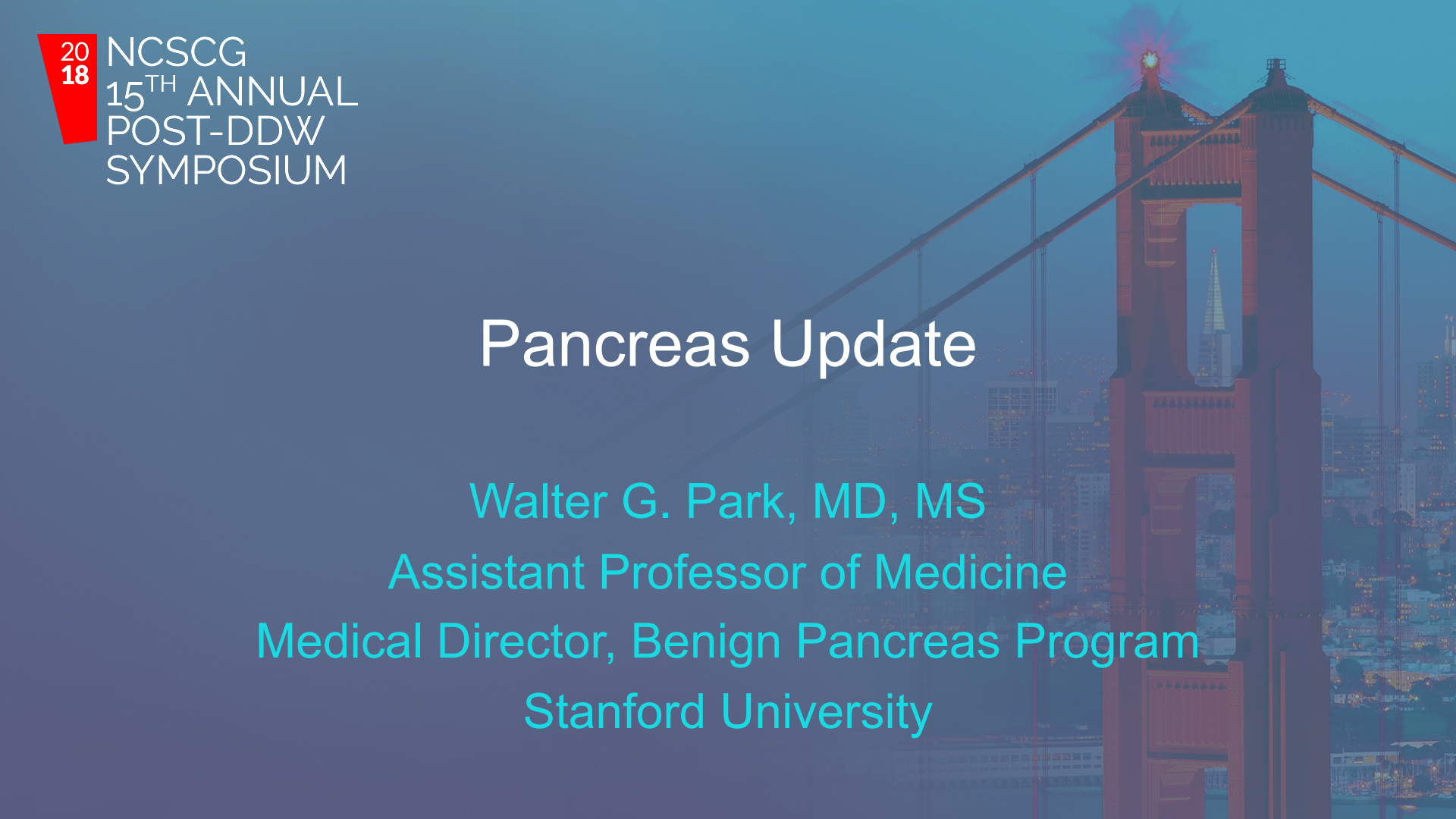


# Pancreas Update

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# Disclosures

- Advisory Board:
  - Abbvie
  - Interpace
  - Alnylam
  - Akcea
  - Ariel Medicine
- Consultant:
  - Recro Pharma
  - Eagle Pharmaceuticals

# Pancreatic Disorders

- Acute Pancreatitis
- Chronic Pancreatitis
- Pancreatic Cysts
- Pancreatic Cancer Screening

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# Acute Pancreatitis

# AGA Guidelines on Initial Management of Acute Pancreatitis: Management Point #3

- In patients with acute biliary pancreatitis and no cholangitis, urgent ERCP not indicated
  - Conditional Recommendation/Low quality Evidence
  - 8 RCTs
    - Urgent ERCP had no impact on critical outcomes such as organ failure or mortality.

Gastroenterology 2018: 1096-1101

# DDW Abstract #Mo570

- **Early Endoscopic Retrograde Cholangiography with Biliary Sphincterotomy or Conservative Treatment in Predicted Severe Acute Biliary Pancreatitis: A Multicenter Randomized Trial (Schepers et. al, Dutch Pancreatitis Study Group)**
- **Inclusion:** Biliary etiology + predicted severed dx (CRP > 150, Imrie > 2, APACHE II score > 7)
- **Exclusion:** Cholangitis
- **Primary Outcome:** Severe Complications (persistent organ failure, cholangitis, bacteremia, PNA, pancreatic necrosis, EPI) & Death
- **Results:** 232 patients randomized (118 ERC with sphincterotomy/114 conserv. Rx)
  - Primary composite outcome: 39% ERC with sphincterotomy vs. 44% conservative Rx ($p = 0.37$); only reduction seen in cholangitis (2% vs 10%)
- **Conclusion:** NO superiority observed with early ERC for those with predicted severed biliary AP

# AGA Guidelines on Initial Management of Acute Pancreatitis: Management Point #4

- Early (within 24 hours) oral feeding rather than keeping patient NPO.
  - Strong Recommendation/Moderate quality Evidence
  - 11 RCTs early vs delayed feeding
    - No difference in mortality.
    - Infection rate in delayed feeding (OR 2.69; 95% CI: 0.8 – 3.6)
    - Multi-organ failure in delayed feeding (OR 2.0; 95% CI: 0.49 – 8.2)
  - Starting with clear liquids is NOT required.
  - Maintaining enteral nutrition helps protect the gut mucosal barrier and reduce bacterial translocation

Gastroenterology 2018: 1096-1101

# AGA Guidelines on Initial Management of Acute Pancreatitis: Management Point #7

- For acute biliary pancreatitis, cholecystectomy before discharge
  - Strong Recommendation/Moderate quality Evidence
  - 1 RCT: in-hospital cholecystectomy reduced:
    - Composite of mortality and gallstone related complications (OR 0.24, 95% CI 0.09 – 0.61)
    - Readmission for recurrent pancreatitis (OR 0.25, 95% CI 0.07 – 0.90)
    - Pancreatico-biliary complications (OR 0.24 95% CI 0.09 – 0.61)
  - No difference in conversion rates (lap to open)

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# Chronic Pancreatitis

# Chronic Pancreatitis & Osteoporosis

- Prevalence of osteoporosis is ~ 30% among CP patients.
  - Low Vitamin D from fat malabsorption
  - Increased bone turnover related to systemic inflammation
- Guidelines recommend baseline bone density testing and then every 2-3 years along with annual Vitamin D Assay testing.

Duggan S, et. al Am J Gastroenterol 2015: 336-45
Lohr M, et. Al. United European Gastroenterol J 2017: 153-99

# DDW Abstract: Su1449

- **Do Patients with Chronic Pancreatitis Receive Optimal Bone Health Care (Srivoleti et. al.)**
- Aim: To assess BMD and Vit D testing compliance
- Methods: Single-center retrospective analysis within 1 year
- Results: 478 CP patients reviewed
  - BMD testing in 52% of patients
    - 30% had osteoporosis.
  - Vit D testing in 82% of patients
- Conclusion: Quality gap in getting BMD and Vit D Testing.

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# Pancreatic Cysts

# Multiple Guidelines

- Revised Sendai Guidelines (Fukuoka Criteria) (2012 & 2017)
- American Gastroenterological Association Guidelines (2015)
- American Society for Gastrointestinal Endoscopy (2016)
- American College of Radiology (2017)
- American College of Gastroenterology (2018)
- European Evidence-Based Guidelines (2018)

# Molecular Analysis (Panc. Cyst Fluid)

| | *KRAS* | *GNAS* | *VHL* | *CTNNB1* |
|---|---|---|---|---|
| IPMN | + | + | - | - |
| MCN | + | - | - | - |
| SCA | - | - | + | - |
| SPN | - | - | - | + |
| Non | - | - | - | - |

- Intraductal papillary mucinous neoplasms (**IPMN**): *KRAS* and *GNAS*
- Mucinous cystic neoplasms (**MCN**): *KRAS*
- Serous cystadenomas (**SCA**): *VHL*
- Solid pseudopapillary neoplasms (**SPN**): *CTNNB1*

**Non-neoplastic cysts:**
**Absent**

Courtesy: A. Singhi

# Molecular Analysis (Panc. Cyst Fluid)

| Surgical Resection Dx | Total, n = 102 (18%) |
|---|---|
| AdenoCA arising in an IPMN | 13 |
| IPMN with HGD | 4 |
| MCN with HGD | 2 |
| IPMN with LGD | 39 |
| MCN with LGD | 8 |
| Serous cystadenoma | 3 |
| Cystic PanNET | 9 |
| Acinar cell cystadenoma | 1 |
| Pseudocyst | 17 |
| Retention cyst | 2 |
| Lymphoepithelial cyst | 2 |
| Epidermoid cyst | 1 |
| Squamoid cyst | 1 |

**IPMNs & MCNs**
*KRAS* &/or *GNAS* mutations
Sensitivity: 89%
Specificity: 100%

Elevated CEA*
Sensitivity: 57%
Specificity: 80%

**IPMNs**
*KRAS* &/or *GNAS* mutations
Sensitivity: 100%

**MCNs**
*KRAS* mutations
Sensitivity: 20%

Courtesy: A. Singhi et al. Gut 2017:1-11

# Molecular Analysis (Panc. Cyst Fluid)

| Surgical Resection Dx | Total, n = 102 (18%) |
|---|---|
| AdenoCA arising in an IPMN | 13 |
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| Lymphoepithelial cyst | 2 |
| Epidermoid cyst | 1 |
| Squamoid cyst | 1 |

**Advanced Neoplasia**

***KRAS*** **and/or** ***GNAS*** **and** ***TP53***, ***PIK3CA***, **and/or** ***PTEN***

- **Sensitivity: 79%**
- **Specificity: 96%**

**Cytology**

- **Sensitivity: 32%**
- **Specificity: 98%**

Courtesy: A. Singhi et al. Gut 2017:1-11

# DDW Abstract: Sa78

- **A Multi-modality test to Guide the Management of Patients with Pancreatic Cysts (Dal Molin, M, et. al)**
- **Methods:** International Multi-center Retrospective Study of mutational profiles of pancreatic cysts along with supervised machine learning of clinical & imaging markers
- **Results:** 862 cysts analyzed. CompCyst trained in half of the cohort to classify those that *required surgery, monitoring, or no further surveillance*. Independent validation with 2nd half of the cohort.
- **Conclusion:** Use of CompCyst would have reduced unnecessary surgery by 60%.

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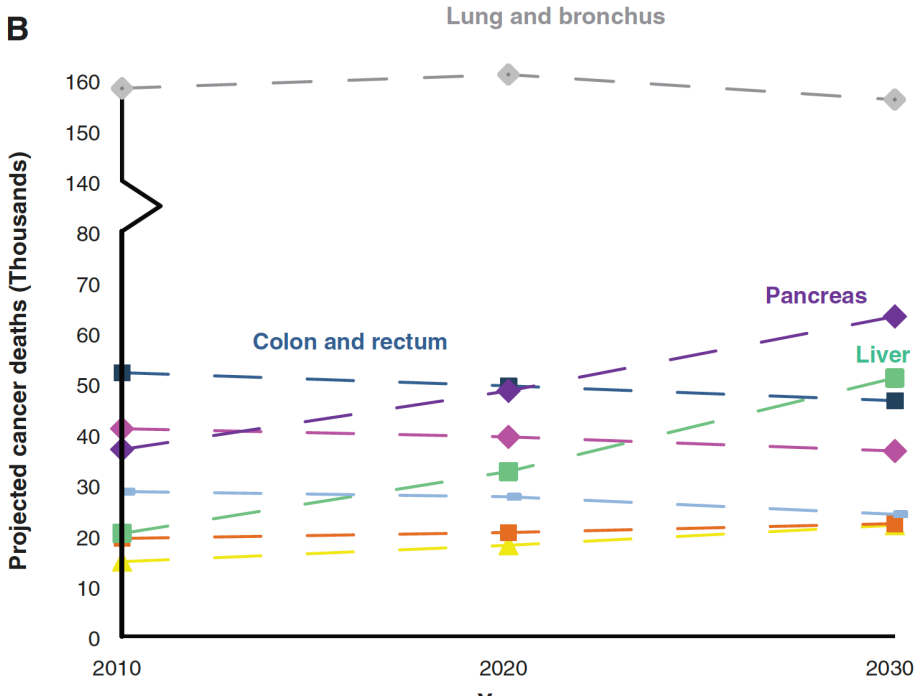
# Pancreatic Cancer Screening

# Pancreas Cancer to become 2nd leading cause of Cancer Death




Rahib et. al. Cancer Res 2014:2913-21

# Presentation and Prognosis

| Stage | Presentation | Median OS | 5-Year OS |
|---|---|---|---|
| Local resectable | 15 – 20% | 20 – 28 mo. | 20 – 25% |
| Locally advanced | 30 – 35% | 10 – 12 mo. | < 5% |
| Metastatic | 50 – 55% | 6 – 10 mo. | 0% |

~80%

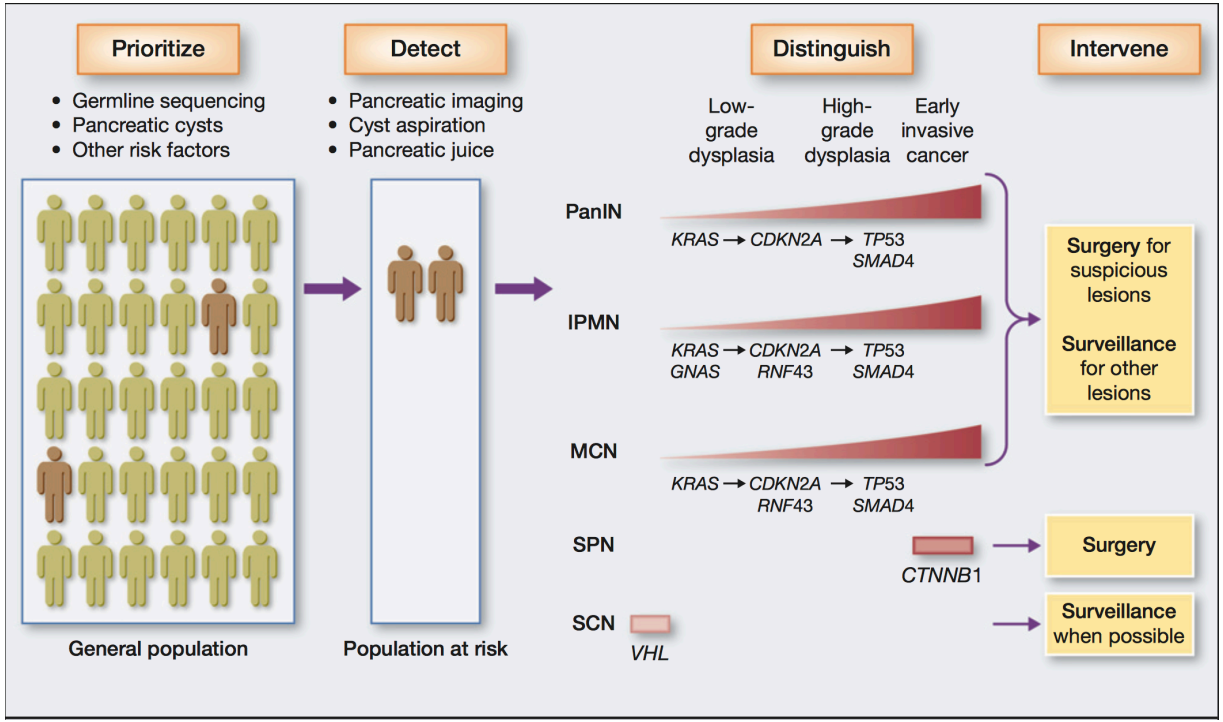
~6 months

# Screening Program Yields

| | Population | Tests | Clinical Relevant Lesions |
|---|---|---|---|
| Canto 2012<br>N=225 | FPC, BRCA, CDKN2A, PJS (Initial Screen) | EUS<br>MRI<br>CT | 42% any lesion<br>1.3% HGD |
| Harinck 2016<br>N=139 | FPC, BRCA, CDKN2A (Initial Screen) | EUS<br>MRI | 6% prevalence (solid lesions/cysts>1 cm/MD-IPMN) |
| Bartsch 2016<br>N=253 | FPC, BRCA, PALB2 (median F/U 28 m) | MRI<br>EUS (PRN) | 6% incidence (PanIN 2 or greater) |
| Vasen 2016<br>N=411 | CDKN2A, FPC, BRCA, PALB2 | EUS<br>MRI | 4.8% incidence (PanIN 2 or greater) |

Canto, et al. Gastroenterology 2012: 796, Harinck et al. Gut 2016: 1505, Bartsch et al Gut 2016:1314, Vasen et al. JCO 2016: 2010, Courtesy MI Canto: NIDDK Workshop 2017

# Paradigm for Early Detection



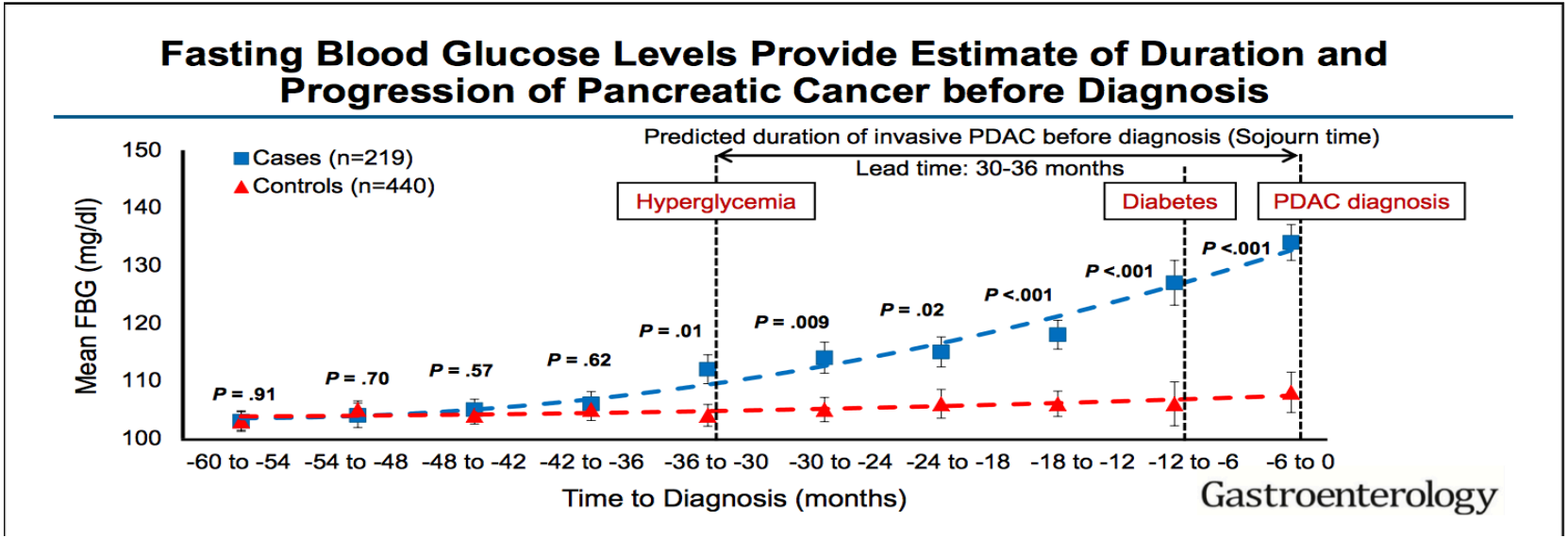

Lennon AM, et. al.Cancer Res 2014:3381-9

# International Cancer of the Pancreas Screening Consortium Recommendations

- Who should be screened?
  - ≥ 2 affected family members with at least 1 first degree relative (FDR)
  - Peutz-Jeghers Syndrome (STK11/LKB11)
  - BRCA2/PALB2/p16 mutation carriers or Lynch Syndrome with at least 1 FDR (or 2 affected family members)
  - Hereditary Pancreatitis (PRSS1)
- Initial Screening & Surveillance
  - (1) EUS or (2) MRI

Canto MI, et al. Gut 2013:339-347

# New Onset Diabetes & PDAC




- ~1% of subjects >50 years with NOD will be diagnosed with Pancreatic Cancer within 3 years of meeting biochemical criteria for NOD.
- Subjects with NOD have 6-8 fold higher 3-year risk of PC than general population.

Sharma A, et. al. Gastroenterology 2018;490-500
Chari ST, et. Al. Gastroenterology 2008;981-7

# Disproportionate High Prevalence of DM in PDAC compare to other Cancers

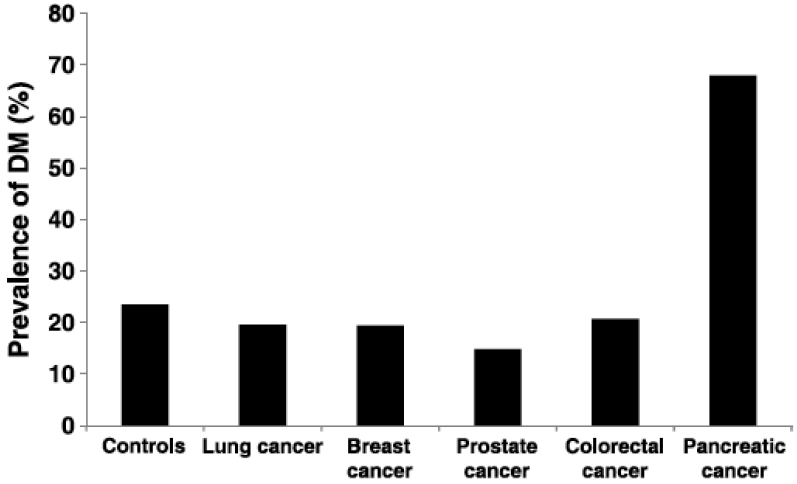



FIGURE 1. Prevalence of DM in various cancers and noncancer controls.

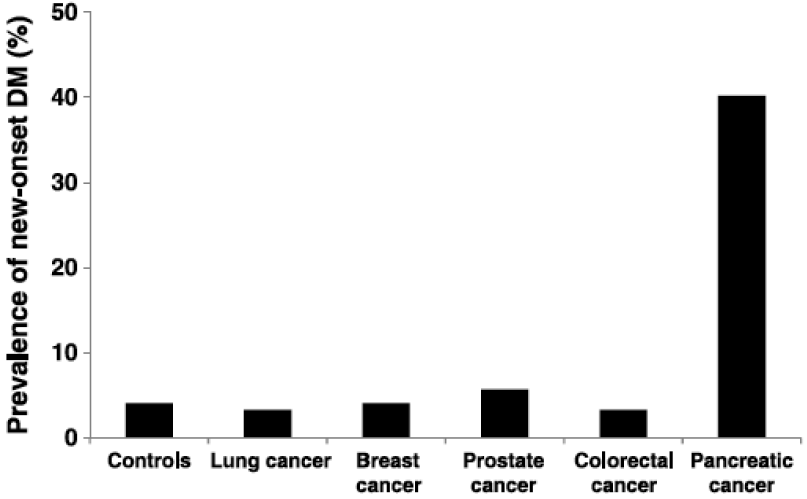



FIGURE 2. Prevalence of new-onset DM in various cancers and noncancer controls.

Aggarwal et al. Pancreas 2013: 198

# DDW Abstract: Sa162

- **Glycemic profile of subjects with FPC: Mayo Clinic Experience from 2000-2018 (Garg, S. et al.)**
- **Methods:** Single center retrospective review of the Mayo Clinic Tumor Registry of those with PDAC and family hx of PDAC. Assessed for DM status.
- **Results:** 236 patients included. No difference in DM prevalence in FPC vs sporadic PDAC (50% vs. 47%), pre-DM (29% vs 38%) and normoglycemia (21% vs 14%). In FPC subjects, 42% reported weight loss.
- **Conclusion:** Glycemic profiles in FPC subjects mimic that of sporadic cases

# Ongoing Research Studies

- **NIDDK/NCI** Prospective Cohort of Adult (PROCEED) and Pediatric (INSPIRRE2) Chronic Pancreatitis
- **NIDDK/NCI** Mixed Meal test to Diagnose Type 3c DM
- **NIDDK/NCI** New Onset Diabetes Cohort for PDAC
- **NCI** Prospective Registry for Early Detection in Pancreatic Cancer for Pancreatic Cysts and Familial Pancreatic Cancer
- **Industry** sponsored Phase 2 RCT for Pain in Chronic Pancreatitis
- **NCI** Molecular US and EUS Imaging Trials in Pancreatic Cancer of Targeted Microbubbles
- **NCI** Molecular PET Imaging Trial in Pancreatic Cancer using an αVβ6 tracer

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# Thank you

wgpark@Stanford.edu

NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Early Detection Research Network
*Biomarkers: the key to early detection*

NATIONAL CANCER INSTITUTE