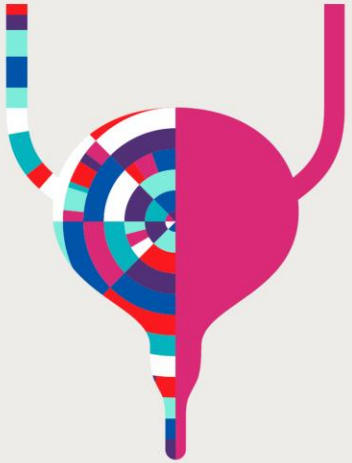
MasterClass in Bladder Cancer 2024



Molecular biology for NMIBC: current landscape

Bishoy M. Faltas MD

Director, Bladder Cancer Research, Englander Institute for Precision Medicine
Gellert Family-John P. Leonard, MD Research Scholar
Assistant Professor of Medicine, Cell and Developmental Biology

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Disclosures

Consulting: QED therapeutics, Boston Gene

Advisory board: Merck, Immunomedics/Gilead, QED therapeutics, Gilead, Janssen

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Honoraria: Urotoday

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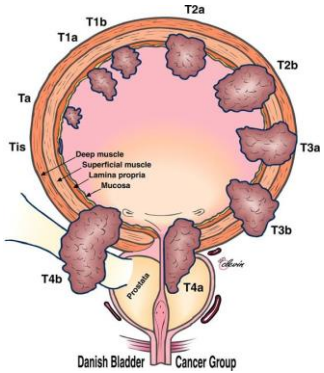
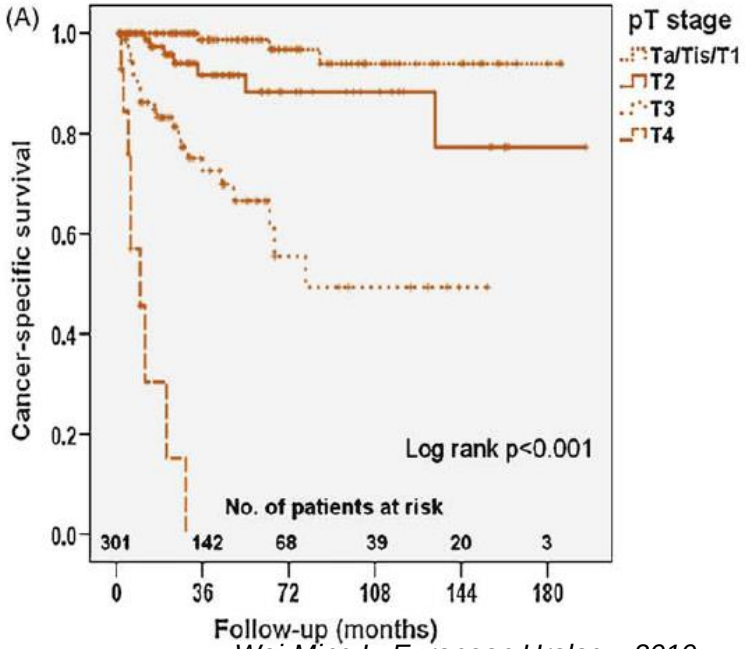
Bladder cancer

- Bladder cancer is the 9th most commonly diagnosed cancer worldwide
- 165,000 deaths annually worldwide
- ~75 % of the tumors are non-muscle invasive (Ta, T1 and CIS) at diagnosis
- ~ 25% T2-T4 at diagnosis
- NMIBC is a very prevalent disease
    - High risk of recurrence (75 %)
    - Moderate risk of progression (5-25 %)





Slide credit: Lars Dryskot

Wei-Ming L, European Urology, 2010

Main clinical challenges for patients with NMIBC

Predict disease course in early-stage bladder cancer

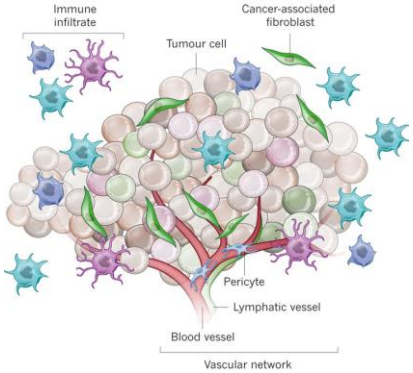
- Better risk assessment for surveillance, follow-up planning
- Better selection of high-risk patient to therapy (BCG/IO/targeted treatment)

Predict response before (or during) treatment

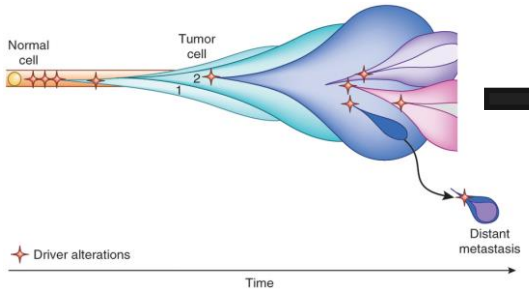
- BCG, MMC, IO, targeted treatment
- Change treatment regimens

Slide credit: Lars Dryskot

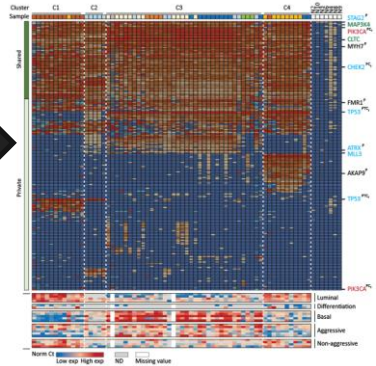
Biological challenges



Tumor micro-environment



Tumor evolution

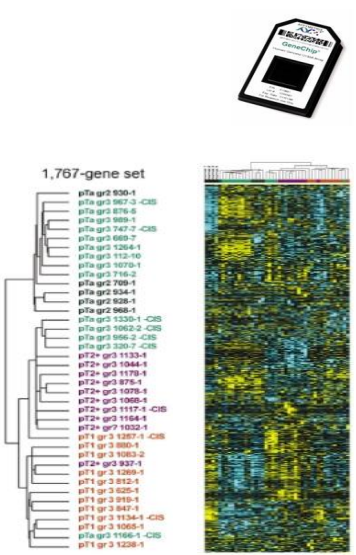


Tumor heterogeneity

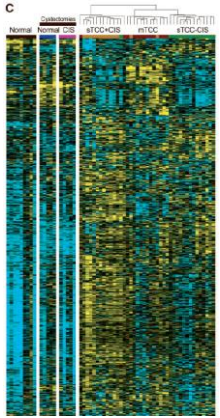
Slide credit: Lars Dryskot

Identification of subtypes and predicting outcome in NMIBC

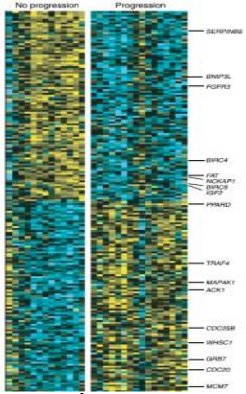
Cohorts selected from biobank materials based on clinical outcome (recurrence, CIS and progression)



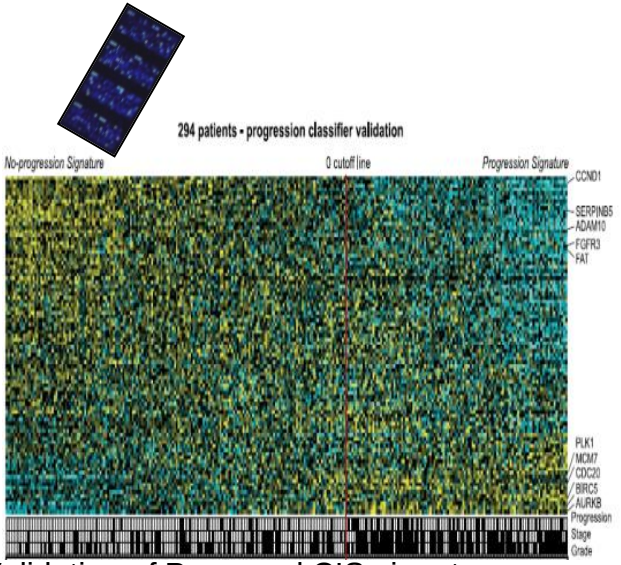
Rec. signature



CIS signature



Prog. signature



Validation of Prog. and CIS signatures

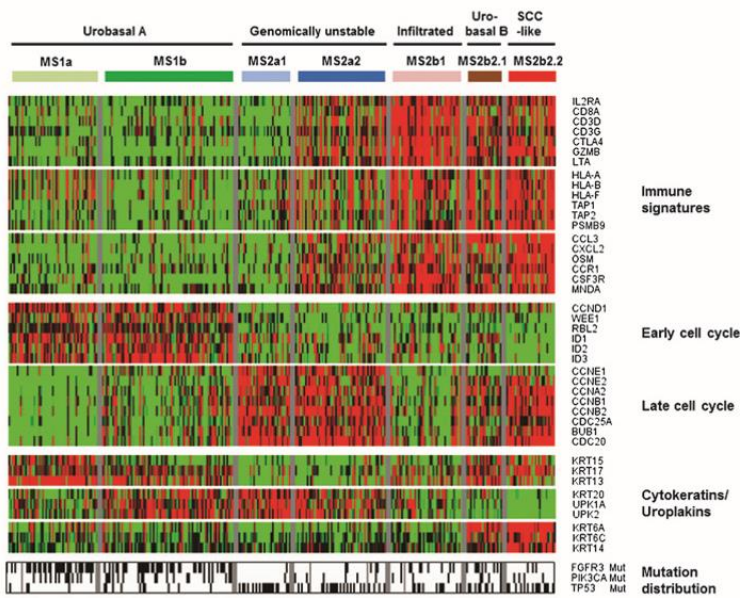
Two major risk classes identified and validated

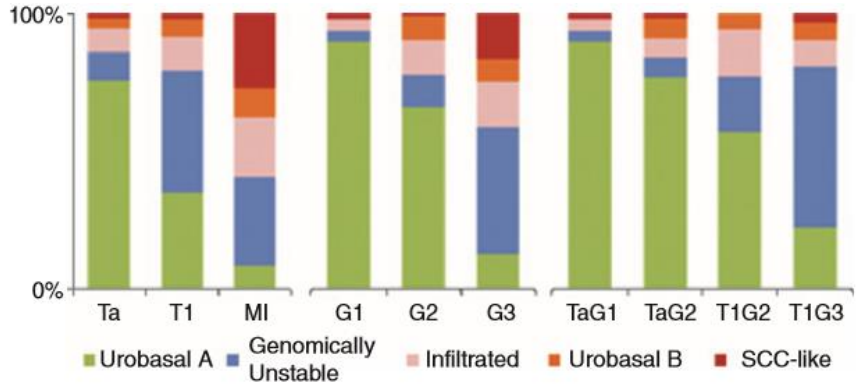
Nat. Genet. 2003
Can. Res 2004
Clin. Can. Res. 2005
Clin. Can. Res. 2007

Slide credit: Lars Dryskot

Lund Taxonomy approach - NMIBC and MIBC combined

Samples selected to represent the entire disease spectrum
3 major groups identified in NMIBC





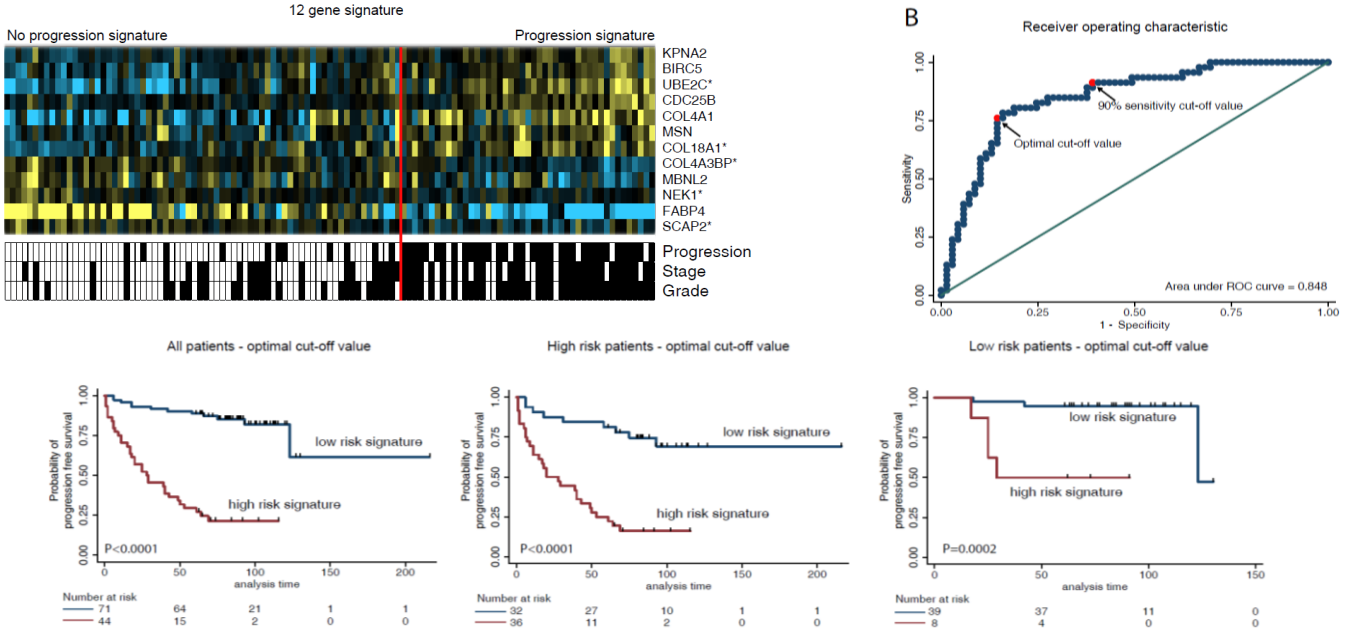
Slide credit: Lars Dryskot

Sjodahl et al, Clinical Cancer Research 2012

Development of a 12-gene progression score qPCR assay

Transferred microarray signature to a 12-gene RT-qPCR test

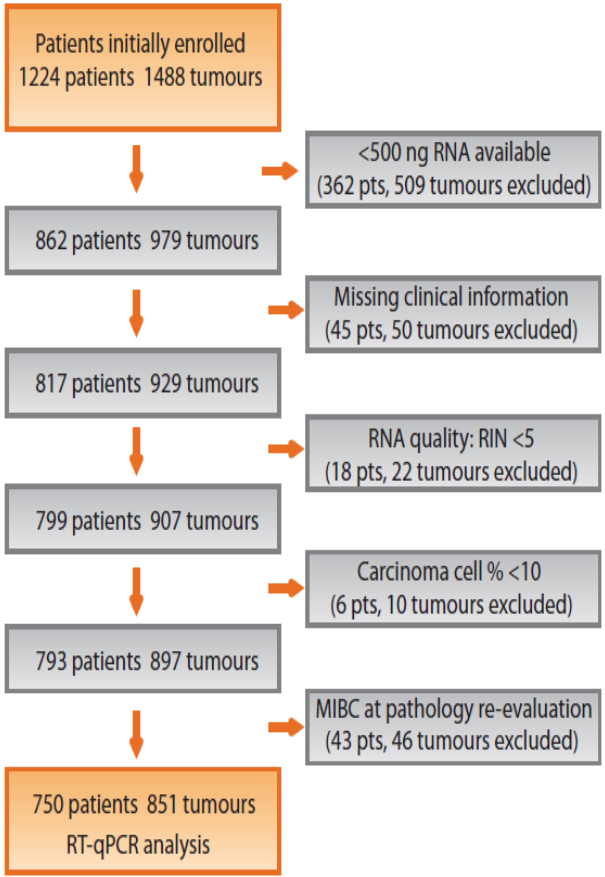
Progression score = *average (Ct (COL4A3BP, MBNL2, NEK1, FABP4, SCAP2) – average (Ct (KPNA2, BIRC5, UBE2C, CDC25B, COL4A1, MSN, COL18A1))*

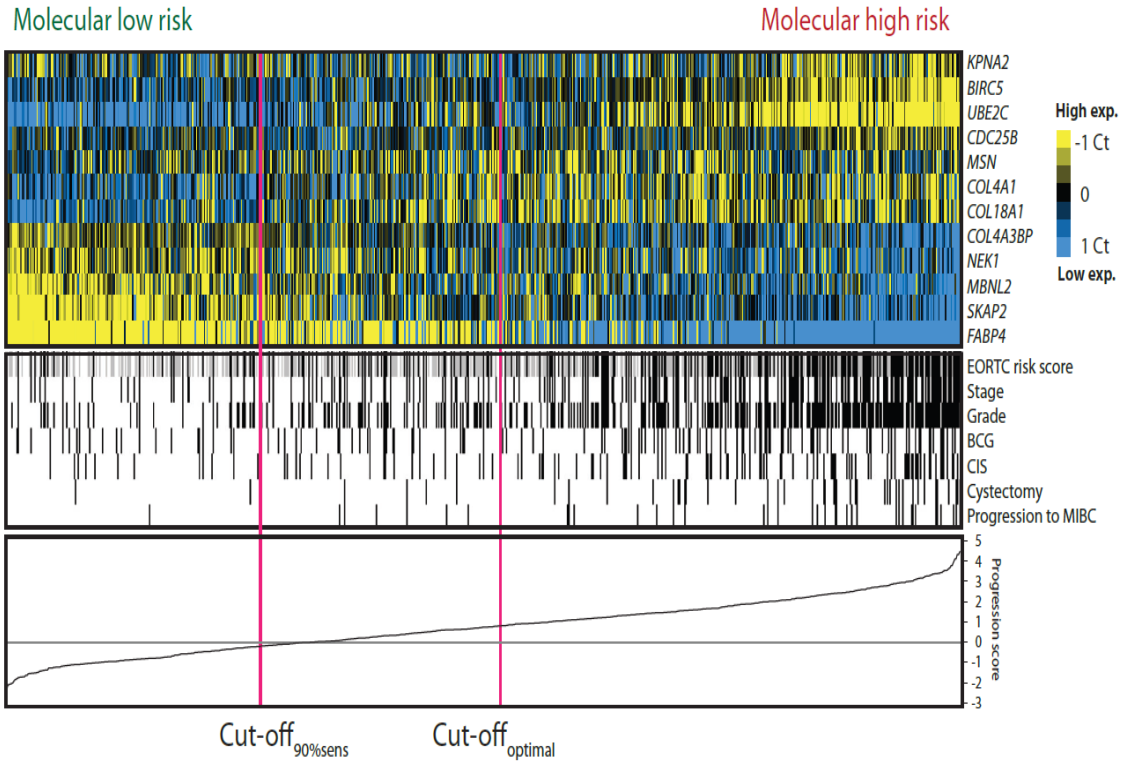


Dyrskjøt et al, BJC. 2012

Slide credit: Lars Dryskot

Prospective study of 12-gene progression score in UROMOL





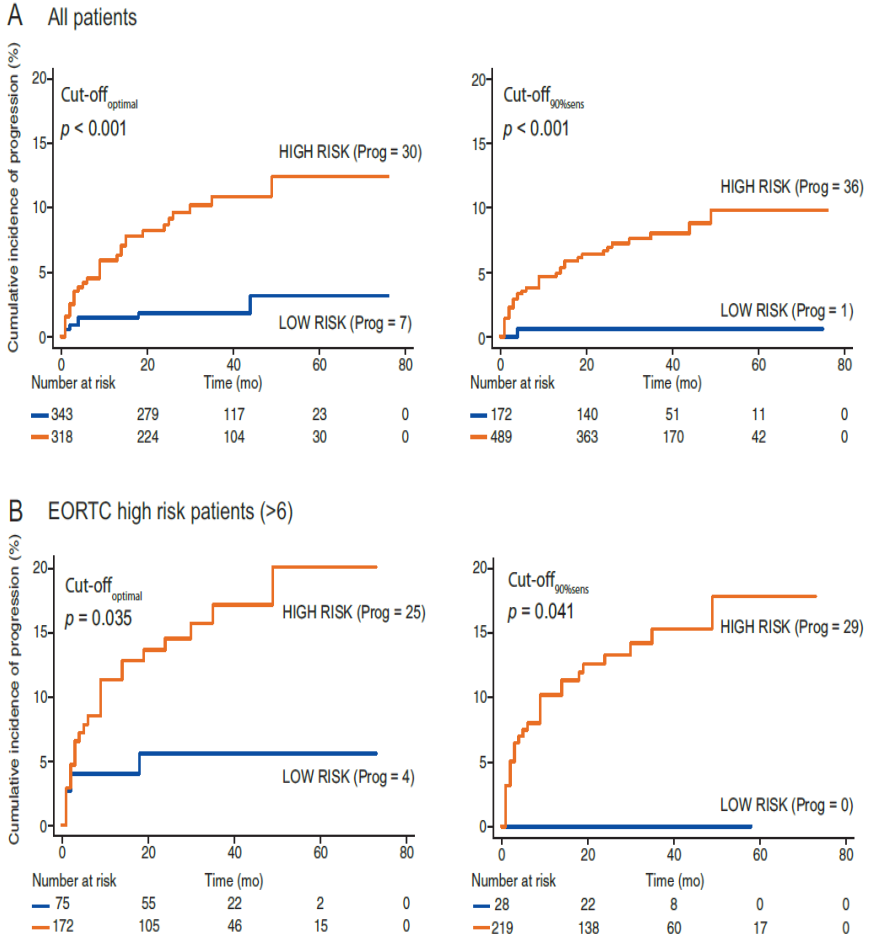
Slide credit: Lars Dryskot

Dyrskjøt et al, Eur Urol 2017

Prospective study of 12-gene progression score

All patients

EORTC high-risk



Slide credit: Lars Dryskot

Dyrskjøt et al, Eur Urol 2017

Table 2 – Cox regression analysis of progression-free survival with the first tumour in the disease course as the baseline [a]

	HR (95% CI)	χ^2 (df)	*p* value	PA (%)
Univariate analysis (n = 578, 37 events)				
Age	1.03 (1.00–1.06)	3.92 (1)	**0.040**	58.4
Gender (female vs male)	0.93 (0.43–2.05)	0.03 (1)	0.878	49.5
Stage (T1 + Cis vs Ta)	7.42 (3.67–15.04)	34.87 (1)	**<0.001**	75.5
Grade (high vs low + PUNLMP)	4.94 (2.32–10.51)	20.58 (1)	**<0.001**	70.1
Bacillus Calmette-Guérin (yes vs no)	0.63 (0.24–1.61)	1.07 (1)	0.329	53.8
Size (≥3 cm vs <3 cm)	1.40 (0.63–3.11)	0.63 (1)	0.415	53.2
Growth pattern (solid + mixed vs papillary)	4.45 (1.72–11.51)	6.70 (1)	**0.002**	55.5
Primary (yes vs no)	1.01 (0.53–1.93)	<0.001 (1)	0.978	49.8
Multiplicity (multiple vs solitary)	1.48 (0.76–2.88)	1.29 (1)	0.248	53.0
Concomitant CIS (yes vs no)	3.59 (1.58–8.18)	7.03 (1)	**0.002**	56.5
EORTC risk score (>6 vs ≤6)	7.17 (3.28–15.71)	31.20 (1)	**<0.001**	73.3
EORTC risk score (continuous)	1.21 (1.14–1.28)	35.88 (1)	**<0.001**	78.4
Progression score (high vs low risk)	5.08 (2.23–11.57)	19.56 (1)	**<0.001**	68.1
Progression score (continuous)	2.39 (1.82–3.16)	41.85 (1)	**<0.001**	78.6
PA model (clinical)				81.8
PA model (clinical + Progression score [continuous])				85.7
Multivariable model 1 (n = 517, 34 events)		55.84 (2)	**<0.001**	85.7
Progression score (continuous)	1.95 (1.44–2.65)		**<0.001**	
Stage (T1 + CIS vs Ta)	4.21 (1.89–9.39)		**<0.001**	
Multivariable model 2 (n = 578, 37 events)		53.36 (2)	**<0.001**	82.2
Progression score (continuous)	1.90 (1.39–2.58)		**<0.001**	
EORTC risk (continuous)	1.13 (1.05–1.21)		**0.001**	

Slide credit: Lars Dryskot

UROMOL 2016 study

European multicenter study of total RNA-Sequencing from 460 NMIBC tumors.

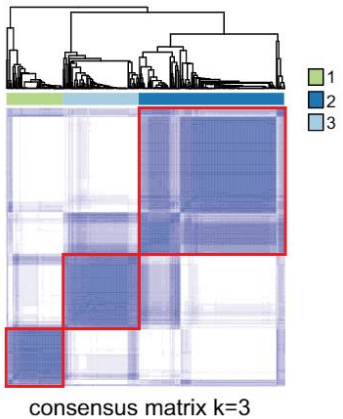
Major finding: Three molecular subclasses of NMIBC with different clinical outcomes and biological characteristics.

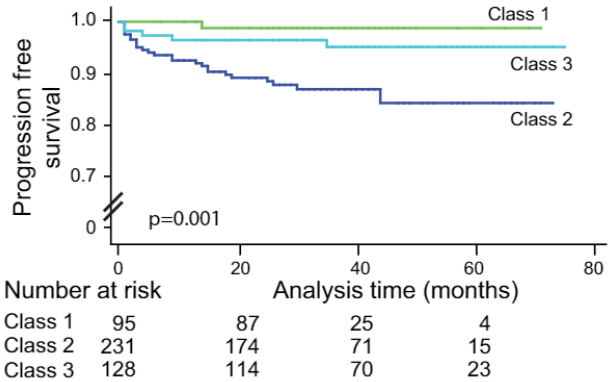
Cancer Cell
Volume 30, Issue 1, 11 July 2016, Pages 27-42
CellPress

Article

Comprehensive Transcriptional Analysis of Early-Stage Urothelial Carcinoma

Jakob Hedegaard [1], Philippe Lamy [1], Iver Nordentoft [1], Ferran Algaba [2], Søren Høyer [3], Benedicte Parm Ulhøi [3], Søren Vang [1], Thomas Reinert [1], Gregers G. Hermann [4], Karin Mogensen [4], Mathilde Borg Houlberg Thomsen [1], Morten Muhlig Nielsen [1], Mirari Marquez [5], Ulrika Segersten [6], Mattias Aine [7], Mattias Höglund [7], Karin Birkenkamp-Demtröder [1], Niels Fristrup [1] ... Lars Dyrskjøt [1]





	Luminal-like Differentiation	Basal-like	EMT TF activity	CSC activity	Cell cycle activity	Molecular signature	Mutations
Class 1	UPKs PPARG GRHL3 BAMBI SPINK1			SHH RPSA ALDH1A3 ITGA6	*Early:* CCND1 ID1 RBL2		*FGFR3*
Class 3	GATA3	KRT5 KRT14 KRT15 CD44		ITGA6		BASE47+	*FGFR3* RNA-editing signature
Class 2	UPKs PPARG KRT20 GRHL3 BAMBI SPINK1	KRT14	SOX9 TWIST1 FOXF1 ZEB1 ZEB2 GATA6	PROM1 ALDH1A1 ALDH1A2 ALDH1A3 NES THY	*Late:* CDC20 CDC25A CDKs PLK1	CIS+ Prog.+	*TP53* *ERCC2* APOBEC mutation signature

Slide credit: Lars Dryskot

Hedegaard et al, Cancer Cell 2016

UROMOL 2021 study

Multi-omics analysis of 862 NMIBC tumors

- Transcriptomic analysis (total RNA-Seq): **535 tumors**
- Copy number analysis (SNP arrays): **473 tumor-leukocyte pairs**
- Methylation analysis (EPIC BeadChip): **29 tumors**
- Spatial proteomics analysis (multiplex immunofluorescence): **167 tumors**

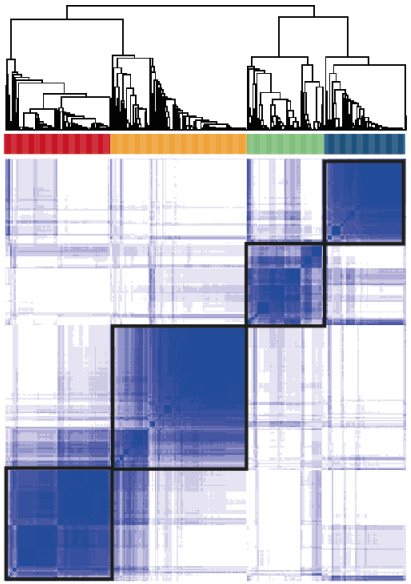
- Validation using expression data from **1309 independent tumors**

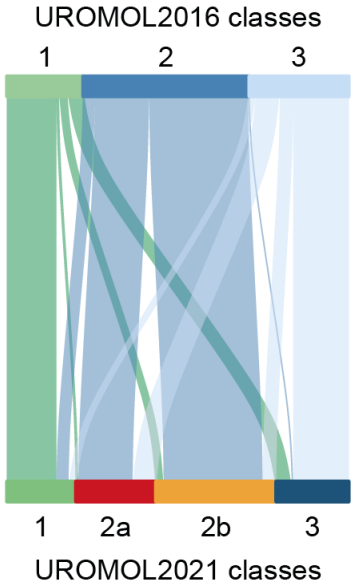
- Updated clinical follow-up
- Updated bioinformatics analysis pipelines

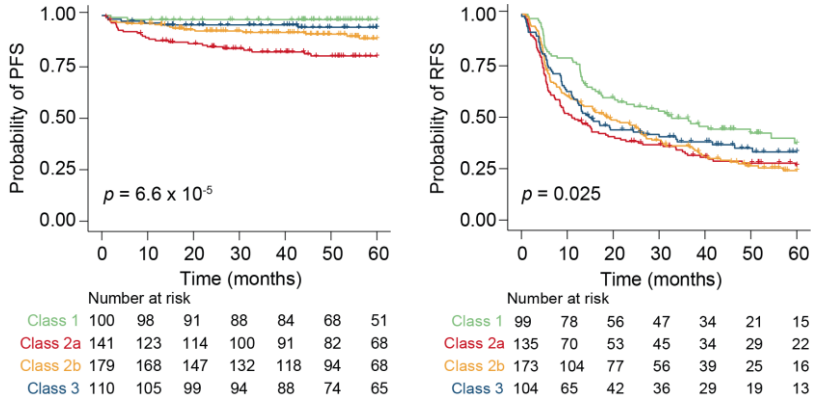
Slide credit: Lars Dryskot

Lindskrog et al, Nature Communications 2021

Four transcriptomic classes (n=535 NMIBC)



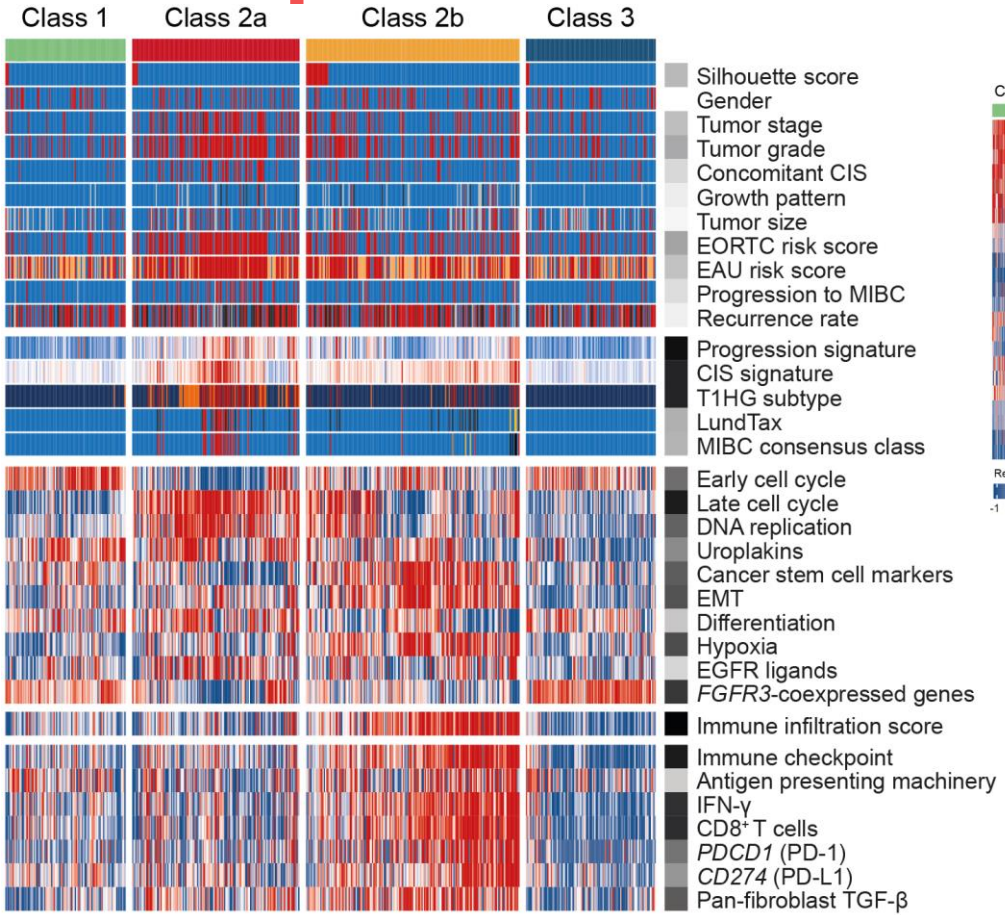




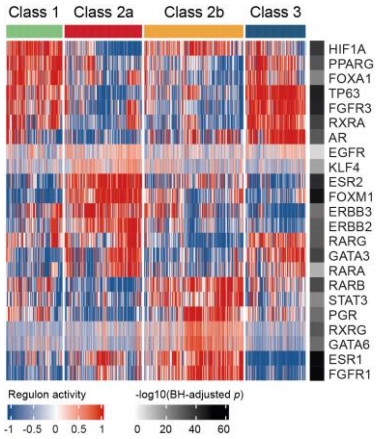
Slide credit: Lars Dryskot

Lindskrog et al, Nature Communications 2021

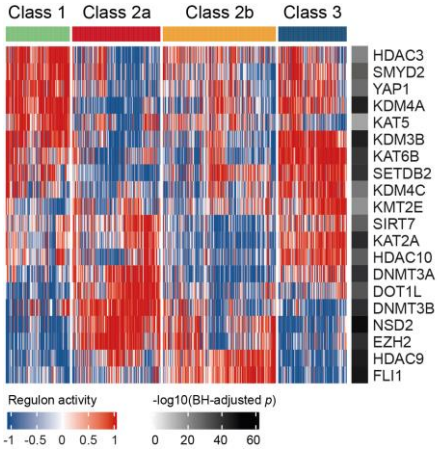
Transcriptomic class characteristics

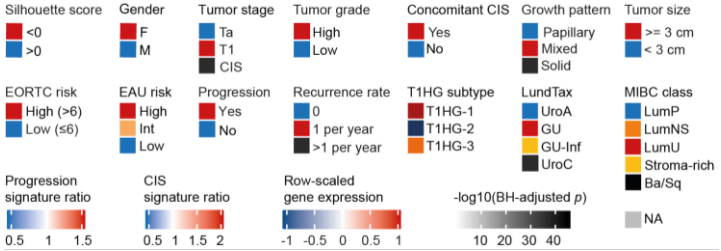


Regulons: TFs



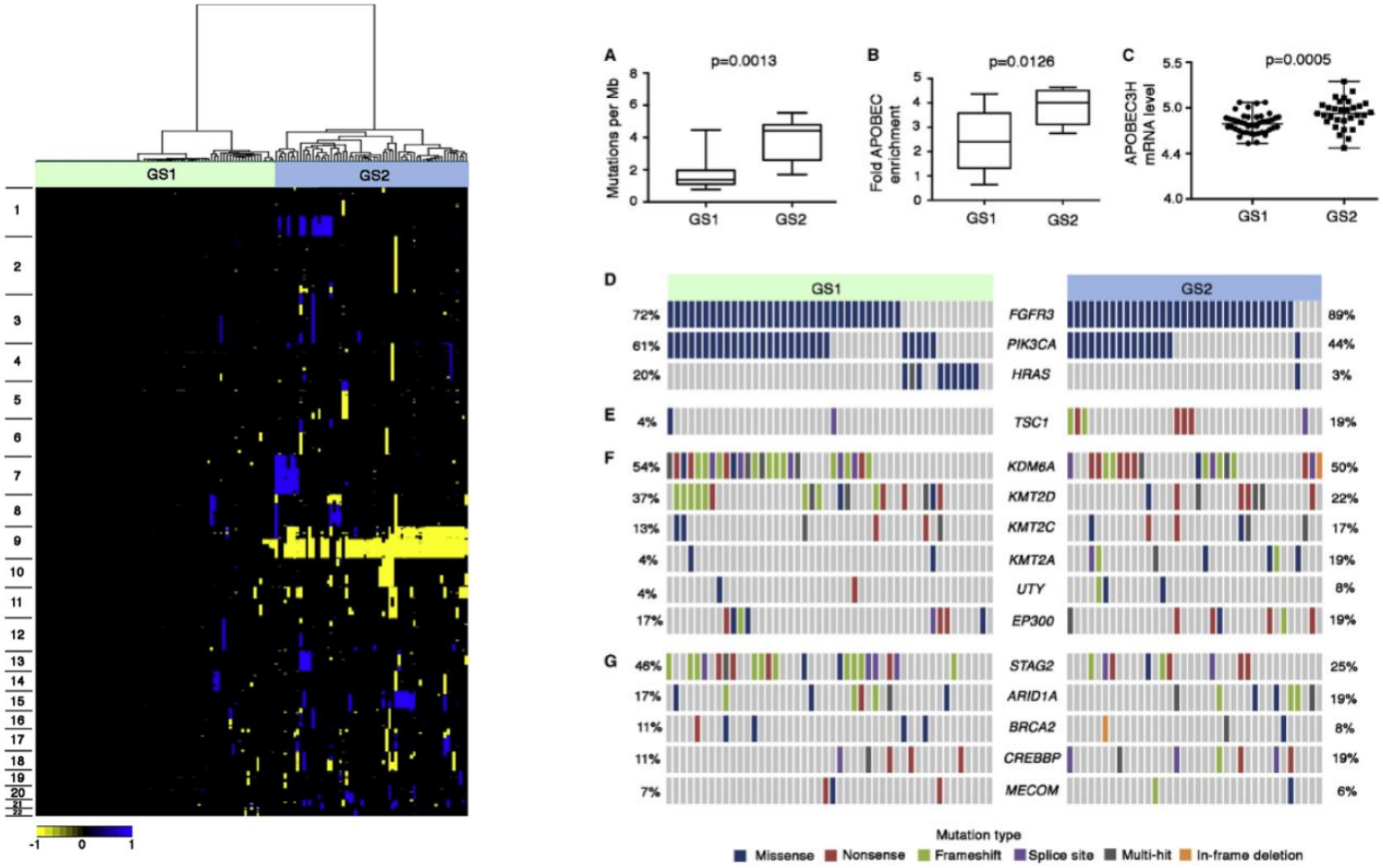
Regulons: Chromatin remodelling





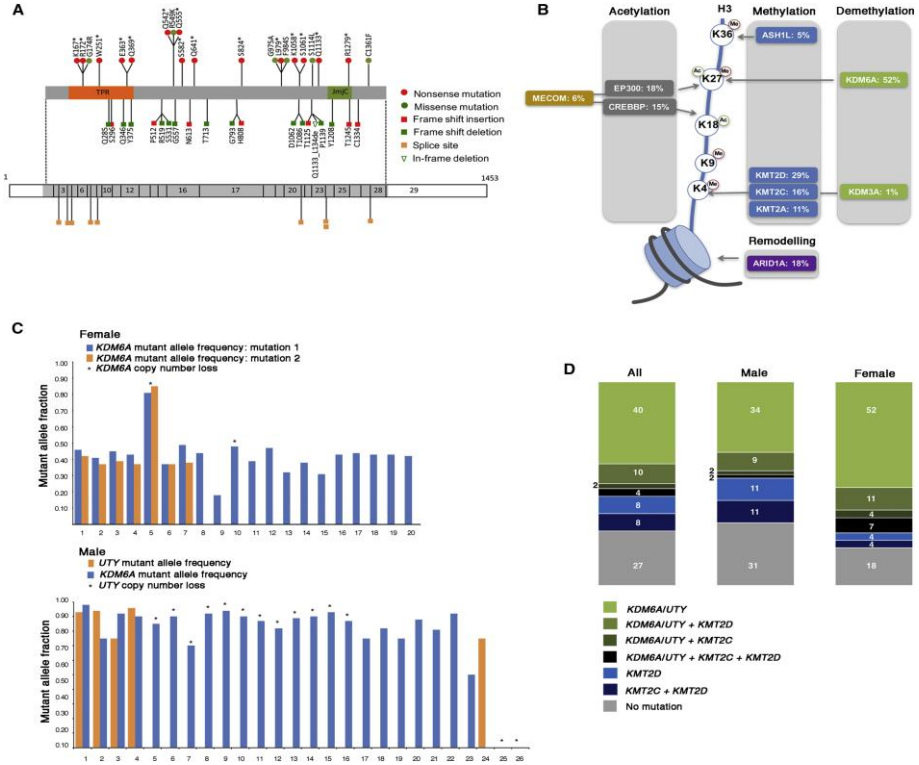
Lindskrog et al, Nature Communications 2021

Genomic alteration in 140 Ta tumors



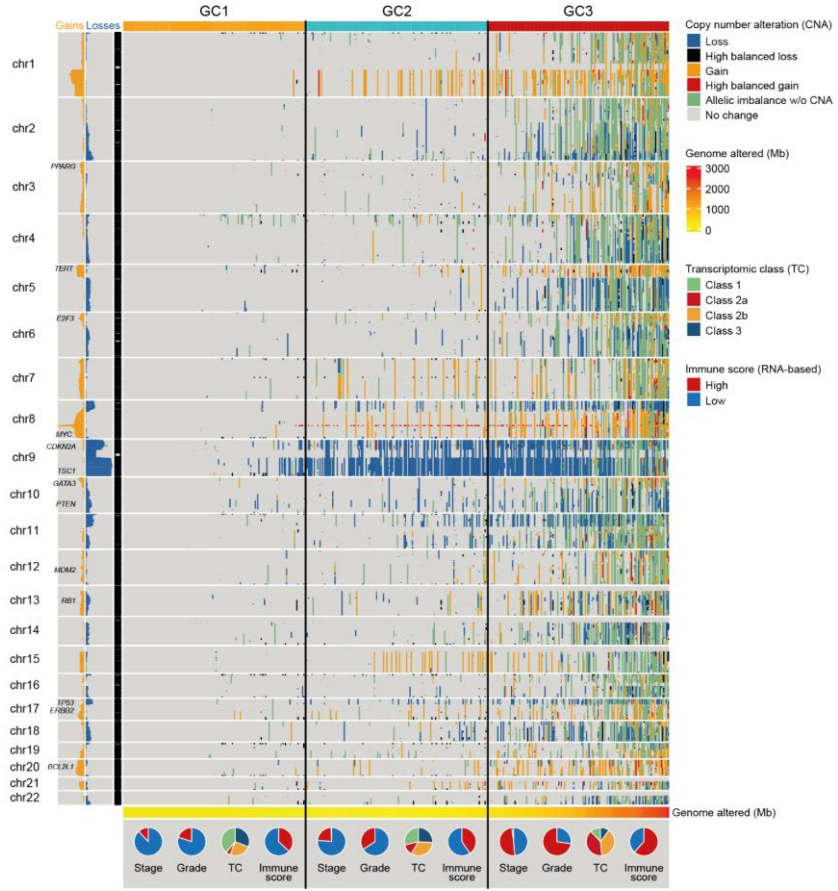
Hurst et al, Cancer Cell 2017

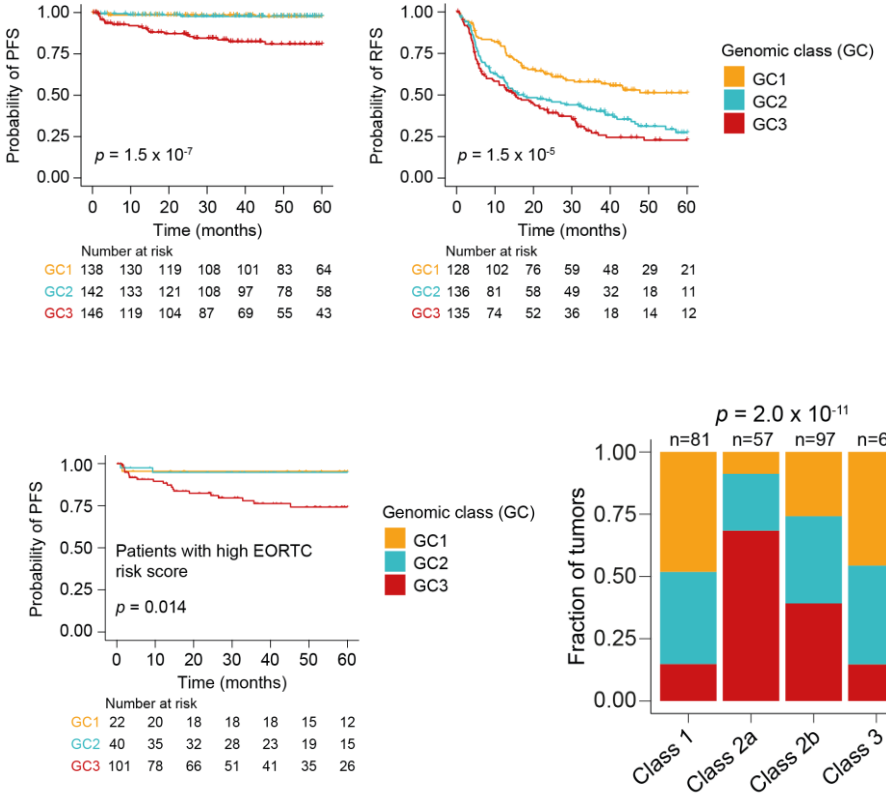
Sex-specific differences in prevalence of KDM6A mutations in NMIBC



Hurst et al, Cancer Cell 2017

Copy number alterations (n=473 NMIBC)

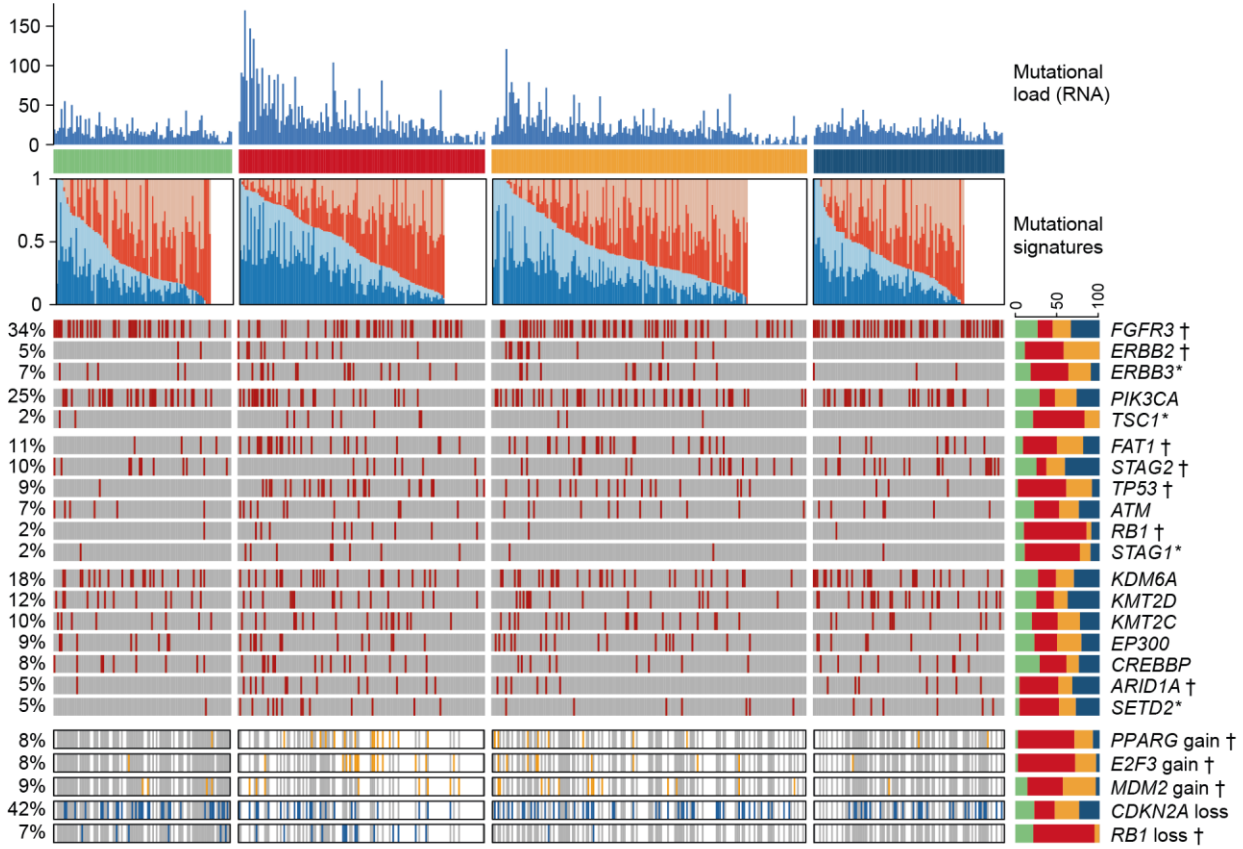


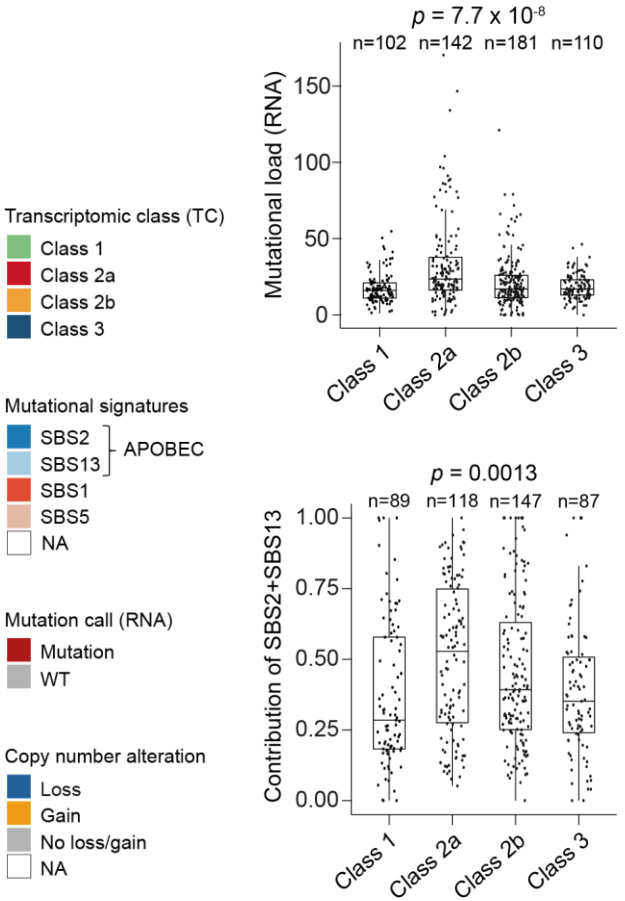


Slide credit: Lars Dryskot

Lindskrog et al, Nature Communications 2021

Mutational analysis (RNA-Seq based)

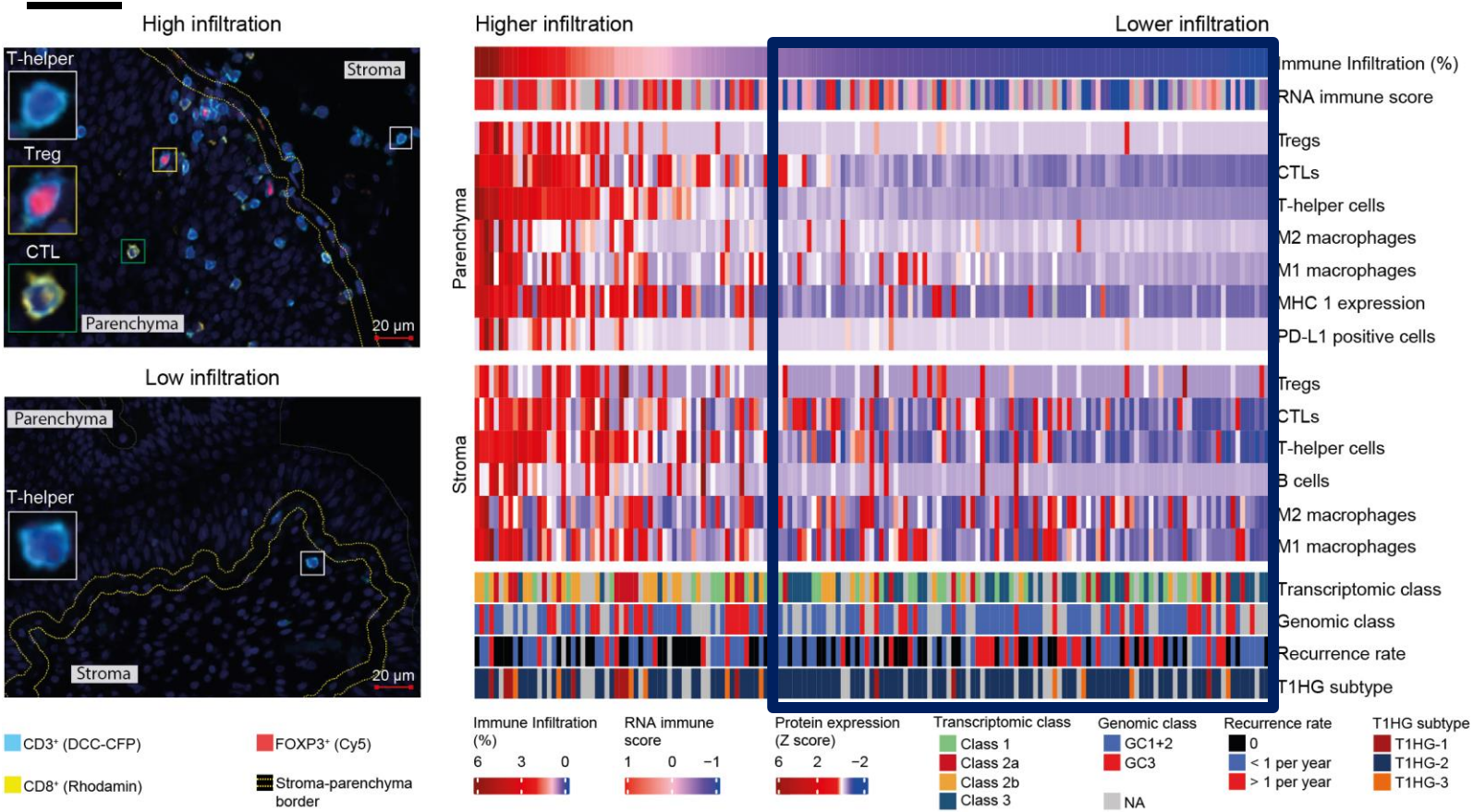




Slide credit: Lars Dryskot

Lindskrog et al, Nature Communications 2021

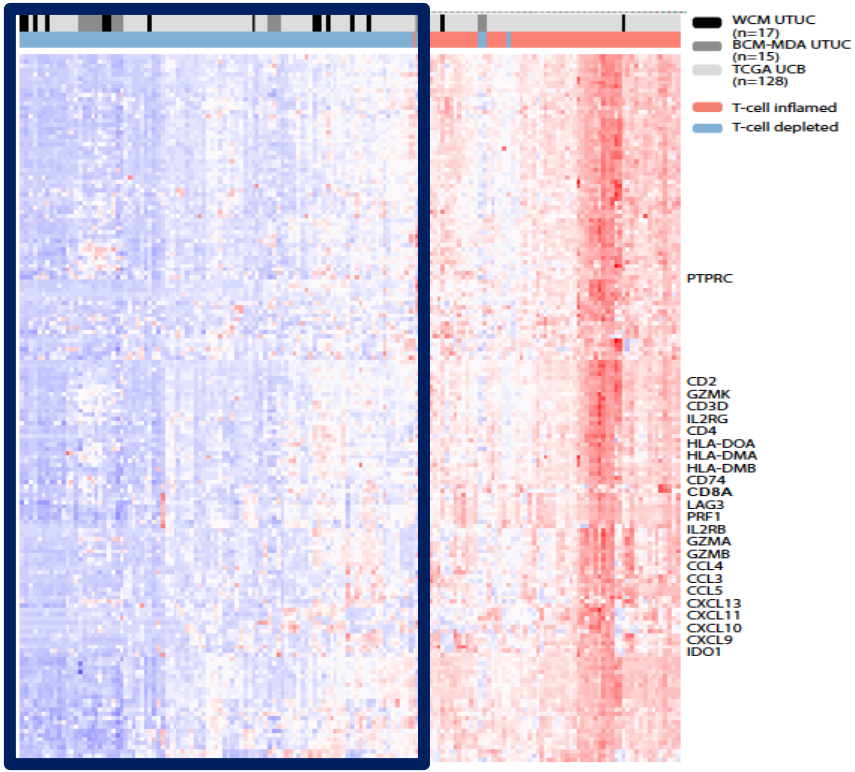
Class 3 tumors are luminal-papillary and immune-depleted



Slide credit: Lars Dryskot

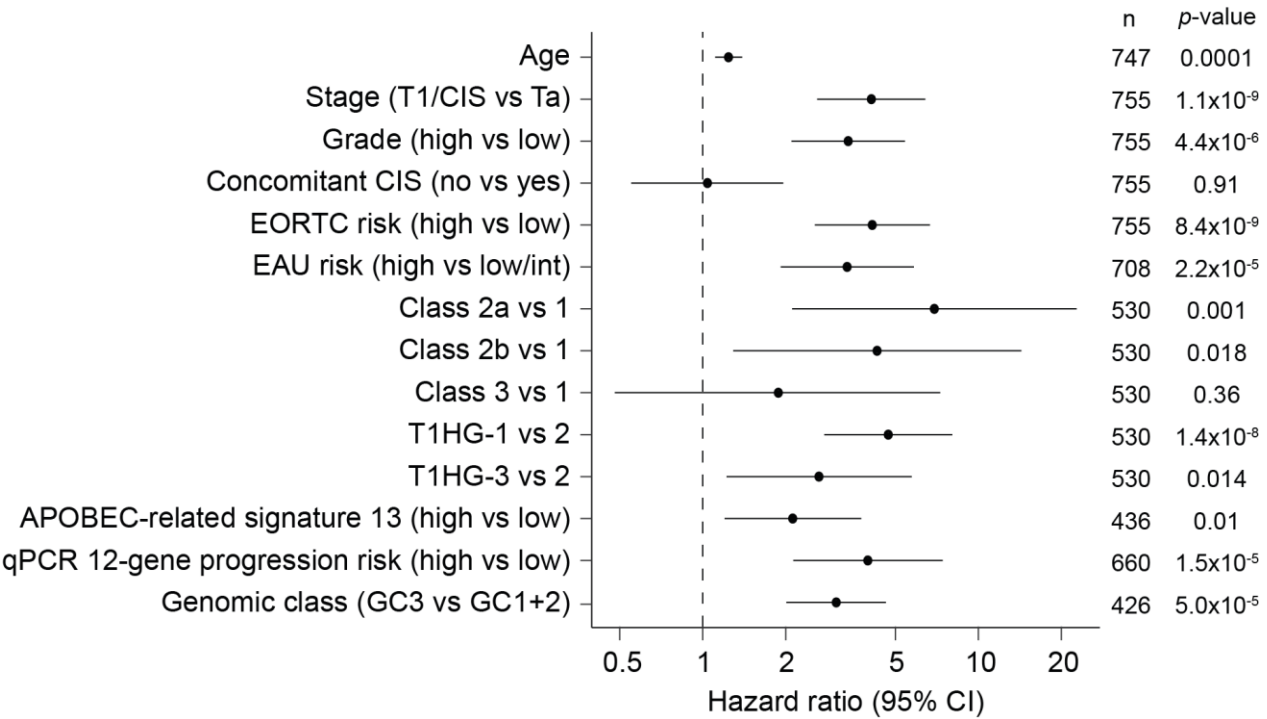
Lindskrog et al, Nature Communications 2021

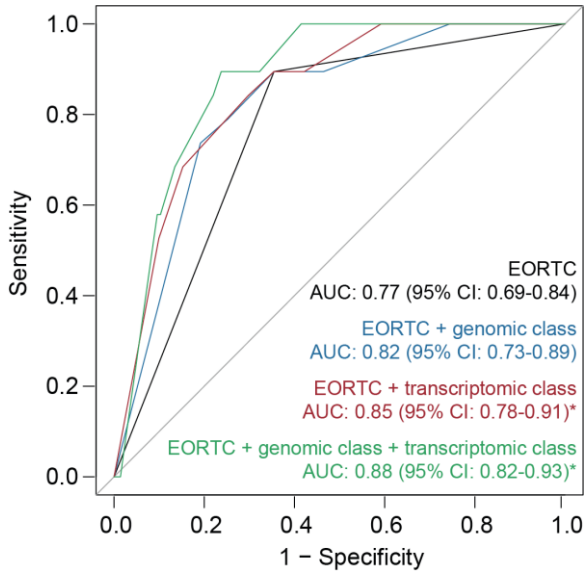
Class 3 NMIBC similar to UTUC with a luminal-papillary and T-cell depleted immune contexture



Robinson, Vlachostergios et al. Nature Communications, 2019

Prediction models

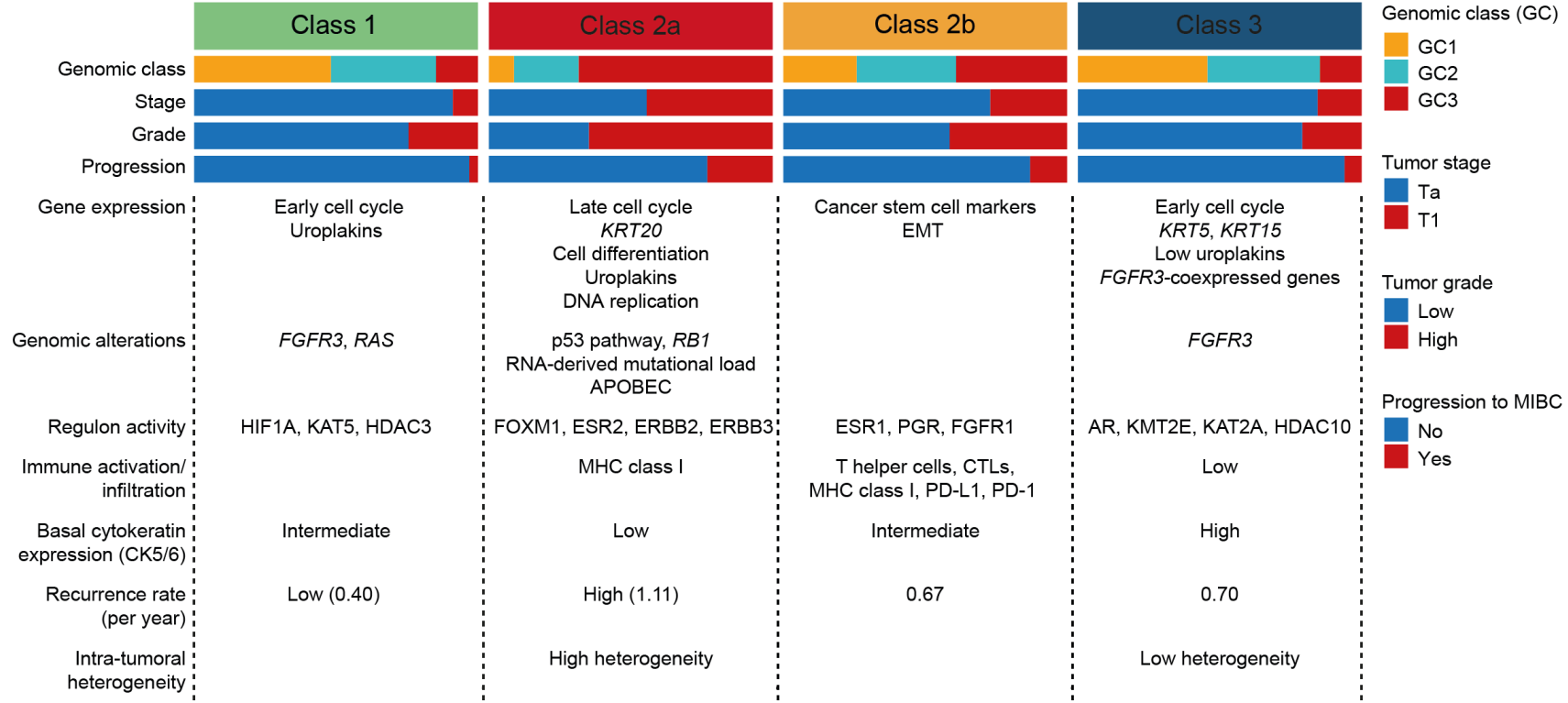




Slide credit: Lars Dryskot

Lindskrog et al, Nature Communications 2021

Summary of biological characteristics



Slide credit: Lars Dryskot

Lindskrog et al, Nature Communications 2021

Summary and conclusions

- NMIBC molecular subtypes are prognostic.
- Biomarkers for predicting response to BCG and newer intravesical agents are needed.
-MIBC molecular subtypes overlap with NMIBC but are not the same.
-Important NMIBC molecular features: FGFR3 alterations, APOBEC3 signatures association with worse outcomes, KDM6A alterations.
-Prospective trials assigning interventions based on molecular subtyping are needed but additional work to translate discoveries of molecular subtypes to clinical-grade biomarkers is needed.