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, patterns of evidence-based treatment selection. This study aimed to examine: (1) the frequency and results of testing, (2) timing of testing by line of therapy, and (3) factors associated with the receipt of testing.

Methods: De-identified data from the Flatiron Health EHR-derived database was used to identify patients who were ≥18 years old with newly-diagnosed CLL/SLL, who had ≥6-month continuous enrollment, and no prior treatment from January 2014 to May 2021. Testing evaluated included IgHV mutation status, FISH cytogenetic (11q deletion [del(11q)], 13q deletion [del(13q)], 17p deletion [del(17p)], Trisomy 12 [+12]) and other biomarkers (including CD38 and ZAP-70) by immunophenotyping. Descriptive analyses were conducted to examine the frequency and results in the overall population, and compared by patient characteristics and across sociodemographic groups. Multivariable logistic regression was conducted to examine factors associated with the likelihood of receiving testing. Statistical significance was determined as a p-value of <0.05.

Results: A total of 3,037 CLL patients were included (median age=73, 62.3% male, 74.6% white). The majority of patients (92%) received treatment in community practices, with 54.1% commercially-insured. We observed over half of CLL patients did not receive risk factor testing (Figure 1): 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 therapy. Significant differences in the receipt of testing were observed between different age, gender, race/ethnicity, and regional subgroups (Table 1). 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%). 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%). We then investigated the impact of risk testing on therapy selection, and noted that 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. Multivariable regression showed that patients who were older (≥65 years), female or those living in the west of U.S. were significantly less likely to receive testing.

Conclusions: 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. Our real-world data highlights not only a significant gap in testing, but that this suboptimal testing is more common in vulnerable populations. We observed that despite identification of del(17), a quarter of CLL patients failed to receive novel agents in the frontline setting. Our analysis identified 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.

Figure 1. Real-world frequency of risk assessment testing

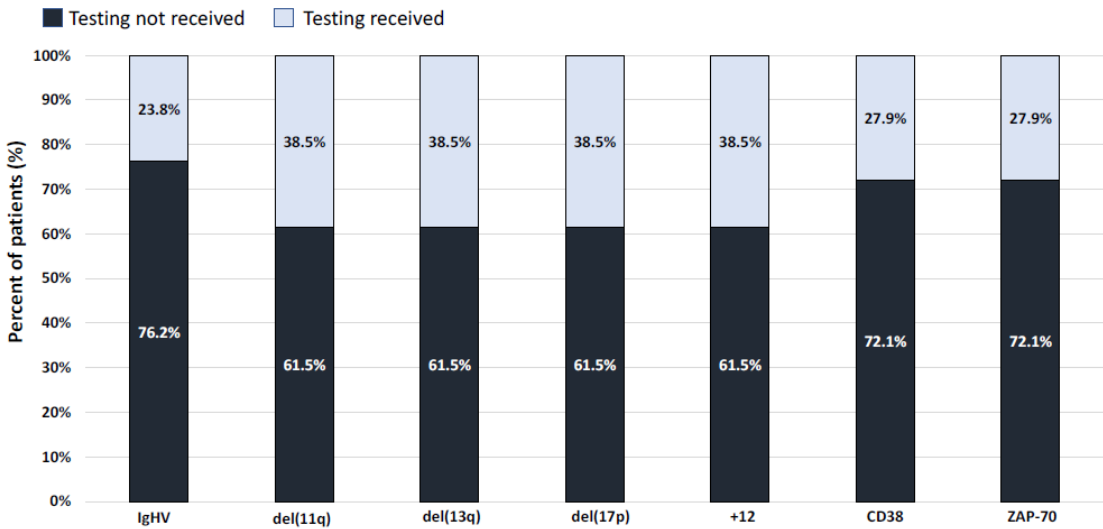

Table 1: Disparity in risk factor testing evaluation among various subgroups of patients with CLL

Testing	SUBGROUPS																
	Age (years)		Sex		Race		Hispanic Ethnicity		Practice type		Insurance type			Geographic region			
	<65	≥65	M	F	White	Non-white	Y	N	Academic	Community	Commercial	Government	Other	MW	NE	S	W
IgHV	32.5%	21.4%*	25.4%	21.0%*	24.7%	21.0%*	16.0%	24.0%	30.0%	23%*	25.2%	22.1%	21.9%	19.6%	24.9%	27.4%	16.5%
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%	38.3%	39.2%	41.0%	40.4%	32.4%
Immunophenotyping	29.0%	26.1%	29.8%	27.4%	28.2%	26.9%	19.1%	28.2%	20.6%	28.5%*	28.2%	27.8%	26.6%	29.4%	27.6%	33.2%	20.3%

Abbreviations: M, male, F, female; MW, midwest; NE, northeast; S, south; W, West.
FISH cytogenic testing includes del(11q), del(13q), del(17p), +12. Immunophenotyping includes CD38 and ZAP-70.
*$P<0.05$