Mutational Landscape of Therapy-related versus Other Secondary Leukemias

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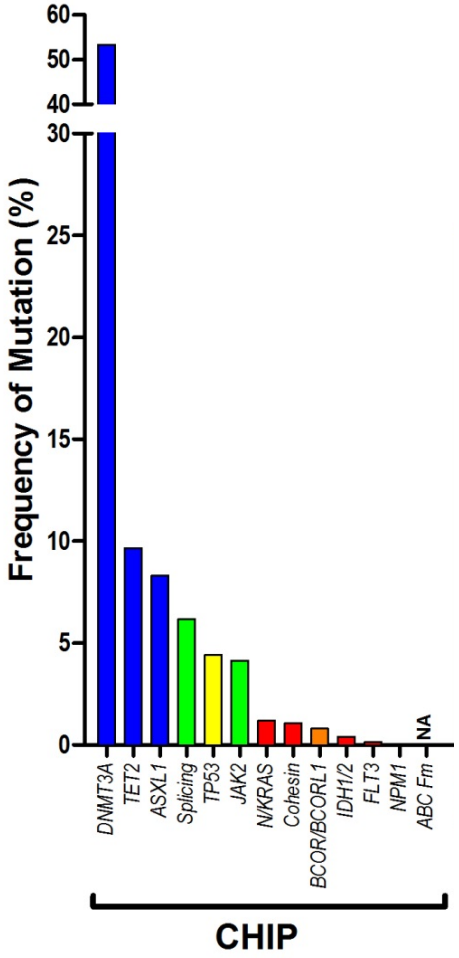
Mutational Landscape of Myeloid Diseases

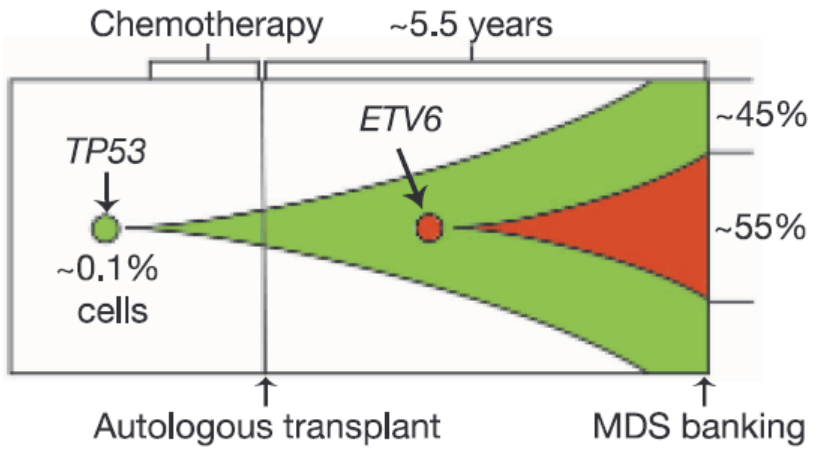


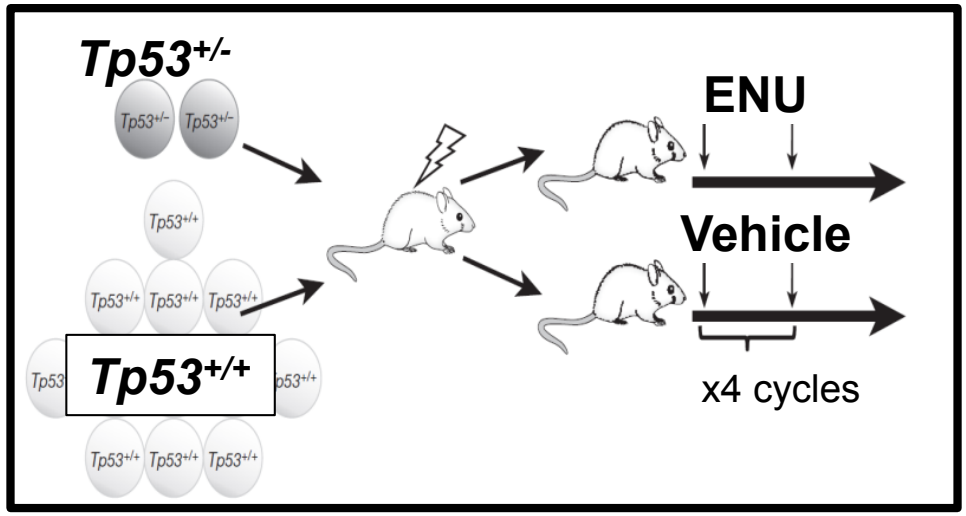
DNMT3A
TET2
ASXL1
Splicing
TP53
JAK2
N/KRAS
Cohesin
BCOR/BCORL1
IDH1/2

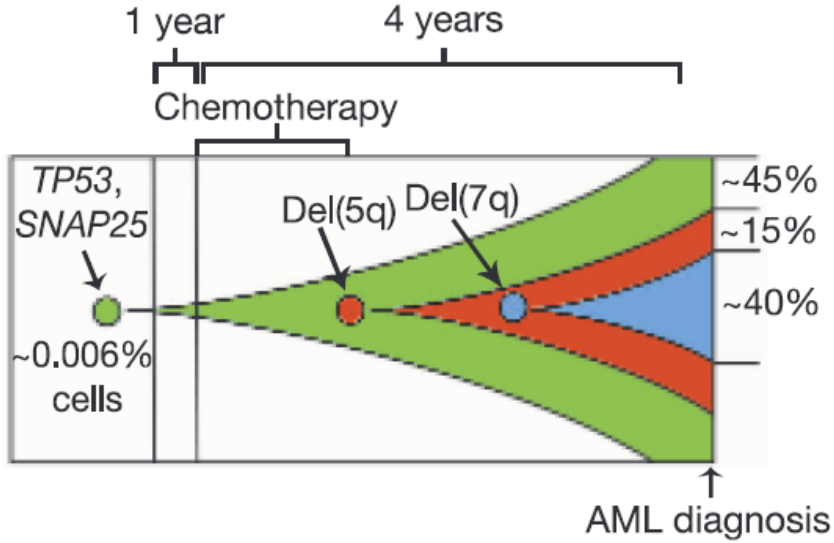
Link & Walter, *Leukemia,* 2016

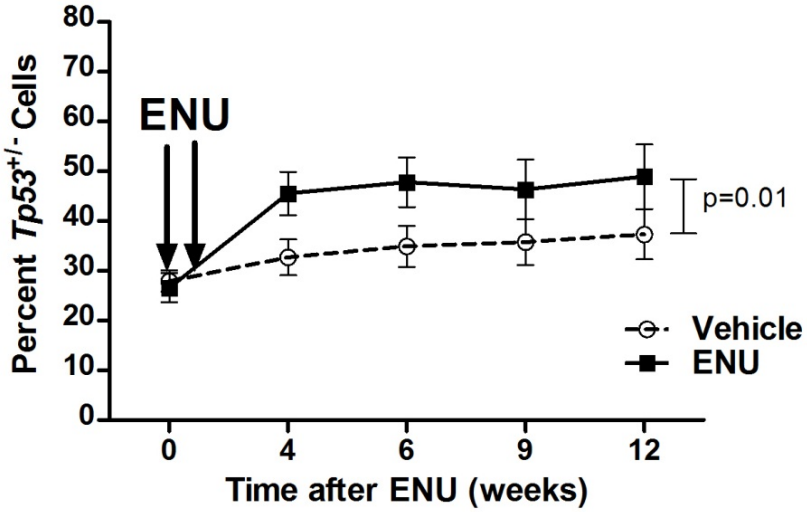
Jaiswal, *NEJM*, 2014; TCGA, *NEJM*, 2013; Wong, *Nature,* 2015; Lindsley, *Blood,* 2015; Papaemmanuil, *Blood*, 2013

TP53 Mutations can Pre-Exist in t-MN



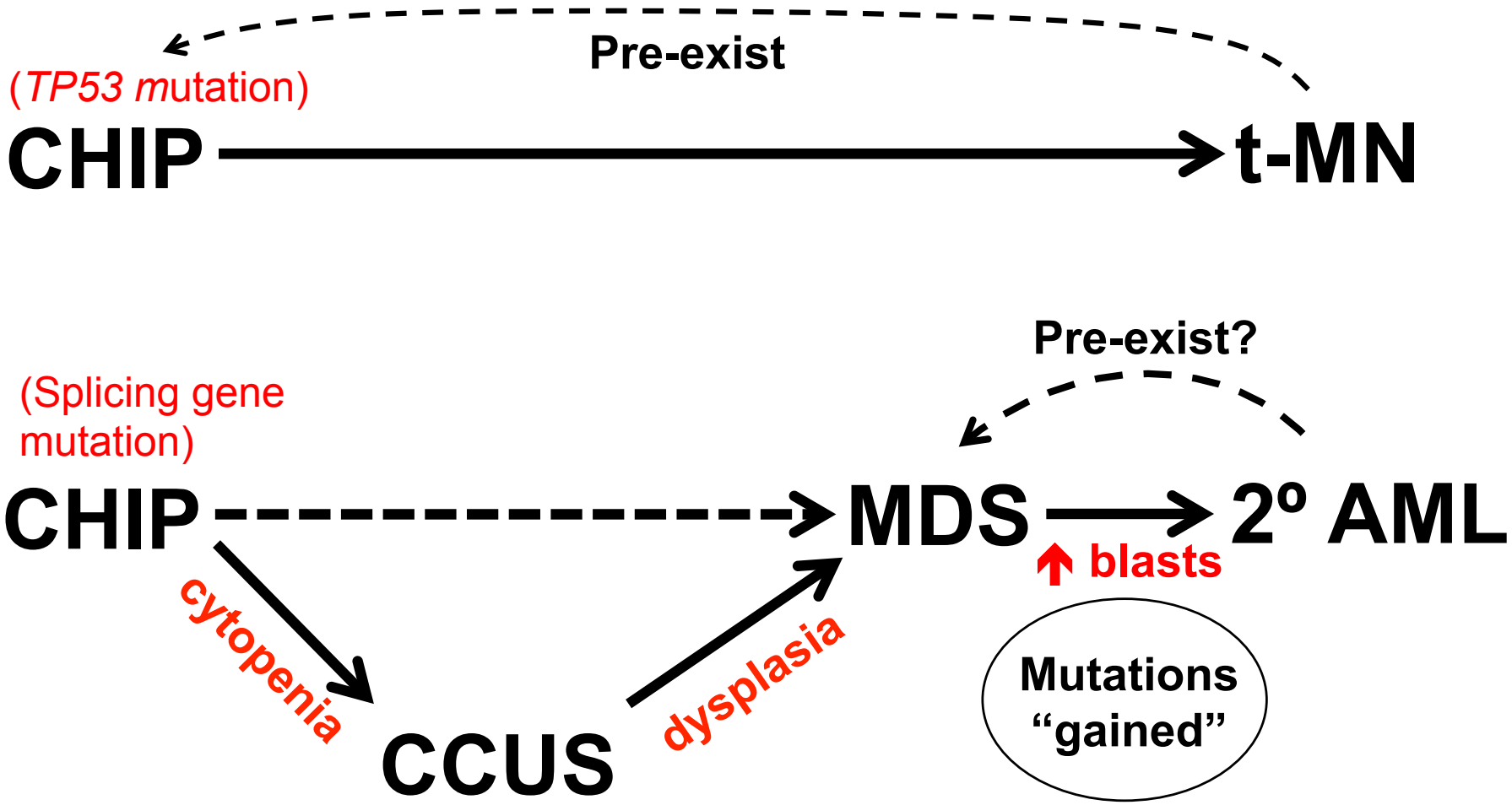






Wong, *Nature,* 2015

Disease Progression Model

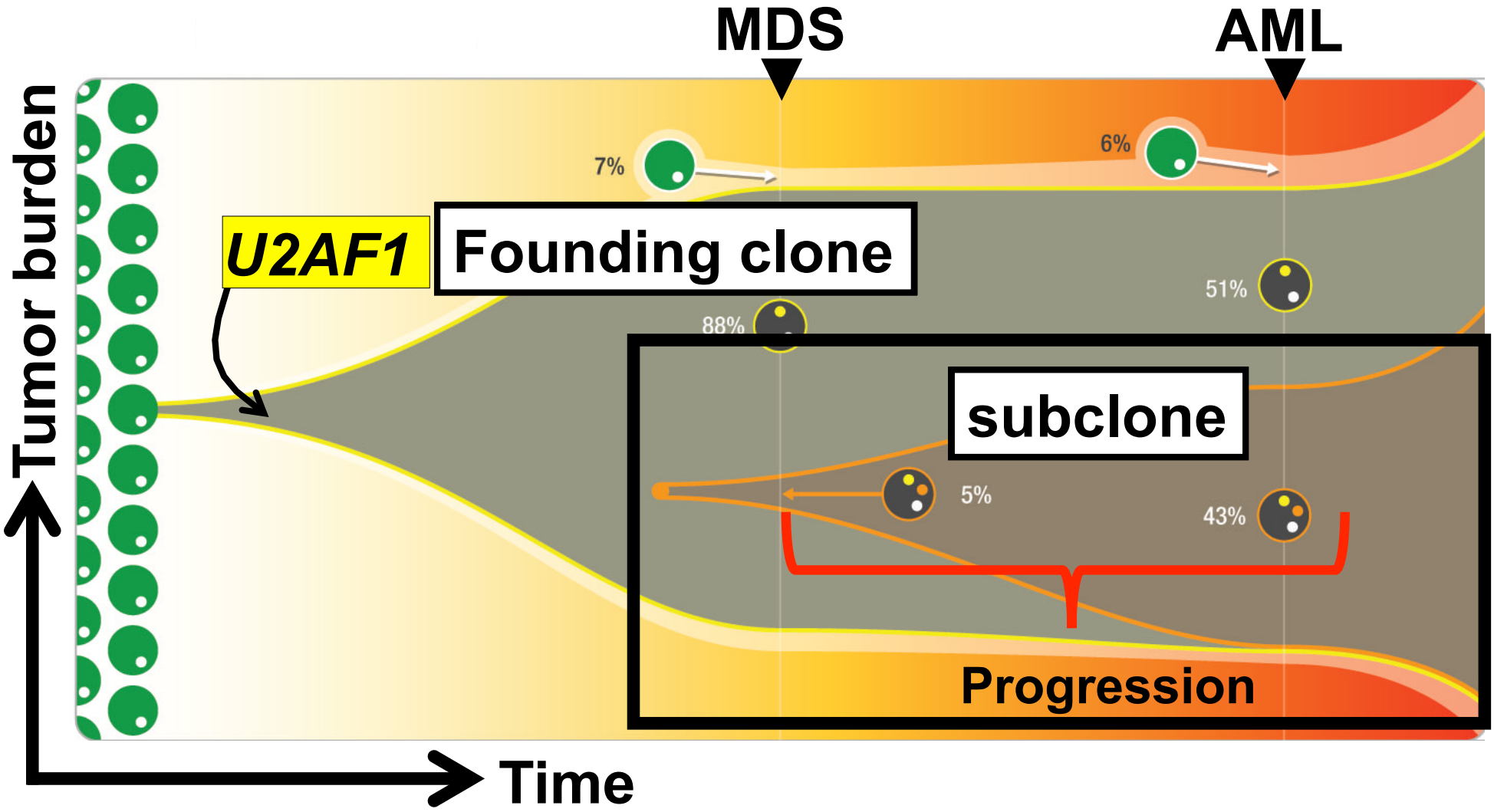


Gene Mutations "Gained" at Progression to 2º AML

	Lindsley, *Blood*, 2015	Walter, *NEJM*, 2012; *Leukemia*, 2013
MDS/2°AML pairs	17	8
2°AML with new mutations	10	4
Genes mutated	*N/KRAS (5), RUNX1 (3), CEBPA (3), NPM1 (2), FLT3/NF1/TET2/IDH2/ RAD21 (1* each)	*RUNX1, PTPN11, WT1* (1 each)
Gene category	signal transduction & transcription factors	2 patients without new coding recurrently mutated genes

Do these "gained" mutations (i.e., subclones) pre-exist in MDS?

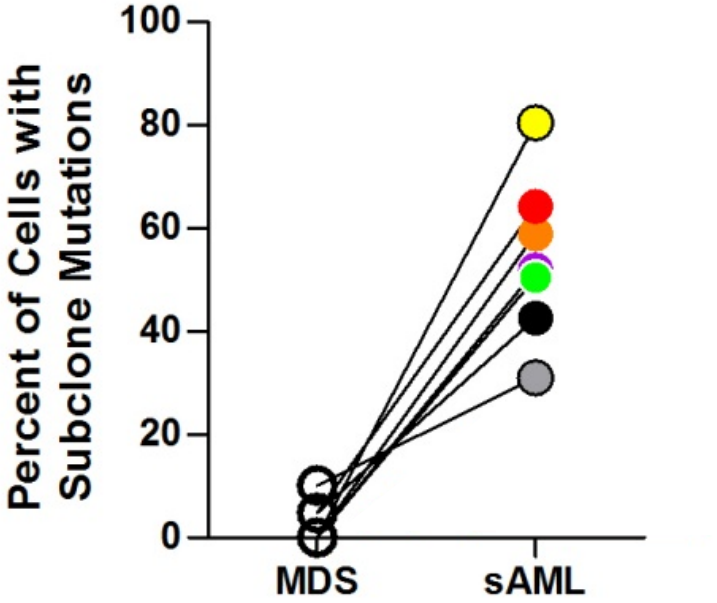
Clonal Evolution Model: Founding Clone and Subclone



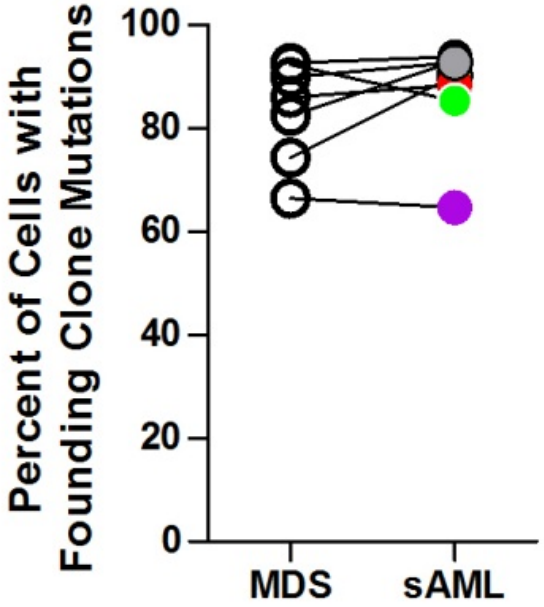
Walter, *NEJM,* 2012

A Subclone(s) Expands in 2° AML & the Founding Clone Persists

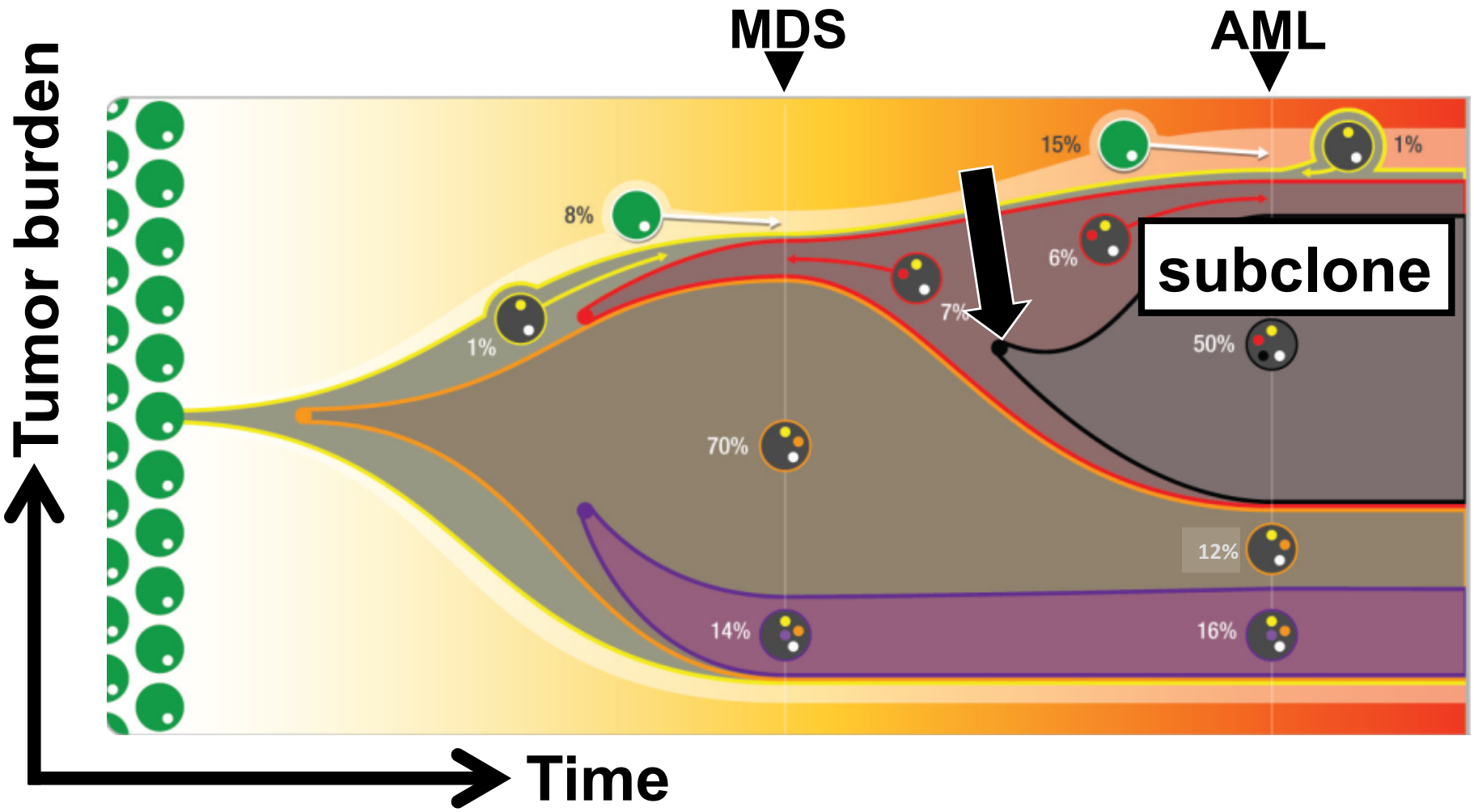
Subclones



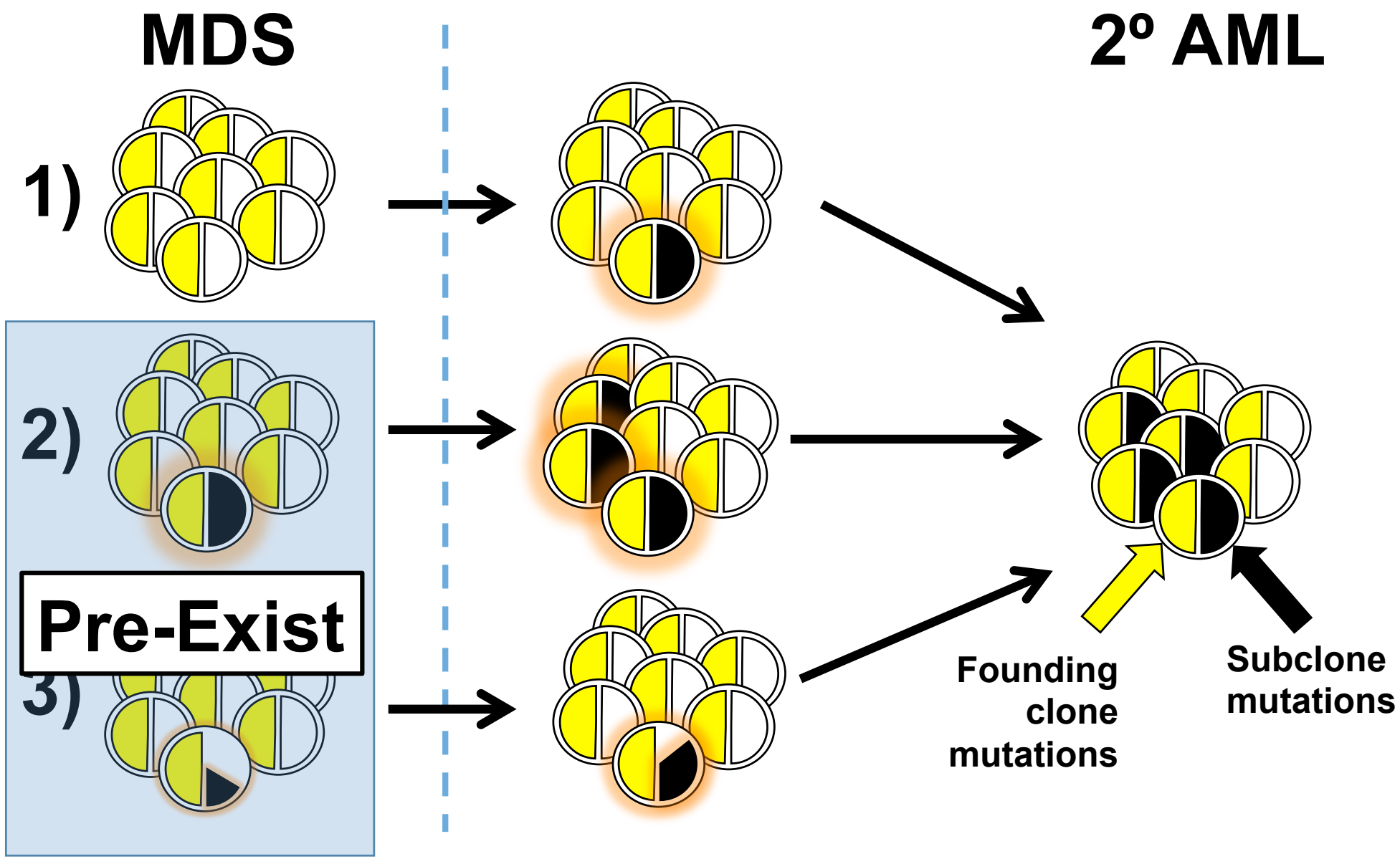
Founding Clone



Do “2º AML-specific” subclones pre-exist in MDS?

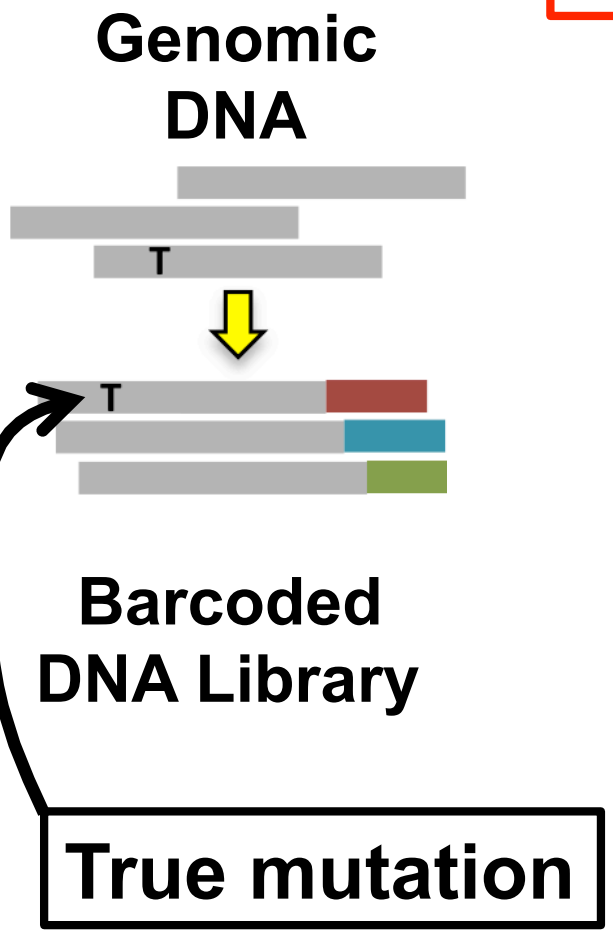


3 Models:


MDS
2º AML
1)
2)
Pre-Exist
3)
Founding clone mutations
Subclone mutations

Molecular Barcodes

PCR & sequencing errors

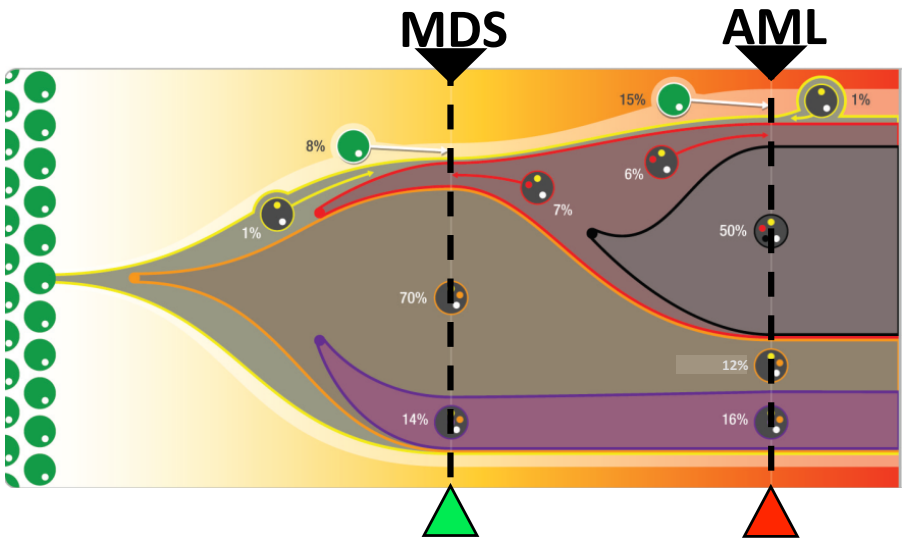


VAF, Variant Allele Fraction

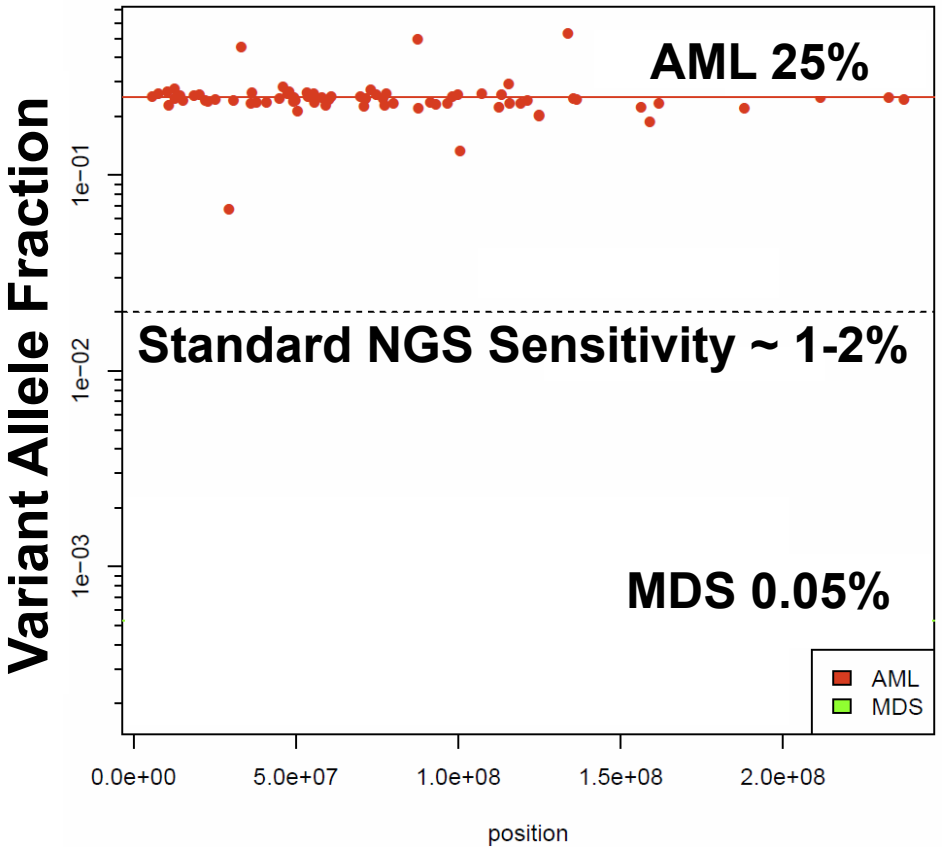
Kinde, *PNAS*, 2011; Schmitt, *PNAS,* 2012

Rare Subclones can Pre-exist in MDS

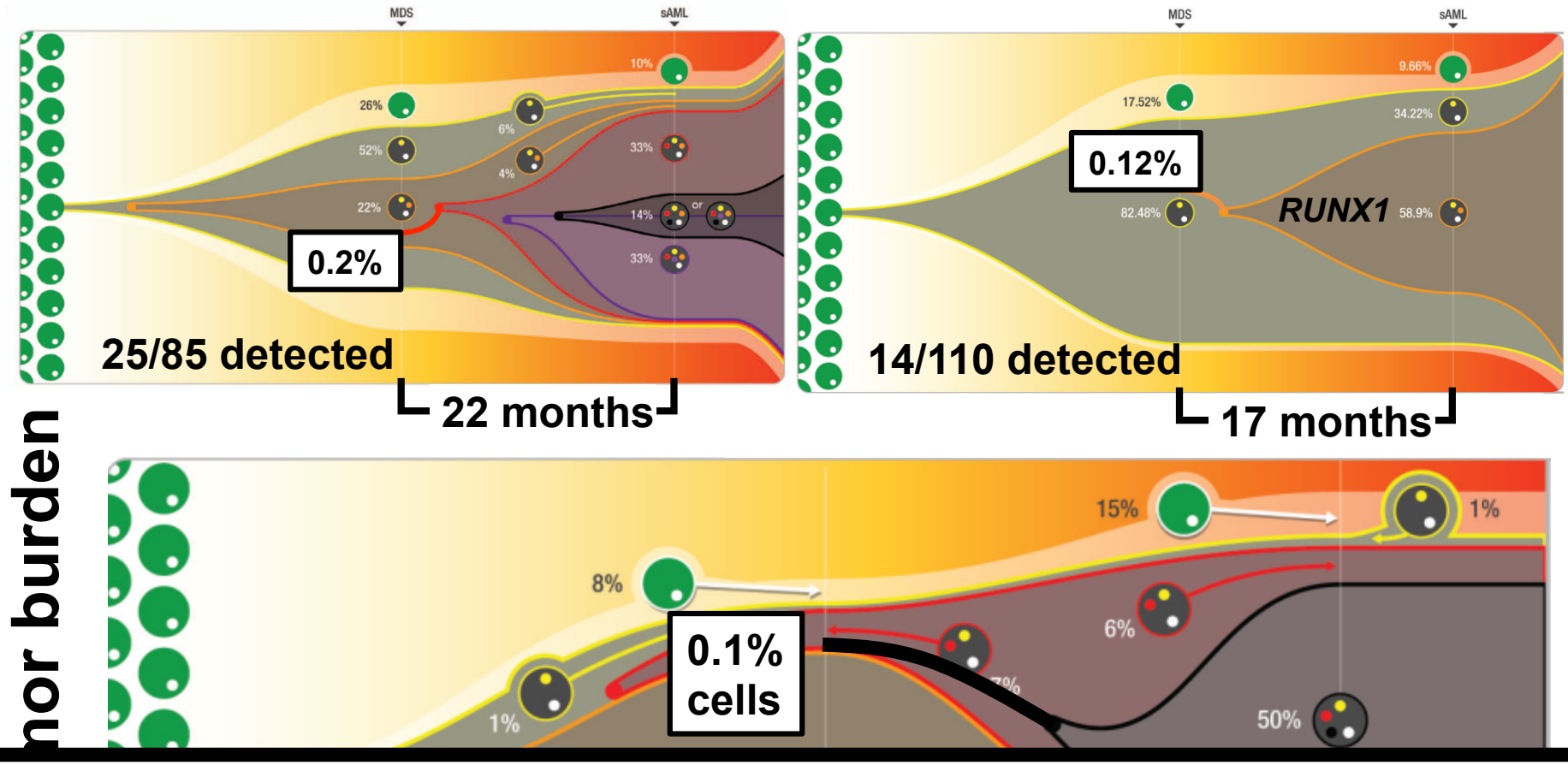
"Standard" next-gen sequencing



Molecular barcode sequencing

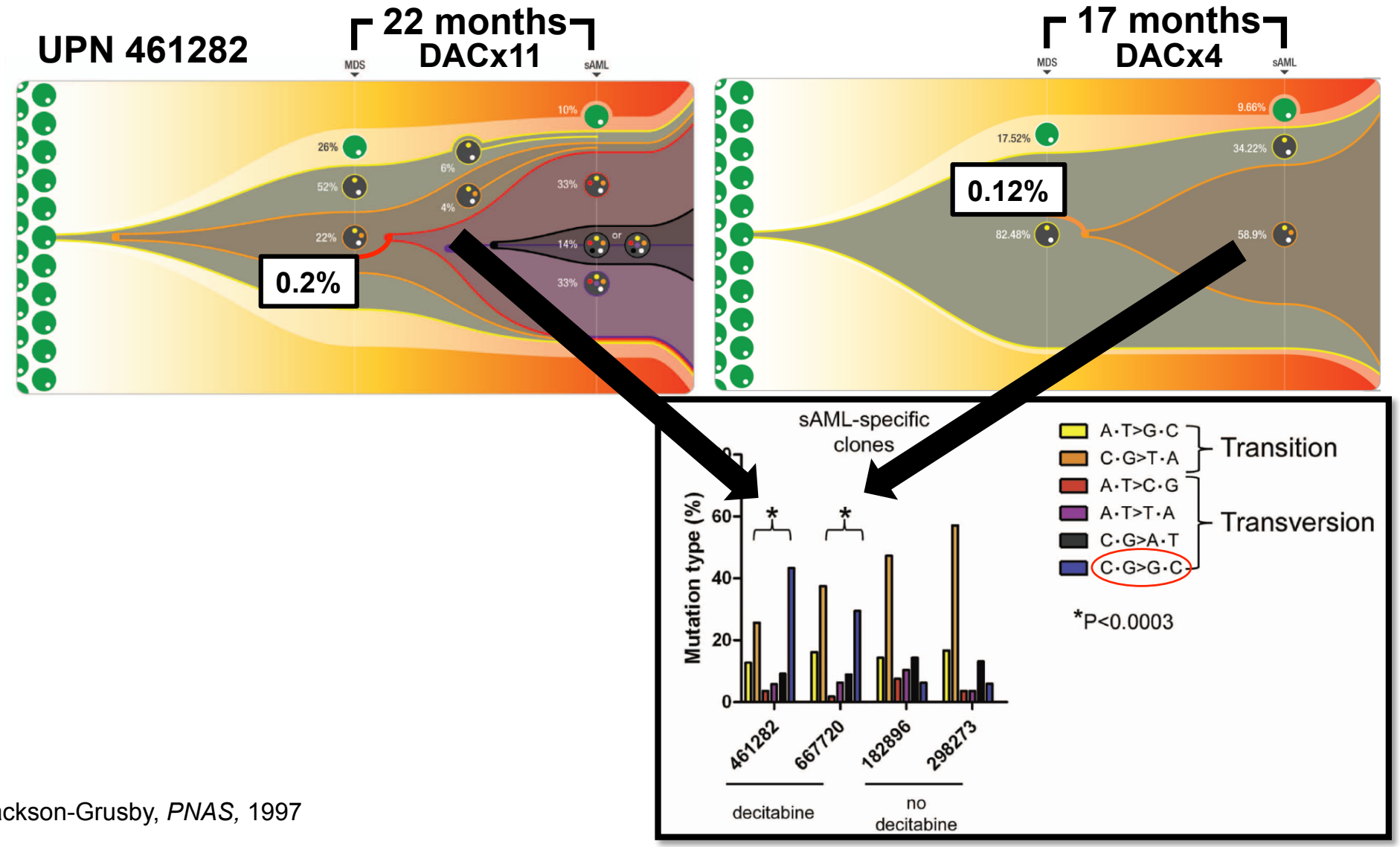


15/80 subclone mutations detected at MDS

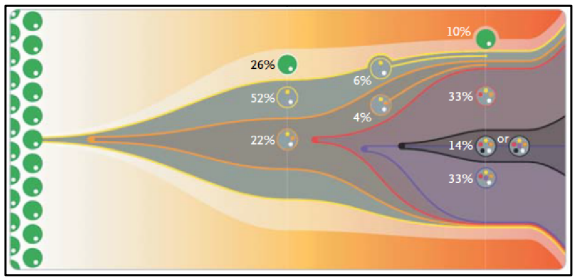


Why do only a subset of subclone mutations pre-exist in MDS?

Decitabine Induces Mutations



Jackson-Grusby, *PNAS,* 1997



UPN 461282

Clone 3 (VAF 40%)

Clone 4 (VAF 24%)

Clone 5 (VAF 7%)

VAF(%)

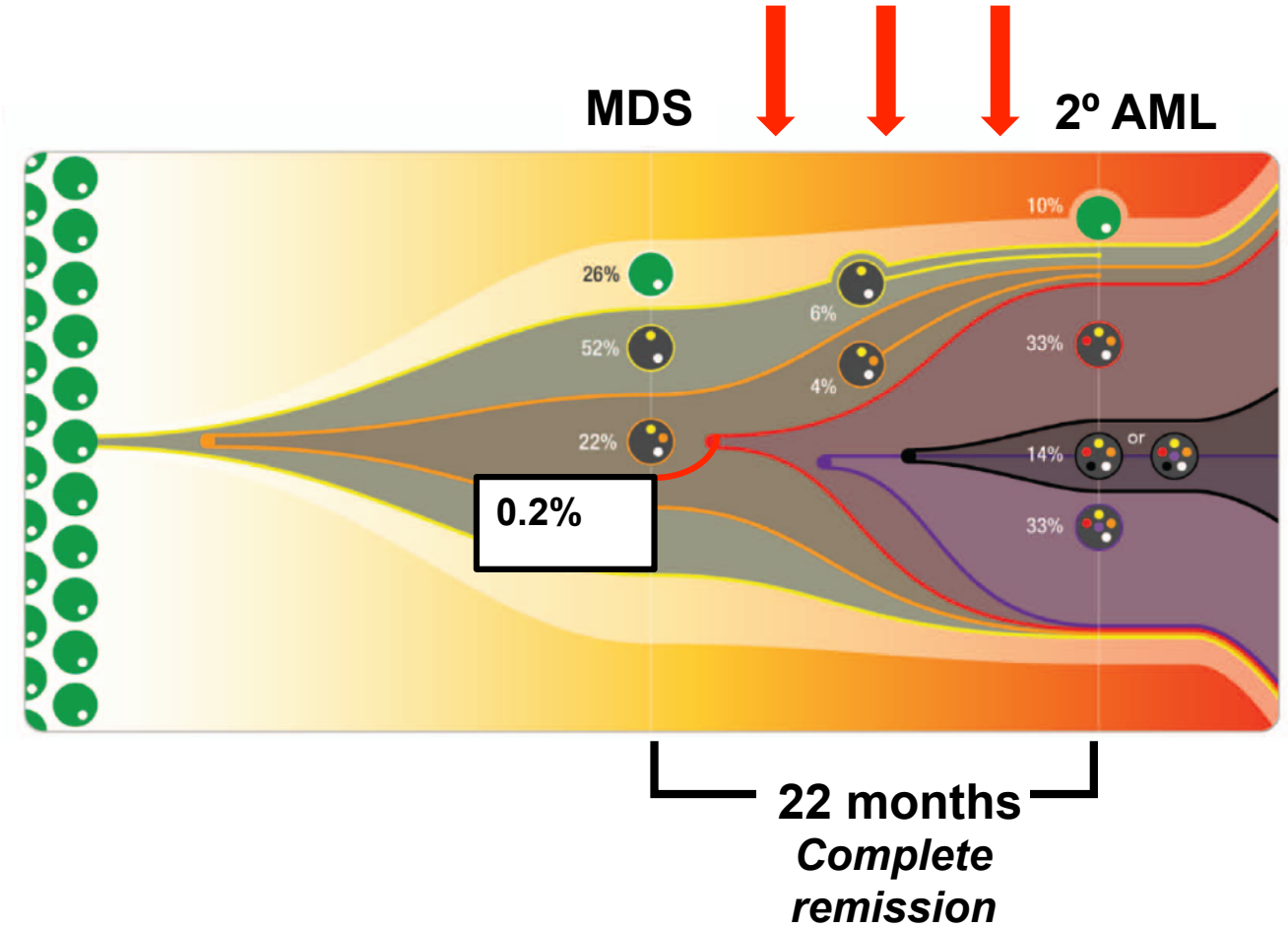
100
50
40
30
20
10
0.3
0.2
0.1
0.05

0
20
40
60
80

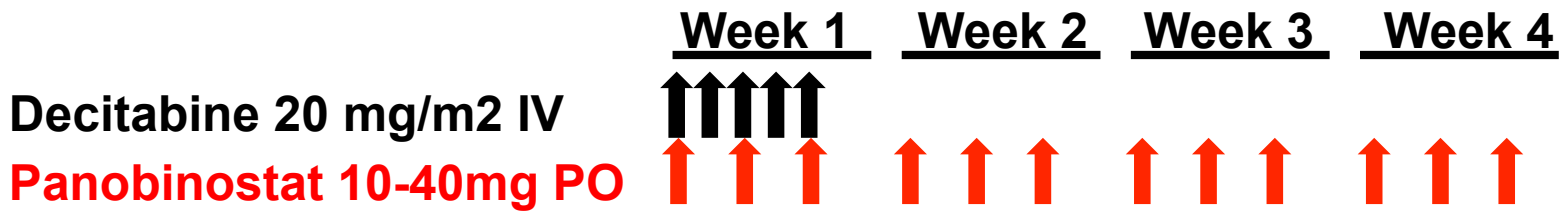
AML
MDS

A->G
A->T
A->C
C->A
C->T
C->G
none

What happens to clones during treatment?

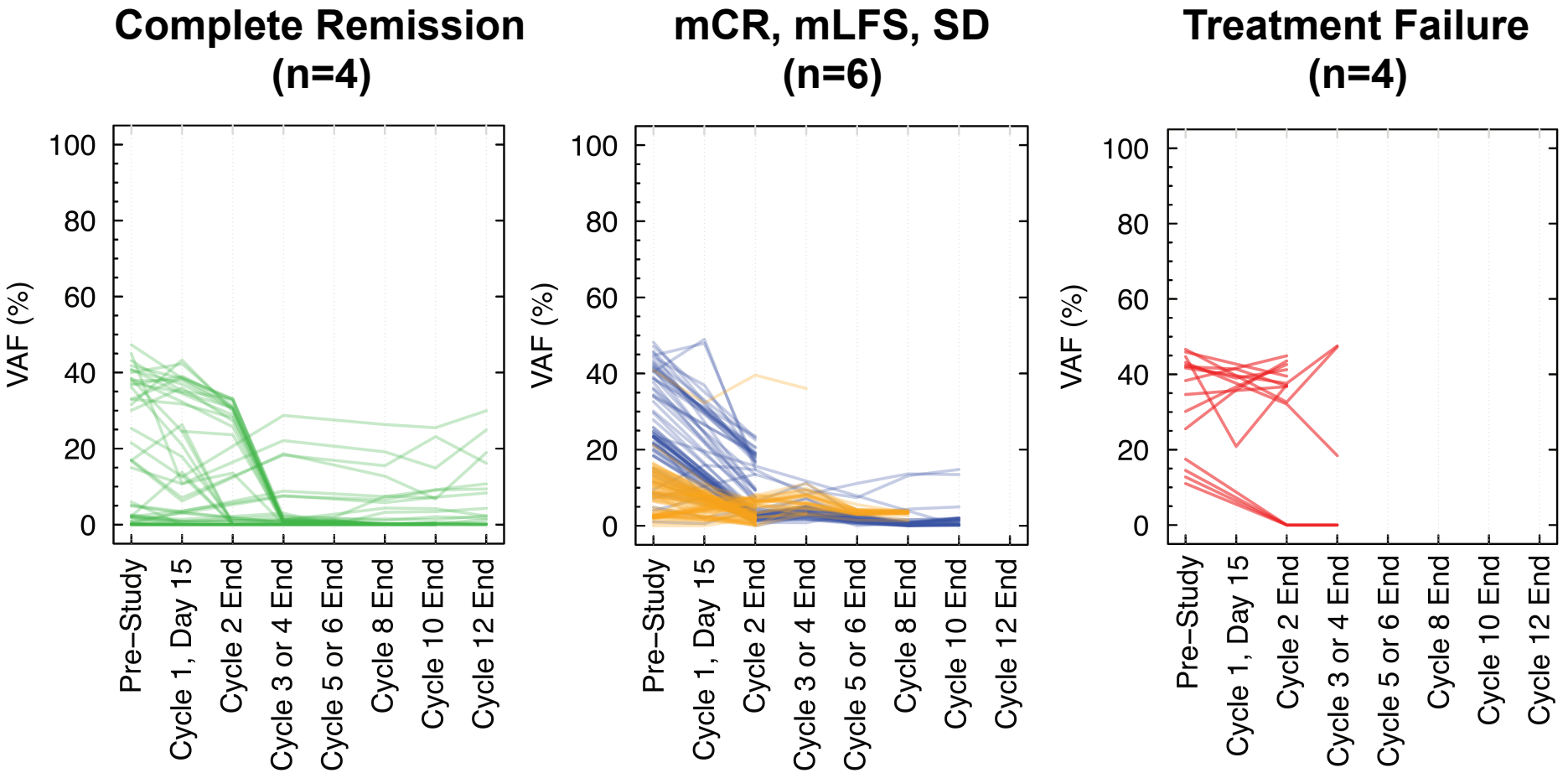


Phase I/II Panobinostat+Decitabine (AML, high-risk MDS, age≥60)



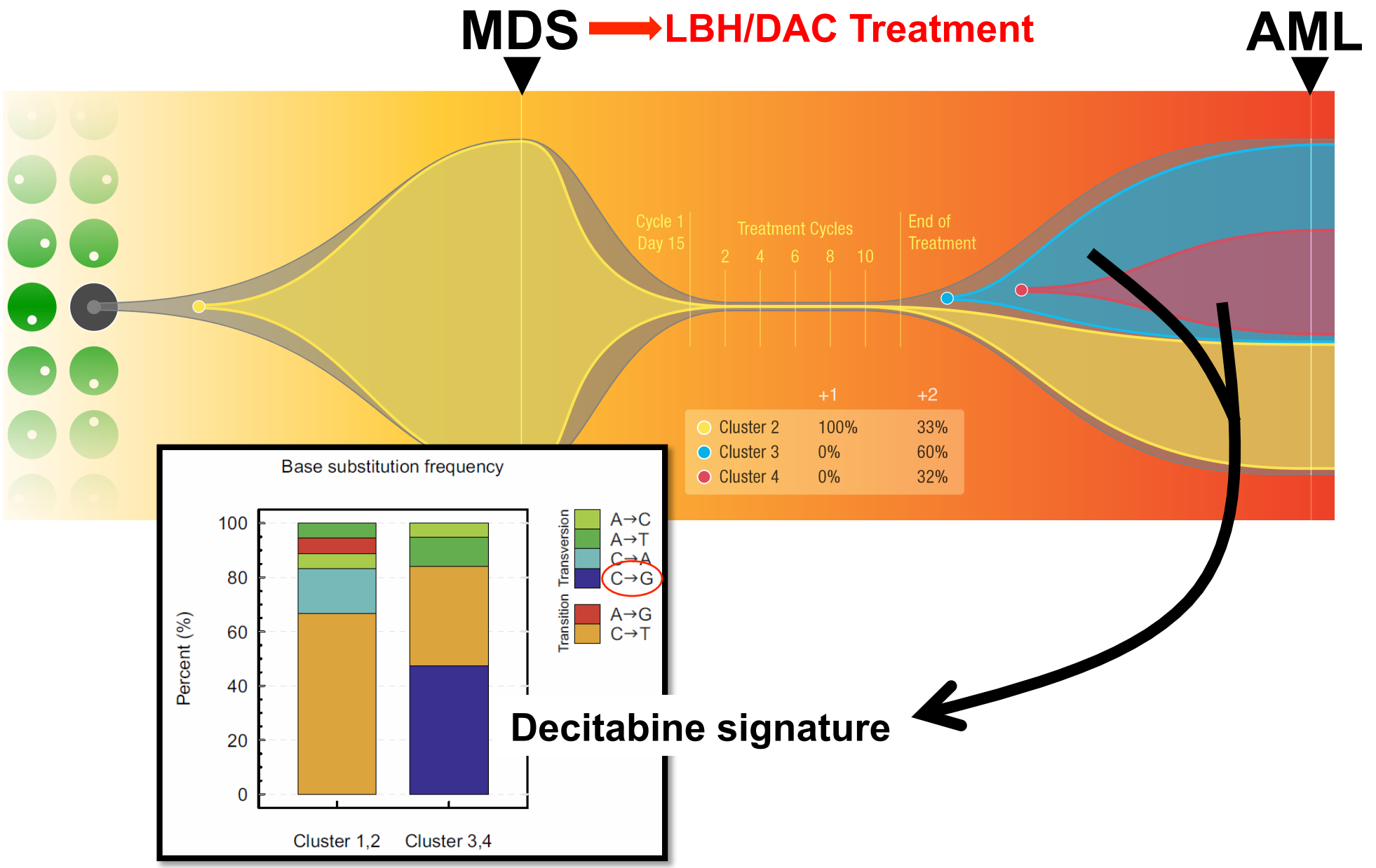
- **52 patients enrolled** (median 2 cycles, range 1-12)
- **Bone marrow**: pre-study, cycles 2, 4, 6, 8, 10, 12
- **25 patients sequenced** (284 genes, standard NGS)
  - **Subset exome sequenced**
  - **Subset barcode sequenced**

Tracking VAFs in Serial Samples



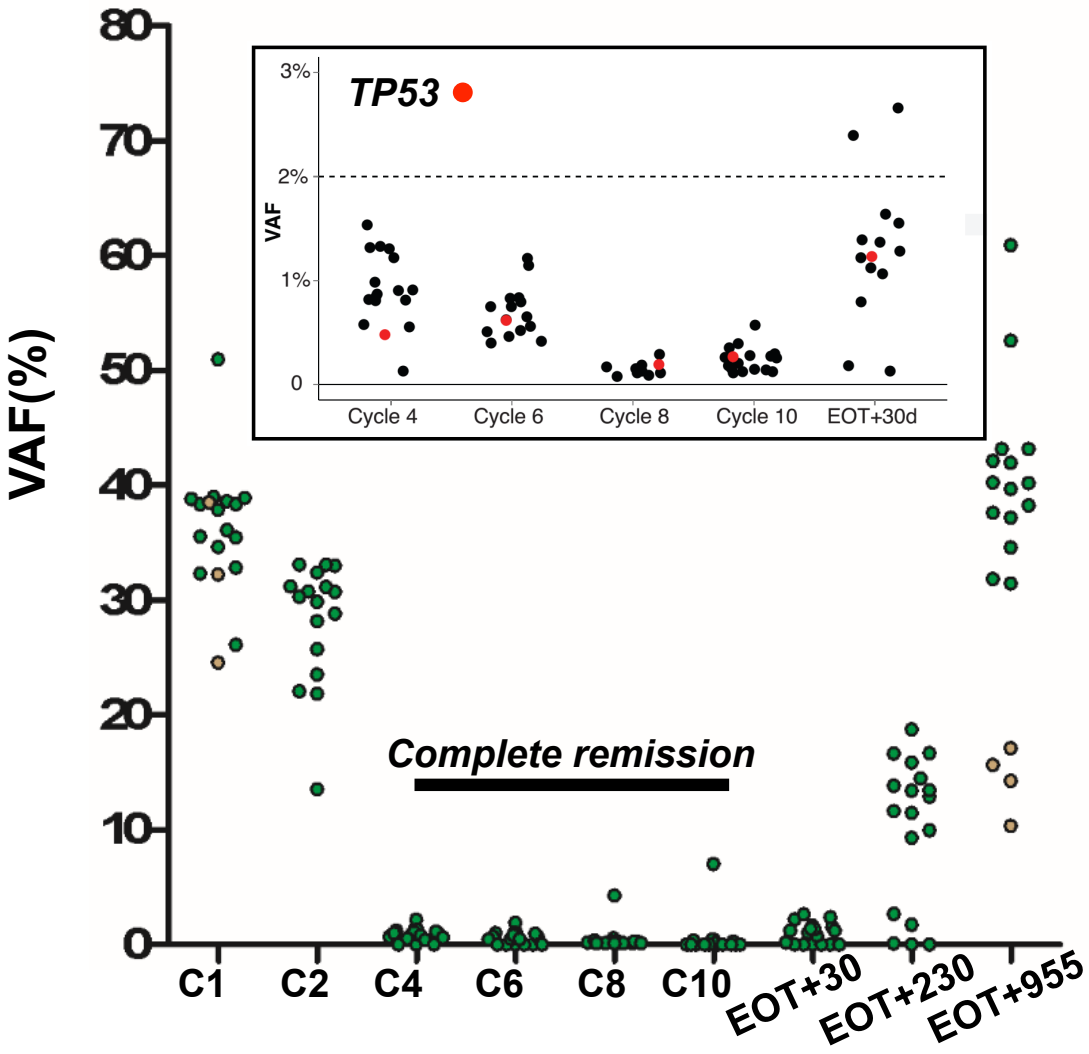
Uy, *Leukemia,* in press

Clonal Evolution: MDS in CR→2ºAML

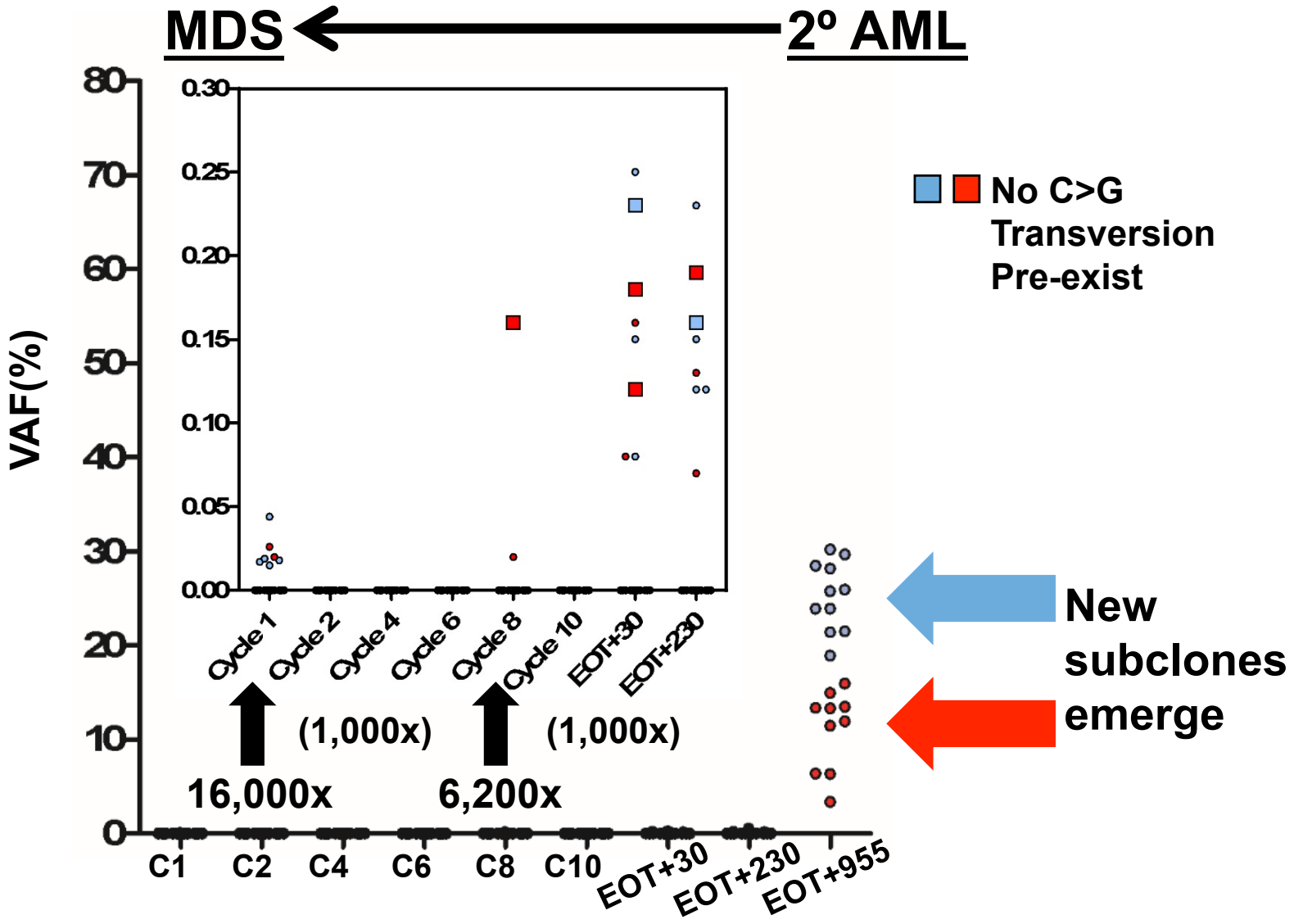


Mutations Persist in CR with LBH/DAC

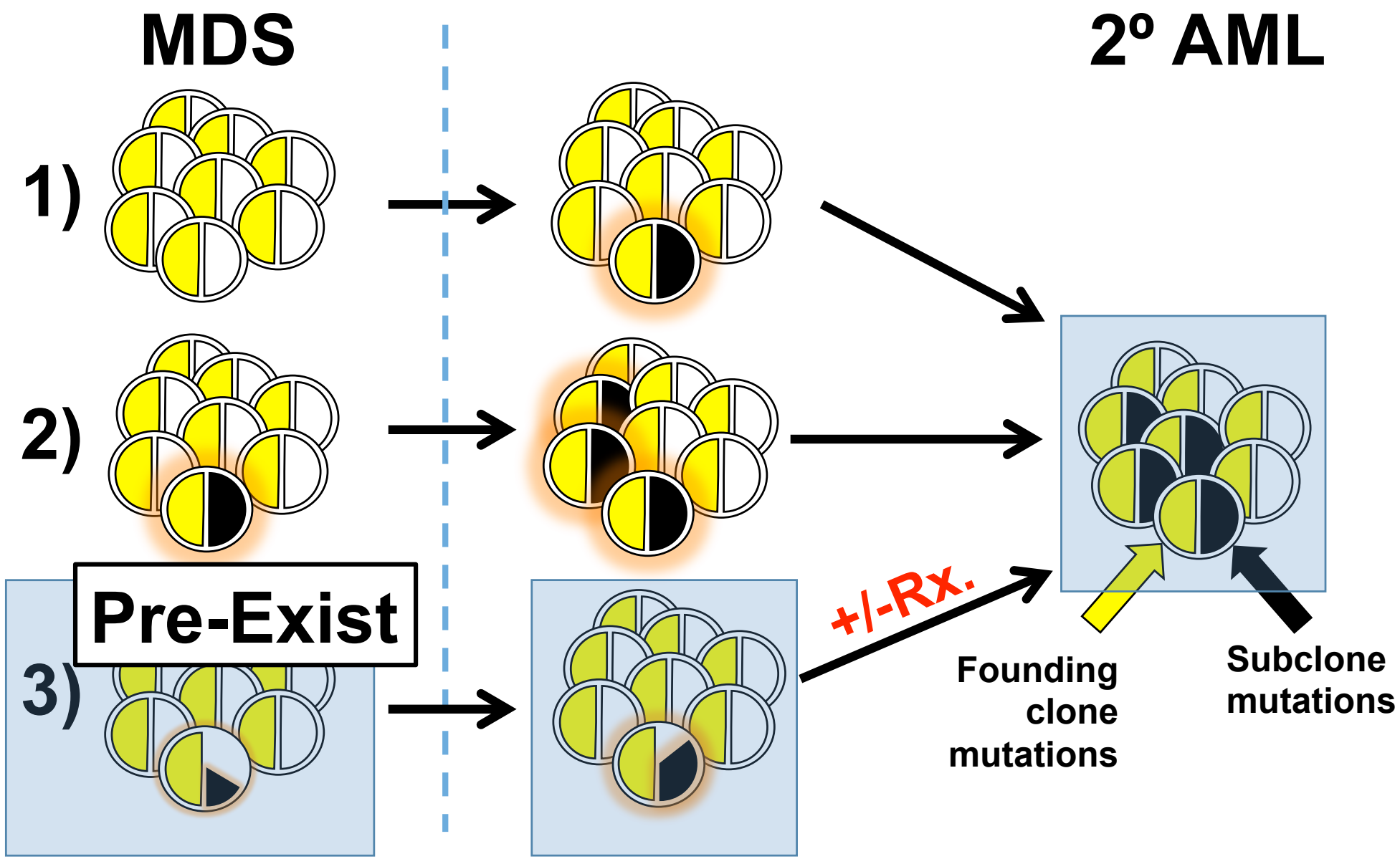
*Mutations were detectable in all cases following LBH/DAC



Some Subclone Mutations Pre-Exist



3 Models:


MDS
2º AML
1)
2)
3)
Pre-Exist
+/-Rx.
Founding clone mutations
Subclone mutations

Subclone questions:

1. Are certain gene mutations typically gained (or pre-exist)?
2. Do specific therapies have predictable effects on subclones?
3. Can we detect rising subclones prior to clinical progression to secondary AML?

Treatment Implications:

1. Know the clone a mutations occurs in if using targeted therapy.
2. Treat all clones, or at least the founding clone.

Acknowledgements

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