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A Data-Driven Approach to Define Parsimonious Eligibility Criteria in First-Line Clinical Trials for Diffuse Large B-Cell Lymphoma

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A Data-Driven Approach to Define Parsimonious Eligibility Criteria in First-Line Clinical Trials for Diffuse Large B-Cell Lymphoma

By

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An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2020

Abstract

A Data-Driven Approach to Define Parsimonious Eligibility Criteria in First-Line Clinical Trials for Diffuse Large B-Cell Lymphoma
By R. Andrew Harkins

Background: Diffuse large B-cell lymphoma (DLBCL) is clinically and genetically heterogeneous. Forty percent of patients relapse or are refractory to first-line therapy and have inferior outcomes, indicating unmet treatment needs for high-risk disease. Randomized controlled trials (RCTs) designed to improve outcomes for these high-risk groups have been largely unsuccessful, potentially due to restrictive eligibility criteria that in fact limit enrollment of high-risk patients. We define evidence-based methods to streamline enrollment of patients with high-risk disease for first-line DLBCL clinical trials incorporating novel therapeutics.

Methods: We enumerated enrollment criteria from 19 first-line DLBCL RCTs. We proposed eligibility criteria for four eligibility criterion categories: International Prognostic Index (IPI) score, age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and Ann Arbor stage. Using study-specific eligibility criteria and proposed criteria, we identified eligible patients in eight DLBCL data sets representing institutional, regional, and national populations. We performed survival analysis according to eligibility status to determine whether prior RCTs and proposed criteria targeted high-risk groups. We calculated sensitivity and specificity of combinations of proposed criteria to identify patients meeting eligibility criteria for prior studies and developed receiver operating characteristic plots to identify optimal combinations. We characterized the mutational profile of the eligible patient population.

Results: We identified 52 eligibility criterion categories across 19 trials. We proposed the inclusion criteria IPI score ≥ 2, age at diagnosis ≥ 18, ECOG PS 0–2, and stage II–IV. Proposed criteria risk-stratified patients with hazard ratios for eligible versus ineligible patients of 1.37–3.58 for overall survival across data sets and defined eligibility for high-risk subgroups. Subsets of the proposed criteria lacking full IPI factors identified patients who were eligible for prior RCTs with sensitivity ≥ 0.75 for at least 14 of 19 RCTs when using data sets containing data for all data types included in analysis. We described patterns of DLBCL mutations for high-risk, eligible patients.

Conclusion: Subsets of modernized eligibility criteria for first-line DLBCL RCTs identified high-risk, eligible patient groups with high sensitivity. We identified relationships between eligibility status and cohort genomics that facilitate precision medicine RCT design for DLBCL.

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ACKNOWLEDGMENTS

I wish to express my sincere gratitude to my research mentor, Dr. Christopher Flowers, for providing invaluable guidance and support throughout the completion of this project and others.

I wish to express my appreciation to Dr. Jean Koff for helpful advice and input pertaining to both my oral defense and manuscript.

In addition, I wish to express my thanks to Dr. Jeffrey Switchenko for statistical assistance.

I wish to acknowledge the abiding love and support of my family.

Lastly, I wish to acknowledge the contribution of patients and families of patients who enrolled in data sets included in the analysis for the present study, without whom this research would not be possible.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common adult lymphoma and exhibits significant clinical and genetic heterogeneity (1, 2). For 60% of patients with DLBCL, standard first-line treatment is curative (3). The remaining 40% of patients experience relapse or are refractory to first-line therapy and exhibit poor outcomes with median overall survival (OS) under one year (4). Attempts to improve on standard first-line therapy for patients who have an increased likelihood of refractory or relapsed disease have shown consistent negative results, due in part to time-intensive pre-enrollment steps for determination of eligibility status that paradoxically impedes enrollment of patients with high-risk disease who require urgent therapy (5). In addition, recent DLBCL genomics studies indicate that the profound genetic heterogeneity underpinning DLBCL biology requires enrichment of genetic subtypes in study populations for DLBCL randomized controlled trials (RCTs) in order to uncover true effects of novel precision drugs (6-9). In the present study, we propose data-driven methods leveraging eligibility criteria from previous first-line DLBCL RCTs and large DLBCL patient data sets to streamline eligibility criteria and promote enrollment of high-risk groups in future first-line RCTs for DLBCL. We then link eligible patients with individual-level genetic profiles to characterize the mutational profile of the eligible cohort, facilitating adaptive precision medicine clinical trial design for patients with DLBCL.

BACKGROUND

DLBCL is a malignancy of mature lymphoid cells expressing B-cell antigens and is the most common adult non-Hodgkin lymphoma (NHL), comprising 25%–40% of the estimated 72,400 NHL diagnoses in the US in 2019 (1, 10-12). DLBCL incidence increases after 50 years of age and is more common in men, exhibiting a male:female incidence rate ratio of approximately 1.5 (1). Clinical presentation for DLBCL typically includes an enlarging nodal mass and constitutional symptoms (13). DLBCL staging follows Ann Arbor staging criteria, with stages I and II representing localized disease on one side of the diaphragm and stages III and IV representing advanced stage disease with involved sites present on both sides of the diaphragm (14). DLBCL exhibits distinct clinical heterogeneity, with patient outcomes ranging from cure following frontline treatment to poor with OS under one year in patients who do not respond to available therapies (3, 15). The primary clinical predictor for DLBCL is the International Prognostic Index (IPI), which estimates patient outcomes based on adverse clinical factors including older age, advanced stage disease, poor performance status, elevated serum lactate dehydrogenase (LDH), and disease involvement at two or more extranodal sites such as bone marrow, liver, or lung (16, 17). The IPI categorizes patients into risk groups ranging from low- to high-risk disease, with a greater number of adverse risk factors predicting inferior survival when treated with standard first-line chemoimmunotherapy (17). Advances in gene-expression profiling (GEP) (18), immunohistochemistry (IHC) (19), and next-generation sequencing (NGS) (6-9) have elucidated a profound histologic and genetic heterogeneity underpinning DLBCL and may identify new methods of prognostic modeling (20) as well exciting opportunities for precision medicine, particularly in the development of novel first-line drugs (2, 21).

First-line treatment for DLBCL has remained essentially unchanged for two decades and leads to highly variable clinical outcomes (3). Recommended first-line therapy comprises the anti-CD20 immunotherapy rituximab with the chemotherapeutic regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered every 21 days for between three and eight cycles (22). For approximately 60% of patients, first-line treatment with R-CHOP is curative (3), and patients who remain free of relapse or disease progression for two years following first-line therapy experience a life expectancy approaching that of the general population (23). The remaining 40% of patients will be refractory to R-CHOP or will relapse following first-line treatment, with most DLBCL-related events occurring in the first two years following initial therapy (24). Patients who relapse or are refractory to first-line treatment may receive multiple subsequent treatment modalities including salvage- and later-line chemoimmunotherapy, hematopoietic cell transplant (HCT), and chimeric antigen receptor T-cell therapy (22). For patients with relapsed or refractory DLBCL, outcomes are poor (3). Available data show that patients with disease progression within 24 months following initial therapy or with primary refractory DLBCL exhibit median OS under 8 months (4, 24), indicating significant unmet treatment needs in the first line for patients with high-risk disease.

Attempts to improve on R-CHOP as first-line therapy for patients with poor prognoses have yielded recurrent negative results (25-31). RCTs designed to identify effective first-line treatment in patients with high-risk DLBCL have examined R-CHOP versus "R-CHOP + X," which combines a standard R-CHOP backbone (or a similar variant) with an additional chemotherapeutic or precision drug. Despite multiple trial therapies showing promising results in early-phase clinical trials (32-36) and improved outcomes in other hematologic malignancies

(37-40), subsequent RCTs have failed to meet primary survival endpoints for untreated patients with DLBCL in head-to-head comparisons with R-CHOP. Unsuccessful R-CHOP + X clinical trials from the last five years have incorporated the proteasome inhibitor bortezomib (LYM-2034, NCT01040871; PYRAMID, NCT00931918; REMoDL-B, NCT01324596) (25, 27, 29), the anti-CD20 monoclonal antibody obinutuzumab (GOYA, NCT01287741) (26), the topoisomerase inhibitor etoposide (CALGB 50303, NCT00118209) (28), the Bruton's tyrosine kinase inhibitor ibrutinib (PHOENIX, NCT01855750) (30), and the immunomodulatory drug lenalidomide (ROBUST, NCT02285062) (31) in study regimens, illustrating recurrently negative results from precision therapies spanning a variety of cellular and molecular targets.

Data indicate that failures of these first-line DLBCL RCTs are likely due to 1) modern eligibility criteria that limit the enrollment of patients who require urgent therapy (5), and 2) study designs that fail to sufficiently enrich trial populations with patients whose tumors harbor certain molecular abnormalities or profiles that are more likely to respond to targeted drugs (21). A 2018 investigation of the association between diagnosis-to-treatment interval (DTI) and outcomes in newly diagnosed DLBCL revealed implications for bias in DLBCL RCTs pertaining to the enrollment of high-risk patients who require urgent therapy (5). Analysis of DTI and event-free survival showed that shorter DTI was strongly associated with inferior outcomes, indicating that an oncologist's decision to treat a patient within the first 0–6 days following diagnosis accurately identifies a patient with high-risk DLBCL who is likely to have a poor outcome following first-line treatment with R-CHOP. Critically, patients requiring urgent therapy are unable to participate in the extensive enrollment process necessary to determine clinical trial eligibility, thereby preventing high-risk patients who require urgent therapy from enrolling in DLBCL

RCTs. DLBCL clinical trials designed to enroll high-risk patients thus become enriched in patients who are able to undergo pre-enrollment testing due to their ability to tolerate a longer DTI (i.e., patients with lower-risk disease and increased likelihood for good prognosis following first-line treatment with R-CHOP). In a trial comparing R-CHOP + X and a standard R-CHOP control, the control arm will perform better than anticipated due to the enrolled population enriched in lower-risk disease, leading to negative study results overall. Authors from multiple recent negative studies highlight longer DTI and resulting improved outcomes in the R-CHOP control arm as contributors to negative trial results (25, 27, 28, 30). Of note, ECOG-ACRIN 1412, a phase 2 study of R-CHOP ± lenalidomide, recently showed improved progression-free survival (PFS) in newly diagnosed DLBCL in comparison with R-CHOP, in contrast with negative results from the ROBUST trial comparing the same study drugs (41). In subsequent analysis comparing the discordant outcomes in ECOG-ACRIN 1412 and ROBUST, authors including investigators from each trial concluded that negative results in ROBUST were likely due to time-consuming prospective laboratory analysis prior to trial enrollment that ultimately favored selection of low-risk patients with longer DTI (42). ECOG-ACRIN 1412, meanwhile, stratified patients retrospectively according to the same laboratory marker, allowing for more rapid enrollment and a study population more inclusive of high-risk patients. The positive study findings in ECOG-ACRIN 1412 compared with negative study findings in ROBUST illustrate the importance of minimizing bias associated with DTI in study design of first-line DLBCL RCTs. While retrospective stratification with respect to time-intensive laboratory techniques is an important first step to address DTI in clinical trial design, additional efforts to further streamline enrollment will increase the likelihood of identifying true effects of novel precision drugs.

Clinical trial results and recent genomic studies suggest that first-line RCTs for treatment of high-risk DLBCL have failed to sufficiently enrich study populations in patients with genetic mutations that may respond to investigational precision therapies, likely contributing to recurrent negative DLBCL RCT findings. In the 2000s, efforts to uncover the molecular bases for DLBCL leveraged GEP and later IHC to identify the so-called cell-of-origin (COO) subtypes germinal center B-cell-like (GCB) DLBCL and activated B-cell-like (ABC) DLBCL (18, 19). The advent of novel sequencing methods enabled subsequent investigation of genetic alterations underlying DLBCL biology and illustrated significant genetic heterogeneity with inconsistent results across early sequencing studies regarding which mutations were most prevalent in the DLBCL patient population (43). Four large-scale DLBCL genomic studies published since 2017 advanced understanding of DLBCL genetics and highlight a considerable number of putative driver mutations present at low prevalence in the DLBCL cases (6-9). Co-occurring mutations consistently stratify into recurrent genetic subtypes, indicating that DLBCL biology is determined by reproducible groups of genetic aberrations associated with discrete biochemical pathways, rather than individual mutations in select genes (7, 8). Notably, genetic subtypes display variable survival after treatment with R-CHOP that is independent of other prognostic markers, suggesting a genetic basis for defining high-risk patient groups (7, 8, 20, 21). Biological pathways identified as aberrant in DLBCL genetic subtypes may be targetable, and precision drugs in preclinical development designed to target actionable pathways number in the hundreds (44). Some currently available precision drugs target implicated pathways, including investigational drugs tested in recent DLBCL RCTs that led to negative overall results (45). Of note, recent negative RCTs either omitted the use of biomarkers during patient selection (26, 28)

or relied on stratification into COO subtypes using GEP (29, 31, 46) or IHC (25, 27, 30) rather than stratification based on presence of specific genetic abnormalities or dysregulated molecular pathways. Multiple study authors cite lack of or imprecise stratification using COO subtypes (25-27) and the failure to anticipate significant underlying genetic mutations during patient selection (27-29, 46) as likely factors in negative trial findings, consistent with the notion that successful DLBCL trials will require enrichment of study populations with patients whose tumors are likely to respond to investigational drugs (21). Indeed, genomic data indicate that stratification using COO—regardless of the accuracy of the laboratory technique—is insufficient to account for the nuance of underlying genetic subtypes in DLBCL, as COO designations overlap with multiple genetic subtypes that exhibit differential survival when treated with R-CHOP (7, 8, 44). Given the profound heterogeneity in the genetic landscape of DLBCL and the associated need to enrich study populations with patient groups likely to respond to targeted agents, the next generation of DLBCL RCTs will likely require patient stratification based on NGS identification of genetic subtypes followed by treatment with subtype-specific precision therapies (47). Implementation of novel trial designs, such as umbrella trials that allow for the broad enrollment of high-risk patients followed by molecular subtyping and subsequent pairing with appropriate precision drugs in concurrent study arms, will be necessary for the efficient and cost-effective identification of novel, subtype-specific treatment (44).

The American Society of Clinical Oncology, Friends of Cancer Research, and the Food and Drug Administration have recommended modernization of clinical trial eligibility criteria throughout the field of oncology in an effort to broaden enrollment and increase generalizability of results (48-52). In the present study, we propose data-driven methods to streamline eligibility criteria for

first-line precision medicine DLBCL RCTs to permit inclusion of high-risk patients who require urgent therapy and thereby increase the likelihood of identifying positive effects of novel treatment. In addition, we characterize the genetic landscape of this eligible, high-risk patient population to facilitate pairing of study populations enriched in recently defined genetic subtypes with appropriate targeted drugs in an effort to account for the significant genetic heterogeneity of DLBCL in first-line clinical trial design.

METHODS

Aims

The present study has two principal aims.

Aim 1: Define a data-driven methodology for streamlining eligibility criteria in first-line DLBCL RCTs to increase enrollment of patients with high-risk disease.

Aim 2: Characterize prevalent genetic alterations in the eligible, high-risk patient group to facilitate pairing of genetic subtypes with effective precision therapies in first-line DLBCL RCTs.

Study design

The study design for Aim 1 is novel and leverages eligibility criteria from previous first-line DLBCL RCTs in conjunction with large-scale DLBCL patient data sets to demonstrate methods for reducing the quantity of enrollment criteria while retaining the capacity to target high-risk patient groups. Specifically, piloted methods analyzed patient outcomes following patient selection using modernized criteria for IPI score and IPI risk factors in comparison with patient outcomes following patient selection using criteria for IPI score and IPI risk factors in previous first-line DLBCL RCTs. We then identified reduced subsets of modernized criteria for IPI risk factors that exhibited high sensitivity for selecting high-risk patient groups that had been targeted in past first-line DLBCL RCTs.

To address Aim 2, the patient population identified as high-risk and eligible in Aim 1 using modernized criteria was categorized into genetic subtypes based on patient-specific genetic

profiles in anticipation of future first-line DLBCL RCTs designed to match appropriate precision therapies to individual-level molecular markers.

Study population

The study population comprises patients with DLBCL from eight large DLBCL patient data sets representing institutional, regional, and national patient groups. Data sets include an Emory University DLBCL patient cohort (n = 329), cohorts from three recent DLBCL genomics publications (the Reddy *et al.* cohort [n = 761], the Schmitz *et al.* cohort [n = 361], and the Chapuy *et al.* cohort [n = 264]), and four Surveillance, Epidemiology, and End Results (SEER) Program data sets (national SEER 1975–2016 [n = 6,095], SEER Georgia 1975–2016 [n = 591], SEER Iowa 1975–2016 [n = 684], and national SEER-Medicare 2002–2009 [n = 11,066]). SEER data sets were produced using SEER*Stat 8.3.6 and the SEER 1975–2016 Research Database File.

Patients were included for analysis if the corresponding data set contained complete patient data for IPI and for the IPI risk factors age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and Ann Arbor stage when those data types were present in the data set. Only the Emory University DLBCL cohort and the Schmitz *et al.* cohort included data for all four criteria. For the remaining data sets, "complete case" was defined as the greatest possible combination of IPI, age at diagnosis, ECOG PS, and Ann Arbor stage attainable. While the Reddy *et al.* and Chapuy *et al.* cohorts included data for all four criterion categories, values for ECOG PS and Ann Arbor stage were dichotomized according to ECOG PS ≤ 1 versus ≥ 2 and stage $\leq$ II versus $\geq$ III and were insufficiently granular to address all variations in eligibility.

The national SEER, SEER Georgia, and SEER Iowa data sets included data for IPI score, age at diagnosis, and Ann Arbor stage. SEER-Medicare included data for age at diagnosis and Ann Arbor stage. Logistic regression was used to assess for bias due to complete case analysis within each data set.

Analytic plan

Enumerating inclusion and exclusion criteria

We enumerated inclusion and exclusion criteria from 19 DLBCL RCTs spanning the R-CHOP era from the initial investigation of R-CHOP to recent studies comparing R-CHOP with R-CHOP + X treatment regimens. Study-specific enrollment criteria were drawn from study protocols, study publications, and ClinicalTrials.gov. Study protocols were prioritized as the resource for eligibility criteria when available. Enrollment criteria from the 19 RCTs were then tabulated according to criterion categories. For example, the enrollment criteria "creatinine ≤ 1.7 mg/dL" and "creatinine ≤ two times the upper limit of normal" were both tabulated under the criterion category "renal function." Criterion categories were defined as Common if they were present in ≥ 2/3 of selected DLBCL RCTs, Moderately Common if included in ≥ 1/3 but < 2/3 of the 19 studies, and Uncommon if present in < 1/3 of DLBCL RCTs.

Criterion categories selected for piloted methodology

To pilot data-driven methods for streamlining eligibility criteria, we selected the four Common criterion categories IPI, age at diagnosis, ECOG PS, and Ann Arbor stage for inclusion in the present analysis. These criterion categories enabled the comparison of using the full IPI score representing the sum total of five risk factors in patient selection versus subsets of the IPI score

composed of various combinations of age at diagnosis, ECOG PS, and Ann Arbor stage in patient selection. In other words, the piloted methodology tests whether the full IPI is necessary to identify high-risk, eligible patients, or whether a reduced assessment using selected components of the IPI score could target a similar high-risk group with less extensive requirements for data collection and potentially more rapid assessment and enrollment into clinical trials. The remaining IPI risk factors (elevated serum LDH and extranodal involvement by DLBCL) were insufficiently represented in study data sets and were not included in analysis.

Analysis of study-specific criteria over time

We analyzed study-specific criteria for IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage to identify trends for each criterion category over time. Linear regression models were used to assess for association between study-specific lower bounds, upper bounds, and ranges for each criterion over time throughout the R-CHOP era. Statistical analyses for these steps and all other statistical methods in the study were conducted using R version 3.6.2.

Determination of the proportion of patients eligible from each population data set based on the study-specific eligibility criteria for each study

Within each data set, we determined patient eligibility status for each of the 19 DLBCL RCTs using study-specific criteria for IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage. We compared the percentage of eligible patients for each study across data sets using chi-square tests or Fisher's exact test when appropriate. The proportions of patients included in the eligible group for a given study were compared between data sets that included the same data types (for example, eligibility percentages in the Reddy *et al.* cohort were compared with percentages in

the Chapuy *et al.* cohort because both data sets contained values for IPI score and age at diagnosis and lacked values for ECOG PS and Ann Arbor stage). We determined significance using a significance level of 0.0025 after applying a Bonferroni correction to account for comparison between 19 DLBCL RCTs and subsequent comparison of patient eligibility using proposed criteria for 20 total comparisons.

Determination of study-specific outcomes

We assessed study-specific outcomes for each of the 19 DLBCL RCTs across data sets to determine whether study-specific eligibility criteria for IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage effectively targeted high-risk patient groups. Within a given data set and for a given DLBCL RCT, we stratified patients according to eligibility status based on study-specific criteria, and we compared PFS and OS for the eligible and ineligible groups using Cox proportional hazards models to determine hazard ratios (HRs) for eligible versus ineligible status for each of the 19 studies. We analyzed HRs to identify trends over time associated with survival in target populations for first-line DLBCL RCTs in the R-CHOP era. Analysis of study-specific outcomes using Cox proportional hazards models was repeated across data sets. Available data for survival analysis included PFS data in the Schmitz *et al.* and Chapuy *et al.* cohorts and OS data in the Reddy *et al.*, Schmitz *et al.*, Chapuy *et al.*, SEER national, SEER Georgia, SEER Iowa, and SEER-Medicare cohorts.

Proposed criteria

The piloted data-driven methods tested whether a reduced subset of modernized criteria could target the same high-risk patient groups that were targeted by past studies using a greater number

of criteria. Determination of whether a subset of modernized criteria would be effective required first proposing modernized criteria for the full complement of criterion categories used in the present analysis. Specifically, we proposed modernized criteria for the total IPI score as well as modernized criteria for age at diagnosis, ECOG PS, and Ann Arbor stage (Figure 1) in order to permit comparison of patient selection using total IPI score with patient selection using subsets of IPI risk factors. Modernized criteria were selected based on historical trends and clinical judgment in the interest of promoting inclusion of high-risk patient groups in first-line clinical trials for DLBCL. Proposed criteria included IPI score ≥ 2, age at diagnosis ≥ 18 years, ECOG PS 0–2, and Ann Arbor stage II–IV.

Determination of patient eligibility using the proposed eligibility criteria

Within each data set, we determined patient eligibility status using proposed criteria for IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage. We compared the percentage of eligible patients using proposed criteria across data sets using chi-square tests.

Determination of outcomes using the proposed eligibility criteria

We analyzed PFS and OS based on eligibility status using proposed criteria to determine whether proposed criteria effectively risk-stratified patients by eligibility status and targeted the high-risk group for enrollment. Survival analysis was conducted using Cox proportional hazards models to determine HRs for eligible versus ineligible status.

Comparison of outcomes using prior criteria and proposed criteria

To determine whether the proposed limited eligibility criteria targeted similar high-risk patient groups as were targeted in prior DLBCL RCTs, we used the eight DLBCL patient data sets and compared outcomes for the eligible populations defined using study-specific criteria from each of the 19 DLBCL RCTs with outcomes from the eligible population defined using the proposed limited criteria. We performed survival analysis using Cox proportional hazards models for clustered events to account for instances of paired data when the same study participant was eligible using study-specific criteria and proposed criteria.

Identification of parsimonious subsets of proposed criteria for effective targeting of high-risk patient groups

We tested whether combinations of proposed criteria for the IPI risk factors age at diagnosis, ECOG PS, and Ann Arbor stage could target high-risk groups that were identified as eligible for previous first-line DLBCL RCTs using study-specific criteria for total IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage. For each of the 19 DLBCL RCTs, we constructed 2x2 contingency tables wherein the columns stratified patients according to eligibility status using study-specific criteria and the rows stratified patients according to eligibility status using each of the 15 possible combinations of proposed criteria in turn. This approach generated 15 total 2x2 tables for each of the 19 DLBCL RCTs (data sets lacking data for IPI score, ECOG PS, or Ann Arbor stage had fewer possible combinations of proposed criteria). For example, for a given study and within a given patient cohort, we constructed a 2x2 table comparing eligibility status using all study-specific criteria versus eligibility status using the proposed criterion for age at diagnosis alone. For the same study and same cohort, we then constructed a second 2x2 table using the same study-specific criteria to stratify patients across columns but stratified patients

across rows using proposed criteria for ECOG PS rather than age at diagnosis. We repeated these steps for all individual proposed criteria, all combinations of two proposed criteria, all combinations of three proposed criteria, and lastly for the full complement of proposed criteria including IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage. Each 2x2 table provided values for "true positives," representing patients deemed eligible using study-specific criteria and proposed criteria; "true negatives," representing patients who were ineligible using study-specific and proposed criteria; "false positives," representing patients who were eligible using the proposed criteria but not eligible using study-specific criteria; and "false negatives," representing patients who were ineligible using the proposed criteria but were eligible using study-specific criteria. Each 2x2 table enabled calculation of the sensitivity and specificity for a combination of proposed criteria to identify the target population selected using study-specific criteria for a given prior first-line DLBCL RCT. We plotted sensitivities and specificities for each combination of proposed criteria in receiver operator characteristic (ROC) plots and identified the combinations of proposed criteria with the highest sensitivity and specificity for selecting the target population for each prior first-line DLBCL RCT. These steps were repeated across all 19 DLBCL RCTs for all patient cohorts as able given the data available for analysis in each data set.

Characterizing the genetic landscape of the eligible patient population

We next analyzed the genetic alterations common to the eligible patient subgroup when using the proposed criteria for determination of eligibility status. We linked eligible patients from the Reddy *et al.* and Chapuy *et al.* cohorts with individual-level genetic alterations available in each genomic data set and then calculated the prevalence of genetic alterations by mutation in the

eligible group. To assess for enrichment of genetic alterations, we compared the mutation prevalence in the eligible group with mutation prevalence in the overall patient cohort for the Reddy *et al.* and Chapuy *et al.* data sets using chi-square and Fisher's exact tests when necessary, with a false-discovery rate at threshold q = 0.05. For the Chapuy *et al.* patient cohort, we further categorized eligible patients according to genetic clusters defined in the Chapuy *et al.* data set to determine the prevalence of alterations common to eligible patients within each genetic subtype. We assessed for significant enrichment of genetic alterations after categorization into genetic subtypes by comparing the mutation prevalence in the eligible group in each subtype with mutation prevalence in the overall cohort using chi-square and Fisher's exact tests when necessary, with a false-discovery rate at threshold q = 0.05. The Schmitz *et al.* genomic data set did not provide sufficient patient-level genetic information for analysis of common genetic alterations in the eligible patient group.

RESULTS

Study population

We analyzed eight large DLBCL patient data sets representing institutional, regional, and national DLBCL patient populations (Table 1). Mean age for each data set ranged from 55.6 years in the Emory cohort (standard deviation [SD] 16.4 years) to 77.5 years in the national SEER-Medicare cohort (SD 7.0 years), with the SEER-Medicare population notably older than patients in all other data sets. The percentage of female participants in data sets ranged from 41% (SEER Georgia) to 54% (national SEER-Medicare), with more male patients than female patients in all data sets other than SEER-Medicare. Patients with better performance status (i.e., lower ECOG PS values) were represented in greater number than patients with poor performance status in all four data sets that included ECOG PS data. The percentage of patients with favorable performance status (ECOG PS values of 0 or 1) ranged from 58% in the Schmitz *et al.* cohort to 86% in the Chapuy *et al.* cohort, reflecting a notably more fit patient population in the latter data set. Ranges for IPI score values were similar across data sets that included IPI score. The Emory cohort had the greatest percentage of patients with low-risk disease, with 42% of patients having an IPI score of 0 or 1. The SEER Iowa data set had the greatest number of patients with high-risk disease, with 26% of patients exhibiting an IPI score of 4 or 5. Ann Arbor stage ranges were also similar across data sets. Frequency of patients with localized disease (Ann Arbor stage I or II) ranged from 37% in the SEER Iowa cohort to 51% in the SEER-Medicare data set. Frequency of patients with advanced stage disease (Ann Arbor stage III or IV) ranged from 49% in the SEER-Medicare cohort to 63% in the SEER Iowa data set. All data sets other than SEER-Medicare had a greater percentage of patients with advanced stage disease than localized disease.

We performed logistic regression to determine whether IPI score, age at diagnosis, ECOG PS, or Ann Arbor stage was significantly associated with missingness across data sets. IPI score was associated with missingness in the Emory cohort ($P < 0.001$), with a higher IPI associated with an increased likelihood of being a complete case, and in the Schmitz *et al.* data set ($P < 0.001$), with IPI scores of 0, 1, and 3 poorly represented in incomplete cases. Age at diagnosis was associated with missingness in the SEER national ($P < 0.001$) and SEER Iowa ($P < 0.001$) data sets, with a greater proportion of patients receiving a DLBCL diagnosis at either end of the age spectrum among incomplete cases, and in the SEER-Medicare data set ($P < 0.001$), with a significantly younger population of SEER-Medicare patients represented in complete cases. ECOG PS was associated with missingness in the Emory cohort ($P < 0.001$) with worse performance status enriched among complete cases. Ann Arbor stage was associated with missingness in the SEER national ($P < 0.001$), SEER Georgia ($P < 0.001$), and SEER Iowa ($P < 0.001$) data sets, with patients possessing higher-stage disease exhibiting an increased likelihood of being a complete case.

Enumerating inclusion and exclusion criteria

The 19 DLBCL RCTs selected for analysis ranged in accrual start year from 1998–2017 (Table 2), spanning the R-CHOP era. Selected RCTs were broadly categorized according to study therapy type, with the 13 earlier studies (LNH-98.5 through R-CHOP-14 vs. R-CHOP-21) investigating chemoimmunotherapy regimens incorporating rituximab, and the six more recent studies (MAIN through POLARIX) investigating precision medicine alternatives to R-CHOP in the form of R-CHOP + X. We tabulated all inclusion and exclusion criteria from each of the 19 trials. Across all 19 trials, there were 451 total enrollment criteria, with an average of 23.7

enrollment criteria per study (SD 6.3, range 14–37). From the tabulated criteria, we identified 52 discrete criterion categories (Table 3). Among the 52 criterion categories, 18 categories were Common (present in ≥ 2/3 of selected DLBCL RCTs), 11 criterion categories were Moderately Common (present in ≥ 1/3 but < 2/3 of the studies), and 23 categories were Uncommon (present in < 1/3 of studies). Five criterion categories were included in 100% of studies: age at diagnosis, tumor histology, history of other malignancies, prior DLBCL treatment, and renal function.

Analysis of study-specific criteria over time

We examined trends for study-specific criteria spanning the R-CHOP era (Figure 1). We used linear regression models to assess for association between study-specific criteria for IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage with study accrual start year across the 19 studies included in analysis. The upper bound ($P = 0.016$, $R^2 = 0.42$) and lower bound ($P = 0.035$, $R^2 = 0.34$) for the IPI range in a given study were significantly associated with study accrual start year, with both the upper and lower bounds for IPI score increasing over time. The lower bound ($P = 0.030$, $R^2 = 0.52$) and overall range ($P < 0.001$, $R^2 = 0.51$) for age at diagnosis were significantly associated with study accrual start year, with an increasing upper age limit for study inclusion and increasing overall age range observed over time. No statistically significant associations were observed between enrollment criteria for ECOG PS or Ann Arbor stage and study accrual start year across the R-CHOP era.

Determination of the proportion of patients eligible from each population data set based on the study-specific eligibility criteria for each study

We determined individual-level eligibility status within each data set based on study-specific enrollment criteria for 19 DLBCL RCTs and calculated the percentage of patients in each data set meeting eligibility criteria for each study (Figure 2). Across all data sets, study-specific criteria for study LNH03-1B most frequently yielded the lowest percentage of eligible cohort participants, with eligibility ranging from 0% in the SEER-Medicare data set to 15.2% in the Emory cohort. The eligibility criteria for the NHL13, R-CHOP-14 vs. R-CHOP-21, and PYRAMID studies most frequently included the greatest percentage of patients among the eligible cohort for a given data set, with eligibility ranging from 83.1% for all three studies in the Schmitz *et al.* data set to 100% for all three studies in the Chapuy *et al.*, SEER Georgia, and SEER-Medicare data sets.

Among data sets containing values for all four types of study criteria, only the ECOG 4494/CALGB 9793 study yielded statistically different proportions of eligible patients between data sets. Among data sets that included data for IPI score, age at diagnosis, and Ann Arbor stage, the proportions of patients eligible for the studies ECOG-ACRIN 1412 and ROBUST were significantly different. Among data sets containing values for only IPI score and age at diagnosis, the proportions of eligible patients for eight studies were statistically different, including LNH-98.5, ECOG 4494/CALGB 9793, LNH-98.3, RICOVER-60, MInT, DSHNHL 2002-1, ANZINTER3, and LNH03-6B.

Determination of study-specific outcomes

We determined HRs based on eligibility status (eligible versus ineligible) for the 19 DLBCL RCTs across all data sets containing outcomes data permitting survival analysis (Figure 3). In

assessment of OS, the MInT, LNH03-1B, and LNH03-2B studies consistently exhibited statistically significant HRs that indicated superior outcomes among the eligible population across data sets containing OS data. Significant HRs for the MinT study ranged from 0.20 (SEER Iowa, 95% CI 0.10–0.44) to 0.41 (SEER Georgia, 95% CI 0.27–0.62). Significant HRs for the LNH03-1B study ranged from 0.11 (Schmitz *et al.* cohort, 95% CI 0.03–0.47) to 0.40 (SEER Georgia, 95% CI 0.20–0.77). Significant HRs for the LNH03-2B study ranged from 0.27 (SEER Georgia, 95% CI 0.13–0.55) to 0.55 (Reddy *et al.* cohort, 95% CI 0.33–0.94).

The ECOG 4494/CALGB 9793, ECOG-ACRIN 1412, and ROBUST studies showed statistically significant inferior survival among the eligible patient group in comparison with ineligible patients in terms of OS. Significant HRs for the ECOG 4494/CALGB 9793 study ranged from 1.66 (Schmitz *et al.* cohort, 95% CI 1.07–2.59) to 2.76 (SEER Iowa, 95% CI 1.86–4.09). Significant HRs for the ECOG-ACRIN 1412 study ranged from 1.37 (SEER-Medicare, 95% CI 1.30–1.45) to 3.58 (Chapuy *et al.* cohort, 95% CI 2.06–6.23). Significant HRs for the ROBUST study ranged from 1.73 (SEER Georgia, 95% CI 1.30–2.31) to 3.58 (Chapuy *et al.* cohort, 95% CI 2.06–6.23).

Regarding PFS, outcomes for the eligible group versus the ineligible group in the MInT and LNH03-1B studies exhibited statistically significant HRs, indicating superior survival among the eligible patient group. In the Schmitz *et al.* data set, the HR for the MInT study was 0.33 (95% CI 0.19–0.57). The HR for the LNH03-1B study was 0.19 (95% CI 0.07–0.53). Among data sets with PFS data, only the Schmitz *et al.* data set yielded HRs showing an eligible population with superior survival compared with outcomes for the ineligible group.

Lastly, assessment of PFS across data sets showed that ECOG-ACRIN 1412 and ROBUST most consistently demonstrated HRs showing significantly inferior survival for eligible patients. Significant HRs for the ECOG-ACRIN 1412 study ranged from 1.75 (Schmitz *et al.* cohort, 95% CI 1.16–2.62) to 2.55 (Chapuy *et al.* cohort, 95% CI 1.61–4.05). Significant HRs for the ROBUST study ranged from 2.55 (Chapuy *et al.* cohort, 95% CI 1.61–4.05) to 2.60 (Schmitz *et al.* cohort, 95% CI 1.66–4.09). As with OS, recent studies exhibited a trend toward worse outcomes for eligible patient groups in comparison with ineligible patients for PFS.

Determination of patient eligibility using the proposed eligibility criteria

We determined patient eligibility using the proposed criteria across all data sets (Figure 2). The proportion of patients meeting eligibility requirements based on proposed criteria ranged from 43% (Emory cohort) to 69% (SEER-Medicare cohort). We compared proportions of eligible patients across data sets that shared common data types. The proportion of patients eligible in data sets using IPI score, age at diagnosis, and Ann Arbor stage was significantly different after applying a Bonferroni correction ($P < 0.001$). In comparing the proportion of eligible patients by proposed criteria across data sets that included IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage vs. only IPI score and age at diagnosis, the proportions of eligible patients by proposed criteria were not significantly different.

Determination of outcomes using the proposed eligibility criteria

Proposed criteria led to statistically significant HRs (eligible versus ineligible) indicating inferior survival in the eligible group by both OS and PFS across all data sets that included data

permitting survival analysis (Figure 3). The HRs for OS among the eligible group using proposed criteria ranged from 1.37 (SEER-Medicare, 95% CI 1.30–1.45) to 3.58 (Chapuy *et al.* cohort, 95% CI 2.06–6.23). The HRs for PFS among the eligible group using proposed criteria ranged from 1.74 (Schmitz *et al.* cohort, 95% CI 1.16–2.62) to 2.55 (Chapuy *et al.* cohort, 95% CI 1.61–4.05).

Comparison of outcomes using prior criteria and proposed criteria

We compared outcomes of each eligible group using study-specific criteria with the eligible group using proposed criteria across all data sets (Figure 4). Survival analysis using Cox proportional hazards models with clustered events was conducted such that the eligible group using proposed criteria was the reference group, with resulting HRs indicating the HR for OS or PFS for the eligible group using study-specific criteria in comparison with the eligible group using proposed criteria. The eligible group using proposed criteria consistently exhibited inferior survival by OS and PFS in comparison with the overwhelming majority of eligible groups using study-specific criteria across all data sets. Notably, outcomes by OS and PFS for the eligible populations from the ECOG-ACRIN 1412 and ROBUST studies were consistently not significantly different in comparison with outcomes for the eligible group using proposed criteria across all data sets, with the exception of the ROBUST trial using the SEER-Medicare cohort.

Identification of parsimonious subsets of proposed criteria for effective targeting of high-risk patient groups

We developed ROC plots illustrating the capacity for subsets of proposed criteria to target patients who were eligible for prior DLBCL RCTs (Figure 5). Across studies and across data

sets, subsets of proposed criteria that did not include IPI score consistently identified the target population for prior first-line DLBCL RCTs with high sensitivity. For example, in the Emory data set, use of the proposed criteria for age at diagnosis, ECOG PS, and Ann Arbor stage identified the target population in 14 out of 19 prior DLBCL RCTs with a sensitivity of 0.75 or greater and identified five target populations with a sensitivity of 1.0. Using proposed criteria for age at diagnosis, ECOG PS, and Ann Arbor stage in the Schmitz *et al.* cohort yielded similar trends, identifying the target population in 15 out of 19 prior DLBCL RCTs with sensitivity of 0.75 or greater and five target populations with a sensitivity of 1.0. Notably, use of proposed criteria for age at diagnosis, ECOG PS, and Ann Arbor stage identified patients in the target populations for the ECOG-ACRIN 1412 and ROBUST studies—studies that consistently targeted high-risk groups for inclusion—with sensitivities greater than 0.7 across the two data sets that provided all four data types for analysis.

Addition of IPI score to the proposed criteria increased specificity, and specificity without inclusion of the IPI score was inconsistent and often low. For example, in the Schmitz *et al.* cohort, use of all four proposed criteria yielded the highest specificity across all 19 studies, including targeting the population from seven studies with a specificity of 1.0. Removing IPI score and using proposed criteria for age at diagnosis, ECOG PS, and Ann Arbor stage reduced specificity, identifying the target population from 11 of the 19 studies with a specificity of 0.5 or less.

Subsets of proposed criteria that did not include IPI score often yielded the greatest combined sensitivity and specificity of all possible combinations for a given data set. For the Emory cohort,

maximum combined sensitivity and specificity was achieved without use of IPI score for eight out of 19 studies. For the Schmitz *et al.* cohort, combined sensitivity and specificity was maximized using subsets of proposed criteria without IPI score for nine out of 19 DLBCL RCTs. This trend was consistent across data sets, with combined sensitivity and specificity maximized by subsets of proposed criteria that did not include IPI for at least seven of the 19 studies in any one data set.

Characterizing the genetic landscape of the eligible patient population

Prevalent mutations for the eligible patient population from the Reddy *et al.* cohort (Figure 6) included alterations in *MLL2* (present in 28% of eligible patients), *MYD88* (19%), *PIM1* (19%), and *HIST1H1E* (19%). Prevalence of the most frequently observed mutations in the eligible group was consistent with the genes most commonly affected in the overall Reddy *et al.* cohort, though the proportion of participants exhibiting highly prevalent alterations was moderately lower in the overall population in comparison with the eligible population. No genes were significantly enriched in the eligible population in the Reddy *et al.* cohort when using proposed criteria to determine eligibility status.

The most common genetic alterations in the eligible Chapuy *et al.* cohort (Figure 7) included 18q amplification (present in 33% of eligible patients), *PIM1* mutation (32%), 7p amplification (29%), and 18p amplification (28%). Once again, observed prevalence was consistent with common genetic alterations in the overall population. Comparison of mutation prevalence using false-discovery rate yielded similar results to those seen with the Reddy *et al.* data set, indicating

no genes occurring at significantly different prevalence in the eligible population using proposed criteria.

When patients in the Chapuy *et al.* cohort were categorized by genetic cluster according to the consensus clusters identified in the Chapuy *et al.* study (Figures 8–12), prevalent mutations in Cluster 1 included a structural variant in *BCL6* (present in 59% of eligible patients in Cluster 1 versus 15% in the total Chapuy *et al.* cohort), *B2M* mutation (35% versus 9%), and 5p amplification (35% versus 15%). Prevalent alterations in Cluster 2 included 17p deletion (71% versus 22%), *TP53* mutation (69% versus 21%), and 2p16.1 amplification (57% versus 27%). Common alterations in the eligible group for Cluster 3 included a *BCL2* structural variant (73% versus 21%), *BCL2* mutation (70% versus 20%), and *KMT2D* mutation (46% versus 25%). The most prevalent alterations in Cluster 4 included mutations in *SGK1* (57% versus 15%), *HIST1H1C* (48% versus 16%), and *PIM1* (48% versus 30%). For participants who were eligible by proposed criteria and categorized into Cluster 5, common alterations included 18q amplification (74% versus 33%), 3q amplification (67% versus 25%), and *PIM1* mutation (52% versus 30%). Comparison of mutation prevalence between genetic subtypes and the overall Chapuy *et al.* study population using a false-discovery rate threshold of $q = 0.05$ revealed significant enrichment in a *BCL6* structural variant and mutations in *B2M*, *BCL10*, *TNFAIP3*, and *NOTCH2* in Cluster 1; 17p deletion, *TP53* mutation, 9p21.3 deletion, and 9q21.13 deletion in Cluster 2; *BCL2* structural variant and mutation as well as mutations in *EZH2* and *GNA13* in Cluster 3; *SGK1* and *RHOA* mutations in Cluster 4; and amplifications in 18q, 3q, 18p, and 3p in Cluster 5.

DISCUSSION

In the present study, we define data-driven methods for identifying parsimonious subsets of eligibility criteria capable of targeting high-risk patient groups for enrollment in first-line DLBCL RCTs. We utilized large DLBCL patient data sets to demonstrate that the use of eligibility criteria from prior first-line DLBCL RCTs can 1) identify previous studies that effectively targeted high-risk groups, 2) confirm successful targeting of high-risk groups using proposed modern criteria, and 3) characterize the expected genomic alterations and clinical outcome for patient groups selected by these eligibility criteria. Moreover, we illustrate evidence-based techniques employing ROC plots to identify parsimonious subsets of proposed criteria capable of identifying high-risk patients with high sensitivity. Use of subsets of proposed criteria in this manner has important implications for selection of criteria for preliminary eligibility screening in an effort to streamline enrollment for patients with high-risk disease who require urgent therapy in first-line RCTs for DLBCL. In addition, we demonstrate the use of large DLBCL genomic data sets to link patient-specific genetic profiles with eligibility status and thereby characterize the genetic makeup of the eligible cohort for future first-line DLBCL RCTs. Our results highlight the importance of defining therapeutic subgroups enriched in genetic subtypes for the appropriate pairing of mutational profiles with precision medicine drugs in treating DLBCL. Taken together, our work provides a data-driven road map from development of enrollment criteria for patient selection to stratification of the ensuing eligible cohort based on genetic subtype, and will facilitate development of first-line precision medicine clinical trials effectively targeting high-risk DLBCL patients with unmet treatment needs.

While multiple evidence-based approaches for modernizing eligibility criteria for clinical trials in oncology have been conducted in recent years pertaining to minimum age thresholds (48), comorbid organ dysfunction (49), HIV status (51), and other considerations, no studies to our knowledge have utilized data-driven techniques similar to the methods employed in the present study. Moreover, studies employing data-driven techniques for the development of novel eligibility criteria for clinical trials in hematological malignancies are lacking. The present study addresses an urgent research gap with important ramifications for the inclusion of high-risk patients in future first-line studies for DLBCL.

Analysis of study-specific criteria over time indicate that first-line DLBCL RCTs have increasingly targeted high-risk groups for inclusion. Significant linear associations between the upper and lower bounds for IPI score with study accrual start year illustrate a progression in first-line DLBCL RCTs over the R-CHOP era: early first-line RCTs designed to determine the efficacy of R-CHOP targeted patients with low-risk disease, while more recent studies designed to identify novel precision therapies with improved performance in comparison with R-CHOP target high-risk groups. Analysis of trends for age at diagnosis, ECOG PS, and Ann Arbor stage showed a significant trend toward inclusion of all adults rather than specific age groups, as well as trends toward targeting lower ECOG PS (i.e., patients more likely to tolerate study therapies) and advanced-stage disease. Examination of calculated study eligibility across data sets consistently shows that first-line DLBCL RCTs have become more inclusive over the R-CHOP era, driven predominantly by 1) criteria for age at diagnosis targeting most or all adult patients with DLBCL and 2) a trend toward wider ranges for IPI score in enrollment criteria. In general, recent DLBCL RCTs are more likely to have targeted adult patients with advanced stage, high-

risk disease who are capable of tolerating study drugs. Prior investigation of DTI in relation to patient outcomes has shown that recent studies fail to enroll the high-risk patients they ostensibly target for inclusion, emphasizing the need for streamlined enrollment criteria that maximize inclusion of high-risk groups in first-line DLBCL RCTs.

Survival analysis conducted to identify study-specific outcomes shows a trend toward effective risk-stratification based on eligibility status for the majority of DLBCL RCTs included in analysis, with the eligible patient group exhibiting inferior outcomes relative to the ineligible group. Recent studies were particularly likely to target high-risk patient populations, with five out of the six DLBCL RCTs that investigated R-CHOP + X treatment modalities observed to target higher-risk groups across multiple data sets. Notably, the MInT, LNH03-1B, and LNH03-2B studies identified eligible patients with superior outcomes rather than inferior outcomes, consistent with study-specific enrollment criteira for the MInT, LNH03-1B, and LNH03-2B studies targeting younger patients with low-risk disease. Results from Cox proportional hazards models further indicate that eligibility criteria for first-line DLBCL RCTs in the precision medicine era effectively target high-risk groups for enrollment despite the failure to successfully enroll high-risk patients requiring urgent therapy in the ensuing study population.

Proposed criteria are in line with historical trends for identification of eligible patients. Determination of eligibility status by proposed criteria showed that the majority of patients targeted using proposed criteria were also identified as eligible for the nine more recent DLBCL RCTs analyzed in the present study. Beginning with the study NHL13 and including all studies in the precision medicine era, all or nearly all of patients who were eligible using proposed

criteria were also eligible using study-specific criteria, indicating significant overlap between the eligible group using proposed criteria and the eligible cohorts for recent precision medicine clinical trials. Additionally, survival analysis for patients targeted using proposed criteria indicate that proposed criteria effectively risk-stratified patients by eligibility status across multiple data sets, with eligible patients exhibiting significantly inferior survival. Proposed criteria thereby achieve the desired result of targeting high-risk patient groups for future DLBCL RCTs.

We compared outcomes of eligible groups targeted using proposed criteria with outcomes of eligible groups defined using study-specific criteria to further determine whether proposed criteria targeted similar high-risk groups targeted by prior DLBCL RCTs. HRs using both OS and PFS across data sets indicate that the eligible group using proposed criteria exhibited inferior survival in comparison with most target populations from prior DLBCL RCTs. Only the ECOG-ACRIN 1412 and ROBUST studies from the R-CHOP + X era targeted populations with similarly poor survival in comparison with outcomes from populations targeted using proposed criteria. These results provide further evidence that use of proposed criteria in future DLBCL RCTs will effectively target the patient populations with high-risk disease that prior DLBCL RCTs were designed to enroll.

Our piloted methods for defining a parsimonious subset of proposed eligibility criteria illustrate that the full IPI score is not necessary to identify patients who were eligible for prior DLBCL RCTs with high sensitivity. We have thus demonstrated that 1) proposed criteria are capable of targeting high-risk groups, and 2) subsets of proposed criteria can identify high-risk groups with

high sensitivity. Taken together, these findings have important clinical implications for streamlining enrollment of high-risk patients who require urgent therapy. Development of a subset of eligibility criteria comprising readily attainable clinical factors with high sensitivity for identifying patients who will ultimately be eligible using all eligibility criteria (i.e., after the patient has proceeded through all pre-enrollment testing to determine eligibility status) will enable clinicians to rapidly assess the likelihood of eligibility for patients who require urgent therapy without necessitating assessment of all eligibility criteria for that patient. Patients who fail to meet the screening criteria for eligibility can proceed to standard therapy without participation in the clinical trial, while patients who do meet screening criteria can begin a bridging cycle of standard chemoimmunotherapy and proceed with the remaining steps for eligibility assessment. If deemed eligible after completion of the full eligibility assessment, the patient can then begin study therapy (or continue with R-CHOP if randomized into the control arm of the RCT). Implementation of our data-driven methodology in future trial design has the potential to significantly increase enrollment of high-risk patients who require urgent therapy and thereby increase the likelihood of identifying true effects of novel precision treatment for a DLBCL patient population known to exhibit poor survival with R-CHOP alone.

For both the Reddy *et al.* and Chapuy *et al.* patient cohorts, selection of high-risk patients based on eligibility status using proposed criteria failed to significantly enrich the resulting eligible group in genetic alterations, indicating that selection based on clinical markers for high-risk disease such as IPI score is insufficient to adequately enrich the study population in targetable mutations. Subsequent patient stratification based on genetic subtypes using the consensus clusters proposed in the Chapuy *et al.* study successfully enriched genetic subgroups in

mutations common to each subtype, highlighting the importance of subtype-specific investigational arms in future clinical trials for DLBCL. Our results build the foundation for DLBCL trial designs incorporating NGS methods for determination of patient-specific genetic subtype followed by categorization of each patient into subtype-specific trials comparing the R-CHOP control with R-CHOP plus a precision therapy tailored to a particular genetic subtype. Work by our group (53) and others (7, 45) has begun pairing genetic profiles with targeted therapies in preparation of future trials incorporating similar adaptive trial techniques.

Strengths of the present study include use of multiple large DLBCL data sets representing institutional, regional, and national populations. Additionally, incorporation of inclusion and exclusion criteria from 19 clinical trials throughout the R-CHOP era places proposed criteria in context with pivotal trials spanning the recent history of DLBCL care. Analytic techniques for the identification of parsimonious subsets of criteria are novel and robust and are readily applicable to clinical trials for other malignancies and disease states beyond oncology. In particular, the use of ROC plots to identify subsets of eligibility criteria capable of identifying eligible patients with high sensitivity represents an innovative statistical application with significant potential to streamline enrollment in clinical trials. Lastly, our analysis incorporated data from recent genomic studies, ensuring that study results reflect the forefront of the current understanding of DLBCL genomics in preparation for future first-line DLBCL RCTs.

Limitations include complete-case analysis with significant associations between study clinical factors and missingness. In addition, the data sets selected for analysis included a limited number of variables, allowing for development of piloted methods using only data for IPI score, age at

diagnosis, ECOG PS, and Ann Arbor stage. A given clinical trial will utilize many more criteria than the four selected for analysis in the present study. Notably, the limited number of data types across data sets prevented use of imputation methods to account for missingness in the complete-case analysis. Data types were also not present in all available data sets, with only the Emory cohort and the Schmitz *et al.* cohort allowing for full analysis using all four data types. Lastly, not all data sets included survival data, further limiting application of the full methodology with available data.

Future directions include application of piloted methods to a robust DLBCL data set. Validation in a robust data set incorporating significantly more data types will allow for more accurate estimation of target populations using study-specific and proposed criteria and will permit true identification of a parsimonious subset of eligibility criteria that are readily applied in a routine clinical setting. Additionally, our group is currently working to define comprehensive proposed criteria for future first-line DLBCL RCTs based on expert recommendation. We are conducting a Delphi-method survey with participation from 17 nationally recognized clinical investigators across the US to develop consensus, streamlined criteria for first-line clinical trials in DLBCL. Consensus criteria from the survey will replace proposed criteria in future applications of our data-driven methods. Finally, we will replicate our analysis with other lymphoma subtypes to further modernize criteria in clinical trials for hematologic diseases.

It is our hope that the data-driven methods piloted in the present study will streamline eligibility criteria and facilitate enrollment of high-risk patient groups in first-line DLBCL RCTs. We believe that this research lays the groundwork for precision medicine clinical trials capable of

pairing patient-specific genetic profiles with tailored targeted therapy in an effort to define the next generation of DLBCL care for patients with high-risk disease.

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TABLES

Table 1. Patient demographics and baseline disease characteristics from all data sets

Characteristic	Emory University cohort (n = 329)	Reddy *et al.* cohort (n = 761)	Schmitz *et al.* cohort (n = 361)	Chapuy *et al.* cohort (n = 264)	SEER (national) (n = 6,095)	SEER (Georgia) (n = 591)	SEER (Iowa) (n = 684)	SEER-Medicare (national) (n = 11,066)
Age (continuous), y								
Mean	55.6	60.8	60.4	65.7	63.5	61.9	63.8	77.5
SD	16.4	15.5	15.0	11.5	16.0	15.9	15.4	7.0
Median	55.8	62.4	62.0	67.0	65.0	65.0	65.0	77.0
Range	17–92	3–93	14–92	26–88	3–99	18–97	12–99	66–104
Age (categorical), y								
< 60	195 (59)	328 (43)	156 (43)	54 (21)	2,211 (36)	235 (40)	244 (36)	0 (0)
60–69	55 (17)	204 (27)	92 (26)	109 (41)	1,440 (24)	135 (23)	171 (25)	1,690 (15)
≥ 70	79 (24)	229 (30)	113 (31)	101 (38)	2,444 (40)	221 (37)	269 (39)	9,376 (85)
Sex*								
Missing	6 (2)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Female	145 (45)	329 (43)	156 (43)	119 (45)	2,636 (43)	245 (41)	315 (46)	5,954 (54)
Male	178 (55)	431 (57)	205 (57)	145 (55)	3,459 (57)	346 (59)	369 (54)	5,112 (46)
ECOG performance status*								
Missing	0 (0)	0 (0)	0 (0)	0 (0)	6,095 (100)	591 (100)	684 (100)	11,066 (100)
0–1	240 (73)	546 (72)	208 (58)	228 (86)	–	–	–	–
≥ 2	89 (27)	215 (28)	153 (42)	36 (14)	–	–	–	–
IPI score*								
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	11,066 (100)
0 or 1	139 (42)	244 (32)	113 (31)	90 (34)	1,954 (32)	207 (35)	189 (28)	–
2	76 (23)	180 (24)	90 (25)	59 (22)	1,342 (22)	143 (24)	159 (23)	–
3	52 (16)	192 (25)	84 (23)	78 (30)	1,323 (22)	115 (19)	156 (23)	–
4 or 5	62 (19)	145 (19)	74 (21)	37 (14)	1,476 (24)	126 (21)	180 (26)	–
Ann Arbor stage*								
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
I/II	133 (40)	297 (39)	164 (45)	115 (44)	2,452 (40)	246 (42)	256 (37)	5,662 (51)
III/IV	196 (60)	464 (61)	197 (55)	149 (56)	3,643 (60)	345 (58)	428 (63)	5,404 (49)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; SD, standard deviation
*Percentages were calculated within each group after subtraction of missing data.

Table 2. Randomized controlled trials included in analysis (n = 19)

Study identifier	Accrual start year	n	Treatment
LNH-98.5 (54-56)	1998	399	CHOP-21 vs. R-CHOP-21
ECOG 4494/CALGB 9793 (57)	1998	546; 342	R1: CHOP-21 vs. R-CHOP-21; R2: observation vs. rituximab
LNH-98.3 (58)	1999	474; 269	R1: ACE vs. ACVBP*; R2: observation vs. rituximab
RICOVER-60 (59)	2000	1,215	6 cycles CHOP-14 vs. 8 cycles CHOP-14 vs. 6 cycles R-CHOP-14 vs. 8 cycles R-CHOP-14
MInT (60, 61)	2000	796	CHOP-like vs. R-CHOP-like
DSHNHL 2002-1 (62)	2003	261	R-CHOEP-14 vs. R-MegaCHOEP followed by ASCT
ANZINTER3 (63)	2003	224	R-CHOP-21 vs. R-miniCEOP
LNH03-1B (64)	2003	223	ACVBP** vs. R-ACVBP**
LNH03-2B (65)	2003	379	R-CHOP-21 vs. R-ACVBP**
LNH03-6B (66)	2003	600	R-CHOP-14 vs. R-CHOP-21
NHL13 (67)	2004	681	Observation vs. rituximab
PIX203 (68)	2005	122	R-CHOP-21 vs. R-CPOP
R-CHOP-14 vs. R-CHOP-21 (69)	2005	1,062	R-CHOP-14 vs. R-CHOP-21
MAIN (70)	2007	748	R-CHOP-14 or R-CHOP-21 vs. RA-CHOP-14 or RA-CHOP-21
PYRAMID (27)	2009	206	R-CHOP-21 vs. VR-CHOP
ECOG-ACRIN 1412 (41)	2013	280	R-CHOP-21 vs. R2CHOP
PHOENIX (71)	2013	844	R-CHOP-21 vs. R-CHOP + ibrutinib
ROBUST (31)	2015	570	R-CHOP-21 vs. R-CHOP + lenalidomide
POLARIX (72)	2017	875	R-CHOP-21 vs. R-CHP + polatuzumab vedotin

Abbreviations: ACE, doxorubicin, cyclophosphamide, and etoposide; ACRIN, American College of Radiology Imaging Network; ACVBP*, doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone; ACVBP**, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; ANZINTER, Intergruppo Italiano Linforni; ASCT, autologous stem cell transplantation; CALGB, Cancer and Leukemia Group B; CHOP-21, cyclophosphamide, doxorubicin, vincristine, and prednisone given every 21 days; DSHNHL, German High-Grade Lymphoma Study Group; ECOG, Eastern Cooperative Oncology Group; HDT, high-dose therapy; LNH, lymphomes non Hodgkiniens; MAIN, MabThera plus Avastin in aggressive non-Hodgkin lymphoma; MInT, MabThera International Trial; NHL, non-Hodgkin lymphoma; PIX, pixantrone; PYRAMID, Personalized Lymphoma Therapy: Randomized Study of Proteasome Inhibition in Non-GCB DLBCL; R-ACVBP**, ACVBP** plus rituximab; R-CHOEP-14, rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone given every 14 days; R-CHOP-21, rituximab + CHOP given every 21 days; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CPOP, rituximab, cyclophosphamide, pixantrone, vincristine, and prednisone; R-MegaCHOEP, R-CHOEP with dose-escalated cyclophosphamide, etoposide, and doxorubicin; R-miniCEOP, rituximab, cyclophosphamide, epirubicin, vinblastine, and prednisone; R1, 1st randomization; R2, 2nd randomization; R2CHOP, R-CHOP plus lenalidomide; RA-CHOP, R-CHOP plus bevacizumab; RICOVER-60, rituximab with CHOP over age 60 years; VR-CHOP, R-CHOP plus bortezomib

Table 3. Criterion categories in 19 diffuse large B-cell lymphoma randomized controlled trials

Common criterion categories (present in > 66% of RCTs; n = 18 categories)	Number of studies with criterion category n (%)	Moderately Common criterion categories (present in 33%–66% of RCTs; n = 11 categories)	Number of studies with criterion category n (%)	Uncommon criterion categories (present in < 33% of RCTs; n = 23 categories)	Number of studies with criterion category n (%)
Age (years)	19 (100)	HCV status	11 (58)	Pulmonary function	6 (32)
Histology	19 (100)	Participation in other study	11 (58)	Sex	6 (32)
History of other malignancies	19 (100)	Other neurologic pathology	10 (53)	Surgical history	6 (32)
Prior DLBCL treatment	19 (100)	Immunologic history	9 (47)	Diabetes mellitus	5 (26)
Renal function	19 (100)	Other infectious disease status	9 (47)	Patient compliance	5 (26)
Hepatic function	18 (95)	Imaging	8 (42)	Adult patient under tutelage	4 (21)
HIV status	18 (95)	Minimum life expectancy	8 (42)	Uncontrolled hypertension	4 (21)
Cardiac function	17 (89)	Contraindicated therapies	7 (37)	Hemoglobin (g/dL)	3 (16)
CNS involvement by lymphoma	16 (84)	History of transformed lymphoma	7 (37)	History of PTLD	3 (16)
Performance status	16 (84)	Male reproductive	7 (37)	Hypercoagulability	3 (16)
Contraindications to study therapy	15 (79)	Psychiatric history	7 (37)	Organ transplant history	3 (16)
IPI score	15 (79)			Bone marrow infiltration	2 (11)
Female reproductive	14 (74)			Coagulopathy	2 (11)
HBV status	14 (74)			Gastrointestinal function	2 (11)
Other organ dysfunction	14 (74)			HTLV-1 status	2 (11)
Platelet count (platelets/μL)	14 (74)			CGA score	1 (5)
WBC count (cells/μL)	14 (74)			LDH level	1 (5)
Ann Arbor stage	13 (68)			Orthopedic history	1 (5)
				Physical exam findings	1 (5)
				Rheumatologic disease	1 (5)
				Substance use	1 (5)
				Tumor invasion of blood vessels	1 (5)
				Vaccination history	1 (5)

Abbreviations: CGA, Comprehensive Geriatric Assessment; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus 1; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PTLD, post-transplant lymphoproliferative disorder; RCT, randomized controlled trial; WBC, white blood cell

FIGURES

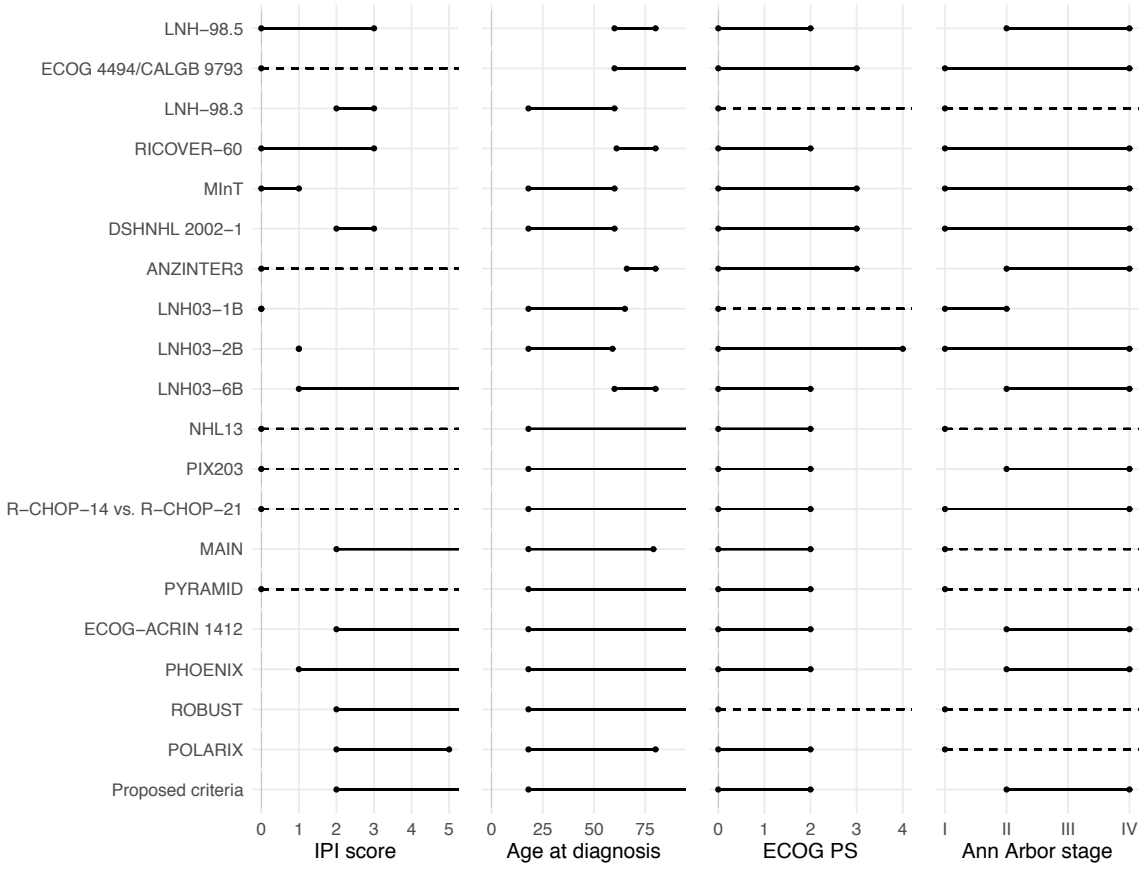
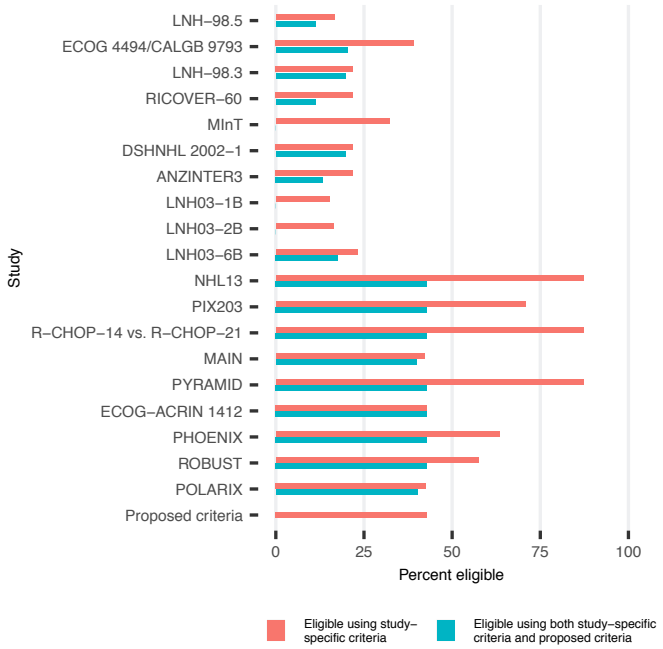


Figure 1. Eligibility criteria trends for IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage in DLBCL RCTs spanning the R-CHOP era. Eligibility criteria ranges for IPI score, age at diagnosis, ECOG PS, and Ann Arbor stage across 19 RCTs for DLBCL included in analysis and in proposed criteria. Dashed lines indicate studies that did not include a given criterion in enrollment criteria. Studies are arranged chronologically by study accrual start year with the earliest studies at the top. Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; RCT, randomized controlled trial

A



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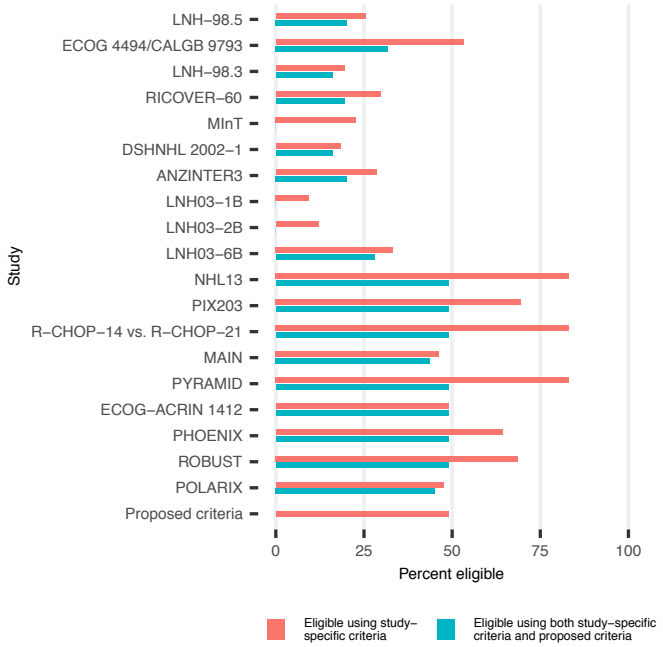
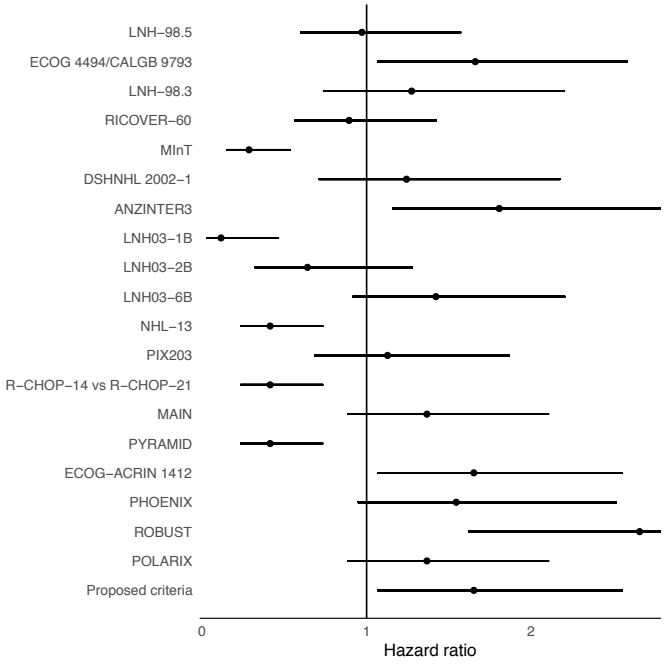


Figure 2. Study eligibility in the Emory University and Schmitz *et al.* DLBCL cohorts using study-specific and proposed criteria. Eligibility by percentage of overall patients in a given cohort using study-specific and proposed criteria in (A) the Emory University DLBCL cohort and (B) Schmitz *et al.* DLBCL cohort. Red columns indicate percentage of eligible patients using study-specific or proposed criteria. Blue columns indicate the percentage of patients who are eligible for a given study using study-specific criteria and are also eligible using proposed criteria. Abbreviations: DLBCL, diffuse large B-cell lymphoma

A



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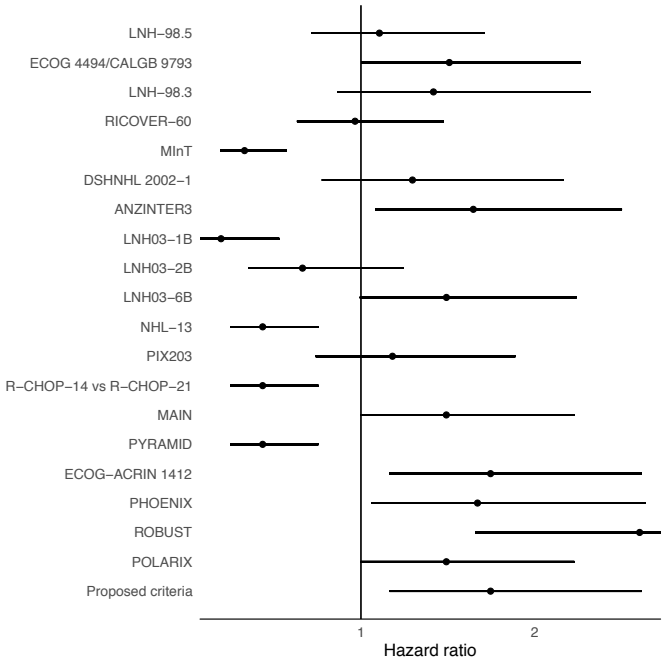

Figure 3. Study specific HRs for OS and PFS comparing eligible and ineligible groups across 19 DLBCL RCTs and using proposed criteria. HRs (eligible versus ineligible) among the Schmitz *et al.* cohort for (A) OS and (B) PFS using study-specific eligibility criteria for 19 DLBCL RCTs spanning the R-CHOP era and using proposed criteria. Studies are arranged chronologically beginning from the top by study accrual start year. Abbreviations: DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial

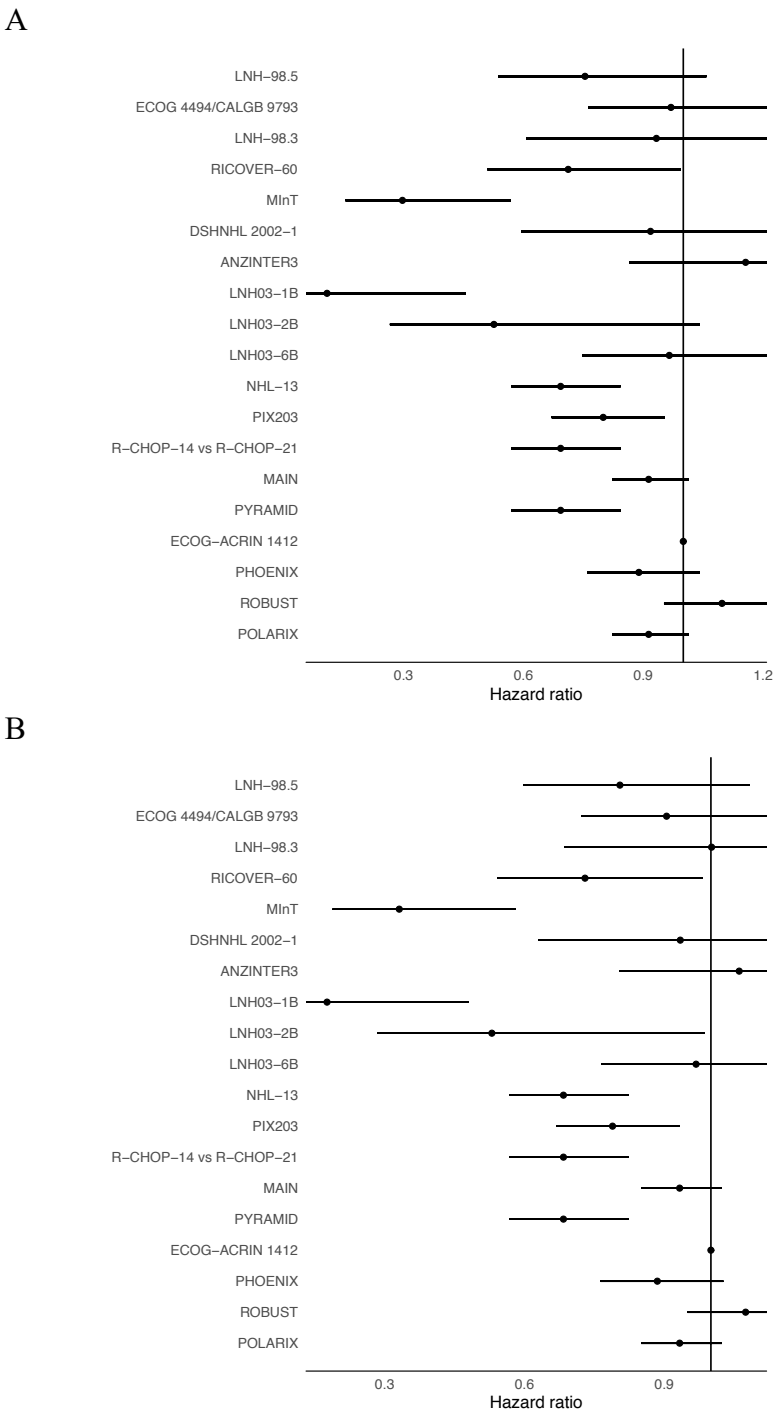

Figure 4. Cox proportional hazards results comparing eligible groups from 19 DLBCL RCTs with eligible groups defined using proposed criteria. HRs (eligible using study-specific criteria versus eligible using proposed criteria) among the Schmitz *et al.* cohort for (A) OS and (B) PFS for 19 DLBCL RCTs spanning the R-CHOP era. Studies are arranged chronologically beginning from the top by study accrual start year. Abbreviations: DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial

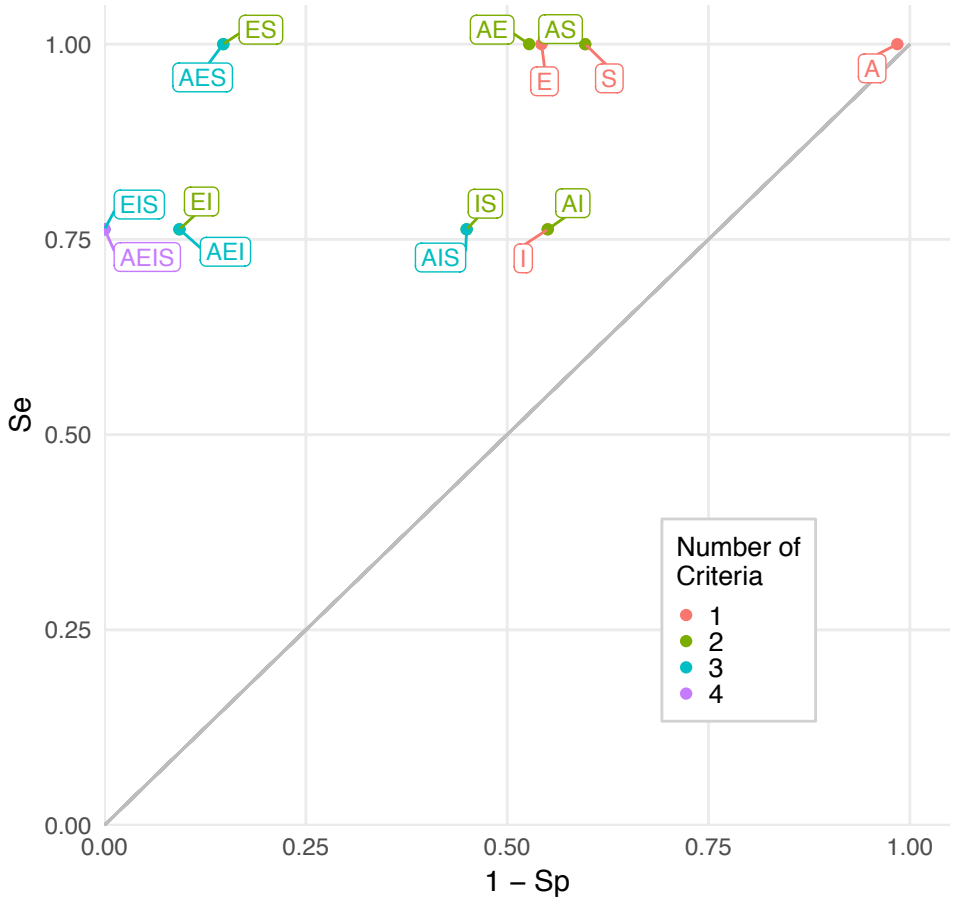

Figure 5. ROC plot illustrating the capacity of combinations of proposed criteria to identify patients eligible for the PHOENIX trial in the Schmitz *et al.* cohort. ROC plot depicting sensitivity and specificity for all possible combinations of proposed criteria to identify patients who met study-specific eligibility criteria for the PHOENIX trial. Abbreviations: A, age at diagnosis; E, Eastern Cooperative Oncology Group performance status; I, International Prognostic Index score; ROC, receiver operating characteristic;
S, Ann Arbor stage; Se, sensitivity; Sp, specificity

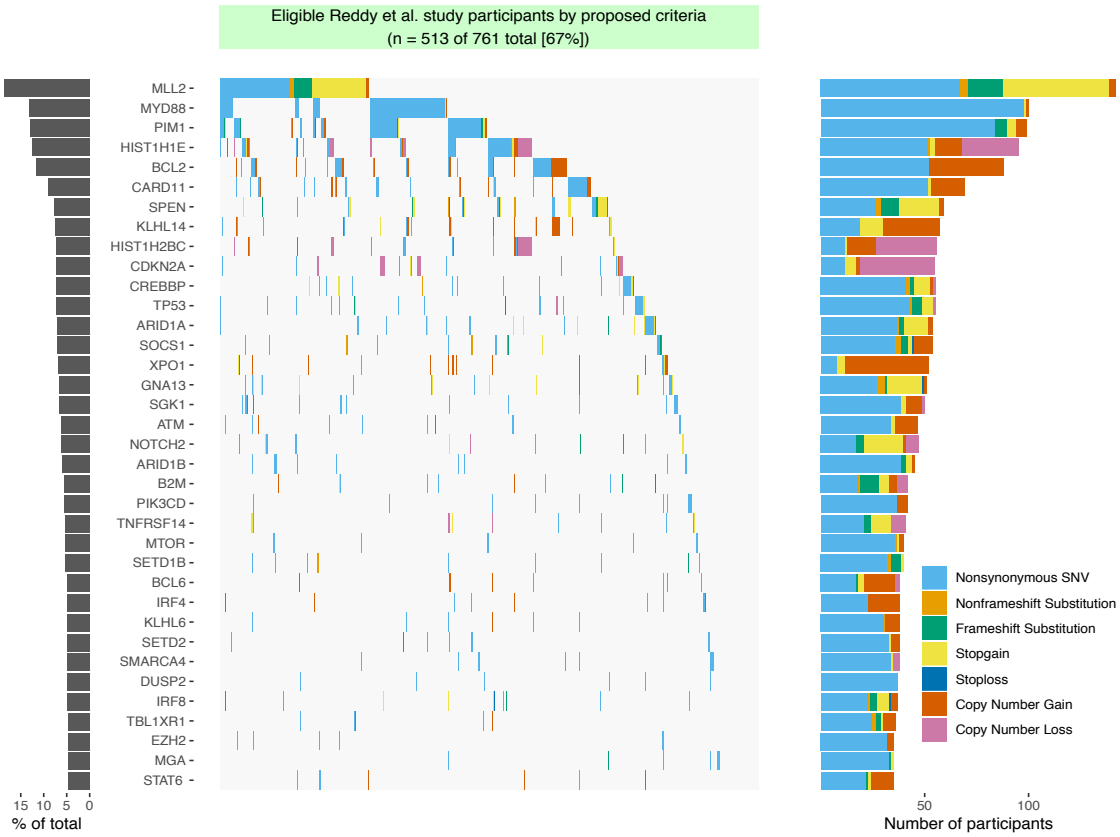

Figure 6. Impact of eligibility criteria on genetic alteration prevalence in the Reddy *et al.* data set. Left: percentage of study participants who 1) were eligible according to proposed criteria and 2) had a mutation in the corresponding gene; middle: mutational heatmap for the eligible patient population according to proposed criteria in the Reddy *et al.* cohort data set; right: prevalence of genetic alterations in each gene by number of study participants along with indications for type of genetic alteration.

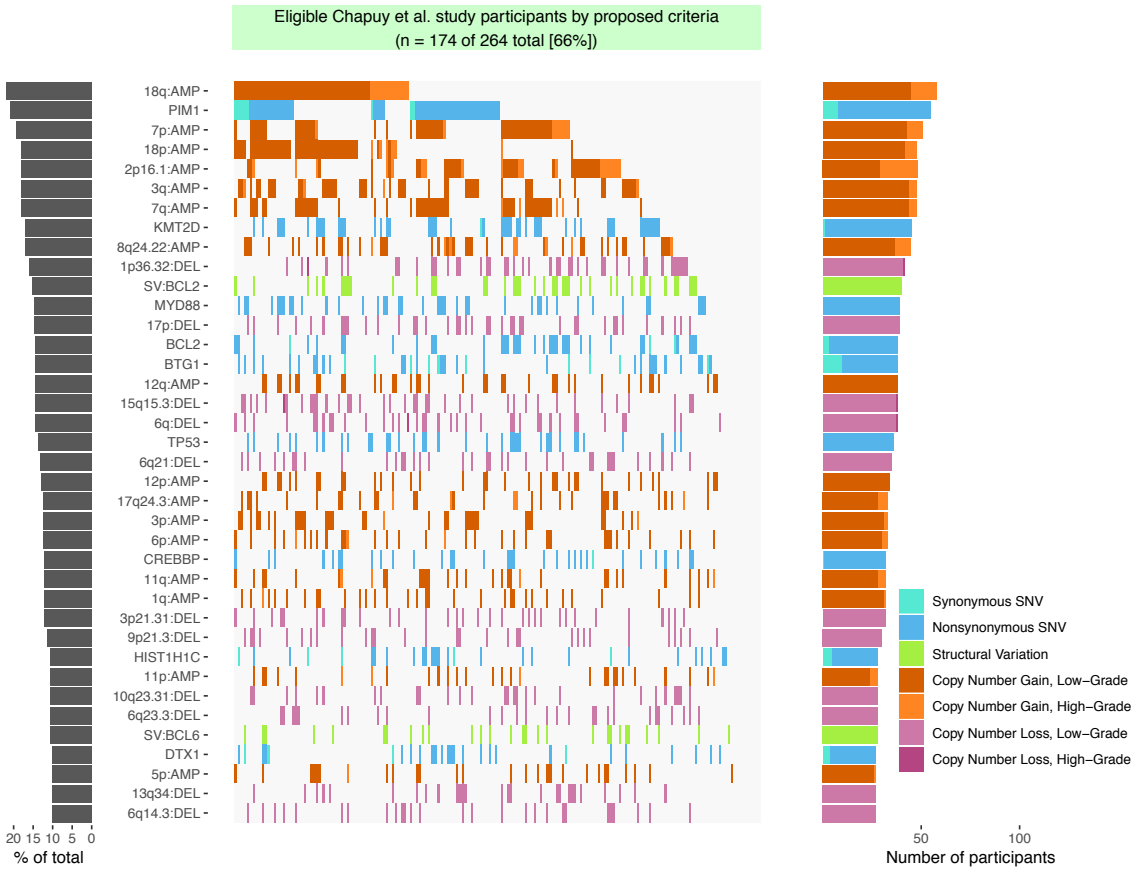

Figure 7. Impact of eligibility criteria on genetic alteration prevalence in the Chapuy *et al.* data set. Left: percentage of study participants who 1) were eligible according to proposed criteria and 2) had a mutation in the corresponding gene. Middle: mutational heatmap for the eligible patient population according to proposed criteria in the Chapuy *et al.* cohort data set. Right: prevalence of genetic alterations in each gene by number of study participants along with indications for type of genetic alteration.

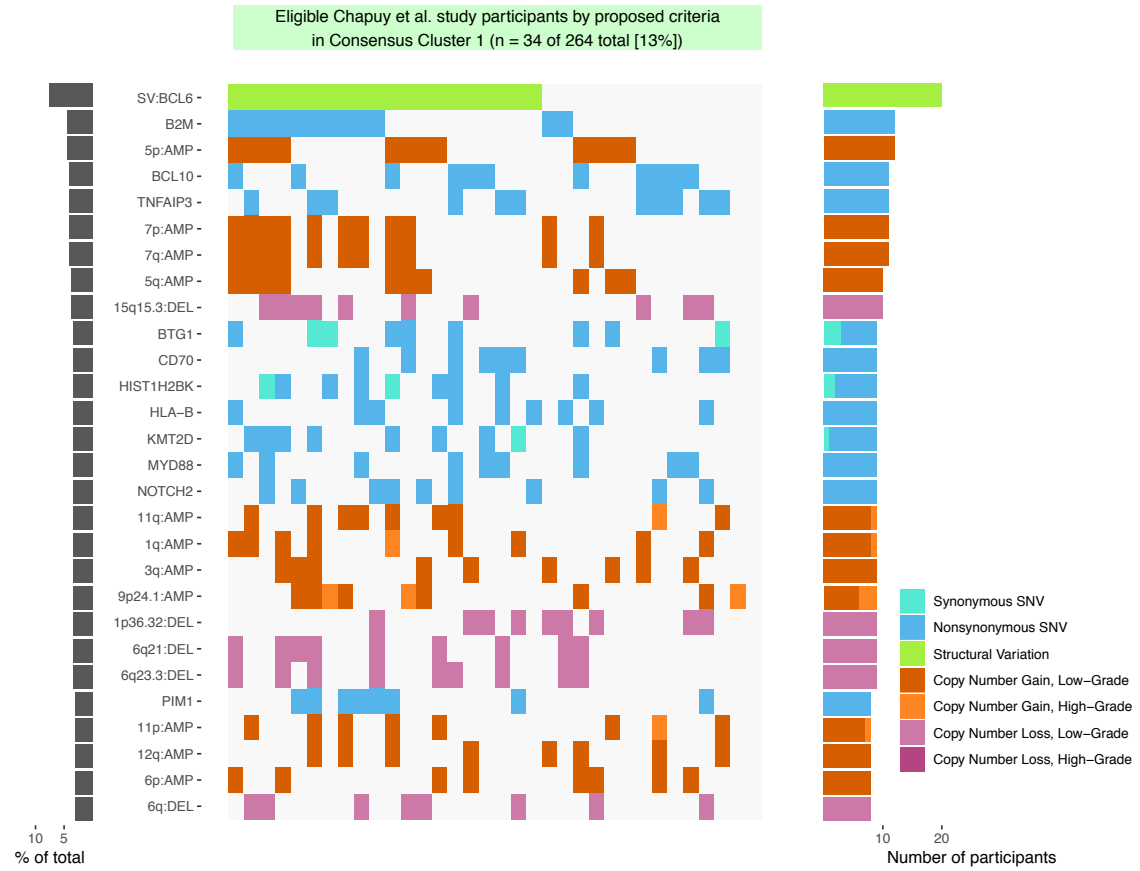

Figure 8. Impact of eligibility criteria on genetic alteration prevalence for patients in genetic Cluster 1 in the Chapuy *et al.* data set. Left: percentage of study participants who 1) were eligible according to proposed criteria, 2) categorized into genetic cluster one, and 3) had a mutation in the corresponding gene. Middle: mutational heatmap for the eligible patient population in genetic cluster one according to proposed criteria in the Chapuy *et al.* cohort data set. Right: prevalence of genetic alterations in each gene by number of study participants along with indications for type of genetic alteration.

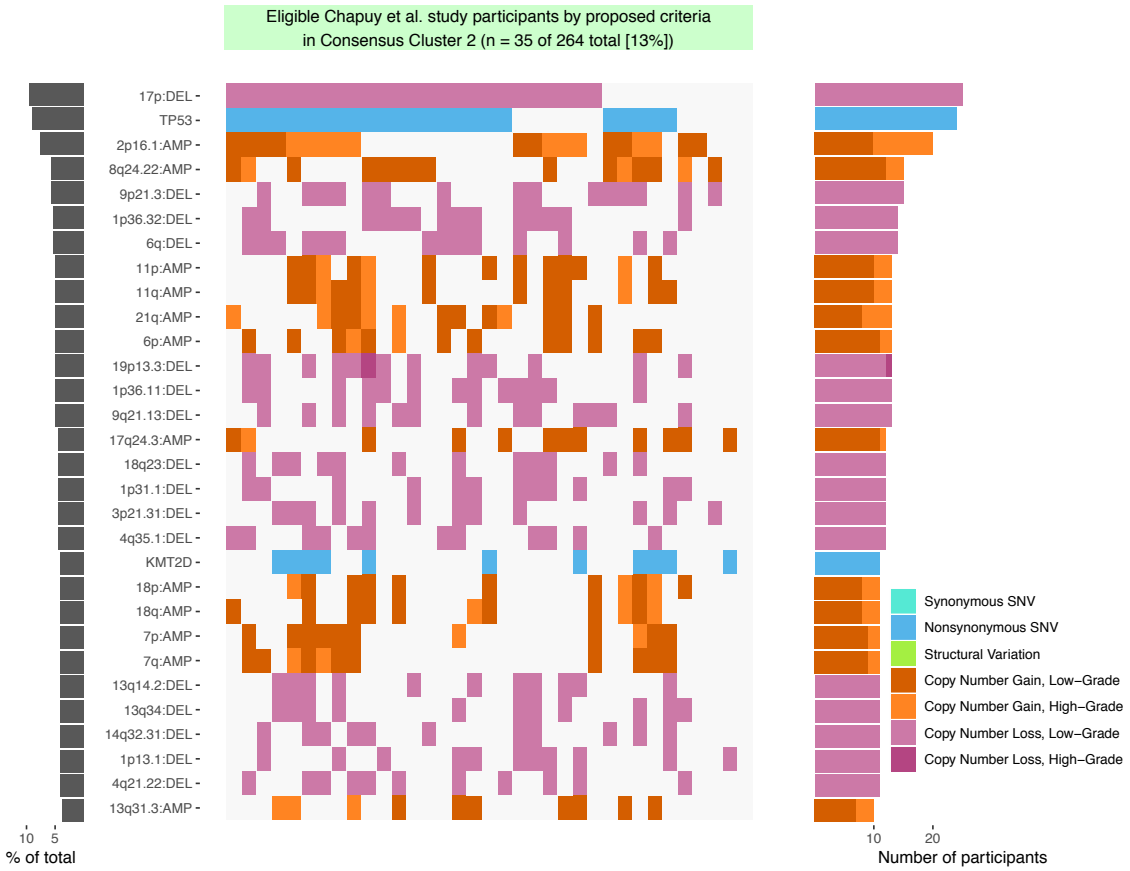

Figure 9. Impact of eligibility criteria on genetic alteration prevalence for patients in genetic Cluster 2 in the Chapuy *et al.* data set. Left: percentage of study participants who 1) were eligible according to proposed criteria, 2) categorized into genetic cluster two, and 3) had a mutation in the corresponding gene. Middle: mutational heatmap for the eligible patient population in genetic cluster two according to proposed criteria in the Chapuy *et al.* cohort data set. Right: prevalence of genetic alterations in each gene by number of study participants along with indications for type of genetic alteration.

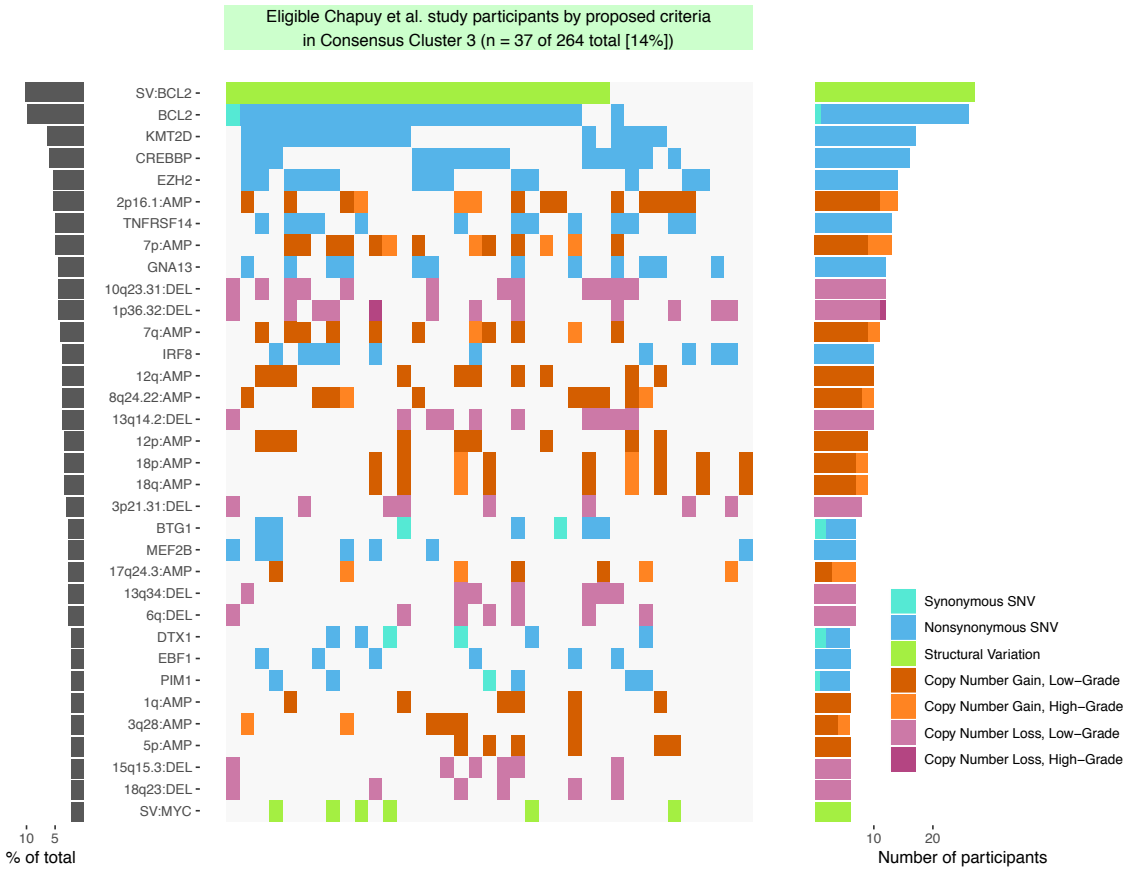

Figure 10. Impact of eligibility criteria on genetic alteration prevalence for patients in genetic Cluster 3 in the Chapuy *et al.* data set. Left: percentage of study participants who 1) were eligible according to proposed criteria, 2) categorized into genetic cluster three, and 3) had a mutation in the corresponding gene Middle: mutational heatmap for the eligible patient population in genetic cluster three according to proposed criteria in the Chapuy *et al.* cohort data set. Right: prevalence of genetic alterations in each gene by number of study participants along with indications for type of genetic alteration.

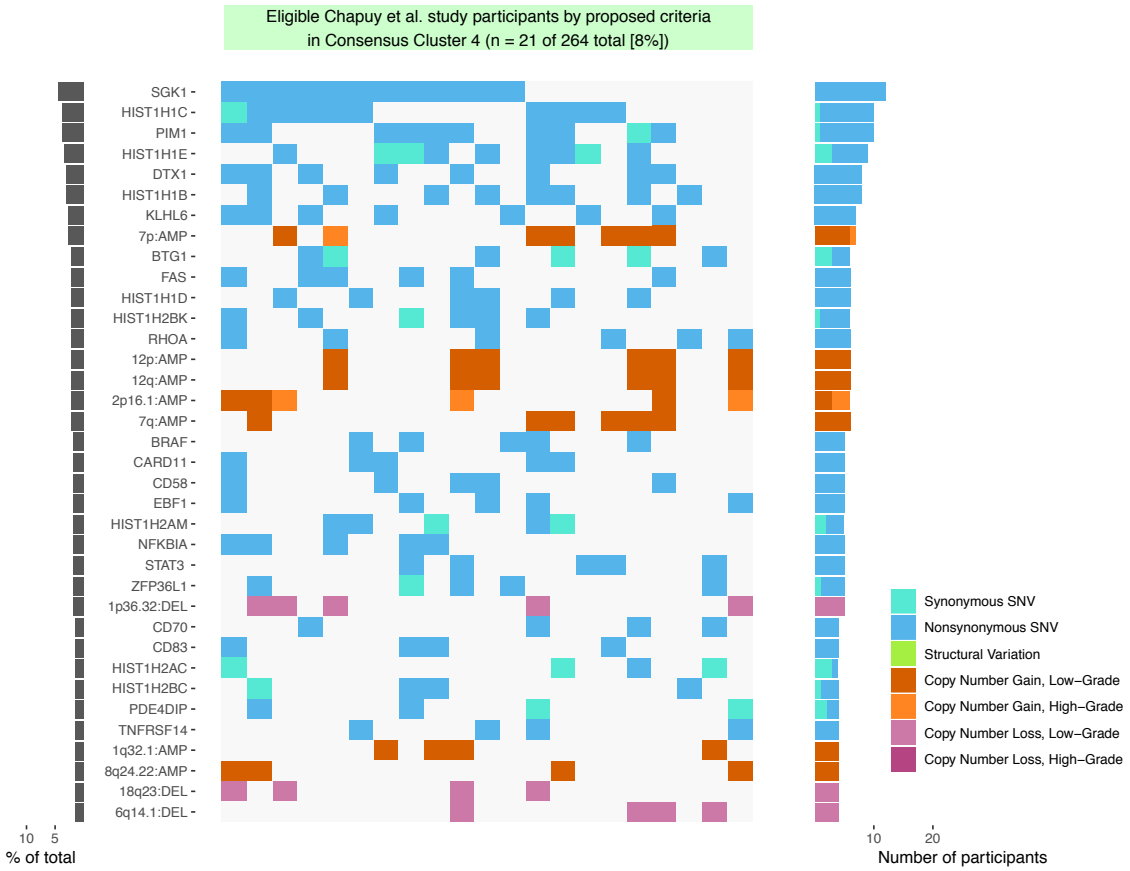

Figure 11. Impact of eligibility criteria on genetic alteration prevalence for patients in genetic Cluster 4 in the Chapuy *et al.* data set. Left: percentage of study participants who 1) were eligible according to proposed criteria, 2) categorized into genetic cluster four, and 3) had a mutation in the corresponding gene. Middle: mutational heatmap for the eligible patient population in genetic cluster four according to proposed criteria in the Chapuy *et al.* cohort data set. Right: prevalence of genetic alterations in each gene by number of study participants along with indications for type of genetic alteration.

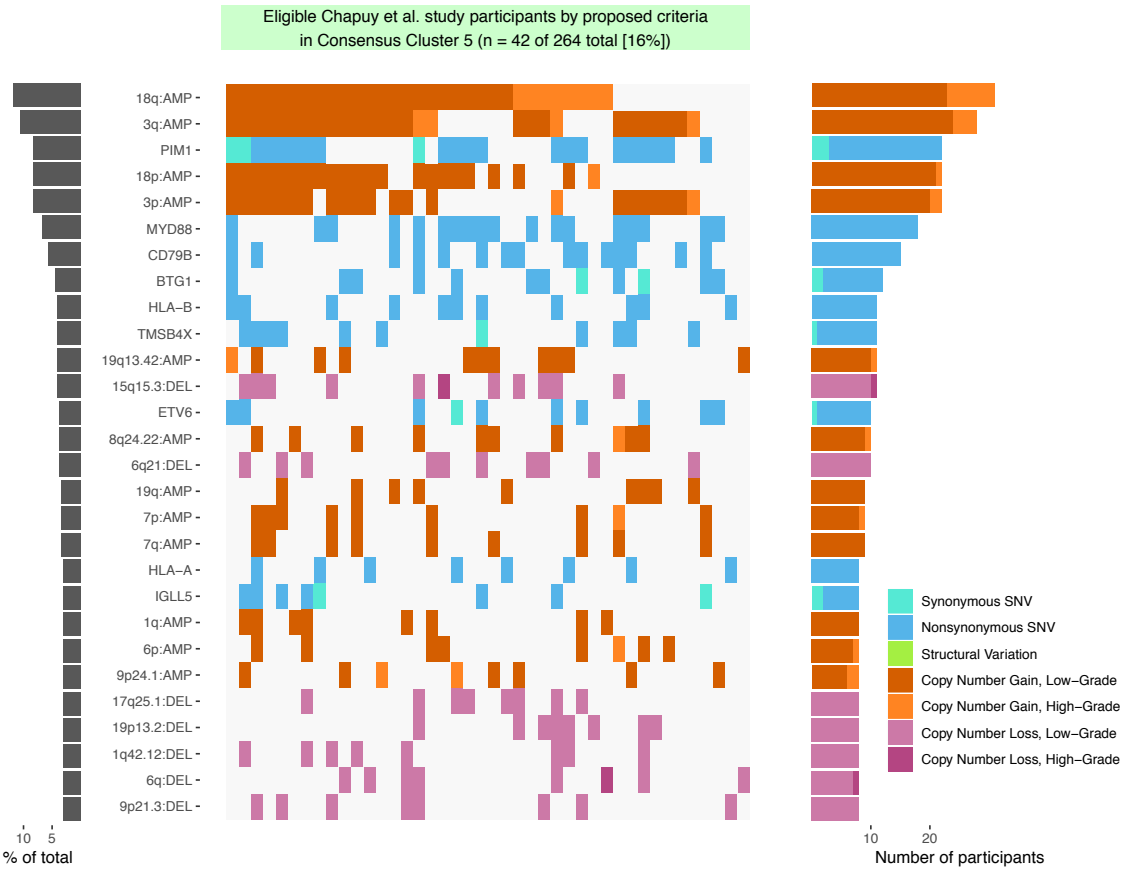

Figure 12. Impact of eligibility criteria on genetic alteration prevalence for patients in genetic Cluster 5 in the Chapuy *et al.* data set. Left: percentage of study participants who 1) were eligible according to proposed criteria, 2) categorized into genetic cluster five, and 3) had a mutation in the corresponding gene. Middle: mutational heatmap for the eligible patient population in genetic cluster five according to proposed criteria in the Chapuy *et al.* cohort data set. Right: prevalence of genetic alterations in each gene by number of study participants along with indications for type of genetic alteration.