CELLS TO SOCIETY:
Overcoming Health Disparities

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CENTERS FOR POPULATION HEALTH AND HEALTH DISPARITIES (CPHHD)

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FOREWORD

Understanding health disparities and determining the most effective strategies for reducing them is one of our Nation's most important and complex challenges. The National Institutes of Health can and should play a central role in providing the evidence necessary to inform not only biomedical intervention strategies to address health disparities but also sound public health policies and practice. The Centers for Population Health and Health Disparities (CPHHD) initiative was designed to accelerate scientific progress in this domain by supporting sophisticated, transdisciplinary research that employs evidence and methods from many disciplines to address the problem at multiple levels of analysis. The CPHHD initiative is a trans-NIH collaboration among the NCI, the National Institute of Environmental Health Sciences, the National Institute on Aging, and the NIH Office of Behavioral and Social Sciences Research.

How does the CPHHD initiative differ from previous NIH-funded efforts in health disparities research? Using the P50 research center grant mechanism, the initiative supports interrelated projects that are scientifically ambitious, addressing a more comprehensive set of pathways (e.g., biological, behavioral, environmental, economic) leading to disparate outcomes than traditional studies. This strategy is essential to informing and resolving long-standing debates about the relative importance of various biomedical and sociological factors in accounting for differences in disease incidence, morbidity, and mortality. Through the study of disparities across multiple risk factor and disease domains, the consortium of investigators is able to deploy the best expertise, tools, and theoretical models from a variety of research traditions. Although focused on the rigorous testing of prior research

questions, the initiative also includes a community-based participatory research component to ensure that solutions derived from academic research are informed by the experience and unique perspectives of community members.

This progress report is intended to provide NCI's advisors and partners with an overview of accomplishments to date, highlighting some of the innovative strategies used by the investigators to advance our understanding of health disparities. Although still in its initial, five-year funding period, the centers are already making headway toward a more effective convergence of rigorous behavioral and biomedical research with the pressing needs and realities of local communities and their leaders. As we await the final results from many of the larger studies in the consortium, preliminary findings have already provided important insights into the complex interplay of contextual, behavioral, and genetic factors in disease risk and outcomes. Together with our NIH funding partners, we look forward to continued collaborations with the investigators and their communities to strengthen the empirical foundation of future efforts to reduce the intolerable disparities in cancer and other chronic diseases.

ROBERT T. CROYLE, PHD
Director
Division of Cancer Control and Population Sciences
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EXECUTIVE SUMMARY

The Centers for Population Health and Health Disparities (CPHHD) have demonstrated the ability to catalyze transdisciplinary research to improve the understanding of complex interactions of biological, social, cultural, environmental, and behavioral factors that contribute to health disparities, with a particular emphasis on cancer-related disparities. The implications of this paradigm-setting initiative are wide ranging. The multicenter, transdisciplinary infrastructure for research and dissemination allows the CPHHD to capitalize on immediate and long-term opportunities in a number of areas:

A New Transdisciplinary Paradigm

The CPHHD have built on existing research and developed new approaches that show the causes of health disparities to be multifactorial and complex. Most health disparities research prior to the inception of the CPHHD did not take a comprehensive approach that considered the multilevel contributions of many factors. The CPHHD represent a paradigm for transdisciplinary research that can serve as a model for other settings. Similarly, they have shown that the solutions needed to address these disparities must use a multilevel transdisciplinary research approach to develop and implement proven interventions that will eliminate disparities.

Biological Determinants of Disparities

The inclusion of the basic sciences including molecular biology, biochemistry, and animal models into health disparities research allows the CPHHD to build on laboratory-based studies related to allostatic load, biological determinants of stress and social isolation, and the implementation of biomarkers to better understand the biological mechanism and processes that contribute to health disparities. Laboratory methods and infrastructure developed in these areas will facilitate additional biologically oriented studies of health disparities. These studies can proceed rapidly in the coming years to inform clinical interventions, clinical practice, and population-based studies.

Clinical Opportunities and Interventions

The incorporation of clinicians and the clinical sciences in CPHHD initiatives has facilitated the rapid development of proactive research and interventions that address access, screening, and treatment factors influencing health disparities. Studies that have begun with database-driven research and observational studies of cancer screening and treatment for diseases such as breast, prostate, and cervical cancers will lead to interventions

"Grantees who are working in communities to reduce cancer health disparities through transdisciplinary initiatives such as the Community Network Program, the Patient Navigation Research Program, and the Centers for Population Health and Health Disparities are crucial partners in our goal of making sure the exciting science happening here at NCI reaches all patients."
JOHN E. NIEDERHUBER, MD
Director NCI at the 2007 Cancer Health Disparities Summit.

aimed at eliminating disparities in these diseases. This work will require a number of generations of research, including clinical and interventional studies that evaluate intermediate outcomes such as screening behaviors and the modulation of risk factor exposures (e.g., smoking, diet, obesity, treatment access). Building on these findings, the next generation of studies will be positioned to evaluate the effect of interventions on disease incidence and mortality and to reduce/eliminate disparate health outcomes.

"In 2004, I received pilot study funding from the UIC center. This funding came at a crucial time early in my career and provided support to initiate research in an area that is highly understudied, yet represents a serious issue in treatment of breast cancer. Dr. Warnecke was very supportive of our project to study the biological basis of racial disparity in breast cancer outcome and greatly strengthened my research program."

DEBRA TONETTI, PHD
Associate Professor, Department of Biopharmaceutical Sciences, University of Illinois at Chicago

Affecting Policy to Eliminate Health Disparities

The CPHHD have a forward-looking emphasis on dissemination of research results that can be translated to policy change to eliminate health disparities. The CPHHD have and will continue to identify factors in health disparities that can be directly addressed by policymakers. These elements include access to cancer screening and early detection, reduction of risk factors such as smoking or obesity in at-risk populations, as well as primary prevention by novel means such as immunization.

Value-Added Relationships with Other Initiatives

The CPHHD initiative's strong link to community groups provides rapid access to the communities that suffer from disparities for dissemination of research results as well as implementation of new interventions aimed at eliminating disparities. Numerous connections with other National Institutes of Health (NIH)– and National Cancer Institute (NCI)–funded initiatives will also facilitate research and interventions related to health disparities. Most CPHHD centers have links with other disparities initiatives, including the Patient Navigation Research Program, and the Community Networks Program. CPHHD also have links with other funders and programs, including the Robert Wood Johnson Foundation, that are building health disparities initiatives. Therefore, the CPHHD form a central nodal point for health disparities research that links a variety of community, policy, research, and intervention agencies and groups.

Training the Next Generation of Health Disparities Researchers

While the CPHHD were not funded specifically to provide training, each center has made transdisciplinary training of health disparities researchers a major priority. Every CPHHD center has received diversity supplement funding to provide research training support for young minority investigators. Every center has built links with undergraduate, graduate, and postgraduate training programs to extend the capacity for research training in health-disparities-related fields. Centers have brought in new investigators to their research groups and have drawn experienced researchers from various disciplines into the field of disparities research.

SECTION I: INTRODUCTION

The challenge to reduce and ultimately eliminate health disparities requires a new transdisciplinary research framework that fosters an integrated approach across biomedical, behavioral, and social sciences to advance our understanding of the nature and importance of the complex determinants of health disparities, including those that act at the societal level. With respect to racial and ethnic group disparities, understanding the interface between biology, behavior, and life circumstances is essential to separating myth from methodology concerning their complex etiologies. Ultimately, interventions that target the intersections between biology, behavior, and social circumstances are needed to reduce the unequal burden of cancer.

Health disparities represent a significant public health problem in the United States. Inequities in screening, incidence, treatment, prognosis, and mortality are hallmarks of many common diseases [1], including cancer. These disparities exist across groups defined by race, ethnicity, gender, age, and socioeconomic status. To cite but one example, African American men have a 34% greater prostate-cancer-specific incidence and 123% greater prostate-cancer-specific mortality than European American men [2]. The greater disparity in mortality relative to the disparity in incidence suggests that factors related to biology, behavior, social circumstances, access to care, and other post-diagnosis factors influence clinical outcomes. Elimination of health disparities in outcomes, therefore, requires a multifaceted, transdisciplinary approach capable of accounting for the many complex interrelated factors that can affect the development and progression of disease.

There have been some important strides made in understanding the relationship between human biology and its interaction with behavioral and social factors in the development, detection, diagnosis, and treatment of cancer. The mapping of the human genome provided an important platform for addressing the causes of cancer disparities in individuals and pop-

Key Definitions:

Health Disparity: Differences in the incidence, prevalence, mortality, and burden of diseases, and other adverse health conditions that exist among specific population groups in the United States.

Multilevel Research: Studies that incorporate data from multiple levels of inference. For example, studies that simultaneously consider both individual (e.g., genotypes, individual risk factors) and neighborhood (e.g., neighborhood-level income or education) data.

Transdisciplinary Research: Scientists from different disciplines working jointly to create a shared conceptual framework that integrates and moves beyond discipline-specific theories, concepts, and approaches, to address a common problem [40].

ulations. New personalized medicine technologies also promise to help many individuals with cancer. However, while such approaches are essential, they are insufficient on their own for the development of an "effective and efficient long-term strategy for gaining knowledge and preventing disease at the population level" [4]. Indeed, the explanations for disease occurrence in a population may be quite different from the causes of interindividual differences in disease occurrence [5-7]. Without special population-targeted approaches, new technologies that help many individuals with cancer are likely to worsen disparities, because their uptake and diffusion will likely be much faster in affluent, educated, and non-minority communities [8, 50].

Determinants of population health outcomes include population characteristics such as aggregate poverty, levels of education, economic opportunity, gender distributions, racial or ethnic distribution, and patterns of segregation [8-13]. Individual or familial risk factors include characteristics of individuals within populations such as socioeconomic status (SES), educational attainment, behavior, heredity, or genes that are directly associated with the onset of disease or health outcomes in the individual, regardless of the population determinants [3, 9, 11-17]. Studies have shown repeatedly that population characteristics have effects on health outcomes, independent of the characteristics of individuals. However, the complex interactions of race and ethnicity with socioeconomic status, culture, and the environment as they affect cancer incidence and outcomes are poorly understood [18]. Thus, a more complete *multilevel* understanding is needed of the broader biomedical, social, and environmental contexts that contribute to cancer initiation and progression.

The National Cancer Institute's Rationale for the Centers for Population Health and Health Disparities

When the National Center on Minority Health and Health Disparities was established as part of the Minority Health and Health Disparities Research and Education Act of 2000, all the institutes and centers of the National Institutes of Health (NIH) were required to develop plans for modifying and eliminating health disparities across cancer and other diseases. These plans explicitly introduced the idea that disparities in health outcomes are not immutable facts of life. By using new models of research that combine social, behavioral, clinical, and basic science, more can be done than simply controlling for these factors in analyses. At the same time, several reports developed by the Institute of Medicine (IOM) and the National Academy of Sciences (NAS) described new transdisciplinary research paradigms that used multilevel approaches to integrate social and behavioral science theory with the newly emerging focus on genetics and molecular biology to expand the scientific understanding of health disparities determinants [1, 7, 8, 16-17, 20, 22- 23]. The Centers for Disease Control and Prevention (CDC) Racial and Ethnic Approaches to Community Health (REACH) program, the health disparities strategic planning by NIH, and the publication of the IOM and NAS reports created a strong stimulus for a more sophisticated approach to health disparities research [19-20, 22-23]. Several institutes, led by the National Institute of Environmental Health Sciences (NIEHS), proposed a trans-NIH effort to study the complex determinants of population health and health disparities.

Prior to the trans-NIH effort in January 2001, a working group of distinguished behavioral, social, and biomedical scientists held a meeting entitled "Social Determinants of Cancer" (http://obssr.od.nih.gov/Documents/Conferences_And_Workshops/HigherLevels_Final.PDF). The meeting was convened in Washington, D.C., under the auspices of the NCI's

Division of Cancer Control and Population Sciences (DCCPS). This working group discussed the state of fundamental and applied research on the social, cultural, environmental, and behavioral determinants of cancer incidence and outcomes. This discussion, together with contemporary reports and literature, highlighted several themes relevant to the need for interdisciplinary research specifically to address health disparities in cancer:

"The work of CPHHD is critical to improving systems of health care by providing deeper insights into racial and ethnic disease disparities. My project at WSU Center for Urban and African American Health (CUAAH), is giving me the necessary skills to integrate basic and clinical science in the attempt to better understand the pathophysiology of diseases."

ANNA LIZA B. VALINA-TOTH MS
MD PhD Student, School of Medicine, Department of Physiology
Wayne State University

• Theory-based behavioral and social science research is needed for a comprehensive approach to the reduction of disparities in cancer morbidity and mortality [12, 49, 51].

• At the social and environmental levels, measures such as socioeconomic status, sociocultural groupings, social support, income distribution, social hierarchies, environmental hazards, and neighborhood characteristics have potentially important influences on health behaviors and disease, including cancer [25-28, 52].

• Individual behaviors mediate major determinants of cancer and other diseases, such as tobacco use, dietary practices, physical activity, alcohol intake, and drug abuse, but these behaviors in turn are influenced at a societal level. The magnitude and relative contribution of known behavioral risk factors in explaining social gradients and health disparities are not known [29, 30].

• Once cancer has occurred, the role of providers and the health-care system in providing access to and delivering quality care for early detection, diagnosis, treatment, and long-term and end-of-life care must also be further studied. Racial, ethnic, and SES disparities in access to and receipt of care

have been documented [13-14, 41-45], but the nature and relative importance of such factors compared with antecedent social, environmental, and behavioral factors is not known.

• Insofar as social gradients in cancer incidence and outcomes cannot be explained by known behavioral, environmental, and health-care factors, biological mechanisms must be further explored. Biological mechanisms, including genetic, endocrine, and immunologic factors, must be sought to explain how social-level variables interact with human behavior, physiology, and genetic susceptibility to influence cancer incidence and survival [3, 31, 46].

The working group concluded that since the determinants of cancer at the population level are broad and influence other chronic diseases and overall mortality, other outcomes must also be considered. The group, therefore, recommended that lessons from the study of cardiovascular diseases, which provide a larger research base with regard to the social determinants of disparities, should be examined for possible relevance to cancer. Above all a transdisciplinary team science infrastructure is needed. Within this infrastructure, researchers could work jointly using a shared conceptual framework that integrates discipline-specific theories, concepts, and approaches to address common problems.

In September 2003, the NIH funded eight Centers for Population Health and Health Disparities designed to support cutting-edge research to understand and reduce disparities in health outcomes, access, and care. In recognition of the complementary nature of the causal factors involved in understanding the disparities in health outcomes, the CPHHD program was announced by the NIEHS, NCI, the NIH Office of Behavioral and Social Sciences Research (OBSSR), and the National Institute on Aging (NIA). The use of the NIH specialized center grant mechanism (P50) was deemed the most appropriate for this initiative. Thirty applications were received, focusing on a wide range of outcomes including cancer, as well as oxidative stress, obesity, diabetes, cardiovascular disease, health promotion, and asthma.

Purpose of the CPHHD

The CPHHD were established as a means to encourage transdisciplinary research to improve the understanding of the complex interactions of biological, social, cultural, environmental, and behavioral factors that affect disease incidence and mortality and that contribute to disparate health outcomes including cancer-related health disparities. In particular, the CPHHD initiative was designed to accelerate knowledge about the social determinants of cancer and other diseases, the psychosocial factors that mediate them, and the biological pathways that can explain their etiology and impact. Centers would bring together the skills of basic, clinical, and cancer control scientists with other population scientists, such as sociologists, anthropologists, economists, and behavioral and political scientists, in medical schools, cancer centers, schools of public health, and community-based organizations.

The eight centers established were (listed with their funding sources; see also Appendix A):

- University of Chicago (UC)—(NIEHS/NCI)

- University of Pennsylvania (Penn)—(NCI)

- RAND Corporation (RAND)—(NIEHS)

- University of Illinois at Chicago (UIC)—(NCI)

- Ohio State University (OSU)—(NCI)

- University of Texas Medical Branch (UTMB)—(NCI)

- Tufts University/Northeastern (Tufts)—(NIA)

- Wayne State University (Wayne State)—(NIEHS).

Each center established a research agenda with the goal of supporting transdisciplinary, multilevel research, leading to a broader and more in-depth understanding and, ultimately, elimination of health disparities in the United States. Each CPHHD undertakes research that embraces transdisciplinary approaches to examine the role of biology, social factors, environment, behavior, clinical practice, and health economics on health disparities.

To achieve this key objective, the CPHHD provide leadership in the field of health disparities research by

- Identifying fundamental causes of health disparities;

- Identifying ways to eliminate health disparities and change current policies that create or support disparities;

- Developing and training new investigators in transdisciplinary health disparities research;

- Forming research/practice partnerships with community groups impacted by or with the capacity to impact adverse health outcomes associated with disparities;

- Developing innovative conceptual models, methods, and interventions for conducting transdisciplinary research on adverse health outcomes related to health disparities; and

- Disseminating and translating successful efforts to suggest and evaluate policies that effectively address disparity-related health outcomes in community settings.
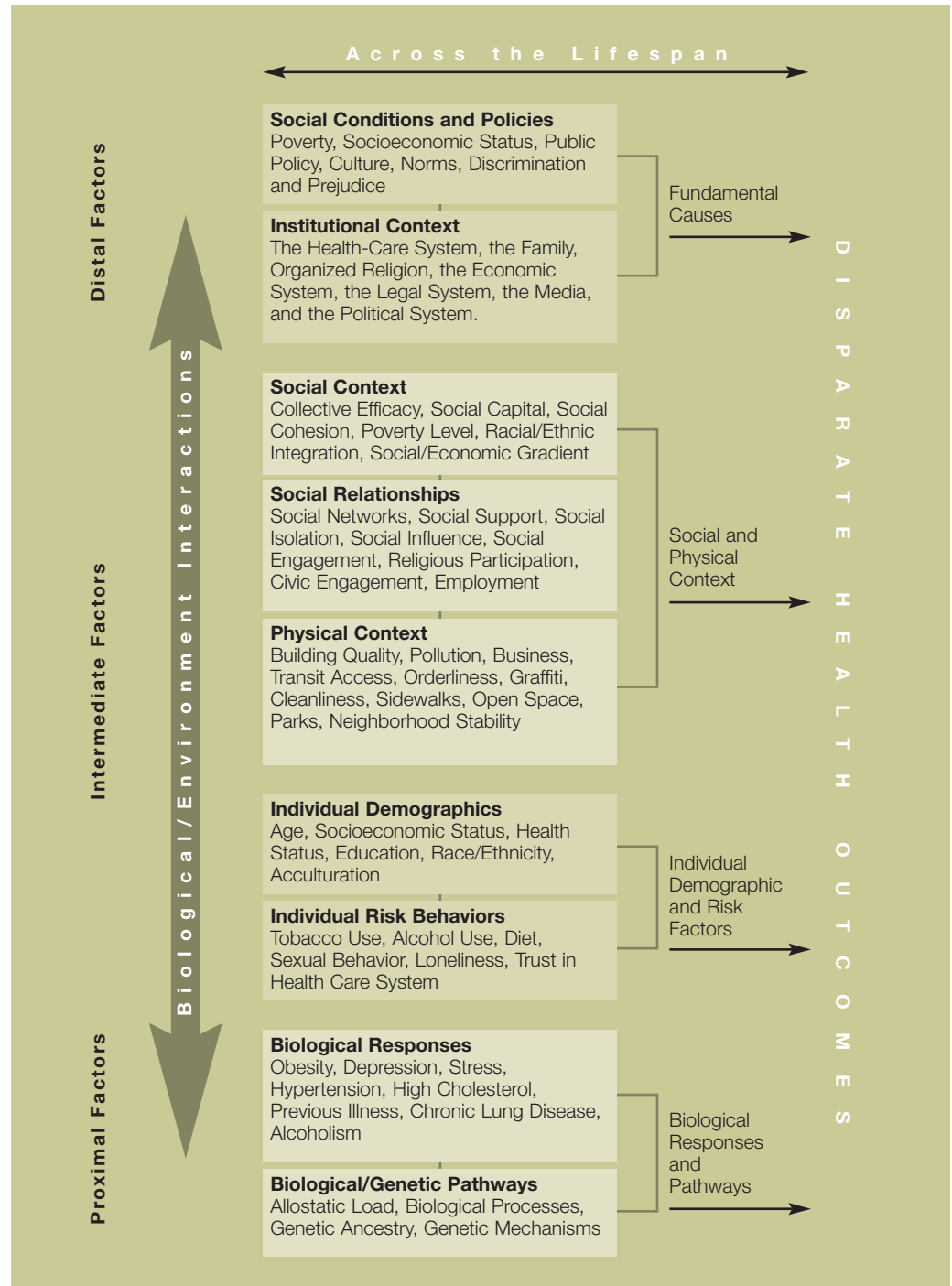
Figure 1: Model for Analysis of Population Health and Health Disparities

CPHHD Framework: From Cells to Society

An underlying question addressed by the CPHHD is "How does the environment get under the skin?" [16] Or, put otherwise, "How do population risks relate to individual risks?"

The CPHHD approach population health and health disparities research with a multilevel framework established by the leadership of the eight CPHHD. This approach focuses on multiple levels of analysis in health sciences to examine factors operating at the biological (organ system, cellular, and molecular), behavioral, social, and environmental levels. It also has widened the centers' shared perspective and led to the theme "From Cells to Society," which implies a common research thread from basic science and clinical science to implementation and policy. Centers have undertaken mechanistic and intervention studies across multiple levels of analysis and across diseases and conditions relevant to the mission of the sponsoring institutes.

The framework established by CPHHD is shown in Figure 1 [17, 31, 32]. In this figure, there are three levels of determinants of health outcomes. *Distal factors* include population social conditions, the policies that affect social conditions, and the policymaking bodies that influence or determine them [ibid.] The influence of distal factors occurs primarily at the population level and is reflected in the variation in rates of disease or poor health such as the epidemic

of HIV in Africa, or high rates of obesity in the United States. These factors have systemic roots, which are embedded in policy, norms about health or social practices, or extreme socioeconomic disadvantage in policies that affect the public availability of support for health services, who receives them, and the level and quality of service.

Across the Lifespan

Distal Factors

Social Conditions and Policies
Poverty, Socioeconomic Status, Public Policy, Culture, Norms, Discrimination and Prejudice

Institutional Context
The Health-Care System, the Family, Organized Religion, the Economic System, the Legal System, the Media, and the Political System.

Fundamental Causes

Intermediate Factors

Social Context
Collective Efficacy, Social Capital, Social Cohesion, Poverty Level, Racial/Ethnic Integration, Social/Economic Gradient

Social Relationships
Social Networks, Social Support, Social Isolation, Social Influence, Social Engagement, Religious Participation, Civic Engagement, Employment

Physical Context
Building Quality, Pollution, Business, Transit Access, Orderliness, Graffiti, Cleanliness, Sidewalks, Open Space, Parks, Neighborhood Stability

Social and Physical Context

Proximal Factors

Individual Demographics
Age, Socioeconomic Status, Health Status, Education, Race/Ethnicity, Acculturation

Individual Risk Behaviors
Tobacco Use, Alcohol Use, Diet, Sexual Behavior, Loneliness, Trust in Health Care System

Individual Demographic and Risk Factors

Biological Responses
Obesity, Depression, Stress, Hypertension, High Cholesterol, Previous Illness, Chronic Lung Disease, Alcoholism

Biological/Genetic Pathways
Allostatic Load, Biological Processes, Genetic Ancestry, Genetic Mechanisms

Biological Responses and Pathways

Biological/Environment Interactions

DISPARATE HEALTH OUTCOMES

The second level of population-level determinants is labeled *intermediate factors* in Figure 1. Determinants at this level include the immediate social and physical contexts and social relationships in which the distal effects are experienced, and usually exist at the neighborhood or community level. The social environment may include the neighborhood or community poverty level, the extent of residential segregation, median income and education, and opportunities for social interaction to address the impact of the distal factors. Forms of social capital that may buffer these effects include relationships such as social networks, social engagement with neighbors, or their absence. The physical environment includes availability and accessibility of local health-care resources, availability of transportation, air and water quality, availability of healthy food, the presence or absence of crime or neighborhood disorderliness, and the quality of the built environment.

Proximal factors are the characteristics of individuals: physical, social, and biological conditions that determine the pathways leading to the onset and severity of health outcomes. Individual resources include socioeconomic status, level of education, race/ethnicity, gender, and level of acculturation. These factors determine the individual-level capacity to respond to environmental resources and challenges, and thus

influence where the individual lives, his or her capacity to respond to health-care needs, the degree to which the individual has social support, and his or her level of social integration or social isolation. Also included at this proximal level are the individual's behaviors such as dietary practices, exercise, sexual practices, tobacco use, cultural beliefs, and regular contact with health-care services, including disease screening. These behaviors are usually addressed through interventions geared toward limiting risk behaviors or exposures.

Separate from risk behaviors are individual biological markers that result from behavior or indicate risk due to heredity. These markers may include elevated cholesterol, prolonged or intense stress, obesity, high blood pressure, abnormal cells in the cervix, or a lump in the breast. Finally, there are also biological pathways that may be familial or somatic responses to biological, social, or physical context or events.

In summary, the model depicted in Figure 1 assumes that the environmental context profoundly affects individual health outcomes and their distribution in the population. The capacity to respond to disparities in the distribution of health outcomes and the ultimate effectiveness of interventions at the individual level require interventions capable of addressing both higher-level contextual factors as well as individual factors. Thus, behavioral or environmental interventions designed to impact the biological or genetic pathways to risk of disease, or poor outcomes when disease occurs, need to be multi-level. They need to address context or environmental

"As a survivor and advocate, I cannot think of a greater honor than to be asked to provide input from the community perspective. Every aspect of this study was strategically planned, reviewed, and executed with the community in mind…If community-based participatory research is going to be successful, the community has to be viewed as an equal partner."

BARBARA J. AKPAN, RN, MSN
Breast Cancer Survivor and Advocate
Chicago, Illinois

Figure 2: The CPHHD and Pathways of Disease Causation
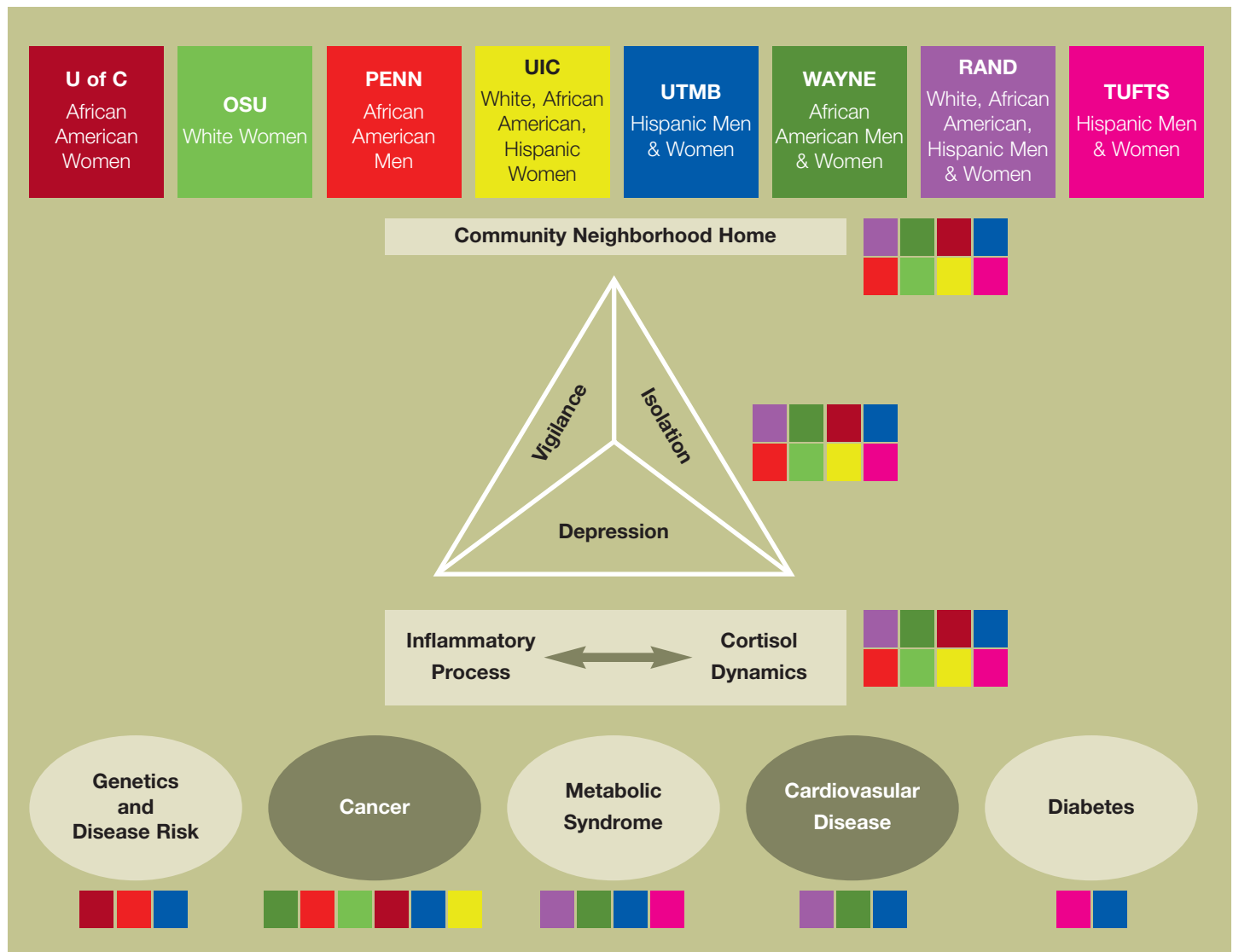
policy issues that may influence health outcomes.

Figure 2 provides an example of the ways in which the eight CPHHD are working together to investigate shared pathways of downward causation from the social environmental level to the level of disease, tracing the path from

- the community, neighborhood, and home to
- psychological and behavioral responses to
- biological responses to stress (i.e., inflammatory process and cortisol dynamics) to
- disease-level variables (i.e., molecular functioning,

morbidity, and mortality).

Preliminary findings reveal *one shared pathway of downward causation* based on the work from three centers (Fig. 2) and another potential pathway based on a fourth (not illustrated) from community-level factors, in which dilapidated housing, crime, and generally fractured communities—through a multifaceted "psychological suite" of isolation, depression, and vigilance—lead to alterations in stress hormone responses, specifically inflammatory process and cortisol dynamics. As investigations continue, we expect additional pathways will be revealed.

Each center conducts at least three research projects focused on population health and/or significant disparity-related health outcomes. At least one of these research projects includes community-based participatory research (CBPR), in which academic researchers and community-based organizations collaborate. Community-based organizations are broadly defined as groups focused on addressing community concerns about the environment and/or health. These organizations often serve as conduits to individual stakeholders who are most affected by the health conditions under study. These CBPR projects meet the same standards of scientific rigor as other types of research projects but also include a strategy for effective interaction and collaboration with community members. These partnerships help inform researchers about important issues and provide research teams with "action partners" that can help translate findings into policy.

Current Role of CPHHD in Addressing NCI Priorities

The CPHHD are well equipped to support the NCI's 2006 Strategic Plan on health disparities. The focus on health disparities within the Strategic Plan, which was developed after the initiation of the CPHHD, is closely connected with NCI's original rationale for the creation of the CPHHD. This plan laid out areas for research to eliminate cancer disparities:

• Understand the factors that cause cancer health disparities

—Assemble interdisciplinary teams of scientists and practitioners to further elucidate the complex interplay of social, behavioral, environmental, genetic, public health, and economic factors, as well as political and health system forces, that may contribute to disparities.

—Advance research to identify and investigate race, ethnicity, and socioeconomic status and how they influence trends and rates of cancer incidence and mortality.

—Support efforts to disaggregate large population studies in order to identify geographic areas of high cancer mortality and investigate the complex mechanisms that underlie the disparities identified across age groups and stages of cancer.

• Provide the knowledge base for and develop interventions to enhance the integration of cancer services for underserved populations.

Organization of This Report

This report describes the progress of the CPHHD in their first four years. Section I has highlighted a research agenda. The remainder of this report is organized into three sections:

• Section II provides an overview of CPHHD accomplishments, emphasizing both individual center achievements as well as cross-center initiatives;

• Section III provides highlights of research findings and activities for each of the eight CPHHD;

• Section IV describes future activities and initiatives for the CPHHD.

SECTION II: OVERVIEW OF CPHHD ACCOMPLISHMENTS

This section describes some of the key cancer health disparities issues addressed and scientific accomplishments enabled by the CPHHD structure and its transdisciplinary research focus. The progress of the centers is discussed under five subheadings:

- *Focusing on health disparities in cancer and related disease outcomes;*
- *Transdisciplinary collaborations investigating multilevel factors on health outcomes;*
- *Developing cross-center collaborations;*
- *Building an infrastructure to facilitate transdisciplinary research; and*
- *Moving science into the community.*

Focusing on Health Disparities in Cancer and Related Disease Outcomes

The research conducted by the CPHHD addresses health outcomes related to cancers of major public health importance, including breast, prostate, and cervical cancers. Understanding the causes of these cancers is important to an understanding of health disparities:

- A recent report from the Urban Health Institute at Mount Sinai Hospital indicated that, between 1994 and 2000, cancer mortality rates in Chicago decreased annually for white women, but unchanged for African American women. Moreover, breast cancer mortality among African American women in Chicago was twice the rate for African American women in New York City and 10% higher than the national rate.

- Other research has shown that African American and Hispanic women tend to be diagnosed at a later stage of breast cancer with more aggressive tumors than white women, despite similar use of mammography screening.

- Prostate cancer is the leading cause of cancer death among men in the United States that disproportionately affects African American men in terms of incidence, morbidity, and mortality.

- Although cervical cancer rates in the United States have declined drastically since the 1950s, rates have remained high among white women in the Appalachian regions of the United States.

Research within the centers also examines other conditions—obesity, diabetes, cardiovascular disease, and hypertension—for which significant disparities in morbidity and/or mortality between populations have been demonstrated.

Table 1: Disciplines Represented at the CPHHD

	UC	Penn	RAND	UIC	OSU	UTMB	Tufts	Wayne State
Biological Sciences								
Biopsychology	●			●	●		●	
Genetics	●	●		●	●		●	●
Nutrition							●	●
Oncology	●	●		●	●			●
Clinical Sciences								
Clinical/community/health psychology		●			●	●	●	
Geriatrics						●	●	
Nursing				●	●	●		●
Pathology	●			●		●		●
Other medical specialties/ general practice	●	●	●	●	●	●	●	●
Media and Communications								
Communication research		●			●			
Journalism/media relations			●					
Marketing research/management			●		●	●		
Public Health, Policy and Planning								
Environmental health			●		●	●	●	●
Epidemiology	●		●	●	●			●
Health services research		●	●	●	●	●	●	
Law, public policy, & administration		●	●	●	●			
Public health education/behavior		●	●		●	●		●
Urban planning				●				
Social and Behavioral Sciences								
Demography			●	●		●	●	●
Economics			●		●	●		
Education						●		
Psychology[1]	●			●	●		●	●
Sociology/anthropology		●	●	●		●	●	●
Social work	●			●				
Biomechanics/Statistics								
Biostatistics	●	●	●	●	●	●	●	●
Computer sciences		●						
Engineering		●	●					
Informatics		●						

1 Includes cognitive, developmental, educational, and social psychology

Transdisciplinary Collaborations Investigating MultiLevel Factors on Health Outcomes

Significantly, CPHHD have achieved new levels of transdisciplinary interaction that have allowed investigators to greatly expand the understanding of health disparities across population groups and diseases. This approach has widened researchers' shared perspectives from basic science and clinical science to implementation and policy. Investigators from an almost unparalleled array of disciplines have worked together with community partners from the inception of CPHHD operations. The benefits of the transdisciplinary approaches to disparities research across the CPHHD are quite evident in the ways in which investigators have informed one another's work. Table 1 lists the full range of 40 disciplines included in the CPHHD.

The benefits of the transdisciplinary approach developed by the CPHHD to advance the understanding and ability to address health disparities lie in the investigations not only of multiple pathways from the population to the disease levels, but of the interrelationships and interactions within and between different levels of determinants of individual and population health outcomes. Appendix B contains two tables that illustrate the common concepts and variables across the CPHHD.

CPHHD investigators have increasingly gone back and forth between animal and human models to mutually inform their understanding of the interactions between the social environment and biology. This type of collaborative interaction is illustrated by the following example, reported from the University of Chicago's CPHHD:

Project #1 established that socially isolated rats died with mammary tumors at younger ages than their group housed peers and became vigilant, i.e., they stayed in one corner of their cages and failed to explore their environments. Project #2 confirmed the relationship using SV 40 Tag mice. Meanwhile, Project #3 ran focus groups with 503 community

stakeholders and found that social isolation was associated with lack of social support and frequent residential moves. In response, Projects #1 and #2 initiated experiments in which they moved rats to new environments and measured their responses. In turn, Project #3 added a Built Environment Team to examine neighborhood factors that impede or enhance social interactions, to understand why some women reported isolation and vigilance in response to neighborhood threats such as crime. On the latter task, the University of Chicago team benefited from the research undertaken by the RAND team, with its focus on neighborhood effects.

Indeed, each of the centers examines the interaction of multiple levels. To cite a few additional examples:

- The University of Pennsylvania center research is integrating genetic information with community data (e.g., socioeconomic status, educational attainment, poverty level) to provide a more holistic picture of prostate cancer prognosis.

- The RAND center is looking at the relationship between neighborhood factors (e.g., socioeconomic status, alcohol outlets, food pricing, and availability) and cumulative physiologic dysregulation, known as allostatic load, as well as health behaviors, including active/sedentary lifestyle, fruit/vegetable intake, and binge drinking.

- The University of Chicago center is exploring the interaction of biological, behavioral, and community factors to understand the causes of health disparities in breast cancer among African American and white women. The research has identified a downward causal pathway between the population and disease levels in which a multifaceted state (most closely associated with social isolation and vigilance) linked to the physiological stress system represents how the environment "gets under the skin" to change endocrine function and ultimately increase risk for mammary cancer.
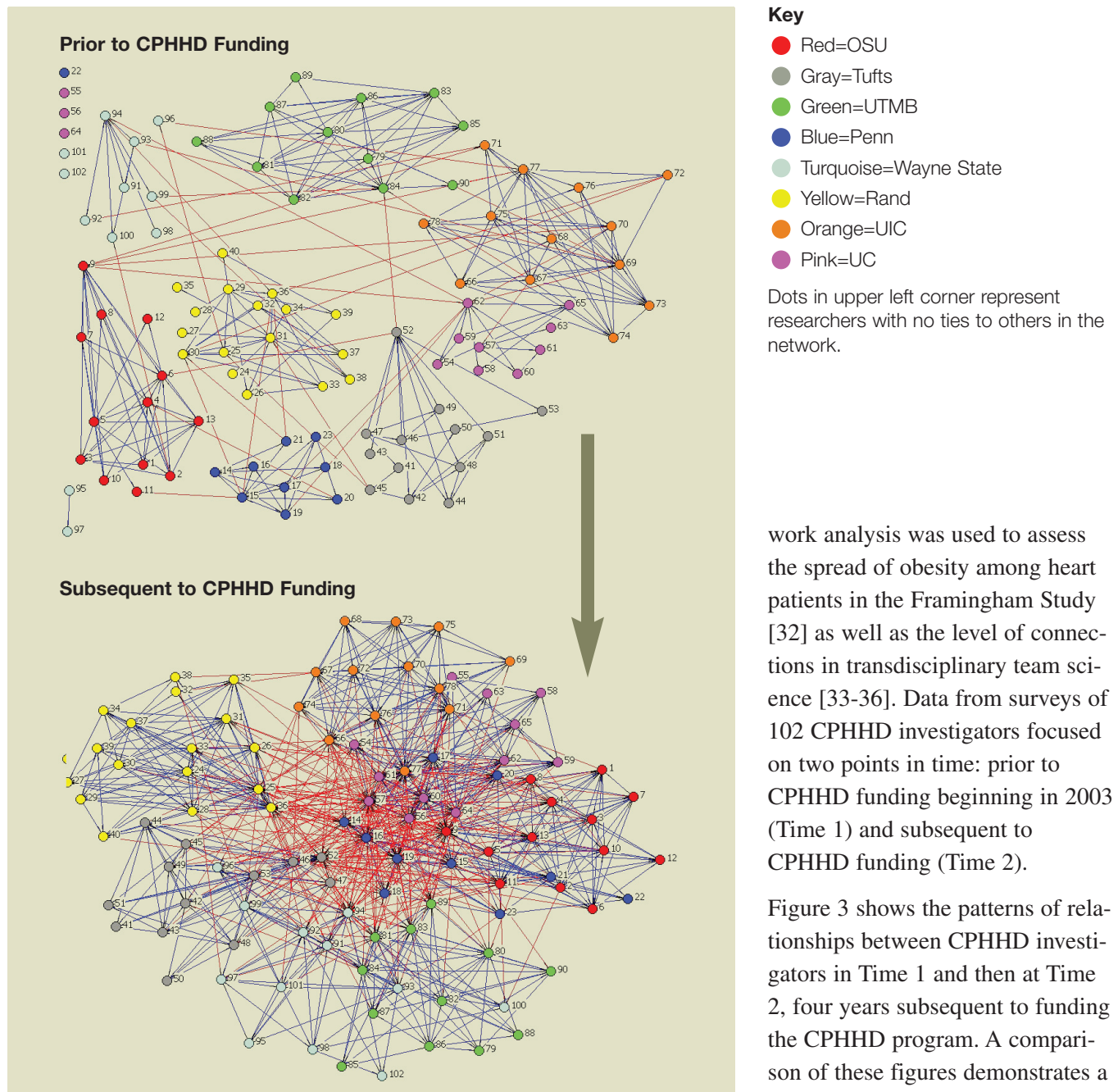
- The Ohio State University CPHHD is seeking to advance understanding of the environmental, societal, behavioral, and biological factors that contribute to health disparities in cervical cancer incidence and mortality among residents of Appalachia Ohio.

- The University of Texas Medical Branch CPHHD is using an integrated framework, which combines analysis of acute and chronic stressors, acculturation/assimilation, coping behaviors and beliefs, self-reported and physiological stress, and health outcomes, to understand how the characteristics of communities in which Hispanics live influence the health of this group, given the paradox of unexpectedly low mortality for this disadvantaged population.

- The Boston Puerto Rican Center CPHHD at Tufts University/Northeastern is evaluating associations between stress, allostatic load, and functional decline (specifically depression, cognitive decline, and physical disability) among older adults of Puerto Rican heritage, as well as the role of social support, vitamin intake, and status in modifying these associations.

- The Wayne State University Center for Urban and African American Health (CUAAH) is exploring the individual and interactive effects of obesity/body composition, environmental and personal stressors, and genetic factors (including ancestral informative markers) in mediating salt sensitivity and non-invasively measured vascular function (e.g., arterial stiffness) and a milieu favorable to breast cancer recurrence in African American breast cancer survivors.

- The University of Illinois at Chicago is examining biological, social, environmental, and behavioral factors associated with the disparity in stage-at-diagnosis and prognosis for breast cancer. One particular focus of this center is how the interplay between biological and environmental factors contributes to the racial and ethnic disparity in breast cancer prognosis.

The value added by transdisciplinary approaches to traditional health disparity research models, typically characterized by isolated specialty foci or "silos," is clearly evident within the CPHHD and across the program as a whole. The CPHHD program has provided a single, network-based organizational structure that supports and encourages the unique type of research required to address health disparities. By providing this structure, the CPHHD program has established new ground in health disparities research never explored fully before the program existed.

Additional evidence of transdisciplinary research is seen in centers shifting from solo to joint-project and centerwide meetings as their science advanced. In the process, new challenges have arisen, which range from synchronizing the schedules of junior and senior investigators and community members for more frequent meetings, to encouraging scientific collaborators to understand each other's disciplines to the extent that the emergence of "new science" is possible. Transdisciplinary research is not simply "interdisciplinary"; rather, it pushes science forward in new and exciting, yet grounded, ways. The CPHHD have continually met these challenges. For example, at one center a clinical investigator, Dr. Funmi Olopade, reported that she had never considered patients in relation to their physical environments prior to working with colleagues from other disciplines in her CPHHD; this interaction changed the way she practiced medicine. Dr. Olopade now considers potential modes of treatment in terms of social supports and their impact on patients' ability to function socially.

Fig 3: Cross-Discipline Network Ties Prior to and Subsequent to Funding of the CPHHD Represented at the CPHHD

Prior to CPHHD Funding

Subsequent to CPHHD Funding

Key

- Red=OSU
- Gray=Tufts
- Green=UTMB
- Blue=Penn
- Turquoise=Wayne State
- Yellow=Rand
- Orange=UIC
- Pink=UC

Dots in upper left corner represent researchers with no ties to others in the network.

Social Network Analysis

The CPHHD aim to achieve transdisciplinary interactions and collaborations that form the basis of a truly multilevel approach to understanding and resolving health disparities. In order to assess progress toward this goal, social network analysis was used to measure progress in building relationships among investigators within and between centers. In the past, social network analysis was used to assess the spread of obesity among heart patients in the Framingham Study [32] as well as the level of connections in transdisciplinary team science [33-36]. Data from surveys of 102 CPHHD investigators focused on two points in time: prior to CPHHD funding beginning in 2003 (Time 1) and subsequent to CPHHD funding (Time 2).

Figure 3 shows the patterns of relationships between CPHHD investigators in Time 1 and then at Time 2, four years subsequent to funding the CPHHD program. A comparison of these figures demonstrates a clear increase in the number of lines, and thus ties, between CPHHD investigators from the first and second time points. The increased number of lines signifies greater number of cross-disciplinary efforts, indicating the emergence of new collaborative relationships. Further analyses demonstrate that interaction increased substantially both within and across centers.

The emergence of transdisciplinarity also is evident in the number of new disciplines with which investigators identified themselves. The average number of new disciplines that had been added into an investigator's research portfolio over the four years of the CPHHD program ranged from 0 to 17 per investigator, with a mean of 4. A total of 37 specific disciplines were identified by investigators as newly incorporated into their research since the funding of the CPHHD program. Those disciplines with the highest frequency are (in descending order): environmental health, epidemiology, demography, and biostatistics. This finding suggests that investigators recognized new opportunities for communication and collaboration with colleagues in other disciplines, and in turn, broadened their definitions of their own research and its intended audience. Important "broker" relationships were also identified among CPHHD investigators. Brokers are investigators who link to otherwise unconnected people in the network and serve an important bridging function between investigators from disparate disciplines. Brokers not only serve as bridges, but also assume new disciplinary identities, significantly more so than non-broker investigators. Finally, brokers demonstrated a significantly higher degree of research orientation that favors transdisciplinarity than other members of the network. This arrangement suggests a possible avenue to achieving transdisciplinary research: identifying brokers early in a cross-center initiative and fostering their efforts as catalysts and change agents. Consequently, this finding indicates an added value of supporting centers that encourage such connections rather than simply funding multiple R01s.

The CPHHD continue to analyze results of their social network survey and will use them not only to foster their own transdisciplinary functioning, but to further knowledge on transdisciplinary science in general—another contribution of the CPHHD.

Developing Cross-Center Collaborations

One of the unique aspects of the CPHHD is that many centers can examine a common area of health disparities among different populations. Currently, investigators from the centers are focusing on cross-center initiatives in several areas. One cross-center initiative relates to the role of social isolation and health outcomes. The animal and human research done at the University of Chicago (see p. 23) suggests that social isolation is linked to adverse health outcomes through dysregulated stress hormone levels. Because all CPHHD had an interest in this topic, a cross-center CPHHD initiative was developed to determine whether social isolation influences the aggressiveness of disease (e.g., cancer) and whether the effect is mediated by dysregulated neurohormonal and immuno-inflammatory system responses, as indicated by selected markers of allostatic load. This investigation also assesses whether the relationships among social isolation, indicators of allostatic load, and aggressiveness of disease (e.g., cancer) vary by age, socioeconomic status, or neighborhood characteristics. Finally, the cross-center studies will investigate whether relationships among social isolation, allostatic load, and aggressiveness or early onset of disease hold across disease entities, and in particular, across cancer sites.

A second cross-center example relates to socioeconomic status, age, race, and ethnicity as predictors of stage-at-diagnosis. An analysis conducted by the University of Illinois at Chicago CPHHD included several innovations in statistical analysis relative to common practice, including (a) analysis of breast cancer stage using an ordered logistic regression (rather than an arbitrary dichotomization such as late-stage versus others); and (b) analysis based on a random effects model to account for the nesting of cases within census tracts. The results from these analyses have been provided to community members and policymakers. These approaches enabled researchers to partially disentangle the effects of race and poverty. These analyses will be extended to data from the other geographic areas represented in the cross-center project. Doing so will allow the CPHHD to demonstrate the degree to which the findings from Chicago are stable and can be replicated across a wide range of urban areas with varying racial, ethnic, and socioeconomic mixes. These analyses may include involvement from the CPHHD centers and populations in Boston, Detroit, Los Angeles, Philadelphia, and Washington, D.C.

Furthermore, representatives from each of the eight CPHHD have collaborated on an original manuscript, entitled "Challenges for Multilevel Analysis in Health Disparities Research." This working group of basic scientists, epidemiologists, statisticians, social scientists, and others addresses the challenges of incorporating factors at multiple levels, from the molecular to community levels, into the same analyses. A manuscript on biomarkers of stress was recently accepted for publication.

Building an Infrastructure to Facilitate Transdisciplinary Research

Many of the centers have established research infrastructures and resources that facilitate cross-site projects. For example, the RAND Corporation CPHHD Data Core supports cross-site projects. This resource houses a large number of measures derived for a variety of substantive areas in several distinct data series including cost of living, disability, pollution, population and housing characteristics, segregation indices, and street connectivity. Researchers can derive smaller data sets from the Data Core to support place-based analyses. Currently, the RAND center works in collaboration with the Penn center as well as with other recently funded projects using national data. These projects include a study at the University of Washington, which examines neighborhood influence on veterans' health, another study on neighborhood influences on women's health in collaboration with investigators from the Women's Health Initiative, and additional studies with UCLA collaborators on allostatic load.

The RAND center has capitalized on national data sets linked with spatial attributes to (a) analyze how the physical and social aspects of neighborhoods affect functional and cognitive disabilities among the elderly; (b) understand the relationships between

"Healthy South Chicago (HSC), as a community partner in a community-based participatory research (CBPR) project continues to find other opportunities to utilize our experiences in a variety of arenas: academia, grants, task forces, and city-wide committees. HSC is now identified as an experienced CBPR partner and it has validated our grassroots work."

DINAH RAMRIEZ, RN
Executive Director , Healthy South Chicago

The center has been a wonderful opportunity to learn about interdisciplinary research on a grand scale. Not only have I learned more about other disciplines, I have expanded my abilities to collaborate with individuals from other disciplines and from other institutions, working with different populations.

KIMBERLY M. KELLY, PHD
Assistant Professor, Human Cancer Genetics
The Ohio State University

neighborhood characteristics and the cumulative wear and tear on multiple organ systems as a result of life stress; and (c) examine how the built environment affects mental health.

Another example of a cross-site resource is the Reference Center established by the University of Texas Medical Branch to provide access to stored plasma and frozen samples of peripheral blood mononuclear cells. The goals of the Reference Center are to

• Provide collection, processing, and long-term storage of longitudinally collected blood samples;

• Provide a specimen bank within and across CPHHD for future studies; and

• Add data from Reference Center–supported studies to the CPHHD database. Future investigators can data mine the information for retrospective studies, or use data for new prospective studies.

In addition to developing cross-site research tools, the CPHHD have taken on a leadership role by developing research infrastructure for appropriate methods in population health and health disparities research. For example, the Project Managers Working Group of the CPHHD has developed a web-based "Health Disparities Toolkit" for use by research project managers within the centers, and ultimately for project managers within the broader scientific community. The toolkit was developed by experienced project managers from the CPHHD institutions who have come together to document their experience of fielding research for the CPHHDs. The toolkit documents overarching practices common to the coordination and management of research involving many departments at any large academic institution. The toolkit provides hands-on practical tips for project managers to use from the beginning to the end of the research process. It can also be used as a training guide for novice project managers and can impact health disparities research by facilitating a better understanding of the varied roles that project managers play and by providing insight into aspects of project management that are common across all studies. The toolkit can be found at http://cancercontrol.cancer.gov/populationhealthcenters/cphhd/toolkit.html.

To cite another example, investigators at the University of Chicago's CPHHD have developed a toolkit for working with animal models, including a method of non-invasive, stress-free measurements of cortiscosterone, enabling repeated measurement at two- to three-hour periods for an indefinite period. The method allows the measurement of the effects of social interactions or stressors on rodents without disrupting their usual activity patterns. Laboratory studies have also established the Sprague-Dawley rat as a model system for spontaneous mammary cancers that parallel the diversity of spontaneous mammary cancers seen in humans.

Moving Science into the Community

Research conducted by the CPHHD is unique not only because it is moving science from "bench to trench," but because it includes underserved and minority communities as partners to identify, address, and ultimately reduce health disparities.

"As a subcontractor and community partner, the UIC center has provided our organization the opportunity to be actively involved in the research process. The presence and accomplishments of the CPHHD have allowed us to begin to see how communities can receive tangible gains from research initiatives."

MARGARET DAVIS, RN, MSN, FNP
Executive Director, Healthcare Consortium of Illinois

As a central feature of the CPHHD, members of the community are involved in the development, execution, and dissemination of research that impacts them directly. Using principles of CBPR, CPHHD researchers have established a wide variety of successful relationships between academic researchers and community groups. A table listing key partnerships established by the centers is found in Appendix C. Examples of these partnerships include the following:

- Tufts University/Northeastern CPHHD and La Alianza Hispana;

- The University of Pennsylvania and the National Black Leadership Initiative on Cancer;

- The University of Texas Medical Branch; Healthy City Assessment Project–Texas City; Community Advisory Panel, Galveston County Health District; League of United Latin American Citizens (LULAC) Council 151; Galveston County Medical Society; Galveston Family, Children and Youth Board; and the Liberty County Health Awareness Network;

- The Ohio State University, Appalachian Community Cancer Network, Meigs County Cancer Initiative, Ohio Department of Breast and Cervical Cancer, Ohio Colorectal Cancer Task Force, Holzer Medical Center/Cancer Center, and Ohio Amish Communities;

- RAND and Altamed, as well as the Los Angeles County Parks and Recreation Department and the District of Columbia City Council;

- University of Illinois at Chicago, Illinois State Cancer Tissue Registry, the Healthcare Consortium of Illinois, Greater Roseland Breast Health District, and Healthy South Chicago.

Centers have also worked to disseminate results within local communities where the research is being conducted. For example,

- The Wayne State University CUAAH has held several "Taste of CUAAH" events, which are designed to encourage healthy eating.

- The University of Pennsylvania center has worked with community stakeholders to develop and implement strategies for disseminating findings to men at risk for prostate cancer by holding regular community outreach events. Through an interactive series of community information symposia, men from the Philadelphia metropolitan area have received training about issues related to prostate cancer screening, decision-making about treatment options, and strategies for navigating the health-care system for prostate cancer care.

- The University of Chicago's center held the first South Side Breast Cancer Summit at a local church to disseminate results from the community-based focus groups held during its first year of operation. After presentations by UIC investigators and local clinicians, the 250 attendees broke into small groups to develop a series of action steps geared at multiple levels of intervention, which the group as a whole later prioritized. The first action step, to provide training in breast health and wellness to 12- to 16-year-old African American youth, resulted in the production of a DVD entitled *Livin' in Your Body 4 Life* that is shown on Chicago cable television and in Chicago public schools. The DVD emphasizes techniques developed by African American youth to deal with stress that comes from community and neighborhood violence. Other action steps focus on organizing residents to address health policy changes affecting inner-city neighborhood areas.

- In work based on methods developed in the CPHHD, RAND is collaborating with ten large health insurers to address health disparities. By merging health plan data with data from the RAND Data Core, these plans can identify community partnerships for intervention.

- The University of Illinois at Chicago center is working with a Patient Navigation Research Program (NCI funded) and a breast and cervical REACH project to develop and evaluate the effect of community navigation on the use of the Illinois Breast and Cervical Cancer Screening Program for early detection. The project also uses in-clinic navigators from the community to assess the effects on follow-up of anomalies found by screening and also rescreening for early detection. This multilevel intervention will move from community organization to individual and policy implications for use of screening resources.

These activities and many others demonstrate that the substantive interaction of the academic research groups and community-based organizations affiliated with the CPPHD is significant and critical for the development and implementation of interventions that will reduce and eventually lead to elimination of health disparities in the future.

SECTION III: RESEARCH HIGHLIGHTS FROM INDIVIDUAL CENTERS

This section provides highlights of work conducted at each of the eight centers:
- *University of Chicago*
- *University of Pennsylvania*
- *RAND Corporation*
- *University of Illinois at Chicago*
- *Ohio State University*
- *University of Texas Medical Branch*
- *Tufts University/ Northeastern*
- *Wayne State University*

University of Chicago:
Biological, Social, and Neighborhood Influence on Fatal Breast Cancer

The four projects and Tissue Core of the University of Chicago Center for Interdisciplinary Health Disparities Research are united by a central question: *Why, despite the fact that white women are more likely to develop breast cancer, are African American women more likely to die from it?* Based on the knowledge that breast cancer develops only after a series of complex genetic interactions, UC center's investigators designed four mutually informative, interdependent research projects to determine the causal links between these genetic mechanisms and the social circumstances and neighborhoods of some African American women. Scientists from inside and outside the university, as well as members of the community who are especially vulnerable to adverse health conditions, contribute to the center's scientific agenda. Taking a multilevel transdisciplinary approach, the center's goal is to move beyond correlations to identify causal steps that start with a person's reaction to his or her social and physical environment and psychological states, and which in turn become embodied by specific endocrine, immune, and neural events that regulate cell death (apoptosis), as well as the function of genes that both promote and inhibit carcinogenesis.

The University of Chicago assembled a transdisciplinary team of physicians, social and behavioral scientists, and community members who not only mutually inform one other, but provide guidance to and receive guidance from two teams working with animal models. These animal models enable laboratory animal manipulations to establish causation, as determined by biopsychologists, molecular biologists, pathologists, and geneticists. In both human and animal research, the center focuses on measuring a range of environments that create daily stressors (e.g., high-crime neighborhoods) or ameliorate them (e.g., neighborhood resources), as well as the lack or presence of social support in the face of these stressors. Psychological measures include vigilance, anxiety, loneliness, and depression along with successful coping strategies. All studies measure tumor stage and grade, receptor status for stress and reproductive hormones,

apoptotic mechanisms, and hyper-methylation in the promoter region of hormone receptors (Fig. 4).
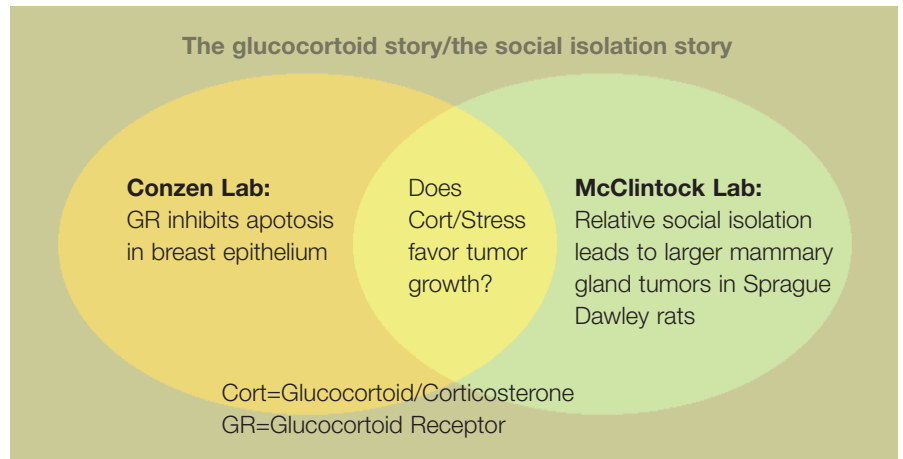
Among the key findings to date:

Preliminary findings from the center's work with animal models suggest that the natural variation in the glucocorticoid response to social isolation predict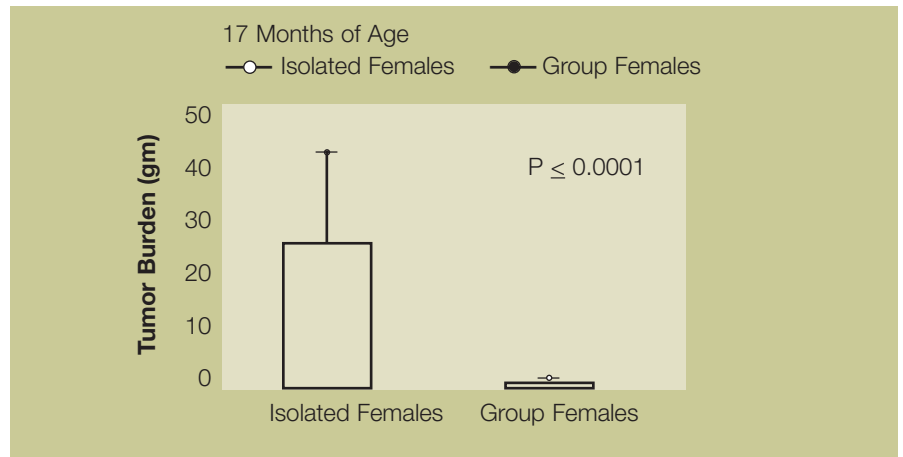s the timing of mammary tumorigenesis. Researchers focused on the regulation of the glucocorticoid system since it (a) is modulated by psychological and social conditions (Fig. 5), and (b) suppresses apoptosis in breast cancer cells, allowing microscopic lesions to grow to a palpable volume (Fig. 6).

The activation of glucocorticoid receptors initiates a downstream signaling pathway that ultimately results in cell survival through suppression of apoptosis. Thus, higher reactivity to stress may predict earlier tumor development through heightened secretion of glucocorticoids (Fig. 7).
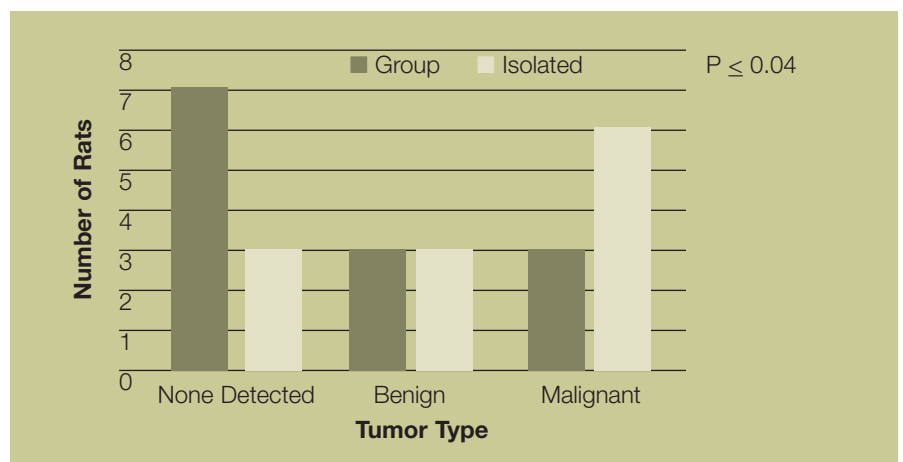
Fig. 4: Rationale for the CPHHD Animal Studies

The glucocortoid story/the social isolation story

Conzen Lab: GR inhibits apotosis in breast epithelium

Does Cort/Stress favor tumor growth?

McClintock Lab: Relative social isolation leads to larger mammary gland tumors in Sprague Dawley rats

Cort=Glucocortoid/Corticosterone
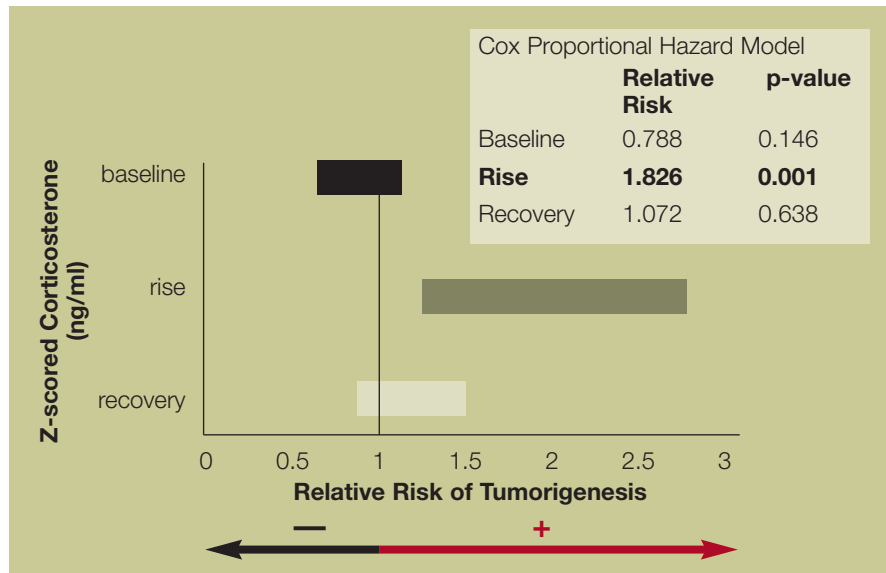GR=Glucocortoid Receptor

Fig. 5: Total Tumor Burden among Isolated and Group-Housed Sprague-Dawley Rats
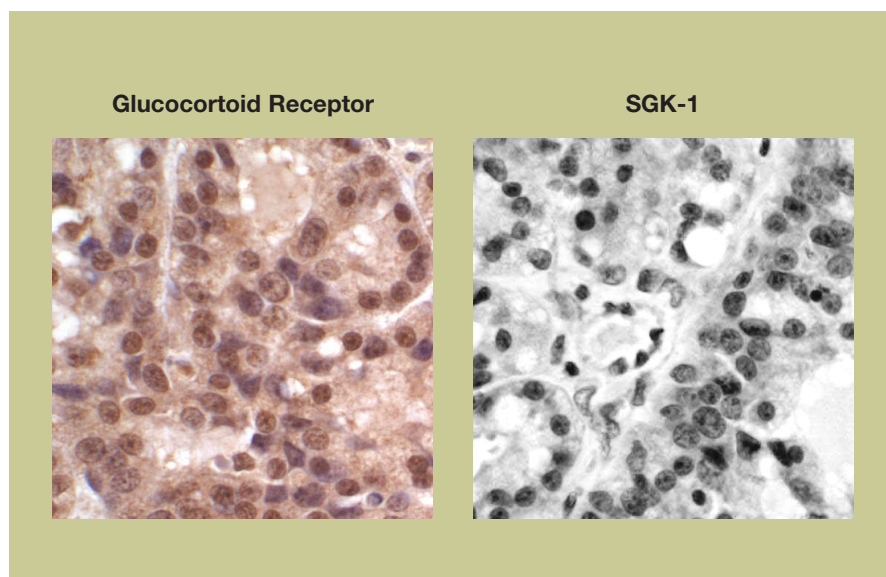

Fig. 6: Isolated Sprague-Dawley Rats Have More Malignant Tumors

Fig. 7: Tumorigenesis Predicted by Rise in Corticosterone in Sprague-Dawley Rats

Cox Proportional Hazard Model		
	Relative Risk	p-value
Baseline	0.788	0.146
Rise	**1.826**	**0.001**
Recovery	1.072	0.638

Fig. 8: IHC Staining Demonstrates GR Expression in Sprague-Dawley Rat Mammary Tumors
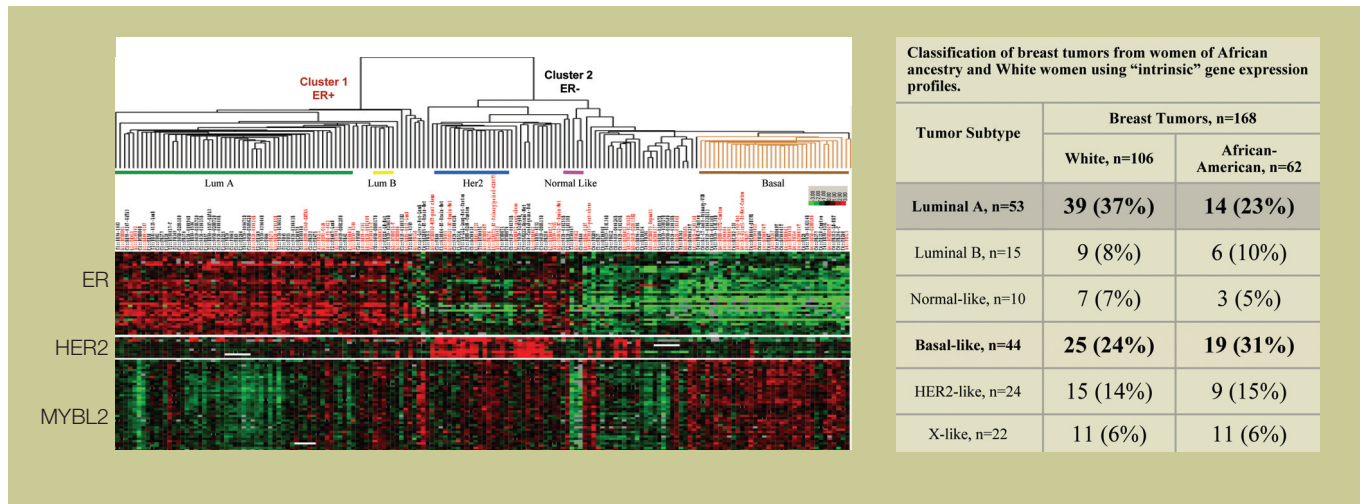

Glucocortoid Receptor   SGK-1

The study tested this hypothesis by subjecting all animals to the same physical restraint stressor and steadily monitoring the development of spontaneous mammary tumors (Fig. 8). High glucocorticoid reactivity to a restraint was found to be associated with earlier tumor development.

Analysis of breast cancer gene expression profiles in a cohort of African American and white women revealed no "race-specific" gene expression. The center has made substantial progress in characterizing mammary cancers suffered by African American women. Self-reported African American women were found to have a higher proportion of tumors within the basal-like (triple negative or ER-/PR-/HER2-negative tumors) and unclassified "intrinsic gene expression" subtypes (Fig. 9).

These tumors do not depend on estrogen and therefore will not respond to hormonal therapy such as tamoxifen or aromatase inhibitors, leaving chemotherapy as the only available treatment option. In a study comparing breast cancers from Nigeria, Senegal, and North America, researchers found that women of African ancestry are more likely to be diagnosed with triple negative and unclassified breast cancer (Table 2).

The study found a high rate of BRCA1 promoter methylation in breast cancers characterized by the so-called triple negative (ER/PR/HE2) tumors from the United States and Nigeria. To date about 30% of tumors from Nigeria and 20% of tumors from African American women exhibit BRCA1 promoter methylation.

Fig. 9: Gene Expression Profiles of Breast Cancers from African American and White Women

Classification of breast tumors from women of African ancestry and White women using "intrinsic" gene expression profiles.

Tumor Subtype	Breast Tumors, n=168	
	White, n=106	African-American, n=62
Luminal A, n=53	39 (37%)	14 (23%)
Luminal B, n=15	9 (8%)	6 (10%)
Normal-like, n=10	7 (7%)	3 (5%)
Basal-like, n=44	25 (24%)	19 (31%)
HER2-like, n=24	15 (14%)	9 (15%)
X-like, n=22	11 (6%)	11 (6%)

Table 2: Molecular Characterization of Breast Cancer and Treatment

ER+	HER2+ (ER–)	BRCA1-mutated (ER–)	From African ancestry (ER–)
Older Age	Younger Age	Younger Age	Younger Age
Well Differentiated	High Grade	High Grade	High Grade
Indolent	Aggressive	Aggressive	Aggressive
HER2–	HER2+	HER2–	?
Tamoxifen	Heceptin	?	?

Researchers have also identified statistically significant links along a downward causal pathway between the population and disease levels in humans. These links are between neighborhood/community-level factors (e.g., violent crime), psychosocial responses (sexual assault, social isolation, vigilance, and depression), and cortiso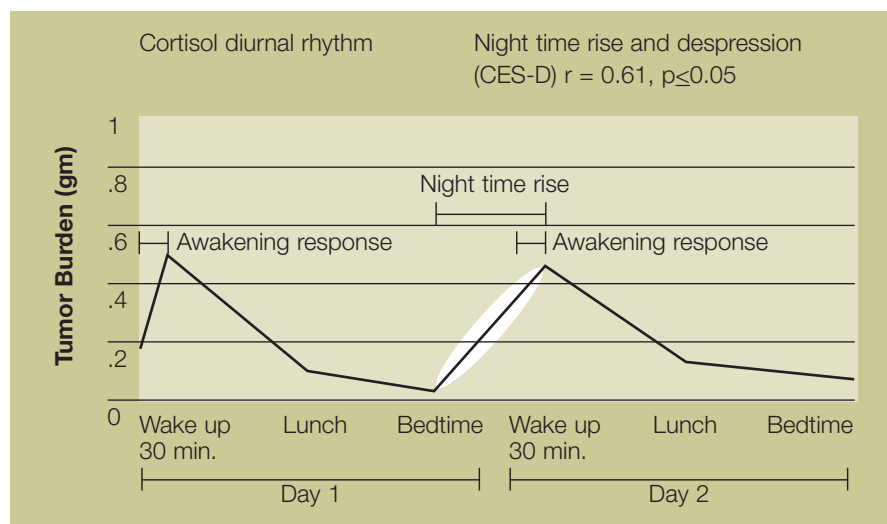l response. The center's human work builds on the animal models by examining the connections between the social environment, psychosocial processes, and biological processes in African American women living on Chicago's South Side who were newly diagnosed with breast cancers. This study involved the development of a Built Environment Team, which measured features in the four-block area around women's homes that might either impede or enhance social interactions (e.g., vacant buildings and lots) and collected data on violent crime, collective efficacy, socioeconomic indicators, and other elements in the vicinity of women's homes. The study found that social isolation, vigilance, and depression were highly correlated and represent facets of a "psychosocial suite" that represents how the social environment gets "under the skin" to alter the body's ability to repair cells (Fig. 10).

Fig. 10: Diurnal Rhythm of Sample of African American Women

UC center's research to date suggests that stress-signaling pathways may be tumorigenic and that women exposed to social isolation may require screening at a younger age than is currently recommended. Prevention agents against breast carcinomas may include inhibitors of glucocorticoid signaling.

In addition, understanding the suite of psychosocial factors that contribute to a woman's vulnerability to stress and development of breast cancers can help clinicians providing treatment identify high-risk individuals and thus allow resources to be maximized. Center researchers are better able to contribute to cancer detection, prevention, and treatment through additional resources leveraged through the entire CPHHD initiative. Based on UC center's investigations, researchers have successfully competed for a Specialized Program of Research Excellence (SPORE) in Breast Cancer. Several of the SPORE projects will translate advances in breast imaging, genetics, and drug development to the benefit of patients with triple negative disease. The center uses knowledge gained from this work to develop better tools for risk assessment, prevention, early detection, and treatment of breast cancer among African American women.

University of Pennsylvania:
Effects of Genetic and Community Factors
on Prostate Cancer Outcomes

The goal of the University of Pennsylvania center is *to address significant gaps in knowledge about the factors that predict prostate cancer outcomes, particularly the causes of disparities in outcomes between men of African and European descent.* Prostate cancer is the leading cause of cancer death among men in the United States that disproportionately affects African American men in terms of incidence, morbidity, and mortality. By integrating diverse scientific disciplines, methods, and analytic approaches from psychology, sociology, epidemiology and genetics, health services, and information science, the Penn center can identify the social, environmental, behavioral, biological, sociological, and psychological factors that contribute to racial disparities in prostate cancer. The Penn center builds on the University of Pennsylvania's existing research resources, which include studies of genetics, quality of life, patterns of care, physical environment, and social environment after the diagnosis of prostate cancer.
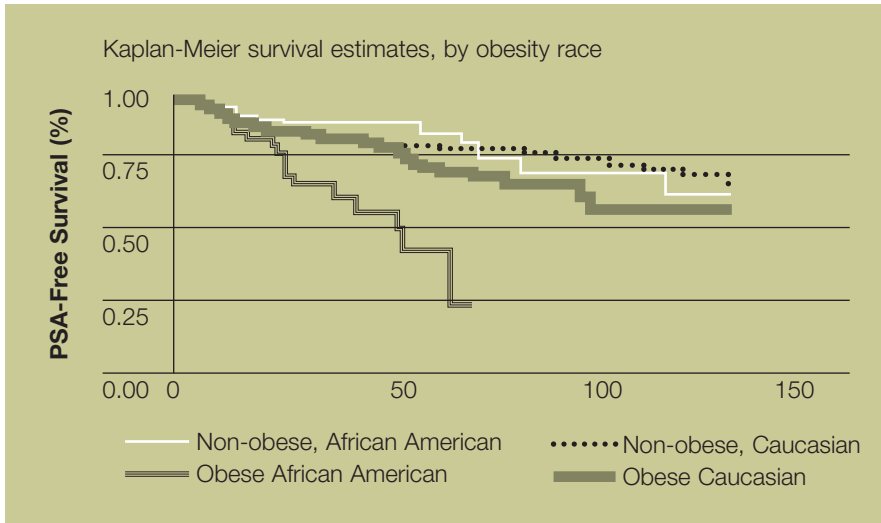
The Penn center has studied approximately 1,300 prostate cancer cases through the University of Pennsylvania Health System. Each project addresses multiple levels of determinants of disparity in prostate cancer outcomes, including factors associated with the social environment (e.g., economic status, access to health care, social isolation), the physical environment (e.g., location or type of residence or medical care setting), behavior (e.g., attitudes, beliefs, and practices associated with prostate cancer screening), and biology (e.g., inherited genotypes that may predict the aggressiveness of a prostate tumor).
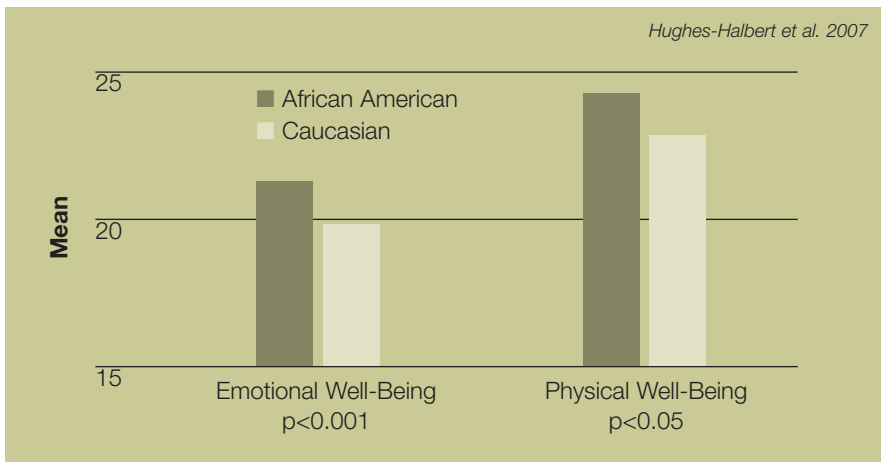
The following are among the key findings to date:

Penn center researchers have found that differences in prostate cancer severity (and associated clinical outcomes) may be affected by both traits such as obesity as well as genetic influences on these risk factor traits. The center has undertaken research that attempts to integrate genetic information with community data to provide a more holistic picture of prostate cancer prognosis. Researchers evaluated the joint relationship of socio-economic status and educational attainment of residential census, including low per-capita income (<$25,319), high poverty (<4.9%) and low high school graduation (<88.3%) as well as genotypes such as the androgen receptor (AR). Genotype effects were observed primarily in men residing in the least deteriorated census tracts. Obesity was found to be associated with tumor severity and shorter time to disease recurrence in African American men but not in white men (Fig. 11). In addition, the effect of obesity on prostate cancer severity differed across AR genotypes. Researchers found that the effect of obesity on prostate cancer outcomes may be modified by androgen metabolism genotypes such as the AR.

Researchers have identified differences in cultural values between African American and white men newly diagnosed with prostate cancer. As a first step toward evaluating the relationship between cultural factors and quality of life following prostate cancer diagnosis, center researchers evaluated racial differences in cultural beliefs and values in African American and white men newly diagnosed with prostate cancer. Standardized instruments were administered to measure cultural values related to religiosity, temporal orientation, and collectivism in 119 African American and white men newly diagnosed with prostate cancer. This research found that African American men reported significantly greater levels of religiosity compared with white men after controlling for clinical factors and sociodemographic characteristics. In addition, African American men had signifi-

Fig. 11: Kaplan-Meier Estimates of Biochemical (PSA) Relapse-free Survival after Radical Prostatectomy in 924 Men Comparing Obese (BMI≥30kg/m²) vs. Non-obese (BMI<30kg/m²) Men by Race, with a Mean Average Follow-up of 42 months

Kaplan-Meier survival estimates, by obesity race

PSA-Free Survival (%)

— Non-obese, African American
····· Non-obese, Caucasian
— Obese African American
— Obese Caucasian

Fig. 12: Quality of Life by Race

Hughes-Halbert et al. 2007

Mean

■ African American
☐ Caucasian

Emotional Well-Being
p<0.001

Physical Well-Being
p<0.05

To facilitate the translation of these findings and other results from CPHHD projects into interventions in the areas of education and to enhance communication skills for negotiating the health-care system, Penn faculty and community stake-holders have developed and imple-mented strategies for disseminating findings to at-risk men. Through an interactive series of community information symposia, men from the Philadelphia metropolitan area have received education about prostate cancer screening, decision-making about treatment options, and strategies for navigating the health-care system for prostate can-cer care.

Research has also identified why some men may not have discus-sions about prostate cancer screening with their general med-ical care providers. In a qualita-tive, chart-stimulated recall study involving 18 primary care physi-cians, Penn center researchers found that physicians did not rou-tinely discuss prostate cancer screening with their patients (discussions occurred in 36% of the clinical encounters evaluated). Barriers to discussion included existence of co-morbidity, lower patient education level or capacity for health literacy, physician forgetfulness, and whether the purpose of the encounter was acute care. Factors that helped stimulate discussion about screening included patient-requested screening, higher patient education level, family history of prostate cancer, and African American race of the patient.
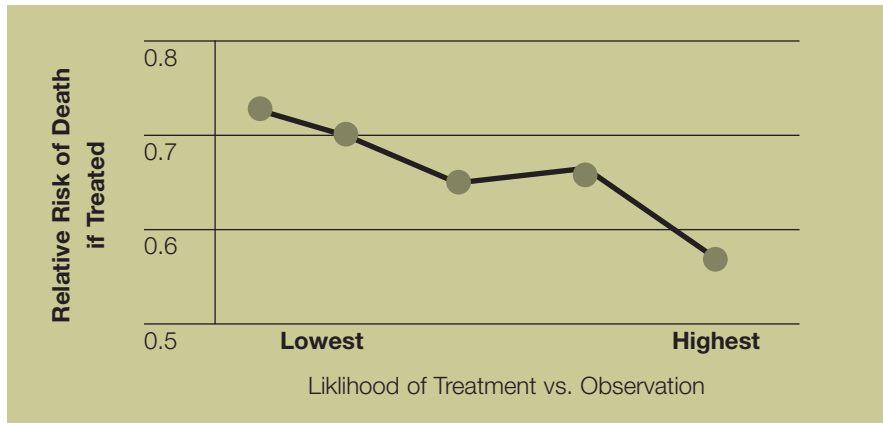
cantly higher levels of emotional and physical well-being than European American men after a prostate cancer diagnosis (Fig. 12). In part, this difference may be explained by the context in which a cancer diagno-sis is made: for African American men, a cancer diag-nosis may be made in the context of a more stressful setting than for European Americans, or African American men may have developed mechanisms to cope with stress that are more effective than those in European American men [37].

Fig. 13: Relationship of Likelihood Treatment for Prostate Cancer and Subsequent Mortality

Liklihood of Treatment vs. Observation

Findings indicate that, among elderly men aged 65 to 80 years with low- and intermediate-risk prostate cancer, those who received treatment for prostate cancer had a statistically significant survival advantage over those who did not receive treatment (Fig 13). Researchers estimated the association between treatment (with radiation therapy or radical prostatectomy) compared with observation and overall survival. Men who were treated had a statistically significant survival advantage (hazard ratio, 0.69; 95% confidence interval, 0.66-0.72). A benefit associated with treatment was seen in all subgroups examined, including older men (aged 75-80 years at diagnosis), African American men, and men with low-risk disease [38].

This research has intervention and policy implications for reducing or eliminating disparities in prostate cancer severity, including ultimately mortality. The Penn center studies are identifying biomarker-environment interactions not previously explored. These interactions suggest that the action of certain biomarkers is only relevant in the context of certain specific exposures, including those at the neighborhood level. Because these studies are aimed at identifying men most likely to have poor outcomes once diagnosed, the potential exists for these biomarkers to aid in identifying the highest-risk groups, so that they can be targeted for screening and prevention. Because these studies link directly with Penn center behavioral research to apply biomarkers to relevant populations, their implementation will allow them to target the segments of the population most appropriate for cancer prevention and control. Similarly, the first-generation studies of cancer treatment that used large databases will lead to the next generation of studies aimed at reducing disparities in prostate cancer severity.

RAND Corporation:
Neighborhood Influences on Health

The overriding focus of the RAND Corporation center is *to understand how the social and built environments where people live affect the health of residents, and how those effects can lead to disparities among different population groups.* The RAND center's work is based on the premise that neighborhoods have their own "genomes," which can be measured and mapped with a wealth of social, environmental, and biological data that contribute to the understanding of health on both population and individual levels. Making strong connections between the social and built aspects of neighborhoods and the health of different groups of people over the life cycle has likely payoffs for the way medicine is personalized and public health is practiced.
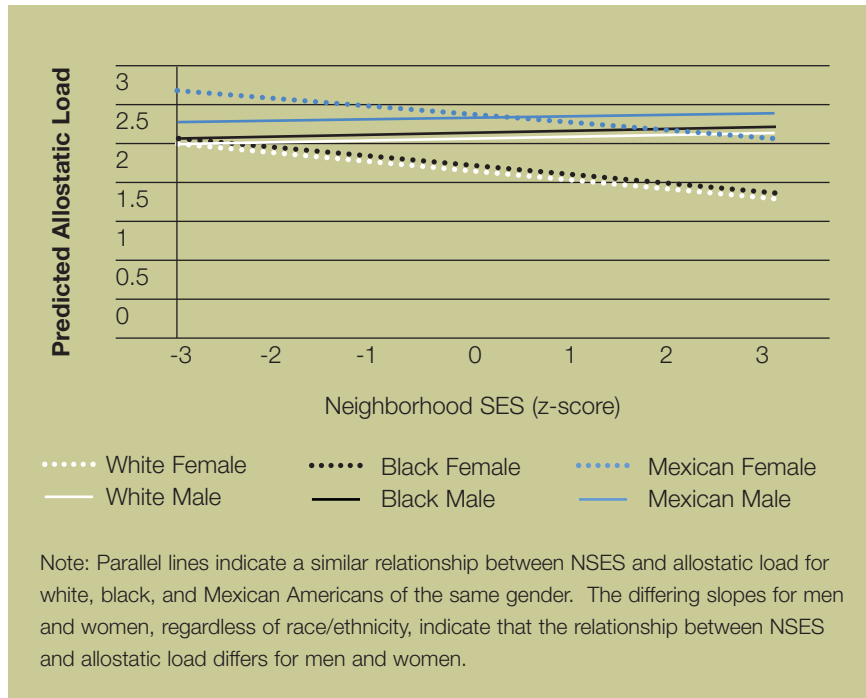
The goal of the RAND center is to study the effects of neighborhoods on health throughout the life cycle and the pathways by which these effects are felt. The center examines neighborhood influences on a variety of health outcomes, including measures of cumulative biological stress, or allostatic load. The center has also developed a rich data resource that can enhance understanding of how neighborhoods influence health. The RAND Data Core contains a host of derived variables, interpolated from 1990-2005, that describe the built and social environments of neighborhoods. Data from the Data Core have been linked with large, national-level data sets to enable national-level analyses of neighborhood effects. The center is developing robust community-based participatory research partnerships within each of the three major U.S. metropolitan areas in which RAND is located (Santa Monica, California; the Washington, D.C. area; and Pittsburgh, Pennsylvania). Disciplines represented on the RAND center team include sociology, demography, economics, medicine, policy analysis, epidemiology, and public health.

The following are among the key achievements and findings to date:

The CPHHD has built the RAND Data Core, which has created a library of contextual data on neighborhoods and neighborhood characteristics. These variables are used to support analyses that investigate the impact of neighborhood characteristics on health. In the process of creating these variables, the development of common approaches to the construction of measures and empirical estimation problems have been resolved or documented. Among the data sets included in the Data Core are Census data from 1990, 2000, and intercensal years; Census TIGER Files from 1990 and 2000; Census Transportation Planning and Package for 1990 and 2000; American Housing Survey for 1990 and 2000; Environmental Protection Agency Data for 1990-2000 on U.S. air quality; and Cost of Living Indices for 1990-2000. In addition to the cross-institutional studies referenced above, the Data Core supports the CPHHD studies related to allostatic load, diet, and health behaviors. These projects use National Health and Nutrition Examination Surveys (NHANES). The NHANES studies examine the role of early life course and of the disablement process, using the Panel Study of Income Dynamics and Health and Retirement Study and studies related to the food and alcohol environment from the California Health Interview Survey.

The RAND center has demonstrated that neighborhood socio-economic status (NSES) has an effect on biological measures of cumulative physiologic dysregulation—known as allostatic load—and that the neighborhood effect differs by gender but not by race/ethnicity (Fig. 14). Using individual-level data from the Third National Health and Nutrition Examination Survey (NHANES III) linked with census-tract level data from the U.S. Census, researchers examined the relationship between

Fig. 14: Neighborhood Socioeconomic Status and Allostatic load

Note: Parallel lines indicate a similar relationship between NSES and allostatic load for white, black, and Mexican Americans of the same gender. The differing slopes for men and women, regardless of race/ethnicity, indicate that the relationship between NSES and allostatic load differs for men and women.

chronic everyday stressors in neighborhoods (ranging from air pollution to fear of crime) and biological precursors of overt disease (allostatic load). The study found that, while allostatic load levels differed across individuals, neighborhood SES had a similar effect on whites, African Americans, and Mexican Americans. The RAND center has also demonstrated, through three different studies and data sources, that neighborhood features impact health of men and women differently. One study found that the neighborhood social environment played a more important role in health outcomes for women, while the economic environment was more important for men.

RAND center's research has demonstrated that neighborhood factors (NSES, alcohol outlets, food pricing and availability) can also affect health behaviors, including binge drinking, active/sedentary lifestyle, and fruit/vegetable intake. However, not all behaviors are impacted in the same way or for the same populations. In one study, individual income, age, education, being male, and being

Hispanic were negatively associated with sedentary lifestyle. Adjusting for these traits, residing in a census tract in a lower-income neighborhood was positively associated with binge drinking (adjusted for individual characteristics). Another study found that lower real price for vegetables and fruits was associated with a significantly lower gain in body mass index (BMI) for children in grades K-3. The estimated effects were meaningfully larger for children in poverty, children already at risk for being overweight or overweight in kindergarten, and Asian and Hispanic children.

In addition, the RAND Center has explored linkages between neighborhood features and stages of the disablement process. Researchers used the Health and Retirement Study to examine these relationships among adults ages 55 and older in the United States. They also examined the relationship of such features to the prevalence of chronic conditions and obesity. They considered multiple dimensions of the neighborhood environment including environmental stressors; safety, mobility and access to services; and social and economic conditions, and used state of the art multi-level statistical techniques to explore these relationships. Findings suggest that economic advantage matters earlier in the disablement process and economic disadvantage is linked to stages of disablement in later life. Consistent with the findings from the National Health and Nutrition Examination Survey (NHANES) study, there also appear to be important differences by gender; street connectivity and economic disadvantage is associated with disablement outcomes only for men.

The chances of having lung disease and arthritis increase with air pollution for men, whereas cancer and heart problems increase with the extent of crime/segregation for women. Onset of hypertension and cancer for men and cancer and lung disease for women are linked to the extent of crime/segregation. Also of note, women living in areas with higher street connectivity are less likely to be overweight. Regarding the social environment, men living in areas with high concentrations of immigrants and women living in areas of high residential stability are more likely to be obese.

Johnson et al (manuscript in preparation) also explored the role of early versus mid-life neighborhood environments using the 1968-2005 Panel Study of Income Dynamics. They estimated four-level hierarchical random effects models of self-assessed general health status and the onset of health-limiting conditions. Findings to date suggest a potentially more prominent role in mid-to-late-life health of neighborhood origins than contemporaneous environments. Taken together, these findings have implications for both the timing and focus of interventions to reduce disparities.

Table 3: A Multilevel Logistic Regression Model of Neighborhood Upward Change and Distant Breast Cancer Stage Diagnosis, 1994-2000

	Odds Ratio	95% CI	p
Intercept	0.08	(0.07,0.08)	0.00
Disadvantage (1990)	1.23**	(1.12,1.36)	0.00
Affluence (1990)	0.86**	(0.79,0.93)	0.00
Immigration (1990)	1.11**	(1.02,1.21)	0.02
Upward Change (1990-2000)	1.09*	(1.01,1.18)	0.03
Age (At diagnosis)	1.01	(1.01,1.02)	0.00
African American	1.24	(1.03,1.48)	0.02
Hispanic	0.71	(0.53,0.95)	0.02

Note: *Significant increase in late-stage diagnosis
     ** Significant predictors in addition to change

University of Illinois at Chicago: Impact of Biological and Environmental Factors on Racial and Ethnic Disparities in Breast Cancer Diagnosis and Prognosis

The goal of the University of Illinois at Chicago center is *to understand why— although data showing that the rates of mammography screening for breast cancer are converging—disparities remain in stage-at-diagnosis and mortality rates.* For example, data from the National Center for Health Statistics indicate that the rate ratio for U.S. breast cancer mortality expanded from near unity in 1980 to 1.37 in 2003 [53]. Using the Illinois State Cancer Registry (ISCR), the Illinois Department of Vital Records tapes, and the Illinois Behavioral Risk Factor Surveillance system to analyze female breast cancer mortality between 1980 and 2003 in Chicago, center researchers found that the death rate due to female breast cancer in Chicago was 49% greater for African American women compared with white women. These data indicate that the difference is not significantly due to increased mortality in African American women, but instead to a substantially greater decrease in mortality among white women (36%). Moreover, a higher number of African American women die at a younger age, namely 19.5% of African American women compared to 9.1% of white women.

The four projects at the UIC center have, since its inception, focused on understanding the impact of biological and social factors in differences in stage, which are considered the best predictor of mortality. Among the key achievements and findings to date:

The UIC center has established a relationship between neighborhood change (gentrification) and the presentation of breast cancer at an advanced stage [54]. CPHHD researchers have found that neighborhood context and upward change

(gentrification) are independently and significantly associated with the probability of a breast cancer patient presenting with a distant metastasis at diagnosis. Specifically, for one standard deviation increase in the rate of neighborhood change, there was a 9% increased risk of distant stage at diagnosis, controlling for neighborhood composition, in 1990. Neighborhood compositional factors such as concentrated disadvantage and concentrated immigration in 1990 were also independently related to distant-stage diagnosis (Table 3).

These results are consistent with findings from the RAND Corporation and the University of Chicago suggesting that environmental disorder and change are stress producing because they disrupt customary patterns of support and access to service including health care.

Researchers have also found that while, at younger ages, African American women are substantially more likely to be diagnosed at later stages of breast cancer than whites, the disparity gradually declines with age and disappears after age 50, although poverty is still important. Disparity in stage-at-diagnosis between whites and the other two groups declines with age. At younger ages, African Americans are much more likely than whites to be diagnosed at the regional or distant stages, but the disparity is far less pronounced at older ages. A similar

but less pronounced result occurs for Hispanics.

Analysis of interview data suggests that the racial/ethnic differences may be strongly related to finding the cancer by mammography. At younger ages, white women are more likely than younger African American women to be diagnosed at the in-situ stage, which is almost always detected via mammography. The results are similar for Hispanic breast cancer patients. Replication of these findings in other participating cities will provide guidance for policy that addresses more effective use of screening in identification of populations that may be at greater risk of advanced disease. Outcomes from the initial Chicago/Cook County research are being replicated in Detroit, Boston, Los Angeles, Philadelphia, and Washington, D.C. as part of a multi-center collaboration with the center at the University of Chicago, the University of Pennsylvania, RAND, and Tufts.

Researchers have found variation in time to diagnosis, treatment offered, and treatment refused.
Interviews with 610 breast cancer patients, identified by rapid case ascertainment, which the CPHHD helped the Illinois State Cancer Registry (ISCR) develop with project funds, have supported research on the role of patient support through social networks and on variation in time to diagnosis, treatment offered, and treatment refused. The results are used to develop strategies for community education in collaboration with the Illinois Breast and Cervical Cancer program. Additional interviews with patients waiting for results of follow-up for suspicious findings indicate that cultural beliefs may be a deterrent to care.

Preliminary results based on the first 610 patient interviews indicate that African American/Hispanic patients are less likely than whites to have a screen-detected cancer (47% and 43% vs. 58%, p=0.01); more likely to wait at least three months from first medical visit to treatment; and more likely to wait at least six months from initial discovery to treatment (20% and 20% vs. 9%, p=0.01) (Table 4). The crude odds ratios for late stage diagnosis (stages 2, 3, 4 vs.

0, 1) was 2.1. Path analyses revealed that these timing-of-care variables mediated approximately half of African American-white and Hispanic-white stage disparity. These results indicate that African American and Hispanic women experienced less optimal timing of health care compared to whites. Abstracting medical records will enable researchers to better measure how these mediating variables may account for stage disparities.

Discovery of a symptomatic lump following (despite) a recent routine mammogram was more common among African American and Hispanic breast cancer patients than for white patients (33% and 44% vs. 22%, respectively), suggesting that differences in the effectiveness of mammography as currently practiced could explain the later stage at diagnosis for African American and Hispanic women (Table 5).

Preliminary results suggest that African American and Hispanic women are less likely to be offered optimal treatment for their breast cancer. For patients diagnosed with stage 0, I, or II disease (when lumpectomy may be appropriate), African American patients (12%) were more likely than white patients (5%) not to be offered lumpectomy (p=0.06). For patients diagnosed with stage I, II, or III disease (when radiation therapy may be appropriate), African American patients (30%) were more likely than white patients (21%) not to be offered radiation therapy (p=0.09). For patients diagnosed with stage 0, I, or II disease, African American patients (69%) and Hispanic patients (35%) were both more likely than white patients (24%) not to be offered hormone therapy (p=0.0004).

Preliminary results suggest that, while Hispanic women may be less likely than white patients to refuse treatment, African American women appear more likely to refuse treatment for breast cancer. Fifteen percent of white, 23% of African American, and 7% of Hispanic patients report refusing surgery, radiation therapy, chemotherapy, and/or hormone therapy (p=0.006). Associations were unchanged with adjustment for stage-at-diagnosis and age.

Table 4: Racial and Ethnic Disparity in the Timing of Health Care for Breast Cancer

	White (N=209) (%)	Black (N=315) (%)	Hispanic (N=86) (%)	p-value
Initial patient awareness				
Through screening imaging	58	47	43	
Through symptoms or clinical exam	42	53	57	0.01
Time from awareness to first contact with health care system				
None (medically detected)	66	56	52	
< 1 month	18	23	20	
1-3 months	9	11	14	
> 3 months	4	5	7	
Time in the system before treatment initiation				
< 1 month	10	11	11	
< 3 months	83	56	53	
> 3 months	17	34	37	0.0007
Total time from awareness to treatment initiation				
< 3 months	72	51	45	
3-6 months	19	29	35	
≥ 6 months	9	20	20	0.0001

Table 5: Racial and Ethnic Disparity in the Proportion of Symptomatic Cancers among Women with a Recent, Asymptomatic Screening Mammogram

Timing of Last Mammogram	White (N=162) (%)	Black (N=232) (%)	Hispanic (N=71) (%)	p-value
Within 2 Years	25	36	48	0.002
Within 1 Year	17	29	43	0.0003

Ohio State University: Biological, Behavioral, and Community Factors Affecting Cervical Cancer Disparities in Appalachia Ohio

Although cervical cancer has significantly declined in the United States since the 1950s, certain regions, including the Appalachia area of Ohio, still report high rates of this cancer. Incidence of and mortality rates for cervical cancer in the Appalachia area of Ohio, a 29-county region in the southeastern area of the state, are 38.6% higher and the mortality rates are 44.4% higher than in non-Appalachia Ohio (Tables 6 and 7). To address this difference in rates, the Ohio State University (OSU) center *seeks to understand why Ohio Appalachian women have higher rates of cervical cancer than found in other regions*.

The ultimate goal of the OSU center is to advance understanding of the environmental, societal, behavioral, and biological factors that contribute to health disparities in cancer incidence and mortality among this population. The CPHHD focuses on the three major factors associated with cervical cancer—lack of Pap testing, smoking, and infection with human papillomavirus (HPV)—in order to investigate why rates of cervical cancer are so high in Ohio Appalachia and to test culturally appropriate interventions to reduce risk. The center's research involves a number of disciplines, including public health, nursing, biostatistics, family medicine, pathology, gynecology, cancer genetics, medicine, dentistry, psychiatry, and virology.

A baseline survey of 571 women was used to provide information about factors related to Pap smear and tobacco use, respectively. A similar survey was administered to participants in a case-control study that focused on the role multilevel factors play in causing cervical abnormalities. One hypothesis is that women who smoke are more likely to have a weakened immune system. In turn, this weakness leads to greater difficulty in clearing an HPV infection, thereby raising the risk for a cervical abnormality. Center researchers are also investigating the frequency of
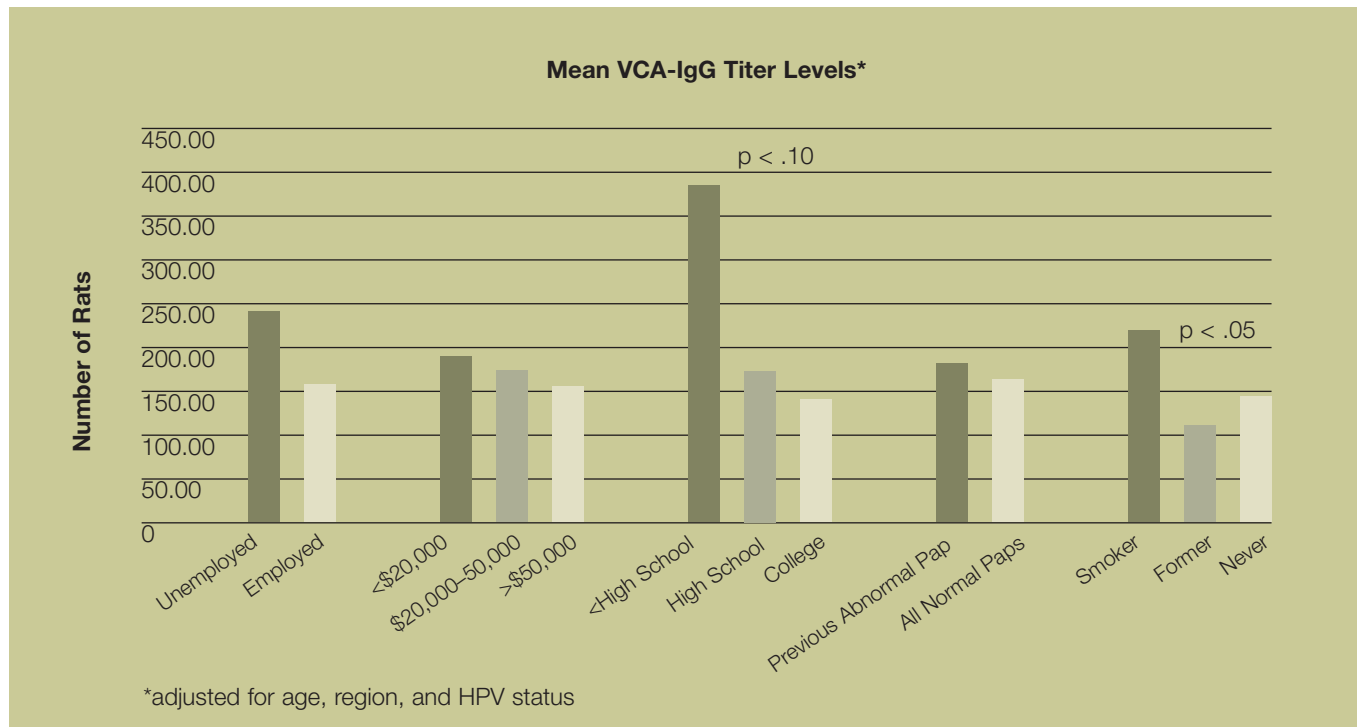
TGFBR1*6A germline alleles in women with abnormal Pap smears compared to women with normal Pap smears. This mutation may affect the expression of HPV oncoproteins.

The following are among the key findings to date:

CPHHD researchers found that rates of abnormal Pap tests among women receiving those tests in Appalachian clinics were fourfold higher than the national average (Fig. 15). Among Appalachian women with abnormal Pap tests, Epstein-Barr virus antibody titer levels (a marker of chronic stress) were elevated among those with lower socio-economic status (SES), high-risk status for cervical cancer, and current tobacco use.

Factors associated with receiving Pap tests within guidelines among Appalachian women included SES measures (education, income, poverty index), life stressors, trust in the health-care system, tobacco use, and perceived discrimination. In terms of Pap cancer screening behavior, women who were not within guidelines for Pap testing tended to be older ($\geq$ age 50), less likely to be high school graduates, more likely to be of lower income, and more likely to smoke cigarettes compared with women within guidelines for Pap testing.

Studies also found that female Appalachian smokers experienced more disadvantage compared with ex-smokers and those who had never smoked. Researchers identified several individual-level factors associated with smoking. In particular, current smokers tended to have lower education and income, and were less likely to be employed. Forty-seven percent of women who reported being current smokers had Center for Epidemiologic Studies Depression Scale (CES-D) scores indicative of depression and smokers were more likely to be heavier alcohol drinkers. These women also tended to have fewer ties in their social networks. Because limited information exists on the mechanisms responsible for smoking among disadvantaged adults, it is not possible to say if and how

Fig. 15: Epstein-Barr Virus Results (N=98)

Mean VCA-IgG Titer Levels*

p < .10

p < .05

Number of Rats

450.00
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0

Unemployed / Employed / <$20,000 / $20,000-50,000 / >$50,000 / <High School / High School / College / Previous Abnormal Pap / All Normal Paps / Smoker / Former / Never

*adjusted for age, region, and HPV status

Appalachian women are unique among poor women who smoke. Nevertheless, the OSU studies, though preliminary, suggest ways in which factors such as social networks, alcohol, and depression influence persistent smoking among poor women.

Results indicate that the Amish population in Appalachia Ohio has lower cancer incidence and mortality rates than other populations in this region. In the Amish settlement in Holmes County, Ohio, the largest settlement in North America, members had lower cancer incidence rates, especially for tobacco and alcohol-related cancers. Survey results indicate that Amish men and women were significantly less likely to currently smoke cigarettes or to have had recent cancer screening tests (for men: prostate, oral, colorectal cancers; for women: cervical, breast, colorectal, and oral cancers) compared with their non-Amish neighbors. Amish men and women also walked a significantly higher number of steps each day (as measured by pedometer). Thus, following cultural norms appears to have provided some protection

in terms of tobacco and physical inactivity, but the lower utilization of cancer screening tests, perhaps due to lack of transportation, trust, or health insurance coverage, is of concern. As an example, like the Amish, Mormons in Utah have a proscription for tobacco, alcohol, and risky sexual behaviors. Unlike the Amish, they do not have cultural norms that encourage walking or discourage the use of screening tests. Cancer incidence and mortality rates among the Amish are similar to those of the Mormons in Utah and the Seventh Day Adventists in California.

Table 6: Average Annual, Age-adjusted Invasive Cervical Cancer Incidence Rates in the US, Ohio, Non-Appalachia Ohio and Appalachia Ohio, per 100,000 Females, According to Age Group and Race for the Years 1996 to 2003

	15 Years and Older		15 Years to 49 Years		50 Years and Older	
	All Races	White Only	All Races	White Only	All Races	White Only
United States[1]	11.6	11.2	9.8	10.0	15.0	13.5
Ohio[2]	11.1	10.9	9.9	9.9	13.4	12.7
Non-Appalachia Ohio[2]	10.1	10.3	9.3	9.3	13.0	12.1
Appalachia Ohio[2]	14.7	14.5	13.7	13.6	16.5	16.2

1 US incidence rates are based on the following: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 13 Regs Public-Use, Nov 2005 Sub (1992-2003), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006, based on the November 2005 submission.

2 Ohio incidence rates and incidence rates for selected geographic regions within Ohio are based on The Ohio Cancer Incidence Surveillance System, Ohio Department of Health, April 2006 data release.

Table 7: Average Annual, Age-adjusted Invasive Cervical Cancer Mortality Rates in the US, Ohio, Non-Appalachia Ohio and Appalachia Ohio, per 100,000 Females, According to Age Group and Race for the Years 1996 to 2003 for Ohio and the Years 2000 to 2004 for the US

	Under 50 Years		50 Years and Older		All Ages	
	All Races	White Only	All Races	White Only	All Races	White Only
United States[1]	1.3	1.2	5.9	5.2	2.6	2.3
Ohio[2]	1.5	1.4	6.5	6.0	2.9	2.7
Non-Appalachia Ohio[2]	1.4	1.3	6.2	5.6	2.7	2.5
Appalachia Ohio[2]	2.1	2.1	8.4	8.1	3.9	3.8

1 Ries LAG, Melbert D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Horner MJ, Howlader N, Eisner MP, Reichman M, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2004, based on November 2006 SEER data submission, posted to the SEER Web site, 2007.

2 Source: Ohio Vital Statistics Program, Ohio Department of Health (data release January 2006).

Fig. 16: Cell Proliferation of Cervical Carcinoma Cells after Treatment with PK3-46-3B
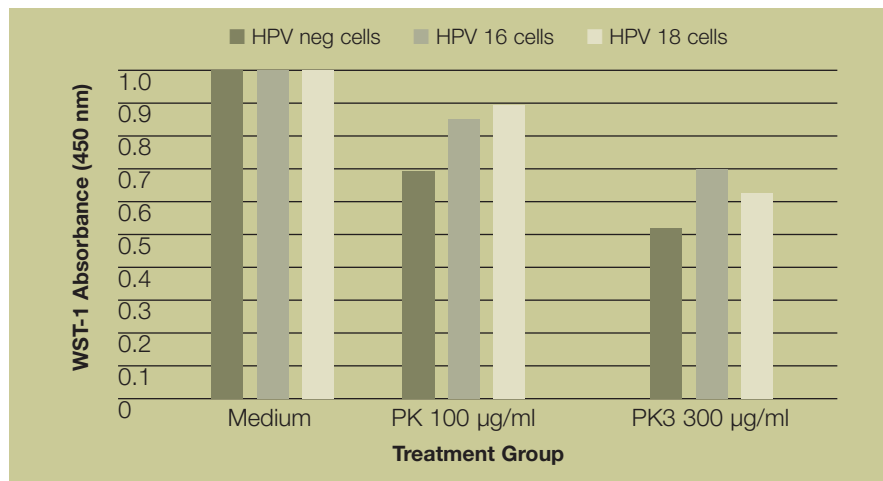
In vitro studies using an extract of lyophilized black raspberries (LBR) suggest that the responsiveness of human cervical cancer cells in vivo to the chemopreventive effects of LBR is a real possibility, perhaps providing an intervention to reduce cervical cancer rates in Appalachia Ohio (Fig. 16).

Numerous epidemiological studies have shown the strong correlation between frequent consumption of fresh fruits and vegetables and a decreased cancer risk. In support of that data, several preclinical animal studies have been conducted that demonstrate the remarkable chemopreventive activity of black raspberries on chemically-induced aerodigestive tract tumor development from epithelial cells, including oral, esophagus, and colon. Specifically at OSU, an extract of lyophilized black raspberries (LBR) dramatically inhibited the *in vitro* proliferation of epithelial cells derived from a human oral squamous cell carcinoma, suggesting that the chemoprevention of human cancer by LBR components *in vitro* is possible, perhaps by the down-regulation and up-regulation of 31 and 23 genes, respectively, in these epithelial cells. Since there is little difference between the squamous epithelium of the oral cavity and cervix, we would expect a similar anti-proliferative effect to be elicited by the LBR extract on cervical cancer cell growth. Initial proliferation experiments demonstrate that the LBR

extract significantly decreased the levels of cell proliferation in C33-A cells (HPV negative) by 47% at 3 days; SiHa cells (HPV 16) by 30% by 7days; and HeLa cells (HPV 18) by 37% by 7days.

The ability to examine cervical cancer disparities using a transdisciplinary approach, in which researchers examine risk factors from the cellular to the societal level, has helped the OSU center identify areas for intervention. For example, preliminary results indicating high rates of HPV infection suggest future research should look at ways to 1) identify ways to inform and educate the population at risk about HPV, the HPV vaccine, and cervical cancer; and 2) assess the characteristics of HPV infection in the population, eg type, load, partner factors. High EBV titer levels indicate low immune functioning and/or high levels of stress. Young women participating in focus groups aimed at identifying reasons for lack of health care report "stress" as a common problem faced by women in their communities due to crime, loss of jobs, poor economic situations, and geographic/social isolation. Thus, our biological measures may be reporting effects related to social and economic factors

Lastly, our results point to the need to engage policy and health officials in the state to address these identified areas of disparity. As an example, the high rates of abnormal Pap tests and the influence of SES on Pap test completion suggest that state screening programs, like the Breast and Cervical Cancer Detection Program, should focus efforts on screening women in this geographic area. Funding for smoking cessation programs may need to be expanded to address co-occurring problems, such as alcohol use and depression.

Table 8: Distance from Petrochemical Complex and Stressful Life Events Predict Interleukin 10 and 6

	IL-10	IL-6
Mean ± SD	4.85 ± 15.76	1.93 ± 4.68
Distance, ß, (p-value)	0.229 (**0.018**)	-0.438 (**<0.001**)
Life Events, ß, (p-value)	0.061 (**0.011**)	-0.065 (**0.033**)

Adjusted for gender, age, marital status, education, race/ethnicity, income

University of Texas Medical Branch: Understanding the Individual, Social, and Community Mechanisms Underlying the "Hispanic Paradox"

The University of Texas Medical Branch (UTMB) center *focuses on ethnic differences in cancer treatment outcomes, especially toxicity from treatment, among Hispanic populations in the United States.*

The center systematically investigates mechanisms operable in the so-called "Hispanic paradox," the finding that the health of many Hispanic populations in the United States is similar to that of non-Hispanic whites, even though Hispanic populations are clearly disadvantaged in terms of income, health insurance, housing, education, and other factors that correlate strongly with health.

The center's research was stimulated by the UTMB researchers' recent finding that overall mortality and the incidence of most major cancers are significantly lower among Hispanics living in census tracts with high percentages of Hispanics compared with those living in neighborhoods with low percentages of Hispanics. The UTMB center was built on a foundation of two groups of investigators conducting separate but related research: (a) population-based studies of cancer and cancer outcomes, focusing on disparities in diagnosis, treatment, and outcomes associated with advanced age, minority ethnicity, or rural residence; (b) population-based longitudinal studies of the health of Hispanic populations, assessing predictors of continued health and functional independence in older Hispanics.
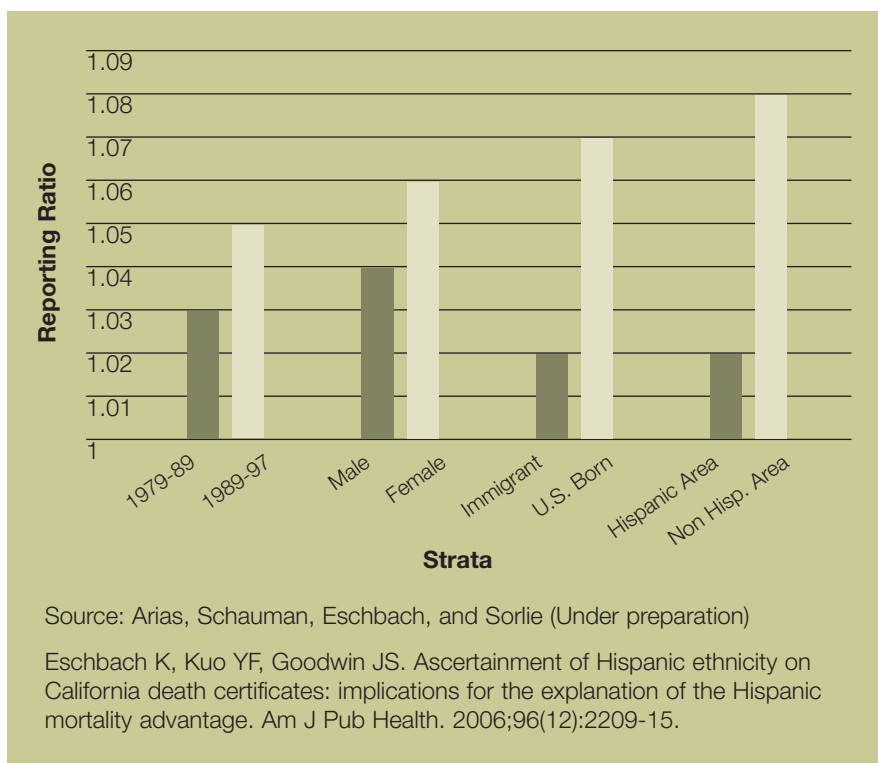
The research aims to add to the explicit understanding of stress and its moderators in the social epidemiology of Hispanics. Underlying these global goals is an attempt to link social-, individual-, and physiological-level data to better understand their interrelationships in the health of Hispanics. The center seeks to understand how the characteristics of communities in which Hispanics live influence the health of this group, given the paradox of unexpectedly low mortality for a disadvantaged population. Using an integrated framework, research has combined an analysis of acute and chronic stressors (e.g., daily hassles, life events, perception of risk associated with a technological hazard such as nuclear power plants, nerve-gas storage facilities, or hazardous waste sites) and acculturation/assimilation, coping behaviors and beliefs, self-reported and physiological stress, and health outcomes.

The following are among the key findings to date:

The UTMB center has found an association between living in close proximity to an oil refinery and increased levels of psychological stress. One study focused on residents of Texas City, a town of 43,095, home to three of Texas's refineries (16% of Texas's capacity). The study examined the relationships among technological hazards, psychosocial processes, contextual effects, and health outcomes among a randomly selected sample of Mexican American and non-Hispanic Texas City residents 25 years of age or older. A total of 2,751 residents completed surveys; their blood was collected, and their blood pressure, pulse, height, and weight were measured. A majority were U.S.-born Hispanic (36%), 17% were foreign-born Hispanic, 34% were non-Hispanic white, and 12% were African American.

In terms of proximity to the refineries, the distance between the fence line to the refinery and the respondents' homes ranged from 0 to 3 miles. For each mile increase from the fence line, inflammatory and stress

markers (IL-6 and IL-10) were significantly affected. The findings suggest that proximity to large petrochemical complexes may increase exposure to pollutants that can lead to an increase in health problems and an increase in inflammatory cytokines, or may lead to an increase in the psychological stress response reflected in an increase in inflammatory cytokines (Table 8).

Data have generally not shown evidence of lower risk for Hispanics or for residents of barrio settings; however, Hispanics living in low-concentrated Hispanic neighborhoods were found to be at higher risk of prostate cancer. The UTMB center uses NHANES III[*] data to investigate neighborhood variation in risk behaviors and risk biomarkers. The research has found, in general, that risks for Hispanics appear to be concordant with expectations based on their socioeconomic disadvantage, and that neighborhood socioeconomic conditions are more robust predictors of risks than ethnic composition variables.

Another important finding is the validating of the reported lower mortality among Mexican Americans and to address whether a high percentage of Mexican Americans in the neighborhood (i.e., ethnically homogenous neighborhood) is a protective factor (Fig. 17).

Based on validation of death certificate classification of Hispanic origin by comparing classification on the death certificate to classification based on place of birth and Spanish surname coding, it was found that death certificate classification is largely accurate: Mexican American mortality rates really are lower than those of non-Hispanic whites; lower mortality is

Fig. 17: Death Certificate Reporting Errors are Modest

Source: Arias, Schauman, Eschbach, and Sorlie (Under preparation)

Eschbach K, Kuo YF, Goodwin JS. Ascertainment of Hispanic ethnicity on California death certificates: implications for the explanation of the Hispanic mortality advantage. Am J Pub Health. 2006;96(12):2209-15.

mostly among immigrant Mexican Americans compared to US native-born Mexican Americans and vital statistics are particularly reliable for immigrants.

The UTMB center has established a Reference Center using pilot funding so that future studies can have access to stored plasma. The Reference Center will provide collection, processing, and long-term storage of longitudinally collected blood samples; provide a specimen bank for future studies within and across the CPHHD; and add data from Reference Center–supported studies to the CPHHD database. In addition to the stored plasma, frozen samples of peripheral blood mononuclear cells are also available. Other investigators in the future can data mine the information for retrospective studies, or use information for new prospective studies.

[*]National Health and Nutrition Examination Survey III

Tufts University/Northeastern: Stress and Nutrition in Relation to Chronic Disease Risk in Older Puerto Ricans

The Boston Puerto Rican center at Tufts University/Northeastern was designed *to perform a series of interrelated studies focusing on older adults of Puerto Rican origin in order to evaluate specific stressors affecting the Puerto Rican community, and to determine the effect of these stressors on allostatic load (a measure of stress) and, in turn, on disease-specific outcomes.* This focus stems from a recognition that older Puerto Rican adults living on the U.S. mainland have been identified as a group highly at risk for excess chronic conditions, particularly diabetes, depression, and physical impairment. Puerto Ricans make up the majority of the Hispanic population in the northeastern United States.

Activities in the center revolve around a two-year prospective cohort study, which is evaluating (a) associations between stress, allostatic load, and functional decline (specifically depression, cognitive decline, and physical disability), and (b) the role of social support, vitamin intake, and status in modifying these associations. Because poverty, environment, changes in acculturation, and family mobility may all contribute to the burden of stress that may, in turn, affect risk of chronic disease, the center is focusing on a sociological investigation of psychosocial stressors and their measurement. Researchers also hypothesize that poor diet may contribute to the effects of stress on this population, and therefore measure both dietary intake and plasma status of several nutrients. Finally, researchers recognize that genetic variations may contribute to health disparities, and they are exploring relationships between selected gene variants and allostatic load and other chronic conditions. The center format has allowed researchers from social sciences, epidemiology, biology, and genetics to work together to examine these complex issues.

The following are among the key findings to date:

Descriptive data confirm the presence of health disparities in this population with high risk levels for several conditions. Based on findings from 1,000 interviews in a baseline survey, researchers found that the majority of Puerto Rican elders in the Boston area lived in poverty; more than 50% had less than or equal to an eighth grade education; and 76% received health services through Medicare. Further, subjects had significantly higher disability scores than did neighborhood-based non-Hispanic whites, with more than half of those aged 60 and older reporting difficulty with at least one activity of daily living (ADL). Almost 40% of these Puerto Rican elders had diabetes, and among those with diabetes, Puerto Ricans were more than twice as likely to have high glycosylated hemoglobin (>7%) indicating poor control. More than 40% reported depressive symptomatology, reinforcing the complex nature of their health conditions.

Moreover, preliminary results show that Puerto Rican adults (45-75 years) in the Boston area were, as a group, not highly acculturated, despite living on the U.S. mainland for many years (median=36 years). Acculturation refers to the degree of adaptation to culture of the United States, including residence history, country of origin, ancestry, immigration, and adaptation to new physical, cultural, social, and economic environments. The process of acculturation is associated with stress, and those least acculturated may experience more difficulty in meeting their needs. Using a measure based on language, researchers found that median acculturation scores were 25% on a scale of 0-100%. Interestingly, unlike several findings on Mexican Americans, which show that dietary quality deteriorated with acculturation in the United States (due to greater use of convenience and snack foods), an earlier analysis by the center showed that greater acculturation among Hispanic elders of Caribbean origin in Boston was associated with better quality diet, due to a broadening of food choice [39].

Fig. 18: APOE Allele Frequencies
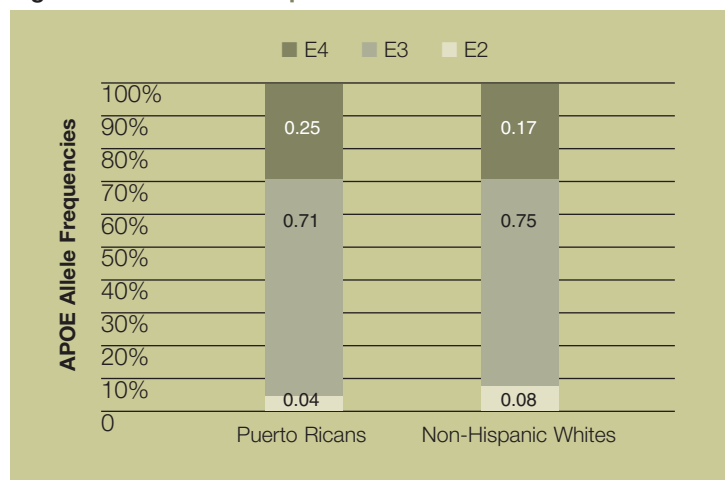
Findings from qualitative data suggest that social networks can be a great source of support for this population, but at the same time a major source of stress as individuals share burden in a collective way. Networks composed of individuals facing a large number of stressors may, in fact, contribute to increasing stress among members of this group rather than serving as sources of support. The process of migration was also found to contribute to stress in many ways, as it disrupts existing social networks either through the migration of the subject or through the migration of members of his or her network. Researchers also found significant associations between depression and level of stress, and between depression and the number of important life events the respondent has experienced. The size (number of contacts) of the respondent's social network was inversely correlated with depression but did not show a significant association with the level of stress. In addition, the length of the relationship to people in one's network was not as important as the amount of assistance the individual received from the network.

Preliminary analysis of genetic variation shows that Puerto Ricans are more likely to have genetic variants associated with disease risk relative to non-Hispanic white populations (Figures 18, 19, and 20). Candidate genes, potentially associated with metabolic syndrome, inflammation, stress, and cognitive function were analyzed and compared with similar analyses of the non-Hispanic white Framingham study population; 32 of 46 polymorphisms showed genotype frequency distribution significantly different than those in the Framingham population, the majority showing higher risk in the Puerto Rican population, including Apolipoprotein E (*APOE*) 4 variant, *PPARG* Pro-12-Ala dominant variant, *LPL* N219S minor allele, *LPL*-93 G allele, Apolipoprotein B (APOB) XBA1 variant, and *APOC*3 SST1 variant. This higher genetic risk, in combination with high stress and poor nutritional status is likely to be an important factor in explaining observed health disparities. Prelminary review of polymorphisms associated with allostatic load, identified several candidates, including *APOE*, *APOC*3, *PPARG*, which are more prevalent in this population. Another contributor to observed disparities may be DNA damage, which is accelerated in the presence of stress. Analysis of 8-hydroxyguanisine (8-OHdG) urine showed significantly higher DNA damage in women, relative to men, in smokers, relative to non-smokers and in those with diabetes and cardiovascular disease in this population.
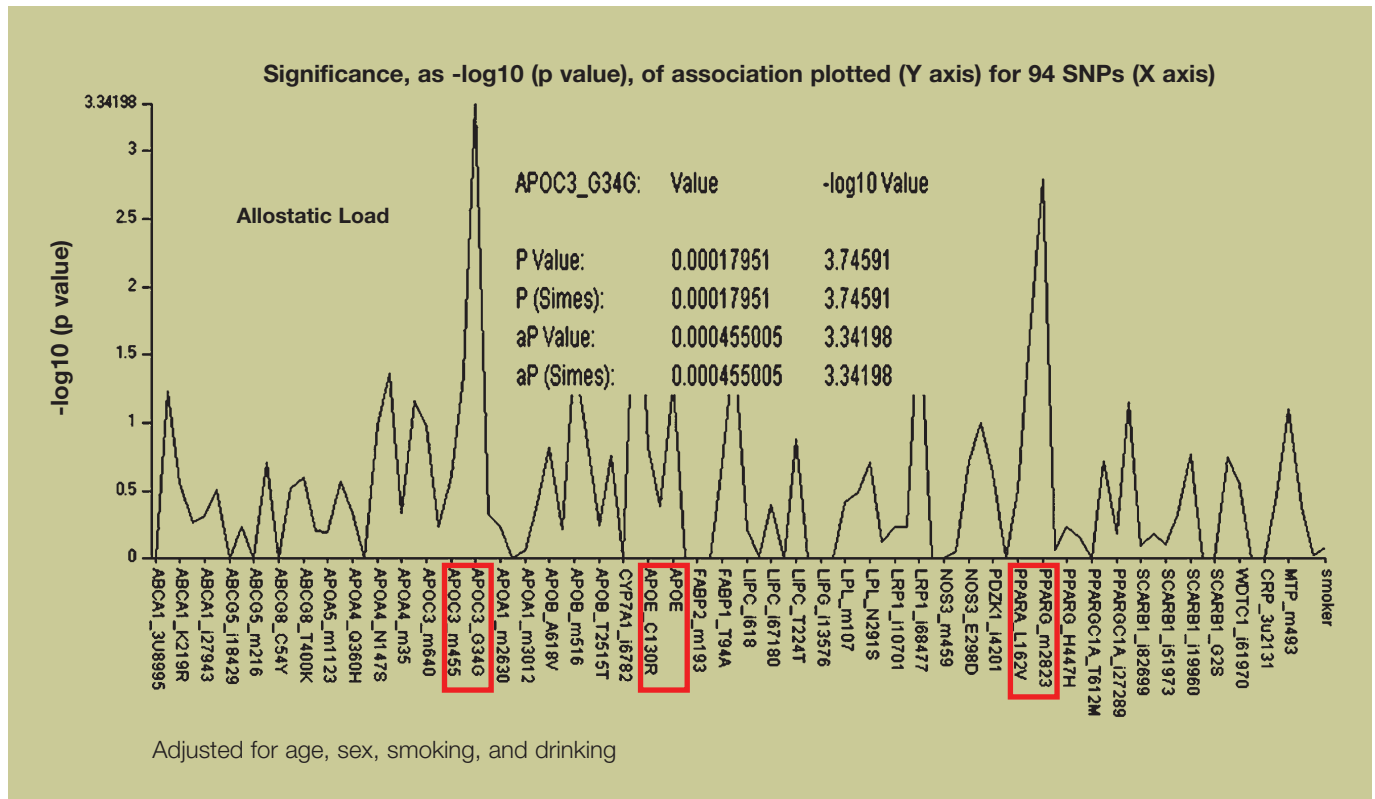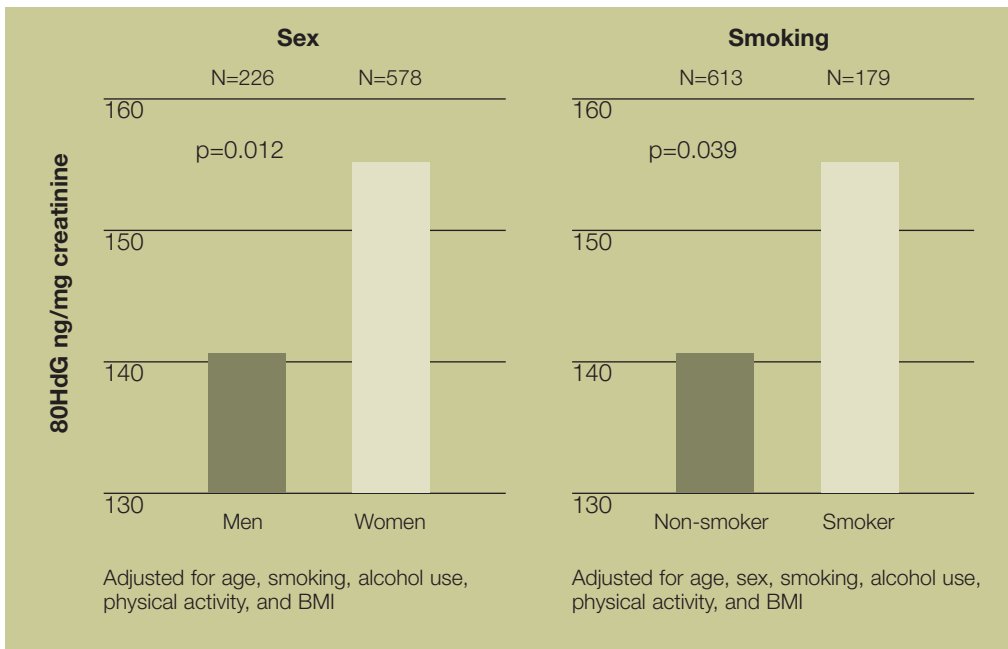
Fig. 19: Genetic Variants and Allostatic Load

Significance, as -log10 (p value), of association plotted (Y axis) for 94 SNPs (X axis)

Allostatic Load

APOC3_G34G:	Value	-log10 Value
P Value:	0.00017951	3.74591
P (Simes):	0.00017951	3.74591
aP Value:	0.000455005	3.34198
aP (Simes):	0.000455005	3.34198

Adjusted for age, sex, smoking, and drinking

Fig. 20: DNA Damage (8-OHdG) by Sex and Smoking Status in Puerto Rican Adults

Adjusted for age, smoking, alcohol use, physical activity, and BMI

Adjusted for age, sex, smoking, alcohol use, physical activity, and BMI

Table 9: Relationship of Vitamin D and PTH Categories to Body Mass (n=61)

Vitamin D/PTH Category	Body Mass (g)		
	Fat	Lean	%Fat
Normal	28,575	54,520	34.4
▼ Vitamin D/ PTH Normal	31,544	55,188	36.4
▼ Vitamin D/ ▲ PTH (secondary hyperthyroidism)	33,383	54,976	37.8

Wayne State University: Obesity-Linked Oxidative Stress and Physiological Pertubations Contributing to Hemodynamic and Vascular Abnormalities and Cancer Risk

The focus of the Wayne State University Center for Urban and African American Health (WSU-CUAAH) is *to uncover new ways to address health disparities among African Americans by improving diet and other lifestyle factors,* including physical activity, and reducing obesity and other risk factors for cardiovascular disease, cancer, and other chronic diseases. The center chose African Americans as the sole study population for its projects because this is the largest minority group in the Detroit area and they suffer excessively from a wide range of obesity- and lifestyle-related health conditions.

The center focuses on obesity, diet, and nutrition as underlying risk factors associated with breast cancer and cardiovascular disease. Obesity-related chronic conditions such as stroke, coronary heart disease, heart failure, and kidney disease are all prevalent among African Americans. Cancer is the second leading cause of death among Americans and is responsible for one of every four deaths in the United States. African Americans are more likely to develop and die from cancer than any other racial or ethnic group, and African American women with breast cancer have more aggressive disease and lower survival than white women.

The WSU-CUAAH research projects explore the individual and interactive effects of obesity/body composition, environmental and personal stressors, and genetic factors (including ancestral informative markers) in mediating salt sensitivity and non-invasively measured vascular function (e.g., arterial stiffness) and a milieu favorable to breast cancer recurrence in African American breast cancer survivors. The WSU-CUAAH team is comprised of a diverse group of investigators from a wide range of disciplines, includ-

ing exercise physiology, sociology, psychology, internal medicine/hypertension, oncology, family medicine, nursing, epidemiology, biostatistics, bioinformatics, obstetrics and gynecology, genomics, gerontology, anthropology, and demography.

The following are among the CUAAH's key activities to date:

The center has successfully genotyped 101 ancestry informative markers on 223 individuals across all three studies in the center. Researchers have performed individual ancestry analyses that showed that African American individuals in the studies have on average 30% European ancestry and 70% West African ancestry. These measures will be incorporated into other disease models and used to elucidate how environmental exposures/stressors interact with body composition, diet, and genetics to cause oxidative stress that plausibly leads to cardiovascular disease and breast oncogenesis.

Wayne State center has found an association between low vitamin D levels and increased fat mass in African Americans (Table 9). The study found that low circulating serum vitamin D level, which is largely derived from sunlight-triggered conversion of its precursor in the skin—7-dehydrocholesterol—to a more active form, was associated with increased fat mass compared with African Americans with more normal vitamin D levels. The study also found that the fat mass was even greater among those with low vitamin D levels and high levels of parathyroid hormone compared with normals. However, lean muscle mass, which should rise in parallel with fat mass, remained relatively constant despite higher fat

mass in participants with low vitamin D level or low vitamin D/high parathyroid hormone levels. These data raise the possibility that vitamin D deficiency may have a significant role in obesity, per se, as well as in obesity-related conditions that disproportionately affect African Americans, such as insulin resistance, diabetes, salt sensitivity, and hypertension.

Among obese African American breast cancer survivors, heart rate variability (HRV) is linked to ventilatory threshold (VT) responses. There was an immediate and dramatic drop in HRV between rest and 25 Watts of exercise; most subjects ended the test by 75 W of exercise. Changes in HRV correlated highly with VT in this population, the latter previously measured at 12 and 24 months of follow-up. Thus, exercise prescription based on a HRV threshold, an important component of the lifestyle modifications to prevent weight gain in breast cancer survivors, might not be appropriate in these largely de-conditioned women. Exercise programs geared toward weight loss and maintenance for African American breast cancer survivors should take into account their level of deconditioning.

Recent analysis found different rates of depression, respectively, in African American men and women enrolled in cardiac rehabilitation programs and found a high burden of depression linked to factors that may minimize the likelihood of successful rehabilitation. The project examined the relationship of depression (defined by CES-D score > 16) to biological, social psychological, and behavioral factors. Twenty-nine percent of participants were found to be depressed. Almost 75% of the depressed patients were women. Depressed patients had lower dispositional optimism, more maladaptive coping, higher levels of stress, and higher systolic blood pressure (~10 mm Hg) than non-depressed patients. These data suggest a gender difference in African Americans enrolled after major cardiac events and a high burden of depression linked to factors that may minimize the likelihood of successful rehabilitation outcomes.

Analyses also explore how a known deleterious physiological response—a persistent rise in blood pressure related to increased intake of dietary sodium—results from the interaction of environmental stressors/exposures, body composition, genetic profile, including ancestral origins, the level of nitric oxide production, free radical formation, and the level of oxidative stress. This research should yield new conceptual models regarding how these exposures interact to cause a sustained and deleterious rise in blood pressure. This enhanced understanding will lead to potentially new therapeutic targets (e.g., vitamin D supplementation) for interventions to prevent these physiological changes. Greater understanding of the environmental and dietary determinants of oxidative stress may shed light on the biological link between obesity and breast cancer recurrence, which plausibly occurs, at least in part, from high local oxidative stress.

SECTION IV: FUTURE OF HEALTH DISPARITIES RESEARCH

The CPHHD program has established a multilevel research framework for answering fundamental questions concerning health disparities using a unique transdisciplinary approach that includes community stakeholders as partners in research. This framework, along with the research and outreach resources that have been developed, have begun to demonstrate the value of a more rigorous science of health disparities research. The CPHHD will continue to develop and implement novel and sophisticated strategies to better understand the etiology and potential reduction of health disparities. A transdisciplinary agenda, that is multifaceted, has imparted some lessons, and its research has implications for scientific innovation, as well as academic, clinical practice, and policy approaches to eliminating cancer health disparities.

Lessons Learned

Establishing a program of transdisciplinary centers involving over 40 disciplines and conducting multilevel research in diverse populations can pose several challenges, especially in terms of methodology and building effective teams of researchers. While these challenges initially seemed daunting, the CPHHD were able to adapt and adopt new models because of their commitment to transdisciplinary research. For example, in the area of methodology, when research surveys were developed, it was apparent that there was limited opportunity to collect similar data and pool the data for analysis because of the diverse social, cultural, economic, and health access issues in different regions of the country. Therefore, the CPHHD shifted to replication of models of health disparities outcomes across the centers to understand and explain whether the patterns were similar across regions given variations in biological, social, economic, and behavioral conditions.

Another challenge has been building teams composed of basic, social, and behavioral scientists, clinicians, and community members. This process is time consuming and requires considerable effort from the principal investigators. Hence, the start-up time for such programs is considerably longer, especially since they require an understanding of the importance of various (and sometimes competing) theories of health disparities tested within an overall framework in the studies. The funding of centers by NIH was a critical incentive to develop and subsequently sustain these teams within their universities, and to address health disparities phenomena in a comprehensive manner.

Developing transdisciplinary projects that extend from cells to society also pose challenges to existing institutional review boards. The complexity of the protocols resulted in time lags launching the projects. The need to reach underserved populations in remote areas added further complexity to the recruitment of subjects. Some centers had to develop completely new approaches to gaining access to the populations and/or systems.

Scientific Innovation

The CPHHD program is advancing research on health disparities by integrating approaches from the basic, clinical, and population sciences to understand how disparities "get under the skin," and to identify practice and policy approaches to addressing these disparities. To that end, the science emerging from the CPHHD offers new foundations for transdisciplinary science in general. For example, the evidence will inform our understanding of how the social and built environments interact with biological processes, such as gene expression, methylation, inflammation, tumor growth, and aggressiveness. As our understanding of the effect of social environment on health has increased, it is important to further elucidate how this knowledge impacts genetics and predisposes certain subpopulations to worse health outcomes. Thus, this transdisciplinary science operates simultaneously in the laboratory (e.g., in cell and tissue culture and in animal models), in individual patients (e.g., by determining their exposure to violence or social isolation), and in populations (e.g., by examining how geographic location relates to biological risk variables).

Further, the CPHHD as a network will continue to create important synergies as they attempt to answer similar questions about cancer causation and mitigation with very different methodologies, populations, and community partners. One of the most valuable contributions of the CPHHD has been to unite nationally recognized experts in the social and medical aspects of health disparities with a range of community stakeholders.

What we learn about the health of Hispanics, rural whites, and African Americans and the potential effects of biology, neighborhoods, social contexts, and culture will inform studies of other subpopulations and should lead the way to a better understanding of how ethnic group dynamics interact with biological factors and social circumstances at the neighborhood and community levels.

The contributions of this kind of a scientific inquiry lead to a better understanding of disease causation, and the differences in those causative factors that lead to health disparities. For example, CPHHD research is unraveling factors that may explain the "Hispanic paradox," i.e., relatively high morbidity and disability, but relatively low mortality and lower cancer rates among Hispanics, even though Hispanics are clearly disadvantaged with respect to income, education, and access to health care.

The activities of the CPHHD are leading to an understanding of how to answer more difficult and complex questions regarding health disparities in general and cancer health disparities in particular. The significant findings regarding the health of disadvantaged populations have provided paradigms around which additional observational and intervention research can be initiated. These results suggest that a transdisciplinary, multilevel approach will increase the potential to maximize efforts based on collaboration among the various CPHHD. An example is the multicenter, multilevel, transdisciplinary research that evaluates social isolation, biological dysregulation of the stress response, and disease severity.

Impact on Academia

The CPHHD program has also been committed to training the next generation of investigators in transdisciplinary science to understand health disparities. These leaders of the future will have the advantage of learning research through a transdisciplinary lens rather than coming to it with more disciplinary-based thinking and habits in place.

Opportunities for the CPHHD to train young investigators have already been widely integrated throughout all of the centers. Junior investigators and established researchers who are retraining to become transdisciplinary health disparities researchers are better equipped to analyze scientific and community problems from a broader perspective than available in an individual laboratory or department.

"As a junior investigator, the CPHHD have provided me with the opportunity to share my ideas and receive feedback from senior investigators, it has exposed me to the challenges of doing transdiciplinary research, it has made me think about cancer health disparities from a multi-level (from basic biology to the population level) perspective, and it has provided me with funding for a pilot study to collect data that will be used in future grant applications."

MIRA L. KATZ, PHD, MPH
Assistant Professor, Division of Health Behavior and Health Promotion, College of Public Health, The Ohio State University

Additionally, these researchers are much more likely to work collaboratively and to integrate interdisciplinary perspectives into their research.

Promotion of junior faculty working in transdisciplinary teams presents challenges to individuals, groups, and institutions. To address the latter issue, some of the centers work within their institutions to redefine promotion and retention criteria in order to foster a more transdisciplinary-friendly academic environment that recognizes and rewards team science. An example is a campus-wide committee at the University of Chicago that addresses ways to acknowledge cross-disciplinary science and teaching. It is anticipated that such changes will be adopted at all transdisciplinary health disparities programs.

Creating an institutional environment that encourages and rewards transdisciplinary collaboration and investigation becomes integral to success in CPHHD research. For successful transdisciplinary work, the academic environment must recognize and promote shared methods and models from a variety of disciplines in research and help to build bridges across disciplines. The CPHHD program has increased visibility for transdisciplinary research, and university communities have responded by recognizing the need for this type of research. Some institutions, such as Wayne State University, have committed additional funding to build center infrastructure. Others have committed additional resources to fund pilot studies on health disparities to their existing programs. This institutional support occurred in the University of Chicago's 75-year-old Center for Health Administration Studies, an example which demonstrates the changing values and enhances the promise and acceptability of cross-disciplinary collaboration.

Practice

Continuous information exchanged between academic centers and communities will also help communities assume leadership and help select key points of focus for health disparities research, develop interventions to address these disparities, and determine the effectiveness of those interventions. The development and evaluation of interventions in various settings will impact both public health and clinical practice. Already, clinicians in each of the centers have reported "thinking differently" at the bedside. Dr. Suzanne Conzen, clinician/scholar and co-investigator at University of Chicago, for instance, reports that, based on her CPHHD experiences, she has begun to incorporate questions about social networks and loneliness and neighborhood crime into her interviews with patients in the high-risk cancer clinic in which she works. She is now more likely to refer these women to support services and is actively advocating an increase in the number and quality of those services in her health-care institution. Similarly, basic scientists are attempting to replicate in the laboratory the kinds of social and built environment conditions uncovered in clinical or community settings.

Animal model work at the University of Chicago exemplifies this shift, which was strongly influenced by research conducted with their social and behavioral science colleagues.

"I have become a stronger advocate for breast cancer issues and policy changes for my community as a result of the support of the members at the Centers for Population Health and Health Disparities."

BARBARA J. AKPAN, RN, MSN
Breast Cancer Survivor and Advocate
Chicago, Illinois

All centers work with community partners and health-care providers, and all partners mutually empower one another through asking questions, exchanging information, and collaboratively testing interventions to address disparities. These partnerships ultimately enhance public visibility about the outcomes related to health disparities in their communities. For example, the OSU center is examining community knowledge, attitudes, and acceptance of the new HPV vaccine within Appalachian Ohio. Four Appalachian community coalitions, in partnership with researchers from the OSU center, are conducting 20 focus groups with parents, community leaders, and young adult women. The results will be used to develop an intervention to educate and promote informed decision-making regarding HPV vaccination in this region, which has higher rate of cervical cancer.

CPHHD have also used information concerning the multilevel determinants of disparities to develop risk profiles for determining who most need services and education. The Penn center, for example, is identifying biomarker-environment interactions that suggest the action of certain biomarkers is relevant only in the context of specific exposures, including those at the neighborhood level. These biomarkers can aid in identifying the highest-risk groups, so that they can be targeted for screening and prevention. Similarly, the center at the University of Chicago is constructing a risk profile that combines neighborhood- and individual-level data to target interventions and services and maximize the impact of limited intervention resources. This information will be combined with evidence from other studies to develop individualized treatment approaches.

Policy

Ultimately, some of the factors underlying disparities will need to be addressed by policy, whether at an institutional, local (community), or national level. For example, RAND center is undertaking interventions that have both policy and practice implications. RAND has been working in a community coalition with the Washington, D.C. Primary Care Association and other community groups to develop a primary-care system for the District. RAND provides analytic and technical support to the coalition. One component of the project strengthens the health-care safety net, including increased cancer screening, patient navigation systems, access to specialists such as medical, radiation, and surgical oncologists, and construction of new clinics.

Development of new clinical settings can also stimulate job growth and economic development in the surrounding areas. In Los Angeles, the community already uses RAND's work on park renovation as it considers further planning and programming. In both Washington and Los Angeles, as the work progresses, RAND is being asked to conduct community-based participatory research (CBPR), share findings with community partners, and work collaboratively with policymakers to develop actionable plans to impact policy with regard to the built environment.

While, to date, the CPHHD have focused largely on local policymaking, they are poised to move toward influencing regional and national disparities policy.

First, as CBPR relationships mature, community partners are in stronger positions to inform their congressional legislators and advocate for change. In addition, the use of the RAND center methods and its Data Core to support the disparities-reducing work of health plans covering 90 million people is a reminder that policy change comes from both the public and private sector. Secondly, because research from multiple centers is leading to consistent findings on how the interplay of biological and social processes cause disparities, the results will be considered on a more national scale. Moreover, the mix of studies using local data conducted in the university-based centers and those using national data conducted in the RAND center and in the cross-center projects, further strengthens the applicability of findings to national-level policy. To that end, several of the centers, such as the University of Chicago, University of Illinois at Chicago, and RAND Corporation, have already briefed high-level policymakers in Congress and DHHS on the findings of their studies and their implications. As the centers mature, the policy influence of the CPHHD is likely to expand further.

Conclusion

The challenges faced by the CPHHD are inherent to the conduct of transdisciplinary research. The centers' ability to address these challenges and develop innovative models was possible because of the comprehensive nature of this initiative and the willingness of NIH and its partners to adapt to changing structures. The contributions of the CPHHD argue for a multifaceted approach to address the scientific and translational challenges associated with health disparities. Prior to the initiation of the CPHHD, approaches aimed at understanding and eventually eliminating health disparities were limited to one level of analysis or intervention and as such had only limited success. Solutions to health disparities must involve multilevel approaches informed by proven scientific methods, clinically meaningful interventions, and sustainable, evidence-based policies that will lead to the elimination of health disparities in the future.

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APPENDIX A: CPHHD LEADERSHIP

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RAND Center for Population Health and Health Disparities
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PI: Nicole Lurie

University of Illinois—Chicago Center for Population Health and Health Disparities
P50-CA106743
PI: Richard Warnecke

Ohio State University Center for Population Health and Health Disparities
P50-CA105632
PI: Electra Paskett

University of Texas Medical Branch Center for Population Health and Health Disparities
P50-CA105631
PI: James Goodwin

Tufts University/Northeastern Boston Puerto Rican Center for Population Health and Health Disparities
P01-AG023394
PI: Katherine L. Tucker

Wayne State University Center for Urban and African American Health (CUAAH)
P50-ES012395
PI: John Flack

APPENDIX B: MATRICES

Cross-Center Collaborations:
Biobehavioral Influences

Cross-Center Collaborations:
Socioeconomic Data

APPENDIX C: CPHHD PARTNERSHIPS

University of Chicago

http://cihdr.uchicago.edu

Inter-University Partners

- University of Ibadan, Nigeria
- Other seven CPHHDs through supplemental funding from NCI to do parallel analyses across centers

Intra-University Partners

- School of Social Service Administration
- Center of Excellence in Health Promotion Economics (CDC)
- Biological Sciences Division
- Social Sciences Division
- Institute for Mind and Biology
- Robert Wood Johnson National Program Office for Health Disparities Solutions

Federal, State, or Local Government or Quasi-Government Partners

- John H. Stroger, Jr. Hospital of Cook County, Illinois
- Mt. Sinai Hospital of Chicago, Illinois
- Methodist Hospitals of Gary, Indiana

Community-Based Organizational Partners

- Faith Based Wellness Network

University of Pennsylvania

http://www.cceb.upenn.edu/cphhd

Inter-University Partners

- Cheikh Anta Diop University, Dakar, Senegal

Intra-University Partners

- Robert Wood Johnson Health and Society Scholars Program
- Leonard Davis Institute for Health Economics
- Abramson Cancer Center
- Institute on Aging
- Wharton School of Business
- Annenberg School of Communication
- School of Social Work Law

Federal, State, or Local Government or Quasi-Government Partners

- U.S. Veteran's Administration Hospitals

Community-Based Organizational Partners

- National Physician and Family Referral Project
- Philadelphia Chapter, National Black Leadership Initiative on Cancer

RAND Corporation

http://www.rand.org/health/pophealth/

Inter-University Partners

- University of Michigan
- University of California, Berkeley
- University of California, Los Angeles
- Rutgers University

Federal, State, or Local Government or Quasi-Government Partners

- Los Angeles Department of Parks and Recreation
- District of Columbia City Council

Community-Based Organizational Partners

- Multicultural Area Health Education Center
- District of Columbia Primary Care Association

University of Illinois at Chicago

http://cphhd.hrpc.uic.edu

Inter-University Partners

- Boston: Tufts/Northeastern University Center
- Washington, DC and Los Angeles, CA: RAND Center
- Philadelphia: Penn Center
- Chicago: Cook County, UIC and UC Center
- Detroit: Wayne State Center

Intra-University Partners

- Institute for Research on Race and Public Policy
- Midwest Latino Health Research Training and Policy Center
- International Center for Health Leadership Development
- UIC Cancer Center
- School of Public Health
- College of Nursing
- Department of Sociology
- Vice Chancellor for Research
- Institute for Health Research and Policy
- Survey Research Lab

Federal, State, or Local Government or Quasi-Government Partners

- Illinois Department of Public Health—Illinois State Cancer Registry
- Chicago Department of Public Health
- John H. Stroger Jr. Hospital of Cook County
- Illinois State Cancer Plan
- Institute for Health Care Quality (Medicare)

Community-Based Organizational Partners

- Healthcare Consortium of Illinois (Greater Roseland Health District & Healthy South Chicago)
- Cook County Breast Health Consortium
- Illinois Division-American Cancer Society

Ohio State University

http://www.osuccc.osu.edu/cphhd

Inter-University Partners
- University of Kentucky
- Ohio University
- University of Michigan

Intra-University Partners
- Ohio State Agricultural Extension Service
- College of Public Health
- College of Medicine
- Economics Department
- Psychology Department
- Comprehensive Cancer Center

Federal, State, or Local Government or Quasi-Government Partners
- Ohio Department of Breast Health and Cervical Cancer
- National Cancer Institute Cancer Information Service
- Centers for Disease Control and Prevention

Community-Based Organizational Partners
- Ohio Division, American Cancer Society
- Appalachia Community Cancer Network
- Meigs County Cancer Initiative
- Fight Cancer, Save Lives—ACT
- Now Coalition of Sceato County
- Cancer Concern Coalition, Inc. of Morgan, Muskingum, and Perry Counties
- Women in Action Against Cancer Coalition, Inc. of Jefferson County

University of Texas Medical Branch

http://www.catchum.utmb.edu/cphhd/index.htm

Inter-University Partners
- University of Maryland—Population Center
- University of Texas, Austin—Population Research Center
- Baylor College of Medicine—Department of Medicine, Health Services Research

Intra-University Partners
- School of Nursing
- Department of Preventive Medicine and Community Health
- Infectious Disease
- Obstetrics and Gynecology Division

Federal, State, or Local Government or Quasi-Government Partners
- Area Health Education Center
- Social Security Administration
- Galveston County Health District
- National Center for Health Statistics—Mortality Division

Community-Based Organizational Partners
- Liberty County Cancer Awareness Network
- Parent-Teacher Association of LA Morgan School
- Galveston County Cancer Coalition
- Jesse Tree

Tufts University/Northeastern

http://cphhd.hnrc.tufts.edu

Intra-University Partners

- Jean Mayer, USDA, Human Nutrition Research Center on Aging at Tufts University
- Tufts Friedman School of Nutrition Science and Policy
- Tufts School of Medicine
- Northeastern University Department of Sociology
- Northeastern Center for Urban Health Research

Federal, State, or Local Government or Quasi-Government Partners

- USDA Agricultural Research Service
- Massachusetts Department of Public Health

Community-Based Organizational Partners

- La Alianza Hispana
- Tufts-New England Medical Center

Wayne State University

http://www.med.wayne.edu/intmed/cuaah/cuaah.htm

Inter-University Partners

- University of Michigan—Inter-University Consortium for Political and Social Research
- Case Western Reserve University

Intra-University Partners

- African American Initiative for Male Health Improvement (Henry Ford Hospital)
- Minority Center for Urban African American Aging Research (MCUAAR)
- College of Nursing
- College of Liberal Arts
- Center for Urban Studies
- Karmanos Cancer Institute
- Wayne State University Community Relations

Federal, State, or Local Government or Quasi-Government Partners

- Detroit Department of Public Health
- Detroit Medical Center Tri-Counties Multi Trade

Community-Based Organizational Partners

- Movement for Life Initiative
- American Heart Association/ Detroit
- Healthy Black Elders
- Project Health Living
- Metropolitan Christian Council

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University of Illinois at Chicago

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