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ORIGINAL REPORT

Impact of Expert Pathologic Review of Lymphoma Diagnosis: Study of Patients From the French Lymphopath Network

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ABSTRACT

Purpose
To prospectively assess the clinical impact of expert review of lymphoma diagnosis in France.

Materials and Methods
From January 2010 to December 2013, 42,145 samples from patients with newly diagnosed or suspected lymphomas were reviewed, according to the 2008 WHO classification, in real time by experts through the Lymphopath Network. Changes in diagnosis between referral and expert review were classified as major or minor according to their potential impact on patient care.

Results
The 42,145 reviewed samples comprised 36,920 newly diagnosed mature lymphomas, 321 precursor lymphoid neoplasms, 314 myeloid disorders, and 200 nonhematopoietic neoplasms, with 4,390 benign lesions. There were 4,352 cutaneous and 32,568 noncutaneous lymphomas. The most common mature noncutaneous lymphomas were diffuse large B-cell lymphomas (32.4%), follicular lymphomas (15.3%), classic Hodgkin lymphomas (13%), peripheral T-cell lymphomas (6.3%) of which angioimmunoblastic T-cell lymphomas (2.3%) were the most frequent, and mucosa-associated lymphoid tissue lymphomas (5.8%). A diagnostic change between referral and expert review occurred in 19.7% of patients, with an estimated impact on patient care for 17.4% of patients. This rate was significantly higher for patients sent with a provisional diagnosis seeking expert second opinion (37.8%) than for patients sent with a formal diagnosis (3.7%). The most frequent discrepancies were misclassifications in lymphoma subtype (41.3%), with 12.3% being misclassifications among small B-cell lymphoma entities. Fewer than 2% of changes were between benign and malignant lymphoid conditions. Minor changes (2.3%) mostly consisted of follicular lymphoma misgrading and diffuse large B-cell lymphoma subtype misclassification.

Conclusion
To our knowledge, this study provides the largest ever description of the distribution of lymphoma entities in a western country and highlights how expert review significantly contributes to a precise lymphoma diagnosis and optimal clinical management in a proportion of patients.

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INTRODUCTION

Lymphoma diagnosis has become more accurate since the introduction of the WHO classification in 2001,[1] but the risk of error remains higher than in other areas of pathology, which supports the requirement for expert review.[2-4] The 2008 WHO classification[5] includes more than 80 lymphoma entities, with some being rare and difficult for inexperienced pathologists to recognize. Furthermore, the diagnosis of hematologic malignancies currently requires multiple immunohistochemical (IHC) studies[4-6] and additional tests such as fluorescent in situ hybridization (FISH) or polymerase chain reaction techniques that are not available in all

ASSOCIATED CONTENT

Appendix
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routine laboratories. Thus, there have been calls for expert review of patients with lymphoma. In addition, with the advent of individualized therapeutic approaches for distinct lymphoma subtypes, it is increasingly critical to render an accurate diagnosis before treatment is started.[7-18]

Previous studies have supported the impact of expert review on lymphoma management by comparing tumor diagnosis on referral with diagnosis of the same sample by an expert and have reported a highly variable rate of discrepancy.[19-23] Most of these studies were based on the retrospective analyses of limited cohorts of patients with lymphoma at monocentric or regional levels[19-23] and/or were focused on the most common lymphoma entities.[22] Most were also conducted before the publication of the current WHO classifications,[5,24] which introduced new lymphoma entities and reinforced the importance of an integrated morphologic, immunophenotypic, and molecular approach for lymphoma diagnosis.[20,22,23]

The Lymphopath Network is a national hematopathology network established in France in 2010 and funded by the French National Cancer Agency that aims to provide an expert pathologic review of every newly diagnosed lymphoma before therapy is started.[25,26] Here, we provide data on 36,920 lymphomas diagnosed between 2010 and 2013 that were reviewed and classified according to the WHO 2008 classification criteria.[5] We present the overall frequency and relative distribution of specific entities and show the importance of expert pathologic review on the clinical management of patients with lymphoma.

MATERIALS AND METHODS

The Lymphopath Network Review Process

Since 2010, pathologists in France have been encouraged to send samples of every newly diagnosed or suspected lymphoma to a reference center belonging to the Lymphopath Network in which experienced hematopathologists have unlimited access to IHC and molecular tests.[25,26] Lymphopath aims to provide expert diagnoses within a reasonable time frame (mean, 8 days), which allows for real-time therapeutic decision making on the basis of a revised diagnosis. Both the final and submitted diagnoses are recorded in the Lymphopath database and take into account whether patients had a formal diagnosis or were sent with a provisional diagnosis to obtain an expert second opinion. The Lymphopath review process is detailed in the Appendix (online only).

Evaluation of Diagnostic Changes Between Referral and Expert Review

A total of 31,910 patients were eligible for comparison of referral and expert diagnoses, after excluding those sent without a diagnosis proposed by the referral pathologist (n = 4,289) and patients with cutaneous lymphoid lesions (n = 5,946), which commonly require clinicopathologic integration for a definitive diagnosis (Fig 1). We calculated the percentage of patients whose diagnosis did not change between referral and expert histopathologic review (Table 1). Diagnostic changes included patients referred with a lymphoma diagnosis not conforming to the WHO classification.[5] To assess the reproducibility of expert diagnoses,[22,27] quality control of 319 patients randomly selected from the database showed an expert concordance rate of 99.05%. Additional details are provided in the Appendix.

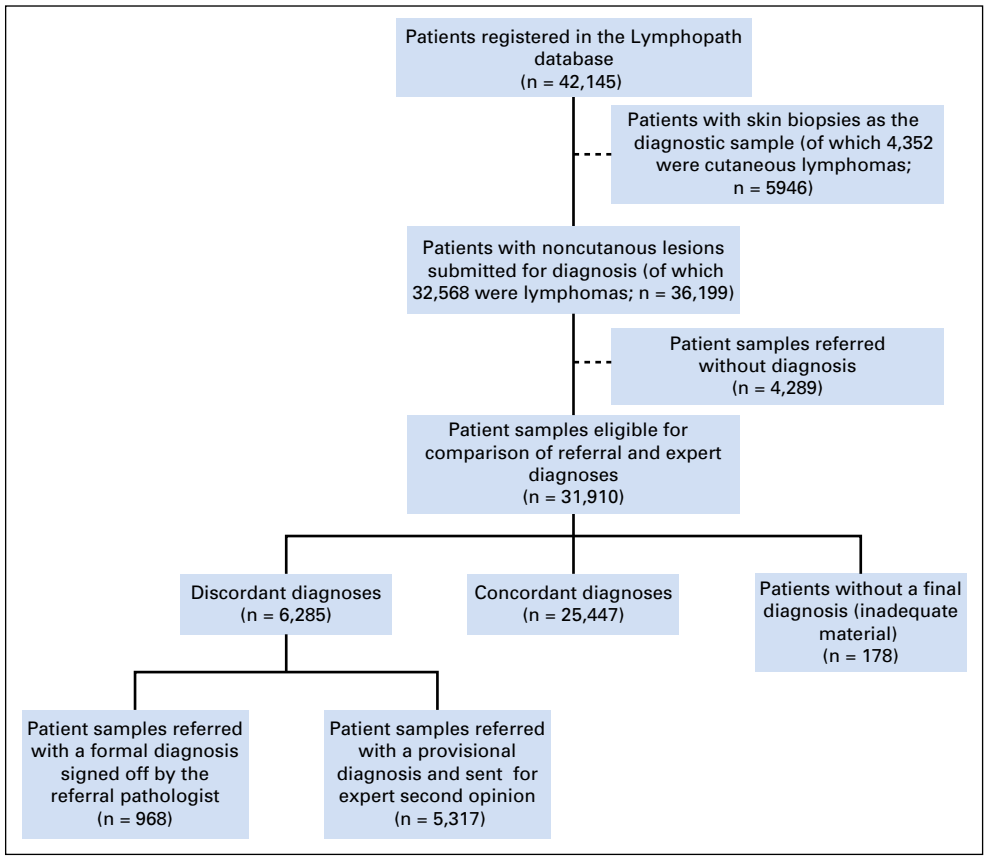

Fig 1. Flowchart of the Lymphopath Network study.

Table 1. Comparison of Referral and Expert Diagnoses Among the Major Categories of Noncutaneous Disorders (N = 31,910)

Main Categories	Overall Concordance No.	%
Mature B-cell lymphomas		
DLBCL-NOS	8,060/9,618	83.8
BL	298/392	76
FL grade 1, 2, or 3A	3,910/4,572	85.5
FL grade 3B	87/188	46.3
CLL/SLL	1,321/1,690	78.1
MCL	963/1,310	73.5
LPL/WM	662/789	83.9
MALT lymphomas	1,351/1,628	83
SMZL	247/310	79.6
NMZL	314/530	59.2
HCL	131/153	85
PCN	977/1,060	92.1
PTCLs		
AITL	429/624	68.7
PTCL-NOS	309/484	63.8
ALK^+ ALCL	130/158	82.3
ALK^- ALCL	69/146	47.2
Extranodal NKTCL	71/107	66.3
EATL	49/66	74.2
ATLL	23/49	47
T-LGL	29/34	85
HSTL	14/17	82
HLs		
cHL	3,744/4,010	93.3
NLPHL	254/404	62.8
Precursor lymphoid neoplasms		
B-cell lymphoblastic leukemia/lymphomas	80/114	70.17
T-cell lymphoblastic leukemia/lymphomas	138/188	73.4
Post-transplant lymphoproliferative disorders	123/148	83
Myeloid neoplasms	84/108	77.7
Benign lymphoid conditions	1,040/1,289	80.6

NOTE. The 4,289 patients sent without diagnosis have been excluded. The concordance rate (No. and %) was established as the number of patients of each lymphoma subtype with the same diagnosis from both the referral and expert pathologists among the total number of that subtype according to expert review.

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukemia/lymphoma; BL, Burkitt lymphoma; cHL, classic Hodgkin lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell lymphoma; HL, Hodgkin lymphoma; HSTL, hepatosplenic T-cell lymphoma; LPL/WM, lymphoplasmocytic lymphoma/Waldenström macroglobulinemia; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; NKTCL, natural killer T-cell lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; NMZL, nodal marginal zone lymphoma; NOS, not otherwise specified; PCN, plasma cell neoplasm; PTCL, peripheral T-cell lymphoma; SMZL, splenic marginal zone lymphoma; T-LGL, T-cell large granular lymphocytic leukemia.

Potential Impact of a Change in Diagnosis on Clinical Management

To evaluate the potential impact of expert review on clinical management of patients, diagnostic changes were evaluated a posteriori by a hematologist and were divided into major and minor changes according to the guidelines of the National and European Onco-Hematology Societies (Société Française d'Hématologie and European Society of Medical Oncology).[28,29] The rates of major and minor changes between referral and expert diagnoses (definitions are provided in the Appendix) were assessed among the 31,910 eligible patients with noncutaneous disorders and included both patients sent with formal diagnoses (n = 19,112) and those with provisional diagnoses who were sent for expert second opinion (n = 12,798; Tables 2 and 3).

Statistical Analysis

The χ^2 test was used to evaluate the frequency of ancillary tests performed by the experts among the discordant and concordant diagnoses. Because of the epidemiologic nature of the study, *P* values of .001 or less were considered to be statistically significant. Analyses were performed by using GraphPrism and R.3.1.0 software.

RESULTS

Distribution of Lymphoma Entities From the Lymphopath Survey

From January 2010 to December 2013, the samples of 42,145 patients, including 5,946 cutaneous and 36,199 noncutaneous samples, were referred to Lymphopath for a newly diagnosed or suspected lymphoma. Of the 42,145 samples, 36,920 were newly diagnosed mature lymphomas, 321 were precursor lymphoid neoplasms with 193 T-cell and 128 B-cell lymphoblastic lymphoma/leukemias, and 314 were myeloid disorders. The remaining patients (n = 4,590) had reactive lymphoid conditions (n = 4,390) and nonhematopoietic neoplasms (n = 200).

The 36,920 mature lymphomas comprised 4,352 cutaneous lymphomas and 32,568 noncutaneous lymphomas. Cutaneous lymphomas comprised 34% B-cell lymphomas (n = 1,480) and 65.2% T-cell lymphomas (n = 2,838), mostly mycosis fungoides (n = 1,922) and Sézary syndrome (n = 130). Among the noncutaneous lymphomas, 78.3% were B-cell lymphomas, 6.3% were peripheral T-cell lymphomas (PTCLs), and 14.5% were Hodgkin lymphomas (HLs), with 1% remaining as unclassified non-Hodgkin lymphomas (NHLs; Fig 2A). As shown in Figure 2B, diffuse large B-cell lymphomas (DLBCLs), including primary mediastinal B-cell lymphomas (PMBLs), were the most prevalent subtype of noncutaneous mature B-cell lymphomas (41.4%), followed by follicular lymphomas (FLs; 19.61% were grade 1, 2, or 3A and 0.82% were grade 3B). Mucosa-associated lymphoid tissue (MALT) lymphomas, chronic lymphocytic leukemias/small lymphocytic lymphomas (CLLs/SLLs), mantle cell lymphomas (MCLs; 1,231 common-type and 163 blastoid variant), and plasma cell neoplasms (PCNs) accounted for 7.5%, 7.1%, 5.5%, and 4.6% of mature B-cell neoplasms, respectively, and Burkitt lymphomas (BLs) were less than 2%. Lymphoplasmacytic lymphomas/Waldenström macroglobulinemias (LPLs/WMs) were slightly more prevalent (3.3%) than nodal marginal zone lymphomas (NMZLs; 2.4%). Among specific DLBCL subtypes, there were 153 Epstein-Barr virus–positive (EBV-positive), 124 plasmablastic, and 13 primary effusion lymphomas (PELs). Among noncutaneous PTCLs, angioimmunoblastic T-cell lymphomas (AITLs; 36.1%) were more frequent than PTCL not otherwise specified (PTCL-NOS; 26.9%), whereas anaplastic lymphoma kinase (ALK^+) and ALK^- anaplastic large cell lymphomas (ALCLs) each represented approximately 8% of the PTCLs. Nasal-type extranodal natural killer T-cell lymphomas (NKTCLs) and enteropathy-associated T-cell lymphomas (EATLs) accounted for 6% and 3.8%, respectively (Fig 2C).

Among 4,713 HLs, 89.8% were classic HLs (cHLs), whereas nodular lymphocyte-predominant Hodgkin lymphomas (NLPHLs) accounted for 10.2% (Fig 2D). Among cHLs, 62.85% were nodular sclerosis cHLs, and 17.5% were mixed cellularity cHLs, whereas

Table 2. Major and Minor Changes Between Referral and Expert Diagnoses for Noncutaneous Disorders

Major and Minor Diagnostic Changes	Diagnostic Changes Among All Diagnostic Changes		Percentage Among All Patients (N = 31,910)
	No.	%	
Major changes (ie, with a potential impact on patient care)	5,553	88.3	17.4
Category A: Misclassification of lymphoma subtype	2,592	41.3	8.12
Mature B-NHL to PTCL or vice versa	118	1.9	0.37
cHL to mature B-NHL or vice versa	137	2.2	0.43
cHL to PTCL or vice versa	98	1.6	0.3
NLPHL to other lymphoma subtypes or vice versa	139	2.2	0.44
BL to other mature B-NHLs or vice versa	139	2.2	0.44
MCL to other mature B-NHL or vice versa	344	5.5	1.08
DLBCL to low-grade B-NHL*	202	3.2	0.63
Low-grade B-NHL to DLCBL†	359	5.7	1.13
Misclassifications in low-grade B-NHL with therapeutic impact‡	773	12.3	2.42
Misclassifications in PTCL with therapeutic impact§	196	3.1	0.61
Lymphomas to PCN or vice versa	87	1.4	0.27
Category B: Malignant to benign lesions or vice versa	466	7.4	1.46
Lymphomas or other neoplasms to benign lesions	255	4.1	0.8
Benign lesions to lymphomas or other neoplasms	211	3.3	0.66
Category C: Lymphomas to other malignancies or vice versa	192	3	0.6
Lymphomas to nonhematopoietic neoplasms or vice versa	97	1.5	0.3
Lymphomas to myeloid neoplasms or vice versa	39	0.6	0.12
Mature lymphomas to T-cell precursor neoplasms or vice versa	28	0.4	0.09
Mature lymphomas to B-cell precursor neoplasms or vice versa	28	0.4	0.09
Category D: Unclassified lymphomas to classified lymphomas	2,303	36.6	7.22
Minor changes (ie, without a potential impact on patient care)	732	11.7	2.3
FL grade 1 or 2 to FL grade 3A or vice versa	176	2.8	0.55
FL grade 3B to DLBCL-NOS or vice versa	30	0.5	0.09
DLBCL subtypes to other DLBCL subtypes without therapeutic impact‖	359	5.7	1.13
DLBCL to B-cell lymphomas with features intermediate between DLBCL and cHL without therapeutic impact in France	5	0.08	0.01
DLBCL to B-cell lymphomas with features intermediate between DLBCL and BLs without therapeutic impact in France	40	0.62	0.13
Blastoid MCL to classic MCL or vice versa	42	0.7	0.13
PTCL to other PCTL subtypes without therapeutic impact¶	80	1.3	0.25
Total changes in diagnosis	6,285		19.7

NOTE. The 4,289 patients submitted without diagnosis have been excluded.

Abbreviations: BL, Burkitt lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; cHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; NOS, not otherwise specified; PCN, plasma cell neoplasm; PTCL, peripheral T-cell lymphoma.

*Of the 202 patients, 183 patients referred as DLBCL-NOS, 15 as FL grade 3B, and 4 as primary mediastinal B-cell lymphomas (PMBLs) changed to 100 FL grade 1, 2, or 3A, 43 chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), 5 lymphoplasmocytic lymphoma/Waldenström macroglobulinemia (LPL/WM), 14 mucosa-associated lymphoid tissue (MALT) lymphoma, 20 marginal zone lymphoma (MZL), and 20 unclassified low-grade B-NHL.

†Three hundred fifty-nine patients initially referred as low-grade B-NHL (197 FL grade 1, 2, or 3A, 12 CLL/SLL, 11 LPL/WM, 54 MALT lymphoma, 11 nodal marginal zone lymphoma [NMZL], 11 splenic marginal zone lymphoma [SMZL], and 63 unclassified low-grade B-NHL) were changed to DLBCL-NOS (n = 302), FL grade 3B (n = 55), and PMBL (n = 2).

‡This category includes 76 patients referred as FL grade 1, 2, or 3A who were changed to CLL/SLL (n = 16), MALT lymphoma (n = 15), NMZL (n = 20), SMZL (n = 1), HCL (n = 1), and unclassified low-grade B-cell lymphomas (n = 23); 64 patients referred as CLL/SLL were changed to FL grade 1, 2, or 3A (n = 18), MALT lymphoma (n = 7), marginal zone lymphoma (MZL; n = 10), SMZL (n = 4), hairy cell lymphoma (HCL; n = 1), and unclassified low grade B-cell lymphomas (n = 24); 47 referred as LPL/WM were changed to FL grade 1, 2, or 3A (n = 1), CLL/SLL (n = 8), MALT lymphoma (n = 12), NMZL (n = 12), SMZL (n = 2), and unclassified low-grade B-cell lymphomas (n = 12); 57 referred as MALT lymphoma were changed to FL grade 1, 2, or 3A (n = 18), CLL/SLL (n = 9), SMZL (n = 7), and unclassified low-grade B-cell lymphomas (n = 23); 29 referred as NMZL were changed to FL grade 1, 2, or 3A (n = 9), CLL/SLL (n = 13), SMZL (n = 1), and unclassified low-grade B-cell lymphomas (n = 6); 12 referred as SMZL were changed to FL grade 1, 2, or 3A (n = 3), CLL/SLL (n = 1), NMZL (n = 2), HCL (n = 2), and unclassified low-grade B-cell lymphomas (n = 4); 4 referred as HCL were changed to CLL/SLL (n = 4); and 413 referred as low-grade B-NHL were changed to FL grade 1, 2, or 3A (n = 135), CLL/SLL (n = 119), MALT lymphoma (n = 86), NMZL (n = 46), SMZL (n = 18), and HCL (n = 9).

§This category included 196 patients referred as PTCL that were changed to another PTCL subtype with a predicted therapeutic impact, of which 21 specified as PTCL (15 PTCL-NOS, 1 angioimmunoblastic T-cell lymphoma [AITL], and 5 anaplastic lymphoma kinase (ALK^-) anaplastic large cell lymphoma [ALCL]) were changed to ALK^+ ALCL (n = 3), enteropathy-associated T-cell lymphoma (EATL; n = 5), natural killer T-cell lymphoma (NKTCL; n = 3) and adult T-cell leukemia/lymphoma (ATLL; n = 10); 4 referred as NKTCL were changed to PTCL-NOS (n = 4); 5 ALK^+ ALCL were changed to PTCL-NOS (n = 2), ALK^- ALCL (n = 2) and NKTCL (n = 1); 3 referred as EATL were changed to PTCL-NOS (n = 2) and ALK^- ALCL (n = 1); 4 referred as T-LGL were changed to ATLL (n = 2), NKTCL (n = 1), and PTCL-NOS (n = 1); and 159 patients referred as unclassified PTCL were changed to PTCL (n = 116 with 55 PTCL-NOS, 47 AITL, and 14 ALK^- ALCL), NKTCL (n = 17), EATL (n = 6), ALK^+ ALCL (n = 2), and ATLL (n = 18).

‖Changes in DLBCL subtypes without therapeutic impact (n = 359), that is, DLBCL to Epstein-Barr virus–positive DLBCL of the elderly (n = 42), DLBCL to T-cell/histiocyte-rich large B-cell lymphomas (n = 10), T-cell/histiocyte-rich large B-cell lymphomas to DLBCL-NOS (n = 28), DLBCL to lymphomatoid granulomatosis (n = 5), DLBCL to primary DLBCL of the CNS (n = 11), primary DLBCL of the CNS to DLBCL-NOS (n = 3), DLBCL to primary effusion lymphoma (n = 1), DLBCL to plasmablastic lymphoma (n = 5), plasmablastic lymphoma to DLBCL-NOS (n = 4), DLBCL to ALK^+ large B-cell lymphoma or vice versa (n = 2), DLBCL to intravascular large B-cell lymphoma or vice versa (n = 2), DLBCL to transformation of low-grade B-NHL to DLBCL-NOS (n = 131), unclassified high-grade B-NHL to DLBCL-NOS (n = 71), and changes between DLBCL and PMBL (n = 44).

¶Changes in PTCL subtypes without therapeutic impact (n = 80), that is, 53 PTCL-NOS changed to ALK^- ALCL (n = 28) and AITL (n = 25); 14 AITL changed to PTCL-NOS (n = 12), ALK^- ALCL (n = 1), and T-cell FL (n = 1); and 13 ALK^- ALCL changed to PTCL-NOS (n = 10) and AITL (n = 3).

Table 3. Major and Minor Changes Between Referral and Expert Diagnoses for Patients Sent With a Formal Diagnosis and Patients Sent With a Provisional Diagnosis for Expert Second Opinion

	All Eligible Patients (N = 31,910)			
	Patients Sent With a Formal Diagnosis (n = 19,112)		Patients Sent With a Provisional Diagnosis for Expert Second Opinion (n = 12,798)	
Major and Minor Diagnostic Changes	No.	%	No.	%
Major changes (ie, with a potential impact on patient care)	709	3.7	4,844	37.85
Category A: Misclassification in lymphoma subtypes	483	2.52	2,109	16.48
Mature B-NHL to peripheral T-cell lymphoma or vice versa	16	0.08	102	0.80
cHL to mature B-NHL or vice versa	28	0.15	109	0.85
cHL to PTCL or vice versa	5	0.02	93	0.73
NLPHL to other lymphoma subtypes or vice versa	30	0.16	109	0.85
BLs to other mature B-NHL or vice versa	33	0.17	106	0.83
MCL to other mature B-NHL or vice versa	65	0.34	279	2.18
DLBCL to low-grade B-NHL	59	0.31	143	1.12
Low-grade B-NHL to DLCBL	73	0.38	286	2.23
Misclassifications in low-grade B-NHL with therapeutic impact	142	0.74	631	4.93
Misclassifications in PTCL with therapeutic impact	17	0.09	179	1.4
Lymphomas to PCNs or vice versa	15	0.08	72	0.56
Category B: Malignant to benign lesions or vice versa	61	0.32	405	3.17
Lymphomas or other neoplasms to benign lesions	27	0.15	224	1.75
Benign lesions to lymphomas or other neoplasms	34	0.17	181	1.42
Category C: Lymphomas to other malignancies or vice versa	16	0.08	176	1.37
Lymphomas to nonhematopoietic neoplasms or vice versa	10	0.05	87	0.68
Lymphomas to myeloid neoplasms or vice versa	3	0.01	36	0.28
Mature lymphomas to T-cell precursor neoplasms or vice versa	1	0.01	27	0.21
Mature lymphomas to B-cell precursor neoplasms or vice versa	2	0.01	26	0.20
Category D: Unclassified lymphomas to classified lymphomas	149	0.78	2,154	16.83
Minor changes (ie, without a potential impact on patient care)	259	1.36	473	3.7
FL grade 1 or 2 to FL grade 3A or vice versa	59	0.31	117	0.92
FL grade 3B to DLBCL-NOS or vice versa	13	0.07	17	0.13
DLBCL subtypes to other DLBCL subtypes without therapeutic impact	121	0.64	238	1.9
DLBCL to B-cell lymphomas with features intermediate between DLBCL and cHL without therapeutic impact in France	1	0.005	4	0.03
DLBCL to B-cell lymphomas with features intermediate between DLBCL and BL without therapeutic impact in France	16	0.08	24	0.19
Blastoid MCL to classic MCL or vice versa	23	0.12	19	0.15
PTCL to other PTCL subtypes without therapeutic impact	26	0.14	54	0.42
Total number of changes in diagnosis	968	5.06	5,317	41.55

NOTE. The 4,289 patients submitted without diagnosis have been excluded.
Abbreviations: BL, Burkitt lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; cHL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; NOS, not otherwise specified; PCN, plasma cell neoplasm; PTCL, peripheral T-cell lymphoma.

only 3.29% and 1.63% corresponded to lymphocyte-rich and lymphocyte-depleted cHL variants, respectively, with the remaining 14.72% recorded as unclassified cHLs.

Concordance Between Referral and Expert Diagnoses Among Noncutaneous Lymphomas

Among the 31,910 eligible patients, the concordance rate was high for the most common B-cell lymphomas such as FL grades 1, 2, or 3A (85.5%) and DLBCL-NOS (83.8% overall concordance; Table 1). However, among the 9,618 samples with a final diagnosis of DLBCL, 1,558 patients were initially referred as low-grade B-cell NHL (B-NHL; n = 786), unclassified lymphomas (n = 521), BL (n = 70), or other conditions (n = 181; Appendix Fig A1A, online only), whereas among 4,572 FL grade 1, 2, or 3A final diagnoses, 662 patients had been submitted as other low-grade B-NHLs (n = 287), unclassified lymphomas (n = 202), or other conditions (n = 173; Appendix Fig A1B). Regarding other B-cell lymphomas, the diagnoses of LPL/WM, MALT lymphoma, splenic marginal zone lymphoma (SMZL), CLL/SLL, and PCN were confirmed after expert review in 83.9%, 83%, 79.6%, 78.1%, and 92.1% of patients, respectively (Table 1). Diagnoses of BL and MCL were less commonly concordant (76% and 73.5% overall concordance, respectively) with most changes being from DLBCL-NOS to BL (n = 60 of 94 misdiagnosed BLs) and from low-grade B-NHL to MCL (n = 184 of 347 misdiagnosed MCLs) after review. The concordance rate was lower for challenging diagnoses and/or less common lymphoma subtypes, such as FL grade 3B (46.3% concordance), with 60% of misdiagnoses due to misgrading between FL grade 1, 2, or 3A and grade 3B and NMZL (59.2% concordance), for which a change from low-grade B-NHL to NMZL was the most frequent (88% of patients). The concordance rate between referral and final ALK$^+$ ALCL diagnoses was 82.3%, but was lower for other PTCLs: AITL (68.7%), PTCL-NOS (63.8%),

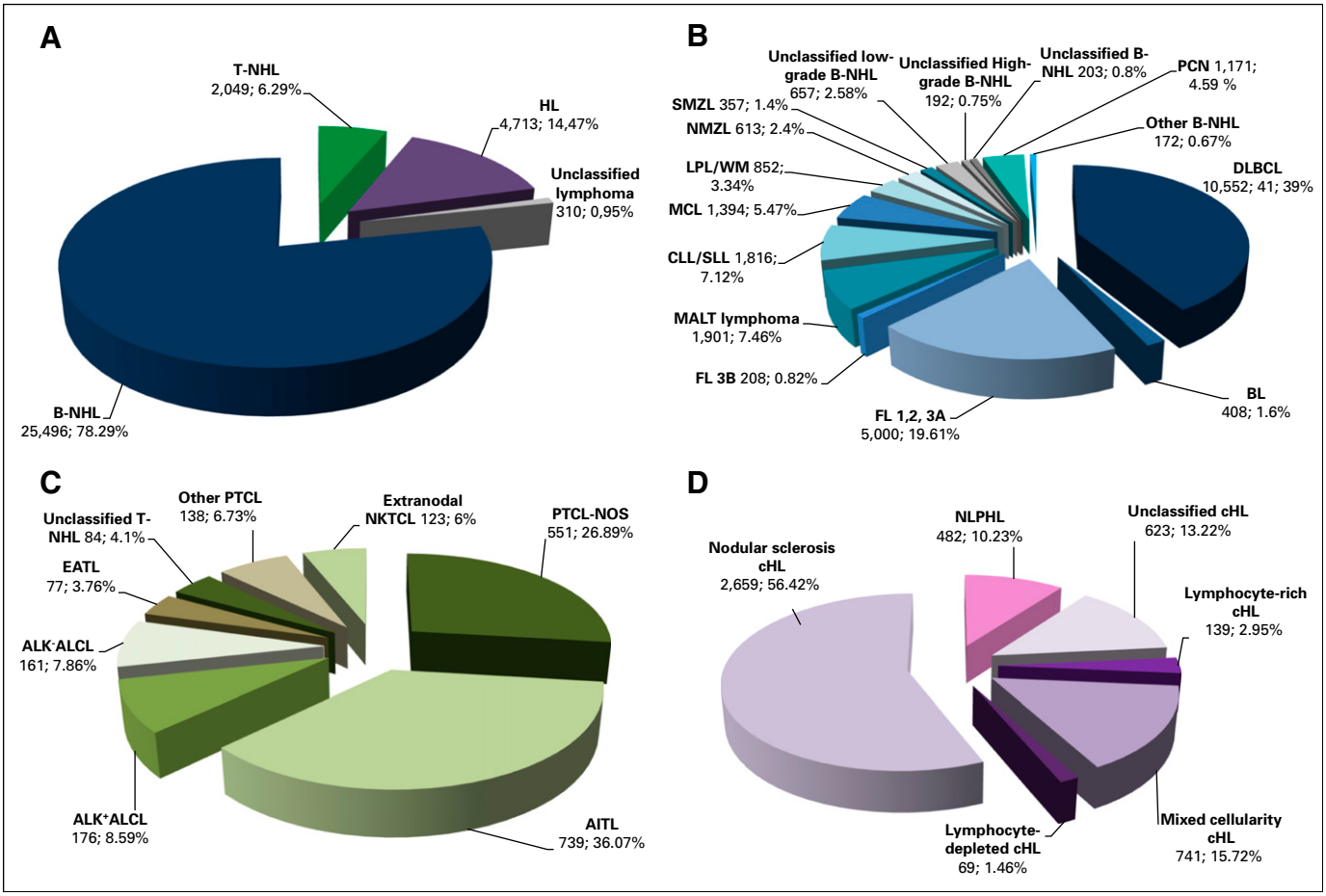

Fig 2. (A) Distribution of B-cell, T-cell, and Hodgkin lymphomas among the 32,568 nodal or extranodal lymphomas (excluding 321 precursor lymphoid neoplasms and 4,352 cutaneous lymphomas) diagnosed through the Lymphopath Network over the 2010-2013 period. Relative frequencies of (B) B-cell lymphoma, (C) peripheral T-cell lymphoma, and (D) Hodgkin lymphoma subtypes. Other B-cell non-Hodgkin lymphomas (B-NHLs) include B-cell prolymphocytic leukemia and hairy cell leukemia. Other peripheral T-cell lymphomas (PTCLs) include T-cell prolymphocytic leukemia, T-cell large granular lymphocytic leukemia, hepatosplenic T-cell lymphoma, chronic lymphoproliferative disorder of natural killer (NK) cells, aggressive NK cell leukemia, chronic systemic Epstein-Barr virus–positive T-cell lymphoproliferative disease of childhood, and human T-cell leukemia-lymphoma virus-I–associated adult T-cell leukemia/lymphoma. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BL, Burkitt lymphoma; cHL, classic Hodgkin lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; LPL/WM, lymphoplasmocytic lymphoma/Waldenström macroglobulinemia; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; NKTCL, natural killer T-cell lymphoma, nasal type; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; NMZL, nodal marginal zone lymphoma; NOS, not otherwise specified; PCN, plasma cell neoplasm; SMZL, splenic marginal zone lymphoma; T-NHL, T-cell non-Hodgkin lymphoma.

ALK^- ALCL (47.2%), EATL (74.2%), and extranodal NKTCLs (66.3%). Among the 624 samples with a final diagnosis of AITL, discrepancies (n = 195) were represented by patients referred as other PTCL subtypes (12%), unclassified lymphomas (10%), HL (4%), B-NHL (4%), and benign lymphoid conditions (1%; Appendix Fig A1C).

Most cHLs (93.3%) were accurately referred, in contrast to an accuracy of only 62.8% for the NLPHL diagnosis (Appendix Fig A1D). Indeed, 266 (6.7%) of 4,010 cHLs were initially diagnosed as unclassified lymphomas (n = 138), PTCLs (n = 44), B-cell lymphomas (n = 40), NLPHLs (n = 27), myeloid neoplasms (n = 2), or other benign lymphoid conditions (n = 15), whereas 150 (37.2%) of 404 NLPHLs were initially diagnosed as unclassified lymphomas (n = 55), cHLs (n = 47), B-NHLs (n = 28), PTCLs (n = 1), or benign lymphoid conditions (n = 19; Appendix Fig A1E).

The diagnosis of myeloid neoplasms showed 77% concordance. Many patients with atypical benign conditions were also diagnosed by the experts (n = 1,289 of 31,910 eligible patients), 80.6% of whom had been accurately referred to Lymphopath (Table 1).

We next investigated the number of additional studies performed by expert reviewers to reach final diagnoses based on the lymphoma classification decision algorithm used by the expert centers (Appendix Table A1 and Appendix Fig A2, online only). Ancillary tests were more frequently performed for discordant than for concordant diagnoses, with 92%, 15%, and 11% of the 6,285 discordant diagnoses requiring IHC, FISH, and *IGH* or *TCR* gene rearrangement analysis, respectively, versus 86.5%, 9%, and 9.4% of the 25,447 concordant diagnoses ($P < .001$ for all).

Categorization of Diagnostic Changes According to Their Impact on Clinical Management

Among the 31,910 noncutaneous samples, referral and expert diagnoses were divergent in 6,285 patients (19.7%; 95% CI, 19.3%

to 20.1%) with 5,553 major changes (17.4%; 95% CI, 16.9% to 17.8%) and 732 minor changes (2.3%; 95% CI, 2.1% to 2.5%), measured according to their potential impact on patient care (Fig 3; Tables 2 and 3).

Within the major changes, lymphoma misclassification with a predicted impact on patient management (category A) represented the largest group (n = 2,592; 41.3% of all changes; Table 2). This category included diagnostic changes between B-cell and T-cell lymphomas (n = 118), NHLs and cHLs (n = 235), NLPHLs and other lymphomas (n = 139), and misclassifications of BLs (n = 139) and MCLs (n = 344). It also included changes between low-grade B-NHLs and DLBCLs (n = 561), lymphomas and PCNs (n = 87), and diagnostic changes with a potential clinical impact among PTCLs (n = 196) or low-grade B-NHLs (FL grade 1, 2, or 3A *v* MALT lymphoma *v* NMZL *v* SMZL *v* LPL/WM *v* SLL/CLL *v* hairy cell leukemia (HCL) *v* unclassified low-grade B-NHL; n = 773). Major category B and C changes comprised reclassification of benign lesions to lymphomas or other malignant neoplasms (n = 211) and vice versa (n = 255; category B; 7.4%) and 192 changes between lymphomas and other malignancies (including 56 T-cell acute lymphoblastic leukemia [T-ALL] or B-ALL, 39 myeloid neoplasms, and 97 nonhematopoietic neoplasms; category C; 3%). The last category of major changes (category D) corresponded to changes from initially unclassified lymphomas to a subtype within the WHO classification[5] (n = 2,303; 36.6%).

The minor diagnostic discrepancies (n = 732; 11.7% of all changes) included mostly the reclassification of DLBCL subtypes (n = 404), which included changes from DLBCL to B-cell lymphomas, with features intermediate between DLBCL and BL (n = 40) or features intermediate between DLBCL and cHL (n = 5) that were thought to have no significant impact on patient care received in France between 2010 and 2013.[28] The other most common minor misdiagnoses were FL misgrading between grades 1 and 2 and grade 3A (n = 176), misgrading between classic and blastoid MCL (n = 42), and changes between FL grade 3B and DLBCL (n = 30). Minor changes also occurred in 80 patients with PTCL with no therapeutic impact.[28]

The rate of diagnostic changes was significantly lower in patients sent with a formal diagnosis (n = 968 [5.1%] of 19,112 patients) than in those with a provisional diagnosis sent for expert second opinion (n = 5,317 [41.5%] of 12,798 patients; Table 3). Major changes represented 37.8% (n = 4,844) of patients sent with a provisional diagnosis but only 3.7% (n = 709) of patients with a formal submitted diagnosis. Among the patients sent for expert second opinion, the largest category of changes corresponded to lymphomas referred without a precise classification (n = 2,154), whereas the most frequent major changes in patients sent with a formal diagnosis were lymphoma subtype misclassifications with potential clinical impact (n = 483). Of note, the annual discordance rate showed no significant variation over the 4-year period for patients sent with both formal and provisional diagnoses (Appendix Fig A3, online only).

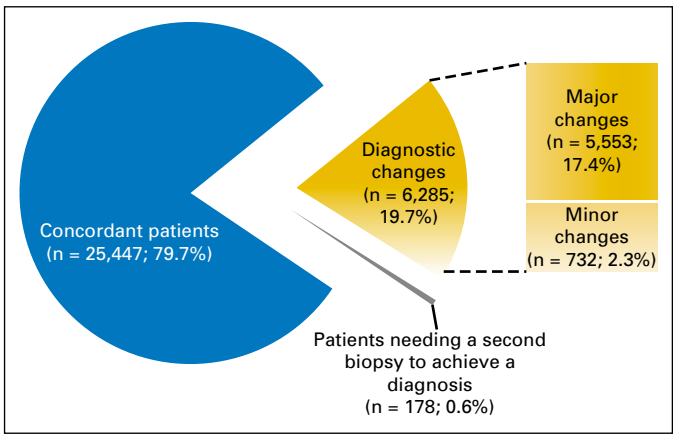

Fig 3. Schematic representation of the rates of concordance and change between referral and expert diagnoses among the 31,910 noncutaneous samples. The 4,289 patients submitted without diagnosis have been excluded. Diagnostic changes were scored as major or minor according to their potential impact on patient care.

DISCUSSION

We report here a large prospective review of newly diagnosed or suspected lymphomas. Over the 4-year period from 2010 through 2013, the Lymphopath Network covered more than 70% of all new lymphoma diagnoses in France and provided an expert review of patients with lymphoma, a service that is usually limited to those enrolling in clinical trials. The number of lymphomas reviewed here and classified according to the WHO classification,[5] provides a comprehensive description of the distribution of all B-cell and T-cell lymphoma subtypes and HLs in a western country and is in overall agreement with previously published data.[5,21,24,30] This survey also provides novel insights into the frequency of uncommon entities such as PEL, plasmablastic lymphoma, and EBV-positive DLBCL of the elderly, which accounted for 0.12%, 1.17%, and 1.44% of DLBCLs, respectively. It also highlights a twofold higher incidence of NLPHLs than was previously reported[5,24,30-33] and a high prevalence of AITLs, as was recently reported.[25] These observations may reflect geographical variations and/or ethnic differences in the incidence of lymphoma subtypes, as suggested previously,[30-36] but may also be the result of difficulties in diagnosing these entities, which can require an extensive panel of antibodies and molecular tools. Finally, our large-scale study provided the exact prevalence of newly described or provisional entities such as breast implant–associated ALCL,[24,26] which represents only 0.06% of noncutaneous lymphomas.

Another key finding of this study is that real-time prospective expert review resulted in diagnostic changes that were deemed to have a potential impact on patient care in 17.4% of patients. This rate is in agreement with a recent report[19] but differs from other studies showing lower rates of discordance.[20-23,37] These latter studies comprised a limited number of patients and/or were restricted to diagnosed lymphomas, thus excluding the review of atypical benign lymphoid conditions and lymphomas without precise subclassification, which were particularly frequent among

the patients sent for expert second opinion in Lymphopath. For example, the study by LaCasce et al[22] was restricted to the five most common lymphoma subtypes (FL, DLBCL, MCL, CLL, and MZL) and did not include PTCL or NLPHL for which diagnoses are more challenging, as shown in this study. Our study also included a significant number of atypical benign lymphoid conditions that were reclassified as lymphomas, as well as suspected lymphomas sent for expert second opinion. As expected, patients sent with a formal diagnosis showed a lower rate of diagnostic change than patients sent with a provisional diagnosis for expert second opinion, particularly patients with a formal diagnosis based on the use of a unique IHC marker such as MCL and ALK$^+$ ALCL (only 22 of 710 MCLs and two of 90 ALK$^+$ ALCLs referred with a formal diagnosis were reclassified as other B-cell–derived neoplasms or ALK$^-$ ALCL, respectively). The higher rate of diagnostic change in patients sent for expert second opinion highlights the importance of this service, especially for challenging diagnoses. We did not observe a significant decline in the overall discordance rate over the 4-year period, in contrast to Proctor et al.[21] This may result from prematurely sending patient samples with unspecified lymphoma for expert review and, in contrast to previous studies,[19,21] from the large number of pathologists from private and nonacademic laboratories (more than 500) involved in the Lymphopath Network who may be faced with a limited number of patients with lymphoma per year and/or who may not have access to ancillary tests. To the best of our knowledge, this is the first time that referral and expert pathologists have contributed to a comprehensive network on a national scale with the aim of confirming or providing an accurate lymphoma diagnosis. In our study, the concordance rate between experts (99.05%) seemed significantly higher than in another study conducted before the introduction of the WHO classification[1,5] (which reported 85% concordance). This discrepancy likely reflects improvements in consistency among the experts themselves as a result of more accurate diagnostic criteria as well as new tools, including novel antibodies, polymerase chain reaction assays, and FISH tests applicable on routine formalin-fixed paraffin-embedded samples.[27]

This study shows that without expert review, a significant proportion of patients with lymphoma would have been misdiagnosed and given an inappropriate therapeutic regimen. Most critically, 200 patients referred as benign conditions were subsequently diagnosed as lymphomas after Lymphopath review, which resulted in major changes to their clinical management. However, the most frequent diagnostic changes were the misclassification of lymphoma subtypes, such as changes between DLBCL and low-grade B-NHL, and the misclassification of low-grade B-NHL, NLPHL, and PTCL. For example, the confusion between DLBCL and low-grade B-NHL has important implications, because patients with DLBCL require first-line immunochemotherapy followed in one subset by intensification with high-dose chemotherapy and autologous stem-cell transplantation.[38-40] Young patients (age $<$ 65 years) with MCL also require intensive immunochemotherapy based, for example, on the addition of high-dose cytarabine,[41] whereas patients with FL benefit from rituximab maintenance after chemotherapy with rituximab.[42] Among patients with PTCL, the recognition of ALK$^+$ ALCL, ALK$^-$ ALCL, and NKTCL has prognostic relevance and could also have therapeutic implications[43,44]; for example, patients with refractory ALCL may benefit from the anti-CD30 antibody conjugate brentuximab-vedotin and from ALK inhibitors for those expressing ALK.[43,45] Among B-cell lymphomas, patients with CLL with TP53 inactivation and patients with relapsed/refractory MCL may also benefit from Bruton tyrosine kinase inhibitors.[46,47] Finally, on the basis of the upcoming 2016 WHO classification,[24] which identifies an increasing number of lymphoma subtypes with unmet needs for therapy, especially those with unfavorable outcomes such as DLBCL/HL and DLBCL/BL (double-hit lymphoma) intermediate forms, it will be even more important to assess the accuracy of diagnoses in the near future.[48-50]

Two critical findings arise from this study. First, we believe it provides the largest description of the distribution of NHL and HL entities in a western country, highlighting the epidemiology of all lymphoma entities, including rare subtypes. Second, it shows that expert review helps to ensure an accurate lymphoma diagnosis in approximately 17% of patients. This will become increasingly relevant in this new era of personalized medicine.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impact of Expert Pathologic Review of Lymphoma Diagnosis: Study of Patients From the French Lymphopath Network

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Appendix

Expert Review Process of the Lymphopath Network

Since 2010, referral pathologists working in nearly 500 laboratories throughout France have been encouraged to send tumor blocks, and in a proportion of patients' stained slides, of every newly diagnosed or suspected lymphoma (excluding a subset of patients with a leukemic presentation such as B-cell chronic lymphocytic leukemia) to one of the Lymphopath Network expert centers. The Lymphopath pathology network is composed of recognized experts in hematopathology working across 36 expert sites who have been selected according to three main criteria: (1) they diagnose more than 200 patients per year with lymphoma, (2) they participate in translational or clinical research in the lymphoma field (ie, they have national and/or international renown, and they have conducted clinical and biological studies in the lymphoma field) and/or are in charge of training or postgraduate courses on lymphoma diagnosis (lectures, e-learning, and hematopathology training), and (3) they work in an academic institution (a university hospital or comprehensive cancer center) with unlimited access to immunohistochemical techniques and molecular tests.

In France, referral pathologists have access to some clinical information (age, sex, and site of the biopsy) and additional information can be obtained upon request. In referral laboratories, immunohistochemstry is almost systematically performed by using an extended panel of antibodies. For each patient, the Lymphopath expert center receives the diagnostic material which contains formalin-fixed paraffin-embedded block(s) of the tumor sample and, in most instances, the original slides (hematoxylin and eosin and immunohistochemical stains) as well as the clinical information (consisting of at least age, sex, and site of the biopsy). At Lymphopath expert centers, immunohistochemstry is almost always rechecked or performed. In addition, when needed, molecular studies are performed, including in situ hybridization (Epstein-Barr virus–encoded RNA, kappa and lambda probes), fluorescent in situ hybridization translocation analysis (eg, *MYC*, *BCL2*, and *BCL6* rearrangements) and polymerase chain reaction assessment of *IGH*, *IGK*, *TCRβ*, and *TCRγ* rearrangements (according to the EuroClonality (BIOMED-2) guidelines; van Dongen JJ, et al: Leukemia 17:2257-2317, 2003). These molecular studies are not available in referral pathologist laboratories. After taking into account each patient's age, sex, and site of biopsy (and in some instances, additional clinical data), the expert's diagnosis is made on the basis of the combination of histology and immunophenotyping (if necessary, associated with molecular tests), which have been shown (in an international study) to provide a consensus diagnosis between experts for most histologic subtypes.[27] The decision algorithm (based on the above data) in Appendix Figure A2 shows the major techniques performed by the expert centers to classify the main categories of noncutaneous mature lymphomas. In addition, when the expert diagnoses are submitted to the Lymphopath database, information is recorded on whether the patient was sent with a formal diagnosis by the referral pathologist or with a provisional diagnosis for which a second opinion was needed (ie, patients sent for expert second opinion). The rate of concordance between experts within the Lymphopath Network was also evaluated through a quality control blind assessment of 319 patients randomly selected from the database. The concordance rate was 99.05%, which included three discordant diagnoses. These were reviewed again on a multihead microscope by the experts: in two patients, discordant diagnoses were mainly a result of the small size of the biopsy specimen, and in the other patient, there was no agreement between expert sites, suggestive of an unusual lymphoproliferative disorder. These results confirmed the reliability of the diagnoses made by the different expert sites in the Lymphopath Network.

Potential Impact of a Change in Diagnosis on Clinical Management

Changes to diagnoses were evaluated a posteriori by a physician (hematologist) and divided into major and minor discordances according to their impact on clinical management of the patient. A major discrepancy was defined as a significant change to the diagnosis that had a potential impact on patient care. In accordance with other studies,[19-21] these were further divided into four categories: misclassification of lymphoma subtypes with a potential impact on patient care (category A), changes from malignant to benign lesions or vice versa (category B), changes from lymphoma to other malignancies or vice versa (category C), and changes from unclassified lymphoma to classified lymphoma (category D). A minor discrepancy was defined as a change without significant impact on patient care.

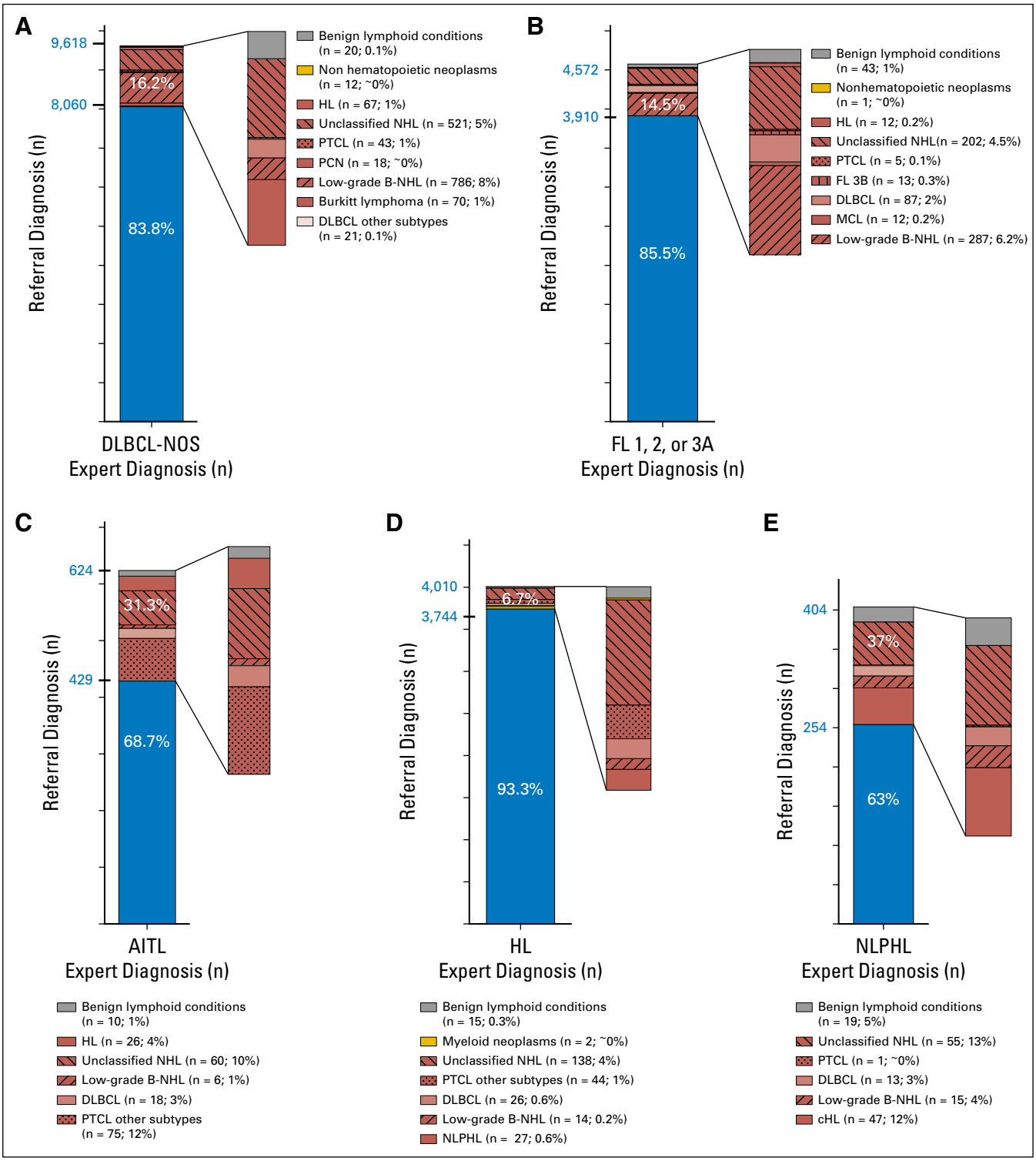

Fig A1. Graphical representation of the changes between the referral and final diagnoses for several common entities. The 4,289 patients submitted without diagnosis have been excluded. Summary of concordances and changes for all final diagnoses of (A) diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS; n = 9,618), (B) follicular lymphoma (FL) grade 1, 2, or 3A (n = 4,572), (C) angioimmunoblastic T-cell lymphoma (AITL; n = 624), (D) classic Hodgkin lymphoma (cHL; n = 4,010), and (E) nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL; n = 404). Blue, concordant diagnoses; red, changes from other non-Hodgkin lymphomas (NHLs) to the specified lymphoma subtype after expert review; orange, changes from nonlymphoid neoplasms to the specified lymphoma subtype after expert review; brown, changes from Hodgkin lymphoma (HL) to the specified lymphoma after expert review; gray, changes from benign conditions to the specified lymphoma subtype after expert review. BL, Burkitt lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; MCL, mantle cell lymphoma; PCN, plasma cell neoplasm; PTCL, peripheral T-cell lymphoma.

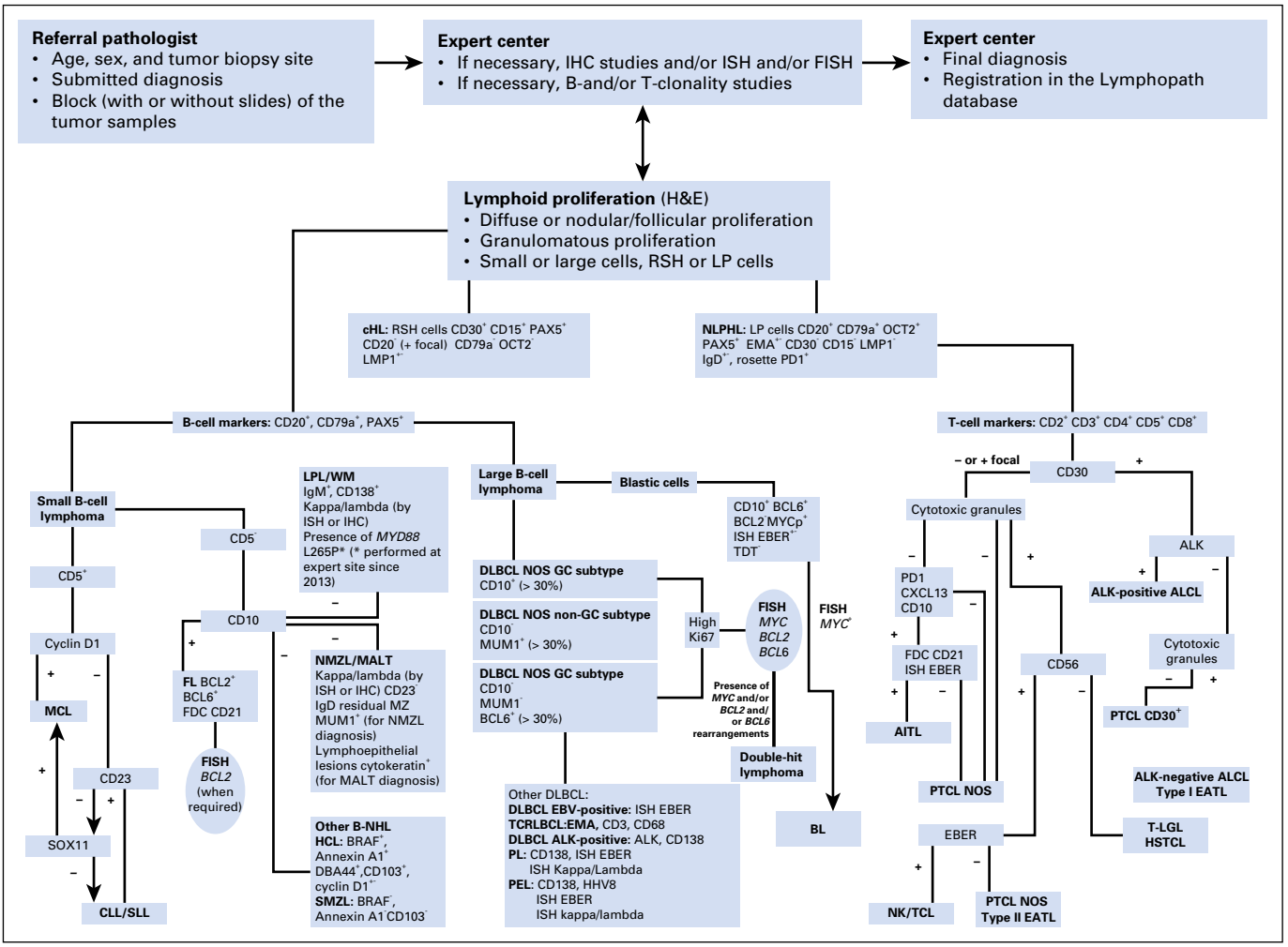

Fig A2. Decision algorithm based on the histologic criteria and ancillary techniques used for classifying the main categories of mature noncutaneous lymphomas. Patient samples (formalin-fixed paraffin-embedded blocks and, for a proportion of patients, hematoxylin and eosin (H&E) –stained slides and immunohistochemistry [IHC] staining) were sent to an expert center for review. To classify the main categories of noncutaneous mature lymphomas at the expert center according to the 2008 WHO classification,[5] antibody panels were used (Soo KL, et al: Pathology 43:673-681, 2011). A typical panel included antibodies against CD2, CD3, CD4, CD5, CD8, CD10, CD15, CD20, CD21, CD23, CD30, CD56, CD79a, CD138, immunoglobulin D (IgD), IgM, Ig kappa, Ig lambda, anaplastic lymphoma kinase (ALK), Annexin A1, BCL2 (clone SP66 or clone E17), BCL6, $BRAF^{V600E}$, CXCL13, cyclin D1 (clone SP4), cytotoxic molecules, DBA44, HHV8, LMP1, MUM1, MYC protein (MYCp), PAX5, PD1, and SOX11. The positivity or negativity of the IHC staining with each antibody is defined as "+" or "−", respectively. If material was available, samples were processed for routine histopathologic and IHC analyses. If necessary, Epstein-Barr virus (EBV) detection and light chain restriction were also performed by in situ hybridization (ISH) by using EBV-encoded RNA (EBER) and kappa/lambda probes. When required, *MYC*, *BLC2*, and *BCL6* rearrangements were detected by using fluorescent in situ hybridization (FISH). If necessary, B-cell and/or T-cell clonality studies were carried out by using multiplexed polymerase chain reaction and assessed according to the EuroClonality (BIOMED-2) guidelines (van Dongen JJ, et al: Leukemia 17:2257-2317, 2003). Institutional ethical approval was obtained in compliance with the Helsinki agreement. AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; BL, Burkitt lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; cHL, classic Hodgkin lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; FDC, follicular dendritic cell; FL, follicular lymphoma; GC, germinal center; HCL, hairy cell leukemia; HSTCL, hepatosplenic T-cell lymphoma; LP, lymphocyte-predominant; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MZ, mantle zone; NKTCL, extranodal natural killer T-cell lymphoma, nasal type; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; NMZL, nodal marginal zone lymphoma; NOS, not otherwise specified; PEL, primary effusion lymphoma; PL, plasmablastic lymphoma; PTCL, peripheral T-cell lymphoma; RSH, Reed-Sternberg Hodgkin; SMZL, splenic marginal zone lymphoma; TCRLBCL, T-cell/histiocyte-rich large B-cell lymphoma; T-LGL, T-cell large granular lymphocytic leukemia.

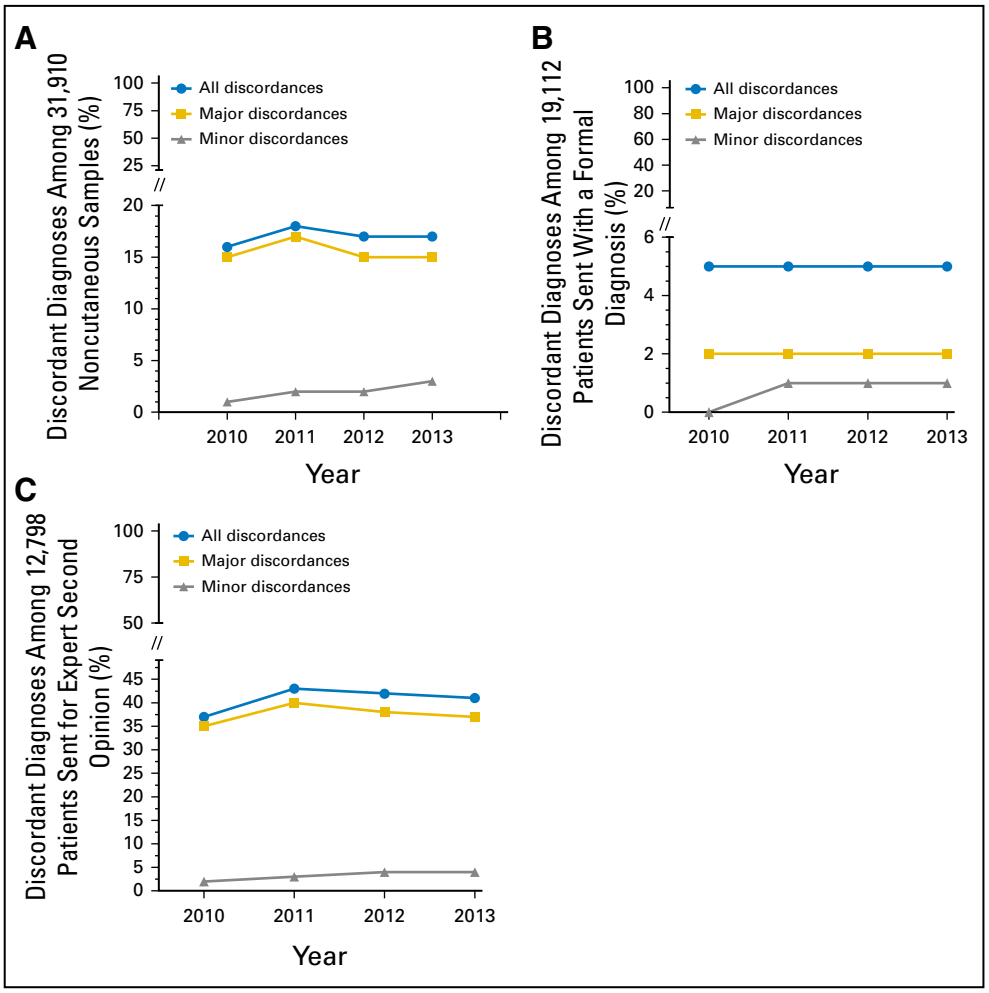

Fig A3. Annual frequency of diagnostic changes between referral and expert diagnoses over the 2010-2013 period among (A) the 31,910 noncutaneous eligible samples, (B) the 19,112 patients submitted with a formal diagnosis, and (C) the 12,798 patients sent with a provisional diagnosis for expert second opinion. (*) The 4,289 patients submitted without diagnosis have been excluded.

Table A1. Number and Types of Techniques Performed at the Expert Sites for Concordant and Discordant Diagnoses Among Noncutaneous Lesions

	All Eligible Patients (N = 31,910)			
	Patients With Concordant Diagnoses (n = 25,447)		Patients With Discordant Diagnoses (n = 6,285)	
Type of Additional Study Performed at the Expert Site	No.	%	No.	%
IHC				
Yes	22,011	86.5	5,769	92
No	2,021	7.9	361	5.7
Not mentioned	1,415	5.6	155	2.3
ISH				
Yes (EBER kappa/lambda)	3,580	14.1	1,291	20.6
No	15,235	59.8	3,829	60.9
Not mentioned	6,632	26.1	1,165	18.5
FISH				
Yes (presence of *MYC* and/or *BCL2* and/or *BLC6* rearrangements)	2,290	9	939	15
No	19,523	76.7	4,920	78.3
Not mentioned	3,634	14.3	426	6.7
Ig heavy chain rearrangement				
Yes	1,832	7.2	522	8.3
No	21,059	82.8	4,775	76
Not mentioned	2,556	10.0	988	15.7
T-cell receptor rearrangement				
Yes	559	2.2	179	2.8
No	22,332	87.8	5,118	81.5
Not mentioned	2,556	10.0	988	15.7
IHC + FISH	1,736	6.8	744	11.8
IHC + clonality	1,826	7.2	546	8.7
IHC + FISH + clonality	296	1.2	136	2.2

NOTE. The 4,289 patients submitted without diagnosis have been excluded.
Abbreviations: EBER, Epstein-Barr virus–encoded RNA; FISH, fluorescent in situ hybridization; Ig, immunoglobulin; IHC, immunohistochemistry; ISH, in situ hybridization.