The Search for Improved Outcomes in Pancreatic Cancer: From Altered Systemic Metabolism to Novel Early Detection Approaches

PancreasFest 2019

Brian Wolpin, MD, MPH
Dana-Farber Cancer Institute
Harvard Medical School
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Disclosures

- Sponsored research funding: Celgene, Eli Lilly
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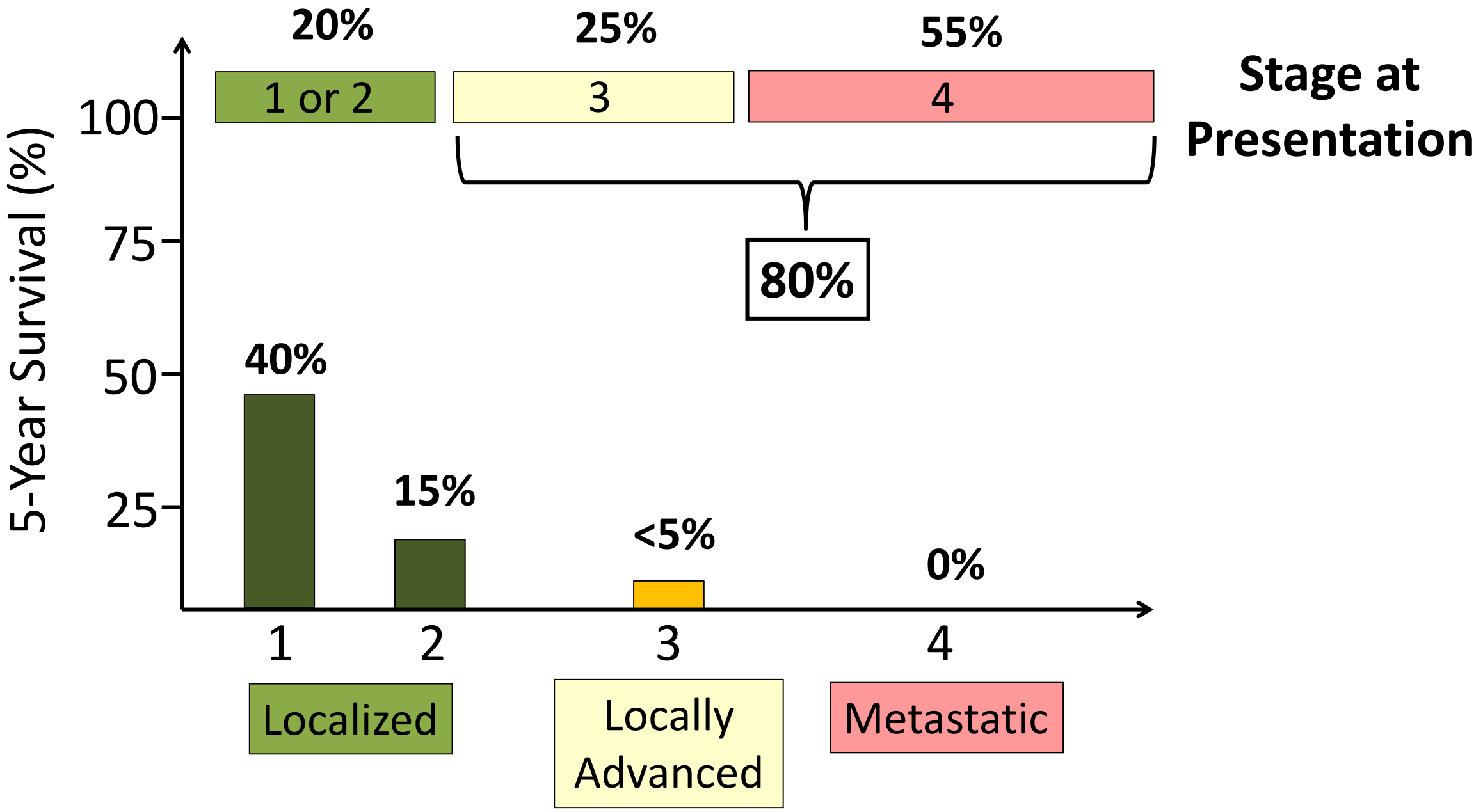

20%
25%
55%
1 or 2
3
4
Stage at Presentation
100
75
50
25
5-Year Survival (%)
80%
40%
15%
<5%
0%
1
2
3
4
Localized
Locally Advanced
Metastatic

Pancreatic Cancer Early Detection

- Data overload: Weighing numerous inputs for earlier diagnosis of pancreatic cancer
- What to look for: Host reactions to an early tumor - altered systemic metabolism
- Imaging: Latent information beyond looking for a tumor in a specific organ
- Change over time: Information in repeated measures
- Personalized medicine for early detection

The New England
Journal of Medicine

VOLUME 211 AUGUST 23, 1934 NUMBER 8

DIABETES AND CANCER*

BY ALEXANDER MARBLE, M.D.†

THE presence of diabetes and cancer in the same individual is an association which promotes speculation and calls for a consideration of the possible relationship between the two diseases.

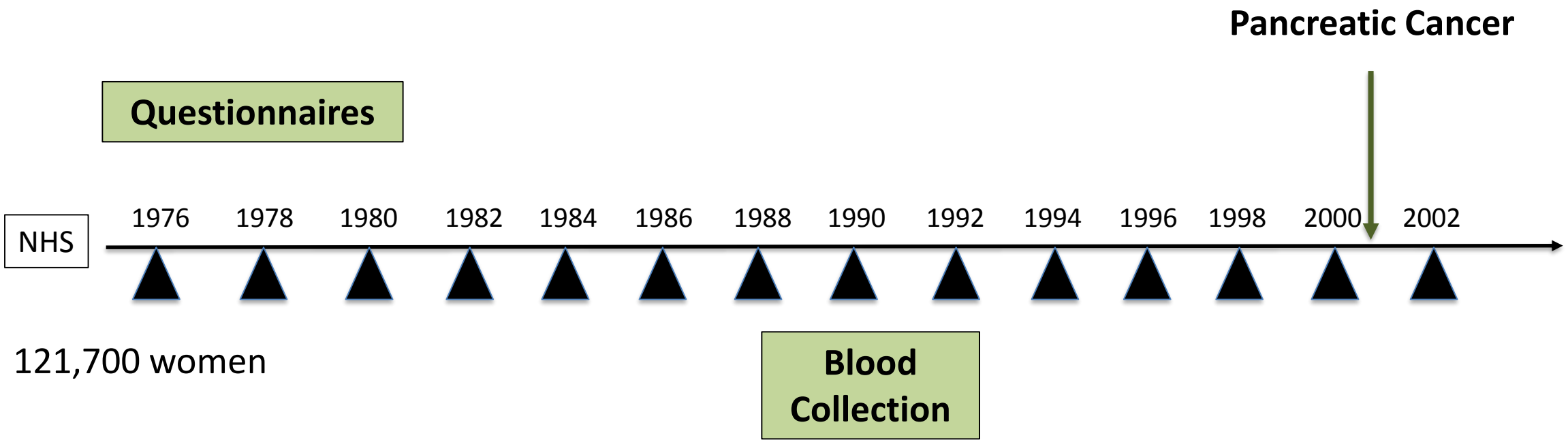
SUMMARY

The incidence of carcinoma of the pancreas was therefore extraordinarily high. In this series it was 12.9 per cent of the total number of cases as contrasted with less (often considerably less) than 5 per cent in general cancer statistics reported by others.

Material. The 256 cases of malignant disease (which include eight cases of malignancy of types other than carcinoma) represent patients seen by Dr. Elliott P. Joslin and associates from 1898 to 1933.

*From the George F. Baker Clinic, Elliott P. Joslin, M.D., Medical Director, New England Deaconess Hospital, Boston.

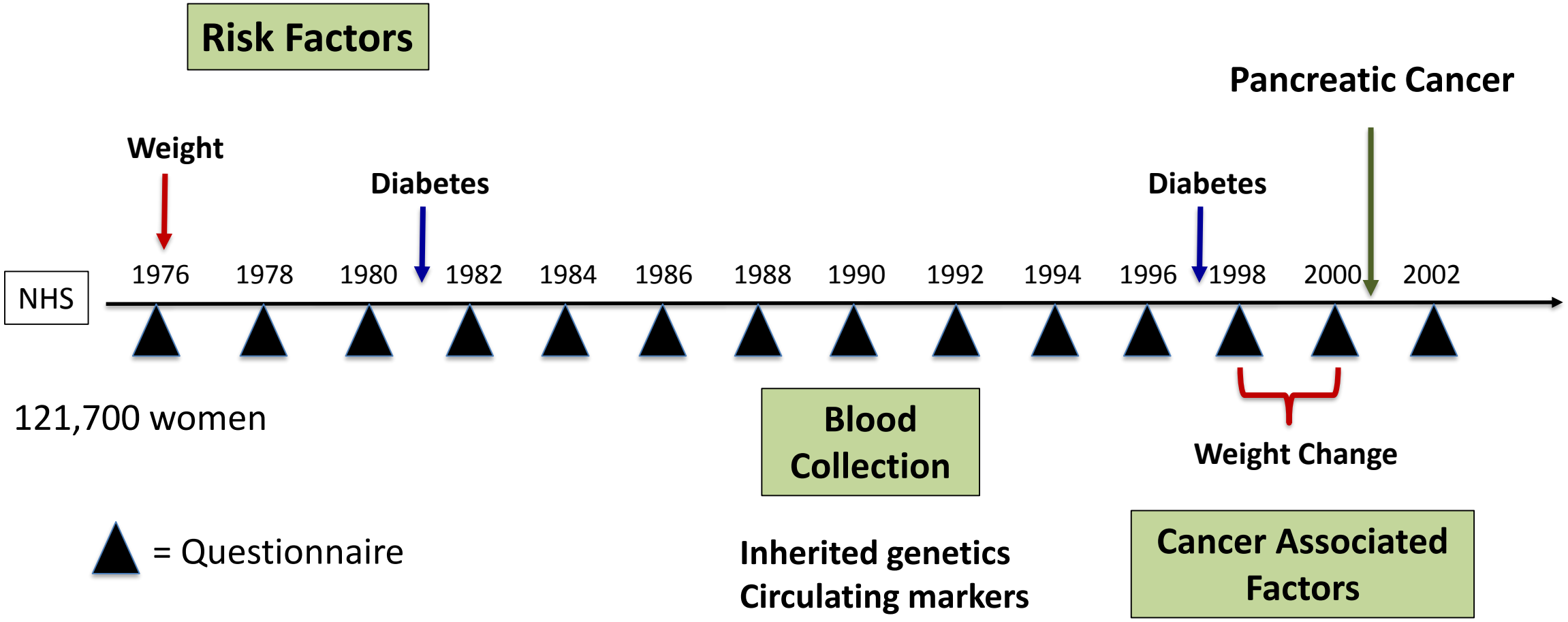
Longitudinal Cohorts



▲ = Questionnaire

- Demographics
- Exposures
- Diet
- Medical diagnoses
- Medications

Longitudinal Cohorts



Pancreatic Cancer Risks by Weight and Diabetes

	Diabetes Status	
	No diabetes	Diabetes
Person-years	4,344,683	340,410
No. cases*	764	236
Age-adjusted RR (95% CI)	1	2.37 (2.04, 2.75)

	Body-Mass Index (kg/m2)		
	Normal Weight	Overweight	Obese
Person-years	3,262,564	1,259,687	391,131
No. cases*	653	382	133
Age-adjusted RR (95% CI)	1	1.23 (1.09-1.40)	1.55 (1.29-1.87)

* Participants who developed pancreatic cancer in NHS or HPFS

Chen Yuan

Germline Common Risk Variants

N=22

PanScan and PanC4 Consortia

Amundadottir et.al, *Nature Genetics* 2009; N=1.

Petersen et.al, *Nature Genetics* 2010; N=3.

Wolpin et.al, *Nature Genetics* 2014; N=6.

Childs et.al, *Nature Genetics* 2015; N=4.

Zhang et.al, Oncotarget 2016; N=3.

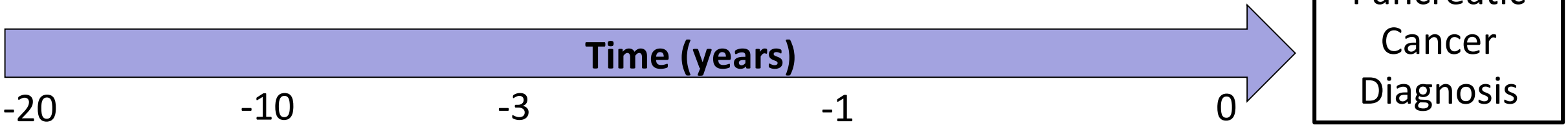
Klein et al, *Nature Commun* 2018; N=5.

Chr	Gene(s)	SNP	Alleles	OR (95% CI)	MAF	*P*	
1q32.1	*NR5A2*	rs2816938	A/T	1.21 (1.17-1.26)	0.23	3.4×10^{-15}	
1q32.1	*NR5A2*	rs3790844	G/A	0.81 (0.76-0.86)	0.24	7.6×10^{-16}	
1p36.33	*NOC2L*	rs13303010	G/A	1.26 (1.19-1.35)	0.11	8.4×10^{-14}	*
2p13.3	*ETAA1*	rs1486134	G/T	1.13 (1.09-1.17)	0.28	4.6×10^{-9}	*
3q29	*TP63*	rs9854771	A/G	0.90 (0.86-0.94)	0.36	4.5×10^{-8}	*
5p15.33	*TERT*	rs2736098	T/C	0.84 (0.79-0.88)	0.27	6.9×10^{-15}	*
5p15.33	*TERT*	rs35226131	T/C	0.67 (0.53-0.81)	0.03	2.2×10^{-8}	
5p15.33	*CLPTM1L*	rs401681	T/C	1.19 (1.15-1.23)	0.45	9.3×10^{-17}	
7p12	*TNS3*	rs47488569	T/A	0.83 (0.77-0.88)	0.12	4.4×10^{-8}	
7p14.1	*SUGCT*	rs17688601	A/C	0.88 (0.84-0.93)	0.25	1.1×10^{-8}	*
7q32.3	*LINC-PINT*	rs6971499	C/T	0.81 (0.76-0.87)	0.15	7.4×10^{-14}	*
8q21.11	*HNF4G*	rs2941471	G/A	0.89 (0.85-0.93)	0.43	6.6×10^{-10}	*
8q24.21	*MYC*	rs10094872	T/A	1.14 (1.10-1.19)	0.36	1.2×10^{-9}	
8q24.21	*PVT1*	rs1561927	C/T	0.89 (0.85-0.93)	0.27	7.1×10^{-8}	*
9q34.1	*ABO*	rs505922	C/T	1.27 (1.22-1.31)	0.35	7.4×10^{-27}	
13q12.2	*PDX1*	rs9581943	A/G	1.15 (1.12-1.19)	0.40	5.1×10^{-14}	*
13q22.1	*KLF5, KLF12*	rs9543325	C/T	1.23 (1.18-1.30)	0.37	1.2×10^{-22}	
16q23.1	*BCAR1*	rs7190458	A/G	1.36 (1.27-1.44)	0.04	1.3×10^{-11}	*
17pq12	*HNF1B*	rs4795218	A/G	0.88 (0.84-0.92)	0.23	1.3×10^{-8}	*
17q24.3	*LINC00673*	rs7214041	T/C	1.25 (1.19 1.30)	0.11	9.5×10^{-15}	*
18q21.32	*GRP*	rs1517037	T/C	0.86 (0.80-0.91)	0.19	3.3×10^{-8}	
22q12.1	*ZNRF3*	rs16986825	T/C	1.15 (1.10-1.20)	0.16	1.2×10^{-8}	*

* All GWAS plus Pandora for replication

Risk Stratification

Risk Factors
Demographics: Older Age, Men, AA, AJ
Exposures: Cigarettes, Obesity, Low Physical Activity, Heavy Alcohol, Unhealthy Diet
Comorbidities: Diabetes, Chronic Pancreatitis, Pancreatic cysts
Family History



Genetics
Rare, Medium-High Penetrance: *BRCA1/2, PALB2, ATM, CDKN2A, TP53, PRSS1, MMR genes*
Common, Low Penetrance: 22 loci from GWAS – polygenic risk score

Risk Models for Pancreatic Cancer

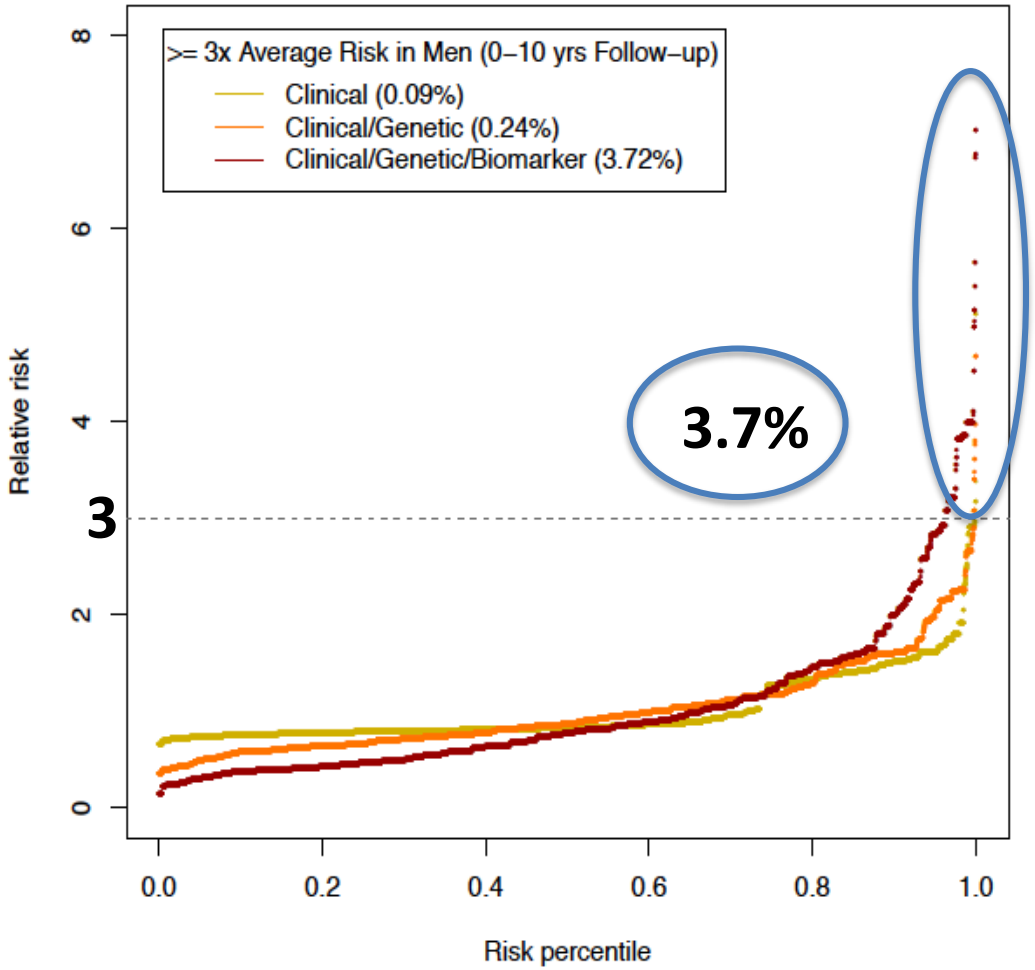
Pooled Data from 4 Prospective Cohorts: HPFS, NHS, PHS, WHI

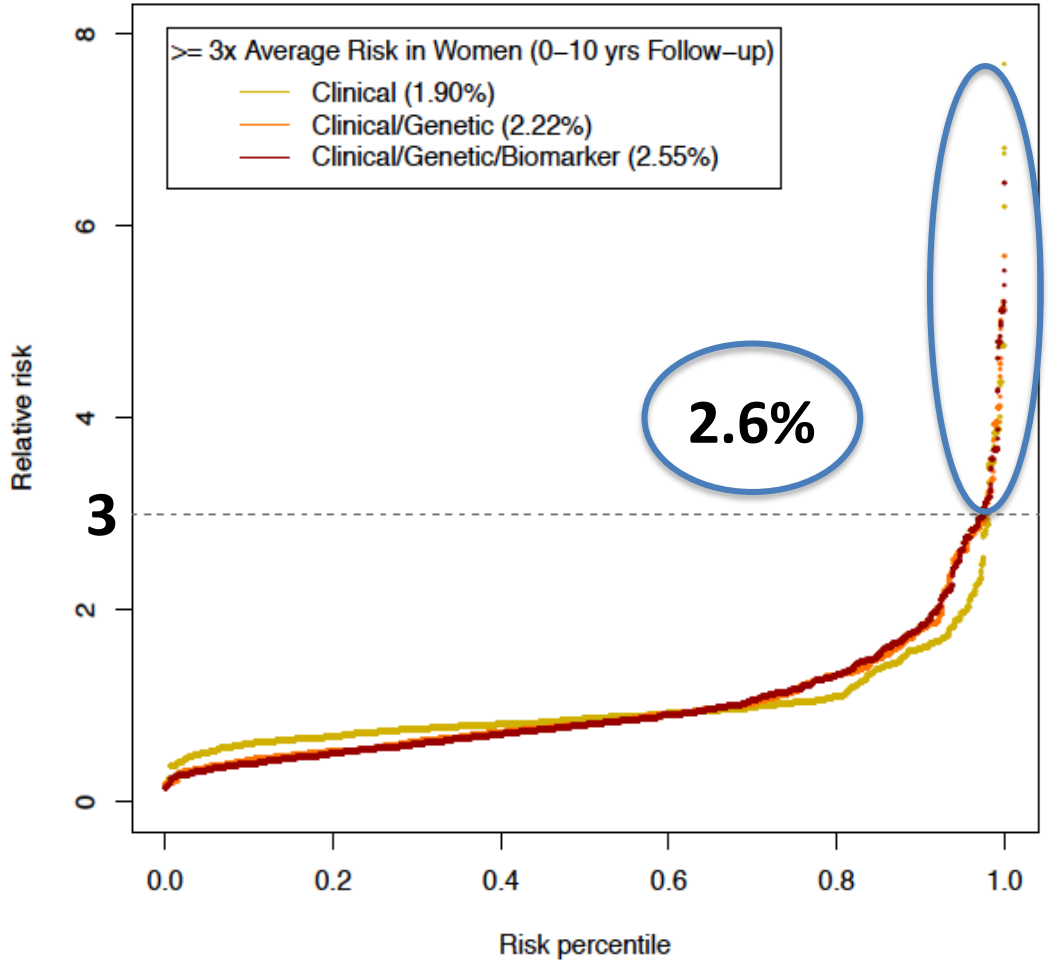
0-10 Yrs Population
N=956: 304 cases, 652 controls

0-10 Year Follow-up Population	Base Model	+ Genetic Risk Score	+ Circulating Markers
Covariates	Body-mass index Waist-hip ratio Physical activity Diabetes history Age, Sex Race/ethnicity, Smoking status, Family history, Chronic pancreatitis	wGRS (22 common risk loci in Caucasions)	Proinsulin Adiponectin Interleukin-6 Total BCAAs
LR *P*-value	--	2.9×10^{-9}	0.003
ROC AUC	0.61	0.67	0.69

Pete Kraft
Jihye Kim
Chen Yuan

Identify Subjects with High Relative Risk

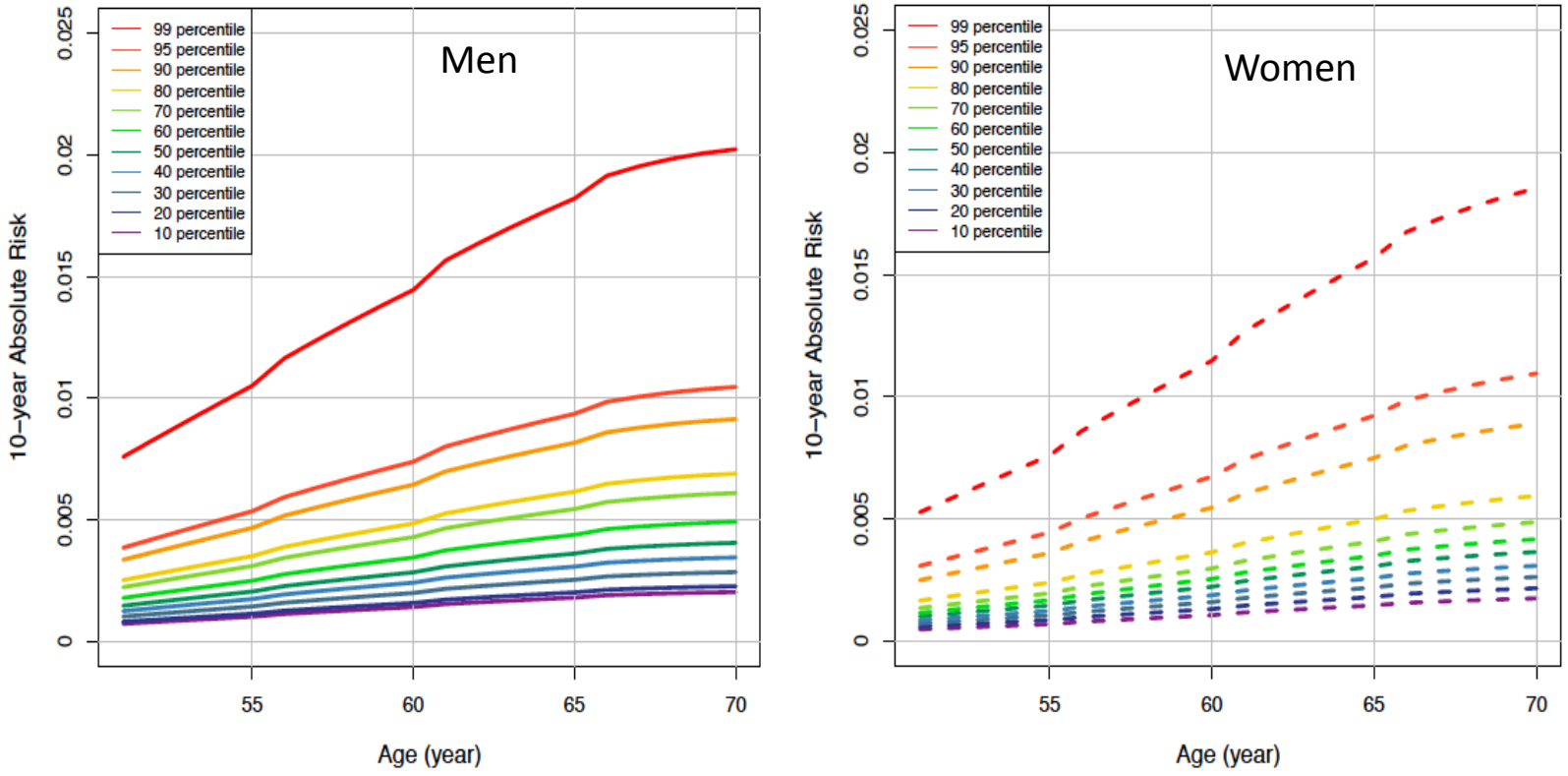




Absolute Risk Models for Pancreatic Cancer

Clinical + Genetic + Circulating Biomarker Model

10-Year Pancreatic Cancer Risk



Study Considerations

Improved Fit for Future Models	Reduced Fit for Future Models
“Missing” data: Smoking status (matched), history of pancreatitis or pancreatic cyst, and family history	Data not (yet) commonly available in standard clinical practice: e.g., germline genetic variants
Self-reported data from mailed questionnaires	Sample size
No changes in measurements over time	Model overfitting
No data on “early” symptoms, such as abdominal discomfort, back pain, weight loss, anorexia etc.	

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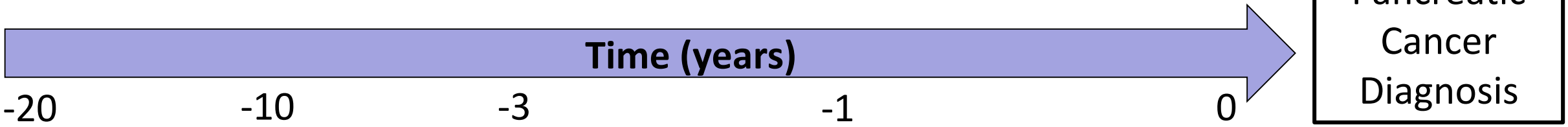
- BP medications
- Hypoglycemics

Vital Signs
- Weight loss
- Decreased BP

Dietary Changes
- Malabsorption
- Food preferences



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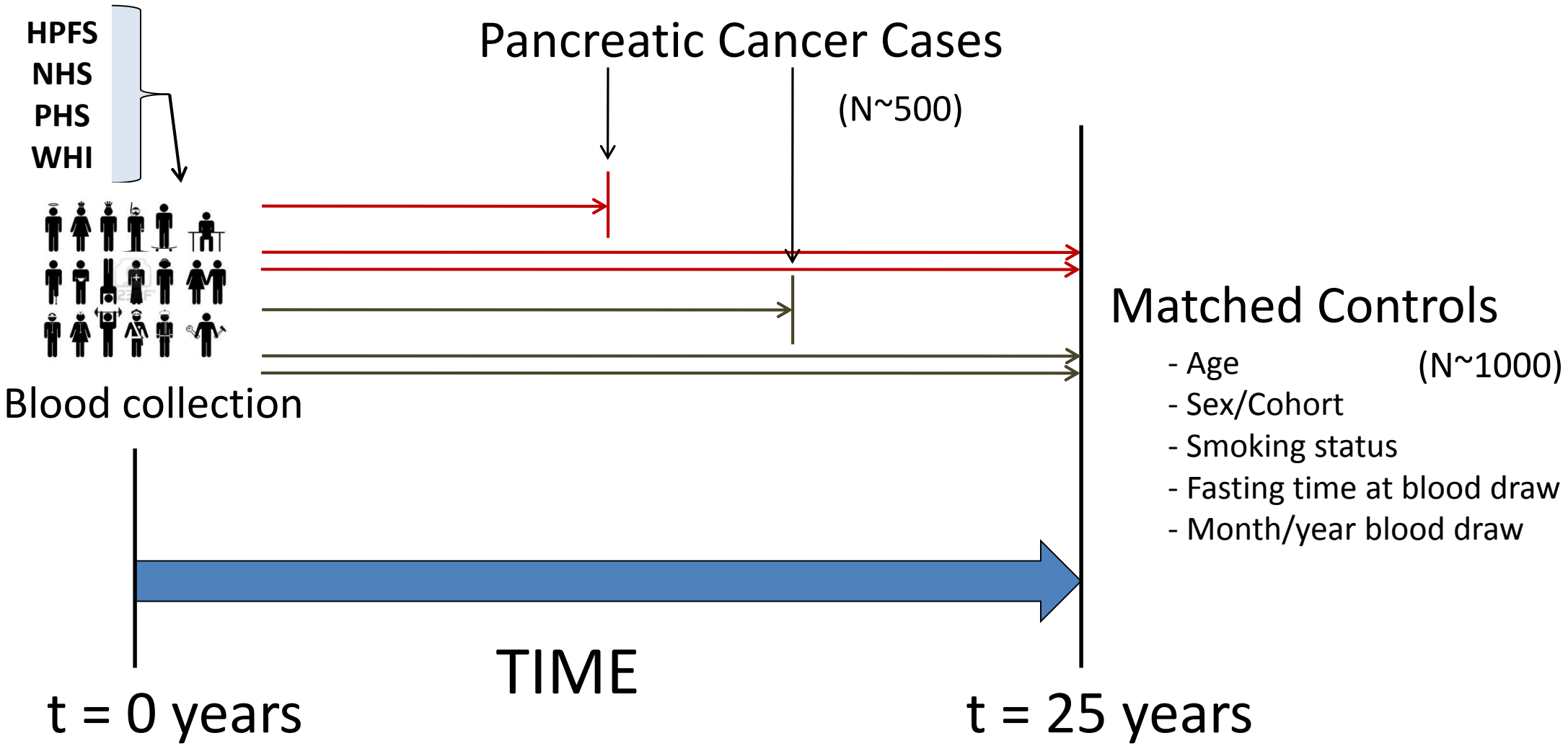
New Diagnoses
- Diabetes
- Gastritis/Indigestion
- Heartburn/Reflux
- MSK back pain

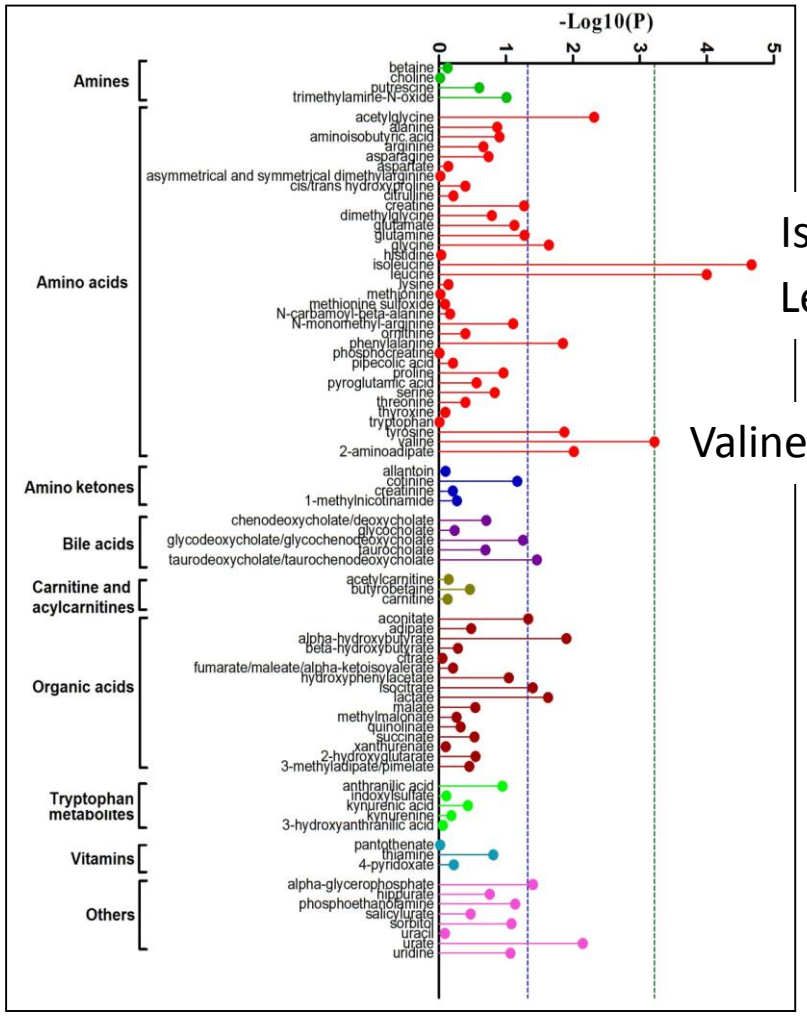
Procedures
- EGD
- Spine MRI
- RUQ ultrasound

Imaging Features
- AP CT scan
- AP MRI
- EUS

Assessment of prediagnosis metabolic changes in PDAC



Prediagnosis Metabolic Alterations



N=83 metabolites

Conditional logistic regression

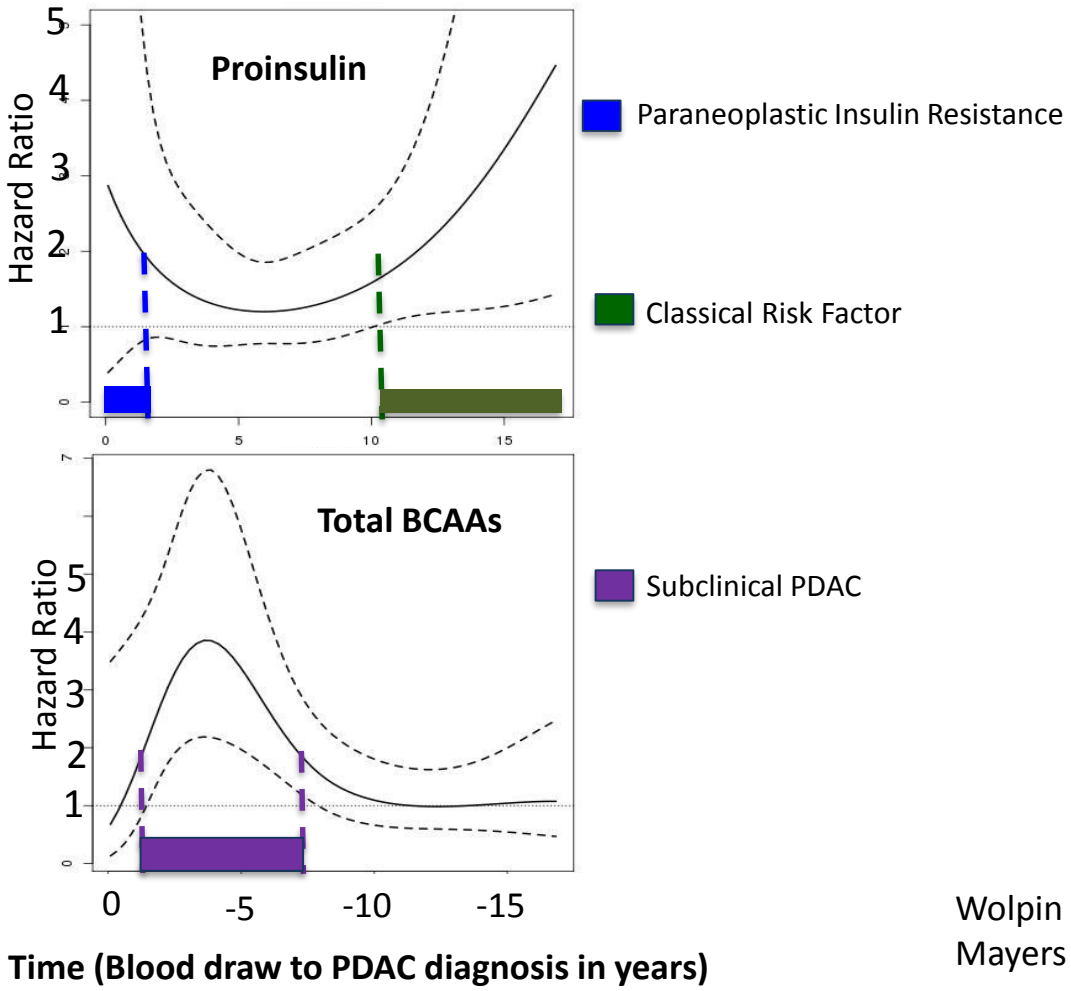
Branched Chain Amino Acids (BCAAs)

Independent of:

Body-mass index
Physical activity
Current diabetes
Future diabetes
Hemoglobin A1c
Insulin markers

Mayers et al. *Nat Med*. 2014;20:1193.

Prediagnosis BCAA Elevations in Humans

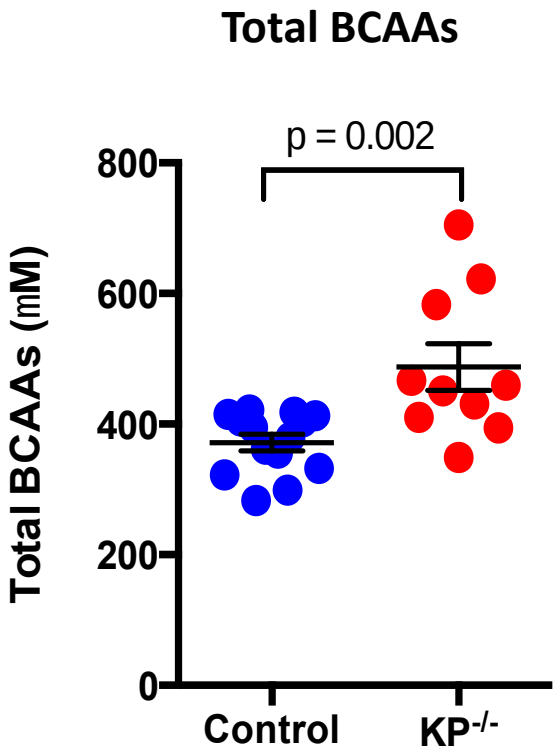


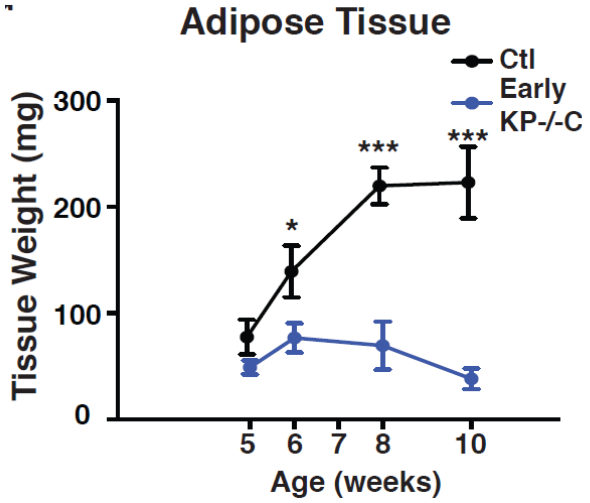
Wolpin et al. JNCI 2013;105:1027.
Mayers et al. *Nat Med*. 2014;20:1193.

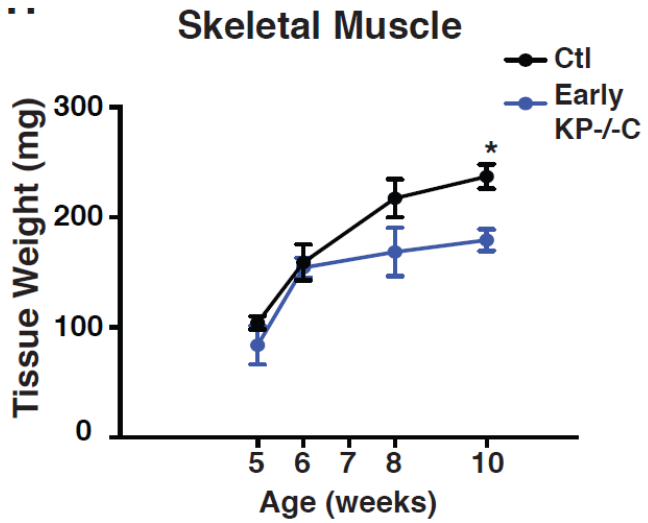
BCAA elevations are associated with early pancreatic cancer in mouse models

Jared Mayers
Laura Danai
Matt Vander Heiden

KP$^{-/-}$C Model:
LSL-Kras$^{G12D/+}$
Tp53$^{fl/fl}$
Pdx1-Cre





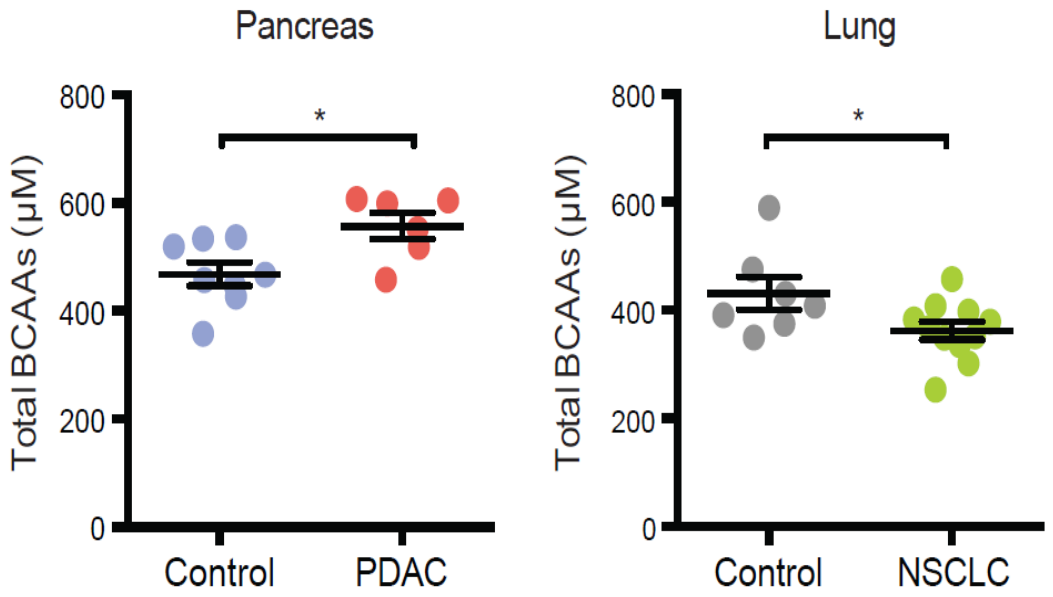


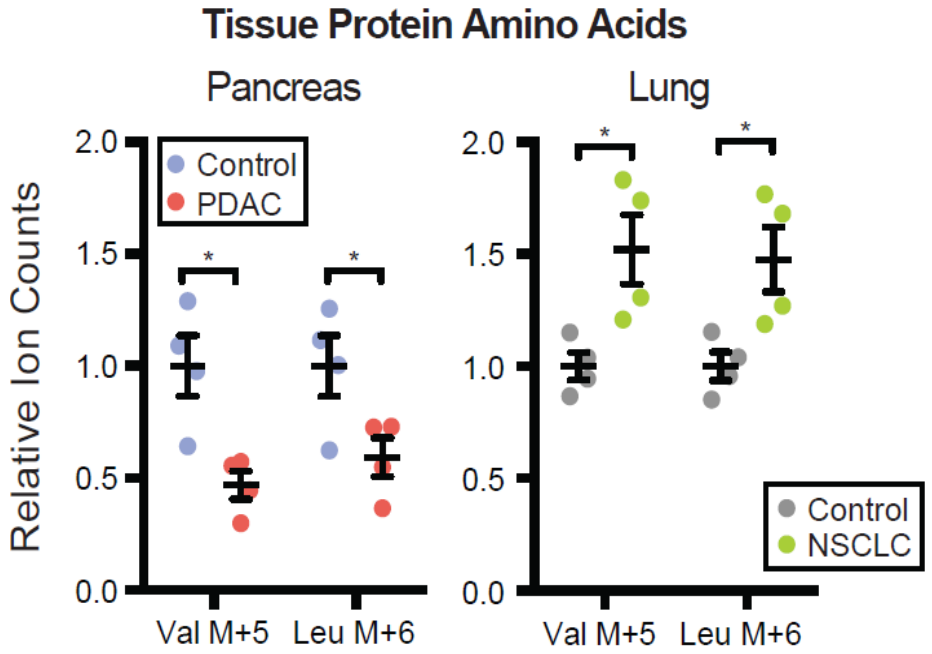
Mayers et al. *Nat Med*. 2014;20:1193.

Danai, Babic, Rosenthal et al. *Nature*. 2018;558:600.

Pancreas tumors do not directly utilize liberated BCAAs

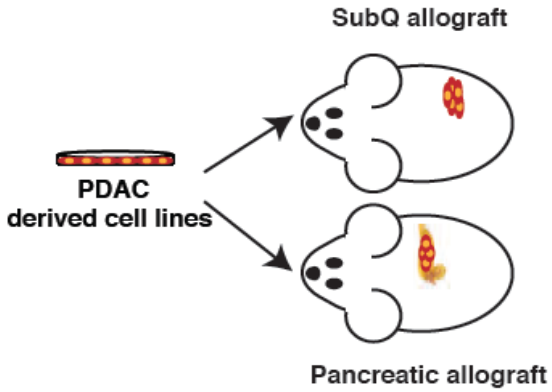
KP$^{-/-}$C Model:
LSL-Kras$^{G12D/+}$
Tp53$^{fl/fl}$
PDAC: *Pdx1-Cre*
NSCLC: Inhaled *Cre*





Mayers et al. *Science*. 2016;353:1161.

Pancreatic Exocrine Insufficiency

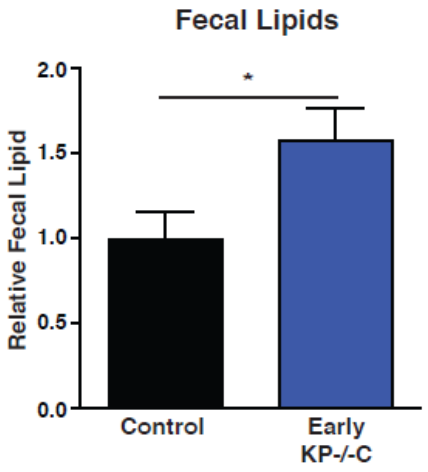


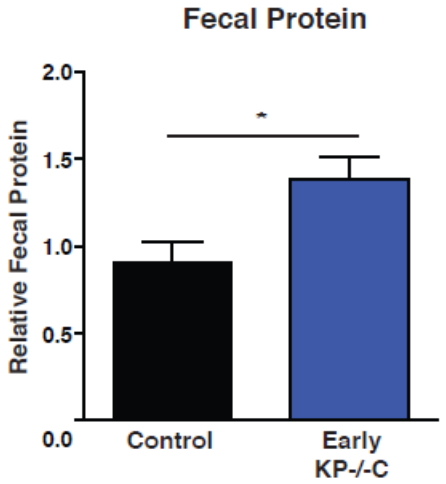
Peripheral
Tissue Wasting

No

Yes

KP$^{-/-}$C Model:
LSL-Kras$^{G12D/+}$
Tp53$^{fl/fl}$
Pdx1-Cre





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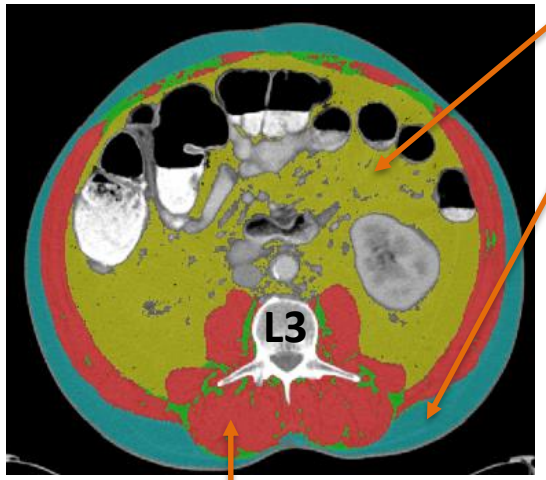
Body Composition Measurements



Visceral adipose (yellow)

Subcutaneous adipose (blue)

Skeletal muscle (red)

DFCI/BWH
Mayo Clinic
MGH
Stanford Univ
UNC-Chapel Hill

Body composition segmentation in 679 pts with newly diagnosed, previously-untreated pancreatic cancer

65% of 679 pts with PDAC of all stages had sarcopenia

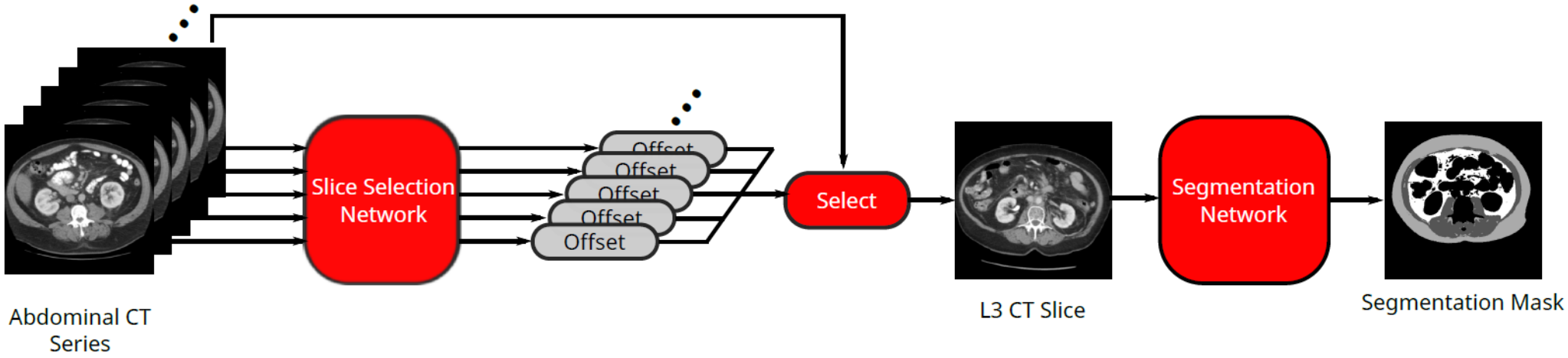
64% of 213 pts with localized PDAC had sarcopenia

Sarcopenia defined as skeletal muscle index (SMI): men, <55.4 cm^2/m^2; women, <38.9 cm^2/m^2

Michael Rosenthal
Ana Babic

Danai, Babic, Rosenthal et al. *Nature*. 2018;558:600.

Automated Peripheral Tissue Segmentation



Two-part Neural Network

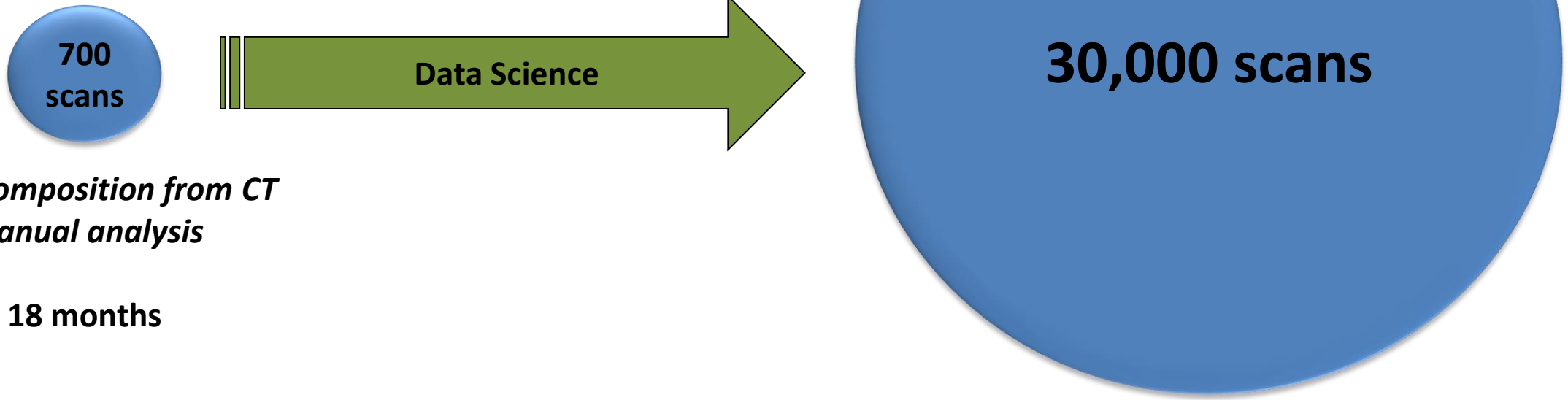
Training set of 600 manually segmented scans from pancreatic cancer patients

Testing set of 560 manually segmented scans from patients with lymphoma

Testing set correlation coefficients for three compartments by machine vs. human = 0.986-0.994

Michael Rosenthal
MGH/BWH Center for Clinical Data Science

Case Series to Population Scale



Body Composition from CT
Manual analysis

18 months

Body Composition from CT
Fully automated analysis

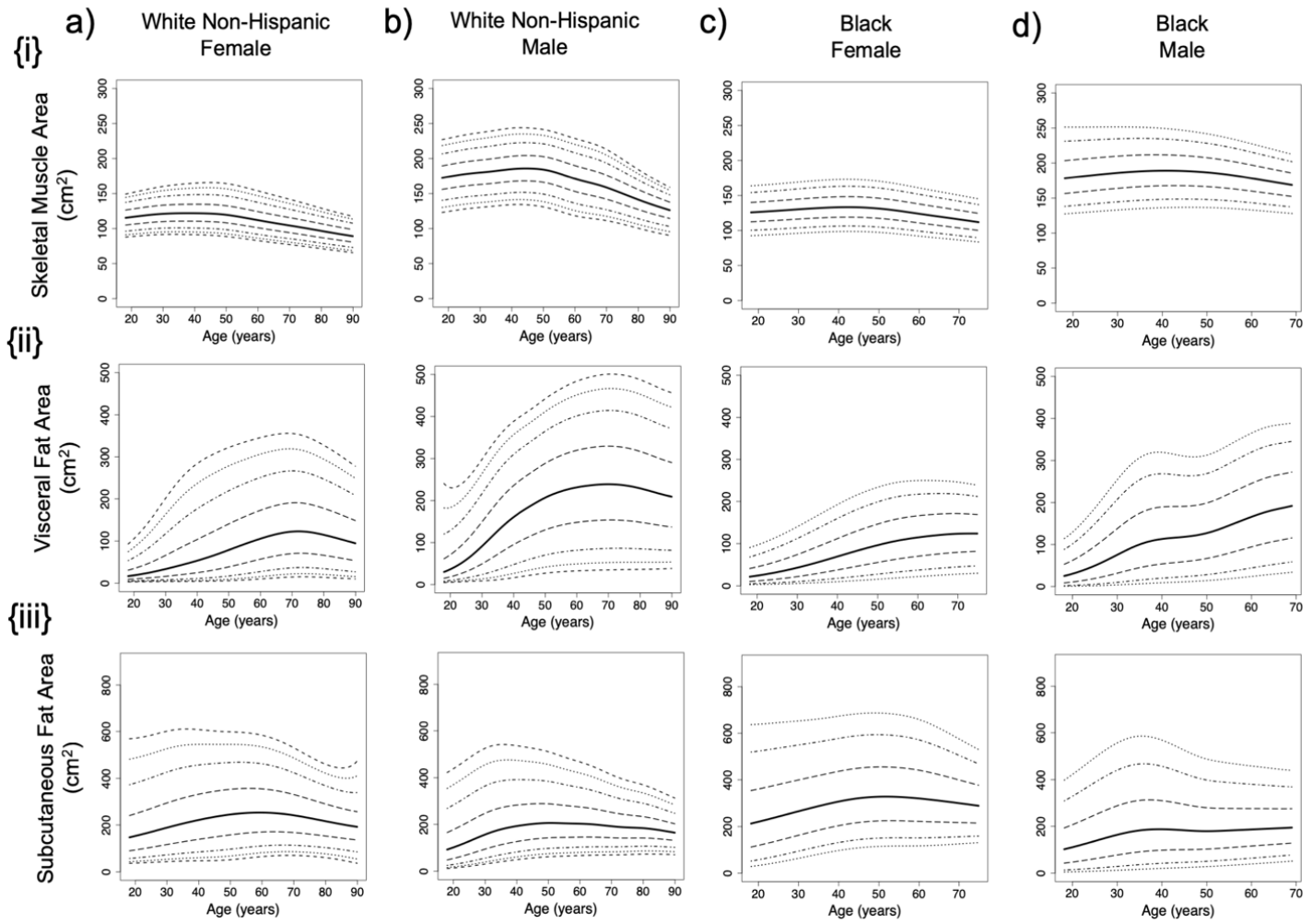
1-2 months

Michael Rosenthal
MGH/BWH Center for Clinical Data Science

Population Metrics

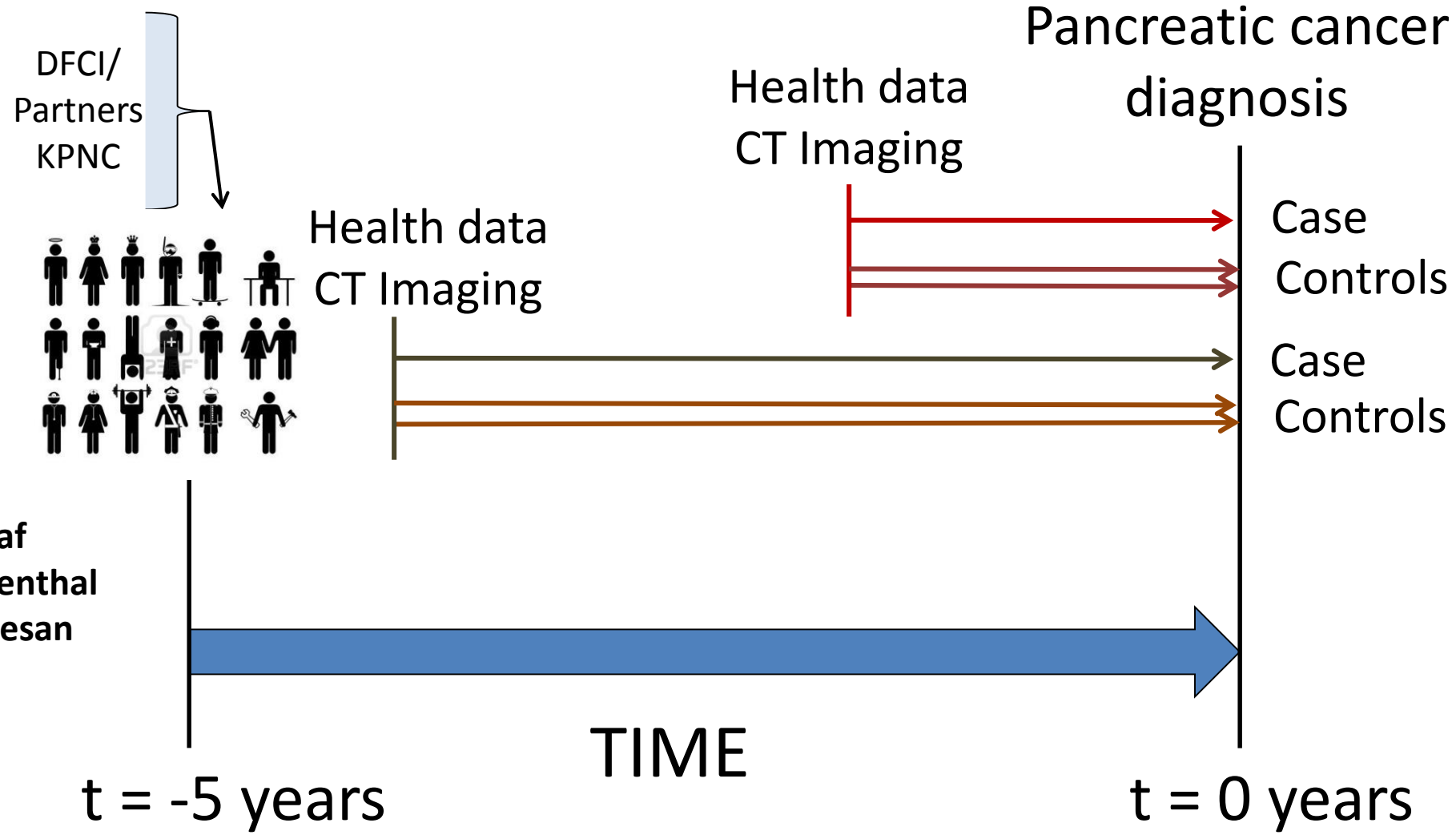
28,411 outpatient AP CT exams from patients seen within Partners Healthcare in 2012

Kirti Magudia
Michael Rosenthal
MGH/BWH Center for Clinical Data Science



From inferior to superior, the lines represent the 3rd (short dashed line), 5th (dotted line), 10th (dashed and dotted line), 25th (long dashed line), 50th (solid line), 75th (long dashed line), 90th (dashed and dotted line), 95th (dotted line) and 97th (short dashed line) percentiles.

Imaging-Based Risk Modeling within Large Health Systems



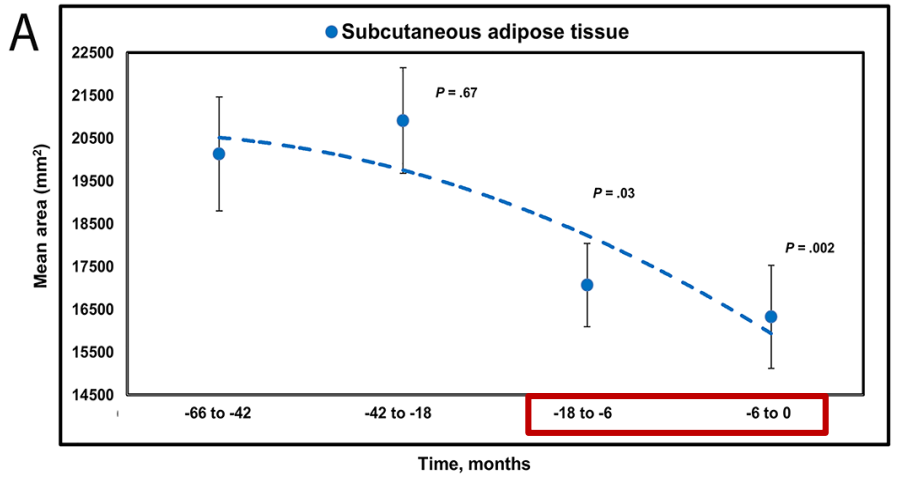
Natalia Khalaf
Michael Rosenthal
Tilak Sundaresan
Bette Caan

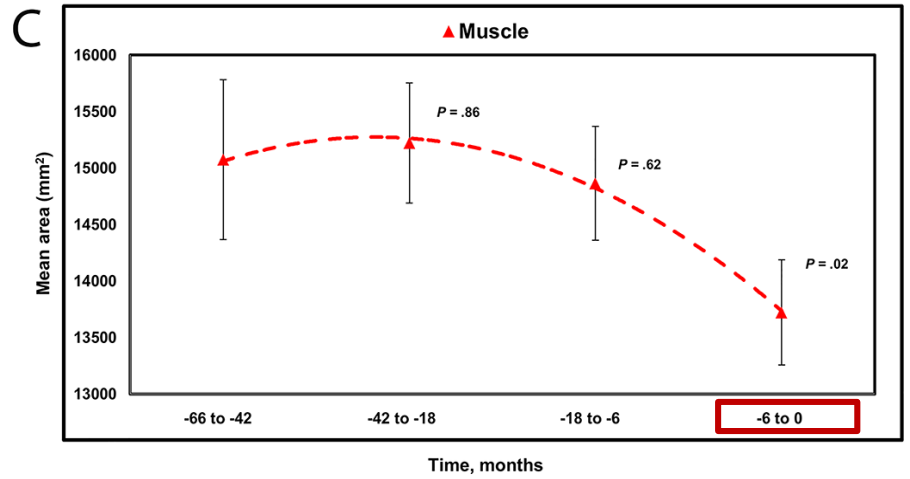
Sah RP et al. Phases of Metabolic and Soft Tissue Changes in Months Preceding a Diagnosis of Pancreatic Ductal Adenocarcinoma. *Gastroenterology*. 2019.

Suresh Chari's group (Mayo Clinic)

68 patients with 2 or more CT scans before pancreatic cancer diagnosis

Muscle and AT wasting before diagnosis





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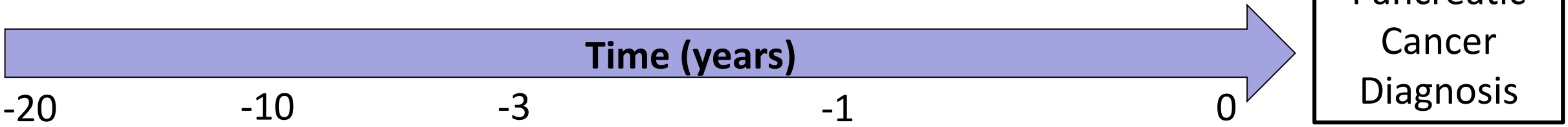

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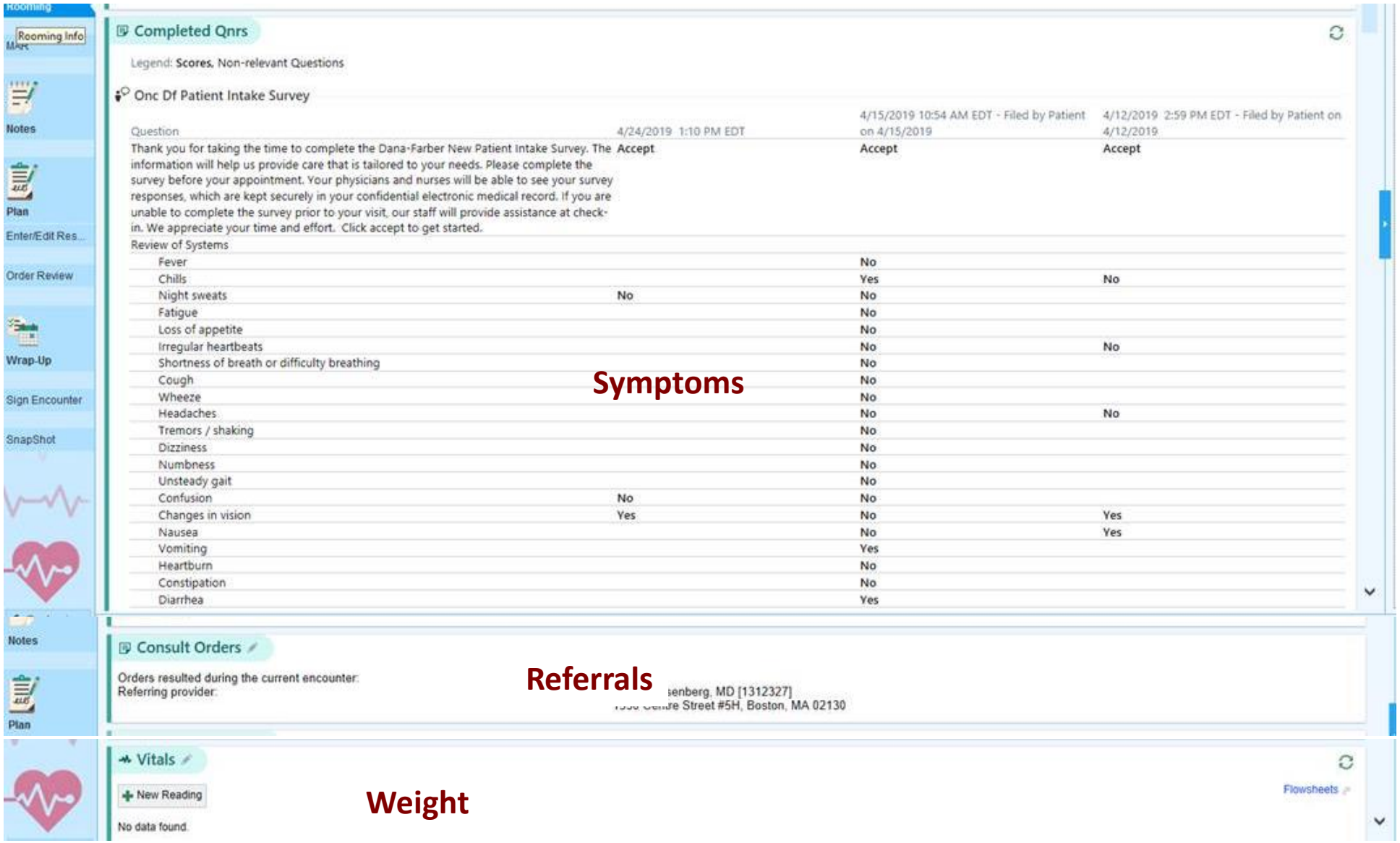
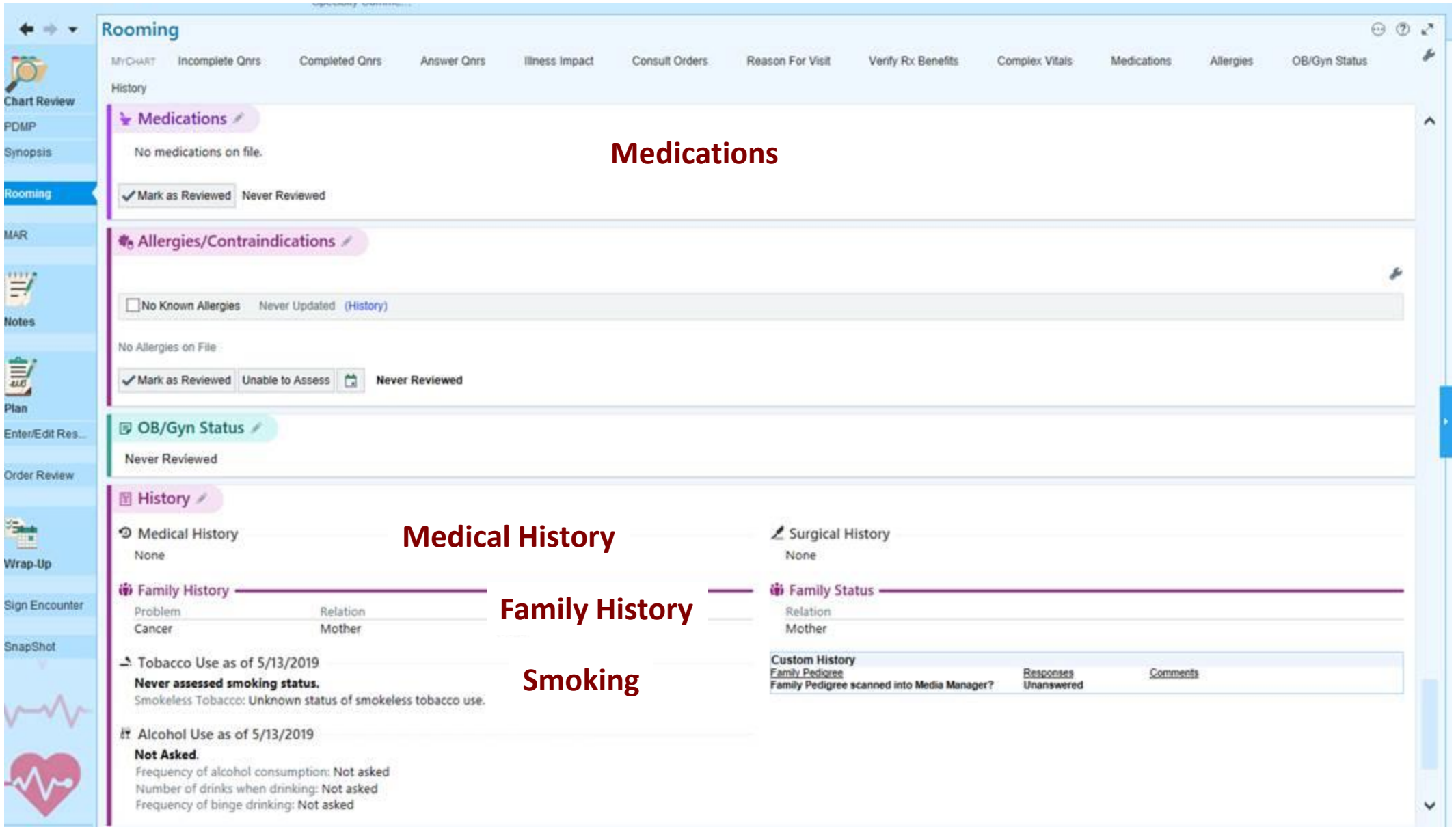

Rooming Info
Notes
Plan
Enter/Edit Res...
Order Review
Wrap-Up
Sign Encounter
SnapShot
Notes
Plan
Completed Qnrs
Legend: Scores, Non-relevant Questions
Onc Df Patient Intake Survey
Question
4/24/2019 1:10 PM EDT
4/15/2019 10:54 AM EDT - Filed by Patient on 4/15/2019
4/12/2019 2:59 PM EDT - Filed by Patient on 4/12/2019
Thank you for taking the time to complete the Dana-Farber New Patient Intake Survey. The information will help us provide care that is tailored to your needs. Please complete the survey before your appointment. Your physicians and nurses will be able to see your survey responses, which are kept securely in your confidential electronic medical record. If you are unable to complete the survey prior to your visit, our staff will provide assistance at check-in. We appreciate your time and effort. Click accept to get started.
Accept
Accept
Accept
Review of Systems
Fever
No
Chills
Yes
No
Night sweats
No
No
Fatigue
No
Loss of appetite
No
Irregular heartbeats
No
No
Shortness of breath or difficulty breathing
No
Cough
No
Wheeze
No
Headaches
No
No
Tremors / shaking
No
Dizziness
No
Numbness
No
Unsteady gait
No
Confusion
No
No
Changes in vision
Yes
No
Yes
Nausea
No
Yes
Vomiting
Yes
Heartburn
No
Constipation
No
Diarrhea
Yes
Symptoms
Consult Orders
Orders resulted during the current encounter:
Referring provider:
senberg, MD [1312327]
e Street #5H, Boston, MA 02130
Referrals
Vitals
New Reading
No data found.
Flowsheets
Weight


Rooming
MyCHART
Incomplete Qnrs
Completed Qnrs
Answer Qnrs
Illness Impact
Consult Orders
Reason For Visit
Verify Rx Benefits
Complex Vitals
Medications
Allergies
OB/Gyn Status
History
Chart Review
PDMP
Synopsis
Rooming
MAR
Notes
Plan
Enter/Edit Res...
Order Review
Wrap-Up
Sign Encounter
SnapShot
Medications
No medications on file.
Mark as Reviewed
Never Reviewed
Allergies/Contraindications
No Known Allergies
Never Updated
(History)
No Allergies on File
Mark as Reviewed
Unable to Assess
Never Reviewed
OB/Gyn Status
Never Reviewed
History
Medical History
None
Surgical History
None
Family History
Problem
Relation
Cancer
Mother
Family Status
Relation
Mother
Tobacco Use as of 5/13/2019
Never assessed smoking status.
Smokeless Tobacco: Unknown status of smokeless tobacco use.
Custom History
Family Pedigree
Responses
Comments
Family Pedigree scanned into Media Manager?
Unanswered
Alcohol Use as of 5/13/2019
Not Asked.
Frequency of alcohol consumption: Not asked
Number of drinks when drinking: Not asked
Frequency of binge drinking: Not asked
Medications
Medical History
Family History
Smoking

Machine Learning for Pancreatic Cancer Early Detection

Identifying individuals at high risk for pancreatic cancer through machine learning analysis of clinical records and images

DFCI: Michael Rosenthal, Chris Sander, Brian Wolpin
HSPH: Peter Kraft
MIT: Regina Barzilay

End Goal

Develop practical tool to identify individuals in the general population at elevated risk for pancreatic cancer who should be enrolled in **interception programs** for disease **prevention** and **early detection**.

Pancreatic Cancer Early Detection

- Data overload: Weighing numerous inputs for earlier diagnosis of pancreatic cancer
- What to look for: Host reactions to an early tumor - altered systemic metabolism
- Imaging: Latent information beyond looking for a tumor in a specific organ
- Change over time: Information in repeated measures
- Personalized medicine for early detection

Early Detection Team

DFCI

Michael Rosenthal
Ana Babic
Natalia Khalaf
Chen Yuan
Jonathan Nowak
Vicente Morales
Lauren Brais
Zunelly Odhiambo
Marisa Welch
Natalia Boos
Maureen Loftus
Leah Caplan

MIT

Matthew Vander Heiden
Laura Danai
Jared Mayers

Harvard Cohort Studies

Peter Kraft
Charlie Fuchs
Ed Giovannucci
JoAnn Manson
Jihye Kim
Meir Stampfer
Howard Sesso
Julie Buring

Collaborating Institutions

Clary Clish (Broad Inst)
Julian Avila (Broad Inst)
Gloria Peterson (Mayo Clinic)
Albert Koong (MDACC)
Nabeel Bardeesy (MGH)
Carlos Fernandez (MGH)
Pari Pandharipande (MGH)
Jen Jen Yeh (UNC)
Alison Klein (JHU)
Laufey Amundadottir (NCI)
Rachael Solomon (NCI)
Tilak Sundaresan (KPNC)
Bette Caan (KPNC)

LUSTGARTEN FOUNDATION PANCREATIC CANCER COLLECTIVE
STAND UP TO CANCER

NATIONAL CANCER INSTITUTE

DANA-FARBER CANCER INSTITUTE
HALE FAMILY RESEARCH CENTER

LUSTGARTEN FOUNDATION PANCREATIC CANCER RESEARCH

DFCI-LF Dedicated Pancreatic Cancer Research Laboratory

Team Approach

Thank you.

SU2C-LF Interception Dream Team
PIs: Anirban Maitra (MDACC), Mike Goggins (JHU), Scott Lippman (UCSD)
Judy Garber, Sapna Syngal, Brian Wolpin, Matt Yurgelun (DFCI)
Elliott Fishman Liz Jaffee, Ken Kinzler, Alison Klein, Bert Vogelstein (JHU)
Gloria Petersen (Mayo)
Sam Hanash, Eugene Koay, Florencia McAllister (MDACC)
Tyler Jacks (MIT)
Barbara Kenner, Scott Nelson (Advocates)

Pancreatic Cancer Detection Consortium
NIH/NCI U01 CA 210171
PI: Brian Wolpin
Pasi Janne, Cloud Paweletz, Michael Rosenthal, Sapna Syngal (DFCI)
Nabeel Bardeesy, Dan Chung, Ralph Weissleder, (MGH)
Yuval Dor (Hebrew Univ)
Clary Clish (Broad Inst)
Peter Kraft (HSPH)
Jeanine Genkinger (CUMC)
Andrea Bullock (BIDMC)
David Kelsen (MSKCC)