Cancer bioinformatics: identification of diagnostic and prognostic biomarkers from gene expression data

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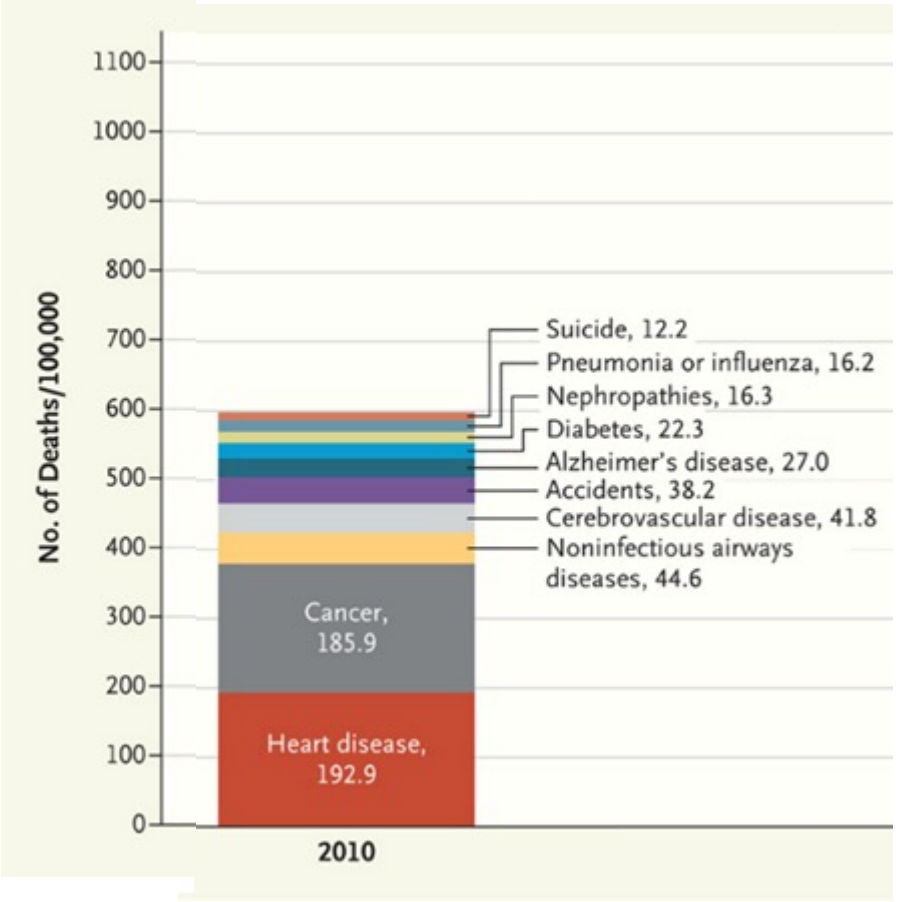
Leading causes of death (2010)



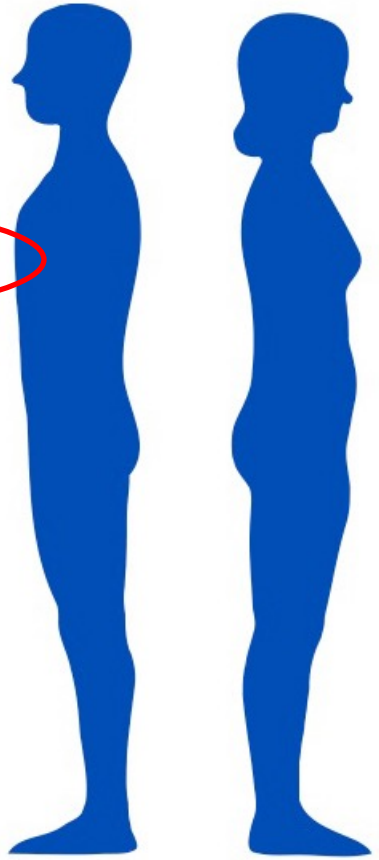
Lifetime probability of developing cancer

Males: 50%
Females: 33%

Also see: https://tinyurl.com/2mt2z7ae

Jones et al. N Engl J Med 2012; 366:2333-2338

2010 Estimated US Cancer Cases*



Men 789,620		Women 739,940	
Prostate	28%	28%	Breast
Lung & bronchus	15%	14%	Lung & bronchus
Colon & rectum	9%	10%	Colon & rectum
Urinary bladder	7%	6%	Uterine corpus
Melanoma of skin	5%	5%	Thyroid
Non-Hodgkin lymphoma	4%	4%	Non-Hodgkin lymphoma
Kidney & renal pelvis	4%	4%	Melanoma of skin
Oral cavity	3%	3%	Kidney & renal pelvis
Leukemia	3%	3%	Ovary
Pancreas	3%	3%	Pancreas
All Other Sites	19%	20%	All Other Sites

Source: American Cancer Society, 2010.

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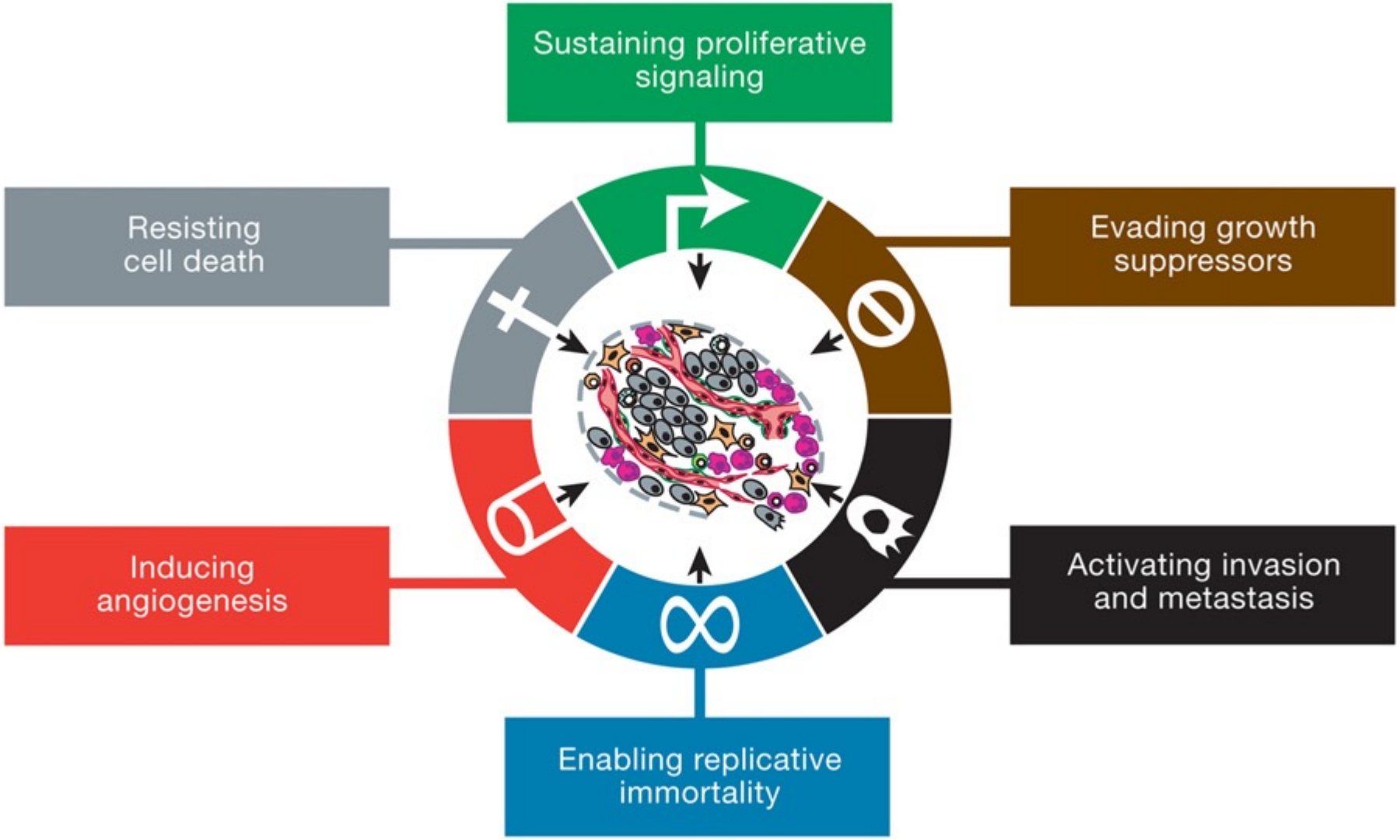
*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

http://www.cancer.org

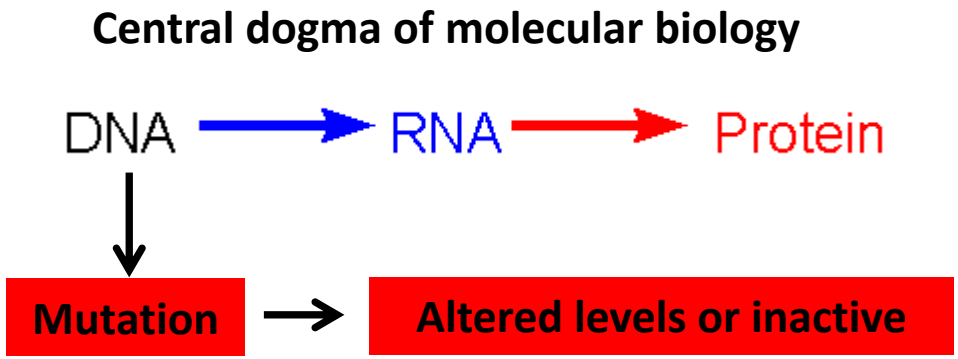
What is cancer?

Hallmarks of cancer



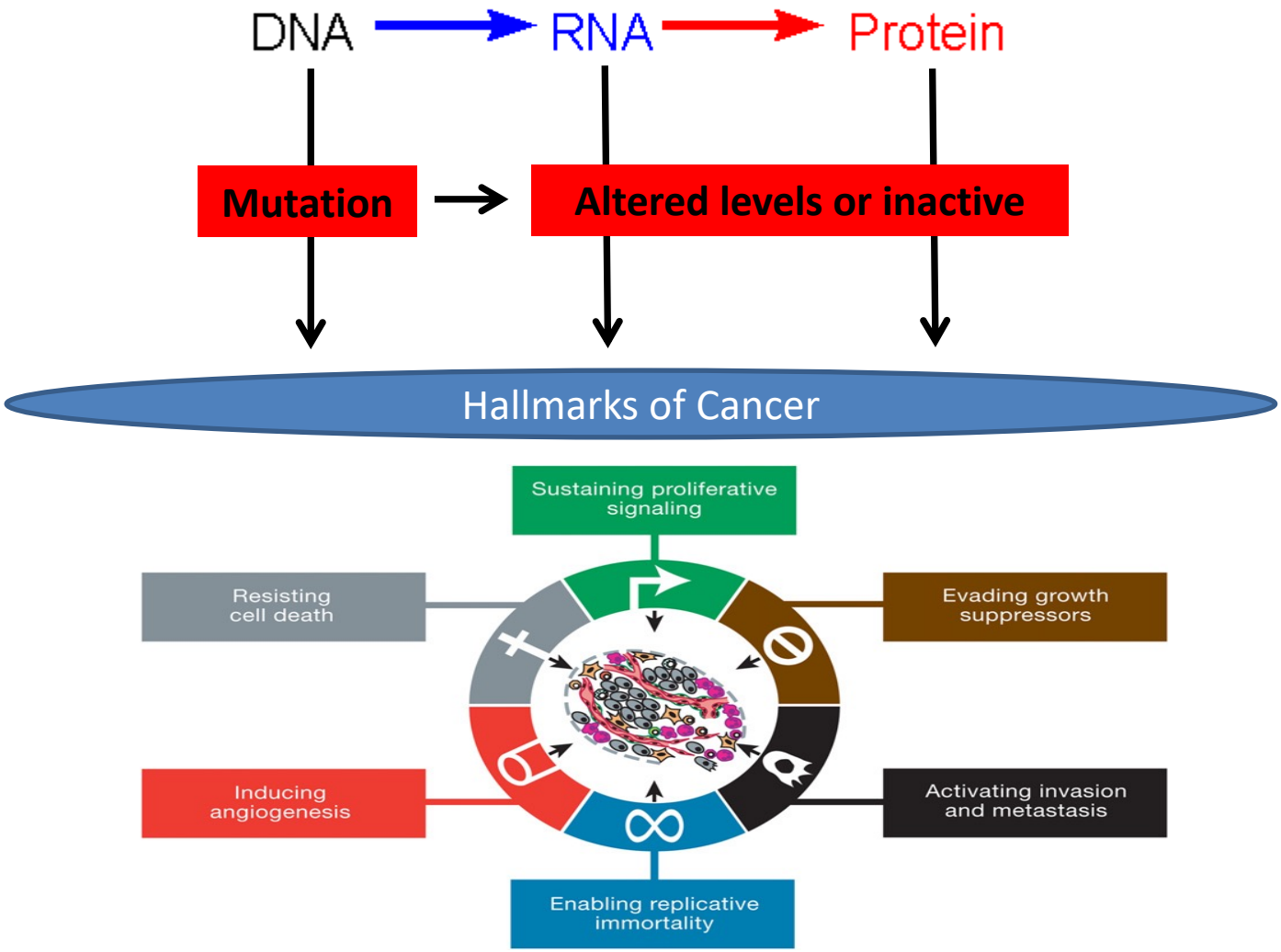
Hanahan and Weinberg. Cell 2011; 144(5):646–674.

Cancer is a genetic disease



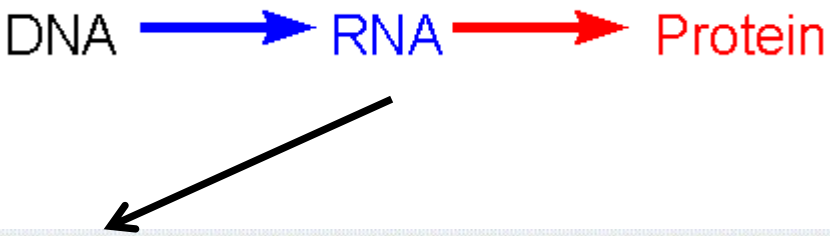
Cancer is a genetic disease

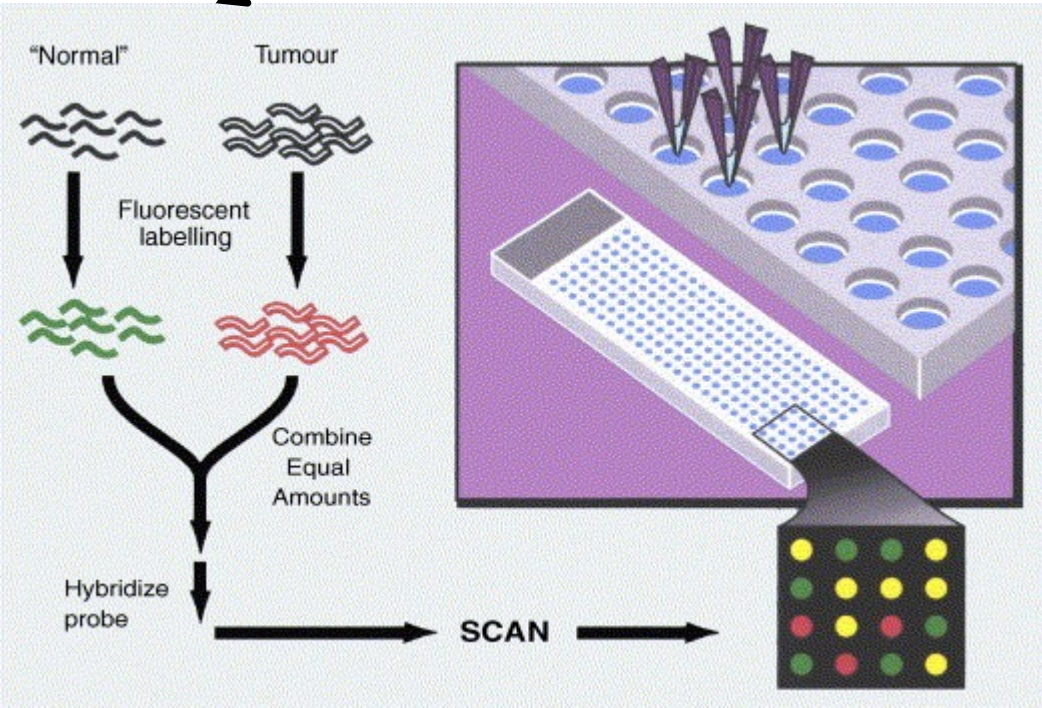
Central dogma of molecular biology



Gene expression profiling by microarray

Central dogma of molecular biology

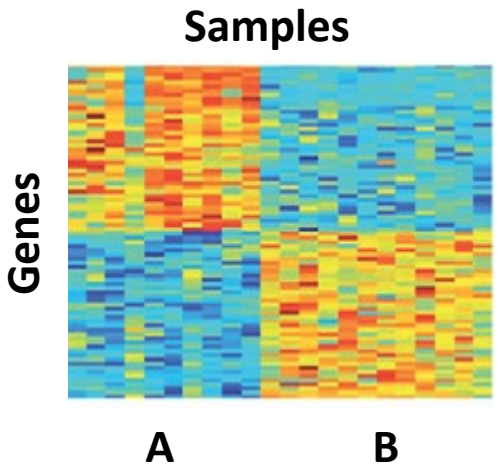




Bowden and Brennan. Br J Oral Maxillofac Surg 2004; 42(6): 42-545

Biomarkers and personalized medicine

Gene expression profiles



Class comparison
- A,B: clinical variable or outcome
  - Tumor type
  - High risk vs. low risk (survival)
  - Responders vs. non-responders
- Classification of new samples:
  - Gene signature
  - Classification method:
    - KNN, SVM, PCA, NCC, etc.

- **Diagnostic biomarker:** a gene or gene signature that is predictive of a clinical variable (e.g., tumor grade)
- **Prognostic biomarker:** a gene or gene signature that is predictive of disease outcome (e.g., survival)

Nature Reviews | Genetics

A framework to select clinically relevant cell lines by establishing their molecular similarity with patient tumors

Dancik *et a*l. Can. Res. 2011; 71:7398

Background and motivation

- Cell lines as model systems in cancer
  - Characterization of molecular mechanisms of disease
  - Characterization of activity of therapeutic agents
  - High throughput drug discovery programs
- But….cell lines do not always represent patient tumors
  - Adaptation in culture
  - Cross-contamination
- *In vitro* (cell line) drug sensitivity often does not correlate with drug efficacy in patients

Motivation and approach

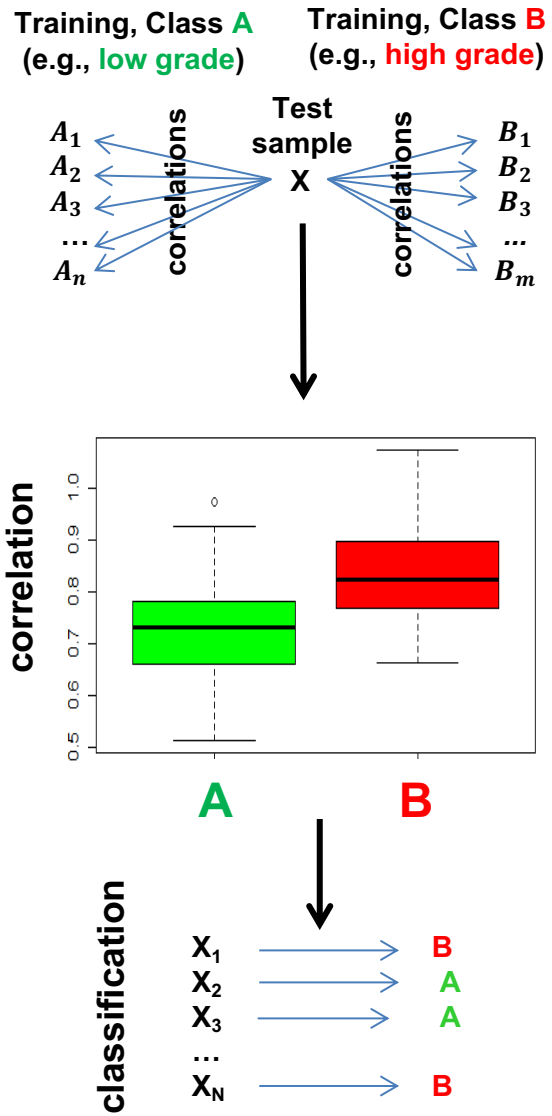
- Objective: identify and **select clinically relevant cell lines** based on their **gene expression profiles**
  - Classify a panel of 36 bladder (BLA-36) cell lines
- Classification objectives
  - **Tissue of origin** (from 10 epithelial tumors)
  - **Stage** (NMI vs. MI)
  - **Grade** (high grade vs. low grade)
  - **Disease specific survival** (high vs. low risk)

Spearman rank correlation classification method (SRCCM)

Step 1: Calculate Spearman correlation between the gene expression profile of test sample (*X*) and gene expression profiles of samples from known classes (classes *A* and *B* here) using a relevant gene signature

Step 2: Classification/prediction: the test sample is assigned the class with the highest mean correlation (class B here).

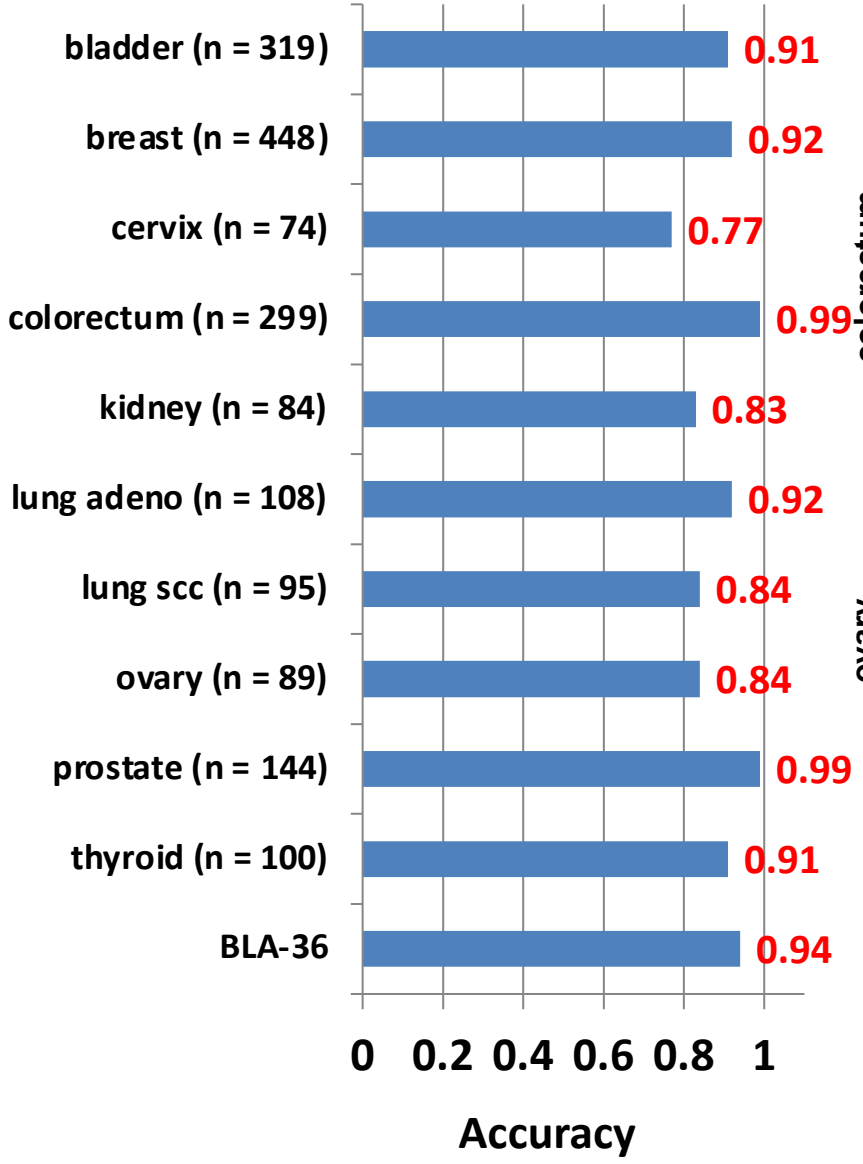
Step 3: Repeat steps 1-2 to classify all test samples

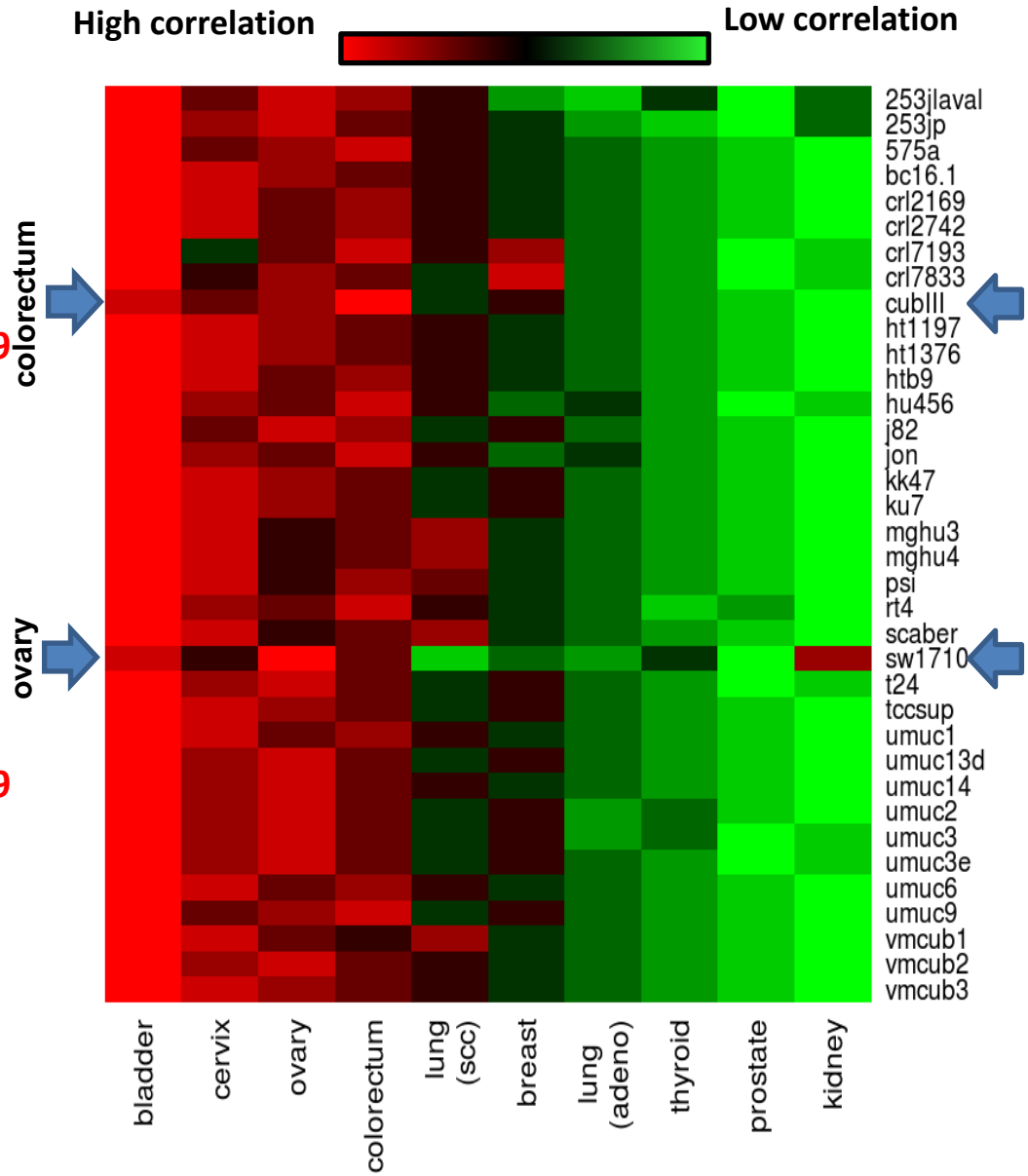


Tissue of origin classification

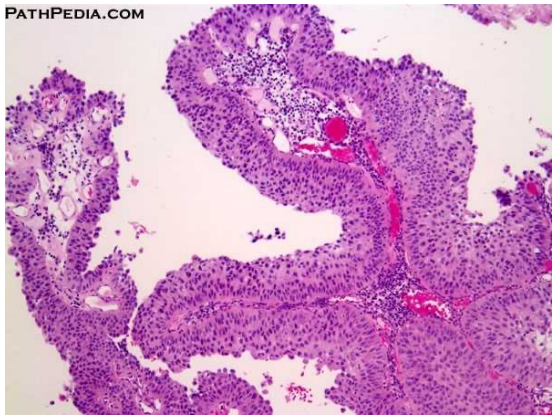
- Clinical relevance of tissue of origin
  - Chemotherapy and radiation therapy efficacy depends on tumor type (Kemp CJ, et al. *Cancer Res* 2001;61(1):327-332)
  - Metastatic site preference is tissue specific
- Do cell lines resemble their derived tissues
  - Previous studies: Only 57% of NCI-60 cell lines resemble presumed tissue of origin (Sandberg R, Ernberg I. *PNAS* 2005;102(6):2052-2057).
  - Survey of 500 leukemia-lymphoma cell lines finds 15% mislabeled. (Drexler HG et al. *Leukemia*. 2003;17(2):416-426)

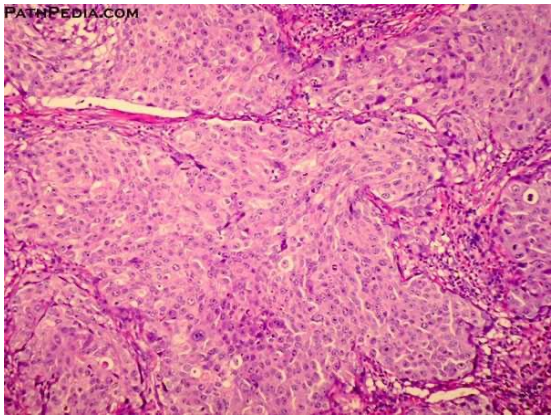
Tissue of origin classification





Grade classification



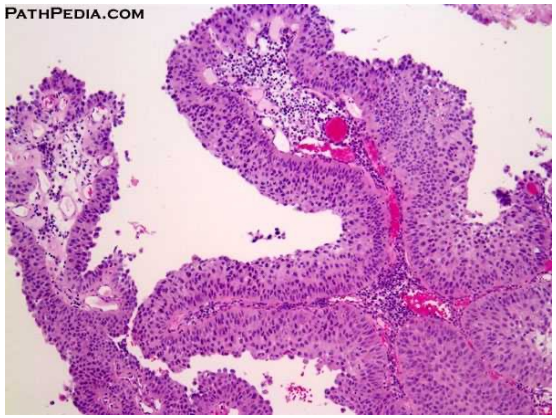


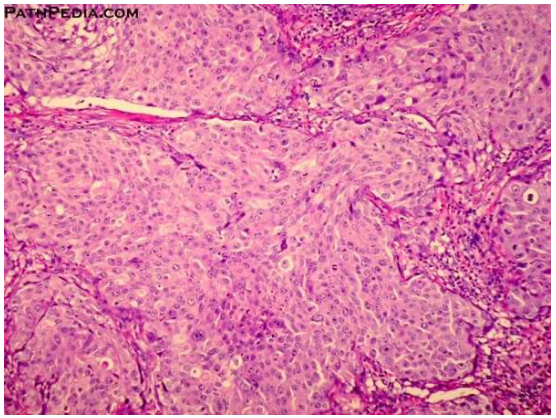
Low grade **vs.** **High grade**

Well differentiated vs. poorly differentiated

Dataset	SRCCM accuracy
Lindgren (LOOCV)	0.875
SC	0.813

Grade classification



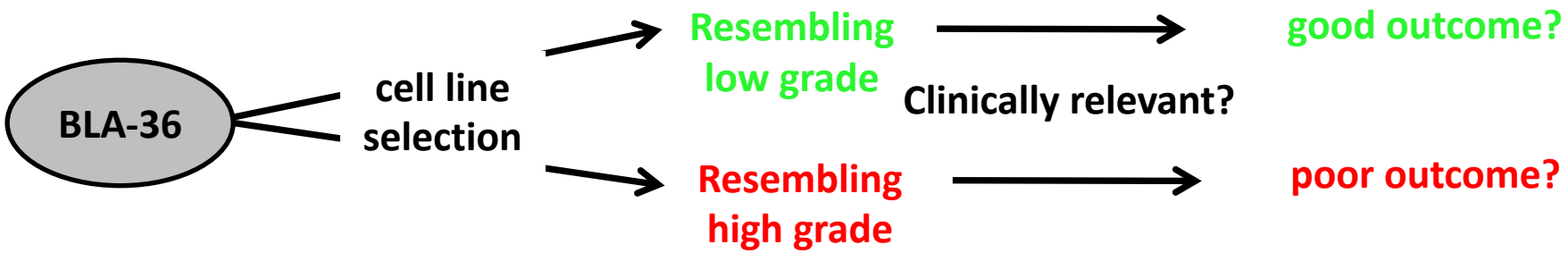


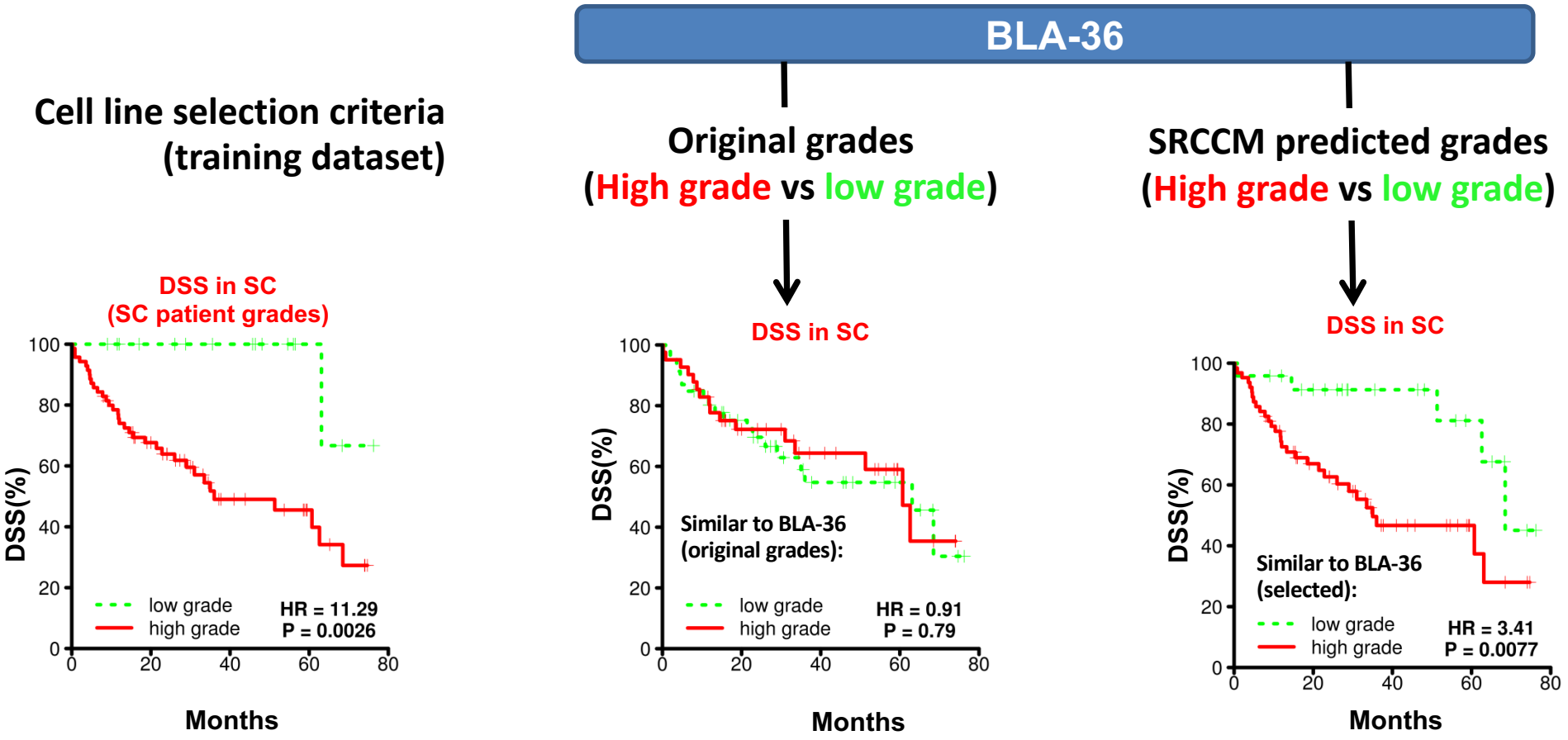
Low grade **vs.** **High grade**

Well differentiated vs. poorly differentiated

Dataset	SRCCM accuracy
Lindgren (LOOCV)	0.875
SC	0.813
BLA-36	.571

Original tumor grades no longer correlate with survival; correlation is restored through cell line selection via SRCCM

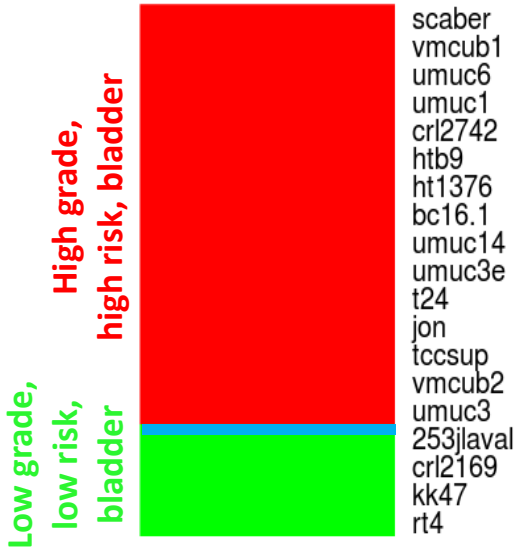




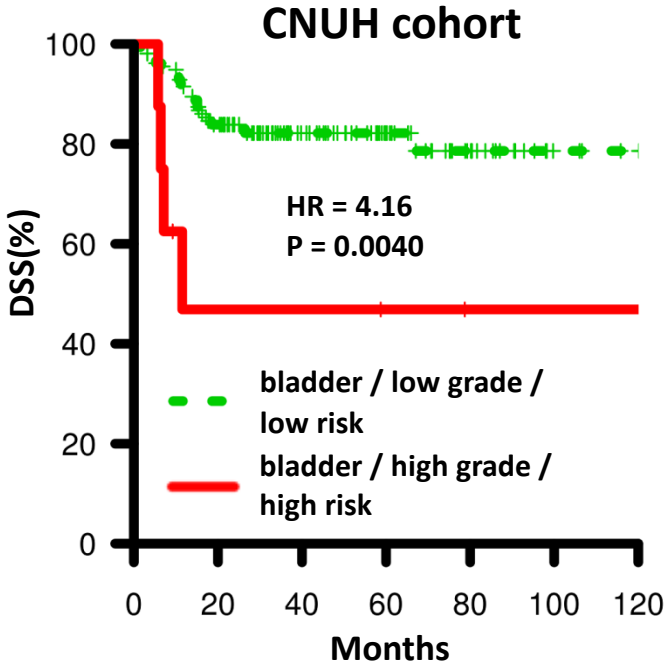
Selection of the most clinically relevant cell lines by survival risk, grade, and tissue type

CELL LINE PANEL

Selection of cell lines based on characteristics of interest using SRCCM



Training: cell lines
Testing: new patient cohort



Summary

- SRCCM algorithm for classification and cell line model selection
- BLA-36
  - Grade: accuracy < 60%, suggesting that many cell lines no longer resemble original tumors with respect to grade
  - Original tumor grade no longer correlates with survival; correlation is restored through SRCCM selection
- Software: Correlation classification method (CCM) http://cran.r-project.org/web/packages/CCM/index.html

Acknowledgements

- Theodorescu Lab
  - Dan Theodorescu, MD, PhD (PI)
  - Yuanbin Ru, PhD
  - Chuck Owens (lab technician)
- Funding: NIH CA075115.

Thank You!

Cancer grade and staging

- Tumor grade
  - Normal vs. abnormal
  - Low vs. high grade
- Tumor stage
  - How far has the cancer spread
- Bladder cancer stages
  - Non-muscle invasive (NMI): Ta, T1
    - 5 year survival rate of ~ 90%
    - Progression rate of ~ 20%
  - Muscle invasive (MI): T2-T4
    - 5 year survival rate ~ 50%

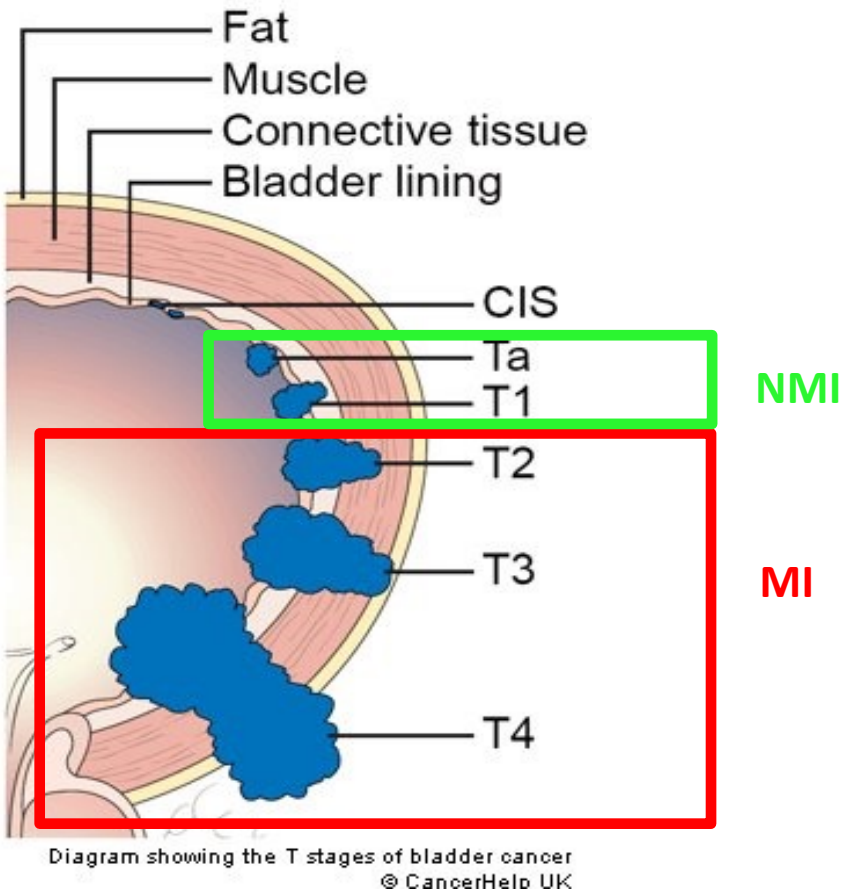


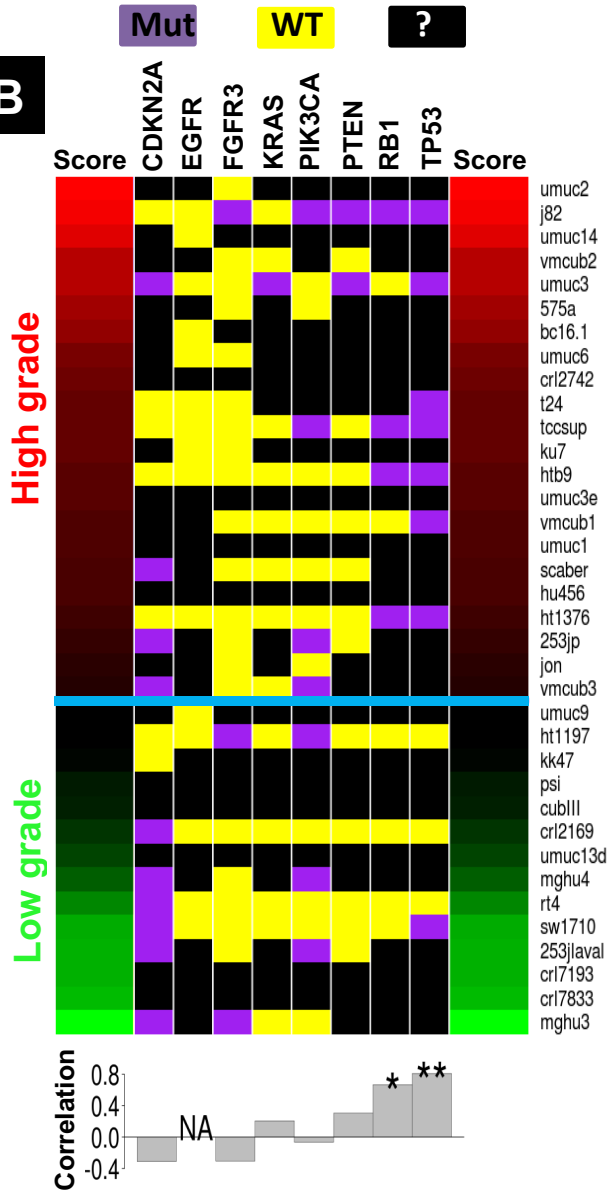
Image: http://www.cancerhelp.org.uk/type/bladder-cancer/treatment/bladder-cancer-stage-and-grade

Bladder cancer grade classification

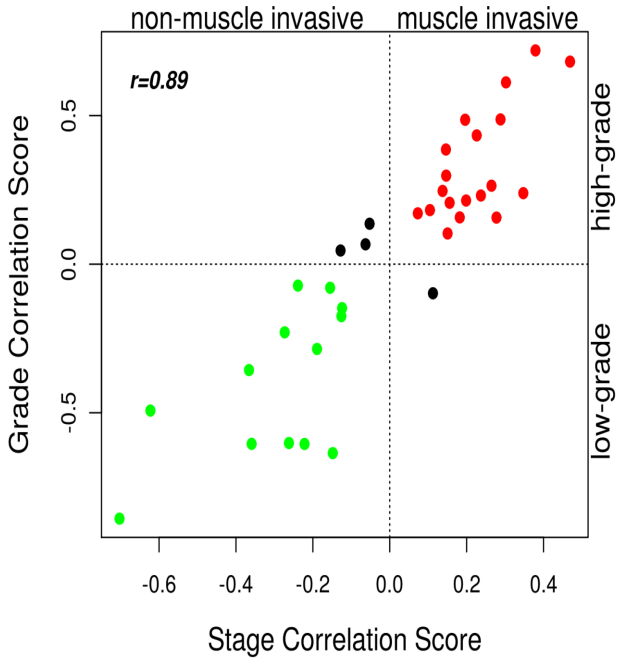
A

	Accuracy
LOOCV in Lindgren	0.875
Independent Validation in SC	0.813
BLA-36	.571

B



C



Presentation Tips

- You are presenting your paper:
  - background, significance, objective, methods, results
- Almost every slide is a picture (or table)
  - From the internet (with reference)
  - From another publication (with reference)
  - From original research

Presentation Tips

- Presentation is written out and practiced ahead of time
- You do NOT read off of the page
- Additional slides are included at the end
  - For results or background not presented do to time
  - To answer possible questions