HEMATOLOGIC MALIGNANCIES

Chronic Lymphocytic Leukemia: Prognostic Factors at Presentation in a Resource-Limited Center

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PURPOSE Determining chronic lymphocytic leukemia (CLL) prognosis using the International Prognostic Index markers such as TP53 and immunoglobulin heavy-chain variable region gene mutation in a resource-limited setting is difficult to achieve because of cost and equipment unavailability. The aim of this study is to determine prognostic factors easily available to hematologists in low- or medium-income countries.

MATERIALS AND METHODS This was a retrospective study conducted at the University of Port Harcourt Teaching Hospital, Nigeria. Data were retrieved from CLL patient records from January 2004 to December 2019 (15 years). Data collected were analyzed using SPSS software version 25.

RESULTS A total of 46 records were reviewed, with a median age of 55 years and a male:female ratio of 1:1.2. All patients were symptomatic at presentation, with splenomegaly (91.3%), anemia (82.6%), and lymphadenopathy (76.1%) predominating. About 89.1% of the patients presented at Binet stage C and/or high-risk Rai (Rai stages III and IV) with 10.9% presenting at Binet stage B and/or intermediate-risk Rai (Rai stage II). Only 13% of the patients had immunophenotyping done with 6.5% being done for the Matutes CLL score. The 5-year overall survival (OS) was 15.7% with a median survival of 26 months. WBC count and absolute lymphocyte count (ALC) $> 100 \times 10^9$/L were significant poor prognostic markers ($P = .013$ and .021, respectively). Thirty-five (76.1%) received chemotherapy, and they had a better median survival than those who did not (26 *v* 17.5 months). The most common regimen used was cyclophosphamide, vincristine, and prednisolone for 15 (42.9%) patients.

CONCLUSION WBC count and ALC $> 100 \times 10^9$/L were poor prognostic markers. Patients who received chemotherapy had a better OS.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a clonal B cell malignant disease with attendant lymphocytosis characterized by progressive accumulation of clonal B cells in the blood, bone marrow, lymph nodes, and spleen permitting easy diagnosis from the peripheral blood. The clinical features of CLL at presentation are related to the accumulation of these leukemic cells.

CLL is predominantly a disease of the elderly, with a median age of 65-72 years at diagnosis.[1,2] It is a slowly progressive disease, with an 81.7% 5-year survival rate.[1] It accounts for 17%-20% of all hematologic malignancies in Nigeria with 2-6 per 100,000 new cases diagnosed annually.[3,4] CLL accounts for one quarter of the new cases of leukemia with an age-adjusted incidence of 4.5 per 100,000 persons in the United States.[1] The incidence varies widely across geographical locations, with Asia having a 5-10-fold lower prevalence.[5,6] It is more common in males, mostly seen in the elderly (age > 65 years) with some familial tendency being alleged.[2,7]

Diagnosis requires peripheral blood lymphocytosis, an absolute lymphocyte count (ALC) of $\geq 5 \times 10^9$, and clonality confirmed by immunophenotyping (IMPT). Staging of the tumor is usually done at diagnosis, using Rai or Binet staging,[2] both of which are used for prognosis and decision on the commencement of therapy. The system uses lymphadenopathy, organomegaly, and cytopenias (anemia and thrombocytopenia) to establish prognostic groups that can be used to predict median survival. The Rai and Binet staging systems were the first prognostic markers to affect disease management. Although still widely used, they do not predict disease progression or response to therapy. There are numerous ongoing efforts to identify and characterize additional prognostic markers at the cellular and molecular level.[1,2,8]

Serum β_2-microglobulin (β_2m), thymidine kinase, and soluble CD23 have all been described as independent

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CONTEXT

Key Objective

Prognostic factors such as del(11q), del(17p)/TP53, and immunoglobulin heavy-chain variable region gene mutation are unavailable in many resource-limited settings. What other available factors could aid prognostication in patients diagnosed with Chronic Lymphocytic Leukemia?

Knowledge Generated

Patients with WBC count and absolute lymphocyte count (ALC) $> 100 \times 10^9$/L at presentation had a poor prognostic outlook when compared with those with WBC count and ALC $< 100 \times 10^9$/L ($P = .013$ and .021, respectively).

Relevance

A majority of patients could not afford novel drugs such as ibrutinib, obinutuzumab, or venetoclax; hence, older management protocols such as CP (chlorambucil and prednisolone), CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone), and CVP (cyclophosphamide, vincristine, and prednisolone) were used. Patients on CHOP appeared to have a better prognostic outlook.

prognostic markers in CLL.[9,10] Other newer prognostic factors include mutational status of the immunoglobulin heavy chain variable region (IGVH) genes and surrogate markers such as CD38 and zeta-associated protein (ZAP)-70 gene expression, telomerase length, and telomerase activity.[9,11] In a resource-limited setting like Nigeria, most of these investigations cannot be done and hence the need to investigate the usefulness of some clinical and laboratory parameters in assessing the prognosis and survival of patients with CLL.

Not all patients require treatment at diagnosis. Indications for treatment include a rapid doubling time, worsening cytopenias and symptomatic nodal or extranodal disease. Treatment options include the use of alkylating agents, purine analogs, anti-CD20 monoclonal antibodies, Bruton Tyr kinase inhibitors, and BCL-2 inhibitors.[12]

The aim of this study was to identify some clinical and laboratory prognostic markers for patients with CLL in a resource-limited setting.

MATERIALS AND METHODS

This was a retrospective study conducted at the University of Port Harcourt Teaching Hospital. Data were retrieved from the files of all patients diagnosed with CLL from January 2004 to December 2019. Inclusion criteria were asymptomatic and symptomatic patients with ALC $> 5 \times 10^9$/L and peripheral blood film showing predominantly mature lymphocytes with a Matutes score of 4 or 5 (if IMPT was done). Those with $\geq$ 10% prolymphocytes on blood film or Matutes score ≤ 3 were excluded. Data collected were analyzed using SPSS software version 25 (IBM, Armonk, NY). The results were expressed in charts and tables. A P value of < 0.05 (at 95% CI) was taken as statistically significant.

RESULTS

A total of 46 patients (making up 21.1% of 218 hematological malignancies) were diagnosed with CLL from January 2004 to December 2019 (15 years). There were 21 (45.7%) males and 25 (54.3%) females with a male to female ratio of 1:1.2. The median age at presentation for all the cases was 55 years (range, 39-83 years). Twenty-four patients (52.2%) were $\leq$ 55 years at presentation. Females had a lower median age at presentation (55 years) compared to the males (58 years); however, this was not statistically significant ($P = .35$).

There was no asymptomatic case, and the median duration of symptoms was 5 months (range, 3 weeks to 168 months). The most common symptoms were splenomegaly seen in 42 (91.3%) of the cases, followed by anemia (n = 38, 82.6%) and lymphadenopathy (n = 35, 76.1%). A little over a quarter of them (n = 12, 26.1%) had fever. The mean spleen size was 14 cm ($\pm$ 6.7 cm). Of the 42 patients with splenomegaly, 6 (14.3%) had a spleen size $>$ 20 cm (massive splenomegaly). One patient presented with asplenia following splenectomy for hypersplenism. Figure 1 shows a summary of the clinical features of the patients with CLL.

The median packed cell volume (PCV), total WBC count, ALC, and platelet count were 24% (range, 8.7%-39%), 101.0×10^9/L (range, 26.3-642.0 $\times 10^9$/L), 88.7×10^9/L (range, 21.3-622.7 $\times 10^9$/L), and 131.5×10^9/L (12-392 $\times 10^9$/L), respectively. Using the PCV and platelet count cutoff from the Rai staging criteria, there were 33 patients (71.7%) with anemia and 18 (39.1%) with thrombocytopenia. Eighteen patients (39.1%) presented at Rai stage 4, whereas 23 (50%) presented at Rai stage 3 and 5 (10.9%) at Rai stage 2. None of the patients presented at Rai stage 0 or 1 or Binet stage A, 41 patients (89.1%) presented at Binet stage C, and 5 (10.9%) at Binet stage B.

IMPT was done for only six patients (13.0%); half of them (n = 3, 50%) had only CD20 done, whereas the other three (50%) were tested using the Matutes CLL score. All the six cases who had IMPT done were CD20+ (Table 1).

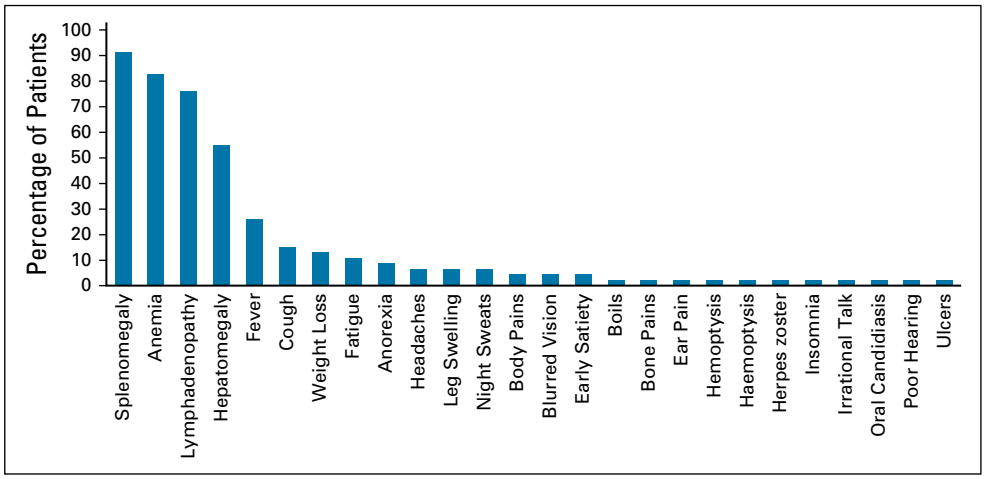

FIG 1. Clinical features at presentation.

All 46 patients had indications for treatment: 35 (76.1%) received chemotherapy and 11 (23.9%) did not receive chemotherapy (of these, 2 [18.1%] patients were referred to chemotherapy and 4 [36.4%] died before commencing treatment, whereas 5 [45.5%] refused to undergo chemotherapy). The mean duration of treatment for all regimens was 4.2 months (± 3.2 months). The major first-line chemotherapy used was cyclophosphamide, vincristine, and prednisolone (CVP) for 15 patients (42.9%), followed by chlorambucil and prednisolone (CP) for 11 (31.4%). Only three (8.6%) patients had rituximab with cyclophosphamide, hydroxodaunorubicin, oncovin, and prednisolone (R-CHOP). Fludarabine, cyclophosphamide, and prednisolone (FCP) was received by two patients (Table 1).

Patients on chemotherapy were grouped into those who received older forms of therapy (such as CP, CVP, and cyclophosphamide, hydroxodaunorubicin, oncovin, and prednisolone [CHOP]; n = 30, 85.7%) and those who received newer therapy, which were either FCP or R-CHOP (n = 5, 14.3%). Patients who received older therapy had a median survival of 26 months, whereas those who had newer therapy had a median survival of 38 months, although this was not statistically significant ($P = .8$). Patients who had CHOP had the longest median survival of 48 months (Table 2). The median survival was 26 months for all patients, with a 3-year overall survival (OS) of 47.2%, whereas the 5-year OS was 15.7%. Females had a better median survival than males (26 months *v* 13 months); however, this was not statistically significant ($P = .3$). Survival rate of younger patients (≤ 55 years) was better than patients of age > 55 years (29.9% *v* 11.08%), $P = .9$. Patients with massive splenomegaly (> 20 cm) had a shorter median survival (6 months) compared with those with splenomegaly < 20 cm (26 months), although this was not statistically significant, $P = .3$.

Patients with WBC count > 100×10^9/L (n = 24, 52.2%) had a significantly lower 5-year survival rate of 13.3% (a median survival of 41 months) compared with those with WBC count < 100×10^9/L (n = 22, 47.8%) whose 5-year OS was 18.2% (a median survival of 6 months), which was significant ($P = .013$) (Fig 2, Table 3). Also, patients with ALC > 100×10^9/L (n = 22, 47.8%) had a significantly lower median survival of 6 months compared with those with ALC < 100 (41 months), which was also significant ($P = .021$).

Patients who received chemotherapy had a higher median survival of 26 months with a 5-year survival rate of 14.7%, those without chemotherapy had a median survival of 17.5 months, and 5-year survival rate was zero. The median follow-up duration for all patients was 5 months (range, 0.5-72 months).

TABLE 1. Immunophenotyping and Matutes Score Results

Serial Number	Matutes Positive Markers	Matutes Negative Markers	Number of Markers Used for Matutes Score	Total Matutes/CLL Score (of 5)	Other CDs Tested for
1	**CD5+** and **CD23+**	**CD22**– and **sIg**	4	4/5	CD19+, CD20+, CD200+, and CD10–
2	**CD5+** and **CD23+**	**CD22**– and **sIg**	4	4/5	CD19+, CD43+, CD200+, and CD20+
3	**CD5**	**sIg, CD22,** and **FMC7**	4	4/5	CD7+, CD20+, and CD23–
4	CD20+		NA	NA	
5	CD20+		NA	NA	
6	CD20+		NA	NA	

NOTE. Components of CLL score highlighted in bold font.

Abbreviations: CLL, chronic lymphocytic leukemia; NA, not applicable; sIg, surface immunoglobulin.

TABLE 2. Chemotherapy Regimens Used for Patients With Chronic Lymphocytic Leukemia

Regimen	Number (%)	Median Duration of Rx (Months)	Range of Duration (Months)
CHOP	4 (11.4)	5.5	2-8
CP	11 (31.4)	4.0	1-8
CVP	15 (42.9)	2.0	1-11
FCP	2 (5.7)	8.0	3-13
R-CHOP	3 (8.6)	4.0	1-6
Total	35 (100)	4.0	1-19

Abbreviations: CHOP, cyclophosphamide, hydroxodaunorubicin, oncovin, and prednisolone; CP, chlorambucil and prednisolone; CVP, cyclophosphamide, vincristine, and prednisolone; FCP, fludarabine, cyclophosphamide, and prednisolone; R-CHOP, rituximab plus CHOP.

DISCUSSION

The median age at diagnosis of CLL was 55 years, showing a younger age at presentation when compared with other studies.[1,2] Salawu et al[13] showed a median age of 60 years in Ile-Ife, South-West Nigeria. However, western studies have shown a median age of between 65 and 72 years.[1,2,14] More than half of our patients with CLL were young (< 55 years) compared with those in the United States and Europe where only about 5%-11% of cases are younger than 55 years.[14,15] Although the epidemiology of CLL both in Nigeria and globally generally shows a male predominance,[16] our study showed a slight female preponderance. A female preponderance has also been reported in our environment.[17]

No patient was asymptomatic, unlike in western studies where 25%-50% of patients are asymptomatic at presentation.[18] This could be due to the poor health seeking behavior and the low socioeconomic status of the populace. This is further buttressed by the long median duration of symptoms. More than 90% of our patients had splenomegaly, which is higher than the results found by Basabaeen et al in Sudan and Salawu et al in Nigeria (49.1% and 70.9%, respectively).[12,19] Patients with massive splenomegaly had a lower median survival, albeit not statistically significant.

Slightly more than half of the patients presented with WBC count and ALC > 100×10^9/L, representing a high tumor burden, possibly associated with bone marrow suppression (because anemia was seen in more than three quarters of them, whereas thrombocytopoenia was present in more than a third of the cases). The presence of anemia and thrombocytopoenia explains why a majority had a high-risk Rai (III and IV) and Binet C at the time of presentation.

Only 13% of our patients could afford the cost of IMPT, of which half of them tested for the Matutes CLL score (CD5, CD23, FMC7, surface immunoglobulin, and CD22/CD79b) and the remaining half were tested for CD20 only. IMPT should be performed routinely as part of the workup for diagnosis of CLL as this aids confirmation of diagnosis and excludes other lymphoid neoplasms whose blood or marrow morphology may mimic CLL.[2]

The median survival was 26 months, which is only slightly above 2 years. This is poor when compared with some western studies like the one conducted by Weide et al,[20] in

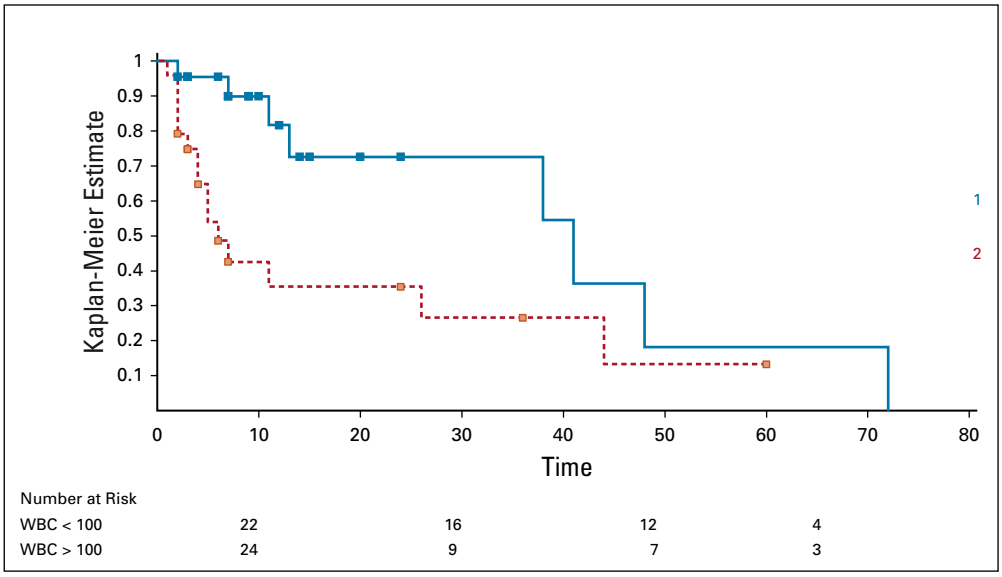

FIG 2. Survival curve showing the survival rates of those with WBC count < 100×10^9/L (1, blue line) compared with WBC count > 100×10^9/L at presentation (2, red line) (Note: Time in months).

TABLE 3. Median Survival and Survival Rates Based on Clinical and Laboratory Parameters

Parameter	Group	Total Number (%)	Median Survival (Months)	5-Year Survival Rate (%)	*P*
Sex	Female	25 (54.3)	26	23.89	.319
	Male	21 (45.7)	13	0	
Age group	< 55 years	24 (52.2)	41	29.91	.963
	> 55 years	22 (47.8)	26	11.08	
Splenomegaly	< 20 cm	38 (82.6)	26	16.52	.315
	> 20 cm	8 (17.4)	8	0	
WBC	$< 100 \times 10^9$/L	22 (47.8)	41	18.15	**.013***
	$> 100 \times 10^9$/L	24 (52.2)	6	13.29	
ALC	$< 100 \times 10^9$/L	23 (50.0)	41	16.73	**.021***
	$> 100 \times 10^9$/L	23 (50.0)	6	14.76	
PCV	> 30%	13 (28.3)	38	39.91	.699
	< 30%	33 (71.7)	26	28.96	
Platelets	$> 100 \times 10^9$/L	28 (60.9)	41	17.86	.182
	$< 100 \times 10^9$/L	18 (39.1)	11	12.43	
Rai	Stage 2	5 (10.9)	41	29.14	.442
	Stage 3	23 (50.0)	26	24.46	
	Stage 4	18 (39.1)	11	12.43	
Binet	Stage B	5 (10.9)	41	28.7	.703
	Stage C	41 (89.1)	26	17.73	
Time of presentation	< 12 months	34 (73.9)	38	18.94	.081
	> 12 months	12 (26.1)	6	0	
Chemotherapy	No chemotherapy	11 (23.9)	17.5	0	.849
	Chemotherapy	35 (76.1)	26	14.7	

NOTE. Normal$^+$/high$^\#$—uric acid based on sex (males, 180-420 μmol/L; females, 140-380 μmol/L).
Abbreviations: ALC, absolute lymphocyte count; PCV, packed cell volume.
*indicates *P* value < 0.05, which is statistically significant.

which the median survival from the time of diagnosis was 12.3 years for patients diagnosed in 2001 or earlier and 13.3 years for patients diagnosed between 2002 and 2008, whereas the median survival was not achieved in those diagnosed between 2009 and 2017. This short median survival may be due to misdiagnosis of patients who may have had other more severe lymphoproliferative neoplasms, since IMPT was not routinely performed. Our study showed that young patients < 55 years had a better OS than those > 55 years, even though it was not statistically significant. This is similar to studies where patients younger than 55 years had better OS than older patients.[14,15] The better survival in the younger age group (despite having more poor prognostic markers such as ZAP-70 expression or unmutated immunoglobulin heavy-chain variable status) could be due to their fewer comorbidities and shorter time to treatment, when compared with the older age group.[15] The females in our study had a slightly younger median age than males (55 years *v* 58 years), which may have contributed to the better median survival than the males (26 months *v* 13 months).

Patients with WBC count and ALC $< 100 \times 10^9$/L had a statistically significant better median survival than those with higher WBC counts or ALC, suggesting that a high tumor burden at presentation is a poor prognostic feature. This is validated by other studies that showed similar results.[9,21] However, Madu et al showed that there was no association between the ALC and median survival.[14] The hematocrit, platelet count, and Rai and Binet staging did not have any statistically significant impact on OS in our patients, unlike several other studies where these factors were associated with a shorter OS, with the exception of Salawu et al who noted that their patients with anemia had a better median OS.[2,22]

The later the stage at presentation using Rai or Binet, the shorter the median survival. Since our patients presented late, this was not statistically significant in our findings but might have been due to not having patients who presented with Rai 0 or I or Binet-A, which is yet to be compared. Other studies have shown a similar pattern in median survival, with it declining at later stages of presentation (Rai stage 0 > 150 months; stage I, 101 months; stage II, 71 months; stages III and IV, 19 months each).[13] Patients with Binet-A had a longer median OS of 100 months; stage B patients, 55 months; and stage C patients, 45 months.[23]

TABLE 4. Treatment Regimen and Median Survival

Regimen	Number (%)	Median Survival	Median Duration of Rx (Months)
Older regimen (CP, CVP, and CHOP)	30 (85.7)	26	3 (1-11)
Newer regimen (FCP and R-CHOP)	5 (14.3)	38	4 (1-13)
CHOP	4 (11.4)	48	5.5 (2-8)
CP	11 (31.4)	26	4 (1-8)
CVP	15 (42.9)	7	2 (1-11)

Abbreviations: CHOP, cyclophosphamide, hydroxodaunorubicin, oncovin, and prednisolone; CP, chlorambucil and prednisolone; CVP, cyclophosphamide, vincristine, and prednisolone; FCP, fludarabine, cyclophosphamide, and prednisolone; R-CHOP, rituximab plus CHOP.

Our patients with Rai stages II, III, and IV had the median survival of 41, 26, and 11 months, respectively. None of our patients presented in Binet-A, but patients with Binet-B had a better median survival than those at stage C.

Patients who received chemotherapy had a higher median survival than those who did not (26 *v* 17.5 months). A majority of our patients were not exposed to newer regimens because of nonavailability and financial implications. Although CVP was the most used older regimen, patients who received CHOP had the best median survival. This is similar to the 1989 findings by the French Cooperative Group on CLL.[24] In recent years, CLL treatment has evolved. First-line regimens now include novel drugs such as BTK inhibitors (ibrutinib), newer anti-CD20 monoclonal antibodies (obinituzumab), or BCL-2 inhibitors (venetoclax).[12] Therefore, comparatively speaking, our five patients who had the newer regimens did not *actually* receive novel therapy, and this may explain the poor survival in our patients with CLL compared with other climes. Those five patients in the newer therapy group (FCP and R-CHOP) had better median survival unlike the older therapy group (38 *v* 26 months); however, patients on CHOP had the longest median survival (Table 4).

In conclusion, while striving for better diagnostic and therapeutic availability and reduced costs, there is a need to use the limited available investigations and drugs at our disposal to patients with prognosticate CLL in our environs. Our patients presented at a younger median age of 55 years. At presentation, WBC count and ALC $> 100 \times 10^9$/L are poor prognostic markers. Patients who received chemotherapy had a longer median survival. It is recommended that full blood count is done for all patients for earlier detection of CLL, which may affect survival.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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