18th Annual Fall Midwest Thoracic and GI Oncology Conference
University of Nebraska Medical Center, Omaha, NB

FRIDAY, SEPTEMBER 8, 2023
11:00 AM - 11:40 AM

Prevention of Pancreatic Cancer by:

TARGETING PANCREATIC NEOPLASTIC CYSTS

Mokenge (MO), Malafa, MD, FACS
Senior member & surgical oncologist, Moffitt Cancer Center
Professor, University of South Florida

DISCLOSURES

I am a Principal Investigator of a clinical trial which is being funded by the NIH.

I am an inventor of a patent through Moffitt Cancer Center for the use of Delta-Tocotrienol to prevent cancer.

Targeting Pancreatic Neoplastic Cysts

LEARNING OBJECTIVES

1

Articulate

Articulate the importance of pancreatic neoplastic cysts in healthcare.

2

Recognize

Recognize the absence of any FDA approved agents to treat pancreatic neoplastic cysts.

3

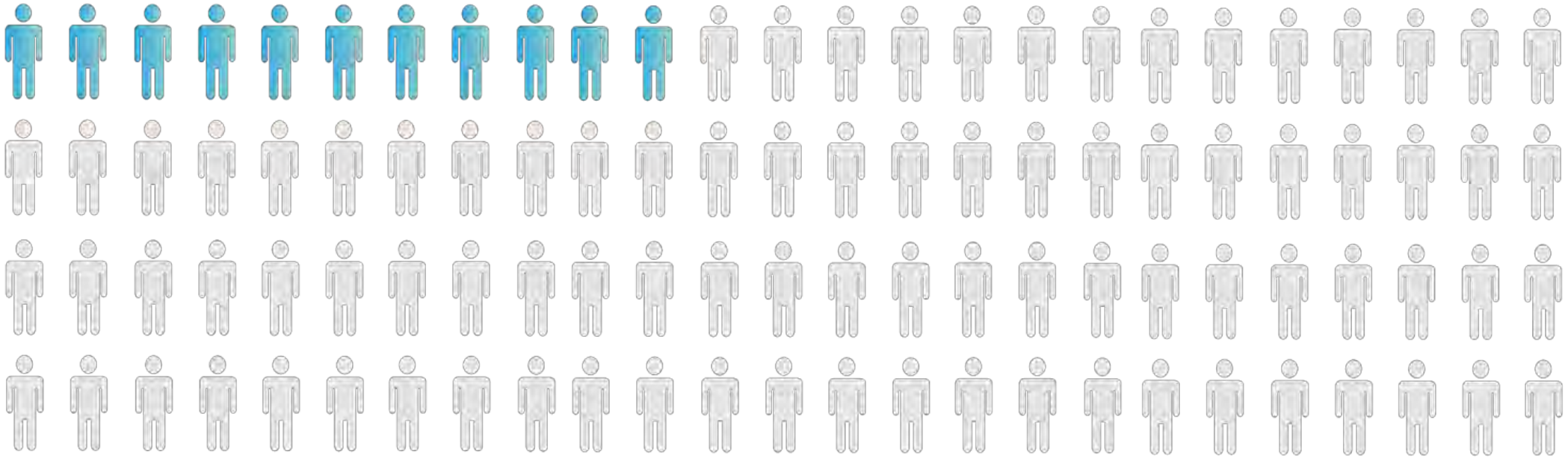
Describe

Describe the rationale and design of an NIH sponsored trial targeting pancreatic neoplastic cysts for the prevention of pancreatic cancer.

Problem:

PANCREATIC CANCER

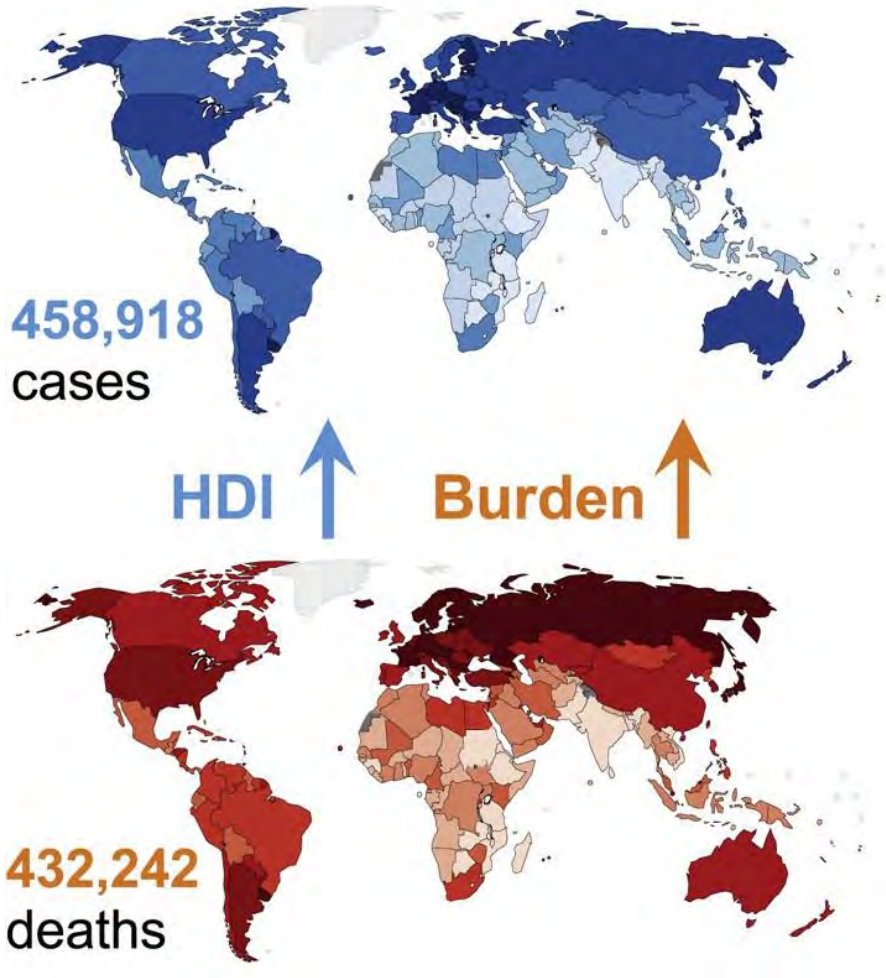
- Pancreatic cancer is an enormous and worsening healthcare burden
  - **Reducing the risk of developing PDAC will be impactful to human health.**

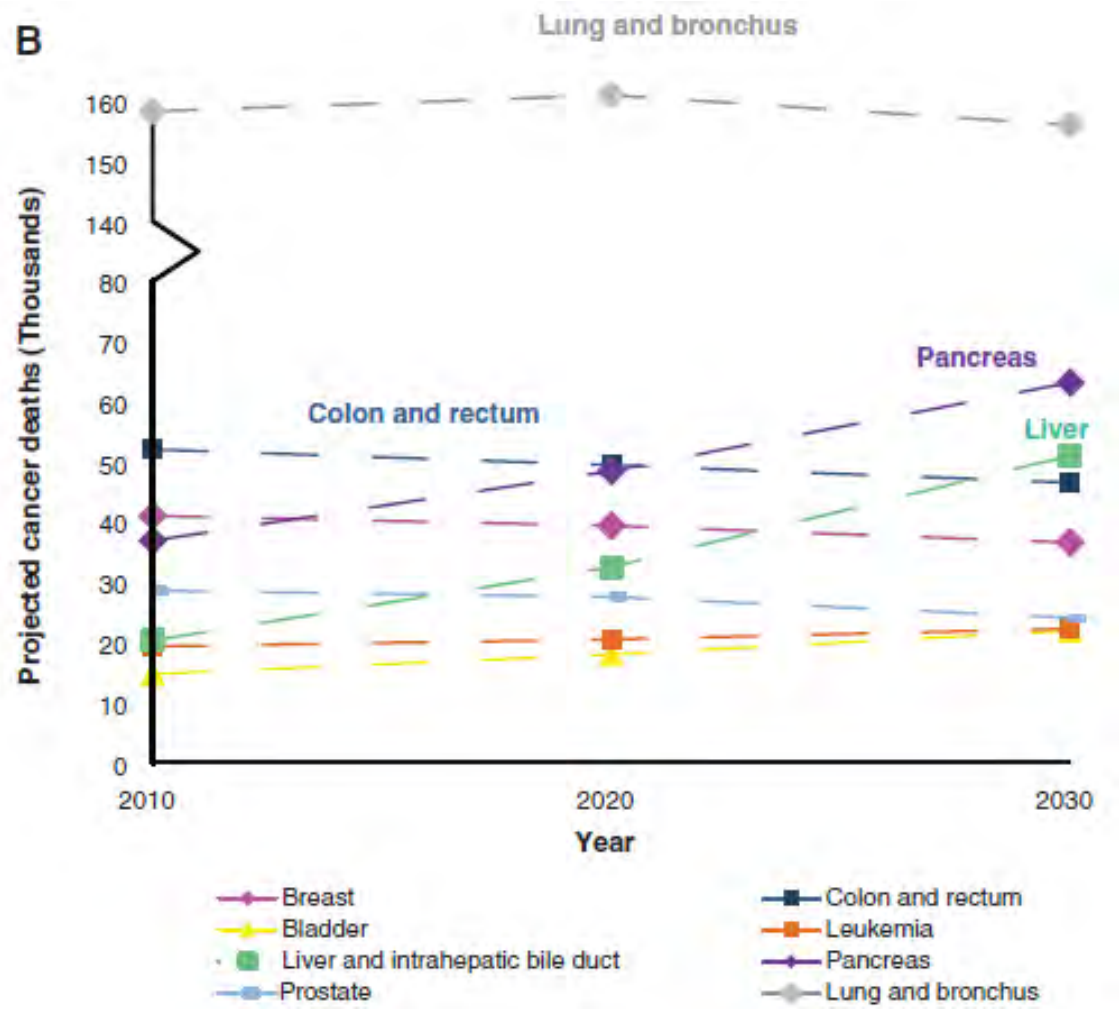


Problem:

PANCREATIC CANCER

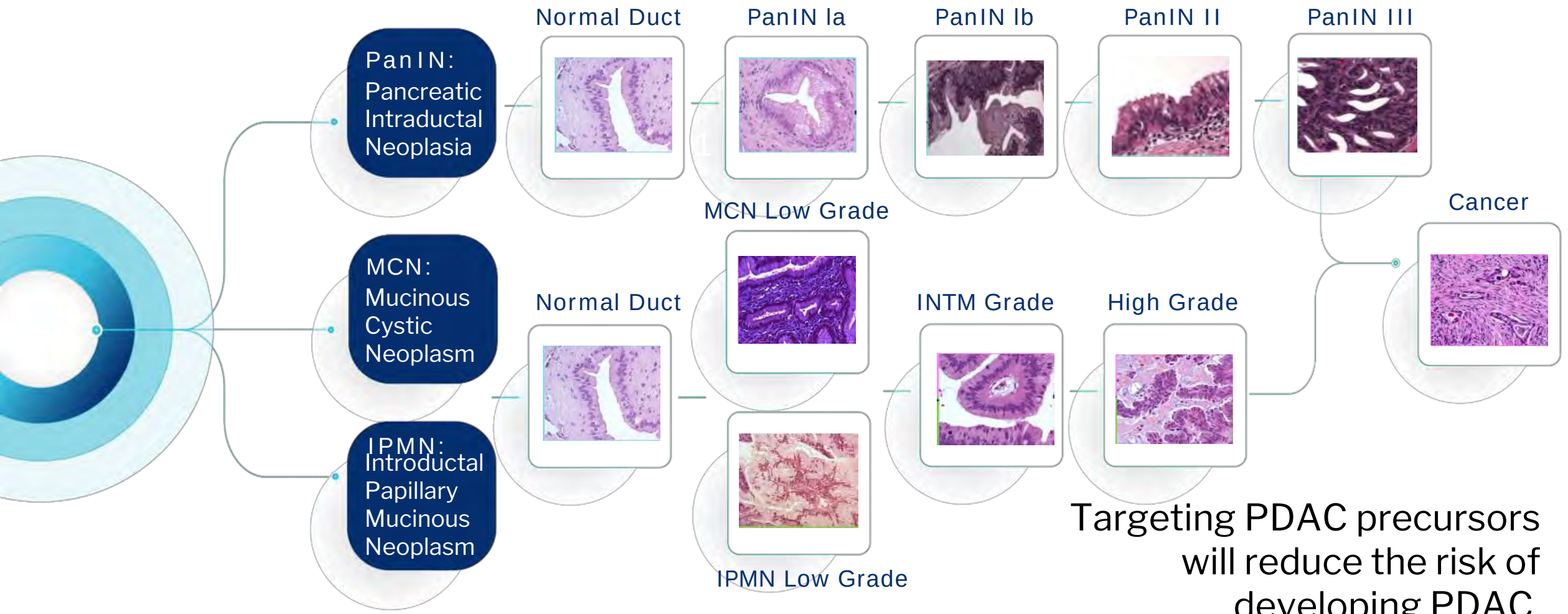
Rahib,L et al. Cancer Research, 2014.





Pancreatic Ductal Adenocarcinoma:

PRECURSOR LESIONS

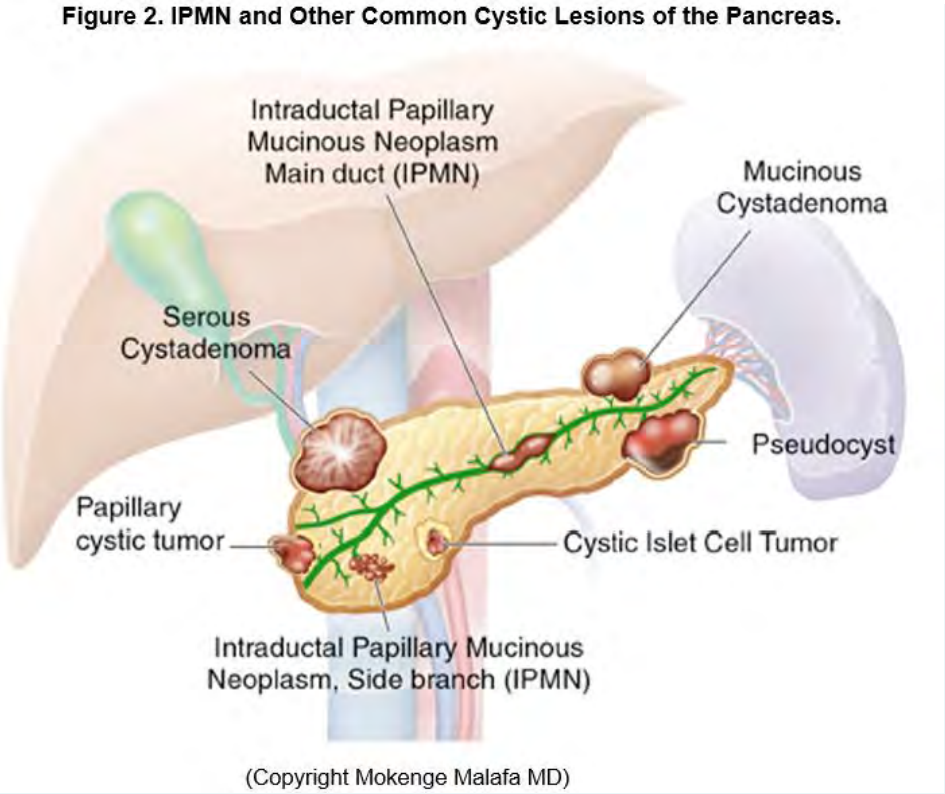


Targeting PDAC precursors will reduce the risk of developing PDAC.

Pancreatic Ductal Adenocarcinoma:

IPMN OF THE PANCREAS

- First described by Ohashi et al in 1982.
- Incidence is unknown since most asymptomatic
  - CT Study 2.6%
  - MRI Study 13.5%
- More common in: smokers, DM, family history and familial PDAC, Peutz-Jeghers syndrome, and FAP.
- 30% Resected PDAC arise from IPMN.



Management:

IPMN OF THE PANCREAS

1982

Described
Ohashi et al.

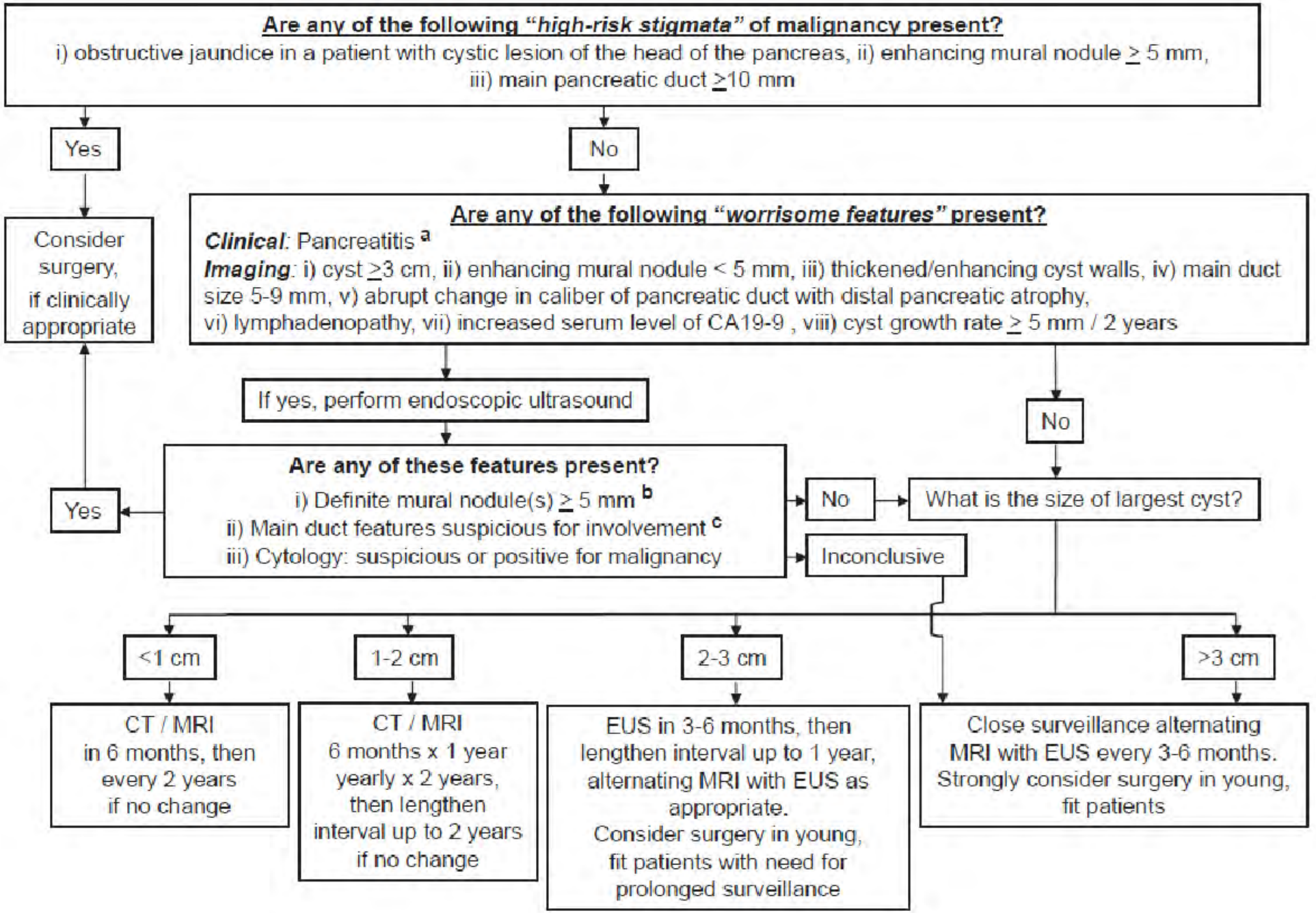
2006

International
Consensus
(IAP)

2012

International
Consensus
(IAP)

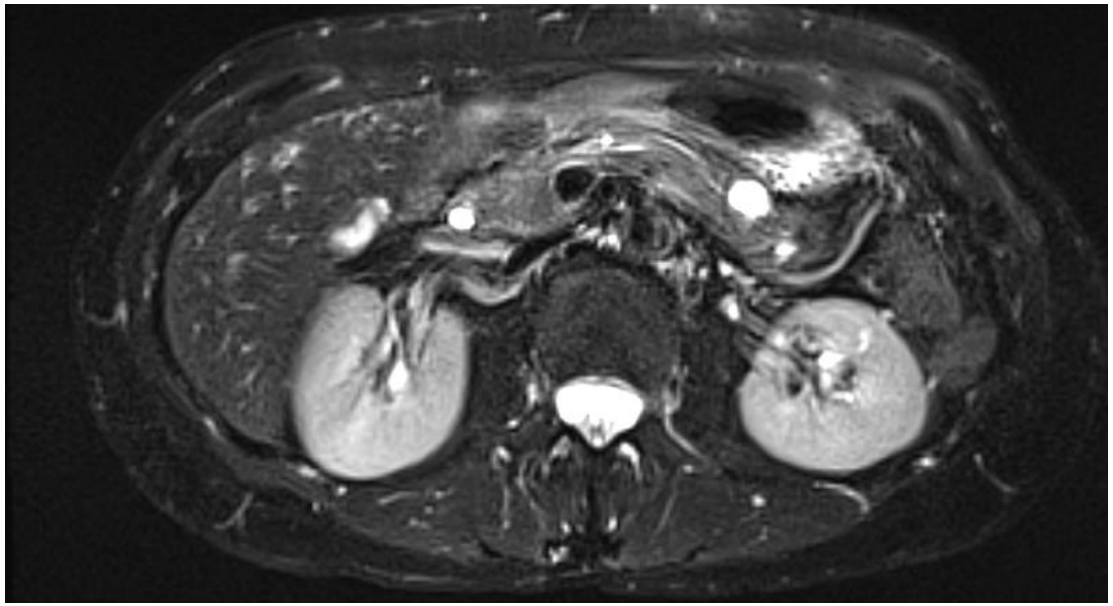
2017

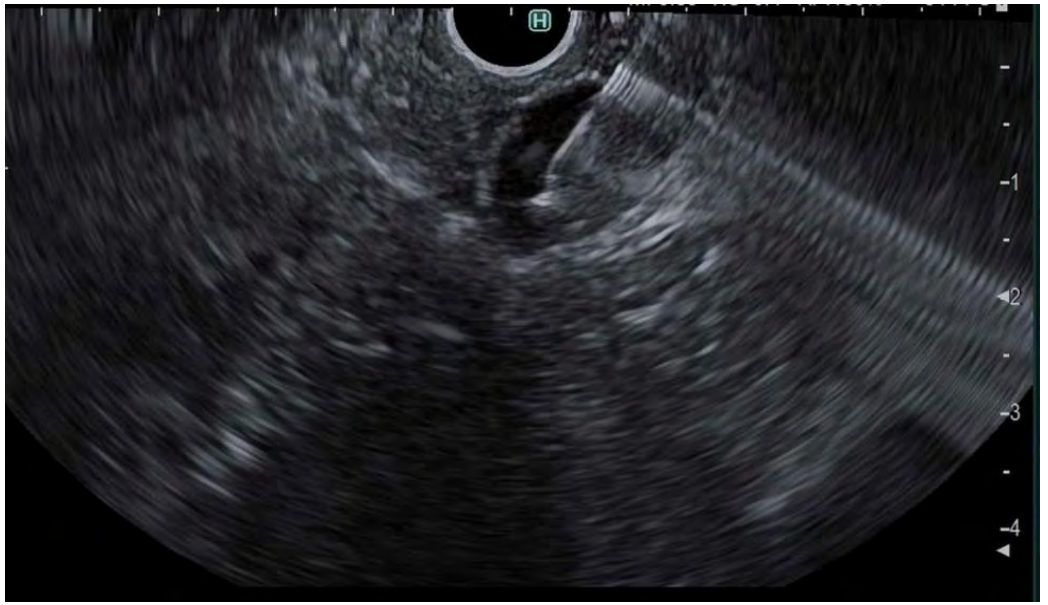


Tanaka.Pancreatology.2017

IPMN of the Pancreas

72 F 2.5 cm SB-IPMN





Pancreas Results Summary: Genomic Alterations Identified

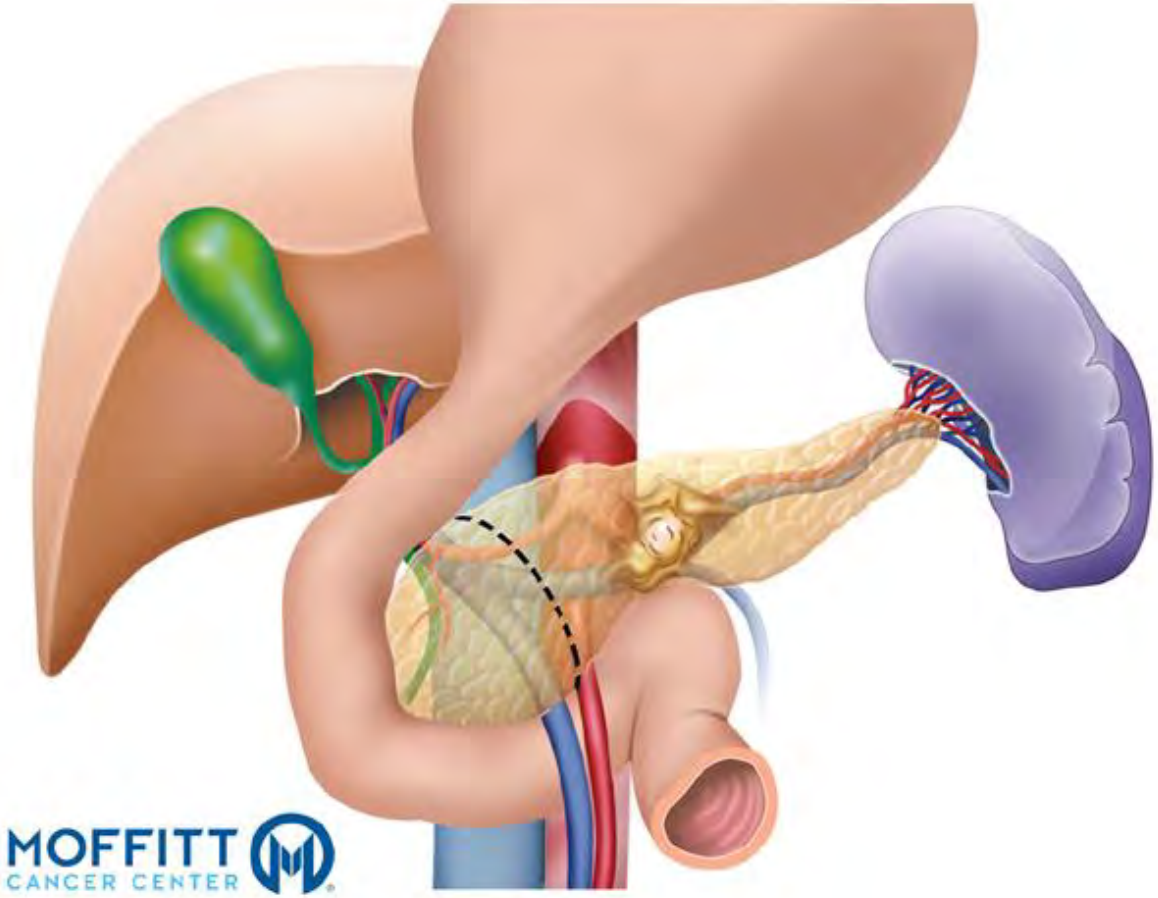
- **GNAS mutation** p. R201H
- **BRAF mutation** p.N486_Q493delinsTOE
- **PIK3CA mutation** p.E110del

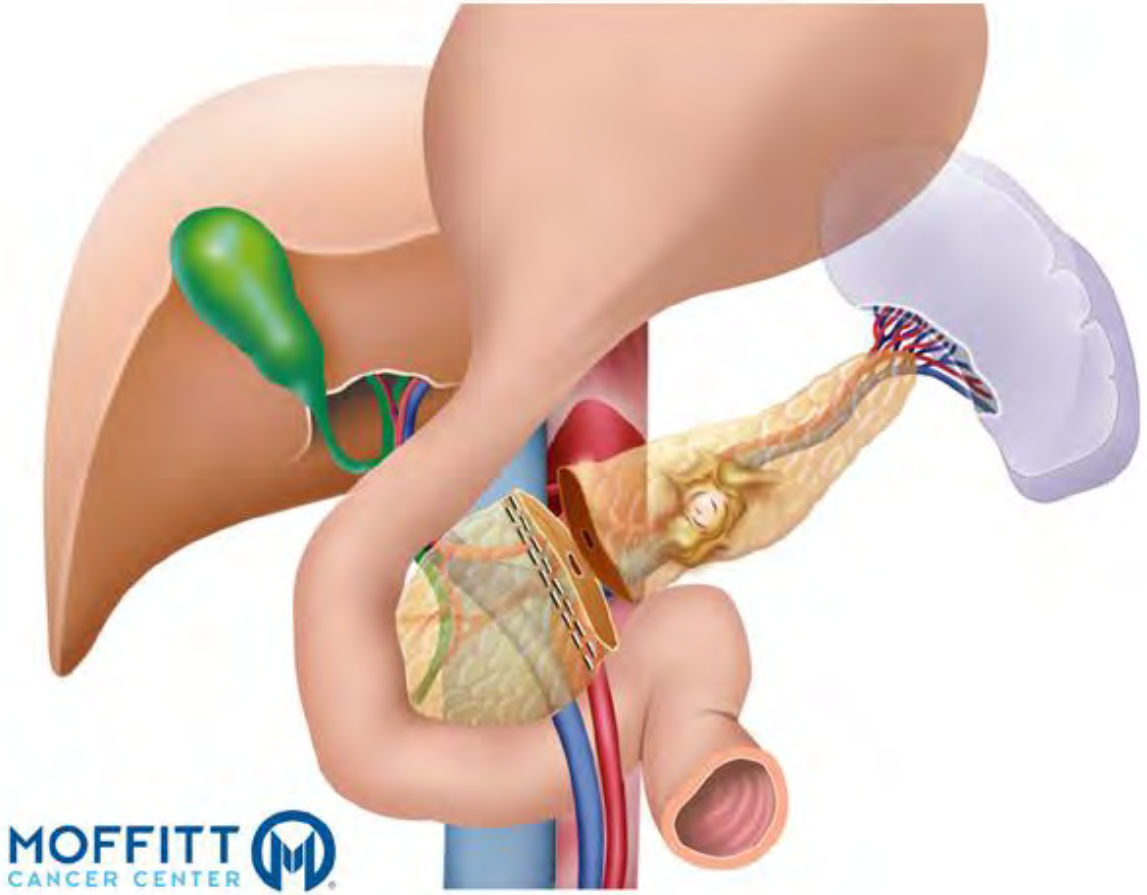
See interpretation and Detailed Results

PancreaSeq®

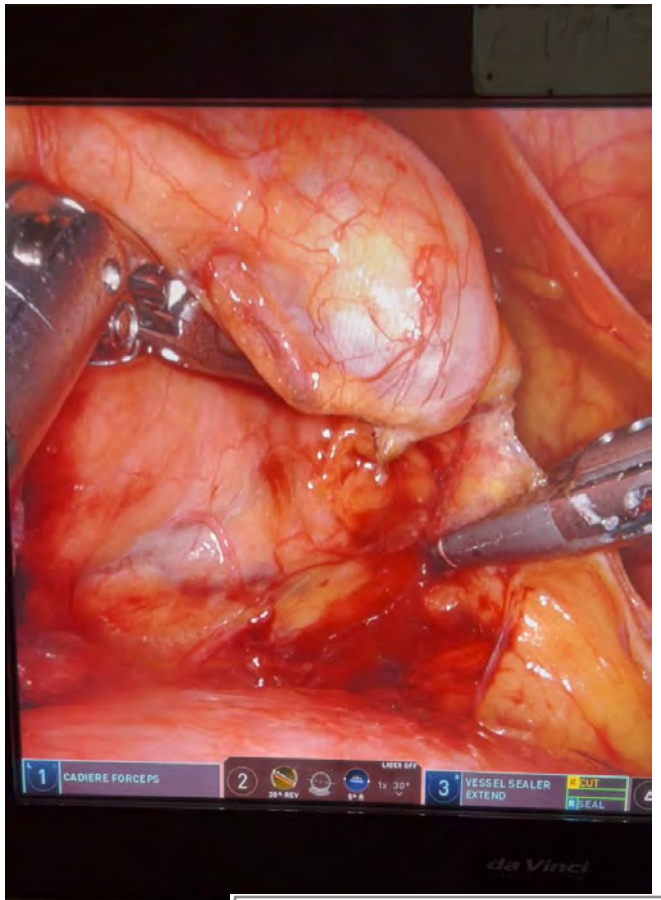
Graphic examples:

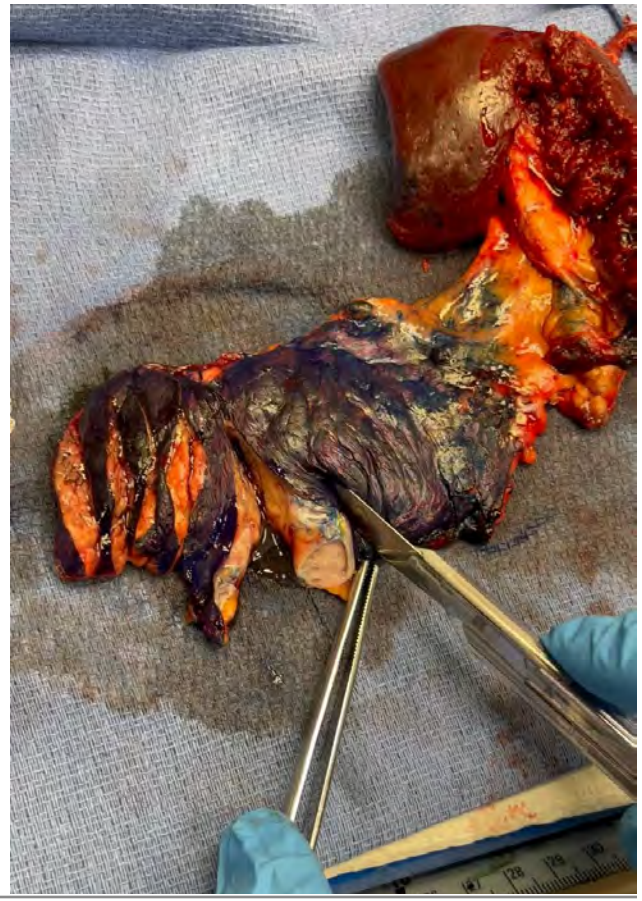
DISTAL PANCREATECTOMY & SPLENECTOMY





72 F 2.5 cm SB-IPMN





Final Diagnosis

A. NECK, BODY AND TAIL OF PANCREAS WITH SPLEEN, DISTAL PANCREATECTOMY AND SPLENECTOMY:

Intraductal papillary mucinous neoplasm, within branching ducts, entirely excised.

The first IPMN measures 2.5 cm; the second measures 1.0 cm; consistent with gastric type IPMN.

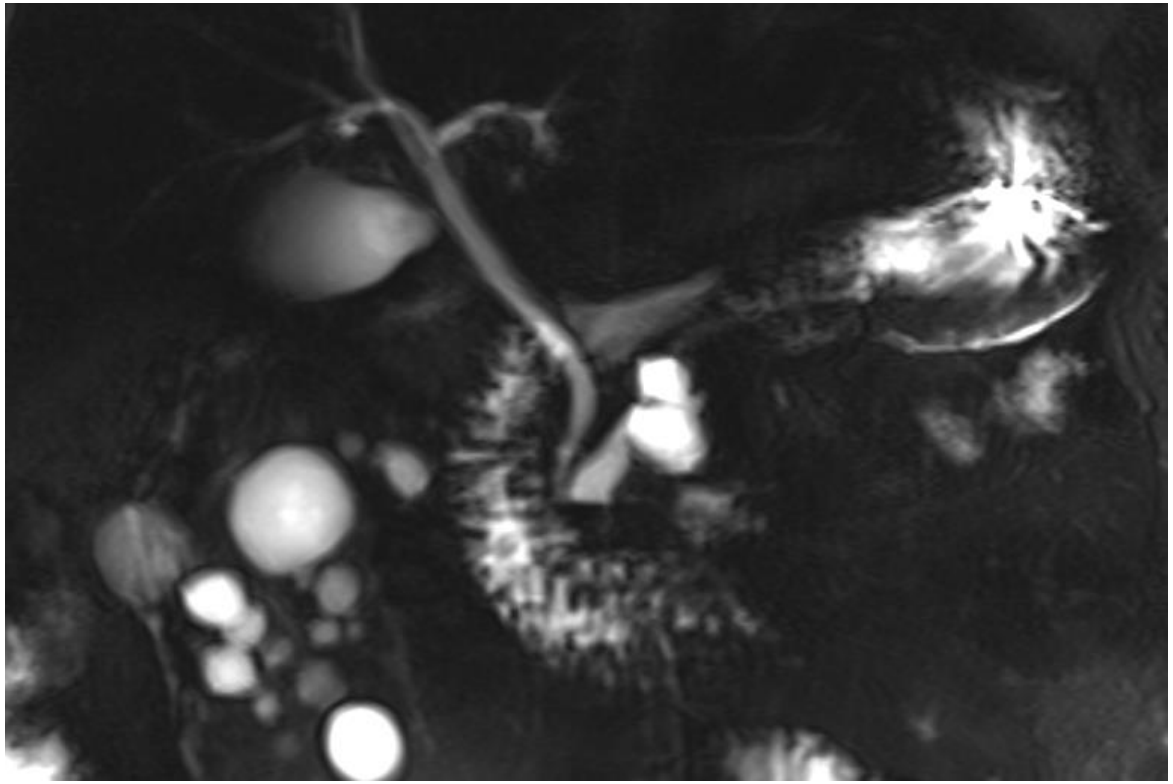
Resection margins are benign.

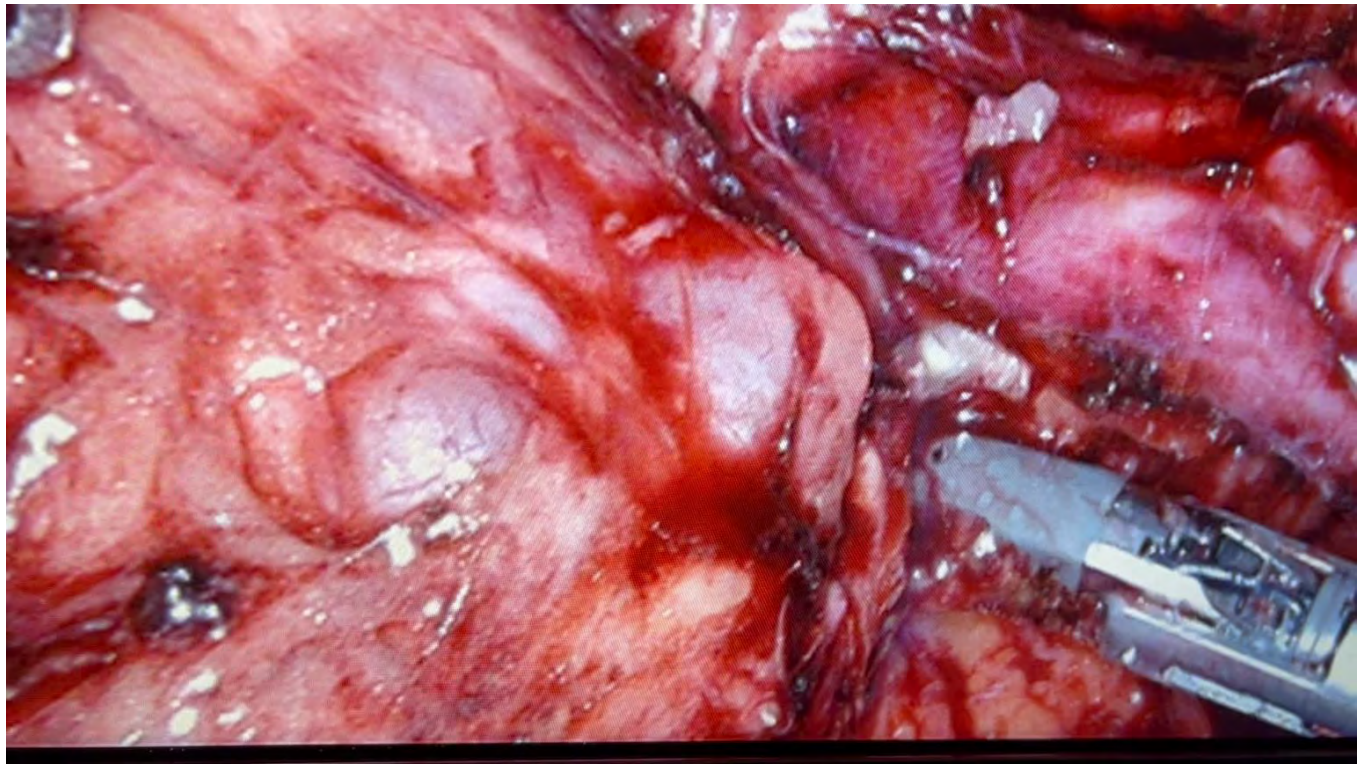
Microscopic foci of high-grade dysplasia seen.

No invasive carcinoma identified in the entirely submitted cysts.

IPMN of the Pancreas

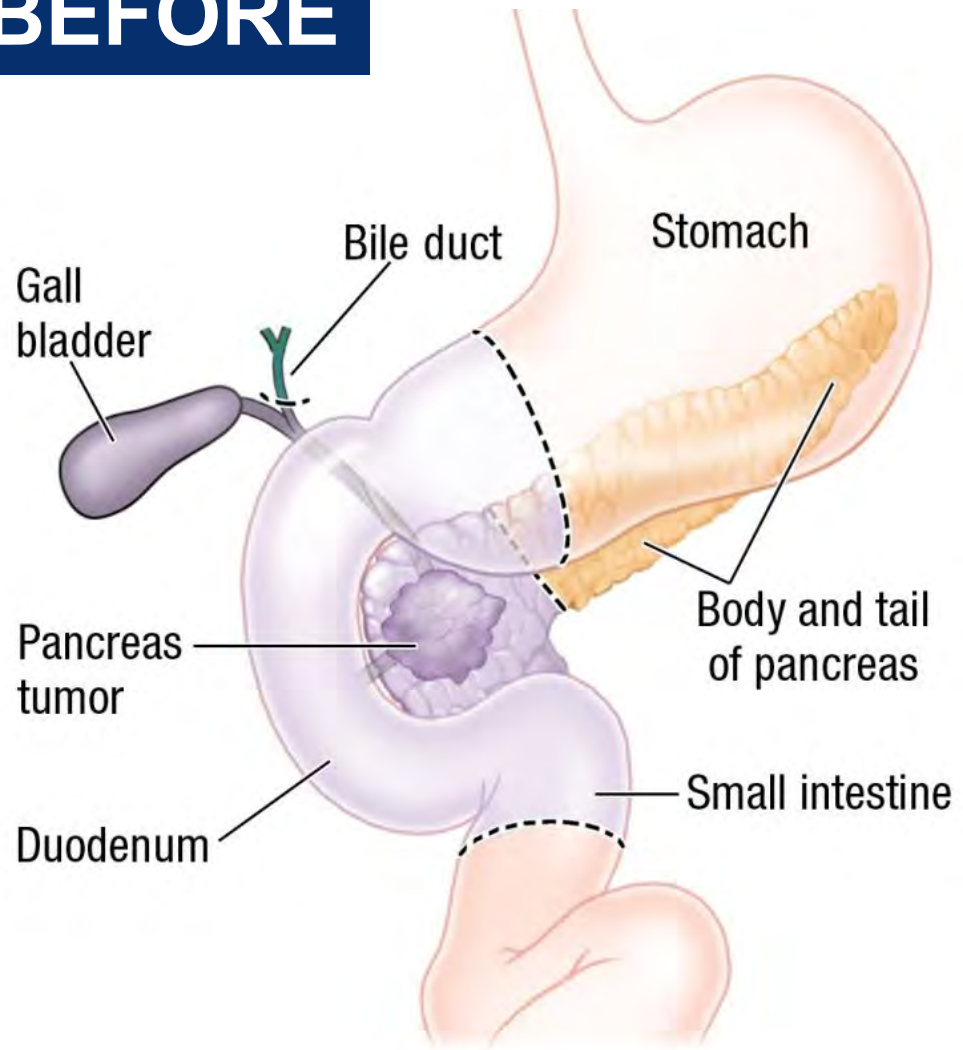
77 M 2.5 cm Mixed Type-IPMN



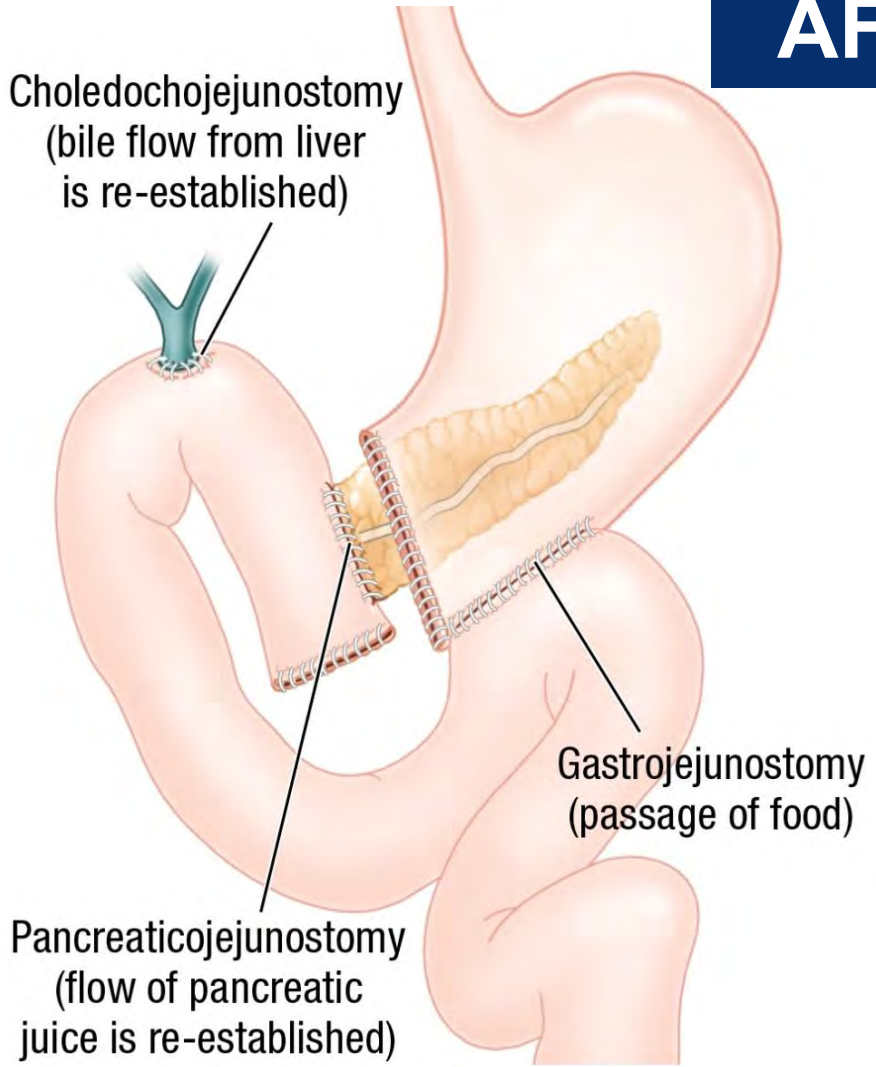


THE WHIPPLE PROCEDURE

BEFORE

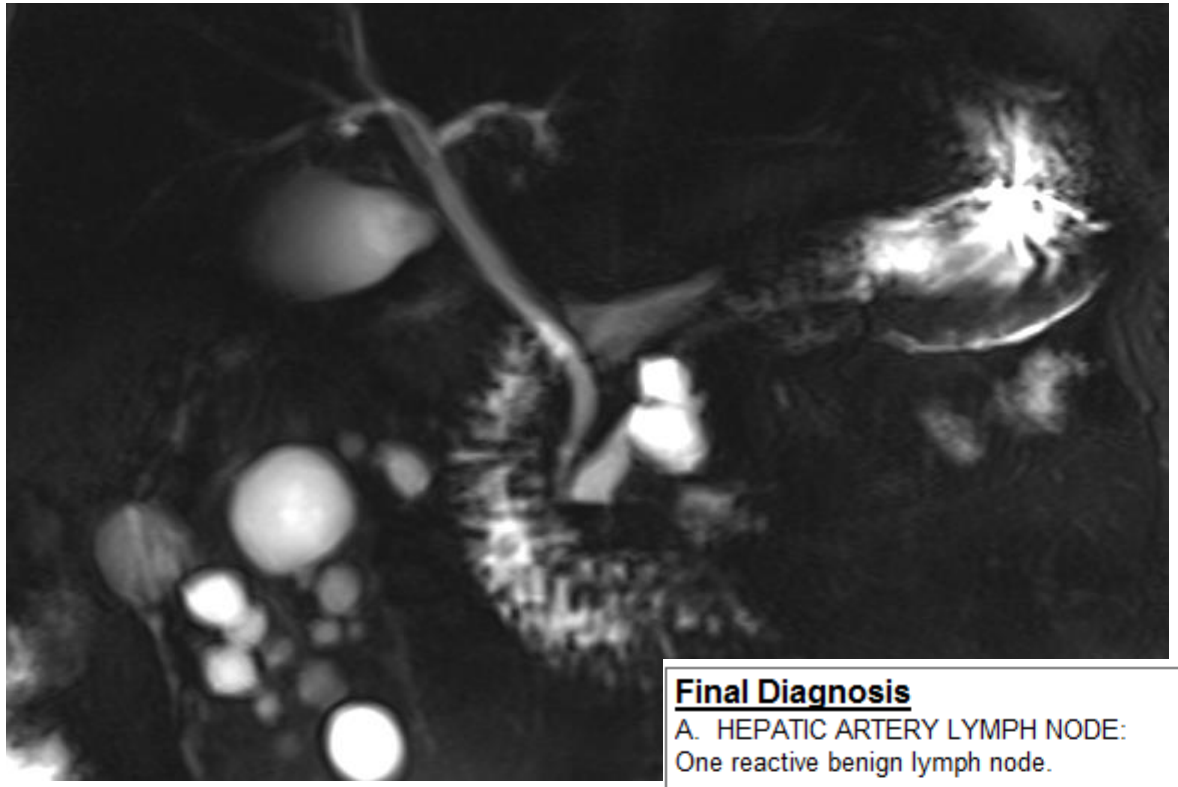


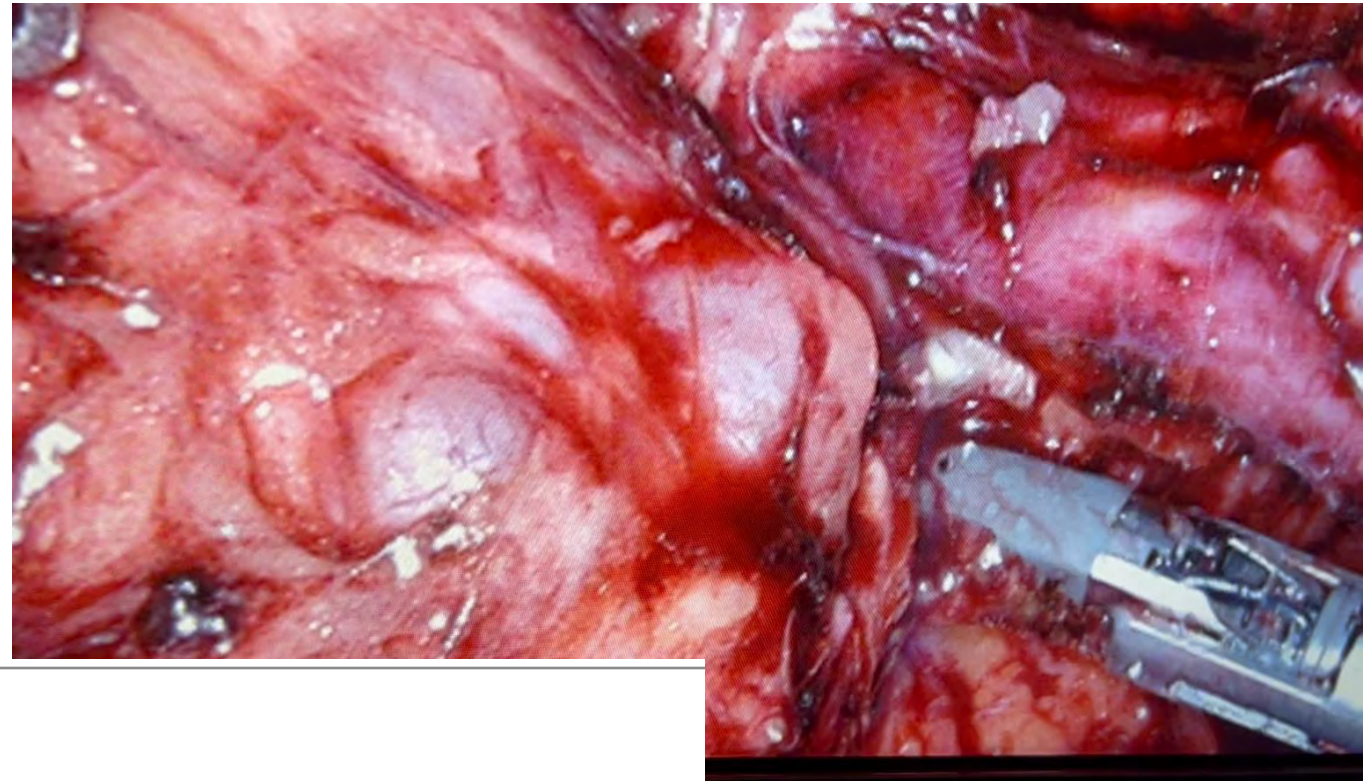
AFTER



IPMN of the Pancreas

77 M 2.5 cm Mixed Type-IPMN





Final Diagnosis

A. HEPATIC ARTERY LYMPH NODE:
One reactive benign lymph node.

B. PANCREAS, STOMACH, COMMON BILE DUCT, GALLBLADDER AND DUODENUM, WHIPPLE RESECTION:
Intraductal papillary mucinous neoplasm (IPMN), grossly 2.5 cm, with low and focally high-grade dysplasia; see comment.
No invasive adenocarcinoma was identified in the entirely submitted and examined IPMN.
IPMN is gastric type, involving main and branching pancreatic ducts.
Background microscopic foci of pancreatic intraepithelial neoplasia, with low and high grade dysplasia.
15 benign lymph nodes.

IPMN OF THE PANCREAS: TREATMENT LANDSCAPE

1982 — Described Ohashi et al.

2006 — International Consensus (IAP).

2012 — International Consensus (IAP).

2017

2009

SB-IPMN Sulindac Trial (n=22)

- Sulindac 150 mg BID with Omeprazole 20mg QD (n=10) for 18 months.
- Neither randomized or controlled.
- Decreased cyst size and mural nodule height in Rx group.
- *Hayashi et al. J. Gastroenterology 2009.*

2011

IPMN Erlotinib Trial (n=6)

- Erlotinib 100 mg QD for 21-42 days before surgical resection.
- Primary Endpoint was MUC5AC change. Occurred in 2/3.
- ? 1 patient with complete response.
- *Lipkin et al. CCR 2011.*

2020

NCI Phase 2 IPMN Sulindac Trial.
PI: Peter Allen, MD

2022

NCI Phase 2 IPMN Tocotrienol Trial.
PI: Mokenge Malafa, MD

❖ **There is an unmet need to develop noninvasive therapy for IPMN.**

Cancer Prevention:
INTERVENTIONS

Available today because of research.

Lifestyle Choices
Such as avoid or quit tobacco, limit alcohol, avoid known carcinogens, keep active and avoid obesity.

Medications
Proven to reduce risk of breast and colon cancers in those at increased risk.

Treatments for Infections
Known to increase cancer risk, including hepatitis C, HIV, and H. pylori.

Surgery
To remove tissues at risk, such as for women with increased risk of breast and ovarian cancer..

Screening Tests
That allow removal of precancerous lesions such as colon polyps.

Vaccines to Protect
Against infection with the human papillomavirus (HPV and hepatitis B.).

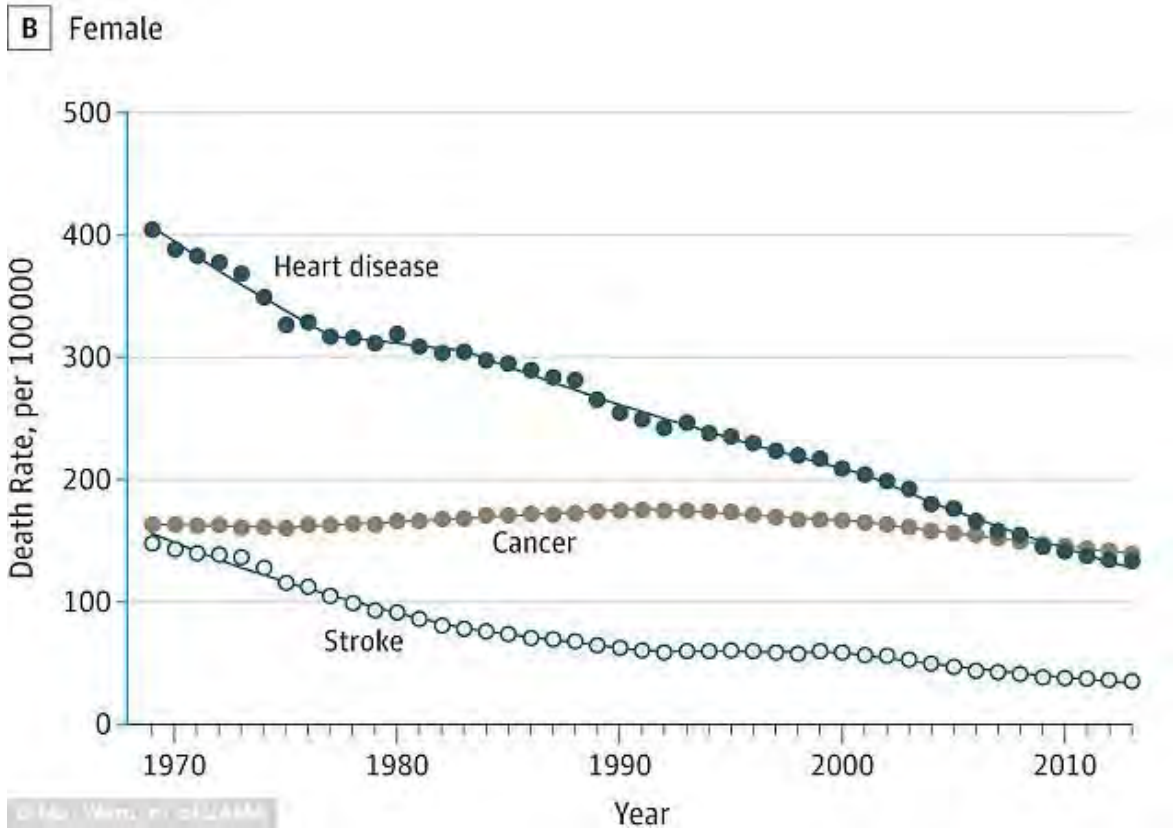
Definition

CHEMOPREVENTION

- Sporn (1976)
  - Use of drugs, biologics, or nutrients to inhibit carcinogenesis.

The Value of CHEMOPREVENTION

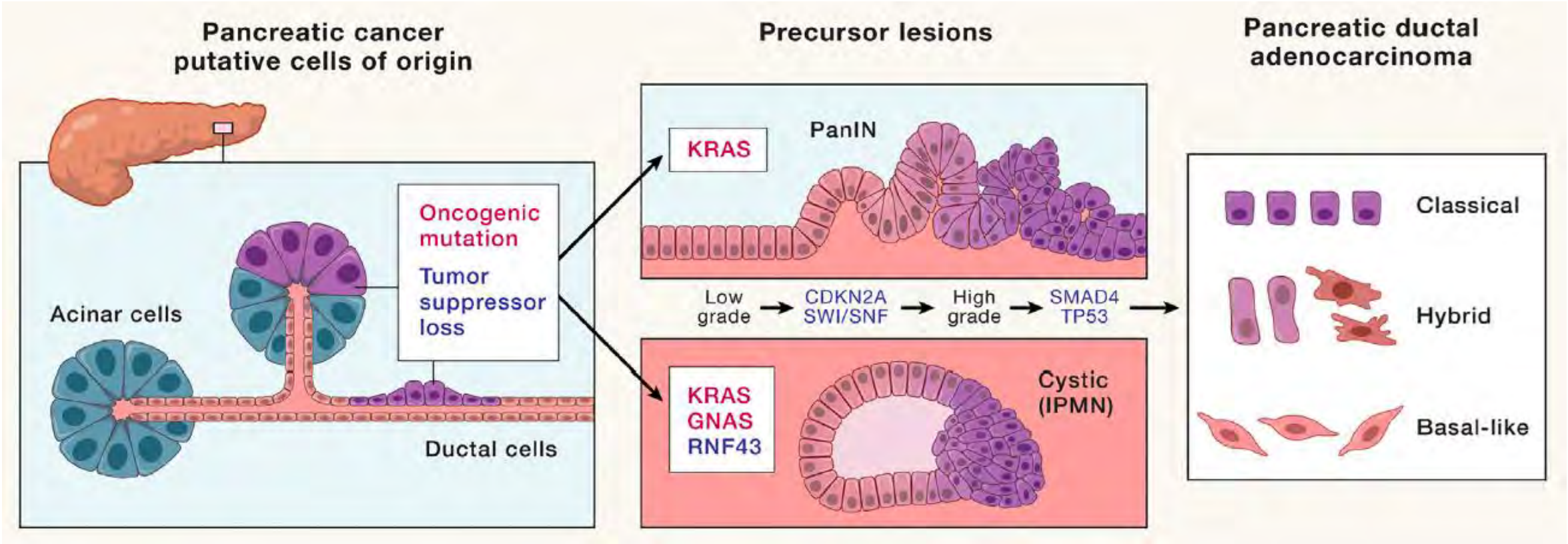
Lessons from heart disease.



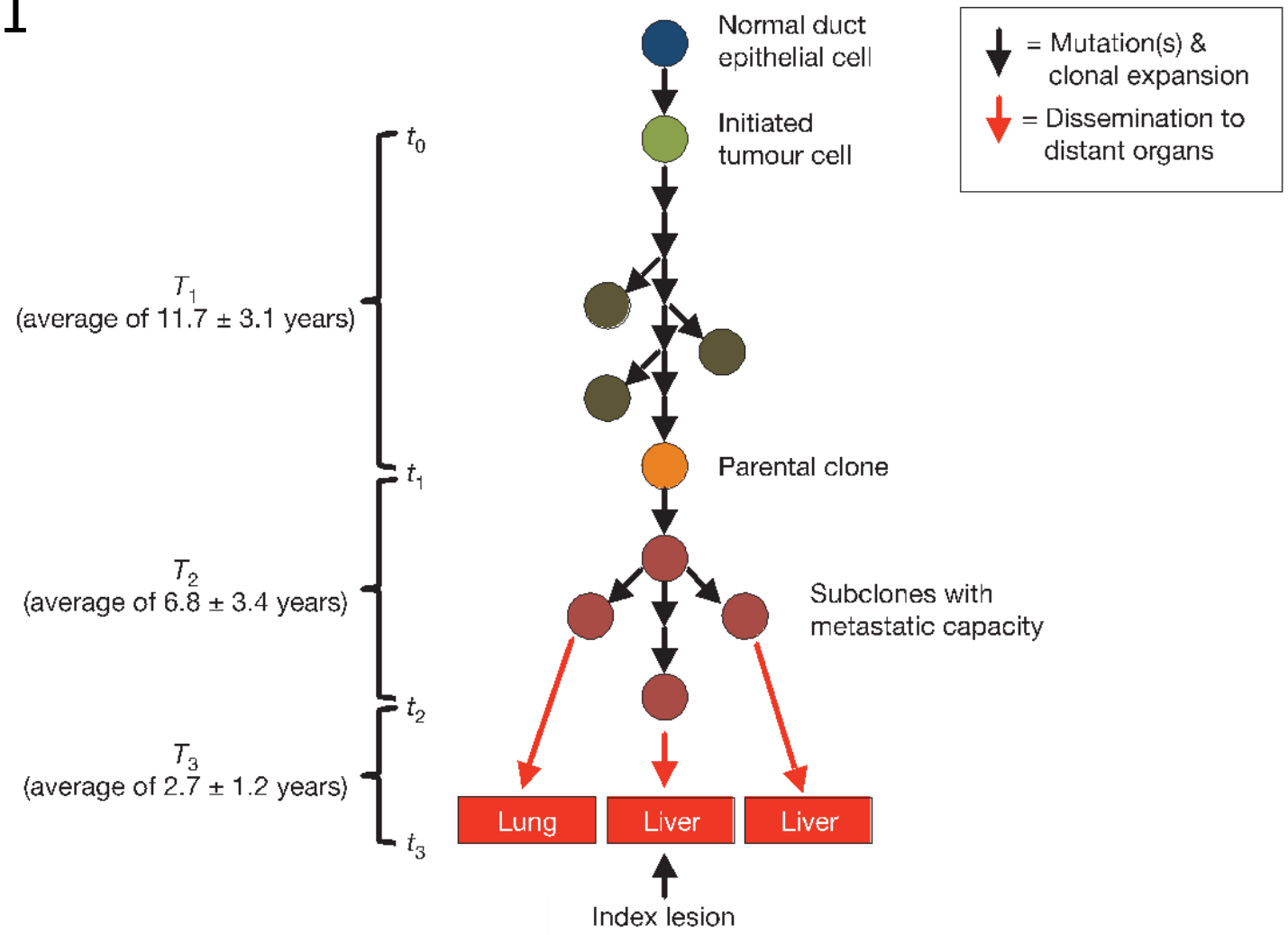
Rationale 1

Pancreatic Ductal Adenocarcinoma:

INITIATION & PROGRESS

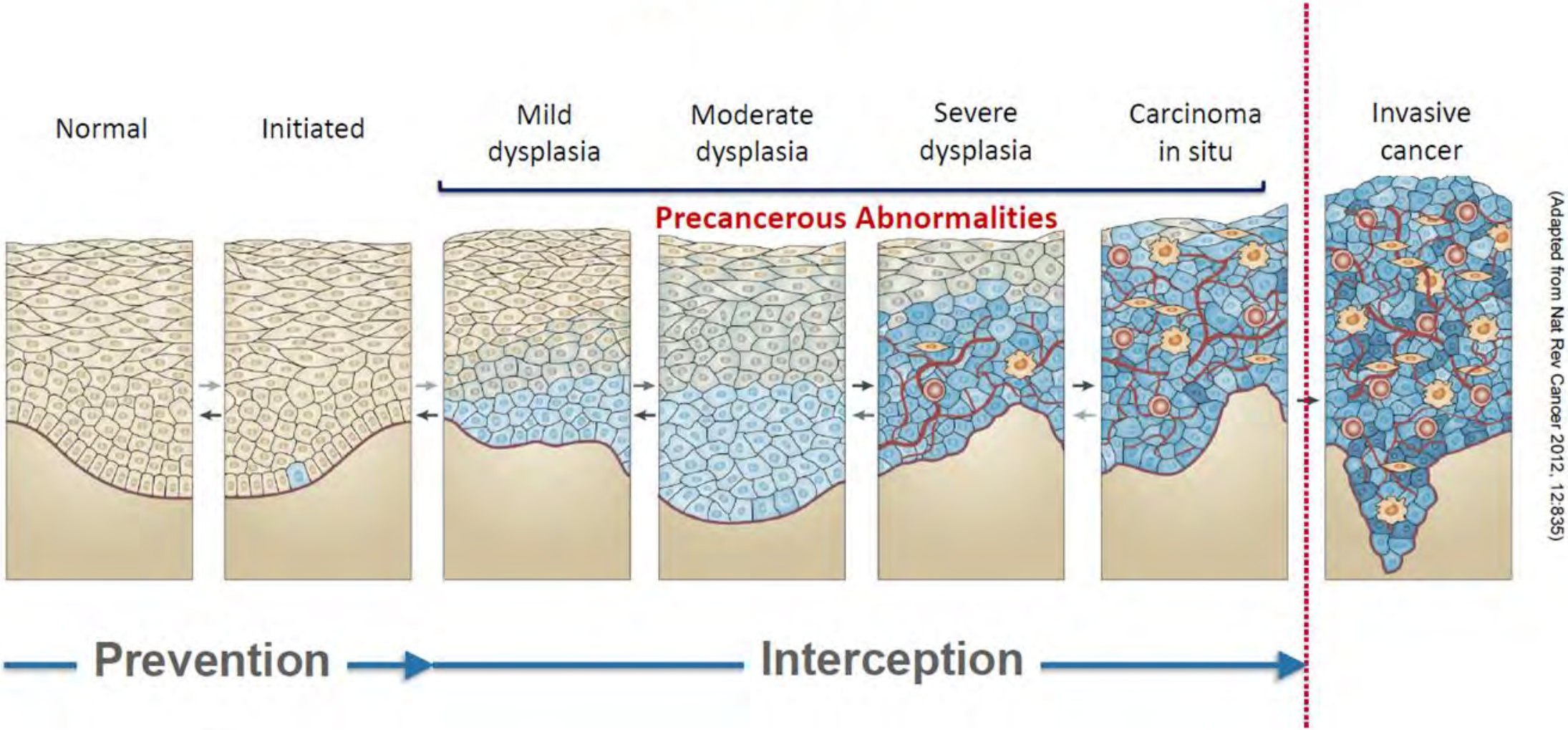


Rationale 1



Yachida S et al, Nature 2010

Working Definition of Cancer Prevention – Interception by CAP-IT



Precision Cancer Prevention for High-risk Groups

Individuals with heritable cancer syndromes (HCS) with/without precancerous abnormalities (precancer)

Individuals exposed to carcinogens without HCS with/wo precancer

Individuals with precancer without HCS & carcinogen exposure

Cancer Patients:

Efficacious therapeutics

STOP

High Risk Cohorts:

Preventive Strategies Tailored for Each High-risk Group

Precision Cancer Prevention-Interception

General Population:

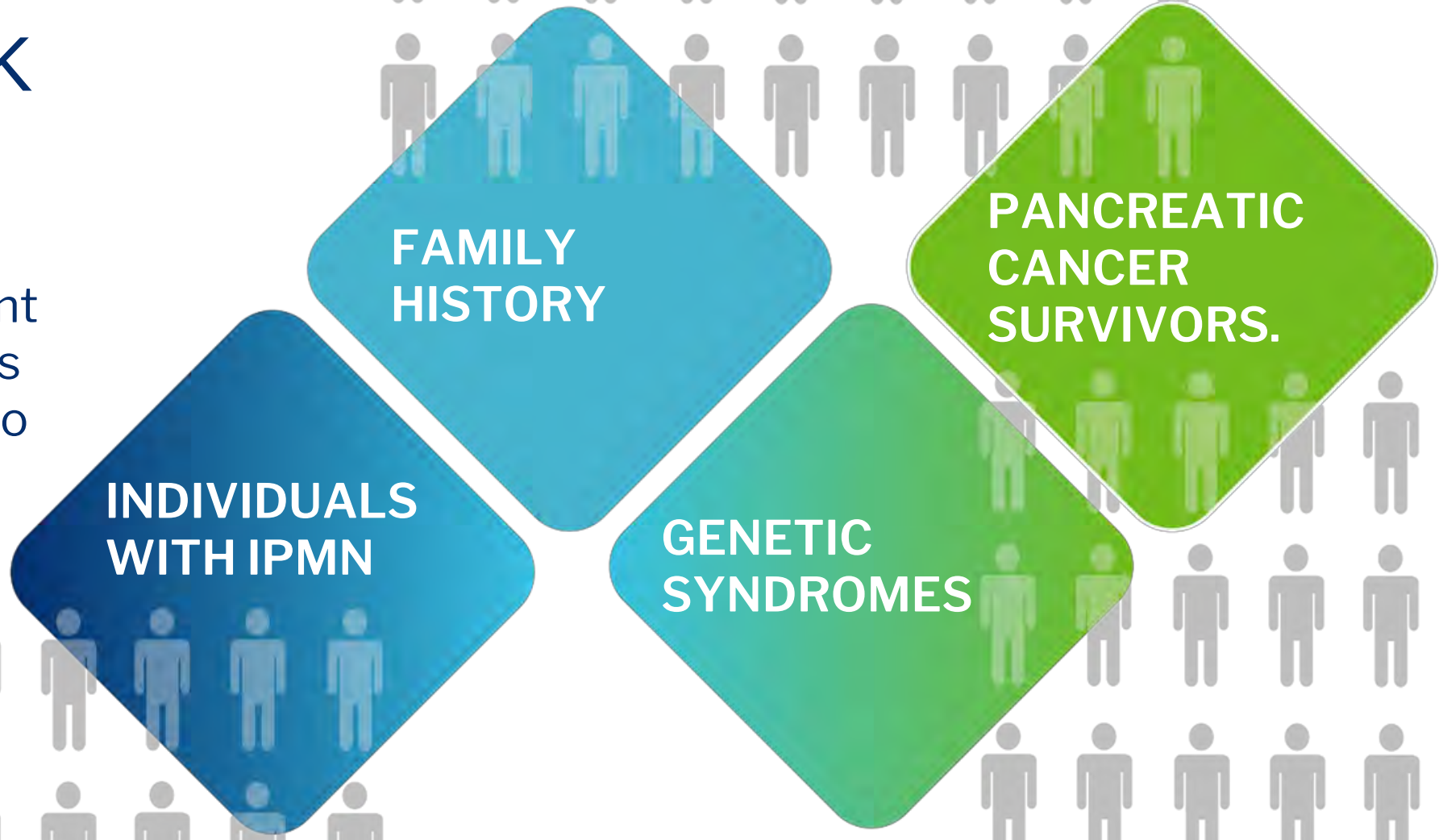
Avoid/Reduce Cancer Risks

(e.g. Smoking cessation, Healthy lifestyle, HBV vaccine, HPV vaccine, HCV Rx, etc)

Rationale 2

HIGH-RISK GROUPS

There are a significant number of individuals that are at high risk to develop pancreatic cancer.

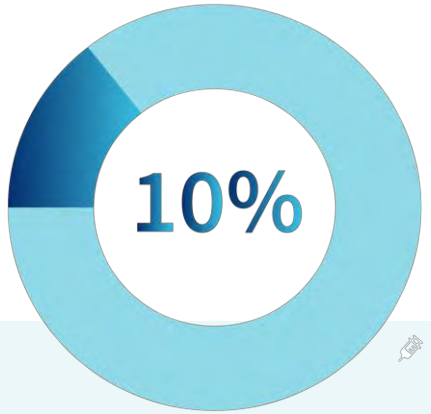


Rationale 3:

CHEMOPREVENTION

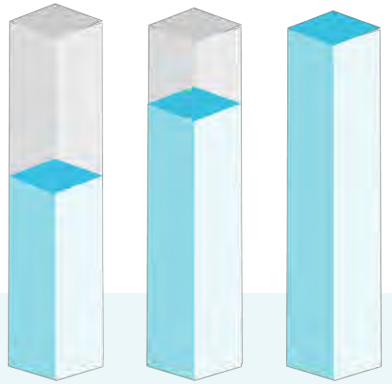
2012

- 330,000 individuals die of pancreatic cancer every year worldwide.



10% Decrease

- A 10% decrease in PDAC would prevent > 30,000 deaths per year.



USA

- Projected to be the 2nd most common cause of cancer death in 2030 (behind lung; ahead of liver.)

Chemoprevention of Pancreatic Cancer

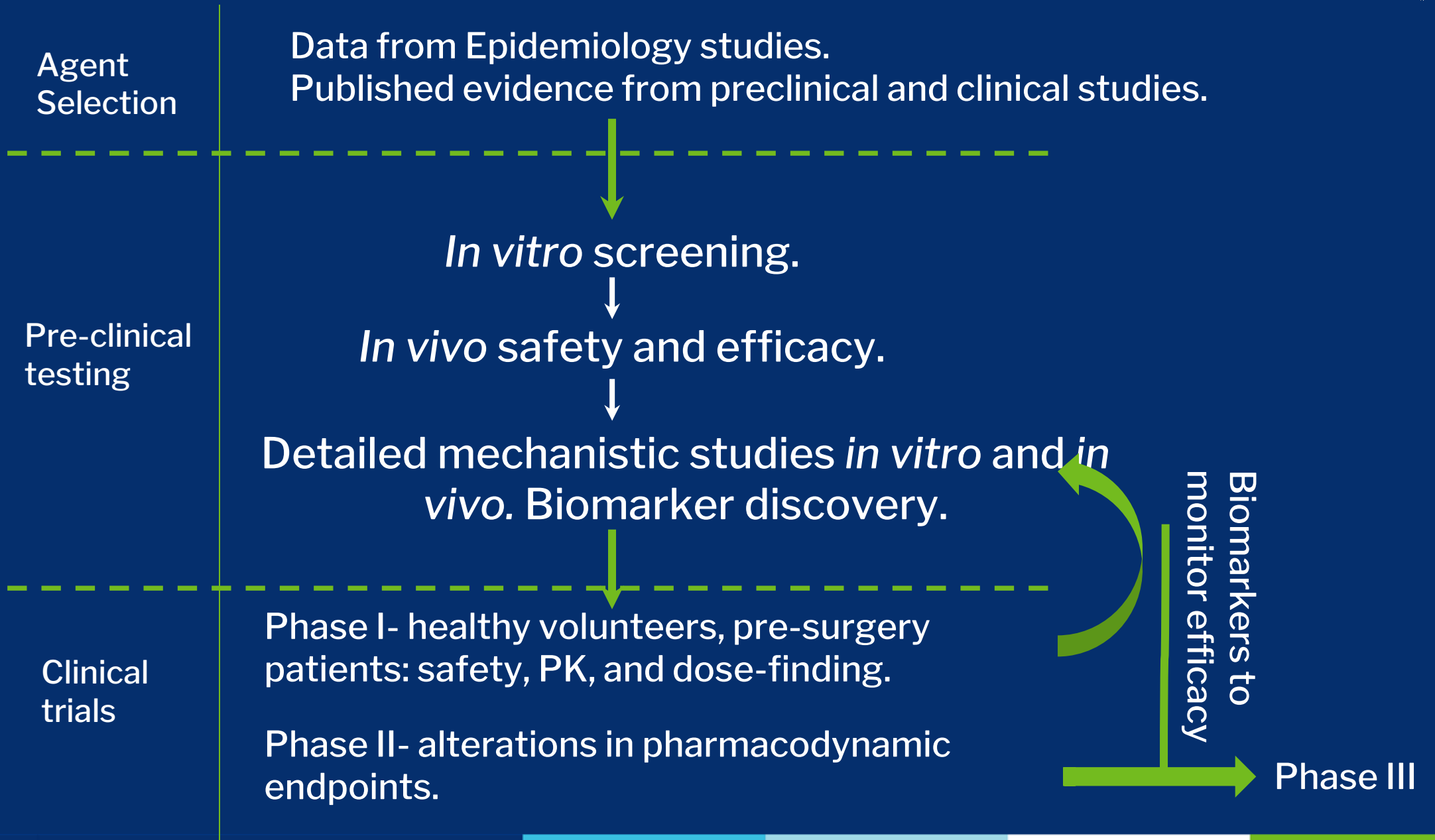
SUMMARY OF RATIONALE

Pancreatic carcinogenesis is a multi-year process with well known driver mutations thus providing many opportunities to intervene.

There are a significant number of individuals that are high risk to develop pancreatic cancer.

Potential to save many lives.

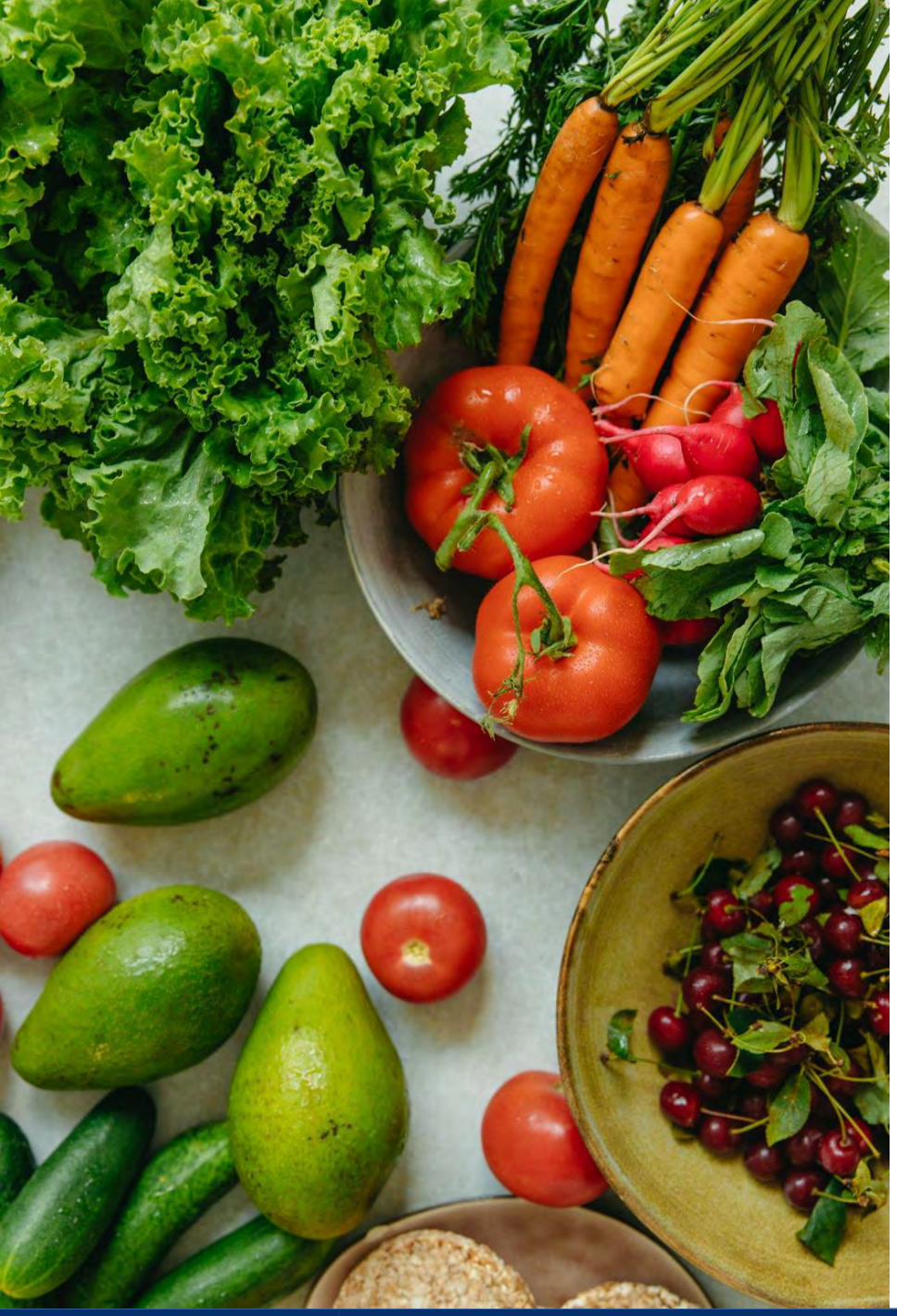
Development of a Chemoprevention Agent



Development of a Chemoprevention Agent

Agent Selection

Data from Epidemiology studies.
Published evidence from preclinical and clinical studies.



Pancreatic Cancer Prevention

NUTRITION

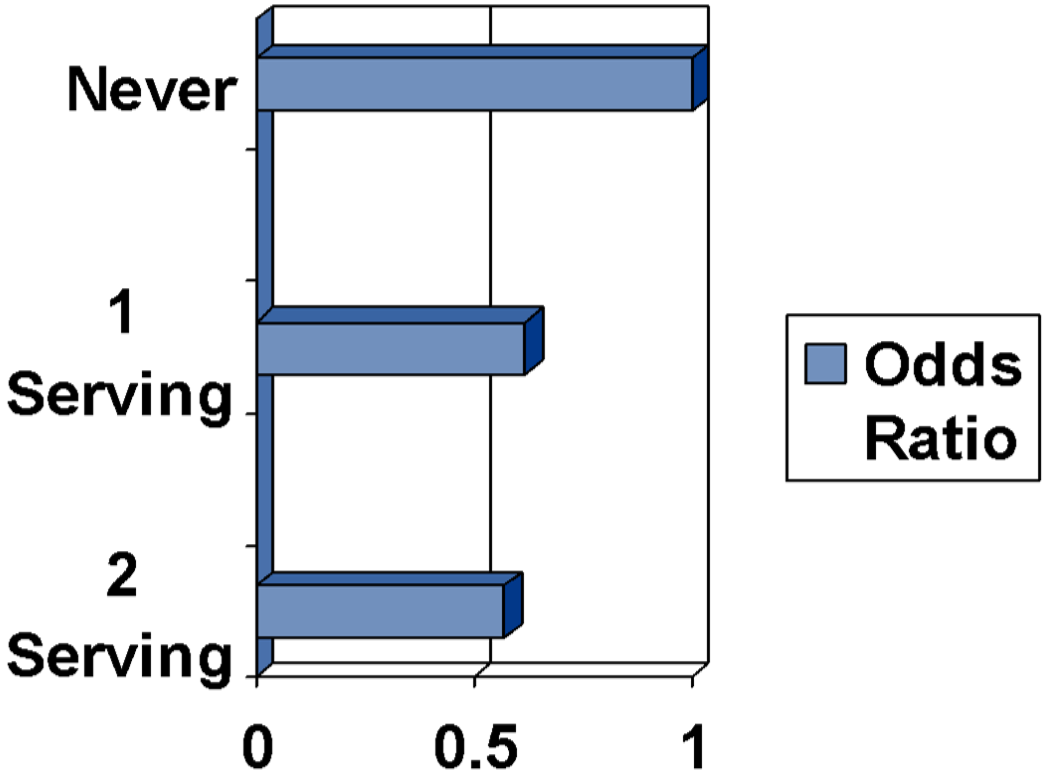
Studies	Benefit	No Benefit
Prospective	**4**	**2**
Case Control	**11**	
Cohort	**2**	

- Increasing vegetable fruit and cereal consumption may protect against pancreatic cancer.

Mo Malafa, MD

WHOLE GRAIN DECREASES RISK

- The risk of pancreatic cancer reduced by nearly 50% with whole grain consumption.
- HOW?
  - **Bioactive food components?**



Chan, JM, Am J Epidemiol 2007: 1174-1185

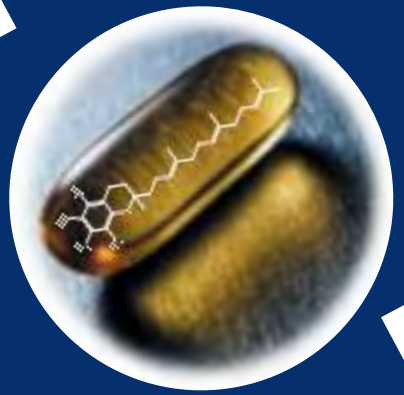
TOCOTRIENOL SOURCES

Palm

Annatto

Oats

Barley



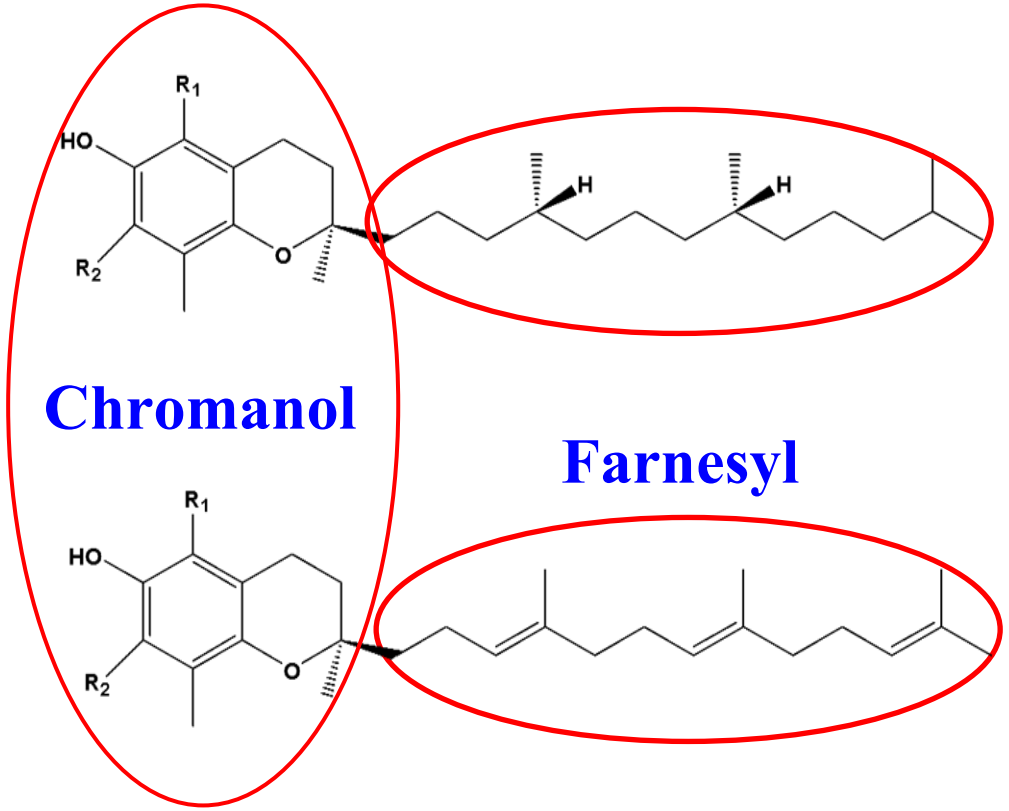
Rice Bran

Rye

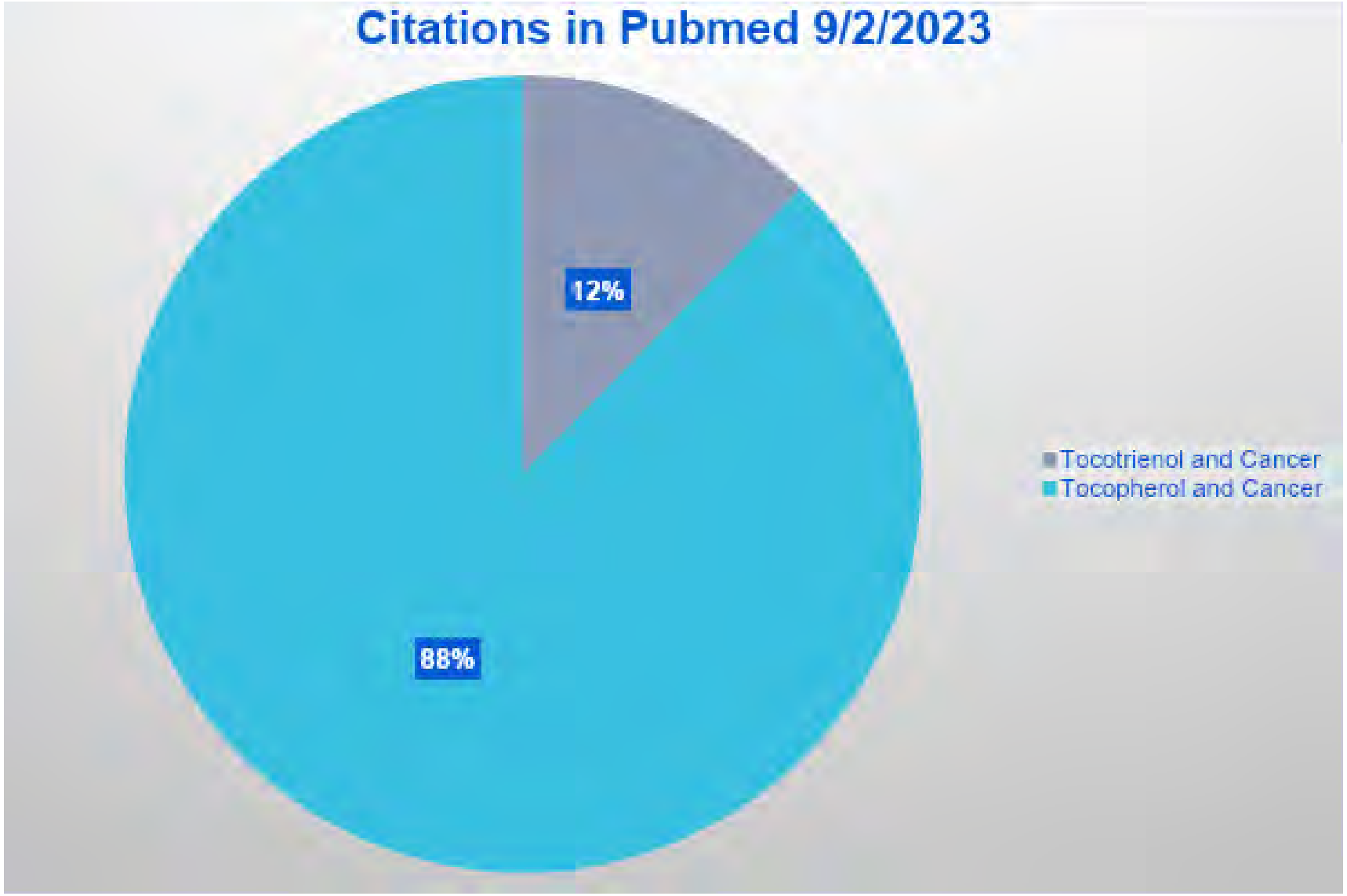
VITAMIN E.

R_1	R_2	
CH_3	CH_3	α-tocopherol (α-TP)
CH_3	H	β-tocopherol (β-TP)
H	CH_3	γ-tocopherol (γ-TP)
H	H	δ-tocopherol (δ-TP)

R_1	R_2	
CH_3	CH_3	α-tocotrienol (α-T_3)
CH_3	H	β-tocotrienol (β-T_3)
H	CH_3	γ-tocotrienol (γ-T_3)
H	H	δ-tocotrienol (δ-T_3)



- Saturated Phytyl side chain for tocopherols (TP)
- Unsaturated Farnesyl side chain for tocotrienols (T3)


Citations in Pubmed 9/2/2023
12%
88%
Tocotrienol and Cancer
Tocopherol and Cancer

Development of a Chemoprevention Agent

Agent Selection

Data from Epidemiology studies.
Published evidence from preclinical and clinical studies.

Pre-clinical testing

In vitro screening.

↓

In vivo safety and efficacy.

↓

Detailed mechanistic studies *in vitro* and *in vivo*. Biomarker discovery.

Tocotrienol Chemoprevention of Pancreatic Cancer

PRECLINICAL STUDIES

Carcinogenesis vol.34 no.4 pp.858–863, 2013
doi:10.1093/carcin/bgt002
Advance Access publication January 9, 2013

Prolonged survival and delayed progression of pancreatic intraepithelial neoplasia in *LSL-Kras$^{G12D/+}$;Pdx-1-Cre* mice by vitamin E δ-tocotrienol

Kazim Husain[1], Barbara A.Centeno[1], Dung-Tsa Chen[2], William J.Fulp[2], Marta Perez[1], Guo Zhang Lee[1], Noreen Luetteke[3], Sunil R.Hingorani[4], Said M.Sebti[5] and Mokenge P.Malafa,[1,5,*]

neoplastic cysts in the pancreas (6,7). A new study indicates a long latent phase (more than 12 years) from initiation of a pancreatic tumor to clinical symptoms, allowing ample time to deliver chemopreventative and therapeutic agents (8).

Kras mutations are prevalent (55–60%) in human pancreatic cancer as

-13-0157

Cancer Prevention Research

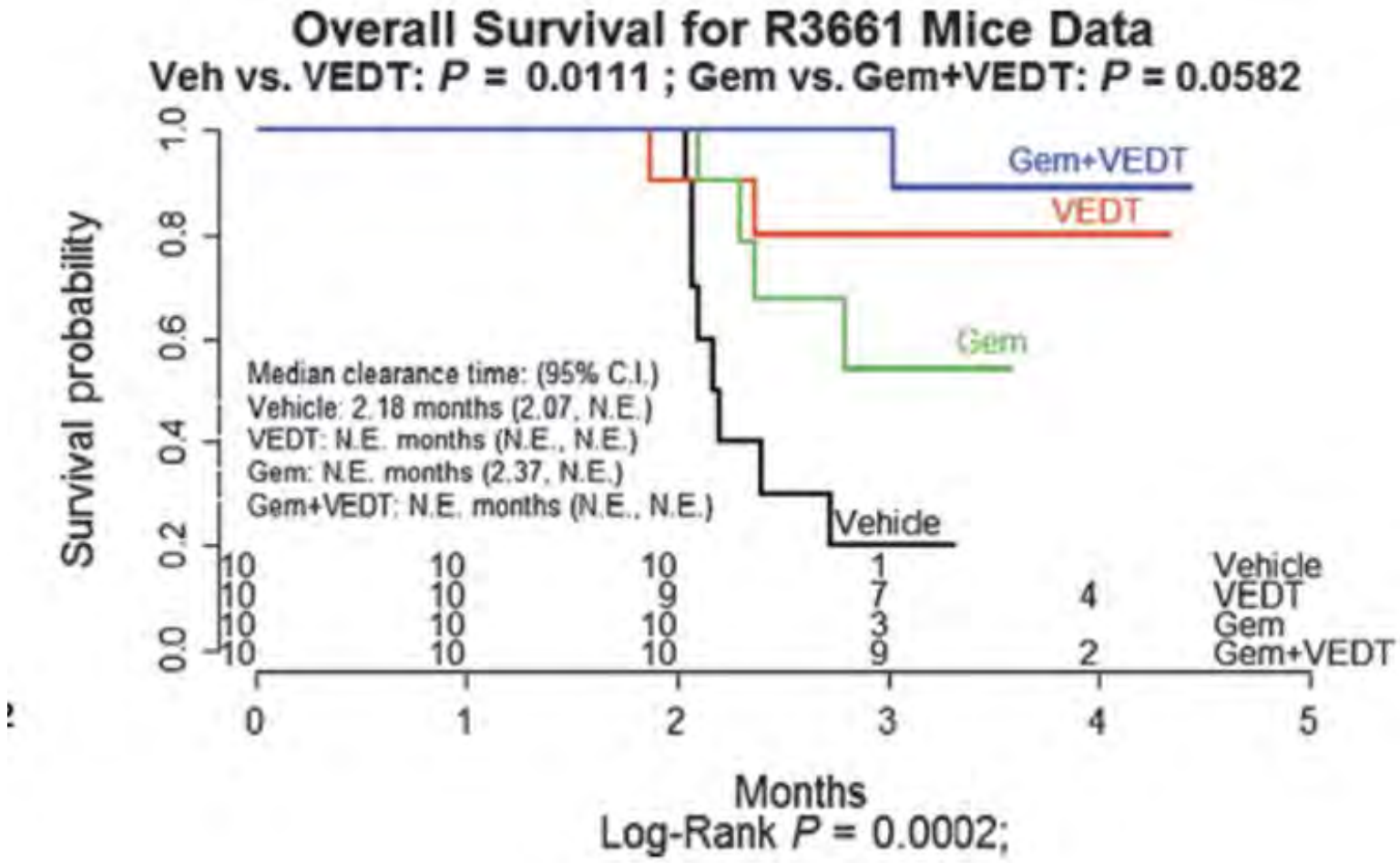
Research Article

Vitamin E δ-Tocotrienol Prolongs Survival in the *LSL-Kras$^{G12D/+}$;LSL-Trp53$^{R172H/+}$;Pdx-1-Cre* (KPC) Transgenic Mouse Model of Pancreatic Cancer

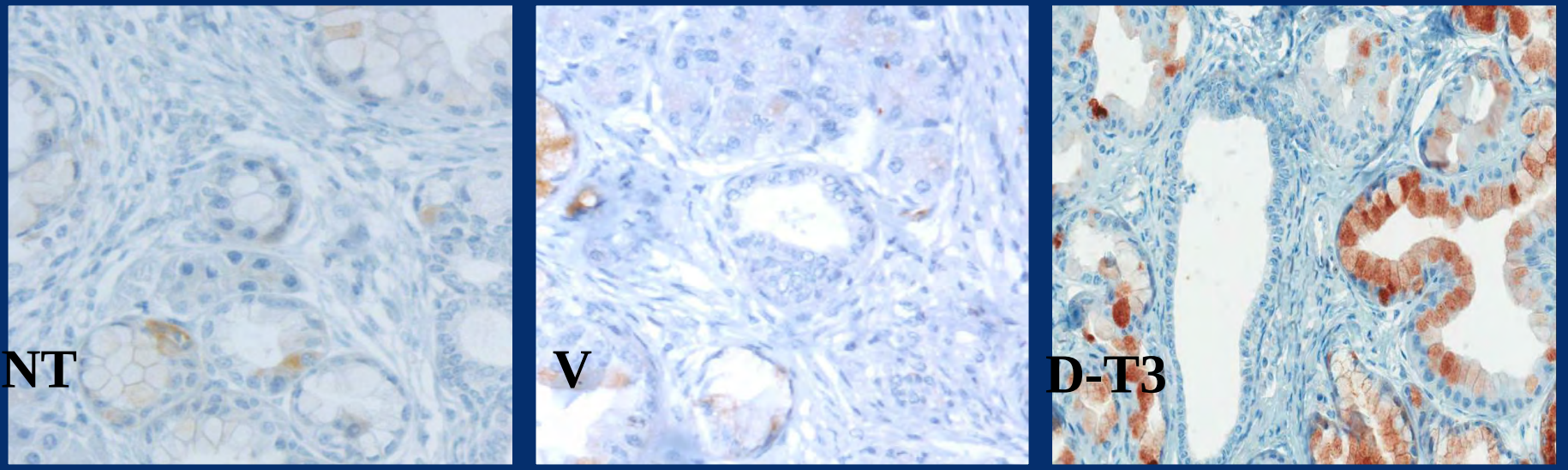
Kazim Husain[1], Barbara A. Centeno[2], Dung-Tsa Chen[4], Sunil R. Hingorani[5], Said M. Sebti[3], and Mokenge P. Malafa[1,3]

Tocotrienol Chemoprevention of Pancreatic Cancer

PRECLINICAL STUDIES



Tocotrienol in LSL-KRAS^{G12D};PDX-1-Cre mice



Caspase-3

Husain et al, Carcinogenesis, 2013.

Preclinical studies:

TOCOTRIENOL IN PANCREATIC CANCER

- ➔ Delta-tocotrienol was the most effective vitamin E compound against pancreatic cancer[1].
- ➔ Mice receiving delta-tocotrienol showed inhibition of pancreatic tumor growth[1] and carcinogenesis[2].
- ➔ Adequate levels of delta-tocotrienol in the pancreas of mice was achieved with well tolerated oral dosing[3].
- ➔ Tocotrienols target many hallmarks of cancer including cell survival.[1,2]

1. Husain et al., *Molecular Cancer Therapeutics*, 2011.
2. Husain et al., *Carcinogenesis*, 2013.
3. Husain et al., *Pharmacology*, 2009.

Development of a Chemoprevention Agent

Agent Selection

Data from Epidemiology studies.
Published evidence from preclinical and clinical studies.

Pre-clinical testing

In vitro screening.

↓

In vivo safety and efficacy.

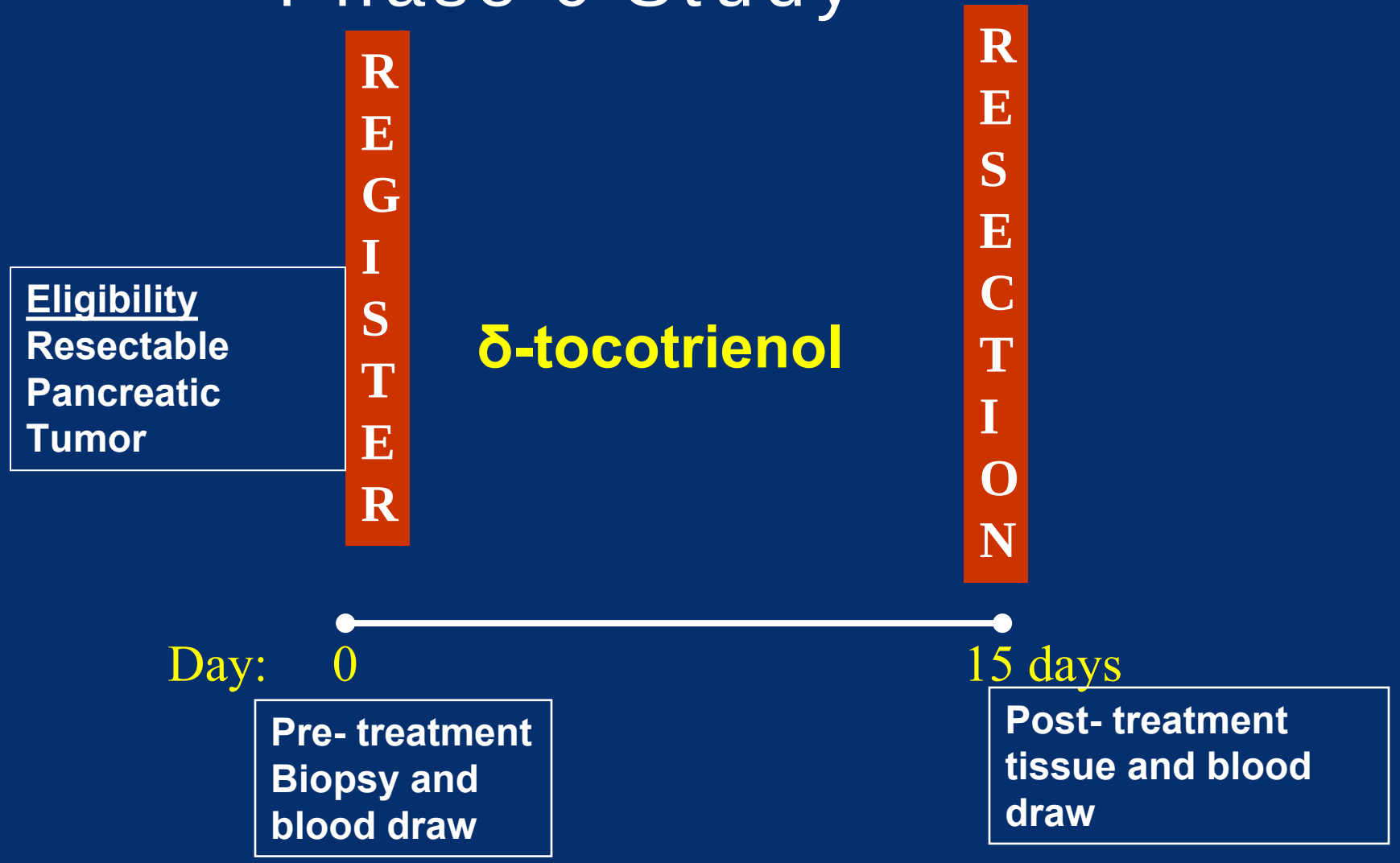
↓

Detailed mechanistic studies *in vitro* and *in vivo*. Biomarker discovery.

Clinical trials

Phase I- healthy volunteers, pre-surgery patients: safety, PK, and dose-finding.

Tocotrienol and Pancreatic Cancer Phase 0 Study



Springett et al., *EBIOMEDICINE*, 2015.

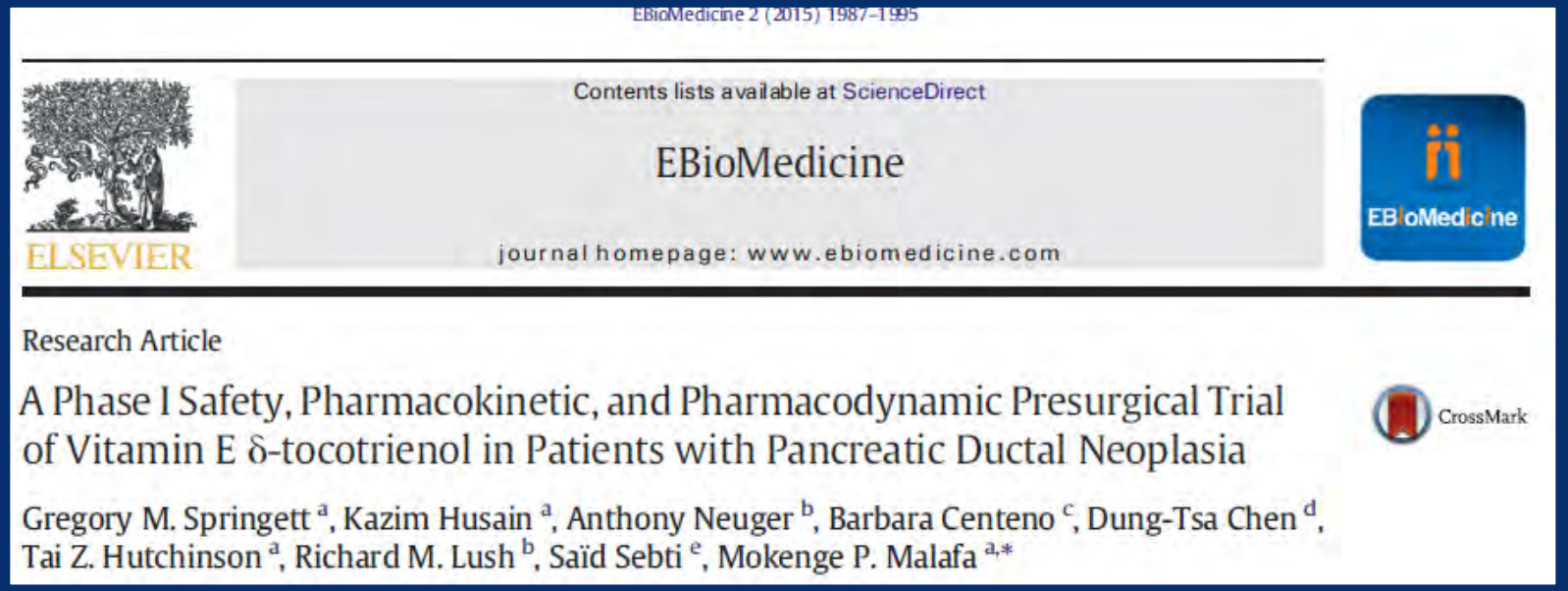
OBJECTIVES

Phase I Study of Vitamin E & Tocotrienol in pancreatic neoplasia.

- Primary:
  - Safety and tolerability
    - (5.6X the predicted BED)
  - **Phase II dose = Biologically Effective Dose (BED).**
    - Significant induction of apoptosis in neoplastic cells.

Springett et al., *EBIOMEDICINE*, 2015.

Tocotrienol and Pancreatic Cancer Clinical



EBioMedicine 2 (2015) 1987–1995

Contents lists available at ScienceDirect

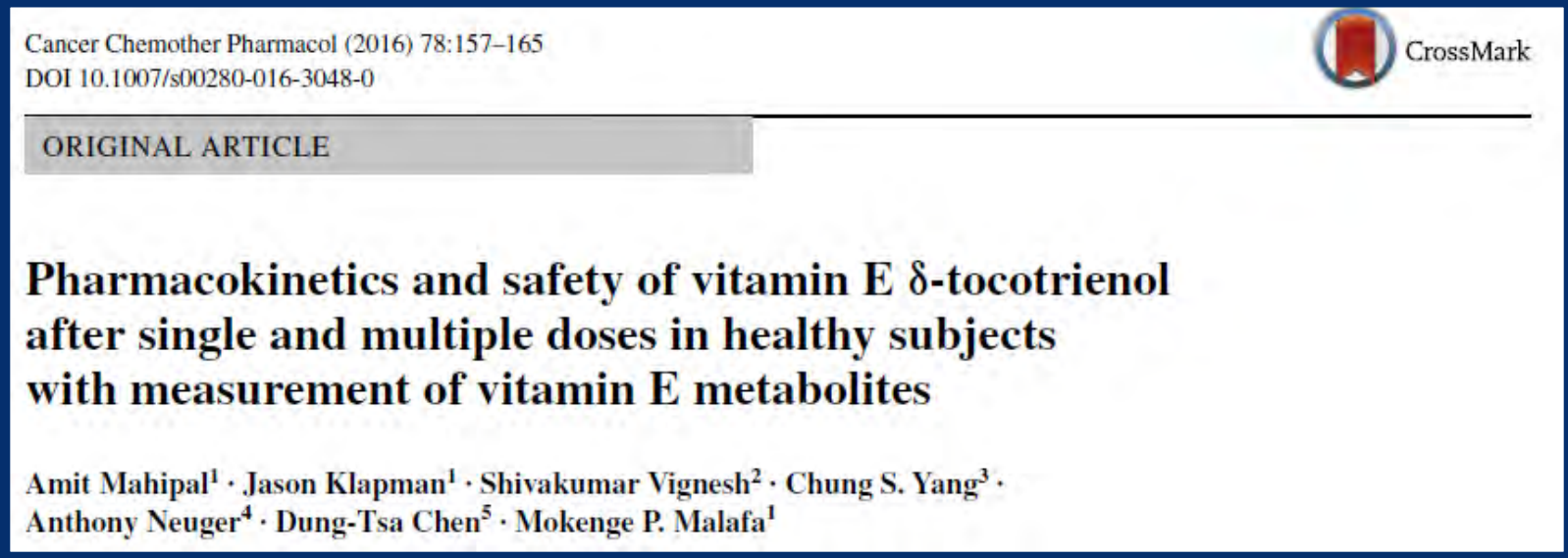
EBioMedicine

journal homepage: www.ebiomedicine.com

Research Article

A Phase I Safety, Pharmacokinetic, and Pharmacodynamic Presurgical Trial of Vitamin E δ-tocotrienol in Patients with Pancreatic Ductal Neoplasia

Gregory M. Springett [a], Kazim Husain [a], Anthony Neuger [b], Barbara Centeno [c], Dung-Tsa Chen [d], Tai Z. Hutchinson [a], Richard M. Lush [b], Saïd Sebti [e], Mokenge P. Malafa [a,*]



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ORIGINAL ARTICLE

Pharmacokinetics and safety of vitamin E δ-tocotrienol after single and multiple doses in healthy subjects with measurement of vitamin E metabolites

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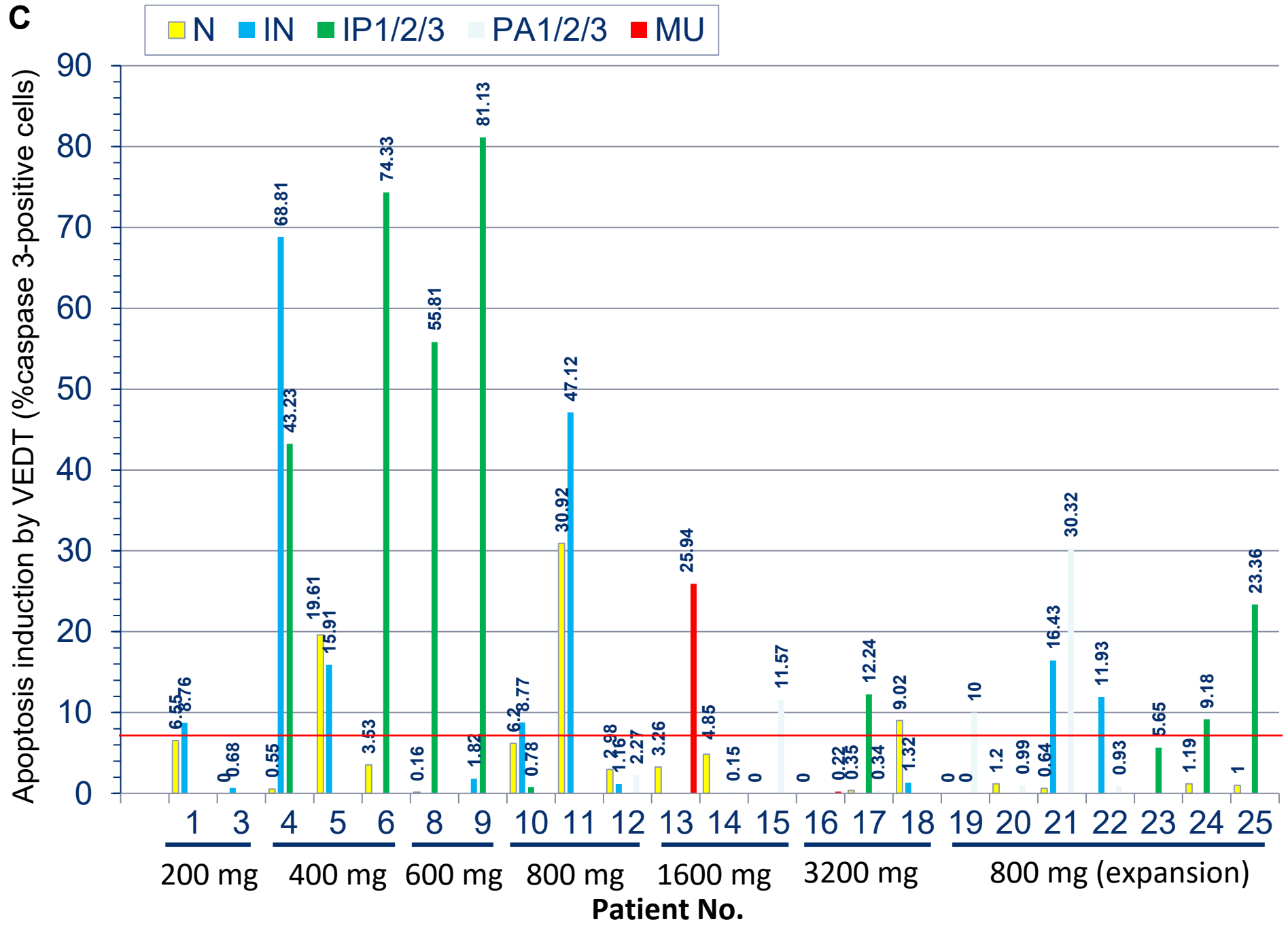
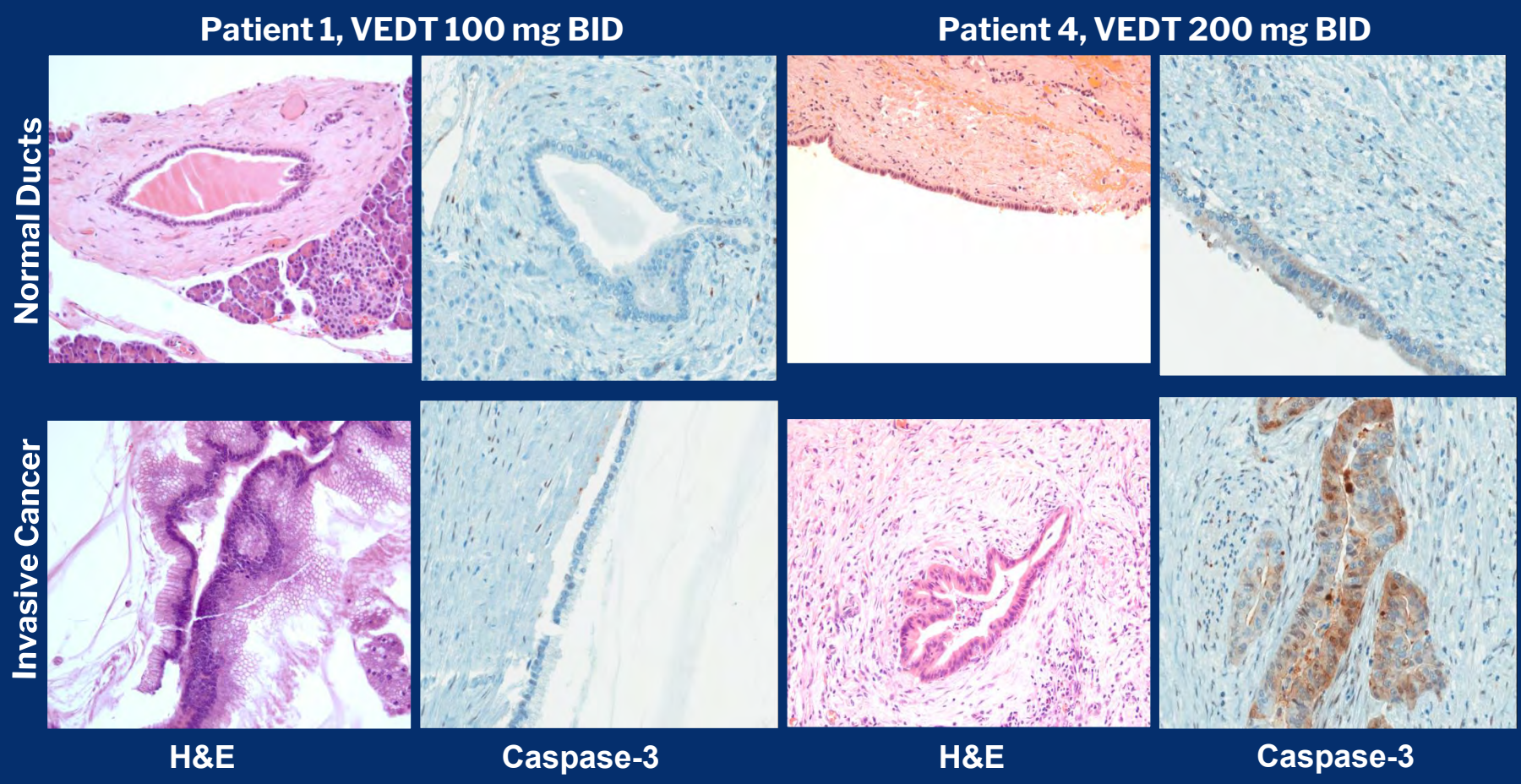

C
N
IN
IP1/2/3
PA1/2/3
MU
Apoptosis induction by VEDT (%caspase 3-positive cells)
0
10
20
30
40
50
60
70
80
90
6.55
8.76
0
0.68
0.55
68.81
43.23
19.61
15.91
3.53
74.33
0.16
55.81
1.82
81.13
6.2
8.77
0.78
30.92
47.12
2.98
1.16
2.27
3.26
25.94
4.85
0.15
0
11.57
0
0.22
0.35
12.24
0.34
9.02
1.32
0
0
10
1.2
0.99
0.64
16.43
30.32
11.93
0.93
5.65
1.19
9.18
1
23.36
1 3 4 5 6 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
200 mg
400 mg
600 mg
800 mg
1600 mg
3200 mg
800 mg (expansion)
Patient No.

Phase I Study of Vitamin E δ-Tocotrienol in Pancreatic Neoplasia

Results: Phase II dose= Biologically Effective Dose (BED).



Springett et al., *EBIOMEDICINE*, 2015.

Vitamin E Delta-Tocotrienol in Pancreatic Neoplasia

PHASE 0 / I STUDIES

1. **Tocotrienol is safe up to a dose of 3.6gms daily for 2 weeks.**
2. **Tocotrienol induces selective apoptosis in pancreatic neoplastic cells from 200 mg BID to 1600 mg BID with possibly greater effects at 200-400 mg BID doses.**
3. **Tocotrienol PK demonstrates variability but reaches bioactive levels in blood above 200 mg. BID.**

Development of a Chemoprevention Agent

Agent Selection

Data from Epidemiology studies.
Published evidence from preclinical and clinical studies.

Pre-clinical testing

In vitro screening.

↓

In vivo safety and efficacy.

↓

Detailed mechanistic studies *in vitro* and *in vivo*. Biomarker discovery.

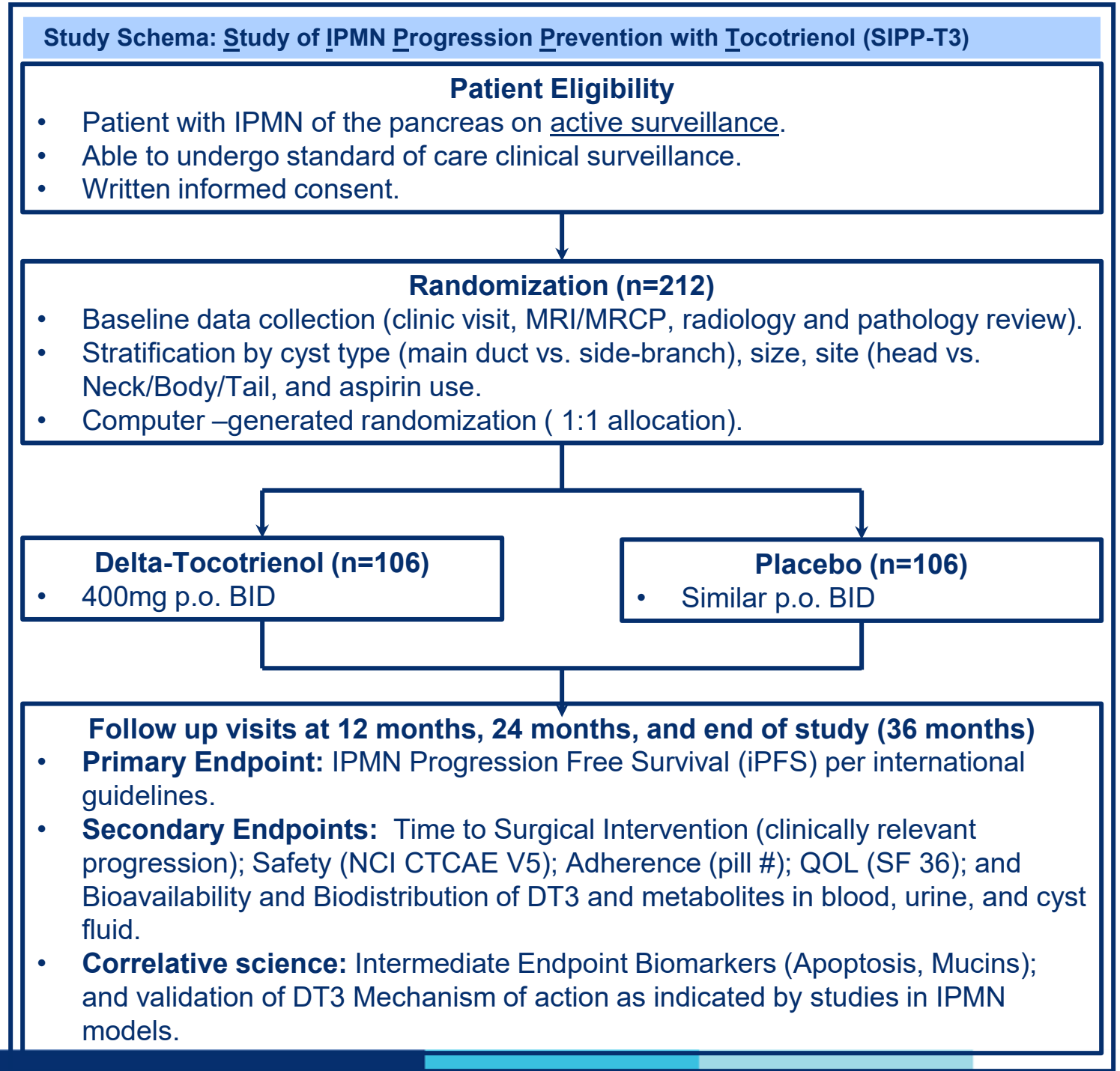
Clinical trials

Phase I- healthy volunteers, pre-surgery patients: safety, PK, and dose-finding.

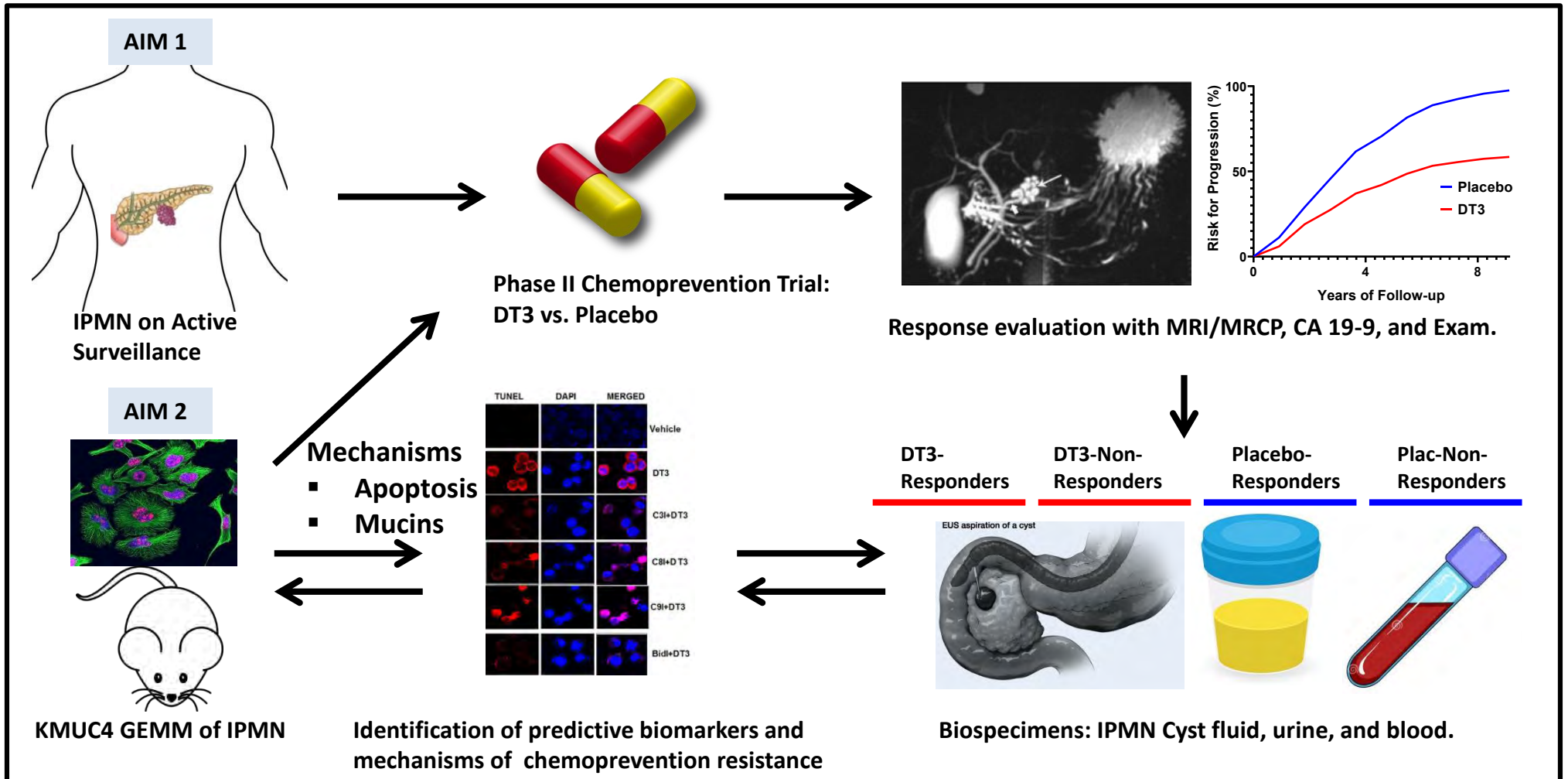
Phase II- alterations in pharmacodynamic endpoints.

Biomarkers to monitor efficacy

Phase III


Study Schema: Study of IPMN Progression Prevention with Tocotrienol (SIPP-T3)
Patient Eligibility
• Patient with IPMN of the pancreas on active surveillance.
• Able to undergo standard of care clinical surveillance.
• Written informed consent.
Randomization (n=212)
• Baseline data collection (clinic visit, MRI/MRCP, radiology and pathology review).
• Stratification by cyst type (main duct vs. side-branch), size, site (head vs. Neck/Body/Tail, and aspirin use.
• Computer –generated randomization (1:1 allocation).
Delta-Tocotrienol (n=106)
• 400mg p.o. BID
Placebo (n=106)
• Similar p.o. BID
Follow up visits at 12 months, 24 months, and end of study (36 months)
• Primary Endpoint: IPMN Progression Free Survival (iPFS) per international guidelines.
• Secondary Endpoints: Time to Surgical Intervention (clinically relevant progression); Safety (NCI CTCAE V5); Adherence (pill #); QOL (SF 36); and Bioavailability and Biodistribution of DT3 and metabolites in blood, urine, and cyst fluid.
• Correlative science: Intermediate Endpoint Biomarkers (Apoptosis, Mucins); and validation of DT3 Mechanism of action as indicated by studies in IPMN models.

MPI R01 (Malafa and Batra) "Novel Therapy to Inhibit IPMN Progression"



Schema 1: Schematic representation of the overall rationale, hypothesis, and design of the project.

Chemoprevention of Pancreatic Cancer

SUMMARY

There is a potential for high impact with a chemoprevention strategy for pancreatic cancer.

Tocotrienol is a promising agent in Phase I trials.

Next step is to complete Phase II “proof of concept” trials to justify Phase III efficacy trials.

Chemoprevention of Pancreatic Cancer

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2 Coinvestigators

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4 Current Funding: NIH 1R01CA263575


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