Management of Patients with Neuroendocrine Tumors of the Pancreas and the Gastrointestinal Tract

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Surgeon-Scientist at NIH

Neuroendocrine Cancer Therapy Section

Agenda:

- Defining management of PNETs in familial NET syndromes
- Research to discover targets for therapy of high-grade NETs

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Overview

- Epidemiology and Diagnosis
- Non-functioning PNETs
- Functioning PNETs
  - Insulinoma
  - Other rare-omas
- Research in Targeted Therapies for High Grade NETs

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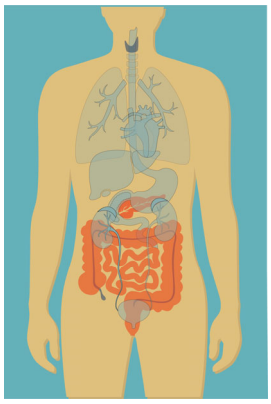
NETs of the Pancreas and Gastro-Intestinal Tract

- Neuroendocrine Tumors (NETs): secretory, hereditary
- Incidence 7 per 100,000 in the US
- Treatment: Surgery- complete resection



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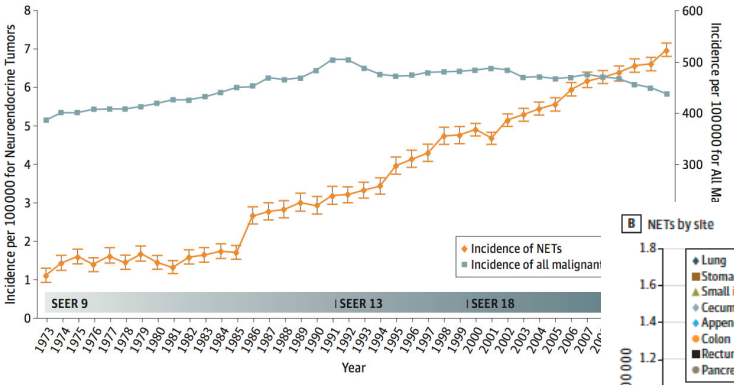
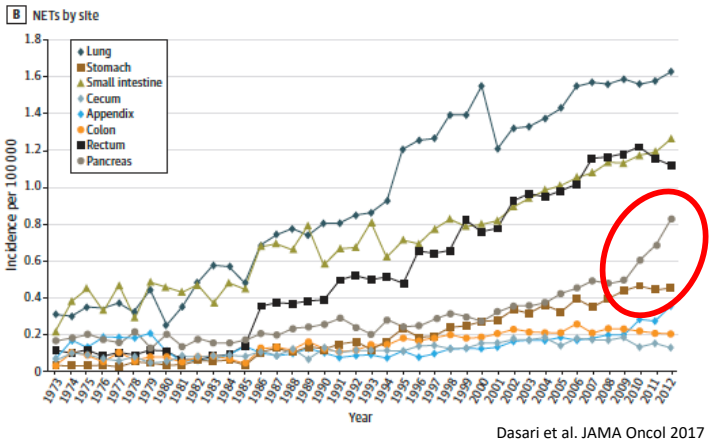
Pancreatic NETs: Increasing Incidence



All NET Annual incidence per 100,000:
1.09 (1973) to 6.98 (2012)
Most non-functioning PNET are "Incidentalomas"



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Dasari et al. JAMA Oncol 2017

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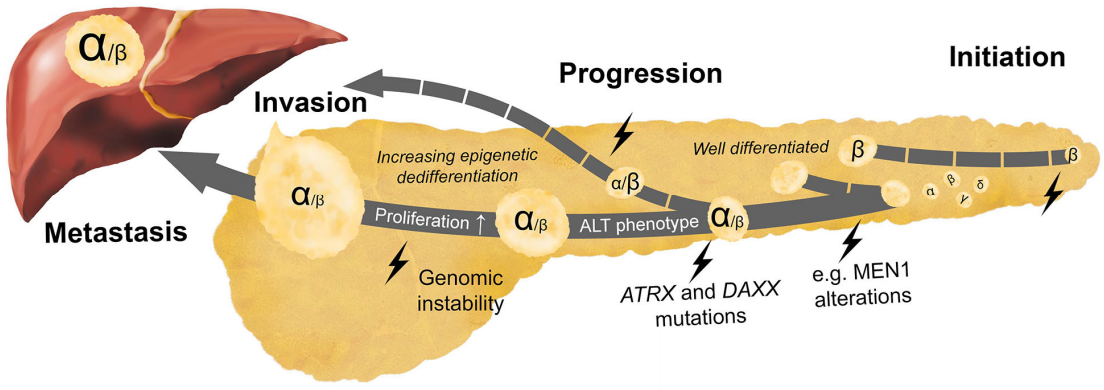
Cells of origin in NETs: Islet of Langerhans



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Dreijerink et al. Journal of Pathology 2021, Yashida et al. Am J Surg Pathol 2012
Francis et al. Nat Genet 2013, Simbolo et al. Virchows A 2018

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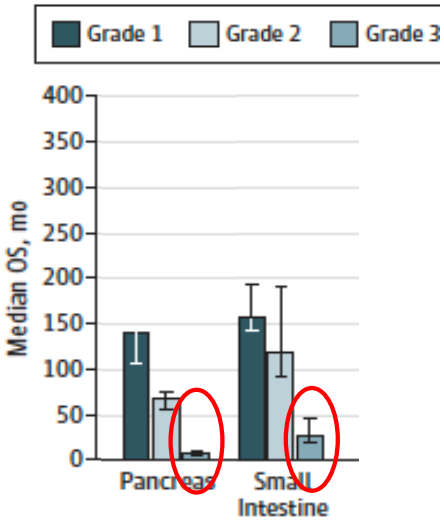
NETs of the Pancreas and Gastro-Intestinal Tract

- NETs express Somatostatin Receptor 2
  - Receptor that inhibits secretion of hormones and negatively regulates cell proliferation
  - No mutations -> epigenetic mechanisms
  - SSTR2 expression correlates inversely with grade
    - Worse prognosis



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Dasari et al. JAMA Oncol 2017, Sadowski et al. Ann Surg Oncol 2015, Refardt et al. ERC 2020

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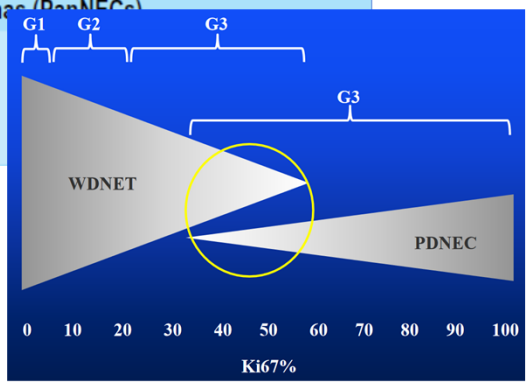
Classification of PNETs (WHO 2017)

Classification/grade	Ki-67 proliferation index[a]	Mitotic index[a]
Well-differentiated PanNENs: pancreatic neuroendocrine tumours (PanNETs)		
G1 PanNET	< 3%	< 2
G2 PanNET	3–20%	2–20
G3 PanNET	> 20%	> 20
Poorly differentiated PanNENs: pancreatic neuroendocrine carcinomas (PanNECs)		
PanNEC (G3)	> 20%	
Small cell type		
Large cell type		

Rindi et al endocrine pathology 2022



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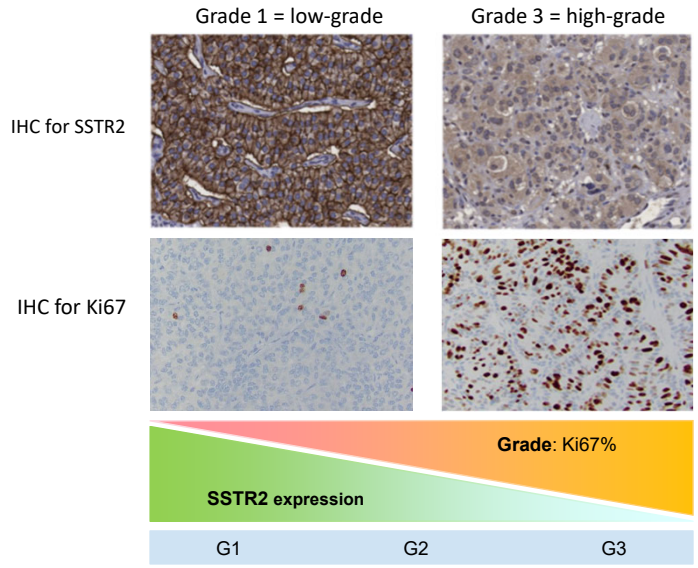
PNETs express Somatostatin receptor type 2 (SSTR2)



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Sadowski *et al. Gland Surg* 2014, **Sadowski** *et al. Ann Surg Oncol* 2015
Dasari *et al. JAMA Oncol* 2017, Refardt *et al. ERC* 2020

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SSTR2 as a Target for Diagnosis

VOLUME 34 · NUMBER 6 · FEBRUARY 20, 2016
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Prospective Study of ^{68}Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites

Samira M. Sadowski, Vladimir Neychev, Corina Millo, Joanna Shih, Naris Nilubol, Peter Herscovitch, Karel Pacak, Stephen J. Marx, and Electron Kebebew

- ^{68}Ga-DOTATATE PET/CT for accurate staging and selection of appropriate therapy
- Change in management in 32.8% of patients

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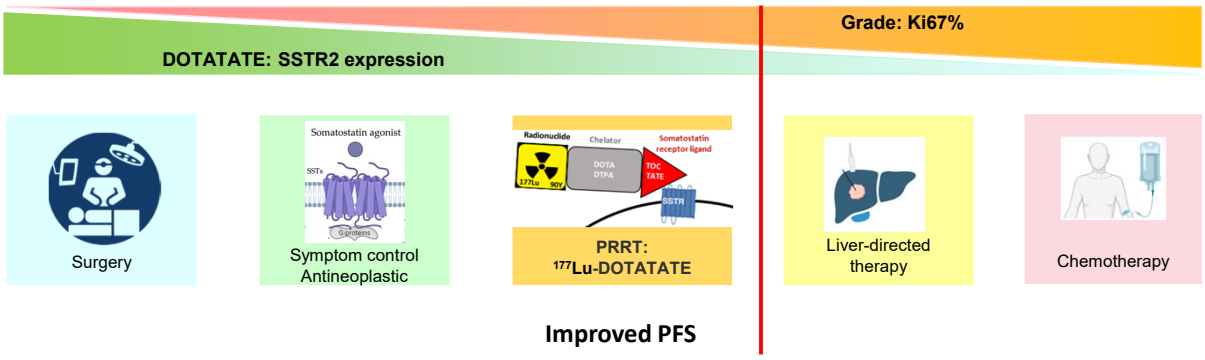
Current therapy regimen for high-risk PNET

Upfront therapy: multi-modal



Improved PFS

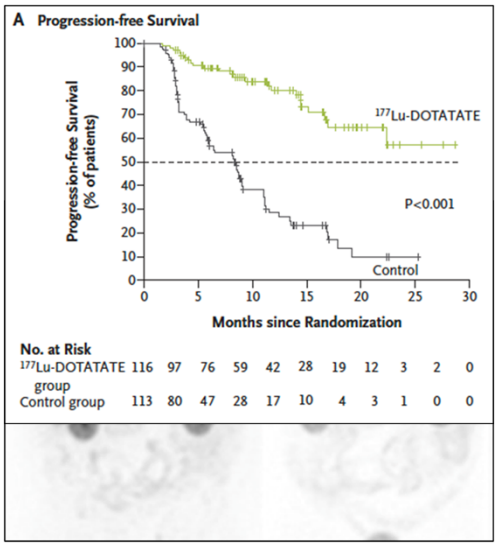
Unmet clinical need

- Loss of SSTR2 renders high-risk PNETs ineligible for SSTR2-targeted therapy
- Lack of therapeutic options: Despite multimodal therapy, there is **less than 30% ORR** in WD high-risk PNETs

Strosberg *et al. NEJM* 2017, Das *et al. Cancers* 2021[11]

SSTR2 as a Target for Therapy

- 177Lu-DOTATATE for therapy in WD NET
  - Requires SSTR2 positive status
  - Survival benefit



Sadowski et al. JCO 2016, Strosberg et al. NEJM 2017 12

SSTR2 as a Prognostic Factor

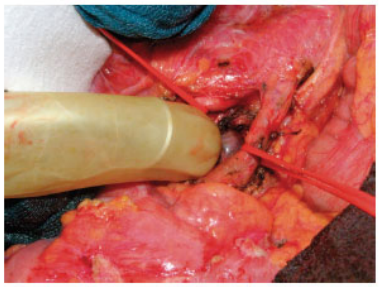
Ann Surg Oncol (2015) 22:S676–S682
DOI 10.1245/s10434-015-4857-9

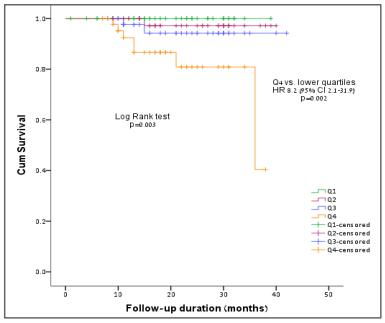
Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Feasibility of Radio-Guided Surgery with ^{68}Gallium-DOTATATE in Patients with Gastro-Entero-Pancreatic Neuroendocrine Tumors

Samira M. Sadowski, MD[1], Corina Millo, MD[2], Vladimir Neychev, MD, PhD[1], Rachel Aufforth, MD[1], Xavier Keutgen, MD[1], Joanne Glanville, MD[1], Meghna Alimchandani, MD[3], Naris Nilubol, MD, FACS[1], Peter Herscovitch, MD[2], Martha Quezado, MD[3], and Electron Kebebew, MD, FACS[1]





Tirosh et al Gastroenterology 2018

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Three Questions in NET

1. Functioning?
2. Risk of metastasis?
3. Hereditary?

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Pancreatic Neuroendocrine Tumors (PNETs)

Functioning

- Insulinoma 55%
- Gastrinoma 36%
- VIPoma 5%
- Glucagonoma 3%
- ACTHoma 1%
- Somatostatinoma 1%

Nonfunctioning

Up to 90% of PNETs are non-functioning

(ENETS guidelines Neuroendocrinology 2016)

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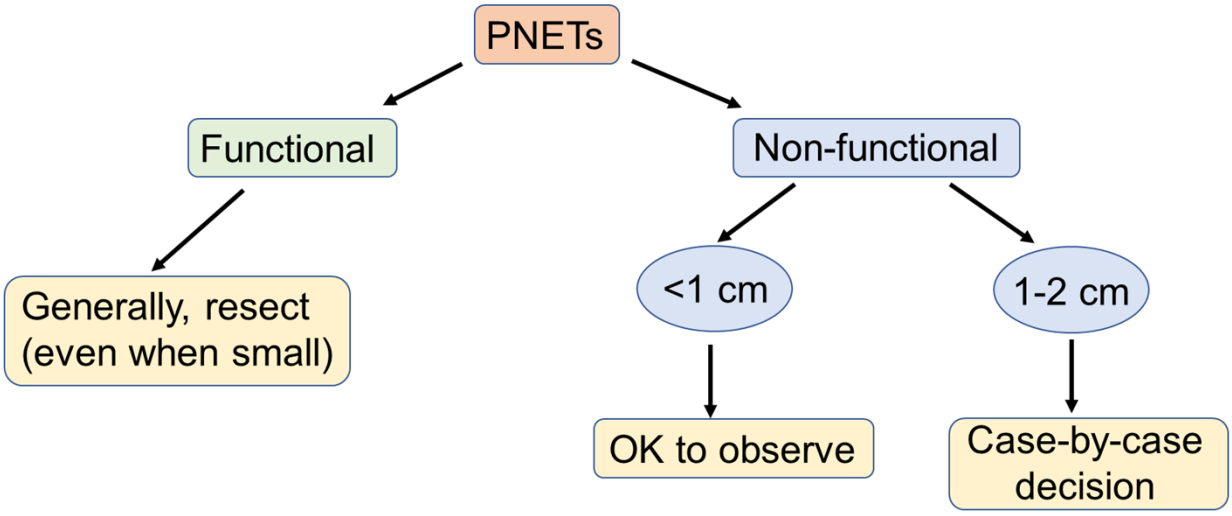
2020 NANETS Guidelines for localized PNETs



Halfdanarson et al. NANETS guidelines 2020
Partelli et al. ASPEN Trial, BJS 2023

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Nonfunctioning PNETs

- Absence of clinical syndrome
  - May not produce hormones or produce insufficient amount, inactive form
- ~50% are incidental finding
- ~50% present with liver metastasis
- Histology similar to functioning PNETs
- Age: 40-50s
- 40%-80% locate in the head of pancreas

Norton et al. Curr Prob Surg 2013
Gorelik et al Surg Clin N Am 2018

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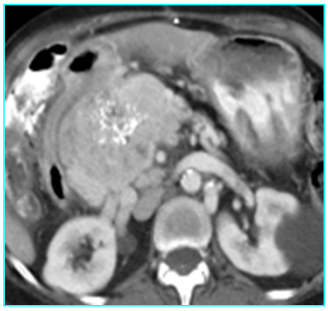
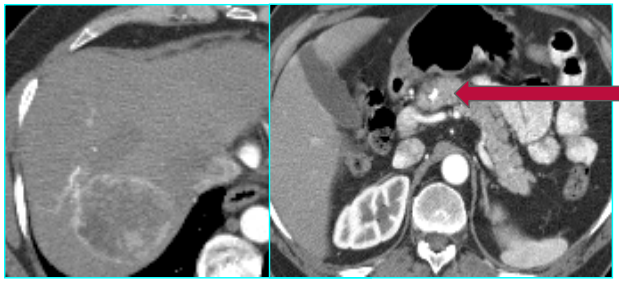
Presentation



- Most are incidentally found
- Jaundice (20%-70%)
- Locally advanced disease
  - Abdominal pain, mass effect
  - Invasion to vessels, nearby structures
- Metastasis→ Liver



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Diagnostic Studies

- CT scan: pancreatic protocol
- MRI, MRCP or MR angiography
- Somatostatin Receptor Imaging
  - Octreotide scan: 30.9%
  - **68-Gallium DOTATATE 95.1%**
- 18F-FDG/PET: poorly diff. NET
- EUS +/- FNA
  - FNA for Ki-67 expression to guide Rx

Sadowski et al JCO 2016

Biochemical studies

- **serum Chromogranin A:** tumor burden [1]
- 30% have elevation PP
- serum pancreastatin: PFS and OS [2]
- Hormonal work up per clinical symptoms

1. Modlin et al. Ann Surg Oncol 2010
2. Sherman et al. Ann Surg Oncol 2014

Sporadic NF PNETs

- Management of incidentally found PNETs
  - Most favor 2 cm. cutoff:
    - 34 mo FU (n=41), no LN or distant metastasis[1]
    - Mayo: 45 mo FU→ n=77 observed (median size 1 cm.): none progressed[2]
    - Size >2cm and symptoms: predictor for mets[3]
- EUS FNA for Ki-67% controversial
- Predictor of aggressive behavior [4]
  - Calcification, Ki-67 $\geq 3\%$, HYPOenhancing tumor

1. Gaujoux et al. JCEM 2013
2. Lee et al. Surgery 2012
3. Bettini et al. Surgery 2011
4. Golerlik et al. Surg Clin N AM 2018

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Sporadic NF PNETs – ASPEN Trial in <2cm

- Interim analysis 500 patients
- Young age, tumor >1cm, main pancreatic duct dilatation

Partelli S et al BJS Dec 2022

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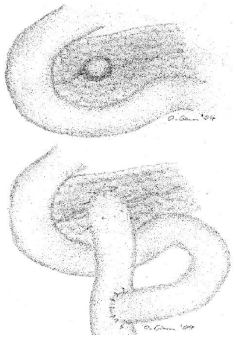
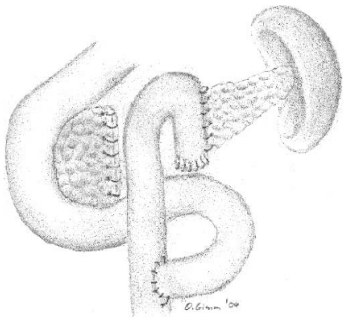
Sporadic NF PNETs

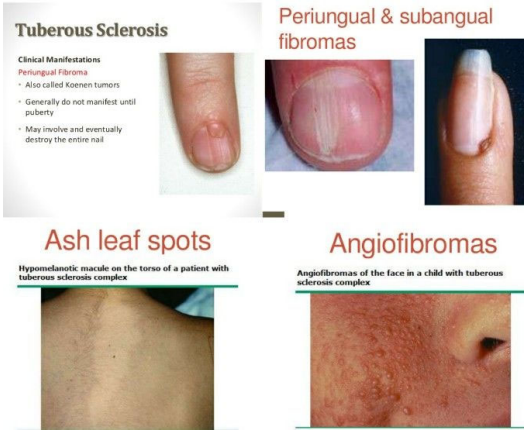
- Procedures: “all about pancreatic duct”
  - Resection: Distal pancreatectomy +/- splenectomy, central pancreatectomy, Whipple’s procedure
  - Enucleation: When multiple tumors, no duct involvement, no evidence of malignancy, exophytic





Hereditary Syndromes in PNETs

- MEN1
- VHL
- NF1
- Tuberous sclerosis



MEN1- NF PNETs

- **Almost always multiple**: patients with a hormone excess syndrome have other nonfunctioning macro- or microadenomas
- Risk of malignancy~ 30-50%
- Dutch: 2/115 PNETs **<2 cm** had liver mets[1]
- French: **> 2cm**, age 40, and ZE syndrome independent factors for mets (n=603).[2-4]

-> New Guidelines 2024

1. Pieterman et al JCEM 2017
2. Vinault et al. Ann Surgery 2018
3. Triponez et al Ann Surgery 2019
4. International consensus statement 2020

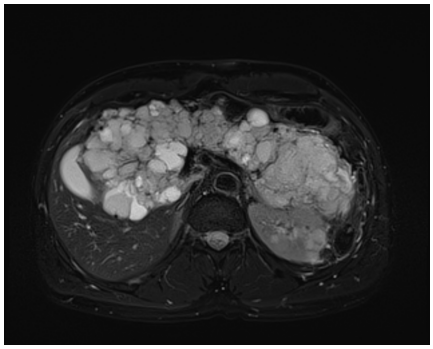
Procedures for MEN-1 with NF PNETs

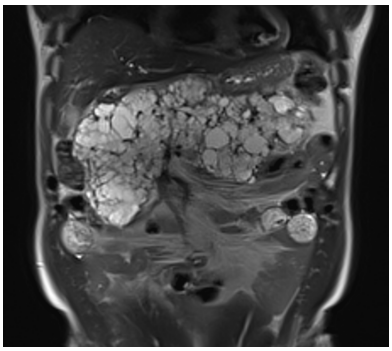
1. Distal pancreatectomy +/- splenectomy combined with enucleation of head tumors (historic)
2. Enucleation or resection of macronodules without routine distal pancreatectomy

- No study has compared these procedures

VHL- PNETs

- Always non-functioning
- 15% of patients with VHL
- Risk of metastasis
  - Tumor > 3cm.
  - Missense mutation
  - Exon 3 mutation
  - Doubling time <500 days





Blansfield et al. Surgery 2007
Tirosh et al. JAMA Oncol 2018

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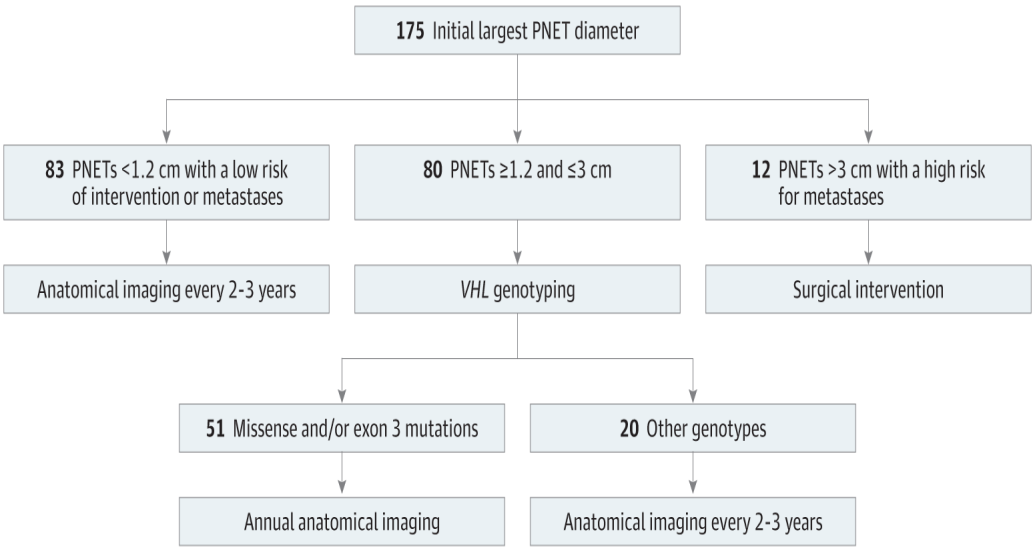
VHL- PNETs



Tirosh et al. JAMA Oncol 2018

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Functioning PNETs

- Insulinoma 55%
- Gastrinoma 36%

VIPoma
Glucagonoma
ACTHoma
Somatostatinoma

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Insulinoma

- Most common functioning PET
- Incidence: 1-4 per million
- Median age of diagnosis of 50 yrs (sporadic)
- 1.5-2 times more common in women
- Younger presentation in MEN-1 (30s)
- 5-10% associated with MEN-1 syndrome

90% sporadic disease
90% less than 2 cm
90% solitary
90% benign

Krampitz and Norton. Curr Prob Surg 2013

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Insulinoma Diagnosis

- **Whipple's triad** (1938)
  - Serum glucose <45 when symptomatic
  - Neuroglycopenic symptoms with fasting
  - Symptoms relieved with glucose
- Inappropriately elevated serum insulin > 5 mcU/ml
- Insulin/glucose ratio >0.3

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Diagnostic tests for patient with insulinoma

Test	Diagnostic criteria	Normal range	Sensitivity (%)
Supervised 72-hr fast serum glucose	<40 mg/dl	90-150 mg/dl	99
Immunoreactive insulin	> 5 uU/ml	<5 uU/ml	~100
C-peptide	>1.7 ng/ml	<1.7 ng/ml	78
Pro-insulin	>25%	<25%	87

Krampitz and Norton. Curr Prob Surg 2013

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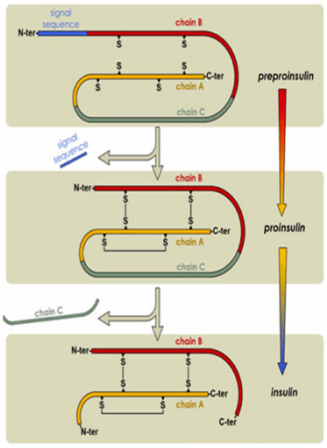
Insulinoma Diagnosis



- C-peptide: endogenous insulin
  - Elevated in insulinoma and sulfonylurea
  - Normal in hyperinsulinemia→ exogenous insulin
- Rule out sulfonylurea (Urine or serum)
- Increase proinsulin level
  - Typically higher proinsulin:insulin ratio in patients with insulinoma (> 25%)

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Insulinoma Non-invasive Preoperative Localization

- CT scan: bi or triphasic,(spiral) thin cut→ arterial enhancing pancreatic lesion: sensitivity ~44% (40%-94%).[1,2]
- MRI: low intensity on T1, after Gadolinium→ enhancing lesion: sensitivity ~ 50% (0-100%)
- Octreotide scan: sensitivity ~20% (0-47%)
- 68-Gallium DOTATATE: 90% (n=9/10) [3]

1. Krampitz and Norton. Curr Prob Surg 2013
2. Mehrabi et al. Pancreas 2014
3. Nockel et al. JCEM 2017

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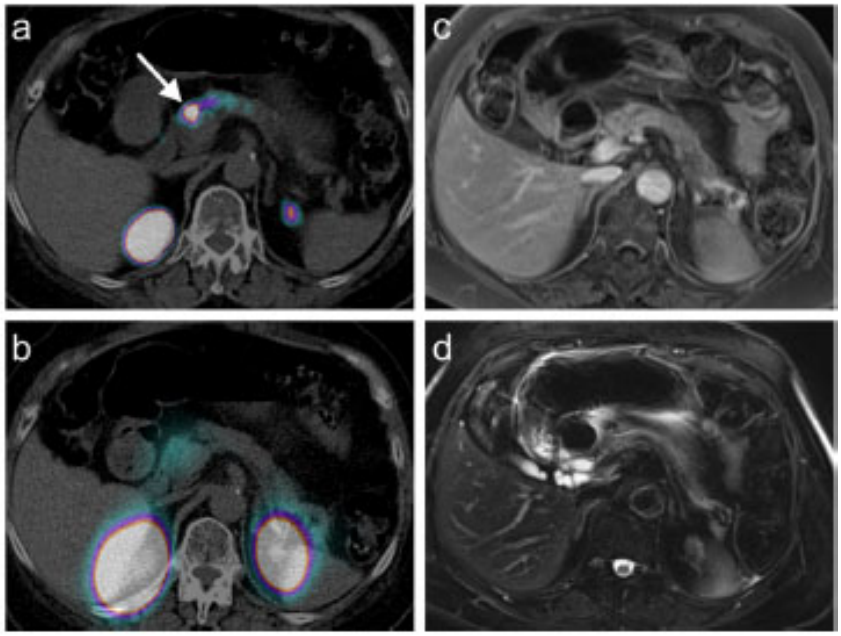
Insulinoma Non-invasive Preoperative Localization

^{68}Ga-DOTA-exendin-4 PET/CT (GLP-1R)

- GLP1-R > SSTR2 on WD insulinoma[1]
- Compared to ^{111}In-DOTA-exendin-4 SPECT/CT and 3T MRI[2]
  - 38 patients (total 52, 6 MEN1), prospective
    - accuracy of 93.9% for PET/CT
    - 67.5% for SPECT/CT
    - 67.6% for MRI for detecting insulinoma
  - Differentiate Insulinoma from other pNET

1 Reubi Eur J Nucl Med Mol Imaging 2003
2 Antwi et al Eur J Nucl Med Mol Imag 2018

68Ga-DOTA-exendin-4 PET/CT (GLP-1R)



Antwi et al Eur J Nucl Med Mol Imag 2018

Insulinoma Invasive Preoperative Localization

- EUS: 70%-94% procedure of choice when axial imaging are negative
- Selective arterial calcium stimulation with hepatic venous sampling.
  - 2-fold increase
  - Arteriography: lower sensitivity 27%-80% for recurrent or persistent disease
  - Useful in MEN-1 patients with multiple pancreatic tumors

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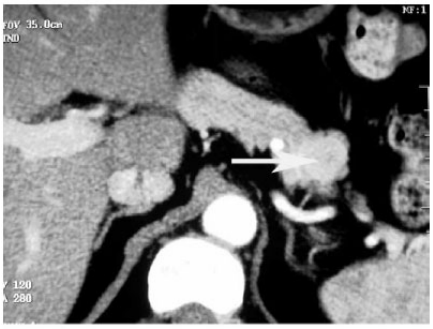
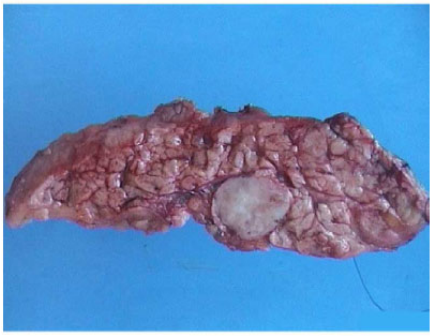
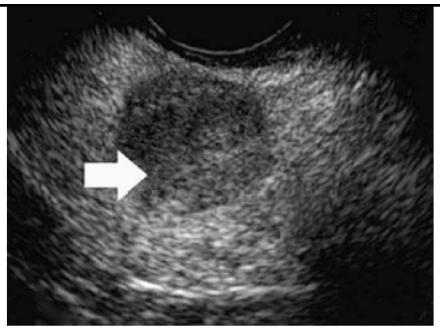
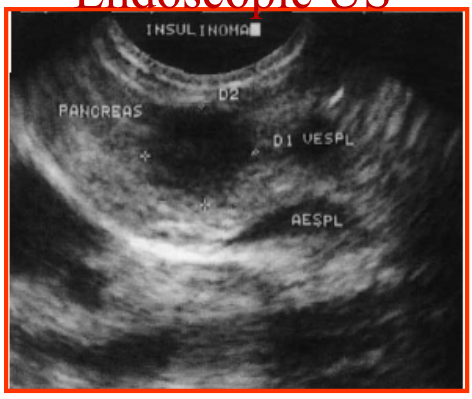


CT scan (a)





Endoscopic US



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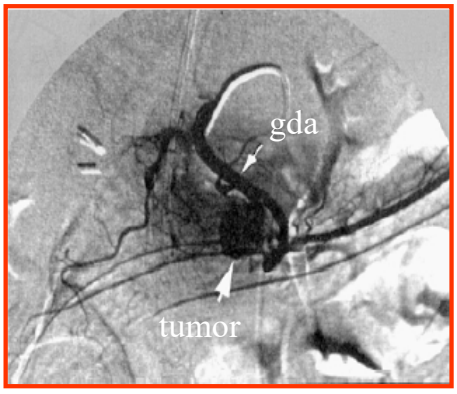
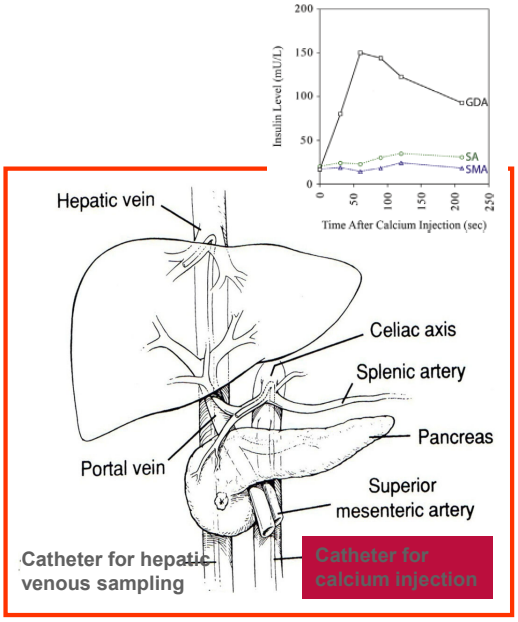
Arteriography



Selective Arterial Calcium Stimulation



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Insulinoma Medical Management

- Dietary modification
- Diazoxide: inhibits insulin release, increases glycogenolysis.
  - Na retention, edema
- Somatostatin analogue: effective in 40%-60% of patients

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Insulinoma Surgical Management

- Open Kocherization→ bimanual palpation (42%-95%), body and tail mobilization
- Intraop US: sensitivity 75%-100%
- Laparoscopic with intraop US, hand port: pre-op localization is helpful
- Enucleation or resection
- MUST send FROZEN section

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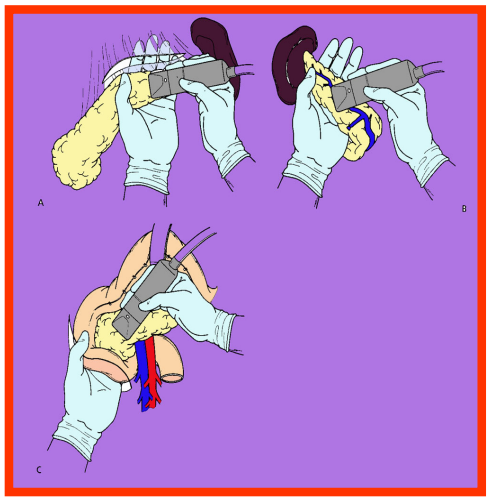
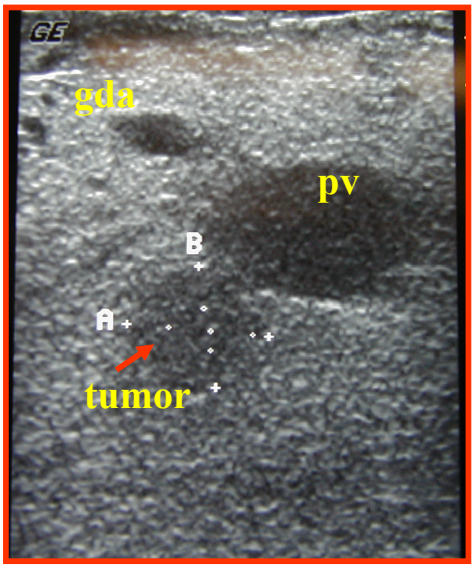
Intraoperative US and Palpation





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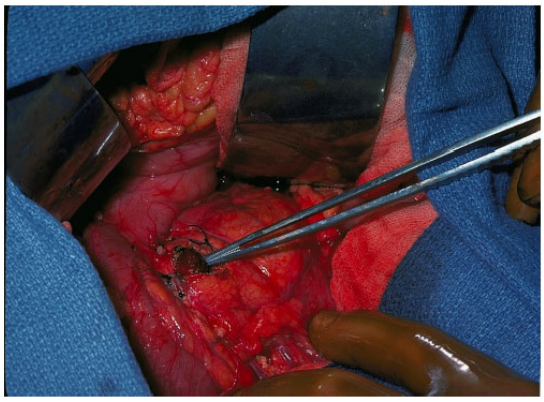

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What if….. NO mass found in OR!!

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NO blind distal pancreatectomy

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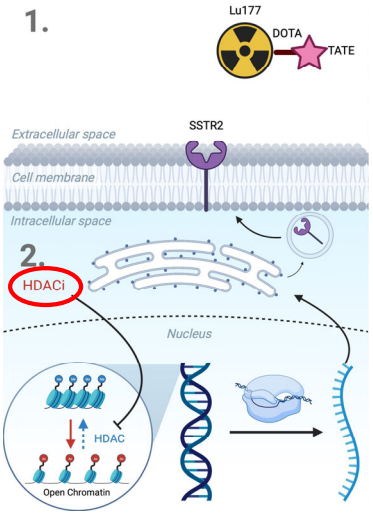
Research scope of the Sadowski Lab

To develop targeted therapy for high-grade PNETs



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Histone Deacetylase Inhibitor (HDACi) created in BioRender.com 45

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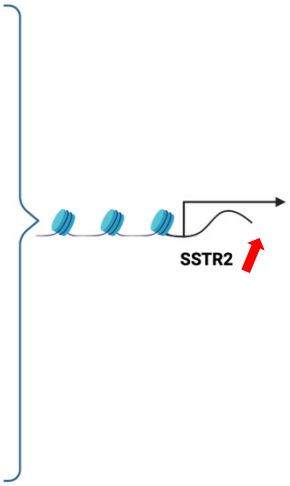
Multiple epigenetic mechanisms cooperate to modify expression of the SSTR2 gene

1. LSH affects chromatin remodeling
2. DNMT3B is responsible for the DNA CpG methylation



Relevant Question:
Can we develop novel, very **targeted** epigenetic-based therapies with improved patient **toxicity profiles** and few **off-target effects?**

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Staff scientist
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Unpublished data: Madigan.....**Sadowski**, in preparation 46

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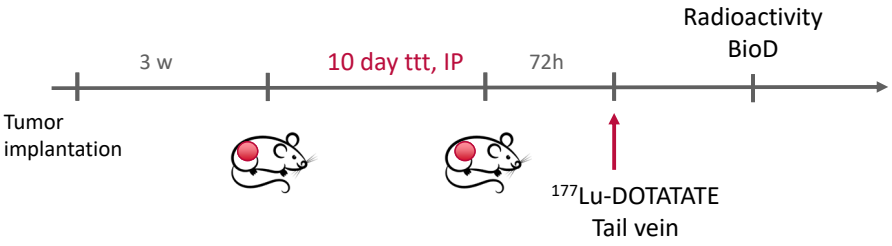
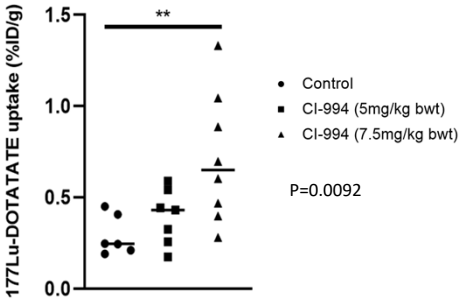
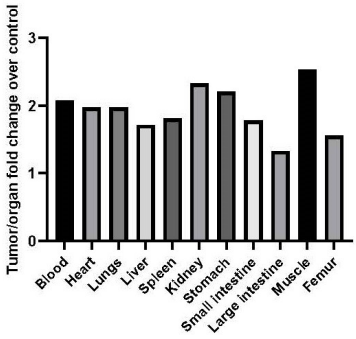
In vivo SSTR2 upregulation: Clinical relevance







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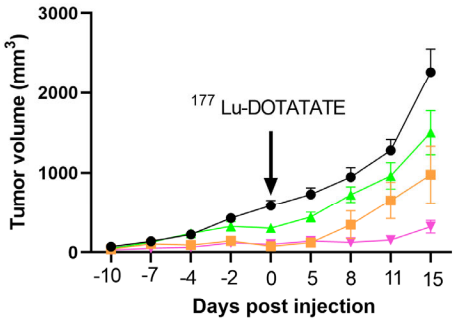
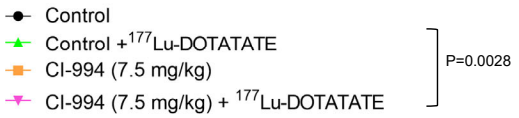
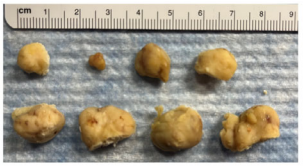
Upregulation of SSTR2 for therapeutic targeting in advanced PNET







CI-994 (7.5 mg/kg)+^{177}Lu-DOTATATE

Control+ ^{177}Lu-DOTATATE

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GEP-NET Organoid Workflow

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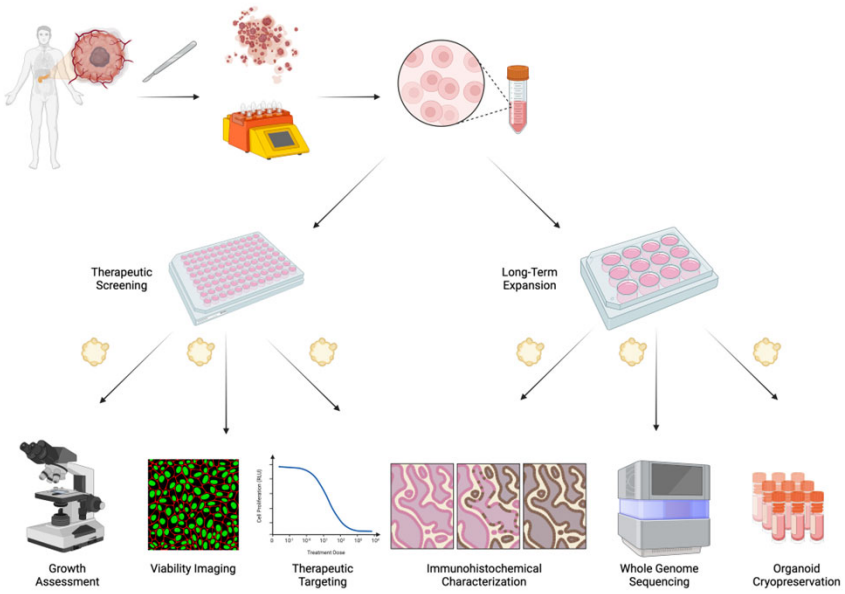
Early-Stage Surgeon Scientist Program (ESSP)



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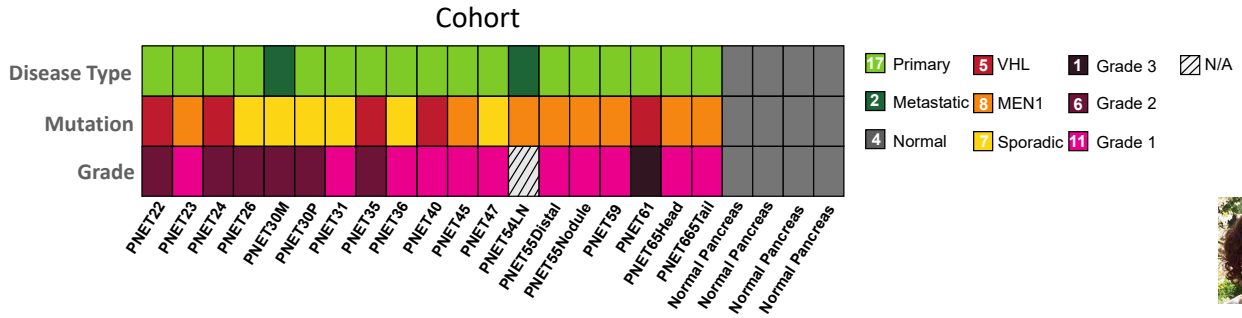
Epigenetic mechanisms governing PNET differentiation and progression

Relevant Questions:

1. What are the **cells of origin and composition of tumors** and how do they influence outcome?
2. How do **tumor heterogeneity and differences in SSTR2 expression** affect therapy response?
3. What are the **drivers of tumor progression** (transcription factors), and are they targetable?



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Collaboration with Dr Efsun Arda Lab 50

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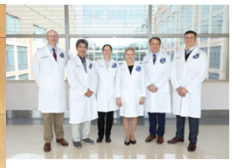
Acknowledgments



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Early-Stage Surgeon Scientist Program (ESSP)

Patients and families

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