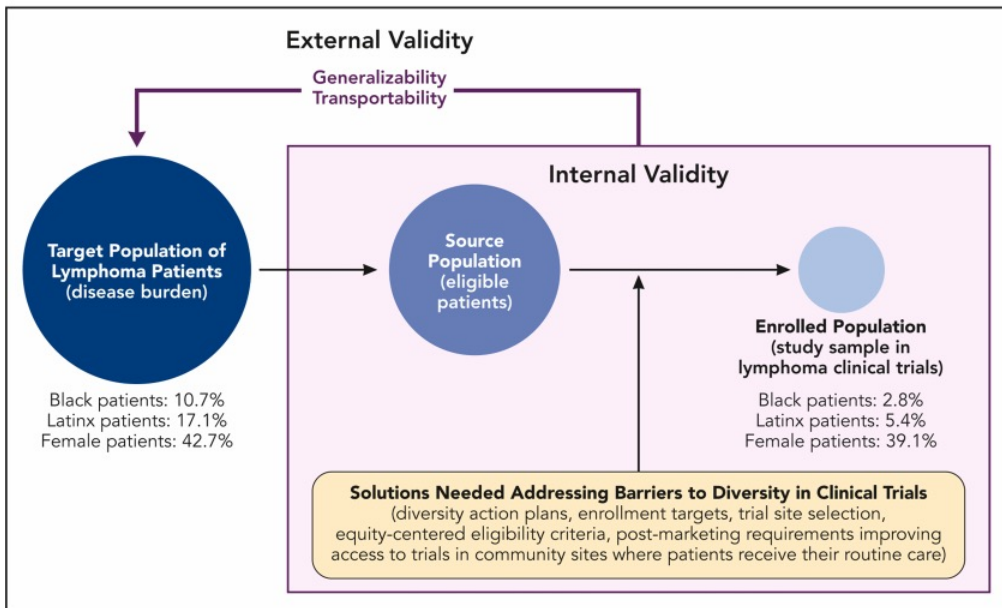


External Validity of Lymphoma Clinical trials



Generalizability and Transportability of Clinical Results

- **Generalizability** refer to concerns with making inference on the average treatment effect from a possibly biased sample of the target population back to the full target population.
- **Transportability** refers to making inference on the treatment effect for a target population when the study sample and target population do not overlap (partially or entirely)

Peter M Rothwell et al:

"In making treatment decisions, doctors and patients must take into account relevant randomised controlled trials and systematic reviews. Relevance depends on external validity (or generalisability)--ie, whether the results can be reasonably applied to a definable group of patients in a particular clinical setting in routine practice. There is concern among clinicians that external validity is often poor, particularly for some pharmaceutical industry trials, a perception that has led to underuse of treatments that are effective"

Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?"

Lancet. 2005 Jan 1-7;365(9453):82-93.

1. Calip GS, Royce TJ. External validity of lymphoma clinical trials. *Blood*. 2023 Aug 31;142(9):757-759.
2. Casey M, Odhiambo L, Aggarwal N, Shoukier M, Islam KM, Cortes J. Representation of the population in need for pivotal clinical trials in lymphomas. *Blood*. 2023 Aug 31;142(9):846-855.



Advancing Equitable Lymphoma Care

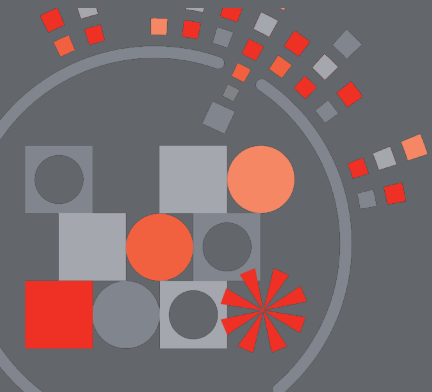
Christopher Flowers, MD, MS, FASCO

Division Head
Chair, Professor

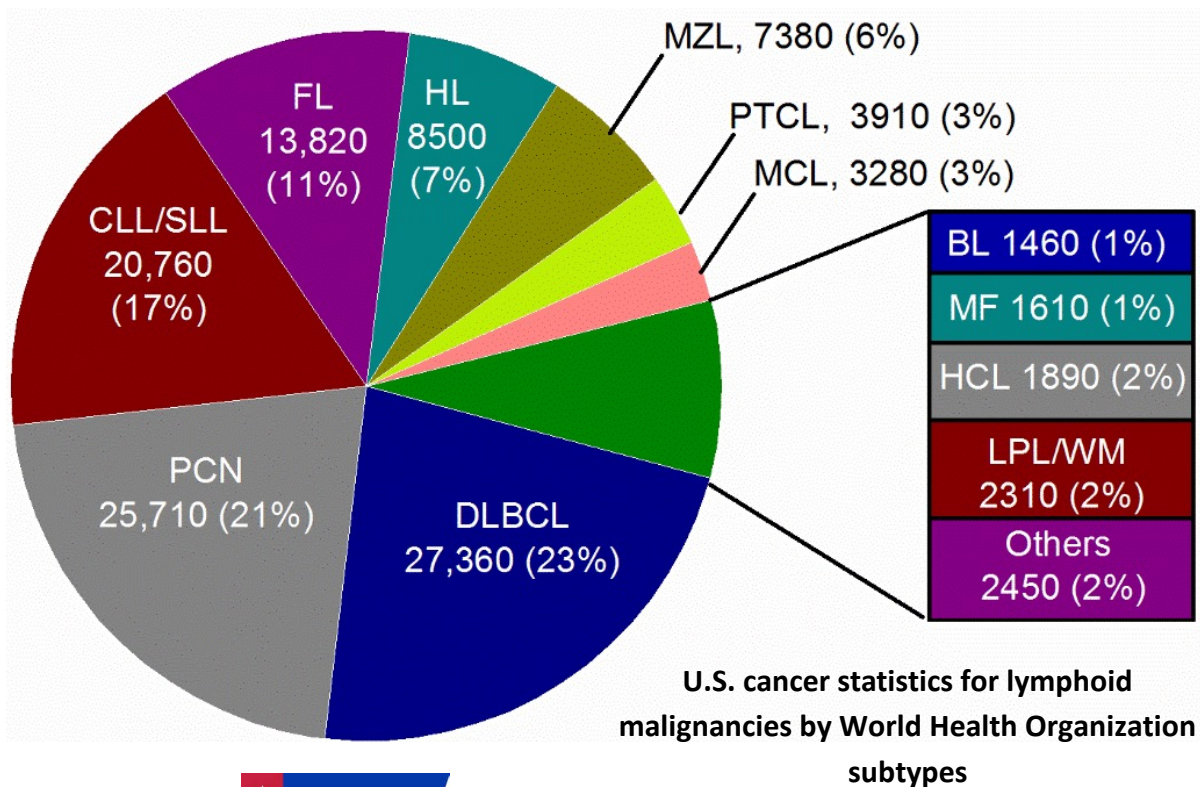
Division of Cancer Medicine
Department of Lymphoma/Myeloma

THE UNIVERSITY OF TEXAS
MDAnderson
Cancer Center

Making Cancer History®



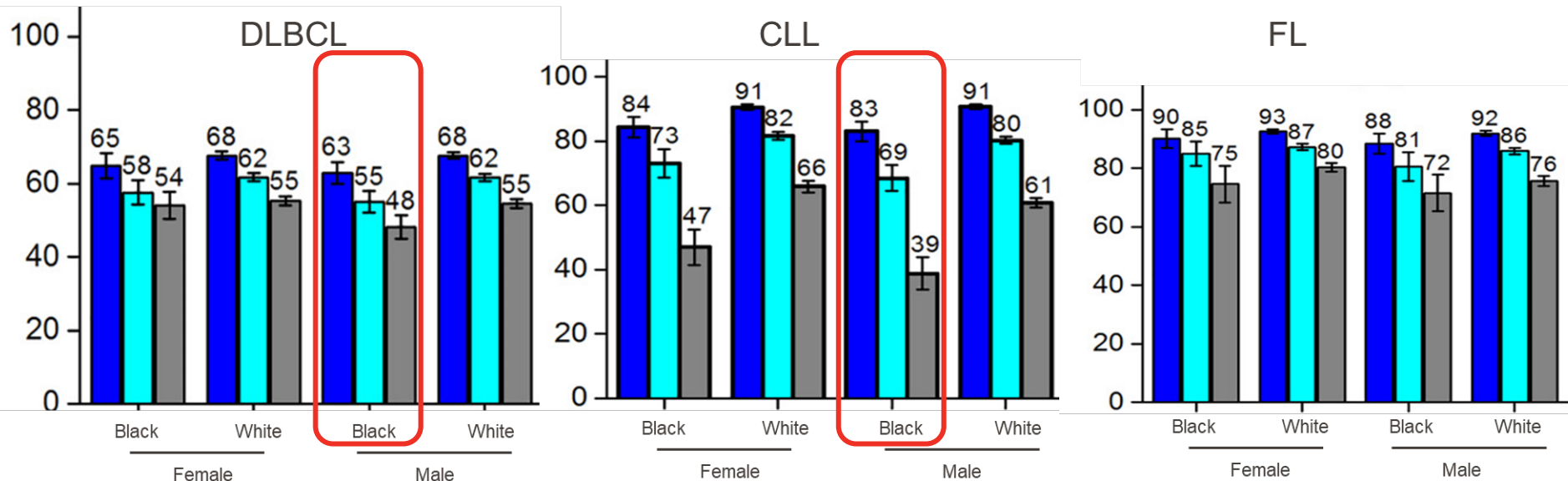
Annual Incidence of Lymphoid Cancers in the United States



Teras LR, DeSantis CE, Morton LM, Cerhan JR, Jemal A, Flowers CR

CA Cancer J Clin. 2016

Survival by Gender and Race for Lymphoma Subtypes



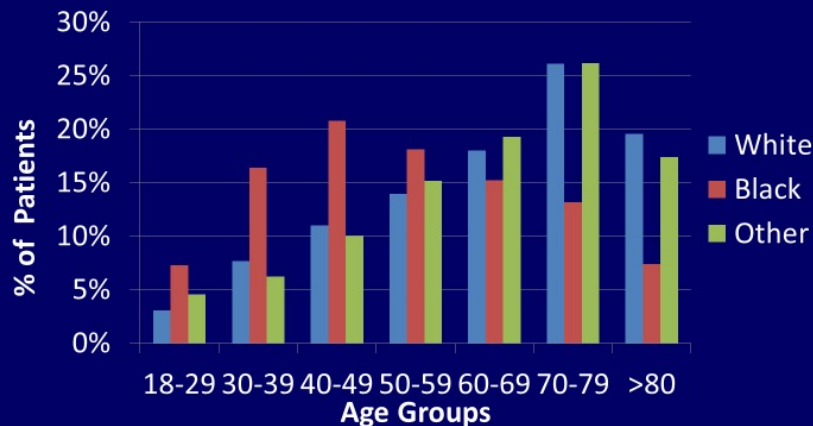
U.S. cancer statistics for lymphoid malignancies by World Health Organization subtypes

■ 2-year ■ 5-year ■ 10-year

Teras LR, DeSantis CE, Morton LM, Cerhan JR, Jemal A, Flowers CR

Disparities in Lymphoma

Age Distribution of DLBCL by Race: SEER



African American Present 10 year Younger Across WHO Classified Lymphoid Malignancies

NHL Subtype	ICD-O-3	Median Age		
B-CELL NEOPLASM		White	Black	Other
B-cell prolymphocytic leukemia	9833	75.5	57	46.5
Lymphoplasmacytic lymphoma	9671	71	60	69
Follicular lymphoma, NOS	9690	66	56	65
Follicular lymphoma Grade 1	9695	63	58	59
Follicular lymphoma Grade 2	9691	64	60	62
Follicular lymphoma Grade 3	9698	65	55	67
Diffuse large B-cell lymphoma	9680	68	52	66
Immunoblastic diffuse large B-cell lymphoma	9684	60	48	67
Primary effusion lymphoma	9678	58	50.5	
Mediastinal (thymic) large cell lymphoma	9679	35	21.5	39
Burkitt lymphoma	9687	41	39.5	49
T-CELL AND NK-CELL NEOPLASM				
Peripheral T-cell lymphoma, unspecified	9702	65	54	65.5
Classical Hodgkin lymphoma	9650	50	39	41

[Disparities in survival by insurance status in follicular lymphoma.](#) Goldstein JS, Nastoupil LJ, Han X, Jemal A, Ward E, **Flowers CR.** *Blood.* 2018 Sep 13;132(11):1159-1166

[Impact of Treatment and Insurance on Socioeconomic Disparities in Survival after Adolescent and Young Adult Hodgkin Lymphoma: A Population-Based Study.](#) Keegan TH, DeRouen MC, Parsons HM, Clarke CA, Goldberg D, **Flowers CR,** Glaser SL. *Cancer Epidemiol Biomarkers Prev.* 2016 Feb;25(2):264-73.

[Population-specific prognostic models are needed to stratify outcomes for African-Americans with diffuse large B-cell lymphoma.](#) Chen Q, Ayer T, Nastoupil LJ, Koff JL, Staton AD, Chhatwal J, **Flowers CR.** *Leuk Lymphoma.* 2016;57(4):842-51

[Racial differences in chronic lymphocytic leukemia. Digging deeper.](#) **Flowers CR,** Pro B. *Cancer.* 2013 Oct 15;119(20):3593-5.

[Examining racial differences in diffuse large B-cell lymphoma presentation and survival.](#) **Flowers CR,** Shenoy PJ, Borate U, Bumpers K, Douglas-Holland T, King N, Brawley OW, Lipscomb J, Lechowicz MJ, Sinha R, Grover RS, Bernal-Mizrachi L, Kowalski J, Donnellan W, The A, Reddy V, Jaye DL, Foran J. *Leuk Lymphoma.* 2013 Feb;54(2):268-76.

[Disparities in the early adoption of chemioimmunotherapy for diffuse large B-cell lymphoma in the United States.](#) **Flowers CR,** Fedewa SA, Chen AY, Nastoupil LJ, Lipscomb J, Brawley OW, Ward EM. *Cancer Epidemiol Biomarkers Prev.* 2012 Sep;21(9):1520-30

[Racial differences in presentation and management of follicular non-Hodgkin lymphoma in the United States: report from the National LymphoCare Study.](#) Nabhan C, Byrtek M, Taylor MD, Friedberg JW, Cerhan JR, Hainsworth JD, Miller TP, Hirata J, Link BK, **Flowers CR.** *Cancer.* 2012 Oct 1;118(19):4842-50.

[Racial differences in the presentation and outcomes of chronic lymphocytic leukemia and variants in the United States.](#) Shenoy PJ, Malik N, Sinha R, Nooka A, Nastoupil LJ, Smith M, **Flowers CR.** *CLML* 2011 Dec;11(6):498-506.

[Racial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the United States.](#) Shenoy PJ, Malik N, Nooka A, Sinha R, Ward KC, Brawley OW, Lipscomb J, **Flowers CR.** *Cancer.* 2011 Jun 1;117(11):2530-40.

[Charting the Future of Cancer Health Disparities Research: A Position Statement from the American Association for Cancer Research, the American Cancer Society, the American Society of Clinical Oncology, and the National Cancer Institute.](#) Polite BN, Adams-Campbell LL, Brawley OW, Bickell N, Carethers JM, **Flowers CR,** Foti M, Gomez SL, Griggs JJ, Lathan CS, Li CI, Lichtenfeld JL, McCaskill-Stevens W, Paskett ED. *J Clin Oncol.* 2017 Sep 10;35(26):3075-3082.

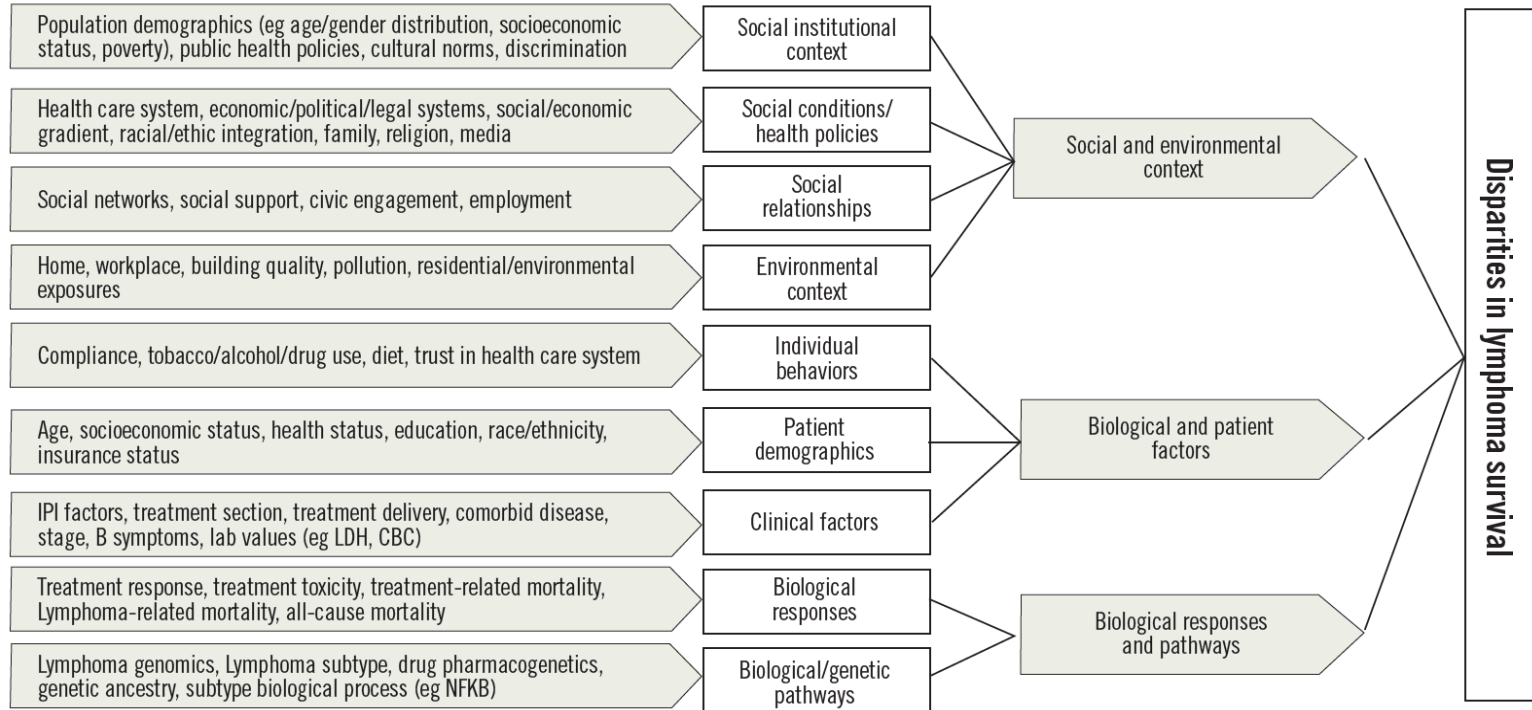
“ It’s not enough that oncologists deliver excellent care; we must also investigate how our healthcare system can be restructured to ensure equitable cancer care for all. ”



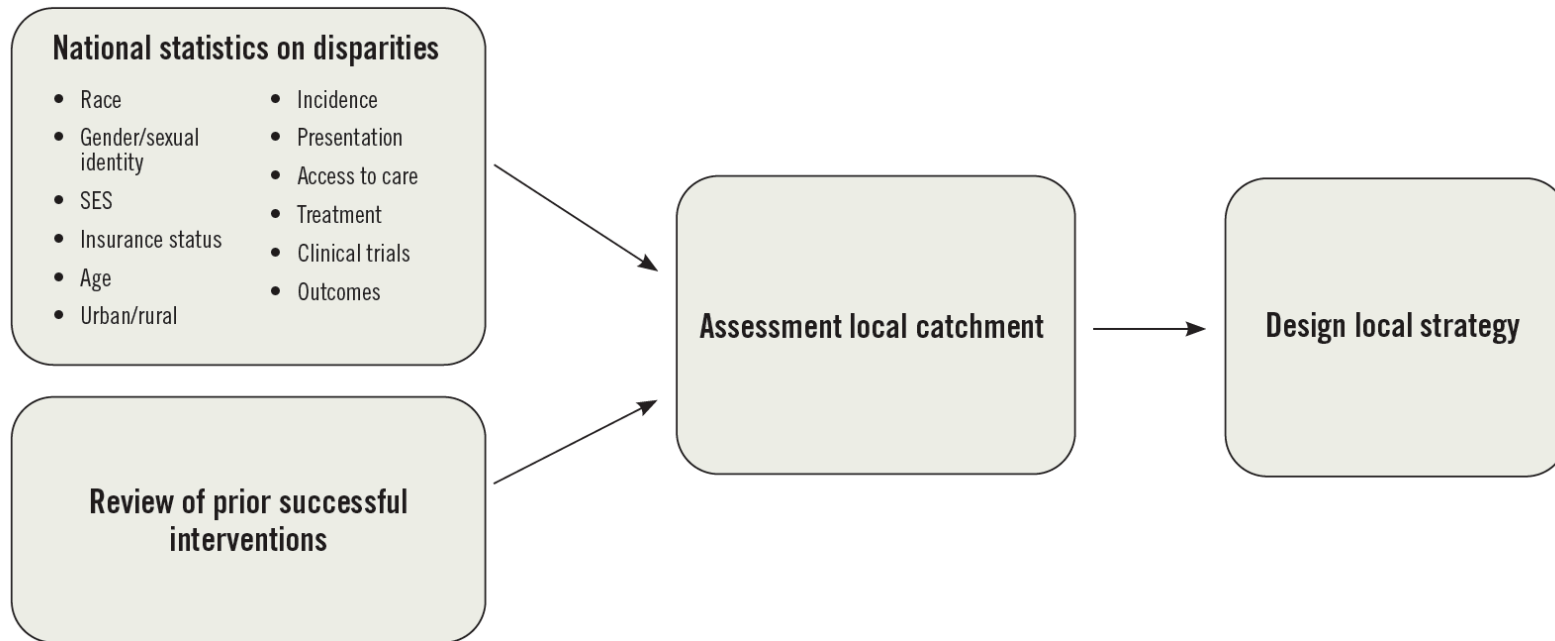
Chijioke Nze, MD
MD Anderson Cancer Center

Approaches For Clinicians to Address Disparities in Hematologic Malignancies

Multilevel approaches are required to improve outcomes



Proposed Framework for Addressing Disparities



905.OUTCOMES RESEARCH-MALIGNANT CONDITIONS (LYMPHOID DISEASE) |
NOVEMBER 5, 2020

The Impact of Race and Ethnicity on Diffuse Large B-Cell Lymphoma (DLBCL) Outcomes within the Veterans Health Administration (VHA)

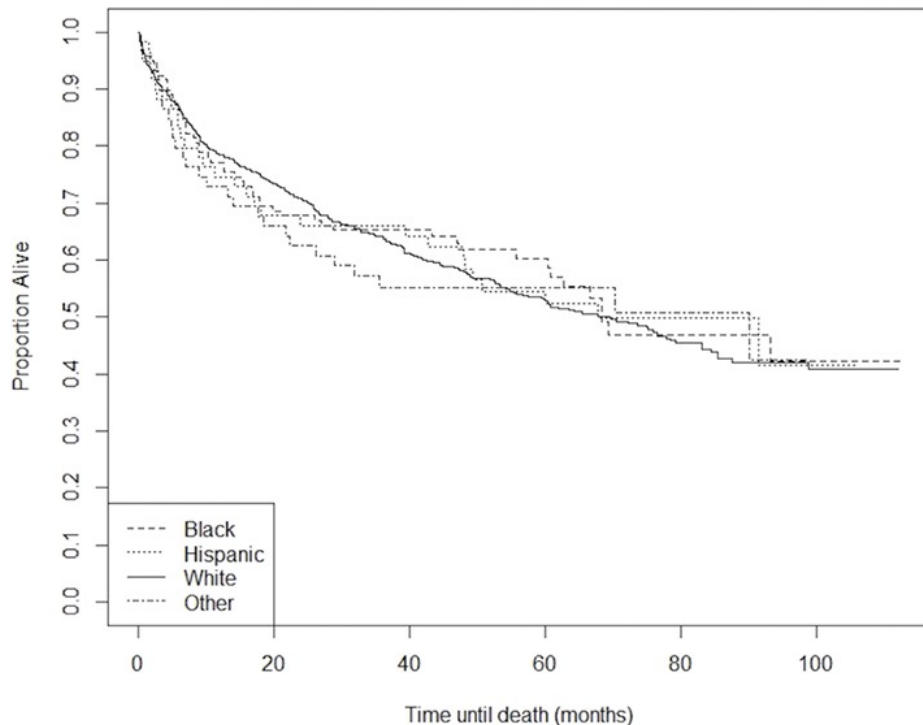
Madison H. Williams, MD, Ryan A. Williams, MD, Jean Pierre Blaize, MD, Snegha Ananth, MBBS, David Gregorio, DO, Gerardo Manuel Rosas, MD, Michael M. Song, MDPhDPharmD, Brian Warnecke, DO, Abhishek Pandya, DO, Lakene Raissa Djoufaok Djoumessi, MD, Vivian Dee, NP, Phillip Nazarewicz, Kathleen Franklin, Juan J. Toro, MD MS, Michael Mader, MS, Zohra Nooruddin, MD

Table 2. Response rate to first-line chemotherapy and survival



	All Patients	Black	Hispanic	White	Other/Unknown
Response to Chemo					
CR	641 (66%)	80 (66.7%)	42 (68.9%)	477 (65.3%)	42 (70%)
PR	66 (6.8%)	4 (3.3%)	4 (6.6%)	54 (7.4%)	4 (6.7%)
SD	18 (1.9%)	3 (2.5%)	1 (1.6%)	13 (1.8%)	1 (1.7%)
PD	84 (8.7%)	14 (11.7%)	4 (6.6%)	62 (8.5%)	4 (6.7%)
Response unknown/no therapy given	162 (16.7%)	19 (15.8%)	10 (16.4%)	124 (17%)	9 (15%)
ORR	87.4%	83.2%	90.2%	87.6%	90.2%
Survival from time of diagnosis					
1-year survival	736 (75.8%)	91 (75.8%)	44 (72.1%)	558 (76.4%)	43 (71.7%)
2-year survival	655 (67.5%)	80 (66.7%)	39 (63.9%)	500 (68.5%)	36 (60%)
Median OS, months	40.5	43	49.2	40.5	33.3

When similar treatments can be administered, similar outcomes can occur

KM survival curve by Race

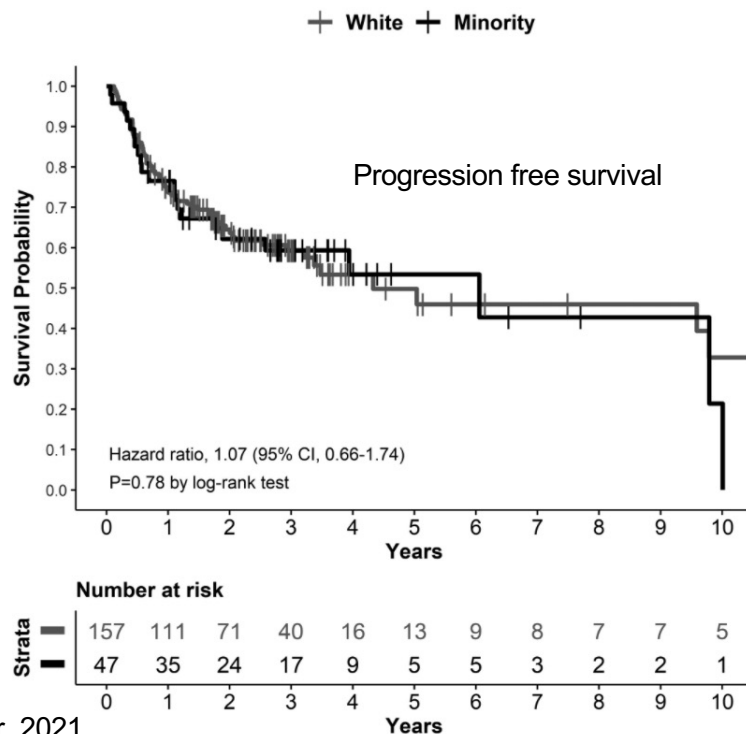


Equal Access to Care and Nurse Navigation Leads to Equitable Outcomes for Minorities With Aggressive Large B-Cell Lymphoma

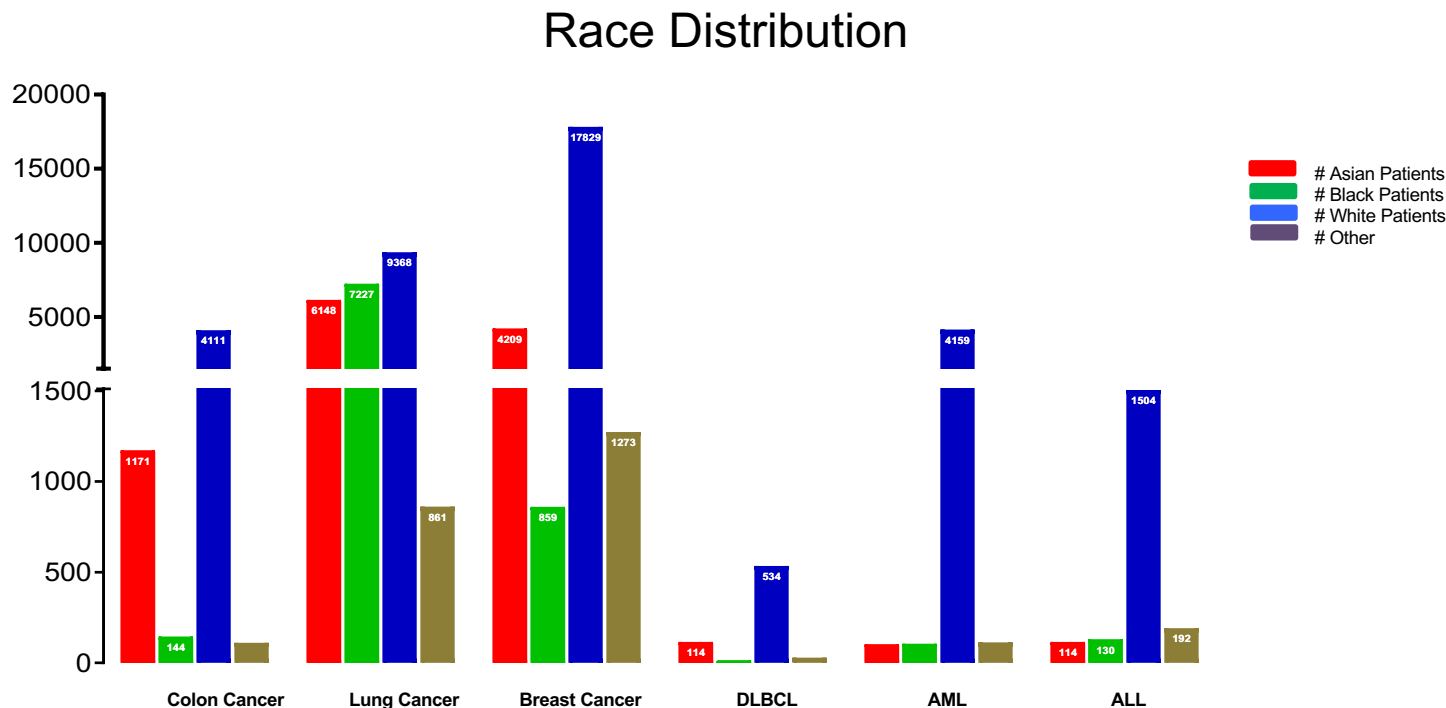
Bei Hu, MD¹; Danielle Boselli, MS²; Lisa M. Pye, BSN³; Tommy Chen, BS²; Rupali Bose, MS, MBA²; James T. Symanowski, PhD²; Kris Blackley, MSN³; Tamara K. Moyo, MD, PhD¹; Ryan Jacobs, MD¹; Steven I. Park, MD¹; Amy Soni, MD¹; Belinda R. Avalos, MD¹; Edward A. Copelan, MD¹; Derek Raghavan, MD, PhD⁴; and Nilanjan Ghosh, MD, PhD¹  

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Age at diagnosis (every 5 y)	1.33 (1.19-1.49)	<.001	1.41 (1.22-1.63)	<.001
Race		.27		.62
White	Reference		Reference	
Minority	0.68 (0.34-1.35)		1.20 (0.59-2.45)	
Sex		.49		
Female	Reference			
Male	1.21 (0.71-2.05)			
Driving distance to LCI		.002		.02
<20 miles	Reference		Reference	
≥20 miles	2.75 (1.45-5.22)		2.34 (1.17-4.67)	

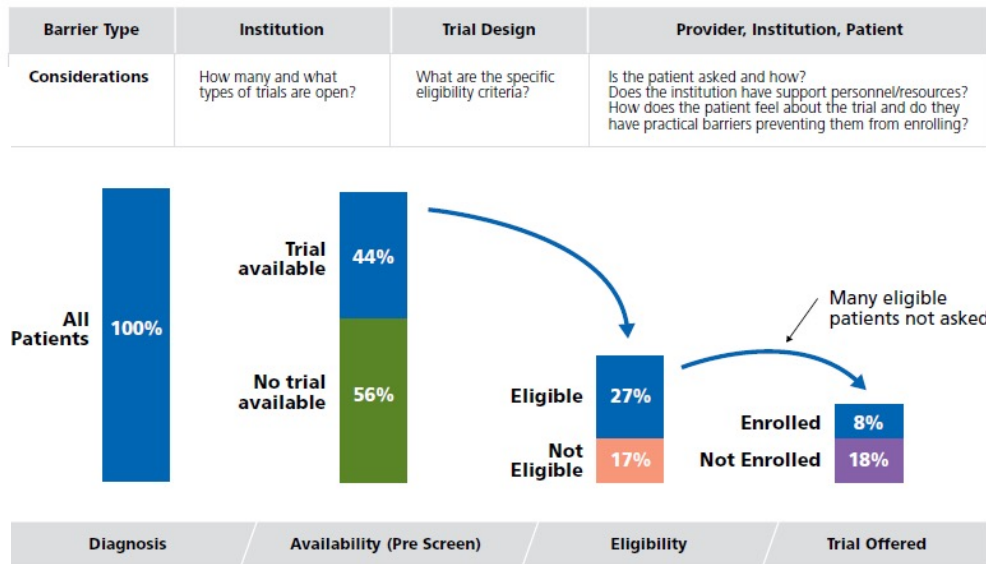
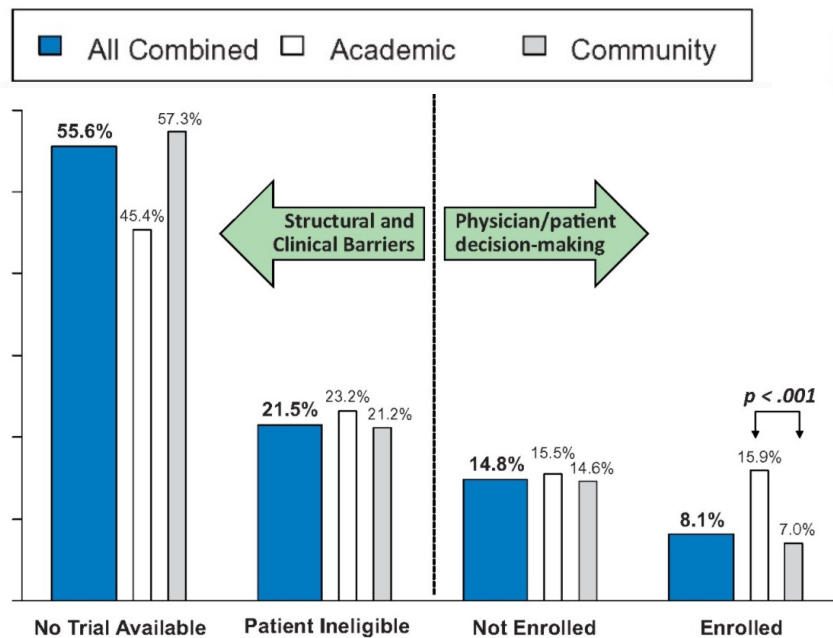
When similar treatments can be administered, similar outcomes can occur



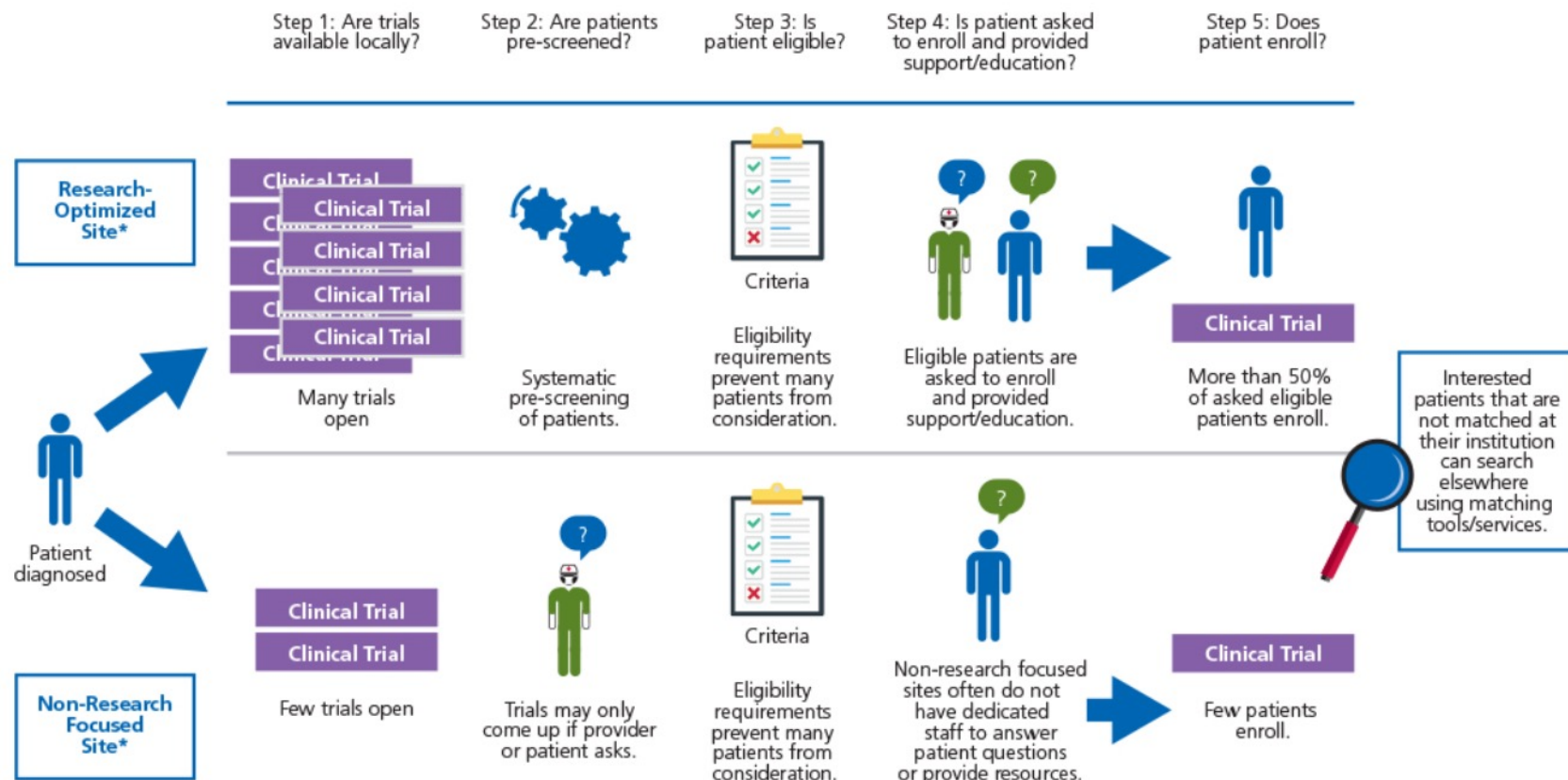
Significant under-representation of minority populations in heme malignancy clinical trials



Enrollment barriers vary by clinical setting

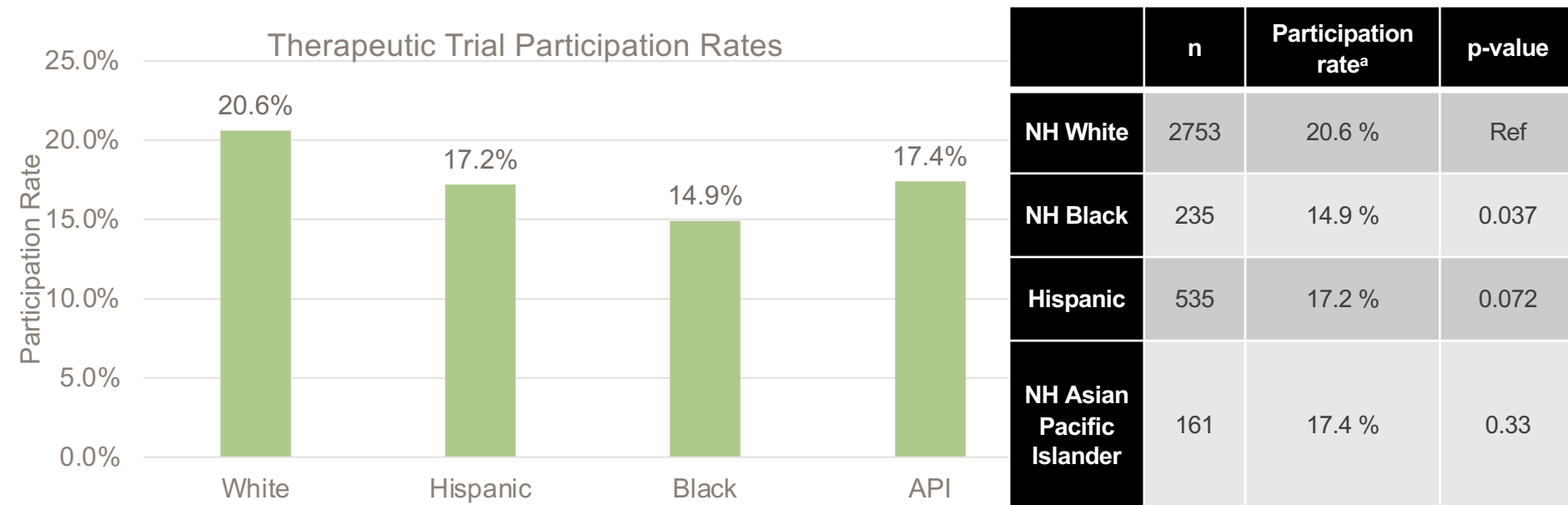


PATIENT ENROLLMENT BARRIERS VARY BY LOCATION



*Comparisons are illustrative only, and individual sites vary.

MDACC TMC Data: Participation Rates in Therapeutic Trials, FY17-FY20



(U01 CA195568) **The Lymphoma Epidemiology of Outcomes Cohort Study**



Chris Flowers MD, MS



Jim Cerhan MD, PhD



Weill Cornell Medical College

GOAL:
TO FACILITATE
RESEARCH THAT
USES **LEO**
INFRASTRUCTURE
AND SUPPORTS
INTERACTION WITH
LYMPHOMA NCTN

- AIMS:**
- 1) Recruit 12,900 newly diagnosed NHL pts including 3,600 DLBCL and 3,100 FL
 - 2) Build a NHL tumor bank w/ TMA, tumor DNA and RNA
 - 3) Central biorepository: PB, serum, plasma, DNA
 - 4) Collect clinical, epidemiologic, pathology and treatment data
 - 5) Prospectively follow patients for clinical and patient-reported outcomes

Leveraging Research to Overcome Cancer Disparities

(U01 CA195568) **Lymphoma Epidemiology of Outcomes Cohort Study Supports Additional Research**



LEO NCI Diversity Supplements: U01 CA195568

Support the research training for members of an underrepresented group



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

LEO Retreat | October 20th, 2022

Core Infrastructure and Methodological Research for Cancer Epidemiology Cohorts (U01)
U01 CA195568) **The Lymphoma Epidemiology of Outcomes Cohort Study**



Chris Flowers MD, MS Jim Cerhan MD, PhD



GOAL:
TO FACILITATE
RESEARCH THAT
USES LEO
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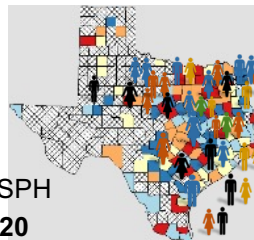
- AIMS:**
- 1) Recruit 12,900 newly diagnosed NHL pts including:
 - 3,600 DLBCL and 3,100 FL
 - 1,000 African American and 1,400 Hispanic patients
 - 2) Build a NHL tumor bank w/ TMA, tumor DNA and RNA
 - 3) Central biorepository: PB, serum, plasma, DNA
 - 4) Collect clinical, epidemiologic, pathology and treatment data
 - 5) Prospectively follow patients for clinical and patient-reported outcomes



- **W. Brad Jones** (Ga Tech PhD ISyE)
- mHealth Approaches for LEO 7/16–5/17
- **Jacob Jordan** (U Penn undergraduate)
- Pathology Informatics 7/16–5/18



- **Lauren McCullough, PhD, MPH** Emory SPH
- Adiposity & lymphoma disparities 7/18–5/20



Epidemiology of Lymphomas in Latin America (ELLA)

Luis Malpica, MD
Assistant Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
LEMalpica@mdanderson.org

Christopher Flowers, MD, MS, FASCO
Professor, Chair
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
CRFlowers@mdanderson.org



Informatics Tools for Quantitative Digital Pathology Profiling and Integrated Prognostic Modeling (U01 CA220401)

Emory (ITCR + LEO):

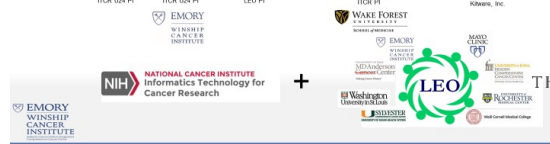


Lian Cooper, PhD David Goltzman, MD, PhD Chris Freeman, MD, MS

Wake Forest (ITCR):



Mark Glickson, PhD Douglas Critchley, PhD



U01CA195568

K24CA208132



THE FOUNDATION* for Cancer Research

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Grupo de Estudio Latinoamericano de Linfoproliferativos GELL



Christopher Flowers, MD



Jonathon Cohen, MD



James Cerhan, MD, PhD



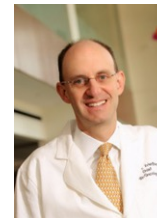
Loretta Nastoupil, MD



Brian Link, MD



Brad Kahl, MD



Jonathon Friedberg, MD



Weill Cornell Medical College



Izidore Lossos, MD



Peter Martin, MD



John Leonard, MD

**ECOG Lymphoma
Chair**

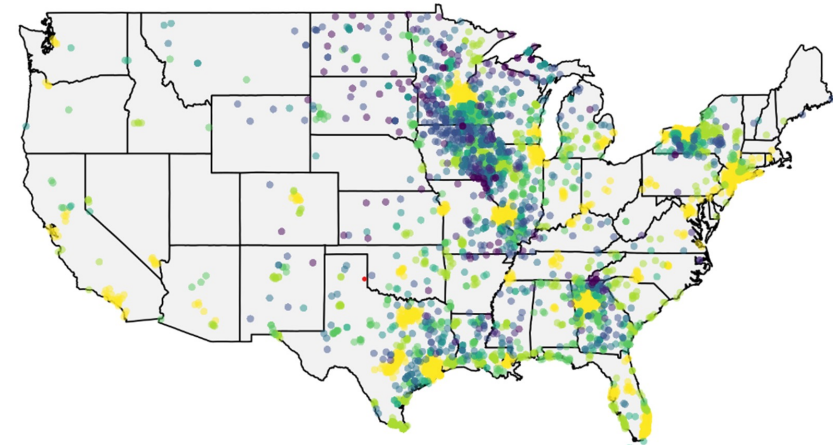
SWOG Lymphoma Chair

Alliance Lymphoma Chair

LEO Geography and Comparison of to SEER

(n=7735)

Residence of LEO participants enrolled 2015-2020 by Rural Urban Code



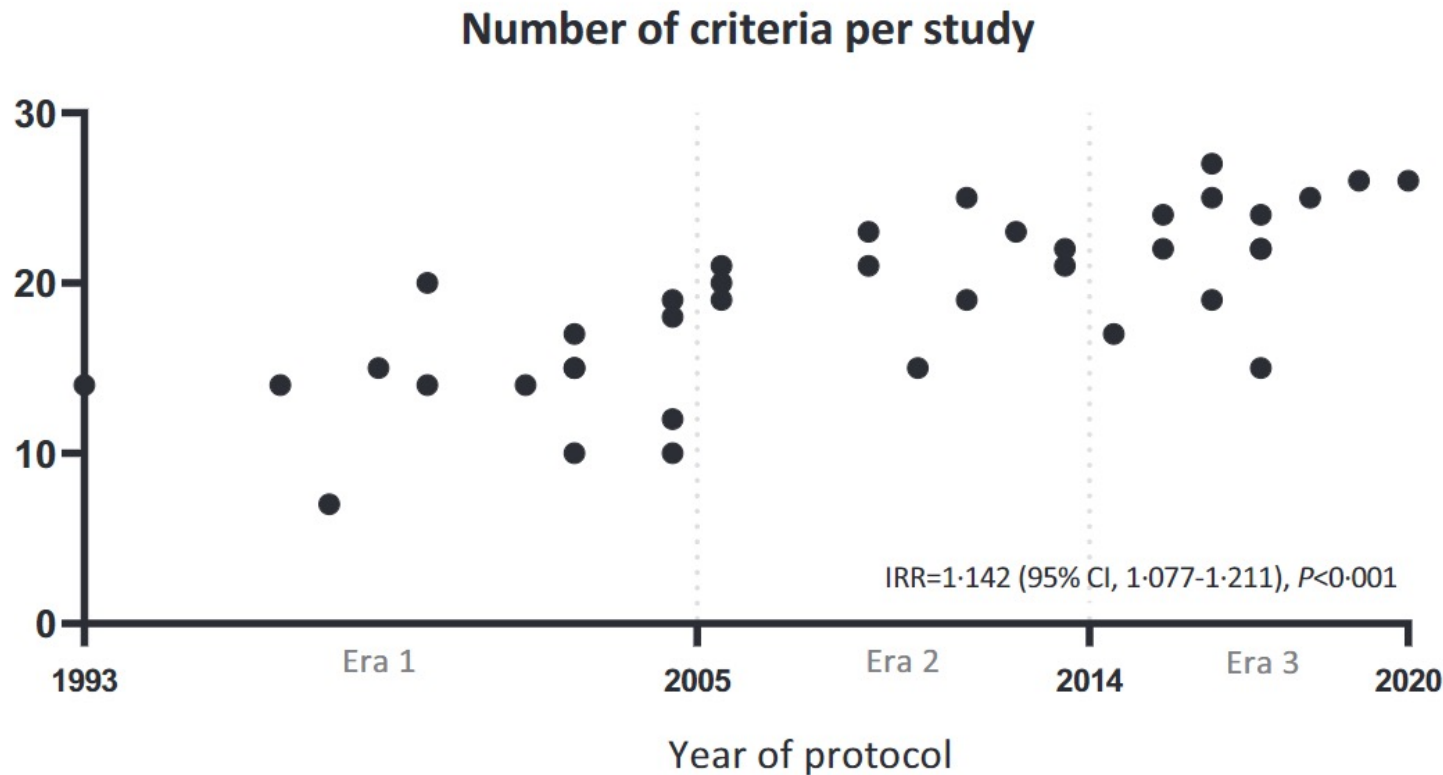
- Nonmetro - Completely rural or less than 2,500 urban population, not adjacent to a metro area
- Nonmetro - Completely rural or less than 2,500 urban population, adjacent to a metro area
- Nonmetro - Urban population of 2,500 to 19,999, not adjacent to a metro area
- Nonmetro - Urban population of 2,500 to 19,999, adjacent to a metro area
- Nonmetro - Urban population of 20,000 or more, not adjacent to a metro area
- Nonmetro - Urban population of 20,000 or more, adjacent to a metro area
- Metro - Counties in metro areas of fewer than 250,000 population
- Metro - Counties in metro areas of 250,000 to 1 million population
- Metro - Counties in metro areas of 1 million population or more

Comparison of LEO Characteristics with SEER-18 data

	LEO (2015-2020)		SEER (2015-2019)	
	N	%	N	%
Age at diagnosis (years)				
<40	716	9.3%	6,332	7.0%
40-49	870	11.2%	6,741	7.4%
50-59	1,686	21.8%	15,009	16.5%
60-69	2,270	29.3%	23,331	25.6%
70-79	1,639	21.2%	23,313	25.6%
80+	554	7.2%	16,354	18.0%
Gender				
Women	3,386	43.8%	40,552	44.5%
Men	4,349	56.2%	50,528	55.5%
Men:Women		1.28		1.25
Ethnicity				
Hispanic/Latino	822	10.9%	13,706	15.0%
Non-Hispanic/Latino	6,728	89.1%	77,374	85.0%
Unknown	185		0	
Race				
Asian/Pacific Islander	205	2.7%	7,338	8.2%
American Indian/Alaska Native	27	0.4%	576	0.6%
Black/African American	538	7.2%	6,616	7.4%
White	6652	89.1%	74,886	83.8%
Other or >one race	43	0.6%	0	0.0%
Unknown	270		1,664	
NHL subtype				
DLBCL	2686	35.5%	33,865	37.2%
Follicular	1632	21.6%	15,616	17.1%
Mantle Cell	766	10.1%	4,085	4.5%
Marginal Zone	724	9.6%	9,642	10.6%
T-cell	688	9.1%	10,123	11.1%
All other NHL	1076	14.2%	17,749	19.5%
Ann Arbor Stage*				
I-II	2571	35.5%	6,307	43.6%
III-IV	4662	64.5%	8,162	56.4%
Missing	502		3,433	
B-Symptoms				
No	5552	73.7%	42,514	72.7%
Yes	1980	26.3%	15,952	27.3%
Unknown	203		32,614	

*Only available for 2015 in SEER

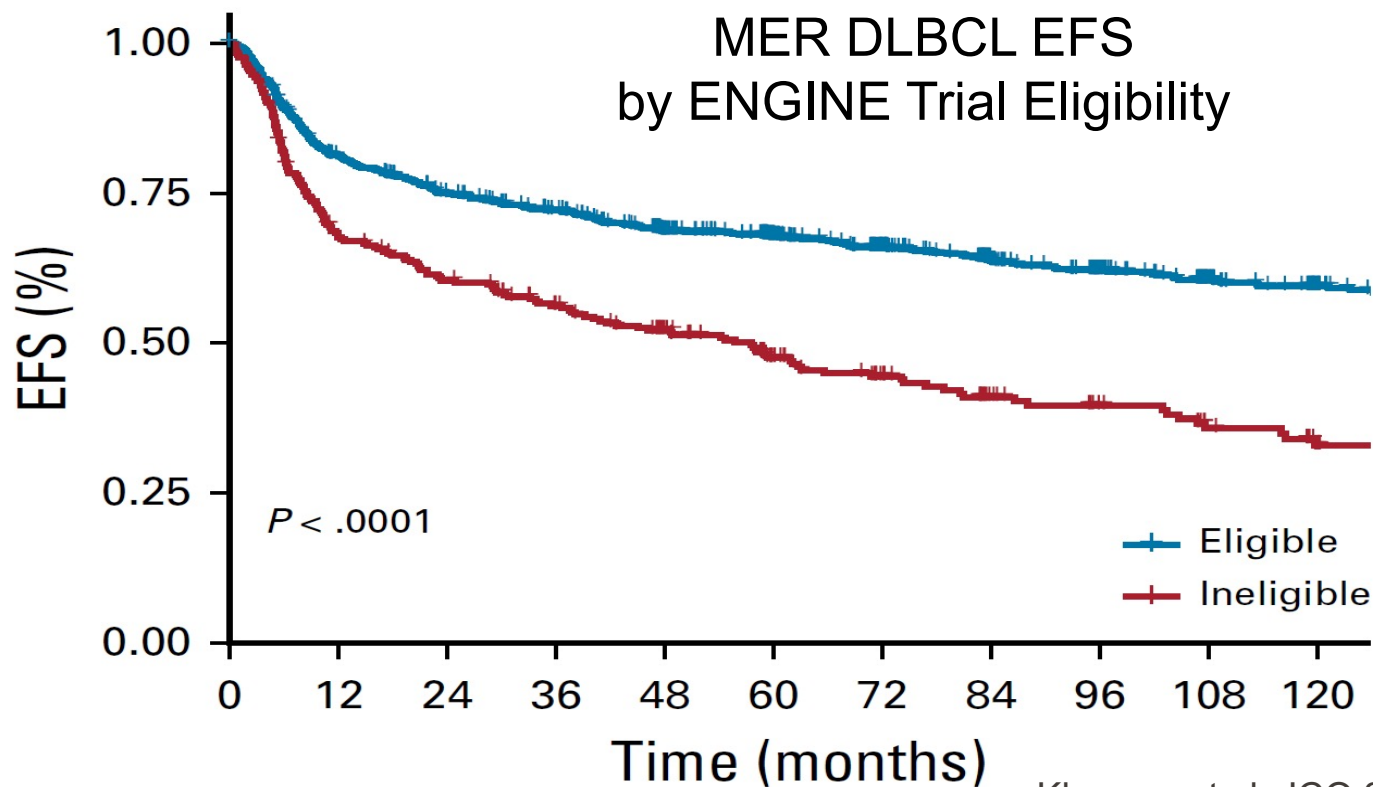
Eligibility criteria for 1L DLBCL trials increasingly more restrictive



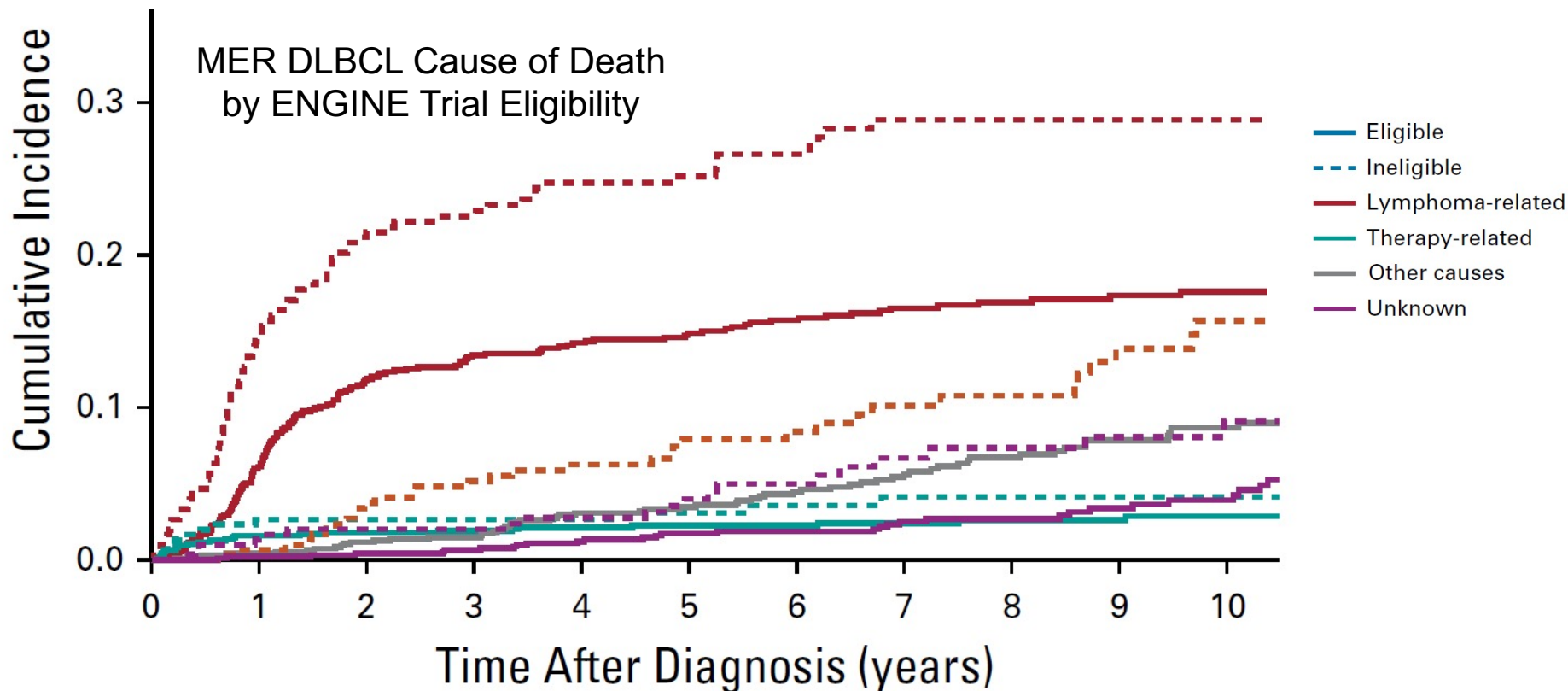
Who gets left behind in clinical trials of DLBCL?

	PHOENIX	ROBUST	GOYA	ENGINE
Total	12.3%	10.0%	15.9%	24.1%
ANC	1.3%	2.5%	2.5%	2.5%
PLT	3.2%	3.2%	3.2%	3.2%
Hepatic	3.8%	3.8%	3.8%	3.8%
Renal	5.2%	2.0%	5.2%	10.5%
HGB	0%	1.3%	6.3%	12.7%

Trial ineligible patients have worse outcomes



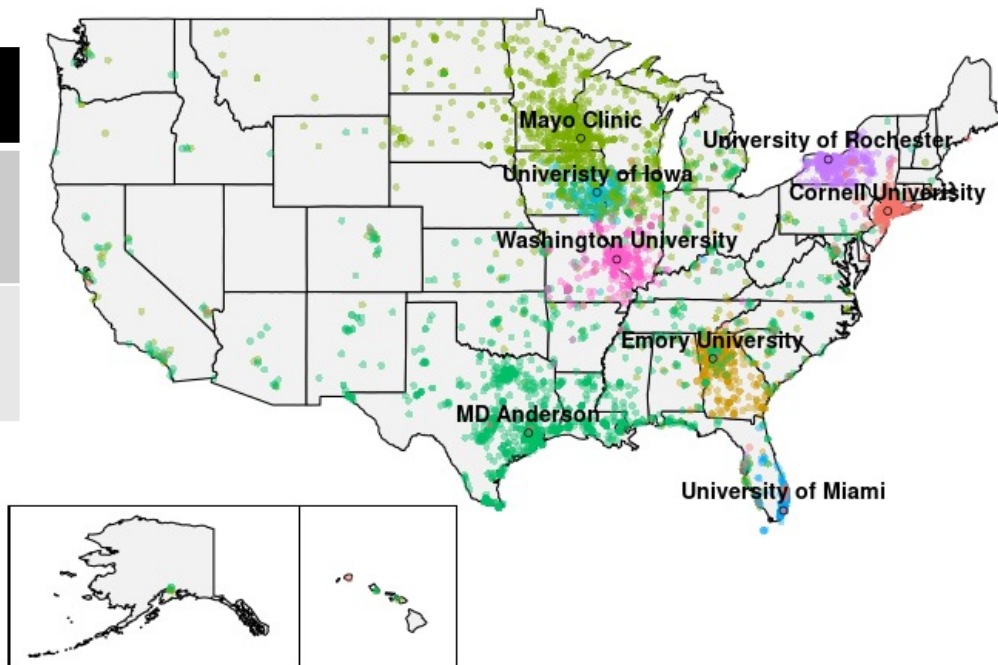
Trial ineligible patients have worse outcomes



LEO Cohort Enrollment (DLBCL n=2185)

• Cornell University • MD Anderson • University of Rochester
 • Emory • University of Iowa • Washington University
 • Mayo Clinic • University of Miami

	White	Black/AA	Hispanic	Other
LEO DLBCL	76%	7%	13%	4%
SEER DLBCL	67%	7%	16%	10%



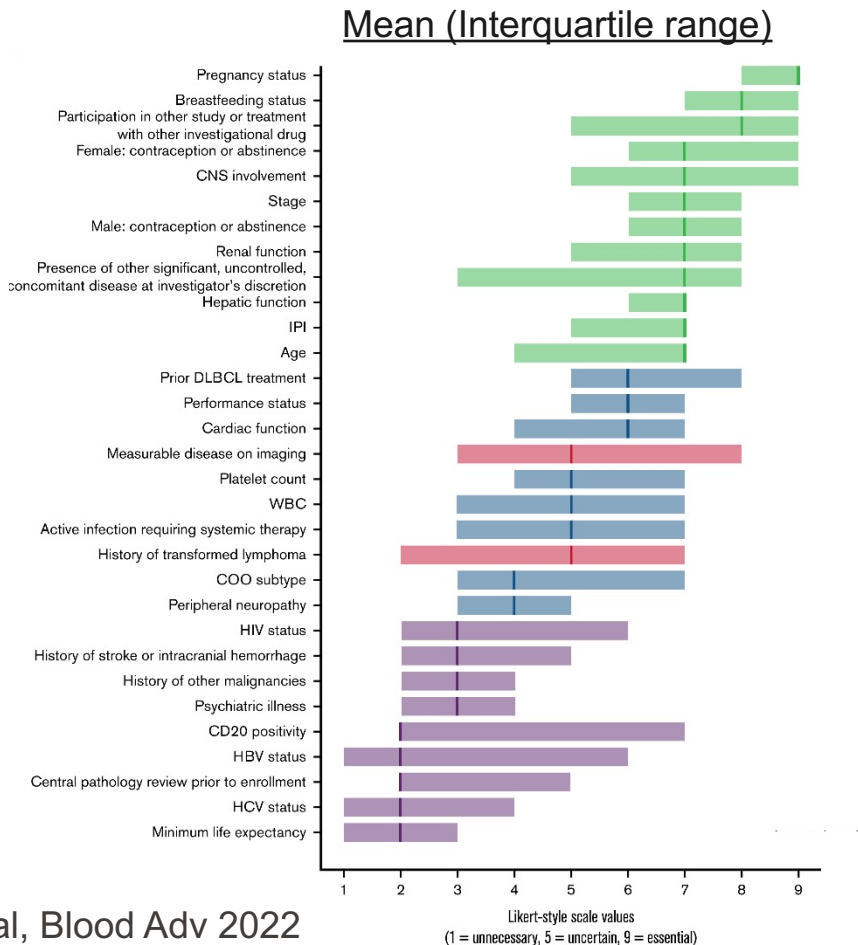
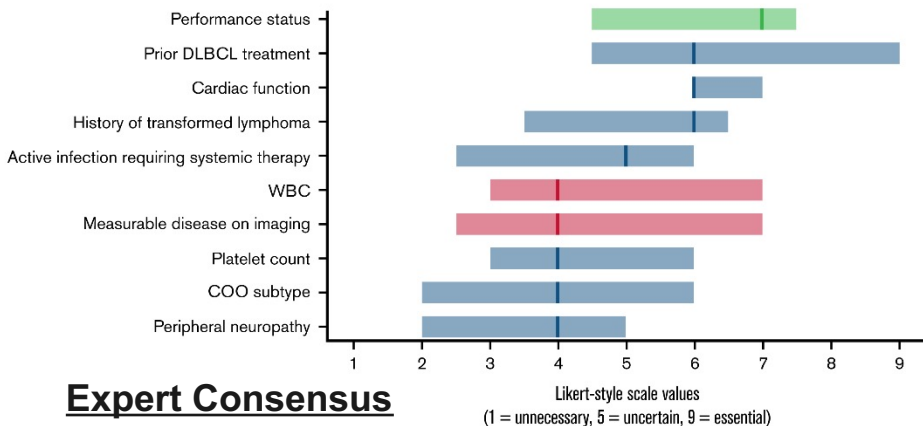
LEO Cohort DLBCL (n=2185)

Organ Function Lab Based Ineligibility by Race/Ethnicity

Clinical Trial	All Patients	White (Non-Hispanic)	Black/AA (Non-Hispanic)	Hispanic (Any)	Other Minority (Non-Hispanic)	P-Value
	(N=2185)	(N=1666)	(N=155)	(N=288)	(N=76)	
GOYA, n (%)	372 (17.0%)	269 (16.1%)	39 (25.2%)	47 (16.3%)	17 (22.4%)	0.020
ENGINE, n (%)	571 (26.1%)	409 (24.5%)	57 (36.8%)	82 (28.5%)	23 (30.3%)	0.0052
POLARIX, n (%)	360 (16.5%)	262 (15.7%)	34 (21.9%)	47 (16.3%)	17 (22.4%)	0.11

Simplifying Eligibility for DLBCL Trials

Recommendations for eligibility criteria in 1L DLBCL RCTs using Delphi-method with lymphoma experts from LEO



Consensus recommendations for eligibility criteria in 1L DLBCL RCTs using Delphi-method with lymphoma experts

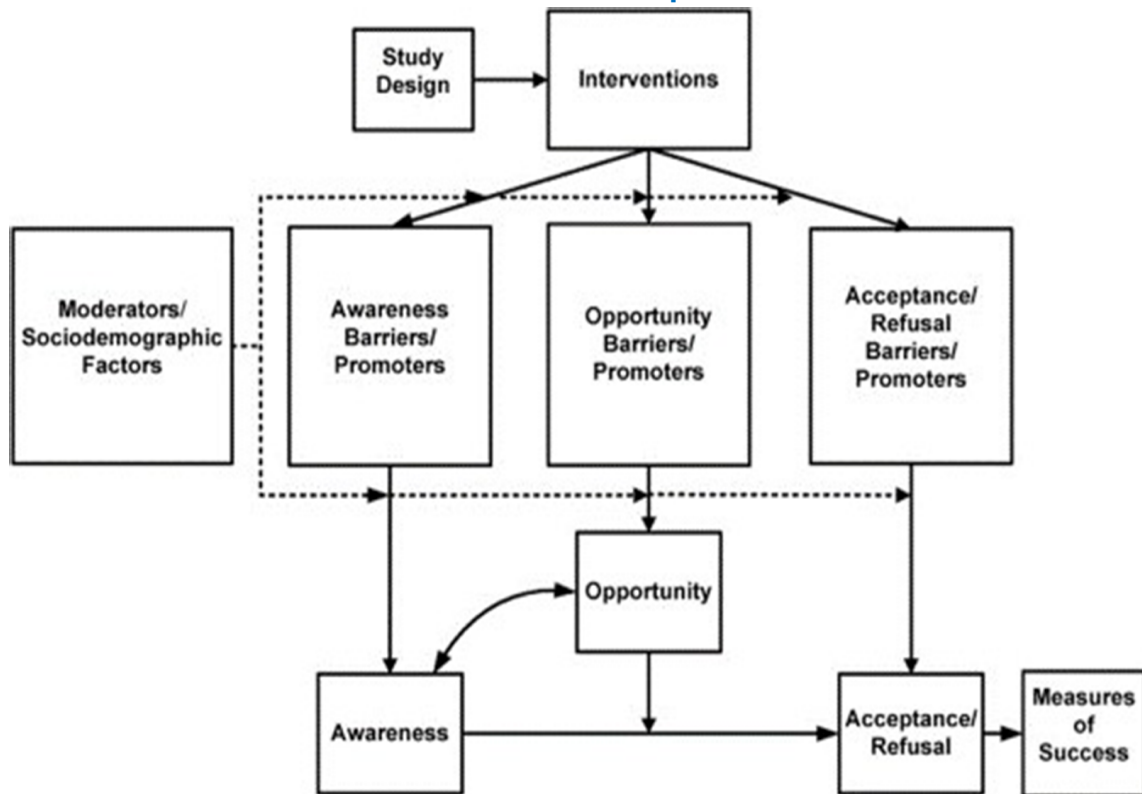
Essential Criteria

1.	Pregnancy status
2.	Breastfeeding status
3.	Female: contraception or abstinence
4.	Male: contraception or abstinence
5.	Participation in other study with investigational drug
6.	IPI score
7.	Ann Arbor stage
8.	Age at diagnosis
9.	Performance status
10.	Renal function
11.	Hepatic function
12.	CNS involvement
13.	Presence of other significant, uncontrolled, concomitant disease

Harkins et al, Blood Adv 2022

Improving Clinical Enrollment and Outcomes for African American and Hispanic lymphoid cancer patients

Barriers and Facilitators to Clinical Trial Participation



Patient Navigation

Identification

Coordinate with the Research Team to determine list of patients who might be eligible



Initial Contact

Navigator Prospectively contacts AA/H patients to discuss navigation



Clinic Contact

Meet participants to provide clinical trial education and administer needs assessment



Enrollment Participation

Develop plan to address barriers and provide support throughout trial

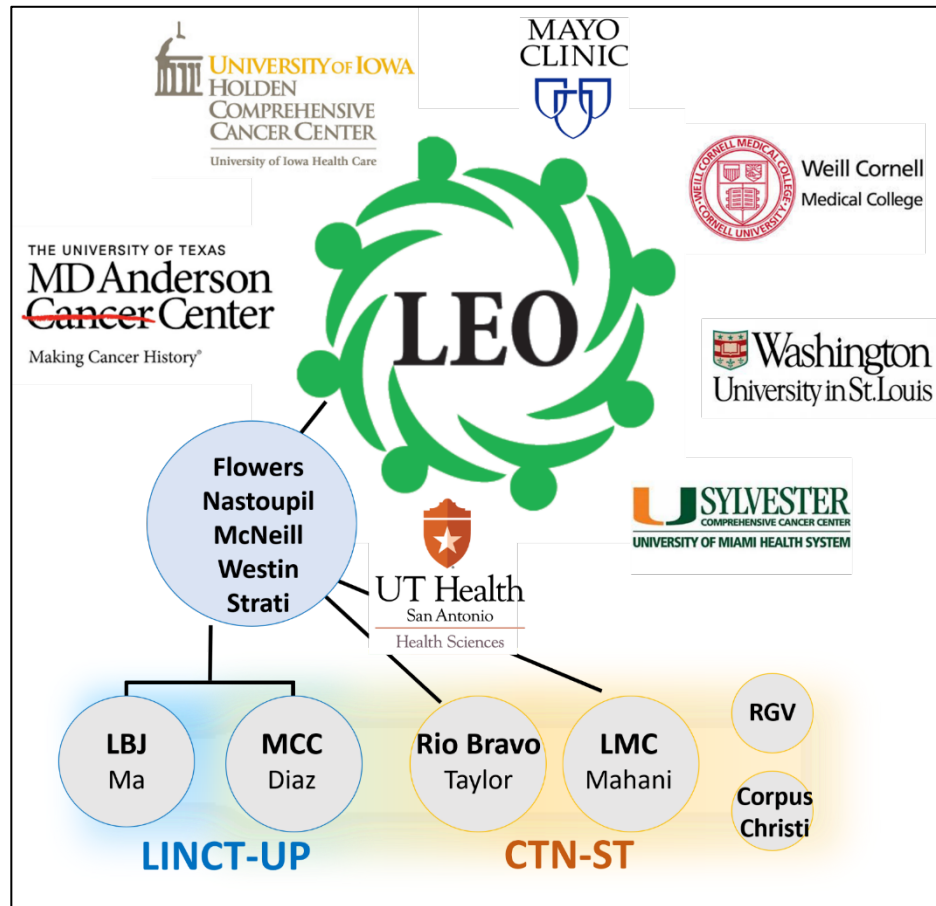
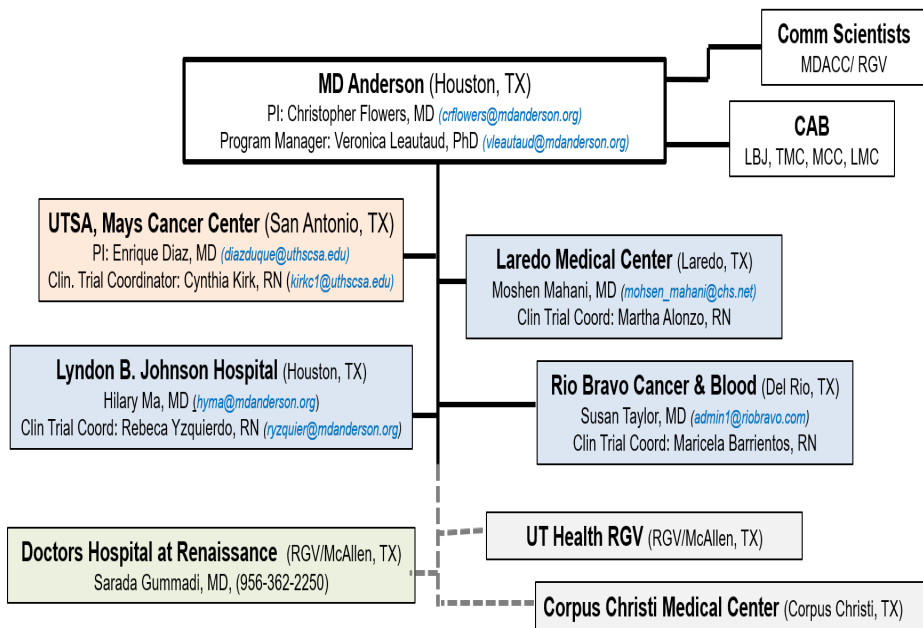


Documentation

Patient caseload, navigation services offered and patient trial status

LLS Influential Medicine Providing Access to Clinical Trials (IMPACT)

GOAL: Expand access to high-quality clinical trials to patients with blood cancers in academic and community health settings

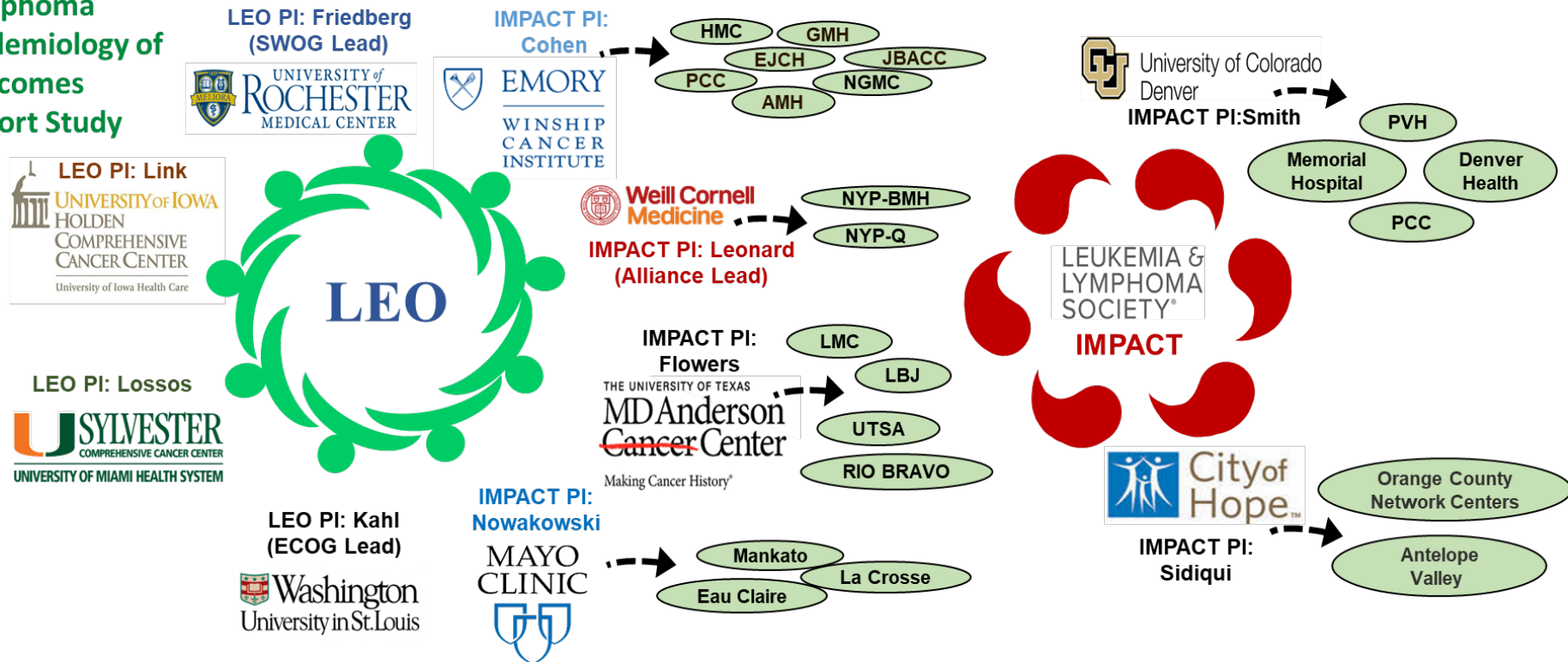


LLS Influential Medicine Providing Access to Clinical Trials (IMPACT)

GOAL: Expand access to high-quality community-care focused clinical trials to patients with blood cancers in academic and community health settings

(U01 CA195568)

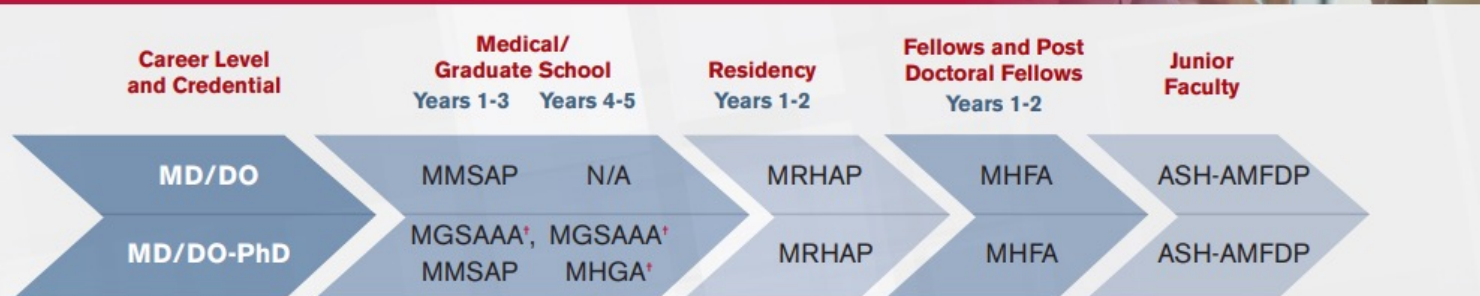
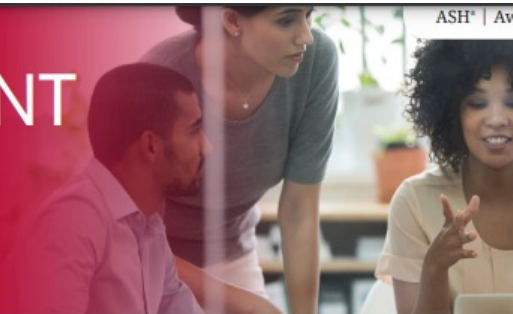
**Lymphoma
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Thank you!

Lymphoma Epidemiology of Outcomes



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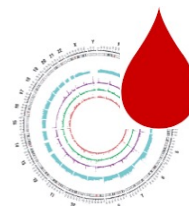
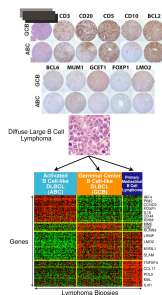
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