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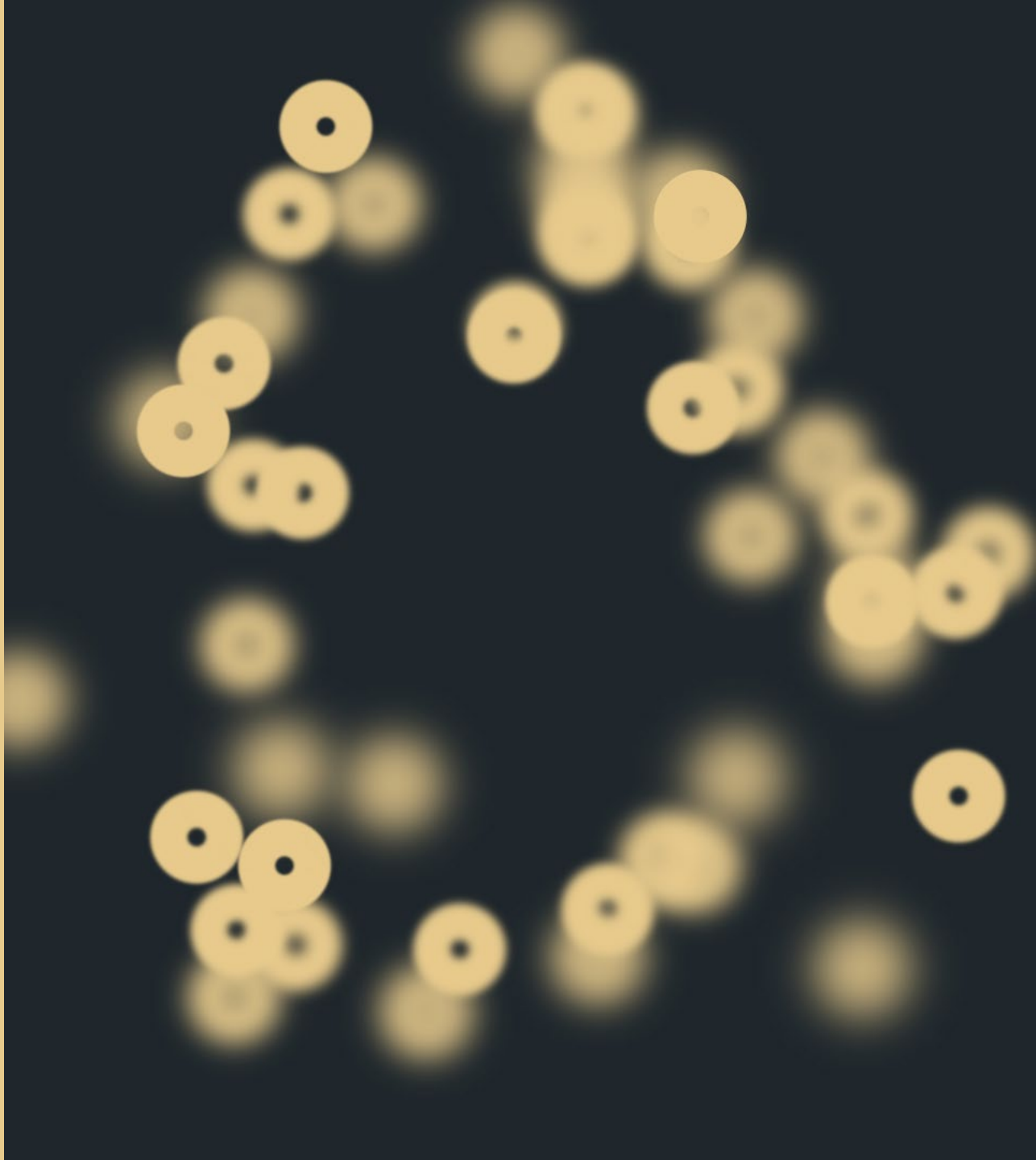
EHA-SWG Scientific Meeting on Recent Advances in the Pathogenesis and Treatment of Secondary Acute Myeloid Leukemias

Berlin, Germany
April 25-26, 2025



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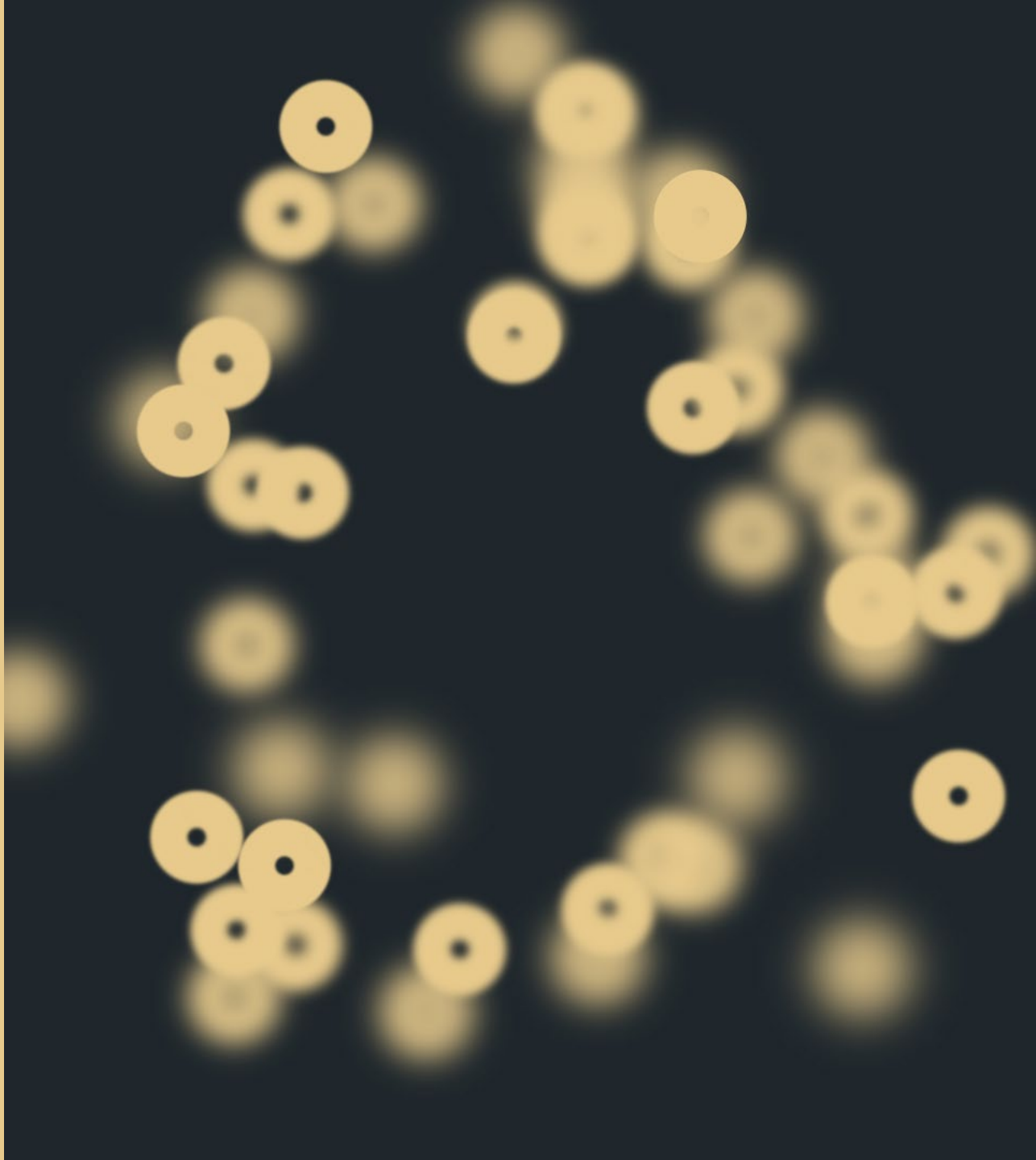
Quantitative dynamics driving transformation to MDS and AML

EHA-SWG Scientific Meeting, Berlin

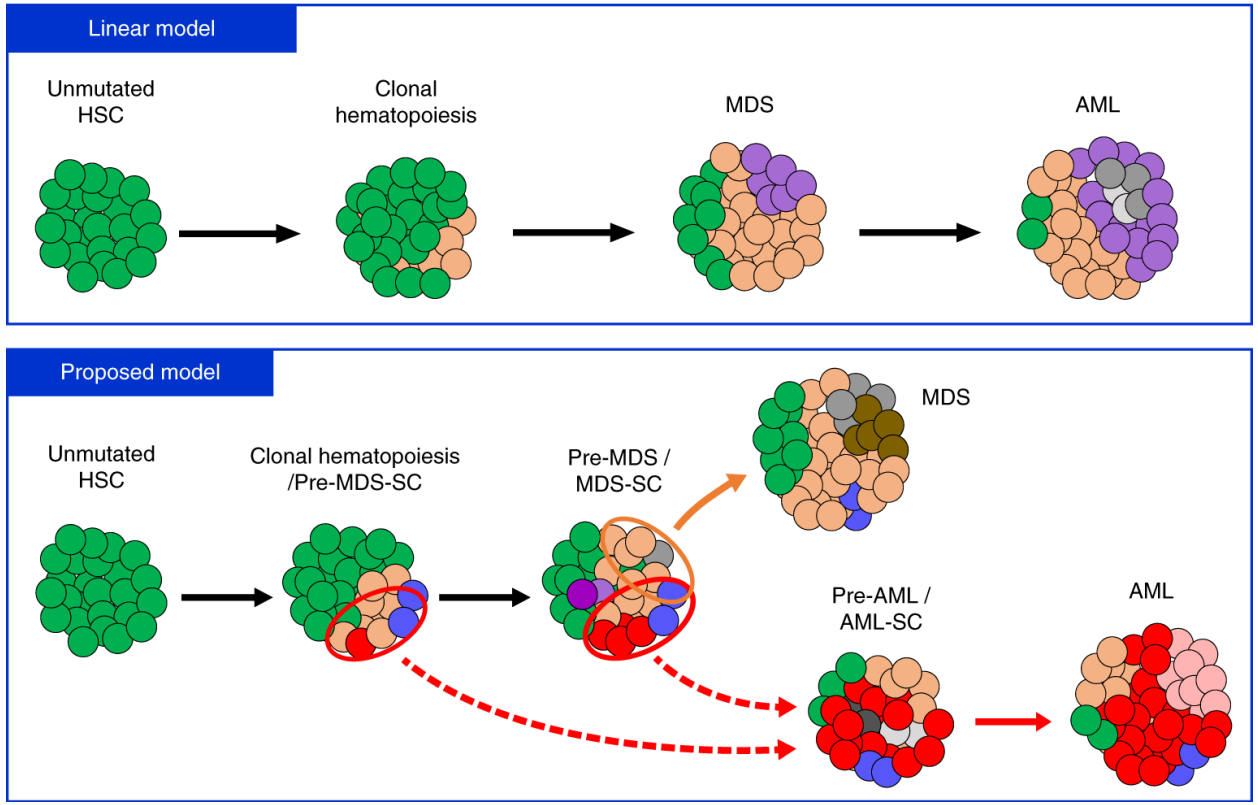
Verena Körber, Weatherall Institute of Molecular Medicine, Oxford, April 25th, 2025



Disclosure

I have nothing to disclose.

Clonal evolution during progression from myelodysplastic syndrome (MDS) to acute myeloid leukemia (AML)



Chen et al., Nature Medicine, 2018

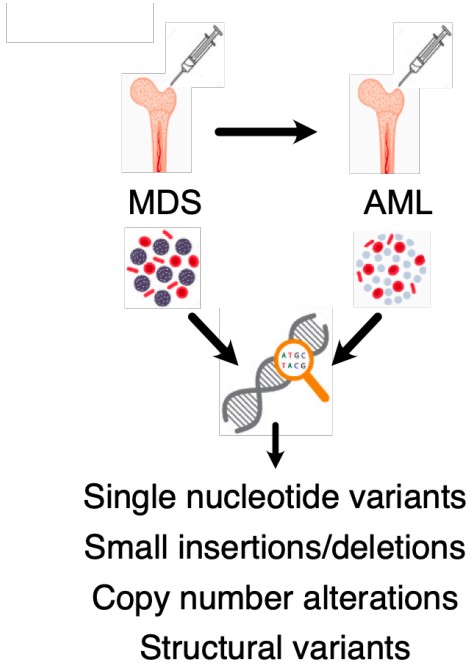
When in life do selected clones identified at MDS and AML stage emerge?

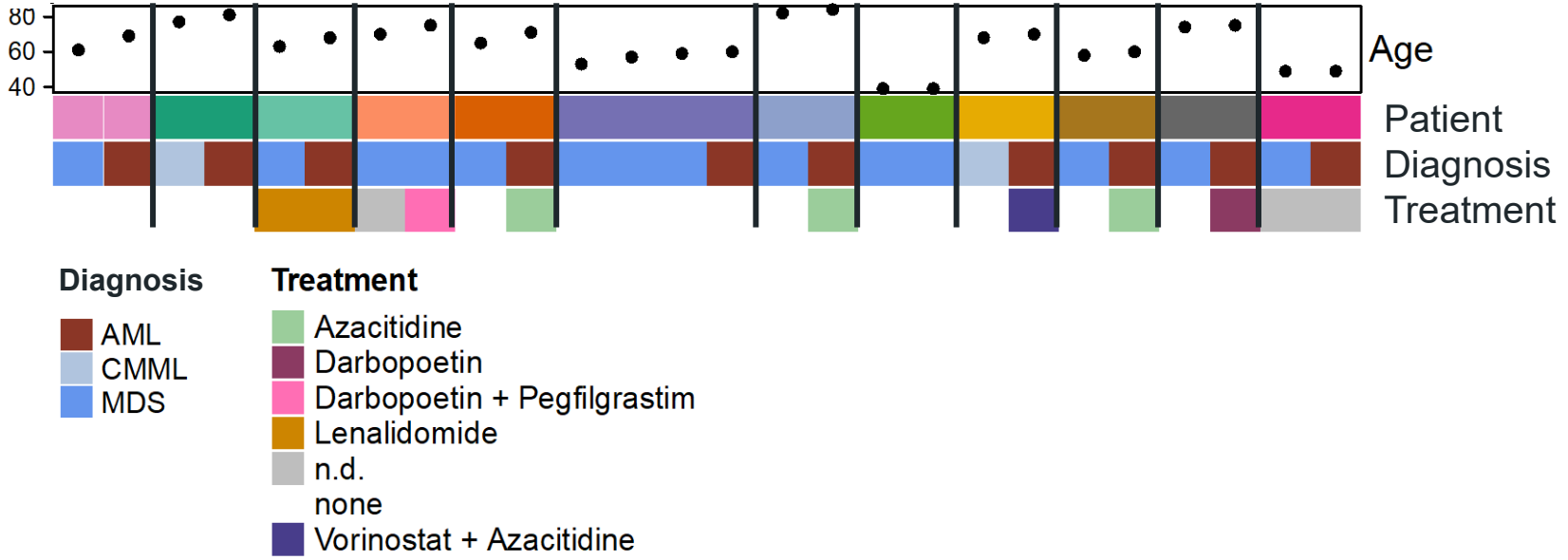
How fast do they expand?

Do the rates of clonal emergence and expansion change over time?

How do mutant clones perturb normal division and differentiation dynamics?

Reconstructing clonal evolution with deep whole genome sequencing data

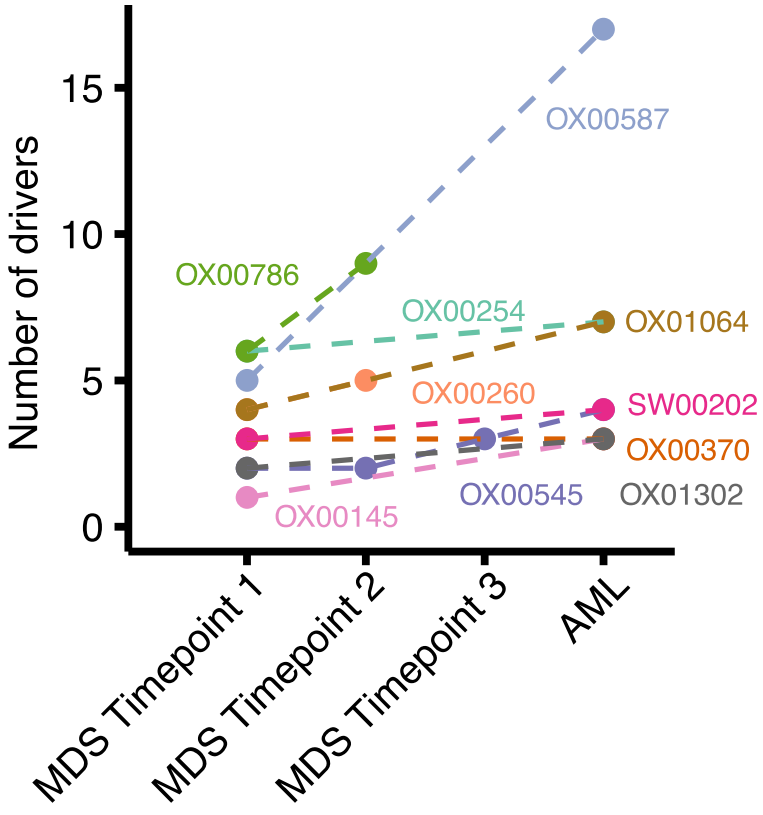


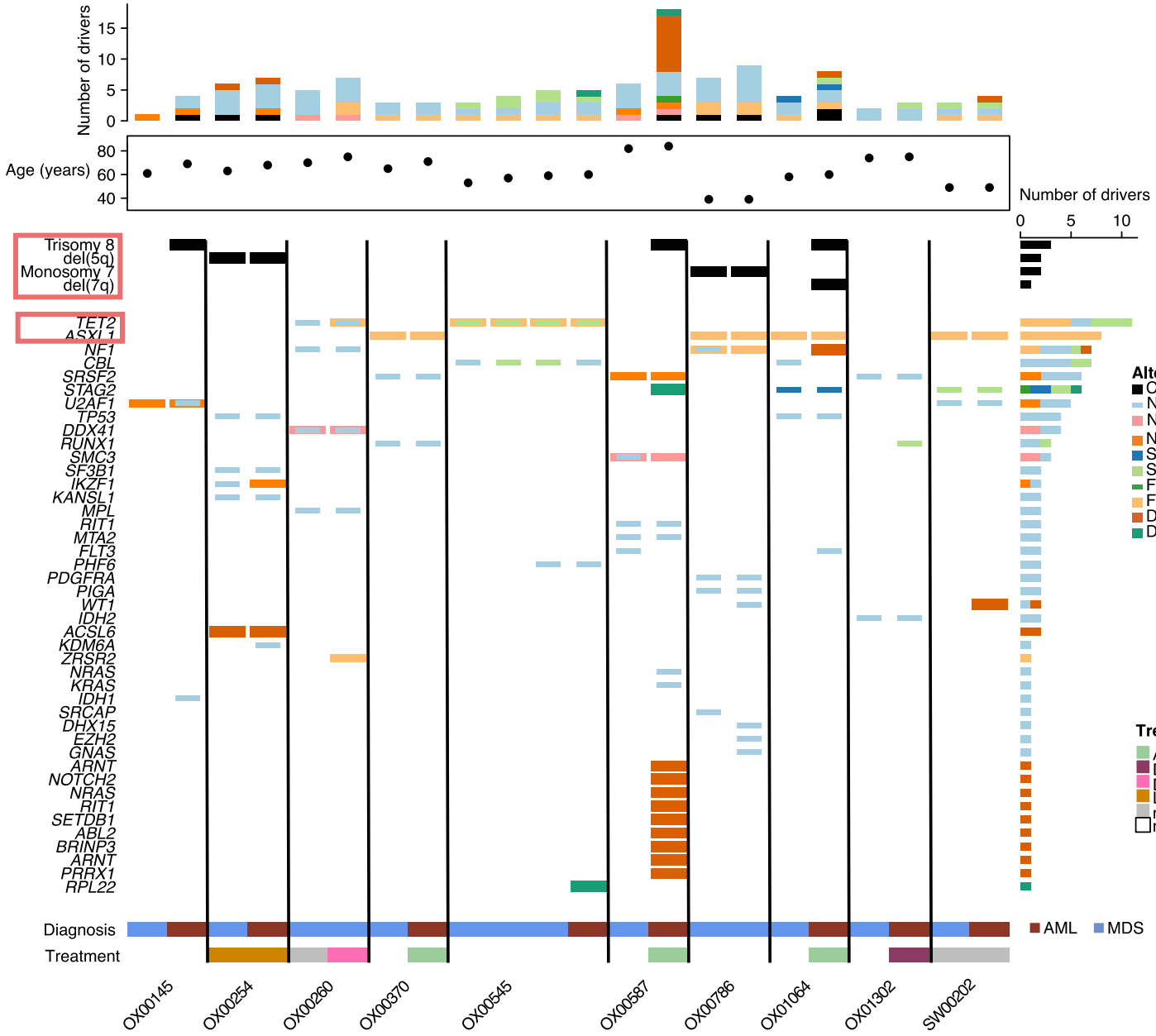


- Longitudinal data from 12 MDS/sAML patients
- Median age at diagnosis: 64 years (57, 71)
- 5 females, 7 males

With Paresh Vyas, Oxford

Driver landscape in MDS/AML





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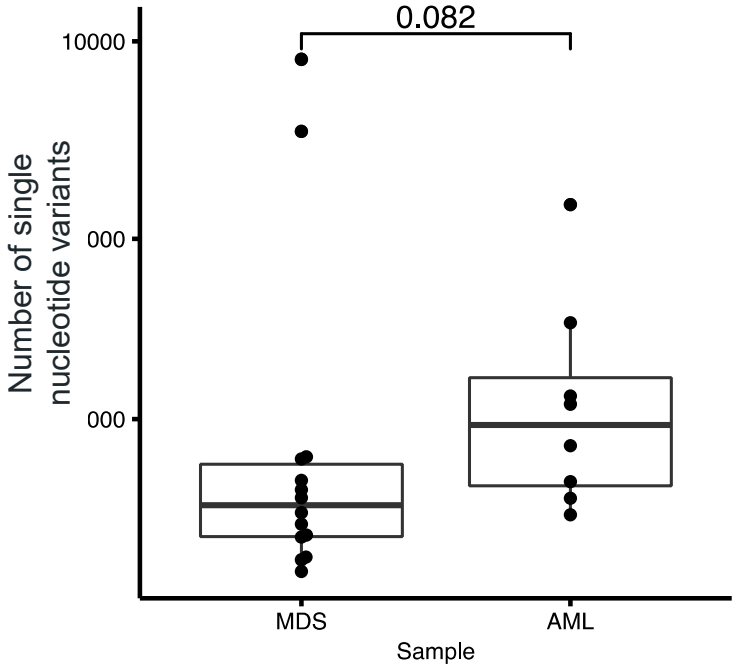
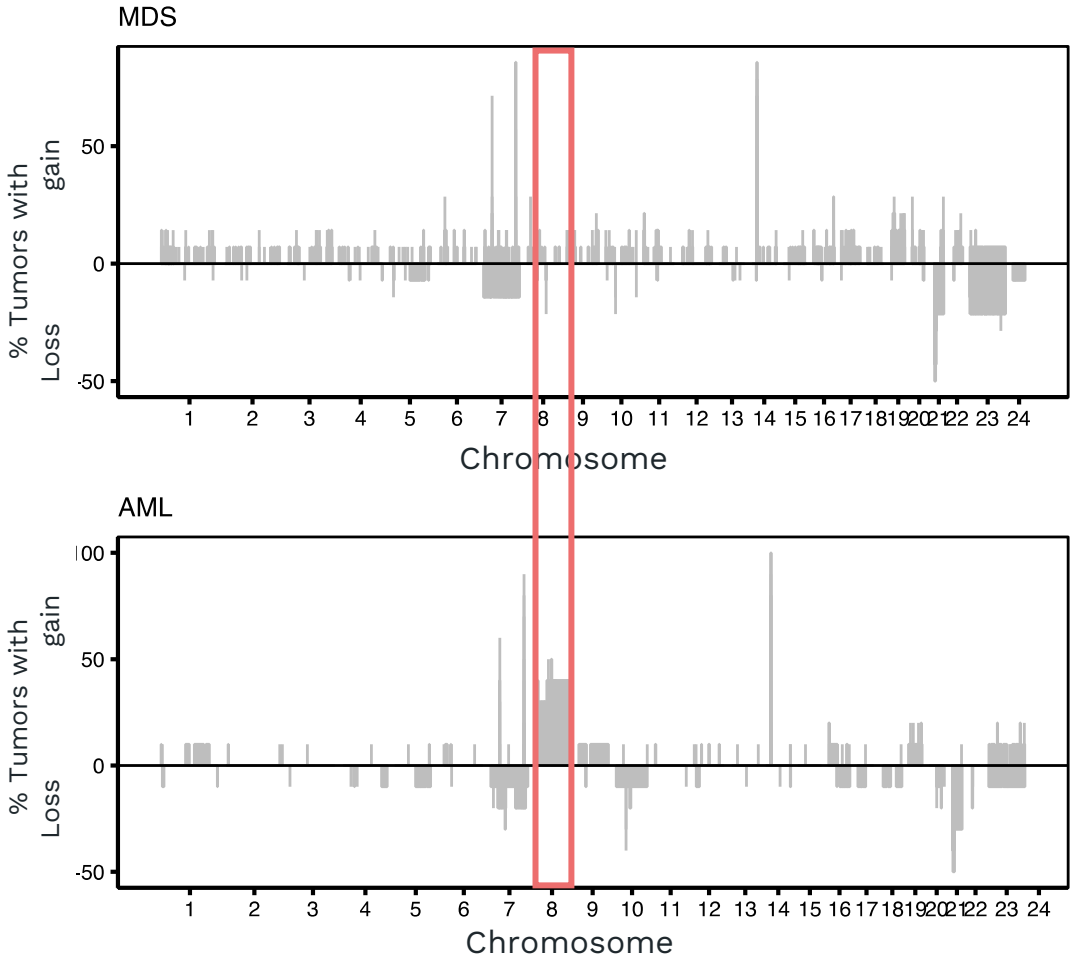
Ongoing genetic evolution between MDS and AML

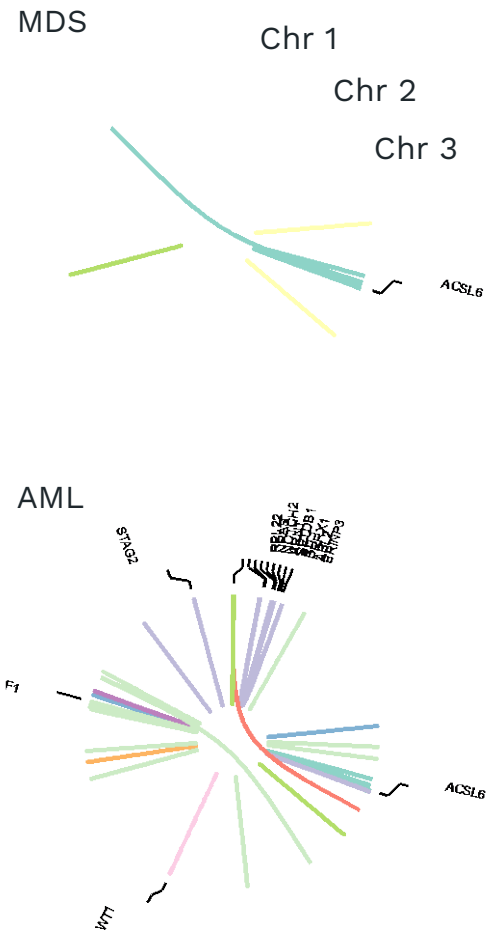
Single nucleotide variants



Copy number alterations



Structural variants



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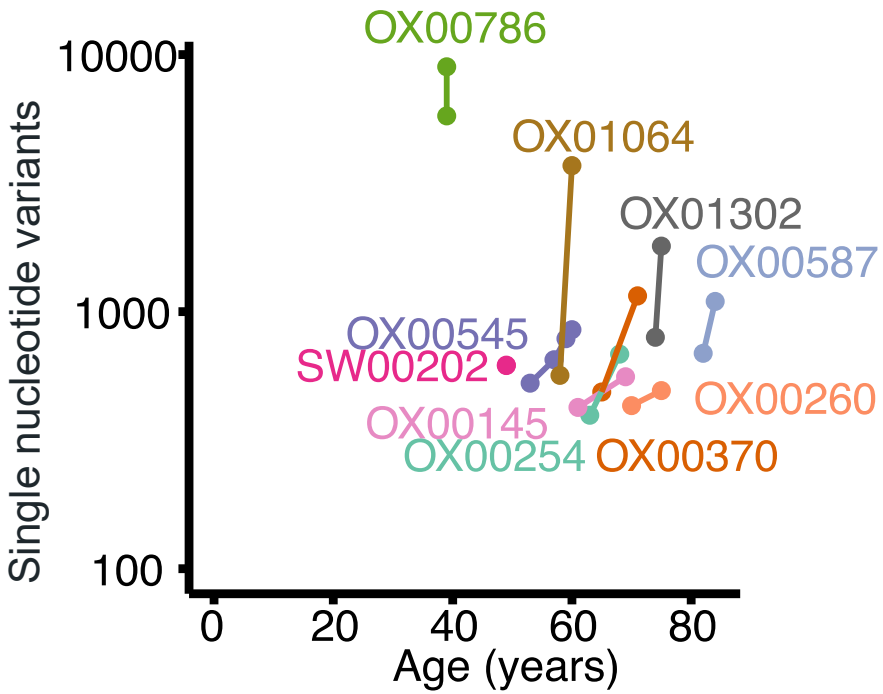
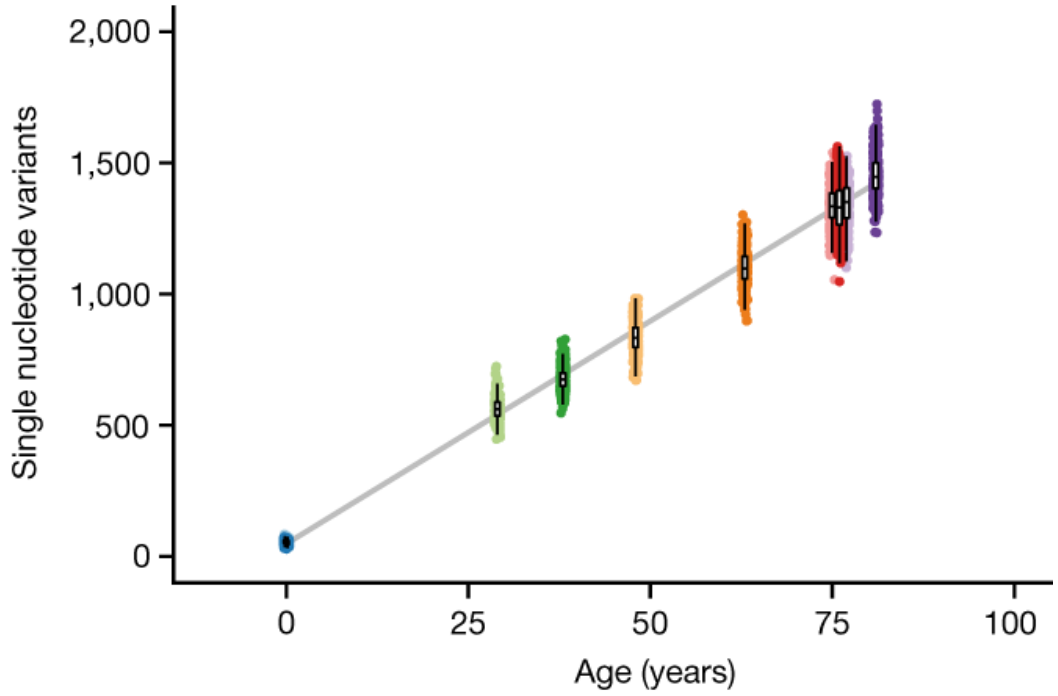
Decorrelation between mutational burden and age

Mutational burden in MDS/AML samples

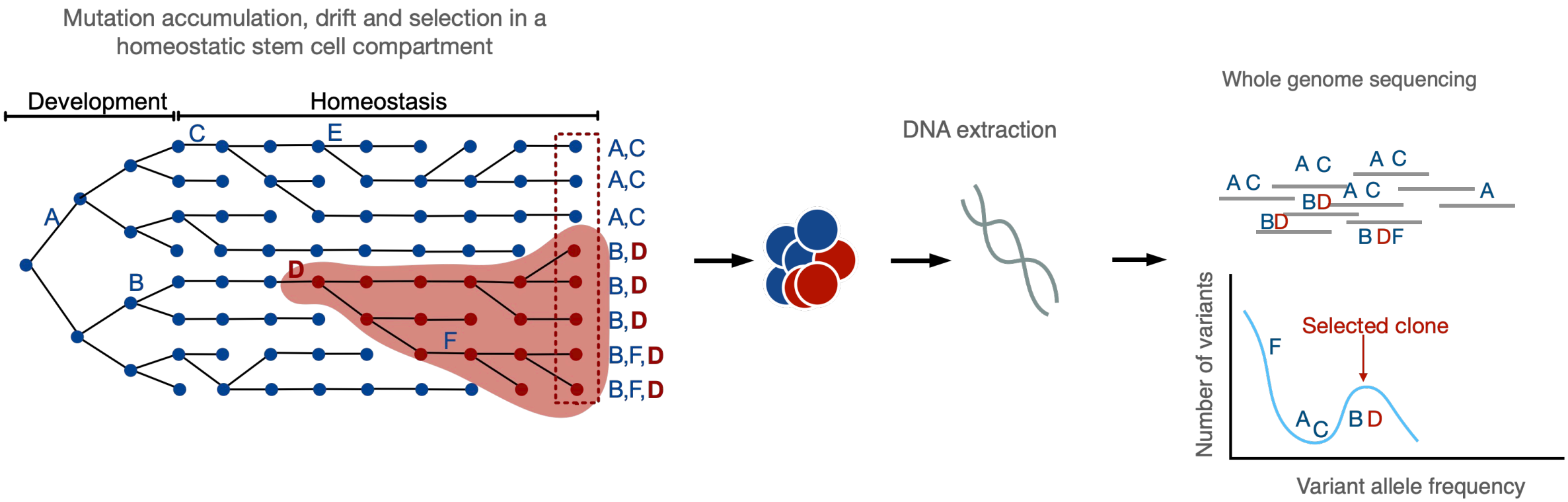


Mutational burden in normal hematopoietic stem cells



Mitchell et al., Nature, 2020

Understanding tissue evolution using somatic mutations as a molecular clock



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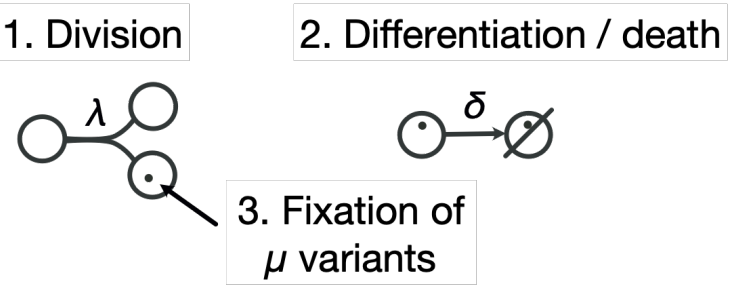
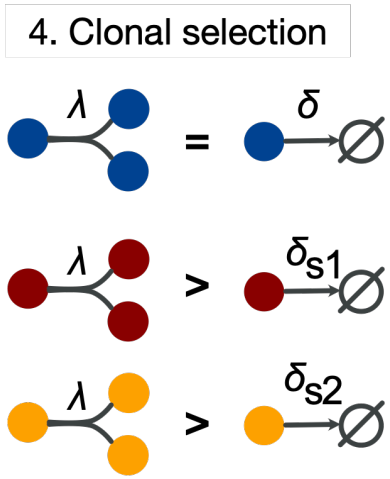
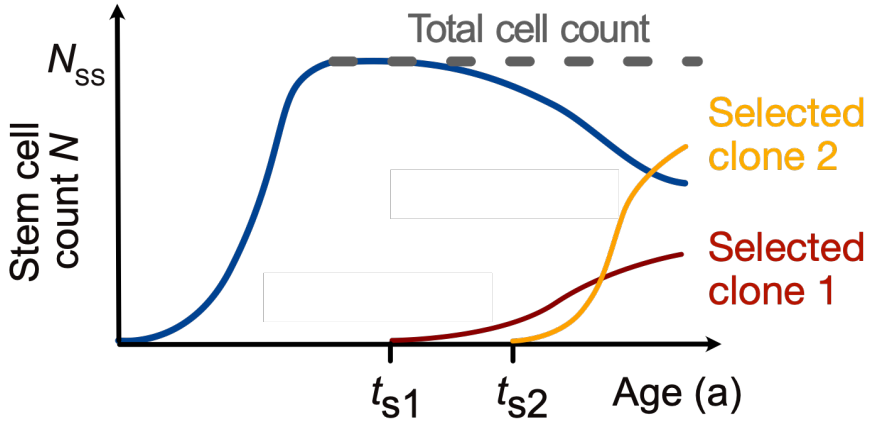
Modelling drift & selection in homeostatic stem cell populations







With Thomas Höfer, Heidelberg

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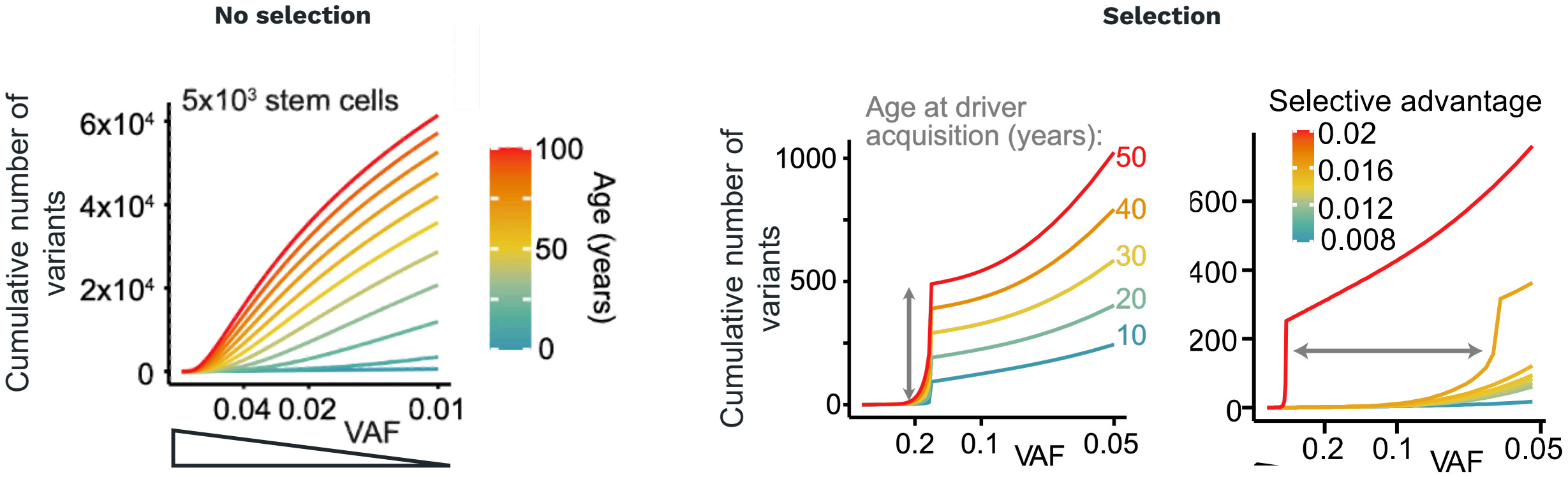
Selection manifests itself in a subclonal shoulder whose height & position reflect age at driver acquisition and selective advantage



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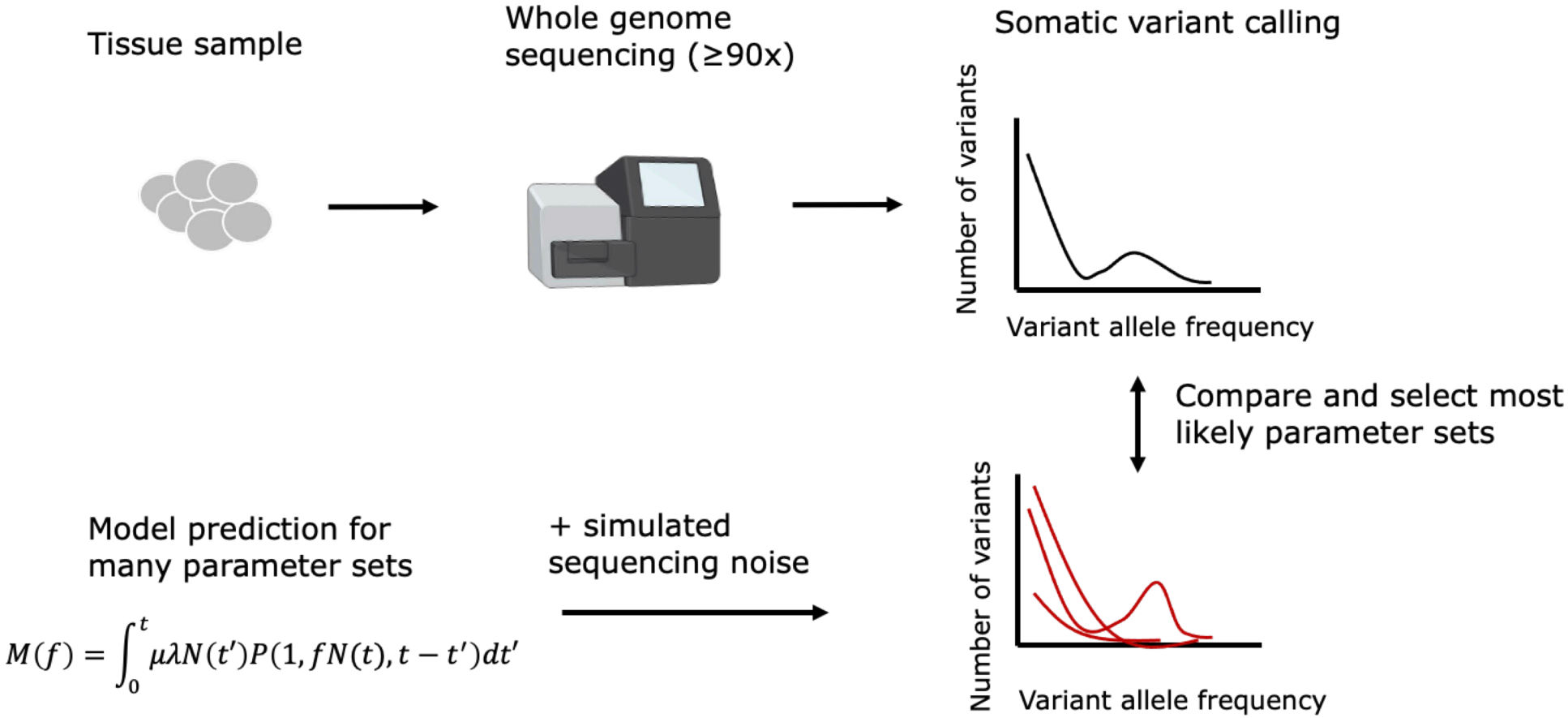
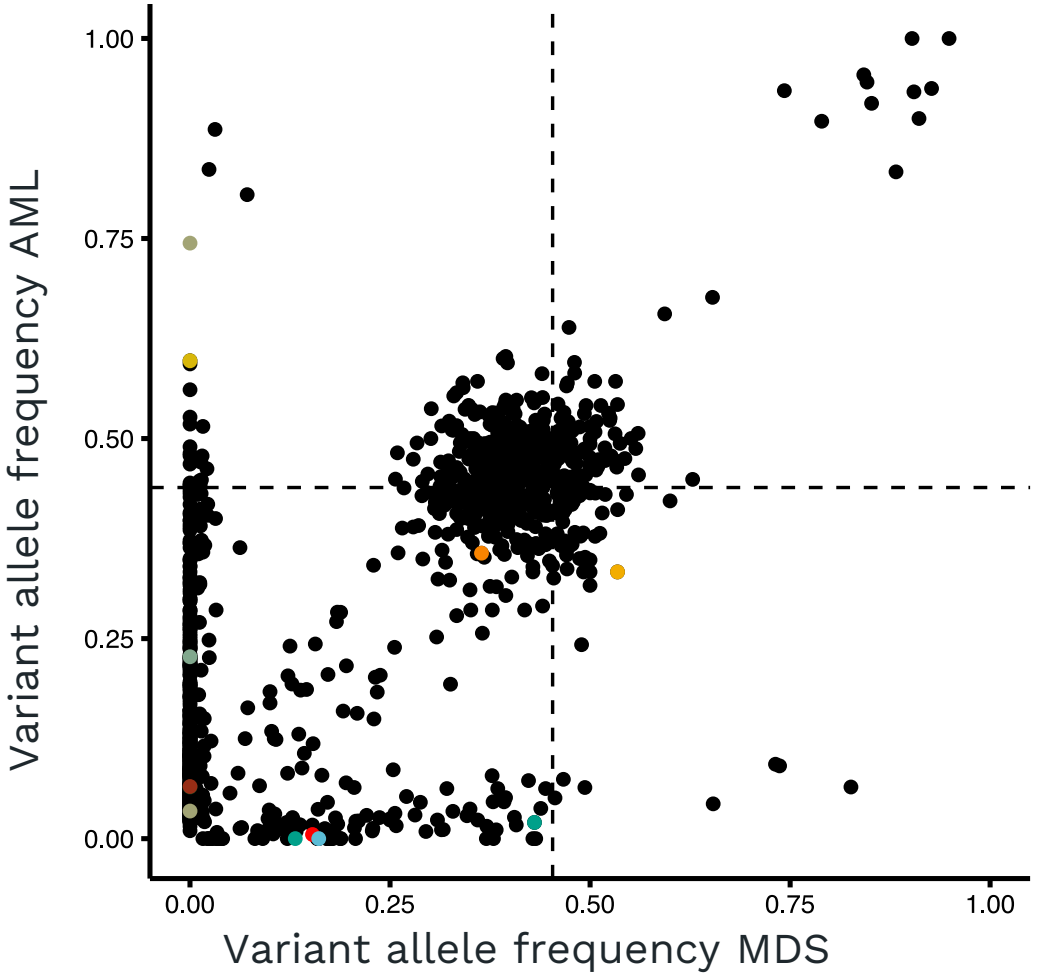
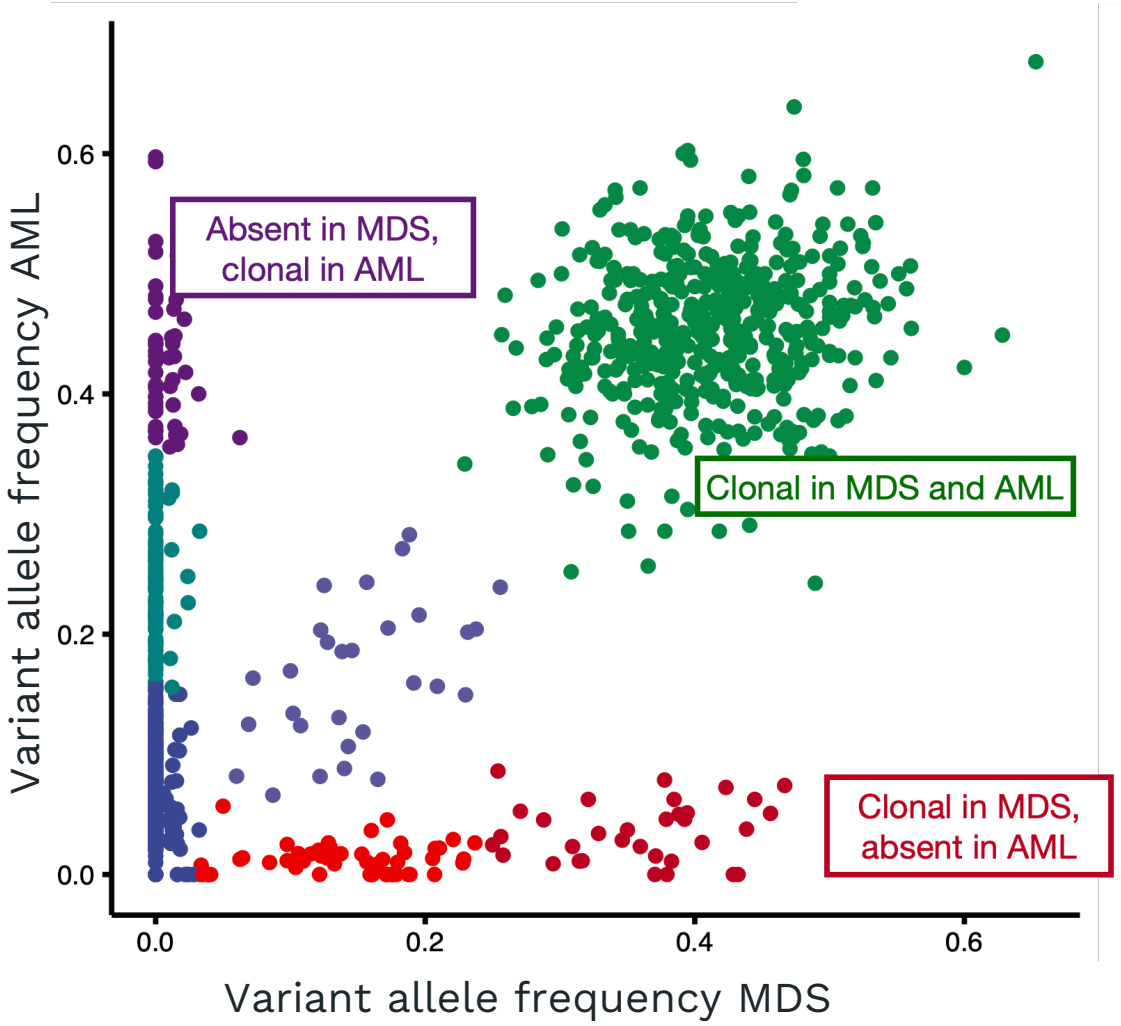
SCIFER: a population-genetics tool to detect selection in a single bulk-whole genome sequencing sample



Körber et al., accepted by Nature Genetics

Example: 82 years-old male, diagnosed with MDS, progression to AML 2 years later





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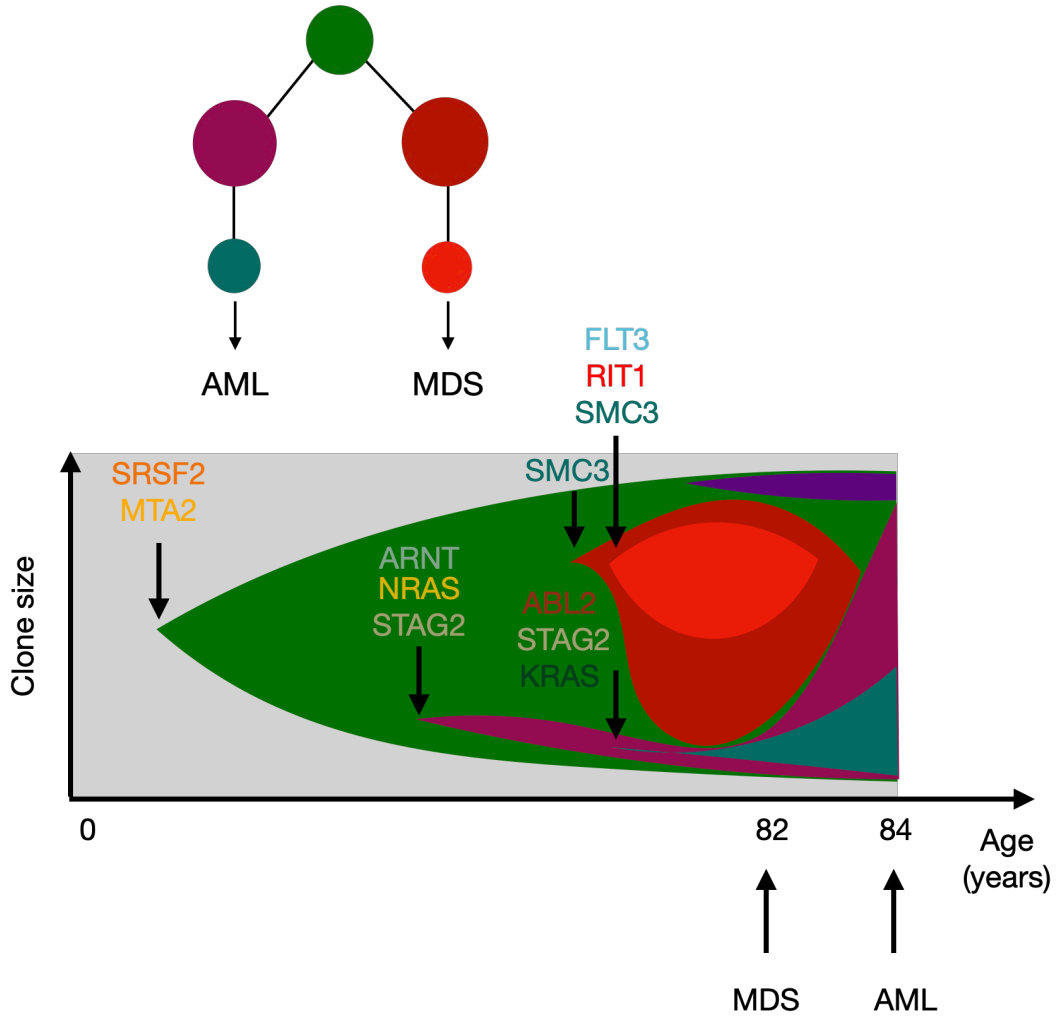

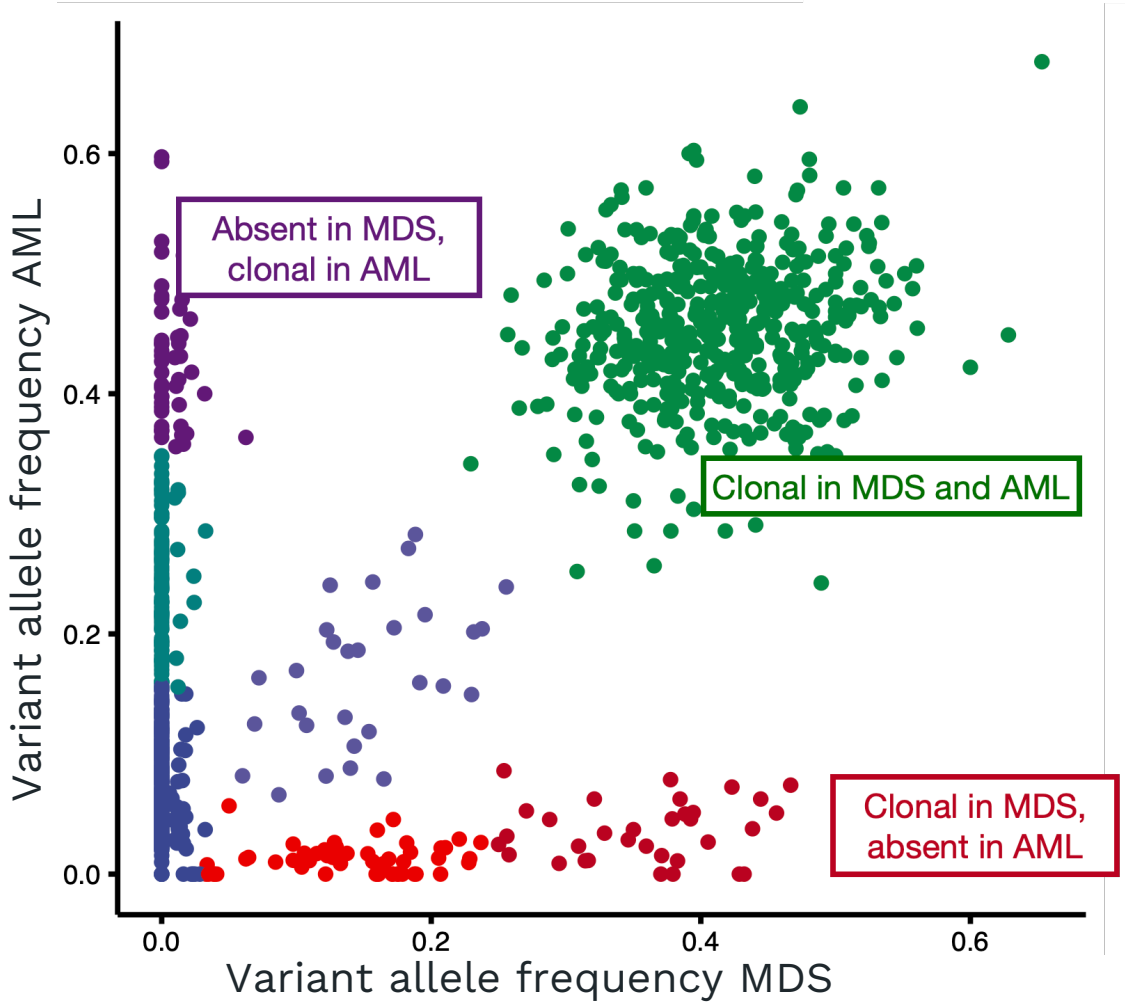

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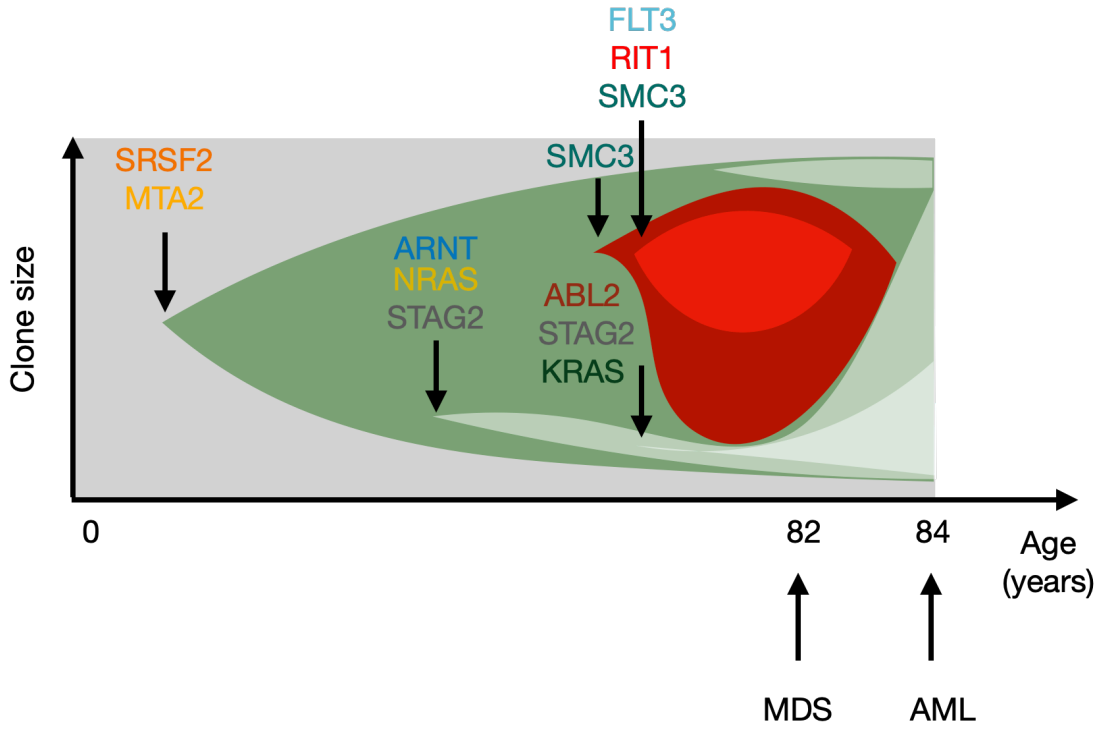

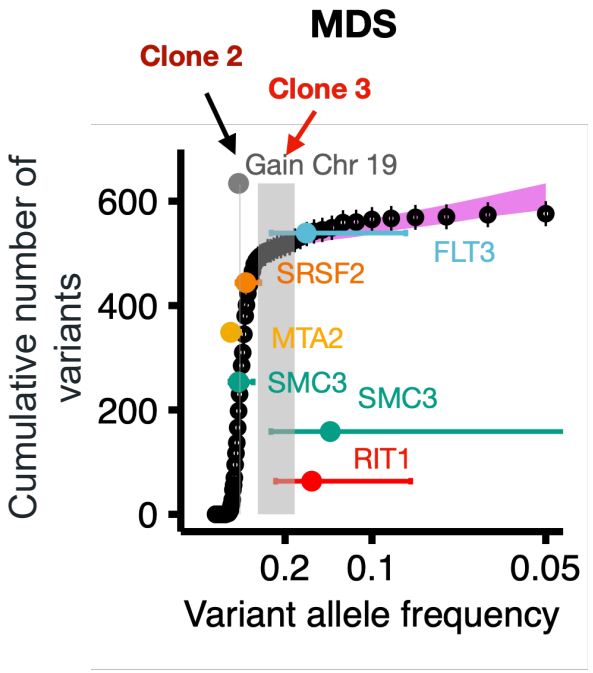

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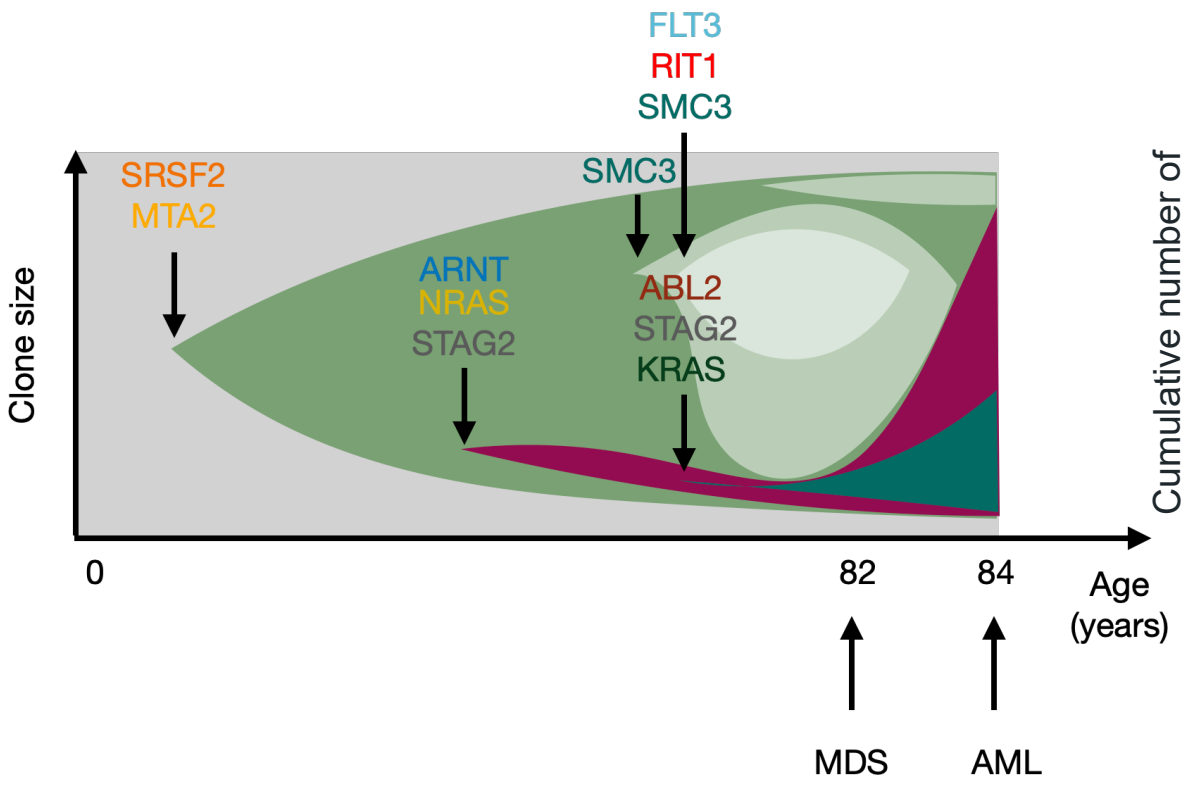
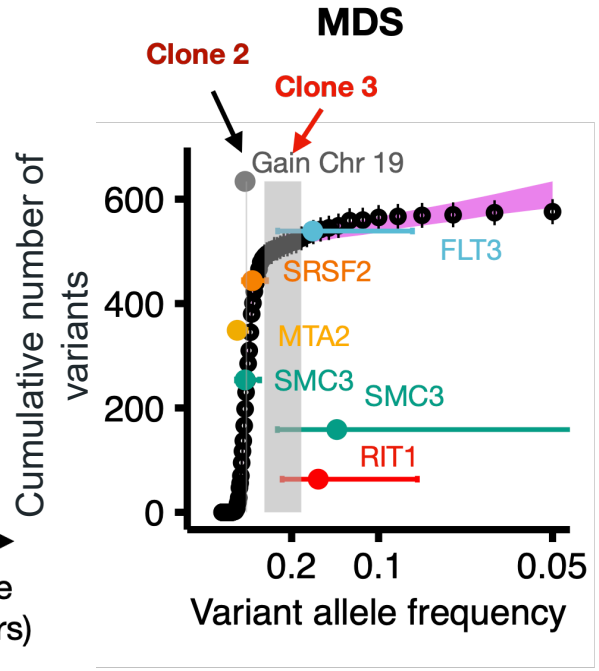
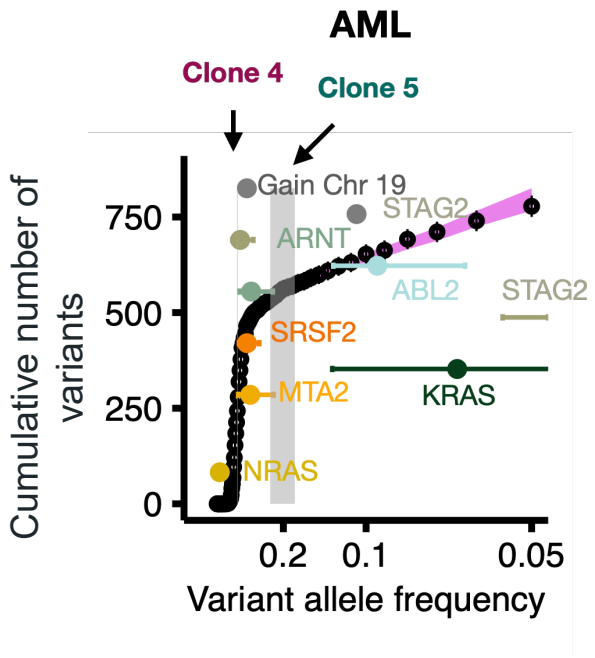
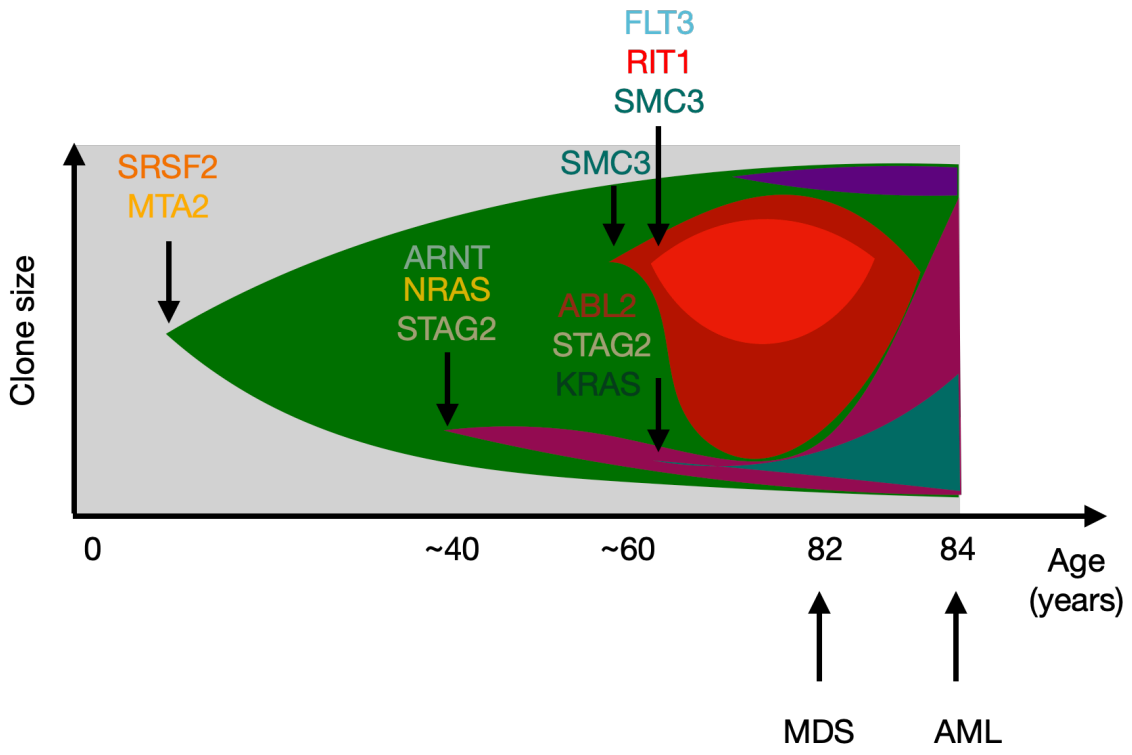
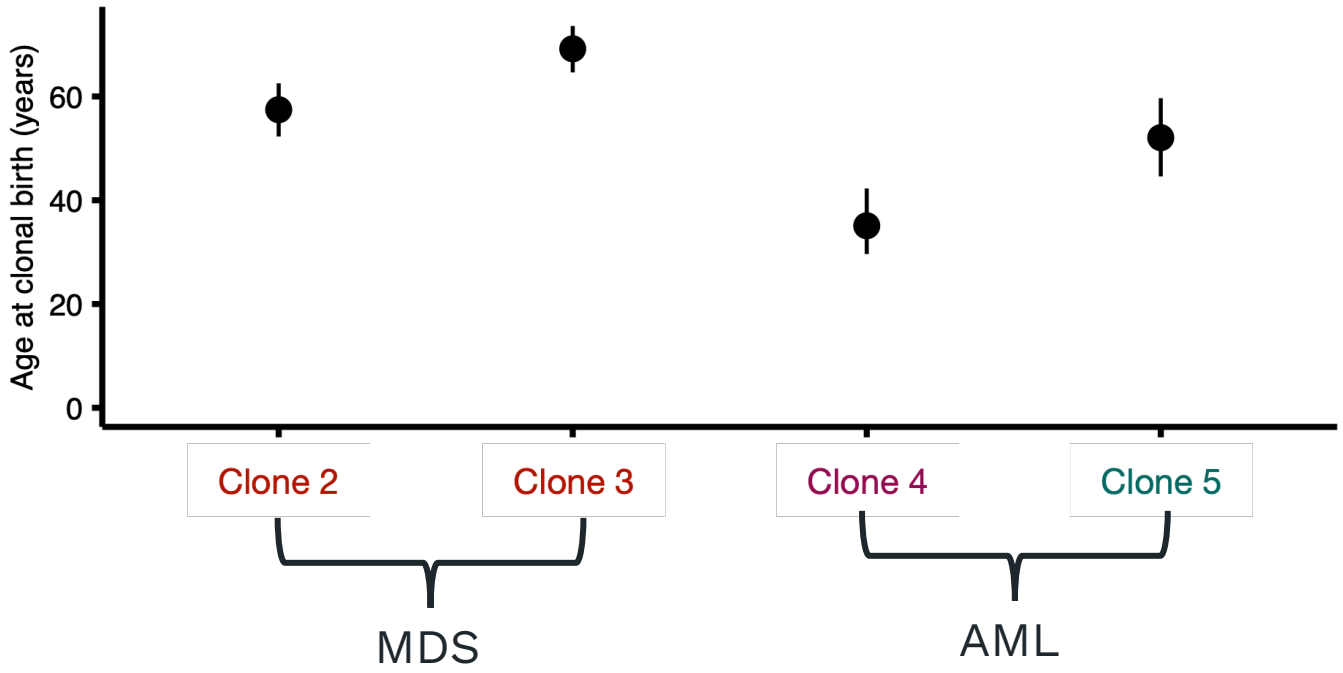






SCIFER infers early acquisition of the leukemic clone but transient replacement by the MDS clone





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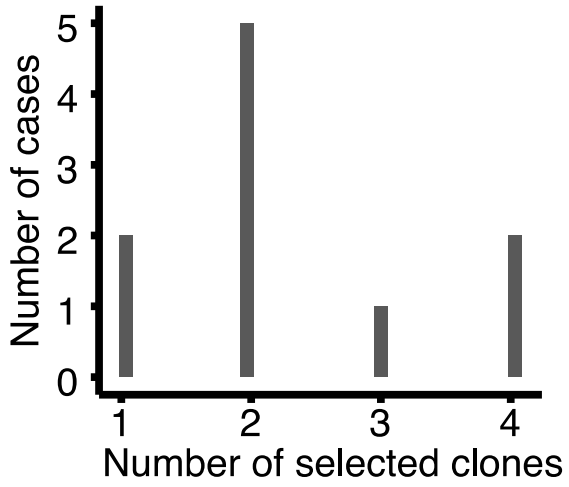
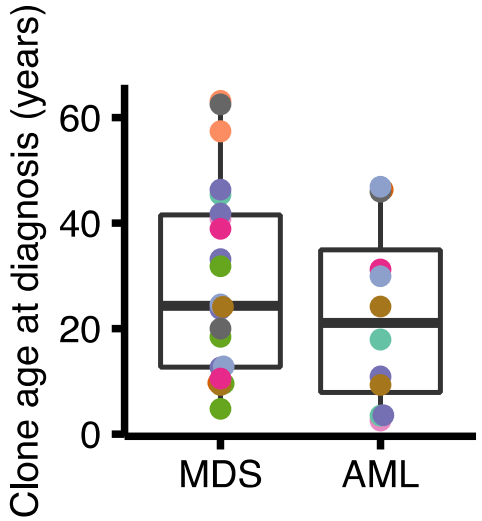
SCIFER infers years to decade-long clonal evolution that accelerates with time

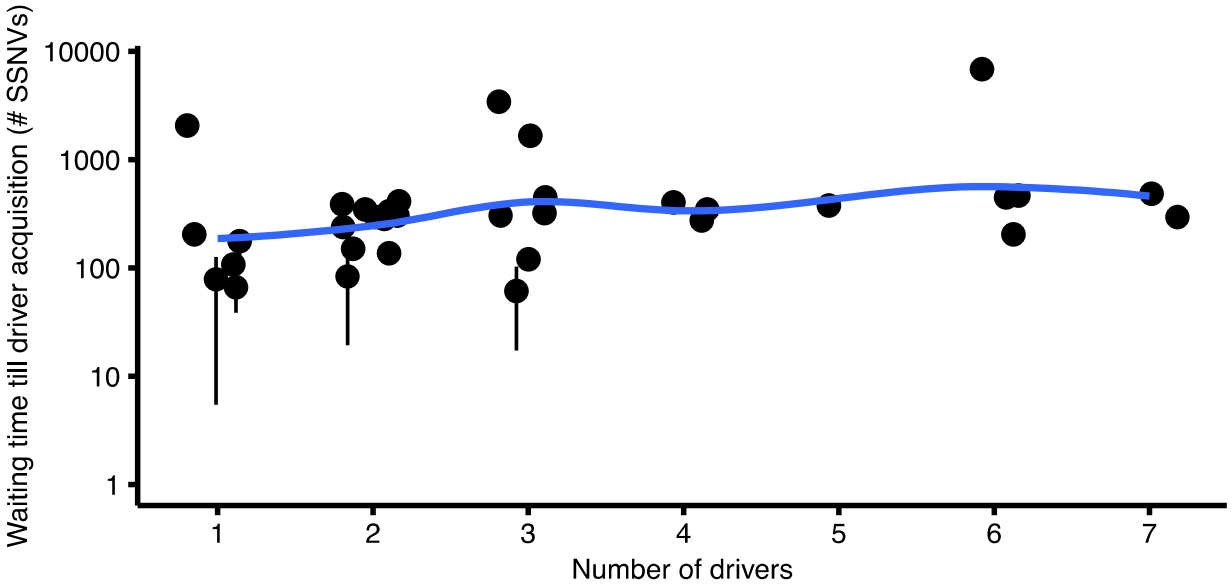
1-4 selected clones per patient



Decade-long clonal age at diagnosis



Accelerated evolution after 1st driver



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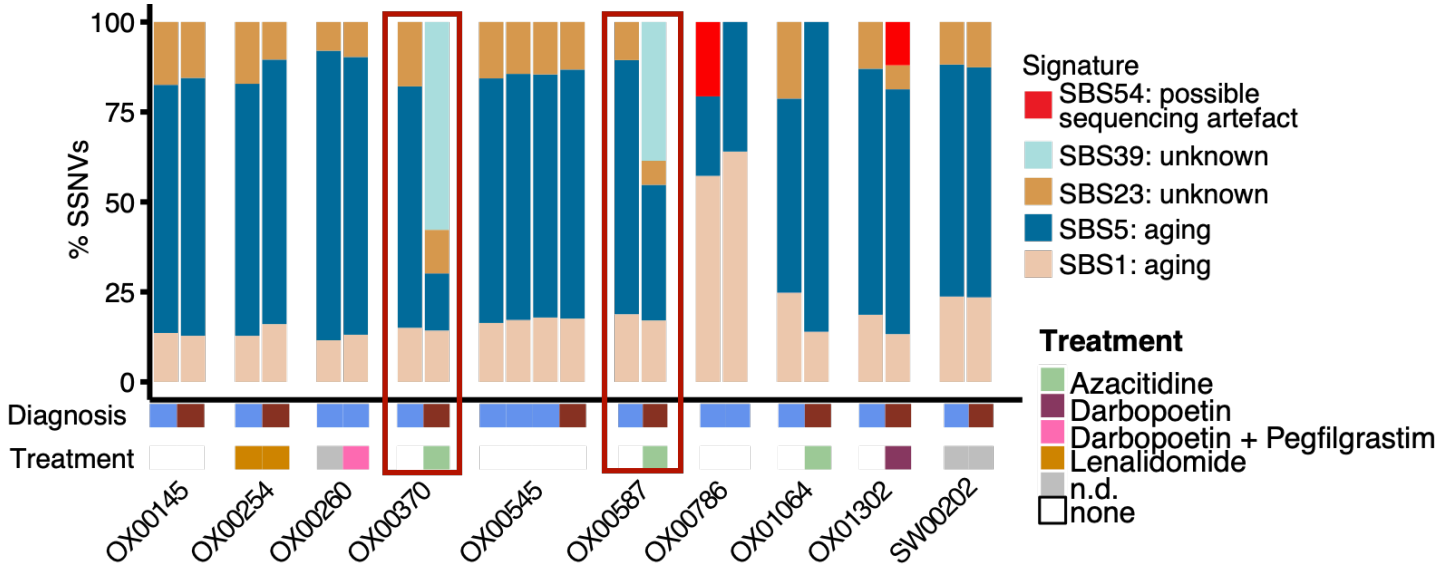
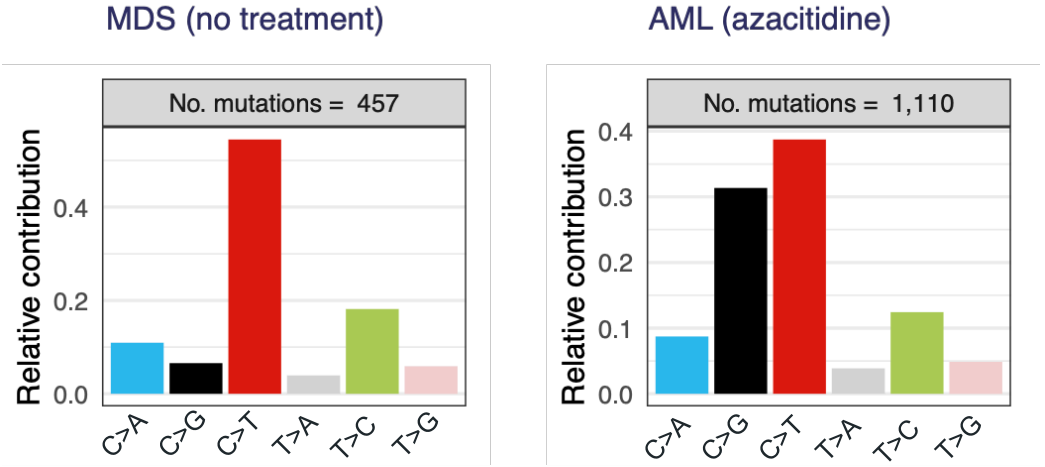
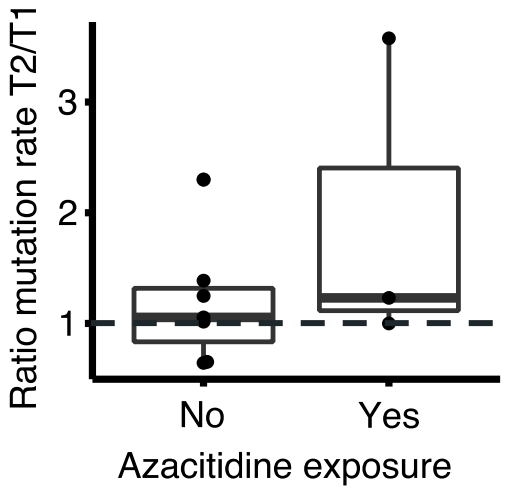
What determines the pace of evolution during progression from MDS to AML?

1. Therapy?
2. Environmental factors?
3. Aging?
4. Different selective forces along the hematopoietic hierarchy?
5. Something else?

Accelerated evolution after Azacitidine exposure







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Summary

- Genetic clones driving MDS and sAML emerge years to decades prior to diagnosis
- Clonal evolution accelerates over the course of the disease
- Azacitidine treatment is associated with characteristic C>G substitutions, suggesting induced mutagenesis

Acknowledgments

Weatherall Institute of Molecular Medicine, Oxford

Paresh Vyas
Sven Turkalj
Felix A. Radtke
Rabea Mecklenbrauck
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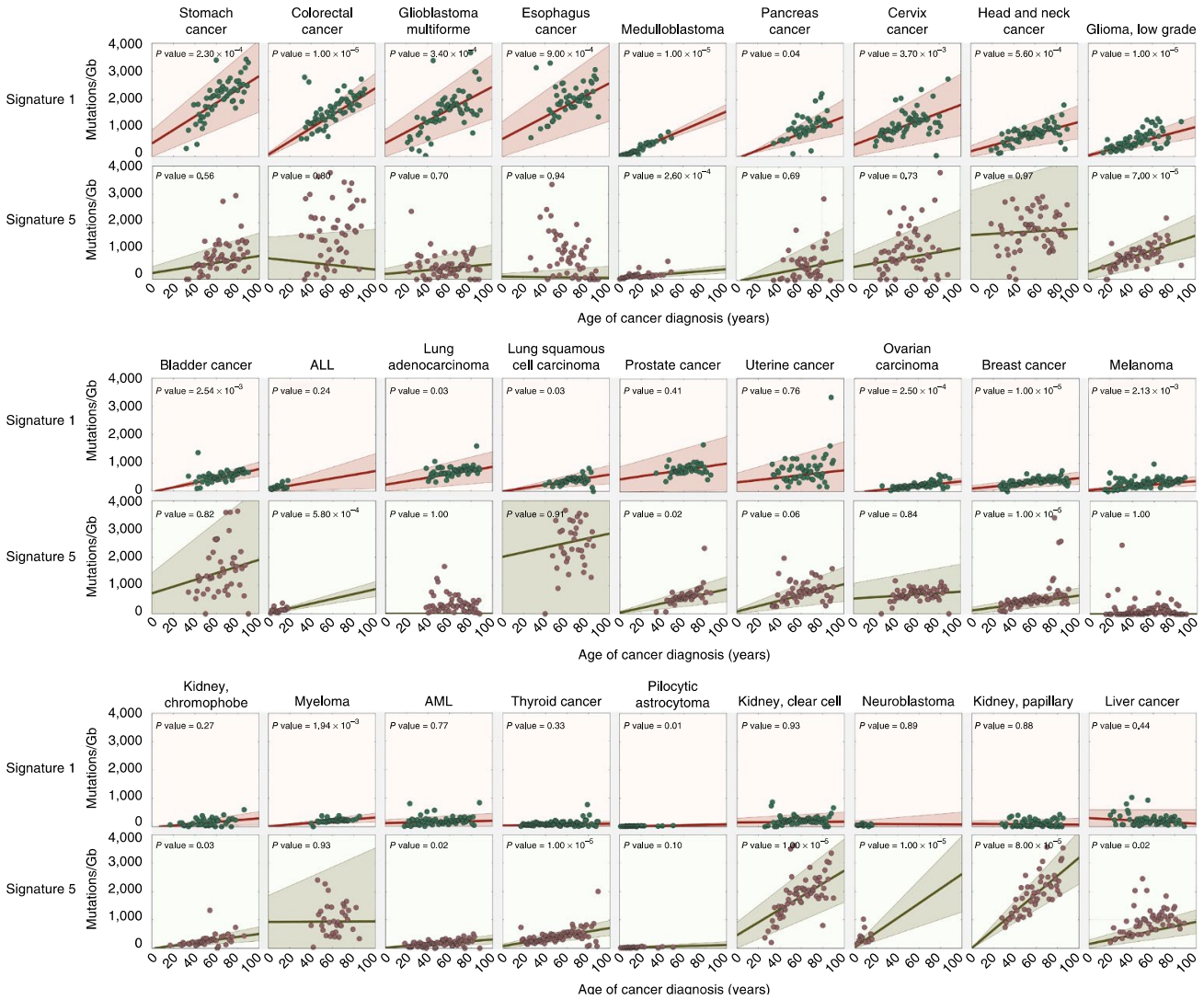
Niels Asger Jakobsen
Marlen Metzner
Batchimeg Usukhbayar

German Cancer Research Center, Heidelberg

Thomas Höfer
Nina Claudino

Patients and their families

Clock-like mutation accumulation in human cancer



Alexandrov et al., Nature, 2015

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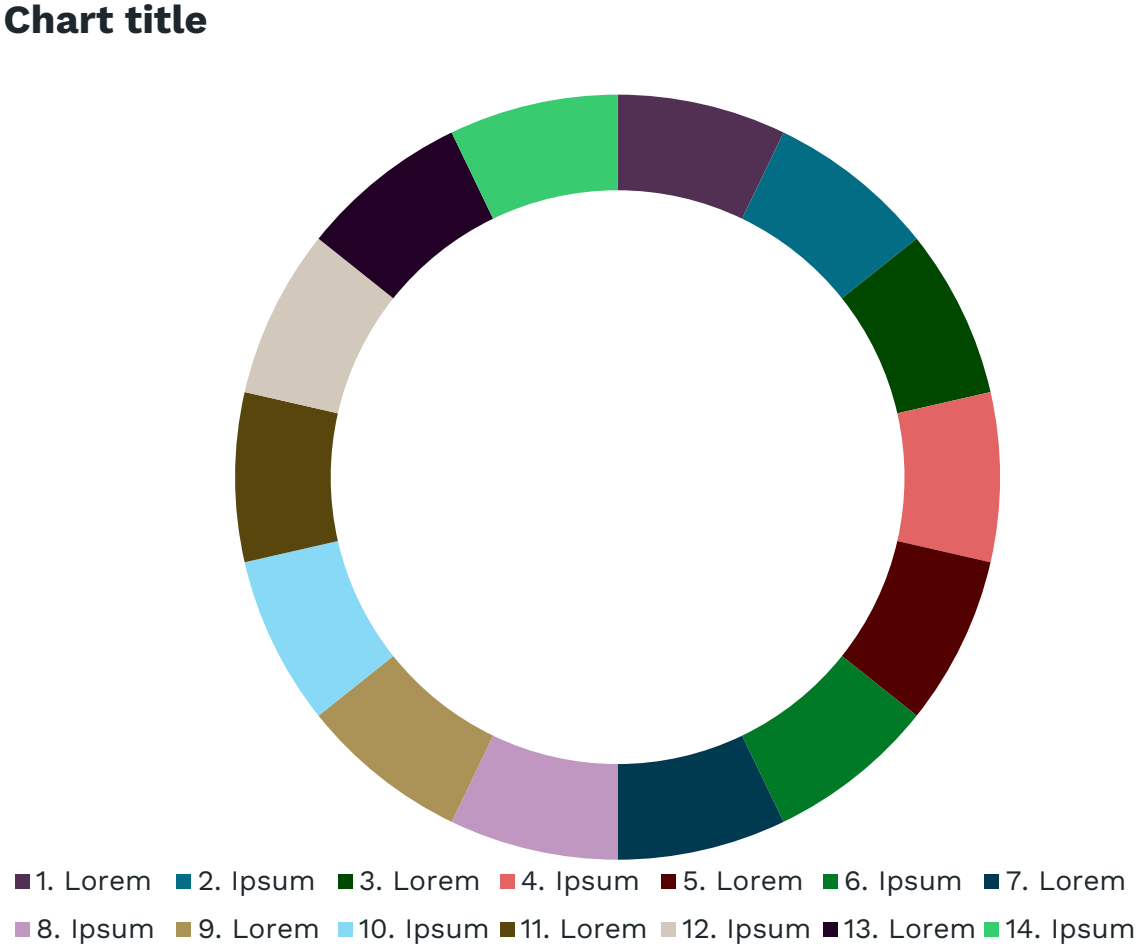

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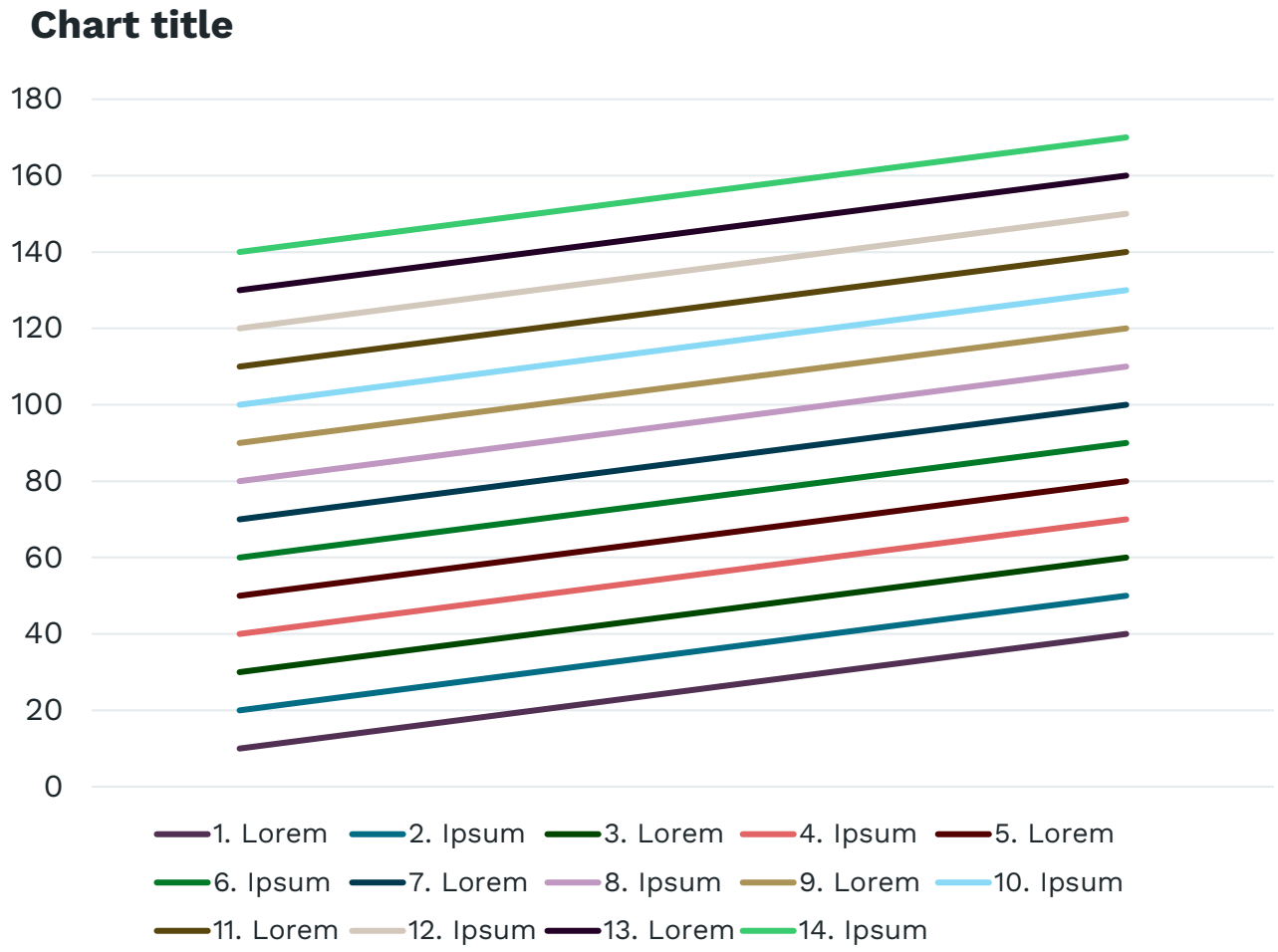

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