

New Platforms Designed to Improve Survival in Pancreatic Cancer

The Ruth C. Brufsky Award Lecture

Diane M. Simeone, M.D.

Laura and Isaac Perlmutter Professor of Surgery
Director, Pancreatic Cancer Center
Associate Director, Perlmutter Cancer Center
NYU Langone Health







Pancreatic Cancer: The Challenge

- Deadliest common cancer
 – a dismal survival rate of 11% and few tools to combat it.
- Projected to become the second leading cause of cancer death in the U.S. by 2030.
- Incidence continues to increase (62,210 cases in U.S. 2022).

Our current approach to making inroads is not adequate

The Surgical Approach to the Disease

- 1) appropriately select operative patients
- 2) optimize therapeutic approaches to achieve negative resection margins
- 3) expand surgical approaches (i.e. vascular resection) to increase benefit to patients
- 4) identify and resect high risk lesions



reflection by Murray Brennan in article about his surgical career in treating pancreatic cancer

If surgery is often not an option, or curative in only a small percentage of patients, and medical therapy largely ineffective, what can we do to help these patients?

The key is a better understanding of the molecular mechanisms of pancreatic cancer development and progression

- -Develop more effective therapeutics
- -Detect the disease early

What's in Our Favor to Make an Impact in Pancreatic Cancer

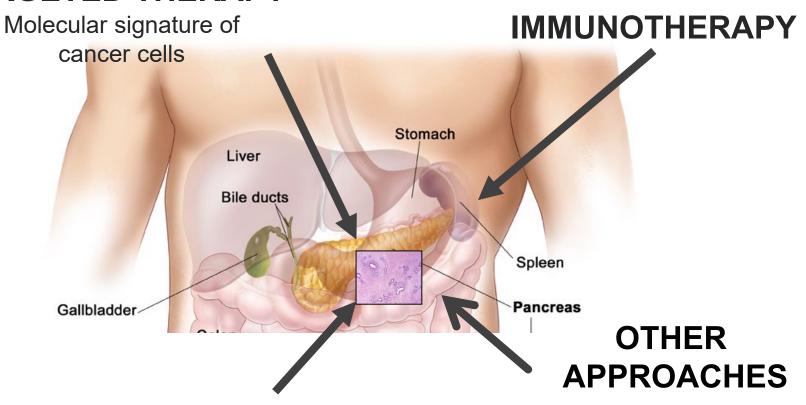
- 1) The scientific community has grown and a more complex understanding of PDA biology exists
- 2) We know pancreatic cancers may respond to specific treatments based on the molecular signature
- 3) increasing number of therapeutic agents are available (and PDA likely need unique combinations of drugs to eradicate it)

Active Areas of Research in Pancreatic Cancer

- Genomics and Precision Medicine
- Targeting Kras
- Activating the dormant immune system
- Metabolic reprogramming of pancreatic cancer
- Understanding molecular mechanisms driving early metastasis
- Intratumoral heterogeneity
- Developing and testing novel therapeutics

Ultimately needs a comprehensive, coordinated approach for drug development

TARGETED THERAPY



STROMAL DISRUPTION

Biologic targets
Cancer stem cells
Metabolic vulnerabilities

Issue: Clinical Trials for PDA

- Hard to move compelling science forward into clinical trials
- Access to therapeutics challenging; funding for trials is limited
- Lack of data sharing
- Predictive biomarkers not developed
- Inadequate study of patient tumor responses to treatment
- Only 4% of PDA patients entering clinical trials

If current strategy inadequate, let's change our strategy

Approached PanCAN 5 years ago

Proposal: Develop a more effective clinical trial apparatus

Why PanCAN: honest broker, serves as fabric and glue for effort

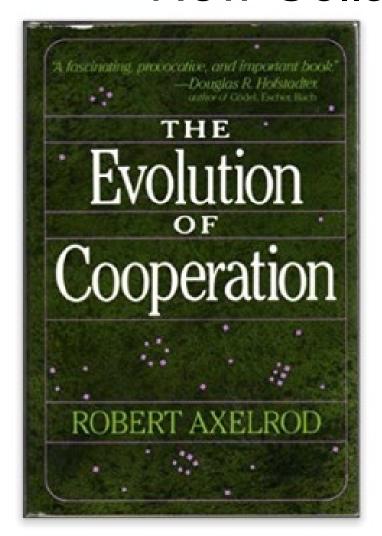


A new clinical trial ecosystem

Basic Tenets of Precision Promise

- novel model of <u>cooperation</u>
- Trial concepts rigorously vetted by expert scientific teams
- adaptive clinical trial design
- deep learning and multiple treatment options for every patient
- open ongoing sharing of data
- flexibility
- establishing pharma consortium as partner
- focus always to put the <u>patient</u> at the center of every decision

New Collaborative Model





Robert Axelrod
Walgreen Professor of the Study of Human Understanding
Professor of Public Policy and Political Science
University of Michigan

National Medal of Science 2014

<u>Axelrod's findings</u>: cooperation is evolutionary advantagious For relationships with repeated encounters, modeling shows player wins the most if elicits cooperation and promotes mutual interest

Adaptive Platform Trial

Single clinical trial to evaluate multiple therapies simultaneously

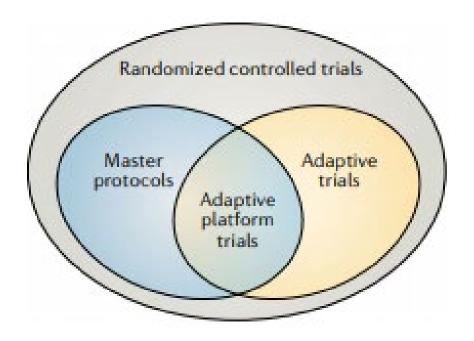
Benefits

- Shared use of control patients across treatment arms
- Assigns better-performing treatments to future patients entering the trial (helps patients <u>on</u> trial, not just <u>after</u> trial)
- Smaller trials than traditional designs
- Shortens the evaluation time for the best therapies
- More effective apparatus to develop and validate biomarkers
- More efficient use of resources (time/money)

OPINION

Adaptive platform trials: definition, design, conduct and reporting considerations

The Adaptive Platform Trials Coalition



Topics Discussed:

- 1) Design elements
- 2) Regulatory issues
- 3) Oversight
- 4) Data sharing (when/how)
- 5) Reporting results
- 6) Financial models

Considerations for Use of an Adaptive Platform Trial



upfront planning and cost to establish trial infrastructure



coordination to satisfy multiple stakeholders

Discussion points

Data sharing plan

Publication strategy

Coordinating regulatory submissions (central IRB)

Funding model

Design Overview of Precision Promise

- First and second line metastatic PDAC patients
- Primary end point: OS
- Many experimental arms screened (Phase 2; Max n=100)
- Two standard of care control arms: 30% (15% each Gem/Abrax and mFFX)
- Possible registration via seamless shift to Phase 3 (Max n=75)
- Response-adaptive randomization incorporated into Master Protocol
- Patients can be re-randomized from 1st line therapy into a 2nd line therapy

Precision Promise Platform

Clinical trial concepts vetted by Arms Selection Committee

Platform trial Phase II – III

deep study of every patient's tumor

Accelerated path to FDA approval

Fast failure of non-effective therapies

Supportive care research, financial models, patient reported outcomes, large scale genomic analyses, comprehensive biomarker discovery

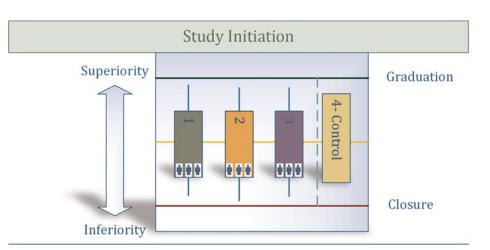
Biomarker Development and Validation Plan

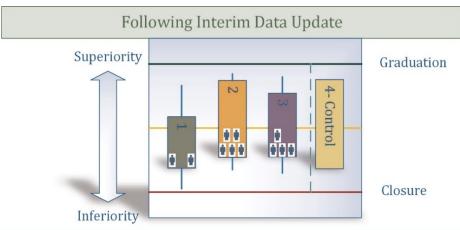
- Standardized Collections
 - Required Tumor Biopsies (baseline, 8 weeks on treatment)
 - Research Blood (cfDNA, serum/plasma: baseline and every 8 weeks)
- Uniform analyses at baseline
 - xT 595 Gene Panel (Tempus), germline testing, transcriptome analysis, immune signature
- Arm specific analyses
 - Prospective to stratify subtypes and evaluate efficacy signal
 - Retrospective to mine mechanism, PD, and response
- Imaging
 - Thin cut abdominal CT and chest CT every 8 weeks
 - Uniform imaging criteria (Imaging committee)

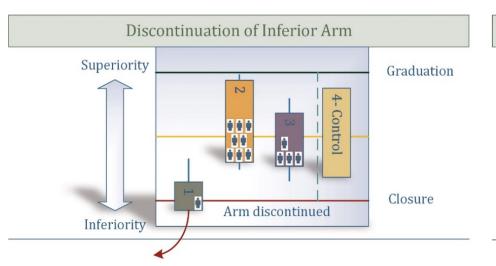
Control Arm(s) for Precision Promise

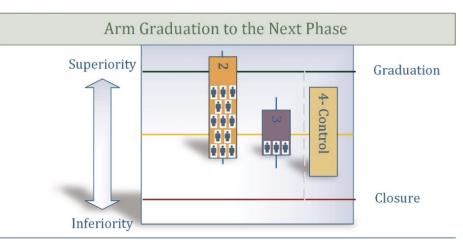
- FDA supportive of experimental arms built with either backbone of Gem/Abraxane (GA) or FOLFIRINOX.
- FDA mandates use of two control arms based on experimental arms with either GA or FOLFIRINOX backbones.
- Both GA and FOLFIRINOX open to all patients (1st and 2nd line)- assignment based on randomization
- 2nd line patients will only be eligible to receive opposite backbone of what they received 1st line

Response Adaptive Randomization

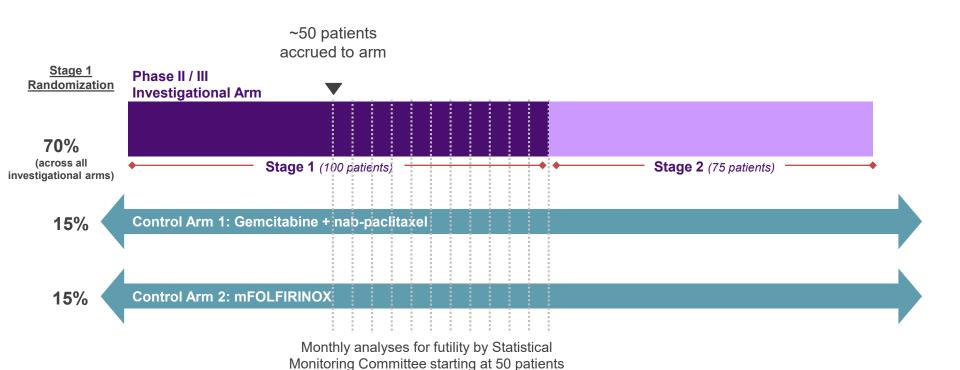




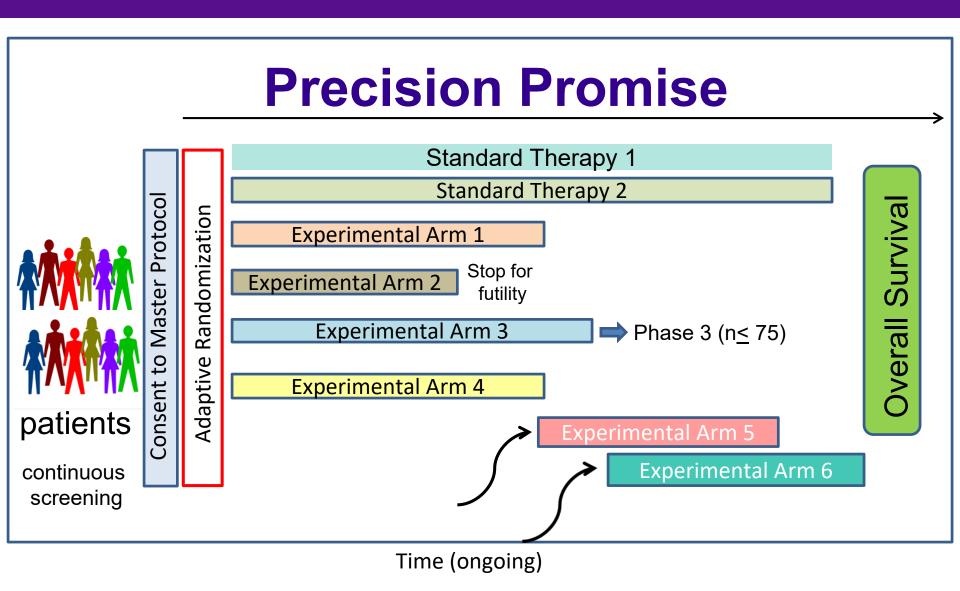




How Does an Investigational Arm Look in Precision Promise?



- Indication: L1 and L2 patients with metastatic PDAC; if the treatment assigned in L1 fails, patient can be re-randomized to a L2 treatment.
- Patient assignment is stratified by line of therapy, so the 3 possible graduating signatures are L1, L2, L1+L2.



Arm 3 graduates to a small focused Phase 3 trial

Re-Randomization of Patients



Don Berry

- Key feature of Precision Promise: multiple options for patient and not just initial therapy
- Re-randomization, with possibility for registration, a significant innovation in clinical trial design and in the field of cancer
- Baseball analogy- wins above average (WAA)
- Clinical trial analogy- survival above control, where
 an experimental arm= player and control=league average or any player

1 of 12 new clinical trial innovations in Precision Promise approved by the FDA!

Pharma Pipeline Critical for Arm Development

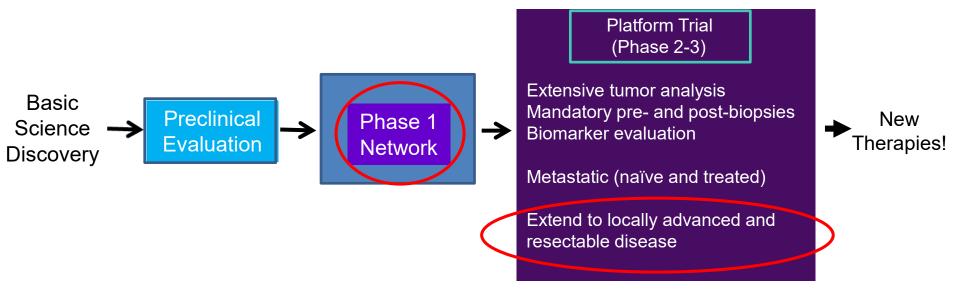
1) Monthly Pipeline Business Report

Company	Physician Champion(s)	Therapy	Mech of Action	Status/Next Steps	

- 2) Development of New Clinical Trial Concepts
- a) Translational and Arms Development Committees
- b) Big Kahuna monthly presentations from each site
- c) Scientific or pharma community
- 3) Add in exciting Phase 1 trials to feed into Phase 2/3 platform
- 4) Help companies complete needed pre-clinical studies to support clinical trial concept (using research base in Precision Promise)

Plan: 6-7 concepts vetted per year to lead to 2 new arms per year

Planned Growth of Precision Promise



Supportive care research, novel financial models, incorporate patient reported outcomes, large scale genomics analysis, comprehensive biomarker analysis

Supportive Care Research

Develop best practices and establish a framework for supportive care interventions

PATIENT REPORTED OUTCOME (PRO) and QOL QUESTIONNAIRES

 Ongoing assessment of quality of life, performance, anorexia/cachexia, patient-reported adverse events and toxicity

ACTIGRAPHY SUB-STUDY

- Daily activity patterns will be tracked/quantified: Fitbit devices
- Changes in activity may be an early marker for disease progression

BODY COMPOSITION ANALYSIS

- Radiological quantification of muscle and fat loss over time
- Opportunity to correlate muscle and fat loss with tumor biology and clinical responses

FREE ACCESS TO PANCREATIC ENZYME REPLACEMENT THERAPY

Precision Promise: a Unique Business Model and Stakeholder Partnerships

Operations

Investigational New Drug (IND) holder:



Contract Research Organization (CRO):

Statistical Design:



Genomics Sequencing and Analysis:



TEMPUS

6 Committees with 150+ Leading Experts **Advising Precision Promise**









Supportive Care Committee

Translational. Research Committee

> 40 companies

Industry Members











































































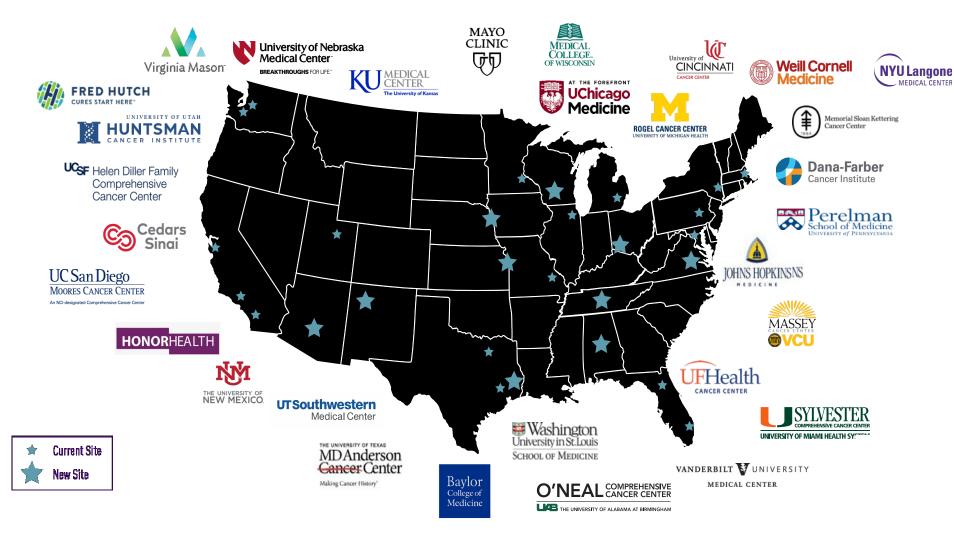








PRECISION PROMISE Clinical Trial Sites



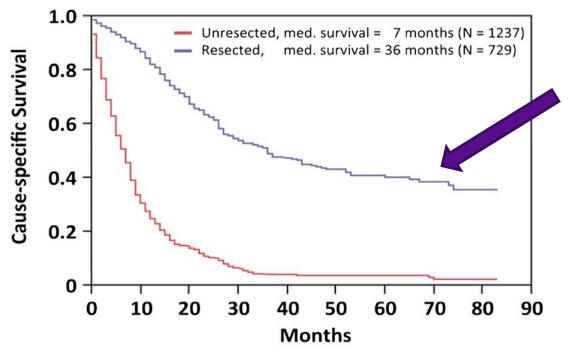
Summary

- 1) Precision Promise has created an entirely new clinical trial "learning ecosystem"
- 2) Detailed studies to learn from every patient during the trial
- 3) Multiple investigational treatments can be evaluated in parallel (with increased efficiency)
- 4) Only 175 pts per experimental arm required for regulatory registration (if supportive data)
- 5) Marked acceleration of drug development for PDA with time and cost savings
- 6) Aligns key stakeholders (patients, families, researchers, clinicians, pharma, FDA) to increase the <u>pace and scale</u> in we can impact change

Opportunities

- Engage pharma to provide greater access to promising therapeutics and translational science in the earlier phases of drug development
- Further expand network to improve patient access and consider innovative funding models
- 3. Link Precision Promise to other efforts to amplify impact (NCI, ASCO, SPORES, private sector)
- 4. Use the Precision Promise model to expand use of in other disease settings (locally advanced PDA) and other cancer types
- 5. Develop similar platform for early detection/prevention (PRECEDE Consortium)

Early Detection Improves Survival



Effect of surgical resection on survival for resected cases (SEER data analysis)

Removal of earlier stage tumors increases survival rate

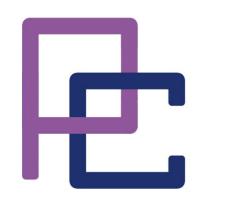
Japanese data: Resection of tumors <10 mm 5-year survival approaches 75%

Ishikawa et al, 1999

We still don't really understand:

- a) Who is at risk for pancreatic cancer?
- b) What is that 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 may be the **most** important to changing survival in pancreatic cancer



PRECEDE

The Pancreatic Cancer Early Detection Consortium

What is PRECEDE?



The PRECEDE Consortium is a **collaborative research effort** by 40 academic medical centers around the world. New York University 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 <u>50%</u> within the **next 10 years**.



It is the **largest effort of its kind**, using a novel model of data sharing across medical centers around the world. By combining data from all these sites, we will be able to more effectively and quickly identify methods of early detection.

SPECIFIC AIMS

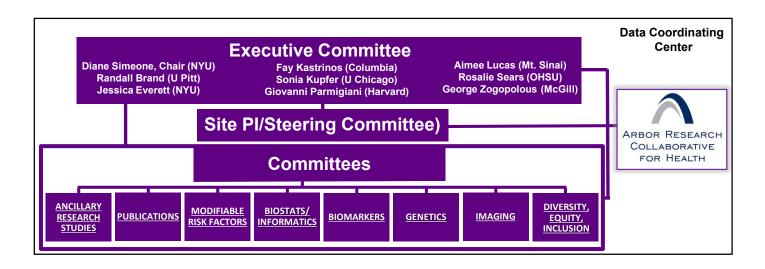
- Standardize collection of demographic, clinical, imaging data, and biosamples for a large high-risk familial PDA cohort at consortium centers worldwide.
- Generate proof of the importance of high-risk surveillance programs for PDA for both clinicians and health authorities through longitudinal follow up of clinical outcomes.
- 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.
- 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.
- Identify new pancreatic cancer susceptibility genes.
- Develop and/or validate biomarker assays (blood test/imaging/AI) that detects PDA at its earliest stage.

Study Design

- The PRECEDE Consortium will collect data, biosamples and imaging results from individuals who have been identified as being at high risk for developing pancreatic cancer. We will be following 10,000 high risk individuals over time.
- All medical 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 biosample collection and storage
 - Staff to manage patient consent, data collection and entry, biosample collection

Can't join unless you agree to share data

PRECEDE Organizational Structure



Cohorts for Study

Cohort 1 (largest cohort)

- 1. 2+ relatives with PDAC on same side of family with at least 1 affected is first degree related to subject; **age 50+** or ≤10 years younger than earliest case.
- 2. 2 affected first degree relatives with PDAC; age 50+ or 10 years younger than earliest case
- 3. BRCA1, BRCA2, PALB2, ATM, MLH1, MSH2, MSH6, PMS2 pathogenic variant AND 1 first or second degree relative with PDAC; age 50+ or 10 years younger than earliest case
- 4. Familial Atypical Moles and Malignant Melanoma (FAMMM) with pathogenic CDKN2A variant; age 40+
- 5. Peutz-Jegher syndrome with *STK11* pathogenic variant; **age 35+**
- 6. Hereditary pancreatitis with PRSS1 pathogenic variant and history of pancreatitis; age 40+

Cohort 2

- 1. ATM, BRCA2, or PALB2 pathogenic variant regardless of family history, age 50+
- 2. 2+ relatives with PDAC on the same side of family, any relation; age 50+ or 10 years younger than earliest case
- 3. 1 FDR with PDAC ≤ age 45; age ≤10 years younger than PDAC diagnosis in family member

Cohort 3

Individual meeting criteria for Cohorts 1 or 2 EXCEPT too young to qualify

Cohort 4

Individual with a single relative first degree relative with PDAC

Cohort 5

Relatives of individuals in Cohorts 1-4, allows data/biosamples for research studies.

Cohort 6

PDAC patients with FPC or relevant PGVs (tissue collection key)

PRECEDE Enrollment (as of 4/29/22): 2578 pts

1st site open (NYU): May, 2020

Yellow = site enrolled in the last 7 days

Central IRB in place for all US sites (some sites joined more recently than others)

Arbor Research assists each site with

- a) Sharing requirements to join
- b) Getting regulatory documents in place
- c) Onboarding for data/biosample collection

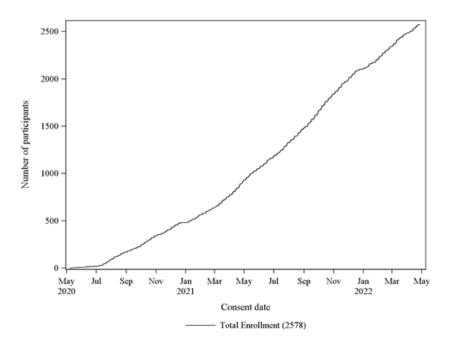
Biosamples are barcoded and stored locally

Plan this year: to centralize biorepository

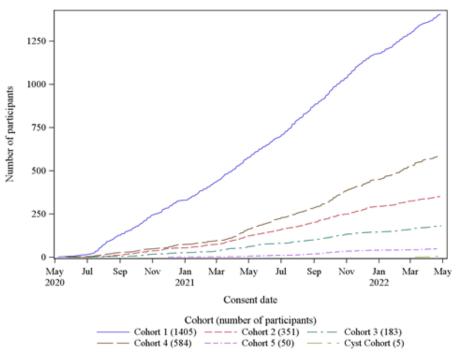
												n4		
	Col	hort 1	Со	hort 2	Со	hort 3	Co	hort 4	Co	hort 5		Cyst ohort		
														Most recent
														date participant
														was
Site	N	% in cohort	N	% in cohort	N	% in cohort	N	% in cohort	N	% in cohort	N	% in cohort	Total*	approached for consent
Total	1405	54%	351	14%	183	7%	584	23%	50	2%	5	0%	2578	tot conzent
NY-NYU	230	38%	102	17%	20	5%	223	37%	18	3%	5	1%	607	04/22/2022
							0				<u> </u>			
CN-BCC	9	90%	0	0%	1	10%	_	0%	0	0%	0	0%	10	03/10/2021
ES-RYC	25	56%	14	31%	0	0%	5	11%	1	2%	0	0%	45	03/14/2022
PA-PEN	169	65%	53	20%	14	5%	22	8%	1	0%	0	0%	259	04/28/2022
WA-UWA	19	76%	1	4%	0	0%	4	16%	1	4%	0	0%	25	03/18/2022
IT-VER	88	69%	10	8%	20	16%	4	3%	5	4%	0	0%	127	04/23/2022
CT-YAL	56	86%	4	6%	3	5%	2	3%	0	0%	0	0%	65	09/10/2021
OR-OHS	40	41%	21	22%	6	6%	30	31%	0	0%	0	0%	97	04/28/2022
PA-PIT	178	70%	22	9%	17	7%	35	14%	4	2%	0	0%	256	04/27/2022
MA-MGH	47	92%	3	6%	1	2%	0	0%	0	0%	0	0%	51	04/25/2022
IS-SHE	20	67%	3	10%	5	17%	2	7%	0	0%	0	0%	30	04/27/2022
MI-UMI	42	82%	5	10%	1	2%	3	6%	0	0%	0	0%	51	04/21/2022
FL-UMI	21	51%	7	17%	9	22%	4	10%	0	0%	0	0%	41	04/26/2022
IL-CHI	47	38%	11	9%	4	3%	59	48%	3	2%	0	0%	124	04/15/2022
CA-CES	0	0%	0	0%	0	0%	1	100%	0	0%	0	0%	1	08/23/2021
UT-HCI	36	72%	2	4%	10	20%	2	4%	0	0%	0	0%	50	04/27/2022
NE-UNE	65	45%	23	16%	20	14%	36	25%	0	0%	0	0%	144	04/04/2022
CA-SAN	15	38%	8	20%	1	3%	16	40%	0	0%	0	0%	40	04/12/2022
MA-UMA	12	35%	9	26%	3	9%	10	29%	0	0%	0	0%	34	04/08/2022
FL-MOF	32	40%	5	6%	8	10%	26	32%	10	12%	0	0%	81	03/29/2022
NY-COL	15	58%	10	38%	0	0%	1	4%	0	0%	0	0%	26	12/15/2021
FL-MAY	30	42%	3	4%	1	1%	35	49%	2	3%	0	0%	71	04/12/2022
NY-ROC	3	75%	0	0%	0	0%	1	25%	0	0%	0	0%	4	07/09/2021
CN-MCG	96	83%	5	4%	10	9%	4	3%	0	0%	0	0%	115	04/22/2022
NY-MTS	100	48%	29	14%	19	9%	58	28%	3	1%	0	0%	209	03/17/2022
VA-INS	10	67%	1	7%	1	7%	1	7%	2	13%	0	0%	15	04/25/2022

Cohort Enrollment

Cumulative Enrollment



Enrollment by Cohort (Largest is Cohort 1)



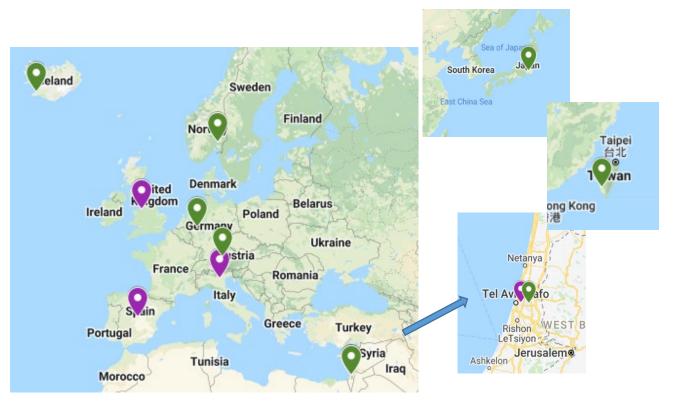
Current enrollment 2578 pts
Expect enrollment of 3000 pts by July, 2022

PRECEDE Consortium: 25 Sites US/Canada Enrolling



- British Columbia Cancer Agency Vancouver, Canada
- Cedars Sinai Los Angeles, CA
- Columbia University, New York, NY
- ♣ Huntsman Cancer Institute Salt Lake City, UT
- Inova Schar Cancer Institute Falls Church, VA
- Mass General/Harvard Boston, MA
- Mayo Clinic Jacksonville, FL
- McGill University Montreal, Canada
- A MD Anderson, Houston, TX
- A Moffitt Cancer Center Tampa, FL
- Mount Sinai New York, NY
- NYU Langone New York, NY
- Oregon Health & Science Portland, OR
- Penn Medicine Philadelphia, PA
- University of Chicago Chicago, IL
- University of Massachusetts Worcester, MA
- University of Miami Miami, FL
- University of Michigan Ann Arbor, MI
- University of Rochester Rochester, NY
- University of Toronto/Mt. Sinai Toronto, Canada
- University of Washington/SCCA Seattle, WA
- UNMC Omaha, NB
- UPMC/Pittsburgh Pittsburgh, PA
- UCSD San Diego, CA
- Yale New Haven, CT

PRECEDE Consortium: International Sites



Open to enrollment:

- Ramón y Cajal Hospital Madrid, Spain
- Sheba Medical Center Ramat Gan, Israel
- University of Verona Verona, Italy
- University of Liverpool Liverpool, England

In approval process:

- Medical University of Munich Munich, Germany
- University Hospital Essen Essen, Germany
- A National University Hospital Iceland
- National Cancer Center Japan
- Oslo University Hospital Norway
- Rabin Medical Center Israel
- National Cheng Kung University Hospital Taiwan

Purple = actively enrolling Green = being on-boarded > Gastroenterology. 2021 Aug 27;S0016-5085(21)03416-8. doi: 10.1053/j.gastro.2021.08.036. Online ahead of print.

Recommendations for a More Organized and Effective Approach to the Early Detection of Pancreatic Cancer From the PRECEDE (Pancreatic Cancer Early Detection) Consortium

Tamas A Gonda ¹, Jessica N Everett ¹, Michael Wallace ², Diane M Simeone ³, PRECEDE Consortium

Standardizing Family History and Genetic Testing

Areas of standardization	Proposed elements	Examples
Family history	Pedigree templates (e.g. Progeny)	3 generation pedigree with PGV information Confirmation of reported PDAC cases with records
Genetic testing	Minimum gene list and plan for updating	Panels including all known genes linked to PDAC risk Updated testing for families with outdated results

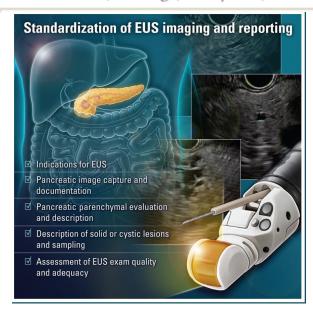


ORIGINAL ARTICLE

Standardization of EUS imaging and reporting in high-risk individuals of pancreatic adenocarcinoma: consensus statement of the Pancreatic Cancer Early Detection Consortium

Tamas A. Gonda, MD, ¹ James Farrell, MD, ² Michael Wallace, MD, ³ Lauren Khanna, MD, ¹ Eileen Janec, MD, ¹ Richard Kwon, MD, ⁴ Michael Saunders, MD, ⁵ Uzma D. Siddiqui, MD, ⁶ Randall Brand, MD, ⁷ Diane M. Simeone, MD⁸ for the PRECEDE Consortium*

New York, New York; New Haven, Connecticut; Jacksonville, Florida; Ann Arbor, Michigan; Seattle, Washington; Chicago, Illinois; Pittsburgh, Pennsylvania, USA



MRI standardization in progress



Current Projects Utilizing PRECEDE Resources						
Projects	Principal Investigators and Affiliations					
Estimating the Impact of PDAC Screening	Giovanni Parmigiani (Harvard) Diane Simeone (NYU)					
Discovery and Validation of Early Detection Biomarkers	Randall Brand (U Pitt) Aatur Singhi (U Pitt) Thomas Wilkie (UTSW) Giulio Innamorati (Verona) Davide Lyden (Cornell) Rosalie Sears (OHSU) Diane Simeone (NYU)					
Genome-Wide Association Studies and Polygenic Risk Scores for Pancreatic Ductal Adenocarcinomas	Fay Kastrinos (Columbia)Giovanni Parmigiani (Harvard)Laufey Amundadottir (NCI)					
Monitoring Heart Rate Variability for the Early Detection of Pancreatic Cancer	Aaron Grossberg (OSHU)Kelsey Klute (Nebraska)					
5) The Undiscovered Heritable Component of Familial Pancreatic Cancer	George Zogopoulos (McGill) Steve Gallinger (Univ Toronto)					
6) Genetic Predisposition Study (GPS): Identification of Inherited Risk Factors in a High-Risk Familial Pancreatic Cancer Cohort	Rachid Karam (Ambry Genetics) Jessica Everett (NYU)					
7) Single Nucleotide Polymorphisms in carriers of PGVs in the <i>ATM</i> , <i>BRCA1</i> , <i>BRCA2</i> , and <i>PALB2</i> genes	Fay Kastrinos (Columbia) Giovanni Parmigiani (Harvard)					
8) PRECEDE Imaging and Clinico-laboratory Biomarkers of Pancreatic Cancer: A Hypothesis Generating Study	Alex Guimaraes (OHSU) Hersh Chandarana (NYU) Jacob Hesterman (Invicro)					
Biobehavioral Assessment and Psychosocial Support for High-Risk Individuals	Naomi Simon (NYU)					
10) P-CARE: a Strategic Approach to Develop Equitable Genetic Testing and Screening for Pancreatic Cancer	Sonia Kupfer (Univ Chicago) Diane Simeone (NYU) Larry An (Univ Michigan)					
11) The Fecal Microbiome as an Early Detection Biomarker in Pancreatic Cancer	Florencia McAllister (MDACC) Gregory Poore (UCSD)					
12) Diversity, Equity and Inclusion in Pancreatic Cancer Screening	Bryson Katona (UPenn) Aimee Lucas (Mt. Sinai)					
13) Harnessing Multimodal Data Integration to Early Cancer Detection	Aris Tsirigos (NYU) Lisa McFerrin (AWS)					

"Most people overestimate what they can do in 1 year and underestimate what they can do in 10 years"

Bill Gates





January 27, 2021 @ 11:00pm by Stephen J. Dubner Produced by Matt Hickey and Daphne Chen



diane.simeone@nyulangone.org

MadamSurgeon



Funding: NIH, DOD, Pancreatic Cancer Action Network, Lustgarden Foundation, Thompson Family Foundation, Novartis, Immunovia, Bluestar Genomics, Micronoma, Cyteir Therapeutics, Tempus, TrovaNOW, Project Purple