23rd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

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JW MARRIOTT CHICAGO

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All Patients with lymphoma should undergo Next Gen Sequencing/Next Gen Profiling

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No

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Disclosures

1) Advisory Board for Bristol Meyers Squibb, Novartis and Kite Pharmaceuticals,

2) DSBM for Umoja

3) cofounder of Zylem Biosciences

4) Patents: a) nanoparticles for cancer therapy (HDL NP As Inducers of Ferroptosis in Cancer, PCT/US2020/051549; b) Nanostructures for Treating Cancer and Other Conditions, PCT/US2013/027431).

5) I used AI to obtain data for this discussion

What is the current Standard?

The NCCN guidelines (NCCN B-cell 2025) support use of NGS in certain circumstances

Entity	NCCN Molecular Recommendation	Actionability
DLBCL	IHC + FISH (not NGS) at diagnosis	Identifies DH/TH → treatment intensity
DLBCL post-treatment	ctDNA-MRD if PET+ (narrow indication)	Avoids unnecessary biopsy
MCL	*TP53* sequencing preferred	Guides BTK inhibitor vs. chemotherapy
CLL/SLL	*TP53* + *IGHV* by sequencing	Directs frontline therapy
FL, MZL, PTCL	No broad NGS recommendation	Clinical scoring tools used

So why not for all?

Overview

1	2	3	4	5
Clinical Utility Do results change treatment?	Cost Who should pay?	Tissue Availability Is there enough tissue and should we re-biopsy?	Turnaround Time Should we wait to treat?	Interpretation How do we interpret results? VAF? VUS?

1. Clinical Utility

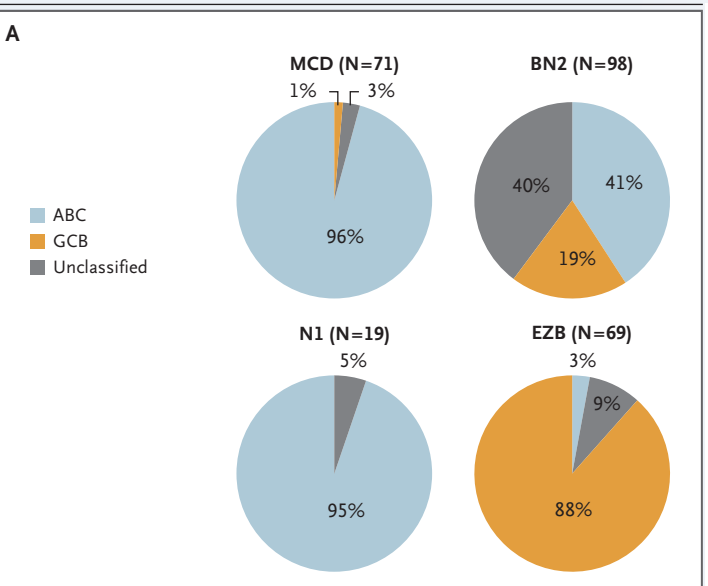
NGS has given us transformative insight into lymphoma biology: Example DLBCL

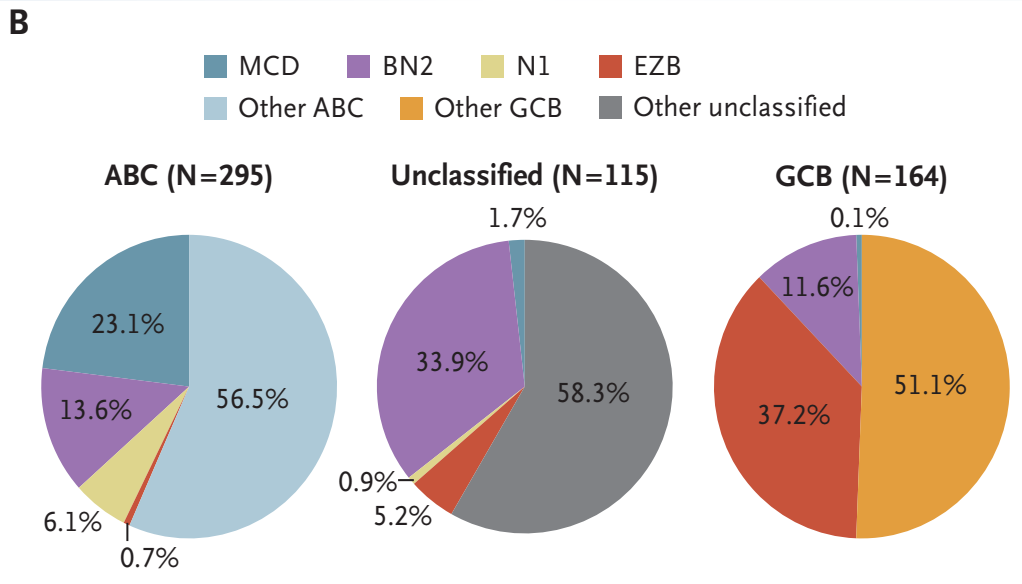
Schmitz et al (NEJM 2018, 378;15) have identified 4 genetic subtypes of DLBCL from 574 DLBCL biopsy samples

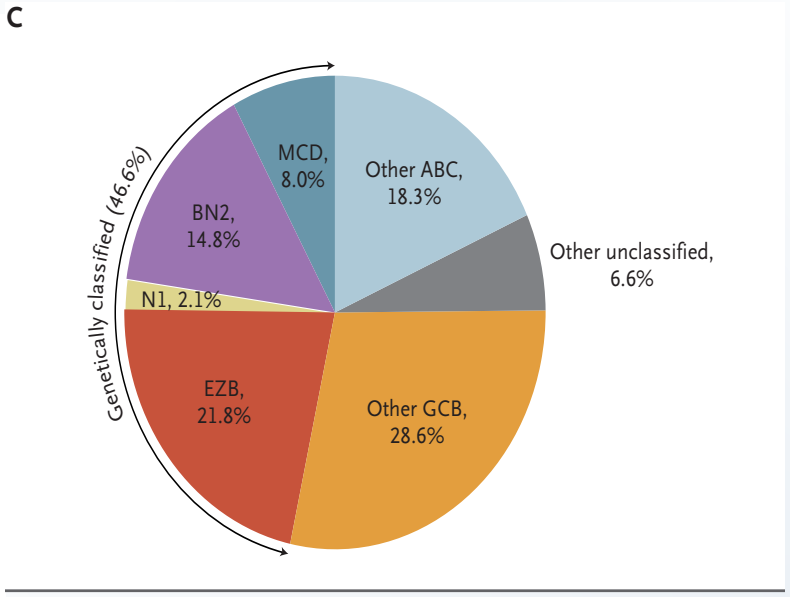
Used exome and transcriptome sequencing, targeting amplicon resequencing of 372 genes

Used an algorithm to find patterns

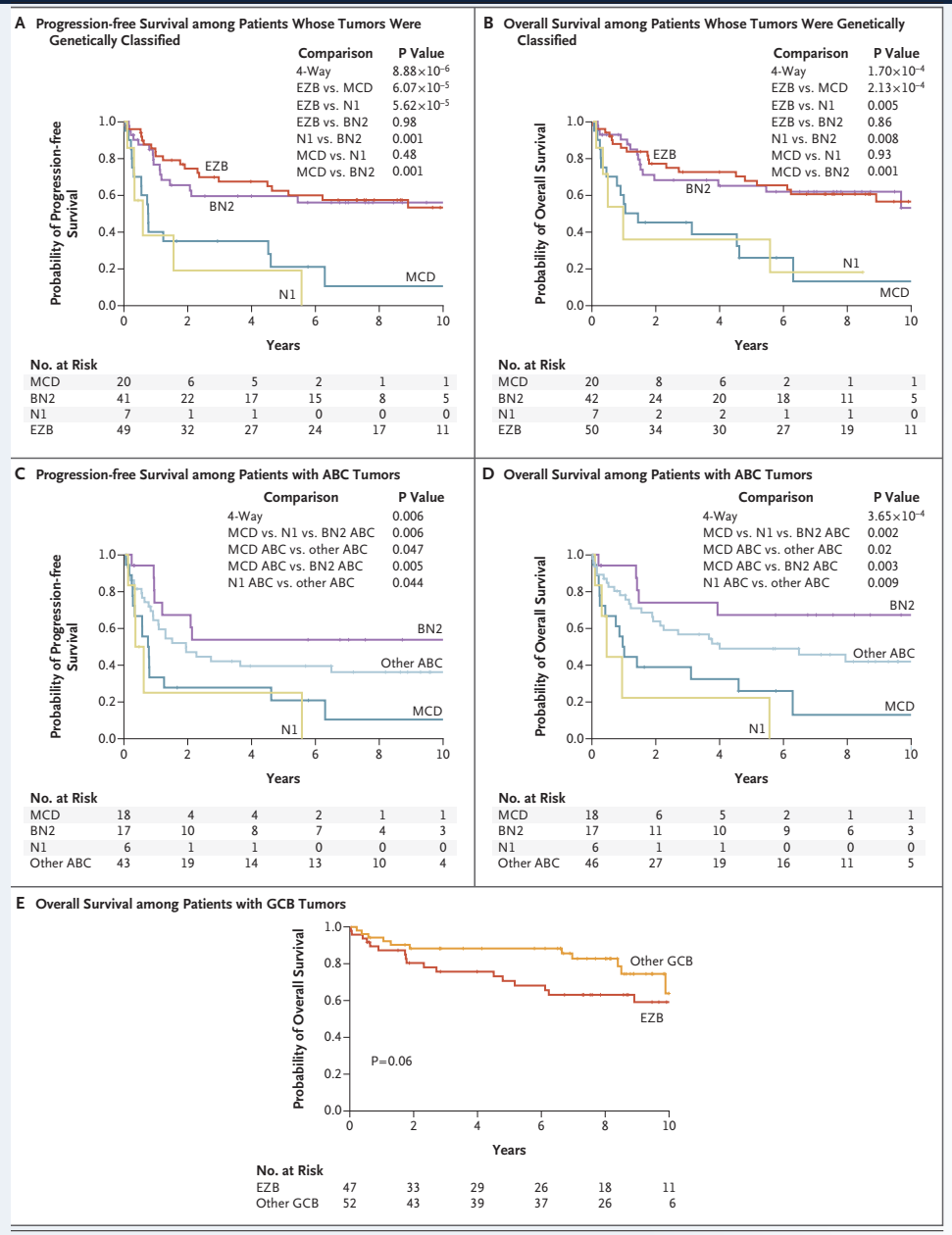
- MCD (*MyD88* and *CD79* mutations)
- BN2 (*BCL6* fusions and *NOTCH2* mutations)
- N1 (*NOTCH 1* mutations)
- EZB (*EZH2* mutations and *BCL2* translocations







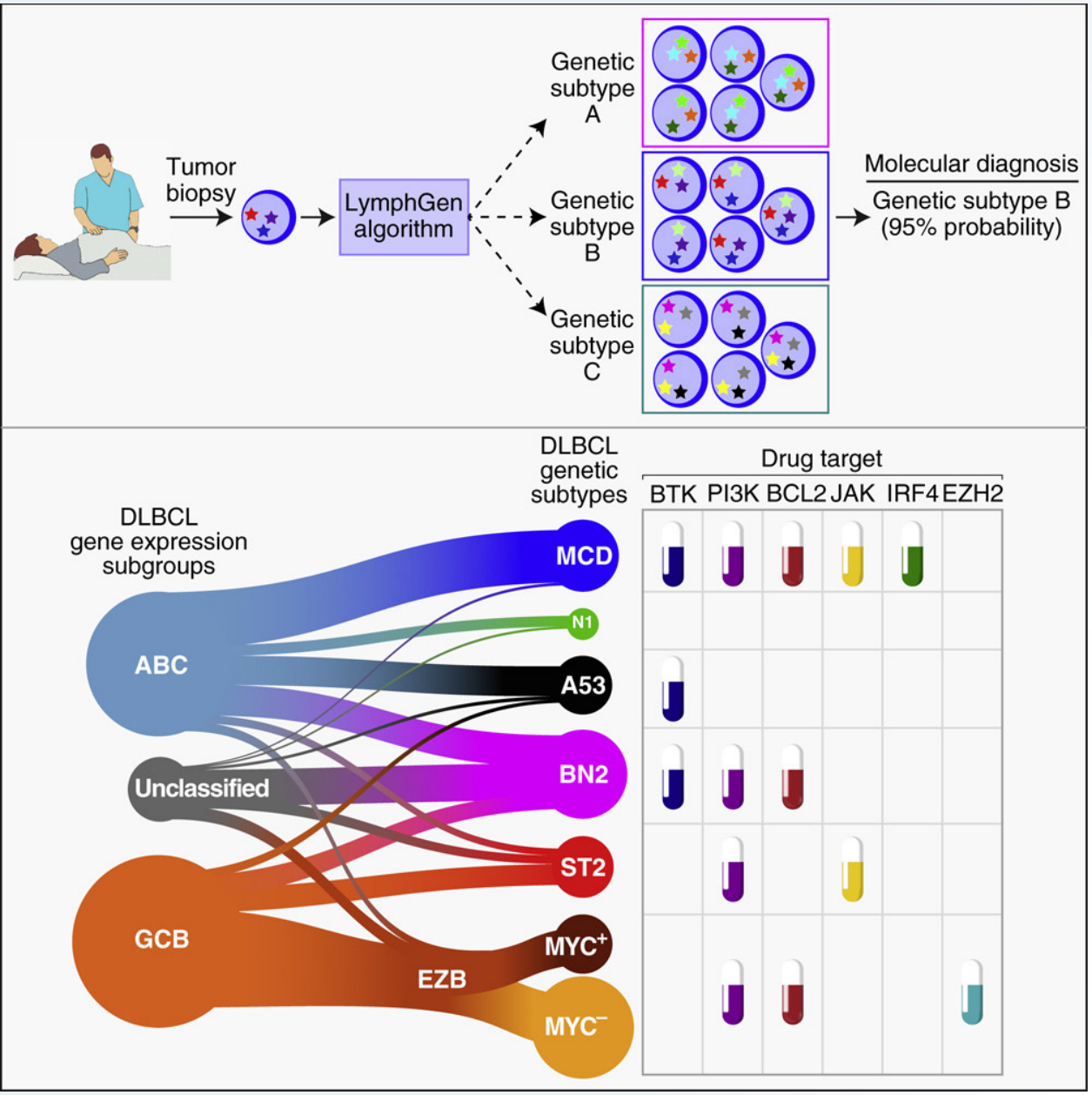
NGS has given us transformative insight into lymphoma biology: Example DLBCL

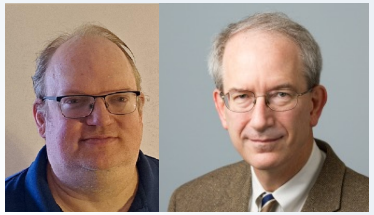


- Panels A and B: PFS and OS according to genetic subtype
- Panels C and D: PFS and OS among ABC subtypes and non subtyped
- Panel E: OS for GB and EZB subtype

Schmitz et al NEJM 2018, 378;15

Lymph Gen Classification of DLBCL





Highlights

- Diffuse large B cell lymphoma (DLBCL) consists of seven genetic subtypes
- The LymphGen algorithm classifies a DLBCL biopsy into one or more genetic subtypes. The genetic subtypes have distinct clinical outcomes and pathway dependencies
- The genetic subtypes will aid the development of rationally targeted therapy of DLBCL

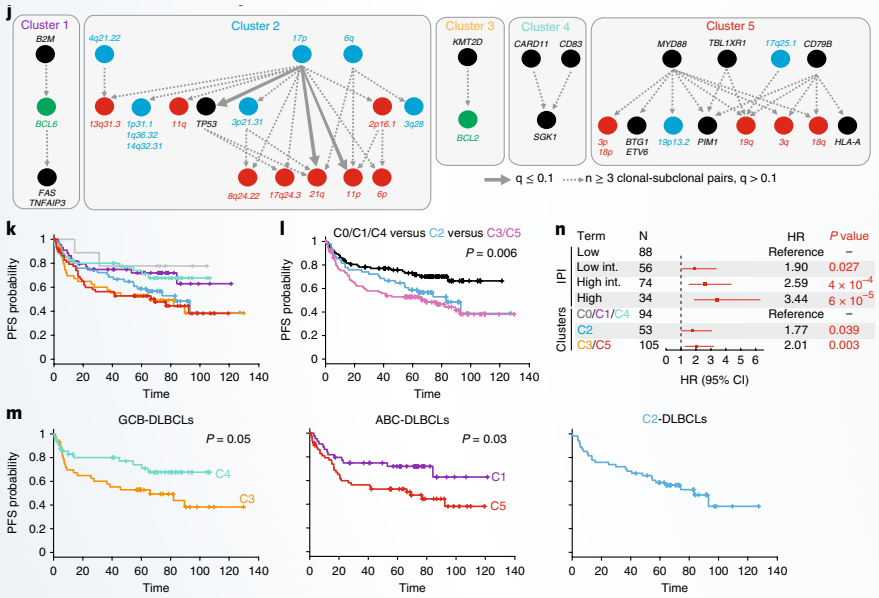
Wright et al, 2020, Cancer Cell 37, 551-658

NGS has given us transformative insight into lymphoma biology: Example DLBCL

Chapuy et al (Nature Medicine 2018, Vol 24, May 2018: 679) studied 304 primary DLBCL samples

Identified 5 DLBCL subsets

- Low risk-ABC of extrafollicular/marginal zone origin
- 2 subsets of GCB DLBCL with targetable alterations
- ABC/GCB independent group with activation of TP53, CDKN2A loss and genomic instability
- Outcome is predicted independent of the IPI
- Possible new strategies



Chapuy et al Nature Medicine 2018, Vol 24: 679

NGS has given us transformative insight into lymphoma biology: Clinical Utility

The Genomic Revolution in NHL

Over the past decade, NGS produced landmark discoveries — from the Chapuy, Schmitz and Wright DLBCL subtypes to comprehensive mutational atlases in follicular, mantle cell, and marginal zone lymphoma.

We gained understanding of disease pathogenesis and identified rational therapeutic targets.

But research value is not equal to routine clinical utility.

30 + Recurrent somatic mutations identified in DLBCL alone

7 Lymph Gen genetic subtypes in DLBCL

0 FDA-approved frontline subtype specific regimens

NGS has given us transformative insight into lymphoma biology: Clinical Utility

LymphGen Genetic Subtypes (2020)

BN2 · EZB (Myc+ and Myc-) · MCD · N1 · ST2 · A53

These molecularly distinct subtypes are biologically compelling — yet none drives a different frontline treatment in standard practice today.

R-CHOP (or a variation) remains the standard of care regardless of genomic subtype in the first-line setting.

In follicular lymphoma: FLIPI and FLIPI-2 — based on clinical parameters — remain the dominant risk tools in routine practice.

R-CHOP or possibly DA-EPOCH-R for double hit

Wright et al, 2020, Cancer Cell 37, 551-658

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Ongoing study of NGS in low grade lymphomas

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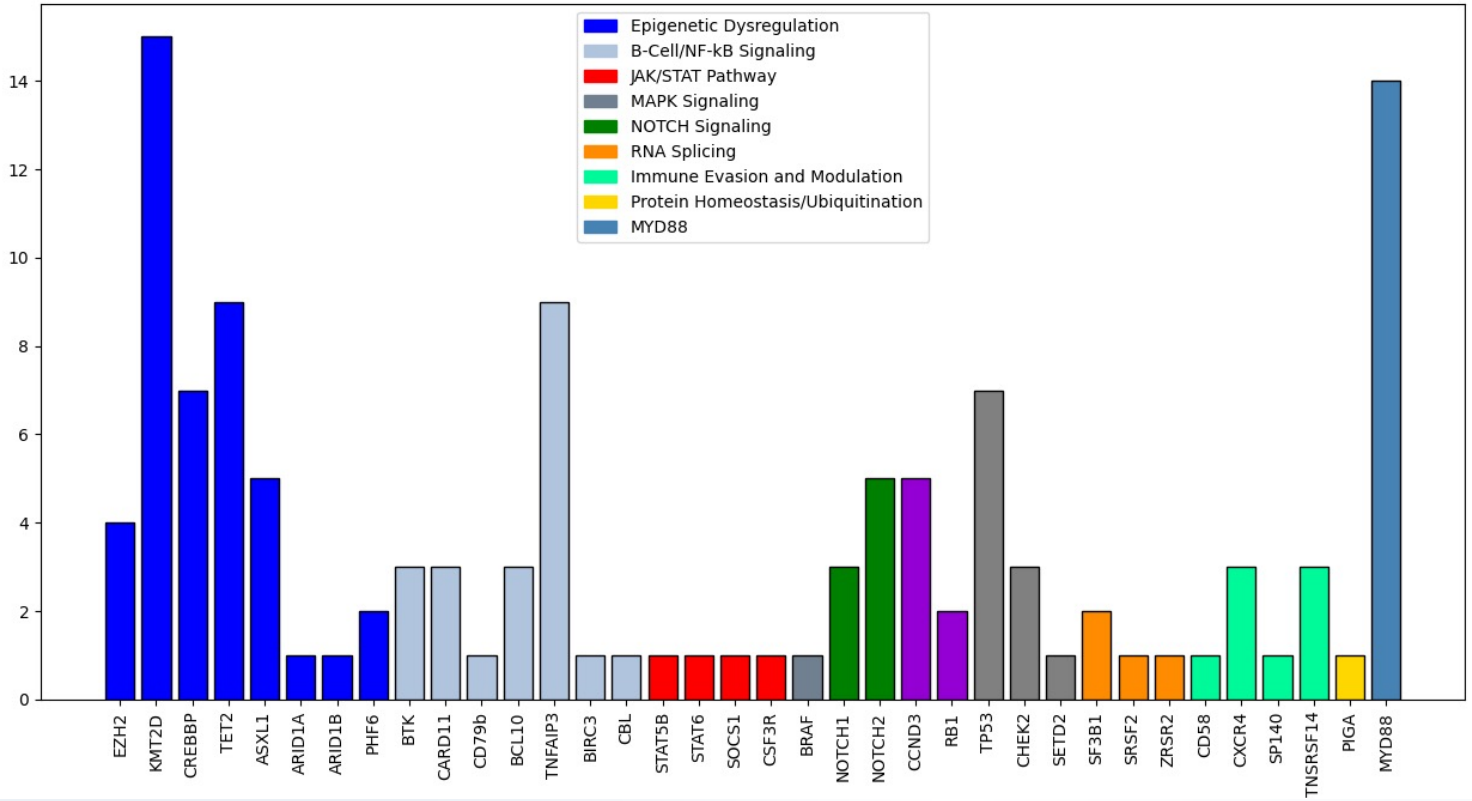
NGS has given us transformative insight into lymphoma biology: Example Low Grade Lymphomas

Disease	Alteration (Frequency)
Lymphoplasmacytic Lymphoma (LPL) / Waldenström Macroglobulinemia (WM)	• MYD88 L265P mutation (87-97%) • CXCR4 mutations (30-40%)
Hairy Cell Leukemia (HCL)	• BRAF V600E mutation (>95%)
Follicular Lymphoma (FL)	• KMT2D mutations (50-89%) • CREBBP mutations (40-70%) • TNFRSF14 mutations (18-40%) • EZH2 mutations (20-30%) • STAT6 mutations (10-29%) • TP53 mutations (5-15%, higher in relapsed/transformed)
Splenic Marginal Zone Lymphoma (SMZL)	• NOTCH2 mutations (10-25%) • KLF2 mutations (12-20%) • TP53 mutations (10-16%)
Extranodal Marginal Zone Lymphoma (EMZL)	• TNFAIP3 mutations/deletions (10-30%, varies by site) • TET2 mutations (10-30%, particularly thyroid)
Nodal Marginal Zone Lymphoma (NMZL)	• NOTCH2 mutations (20-25%)
Mantle Cell Lymphoma (MCL)	• ATM mutations (37-50%) • TP53 mutations (16-32%) • KMT2D mutations (11-15%) • NOTCH1/NOTCH2 mutations (6-15%) • BIRC3 mutations (5-10%)

Yellow highlights the only 2 specific enough to be used as diagnostic evidence

NGS has given us transformative insight into lymphoma biology: Clinical Utility

Frequency of Genetic Alterations by NGS Across All low-grade subtypes



- n=50 (Illumina assay Hybrid capture)
  - Marginal zone lymphoma (n=16; 32.0%)
  - Lymphoplasmacytic lymphoma (n=15; 30.0%)
  - Low-grade B-cell lymphoma not specified (n=8; 16.0%)
  - CD10- follicular lymphoma (n=7; 14.0%)
  - Splenic marginal zone lymphoma (n=4; 8.0%)
  - 47 of the 50 cases had at least one identifiable pathogenic or likely pathogenic alteration

Coty-Fatal et al unpublished data

2. Cost

2. Cost

Inconsistent Insurance Coverage

Payers increasingly scrutinize molecular testing. Denials shift cost onto patients — with financial consequences.

The Two-Tiered Oncology Problem

Academic centers have comprehensive genomic profiling; community hospitals have no testing or inconsistent access. Most lymphoma patients are treated in community settings.

At cost equivalent to NU, if we were to do NGS on all patients with lymphoma, cost would be $400,000,000

$1,500 to $5,000 per NGS panel

At Northwestern, NGS panel is $5,000

Costs may come down

3. Tissue Limitations

3. Tissue Limitations

Core needle Biopsy

Is there enough tissue??

Morphology and IHC

required

Flow Cytometry

required

FISH (MYC/BCL2/ BCL6 required

NGS

Maybe this will replace steps 1-4, but not yet

The Re-Biopsy Dilemma

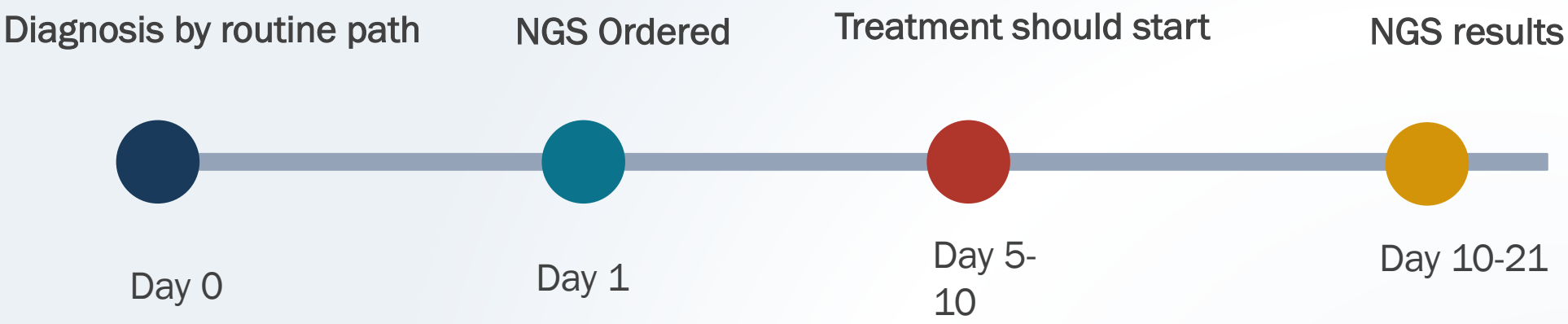
Obtaining a second biopsy to enable NGS carries real risk: pain, bleeding, infection, patient anxiety, and treatment delay. For elderly patients or deep retroperitoneal disease, these are not trivial concerns.

Liquid Biopsy: A Partial Solution

ctDNA-based approaches are promising, but sensitivity varies widely by subtype and tumor burden. Not yet a validated substitute for tissue profiling in the routine newly diagnosed setting.

4. Turnaround time

4. Turnaround time vs Clinical urgency



In some patients, not in all, treatment of DLBCL cannot wait 2-3 weeks for NGS data. If clinical utility were higher, then this wait time could be accepted in some patients. In low grade lymphomas or watch and wait, then this is not an issue

5. Interpretation of Results

5. Interpretation of Results

NGS reports contain dozens of variants — many classified as VUS — whose clinical significance is unknown.

How do we interpret these data?

Risks:

- Inappropriately alter risk stratification
- Refer for unnecessary germline counseling
- Generate patient anxiety without clinical basis
- Trigger cascade testing with no actionable endpoint

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Counter Arguments

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Why Yes?

"NGS will be useful when new drugs are approved"

- When subtype-specific approvals with companion diagnostics arrive, test — in that context, for that indication.
- Targeted, evidence-based testing.
- Not reflexive universal NGS at diagnosis

"NGS enables enrollment in clinical trials"

- Valid at academic centers with active trial portfolios.
- Does not justify universal testing
- Clinical trials have specific molecular inclusion criteria

"The cost will soon be negligible and turnaround time will be manageable"

- Guidelines made on current evidence, not anticipated evidence
- Show utility, cost effectiveness, this debate should be revisited

Key Takeaways

1. NGS results rarely change treatment in newly diagnosed patients with lymphoma
2. Not to be confused with MRD testing, which uses similar technology
3. Tissue limitations, cost, turnaround time and interpretation of results make routine use premature
4. NGS has selective value in some lymphomas (MCL, CLL) or when pathology short of NGS is still equivocal (e.g.Burkitt vs High Grade Lymphoma
5. For certain clinical trials NGS will be standard