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Clinical impact of recurrently mutated genes on lymphoma diagnostics: state-of-the-art and beyond

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ABSTRACT

Similar to the inherent clinical heterogeneity of most, if not all, lymphoma entities, the genetic landscape of these tumors is markedly complex in the majority of cases, with a rapidly growing list of recurrently mutated genes discovered in recent years by next-generation sequencing technology. Whilst a few genes have been implied to have diagnostic, prognostic and even predictive impact, most gene mutations still require rigorous validation in larger, preferably prospective patient series, to scrutinize their potential role in lymphoma diagnostics and patient management. In selected entities, a predominantly mutated gene is identified in almost all cases (e.g. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma and hairy-cell leukemia), while for the vast majority of lymphomas a quite diverse mutation pattern is observed, with a limited number of frequently mutated genes followed by a seemingly endless tail of genes with mutations at a low frequency. Herein, the European Expert Group on NGS-based Diagnostics in Lymphomas (EGNL) summarizes the current status of this ever-evolving field, and, based on the present evidence level, segregates mutations into the following categories: i) immediate impact on treatment decisions, ii) diagnostic impact, iii) prognostic impact, iv) potential clinical impact in the near future, or v) should only be considered for research purposes. In the coming years, coordinated efforts aiming to apply targeted next-generation sequencing in large patient series will be needed in order to elucidate if a particular gene mutation will have an immediate impact on the lymphoma classification, and ultimately aid clinical decision making.

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Introduction

Most, if not all, lymphoma subtypes display considerable heterogeneity in their clinical and pathological characteristics, intricately linked to the underlying biological heterogeneity.[1] Indeed, the genomic landscape of lymphomas is remarkably diverse, although an increasing number of 'shared' genetic lesions have recently emerged, affecting similar mechanisms and processes that in certain instances are

important for 'generic' cell homeostasis (e.g. DNA repair) while in others they are 'lymphocyte-specific' (e.g. antigen receptor signaling) (Figure 1).

Thanks to next-generation sequencing (NGS), it has become possible to appreciate the panorama of recurrently affected genes that contribute to disease pathogenesis and/or evolution, at least in major lymphoma subtypes. Mounting evidence suggests that certain gene mutations have diagnostic, prognostic and/or predictive impact. However, for most mutations, functional *in vitro* validation and confirmation in larger patient series are warranted in order to fully elucidate their role in the pathobiology of a particular lymphoma as well as their relevance for routine diagnostics.

In few circumstances, a single recurrent mutation is identified in almost all cases of a given lymphoma and predominates by far in the genomic landscape of that particular tumor, e.g. the MYD88^{L265P} mutation in Waldenström's Macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL)[2] and the BRAF^{V600E} mutation in hairy-cell leukemia (HCL).[3] However, for the great majority of lymphomas, including chronic lymphocytic leukemia (CLL),[4] diffuse large B-cell lymphoma (DLBCL),[5] follicular lymphoma (FL),[6] mantle cell lymphoma (MCL),[7] Burkitt lymphoma (BL),[8] splenic marginal zone lymphoma (SMZL)[9] and most peripheral T-cell lymphoma (PTCL) subtypes,[10-13] NGS studies have revealed a quite diverse and complex mutation pattern, with a limited number of frequently mutated genes accompanied by a long tail of genes with low-frequency mutations. In addition, while some genes are biased to certain lymphoma entities, e.g. *SF3B1* mutations in CLL,[14,15] *KLF2* mutations in SMZL,[16-18] *ID3* and *TCF3* mutations in BL,[19] *STAT3* mutations in large granular lymphocyte (LGL) leukemia,[11] and *RHOA* mutations in angioimmunoblastic T-cell lymphoma (AITL),[20,21] other genes found recurrently mutated, such as genes involved in DNA repair, epigenetic modification and regulation of transcription (Figure 1), can be detected in multiple subtypes (Table 1) and even in other cancer types.

Considering the genetic heterogeneity of lymphomas, also highlighted by diverse results reported in hitherto published NGS studies, it will require large-scale initiatives encompassing thousands of patients to clarify if a specific gene mutation has an impact on the current lymphoma classification/diagnostics and aids clinical decision-making, including therapy selection and response prediction.

In an effort to summarize the current status of this ever-evolving field and provide guidelines regarding the clinical relevance of recent genetic findings, we have established the European Expert Group on NGS-based Diagnostics in Lymphomas (EGNL), with expertise in hematopathology, molecular pathology, clinical genetics, hematology, and oncology. The EGNL Group is supported by the European Research Initiative on CLL (ERIC; Scientific Working Group within the European Hematology Association, EHA) and the European Association for Haematopathology (EAHP).

As our first task, we took advantage of the published literature on lymphomas to identify recurrently mutated genes with a potential clinical relevance that were reported in at least two independent studies; other genomic aberrations, e.g. translocations and copy number aberra-

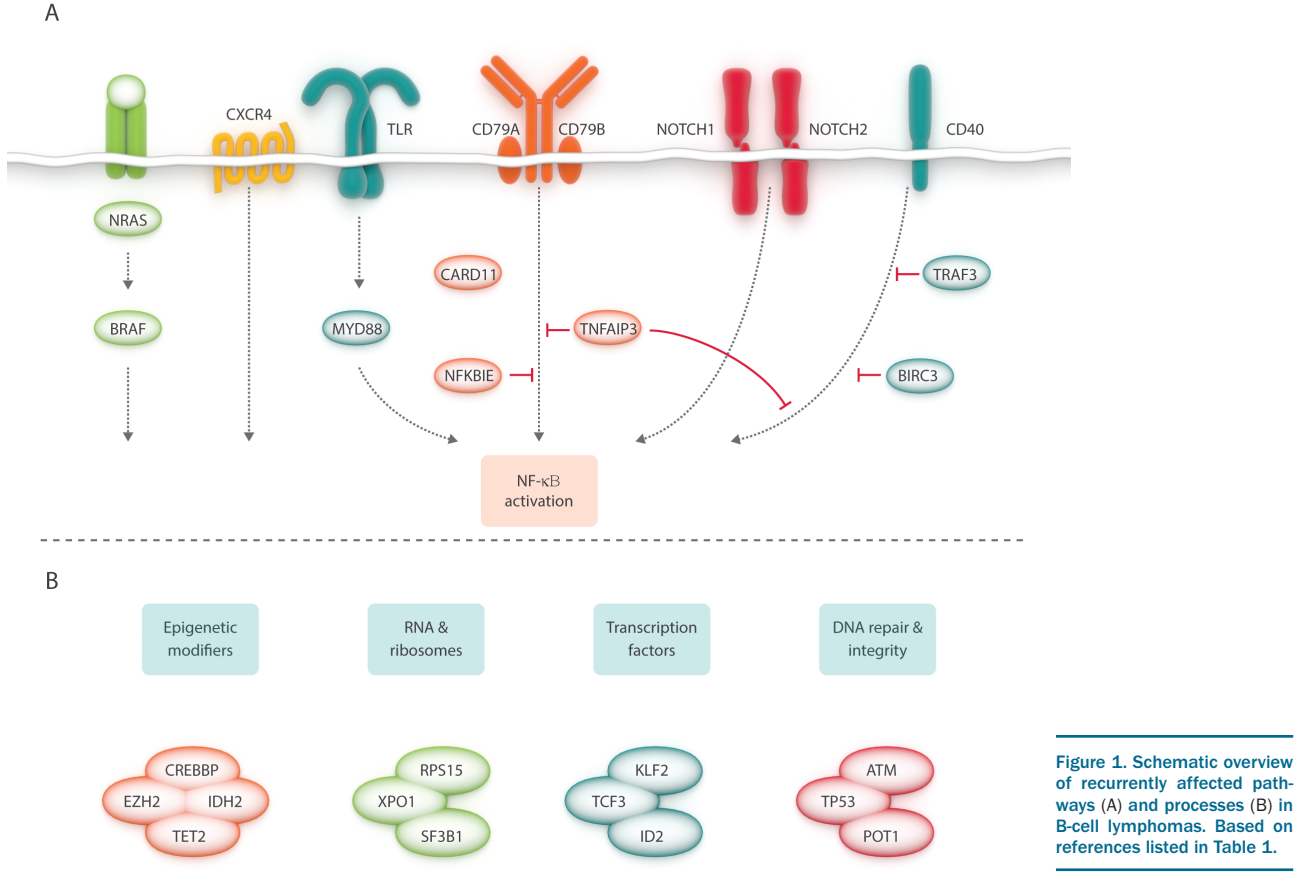

Figure 1. Schematic overview of recurrently affected pathways (A) and processes (B) in B-cell lymphomas. Based on references listed in Table 1.

tions, may also be clinically relevant, though they are not discussed in this review. As the next step, we grouped the identified genes into the following categories based on: i) immediate impact on treatment decisions, ii) diagnostic impact, ii) prognostic impact, iv) potential clinical impact in the near future, or v) interest for research purposes only. In the end, only few genes were deemed to have direct therapeutic or diagnostic implications, while a sizeable proportion of genes were judged as prognostic and/or with a potential role for patient management within the next few years (Table 2). Though this latter category is evidently difficult to define, we decided to include genes for which recent evidence strongly suggests a diagnostic and/or predictive role, sometimes limited to retrospective studies, or for which targeted therapy is under development. In the following sections, we outline our arguments for including a particular gene in one of these categories; highlighted genes in each category are summarized in Table 2.

I. Genes with immediate impact on treatment decisions

Currently, there are few genetic lesions with documented impact on therapy selection and patient management in patients with lymphoma. This category is best exemplified by *TP53* aberrations in CLL.[22] Such aberrations are due to (i) deletions of chromosome 17p (covering the *TP53* gene) seen in 5-10% of patients at diagnosis, which are often associated with *TP53* mutations on the remaining allele; and, (ii) in a small fraction of CLL patients (3-6%), mutations within the *TP53* gene only.[23-25] Both types of aberrations (i.e. 17p-deletions and *TP53* mutations) are equally adverse in CLL, portending for refractoriness to standard chemoimmunotherapy and poor overall survival.[26-29] Notably, such patients experience major clinical benefit by the recently approved novel agents targeting B-cell receptor signaling, namely, the Bruton tyrosine kinase inhibitor ibrutinib and the phosphatidylinositol 3-kinase delta inhibitor idelalisib that are approved for the treatment of patients carrying either of these lesions;[30] however, these patients still constitute a high-risk group with an increased risk of disease recurrence with time.

On these grounds, the assessment of *TP53* status is essential for clinical decision-making. Hence, sequencing of the *TP53* gene is now recommended for all CLL patients, in addition to FISH analysis, before the start of any line of therapy (except in the palliative situation).[31,32] Indeed, testing for *TP53* aberrations should be considered companion diagnostics for signaling inhibitor treatment in

Table 1A. Mutation frequencies in different B-cell lymphoma entities.

Pathway/cellular function	CLL[a]	MCL[b]	BL[c]	FL[d]	ABC-DLBCL[e]	GCB-DLBCL[e]	SMZL[f]	HCL[g]	WM[h]
B-cell receptor signaling									
CD79A/CD79B	<1%	-	-	4%	10-20%	<5%	-	-	10%
CARD11	1%	-	-	10%	10%	5%	4%	-	-
Toll-like receptor signaling									
MYD88	3%	-	5%	-	20-30%	<5%	7%	-	>90%
NF-κB signaling pathway									
TNFPAI3	-	-	-	10%	20%	<5%	8%	-	40%*
BIRC3	<3%	5-10%	-	-	-	-	5%	-	-
TRAF3	<1%	-	-	-	-	-	5%	-	-
NFKBIE	<2%	5%	-	-	<5%	<5%	2%	-	-
Notch signaling									
NOTCH1	10%	10-15%	-	-	-	-	6%	-	-
NOTCH2	<1%	5%	-	-	-	-	15-20%	-	-
Other signaling pathways									
BRAF	3%	-	-	-	4%	-	<1%	>90%	-
CXCR4	<1%	-	-	-	<10%	-	<1%	-	25%
Transcription factors									
ID3	-	-	35-60%	-	-	-	-	-	-
TCF3	-	-	10-25%	-	-	-	-	-	-
KLF2	-	-	-	-	-	-	14%	-	-
DNA repair/genomic integrity									
ATM	11%	40-50%	-	-	-	-	6%	-	-
TP53	5%	15-20%	35%	5%	10-25%	10-20%	18%	-	-
POT1	5%	<3%	-	-	-	-	<1%	-	-
Epigenetic modifiers									
TET2	<1%	<5%	-	-	5-10%	5-10%	3%	-	-
EZH2	<1%	-	-	10-20%	-	20%	<1%	-	-
IDH2	-	-	-	-	-	-	-	-	-
CREBBP	<1%	-	-	50%	15-20%	40%	6%	-	-
EP300	<1%	-	2%	10-15%	<5%	<10%	4%	-	-

*CLL: chronic lymphocytic leukemia; MCL: mantle cell lymphoma; BL: Burkitt lymphoma; FL: follicular lymphoma; ABC-DLBCL: activated B-cell-like diffuse large B-cell lymphoma; GCB-DLBCL: germinal center B-cell-like diffuse large B-cell lymphoma; SMZL: splenic marginal zone lymphoma; HCL: hairy-cell leukemia; WM: Waldenström's Macroglobulinemia. *Genomic deletions. [a]Frequencies are based on the combined cohort included in Puente* et al., *Nature 2015[86] and Landau* et al., *Nature 2015[87], though the former encompasses more general practice CLL patients and the latter more advanced, clinical trial patients. [b]Based on Bea* et al., *PNAS 2013[7] Meissner* et al., *Blood 2013[101], Rahal* et al., *Nat Med 2014[91]. [c]Based on Schmitz* et al., *Nat Med 2012[19] [d]Based on Morin* et al., *Nat Genet 2010[61] Okosun* et al., *Nat Genet 2014[6] Okosun* et al., *Nat Genet 2016[60]. [e]Based on Compagno* et al., *Nature 2009[102], Davis* et al., *Nature 2010[93] Ngo* et al., *Nature 2011[5], Pasqualucci* et al., *Nat Genet 2011103, de Miranda* et al., *Blood 2014[104], Bohers* et al., *Genes Chrom Cancer 2014[105]. [f]Based on Rossi* et al., *JEM 20129 Parry* et al., *Clin Cancer Res 2015[16], Piva* et al., *Leukemia 2015[18]. [g]Based on Tiacci* et al., *NEJM 2011[41]. [h]Based on Treon* et al., *NEJM 2012[2] Poulain* et al., *Clin Cancer Res 2015[106].*

CLL, in order to identify patients with aberrant *TP53* for whom the new targeted therapies, described above, represent the current treatment of choice. Furthermore, the fact that the frequency of *TP53* mutations gradually increases as the disease becomes more aggressive and chemorefractory supports the need to repeat *TP53* mutation analysis prior to any subsequent line of chemotherapy.[31,32] Of note, it has also been demonstrated that *TP53* microclones at diagnosis, i.e. subclones with a low-allelic burden detected only by NGS but not by Sanger sequencing, were selected by repeated rounds of chemoimmunotherapy and conferred a poor outcome similar to clonal *TP53* mutations.[33,34] If this finding is confirmed within the context of prospective clinical trials including signaling inhibitors, it is very likely that NGS-based protocols will become the recommended method for *TP53* mutation screening in routine clinical practice.

Mutations within *TP53* have been described in most other lymphoid malignancies besides CLL, albeit with varying frequency. Although they have been linked to poor clinical outcome in DLBCL,[35] SMZL[16] and MCL,[36,37] this information does not currently have any impact on treatment decisions or follow-up strategies for the individual lymphoma patient.

II. Genes of diagnostic potential

Few lymphoma entities show a predominating, recurrent mutation, such as: the hotspot MYD88^{L265P} mutation in more than 90% of WM/LPL,[2,38-40] the hotspot BRAF^{V600E} mutation in ~90% of HCL,[41-43] and the STAT3 mutations detected in up to 40% of LGL leukemia.[11,44] None of these mutations are pathognomonic of (i.e. exclusive to) a particular entity and can also be found in other lymphomas, though generally at lower frequencies (Table 1). For instance, the MYD88^{L265P} mutation is detected in a significant fraction of DLBCL of the activated B-cell-like subtype (ABC DLBCL),[5] as well as in primary cutaneous,[45] the central nervous system[46] and testicular large B-cell lymphomas,[47] but also in a minority of patients with CLL[4,48-50] and SMZL.[16,51] As another example, *STAT3* mutations have been reported, albeit rarely, in immune, mainly hypoplastic, bone marrow failure characterizing a subset of patients with severe aplastic anemia or myelodysplastic syndrome.[52] Moreover, some gene mutations are mainly found in a specific lymphoma entity at a relatively high frequency, whereas they are rare in other subtypes, e.g. *ID3* and *TCF3* mutations in BL,[19] *KLF2* in SMZL,[16-18] *SF3B1* mutations in CLL,[14,15] *RHOA* mutations in AITL and other PTCL with a follicular helper T cell (T_{FH}) phenotype,[13,20,21,53-59] and, very recently, the novel somatic mutations in *RRAGC* encoding a Rag GTPase protein (RagC) that were enriched in FL (16%) but were absent in other mature B-cell lymphomas.[60]

That said, a pattern has started to emerge in recent years where certain lymphoma entities 'share' common types of genetic events affecting selected pathways or biological mechanisms (Figure 1). For instance, germinal center derived B-cell malignancies, such as DLBCL of the germinal center B-cell-like type (GCB DLBCL) and FL, appear to have higher frequencies of aberrations in epigenetic-related genes (e.g. *EZH2*, *CREPPB*, *TET2*, *IDH2*),[61,62] while other B-cell lymphomas demonstrate common mutations of members in the NOTCH, B-cell receptor (BcR), and NF-κB signaling pathways (Table 1).[63,64] Similarly, different PTCL subtypes, such as mycosis fungoides and Sézary syndrome, AITL and other T_{FH}-derived PTCL, and adult T-cell leukemia/lymphoma (ATLL) share frequent alterations affecting both epigenetic regulation and T-cell receptor

Table 1B. Mutation frequencies in different T-cell lymphoma entities.

Pathway/cellular function	AITL	MF/SS	PTCL-NOS	LGL	HSTL	P-TLL	ALK-neg ALCL	NKTCL	ATLL
Co-stimulatory/TCR signaling elements									
CD28	11%	-	-	-	-	-	--	2%	
FYN	3%	-	-	-	-	-	--	3%	
PLCG1	12%	20%	15%	-	-	-	--	36%	
Epigenetic modifiers									
TET2	50-70%	-	20-48°	-	-	-	--	-	
IDH2	20-40%	-	-	-	-	-	--	-	
DNMT3	20-30%	-	10-27°	-	-	-	--	-	
JAK-STAT signaling pathway		-	-	-		-	-		-
STAT3	-	-	-	35%	-	-	38%#	5-10%	22%
STAT5B (N642H)*	-	-	-	<5%	25%	35%	-6%	-	
JAK1	-	-	-	-	-	<10%	38%#	-	-
JAK3	-	-	-	-	-	30-40%	-20%	-	
NF-κB signaling pathway									
PRKCB	-	-	-	-	-	-	--	33%	
CARD11	-	15%	-	-	-	-	--	24%	
TNFRSF1B	-	6%	-	-	-	-	--	-	
Other genes									
RHOA (G17V)¤	60-70%	7%	18%°	-	-	-	--	<15%	
DDX3X	-	-	-	-	-	-	-20%	-	
CCR4	-	7%	-	-	-	-	--	-	

AITL: angioimmunoblastic T-cell lymphoma; MF: mycosis fungoides, SS: Sézary syndrome; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified; LGL: large granular lymphocytic leukemia; HSTL: hepatosplenic T-cell lymphoma; TPLL: T-cell prolymphocytic leukemia; ATLL: adult T-cell leukemia/lymphoma; ALK-neg ALCL: ALK-negative anaplastic large cell lymphoma, NKTCL, extranodal NK/T-cell lymphoma, nasal-type. *STAT5B *mutations were also reported in 36% of EATL type 2 (Kücück et al Nat Commun 2015[107]).* °*Mutations in* TET2, RHOA *and* DNMT3A *also reported in the subgroup of PTCL-NOS with TFH phenotype.* #*38% of systemic ALK-negative ALCL patients were reported to carry both* JAK1 *and* STAT3 *mutations (Crescenzo et al, Cancer Cell 2015[65]).* ¤*Whereas* RHOA *mutations in AITL almost invariably involve the hotspot G17V, RHOA mutations in ATLL are more widely distributed (Kataoka et al, Nat Genet, 2015[56]; Nagata et al, Blood 2016[108]).*

(TCR) signaling, whereas mutations of members of the JAK-STAT signaling pathway (*STAT3*, *STAT5B*) are shared by several cytotoxic T-cell or NK-cell lymphomas, such as T-LGL, nasal NK/T-cell lymphomas, hepatosplenic T-cell lymphoma, enteropathy-associated T-cell lymphoma (type 2) and ALK-negative anaplastic large cell lymphomas[11,56,65,66] (Table 1).

Subgroups of patients within a lymphoma entity may also display differential mutation profiles, initially shown for the GCB *vs*. ABC subtypes of DLBCL (Table 1) and, more recently, also demonstrated in other lymphomas e.g. HCL, where cases expressing the IGHV4-34 gene in the clonotypic B-cell receptor lack the canonical $BRAF^{V600E}$, and instead display enrichment for *MAP2K1* mutations with an overall similar profile to the HCL-variant.[67,68] Similarly, a subgroup of SMZLs with IGHV1-2 expressing B-cell receptor commonly harbors inactivating *KLF2* mutations and 7q deletions.[16,17] Potentially, this might aid future diagnostics aiming to distinguish these subtypes, however the utility and applicability of this approach have to be studied further.

In summary, presently, *MYD88*, *BRAF*, *ID3*, *TCF3*, *STAT3*, *STAT5B*, *RHOA*, *TET2*, and *IDH2* mutations are the only genes that can be considered as a complement to the current set-up for lymphoma diagnostics. However, the list is rapidly expanding as evidenced by the case of *RRAGC* mutations, for example.

III. Genes with prognostic potential

Several gene mutations have been associated with clinical outcome in various lymphoma subtypes. In CLL, besides *TP53* and *ATM* mutations, which are both known to confer poor prognosis, recent high-throughput NGS studies have revealed recurrent mutations within *NOTCH1*, *SF3B1*, and *BIRC3* for example, that were reported to be associated with poor clinical outcome with higher frequencies in relapsing/treatment-refractory CLL and in Richter's syndrome.[48,69-79] More recent studies have also identified additional gene mutations that may confer a worse outcome in CLL, e.g. *NKFBIE*, *EGR2*, and *RPS15*, although they have been studied less.[78-79] In a recent multicenter study conducted within ERIC, sequencing of *TP53*, *NOTCH1*, *SF3B1*, *BIRC3* and *MYD88* was performed in a large patient series (totaling 3,490 patients), revealing that *TP53* and *SF3B1* mutations, but not *NOTCH1* mutations, remained as independent prognostic markers of shorter time to first treatment in multivariate analysis, even amongst patients expressing unmutated *IGHV* genes.[50] A few published clinical trials have also pointed to a prognostic and even predictive role of *SF3B1* and *NOTCH1* mutations in CLL,[28] where, in particular, the latter confers resistance to the anti-CD20 monoclonal antibodies rituximab[29] and ofatumumab,[80] however, this needs further exploration and validation. Currently, as a new ERIC project, a dedicated NGS-based gene panel (including 11 genes) has been designed with the purpose to test different targeted enrichment techniques and evaluate inter-center variability and reproducibility.

Similar gene panel-based efforts have also been performed for SMZL, revealing a high frequency of *TP53*, *KLF2*, *NOTCH2*, *TNFAIP3*, and *MYD88* mutations,[17,18] and demonstrating *NOTCH2* and *TP53* mutations as independent markers of short treatment-free and overall survival, respectively.[16] Nonetheless, caution is required given the retrospective nature of the published studies and the overall rarity of SMZL raising concerns about potential selection biases.

MCL is characterized by a relatively high number of recurrent secondary genomic aberrations, but few of them have demonstrated additional prognostic value. From recent NGS studies, the prognostic value of *NOTCH1/NOTCH2* mutations was recently highlighted[7,81] in addition to *TP53* defects.

In DLBCL, the prognostic impact of *MYC* translocations critically depends on the second hit, with cases harboring *TP53* mutation and *MYC* translocation showing the worst overall survival, followed by those cases carrying *MYC* and *BCL2* translocation.[82,83] Indeed, DLBCL with *TP53* mutation and *MYC* translocation is a newly recognized subset of 'double-hit' lymphoma, accounting for one-third of *MYC* translocation positive DLBCL. Hence, it is pivotal to perform *TP53* mutation screening, in addition to the detection of *BCL2* translocation in *MYC* translocation positive DLBCL, in order to distinguish the double-hit DLBCL from those with an isolated *MYC* translocation.[84]

Among PTCL, *TET2* mutations in AITL patients were reported to associate with a more aggressive clinical presentation and a shorter progression-free survival,[53] whereas in a recent study of NK-TCL *DDX3X* mutations conferred a particularly poor prognosis.[85]

Considering the significant differences in mutation frequencies observed between different studies, best exemplified by DLBCL, large-scale efforts are now needed, in particular for rarer entities, to fully understand which genes are the most relevant and will retain independent prognostic impact in relation to other known clinical/molecular markers. This is particularly relevant in light of recent studies[86-88] pointing to a prognostic relevance of particular combinations of mutations and/or an increasing

Table 2. Categorization of gene mutations based on current evidence levels.

Category	Gene mutations
1. Immediate impact on patient care	*TP53* mutations (exons 4-10) in CLL
2. Diagnostic impact	$MYD88^{L265P}$ mutation in WM/LPL $BRAF^{V600E}$ mutation in HCL *KLF2* mutations in SMZL *ID3* and *TCF3* mutations in BL *STAT3* mutations in LGLL *RHOA*, *TET2*, *IDH2* and DNMT3A mutations in AITL and other T_{FH}-derived PTCL
3. Prognostic impact	*CLL*: *TP53*, *ATM*, *BIRC3*, *NFKBIE*, *NOTCH1*, *SF3B1* MCL: *TP53*, *NOTCH1*, *NOTCH2* mutations SMZL: *NOTCH2*, *TP53* mutations DLBCL: *TP53* mutation & MYC translocation NKTCL: *DDX3X* mutations
4. Potential clinical impact in the near future	Therapy response to BcR inhibitors: WM: *MYD88*, *CXCR4* mutations DLBCL: *CD79B* mutations (responsive) *CARD11*, MYD88 mutations (non-responsive) Resistance to BcR inhibitors: BTK^{C481S}, PCLG2 mutations New inhibitors under development: *EZH2*, *SF3B1* & *NOTCH1*

[a]*Based on references listed in Table 1. CLL: chronic lymphocytic leukemia; WM: Waldenström's Macroglobulinemia; LPL: lymphoplasmacytic lymphoma; HCL: hairy-cell leukemia; BL: Burkitt lymphoma; AITL: angioimmunoblastic T-cell lymphoma; MCL: mantle cell lymphoma; SMZL: splenic marginal zone lymphoma; DLBCL: diffuse large B-cell lymphoma; NKTCL: NK T-cell lymphoma.*

number of 'driver mutations'. In addition, the time point of mutation screening may also differ depending on the disease entity and response to therapy.

IV. Genes with potential clinical impact in the near future

Recent studies in different lymphoma subtypes have highlighted relevant associations between certain recurrent gene mutations and response to treatment. The most striking example is perhaps offered by *MYD88* and *CXCR4* mutations, which were shown to affect responses to ibrutinib in WM. Indeed, patients with $MYD88^{L265P}CXCR4^{WT}$ (with WT indicating wild-type) status had 100% overall response rate (91% major response rate) as opposed to 86% (62%) and 71% (29%) for $MYD88^{L265P}CXCR4^{WHIM}$ and $MYD88^{WT}CXCR4^{WT}$ patients, respectively.[89] Although these results were obtained from a small cohort of patients with WM, they offer a tantalizing glimpse into the future of lymphoma treatment with novel companion diagnostics tailored to novel therapeutic agents.

From recent studies, we have also learnt that mutations within the *BTK* (C481S) and *PLCG2* genes may emerge in CLL patients relapsing after and/or refractory to ibrutinib treatment, and we foresee that the assessment of these genes may soon be incorporated in the diagnostic set-up.[90] Preliminary results also indicate that the divergent responses of patients with MCL or DLBCL to ibrutinib may be linked to distinct profiles of genomic aberrations, e.g. *BIRC3* mutations in MCL[91] and isolated *MYD88* mutation in DLBCL[92] as well as mutations downstream of BTK, such as activating mutations of *CARD11* in DLBCL,[93,94] may make these tumors resistant to BTK inhibition.

Recent reports of genes linked to particular physiological processes have revealed new types of mechanisms that may be suitable for targeted therapy. For mutant *BRAF*, the inhibitor vemurafenib is already in clinical trials in relapsed/refractory HCL, demonstrating high activity even among heavily pre-treated patients.[3,95] New types of promising inhibitors have also been developed for EZH2 (a histone methyl transferase),[96] SF3B1 (a splicing factor),[97] NOTCH1[98] and IDH2,[99] and in some cases have already entered early phase clinical trials. The high frequency of *TET2* and/or *DNMT3A* mutations in AITL and other T_{FH}-derived PTCL may also support the rationale to use demethylating agents as an alternative way to treat patients, supported by the results of a recent single report.[100] More generally, targeting certain epigenetic abnormalities or alterations in pathways frequently involved in patients with PTCL (TCR, JAK-STAT, NF-κB; Table 2) represents an attractive approach, also taking into consideration the overall poor outcome of the majority of such patients with conventional chemotherapy-based approaches.

In conclusion, we expect that the list of potential therapeutic targets will expand quickly in coming years, once markers have been functionally validated and new compounds have been discovered.

V. Genes for research purposes only

Finally, for most recurrently mutated genes identified thus far, we do not yet understand their functional role and/or their clinical association, either alone or in the presence of cooperating events. These genes might still be of interest, however, before large-scale studies are performed, it will not be possible to discern their potential contribution to disease pathobiology. Having said that, and similar to category IV above, this subgroup of genes will be a 'moving target' depending on the evidence level ascertained for a particular mutation in the coming years, and genes may be taken out if a certain type of mutation is judged to have minor impact for a specific lymphoma entity.

How to move forward in the diagnostic field using NGS?

As mentioned, targeted NGS allows us to select and test many genes and samples simultaneously, and this approach has now been validated for CLL, SMZL and DLBCL, amongst others. In addition, targeted NGS permits a high sequence read depth, an important factor for studying minor subclones and thus clonal heterogeneity, and can also be adapted to formalin-fixed, paraffin-embedded (FFPE) tumor material, which in reality is the source of material for most diagnostic lymphoma specimens.

To gain further insight into NGS-based diagnostics in lymphoma, the EGNL Group has participated in the design of a lymphoma gene panel, compatible with FFPE material, that includes 30 recurrently mutated genes. Our ambition now is to perform a multi-center validation study using a defined number of matched FFPE/fresh-frozen lymphoma specimens to set the technical requirement for NGS-based diagnostics (including metrics such as sequence coverage, specificity, sensitivity and reproducibility of the technique). Once validated, large-scale international collaborative efforts can be conducted for each lymphoma entity, in particular within ongoing or planned treatment studies, to fully understand how to adapt and implement NGS-based diagnostics in day-to-day routine diagnostics.

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