General Session V

Blue Ribbon Presentations: 10 Year Anniversary – Lessons Learned
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DISCLOSURE STATEMENT

Speakers for this session have nothing to disclose. Any updates in disclosure will be made from the podium.
Transdisciplinary Team Science: Applying an Exposome Paradigm to Health Disparities

Xavier Health Disparities Conference
New Orleans, Louisiana
March 17, 2017

Paul D. Juarez, PhD
Professor & Vice Chair, Department of Family & Community Medicine
Director, Health Disparities Research Center of Excellence
Meharry Medical College
Health Disparities

**Inputs**
- Individual Traits
- Environmental Exposures

**Processes**
- Pathways
- Mechanisms

**Outputs**
- Personal Health
- Health Disparities
Exposome

**Definition:** Cumulative exposures from conception to death that affect health

* (C. Wild, 2005)
Paradigm Shift

Conceptual
• Systems Approach
• Transdisciplinary
• Life Course
• Critical Periods

Methodological
• Taxonomy
• Big Data
• Spatial
• Temporal

Exposome

Systems Approach Taxonomy
Transdisciplinary Life Course Critical Periods
Exposome
Complete Exposure Pathway

- Source of Exposure
- Transport Mechanism
- How it gets Under the Skin
- Biomarkers of Exposure
- Biomarkers of Disease
- Disease Phenotype
- Personal Health Outcomes
- Population Level Health Disparities
Etiological, Mediating, & Moderating Factors
Transdisciplinary Team

- Paul D. Juarez*, PhD, Social Policy
- Darryl B. Hood, PhD, Environmental Toxicology
- Gary L. Rogers, PhD, Computer Science
- Suzanne H. Baktash, MPH, Epidemiologist
- Arnold M. Saxton, PhD, Statistician
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- Wansoo Im, PhD, Urban Planning/GIS
- Myriam Patricia Cifuentes, MD, PhD, Public Health
- Charles A. Phillips, PhD, Computational Biology
- Michael A. Langston, PhD, Engineering
Thank You!
Xavier University Tenth Health Disparities Conference: Blue Ribbon

Presentation: 10 Year Anniversary-Lessons Learned

Mississippi Delta Health Collaborative
Jackie Hawkins, MS
Community Project Manager
Mississippi State Department of Health
March 16-17, 2017
New Orleans, LA
Disclosure

- Funded by the Centers for Disease Control and Prevention, Cooperative Agreement #2 U50DP003088-6-00

- Centers for Disease Control and Prevention to the Mississippi State Department of Health to establish the Mississippi Delta Health Collaborative in the 18 counties of the MS Delta region to reduce risk factors for cardiovascular disease.
Learning Objectives

- Discuss ways local health departments can build strategic alliances to implement successful collaborations that address health threats in the community.

- Compare innovative ways to structure local health departments that maximize resources to enhance service delivery to the community.
Delta Health Collaborative Overview

The Mississippi Delta Health Collaborative (MDHC) provides leadership in the Mississippi Delta region to implement heart disease and stroke prevention interventions to reduce morbidity, mortality, and related health disparities.

The MDHC works with partners to educate and implement policy, environmental, and healthy system changes to increase heart disease and stroke prevention with emphasis on the **ABCS** among priority populations in high burden, underserved, rural areas.

- **A**spirin: Increase low dose aspirin therapy according to recognized guidelines
- Hemoglobin **A**1c (HbA1c): Monitor and control blood glucose
- **B**lood pressure: Prevent and control high blood pressure
- **C**holesterol: Prevent and control high LDL-cholesterol
- **S**moking: Prevent initiation and increase cessation of smoking, and increase the percentage of population protected by smoke-free air laws or regulations.
Mississippi Delta Region

- 50% African-American (Range: 22%-83%)
  - Mississippi: 37%
  - U.S.: 13%

- 33% below poverty level (Range: 9-48%)
  - Mississippi: 22%
  - U.S.: 14%

- 29% < HS education (Range: 13-40%)
  - Mississippi: 21%
  - U.S.: 15%

Medically Underserved Area\(^1\)

\(^1\) Health Resources and Services Administration (HRSA): http://muafind.hrsa.gov/
MDHC: 2008 – 2010

Goals

- Develop infrastructure at the community level to facilitate policy and environmental system changes to support healthier lifestyles and decrease risk factors for heart disease and stroke, leading to the reduction in chronic disease prevalence and incidence.

- Improve management of hypertension among consumers and reduce the incidence of hypertension among adults at-risk for developing the disease.

- Address social determinants of health and eliminate health disparities by reaching beyond public health and bringing together diverse representation from the community, government, law enforcement, recreation, business, transportation, health, public and private organizations, and academia.
MDHC: 2008 - 2010

Program Objectives:
- Increase access to **physical activity**
- Increase access to **healthy foods**
- Increase access to **quality care**
- Improve **management of hypertension**
- Reduce **Tobacco Use**
- Reduce **health disparities** by addressing the social determinants of health
Mississippi Delta Health Collaborative Evidence-Based Interventions

1. Policy, Systems and Environmental Change through Mayoral Health Councils and County Health Networks
2. Delta Alliance for Congregational Health/ABCS Screening Program
4. Clinical Community Health Worker Initiative
5. Medication Therapy Management
6. Cardiovascular Health Examination Survey
What is a Mayoral Health Council

Mayor Health Council is a partnership with Delta municipalities to establish coalitions governed by the Mayor’s Office with the responsibility of creating healthy environments through policy systems and environmental changes which support:

- Increased access to physical activity, healthy foods, reduced exposure to tobacco smoke
- Reducing the prevalence of heart disease and stroke; and
- Engaging key stakeholders to enact policies which support the reduction of risk factors for heart disease and stroke prevention.
Mayoral Health Council Initiative

- The Mayoral Health Council Initiative (MHC) serves as a foundation for implementing policy, systems and environmental change:
  - Established in 2010
  - Diverse council with community stakeholders
  - Led by Mayor’s Office
  - Designated Coordinator
  - Required focus on physical activity, nutrition, and tobacco free environments through policy, systems, and environmental change strategies
“BUILDING COMMUNITY CAPACITY IN RURAL MISSISSIPPI DELTA FOR POLICY AND ENVIRONMENTAL SYSTEMS CHANGE.”

Jackie S. Hawkins, MS, BS
Mississippi Delta Health Collaborative
Mississippi State Department of Health
Fourth Health Disparities Conference,
Xavier University, New Orleans, La
March 28, 2011
What does your neighborhood look like?
- Run Down
- No Recreation
- No Parks
- No Grocery Stores
- Needs Supermarkets
- Pesticide (cars, houses, lungs)
- Too Much Dust

What are the strengths in your neighborhood?
- Crime Rate
- A lot of Open Ground
- A lot of Young People
- A MAYOR THAT CARES!!
- Someone from every sections of town came to the meeting

What actions could be taken to sustain those strengths?
- Unity/Commitment
- Working Together
- Keeping Citizens Informed
- Leadership Keys
- Motivation
- Knowing what to ask
- Leaders in Different Areas (team captains).
What actions could be taken to sustain those strengths
• Unity/Commitment
• Working Together

Who can help us take those actions?
• MS Delta Health Collaborative
• Mayor and Board
• Citizens of Town

What actions could be taken to make those improvements
• Enforce the 911 rule
• Lighting in the community
• Signs (Street)
• Farmer’s Market

What things in your neighborhood need to be improved to reduce chronic stress, give residents better access to healthy choices, and/or give people a greater control over their lives?

• Visible addresses of homes for emergencies
• Keep trash picked up
• Recreation Center
• Walking Trails/Sidewalks
• Street...
Common Themes

- Stray dogs
- No parks
- No grocery stores
- Travel 20 miles for nearest grocery store for fresh fruits and vegetables
- Not enough lighting
- No walking trails
- Too much trash
- Pesticides
Results

During a 9-month time frame:

- Five (5) municipalities worked with their local school districts to implement joint-use agreements allowing community members to use school facilities

- Four (4) municipalities implemented smoke-free air policies

- Eleven (11) municipalities developed community gardens
Outcomes 2008 – 2010
Mayoral Health Councils

- 80% of Mayor’s Health Councils reported adopting a land use plan or complete streets plan to support walking and biking
- 74% of Mayor’s Health Councils reported providing access to or making improvements to places for physical activity
- 63% of Mayor’s Health Councils reported they had either encouraged or established community gardens
- 47% of Mayor’s Health Councils instituted a 24/7 smoke-free policy for indoor public places
Mayoral Health Council Initiative as an Evidence-Based Model for Policy, Systems, and Environmental Change!!!
ABCS Goals
- Aspirin Use
- Hemoglobin A1c Control
- Blood Pressure Control
- Cholesterol Control
- Smoking Cessation

Policy, Systems, and Environmental Change

Cardiovascular Health Examination Survey
Impact Since 2010

- 69 MHCs have been established
- 40 comprehensive smoke-free ordinances serving 170,266 people
- 9 complete streets serving 22,058 people
- 25 physical activity shared-use agreements serving 148,843 people
- 9 land-use agreements serving 17,937 people
- 12 SNAP Certified Farmer Markets
- 12 Corner/Convenient Stores offering Fresh Fruits and Vegetables
- 1 Bike Friendly Town
- 2 Built Environment Policies
“Access to Healthy Food & Marketing Healthy Behaviors”
Indianola MHC partners with Love’s Gas Station to offer Fresh Fruits
Expanded our Reach Across the State
Smoke-Free and Shared Use Agreements Policies
Let's Play Mayors Challenge

- 27 cities and towns
  - 4 municipalities in the MS Delta Participated: Marks, Tchula, Vaiden, Greenville, and Gunnison
  - Devote at least 1 additional hour to active play
  - Receive the most pledges as a percentage of population will win the opportunity to build a new playground in their community
  - Sponsored by Dr. Pepper Snapple Group

The Town of Vaiden, MS; Carroll County won second place out of the 27 participating cities and towns in Mississippi.
Mayoral Health Council Activities
Community Raised Funds to Construct this Playground
City of Vicksburg Walking Trial in Partnership with My Brothers Keeper
Leveraging Funding

- Cities and towns have been able to leverage additional funding from sources such as:
  - Kaboom
  - Safe Routes to School
  - Blue Cross and Blue Shield of Mississippi
  - MS Wildlife Fisheries and Parks
  - MS Department of Transportation
  - Foundation for the Mid-South,
  - Dreyfus Foundation, Kellogg Foundation,
  - Mississippi Emergency Management,
  - United Healthcare
  - American Heart Association

- An estimated total of $3.5 million in funding
  - Construction of sidewalks, street lights and signs
  - Parks and Walking trails,
  - Community and church gardens,
  - Summer feeding,
  - Satellite library
  - Construction of community centers and recreation centers
  - 911 systems and weather sirens
  - Farmers markets, smoke free air, joint use agreements,
  - Bike lanes and playground equipment
  - Commercial blood pressure machines
Success Stories
Success Stories

In partnership with Tallahatchie General Wellness Center, the City of Charleston submitted an essay for the Robert Wood Johnson Foundation Cultural of Health Prize and was asked to submit an application. Applicants will be notified March 2017.
Town of Pickens
The Mayoral Health Council started a walking group titled “Walk By Faith,” which participates Monday thru Thursday in the early morning times at 6:00am. The group is led by the Mayor himself. As the town focused on improving the community’s involvement in physical activity, the Mayoral Health Council began hosting a Aerobics Class twice a week on Tuesday and Thursdays evenings for a hour each session in The Court Room.

The Town of Alligator
Thanks to the Mississippi Delta Health Collaborative, we, the town of Alligator now have our first community food pantry in Partnership with the Ms Food Network. We serve 68 families in all in Alligator, which equates to 167 people, ranging from ages 1-85. As a result of this feeding program, we have increased volunteers and health council support. The health council continues to provide residents with information that helps to improve the health outcome of our residents. Thanks Mississippi Delta Health Collaborative for all the support!

The Town of Louise
Our Mayor’s health council was just formed in October of 2015, but it has already been very effective at bringing people together. The town of Louise has always been somewhat divided racially, but since we have gotten a Shared Use Agreement to use our abandoned fire station for exercise, we have seen different races of people come together that probably would not have come together under other circumstances. So that has been a plus for us. Also, we have seen quite a few of our community members coming out to support us in other endeavors, like our breast cancer awareness walk this year. Both adults and youth were line up at city hall downtown, and we all walked together for two miles until we reached the ball park area. Once there, some of the participants even hung around to get screened. So our council has been a good thing in terms of bringing people together.
Success Stories

Town of Cary
The Mayoral Health Council was able to build partnership with the most active church in town, Mt. Zion Baptist Church. During the partnership, the two started a 90 day Biggest Loser Challenge to encourage community members to partake in physical activity. A Share Use Agreement was approved between the two entities to utilize the exterior field area outside on church grounds for future physical activity programs. Also, the Mayoral Health Council and Mt. Zion Baptist Church was able to establish a community garden in which tomatoes, onions, squash, greens and other vegetables were produced and later distributed among the community. The partnership hosted a Fun Day in which the Mayoral Health Council. The town received a $2,500 grant from the Mississippi Department of Transportation for repaving the main street leading to the Cary Christian Center behind Town Hall and adding new street bumps to slow down the flow of traffic.

Town of Goodman
The Mayoral Health Council was able to partner with Holmes Community College Summer Basketball Program with a agreement to provide a healthy concession during the program tenure. These healthy options consisted of fruit, vegetables, popcorn, and water. (Fruits and Vegetables were provided from F.S.H.S. Micro Mall, a Fruit & Vegetable Stand in Downtown Goodman).

Town of Durant
The City of Durant in partnership with the Mississippi State Department of Health Division of Nutrition, Physical Activity and Obesity and Alcorn Extension service established a Farmers Market.
TOOLKIT CONTENTS
Mayoral Health Council Toolkit

- *Working Together for a Healthy City (WTHC)*
- Five phases
  - Phase 01: Collect information
  - Phase 02: Identify leadership
  - Phase 03: Engage the community
  - Phase 04: Establish the council & community action plan
  - Phase 05: Sustain the council
- Guides:
  1. Telling Your Story
  2. Effective Meetings
  3. Using the Media
  4. Evaluation
  5. Role of the Coordinator
  6. Role of the Mayor
  7. Reference
- Organizations will be required to complete WTHC certificate training program
Delta Alliance for Congregational Health

- 77 churches since 2009
- 73 congregational health nurses and advocates
- 5,641 individual ABCS health screenings performed
- 3,154 individual blood pressure screenings performed, revealing
  - 1,593 individuals with high blood pressure
  - (170 of these displayed undiagnosed hypertension and 1,223 were pre-hypertensive)
- 523 were referred to a community health worker for follow-up
B.R.O.T.H.E.R.S.
Barbers Reaching Out to Help Education on Routine Screenings

- 27 participating barbershops
- 17 barbershops smoke-free
- 3,400 individual blood pressure screenings performed revealing
  - 520 individuals were hypertensive
  - 1,320 individuals were pre-hypertensive
  - 813 individuals were referred to a community health worker for follow-up
National Recognition

- Health Education and Behavior Journal
  - MDHC 2008 - 2010

- Centers for Disease Control and Prevention Preventing Chronic Disease Journal
  - BROTHERS Barbershop Hypertension Reduction Initiative

- Centers for Disease Control and Prevention Division of Heart Disease and Stroke Prevention, Evaluation Branch
  - Field Notes on CHWs, DACH, CHES, and MTM

- Association of State and Territorial Health Officers – National Prevention Strategy
  - Mayoral Health Council Initiative

- National Association of City and County Health Officials
  - Cardiovascular Health Examination Survey

- University of Mississippi Medical Center
  - Rural Health Champion Award

- Presented at Several National Conferences
  - APHA, NACCHO, Obesity Summit, NIH Minority Health, Xavier Health Disparities, CHW Conference
Thank You!

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www.healthyms.com/MDHC
Inequity and Health Care diversity: Challenges that are facing patients with Sickle Cell Disease

Cassandra Dobson, PhD, RN-BC
Associate Professor, Lehman College, CUNY
Xavier Health Disparities Conference: March 16-18, 2017
Diversity =

Different Individuals
Valuing Each other Regardless of Skin
Intellect
Talents
Years

DUP ICATION PROHIBITED
History of SCD, Myths and Scientific findings

- James B. Herrick: First to draw “sickle-shaped” red blood cells, in a paper about a dental student from Grenada with pain episodes, anemia and yellow eyes. (1910)

- R. Janet Watson: First to suggest that fetal hemoglobin might protect from sickle cell problems in newborn infants. (1948)

- Linus Pauling: Attributed the many problems of sickle cell disease to a single abnormal molecule - sickle hemoglobin. (1949)
Red Blood Cells have hemoglobin in them

Hemoglobin carries oxygen from the lungs to the tissues of the body. In sickle disease, unloading the oxygen can cause the cell to change shape and get stuck in the blood vessel.
Normal Human Hemoglobins
(Adult Distribution)

<table>
<thead>
<tr>
<th>Hemoglobin Type</th>
<th>Structure (4 globins/hemoglobin molecule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb A</td>
<td>$\alpha_2\beta_2$ (&gt;95.5%)</td>
</tr>
<tr>
<td>Hb F</td>
<td>$\alpha_2\gamma_2$ (&lt; 1% in adults; 90+%</td>
</tr>
<tr>
<td></td>
<td>in newborns)</td>
</tr>
<tr>
<td>Hb A$_2$</td>
<td>$\alpha_2\delta_2$ (2-3.5%)</td>
</tr>
<tr>
<td></td>
<td>(uncertain function, elevated in beta</td>
</tr>
<tr>
<td></td>
<td>thalassemia trait)</td>
</tr>
</tbody>
</table>

There are two beta globin producing genes, one on each chromosome #16. A specific mutation in a beta globin gene causes it to produce sickle, rather than normal, beta globin.
Sickle Cell Trait (Hb AS)

- Normal blood counts, normally shaped red blood cells
- Most have NO symptoms

Most people with sickle cell disease in this country have ancestors from Africa, because having sickle cell trait protects from dying of malaria. One in 12 African Americans have sickle cell trait.
Parents with sickle cell trait: hemoglobin AS

- Probability of child with hemoglobin AA: 25%
- Probability of child with sickle cell trait AS: 50%
- Probability of child with sickle cell disease SS: 25%

Trait status can ONLY be determined by a test for hemoglobin analysis (usually HPLC). This test will also detect other types of hemoglobin that, combined with Hb S, will cause sickle cell disease!
<table>
<thead>
<tr>
<th>Hb Type</th>
<th>Sickle Cell Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb SS</td>
<td>Sickle Cell Anemia</td>
</tr>
<tr>
<td>Hb SC</td>
<td>Milder (except eyes and hips)</td>
</tr>
<tr>
<td>Hb Sβ⁰-thalassemia</td>
<td>Similar to SS</td>
</tr>
<tr>
<td>Hb Sβ⁺-thalassemia</td>
<td>Milder</td>
</tr>
<tr>
<td>Hb SD</td>
<td>Similar to SS</td>
</tr>
<tr>
<td>Hb SE</td>
<td>Often no symptoms</td>
</tr>
<tr>
<td>Hb SG</td>
<td>Generally no symptoms</td>
</tr>
<tr>
<td>Hb S₀Arab</td>
<td>Similar to SS</td>
</tr>
<tr>
<td>Hb S/HPFH</td>
<td>No symptoms</td>
</tr>
</tbody>
</table>
De-oxy hemoglobin polymerizes into long chains
Elongates red cell
Shortens red cell survival (anemia), impedes blood flow (pain and organ damage), damages blood vessels
Acute and Chronic Problems Related to Sickle Cell Disease

- Acute anemia
  - Spleen sequestration
  - Aplastic crisis (parvovirus B19)
- Infection
- Pain
- Acute chest syndrome
- CNS
  - Stroke, cognitive
- Priapism

- Avascular necrosis
  - Hip most disabling
- Leg ulcers
- Renal
  - Concentrating defect
  - Hyperfiltration
  - Renal insufficiency
  - Pulmonary hypertension
  - Ocular
    - Retinopathy
    - Retinal artery occlusion
- Gallstones, hepatopathy
- Early mortality
  - SS mid-late 40’s
The median age at death among patients with sickle cell anemia was 42 years for males and 48 years for females.
Stem Cell Transplant for Sickle Cell Disease

- Only curative therapy - no more sickle cells!!!

- Problems
  - Rejection/non-engraftment (transplanted cells don’t “take”)
    - Infection, bleeding
  - Graft vs Host Disease (transplanted cells attack the host)
Stem Cell Transplant for Sickle Cell Disease

- **Donors**
  - 1 in 4 chance any full sib will match (safest)
  - Umbilical cord blood from placenta can be used - free storage available for newborns sibs of children with SS (Via cord)
  - Alternatives: Unrelated matched donors (including cord blood) (Marrow Registry); related partially matched donors (parent)

- **Toxicity**
  - Less chemotherapy to remove sickle marrow may be possible; fewer risks and side effects

- **Alternatives**
  - Gene therapy?
Stem Cell Transplant for Sickle Cell Disease

50 transplants, compatible (matched) sibs

Walters MC. Blood 2000
Hydroxyurea

- Only approved medication for specific treatment of sickle cell disease
- Inhibits ribonucleotide reductase (Interferes with DNA synthesis)
- Increases fetal hemoglobin
- Makes cells less sticky
- Reduces cellular dehydration
- Improves deformability
- Releases/replenishes nitric oxide (Improves blood vessel function)
- Decreases white blood cell (WBC) count
  - High WBC poor prognostic factor
<table>
<thead>
<tr>
<th>Event</th>
<th>HU (N=152)</th>
<th>Placebo (N=147)</th>
<th>Δ (%)</th>
<th>P-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Evts/Yr</td>
<td>2.5</td>
<td>4.6</td>
<td>-46</td>
<td>.001</td>
</tr>
<tr>
<td>Time to 1st</td>
<td>2.76 mo</td>
<td>1.35 mo</td>
<td>+104</td>
<td>.014</td>
</tr>
<tr>
<td>Time to 2nd</td>
<td>6.58 mo</td>
<td>4.13 mo</td>
<td>+59</td>
<td>.002</td>
</tr>
<tr>
<td>ACS Episodes</td>
<td>56</td>
<td>101</td>
<td>-45</td>
<td>.003</td>
</tr>
<tr>
<td>Pts Tx’d</td>
<td>55</td>
<td>79</td>
<td>-30</td>
<td>.002</td>
</tr>
</tbody>
</table>


FDA-approved for adults with sickle cell anemia 1998
MSH 17.5 yr F/U
Overall death rate 43%
87% of deaths in HU
(never or <5yr)
3 malignant deaths
(uterus, breast, adeno ca)
(<5y (1); 5-10y (2))

Steinberg. AJH 2010
Pediatric Hydroxyurea Phase III Clinical Trial
(BABY-HUG): OVERVIEW

- 14 Clinical Centers, 1 Coordinating Center
- Double-Blind, Placebo controlled
- 193 infants randomized
  - Hb SS
  - Age 9-17 months
  - Informed consent
  - Follow-up 2 years (final exit 10/09)
  - Markers for organ damage (1st spleen, kidney)
  - Safety/Toxicity/Compliance
BABY HUG Results

- Primary endpoints: No impact on spleen or kidney damage
- Improved blood counts
- Reduced complications
  - Pain (50%)
  - Acute chest (70%)
  - Hospitalizations (30%)
- May reduce early brain injury, stroke risk
- No unexpected/severe side effects

The Lancet. May 2011
Limitations/Toxicity

- Birth defects? Not in humans.
- Reduced fertility? Reduced sperm, ?impact?
- Hair loss? Sometimes, minimal
- Nausea? Take it at night.

Requires monitoring of blood counts every 1-2 months
Side Effect

Short-term
- Decreased leukocyte count (leukopenia)
- Decreased platelet count (thrombocytopenia)
- Decreased erythrocyte count (anemia)
- Nausea (usually mild)*
- Skin rash
- Pneumonitis (lung inflammation)
- Temporarily decreased sperm count or sperm abnormalities*

Long-term
- Increased risk for superficial skin cancer*
- Skin and nail darkening (hyperpigmentation)
- Permanently decreased sperm count*

Reproductive*
* Evidence is insufficient or low that this side effect is associated with hydroxyurea.
Greece
Mostly sickle thalassemia (33 SS)
131/330 commenced HU mean age 33 yr (non-random (severity))
Median FU 8 (HU) and 5 (no HU) yr
Dramatic reduction pain, chest syndrome, transfusions
Management of Acute Pain Episodes

- Hydration ([Na])
- Analgesia
  - NSAID’s (Ketorolac?)
  - Morphine, Hydromorphone (PCA?)
- Non-pharmacologic
  - Guided Imagery, Behavioral, Psychological, Physical
- Pulse Oximetry (monitor for acute chest syndrome (ACS), respiratory depression)
- Incentive Spirometry (reduce risk of ACS)
Addiction?

- Tolerance
- Physical Dependence

- Expected
  - Increased dose required
  - Tapering required

Addiction – Compulsive drug use characterized by continued craving for an opioid and a need to use the opioid for effects other than pain control
A patient who believes that a medication will not be given unless he or she appears to be in severe pain may lie quietly when alone but begin to writhe and moan when a nurse or physician enters the room.

Pseudo-addiction or clock-watching behavior usually can be resolved by effective communication with the patient to ensure accurate assessment and by adequate opioid doses.
Patients with SCD are often quite knowledgeable about the medications they take for their condition and the doses that have worked in the past.

Requests for these specific medications and doses should not be interpreted as drug-seeking behavior.
Acute Chest Syndrome in Sickle Cell Disease

- Fever
- Chest Pain
- New Pulmonary Findings
  - Clinical
  - Radiographic
  - Laboratory
- Etiology Variable, Multi-factorial
  - Infection
  - Sickle cell related

Leading Cause of Death in Children and Adults
National Acute Chest Syndrome Study Group

- 1993-97
- 30 centers
- 671 episodes, 538 pts

Specific cause in 38% (70% of those with complete data)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Fat embolism</td>
<td>8.8%</td>
</tr>
<tr>
<td>Chlamydia pn.</td>
<td>7.2%</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>6.6%</td>
</tr>
<tr>
<td>Virus (RSV, parvovirus B19)</td>
<td>6.4%</td>
</tr>
<tr>
<td>Bacteria</td>
<td>4.5%</td>
</tr>
<tr>
<td>Mixed</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Management: Macrolide Antibiotic

Vichinsky, NEJM 2000
Acute Chest Syndrome: Management

- Continuous O₂ monitoring
- Oxygen therapy if tachypnea or hypoxemia
- Antibiotics (Macrolide)
- Fluids (1 maintenance; do not overhydrate)
- Incentive spirometry
- Pain management
- Bronchodilator/steroids if RAD
- Transfusion
Improvement in the clinical treatment of patients with SCD Treatment

- Fluids
- Pain Medication
  - Adequate (opioid) medication?
- Antibiotics
- Red blood cell transfusion
Stigmatization of patients with SCD

- Negro /Black Disease
- Bad blood/gene
- Punishment
- Drug seekers
- Frequent Flyers
Challenges facing the Sickle Cell patients

- Access to care??
- Care given when access is granted?
- Lack of Educated health care providers who specialized in SCD
- American Society of Hematology (2016) Reported that “The health outcomes and treatment disparities related to SCD make it a public health priority both in the United States and globally.”
- “There is enormous opportunity to improve the state of SCD. There are actions we can take today to address unmet needs - both in the United States and around the world”.
Implications for Clinical Practice

- Assess the need for pain medications
- **Do not focus on the pain only**
- Treat the patient holistically
- Treat SCD patient individually
- Listen, to the patient
- Engage patient into his/her care
- Advance Practice Registered Nurse (APRN) needs to meet and educate policy makers on the need for funding, education and research
- More educated MD’s and nurses to provide care for this population
In conclusion:

WE all SHOULD Know that DIVERSITY makes for a rich tapestry, AND WE MUST understand that all the threads of the tapestry are EQUAL in value no matter what their color.

— Maya Angelou
Acknowledgment:

- Dr. C. Alicia Georges, Chairperson: Lehman College, CUNY
- Dr. Miller, Downstate University, Brooklyn New York
SPEAKER

Elvin T. Price, PharmD, PhD
Current Trends In Pharmacogenomics: From The Clinic To The Bench And Back

Elvin T. Price, Pharm.D., Ph.D., F.A.H.A
Assistant Professor, Pharmaceutical Sciences
UAMS College of Pharmacy
Seminar Outline

- Understand the history and principles of pharmacogenetics/genomics (PGx)
- Present data on the effects of genetic variants in Nuclear Hormone Receptors (NR) as contributors to comorbid cardiometabolic disorders
- Introduce the concept of using a translational PM approach to improve cardiometabolic health trends in older adults
Patients with same diagnosis

- Predicted increased toxicity risk
  - Decrease dose or use different drug

- Predicted good response to tested drug
- Predicted poor or nonresponse
  - Use different drug

The Clinical Potential of PGx:
Can We Increase The Responsiveness To Drugs?
Genetic Variability Influences the Pathogenesis of Disease and the Response to Pharmacotherapy
Medicare Data Identify Hypertension, Hyperlipidemia & Diabetes As Prevalent Comorbidities
Medicare Data Identify Hypertension, Hyperlipidemia & Diabetes As Prevalent Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Ischemic Heart Disease* (N = 8,678,060)</th>
<th>HF* (N = 4,366,489)</th>
<th>AF* (N = 2,556,839)</th>
<th>Stroke* (N = 1,145,719)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1 (81.3)</td>
<td>1 (85.6)</td>
<td>1 (84.5)</td>
<td>1 (89.0)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2 (69.1)</td>
<td>3 (62.6)</td>
<td>2 (64.4)</td>
<td>2 (69.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (41.7)</td>
<td>5 (47.1)</td>
<td>7 (37.1)</td>
<td>6 (41.5)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>4 (40.6)</td>
<td>6 (45.6)</td>
<td>6 (41.7)</td>
<td>5 (44.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (38.7)</td>
<td>4 (51.2)</td>
<td>5 (43.0)</td>
<td>4 (46.8)</td>
</tr>
<tr>
<td>HF</td>
<td>6 (66.3)</td>
<td></td>
<td>4 (50.9)</td>
<td>7 (37.2)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>Index</td>
<td></td>
<td>2 (63.5)</td>
<td>3 (58.1)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>7 (30.2)</td>
<td>7 (44.8)</td>
<td>8 (34.4)</td>
<td>8 (35.2)</td>
</tr>
<tr>
<td>Cataract</td>
<td>8 (31.6)</td>
<td>↑</td>
<td>10 (22.6)</td>
<td>↑</td>
</tr>
<tr>
<td>COPD</td>
<td>9 (21.0)</td>
<td>8 (30.9)</td>
<td>9 (23.8)</td>
<td>↑</td>
</tr>
<tr>
<td>AF</td>
<td>10 (18.7)</td>
<td>9 (28.8)</td>
<td>Index</td>
<td>↑</td>
</tr>
<tr>
<td>Alzheimer's disease/dementia</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>9 (33.8)</td>
</tr>
<tr>
<td>Depression</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>10 (29.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Index</td>
</tr>
</tbody>
</table>

*Data shown as rank and percentage of persons with index condition who also had a comorbidity. The percentage is included parenthetically when applicable. ↑Comorbidity was not in the top 10 for this index condition (N). AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; and HF, heart failure.
Medicare Data Identify Hypertension, Hyperlipidemia & Diabetes As Prevalent Comorbidities

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyads (beneficiaries with ≥2 comorbidities; N = 19,139,696)</strong></td>
<td></td>
</tr>
<tr>
<td>High cholesterol and high BP</td>
<td>57.2</td>
</tr>
<tr>
<td>High BP and ischemic heart disease</td>
<td>36.8</td>
</tr>
<tr>
<td>High BP and arthritis</td>
<td>33.3</td>
</tr>
<tr>
<td>High BP and diabetes mellitus</td>
<td>32.7</td>
</tr>
<tr>
<td>High cholesterol and ischemic heart disease</td>
<td>31.3</td>
</tr>
<tr>
<td><strong>Triads (beneficiaries with ≥3 comorbidities; N = 14,908,988)</strong></td>
<td></td>
</tr>
<tr>
<td>High cholesterol, high BP, and ischemic heart disease</td>
<td>35.8</td>
</tr>
<tr>
<td>High cholesterol, high BP, and diabetes mellitus</td>
<td>31.7</td>
</tr>
<tr>
<td>High cholesterol, high BP, and arthritis</td>
<td>28.8</td>
</tr>
<tr>
<td>High BP, diabetes mellitus, and ischemic heart disease</td>
<td>21.5</td>
</tr>
<tr>
<td>High BP, arthritis, and ischemic heart disease</td>
<td>20.6</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Reproduced with permission from the Centers for Medicare & Medicaid Services (14).
The General Public Is Watching

The Washington Post

Health & Science

‘America’s other drug problem’: Giving the elderly too many prescriptions

By Anna Gorman  August 15 at 3:51 PM

Dominick Bailey sat at his computer, scrutinizing the medication lists of patients in the geriatric unit.
Translational Approaches Are Required
To Reduce The Burdens Of Comorbid Diseases
## The Nuclear Receptor Superfamily

<table>
<thead>
<tr>
<th>Endocrine Receptors</th>
<th>Adopted Orphan Receptors</th>
<th>Orphan Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroid Receptors</strong></td>
<td><strong>Lipid sensors</strong></td>
<td>SHP</td>
</tr>
<tr>
<td>GR</td>
<td>RXRα,β,γ</td>
<td>DAX-1</td>
</tr>
<tr>
<td>MR</td>
<td>PPARα,δ,γ</td>
<td>TLX</td>
</tr>
<tr>
<td>PR</td>
<td>LXRα,β</td>
<td>PNR</td>
</tr>
<tr>
<td>AR</td>
<td>FXR</td>
<td>GCNF</td>
</tr>
<tr>
<td>ERα,β</td>
<td>PXR</td>
<td>TR2,4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR4Aα,β,γ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rev-erbα,β</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COUP-TFα,β,γ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Heterodimeric Receptors</strong></th>
<th><strong>Enigmatic Orphans</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>TRα,β</td>
<td>CAR</td>
</tr>
<tr>
<td>RARα,β,γ</td>
<td>HNF-4α,γ</td>
</tr>
<tr>
<td>VDR</td>
<td>SF-1/LRH-1</td>
</tr>
<tr>
<td></td>
<td>RORα,β,γ</td>
</tr>
<tr>
<td></td>
<td>ERRα,β,γ</td>
</tr>
</tbody>
</table>

- GR: glucocorticoid
- MR: mineralocorticoid
- PR: progesterone
- AR: androgen
- ERα,β: estrogen
- RXRα,β,γ: retinoic acid
- PPARα,δ,γ: vitamin D (bile acid)
- LXRα,β: androstanone
- FXR: fatty acids
- PXR: cholesterol
- CAR: fatty acids
- HNF-4α,γ: phospholipids
- SF-1/LRH-1: retinoic acid
- RORα,β,γ: cholesterol
- ERRα,β,γ: estrogen

**Note:** The table includes several receptors and their roles in various processes, highlighting the complexity and diversity within the nuclear receptor superfamily.
NRs Regulate Homeostasis In Response To Diet: Dietary Substances Turn The Switches On Or Off
LXRA Regulates The Essential Genes Described Below

<table>
<thead>
<tr>
<th>A. Lipid Homeostasis</th>
<th>B. Vascular Homeostasis</th>
<th>C. Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA1</td>
<td>RENIN</td>
<td>MCP-1</td>
</tr>
<tr>
<td>ABCG1</td>
<td>CYP11β2</td>
<td>CRP</td>
</tr>
<tr>
<td>ABCG5</td>
<td>HSD11β1</td>
<td>CCL7</td>
</tr>
<tr>
<td>ABCG8</td>
<td>UCP-1</td>
<td>CXCL10</td>
</tr>
<tr>
<td>APOE</td>
<td>ANGPTL3</td>
<td>IL1β</td>
</tr>
<tr>
<td>APOC1</td>
<td>ARG2</td>
<td>IL6</td>
</tr>
<tr>
<td>CETP</td>
<td>SCD-1</td>
<td>MMP9</td>
</tr>
<tr>
<td>CYP7A1</td>
<td>ENG</td>
<td>NOS2A</td>
</tr>
<tr>
<td>LPL</td>
<td>FSCN1</td>
<td>COX-2</td>
</tr>
</tbody>
</table>
Establishing The Role Of LXRA Variants In CVD

LXRA Genetic Variation

Lipid Homeostasis

Regulation of Inflammation

Atherosclerosis?
Coronary Artery Calcification?
ACS?
Ischemic Stroke?
The International Verapamil SR/Trandolapril Study (INVEST)
- N=22,576
  - International
  - Multicenter
  - Randomized clinical trial
- Enrollment: Sep-97 to Dec-00
- Effectiveness of verapamil SR vs. atenolol, with or without trandolapril and/or hydrochlorothiazide

INVEST GENETic substudy (INVEST GENES) (N=5979)
- case-control subset (N=1059)
- cases: 297
- controls: 762

INVEST-GENES Design:
Hypertension 100%, Dyslipidemia 55%, T2DM 28%

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil SR 240 mg</td>
<td>Verapamil SR 240 mg + Trandolapril 2 mg</td>
<td>Verapamil SR 180 mg twice daily + Trandolapril 2 mg twice daily</td>
<td>Verapamil SR 180 mg twice daily + Trandolapril 2 mg twice daily + HCTZ 25 mg twice daily</td>
</tr>
</tbody>
</table>

INVEST GENES Design:
Hypertension 100%, Dyslipidemia 55%, T2DM 28%

Study drugs could be titrated: verapamil SR 120–480 mg/day; trandolapril 0.5–8 mg/day; atenolol 25–200 mg/day; HCTZ 12.5–160 mg/day/day

Pepine CJ, et al. JAMA 2003;290:2805-16
LXRA (*NR1H3*) Gene Structure
LXRA (*NR1H3*) SNPs & INVEST-GENES Outcomes

Price ET, et al, Pharmacogenetics and Genomics 2011
LXRA (NR1H3) SNPs & INVEST-GENES Outcomes:
Stratified By Hypertension Strategy

Patients with same diagnosis

- Predicted good response to tested drug
- Predicted poor or nonresponse
- Use different drug
- Predicted increased toxicity risk
  Decrease dose or use different drug

Price ET, et al, Pharmacogenetics and Genomics 2011
Independent Clinical Data Support:

LXRA SNPs Increase Risk of Atherosclerotic Diseases

Genetic Variation in Liver X Receptor Alpha and Risk of Ischemic Vascular Disease in the General Population

Stefan Stender, Rith Frikke-Schmidt, Aristomenis Anestis, Dimitris Kardassis, Amar A. Sethi, Borge G. Nordestgaard and Anne Tybjærg-Hansen

Arterioscler Thromb Vasc Biol 2011, 31:2990-2996: originally published online September 8, 2011
doi: 10.1161/ATVBAHA.111.223867

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association.
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Copyright © 2011 American Heart Association. All rights reserved. Print ISSN: 1079-5542. Online ISSN: 1524-4636
Independent Clinical Data Support: LXRA SNPs Increase Risk of Atherosclerotic Diseases
Expanding My Network Of NR Genes
Experimental Methods: Cell Culture

- Cultured HUVECs to 80% confluency
- Fenofibrate 10µM
- Conducted PCR arrays designed to explore NR signaling
Fenofibrate Induces The mRNA Expression Of 21 NRs In Basal HUVECs

Manuscript in prep. ET Price
How Do We Move Forward With Genes That May Be Associated With Risks Of Disease/Pharmacologic Response From This Network?
Determine If NR SNPs Are Associated With CVD Risk Biomarkers In GWAS Data

1A. HyperGEN Whites

1B. HyperGEN Blacks

Nuclear Receptor (NR) Genetic Variants:
GR, MR, TR, PPAR-A, PPAR-G, PPAR-D, LXRA, FXR, ER-A, ER-B, HNF-4A, VDR etc

Cardiometabolic Traits:
Lipids, Glucose, Blood Pressure, Cardiac Structure/Function

2. Replication in the GENOA Family Study

3. Validation in UAMS Cohort:
Cardiometabolic Traits & Functional Assays
Novel NR Associations That Are Consistent In HyperGEN & GENOA Whites & Blacks

- **ESRRB**: Increased TG 15-16 mg/dl per variant allele
- **THR2**: HDL Decreases 2-3 mg/dl, Tchol Increases, Glucose Increases 8-9 mg/dl, LDL Increases
- **PGC1B**: Glucose Increases 13-15 mg/dl per allele and TG increases 28-30 mg/dl
Novel NR Associations That Are Consistent In HyperGEN & GENOA Whites

- LXRA (NR1H3) SNPs: rs3758674 and rs12221497 were associated with a 3.2-3.3 mg/dl increase in HDL per variant allele.
Novel NR Associations That Are Consistent In HyperGEN & GENOA Blacks

- NR6A1 SNPs have a suggestive association with glucose, insulin and TGs.
Interesting phenotypes are associated with 3 genes across the entire cohorts: **THRB, PGC1B, ESRRB**.

**THRB, PGC1B, and ESRRB** are prime candidates for additional sequencing and are promising PGx targets.

There was a novel association that was observed in Blacks only: **NR6A1** associations with insulin, triglycerides and glucose.

**LXRA (NR1H3)** was associated with HDL in Whites only and warrants additional studies for a potential association with HDL function.
UAMS Functional Validation Cohort

Translational Approaches To Personalized Pharmacotherapy
NR SNPs Clinical Associations (BP, Glucose, Lipids) and Personalized Ex-vivo Analyses

Vacutainer A -> Personalized Ex-vivo Analyses -> Vacutainer B

Leukocytes
- Monocytes
- Neutrophils
- T-cells
- Dendritic cells

Clinical Labs and Novel Assays
- Cytokines & Chemokines
- Reverse cholesterol transport
- RNA Seq & Microarrays

iPSCs
NRs CVD GTx/PGx Translational Paradigm

Candidate gene

Whole genome

in silico

ex vivo

in vitro

intermed

in vivo

PK/PD

in vivo

outcome

in vivo

risk

reproducibility

Clinical test
Summary & Conclusions

- NRs appear to be promising biomarkers for predicting CVD risk and treatment outcomes which deserves further study.

- Follow up studies designed to explore the effects of NRs on vascular, cholesterol and inflammatory homeostasis will prove useful for the clinical development of NRs as biomarkers or pharmacologic targets.
Acknowledgments

- Ryan Farris, Pharm.D., Ph.D.
- Charla Wiley, B.S.
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- Bukola Odeniyi, B.S. (M.D., Ph.D. Student)
- Rose Cooper, M.S., (Ph.D. Student)
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