

Day 4. Cancer Genome Analysis - Latin America and the Caribbean

Validation of signature etiologies / clinical examples



November 30th, 2023

Marcos Díaz Gay

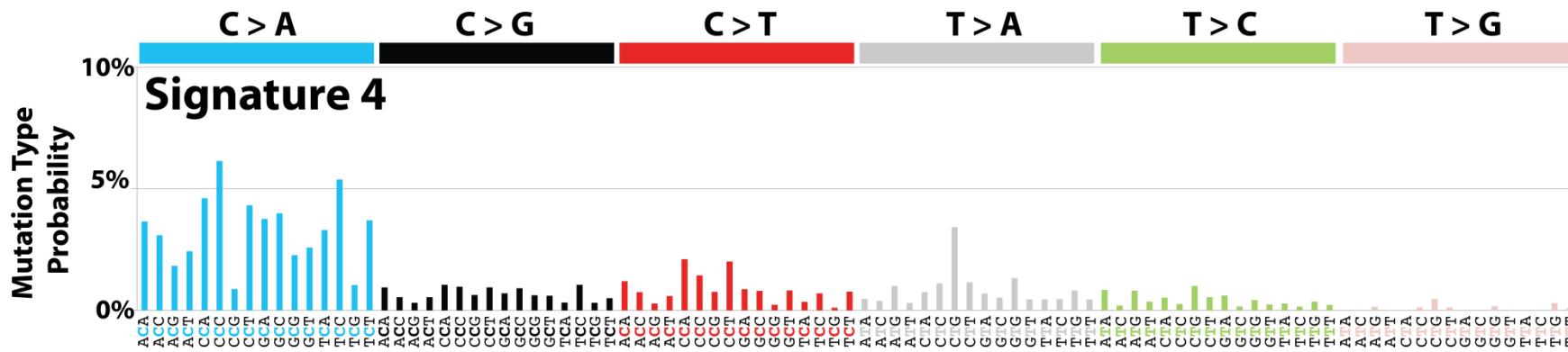
Alexandrov lab, University of California San Diego

UC San Diego



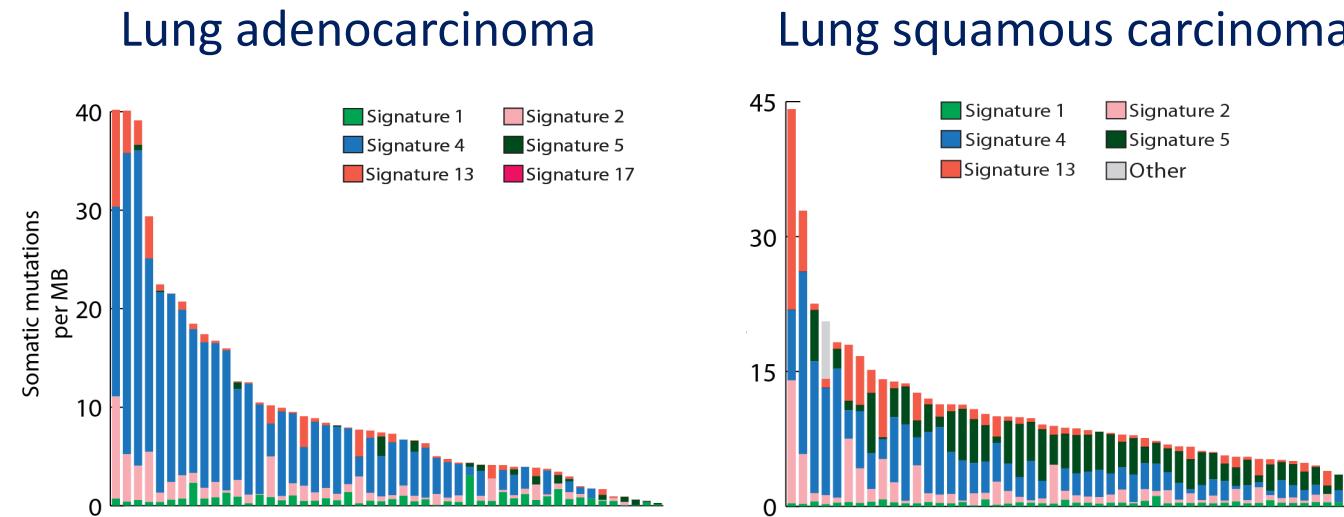
How do you know mutational signature etiologies?

Signature SBS4 is likely due to tobacco smoking

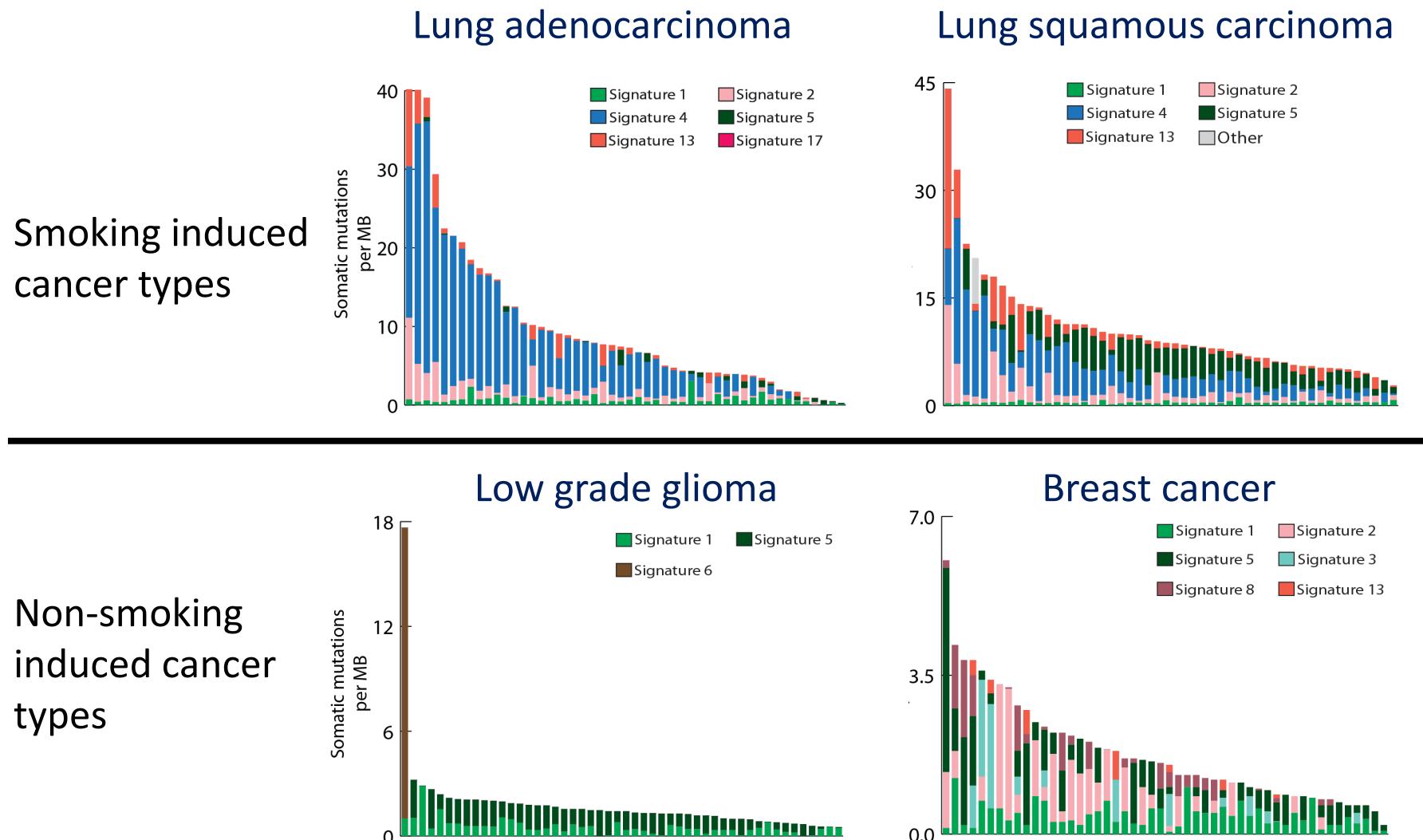


Contributions of mutational signatures to smoking induced and non-smoking induced cancer types

Smoking induced
cancer types



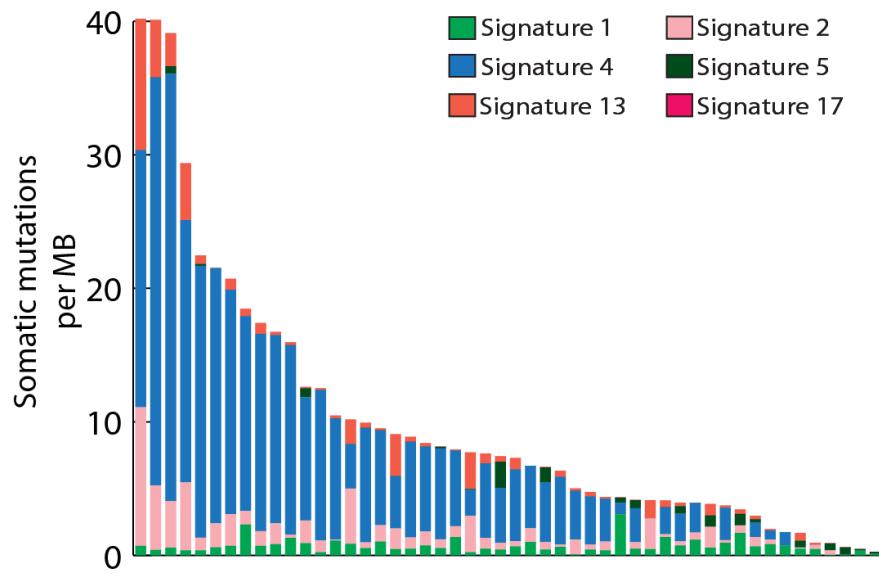
Contributions of mutational signatures to smoking induced and non-smoking induced cancer types



Contributions of mutational signatures to lung adenocarcinomas

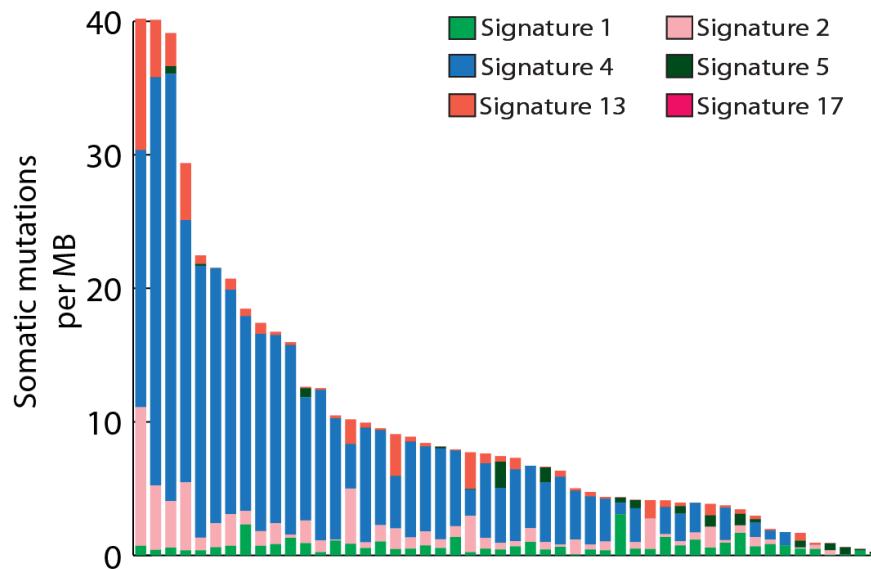
Contributions of mutational signatures to lung adenocarcinomas

Tobacco smokers

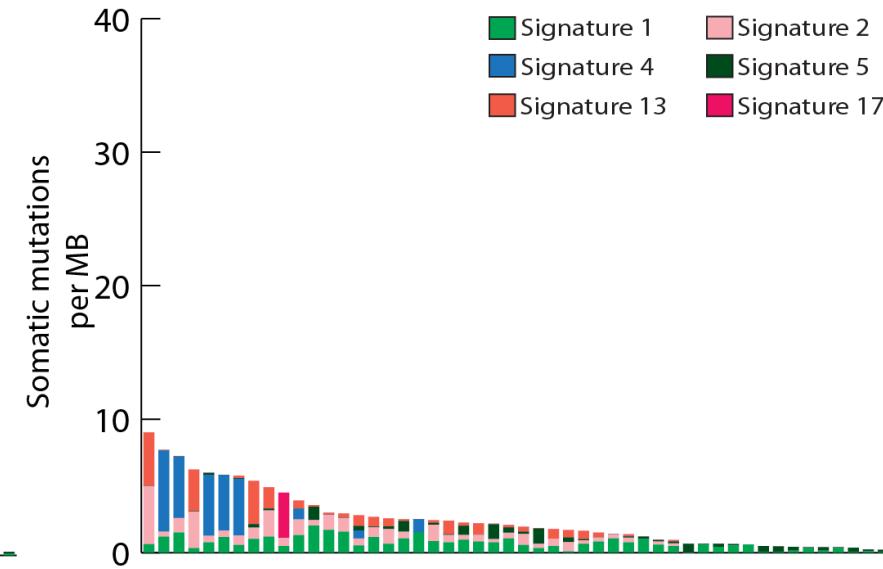


Contributions of mutational signatures to lung adenocarcinomas

Tobacco smokers

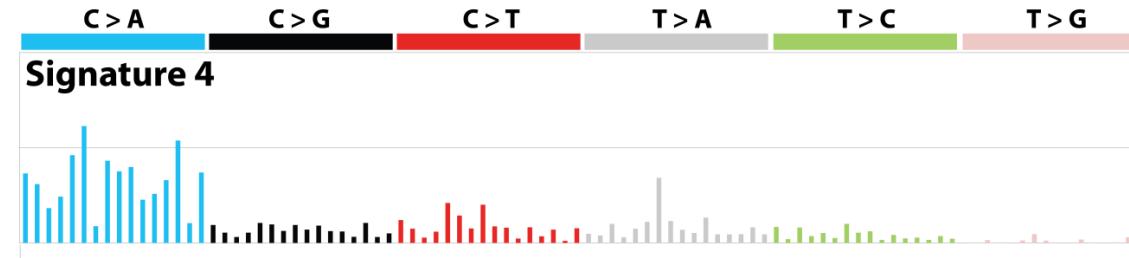


Life-long non-smokers



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

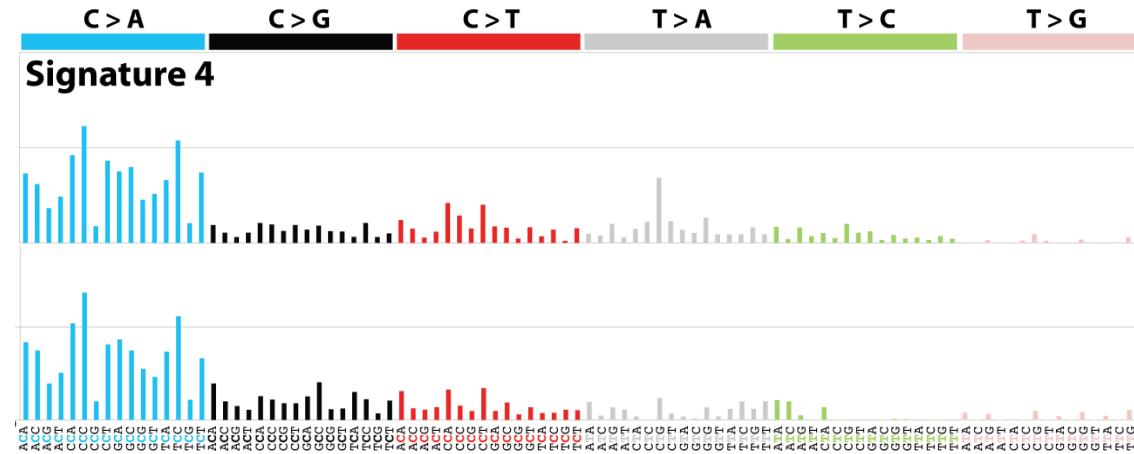
Signature 4 extracted from human cancers



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*



Evidence for the aetiology of signature 4

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Identified only in cancer types epidemiologically known to be caused by tobacco smoking

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The pattern of signature 4 matches *in vitro* experimental results in which cells were exposed to known tobacco carcinogens

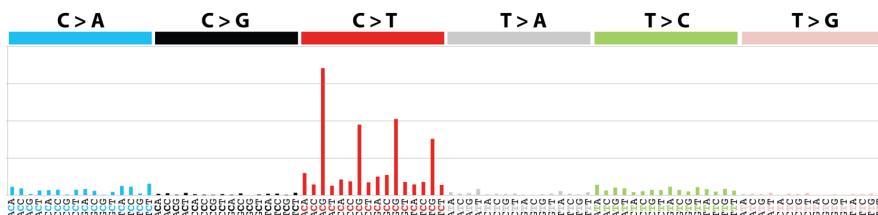
Mutational signature analysis marked a turning point in cancer diagnosis, prognosis and treatment



Cancer Cell
Article

Mutational Signature Analysis Reveals NTHL1 Deficiency to Cause a Multi-tumor Phenotype

Judith E. Grolleman,^{1,36} Richarda M. de Voer,^{1,36,38,*} Fadwa A. Elsayed,^{2,36} Maartje Nielsen,^{3,36} Robbert D.A. Weren,^{1,36} Claire Palles,⁴ Marjolijn J.L. Ligtenberg,^{1,5} Janet R. Vos,⁶ Sanne W. ten Broeke,⁷ Noel F.C.C. de Miranda,² Renske A. Kuiper,¹ Eveline J. Kamping,¹ Erik A.M. Jansen,¹ M. Elisa Vink-Börger,⁸ Isabell Popp,⁷ Alois Lang,⁸ Isabel Spier,^{9,10} Robert Huneburg,^{10,11} Paul A. James,¹² Na Li,^{13,14} Marija Staninova,¹⁵ Helen Lindsay,¹⁶



nature
medicine

HRDetect is a predictor of *BRCA1* and *BRCA2* deficiency based on mutational signatures

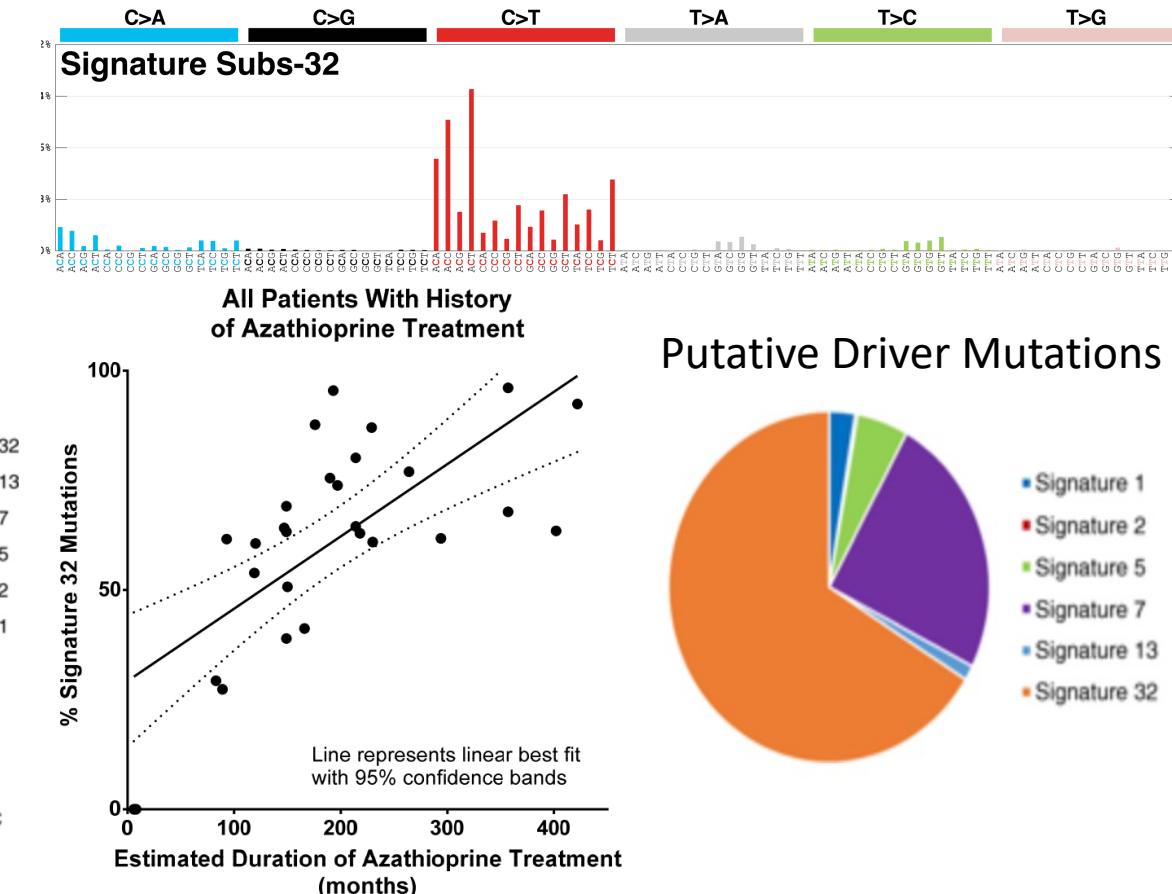
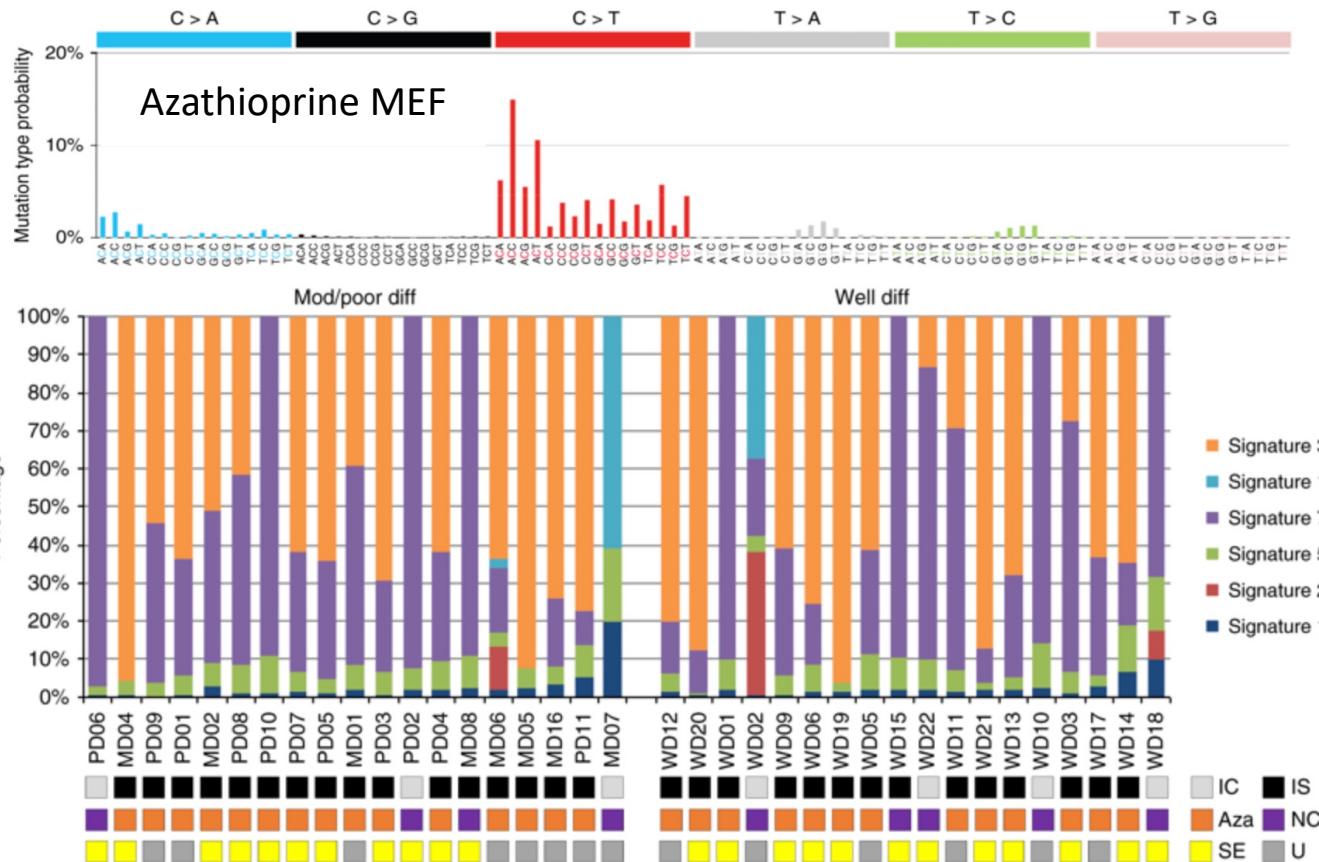
Helen Davies^{1,32}, Dominik Glodzik^{1,32}, Sandro Morganella¹, Lucy R Yates^{1,2}, Johan Staaf³, Xueqing Zou¹, Manasa Ramakrishna^{1,4}, Sancha Martin¹, Sandrine Boyault⁵, Anieta M Sieuwerts⁶, Peter T Simpson⁷, Tari A King⁸, Keiran Raine¹, Jorunn E Eyfjord⁹, Gu Kong¹⁰, Åke Borg³, Ewan Birney¹¹, Hendrik G Stunnenberg¹², Marc J van de Vijver¹³, Anne-Lise Børresen-Dale^{14,15}, John W M Martens⁶, Paul N Span^{16,17}, Sunil R Lakhani^{7,18}, Anne Vincent-Salomon^{19,20}, Christos Sotiriou²¹, Andrew Tutt^{22,23}, Alastair M Thompson²⁴, Steven Van Laere^{25,26}, Andrea L Richardson^{27,28}, Alain Viari^{29,30}, Peter J Campbell¹, Michael R Stratton¹ & Serena Nik-Zainal^{1,31}

Clinical examples

(Somewhat) unexpected carcinogens: Azathioprine



Azathioprine, sold under the brand name Imuran among others, is an immunosuppressive medication. Azathioprine is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Epidemiological studies by International Agency for Research on Cancer have provided "sufficient" evidence of azathioprine carcinogenicity in humans (Group 1), although the methodology of past studies and the possible underlying mechanisms are questioned.

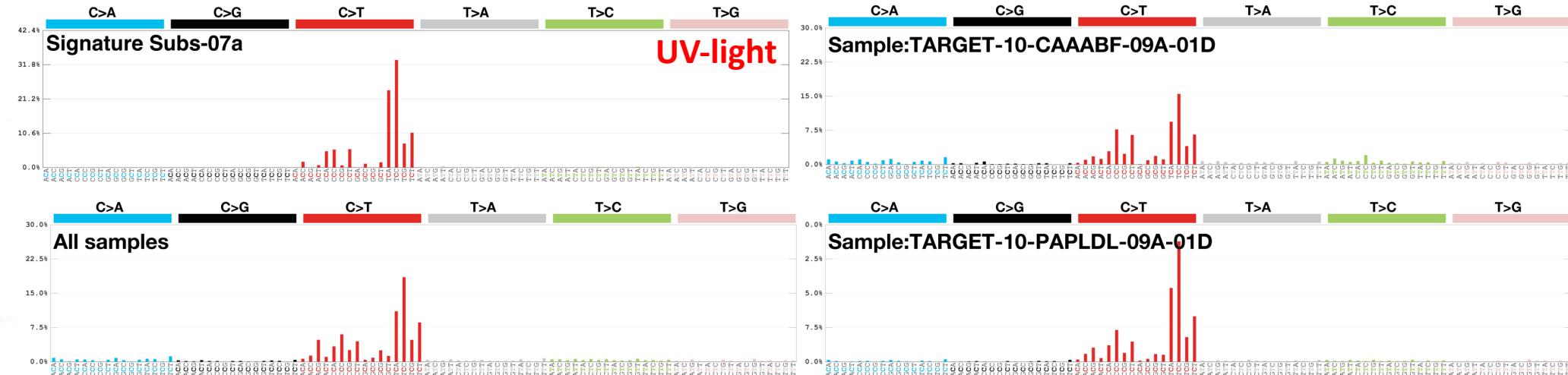
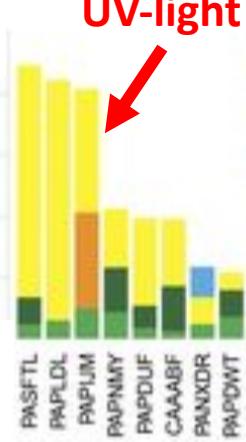


Known carcinogen in unexpected cancer types: UV-light

Somatic Mutation per MB

B-Cell ALL

UV-light



Similarity extends to strand bias, dinucleotide, and indel patterns. Confirmed in three other cohorts.
Signature found only in white Caucasian children. Much lower mutation burden compared to skin cancer.



Cancer Causes & Control

October 2017, Volume 28, Issue 10, pp 1075–1083 | Cite as

Residential exposure to ultraviolet light and risk of precursor B-cell acute lymphoblastic leukemia: assessing the role of individual risk factors, the ESCALE and ESTELLE studies

Authors

Authors and affiliations

Astrid Coste , Denis Hémon, Laurent Orsi, Mathieu Boniol, Jean-François Doré, Laure Faure, Jacqueline Clavel, Stéphanie Goujon

UV-light high confidence cancer types:

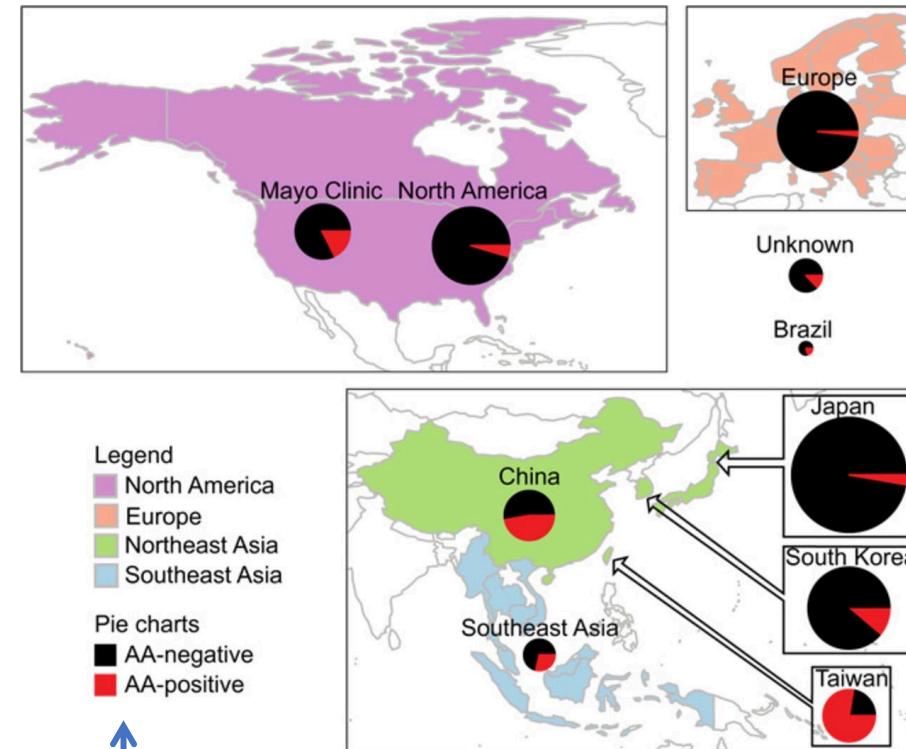
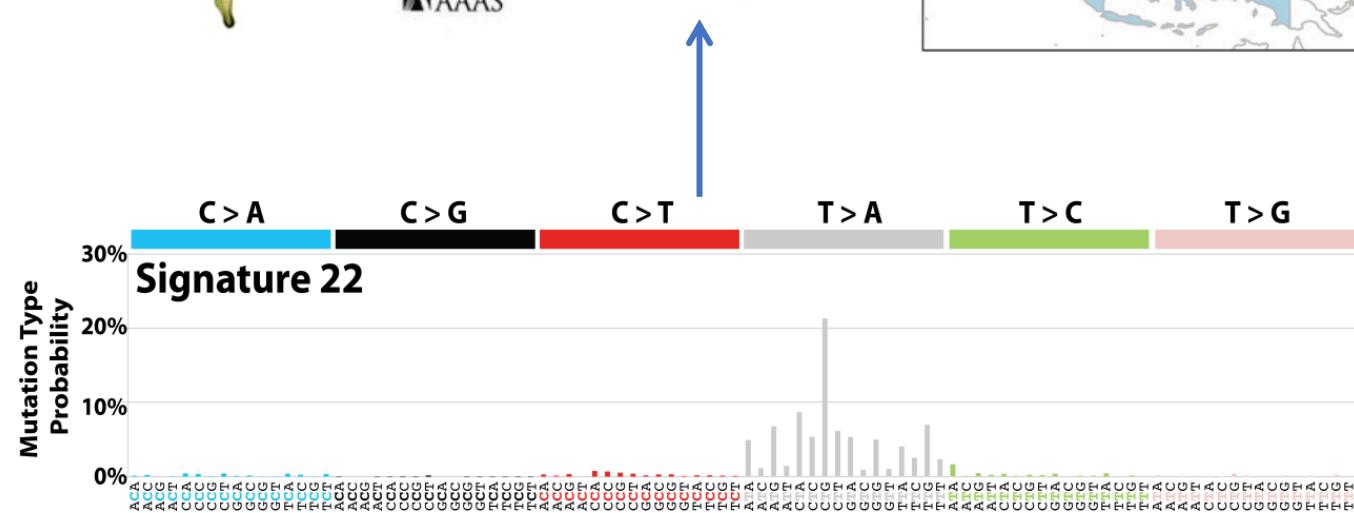
- Basal Cell Carcinoma
- Squamous cell carcinoma
- Cutaneous melanoma (NOT in uveal melanoma)
- Lip cancer (H&N)
- B-cell ALL (childhood)
- Sarcomas (adulthood)
- Squamous cell lung carcinoma (all melanoma metastasis)

Ma et al. 2018 Nature

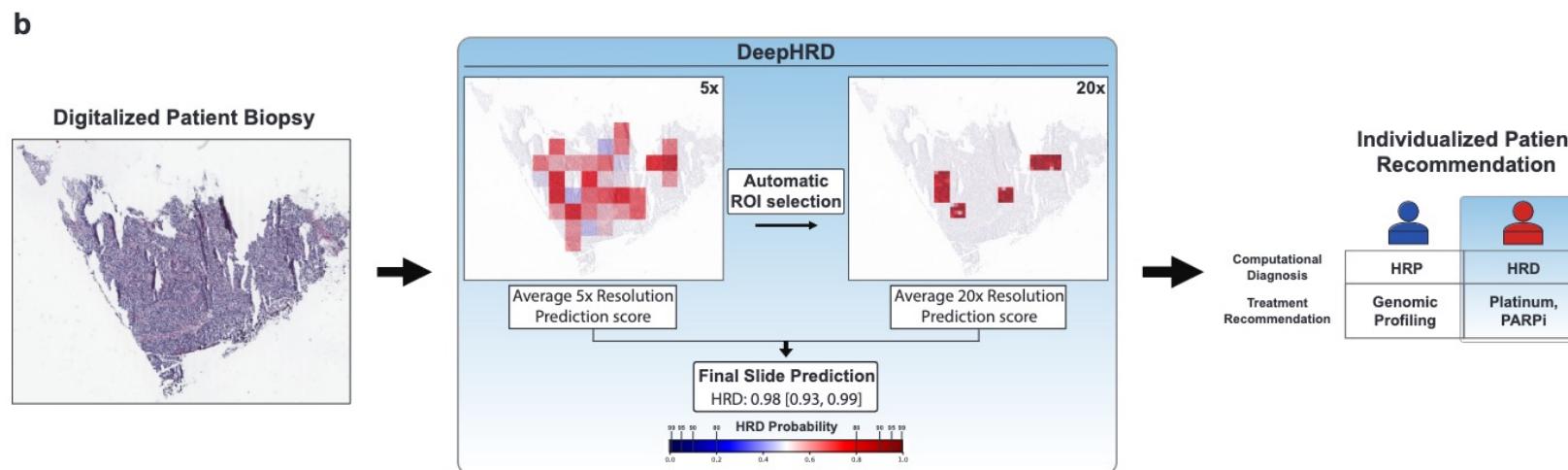
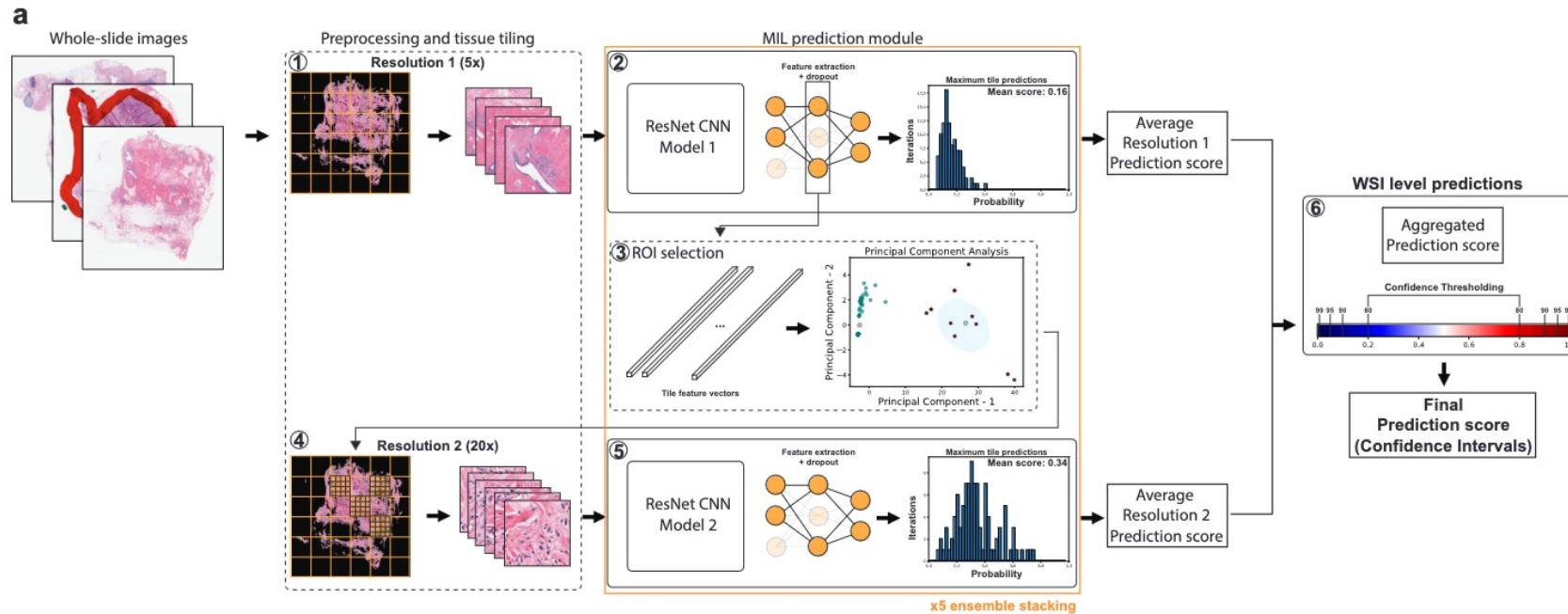
Quantification of known carcinogens in suspected cancer types

Science Translation Medicine





Deep learning image analysis to predict HRD and other signatures



Summary

- Different mutational processes generate somatic mutations, including endogenous and exogenous sources
- The pattern of mutations imprinted by a particular mutational process is known as mutational signature
- Reference mutational signatures have been identified and deposited in COSMIC after the analysis of thousands of cancer samples
- Leveraging these reference signatures, the contributions of the different mutational processes to a given tumor can be quantified
- Mutational signatures can be used clinically as biomarkers for cancer prevention, prognosis and treatment

Acknowledgements



Alexandrov lab

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Stephen Duke

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Wellington Oliveira
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