

Figure S1 Distribution of chromosomal instability score (CIS) among all 49 neuroendocrine neoplasms (NENs) patients (A) and within the stomach cohort only (B). The K-means clustering algorithm separated patients into two groups. Samples to the left of the vertical line are chromosomal stable (CS) and samples to the right are chromosomal instability (CIN).

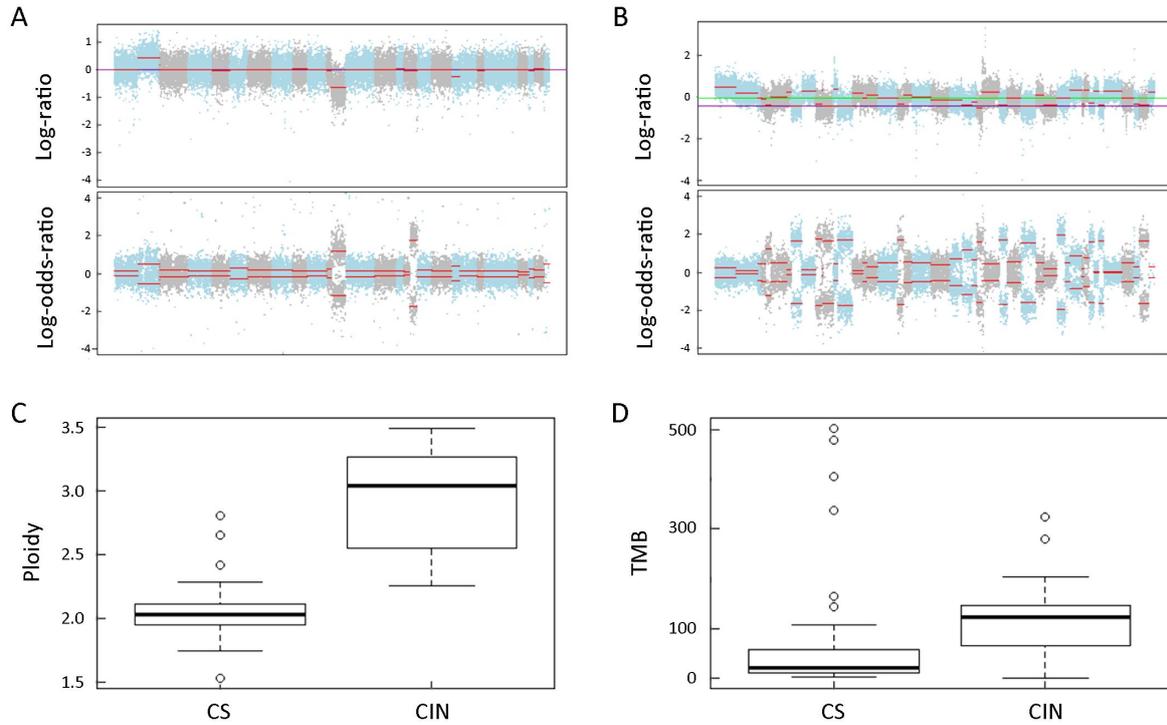


Figure S2 Ploidy and tumor mutation burden (TMB) difference between chromosomal instability (CIN) and chromosomal stable (CS) samples. Top panel: Fraction and Allele-Specific Copy Number Estimates from Tumor Sequencing (FACETS) results showing genome-wide log-ratio and log-odds-ratio of a CS tumor sample (A) and a CIN tumor sample (B); Bottom panel: boxplot of ploidy by CIS subtypes ($P < 0.001$) (C) and TMB by CIS subtypes ($P = 0.004$) (D).

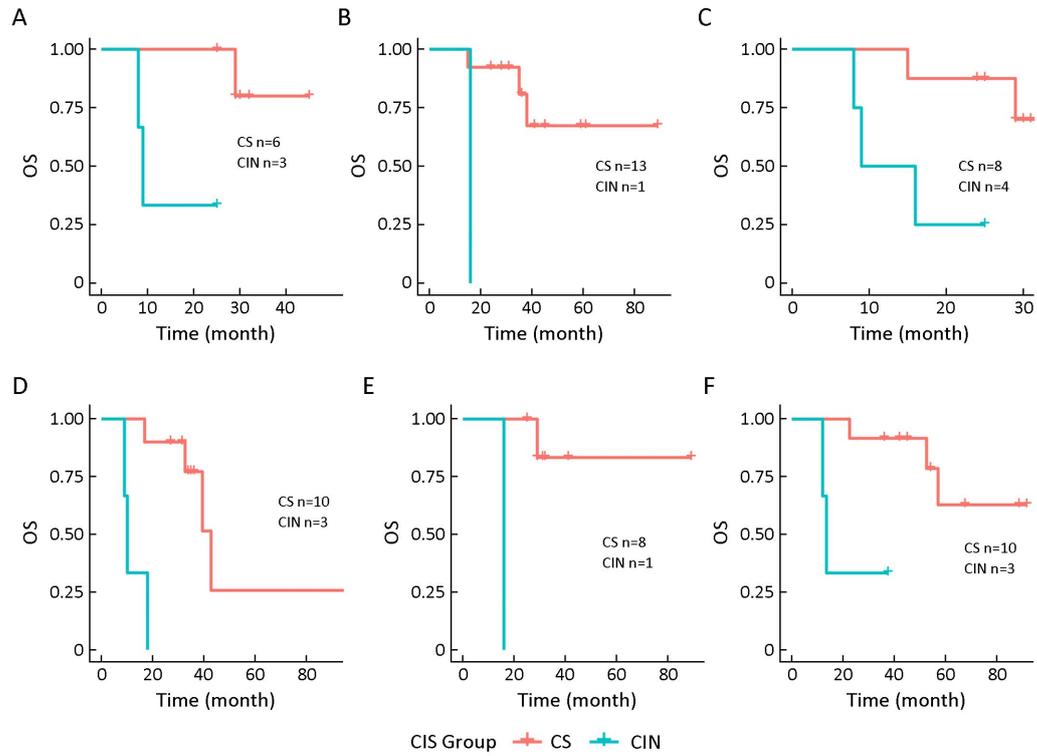


Figure S3 Stratified Kaplan-Meier analysis of survival difference between chromosomal instability (CIN) and chromosomal stable (CS) subtypes. Kaplan-Meier plot of overall survival (OS) between CIN and CS subtypes stratified by gender [male (A): $P=0.027$; female (B): $P=0.022$], G grade [grade G3 (C): $P=0.023$], stage [stage III&IV (D): $P<0.001$] and age [median, 60.5 years old; age high (E): $P=0.008$; age low (F): $P=0.008$].

Table S1 Clinical characteristics of each individual patient

Patient_ID	Gender	Age at diagnosis (year)	Stages at diagnosis	Sites	OS (month)	Death*	G_grade	Ki67_index (%)	Histological diagnosis	NEC cell type	CIN group	CIN index	Tumor content estimated by FACETS (%)	Ploidy
S01	Male	53	IA	Lung	25	0	G3	>75	NEC	Small	Unstable	1.8513	78.4	3.27
S02	Male	79	IIIB	Lung	22	0	G3	80	NEC	Small	Unstable	1.6406	68.8	2.97
S03	Male	62	IIIB	Lung	8	1	G3	90	NEC	Small	Unstable	1.6444	61.2	3.49
S04	Male	70	IB	Lung	17	0	G3	>75	NEC	Small	Unstable	1.4075	64.8	2.53
S05	Male	62	IIIB	Stomach	10	0	G3	70	NEC	Small	Unstable	1.7795	51.2	3.24
S06	Male	71	IIIB	Stomach	6	0	G3	75	NEC	Large	Unstable	2.0379	60.6	3.08
S07	Female	64	IIIB	Stomach	7	0	G3	>75	NEC	Large	Unstable	2.0419	60.4	3.25
S08	Male	64	IIIB	Stomach	7	0	G3	70	NEC	Small	Unstable	1.6527	70.8	3.43
S09	Male	60	IIA	Stomach	4	0	G3	70	NEC	Small	Unstable	1.9519	48.8	2.90
S10	Male	60	IIIB	Stomach	9	1	G3	80	NEC	Small	Unstable	2.2426	87.4	3.23
S11	Male	47	I	Stomach	45	0	G2	5	NET	NA	Stable	0.8445	45.8	2.15
S12	Male	67	IIIB	Stomach	23	0	G3	>75	NEC	Large	Unstable	1.1868	34.7	2.54
S13	Female	74	IIIB	Stomach	16	1	G3	80	NEC	Large	Unstable	1.2501	48.0	2.40
S14	Male	47	IIIB	Stomach	14	0	G3	>75	NEC	Mixed	Unstable	1.0149	68.8	2.57
S15	Male	59	IA	Lung	19	0	G3	>75	NEC	Small	Unstable	1.3014	35.0	3.01
S16	Male	50	IIIB	Stomach	3	0	G3	>80	NEC	Small	Unstable	1.4038	57.5	3.44
S17	Male	69	IIIB	Stomach	9	0	G3	>75	NEC	Large	Unstable	0.9562	62.1	2.25
S18	Female	53	I	Stomach	45	0	G2	2-20	NET	NA	Stable	0.5248	64.0	1.80
S19	Male	72	IIIB	Stomach	29	1	G3	80	NEC	Small	Stable	0.5650	60.9	2.05
S20	Male	65	IIIB	Stomach	32	0	G3	>75	NEC	Large	Stable	0.2595	54.2	2.08
S21	Female	71	IIIB	Lung	31	0	G3	>75	NEC	Small	Stable	0.2730	87.9	2.42
S22	Male	68	IA	Lung	29	0	G3	>75	NEC	Small	Stable	0.3743	75.5	2.05
S23	Male	62	IA	Lung	1	0	G3	>75	NEC	Small	Stable	0.3517	77.5	1.76
S24	Female	61	IIIB	Lung	24	0	G3	>75	NEC	Small	Stable	0.3572	60.2	2.03
S25	Male	74	IIIB	Stomach	1	0	G3	50-75	NEC	Large	Stable	0.5418	62.5	1.75
S26	Female	52	I	Stomach	13	0	G2	5	NET	NA	Stable	0.4359	48.9	1.54
S27	Female	59	IV	Stomach	15	1	G3	30	NET	NA	Stable	0.6413	47.5	2.28
S28	Female	58	IV	Stomach	7	0	G3	32	NET	NA	Stable	0.7896	43.5	2.65
S29	Male	60	IIIB	Stomach	30	0	G3	30	NET	NA	Stable	0.4552	53.4	2.81
S30	Male	70	IIA	Intestines (rectum)	12	0	G2	10	NET	NA	Stable	0.2192	62.6	1.99

Table S1 (continued)

Table S1 (*continued*)

Patient_ID	Gender	Age at diagnosis (year)	Stages at diagnosis	Sites	OS (month)	Death* G_grade	Ki67_index (%)	Histological diagnosis	NEC cell type	CIN group	CIN index	Tumor content estimated by FACETS (%)	Ploidy
S31	Female	44	I	Stomach	61	0 G1	1	NET	NA	Stable	0.0888	32.4	1.93
S32	Female	47	IV	Intestines (duodenum)	38	1 G2	10	NET	NA	Stable	0.1472	54.9	2.09
S33	Female	36	I	Intestines (duodenum)	59	0 G2	5	NET	NA	Stable	0.1615	36.3	2.11
S34	Female	79	IV	Intestines (rectum)	89	0 G2	5	NET	NA	Stable	0.0829	40.8	1.92
S35	Male	45	IIIB	Stomach	NA	0 G2	5	NET	NA	Stable	0.1377	47.9	1.91
S36	Female	67	I	Stomach	41	0 G2	6	NET	NA	Stable	0.1067	49.1	1.77
S38	Female	53	I	Stomach	5	0 G2	3	NET	NA	Stable	0.1261	49.3	1.96
S39	Female	40	I	Stomach	36	0 G1	1	NET	NA	Stable	0.2552	39.1	2.11
S40	Female	52	IV	Intestines (rectum)	35	1 G2	5	NET	NA	Stable	0.0813	84.8	1.96
S41	Female	59	I	Stomach	3	0 G1	1	NET	NA	Stable	0.0224	42.2	2.19
S42	Female	52	IV	Intestines (rectum)	28	0 G2	10	NET	NA	Stable	0.0196	70.1	2.06
S43	Male	65	IA	Lung	25	0 G3	75	NEC	Small	Stable	0.2736	82.3	2.01
S44	Male	81	IIIB	Stomach	NA	0 G2	5	NET	NA	Stable	0.1836	45.7	2.12
S45	Female	27	I	Stomach	21	0 G2	3	NET	NA	Stable	0.0681	45.2	2.13
S46	Male	50	IV	Intestines (duodenum)	12	0 G3	25	NET	NA	Stable	0.2735	57.5	2.15
S47	Male	70	IIA	Intestines (rectum)	12	0 G2	10	NET	NA	Stable	0.1100	38.0	1.95
S48	Male	68	IV	Intestines (sigmoid colon)	11	0 G2	10	NET	NA	Stable	0.1076	70.0	2.01
S49	Male	NA	IV	Intestines (rectum)	9	0 G2	20	NET	NA	Stable	0.0220	54.6	2.02
S50	Female	47	I	Stomach	24	0 G1	1	NET	NA	Stable	0.0000	69.1	1.97

OS, overall survival; NEC, neuroendocrine carcinoma; CIN, chromosomal instability; FACETS, Fraction and Allele-Specific Copy Number Estimates from Tumor Sequencing; NET, neuroendocrine tumor; NA, not available; *, 1=death, 0=no event; Sample from patient S37 was removed due to sample contamination.

Table S2 Mean proportion of 30 COSMIC mutational signatures in PanNENs and NP-NENs

COSMIC signature	Ref (12)	Our data
Signature.1	0.159982238	0.346228362
Signature.10	0.011079643	0.010392651
Signature.11	0.032256010	0.013738497
Signature.12	0.021285641	0.013442374
Signature.13	0.041404037	0.019918897
Signature.14	0.005894283	0.001727616
Signature.15	0.032758491	0.029411381
Signature.16	0.039199494	0.002234721
Signature.17	0.021933895	0.018716511
Signature.18	0.047276639	0.013247281
Signature.19	0.035502515	0.002246793
Signature.2	0.018432333	0.013873117
Signature.20	0.027670301	0.022180302
Signature.21	0.032648917	0.014806427
Signature.22	0.011832450	0.003458886
Signature.23	0.033268548	0.039591606
Signature.24	0.034368941	0.062426407
Signature.25	0.008030420	0.003873105
Signature.26	0.017426507	0.024303159
Signature.27	0.010720511	0.000851746
Signature.28	0.009624432	0.007964046
Signature.29	0.031873880	0.027362037
Signature.3	0.114408516	0.153535185
Signature.30	0.037531756	0.013375991
Signature.4	0.032605106	0.075485003
Signature.5	0.011852951	0.003172427
Signature.6	0.053626062	0.031599656
Signature.7	0.030288502	0.026837840
Signature.8	0.021972256	0.000214536
Signature.9	0.013244725	0.003783440

COSMIC, Catalogue Of Somatic Mutations In Cancer; PanNENs, pancreatic neuroendocrine neoplasm; NP-NENs, nonpancreatic neuroendocrine neoplasm. The sum of 30 signatures is equal 1.

Table S3 Frequency of mutation and LOH of commonly altered genes in PanNENs and NP-NENs

Genes	Ref (12) (%)		Our data (%)	
	Mutation frequency	LOH frequency	Mutation frequency	LOH frequency
<i>MEN1</i>	41	70	6	30.6
<i>DAXX</i>	22	53	0	14.3
<i>ATRX</i>	10	19	6	13.3
<i>PTEN</i>	7	40	2	30.6
<i>TP53</i>	4	–	31	49.0
<i>DEPDC5</i>	2	49	2	38.8
<i>MUTYH</i>	6	47	2	10.2
<i>CHEK2</i>	4	49	0	38.8
<i>BRAC2</i>	1	9	0	44.9
<i>SETD2</i>	5	51	4	38.8
<i>MLL3</i>	5	10	–	–
<i>TSC1</i>	2	17	2	20.4
<i>TSC2</i>	2	43	8	28.6
<i>RB1</i>	2	–	6	53.1
<i>BRAF</i>	0	–	6	14.3
<i>VHL</i>	1	–	2	34.7

LOH, loss of heterozygosity; PanNENs, pancreatic neuroendocrine neoplasm; NP-NENs, nonpancreatic neuroendocrine neoplasm.

Table S4 Frequency of common arm-level copy number alteration in PanNENs and NP-NENs

Arm SCNA	Ref (38) (%)	Our data (%)
11q loss	39	26.5
6q loss	38	12.2
11p loss	34	20.4
3p loss	27	24.5
1p loss	28	8.2
10q loss	26	30.6
1q loss	24	2.0
17q gain	41	12.2
7q gain	35.90	12.2
20q gain	30.70	24.5
9p gain	19.20	12.2
7p gain	28	20.4
9q gain	26.90	16.3

PanNENs, pancreatic neuroendocrine neoplasm; NP-NENs, nonpancreatic neuroendocrine neoplasm; SCNA, somatic copy number alteration.

Table S5 Cox multivariate analysis with several factors and OS

Variables	HR	95% CI	P
CIN vs. CS	15.06	1.01–224.71	0.049
NEC vs. NET	1.52	0.06–40.63	0.802
Male vs. female	1.28	0.18– 9.19	0.804
Age (numeric)	1.02	0.94–1.12	0.617

OS, overall survival; CIN, chromosomal instability; CS, chromosomal stable; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; HR, hazard ratio; 95% CI, 95% confidence interval.