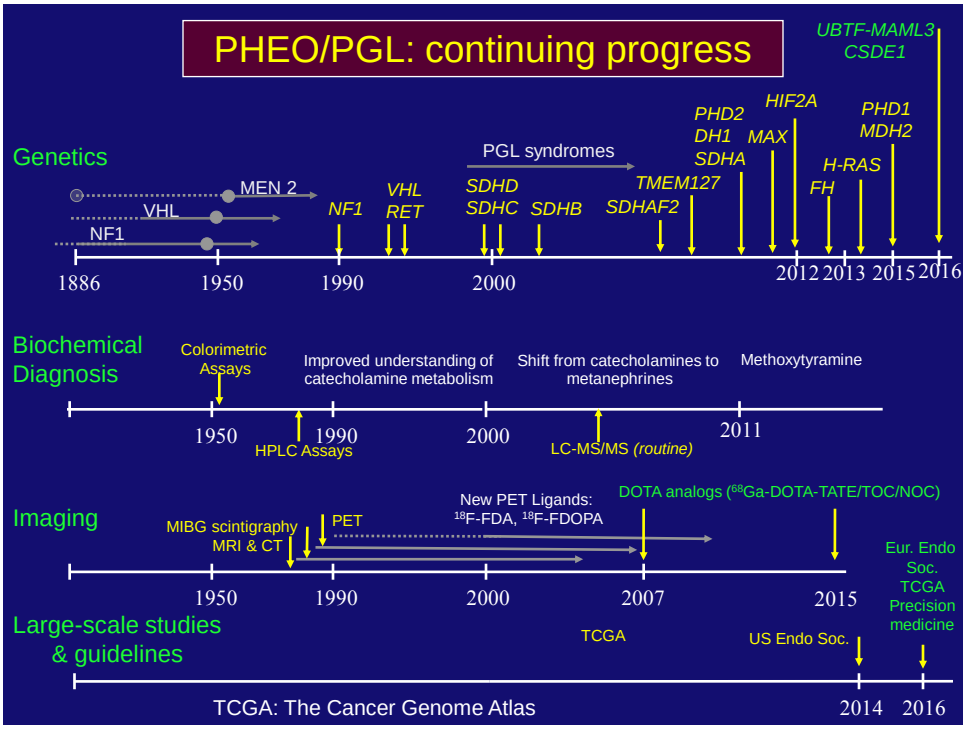
Janssen et al. J. Nucl. Med. 2016; 57:186

Overall performance of ^{68}Ga-DOTATATE PET/CT compared to other imaging modalities

Detection rate	[^{68}Ga]-DOTATATE	[^{18}F]-FDG	[^{18}F]-FDOPA	[^{18}F]-FDA	CT/MRI
Total lesions %	513/525 98%	392/525 75%	325/525 68%	318/525 61%	435/525 83%

Immediate clinical outcome:

- These results suggest modifications in imaging guidelines for metastatic PHEOs/PGLs & HNPGLs
- These results also suggest that metastatic PHEOs/PGLs & HNPGLs may be targeted by ^{177}Lu– or ^{90}Y-DOTA analogs
- These findings resulted in the use of a gamma probe being used for hidden metastatic PHEOs/PGLs



New European Soc. of Endocrinology guidelines

- All patients with PHEO/PGL should be considered for genetic testing
- Plasma or urine metanephrines to be used for screening
- Follow-up for at least 10 years; high-risk patients (children, genetic disease, large tumors) should have lifelong follow up

Plouin et al. Eur. J. Endocrinol. 2016; 174:G1

"A5 PHEO/PGL Genomic Alliance"

"Together we have a chance, separately we fail"

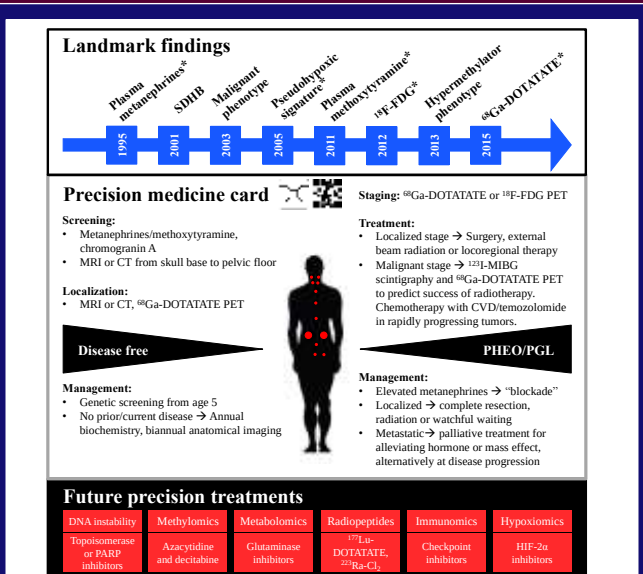
Aim: To develop a *precision medicine* approach for improved treatment of metastatic PHEO/PGL

- **Large-scale international study**
- **Multidisciplinary approach**
- **Excellent clinical assessment**
- **Comprehensive molecular analysis of metastatic PHEO/PGL**

A5: American-Australian-Asian Adrenal Alliance

Tothill et al. Peter MacCallum Cancer Center, Australia
Else et al. University of Michigan Medical School
NICHD/NIH

Current precision medicine card for SDHB-related PHEO/PGL



"Transforming hope to better lives through precision medicine"

Crona & Pacak, in preparation

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TCGA and A5 members and many others

"Patients are our passion and we are their hope "