AMPLab / MSR Genomics reading group: *A Genomics-Based Classification of Human Lung Cancer*

André Schumacher

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Paper

- Title: A Genomics-Based Classification of Human Lung Cancer
- Authors: The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM) (Seidel at al.)
- Reference: *Sci Transl Med*, 30 October 2013, Vol. 5, Issue 209, p. 209ra153 Sci. Transl. Med. DOI: `10.1126/scitranslmed.3006802`

Merits

1. Analysis of classical lung cancer groups according to similarities and differences in SNPs and structural variations

2. Clustering of samples from different groups according to gene expression, leading to similar (and occasionally very different) assignment of samples to lung cancer subclasses

3. Finding of *clinically relevant* variations in cancer subtypes and using these as a *recommendation system for treatment of patients* as part of a larger trial (or actually, a few)

Summary of results

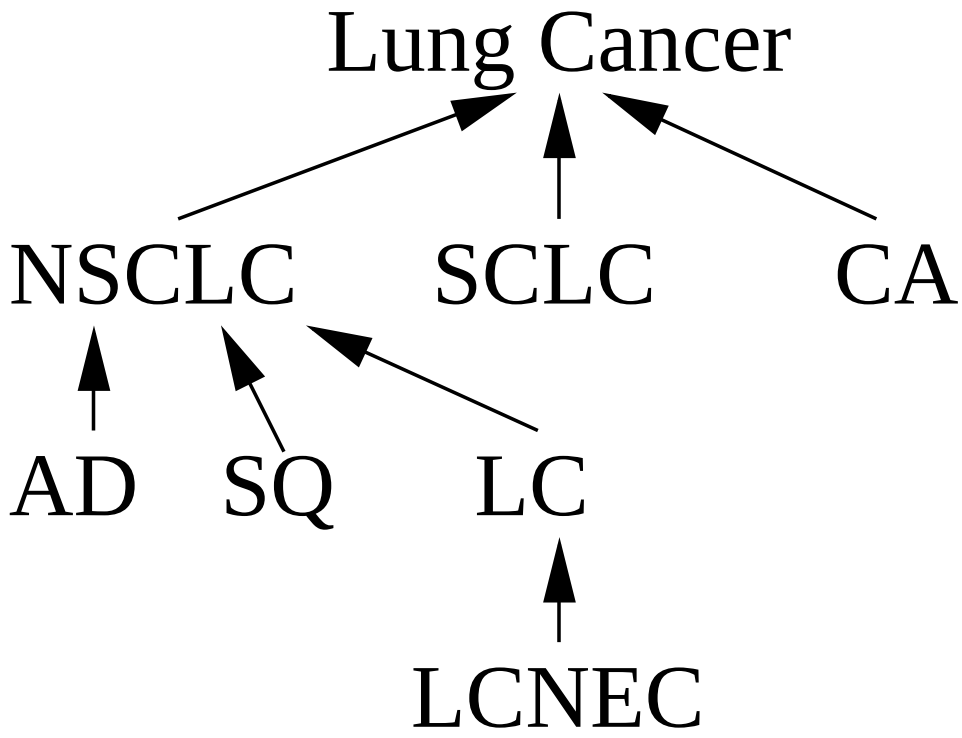
- Two datasets: 1255 patients from a retrospective study and 3863 patients in the prospective dataset
- More than 55% of malignant lung tumors had at least one genetic alteration with features of a potentially tractable target
- The most frequent alterations had no significant impact on survival in (some?) subgroups
- Concurrent mutations can have larger effects: (TP53 + EGFR) and (TP53 + RB1 loss) seem to lead to low survival rates
- Lung cancer subtypes have a mix of variations which can be exploited for classification (in addition to other diagnostic tools)
- Treatment recommendations were provided: 76% of advanced stage patients with EGFR mutated and 50% of patients with ALK translocation

Traditional classification of lung cancer

1. Mostly based on histology (appearance of cells under the microscope)
2. .. and other properties, such as the presence and absence of antibodies (*immunohistochemical* properties)

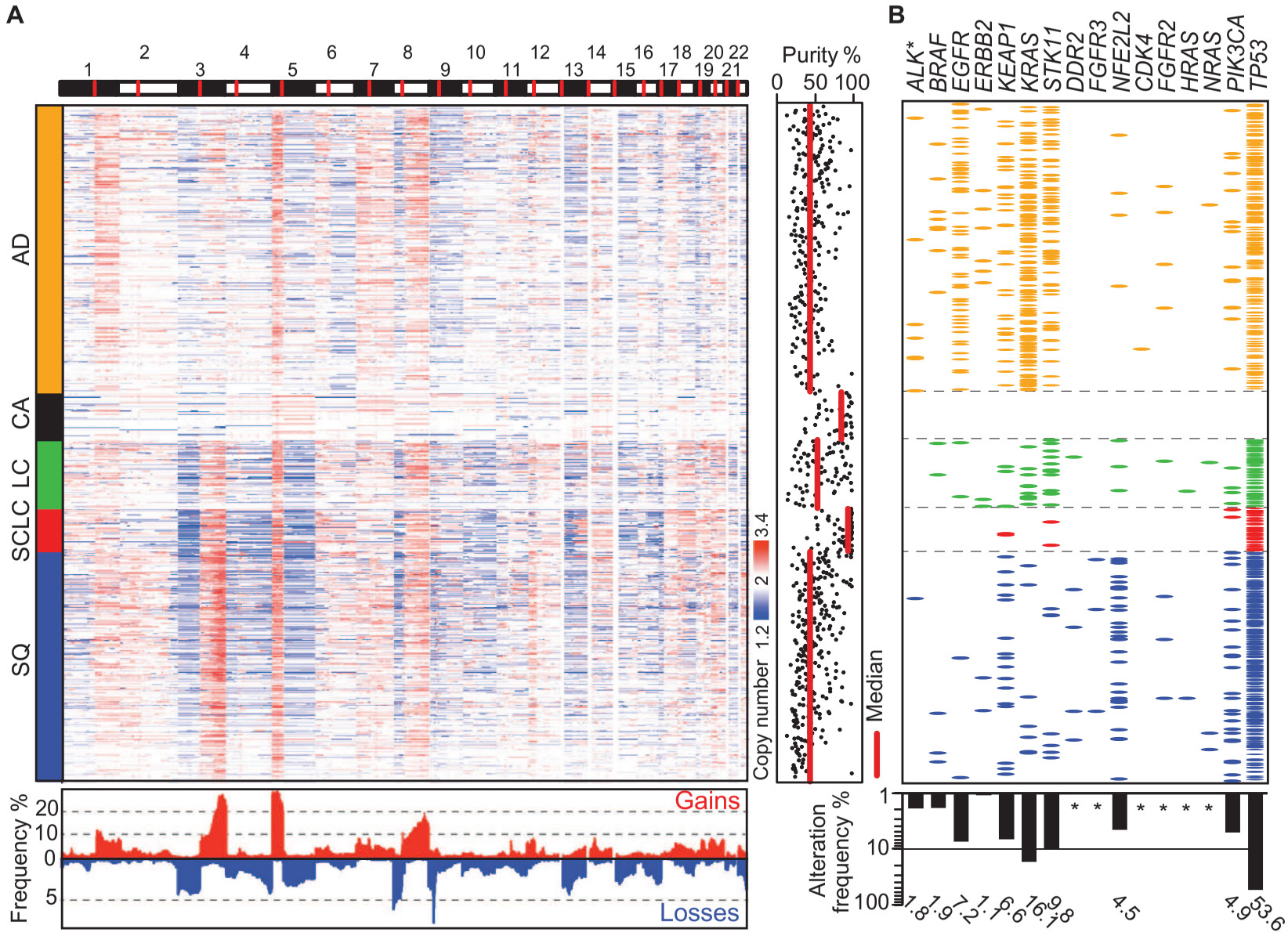
Traditional classification of lung cancer

(cont.)

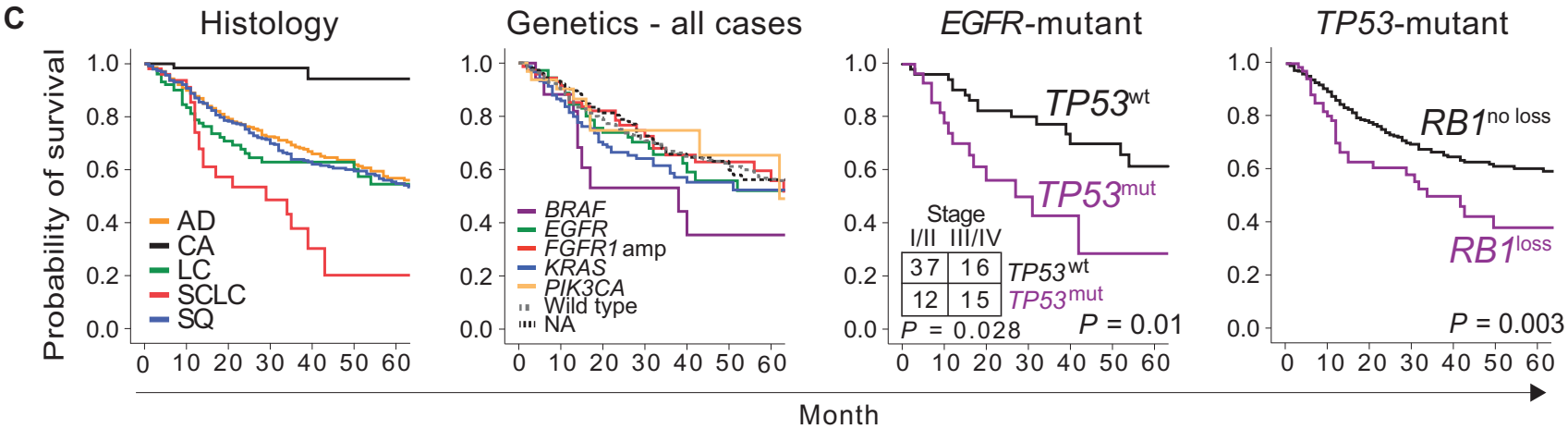


NSCLC: non-small cell lung cancer, SCLC: small-cell lung cancer, CA: carcinoid, AD: adenocarcinoma, SQ: squamous cell carcinoma, LC: large cell carcinoma, LCNEC: large cell carcinoma with neuroendocrine differentiation

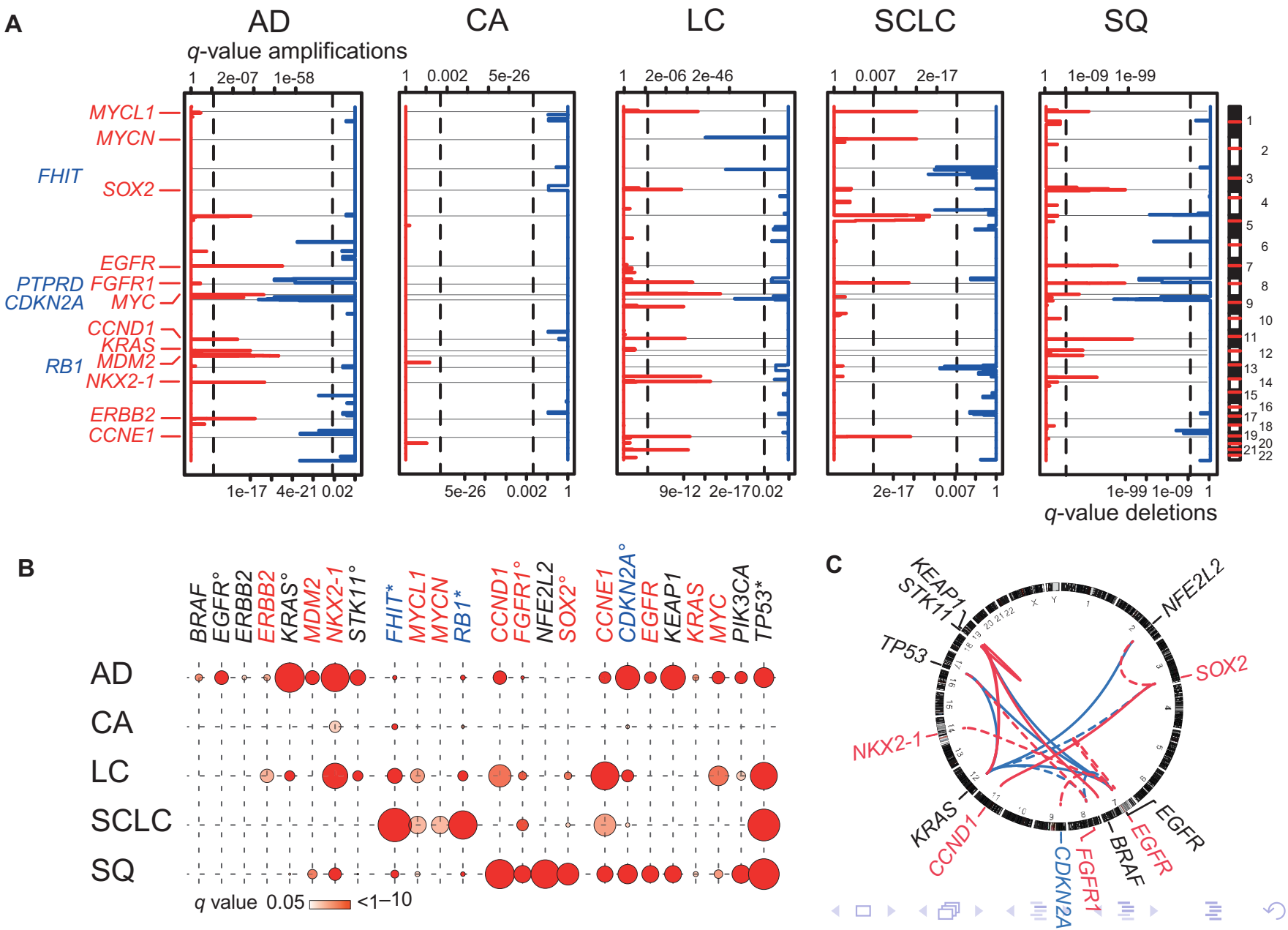
Amplified and deleted genome regions



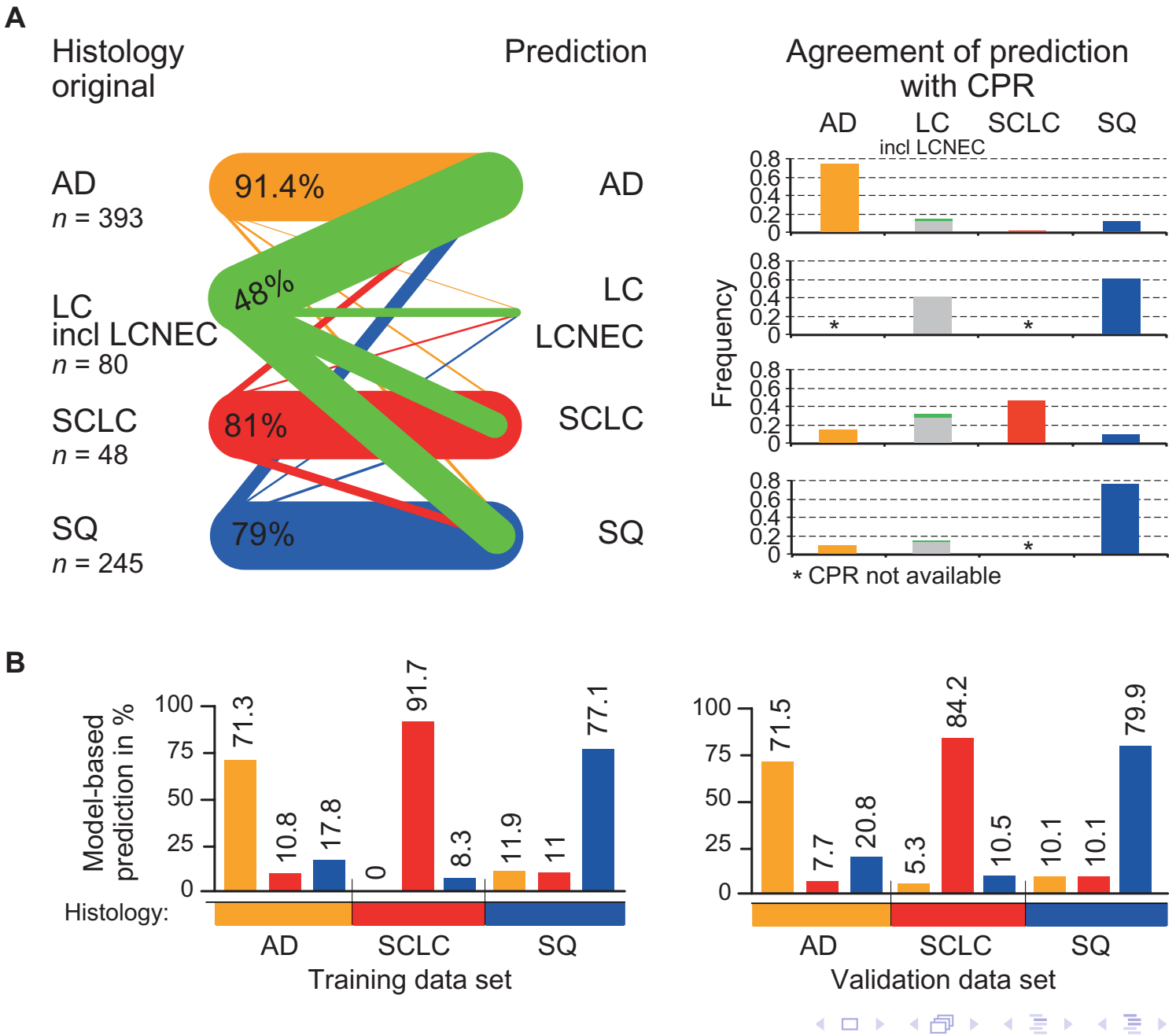
Survival for different patient groups



Genomic alterations in histological subgroups



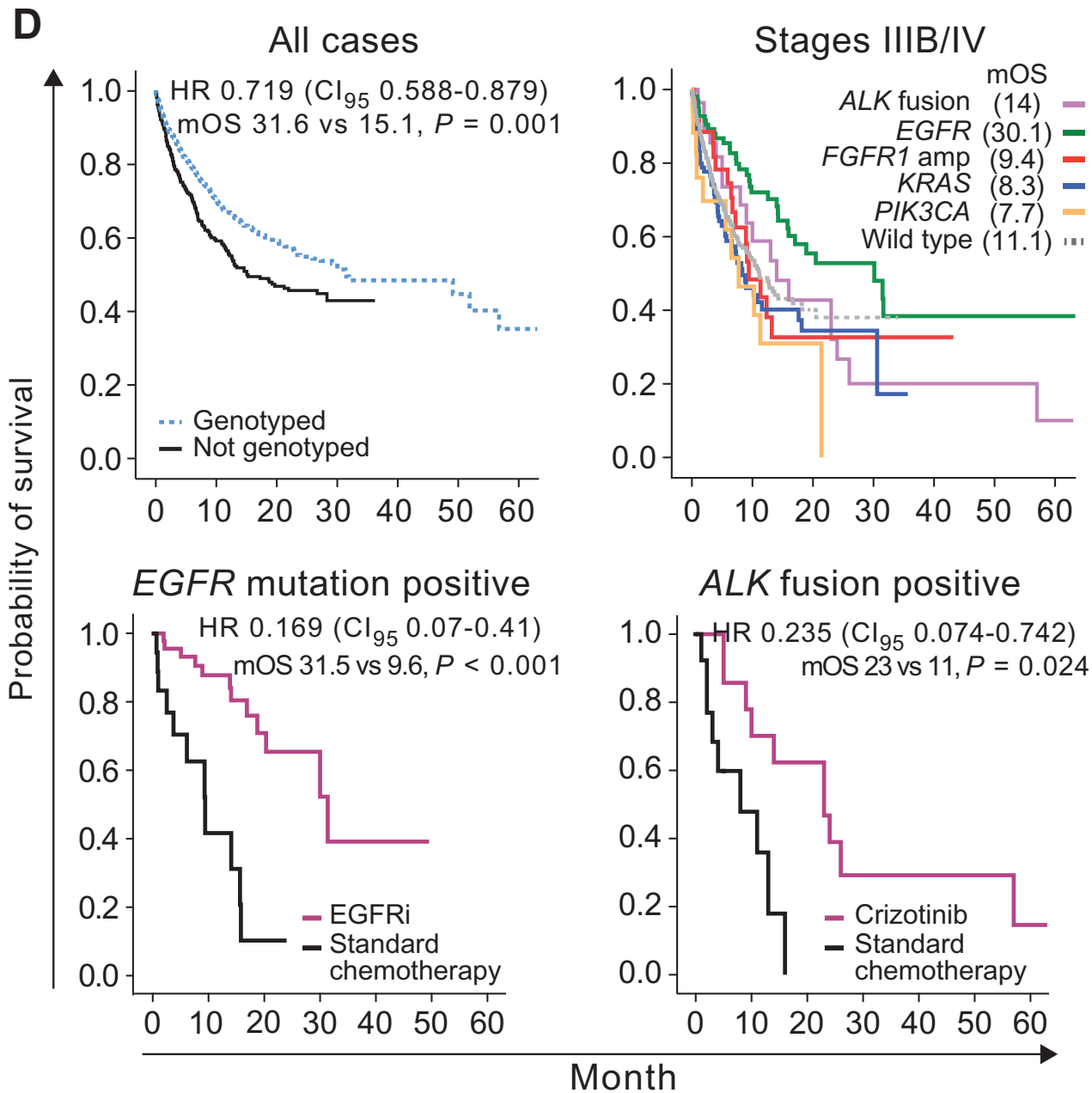
(Re-)classification of samples



Genomics-based lung cancer diagnosis

- 5145 lung cancer patients enrolled in a *molecular screening outreach program* run by Network Genomic Medicine (NGM)
- Genomics based screening supplemented by immunohistochemical screening
- Fewer cases of LC due to re-assignment to other subgroups (compared to retrospective dataset)
- Central genotyping for *key alterations* of 75% of patients
- Treatment recommendations were provided: 76% of advanced stage patients with EGFR mutated and 50% of patients with ALK translocation

Impact of targeted therapy on survival



Discussion (from paper)

- Benefit of reducing size of (potentially) ill-defined subgroup LC
- In some cases targetable mutations were found that are typical of a different subgroup
- Not a real trial (lack of randomization), which would be irresponsible for the control group
- Data has other problems: difference in time of treatment and distribution of stages, quality of clinical data, incomplete data (smoking status, treatment)
- Major results, however, were consistent across both datasets