Christopher Flowers MD, MS, FASCO
• Professor of Hematology and Oncology, Winship Cancer Institute at Emory University School of Medicine
• Clinical Director for Oncology Informatics Program
• Director of the lymphoma program at Emory University
Disparities in Cancer Survival
HICOR Value in Cancer Care Summit

Christopher Flowers, MD, MSc, FASCO
Professor, Hematology and Medical Oncology
Director, Lymphoma Program
Scientific Director, Winship Research Informatics
Emory School of Medicine

May 13, 2019
Consultant: Abbvie, Astra Zeneca, Bayer, Celgene (unpaid), Denovo Biopharma, Genentech/Roche (unpaid), Gilead, OptumRx, Karyopharm, Pharmacyclics/Janssen, Spectrum

Research Funding: Abbvie, Acerta, Celgene, Gilead, Genentech/Roche, Janssen Pharmaceutical, Millennium/Takeda, Pharmacyclics, TG Therapeutics, Burroughs Wellcome Fund, Eastern Cooperative Oncology Group, National Cancer Institute, V Foundation

Social Conditions and Policies
Region Level: Population, Age/sex distribution, poverty, socioeconomic status, public policy, cultural norms, discrimination

Social Institutional Context
Healthcare system, racial/ethnic integration, family, religion, social/economic gradient

Social Relationships
Social networks, social support, civic engagement, employment

Environmental Context
Building quality, pollution, residential/ environmental exposures

Individual Demographics
Age, socioeconomic status, health status, education, race/ethnicity, insurance status

Individual Clinical Factors
Treatment regimen, treatment delivery, stage, B symptoms, lab values (e.g., LDH, CEB), comorbid diseases

Biological Responses
Treatment toxicity, treatment response, treatment-related mortality, DLBCL-related mortality, All cause mortality

Biological/Genetic Pathways
DLBCL subtype, subtype biological processes (e.g., NFκB), genetic ancestry, DLBCL genotype, general subtype specific

Social and Environmental Context

Individual and Demographic Risk Factors

Disparate Health Outcomes

Biological Responses and Pathways

Biological-Environmental Interactions

1 Underlying pilot evaluation in collaboration with CIP/C. Similar to their prior work, described in Warner & Gomez J Community Health 2010

Numbered references refer to our prior publications examining racial disparities in lymphoma at each of these levels.
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

Blaise N. Poitè, MD, MPH1; Lucie L. Adams-Campbell, PhD2; Otis W. Brawley, MD1; Nina Bickell, MD2; John M. Careythers, MD3; Christopher R. Flowers, MD2; Margaret Foti, PhD, MD (Hon)4; Scarlett Lin Gomez, PhD, MPH5; Jennifer J. Griggs, MD, MPH6; Christopher S. Lathan, MD, MS, MPH7; Christopher I. Li, MD, PhD8; J. Leonard Lichtenfeld, MD9; Worta McCaskill-Stevens, MD, MSc10; Electra D. Paskett, PhD11.
Non-Hodgkin Lymphomas

• Non-Hodgkin lymphomas (NHLs)
  – heterogeneous group of B-cell and T-cell neoplasms
  – differing patterns of growth and response to treatment

• Prognosis depends on histologic type, stage, and treatment

Annual Lymphoid Cancers in the US

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

Teras LR, DeSantis CE, Morton LM, Cerhan JR, Jemal A, Flowers CR
Survival by Gender and Race for NHL Subtypes

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

Teras LR, DeSantis CE, Morton LM, Cerhan JR, Jemal A, Flowers CR
Diffuse Large B-Cell Lymphoma

- Most common lymphoid malignancy
  - 31% of adult NHL
- Aggressive: rapid growth and limited survival in the absence/inadequate tx
- Curable in 50% or more of cases
- Clinical outcomes highly variable

Advances in Treatment Improve Survival for Patients with Lymphoma


Gene Expression Defines Molecularly and Clinically Distinct Subgroups in DLBCL

Diffuse Large B-cell Lymphoma

DLBCL Subgroup | 5-Yr OS, %
--- | ---
PMBL | 64
GCB DLBCL | 59
ABC DLBCL | 30

Racial Differences in the Presentation and Outcomes of Diffuse Large B-Cell Lymphoma in the United States

Neha Malik, Pareen J. Shenoy, MBBS, MPH, Kevin Bumpers, MPA, Rajni Sinha, MD, MRCP and Christopher R. Flowers, MD

Winship Cancer Institute
Emory University

Advancing the possibilities...
Data Source: SEER

Surveillance, Epidemiology and End Results (SEER)

- Population-based cancer registry
  - collect information on new cancers and survival from specific geographic areas
  - Represents 26% of the US population

- Contains standardized data elements
  - tumor characteristics (including stage and histopathology)
  - patient demographics, baseline characteristics
  - survival data

Study Population

- Diagnosed with DLBCL 1992 to 2005
Age Distribution of DLBCL by Race
## DLBCL Demographics by HIV Status: SEER

<table>
<thead>
<tr>
<th>HIV Status</th>
<th>White</th>
<th></th>
<th></th>
<th>Black</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>Med Age</td>
<td>N</td>
<td>%</td>
<td>Med Age</td>
</tr>
<tr>
<td>HIV+</td>
<td>353</td>
<td>4%</td>
<td>46</td>
<td>126</td>
<td>17%</td>
<td>44</td>
</tr>
<tr>
<td>HIV-</td>
<td>3295</td>
<td>39%</td>
<td>68</td>
<td>309</td>
<td>42%</td>
<td>56</td>
</tr>
<tr>
<td>Unknown</td>
<td>4852</td>
<td>57%</td>
<td>71</td>
<td>295</td>
<td>41%</td>
<td>56</td>
</tr>
<tr>
<td>Total</td>
<td>8500</td>
<td>69%</td>
<td>730</td>
<td>53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# InterLymph Clustering of Other WHO Classified Lymphoid Malignancies

<table>
<thead>
<tr>
<th>NHL Subtype</th>
<th>ICD-O-3</th>
<th>White median Age</th>
<th>Black median Age</th>
<th>Other median age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-CELL NEOPLASM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cell prolymphocytic leukemia</td>
<td>9833</td>
<td>75.5</td>
<td>57</td>
<td>46.5</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>9671</td>
<td>71</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td>Follicular lymphoma, NOS</td>
<td>9690</td>
<td>66</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>Follicular lymphoma Grade 1</td>
<td>9695</td>
<td>63</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>Follicular lymphoma Grade 2</td>
<td>9691</td>
<td>64</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Follicular lymphoma Grade 3</td>
<td>9698</td>
<td>65</td>
<td>55</td>
<td>67</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>9680</td>
<td>68</td>
<td>52</td>
<td>66</td>
</tr>
<tr>
<td>Immunoblastic diffuse large B-cell lymphoma</td>
<td>9684</td>
<td>60</td>
<td>48</td>
<td>67</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>9678</td>
<td>58</td>
<td>50.5</td>
<td></td>
</tr>
<tr>
<td>Mediastinal (thymic) large cell lymphoma</td>
<td>9679</td>
<td>35</td>
<td>21.5</td>
<td>39</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>9687</td>
<td>41</td>
<td>39.5</td>
<td>49</td>
</tr>
<tr>
<td><strong>T-CELL AND NK-CELL NEOPLASM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precursor T-cell neoplasm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, unspecified</td>
<td>9702</td>
<td>65</td>
<td>54</td>
<td>65.5</td>
</tr>
<tr>
<td><strong>HODGKIN LYMPHOMA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical Hodgkin lymphoma</td>
<td>9650</td>
<td>50</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Lymphocyte-depleted classical Hodgkin lymphoma</td>
<td>9653</td>
<td>58.5</td>
<td>43</td>
<td>69</td>
</tr>
</tbody>
</table>
## Clinical Features at Presentation by Race

### Pts with complete staging (n=7,835)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White (n=31,285)</th>
<th>Black (n=2,511)</th>
<th>Other (n=3,213)</th>
<th>p-value W v. B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>52%</td>
<td>44%</td>
<td>58%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>III/IV</td>
<td>48%</td>
<td>56%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td><strong>B Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.6%</td>
<td>8.5%</td>
<td>5.9%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10.6%</td>
<td>11.4%</td>
<td>13.8%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>83.8%</td>
<td>80.1%</td>
<td>80.3%</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Clinical Features at Presentation by Race

• Black patients with DLBCL
  – Younger Age
  – More Advanced Stage
  – Shorter Survival
Kaplan Meier Curve - OS

Kaplan Meier Curve - OS White

Kaplan Meier Curve - OS Black

Kaplan Meier Curve - OS Other

W vs B p = 0.0007
W vs D p = 0.2439

Black
Other

00-03 04-06
92-95 95-99

00-03 04-05
92-95 96-99
Challenges

- Do all patients with DLBCL in the US receive standard chemo-immunotherapy?
- How does modern treatment of DLBCL impact survival in the US?
- Are there clinically differences in DLBCL that may reflect underlying biological variants (ABC vs GCB)?
Disparities in the Use of Chemo-Immunotherapy for Diffuse Large B-Cell Lymphoma in the United States

Christopher Flowers, MD, MSc¹, Stacey Fedewa, MPH², Amy Chen, MD, MPH², Joseph Lipscomb, PhD¹, Otis Brawley, MD², Elizabeth Ward, PhD²

¹Winship Cancer Institute
Emory University

²American Cancer Society
Data Source: NCDB

**National Cancer Database**
- Hospital-based cancer registry jointly sponsored by American Cancer Society & American College of Surgeons
- Contains standardized data elements
  - tumor characteristics (including stage and histopathology), and first course of treatment
  - patient demographics, patient insurance status, county of residence, facility type in which patients were treated

**Study Population**
- diagnosed with DLBCL (ICD-O codes 9679 & 9680)
  Jan 1, 2001 - Dec 31, 2004
- received all or part of their first course of treatment at the reporting facility
## Black Pts with DLBCL Present at Younger Age: NCDB

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>White (n=31,671)</th>
<th>Black (n=3,001)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age years (IQR)</strong></td>
<td>70 (57-79)</td>
<td>53 (42-68)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>70%</td>
<td>38%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex, female</td>
<td>48%</td>
<td>46%</td>
<td>0.0341</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>I/II</td>
<td>46</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>41</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>13</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>
Features at Presentation by Race

• Black patients with DLBCL
  – Younger Age
  – More Advanced Stage

• Black patients with DLBCL
  – More likely Uninsured
  – More likely Medicaid insured
  – Less likely to receive Chemoimmunotherapy
Study Limitations

- No direct pharmacy data for rituximab or chemotherapy
  - Comparison to SEER:Medicare
- Pt-level SES is not available in the NCDB
- Additional clinical data influence prognosis and treatment decisions
- Insufficient follow-up to describe impact on outcomes

  - Shenoy ASH 2009 (n=348 W and 107 B)
    - No racial differences in R-CHOP use, but differences in OS
Black/White Differences in the Treatment and Outcomes of Diffuse Large B Cell Lymphoma: A Matched Cohort Analysis

Pareen Shenoy, Kevin Bumpers, Nassoma King, Taoying Huang, Neha Malik, Rajni Sinha, Christopher Flowers

To examine Black/White differences in pts with DLBCL across:

- Baseline characteristics at diagnosis
- Use of CHOP vs. R-CHOP
- Treatment outcomes
Kaplan Meier Curve-OS of pts treated with CHOP

All patients

Kaplan Meier Curve-OS of pts treated with R-CHOP

TMA patients

Kaplan Meier Curve-OS of pts treated with CHOP

Kaplan Meier Curve-OS of pts treated with R-CHOP
Conclusions and Future Directions

- Racial differences in the presentation of DLBCL
  - Younger Age, More Advanced Stage, Shorter Survival
- Racial differences present in other lymphomas
  - CLL/SLL, PTCL, FL, HL
- Additional studies are needed to explore etiology and prognostic significance
Whole Exome Sequence Analysis

Figure 4

A

B

DLBCL Tumor

Matched Normal

DLBCL Tumor

Matched Normal
Whole Exome Sequence Analysis

Genetic heterogeneity of diffuse large B-cell lymphoma


*Duke Institute for Genome Sciences and Policy, 1Duke Cancer Institute and Department of Medicine, and 2Department of Statistical Science, Duke University, Durham, NC 27710; 3University of North Carolina at Chapel Hill, Chapel Hill, NC 27599; 4The University of Hong Kong, Queen Mary Hospital, Hong Kong, China; 5Duke University Medical Center, Durham NC 27710; 6Emory University, Atlanta GA 30322; 7Imperial College, London, United Kingdom; 8University of Massachusetts, Worcester, MA 01655; Northwestern University, Chicago IL 60620; 9Indiana University, Indianapolis IN 46202; 10Baylor University Medical Center, Dallas TX 75246; 11Cleveland Clinic, Cleveland, OH 44195; 12Division of Hematology and Comprehensive Cancer Center, Ohio State University, Columbus, OH 43210; 13Genetics and Development Biology Center, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD 20892; and 14Hudson Alpha Institute for Biotechnology, Huntsville, AL 35806

Edited by Elliott Kieff, Harvard Medical School and Brigham and Women's Hospital, Boston, MA, and approved November 27, 2012 (received for review April 2, 2012)

Genetic and Functional Drivers of Diffuse Large B Cell Lymphoma

Anupama Reddy1,2,22, Jenny Zhang1,2,22, Nicholas S. Davis1,2,22, Andrea B. Moffitt1,2,22, Cassandra L. Love1, Alexander Waldrop1, Sirpa Leppa1, Annika Pasanen1, Leo Merinanta1, Marja-Liisa Kajalainen-Lindberg2, Peter Norgaard3, Mette Pedersen1, Anne O. Gang1, Estrid Hogdall1, Tayla B. Heavican2, Waseem Lone2, Javeed Iqbal2, Qiu Qin1, Guojie Li1, So Young Kim1, Jane Healy1, Kristy L. Richards2, Yuri Fedorii1, Leon Bernal-Mizrachi1, Jean L. Koff1, Ashley D. Staton1, Christopher R. Flowers1, Ora Paltiel1, Neta Goldsmith1, Maria Calaminici1, Andrew Clear9, John Gribben2, Evelyn Nguyen1, Magdalena B. Czader10, Sarah L. Ondrejka1, Angela Collie1, Eric D. Hsi11, Eric Tse12, Rex K.H. Au-Yeung12, Yok-Lam Kwong12, Gopesh Srivastava12, William W.L. Choi12, Andrew M. Evens12, Manika Pilichowska13, Manju Sengar13, Nishitha Reddy13, Shaoying Li13, Amy Chadburn12, Leo I. Gordon10, Elaine S. Jaffe12, Shawn Levy12, Rachel Rempel12, Tiffany Tzeng1, Lanie E. Happ13, Tushar Dave12, Deepthi Rajagopal12, Jyotishka Datta12, David B. Dunson12, and Sandeep S. Dave12,23

Cell
DLBCL Genomics

Reddy Cell 2017
Zhang PNAS. 2013
Lee et al.
AACR 2019
A framework for understanding the relationships between social, environmental, biological, and patient-related factors and disparities in DLBCL survival (numbers indicate example publications from the references that address specific factors).

Flowers CR, and Nastoupil LJ Blood 2014;123:3530-3531
Conclusions and Future Directions

- Racial differences in the presentation of DLBCL
  - Younger Age, More Advanced Stage, Shorter Survival
- Racial differences present in other lymphomas
  - CLL/SLL, PTCL, FL, HL
- Additional studies are needed to explore etiology and prognostic significance

- Georgia State Registry
- LEO Cohort Study
**Core Infrastructure and Methodological Research for Cancer Epidemiology Cohorts (U01)**

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

**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

**GOAL:**
To Facilitate research that uses LEO infrastructure and supports interaction with Lymphoma NCTN
Racial Differences in DLBCL: Georgia
Rural and urban patients with DLBCL and follicular lymphoma have reduced overall survival: a National Cancer Data Base study.

- National Cancer Data Base (NCDB)
  - National registry: American College of Surgeons and the American Cancer Society
  - >70% of all new cancer diagnoses in the US from >1,500 CoC-accredited hospitals

- Received treatment 2004-2014
  - **Rural**: counties with <2,500 people
  - **Urban**: 2,500+ people but NO metro areas of at least 50,000 urbanized people
  - **Metro**: urbanized population of at least 50,000 in county

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![Flowchart diagram showing the process of selecting patients from the National Cancer Data Base.](image)

- Patients in National Cancer Database diagnosed with DLBCL 2004-2014 (n = 175674)
  - Excluded 79229 patients who were HIV-positive (n = 96445)
  - Excluded 3363 patients missing degree of urbanization data (n = 93082)
  - Excluded 9974 patients missing survival data (n = 83108)
  - Stratified rural patients (n = 1413)
  - Stratified urban patients (n = 10887)
  - Stratified metro patients (n = 70808)

- Patients in National Cancer Database diagnosed with Fl 2004-2014 (n = 90026)
  - Excluded 40652 patients who were HIV-positive (n = 49374)
  - Excluded 1625 patients missing degree of urbanization data (n = 47749)
  - Excluded 4456 patients missing survival data (n = 43293)
  - Stratified rural patients (n = 715)
  - Stratified urban patients (n = 5641)
  - Stratified metro patients (n = 36397)

- 1.7% rural 13.1% urban 85.2% metro 1.7% rural 13.0% urban 85.3% metro
Examinaing Memo/Urban/Rural Lymphoma Patients in LEO

LEO Center: 330
Emory: 330
University of Iowa: 222
Mayo Clinic: 736
MD Anderson: 887
University of Miami: 262
University of Rochester: 310
Cornell University: 272
Washington University: 218
Program Goals:
To eliminate death and suffering from lymphoma

Physician Team:
- Chris Flowers
- Mary Jo Lechowicz
- Jonathon Cohen
- Leon Bernal-Mizrachi
- Jean Koff
- Pamela Allen
- Kristie Blum

Winship CPC Pilot Grant
ACTSI Healthcare Innovation Grant

U01 CA220401
K24 CA208132
R01 CA206019
U01 CA195568
U01 supplements