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Minimal residual disease in smoldering myeloma


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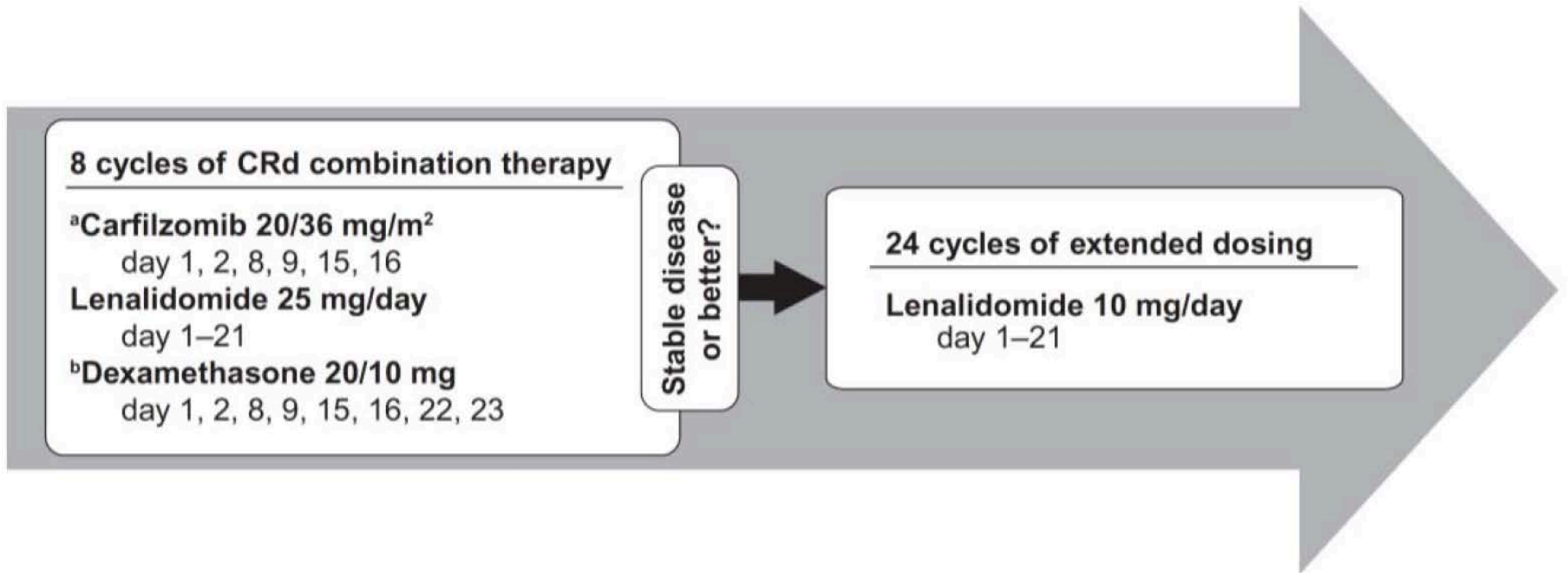
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- **MRD by flow cytometry and NGS**
 - **Genetic landscape**
 - **Future directions**



Korde et al, JAMA Oncology, 2015

17 patients with smoldering myeloma



Patients and treatment response

Best treatment response after combination therapy	Smoldering myeloma (N=17)
CR	16 (94%)
non-CR	1 (6%)

CR = complete response

MRD assessment

- MRD assessment at CR
- Multiparametric flow cytometry
 - Two tube eight color flow cytometry, sensitivity 10^{-5}
- Next generation sequencing for VDJ rearrangement using LymphoSIGHT
 - Sensitivity 10^{-6}

MRD assessment in SMM

		SMM
MRD by two-tube 8 color flow cytometry	Negative	16/17 (94%)
	Positive	1/17 (6%)
MRD by VDJ next generation sequencing	Negative	9/12 (75%)
	Positive	3/12 (25%)

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Mutational landscape

SMM patients n=17, NDMM patients=39

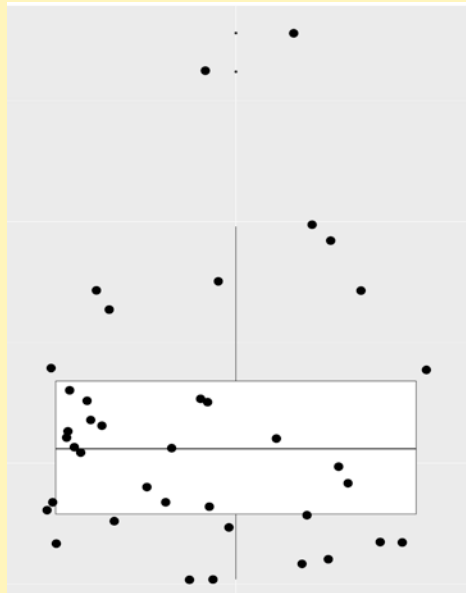
Tumor only DNA from CD138+ plasma cells from baseline

Whole exome sequencing, median coverage of 125x (range 105-185x)

Median number of mutations per patient

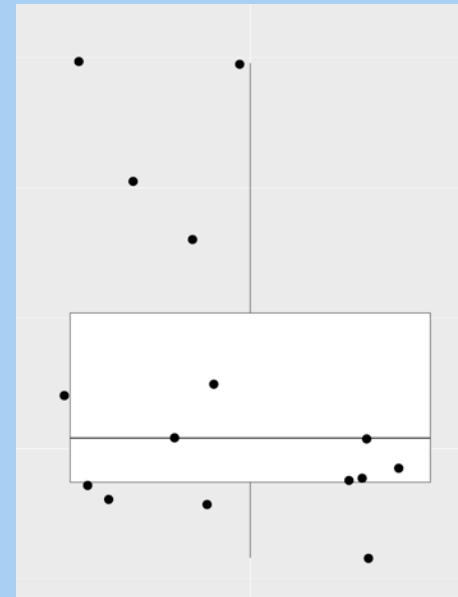
Non-synonymous mutations

Median number = 53



Newly diagnosed
multiple myeloma
N=39

Median number = 52



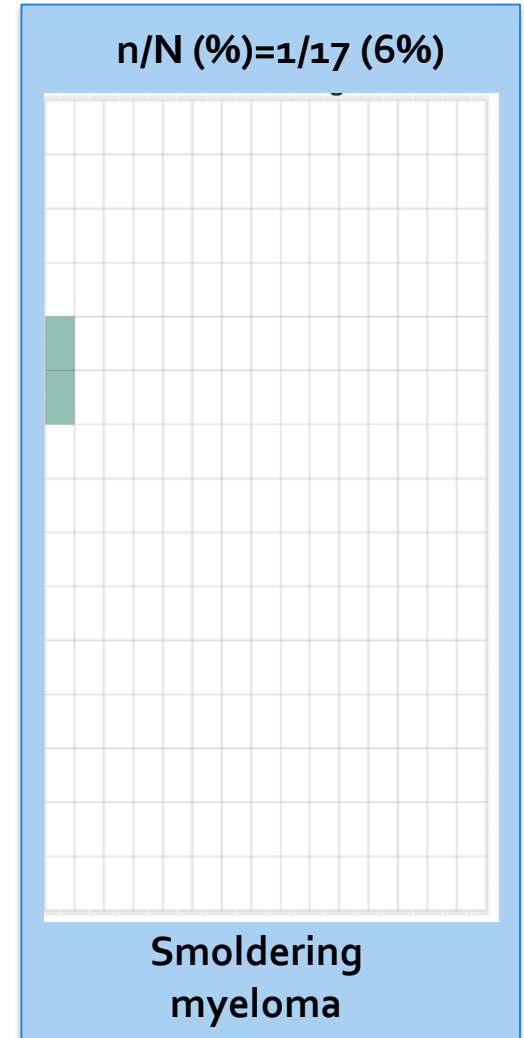
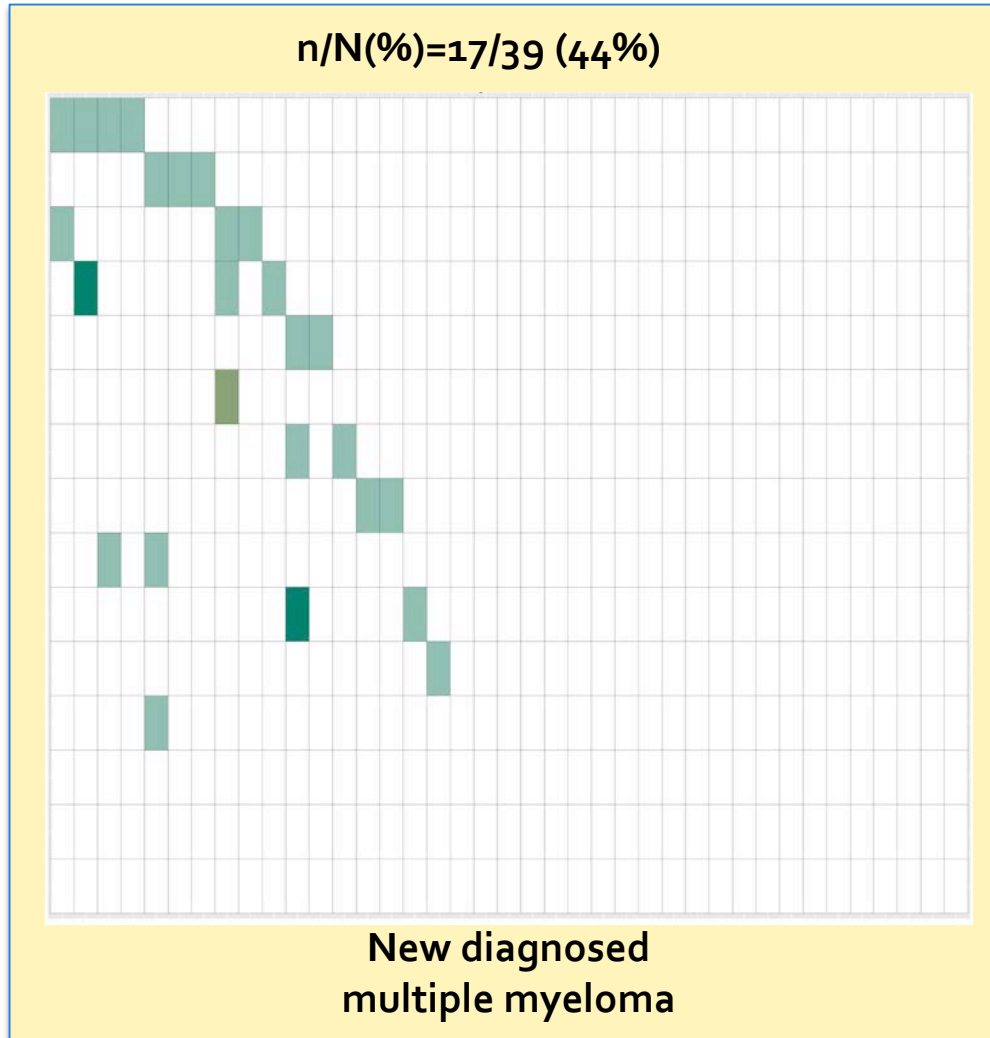
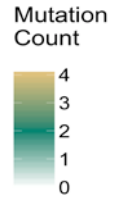
Smoldering
myeloma
N=17

Significantly recurrent mutations of individual genes in multiple myeloma

- KRAS
- NRAS
- BRAF
- CYLD
- FAM46C
- TRAF3
- DIS3
- IRF4
- HIST1H1E
- ACTG1
- TP53
- LTB
- PRDM1
- RB1
- MAX



Patients with mutations in significantly recurrent multiple myeloma genes



NDMM versus SMM, Fisher's exact test: P=0.005



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Future directions

- Relationship between molecular MRD positivity and immunophenotype?
- Relationship between mutations at MRD and clinical phenotype?
- Prognostic impact of the above?





Lessons learned from AML





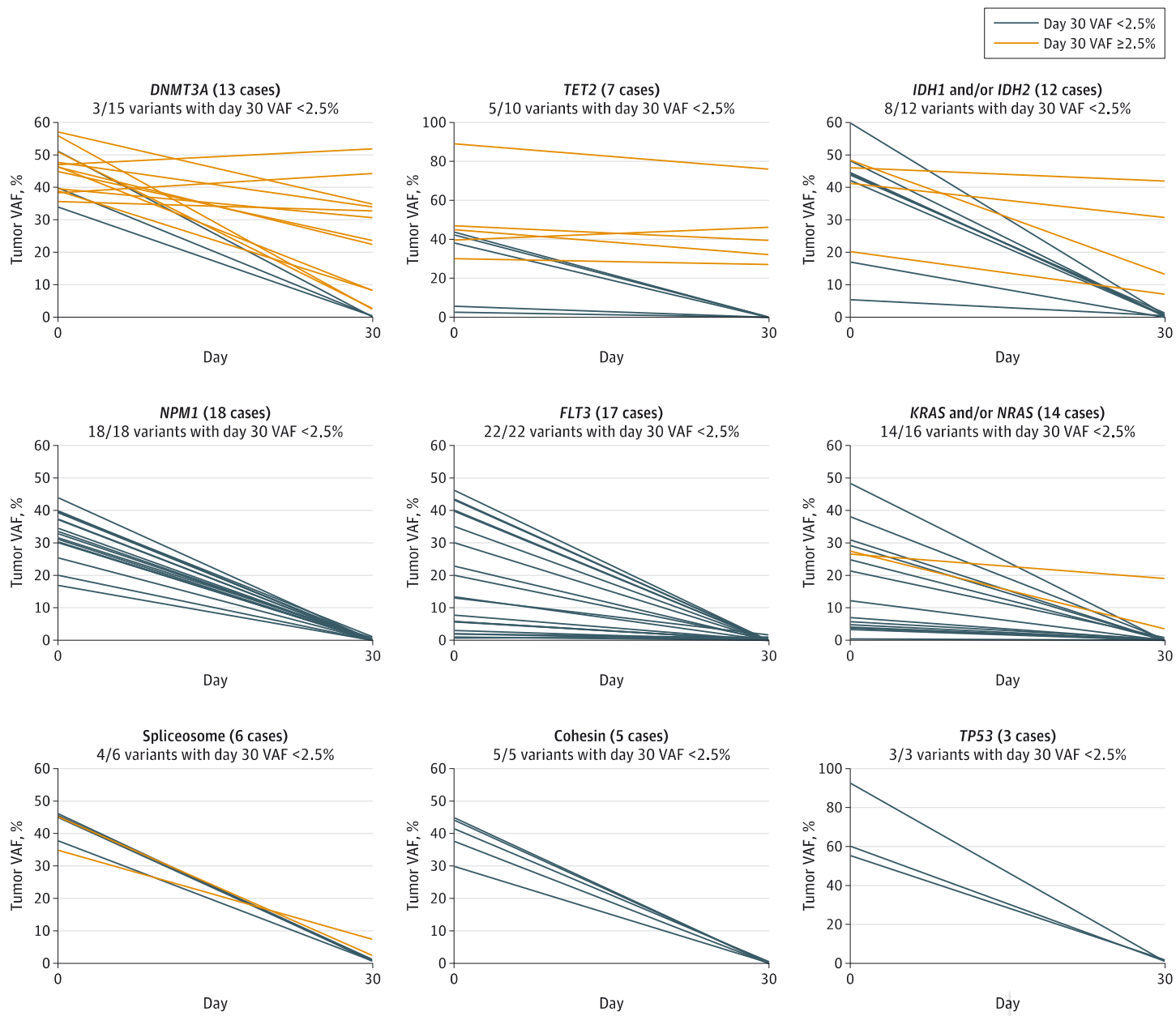
Association Between Mutation Clearance After Induction Therapy and Outcomes in Acute Myeloid Leukemia

Jeffery M. Klco, MD, PhD; Christopher A. Miller, PhD; Malachi Griffith, PhD; Allegra Petti, PhD; David H. Spencer, MD, PhD; Shamika Ketkar-Kulkarni, MS; Lukas D. Wartman, MD; Matthew Christopher, MD, PhD; Tamara L. Lamprecht, BS; Nicole M. Helton, BS; Eric J. Duncavage, MD; Jacqueline E. Payton, MD, PhD; Jack Baty, BA; Sharon E. Heath; Obi L. Griffith, PhD; Dong Shen, PhD; Jasreet Hundal, MS; Gue Su Chang, PhD; Robert Fulton, MS; Michelle O'Laughlin, BS; Catrina Fronick, BS; Vincent Magrini, PhD; Ryan T. Demeter, BE; David E. Larson, PhD; Shashikant Kulkarni, MS, PhD; Bradley A. Ozenberger, PhD; John S. Welch, MD, PhD; Matthew J. Walter, MD; Timothy A. Graubert, MD; Peter Westervelt, MD, PhD; Jerald P. Radich, MD; Daniel C. Link, MD; Elaine R. Mardis, PhD; John F. DiPersio, MD, PhD; Richard K. Wilson, PhD; Timothy J. Ley, MD

JAMA. 2015;314(8):811-822. doi:10.1001/jama.2015.9643.



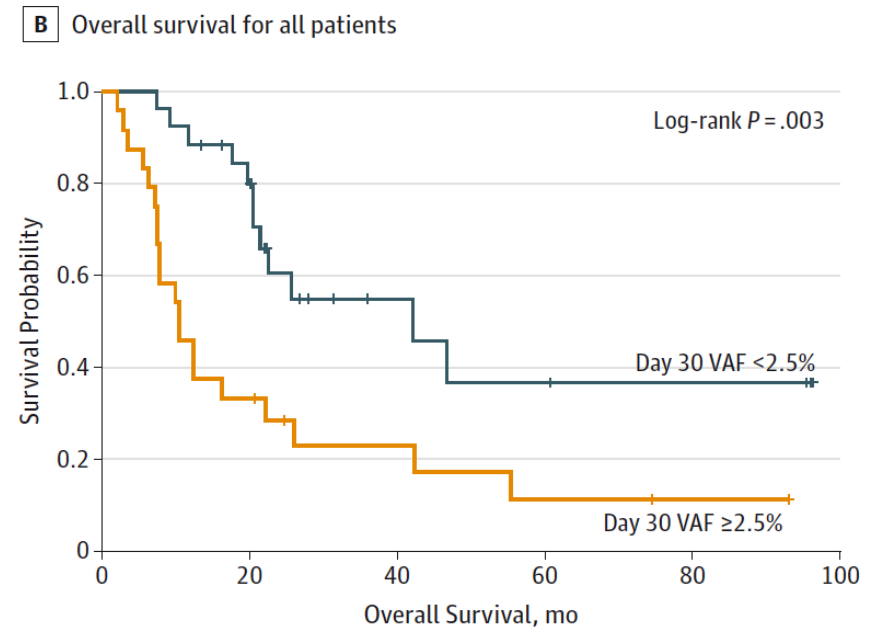
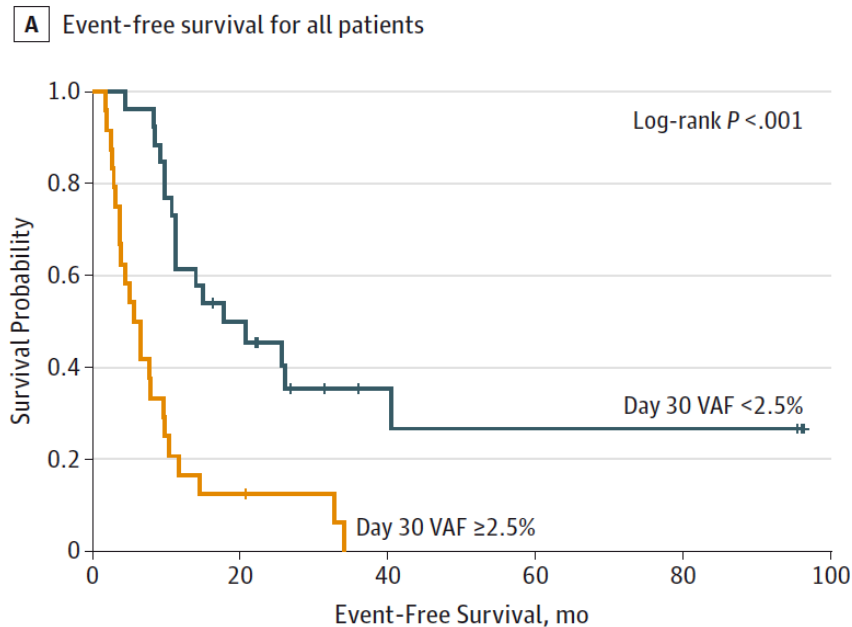
Figure 4. Day 30 Mutation Clearance by Gene for 50 Acute Myeloid Leukemia Cases



VAF indicates variant allele frequency. Serial VAF measurements demonstrating the clearance patterns of several recurrently mutated acute myeloid leukemia genes in the set of 50 cases. Orange lines indicate a day 30 VAF of 2.5% or more; blue lines indicate a day 30 VAF of less than 2.5%.

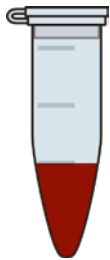
Mutation clearance and outcomes

Figure 5. Association Between Mutation Clearance and Outcomes

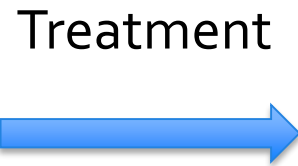


Profiling at diagnosis and MRD

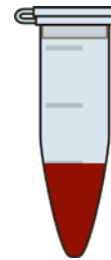
Diagnosis



M+ / M-



MRD



F+ M+

F+ M-

F- M+

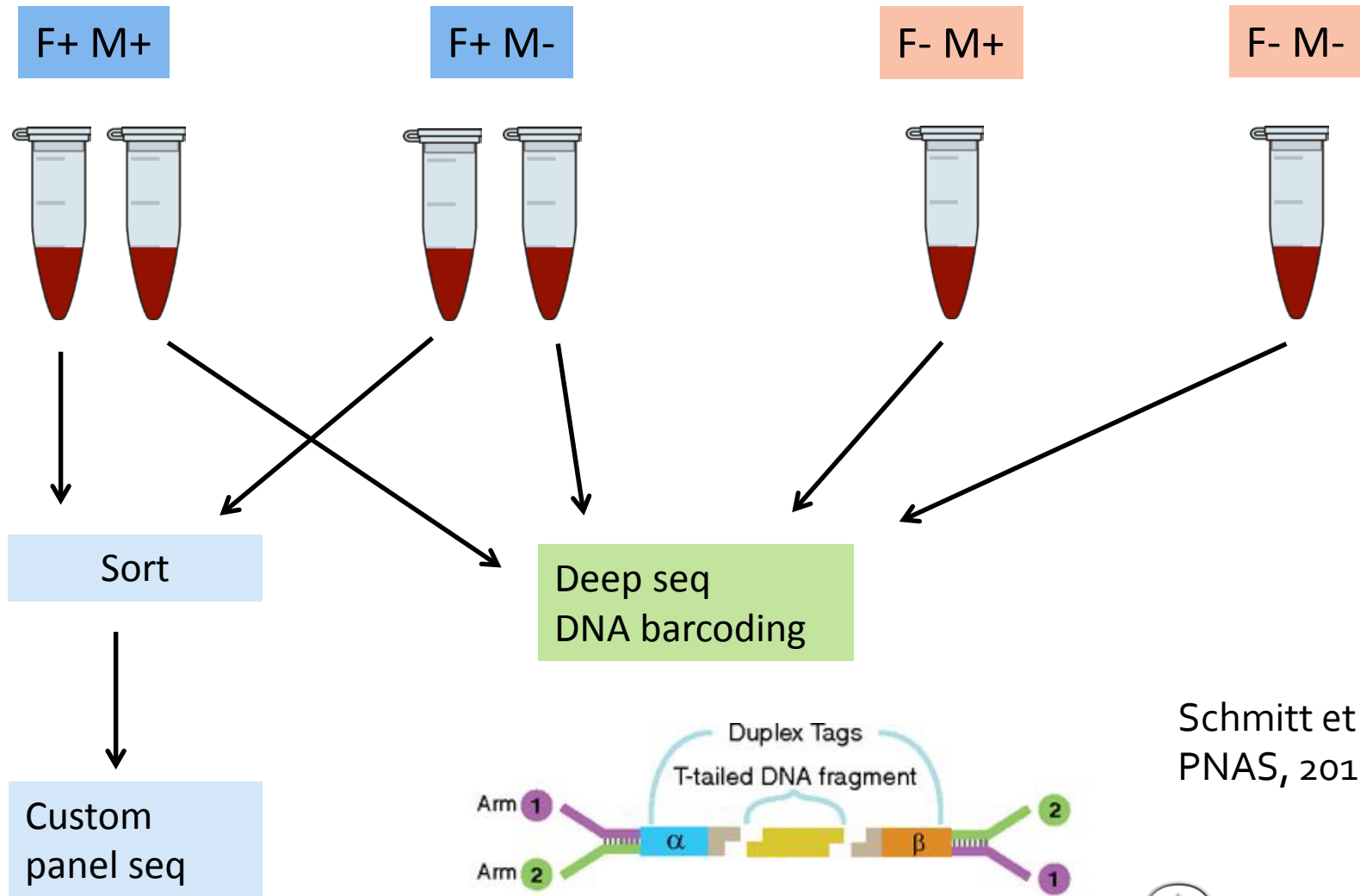
F- M-

M=mutations by NGS, F=flow cytometry



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Flow sort and sequencing of MRD



Schmitt et al,
PNAS, 2012



Future studies at MSKCC

- Profiling of MRD in smoldering and newly diagnosed myeloma
- Profiling of precursor disease
 - Case control study
 - iStopMM



iStopMM

Iceland Screens,
Treats or Prevents
Multiple Myeloma



Collaborators

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Austin Christofferson



Thank you!



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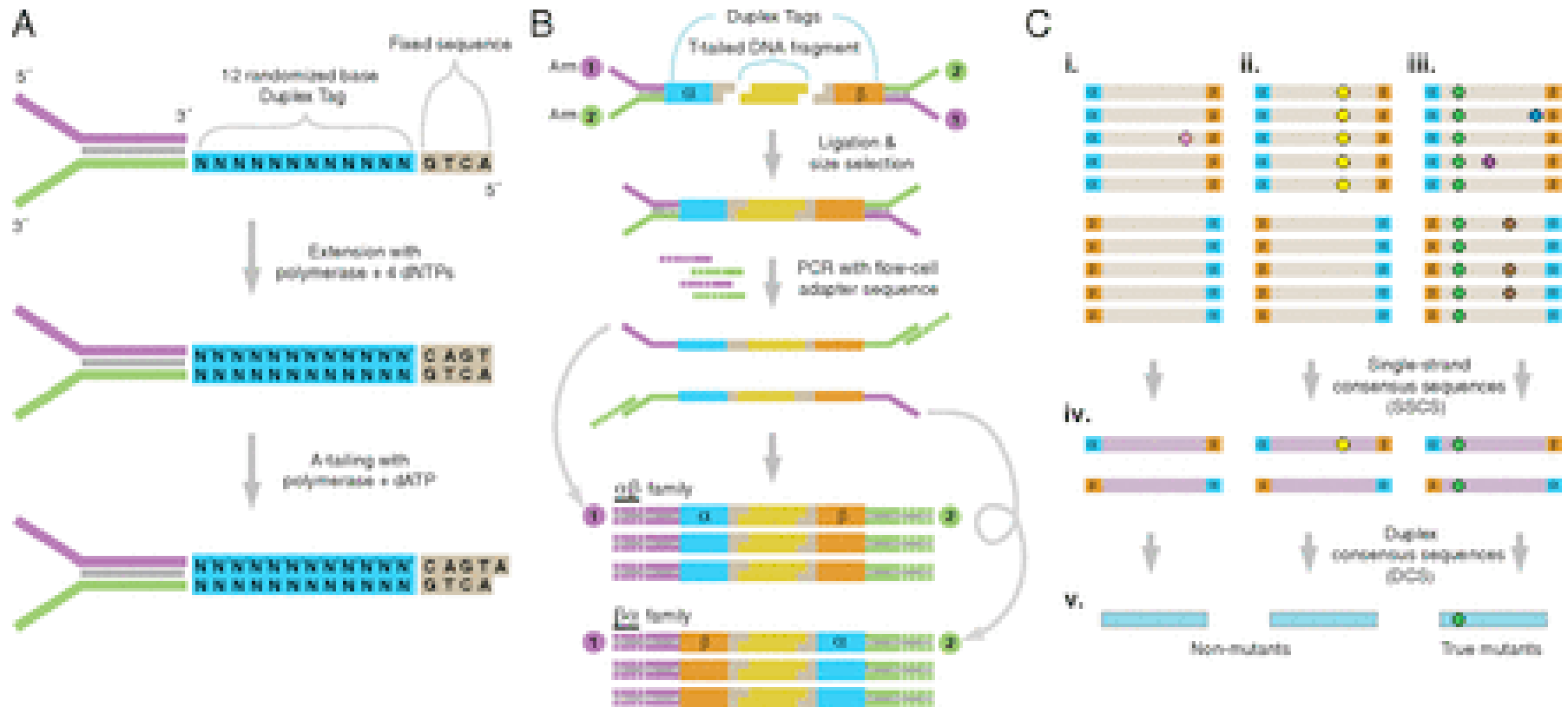


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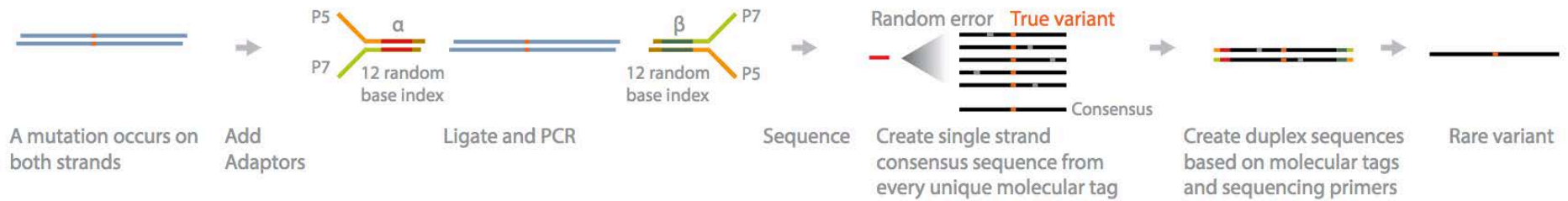




Schmitt et al, *PNAS*, 2012



Duplex sequencing



UMI deep sequencing



UMI=unique molecular identifiers





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