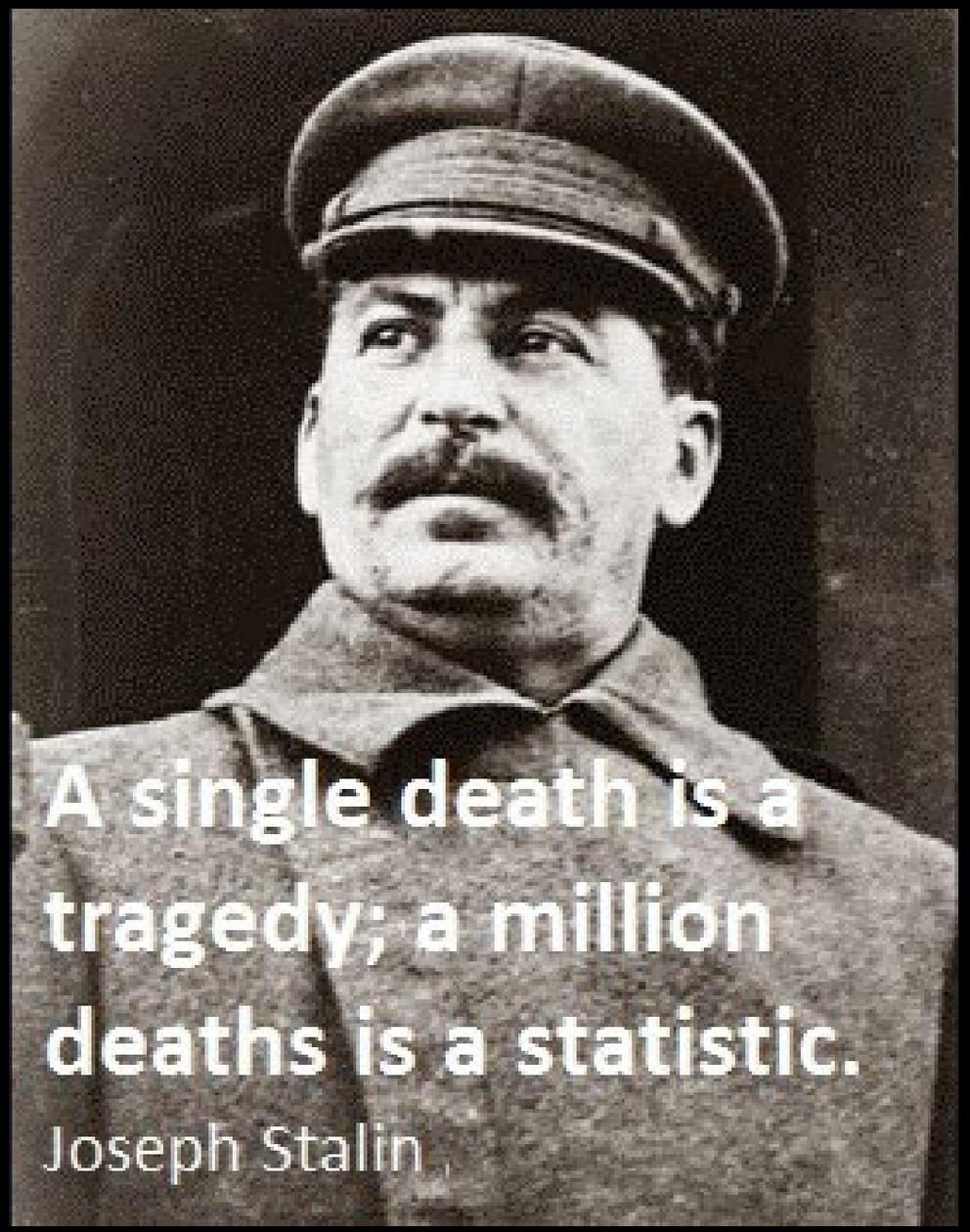
CPAT VIRTUAL KEYNOTE

THE FORTUNE & FOLLY OF SELF-DIAGNOSIS

September 6th, 2024

Mark A. Lewis, M.D.

A surprising source of wisdom



The index patient

- A minister in Belfast develops dysphonia during his sermons
- Progresses to dysphagia
- Develops amnesia, found to have brain metastases
- Dies at age 64 without a firm diagnosis

His older son

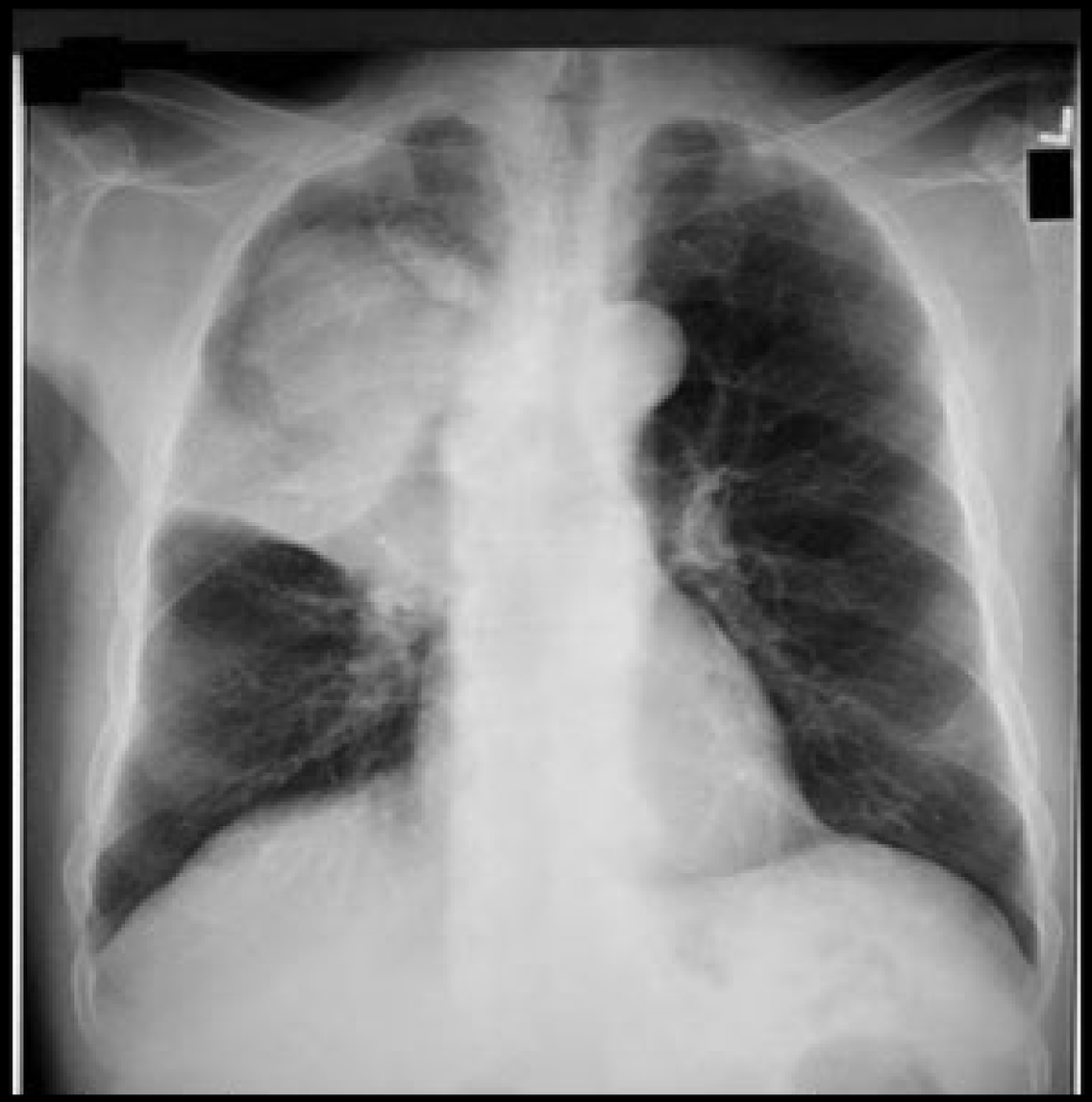
42-year-old male

* Lifelong non-smoker

* In usual state of health

* CXR obtained through pre-employment screening

* Past medical history remarkable only for kidney stones since his 20s



Treatment course

* “Lung cancer”

* Pneumonectomy

* Adjuvant radiation therapy to mediastinum

Relapse

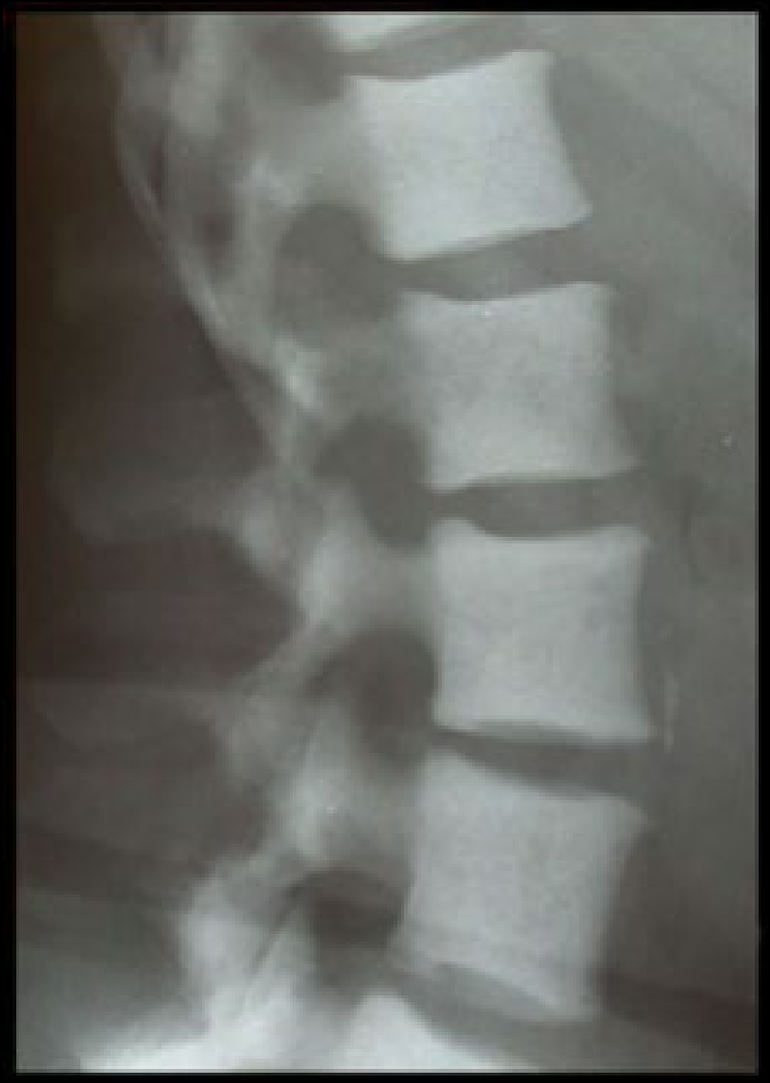
* Develops severe back pain while on holiday

* Plain X-rays reveal bone metastases

* Begins cisplatin/etoposide chemotherapy

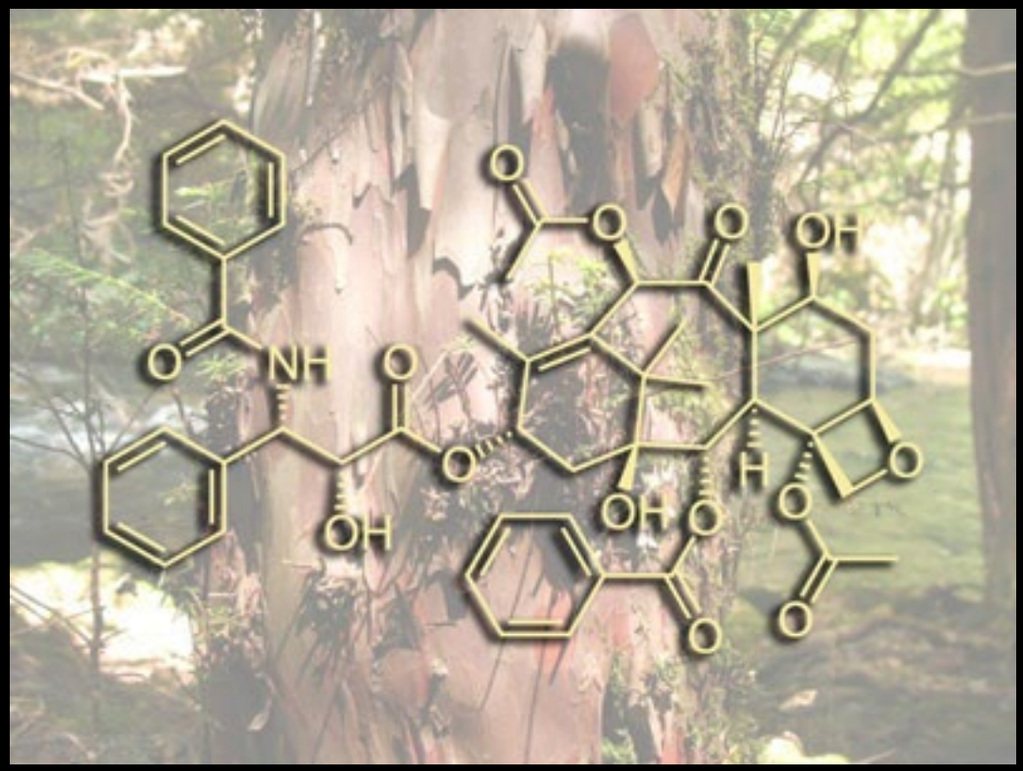
* Nearly dies after the 1st cycle from infection

* Filgrastim given to counter neutropenia



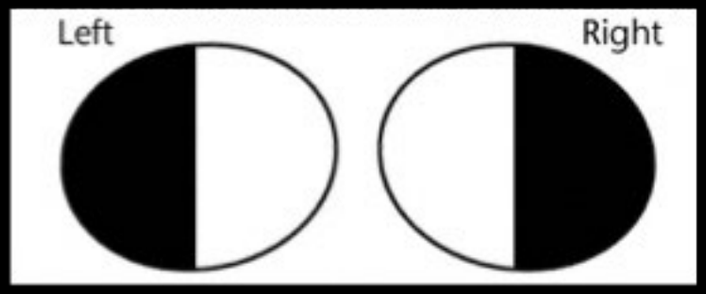
Further history

* Disease stabilization after 6 cycles of cisplatin/etoposide
* More metastases develop after a 2-year dormancy
* Transition to a new chemo
* Dies within 8 hours of first paclitaxel exposure



His younger son

* 5 years later, the index patient's younger son developed headaches and visual changes

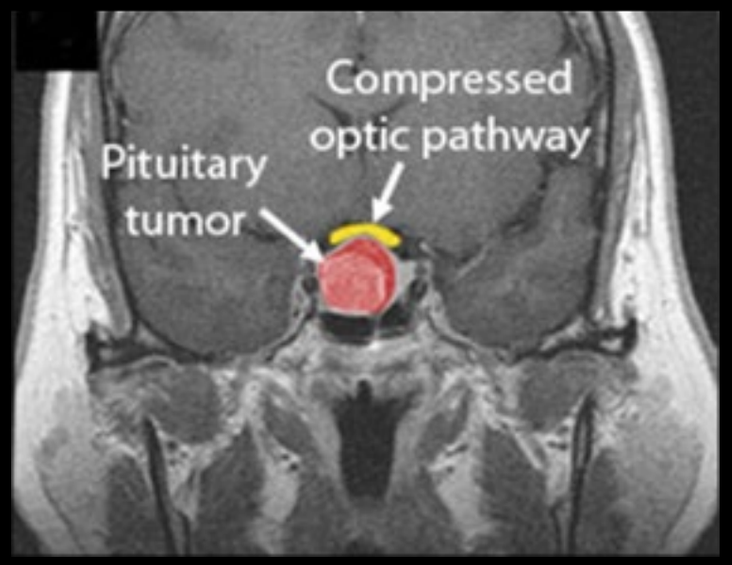


* MRI reveals a pituitary tumor (macroadenoma)

* Undergoes surgical removal

* Complicated by hemorrhage

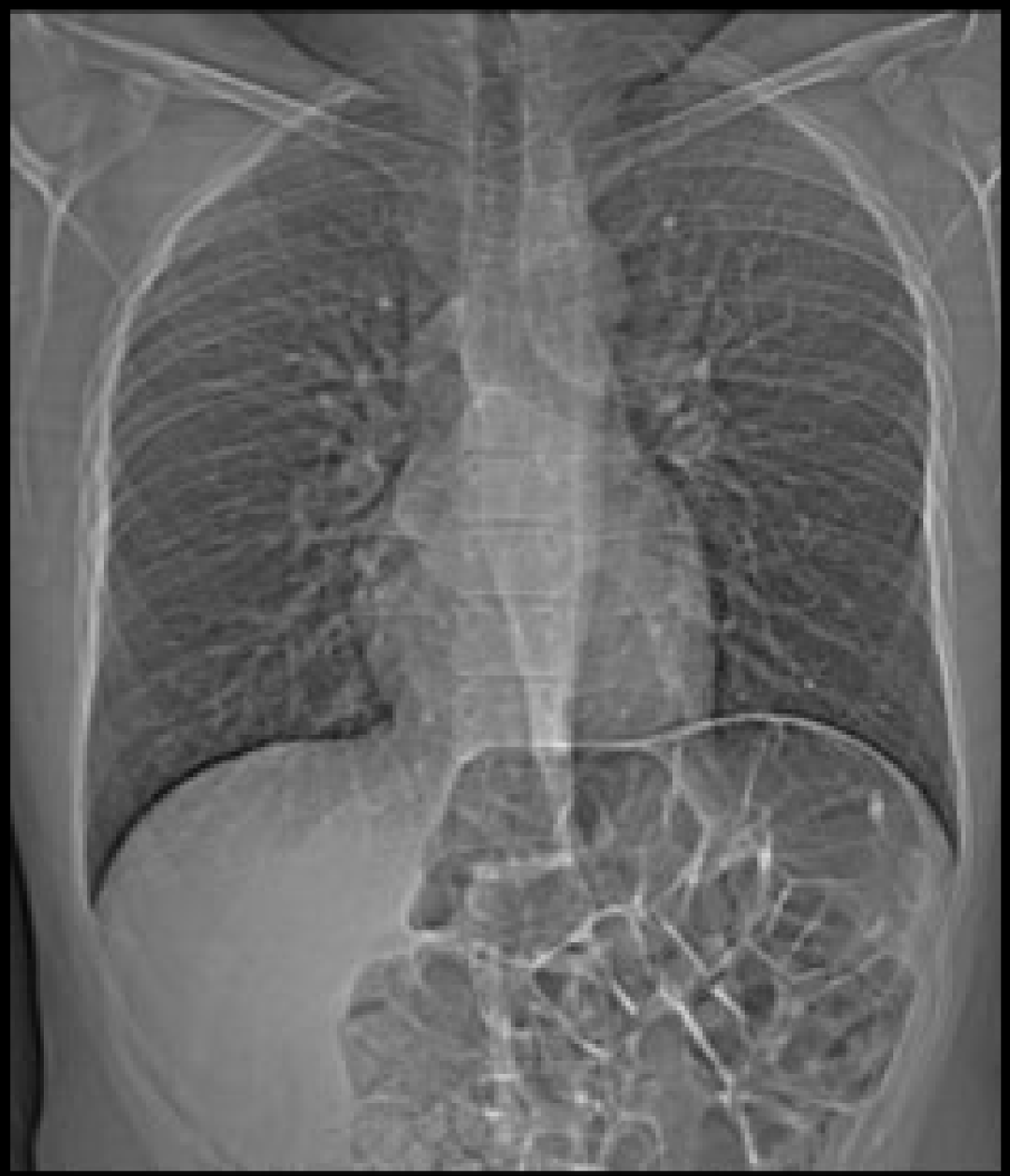
* Dies of pituitary apoplexy



His grandson

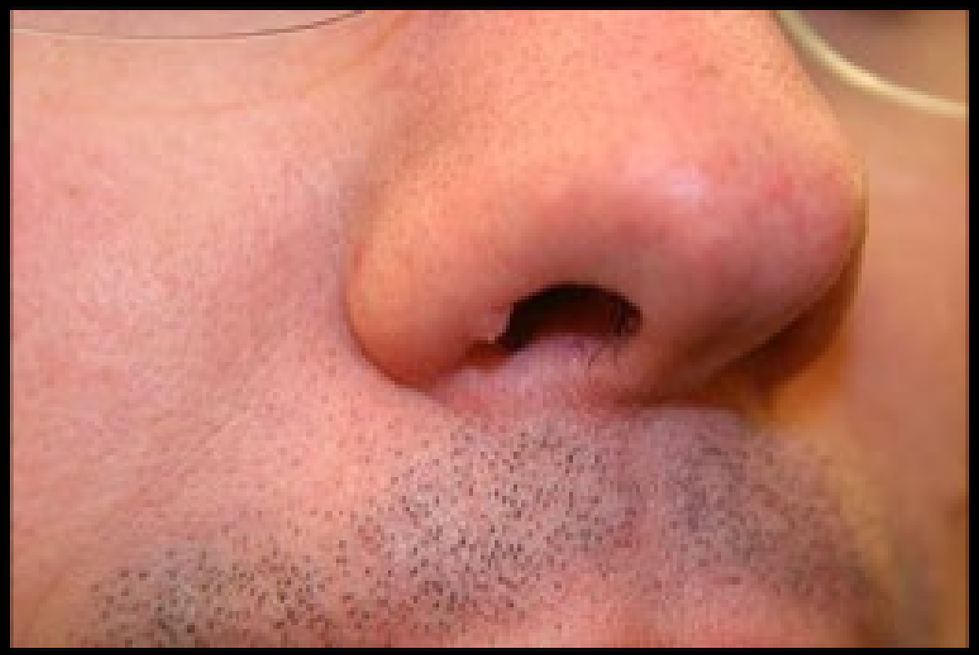
* 50 years after his grandfather's death, the grandson develops severe abdominal pain at age 30

* Calcium = 10.8 mg/dL



The grandson’s history

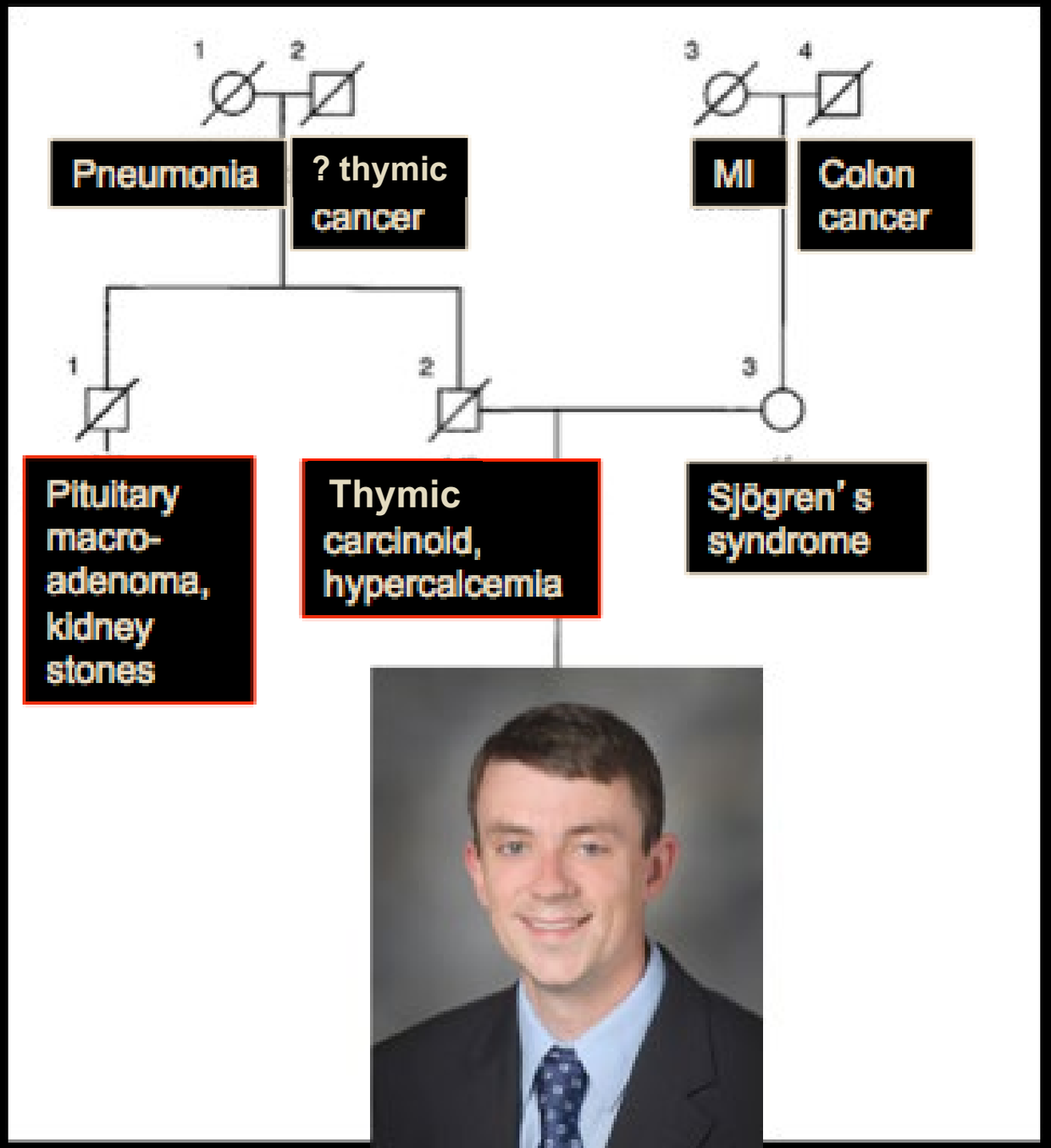
* 2 years prior to onset of abdominal pain, developed tiny red bumps over the nose



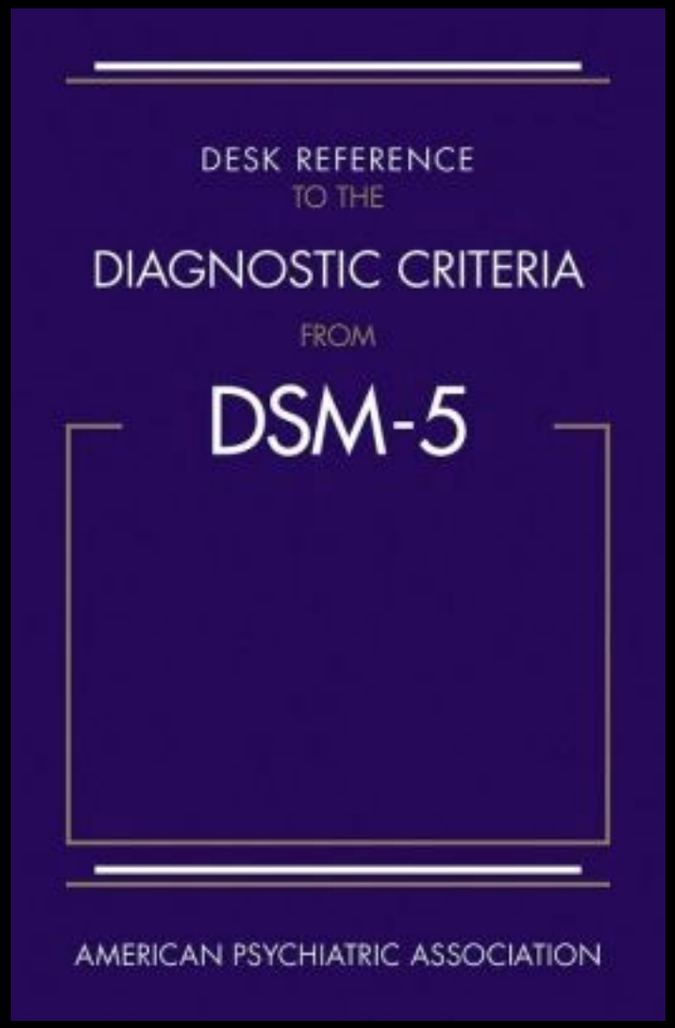
* Diagnosed as angiofibromas

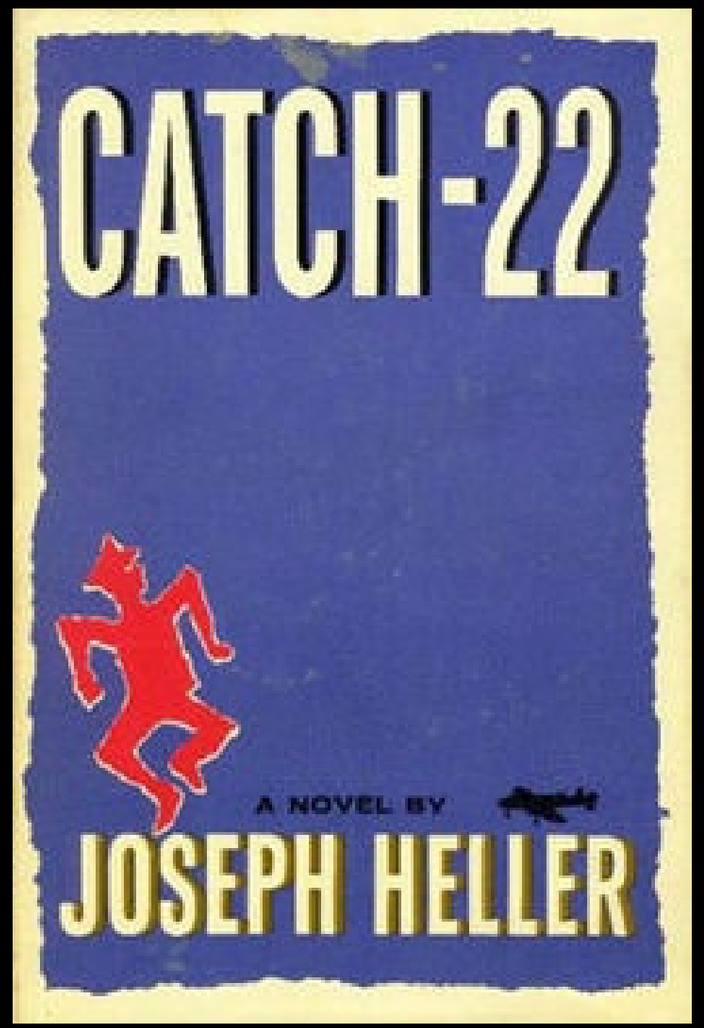
* “Pathognomonic for tuberous sclerosis”

I am the proband



The folly of self-diagnosis





A 30-year-old doctor starting his specialized training in oncology convinces himself he has a tumor syndrome

Nerves or something worse?

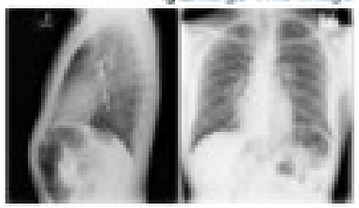
DIAGNOSIS

Nerves or Something Worse?

By LISA SANDERS, M.D.
Published: December 2, 2011 | 10 Comments

It felt like a knife slicing through his right side. The young man lay in bed and tried not to move. He'd had this pain off and on for years — usually when he was nervous, and he was very nervous that Sunday morning. He was supposed to start a new job the next day.

Enlarge This Image



The patient's chest X-rays.

Multimedia

Graphic

Readers' Responses

WELL
Think Like a Doctor
How this diagnosis unfolded, thanks to Well readers' responses.

Readers' Comments

1. THE PATIENT'S STORY

The pain had never been that bad before. A hot shower helped, but not for long; afterward, he couldn't bend at the waist without gasping. Slowly the pain began to ease, and the next day, he was well enough to start his new position — as a doctor, training for a specialty in cancer.

Although he felt comfortable with his self-diagnosis of a jittery stomach, his wife — also a doctor — did not. At her insistence, he made an appointment with the primary-care doctor he'd been assigned at the Mayo Clinic.

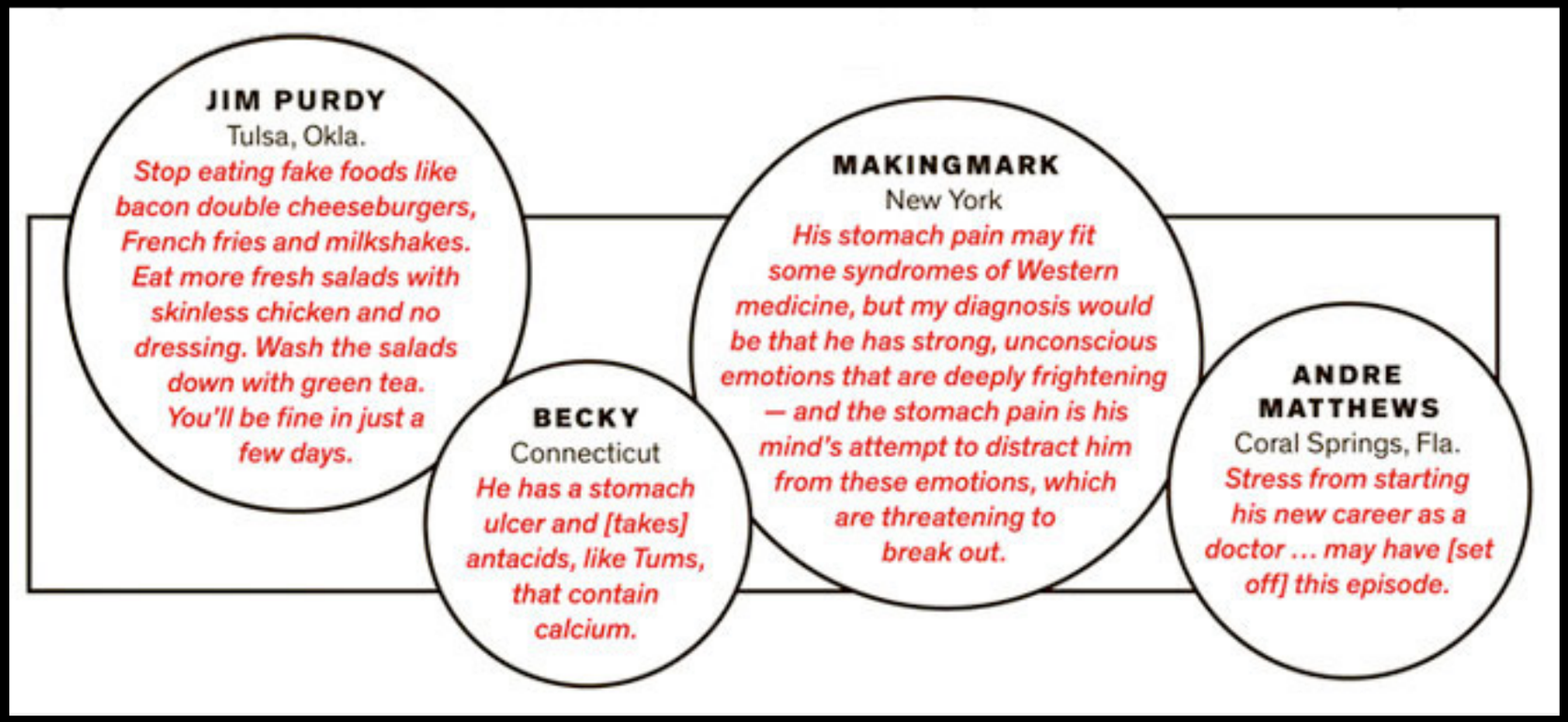
2. THE DOCTOR'S STORY

When Dr. Eric Tangalos met his new patient, his impression was that he was a pretty healthy guy. Tall and slender, he had a ready smile and an earnest, easygoing manner. "Tell me what brought you in," he asked the patient.

3. THE PATIENT'S LIST

a) Abdominal pain: Normally it was intermittent and manageable, but it became quite severe that one time. He

Crowdsourcing my problem



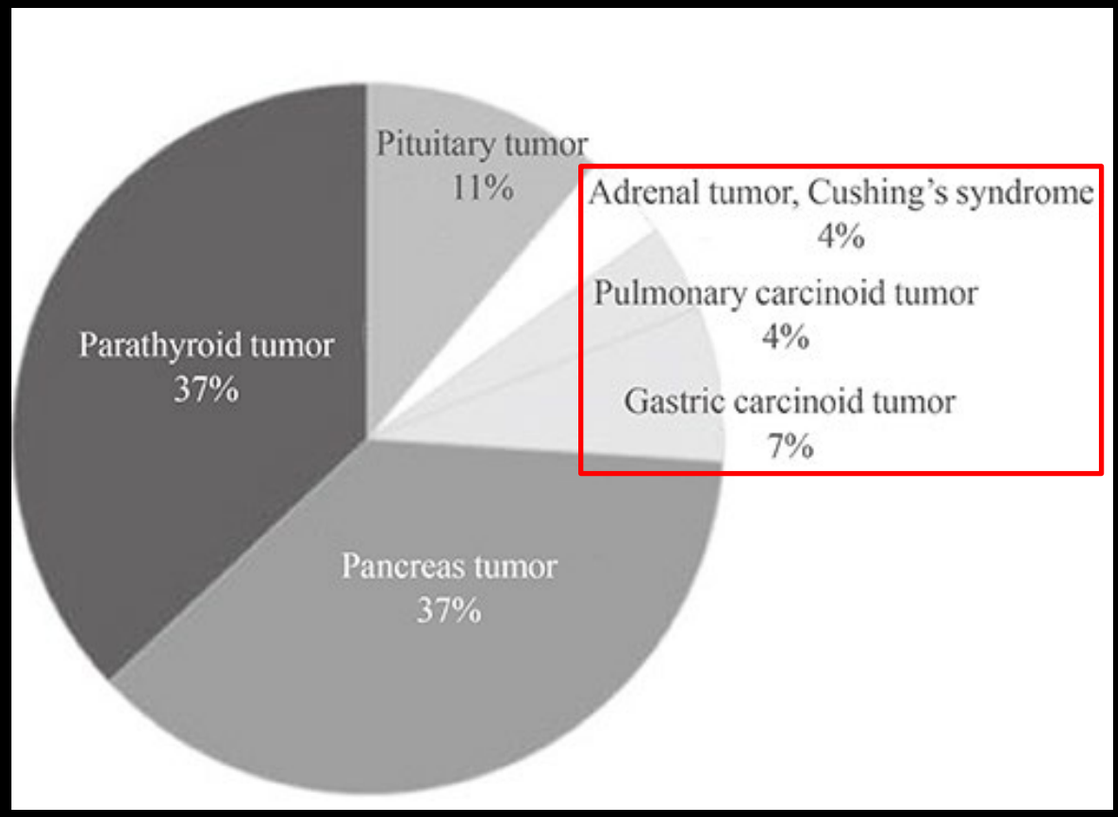
Beyond the 3 Ps

<u>Other tumor locations/types in MEN1</u>:

Bronchial & thymic carcinoids
Adrenal cortex

<u>Cutaneous manifestations:</u>

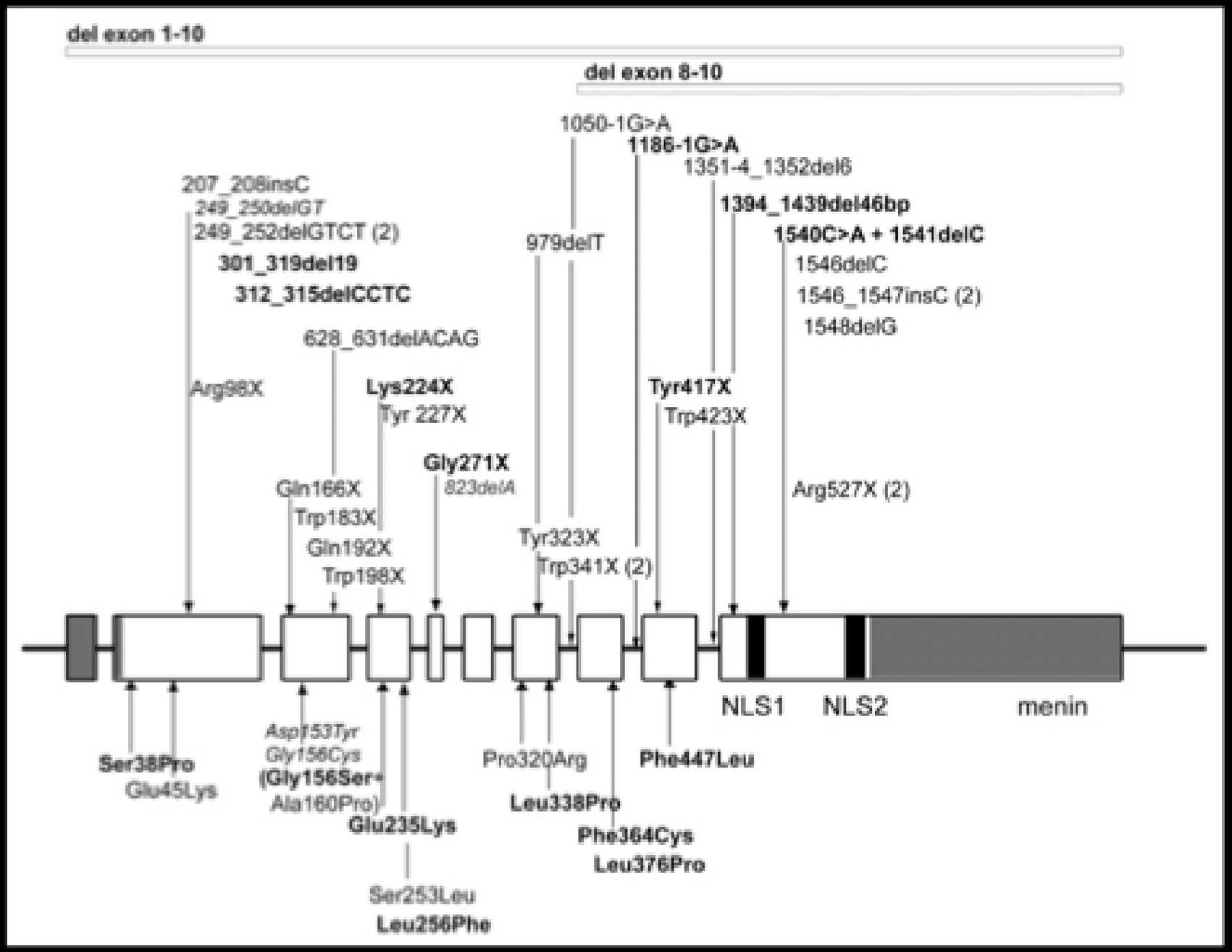
Angiofibroma
Collagenoma
Lipoma



“Localizing the lesion”

Test(s) requested:	MEN1 Gene / Multiple Endocrine Neoplasia Type 1 (MEN1)
Result:	**POSITIVE. Heterozygous for the c.1540_1541delCCinsA Mutation** This individual is heterozygous for a deletion of two nucleotides and an insertion of 1 nucleotide in exon 10 of the MEN1 gene. The normal sequence with the bases that are deleted in braces and the base that is inserted in brackets is: AGGA{CC}[A]CCCC. This mutation is denoted c.1540_1541delCCinsA at the cDNA level or at the protein level as p.Pro514ThrfsX45.
Interpretation:	The c.1540_1541delCCinsA mutation in the MEN1 gene has been reported previously in association with Multiple Endocrine Neoplasia Type 1 (Tham et al., 2007), and is consistent with the diagnosis in this patient. The deletion and insertion causes a frameshift starting with codon Proline 514, changes this amino acid to a Threonine residue and creates a premature Stop codon at position 45 of the new reading frame, denoted p.Pro514ThrfsX45. This mutation is predicted to result in premature protein truncation.

A (relatively) novel mutation



Bold = not previously reported

Tham *et al*. Clinical Testing for Mutations in the *MEN1* Gene in Sweden: A Report on 200 Unrelated Cases. *J Clin Endocrinol Metab.* **2007** Sep;92(9):3389-95.

Phenotype-genotype correlation?

c1540_1541delCCinsA, *n = 5*?

* Paternal grandfather died in his late 60s of an unspecified malignancy

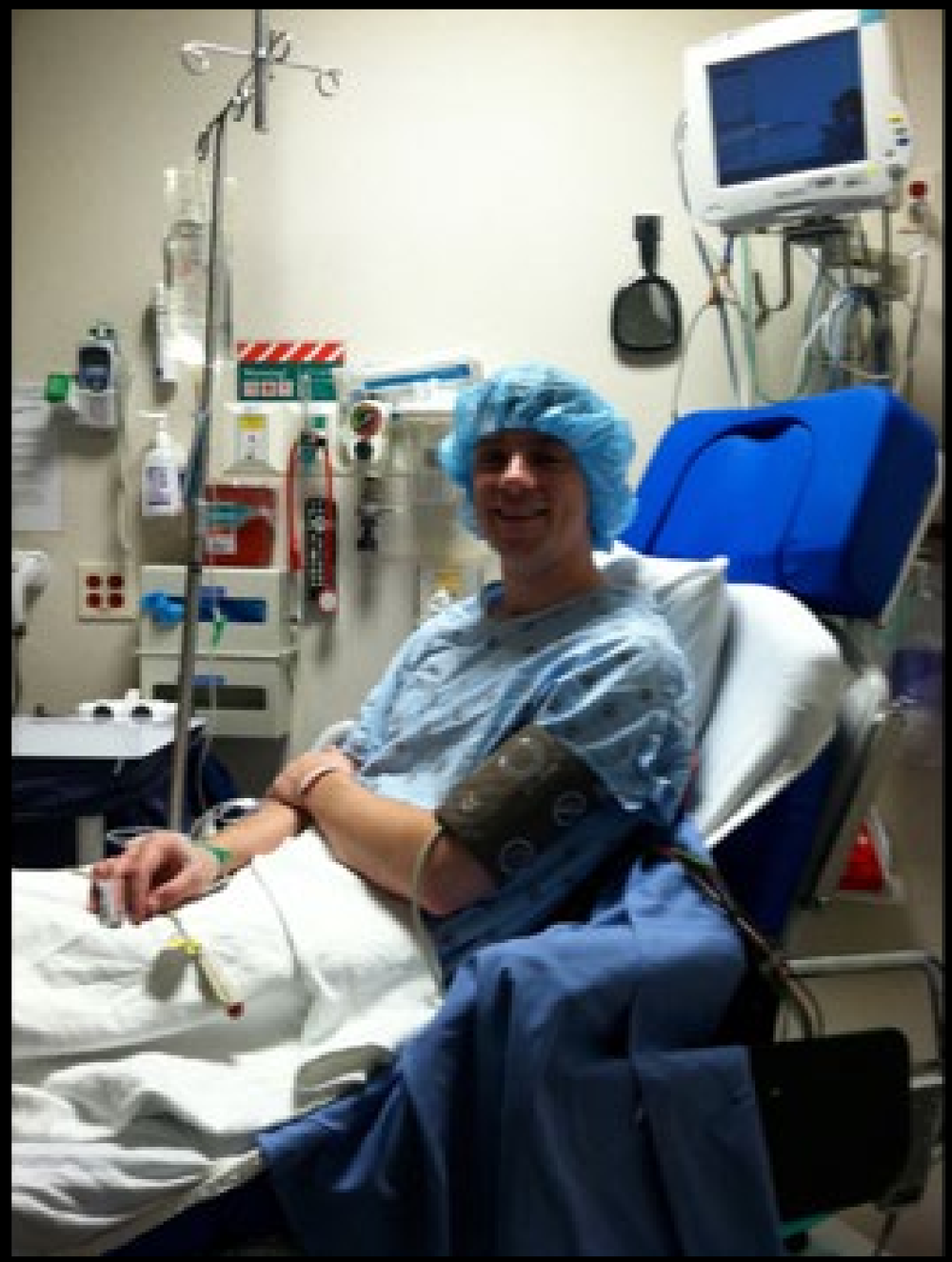
* Father died in his late 40s of metastatic atypical bronchial carcinoid

* Uncle died in his early 50s from pituitary macroadenoma

* From the Tham paper:

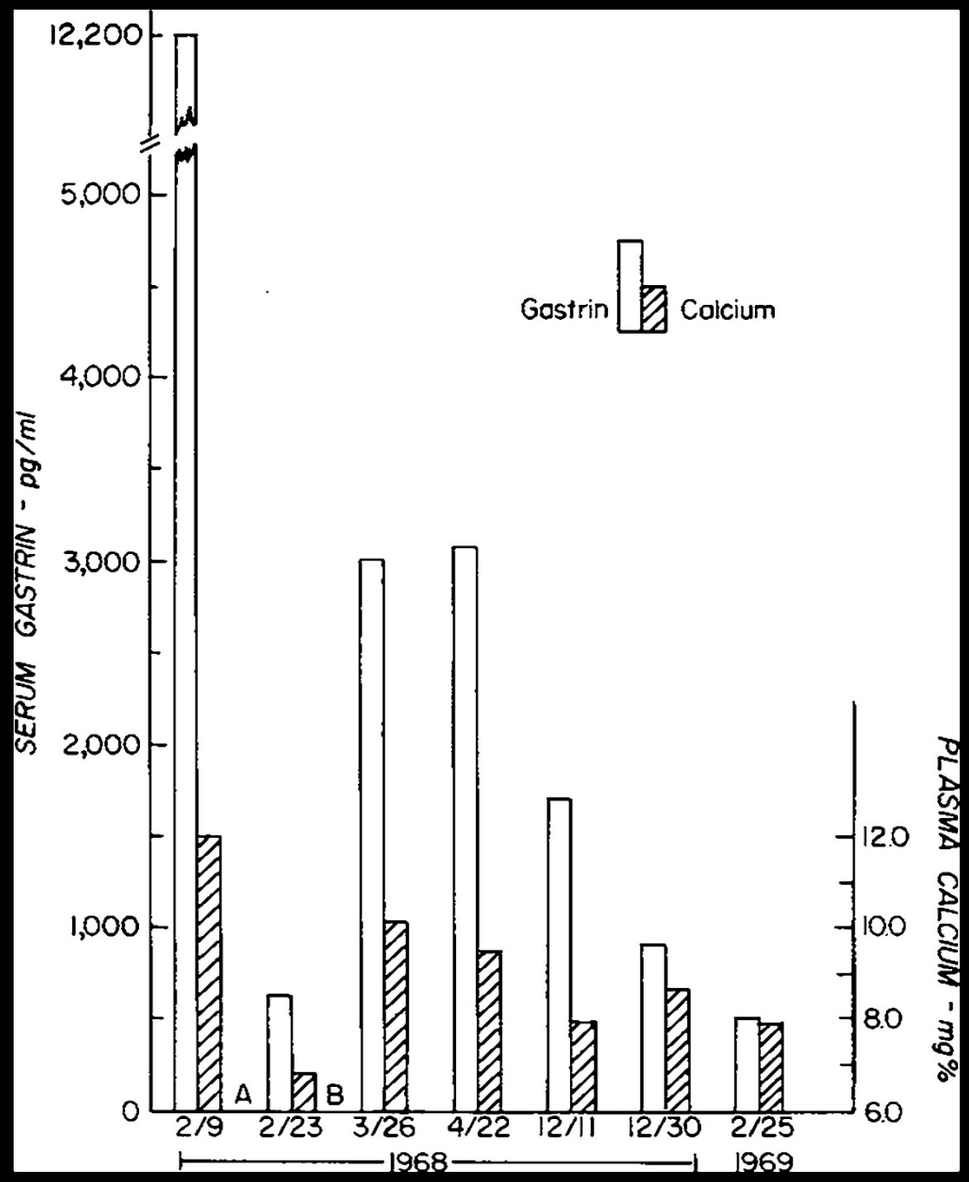
	Proband tumors (age at dx/surg/referral)	*Tumors in family members*		*Mutation type*		*Mutation in sequence*	*Effect on protein*	
38	HPT-h, PIT (PRL), ADR-uni (?/40/62)	*HPT-h, malignant schwannoma (†); hypercalcemia*		frameshift deletion/insertion	10	1540_1541delinsA (i.e. 1540C>A + 1541delC)	Pro514Thr CCC>ACC and 515fs	not reported

First things first



A surprising link

- Primary hyperparathyroidism can lead to elevated gastrin levels in more than 20% of MEN1 patients
- After parathyroidectomy, gastrin tends to normalize
- Seems more linked to the calcium level than the PTH itself
- Gastrin-secreting G cells in the stomach have calcium-sensing receptors (CaRs)



Trudeau WL & McGuigan JE. Effects of Calcium on Serum Gastrin Levels in the Zollinger-Ellison Syndrome. N Engl J Med. 1969; 281:862-866.

Zaniewski M, et al. Serum Gastrin Level Is Increased by Chronic Hypercalcemia of Parathyroid or Nonparathyroid Origin. *Arch Intern Med.* 1986;146(3):478-482.

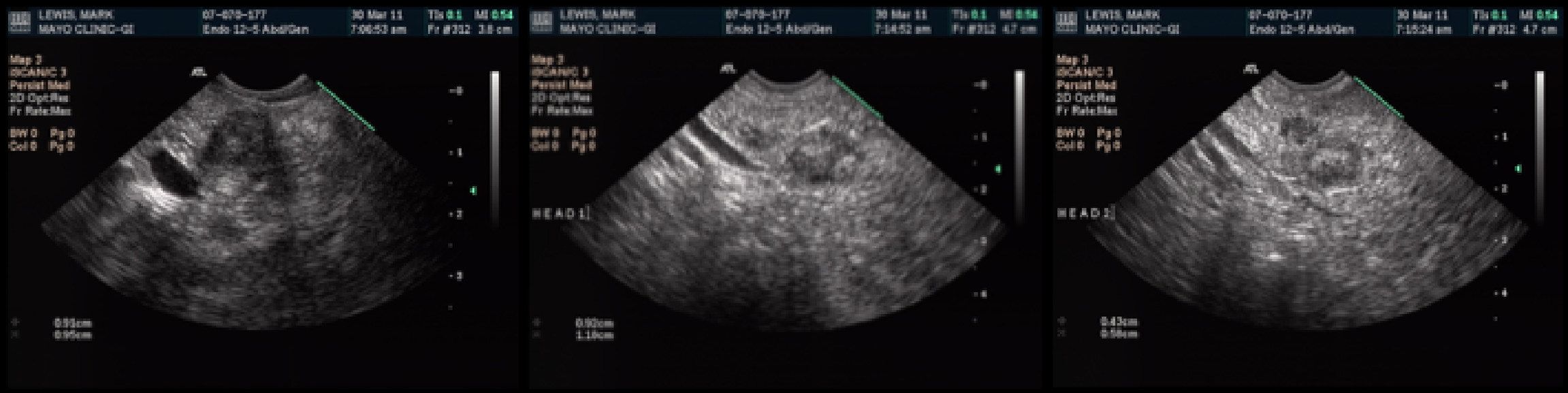
Feng J, et al. Calcium-sensing receptor is a physiologic multimodal chemosensor regulating gastric G-cell growth and gastrin secretion. *PNAS*. 2010; 107(41): 17791-17796.

A risk assessment

- Historically the main cause of mortality in MEN1 was ulcers
- Since the advent of H2 blockers and PPIs, metastatic pancreatic NETs have become the #1 source of MEN1-related mortality
- The Dutch MEN1 cohort studied MEN1 patients whose PNETs metastasized to the liver and found a 50% life expectancy at 10 years
- But the same research group studied 99 patients with localized PNETs < 2cm in size for up to 16 years and found that most (66%) had stable tumors under that threshold over serial scans (median = 4)

Pieterman CRC et al. Long-Term Natural Course of Small Nonfunctional Pancreatic Neuroendocrine Tumors in MEN1—Results From the Dutch MEN1 Study Group. *J Clin Endocrinol Metab*. 2017 Oct 1;102(10):3795-3805

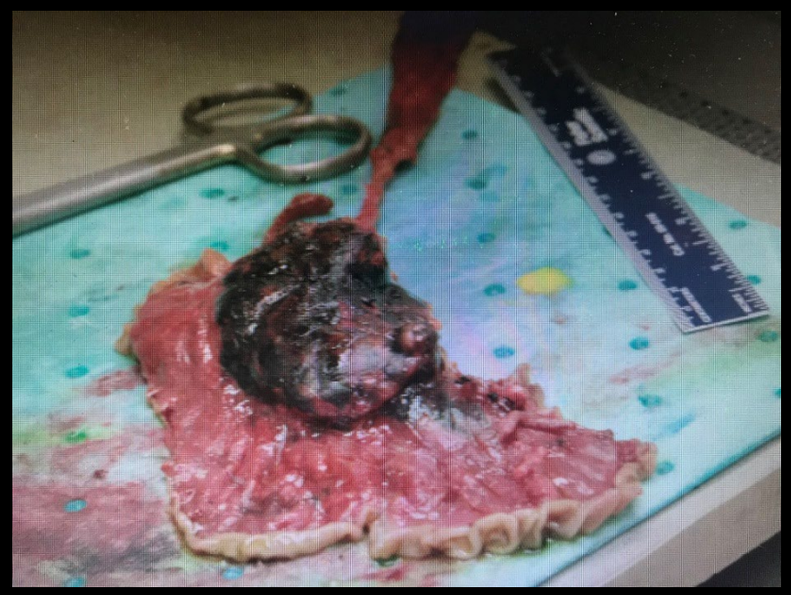
EUS still images

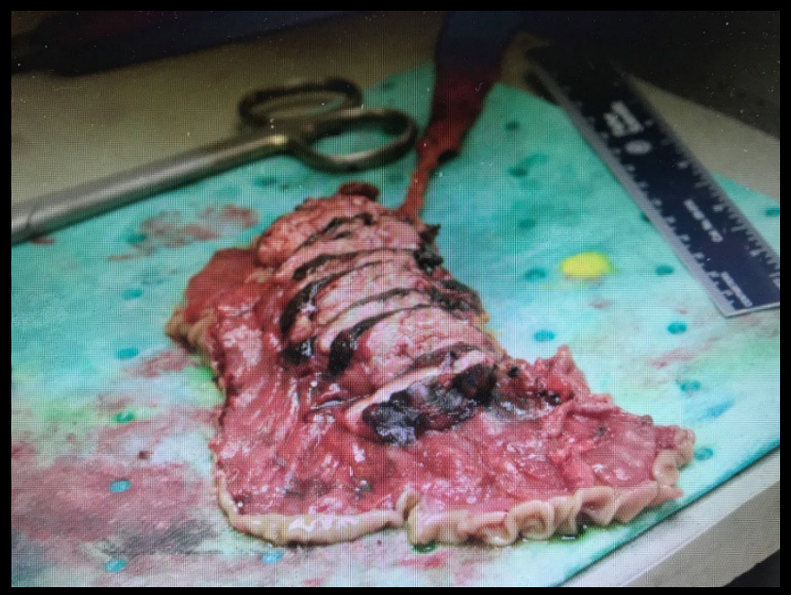


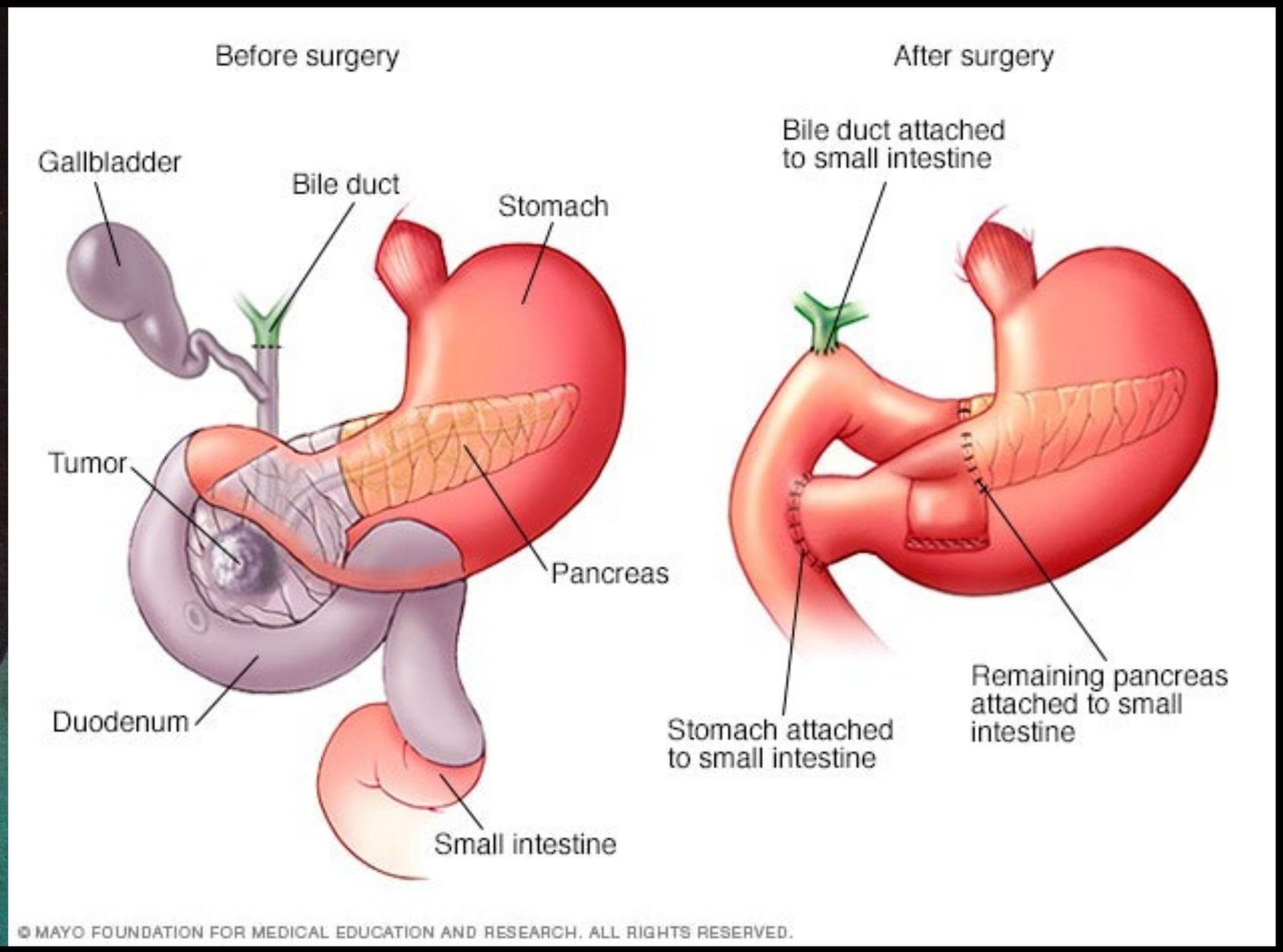
"**The pancreas was markedly abnormal with a hyperechogenic pancreatic duct and multiple 2- to 3-mm hyperechoic lesions throughout the pancreas**. In addition, there was a mass lesion in the tail of the pancreas, which measured 12 mm in diameter, round, well-defined, variably hypoechoic with Doppler flow. In the head of the pancreas and anterior to the pancreatic duct, there were two additional well-defined solid lesion measuring 10 mm in diameter, round, well-defined, and variably hypoechoic, and immediately inferior to this a smaller lesion measuring 5 mm in diameter. Adjacent to the superior mesenteric artery, there was **a cluster of cysts, consistent with branch duct IPMN**, and there was no ductal communication demonstrated."

Proof positive

- July 2017: dominant PNET in head of pancreas grew to 3.1cm from 1.7cm the year prior
- August 2017: Whipple procedure removed this mass and innumerable tumorlets







Over-sharing

Local physician live tweets unique cancer surgery

Intermountain Medical brings awareness to type of cancer

By: Surae Chinn

Posted: Aug 11, 2017 10:23 AM MDT

Updated: Aug 11, 2017 10:23 AM MDT

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Out-of-body experience

Intermountain Cancer @intermtncancer · 7 Aug 2017

Whipple surgery has officially begun with Dr. Ott. #IMTNLive #pancsm

Bile duct is now disconnected, to eventually connect into the small bowel. -Dr. Ott #IMTNLive #pancsm

Mark Lewis @marklewismd · 7 Aug 2017

The **dunked** anastomosis is complete. Up next, the bile duct reconstruction. #pancsm #IMTNLive

Putting it all out there

#IMTNlive

Intermountain Cancer @intermtncancer

Portal vein is now being tied off- main vein taking blood from gut over to the liver. This vein is about the size of thumb.#IMTNlive #pancsm

Intermountain
@Intermountain

After ¼ of the pancreas was removed, we took it to pathology to make sure there wasn't more cancer. #IMTNLive #pancsm

https://wakelet.com/wake/e82752c4-9eb5-4497-9b36-af6935cb579f

Life as a patient-physician

My Inherited Condition Has Led to a Life and Career I Love

My patients with endocrine tumors are preparing me for whatever the future might hold, and I feel privileged to be both patient and physician.

By Mark A. Lewis, MD, as told to Jo Cavallo

October 10, 2020

Get Permission

Mark A. Lewis, MD

My father died of thymic cancer when I was 14, and that's when I decided to become an oncologist. Ironically, the first patient I diagnosed with cancer was me. In 2009, during my first week of training in hematology/oncology at the Mayo Clinic, I began having severe abdominal pain, which had plagued me on and off for years, and laboratory tests showed that I had high levels of calcium in my blood. I remembered my father had suffered from hypercalcemia his whole life. In fact, several members of the paternal side of my family had an unusual run of bad luck when it came to their health and died in middle age.

Two-face

A family curse

* Past — my father —> uncle —> grandfather

* Present — me

* Future — my children

Life as a parent-physician

Wermer P. Endocrine adenomatosis and peptic ulcer in a large kindred:
Inherited multiple tumors and mosaic pleiotropism in man. American J Med. 1963 Aug; 35 (2): 205-212

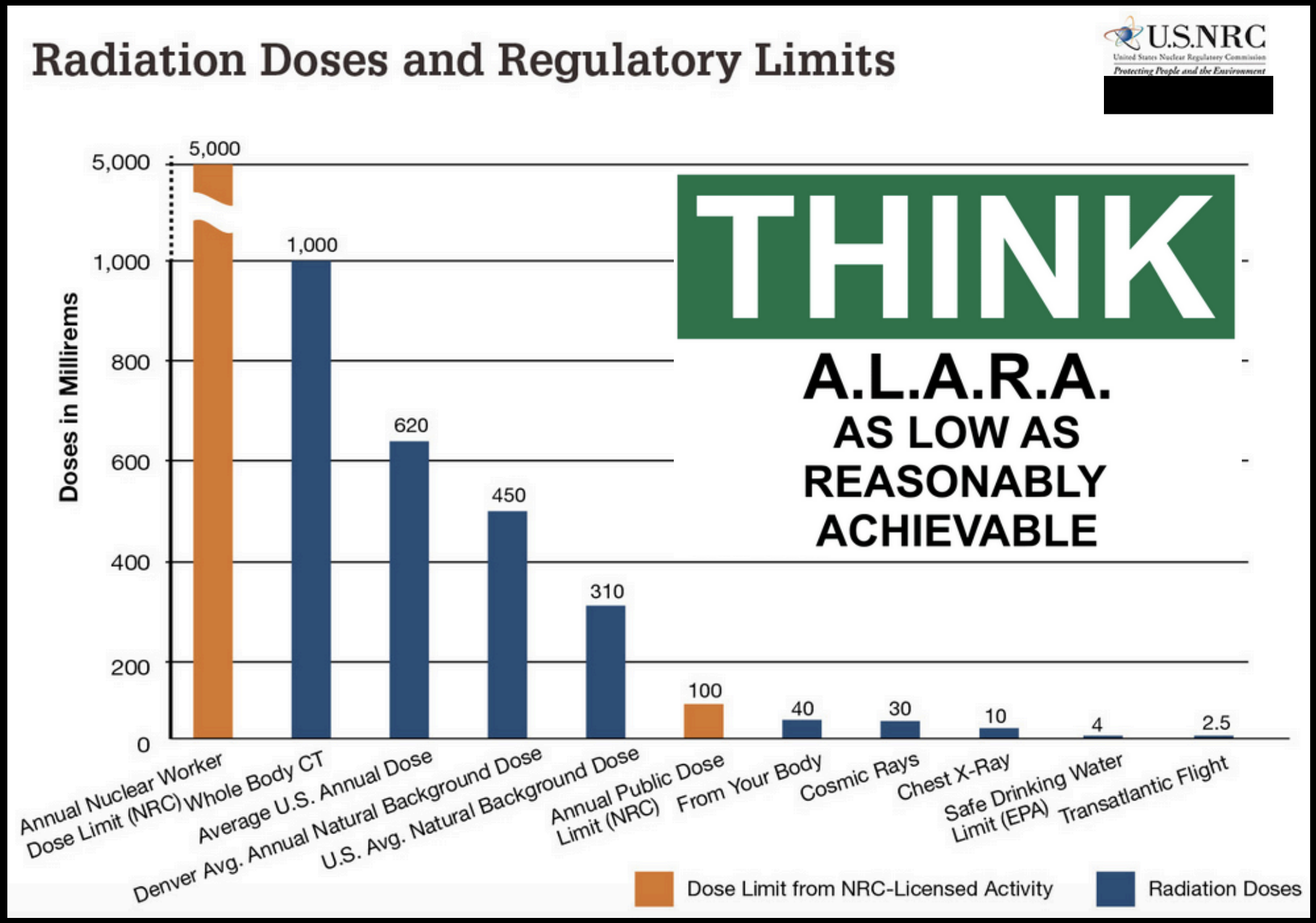
Guidelines as gospel

TABLE 2. Suggested biochemical and radiological screening in individuals at high risk of developing MEN1

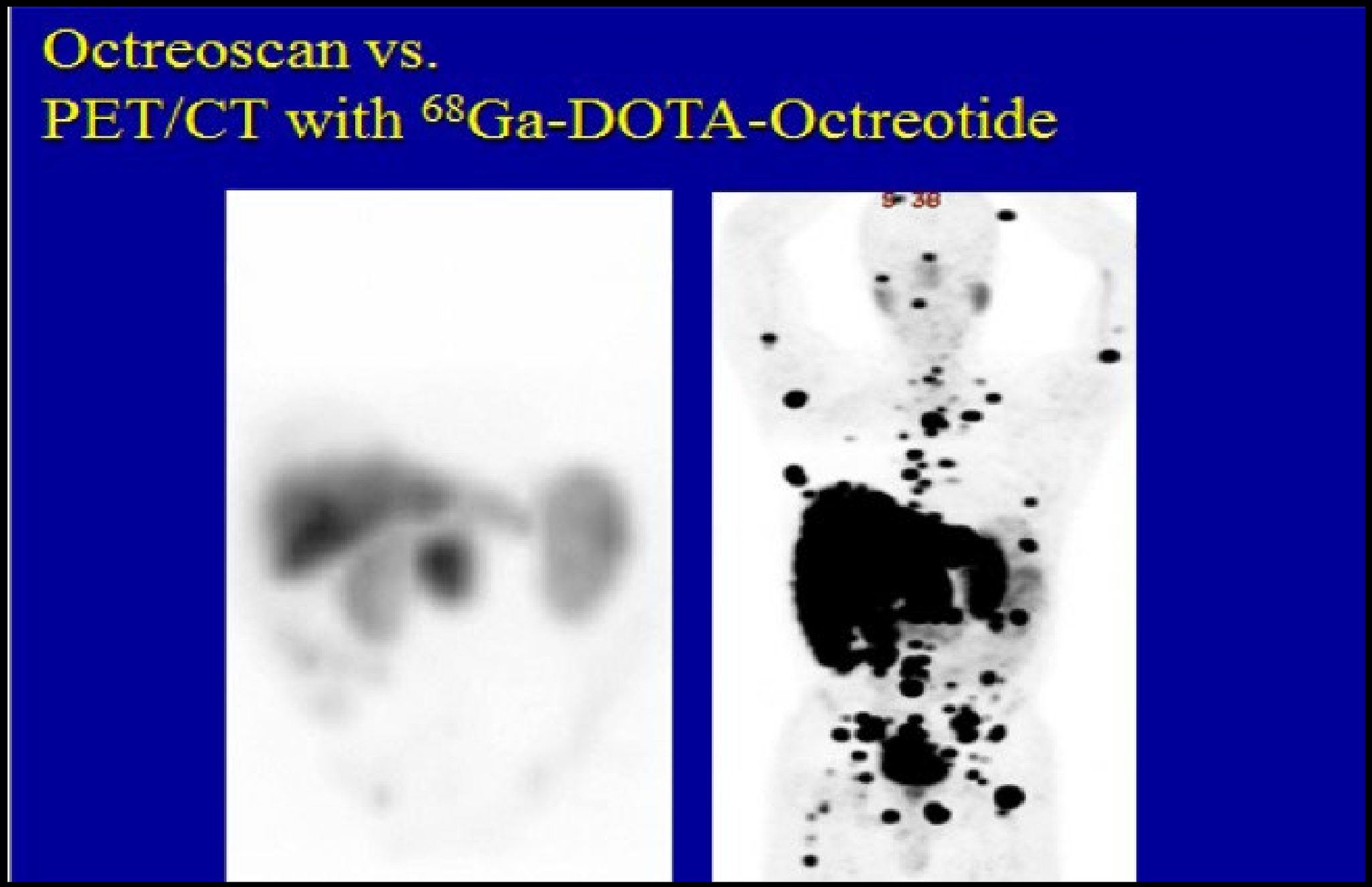
Tumor	Age to begin (yr)	Biochemical test (plasma or serum) annually	Imaging test (time interval)
Parathyroid	8	Calcium, PTH	None
Pancreatic NET			
Gastrinoma	20	Gastrin (± gastric pH)	None
Insulinoma	5	Fasting glucose, insulin	None
Other pancreatic NET	<10	Chromogranin-A; pancreatic polypeptide, glucagon, VIP	MRI, CT, or EUS (annually)
Anterior pituitary	5	Prolactin, IGF-I	MRI (every 3 yr)
Adrenal	<10	None unless symptoms or signs of functioning tumor and/or tumor >1 cm are identified on imaging	MRI or CT (annually with pancreatic imaging)
Thymic and bronchial carcinoid	15	None	CT or MRI (every 1–2 yr)

Thakker et al J Clin Endocrinol Metab, 2012, 97: 2990-3011

“Of one that lov'd not wisely but too well"

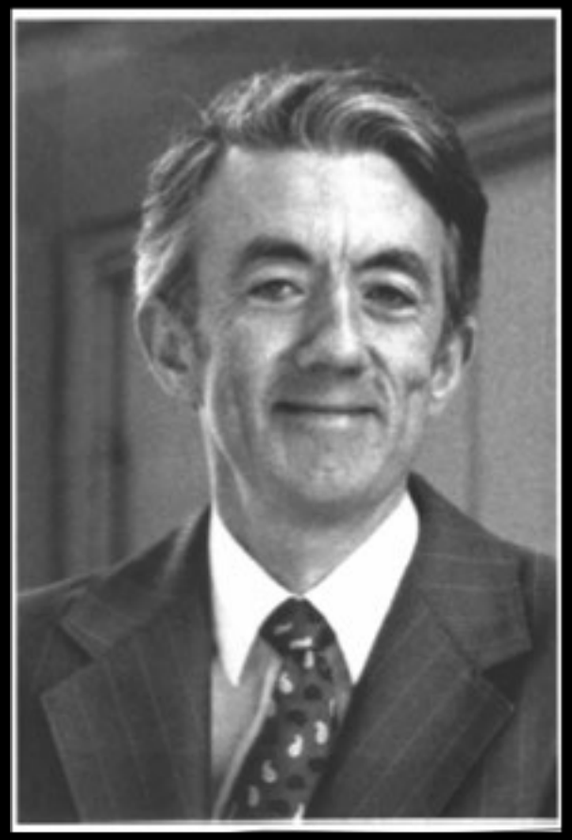


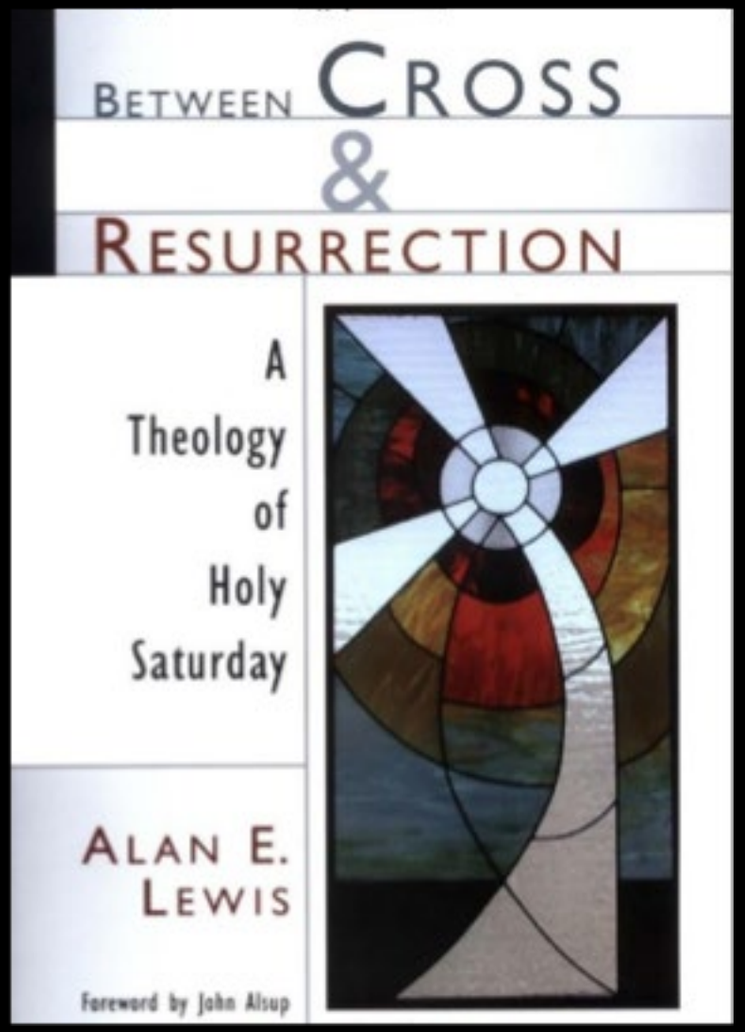
Turning on the light



Vinik A, et al. Pathophysiology and Treatment of Pancreatic Neuroendocrine Tumors (PNETs): New Developments. Endotext. https://www.ncbi.nlm.nih.gov/books/NBK279074/ Updated: 6/12/18.

Learning by example





Wise words (I)

“The question ‘why me?’ is just too myopic to be asked in situations such as mine, although one knows it often is. Much more realistic is the question ‘why not me?’ Why should I be exempt from the floods and famines, accidents and disasters, that bedevil brothers and sisters? By what extravagant mercy have I so far survived that to which so many others tragically succumb?”

Wise words (II)

“Grounds for gratitude multiply: spine-tingling miracles of providential timing; the banter and much laughter that frequently echoed through my valley of darkness; the discovery with family and friends of whole new levels of resourcefulness and love; and **the opportunity now, however brief or lengthy, to discard the trivial and shallow and to fill every moment and relationship with meaning, intensity, and value.**”

-- Rev. Prof. Alan E. Lewis

Thank you so much!