



93 yo F with polyuria/polydypsia

Jess Hwang

June 27, 2013

HPI

- Worsening confusion x 2 days
- Fatigue, weakness
- Anorexia
- Polyuria/polydypsia
- Weight loss >20 lb over 6 months
- No nausea, vomiting, diarrhea, abdominal pain

More history...

PMHx

R breast cancer (DCIS s/p
mastectomy in 2001)

HTN

Dementia

Glaucoma

FHx

No diabetes

SHx

No tobacco/EtOH

Lives with daughter

Meds

HCTZ 12.5 mg

Xalatan/Timolol eye drops

Cozaar 25 mg

Remeron 7.5 mg

Physical Exam

Vitals: 35.7, HR 100, BP 130/53, RR 24, SpO2 100%, BMI 24

Constitutional: Patient appears thin, in no acute distress.

Eyes: No scleral icterus.

ENT: Mucous membranes moist. + thrush.

Neck: No thyromegaly or nodules palpated.

Cardiovascular: tachycardic. No murmurs appreciated.

Respiratory/Chest: clear lung fields. Slightly tachypneic.

Gastrointestinal/Abdomen: soft, nontender, nondistended. No palpable masses.

Musculoskeletal/extremities: No peripheral edema.

Neurological: A+Ox1 to person/birthdate. (BL for 6 months)

Skin: Skin is warm and dry. No acanthosis.

Initial Labs HD #1

132	83	36
4.6	32	1.4

AG 17

723

9.9

2.5

3.9

11.9	271
4.2	36

7.4	4.6
0.8	117
49	10

B-OH 3.98 (RR <0.3)

HbA1c 14.9 %

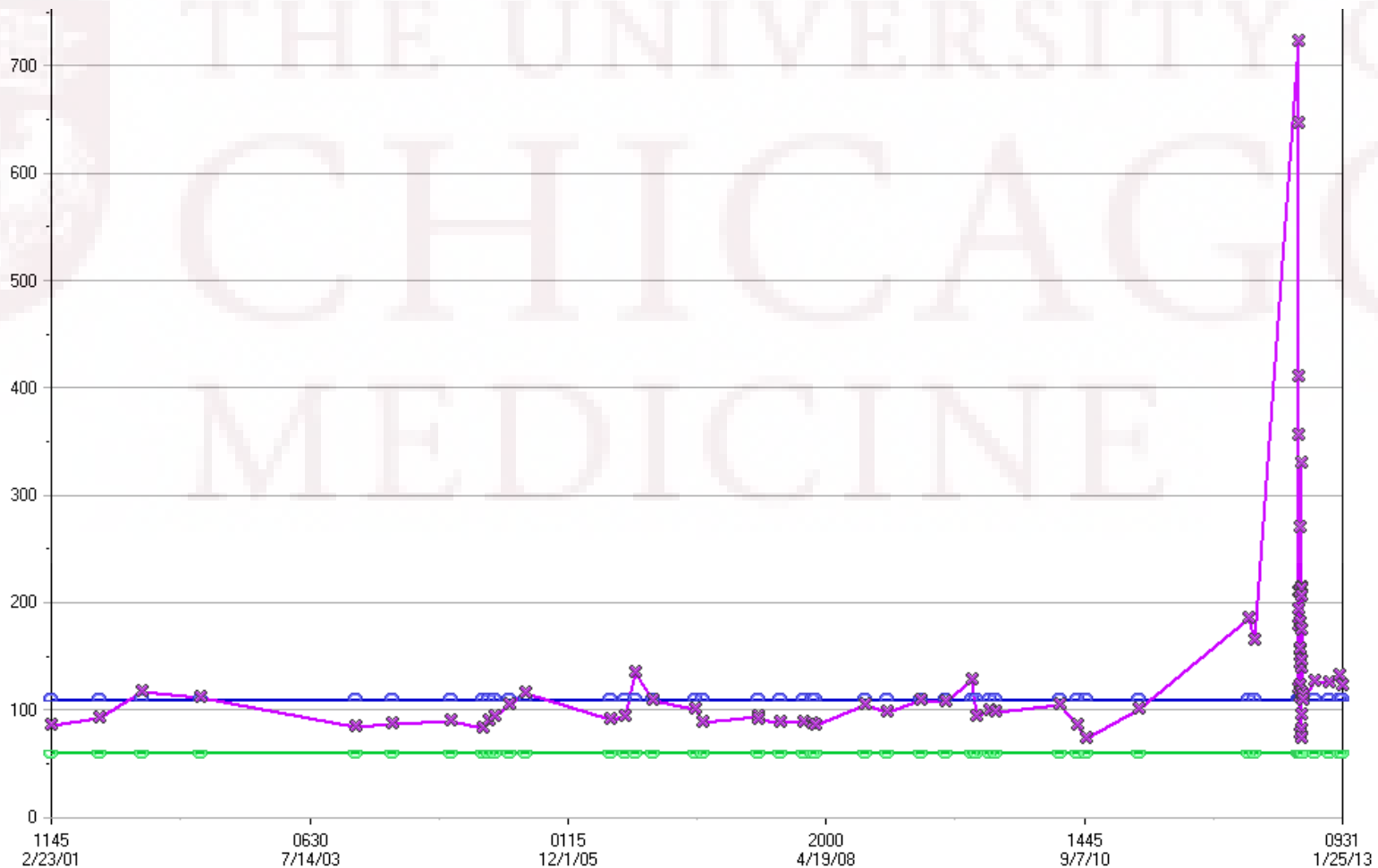
Lipase 76 (13-60)

GAD65 negative

IA2 negative

Recent labs prior to admission

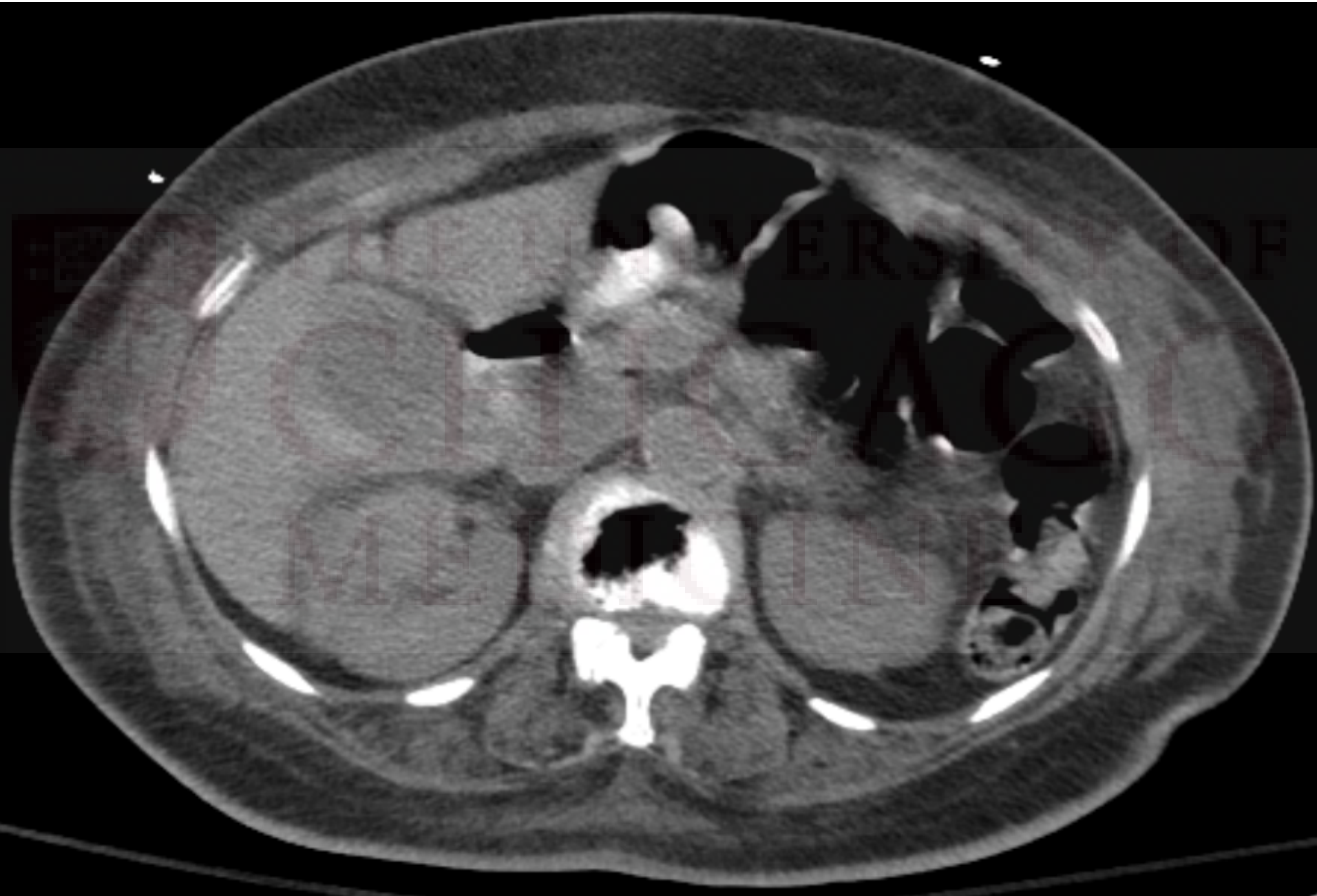
- 7/7/2011: HbA1c 6.2%



Hospital Course

- Totally occluding acute DVT of BLE
- TTE showed large mass vs thrombus in RA/RV originating from SVC. RV moderately dilated. RV severely reduced. LV 59.3%.

CA 19-9: 9754 (RR <37)



Post-discharge course

- No plan for tube feeding at home or any supplemental nutrition
- Discharged on Lantus 5U qhS
- Enrolled in hospice → passed away 2 months later

Clinical Concepts

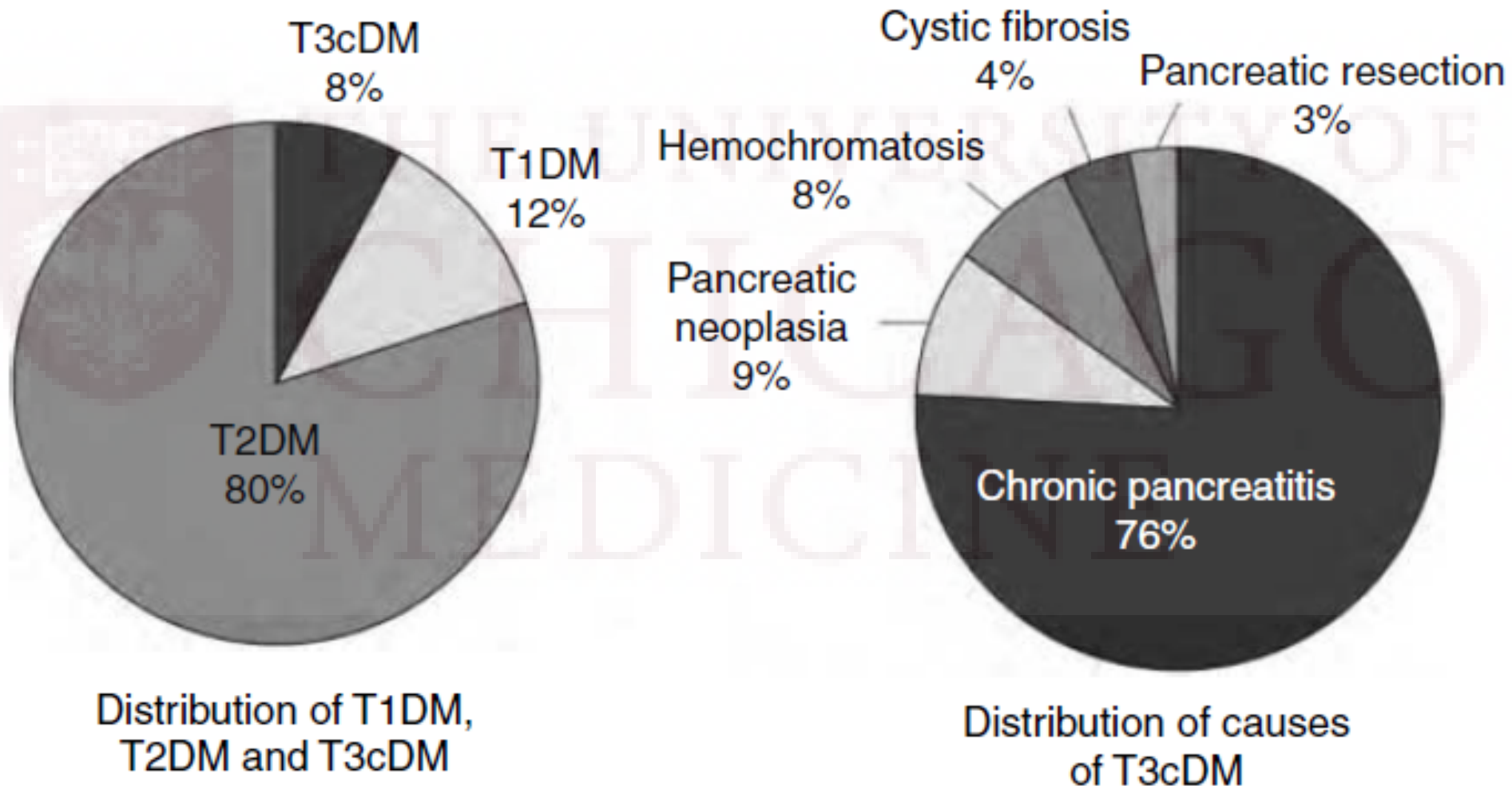
- Definition of type 3c diabetes
- Does diabetes cause pancreatic cancer or vice versa?
- Tumor markers to screen new-onset diabetics for pancreatic cancer?

- I. Type 1 diabetes (β -cell destruction, usually leading to absolute insulin deficiency)
 - A. Immune mediated
 - B. Idiopathic
- II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
- III. Other specific types
 - A. Genetic defects of β -cell function
 - 1. MODY 3 (Chromosome 12, HNF-1 α)
 - 2. MODY 1 (Chromosome 20, HNF-4 α)
 - 3. MODY 2 (Chromosome 7, glucokinase)
 - 4. Other very rare forms of MODY (e.g., MODY 4: Chromosome 13, insulin promoter factor-1; MODY 6: Chromosome 2, NeuroD1; MODY 7: Chromosome 9, carbonyl ester lipase)
 - 5. Transient neonatal diabetes (most commonly ZAC/HYAM1 imprinting defect on 6q24)
 - 6. Permanent neonatal diabetes (most commonly KCNJ11 gene encoding Kir6.2 subunit of β -cell K_{ATP} channel)
 - 7. Mitochondrial DNA
 - 8. Others
 - B. Genetic defects in insulin action
 - 1. Type A insulin resistance
 - 2. Lipodystrophy
 - 3. Rabson-Mendenhall syndrome
 - 4. Lipodystrophic diabetes
 - 5. Others
 - C. Diseases of the exocrine pancreas
 - 1. Pancreatitis
 - 2. Trauma/pancreatectomy
 - 3. Neoplasia
 - 4. Cystic fibrosis
 - 5. Hemochromatosis
 - 6. Fibrocalculous pancreatopathy
 - 7. Others
 - D. Endocrinopathies
 - 1. Acromegaly
 - 2. Cushing's syndrome
 - 3. Glucagonoma
 - 4. Pheochromocytoma
 - 5. Hypothyroidism
 - 6. Somatotrophinoma
 - 7. Aldosteronoma
 - 8. Others
 - E. Drug or chemical induced
 - 1. Vacor
 - 2. Pentamidine
 - 3. Nicotinic acid
 - 4. Glucocorticoids
 - 5. Thyroid hormone
 - 6. Dantrolene
 - 7. β -Adrenergic agonists
 - 8. Thiazides
 - 9. Diuretics
 - 10. γ -lithium
 - 11. Others
 - F. Infections
 - 1. Congenital rubella
 - 2. Cytomegalovirus
 - 3. Others
 - G. Uncommon forms of immune-mediated
 - 1. "Stiff-man" syndrome
 - 2. Anti-insulin receptor antibodies
 - 3. Others
 - H. Other genetic syndromes sometimes associated
 - 1. Down syndrome
 - 2. Klinefelter syndrome
 - 3. Turner syndrome
 - 4. Wolfram syndrome
 - 5. Friedreich ataxia
 - 6. Huntington chorea
 - 7. Laurence-Moon-Biedl syndrome
 - 8. Myotonic dystrophy
 - 9. Porphyria
 - 10. Prader-Willi syndrome
 - 11. Others
- IV. Gestational diabetes mellitus

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7. Others

Type 3c diabetes



Type 3c diabetes

Proposed diagnostic criteria

- Low fecal elastase-1 levels
- Pathologic pancreatic imaging (EUS/MRI/CT)
- Absence of type 1 DM autoAb

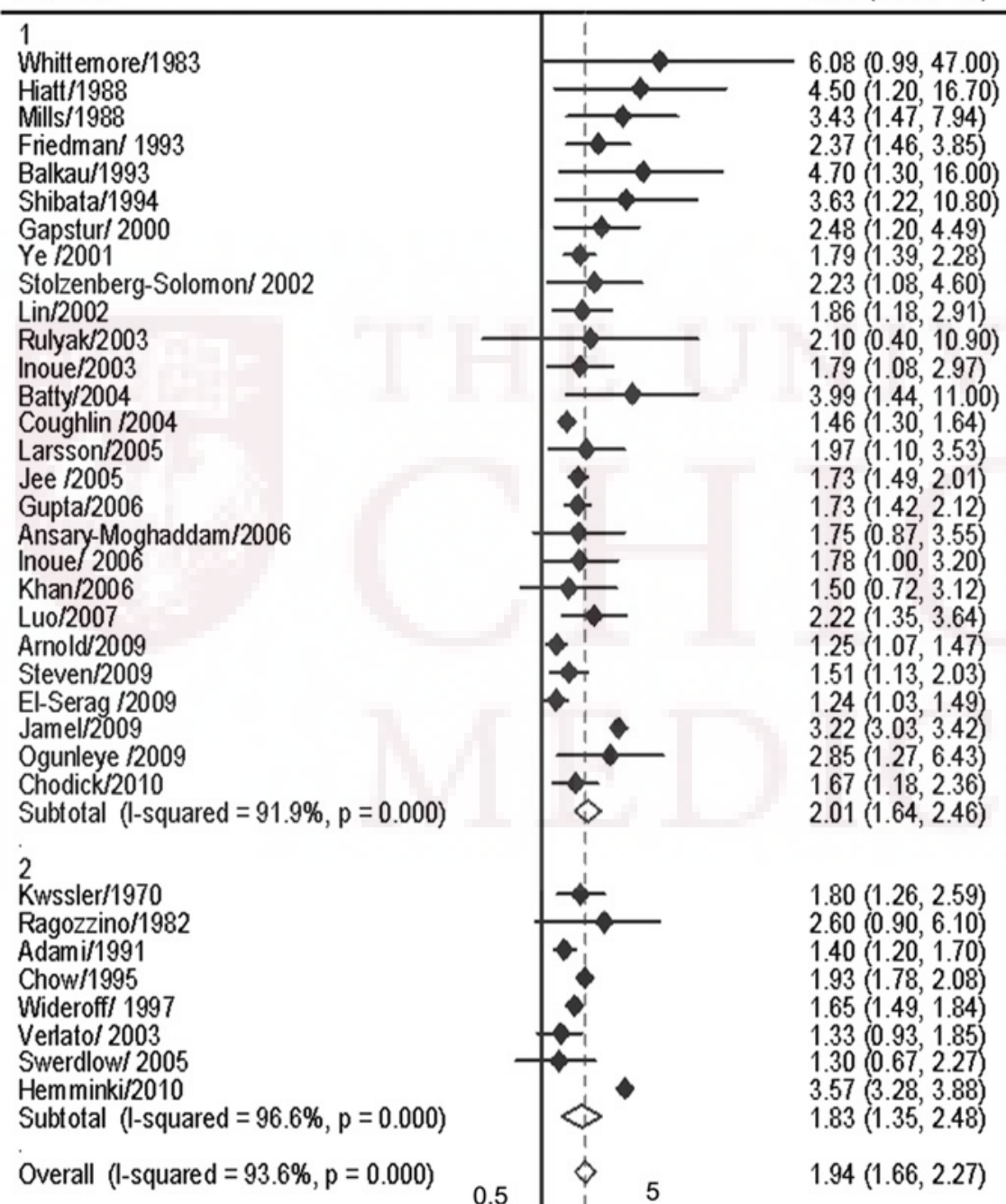
Supporting criteria

- Low fat soluble vitamin levels
- No excessive insulin resistance
- Deficiency of glucoregulatory hormones

Association between DM + PC

- Eur J Ca 2011 Meta-analysis: 35 cohort studies
- Countries: Japan (5), US (14), Europe (13), Israel (1), Korea (1), Other Asia (1)
- Secondary analysis of confounding factors-stratified by geography, sex, EtOH, BMI, smoking.
- Did not analyze effect of anti-DM drugs or detection bias

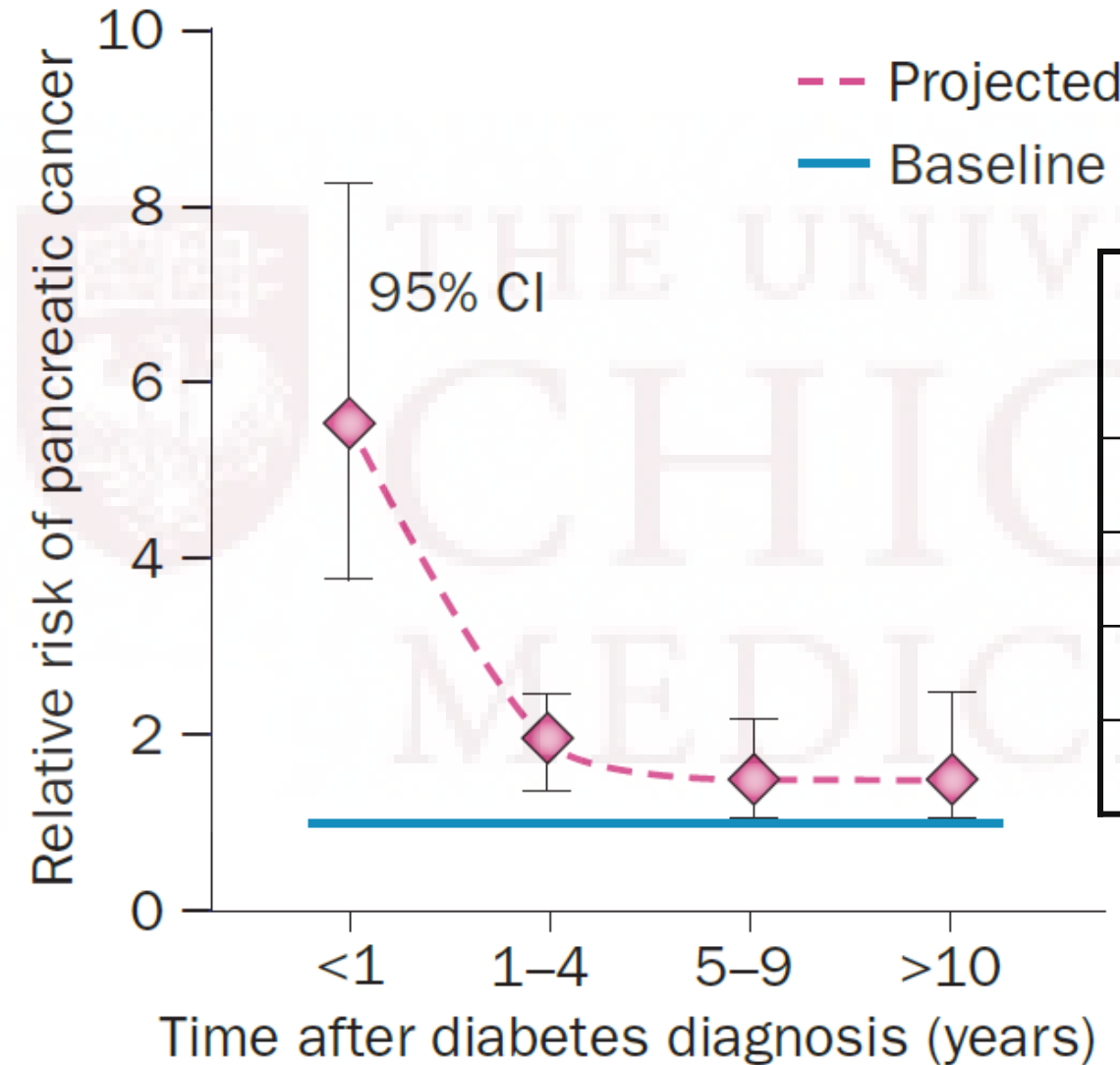
Studies RR (95% CI)



RR 1.94 (95% CI 1.66-2.27)

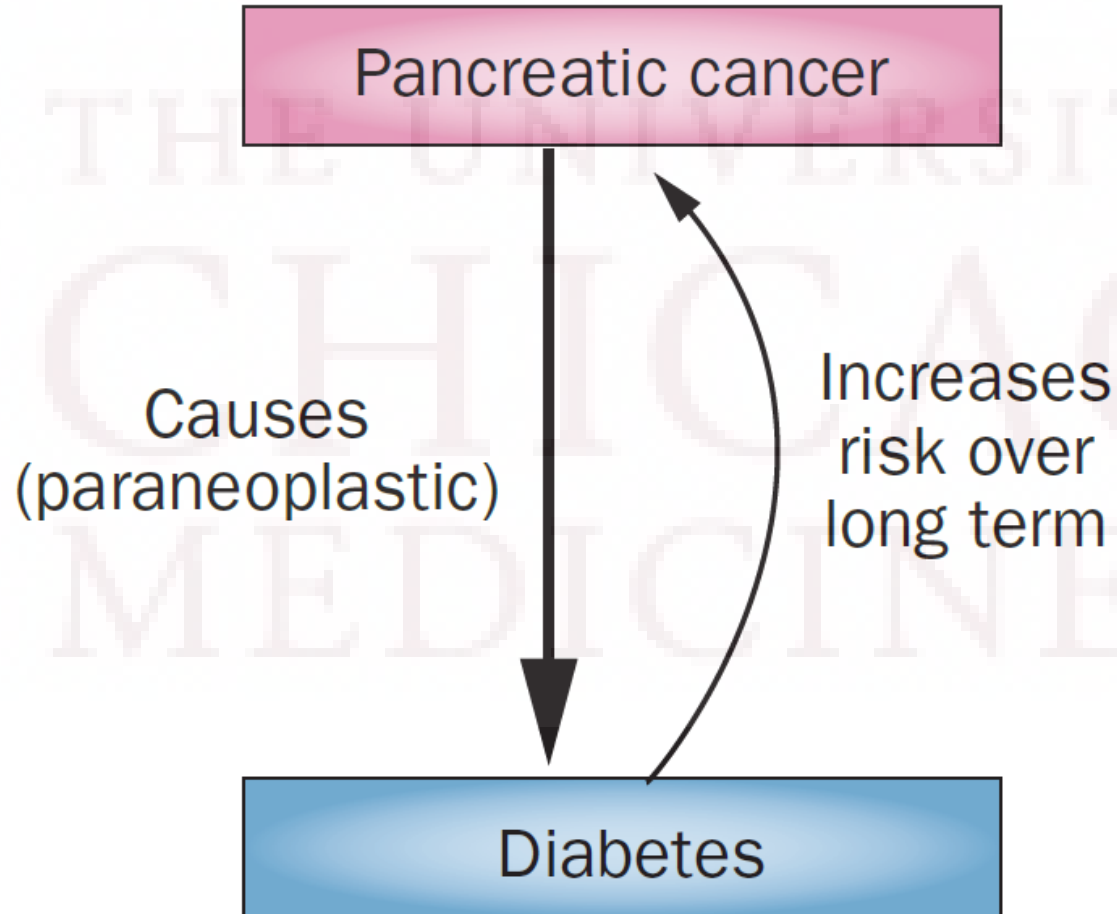
Increased risk is independent of alcohol, smoking, gender, BMI

Association between DM + PC

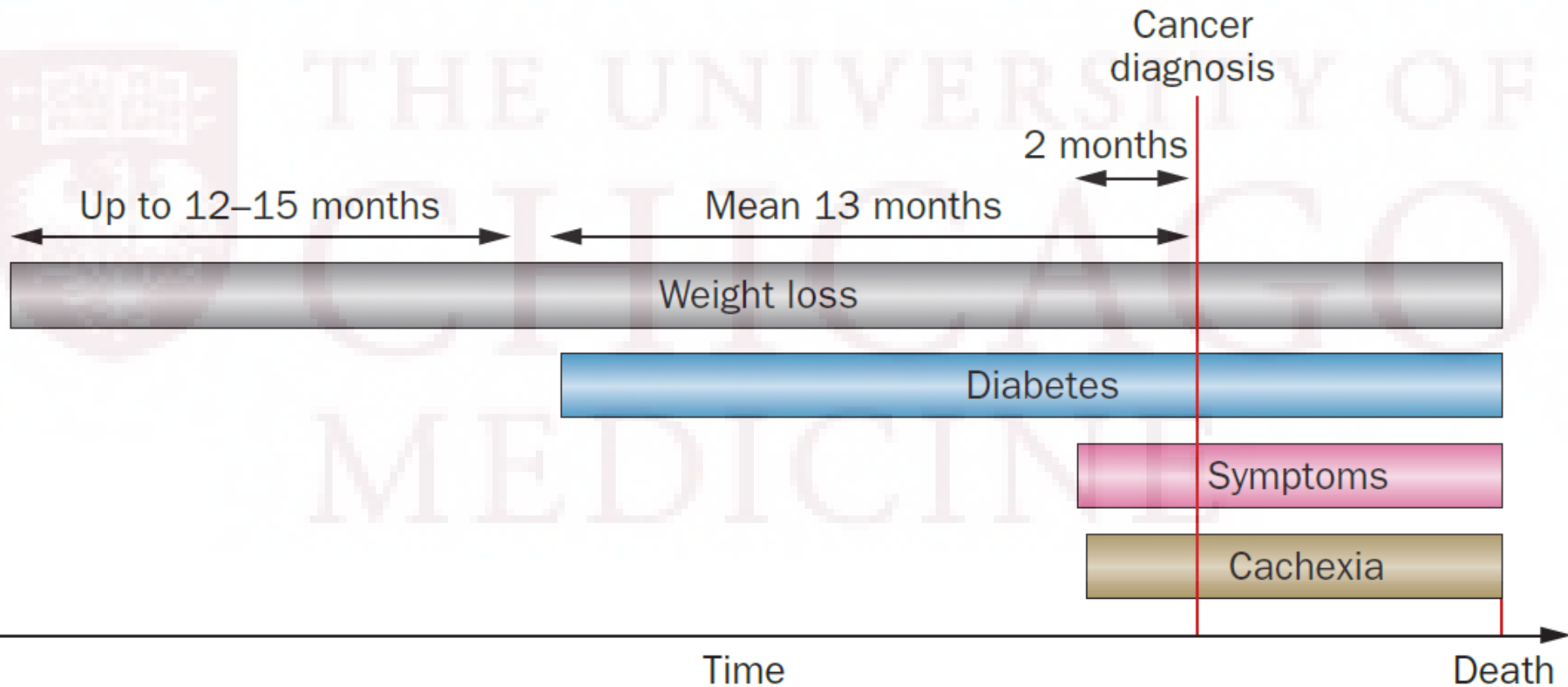


Diabetes duration	RR	95% CI
<1	5.4	3.5-8.3
1-4	2.0	1.6-2.3
5-9	1.5	1.1-2.1
>9	1.5	0.9-2.3

PC + DM = bidirectional association



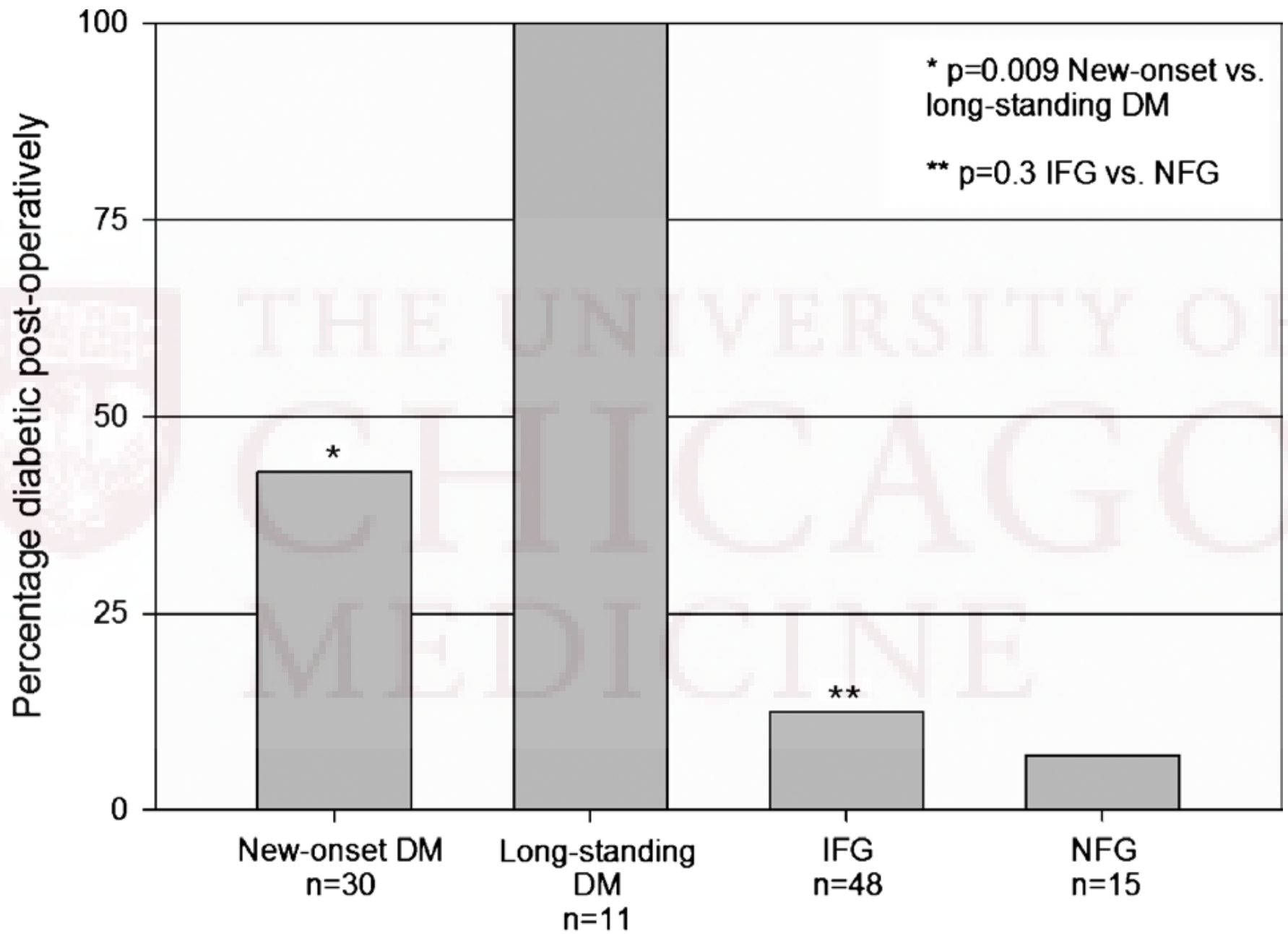
Diabetes as paraneoplastic syndrome



Diabetes as paraneoplastic syndrome

“Metabolic... symptoms, which are consequences of humoral or hormonal factors that present distant to the site of the primary cancer or metastases. However, they are closely associated with the malignant disease.”

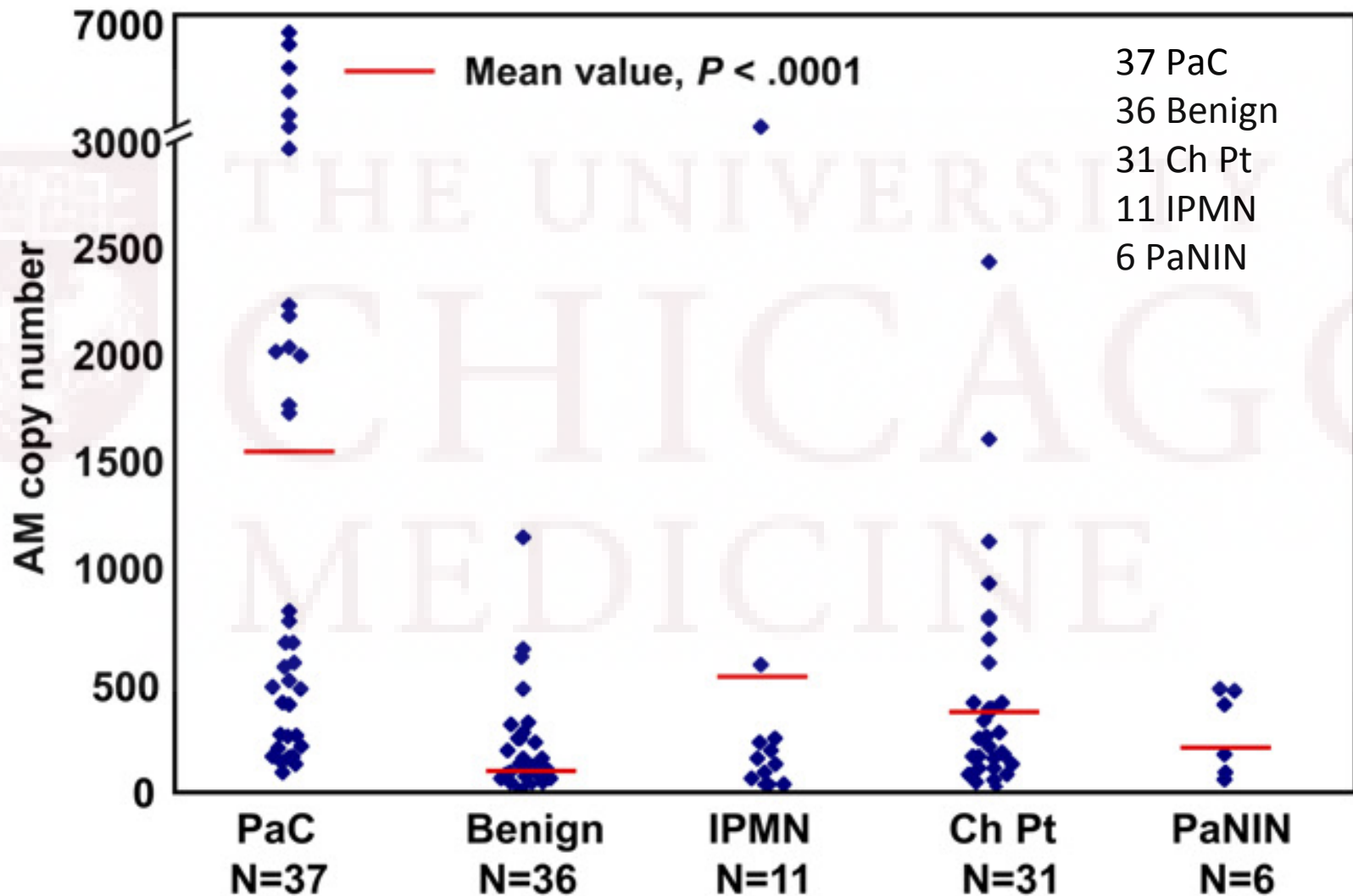
- Onset temporally associated with diagnosis
- AdenoCa involving a small portion of the pancreas has been associated with diabetes
- Diabetes can improve after tumor resection despite surgical removal of a significant amount of pancreas



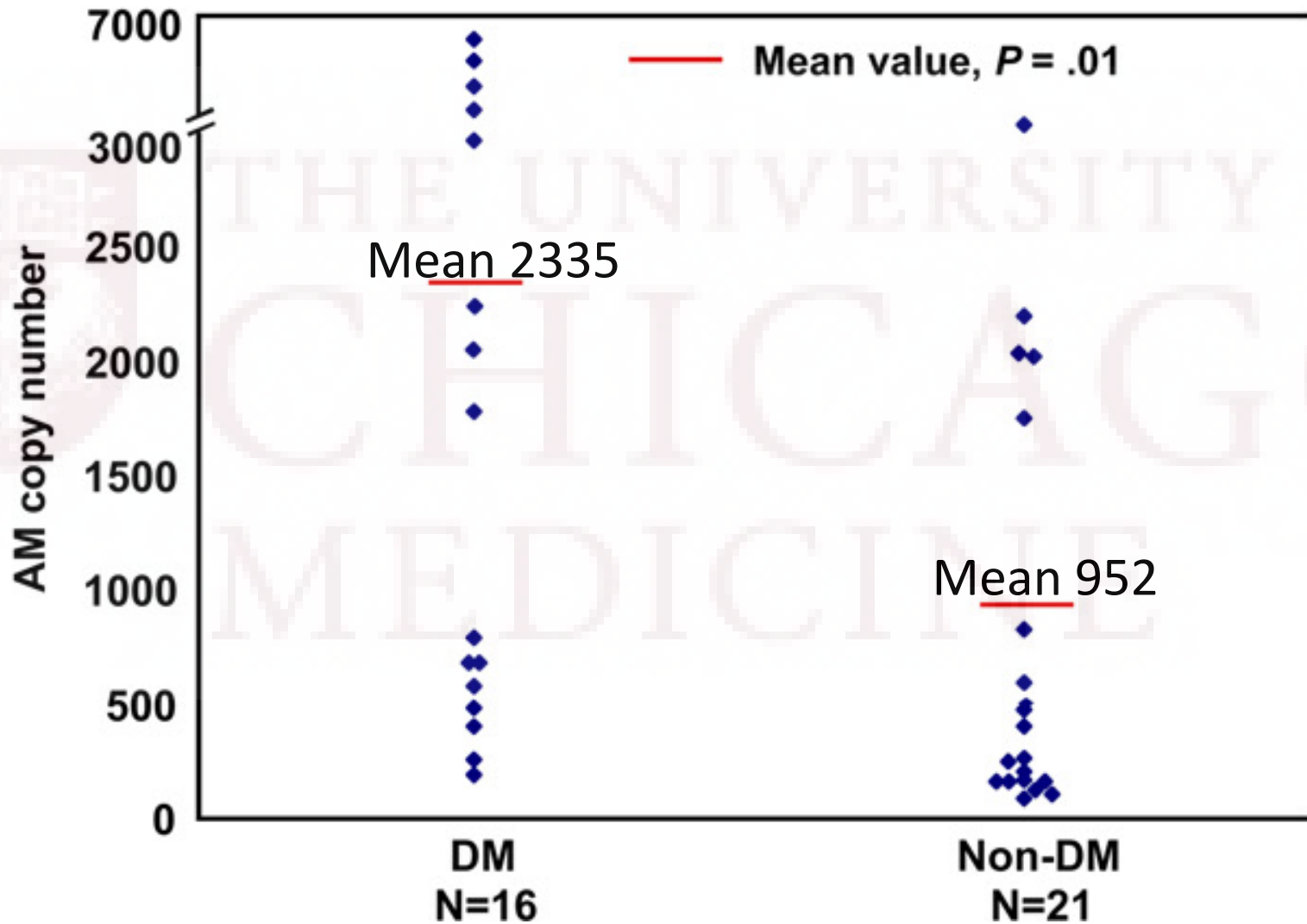
Need for improved screening

- Pancreatic cancer can be resectable in as little as 6-18 months before clinical diagnosis
 - At diagnosis, 85% have unresectable disease
- Prognosis is poor
 - 5 year survival rate = 10-20%
- Screening should include new-onset DM or aggravation of long-standing DM + biomarkers

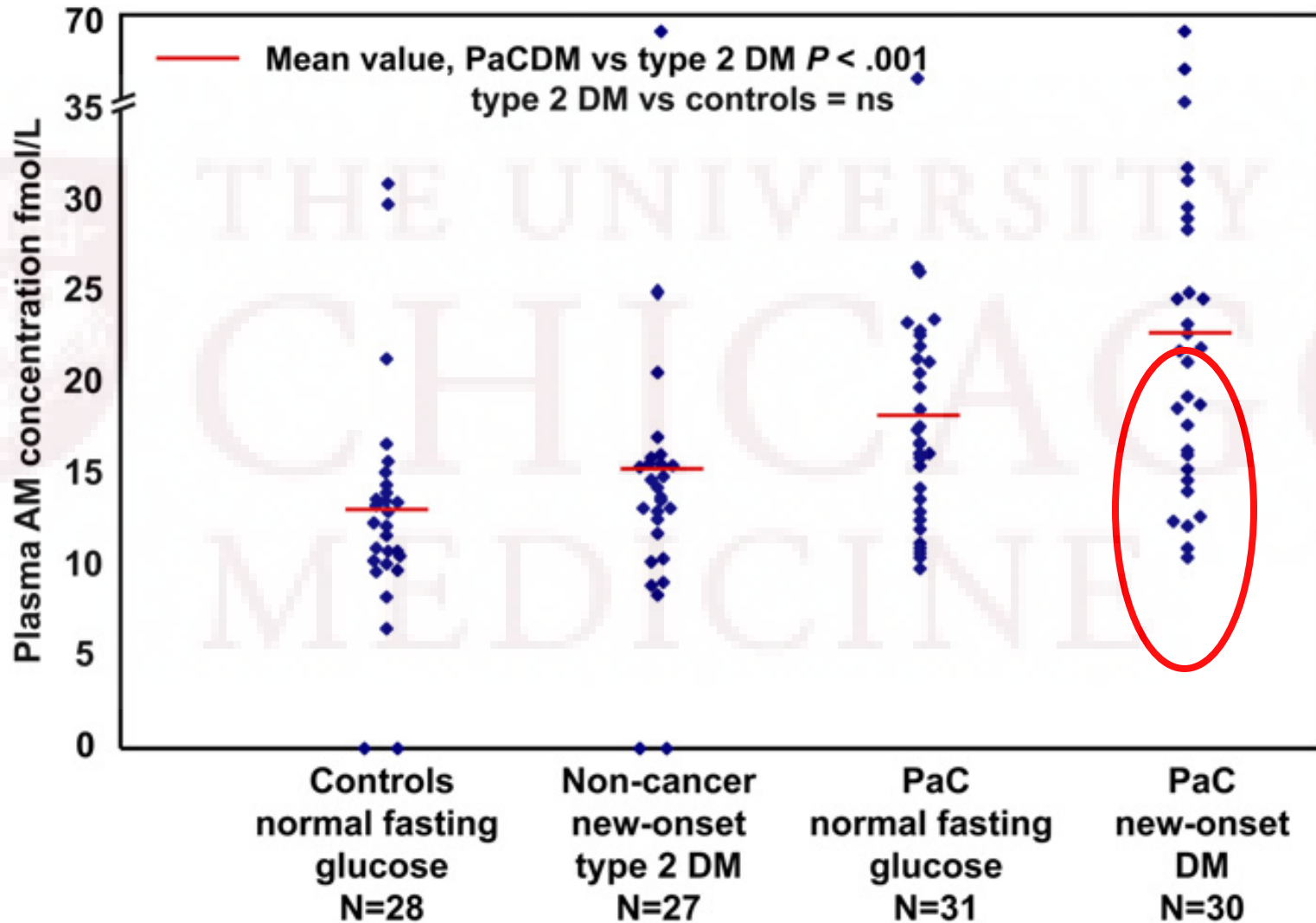
Biomarkers- adrenomedullin



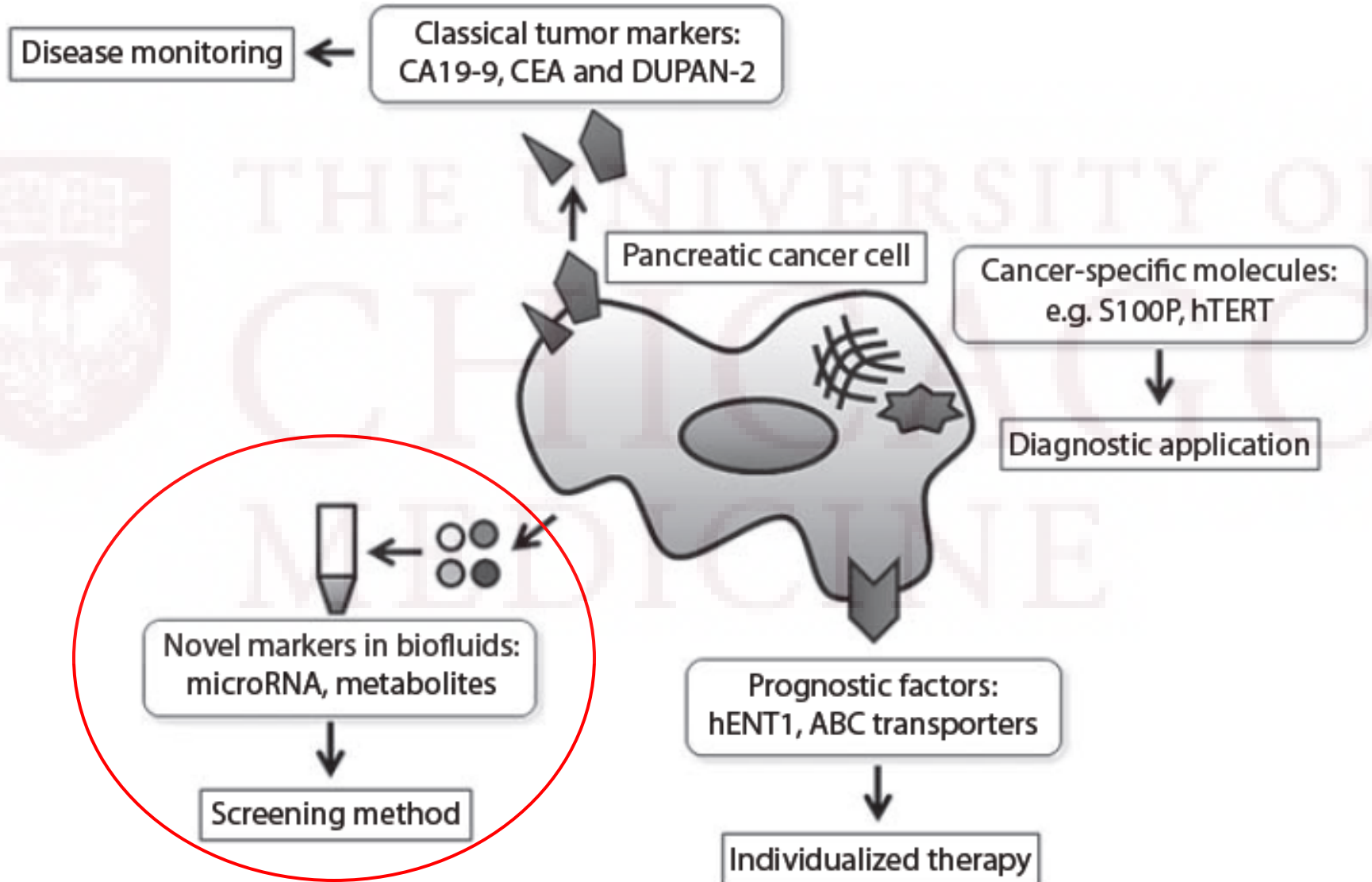
Biomarkers- adrenomedullin



Biomarkers- adrenomedullin



Other biomarkers



Salivary Transcriptomic Biomarkers

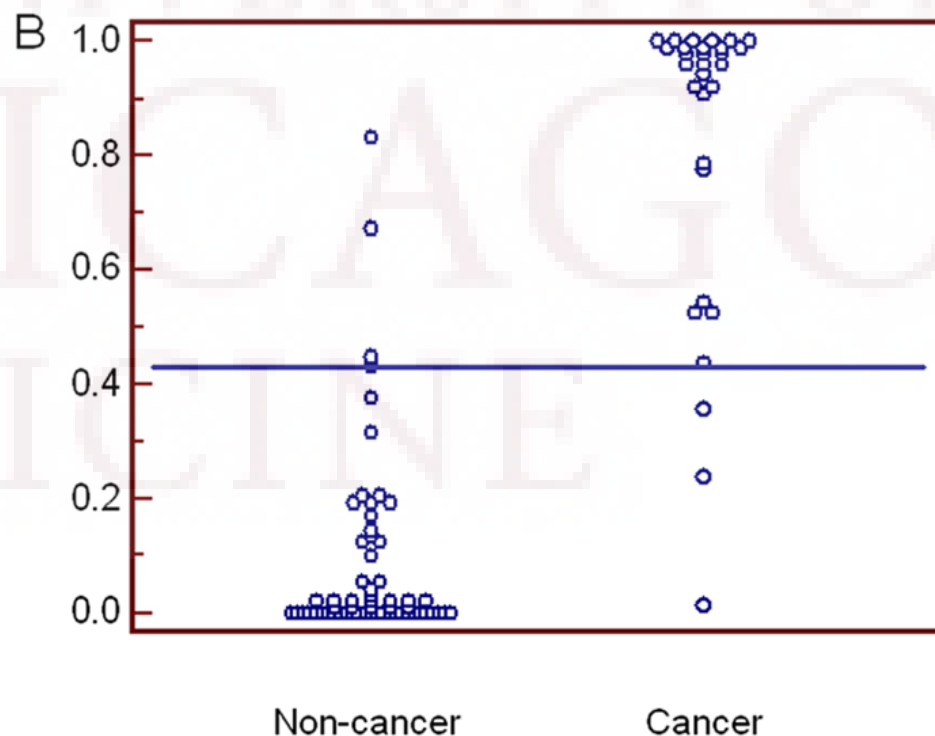
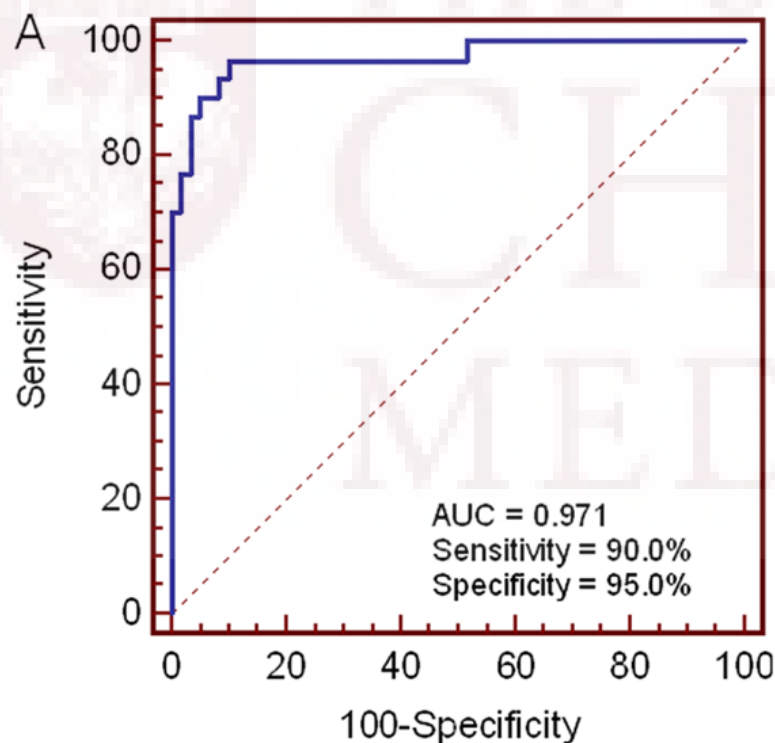
Pancreatic cancer vs. Healthy control				Pancreatic cancer vs. Chronic pancreatitis		
Gene symbol	P	AUC	Fold change	P	AUC	Fold change
<i>MBD3L2</i>	< 0.001	0.788	8.0 ↑	0.003	0.718	4.3 ↑
<i>KRAS</i>	<0.001	0.823	6.1 ↑	0.001	0.759	4.2 ↑
<i>STIM2</i>	< 0.001	0.759	4.3 ↑	0.002	0.733	3.1 ↑
<i>DMXL2</i>	0.007	0.699	4.6 ↑	0.106	0.622	2.8 ↑
<i>ACRV1</i>	< 0.001	0.745	3.9 ↑	< 0.001	0.753	4.9 ↑
<i>DMD</i>	< 0.001	0.758	4.1 ↑	0.003	0.718	2.9 ↑
<i>CABLES1</i>	< 0.001	0.783	4.1 ↑	0.003	0.721	2.7 ↑
<i>TK2</i>	0.002	0.731	4.7 ↓	0.015	0.682	4.5 ↓
<i>GLTSCR2</i>	< 0.001	0.785	4.8 ↓	< 0.001	0.769	5.4 ↓
<i>CDKL3</i>	0.014	0.682	3.8 ↓	0.035	0.659	4.5 ↓
<i>TPT1</i>	0.003	0.720	2.0 ↓	0.061	0.641	0.7 ↓
<i>DPM1</i>	0.004	0.712	2.6 ↓	0.123	0.617	0.6 ↓

30 PC patients, 30 healthy control subjects, and 30 chronic pancreatitis patients

12 mRNA biomarkers all showed significant difference between PC and healthy controls

Salivary Transcriptomic Biomarkers

Biomarkers used in model: KRAS, MBD3L2, ACRV1, DPM1



Potential secondary/tertiary filters

- BMI < 25
- Age > 55
- Family history of DM (unclear association)
- Family history of pancreatic cancer
- Family history of multiple other cancers
- Exacerbation of DM
- Biomarkers

Take home points

- There is an association between pancreatic cancer and diabetes (bi-directional)
- Pancreatic cancer-induced DM does not fit criteria of type 3c diabetes
- More research is needed using new-onset diabetes +/- other risk factors +/- biomarkers for effective screening

References

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