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Smart Patients Get Smart Care™

Understanding How Biomarkers Help Guide Treatment Decisions for Those with CLL/SLL

May 22, 2023

11 AM PT, 12 PM MT,
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Speakers

Moderator
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23-year CLL Patient and Advocate, Director, CLL Society Support Network

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CLL Society

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Catherine C. Coombs
Associate Clinical Professor
University of California, Irvine

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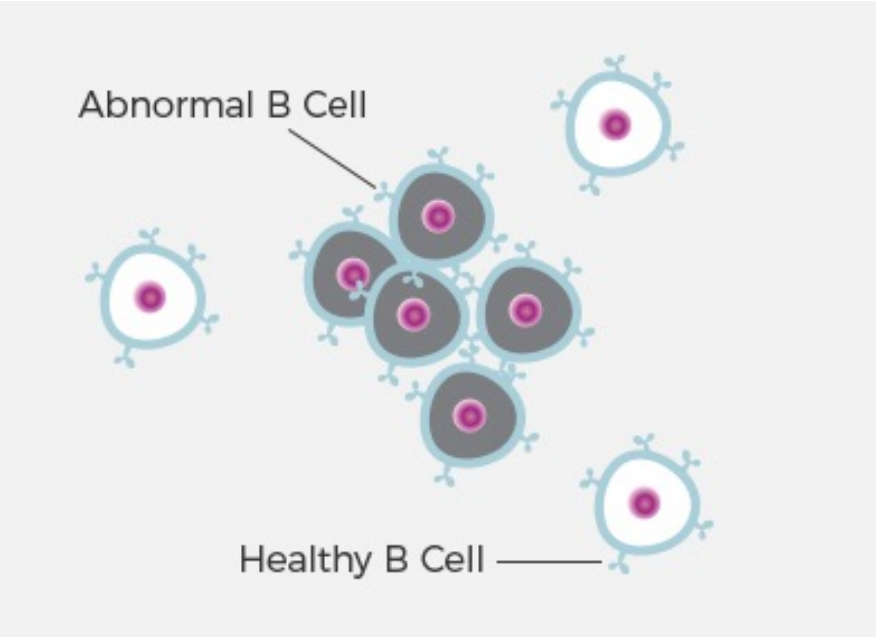
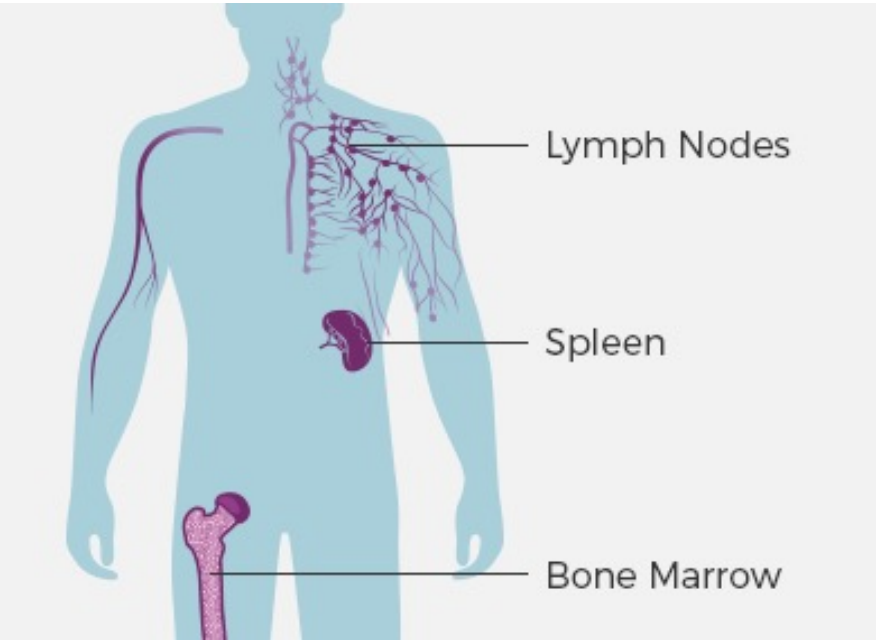
How Is CLL/SLL Diagnosed

- CLL = chronic lymphocytic leukemia; SLL= small lymphocytic lymphoma
- Most commonly, CLL is diagnosed after routine blood work shows an elevated WBC count (and an increased absolute lymphocyte count – ALC)
- Some patients can present with symptomatic disease – symptoms can depend on what “compartment” the disease is affecting the most





CLL by definition involves the blood – SLL is the preferred term when there is not significant blood involvement but lymph nodes are involved

How Is CLL/SLL Diagnosed

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- CLL = can be diagnosed with blood testing
- SLL = usually a lymph node biopsy is required for diagnosis

- A bone marrow biopsy is not mandatory for diagnosis as most tests can be done on the blood – “flow cytometry” is a blood test needed to diagnose CLL though cytogenetics are helpful to exclude other types of lymphoma that can mimic CLL (and to help with prognostication)
- Bone marrow biopsies are often considered if low blood counts are also present

How Is CLL Staged?

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Rai stage 0:	**Lymphocytosis (high blood count of lymphocytes) and no enlargement of the lymph nodes, spleen, or liver, and with near normal red blood cell and platelet counts.**
Rai stage I:	**Lymphocytosis plus enlarged lymph nodes. The spleen and liver are not enlarged, and the red blood cell and platelet countsare normal or only slightly low.**
Rai stage II:	**Lymphocytosis plus an enlarged spleen (and possibly an enlarged liver), with or without enlarged lymph nodes. The red blood cell and platelet counts are normal or only slightly low.**
Rai stage III:	**Lymphocytosis plus anemia (too few red blood cells), with or without enlarged lymph nodes, spleen, or liver. Platelet counts are near normal.**
Rai stage IV:	**Lymphocytosis plus thrombocytopenia (too few platelets), with or without anemia, enlarged lymph nodes, spleen, or liver.**

Modified Rai and Binet Staging Systems

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Risk Status	Modified Rai Stage	Binet Stage
Low risk	0: Lymphocytosis	A: < 3 involved nodal areas
Intermediate risk	I: Lymphadenopathy II: Splenomegaly and/or hepatomegaly	B: ≥ 3 involved nodal areas
High risk	III: Hemoglobin < 11 g/dL IV: Platelets < 10 x 10^4 /μL	C: Hemoglobin < 10 g/dL and/or platelets < 10 x 10^4 /μL

Role of CT Scans

Recommendation: Don't perform baseline or routine surveillance computed tomography (CT) scans in patients with asymptomatic, early-stage chronic lymphocytic leukemia (CLL).

- In patients with asymptomatic, early-stage CLL, baseline and routine surveillance CT scans do not improve survival and are *not necessary* to stage or prognosticate patients. CT scans expose patients to small doses of radiation, can detect incidental findings that are not clinically relevant but lead to further investigations and are costly. For asymptomatic patients with early-stage CLL, clinical staging and blood monitoring is recommended over CT scans.

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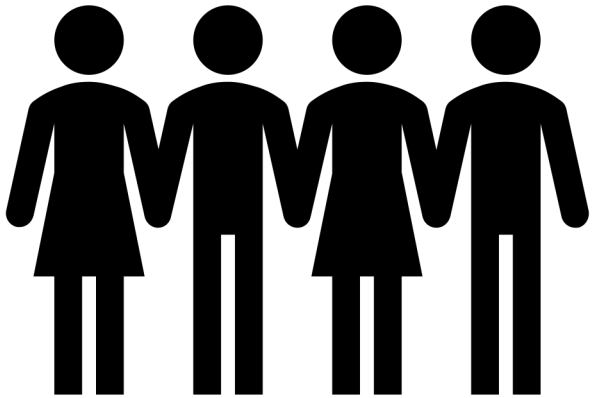
What Are the Limitations of Clinical Staging?



Consider these 4 hypothetical patients

- Patient A presents with Rai stage 0 but progresses rapidly needing therapy
- Patient B presents with Rai stage 1 or 2 and progresses after several years to need therapy
- Patient C presents with Rai stage 3 disease but needs therapy after a brief period of observation
- Patient D presents with Rai stage 4; platelets remain stable ~90 for a decade

What Are Biomarkers?

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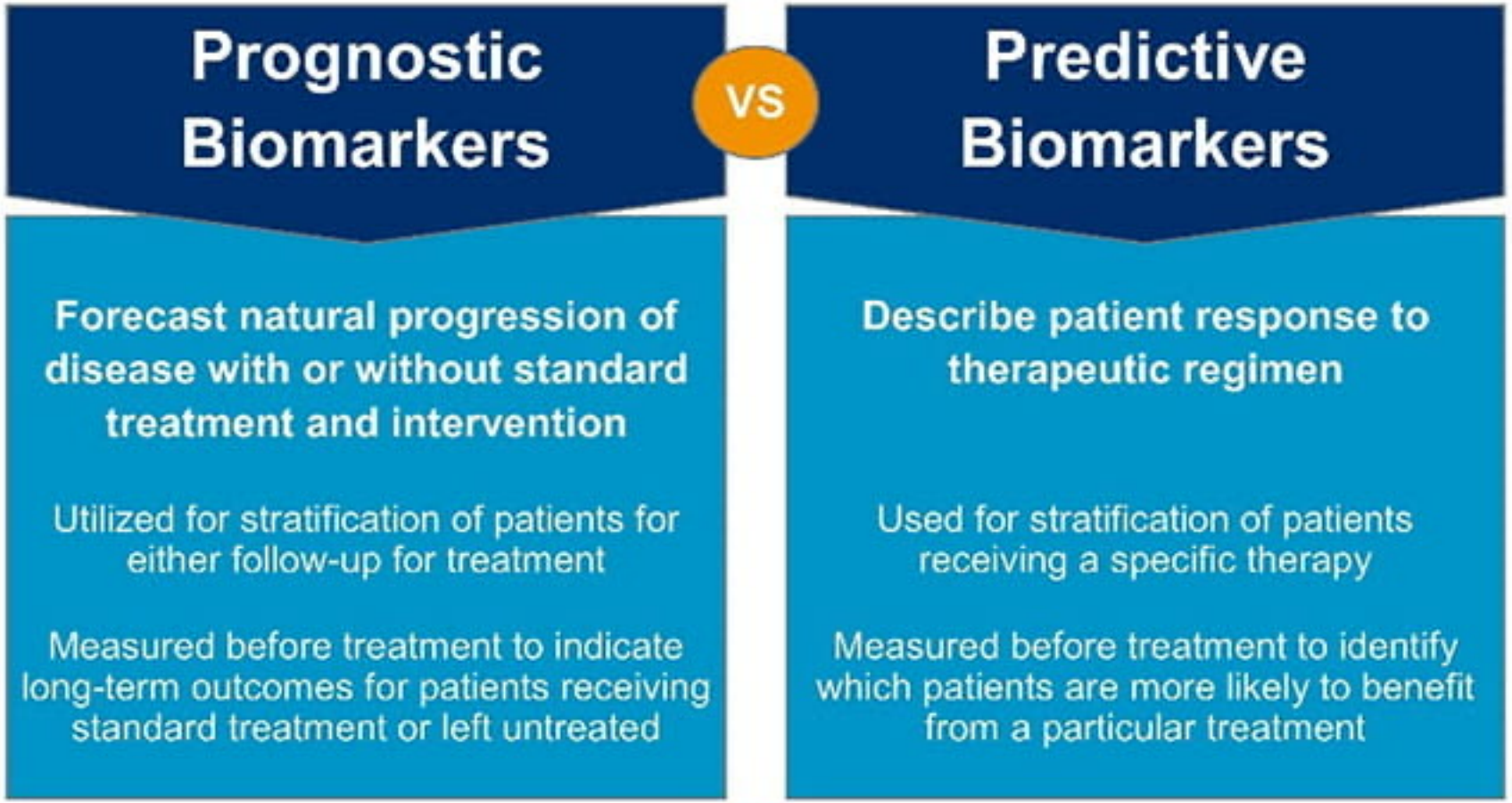

What Are the Important Biomarkers in CLL?

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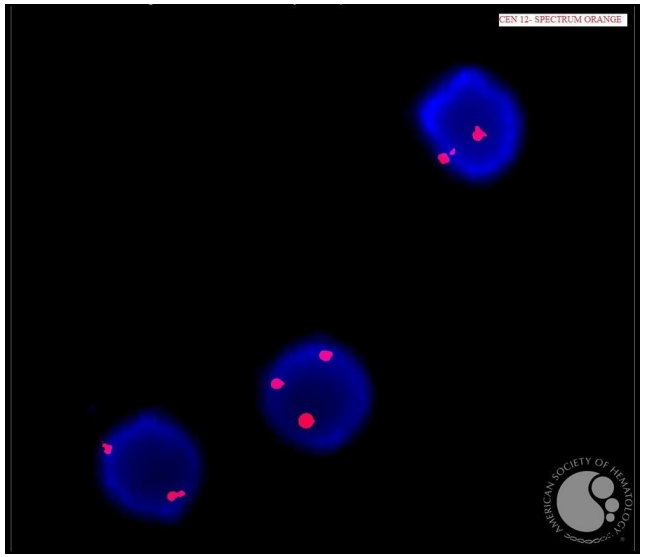
- Cytogenetics (CLL FISH panel +/- karyotype)
- Molecular testing for *TP53* mutations (note this is a different test than FISH)
- IGHV mutation status testing
- B2 microglobulin level – included in CLL-IPI (a prognostic scoring system used in CLL)



Abnormality	*Frequency (FISH)*	*Prognosis*
Del(13q)	30–50%	Favorable
+12	15–20%	Intermediate
None	20%	Intermediate
Del(11q)	15–20%	Unfavorable
Del(17p)	5–10%	Unfavorable

Abbreviation: CLL, chronic lymphocytic leukemia.

Can Biomarkers Change Over Time?

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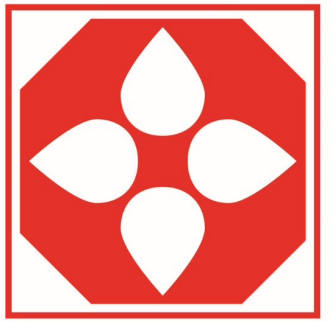
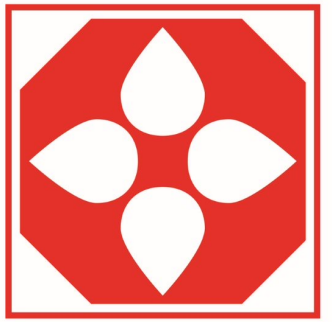
- Yes and no
  - The IGHV mutation status does *not* change over time and only needs to be tested once
  - Cytogenetics and other molecular tests (primarily *TP53* mutations) can change over time
    - Important to repeat these tests upon relapse
    - 17p deletions and *TP53* mutations are uncommon at diagnosis but are more common after subsequent lines of therapy

How Can Biomarkers Influence Therapy Selection?



- If a 17p deletion and/or *TP53* mutation is present, patient should never receive cytotoxic chemotherapy (such as FCR, BR, chlorambucil)
  - Historically, patients with these abnormalities did very poorly and had short survival from time of diagnosis (using the CLL-IPI model, patients with these aberrations had a survival time of ~3-6 years from diagnosis
  - Nowaday, survival is much longer because of how well novel agents such as BTK inhibitors and venetoclax work for patients with these findings

How Can Biomarkers Influence Therapy Selection?



- If unmutated IGHV, also should not receive cytotoxic chemotherapy
  - Novel therapies like BTK inhibitors work essentially just as well in unmutated IGHV patients as mutated IGHV patients
- If mutated IGHV and no other unfavorable markers, occasionally can consider FCR chemo regimen if patients are and young and fit though most CLL experts are not recommending nowadays due to potential for long term toxicity (can induce a second leukemia – AML/MDS)
  - Patients with mutated IGHV generally have long remissions with all therapies

CLL Society's Test Before Treat Educational Resource

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Additional Testing For Disease Monitoring and Measurement

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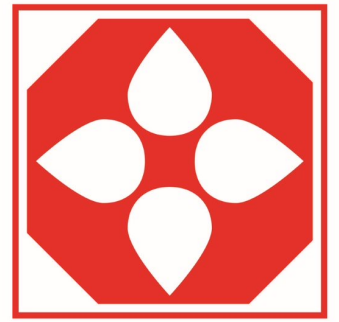
- MRD testing is often considered following venetoclax-containing regimens
- MRD = measurable residual disease (previously minimal residual disease)
- MRD is a way to look for very low levels of CLL and patients who are negative for MRD following venetoclax regimens have a longer time till progression and longer overall survival compared to patients who are detectable
- Different tests for MRD have different limits of detection
  - Flow based (1 out of 10,000 cells)
  - PCR (1 out of 100,000 cells)
  - Clonoseq (1 out of 1,000,000 cells)

Questions?

- Thank you for your attention!



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Audience Questions & Answers

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