Concordance in survival among first-degree relatives diagnosed with indolent lymphoid malignancies including chronic lymphocytic leukemia

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Abstract

Objectives: To investigate concordance in survival time among first-degree relatives with lymphoid malignancies.

Methods: By linkage of national Swedish registers, we identified 66 430 patients diagnosed with a lymphoid malignancy 1958-2016 with information on first-degree relationships and follow-up until 2017. Among these, we identified pairs of first-degree relatives with any (N = 3326) or a similar (N = 690) lymphoid malignancy subtype. We defined survival in the first-degree relative as good, expected, or poor based on tertiles of deviance residuals from a multivariable Cox regression model. Next, we used Cox regression to estimate hazard ratios (HR) of death with 95% confidence intervals (CI) among patients, using the survival of their first-degree relative as exposure and adjusting for confounders.

Results: There was no concordance in survival among first-degree relatives with any lymphoid malignancy (HR good = 1.00 (reference), HR Expected = 1.02, 95% CI: 0.89-1.17, HR Poor = 1.12, 95% CI: 0.98-1.27, \( P_{\text{trend}} = .08 \)). Among first-degree relatives with indolent lymphoma, including chronic lymphocytic leukemia, those with a first-degree relative to an expected or poor survival had worse outcome compared to those with a first-degree relative with good survival (HR Expected = 1.44, 95% CI: 0.82-2.53, HR Poor = 1.79, 95% CI: 1.07-3.00, \( P_{\text{trend}} = .03 \)).

Conclusion: Our results support a role of inherited factors in the outcome of indolent lymphoma, including chronic lymphocytic leukemia.

Keywords: family history, first-degree relative, lymphoid malignancy, survival

Novelty Statements: For the first time, we tested the hypothesis of inherited factors affecting lymphoma prognosis by investigating concordance in survival time among first-degree relatives with lymphoid malignancies. Our novel results provide evidence to support a role of inherited factors in the outcome of indolent lymphoma and chronic lymphocytic leukemia. In counseling patients with an indolent lymphoma, the survival of relatives affected by indolent lymphoma may add information about the predicted clinical course.
1 | INTRODUCTION

Lymphoid malignancies may arise anywhere along the normal path of maturation of B or T/NK cells, resulting in the recognition of more than 50 distinct lymphoid neoplasms with different morphological, immunophenotypical, clinical, and/or genetic features. Survival varies considerably between and also within specific subtypes, and depend on host factors, tumor-specific characteristics, disease stage and location, and treatment schemes. Several observations suggest that prognosis may also depend on variation in normal cell functions in the tumor microenvironment and in the germline genome. In follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL), the malignant cells are dependent on normal stromal cells for their survival in vitro. Further, gene expression profiling studies have shown that expression signatures of non-malignant cells in the tumor microenvironment have strong impact on survival in patients with Hodgkin lymphoma, FL, and diffuse large B-cell lymphoma (DLBCL). In addition, candidate gene and genome-wide studies have found associations between germline polymorphisms and survival in Hodgkin lymphoma, CLL, FL, DLBCL, and multiple myeloma.

If the survival of lymphoid malignancies is, at least in part, dependent on germline genetic variation and normal cell function, a concordance in survival among first-degree relatives diagnosed with lymphoid malignancies would be expected. Such a concordance has previously been reported for breast, lung, prostate, and colorectal cancer. To investigate this hypothesis in lymphoid malignancies, we performed a large multi-generational cohort study using data from Swedish national population-based registers.

2 | METHODS

2.1 | Study cohort and definition of variables

We identified patients with lymphoid malignancies and their first-degree relatives along with relevant individual-level data by using the unique Swedish personal identity number to link several national registers (specified below). Health care in Sweden is publicly financed and decentralized ensuring full access to specialized cancer care for all residents.

We identified all patients with a first lymphoid malignancy (seventh revision of the International Classification of Diseases (ICD-7) codes 2000-2049) in the Swedish Cancer Register diagnosed 1958-2011 that also had data on at least one first-degree relative. The Cancer Register includes date of diagnosis, ICD-7 codes, and, since 1993, histopathologic type as Systematized Nomenclature of Medicine (SNOMED) codes. To classify the lymphoid malignancies into subtypes with as much detail as possible, we used SNOMED codes when available and ICD codes otherwise (Table S1). Because of few observations for several uncommon subtypes and less detail before 1993, the cases were mainly categorized into seven subgroups: aggressive and indolent lymphoma of non-Hodgkin type, Hodgkin lymphoma, CLL, plasma cell malignancies, acute lymphoblastic leukemia (ALL), and lymphoma unspecified (Table S2). By linking the patients to the Multi-Generation Register, we identified first-degree relationships among them (parents, children, and siblings). Among pairs of first-degree relatives diagnosed with a lymphoid malignancy, we defined the index patient as the individual diagnosed last in terms of calendar time and the other member as the affected relative. For individuals born in Sweden and alive in 1991 or later, information on the mother and father is close to complete. Therefore, index patients were identified from 1991 and onwards. In families with three members affected by a lymphoid malignancy (N = 110), we constructed two pairs of index patients and affected relatives, such that the individual diagnosed last (in terms of calendar time) was the index patient and the individual diagnosed second the affected relative in one pair, and the individual diagnosed second was the index patient and the individual diagnosed first the affected relative in the other pair. Pairs of index patients and affected relatives were formed in the same manner in families with four (N = 2; 3 pairs per family) and five (N = 1; 4 pairs per family) members affected by a lymphoid malignancy.

Data on socioeconomic status at diagnosis were obtained from the Longitudinal Integration Database for Health Insurance and Labor Market Studies 1991-2016, and the National censuses of 1960, 1970, 1980, and 1990. We used the highest achieved educational level as measure of socioeconomic status for most study participants. However, because the censuses of 1960 and 1980 did not include educational level, we instead used employment-derived educational level as defined by Statistics Sweden in some instances. Low socioeconomic status was defined as 9 years of education or less (or employment demanding 9 years or less of education), intermediate as 10-12 years of education (or employment demanding 10-12 years of education), and high socioeconomic status as >12 years of education (or employment demanding >12 years of education). Linkage with the Total Population Register provided virtually complete follow-up with regard to vital status, dates of death, and dates of emigration from Sweden.

2.2 | Statistical methods

Follow-up time for the survival analysis was counted from date of diagnosis until all-cause death, emigration, or December 31, 2017, whichever came first. We defined the survival of the affected relatives as either good, expected, or poor based on deviance residuals retrieved from a multivariable Cox proportional hazards model. The Cox model was adjusted for sex, calendar period of diagnosis (in 10-year intervals except 1958-1969 and 2010-2016) and socioeconomic status, age at diagnosis (in 10-year intervals except 0-19 and 80+), and with the baseline hazard stratified by type of lymphoid malignancy (seven subgroups as defined above). To satisfy the assumption of proportional hazards, follow-up time was restricted to 10 years maximum and split into two intervals, 0-1 and 1-10 years. The model was fitted to all patients with a lymphoid malignancy identified in...
| Variable                      | All patients | Index patients and relatives with any subtype | Index patients and relatives with concordant subtypes |
|------------------------------|--------------|-----------------------------------------------|------------------------------------------------------|
|                              | Frequency    | %                                             | Frequency    | %                                             | Frequency    | %                                             |
| Number of patients           | 66 430       |                                               | 3326         |                                               | 690          |                                               |
| Sex                          |              |                                               |              |                                               |              |                                               |
| Males                        | 39 011       | 59                                            | 1967         | 59                                            | 393          | 57                                            |
| Females                      | 27 419       | 41                                            | 1359         | 41                                            | 297          | 43                                            |
| Age at diagnosis             |              |                                               |              |                                               |              |                                               |
| 0-19                         | 6611         | 10                                            | 65           | 2                                             | 12           | 2                                             |
| 20-29                        | 3531         | 5                                             | 54           | 2                                             | 9            | 1                                             |
| 30-39                        | 3926         | 6                                             | 102          | 3                                             | 22           | 3                                             |
| 40-49                        | 6502         | 10                                            | 223          | 7                                             | 48           | 7                                             |
| 50-59                        | 11 643       | 18                                            | 697          | 21                                            | 161          | 23                                            |
| 60-69                        | 16 962       | 26                                            | 1088         | 33                                            | 233          | 34                                            |
| 70-79                        | 13 437       | 20                                            | 804          | 24                                            | 145          | 21                                            |
| 80-99                        | 3818         | 6                                             | 294          | 9                                             | 60           | 9                                             |
| Year of diagnosis            |              |                                               |              |                                               |              |                                               |
| 1958-1969                    | 2804         | 4                                             | 0            |                                               | 0            |                                               |
| 1970-1979                    | 4237         | 6                                             | 0            |                                               | 0            |                                               |
| 1980-1989                    | 7049         | 11                                            | 0            |                                               | 0            |                                               |
| 1990-1999                    | 11 739       | 18                                            | 469          | 14                                            | 117          | 17                                            |
| 2000-2009                    | 19 420       | 29                                            | 1192         | 36                                            | 244          | 35                                            |
| 2010-2016                    | 21 181       | 32                                            | 1665         | 50                                            | 329          | 48                                            |
| Socioeconomic status         |              |                                               |              |                                               |              |                                               |
| Low                          | 23 656       | 36                                            | 1107         | 33                                            | 1356         | 41                                            |
| Intermediate                 | 26 088       | 39                                            | 1279         | 38                                            | 1403         | 42                                            |
| High                         | 13 205       | 20                                            | 871          | 26                                            | 423          | 13                                            |
| Unknown                      | 3481         | 5                                             | 69           | 2                                             | 144          | 4                                             |
| All-cause deatha             | 30 899       | 47                                            | 1464         | 44                                            | 2579         | 78                                            |
| Lymphoid malignancies        |              |                                               |              |                                               |              |                                               |
| Plasma cell malignancies     | 10 864       | 16                                            | 576          | 17                                            | 568          | 17                                            |
| Indolent lymphoma excl CLL    | 10 261       | 15                                            | 657          | 20                                            | 333          | 10                                            |

(Continues)
We identified 66,430 patients with a first lymphoid malignancy diagnosed 1958-2016 in the Swedish Cancer Register and at least one first-degree relative in the Multi-Generation Register (Table 1). Among these, we identified families with two (N = 3096), three (N = 110), four (N = 2), or five (N = 1) first-degree relatives diagnosed with a lymphoid malignancy. In relation to the index patient, the first-degree relative was a parent in 55% of the pairs, sibling in 29%, and offspring in 15%. For 690 index patients, the first-degree relative was diagnosed with a lymphoma within the same lymphoid malignancy subgroup (seven subgroups, Table 1). We noted an increasing proportion of CLL cases among the familial cases, rising from 14% among all patients with a lymphoid malignancy (N = 66,430) to 22% among all index patients with any affected relative (N = 3326) to 34% among index patients with concordant subtypes (N = 690; Table 1). In line with a strong heritability of CLL, a less marked accumulation was also noted for plasma cell malignancies.

### RESULTS

**Table 1** (Continued)

| Variable | All patients | Index patients and relatives with any subtype | Index patients and relatives with concordant subtypes |
|----------|-------------|---------------------------------------------|--------------------------------------------------|
|          | Frequency   | Index patients | Relatives | Index patients | Relatives |
|          | %           | Frequency | % | Frequency | % | Frequency | % |
| CLL      | 9168        | 730       | 22 | 605       | 18 | 233       | 34 |
| Aggressive lymphoma | 10 262     | 651      | 20 | 249       | 7  | 56        | 8  |
| Hodgkin lymphoma | 7098        | 193      | 6  | 342       | 10 | 35        | 5  |
| ALL      | 6476        | 131       | 4  | 167       | 8  | 14        | 2  |
| Lymphoma, unspecified | 12 301     | 388      | 12 | 962       | 29 | 132       | 19 |

| Abbreviations: ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; Lymphoma unspecified, lymphoma not otherwise specified (NOS), non-Hodgkin lymphoma (NHL) NOS, B-cell NHL NOS, B-cell lymphoma cutaneous, leukemia NOS; Hodgkin lymphoma, classical Hodgkin lymphoma; nodular lymphocyte-predominant Hodgkin lymphoma; Aggressive lymphoma, aggressive NHL NOS, T-cell NHL NOS, diffuse large B cell, primary mediastinal B cell, Mantle cell, Burkitt, B-cell intravascular, peripheral T-cell lymphoma NOS, Sezary, T-cell angioimmunoblastic, T-cell enteropathy-associated, T/NK cell extranodal kind, NK cell lymphoma NOS; Indolent lymphoma, indolent NHL NOS, B-cell lymphocytic, follicular, marginal zone, Waldenstrom, lymphoplasmacytic, hairy cell leukemia, mycosis fungoides, other cutaneous T-cell lymphomas, gamma-heavy chain disease; CLL, chronic lymphocytic leukemia, small cell lymphocytic lymphoma, B- and T-cell prolymphocytic leukemia; Plasma cell malignancy, multiple myeloma, plasmacytoma, plasma cell leukemia; ALL, ALL NOS, B- and T-cell ALL, B- and T-cell lymphoblastic lymphoma. |

| Follow-up time of 10 y maximum for all patients, and unlimited for index patients and relatives with any subtype and index and relative patients with concordant subtypes. |

### Discussion

In the main analysis, we assessed the relative rate of all-cause death among the index patients given the all-cause survival of their affected first-degree relative by estimating hazard ratios (HR) with 95% confidence intervals (CI). For this, we used a similar Cox model to the one described above, additionally including the categorical representation of survival of the relative (good, expected, poor) as the exposure, and accounting for potential family cluster effects. First, the model was fitted to all index patients combined (ie all subtypes of lymphoid malignancies; N = 3326) stratified by subtype. Second, we limited the analysis to index patients with an affected first-degree relative with a concordant subtype of lymphoid malignancies (N = 690). In these analyses, we did not have to split or limit the follow-up time in order to satisfy the proportional hazards assumption. Because of few patients with ALL, Hodgkin lymphoma, and other subtypes of lymphoid malignancies, we collapsed good and expected survival of the relative into one category when performing subgroup-specific analyses.

**Table 1** (Continued)

| Variable | All patients | Index patients and relatives with any subtype | Index patients and relatives with concordant subtypes |
|----------|-------------|---------------------------------------------|--------------------------------------------------|
|          | Frequency   | Index patients | Relatives | Index patients | Relatives |
|          | %           | Frequency | % | Frequency | % | Frequency | % |
| CLL      | 9168        | 730       | 22 | 605       | 18 | 233       | 34 |
| Aggressive lymphoma | 10 262     | 651      | 20 | 249       | 7  | 56        | 8  |
| Hodgkin lymphoma | 7098        | 193      | 6  | 342       | 10 | 35        | 5  |
| ALL      | 6476        | 131       | 4  | 167       | 8  | 14        | 2  |
| Lymphoma, unspecified | 12 301     | 388      | 12 | 962       | 29 | 132       | 19 |

In the Cancer Register except the index patients (N = 64,430). The relative rate of all-cause death among the index patients given the all-cause survival of their affected first-degree relative by estimating hazard ratios (HR) with 95% confidence intervals (CI). For this, we used a similar Cox model to the one described above, additionally including the categorical representation of survival of the relative (good, expected, poor) as the exposure, and accounting for potential family cluster effects.
We observed no concordance in survival among two first-degree relatives affected by any type of lymphoid malignancy (Table 2). However, when limiting the analyses to index patients diagnosed with a similar lymphoid malignancy subtype as their affected relative (N = 690), we observed statistically significant concordance in survival among two first-degree relatives diagnosed with an indolent non-Hodgkin lymphoma including CLL. In this group, index patients with a first-degree relative with expected or poor survival had a statistically significantly worse overall survival (HR$_{good} = 1.00$ (ref), HR$_{Expected} = 1.44$, 95% CI: 0.82-2.53, HR$_{Poor} = 1.79$, 95% CI: 1.07-3.00, $P_{trend} = .03$; Table 2) compared to index patients with a first-degree relative with good survival. A similar but not statistically significant result was observed among index patients with CLL that had a first-degree relative with CLL (HR$_{good} = 1.00$ (ref), HR$_{Expected} = 1.43$, 95% CI: 0.78-2.64, HR$_{Poor} = 1.63$, 95% CI: 0.93-2.86, $P_{trend} = .10$).

There was no interaction between age at diagnosis and sex in any of the survival analyses performed (data not shown).

4 | DISCUSSION

In this nationwide multi-generational cohort study, we observed statistically significant concordance in survival time among two first-degree relatives diagnosed with an indolent lymphoma including CLL.

This is the first large study to explore the potential concordance in survival time among first-degree relatives with a lymphoid malignancy accounting for subtype. Previously, the survival of lymphoma patients with a family history of any lymphoma, non-Hodgkin lymphoma, or a hematological malignancy was explored and found to be no different than the survival of non-familial cases. In complementary analyses, one of the studies investigated the potential concordance of survival between 98 parents and 98 offspring with non-Hodgkin lymphoma and found a statistically non-significant worse survival among offspring with a parent surviving <24 months after diagnosis as compared to offspring with a parent surviving ≥24 months. They noted the same trend for parents with offspring surviving more or less than 60 months. However, there was no account of non-Hodgkin lymphoma subtype, and reported differences in heritability and survival between low- and high-grade non-Hodgkin lymphoma could have influenced the results. The heritability in risk of CLL, multiple myeloma (the majority of plasma cell neoplasms), DLBCL, HL, and ALL has been estimated to 46%, 20%, 16%, 24%, and 12%, respectively. The strong accumulation of CLL among the familiar cases in our study is in line with the known high heritability in risk of CLL. In addition, this fact resulted in higher power to detect concordance in survival time among first-degree relatives with indolent lymphomas, of whom the majority had CLL (232 of 301 index cases, 77%). Conversely, the comparably low heritability in risk of aggressive B-cell lymphoma, HL, and ALL in combination with lower incidence for the latter two subtypes resulted in small numbers of familial cases. Consequently, we had low power to detect concordance in survival time among first-degree relatives with these lymphoma subtypes.

We cannot exclude the possibility that unmeasured confounding explains our results. Nor can we exclude that inherited genetic factors affecting survival in general, that is, factors unrelated to the development and progression of lymphoid malignancies, drive the familial concordance in survival observed in our data. Since human lifespan has low heritability in the general population, this explanation is, however, unlikely. Furthermore, significant familial concordance in survival was only observed among index cases and first-degree relatives with similar subtypes of lymphoid malignancy and not among relatives with different subtypes, strengthening the argument for a role of heritability of lymphoma subtype-specific factors affecting the prognosis. In addition, we adjusted for socioeconomic status using educational level as a proxy. This should have reduced the influence of familial comorbidities associated with socioeconomic status, such as cardiovascular diseases, on our estimates. Also, specialized health care was publicly financed and available to all Swedish residents during the study period (1958-2017), acting to reduce potential health consequences of differences in socioeconomic status.

Survival of lymphoid malignancies has improved over time in Sweden, which was also reflected in our dataset (Figure S1). Known reasons for this include improvements in chemo- and radiotherapy schemes, the addition of anti-CD20 antibody therapy, and diagnostic improvements. By adjusting the Cox model for calendar period of diagnosis (and other variables) and then using the deviance residual instead of the actual survival time for each study subject, we could make fair comparisons of prognosis among individuals diagnosed with lymphoma at different time periods. Hence, this methodology reduced any bias due to changes in treatment or other factors improving survival after lymphoma diagnosis over time.

Several studies have found an association between germline polymorphisms in genes related to immune response, metabolism, and DNA repair and outcome in lymphoid malignancies. However, few attempts have been made to validate these findings, and the mechanisms behind the observations are yet to be elucidated. Nevertheless, there is a growing interest in normal cells and structures in the tumor microenvironment and their role in tumor growth. There is strong evidence of a close interplay and co-dependence between the tumor microenvironment and the malignant B cells in several lymphoid malignancies, including CLL, FL, and plasma cell malignancies. The lymphoid tumor microenvironment consists of immune cells, stromal cells, osteoclasts, endothelial cells, and extracellular matrix in variable proportions depending on lymphoma subtype. The ratio of normal versus malignant cells goes from high in indolent lymphomas to low in aggressive lymphomas. FL and CLL rarely harbor mutations in the B-cell receptor or associated proteins that would make them self-sufficient of signals to survive and proliferate. Instead, FL and CLL are dependent on external signals from the tumor microenvironment, such as cell-cell interaction, (auto)antigens, and cytokines, for such stimuli. One could speculate that these external signals may be modified by germline genetic polymorphisms with possible implications for the prognosis (and risk) of indolent
lymphomas in particular. Alternatively, genetic polymorphisms could alter gene expression or protein structures resulting in variations in enzymatic activity or drug metabolism with implications for prognosis. 29 Genetic polymorphisms have also been associated with risk of histologic transformation of FL and CLL to aggressive lymphoma, resulting in worse survival as compared to non-transformed FL and CLL. 30,31 In summary, genetic polymorphisms have the potential to influence the risk of developing distinct molecular subtypes within existing lymphoma entities (e.g., CLL or FL more prone to transforming into aggressive lymphoma), as well as host factors affecting drug efficacy and the immune response to the lymphoma, all with possible implications for prognosis. Because genetic polymorphisms are inherited from one generation to the next, they have the potential to influence the survival time in both the parent(s) and the offspring affected by lymphoma. In this way, genetic polymorphisms could possibly explain the observed concordance in survival time between first-degree relatives with indolent lymphoma.

Strengths of the study include the novel findings, the population-wide approach, and the careful statistical methods to define exposure and achieve comparability across a long period of calendar time. Limitations include lack of information on established prognostic factors. We reason, however, that most prognostic factors would be steps in the causal path between inherited factors such as genetic polymorphisms and survival following the diagnosis of a lymphoid malignancy. Hence, including established prognostic factors in the model could then risk to attenuate a true association.

In conclusion, our results support the hypothesis that survival of indolent lymphomas is affected in part by inherited factors. This encourages further studies in this field. In counseling patients with an indolent lymphoma with a family history of a similar lymphoma

### TABLE 2

Relative risk of death estimated as hazard ratios (HR) with 95% confidence intervals (CI) in index patients with lymphoid malignancy given the prognosis (good, expected, poor) of their respective affected first-degree relative. Analyses were performed in all subtypes combined and separately among all index patients and limited to index patients with a first-degree relative with a concordant subtype.

| Lymphoma subtype       | Survival of first-degree relative | Index patients with relatives with any lymphoma subtype | Index patients with relatives with concordant lymphoma subtype |
|------------------------|-----------------------------------|-------------------------------------------------------|---------------------------------------------------------------|
|                        | #obs. | #deaths | HR 95% CI | #obs. | #deaths | HR 95% CI |
| All subtypes           |       |         |          |       |         |          |
| Good                   | 941   | 415     | ref      | 184   | 80      | ref      |
| Expected               | 1114  | 489     | 1.02     | 0.89-1.17 | 225   | 116     | 1.14     | 0.85-1.55 |
| Poor                   | 1271  | 560     | 1.12     | 0.98-1.27 | 281   | 129     | 1.24     | 0.93-1.66 |
| P for trend            |       |         | .08      |       |         | .15      |
| Plasma cell            |       |         |          |       |         |          |
| Good                   | 157   | 90      | ref      | 28    | 43      | ref      |
| Expected               | 113   | 113     | 1.13     | 0.85-1.50 | 66    | 18      | 0.85     | 0.48-1.51 |
| Poor                   | 138   | 138     | 1.23     | 0.94-1.62 | 58    | 30      | 1.03     | 0.56-1.89 |
| P for trend            |       |         | .13      |       |         | .82      |
| Indolent lymphoma      |       |         |          |       |         |          |
| Good                   | 358   | 124     | ref      | 81    | 26      | ref      |
| Expected               | 502   | 172     | 1.07     | 0.84-1.35 | 83    | 33      | 1.44     | 0.82-2.53 |
| Poor                   | 527   | 181     | 1.14     | 0.90-1.44 | 137   | 54      | 1.79     | 1.07-3.00 |
| P for trend            |       |         | .26      |       |         | .03      |
| Including CLL          |       |         |          |       |         |          |
| Good                   |       |         |          |       |         |          |
| Expected               | 264   | 100     | 1.24     | 0.90-1.69 | 71    | 29      | 1.43     | 0.78-2.64 |
| Poor                   | 283   | 103     | 1.19     | 0.87-1.63 | 101   | 43      | 1.63     | 0.93-2.86 |
| P for trend            |       |         | .33      |       |         | .10      |
| Aggressive lymphoma    |       |         |          |       |         |          |
| Good + expected        |       |         |          |       |         |          |
| Poor                   | 256   | 121     | 1.16     | 0.92-1.47 | 26    | 9       | 0.56     | 0.22-1.44 |
| P value                |       |         | .21      |       |         | .23      |
| Hodgkin lymphoma       |       |         |          |       |         |          |
| Good + expected        |       |         |          |       |         |          |
| Poor                   | 65    | 17      | 0.92     | 0.48-1.76 | 11    | 4       | Inestimable | |
| P value                |       |         | .80      |       |         |          |
| ALL                    |       |         |          |       |         |          |
| Good + expected        |       |         |          |       |         |          |
| Poor                   | 96    | 61      | 0.86     | 0.48-1.56 | 10    | 8       | 1.18     | 0.13-11.2 |
| P value                |       |         | .63      |       |         | .89      |

Abbreviations: ALL, acute lymphoblastic leukemia, CLL, chronic lymphocytic leukemia.
subtype, the survival of affected relatives may add information when predicting the clinical course.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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