TP53 and other classifier mutations

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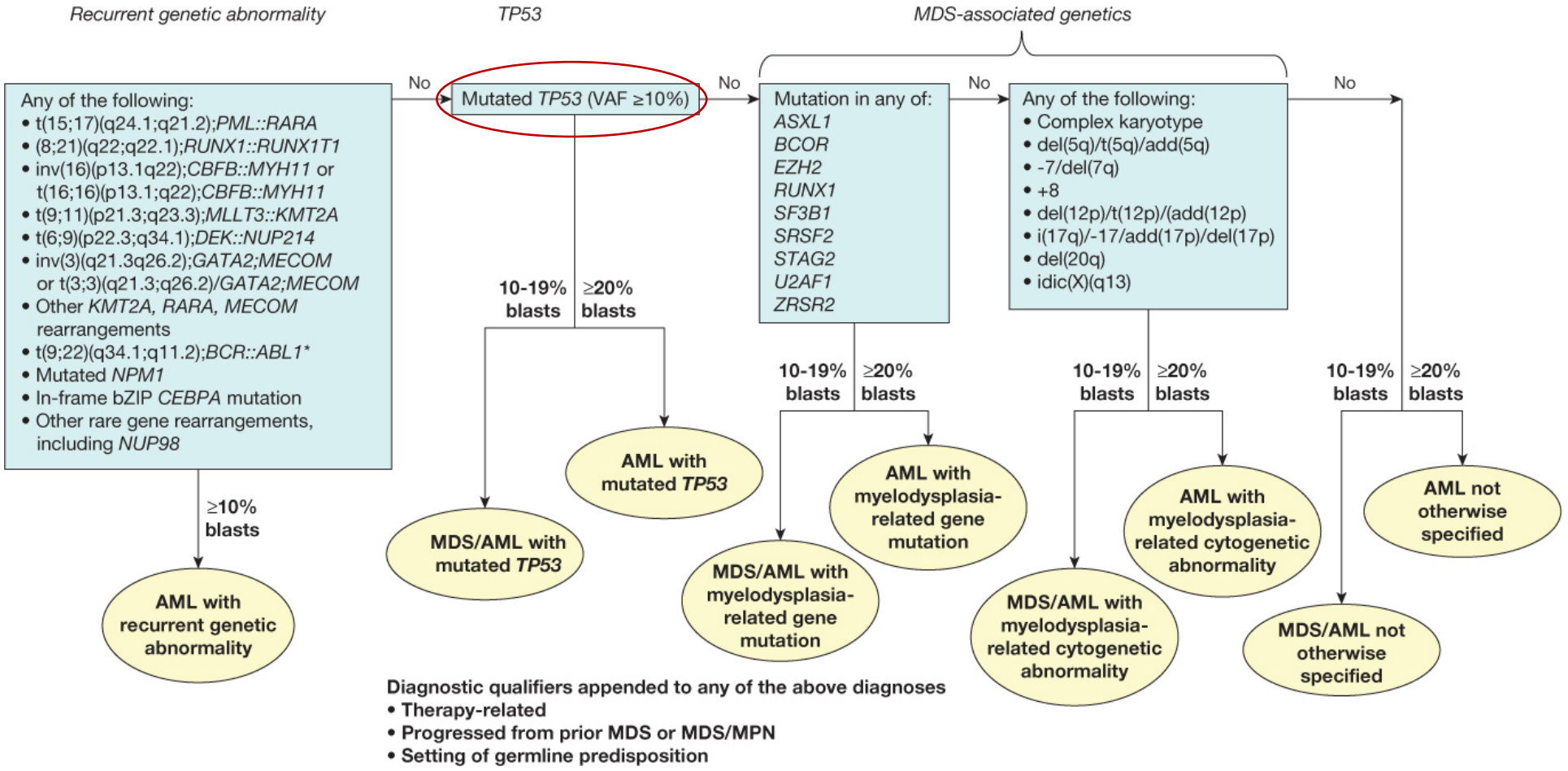
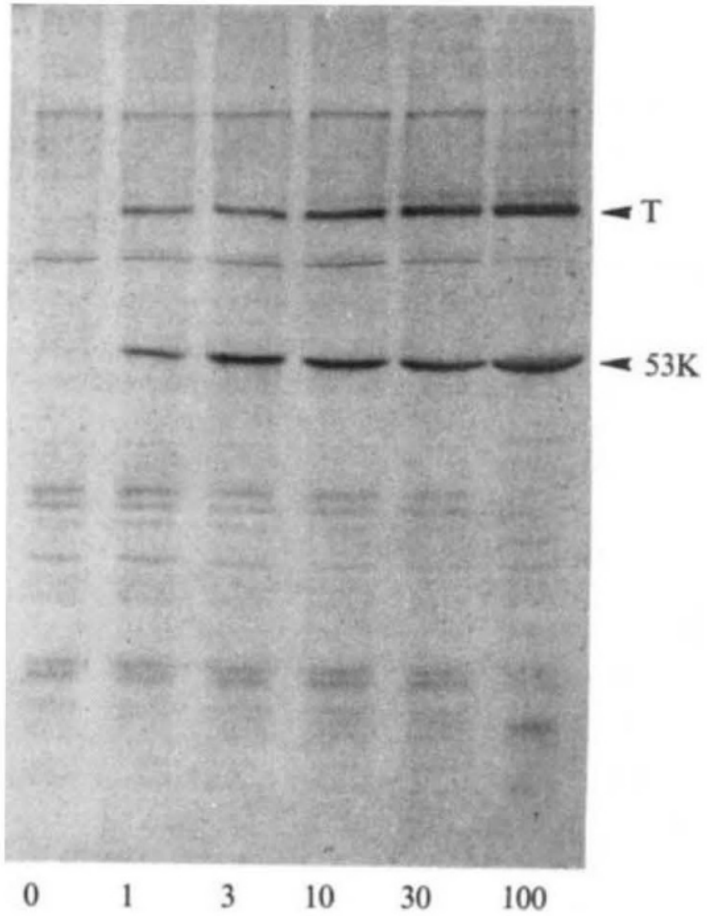
TP53 mutation and ICC 2022 classification



Arber, Daniel, A. et al. The International Consensus Classification of Myeloid and Lymphoid Neoplasms. Available from: Wolters Kluwer, Wolters Kluwer Health, 2024

A novel protein co-immunoprecipitated by anti-SV40 T serum



Lane and Crawford, Nature 1979

Similar protein found in uninfected embryonal carcinoma cells

Linzer DI, Levine AJ. Characterization of a 54K dalton cellular SV40 tumor antigen present in SV40-transformed cells and uninfected embryonal carcinoma cells. ***Cell.*** **1979**;17:43–52.

Kress M, May E, Cassingena R, May P. Simian virus 40-transformed cells express new species of proteins precipitable by anti-simian virus 40 tumor serum. ***J Virol.*** **1979**;31:472–83.

Melero JA, Stitt DT, Mangel WF, Carroll RB. Identification of new polypeptide species (48-55K) immunoprecipitable by antiserum to purified large T antigen and present in SV40-infected and -transformed cells. ***Virology.*** **1979**;93:466–80.

Smith AE, Smith R, Paucha E. Characterization of different tumor antigens present in cells transformed by simian virus 40. ***Cell.*** **1979**;18:335–46.

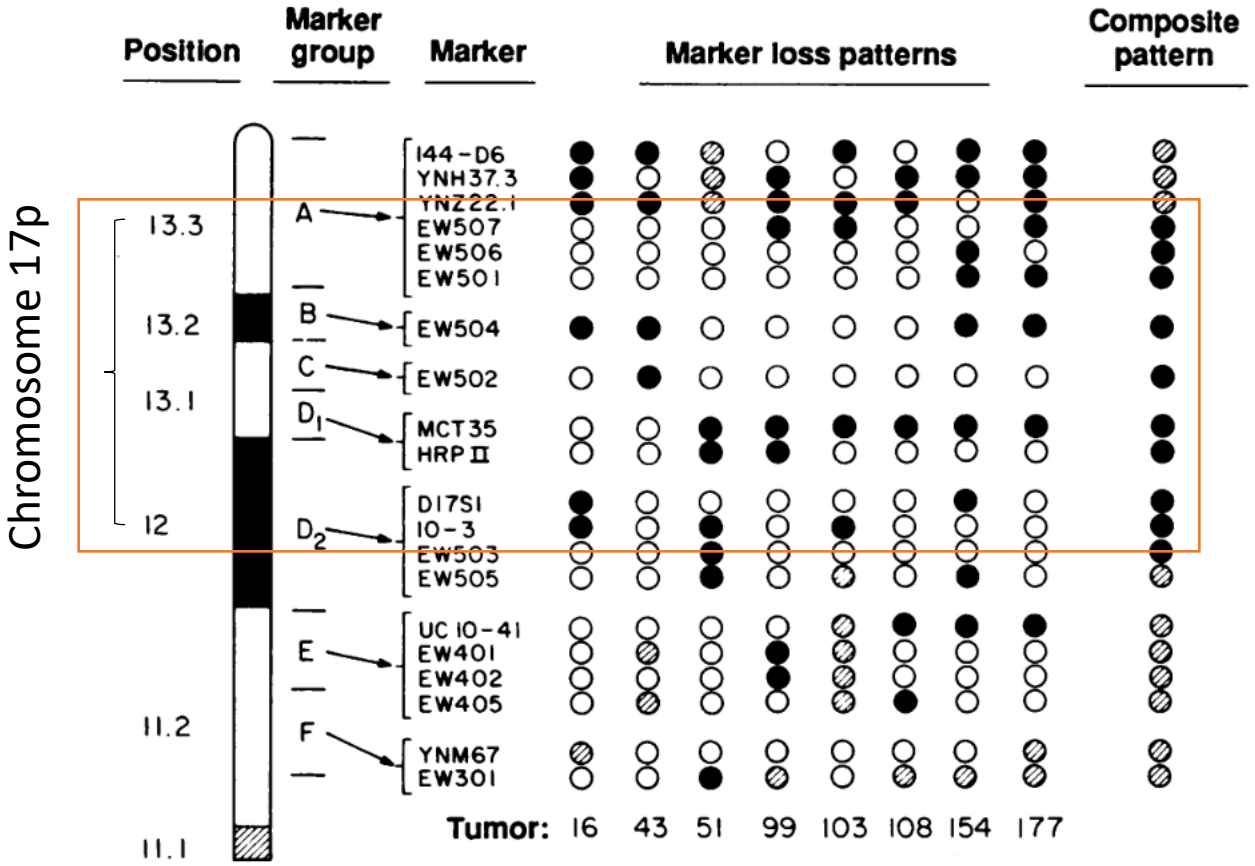
Transduction of mutant *TP53* cDNA transforms targeted cells

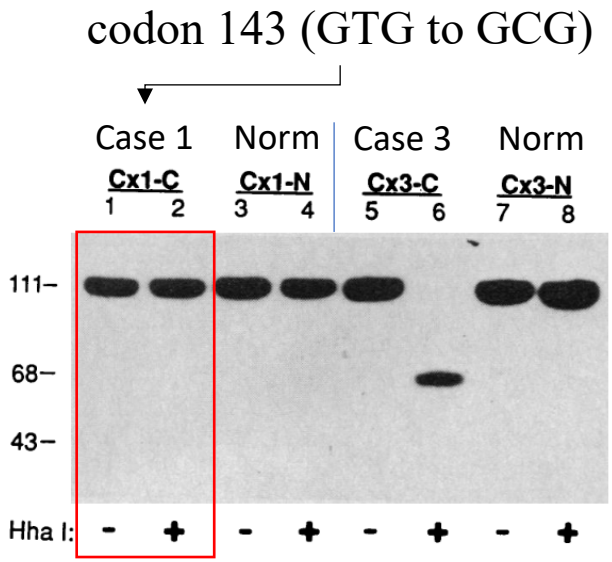
1. Eliyahu D, Raz A, Gruss P, Givol D, **Oren M.** Participation of p53 cellular tumour antigen in transformation of normal embryonic cells. ***Nature.*** **1984**;312:646–9

2. Jenkins JR, Rudge K, Currie GA. Cellular immortalization by a cDNA clone encoding the transformation-associated phosphoprotein p53. ***Nature.*** **1984**;312:651–4

3. Parada LF, Land H, Weinberg RA, Wolf D, Rotter V. Cooperation between gene encoding p53 tumour antigen and ras in cellular transformation. ***Nature.*** **1984**;312:649–51

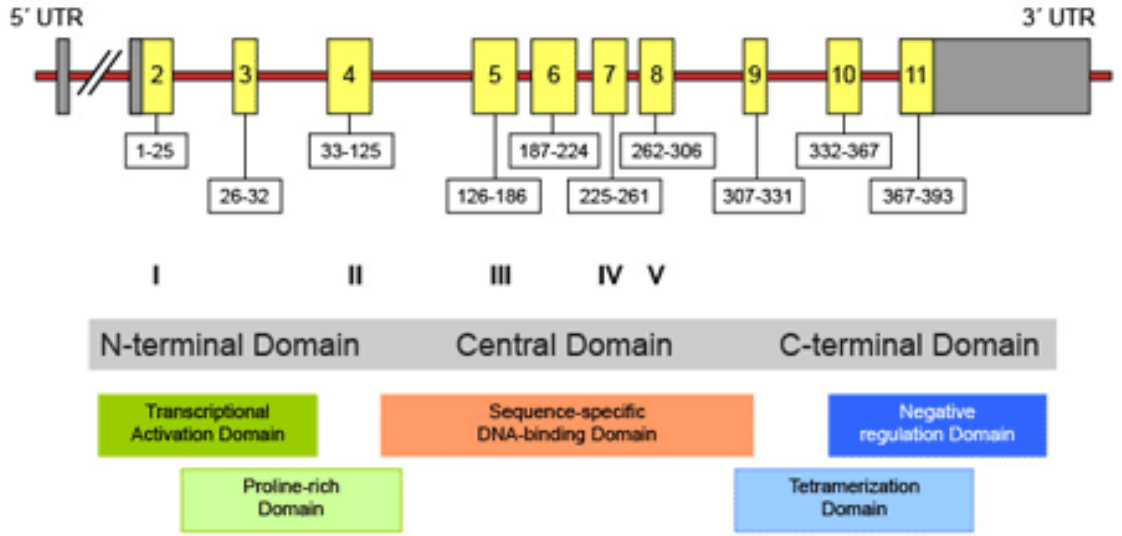
TP53 is a tumor suppressor gene

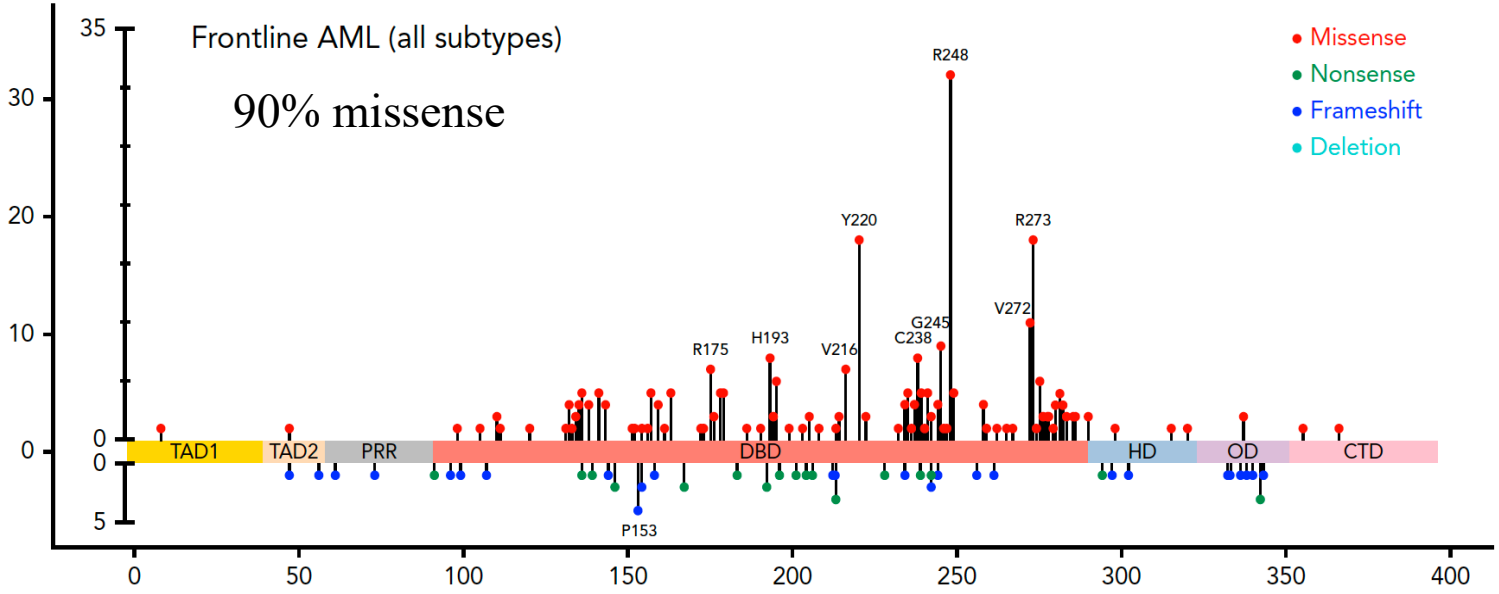




Baker…Vogelstein, Nature 1989

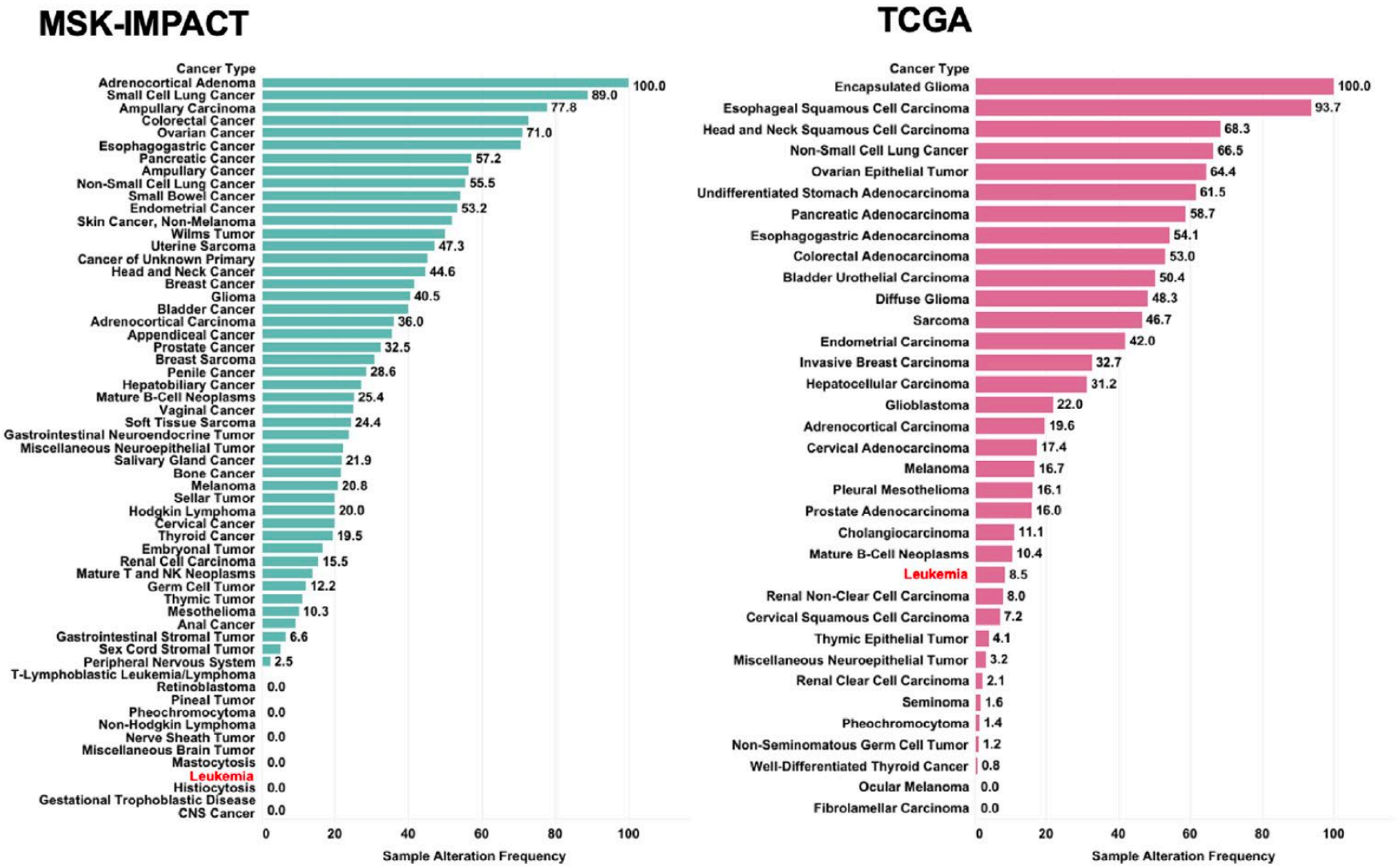
In AML *TP53* mutations concentrated in the core domain





Tashakori et al, Blood 2022

Frequency of *TP53* mut across human cancers



Barbosa et al, *Genes Chromosomes Cancer. 2019*

Mutated *TP53* more common in older AML

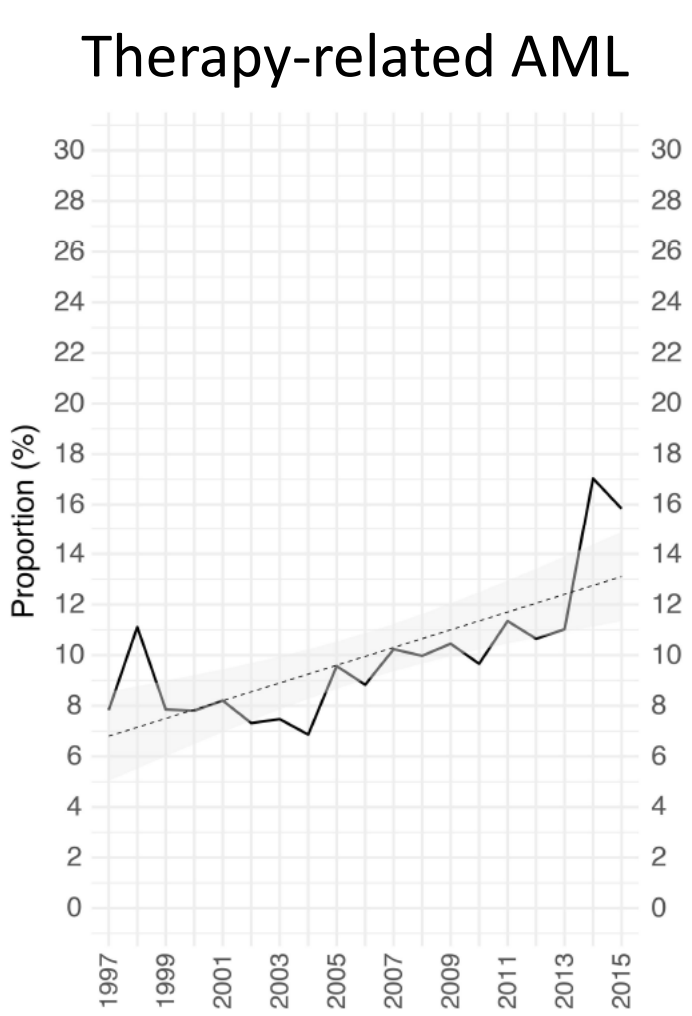
Reference	Age (years)	N	TP53 mutant
Tsai, ASH 2015	15-59	285	4%
Metzeler, Blood 2016	18-59	376	4%
Dohner, Leukemia 2018	≥65	156	21%
DiNardo, NEJM 2020	≥65	52	19%
Metzeler, Blood 2016	≥60	288	18%
Kadia, Lancet Hematol 2018	≥60	196	18%
Welch, NEJM 2016	≥60	54	17%
Prassek, Haematologica 2018	≥75	151	14%
Renaud, Am J Hematol 2018	≥80	88	17%
Tsai, ASH 2015	≥60	177	13%

TP53 mut prevalent in t-MN

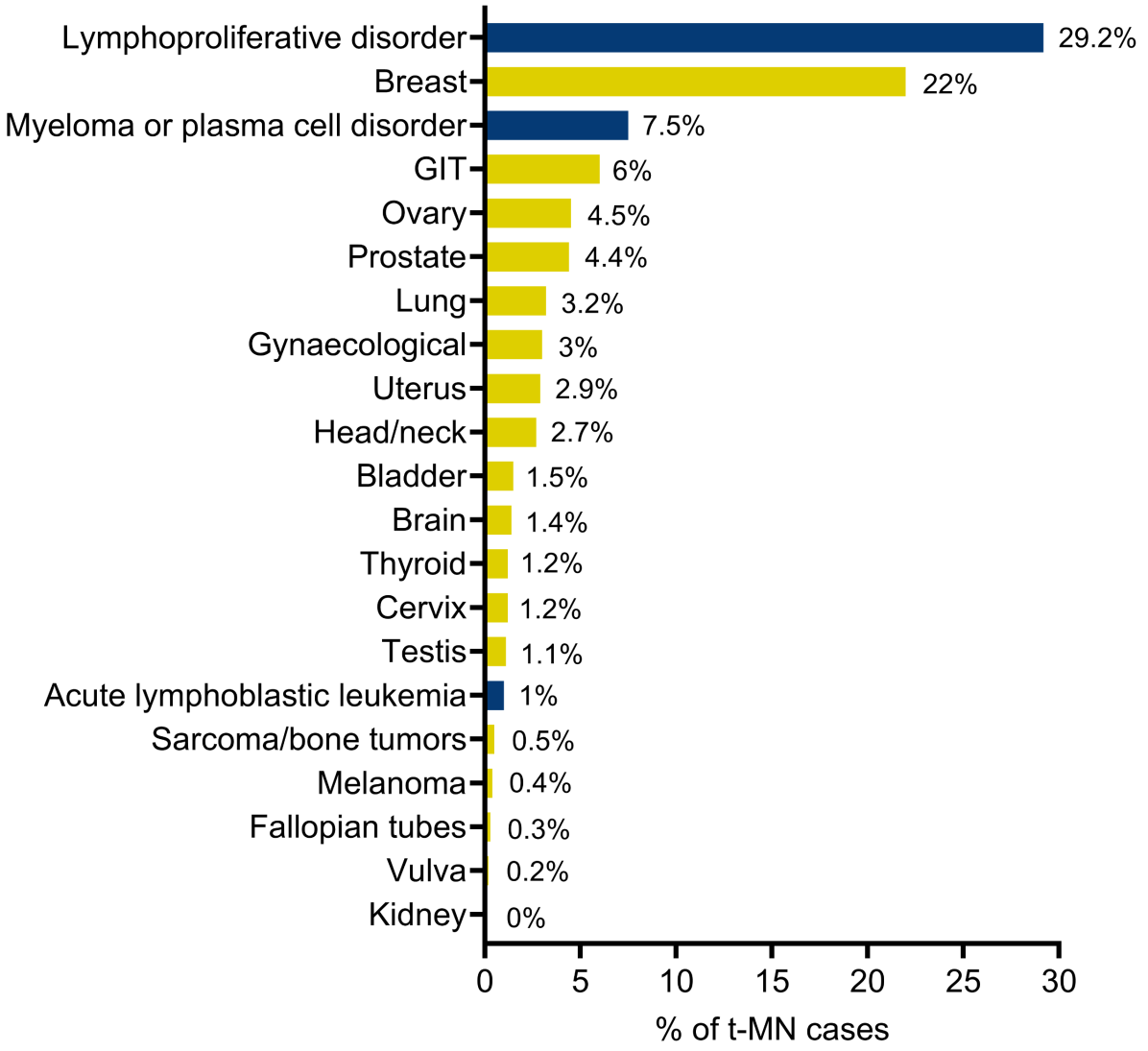
Gene mutation	t-MN(%)
ASXL1	3–17
CEBPA	0–5
DNMT3A	8–27
EZH2	3–4
FLT3	8–16
IDH1	3–5
IDH2	0–5
KMT2A	3
KRAS	11
NPM1	4–16
NRAS	10–13
PTPN11	3–9
RUNX1	11–16
SF3B1	0–3
SRSF2	8–11
TET2	6–14
TP53	**23–37**
U2AF1	5–8

Lindsley, Blood 2015
Christiansen, Leuk 2005
Shih, Haematologica 2013
Wong, Nature 2015
Bacher, Haematologica 2007
Voso, Leuk 2013

TP53 mutated AML is increasing in frequency



Nilsson et al, Hematologica 2023

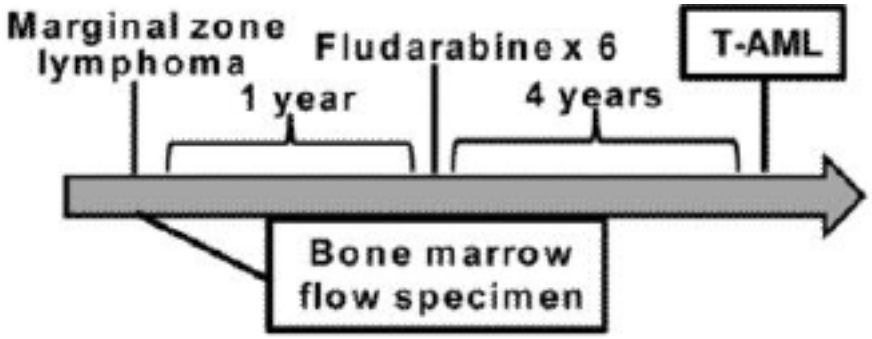


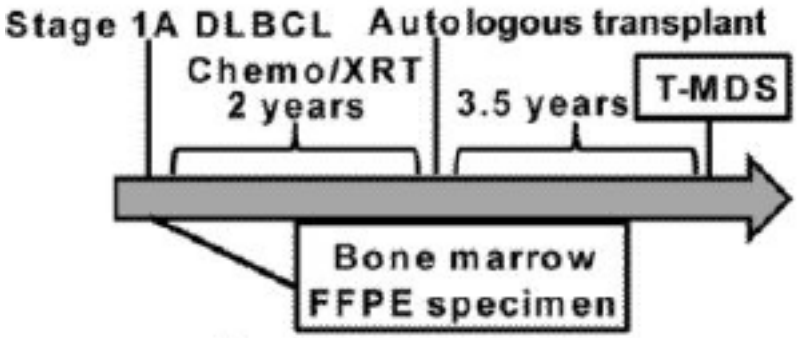
Singhal et al, Blood Cancer Discovery 2024

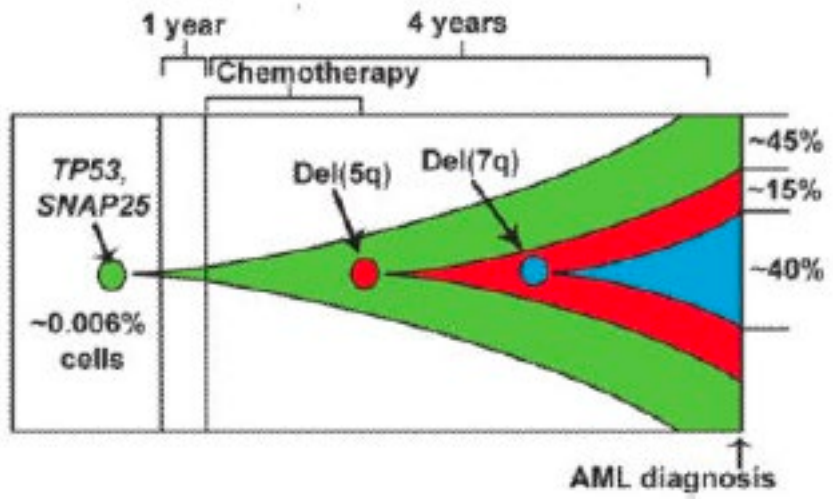
Therapy-related MN after prior hematological malignancy

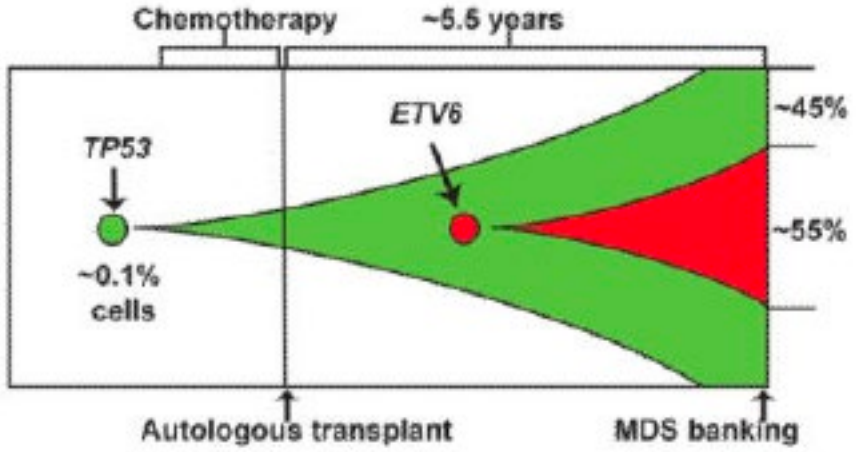
Scenario	Occurrence of t-MDS/AML
FCR/FC for CLL	1.9 % (Laribi et al Hemasphere 2022)
BEACOPP for HL	~1 % (Eichenauer et al, Blood 2014)
CAR-T for R/R NHL	11 % at 2 years (Alkhateeb et al, BCJ 2022)
CAR-T for R/R MM	9 % at 2 years (Martin et al, JCO 2023)
CAR-T for R/R NHL CAR-T for R/R MM	~9 % at 3 years (Gurney et al, JAMA 2024) ~9 % at 3 years (Gurney et al, JAMA 2024)
CAR-T for R/R NHL	11 % at 3 years (Yeoh et al, ASH 2024)
CAR-T for R/R NHL	If CH at time of CAR-T, 19% tMN at 2 years (Saini et al, Blood Canc Disc 2022)
CAR-T for R/R NHL	If CH at time of CAR-T, 17% tMN at 3 years If TP53 or PPM1D mut at time of CAR-T, 22% tMN at 3 years (Yeoh et al, ASH 2024)

Mutated *TP53* precedes clinical presentation of t-MN









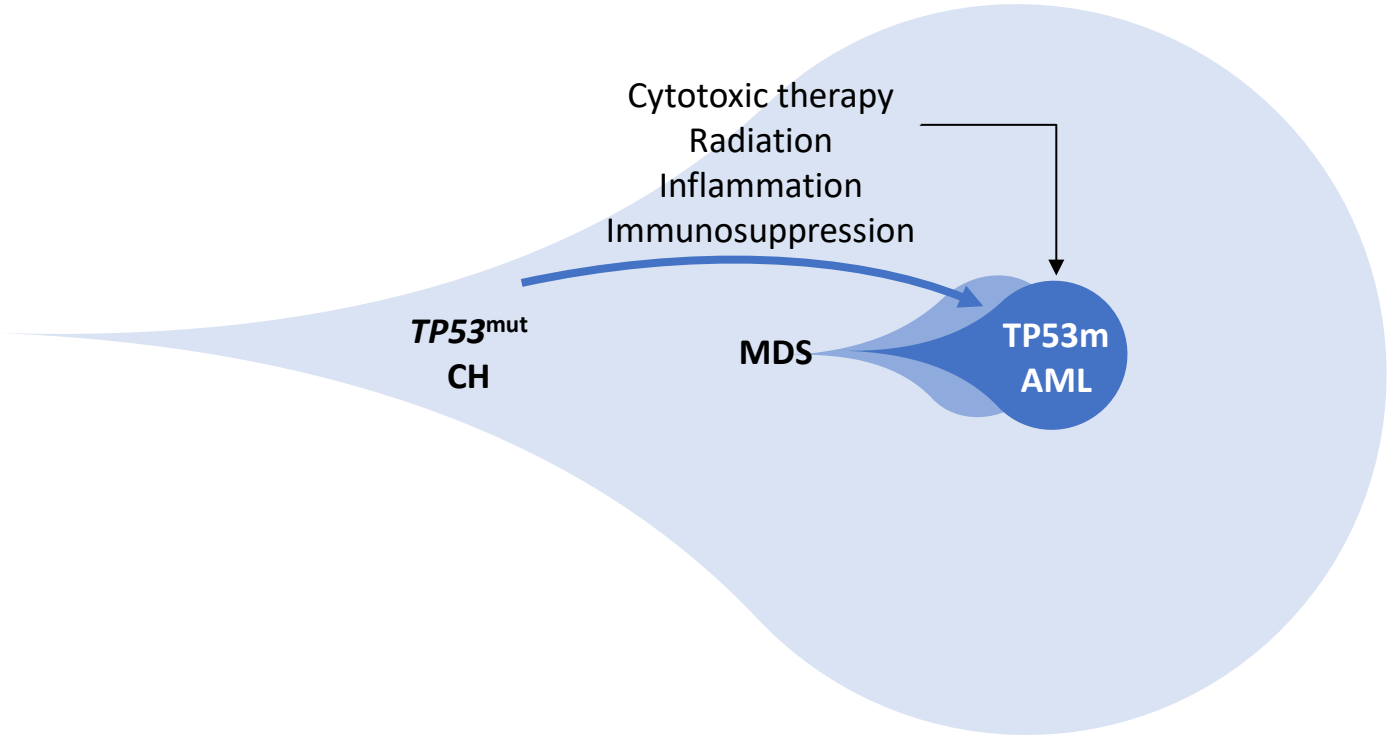
Wong et al, Nature. 2015

Pathogenic *TP53* variants in 9/19 WBC donors 68-89 yo

Sample	Chr	Exon	Start	Stop	Ref	Var	Amino acid	COSMIC ID	Var count	Total read family count	VAF (read-family	VAF (ddPCR)
34	17	7	7518230	7518230	T	G	D259A	none	13	33085	0.039%	N.D.
99	17	7	7518273	7518273	C	T	G245S	COSM6932	18	41836	0.043%	N.D.
99	17	8	7517849	7517849	C	T	V272M	COSM10891	26	81015	0.032%	N.D.
269	17	8	7517845	7517845	C	T	R273H	COSM10660	489	420026	0.12%	N.D.
271	17	5	7519138	7519138	C	T	V173M	COSM11084	177	182809	0.097%	0.081%
271	17	5	7519174	7519174	C	T	A161T	COSM10739	25	164591	0.015%	N.D.
271	17	NA	7520035	7520035	A	T	SPLICING	COSM152274	23	165672	0.014%	N.D.
271	17	NA	7517934	7517934	C	T	INTRONIC	none	36	333996	0.011%	N.D.
273	17	6	7518990	7518990	A	G	I195T	COSM11089	57	15540	0.37%	0.28%
300	17	6	7518915	7518915	T	C	Y220C	COSM10758	91	316765	0.029%	0.029%
324	17	8	7517819	7517819	G	A	R282W	COSM10704	51	86090	0.059%	N.D.
335	17	7	7518264	7518264	G	C	R248G	COSM11564	245	218077	0.11%	N.D.
338	17	7	7518264	7518264	G	A	R248W	COSM10656	188	51001	0.37%	N.D.

Wong et al, *Nature*. 2015 February 26; 518(7540): 552–555

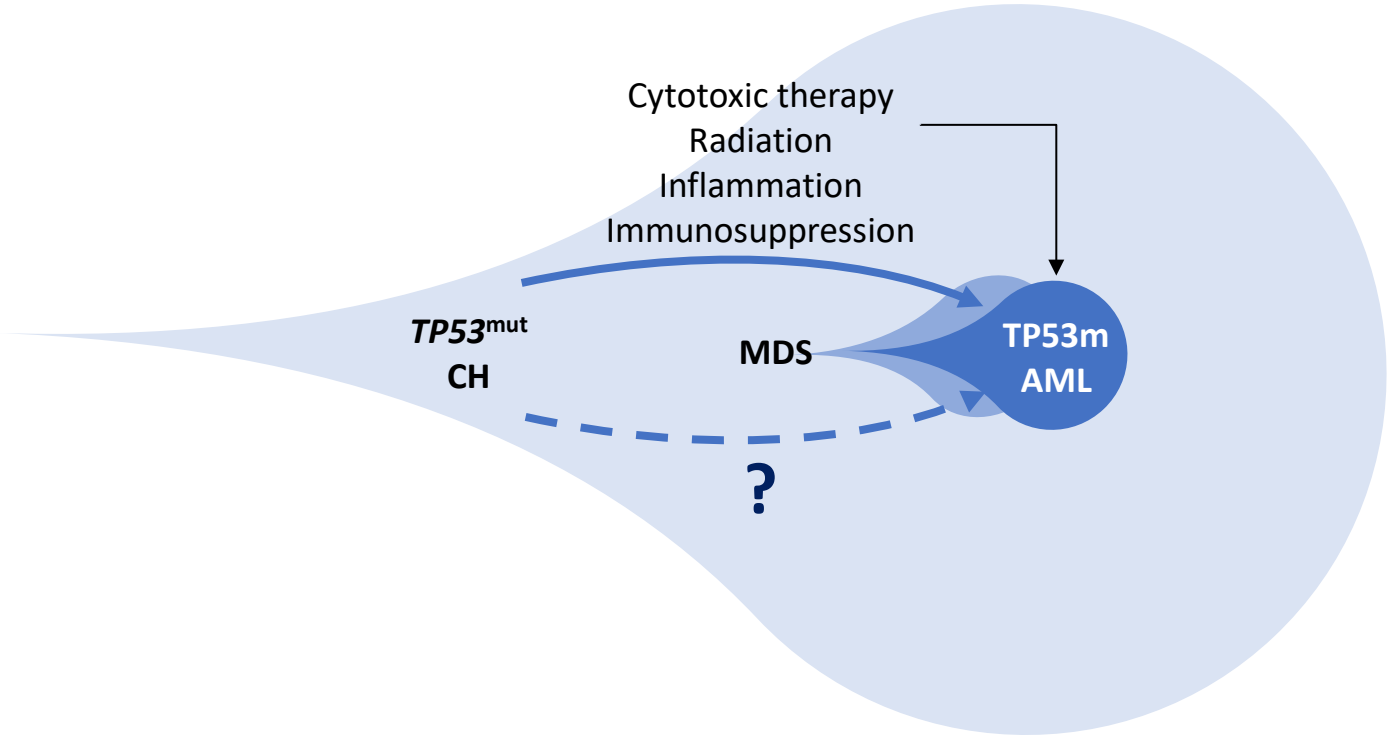
TP53^{mut} feature of older populations



Age	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
TP53 ^{mut} AML	0	0	0	5%	5%	6%	**16%**	**19%**
TP53 ^{mut} MDS	0	0	0	0	0	6%	**8%**	**7%**

Stengel et al. Leukemia 2017

What are the genomic events leading to *TP53*^{mut} AML?



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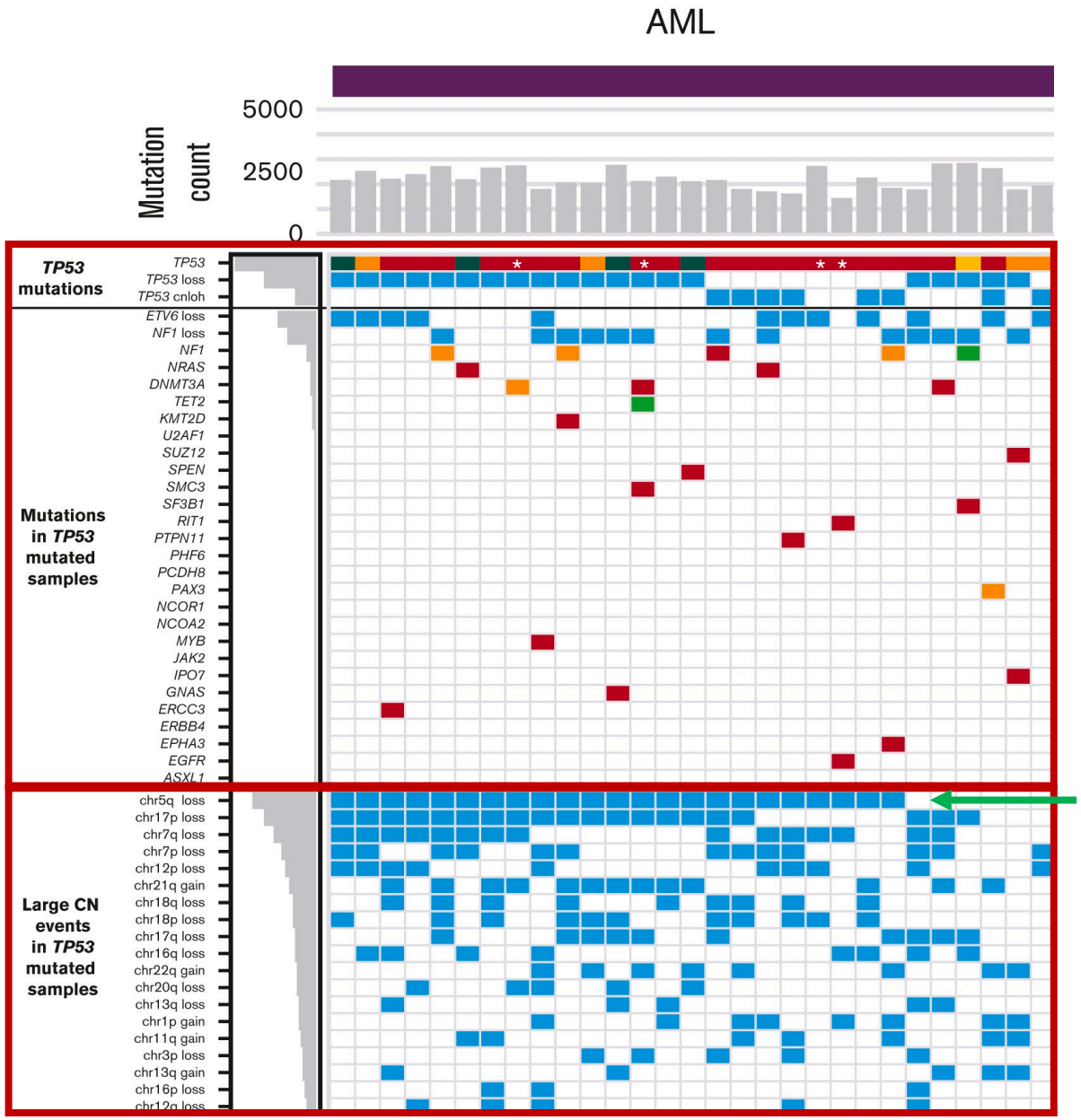
Stengel et al. Leukemia 2017

Typical AML driver mutations lacking in *TP53* mutated AML

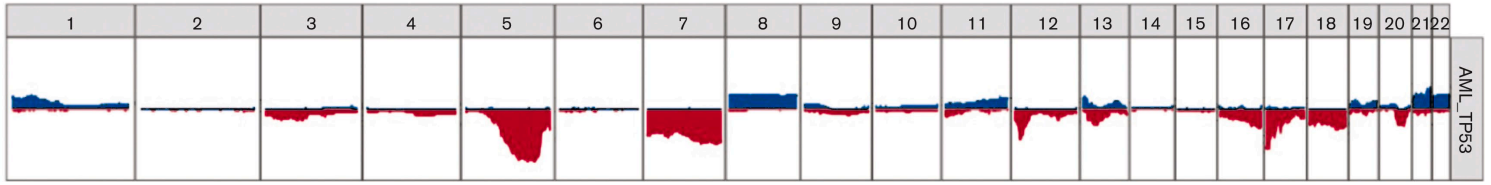


Chr 5q loss

Abel *et al.* (2023) *Blood Adv.*

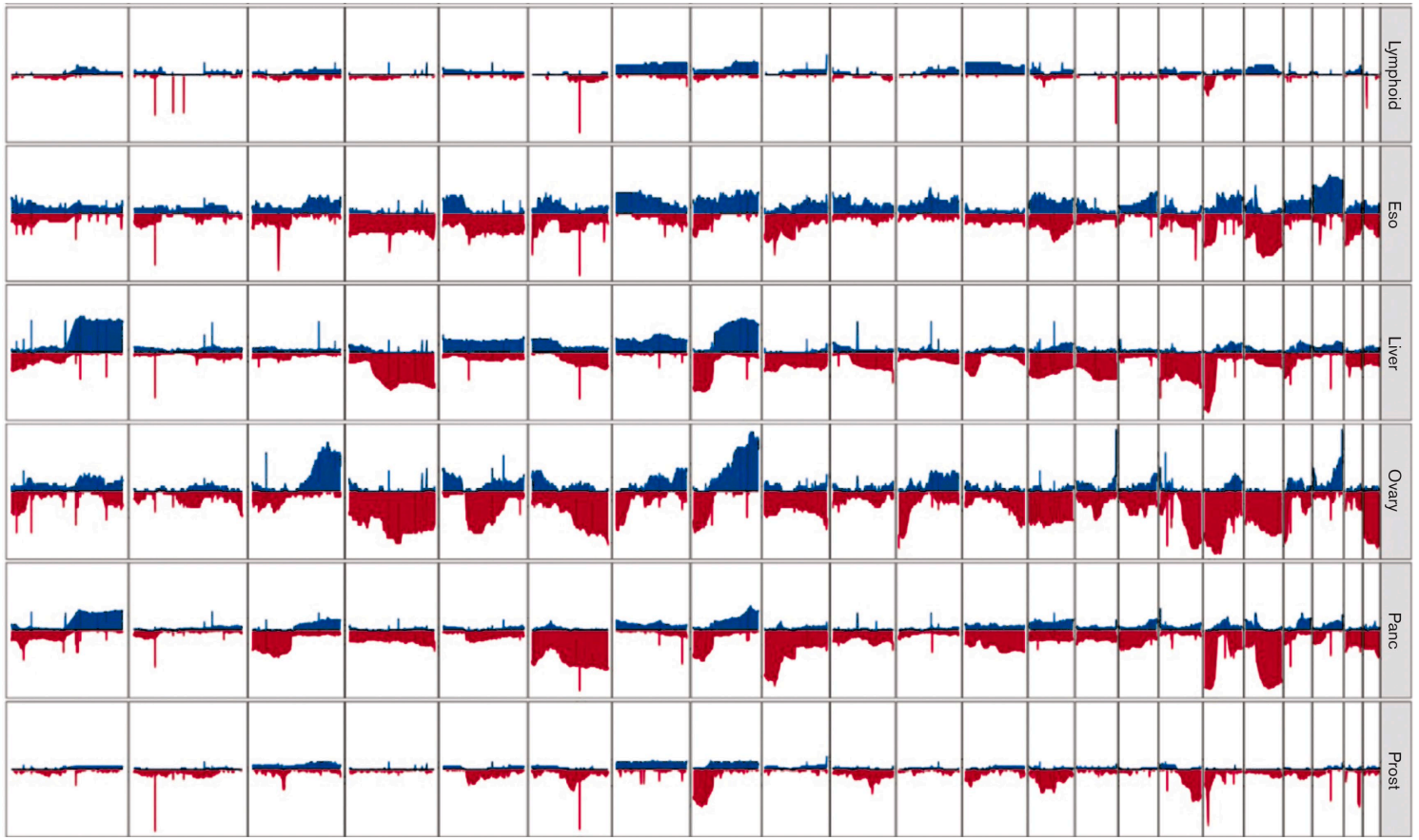
Copy number landscape of TP53 mut cancer is tissue specific

Myeloid malignancies



TP53 mut AML/MDS

Other cancers

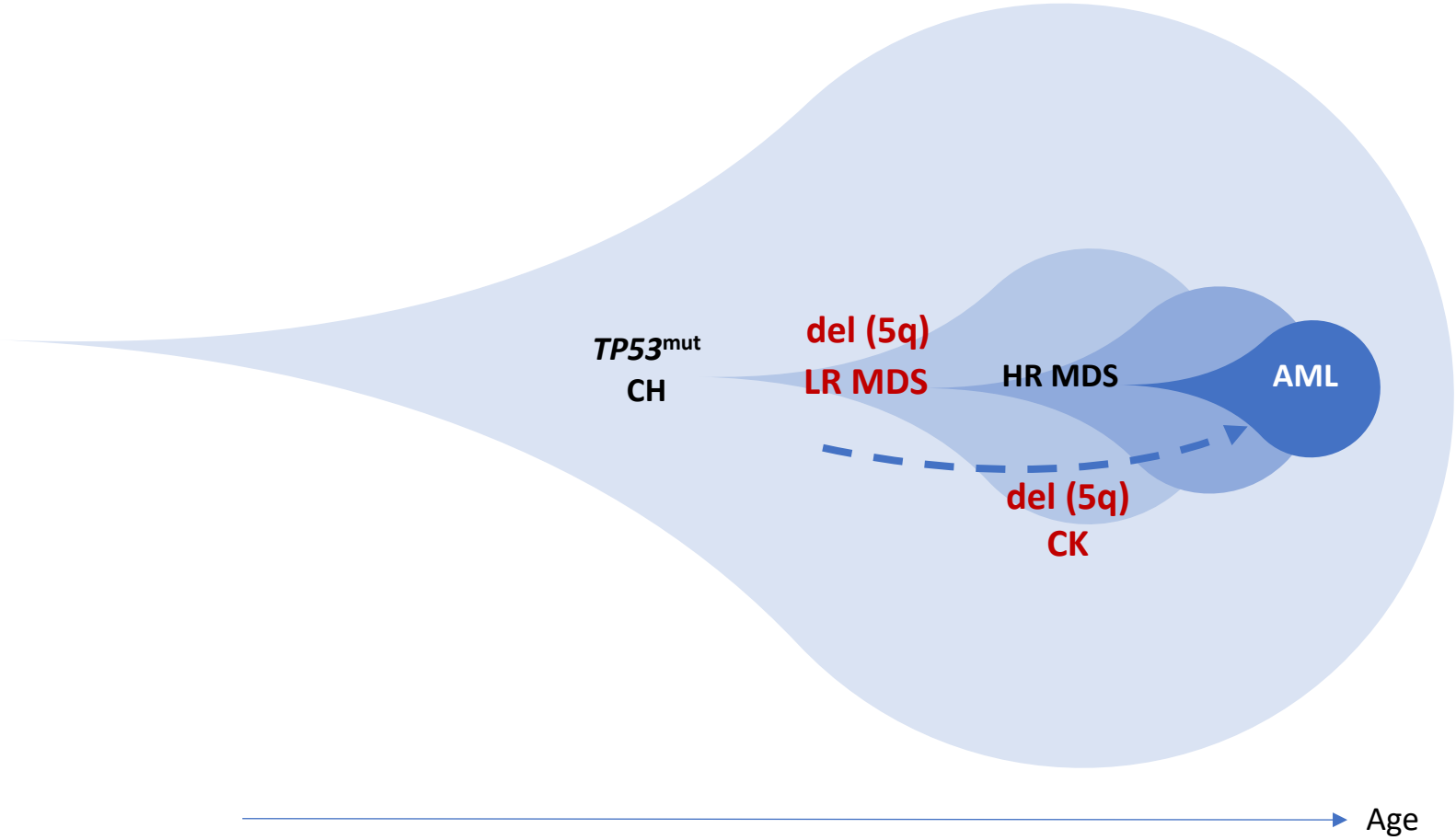


Lymphoid malignancies

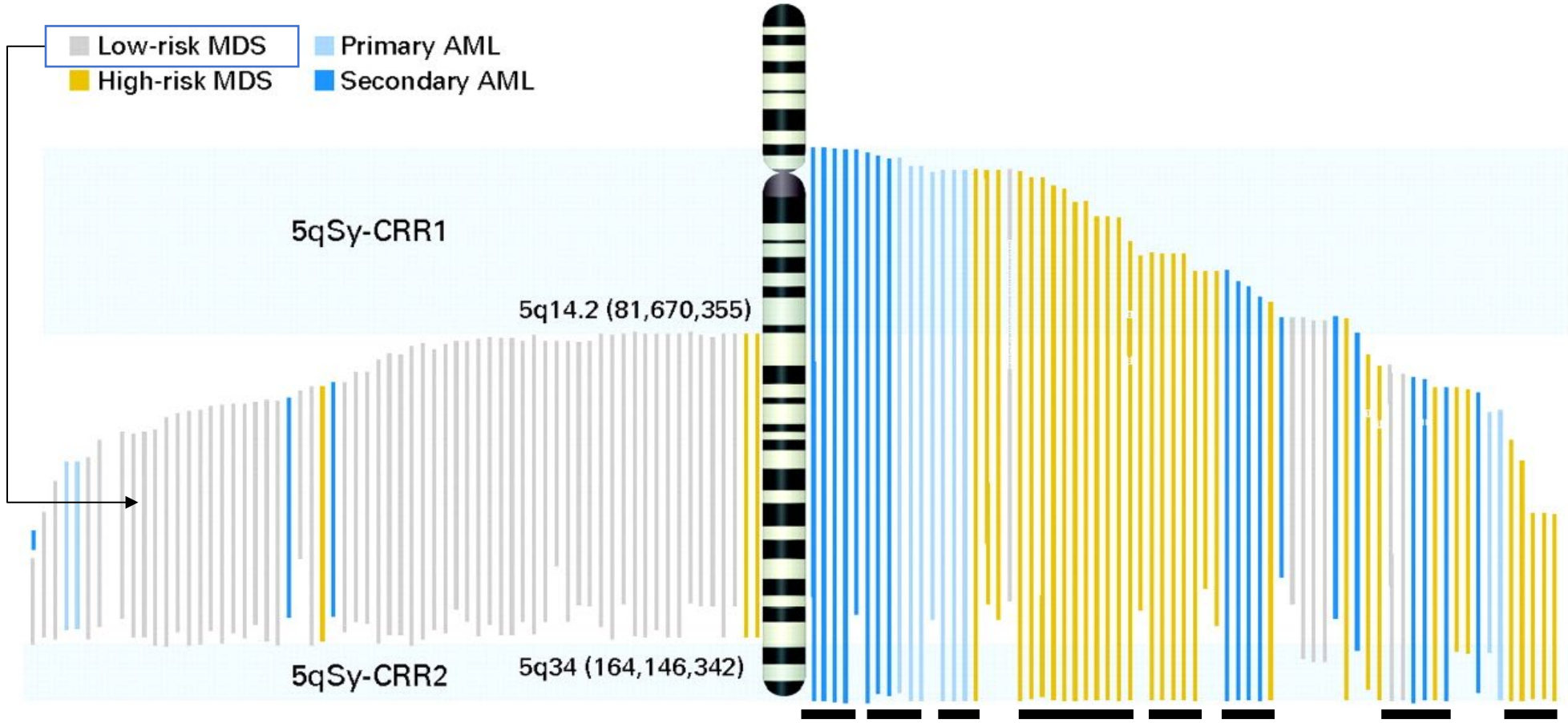
Solid cancers

Abel *et al.* (2023) *Blood Adv.*

Two faces of del(5q)



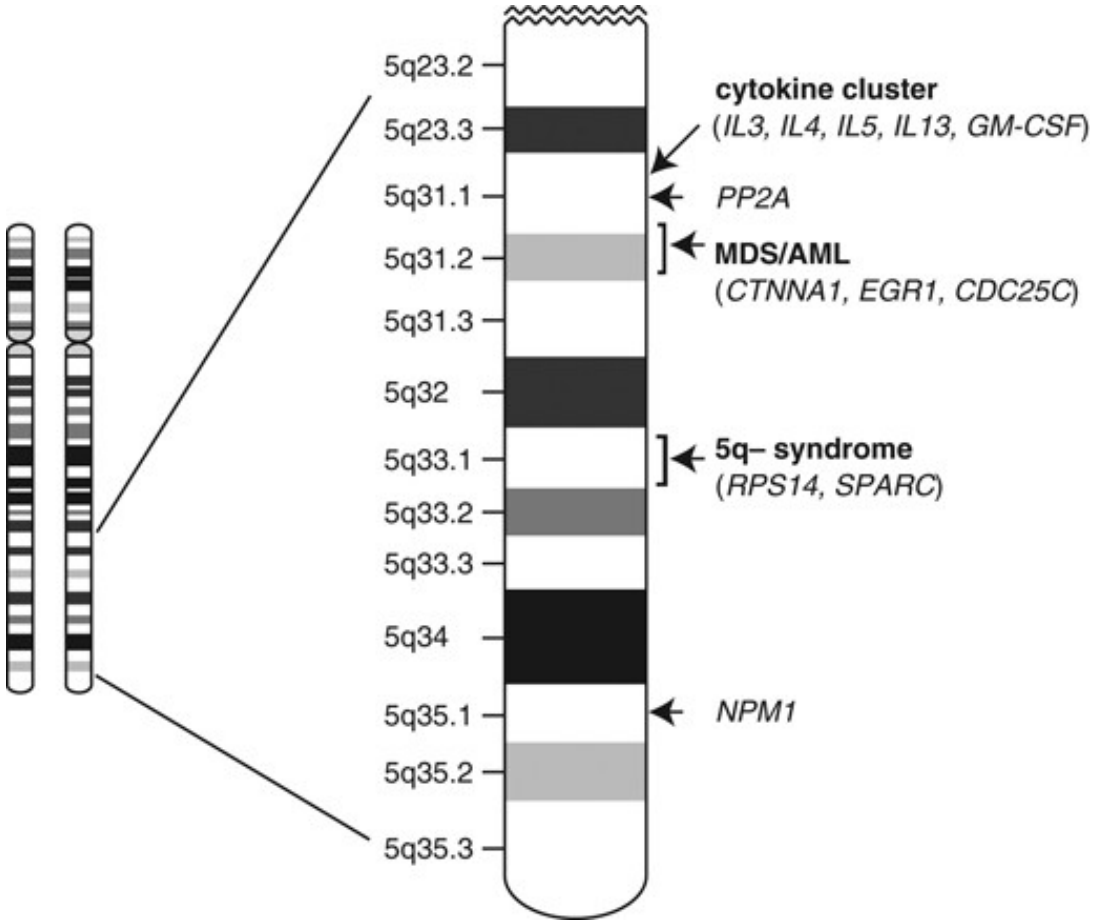
Patterns of del(5q) loss in MN



>5q35 CDR more associated with CK

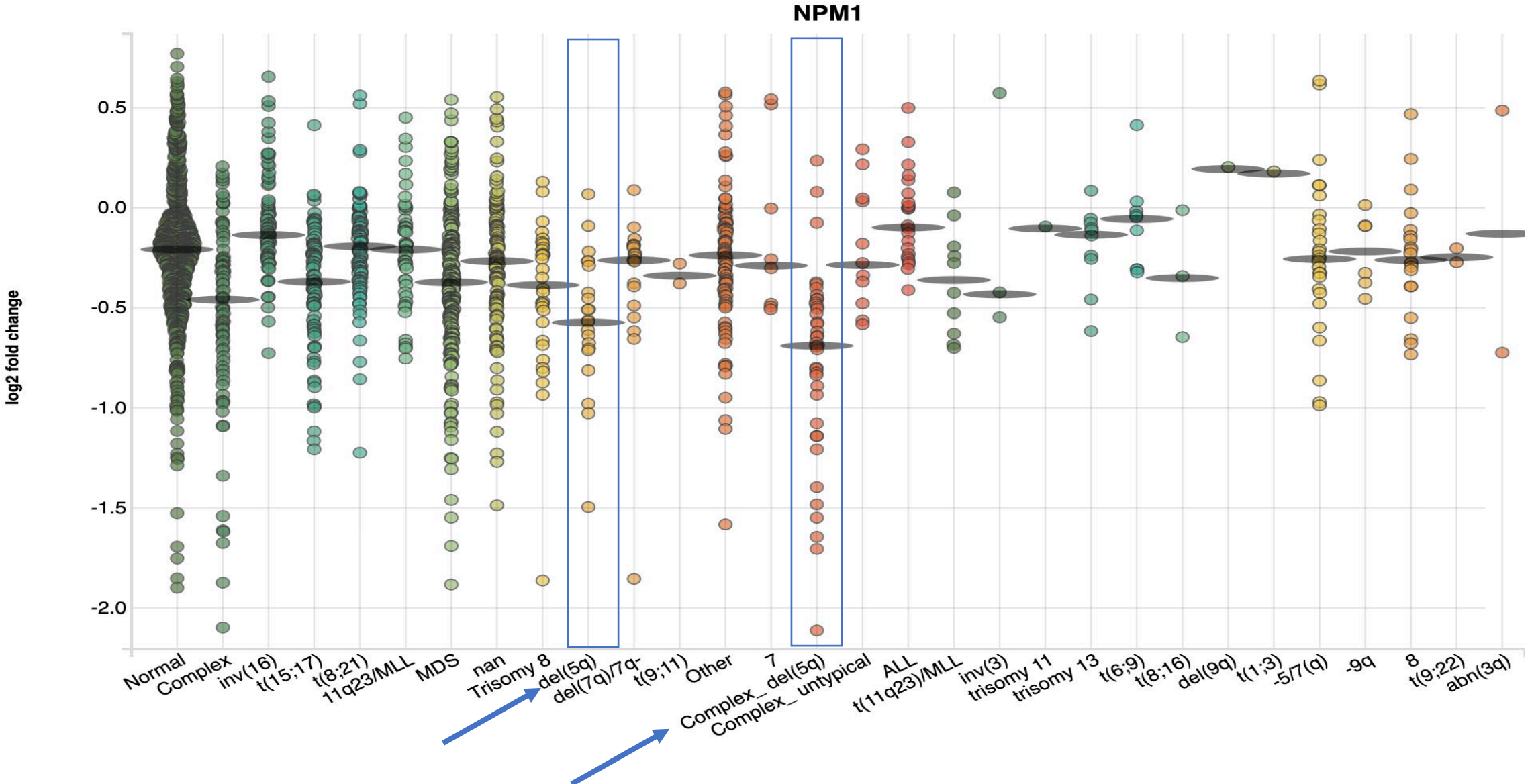
Jerez et al. *JCO*. 2012

Candidate 5q genes

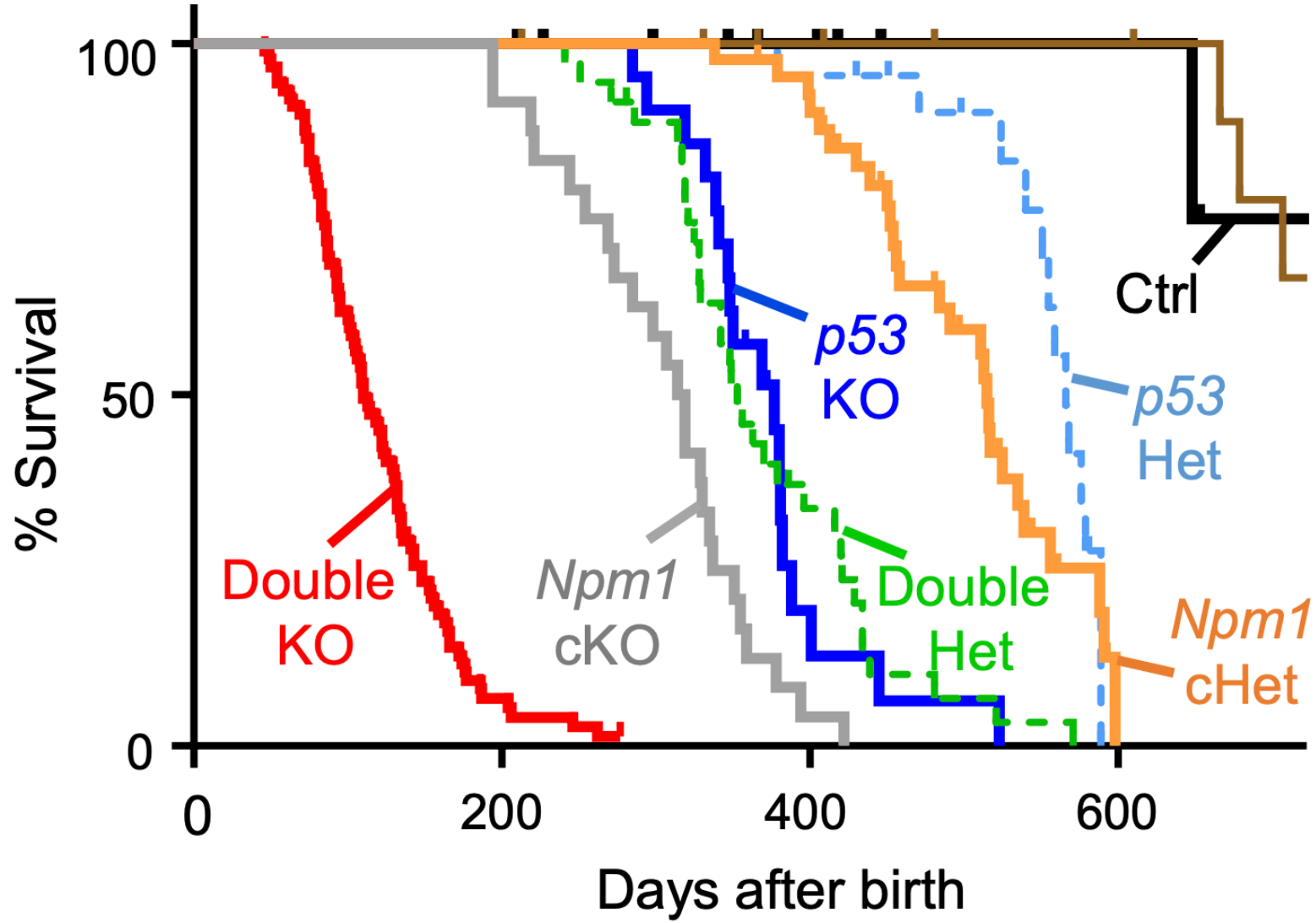


Ebert, Leukemia 2009

Reduced NPM1 expression in del(5q) AML



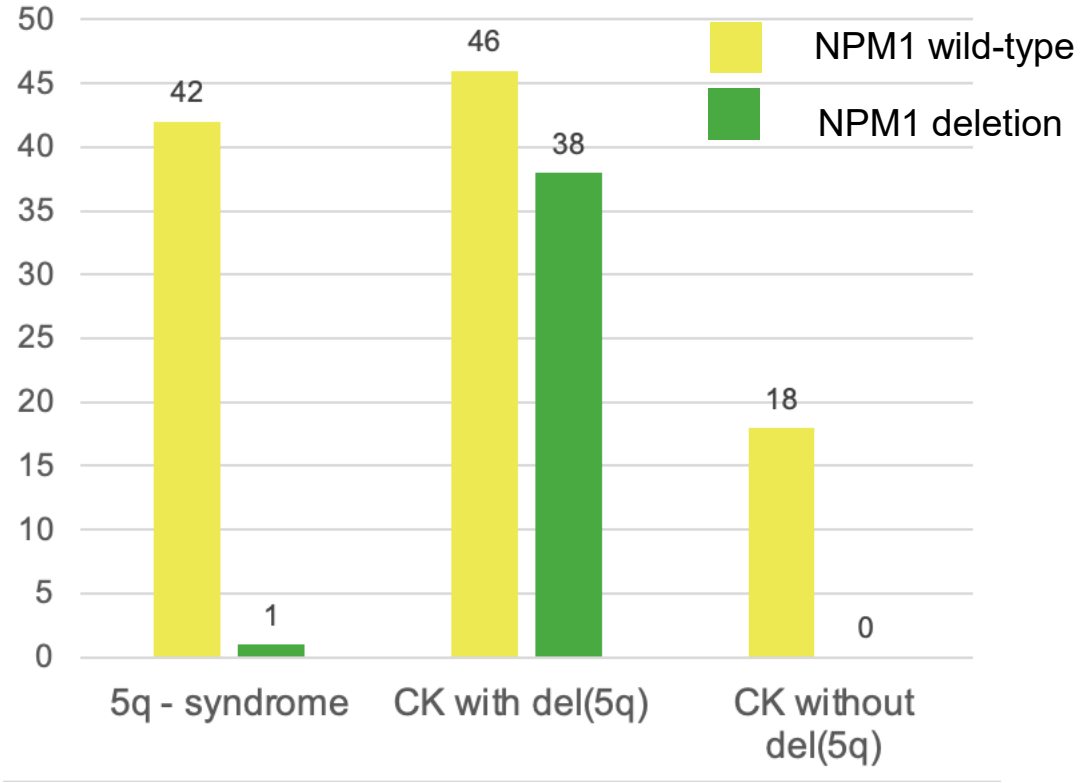
Npm1$^{F/F}$*p53*$^{-/-}$ *Vav1Cre*$^{+}$ DKO mice develop rapid AML



Morganti et al. *EMBO.* 2022

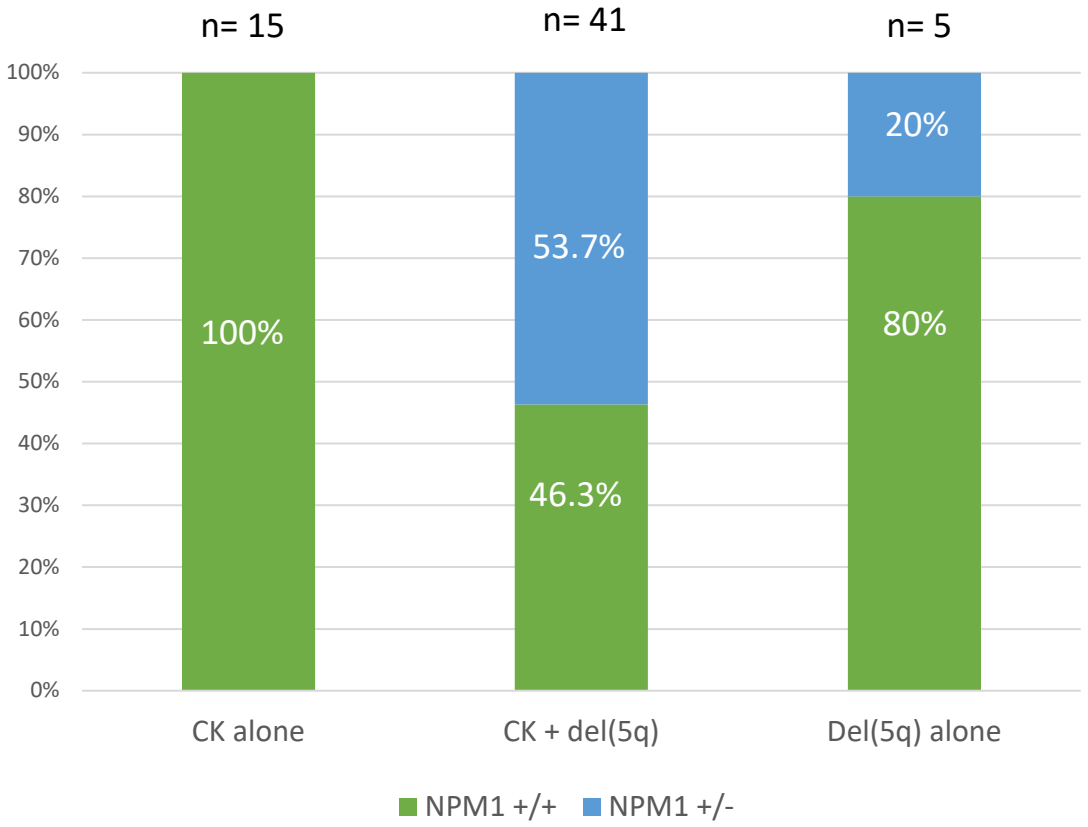
NPM1 loss in CK with del (5q)

NPM1 deletion in 45%



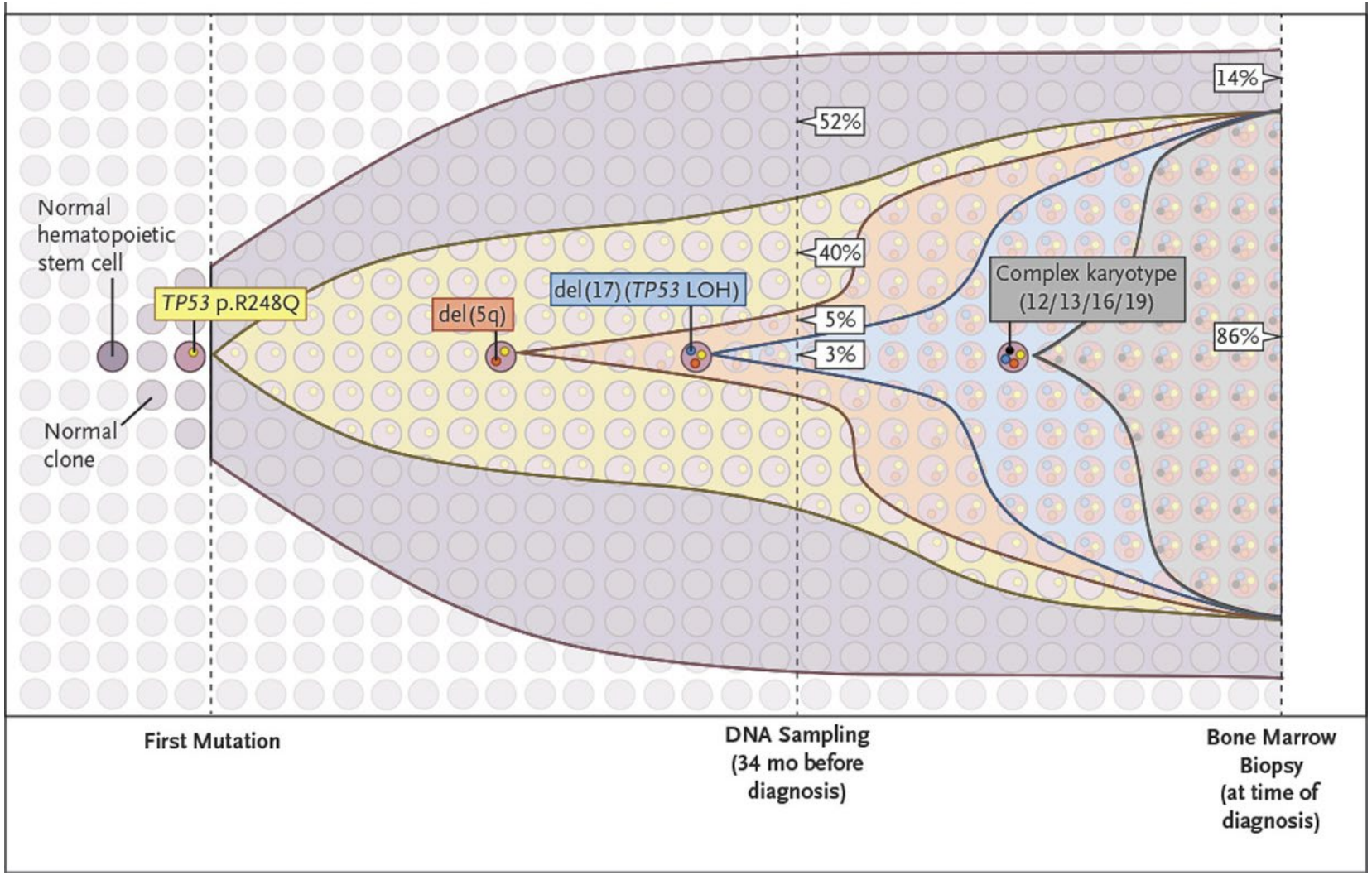
La Starza. *PLoS One.* 2010.

NPM1 deletion in 54%



Malalasakera et al, unpublished

Is there an ordered process to the development of *TP53* mut AML?



Genovese *et al.* (2014) *NEJM.*

Conclusions

- Frequency of *TP53* mut AML increasing
- Copy number changes associated with leukemic transformation
- Whether events leading to *TP53* mut myeloid transformation stochastic or iterative remains to be determined