PROJECT SUMMARY (See instructions):

BACKGROUND: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. DLBCL has a life expectancy of < 1 year, but > 50% of patients can be cured with combined chemo-immunotherapy. Despite the high cure rate of standard treatment, DLBCL presents marked disparities in patients' survival. Recent emerging evidences have shown that in addition to clinical factors, genomic and socioeconomic factors have substantial predictive and prognostic values. However, at present there is no unifying, comprehensive risk prediction model that incorporates these parameters.

OBEJCTIVE: To develop a risk prediction model that incorporates data on known differences in demographic, socioeconomic, clinical, and biological factors and provides an online risk prediction tool for DLBCL as a decision support tool for clinicians, health services researchers, and other investigators.

METHOD: We will develop a micro-simulation model to replicate DLBCL patients' survival process and incorporate biological data on DLBCL biological subtype and socioeconomic data on insurance status and race that are affect patient's cancer-specific and overall survival. We will calibrate the effect of each factor (e.g., estimate the hazard ratio) using patient-level datasets and survival curves from published studies. The final model, will be implemented in a web-based risk assessment tool that can generate expected survival under specific scenarios.

SIGNIFICANCE: A well-calibrated risk prediction model can aid patients, clinicians, and health policy makers to optimize management strategies for patients and improve survival outcomes. Moreover, this risk model can predict the value of information gained from novel genomic tests, project the survival benefit required for novel treatments to provide population benefit, and can be easily updated to incorporate emerging genomic

RELEVANCE (See instructions):

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PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location			
Organizational Name: Emory University			
DUNS: 066469933			
Street 1: 1599 Clifton Road NE		Street 2:	
City: Atlanta	County: Dekalb		State: Georgia
Province:	Country: Unites States		Zip/Postal Code: 30322-4250
Project/Performance Site Congressional Districts: 05			

Additional Project/Performance Site Location			
Organizational Name: Georgia Institute of Technology			
DUNS: 097394084			
Street 1: 225 North Avenue		Street 2:	
City: Atlanta	County: Fulton		State: Georgia
Province:	Country: Unites States		Zip/Postal Code: 30322
Project/Performance Site Congressional Districts: GA005			

SENIOR/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other senior/key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Christopher Flowers	CHRISTOPHERFLOWERS	Emory University	Co-PI
Turgay Ayer	TURGAYAYER	Georgia Institute of Tech	Co-PI

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project
Qiushi Chen (Predoctoral Student)	Georgia Institute of Technology	Co-I
Jean Koff (Fellow)	Emory University	Co-I
Ashley Staton (Fellow)	Emory University	Co-I
Kevin Ward	Emory University	Co-I

Human Embryonic Stem Cells ☒ **No** ☐ **Yes**

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

BACKGROUND AND SIGNIFICANCE

Diffuse large B-cell lymphoma (DLBCL) represents a significant clinical problem for cancer outcomes research in that it is a curable disease, but one that is universally fatal if untreated or improperly treated.[1] DLBCL is the most common lymphoma in the US, affecting ~22,000 people/year, and accounting for about one-third of adult cases of non-Hodgkin lymphoma (NHL) [1] Untreated DLBCL patients have an expected survival of <1 year,[1] whereas with modern chemo-immunotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) >58% of patients are alive and cured at 5 years.[2-4] Despite the high cure rates for DLBCL, outcomes remain heterogeneous and are significantly worse for patients who are African American (AA), uninsured, have activated B-cell-like (ABC) biological subtype or a high international prognostic index (IPI) clinical risk factor score. In prior work, Dr. Flowers [1, 5-22] and colleagues have identified factors that impact DLBCL outcomes, and in recent editorial for *Blood*, he modeled how race/ethnicity, biological, and socioeconomic factors interact to influence DLBCL survival.[23] However, at present there is no unifying, comprehensive risk prediction model that incorporates these parameters.

Our group of investigators found that the IPI (the prevailing system for DLBCL prognosis) does not adequately stratify survival for AA DLBCL patients in the US.[13] Other investigators also have identified that IPI does not adequate stratify outcomes for elderly patients with DLBCL [24, 25] or when biological subtype is considered. [26-29] We propose to develop a computer micro-simulation risk prediction model that incorporates data on known differences in demographic, socioeconomic, clinical, and biological factors and incorporate this model into an online prognostic tool for DLBCL as a decision support tool for patients, clinicians, health services researchers, and other investigators. Patients with DLBCL are commonly told by clinicians that they are likely to be cured based on the average expected outcomes noted above or based on the outdated IPI scoring system. For AA, elderly, uninsured, and/or ABC-subtype patients this is not true! **It is a moral imperative that we develop accurate prognostic model for the modern era so that clinicians can convey realistic expectations of the outcomes of treatment to their patients.**

Biological variants within DLBCL have distinct outcomes Gene expression profiling (GEP) studies have identified two major subtypes of DLBCL associated with marked differences in survival. These groups resemble normal cells from distinct stages of B cell differentiation, namely germinal center B-cell-like (GCB) and activated B-cell-like (ABC) DLBCL.[30, 31]. Subsequent GEP studies upheld and expanded on these findings.[30, 32, 33] Because GEP does not translate easily to clinical practice, immunohistochemistry (IHC) algorithms were developed and validated to classify DLBCL into subtypes. An initial algorithm proposed by Hans et al.[34] used CD10, BCL6, and MUM1 to distinguish GCB and non-GCB subtypes but misclassified 20% of cases. A consortium improved on the Hans method (Choi) with 93% concordance with GEP.[35] Independent of IPI, GCB and ABC subtypes have significantly different OS even in patients treated with RCHOP.[30, 31, 34-36]

Our group recently performed a systematic review and meta-analysis comparing the ability of GEP and IHC to predict DLBCL survival in patients treated with R-CHOP. We found that IHC algorithms are useful but this analysis identified GEP as the preferred method for predicting DLBCL outcomes and informing treatment decisions.[37] Patients with ABC DLBCL treated with RCHOP had significantly worse 5-year OS: 73% GCB vs. 52% ABC, p<0.001 As part of this meta-analysis, we digitized Kaplan–Meier progression-free survival (PFS) and OS curves to produced composite survival estimates for ABC and GCB and the hazard ratios comparing these groups. This work is being presented in June at the 13th International Conference on Malignant Lymphoma in Lugano, Switzerland. In three other recent studies, we applied similar techniques for digitizing PFS and OS curves to incorporate data from individual studies or multiple studies into mathematical modeled survival distributions. We then integrated these mathematical models of survival with individual patient-level survival data from the national Surveillance, Epidemiology and End Results (SEER) registry into computer simulation models of cancer survival.[38-41] This approach will be used to incorporate published survival data from the studies in our meta-analysis describing PFS and OS for patients with GCB and ABC DLBCL treated with R-CHOP into our individual-patient data outcome prediction models based on national DLBCL data from SEER and SEER-Medicare.

DLBCL treatment and outcomes Since the 1970s, the combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the standard therapy for DLBCL.[42, 43] In 2002, a randomized trial comparing CHOP and CHOP with rituximab (R), the first monoclonal antibody anti-cancer therapy, demonstrated that R-CHOP improved 2-year OS from 57% to 70%.[44] Follow-up data from this and other randomized trials confirmed the benefits of R-CHOP, demonstrating cure in nearly 60% of patients.[2-4, 45-47] Other approaches have not improved OS beyond standard R-CHOP given every 21 days.[48-50] For eligible patients with relapsed DLBCL, autologous stem cell transplantation can cure 30-50% of

relapsed patients[51, 52] as compared to additional chemotherapy which cures <10%.[52] Despite these advances, patients with DLBCL have disparate outcomes based on clinical factors, subtype, and race. Stage 3/4 disease, elevated lactate dehydrogenase (LDH), age >60 years, ECOG performance status ≥ 2, and involvement of >1 extranodal site are poor prognostic factors in the IPI score for DLBCL.[53] However, the IPI prognostic scoring system was not developed using patients who received R-CHOP, the current standard of care. We demonstrated that the IPI model did not predict OS well for black patients in the US.[13] Other investigators also have shown that the IPI does not adequate stratify patients treated with R-CHOP[25, 54] and does not predict outcomes well for elderly DLBCL patients.[24, 25] Novel adaptive, patient-specific risk prediction models are needed that incorporate the biological, socioeconomic, and clinical factors that are known to impact survival.

Disparities in DLBCL Survival In a series of studies we have identified racial, socioeconomic, and age-related disparities in DLBCL survival. While there has been a longstanding recognition of racial differences in the incidence of lymphoma,[55] and many groups including ours have contributed to a developed understanding of racial differences in solid tumors,[56-60] our group has been the first to systematically examine disparities in the presentation and survival of lymphoma.[20-23, 61-66] In studies of two national cancer datasets, the SEER registry and the National Cancer DataBase (NCDB), we discovered that black patients in the US with DLBCL were diagnosed at a mean age 10 years younger than whites, were significantly more likely to have advanced stage disease, and were less likely to be insured, less likely have received standard of care therapy, and less likely to be alive 5 years following diagnosis (38% vs. 46%).[20] In independent and joint studies of patients with DLBCL from the University of Alabama at Birmingham (UAB) and Emory University with more detailed ascertainment of the type of chemotherapy administered, we found no racial differences in treatment, but black patients still had inferior survival.[20, 67, 68] In a follow-up study of DLBCL patients using the NCDB we found that even after controlling for race and clinical components of the IPI uninsured and Medicaid insured patients with DLBCL in the US had worse survival.[6] In recent work, we examined 4,635 patients with DLBCL in the linked SEER-Medicare dataset and found that elderly patients with DLBCL had worse lymphoma-related survival and OS.[69] As noted above, the existing IPI does not adequately segregate expected outcomes for elderly patients and AAs with DLBCL. A comprehensive risk prediction system is needed to improve our survival estimates for these patient populations and integrate information on these demographic and clinical factors with data regarding DLBCL biology.

Incorporating Next Generation Sequencing can enhance future prognostic models Additional preliminary data for our work emerge from Dr. Flowers' R21 investigations into the biology of racial disparities in DLBCL and his ongoing collaborations on DLBCL genetic and genomic studies through International Lymphoma Epidemiology Consortium (InterLymph) and the Hematologic Malignancies Research Consortium (HMRC). Given the established biological subtypes of DLBCL that are associated with known differences in OS, we hypothesized that differences in the prevalence of the ABC variant between blacks and whites may underlie racial disparities in DLBCL and that gene mutations associated with ABC DLBCL will be more common in black patients. Our preliminary data supported by Dr. Flowers' R21 indicate that there are racial differences in the prevalence of ABC DLBCL (64% in Blacks vs. 37% in Whites, p=0.01),[66, 70] and we have begun to identify genes and gene pathways that may contribute to the increased likelihood of ABC DLBCL in AA patients.[9-11] Our proposed modeling system can integrate mathematical models derived from survival curves from the published literature and individual patient level data used to populate machine learning micro-simulation models. Thus, our approach is prepared to address interactions between racial, socioeconomic, and biological factors associated with poor outcomes and recalibrate the models accordingly. We have previously used this approach in computer simulation models of cancer outcomes.[39, 40, 71, 72]

As a member of InterLymph, Dr. Flowers was involved in the largest genome wide association study (GWAS) of DLBCL,[73] the largest multivariable assessment of lifestyle, medical history, family history, and occupational risk factors for DLBCL[74] and a study examining the interactions between genes and environment in NHL risk.[75] Future InterLymph studies are applying these findings to investigate their impact on DLBCL survival. Dr. Flowers is a consultant on a recently submitted R01 with Dr. Jim Cerhan (Mayo/InterLymph) to address this aim. Drs. Flowers and Cerhan are also co-PIs on a U01 grant that aims to construct a cohort of 12,000 NHL patients (including ~3,000 DLBCL) with clinical data and tissue samples that they anticipate will be funded by June 2015. These collaborations provide means to augment our model.

Dr. Flowers' work with the HMRC led by Dr. Sandeep Dave, generated the most comprehensive analysis based on high-depth coverage of a human lymphoma genome by sequencing a human DLBCL tumor and paired normal tissue along with whole exome sequencing of 95 DLBCLs. To better understand subgroup differences in the observed patterns of DLBCL mutations, we successfully performed GEP on 93/95 DLCBL

cases using Affymetrix microarrays, and examined the differential presence of mutations in ABC versus GCB DLBCLs. We found 15 genes with a frequency of at least 10% in each subgroup that were differentially mutated between ABC and GCB subtypes ($p<0.05$, Fisher's exact test). While other investigators have published on MYD88[76] and CD79B[77, 78] (both ABC), as well as BCL2,[79] and EZH2[80, 81] (both GCB), we identified several novel genes that were differentially mutated in the two subgroups. These data provide a comprehensive genetic portrait of human DLBCLs, offer new insights into the observed heterogeneity of the disease, and support our efforts to determine the factors underlying the biological differences in DLBCL outcome. Individual patient-level data from our follow-up study on the genomics and outcomes of 1500 DLBCL patients is underway with the HMRC. These data eventually can be incorporate to refine our computer micro-simulation prognostic model and provide patient-specific predictions of cancer-related survival and OS based on demographic, clinical, socioeconomic, and genomic data.

Developing models for DLBCL outcome prediction In preliminary analyses, we examined racial disparities in risk prediction.[13] We used the SEER dataset and included the DLBCL cases diagnosed between 1992 and 2010. After excluding the cases with age unknown or <18 years, we utilized a population of 43,794 cases with 40,517 white and 3,277 AA patients for the risk prediction analysis. Logistic regression (LR) and artificial neural network (ANN) models were developed for predicting 5-year OS. Input factors included age category, sex, race, Ann Arbor stage, presence of B-symptoms, and IPI scores. A random data-splitting approach was used for cross-validation. To evaluate the model performance, we used the Hosmer-Lemeshow test to assess the goodness-of-fit of the model (i.e., the model calibration), and the area under curve (AUC) of receiver operating characteristics (ROC) curve (equivalent to the c-statistic) for model discrimination. In particular, we have compared the model performance in the following scenarios:

1) General model (GM): trained on the general population of patients with DLBCL (~7% AA) [22] and tested on general and AA populations separately. This model was tested in a larger general testing population and a general population (~7% AA) selected to use the same number of testing patients as the AA testing population.
2) General model (GM2): trained on 1,500 patients from the general population (~7% AA) but selected to use the same number of training patients as the AA model, and
3) AA model (AAM): trained on the AA population. GM2 and AAM were tested on the same AA population (separate from the training set).

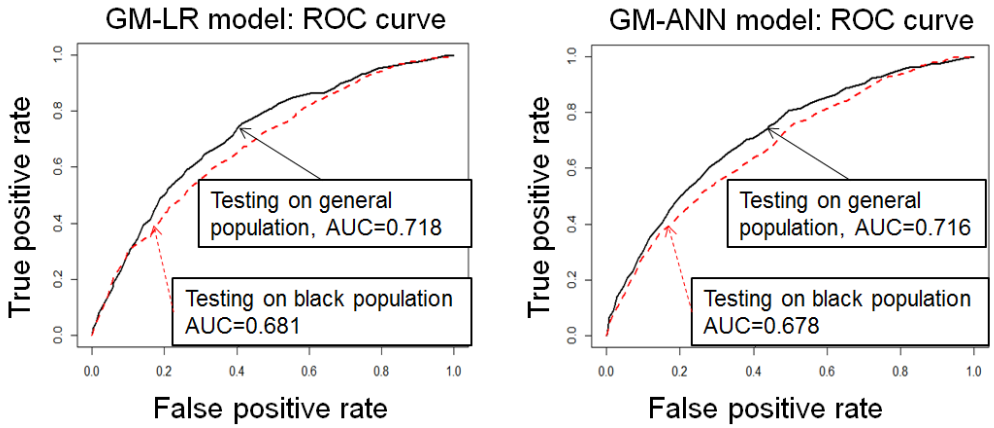
Table 1 Risk prediction model for general population

Model	Training Population			Testing Population			
	Patients Sampled	chi-square*	p*	Patients Tested	chi-square*	p*	AUC
GM-LR	General Population [n=10,800]	13.208	0.105	General-2 Population [W=1,665, AA=135]	11.55	0.172	0.714
				AA Population [AA=1,800]	89.59	**<0.001**	0.684
GM-ANN		2.143	0.976	General-2 Population [W=1,665, AA=135]	10.64	0.223	0.713
				AA Population [AA=1,800]	91.2	**<0.001**	0.685

W=white population; AA=AA population; * reported values of χ^2 and p-value are the median values from all replications of model training/testing on randomly split data.

From Table 1 we observe that in both models, the general model is a well-calibrated model for the general population, but has significantly poorer model calibration and discrimination (also see Figure 1) for the AA population with DLBCL. As displayed in Table 1, the Hosmer–Lemeshow statistical test for goodness-of-fit for the GM risk prediction models

Figure 1 ROC curves of models for general population



assesses whether or not the observed event rates (e.g. OS) match expected event rates in subgroups of the model population. The Hosmer–Lemeshow test indicates that the model is poorly calibrated when the p-value is <0.05. This finding implies that a different risk prediction model is needed to adequately predict survival for African-Americans with DLBCL.

These models currently incorporate all individual patient-level data available in SEER for DLBCL and can be optimized for risk prediction using each of these clinical parameters similar the approach described to improve risk prediction for AA patients with DLBCL. In addition, we can apply similar techniques to our recently published cancer modeling studies [38-41] to integrate SEER survival data with published studies included in our meta-analysis [5] describing outcomes for patients with GCB and ABC DLBCL.

OBJECTIVES AND SPECIFIC AIMS

The objective of this research is to develop a comprehensive, evidence-based model for risk prediction and stratification for DLBCL as a decision support tool for patients, clinicians, health services researchers, policy makers, and other investigators.

In particular, we will:

- Build an outcome prediction model to incorporate known demographic, socioeconomic, clinical, and biological factors prognostic factors into a comprehensive and unified computational system
- Calibrate and validate the model using (1) de-identified individual patient level data from SEER the largest and longest-running US cancer registry database with longitudinal follow-up and survival data and (2) survival data from published clinical trials and studies of biological subtypes
- Augment, recalibrate, and validate this model with national datasets that add more detailed information on socioeconomic status and treatment: NCDB and SEER-Medicare

PROPOSED RESEARCH PLANS Standard statistic procedures, such as logistic regression and survival analysis, have been heavily used in developing prognostic models in various clinical contexts. However, currently they are not suitable for building a comprehensive risk model for DLBCL. Standard statistic methods fit the risk model based on one dataset, but it is impractical to collect patient-level data for all risk factors for DLBCL over a wide spectrum of biological, social, and demographic factors in one single dataset. Moreover, the publication of novel prognostic findings rapidly outpaces the resources available from a single data source. Given the rapidly updated evidence in DLBCL treatment, we need an *additive* modeling framework, which is can able to incorporate new information as it emerges from published studies of new biological prognostic factors and clinical outcomes.

Model development To overcome the limitations in traditional methods of developing risk prediction models, we use a simulation calibration-based framework to achieve the objective of this study. We use Monte Carlo micro-simulation to replicate a patient's survival process, where the mortality risks are adjusted by the patient's characteristics. The effect of each characteristic on the survival (e.g., hazard ratio) will be calibrated based on patient-level data and survival curves from published clinical studies. Moreover, we can additively introduce new factors and calibrate their effect when new clinical evidence emerges. Our research plan has two stages.

Stage I: Baseline model based on patient-level data

Dr. Ayer has considerable experience with building microsimulation models in cancer[38, 82-85] and Drs. Flowers and Ayer have a longstanding track record of collaboration leading to peer-reviewed publication in computer simulation models.[13, 38-40, 71, 72] In the simulation model, patient may die from lymphoma (i.e., cause-specific mortality) or other causes (i.e., background mortality). Gender- and age-specific estimates of background mortality are available from a defined life table for the United States population stratified by demographic factors. [86] As in the preliminary study above, we estimate the cause-specific mortality (or equivalently the cause-specific survival) adjusted by each input risk factor in the following two steps. First, we estimate the lymphoma-specific survival in a baseline parametric form for the general population. We will utilize SEER registry data for DLBCL patients ≥ 18 years diagnosed from 1992 to 2011. Because the SEER dataset is larger than any other clinical study, it provides the most reliable and representative estimate of OS for general population with DLBCL. We have considerable experience with manipulating and performing analyses with SEER data [22, 56, 62, 64, 87-92] and have previously used SEER data to construct models of cancer outcomes [38, 40, 41] and to examine risk prediction for DLBCL.[13] We will assume the same shape of the cause-specific survival function for each patient subgroup. Second, we will adjust the scale of the survival function for each patient subgroup by each risk factor. In other words, we will estimate the hazard ratio of each factor by calibrating the simulated OS against the observed survival in that subgroup. We can estimate the effects of demographic factors such as age at diagnosis, race, and gender which are available in the SEER data, and the effects of socioeconomic factors, clinical factors, and treatment which are available in the NCDB and SEER-

Medicare datasets. Dr. Flowers has experience with using individual patient level data from each of these data sources for studies in DLBCL.[6, 21, 69]

A. Stage II: Extended model based on published survival curves

Besides the patient-level data, emerging evidence in survival outcomes by various treatment or biological factors from published studies are valuable sources to enrich the risk model as noted above. Although we cannot obtain patient-level data used in each clinical study, we can sample the values of calibrated factors (e.g., demographic and clinical factors in phase I) based on the summary of patient characteristics in the published paper. As in prior studies, Engauge Digitizer[93] will be used to extract the data points from the published survival plots, and these data points are then used to fit Gompertz ,Weibull, and log-logistic parametric survival models.[94] We compare these modeled survival distributions for goodness of fit to the published survival curves according to the Akaike information criterion and the Schwarz Bayesian criterion.[95] Then we will calibrate the new factor by comparing the simulated OS and the survival curve presented in the published paper for all DLBCL patients in the study and for patients stratified by clinical, biological or treatment factors. This follows the approach for integrating individual patient-level data from SEER and modeled distributions for published survival curves in our prior studies.[40, 71, 72] In particular, we will expand our DLBCL micro-simulation model by incorporating data from publications for the following previously identified prognostic factors that are not addressed by the IPI:

- Biological subtype of DLBCL: PFS and OS by ABC and GCB subtype [5, 29-36, 96, 97]
- Most common treatment: R-CHOP from phase 3 clinical trials [2-4, 44, 46, 47, 49]
- Novel treatments: lenalidomide + R-CHOP, ibrutinib + R-CHOP, obinotunzimab+CHOP, bortezomib+R-CHOP, carfilizomib+R-CHOP [98-103]
- Biology-specific treatment effect: study of lenalidomide + R-CHOP stratified by ABC/GCB subtype [100]

B. Model validation

In each step of the model development, we will validate the model after model training (i.e., calibrating the effect of each risk factor). To perform the model validation, we will reserve a part of the data for validation which are not used in the model training step. We can apply 10-fold cross validation and bootstrapping approaches to measure the accuracy of model prediction in the unseen dataset, similar to the methods used in our preliminary model.[13]

Model implementation Once our final, validated prediction model is constructed, for any given values of patient risk factors, we can generate the predicted survival curves or point estimates (e.g., 1-, 2-, or 5-year overall survival) by running the simulation model for the particular scenario. We can provide the estimates in the uncertainty of prediction results (e.g., 95% CI) by running simulation with multiple replications. We also can calculate the risk prediction results for every possible combination of risk factors, and implement these results in a web-based risk assessment tool (similar to an interactive tool for breast cancer [104]). Health professionals and patients can choose the input value of each factor, and then obtain the estimates of survival risks. **The Emory prognostic model for DLBCL would provide an international resource that could be widely utilized by patients, clinicians, and investigators and our approach facilitates continued updates to improve our model based on emerging data.**

Plan of Work Our research team started collaboration in September 2011. Dr. Flowers serves on the American Cancer Society Guidelines Development Committee that oversees development and integrates results of such risk prediction models into ACS guidelines and policies [105], and Dr. Ayer has longstanding experience with developing Cancer Intervention and Surveillance Modeling Network (CISNET) disease simulation models that incorporate information on cancer biology into predictive models. [82-84] Dr. Flowers and Dr. Ayer currently jointly supervise an engineering PhD student (Qiushi Chen). Our research team meets weekly at the Winship Cancer and presented our work on racial disparities in DLBCL survival prediction at the 2013 American Society of Hematology Annual Meeting. [38] We have collaborated and published a series of modeling studies. [38, 40, 41]

Establishing this model is central to our future work aimed at submitting a U01 in response to the RFA "Bridging the Gap Between Cancer Mechanism and Population Science" ***that requires an established computer simulation model*** **that links data from biological models to population-based disease outcomes prior to application.** Without this funding this model will not be developed and we will continue collaboration on cost-effectiveness analyses. Thus, the proposed model has the capacity to influence the successful funding of several future endeavors. In addition, this model can be integrated into R21 and R01 applications that utilize biological data generated from InterLymph and the HMRC to explore or validate novel prognostic markers generated through these resources.