School of Molecular and Cellular Biology
FACULTY OF BIOLOGICAL SCIENCES
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Machine learning and big data for prognosis and prediction in aggressive lymphomas

David R. Westhead

With thanks to

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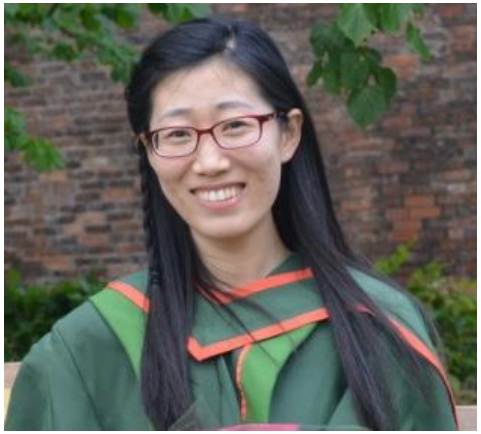

B cell related malignancies

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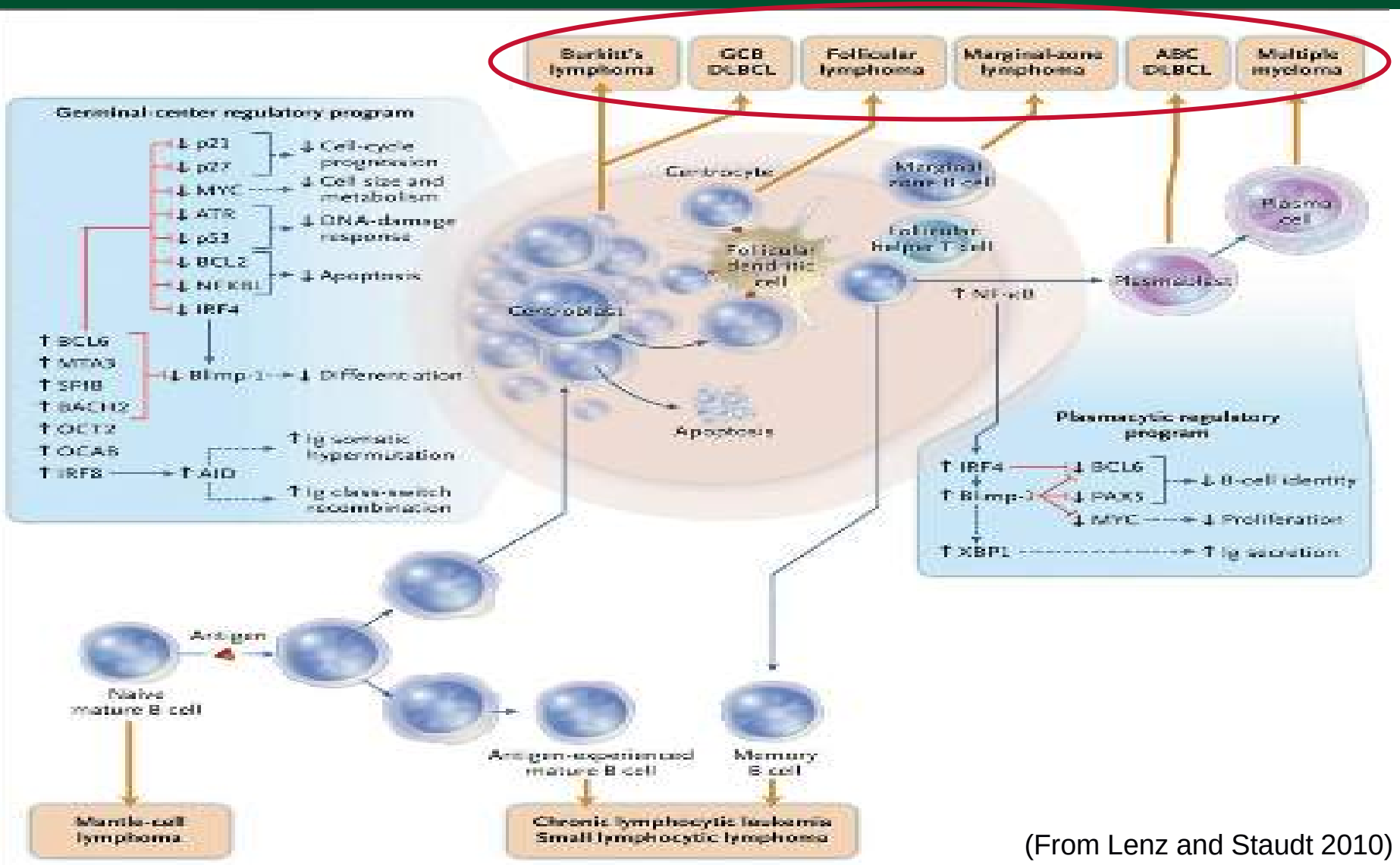

(From Lenz and Staudt 2010)

Where this all started: Classification of DLBCL

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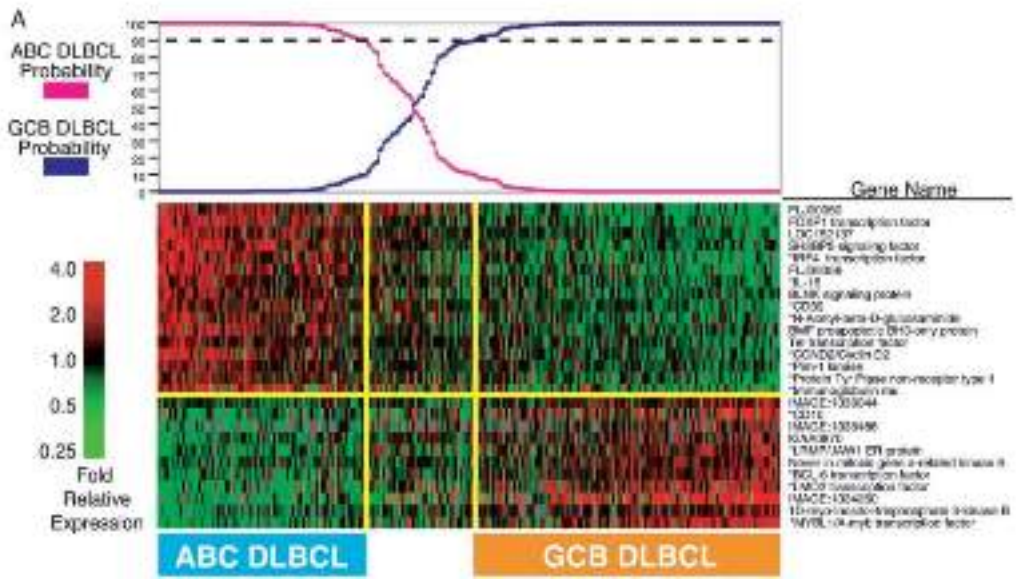
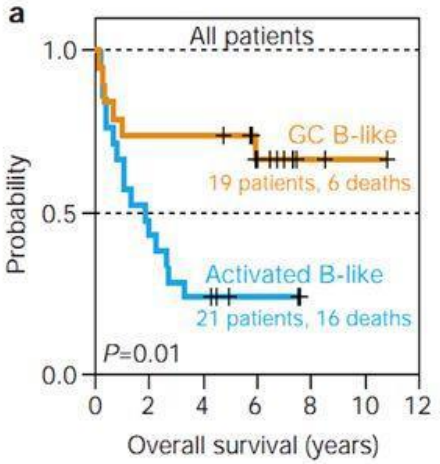
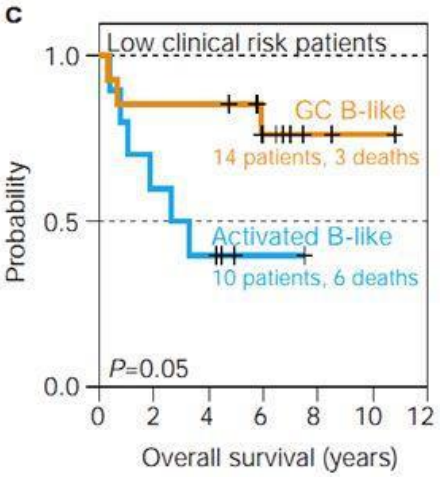
Alizadeh et al. (2000) recognised two distinct types based on gene expression

- ABC – activated B cell like
- GBC – germinal centre B cell like
- Different survival on (R-)CHOP therapy







Where this all started

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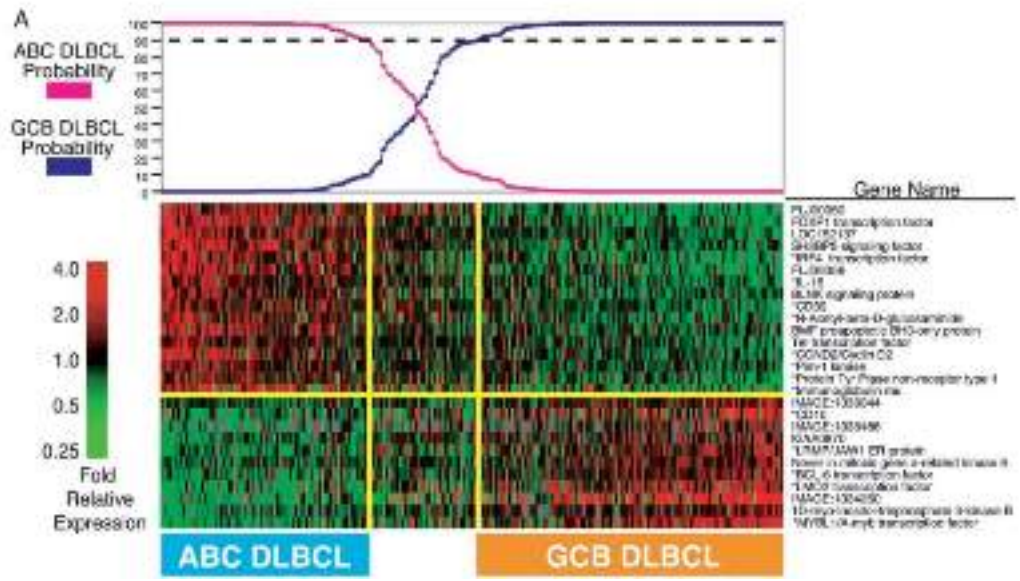

For the purposes of a clinical trial, we were asked if we could recapitulate this work based on gene expression measurements from formalin fixed paraffin embedded (FFPE) tumour biopsies.

Illumina DAZL array platform.

Trial: Bortezomib

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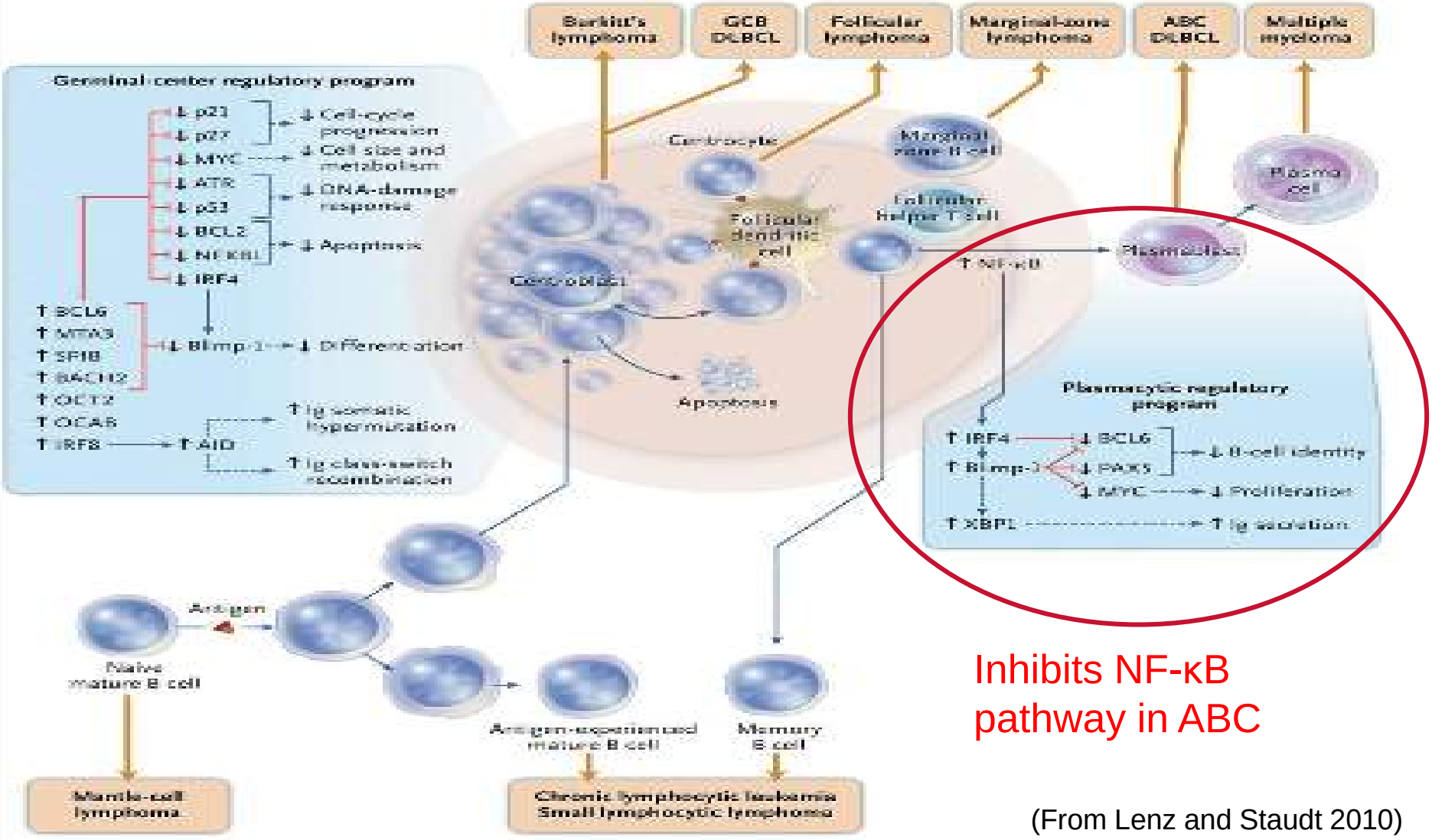

Inhibits NF-κB pathway in ABC

(From Lenz and Staudt 2010)

Gene expression classification works with FFPE samples

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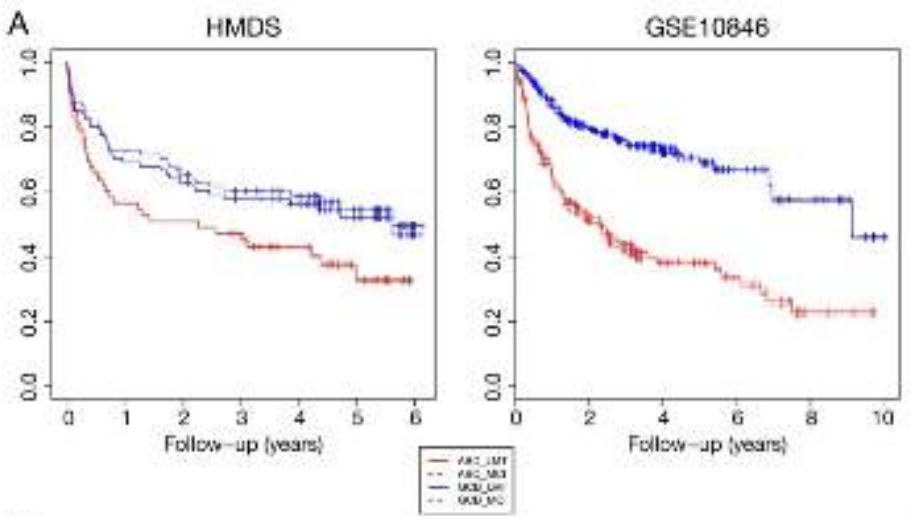
The best single classifier and the best meta classifier produce effective survival separation in both data sets



A great deal of effort: - the DAC classifier

Data quality and normalisation

Training

Transferability – data sets and platforms

Validation on several independent data sets

(Care MA, Barrans S, Worrillow L, Jack A, Westhead DR, Tooze RM A microarray platform-independent classification tool for cell of origin class allows comparative analysis of gene expression in diffuse large B-cell lymphoma. PLoS One **8** e55895-, 2013)

Burkitt's lymphoma

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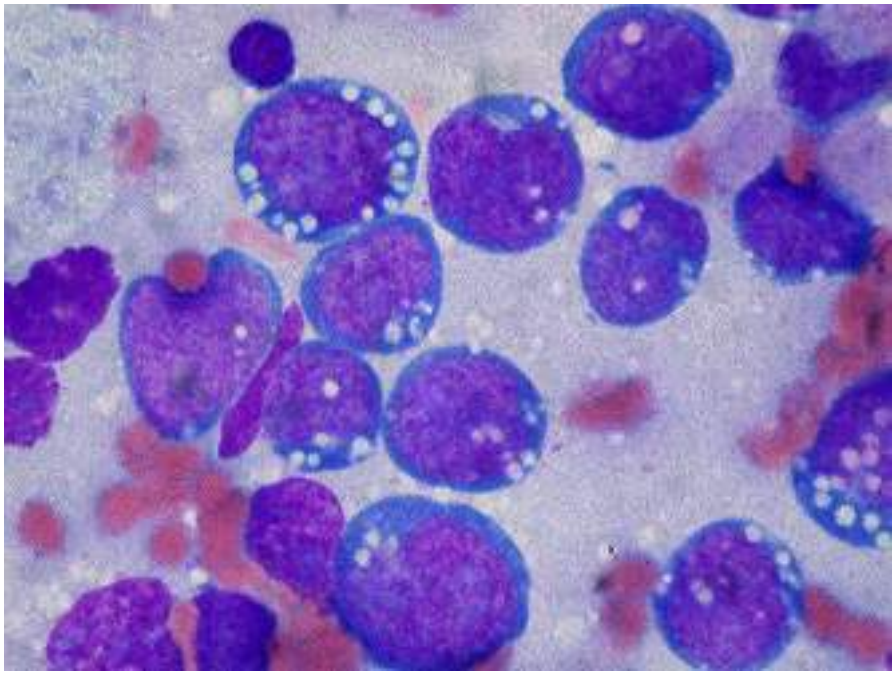
Burkitt's lymphoma

- Related to DLBCL
- More aggressive and fast growing
- Treatment is different
  - Typically R-CODOX-M/IVAC
- Again there are intermediate cases and classification is an issue



From Wikipedia…

Burkitt's lymphoma

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Literature classifiers

- Two seminal works in this area
  - Dave et al. (2006), Hummel et al. 2006.
- Different approaches and gene numbers

Data Set	HGNC matched genes on platform	Genes used in authors' classifier	Classifier genes located in data[1]	Classifier genes available in other data set[2]
Dave	2411	217	214	172
Hummel	12495	58	58	28
Overlap	1913	21	21	-

(Note that other classifiers have emerged since – Masque-Solar et al. 2013 – Nanostring – 10 genes.)

Cross-validation results

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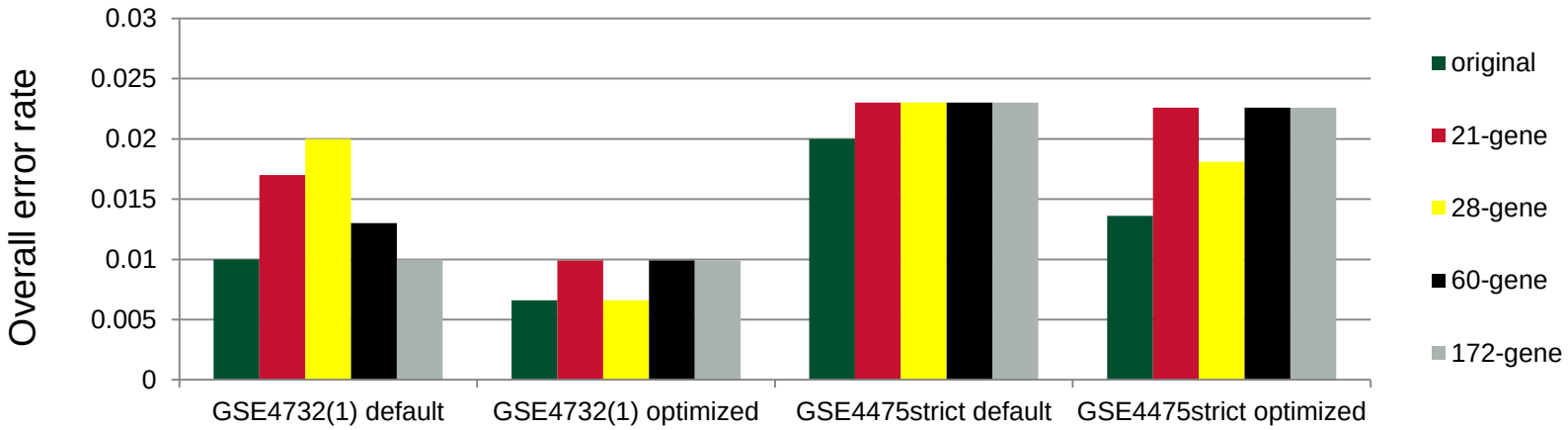
Re-capitulating the results of others

- Possible with reasonable accuracy
- Can work with a much reduced gene set!



Transferability between data sets

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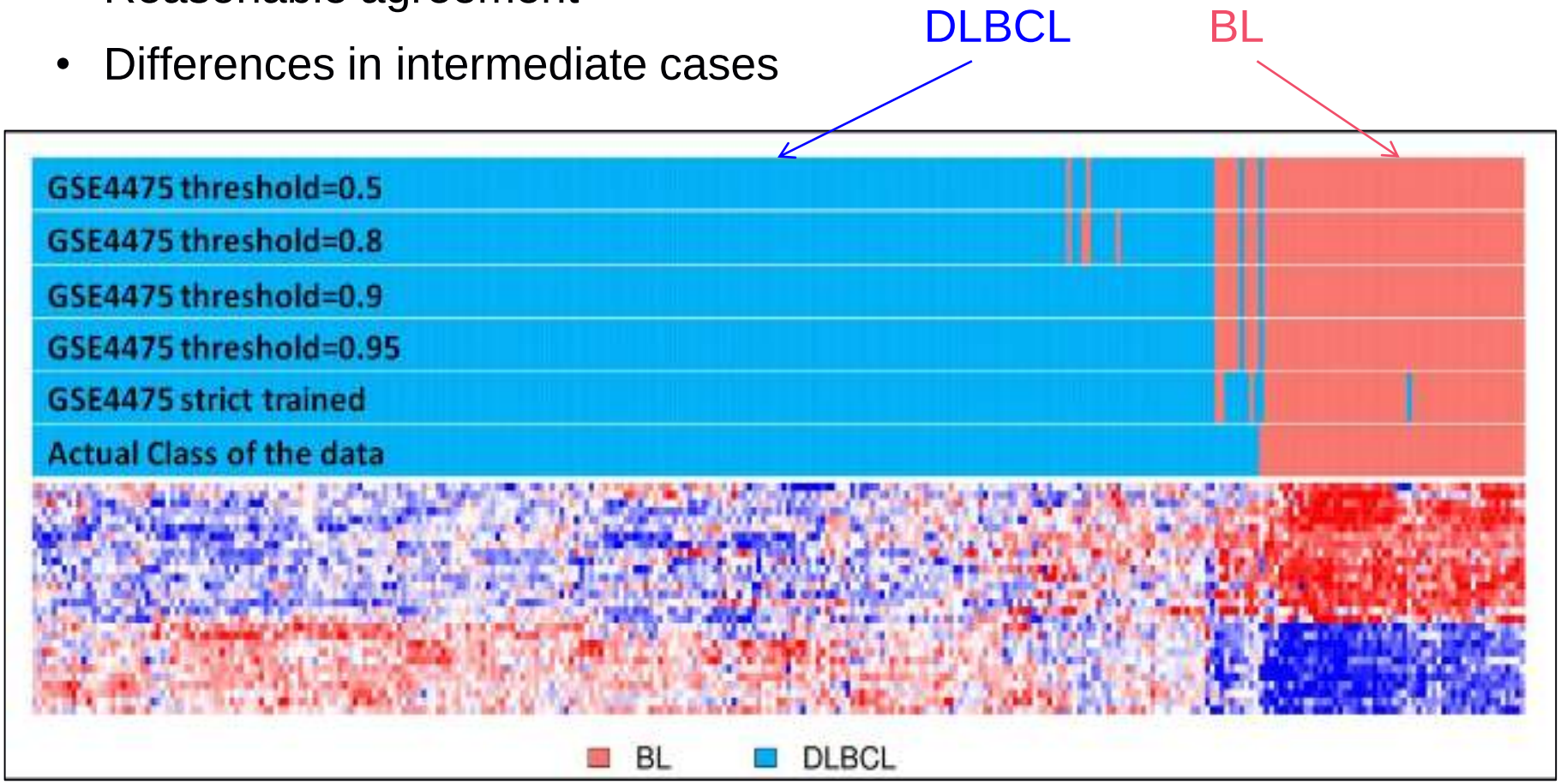
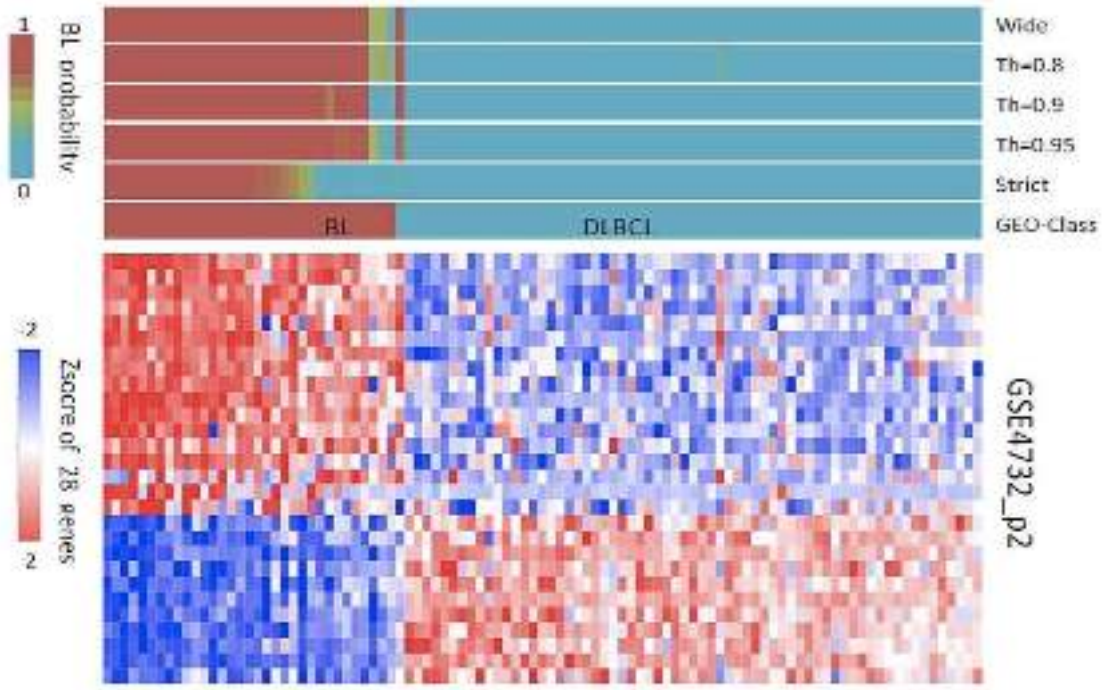
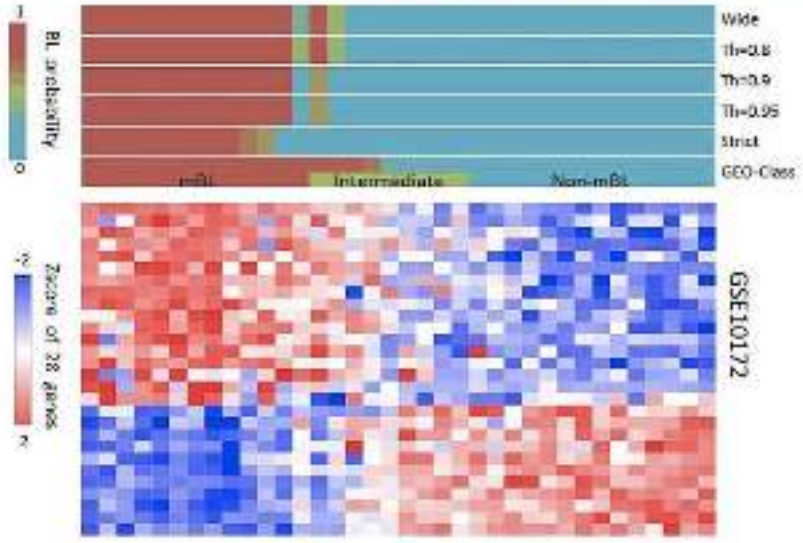
Train on one data set and definition, test on the other

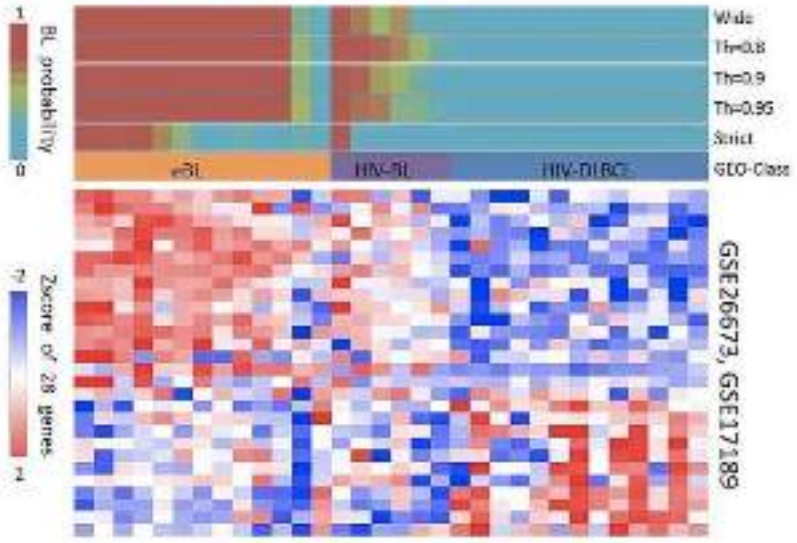
- Reasonable agreement
- Differences in intermediate cases





Applying to other public data sets





Our own clinical DAZL data

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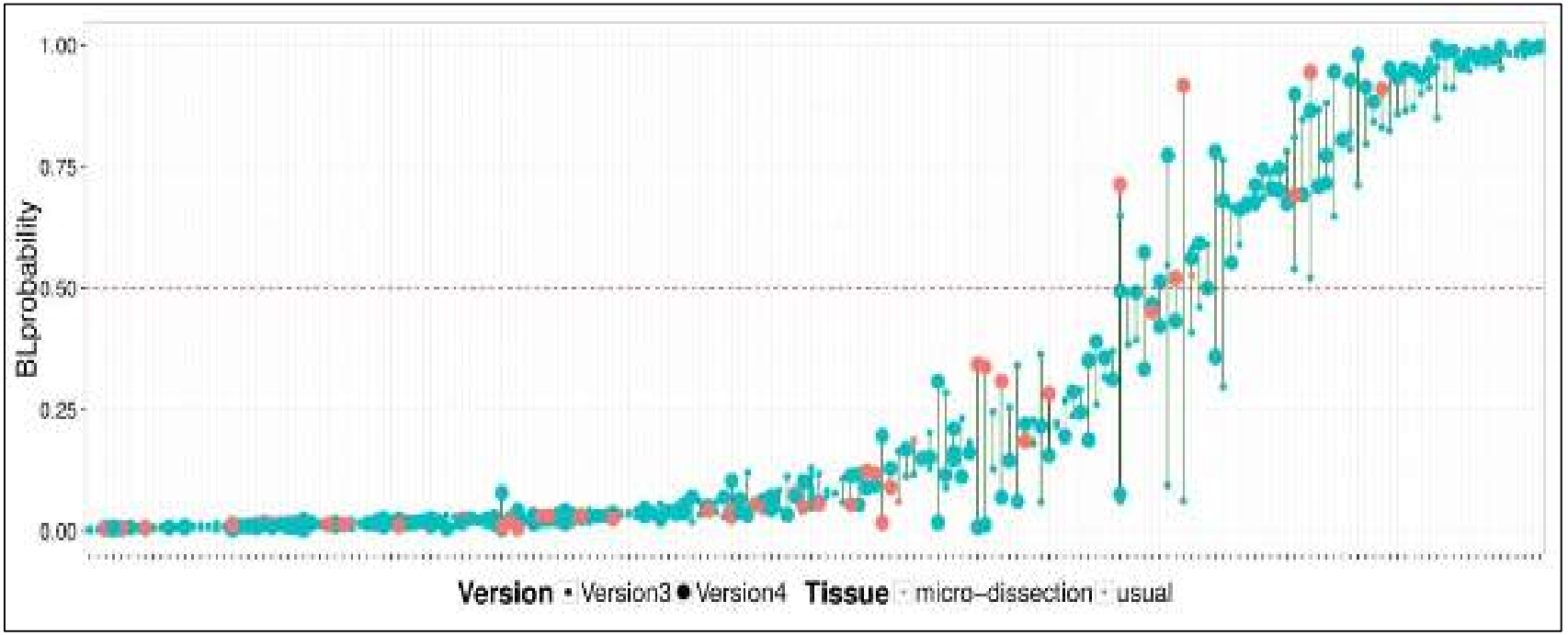
A careful look at reproducibility

- Different DAZL platforms
- Effect of careful micro-dissection



And with our clinical DAZL data

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Pathology based diagnosis - good agreement

- Most interesting are those DLBCL(path.) diagnosed as BL (exp.)
- For these death rate for BL(exp) is high 74% - different treatment?

Table 5: Classification correlation with current clinical diagnosis

		Diagnosed			
		BL	DLBCL(MYC-R)	DLBCL	
Classified	BL	61 (85%)	14 (30%)	34 (4.5%)	109
	DLBCL	11 (15%)	33 (70%)	720 (95.5%)	764
		72	47	754	

Sha C, Barrans S, Care MA, Cunningham D, Tooze RM, Jack A, Westhead DR Transferring genomics to the clinic: Distinguishing Burkitt and diffuse large B cell lymphomas. **Genome Medicine 7 -, 2015**.

Big data for an interesting group of patients

Somatic mutation data now including – but difficult for FFPE

Diagnosed as DLBCL (path) but significant numbers of BLs by our classifier

LMO2…

Grey areas: intermediates cases

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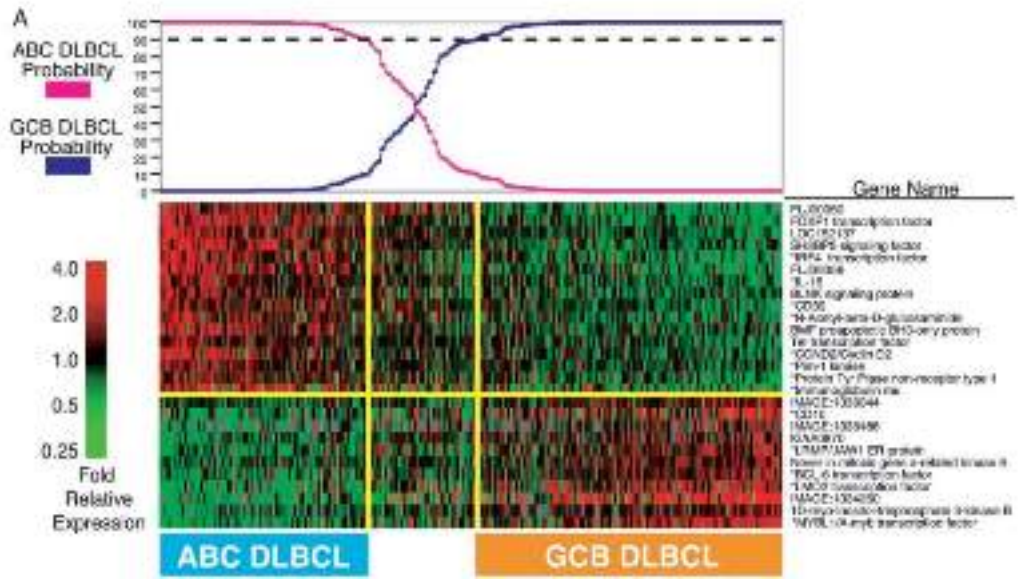

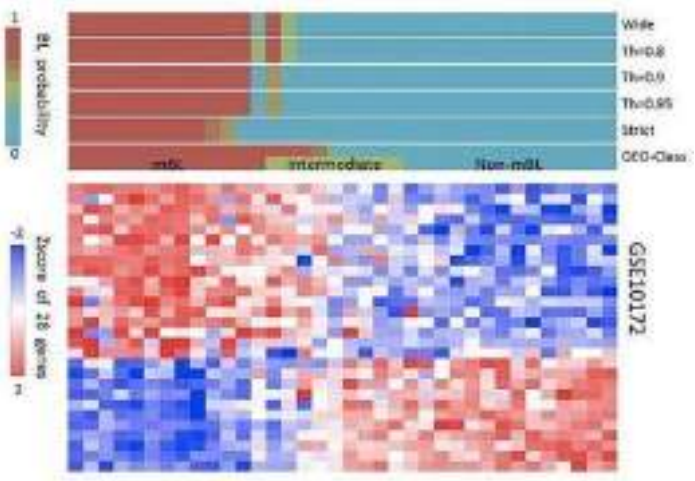

Similarity searches vs classifications

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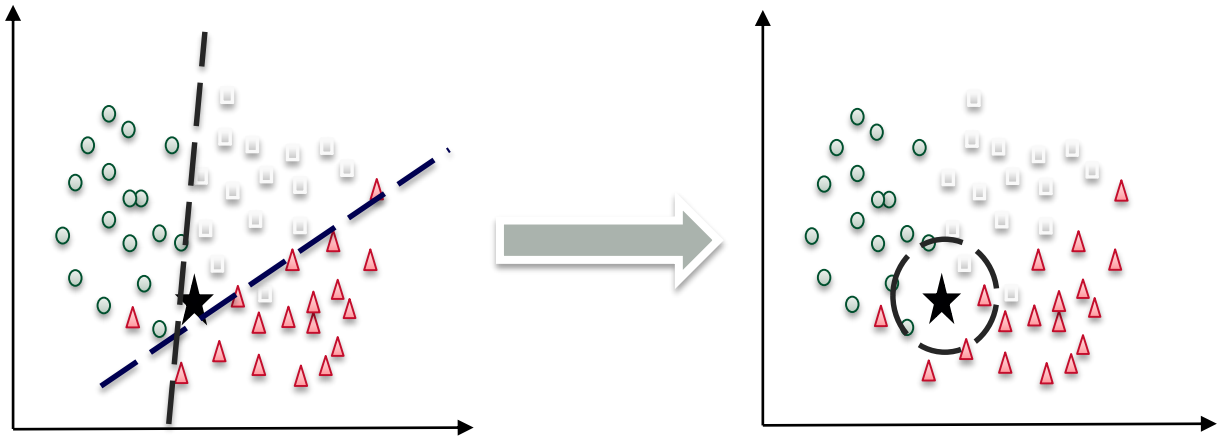

Use ‘similar’ or ‘neighbour’ cases in prognosis and prediction

Requires machine learning of a gene expression based similarity or distance metric

Learning a similarity measure

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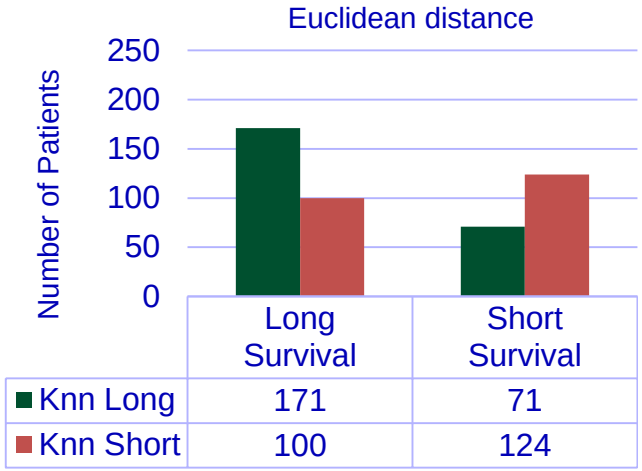

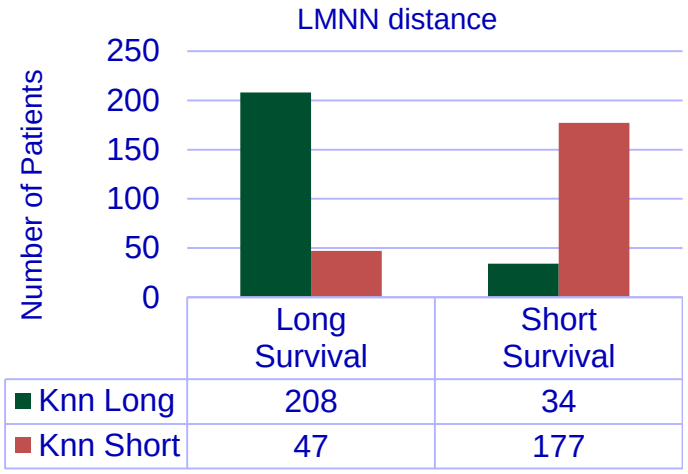

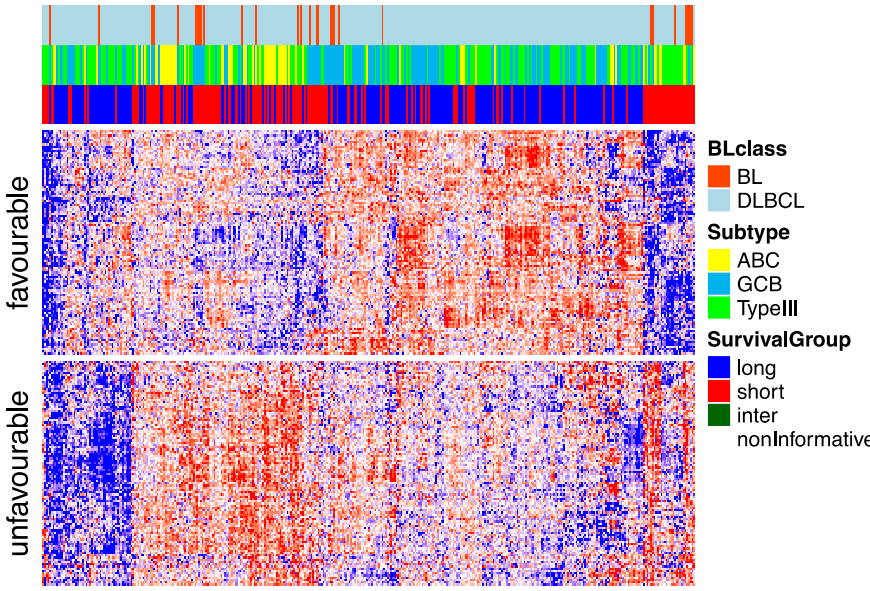

Conclusions

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Summary

- Gene expression classifiers using data from FFPE can work and can be useful
  - For BL and DLBCL subtypes
- Our classifiers have been evaluated carefully
  - Transfer between data sets – local and public
  - Transfer between different expression measurement platforms
- Watch this space for clinical trial results
- Beginning to progress with category free methods
  - Similarity searches

Thank you for listening

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