Temporal-weight Estimation Of The Copy Number Alterations Of 1384 Multiple Myeloma Patients Defines An Ancestrality Index Impacting Patients Survival

Andrea Poletti

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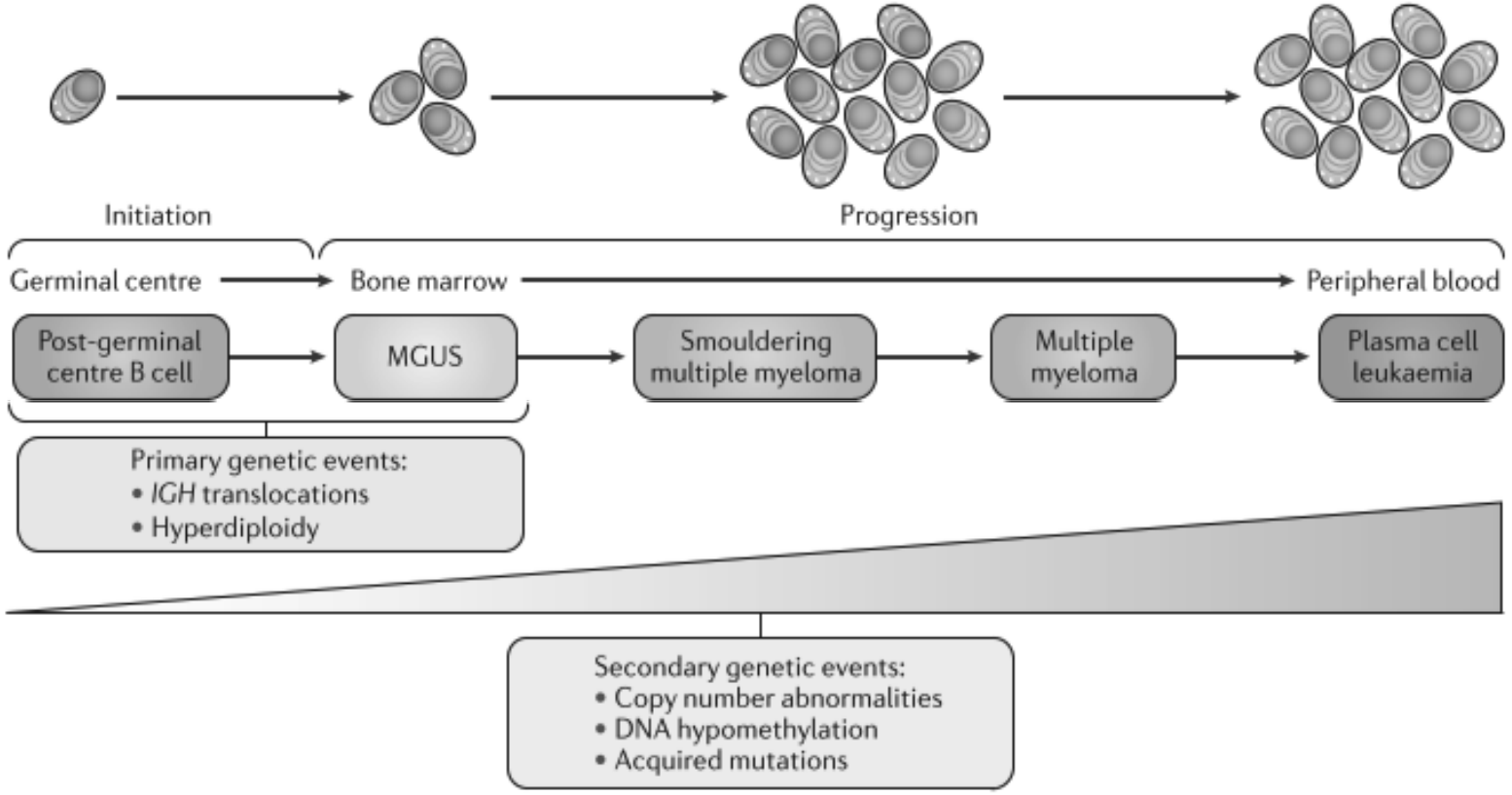
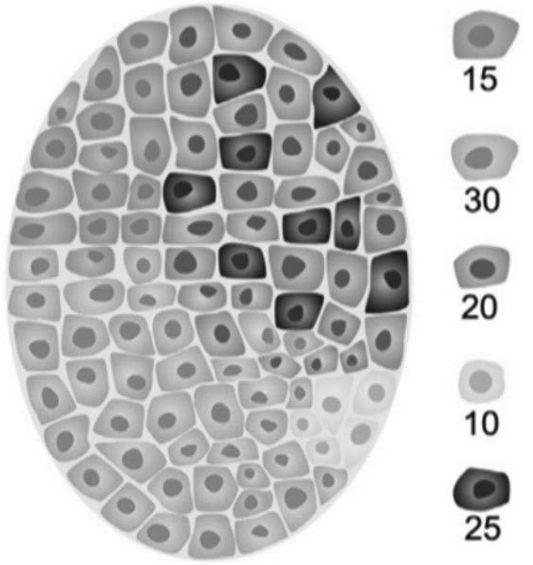
The Multiple Myeloma CNAs heterogeneity





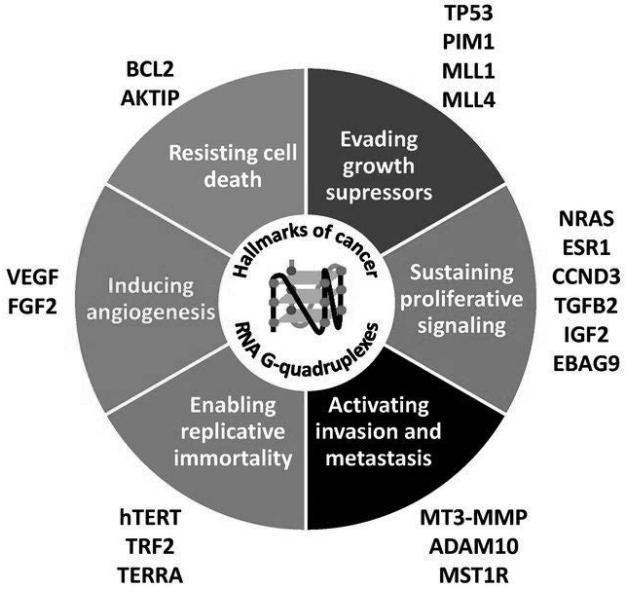
Kumar, S. *et al.* (2017) Nature Reviews

Davis, A. *et al.* (2017) Reviews on Cancer

The Multiple Myeloma clinical and genetic onset

- Active MM is defined by the onset of clinical symptoms, but there is ***no clear connection*** between the MM diagnosis and the genomic lesions in the tumor cells.

- However, genetic alterations are widely recognized to have a ***driving*** role for tumors onset as they can cause all the biological **"hallmarks of cancer"**



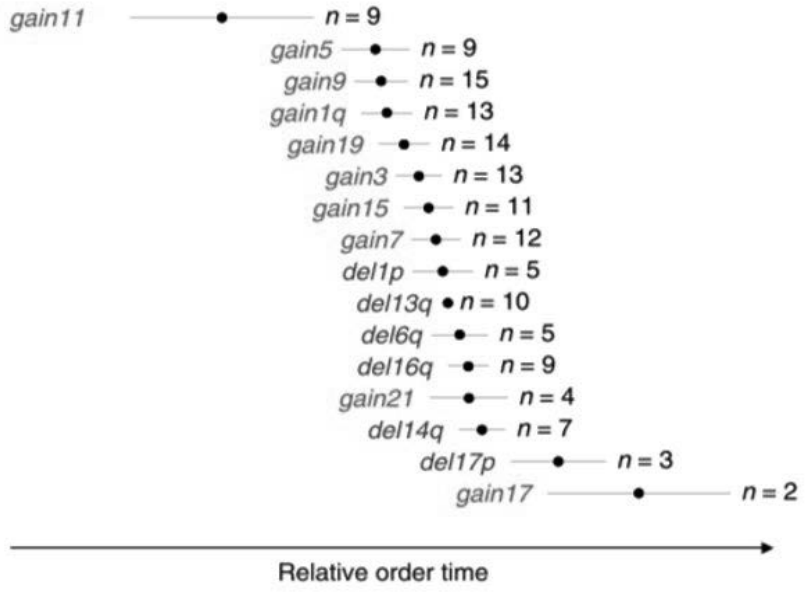
- Alterations present in the MM tumors at diagnosis are often found in MGUS and SMM, so if precisely characterized, they could support a correct MM diagnosis in "ambiguous" SMM patients

The importance of ***timing*** the genetic cancer alterations

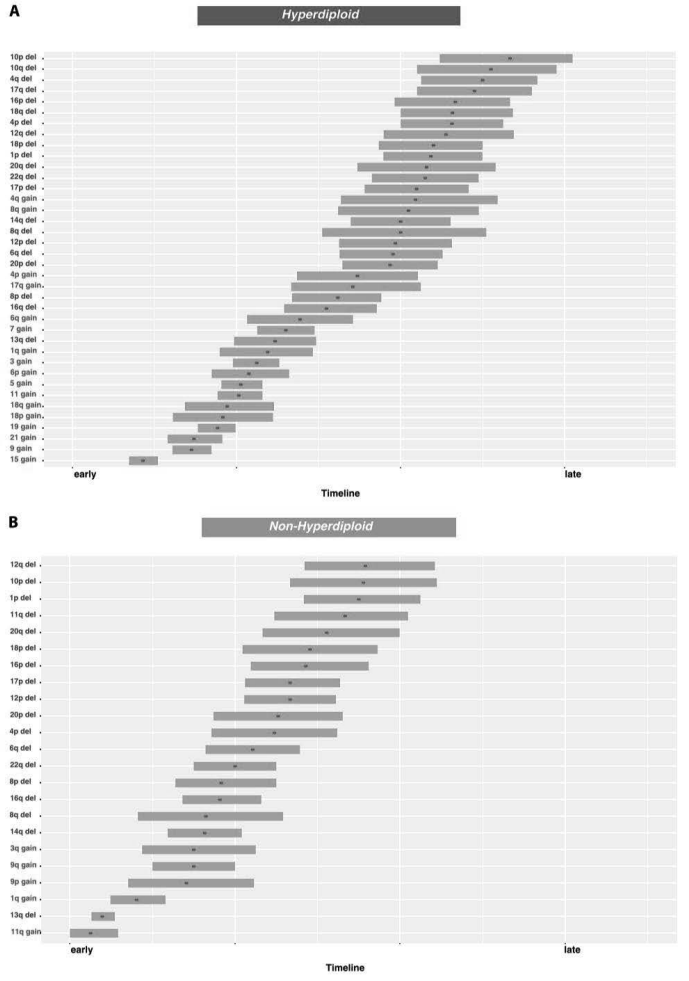
- The recognition of ***ancestral alterations*** can help identify true «driver» lesions, relevant for the onset of the MM and clinical symptoms

- Using statistical algorithms, its's possible to create a **time-map** of the of the acquired **CNAs** during **MM oncogenesis** and rank them as "late" or "early".

- The correct CNAs' timing in previous works is biased by the low number of patients analysed (< 100)



Maura *et al.* Nat Comm (2019)



Samur *et al.* Blood Cancer Journal (2019)

Harmonizing datasets – the importance of statistical power

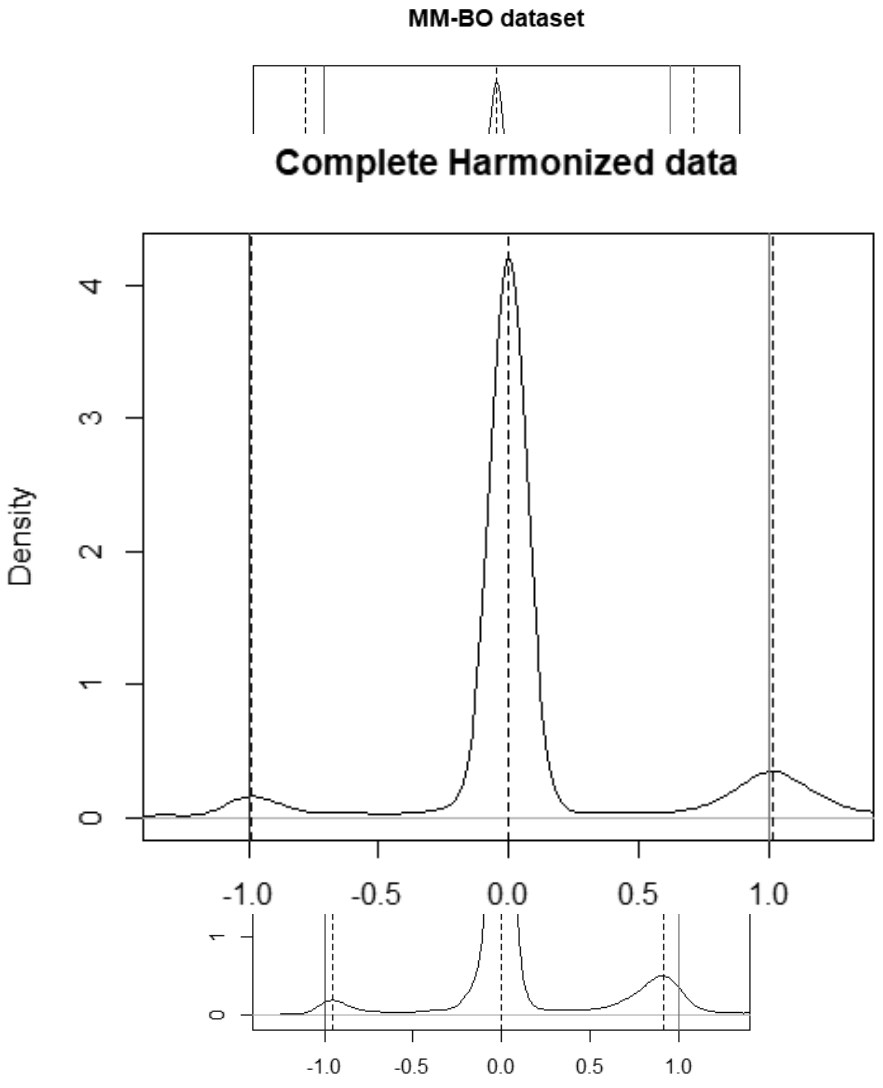
High statistical power is required to precisely time CNAs, especially rare ones.

We combined two huge (but different) different datasets:

- MM-BO: **512 samples** profiled with SNP-arrays
- CoMMpass cohort: **871 samples** profiled with WGS

BUT

- Need for ***data-harmonization*** to compare CN profiles, since clonal and subclonal CN events can be biased by multiple methodological aspects:
  - different **assays methods**
  - different **tools/pipelines**
  - different analysis **algorithm parameters**

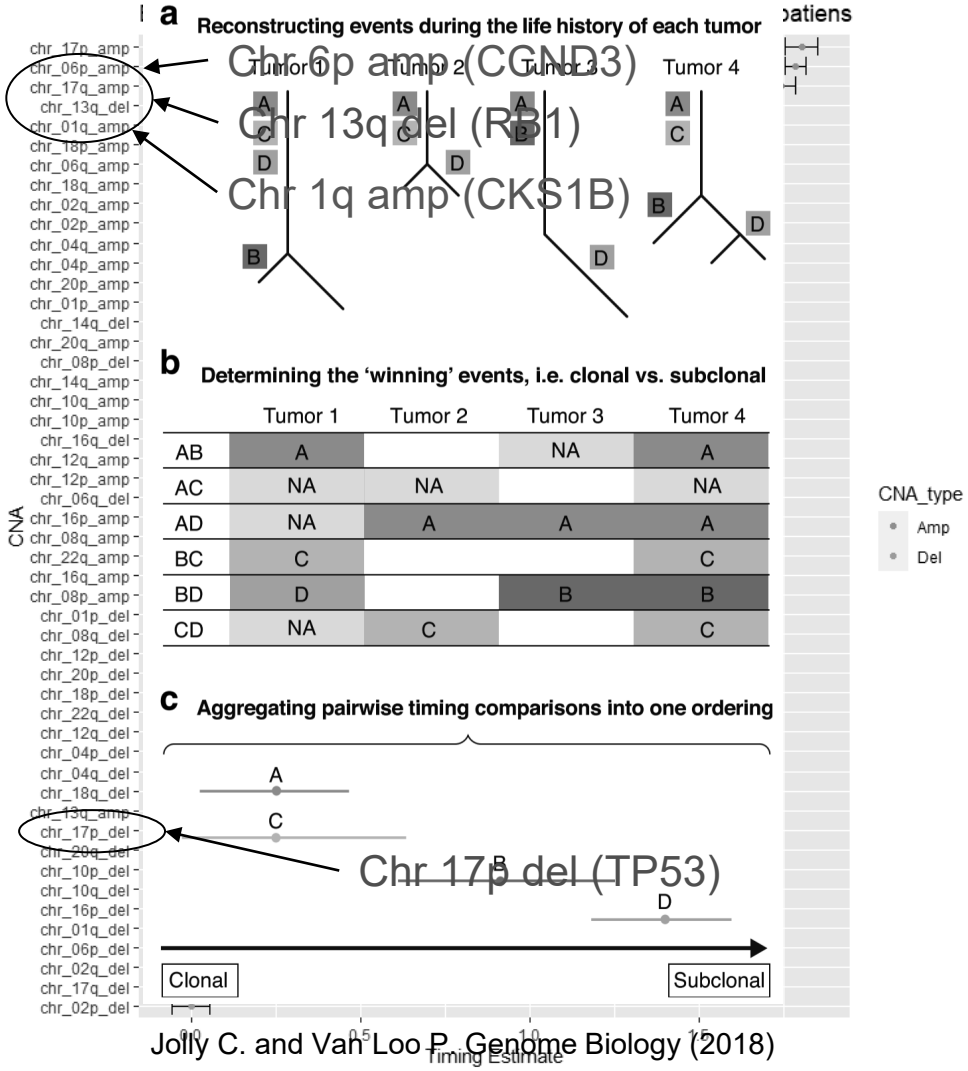


Bradley-Terry algorhitm to date MM CNAs – a precise time map

- SPORT classification algorhitm
  - **PLAYERS = any secondary (non-HD) CNAs**
  - **MATCHES = clonality contest**

    => any clonal and subclonal CNAs «competed», according to 10% clonality difference threshold

    => only secondary CN events do participate to the competition since IgH traslocations and Hyperdiploidy are primary ancestral events (they are always *clonal*)



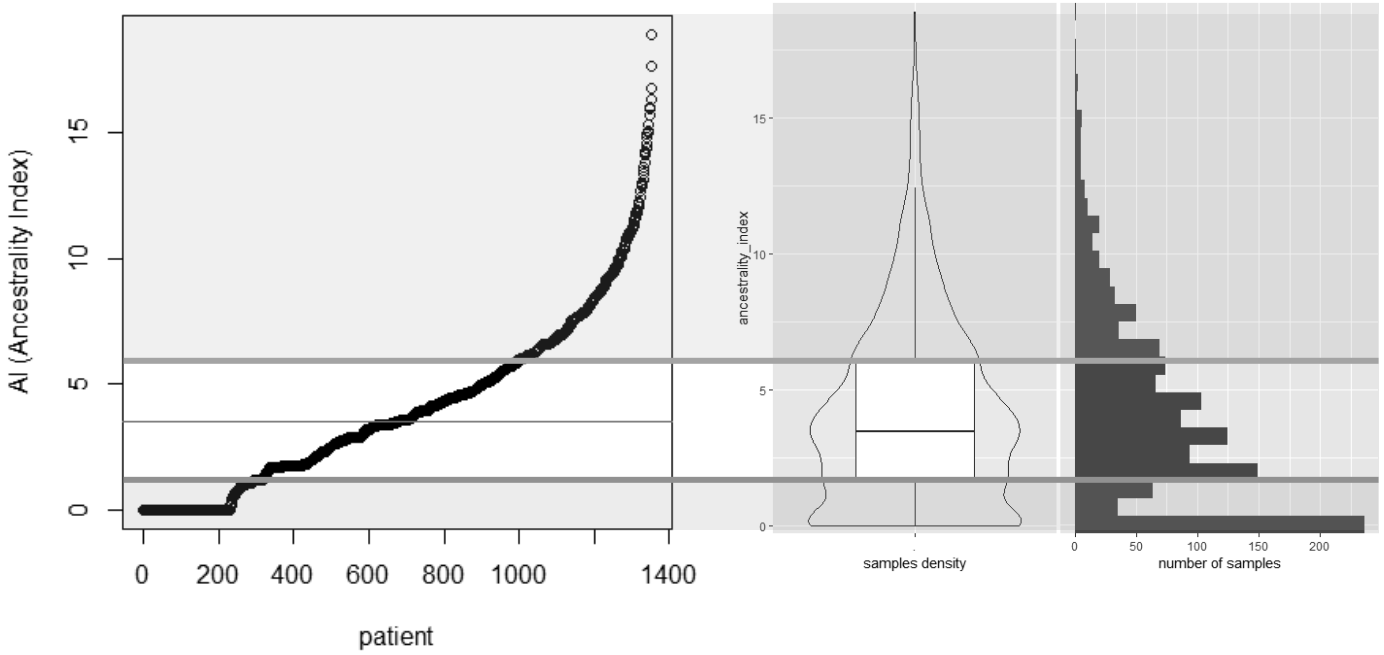
Jolly C. and Van Loo P. Genome Biology (2018)

Implemetation of CNAs timing information to date MM patients' ***ancestrality***

- We developed a **combinatorial scoring model** to produce an **ANCESTRALITY INDEX (AI)** that weights each CNA in any given sample for its relative Timing Estimate (TE).

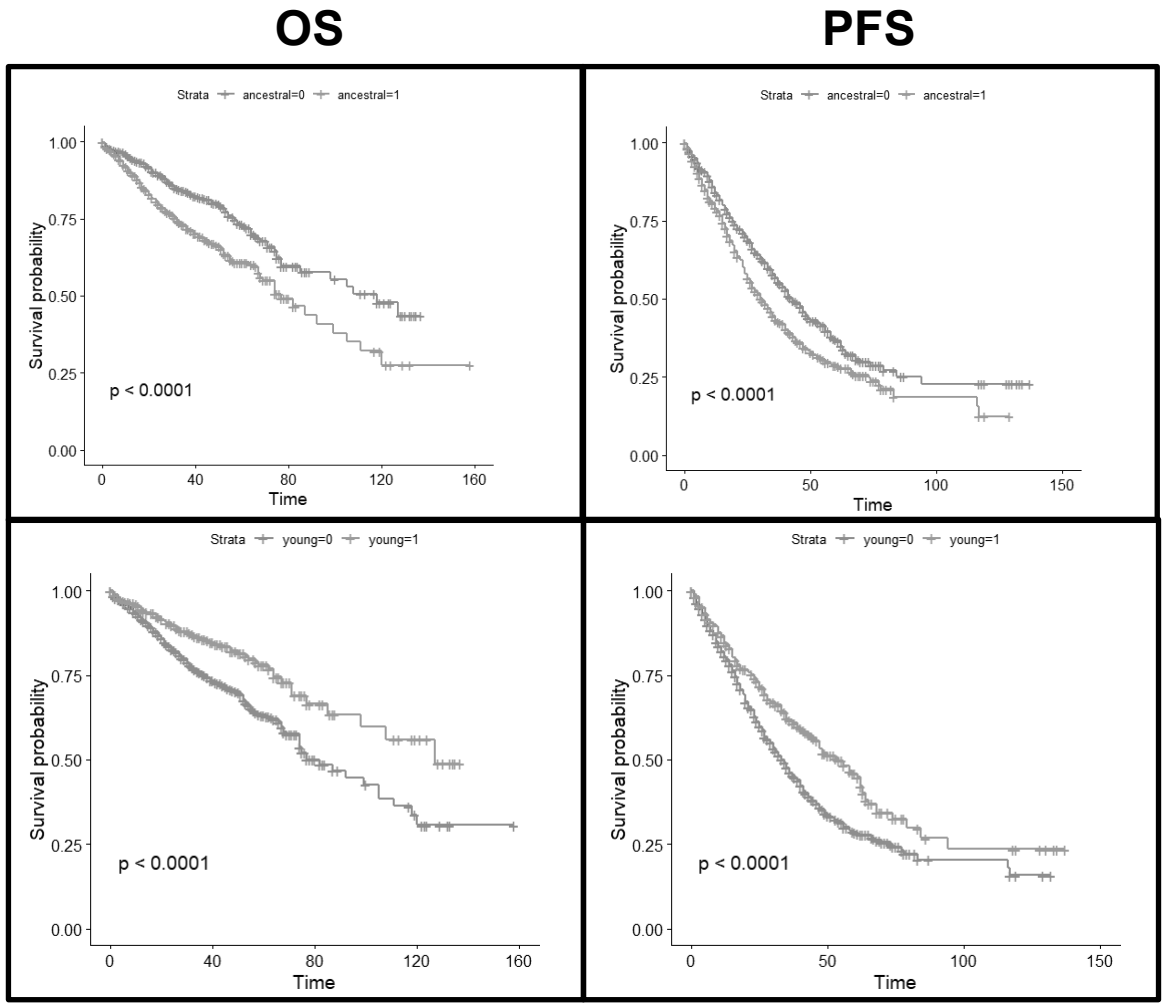
For each patient (p):

$$AI_p = \sum_{i=1}^{n} (CNA_i \times TE_i)$$
$$= (CNA_1 \times TE_1) + (CNA_2 \times TE_2) + (CNA_3 \times TE_3) \ldots$$



- Statistical categorization of patients according to the ***AI quartiles***:
  - «***ancestral***» (high AI) patients
  - «***young***» (low AI) patients

“ancestral” and “young” MM patients => survival analysis



- Patients included in the «ancestral» time-weighted category present ***worse*** prognosis, as compared to patients included in the «young» time-weighted category, in terms of both OS and PFS
- At the time of MM diagnosis, the timing characterization of the whole CNAs landscape significantly impact patients’ survival

CONCLUSIONS 1

➔ the whole CNAs landscape carries information concerning the MM evolution ancestrality state and this impacts patients' survival

- CNAs can be dated during MM oncogenesis and evolution
- ***OLD*** CNAs are probably ***driver alterations*** => patients with ***high AI*** have bad prognosis;
- The ***timing analysis*** of molecular lesions (particularly CNAs) help in defining newly diagnosed patients' clinical characteristics and might identify ***driver lesions***
- The use of AI score in SMM patients might help in defining their ***evolutive status*** by distinguish either MGUS-like or high-risk SMM subtypes

CONCLUSIONS 2

- By this approach, it has been possible to **define genomically distinct states at the onset of MM**, i.e.
  - *"young/simple" MM tumors* with ***low*** temporal-genomic heterogeneity
  - *"ancestral/evolved" tumors* with ***multiple*** different driver ancestral alterations distributed across the genomic profile

- Clinical correlations highlighted that:
  - novel biomarkers can be defined, based on the *genome ancestrality*, useful for the clinical management of MM patients
  - MM evolution in *pre-clinical phases* can be elucidated, thus possibly improving knowledges on high-risk SMM patients

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Federica Pedali

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