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# New Molecular Assay for the Proliferation Signature in Mantle Cell Lymphoma Applicable to Formalin-Fixed Paraffin-Embedded Biopsies

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#### ASSOCIATED CONTENT

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#### Purpose

Mantle cell lymphoma is an aggressive B-cell neoplasm that displays heterogeneous outcomes after treatment. In 2003, the Lymphoma/Leukemia Molecular Profiling Project described a powerful biomarker—the proliferation signature—using gene expression in fresh frozen material. Herein, we describe the training and validation of a new assay that measures the proliferation signature in RNA derived from routinely available formalin-fixed paraffin-embedded (FFPE) biopsies.

#### Methods

Forty-seven FFPE biopsies were used to train an assay on the NanoString platform, using microarray gene expression data of matched fresh frozen biopsies as a gold standard. The locked assay was applied to pretreatment FFPE lymph node biopsies from an independent cohort of 110 patients uniformly treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. Seventeen biopsies were tested across three laboratories to assess assay reproducibility.

#### Results

The MCL35 assay, which contained a 17-gene proliferation signature, yielded gene expression of sufficient quality to assign an assay score and risk group in 108 (98%) of 110 archival FFPE biopsies. The MCL35 assay assigned patients to high-risk (26%), standard-risk (29%), and low-risk (45%) groups, with different lengths of overall survival (OS): a median of 1.1, 2.6, and 8.6 years, respectively (log-rank for trend, P < .001). In multivariable analysis, these risk groups and the Mantle Cell Lymphoma International Prognostic Index were independently associated with OS (P < .001 for both variables). Concordance of risk assignment across the three independent laboratories was 100%.

#### Conclusion

The newly developed and validated MCL35 assay for FFPE biopsies uses the proliferation signature to define groups of patients with significantly different OS independent of the Mantle Cell Lymphoma International Prognostic Index. Importantly, the analytic and clinical validity of this assay defines it as a reliable biomarker to support risk-adapted clinical trials.

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# INTRODUCTION

Mantle cell lymphoma (MCL) is an incurable B-cell malignancy with a broad array of clinical and biologic features.<sup>1,2</sup> The vast majority of cases harbor the t(11;14)(q13;q32) translocation, leading to overexpression of cyclin D1 and dysregulation of the cell cycle. Although most patients have aggressive disease that requires immediate treatment, there is a group of patients in whom the disease is indolent and can be observed for years without treatment. Recently, it was recognized that MCL encompasses two subtypes, each with distinct biology: conventional MCL and a leukemic non-nodal variant characterized by lymphocytosis, splenomegaly, no (or minimal) lymphadenopathy, and an indolent clinical course.<sup>3-5</sup>

There is no universally accepted treatment regimen for MCL at this time. Most centers make

treatment decisions on the basis of the patient's age, with intensive regimens offered to younger patients. New therapeutic agents have shown impressive activity and are being incorporated into combination regimens in the frontline and relapse settings (recently reviewed by Cheah et al<sup>6</sup>). There is a critical need for reproducible biomarkers that can be incorporated into clinical trial design and ultimately used to guide management decisions.

A number of prognostic tools have been developed for MCL. The most prominent is the MCL International Prognostic Index (MIPI), which combines clinical and laboratory values to assign patients to low-, intermediate-, or high-risk groups. MIPI has been validated in randomized clinical trials.<sup>7-9</sup> In 2003, the Lymphoma/ Leukemia Molecular Profiling Project performed gene expression profiling on MCL and demonstrated that a coordinated signature of gene expression associated with proliferation was the strongest molecular predictor of survival and integrated the prognostic power of other molecular markers.<sup>10</sup>

However, this proliferation signature, requiring fresh frozen (FF) material and using a microarray-based platform, has not penetrated clinical practice. Ki-67 proliferation index (PI), measured using immunohistochemistry (IHC), has been proposed as a surrogate measure of the proliferation signature and has been shown to be prognostic in numerous studies, both alone and in combination with the MIPL<sup>7,11-14</sup> However, serious concerns have been raised regarding the analytic validity of the Ki-67 PI in lymphoma and other malignancies, particularly regarding interlaboratory and interobserver variability.<sup>15</sup>

Recently, technologies have been developed to reliably quantify gene expression in RNA from formalin-fixed paraffinembedded (FFPE) tissue, allowing the development of clinically relevant, intermediate-density, gene expression–based assays.<sup>16-18</sup> Herein, we describe the development, analytical validation, and evaluation of the clinical impact of a gene expression–based assay for measuring the proliferation signature in RNA derived from routinely available FFPE biopsies in MCL.

# METHODS

# Study Design and Patient Population

The overall design of the process for developing and characterizing the new assay for the proliferation signature in MCL is shown in the Data Supplement. The study involved retrospective gene expression profiling of samples from patients with MCL, confirmed by expert pathology consensus review. Biopsies contributing to the training of the new assay included 80 biopsies described in Rosenwald et al,<sup>10</sup> along with an additional 51 biopsies gathered from the clinical sites of the Lymphoma/Leukemia Molecular Profiling Project. These biopsies, with tumor content  $\geq$  60%, were obtained from patients who subsequently received a broad range of treatment regimens.

The assay was validated using 110 pretreatment biopsies from an independent cohort of patients treated at the BC Cancer Agency (BCCA; Table 1; Fig 1). Patients diagnosed with MCL at the BCCA between 2003 and 2012 were identified using the BCCA Lymphoid Cancer Database. Inclusion in the validation cohort required a diagnostic excisional FFPE biopsy of a lymph node with tumor content  $\geq 60\%$  and treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) within 3 months of the diagnostic biopsy. Biopsies with a predominantly mantle zone involvement by lymphoma cells were excluded.

All biopsies were centrally reviewed to confirm a diagnosis of conventional MCL and were positive for cyclin D1 by IHC.<sup>1</sup> The BCCA policy during this era was to treat MCL using the R-CHOP regimen with a planned consolidative autologous stem-cell transplantation (ASCT) for appropriate patients  $\leq 65$  years of age. A policy to provide maintenance rituximab (375 mg/m<sup>2</sup> intravenously every 3 months for 2 years) to patients who did not receive a consolidative ASCT was introduced in 2011. The study was approved by the University of British Columbia–BCCA Research Ethics Board.

# Gene Expression Profiling

Gene expression profiling of RNA extracted from FF biopsies used in the training of the assay was performed on Affymetrix U133 plus 2.0 (Thermo Fisher Scientific, Waltham, MA) microarrays.<sup>19</sup>

Nucleic acids were extracted from 10- $\mu$ m sections of FFPE biopsies using the QIAGEN AllPrep DNA/RNA FFPE Kit (QIAGEN, Hilden, Germany) after deparaffinization according to the manufacturer's instructions. Gene expression was quantitated in 200 ng of RNA on the NanoString platform (NanoString Technologies, Seattle, WA), using the "high sensitivity" setting on the nCounter Prep Station and 490 fields of view on the nCounter analyzer (generation 2) or 1,155 fields of view when a generation 1 analyzer was used. Normalization for RNA loading was performed using the geometric mean of 18 housekeeping genes. Samples in which this geometric mean was > 10-fold below the median were deemed to have failed. Probes to exon 3 and the 3' untranslated region (UTR) of *CCND1* were used to assess the status of the *CCND1* 3' UTR (Data Supplement).

# IHC and the MIPI

Ki-67 IHC (MIB-1) was performed on whole-tissue sections on a Ventana BenchMark platform (Ventana Medical Systems, Tucson, AZ) and scored by counting 200 cells per biopsy, according to the recommendations of Klapper et al.<sup>20</sup> The Ki-67 PI was defined as the proportion of positive tumor cells. TP53 IHC (clone DO-7) was performed on tissue microarrays comprising duplicate 0.6-mm cores from FFPE blocks of the biopsies, with positivity defined as strong uniform nuclear staining of tumor cells; all positive biopsies had staining in > 30% of tumor cells. The MIPI was calculated per Hoster et al.<sup>7</sup>

#### Statistical Analysis

The statistical analysis plan was specified before the evaluation of gene expression from the validation cohort. Fisher's exact and Kruskal-Wallis exact tests were used to examine the significance of differences in patient and pathology characteristics between groups. The median follow-up was estimated using the reverse censoring method.<sup>21</sup> The primary end point of the study was overall survival (OS), which was calculated from the date of diagnosis to date of death from any cause. OS was estimated using the Kaplan-Meier method. A planned subgroup analysis was performed, which was limited to patients for whom there was a per-policy intention-to-treat with a consolidative ASCT.

Univariable analyses using Cox models were implemented to examine the relationship between continuous variables and OS. Log-rank tests were used to test the relationship between discrete variables and OS. Cox proportional hazards regression model score tests were used to test the association of variables with OS in combination with other variables. It was prespecified that one-sided *P* values < .05 would be considered significant.

# RESULTS

# Development of the MCL35 Assay

The proliferation signature was originally described using gene expression defined on the basis of RNA derived from 92 FF tissue biopsies on custom Lymphochip microarrays.<sup>10</sup> In a first step toward producing a new assay, gene expression analysis was performed on the 80 available samples from the original 92 FF

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Table 1. Patient Demographic Data and Disease Characteristics					
		MCL35 Categories			
Variable	Total Cohort	Low-Risk Group	Standard-Risk Group	High-Risk Group	P*
Patients					
Assessable patients	108	49 (45)	31 (29)	28 (26)	
Male	86 (80)	39 (80)	26 (84)	21 (75)	.75
Female	22 (20)	10 (20)	5 (16)	7 (25)	
Age in years, median (range)	62 (41-84)	60 (41-84)	64 (45-74)	68 (41-81)	.18
> 65	39 (36)	12 (24)	12 (39)	15 (54)	.04
ECOG performance status		20 (02)	20 (74)	10 (04)	.20
0-1	/5 (/6)	39 (83)	20 (74)	16 (64)	
Z-4	24 (24)	8(17)	/ (26)	9 (36)	
Wissing	9		4	3	02
vvnite cell count, median (range)	0.9 (1.7-79.2)	0.4 (Z./-1Z./)	8.7 (1.7-41.4)	7.9 (2.3-79.2)	.02
Normal	54 (57)	20 (69)	17 (62)	7 (20)	.007
	04 (07) A1 (A3)	14 (32)	10 (27)	17 (23)	
Missing	13	5	10 (27)	17 (71)	
MIPI	10	0	-	-	001
$ _{0W} (< 5.7)$	38 (41)	27 (61)	8 (31)	3 (13)	.001
Intermediate $(5.7-6.2)$	20 (22)	7 (16)	8 (31)	5 (22)	
High $(\geq 6.2)$	35 (38)	10 (23)	10 (38)	15 (65)	
Missing	15	5	5	5	
Pathology					
Morphology					< .001
Classic	95 (88)	49 (100)	29 (94)	17 (61)	
Pleomorphic	3 (3)	0	0	3 (11)	
Blastoid	10 (9)	0	2 (6)	8 (29)	
Ki-67 proliferation index (%)					< .001
< 30	53 (49)	45 (92)	6 (19)	2 (7)	
≥ 30	55 (51)	4 (8)	25 (81)	26 (93)	
TP53 immunohistochemistry					< .001
Negative	93 (87)	49 (100)	26 (87)	18 (64)	
Positive	14 (13)	0	4 (13)	10 (36)	
Fail	1	0	1	0	
CCND1 3' UTR					< .001
Wildtype	89 (82)	49 (100)	27 (87)	13 (46)	
Truncated	19 (18)	0	4 (13)	15 (54)	
Ireatment	100 (100)	40 (400)	04 (400)	00 (100)	
R-CHUP	108 (100)	49 (100)	31 (100)	28 (100)	001
Consolidative ASCI	EQ (Q4)	21 (04)	17 (00)	10 (77)	.967
Per-protocol Intention-to-treat+	58 (84)	31 (84)	17 (89)		
Received transplantation per protocols	4Z (/Z)	24 (77)	∠ (/  )	0 (00)	
Median follow up, months	70	0	69	75	
weulan lollow-up, months	/0	30	00	/5	

NOTE. All values are expressed as the number (%) unless indicated otherwise.

Abbreviations: ASCT, autologous stem-cell transplantation; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MIPI, mantle cell lymphoma International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; ULN, upper level of normal; UTR, untranslated region.

\*P values are for comparisons across the three risk groups determined by the MCL35 score.

†Comparison (across groups) of the number of patients who received an ASCT with the number of patients for whom there was an intention to consolidate with an ASCT.

§Percentage of patients for whom there was an intention to consolidate with an ASCT.

RNA samples using Affymetrix U133 plus 2.0 microarrays because these arrays provide broader coverage of the coding genome. Comparison of the correlation of expression of individual genes and the proliferation signature with the relationship between gene expression and overall survival, expressed as the Z-score from univariable Cox models, is shown in Figure 2. The strong association observed ( $r^2 = 0.82$ ) suggests that the proliferation signature encompasses much of the prognostic information present in gene expression in MCL. Furthermore, whereas the original proliferation signature solely contained genes that were overexpressed in biopsies with a high proliferation score, it is evident that a number of genes are underexpressed in these biopsies, allowing the design of a "balanced" gene expression model. Sixty-nine genes of interest, along with 30 potential housekeeping genes, were selected for further assay development, on the basis of this analysis and other published studies that have described the relationship between gene expression and outcomes in MCL<sup>22,23</sup> (Data Supplement).

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Fig 1. Patient flow for the validation cohort. B+R, bendamustine plus rituximab; CLB, chlorambucil; MCL: mantle cell lymphoma; R, rituximab; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R+CP, rituximab plus cyclophosphamide and prednisone; R+CVP, rituximab plus cyclophosphamide, vincristine, and prednisone.

Digital gene expression was performed to quantitate these 99 genes in RNA extracted from 47 FFPE biopsies, including all 39 suitable biopsies with matched Affymetrix gene expression data on RNA from FF biopsies. Seventeen genes were selected to replicate the proliferation signature based on the following criteria: being highly correlated across the NanoString (FFPE) and Affymetrix (FF) platforms, being moderately to highly expressed on the NanoString platform, and having high variance across the samples. Eighteen housekeeping genes were also selected on the basis of



**Fig 2.** Gene expression data in the training cohort. The correlation of the expression of individual genes to the proliferation signature calculated in Rosenwald et al<sup>10</sup> plotted against the Wald test Z-score for overall survival (OS) for that gene. The data are from gene expression profiling of 80 fresh frozen biopsies from Rosenwald et al<sup>10</sup> using Affymetrix U133 plus 2.0 microarrays. Gold and gray dots represent genes that were included in the NanoString gene set, which was used to select genes to replicate the proliferation signature. Gray dots represent genes that were selected for the MCL35 assay.

having low variance across the samples and moderate to high expression levels. Digital gene expression was then performed on the same 47 FFPE RNA samples using a smaller code set containing these 35 genes.

After normalization with the 18 housekeeping genes, a model was developed using expression of the 17 proliferation genes to replicate the proliferation signature score described by Rosenwald et al<sup>10</sup> (Fig 3A). Optimal thresholds for defining three groups with distinct outcomes (ie, OS) were determined using Affymetrix data from 123 FF biopsies, including the 80 biopsies from Rosenwald et al<sup>10</sup> (Fig 3B). The final model, named the MCL35 assay, including the gene coefficients and thresholds, was then locked and validated in an independent cohort of patients. Details of the model building are presented in the Data Supplement.

# MCL35 Assay Is Prognostic in Patients Treated With R-CHOP

The MCL35 assay was then applied to pretreatment FFPE lymph node biopsies from 110 patients treated with R-CHOP, with or without ASCT, at the BCCA (Table 1; Fig 1). Adequate gene expression was obtained in 108 (98%) of the biopsies. As a continuous variable, the MCL35 score was significantly associated with OS (univariate P < .001; Harrell's C-index, 0.74 [95% CI, 0.66 to 0.82]). The assay assigned 28 (26%) patients to the high-risk group, 31 (29%) to the standard-risk group, and 49 (45%) to the low-risk group (Fig 4A). The outcomes were significantly different among these three groups, with median OS of 1.1, 2.6, and 8.6 years in the high-, standard-, and low-risk groups, respectively, (log-rank for trend, P < .001; Fig 4B).

Recognized high-risk MCL features were more frequently encountered in the high-risk group, including morphologic characteristics (pleomorphic and blastoid variants<sup>24,25</sup>), TP53



Fig 3. The gene expression-based model for the proliferation signature in the training cohort. (A) The MLC35 assay is shown in the form of a heat map, with the 17 informative genes shown as rows and the 47 patient biopsies shown as columns. The three patient groups identified by the assay are shown below the heat map. (B) Kaplan-Meier curves of the overall survival (OS) of the three patient groups identified by the MCL35 assay. Outcome data were available for 44 of the 47 patients.

positivity by IHC,<sup>26</sup> and the presence of *CCND1* mRNA with truncated 3' UTRs<sup>10</sup> (Table 1; Fig 4A; Data Supplement). In a planned subgroup analysis, the assay also defined groups with significantly different OS in patients  $\leq$  65 years of age for whom there was intention-to-treat with R-CHOP followed by a consolidative ASCT. In this group, the median OS was 1.4 years, 5.9 years, and not reached in the high-, standard-, and low-risk groups, respectively, (log-rank for trend, *P* < .001; Fig 4C).

The MIPI also identified groups of patients with significantly different OS in the total validation cohort (log-rank for trend, P < .001; Harrell's C-index, 0.74 [95% CI, 0.66 to 0.82]). In multivariable analyses, both the MCL35 and the MIPI independently contributed to OS (P < .001 for both variables) whether the variables were continuous or grouped (Data Supplement).

There was a significant positive correlation between the Ki-67 PI and the MCL35 score ( $r^2 = 0.72$ ; Data Supplement). As a continuous variable, the Ki-67 PI was significantly associated with OS (univariable P < .001; Harrell's C-index, 0.69 [95% CI, 0.61 to

0.77]). Applying previously published thresholds,<sup>14</sup> 55 (50%) of the biopsies had a Ki-67 PI  $\geq$  30%, 38 (35%) had a Ki-67 PI of 10% to 29%, and 17 (15%) had a Ki-67 PI < 10%. A Ki-67 PI  $\geq$  30% was associated with inferior OS (median, 2.2 years; log-rank *v* Ki-67 PI 10% to 29%, *P* < .001), whereas the lengths of OS when the Ki-67 PI was 10% to 29% and < 10% were not significantly different from one another (median, 6 and 7.2 years, respectively; log-rank *P* = .75; Data Supplement). In multivariable Cox models, the Ki-67 PI (*P* = .36) did not contribute prognostically when adjusted for the MCL35 assay results, whereas the MCL35 did contribute (*P* < .001) when adjusted for the Ki-67 PI, whether the variables were continuous or grouped (Ki-67 PI groups: 0% to 29% and  $\geq$  30%; Data Supplement).

# Analytic Validity of the MCL35 Assay

Experiments were then performed to determine the intra- and interlaboratory reproducibility of the MCL35 assay. Seventeen biopsies were selected on the basis that the MCL35 scores were



Fig 4. The gene expression-based model for the proliferation signature in the validation cohort. (A) The MLC35 assay is shown in the form of a heat map, with the 17 informative genes shown as rows and the 108 patient biopsies shown as columns. The three patient groups identified by the assay are shown below the heat map. Shown below are the Ki-67 proliferation index (PI), pathologic characteristics, and the mantle cell lymphoma International Prognostic Index (MIPI). (B) Kaplan-Meier curves of the overall survival (OS) of the three patient groups in the validation cohort identified by the MCL35 assay. Hazard ratios (HR) are reported with the standard-risk group used as the reference. (C) Kaplan-Meier curves of the overall survival of the three patient groups within the subgroup of patients for whom there was an intention to consolidate response with an autologous stem-cell transplantation (ASCT). HRs are reported with the standard-risk group used as the reference. IHC, immunohistochemistry; UTR, untranslated region.

equally distributed across the population (Fig 5A) and thus representative of the distribution of MCL35 scores in the validation cohort. For intralaboratory comparison, the RNA from each of these biopsies was run on the MCL35 assay in triplicate, with each run performed on a different aliquot of RNA and on different NanoString cartridges. The results showed 100% concordance of risk group assignment (Fig 5B) across the triplicates.

One outlier result was observed, where the gene expression was disparate from the other replicates. This outlier result was removed from further analyses. The standard deviation of the intralaboratory error was four points, compared with a range of scores across the validation cohort of 586 points. For interlaboratory comparison, scrolls of tissue from the 17 biopsies were distributed to two independent laboratories in Barcelona, Spain and Würzburg, Germany, where RNA was extracted and run on the MCL35 assay (Fig 5C). There was 100% concordance of risk group assignment and no significant bias was seen compared with the mean of the triplicate results from the laboratory in Vancouver,



Fig 5. Studies of the analytic validity of the MCL35 assay. (A) MCL35 scores are shown in ascending order, left to right, in the validation cohort. Gold dots represent the scores of the 17 biopsies (equally spread across the spectrum of scores) selected for the analytic validation studies. Blue dots represent the scores of the biopsies not selected. (B) MCL35 scores of RNA from the 17 biopsies identified in (A) run in triplicate (y-axis) plotted against the average of the three scores (continued on next page)

British Columbia, Canada (95% CIs of bias: Barcelona, -6.1 to 0.6; Würzburg, -3.7 to 3.0 points).

The standard deviation of the interlaboratory error was three points, giving a standard deviation of the total (intra- plus interlaboratory) error of five points. Given that the examination of a small number of samples provides an imprecise estimate of concordance over a population, the distribution of the MCL35 score in this study and the calculated distributions of error were used to estimate concordance of risk group assignment between laboratories over a large population (Data Supplement). This model estimated that 1.2% of biopsies would change risk group assignment between laboratories. The Data Supplement contains these analyses if the outlier result was retained.

Finally, to determine the lower limit of RNA input for the MCL35 assay, RNA from the same 17 biopsies was run on the assay with input of 100 ng, 50 ng (in duplicate), and 25 ng (Figs 5D–F). No significant bias was observed at 100 and 50 ng compared with the mean of the triplicates at 200 ng. However, at 25 ng, there was a consistent trend toward higher MCL35 scores.

#### DISCUSSION

To our knowledge, this is the first description of a molecular assay that translates the research-derived proliferation signature in MCL into a test applicable to routinely available FFPE biopsies. The clinical validity of the MCL35 assay, identifying patient groups at significantly different risk of death, was demonstrated in an independent cohort of uniformly treated patients. The assay was demonstrated to be a powerful prognostic biomarker in patients treated with R-CHOP, identifying sizeable groups of patients with dismal or excellent outcomes. Furthermore, the prognostic power of the assay was maintained in younger patients for whom there was a plan to consolidate with an ASCT.

Similar to the original proliferation signature, the assay summates established high-risk disease features, including blastoid and pleomorphic morphology, TP53 overexpression, and truncation of the 3' UTR of *CCND1* mRNA transcripts. In addition, the prognostic power of the assay was independent of the MIPI.

This initial study was restricted to lymph node biopsies with a tumor content  $\ge 60\%$ , which encompasses the vast majority of patients with conventional MCL. Further studies are required to establish the clinical validity of the assay in biopsies that have low tumor content or are from extranodal sites. Similarly, this study exclusively used biopsies fixed in formalin, which is the methodology used by the vast majority of clinical laboratories. Further study would be required to determine whether the performance of the assay is affected by alternative fixation methodologies.

Proliferation of MCL cells in peripheral blood is typically, but not universally, lower than in matched lymph-node infiltrates; this effect is thought to reflect activation of the NF-κB pathway in the malignant cells by the tumor microenvironment, which dissipates upon exit from the lymph node.<sup>27</sup> This inconsistent relationship of proliferation between different tumor compartments would require alteration of the assay parameters and may affect the clinical validity of the MCL35 assay in peripheral blood samples. Similarly, it is also not known whether the assay will have clinical validity in the rare leukemic non-nodal subtype of the disease.

The analytic validity of the assay was demonstrated by examining both intra- and interlaboratory variability, showing a low estimated 1.2% rate of discordance across laboratories. This reproducibility sharply contrasts with the published literature regarding the Ki-67 PI as a surrogate marker for the proliferation signature, which has high interlaboratory and interobserver variability in lymphoma.<sup>15,20</sup> This study was not designed or powered to directly compare the clinical validity of the new assay with this surrogate marker, but the MCL35 assay subsumed the prognostic power of the Ki-67 PI in pairwise multivariable analyses. Finally, the demonstration that there is no appreciable bias with RNA loading down to 50 ng will allow the assay to be applied to the majority of tissue biopsies, including core needle biopsies.

Clinical utility, as defined by improving patient outcomes, relies on the ability of the biomarker to guide clinical management. It is appreciated that the design of this study does not establish the assay as a predictive biomarker because it was tested in a homogeneously treated population. To establish the MCL35 assay as a predictive biomarker, it will need to be applied to prospectively collected samples from clinical trials testing the efficacy of modern treatment regimens. The recognition of highly variable treatment outcomes in this disease, along with the increasing range of efficacious treatment options, makes risk-stratified approaches attractive whereby toxic and/or expensive therapies are provided to patients in whom the most benefit will be accrued.<sup>28</sup>

In conclusion, the newly developed and validated MCL35 assay for FFPE biopsies uses the proliferation signature to define groups of patients with significantly different OS independent of the MIPI. The analytic and clinical validity of this assay make it the ideal candidate to support future trials of risk-adapted therapeutic strategies.

# AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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(continued) (x-axis). The gold dot represents an outlier score. (C) MCL35 scores of RNA from the 17 biopsies that were extracted and run at two independent laboratories in Würzburg, Germany and Barcelona, Spain (y-axis) plotted against the original MCL35 score (x-axis) generated at the BC Cancer Agency, Vancouver, BC, Canada. Calculation of the MCL35 scores was performed centrally. (D) MCL35 scores from 100 ng of RNA from the 17 biopsies (y-axis) plotted against the score when 200 ng was loaded. The solid line represents the line-of-best-fit. (E) MCL35 scores from 50 ng of RNA run in duplicate from the 17 biopsies (y-axis) plotted against the score when 200 ng was loaded. The solid line represents the line-of-best-fit. (F) MCL35 scores from 25 ng of RNA from the 17 biopsies (y-axis) plotted against the score when 200 ng was loaded. The solid line represents the line-of-best-fit. (F) MCL35 scores from 25 ng of RNA from the 17 biopsies (y-axis) plotted against the score when 200 ng was loaded. The solid line represents the line-of-best-fit. (F) MCL35 scores from 25 ng of RNA from the 17 biopsies (y-axis) plotted against the score when 200 ng was loaded. The solid line represents the line-of-best-fit.

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# **AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

# New Molecular Assay for the Proliferation Signature in Mantle Cell Lymphoma Applicable to Formalin-Fixed Paraffin-Embedded Biopsies

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