An introduction to bladder cancer

…and patient stratification research in the Mason Lab

Andrew Mason

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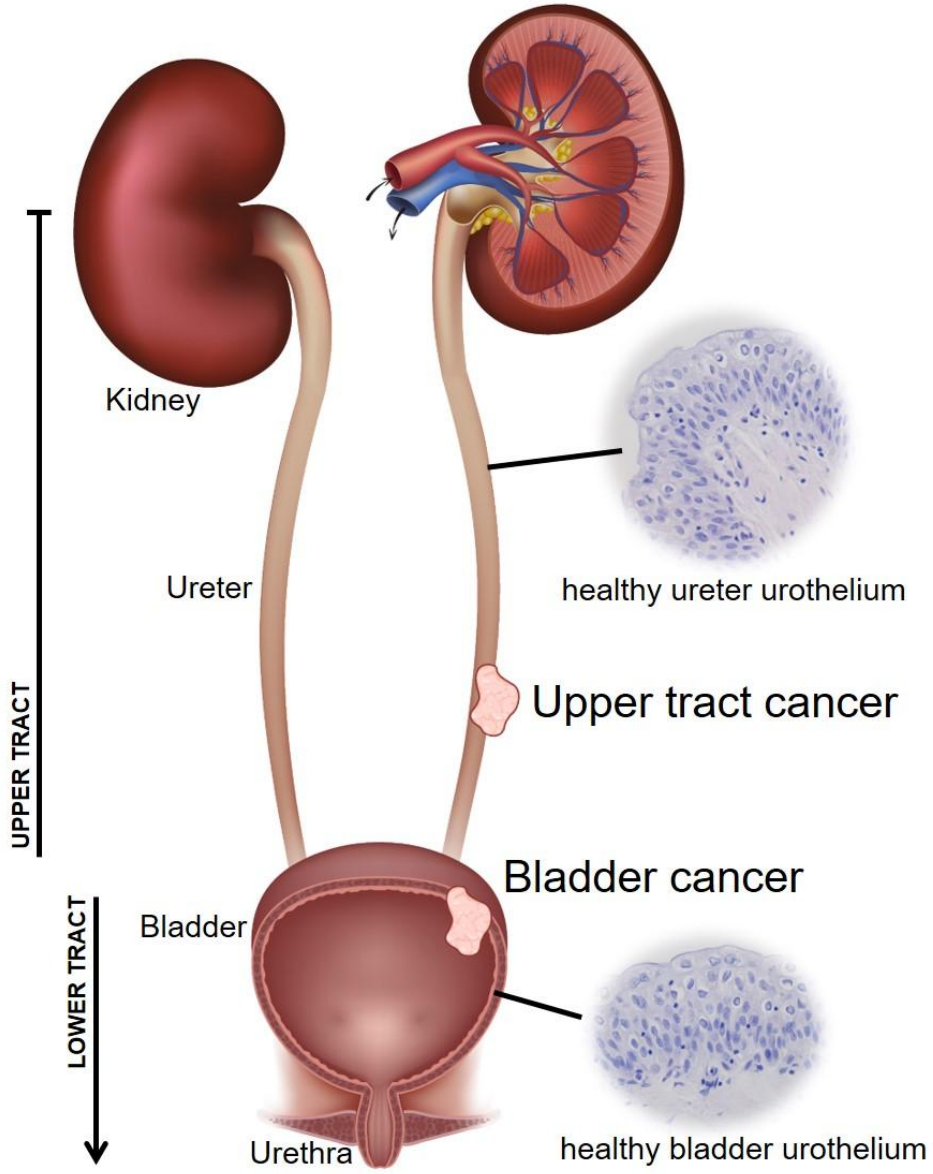
asmasonomics.github.io

An introduction to the urinary tract



The urinary system falls into 2 distinct zones:

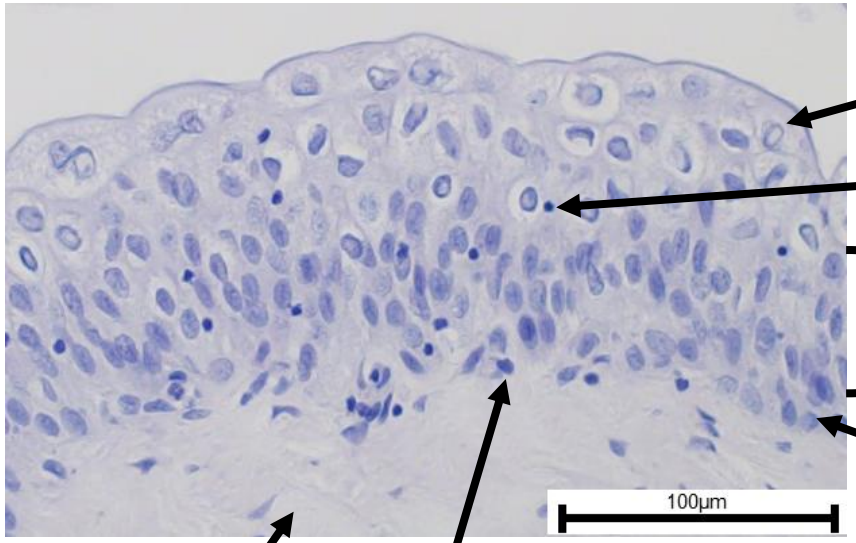
1) Upper urinary tract (kidneys and ureters)
2) Lower urinary tract (bladder and urethra)

The urinary tract experiences many pressures

- Pathogens
- Urinary toxins
- Fluid pressure changes (incl. size/shape changes)

Urothelium – a highly specialised and barrier-forming epithelium

The urothelium is a specialised, transitional epithelial lining which spans the urinary system, from the kidney renal pelvis to the top of the urethra



Superficial “umbrella” cells

Infiltrated immune cells (resident?)

Intermediate cells

Basal cells

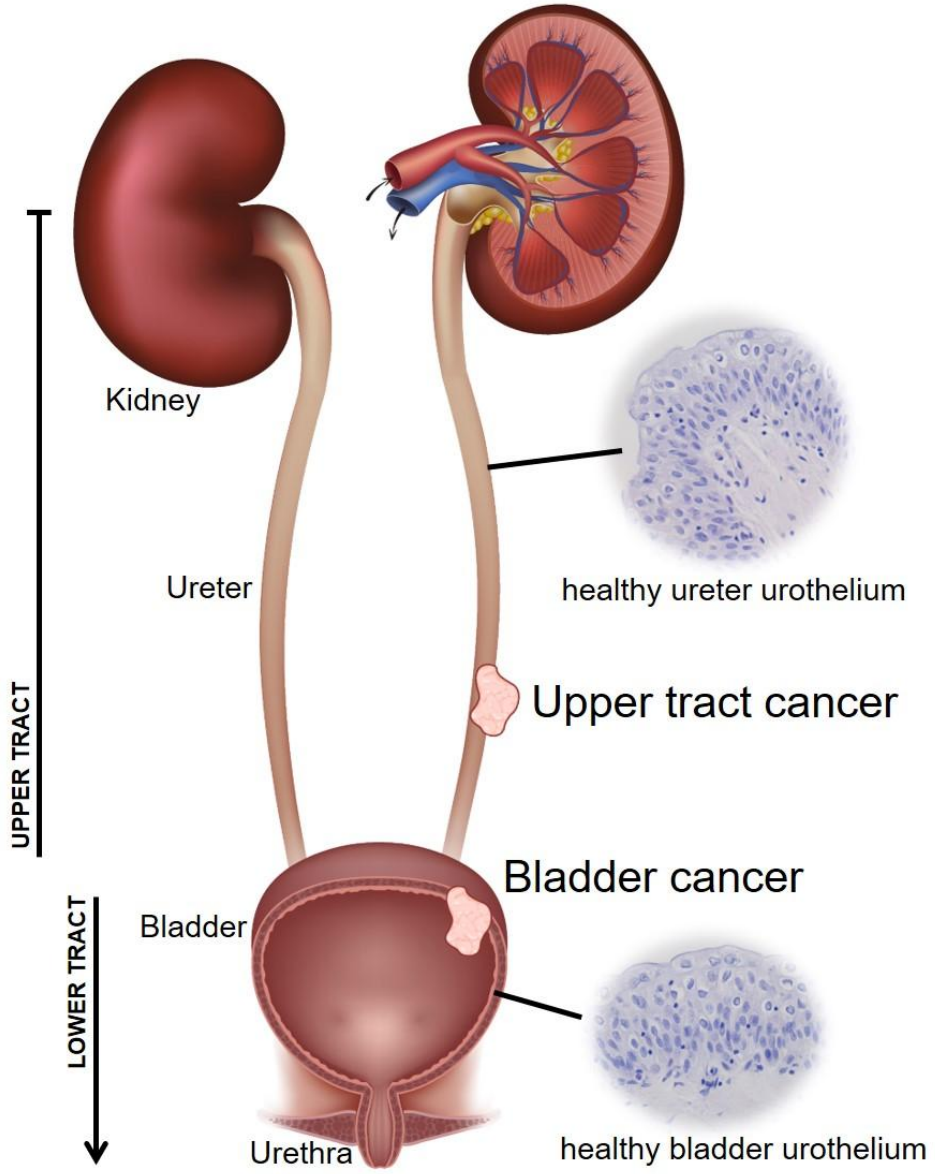
Lamina propria

Basement membrane
(with underlying capillary bed)

Additional relevant info

- Urothelium is quiescent
- There is no evidence for a urothelial stem cell
- Superficial cells are not “more differentiated” than basal cells

Urothelial carcinoma



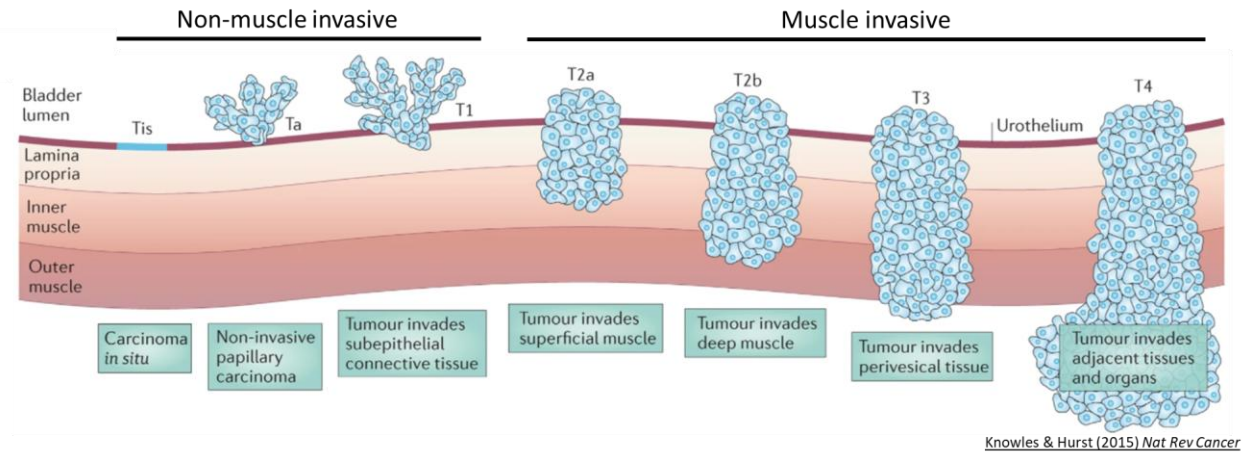
In the global north, >95% of cancers between the renal pelvis and bladder neck are urothelial carcinoma (aka transitional cell carcinoma; TCC)

>92% are urothelial carcinoma of the bladder (UCB)

c.8% are upper tract urothelial carcinoma (UTUC)

UTUC (c.2/100,000)
60% present at T2+
Luminal (immune-poor) tumours
1/3 patients go on to develop UCB
Treatment based on UCB research

UCB (c.20/100,000)
80% present <T2 (non-invasive)
Highly recurrent
Very expensive aftercare
MIBC 5-year survival <50%
MIBC is molecularly diverse



Knowles & Hurst (2015) *Nat Rev Cancer*

What causes urothelial carcinoma?

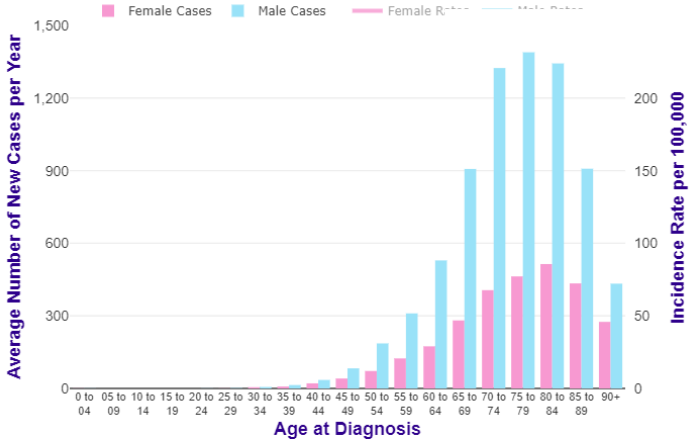
Well established risk factors include age, sex and smoking

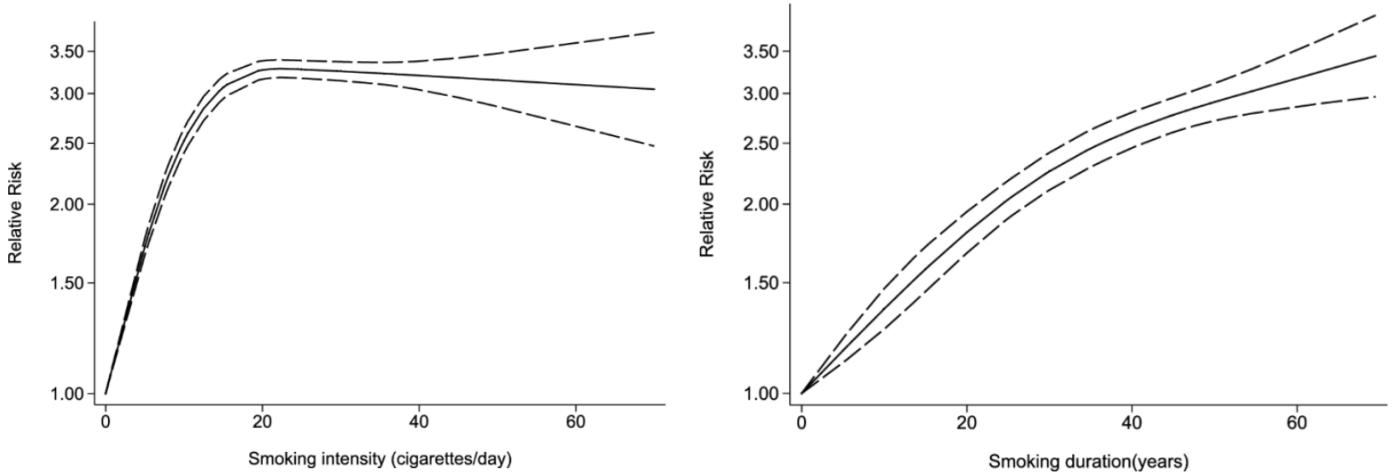
Urothelial carcinoma has **high mutational burden** and, consequently, **diverse driver genes**

CANCER RESEARCH UK

Caused by smoking	Caused by occupation	Caused by radiation
45%	6%	2%
Bladder cancer cases caused by smoking, UK, 2015	Bladder cancer cases linked to occupational exposures, UK	Bladder cancer cases linked to ionising radiation exposure, UK

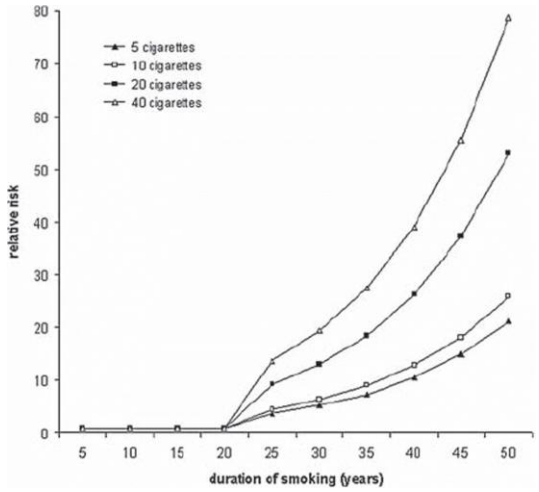
Older age is the main risk factor for cancer. This largely reflects cell DNA damage accumulating over time. Damage can result from biological processes or from exposure to risk factors.





Zhao *et al* (2022) meta-analysis in bladder cancer
PMID:35332429

Smoking relationship different in lung cancer

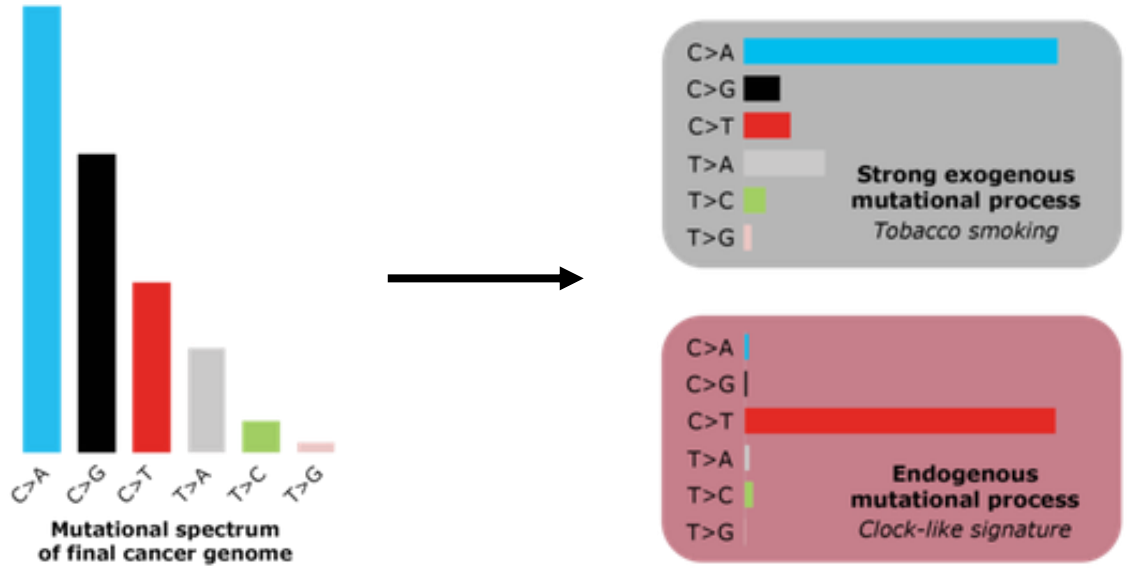


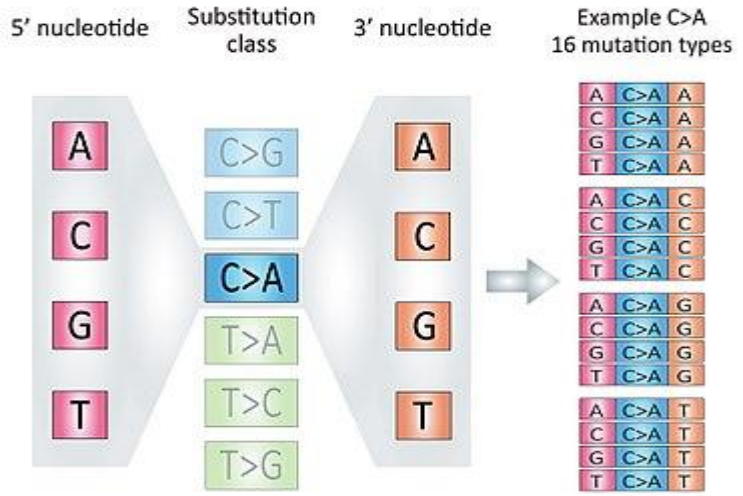
Didkowska *et al* (2011; PMID:20553096) from data in Simonata *et al* (2001; PMID:11275995)

Mutational patterns can tell us more about cancer causes

Urothelial carcinoma has **high mutational burden** and, consequently, **diverse driver genes**

High mutational burden allows us to construct mutational signatures very confidently





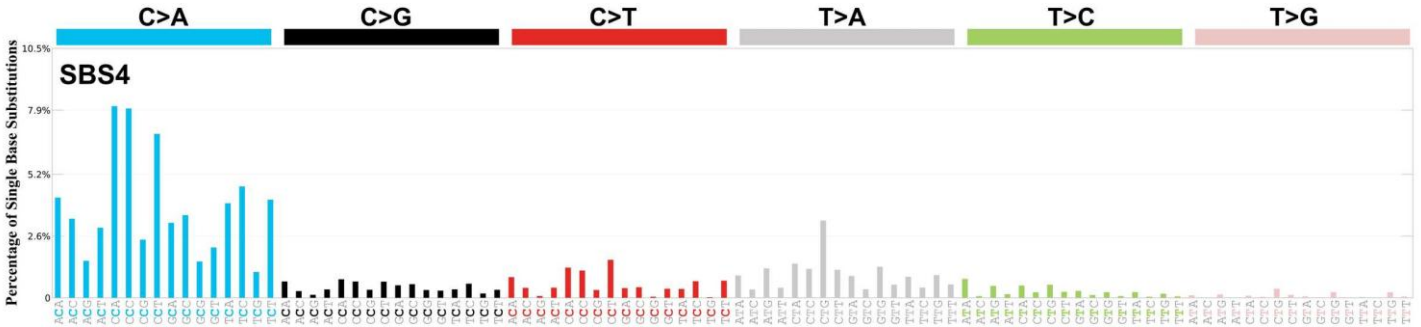
Specific base change, plus surrounding chemistry creates very specific signatures of mutational processes

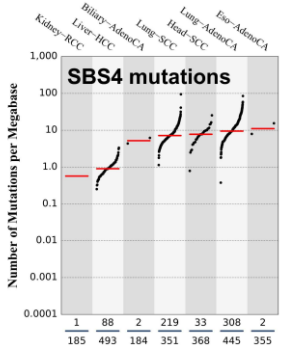
Bladder cancer doesn’t display typical patterns of smoke-based mutagenesis

Urothelial carcinoma has **high mutational burden** and, consequently, **diverse driver genes**

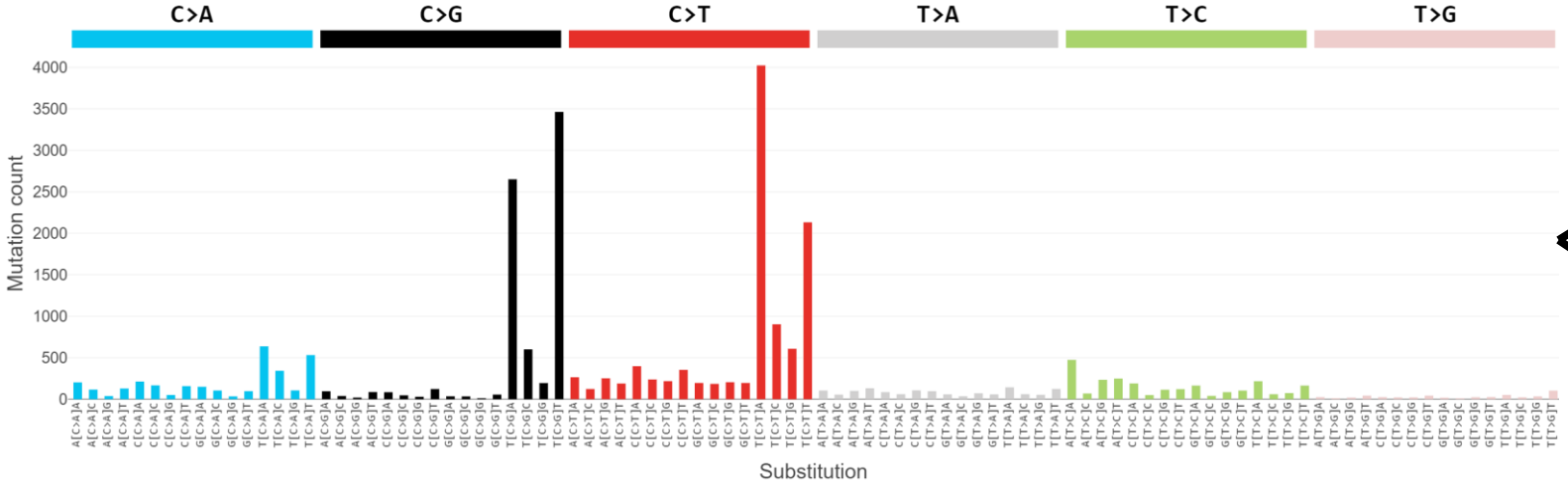
High mutational burden allows us to construct mutational signatures very confidently

Smoking signature characteristic in lung cancer

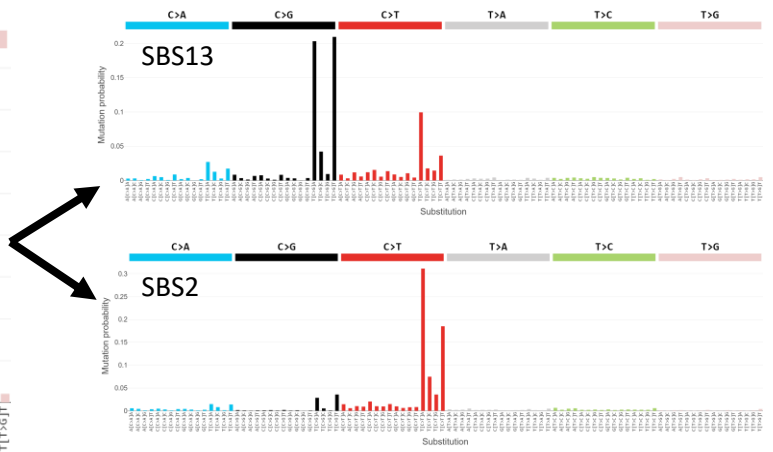




Typical bladder cancer mutational signature



APOBEC mutagenesis

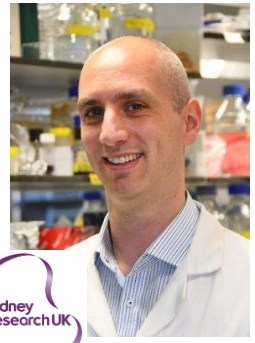


What evidence of viral damage?

Urothelial carcinoma has **high mutational burden** and, consequently, **diverse driver genes**

High mutational burden allows us to construct mutational signatures very confidently

Mutational signatures (and epidemiological data) now support a **viral cause of urothelial carcinoma**



Induction of APOBEC3-mediated genomic damage in urothelium implicates BK polyomavirus (BKPyV) as a hit-and-run driver for bladder cancer

Simon C. Baker, Andrew S. Mason, Raphael G. Slip, Katie T. Skinner, Andrew Macdonald, Omar Masood, Reuben S. Harris, Tim R. Fenton, Manikandan Periyasamy, Simak Ali & Jennifer Southgate

Oncogene **41**, 2139–2151 (2022) | Cite this article

Smoking may dampen the immune system and/or specific toxins may damage urothelium and facilitate viral infection

Additional relevant info

Mice do not get the relevant virus

Mice do not have the relevant APOBEC3 enzymes

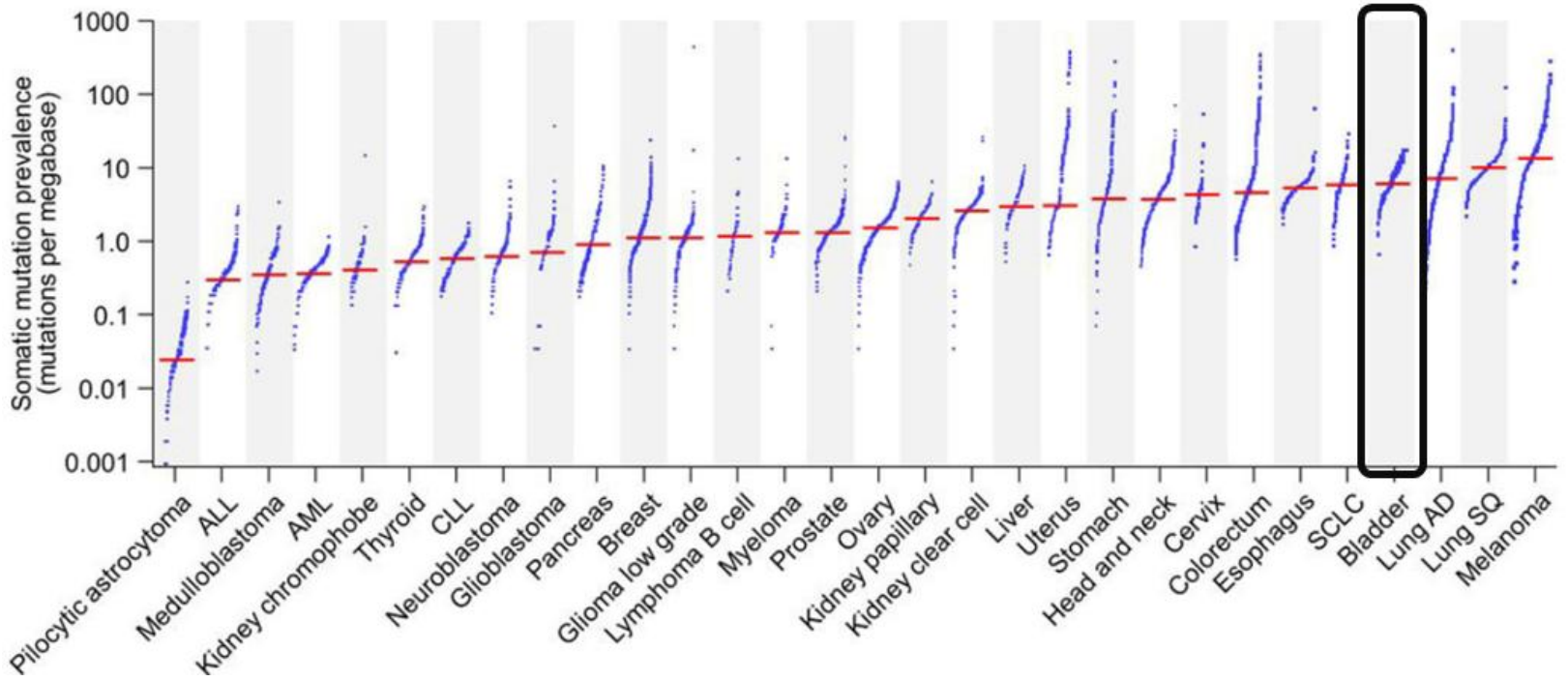
Mice UC models are chemically-induced

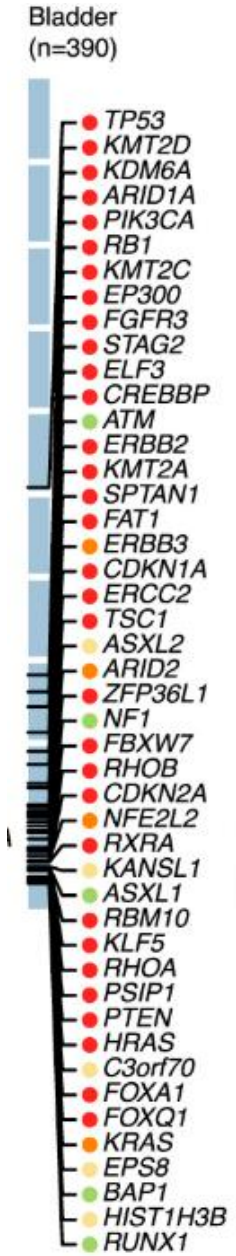
Rodent urothelium is different

Rodents are effectively incontinent

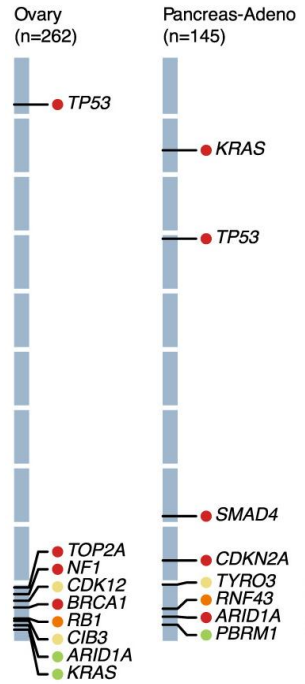
Urothelial carcinoma is a diverse disease without clear mutational subtypes

Very high mutational burden (TMB) and diverse driver genes





For comparison



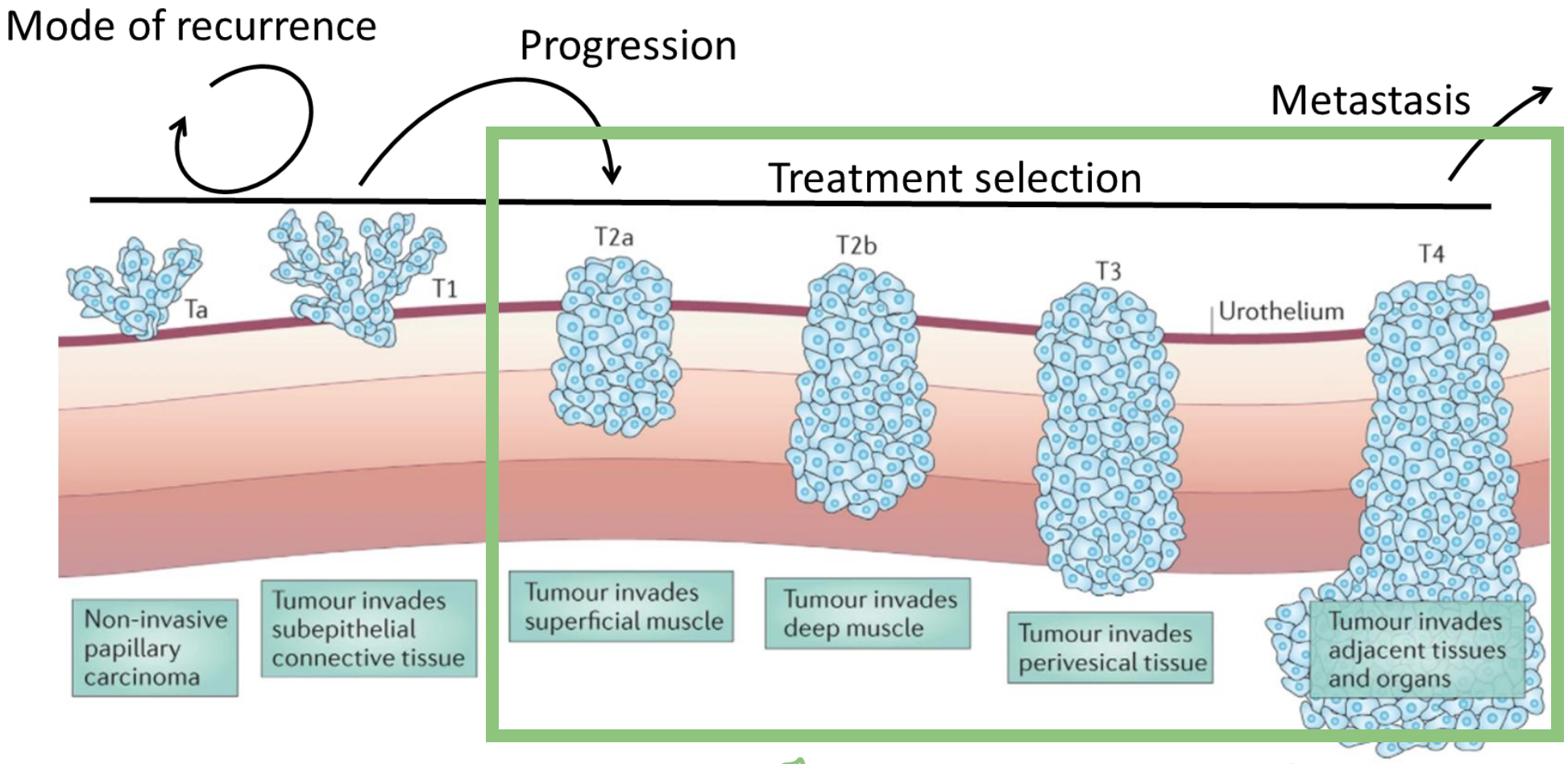
Unclear which are tumour drivers, and which are unimportant passengers

Diverse pathways to try to find druggable targets

Issues with pathway redundancy and pathway interactions

Not all bladder cancers are equal

Can we use data to personalise patient experience and treatment?

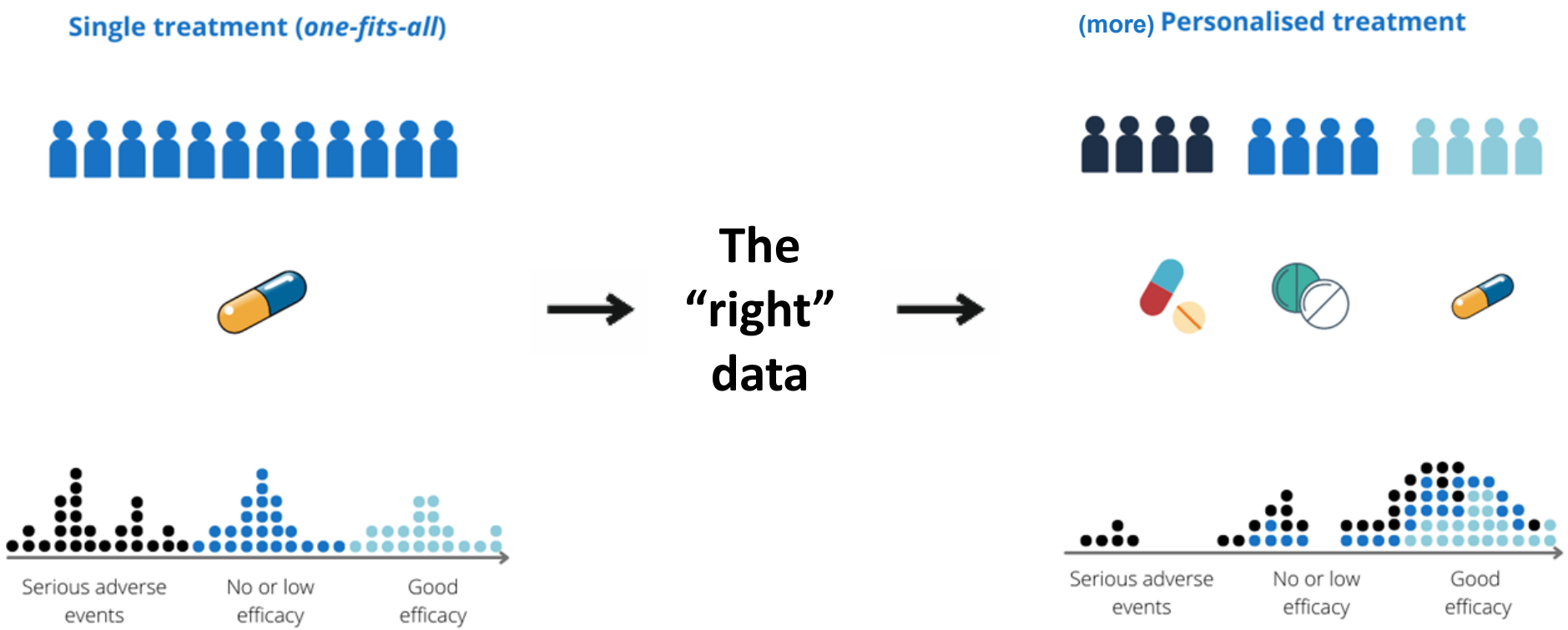


Knowles & Hurst (2015) *Nat Rev Cancer*

TCGA

The problem is stratification

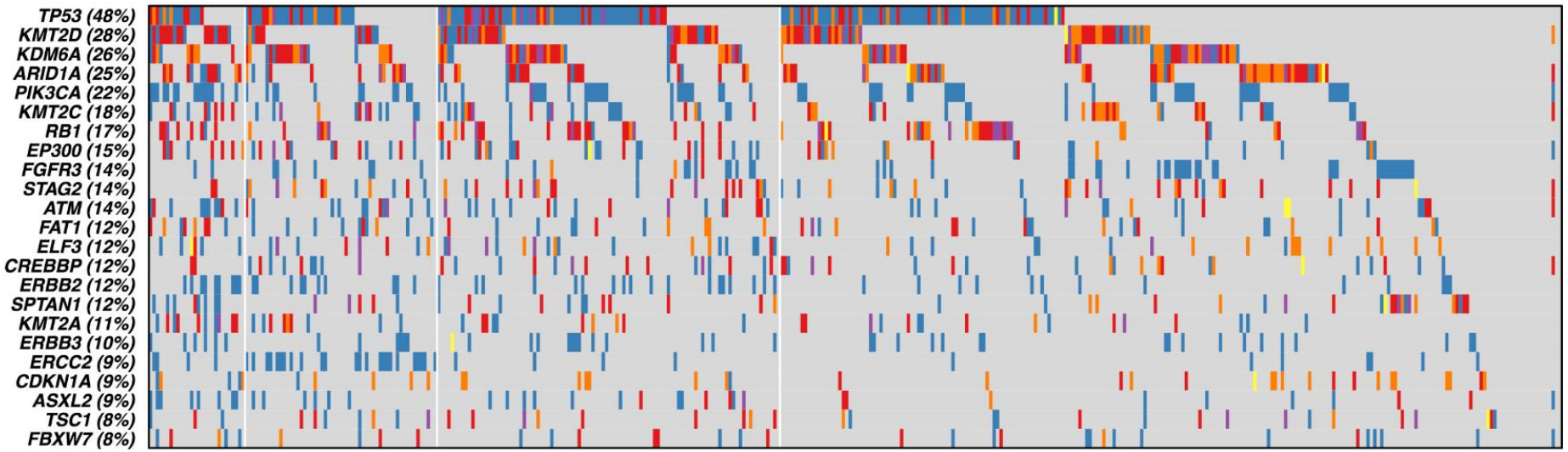
Stratification is an achievable middle ground towards personalised medicine



Unsupervised clustering → finding order without knowing the answer

Mutational subgroups not an option

Mutations are appealing as they are easy and cost-effective to profile, and often give clear binary answers



Overlaps between different mutation types

Difficult to predict the impact of each mutation

Very limited data on mutation interactions

High number of mutations found in only one or two patients

Gene expression subtypes could only describe - the clinical links were weak

As with many cancers, BLCA research focused on gene expression profiles in the 2010s

Standard approach → retain “most variable” genes, dimension reduction, most parsimonious number of groups

Volume 18, Issue 12
15 June 2012
IMAGING, DIAGNOSIS, PROGNOSIS | JUNE 14 2012

A Molecular Taxonomy for Urothelial Carcinoma FREE

Gottfrid Sjödahl; Martin Lauss; Kristina Lövgren; Gunilla Chebil; Sigurdur Gudjonsson; Srinivas Veerla; Oliver Patschan; Mattias Aine; Mårten Fernö; Markus Ringnér; Wiking Månsson; Fredrik Liedberg; David Lindgren; Mattias Höglund

Clinical Cancer Research

Check for updates

ARTICLE · Volume 171, Issue 3, P540-556.E25, October 19, 2017 · *Open Archive* Download Full Issue

Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

A. Gordon Robertson [1,25] · Jaegil Kim [2,25] · Hikmat Al-Ahmadie [3] · … · John N. Weinstein [8,22] · David J. Kwiatkowski [23] · Seth P. Lerner [24,26] … Show more

Cancer Cell

CellPress

Volume 25, Issue 2, 10 February 2014, Pages 152-165

Identification of Distinct Basal and Luminal Subtypes of Muscle-Invasive Bladder Cancer with Different Sensitivities to Frontline Chemotherapy

Woonyoung Choi [1], Sima Porten [1], Seungchan Kim [6], Daniel Willis [1], Elizabeth R. Plimack [7], Jean Hoffman-Censits [8], Beat Roth [1], Tiewei Cheng [1,5], Mai Tran [1,5], I-Ling Lee [1], Jonathan Melquist [1], Jolanta Bondaruk [3], Tadeusz Majewski [3], Shizhen Zhang [3], Shanna Pretzsch [1], Keith Baggerly [4], Arlene Siefker-Radtke [2], Bogdan Czerniak [3], Colin P.N. Dinney [1], David J. McConkey [1,5]

Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology

Jeffrey S. Damrauer, Katherine A. Hoadley, David D. Chism, +7, and William Y. Kim Authors Info & Affiliations

Edited* by William G. Kaelin, Jr., Harvard Medical School, Boston, MA, and approved January 15, 2014 (received for review October 2, 2013)

February 11, 2014 | 111 (8) 3110-3115 | https://doi.org/10.1073/pnas.1318376111

Prognostic Power of a Tumor Differentiation Gene Signature for Bladder Urothelial Carcinomas FREE

Qianxing Mo, Fotis Nikolos, Fengju Chen, Zoe Tramel, Yu-Cheng Lee, Kazukuni Hayashi, Jing Xiao, Jianjun Shen, Keith Syson Chan

JNCI: Journal of the National Cancer Institute, Volume 110, Issue 5, May 2018, Pages 448–459, https://doi.org/10.1093/jnci/djx243

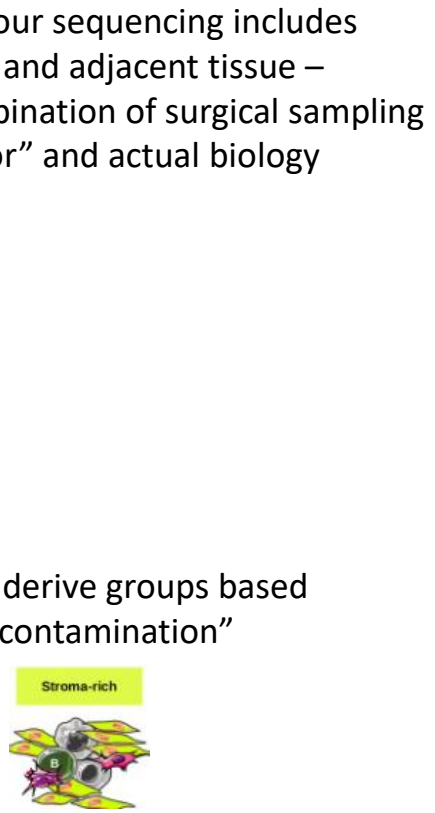
Published: 12 January 2018 **Article history**

Journal of Pathology
J Pathol 2017; 242: 113–125
Published online 28 March 2017 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.4886

ORIGINAL PAPER

Molecular classification of urothelial carcinoma: global mRNA classification versus tumour-cell phenotype classification

Gottfrid Sjödahl[1], Pontus Eriksson[2], Fredrik Liedberg[1] and Mattias Höglund[2]*



Tumour sequencing includes TME and adjacent tissue – combination of surgical sampling “error” and actual biology

Can derive groups based on “contamination”

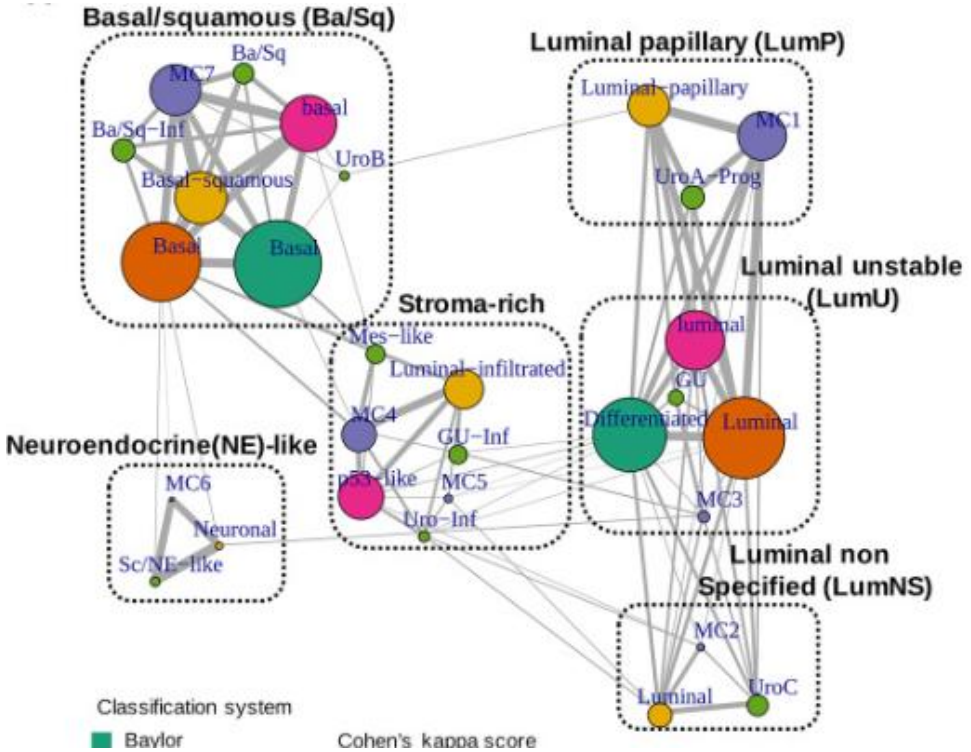
A “consensus” strategy

European Urology
Volume 77, Issue 4, April 2020, Pages 420-433

Platinum Priority – Bladder Cancer – Editor's Choice

Editorial by Kenneth B. Yatai, Mark J. Dunning and Dennis Wang on pp. 434–435 of this issue

A Consensus Molecular Classification of Muscle-invasive Bladder Cancer EU★ACME ☆

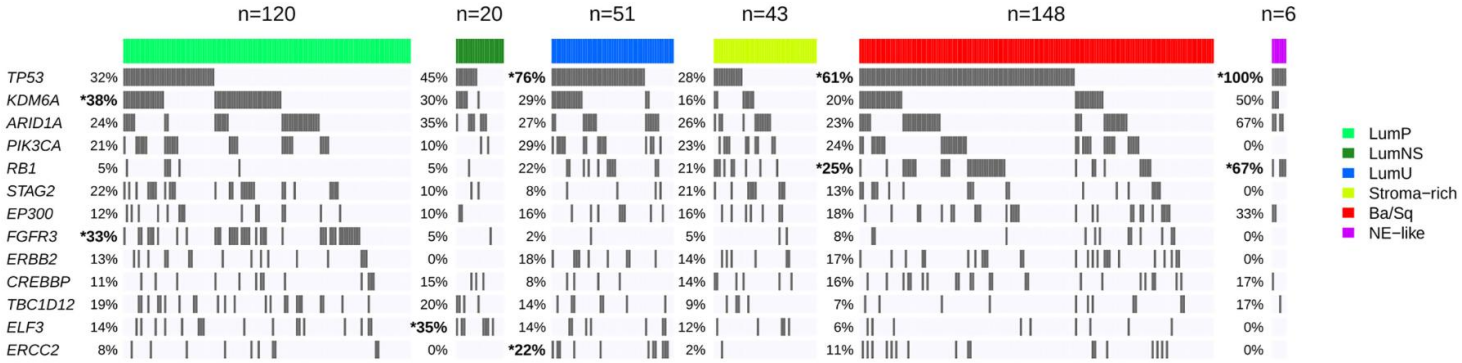


	Luminal Papillary (LumP)	Luminal Non-Specified (LumNS)	Luminal Unstable (LumU)	Stroma-rich	Basal/Squamous (Ba/Sq)	Neuroendocrine-like (NE-like)
% of MIBC	24%	8%	15%	15%	35%	3%
Class Name						
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 + PPARG + CDKN2A -	PPARG +	PPARG + E2F3 +, ERBB2 + Genomic instability Cell cycle +		EGFR +	TP53 -, RB1 -, Cell cycle +
Mutations	*FGFR3* (40%), *KDM6A* (38%)	*ELF3* (35%)	*TP53* (76%), *ERCC2* (22%) TMB +, APOBEC +		*TP53* (61%), *RB1* (25%)	*TP53* (94%) *RB1* (39%)*
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology (59%)	Micropapillary variant (36%)			Squamous differentiation (42%)	Neuroendocrine differentiation (72%)
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

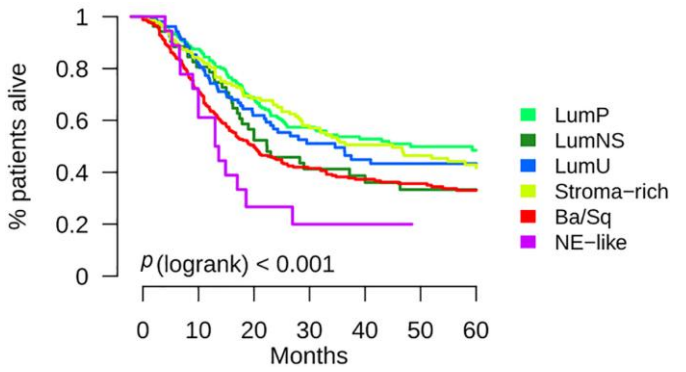
* 94% of these tumors present either RB1 mutation or deletion

The consensus still did not yield clinically relevant groups

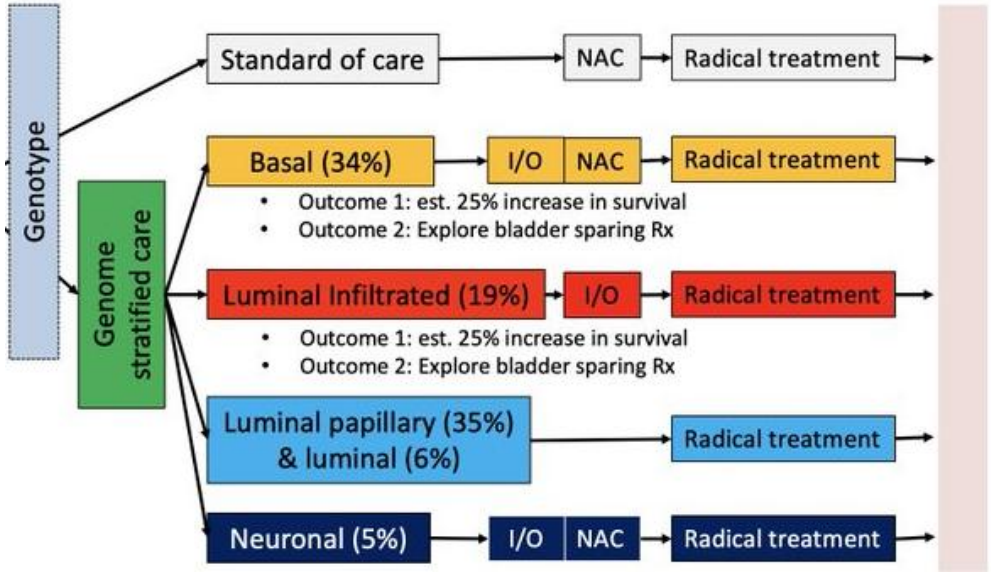
“Clinically relevant” mutations were still very divided



Limited differences in patient outcome



There are some propensities for treatment response → opportunities for trials



Genotype of Urothelial cancer: Stratified Treatment and Oncological outcomes (GUSTO): Phase II study

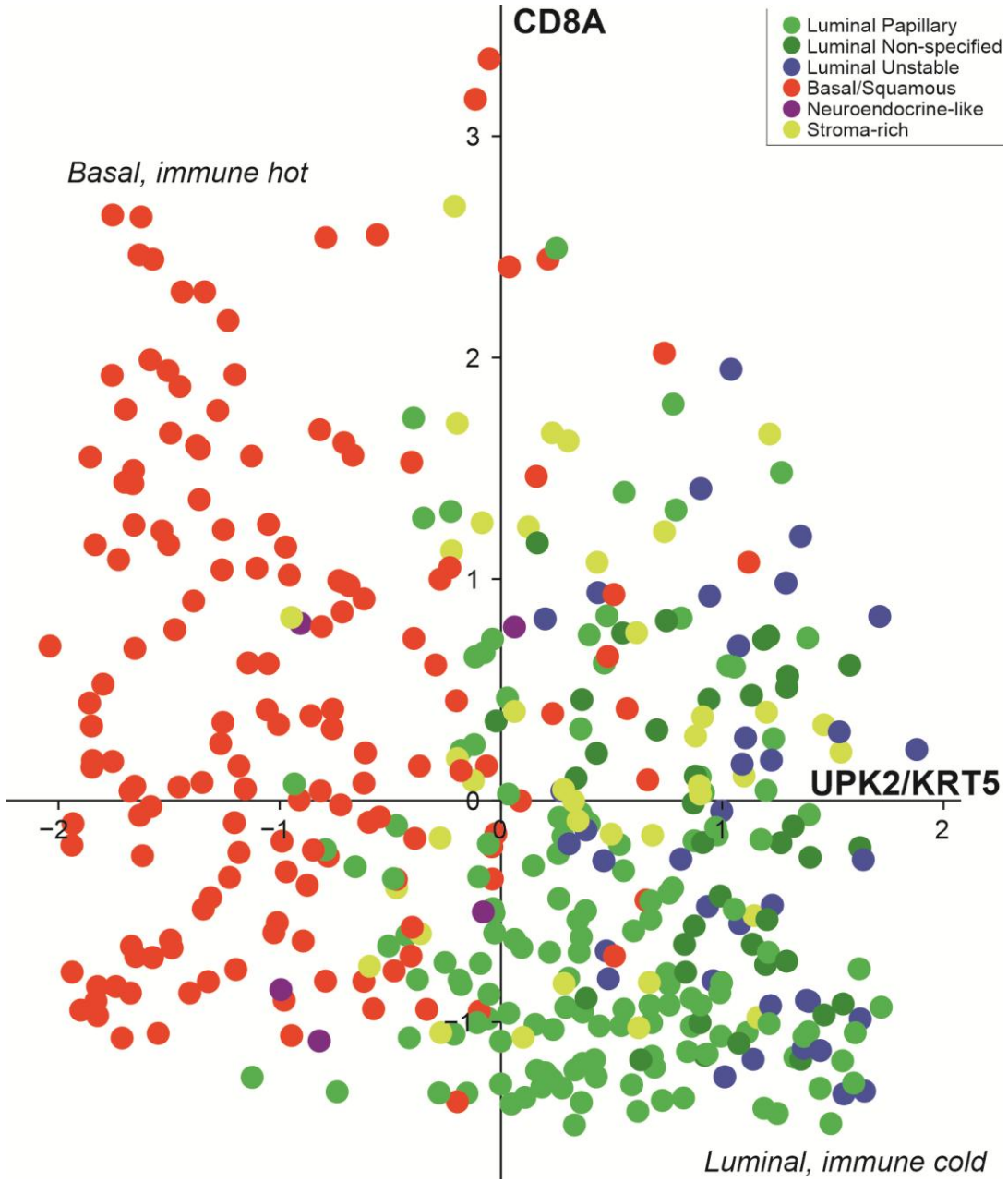
Plain English Summary:

Award: £2,888,145.70

Award ID: NIHR128103

We want to improve the outcomes from Bladder Cancer. We think this can be achieved by using the genetic information within each cancer to tailor treatments to individual patients. However, before testing our approach, we have to understand if this is possible within the NHS and if our choices appear to work.

Bladder cancer is a disease continuum



Despite this work, we can largely represent MIBC molecular subtypes with 3 genes / 2 axes

- basal/luminal differentiation state
- immune activity

New classification systems already proposed

THE PROBLEMS

ML is giving us very limited gains in understanding

Subgroupings are arbitrary

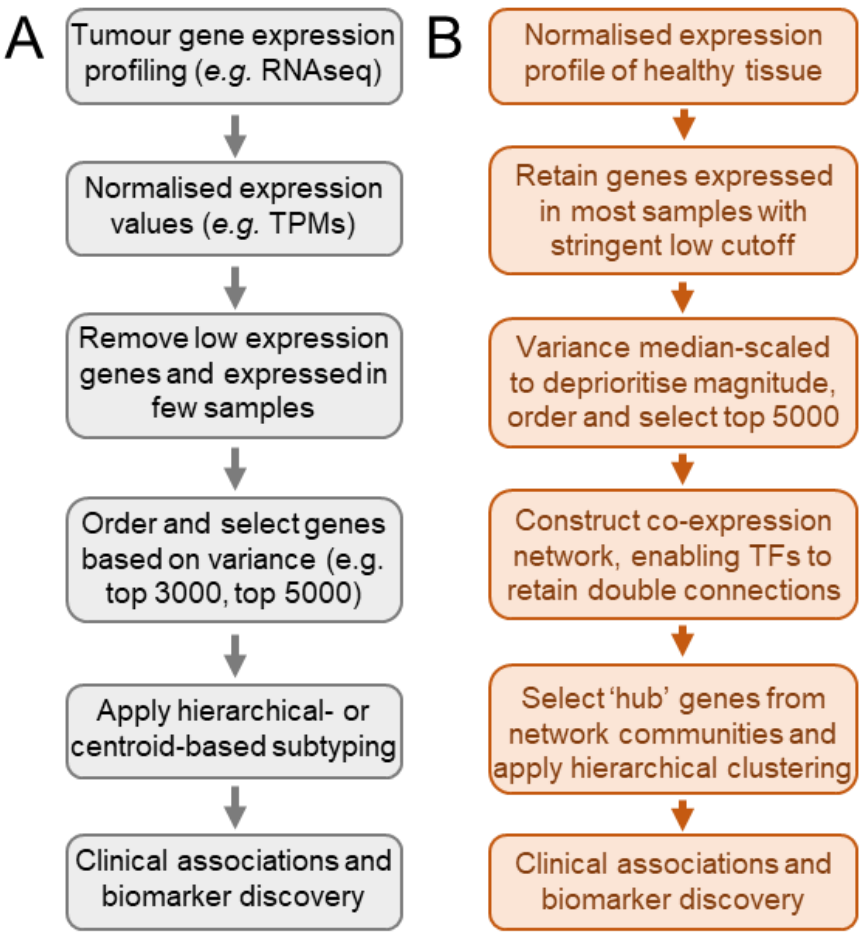
- Even splits
- Group edge cases swap with new annotations, different filtering strategies *etc.*

Subgroupings are academic, not clinical

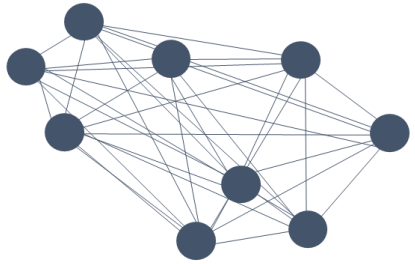
We can’t rely on data alone.

Biological knowledge is essential.

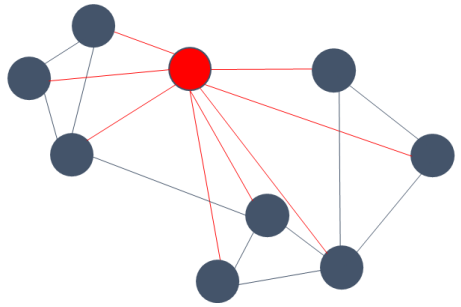
A case study in this strategy (i)



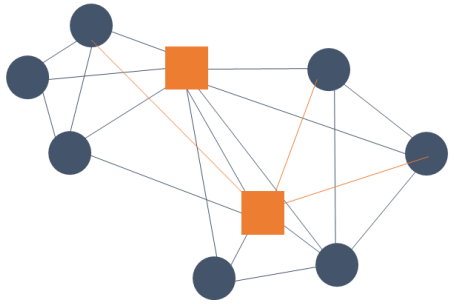
(1) Co-correlation network (Spearman rank)

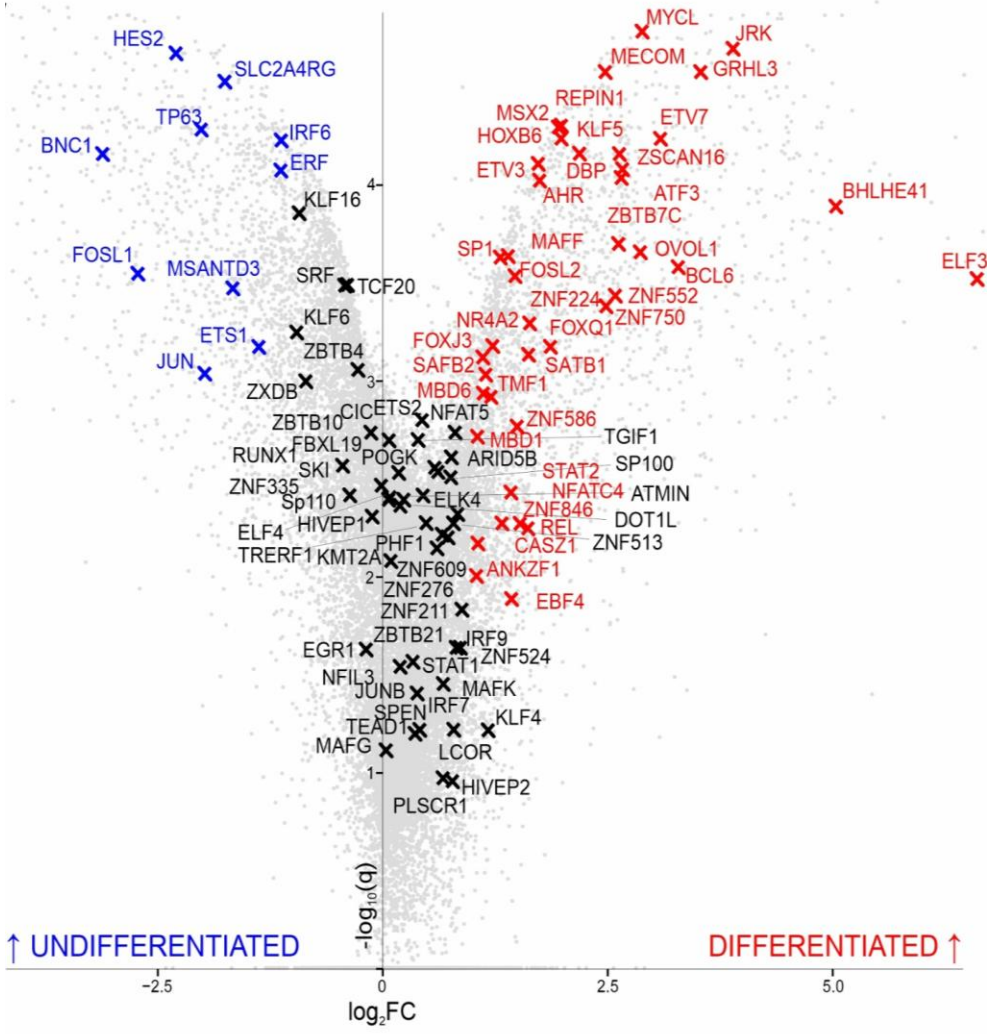


(2) Selective edge pruning



(3) Gene Prioritisation

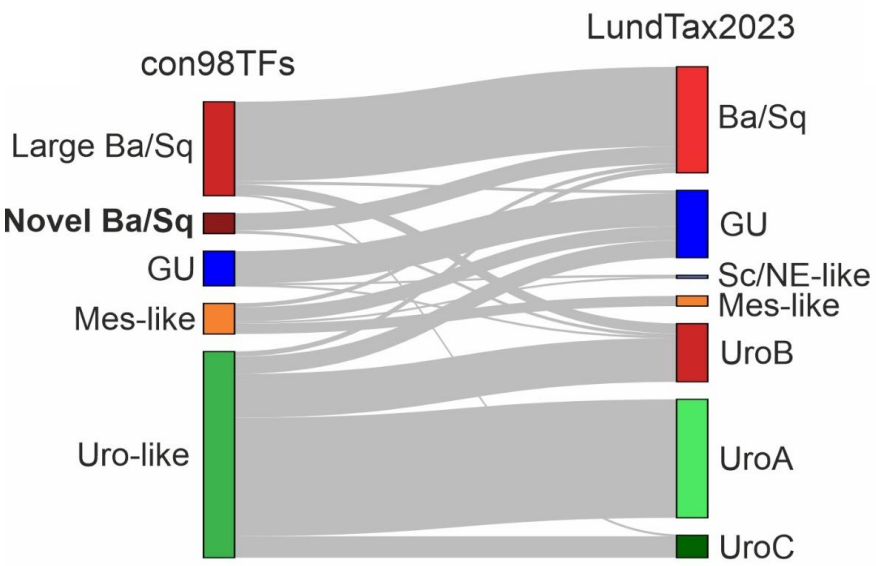


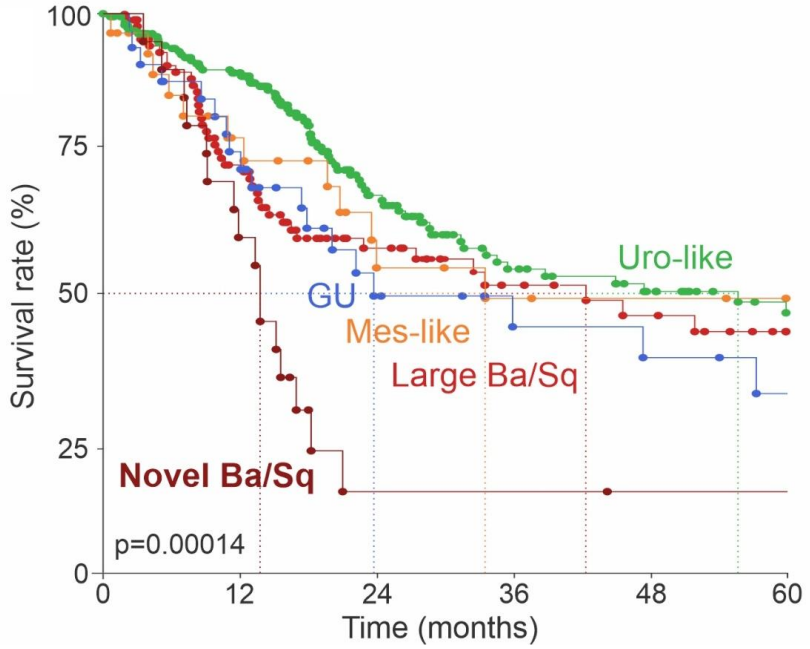


A case study in this strategy (ii)

This approach allowed us to choose different genes to use as markers to stratify the cancers

This revealed a novel group of basal cancers with particularly bad survival



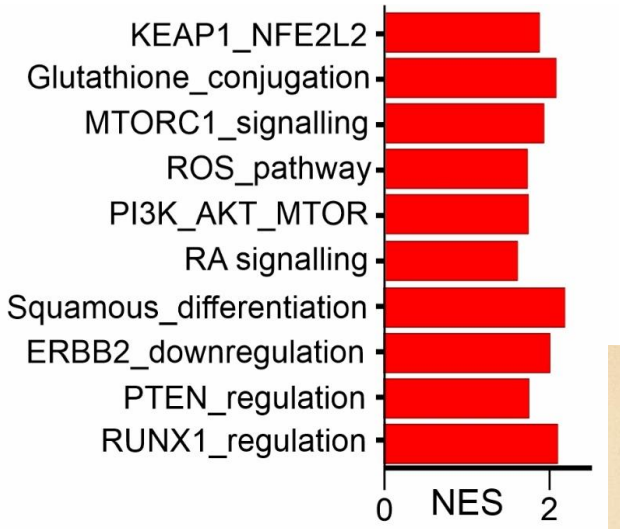


A case study in this strategy (iii)

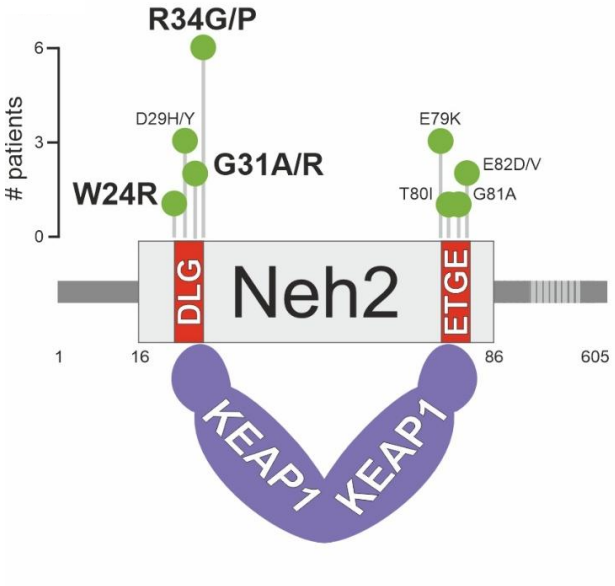
This approach allowed us to choose different genes to use as markers to stratify the cancers

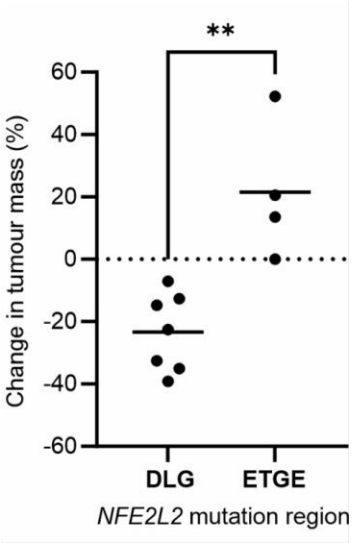
This revealed a novel group of basal cancers with particularly bad survival

Novel group characterised by NRF2 overactivity – this is a druggable target in other cancers



Our work goes beyond a mutation-only classifier





If a single classification strategy is not practical, we need to keep asking biologically and clinically relevant questions to find groups of patients we can treat more effectively.

- END -

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