

16:30 - 18:00 **Type: Educational session**

Valencia Auditorium (Hall 5)

Title: Bronchial neuroendocrine tumours

Chair(s): Christina Thirlwell, GB; Nicola Fazio, IT

Challenges in pathological and molecular classifications

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Milano- Italy

DISCLOSURE OF INTEREST

CONSULTING AND ADVISORY SERVICES, PUBLIC PRESENTATIONS
(NOVARTIS, IPSEN, ROCHE, MERCK SHARP & DHOME)

FINANCIAL SUPPORT FOR CLINICAL TRIALS
(IGNYTA, ROCHE, ADOPT BBMRI-ERIC, TRANSCAN2)

Outline



- ✓ General Features
- ✓ Current WHO Classifications
- ✓ Molecular Landscape & Neoplasm's Heterogeneity

Morphology -Prognosis- Molecular pathogenesis

**Well Differentiated
Neuroendocrine
Neoplasms**

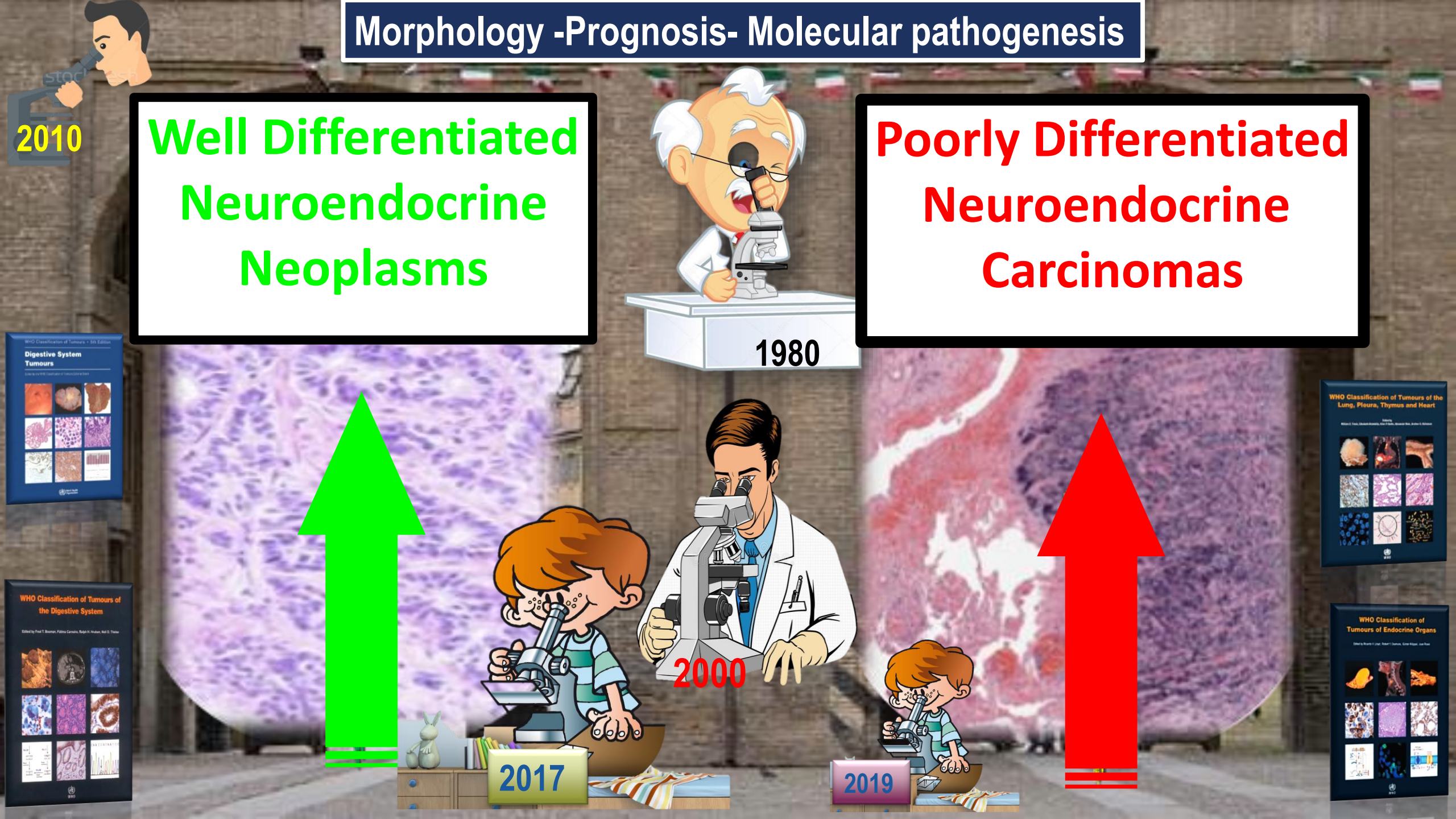
**Poorly Differentiated
Neuroendocrine
Carcinomas**

1980

2000

2017

2019

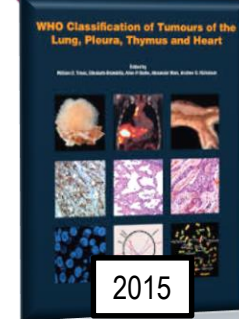
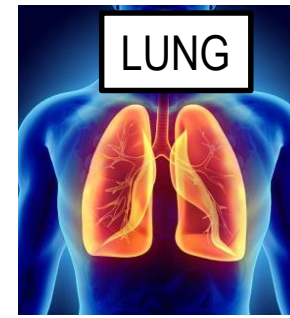
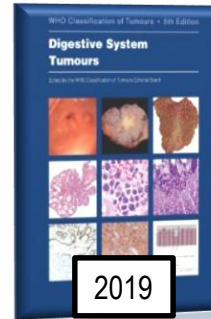
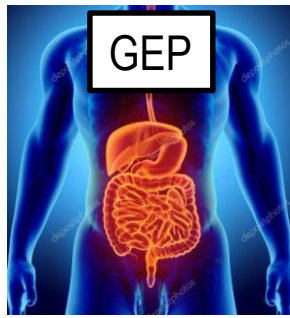


Outline



- ✓ General Features
- ✓ Current WHO Classifications
- ✓ Molecular Landscape & Neoplasm's Heterogeneity

Current WHO Classifications



Morphology

Well Differentiated

**Ki-67
< 3%**

Or
Mitosis
<2*

NET G1

**Ki-67
3-20%**

Or
Mitosis
2-20*

NET G2

**Ki-67
> 20%**

Or
Mitosis
2-20*

NET G3

Ki-67 > 20%

Or
Mitosis
>20*

NEC

Morphology

Well Differentiated

**MITOTIC
INDEX
<2#**

**NECROSIS
ABSENT**

**TYPICAL
CARCINOID**

**MITOTIC
INDEX
2-10 #**

**NECROSIS
RARE**

**ATYPICAL
CARCINOID**

**MITOTIC
INDEX
>10 #**

**NECROSIS
focal/diffuse**

**LARGE CELLS
CARCINOMA**

**MITOTIC
INDEX
>10 #**

**NECROSIS
diffuse**

**SMALL CELLS
CARCINOMA**

counted in 10 HPF/2000 cells/2mm²

Milione M, ESMO 2020 Barcelona

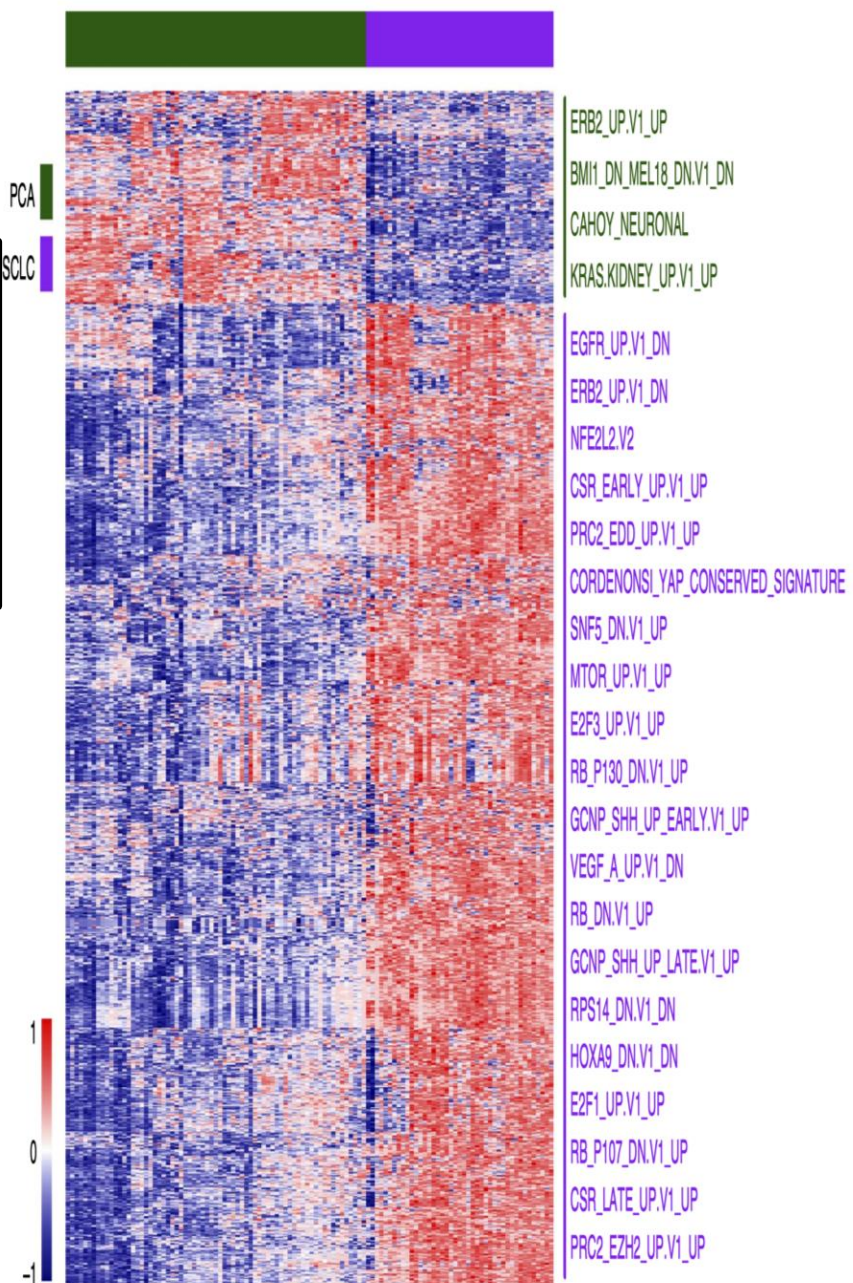
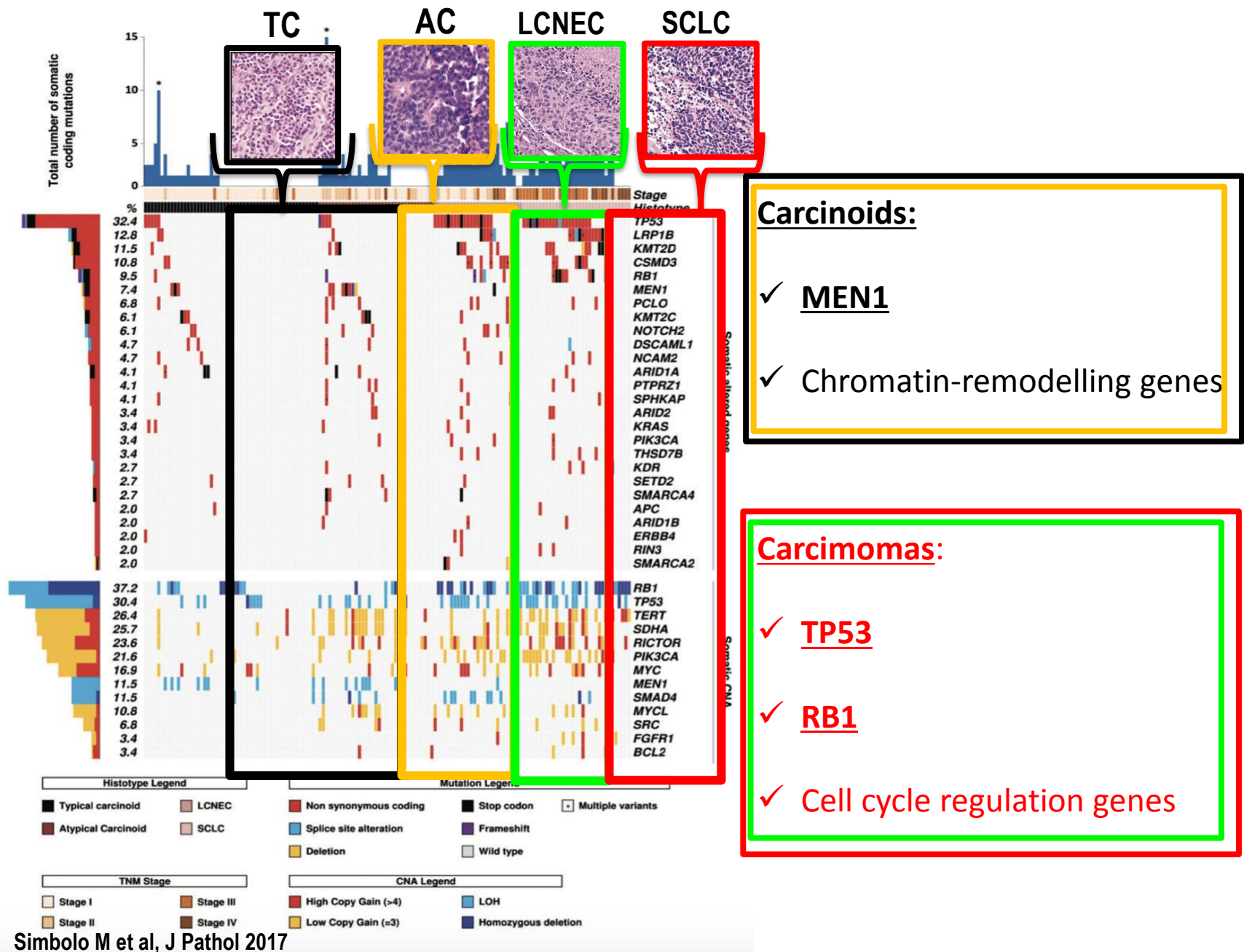
* counted in 10 HPF/2000 cells/2mm²

Outline

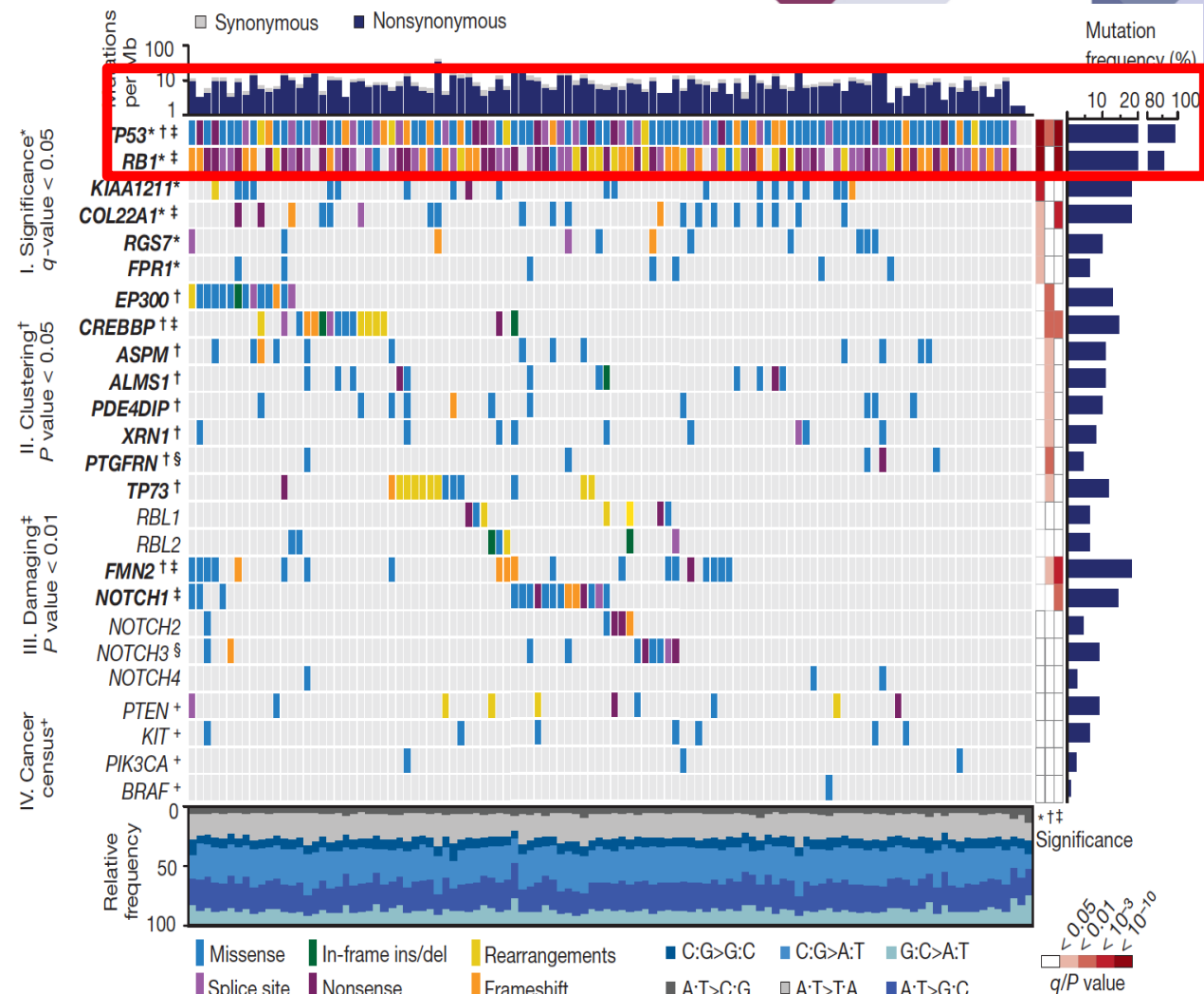
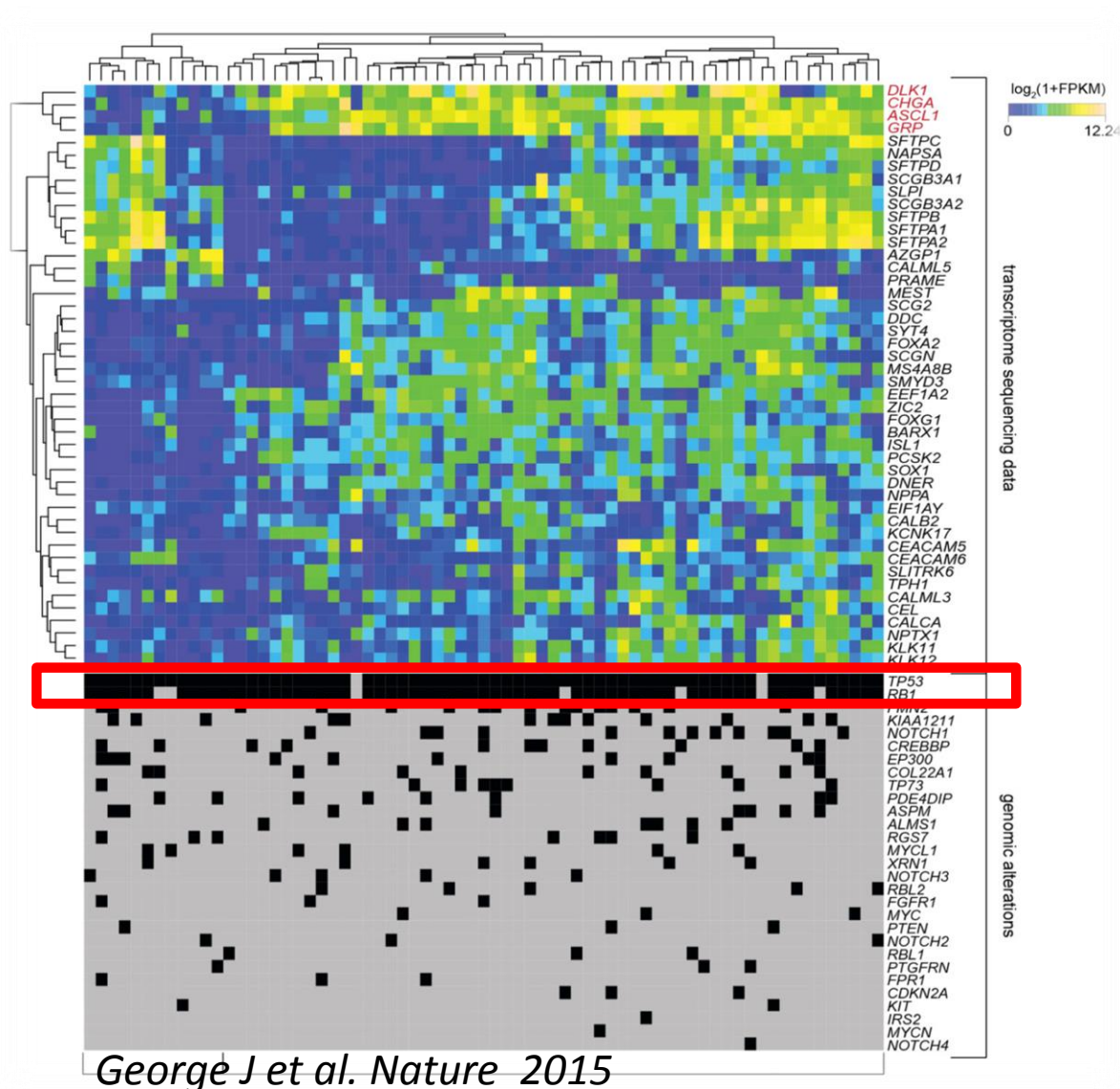


- ✓ General Features
- ✓ Current WHO Classifications
- ✓ Molecular Landscape & Neoplasm's Heterogeneity

The Four WHO 2015 Lung Neuroendocrine Tumours categories: Molecular Landscape



SCLC* Molecular Landscape



George J et al. Nature 2015

Inactivation of *TP53* and *RB1* are obligatory in SCLC

Lung Neoplasms: Molecular Glossary

Carcinoids

- ✓ MEN1
- ✓ Chromatin-remodelling genes

Small Cells Carcinoma

- ✓ TP53+RB1 (Double Hit)
- ✓ MYC

ADENOCARCINOMA

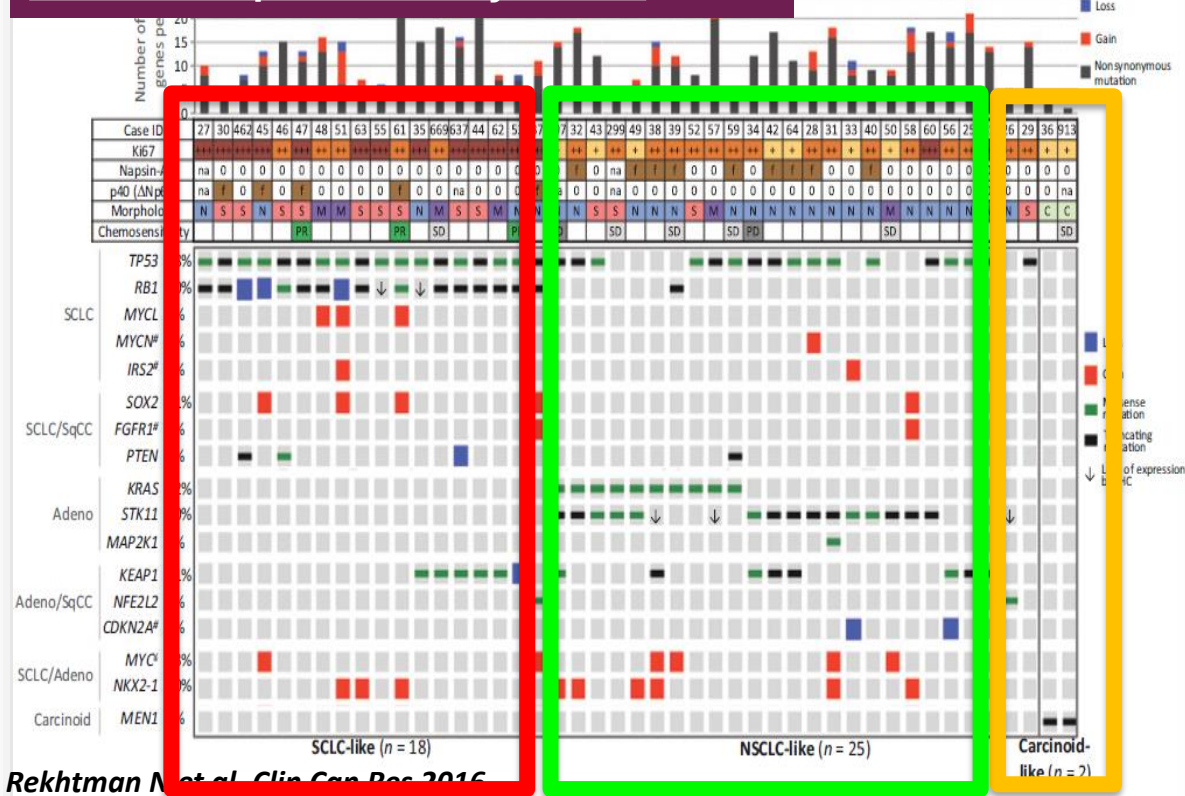
- ✓ K-ras
- ✓ STK11
- ✓ KEAP-1

Large Cells Carcinoma

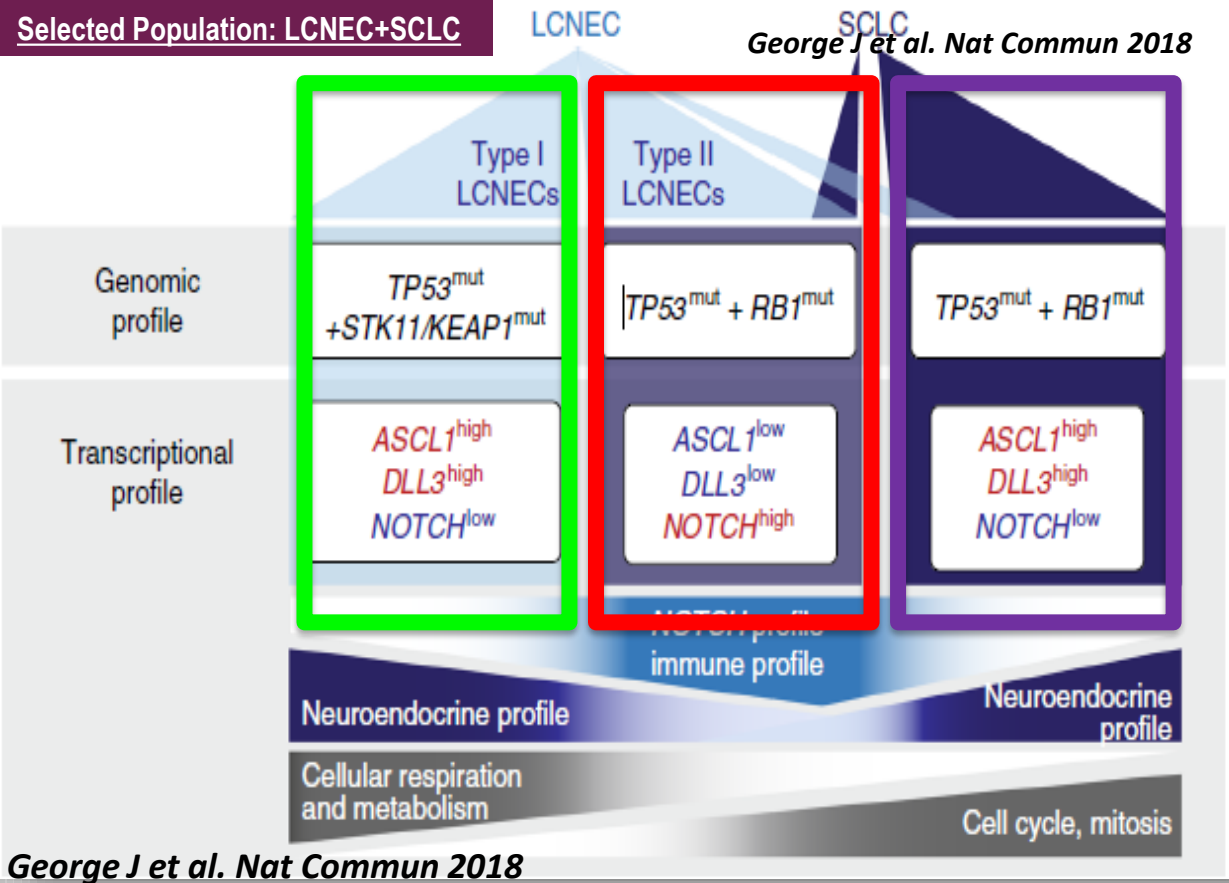
?????????

Neuroendocrine Carcinomas (LCNECs + SCLC): Molecular Landscape

Selected Population: only LCNEC



Selected Population: LCNEC+SCLC



NSCLS GROUP/LCNEC I

LCNEC Morphology + SCLC/ADK Molecular Features

- ✓ RB1 or TP53: YES
- ✓ STK11 and KRAS: YES
- ✓ MYCL, SOX2:NO
- ✓ FGFR1 :NO
- ✓ MEN1: NO

CARCINOID GROUP

LCNEC Morphology + Carcinoid Molecular Features

- ✓ RB1 or TP53: NO
- ✓ STK11 and KRAS: NO
- ✓ MYCL, SOX2:NO
- ✓ FGFR1 :NO
- ✓ MEN1: YES

SCLC GROUP/LCNEC II

LCNEC Morphology + SCLC Molecular Features

- ✓ RB1+TP53: YES
- ✓ STK11 and KRAS: NO
- ✓ MYCL, SOX2:YES
- ✓ FGFR1:YES
- ✓ MEN1:NO

(PURE)SCLC GROUP

SCLC Morphology + SCLC Molecular Features

- ✓ RB1+TP53: YES
- ✓ STK11 and KRAS: NO
- ✓ MYCL, SOX2:YES
- ✓ FGFR1:YES
- ✓ MEN1:NO

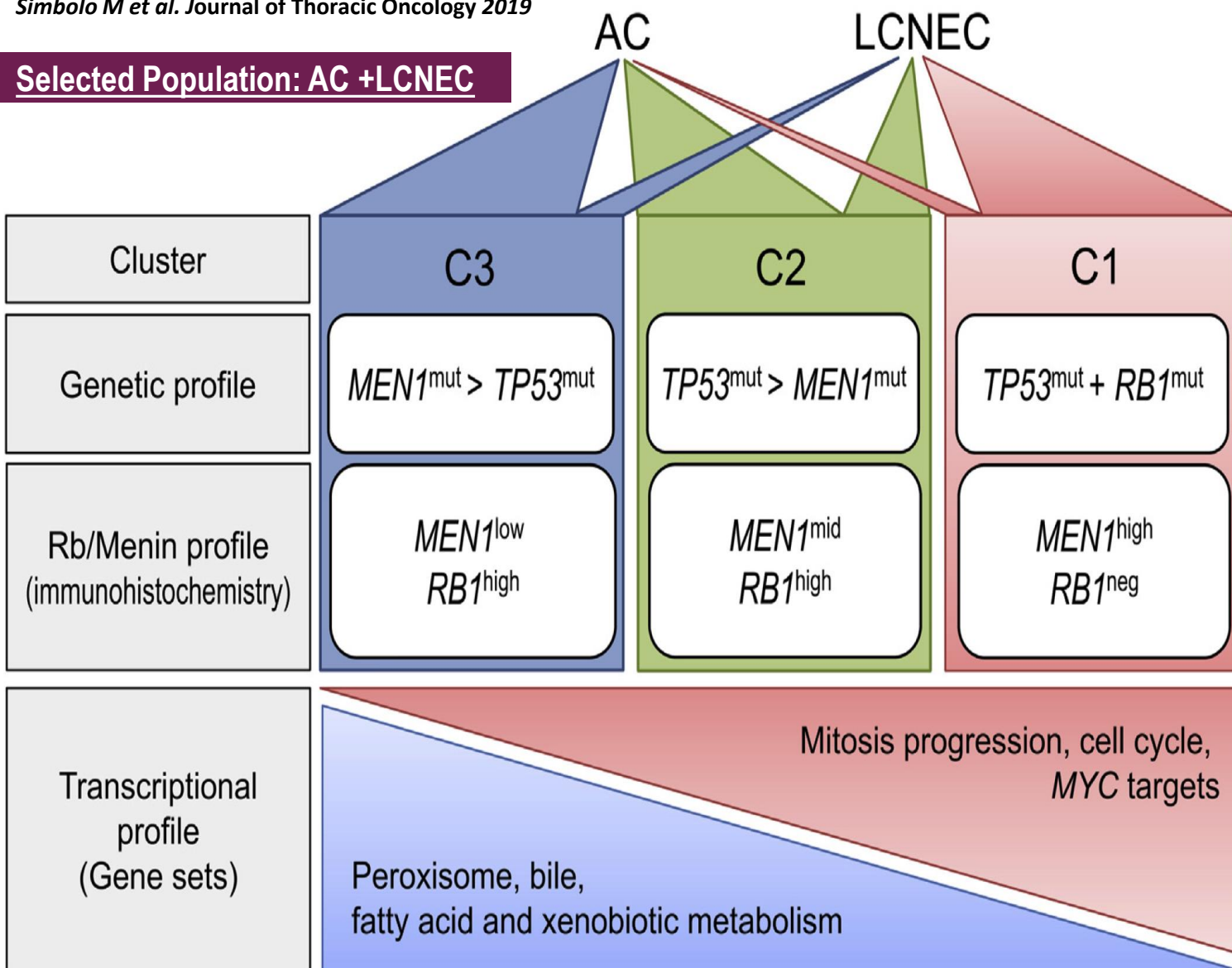


LCNECs + AC: Molecular Landscape



Simbolo M et al. Journal of Thoracic Oncology 2019

Selected Population: AC +LCNEC



C3= AC-enriched cluster (20 ACs +4 LCNECs)

- ✓ MEN1 mutations
- ✓ TP53 mutations
- ✓ **NO RB1 alterations**

C1= LCNEC-enriched cluster (20 LCNECs +1 ACs)

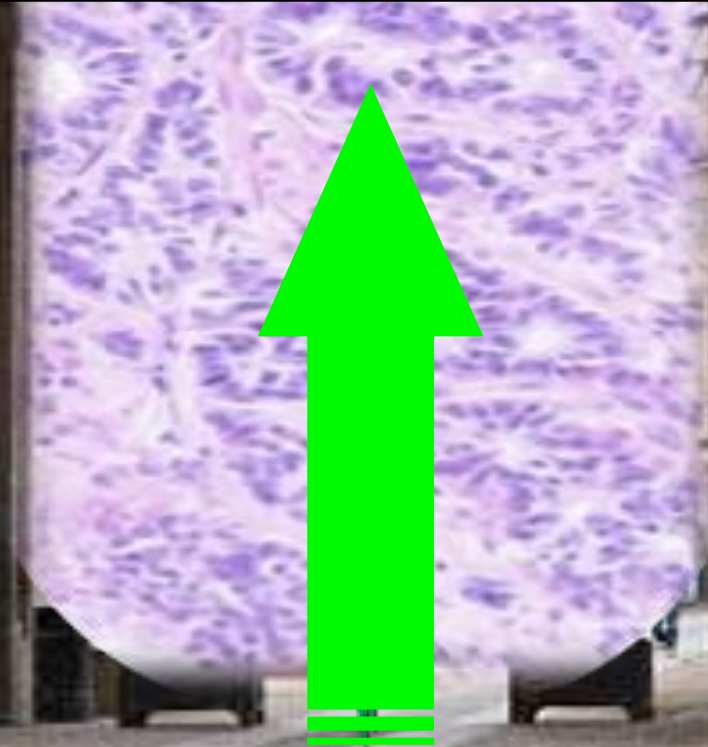
- ✓ TP53 and RB1 inactivation (100%)
- ✓ **NO MEN1 mutations.**

C2: C1+ C3 features (14 ACs+ 8LCNECs)

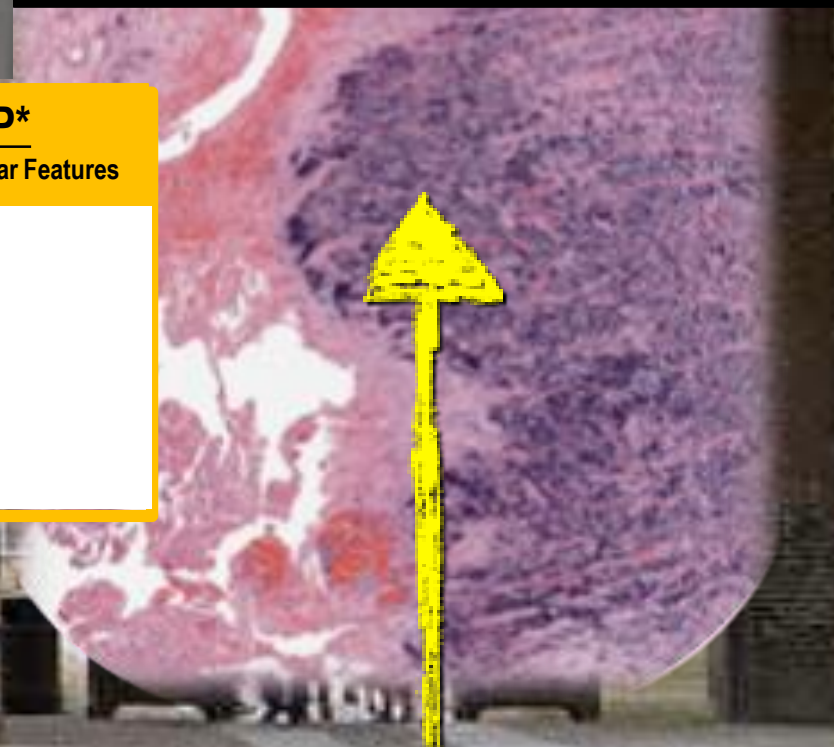
- ✓ TP53 (41%)
- ✓ MEN1 (23%)
- ✓ RB1 (18%)

First leak in the wall?

Well Differentiated Neuroendocrine Neoplasms



Poorly Differentiated Neuroendocrine Carcinomas



CARCINOID GROUP*

LCNEC Morphology + Carcinoid Molecular Features

- ✓ RB1 or TP53: NO
- ✓ STK11 and KRAS: NO
- ✓ MYCL, SOX2:NO
- ✓ FGFR1 :NO
- ✓ **MEN1: YES**

*According to Rekhtman 2016 and Simbolo 2019

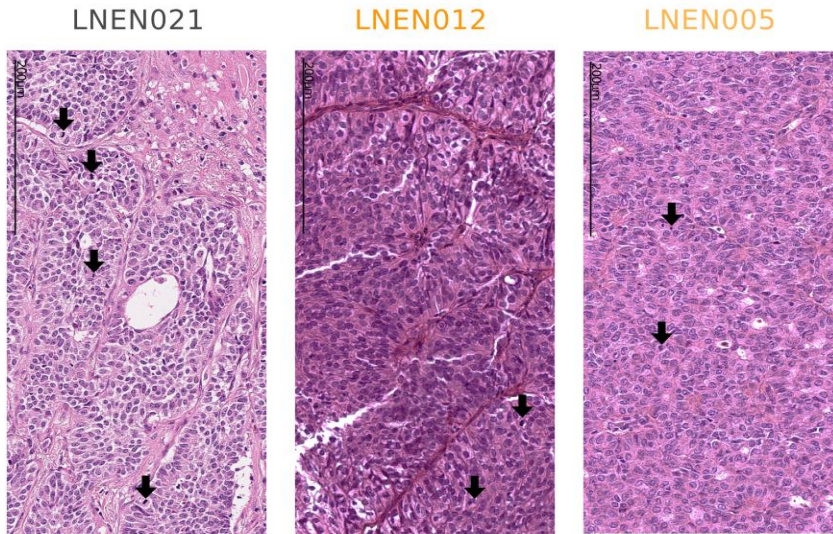
LCNECs + AC: Molecular Landscape

Supracarcinoids

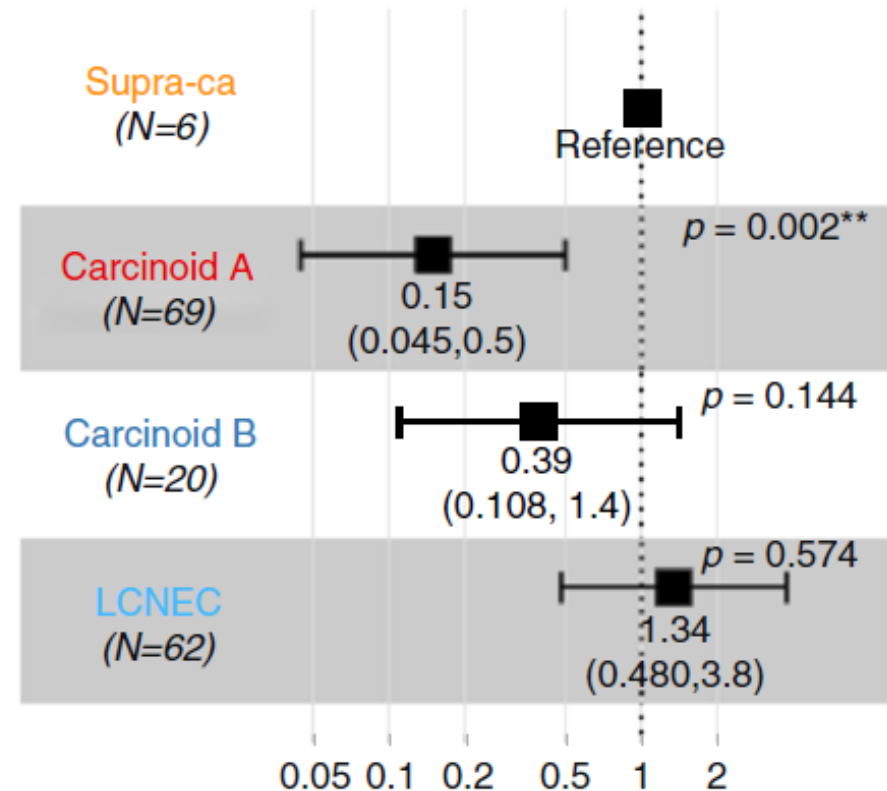
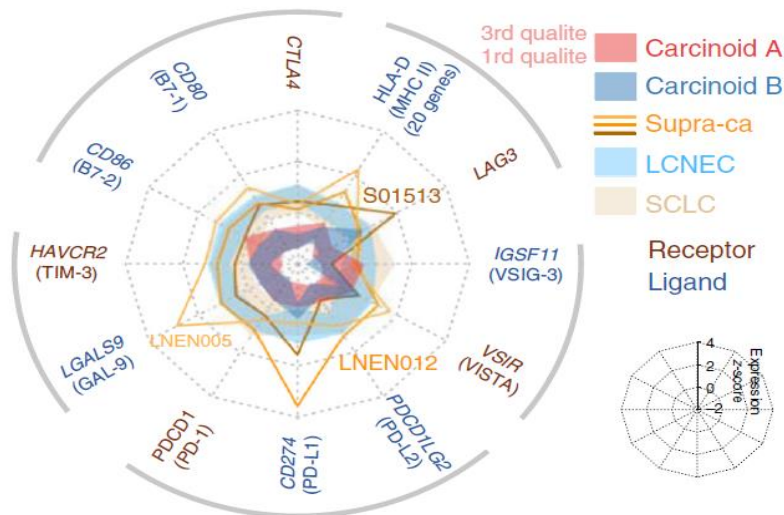
Clear carcinoid morphological pattern

+

Neuroendocrine Carcinoma
molecular characteristics



Alcala N, Fernandez Cuesta L et al, Nature Communications 2019



Alcala N, Fernandez Cuesta L et al, Nature Communications 2019

Second leak in the wall?

*According to Rekhtman 2016 - Simbolo 2019

**Well
Differentiated
Neuroendocrine
Neoplasms**

CARCINOID GROUP*

LCNEC Morphology + Carcinoid Molecular Features

- ✓ RB1 or TP53: NO
- ✓ STK11 and KRAS: NO
- ✓ MYCL, SOX2:NO
- ✓ FGFR1 :NO
- ✓ **MEN1: YES**

**Poorly Differentiated
Neuroendocrine
Carcinomas**

Supracarcinoids#

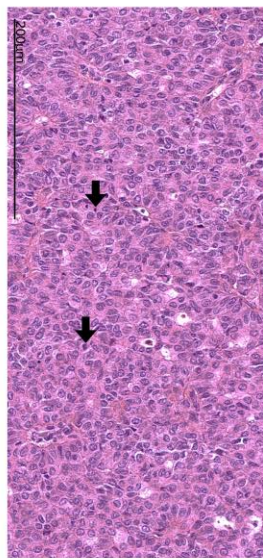
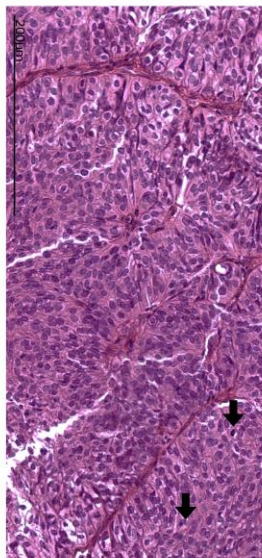
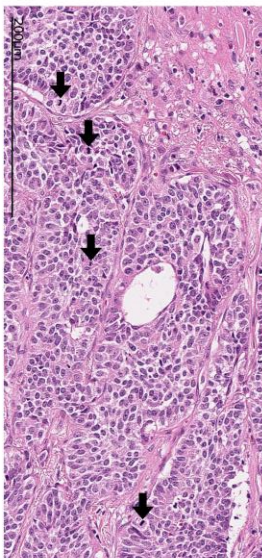
#According to Alkala & Fernandez-Cuesta 2019

Supracarcinoids

LNEN021

LNEN012

LNEN005

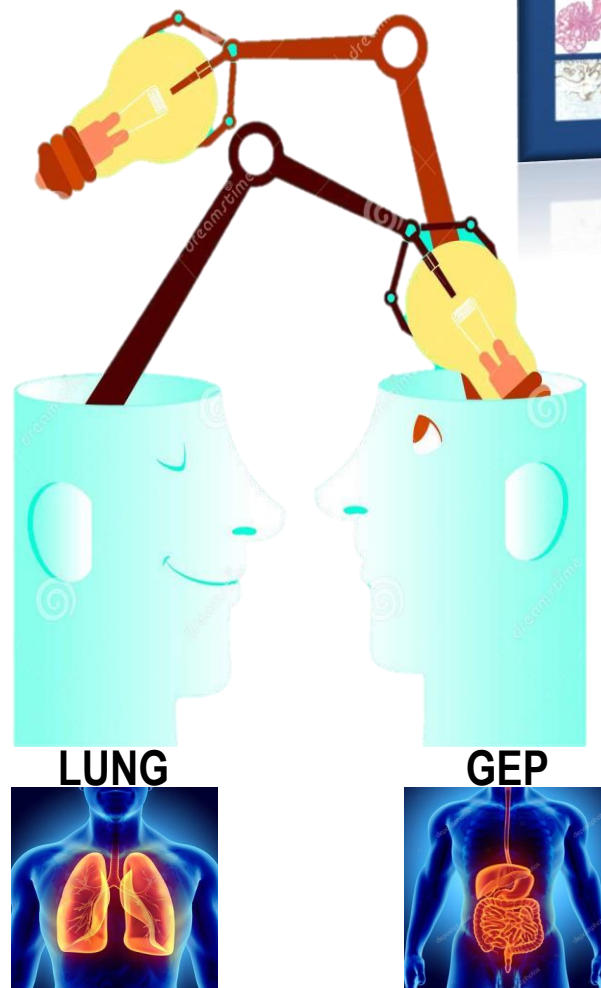


Alcala N, Fernandez Cuesta L et al, Nature Communications 2019

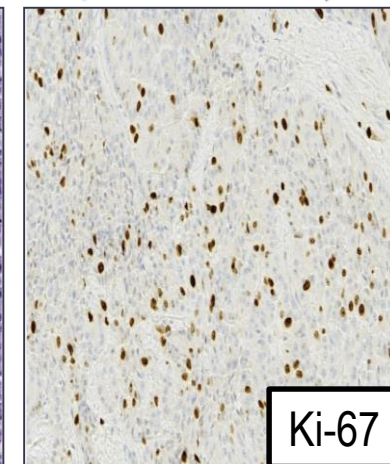
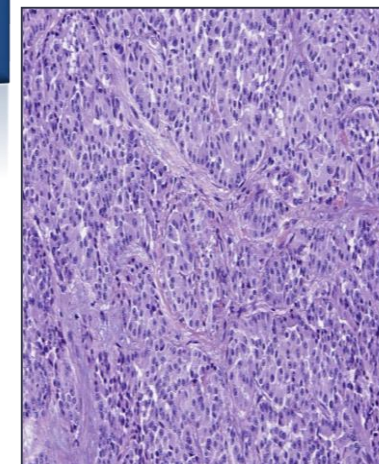
**Clear carcinoid
(Well Differentiated
Morphology)**

+

**Neuroendocrine Carcinomas
molecular characteristics**



NET G3



**Clear NET
(Well Differentiated
Morphology)**

+

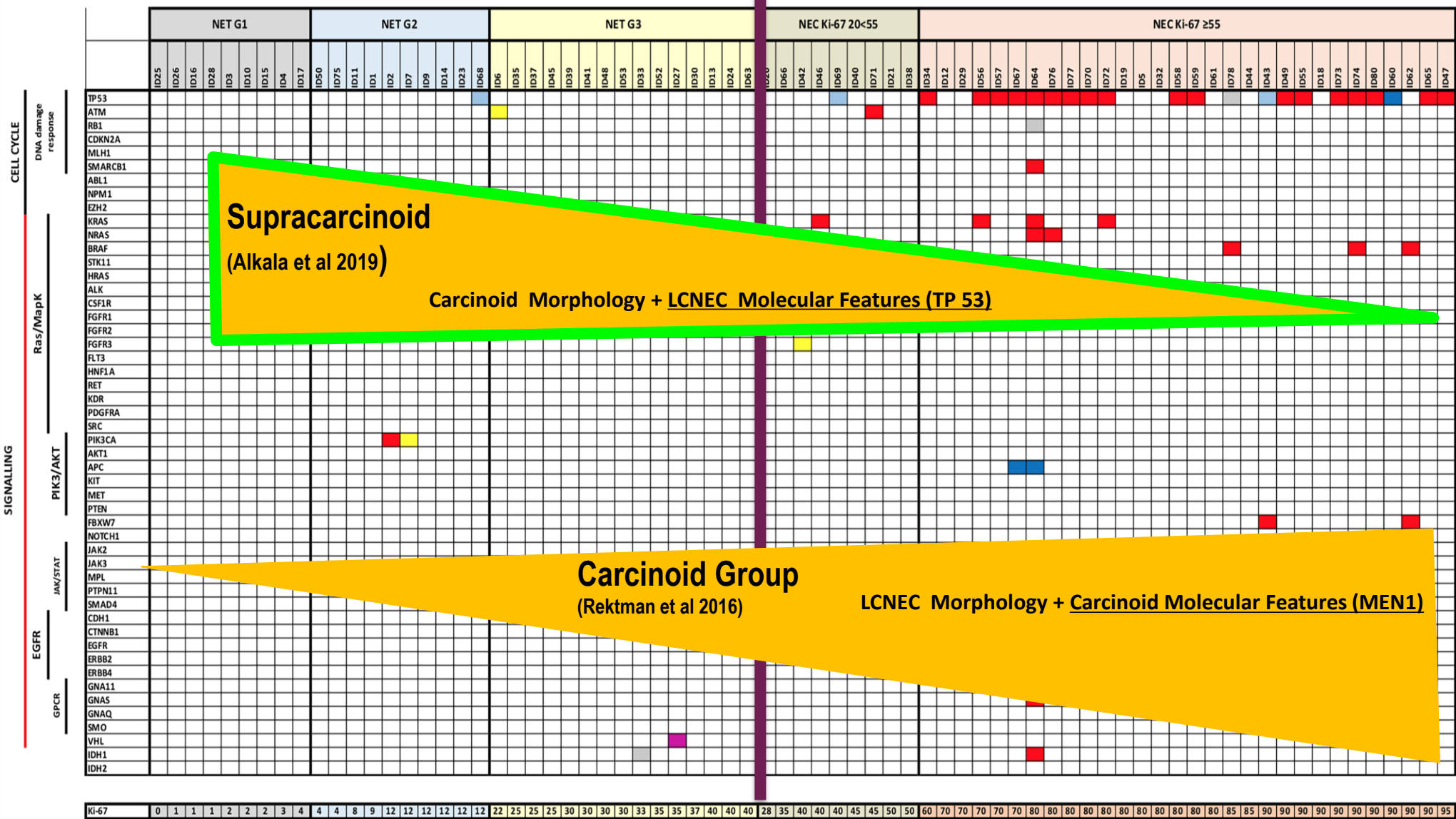
Ki-67 > 20%
(as in GEP Poorly Differentiated
Carcinomas)

ESMO

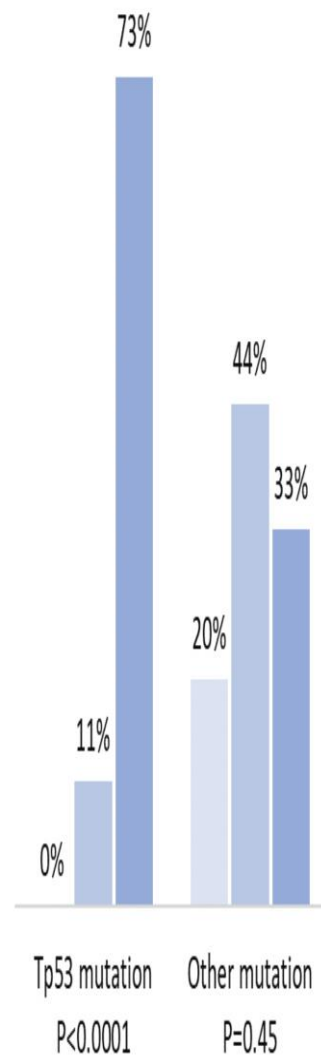
GEP NENs Molecular Landscape

Well Differentiated

Poorly Differentiated



NET G3 NEC<55 NEC≥55



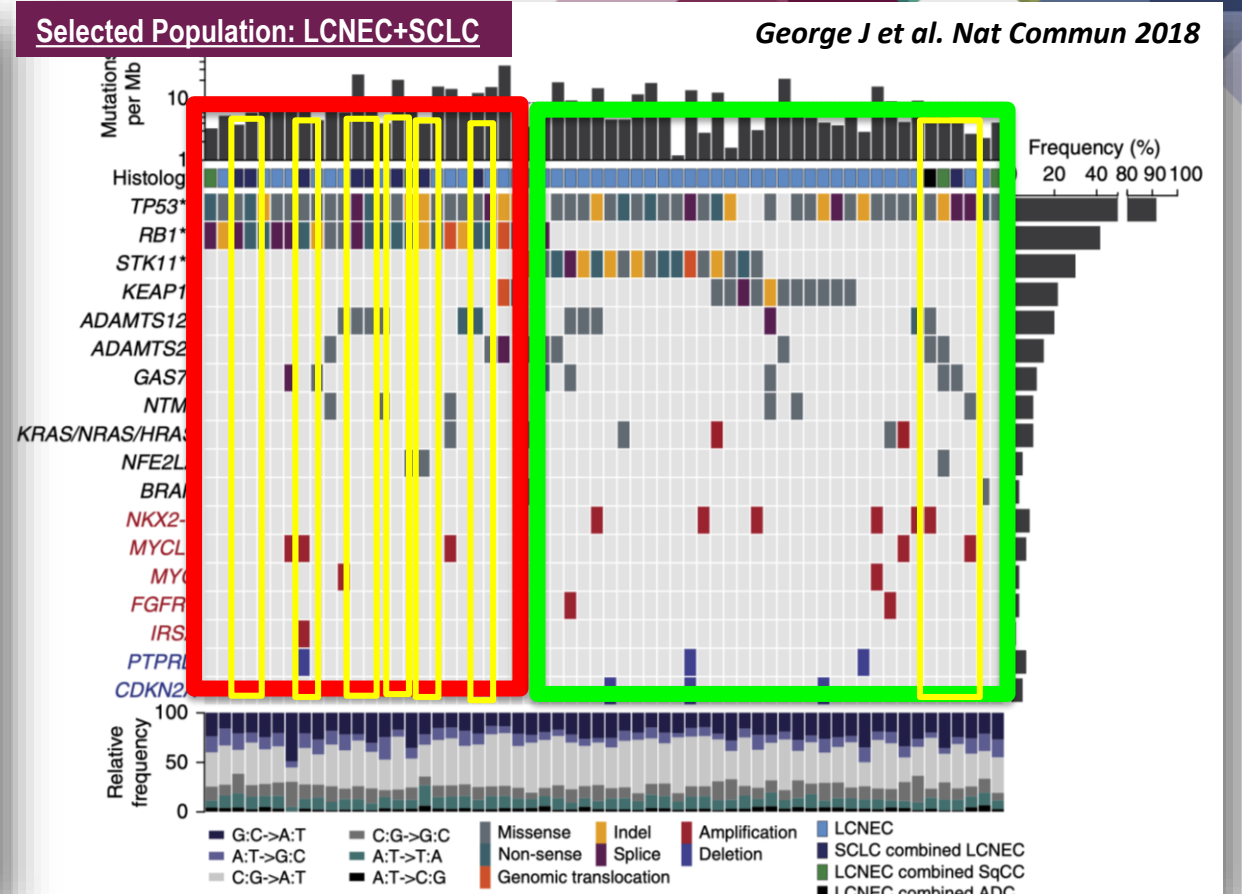
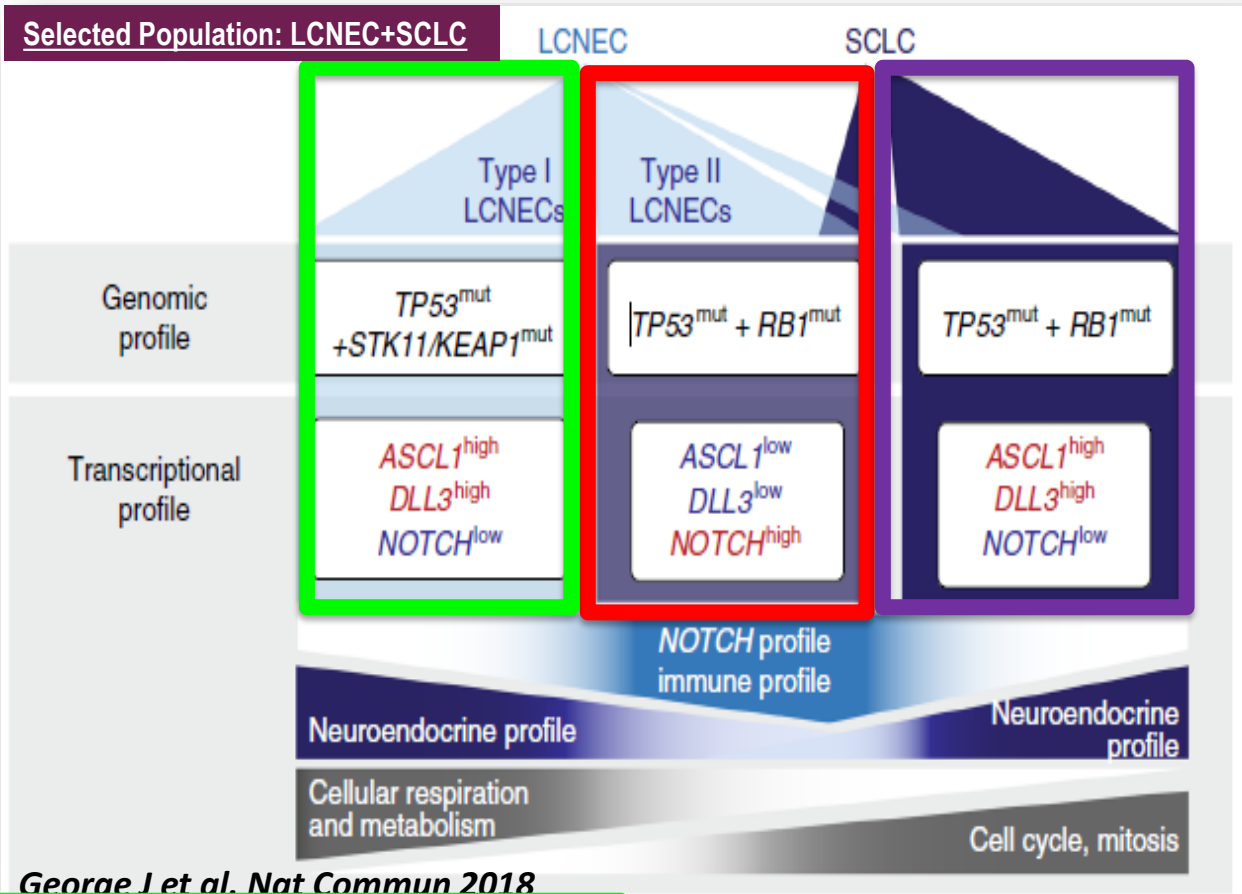
**Well Differentiated
Neuroendocrine
Neoplasms**

**Poorly Differentiated
Neuroendocrine
Carcinomas**

NO leaks in the GEP-NEN wall !!!!



Carcinomas (LCNECs + SCLC) Molecular Landscape



NSCLS GROUP/LCNEC I

LCNEC Morphology + SCLC/ADK Molecular Features

- ✓ RB1 or TP53: YES
- ✓ STK11 and KRAS: YES
- ✓ MYCL, SOX2:NO
- ✓ FGFR1 :NO
- ✓ MEN1: NO

SCLC GROUP/LCNEC II

LCNEC Morphology + SCLC Molecular Features

- ✓ RB1+TP53: YES
- ✓ STK11 and KRAS: NO
- ✓ MYCL, SOX2:YES
- ✓ FGFR1:YES
- ✓ MEN1:NO

Combined LCNEC

LCNEC /ADK Morphology + LCNEC / ADK Molecular Features

- ✓ RB1 or TP53: YES
- ✓ STK11 and KRAS: YES
- ✓ MYCL, SOX2: YES/NO
- ✓ FGFR1 :NO
- ✓ MEN1: NO

(PURE)SCLC GROUP

SCLC Morphology + SCLC Molecular Features

- ✓ RB1+TP53: YES
- ✓ STK11 and KRAS: NO
- ✓ MYCL, SOX2:YES
- ✓ FGFR1:YES
- ✓ MEN1:NO

ESMO

Milione M, ESMO 2020 Barcelona

**LARGE CELLS
CARCINOMA**

**TYPICAL
CARCINOID**

Carcinoid Group

(Rektman et al 2016)

LCNEC Morphology +
Carcinoid Molecular Features

NSCLS GROUP/LCNEC I

LCNEC Morphology + SCLC/ADK Molecular Features

SCLC GROUP/LCNEC II

LCNEC Morphology + SCLC Molecular Features

ADENOCARCINOMA

(PURE) SCLC GROUP

SCLC Morphology + SCLC Molecular Features

**ATYPICAL
CARCINOID**

Supracarcinoid

(Alkala et al 2019)

Carcinoid Morphology + LCNEC Molecular Features

Combined LCNEC

LCNEC /ADK Morphology

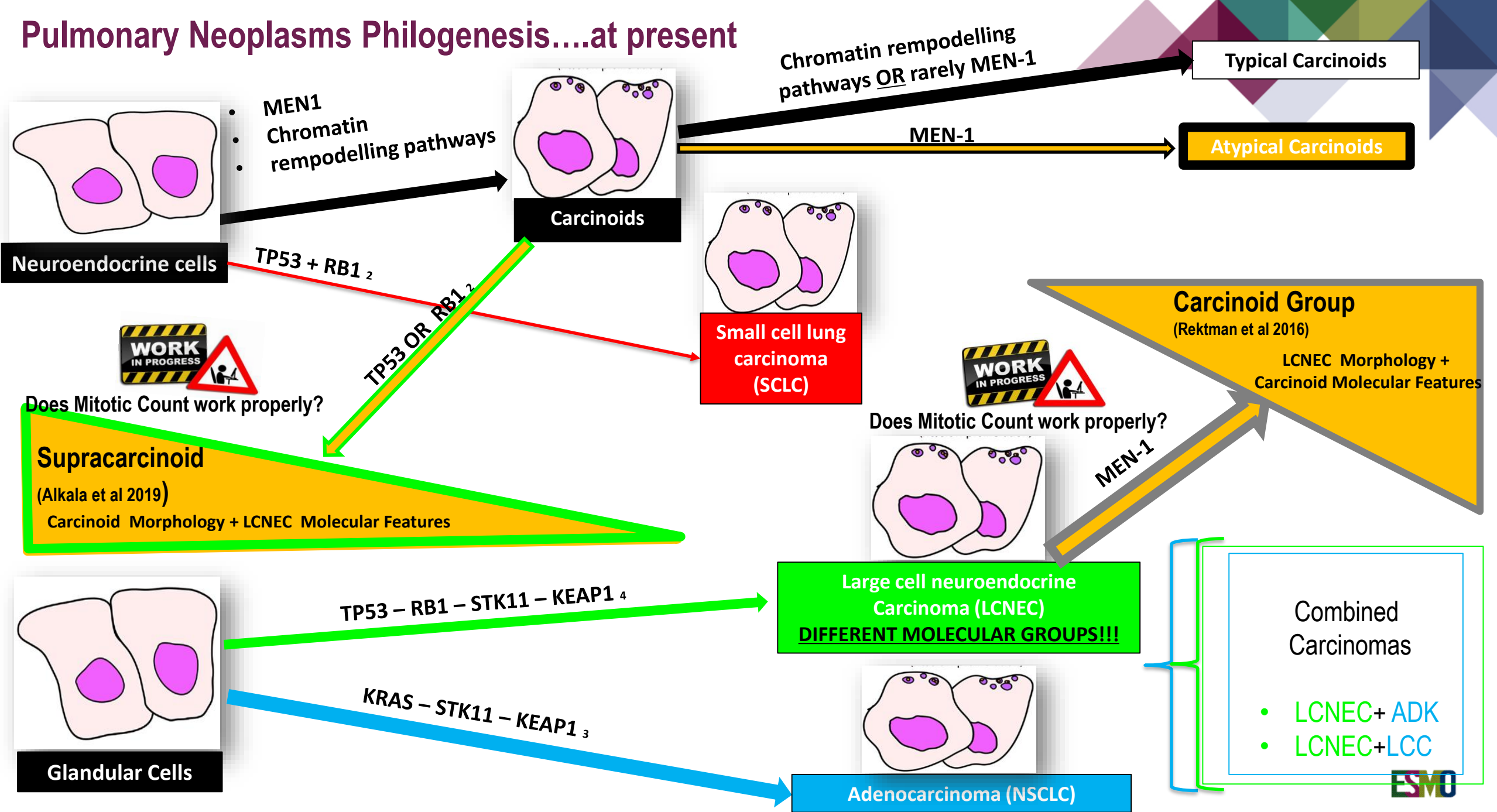
+

LCNEC / ADK Molecular Features

**SMALL CELLS
CARCINOMA**



Pulmonary Neoplasms Philogenesis....at present



1: Fernandez-Cuesta L et al. Frequent mutations in chromatin-remodelling genes in pulmonary carcinoids. Nat Commun. 2014;5:3518.2: George, J. et al. Comprehensive genomic profiles of small cell lung cancer. Nature 524, 47-53 (2015). 3: Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014; 511(7511):543-50. 4: George, J. et al. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors Nat. Commun DOI: 10.1038/s41467-018-03099-x

Take Home Messages



- ✓ Lung Neuroendocrine Neoplasms WHO 2015 categories need urgent refinement
- ✓ Molecular studies properly dissected the WHO 2015 classical Carcinoid and Carcinoma categories, suggesting that Lung Neuroendocrine Neoplasms are more heterogenous than expected

New Molecular Categories will pave the way for new Therapies?



Thank you

Massimo Milione