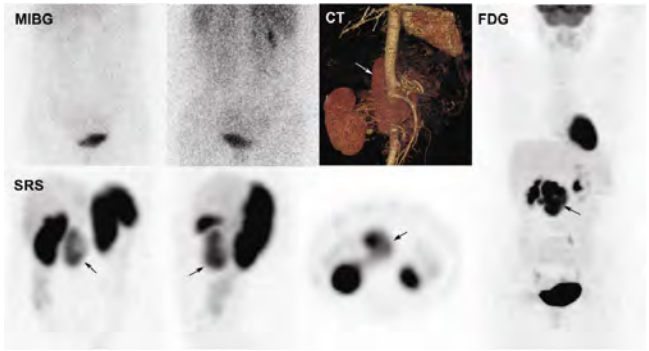
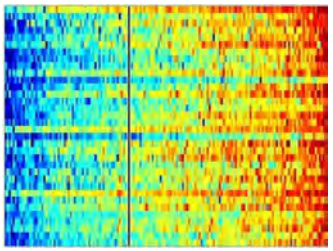
Precision Surgery for Pheochromocytoma (PCC)/Paraganglioma (PGL)

Electron Kebebew, MD, FACS
Professor of Surgery
Chief, Division of General Surgery
Harry A. Oberhelman, Jr. And Mark L. Welton Professor





Disclosure

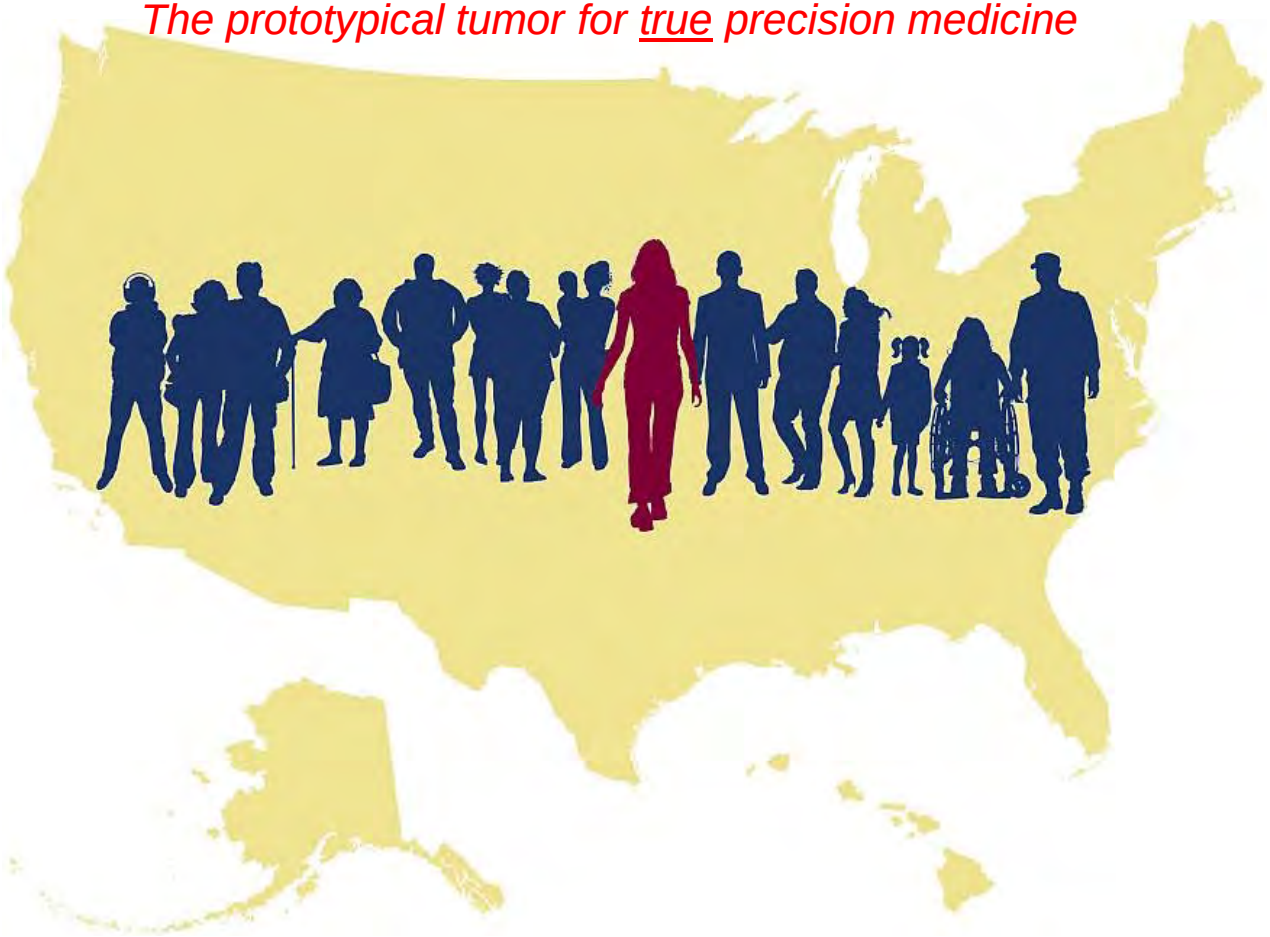
Nothing to disclose

Precision Medicine

Precision Medicine Initiative – Individualize Care

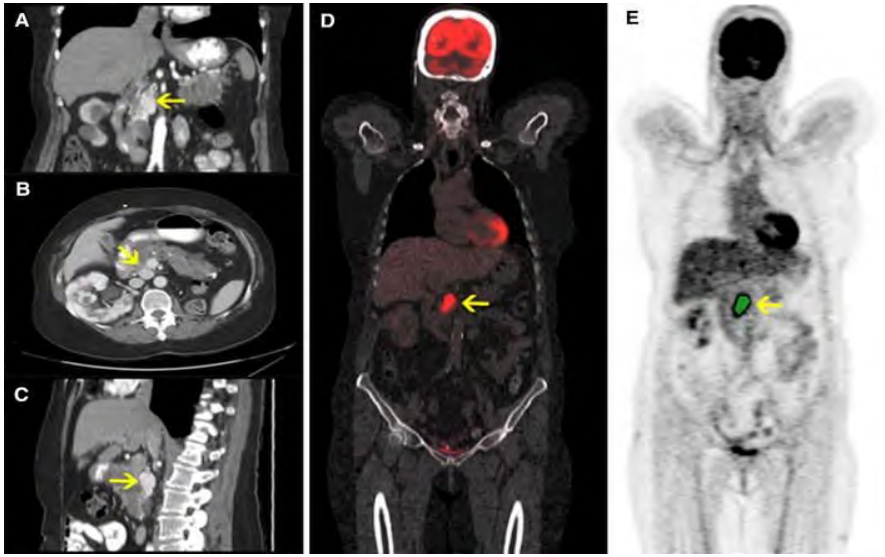
Precision Medicine

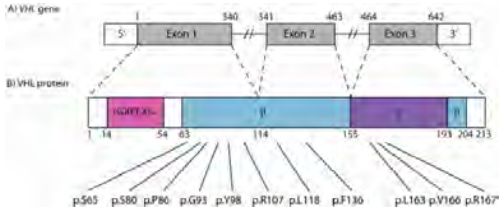
Pheochromocytoma/Paraganglioma –
The prototypical tumor for <u>true</u> precision medicine

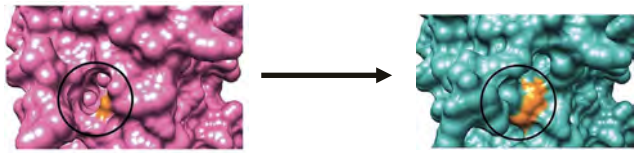


Precision Medicine Initiative – Individualize Care

Precision Surgery







Precision: Exact and accurate in our management.
…or let the crime fit the punishment

Outline

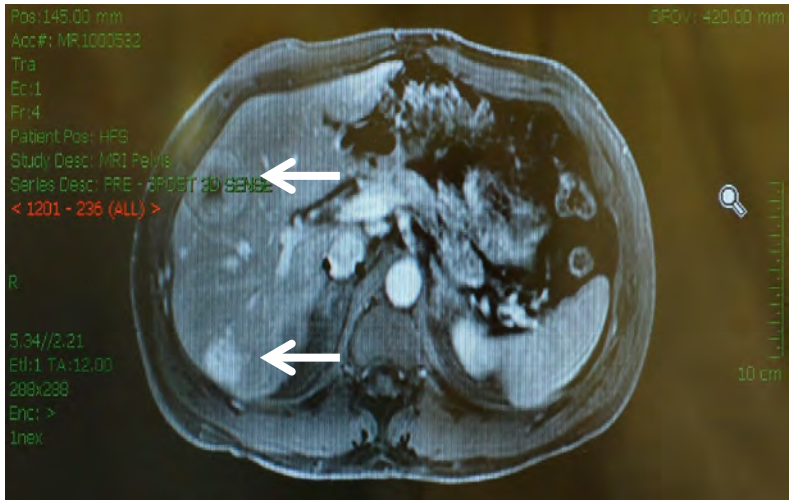
Pheochromocytoma/Paraganglioma (PCC/PGL)

- Genetics
- Imaging
- Personalized surgical management based on genetics and advanced imaging results

PCC/PGL

- Incidence of PCC/PGL is 2-8 cases per million

- Rare but can result in significant morbidity and mortality
  - Functional
  - Mass effect
  - Malignant (metastatic/locally invasive)

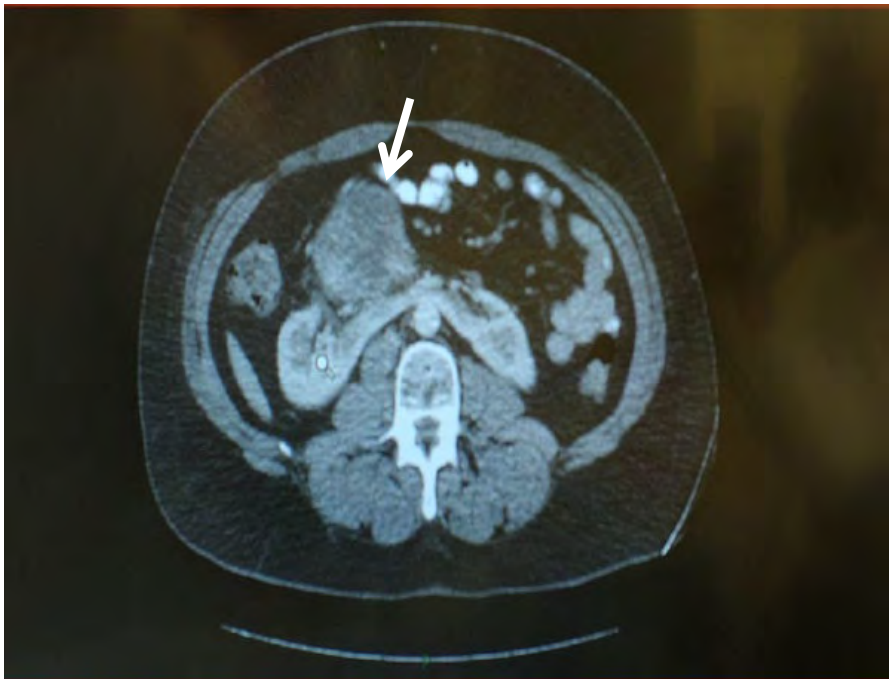


46 year-old man with metastatic paraganglioma resected 2009. Alive and disease-free today.

PCC/PGL

- ~~RULE of 10~~

- Growing list of susceptibility genes
  - Age of onset
  - Tumor site
  - Multiplicity
  - Malignancy….



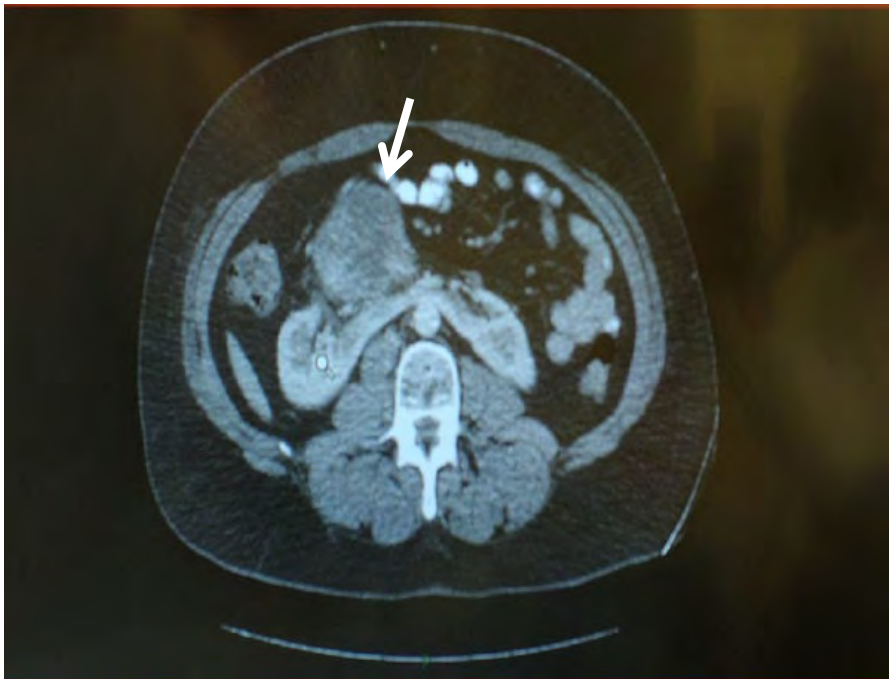
Paraganglioma in a patient with a horseshoe kidney

PCC/PGL

- ~~RULE of 10~~

- Growing list of susceptibility genes
  - Age of onset
  - Tumor site
  - Multiplicity
  - Malignancy….

Commercial PCC/PGL Panel
EGLN1
FH
KIF1B
MAX
MEN1
NF1
RET
SDHA
SDHAF2
SDHB
SDHC
SDHD
TMEM127
VHL



Paraganglioma in a patient with a horseshoe kidney

What we have learnt

Timeline of seminal events in the surgical treatment of PCC/PGL

Almost a century ago…..

1926/27

The first adrenalectomy performed by Roux and Mayo

What we have learnt

Timeline of seminal events in the surgical treatment of PCC/PGL

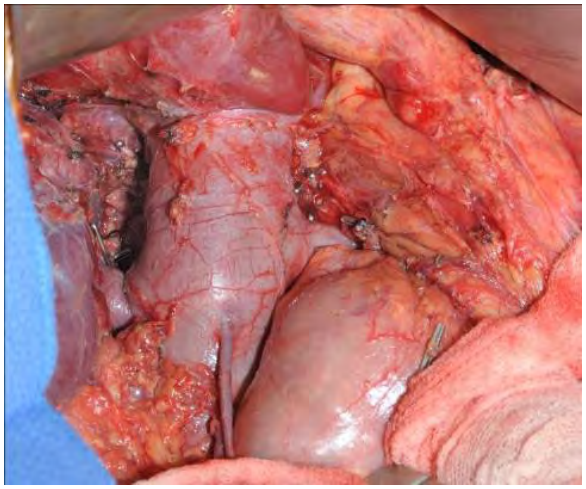
1926/27

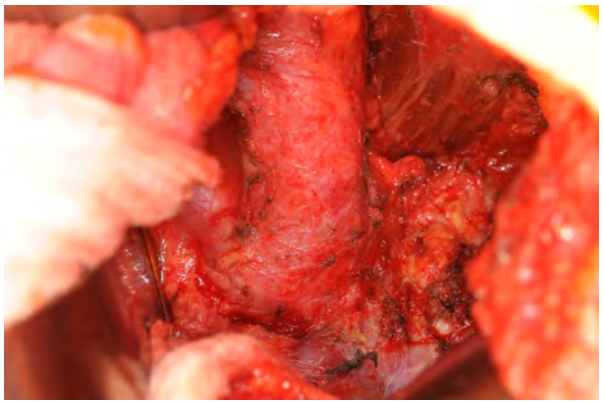
The first adrenalectomy performed by Roux and Mayo

1970-80's

Alpha blockade
Intraoperative hemodynamic monitoring

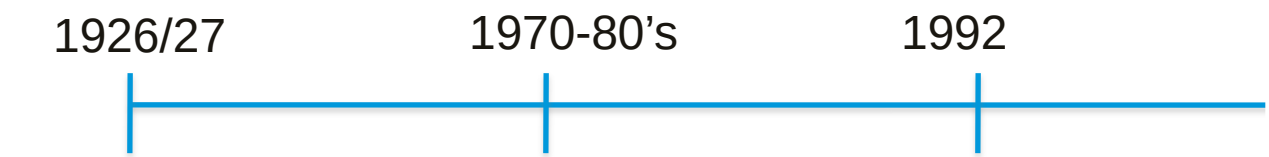
Reduced morbidity and mortality of surgical intervention…..





What we have learnt

Timeline of seminal events in the surgical treatment of PCC/PGL



The first adrenalectomy performed by Roux and Mayo

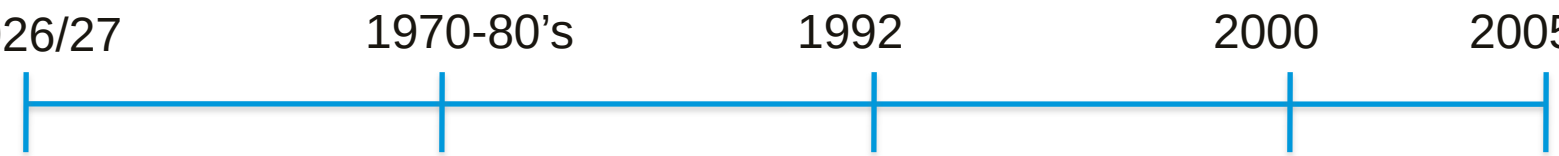
Alpha blockade
Intraoperative hemodynamic monitoring

Minimally invasive adrenalectomy & better localization

What we have learnt

Timeline of seminal events in the surgical treatment of PCC/PGL

Diagnosis
Genetics – syndromes
Refined imaging



The first adrenalectomy performed by Roux and Mayo

Alpha blockade
Intraoperative hemodynamic monitoring

Minimally invasive adrenalectomy & better localization

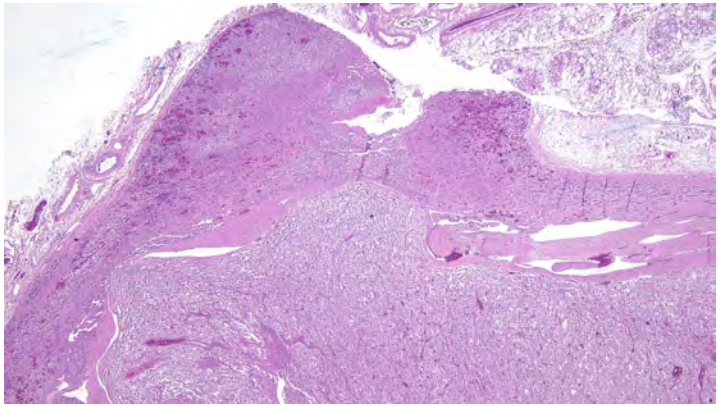
Partial adrenalectomy

Robotic adrenalectomy

Approach

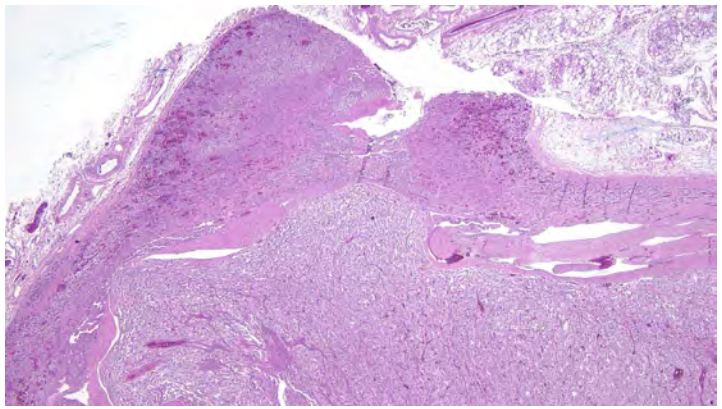
Diagnosis of PCC/PGL

- Biochemical testing is essential for detecting functional tumors
  - Plasma/urine fractionated
    - Normetanephrine(NMN)/metanephrine(MN) levels > 3 upper limit of normal unless prior probability high.
  - Supine
  - Age-adjusted



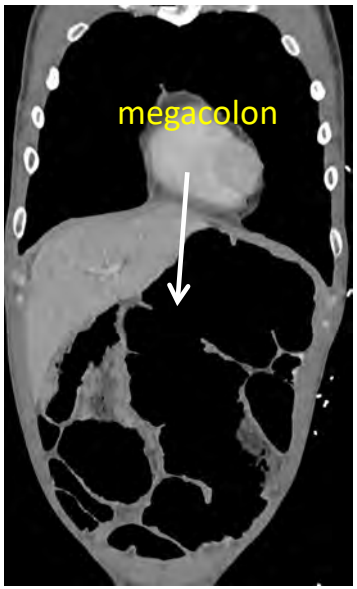
Diagnosis of PCC/PGL

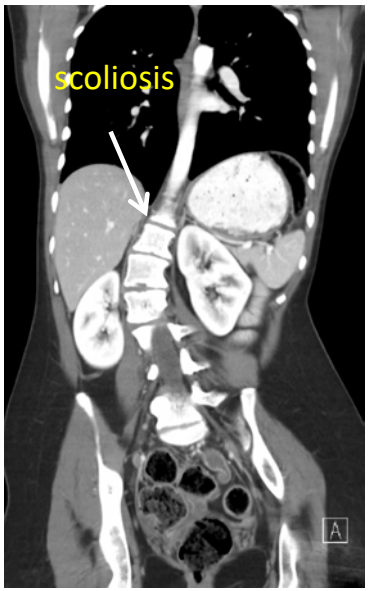
- Biochemical testing is essential for detecting functional tumors
  - Plasma/urine fractionated
    - Normetanephrine(NMN)/metanephrine(MN) levels > 3 upper limit of normal unless prior probability high.
  - Supine
  - Age-adjusted
- Any value above normal should be carefully evaluated.
  - Truly silent – head/neck PGL
  - Psuedo-silent – small tumor burden or episodic

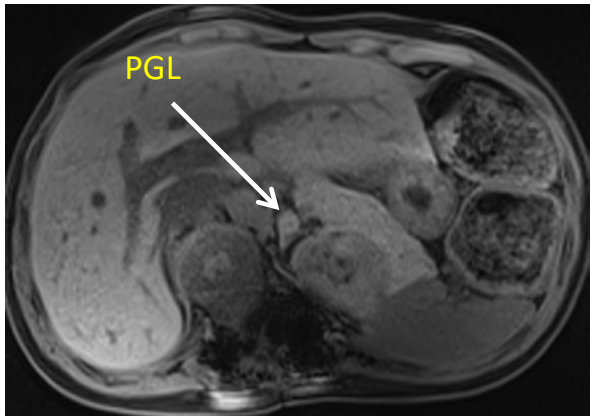


Diagnosis of PCC/PGL - Location

- Noradrenergic phenotype
  - Increased levels in NE/NMN – outside of adrenals







Diagnosis of PCC/PGL - Location

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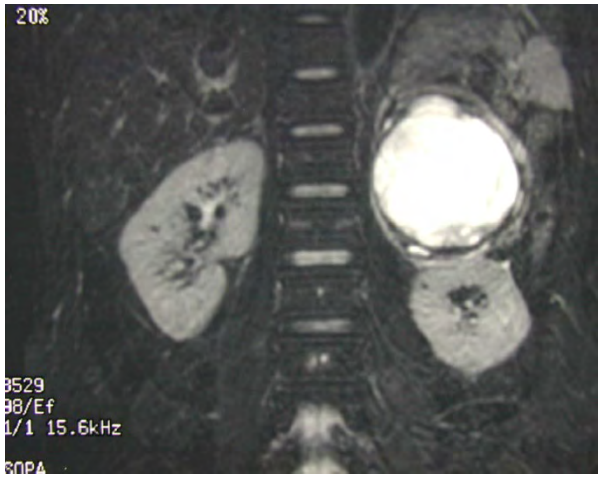
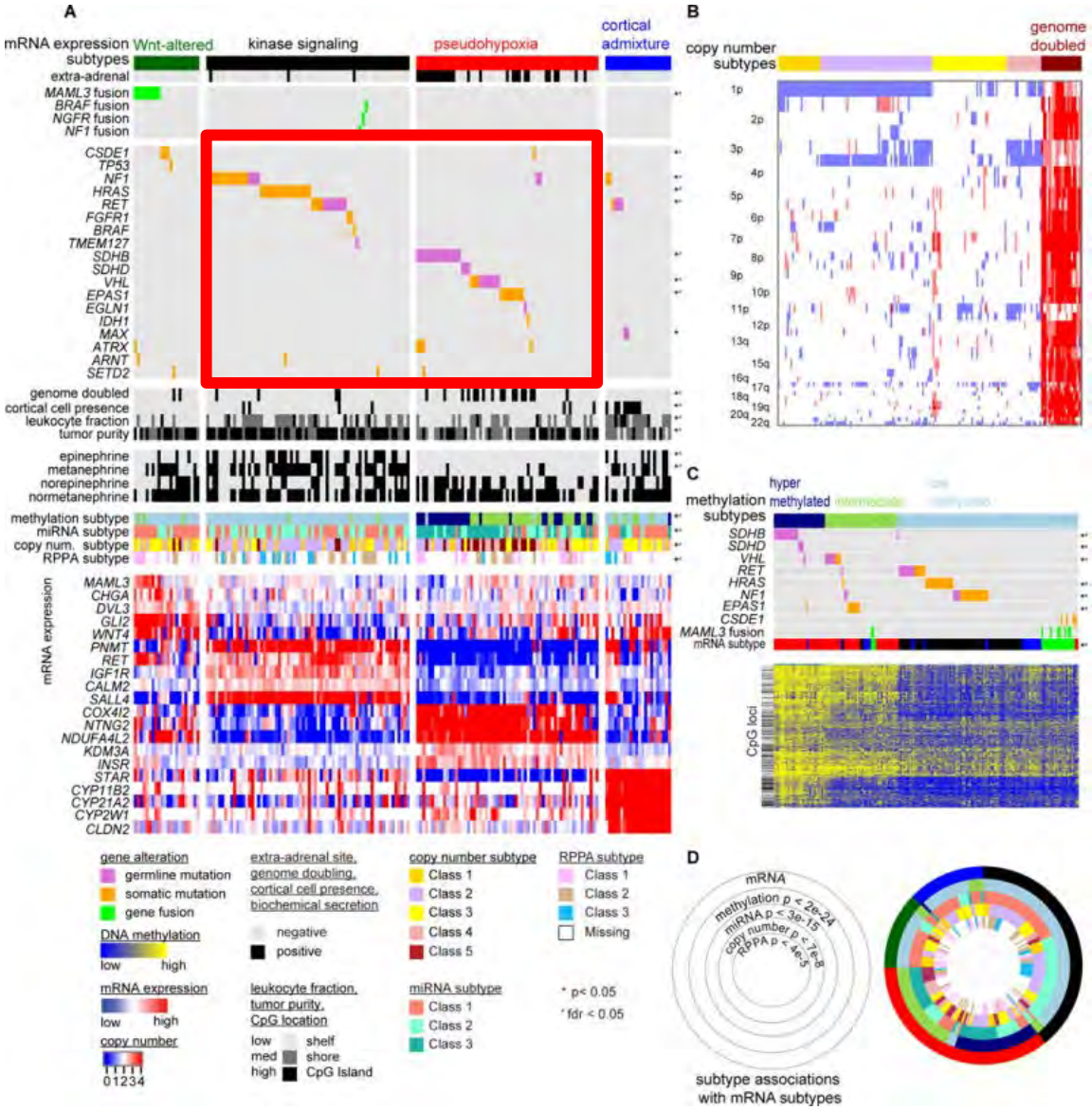
- Adrenergic phenotype
  - Elevated E/MN or both E/MN and NE/NMN – often in adrenals
  - False positive by tricyclic antidepressants, anesthetics, tyramine-rich food



Diagnosis of PCC/PGL - Location

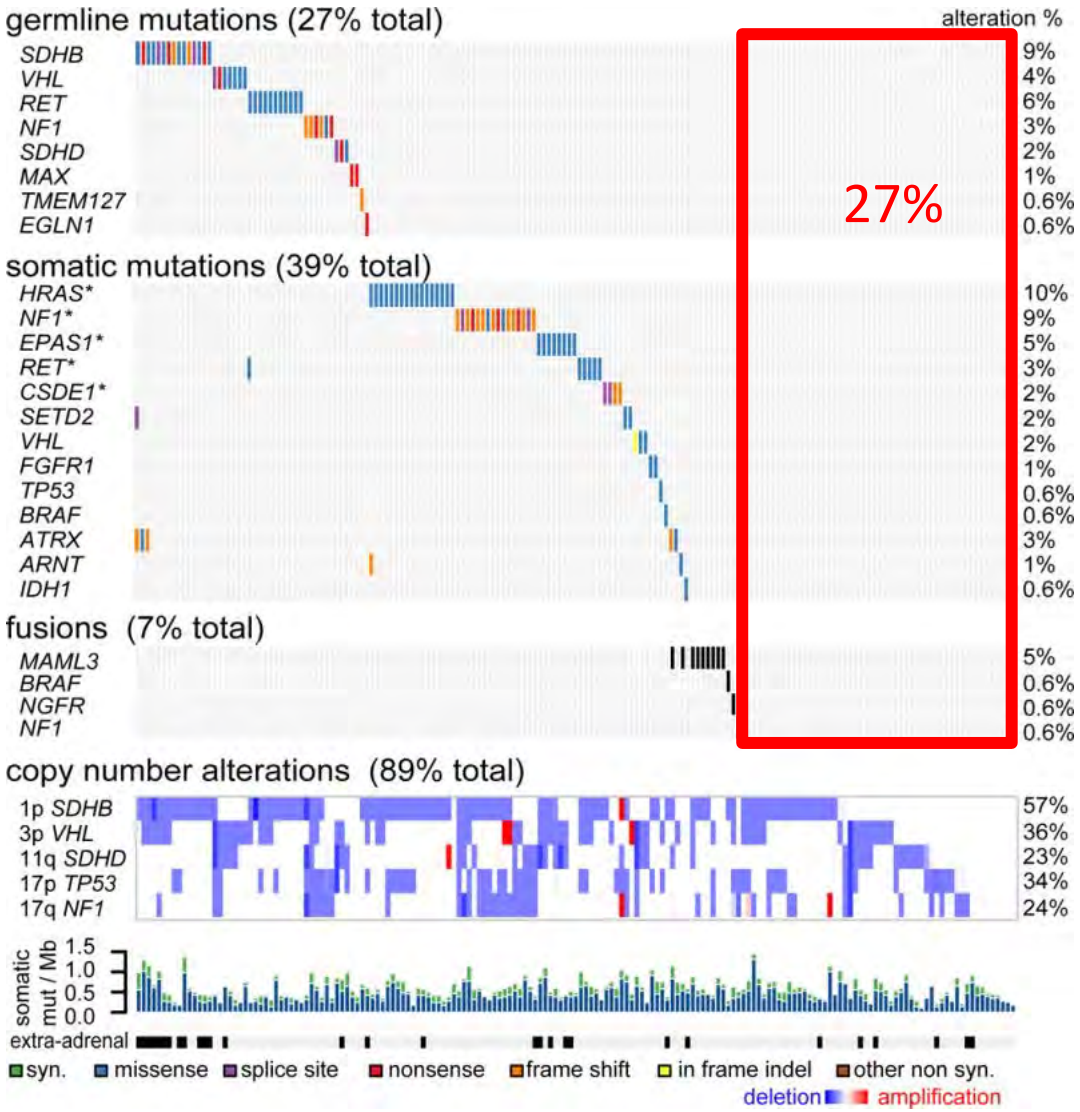
- Noradrenergic phenotype
  - Increased levels in NE/NMN – outside of adrenals
- Adrenergic phenotype
  - Elevated E/MN or both E/MN and NE/NMN – often in adrenals
  - False positive by tricyclic antidepressants, anesthetics, tyramine-rich food
- Dopminergic phenotype
  - High levels of dopamine/3-methoxytyramine and normal or near normal levels in E/MN and NE/NMN
  - Tumors often extra-adrenal and head/neck
  - Asymptomatic or abdominal pain/diarrhea/N/V, hypotension and weight loss

Tumor classifications



Fishbein L, et al. Cancer Cell 2017

Tumor classifications



Germline mutations

Gain-of-function mutations
RET

Loss-of-function

Fishbein L, et al. Cancer Cell 2017

Susceptibility mutations

- PCC/PGL may be sporadic or inherited
  - Half due to *SDHx*
  - 15% of positive are in *SDHx*
- Up to 40% of adult patients may have a susceptibility germline mutation
  - Up to 80% of pediatric patients
- Patients may present without family history of the disease
  - 24%

Disease (phenotype MIM numbers)	Genes	Mutation rate (%)*
Neurofibromatosis type 1 (162200)	*NF1*	3
Multiple endocrine neoplasia type 2 (171400; 162300)	*RET*	6
von Hippel–Lindau disease (193300)	*VHL*	7
Hereditary paragangliomas (168000; 605373; 115310; 601650; 614165)	SDHx genes: *SDHB* *SDHD* *SDHC* *SDHA* *SDHAF2*	 10 9 1 <1 <0.1
Familial phaeochromocytomas (173300; 613403; 154950)	*TMEM127* *MAX*	1 1
Polycythemia paraganglioma syndrome (603349)	*EPAS1*	1
Leiomyomatosis and renal cell cancer (150800)	*FH*	1

Babic B, et al. Surgery 2016
Fliedner SM et al, Semin Oncol. 2011
Neumann HP et al, N Engl J Med. 2002

Case 1

46 year old man with a left PCC

Blocked for 2 weeks with phenoxybenzamine.

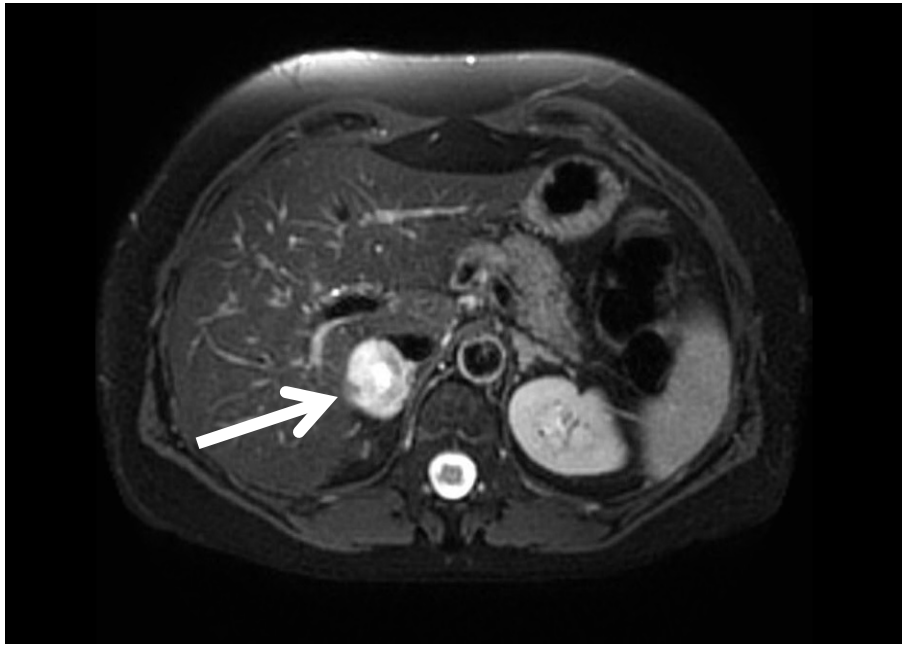
Any further work up?

Case 2

32 year old woman with a right PCC

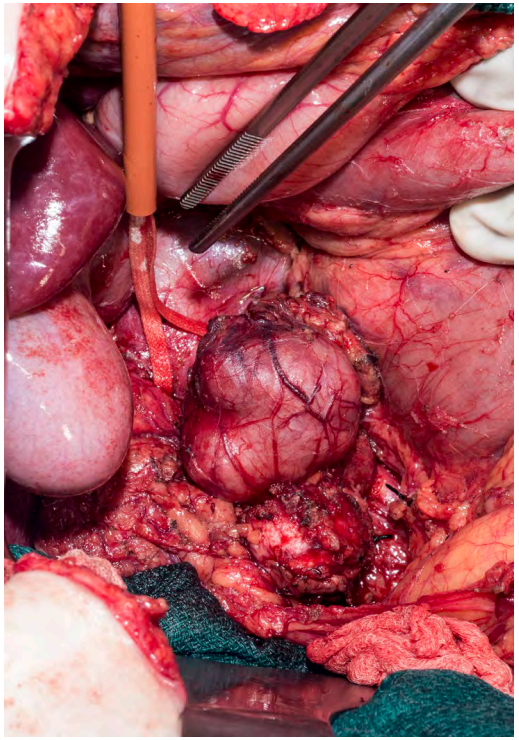
Started blockade 3 days ago.

Any further work up?

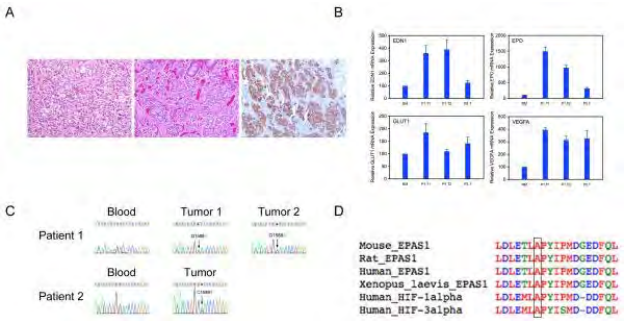


Cardinal Features of Inherited Syndromes are not always present!

- Early age of onset
- Multiplicity
- Bilateral
- Other neoplasms…
- Malignant potential



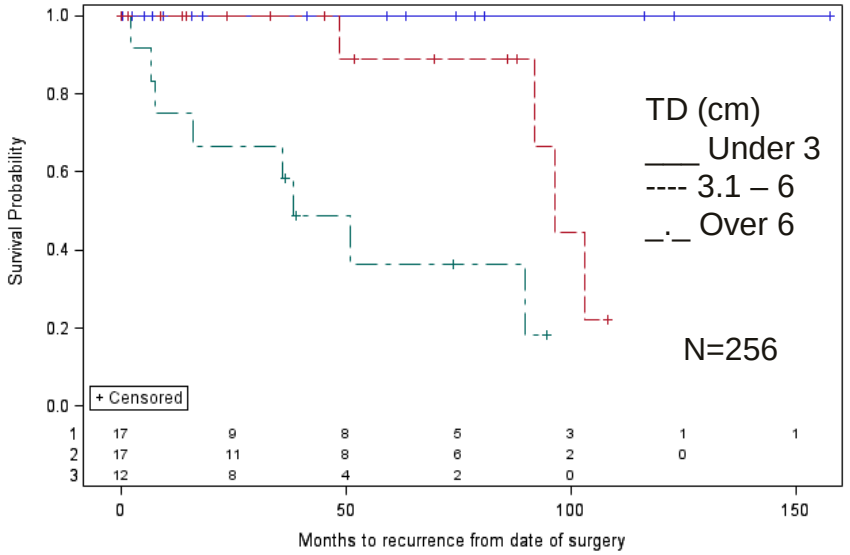
33 year-old woman
@14 had left periaortic paraganglioma,
@15 an aortocaval additional paraganglioma detected.
One year later she presented with a recurrent paraganglioma and 3 years later with at least 5 abdominal paragangliomas.



Zhuang Z, et al. N Engl J Med. 2012

Is preoperative genetic testing imperative for optimal management of PCC/PGL?

- **Surgical resection is the only curative treatment available**
  - **Indication**
    - **All functioning**
    - **All Symptomatic**
    - **Malignant or potentially malignant nonfunctioning tumor(s)**



Tumor diameter (TD) (cm).
Median DFI: not reached vs. 95.4 months, vs. 38.4 months ($p<0.001$).

Assadipour et al. Surgery 2016

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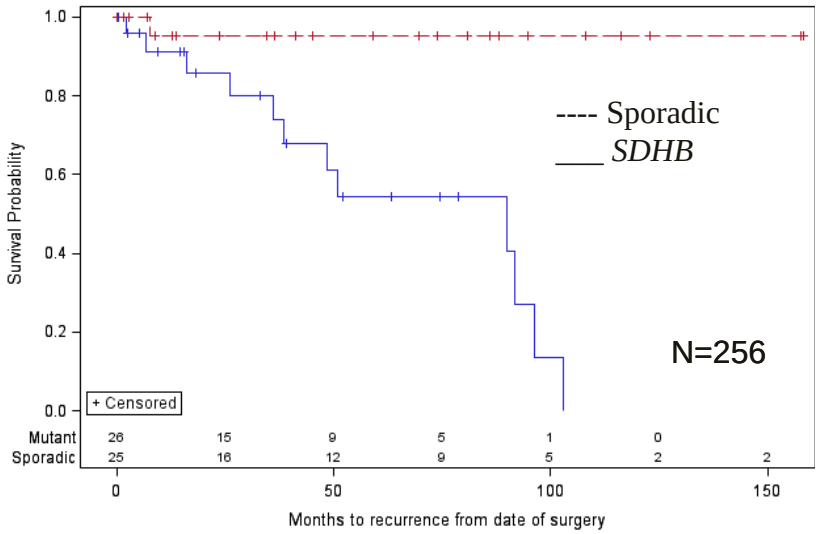


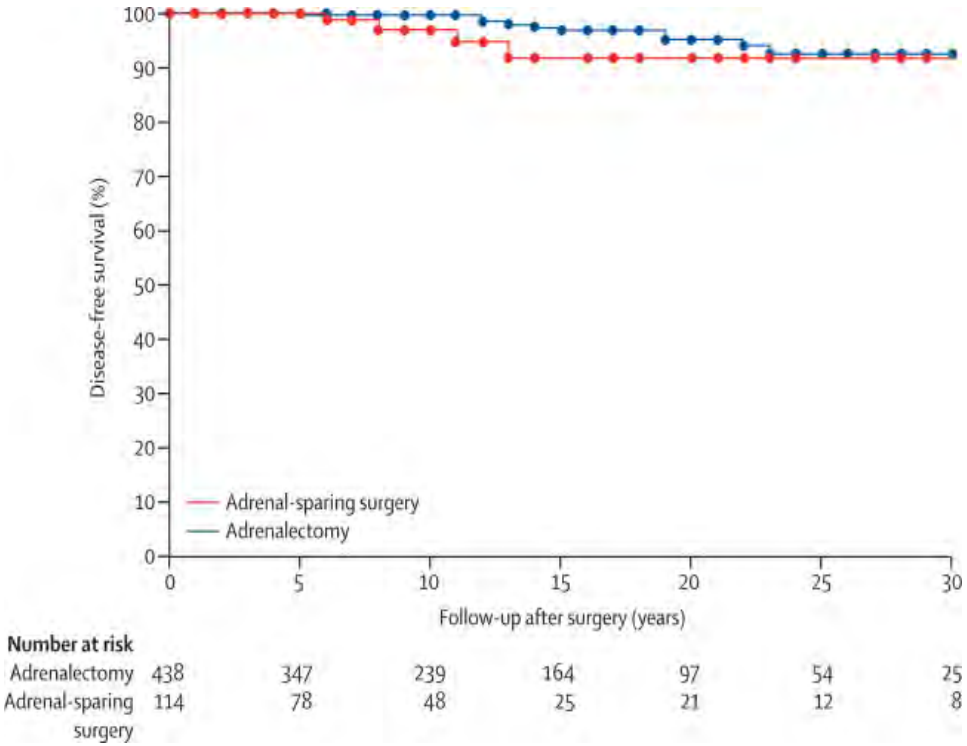
SDHB mutation vs. no mutation Median DFI: 89.8 months vs. median not reached ($p<0.001$).

Assadipour et al. Surgery 2016

Is preoperative genetic testing imperative for optimal management of PCC/PGL?

N = 552 with MEN2/*RET*

- 438 (79%) total adrenalectomy
- 114 (21%) adrenal-sparing surgery
- Recurrence occurred in 3% of the operated glands after adrenal-sparing surgery after 6-13 years

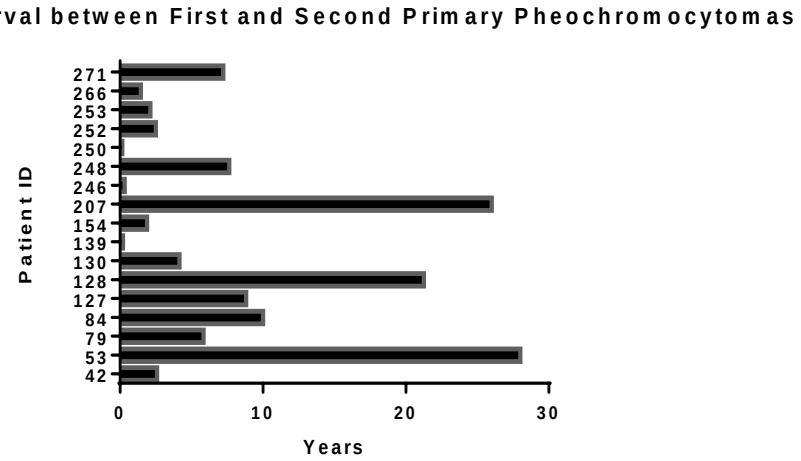


Castinetti et al. Lancet Oncol, 2014

Is preoperative genetic testing imperative for optimal management of PCC/PGL?

VHL-associated PCC (N = 273)

- Follow up: 203.8 months [0.7-912]
- 84 developed PCC
- 62 (74.7%) unilateral PCC & 22 (26.3%) bilateral
- 17 (20.5%) patients developed a contralateral second primary tumor requiring surgical intervention.



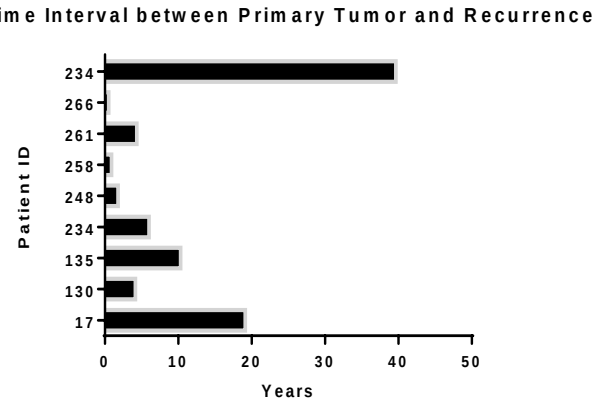
Aufforth et al. J Clin Endocrinol Metab 2015

Is preoperative genetic testing imperative for optimal management of PCC/PGL?

- **Operative approach**
  - **Is partial adrenalectomy reasonable?**
  - **Yes in *VHL, RET & NF1* if**
    - **tumor is small < 2-3cm,**
    - **no history of metastatic disease in the family**

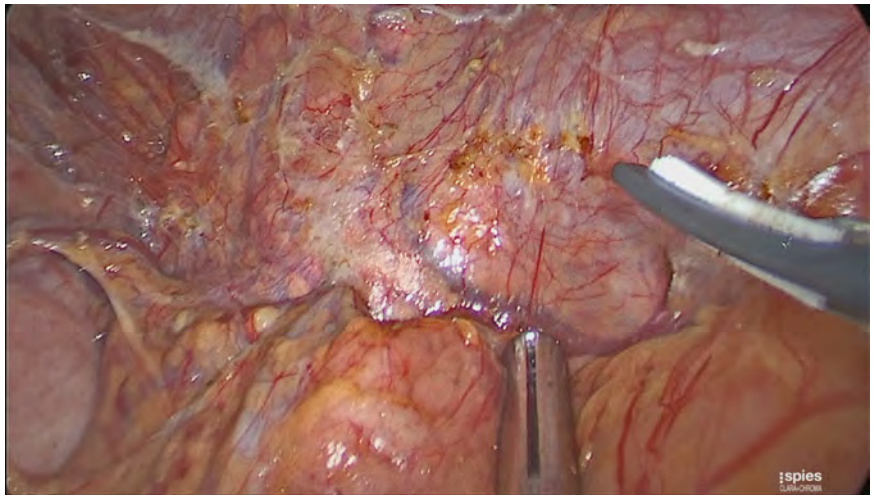
•9 (14%) developed recurrence in remnant gland

a.



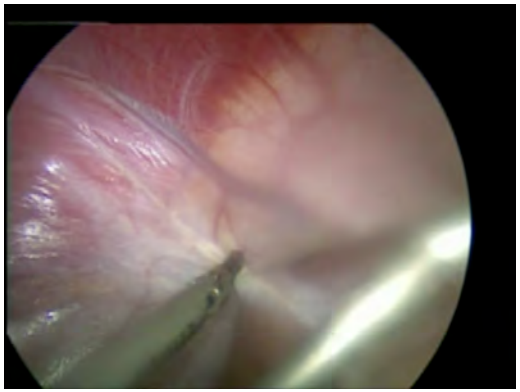
Aufforth et al. J Clin Endocrinol Metab 2015

Genotype-Phenotype Association



- ***SDHB, FH, MAX***
  - Higher rate of metastatic disease

- ***NF1, RET, VHL***
  - Low risk of metastatic disease
  - Synchronous/metachronous bilateral pheochromocytoma



Fliedner SM et al, Semin Oncol. 2011
Neumann HP et al, N Engl J Med. 2002
Maignan A et al, Langenbecks Arch Surg. 2017
Lenders et al. J Clin Endocrinol Metab 2014.

Case 1

46 year old man with a left PCC

Blocked for 2 weeks with phenoxybenzamine.

Any further work up?

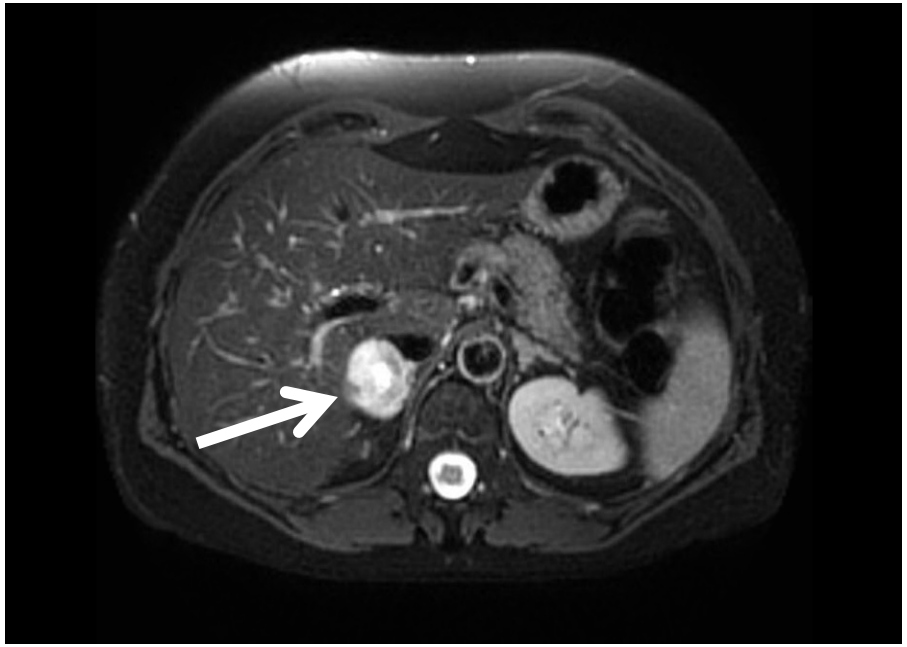
SDHB positive
Open adrenalectomy and retroperitoneal lymph node dissection

Case 2

32 year old woman with a right PCC

Started blockade 3 days ago.

Any further work up?



Genetic testing & family history positive for *VHL*
Partial laparoscopic adrenalectomy

How many imaging studies & which ones?

Imaging Modalities

Anatomic

- CT
- MRI

Functional

- MIBG
- 18F-FDG PET
- 18F-FDOPA PET
- 18F-FDA PET
- 68Ga DOTATATE PET

How many imaging studies & which ones?

Imaging Modalities

Anatomic

- CT
- MRI

Functional

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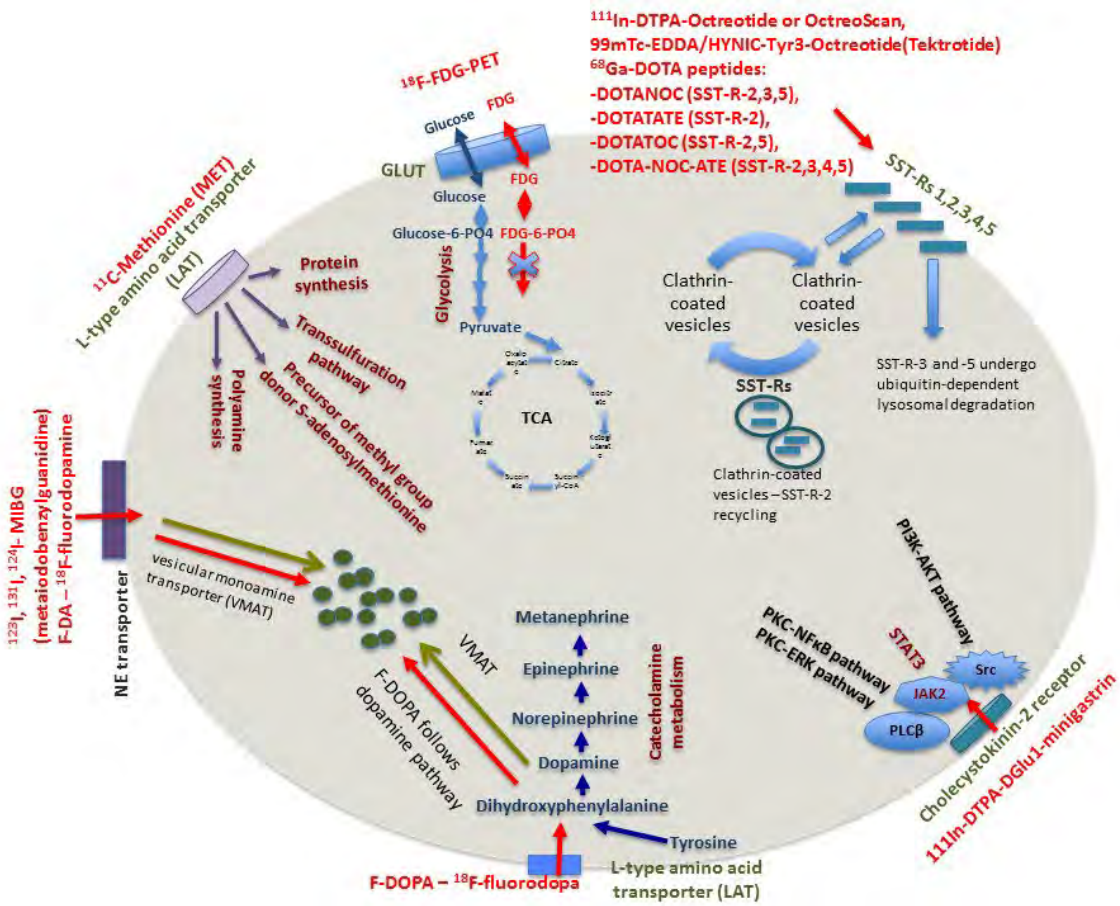

So many targets!

How many imaging studies & which ones?

Imaging Modalities

Anatomic

- CT
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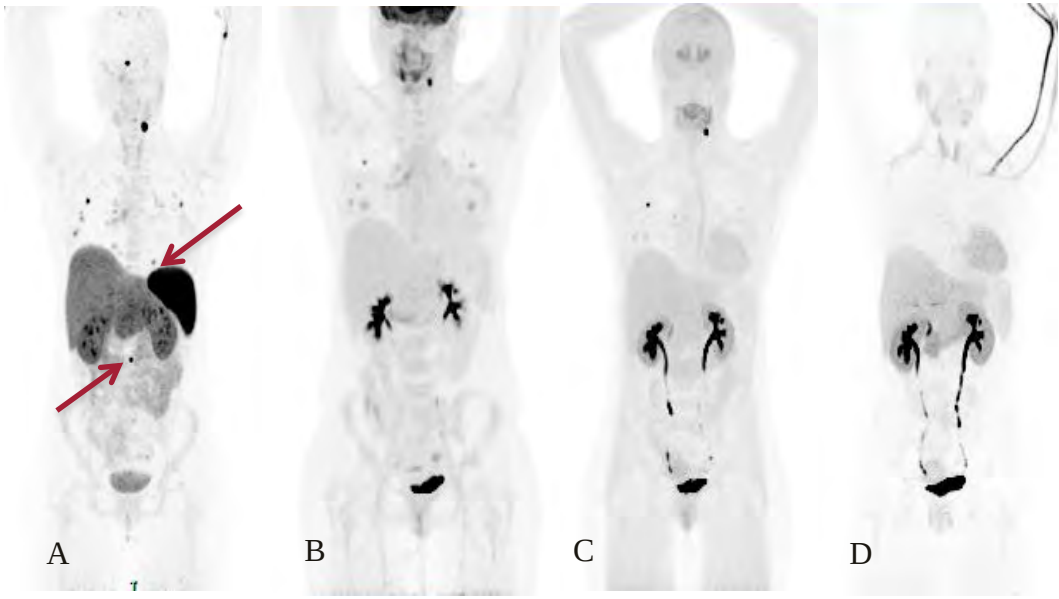

[^{68}Ga]-DOTATATE PET [^{18}F]-FDG PET [^{18}F]-FDOPA PET [^{18}F]-FDA PET (D)

How many imaging studies & which ones?

Imaging Modalities

Anatomic

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Functional

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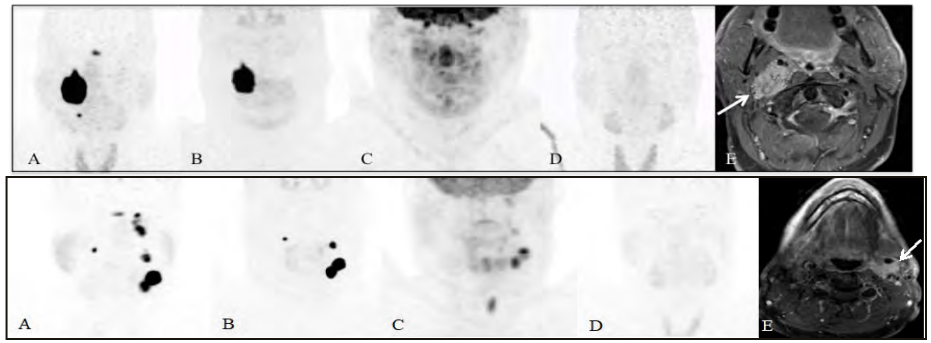
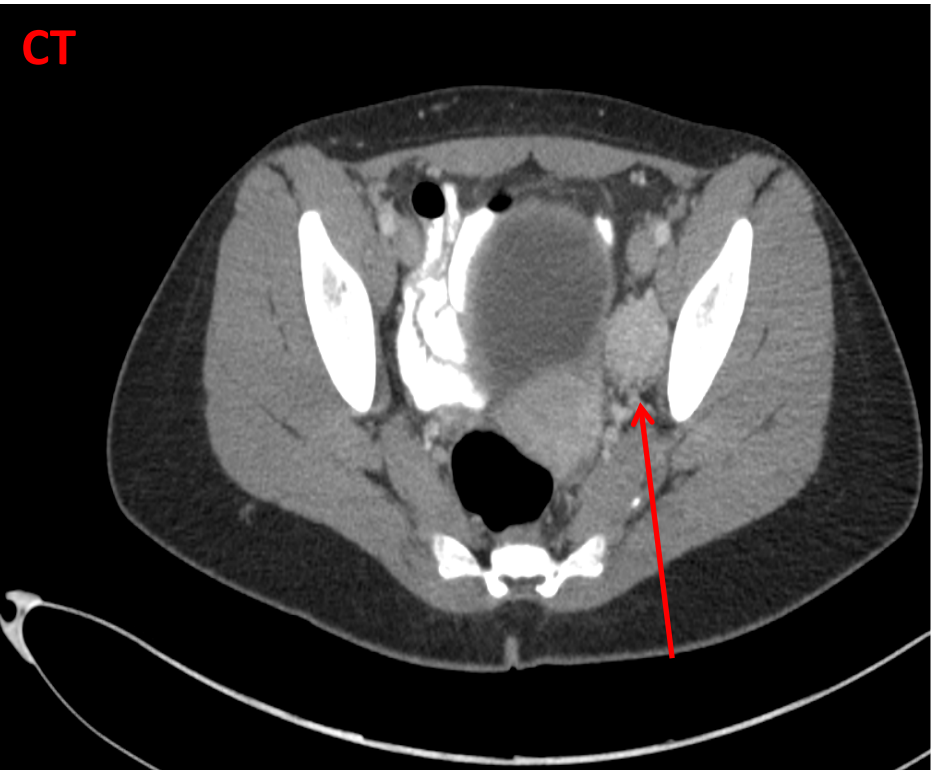


[^{68}Ga]-DOTATATE PET [^{18}F]-FDG PET [^{18}F]-FDOPA PET [^{18}F]-FDA PET (D)

Case and Point

16 year old female with a “left” pelvic paraganglioma – functional



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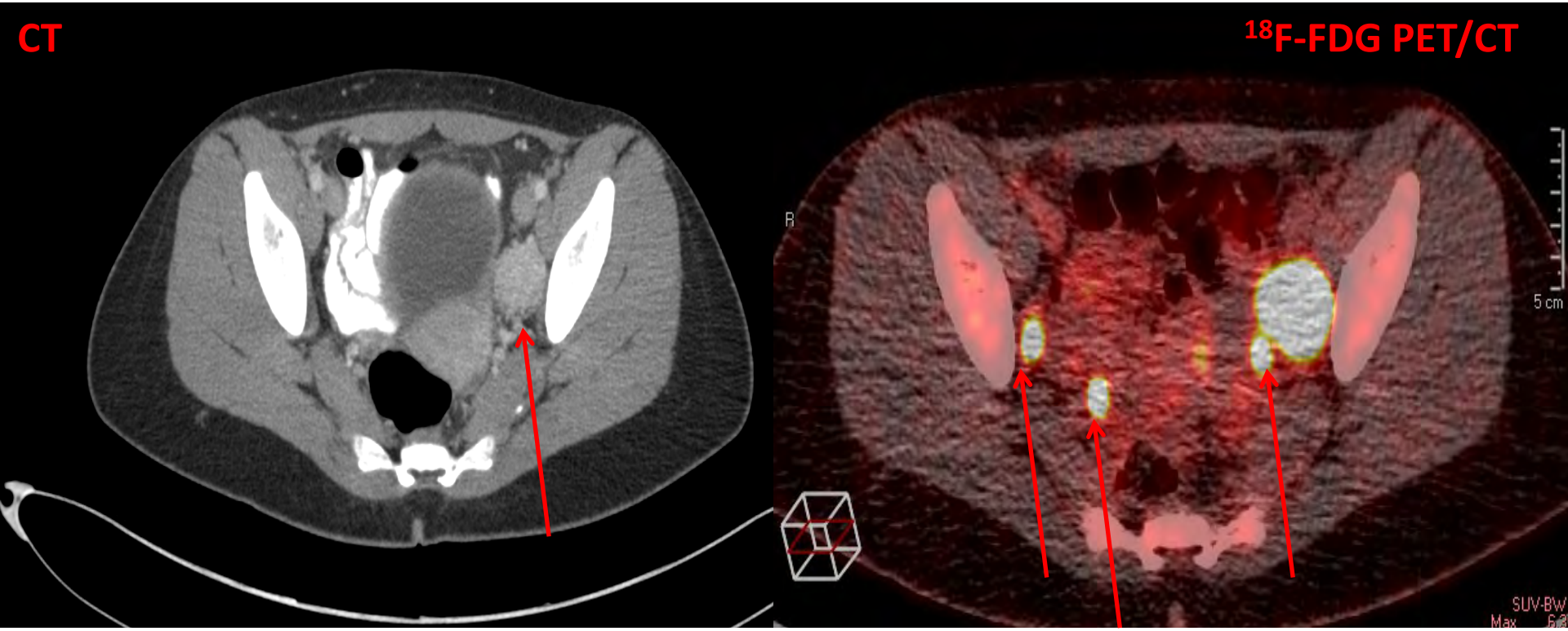

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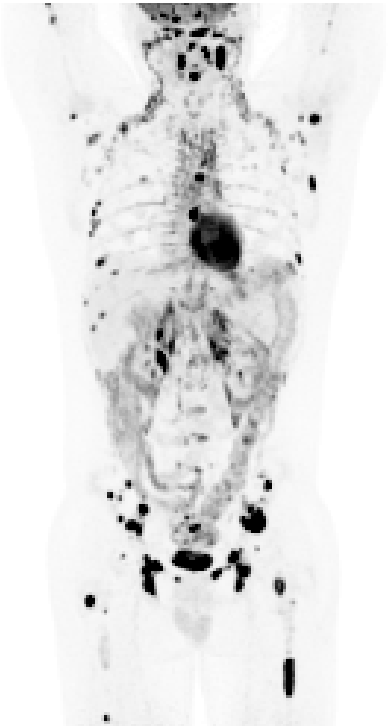
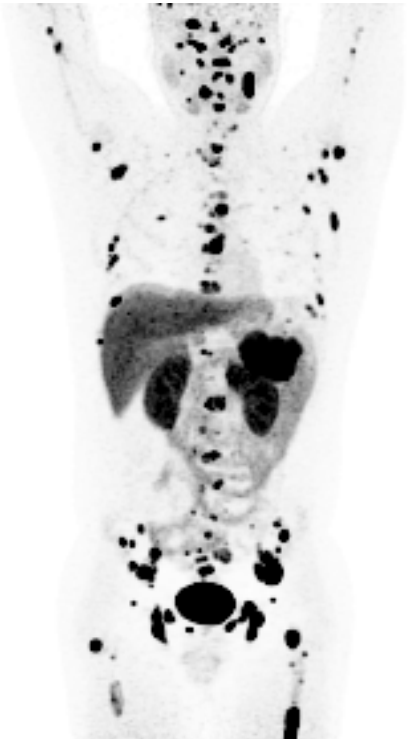


FDG



DOTATATE

FDA

FDOPA

46 year old man with history of left PGL and *SDHB+* referred for adrenal bed recurrence

How many imaging studies & which ones?

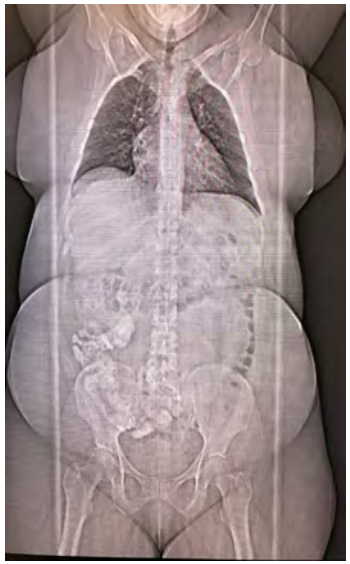
Imaging Modalities

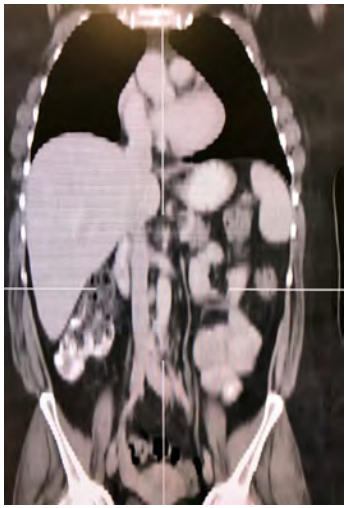
Anatomic

- CT
- MRI

Functional

- MIBG
- 18F-FDG PET
- 18F-FDOPA PET
- 18F-FDA PET
- 68Ga DOTATATE PET





Preoperative genetic testing and functional imaging experience with surgical resection of abdominal PCC/PGL

7/1/2009 – 12/30/2016

N = 137 PCC/PGL

Surgical Approach

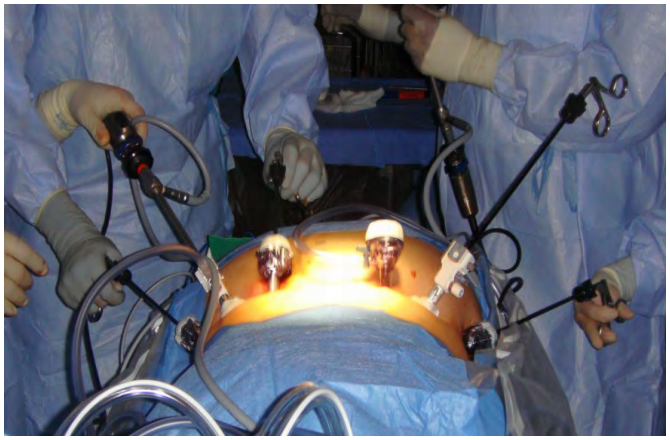
Open: 45 – metastatic/SDHB

Laparoscopic:

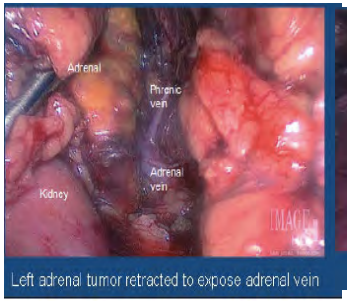
Lateral: 56 (14 partial in MEN2/VHL/NF1)

Retroperitoneal: 24 (4 partial in MEN2/VHL/NF1)

Robotic:12

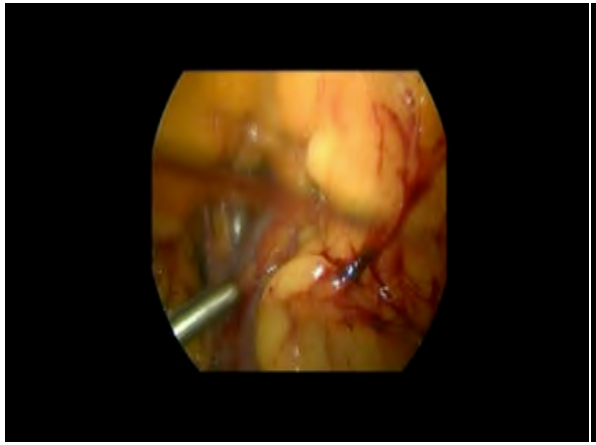


Port placement for the bilateral synchronous laparoscopic posterior retroperitoneal



Left adrenal tumor retracted to expose adrenal vein

Surgical clips on the right adrenal vein.



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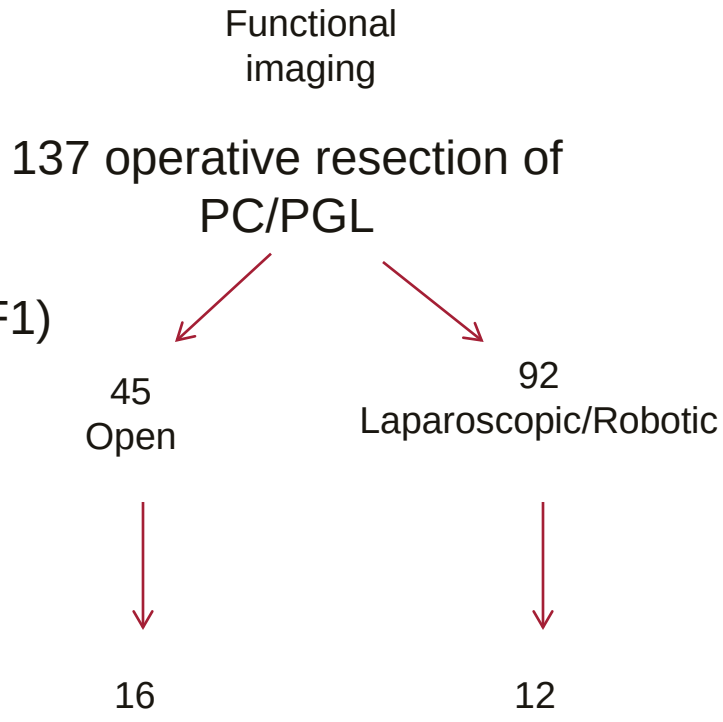
Pavel Nockel

Does preoperative functional imaging and genetic testing impact our surgical intervention?



22% additional sites of disease that needed to be addressed

Nockel P, et al. Ann Surg 2018

Nockel P, et al. Surgery 2018

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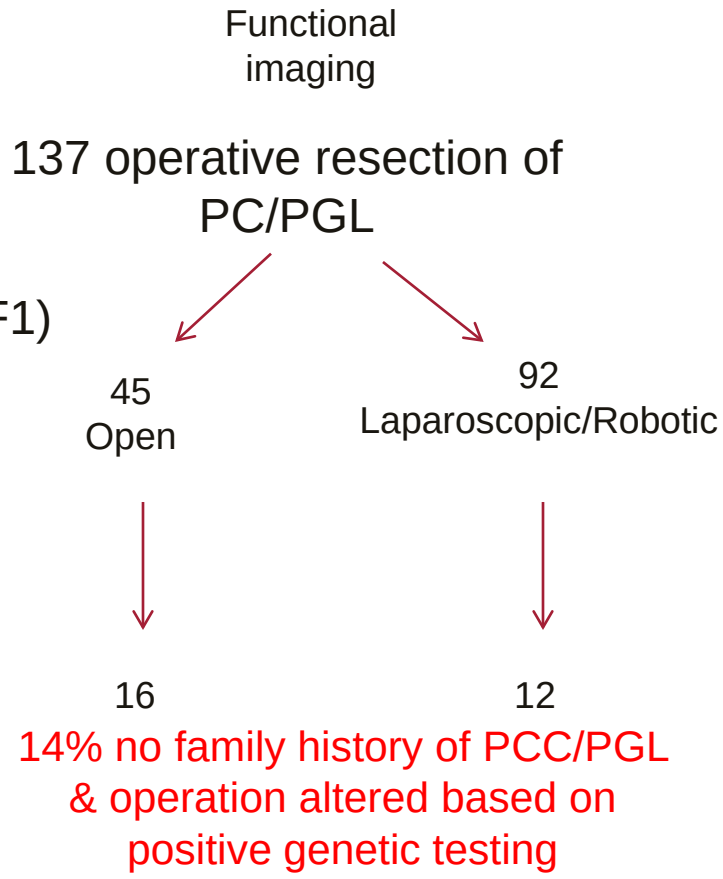

14% no family history of PCC/PGL & operation altered based on positive genetic testing

Nockel P, et al. Ann Surg 2018
Nockel P, et al. Surgery 2018

What is the role of surgery for metastatic/recurrent PCC/PGL?

Response after Surgical Resection of Metastatic Pheochromocytoma and Paraganglioma: Can Postoperative Biochemical Remission Be Predicted?

Ryan J Ellis, BS, Dhaval Patel, MD, Tamara Prodanov, MD, Samira Sadowski, MD, Naris Nilubol, MD, FACS, Karen Adams, RN, Seth M Steinberg, MD, Karel Pacak, MD, PhD, DSc, Electron Kebebew, MD, FACS

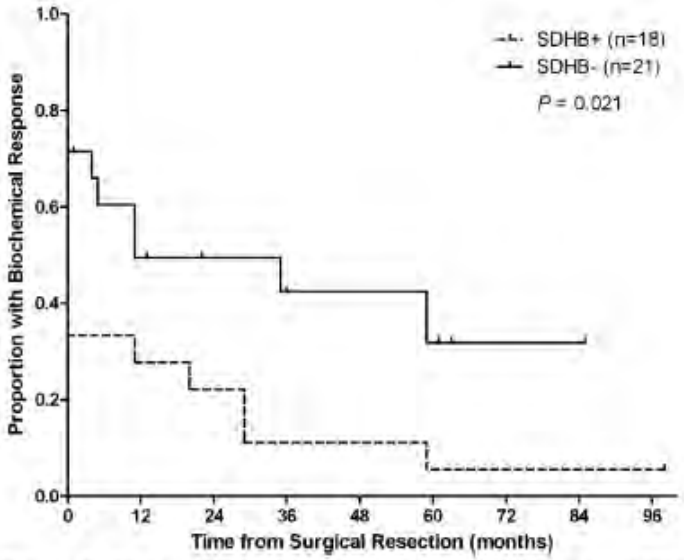

Figure 2. Biochemical response in patients stratified by *SDHB* mutation status.

Ellis RJ, Patel D, et al. J Amer Coll Surg 2013

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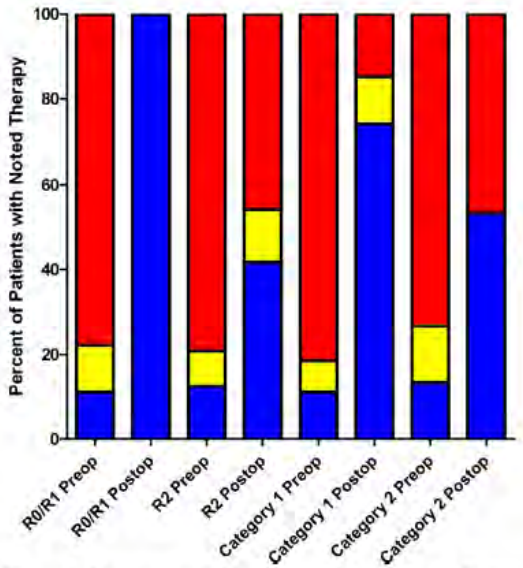

Figure 5. Pharmacotherapy breakdown by subgroups. Postop, postoperative; Preop, preoperative. Blue = No drug therapy; yellow = monotherapy; red = multi-drug therapy.

Ellis RJ, Patel D, et al. J Amer Coll Surg 2013

How can we better predict who is going to benefit from surgical treatment when metastases is present?

Optimizing benefit/success while minimizing risk!

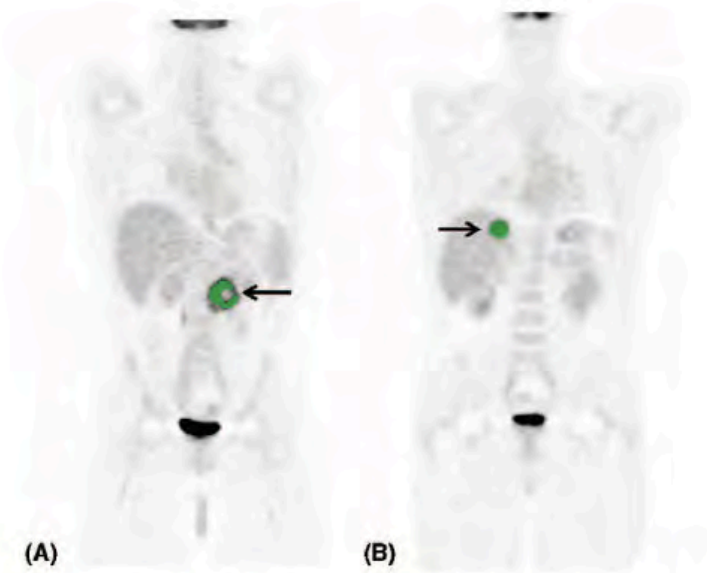

FIGURE 1. 18F-FDG PET/CT scan MTV measurements. A, A patient with a history of primary adrenal PCC with locoregional recurrence. B, A patient with liver metastasis.

Total 18F-FDG PET/CT Metabolic Tumor Volume Is Associated With Postoperative Biochemical Response in Patients With Metastatic Pheochromocytomas and Paragangliomas

Dhaval Patel, MD, Amit Mehta, BS,*† Naris Nilubol, MD,* William Dieckmann, PhD,‡ Karel Pacak, MD, ScD,§ and Electron Kebebew, MD**

- Measured from FDG PET scans
  - Tumor volume per lesion
  - Total SUV uptake per lesion
  - Total lesion glycolysis (TLG) calculated (mean SUV * volume) per lesion

Tumor volumes, Total SUV, and TLG summed for each patient.

Patel D, et al. Ann Surg. 2014

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TABLE 3. Treatment and Tumor Burden Characteristics

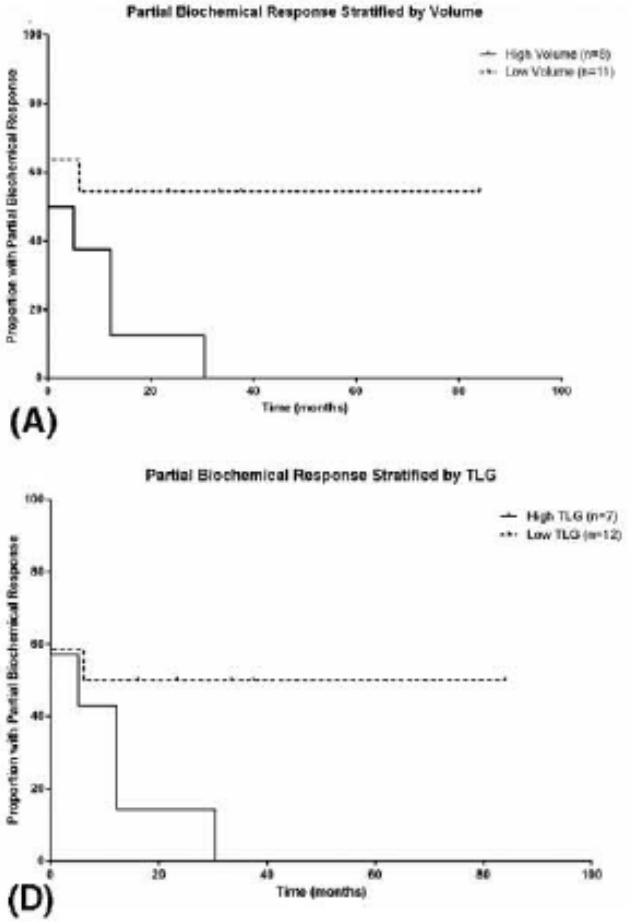
Characteristic	Data
Age at procedure, median (range), yrs	34 (13–68)
Intervention category, n	
Surgery, reoperation	13
Surgery, first operation	2
RFA	4
Disease location per patient, n (%)	
Abdominal metastases	
Liver	3 (17.6%)
Retroperitoneal	14 (82.4%)
Thoracic metastases	2 (11.8%)
Bony metastases	6 (35.3%)
No. tumors per disease location, n (range)	
Abdomen	32 (1–6)
Bone	128 (0–76)
Thoracic	4 (0–3)
Preoperative pharmacotherapy, n (%)*	
None†	2 (10.5%)
1 drug	3 (15.8%)
2 drugs	9 (47.4%)
>3 drugs	5 (26.3%)
Postoperative biochemical response, n (%)	
Partial biochemical response‡	11 (57.9%)
Complete biochemical remission§	6 (31.6%)

*Drugs included alpha-blockers, beta-blockers, calcium channel blockers, and metyrosine.

†Pharmacotherapy refused by a patient.

‡Partial biochemical response was defined as having at least 1, but not all, biochemical laboratory values returning to the normal range postoperatively.

§Complete biochemical remission was defined when all indicative laboratory values returned to the normal range postoperatively.



Patel D, et al. Ann Surg. 2014

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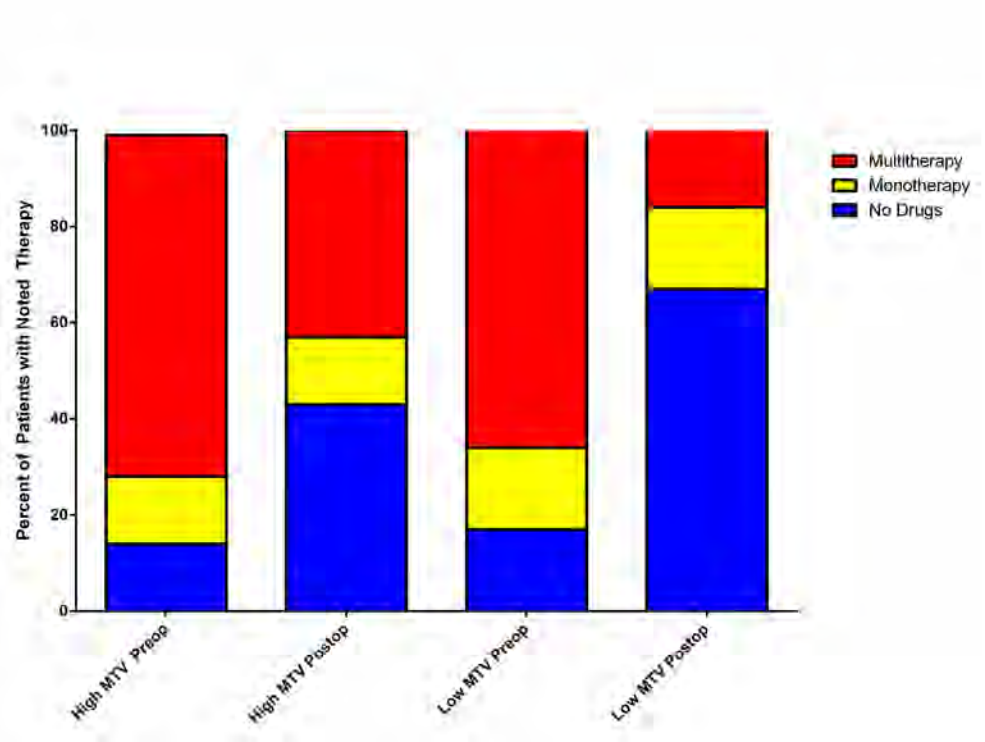


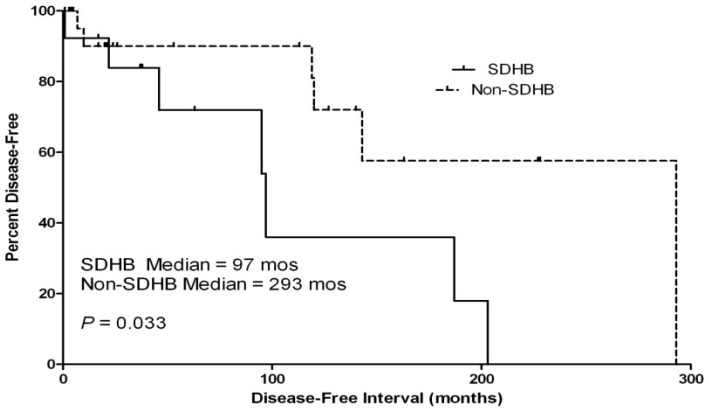
Total SUV Uptake by Biochemical Response

Patel D, et al. Ann Surg. 2014

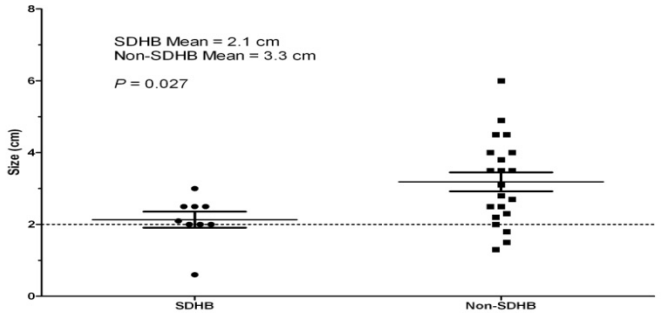
Surgical Resection of Carotid Body Paragangliomas: Should Genetic Background Modify Surgical Indications?

- 36 patients with 43 primary resections
- Median age: 33 years
- Mutation breakdown
  - 17 (47.2%) patients positive for *SDHD*
  - 12 (33.3%) for *SDHB*
  - 7 (19.4%) wildtype (no identified mutation)
- Six patients received medical and/or radiation therapy upon recurrence

Disease-Free Survival



Tumor Size at Resection



Ellis RJ, et al. Ann Surg 2014

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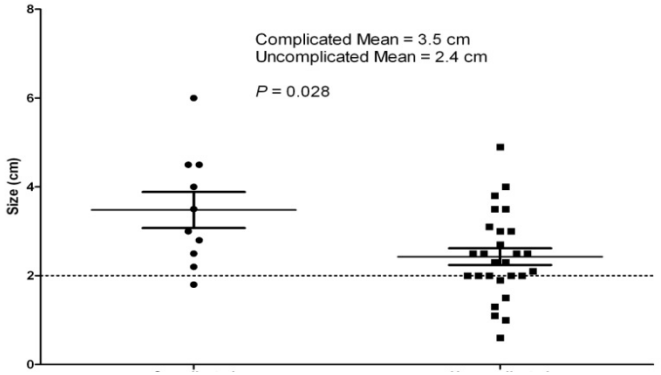
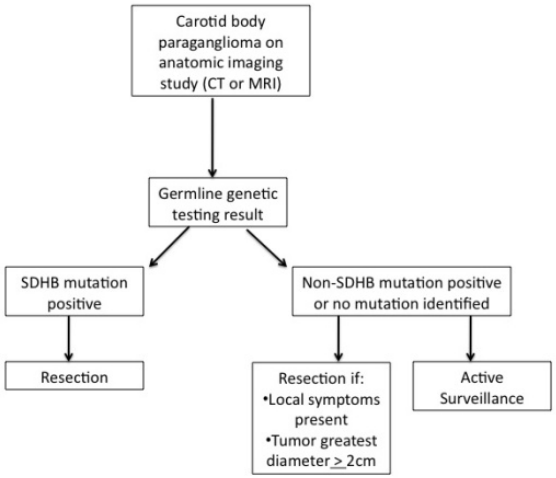
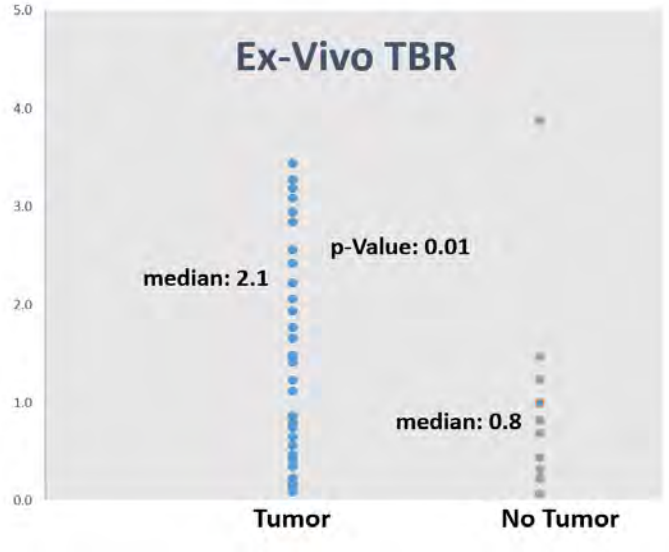


Proposed Surgical Algorithm



Ellis RJ, et al. Ann Surg 2014

Radioguided Surgery using ^{68}Ga-DOTATATE



- Forty-four patients with 133 lesions on preoperative imaging
- Pancreatic NET (43%), gastrointestinal NET (50%), and pheochromocytoma/paraganglioma (7%)
- The omentum had a significantly lower count than other solid organs for background count activity 3 hours after injection (22.1 vs. 34.5; $p < 0.001$).
- The lesions containing NETs had a higher TBR (18.9 vs. 4.4; $p < 0.001$).
- **13% of lesions not visible and or palpable.**

El Lakis, et al. JAMA Surgery 2018

Summary PCC/PGL

- Our understanding of the genetic basis of PCC/PGL has tremendously improved.
- Over half of the patients with PCC/PGL will have germline mutations.
- Thus all patients should undergo genetic counseling & testing before their surgical treatment.
- Genotype-phenotype associations
- The genetic testing results may alter the preoperative evaluation and management of patients with PCC/PGL, the surgical approach used, and the follow up plan.
- Patients should have at least one anatomic (CT/MRI) and one functional imaging study (18F FDG or 68-Ga DOTATATE).

Thank you!