

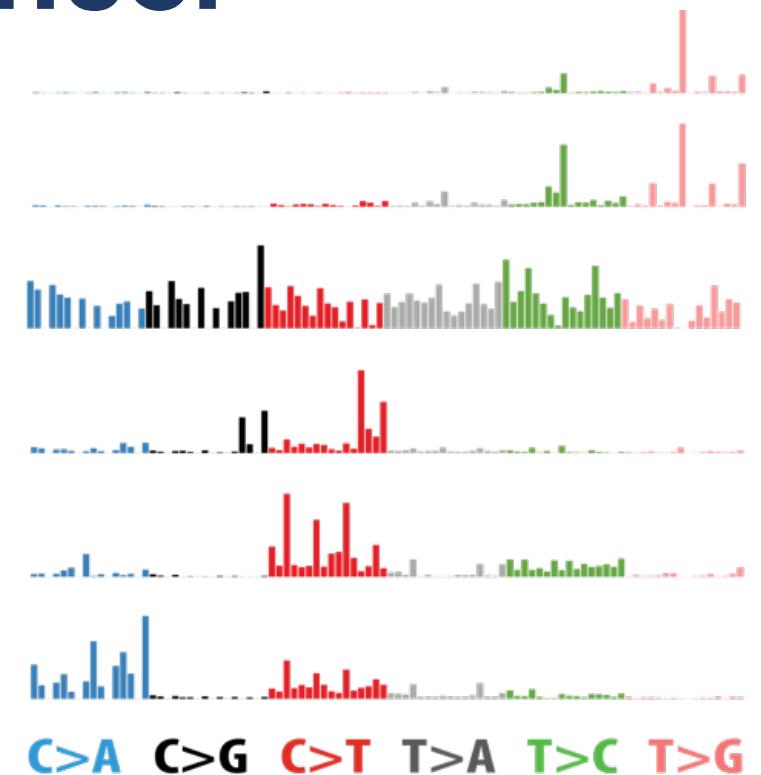
# Reconstructing mutational histories of oesophageal cancer

**Maria Secrier**

Department of Genetics, Evolution and Environment  
University College London

CompBioMed Conference  
September 25<sup>th</sup>, 2019

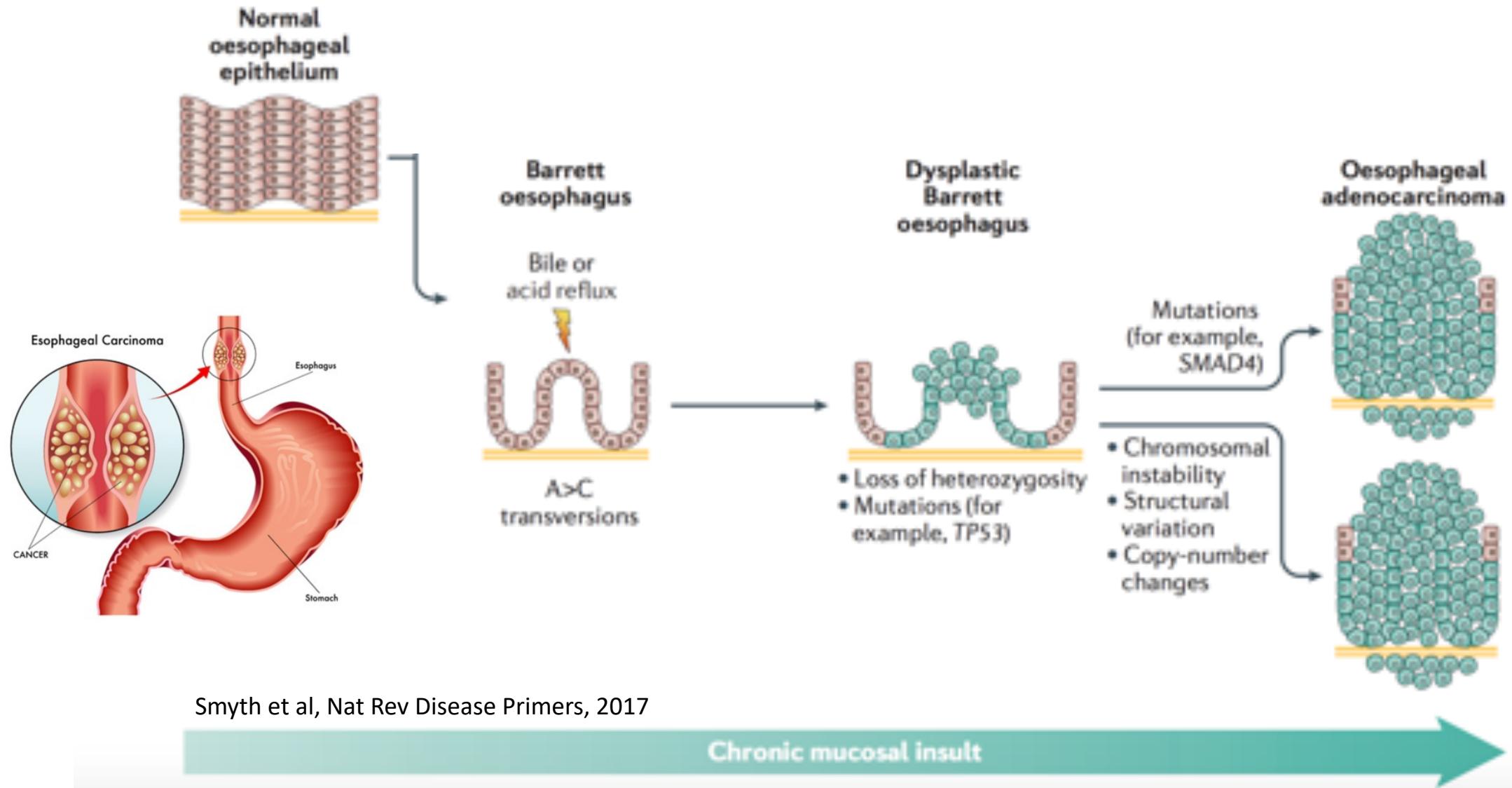
m.secrier@ucl.ac.uk



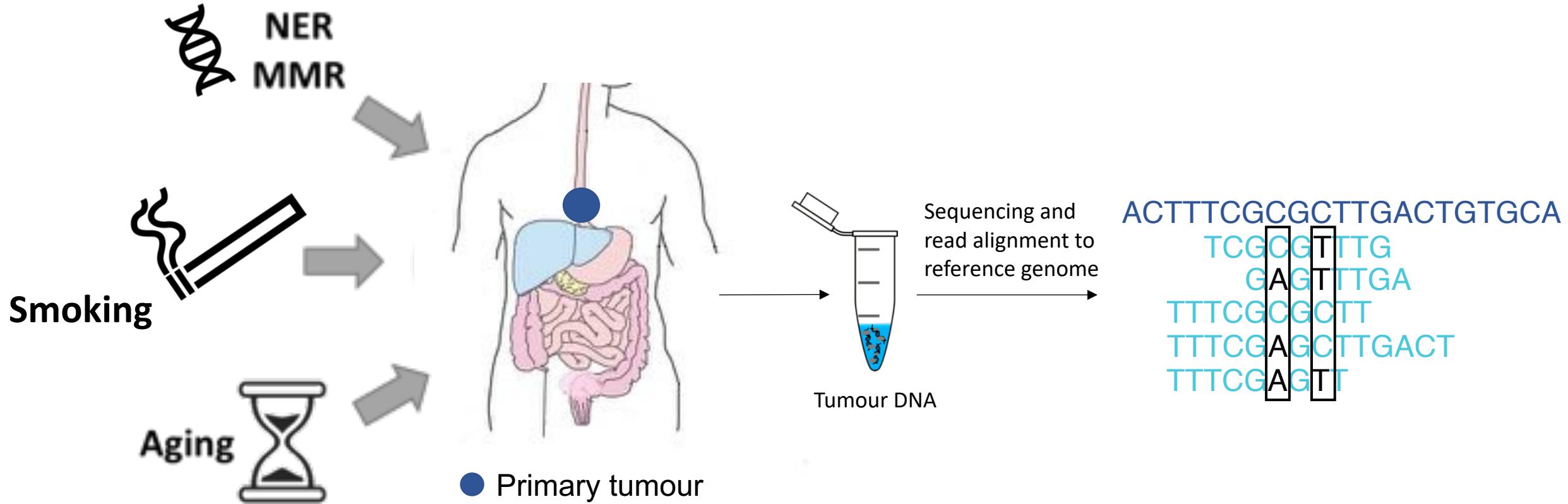
1. Can mutational histories of oesophageal cancer help us understand the aetiology of this disease?
2. Can evolutionary bottlenecks in mutagenesis offer clues to oncogenic reprogramming and pave the way for early intervention?

1. Can mutational histories of oesophageal cancer help us understand the aetiology of this disease?
2. Can evolutionary bottlenecks in mutagenesis offer clues to oncogenic reprogramming and pave the way for early intervention?

# Oesophageal adenocarcinoma development

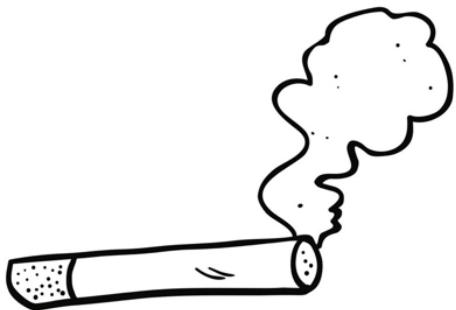


# Risk factors and cancer development



Endogenous + environmental  
risk factors

# Mutational processes in cancer



AACCAT C C C TGTA  
↓  
AACCAT C A C TGTA

**C[C>A]C**

*Signature of smoking*

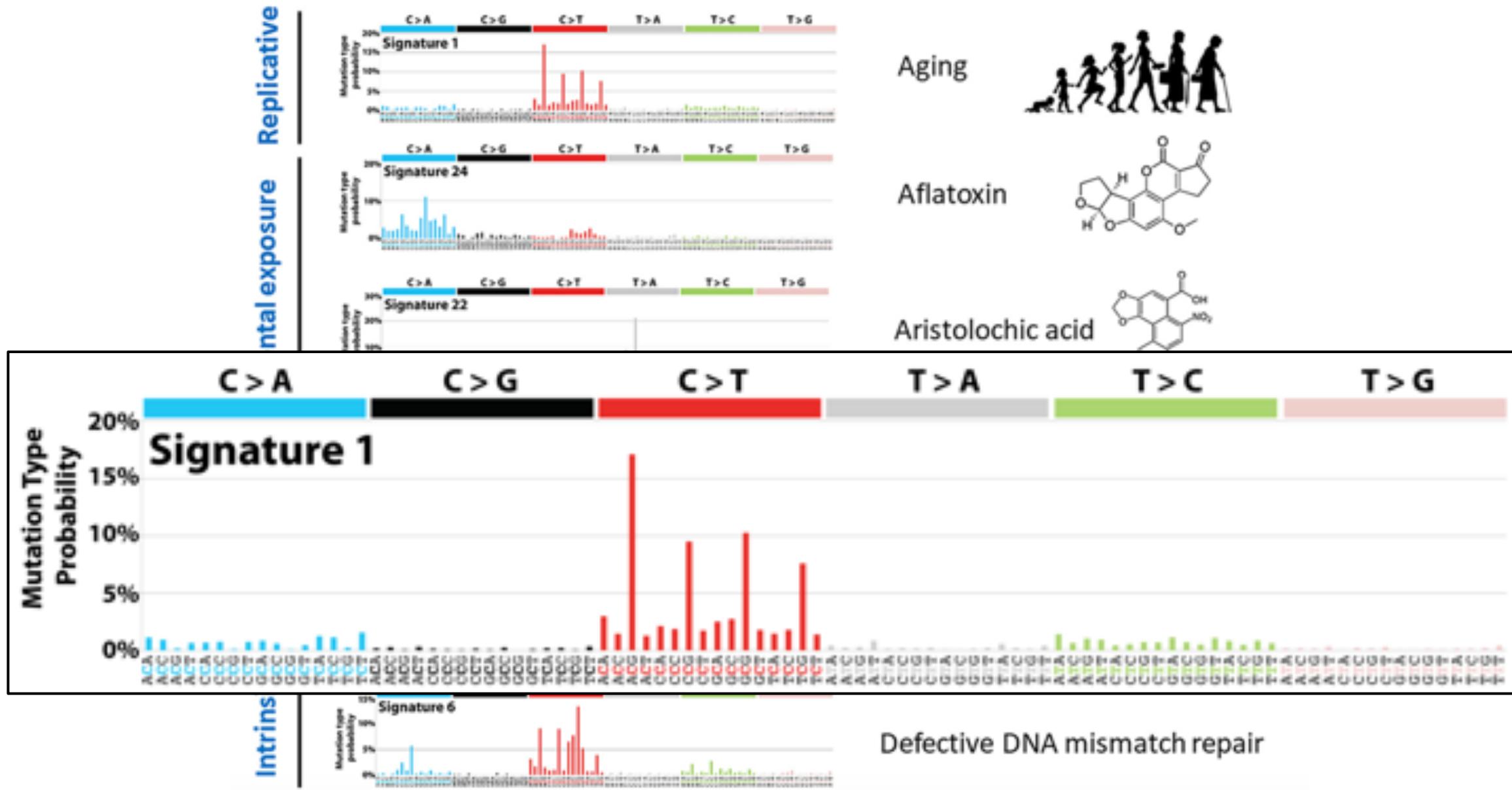
AACCAT A C G TGTA  
↓  
AACCAT A T G TTTA

**A[C>T]G**

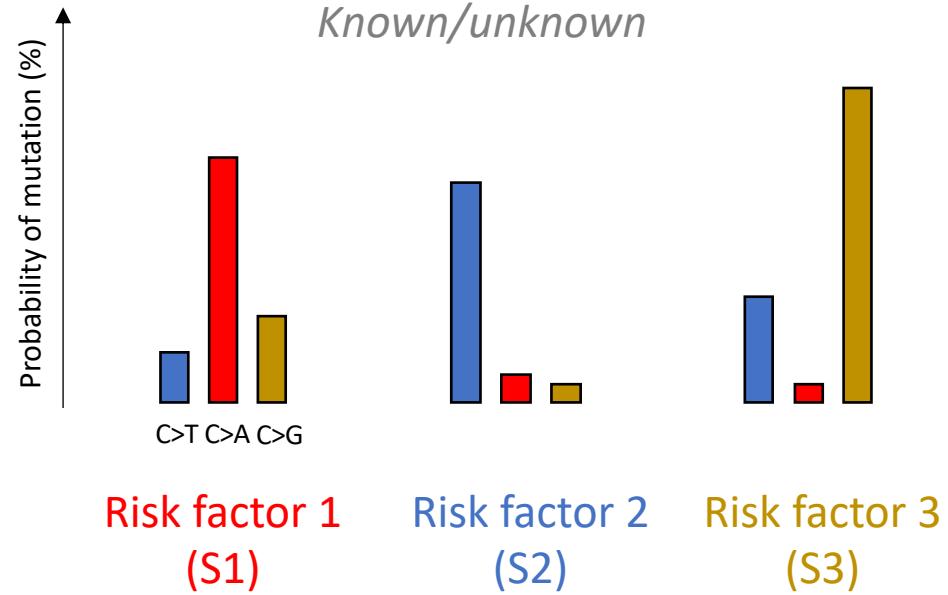
*Signature of ageing*



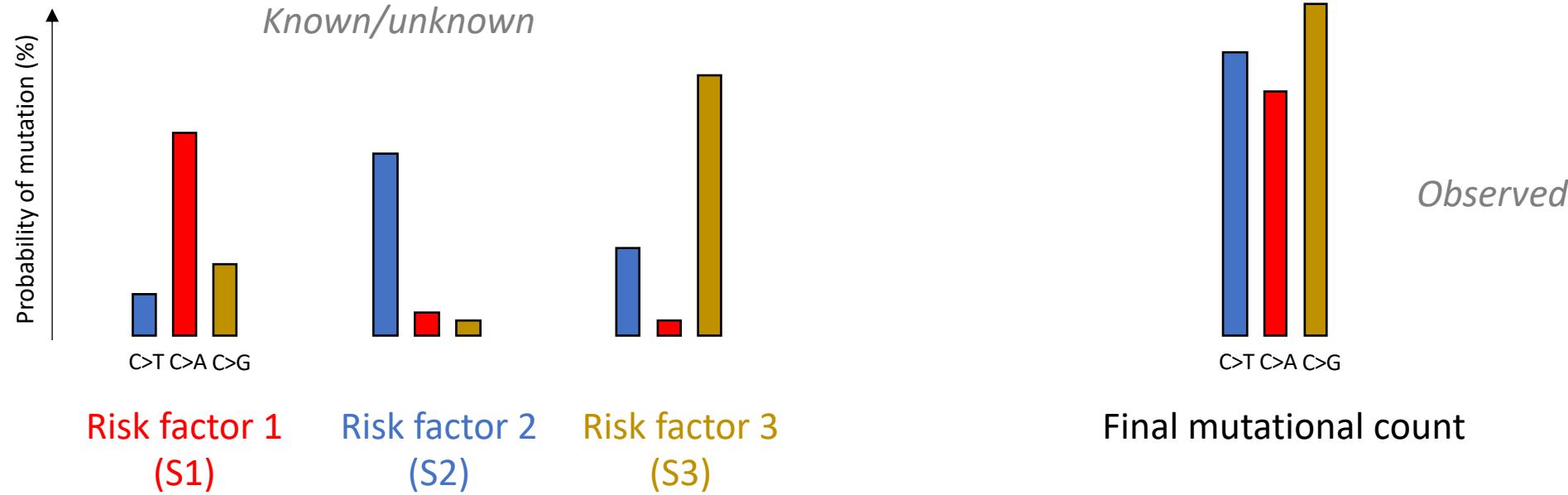
# Mutational signature examples



# Inferring mutational signatures operative in cancer

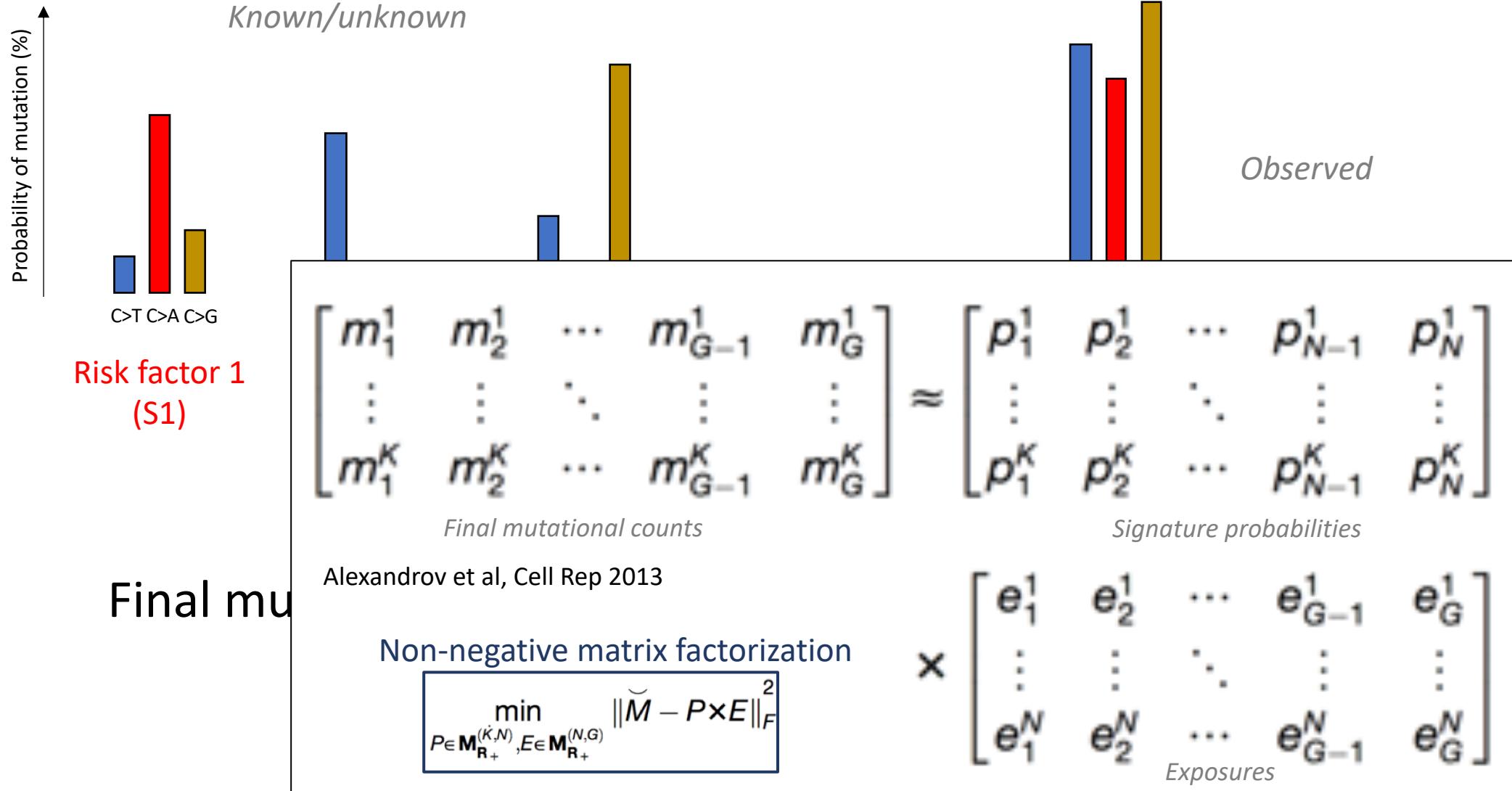


# Inferring mutational signatures operative in cancer

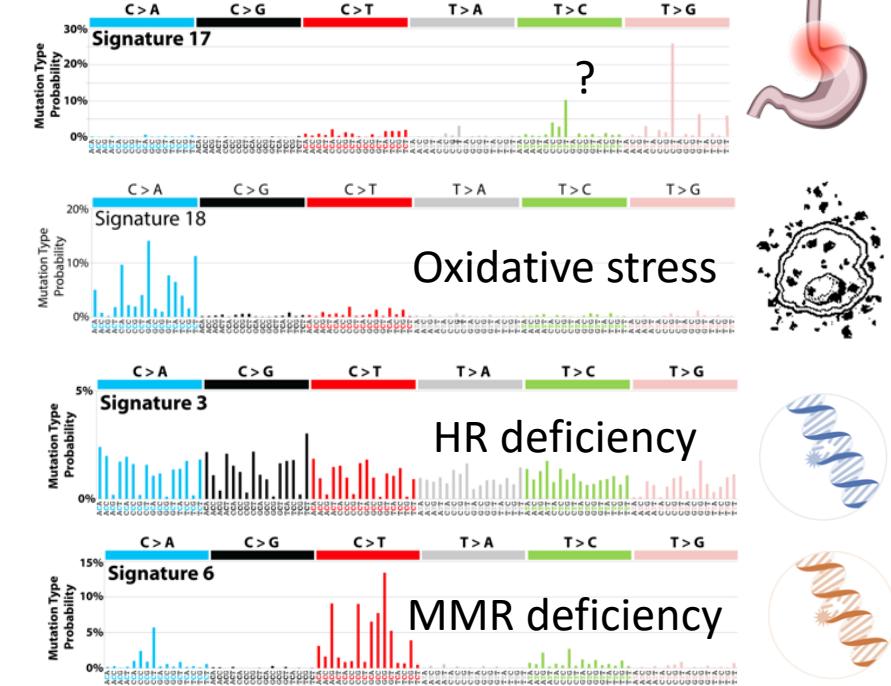
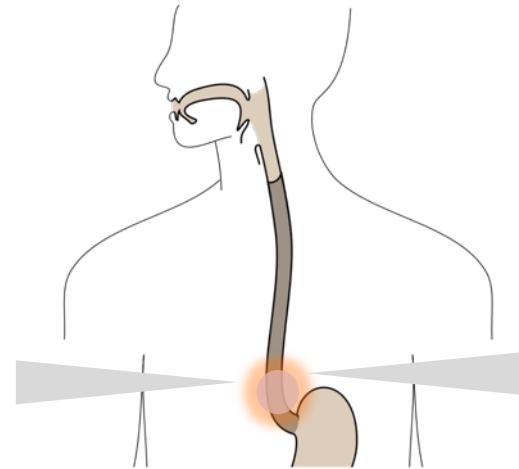
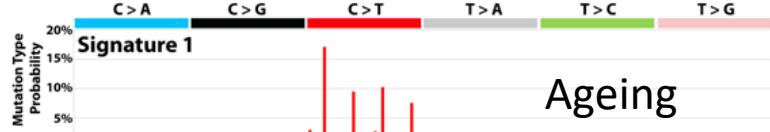


$$\text{Final mutational count} \sim \beta_1 * S1 + \beta_2 * S2 + \beta_3 * S3 + \epsilon$$

# Inferring mutational signatures operative in cancer

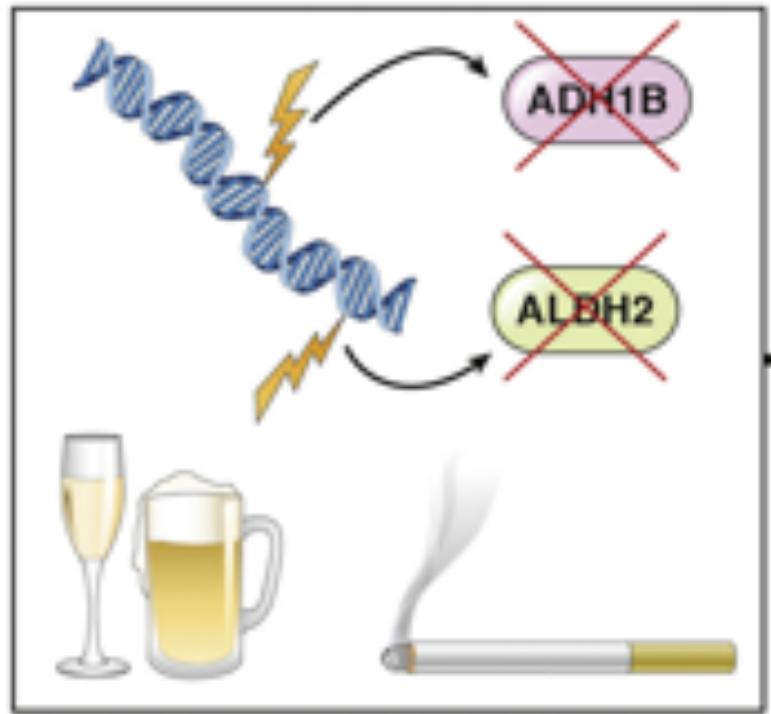


# Mutational processes shaping oesophageal cancer development

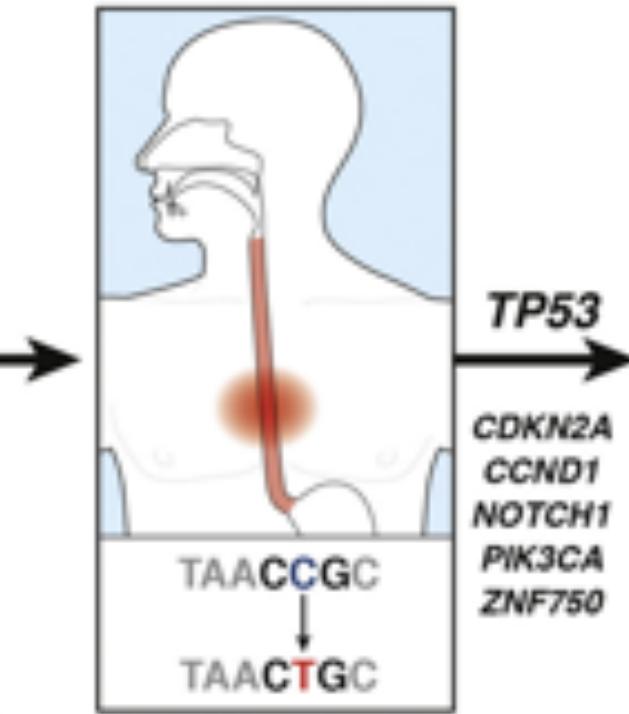


TCGA, Nature 2017; Alexandrov et al, bioRxiv 2018

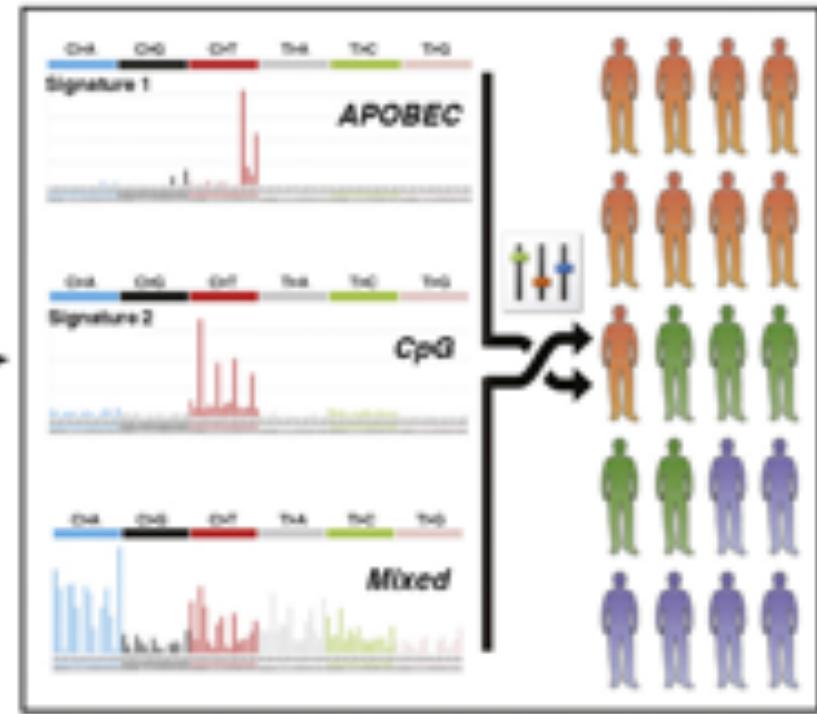
Dulak et al, Nat Genet 2013; Secrier\*, Li\* et al, Nat Genet 2016



*Cancer risk factors*



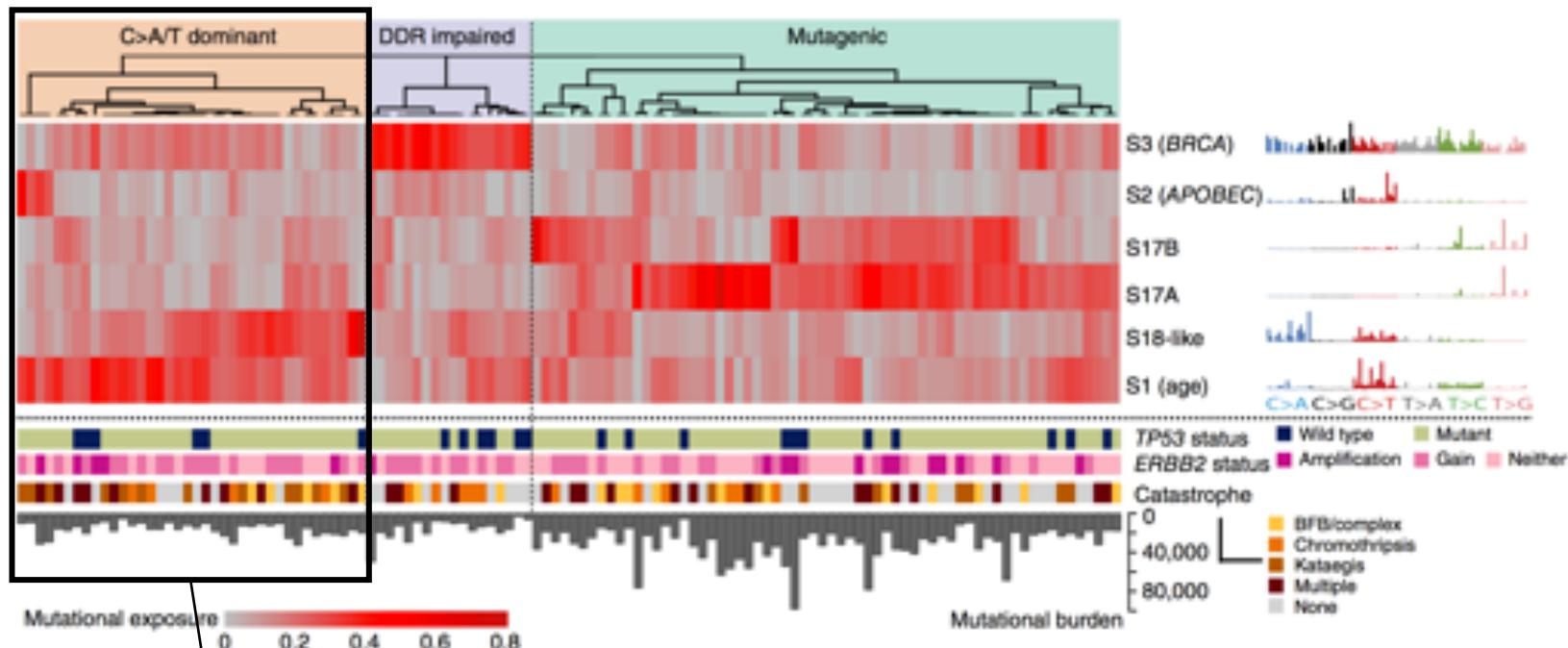
*Mutational footprints*



*Distinct pathways to cancer development*

Secrier and Fitzgerald, Gastroent 2016

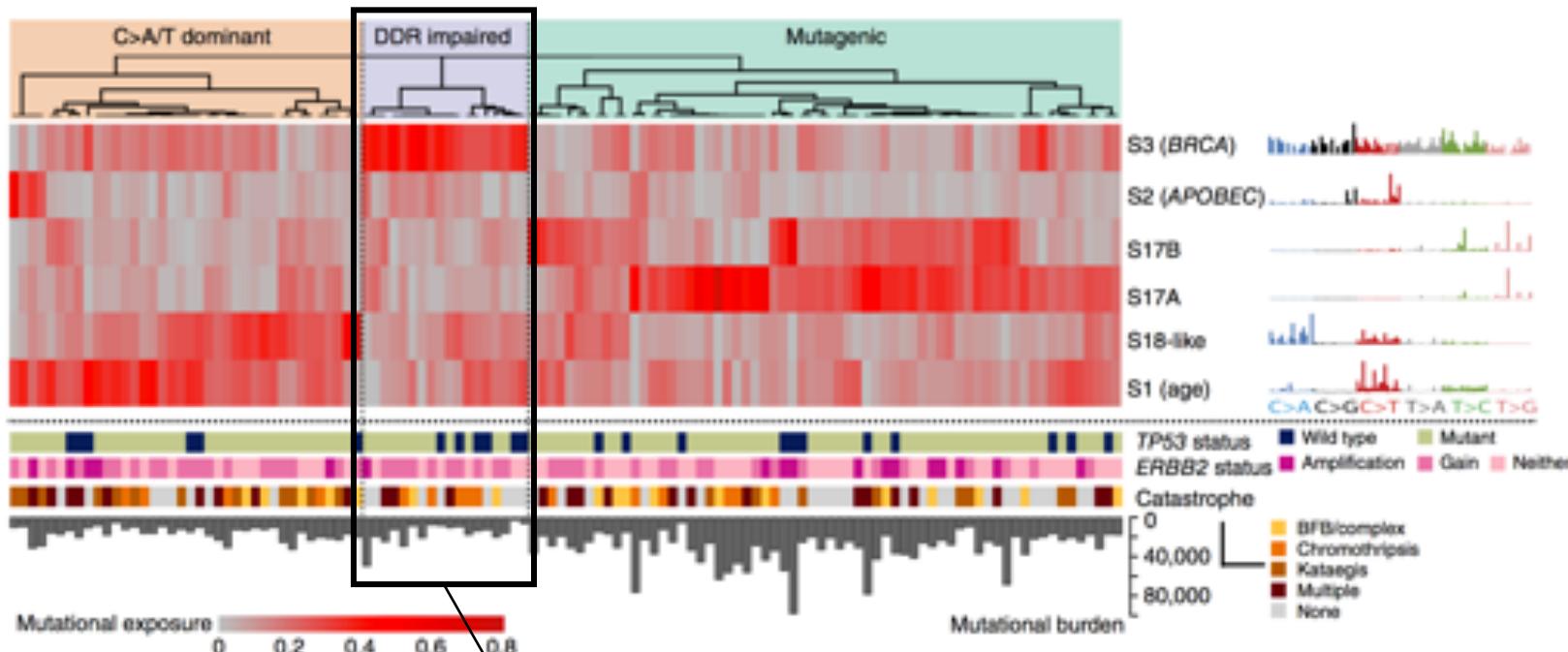
# Mutational signatures shed light on aetiology pathways of OAC



Secrier\*, Li\* et al, Nat Genet 2016

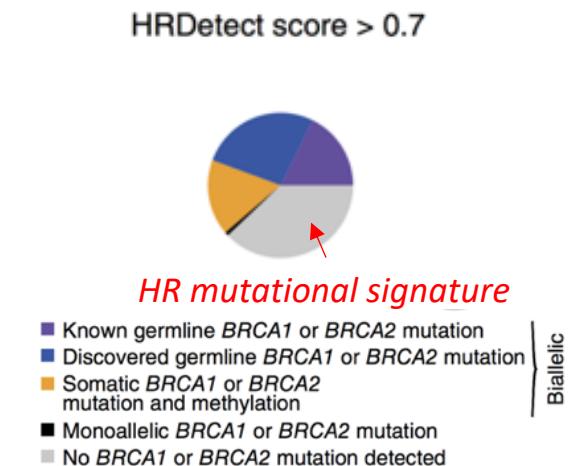
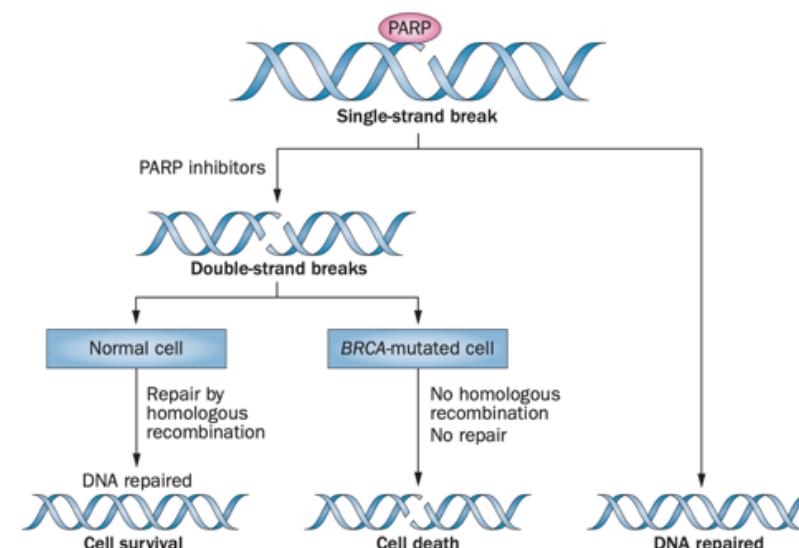
Ageing/oxidative stress

# Mutational signatures shed light on aetiology pathways of OAC



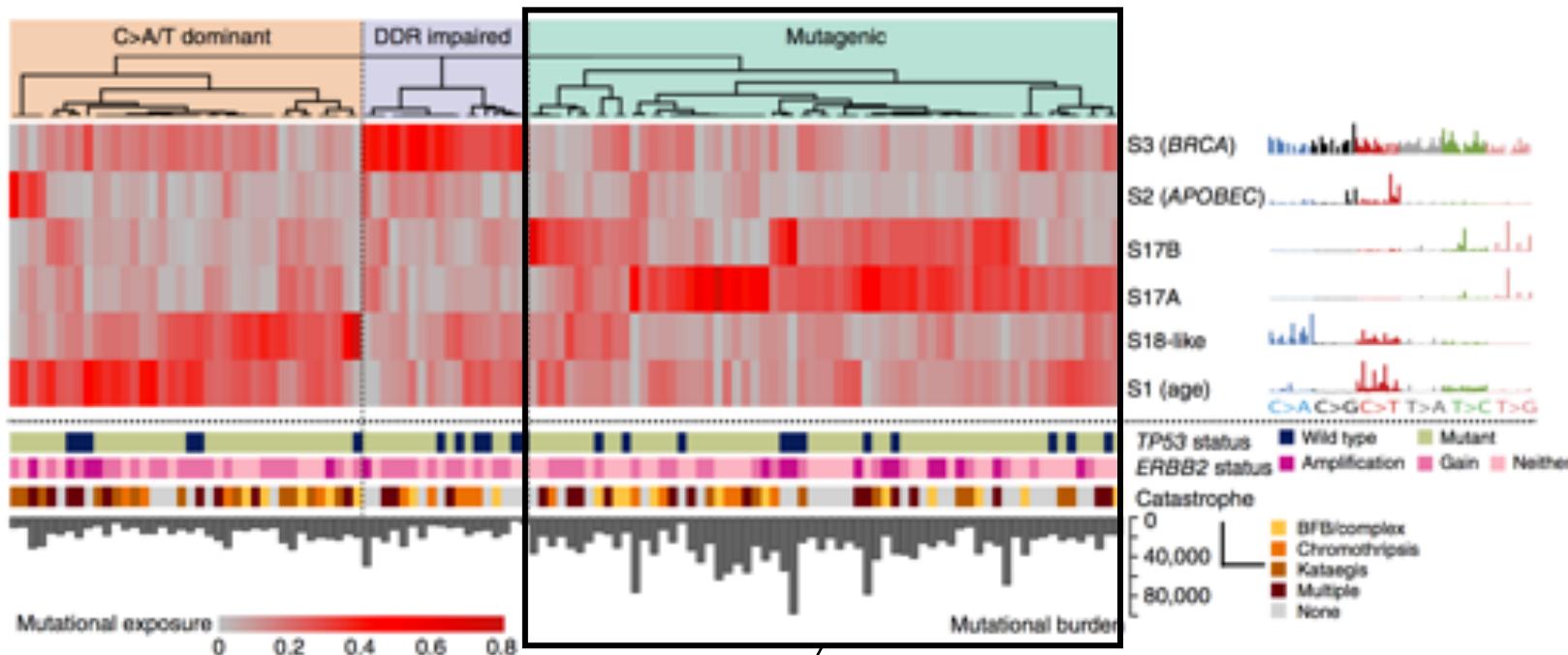
Secrier\*, Li\* et al, Nat Genet 2016

## Homologous recombination deficiency:



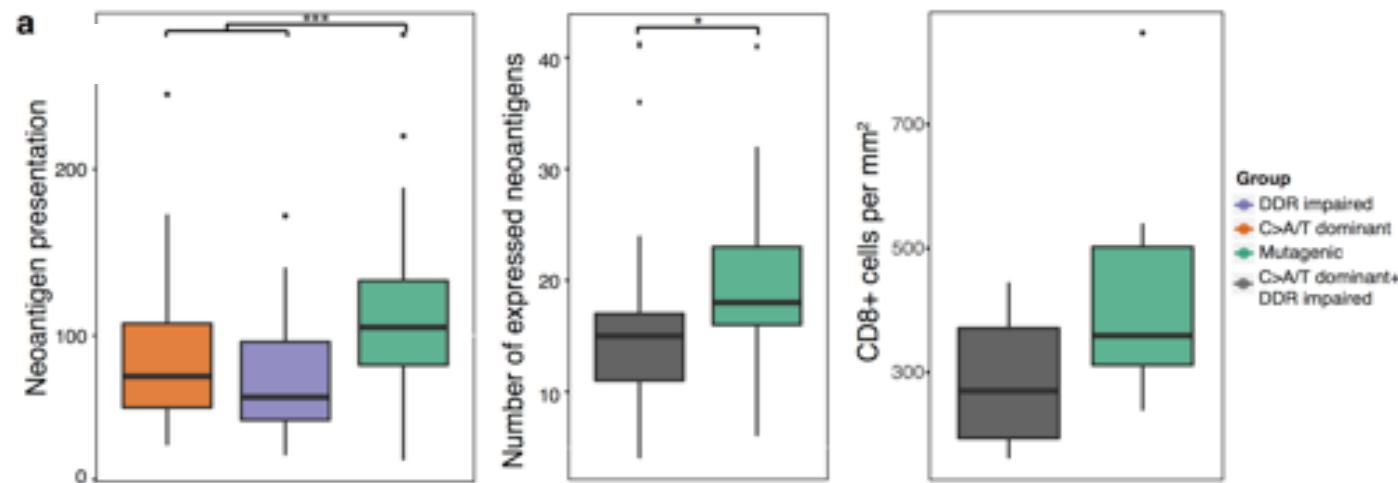
Davies et al, Nature Medicine 2017

# Mutational signatures shed light on aetiology pathways of OAC

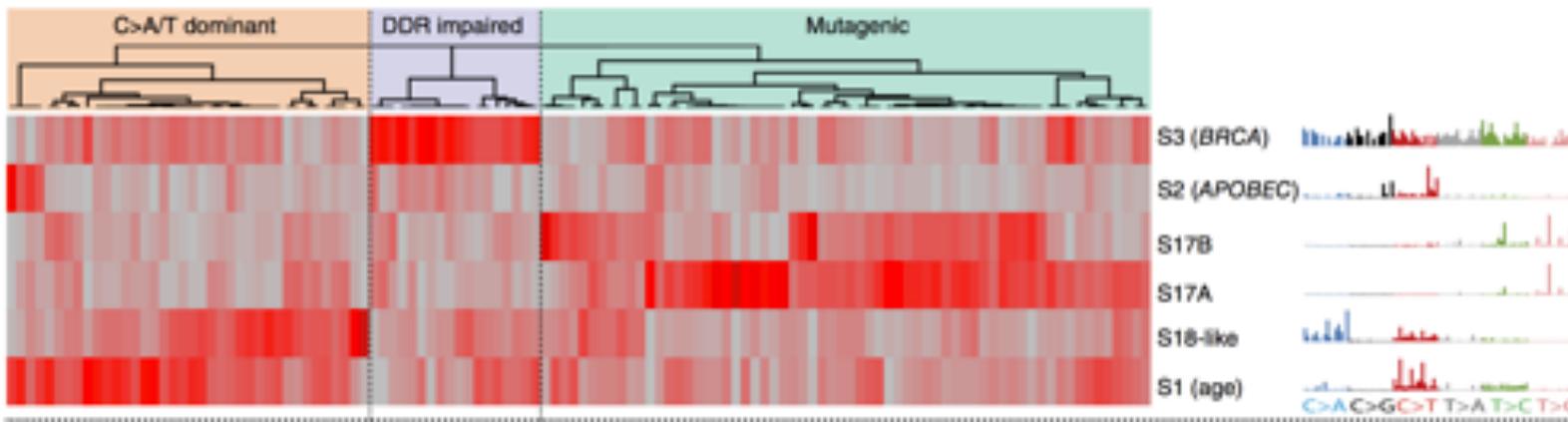


Secrier\*, Li\* et al, Nat Genet 2016

Higher mutational and neoantigen burden:



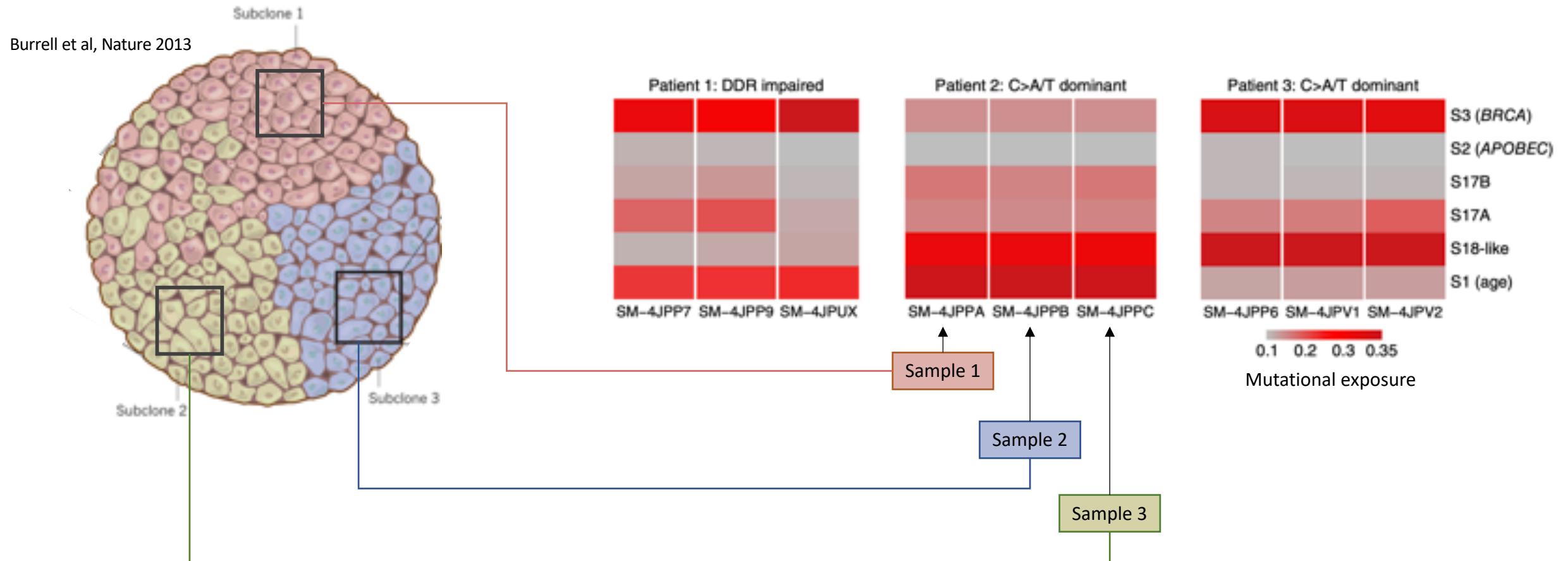
# Mutational signatures shed light on aetiology pathways of OAC



Secrier\*, Li\* et al, Nat Genet 2016

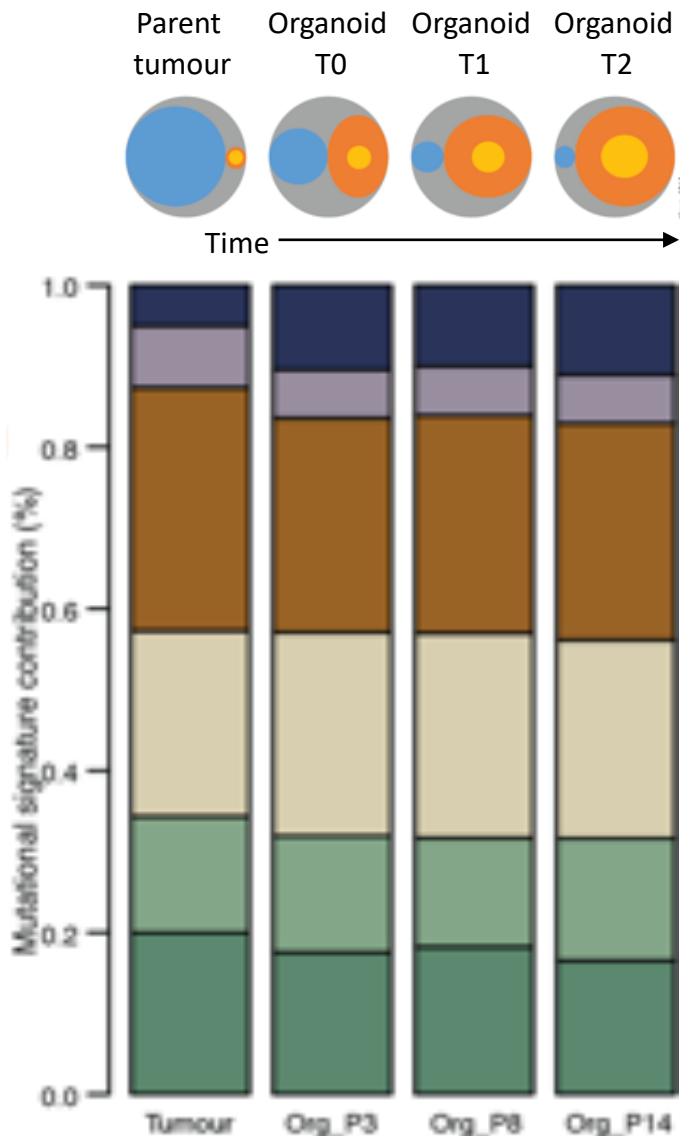
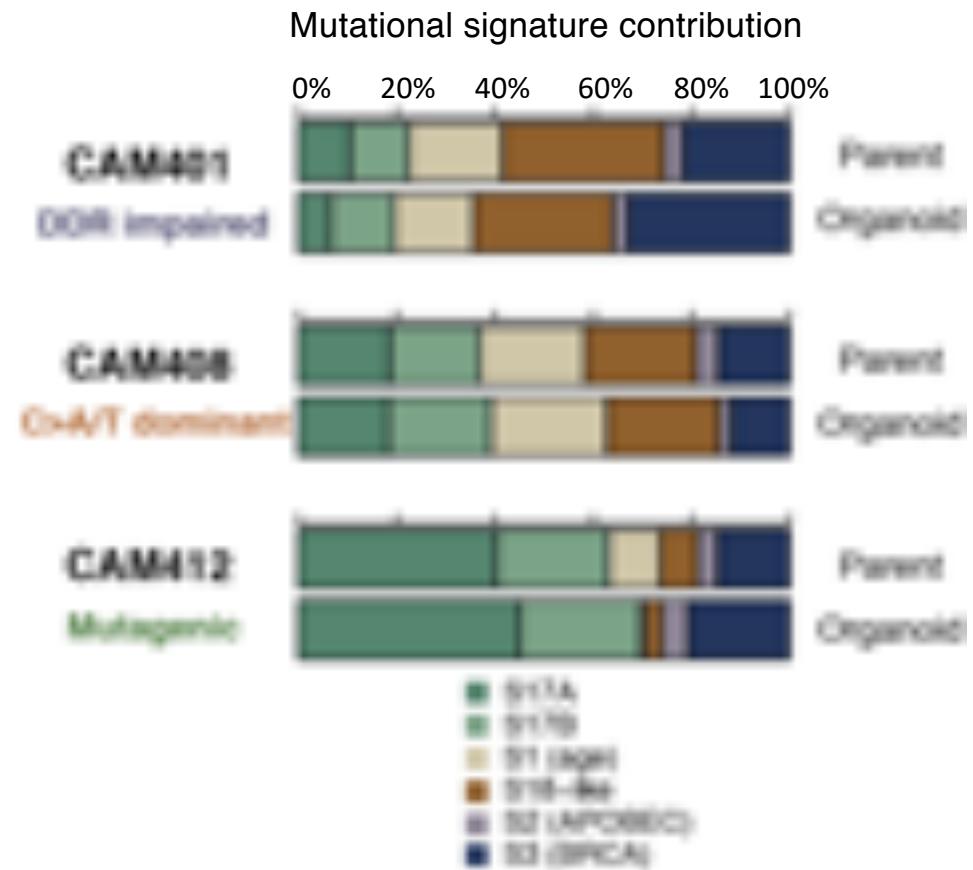
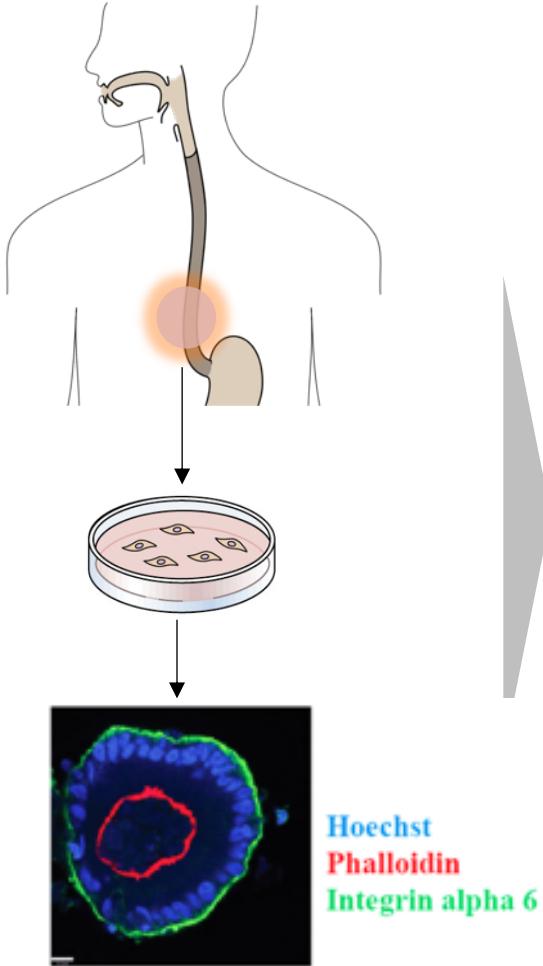
	C>A/T dominant (29%)	DDR impaired (18%)	Mutagenic (53%)
Etiology			
Description	<ul style="list-style-type: none"><li>Dominant C&gt;A/T mutational pattern</li><li>Aging as a pervasive risk factor</li><li>Fewer unstable genomes and large duplication events</li></ul>	<ul style="list-style-type: none"><li>Prevalent defects in homologous recombination and chromosome segregation pathways</li></ul>	<ul style="list-style-type: none"><li>Dominant T&gt;G mutational pattern</li><li>Highest mutational burden</li><li>Highest neoantigen load</li></ul>
Therapy	<ul style="list-style-type: none"><li>Conventional chemotherapy</li><li>Tailored ERBB2/MET inhibition</li></ul>	<ul style="list-style-type: none"><li>DNA-damaging agents combined with PARPi</li><li>Proton irradiation</li><li>Photon irradiation with PARPi</li></ul>	<ul style="list-style-type: none"><li>CHK/WEE1 inhibition</li><li>Immunotherapy:<ul style="list-style-type: none"><li>CTLA4-targeting agents</li><li>PD-1/PD-L1-targeting agents</li></ul></li></ul>

# Mutational signatures are largely homogeneous despite spatial tumour heterogeneity



1. Can mutational histories of oesophageal cancer help us understand the aetiology of this disease?
2. Can evolutionary bottlenecks in mutagenesis offer clues to oncogenic reprogramming and pave the way for early intervention?

# Mutational signature scars are maintained in OAC organoids and persist despite clonal dynamics



# Acknowledgements



**Laura Vo Ngoc**

**Jenny Hu**

Guidantonio Malagoli Tagliazzuchi

Anna Wiecek

University of Cambridge

**Rebecca Fitzgerald**

**Xiaodun Li**

Sujath Abbas

Paul Edwards

Shona MacRae

CRUK Cambridge Institute

**Simon Tavaré**

Matthew Eldridge

Andy Lynch

Lawrence Bower

Achilleas Achilleos

Juliane Perner

Addenbrooke's Hospital

Maria O'Donovan

Nicola Grehan

Barbara Nutzinger

Wellcome Trust Sanger Institute

**Mathew Garnett**

**Hayley Francies**

Oxford Big Data Institute

**David Wedge**



International  
Cancer Genome  
Consortium

**Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) Consortium**



**The Academy of  
Medical Sciences**

