Chronic Kidney Disease – A Window into Understanding Health Disparities

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Constance B. Wofsy Distinguished Professor and
Vice-Chair of Medicine, University of California San Francisco
Overview

• Case illustrating racial/ethnic disparities in kidney disease

• A premise about disparities as a focal point in science and medicine

• Definitions & framework for understanding disparities

• Science of disparities
  – Why kidney disease occurs more often in minorities
  – Glimpse of my research and others
A Patient

• **Chief Complaint:** 46 year old African American male presents to Emergency Room for generalized weakness, nausea and vomiting

• **History of Present Illness:** Increasing lower extremity edema for 2 months. Seen by private physician (primary care physician of his mother). No lab work done, but placed on furosemide. Edema improved, but worsening weakness with 15 pound weight loss over 2 months. Presented to Emergency Room with nausea and vomiting of 3 days duration

• **Past Medical History:** No diagnosis of kidney disease; no other significant past history (no HTN, DM, CVD)

• **Family History:** Diabetes and Hypertension run in family

• **Medications:** No prescription or over the counter meds
A Patient

• **Physical Examination:** Chronically ill appearing young man in no acute distress
  T 97.4F; HR 96; RR 16 BP 141/76; O2 Saturation: 99% (room air)
  HEENT: pale conjunctiva, no icterus, no JVP
  lungs clear, CV exam within normal limits, abdomen soft, nontender, nondistended, remainder of exam normal.

• **Laboratory findings:** Na 137, K 4.4, bicarbonate 19, chloride 90, AG 28, calcium 5.8, phos 13, BUN 240, creatinine 28

• **Hospital Course:** Admitted, seen by nephrology service. Temporary catheter placed, hemodialysis started on admission.
Key features

• African American patient with kidney failure
• Late presentation for care
• Poorly prepared for kidney failure
• Urgent initiation of hemodialysis possibly limiting optimal treatment
Premise
Science on disparities ... clinical care with diverse patients ... and education about disparities ... enhances all of Medicine and human health.

Learning about disparities allows the examination of complex interactions that contribute (often unequally for different clinical problems) to human health.
Race/Ethnic Composition
United States, California and ZSFG

U.S. Now: 69%
U.S. 2050: 47%
California: 49.2%
San Francisco: 44%
ZSFG: 5%

Other
Asian/Pacific Islander
Latino
African American
Caucasian

ZSFG = Zuckerberg San Francisco General Hospital
2015 - A Year of Anniversaries

December 1, 1955

• Rosa Parks changed the course of history and inspired us all

September 1985

• US Dept of Health and Human Services landmark Heckler report
• Documented health disparities among racial and ethnic minorities
• Disparities are "an affront both to our ideals and to the ongoing genius of American medicine."
• Served as driving force for ending health disparities and advancing health equity in America
Disparities: What do we mean?

• Disparity (dis per’ə tē) _n_. a difference or lack of _equality_/ --pl. –ties

• Health Care should be:
  – Safe
  – Effective
  – Patient centered
  – Timely
  – Efficient
  – **Equitable** = providing care that **does not vary** in quality because of personal characteristics such as gender, _ethnicity_, geographic location or socio-economic status

_Institute of Medicine_
Race: What do we mean?

• Race (rās) *n.* a group of people united or classified together on the basis of common history, nationality, or geographic distribution
  
  *Webster’s New World Dictionary, Revised Edition, 1996*

• “a construct of human variability based on perceived differences in biology, physical appearance and behavior”,-- not a biological reality.  *Institute of Medicine, United States*

• “Information about genetic group membership captured by notions of race is, in general, less than that obtained by making inferences of ancestry from geographic or explicit genetic data”  *Bamshad M.*
Inference of Individual Ancestry Proportions From Genetic Data

Non-uniformity of health among racial and ethnic groups is extensively documented

- **Life expectancy at birth** – Blacks vs. Whites, 10 year gap for men, 5 year gap for women
- **Infant mortality rate** – Blacks and Native Americans twice as high vs. Whites.
- **Death rate** – Blacks vs. whites: greater for cancer, diabetes, heart disease, HIV/AIDS, homicide; Hispanics vs. Whites: greater for diabetes
- **Morbidity** – For most ethnic minorities (Blacks, Native Americans, Hispanics and Asians) vs. Whites: higher for kidney failure; also for cancer, diabetes, hypertension, obesity, HIV/AIDS, tuberculosis, hepatitis
- Disparities persist even after accounting for socioeconomic status, insurance, lifestyle, and clinical factors
- Combined costs of health inequalities and premature death in the United States were $1.24 trillion¹

¹ LaVeist TA. Gaskin DJ. Richard P. THE ECONOMIC BURDEN OF HEALTH INEQUALITIES IN THE UNITED STATES. Joint Center for Political and Economic Studies September 2009
Eight Americas: Investigating Mortality Disparities across Races, Counties, and Race-Counties in the United States

Christopher J. L. Murray¹,²,³, Sandeep C. Kulkarni²,⁴, Catherine Michaud²,³, Niels Tomijima³, Maria T. Bulzacchelli³, Terrell J. Landiorio³, Majid Ezzati¹,²*

¹ Harvard School of Public Health, Boston, Massachusetts, United States of America, ² Harvard University Initiative for Global Health, Cambridge, Massachusetts, United States of America, ³ Center for Population and Development Studies, Harvard University, Cambridge, Massachusetts, United States of America, ⁴ University of California San Francisco, San Francisco, California, United States of America

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A B S T R A C T

Background

The gap between the highest and lowest life expectancies for race-county combinations in the United States is over 35 y. We divided the race-county combinations of the US population into eight distinct groups, referred to as the “eight Americas,” to explore the causes of the disparities that can inform specific public health intervention policies and programs.
<table>
<thead>
<tr>
<th>America</th>
<th>General Description</th>
<th>Population (Millions)</th>
<th>Average Income Per Capita</th>
<th>Percent Completing High School</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asian</td>
<td>10.4</td>
<td>$21,566</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>Northland low-income rural white</td>
<td>3.6</td>
<td>$17,758</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>Middle America</td>
<td>214.0</td>
<td>$24,640</td>
<td>84%</td>
</tr>
<tr>
<td>4</td>
<td>Low-income whites in Appalachia and the Mississippi Valley</td>
<td>16.6</td>
<td>$16,390</td>
<td>72%</td>
</tr>
<tr>
<td>5</td>
<td>Western Native American</td>
<td>1.0</td>
<td>$10,029</td>
<td>69%</td>
</tr>
<tr>
<td>6</td>
<td>Black Middle America</td>
<td>23.4</td>
<td>$15,412</td>
<td>75%</td>
</tr>
<tr>
<td>7</td>
<td>Southern low-income rural black</td>
<td>5.8</td>
<td>$10,463</td>
<td>61%</td>
</tr>
<tr>
<td>8</td>
<td>High-risk urban black</td>
<td>7.5</td>
<td>$14,800</td>
<td>72%</td>
</tr>
</tbody>
</table>

Mortality Experiences of the 8 Americas

Kidney Failure (End Stage Renal Disease) is up to 2.9 times greater in racial/ethnic minorities 2013

US Renal Data System Annual Data Report 2015; *adjusted for age, sex, race, ethnicity
Treating ESRD is costly, both personally and financially

<table>
<thead>
<tr>
<th></th>
<th>Age 50-54 expected remaining lifetime</th>
<th>Annual Medicare expenditures per person</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis patient</td>
<td>8 years</td>
<td>$85,000</td>
<td>↓</td>
</tr>
<tr>
<td>Transplant patient</td>
<td>20 years</td>
<td>$30,000</td>
<td>→</td>
</tr>
<tr>
<td>General population</td>
<td>30 years</td>
<td>$10,000</td>
<td>↑</td>
</tr>
</tbody>
</table>

→Need to pre-empt illness upstream through molecular knowledge, clinical therapeutics and behavioral interventions
Over Three Decades

Incidence Rate of ESRD by Race May be Declining but Greater for Minorities

CKD Prevalence May Also be Declining and is Similar in Blacks and Whites

US Renal Data System Annual Data Report 2014; *adjusted for age and sex

Relentlessness of CKD Progression in African Americans:
Cumulative Incidence of Events (Doubling of SCr, ESRD, or Death) in African American Study of Kidney Disease

Cumulative Incidence (%)

Follow-Up Time (Years)

Number At Risk
Usual BP & non-ACEI:
Low BP and ACEI:

0 1 2 3 4 5 6 7 8 9 10

0 10 20 30 40 50 60

Only Trial
Mixed Trial and Post-Trial
Only Post-Trial

Non-ACEI with Usual BP
ACEI with Low BP

0 1 2 3 4 5 6 7 8 9 10

215 210 196 183
168 151 130 120 104 63 23

ASK
Decline in $\text{eGFR}_{\text{cys}}$ Differs by Race at Early Ages, with Faster Annualized Rates of Decline Among Blacks

Risk of Projected* Kidney Failure Among 1,119,816 Adult in Kaiser Permanente Southern California is Greater for Blacks and Hispanics Compared to Whites

<table>
<thead>
<tr>
<th>Time after Entry eGFR</th>
<th>Black vs White</th>
<th>Hispanic vs White</th>
<th>Asian vs White</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 y</td>
<td>2.17 (1.89–2.49)</td>
<td>1.78 (1.56–2.02)</td>
<td>1.47 (1.20–1.80)</td>
</tr>
<tr>
<td>3 y</td>
<td>1.53 (1.45–1.61)</td>
<td>1.30 (1.24–1.36)</td>
<td>1.10 (1.03–1.19)</td>
</tr>
<tr>
<td>5 y</td>
<td>1.34 (1.29–1.39)</td>
<td>1.15 (1.12–1.19)</td>
<td>0.99 (0.94–1.04)</td>
</tr>
</tbody>
</table>

### During Study Period

<table>
<thead>
<tr>
<th></th>
<th>Black vs White</th>
<th>Hispanic vs White</th>
<th>Asian vs White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any entry eGFR</td>
<td>1.34 (1.30–1.38)</td>
<td>1.08 (1.05–1.10)</td>
<td>0.89 (0.85–0.92)</td>
</tr>
<tr>
<td>Entry eGFR ≥60 mL/min/1.73 m²</td>
<td>1.19 (1.47–1.23)</td>
<td>0.92 (0.89–0.94)</td>
<td>0.69 (0.66–0.73)</td>
</tr>
<tr>
<td>Entry eGFR &lt;60 mL/min/1.73 m²</td>
<td>1.54 (1.46–1.62)</td>
<td>1.49 (1.42–1.56)</td>
<td>1.41 (1.32–1.51)</td>
</tr>
</tbody>
</table>


The higher incidence of kidney failure among African Americans appears due to a faster rate of disease progression rather than greater prevalence of early stage CKD.

What are the contributing factors to this acceleration?
Susceptibility, initiation and progression factors contributing to excess ESRD incidence

- Biological
- Environmental
- Behavioral (e.g. lifestyle)
- Quality/adequacy of CKD care
Blacks are more likely to have a family history of ESRD than Whites.

Of 25,883 patients starting dialysis in southeast U.S: 1st or 2nd degree relative who was also being treated for ESRD.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Blacks</th>
<th>Whites</th>
<th>All</th>
<th>Blacks</th>
<th>Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Participants</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>22.8</td>
<td></td>
<td></td>
<td>14</td>
<td></td>
<td>14</td>
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<tr>
<td>20</td>
<td>23</td>
<td></td>
<td></td>
<td>9.5</td>
<td></td>
<td>6.4</td>
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<tr>
<td>15</td>
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<td>10</td>
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<td>5</td>
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<td>0</td>
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<td></td>
</tr>
</tbody>
</table>

12,030 US residents 45 yr and older in NC, SC, GA, TN, MS AL, LA, AR and contiguous states in the Reasons for Geographic and Racial Differences in cohort: parent, sibling, or child with kidney failure (dialysis or transplant).


Overview of the Choices for Healthy Outcomes in Caring for ESRD Study

- **Design**: National prospective cohort study comparing effectiveness of hemodialysis and peritoneal dialysis.
- **Follow-up**: range 6 months to 9 years.
- **Support**: since 1994 by 2 NIDDK, 1 NHLBI, 1 AHRQ grant.
- **Current RO1**: Retained Organic Solutes and Clinical Outcomes in Hemodialysis.
- **K awards and fellow research**: Coresh, Longenecker, Boulware, Astor, Miskulin, Shafer, Unruh, Melamed, Cavanaugh, Crews, Shafi, Scialla.
CHOICE Specimen Bank

- **Enrollment**: ~45 days after start
- **Specimen**
  - 0 1 2 3
  - 6 12 18 24 30 36 42 48

1041 enrolled

<table>
<thead>
<tr>
<th>N</th>
<th>n-Visits</th>
<th>n-Vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>895 13,502</td>
<td>91,231</td>
</tr>
<tr>
<td></td>
<td>(8 routine + 1 special)</td>
<td></td>
</tr>
</tbody>
</table>

- **Measurements**: ~10,000
  - **Serum**: Lp(a) levels + isoforms, CRP, IL-6, MMP3, p-selectin, TNF-beta
  - **Plasma**: Fibrinogen, PTH, iPTH
  - **DNA**: 16 candidates genes
    - Illumina panel - 1536 SNPs; 164 CVD genes; 87 admixture markers
    - 646 genomic DNA + 179 WGA DNA + QC of WGA
Issues Addressed in the CHOICE Study

- **Risk Factors & Prevention**
  - Risk factors for CVD

- **Diagnosis**
  - Detection of Comorbid Disease

- **Etiology**
  - Genetics
    - Small organic solutes and outcomes in dialysis
    - Inflammation

- **Therapy**
  - Hemodialysis vs Peritoneal dialysis
    - Mortality, quality of life, patient satisfaction
  - Dose of dialysis
  - Statin use and sepsis

- **Prognosis**
  - Residual renal function and survival
  - Comorbidity and survival
  - Cholesterol & mortality
  - Phosphate & mortality

- **CKD Complications**
  - Anemia
  - Bone and mineral disease
  - Blood pressure, PAD
  - Sudden cardiac death

- **Access (Equity) to Care**
  - Referral to nephrologist

- **Quality & Safety of Care**
  - Multidisciplinary rounds
  - Clinical practice guidelines
  - Vascular access monitoring
  - Peritoneal dialysis experience and outcomes

- **Resource Use/Costs**
  - Patient-physician contact

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83 study publications, 4 RO1s, multiple K awards and trainee projects
Case-control design in Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study participants

MYH9 is associated with nondiabetic end-stage renal disease in African Americans

W H Linda Kao¹⁻³,²⁵, Michael J Klag¹⁻³,²⁵, Lucy A Meoni²⁻⁴, David Reich⁵,⁶, Yvette Berthier-Schaad¹, Man Li¹, Josef Coresh¹⁻⁴, Nick Patterson⁶, Arti Tandon⁵,⁶, Neil R Powe¹⁻³, Nancy E Fink¹⁻³, John H Sadler⁷, Matthew R Weir⁷, Hanna E Abboud⁸, Sharon G Adler⁹, Jasmin Divers¹⁰, Sudha K Iyengar¹¹, Barry I Freedman¹⁰, Paul L Kimmel¹², William C Knowler¹³, Orly F Kohn¹⁴, Kristopher Kramp¹¹, David J Leehey¹⁵, Susanne B Nicholas¹⁶, Madeleine V Pahl¹⁷, Jeffrey R Schelling¹⁸, John R Sedor¹⁸,¹⁹, Denyse Thornley-Brown²⁰, Cheryl A Winkler²¹, Michael W Smith²¹,²⁴ & Rulan S Parekh¹⁻³,²², on behalf of the Family Investigation of Nephropathy and Diabetes (FIND) Research Group²³

Summary of studies of MYH9 or APOL1 genetic variants

Table 1 | Summary of studies of MYH9 or APOL1 genetic variants

<table>
<thead>
<tr>
<th>Population and etiology</th>
<th>Variant</th>
<th>OR</th>
<th>P value</th>
<th>Patients (cases/controls)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondiabetic ESRD (not biopsy-proven)</td>
<td>MYH9 E1</td>
<td>2.2</td>
<td>1.72×10⁻¹¹</td>
<td>669/806</td>
<td>Kao et al. (2008)²²</td>
</tr>
<tr>
<td></td>
<td>MYH9 E1</td>
<td>2.5</td>
<td>8.48×10⁻¹⁷</td>
<td>871/948</td>
<td>Freedman et al. (2009)³¹</td>
</tr>
<tr>
<td></td>
<td>MYH9 E1</td>
<td>2.0</td>
<td>2.57×10⁻⁰³</td>
<td>346/140</td>
<td>Behar et al. (2010)³⁶</td>
</tr>
<tr>
<td></td>
<td>APOL1 G1</td>
<td>4.9</td>
<td>3.50×10⁻⁰⁴</td>
<td>346/140</td>
<td>Tzur et al. (2010)³⁷</td>
</tr>
<tr>
<td>Biopsy-proven FSGS</td>
<td>MYH9 E1</td>
<td>4.5</td>
<td>1.00×10⁻¹³</td>
<td>188/370</td>
<td>Kopp et al. (2008)²³</td>
</tr>
<tr>
<td></td>
<td>MYH9 E1</td>
<td>3.7</td>
<td>3.98×10⁻⁰⁶</td>
<td>87/806</td>
<td>Kao et al. (2008)²²</td>
</tr>
<tr>
<td></td>
<td>APOL1 G1 or G2</td>
<td>10.5</td>
<td>1.07×10⁻²³ (G1)<em>; 4.38×10⁻⁰⁷ (G2)</em></td>
<td>192/176</td>
<td>Genovese et al. (2010)³⁶</td>
</tr>
<tr>
<td>Biopsy-proven HIVAN</td>
<td>MYH9 E1</td>
<td>5.3</td>
<td>2.00×10⁻⁰⁶</td>
<td>53/241</td>
<td>Kopp et al. (2008)²³</td>
</tr>
<tr>
<td>Biopsy-proven HIVAN and FSGS</td>
<td>MYH9 E1</td>
<td>4.9</td>
<td>2.20×10⁻²⁰</td>
<td>241/611</td>
<td>Nelson et al. (2010)³⁷</td>
</tr>
<tr>
<td>Hypertensive ESRD (not biopsy-proven)</td>
<td>MYH9 E1</td>
<td>1.9</td>
<td>2.00×10⁻⁰³</td>
<td>288/192</td>
<td>Kopp et al. (2008)²³</td>
</tr>
<tr>
<td></td>
<td>MYH9 E1</td>
<td>2.1</td>
<td>3.70×10⁻⁰⁷</td>
<td>347/806</td>
<td>Kao et al. (2008)²²</td>
</tr>
<tr>
<td></td>
<td>MYH9 E1</td>
<td>2.6</td>
<td>3.20×10⁻¹¹</td>
<td>696/948</td>
<td>Nelson et al. (2010)³⁶</td>
</tr>
<tr>
<td></td>
<td>MYH9 E1</td>
<td>2.4</td>
<td>8.66×10⁻¹⁴</td>
<td>696/948</td>
<td>Freedman et al. (2009)³¹</td>
</tr>
<tr>
<td></td>
<td>APOL1 G1 or G2</td>
<td>7.3</td>
<td>1.00×10⁻⁶¹*</td>
<td>1,002/923</td>
<td>Genovese et al. (2010)³⁶</td>
</tr>
<tr>
<td>T2DM and ESRD (not biopsy-proven)</td>
<td>MYH9 E1</td>
<td>NS</td>
<td>NS</td>
<td>284/192</td>
<td>Kopp et al. (2008)²³</td>
</tr>
<tr>
<td></td>
<td>MYH9 E1</td>
<td>1.3</td>
<td>5.6×10⁻⁰³</td>
<td>751/925</td>
<td>Freedman et al. (2009)³⁴</td>
</tr>
<tr>
<td>Hispanic American</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes-unrelated ESRD (not biopsy-proven)</td>
<td>MYH9 E1</td>
<td>3.7</td>
<td>6.88×10⁻⁰³</td>
<td>89/308</td>
<td>Behar et al. (2010)³⁶</td>
</tr>
<tr>
<td></td>
<td>APOL1 G1</td>
<td>15.5</td>
<td>8.80×10⁻⁰⁴</td>
<td>89/308</td>
<td>Tzur et al. (2010)³⁷</td>
</tr>
<tr>
<td>European American</td>
<td>Biopsy-proven FSGS</td>
<td>MYH9 E1</td>
<td>9.7</td>
<td>2.00×10⁻²⁰</td>
<td>221/125</td>
</tr>
<tr>
<td>American Indian</td>
<td>Kidney dysfunction (not biopsy-proven)</td>
<td>MYH9 SNPs</td>
<td>NS</td>
<td>NS</td>
<td>1,119</td>
</tr>
</tbody>
</table>

For consistency, all ORs and P values presented for MYH9 are for the SNP E1 rs4821480, after global ancestry adjustments, when available. The risk for the variants shown is for a recessive mode of inheritance, except the P values for Genovese et al. (2010)³⁶, marked by *, which are of an allelic test. Some cohorts have been used more than once in these studies. Abbreviations: ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; NS, not significant; OR, odds ratio; SNP, single nucleotide polymorphism.
Structure of the ApoL1 gene

- 14.5 kb gene on chromosome 22
- Located 14 kb downstream of MYH9
- Encodes 398 amino acids

Structure of ApoL1 (with annotated domains)

- 43 kDa protein - apolipoprotein family
- Produces a secreted protein bound to circulating HDL particles
- Expressed in various organs including kidney (podocytes, renal tubule cells, and glomerular endothelial cells)
- Involved in the autophagy pathway
Contour maps of allele frequency distributions of identified *APOL1* risk variants in a number of African countries.


Tryset flies live today in moist savanna and woodlands, regions with > 500 mm of rain a year.

Tryset flies carry a parasite which can infect livestock and people with trypanosomiasis (sleeping sickness).
AASK: APOL1 and CKD Progression in Longitudinal Studies

Factors contributing to Excess ESRD Incidence

• Biological
• **Environmental**
• Behavioral (e.g. lifestyle)
• Quality/adequacy of CKD care
Association of Poverty with CKD (eGFR <60) is Modified by Race

Total 25-Hydroxyvitamin D and Vitamin D–Binding Protein Levels in Community-Dwelling White and Black Participants

Factors contributing to Excess ESRD Incidence

• Biological
• Environmental
• Behavioral (e.g. lifestyle)
• Quality/adequacy of CKD care
Socioeconomic Status and Lifestyle Factors Explains 44% of the 3-fold excess risk of CKD in African Americans vs Whites

NHANES II (nationally representative)

High Dietary Acid Load and Progression to End Stage Renal Disease

- Study Design: National cohort study of 1486 adults with CKD enrolled in the NHANES III
- Exposure: Dietary acid load determined by 24-hour dietary recall questionnaire
- Outcome: ESRD over a median 14.2 years of follow-up through linkage with the Medicare ESRD Registry
- Confounders: demographics, nutritional factors, clinical factors, and kidney function/damage markers and accounting for intervening mortality events


Adjusted $\beta$ coefficients, from median regression. Points show $\beta$ coefficients per quintile, and bars show 95% confidence intervals.
Cumulative probability of ESRD with varying levels of dietary acid load

Factors contributing to Excess ESRD Incidence

• Biological
• Environmental
• Behavioral (e.g. lifestyle)
• Quality/Adequacy of CKD care
Minorities in the U.S. with Chronic Kidney Disease are more likely to have uncontrolled blood pressure

P=0.020, CKD

P=0.001, No CKD

*Adjusted for survey year, age, sex, education, income, insurance, obesity, diabetes, and treatment.

Socioeconomic Status, Lifestyle and Quality of Care Explains 44% of the 3-fold excess risk of CKD in African Americans vs Whites

NHANES II

Questions to Ponder

• How much does ApoL1 or other genes contribute to the disparity in ESRD incidence between African Americans and whites?
  – How important is ApoL1 or other genes in comparison to other modifiable risk factors? (population attributable risk – incidence reduction if all unexposed)
Questions to Ponder

• How much does ApoL1 contribute to the disparity in ESRD incidence between African Americans and whites?
  – How important is ApoL1 in comparison to other modifiable risk factors? (population attributable risk – incidence reduction if all unexposed)

• Are ApoL1 risk variants more susceptible to known kidney injury agents?
  – Do APOL1 variants alter response to an environmental factor or to treatment?

• Does knowing ApoL1 risk status lead to better health outcomes? What can be done?
  – better blood pressure and diabetes control, avoidance of nephrotoxins (contrast media, medications, NSAIDS), less acidic diets
  – decision to be a live kidney donor and donor outcomes
Questions to Ponder - Mechanism?

• APOL1 has an endogenous function in podocyte necessary to resist environmental stress and maintain podocyte health?
  – Pathways are dysregulated in presence of two risk variants where clinical disease manifests with the introduction of an environmental stress.

• Gene/gene interactions?
  – Modifier loci may explain the differences in kidney pathologies between FSGS, HIVAN and hypertensive-attributed nephropathy.

• Gene/environment interactions?
  – Modifiable environmental second hits (viruses, antiviral pathway) may explain gaps between lifetime risks in individuals with same genetic background

• Risk in circulating APOL1 or APOL1 expressed in kidney?

• Apoptosis in podocytes?
  – biosynthesis, trafficking, ion channel properties, endocytosis, and effects on organellar structure and function
### Insights from Studies Conducted in Diverse Race/Ethnic Groups

<table>
<thead>
<tr>
<th>Trait</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Breast cancer                       | Differences in Native American ancestry at the estrogen receptor locus led to discovery of a genetic variant that was protective against breast cancer in Latinas.  
[11]                                                                                  |
| Heart failure                       | A post-hoc analysis of clinical trials of fixed-dose combination of hydralazine and isosorbide dinitrate suggested that black, but not white patients had a significant reduction in mortality compared to placebo.  
[12]                                                                                  |
| Increased preterm birth rate        | Exposures to endocrine disrupting chemicals such as bisphenol-A (BPA) are more common among minorities who live in low socioeconomic strata. BPA causes epigenetic alterations of the germ line resulting in increased preterm birth rate; these alterations can pass down to future generations.  
[13]                                                                                  |
| Stevens-Johnson syndrome            | The risk of carbamazepine-induced Stevens-Johnson syndrome due to HLA-B*1502 is highest in populations of Southeast Asian and East Asian ancestry.  
[14]                                                                                  |
| Kidney disease                      | Genetic variants of APOL1 have been associated with kidney disease in individuals of African ancestry whose ancestors lived in regions of Africa endemic with trypanosomiasis; these renal risk variants are largely absent in individuals of European or Asian ancestry.  
[15]                                                                                  |
| Response to efavirenz               | Blood levels and treatment response to this antiretroviral drug are influenced by individual ancestral makeup, which can be accounted for by polymorphisms of cytochrome 2B6 and genetically defined ancestry.  
[16,17]                                                                             |
Factors contributing to Excess ESRD Incidence

• Biological
• Environmental
• Behavioral (e.g. lifestyle)
• Quality/Adequacy of CKD care - downstream
Over One Third of Black Dialysis Patients Receive a Late Evaluation by a Nephrologist < 4 months before dialysis

Adjusted for age race, sex, education, lack of health insurance, Index of Coexistent Disease (ICED), marital status, and exercise status
Late evaluations are associated with poor preparation for dialysis\(^1\)

<table>
<thead>
<tr>
<th>Timing* of Evaluation</th>
<th>Early (n=399)</th>
<th>Intermediate (n=184)</th>
<th>Late (n=245)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Albumin &lt;3.6mg/l</td>
<td>60%</td>
<td>63%</td>
<td>78%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit &lt;30%</td>
<td>56%</td>
<td>66%</td>
<td>68%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Erythropoietin before dialysis</td>
<td>25%</td>
<td>31%</td>
<td>12%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*time from first nephrologist evaluation to first dialysis <4 months (late); 4-12 months (intermediate); greater than 12 months (early)

Other studies: At start of dialysis, Blacks less likely to initiate dialysis with a fistula\(^2,3\), have hypertension controlled\(^4\) and have anemia managed\(^5,6\)

2.USRDS Annual Data Report 2013
3. Healthy people 2020
Late specialty referrals resulted in worse mortality overall; up to 7-fold greater for Blacks.

Poorly prepared patients miss opportunities to make informed treatment choices

Hemodialysis (HD)
- In Center
- At home

Peritoneal Dialysis (PD)
- At home

Transplant
- Living
- Deceased

Graphics courtesy of National Kidney and Urologic Diseases Information Clearinghouse; NIDDK, NIH
Does choice of therapy matter?

- Debate on hemodialysis versus peritoneal dialysis
  - Risk of death in first year of treatment equivalent¹
  - Hemodialysis may yield better long-term outcomes¹
  - More frequent hemodialysis at home may be better²
  - Self-care modalities enhance quality of life

- Transplant yields better (up to 2-fold) length and quality of life and less cost compared to dialysis³,⁴
  - Live donor transplant better⁵
  - Pre-emptive transplant better⁶,⁷

African Americans versus Whites

• Less likely to be waitlisted and transplanted\(^1\)
• Less likely to receive live kidney transplants\(^2\)
• Less likely to have knowledge of kidney replacement therapies\(^3\)
• Less knowledge of transplant prior to dialysis initiation\(^4\)
• Lower health literacy – health literacy associated with transplantation\(^5\)
• Less knowledgeable when being evaluated for transplant; when knowledge is accounted for race differences in transplant evaporate\(^6\)

1. United States Renal Data System 2015 Annual Report
2. Gore JL, Danovitch GM, Litwin MS, Pham PTT, Singer JS. Disparities in the Utilization of Live Donor Renal Transplantation. AJT 2009 9:1124-1133
Summary and Conclusions

- African American patient with late presentation for care, poor preparation for ESRD, urgent hemodialysis initiation
- Treating disease at end-stage is costly, both personally and financially, and limits access to optimal therapies
- Biologic, socioeconomic, behavioral & clinical determinants conspire to compromise health & healthcare
- Need to develop and rigorously test interventions created to address these determinants to human health
  - Learn how to pre-empt illness through molecular knowledge, therapeutics and behavioral interventions
- Disparities research allows examination of complex interactions that contribute (often unequally) to health
Summary and Conclusions

• A growing proportion of Americans are not fully benefiting from clinical and biomedical advances since racial and ethnic minorities make up ~ 40% of the United States population\(^1\)
• Most physicians and scientists are informed by research extrapolated from a largely homogenous population\(^1\)
• Ignoring diversity of US population is a missed scientific opportunity to understand factors that lead to disease or health\(^1\)
• US biomedical research and study populations must better reflect the country’s changing demographics. \(^1\)
• **Science on disparities, clinical care with diverse patients, and education about disparities enhances all of Medicine and human health.**

THANK YOU!