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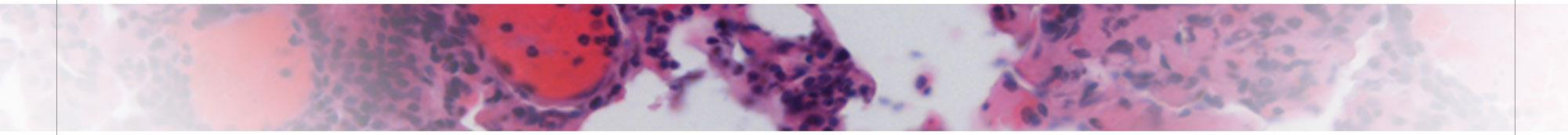

Real-World Testing Patterns for Risk Assessment and Implications on the Adoption of Novel Therapeutics in Chronic Lymphocytic Leukemia: IgHV Mutation Status, FISH Cytogenetic, and Immunophenotyping

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Introduction

- Prognostic testing, including immunoglobulin heavy-chain variable region gene (IgHV) mutation status, cytogenetic abnormalities by fluorescence in situ hybridization (FISH), and immunophenotyping, has been recommended in all newly diagnosed patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) prior to treatment initiation, and even in previously treated patients in some settings

- Recent data have shown that disease with high-risk genetic features is better managed with novel agents than traditional chemoimmunotherapy. As such, the need for testing has become more relevant for disease management

- However, there is limited recent data on real-world patterns of testing for risk factor assessment and in-turn, pattern of evidence-based treatment selection

Objectives

To examine:

- Frequency and results of testing
- Timing of testing by line of therapy
- Factors associated with the receipt of testing

Methods

- **Study design**: Retrospective, observational study
- **Data source**: Flatiron Health EHR-derived database
- **Study period**: January 2014 to May 2021
- **Study population**:
  - Adults who were newly diagnosed with CLL/SLL
  - Index date: the first CLL/SLL diagnosis date during the identification period (July 2014 - February 2021)

Inclusion criteria

  - Aged ≥18 years at index date
  - Continuous enrollment of 6 months pre- and 3 months post-index date
  - Patients who died within 3 months post-index date should be retained

Methods: Study Outcomes and Analysis Plan

- **Study outcomes:**
  - Frequency, results and timing of the following tests:
    - IgHV
    - FISH cytogenetic:
      - 11q deletion [del(11q)]
      - 13q deletion [del(13q)]
      - 17p deletion [del(17p)]
    - Trisomy 12 [+12])
    - Other biomarkers (including CD38 and ZAP-70) by immunophenotyping
- **Statistical analysis:**
  - Descriptive analyses: to examine the frequency and results in the overall population and compared by patient characteristics and across sociodemographic groups
  - Multivariable logistic regression: to examine factors associated with the likelihood of receiving testing
  - Statistical significance: p-value <0.05

Results: Patient Characteristics

- A total of 3,037 CLL patients were included
- Most patients were elderly (median age=73), male (62.3%), and white (74.6%)
- Most patients (92%) received treatment in community practices, with 54.1% commercially-insured

Table 1. Demographic and Clinical Characteristics of CLL Patient Population

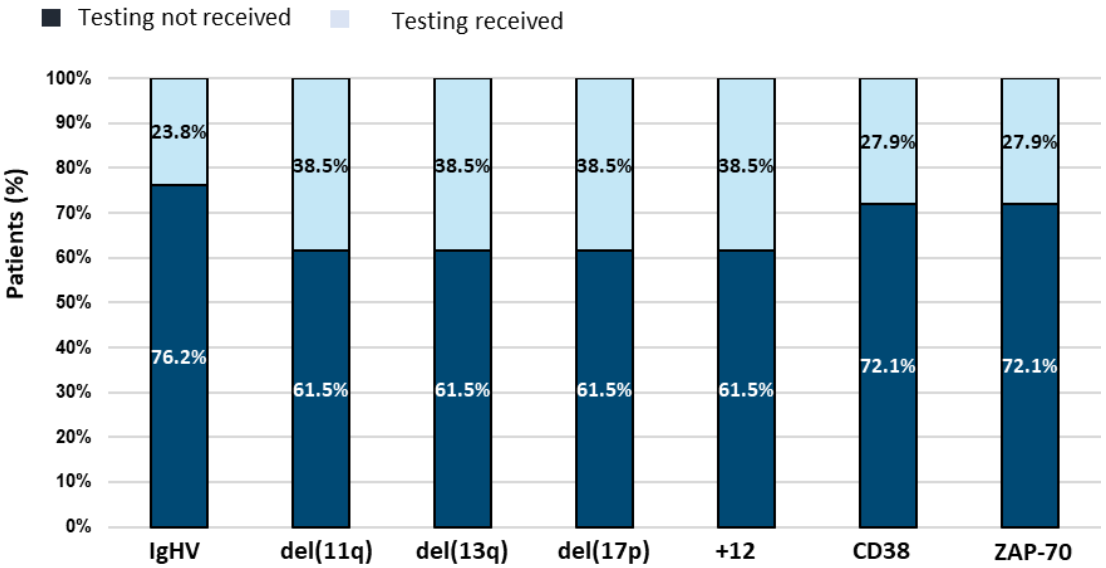
	CLL/SLL Patients (N=3,037)
Age 65+ years, n (%)	2,38 (78.4%)
Male, n (%)	1,892 (62.3%)
Whites, n (%)	2,265 (74.6%)
Hispanics, n (%)	94 (3.1%)
Region, n (%)	
Midwest	367 (12.1%)
Northeast	515 (17.0%)
South	1,217 (40.1%)
West	680 (22.4%)
Other/missing	258 (8.5%)
Health insurance, n (%)	
Commercial	1,643 (54.1%)
Government	1,120 (36.9%)
Other	274 (9.0%)

	CLL/SLL Patients (N=3,037)
Community center, n (%)	2,794 (92.0%)
BMI category at index	
Underweight (BMI < 18.5)	30 (1.0%)
Normal Weight (18.5 <= BMI <25)	620 (20.4%)
Overweight (25 <= BMI < 30)	839 (27.6%)
Obese (>=30)	801 (26.4%)
Unknown	747 (24.6%)
Stage at index	
Stage I-II	299 (9.9%)
Stage III	106 (3.5%)
Stage IV	193 (6.4%)
Stage Missing	2,193 (72.2%)
ECOG status at index (Categorical), n (%)	
0	719 (23.7%)
1	464 (15.3%)
2	95 (3.1%)
>=3	21 (0.7%)
Missing	1,738 (57.2$)

Results: Frequency of Risk Factor Testing

- Testing pattern
  - Over half of CLL patients did not receive risk factor testing: IgHV mutation analyses (76.2%, n=2,315), FISH (61.5%, n=1,868) and immunophenotyping (72.1%, n=2,190)
  - Of those who had testing, the majority (99%) had it done once prior to starting first-line of therapy

Figure 1. Real-world frequency of risk assessment testing



Results: Risk Factor Testing - Subgroup Analyses

- Significant differences in the receipt of testing were observed between different age, gender, race/ethnicity, and regional subgroups
- Among patients who received testing, the presence of high-risk biomarkers was as follows: unmutated IgHV (56.1%), del(17p) present (14.4%), del(11q) present (16.9%), and CD38 present (30.8%)
- Compared to patients <65 years, testing results in elderly patients ≥65 years showed a lower presence of unmutated IgHV (53.8%) and del(11q) (15.7%) while higher del(17p) (14.7%) and +12 (28.1%)

Table 2. Disparity in risk factor testing evaluation among various subgroups of patients with CLL

	Age (<65 vs. 65+) (%)	Sex (M vs. F) (%)	Race (White vs. Non-White) (%)	Hispanic (Yes/No) (%)	Practice type (academic vs. community) (%)	Insurance (commercial vs. government) (%)
IgHV	***32.5, 21.4****	***25.4, 21****	***24.7, 21****	16, 24.0	***30, 23****	25.2, 22.1
FISH	42.7, 37.3*	***40.0, 36.0****	39.0, 37.0	35.1, 38.6	39.5, 38.4	38.1, 39.1
CD38 or ZAP70	29.0, 26.1	29.8, 27.4	28.2, 26.9	19.1, 28.2	***20.6, 28.5****	28.2, 27.8

* p<0.05

Note: FISH cytogenetic tests include 11q deletion [del(11q)], 13q deletion [del(13q)], 17p deletion [del(17p)], Trisomy 12 [+12]

Abbreviations: CLL/SLL, Chronic lymphocytic leukemia /small lymphocytic leukemia

Results: Risk Factor Testing - Subgroup Analyses

- No significant disparity was observed in white vs. non-white patients except for a lower incidence of mutated IgHV and del(13q) presence
- Compared to tested men, tested women had a lower presence of unmutated IgHV (53.9%), del(11q) (11.4%) and CD38+ (25.8%) while higher del(17p) (18.2%)
- The impact of risk testing on therapy selection was investigated: patients with del(17p) had a higher likelihood than those who tested negative (73.6% vs. 48.4%) of being treated with novel agents (ibrutinib, acalabrutinib, or venetoclax)
- In contrast, 26.4% of those who tested del(17p) present and 39.8% among those who did not get tested received chemotherapy

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Results: Factors Associated with the Receipt of Testing

- 3 multivariable logistic regressions were performed to identify factors associated with receipt of IgHV, FISH cytogenetic, and immunophenotyping tests
- Patients who were older, female, or those living in the west of US were significantly less likely to receive IgHV testing
- Similar results were observed in the receipt of FISH cytogenetic testing: patients who were older, female or those living in the west of US were significantly less likely to receive FISH testing
- Multivariable analysis shows patients who live in the northeast or west were less likely to receive immunophenotyping tests

Table 3. Multivariate logistic regression: Factors/predictors associated with CLL patients receiving testing

Effect	Testing (Outcome variable)								
	IgHV			FISH			CD38 or ZAP70		
	Odds Ratio	Lower CL	Upper CL	Odds Ratio	Lower CL	Upper CL	Odds Ratio	Lower CL	Upper CL
Age group: 65+ vs <65	***0.572****	***0.466***	***0.702***	***0.786****	***0.652***	***0.947***	0.891	0.728	1.092
Gender: Female vs Male	***0.815****	***0.682***	***0.974***	***0.857****	***0.736***	***0.999***	0.868	0.734	1.026
Race Non-white vs White	0.854	0.694	1.051	0.958	0.804	1.142	0.974	0.804	1.179
Ethnicity: Hispanic or Latino vs Unknown	0.614	0.344	1.096	0.873	0.559	1.365	0.605	0.353	1.038
Region (Reference: South)									
Mid West	0.64	0.479	0.855	0.956	0.751	1.215	0.834	0.646	1.077
Northeast	0.868	0.683	1.104	1.01	0.817	1.249	***0.758****	***0.603***	***0.953***
Other/Missing	0.759	0.206	2.793	1.014	0.352	2.921	1.207	0.399	3.651
West	***0.549****	***0.431***	***0.698***	***0.716****	***0.587***	***0.874***	***0.520****	***0.416***	***0.650***
Payer type (Reference: Commercial)									
Government	0.970	0.801	1.174	1.11	0.942	1.307	1.030	0.862	1.230
Other	0.846	0.617	1.16	1.011	0.774	1.322	0.988	0.736	1.326
Practice type: Academic vs Community	1.412	0.375	5.32	0.92	0.311	2.716	0.424	0.135	1.331

*** p<0.05**

Note: FISH cytogenetic tests include 11q deletion [del(11q)], 13q deletion [del(13q)], 17p deletion [del(17p)], Trisomy 12 [+12]

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Discussion

- The NCCN guidelines recommend novel agents for patients with high-risk CLL/SLL. Thus, all patients are advised to complete risk-factor testing for both prognostication and selection of optimal, evidence-based therapy

- Despite the recommendations, there remains a significant number of patients who do not undergo FISH and/or IgHV mutation status testing prior to therapy

- Health disparities, across age, gender, race/ethnicity, regional subgroups, and insurance status, in testing are identified

Conclusions

- This real-world data highlights not only a significant gap in testing, but that this suboptimal testing is more common in vulnerable populations
- Despite identification of del(17), a quarter of CLL patients failed to receive novel agents in the frontline setting
- There is an unmet need for further education and refinement of clinical practice
- This is necessary to achieve the best clinical outcome in CLL patients through robust risk-assessment testing and optimal therapeutic triaging.