

Which mutations are relevant? Strategies for identification

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<http://cancer.sanger.ac.uk/cosmic/signatures>
www.mutationsignatures.org



International
Cancer Genome
Consortium

wellcome trust

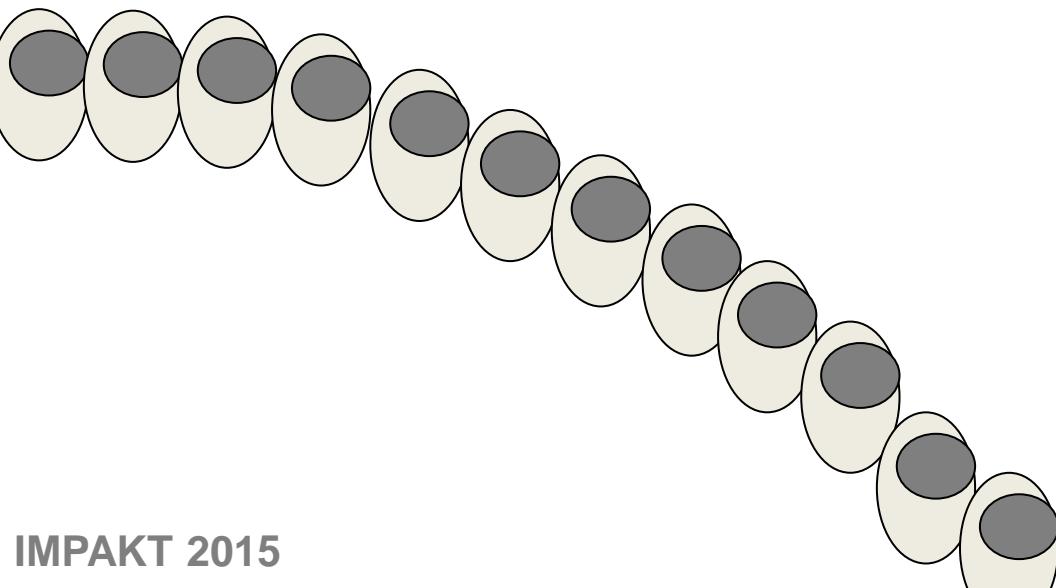




Fertilised
egg

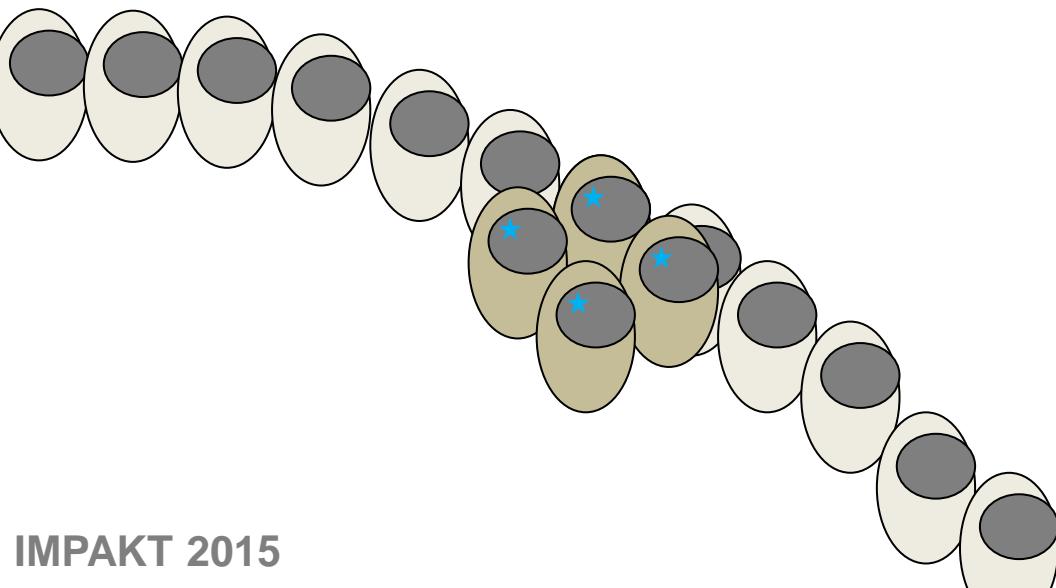


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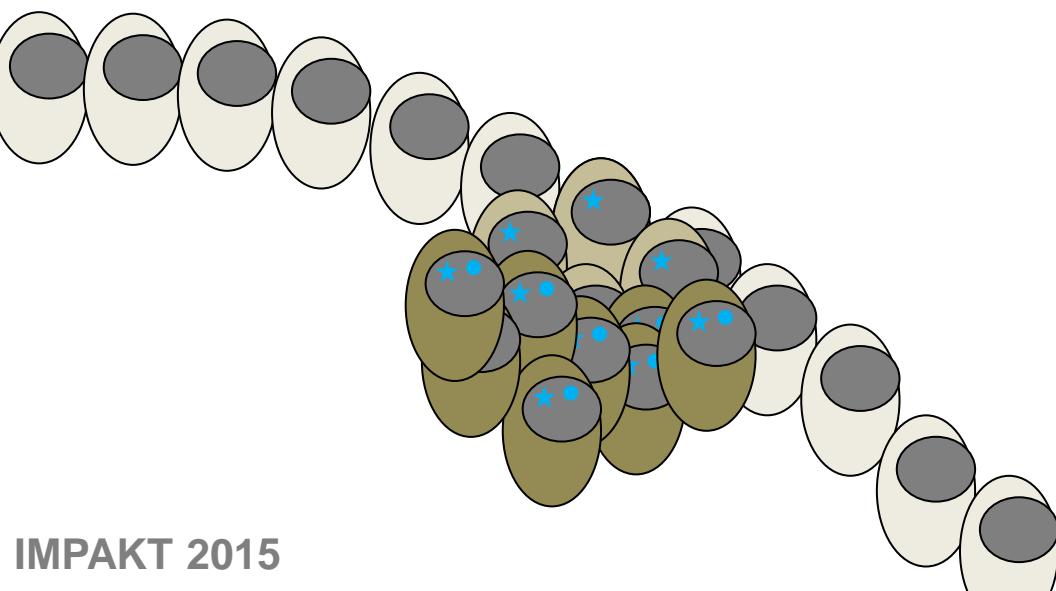


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egg



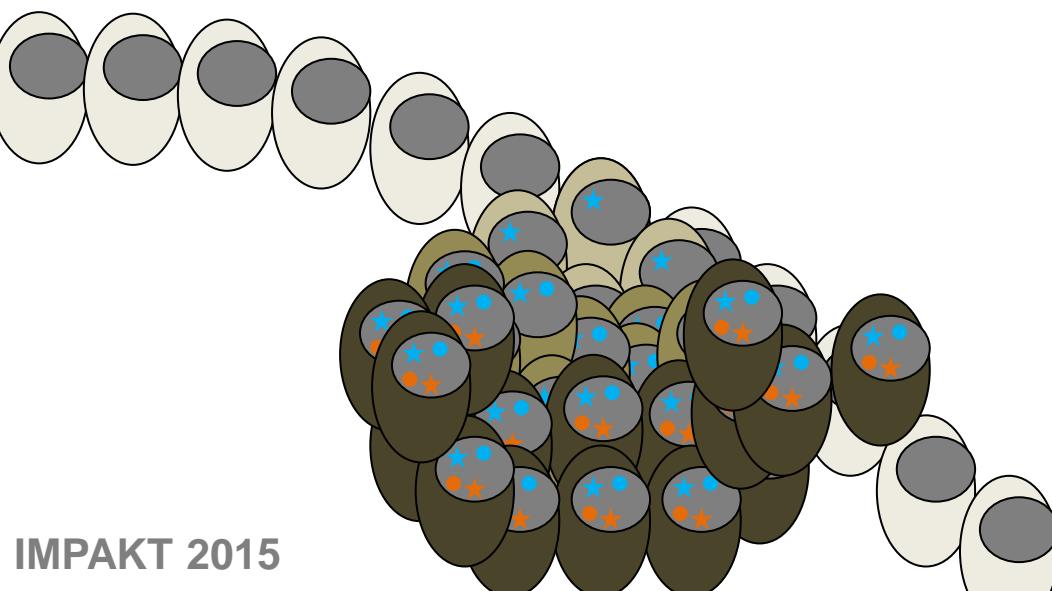


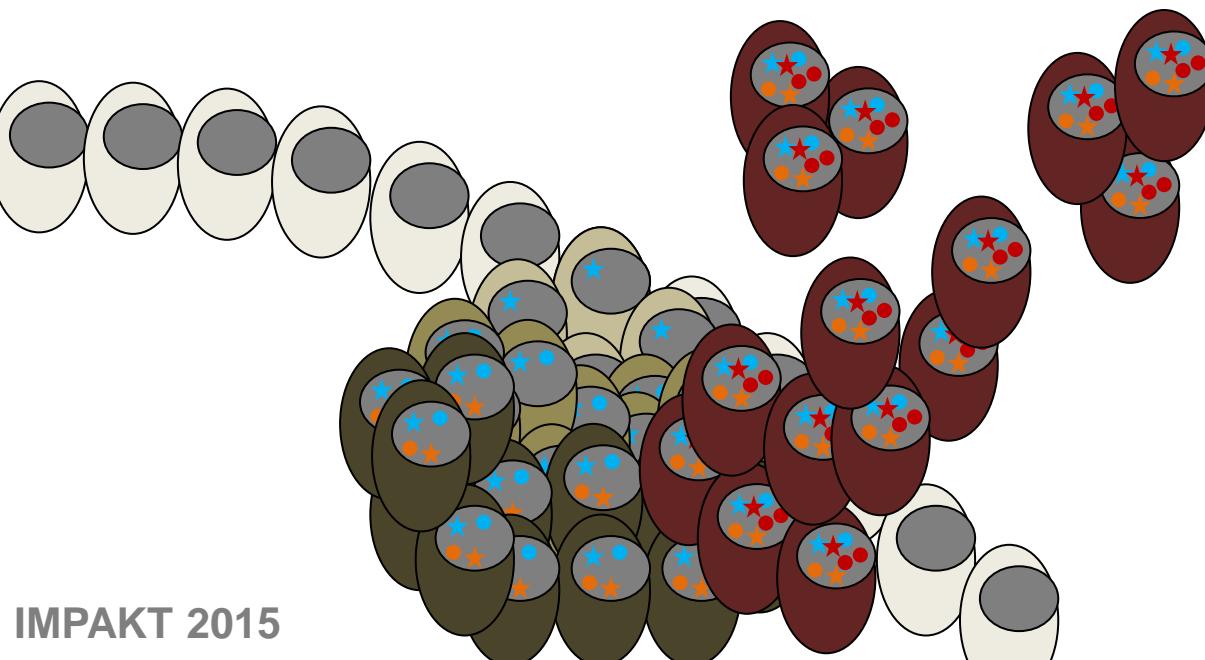
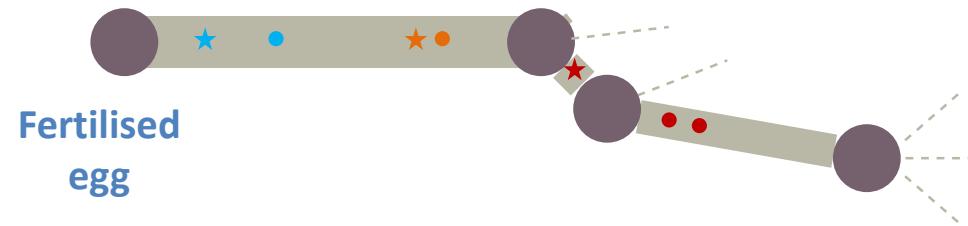
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egg

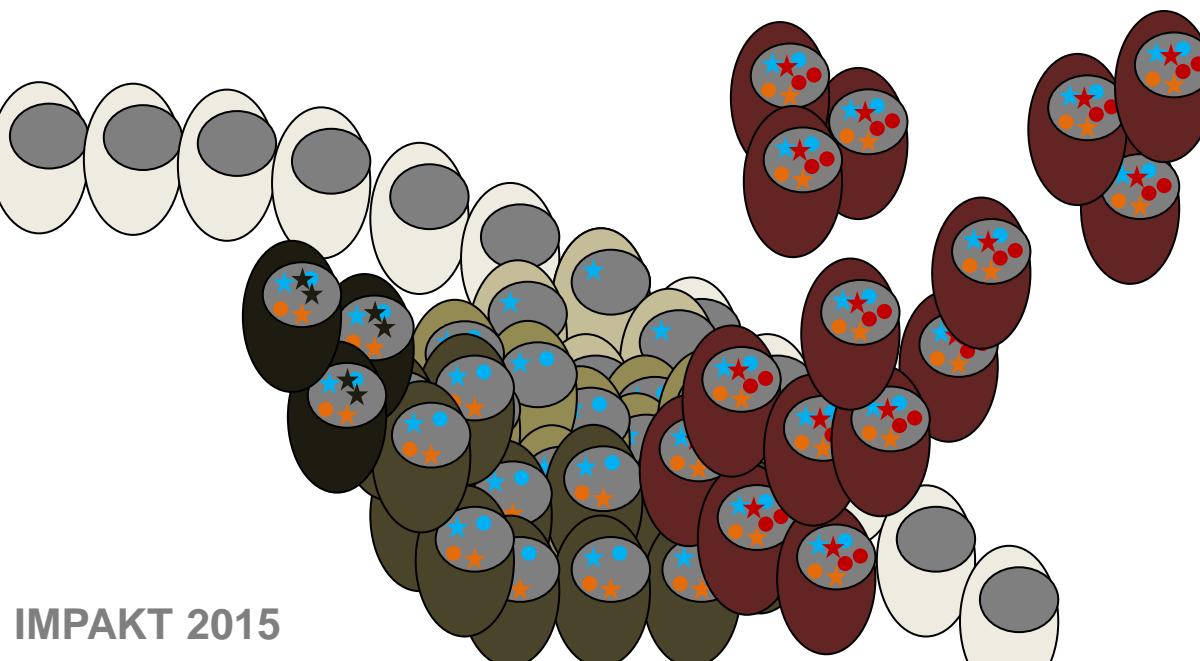
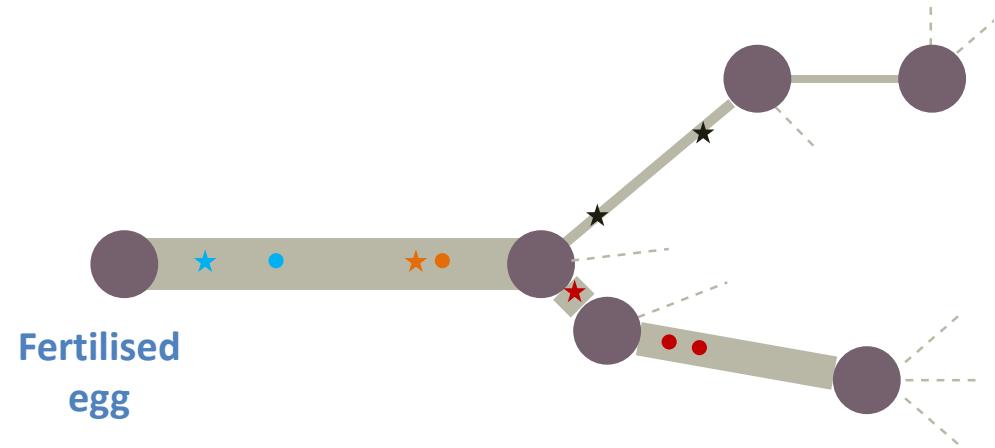


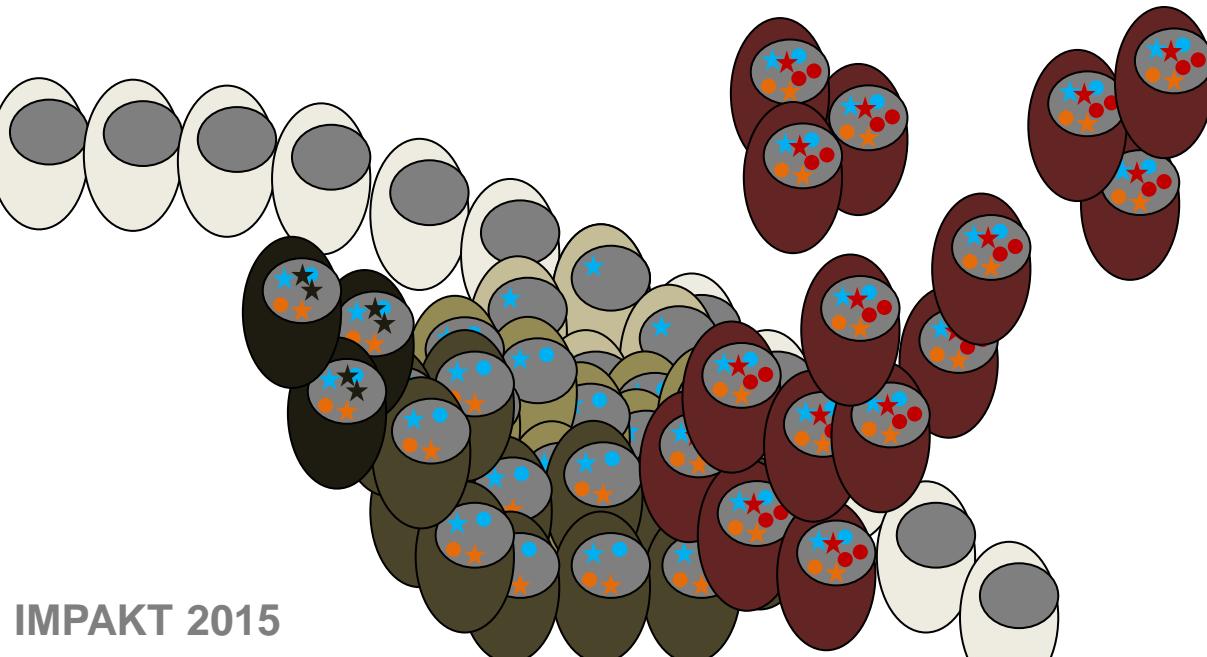
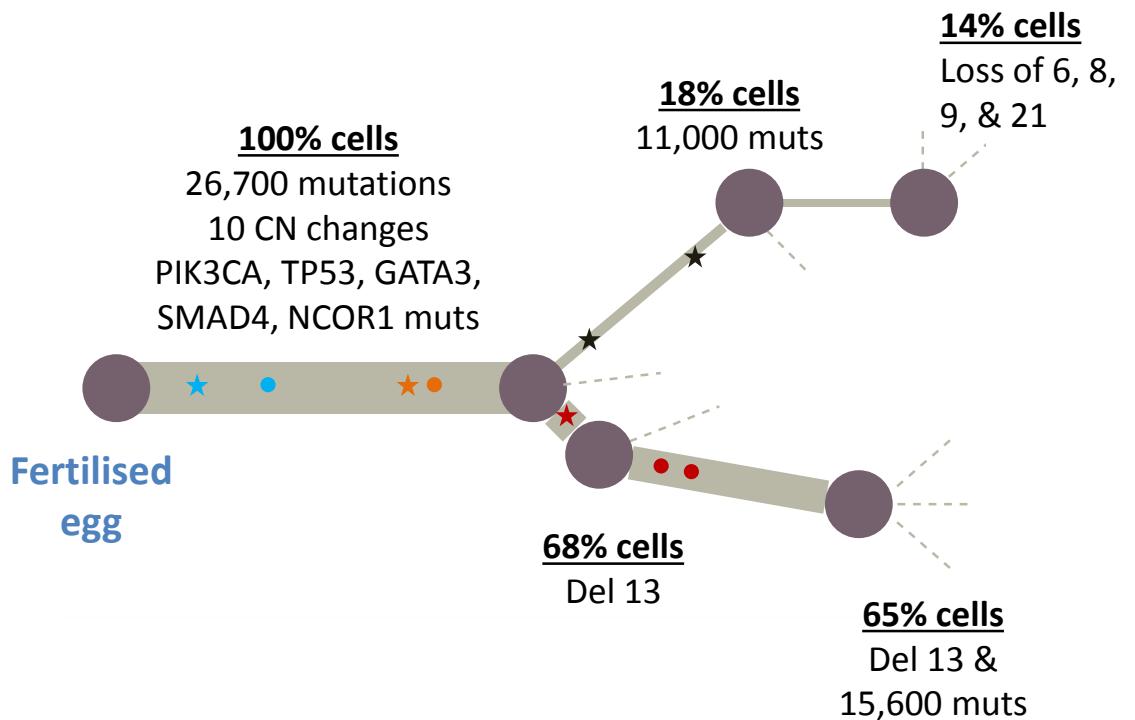


Fertilised
egg









Driver mutations in cancer genes

- Genomic scenario
 - *ERBB2* Amplification
 - (Breast Cancer)
 - *BCR-ABL*
 - (CML)
 - *EGFR*
 - (*NSCLC*)
 - *EML4-ALK*
 - (*NSCLC*)
 - *KRAS*-negative
 - (colorectal cancer)
 - *BRAF(V600E)*
 - (*Metastatic Melanoma*)
- Targeted drug
 - Herceptin & Lapatinib
 - Imatinib (and others)
 - Erlotinib, Gefitinib
 - Crizotinib
 - Cetuximab
 - Vemurafenib

Driver mutations in cancer genes



Pre-treatment



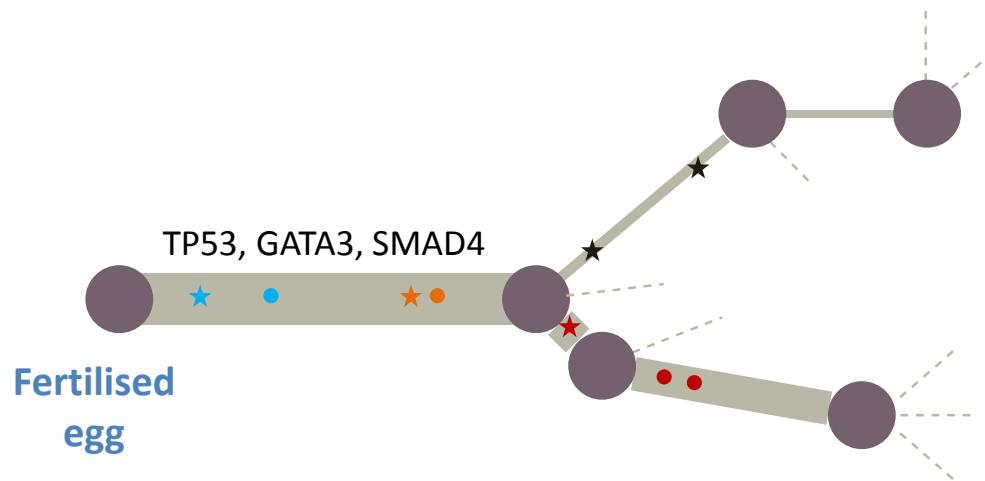
15 Weeks



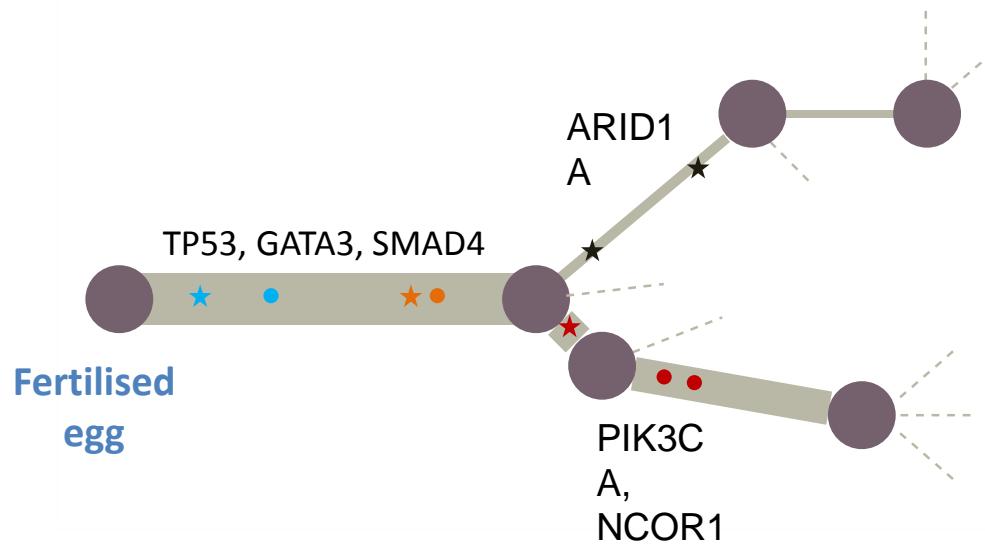
23 Weeks

Wagle et al. *JCO*, 2011

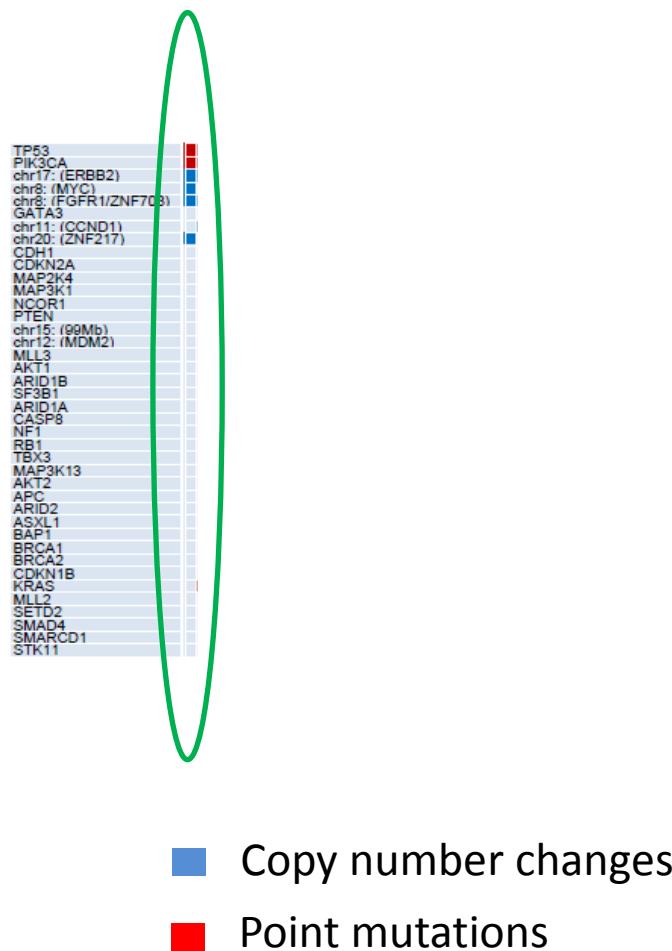
Driver mutations in cancer genes



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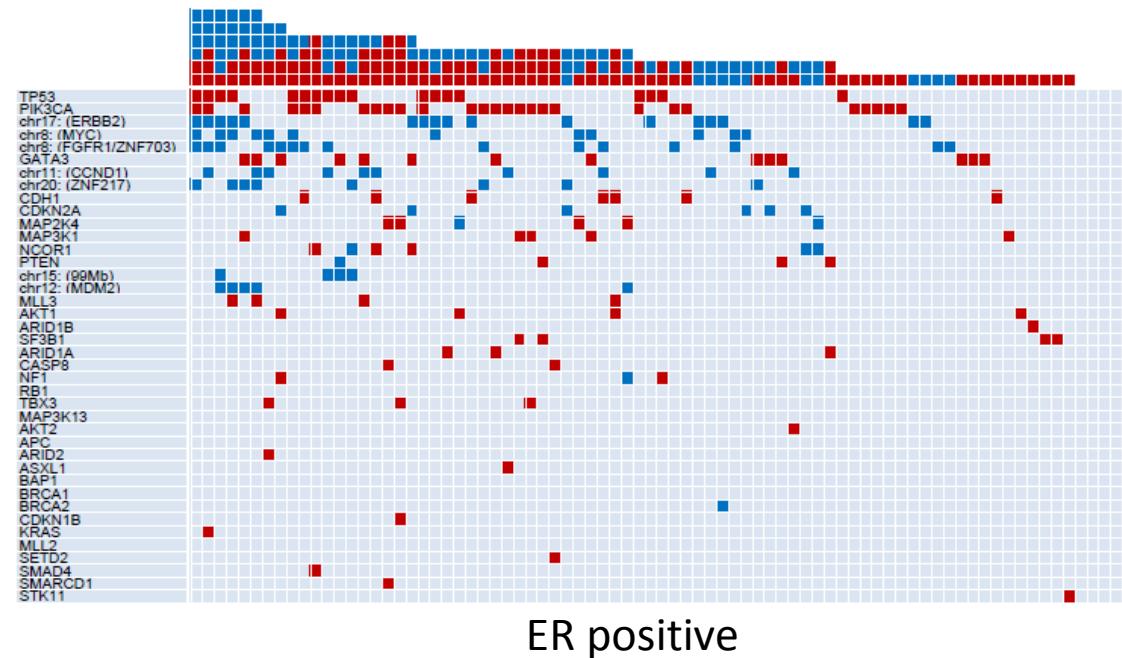


Driver mutations in cancer genes



Stephens et al 2012

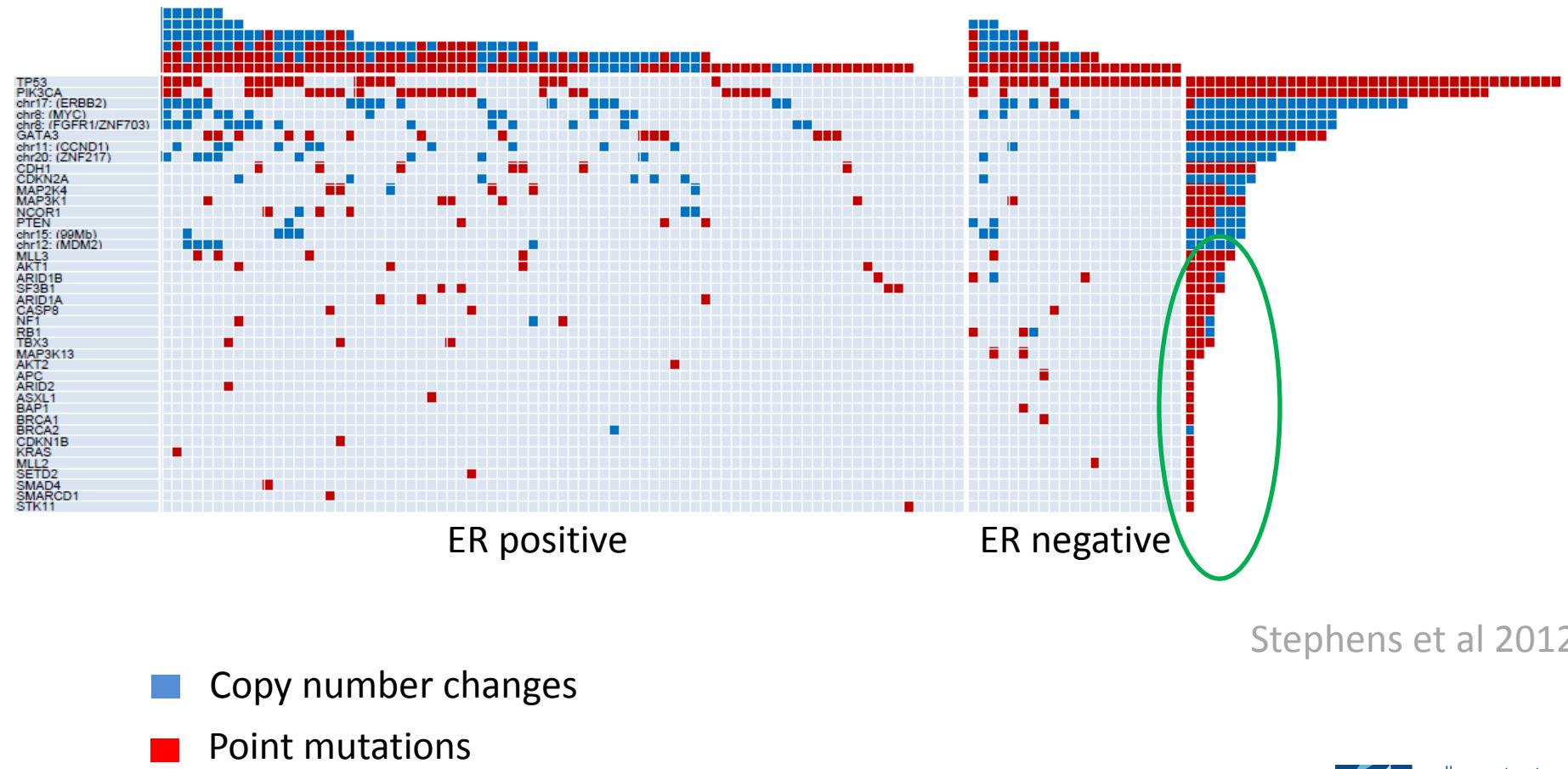
Driver mutations in cancer genes



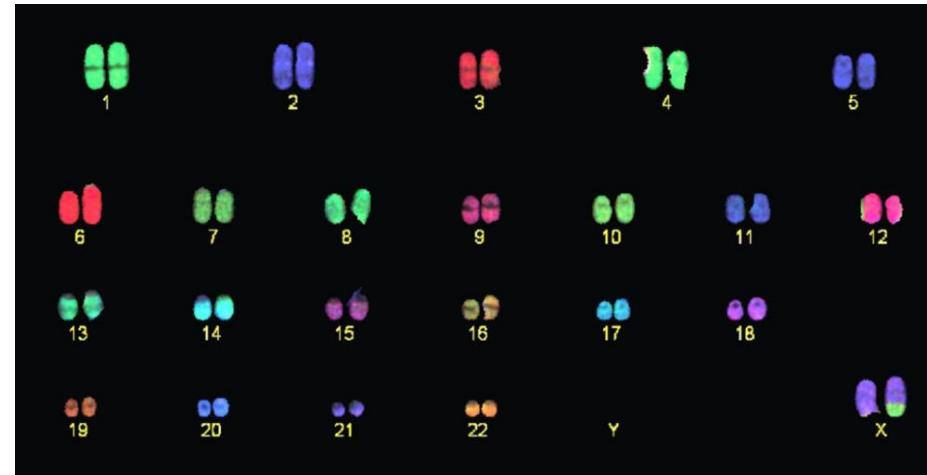
- Copy number changes
- Point mutations

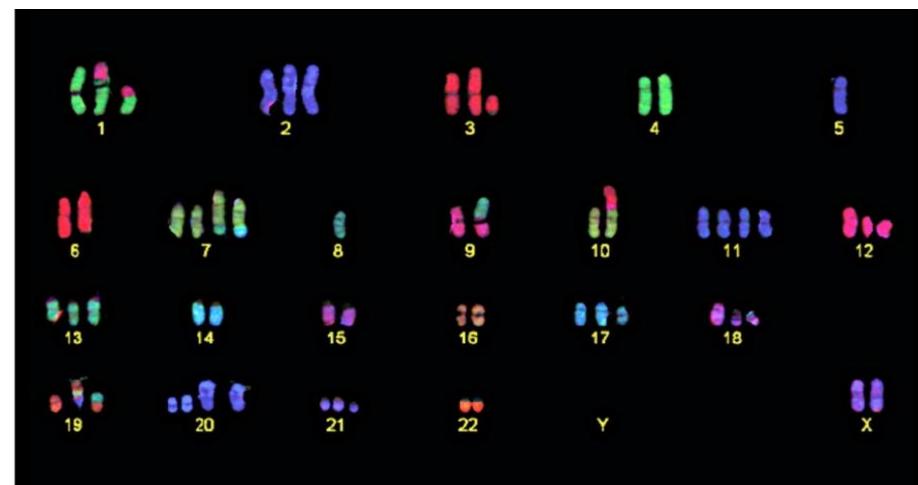
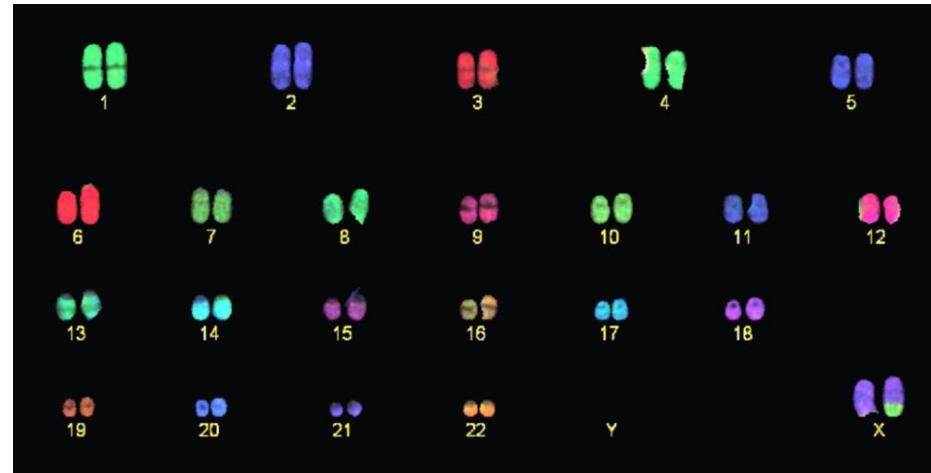
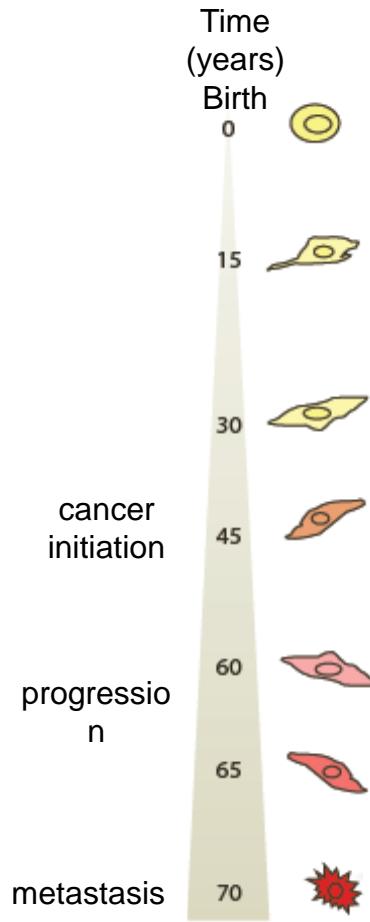
Stephens et al 2012

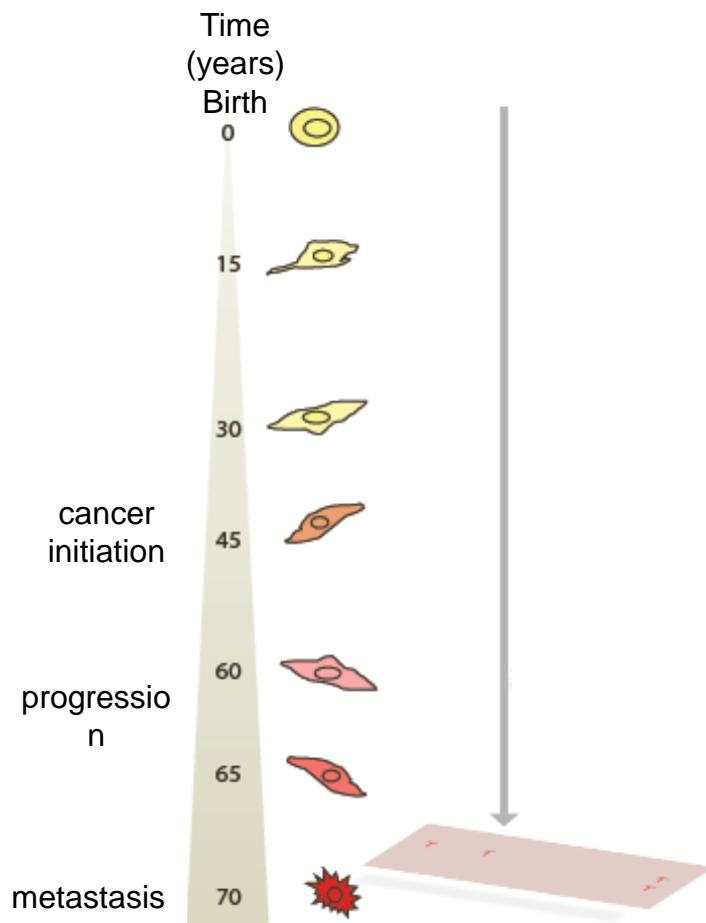
Driver mutations in cancer genes

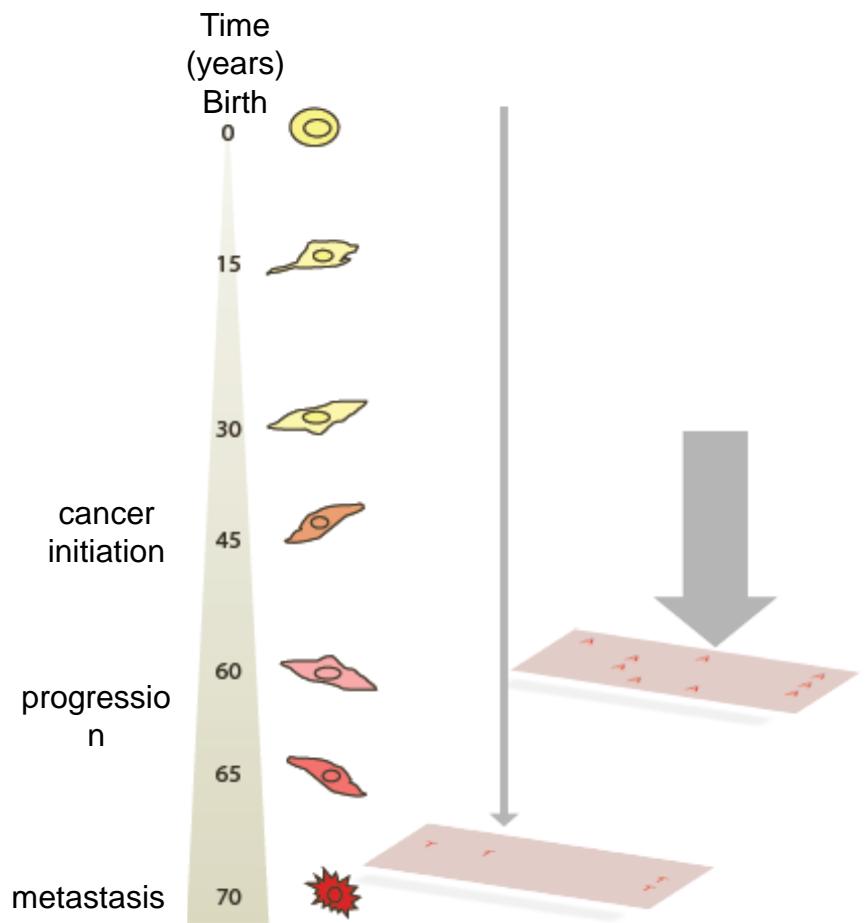


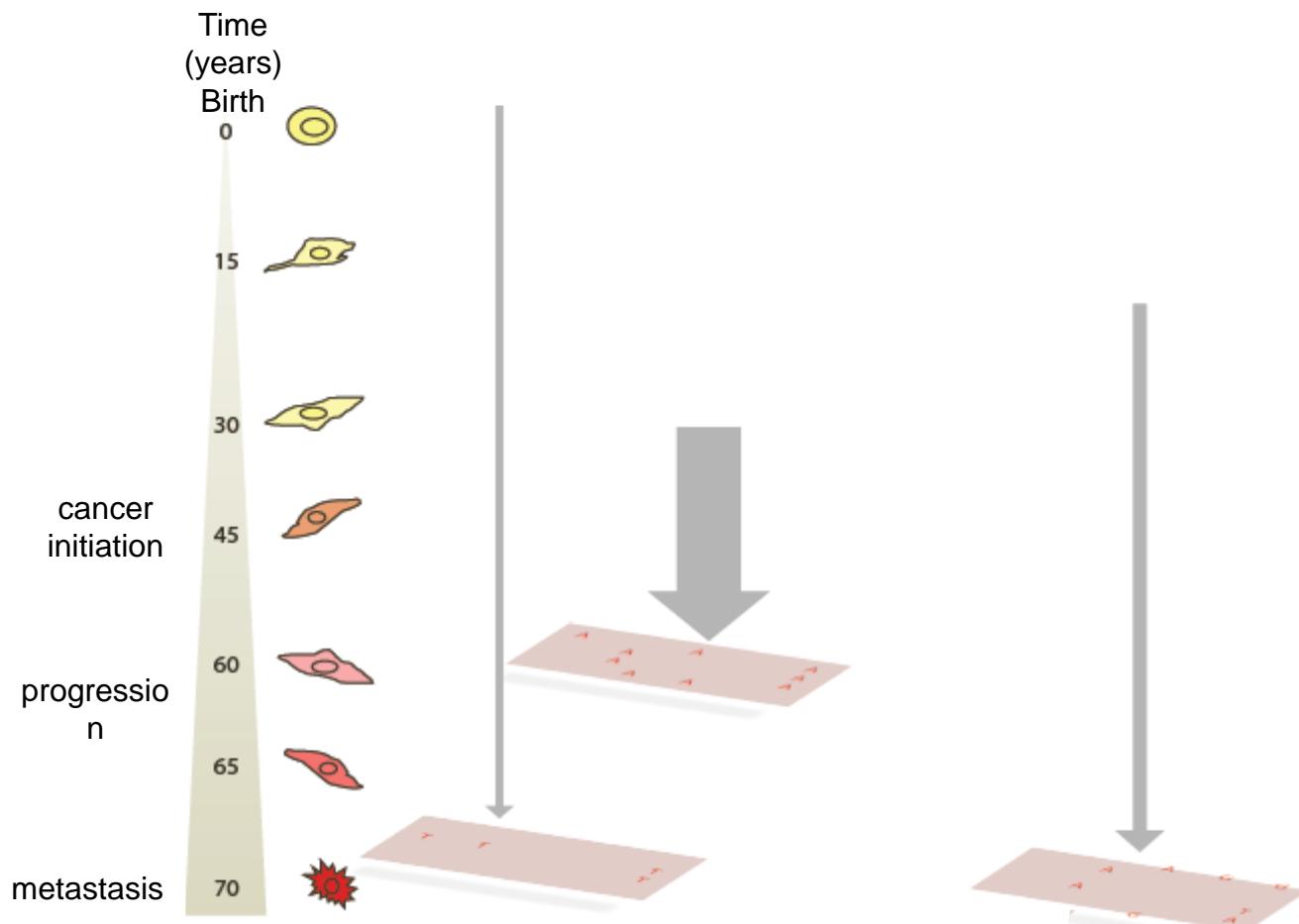
Time
(years)
Birth
0

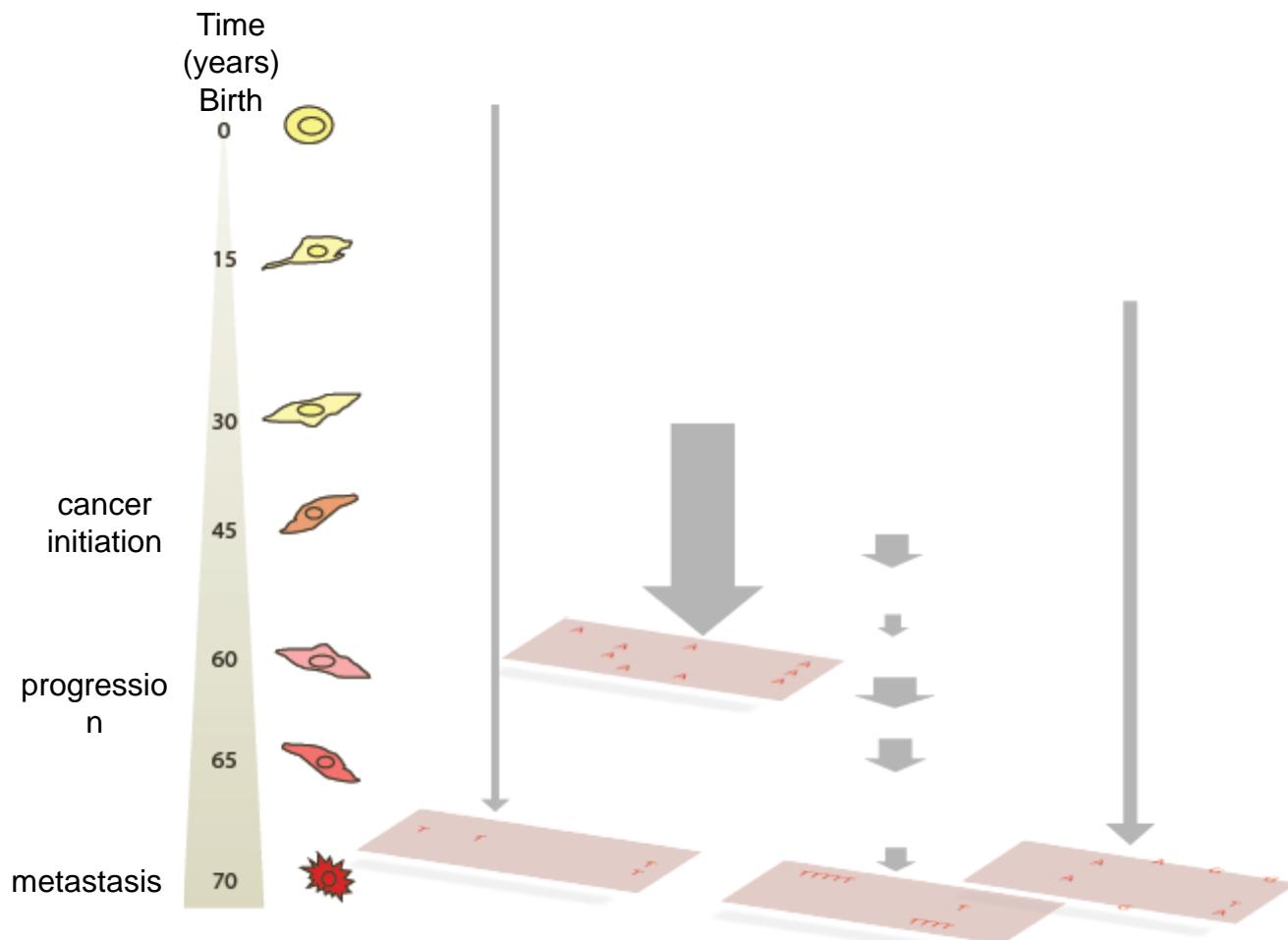


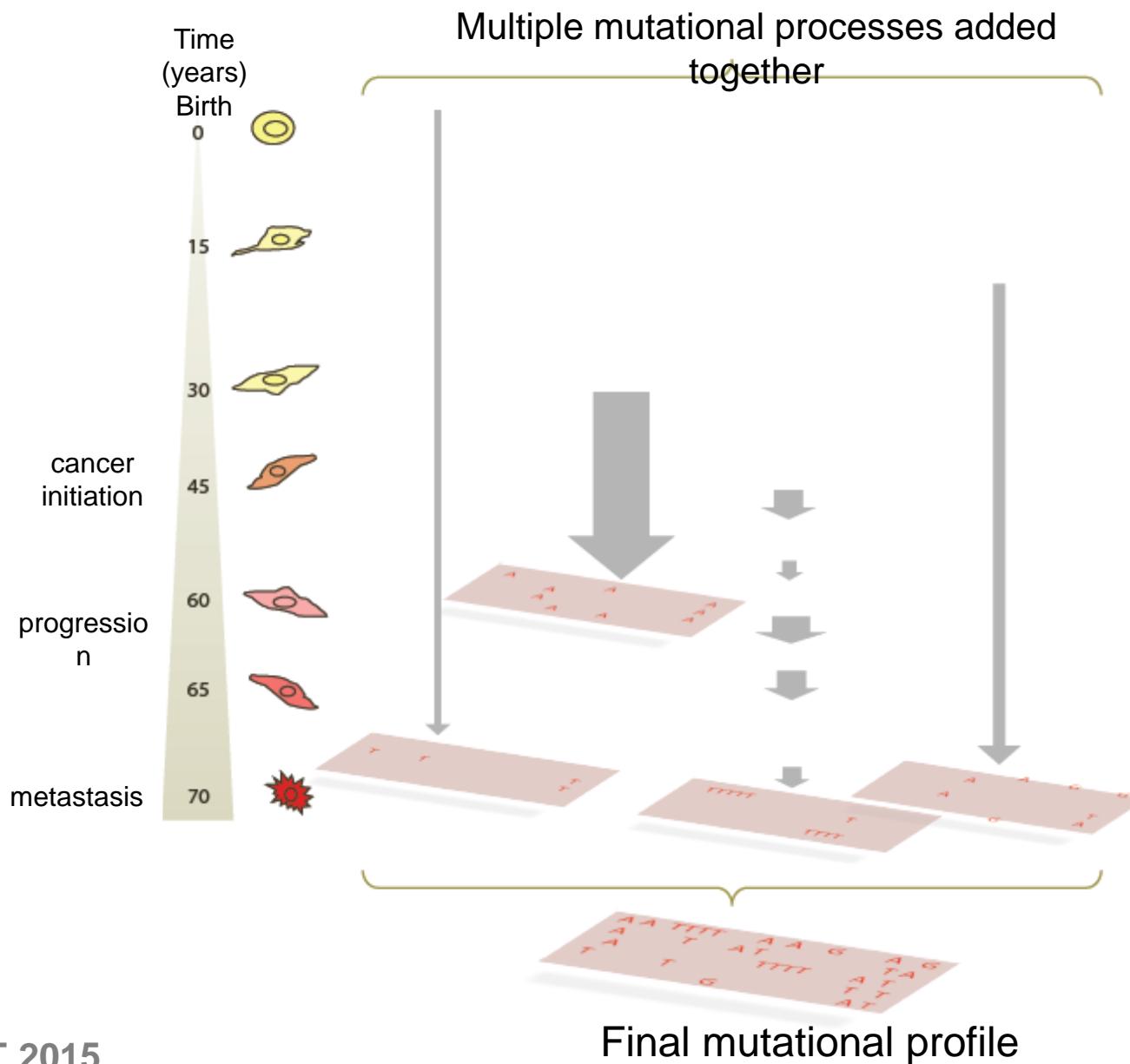












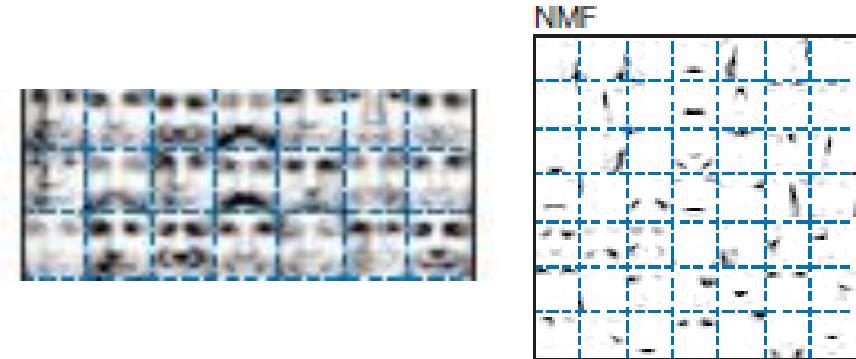
Extracting mutation signatures

Learning the parts of objects by non-negative matrix factorization

Daniel D. Lee* & H. Sebastian Seung*†

* Bell Laboratories, Lucent Technologies, Murray Hill, New Jersey 07974, USA

† Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA



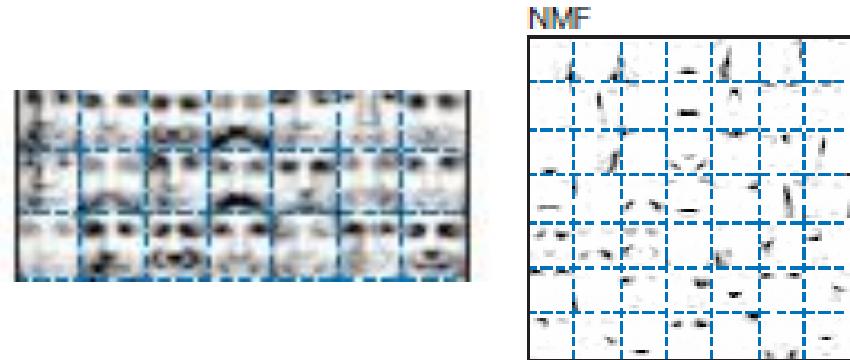
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Cell

Mutational Processes Molding the Genomes of 21 Breast Cancers

Serena Nik-Zainal,¹ Ludmil B. Alexandrov,¹ David C. Wedge,¹ Peter Van Loo,^{1,2,3} Christopher D. Greenman,^{1,4,5}

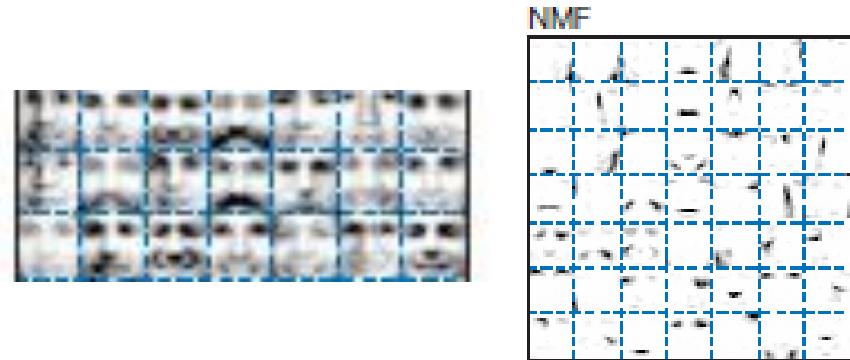
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Open
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Cell Reports
Resource

Deciphering Signatures of Mutational Processes Operative in Human Cancer

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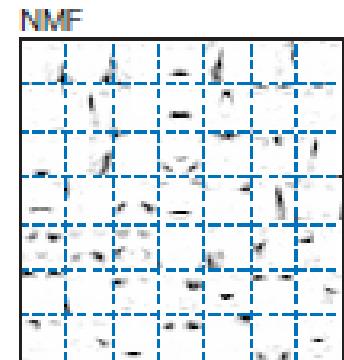
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ARTICLE

doi:10.1038/nature12477

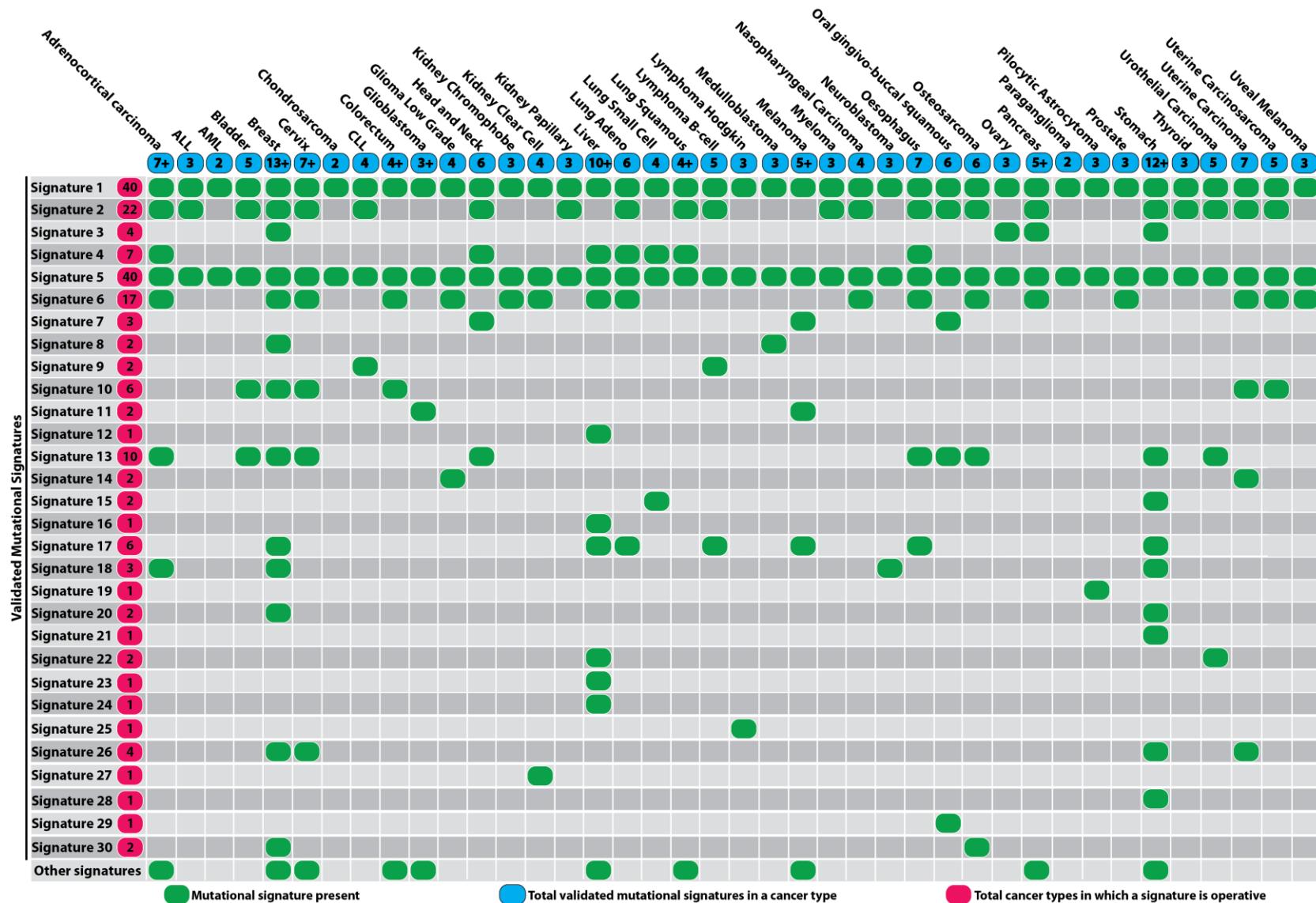
Signatures of mutational processes in human cancer

A list of authors and their affiliations appears at the end of the paper

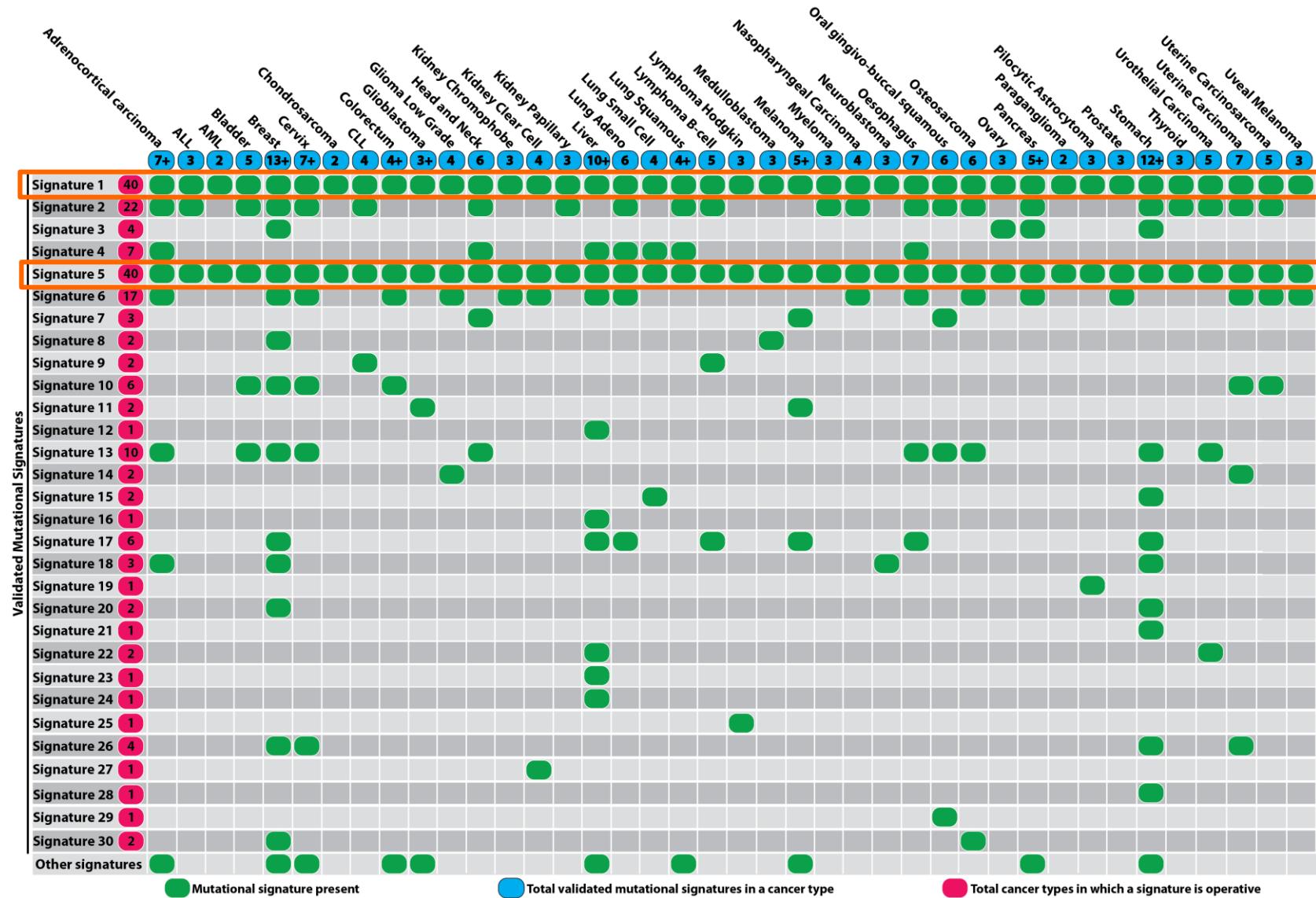
Extracting mutation signatures



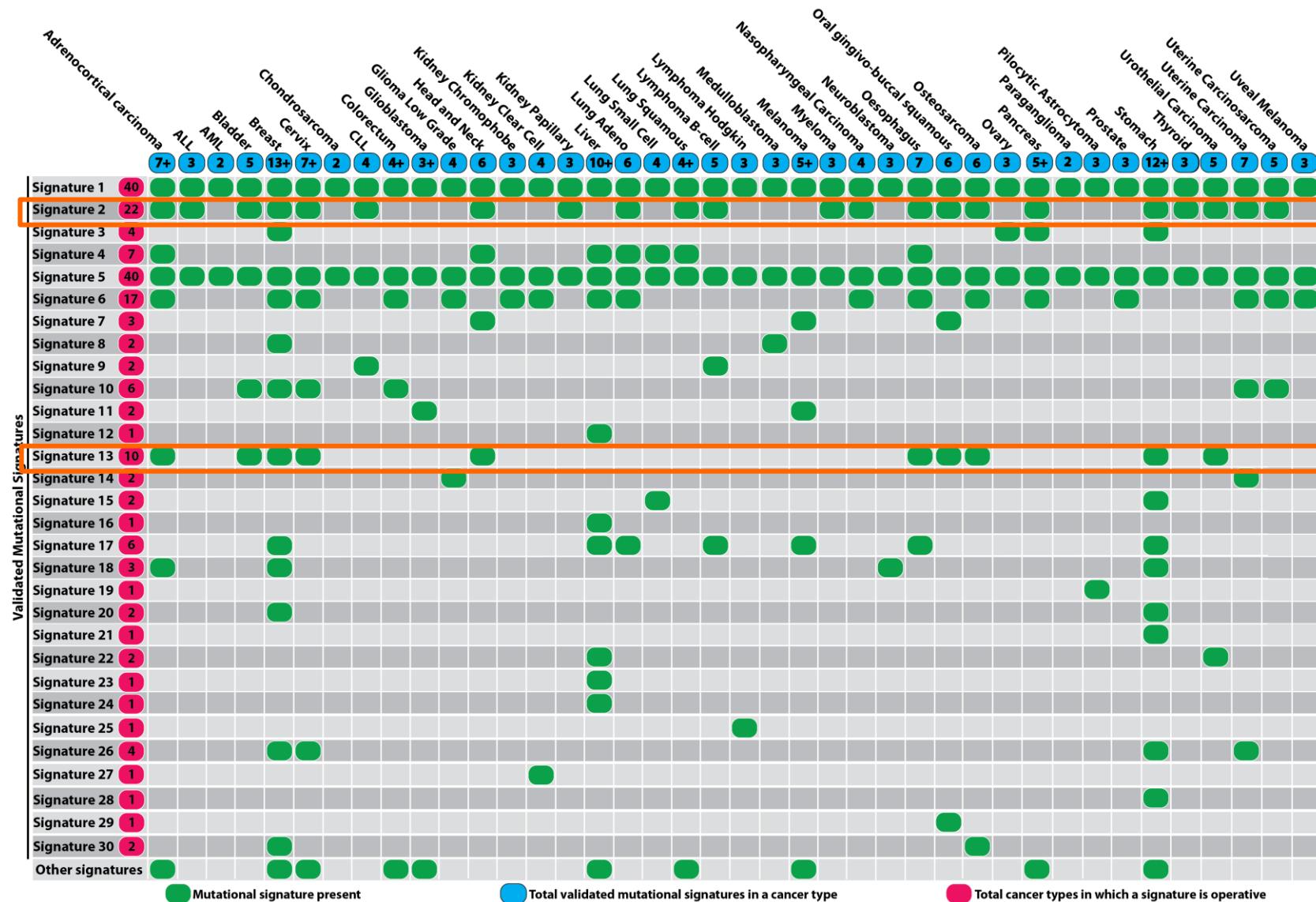
Extracting mutation signatures



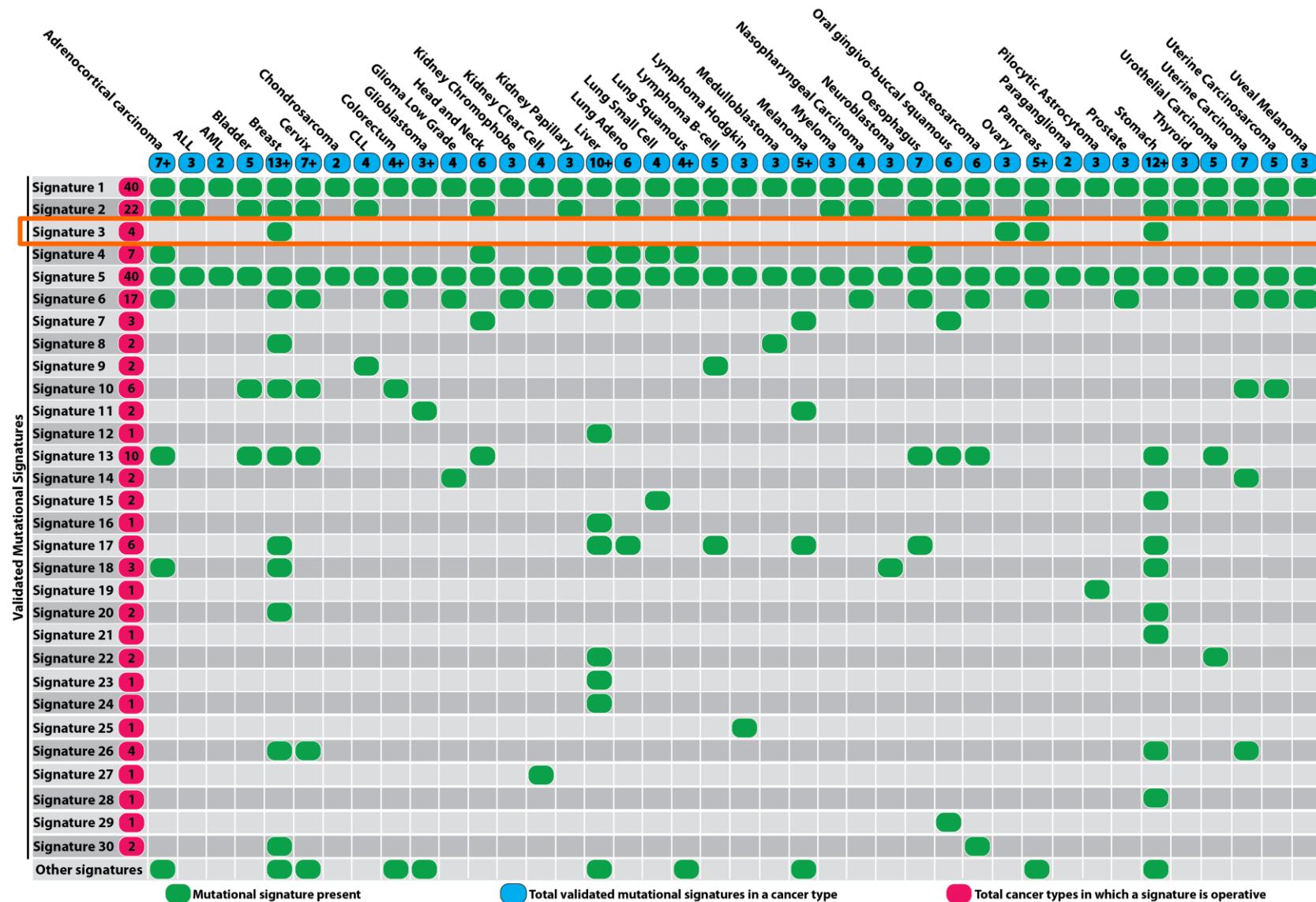
Signatures occurring in many cancer types



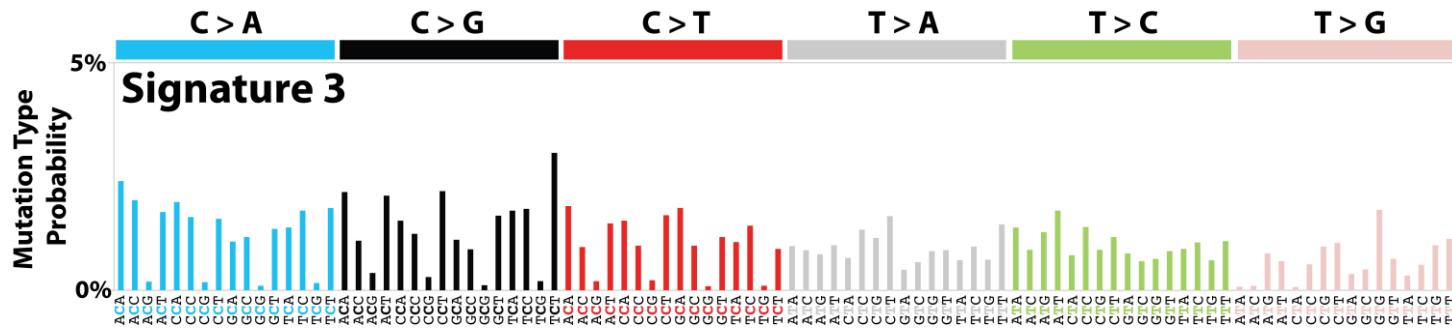
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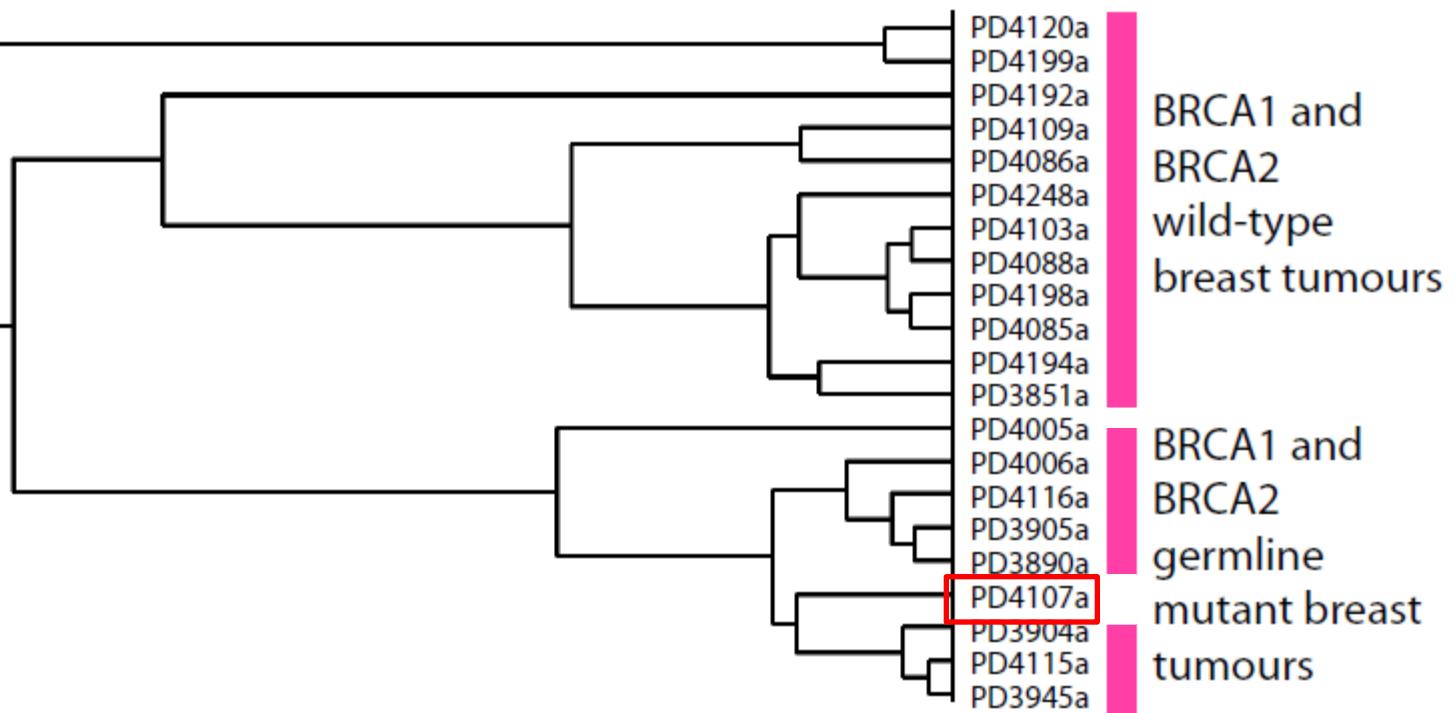
Signatures of DNA repair deficiency



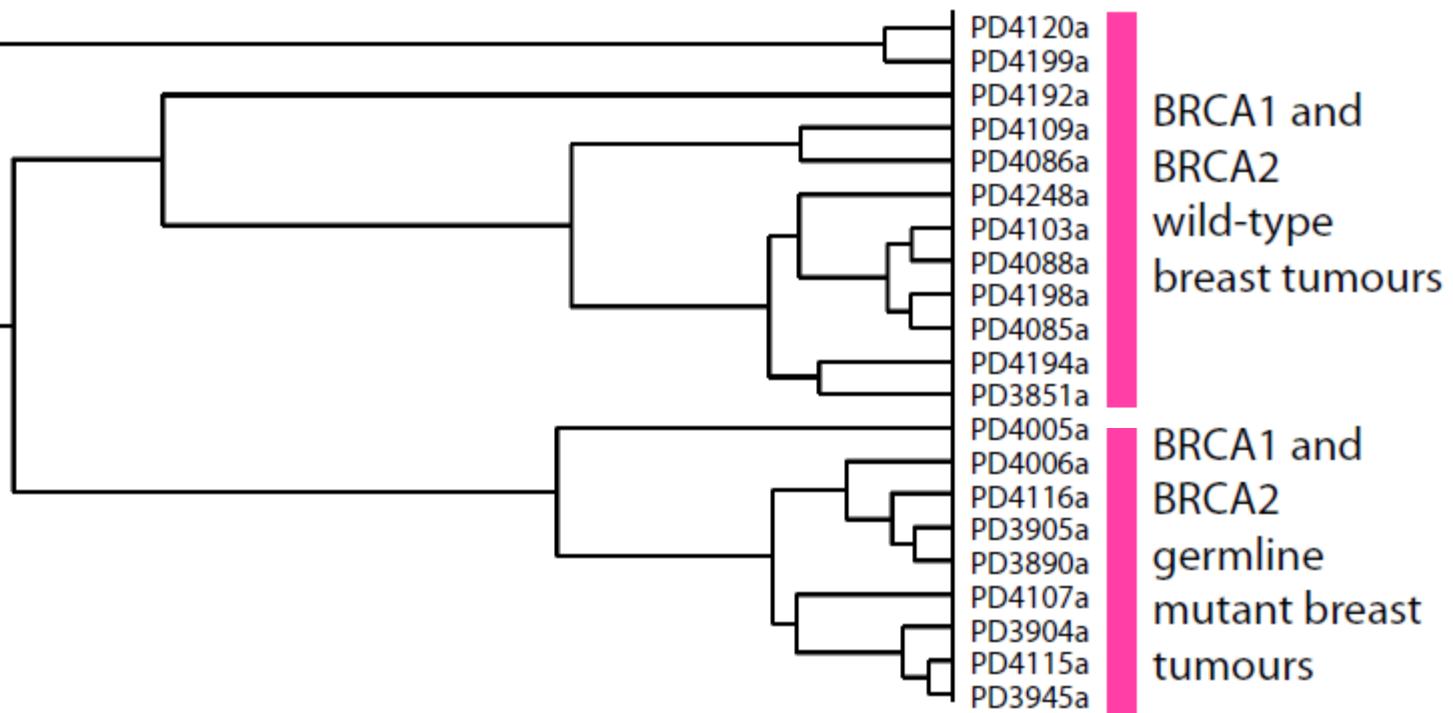
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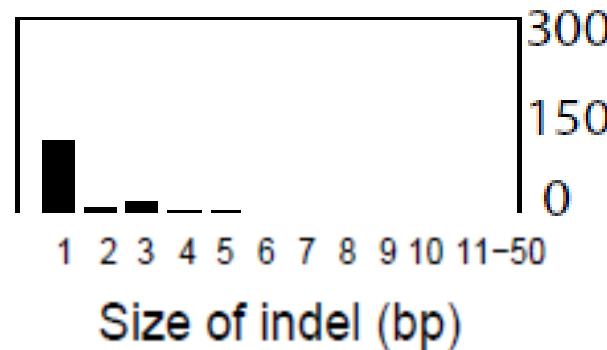


Signatures of DNA repair deficiency

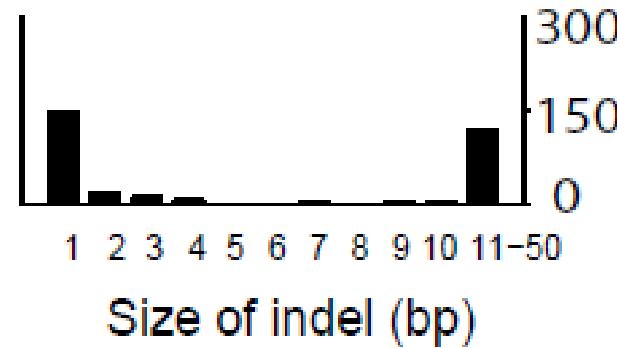


Signatures of DNA repair deficiency

PD4120a



PD4107a



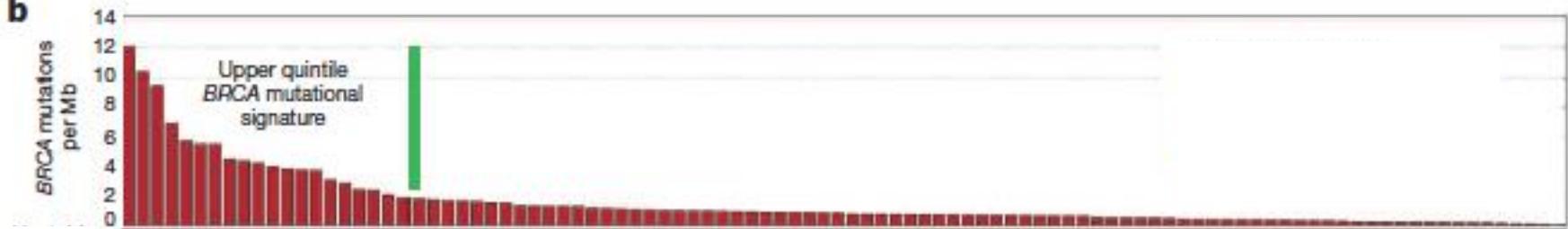
Signatures of DNA repair deficiency

Whole genomes redefine the mutational landscape of pancreatic cancer

Nicola Waddell^{1,2}, Marina Pajic^{3,4}, Ann-Marie Patch¹, David K. Chang^{3,5,6,7}, Karin S. Kassahn¹, Peter Bailey^{1,7}, Amber L. Johns³, David Miller¹, Katia Nones¹, Kelly Quek¹, Michael C. J. Quinn¹, Alan J. Robertson¹, Muhammad Z. H. Fadlullah¹, Tim J. C. Bruxner¹, Angelika N. Christ¹, Ivon Harliwong¹, Senel Idrisoglu¹, Suzanne Manning¹, Craig Nourse^{1,7}, Ehsan Nourbakhsh¹, Shivangi Wani¹, Peter J. Wilson¹, Emma Markham¹, Nicole Cloonan^{1,2}, Matthew J. Anderson¹, J. Lynn Fink¹, Oliver Holmes¹, Stephen H. Kazakoff¹, Conrad Leonard¹, Felicity Newell¹, Barsha Poudel¹, Sarah Song¹, Darrin Taylor¹, Nick Waddell¹, Scott Wood¹, Qinying Xu¹, Jianmin Wu³, Mark Pinese³, Mark J. Cowley³, Hong C. Lee³, Marc D. Jones^{3,7}, Adnan M. Nagrial³, Jeremy Humphris³, Lorraine A. Chantrill³, Venessa Chin³, Angela M. Steinmann³, Amanda Mawson³, Emily S. Humphrey³, Emily K. Colvin³, Angela Chou^{3,8}, Christopher J. Scarlett^{3,9}, Andreia V. Pinho³, Marc Giry-Laterriere³, Ilse Roodman³, Jaswinder S. Samra^{10,11}, James G. Kench^{3,11,12}, Jessica A. Pettitt³, Neil D. Merrett^{5,13}, Christopher Toon³, Krishna Epari¹⁴, Nam Q. Nguyen¹⁵, Andrew Barbour¹⁶, Nikolajs Zeps^{17,18,19}, Nigel B. Jamieson^{7,20,21}, Janet S. Graham^{7,22}, Simone P. Niclou²³, Rolf Bjerkvig²⁴, Robert Grützmann²⁵, Daniela Aust²⁵, Ralph H. Hruban²⁶, Anirban Maitra²⁷, Christine A. Iacobuzio-Donahue²⁸, Christopher L. Wolfgang²⁹, Richard A. Morgan²⁶, Rita T. Lawlor^{30,31}, Vincenzo Corbo³⁰, Claudio Bassi³², Massimo Falconi^{32,33}, Giuseppe Zamboni^{31,33}, Giampaolo Tortora³⁴, Margaret A. Tempero³⁵, Australian Pancreatic Cancer Genome Initiative*, Anthony J. Gill^{3,11}, James R. Eshleman²⁶, Christian Pilarsky²⁵, Aldo Scarpa^{30,31}, Elizabeth A. Musgrove⁷, John V. Pearson^{1,2}, Andrew V. Biankin^{3,5,6,7} & Sean M. Grimmond^{1,7}

Signatures of DNA repair deficiency

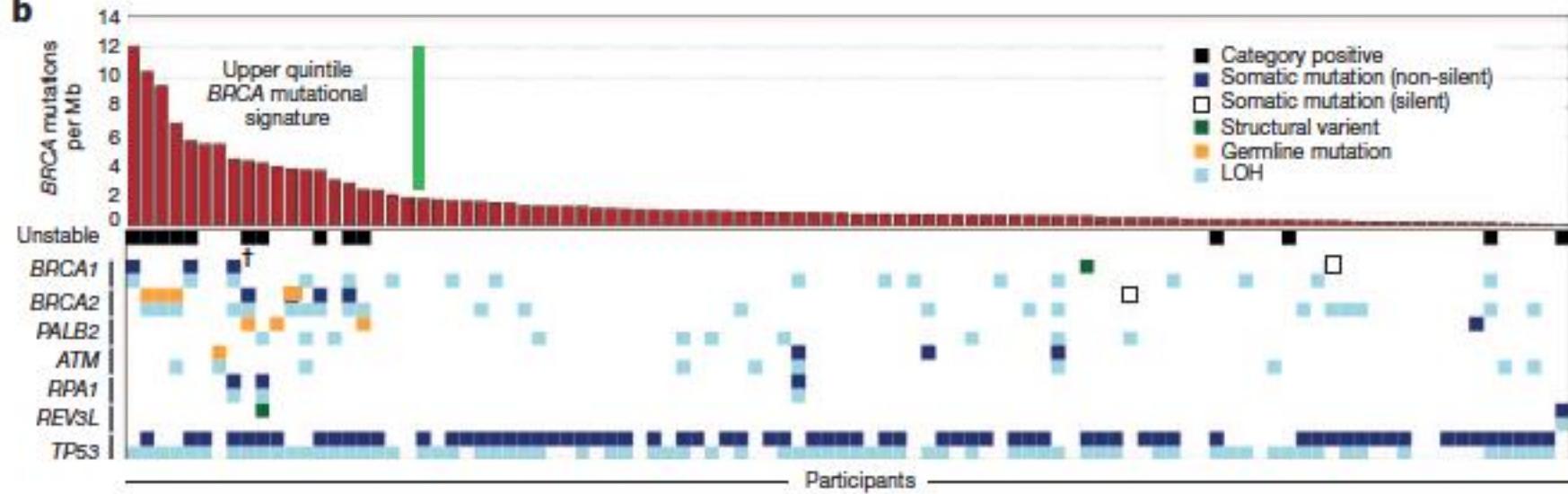
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Waddell et al Nature 2015

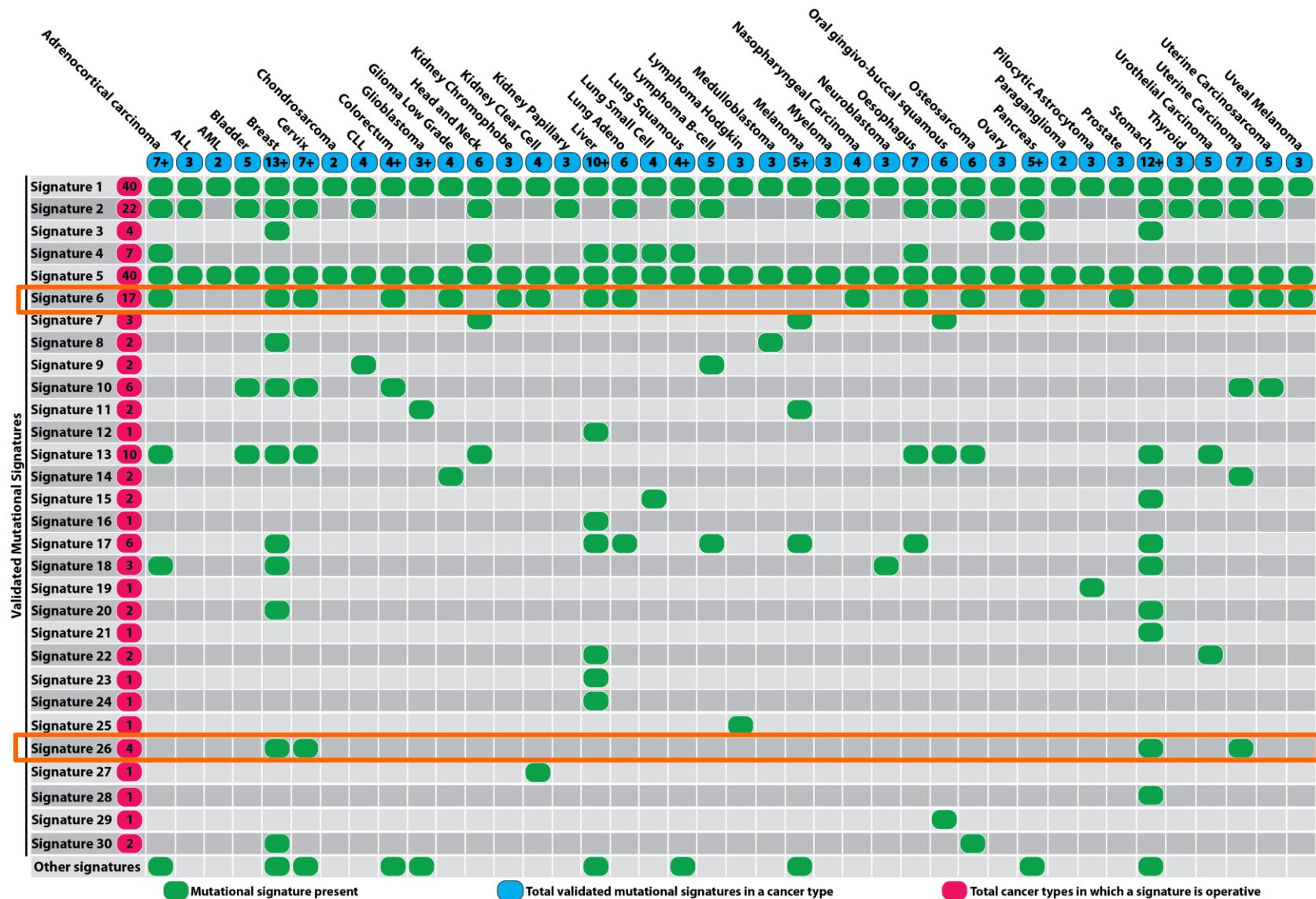
Signatures of DNA repair deficiency

b

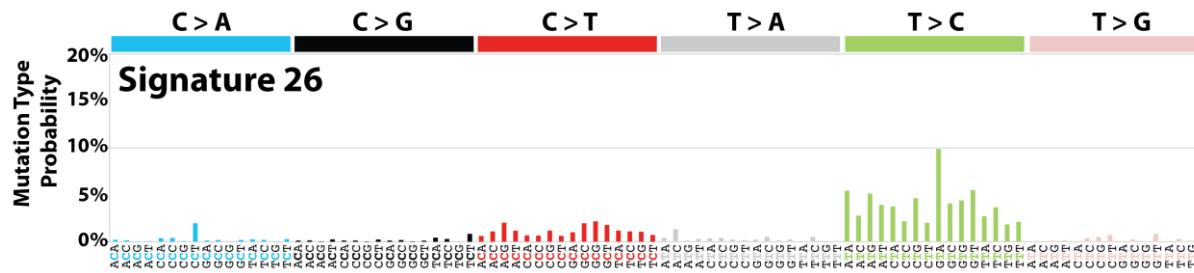
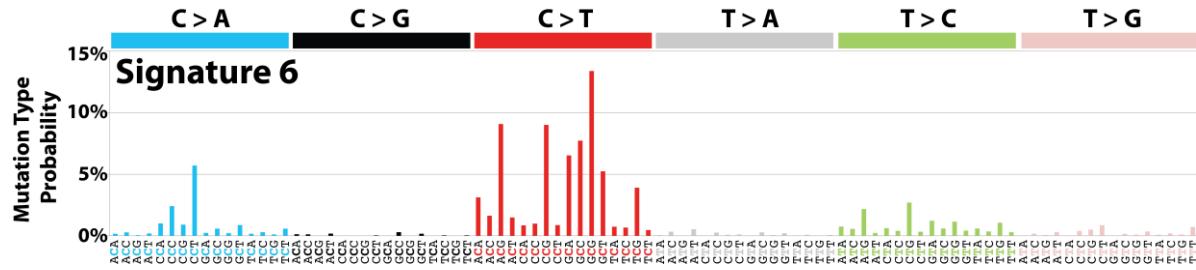


Waddell et al Nature 2015

Signatures of mismatch repair deficiency



Signatures of mismatch repair deficiency



They are all relevant

- Drivers

Cancer genes

- Passengers

Mutation signatures

- Drivers & Passengers

Cancer Evolution

Summary

- All mutations identified in human cancers have potential significance and contribute to the overall understanding of each patient's cancer
- Drivers (not just the clonal ones) are important to recognise
- Passengers are important to analyse
- Integrative work is necessary to extract maximum understanding
- Potential clinical relevance
 - These integrative analyses reveal individuals carrying germline predisposition alleles
 - They potentially identify individual cancers that could have sensitivity to specific chemotherapeutic agents

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- Mike Stratton
- Ludmil Alexandrov
- Helen Davies
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- Xueqing Zou
- Manasa Ramakrishna
- Sancha Martin
- Adam Butler
- Peter Campbell
- BASIS Consortium
- ICGC breast cancer working Group



International
Cancer Genome
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