Genetic Abnormalities and Active Targets in Esophageal Cancer

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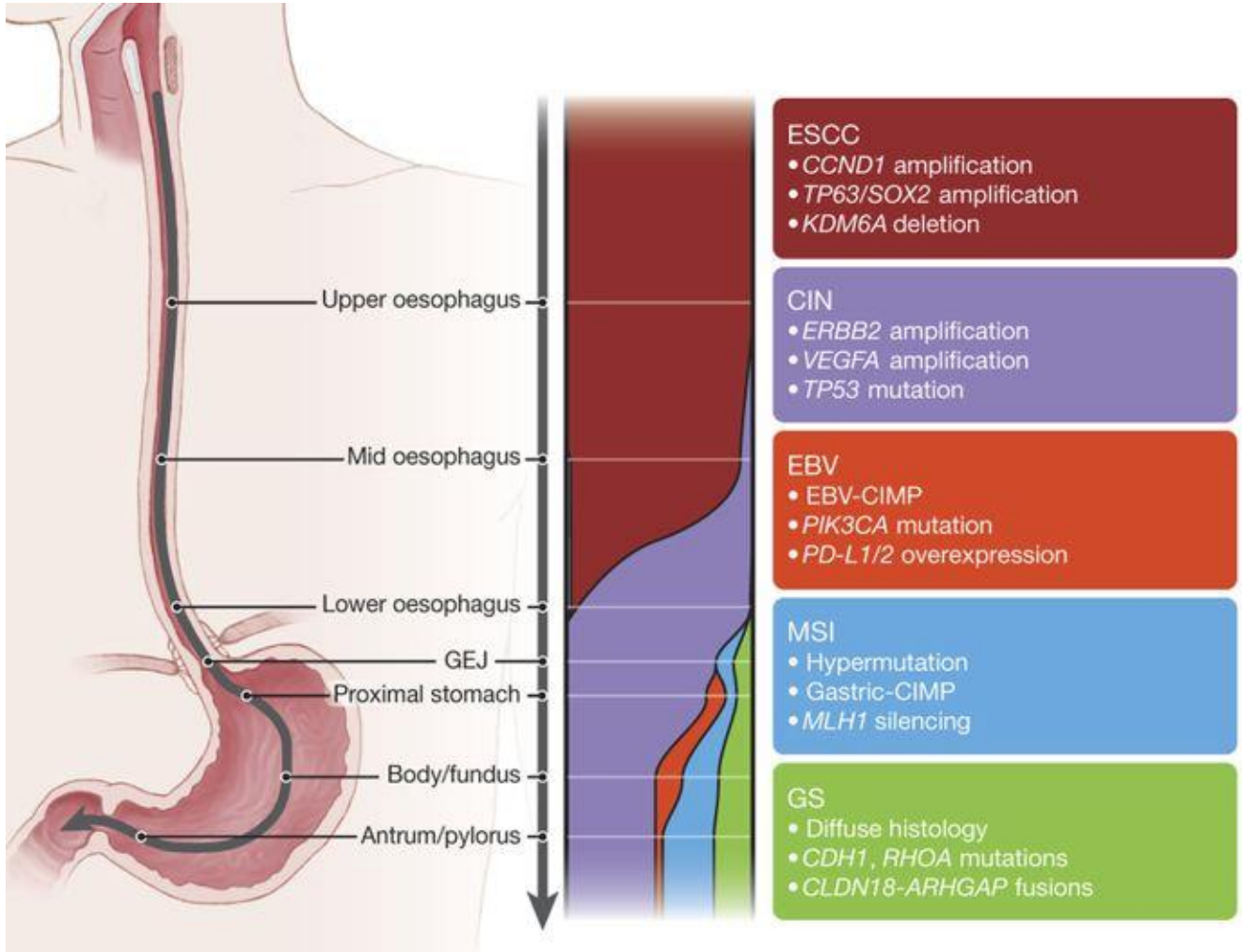
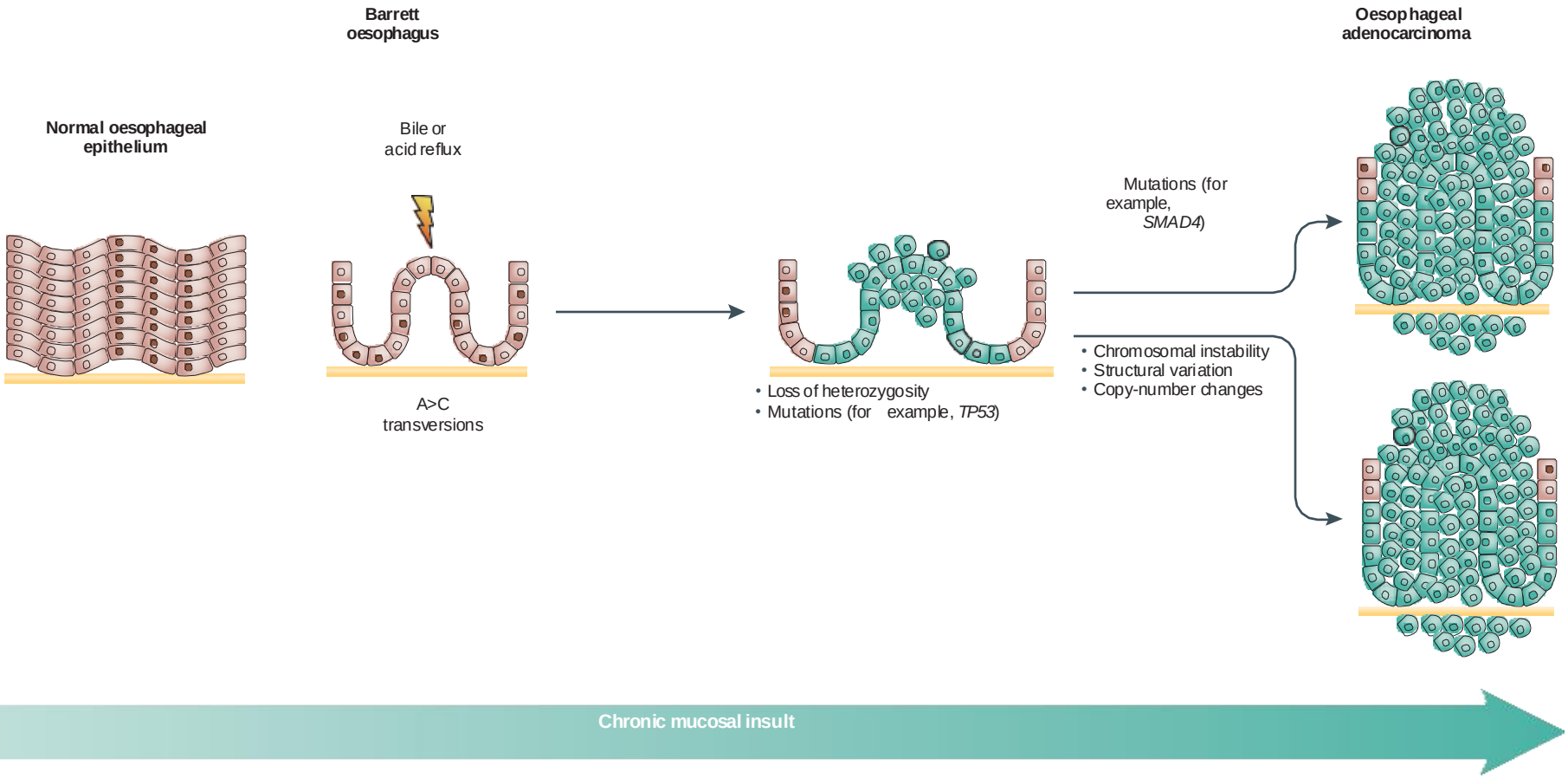
Upper GI Cancer Molecular Subtypes



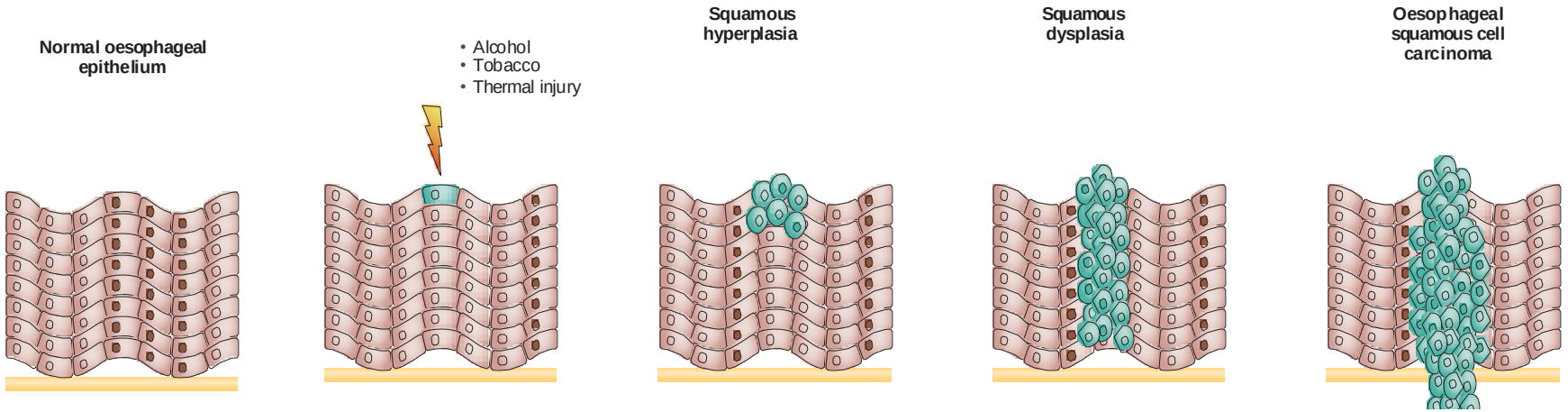
The Cancer Genome Atlas Research Network.
Nature, 2017. 541: 69–175

Pathogenesis of Esophageal Adenocarcinoma



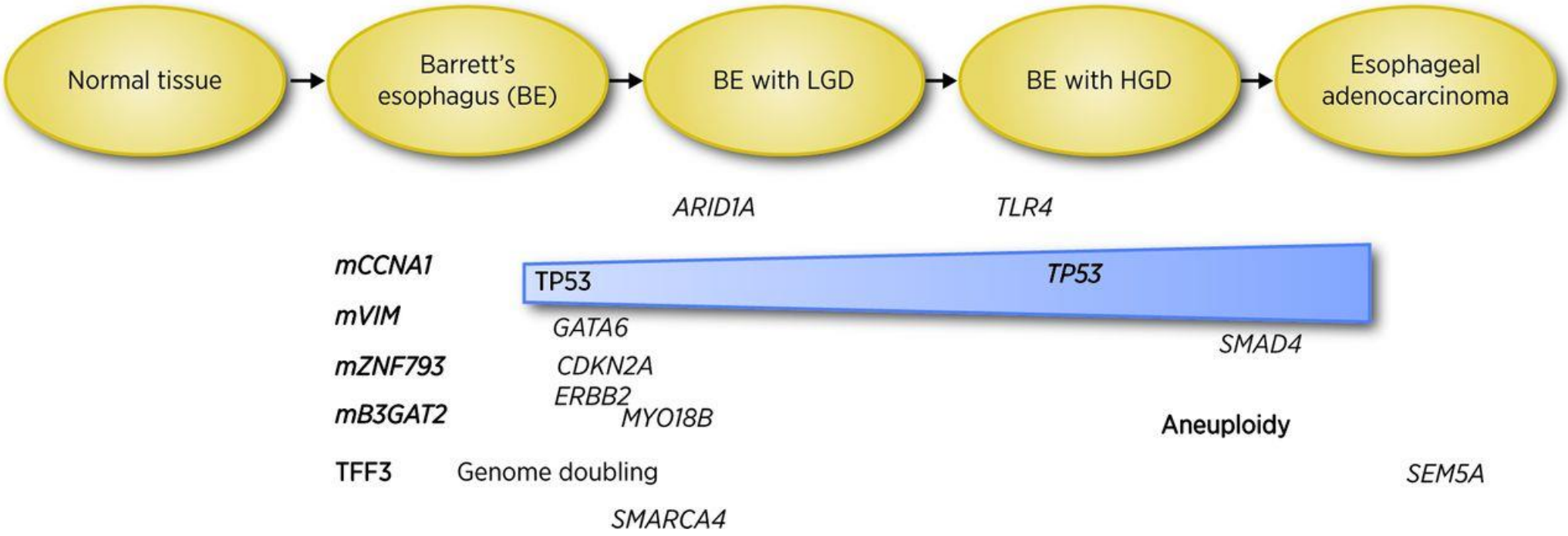
Smythe 2017
Nat. Rev. Dis. Primers

Pathogenesis of Esophageal Squamous Cell Cancer



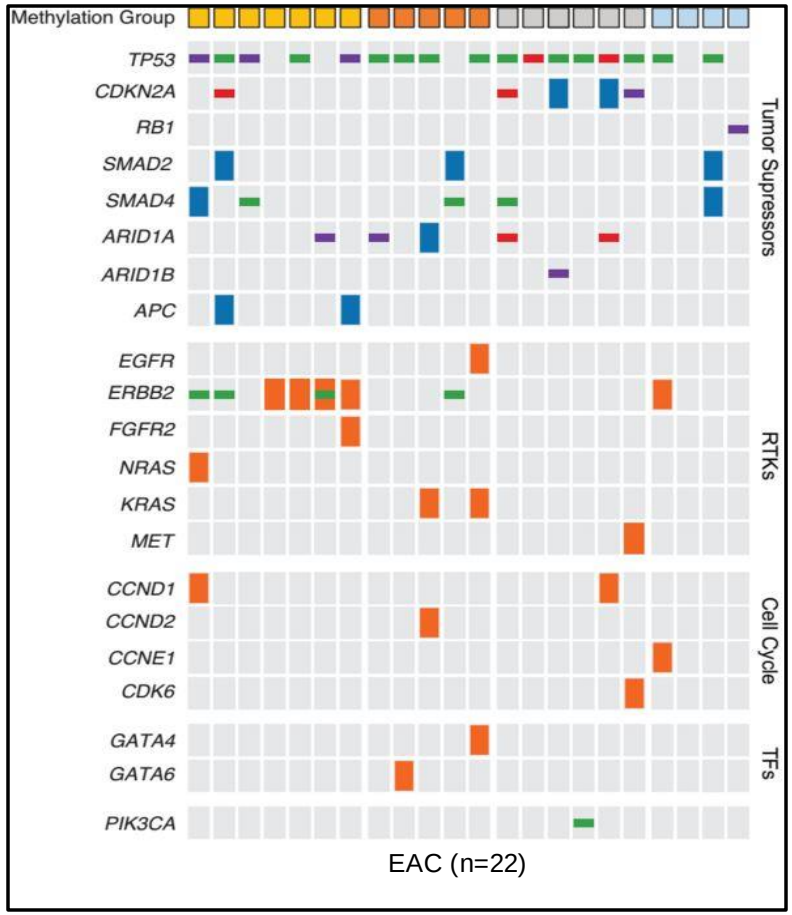
Smythe 2017
Nat. Rev. Dis. Primers

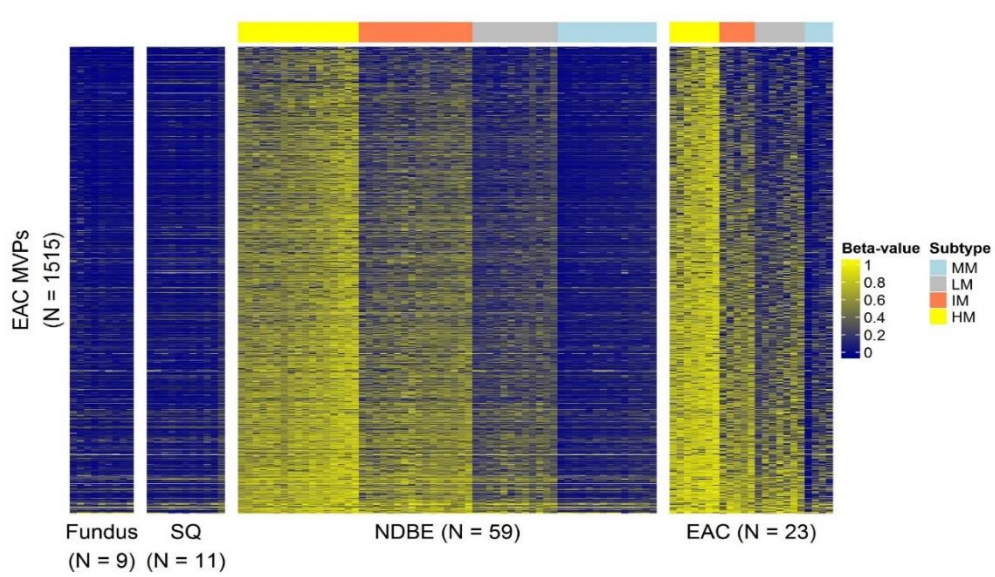
Barrett's Esophagus (BE)→ EAC: Molecular Sequence

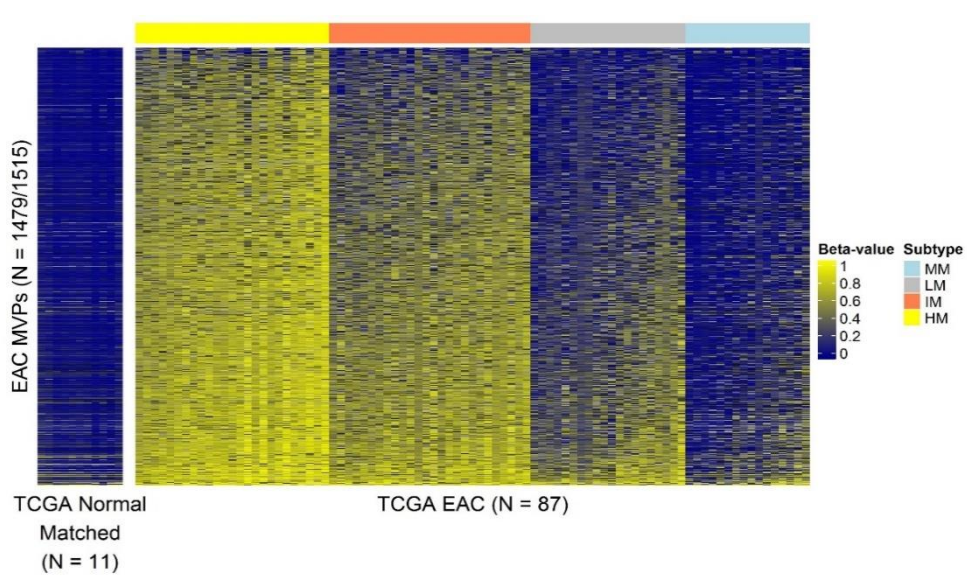


Cancer Epidemiol Biomarkers Prev. 2020;29(12) -20-0223

BE→ EAC: Molecular Landscape

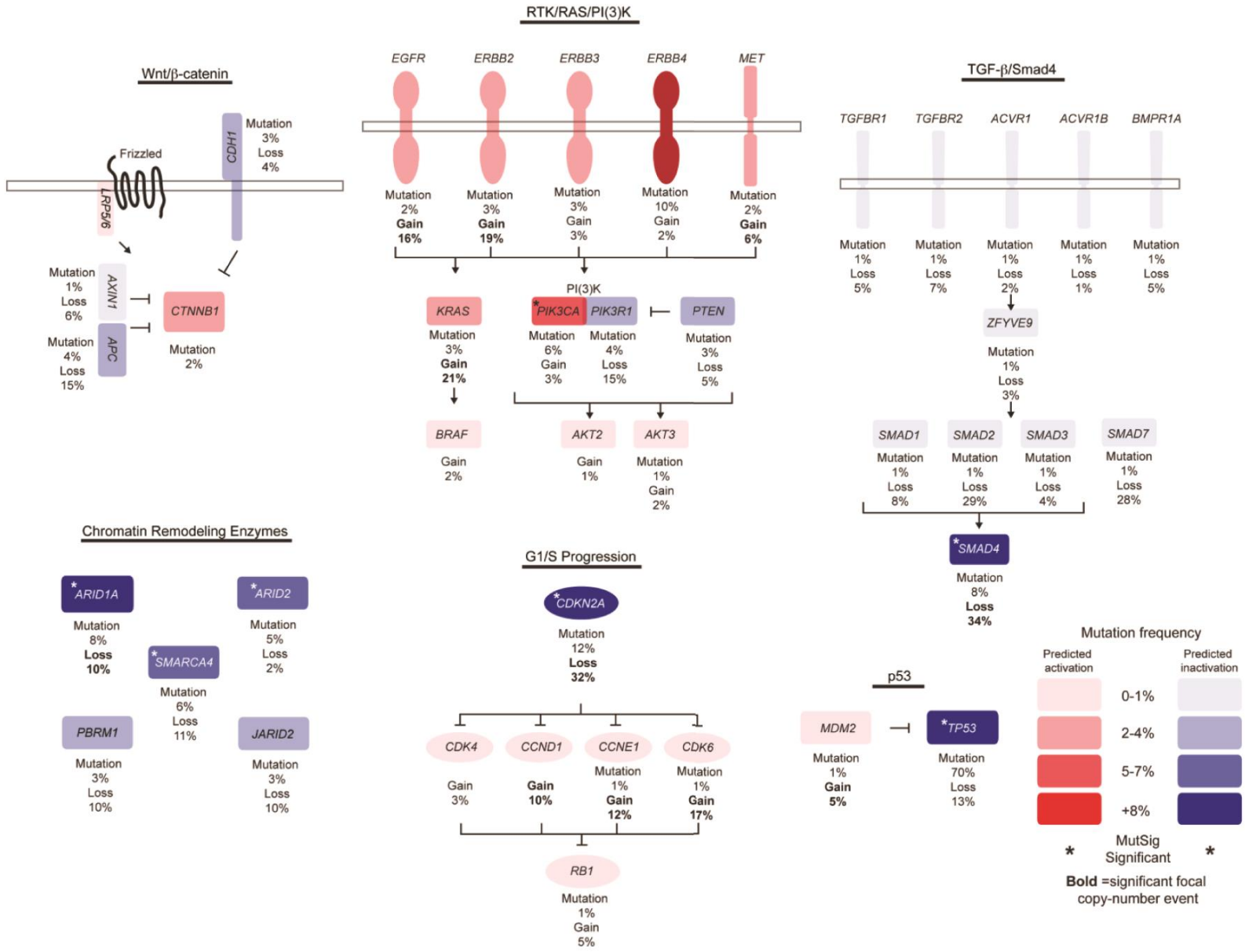






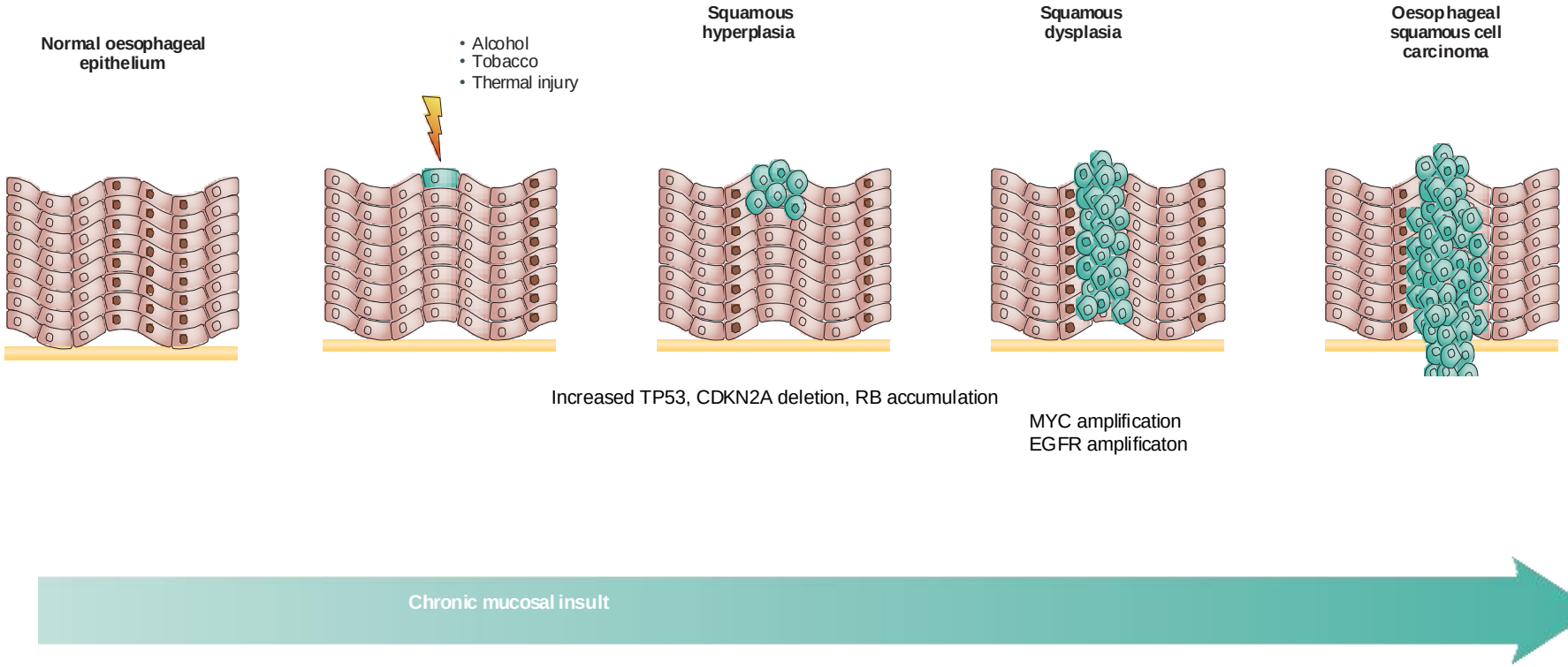
Yu, Gut 2018

EAC: Landscape of mutations



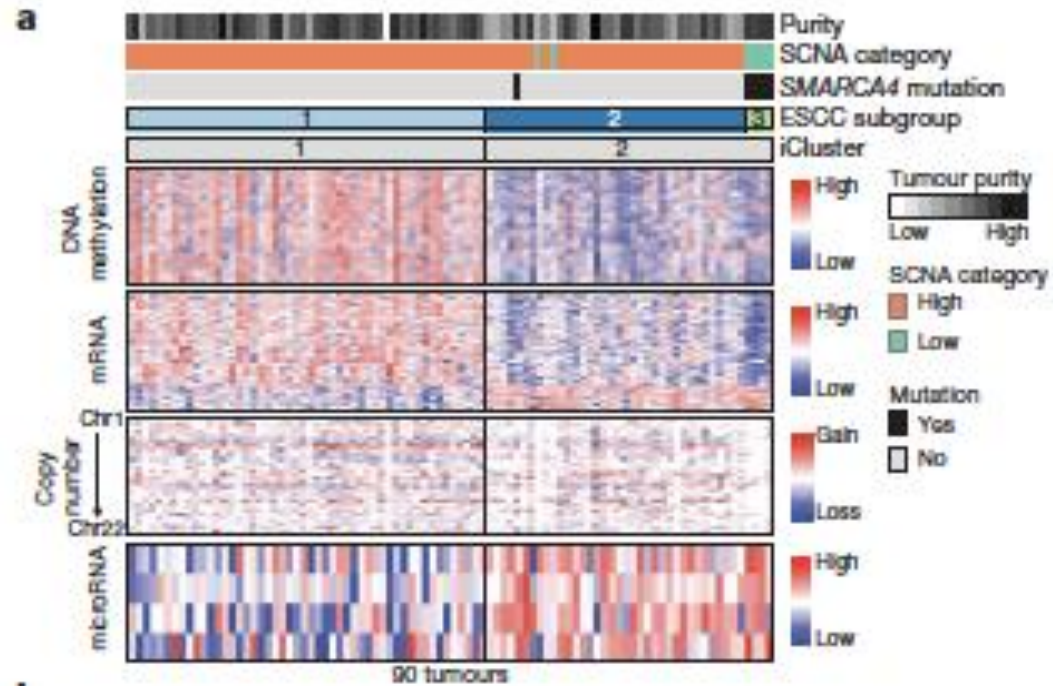
Kaz, 2015

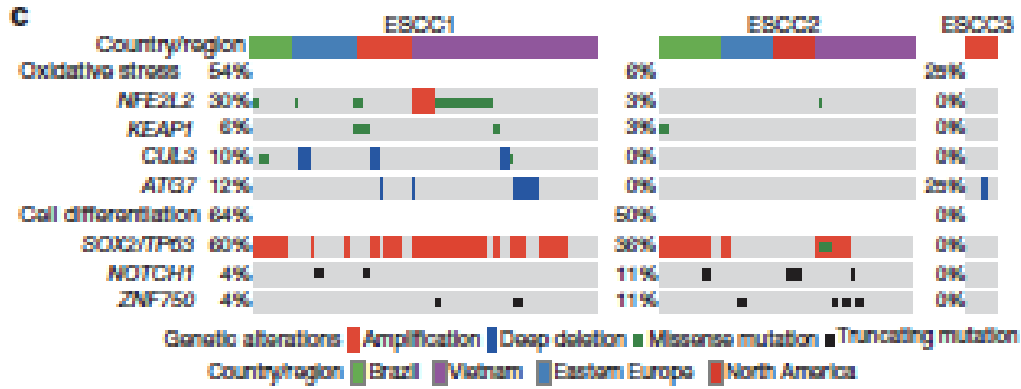
Pathogenesis of Esophageal Squamous Cell Cancer



Smythe 2017
Nat. Rev. Dis. Primers

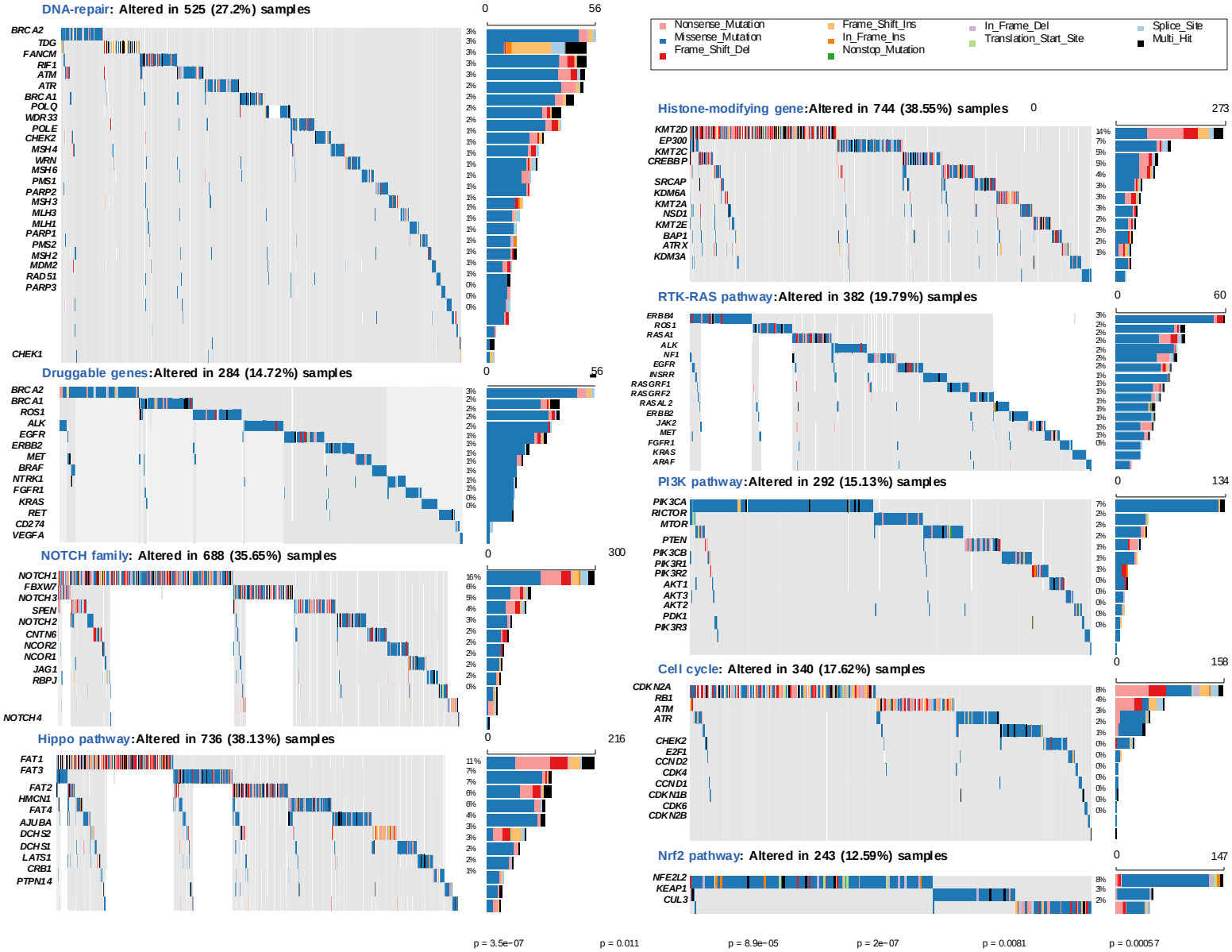
Distinct Molecular Subtypes of ESCC





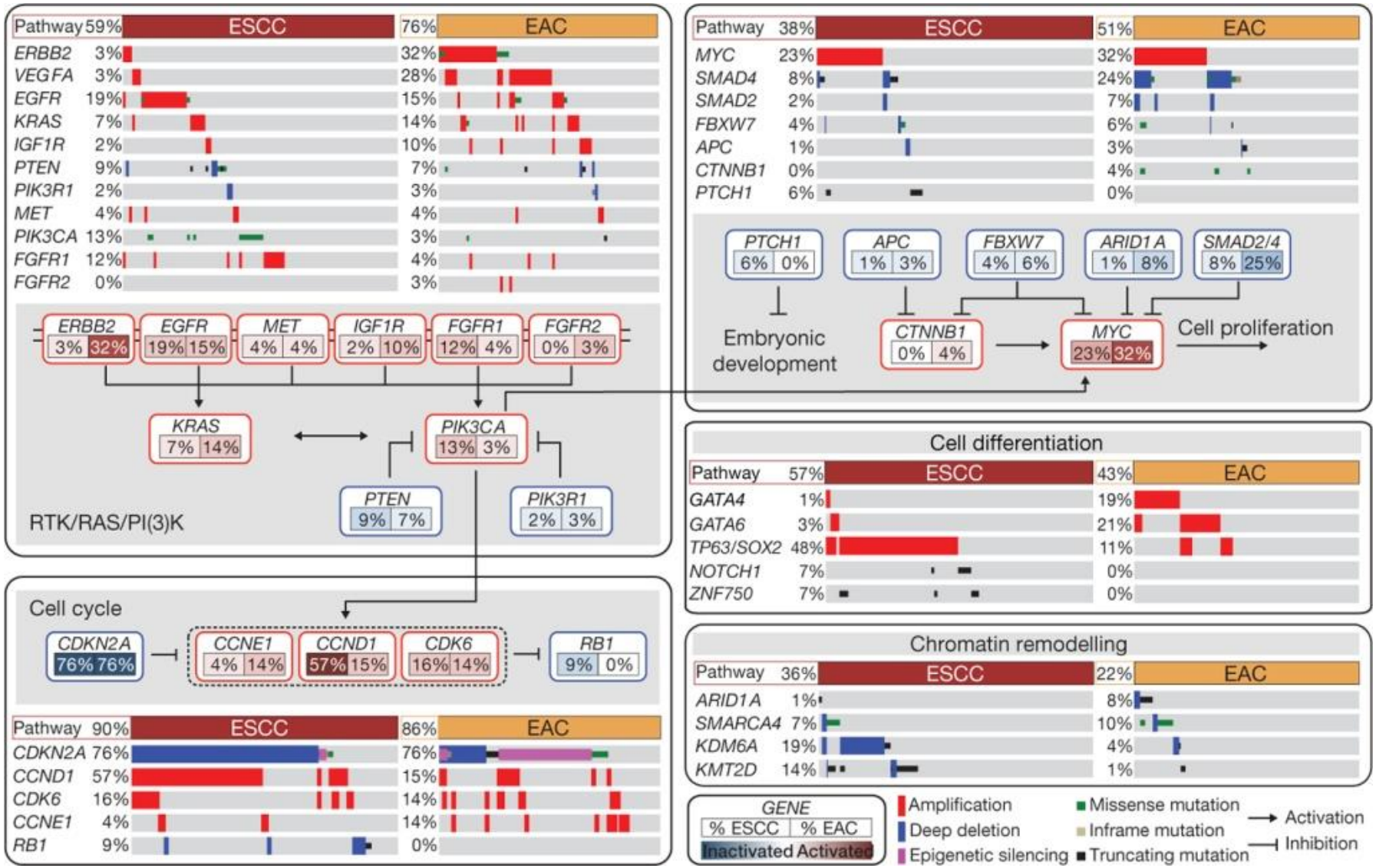
TCGA,
Nature 2017

ESCC: Landscape of Mutations by Target Class



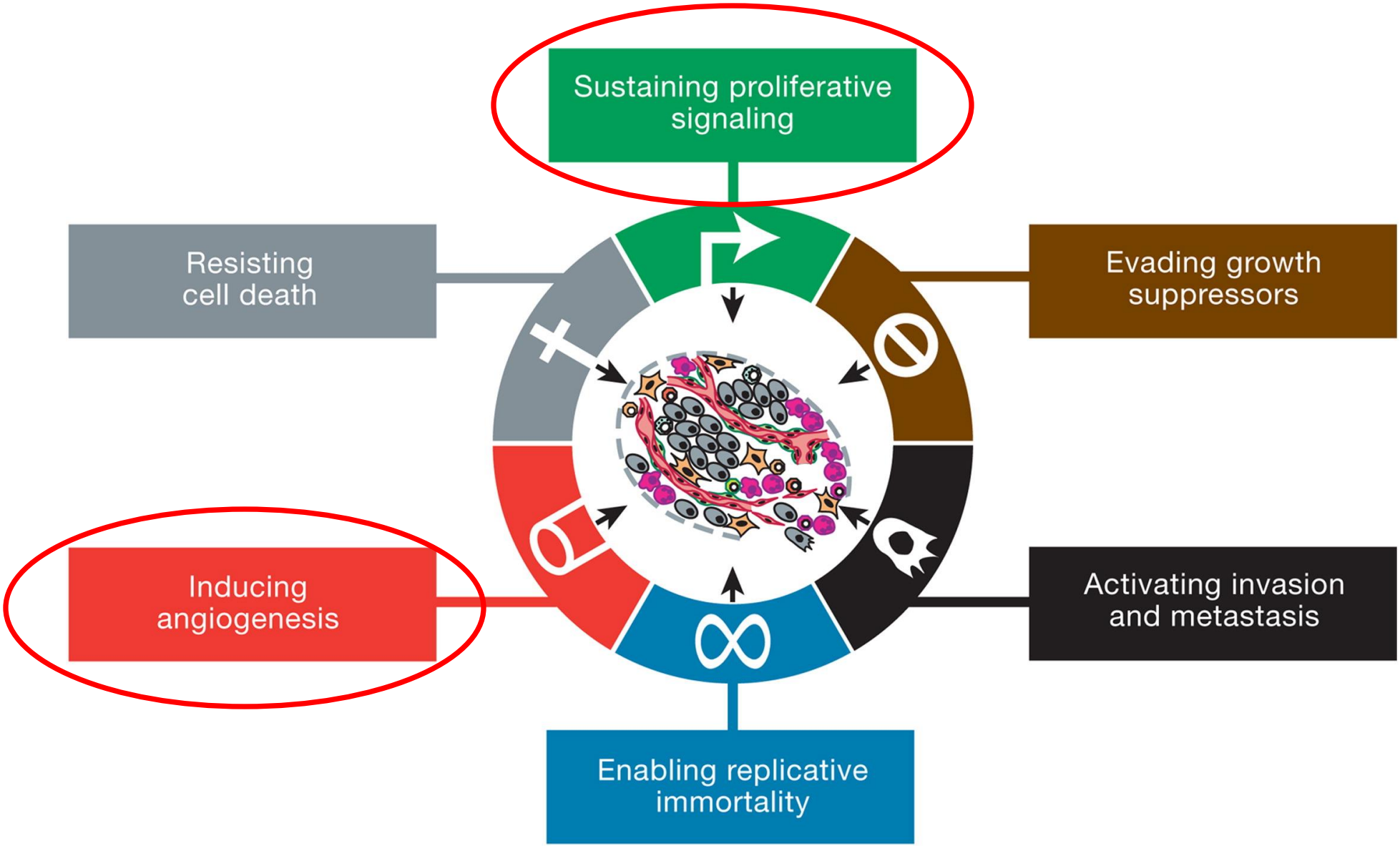
Li Nature Communications 2022

Integrated Molecular Comparison: ESCC vs EAC



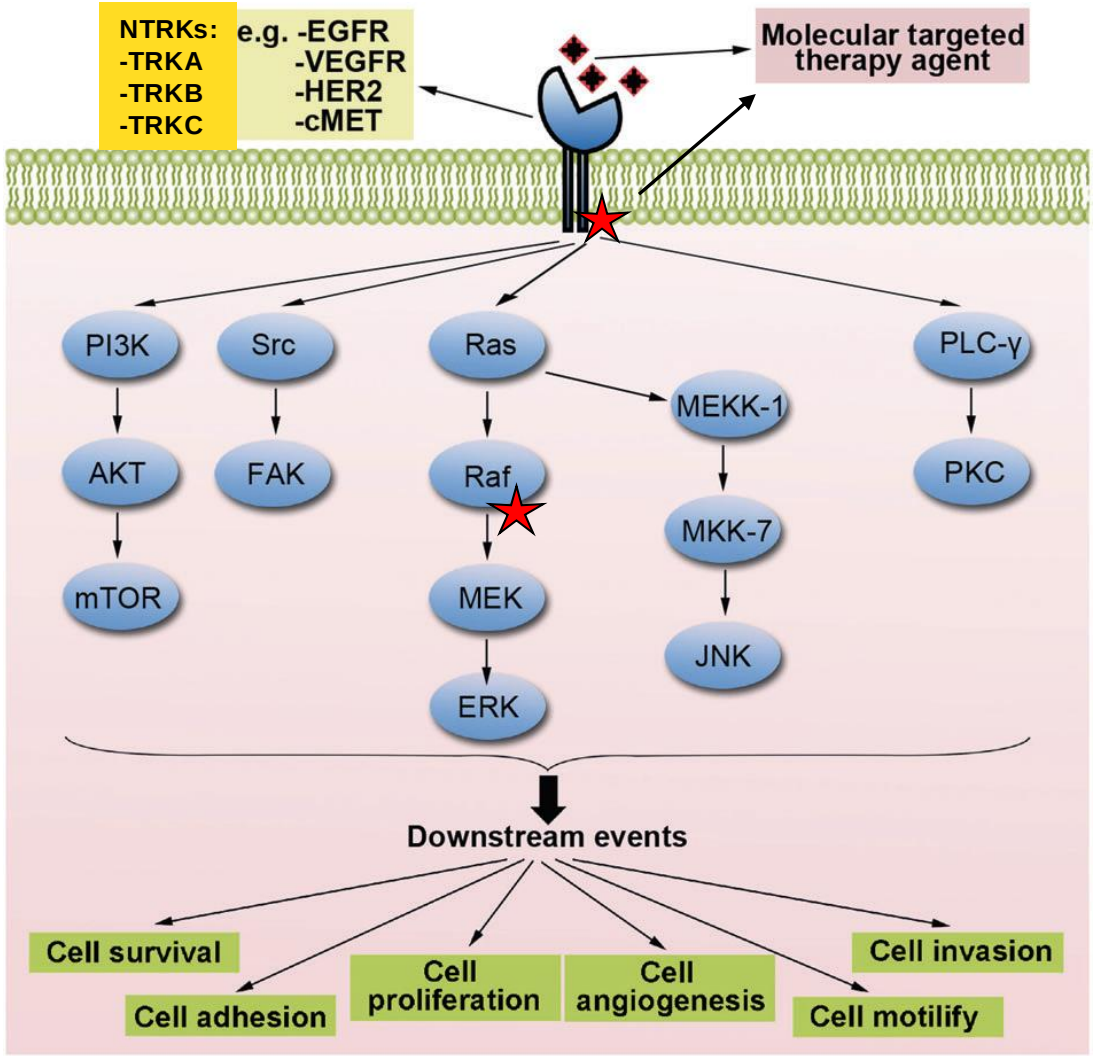
J Kim *et al. Nature* 1–9 (2017)

Hallmarks of Cancer-version 1.0



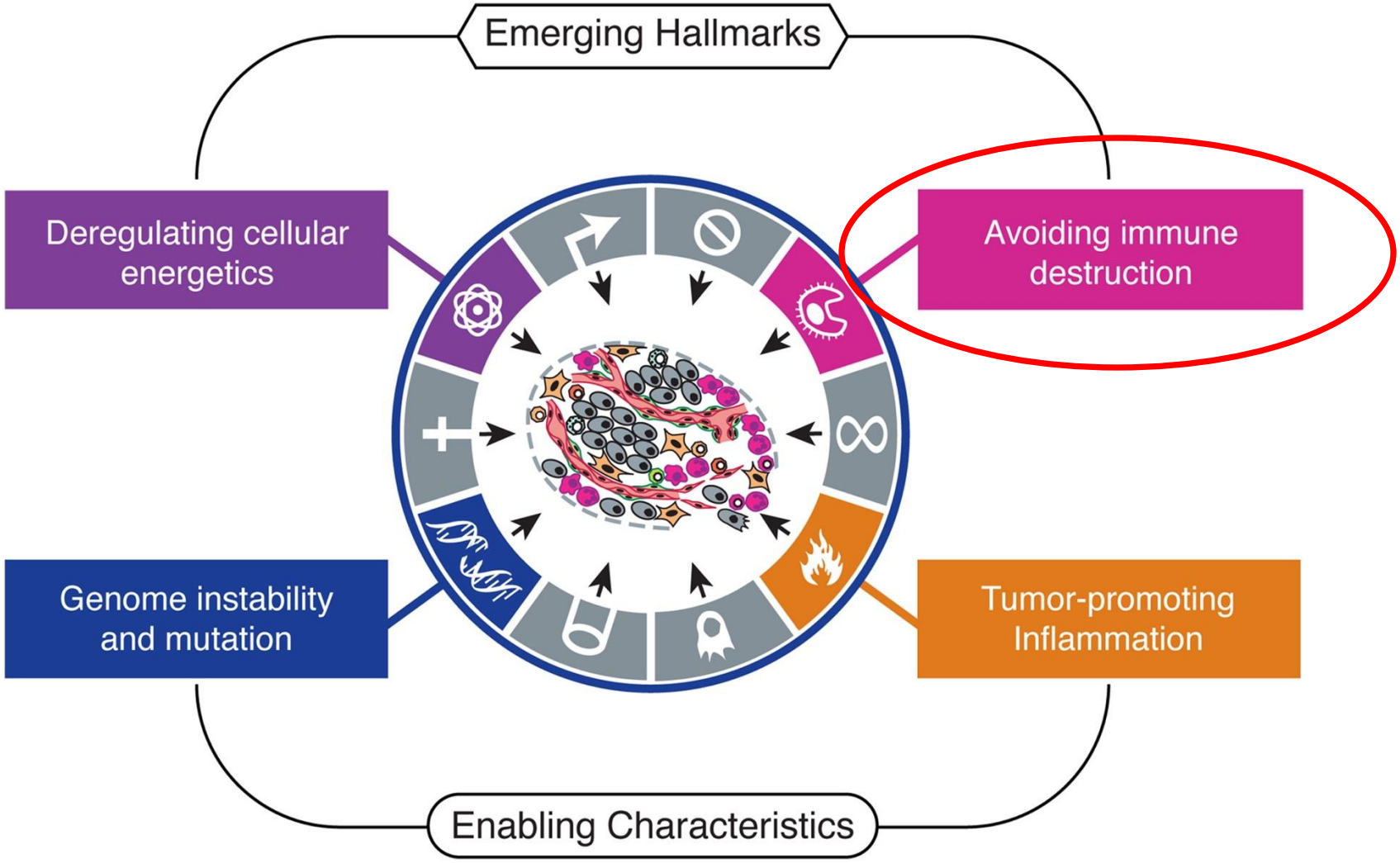
Hanahan and Weinberg, 2011

MAPK and PIK3CA Pathways: EGF, HER2, VEGF, NTRK



Yang, 2020

Hallmarks of Cancer: version 2.0



Hanahan and Weinberg, 2011

ECA Immune Landscape

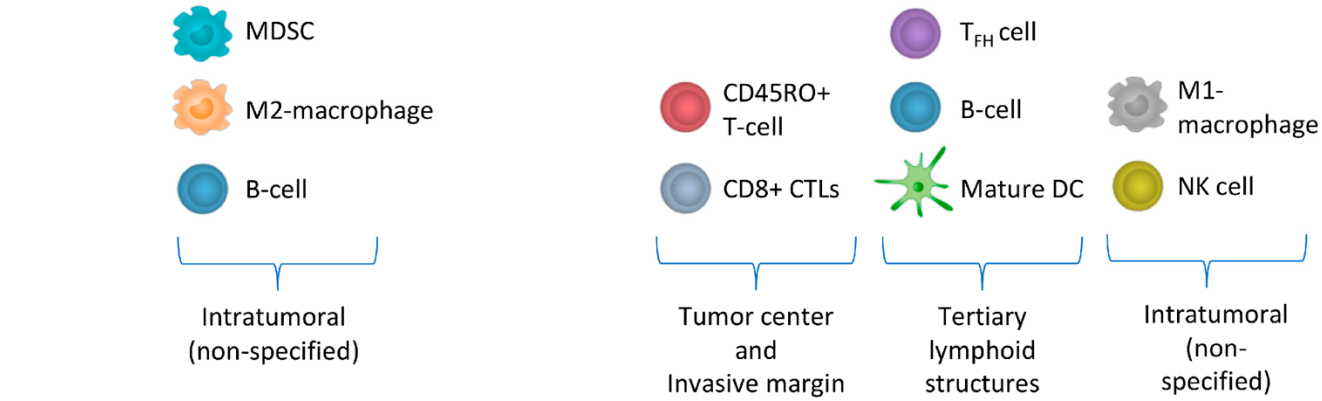
- Immunosurveillance has a central anti-cancer role and is mediated by innate immune cells (NK cells, macrophages, etc) and adaptive immune cells (T cells, B cells, etc).

- Most cancers develop immunoevasion and immunosupression mechanisms, like PD-1 activation.

- Immunotherapy is having success in the clinic, with the most substantial success with immune checkpoint blockade inhibition.

EAC Immune Cells: The players

- **Type**
- **Location**
- **Density**
- **Functional molecular orientation**



Pro-tumorigenic inflammation

↑ myeloid chemokines

↑ immune suppressive molecules

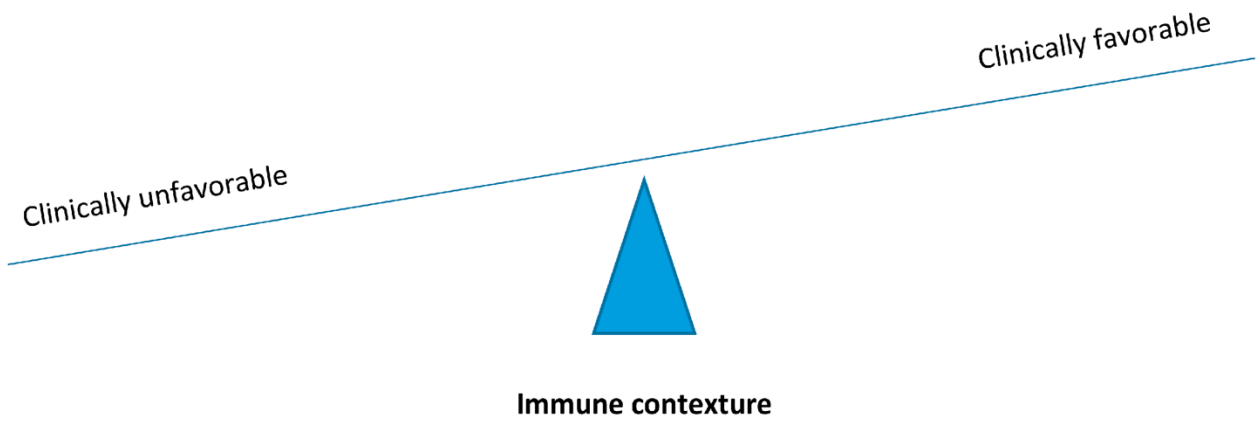
↑ complement factors

Immunologic Constant of Rejection

↑ Th_1 cytokines (CXCL9, CXCL10)

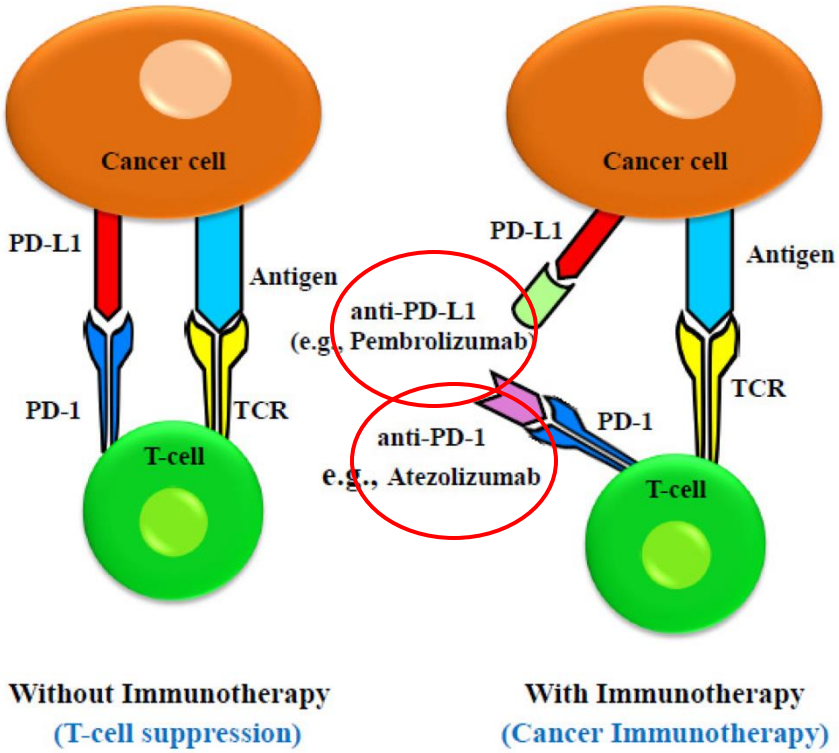
↑ Th_1 signaling

↑ Cytotoxic effector molecules

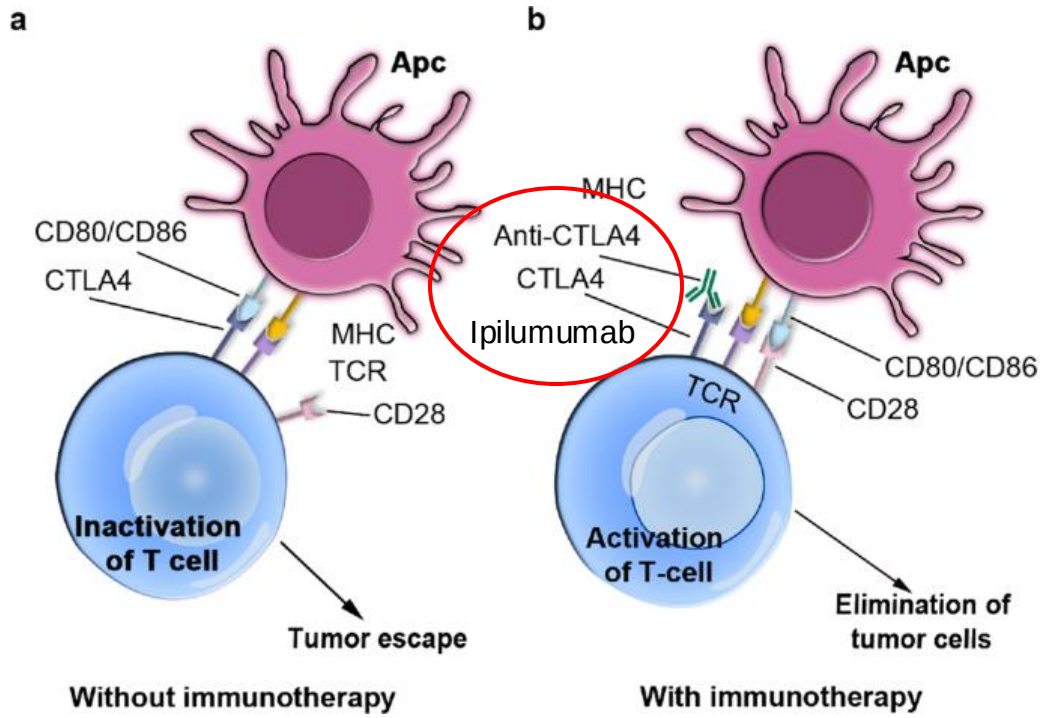


Immunotherapies for Esophageal Cancer

PD-1 and PD-L1

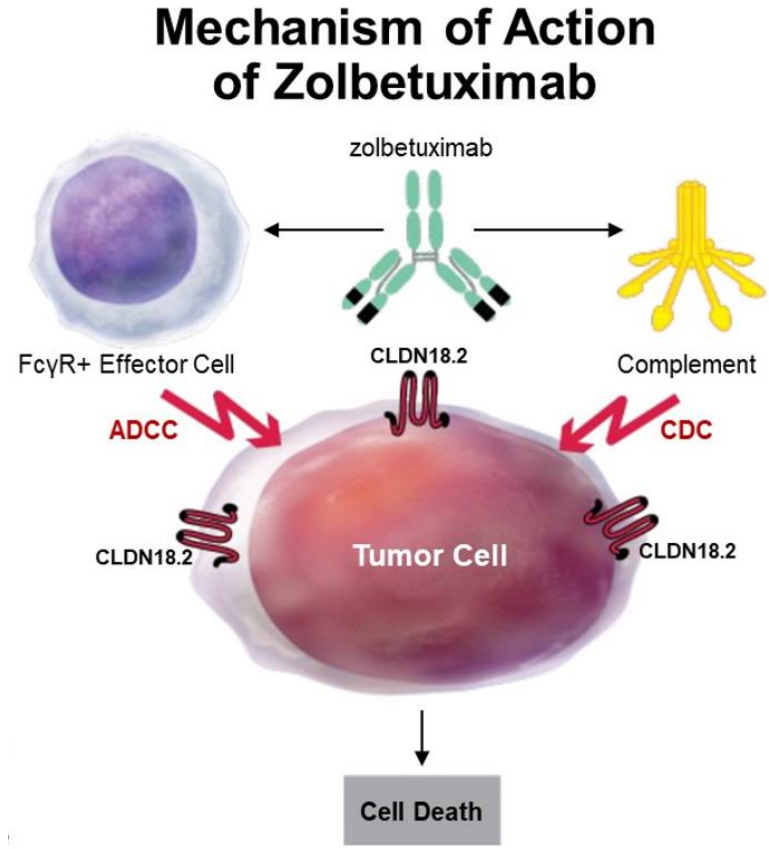


CTLA4



Claudin 18.2 and Gastroesophageal Cancer

- Claudin 18.2 expressed in tight junctions exclusively in the gastric mucosa; expression retained in gastric / GEJ cancers
- Claudin 18.2 positivity = IHC moderate to strong + in at least 75% of cells
- Zolbetuximab is a monoclonal antibody targeting claudin 18.2
- GLOW study: CAPOX + / - Zolbetuximab
- SPOTLIGHT study: mFOLFOX6 + / - Zolbetuximab



Shitara, K. et al. *Lancet*; 401: 1655–68 , Apr 2023
Shitara, K. et al. Abstract LBA292. ASCO GI 2023
Shah, M. et al. *Nature Medicine;* volume 29, pages 2133–2141, July 2023

Esophageal Cancer: Initial Diagnostic Evaluation

Clinical Assessment

- ECOG PS
- Comorbidities
- Nutritional status
  - Stent
  - G or J tube

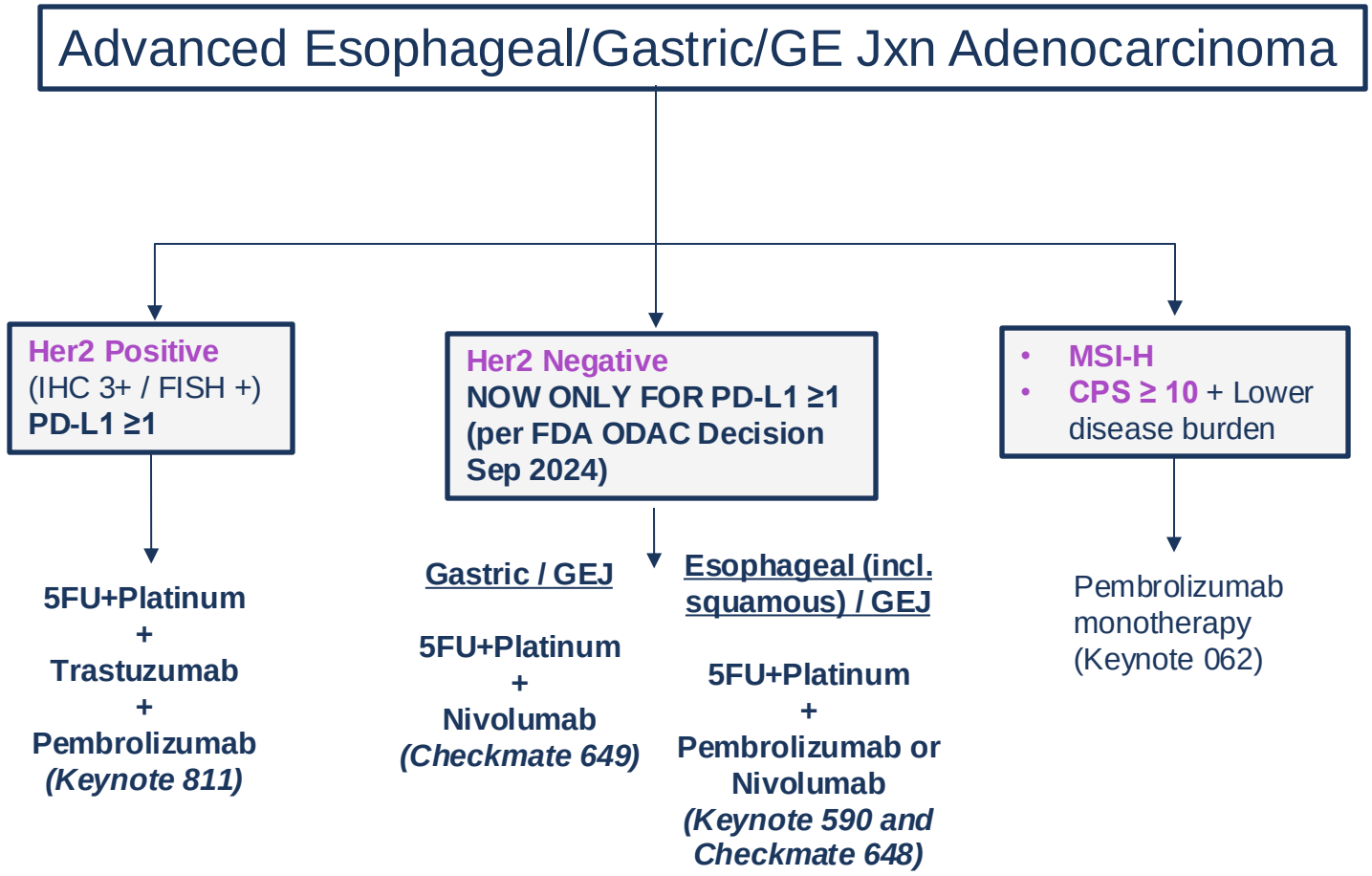
Labs and Imaging

- CT C/A/P w/ IV contrast (peritoneal dz)
- CEA
- CA 19-9

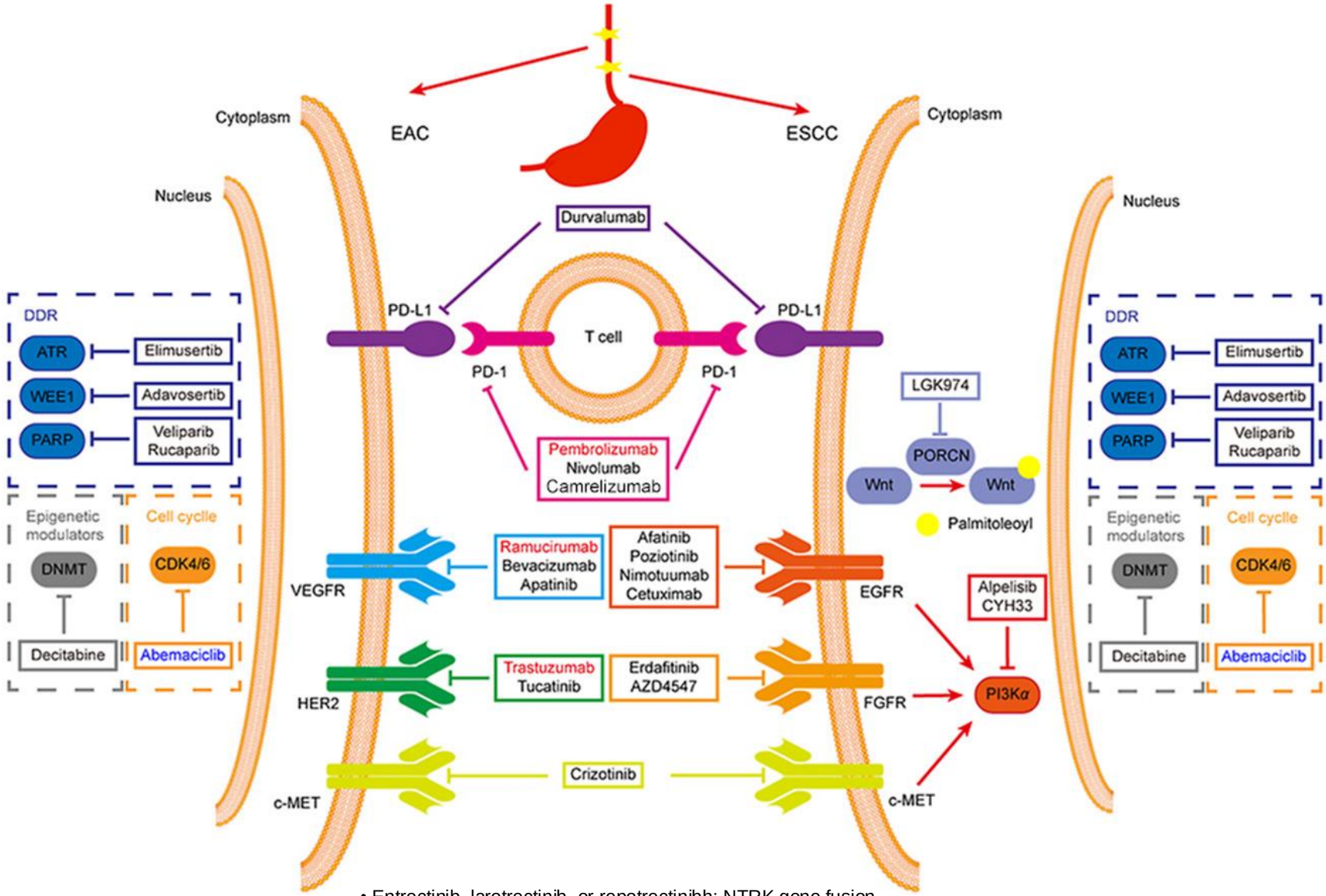
Molecular testing

- Her2 IHC and FISH (3+ or FISH+)
- PDL1 (CPS score)
- MSI
- CLDN18.2
- *NGS for most – tumor mutational burden*
  - *--NTRK fusion*
  - *--RET fusion*
  - *--BRAF V600E*

Esophageal Adenocarcinoma Initial Treatment 2024



Targeted Therapies for Esophageal Cancer



- Entrectinib, larotrectinib, or repotrectinibh: NTRK gene fusion
- Dabrafenib and trametinib: BRAF V600E-mutated
- Selpercatinib: RET gene fusion

Zhang
2022

Summary

- EAC and ESCC have thousands of genetic and epigenetic alterations
- EAC and ESCC have dozens of common genetic alterations that are potentially druggable

- The most commonly used targeted therapies are directed at HER2, VEGFR and PD-1/PD-L1 and CTLA4
- Other targets include Claudin 18.2, BRAF V600E, RET and NTRK

- There are numerous additional targeted therapies under investigation.