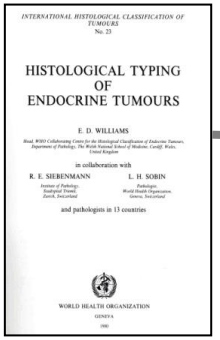
UNIVERSITÄT BERN

Classification of NET

Barcelona, 29.6.2017

Prof. Dr. Aurel Perren
Institute of Pathology
University Bern



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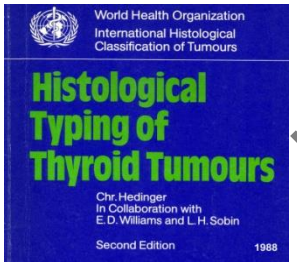

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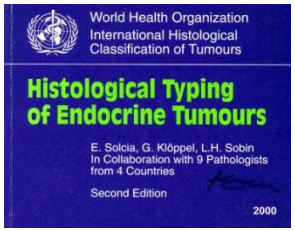

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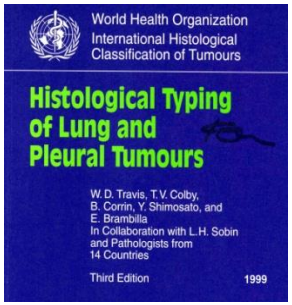

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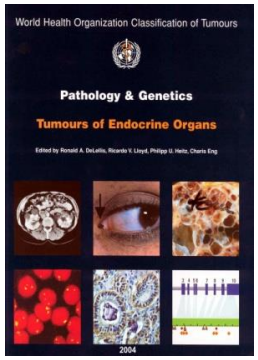

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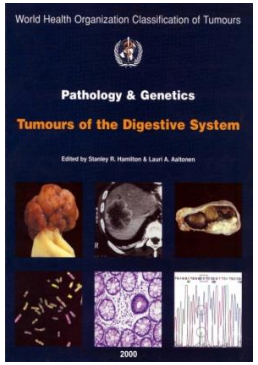

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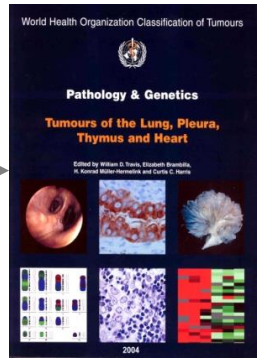

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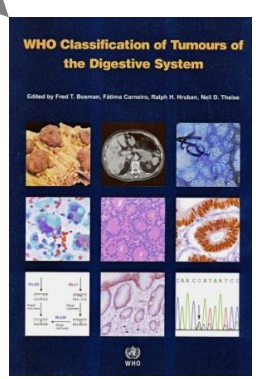

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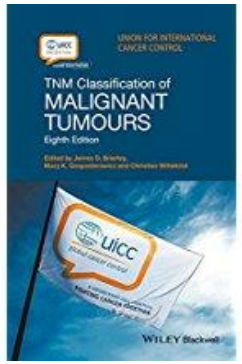
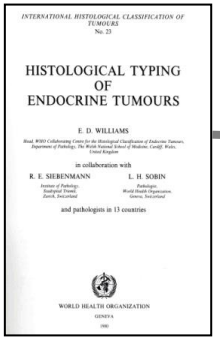
2017





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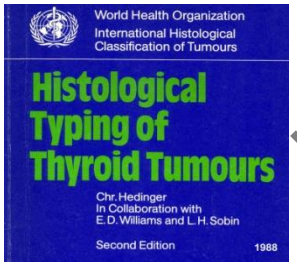

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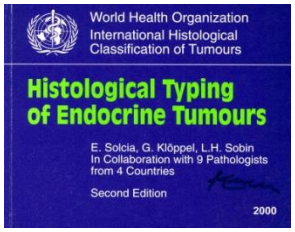

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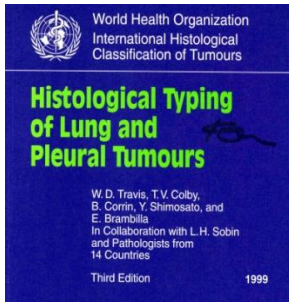

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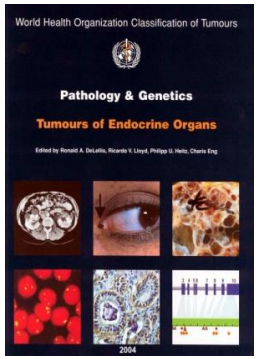

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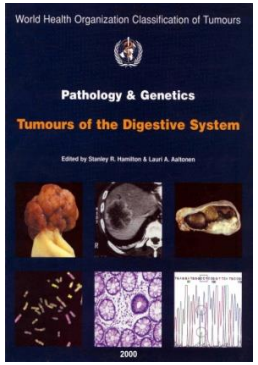

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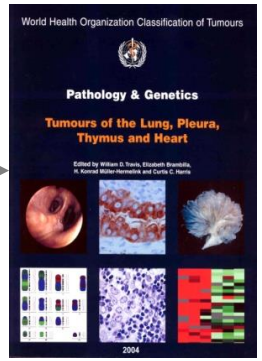
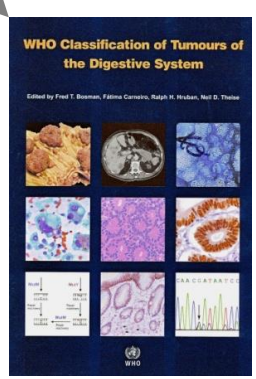


2004

WHO

2017



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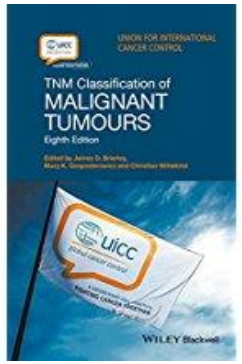

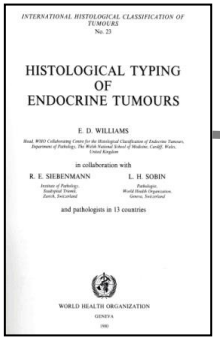

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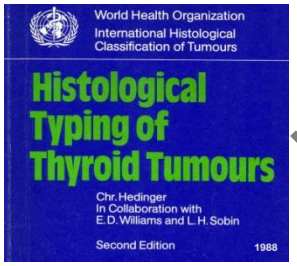

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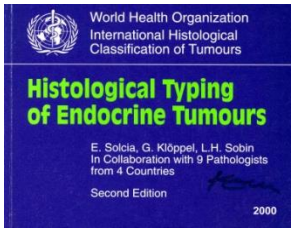

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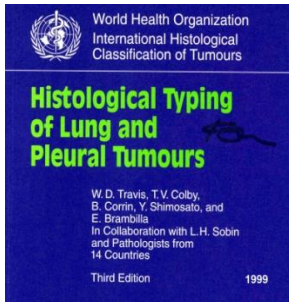

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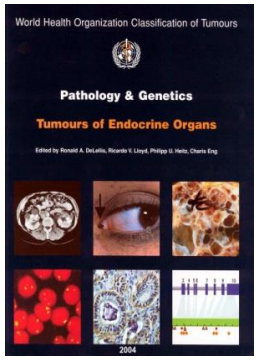

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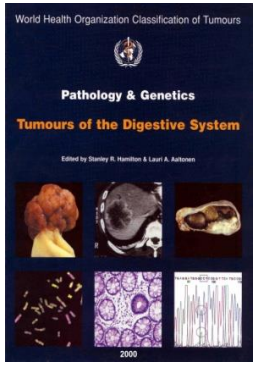

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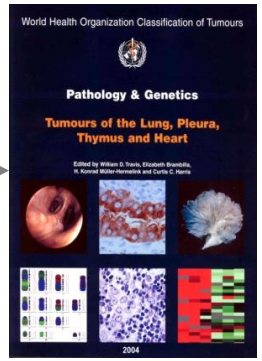

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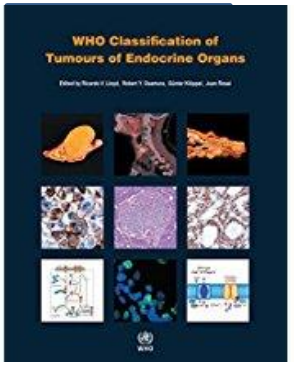

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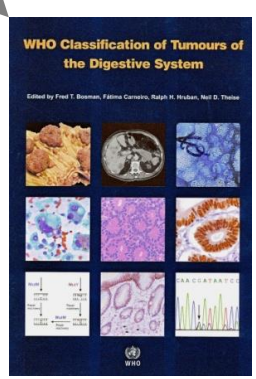

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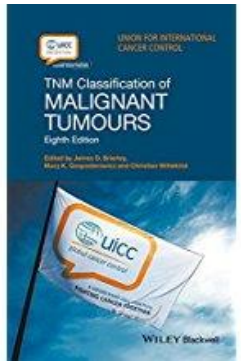

Classification of NET

UNIVERSITÄT BERN

1. Diagnosis, grading and staging
2. Pancreas: Evidence for change of classification
3. Concept of NET G3
4. Outlook

Neuroendocrine neoplasms:

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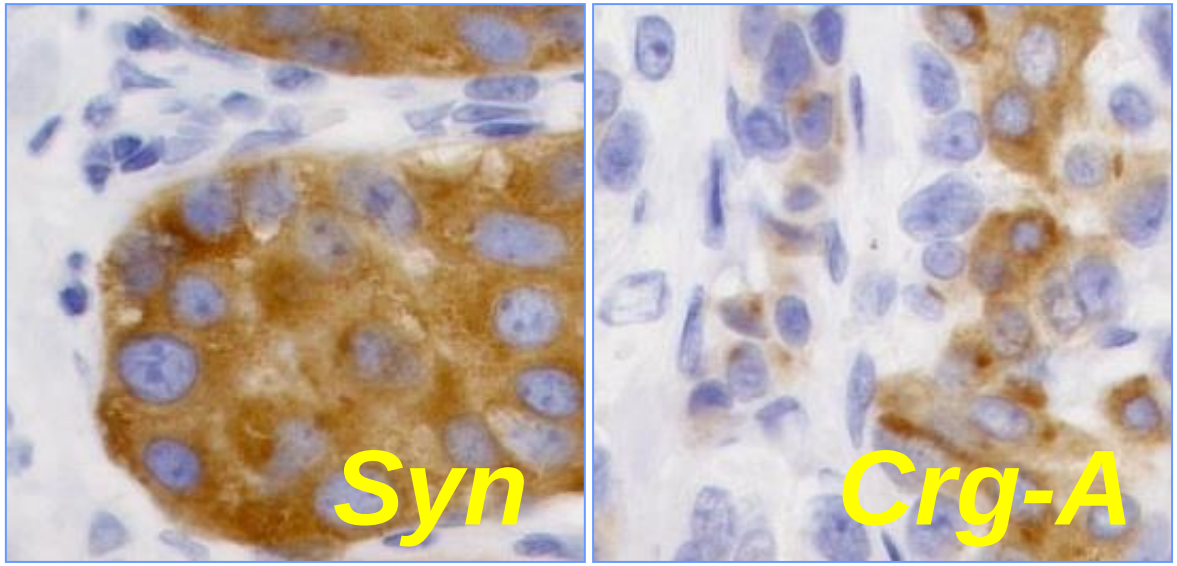
- Rare, in all organs
- Similarities with neurons
- Ability to produce hormones



ENETS Frascati 2006/2007

MBI (Ki67): Grading

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Table 4 Grading proposal for foregut (neuro)endocrine tumors

Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

[a] 10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density

[b] MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

MBI (Ki67): Grading

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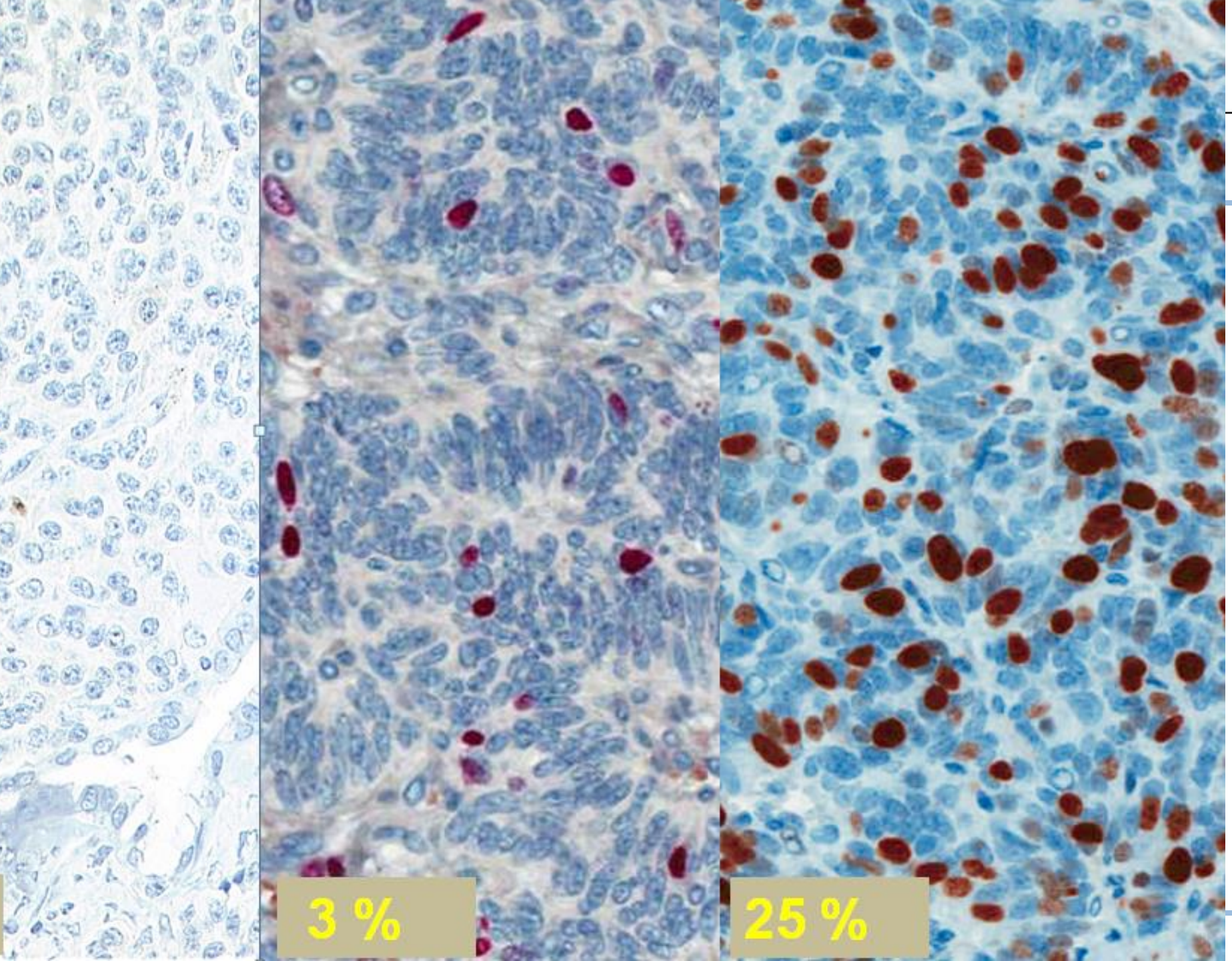
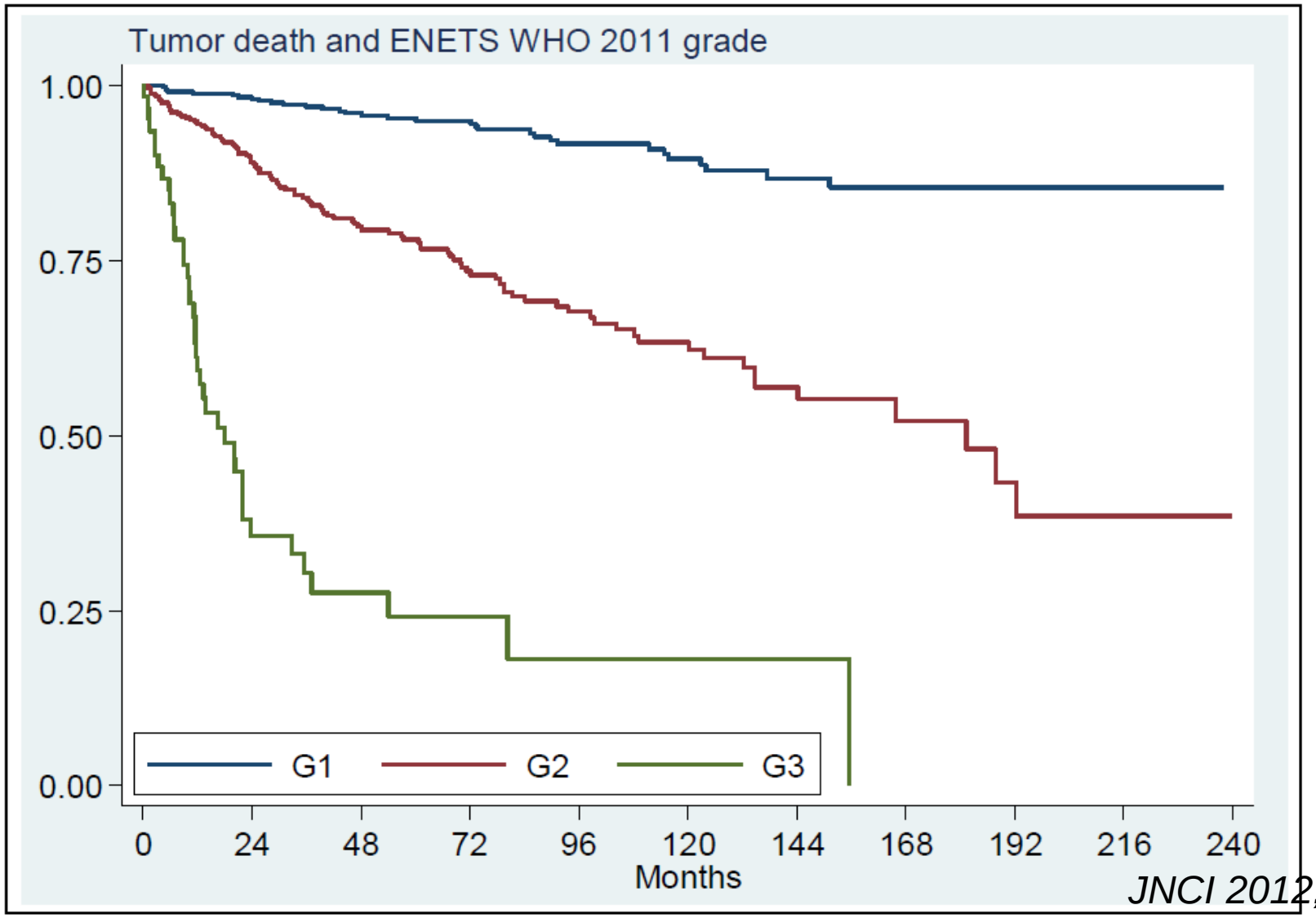

3 %
25 %

TNM-Grading: Evidence pNET



JNCI 2012, Rindi et al.

TNM-Grading: Evidence siNET

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MV analysis, advanced Ileal/Jejunal- NET:

Variable	HR	95% CI	p
Model 1			
Female gender	1.73	0.55–5.44	0.348
Age at diagnosis, years[a]	1.02	0.97–1.07	0.337
Ki67 value[a]	1.18	1.07–1.31	0.001
No primary tumor resection	2.41	0.67–8.61	0.174
Model 2			
Female gender	1.67	0.55–5.10	0.365
Age at diagnosis, years[a]	1.03	0.98–1.07	0.159
Grading (G1: Ki67 ≤2%; G2: Ki67 3–20%)			
G2 vs. G1	2.40	0.89–6.44	0.083
No primary tumor resection	3.13	0.94–10.42	0.063
Model 3			
Female gender	1.87	0.59–5.92	0.288
Age at diagnosis, years[a]	1.02	0.98–1.07	0.265
Grading (G1: Ki67 <5%; G2: Ki67 5–20%)			
G2 vs. G1	3.99	1.46–10.91	0.007
No primary tumor resection	2.41	0.69–8.39	0.168

[a] Continuous variable

- **Biologically, proliferation is a continuous variable**

Panzuto et al, (2012) Neuroendocrinology

WHO Classification 2010

UNIVERSITÄT BERN

1. **Neuroendocrine Tumor, NET G1**
2. **Neuroendocrine Tumor, NET G2**
3. **Neuroendocrine Carcinoma, NEC (small or large-cell)**
4. **Mixed adeno-neuroendocrine carcinoma, MANEC**
5. Hyperplastic and preneoplastic lesions

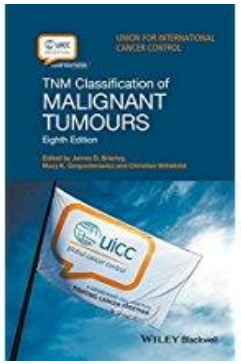
Bosman FT, Carneiro F, Hruban RH, Theise ND WHO Classification of Tumours of the Digestive System, 2010

WHO classification 2010

UNIVERSITÄT BERN

- 1. NET G1
- 2. NET G2
- 3. NEC G3

- + TNM Staging



WHO classification 2010

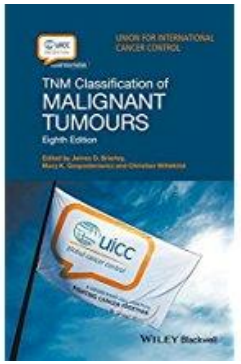
UNIVERSITÄT BERN

Grading

≤2% MIB <2 Mitosis

Differentiation

- **1. NET G1**
- **2. NET G2**
- **3. NEC G3**
- **+ TNM Staging**



Classification of NET

UNIVERSITÄT BERN

1. Diagnosis, grading and staging
2. **Pancreas: Evidence for change of classification**
3. **Concept of NET G3**
4. **Outlook**

USA, grade based on mitosis

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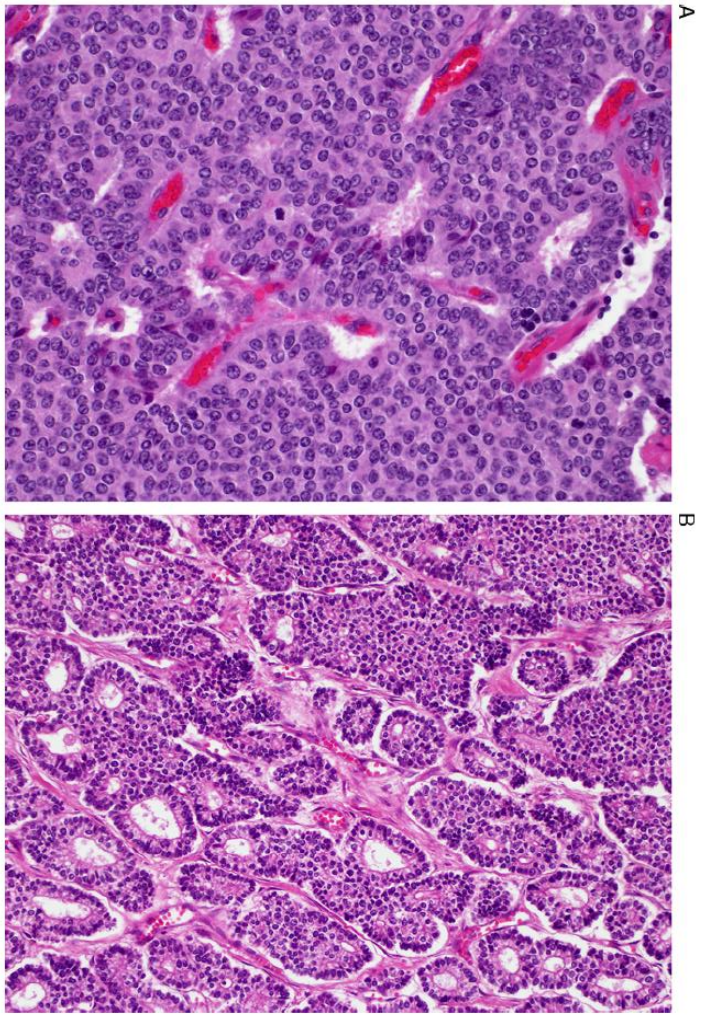
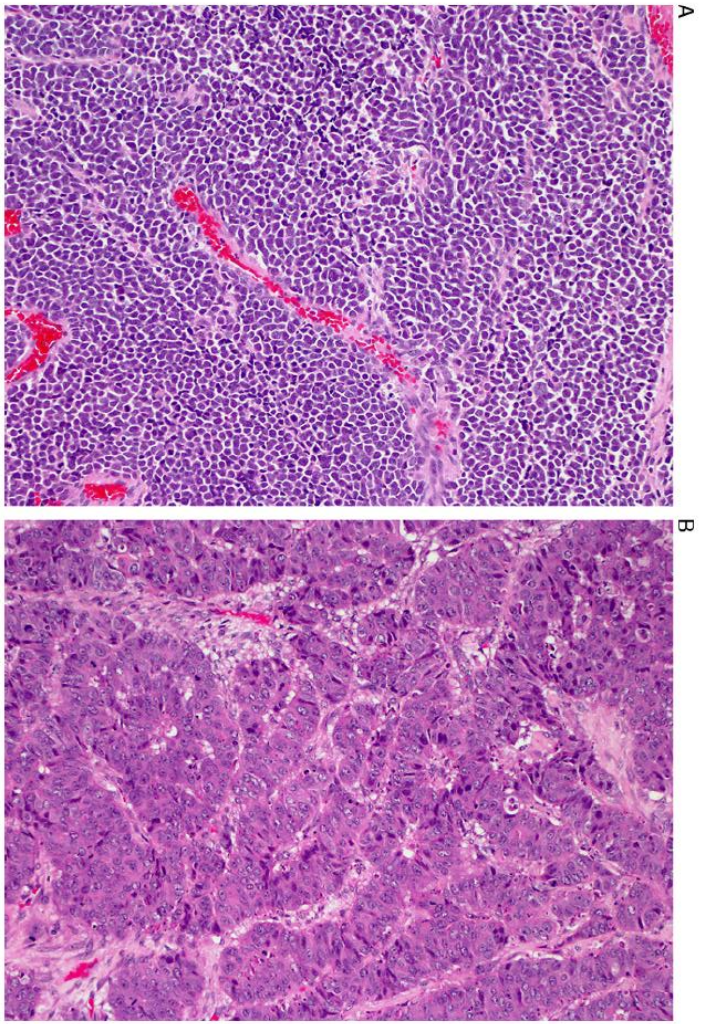
	Ki-67	pN1	2y surv
53 grade concordant pNET G2	2-20%	47%	86%
19 grade discordant pNET	30-50%	52%	74%
43 morphologically pd NEC	50-100%	85%	22%

AJSP 2015, Basturk et al.

Differentiation: grade discordant often WD





AJSP 2015, Basturk et al.

Ki-67

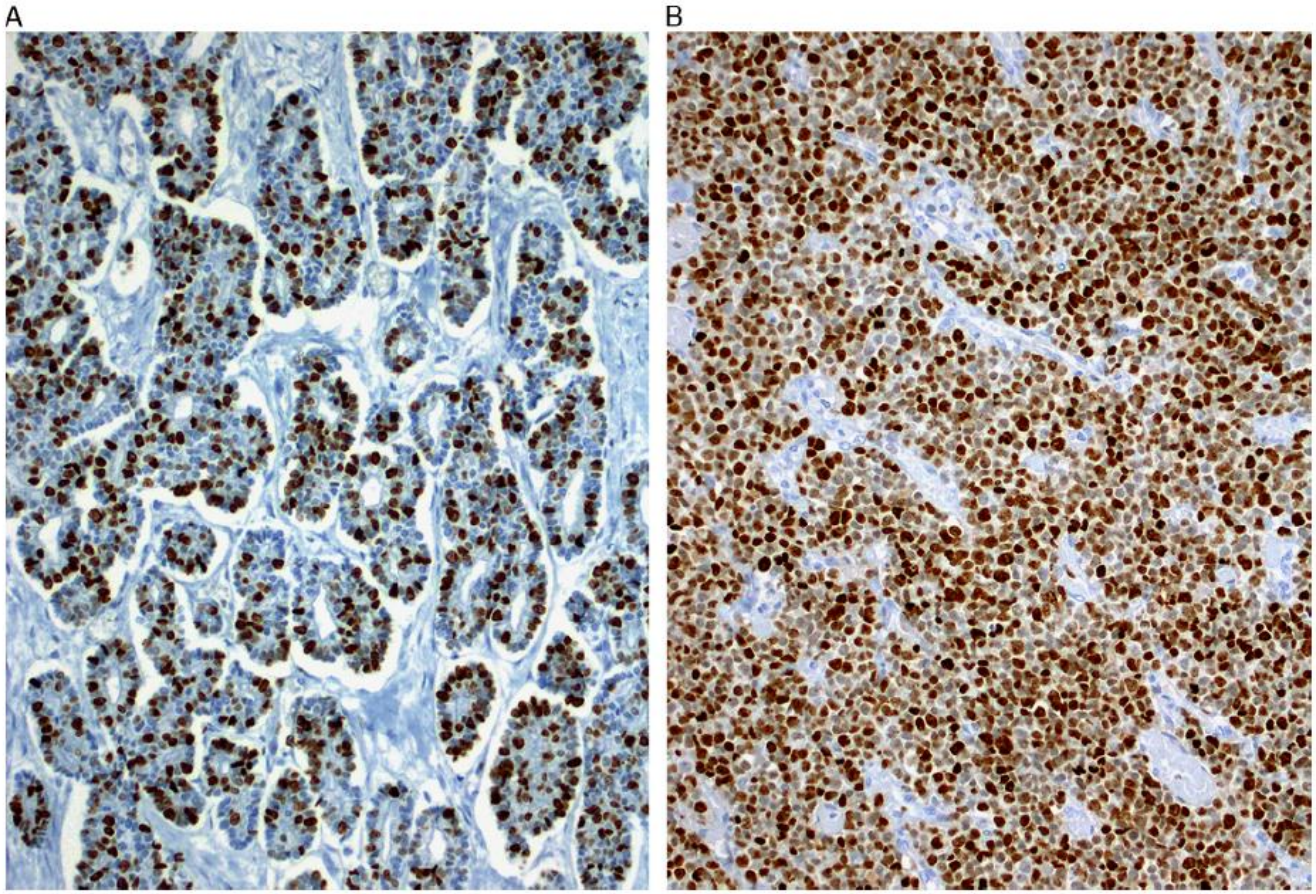
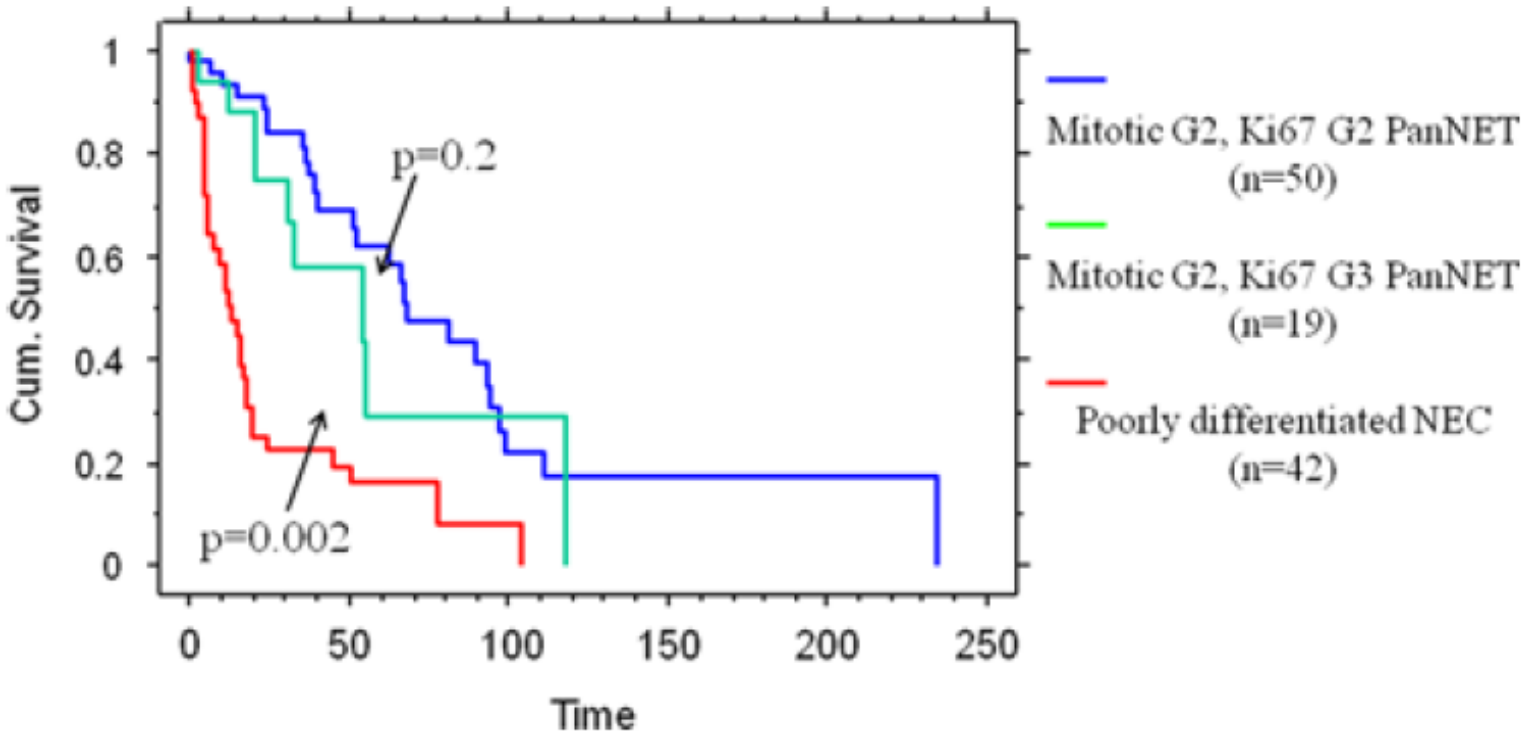


FIGURE 3. A, Average Ki67 proliferation index of grade-discordant PanNETs was 40% (as opposed to 74% of small cell–type and 66% of large cell–type poorly differentiated NECs). B, A small cell carcinoma with a Ki67 proliferation index of >95% is depicted here.

AJSP 2015, Basturk et al.

Survival



AJSP 2015, Basturk et al.

Progression NET to NEC

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31 NET with focal area of poor differentiation

50% in primary, 50% in metastasis

2y and 5y survival 88% und 49%

DAXX/ATRX/MEN1 mutations in secondary

p53 or RB mutations only in true PD

Clin Cancer Research 2015, Tang et al.

G3 NEC, genetically ≠ NET

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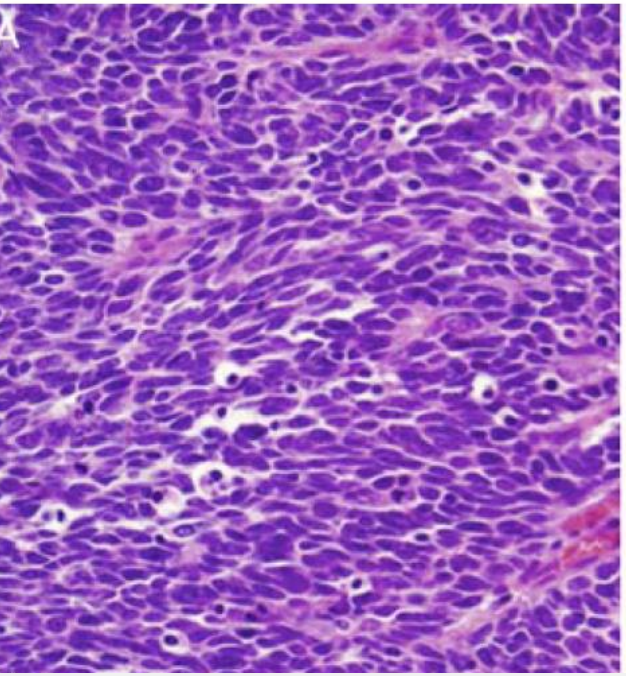
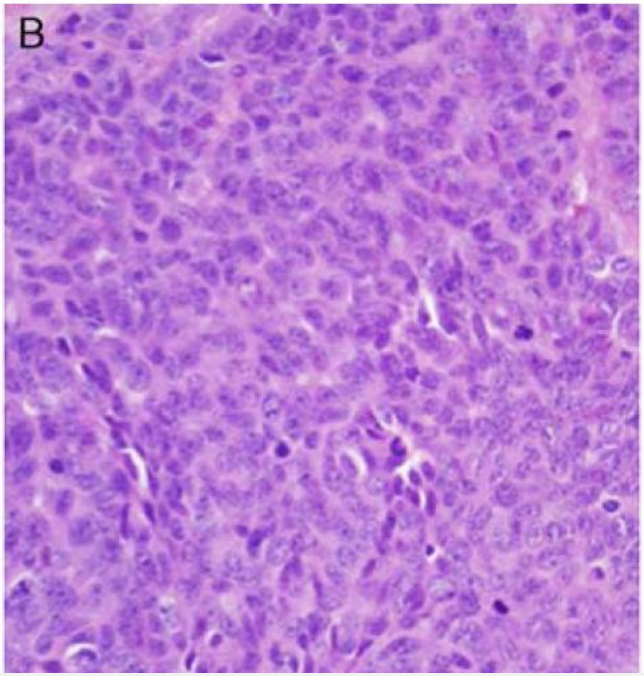
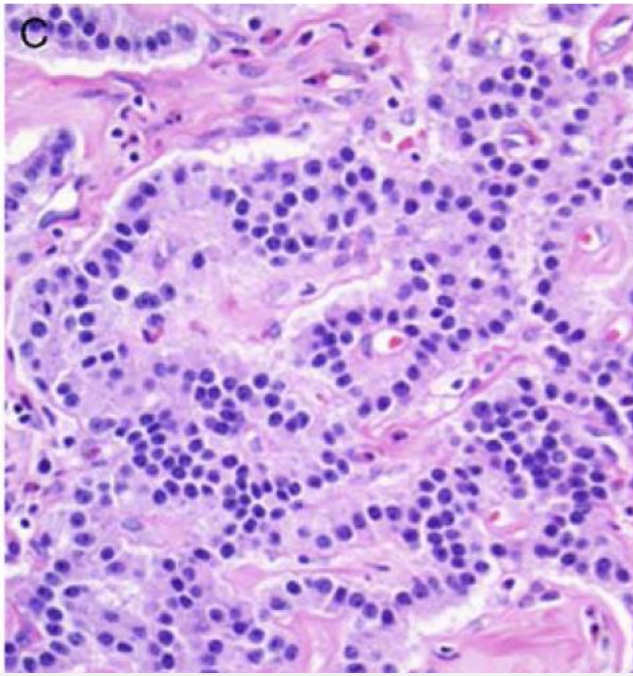


P53 RB mutations

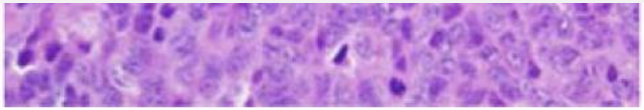


p53 RB Mutation



DAXX/ATRX/Men1/mTOR

11 small cell NEC



9 large cell NEC

11 pNET

AJSP 2012, Yachida et al.

Classification of NET

1. Diagnosis, grading and staging
2. Pancreas: Evidence for change of classification
3. **Concept of NET G3**
4. **Outlook**

Summary PanNET G3

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- **NET G3 and secondary NET G3 behave differently from NEC G3**

- **Important are**
  - **Ki-67**
  - **Differentiation by morphology**
  - **Genetic marks (DAXX/ATRX/(MEN1) vs. P53 RB)**
  - **Clinical history (progression from NET G1/G2)**

~~2010~~ WHO Klassifikation of NEN

old

UNIVERSITÄT BERN

1. **Neuroendocrine Tumor, NET G1**
2. **Neuroendocrine Tumor, NET G2**
3. **Neuroendocrine carcinoma, NEC (small or large-cell)**

Bosman FT, Carneiro F, Hruban RH, Theise ND WHO Classification of Tumours of the Digestive System, 2010

WHO Classification 2017

1. Neuroendocrine Tumor, NET G1

2. Neuroendocrine Tumor, NET G2

3a. Neuroendocrine Tumor, NET G3

3b. Neuroendocrine carcinoma, NEC (small or large-cell)

WHO Classification 2017

UNIVERSITÄT BERN

1. Neuroendocrine Tumor, NET G1
2. Neuroendocrine Tumor, NET G2

3a. Neuroendocrine Tumor, NET G3

3b. Neuroendocrine carcinoma, NEC (small or large-cell)

Differentiation

WHO Classification 2017

UNIVERSITÄT BERN

1. Neuroendocrine Tumor, NET G1
2. Neuroendocrine Tumor, NET G2

3a. Neuroendocrine Tumor, NET G3

3b. Neuroendocrine carcinoma, NEC (small or large-cell)

Grading

<3% MIB <2 Mitosis

Differentiation

WHO Classification 2017

UNIVERSITÄT BERN

1. Neuroendocrine Tumor, NET G1
2. Neuroendocrine Tumor, NET G2

3a. Neuroendocrine Tumor, NET G3

3b. Neuroendocrine carcinoma, NEC (small or large-cell)

Grading

<3% MIB <2 Mitosis

Differentiation

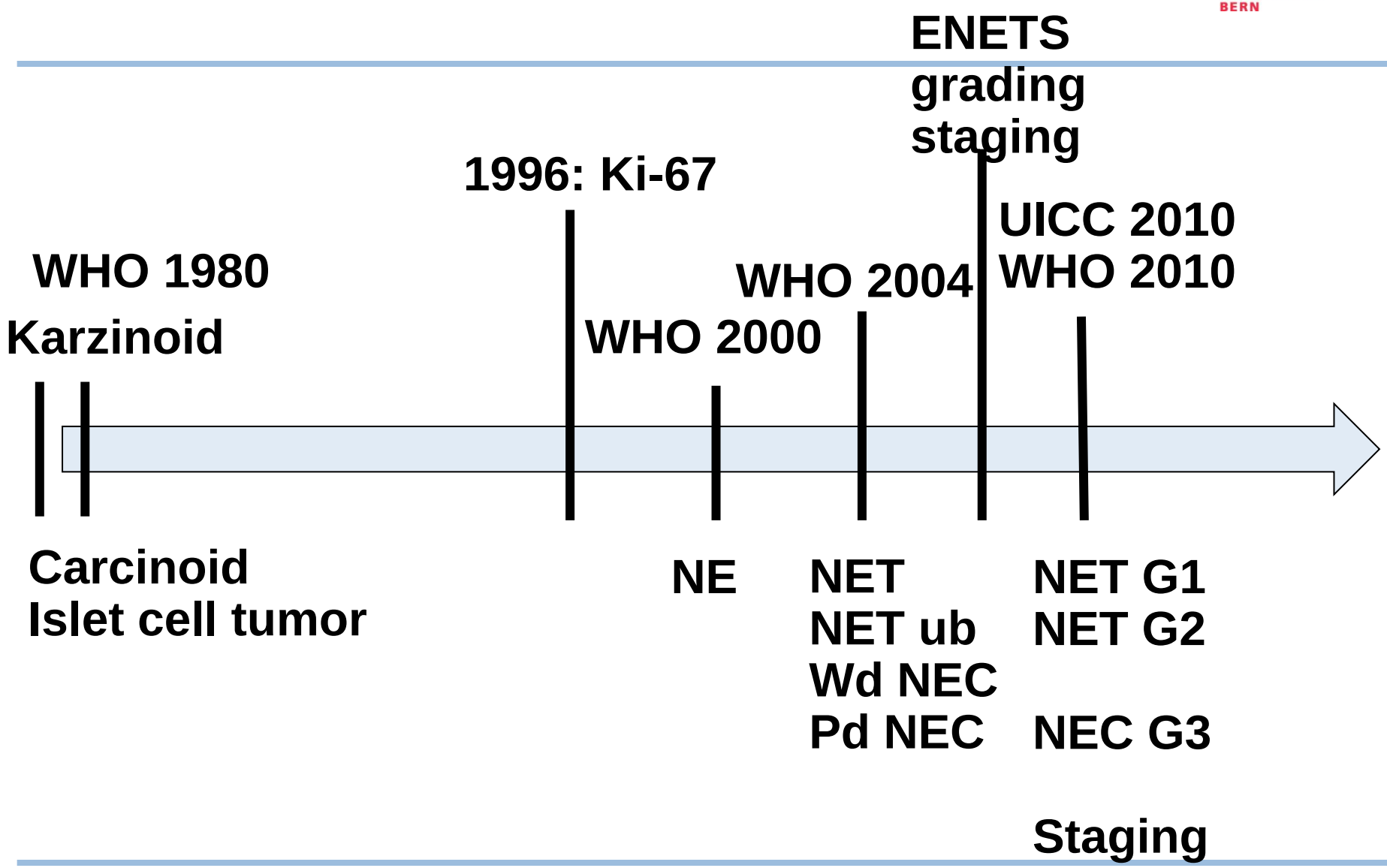
+TNM Staging

Concept of NET G3

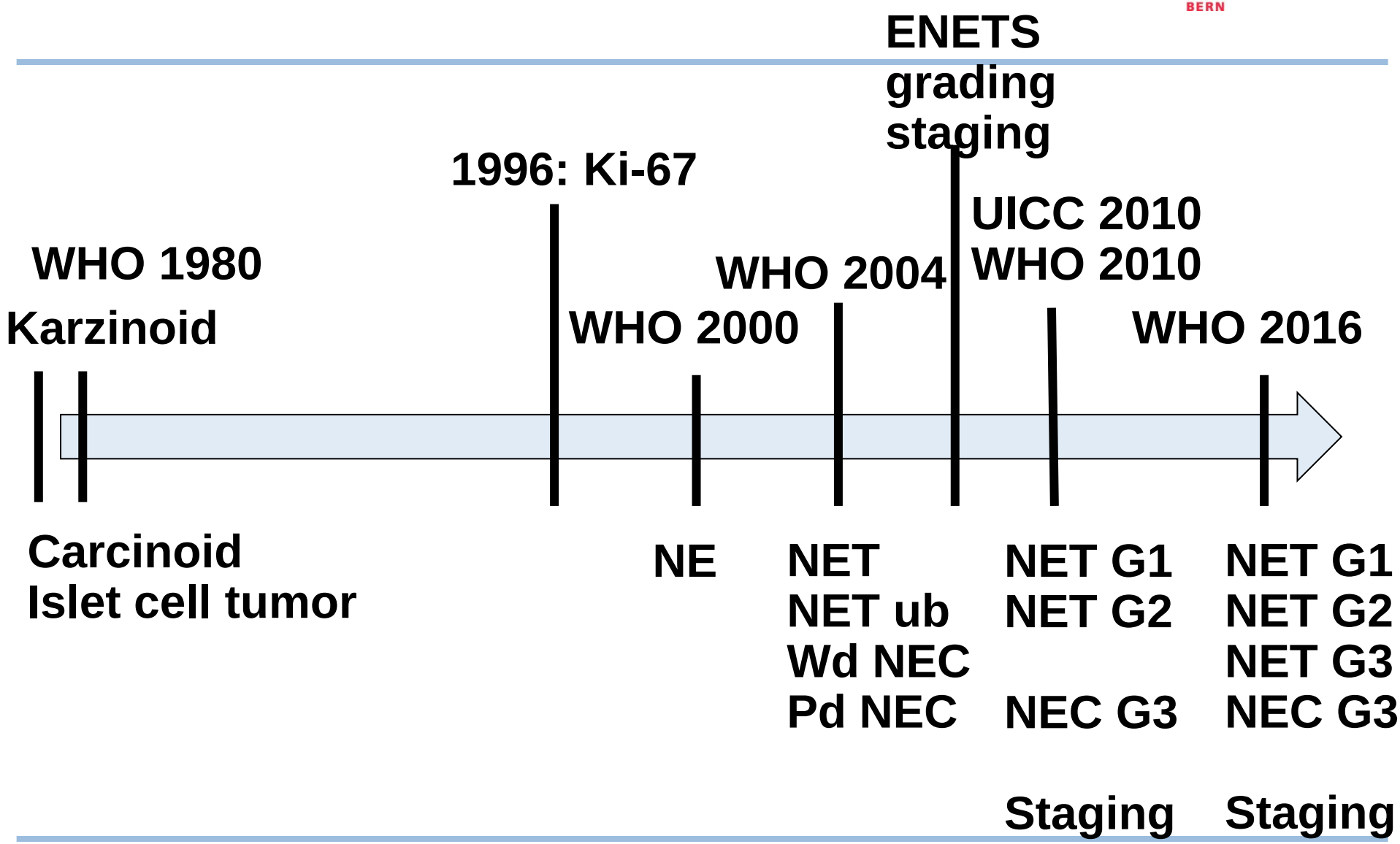
UNIVERSITÄT BERN

1. **Genetically and morphologically group of well differentiated NET**
2. **Clinically less aggressive compared to NEC**
3. **Probably less responsive to Cisplatin than NEC**
4. **Clinical trials needed to determine optimal treatment**
5. **Concept will most likely be implemented in GI (and lung) NET**

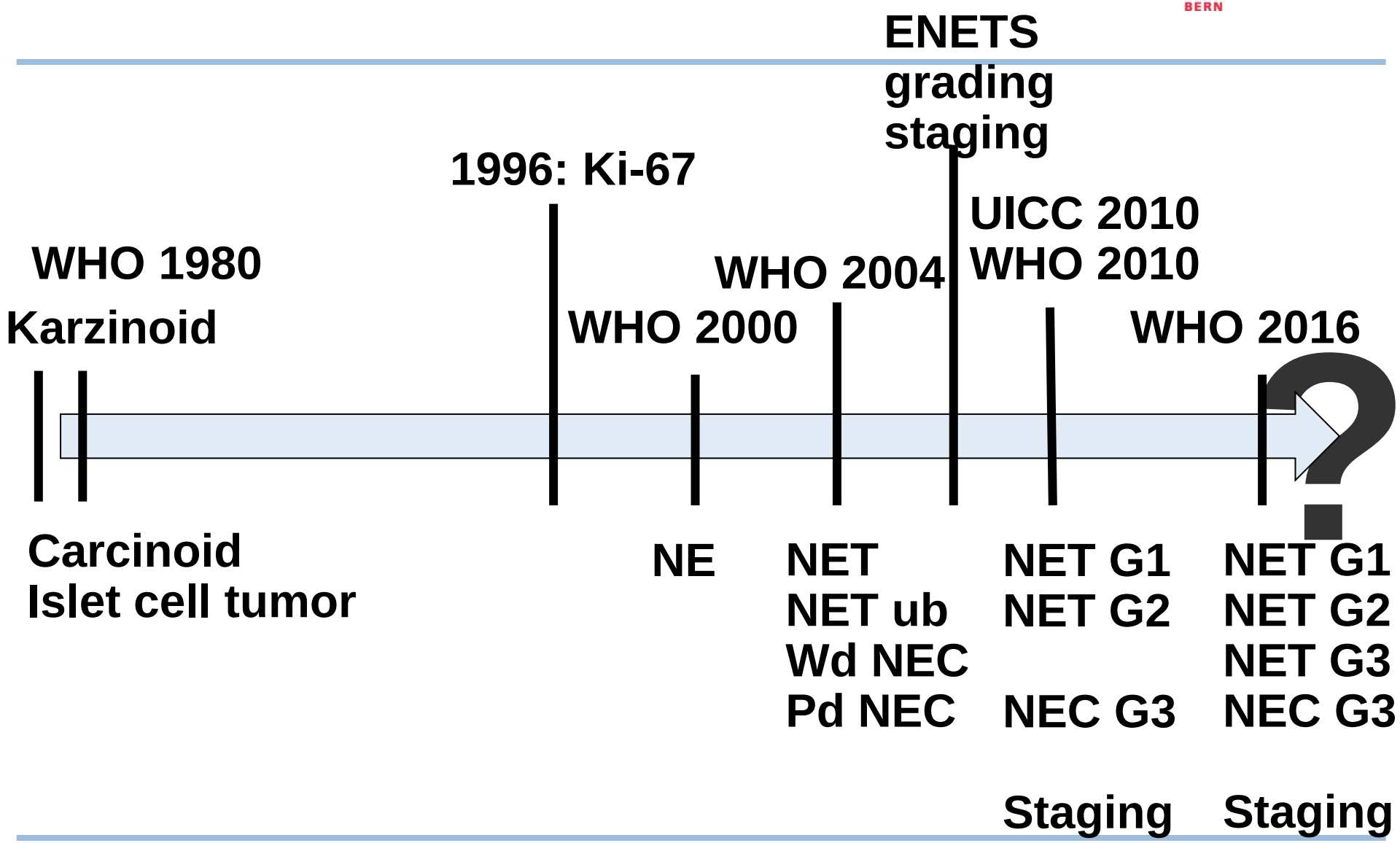
Concept of NEN:



Concept of NEN:



Concept of NEN:



Future classification by Expression/ Genetics/ Epigenetics?

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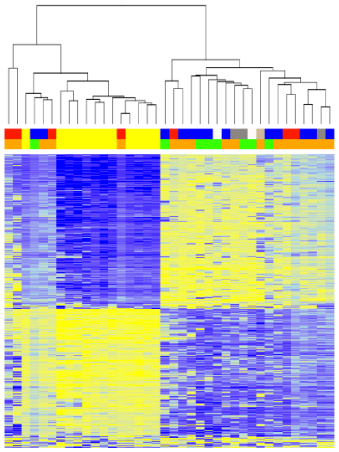
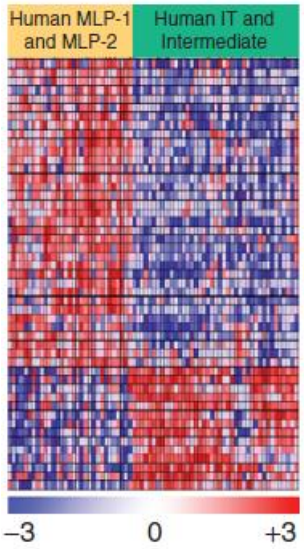
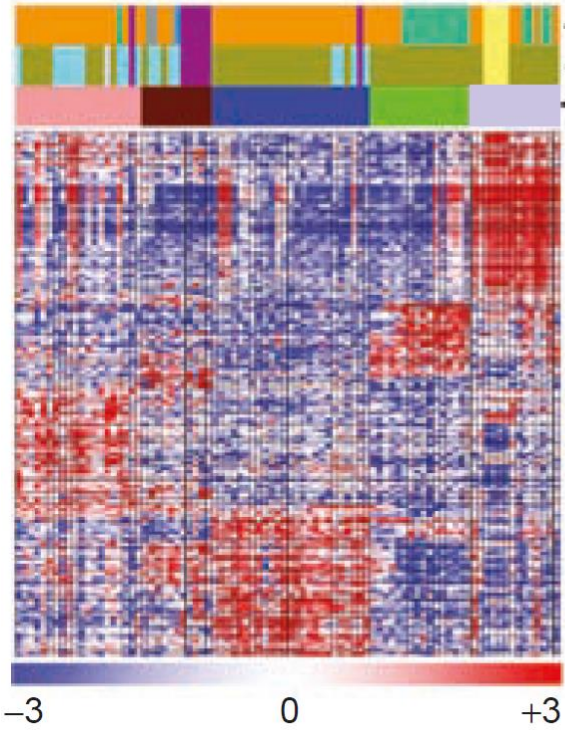
pNET,
RNA expression profiles:
4 Subgroups

pNET,
miRNA expression profiles: 2 Subgroups

pNET,
Methylation data







NEN treatment development: Needs

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- **Collaborations across institutions and disciplines**
- **Clinical trials / follow-up of patients**

European ENETS Neuroendocrine Tumor Society

- **BIO banks**

SWISS BIOBANKING PLATFORM