Cancer Center

NCI-DESIGNATED COMPREHENSIVE CANCER CENTER

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Familial Pancreatic Cancer - Lessons from Registry Data

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South Florida GI Symposium
Hollywood, Florida
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What Needs to be Accomplished to Improve Treatment for Pancreatic Cancer?

Impact on Survival

- Better understanding of molecular events and impaired pathways leading to disease
- Prevention
- Earlier detection
- More effective systemic therapies
- Appropriately resecting more patients with locally advanced disease
- Multidisciplinary care of patients

Impact on Quality of Life and Morbidity of Surgery

- Proper use of laparoscopic/robotic pancreatectomy

Risk Factors for Pancreatic Cancer

Familial Pancreatic Cancer

- 20-30% of pancreatic cancers are considered hereditary.
- 7-10% of patients diagnosed with pancreatic cancer will have an inheritable germline mutation detected.
- 20-30% of families with a history of pancreatic cancer will have a specific gene mutation identified.

Understanding familial risk of pancreatic ductal adenocarcinoma

Raymond M. Paranal[1,2] · Laura D. Wood[1,3] · Alison P. Klein[1,3,4] · Nicholas J. Roberts[1,3]

Familial Cancer 2024

Risk factor	Associated risk
Age	Low risk before the age of 40. Risk sharply increases after age 50. Median age of diagnosis is 72 years.
Body Mass Index	~ 1.6-fold increased risk in individuals with obesity compared with those with normal weight.
Smoking	~ 1.7-fold increased risk for smokers compared with never smokers.
Alcohol Consumption	1.6-fold increased risk in those consuming ≥ 9 alcoholic drinks per day compared with those consuming < 1 alcoholic drink per day.
Personal Medical History	
New-Onset Diabetes Mellitus	< 0.3–0.8% of patients with new-onset diabetes mellitus develop pancreatic ductal adenocarcinoma within 3 years of diabetes diagnosis.
Long Standing Diabetes Mellitus	1.5–2-fold increased risk of pancreatic cancer for individuals with diabetes of > 3 years in duration.
Pancreatitis	A 2.7 (95% CI 1.96–3.74) fold increased risk of individuals with a prior history > 2 years of pancreatitis and a 13-fold (95% CI: 8.72–21.90) risk with a history of pancreatitis in ≤ 2 years.
Family History of Pancreatic Cancer	2.6-fold increased risk (95% CI = 1.95 to 3.34) for one family member with pancreatic cancer. 4.86 (95% CI = 4.01 to 5.90) fold increased risk for individuals from kindreds with two close relatives with pancreatic cancer.
Genetic Status	Individuals with pathogenic variants in pancreatic cancer susceptibility genes (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, PRSS1, STK11*) are at high risk for pancreatic cancer.

Understanding familial risk of pancreatic ductal adenocarcinoma

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Familial Cancer 2024

Gene(s)	Estimated relative risks of PDAC	Estimated lifetime risk of PDAC, %
BRCA1	2–9	2.3–3.8 to age 80 years
BRCA2	2–10	2.3–7.4 to age 80 years
PALB2	2.3–2.4	2.2–2.8 to age 80 years
ATM	5.71–6.5	9.53 to age 80 years
STK11	76–140[#]	11–55[ǂ] to age 65–70 years
CDKN2A	39–52[†]	17 to age 75 years[*]
Mismatch Repair Genes (Including *MLH1*, *MSH2*, *MSH6*, and *PMS2*)	0.7–6.7	3.7 to age 70 years
PRSS1	Likely Increased	7.2–40 to age 70 years
CPA1	Likely Increased	Likely increased
CPB2	Likely Increased	Likely Increased

The New York Times

Deadly Inheritance, Desperate Trade-Off

Share full article

By Denise Grady

Aug. 7, 2007

Dr. Richard D. Schulick briefing Mrs. Platt about the consequences of her choice; she will become diabetic.
Todd Heisler/The New York Times

Mrs. Platt's daughter, Laura Train, and husband, Sam, were by her side at Johns Hopkins.
Todd Heisler/The New York Times

Trading a lethal form of cancer for diabetes

Share full article

By Denise Grady

Aug. 8, 2007

Early Diagnosis and Treatment of Pancreatic Dysplasia in Patients with a Family History of Pancreatic Cancer

Teresa A. Brentnall, MD; Mary P. Bronner, MD; David R. Byrd, MD; Rodger C. Haggitt, MD; and Michael B. Kimmey, MD

1999 · Annals of Internal Medicine

Patient	Symptoms	Endoscopic Ultrasonography Findings	ERCP Findings	Spiral Computed Tomography Findings	Histologic Characteristic
X.III.1	Yes	Heterogeneous parenchyma with scattered 1- to 2-mm echogenic foci, hypoechoic nodules	Irregular and poor filling of the tail and ectatic terminal ducts	Normal	Widespread dysplasia
X.III.2	Yes	Hypoechoic nodules	Poor filling in the tail, ectactic side branches, narrowing of mid-duct	Fatty and atrophic pancreas	Widespread dysplasia
X.III.12	Yes	Heterogeneous parenchyma with scattered 1- to 2-mm echogenic foci, hypoechoic nodules, hyperechoic main-duct walls, discrete masses	Dilated irregular pancreatic duct with ectatic branches	Diffuse calcifications consistent with those seen in chronic pancreatitis, focal decreased attenuation in the head and mid-body	Widespread dysplasia
X.III.14	Yes	Heterogeneous parenchyma with scattered 1- to 2-mm echogenic foci, hypoechoic nodules	Irregular duct in the tail with ectatic branches	Normal	Widespread dysplasia
X.III.17	Yes	Heterogeneous parenchyma with scattered 1- to 2-mm echogenic foci, hypoechoic nodules, discrete masses	Dilated irregular pancreatic duct with strictures and saccules	Diffuse calcifications, 1-cm cystic lesion in pancreatic head	Widespread dysplasia
X.IV.28	No	Normal	Normal	Normal	No surgery
X.IV.29	No	Not available	Dilated irregular pancreatic duct with saccules	Normal	Widespread dysplasia
X.IV.30	Yes	Heterogenous parenchyma with 1- to 2-mm scattered echogenic foci	Normal	Normal	No surgery
Y.IV.5	Yes	Heterogeneous parenchyma with 1- to 2-mm scattered echogenic foci, hypoechoic nodules, hyperechoic main-duct walls	Normal	Not done	No surgery
Z.III.6	No	Normal	Not done	Not done	No surgery
Z.IV.1	Yes	Heterogeneous parenchyma with 1- to 2-mm scattered echogenic foci	Pancreatic divisum with normal ventral and dorsal ducts	Not done	No surgery
Z.IV.2	No	Normal	Normal	Not done	No surgery
Z.IV.4	No	Heterogeneous parenchyma with 1- to 2-mm scattered echogenic foci	Normal	Not done	No surgery
Z.V.3	Yes	Heterogeneous parenchyma with 1- to 2-mm scattered echogenic foci, hypoechoic nodules, hyperechoic main-duct walls	Slightly irregular duct at the tail with small sacculation	Normal	Widespread dysplasia

Increased Prevalence of Precursor Lesions in Familial Pancreatic Cancer Patients

Clin Cancer Res 2009

Chanjuan Shi[1], Alison P Klein[1,2,5], Michael Goggins[1,2,3], Anirban Maitra[1], Marcia Canto[3], Syed Ali[1], Richard Schulick[4], Emily Palmisano[1], and Ralph H Hruban[1,2]

Precursor lesions in the familial (n=49) and sporadic cases (n=40)

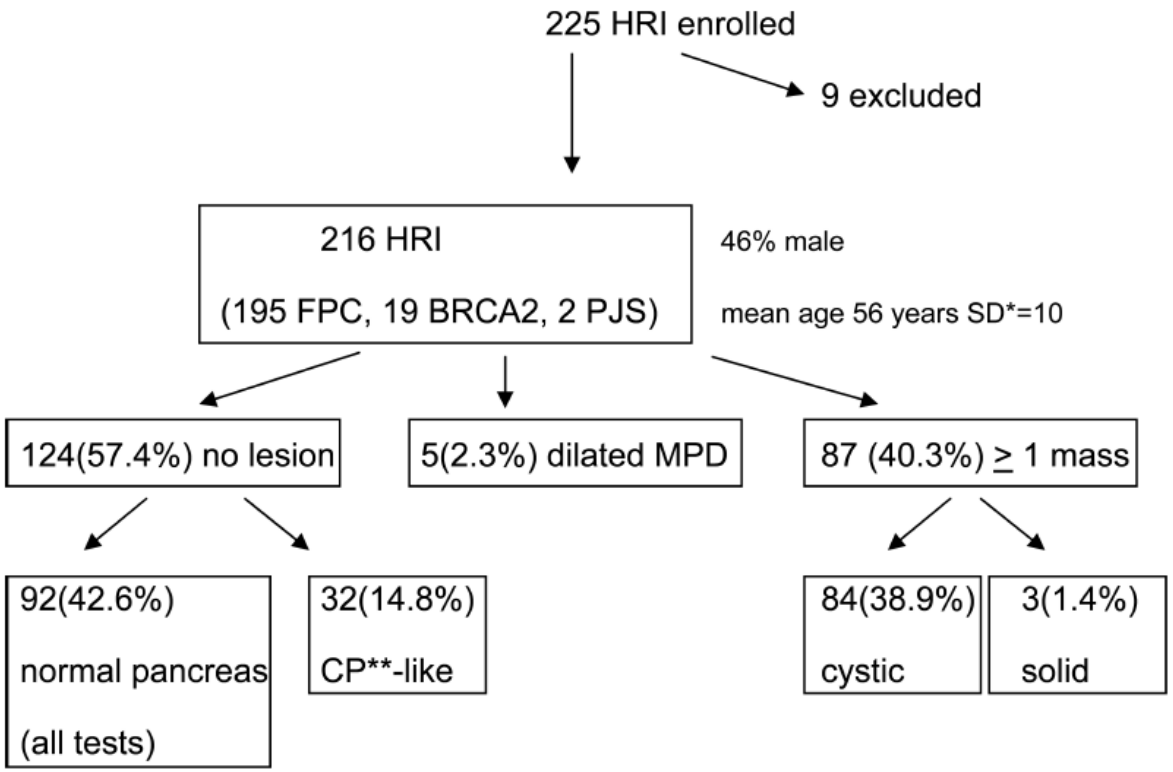
Precursor	Familial (per cm^2)	Sporadic (per cm^2)
Total PanIN	1.51	0.55*
PanIN-1	0.84	0.35
PanIN-2	0.51	0.14
PanIN-3	0.19	0.04
Total incipient IPMN	0.04	0.01*
HG Incipient IPMN	0.03	0
Total Precursor	1.55	0.56*
Total HG precursor	0.22	0.04*

Frequent Detection of Pancreatic Lesions in Asymptomatic High-Risk Individuals:

Screening for Early Pancreatic Neoplasia (CAPS 3 Study)

Gastroenterology. 2012

Marcia Irene Canto[1], Ralph H. Hruban[1], Elliot K. Fishman[1], Ihab R. Kamel[1], Richard Schulick[1], Zhe Zhang[1], Mark Topazian[2], Naoki Takahashi[2], Joel Fletcher[2], Gloria Petersen[2], Alison P. Klein[1], Jennifer Axilbund[1], Constance Griffin[1], Sapna Syngal[3,6], John R. Saltzman[6], Koenraad J. Mortele[6], Jeffrey Lee[5], Eric Tamm[5], Raghunandan Vikram[5], Priya Bhosale[5], Daniel Margolis[4], James Farrell[4], Michael Goggins[1], and For the American Cancer of the Pancreas Screening (CAPS) Consortium



Patient/Age, Risk	CT	MRI/MRCP	EUS	Final Pathologic Diagnosis
Patient 1 73 year 2 FDR	4 cysts (0.6-1.5 cm, non-communicating), 1 cyst with mural nodule), normal MPD Diagnosis BD-IPMN	6 cysts (0.5-2.1 cm, 2 communicating), normal but prominent MPD, multiple dilated branch ducts Diagnosis: BD-IPMN	3 cysts (0.5- 1.5 cm, 2 communicating), multiple non-communicating cysts, focally dilated MPD 3.8 mm with mural nodules and echogenic mucin, multiple dilated branch ducts, EUS-FNA cyst fluid CEA >1000 Diagnosis: combined IPMN	Distal pancreatectomy: MD-IPMN (7 cm body and tail, intestinal type) with extensive HGD, involving multiple branch ducts, multiple PanIN (highest grade 3)
Patient 2 65 years 2 FDR	2 cysts (0.9-1.0 cm, non-communicating) Diagnosis: BD-IPMN	2 cysts (1.7, 1.4 cm, communicating); Diagnosis: BD-IPMN	Dilated MPD 2.8 mm with 2 cysts (0.9, 1.9 cm, communicating, 1 with 5.5 mm mural nodule), multiple dilated branch ducts, Diagnosis: BD-IPMN	Whipple: MD-IPMN (1.3 cm, head and neck, intestinal type) with LGD with BD-IPMN (1.0 with LGD, 1.5 cm with MGD), multifocal PanIN (highest grade 2)
Patient 3 67 years 2 FDR	One 1.2 cm non-communicating cyst (body) Diagnosis: BD-IPMN	2 communicating cysts (body 1.1-1.4 cm) Diagnosis: BD-IPMN	6 communicating cysts (0.5-1.2 cm head, body, tail), 1 cyst with mural nodule; 1 solid mass 0.7 cm (FNA:PNET) Diagnosis: multiple BD-IPMNs, PNET	Total pancreatectomy: Multiple BD-IPMN with LGD (head, body, tail); multifocal PanIN (highest grade 3); multiple PNET (0.6-1.5-cm)
Patient 4 72 years 2 FDR	1.4 cm non-communicating cyst Diagnosis: BD-IPMN	15 cysts (0.5-1.6 cm largest communicating), multiple dilated branch ducts Diagnosis: BD-IPMN	4 cysts (range 0.6 -1.8 cm, largest communicating), multiple dilated branch ducts Diagnosis: BD-IPMN	Distal pancreatectomy: BD-IPMN (1.9 cm, tail) with MGD, incipient IPMN + multifocal PanIN (highest grade 2)
Patient 5 61 years 1 FDR, 1SDR, BRCA2 FBOC	No lesion detected Diagnosis: normal pancreas	No lesion detected Diagnosis: normal pancreas	0.5 cm non-septated communicating cyst (enlarged on follow-up to 0.9 cm) Diagnosis: BD-IPMN	Distal pancreatectomy: Incipient IPMN* (0.9 cm, tail) with LGD + multifocal PanIN (highest grade 2)

International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer

Gut 2013

Marcia Irene Canto,[1] Femme Harinck,[2] Ralph H Hruban,[3] George Johan Offerhaus,[4] Jan-Werner Poley,[2] Ihab Kamel,[5] Yung Nio,[6] Richard S Schulick,[7] Claudio Bassi,[8] Irma Kluijt,[9] Michael J Levy,[10] Amitabh Chak,[11] Paul Fockens,[12] Michael Goggins,[1] Marco Bruno,[2] on behalf of the International Cancer of the Pancreas Screening (CAPS) Consortium

Table 1 Summary of diagnostic yield of familial pancreatic cancer screening and surveillance programmes

Study	High-risk group	Imaging tests	Diagnostic yield*n (%)
Brentnall 1999 (1) n=14	FPC	EUS+ERCP+CT	7/14 (50)†
Kimmey 2002 n=46‡	FPC	EUS; ERCP§	12/46 (26)†
Canto 2004 (2) n=38	FPC, PJS	EUS; ERCP§, EUS-FNA§, CT§	2/38 (5.3)†
Canto 2006 (3) n=78	FPC, PJS	EUS; CT§,EUS-FNA§, ERCP§	8/78 (10.3)¶,†
Poley 2009 (4) n=44	FPC, BRCA, PJS, p16, p53, HP	EUS;CT§, MRI§	10/44 (23)
Langer 2009 (5) n=76	FPC, BRCA	EUS+MRCP; EUS-FNA§	1/76 (1.3)¶,†
Verna 2010 (6) n=51	FPC, BRCA, p16	EUS and/or MRCP	6/51 (12)†
Ludwig 2011 n=109	FPC, BRCA	MRCP; EUS§, EUS-FNA§	9/109 (8.3)¶
Vasen 2011 (7) n=79	p16	MRI/MRCP	14/79† (18)
Al-Sukhni 2011 (8) n=262	FPC, BRCA, PJS, p16, HP	MRI; CT§, EUS§, ERCP§	19/262¶ (7.3)
Schneider 2011 (9)** n=72	FPC, BRCA, PALB2	EUS+MRCP	11/72 (15)¶
Canto 2012 (10) n=216	FPC, BRCA, PJS	CT, MRI/MRCP, EUS; ERCP§	5/216 (2.3)†–92/216 (43)

*Yield is defined as the detection of any pathologically proven (pre)malignant lesion (≥PanIN-2/IPMN and pancreatic adenocarcinoma) and lesions that are morphologically suspicious for branch-duct IPMNs.

International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer

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Table 2 Summary of consensus statements for the management of high risk individuals

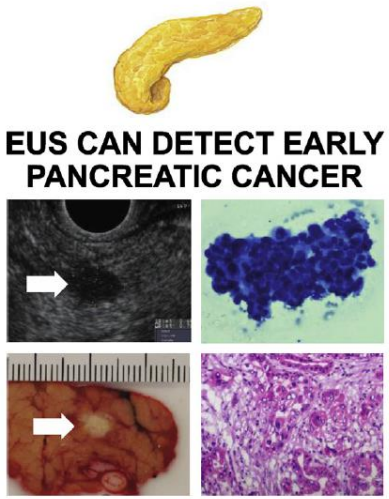
	Who should be screened?
	Statements
A1	Individuals with three or more affected blood relatives, with at least one affected FDR, should be considered for screening.
A2	Individuals with at least two affected FDRs with PC, with at least one affected FDR, should be considered for screening once they reach a certain age.
A3	Individuals with two or more affected blood relatives with PC, with at least one affected FDR, should be considered for screening.
A4	All patients with Peutz–Jeghers syndrome should be screened, regardless of family history of PC.
A5	*p16* carriers with one affected FDR should be considered for screening.
A6	*BRCA2* mutation carriers with one affected FDR should be considered for screening.
A7	*BRCA2* mutation carriers with two affected family members (no FDR) with PC should be considered for screening.
A8	*PALB2* mutation carriers with one affected FDR should be considered for screening.
A9	Mismatch repair gene mutation carriers (Lynch syndrome) with one affected FDR should be considered for screening.
	How should high-risk individuals be screened?
	Statements
B1	Initial screening should include (multiple answers allowed): EUS 83.7%, MRI/MRCP 73.5%, CT 26.5%, abdominal ultrasound 14.3%, ERCP 2.0%.
B2	When previous screening did not detect an abnormality that met criteria for shortening of the interval or surgical resection, follow-up screening should include (multiple answers allowed): EUS 79.6% MRI/MRCP 69.4%, CT 22.4%, abdominal ultrasound 4.1%, ERCP 2.0%.
B3	Standardised nomenclature should be used to define chronic pancreatitis-like abnormalities.
B4	Whenever a cystic lesion is detected, an additional ERCP should not be performed.
B5	Patients with a cystic lesion without worrisome features for malignancy should have an imaging test after 6–12 months.
B6	When a solid lesion is detected, CT should also be performed.
B7	When a solid lesion is detected, ERCP should not be performed.
B8	When a solid lesion is detected at baseline with an indeterminate diagnosis and the patient is not referred for immediate surgery, imaging should be repeated after 3 months.
B9	When a new solid lesion is detected at follow-up with an indeterminate diagnosis and the patient is not referred for immediate surgery, imaging should be repeated after 3 months.
B10	If an indeterminate main pancreatic duct stricture without a mass is detected, repeat imaging should be performed within 3 months.
	When should surgery be performed?
	Statements
C1	Screening should only be offered to individuals who are candidates for surgery.
C2	Pancreatic resections should be performed at specialty centres (taking into account volume, morbidity and mortality rates and expertise available).
C3	*Intraoperatively*, further pancreatectomy (up to a possible total) should be performed in patients with otherwise reasonable life expectancy to achieve R0 resection of cancer.
C4	*Intraoperatively*, further pancreatectomy (up to a possible total) should not be performed in a patient with otherwise reasonable life expectancy and no cancer but with unifocal PanIN-2 in the resected specimen but not at the margin.
C5	*Postoperatively*, further pancreatectomy (up to a possible total) should be not performed in patients with otherwise reasonable life expectancy in a patient without cancer in the resected specimen but with PanIN-2 at margin.
C6	*Postoperatively*, further pancreatectomy (up to possible total) should be not be performed in patients with otherwise reasonable life expectancy in a patient who did not have cancer but had unifocal PanIN-2 in the resected specimens but not at the margin.
C7	*Postoperatively*, further pancreatectomy (up to a possible total) should be not performed in patients with otherwise reasonable life expectancy in a patient without cancer but who has multifocal PanIN-2 in the resected specimens but not at the margin.
	What are the goals of screening? What outcome(s) would be considered a 'success'?
	Statements
D1	Resectable carcinoma is a potential target for early detection and treatment.
D2	PanINs are a potential target for early detection and treatment.
D3	IPMNs are a potential target for early detection and treatment.
D4	Detection and treatment of multifocal PanIN-3 should be considered a success of a screening/surveillance programme.
D5	Detection and treatment of IPMNs with high-grade dysplasia should be considered a success of a screening/surveillance programme.
D6	Detection and treatment of invasive cancer-T1N0M0 detected at baseline should be considered a success of a screening programme.
D7	Treatment of invasive cancer-T1N0M0 detected at follow-up should be considered a success of a screening programme.
D8	Detection and treatment of invasive cancer >T1N0M0 resectable with margins negative at baseline, should be considered a success of a screening programme.

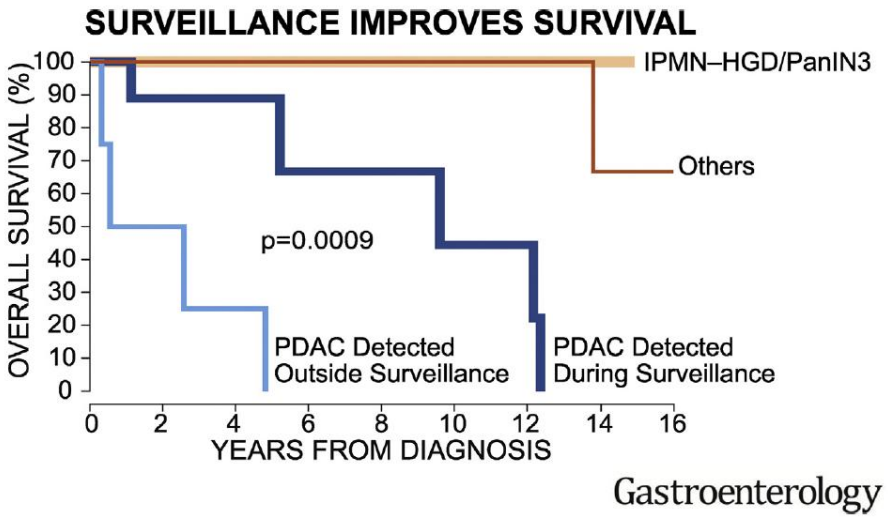
Gastroenterology 2018;155:740–751

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]

1998 to 2014
354 patients at high risk screened
68 patients with lesions detected with worrisome features
24 patients had neoplastic progression (14 cancer and 10 high grade dysplasia)
Of patients who developed cancer:
9 of 10 patients on active surveillance were resectable
All 4 patients not on active surveillance were unresectable





Surgical outcomes after pancreatic resection of screening-detected lesions in individuals at high-risk for developing pancreatic cancer

Marcia Irene Canto, MD MHS[1,*], Tossapol Kerdsirichairat, MD[1,*], Charles J. Yeo, MD[6], Ralph H. Hruban, MD[4], Eun Ji Shin, MD, PhD[1], Jose Alejandro Almario, BS[1], Amanda Blackford, ScM[2], Madeline Ford, BS[4], Alison P. Klein, MHS PhD[2], Ammar A. Javed, MD[3], Anne Marie Lennon, MD, PhD[1], Atif Zaheer, MD[5], Ihab R. Kamel, MD PhD[5], Elliot K. Fishman, MD[5], Richard Burkhart, MD[3], Jin He, MD[3], Martin Makary, MD[3], Matthew J. Weiss, MD[3], Richard D. Schulick, MD MBA[7], Michael G. Goggins, MD[1,4,**], Christopher L. Wolfgang, M,D PhD[3,**]

J Gastrointest Surg 2020

N= 354 High risk individuals
1998 to 2014
57 operations in 48 patients
31 Distal
20 Whipple
6 Total
11 had cancer
10 had high grade precursors
24 had low grade precursors
4 had PNETs

Pathology (n)	Indication for Surgery (n)	Median Age (years) / % Male	Type of Operations (Number of Open/ Minimally Invasive)	Median Tumor Size (cm)	AJCC Stage for PDAC	Median Follow-Up (years)/ % Alive	Overall 1-Year Survival/ 5 year-Survival	Cause of Death, where applicable (n)
PDAC (11)	Solid mass (8) Cyst with duct dilatation (1) Rapid cyst growth (2)	65/54.6%	Whipple (6/0) [a] Distal (3/0) Total (2/0)	2.7 (IQR 1.5-3.5)	Stage IA, T1N0M 0 (2) Stage IIA T3N0M 0 (2) Stage IIB, T2N1M 0 (4) Stage IIB, T3N1M 0 (2) Stage IV, T3N1M 1 after remote Whipple (1) [a]	4.7/45.6 %	90%/60%	PDAC-related(4), non-PDAC related(2)
High-grade PDAC precursors (10)								
IPMN HGD (6) [c]	Mass (1) Cyst with mural nodule (1) Cyst with main duct dilatation and mural nodules(1) Rapid cyst growth (3)	66/16.7%	Whipple (2/0) Distal (3/1)	1.6 (IQR 1.0-2.3)	Tis (including 2 combined IPMN)	7.4/100%	100%/ 100%	No death
PanIN-3 (4)	Cyst with main duct dilatation (1) Main PD stricture with dilation, no mass (1) Rapid cyst growth, multifocal cysts (2)	66/0%	Whipple (2/0) [b] Total (2/0)	1.2 (IQR 0.9-1.5)	Tis (including 1 main duct PanIN3)	7.6/85.7%	100%/ 100%	Non-PDAC related (1) at 7 years
Low-grade PDAC precursors (24): PanIN2, IPMN-LGD, IPMN-MGD	Mass (10) Cyst with duct dilatation (4) Rapid cyst growth (10)	62/56%	Whipple (5/0) Distal (12/5) Total (1/1)	1.6 (IQR 0.7-2.2)	NA	8.4/96%	100%/ 100%	Non-PDAC related (1) at 11.2 years
Pancreatic neuroendocrine tumor > 5 mm (4)	Mass with positive EUS-FNA cytology (4)	51/100%	Whipple (2/0) [c] Distal (1/1) Total (0/0)	1.2 (IQR 1-1.8)	Stage IIB, T3N1M0 (1) Stage 1A (3)	8.4/100%	100%/ 100%	No death

Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium

Michael Goggins ,[1] Kasper Alexander Overbeek ,[2] Randall Brand,[3] Sapna Syngal,[4] Marco Del Chiaro,[5] Detlef K Bartsch,[6] Claudio Bassi,[7] Alfredo Carrato,[8] James Farrell,[9] Elliot K Fishman,[10] Paul Fockens,[11] Thomas M Gress ,[12] Jeanin E van Hooft,[13] R H Hruban,[14] Fay Kastrinos,[15,16] Allison Klein,[17] Anne Marie Lennon,[18] Aimee Lucas,[19] Walter Park ,[15] Anil Rustgi,[16] Diane Simeone,[20] Elena Stoffel,[21] Hans F A Vasen,[22] Djuna L Cahen,[2] Marcia Irene Canto,[18] Marco Bruno,[2] International Cancer of the Pancreas Screening (CAPS) consortium

Gut 2020

Table 3 Summary of the main recommendations of the 2019 International Cancer of the Pancreas Surveillance (CAPS) Consortium

Who?		
► All patients with Peutz-Jeghers syndrome (carriers of a germline *LKB1/STK11* gene mutation) ► All carriers of a germline *CDKN2A* mutation ► Carriers of a germline *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, or *MSH6* gene mutation with at least one affected first-degree blood relative ► Individuals who have at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)		
When (at what age)?		
► Age to initiate surveillance depends on an individual's gene mutation status and family history		
Familial pancreatic cancer kindred (without a known germline mutation)		Start at age 50 or 55* or 10 years younger than the youngest affected blood relative
Mutation carriers: For *CDKN2A*†, Peutz-Jegher syndrome, start at age 40; *BRCA2,ATM, PALB2 BRCA1*, *MLH1/MSH2* start at age 45 or 50 or 10 years younger than youngest affected blood relative		
► There is no consensus on the age to end surveillance		
How?		
At baseline	► MRI/MRCP+EUS + fasting blood glucose and/or HbA1c	
During follow-up	► Alternate MRI/MRCP and EUS (no consensus if and how to alternate) ► Routinely test fasting blood glucose and/or HbA1c	
On indication	► Serum CA 19–9	► If concerning features on imaging
	► EUS-FNA only for	► Solid lesions of ≥5 mm ► Cystic lesions with worrisome features ► Asymptomatic MPD strictures (with or without mass)
	► CT only for	► Solid lesions, regardless of size ► Asymptomatic MPD strictures of unknown aetiology (without mass)
Intervals and surgery		
12 Months	► If no abnormalities, or only non-concerning abnormalities (eg, pancreatic cysts without worrisome features)	
3 or 6 Months	► If concerning abnormalities for which immediate surgery is not indicated (see figure 2 for details)	
Surgery	► If positive FNA and/or a high suspicion of malignancy on imaging (see figure 2 for details)	
► When surgery is indicated, perform an oncological radical resection at a specialty centre		
Goals		
The goal of surveillance is to detect and treat the following pathological lesions		► Stage I pancreatic cancer, confined to the pancreas, resected with negative margins ► Pancreatic cancer precursor lesions with high-grade dysplasia (PanIN or IPMN)

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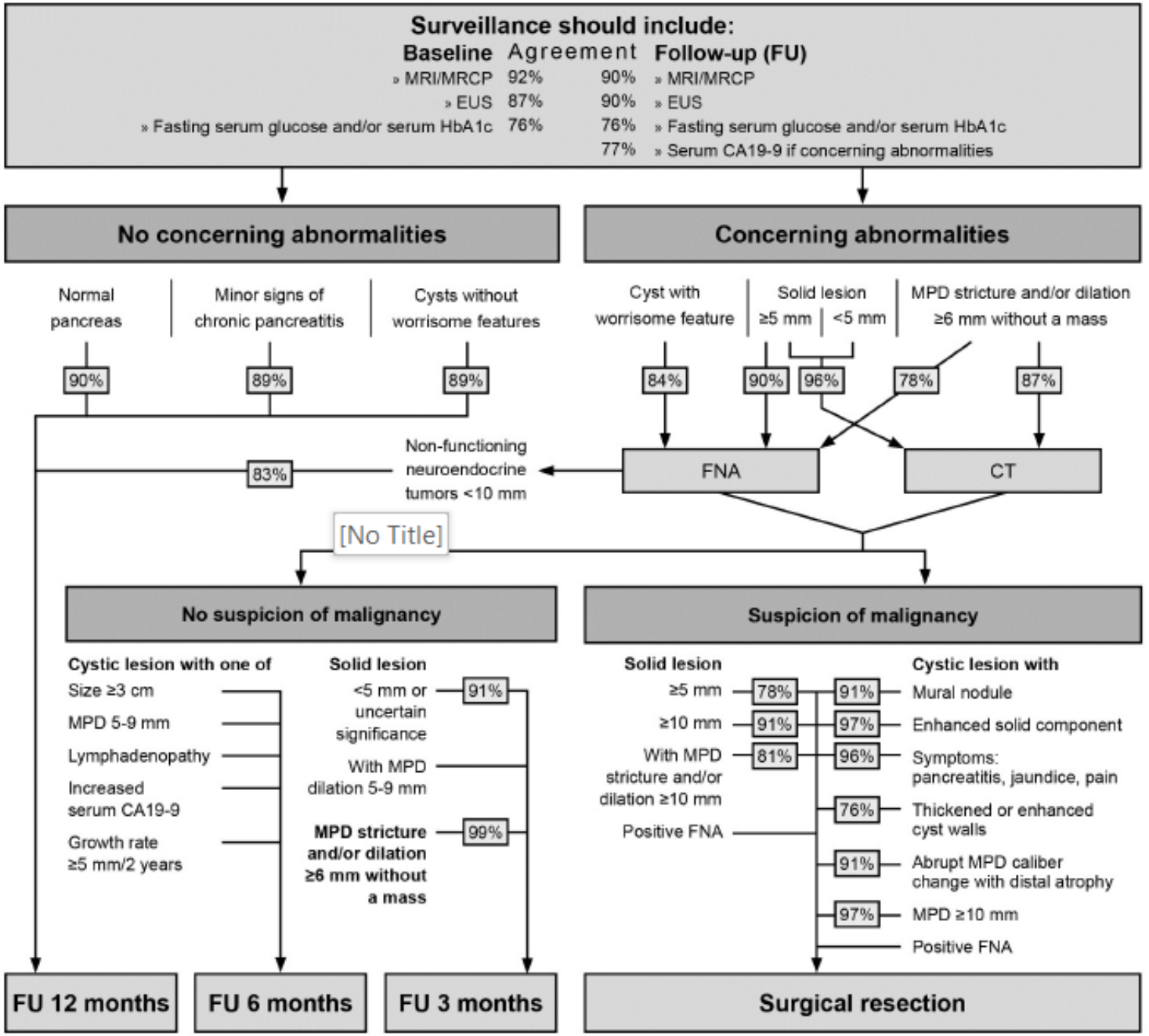
Michael Goggins ,[1] Kasper Alexander Overbeek ,[2] Randall Brand,[3] Sapna Syngal,[4] Marco Del Chiaro,[5] Detlef K Bartsch,[6] Claudio Bassi,[7] Alfredo Carrato,[8] James Farrell,[9] Elliot K Fishman,[10] Paul Fockens,[11] Thomas M Gress ,[12] Jeanin E van Hooft,[13] R H Hruban,[14] Fay Kastrinos,[15,16] Allison Klein,[17] Anne Marie Lennon,[18] Aimee Lucas,[19] Walter Park ,[15] Anil Rustgi,[16] Diane Simeone,[20] Elena Stoffel,[21] Hans F A Vasen,[22] Djuna L Cahen,[2] Marcia Irene Canto,[18] Marco Bruno,[2] International Cancer of the Pancreas Screening (CAPS) consortium

Gut 2020



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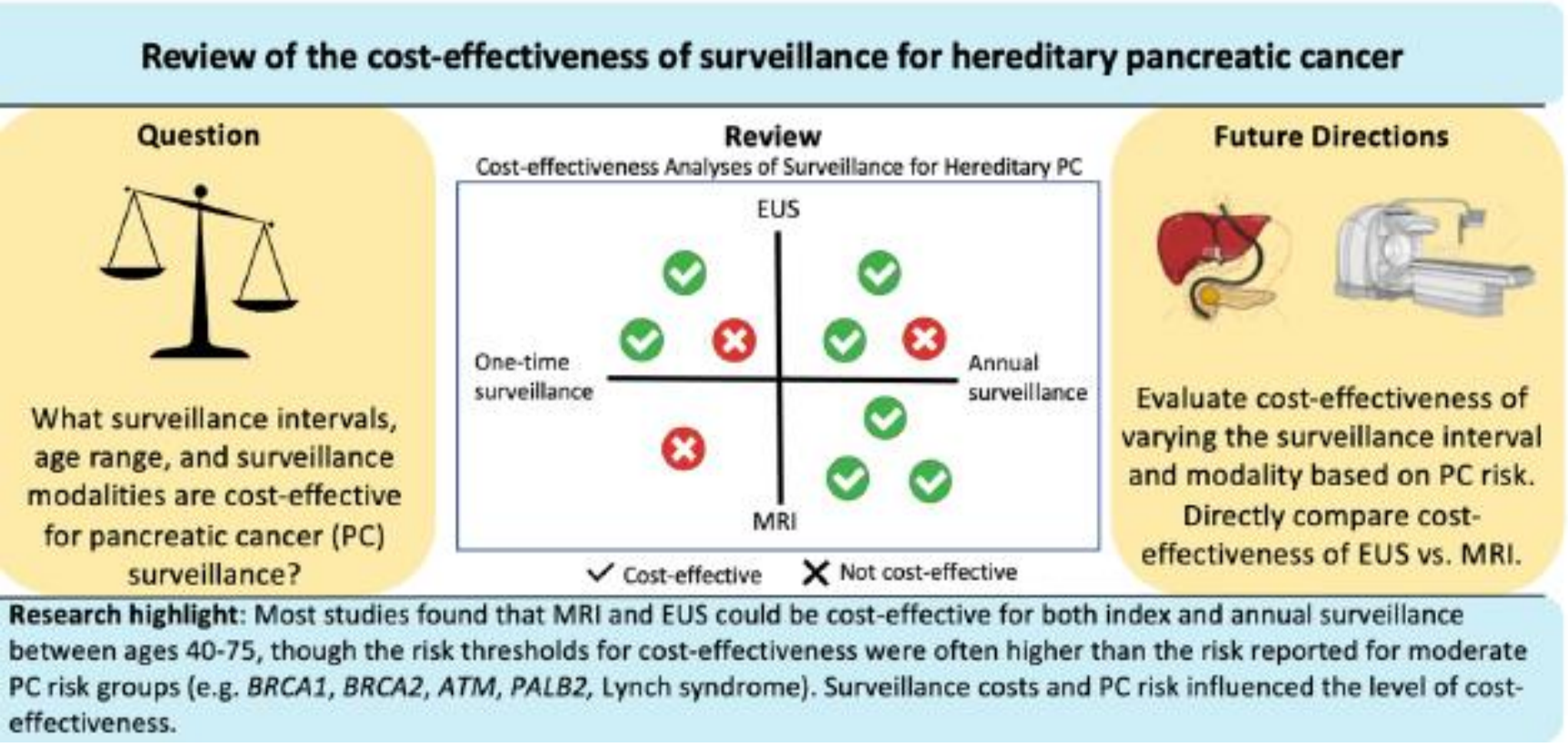
REVIEW

Review of the cost-effectiveness of surveillance for hereditary pancreatic cancer

Louise Wang[1,2,3] · Rachel Levinson[1] · Catherine Mezzacappa[1] · Bryson W. Katona[3]



- Most studies found either EUS, MRI, or both were cost-effective compared to no surveillance
- Surveillance might only be cost-effective in select PGV/familial groups with high lifetime risk (e.g. >10% or RR > 12).
- The most important factors included a high lifetime risk of PC, high life expectancy after resection, or performance characteristics of the testing
- Neither EUS and MRI was dominant and imaging strategy dependent on risk of PC and cost of the surveillance strategy, which varied globally

Pancreatic Cancer Screening among High-risk Individuals

Kevin M. Turner, MD[a,1], Sameer H. Patel, MD, FACS[a,b,*]

Surg Clin N Am (2024)

Summary of societal recommendations

	Screening
Goals?	• Detection of precursor lesions with high-grade dysplasia (PanIN or IPMN) or Stage I PDAC (AGA, ASGE, and CAPS)
Whom?	• Patients with Peutz-Jeghers (*STK11*), FAMM (*CDK2NA*), or Familial Pancreatitis (*PRSS1*, *SPINK1*) • Patients with Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *EPCAM*), pathogenic mutations in *BRCA1*, *BRCA2*, *PALB2*, or *ATM and* ≥1 pancreas cancer affected FDR (AGA, CAPS) or SDR (NCCN) • Patients with FPC (ASGE, CAPS)
How?	• MRI/MRCP and EUS should be used in combination (AGA, ASGE, and NCCN) • Baseline MRI and EUS and fasting blood glucose/HbA1C with follow-up alternating MRI/EUS and routine fasting blood glucose/HbA1C (CAPS)
When?	• Peutz-Jeghers syndrome: Start at age 30–35 y or 10 y prior to the earliest exocrine pancreas cancer (AGA, ASGE, and NCCN); start at age 40 y (CAPS) • FAMM syndrome: Start at age 40 y or 10 y prior to the earliest exocrine pancreas cancer (AGA, ASGE, CAPS, and NCCN) • Familial pancreatitis: Start at age 40 y or 10 y prior to the earliest exocrine pancreas cancer (AGA, ASGE); Start at 20 y after initial symptoms or age 40 y, whichever is earliest (NCCN) • All other pathogenic variants: Start at age 50 y or 10 y prior to the earliest exocrine pancreas cancer (AGA, CAPS, NCCN); Start at age 45–50 y (ASGE) • FPC: Start at age 50–55 y or 10 y prior to the earliest exocrine pancreas cancer (CAPS)
Interval?	• Annual screening if no abnormalities/nonconcerning abnormalities (AGE, ASGE, CAPS, and NCCN) • 3–6 mo based on risk of abnormalities if surgery is not indicated (AGA, CAPS) • NOD in HRI should lead to diagnostic testing (AGA)
Completion?	• When patients are more at risk to die of nonpancreas cancer-related causes and/or not candidates for pancreas resection (AGA)

Informatics strategies for early detection and risk mitigation in pancreatic cancer patients

Di Jin [a,b,c,1], Najeeb Ullah Khan [d,1], Wei Gu [a,b,e], Huijun Lei [a,b], Ajay Goel [f,g,**], Tianhui Chen [a,b,*]

Neoplasia (2025)

Informatics Framework for Early Detection of Pancreatic Cancer.

Category	Description	Key Tools/Technologies	Role in Early Detection
Genomic Informatics	It involves identifying and analyzing genetic mutations that contribute to the development of pancreatic cancer, enabling risk prediction and early diagnosis.	Genome-Wide Association Studies (GWAS) Next-Generation Sequencing (NGS) Bioinformatics Platforms (e.g., GATK, BWA, STAR, HISAT2) Whole Exome Sequencing (WES)	It helps identify early genetic mutations such as KRAS, TP53, and CDKN2A, which are present in most cases of pancreatic cancer. Enables risk assessment based on mutation signatures. Provides a non-invasive method for early detection using blood or tissue samples.
Genetic Mutations of Interest	Describes the significance of specific mutations like KRAS, TP53, and CDKN2A and their role in pancreatic cancer initiation and progression.	KRAS Mutation TP53 Mutation CDKN2A Mutation	KRAS mutation occurs in 90% of pancreatic cancer cases and is a hallmark of the disease. TP53 and CDKN2A mutations often lead to tumorigenesis and are critical in assessing cancer risk.
Biomarker Identification	Informatics tools are used to discover and validate genetic, proteomic, and metabolomic biomarkers to detect pancreatic cancer at an early stage.	NGS-based Bioinformatics Platforms RNA-Seq, microarray analysis Epigenomic Profiling (e.g., Methylation Sequencing)	Identifies genomic, transcriptomic, and epigenomic biomarkers that correlate with pancreatic cancer risk. Helps develop a multi-biomarker signature for early detection. Enhances the accuracy of predictions for high-risk populations.
Imaging Informatics	Utilizes advanced medical imaging technologies and informatics tools to detect early-stage pancreatic tumors that are otherwise undetectable.	CT (Computed Tomography) MRI (Magnetic Resonance Imaging) PET (Positron Emission Tomography) Radiomics, AI/ML Models (e.g., CNNs, SVMs)	Imaging technologies help visualize tumors in early stages, often before they become clinically symptomatic. Radiomics extracts quantitative data from images for precise tumor characterization. AI and ML assist in automating the detection of small, subtle tumors.
Radiomics	Extracts quantitative features from medical images (e.g., CT, MRI) and integrates them with clinical data to improve diagnostic accuracy and predict disease outcomes.	PyRadiomics, Radiomics Software Deep Learning Models (CNNs) Texture and Shape Analysis Tools	Extracts features such as tumor texture, shape, and heterogeneity from radiological images. Correlates image features with patient outcomes, disease stage, and treatment response.

Informatics strategies for early detection and risk mitigation in pancreatic cancer patients

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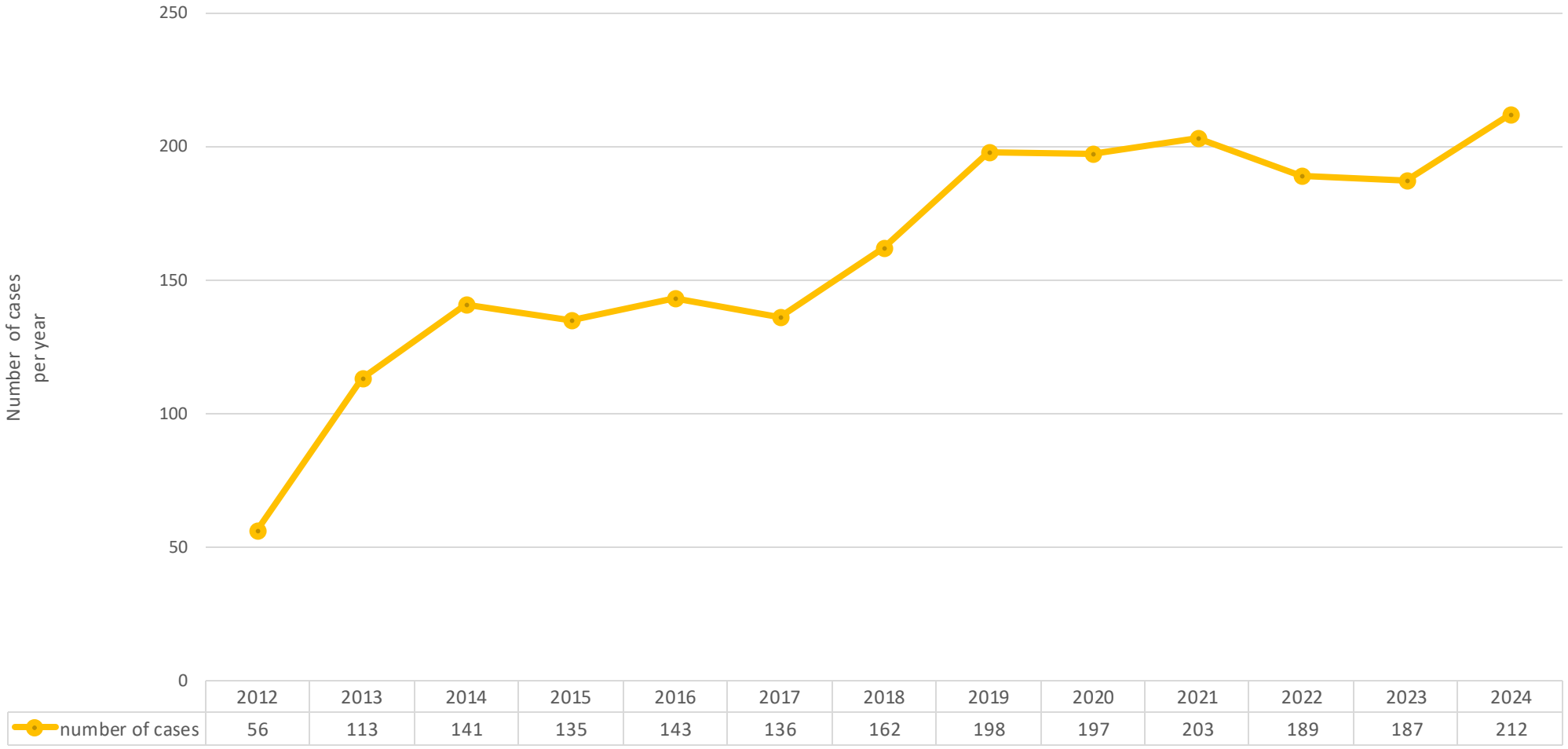
Neoplasia (2025)

Informatics Framework for Early Detection of Pancreatic Cancer.

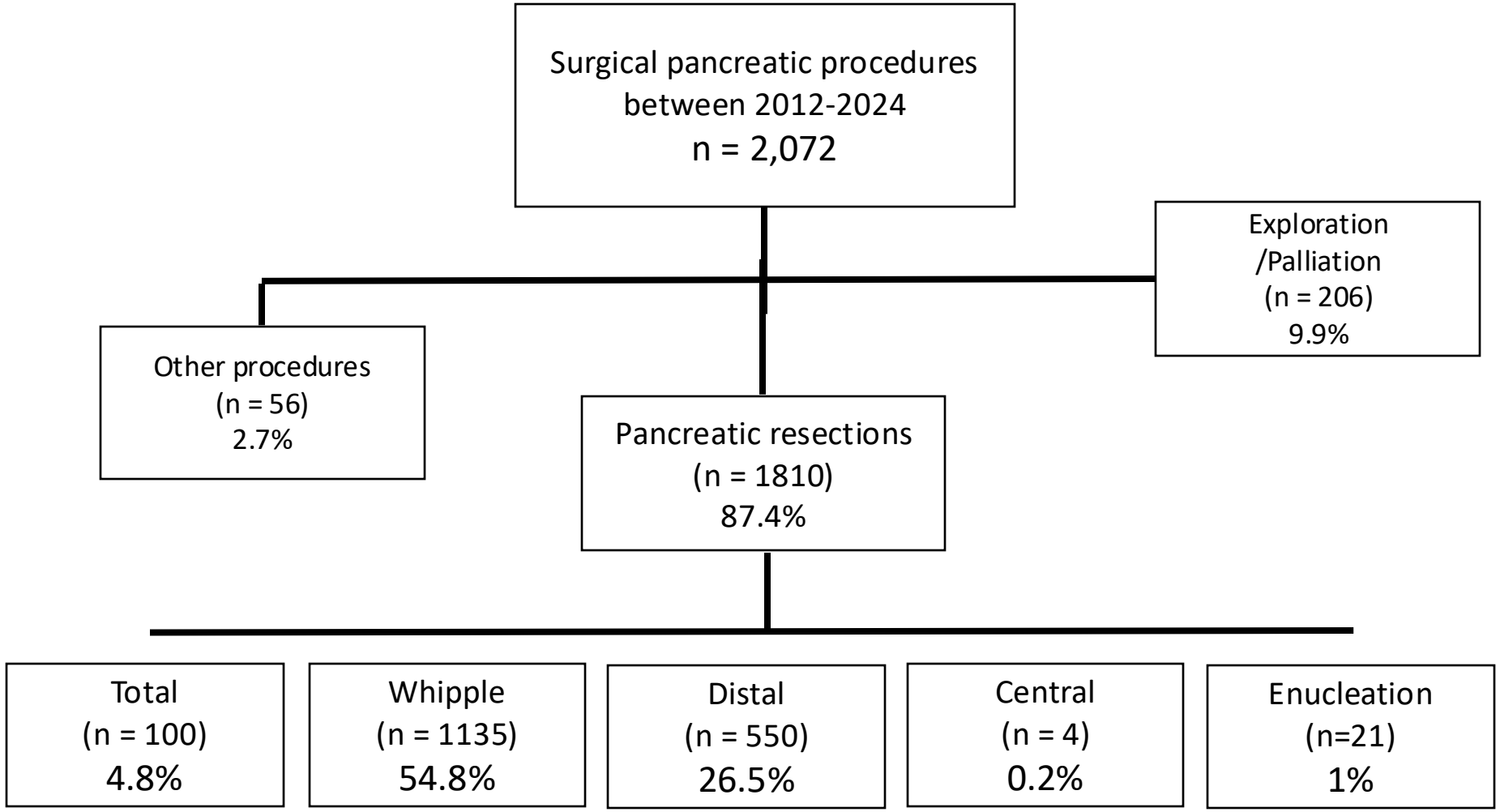
Category	Description	Key Tools/Technologies	Role in Early Detection
AI/ML in Imaging	Applies advanced machine learning and artificial intelligence algorithms to analyze imaging data, aiding in identifying and classifying early pancreatic cancer.	Convolutional Neural Networks (CNNs) Support Vector Machines (SVMs) Recurrent Neural Networks (RNNs) Autoencoders	AI models are trained on large imaging datasets to detect early signs of pancreatic cancer that may not be visible to the human eye. Enhances diagnostic precision, reducing false positives and negatives.
Proteomics and Metabolomics	Involves analyzing proteins and metabolites in biological samples to identify early biomarkers and understand the biochemical pathways involved in pancreatic cancer.	Mass Spectrometry (LC-MS, MALDI-TOF) Nuclear Magnetic Resonance (NMR) Spectroscopy Metabolomic Profiling Tools (e.g., MetaboAnalyst, XCMS)	Provides insights into protein expression changes and metabolic alterations associated with pancreatic cancer. Identifies early biomarkers in blood or urine for non-invasive detection.
Proteomic Tools	Tools used to analyze the proteome (all proteins) in tissues and biofluids to identify cancer-associated proteins and biomarkers for early detection.	Proteome Discoverer Mass Spectrometry (MALDI-TOF, QTOF)	Identifies differentially expressed proteins in early-stage pancreatic cancer. Enables the discovery of novel biomarkers and therapeutic targets based on proteomic alterations.
Metabolomic Tools	Techniques to analyze small molecules (metabolites) in the body, identifying specific metabolites altered in pancreatic cancer.	NMR Spectroscopy GC-MS, LC-MS MetaboAnalyst	Detects specific metabolite profiles linked to pancreatic cancer. Identifies altered metabolic pathways involved in cancer progression. Assists in monitoring disease development and treatment response.
Biomarker Validation	Validate the identified biomarkers through computational and clinical methodologies to ensure their clinical utility.	Bioinformatics Platforms (GATK, MS-DIAL, MetaboAnalyst) Clinical Trials Cross-validation Methods	Ensures that the identified biomarkers are reproducible and reliable for use in clinical settings. Large-scale cohort studies are used to confirm the accuracy and sensitivity of biomarkers.

Pancreatic surgical cases at CU 2012-2024

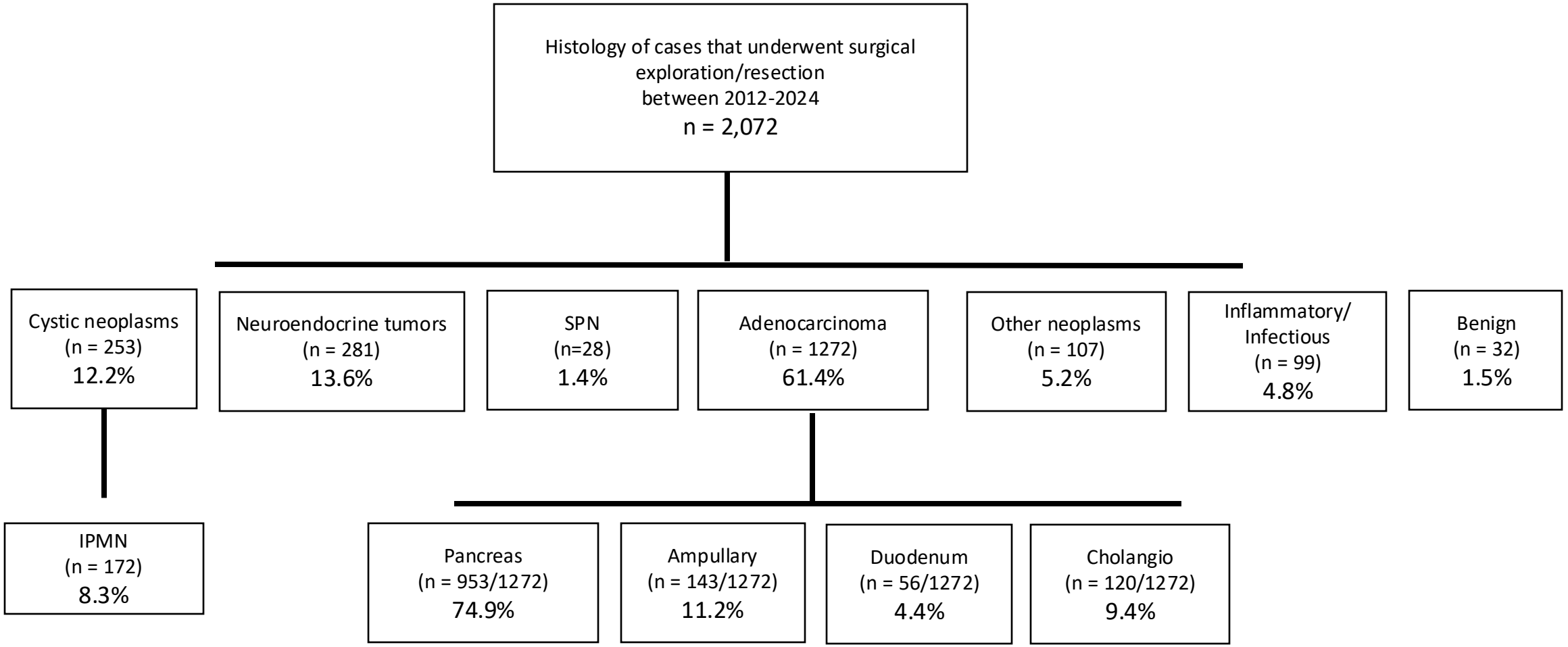


	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
number of cases	56	113	141	135	143	136	162	198	197	203	189	187	212

University of Colorado – Pancreas Surgery Team

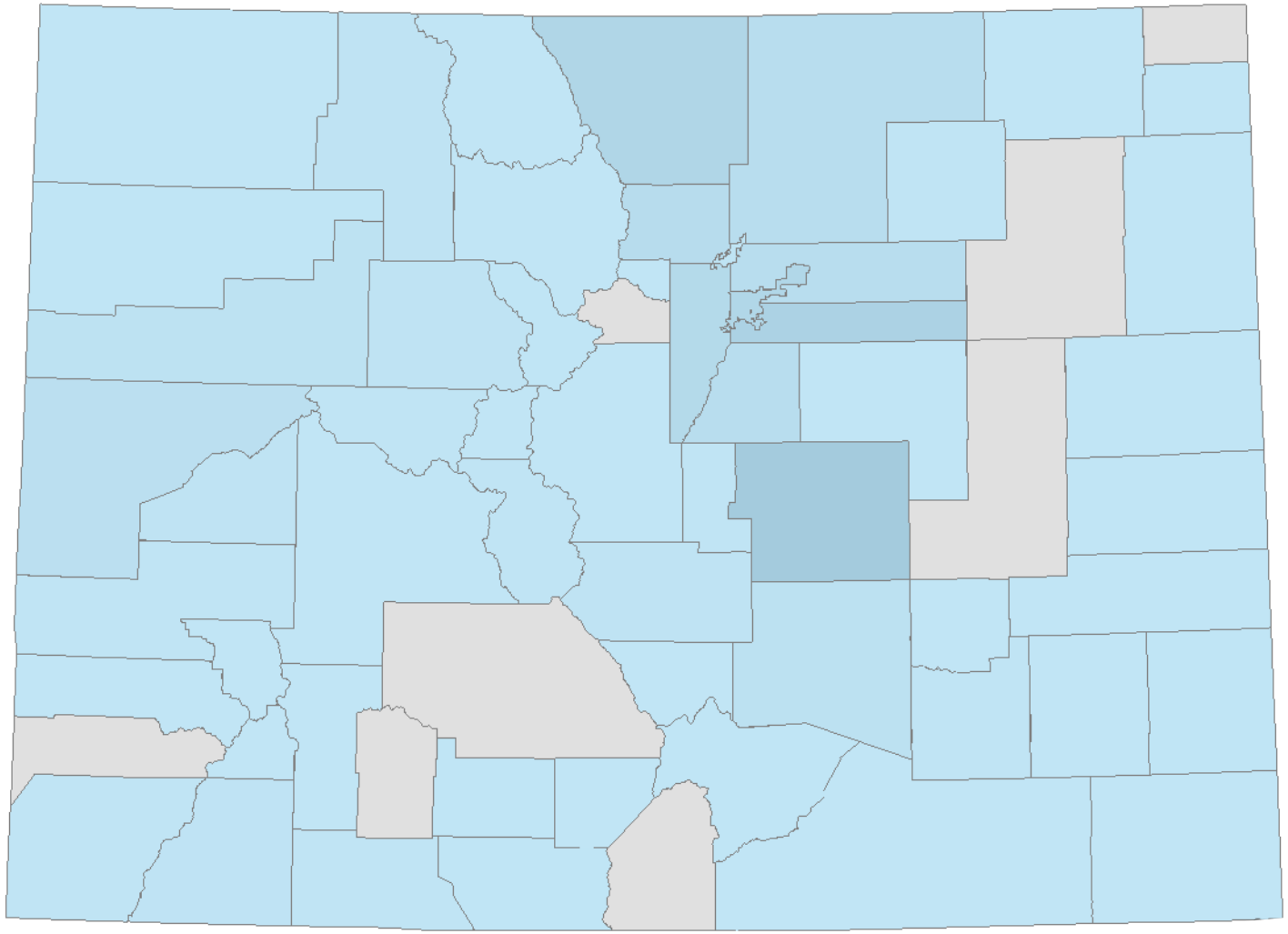


University of Colorado – Pancreas surgery by Diagnosis/Pathology confirmed diagnosis



Where in our state?

Pancreas surgery 2012-2024 - Patients reported home state (n=1716)



Percentage of patients

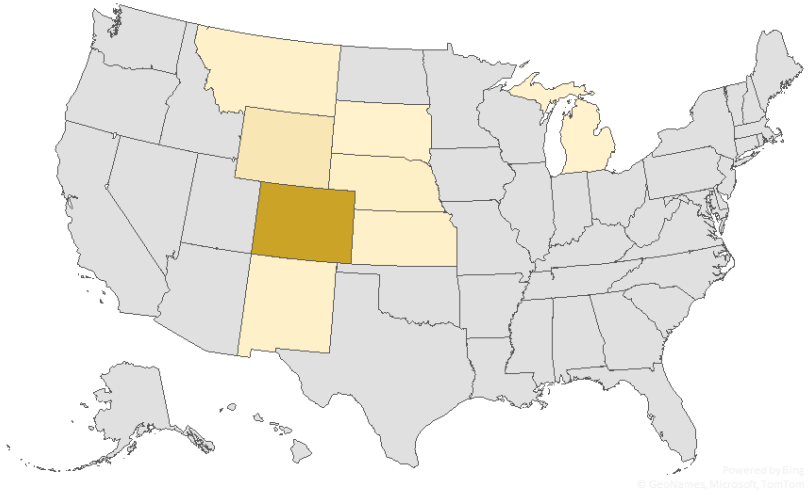
0% 100%

82.8% patients are from our state

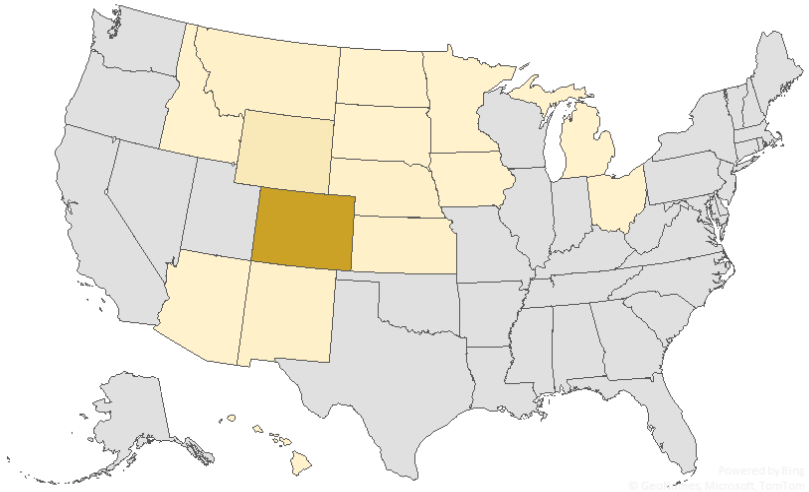
Which states do our patients come from?

Patients reported home state (n=2072)

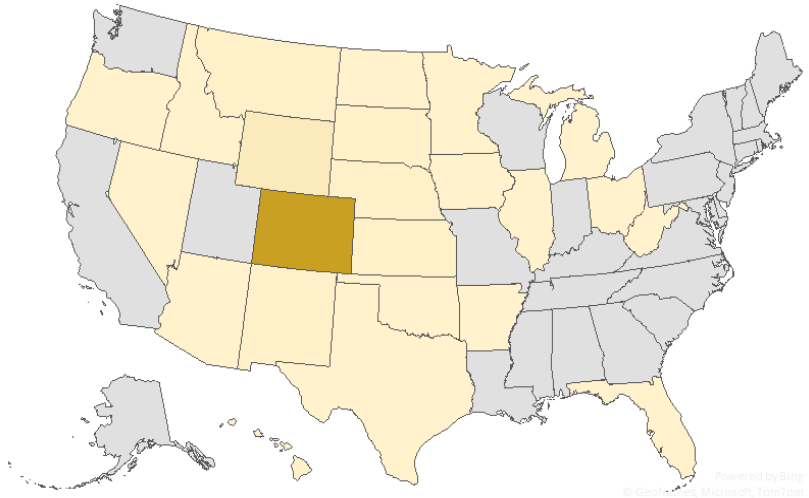
Pancreas surgery 2012-2015



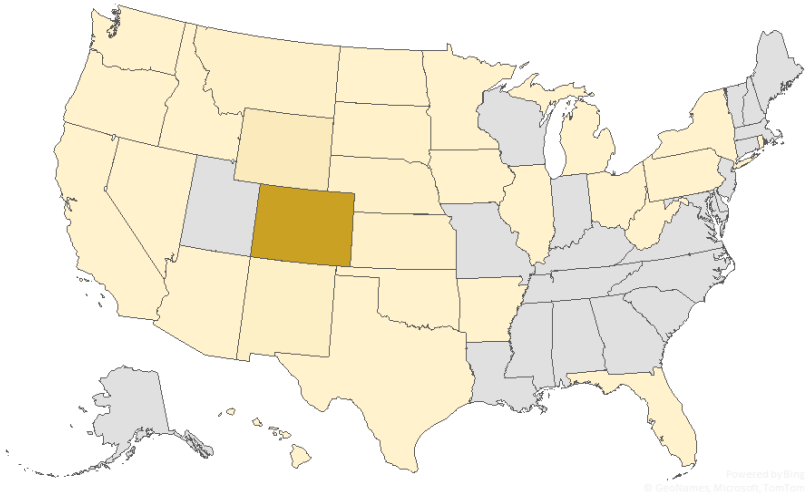
Pancreas surgery 2012-2018



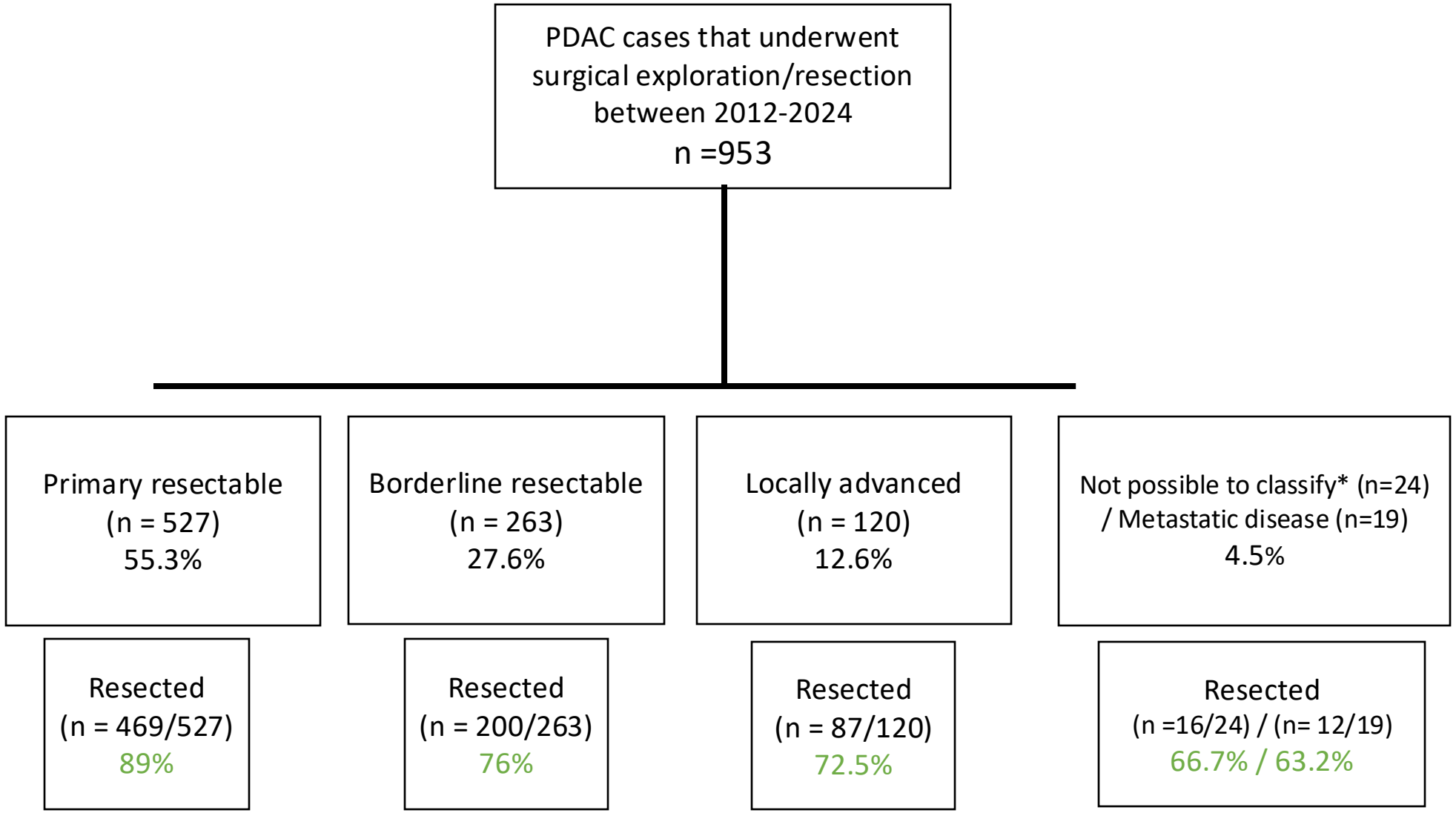
Pancreas surgery 2012-2021



Pancreas surgery 2012-2024

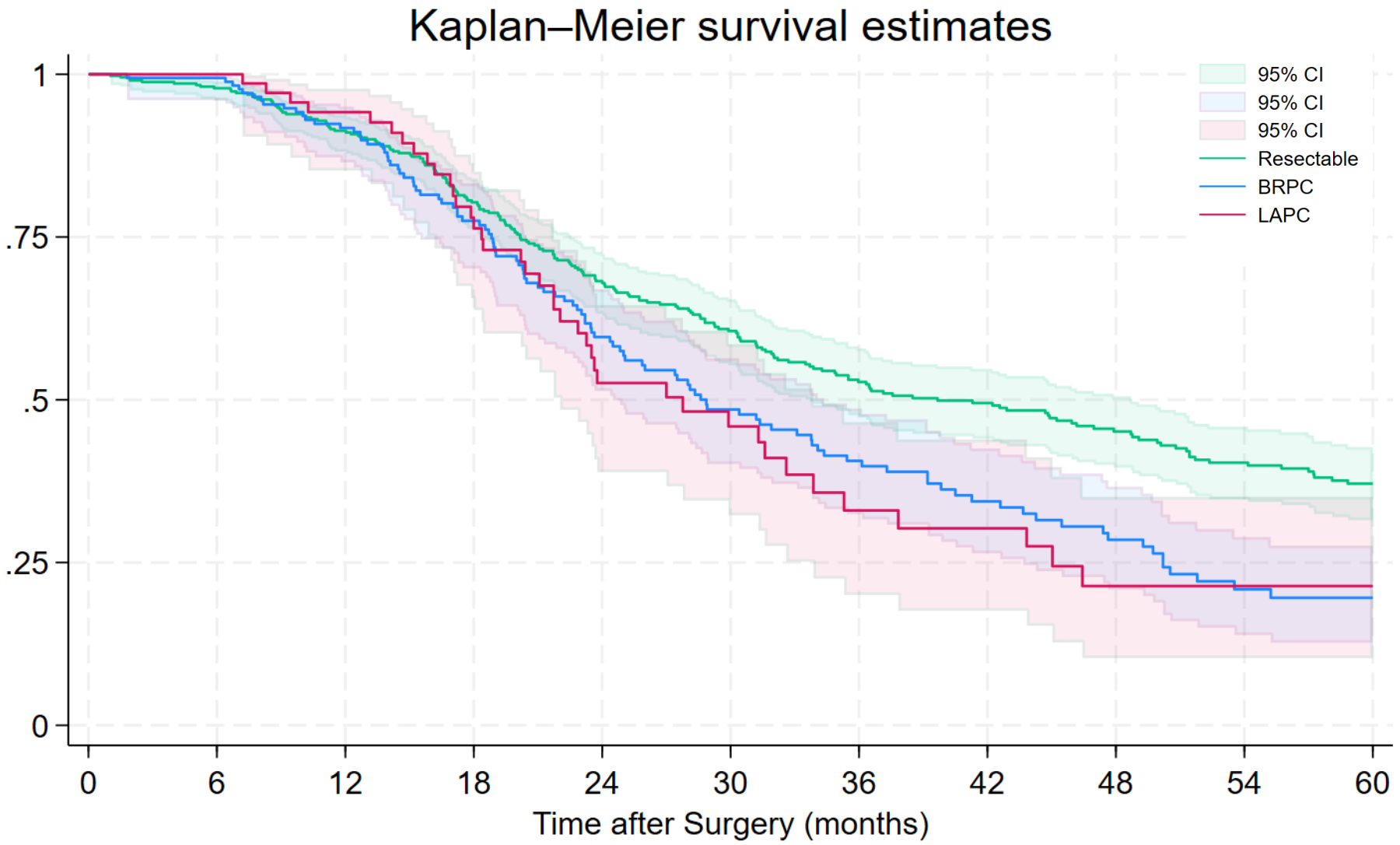


University of Colorado – PDAC cases



* Not possible to classify when imaging at diagnosis was not available and at least a course of treatment (chemotherapy) was already administered.

All resected PDAC cases 2012-2024
(n=694*)



Primary resectable
MST 39.7m (95% CI 33.7-48.8)

Survival rates: 3-year 51.3% (45.9-56.5)
5-year 37.1% (31.5-42.7)

Borderline resectable
MST 28.9m (95% CI 24.5-34.4)

Survival rates: 3-year 39.8% (31.6-47.8)
5-year 19.5% (12.6-27.5)

Locally advanced
MST 27.8m (95% CI 22-33.9)

Survival rates: 3-year 33% (20-46.6)
5-year 21.4% (10.3-35.1)

Overall cohort: MST 33.9m (95% CI 31.2-37.8)
Survival rates: 3-year 46.6% (42.3-50.8)
5-year 31.1% (26.8-35.5)

Summary

Pancreatic cancer is a deadly disease and patients are much better off if it can be prevented or detected very early

Pancreatectomy can be performed with low mortality, but still with high complications rates, and long-term consequences

We continue to learn who to screen, how to screen, and when surgery should be performed

<u>To Impact on Survival</u>

- Better understanding of molecular events and impaired pathways leading to disease
- Prevention
- Earlier detection
- More effective systemic therapies
- Aggressive resection of selected patients
- Multidisciplinary care of patients

<u>To impact on Quality of Life and Morbidity of Surgery</u>

- Proper use of laparoscopic pancreatectomy

Cancer Center

NCI-DESIGNATED COMPREHENSIVE CANCER CENTER

Prevent and conquer cancer. **Together**.

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