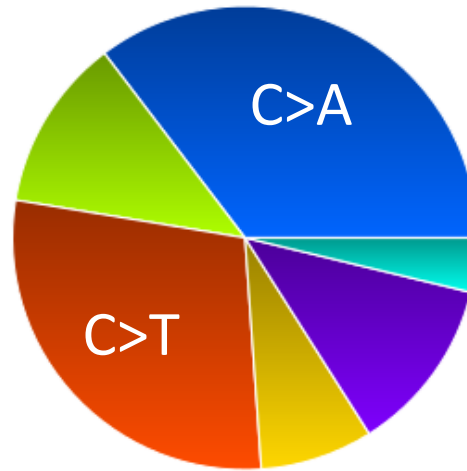


Mutational signatures associated with tobacco smoking in human cancer

Ludmil B. Alexandrov
Oppenheimer Fellow, Los Alamos National Lab
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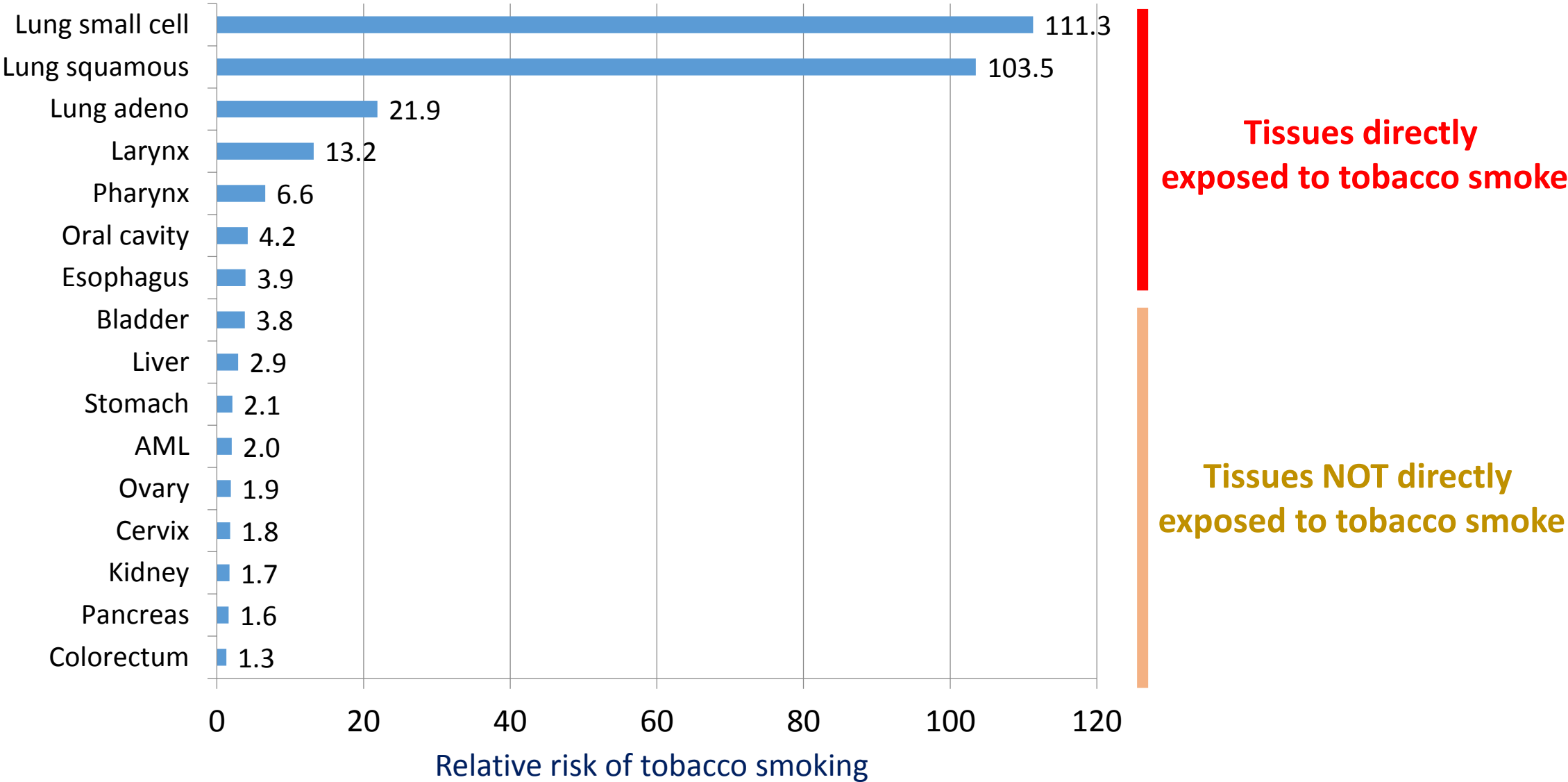
TP53 mutations in human cancer provided initial evidence for mutational signatures

TP53 mutations in
1,647 tobacco associated
lung cancers



Tobacco carcinogens
cause C>A mutations
in vitro

Cancer relative risks of tobacco smoking

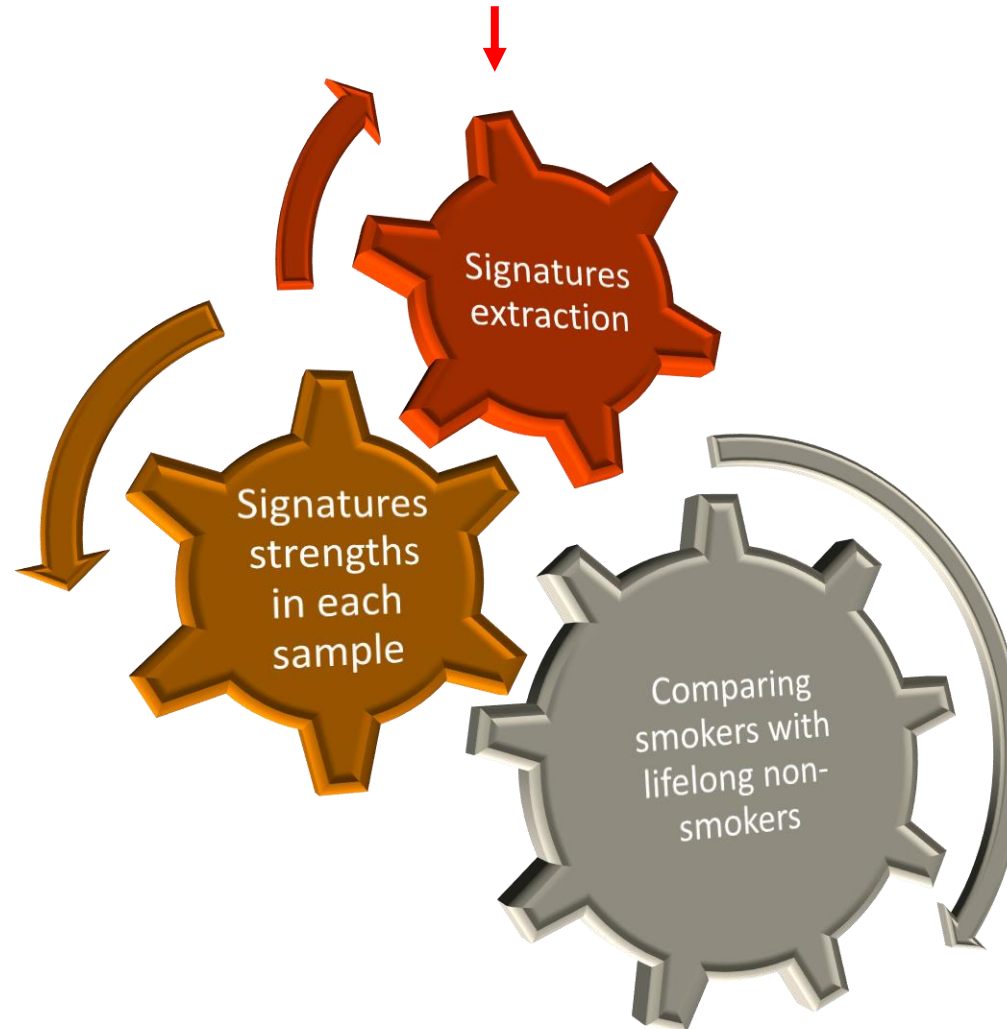


Tobacco smoking induced carcinogenesis



Extracting mutational signatures from human cancers caused by smoking

5,243 cancer genomes of cancer types caused by tobacco smoking

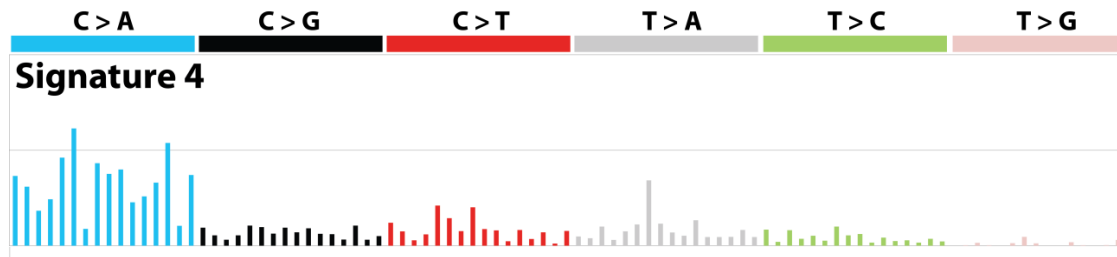


Known or speculative causes of mutational signatures



The mutational signature of *in vitro* benzo[*a*]pyrene exposure is similar to signature 4

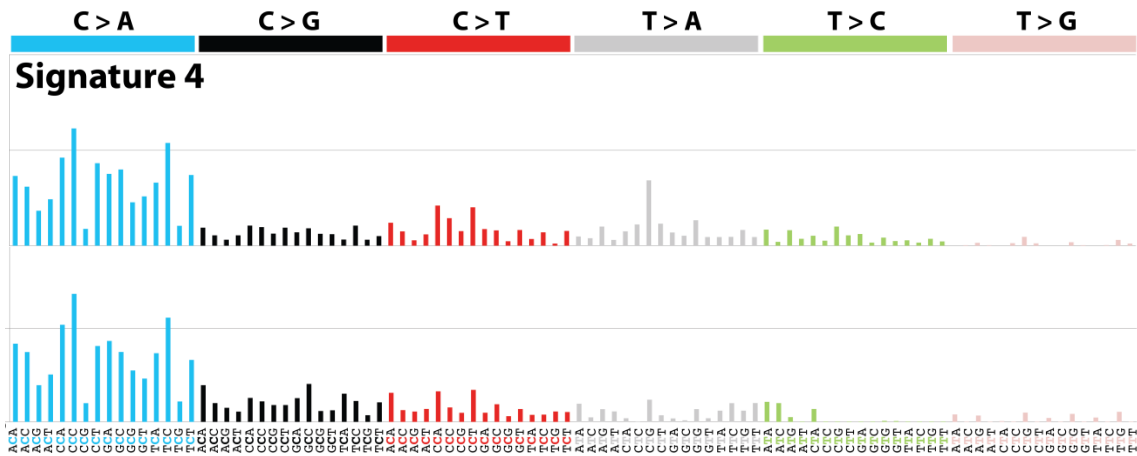
Signature 4 extracted from human cancers



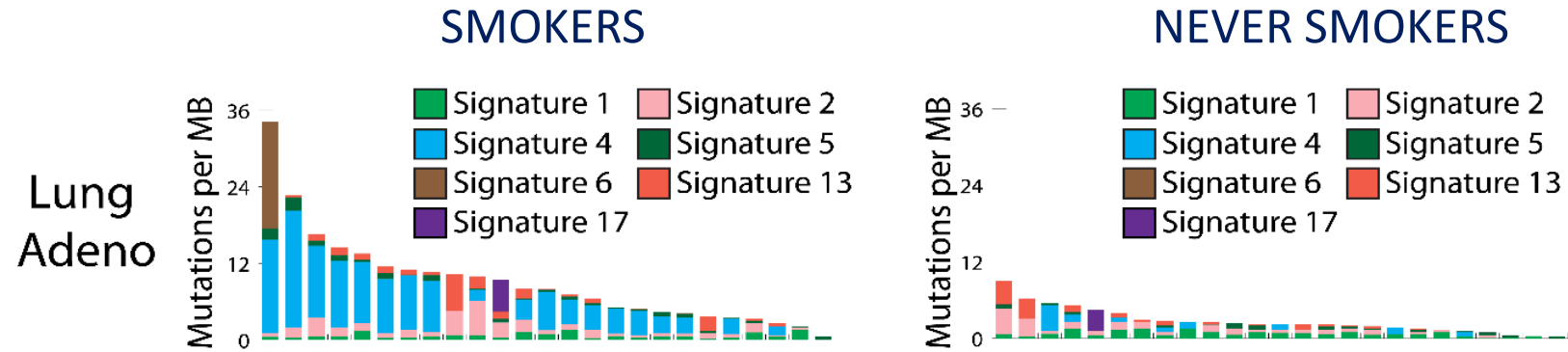
The mutational signature of *in vitro* benzo[*a*]pyrene exposure is similar to signature 4

Signature 4 extracted from human cancers

Signature of benzo[*a*]pyrene exposure *in vitro*



Contributions of signature 4 mutations to cancers from tobacco smokers and non-smokers

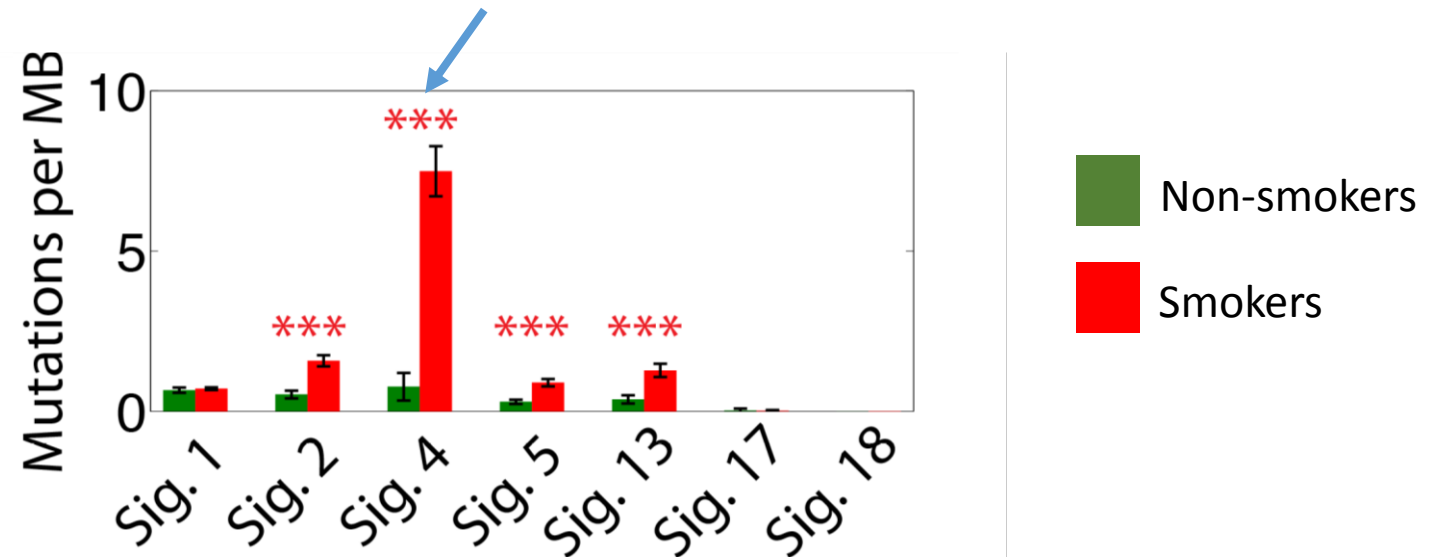


Contributions of signature 4 mutations to cancers from tobacco smokers and non-smokers



Mutational signatures in cancers from smokers compared to non-smokers

Lung
Adeno



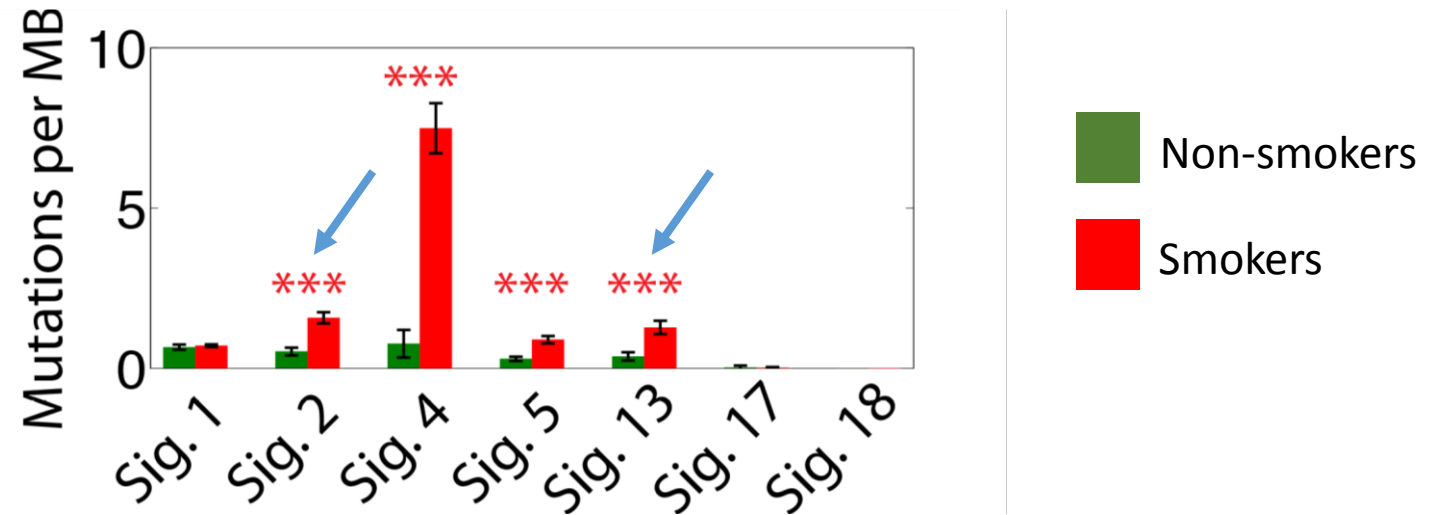
* q-value < 0.05

** q-value < 0.01

*** q-value < 10^{-5}

Mutational signatures in cancers from smokers compared to non-smokers

Lung
Adeno

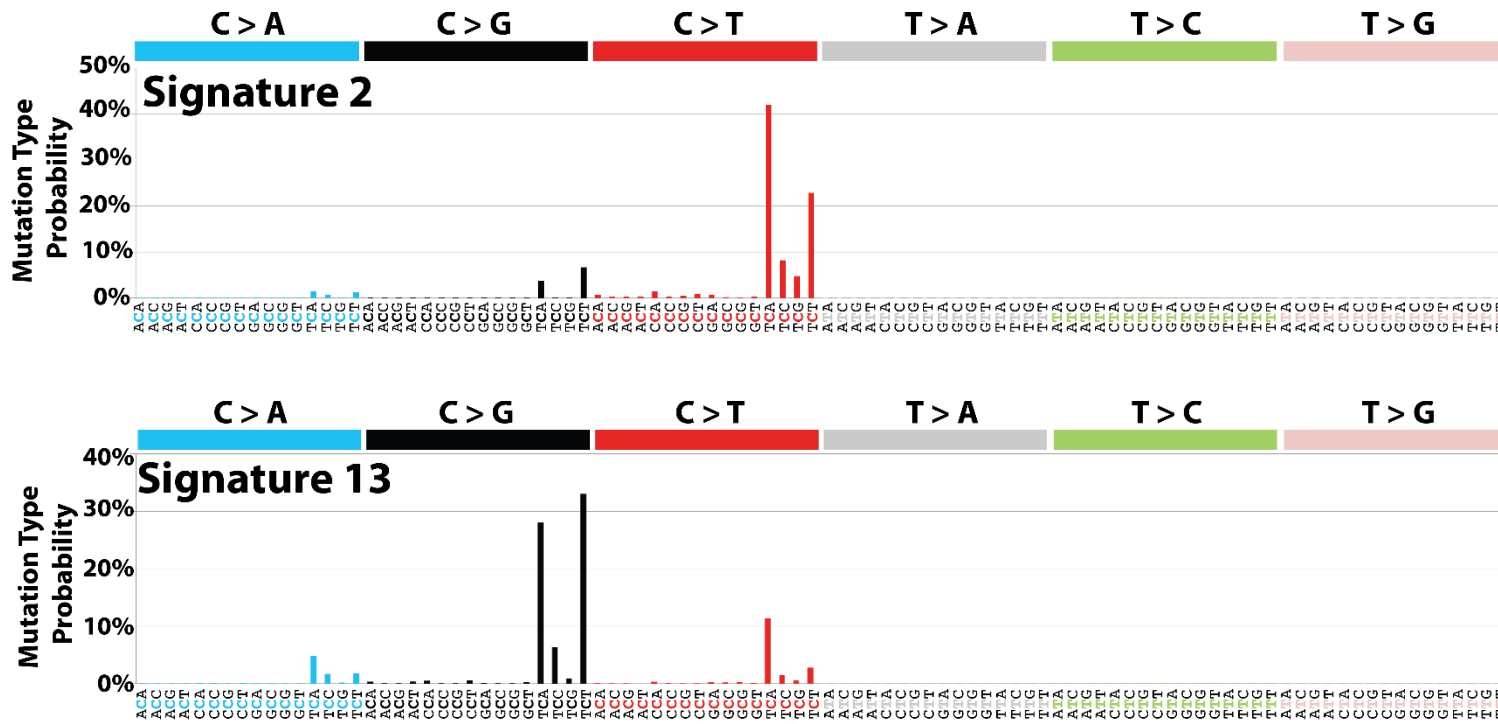


* q-value < 0.05

** q-value < 0.01

*** q-value < 10^{-5}

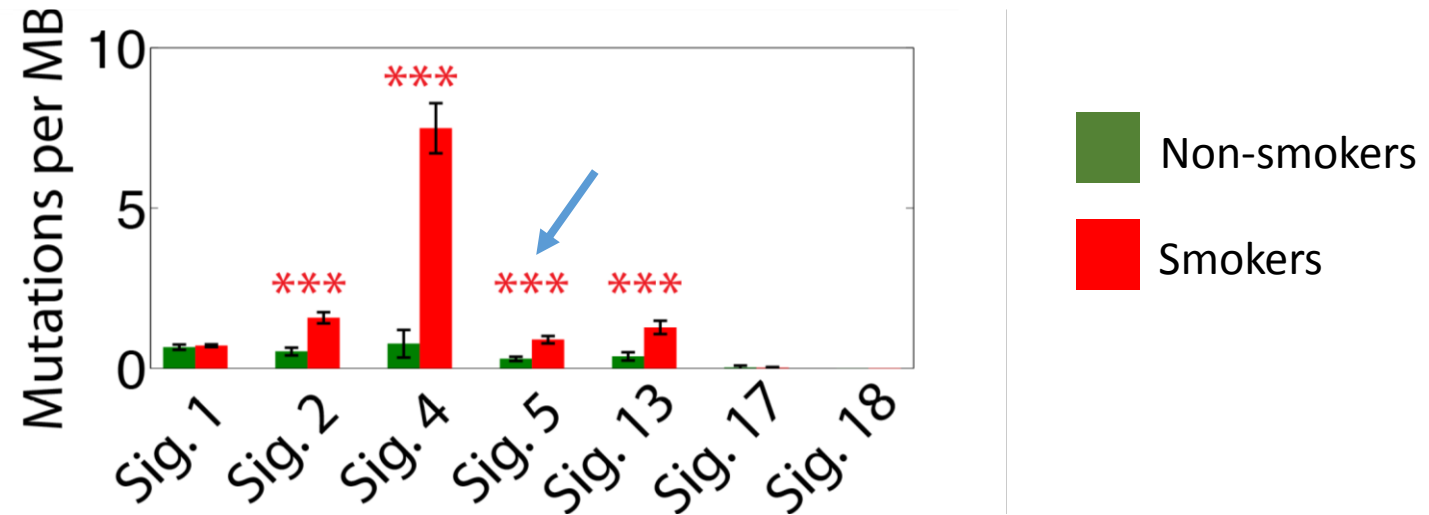
Mutational signatures in cancers from smokers compared to non-smokers



- APOBEC enzymes
- Cytidine deaminases
- Innate immunity
- Common in wide range of cancers
- Activating factors unknown
- Increase due to smoking unlikely to be a direct result of DNA damage

Mutational signatures in cancers from smokers compared to non-smokers

Lung
Adeno

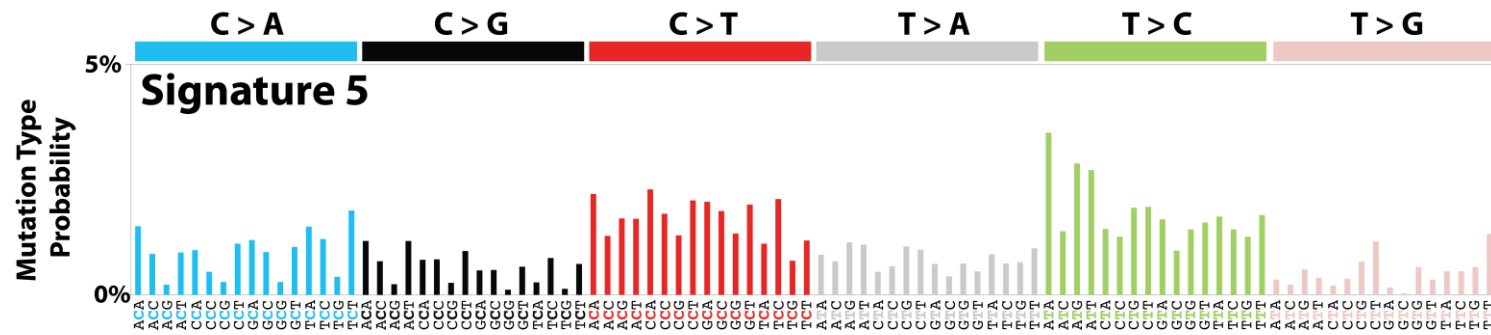


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*** q-value < 10^{-5}

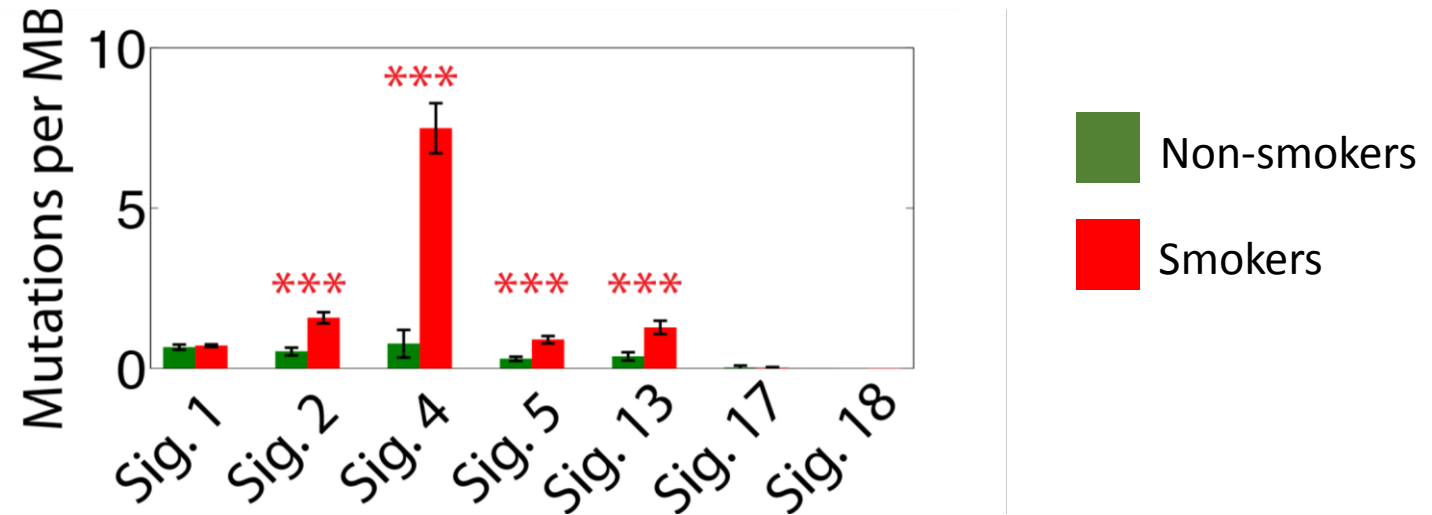
Mutational signatures in cancers from smokers compared to non-smokers



- Uncertain cause
- Found in all normal cell types
- Related to age
- Related to nucleotide excision repair?
- Increase due to smoking unlikely to be a direct result of DNA damage

Mutational signatures in cancers from smokers compared to non-smokers

Lung
Adeno

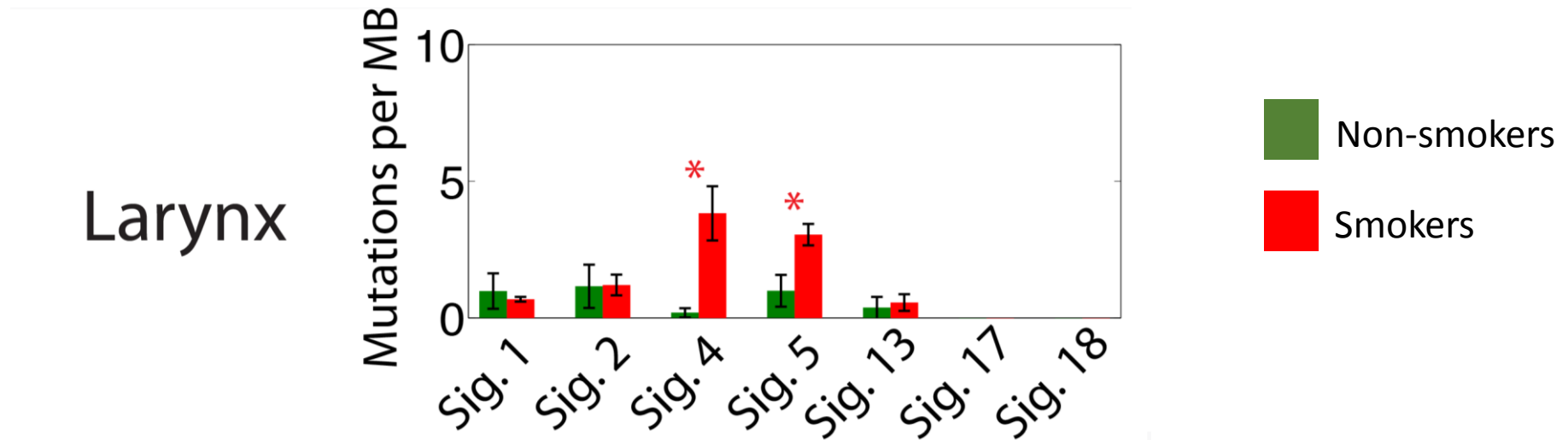


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Mutational signatures in cancers from smokers compared to non-smokers

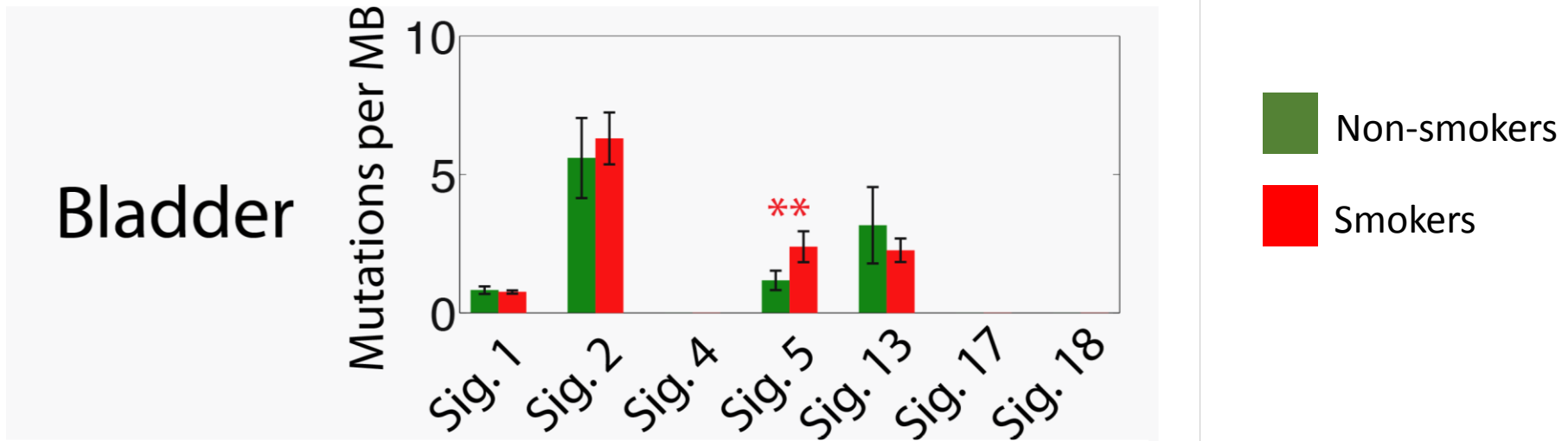


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Mutational signatures in cancers from smokers compared to non-smokers

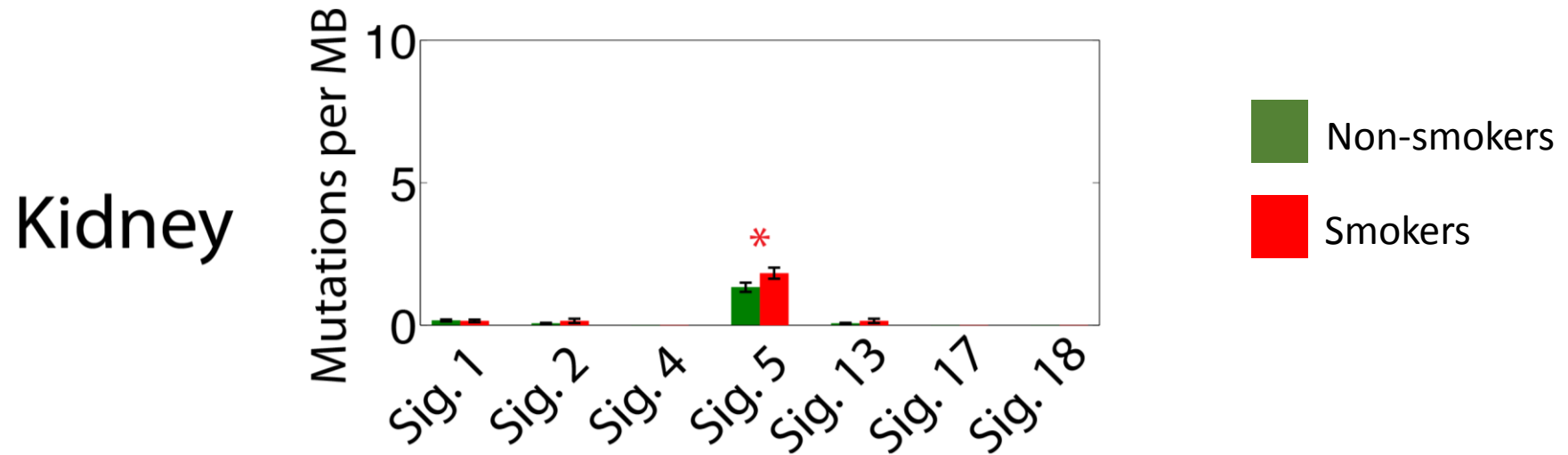


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Mutational signatures in cancers from smokers compared to non-smokers

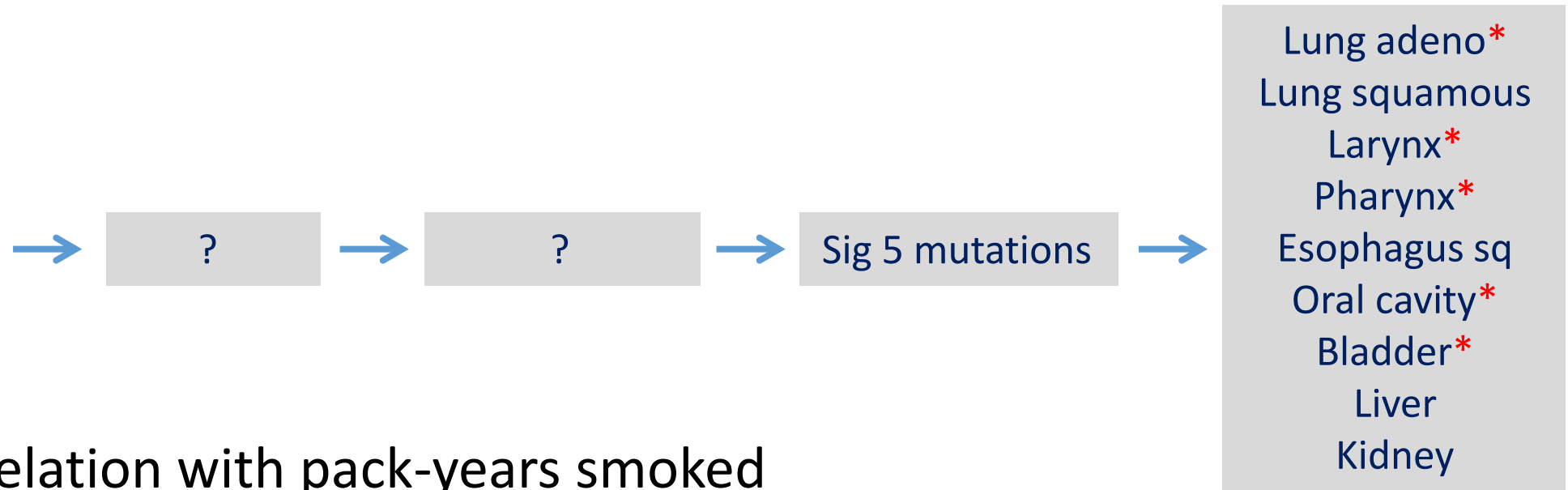
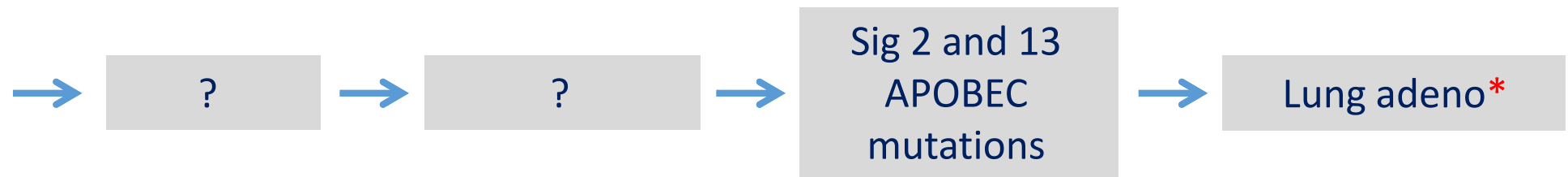


* q-value < 0.05

** q-value < 0.01

*** q-value < 10^{-5}

Tobacco smoking induced carcinogenesis



*Positive correlation with pack-years smoked

Acknowledgements

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Kings College, London



International
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Consortium

THE CANCER GENOME ATLAS

