Clonal trajectories from CH to myeloid malignancies
Why and when does it matter?

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Disclosures

Qiagen
bluebird bio
Vertex Pharmaceuticals
Verve Therapeutics
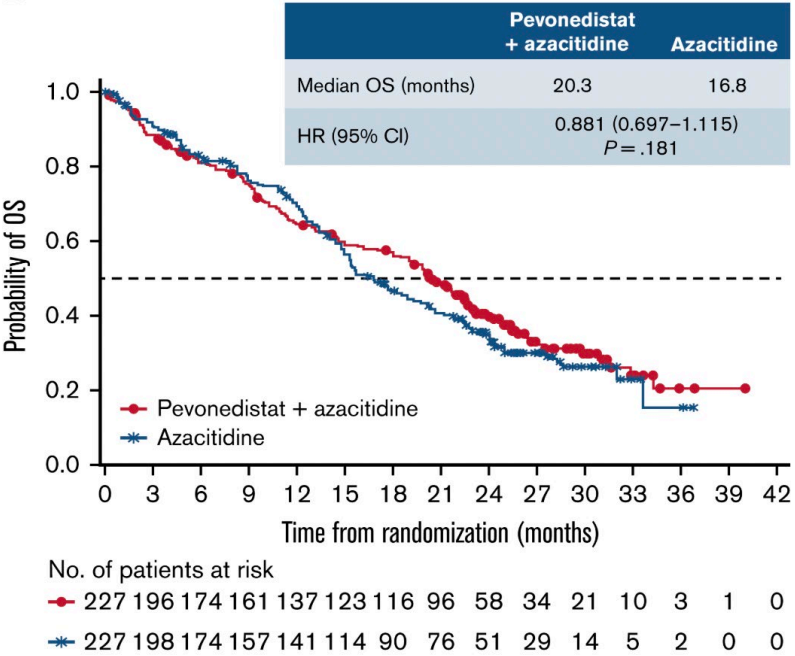*Geron Corporation*
Takeda Pharmaceuticals
Jazz Pharmaceuticals

Challenges (opportunities)
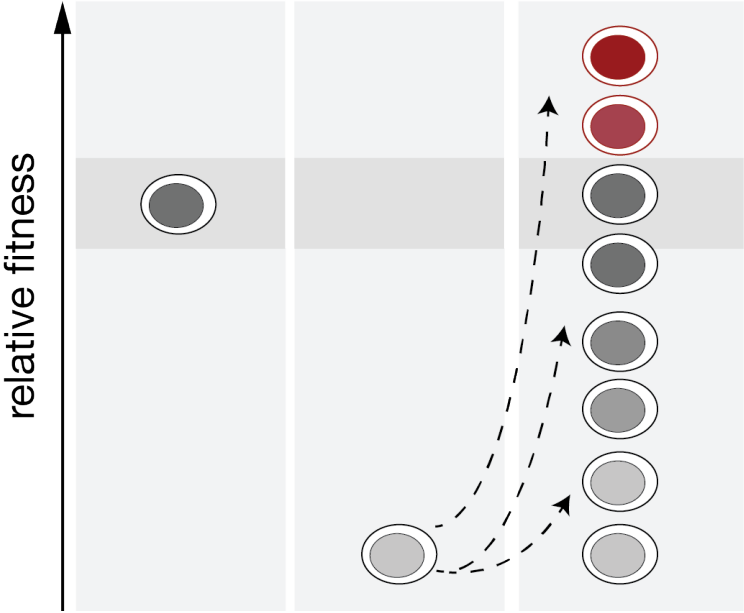
Clonal trajectories in real life

Challenge 1:
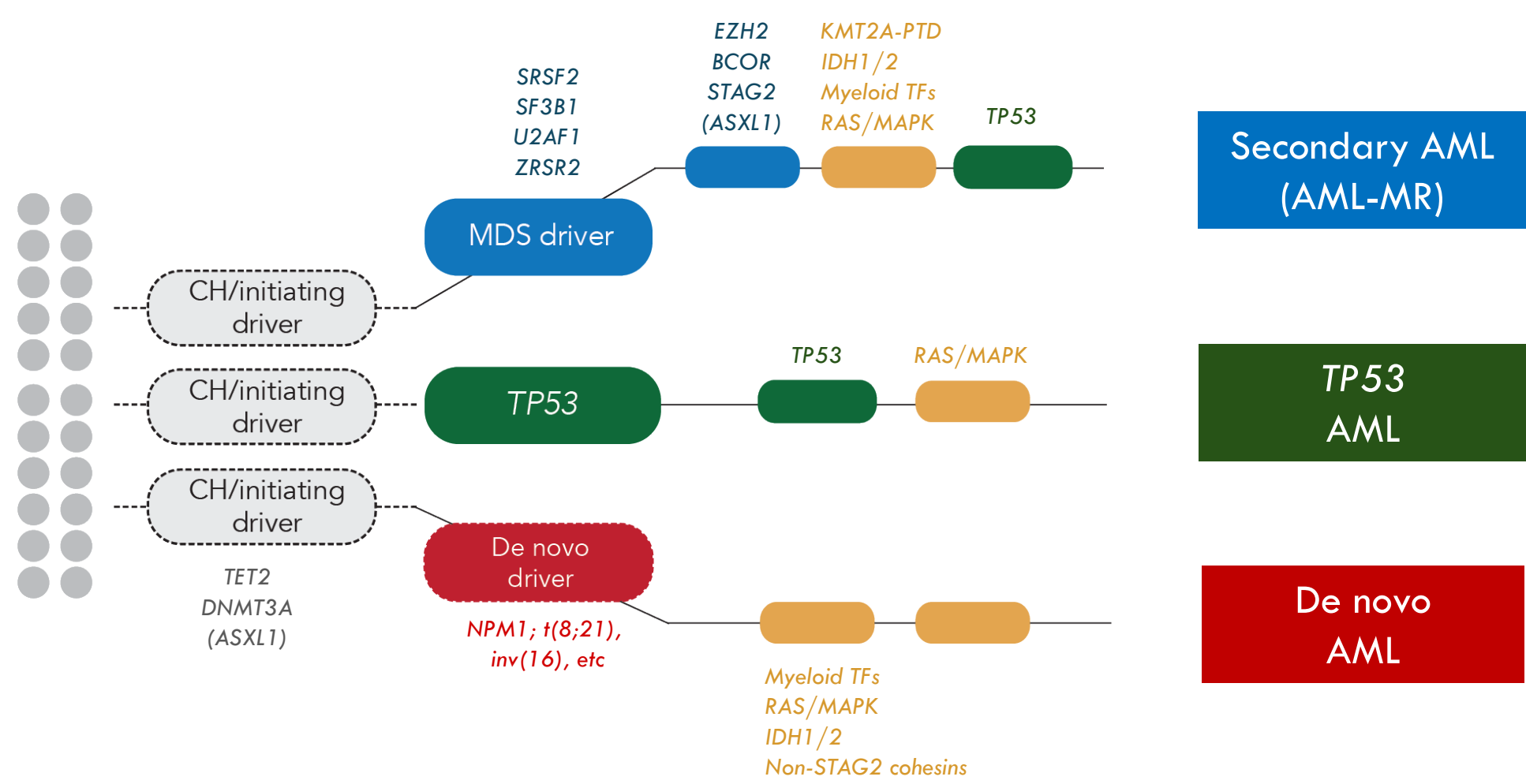Using genomics in clinical trial interpretation and regulatory evaluation

	Pevonedistat + azacitidine	Azacitidine
Median OS (months)	20.3	16.8
HR (95% CI)	0.881 (0.697–1.115) $P = .181$	

Challenge 2:
Rational prediction and surveillance in at-risk precursor states
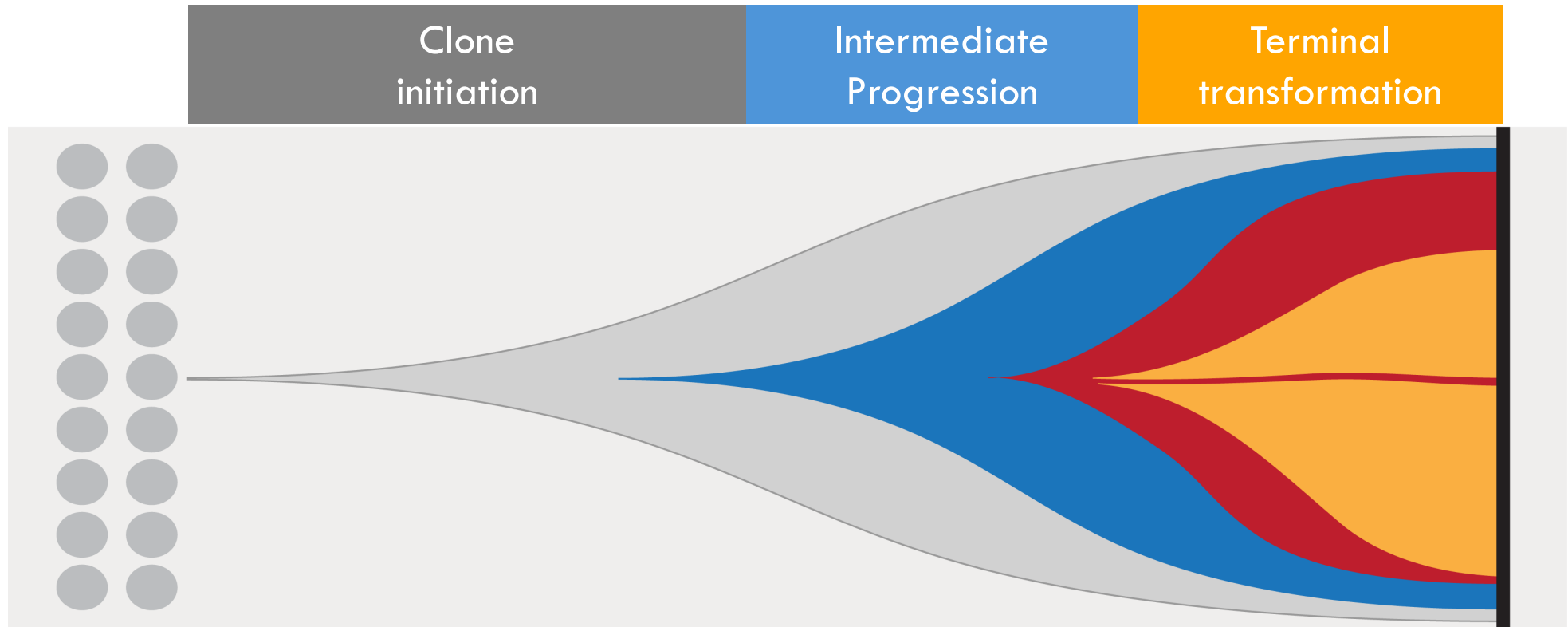
AML ontogeny: a reductionist model
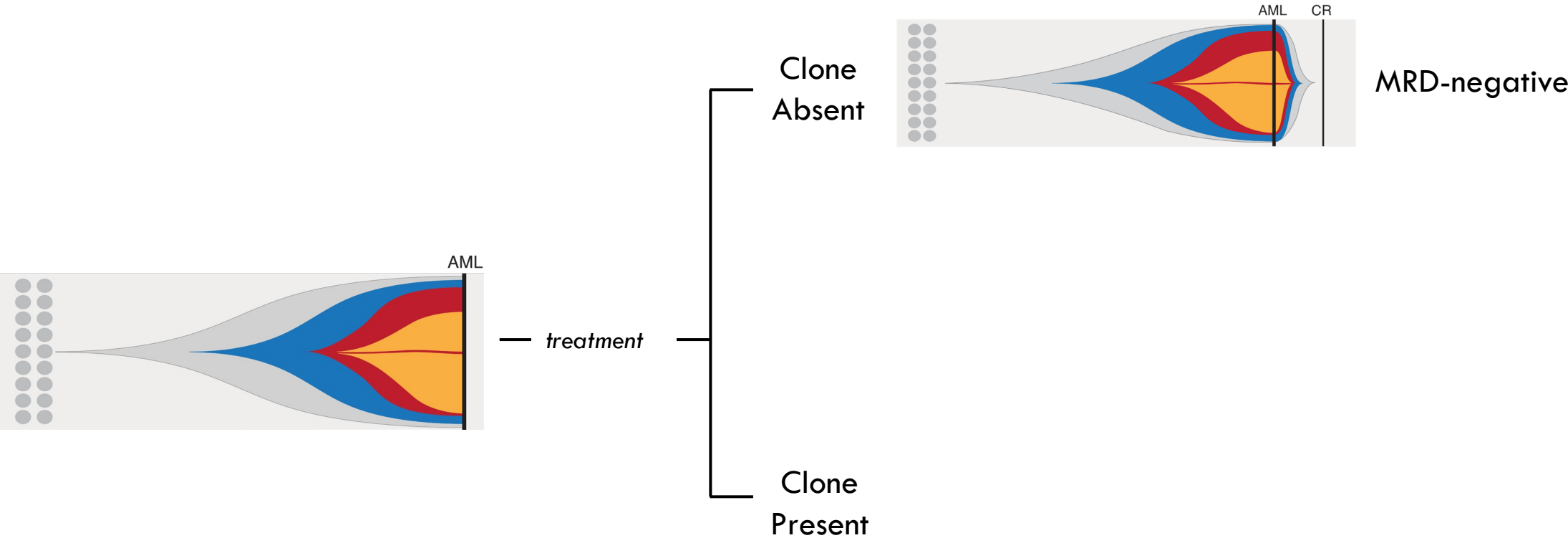

PMID: 25550361

Temporal heuristic

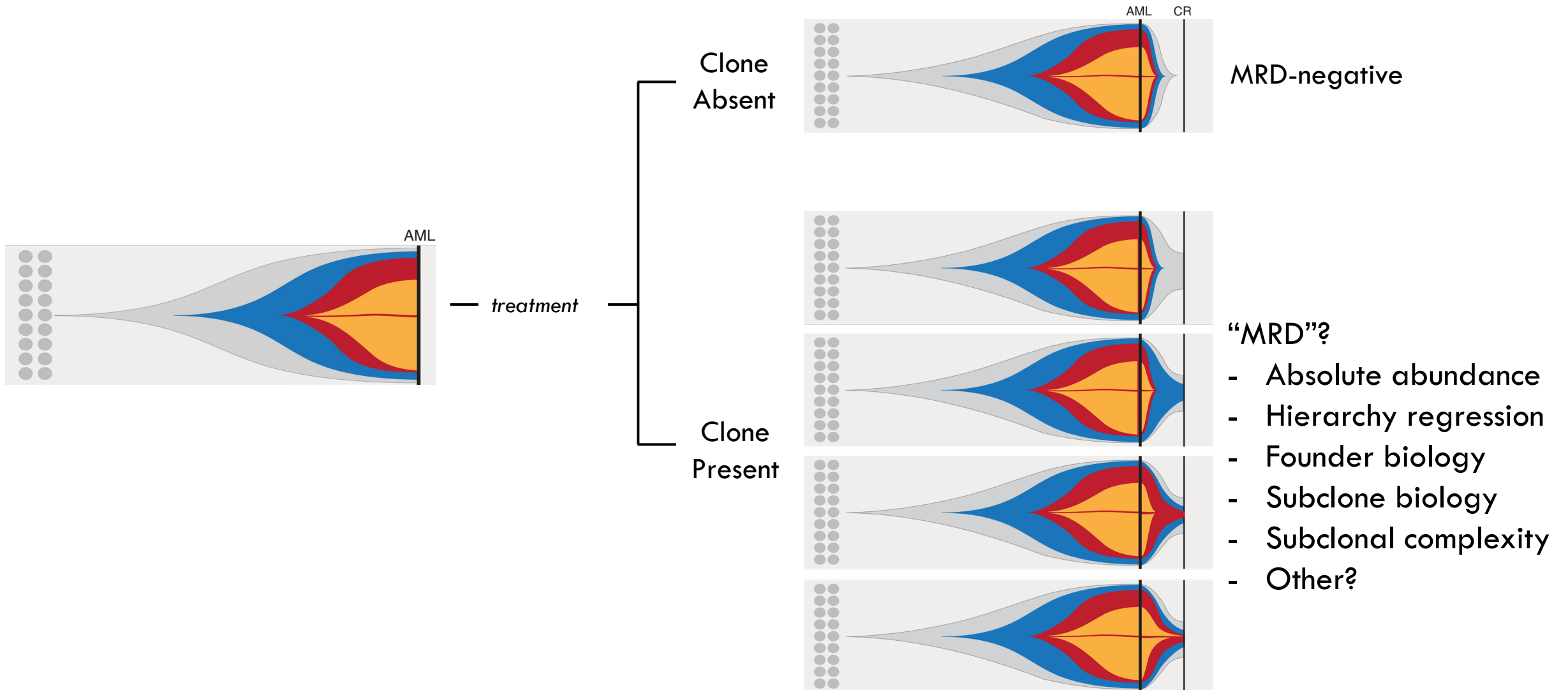*Defining the order of operations*

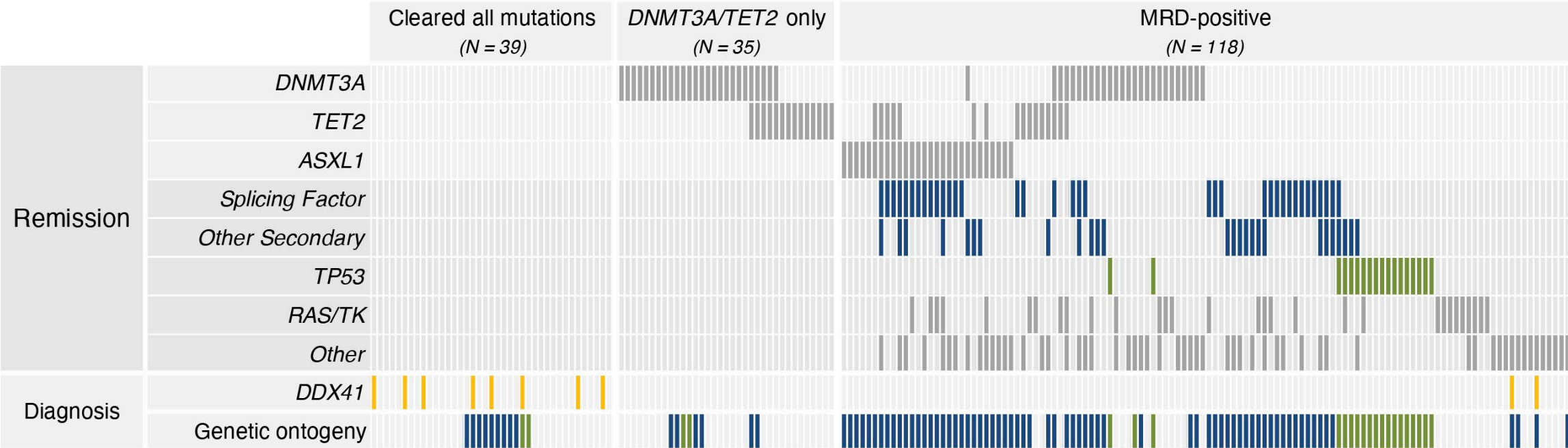# The clonal architecture of response and remission
Quantify what?

The clonal architecture of response and remission
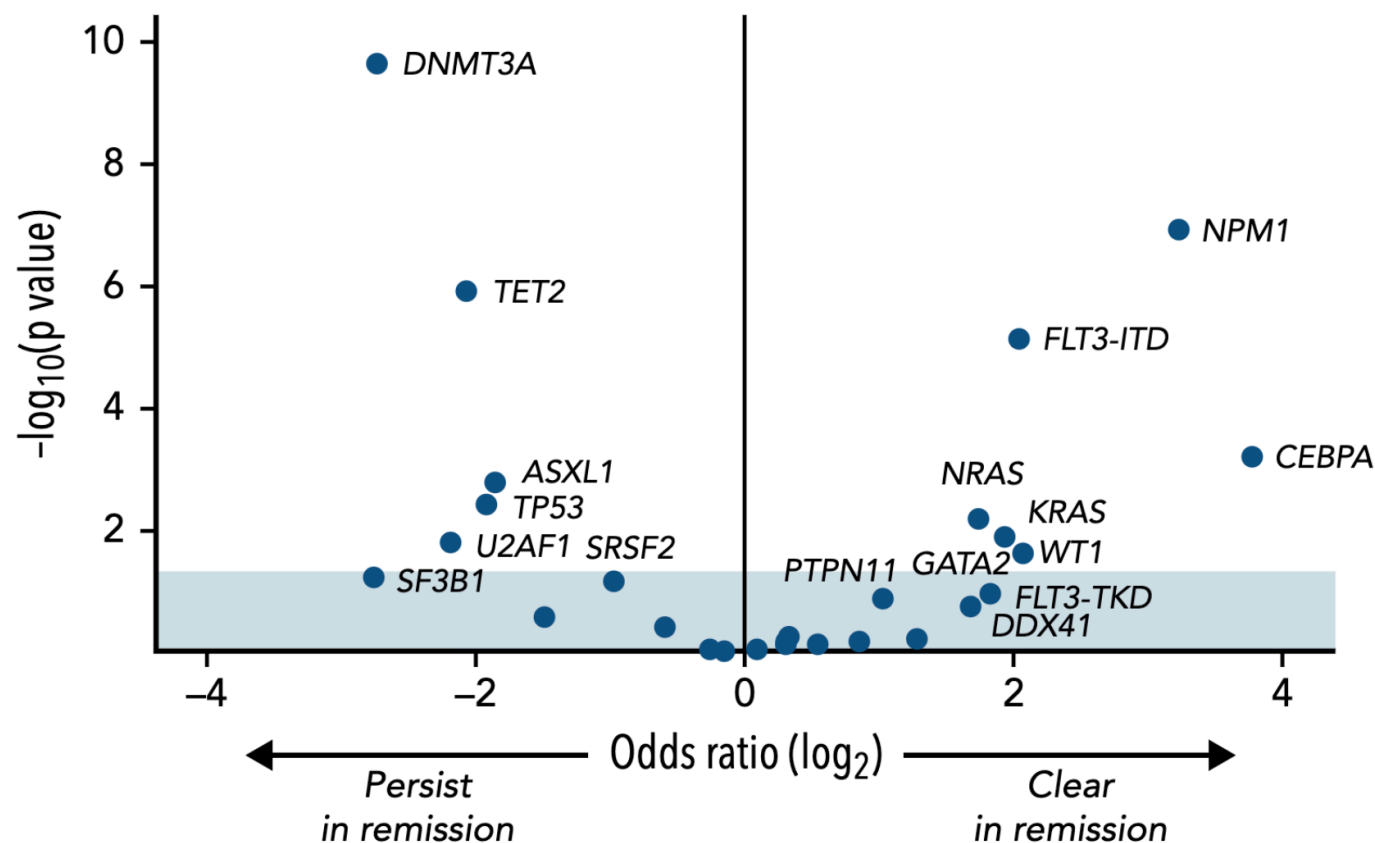## *Quantify what?*

Molecular genetics in remission

80% have persistent mutations

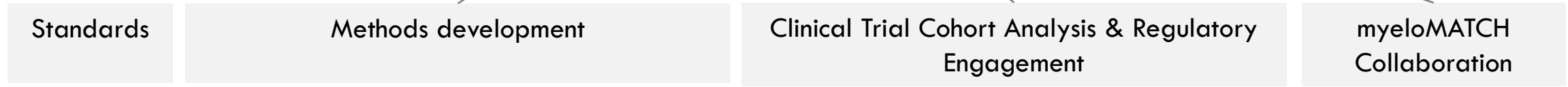# Molecular clearance linked to position in clonal hierarchy

Chris Hourigan

Coleman Lindsley

Jerry Radich

Standards

Methods development

Clinical Trial Cohort Analysis & Regulatory Engagement

myeloMATCH Collaboration

Private sector financial support

Donated services and materials

Academic Partners

Dana-Farber Cancer Institute

Virginia Tech (Fralin Biomededical Research Institute)

Fred Hutchinson Cancer Research Center

Public-Sector Partners

National Cancer Institute (NCI)

National Heart Lung and Blood Institute (NHLBI)

U.S. Food and Drug Administration (FDA)

Private-Sector Partners

AbbVie

Amgen

AccuGenomics, Inc

AstraZeneca

Bio-Rad Laboratories Inc.

Genentech

Gilead Sciences, Inc.

GlaxoSmithKline

Invivoscribe, Inc.

Jazz Pharmaceuticals, Inc.

LGC Clinical Diagnostics
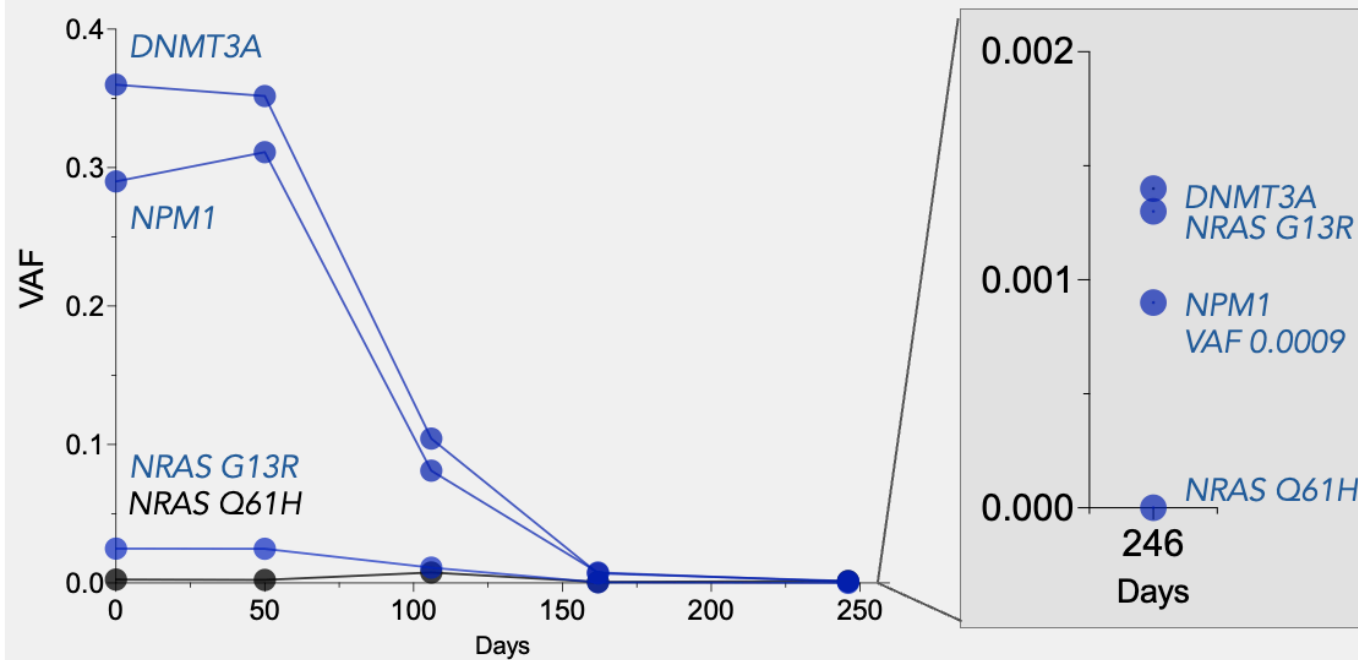
Mission Bio

Novartis

NuProbe

Syndax Pharmaceuticals

Sysmex Inostics, Inc.

10x Genomics, Inc.

Takeda Pharmaceuticals

Thermo Fisher Scientific

TwinStrand Biosciences, Inc

Twist Bioscience Corporation

Molecular dynamics on treatment
PANTHER: Randomized Phase 3 - AZA +/- pevonedistat

Clinical Summary

IWG 2006

IWG 2006 INV: as reported by the trial investigator (INV)

IWG 2006 IRC: as reported by the trial independent review committee (IRC)

IWG 2006: Re-coded by our study team based on response-informing raw data

- aspirate/core/PB blasts %, ANC, Hb and platelet count +/- 14 days within the BM biopsy.
- [No reliable information on timing of blood transfusion, so hematological improvement (HI) not coded]

IWG 2023

Response per IWG 2023 by our study team based on response-informing raw data, as above

CR (Complete remission)
CRbi (Complete remission with bi lineage hematologic recovery)
CRuni (Complete remission with uni lineage hematologic recovery)
CRh (Complete remission with partial hematologic recovery)
PR (Partial remission)
No response
PD (Progressive disease/disease relapse)
Missing data (could not code response because of missing data on blasts, ANC, Hb or platelets)
NA (e.g. baseline marrow or only one marrow obtained)

Sample Summary

Overall

Patient-level

Patients with any sample: 428 of 454 enrolled patients (94.3%)

- Total with screening/pre-treatment sample: 390 (85.9%)

Consequence of Context: re-framing what we know

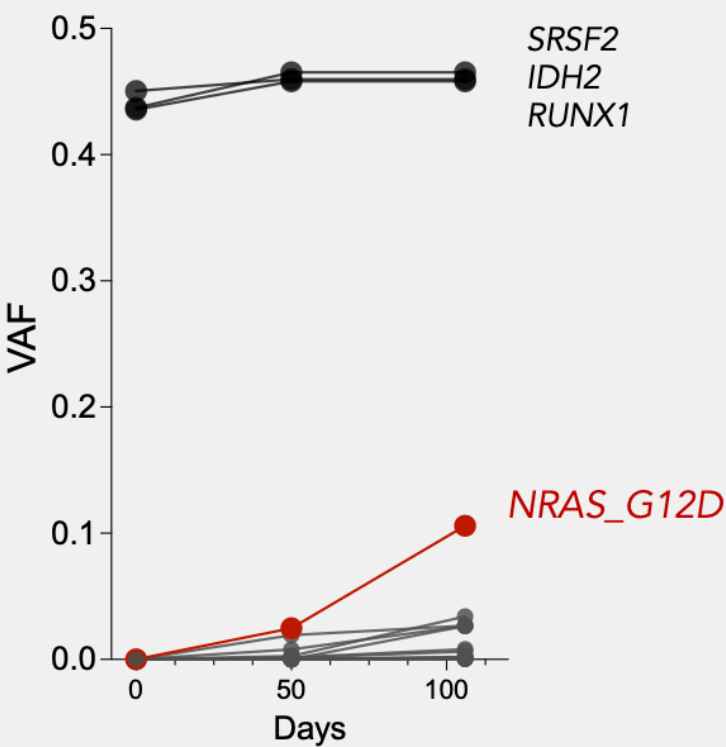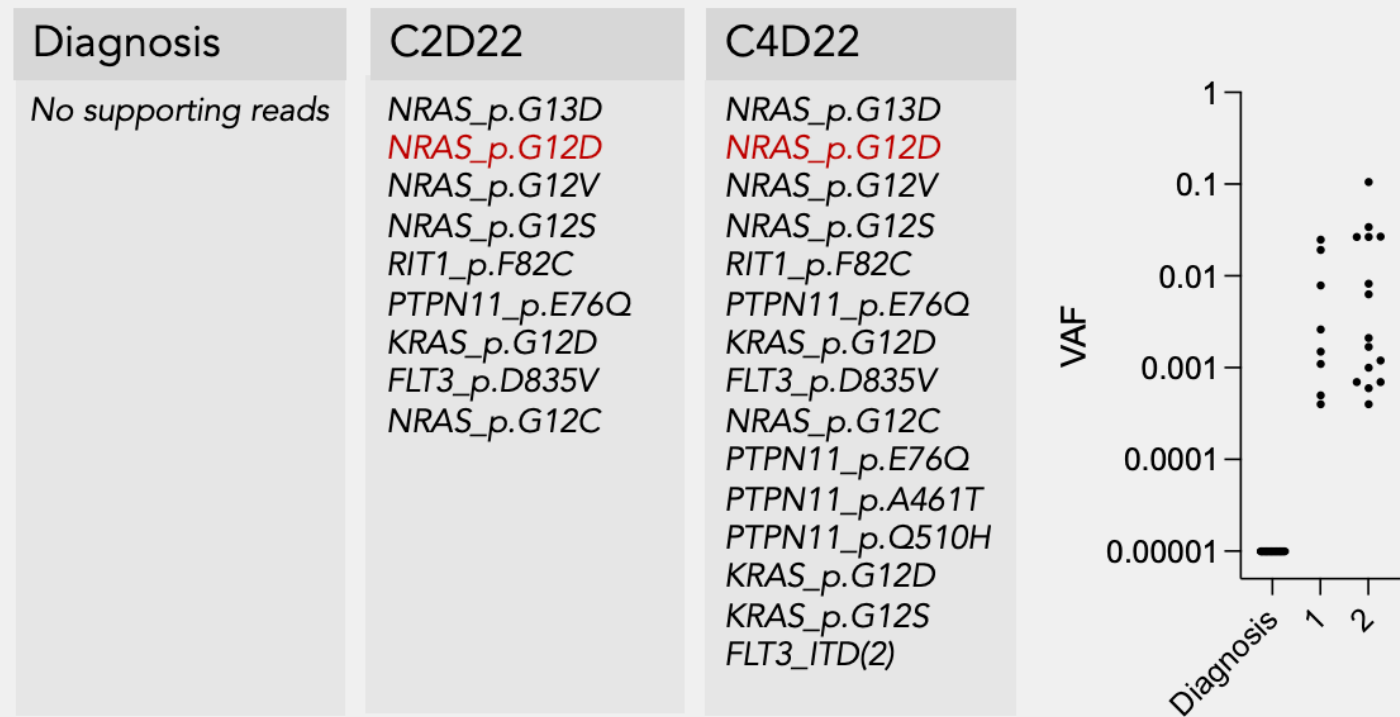*NPM1 mutation dynamics*
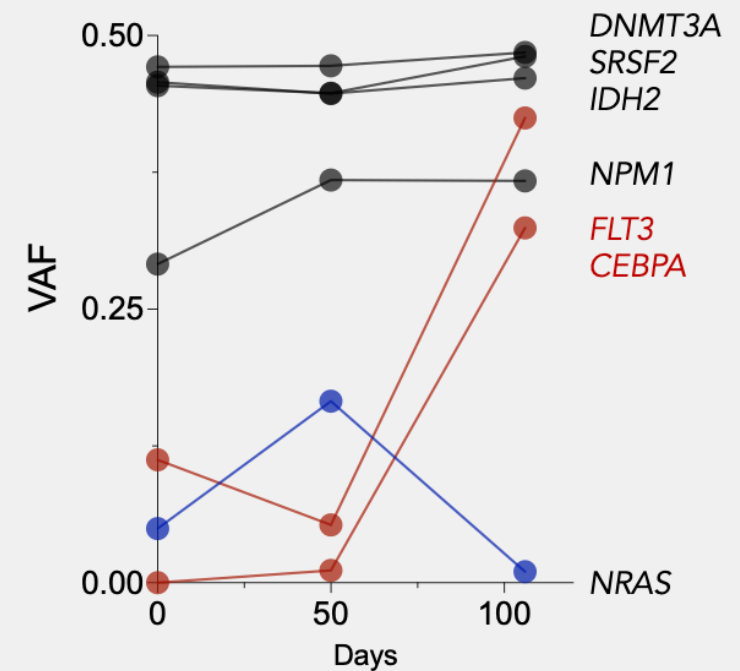
Fitness constraint drives selection

Treatment-emergent resistance pathways

Rapid progression in an MDS genetic context

**Treatment emergent mutations** — *All RAS-MAPK*

Diagnosis	C2D22	C4D22
No supporting reads	NRAS_p.G13D	NRAS_p.G13D
	NRAS_p.G12D	NRAS_p.G12D
	NRAS_p.G12V	NRAS_p.G12V
	NRAS_p.G12S	NRAS_p.G12S
	RIT1_p.F82C	RIT1_p.F82C
	PTPN11_p.E76Q	PTPN11_p.E76Q
	KRAS_p.G12D	KRAS_p.G12D
	FLT3_p.D835V	FLT3_p.D835V
	NRAS_p.G12C	NRAS_p.G12C
		PTPN11_p.E76Q
		PTPN11_p.A461T
		PTPN11_p.Q510H
		KRAS_p.G12D
		KRAS_p.G12S
		FLT3_ITD(2)

Refining the RAS-MAPK heuristic?

Using clinical phenomenology to understand pathway heterogeneity
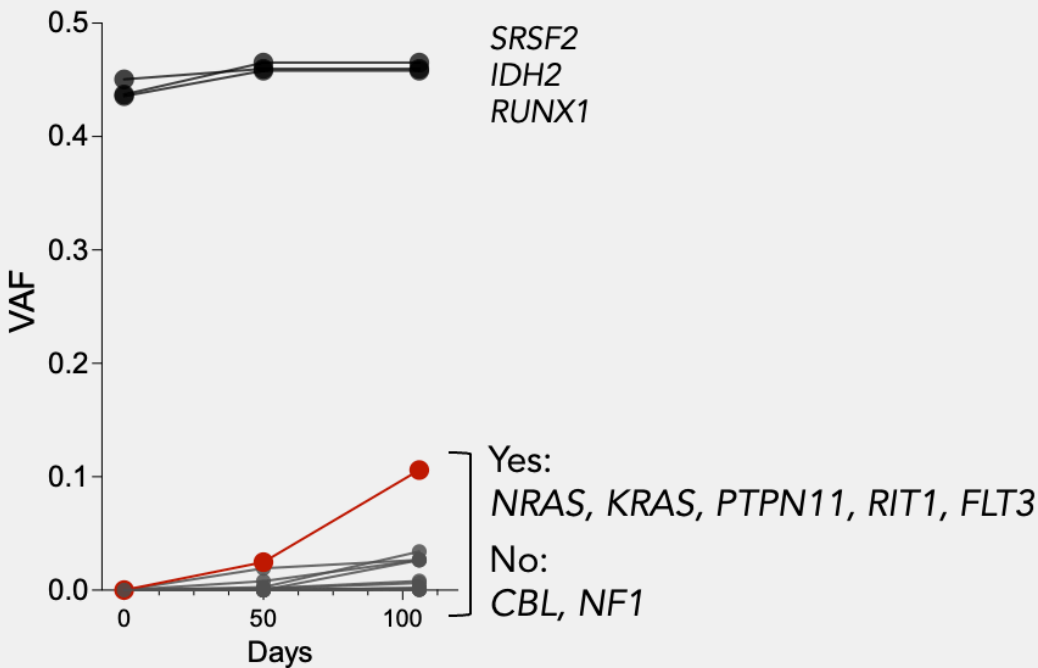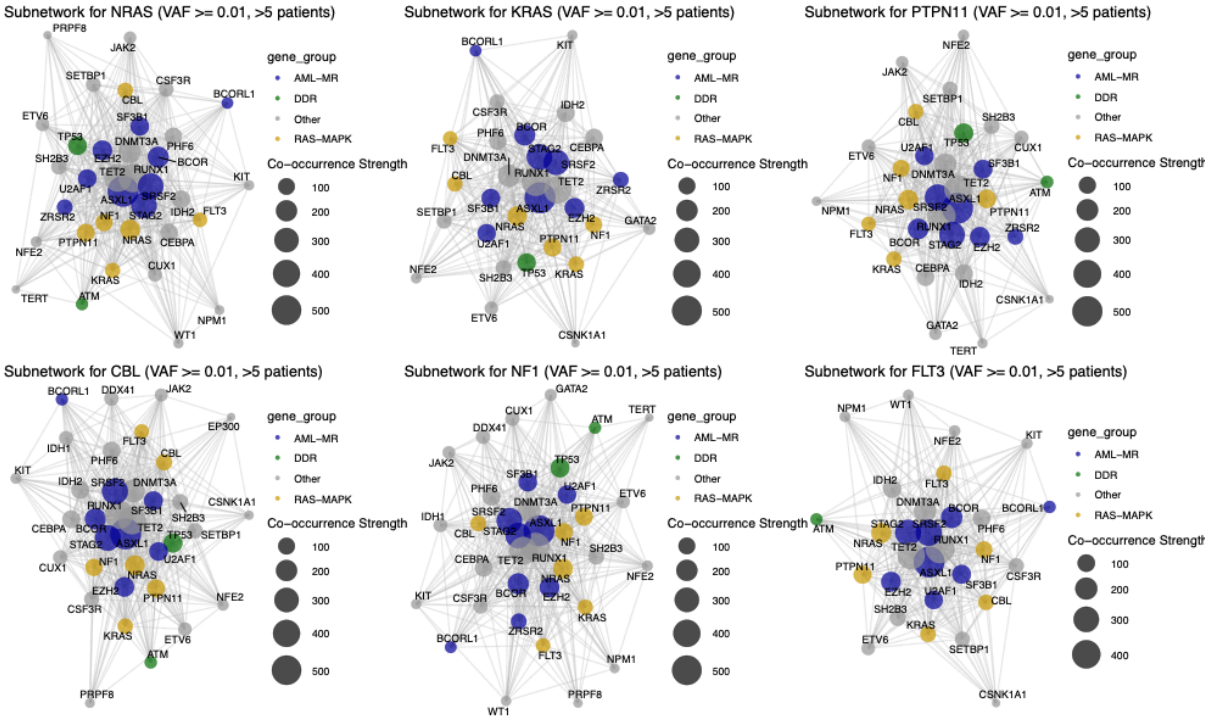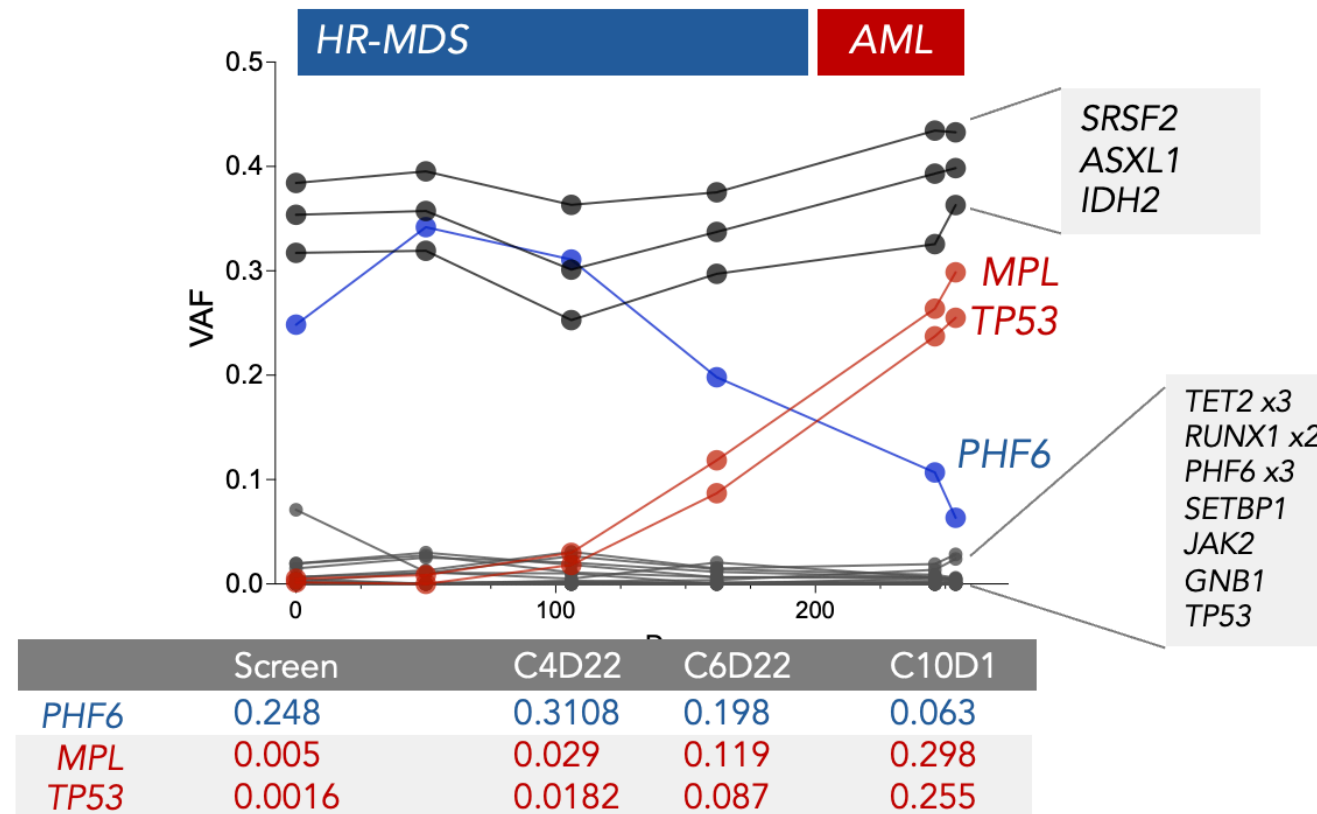
Fitness constraint drives selection

Treatment drives subclone exchange → *PROGRESSION*

False premise: dominant subclone at diagnosis mediates resistance/clinical failure
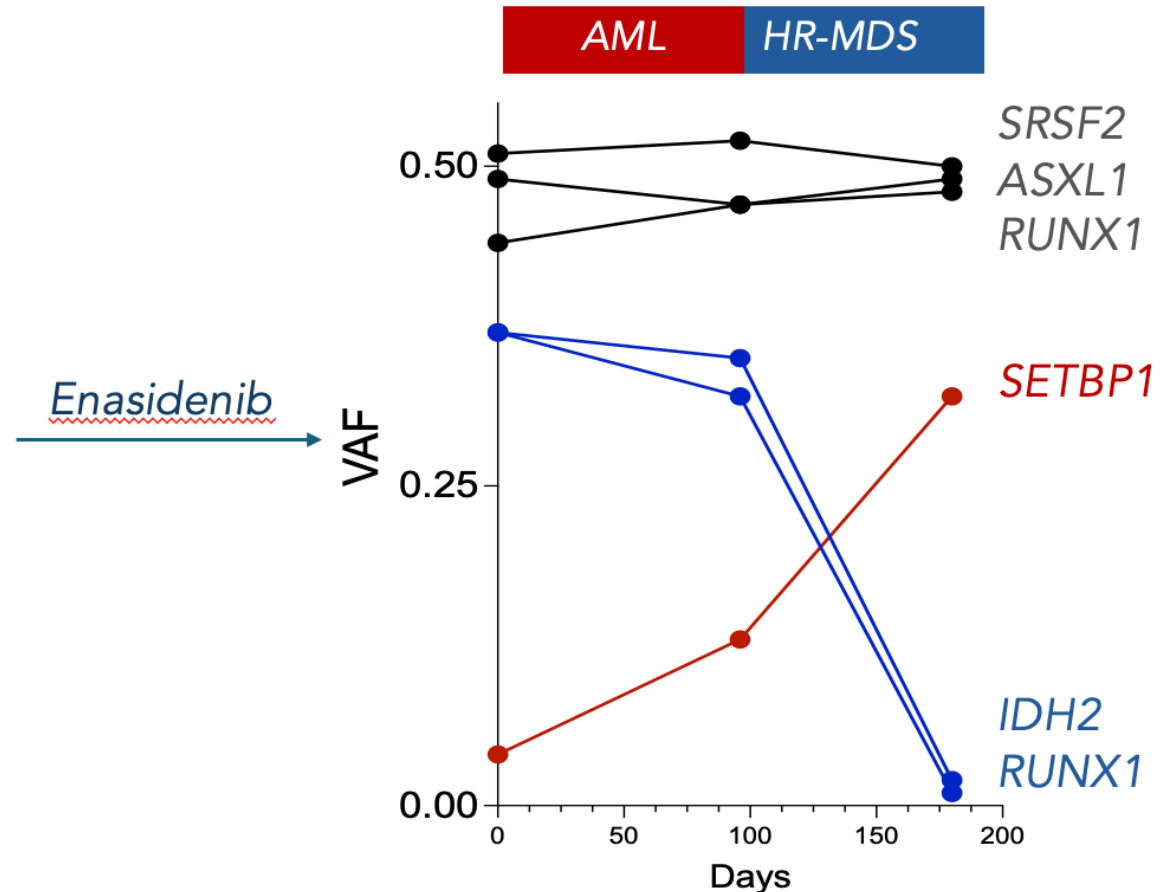

	Screen	C4D22	C6D22	C10D1
PHF6	0.248	0.3108	0.198	0.063
MPL	0.005	0.029	0.119	0.298
TP53	0.0016	0.0182	0.087	0.255

Fitness constraint drives selection

But rules may change as the treatments change…

Subclone-specific constraint drives subclone exchange

→ *Phenotype change*

		Pre-treatment
SRSF2	p.P95H	51%
RUNX1	p.R201*	49%
ASXL1	p.Q760*	44%
IDH2	p.R140Q	37%
RUNX1	p.K110*	37%
SETBP1	p.D868N	4%

Enasidenib

Understanding response and resistance to therapy

Aging , germline, exposures, etc.
Define fitness landscape that mediates clonal selection

Therapeutic Constraint
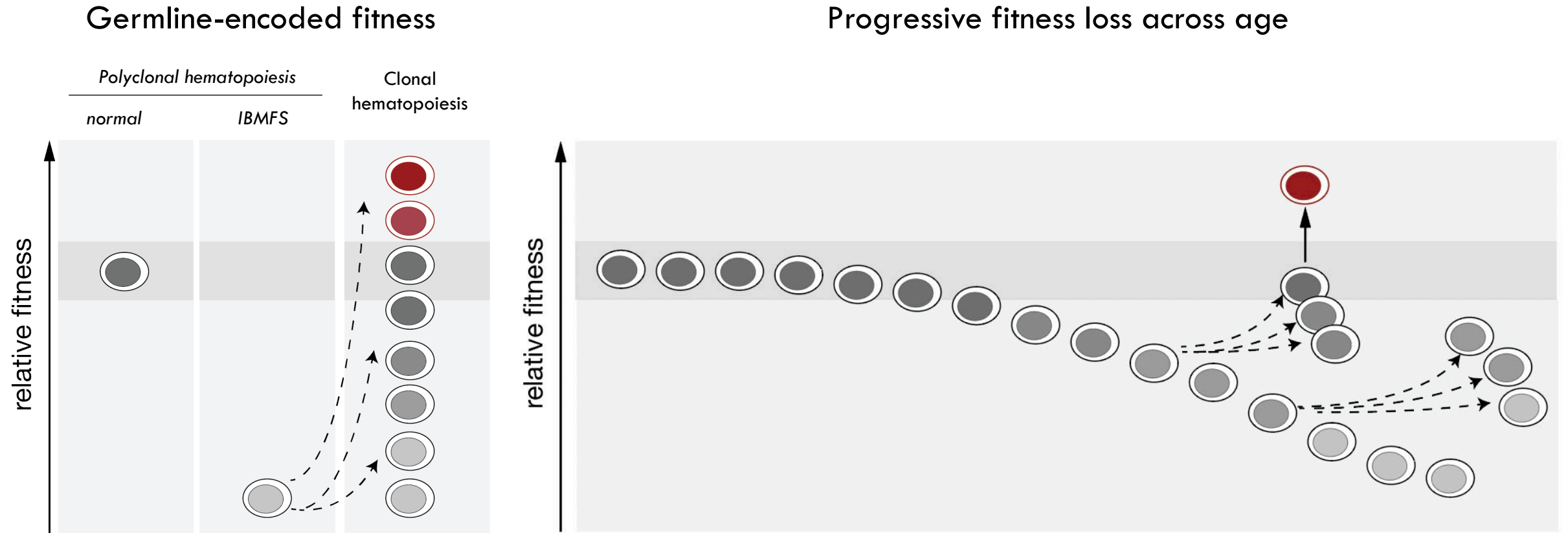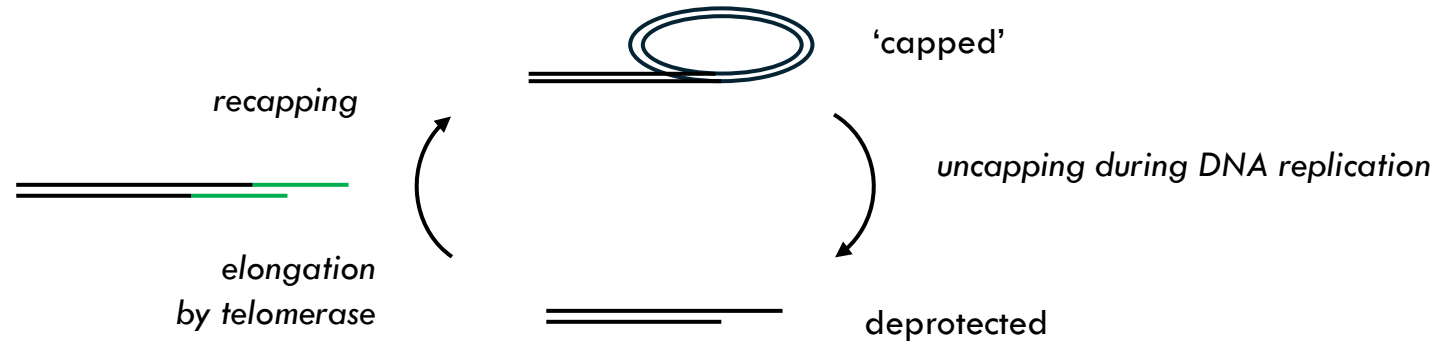
Response/ Resistance
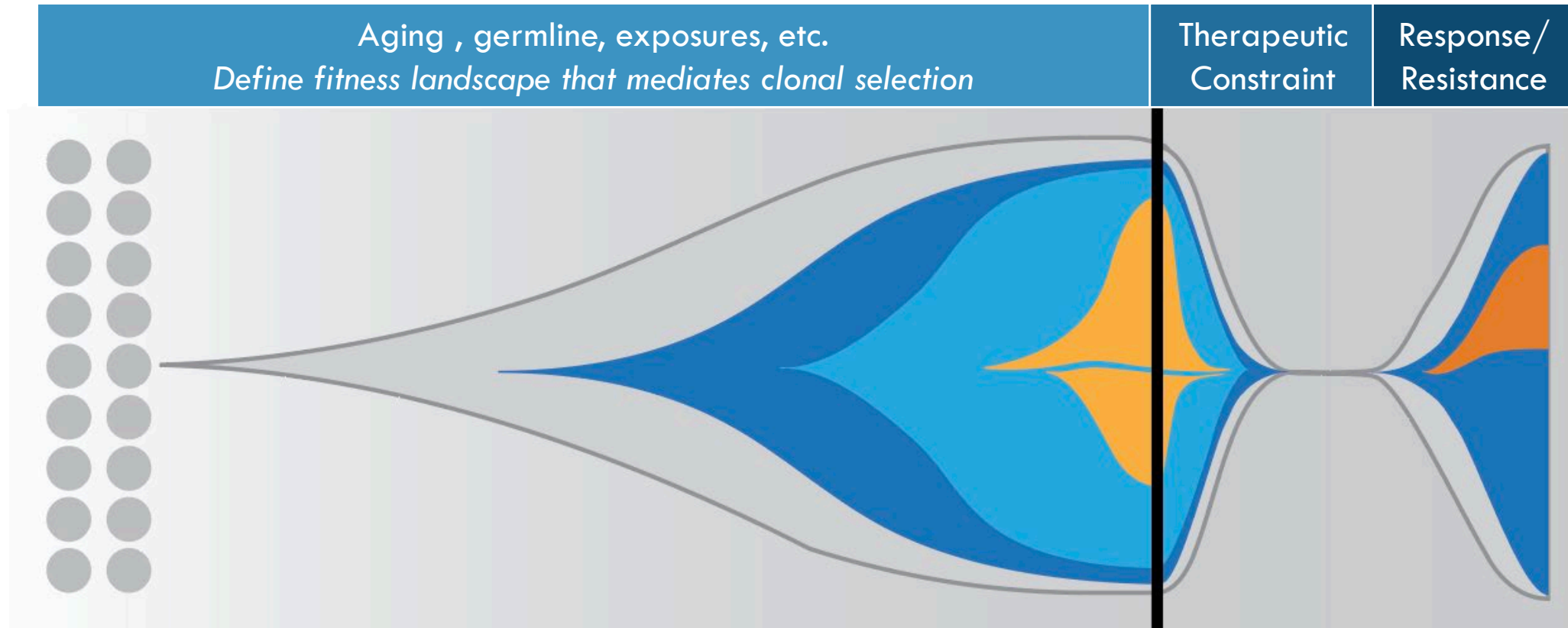
The initiation of clonal myeloid disease
Somatic clones are driven by context-selective fitness constraints
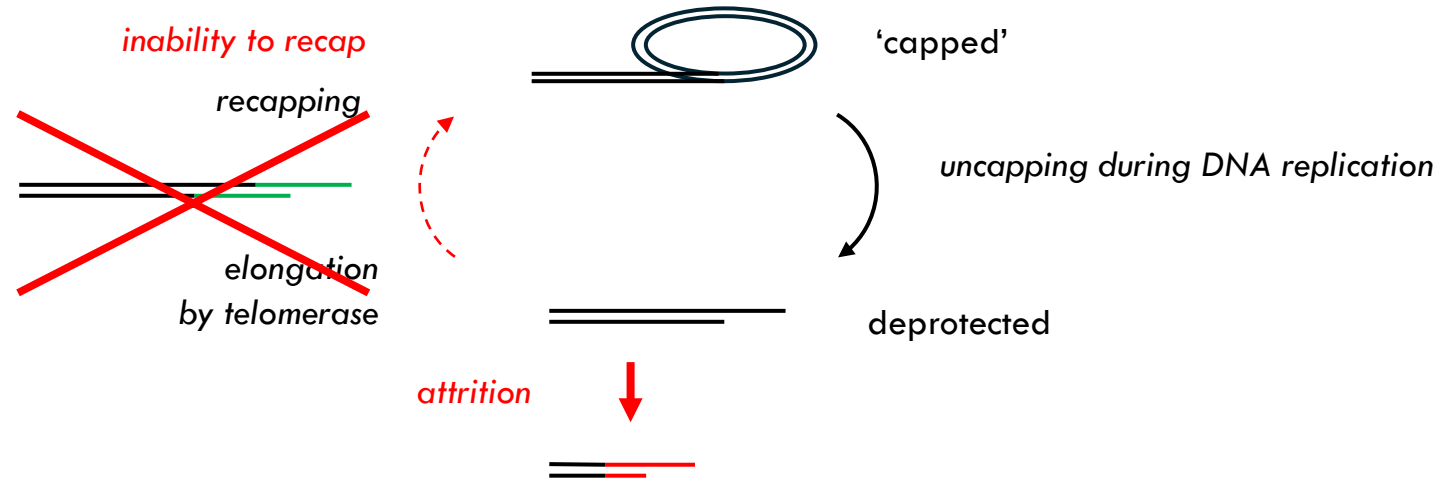

H$_1$: Age and gene distribution of CH reflects the mechanism and magnitude of constraint
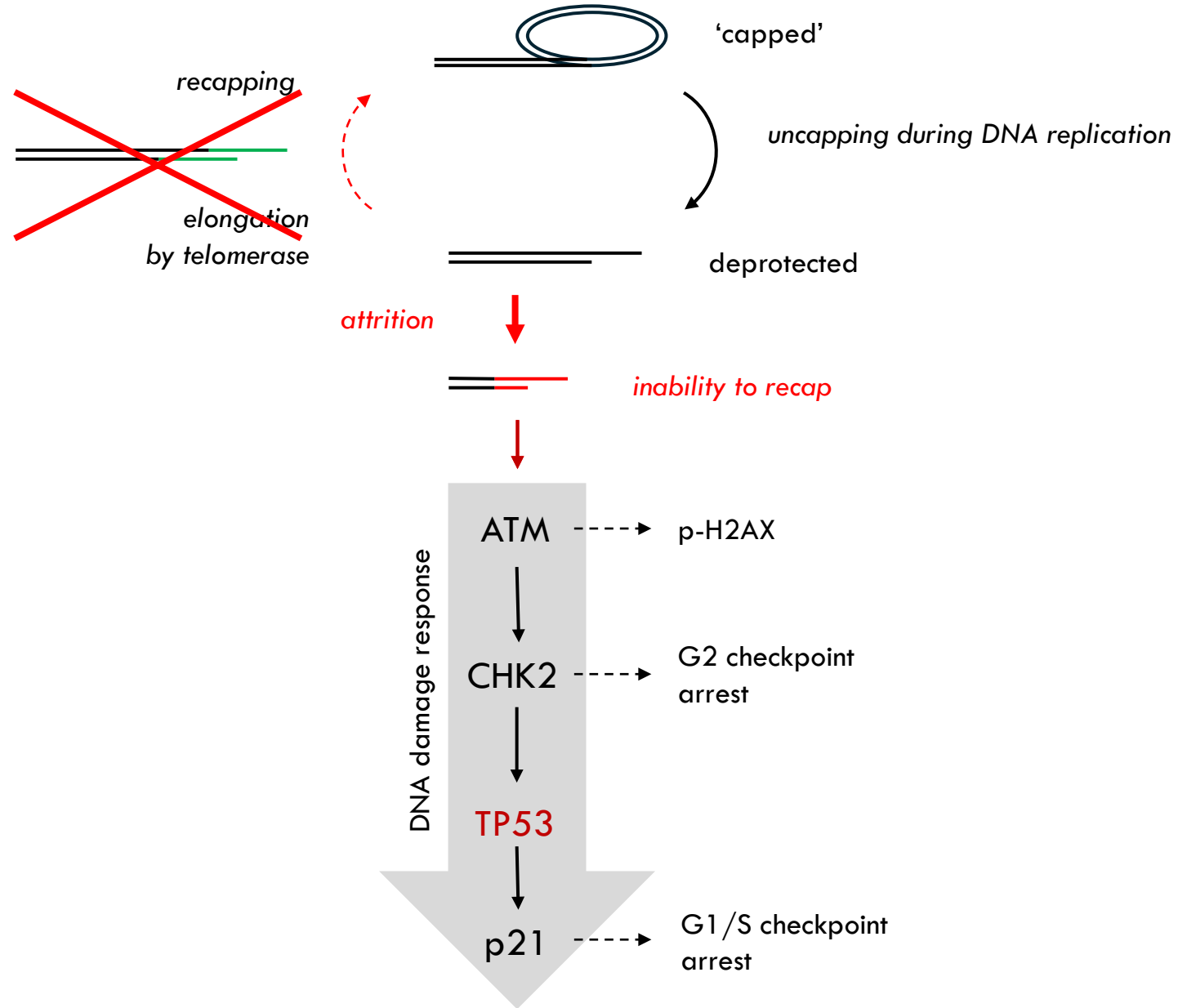
# Telomere attrition activates DDR and leads to checkpoint arrest

'capped'

recapping

uncapping during DNA replication

elongation by telomerase

deprotected

Telomere attrition activates DDR and leads to checkpoint arrest

inability to recap

recapping

'capped'

uncapping during DNA replication

elongation by telomerase

deprotected

attrition

Telomere attrition activates DDR and leads to checkpoint arrest

Hypothesis: *TP53* and *PPM1D* suppress telomeric DDR signaling
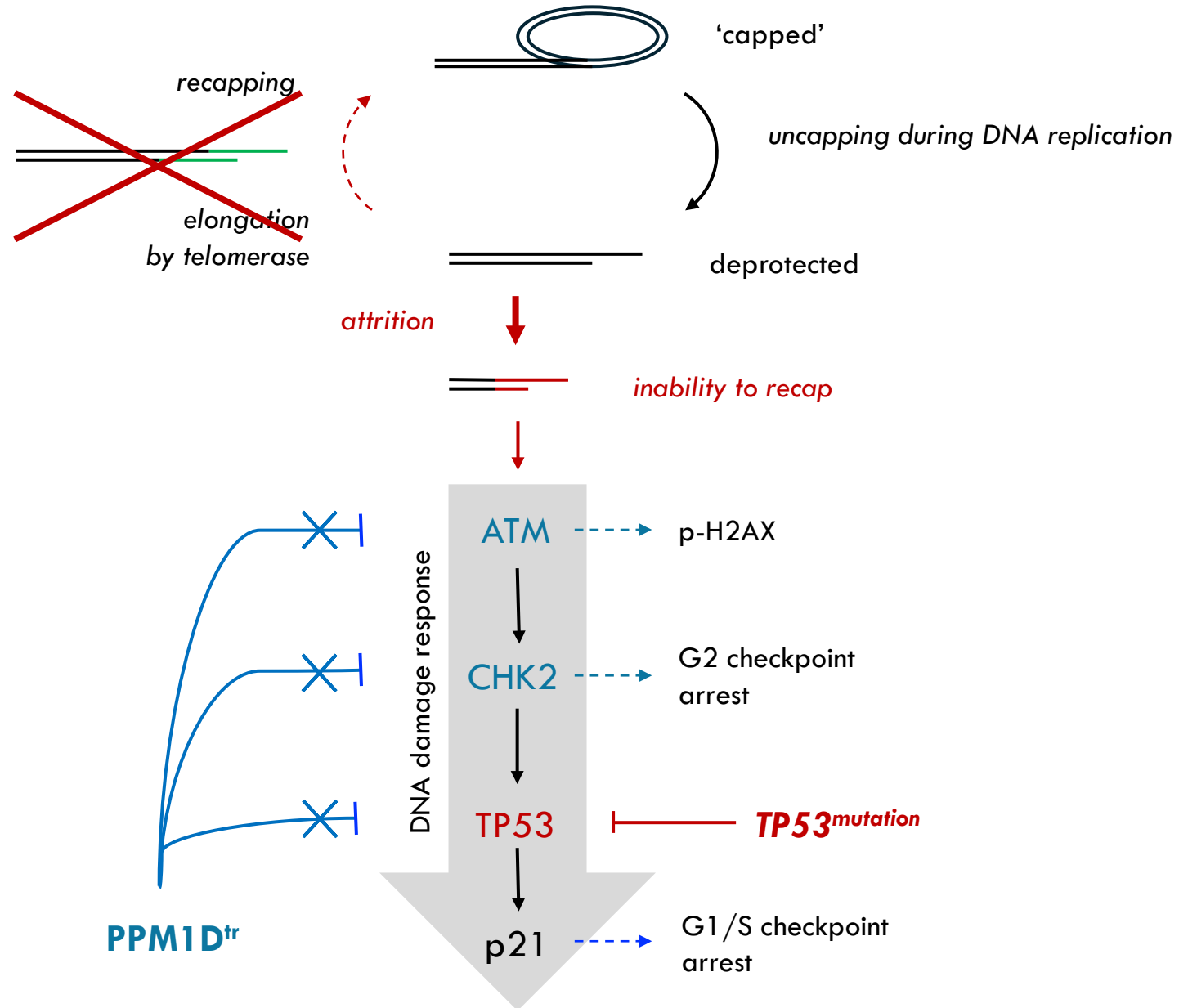
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Moses Murdock
Naomi Kawashima
Chris Reilly
Fred Tsai
Andrew Gehrke
Amelia Grosskopf
Jessica Knapp
Deirdra Venney
Kornelia Gladysz
Felicia Lim
Danielle Morrow
Rishi Thakur
Harrison Tsai
Eva Schaefer

Jianwe Che
Demetris Gazgalis

DFCI Leukemia
Rich Stone
Dan DeAngelo
Marlise Luskjin
Jacqueline Garcia

Niall Lennon
Carrie Cibulskis
Junko Tsuji
Micah Rickles-Young
Mark Fleharty
Sam Pollock

Chris Hourigan

Jerry Radich

George Vassiliou
Margarete Fabre
Sean Wen

Suneet Agarwal
Akiko Shimamura