Request for Renewal of a Trans-NIH RFA Initiative:

Chronic Pancreatitis, Diabetes and Pancreatic Cancer Consortium

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NIH NATIONAL CANCER INSTITUTE

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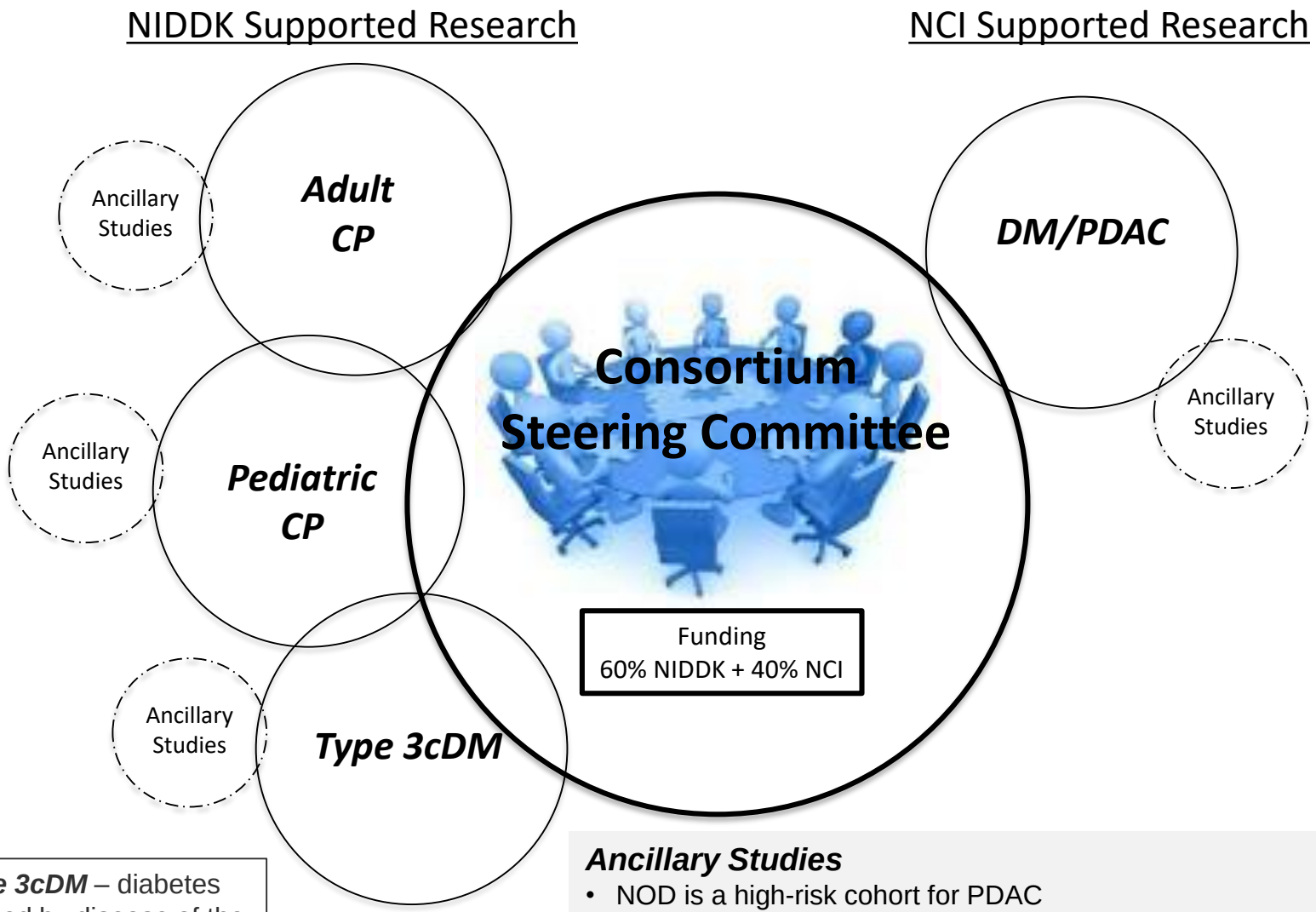
Joint NCI-NIDDK Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) Consortium (RFA-DK-14-027/028)

Purpose

The Consortium was established to gain insight into the pathophysiology of chronic pancreatitis and its sequela: chronic pain, pancreatic insufficiency, T3cDM and the **diabetes/pancreatic cancer association**.

CPDPC Consortium Infrastructure



Type 3cDM – diabetes caused by disease of the exocrine pancreas (e.g. CP, PDAC)

Ancillary Studies

- NOD is a high-risk cohort for PDAC
- Minority populations at increased risk of PDAC in NOD
- Immune Profiling in Patients with Pancreatitis and PDAC Associated DM
- Investigating NMU roles in Type 3c DM associated with CP and PDAC

Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) Consortium

Consortium has 4 large projects –

Chronic Pancreatitis – **PRO**spective Evaluation of **C**hronic Pancreatitis for **E**pid**E**miologic and Translational Stu**D**ies (PROCEED)

Pediatric Pancreatitis – **IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE** (INSPPIRE)

Type 3c Diabetes – Evaluation of a Mixed Meal Test for **D**iagnosis and characterization of Pancr**E**aTog**E**ni**C** Diabe**T**es Secondary to Pancreatic Cancer and Chronic Pancreatitis (DETECT)

New-Onset Diabetes (NOD)

CPDPC Ancillary Studies

- Small exploratory studies (short/intermediate term)
- Hypothesis driven
- Utilize existing consortium resources
- Future validation in prospective cohorts

Examples –

- Immune Profiling in Patients with RAP, CP and PDAC Associated DM
- Investigating NMU (Neuromedin U) roles in Type 3c DM associated with CP and PDAC

New-Onset Diabetes (NOD) Background

New-onset diabetics, age 50-85, are at elevated risk of pancreatic ductal adenocarcinoma (PDAC):

- Cumulative incidence rate over 3 years – 0.85%*
- 6-8 fold higher risk of being diagnosed with PDAC within 3 years of developing diabetes
- 25-40% of patients with PDAC develop diabetes between 6 and 24 months prior to PDAC diagnosis

**Gastroenterology 2005;129:504.*

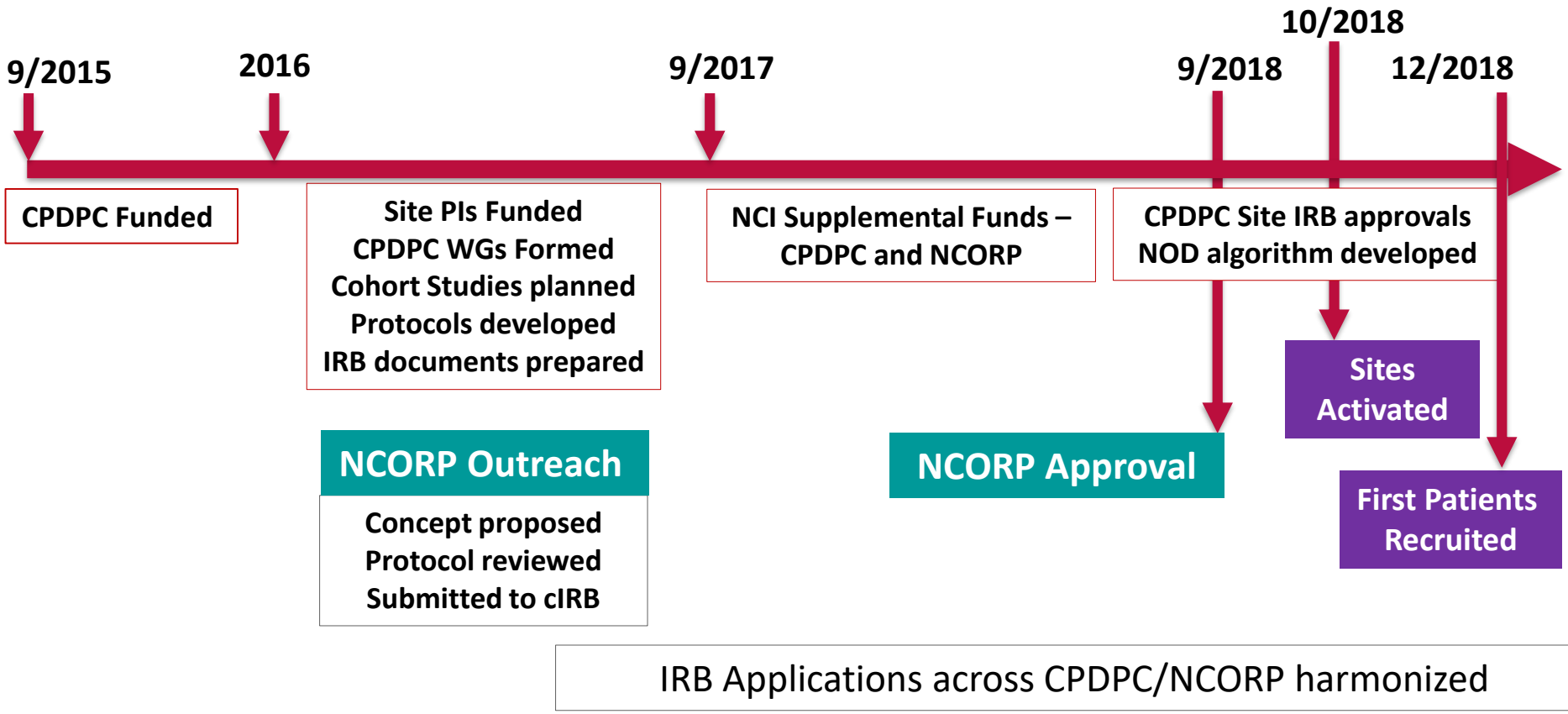
New-Onset Diabetes (NOD) Project

A cohort of 8,000 NOD patients will be recruited with goals:

1. Estimating the probability of PDAC in a cohort of new onset diabetes
2. Establishing a biobank of clinically annotated biospecimens, to establish a reference set of specimens for pre-diagnostic PDAC and other diabetics
3. Performing validation studies of promising biomarkers for identification of occult PDAC
4. Provide a platform to develop future interventional and screening protocols for early diagnosis

- Early detection of PDAC will require asymptomatic subjects in a high-risk population
- New-Onset Diabetes (NOD) is a high-risk population

Timeline



IRB Applications across CPDPC/NCORP harmonized

Participating Sites

***CPDPC Sites* (4000 patients)**

- Baylor College of Medicine
- Cedar Sinai
- Indiana University
- Kaiser Permanente Southern California
- Mayo Clinic
- Ohio State University
- Stanford University
- University of Florida
- University of Pittsburgh

Estimated recruitment rates:

- 2-3 patients / week / site
- 10-12 patients / month / site
- 9 sites = 90-100 patients / month
- One year = 1000-1200 patients

***NCORP Sites* (4000 patients)**

- Kaiser Permanente Northern California
- St. Joseph's Mercy

Additional Sites

- Geisinger
- Intermountain
- LSU Health Sciences Center
- HSHS St. Vincent Hospital

Accrual Challenge

- Beginning in 2018, NOD Study accrual faced several difficulties:
  - Delays in IRB approval
  - Lack of multi-lingual consent forms (e.g. Spanish)
- Recruitment pace is improving and appears promising based on the current numbers and projection for the future.

Addressing the Accrual Challenge

- High volume sites are being identified and prioritized for greater responsibility
- Patient incentives to improve participation
- Appropriate language translations for patient consent forms

Increasing Recruitment

- High volume sites (e.g. KPSC / KPNC / Geisinger)
- Multi-lingual consent forms (e.g. Spanish)
- Satellite sites
- Eligibility criteria (one elevated A1c level [≥6.5])

	TOTAL KPSC Region	KPSC Region (20-30 Miles of Pasadena Facility)				
6 Month Data	***Total # Patients***	***Total # Patients***	***Patients Needing Interpreter***	***English speaking Patients***	***NOD Confirmed Patients***	***Need confirmation***
TOTAL	**3698**	**1583**	**393**	**1191**	**203**	**1028**

Reasonable expectation – patient pool increases by 7-8 fold

- Including Spanish speakers
- Eliminating confirmatory blood test

Renewal of CPDPC Consortium

Goals

- Maintain infrastructure and core facilities
- Provide a platform for clinically relevant studies using the biospecimens and cohorts accrued during the first grant cycle
- Complete enrollment and collection of biospecimens in the prospective cohort studies
- Follow-up to assess clinical outcomes

Proposed NCI Budget

- $2.3M / year for supporting infrastructure: $1.8M for 9 U01 grants for Clinical Centers and $500K for 1 U01 grant for Coordinating Center (institutional/personnel costs)

- $11.5M TOTAL for 5 years

Thank you.

Questions?

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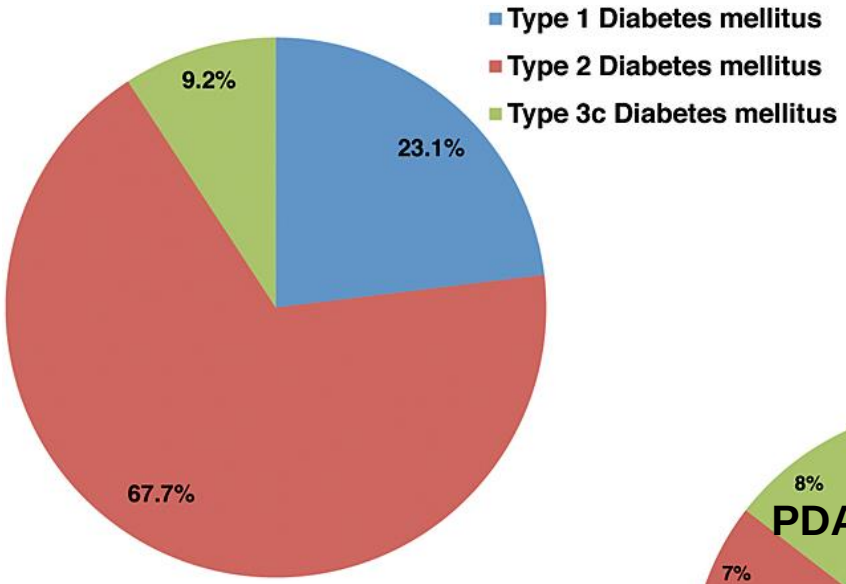
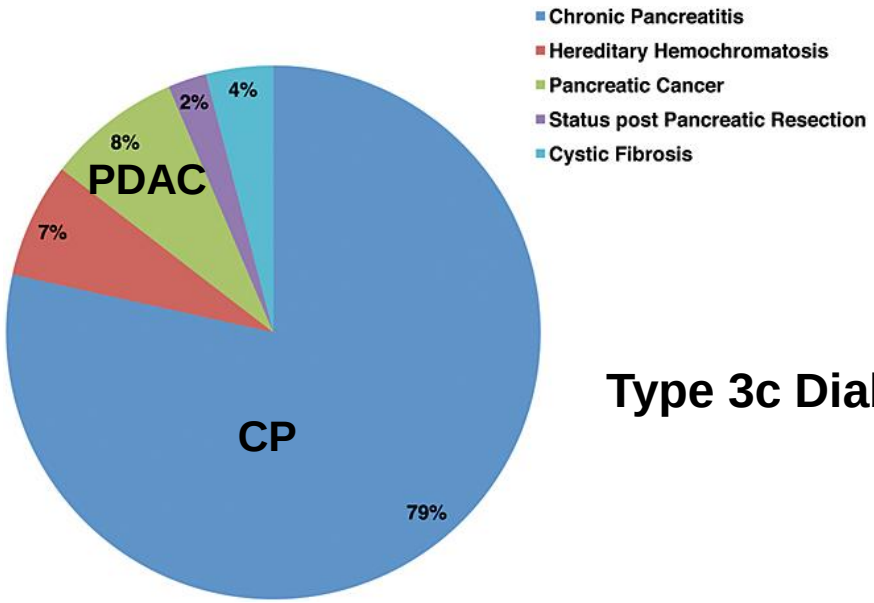
www.cancer.gov/espanol

CPDPC Generation of Projects and Ideas

- SC identifies, deliberates and decides on projects
- Projects are additionally vetted by experts outside the consortium
- Initial funding ($270K Direct Costs) supports personnel, infrastructure, and institutional costs to participate in the consortium
- Initial funding does not include the funding for consortium-wide projects
- Projects are funded by Administrative Supplements from NCI and NIDDK

Types of Diabetes





Type 3c Diabetes

Diabetes Metab Res Rev 2012;28:338.

Ancillary Studies Related to NOD

- NOD is a high-risk cohort for PDAC *Gastroenterology* 2018;3:730.
- Minority populations at increased risk of PDAC in NOD (Multi-ethnic cohort) *JNCI* 2018 Jun 18
- Fasting Blood Glucose Starts Rising 30-36 months before PDAC Diagnosis *Gastroenterology* 2018;155;490.
- Model enriches NOD for PDAC: The ENDPAC score *Gastroenterology* 2018;3:730-39

Significance of PDAC Early Detection

Compelling needs for PDAC

- A strategy to detect PDAC at a potentially curable stage
- A means to identify high-risk groups for preventive interventions

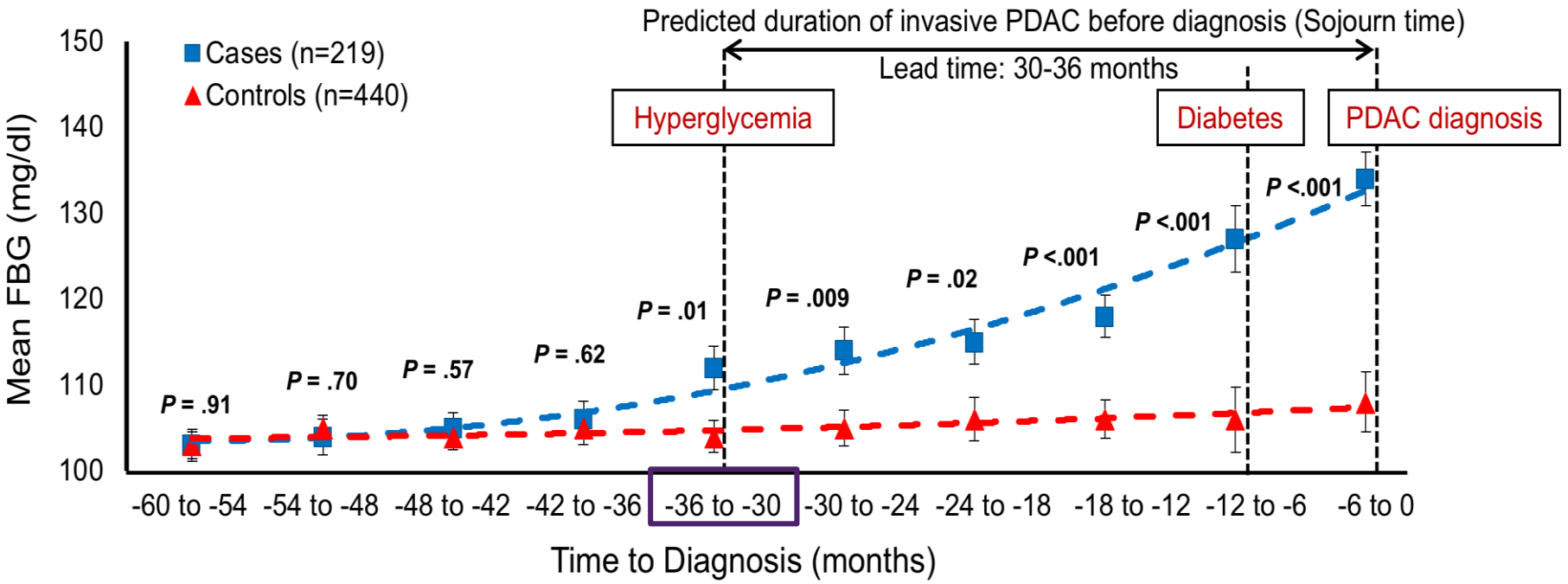
Principal **challenges** to developing an early detection program for sporadic PDAC:

- Lack of an identified high risk group for sporadic PDAC
- Limited availability of high quality biospecimens from pre-symptomatic subjects
- Dearth of biomarkers of early PDAC
- Inability of imaging techniques to identify early PDAC
- Inadequate information about progression rates of preneoplastic lesions → under- and over-treatment

New-Onset Diabetes (NOD) Cohort Assembly: Principles

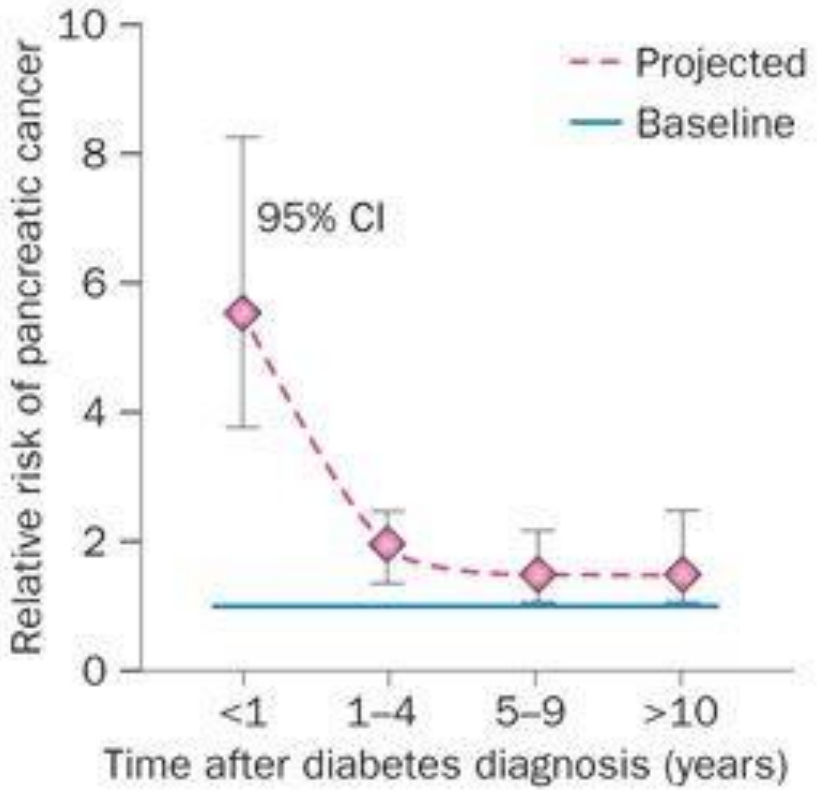
- Identify NOD in primary care settings
  - DM in PDAC is not usually managed by endocrinologists
- Identify NOD as close to its onset as possible
  - Median interval between meeting criteria for DM and PDAC diagnosis is ~13 months
  - 64% of DM-associated PDAC occur within 1 year of DM onset
- Use standardized biochemical criteria for diagnosis rather than physician diagnosis
  - Physician diagnosis could be delayed by months to years

New-Onset Diabetes and Hyperglycemia – Precede PDAC Diagnosis



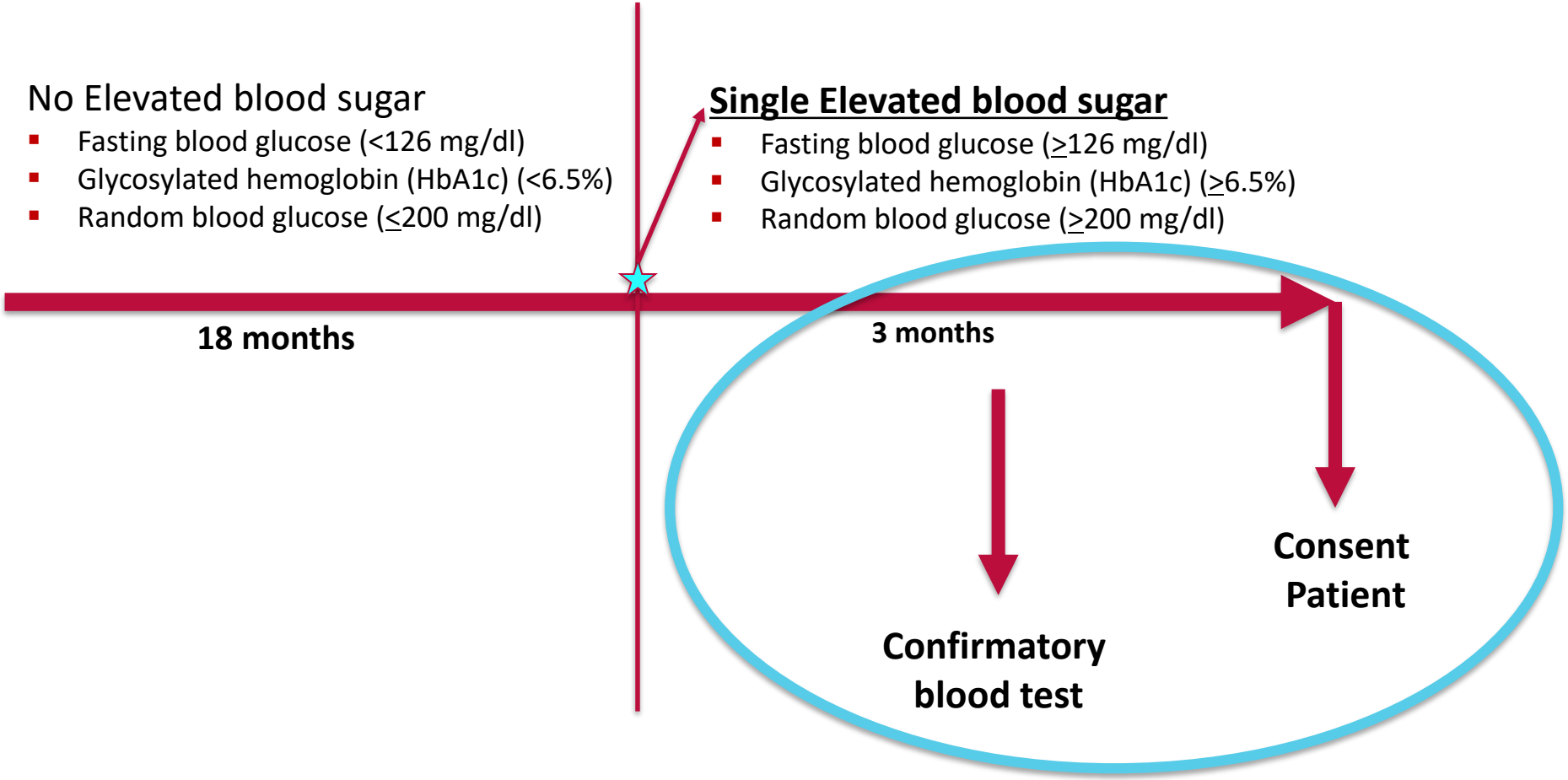
Gastroenterology 2018;155;490

Risk of PDAC in New-Onset Diabetes – 6-8 fold Higher



Nat Rev Gastroenterol Hepatol. 2013;10(7):423-33.

Eligibility Criteria



Biospecimen Collection

NOD Cohort Timeline