Impact of Testing for Genetic Markers on Treatment Selection and Clinical Outcomes Among Patients With Chronic Lymphocytic Leukemia

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CONCLUSIONS

- This large, real-world study suggests that patients who received pre-treatment prognostic genetic marker testing for CLL were more likely to have better clinical outcomes
- These data further emphasize the need for genetic testing before 1L treatment as a likely proxy for optimal care management in CLL

INTRODUCTION

- Genetic markers such as 17p deletion (del17p), *TP53* mutation (*TP53*m), and immunoglobulin heavy chain variable region (IGHV) mutations are important for chronic lymphocytic leukemia (CLL) prognosis and treatment recommendations[1,2]
- Del17p, *TP53*m, and unmutated IGHV are associated with early disease progression, particularly among patients receiving chemoimmunotherapy (CIT) and ibrutinib[3,4]
- While knowledge is limited on the impact of genetic testing on 1L treatment choices and clinical outcomes in CLL, a registry study suggested that biomarker testing was underused in real-world settings[5]

Aim

- This study evaluated the impact of testing for genetic markers before first-line (1L) treatment initiation on 1L treatment selection and real-world clinical outcomes in patients with CLL

METHODS

Data Source and Study Population

- This retrospective cohort study utilized the US electronic health record–derived de-identified Flatiron Health Research Database; 80% of the data were from community practices
- Eligible patients included adults with CLL diagnosis who started 1L treatment between January 1, 2020, and November 30, 2024

Key Variables and Statistical Analysis

- Primary exposures included evidence of testing any time before 1L treatment initiation, regardless of testing status. Tests included fluorescence in situ hybridization (FISH) for del17p and DNA sequencing for *TP53*m and IGHV status
- Outcomes included real-world time to next treatment or death (rwTTNT) and real-world overall survival (rwOS) from 1L initiation using the Kaplan–Meier method to estimate landmark treatment and survival probabilities
- Descriptive statistics were summarized by each test and by combining patients with del17p and *TP53*m
- Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models, adjusting for age, sex, race/ethnicity, insurance, comorbidity, socioeconomic status (SES), practice type, Rai stage, year of 1L treatment initiation, and Eastern Cooperative Oncology Group performance status (ECOG PS). The reference group was patients with documented tests
- Stratified analyses were performed by 1L treatment, including CIT, ibrutinib, and National Comprehensive Cancer Network® (NCCN) guideline–preferred novel therapies (acalabrutinib, zanubrutinib, venetoclax-based therapies)[2]
- Interaction analysis between testing and 1L treatment was assessed for each outcome
- In exploratory analyses, the proportion of patients with 1L treatment by testing result was summarized

RESULTS

Patient Characteristics

- Of the 5481 patients included, the majority received FISH before 1L treatment (81.9%), only 26.5% were tested for *TP53*m, and 51.9% were tested for IGHV status before treatment (**Table 1**)
  - Compared with patients not tested before treatment, tested patients were younger, more likely to be male, be non-Hispanic White, and have ECOG PS 0
  - Patients tested by FISH were more likely to be treated at community practices and patients with *TP53* tests were more likely to be treated at academic practices
  - Compared with the untested group, the tested group had a lower proportion of Medicare coverage and a higher proportion of commercial insurance

Table 1. Patient Demographic and Clinical Characteristics by Receipt of Genetic Testing

	del17p		*TP53*		IGHV	
	Tested (n=4491)	Not tested (n=990)	Tested (n=1454)	Not tested (n=4027)	Tested (n=2847)	Not tested (n=2634)
Age at index (years), median (range)	71 (19-84)	74 (35-84)	70 (19-84)	72 (19-84)	70 (19-84)	73 (35-84)
Gender, n (%)						
Male	2788 (62.1)	610 (61.6)	938 (64.5)	2460 (61.1)	1834 (64.4)	1564 (59.4)
Female	1702 (37.9)	380 (38.4)	516 (35.5)	1566 (38.9)	1012 (35.6)	1070 (40.6)
Missing	1 (0.02)	0	0	1 (0.02)	1 (0.04)	0
Race and ethnicity, n (%)						
White	3301 (73.5)	715 (72.2)	1106 (76.1)	2910 (72.3)	2115 (74.3)	1901 (72.2)
Black or African American	338 (7.5)	76 (7.7)	122 (8.4)	292 (7.3)	225 (7.9)	189 (7.2)
Hispanic or Latino	176 (3.9)	41 (4.1)	52 (3.6)	165 (4.1)	108 (3.8)	109 (4.1)
Asian	35 (0.8)	7 (0.7)	14 (1.0)	28 (0.7)	19 (0.7)	23 (0.9)
Other[a]	314 (7.0)	69 (7.0)	80 (5.5)	303 (7.5)	184 (6.5)	199 (7.6)
Unknown	327 (7.3)	82 (8.3)	80 (5.5)	329 (8.2)	196 (6.9)	213 (8.1)
ECOG PS at baseline, n (%)						
0	1904 (42.4)	338 (34.1)	627 (43.1)	1615 (40.1)	1262 (44.3)	980 (37.2)
1	1343 (29.9)	261 (26.4)	485 (33.4)	1119 (27.8)	858 (30.1)	746 (28.3)
2-4	327 (7.3)	96 (9.7)	111 (7.6)	312 (7.8)	183 (6.4)	240 (9.1)
Unknown	917 (20.4)	295 (29.8)	231 (15.9)	981 (24.4)	544 (19.1)	668 (25.4)
Rai stage at diagnosis, n (%)						
0	1207 (26.9)	226 (22.8)	365 (25.1)	1068 (26.5)	793 (27.9)	640 (24.3)
I	681 (15.2)	86 (8.7)	254 (17.5)	513 (12.7)	485 (17.0)	282 (10.7)
II	269 (6.0)	46 (4.7)	89 (6.1)	226 (5.6)	181 (6.4)	134 (5.1)
III	224 (5.0)	52 (5.3)	82 (5.6)	194 (4.8)	142 (5.0)	134 (5.1)
IV	339 (7.6)	63 (6.4)	128 (8.8)	274 (6.8)	219 (7.7)	183 (7.0)
Not documented	1771 (39.4)	517 (52.2)	536 (36.9)	1752 (43.5)	1027 (36.1)	1261 (47.9)
Year of index (1L start), n (%)						
2020	1082 (24.1)	237 (23.9)	294 (20.2)	1025 (25.5)	644 (22.6)	675 (25.6)
2021	1041 (23.2)	229 (23.1)	316 (21.7)	954 (23.7)	659 (23.1)	611 (23.2)
2022	956 (21.3)	204 (20.6)	338 (23.2)	822 (20.4)	615 (21.6)	545 (20.7)
2023	867 (19.3)	204 (20.6)	319 (21.9)	752 (18.7)	568 (20.0)	503 (19.1)
2024	545 (12.1)	116 (11.7)	187 (12.9)	474 (11.8)	361 (12.7)	300 (11.4)
Comorbidity, n (%)						
0	3601 (80.2)	769 (77.7)	1134 (78.0)	3236 (80.4)	2288 (80.4)	2082 (79.0)
1	597 (13.3)	145 (14.6)	214 (14.7)	528 (13.1)	379 (13.3)	363 (13.8)
2	196 (4.4)	55 (5.6)	69 (4.7)	182 (4.5)	117 (4.1)	134 (5.1)
3	57 (1.3)	12 (1.2)	24 (1.7)	45 (1.1)	37 (1.3)	32 (1.2)
4+	40 (0.9)	9 (0.9)	13 (0.9)	36 (0.9)	26 (0.9)	23 (0.9)
Practice type, n (%)						
Academic	876 (19.5)	251 (25.4)	336 (23.1)	791 (19.6)	597 (21.0)	530 (20.1)
Community	3615 (80.5)	739 (74.6)	1118 (76.9)	3236 (80.4)	2250 (79.0)	2104 (79.9)
SES index, n (%)						
5 (highest)	1077 (24.0)	241 (24.3)	324 (22.3)	994 (24.7)	714 (25.1)	604 (22.9)
4	1015 (22.6)	212 (21.4)	325 (22.4)	902 (22.4)	640 (22.5)	587 (22.3)
3	786 (17.5)	189 (19.1)	266 (18.3)	709 (17.6)	492 (17.3)	483 (18.3)
2	709 (15.8)	151 (15.3)	236 (16.2)	624 (15.5)	448 (15.7)	412 (15.6)
1 (lowest)	533 (11.9)	123 (12.4)	191 (13.1)	465 (11.6)	332 (11.7)	324 (12.3)
Unknown	371 (8.3)	74 (7.5)	112 (7.7)	333 (8.3)	221 (7.8)	224 (8.5)
Insurance coverage, n (%)						
Medicare	2814 (62.7)	708 (71.5)	868 (59.7)	2654 (65.9)	1720 (60.4)	1802 (68.4)
Commercial	767 (17.1)	133 (13.4)	274 (18.8)	626 (15.5)	529 (18.6)	371 (14.1)
Medicaid	81 (1.8)	17 (1.7)	33 (2.3)	65 (1.6)	48 (1.7)	50 (1.9)
Others	279 (6.2)	38 (3.8)	72 (5.0)	245 (6.1)	171 (6.0)	146 (5.5)
Uninsured/unknown	550 (12.2)	94 (9.5)	207 (14.2)	437 (10.9)	379 (13.3)	265 (0.1)

[a]Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or a race description that falls into multiple race categories.

Treatment Outcomes by Receipt of Genetic Testing

- Treatment outcomes were worse among patients not tested before treatment versus those tested (**Figures 1 and 2**, **Supplemental Table 1**; scan QR code to access Supplemental material)
- Median (95% CI) rwTTNT was 30.0 (26.5-36.4) months for patients without del17p/*TP53* testing versus 41.7 (39.1-44.1) months for those tested (aHR 1.10; 95% CI: 0.99-1.22; **Figure 1A**)
  - Patients without IGHV testing had a lower median (95% CI) rwTTNT of 34.0 (31.1-37.8) months, compared with 45.3 (41.6-49.3) months for those tested (aHR: 1.12; 95% CI: 1.03-1.22; **Figure 1B**)
- Median rwOS was not reached (NR) for any group by del17p/*TP53* (**Figure 2A**) or IGHV (**Figure 2B**) testing
  - After adjustment, patients without del17p/*TP53* or IGHV testing had a 28% and 27% higher hazard of death than those with del17p/*TP53* (aHR: 1.28; 95% CI: 1.10-1.49) and IGHV testing (aHR: 1.27; 95% CI: 1.11-1.44), respectively

Figure 1. rwTTNT by Receipt of Genetic Testing

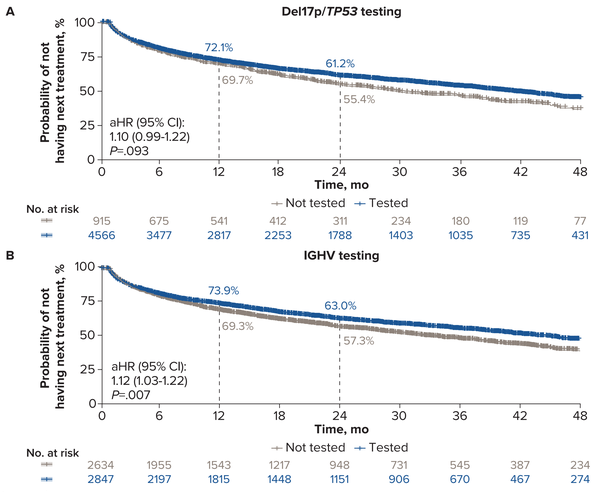

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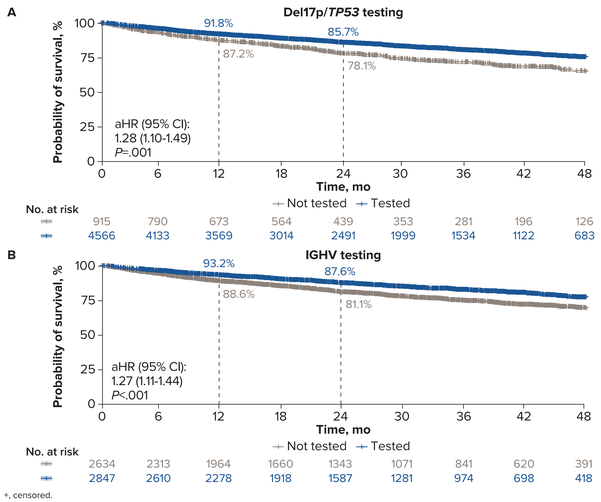
Figure 2. rwOS by Receipt of Genetic Testing



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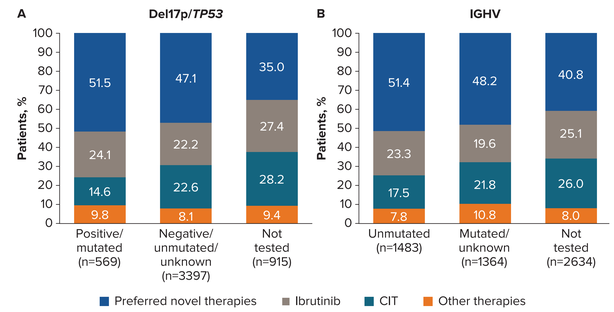
Treatment Access by Receipt of Genetic Testing

- Patients who were not tested before treatment were less likely to receive NCCN guideline–preferred novel therapies and more likely to receive CIT (**Figure 3**)
  - Patients who were del17p/*TP53*m positive were less likely to receive 1L CIT (14.6% vs 22.6%) or 1L venetoclax + obinutuzumab (9.5% vs 14.5%) than those without del17p/*TP53*m (**Figure 3A**)
  - Patients who were tested for IGHV status were less likely to receive 1L CIT (unmutated: 17.5%; mutated/unknown: 21.8%) than those who were not tested (26.0%; **Figure 3B**)

Figure 3. Treatment Patterns by Genetic Testing and Test Results



Treatment Outcomes by 1L Treatment Regimen and Receipt of Genetic Testing

- Among all patients regardless of testing status, median (95% CI) rwTTNT was longest for those who received NCCN guideline–preferred novel therapies (60.2 months; 55.9-NR), followed by ibrutinib (38.7 months; 34.9-42.3) and CIT (9.9 months; 8.4-12.1)
- In the stratified analysis, among patients who received 1L preferred novel therapies, landmark probabilities of staying on current treatment and surviving were higher for patients who received testing than those without testing for IGHV or del17p/*TP53* (**Supplemental Tables 1 and 2**; scan QR code to access)
- There was a statistically significant interaction between testing and 1L treatment on rwTTNT (*P*<.0001) but not on rwOS (*P*>.5), indicating the effect of test status on rwTTNT (**Table 2**)

Table 2. Analysis of Interaction Between Genetic Testing and Treatment Outcomes

Test status × treatment type interaction term *P*-value	IGHV	del17p/*TP53*
rwTTNT	<.0001	<.0001
rwOS	.718	.520

DISCUSSION

- This study showed a trend of higher biomarker testing rates before treatment initiation in patients with CLL compared with earlier studies. However, ~20% of patients did not receive prognostic marker testing before starting treatment
- Our data demonstrated that testing is associated not only with different 1L treatment regimens, but also with improved survival outcomes, suggesting that testing before treatment may be a proxy for both short- and long-term quality of care
  - Patients may not be tested before treatment because of a variety of factors, including quality of care, cost/financial reasons, and/or awareness of testing options

Study Limitations

- Because the Flatiron Health database is derived from electronic health records, patient data may be incomplete or missing. Tests ordered outside the practices may be missing if the documentation is not included in patient records
- The majority of patients in this study were treated at community practices, and may receive different management than in academic practices
- Generalizability of the results to patients outside of the Flatiron Health database and outside of the USA may be limited

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2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.3.2025 © National Comprehensive Cancer Network Inc. 2025. All rights reserved. Accessed October 1, 2025. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
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