

# NET Symptom Management

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CNETs meeting, April 2017

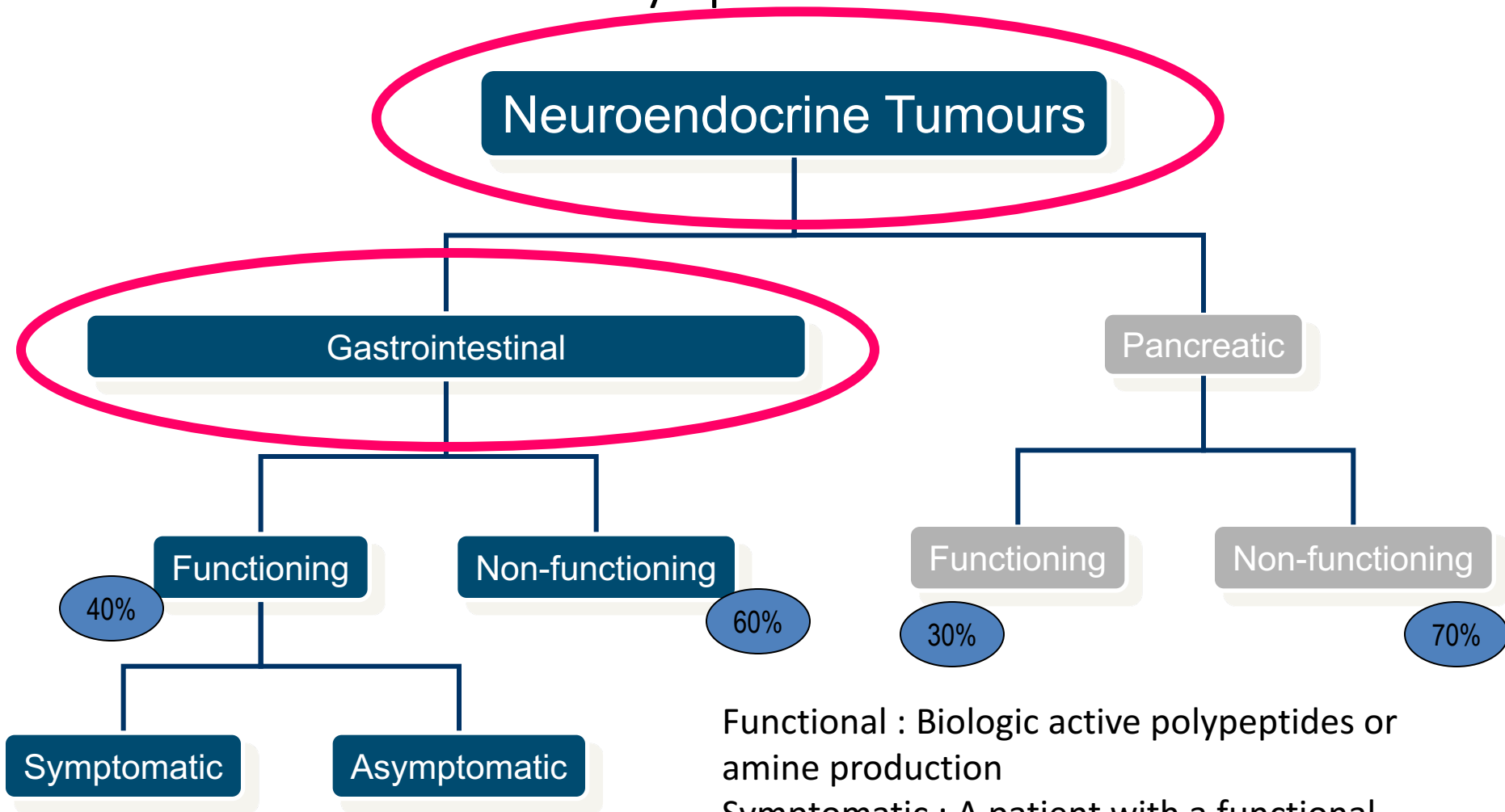
# Disclosures

- Novartis : Consultant, Research funding, fellowship funding
- Ipsen : Consultant, Research funding,

# Objectives

- Define Functional vs Symptomatic Neuroendocrine tumors
- Describe the Carcinoid syndrome
- Describe Medical treatment options of the Carcinoid syndrome

# Neuroendocrine Tumour Classification: Functioning vs Symptomatic



Functional : Biologic active polypeptides or amine production

Symptomatic : A patient with a functional tumor that presents with symptoms

# Case DG

- 49 year old female, with hypertension
- Two year history of diarrhea and flushing
  - Diarrhea, about 8-10 per day
  - Abdominal pain
  - Facial flushing (especially with certain foods and intra-abdominal pressure)
- Exam:
  - Obvious flushing: pinkish and hot face and upper chest
  - Chest clear, Heart sounds normal
  - Abdomen: fullness and palpable liver 2 cm below costophrenic angle



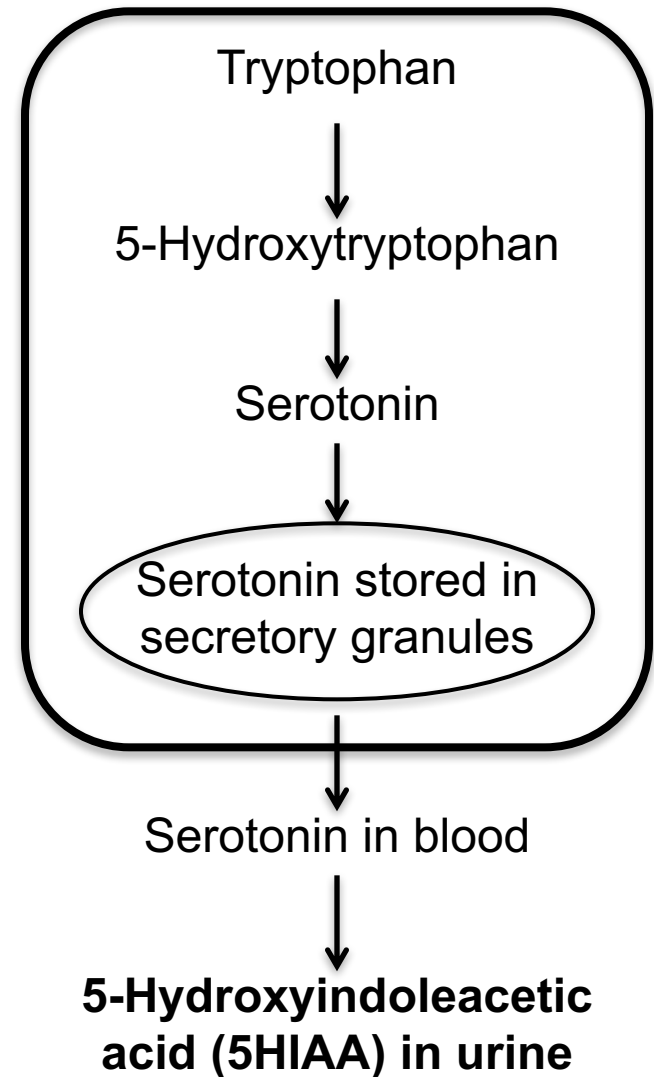
# Case DG

- Went to an allergist about diarrhea, felt it was food intolerance
- Ordered urine 5HIAA= 800.
  - Normal <50 mmol/day

**WHAT Clinical SYNDROME IS THIS?**

# NET Biomarkers - Urinary 5-Hydroxyindoleacetic Acid (5-HIAA)

- Measured in a 24-hour urine specimen
- High levels have prognostic value and can be associated with
  - Reduced survival
  - Progressive carcinoid heart disease



Adapted from :

1.Kocha W, *et al.* *Curr Oncol.* 2010;17(3):49-64.

2.Feldman JM. *Clin Chem.* 1986;32(5):840-4.

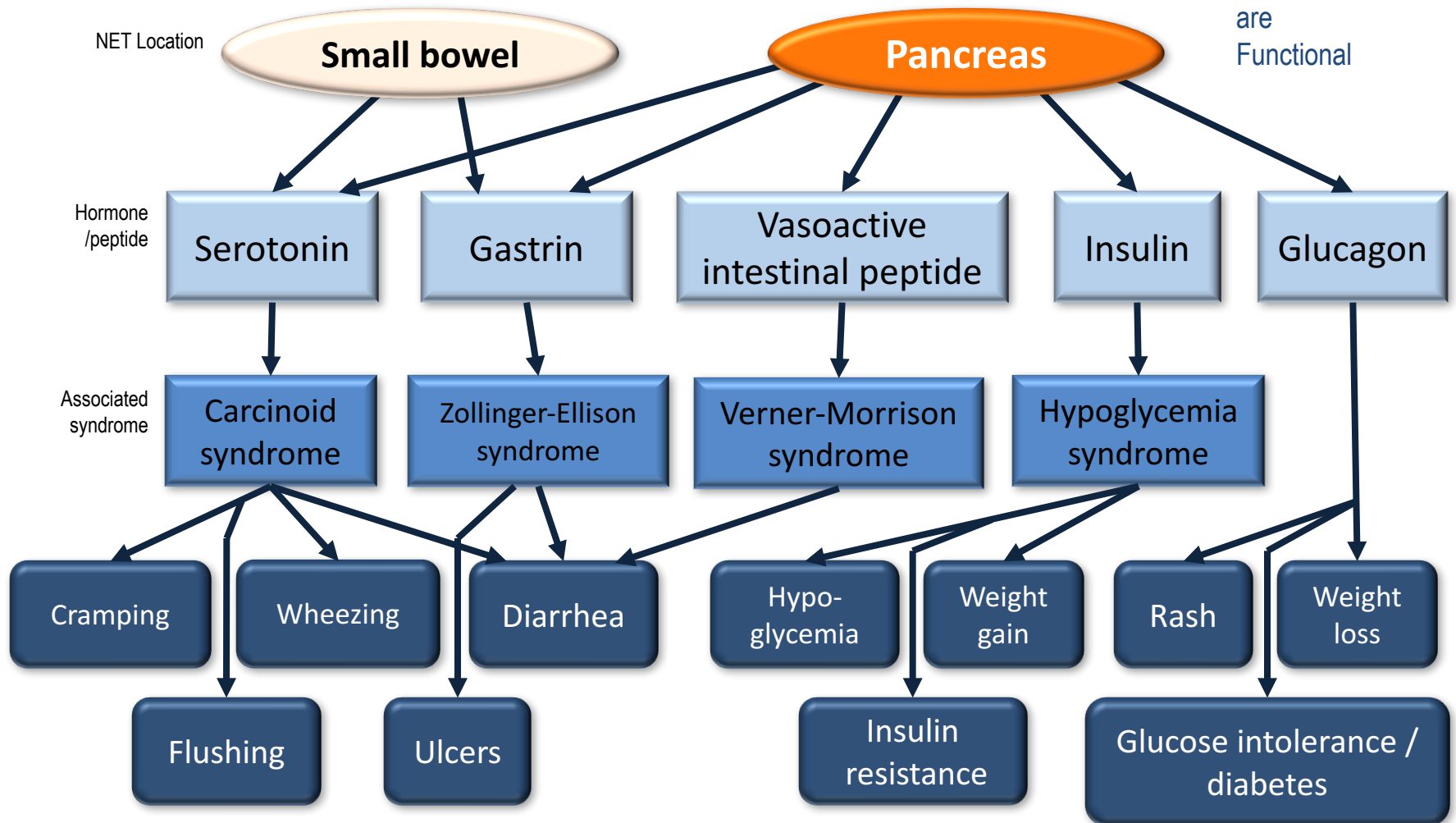
3.Formica V, *et al.* *Br J Cancer.* 2007;96(8):1178-82.

4.de Herder WW. *Best Pract Res Clin Endocrin Metab.* 2007;212(1):33-41

5.Goldfinger SE *et al:* *Clinical features of the carcinoid syndrome* [www.uptodate.com](http://www.uptodate.com). Last updated: September 2014.

# Syndromes with Nonspecific Symptoms Caused by Hormones and Peptides Secreted by Functional NETs\*

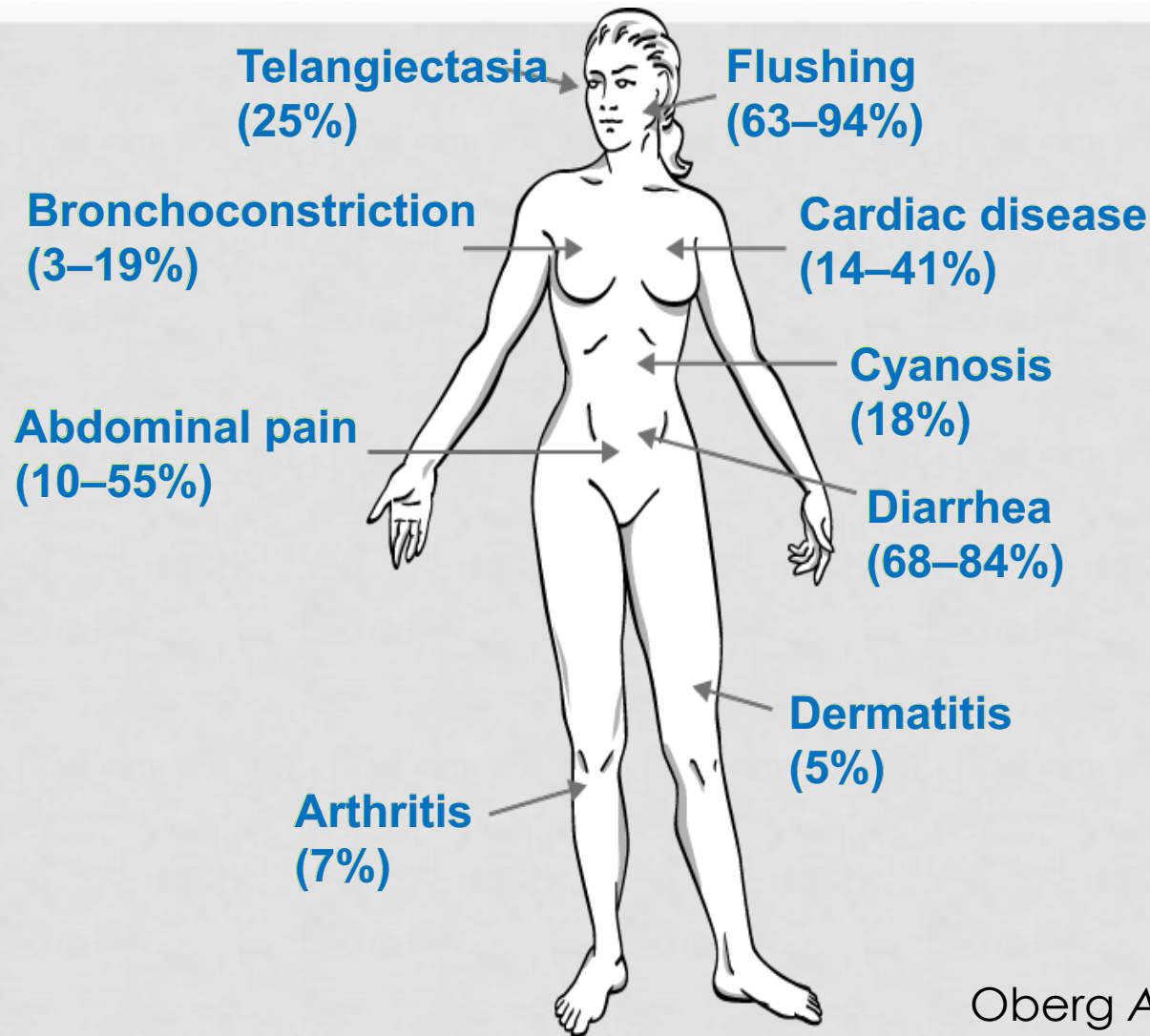
Approx. 2/3 of NETs are Functional

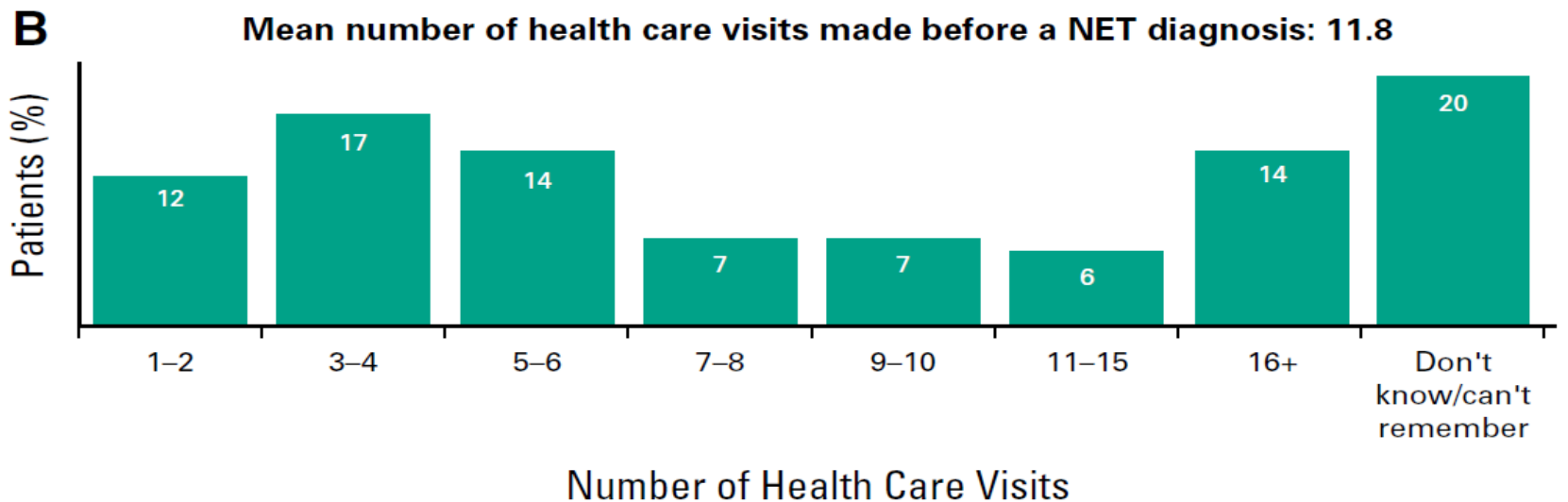
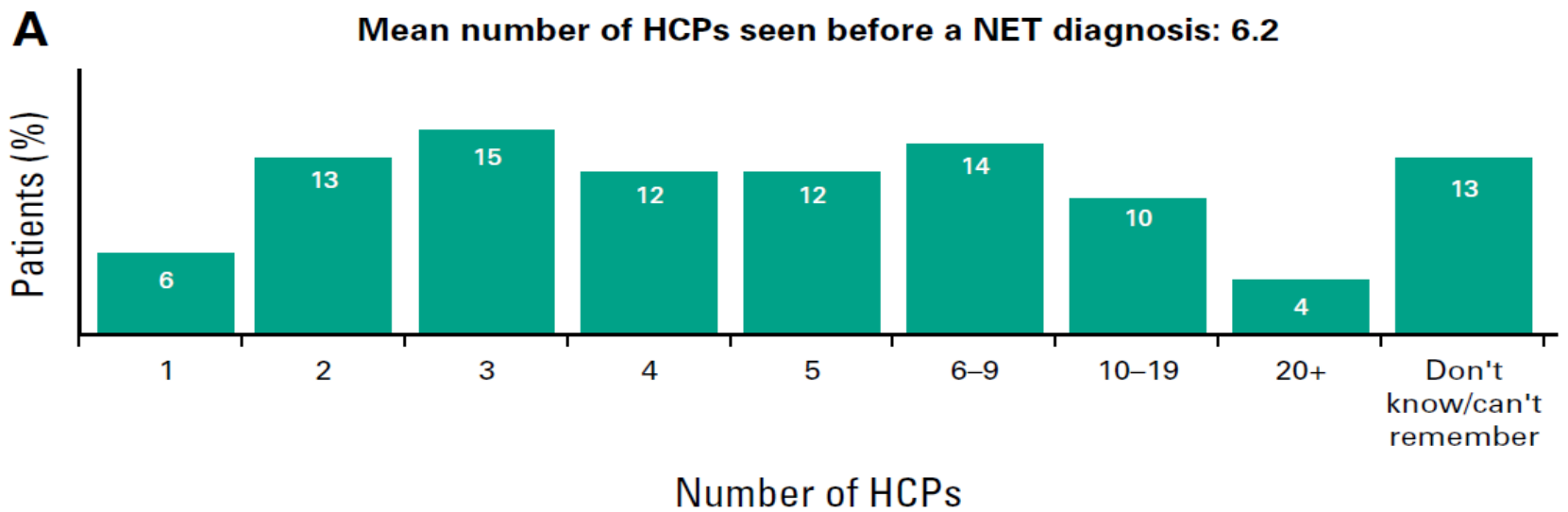


\*There are many other hormones, syndromes and symptoms that can be caused by NETs. These are some of the most common. Adapted from Modlin IM, *et al.* Lancet Oncol. 2008;9(1):61-72; Kaltsas GA, *et al.* Endocr Rev. 2004;25(3):458-511; and Barakat MT, *et al.* Endocr Relat Cancer. 2004;11(1):1-18.



# Carcinoid Syndrome: Clinical Presentation





Mean time from 1<sup>st</sup> symptom onset to diagnosis was 52 months

# Symptoms of carcinoid syndrome:

- A condition associated with tumoral secretion of serotonin
- Vasomotor symptoms (90%): Facial flushing, telangiectasia, chronic facial cyanosis, rhinitis
- Increased intestinal motility (80%): Diarrhea, borborygmi, abdominal pain
- Heart failure (40%): Endocardial fibrosis, right-sided heart insufficiency, pulmonary stenosis
- Bronchoconstriction (15%): Asthma
- Carcinoid Crisis : Severe form of carcinoid syndrome usually triggered by surgery or biopsy.
- **Reference**
- Öberg K, Astrup L, Eriksson B, et al. for the Nordic NE Tumour Group. Guidelines for the management of gastroenteropancreatic neuroendocrine tumours (including bronchopulmonary and thymic neoplasms). Part II-specific NE tumour types. *Acta Oncol.* 2004b;43:626-636.

# Flushing

- 75-80 % of patients with carcinoid syndrome have small bowel carcinoids
- Manifestations and severity vary in individual patients
- Typical flush with a midgut carcinoid lasts 20-30 seconds
- Primarily involves face, neck, upper chest
  - Goes from red to purple and has a mild sensation
  - Could be associated with a fall in blood pressure and a rise in HR

# Diarrhea

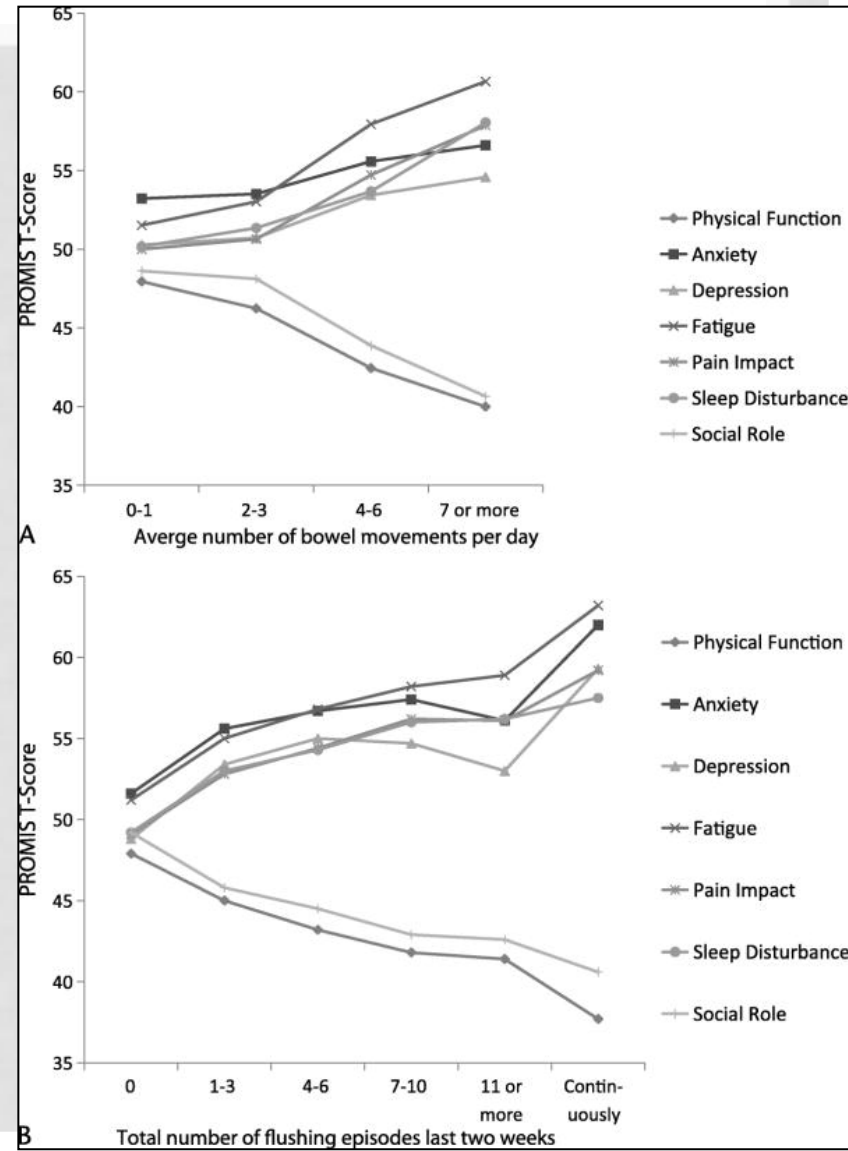
- A common symptom of
- carcinoid syndrome
- Negatively affects quality of life

FIGURE 2 . A, PROMIS scores versus average number of bowel movements per day. B, PROMIS scores versus total number of flushing episodes in the past 2 weeks.

**Comparison of Health-Related Quality of Life in Patients With Neuroendocrine Tumors With Quality of Life in the General US Population.**

Beaumont, Jennifer; Cella, David; Phan, Alexandria; Choi, Seung; Liu, Zhimei; Yao, James

Pancreas. 41(3):461-466, April 2012.  
DOI: 10.1097/MPA.0b013e3182328045



# Symptom Control of Carcinoid Tumor

- Somatostatin Analogs (SSAs) is a standard treatment of patients with carcinoid syndrome
- Octreotide acetate injection (short acting)
- Octreotide for injectable suspension (long acting)
- Octreotide is Indicated by health Canada (since 1989) for the control of symptoms in patients with metastatic carcinoid and VIPomas.
- Octreotide suspension is indicated for the treatment of the severe diarrhea and flushing episodes associated with carcinoid tumors in whom symptoms are adequately controlled on s.c. treatment with Sandostatin. Novartis Product Monograph, Sept. 2016

# Mechanism of action of SSA's

- Binds to somatostatin receptors (SSTRs) and produces a dramatic decrease in Serotonin levels, and the serotonin metabolite, 5 HIAA, and relief of symptoms from the carcinoid syndrome
- Octreotide acetate when administered every 6-8 hours can provide effective therapy
- Two long-acting formulations were developed (Sandostatin LAR and Lanreotide)
- Both provide effective relief, but only Sandostatin LAR is approved for this indication in Canada

# Other treatments for diarrhea

- Opiates or synthetic opiates : disrupts peristaltic movement, increases transit time of intestinal contents, allows fluid to be reabsorbed : useful for mild diarrhea
- Telotristat Ethyl
  - Patients with carcinoid syndrome may develop diarrhea despite SSA therapy
  - Tryptophan hydroxylase (TPH), the rate limiting enzyme in serotonin synthesis, converts tryptophan to 5-hydroxytryptophan, which is subsequently converted to serotonin.
  - Telotristat ethyl is a novel, oral, small-molecule TPH inhibitor, that does not cross the blood brain barrier

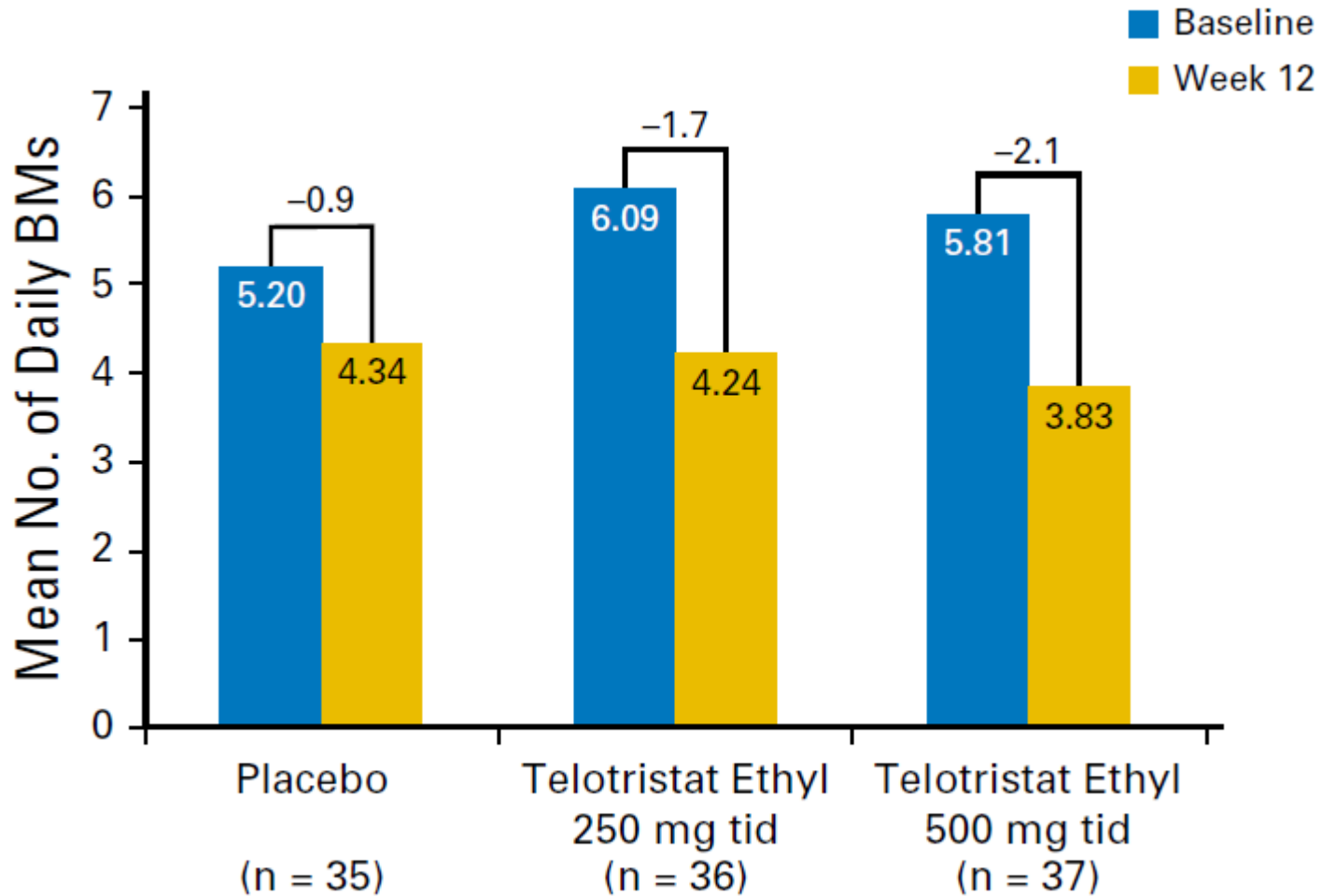


# Telotristat Ethyl TELESTAR Study

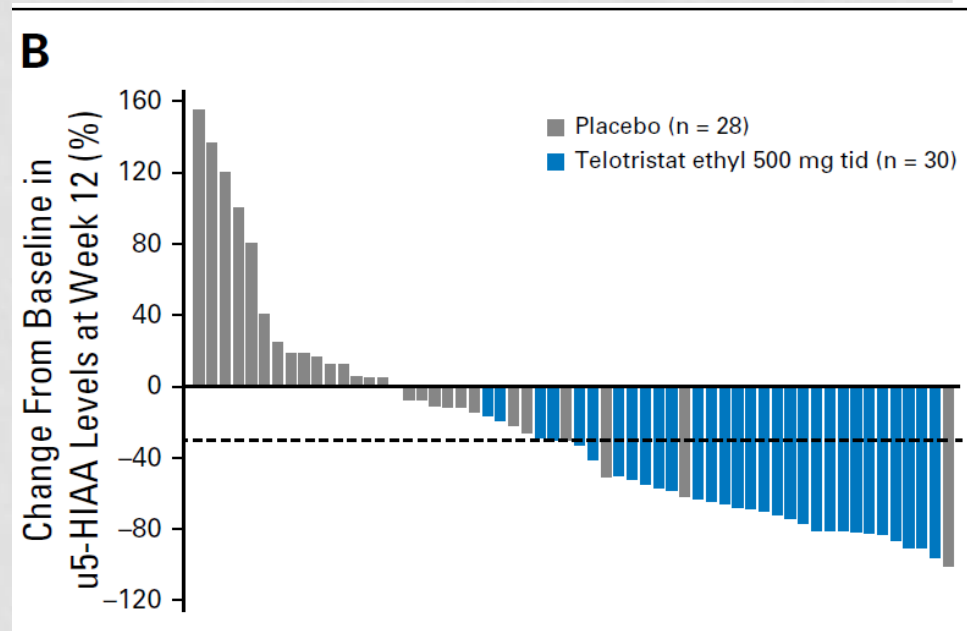
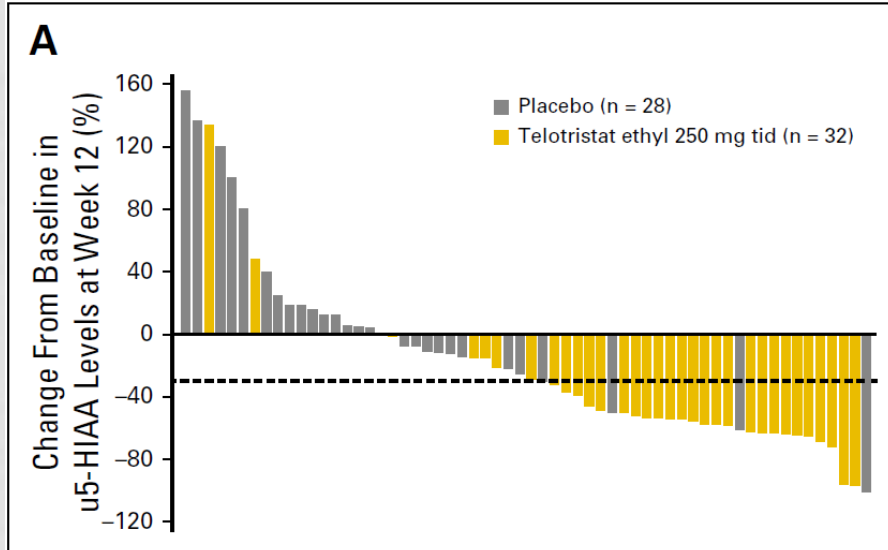
- Eligible patients were  $\geq 18$  years of age, had histopathologically confirmed, well-differentiated metastatic NETs, had a documented history of carcinoid syndrome, were experiencing an average of four or more BMs per day, and were receiving stable-dose SSAs (long-acting release [LAR], depot, or infusion pump) for  $\geq 3$  months before enrollment.
- 135 Patients were randomly assigned 1:1:1 to receive oral doses, three times per day for 12 weeks, of telotristat ethyl 250 mg, telotristat ethyl 500 mg, or placebo.

Kulke MH, Horsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol.* 2017;35(1):14–23.

# Telotristat Ethyl



# Reduction of u5HIAA



# Telotristat Ethyl

- Generally well tolerated :mild nausea, and asymptomatic increases in GGT
- Approved by the FDA Feb. 28, 2017 for the treatment of carcinoid syndrome diarrhea in patients with met NET.
- Dose approved was 250 mg

# Summary

- Many patients with advanced NET have symptoms
- Most common is the carcinoid syndrome
- Effective treatments include Somatostatin Analogs, supportive care, and now Telotristat
- More work needs to be done to understand and improve the patient experience, quality of life, and symptom control