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Incidental vs. symptomatic diagnosis of follicular lymphoma: implications of earlier detection

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Follicular lymphoma (FL) is usually diagnosed at an advanced stage when the patient presents with a palpable lymph node or symptoms such as pain and fatigue. However, due to advances in imaging techniques used for many diseases and cancer screening, incidental diagnosis of FL is expected to rise. In this study, we investigated FL disease characteristics and outcomes in patients diagnosed incidentally versus symptomatically, providing insights into what might be detected with multi-cancer early detection tests (MCEDs). We conducted a review of 908 patients with newly diagnosed FL enrolled in the Mayo Clinic component of the Molecular Epidemiology Resource (MER) from 2002 to 2015. We compared disease characteristics and outcomes between the incidental and symptomatic groups. Of the 908 patients, 259 (28.5%) were diagnosed incidentally. The incidental group was more likely to present with early-stage disease (stage I/II: 43.2% vs. 30.6%, $p = 0.0003$), normal lactate dehydrogenase (LDH) levels (87.2% vs. 80.8%, $p = 0.03$), and trended towards having lower FLIPI scores (49.8% vs. 42.2%, $p = 0.1$). However, there were no significant differences in event-free survival (EFS), overall survival (OS) or lymphoma-specific survival (LSS) between the two groups. In conclusion, incidental detection of FL is associated with earlier stages and more favorable disease characteristics. However, this did not translate into improved survival outcomes. Whether even earlier detection of FL using emerging MCEDs translates into improved outcomes remains an open question requiring further investigation.

Blood Cancer Journal (2025)15:116 ; https://doi.org/10.1038/s41408-025-01322-9

INTRODUCTION

Follicular lymphoma (FL) is the second most common lymphoma globally and accounts for 20–30% of non-Hodgkin lymphoma (NHL) cases. Most FL cases are diagnosed at later stages (III/IV), when patients present with symptoms such as painless palpable lymph nodes, fatigue, B symptoms, or abdominal pain or fullness due to a mass or splenomegaly. However, some individuals are diagnosed incidentally through radiologic exams and/or diagnostic procedures performed for unrelated medical reasons, or abnormal blood work such as cytopenia (e.g., due to previously unknown bone marrow involvement) [1–3].

With advances in diagnostic techniques and an increase in individuals undergoing routine health care visits and cancer screenings, it is expected that incidental diagnoses of FL will rise. We refer to this group as incidental lymphoma or lymphoma diagnosed before symptoms or signs (DB4SS). Understanding how this presentation impacts disease characteristics and outcomes is increasingly relevant, particularly as clinical practice encounters more such cases.

Recent interest has grown around molecular screening methods, including blood-based tests that detect methylated DNA markers (MDMs) for early cancer detection [4–8]. These multi-cancer early detection (MCED) tests may detect lymphomas at even earlier stages. However, the clinical implications of such early detection remain unclear particularly in FL, where a survival benefit of early treatment has not been established and a watch and wait strategy remains acceptable in asymptomatic patients [9–13].

To begin addressing this question, our group previously examined the disease characteristics and outcomes of the DB4SS group among patients with newly diagnosed large B-cell lymphoma as a surrogate of what could be found with MCEDs. We found that the DB4SS group had more favorable prognostic features, including earlier stages and lower IPI scores, compared to patients diagnosed after the onset of signs and symptoms related to their lymphoma. There was a nonstatistical trend in improved event-free survival (EFS) at 24 months but no significant difference in overall survival (OS) [14].

In contrast to diffuse large B-cell lymphoma (DLBCL), which can be cured with chemoimmunotherapy regardless of stage, FL may only be potentially curable when localized at early stages, eg, with radiation [15]. Although FL is the second most common NHL, it tends to present more indolently and is more likely to be discovered incidentally than DLBCL. As incidental detection becomes more common, whether through routine imaging or, in the future, molecular screening, these cases offer a glimpse into what might be uncovered through MCED strategies. Yet whether such early identification translates into better outcomes remains uncertain. To explore this, we examined the clinical characteristics

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Received: 31 March 2025 Revised: 28 May 2025 Accepted: 19 June 2025
Published online: 03 July 2025

and outcomes of patients with FL diagnosed incidentally versus those presenting with signs or symptoms, aiming to better understand the potential implications of earlier detection in this indolent lymphoma.

METHODS

We performed a retrospective analysis of patients with newly diagnosed FL grade 1–3B enrolled into the molecular epidemiology resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE) from 2002 to 2015 [16]. This study received approval from the Mayo Clinic Institutional Review Board. Patient medical records of the Mayo component were reviewed to assign the mode of diagnosis (DB4SS vs symptomatic). We examined disease characteristics and outcome data according to the mode of diagnosis (DB4SS vs symptomatic). DB4SS was defined as asymptomatic FL discovered incidentally after a procedure/imaging performed for medical reasons unrelated to lymphoma, abnormal laboratory tests, or a clinical health care professional palpating a lymph node or mass undetected by the patient.

We describe continuous variables using mean and median, while categorical values are described using frequencies and proportions. EFS was defined as the time from diagnosis to relapse, progression, retreatment, or death from any cause. In patients who were initially observed, therapy initiation was considered a key event. Observation was defined as the initial clinical decision documented at the time of diagnosis to defer treatment, without requiring a minimum duration threshold.

OS was defined as the time from diagnosis to death from any cause. Lymphoma-specific survival (LSS) was defined as the time from diagnosis to death from lymphoma. We compared EFS, OS, and LSS outcomes between DB4SS patients and those presenting with lymphoma-related signs and symptoms using Kaplan–Meier curves. Differences between the two groups were assessed using the log-rank test. Cox proportional hazard models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs), measuring the relative risk of events occurring in the two patient groups. All statistical analyses were performed using R/RStudio version 4.2.2 and SAS version 9.4M5.

RESULTS

We reviewed records from 908 patients diagnosed with FL and summarized their characteristics in Table 1. In total, 28.5% (259/908) of patients met criteria for DB4SS; 71.5% (649/908) presented with lymphoma related symptoms. In the DB4SS group, 82.6% (214/259) were diagnosed after imaging or a diagnostic/surgical procedure performed for medical reasons unrelated to lymphoma; 4.6% (12/259) after an abnormal lab finding, and 12.7% (33/259) after a clinical health care professional incidentally identified a lump or a mass. Patients in the DB4SS group were more likely than those in the symptomatic group to present with stages I/II (43.2% vs. 30.6%, $p < 0.01$), normal LDH levels (87.2% vs. 80.8%, $p = 0.03$), and no bone marrow involvement (57.5% vs. 54.7%, $p = 0.02$). Additionally, DB4SS patients were more likely to have four or fewer nodal groups involvement (73.9% vs. 67.3%, $p = 0.06$) and to have low follicular lymphoma international prognostic index (FLIPI) scores (0–1) (49.8% vs. 42.2%, $p = 0.10$) (Table 1).

There was no difference in EFS between the two groups on univariate (HR = 1.10, 95% CI = 0.91–1.33; $p = 0.32$) or multivariable analysis adjusted for FLIPI score (aHR = 1.06, 95% CI = 0.88–1.27; $p = 0.57$). Also, there was no difference in OS on univariate (HR = 0.98, 95% CI = 0.76–1.28; $p = 0.89$) or multivariable analysis adjusted for FLIPI score (HR = 0.94, 95% CI = 0.73–1.22; $p = 0.66$) (Fig. 1). Additionally, in patients with stages I/II disease, there were no significant differences in EFS (HR = 1.08, 95% CI = 0.77–1.50; $p = 0.65$) or OS (HR = 0.99, 95% CI = 0.62–1.58; $p = 0.97$) between the DB4SS group and the symptomatic group. Similarly, among patients with stage III/IV disease, there were no significant differences in EFS (HR = 1.01, 95% CI = 0.80–1.27; $p = 0.93$) or OS (HR = 0.93, 95% CI = 0.68–1.28; $p = 0.66$) between the two groups. Since therapy initiation was considered a key event in patients who underwent initial observation and given the variability in EFS definitions for this subgroup across other studies, we also performed a sensitivity analysis excluding these patients. There was still no difference in EFS between the DB4SS group and the symptomatic group (HR = 1.16, 95% CI = 0.87–1.56; $p = 0.30$).

For LSS, there was no significant difference between symptomatic and incidental presentations, with an HR of 1.52 (95% CI: 0.90–2.55, $p = 0.12$) and an aHR of 1.41 (95% CI: 0.84–2.38, $p = 0.19$) (Fig. 2).

DISCUSSION

The incidental diagnosis of FL represents a unique opportunity to explore the association between early lymphoma detection and disease outcomes. Our findings indicate that nearly 29% of FL patients at diagnosis were in the DB4SS group and were more likely to have favorable prognostic features, including earlier stages and normal LDH levels, with a trend toward having lower FLIPI scores, compared to those diagnosed after presenting with lymphoma related symptoms. These factors did not translate into improved survival outcomes in terms of EFS, OS, or LSS in the DB4SS group. We recently studied the DB4SS group within a cohort of patients with newly diagnosed large B-cell lymphoma. Among 1140 patients diagnosed with aggressive B-cell lymphoma, 7.5% (85/1140) were identified as having an incidental diagnosis. When comparing the DB4SS group to those with symptomatic presentations, the DB4SS group was more likely to present with Stages I/II (62% vs. 39%, $p < 0.0001$), had a lower International Prognostic Index (IPI) score ($p = 0.025$), a reduced incidence of multiple extranodal organ involvement (15.5% vs. 29.8%, $p = 0.025$), and a lower frequency of elevated lactate dehydrogenase (LDH) levels (40.8% vs. 55.4%, $p = 0.014$) [14].

Moreover, patients in the DB4SS FL group were more likely to be managed with observation and received less immunochemotherapy. This is not surprising, as several studies have demonstrated that initiating treatment in asymptomatic low-grade FL patients does not provide an OS or LSS benefit compared to a watchful waiting approach [9–13]. In one clinical trial, patients with asymptomatic, advanced-stage, low-grade NHL were randomized to receive chlorambucil or observation; OS and LSS were similar in both groups [10]. In another trial involving patients with asymptomatic, advanced-stage, non-bulky FL, no difference in OS was observed between those initiated on rituximab and those assigned to a watch-and-wait strategy [9].

While our study indicates that incidental diagnoses are associated with earlier-stage disease, this did not translate into improved survival outcomes in terms of EFS, OS, or LSS. Although the early DB4SS FL group offers some insight, a key question remains: if FL cases were detected at a preclinical molecular stage, would outcomes differ from those observed in our DB4SS group, in which some patients still had incidental clinical or laboratory abnormalities?

The field of cancer screening is entering an exciting new phase with the development of MCEDs [5, 6]. These tests can detect multiple cancers, including less common ones like lymphomas, by utilizing a distant medium such as blood, where tumor markers are shed [17]. MDMs in plasma show promise to detect lymphoma in asymptomatic individuals and are candidates for inclusion in MCEDs [4, 18]. One such test, the Galleri test, detects and analyzes methylation signatures in circulating free DNA (cfDNA) to help identify the presence of cancer, and potentially the tissue of origin. The PATHFINDER study, a non-randomized clinical trial, applied the Galleri test to 6662 asymptomatic individuals aged 50 or older who had no prior cancer diagnosis. The Galleri test identified alterations in cfDNA in 92 individuals (1.4%), of which 35 were later diagnosed with 26 different types of cancer. Twelve of these were lymphoma, 8 of which were diagnosed at early stages (4 stage I and 4 stage II) [4]. The same assay was tested in patients

Table 1. Baseline characteristics by presentation.

Characteristics	Incidental ($N = 259$)	Symptomatic ($N = 649$)	Total ($N = 908$)	*p*-Value
Age at diagnosis				<0.01[a]
Median	64	59	61	
IQR	55, 71	49, 68	51, 69	
Gender, n (%)				<0.01[b]
Male	156 (60.2%)	322 (49.6%)	478 (52.6%)	
Race, n (%)				0.92[b]
White	237 (91.5%)	580 (89.4%)	817 (90.0%)	
Asian	1 (0.4%)	6 (0.9%)	7 (0.8%)	
American Indian/Alaska Native	1 (0.4%)	5 (0.8%)	6 (0.7%)	
Black or African American	1 (0.4%)	2 (0.3%)	3 (0.3%)	
Native Hawaiian/Pacific Islander	0 (0.0%)	1 (0.2%)	1 (0.1%)	
Other	0 (0.0%)	2 (0.3%)	2 (0.2%)	
Unknown	19 (7.3%)	53 (8.2%)	72 (7.9%)	
Ethnicity, n (%)				0.67[b]
Not Hispanic or Latino	213 (82.2%)	546 (84.1%)	759 (83.6%)	
Hispanic or Latino	3 (1.2%)	6 (0.9%)	9 (1.0%)	
Chose Not to Disclose	32 (12.4%)	64 (9.9%)	96 (10.6%)	
Unknown	11 (4.2%)	33 (5.1%)	44 (4.8%)	
ECOG PS Group, n (%)				0.89[b]
<2	253 (97.7%)	634 (97.8%)	887 (97.8%)	
≥2	6 (2.3%)	14 (2.2%)	20 (2.2%)	
Unavailable	0	1	1	
Stage Group, n (%)				<0.01[b]
I/II	111 (43.2%)	196 (30.6%)	307 (34.2%)	
III/IV	146 (56.8%)	445 (69.4%)	591 (65.8%)	
Unavailable	2	8	10	
FLIPI Group, n (%)				0.10[b]
0–1 Low	129 (49.8%)	274 (42.2%)	403 (44.4%)	
2 Intermediate	73 (28.2%)	220 (33.9%)	293 (32.3%)	
3–5 High	57 (22.0%)	155 (23.9%)	212 (23.3%)	
Number of Nodal Groups, n (%)				0.06[b]
≤4	184 (73.9%)	417 (67.3%)	601 (69.2%)	
>4	65 (26.1%)	203 (32.7%)	268 (30.8%)	
Unavailable	10	29	39	
B Symptoms, n (%)				<0.01[b]
No	259 (100.0%)	592 (91.6%)	608 (91.8%)	
Yes	0 (0.0%)	54 (8.4%)	54 (8.2%)	
Missing	0	3	3	
LDH, n (%)				0.03[b]
≤Normal	191 (87.2%)	450 (80.8%)	641 (82.6%)	
>Normal	28 (12.8%)	107 (19.2%)	135 (17.4%)	
Unavailable	40	92	132	
Treatment Group, n (%)				<0.01[b]
Observation	150 (57.9%)	167 (25.7%)	317 (34.9%)	
Rituximab monotherapy	22 (8.5%)	72 (11.1%)	94 (10.4%)	
Immunochemotherapy	66 (25.5%)	300 (46.2%)	366 (40.3%)	
Radiation Only	4 (1.5%)	61 (9.4%)	65 (7.2%)	
Other Treatments	17 (6.6%)	49 (7.6%)	66 (7.3%)	

[a]Kruskal-Wallis *p*-value.
[b]Chi-square *p*-value.

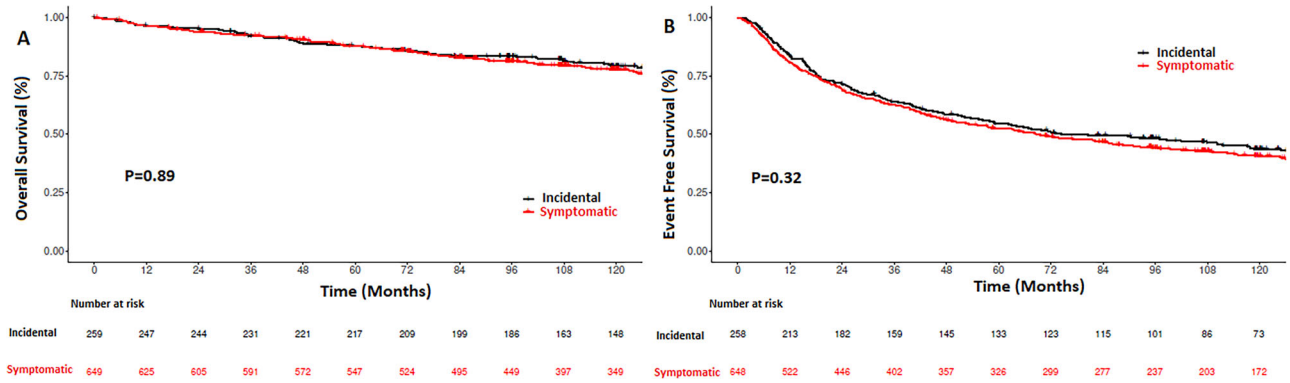

Fig. 1 Overall survival (OS) and event-free survival (EFS) in follicular lymphoma patients based on presentation mode. A OS stratified by incidental presentation versus presentation with lymphoma-related signs and symptoms. **B** EFS stratified by incidental presentation versus presentation with lymphoma-related signs and symptoms.

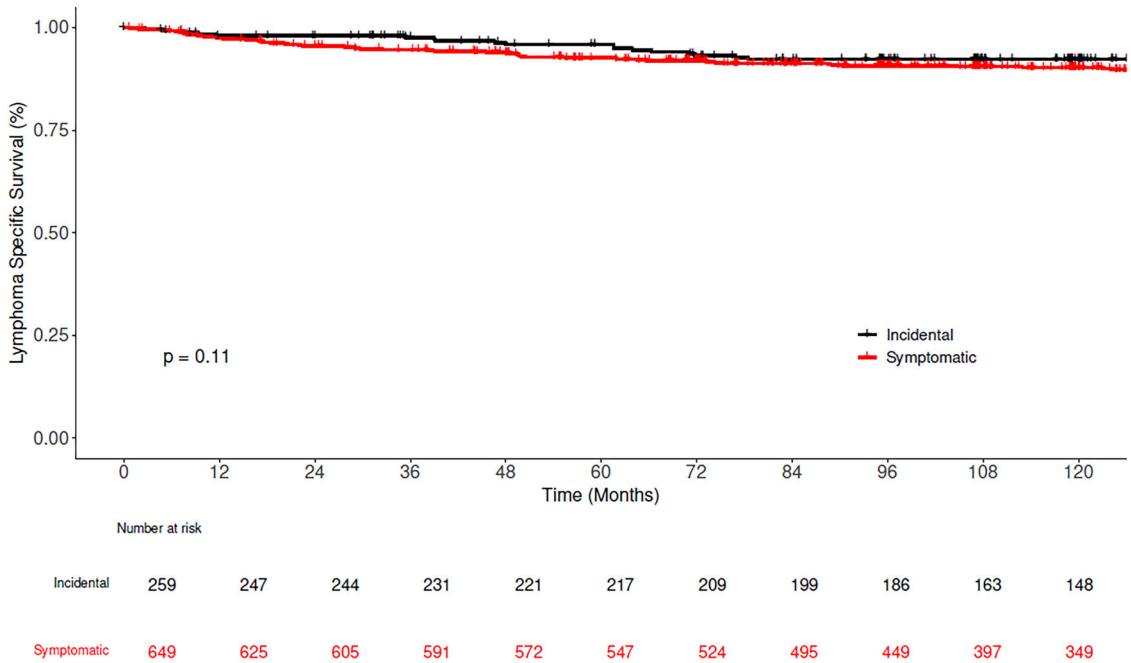

Fig. 2 Lymphoma-specific survival in follicular lymphoma patients based on presentation mode.

with symptoms, and 3.8% ($n = 14$) of the detected cancers were lymphoma [19]. Our group identified a panel of lymphoma-related MDMs capable of effectively differentiating lymphoma from normal lymphoid tissue and other cell lines, showing promise for inclusion in an MCED for lymphoma screening. After validating these markers in lymphoma tissues from independent sample sets, we also assessed the performance of the final panel of 16 MDMs in pre-treatment plasma samples containing DNA from individuals with and without lymphoma, including both NHL and classical Hodgkin lymphoma (cHL). At a specificity of 90%, the panel accurately identified 82% of FL cases (71–90%). The panel successfully identified most stage I/II cases, though its performance was notably higher in advanced stages [18].

While such tests show promise in detecting lymphoma, the impact of early molecular detection, particularly in asymptomatic patients and at stages earlier than those in the DB4SS cases, on both short- and long-term outcomes remains uncertain. Moreover, it is unclear whether adapting treatment strategies to include earlier intervention would meaningfully improve patient-centered outcomes in this subset. This question is especially relevant in FL, where several studies have shown that a watchful wait strategy is acceptable in asymptomatic patients and that some individuals may live an entire life without requiring antilymphoma therapy [9–13]. In the absence of prospective randomized studies demonstrating a survival benefit for detecting FL at a preclinical stage, the potential benefits of early detection must be weighed against the risks of overtreatment, treatment-related toxicity, false positives, and increased healthcare costs [20–22]. The psychological burden is also important to consider. Despite the indolent nature of FL and the possibility of not requiring treatment, receiving the diagnosis earlier may still cause anxiety and lead to unnecessary interventions. For example, in a clinical trial comparing watchful waiting to rituximab in FL, patients in the observation arm had poorer scores on the Illness Coping Style and Mental Adjustment to Cancer scales [9]. However, another study showed that the psychosocial impact of MCEDs is not a long-term issue [23].

Our results represent the traditional approach to FL. However, the treatment landscape of FL has entered a new era with the introduction of cellular therapy agents, including chimeric antigen receptor (CAR) T cells and bispecific antibodies [24–26]. These are approved for refractory/relapsed disease. Indeed, studies of bispecific

antibodies as frontline treatment in the frail (NCT05207670) and even asymptomatic individuals are ongoing. A phase 3 study (NCT06337318) is comparing frontline mosunetuzumab to rituximab in patients with low tumor burden FL. Also, EO2463, a novel microbial-derived peptide therapeutic vaccine, is being tested in a phase 1/2 trial (NCT04669171) for the treatment of FL, including newly diagnosed patients who do not meet criteria for standard of care treatment. However, given the potential toxicities associated with these therapies, including the risk of secondary neoplasms following CAR T-cell therapy [27], and the fact that many FL patients remain treatment-free over the course of their disease, it is important to critically evaluate whether early intervention with novel therapies would lead to meaningful improvements in lymphoma-specific survival among asymptomatic patients enrolled in ongoing clinical trials. If such a benefit is demonstrated, the case for early detection may gain greater clinical relevance.

The strengths of our study are reflected in the large sample size of patients with FL included in the analysis, in addition to the well-annotated treatment and long follow-up, in a prospective fashion. Some limitations to our study include the retrospective nature of the analysis, along with the long span of period of presentations (2002–2015), especially in light of newer treatments now approved for FL. Due to the retrospective nature of the study and the lack of detailed reasoning for therapy decisions in our dataset, we are unable to explain why patients in the DB4SS group received less radiation than those in the symptomatic group, despite having more localized disease. Additionally, we did not have information on the number of treatment cycles, subsequent therapies, incidence of secondary malignancies, and the number of patients who required procedures such as ureteral stenting due to bulky disease or organ compression. If future studies show that these metrics are reduced, they could contribute to the risk-versus-benefit argument for early detection, particularly with respect to non-survival outcomes such as healthcare costs.

In conclusion, our study indicates that incidental detection of FL is associated with earlier stages and more favorable prognostic features; however, this did not result in a significant improvement in patient survival outcomes when compared to symptomatic patients. Whether even earlier detection of FL using emerging MCEDs translates into improved outcomes remains an open question requiring further investigation.

DATA AVAILABILITY

Data is available upon reasonable request.

REFERENCES

1. Cerhan JR. Epidemiology of follicular lymphoma. Hematol Oncol Clin North Am. 2020;34:631–46.
2. Friedberg JW. Update on follicular lymphoma. Hematol Oncol. 2023;41:43–7.
3. Jacobsen E. Follicular lymphoma: 2023 update on diagnosis and management. Am J Hematol. 2022;97:1638–51.
4. Schrag D, Beer TM, McDonnell CH 3rd, Nadauld L, Dilaveri CA, et al. Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study. Lancet. 2023;402:1251–60.
5. Ding W, Chen G, Shi T. Integrative analysis identifies potential DNA methylation biomarkers for pan-cancer diagnosis and prognosis. Epigenetics. 2019;14:67–80.
6. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncol. 2020;31:745–59.
7. Loyfer N, Magenheim J, Peretz A, Cann G, Bredno J, Klochendler A, et al. A DNA methylation atlas of normal human cell types. Nature. 2023;613:355–64.
8. Moss J, Magenheim J, Neiman D, Zemmour H, Loyfer N, Korach A, et al. Comprehensive human cell-type methylation atlas reveals origins of circulating cell-free DNA in health and disease. Nat Commun. 2018;9:5068.
9. Ardeshna KM, Qian W, Smith P, Braganca N, Lowry L, Patrick P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol. 2014;15:424–35.
10. Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, MacLennan KA, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet. 2003;362:516–22.
11. El-Galaly TC, Bilgrau AE, de Nully Brown P, Mylam KJ, Ahmad SA, Pedersen LM, et al. A population-based study of prognosis in advanced stage follicular lymphoma managed by watch and wait. Br J Haematol. 2015;169:435–44.
12. Rueda A, Casanova M, Redondo M, Pérez-Ruiz E, Medina-Pérez A. Has the time to come leave the "watch-and-wait" strategy in newly diagnosed asymptomatic follicular lymphoma patients? BMC Cancer. 2012;12:210.
13. Solal-Céligny P, Bellei M, Marcheselli L, Pesce EA, Pileri S, McLaughlin P, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. J Clin Oncol. 2012;30:3848–53.
14. Atallah-Yunes SA, Rees MJ, Mwangi R, Kuchler RL, Nowakowski GS, Habermann TM, et al. Characteristics and outcomes of incidentally diagnosed diffuse large B-cell lymphoma and implications for cancer screening. Am J Hematol. 2025;100:158–62.
15. Friedberg JW, Byrtek M, Link BK, Flowers C, Taylor M, Hainsworth J, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol. 2012;30:3368–75.
16. Cerhan JR, Link BK, Habermann TM, Maurer MJ, Feldman AL, Syrbu SI, et al. Cohort Profile: the Lymphoma Specialized Program of Research Excellence (SPORE) Molecular Epidemiology Resource (MER) Cohort Study. Int J Epidemiol. 2017;46:1753–4i.
17. Ahlquist DA. Universal cancer screening: revolutionary, rational, and realizable. NPJ Precis Oncol. 2018;2:23.
18. Witzig TE, Taylor WR, Mahoney DW, Bamlet WR, Foote PH, Burger KN, et al. Blood plasma methylated DNA markers in the detection of lymphoma: discovery, validation, and Clinical Pilot. Am J Hematol. 2025;100:218–28.
19. Nicholson BD, Oke J, Virdee PS, Harris DA, O'Doherty C, Park JE, et al. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. Lancet Oncol. 2023;24:733–43.
20. Olivier T, Gill J, Prasad V. Multi-cancer screening tests: communicating about risks should be prioritized. Am J Med. 2022;135:413–5.
21. Robbins HA. Multicancer early detection tests—keeping a high bar for evidence of benefit. N. Engl J Med. 2024;391:292–4.
22. Welch HG, Dey T. Testing whether cancer screening saves lives: implications for randomized clinical trials of multicancer screening. JAMA Intern Med. 2023;183:1255–8.
23. Nadauld L, McDonnell CH 3rd, Dilaveri CA, Klein EA, Reid R, et al. Psychosocial impact associated with a multicancer early detection test (PATHFINDER): a prospective, multicentre, cohort study. Lancet Oncol. 2025;26:165–74.
24. Budde LE, Sehn LH, Matasar M, Schuster SJ, Assouline S, Giri P, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol. 2022;23:1055–65.
25. Linton KM, Vitolo U, Jurczak W, Lugtenburg PJ, Gyan E, Sureda A, et al. Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study. Lancet Haematol. 2024;11:e593–e605.
26. Neelapu SS, Chavez JC, Sehgal AR, Epperla N, Ulrickson M, Bachy E, et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). Blood. 2024;143:496–506.
27. Elsallab, Ellithi M, Lunning MA M, D'Angelo, Ma C, Perales MA J, et al. Second primary malignancies after commercial CAR T-cell therapy: analysis of the FDA Adverse Events Reporting System. Blood. 2024;143:2099–105.

ACKNOWLEDGEMENTS

Supported in part by the University of Iowa/Mayo Clinic Lymphoma SPORE CA97274, U01 CA195568, and the Predolin Foundation Biobank at Mayo Clinic.

AUTHOR CONTRIBUTIONS

TEW and SAAY came up with the conception and design of the study. SAAY, MJR, and RK collected and assembled data. RM analyzed the data. SAAY drafted the paper. SAAY, RM, MJR, RK, AA, GSN, TMH, YW, JCVB, ALF, MJM, JRC, SMA, and TEW contributed to data interpretation, provided expert input and approved the final version of the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with relevant guidelines and regulations. This study was approved by the Mayo Clinic Institutional Review Board (IRB #23-007912). Informed consent was obtained from all participants enrolled in the Molecular Epidemiology Resource cohort.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Suheil Albert Atallah-Yunes.