

Supplementary Table 1. Clinical and pathologic comparison of ARX, PDX1 and ALT status in 137 non-syndromic, primary NF-PanNETs from Utrecht/Amsterdam University and ARC-Net Research Center.

Patient or Tumor Characteristics	Total, n = 137	ARX-positive, n = 107 (78%)	ARX-negative, n = 30 (22%)	<i>p</i>	PDX1-positive, n = 76 (55%)	PDX1-negative, n = 61 (45%)	<i>p</i>	ALT-positive, n = 48 (35%)	ALT-negative, n = 89 (65%)	<i>p</i>
Gender										
Female	69 (50%)	49 (46%)	20 (67%)	0.062	39 (51%)	30 (49%)	0.864	20 (42%)	49 (55%)	0.154
Male	68 (50%)	58 (54%)	10 (33%)		37 (49%)	31 (51%)		28 (58%)	40 (45%)	
Mean age (range), years	57.2 (22 - 77)	57.1 (23 - 77)	57.3 (22 - 74)	0.857	56.4 (23 - 75)	58.1 (22 - 77)	0.227	58.8 (40 - 77)	56.2 (22 - 75)	0.377
Mean tumor size (range), cm	3.7 (0.6 - 18.0)	3.9 (0.7 - 18.0)	2.9 (0.6 - 8.0)	0.153	3.3 (0.6 - 18.0)	4.1 (0.7 - 12.0)	0.072	5.3 (1.5 - 18.0)	2.8 (0.6 - 10.0)	< 0.001
Location										
Head, neck and uncinate	60 (44%)	41 (38%)	19 (63%)	0.051	38 (50%)	22 (36%)	0.203	18 (38%)	42 (47%)	0.331
Body and tail	75 (55%)	64 (60%)	11 (37%)		37 (49%)	38 (62%)		30 (62%)	45 (51%)	
Diffuse	2 (1%)	2 (2%)	0 (0%)		1 (1%)	1 (2%)		0 (0%)	2 (2%)	
WHO grade										
Low (G1)	90 (66%)	67 (63%)	23 (77%)	0.117	54 (71%)	36 (59%)	0.118	17 (35%)	73 (82%)	< 0.001
Intermediate (G2)	45 (33%)	39 (36%)	6 (20%)		22 (29%)	23 (38%)		31 (65%)	14 (16%)	
High (G3)	2 (1%)	1 (1%)	1 (3%)		0 (0%)	2 (3%)		0 (0%)	2 (2%)	
Primary tumor (pT) stage										
T1	33 (24%)	24 (22%)	9 (30%)	0.555	20 (26%)	13 (21%)	0.366	4 (8%)	29 (33%)	< 0.001
T2	56 (41%)	43 (40%)	13 (43%)		34 (45%)	22 (36%)		15 (31%)	41 (46%)	
T3	42 (31%)	34 (32%)	8 (27%)		20 (26%)	22 (36%)		23 (48%)	19 (21%)	
T4	6 (4%)	6 (6%)	0 (0%)		2 (3%)	4 (7%)		6 (13%)	0 (0%)	
Regional node (pN) stage	<i>n = 114</i>	<i>n = 87</i>	<i>n = 27</i>		<i>n = 66</i>	<i>n = 48</i>		<i>n = 44</i>	<i>n = 70</i>	
N0	71 (62%)	57 (66%)	14 (52%)	0.256	40 (61%)	31 (65%)	0.700	22 (50%)	49 (70%)	0.047
N1	43 (38%)	30 (34%)	13 (48%)		26 (39%)	17 (35%)		22 (50%)	21 (30%)	
Metachronous metastases/recurrences										
Absent	87 (64%)	64 (60%)	23 (77%)	0.132	50 (66%)	37 (61%)	0.594	17 (35%)	70 (79%)	< 0.001
Present	50 (36%)	43 (40%)	7 (23%)		26 (34%)	24 (39%)		31 (65%)	19 (21%)	
ARX Expression										
Negative	30 (22%)				22 (29%)	8 (13%)	0.037	3 (6%)	27 (30%)	0.001
Positive	107 (78%)				54 (71%)	53 (87%)		45 (94%)	62 (70%)	
PDX1 Expression										
Negative	61 (44%)	53 (50%)	8 (27%)	0.037				27 (56%)	34 (38%)	0.049
Positive	76 (56%)	54 (50%)	22 (73%)					21 (44%)	55 (62%)	
ATRX/DAXX Expression										
Preserved	97 (71%)	69 (64%)	28 (93%)	0.001	56 (74%)	41 (67%)	0.453	14 (29%)	83 (93%)	< 0.001
Loss	40 (29%)	38 (36%)	2 (7%)		20 (26%)	20 (33%)		34 (71%)	6 (7%)	
ALT status										
Negative	89 (65%)	62 (58%)	27 (90%)	0.001	55 (72%)	34 (56%)	0.049			
Positive	48 (35%)	45 (42%)	3 (10%)		21 (28%)	27 (44%)				

Abbreviations: ALT, alternative lengthening of telomeres; NF-PanNET, non-functional pancreatic neuroendocrine tumor; WHO, World Health Organization

Supplementary Table 2. Clinical and pathologic comparison of ARX, PDX1 and ALT status in 168 non-syndromic, primary NF-PanNETs from Asan Medical Center.

Patient or Tumor Characteristics	Total, n = 168	ARX-positive, n = 132 (79%)	ARX-negative, n = 36 (21%)	<i>P</i>	PDX1-positive, n = 81 (48%)	PDX1-negative, n = 87 (52%)	<i>P</i>	ALT-positive, n = 43 (26%)	ALT-negative, n = 125 (74%)	<i>P</i>
Gender										
Female	87 (52%)	69 (52%)	18 (50%)	0.852	50 (62%)	37 (43%)	0.014	17 (40%)	70 (56%)	0.077
Male	81 (48%)	63 (48%)	18 (50%)		31 (38%)	50 (57%)		26 (60%)	55 (44%)	
Mean age (range), years	53.3 (20 - 77)	52.8 (26 - 77)	54.9 (20 - 77)	0.298	53.1 (20 - 77)	53.5 (29 - 77)	0.910	52.7 (26 - 72)	53.5 (20 - 77)	0.815
Mean tumor size (range), cm	3.1 (0.7 - 15.5)	3.2 (0.7 - 15.5)	2.7 (0.8 - 9.0)	0.193	2.9 (0.7 - 9.0)	3.4 (0.7 - 15.5)	0.577	4.5 (0.7 - 15.5)	2.7 (0.7 - 9.0)	< 0.001
Location										
Head, neck and uncinat	76 (45%)	59 (45%)	17 (47%)	0.883	42 (52%)	34 (39%)	0.088	14 (33%)	62 (50%)	0.035
Body and tail	91 (54%)	72 (54%)	19 (53%)		38 (47%)	53 (61%)		28 (65%)	63 (50%)	
Diffuse	1 (1%)	1 (1%)	0 (0%)		1 (1%)	0 (0%)		1 (2%)	0 (0%)	
WHO grade										
Low (G1)	114 (68%)	89 (67%)	25 (69%)	0.139	58 (72%)	56 (64%)	0.234	20 (46%)	94 (75%)	< 0.001
Intermediate (G2)	51 (30%)	42 (32%)	9 (25%)		23 (28%)	28 (32%)		23 (54%)	28 (23%)	
High (G3)	3 (2%)	1 (1%)	2 (6%)		0 (0%)	3 (4%)		0 (0%)	3 (2%)	
Primary tumor (pT) stage										
T1	63 (37%)	46 (35%)	17 (47%)	0.538	29 (36%)	34 (39%)	0.582	6 (14%)	57 (45%)	< 0.001
T2	61 (36%)	49 (37%)	12 (34%)		33 (41%)	28 (32%)		19 (44%)	42 (34%)	
T3	43 (26%)	36 (27%)	7 (19%)		19 (23%)	24 (28%)		17 (40%)	26 (21%)	
T4	1 (1%)	1 (1%)	0 (0%)		0 (0%)	1 (1%)		1 (2%)	0 (0%)	
Regional node (pN) stage										
N0	144 (86%)	113 (86%)	31 (86%)	1.000	67 (83%)	77 (89%)	0.378	31 (72%)	113 (90%)	0.005
N1	24 (14%)	19 (14%)	5 (14%)		14 (17%)	10 (11%)		12 (28%)	12 (10%)	
Metachronous metastases/recurrences										
Absent	135 (80%)	105 (80%)	30 (83%)	0.813	70 (86%)	65 (75%)	0.079	25 (58%)	110 (88%)	< 0.001
Present	33 (20%)	27 (20%)	6 (17%)		11 (14%)	22 (25%)		18 (42%)	15 (12%)	
ARX Expression										
Negative					27 (33%)	9 (10%)	< 0.001	2 (5%)	34 (27%)	0.001
Positive					54 (67%)	78 (90%)		41 (95%)	91 (73%)	
PDX1 Expression										
Negative	87 (52%)	78 (59%)	9 (25%)	< 0.001				32 (74%)	55 (44%)	0.001
Positive	81 (48%)	54 (41%)	27 (75%)					11 (26%)	70 (56%)	
ATRX/DAXX Expression										
Preserved	130 (77%)	97 (74%)	33 (92%)	0.024	73 (90%)	57 (66%)	< 0.001	6 (14%)	124 (99%)	< 0.001
Loss	38 (23%)	35 (26%)	3 (8%)		8 (10%)	30 (34%)		37 (86%)	1 (1%)	
ALT status										
Negative	125 (74%)	91 (69%)	34 (94%)	0.001	70 (86%)	55 (63%)	0.001			
Positive	43 (26%)	41 (31%)	2 (6%)		11 (14%)	32 (37%)				

Abbreviations: ALT, alternative lengthening of telomeres; NF-PanNET, non-functional pancreatic neuroendocrine tumor; WHO, World Health Organization

Supplementary Table 3. Clinical and pathologic comparison of ARX, PDX1 and ALT status in 256 non-syndromic, primary NF-PanNETs from Barnes-Jewish Hospital and UPMC.

Patient or Tumor Characteristics	Total, n = 256	ARX-positive, n = 167 (65%)	ARX-negative, n = 89 (35%)	<i>P</i>	PDX1-positive, n = 82 (32%)	PDX1-negative, n = 174 (68%)	<i>P</i>	ALT-positive, n = 69 (27%)	ALT-negative, n = 187 (73%)	<i>P</i>
Gender										
Female	119 (46%)	73 (44%)	46 (52%)	0.238	42 (51%)	77 (44%)	0.347	22 (32%)	97 (52%)	0.005
Male	137 (54%)	94 (56%)	43 (48%)		40 (49%)	97 (56%)		47 (68%)	90 (48%)	
Mean age (range), years	59.1 (22 - 93)	59.0 (26 - 83)	59.3 (22 - 93)	0.973	58.9 (22 - 93)	59.2 (26 - 85)	0.746	61.1 (40 - 93)	58.4 (22 - 85)	0.290
Mean tumor size (range), cm	3.2 (0.6 - 14.0)	3.3 (0.7 - 14.0)	3.0 (0.6 - 10.0)	0.196	2.9 (0.6 - 9.5)	3.3 (0.7 - 14.0)	0.138	4.5 (1.2 - 14.0)	2.7 (0.6 - 9.5)	< 0.001
Location										
Head, neck and uncinat	97 (38%)	53 (32%)	44 (49%)	0.007	37 (45%)	60 (34%)	0.129	29 (42%)	68 (36%)	0.468
Body and tail	159 (62%)	114 (68%)	45 (51%)		45 (55%)	114 (66%)		40 (58%)	119 (64%)	
Diffuse	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)	
WHO grade										
Low (G1)	158 (62%)	100 (60%)	58 (65%)	0.277	51 (62%)	107 (62%)	1.000	21 (30%)	137 (73%)	< 0.001
Intermediate (G2)	93 (36%)	65 (39%)	28 (32%)		30 (37%)	63 (36%)		45 (65%)	48 (26%)	
High (G3)	5 (2%)	2 (1%)	3 (2%)		1 (1%)	4 (2%)		3 (4%)	2 (1%)	
Primary tumor (pT) stage										
T1	83 (32%)	50 (30%)	33 (37%)	0.478	30 (36%)	53 (31%)	0.417	3 (4%)	80 (43%)	< 0.001
T2	111 (43%)	76 (45%)	35 (39%)		36 (44%)	75 (43%)		35 (51%)	76 (40%)	
T3	62 (24%)	41 (25%)	21 (24%)		16 (20%)	46 (26%)		31 (45%)	31 (17%)	
T4	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Regional node (pN) stage	<i>n</i> = 220	<i>n</i> = 149	<i>n</i> = 71		<i>n</i> = 66	<i>n</i> = 154		<i>n</i> = 68	<i>n</i> = 152	
N0	147 (67%)	107 (72%)	40 (56%)	0.032	39 (59%)	108 (70%)	0.120	32 (47%)	115 (76%)	< 0.001
N1	73 (33%)	42 (28%)	31 (44%)		27 (41%)	46 (30%)		36 (53%)	37 (24%)	
Metachronous metastases/recurrences										
Absent	201 (78%)	129 (77%)	72 (81%)	0.527	69 (84%)	132 (76%)	0.145	29 (42%)	172 (92%)	< 0.001
Present	55 (22%)	38 (23%)	17 (19%)		13 (16%)	42 (24%)		40 (58%)	15 (8%)	
ARX Expression										
Negative					64 (78%)	25 (14%)	< 0.001	13 (19%)	76 (41%)	0.001
Positive					18 (22%)	149 (86%)		56 (81%)	111 (59%)	
PDX1 Expression										
Negative	174 (68%)	149 (89%)	25 (28%)	< 0.001				56 (81%)	118 (63%)	0.006
Positive	82 (32%)	18 (11%)	64 (72%)					13 (19%)	69 (37%)	
ATRX/DAXX Expression										
Preserved	192 (75%)	117 (70%)	75 (84%)	0.015	68 (83%)	124 (71%)	0.046	8 (12%)	184 (98%)	< 0.001
Loss	64 (25%)	50 (30%)	14 (16%)		14 (17%)	50 (29%)		61 (88%)	3 (2%)	
ALT status										
Negative	187 (73%)	111 (66%)	76 (85%)	0.001	69 (84%)	118 (68%)	0.006			
Positive	69 (27%)	56 (34%)	13 (15%)		13 (16%)	56 (32%)				

Abbreviations: ALT, alternative lengthening of telomeres; NF-PanNET, non-functional pancreatic neuroendocrine tumor; WHO, World Health Organization; UPMC, University of Pittsburgh Medical Center; WHO, World Health Organization

Supplementary Table 4. Clinical and pathologic comparison of 561 primary NF-PanNETs based on the status of ARX and PDX1.

Patient or Tumor Characteristics	ARX-positive/PDX1-negative, n = 280 (50%)	ARX-negative/PDX1-positive, n = 113 (20%)	ARX-positive/PDX1-positive (DP), n = 126 (22%)	ARX-negative/PDX1-negative (DN), n = 42 (8%)	P
Gender					
Female	120 (43%)	60 (53%)	71 (56%)	24 (57%)	0.031
Male	160 (57%)	53 (47%)	55 (44%)	18 (43%)	
Mean age (range), years	57.5 (26 - 83)	58.2 (20 - 93)	54.2 (23 - 76)	56.9 (22 - 85)	0.050
Mean tumor size (range), cm	3.5 (0.7 - 15.5)	2.8 (0.6 - 9.5)	3.2 (0.7 - 18.0)	3.2 (0.7 - 10.0)	0.049
Location					
Head, neck and uncinata	91 (33%)	55 (49%)	62 (49%)	25 (60%)	< 0.001
Body and tail	188 (67%)	58 (51%)	62 (49%)	17 (40%)	
Diffuse	1 (<1%)	0 (0%)	2 (2%)	0 (0%)	
WHO grade					
Low (G1)	175 (63%)	82 (73%)	81 (64%)	24 (57%)	0.003
Intermediate (G2)	101 (36%)	30 (26%)	45 (36%)	13 (31%)	
High (G3)	4 (1%)	1 (1%)	0 (0%)	5 (12%)	
Lymphovascular invasion	n = 227	n = 91	n = 72	n = 34	
Absent	148 (65%)	60 (66%)	51 (71%)	23 (68%)	0.865
Present	79 (35%)	31 (34%)	21 (29%)	11 (32%)	
Perineural invasion	n = 227	n = 91	n = 72	n = 34	
Absent	188 (83%)	69 (76%)	60 (83%)	24 (71%)	0.208
Present	39 (17%)	22 (24%)	12 (17%)	10 (29%)	
Primary tumor (pT) stage					
T1	88 (31%)	47 (42%)	32 (25%)	12 (29%)	0.065
T2	106 (38%)	41 (36%)	62 (49%)	19 (45%)	
T3	81 (29%)	25 (22%)	30 (24%)	11 (26%)	
T4	5 (2%)	0 (0%)	2 (2%)	0 (0%)	
Regional node (pN) stage	n = 250	n = 95	n = 118	n = 39	
N0	193 (77%)	62 (65%)	84 (71%)	23 (59%)	0.031
N1	57 (23%)	33 (35%)	34 (29%)	16 (41%)	
Metachronous metastases/recurrences					
Absent	205 (73%)	96 (85%)	93 (74%)	29 (69%)	0.048
Present	75 (27%)	17 (15%)	33 (26%)	13 (31%)	
ATRX/DAXX Expression					
Preserved	187 (67%)	101 (89%)	96 (76%)	35 (83%)	< 0.001
Loss	93 (33%)	12 (11%)	30 (24%)	7 (17%)	
ALT status					
Negative	171 (61%)	101 (89%)	93 (74%)	36 (86%)	< 0.001
Positive	109 (39%)	12 (11%)	33 (26%)	6 (14%)	

Abbreviations: ALT, alternative lengthening of telomeres; DN, double negative for ARX and PDX1; DP, double positive for ARX and PDX1; NF-PanNET, non-functional pancreatic neuroendocrine tumor; WHO, World Health Organization

Supplementary Table 5. Clinical and pathologic comparison of primary NF-PanNETs based on the status of ARX⁺/DN, PDX1⁺/DP and ATRX/DAXX.

Patient or Tumor Characteristics	ARX ⁺ + DN, n = 322 (57%)	PDX1 ⁺ + DP, n = 239 (43%)	<i>p</i>	Loss of ATRX/DAXX, n = 142 (25%)	Preserved ATRX/DAXX, n = 419 (75%)	<i>p</i>
Gender						
Female	144 (45%)	131 (55%)	0.021	58 (41%)	217 (52%)	0.026
Male	178 (55%)	108 (45%)		84 (59%)	202 (48%)	
Mean age (range), years	57.4 (22 - 85)	56.2 (20 - 93)	0.223	58.6 (26 - 93)	56.3 (20 - 85)	0.135
Mean tumor size (range), cm	3.5 (0.7 - 15.5)	3.0 (0.6 - 18.0)	0.063	4.8 (0.9 - 18.0)	2.8 (0.6 - 10.0)	< 0.001
Location						
Head, neck and uncinata	116 (36%)	117 (49%)	0.002	50 (35%)	183 (44%)	0.133
Body and tail	205 (64%)	120 (49%)		91 (64%)	234 (56%)	
Diffuse	1 (< 1%)	2 (1%)		1 (1%)	2 (< 1%)	
WHO grade						
Low (G1)	199 (62%)	163 (68%)	0.050	55 (39%)	307 (73%)	< 0.001
Intermediate (G2)	114 (35%)	75 (32%)		84 (59%)	105 (25%)	
High (G3)	9 (3%)	1 (< 1%)		3 (2%)	7 (2%)	
Lymphovascular invasion	<i>n</i> = 261	<i>n</i> = 163		<i>n</i> = 102	<i>n</i> = 322	
Absent	171 (66%)	111 (68%)	0.599	37 (36%)	245 (76%)	< 0.001
Present	90 (34%)	52 (32%)		65 (64%)	77 (24%)	
Perineural invasion	<i>n</i> = 261	<i>n</i> = 163		<i>n</i> = 102	<i>n</i> = 322	
Absent	212 (81%)	129 (79%)	0.616	66 (65%)	275 (85%)	< 0.001
Present	49 (19%)	34 (21%)		36 (35%)	47 (15%)	
Primary tumor (pT) stage						
T1	100 (31%)	79 (33%)	0.404	8 (6%)	171 (41%)	< 0.001
T2	125 (39%)	103 (43%)		63 (44%)	165 (39%)	
T3	92 (28%)	55 (23%)		67 (47%)	80 (19%)	
T4	5 (2%)	2 (1%)		4 (3%)	3 (1%)	
Regional node (pN) stage	<i>n</i> = 289	<i>n</i> = 213		<i>n</i> = 139	<i>n</i> = 363	
N0	216 (75%)	146 (69%)	0.132	77 (55%)	285 (79%)	< 0.001
N1	73 (25%)	67 (31%)		62 (45%)	78 (21%)	
Metachronous distant metastases/recurrences						
Absent	234 (74%)	189 (79%)	0.092	61 (43%)	362 (86%)	< 0.001
Present	88 (26%)	50 (21%)		81 (57%)	57 (14%)	
ARX expression						
Negative	42 (13%)	113 (47%)	< 0.001	19 (13%)	136 (32%)	< 0.001
Positive	280 (87%)	126 (53%)		123 (87%)	283 (68%)	
PDX1 expression						
Negative	322 (100%)	0 (0%)	< 0.001	100 (70%)	222 (53%)	< 0.001
Positive	0 (0%)	239 (100%)		42 (30%)	197 (47%)	
ATRX/DAXX expression						
Preserved	222 (69%)	197 (82%)	< 0.001			
Loss	100 (31%)	42 (18%)				
ALT status						
Negative	207 (64%)	194 (81%)	< 0.001	10 (7%)	391 (93%)	< 0.001
Positive	115 (36%)	45 (19%)		132 (93%)	28 (7%)	

Abbreviations: ALT, alternative lengthening of telomeres; DN, double negative for ARX and PDX1; DP, double positive for ARX and PDX1; NF-PanNET, non-functional pancreatic neuroendocrine tumor; WHO, World Health Organization

Supplementary Table 6. Clinical and pathologic comparison of ATRX and DAXX status in 561 non-syndromic, primary NF-PanNETs.

Patient or Tumor Characteristics	Total, n = 561	Loss of ATRX, n = 70 (12%)	Preserved ATRX, n = 491 (88%)	<i>P</i>	Loss of DAXX, n = 87 (16%)	Preserved DAXX, n = 474 (84%)	<i>P</i>
Gender							
Female	275 (49%)	27 (39%)	248 (50%)	0.073	39 (45%)	236 (50%)	0.416
Male	286 (51%)	43 (61%)	243 (50%)		48 (55%)	238 (50%)	
Mean age (range), years	56.9 (20 - 93)	56.8 (29 - 93)	56.9 (20 - 85)	0.604	59.7 (26 - 82)	56.4 (20 - 93)	0.025
Mean tumor size (range), cm	3.3 (0.6 - 18.0)	4.9 (1.1 - 15.5)	3.0 (0.6 - 18.0)	< 0.001	4.7 (0.9 - 18.0)	3.0 (0.6 - 15.5)	< 0.001
Location							
Head, neck and uncinate	233 (41%)	28 (40%)	205 (42%)	0.864	30 (35%)	203 (43%)	0.174
Body and tail	325 (58%)	42 (60%)	283 (57%)		56 (64%)	269 (56%)	
Diffuse	3 (1%)	0 (0%)	3 (1%)		1 (1%)	2 (1%)	
WHO grade							
Low (G1)	362 (65%)	21 (30%)	341 (69%)	< 0.001	38 (44%)	324 (68%)	< 0.001
Intermediate (G2)	189 (33%)	47 (67%)	142 (29%)		47 (54%)	142 (30%)	
High (G3)	10 (2%)	2 (3%)	8 (2%)		2 (2%)	8 (2%)	
Lymphovascular invasion							
Absent	<i>n</i> = 424 282 (67%)	<i>n</i> = 51 18 (35%)	<i>n</i> = 373 264 (71%)	< 0.001	<i>n</i> = 62 23 (37%)	<i>n</i> = 362 259 (72%)	< 0.001
Present	142 (33%)	33 (65%)	109 (29%)		39 (63%)	103 (28%)	
Perineural invasion							
Absent	<i>n</i> = 424 341 (80%)	<i>n</i> = 51 33 (65%)	<i>n</i> = 373 308 (83%)	0.004	<i>n</i> = 62 41 (66%)	<i>n</i> = 362 300 (83%)	0.005
Present	83 (20%)	18 (35%)	65 (17%)		21 (34%)	62 (17%)	
Primary tumor (pT) stage							
T1	179 (32%)	4 (6%)	175 (36%)	< 0.001	4 (5%)	175 (37%)	< 0.001
T2	228 (41%)	30 (43%)	198 (40%)		42 (48%)	186 (39%)	
T3	147 (26%)	34 (48%)	113 (23%)		39 (45%)	108 (23%)	
T4	7 (1%)	2 (3%)	5 (1%)		2 (2%)	5 (1%)	
Regional node (pN) stage							
N0	<i>n</i> = 502 362 (72%)	<i>n</i> = 68 40 (59%)	<i>n</i> = 434 322 (74%)	0.013	<i>n</i> = 86 48 (56%)	<i>n</i> = 416 314 (76%)	< 0.001
N1	140 (28%)	28 (41%)	112 (26%)		38 (44%)	102 (24%)	
Metachronous metastases/recurrences							
Absent	423 (75%)	30 (43%)	393 (80%)	< 0.001	38 (44%)	385 (81%)	< 0.001
Present	138 (25%)	40 (57%)	98 (20%)		49 (56%)	89 (19%)	
ARX Expression							
Negative	155 (28%)	10 (14%)	145 (30%)	0.007	12 (14%)	143 (30%)	0.002
Positive	406 (72%)	60 (86%)	346 (70%)		75 (86%)	331 (70%)	
PDX1 Expression							
Negative	322 (57%)	53 (76%)	269 (55%)	0.001	59 (68%)	263 (56%)	0.034
Positive	239 (43%)	17 (24%)	222 (45%)		28 (32%)	211 (44%)	
ATRX Expression							
Preserved	491 (88%)				73 (84%)	418 (88%)	0.289
Loss	70 (12%)				14 (16%)	56 (12%)	
DAXX Expression							
Preserved	474 (84%)	56 (80%)	418 (85%)	0.289			
Loss	87 (16%)	14 (20%)	73 (15%)				
ALT status							
Negative	401 (71%)	4 (6%)	397 (81%)	< 0.001	7 (8%)	394 (83%)	< 0.001
Positive	160 (29%)	66 (94%)	97 (19%)		80 (92%)	80 (17%)	

Abbreviations: ALT, alternative lengthening of telomeres; NF-PanNET, non-functional pancreatic neuroendocrine tumor; WHO, World Health Organization

Supplementary Table 7. Clinical and pathologic comparison of ARX, PDX1 and ALT status in 196 primary NF-PanNETs of ≤2.0 cm and without lymph node metastases.

Patient or Tumor Characteristics	Total, n = 196	ARX-positive, n = 133 (68%)	ARX-negative, n = 63 (32%)	P	PDX1-positive, n = 87 (44%)	PDX1-negative, n = 109 (56%)	P	ALT-positive, n = 17 (9%)	ALT-negative, n = 179 (91%)	P
Gender										
Female	104 (53%)	64 (48%)	40 (63%)	0.048	57 (66%)	47 (43%)	0.002	9 (53%)	95 (53%)	1.000
Male	92 (47%)	69 (52%)	23 (37%)		30 (34%)	62 (57%)		8 (47%)	84 (47%)	
Mean age (range), years	57.1 (23 - 83)	57.1 (23 - 82)	57.3 (35 - 83)	0.931	56.8 (23 - 83)	57.4 (27 - 82)	0.688	52.9 (41 - 64)	57.5 (23 - 83)	0.066
Mean tumor size (range), cm	1.4 (0.6 - 2.0)	1.4 (0.7 - 2.0)	1.4 (0.6 - 2.0)	0.774	1.4 (0.6 - 2.0)	1.4 (0.7 - 2.0)	0.253	1.6 (0.7 - 2.0)	1.4 (0.6 - 2.0)	0.011
Location										
Head, neck and uncinate	68 (35%)	45 (34%)	23 (37%)	0.749	37 (43%)	31 (28%)	0.050	7 (41%)	61 (34%)	0.599
Body and tail	128 (65%)	88 (66%)	40 (63%)		50 (57%)	78 (72%)		10 (59%)	118 (66%)	
WHO grade										
Low (G1)	162 (83%)	110 (83%)	52 (83%)	1.000	70 (80%)	92 (84%)	0.570	8 (47%)	154 (86%)	< 0.001
Intermediate (G2)	34 (17%)	23 (17%)	11 (17%)		17 (20%)	17 (16%)		9 (53%)	25 (14%)	
Lymphovascular invasion										
Absent	148 (93%)	93 (89%)	55 (100%)	0.017	62 (93%)	86 (93%)	1.000	7 (64%)	141 (95%)	0.003
Present	11 (7%)	11 (11%)	0 (0%)		5 (7%)	6 (7%)		4 (36%)	7 (5%)	
Perineural invasion										
Absent	146 (92%)	95 (91%)	51 (93%)	1.000	62 (93%)	84 (91%)	1.000	10 (91%)	136 (92%)	1.000
Present	13 (8%)	9 (9%)	4 (7%)		5 (7%)	8 (9%)		1 (9%)	12 (8%)	
Metachronous metastases/recurrences										
Absent	178 (91%)	118 (89%)	60 (95%)	0.188	79 (91%)	99 (91%)	1.000	10 (59%)	168 (94%)	< 0.001
Present	18 (9%)	15 (11%)	3 (5%)		8 (9%)	10 (9%)		7 (41%)	11 (6%)	
ARX Expression										
Negative	63 (32%)				47 (54%)	16 (15%)	< 0.001	1 (6%)	62 (35%)	0.014
Positive	133 (68%)				40 (46%)	93 (85%)		16 (94%)	117 (65%)	
PDX1 Expression										
Negative	109 (56%)	93 (70%)	16 (25%)	< 0.001				12 (71%)	97 (54%)	0.214
Positive	87 (44%)	40 (30%)	47 (75%)					5 (29%)	82 (46%)	
ATRX/DAXX Expression										
Preserved	183 (93%)	121 (91%)	62 (98%)	0.065	82 (94%)	101 (93%)	0.777	5 (29%)	178 (99%)	< 0.001
Loss	13 (7%)	12 (9%)	1 (2%)		5 (6%)	8 (7%)		12 (71%)	1 (1%)	
ALT status										
Negative	179 (91%)	117 (88%)	62 (98%)	0.014	82 (94%)	97 (89%)	0.214			
Positive	17 (9%)	16 (12%)	1 (2%)		5 (6%)	12 (11%)				

Abbreviations: ALT, alternative lengthening of telomeres; NF-PanNET, non-functional pancreatic neuroendocrine tumor; WHO, World Health Organization

Supplementary Table 8. RFS rates based on tumor size thresholds for NF-PanNETs of ≤ 2.0 cm and without lymph node metastases.

Tumor size threshold	1, 5 and 10-year RFS rates, below and equal to (\leq) tumor size threshold	1, 5 and 10-year RFS rates, above ($>$) tumor size threshold	<i>p</i>
0.7 cm	92%, 92% and 92%	97%, 89% and 78%	0.883
0.8 cm	95%, 95% and 95%	97%, 89% and 78%	0.529
0.9 cm	96%, 96% and 96%	97%, 89% and 77%	0.394
1.0 cm	98%, 98% and 98%	96%, 87% and 75%	0.099
1.1 cm	98%, 94% and 94%	96%, 88% and 75%	0.150
1.2 cm	99%, 95% and 95%	96%, 87% and 74%	0.059
1.3 cm	97%, 95% and 95%	96%, 86% and 72%	0.054
1.4 cm	97%, 95% and 95%	96%, 86% and 72%	0.042
1.5 cm	97%, 91% and 91%	96%, 86% and 65%	0.046
1.6 cm	98%, 92% and 92%	95%, 85% and 61%	0.017
1.7 cm	97%, 90% and 90%	96%, 88% and 58%	0.040
1.8 cm	97%, 89% and 89%	97%, 92% and 58%	0.095
1.9 cm	97%, 89% and 89%	97%, 91% and 58%	0.074

Abbreviations: *N/A*, not available; *NF-PanNET*, non-functional pancreatic neuroendocrine tumor; *RFS*, relapse-free survival

Supplementary Table 9. Clinical and pathologic comparison of ARX, PDX1, ATRX/DAXX, and ALT status in 107 patients with NF-PanNET metastases.

Patient or Tumor Characteristics	Total, n = 107	ARX-positive, n = 85 (79%)	ARX-negative, n = 22 (21%)	<i>P</i>	PDX1-positive, n = 36 (34%)	PDX1-negative, n = 71 (66%)	<i>P</i>	Loss of ATRX/DAXX, n = 66 (62%)	Preserved ATRX/DAXX, n = 41 (38%)	<i>P</i>	ALT-positive, n = 76 (71%)	ALT-negative, n = 31 (29%)	<i>P</i>
Gender													
Female	53 (49%)	38 (45%)	15 (68%)	0.059	25 (69%)	28 (39%)	0.004	25 (38%)	28 (68%)	0.003	30 (39%)	23 (74%)	0.001
Male	54 (51%)	47 (55%)	7 (32%)		11 (31%)	43 (61%)		41 (62%)	13 (32%)		46 (61%)	8 (26%)	
Mean age at initial presentation (range), years	60.2 (31 - 85)	60.8 (32 - 85)	58.1 (31 - 78)	0.414	58.1 (31 - 85)	61.3 (36 - 83)	0.203	61.3 (31 - 85)	58.6 (31 - 82)	0.290	60.6 (31 - 85)	59.3 (31 - 82)	0.734
Mean primary tumor size (range), cm	5.3 (1.0 - 18.0)	5.6 (1.5 - 18.0)	4.2 (1.0 - 8.0)	0.179	4.5 (1.0 - 10.0)	5.8 (1.5 - 18.0)	0.289	5.4 (1.0 - 15.0)	5.3 (2.4 - 18.0)	0.707	5.6 (1.0 - 18.0)	4.7 (2.4 - 17.0)	0.197
Primary tumor location													
Head, neck and uncinate	43 (40%)	31 (36%)	12 (55%)	0.147	20 (56%)	23 (32%)	0.024	19 (29%)	24 (59%)	0.004	24 (32%)	19 (61%)	0.008
Body and tail	64 (60%)	54 (64%)	10 (45%)		16 (44%)	48 (67%)		47 (71%)	17 (41%)		52 (68%)	12 (39%)	
Primary tumor, WHO grade													
Low (G1)	29 (27%)	20 (24%)	9 (41%)	0.024	11 (31%)	18 (25%)	0.145	17 (26%)	12 (29%)	0.942	20 (26%)	9 (29%)	0.878
Intermediate (G2)	72 (67%)	62 (73%)	10 (45%)		21 (58%)	51 (72%)		45 (68%)	27 (66%)		51 (67%)	21 (68%)	
High (G3)	6 (6%)	3 (3%)	3 (14%)		4 (11%)	2 (2%)		4 (6%)	2 (5%)		5 (7%)	1 (3%)	
Metastatic tumor(s), highest WHO grade													
Low (G1)	20 (19%)	14 (16%)	6 (27%)	0.177	8 (22%)	12 (17%)	0.362	9 (14%)	11 (27%)	0.234	11 (14%)	9 (29%)	0.225
Intermediate (G2)	79 (74%)	66 (78%)	13 (59%)		24 (67%)	55 (77%)		52 (79%)	27 (66%)		59 (78%)	20 (65%)	
High (G3)	8 (7%)	5 (6%)	3 (14%)		4 (11%)	4 (6%)		3 (7%)	3 (7%)		6 (8%)	2 (6%)	
ARX expression													
Negative	22 (21%)				22 (61%)	0 (0%)	< 0.001	8 (12%)	14 (34%)	0.013	9 (12%)	13 (42%)	0.001
Positive	85 (79%)				14 (39%)	71 (100%)		58 (88%)	27 (66%)		67 (88%)	18 (58%)	
PDX1 expression													
Negative	71 (66%)	71 (84%)	0 (0%)	< 0.001				54 (82%)	17 (42%)	< 0.001	62 (82%)	9 (29%)	< 0.001
Positive	36 (34%)	14 (16%)	22 (100%)					12 (18%)	24 (58%)		14 (18%)	22 (71%)	
ATRX/DAXX expression													
Preserved	41 (38%)	27 (32%)	14 (64%)	0.013	24 (67%)	17 (24%)	< 0.001				10 (13%)	31 (100%)	< 0.001
Loss	66 (62%)	58 (68%)	8 (36%)		12 (33%)	54 (76%)					66 (87%)	0 (0%)	
ALT status													
Negative	31 (29%)	18 (21%)	13 (59%)	0.001	22 (61%)	9 (13%)	< 0.001	0 (0%)	31 (76%)	< 0.001			
Positive	76 (71%)	67 (79%)	9 (41%)		14 (39%)	62 (87%)		66 (100%)	10 (24%)				
Timing of metastatic tumor(s)													
Synchronous	14 (13%)	10 (12%)	4 (18%)	0.567	6 (17%)	8 (11%)	0.610	6 (9%)	8 (20%)	0.138	6 (8%)	8 (26%)	0.038
Metachronous	48 (45%)	40 (47%)	8 (36%)		14 (39%)	34 (48%)		34 (52%)	14 (34%)		38 (50%)	10 (32%)	
Both	45 (42%)	35 (41%)	10 (46%)		16 (44%)	29 (41%)		26 (39%)	19 (46%)		32 (42%)	13 (42%)	

Abbreviations: ALT, alternative lengthening of telomeres; NF-PanNET, non-functional pancreatic neuroendocrine tumor; WHO, World Health Organization

Supplementary Table 10. Clinical and pathologic comparison of ARX and PDX1 among primary gastric, duodenal, rectal and appendiceal NETs.

Patient or Tumor Characteristics	Gastric NETs (n = 32)					Duodenal NETs (n = 41)					Rectal NETs (n = 17)					Appendiceal NETs (n = 28)									
	ARX-positive, n = 28 (88%)	ARX-negative, n = 4 (12%)	p	PDX1-positive, n = 4 (12%)	PDX1-negative, n = 28 (88%)	p	ARX-positive, n = 24 (59%)	ARX-negative, n = 17 (41%)	p	PDX1-positive, n = 36 (88%)	PDX1-negative, n = 5 (12%)	p	ARX-positive, n = 17 (100%)	ARX-negative, n = 0 (0%)	p	PDX1-positive, n = 1 (6%)	PDX1-negative, n = 16 (94%)	p	ARX-positive, n = 28 (100%)	ARX-negative, n = 0 (0%)	p	PDX1-positive, n = 2 (7%)	PDX1-negative, n = 26 (93%)	p	
Gender																									
Female	14 (50%)	1 (25%)	0.603	2 (50%)	13 (46%)	1.000	11 (46%)	10 (59%)	0.530	21 (58%)	0 (0%)	0.021	10 (59%)	N/A	0 (0%)	10 (63%)	0.412	16 (57%)	N/A	2 (100%)	14 (54%)	0.492			
Male	15 (50%)	3 (75%)		2 (50%)	15 (54%)		13 (54%)	7 (41%)		15 (42%)	5 (100%)		7 (41%)	1 (100%)		6 (37%)		12 (43%)		0 (0%)	12 (46%)				
Mean age (range), years	57.4 (35 - 82)	45.8 (17 - 62)	0.392	46.0 (17 - 62)	57.3 (35 - 82)	0.424	59.5 (36 - 78)	55.2 (29 - 75)	0.327	59.3 (29 - 78)	46.8 (36 - 59)	0.030	50.2 (25 - 75)	N/A	49.0	50.3 (25 - 75)	0.941	46.0 (17 - 87)	N/A	42.5 (38 - 47)	46.2 (17 - 87)	1.000			
Mean tumor size (range), cm	1.6 (0.3 - 3.0)	1.7 (1.2 - 2.3)	0.721	1.5 (1.0 - 2.3)	1.6 (0.3 - 3.0)	0.891	1.5 (0.3 - 4.5)	1.4 (0.3 - 4.5)	0.605	1.5 (0.3 - 4.5)	1.2 (1.0 - 1.8)	0.632	2.2 (0.3 - 7.0)	N/A	0.5	2.3 (0.4 - 7.0)	0.353	1.1 (0.2 - 3.5)	N/A	0.5 (0.5 - 0.5)	1.2 (0.2 - 3.5)	0.190			
WHO grade																									
Low (G1)	20 (72%)	2 (50%)	0.454	2 (50%)	20 (72%)	0.454	21 (88%)	11 (65%)	0.158	29 (80%)	3 (60%)	0.347	11 (65%)	N/A	1 (100%)	10 (63%)	1.000	27 (96%)	N/A	2 (100%)	25 (96%)	1.000			
Intermediate (G2)	6 (21%)	2 (50%)		2 (50%)	6 (21%)		3 (12%)	5 (29%)		6 (17%)	2 (40%)		6 (35%)	0 (0%)		6 (37%)		1 (4%)		0 (0%)	1 (4%)				
High (G3)	2 (7%)	0 (0%)		0 (0%)	2 (7%)		0 (0%)	1 (6%)		1 (3%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)		0 (0%)		0 (0%)	0 (0%)				
Lymphovascular invasion																									
Absent	23 (82%)	3 (75%)	1.000	3 (75%)	23 (82%)	1.000	13 (54%)	12 (71%)	0.344	23 (64%)	2 (40%)	0.362	8 (47%)	N/A	1 (100%)	7 (44%)	0.471	27 (96%)	N/A	2 (100%)	25 (96%)	1.000			
Present	5 (18%)	1 (25%)		1 (25%)	5 (18%)		11 (46%)	5 (29%)		13 (36%)	3 (60%)		9 (53%)	0 (0%)		9 (56%)		1 (4%)		0 (0%)	1 (4%)				
Peritoneal invasion																									
Absent	24 (86%)	4 (100%)	1.000	4 (100%)	24 (86%)	1.000	22 (92%)	14 (82%)	0.633	33 (92%)	3 (60%)	0.104	11 (65%)	N/A	1 (100%)	10 (63%)	1.000	23 (82%)	N/A	2 (100%)	21 (81%)	1.000			
Present	4 (14%)	0 (0%)		0 (0%)	4 (14%)		2 (8%)	3 (18%)		3 (8%)	2 (40%)		6 (35%)	0 (0%)		6 (37%)		5 (18%)		0 (0%)	5 (19%)				
Primary tumor (pT) stage																									
T1	12 (43%)	0 (0%)	0.138	1 (25%)	11 (39%)	0.632	12 (50%)	9 (53%)	0.308	20 (55%)	1 (20%)	0.373	10 (59%)	N/A	1 (100%)	9 (56%)	1.000	23 (82%)	N/A	2 (100%)	21 (81%)	1.000			
T2	11 (39%)	4 (100%)		3 (75%)	12 (43%)		10 (42%)	4 (23%)		11 (31%)	3 (60%)		2 (12%)	0 (0%)		2 (13%)		0 (0%)		0 (0%)	0 (0%)				
T3	5 (18%)	0 (0%)		0 (0%)	5 (18%)		2 (8%)	3 (18%)		4 (11%)	1 (20%)		5 (29%)	0 (0%)		5 (31%)		5 (18%)		0 (0%)	5 (19%)				
T4	0 (0%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)	1 (6%)		1 (3%)	0 (0%)		0 (0%)	0 (0%)		0 (0%)		0 (0%)		0 (0%)	0 (0%)				
Regional node (pN) stage																									
N0	24 (86%)	3 (75%)	0.512	3 (75%)	24 (86%)	0.512	17 (71%)	12 (71%)	1.000	26 (72%)	3 (60%)	0.620	13 (77%)	N/A	1 (100%)	12 (75%)	1.000	26 (93%)	N/A	2 (100%)	24 (92%)	1.000			
N1	4 (14%)	1 (25%)		1 (25%)	4 (14%)		7 (29%)	5 (29%)		10 (28%)	2 (40%)		4 (23%)	0 (0%)		4 (25%)		2 (7%)		0 (0%)	2 (8%)				
Metachronous metastases/recurrences																									
Absent	22 (79%)	4 (100%)	0.566	4 (100%)	22 (79%)	0.566	21 (88%)	13 (77%)	0.421	31 (86%)	3 (60%)	0.196	10 (59%)	N/A	1 (100%)	9 (56%)	1.000	28 (100%)	N/A	2 (100%)	26 (100%)	N/A			
Present	6 (21%)	0 (0%)		0 (0%)	6 (21%)		3 (12%)	4 (23%)		5 (14%)	2 (40%)		7 (41%)	0 (0%)		7 (44%)		0 (0%)		0 (0%)	0 (0%)				
ARX Expression																									
Negative		2 (50%)		2 (7%)	0.066					15 (42%)	2 (40%)	1.000		0 (0%)		0 (0%)	N/A			0 (0%)	0 (0%)	N/A			
Positive		2 (50%)		26 (93%)						21 (58%)	3 (60%)			1 (100%)		16 (100%)				2 (100%)	26 (100%)				
PDX1 Expression																									
Negative	26 (93%)	2 (50%)	0.066				3 (12%)	2 (12%)	1.000				16 (94%)	N/A				26 (93%)	N/A						
Positive	2 (7%)						21 (88%)	15 (88%)					1 (6%)					2 (7%)							

Abbreviations: N/A, not applicable; NET, neuroendocrine tumor; WHO, World Health Organization