23rd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA

All Patients with Lymphoma Should Undergo Next Generation Sequencing (NGS)/Next Generation Profiling

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I Can See Clearly Now

NGS Brings Light to All Spectrums of Lymphoma

- Diagnosis
- Prognosis
- Treatment
- Disease Monitoring

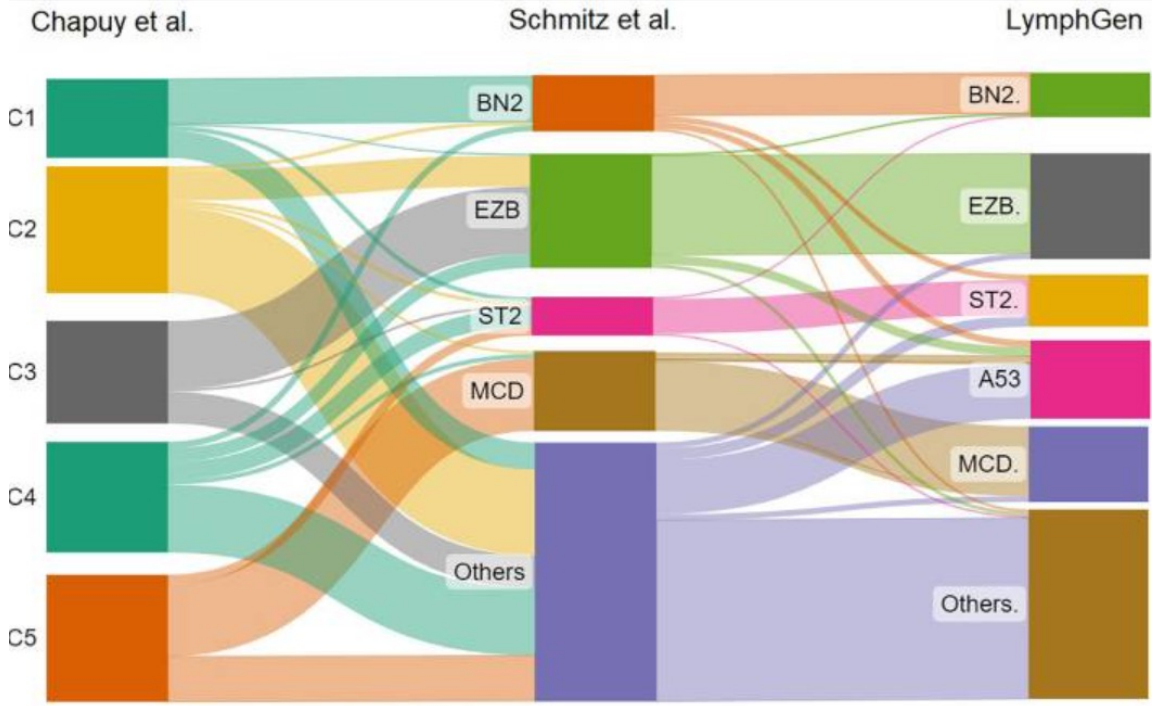
Gone are the Dark Clouds that had me Blind

Diagnosis

- Subtype Classification
- Diagnostic Refinement

Moving Beyond Cell of Origin: NGS Provides More Accurate Classifications and Greater Insight into Biology

DLBCL Type	Genetic Profile
GCB	BCL2/BCL6, EZH2, GNA13, IRF8, MCYY SGK1, STAT3, TNFRI4
ABC	CD79b, EP300, KMT2D, MYD88d, PIM1, PRDM1
PMBCL	STAT6, XPO1, B2M NFKBIE, PTPN1, TNFAIP3



Tomacinschii: Front Onc 2023

Multigene Panel Testing (MGPT) Key in Diagnostic Refinement

- MYD88 and CXCR4 testing recommended in all patients with LPL (Consensus Panel from Intl Workshop on Waldenstrom Macroglobulinemia)
  - Distinguishes from marginal zone

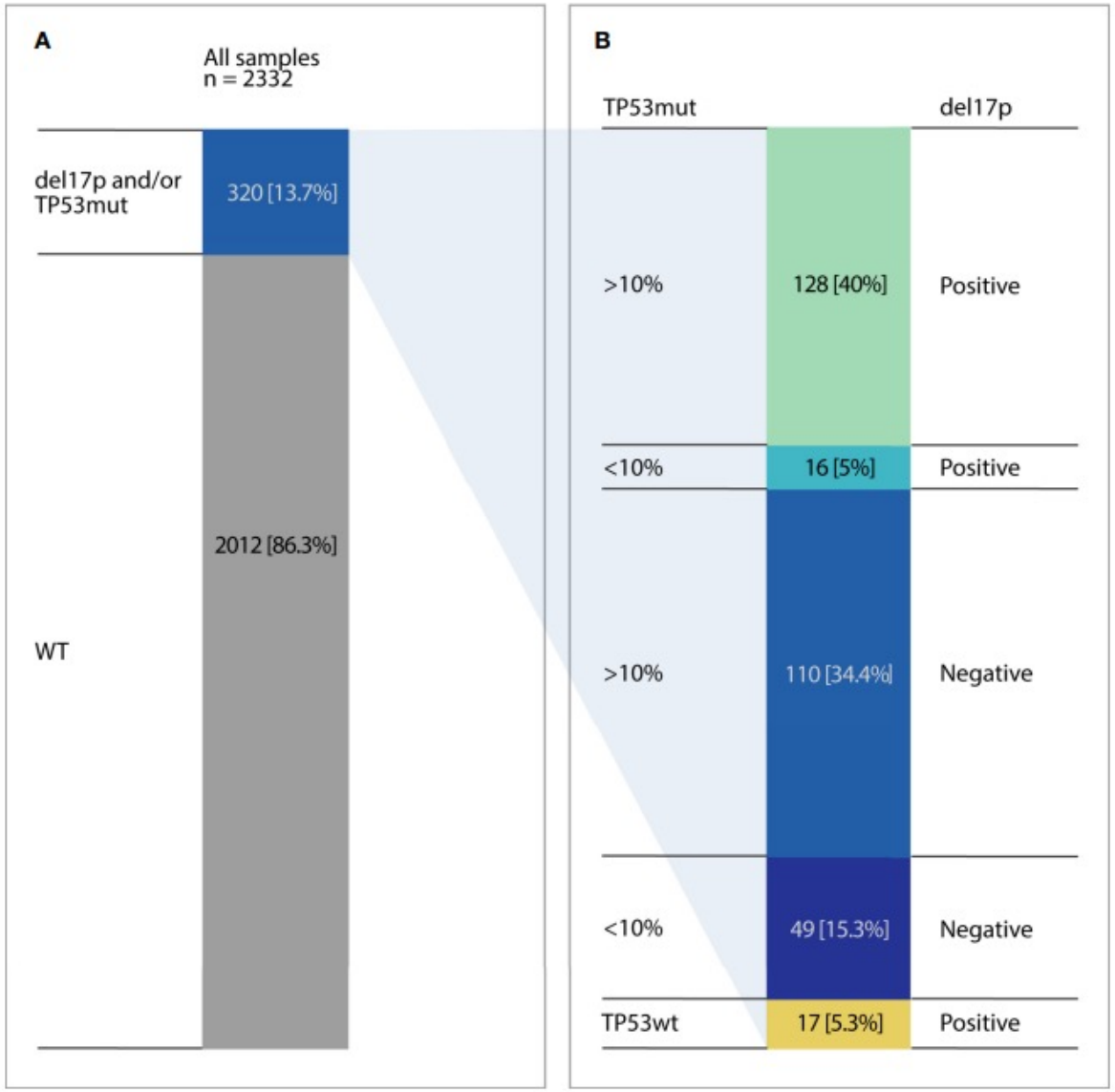
- BRAF V600E mutation distinguishes Hairy Cell Leukemia from Splenic Marginal Zone Lymphoma

- SF3B1 frequent in CLL; rare in other lymphoid malignancies

Buske: Semin Hemat 2023: 60(2), 90-96

The Problem with Relying on FISH Alone

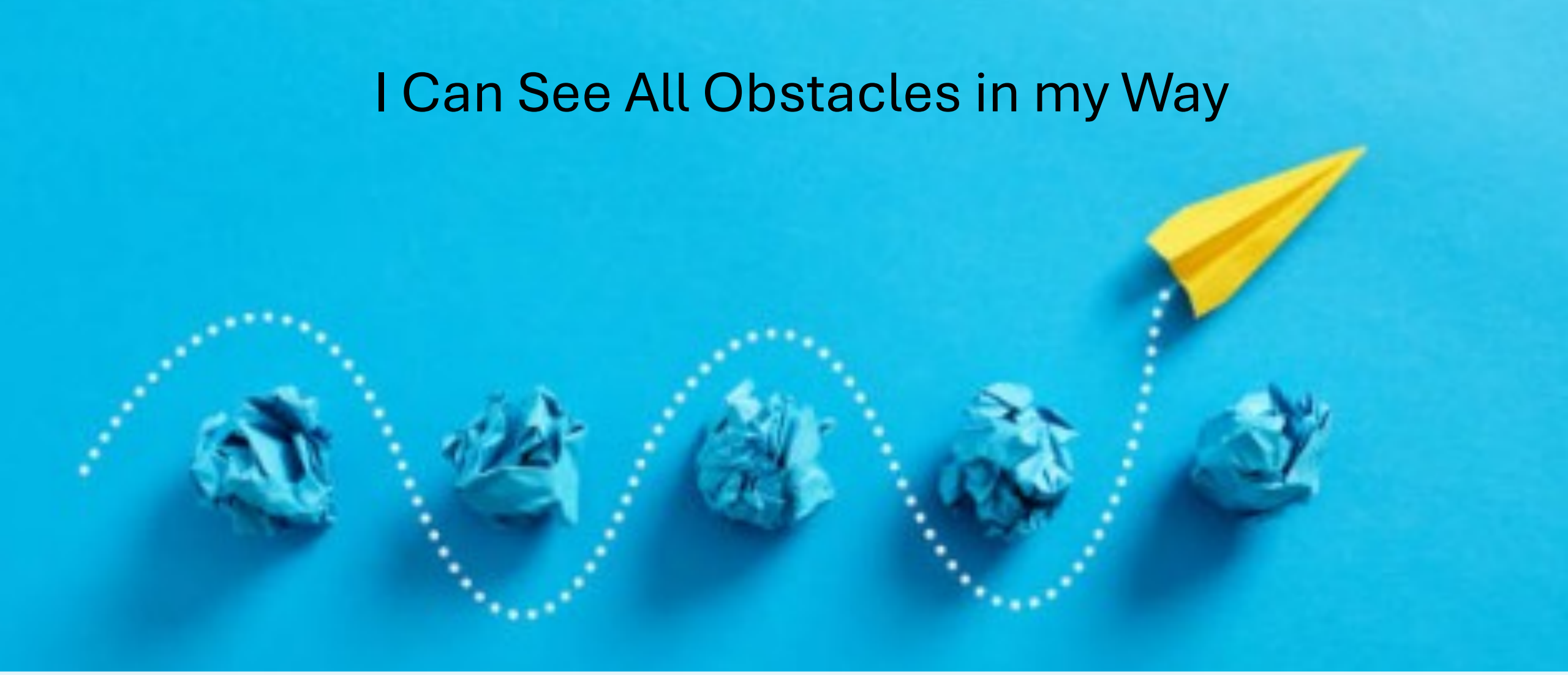
NCCN Recommends
DNA Sequencing
in CLL and MCL for TP53



~50% TP53 mutns
Missed with FISH

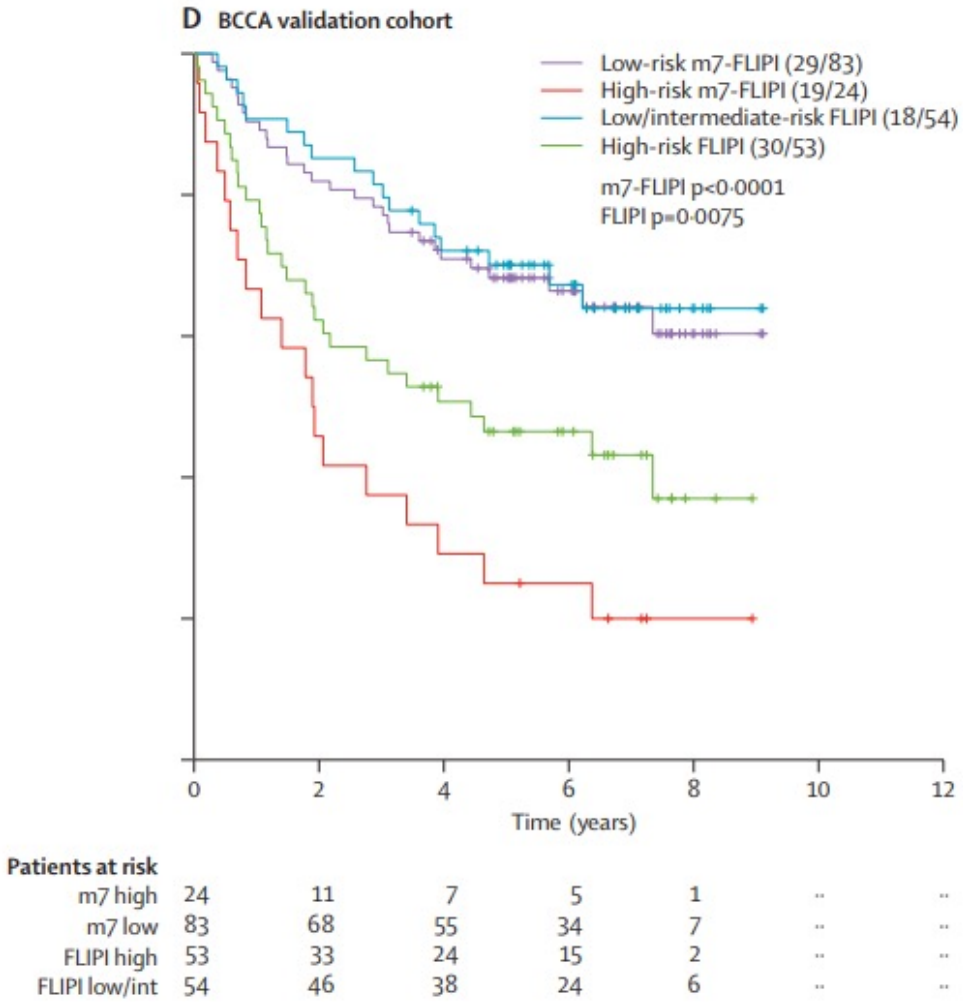
Catherwood: Front Onc 2022: 12, 909615

I Can See All Obstacles in my Way



Prognosis

Improved Stratification for FFS with M7-FLIPI

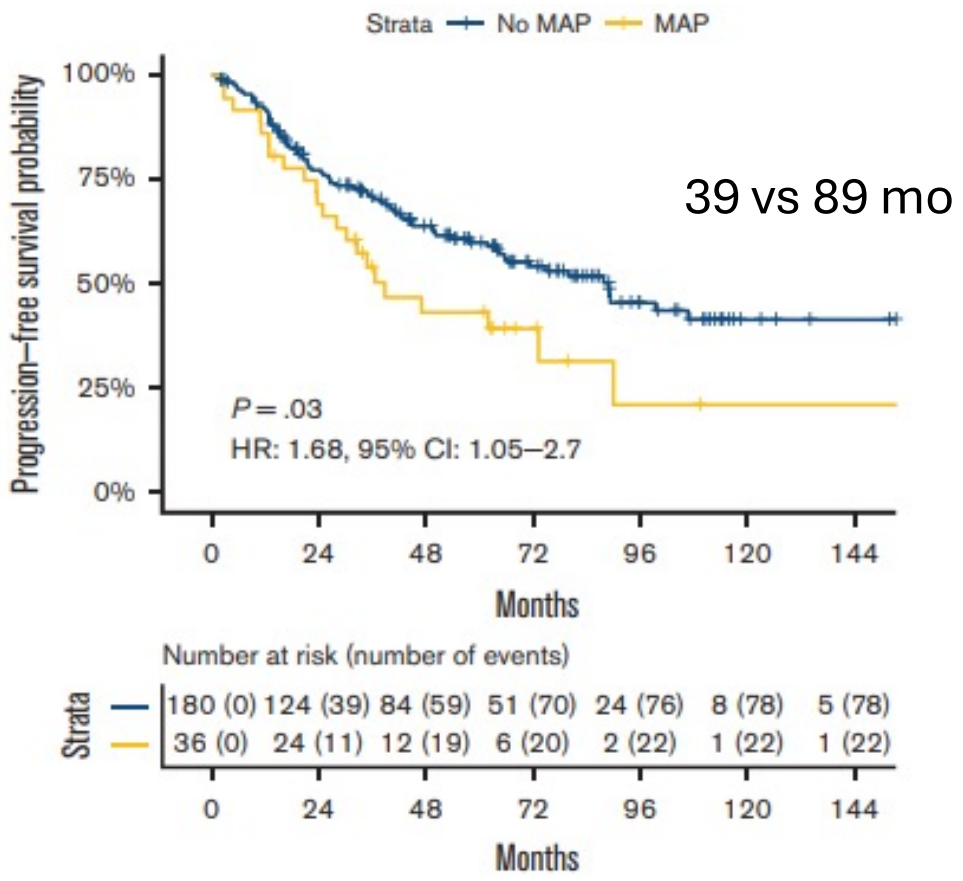


- Symptomatic FL requiring frontline CIT
- 7 Gene Panel
  - EZH2
  - ARIDIA
  - EP300
  - FOXO1
  - CREBBP
  - CARD11
- FLIPI score + ECOG + mutn status
- ? Generalizable

Pastore: Lancet Onc 2015: 16(9), 1111-22; Bantlian: Blood 2023, 142; 3025-7; Russler-Germain Blood Adv 2023: 8(18), 5524-39

Mutations Associated with Progression (MAP) Predict Shorter Frontline PFS at Diagnosis

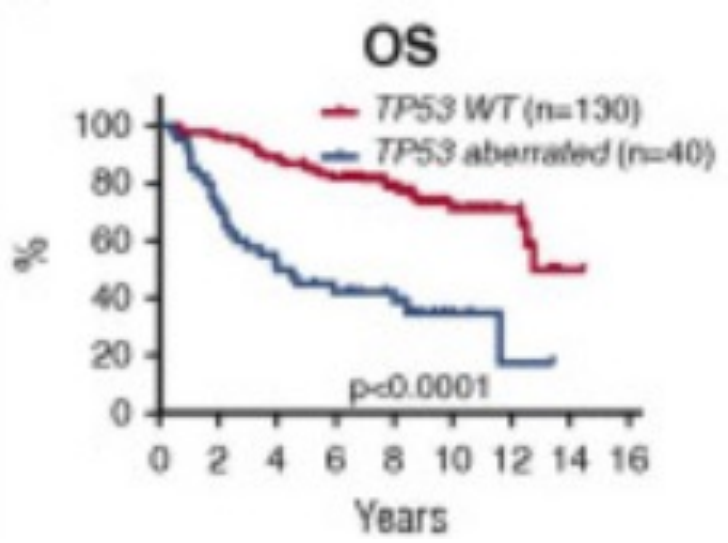
- 370 pts from CALGB trials and real world cohorts: Clinicogenomic analysis
- Tumor burden at dx not assoc with PFS
- ≥ 2 mutations at dx in 7 MAP genes predictive
  - STAT6
  - TP53
  - IGLL5
  - B2M
  - SOCS1
  - MYD88
  - CREBBP



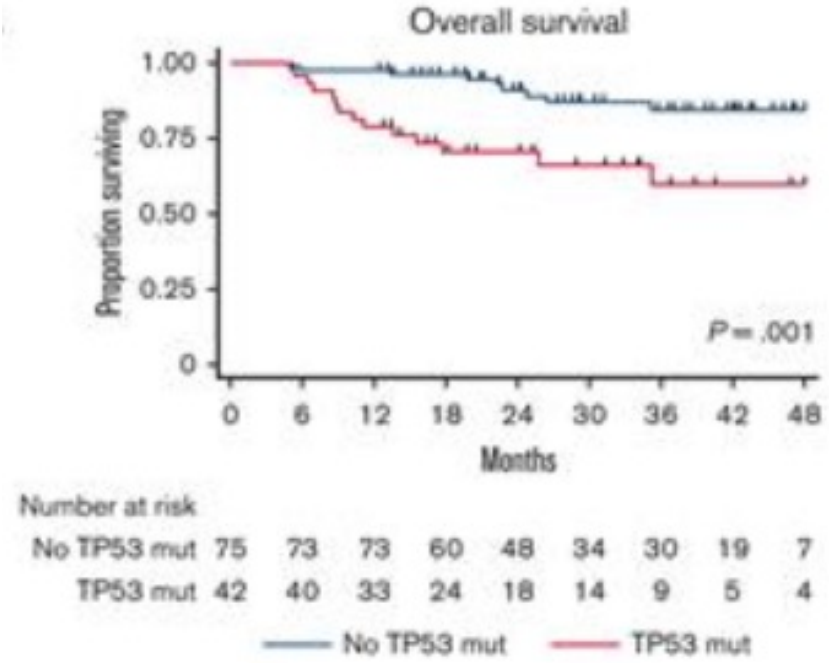
39 vs 89 mo

Russler-Germain: Blood Adv 2023: 8(18), 5524-39

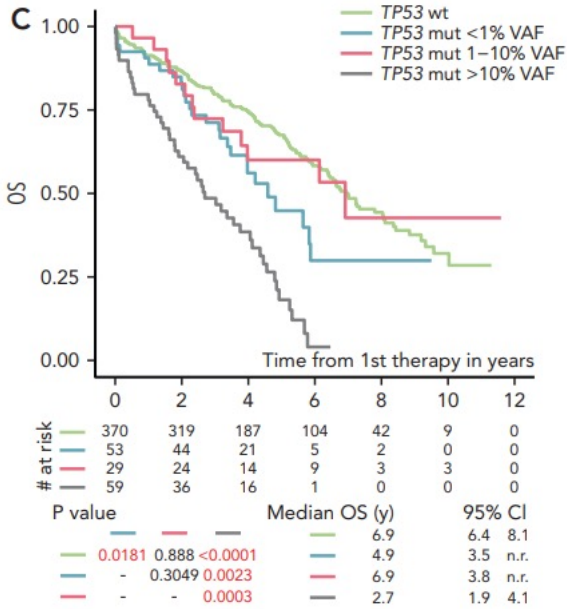
TP53 Mutations Negatively Impact Outcomes; Optimal VAF Thresholds (e.g. > 10%, > 5%) Under Debate



MCL

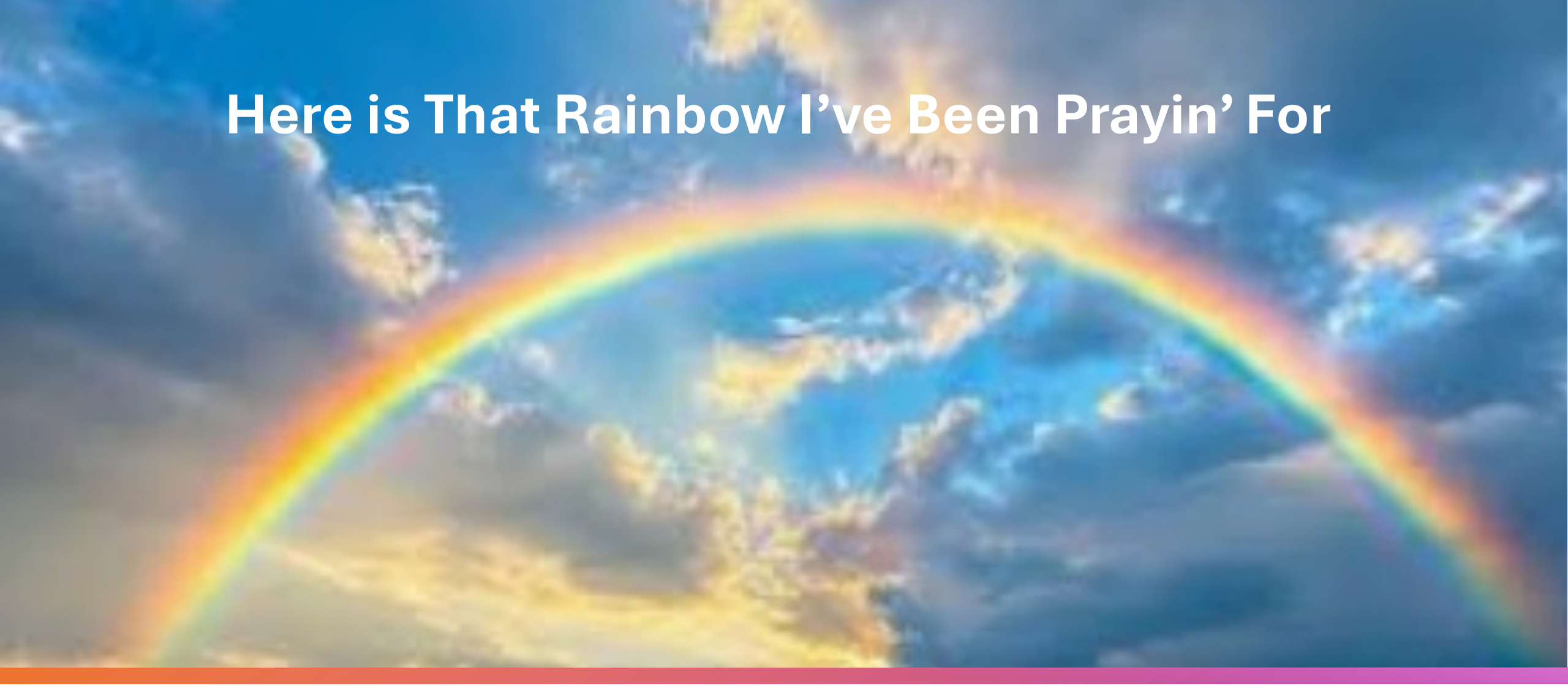


DLBCL



CLL

Eskelund: Blood 2017: 130(17), 1903-10; Landsburg: Bld Adv 2023: 7(23), 7243-53; Malcikova: Blood 2021: 138(25), 2670-85



Treatment:
Actionable and Acquired Mutations

Actionable Mutations/Alterations and Targeted Treatments

Lymphoma Diagnosis	Mutation	Treatment
Follicular	EZH2	Tazemetostat
Lymphoplasmacytic	MYD88 L265p	BTK inhibitor
Mantle Cell	TP53	BTK inhibitor-based regimen
ALK+ ALCL	NMP1: ALK	Crizotinib
ALK – ALCL	DUSP22 rearrangement	Favorable prognosis; tx as ALK+
ALK- ALCL/PTCL	JAK2	JAK2 inhibitor
Hairy cell leukemia	BRAF V600E	Vemurafenib, Dabrafenib, Trametinib
Classic Hodgkin lymphoma	9p24.1/PD-L1	Pembrolizumab/Nivolumab

FDA Orange Book 2026, NCCN Guidelines Hairy cell, T-cell lymphomas, B-cell lymphomas, Hodgkin lymphoma

NGS Identifies Resistance Mutations which Impact Treatment Decisions

- BTK C481, BTK L528, CARD11, and PLCG2 mutations in BTKi treated patients
  - Pirtobrutinib and BTK degraders overcome C481S mutations
- BCL2 mutations in Venetoclax treated patients
- MS4A1 (CD20) mutations in Glofitamab treated patients

NCCN Guidelines v2.2026, CSLL-A-3; Ahn: Sem Hemat 2024: 61(2), 109-18; Landrith: ASCO Abstr 2025, suppl 7042

I Think I Can Make it Now, the Pain is Gone

Disease Monitoring:

Using MRD at end of treatment

Circulating Tumor DNA Methods for MRD Detection

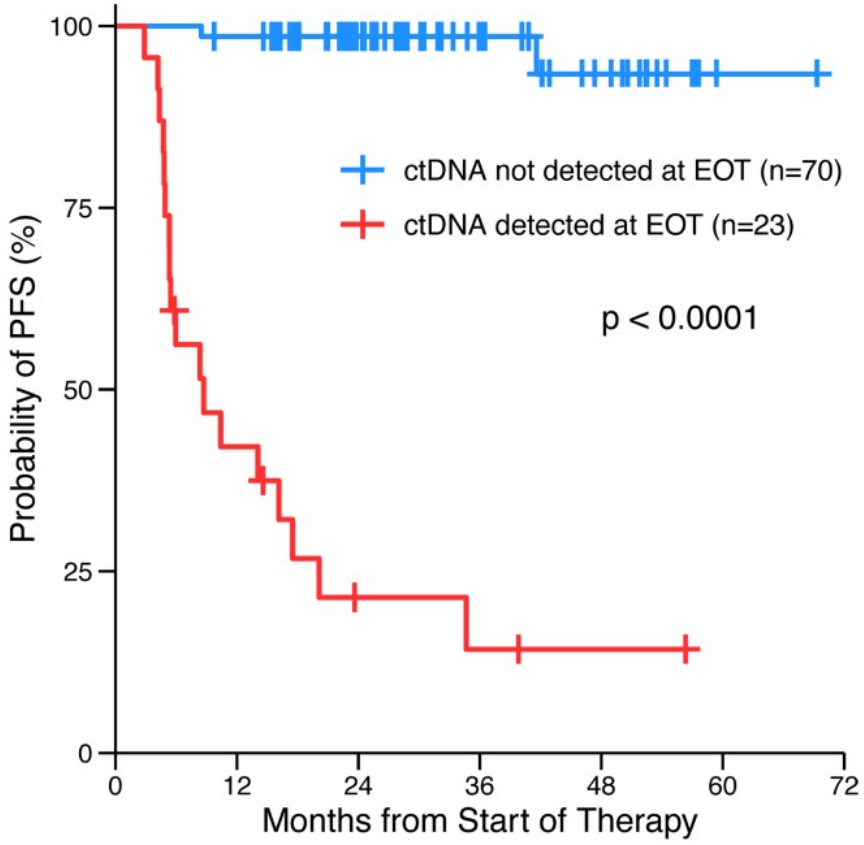
Assay	Approximate analytical sensitivity	Clinical sensitivity at EOT, %	Limitations
Ig sequencing	1:10 000	25-30	Limited by amount of input DNA; light chain IGs are less tumor specific
CAPP-Seq	2.5:100 000	40-50	Limited by background error rate
PhasED-Seq	1:1 000 000	80-90	Limited by background error rate; lower background error rate than CAPP-Seq

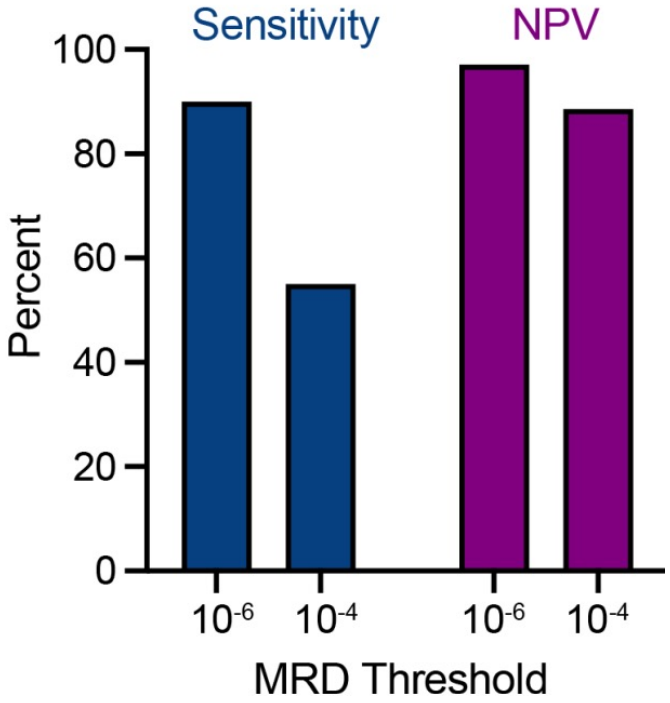
NCCN recommends considering ctDNA for patients with EOT PET + DLBCL. Assay must have limit of detection of at least 1 part per million.

Roschewski: JAMA Oncol 2025: 11(4), 416-22; NCCN B-cell lymphomas, v 3. 2026

Pooled Analysis from 6 Studies Evaluating PhasEd Seq at End of Treatment in DLBCL

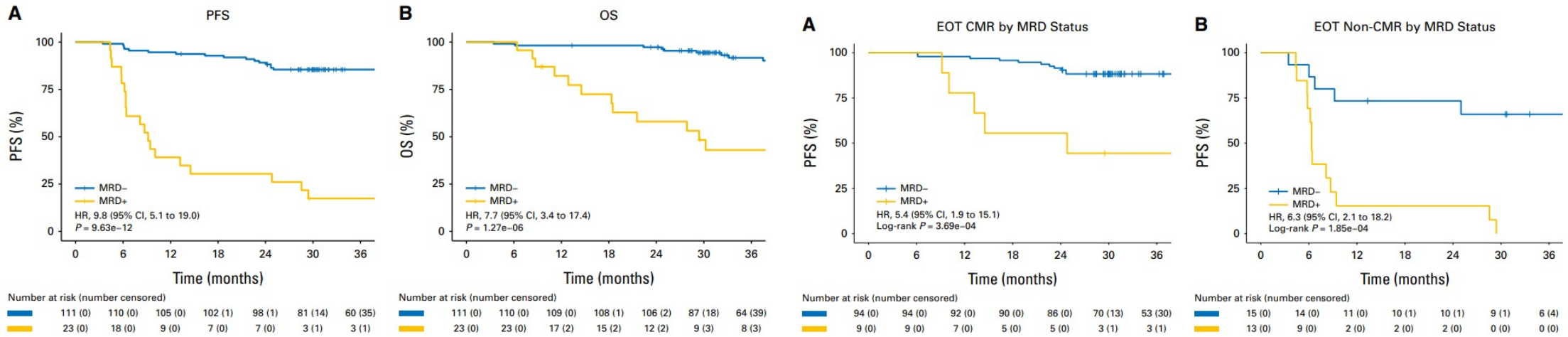
	Pre–Tx	C2D1	C3D1	C4D1	EOT
NCI–acala	27		23		27
Stanford	23	15	12	11	19
MDACC	8	8	1		18
UW–PERCH	17	17	17		17
MOR	12	12		12	12
NHL21	28			28	
TOTAL	115	52	53	51	93





Roschewski: Hemat Oncol 2023: 42(52), 177-79

Prospective Validation of PhasEd Seq ctDNA MRD after First Line Tx in DLBCL



3 yr PFS 17% vs 85%

3 yr OS 43% vs 92%

3 yr PFS 44% vs 88%
PET neg

3 yr PFS 0% vs 66%
PET pos

Wang: JCO 2026:44(5), 400-9

Will NGS be Covered? $$$

- CMS Implemented Natl Covg Determination for NGS in 2018; Expanded in 2020 to include "Clinical indication for germline testing". ?? Insurance: "Lack of medical necessity"
- Median charge amount among denied NGS claims = $3800 (IQR 2650- 3979)
- Pt Assistance Programs

Claims Data 2016- 2021			
	All Claims	**Paid Claims**	**Denied Claims**
Solid Tumors	19077 (64%)	13066 (60%)	5411 (78%)
Heme Malignancies	10842 (36%)	9286 (40%)	1556 (22%)

Kang: JAMA Netw Open 2025: 8(4): e255785

86% Covered

It’s Gonna Be a Bright, Bright Sunshiny Day

It’s a great life, when you can do what you want to do”

- John Ultmann