How will new biomarkers change bladder cancer management?

John Kelly

Professor of Uro-Oncology UCL

What do we mean by biomarker?

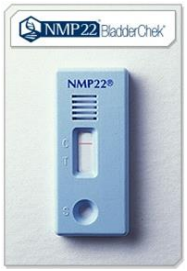
a measurable indicator of the severity or presence of some disease state.

- *Diagnostic*
- *Prognostic*
- *Predictive*

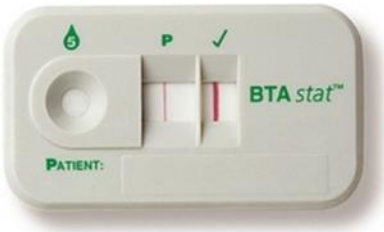
Measured in fluid (liquid biopsy)
Tissue / cells
Physiological
Imaging

Diagnostic Markers for BC

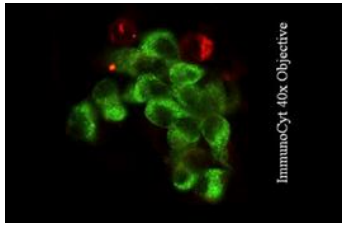
"a littered landscape"



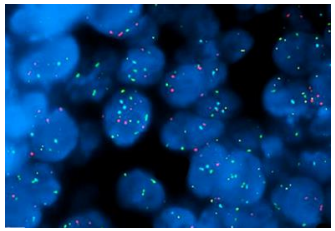
NMP22



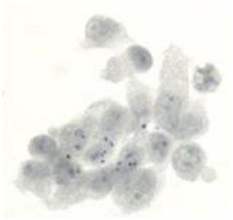
BTA stat (Polymedco)
BTA TRAK



uCYT



Urovision



Cytology

Sensitivity: 57-82%

Specificity: 74-88% (95%) [1]

Bladder Biomarkers in perspective

PSA level >4.0 ng/mL	PPV 30 % NPV 80%

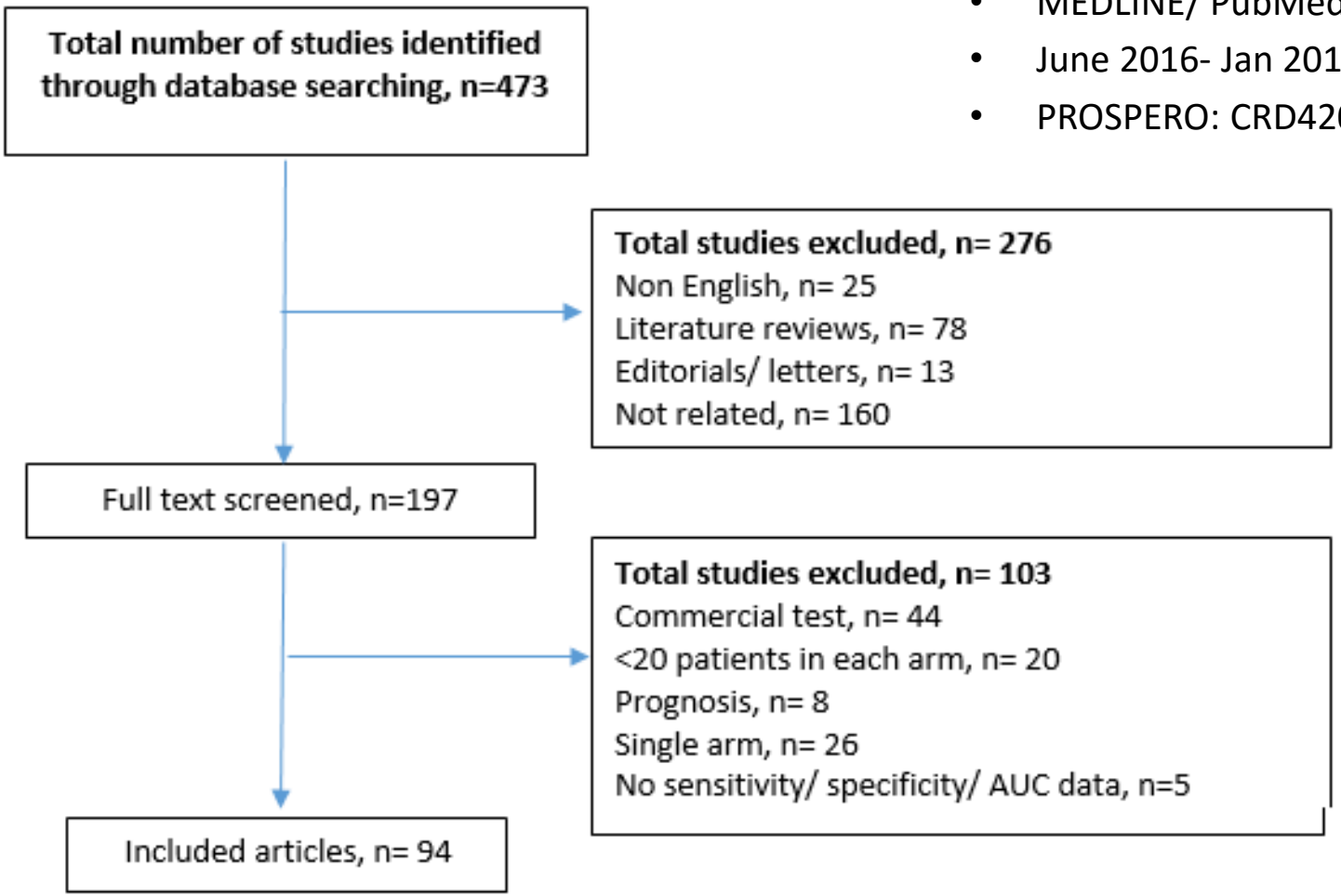
Companion test makes sense for prostate cancer

Flex cystoscopy	PPV 95% NPV 98%

Companion test is not needed for bladder cancer

Active research field: Systematic review of novel urinary biomarkers

- MEDLINE/ PubMed search
- June 2016- Jan 2013
- PROSPERO: CRD42016049918



Wei Shen Tan 2016

Metabolomic testing of urine

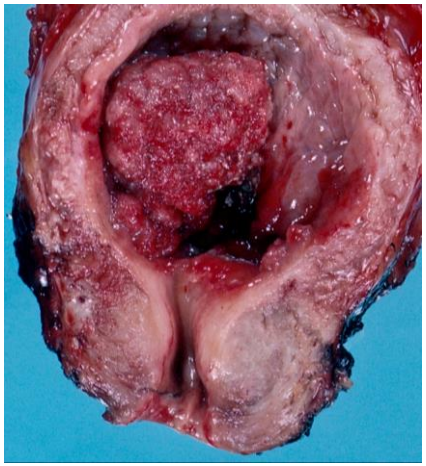
It took 7 months to train Tangle to detect the smell of cancer.

© *Amersham and Wickham Medical Illustration*

Sensitivity 40% !

Urinary metabotyping of bladder cancer using two-dimensional gas chromatography time-of-flight mass spectrometry.

100% specificity and 71% sensitivity



J Proteome Res. 2013

Move towards genomic testing for biomarkers

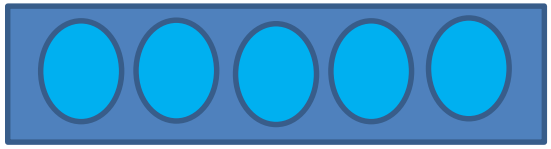
Biomarkers:

- Protein/ cell based: 48.9% (46/94)
- Genomic: 28.7% (27/94)
- Epigenetic: 14.9% (14/94)
- Mass spectrometry: 10.6% (10/94)
- Other: 1.1% (1/94)

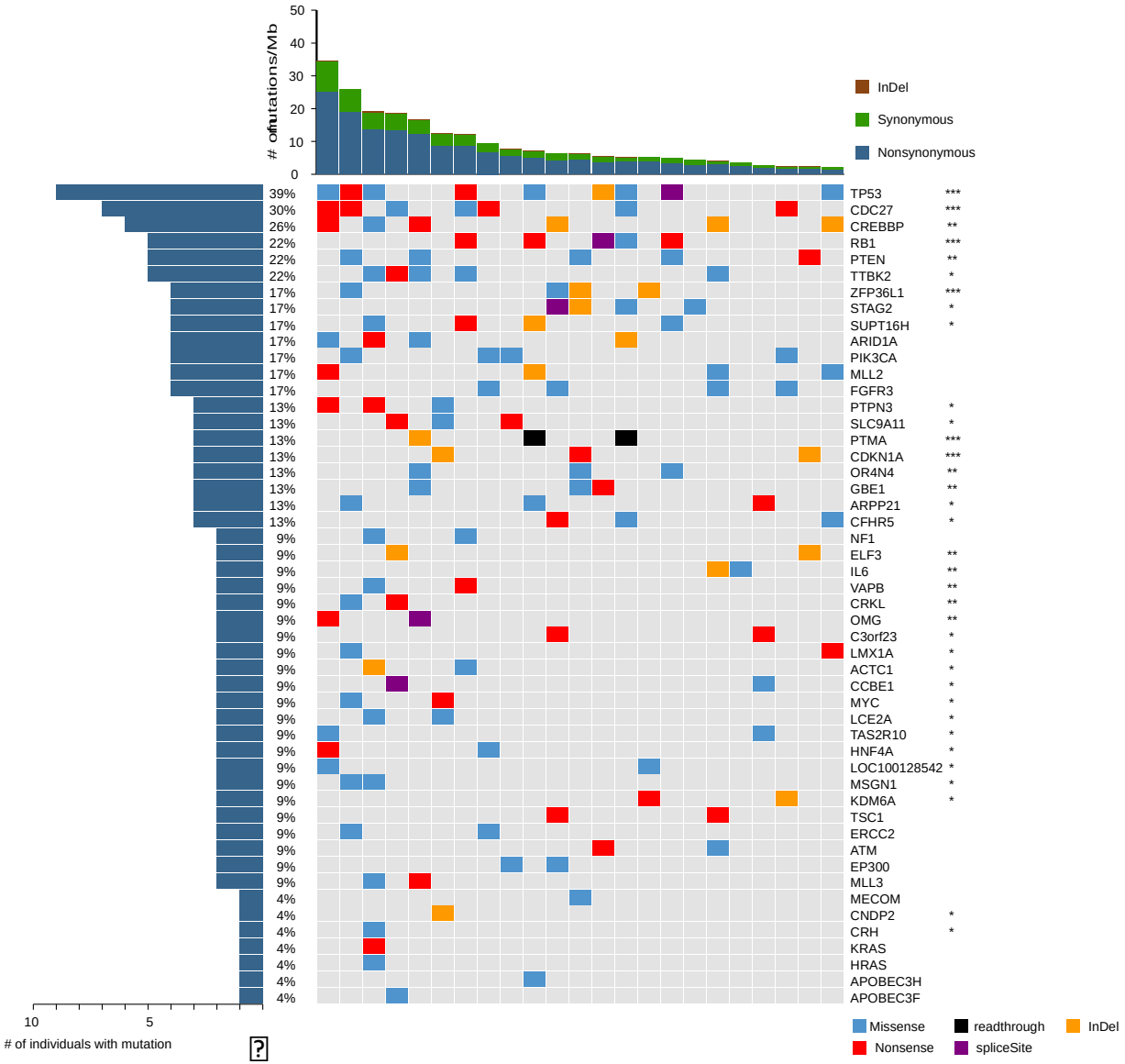
Significant bias in design, reporting.

Only 35% (33/94) had some form of validation

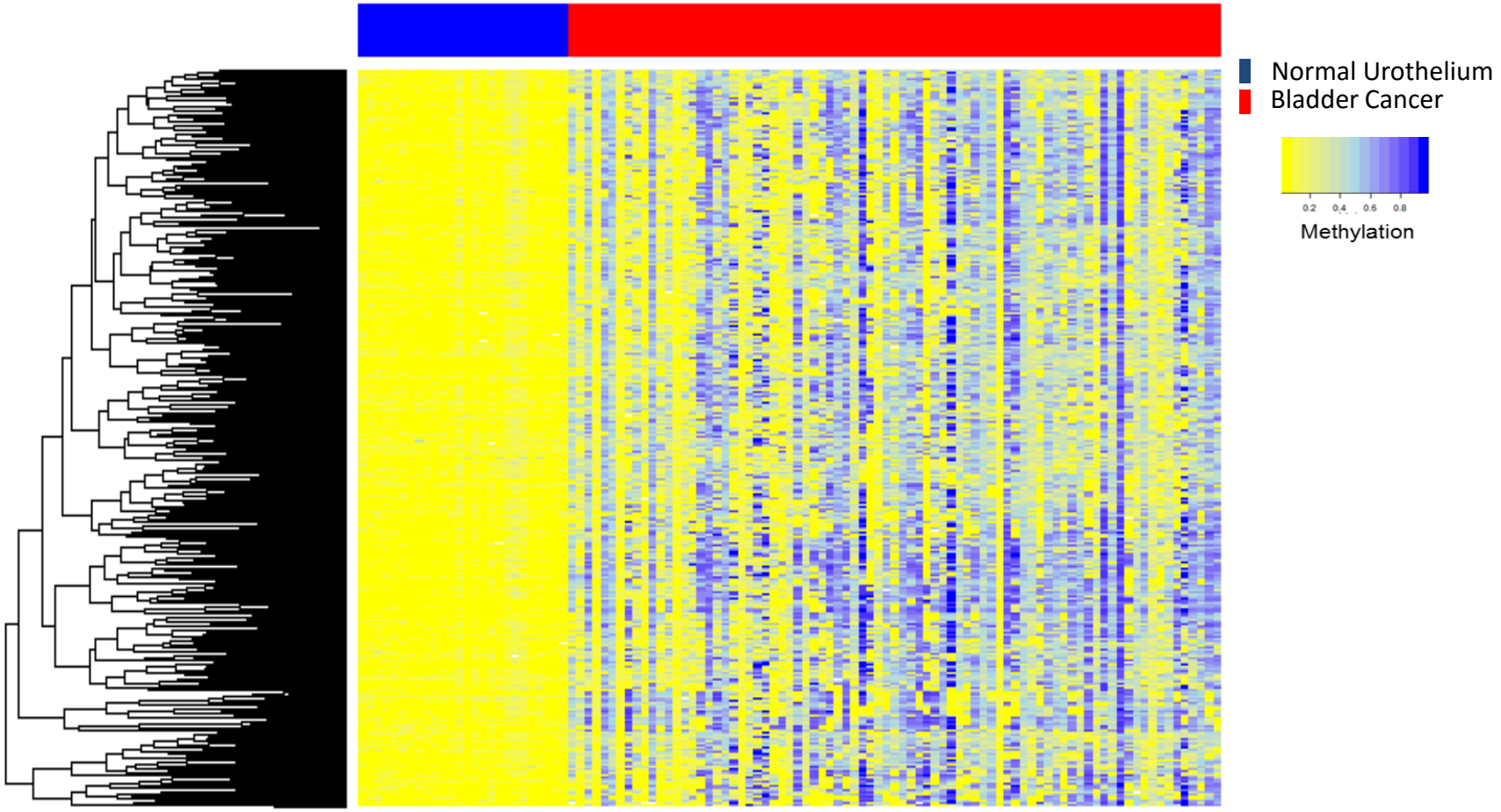
Single or small panel testing



Genomic alterations are not constant across cancer

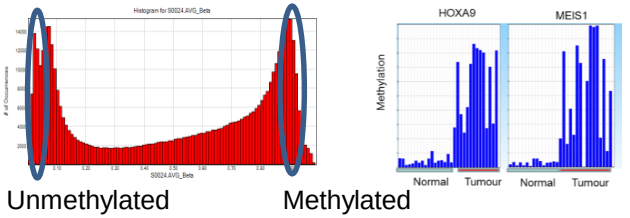


Significant epigenetic variability

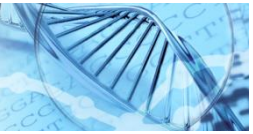


Harnessing NGS for biomarker discovery and design

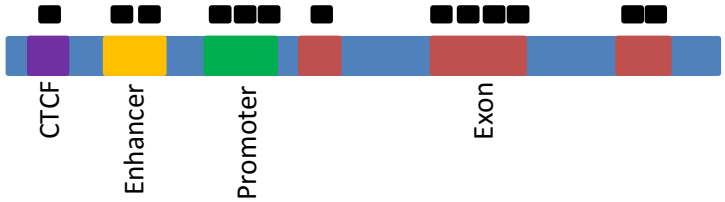
HumanMethylation 950K array

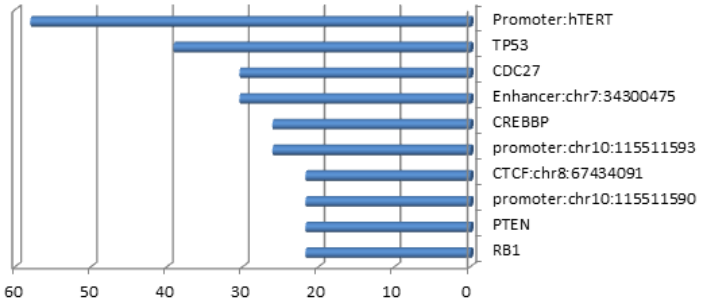


Unmethylated Methylated

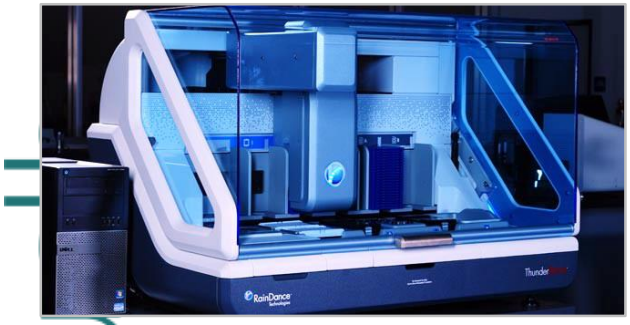


NGS of Regulome



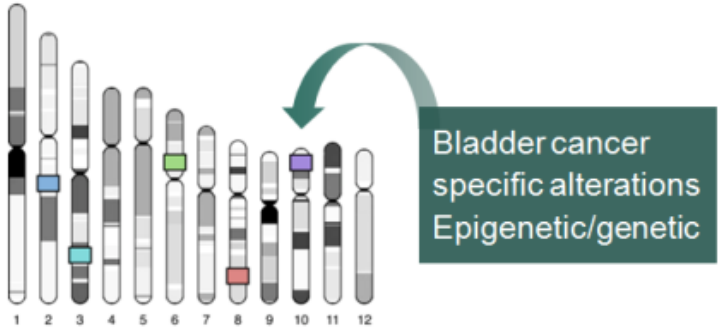


Mutation Frequency (%)



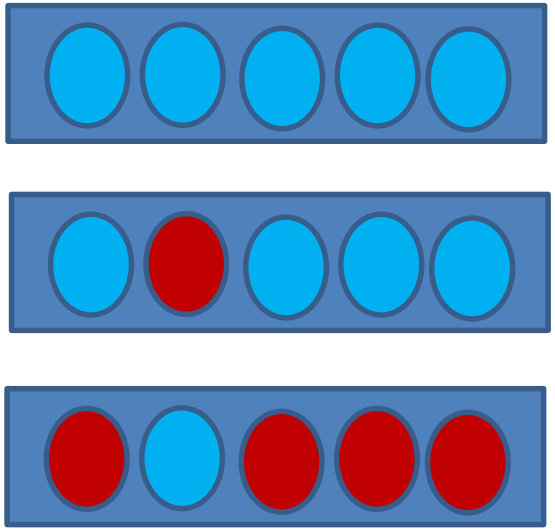
Multiplex PCR high throughput platform

RainDance Thunderstorm

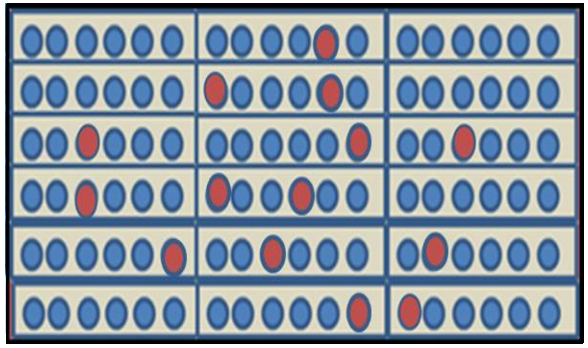


Shifting paradigm in biomarker design

Traditional panel



Classifier (Random Forrest)



-ve

Will a biomarker replace cystoscopy ?

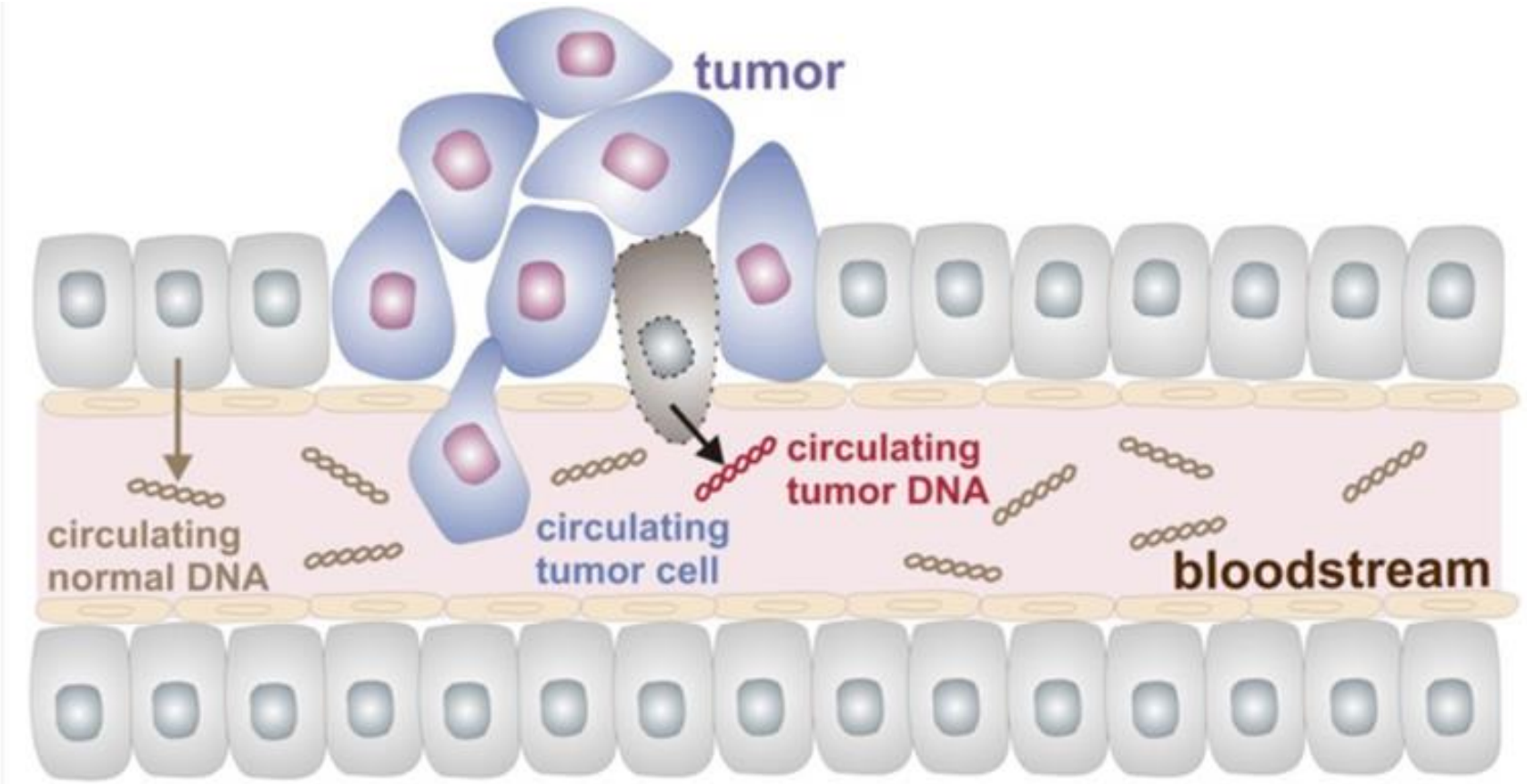
- Single biomarkers have universally failed
- Oligo panels problematic
- Dogs need to be very smart
- NGS sequencing promising but could over fit
- Companion or Replacement
- NGS platforms very stable

Detecting recurrence & monitoring therapy

- Detecting recurrence of NMIBC
  - Test +ve and cystoscopy -ve.
  - Fgfr3 +ve no recurrence.

- MIBC post cystectomy ?
  - Any Test +ve signal could indicate residual or recurrent disease
- Monitoring neo-adjuvant and adjuvant therapy

Blood-based diagnostics



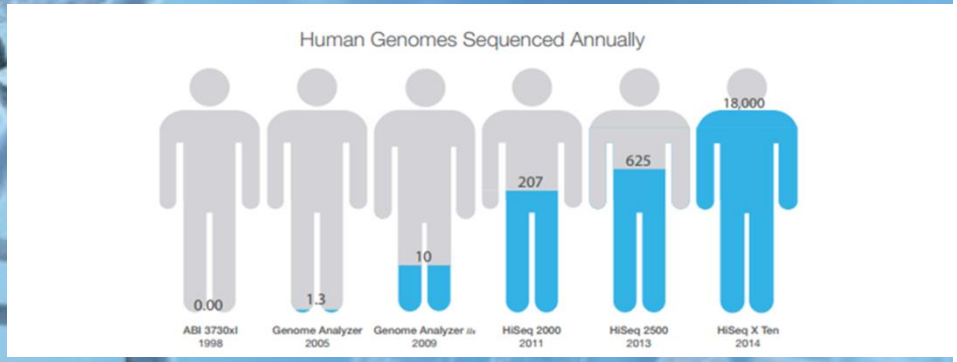
Circulating tumour cells in bladder cancer

- Overall
  - sensitivity 35.1%,
  - specificity 89.4%
- CTC +ve more likely to have advanced disease (OR, 5.05; 95%CI, 2.49 -10.26)

- CTCs are insufficient for diagnostic certainty

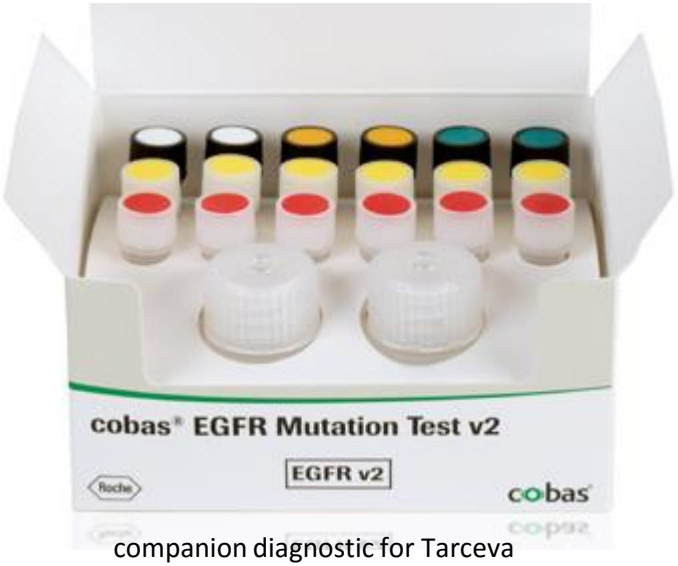
Msaouel P, Koutsilieris M. Diagnostic value of circulating tumor cell detection in bladder and urothelial cancer: systematic review and meta-analysis. BMC Cancer [Internet]. 2011;11:336

Deep sequencing for mutations in cell free cfDNA very attractive



FDA approval for cfDNA cancer testing 2016

- Roche: Cobas EGFR M Test
- 1st FDA cfDNA based biomarker
- Detection of EGFR mutation

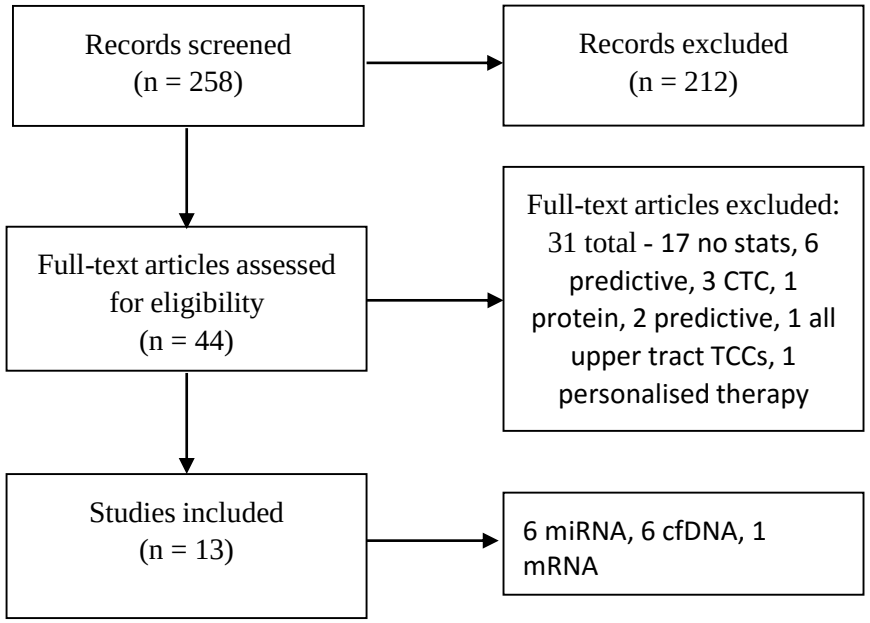


companion diagnostic for Tarceva

- Cobas +ve used to select patients for treatment with erlotinib, a tyrosine kinase inhibitor in lung cancer.

Systematic review of novel blood genomic biomarkers

- MEDLINE/ PubMed search
- August 2016
- PROSPERO: CRD42016051201



Pramit Khetrapal 2016

Liquid biopsy

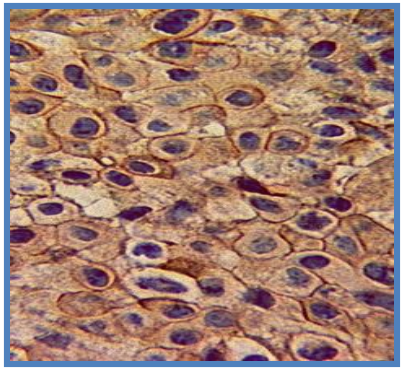
- Increasing activity in field
- NGS platforms are accessible
- Depth of sequencing is cost effective
- Industry and academic groups

Detect recurrence in MIBC
Monitor neo-adjuvant
Monitor adjuvant Immunotherapy
Individualise therapy

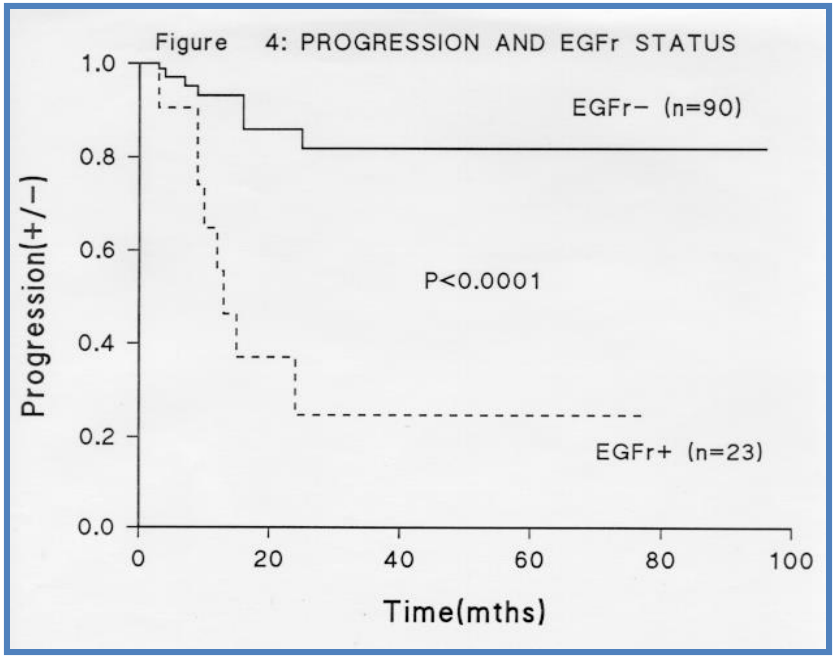
Prognosticators for BC

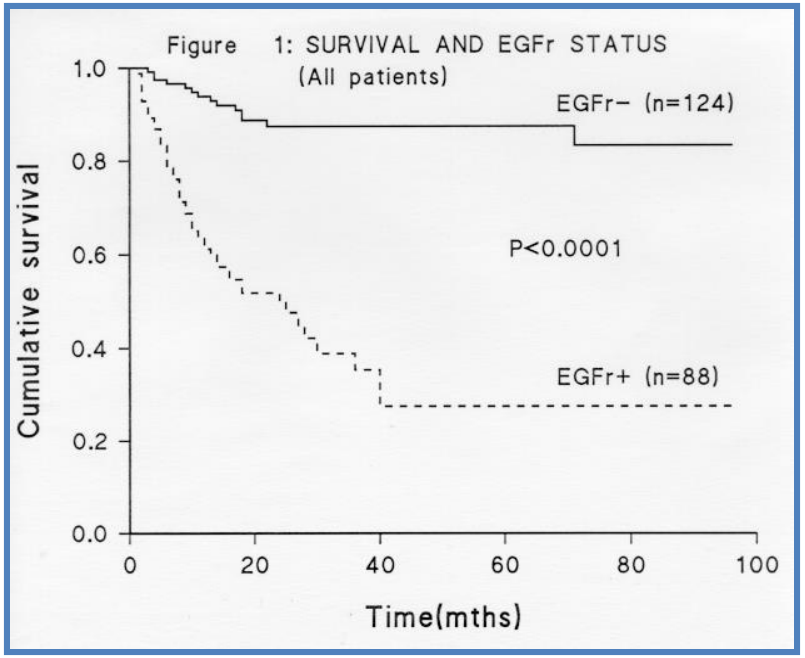
- Progression
- Nodal involvement
- Bladder sparing
- Survival

EGFR is associated with progression and survival in patients with UC.

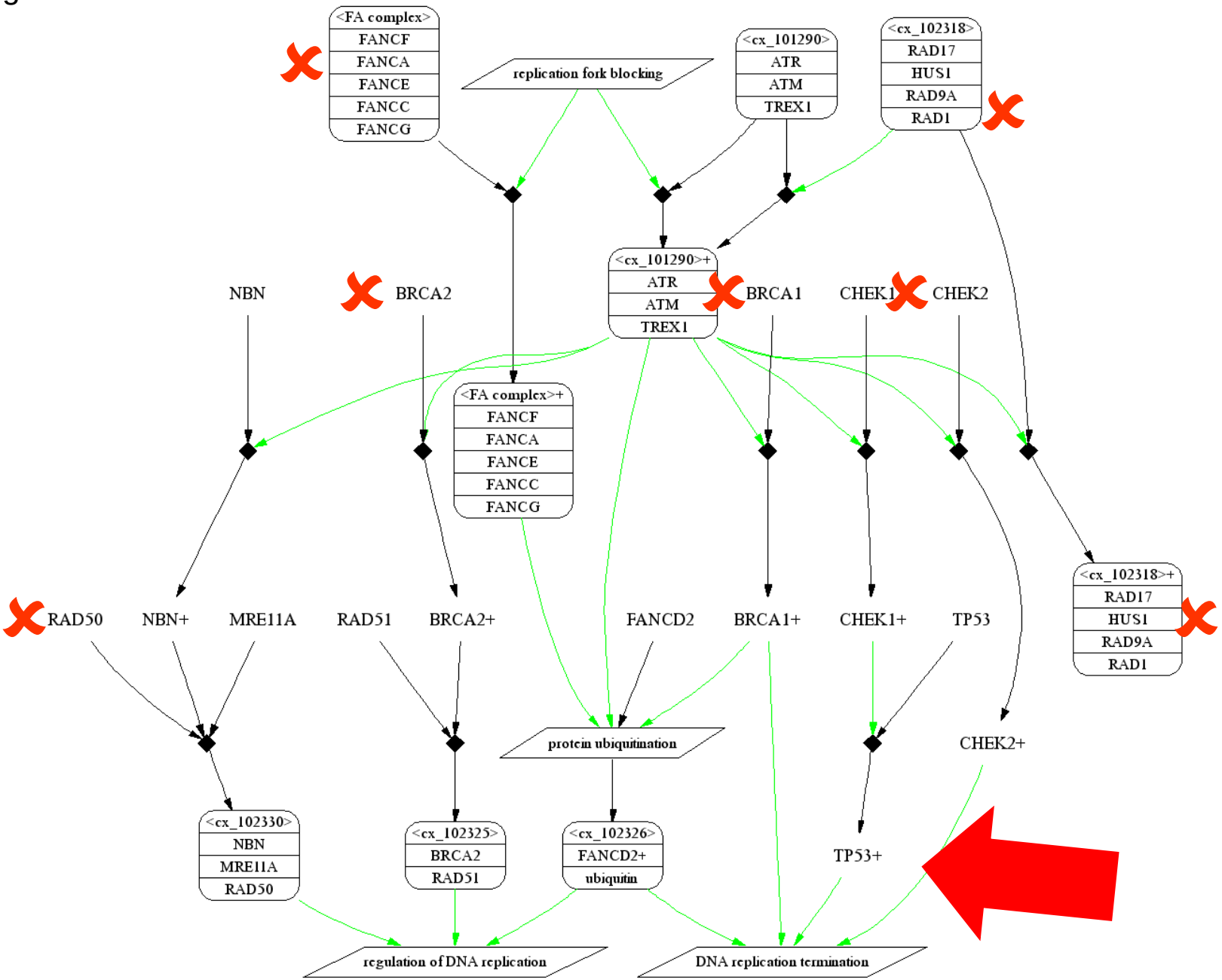


- Immunohistochemical study
- 212 patients
- Cox's proportional hazards regression





DDR genes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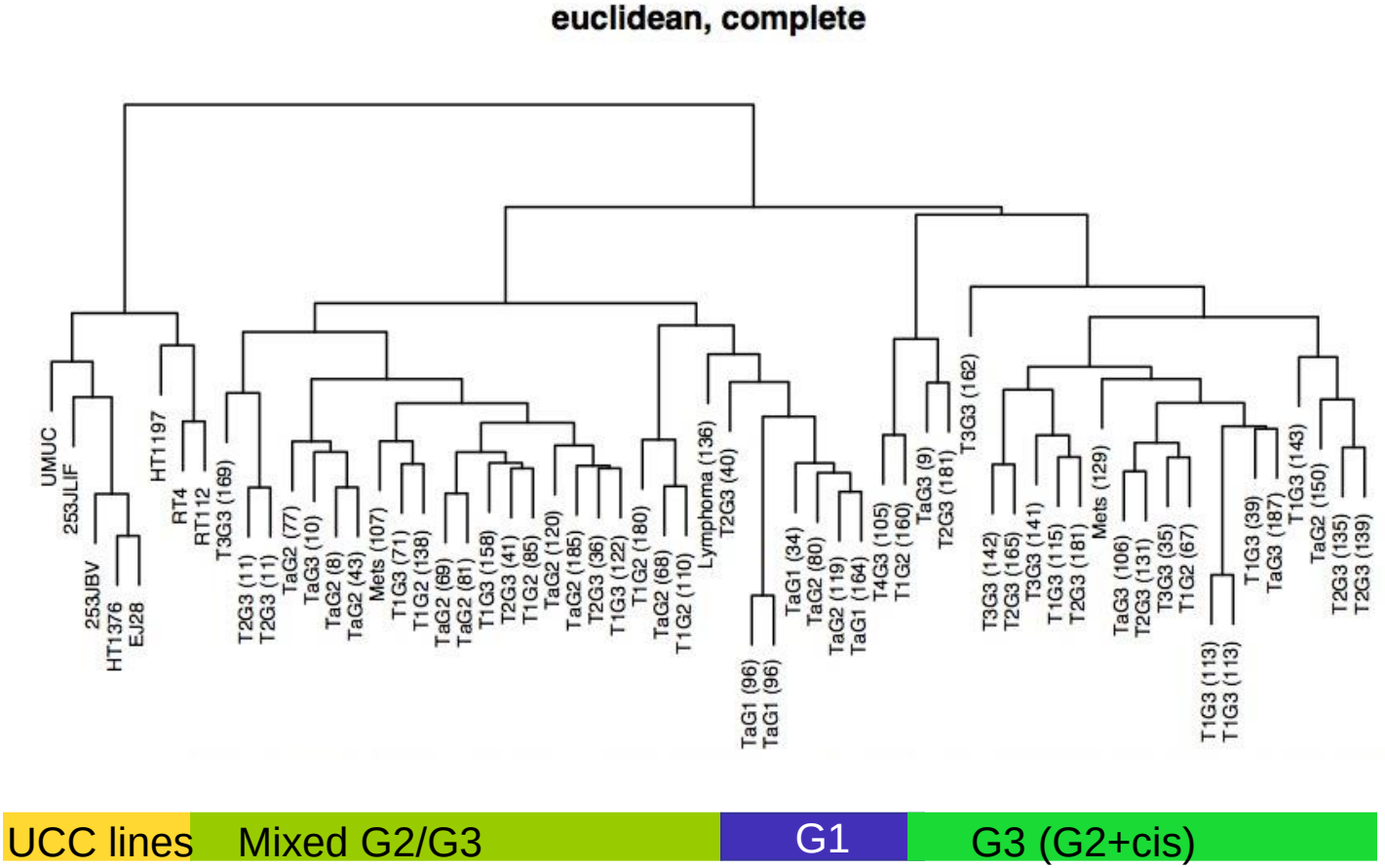
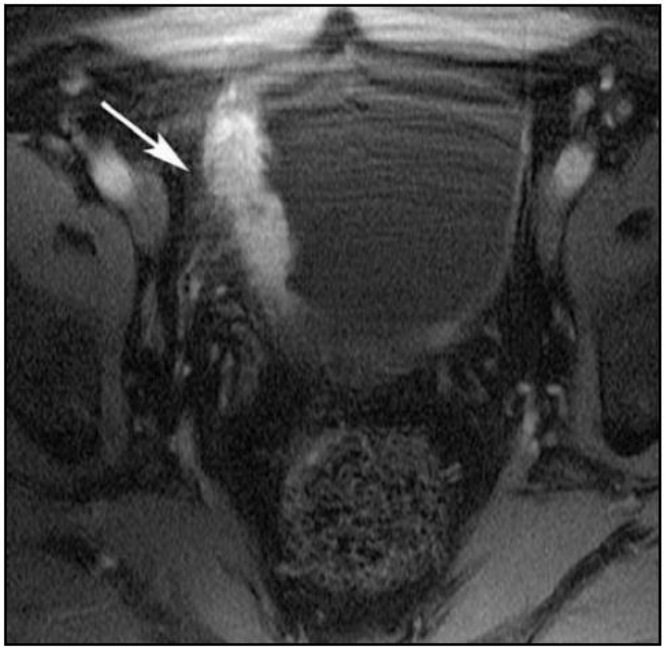
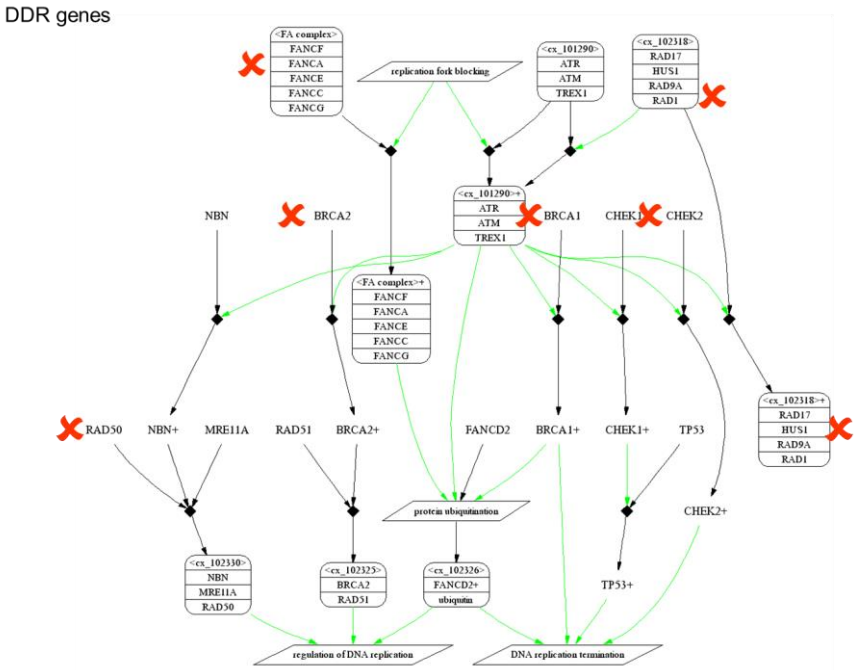
ubiquitin
TP53+
regulation of DNA replication
DNA replication termination

Separating cancer subtypes
Unsupervised hierarchical clustering



Imaging and genomic markers in clinical decision making.



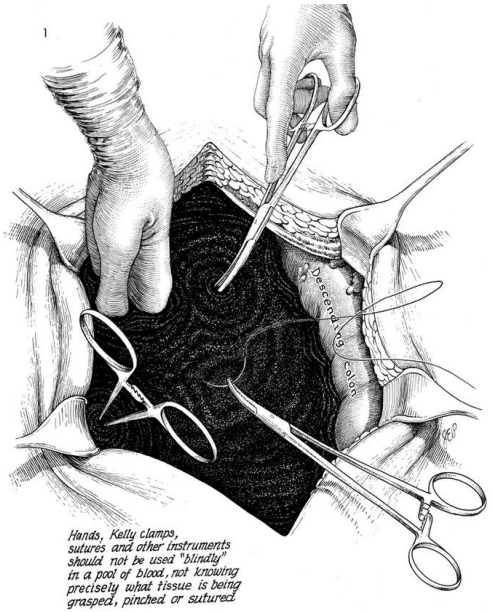


Can we select a proportion of cases following imaging?

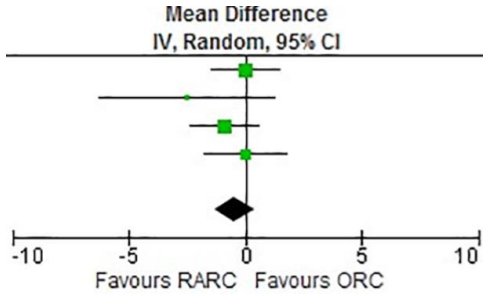
Tekes et al, AJR:184, 2005

Can biomarkers impact on surgical practice

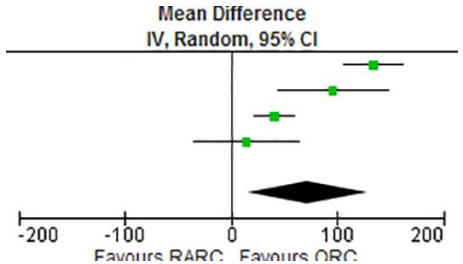
Open radical cystectomy is dead….



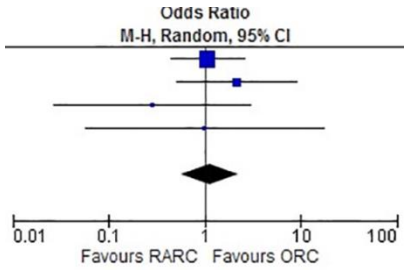
Length of stay



Operating time



Complications



Wei Shen Tan. PlosOne 2016

iRARC versus ORC

Registry data useful but bias and noise!

	LOS	Major complications	Transfusion
UCLH iRARC	10	21%	21%
UCLH iRARC + ERP	7	-	-
BAUS mixed	12	10%	30%

Wei Shen Tan et al. Eur Urol Focus. 2016

Benefits of iRARC for patients with low cardiorespiratory fitness

- Role of CPET in assessing recovery

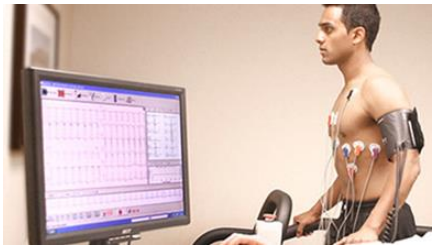


Table 5
Comparison of present study and published series reporting preoperative CPET in patients undergoing cystectomy

Parameter		Lamb et al.	Tolchard et al. [13]	Prentis et al. [12]
	Total, *n*	111	105	82
	Analyzed, *n*	82	105	69
Demographic	Age at treatment, mean	65	71	70
	BMI, mean	27	–	26.9
	Male, %	81	84	70
CPET	AT	10.35 (7.0–19.0)	11.2 (5.8–22)[ab]	12.78[b]
	Peak VO_2	16.11 (7.0–43.0)	15.2 (9–27.6)	16.23
	VE/VCO_2 (AT)	33.92 (23.0–48.0)	31 (21–47.2)[c]	36.12
Outcomes	Length of stay (median)	10	10	17.5
	Major complications at 30 d, *n* (%)	14 (12.6)	–	13 (15.8)
	90 d mortality, *n* (%)	3 (2.7)	6 (6)	2 (2.9)

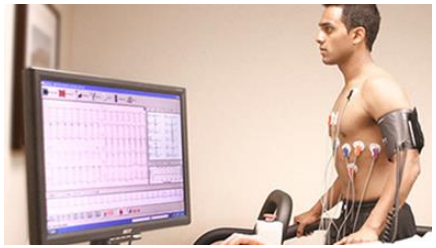
CPET = cardiopulmonary exercise testing.
[a]Predictive of postoperative complications, significant at $P < 0.05$ level.
[b]Predictive of hospital length of stay, significant at $P < 0.05$ level.
[c]Predictive of postoperative complications, significant at $P \leq 0.001$ level.

Lamb BW. Urol Oncol. 2016

iROC: intracorporeal Robotic vs Open Cystectomy

Outcome

- Number of days alive and out of hospital within the first 90 days
- Fitness tracking
- CPET testing at baseline and 12 weeks post-operatively



- Real surgery question iRARC versus ORC biomarkers of performance and activity will probablys deliver the answer.

- NGS and liquid biopsy has great potential for detection of recurrence and monitoiring response to therapy.

Google

DeepMind

AKI