

Table S1. Targeted regions of the 9 genes explored by the AmpliSeq custom panel.

Chromosome	Chr Start	Chr End	Gene
chr3	30648360	30648629	<i>TGFBR2</i>
chr3	30664638	30664810	<i>TGFBR2</i>
chr3	30686059	30686455	<i>TGFBR2</i>
chr3	30691752	30691962	<i>TGFBR2</i>
chr3	30713039	30713979	<i>TGFBR2</i>
chr3	30715562	30715772	<i>TGFBR2</i>
chr3	30729825	30730051	<i>TGFBR2</i>
chr3	30732903	30733134	<i>TGFBR2</i>
chr3	178916617	178917162	<i>PIK3CA</i>
chr3	178921155	178921648	<i>PIK3CA</i>
chr3	178927831	178928156	<i>PIK3CA</i>
chr3	178935837	178936122	<i>PIK3CA</i>
chr3	178951741	178952153	<i>PIK3CA</i>
chr7	140453027	140453242	<i>BRAF</i>
chr7	140481300	140481520	<i>BRAF</i>
chr9	21970876	21971211	<i>CDKN2A</i>
chr9	21974390	21974953	<i>CDKN2A</i>
chr12	25378369	25378743	<i>KRAS</i>
chr12	25380056	25380347	<i>KRAS</i>
chr12	25398182	25398385	<i>KRAS</i>
chr17	7573877	7574094	<i>TP53</i>
chr17	7576782	7577196	<i>TP53</i>
chr17	7577397	7577615	<i>TP53</i>
chr17	7578086	7578560	<i>TP53</i>
chr17	7579287	7579591	<i>TP53</i>
chr17	56432224	56432453	<i>RNF43</i>
chr17	56434765	56436189	<i>RNF43</i>
chr17	56437464	56437658	<i>RNF43</i>
chr17	56438133	56438366	<i>RNF43</i>
chr17	56439832	56440060	<i>RNF43</i>
chr17	56440600	56440826	<i>RNF43</i>
chr17	56440877	56441034	<i>RNF43</i>
chr17	56448215	56448442	<i>RNF43</i>
chr17	56492558	56492950	<i>RNF43</i>
chr18	48573324	48573675	<i>SMAD4</i>
chr18	48575033	48575250	<i>SMAD4</i>
chr18	48575547	48575763	<i>SMAD4</i>
chr18	48580971	48581186	<i>SMAD4</i>
chr18	48581175	48584654	<i>SMAD4</i>
chr18	48584611	48584830	<i>SMAD4</i>
chr18	48586136	48592087	<i>SMAD4</i>
chr18	48593191	48593413	<i>SMAD4</i>
chr18	48593402	48593599	<i>SMAD4</i>
chr18	48602799	48603205	<i>SMAD4</i>
chr18	48604455	48604856	<i>SMAD4</i>
chr20	57480364	57480591	<i>GNAS</i>
chr20	57484315	57484718	<i>GNAS</i>

Table S2.
Twenty
pancreatic
cancer
cell lines
SNV types

Cell line	<i>BRAF</i>	mt effect	<i>CDKN2A</i>	mt effect	<i>GNAS</i>	mt effect	<i>KRAS</i>	mt effect	<i>PIK3CA</i>	mt effect	<i>RNF43</i>	mt effect	<i>SMAD4</i>	mt effect	<i>TGFBR2</i>	mt effect	<i>TP53</i>	mt effect
AsPC-1		wt ³¹		wt ³¹		wt ³¹	p.G12D/ c.35C>T	missense* ³¹		wt ³¹	p.S720X/ c.2159G>C	nonsense**	p.R100T/ c.299G>C	missense* ³¹	wt ³¹		p.C135Afs/c.403delA	fs* ³¹
BxPC3		wt ³¹		wt ³¹		wt ³¹		wt ³¹		wt ³¹		wt ³¹		wt ³¹			p.Y220C/c.659T>C	missense* ³¹
Capan-2		wt ³¹		wt ³¹		wt ³¹	p.G12V/ c.35C>A	missense* ³¹		wt ³¹	p.R330Hfs/ c.989delC	fs**		wt ³¹				wt ³¹
CFPAC-1		wt ³¹		wt ³¹		wt ³¹	p.G12V/ c.35C>A	missense* ³¹		wt ³¹		wt ³¹		wt ³¹			p.C242R/c.724A>G	missense* ³¹
HPAF-II		wt		wt		wt		wt		wt	p.E174X/ c.520C>A	nonsense**		wt			p.P151S/c.451G>A	missense**
Mia PACA-2		wt ³¹		wt ³¹		wt ³¹	p.G12C/ c.34C>A	missense* ³¹		wt ³¹		wt ³¹		wt ³¹			p.R248W/c.742G>A	missense* ³¹
Pa01C		wt ²⁸		wt ²⁸		wt ²⁸	p.G12D/ c.35C>T	missense* ²⁸		wt ²⁸		wt ²⁸		-			p.T155P/c.463T>G	missense* ²⁸
Pa02C		wt ²⁸		-		wt ²⁸	p.Q61H/ c.183T>G	missense* ²⁸		wt ²⁸		wt ²⁸		-			p.L257P/c.770A>G	missense* ²⁸
Pa03C		wt ²⁸		wt ²⁸		wt ²⁸	p.G12D/ c.35C>T	missense* ²⁸		wt ²⁸		wt ²⁸		wt ²⁸			p.L344P/c.1031A>G	missense* ²⁸
Pa07C		wt ²⁸		wt ²⁸		wt ²⁸	p.G12D/ c.35C>T	missense* ²⁸		wt ²⁸		wt ²⁸	p.R445X/ c.1333C>T	nonsense* ²⁸			p.H179R/c.536T>C	missense* ²⁸
Pa08C		wt ²⁸		wt ²⁸		wt ²⁸	p.G12V/ c.35C>A	missense* ²⁸		wt ²⁸		wt ²⁸	p.W268Xfs/ c.804delG	fs** ²⁸			p.L201Cfs/c.602delA	fs** ²⁸
Pa16C		wt ²⁸		wt ²⁸		wt ²⁸	p.G12D/ c.35C>T	missense* ²⁸		wt ²⁸		wt ²⁸		wt ²⁸	p.T180Qfs/ c.539_540insA	fs**	p.I255N/c.764A>T	missense* ²⁸
Pa20C		wt ²⁸		wt ²⁸		wt ²⁸	p.G12D/ c.35C>T	missense* ²⁸		wt ²⁸		wt ²⁸	p.M503Ifs/ c.1508_1509insT	fs** ²⁸			p.D208V/c.623T>A	missense* ²⁸
Pa21C		wt ²⁸		-		wt ²⁸	p.G12D/ c.35C>T	missense* ²⁸		wt ²⁸		wt ²⁸		wt ²⁸			p.G266V/c.797C>A	missense* ²⁸
Pa28C		wt ²⁸		wt ²⁸		wt ²⁸	p.G12V/ c.35C>A	missense* ²⁸		wt ²⁸		wt ²⁸	p.Y95S/ c.284A>C	missense* ²⁸			p.T125Tfs/c.375delC	fs**
Pa222C		wt		wt		wt	p.G12D/ c.35C>T	missense*		wt		wt		wt			p.E339_M340delinsV/ c.1016_1018delTCT	fs**
Panc-1		wt ³¹		wt ³¹		wt ³¹	p.G12D/ c.35C>T	missense* ³¹		wt ³¹		wt ³¹		wt ³¹			p.R273H/c.818C>T	missense* ³¹
PK8	p.V600E/ c.1799A>T	missense*		wt		wt		wt	p.H1047R/ c.3140A>G	missense*	p.H549N/ c.1645G>T	missense*		wt				wt
											p.G659Vfs/c1976delC	fs**						
PK9		wt		-		wt		wt		wt		wt		-			p.R213X/c.637G>A	missense**
Su8686		wt ³¹		wt ³¹		wt ³¹	p.G12D/ c.35C>T	missense* ³¹		wt ³¹		wt ³¹		wt ³¹			p.G245S/c.733C>T	missense* ³¹
																	p.G360V/c.1079C>A	missense**

-, no amplicons; fs, frameshift; mt, mutation; wt, wild type

*, heterozygous mutation; **, homozygous mutation

Table S3. The detection of mutations in diluted cancer cell line DNA reference pools by digital NGS

Cell line	Gene	SNV type		zygosity	0.5% pool		0.1% pool		0.01% pool	
		Amino acid change	Nucleotide change		Predicted%	dNGS#	Predicted%	dNGS#	Predicted%	dNGS#
PK8	<i>BRAF</i>	p.V600E	c.1799A>T	heterozygous	0.25%	3	0.050%	0	0.005%	0
MiaPACA-2	<i>KRAS</i>	p.G12C	c.34C>A	homozygous	0.50%	39	0.100%	7	0.010%	1
Pa01C/Pa03C/Pa07C/Pa16C/Pa20C/Pa21C/Pa222C/AsPC-1/PANC-1/Su8686	<i>KRAS</i>	p.G12D	c.35C>T	mixed	2.75%	96	0.200%	75	0.020%	7
Pa08C/Pa28C/Capan-2/CFPAC-1/	<i>KRAS</i>	p.G12V	c.35C>A	mixed	1.00%	72	0.550%	24	0.055%	3
Pa02C	<i>KRAS</i>	p.Q61H	c.183T>G	heterozygous	0.50%	18	0.100%	8	0.010%	1
PK8	<i>PIK3CA</i>	p.H1047R	c.3140A>G	heterozygous	0.25%	7	0.050%	0	0.005%	2
HPAF-II	<i>RNF43</i>	p.E174X	c.520C>A	homozygous	0.50%	29	0.100%	14	0.010%	0
Capan-2	<i>RNF43</i>	p.R330Hfs	c.989delC	homozygous	0.50%	0	0.100%	0	0.010%	0
PK8	<i>RNF43</i>	p.H549N	c.1645G>T	heterozygous	0.25%	8	0.050%	1	0.005%	0
PK8	<i>RNF43</i>	p.G659Vfs	c.1976delC	homozygous	0.50%	0	0.100%	0	0.010%	0
AsPC-1	<i>RNF43</i>	p.S720X	c.2159G>C	homozygous	0.50%	13	0.100%	1	0.010%	0
AsPC-1	<i>SMAD4</i>	p.R100T	c.299G>C	homozygous	0.50%	5	0.100%	0	0.010%	0
Pa08C	<i>SMAD4</i>	p.W268Xfs	c.804delG	homozygous	0.50%	0	0.100%	0	0.010%	0
Pa07C	<i>SMAD4</i>	p.R445X	c.1333C>T	heterozygous	0.25%	1	0.050%	0	0.005%	0
Pa20C	<i>SMAD4</i>	p.M503delinsIEfs	c.1508_1509insT	homozygous	0.50%	0	0.100%	0	0.010%	0
Pa28C	<i>SMAD4</i>	p.Y95S	c.284A>C	homozygous	0.50%	10	0.100%	1	0.010%	0
Pa16C	<i>TGFBR2</i>	p.T180Qfs	c.539_540insA	homozygous	0.50%	0	0.100%	0	0.010%	0
Pa28C	<i>TP53</i>	p.T125Tfs	c.375CdelC	homozygous	0.50%	1	0.100%	0	0.010%	0
AsPC-1	<i>TP53</i>	p.C135Afs	c.403delA	homozygous	0.50%	1	0.100%	1	0.010%	0
HPAF-II	<i>TP53</i>	p.P151SP	c.451G>A	homozygous	0.50%	13	0.100%	7	0.010%	1
Pa01C	<i>TP53</i>	p.T155P	c.463T>G	homozygous	0.50%	11	0.100%	2	0.010%	0
Pa07C	<i>TP53</i>	p.H179R	c.536T>C	homozygous	0.50%	9	0.100%	3	0.010%	3
Pa08C	<i>TP53</i>	p.L201Cfs	c.602delA	homozygous	0.50%	0	0.100%	1	0.010%	0
Pa20C	<i>TP53</i>	p.D208V	c.623T>AT	homozygous	0.25%	7	0.100%	0	0.010%	3
PK9	<i>TP53</i>	p.R213X	c.637G>A	heterozygous	0.50%	8	0.050%	3	0.005%	1
BxPC-3	<i>TP53</i>	p.Y220C	c.659T>C	homozygous	0.50%	3	0.100%	0	0.010%	0
CFPAC-1	<i>TP53</i>	p.C242R	c.724A>G	homozygous	0.50%	20	0.100%	2	0.010%	2
Su8686	<i>TP53</i>	p.G245S	c.733C>T	homozygous	0.50%	10	0.100%	4	0.010%	1
MiaPACA-2	<i>TP53</i>	p.R248W	c.742G>A	homozygous	0.50%	17	0.100%	6	0.010%	2
Pa16C	<i>TP53</i>	p.I255N	c.764A>T	homozygous	0.50%	6	0.100%	3	0.010%	3
Pa02C	<i>TP53</i>	p.L257P	c.770A>G	homozygous	1.00%	38	0.100%	10	0.010%	3
Pa21C	<i>TP53</i>	p.G266V	c.797C>C	homozygous	0.50%	9	0.200%	2	0.020%	0
PANC-1	<i>TP53</i>	p.R273H	c.818C>T	homozygous	0.50%	17	0.100%	8	0.010%	3
Pa222C	<i>TP53</i>	p.E339_M340delinsV	c.1016_1018delTCT	homozygous	0.50%	0	0.100%	0	0.010%	0
Pa03C	<i>TP53</i>	p.L344P	c.1031A>G	homozygous	0.50%	13	0.100%	3	0.010%	0
Su8686	<i>TP53</i>	p.G360V	c.1079C>A	homozygous	0.50%	11	0.100%	2	0.010%	0

Table S4. Serial pancreatic juice collections from patients who developed pancreatic cancer during surveillance

Case #	Time (months before PDAC diagnosis)	GNAS		KRAS		TP53		SMAD4		RNF43		PIK3CA	
		SNV	dNGS #	SNV	dNGS #	SNV	dNGS #	SNV	dNGS #	SNV	dNGS #	SNV	dNGS #
Case#35_1	13.4	p.R201H	1	p.G12D/p.G13D	8,1	p.R248Q	2						
Case#35 Primary PDAC from case #35	0.1		0	p.G12V	1	p.R248Q	3	p.P198S	3				
	0		0	p.Q61H	29%	p.R248Q	24%						
Case#48_1	15		0		0		0						
Case#48	0		0		0	p.C277R	3	p.M543T	3	p.L109P/p.V480A	3,3		
Case#53_1 Cyst fluid from case#53_1	19		0	p.G12D/p.G12R	1,1	p.Y220C/p.R248W/p.R248Q	4,1,1					p.H1047L/p.H1047R	3,6
Case#53_2 Cyst fluid from case#53_2	28		0	p.G12D/p.G12V/p.Q61H	1,5,1	p.R273H/p.R248Q	1,1						
	28	p.R201C	21	p.G12D/p.G12V	32,1	p.Y220C/p.R196X	1,1						
Case#53_3 Cyst fluid from case#53_3	36	p.Q227R	2	p.Q61H/p.Q61L	1,1	p.R196X	2			p.K108R/p.H420R	3,3		
	36	p.R201C	11	p.G12D/p.G12V	3,1	p.R248Q	1						
Case#53_4	50		0	p.G12D/p.G13D	1,1								
Case#53_PDAC_FNA	0		0	p.G12D/p.G12S	81,4	p.L344P/ p.R248W	3,1	p.H290R	3				
Case#53_PDAC_LCM1 *	0		0	p.G12D	23	p.Q100Rfs	4	p.Q388X	24				
Case#53_PDAC_LCM2	0		0	p.G12D	24	p.Q100Rfs	8	p.Q388X/p.H290R	21,1				
Case#53_PDAC_LCM3	0		0	p.G12D	24	p.Q100Rfs	4	p.G386R/p.Q388X	24,9				
Case#53_PDAC_LCM4	0		0	p.G12D	24	p.Q100Rfs	3	p.G386R/p.Q388X/p.H290R	2,24,1				

*, Laser capture microdissection

Table S5: Mutations detected in patient neoplastic specimens and the matching pancreatic juice results

Patient #	Diagnosis	Sample origin	Mutated gene(s)							
			<i>KRAS</i>	<i>TP53</i>	<i>GNAS</i>	<i>TGFBR2</i>	<i>PIK3CA</i>	<i>SMAD4</i>	<i>RNF43</i>	
#31	PDAC + IPMN	Frozen PDAC		p.G12V						
#31	PDAC + IPMN	Juice		p.G12V						
#33	PDAC + IPMN	Frozen PDAC		p.G12V/p.G12R	p.R273C					
#33	PDAC + IPMN	Juice		p.G13D/p.G12R	p.R273C	p.R201H				
#35	PDAC + IPMN	Frozen PDAC		p.Q61H	p.R248Q					
#35	PDAC + IPMN	Juice		p.G12V	p.R248Q				p.P198S	
#41	PDAC	Frozen PDAC		p.G12R		p.E465K	p.K1030E			
#41	PDAC	Juice		p.G12D/p.G12R		p.R201H				p.C471R
#43	PDAC	Frozen PDAC		p.G12V	p.R209Kfs					
#43	PDAC	Juice		p.G12S/p.G12V	p.R248W					
#17	IPMN	FFPE		p.G13D/p.G12V		p.R201H				
#17	IPMN	Juice		p.G13D/p.G12C/p.G12R/p.G12V/p.Q61R		p.R201H				
#20	IPMN	FFPE		p.G13D/p.G13S/p.G12S						
#20	IPMN	Juice			p.R282W	p.R201C				
#22	IPMN	FFPE		p.G13S/p.G12R		p.R201C/p.R201H				
#22	IPMN	Juice		p.G12V						

Table S6 Characteristics of cases included in this study

Case	M/F	Age	CAPS#	Risk	Group	Lesion (mm)	Pancreatic EUS	Diagnosis
#01	F	27	CAPS4	na	Control	No cyst, no mass	Normal	Diarrhoea, suspected neuroendocrine tumour not identified.
#02	F	79	CAPS4	na	Control	No cyst, no mass	Dilated CBD	Dilated CBD, Whipple Op. benign pathology.
#03	F	77	CAPS3	na	Control	No cyst, no mass	Normal	Chronic abdominal pain.
#04	M	50	CAPS3	na	Control	No cyst, no mass	Normal	Elevated liver enzymes, periportal lymphadenopathy, ?sarcoïd.
#05	F	78	CAPS3	na	Control	No cyst, no mass	Dilated MPD	Main pancreatic duct dilation, 4 mm pancreatic cyst? Chronic pancreatitis.
#06	M	76	CAPS4	na	Control	No cyst, no mass	Normal	Abdominal pain, gastritis, GORD.
#07	F	49	CAPS3	na	Control	No cyst, no mass	Normal	CBD stone.
#08	F	65	CAPS3	na	Control	No cyst, no mass	Normal	Chronic cholecystitis.
#09	M	45	CAPS3	na	Control	No cyst, no mass	Normal	Papillary stenosis.
#10	F	68	CAPS5	na	Control	No cyst, no mass	Chronic pancreatitis	Chronic pancreatitis.
#11	F	48	CAPS5	na	Control	No cyst, no mass	Chronic pancreatitis	Chronic pancreatitis.
#12	F	43	CAPS3	na	Control	No cyst, no mass	Normal	Dilated CBD.
#13	F	44	CAPS3	na	Control	No cyst, no mass	Normal	Cholangitis.
#14	M	48	CAPS3	s	IPMN	8	IPMN	Pathology: IPMN with low-grade dysplasia, head.
#15	M	64	CAPS4	f	IPMNs	20	Cysts	Multiple cystic lesions by EUS, largest 2 cm, head and body.
#16	F	63	CAPS4	f	IPMNs	15	IPMN	Pathology: IPMN with low-grade dysplasia, tail w/PanIN2.
#17	F	60	CAPS3	f	IPMN	10	Dilated MPD	Pathology: IPMN with low-grade dysplasia, tail w/PanIN2
#18	M	75	CAPS5	f	IPMNs	7	Tiny cysts	Pathology: IPMN with low-grade dysplasia, body w/PanIN2.
#19	F	67	CAPS3	s	IPMN	5	Dilated CBD	Pathology: IPMN with intermediate grade dysplasia, head w/PanIN2.
#20	F	73	CAPS3	s	IPMN	20	IPMN	Pathology: IPMN with intermediate grade dysplasia, body w/PanIN1.
#21	F	67	CAPS3	s	IPMNs	60	IPMN	Pathology: IPMN with intermediate grade dysplasia, head.
#22	M	65	CAPS4	f	IPMNs	19	IPMN	Pathology: IPMN with intermediate grade dysplasia, head and neck.
#23	F	64	CAPS4	s	IPMNs	22	IPMNs	Multiple IPMNs by EUS/MRI largest 2 cm, body.
#24	M	21	CAPS4	s	IPMNs	13	Innumerable cysts	McCune-Albright syndrome, many pancreatic cysts (IPMNs) by imaging.
#25	M	67	CAPS5	s	IPMNs	25	Cysts	Multiple IPMNs by EUS/MRI largest >2.5 cm, head and neck
#26	M	51	CAPS4	f	IPMNs	6	Tiny cysts	Subcentimetre pancreatic cysts by EUS, suspected IPMN, tail.
#27	M	62	CAPS5	f	IPMNs	5	Cysts	Subcentimetre pancreatic cysts (suspected IPMN), head.
#28	M	70	CAPS3	s	IPMNs	44	Cyst	IPMN with suspicious features, uncinata.
#29	F	75	CAPS4	s	IPMNs	27	Cyst	IPMN by imaging, tail.
#30	F	63	CAPS5	s	IPMNs	10	Cysts	IPMN by imaging, also a suspected serous cystadenoma by imaging.
#31	M	79	CAPS4	s	PDAC/ IPMNs	45	IPMN	Pathology: Stage IB, body w/IPMN.
#32	M	69	CAPS5	s	PDAC/ IPMNs	60	IPMN	Pathology: Stage IIA, head w/IPMN.
#33	F	74	CAPS4	s	PDAC/ IPMNs	25	PDAC/IPMN	Pathology: Stage IIB, head w/IPMN.
#34	F	55	CAPS2	s	PDAC/ IPMNs	20	PDAC/IPMN	Pathology: Stage IIB, head w/IPMN.
#35	M	65	CAPS4	f	PDAC/ IPMNs	28	PDAC/IPMN	Pathology: Stage IIB, tail w/IPMN.
#36	M	74	CAPS4	f	PDAC/ IPMNs	50	Cysts	Pathology: Stage IIB, head w/IPMN.
#37	M	69	CAPS2	s	PDAC/ IPMN	100	PDAC/IPMN	Pathology: Stage III, head w/IPMN.
#38	M	73	CAPS2	s	PDAC/ IPMNs	38	PDAC/IPMN	Pathology: Stage IV, uncinata w/IPMN.
#39	M	70	CAPS4	f	PDAC	7	PDAC	Pathology: Stage IA, tail.
#40	M	53	CAPS4	s	PDAC	47	PDAC	Pathology: Stage IB, head.
#41	F	46	CAPS3	s	PDAC	30	PDAC	Pathology: Stage IB, head.
#42	M	78	CAPS3	s	PDAC	40	PDAC	Pathology: Stage IIA, head.
#43	F	59	CAPS3	s	PDAC	30	PDAC	Pathology: Stage IIB, uncinata.
#44	F	77	CAPS2	s	PDAC	40	PDAC	Pathology: Stage IIB, head.
#45	M	56	CAPS2	s	PDAC	20	Dilated PD	Pathology: Stage IIB, head.
#46	M	58	CAPS4	s	PDAC	55	PDAC	Pathology: Stage IIB, tail.
#47	F	75	CAPS4	s	PDAC	NA	Mass	Pathology: Stage III, head to body.
#48	M	59	CAPS4	f	PDAC	23	PDAC	Pathology: Stage III, head.
#49	F	69	CAPS2	s	PDAC	35	PDAC	Pathology: Stage IV, body and tail.
#50	F	68	CAPS4	s	PDAC	47	Mass	Pathology: Stage IV, body and tail.

Continued

Table S6 Continued

Case	M/F	Age	CAPS#	Risk	Group	Lesion (mm)	Pancreatic EUS	Diagnosis
#51	F	66	CAPS4	s	PDAC	44	Mass	Pathology: Stage IV, head.
#52	F	62	CAPS5	f	PDAC	18	PDAC	Pathology: Stage IV, head.
#53	F	79	CAPS5	f	PDAC	25	PDAC	Pathology: Stage IIB, head.
#54	M	46	CAPS5	na	Control	No cyst, no mass	Normal	Hepatosplenomegaly.
#55	F	72	CAPS5	na	Control	No cyst, no mass	Normal	Benign pancreatic acinar tissue with acute and chronic inflammation.
#56	M	34	CAPS3	na	Control	No cyst, no mass	Normal	Abdominal pain.
#57	F	52	CAPS4	na	Control	No cyst, no mass	Normal	Post cholecystectomy, ERCP due to sphincter of Oddi dysfunction.
#58	M	66	CAPS4	na	Control	No cyst, no mass	Normal	Abdominal pain.
#59	F	59	CAPS4	na	Control	No cyst, no mass	Normal	Probable pancreatic serous cystadenoma.
#60	M	59	CAPS4	na	Control	No cyst, no mass	Normal	Gallbladder stone.
#61	F	73	CAPS4	na	Control	No cyst, no mass	Normal	Reflux oesophagitis, suspected submucosal nodule not found.
#62	M	48	CAPS4	na	Control	No cyst, no mass	Normal	Abdominal pain, abnormal liver enzymes.
#63	M	40	CAPS4	na	Control	No cyst, no mass	Normal	Abdominal pain.
#64	F	32	CAPS4	na	Control	No cyst, no mass	Normal	Postcholecystectomy, ECRP due to bile leak.
#65	F	58	CAPS4	s	IPMN	11	Cysts	IPMNs by EUS, tail.
#66	M	67	CAPS4	s	IPMN	20	Cysts	IPMNs by EUS, tail.
#67	M	70	CAPS4	s	IPMN	9	Cysts	IPMNs by EUS, head.
#68	M	59	CAPS4	s	IPMN	13	Cyst	Side-branch IPMN by EUS (head).
#69	F	65	CAPS4	s	IPMN	16	Cysts	IPMNs by EUS, head and body.
#70	M	62	CAPS4	s	IPMN	20	Cysts	Cysts by EUS, head.
#71	F	84	CAPS4	s	IPMN	16	Cyst	A cyst by EUS, head.
#72	M	66	CAPS4	s	IPMN	13	Cysts	IPMNs by EUS, head and body.
#73	F	60	CAPS4	s	IPMN	14	Cysts	IPMN vs SCN by imaging.
#74	F	66	CAPS4	s	IPMN	15	Cyst	A cyst by EUS, head, suspected IPMN by MRCP.
#75	M	70	CAPS4	s	IPMN	22	Cyst	IPMN by EUS, head.
#76	M	41	CAPS4	s	IPMN	10	Cyst	IPMN by EUS, tail.
#77	F	55	CAPS4	s	IPMN	15	Cyst	IPMN by EUS, head.
#78	F	74	CAPS4	s	IPMN	26	Cysts	IPMNs by EUS, body and tail.
#79	M	76	CAPS4	s	IPMN	17	Cyst	IPMN by EUS, head.
#80	F	64	CAPS4	s	IPMN	21	Cyst	IPMN by EUS, head.
#81	F	44	CAPS4	s	IPMN	10	Cysts	IPMNs by EUS, head.
#82	F	77	CAPS4	s	IPMN	19	Cyst	IPMN by EUS, head.
#83	F	67	CAPS4	s	IPMN	16	Cysts	IPMNs by EUS, head, body and tail.
#84	M	84	CAPS4	s	IPMN	17	Cysts	Cysts by EUS, body and tail.
#85	M	49	CAPS4	s	IPMN	18	Cyst	IPMN by EUS, tail.
#86	F	74	CAPS4	s	IPMN	24	Cysts	IPMNs by EUS, head, body and tail.
#87	F	77	CAPS4	s	IPMN	21	Cysts	IPMNs by EUS, head, body and tail.
#88	F	83	CAPS4	s	IPMN	19	Cysts	IPMNs by EUS, head, body and tail.
#89	F	83	CAPS4	s	IPMN	19	Cysts	IPMNs by EUS, head, body and tail, chronic pancreatitis.
#90	M	70	CAPS4	s	IPMN	17	Cysts	IPMNs by EUS, head and body.
#91	F	62	CAPS4	s	IPMN	10	Cysts	IPMNs by EUS, head.
#92	F	70	CAPS4	s	IPMN	23	Cysts	IPMNs by EUS, body.
#93	M	62	CAPS4	s	IPMN	21	Cysts	IPMNs by EUS, head, body and tail.
#94	F	66	CAPS4	s	IPMN	17	Cysts	IPMNs by EUS, head and tail.
#95	M	64	CAPS4	s	IPMN	18	Cyst	A cyst by EUS, tail, IPMN by imaging.
#96	M	76	CAPS4	s	IPMN	9	Cysts	IPMNs by EUS, head and tail.
#97	F	83	CAPS4	s	IPMN	15	Cyst	IPMN by EUS, body.
#98	F	68	CAPS4	s	IPMN	14	Cyst	IPMN by EUS, head.
#99	F	60	CAPS4	s	IPMN	12	Cysts	IPMNs by EUS, head, body and tail.
#100	M	78	CAPS4	f	LG-IPMN	6	IPMNs	Pathology: IPMN with low-grade dysplasia, head and tail w/ PanIN2.
#101	M	72	CAPS4	f	LG-IPMN	9	IPMNs	Pathology: IPMN with low-grade dysplasia, head w/ PanIN2.
#102	M	72	CAPS4	s	IM-IPMN	30	IPMNs	Pathology: IPMN with low-to-intermediate grade dysplasia, tail w/ PanIN2.
#103	F	75	CAPS4	f	IM-IPMN	15	IPMNs	Path: IPMN intermediate grade dysplasia, tail w/PanIN2, PanNet (2mm).
#104	M	71	CAPS4	f	IPMN	8	Cysts	Less than 1 cm cysts (1 year later: surgery IPMN high-grade dysplasia (35 mm), body, tail).
#105	M	68	CAPS5	s	PDAC/ IPMNs	60	Cyst (with nodule)	Pathology: stage IIA, head with PanIN3.

Continued

Table S6 Continued

Case	M/F	Age	CAPS#	Risk	Group	Lesion (mm)	Pancreatic EUS	Diagnosis
#106	M	44	CAPS4	s	PDAC/ IPMNs	49	Malignant IPMN	Pathology: stage III, head with PanIN1.
#107	M	59	CAPS5	s	PDAC/ IPMN	7	MD-IPMN	Pathology: mucinous (colloid) carcinoma arising in an IPMN, Stage IA, head.
#108	M	63	CAPS5	s	PDAC	55	Mass	Pathology: stage III, head.
#109	M	71	CAPS5	s	PDAC	25	Mass	Pathology: stage IV, tail.
#110	M	70	CAPS5	f	PDAC	44	Mass	Pathology: stage IV, body.
#111	M	62	CAPS5	s	PDAC	34	Mass	Pathology: stage IV, head.
#112	F	71	CAPS5	s	PDAC	23	Mass	Pathology: stage IB, body with PanIN2.
#113	F	77	CAPS4	s	PDAC	48	PDAC	Pathology: stage IV, body.
#114	M	57	CAPS4	s	PDAC	36	Mass	Pathology: stage IV, head.
#115	M	68	CAPS4	s	PDAC	30	PDAC	Pathology: stage IV, body.

CAPS, Cancer of the Pancreas Screening; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; f, familial; IPMN, intraductal papillary mucinous neoplasm; MRCP, MR cholangiopancreatography; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; s, sporadic.

Table S7. Somatic mutations identified in pancreatic juice by digital NGS*

Case#	M/F	Age	Disease group	Risk**	KRAS		GNAS		RNF43		TP53		SMAD4	
					dNGS#	SNV	dNGS#	SNV	dNGS#	SNV	dNGS#	SNV	dNGS#	SNV
#01	F	27	Control	na	0		0		0		0		0	
#02	F	79	Control	na	1	p.G12D	0		0		0		0	
#03	F	77	Control	na	0		0		0		0		0	
#04	M	50	Control	na	1	p.G12D	0		0		0		0	
#05	F	78	Control	na	0		0		0		0		0	
#06	M	76	Control	na	0		0		0		0		0	
#07	F	49	Control	na	1,2,2	p.G12D/V, G13D	0		0		0		0	
#08	F	65	Control	na	0		3	p.R201C	3	p.Q402R	0		0	
#09	M	45	Control	na	1,2	p.G12D/V	0		0		0		0	
#10	F	68	Control	na	0		0		0		0		0	
#11	F	48	Control	na	0		0		0		0		0	
#12	F	43	Control	na	0		0		0		0		0	
#13	F	44	Control	na	0		0		0		0		0	
#54	M	46	Control	na	0		0		0		0		0	
#55	F	72	Control	na	2	p.Q61L	0		0		0		0	
#56	M	34	Control	na	1	p.Q61L	0		0		0		0	
#57	F	52	Control	na	1	p.G12S	1	p.R201H	0		0		0	
#58	M	66	Control	na	0		2,2	p.R201C/H	0		0		0	
#59	F	59	Control	na	1	p.G12S	0		0		0		0	
#60	M	59	Control	na	1,1	p.G12D/S	0		0		0		0	
#61	F	73	Control	na	0		0		0		0		0	
#62	M	48	Control	na	0		0		0		0		0	
#63	M	40	Control	na	0		1	p.R201C	0		0		0	
#64	F	32	Control	na	1	p.G12D	0		0		0		0	
#15	M	64	IPMNs	f	1	p.G12V	0		0		0		0	
#23	F	64	IPMNs	s	3,4	p.G12D/V	0		0		0		0	
#24	M	21	IPMNs	s	3	p.G13D	29	p.R201C	10,3	p.R343H, Y550C	0		0	
#25	M	67	IPMNs	s	0		0		0		0		0	
#26	M	51	IPMNs	f	0		4,1	p.R201C/H	4,3	p.P634S, Q402X	3	p.R196L	0	
#27	M	62	IPMNs	f	0		0		0		2	p.R248Q	0	
#28	M	70	IPMNs	s	1	p.G12D	4,1	p.R201C/H	0		4	p.K291R	0	
#29	F	75	IPMNs	s	1	p.G12V	2	p.Q227R	0		0		0	
#30	F	63	IPMNs	s	1,2,4	p.G12D/V/ R	0		3	p.S446F	0		0	
#65	F	58	IPMN	s	1,1,1	p.G12D/V, Q61L	1	p.Q227R	0		0		0	
#66	M	67	IPMN	s	9	p.G12C	0		0		0		0	
#67	M	70	IPMN	s	1,1	p.G12D/V	2	p.R201C	0		0		0	
#68	M	59	IPMN	s	1	p.G12V	0		3	p.S464G	0		0	
#69	F	65	IPMN	s	1,1	p.G12S, Q61R	1	p.R201C	3	p.S478P	0		0	
#70	M	62	IPMN	s	1	p.Q61R	0		0		3	p.M246V	0	
#71	F	84	IPMN	s	0		0		0		0		0	
#72	M	66	IPMN	s	1,2	p.G12V, Q61H	1	p.R201H	0		0		0	
#73	F	60	IPMN	s	1	p.Q61L	0		0		0		0	
#74	F	66	IPMN	s	1,1,1	p.G13D, Q61H/R	0		0		0		0	
#75	M	70	IPMN	s	0		0		0		0		0	
#76	M	41	IPMN	s	1,1	p.G12V, Q61R	0		0		2	p.R175H	0	
#77	F	55	IPMN	s	1	p.Q61R	0		0		0		0	
#78	F	74	IPMN	s	1,1,1	p.G12C, G13D, Q61R	0		3	p.A148V	3	p.R175H	0	
#79	M	76	IPMN	s	0		1	p.Q227R	5	p.A629T	0		0	

Continued

Table S7. Continued

Case#	M/F	Age	Disease group	Risk**	KRAS		GNAS		RNF43		TP53		SMAD4	
					dNGS#	SNV	dNGS#	SNV	dNGS#	SNV	dNGS#	SNV	dNGS#	SNV
#80	F	64	IPMN	s	1,8	p.G12V, Q61H	8	p.R201C	0		0		0	
#81	F	44	IPMN	s	2,1,1,1,1	p.G12D//R, p.Q61H/R	1	p.R201H	0		0		0	
#82	F	77	IPMN	s	1	p.Q61H	1	p.R201H	0		0		0	
#83	F	67	IPMN	s	2,1,1,2,1	p.G12D//R/S, G13D	0		0		0		0	
#84	M	84	IPMN	s	1,1	p.G12C/S	1	p.R201H	3	p.G263E	0		0	
#85	M	49	IPMN	s	1,2	p.G12D/V	0		0		0		0	
#86	F	74	IPMN	s	1,1,1	p.G12D, Q61H/R	1	p.R201C	3	p.L122P	3	p.Q165X	0	
#87	F	77	IPMN	s	1,2,1,1	p.G12D//S, Q61L	0		0		0		0	
#88	F	83	IPMN	s	2	p.G12V	1	p.R201H	0		2	p.R282W	0	
#89	F	83	IPMN	s	0		1	p.R201H	0		4	p.R248W	0	
#90	M	70	IPMN	s	1,1	p.G12D, Q61H	1	p.Q227P	0		2	p.G245S	0	
#91	F	62	IPMN	s	1,1,2	p.G12V/R/S	3	p.R201C	0		0		0	
#92	F	70	IPMN	s	5,4,2	p.G12D//C	3,1	p.R201C, Q227R	0		0		0	
#93	M	62	IPMN	s	1,1,1	p.G12C/S, Q61H	0		0		0		0	
#94	F	66	IPMN	s	0		0		0		0		0	
#95	M	64	IPMN	s	0		2	p.R201C	0		0		0	
#96	M	76	IPMN	s	0		0		0		2	p.R248W	0	
#97	F	83	IPMN	s	13	p.G12V	1,1	p.R201C/H	0		0		0	
#98	F	68	IPMN	s	0		0		0		2	p.Q136X	0	
#99	F	60	IPMN	s	1,1	p.Q61L/R	1	p.R201H	3	p.S111G	0		0	
#14	M	48	LG-IPMN	s	0		1	p.R201H	4	p.A618V	0		0	
#16	F	63	LG-IPMN	f	2	p.G12D	0		0		0		0	
#17	F	60	LG-IPMN	f	5,8,1,3,2	p.G13D, G12C/R/V, Q61R	8	p.R201H	15	p.L12Rfs	2	p.R248Q	0	
#18	M	75	LG-IPMN	f	1	p.G12V	2,1	p.Q227R, R201C	0		0		0	
#100	M	78	LG-IPMN	f	1,2	p.G13D, Q61R	1	p.Q227R	0		2	p.R175H	0	
#101	M	72	LG-IPMN	f	0		0		0		0		0	
#19	F	67	IM-IPMN	s	2	p.G13D	2	p.R201C	0		0		0	
#20	F	73	IM-IPMN	s	0		2	p.R201C	0		2	p.R282W	0	
#21	F	67	IM-IPMN	s	1	p.G12V	1	p.R201C	0		0		3	p.W524R^
#22	M	65	IM-IPMN	f	2	p.G12V	0		0		0		0	
#102	M	72	IM-IPMN	s	5	p.Q61H	0		3	p.R127Q	0		0	
#103	F	75	IM-IPMN	f	7,1,18,1,18	p.G12A//R, G13D, Q61H	1	p.R201C	0		0		0	
#104	M	71	HG-IPMN	f	1,1,2,1,7,4,1	p.G12D/R/S, G13D, p.Q61L/H/P	0		0		0		0	
#31	M	79	PDAC/ IPMNs	s	1	p.G12V	0		0		2	p.R196X	0	
#32	M	69	PDAC/ IPMNs	s	1	p.Q61R	0		0		3	p.R175H	0	
#33	F	74	PDAC/ IPMNs	s	4,2	p.G13D, G12R	1	p.R201H	0		0		0	
#34	F	55	PDAC/ IPMNs	s	23,6,3,2,2,2,2,2	p.G12D/S/R/C/V, G13C/D	0		3	p.R454H	26	p.R248Q	0	

Continued

Table S7. Continued

Case#	M/F	Age	Disease group	Risk**	KRAS		GNAS		RNF43		TP53		SMAD4	
					dNGS#	SNV	dNGS#	SNV	dNGS#	SNV	dNGS#	SNV	dNGS#	SNV
#35	M	65	PDAC/ IPMNs	f	1	p.G12V	0		0		3	p.R248Q	0	
#36	M	74	PDAC/ IPMNs	f	21	p.G12D	2	p.R201C	0		0		26,4	p.Q311X, Q256X
#37	M	69	PDAC/ IPMN	s	0		61	p.R201C	0		87	p.L194R	0	
#38	M	73	PDAC/ IPMNs	s	12	p.G12D	1,1	p.R201C/H	0		0		0	
#105	M	68	PDAC/ IPMNs	s	1	p.G12D	6	p.R201C	3,3	p.F322S, H295R	8	p.C141G	0	
#106	M	44	PDAC/ IPMNs	s	10	p.Q61R	0		0		12	p.R175H	3	p.T273fs
#107	M	59	PDAC/ IPMN	s	8,8	p.G12D/S	0		10	p.P470fs	2	p.R175H	0	
#115	M	68	PDAC/ IPMN	s	6,1,1	p.G12C/S, Q61L	1	p.R201H	0		3	p.R181C	0	
#39	M	70	PDAC	f	0		0		0		0		0	
#40	M	53	PDAC	s	0		0		0		6	p. L130Sfs	0	
#41	F	46	PDAC	s	3,6	p.G12D/R	2	p.R201H	4	p.C471R	0		0	
#42	M	78	PDAC	s	6,2	p.G13D, G12V	1	p.R201C	0		0		0	
#43	F	59	PDAC	s	3,5	p.G12S/V	0		0		2	p.R248W	0	
#44	F	77	PDAC	s	1	p.G12D	2	p.R201C	5	p.H556R	3	p.R175H	7	p.A457V^
#45	M	56	PDAC	s	6,2	p.G12D/V	0		4	p.R519X	7	p.Y220C	0	
#46	M	58	PDAC	s	17	p.G12D	0		0		0		0	
#47	F	75	PDAC	s	32,22,4,4	p.G13D, Q61H, G12D/R	0		0		2	p.R273C	0	
#48	M	59	PDAC	f	0		0		3,3	p.L109P, V480A	3	p.C277R	3	p.M543T^
#49	F	69	PDAC	s	23,2	p.G12V/S	2	p.R201C	0		39	p.R196X	0	
#50	F	68	PDAC	s	0		0		0		0		0	
#51	F	66	PDAC	s	0		0		0		0		11	p.K50Kfs
#52	F	62	PDAC	f	4	p.G12D	0		0		0		0	
#53	F	79	PDAC	f	1,1	p.G12D/R	0		0		4,1,1	p.Y220C, R248W/Q	0	
#108	M	63	PDAC	s	0		1	p.Q227R	0		0		0	
#109	M	71	PDAC	s	1	p.Q61H	0		0		0		0	
#110	M	70	PDAC	f	0		0		3	p.H472R	2	p.R248W	0	
#111	M	62	PDAC	s	2,1	p.G12D, G13D	0		0		0		0	
#112	F	71	PDAC	s	1	p.Q61H	1	p.R201C	0		2,2	p.R248W, Y163C	0	
#113	F	77	PDAC	s	11	p.G12V	1	p.R201H	0		2	p.Y220C	0	
#114	M	57	PDAC	s	0		0		0		0		0	

Case #20 had a BRAF K601K mutation (score 4), Case #26 had a TGFBR2 mutation D317Y (score 4), Case #53 had PIK3CA mutations H1047L/R (score 3, 6), Case#105 had a BRAF F595L mutation (score 4), Case # had a Case #107 had a PIK3CA H1047R mutation (score 3).

*, Other four genes shown in supplementary table;**, s: sporadic; f: familial. dNGS#:digital NGS score (mutation concentration); SNV:single nucleotide variant (i.e. somatic mutation).

^suspected pathogenic.

Table S8 Statistical analysis of pancreatic juice mutation concentrations by digital NGS scores

dNGS #	n	<i>KRAS</i> only		<i>GNAS</i> only		<i>TP53</i> only		<i>TP53+SMAD4</i>		All 9 genes	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	24	0.8	1.4	0.4	1.0	0.0	0.0	0.0	0.0	1.3	1.8
IPMN	56	3.9	6.9	1.1	1.8	0.7	1.2	0.8	1.3	7.1	8.9
PDAC	34	8.2	13	2.4	10.4	6.5	16.3	8.2	16.6	20.7	29.6
		<i>KRAS</i> only		<i>GNAS</i> only		<i>TP53</i> only		<i>TP53+SMAD4</i>		All 9 genes	
Mann-Whitney test		p Value		p Value		p Value		p Value		p Value	
PDAC vs controls		0.001		0.098		<0.0001		<0.0001		<0.0001	
IPMN v controls		<0.001		0.006		0.007		0.007		<0.0001	
PDAC vs IPMN		0.335		0.281		0.0003		<0.0001		0.003	

dNGS#, digital NGS score (mutation concentration); IPMN, intraductal papillary mucinous neoplasm; NGS, next-generation sequencing; PDAC, pancreatic ductal adenocarcinoma.