

Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer

Joint RFA Initiative: NIDDK, NCI and NIAAA

June 23-24, 2014

Participating Institutes

National Cancer Institute

Division of Cancer Prevention

- Jo Ann Rinaudo, Ph.D.
- Sudhir Srivastava, Ph.D., M.P.H.

Division of Cancer Control and Population Sciences

- Mukesh Verma, Ph.D.

Division of Cancer Biology

Division of Cancer Treatment and Diagnosis

Participating Institutes

National Institute of Diabetes and Digestive and Kidney Diseases

Division of Digestive Diseases and Nutrition

- Jose Serrano, MD, Ph.D.
- Dana K Andersen, M.D.
- Stephen James, M.D.

National Institute on Alcohol Abuse and Alcoholism

Division of Metabolism and Health Effects

- Gary J. Murray, Ph.D.

Background

Chronic Pancreatitis

- ❑ Progressive, debilitating and incurable disease
- ❑ Fibrosis leads to loss of both endocrine and exocrine pancreatic function
 - Resulting in nutritional and metabolic disease – **diabetes**
- ❑ Risk of **pancreatic carcinoma** increases with duration of disease

Unclear what factors are involved in the initiation of chronic pancreatitis, progression to severe fibrosis, and transformation into pancreatic cancer.

Risk of Pancreatic Ductal Adenocarcinoma (PDAC)

Table 1.	Risk Factor	OR, Confidence Interval*	Reference
Lifestyle	Smoking	1.75 CI 1.61-1.87	Iodice 2008
	Alcohol (>4 drinks/day)	1.5	Lucenteforte 2012
Occupational	Chlorinated hydrocarbons	1.4-4.4	Andreotti, 2012
	Polycyclic aromatic hydrocarbons (PAH)	1.5	Andreotti, 2012
Diet	n-nitroso containing foods	1.27 CI 1.09-1.48	Risch, 2012
	saturated fat / animal fat	1.5	Sanchez, 2012
Medical	Pancreatitis	5.1 CI 3.5-7.3	Raimondi, 2010
	- Chronic pancreatitis	13.3 CI 6.1-28.9	Raimondi, 2010
	- Hereditary pancreatitis	69.9 CI 56.4-84.4	Raimondi, 2010
	Allergies	0.5	Olson 2012
	Diabetes mellitus	1.5	Li 2012
	Obesity	1.3	Bracci, 2012
Genetics	ABO blood group	1.65 CI 1.30-2.09	Risch, 2012
	<i>BRCA2</i>	3.5 CI 1.87-6.58	Klein 2012
	<i>STK11/LKB1</i>	132 CI 44-261	Klein 2012
	<i>PALB2</i>		Familial** Jones, 2012
	<i>CDKN2A</i>	12-38	Klein 2012
	<i>CFTR</i>	5.3-6.6	Raimondi 2009
	<i>TP53</i>		Familial** Raimondi 2009
	<i>APC</i>	4.46 CI 1.2-11.4	Raimondi 2009
	Mismatch repair genes	0 – 8.6	Klein 2012
	<i>PALLD</i>		Familial** Pogue-Geile 2006
	1q32.1	0.77 CI 0.71-0.84	Petersen 2010
13q22.1	1.26 CI 1.18-1.35	Petersen 2010	

Risk of Pancreatic Ductal Adenocarcinoma

At-Risk Group

Hazard Ratio (HR)

Chronic Pancreatitis (CP)

5 – 13

Hereditary Pancreatitis

56 – 84

3 Affected First Degree Family Members

17

Type 2 Diabetes Mellitus (T2DM)

1.5 – 2.0

T2DM + CP

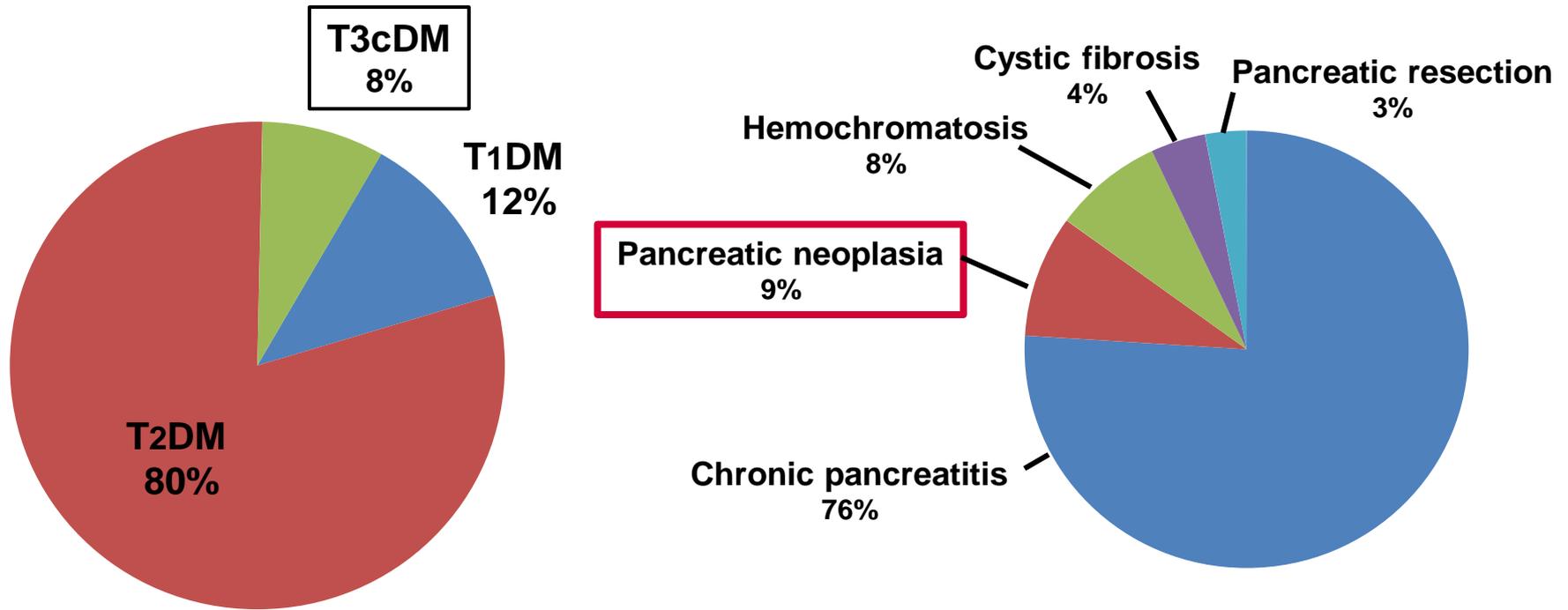
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Type 3c Diabetes Mellitus (T3cDM)

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Distribution of Type 1, 2 and 3c Diabetes

Potential Causes of Type 3c Diabetes



Curr Opin Endocrinol Diabetes Obes 2013, 20:81.

Diabetes and Cancer

- ❑ Diabetes increases risk for cancer
- ❑ 75% of pancreatic cancer patients have diabetes¹
- ❑ 50% of diabetes associated with cancer is secondary or T3cDM (pancreatogenic)¹
- ❑ In 20% of pancreatic cancer patients, the onset of diabetes occurs when patients are asymptomatic for cancer²
- ❑ Potential high risk group for screening

¹*Curr Opin Endocrinol Diabetes Obes* 2013, 20:81.

²*Pancreatology* 2012, 12:156.

Scientific Discussion for Unmet Clinical Needs

- ❑ NIDDK (June 2012) and NIDDK/NCI (June 2013) sponsored workshops to discuss:
 - Type 3c Diabetes Mellitus (T3cDM) and risk of pancreatic cancer
 - Basic and translational studies in the area of chronic pancreatitis
 - Risk factors which link chronic pancreatitis, diabetes, and pancreatic cancer
 - Strategies and therapeutic targets to reduce the burden of disease

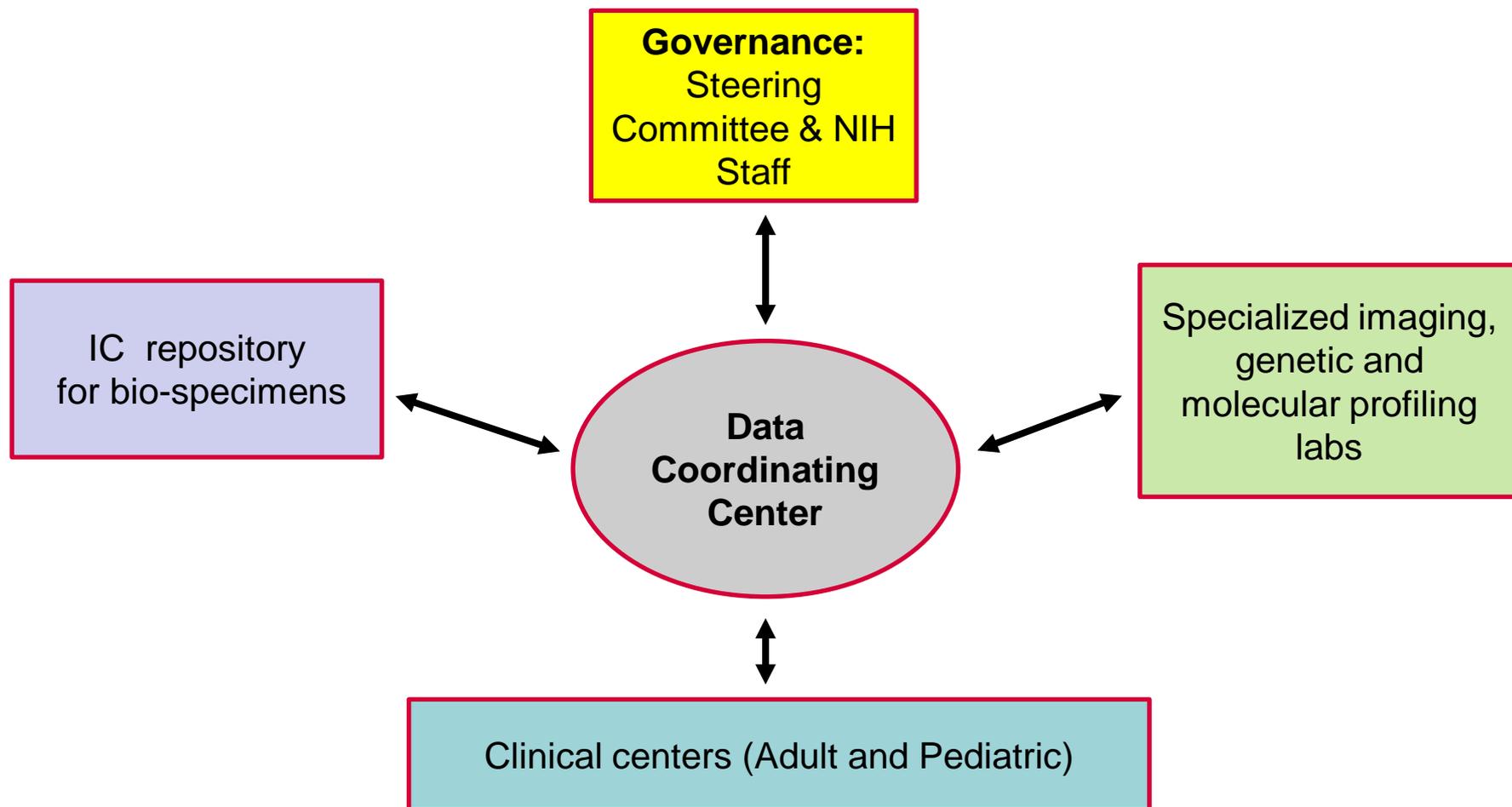
- ❑ NCI's Scientific Framework for Pancreatic Ductal Adenocarcinoma, February 2014

“The NCI will continue to work with NIDDK to develop new funding opportunities for studying the diabetes-PDAC connection.”

NCI Strategic Goals

- ❑ Identify patients at high risk for developing pancreatic cancer
- ❑ Develop methods(e.g. *in vitro* diagnostic and/or imaging) to:
 - Detect early stage pancreatic cancer
 - Detect *Pancreatic intraepithelial lesions* (PanINs)
 - Distinguish low vs. high risk *intraductal papillary mucinous neoplasms* (IPMNs)
 - Distinguish low vs. high risk *mucinous cystic adenomas*
- ❑ Determine the relationship between T3cDM and pancreatic cancer

Organizational Structure of the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer



Research Objectives:

Identify fibrosis markers in patients with acute or recurrent pancreatitis who progress to chronic pancreatitis.

Detect and quantify pancreatic fibrosis and pancreatic cancer.

Trials to determine efficacy of treatment strategies to improve symptoms and outcome (anti-fibrosis for (early) chronic pancreatitis; metformin for prevention of diabetes and pancreatic cancer in patients with chronic pancreatitis.

Determine which combination(s) of genetic and/or environmental factors give rise to pancreatic cancer.

Research Objectives:

Epidemiological studies to establish the incidence and prevalence of Type 3c diabetes (T3cDM).

Studies to establish the risks of acute/chronic pancreatitis and pancreatic cancer in patients with Type 2 (T2DM) diabetes treated with incretin-based therapy.

Studies of “high risk” patients to evaluate genomic, proteomic, and hormonal markers of early pancreatic cancer.

Conduct pilot surveillance studies and generation of survivorship registries; and identification of factors that may contribute to disparity in incidence of pancreatic cancer among populations.

Examples of Deliverables from Consortium:

- ❑ Recruitment: 1200 patients (3-4 patients/month x 48 months x 8 sites)
- ❑ Longitudinal assessment of progression
 - Identify markers for fibrosis progression to chronic pancreatitis and cancer
 - Develop methods to detect pancreatic fibrosis and evaluate T3cDM as a possible biomarker of pancreatic cancer
 - Epidemiological survey for risk factors
- ❑ Serial samples
 - Plasma, serum, DNA
 - Stool, urine
 - Duodenal / pancreatic aspirates
 - Diagnostic biopsies, pancreatic resections
 - Imaging – EUS, secretin–MRCP

Rationale for RFA

This RFA addresses specific high priority needs not adequately met by any other programs at NIDDK, NCI or NIAAA.

The proposed clinical research network will provide the resources (patients and biospecimens) and collaborative opportunities necessary for achieving these goals in pancreatic disease research.

Rationale for Consortium and Cooperative Agreement Award

- Uniform data collection, protocols, and analyses
- Common Data Elements (CDEs) for serial sample collection and clinical annotation
- Reproducibility of data collection including verification and auditing
- Central management of IRB, MTA and protocols
- A consortium of centers will aide in the recruitment of sufficient patients, in the collection of bio-specimens, and will help ensure the sharing of these resources. No single site has resources to achieve these goals.

The cooperative agreement mechanism will allow NIH program staff to guide and support the research to facilitate meeting the IC goals.

U01 Funding Budget

Anticipated Number of Awards:

- 7-9 clinical centers and 1 Data Coordinating Center

Length of Award in Years:

- 5

Repository Data and Bio-specimen repository:

- Consortium and NIDDK repository

Funding Requested:

NIDDK: \$3.5 million/year (Approved NIDDK Council for FY15)

NCI: \$2 million/year

NIAAA: \$0.5-1 million/year

Thank you!

Questions?



National Institute of
Diabetes and Digestive
and Kidney Diseases



NIAAA