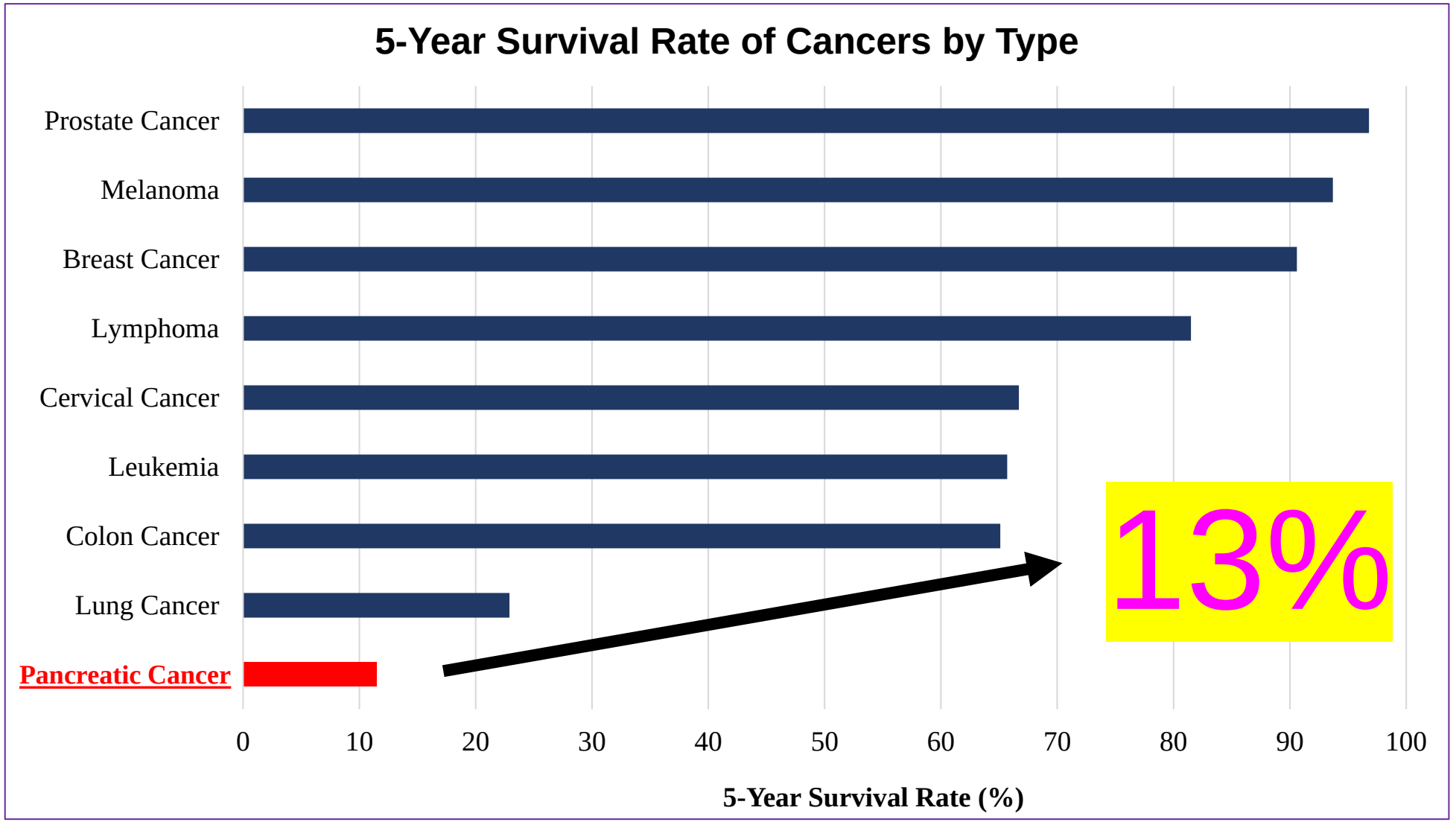
UC San Diego
Moores Cancer Center

Pancreatic Surveillance in High-Risk Individuals

Diane M. Simeone, M.D.
Director, Moores Cancer Center
Chugai Pharmaceutical Chair of Cancer
Professor of Surgery
UC San Diego Health

UC San Diego
Moores Cancer Center



https://seer.cancer.gov/statfacts/

UC San Diego
Moores Cancer Center

Increasing Incidence of Pancreatic Adenocarcinoma

In the past 2 decades, there has been a doubling of PC cases globally.

1990	196,000
2017	441,000

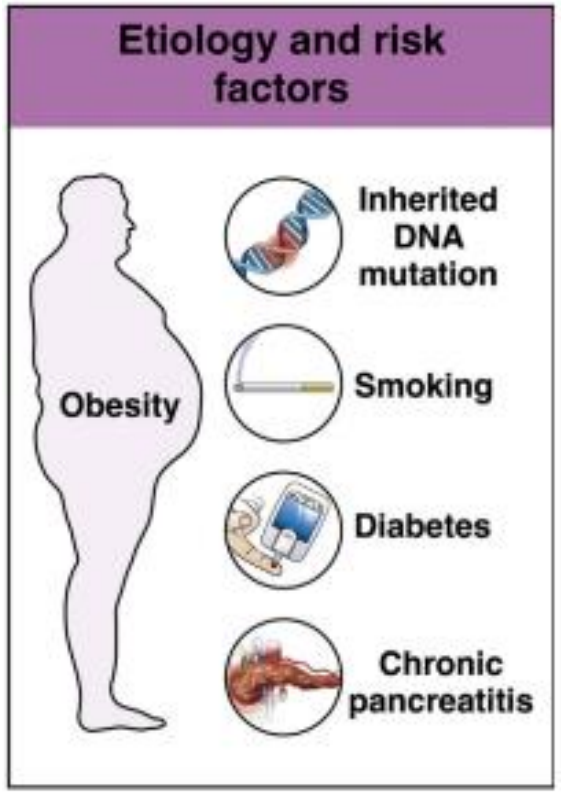
GBD 2017 Lancet Gastroenterol Hepatol 2019; 4: 934-47

The incidence rate for PC in the U.S. has increased by 1% per year since 2000.

ACS Cancer Facts and Figures 2022

UC San Diego
Moores Cancer Center

Risk Factors Linked to Pancreatic Cancer



Smoking
Obesity
Heavy alcohol use
Diabetes
Pancreatitis

For all of these, the relative risk above the general population is generally below 2.0

Race: Blacks/Whites 15.9/13.4 per 100,000 people
Age-adjusted incidence rate (peak in 6-7th decade)

UC San Diego
Moores Cancer Center

We still don't really understand:

a) Who is at risk for pancreatic cancer?
b) What is the level of risk?
c) What we can do about it to help patients,
both in terms of early detection and prevention

Of all the things we do, early detection and prevention are probably the **most important** to changing survival in PDA

Survival for Stage 1A pancreatic cancer: 83.7%

Blackford AL et al. J Natl Cancer Inst 2020

UC San Diego
Moores Cancer Center

Does Screening Work?

Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers

Hans Vasen, Isaura Ibrahim, Carmen Guillen Ponce, Emily P. Slater, Elvira Matthäi, Alfredo Carrato, Julie Earl, Kristin Robbers, Anneke M. van Mil, Thomas Potjer, Bert A. Bonsing, Wouter H. de Vos tot Nederveen Cappel, Wilma Bergman, Martin Wasser, Hans Morreau, Günter Klöppel, Christoph Schicker, Martin Steinkamp, Jens Figiel, Irene Esposito, Evelina Mocci, Enrique Vazquez-Sequeiros, Alfonso Sanjuanbenito, Maria Muñoz-Beltran, José Montans, Peter Langer, Volker Fendrich, and Detlef K. Bartsch

Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance

Marcia Irene Canto,[1,2,*] **Jose Alejandro Almario**,[1,3,*] Richard D. Schulick,[4] Charles J. Yeo,[5] Alison Klein,[2] Amanda Blackford,[2] Eun Ji Shin,[1] Abanti Sanyal,[6] Gayane Yenokyan,[6] Anne Marie Lennon,[1] Ihab R. Kamel,[7] Elliot K. Fishman,[7] Christopher Wolfgang,[8] Matthew Weiss,[8] Ralph H. Hruban,[3] and Michael Goggins[1,3]

Long-term yield of pancreatic cancer surveillance in high-risk individuals

Kasper A Overbeek [1], Iris J M Levink [1], Brechtje D M Koopmann [1], Femme Harinck [1], Ingrid C A W Konings [1], Margreet G E M Ausems [2], Anja Wagner [3], Paul Fockens [4], Casper H van Eijck [5], Bas Groot Koerkamp [5], Olivier R C Busch [6], Marc G Besselink [6], Barbara A J Bastiaansen [4], Lydi M J W van Driel [1], Nicole S Erler [7], Frank P Vleggaar [8], Jan-Werner Poley [1], Djuna L Cahen [1], Jeanin E van Hooft [4], Marco J Bruno [1] on behalf of the Dutch Familial Pancreatic Cancer Surveillance Study Group

The Multicenter Cancer of Pancreas Screening Study: Impact on Stage and Survival

Mohamad Dbouk, MD[1]; Bryson W. Katona, MD[2]; Randall E. Brand, MD[3]; Amitabh Chak, MD, PhD[4]; Sapna Syngal, MD[5,6]; James J. Farrell, MD[7]; Fay Kastrinos, MD[8]; Elena M. Stoffel, MD[9]; Amanda L. Blackford, MS[10]; Anil K. Rustgi, MD, PhD[7]; Beth Dudley, MS[3]; Linda S. Lee, MD[5,6]; Ankit Chhoda, MD[7]; Richard Kwon, MD[9]; Gregory G. Ginsberg, MD[2]; Alison P. Klein, PhD, MHS[1,10,11,12]; Ihab Kamel, MD[10,13]; Ralph H. Hruban, MD[1,10]; Jin He, MD, PhD[10,14]; Eun Ji Shin, MD, PhD[11]; Anne Marie Lennon, MB, PhD[10,11,13,14]; Marcia Irene Canto, MD, MHS[10,11]; and Michael Goggins, MB, MD[1,10,11]

Pancreatic Cancer Surveillance in Carriers of a Germline *CDKN2A* Pathogenic Variant: Yield and Outcomes of a 20-Year Prospective Follow-Up

Derk C.F. Klatte, MD[1]; Bas Boekestijn, MD[2]; Martin N.J.M. Wasser, MD, PhD[2]; Shirin Feshtali Shahbazi, MD[2]; Isaura S. Ibrahim, MD[1]; J. Sven D. Mieog, MD, PhD[3]; Saskia A.C. Luelmo, MD[4]; Hans Morreau, MD, PhD[5]; Thomas P. Potjer, MD, PhD[6]; Akin Inderson, MD[1]; Jurjen J. Boonstra, MD, PhD[1]; Friedo W. Dekker, PhD[7]; Hans F.A. Vasen, MD, PhD[1]; Jeanin E. van Hooft, MD, PhD, MBA[1]; Bert A. Bonsing, MD, PhD[2]; and Monique E. van Leerdam, MD, PhD[1,8]

Surveillance for pancreatic cancer in high-risk individuals

I C A W Konings ✉, M I Canto, J A Almario, F Harinck, P Saxena, A L Lucas, F Kastrinos, D C Whitcomb, R E Brand, J Lachter, G Malleo, S Paiella, S Syngal, J R Saltzman, E M Stoffel, J E Hooft, R H Hruban, J W Poley, P Fockens, M G Goggins, M J Bruno on behalf of the International CAncer of the Pancreas Screening (CAPS) Consortium

UC San Diego
Moores Cancer Center

Data Suggests Screening Works, but Studies have Limitations

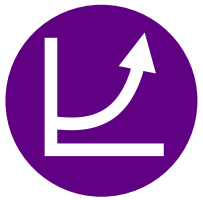
- Recent studies (2017-2023) suggest higher rates of resectable cancers (70-90%), and benefit in 5 year survival (up to 73%)

- Challenges for studies to date:
  - small sample sizes and overlapping publications
  - number of cancers relatively small
  - follow-up short
  - incomplete genetic testing
  - lack of standard approaches, including imaging
  - likely to be gene-specific differences but difficult to sort out
  - overall risk stratification remains crude

It is for this reason we established a new strategy……

What is PRECEDE?

The PRECEDE Consortium is a **collaborative research effort** by 55 academic medical centers (and growing) around the world. UC San Diego is the academic coordinating center.



Its mission is to transform the landscape of pancreatic cancer risk assessment, early detection, **and** prevention and to **increase the 5-year survival rate from 10 to 50% within the next 10 years**.

It is the **largest effort of its kind**, using a novel model of data sharing across well-known medical centers around the world. By combining data and samples, we will more effectively and quickly identify methods of early detection.

Specific Aims

- To generate proof of the importance of high-risk surveillance programs for PDA for both clinicians and health authorities through longitudinal follow up of clinical outcomes.
- To establish evidence-based practice standards for genetic testing and surveillance in individuals with family history of PDA and carriers of gene mutations linked to PDA risk.
- To study modifiers of risk, including genetic and environmental factors, evaluate disease penetrance, and quantify cancer risk in families with PDA and/or carriers of gene mutations linked to PDA risk.
- To identify new pancreatic cancer susceptibility genes.
- To develop comprehensive risk models to estimate PDA risk and guide clinical decision making.
- To develop and/or validate biomarker assays (blood test/imaging/AI) that detects PDA at its **earliest** stage.

Study Design

- The PRECEDE Study will collect standardized data and samples from individuals identified as being at high risk for developing pancreatic cancer. Plan: enroll ≥**10,000** high risk individuals (at 100+ centers) for a 10 year longitudinal study.

- Participating centers must meet minimum requirements to be a part of PRECEDE. Each center must have:
  - At least 75 patients/year who are at increased risk and under surveillance
  - A multidisciplinary team, including GI, advanced endoscopy, surgery and genetics
  - Infrastructure for data and biosample collection
  - Central IRB for US sites
  - **Can't join unless you agree to share data and samples**

PRECEDE Enrollment: 7295 pts (thus far)

1st site open: May 2020

Central IRB in place for all US sites (sites gradually joining since 2020)

Arbor Research assists each site with
a) Sharing requirements to join
b) Getting regulatory documents in place
c) Onboarding for data/biosample collection

Biosamples are barcoded and stored locally until shipment to Azenta central biorepository:
a) US: Indianapolis, Cleveland
b) Canada: Montreal
c) Germany: Griesheim
d) Asia: Singapore

Study Cohorts

Cohort 1 (screening begins age 50 or 10 years younger than earliest PDAC in family unless otherwise noted)

1. 2+ relatives with PDAC; 2 affected are first degree related; at least 1 affected is first degree related to subject
2. 2 affected first degree relatives with PDAC
3. *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM* + AND 1 relative with PDAC
4. *CDKN2A*+; **age 40+**; Peutz-Jegher syndrome *STK11*+; **age 35+**; Hereditary pancreatitis *PRSS1*+; **age 40+**

Cohort 2

1. *ATM, BRCA1, BRCA2,* or *PALB2* +
2. 2+ relatives with PDAC not meeting FPC criteria
3. 1 first degree relative with PDAC ≤ age 45

Sawhney et al, ASGE Guidelines on screening for pancreatic cancer in individuals with genetic suspectibility. Gastrointest Endosc 2022.
Rationale: Most with PGV dx with PDA have no family history of PDA

Cohort 3

Individual meeting criteria for Cohorts 1 or 2 EXCEPT age (i.e. too young to qualify for screening)

Cohort 4

Individuals with a single first degree relative with PDAC (NCCN guidelines: germline testing in this group)

Study Cohorts

Cohort 5
Family members and healthy controls invited to donate a biosample (e.g. blood, saliva) for discovery studies

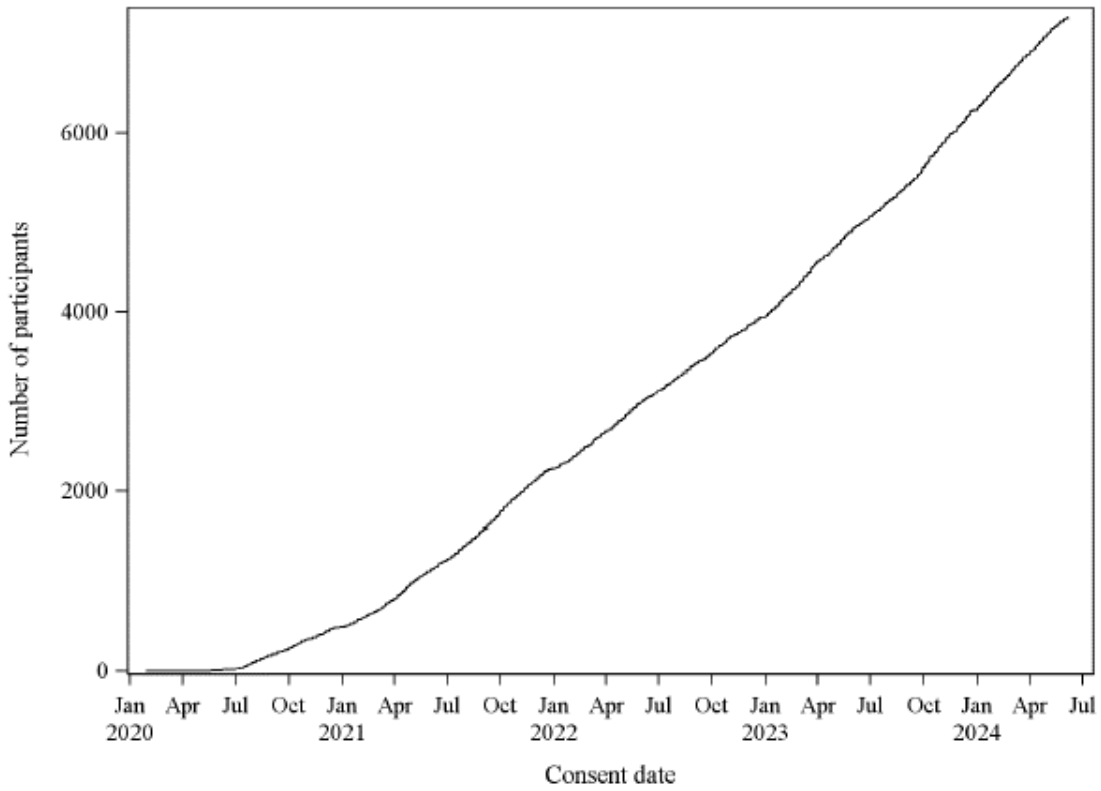
Cohort 6a (estimated to be 1200 individuals through the course of the study)
Individuals initially enrolled in Cohorts 1-3 who have ***progressed to PDAC*** while under surveillance.

Cohort 6b
Individuals ***with a personal history of PDAC*** meeting any of the following criteria:
1. Family history includes at least one first degree relative with PDAC, or 2 relatives with PDAC who are first degree related to each other
2. Personal or family history of a pathogenic or likely pathogenic germline variant in *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*,*PMS2*, *PRSS1*, *STK11*
3. Diagnosed ≤ age 45

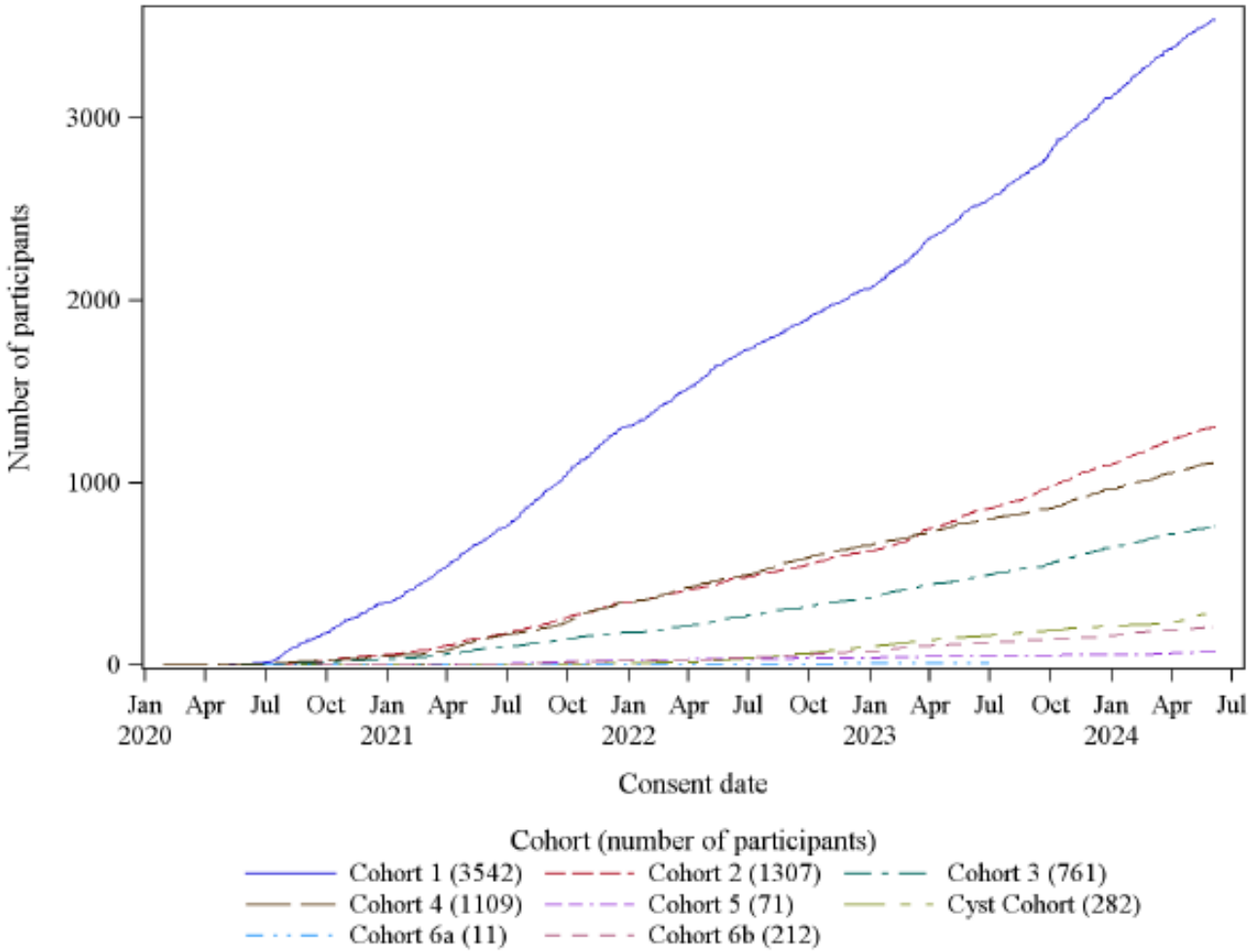
Cyst Cohort
Individuals with a pancreatic cystic neoplasm not meeting any criteria for Cohorts 1-3 or 6 (no known family history of PDAC, no known pathogenic germline variants linked to PDAC risk)
(focus is on cysts that are resected, and those ≥ 2.5 cm in diameter or with MPD ≥ 6 mm)

Cohort Enrollment

Cumulative Enrollment



Enrollment by Cohort (Largest is Cohort 1)



Current enrollment 7295 pts

Enrolling 160-170 pts per month

PRECEDE Consortium Organization

Executive Committee

Diane Simeone, MD (UCSD)-Chair
Randy Brand, MD (Univ Pittsburgh)
Jessica Everett, MS (UCSD)
Fay Kastrinos, MD (Columbia)
George Zogopoulos (McGill)
Aimee Lucas, MD (Mt Sinai)
Sonia Kupfer, MD (Univ Chicago)
Giovanni Parmigiani, PhD (Harvard)
Rosie Sears, PhD (OHSU)

Committees

- MODIFIABLE RISK FACTORS
- GENOMICS
- IMAGING
- BIOSTATS/ INFORMATICS
- BIOSAMPLES & BIOMARKERS
- CLINICAL GENETICS
- DIVERSITY, EQUITY, & INCLUSION
- CANCER OUTCOMES
- ANCILLARY RESEARCH STUDIES
- PUBLICATIONS

Data Coordinating Center

ARBOR RESEARCH

Setting New Standards for the Field

A more organized approach to the early detection of pancreatic cancer. *Gastroenterology* 2021; 161; 1751-1757.

Standardization of Endoscopic Ultrasound (EUS) Imaging and Reporting in High Risk Individuals of Pancreatic Adenocarcinoma: Consensus Statement of the Pancreatic Cancer Early Detection Consortium (PRECEDE). *Gastrointest Endoscopy* 2022; 95:723-732.

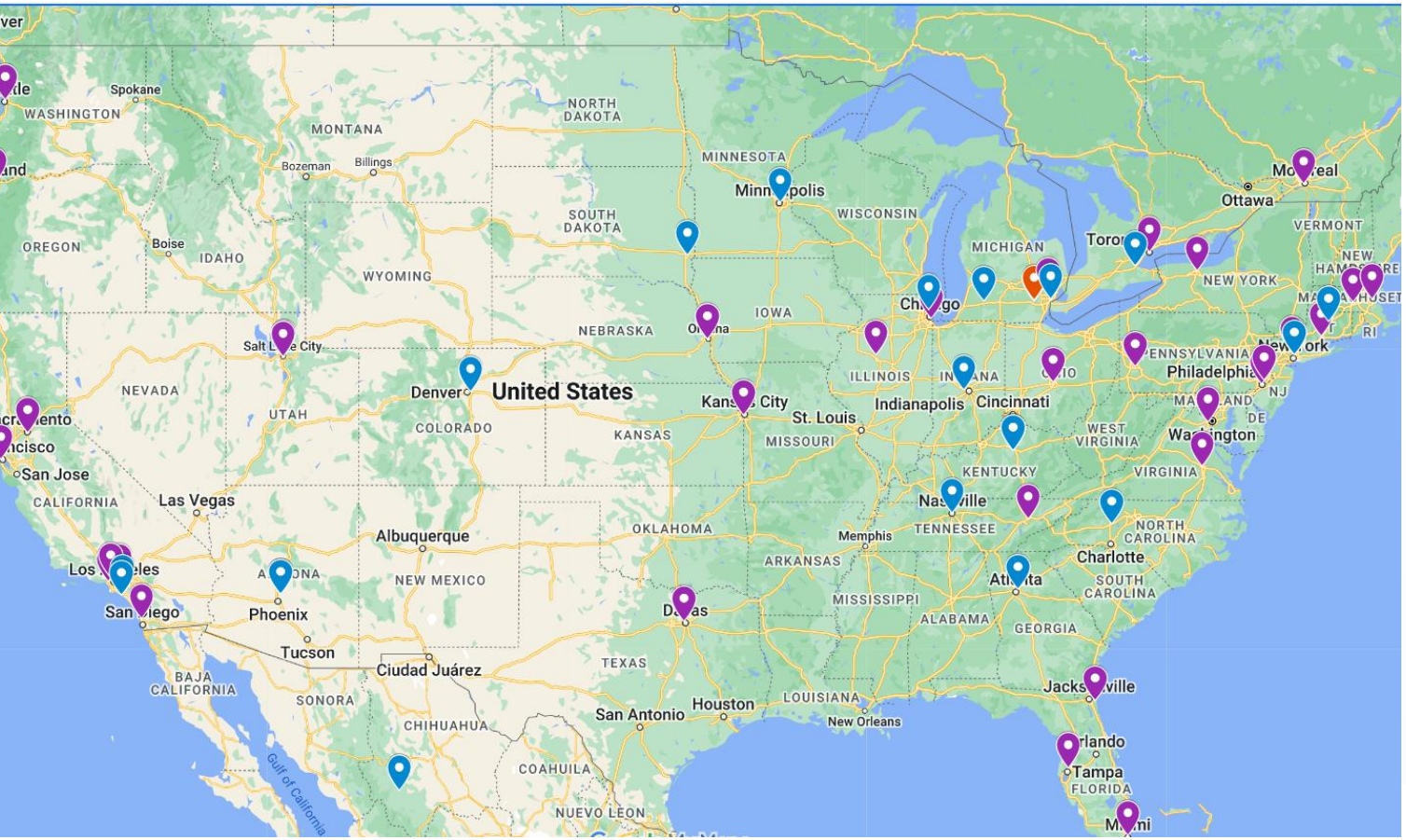
Standardization of MR Imaging and Reporting in Individuals at Elevated Risk of Pancreatic Adenocarcinoma: Consensus Statement of the Pancreatic Cancer Early Detection (PRECEDE) Consortium. *Am J Roentgenol*. 2022; 219:903-914.

Racial, ethnic, and sex-based disparities among high-risk individuals undergoing pancreatic cancer surveillance. *Cancer Prev Res* 2023; 16: 343-352.

The Pancreatic Cancer Early Detection (PRECEDE) Study is a Global Initiative to Drive Early Detection: Baseline Imaging Findings in High-Risk Individuals. *J Natl Compr Canc Netw.* 2024; 22:158-166.

Areas of Standardization	Elements
Family history	Pedigree templates (e.g. Progeny)
Germline genetic testing	Minimum gene panel and plan for updating
Modifiable risk factors	Diabetes, obesity, pancreatitis, smoking, alcohol use (quantify)
Imaging	Using standardized templates
Biosample collection	SOPs in place

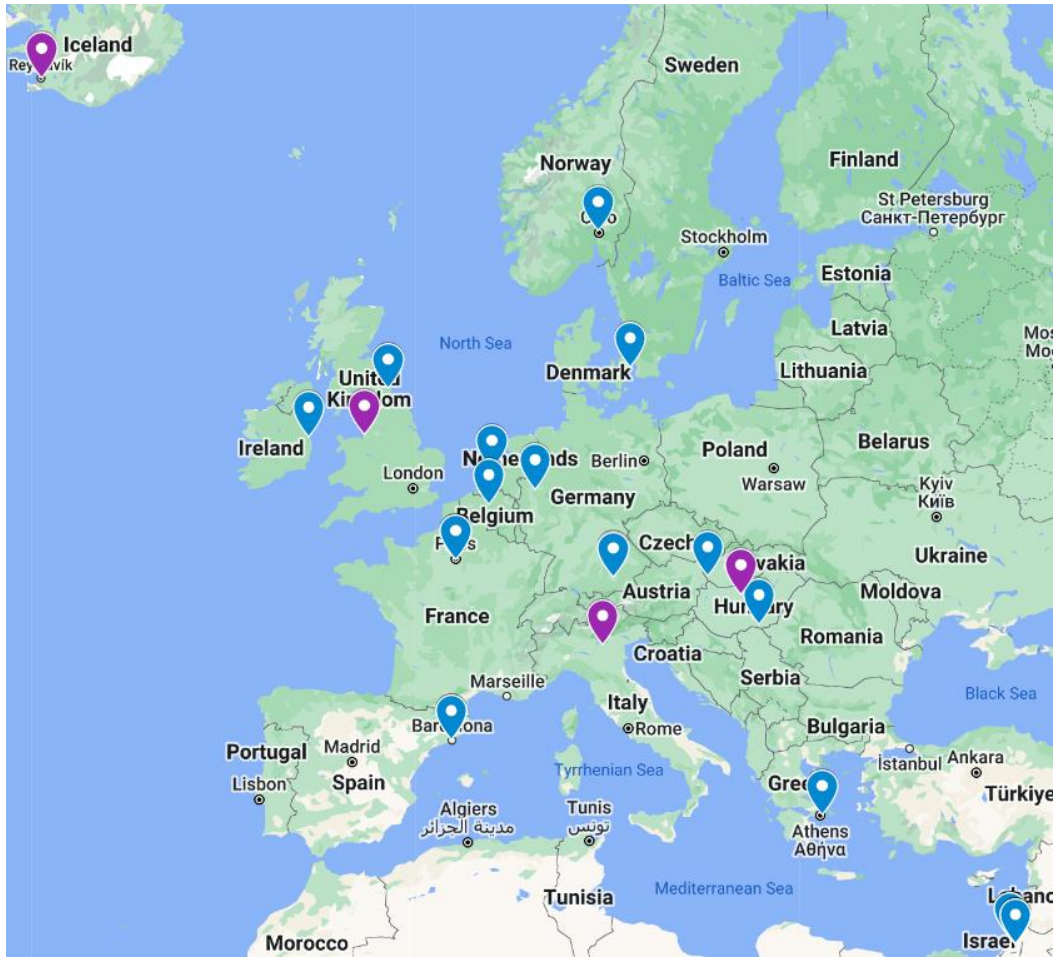
PRECEDE Consortium Sites: US/Canada

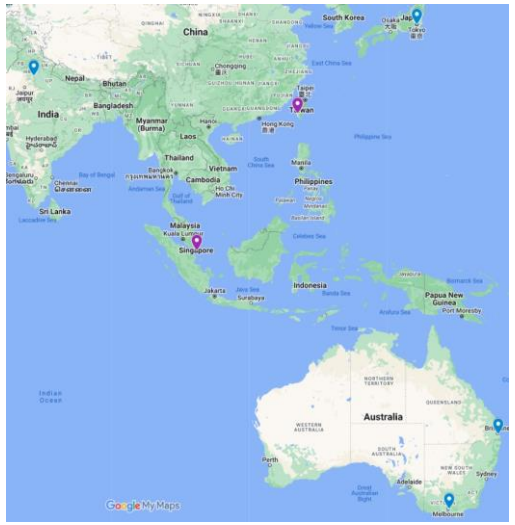


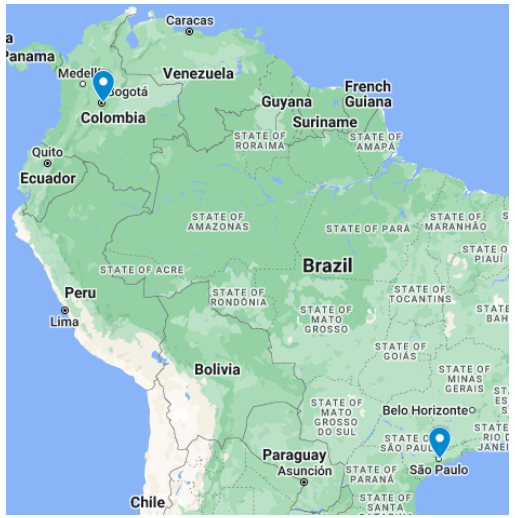
Purple = actively enrolling; Blue = being onboarded
Note: additional sites being on-boarded

- Avera Cancer Institute – Sioux Falls, SD
- Beaumont Health – Detroit, MI
- British Columbia Cancer Agency – Vancouver, Canada
- Cedars Sinai – Los Angeles, CA
- City of Hope – Duarte, CA
- Columbia University – New York, NY
- Emory University – Atlanta, GA
- Fox Chase Cancer Center – Philadelphia, PA
- Hamilton Health Sciences McMaster University
- Hartford General – Hartford, CT
- Henry Ford Health System – Detroit, MI
- Hoag Hospital – Newport Beach, CA
- Honor Health – Phoenix, AZ
- Huntsman Cancer Institute – Salt Lake City, UT
- Illinois CancerCare- Peoria IL
- Indiana University – Indianapolis, IN
- Inova Schar Cancer Institute – Falls Church, VA
- Intermountain Healthcare – Salt Lake City, UT
- John Theurer Cancer Center – Hackensack, NJ
- Mass General/Harvard – Boston, MA
- Mayo Clinic – Jacksonville, FL
- Mayo Arizona – Phoenix, AZ
- McGill University – Montreal, Canada
- Moffitt Cancer Center – Tampa, FL
- Mount Sinai – New York, NY
- Northshore – Evanston, IL
- Ohio State University – Columbus, OH
- Oregon Health & Science – Portland, OR
- Penn Medicine – Philadelphia, PA
- Piedmont Healthcare – Statesville, NC
- Providence Saint Joseph Medical Center – Burbank, C
- University of California Davis – Sacramento, CA
- University of California Irvine – Orange, CA
- University of Chicago – Chicago, IL
- University of Colorado Cancer Center – Aurora, CO
- University of Kansas – Kansas City, KS
- University of Kentucky – Lexington, KY
- University of Massachusetts – Worcester, MA
- University of Miami – Miami, FL
- University of Michigan – Ann Arbor, MI
- University of Minnesota -- Minneapolis, MN
- University of Rochester – Rochester, NY
- University of Tennessee – Knoxville, TN
- University of Texas Southwestern – Dallas, TX
- University of Toronto/Mt. Sinai – Toronto, Canada
- University of Washington/SCCA – Seattle, WA
- UNMC – Omaha, NE
- UPMC/Pittsburgh – Pittsburgh, PA
- UCLA – Los Angeles, CA
- UCSD – San Diego, CA
- UCSF – San Francisco, CA
- Vanderbilt – Nashville, TN
- Virginia Commonwealth University – Richmond, VA
- Weill Cornell Medicine – New York, NY
- West Michigan Cancer Center – Kalamazoo, MI
- Yale – New Haven, CT

PRECEDE Consortium: International Sites







Purple = actively enrolling; Blue = being onboarded
Note: additional sites being on-boarded

Open to enrollment:

- Landspitali University Hospital - Iceland
- National Cancer Center of Singapore - Singapore
- National Cheng Kung University Hospital – Taiwan
- Sheba Medical Center – Israel
- University of Verona – Italy
- University of Liverpool – England

In approval process:

- Centro de Tratamiento e Investigación sobre cáncer Luis Carlos Sarmiento Angulo (CTIC) - Colombia
- Copenhagen University – Denmark
- Epworth Healthcare – Australia
- Hadassah Hebrew University Medical Center – Israel
- Hospital Clinic Barcelona – Spain
- Hospital Paul Brousse – France
- Hospital Sirio Libanes – Brazil
- Ichilov Tel Aviv Medical Center – Israel
- Leiden University Medical Center- Netherlands
- Max Healthcare Institute – India
- Medical University of Munich – Germany
- National Cancer Center – Japan
- National Cancer Institute of Brastislava -- Slovak Republick
- Newcastle University – England
- Oslo University Hospital – Norway
- Rabin Medical Center – Israel
- Semmelweis University -- Hungary
- Sha'are Zedek Medical Center (Jerusalem) – Israel
- Trinity Dublin – Ireland
- University Hospital Essen – Germany
- University of Queensland – Australia
- UZ Brussel – Brussels, Belgium

The PRECEDE Platform Enables Projects by Leading Scientific/Clinical Teams

Scientific/clinical team projects:

Genomic discovery
Early detection biomarkers
Machine learning/AI
Polygenic risk scores
Risk Modeling
Screening in underserved populations
Biology of PDAC development
Environmental risk
Prevention strategies

NIH U01: Biomarker Validation in Pancreatic Cystic Neoplasms

4 PRECEDE Sites, D. Simeone (PI)

Test biomarker (blood and cyst fluid) and multi-variable model performance for detection of early cancer in a prospective cohort of patients with pancreatic cystic neoplasms undergoing surgical resection

Examine biomarker performance and multi-variable model performance for detection of early cancer in a prospective cohort of patients with larger pancreatic cystic neoplasms under serial surveillance

PO1: Submission Date Sept 2024

Overall Goals

1) Develop and validate a genomic risk stratification strategy for PDAC for those at heritable risk of pancreatic cancer

2) Validate blood-based biomarkers using a prospective specimen collection, retrospective blinded evaluation approach

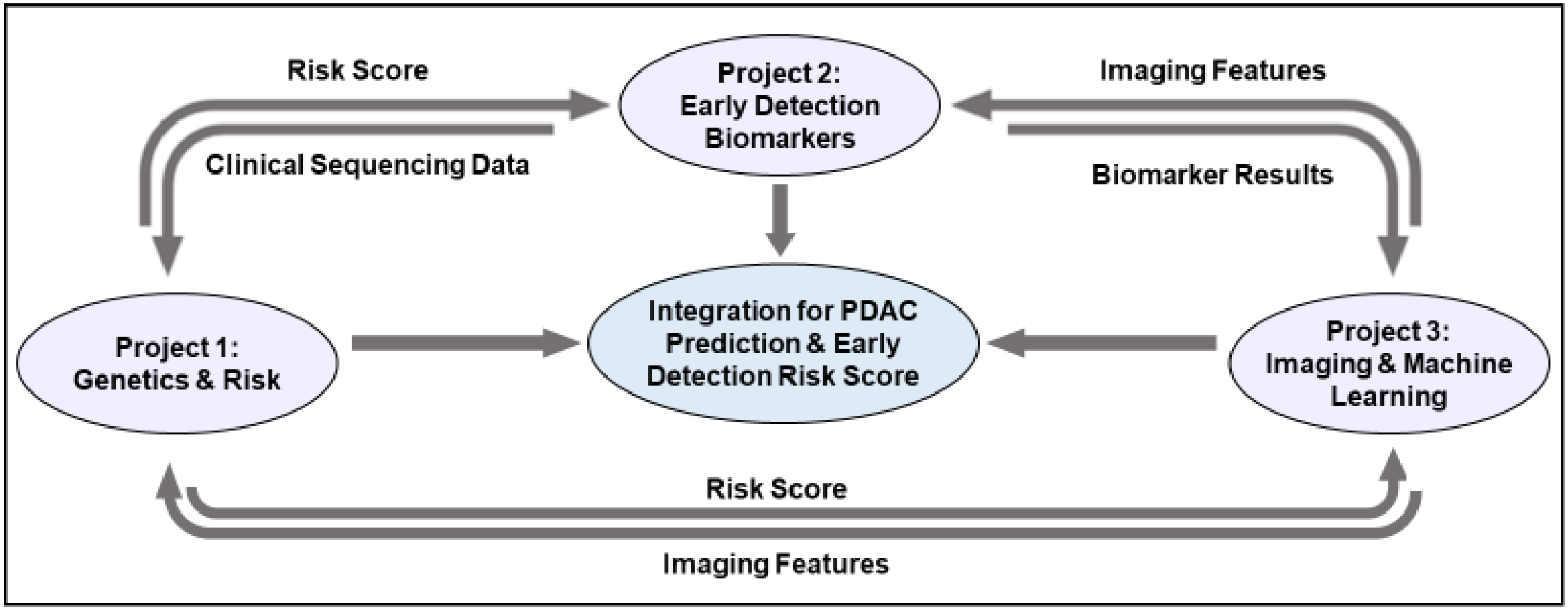
3) Collect and curate a large scale repository of MR images to drive development and testing of machine learning models for PDAC detection and prediction

4) Leverage multi-modal data integration to increase robustness of prediction models

(18 PRECEDE Sites)

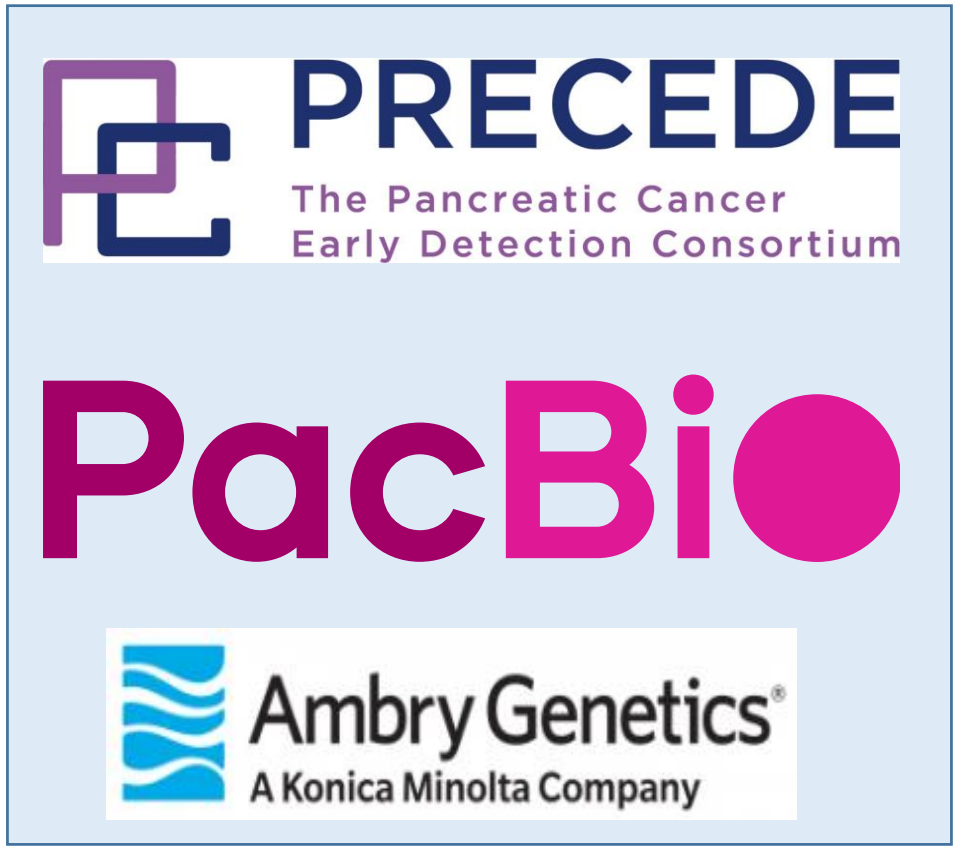
Addressing Early Detection Challenges

Determining Risk of Developing PDAC → Finding & Validating PDAC Detection Biomarkers → Developing Accurate Technologies for Early Detection



Pinpointing heritability factors is fundamental for the prevention and early detection of cancer.

Enhancing Early Detection: PRECEDE consortium and PacBio Collaborate on HiFi whole genome Sequencing for Unlocking Missing Heritability.



In 85% of families with familial pancreatic cancer, the genetic cause is unknown

Long read sequencing has the potential to more comprehensively identify novel genetic causes of PDA

Pilot Project of 200 PDA pts

Candidates: Pancreatic Cancer Patients in the PRECEDE Study with Familial Pancreatic Cancer in whom standard germline genetic testing is negative

First set of samples being analyzed now using the PacBio Human Variant Pipeline

UC San Diego
Moores Cancer Center

Summary

The PRECEDE Consortium is a large scale platform with an innovative data sharing strategy designed to ultimately lead to advances in overall PDA survival.

This new cooperative model better aligns key stakeholders (patients, families, researchers, clinicians, foundations, tech sector, pharma, FDA) to increase the pace and scale in we can impact change.

The data required to define if screening (and in whom) saves lives will be generated from this platform, as will data to refine indications for who and how we screen.

Acknowledgements

www.precedestudy.org

Collaborators
PRECEDE Sites worldwide
Arbor Research

Trovanow
National Pancreas Foundation
John R. Lewis Legacy Institute
Skipper BioMed
Lets Win

<u>PRECEDE Funding/Support</u>: NIH (PCDC), Trovanow, Ambry Genetics, Realm, Amazon Web Services, Biological Dynamics, Canadian Cancer Society, Project Purple, AFFPC, Sky Foundation, Immunovia, ClearNote Health, Micronoma, Pryor Cashman, myCME, FORCE, Ipsen, Janssen Oncology, GE HealthCare, Boston Scientific, Novartis, PacBio

Moores Cancer Center, UCSD Health
dsimeone@health.ucsd.edu
@MadamSurgeon