

Written Testimony Submitted by the Public on the Health Research Priorities for State Fiscal Year 2009-2010

The Pennsylvania Department of Health solicited written testimony on health research priorities for state fiscal year (SFY) 2009-2010 using the form contained on pages 3-8. This document provides a copy of all of the written testimony submitted to the Department by July 18, 2008. To conserve space, instructions for each item on the form and the responses to item 5 were removed from the individual testimonies. See table below for the list of persons who submitted testimony. Note that testimony is ordered by date and time submitted to the Department.

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**Invitation to Submit Written Testimony on Health Research Priorities
Commonwealth Universal Research Enhancement (CURE) Program**

The Pennsylvania Department of Health is inviting the public to submit written testimony to recommend health research priorities for the CURE Program for state fiscal year 2009-2010. Please use the attached form to prepare and submit your recommendations regarding the research priorities. *Before proceeding please review background information on the last page of this form.*

This form must be submitted in MS Word via email no later than July 18, 2008, to: ra-healthresearch@state.pa.us. Only testimony that is submitted to the ra-healthresearch mailbox by the deadline will be accepted. All testimony submitted by the deadline will be posted on the Department’s CURE Web site under the *CURE Health Priorities* link. The Department will not correct the testimony for spelling, grammatical or other errors. Any text that exceeds the page and size limitations specified on this form will be deleted, including any appendices. The Health Research Advisory Committee will review the testimony that has been submitted and then recommend persons who will be invited by the Department to make presentations to the Committee and answer Committee members’ questions. The Committee is not interested in receiving proposals for specific research projects.

Questions? Contact: Cathy Becker, Diane Kirsch or John Koch at 717-783-2548.

1. Contact Information – *please complete the information requested below.*

PERSON SUBMITTING TESTIMONY		
NAME (First Name MI Last Name)	DEGREE(S)	<input type="checkbox"/> Ms. <input type="checkbox"/> Mr. <input type="checkbox"/> Dr.
POSITION TITLE	MAILING ADDRESS (Street, City, State, Zip Code)	
NAME OF ORGANIZATION		
TELEPHONE (Area code, number and extension)	E-MAIL ADDRESS:	

2. Health Research Priority - Only the following types of research may be funded by the CURE Program: biomedical, clinical and health services research. These are defined as follows:

- Biomedical research is comprehensive research pertaining to the application of the natural sciences to the study and clinical practice of medicine at an institution, including biobehavioral research related to tobacco use.
- Clinical research is patient-oriented research which involves direct interaction and study of the mechanisms of human disease, including therapeutic interventions, clinical trials, epidemiological and behavioral studies and the development of new technology.
- Health services research includes any of the following: (1) research on the promotion and maintenance of health including biobehavioral research, (2) research on the prevention and reduction of disease, (3) research on the delivery of health care services to reduce health risks and transfer research advances to community use.

Please describe the health research priority – which disease, disability, injury or health problem is the research designed to prevent or control? Do not exceed the space provided. Any text that exceeds the space provided will be deleted. Use Times New Roman font size no smaller than 12-point.

3. Hypothesis-driven Research Questions - What are the specific hypothesis-driven research questions that need to be addressed? *At least 50% of research to address the selected research priorities for 2009-2010 must be clinical and/or health services research. Please list the specific biomedical, clinical and health services research hypotheses and questions that need to be investigated. See definitions of biomedical, clinical and health services research in Question 2. Responses should not exceed the space provided. Any text that exceeds the space provided will be deleted. Use Times New Roman font size no smaller than 12-point.*

Biomedical research questions and hypotheses:

Clinical research questions and hypotheses:

Health services research questions and hypotheses:

4. Impact on Health of Pennsylvanians – Describe the impact of the health-related issue on Pennsylvanians. What is the health impact of the problem on the statewide population? Are there health disparities – vulnerable segments of the population that are disproportionately affected by the health-related issue? Please provide data or statistics to support your statements. For Pennsylvania health statistics, please visit the Department of Health’s Web site: <http://www.health.state.pa.us/stats>. *Responses should not exceed the space provided. Any text that exceeds the space provided will be deleted. Use Times New Roman font size no smaller than 12-point.*

5. Availability to Testify before the Health Research Advisory Committee – Copies of the written testimony will be provided to the Health Research Advisory Committee. Committee members will review the testimony and determine which persons should be invited to attend the Committee’s fall meeting. During the Committee meeting those persons who were invited to testify will be asked to summarize the critical research questions related to their written testimony in 3 minutes and then answer Committee members’ questions. If invited by the Department to do so, would you be willing to present testimony and answer questions about your proposed research priority at the Committee meeting to be held in Harrisburg during the fall (date to be determined)?

Yes No

Process Used by the CURE Program to Establish Research Priorities and Select Health Research Projects for Funding

Act 2001-77, the Tobacco Settlement Act, authorized the Pennsylvania Department of Health to establish the Health Research Program, known as the Commonwealth Universal Research Enhancement (CURE) Program. Each year, CURE awards two types of health research grants: (1) health research **formula** grants, which are awarded only to hospitals, universities and non-profit organizations that have received three consecutive years of funding from the National Institutes of Health; and (2) **nonformula** grants, which are awarded competitively in response to a Request for Application (RFA) that is issued once a year. Any person or organization located in Pennsylvania is eligible to apply for the nonformula health research grants in response to the RFA.

The nonformula health research grants fund biomedical, clinical and health services research projects that are consistent with specific research priorities. Once a year, the research priorities for both formula and nonformula grants are reviewed and revised as needed. The research priorities are established by the Department in conjunction with a Health Research Advisory Committee, which is chaired by the Secretary of Health.

Prior to establishing the research priorities, the public is invited to submit written testimony on research needs. Copies of the written testimony are provided to the Health Research Advisory Committee. Committee members review the testimony and determine which persons should be invited to attend the Committee's fall meeting. During the fall meeting those persons who were invited to testify are asked to summarize the critical research questions related to their written testimony in 3 minutes and then answer Committee members' questions.

After the research priorities are finalized for the year, a RFA is issued to solicit research projects that address the priorities. Typically, the RFA is issued during late summer or early fall.

The research priorities for the competitive nonformula health research grants have changed each year. They were: bioinformatics related to cancer or infectious diseases (2001-02) and reducing disparities related to cardiovascular disease and mental disorders (2002-03), lung disease and pregnancy outcomes (2003-04), neurodegenerative disease and tobacco use and cessation (2004-05), obesity (2005-06), vaccine development and gene-environment interactions (2006-07), violence prevention and regenerative medicine (2007-08) and autism spectrum disorders and antibiotic resistance (2008-09). Current and past state fiscal year priorities for both formula-funded and nonformula-funded health research are posted on the Department of Health's CURE website (<http://www.health.state.pa.us/cure>). See *CURE Health Research Priorities* for a complete description of the priorities.

The Health Research Program maintains: (1) a public testimony mailing list of persons who want to receive invitations to submit testimony on health research needs; and (2) an RFA mailing list of persons who want to receive copies of the RFA electronically when released. If you would like to be placed on either or both of these lists (public testimony mailing list or RFA mailing list), please email the following information to ra-healthresearch@state.pa.us: your name and professional degree(s), organization, mailing address, email address, and telephone number.

Contact Information

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NAME (First Name MI Last Name) Roseann C. Schaaf, PhD, OTR/L FAOTA	DEGREE(S) PHD; MEd, BS in occupational therapy	<input type="checkbox"/> Ms. <input type="checkbox"/> Mr. <input checked="" type="checkbox"/> Dr.
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Health Research Priority

Health services research - Research on the delivery of occupational therapy services to individual's with Autism Spectrum Disorders (ASD). Occupational Therapy is one of the top 3 requested services by parents of children with ASD, yet there is no systematic protocol for the delivery of these services and limited data on the extent, setting and type of occupational therapy services that are most beneficial and cost effective.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

None

Health services research questions and hypotheses:

Develop and test a systematic application of occupational therapy services for children with ASD
What are the active ingredients? What are meaningful and useful outcome measure to evaluate change? What combination of direct therapy, school consultation and parent training provide the greatest effects?

Impact on Health of Pennsylvanians

Autism Spectrum Disorders (ASD) are a group of developmental disabilities defined by significant impairments in social interaction and communication, unusual behaviors and interests, and unusual ways of learning, paying attention, or reacting to different sensations (CDC, 2007). There has been a 172% growth in individuals diagnosed with ASD over the last 15 years with a projected annual cost to society of 90 billion dollars per year (Jarbrink & Knapp, 2001). ASD is the sixth most common disability in the United States and the most common developmental disability of childhood. It is estimated that 1 out of every 150 children are affected by ASD (CDC, 2007). Data is need to guide educators, health care practitioners and legislators on effective services for children with ASD . This data will guide cost effective use of Pennsylvania's health dollars.

Contact Information

PERSON SUBMITTING TESTIMONY		
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Health Research Priority

Nutrition and dietary factors are directly or indirectly related to certain diseases such as diabetes, cancer, heart disease, bone disease, and hypertension. It has been estimated that about 50% of cancers can be prevented or ameliorated through dietary manipulations. The relationship between malnutrition and disease may not be obvious in the earlier stages of life; however, these effects will appear or become severe as we reach our later years. These diseases include Alzheimer's, depression, cancers, heart disease and osteoporosis. Although aging is an unstoppable process, it is clear that we can manipulate this process through the alteration of our diet. We may not only slow down the aging process but also enhance "natural aging." There are multiple lines of evidence showing that the medical costs of a person who died at the age of 90 or later, which represents a more natural death, are much lower than those who died before the age of 70. Therefore, enhancing natural aging is one of the most powerful avenues in reducing medical costs. Focusing the research priority of the 2009-2010 fiscal year will provide an opportunity to further explore and apply nutritional information to everyday lives of Pennsylvanians. This will not only ensure a better understanding of the relationship between nutrition and aging, but also educate people on the importance of eating smartly and leading a healthy lifestyle with reduced medical costs.

Biomedical research questions and hypotheses:

- (1) Identification of additional nutritional factors that directly or indirectly involved in the biological processes which affect the processes of aging and the status of health.
- (2) Researches to explore the mechanisms of nutrition/nutrients in diseases, health and aging at different levels.
 - a. Molecular levels
 - b. Tissue levels
 - c. Organismal
- (3) Identification or syntheses of more potent nutritional components which can retard aging process and enhance health.

Clinical research questions and hypotheses:

None

Health services research questions and hypotheses:

- (1) Epidemiological studies to establish the relationship between diets and disease, health and aging.

(2) Exploring the educational tools and strategies to make Pennsylvanians aware the importance of eating smartly.

Impact on Health of Pennsylvanians

Although the concepts in this testimony apply to globally, nationally as well as state wise, it is rather important to the state of Pennsylvania because this is one of the states with relatively more aged populations. As I mentioned in the testimony that “the relationship between malnutrition and disease may not be obvious in the earlier stages of life; however, these effects will appear or become severe as we reach our later years”. There is no doubt that this will directly affect the medical costs in treatment of these diseases. On the other hand, if we can alter the aging process through diet manipulating, we will definitely be able to not only improve the life qualities of Pennsylvanians but also reduce the medical casts.

Contact Information

PERSON SUBMITTING TESTIMONY		
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Health Research Priority

This research priority will focus on the state's ever growing, but at-risk population of older citizens. The priority will promote the concept of healthy aging as a statewide public health goal through focus on public education and training of citizen community health advocates/educators across the Commonwealth. Combining research-based preventative education on healthy aging concepts, strategies, and criteria with the training of citizen advocates/educators around Pennsylvania can serve to reduce health care costs, enhance people's quality of life, and help them to live longer and prevent disability and disease.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

None

Health services research questions and hypotheses:

Hypothesis: Creating a statewide cadre of community health advocates/educators will improve quality of life and reduce disability for Pennsylvanians age 65 and older through the dissemination and consequent behavior changes fostered by this educational intervention

Research Questions:

1. What effect does community-based Public Health education have on creating behavior changes among Pennsylvanians age 65 and older?
2. How do the community health advocates/educators affect the accepting of healthy aging concepts, strategies, and criteria in the Pennsylvania population age 65 and older?
3. How does community-based Public Health education advance the goals of social marketing?

Impact on Health of Pennsylvanians

Pennsylvania's population is aging. The population age 65 and older accounted for 4.74% of the state's citizens in 2000 while just 5 years later (2005) that number had risen to 5.77%. (C.D.C. Behavioral Risk Factor Surveillance System--BRFSS). According to the BRFSS data for 2003-2005 there is reason for concerns about the health of Pennsylvania's older population: 27.9% of the age 65+ population report their health as only Fair/Poor; 23.2% of that same age group are obese; 55.7% have been diagnosed with hypertension; 18.1% have been diagnosed with diabetes; 9.2% are cigarette smokers; and 27.2% eat less than 3 servings per day of fruits and vegetables. Those statistics have negative consequences for individual health, longevity, and quality of life. They also have negative impact on the community and the Commonwealth of Pennsylvania through diminished volunteers available to sustain many worthy programs and opportunities for civic engagement as well as causing rising health care costs.

The creation of a statewide cadre of community health advocates/educators, working consistently over time, can have a social marketing impact of disseminating important information and facilitating behavior changes so that the negative trends suggested by the data above can be reversed. Benefits of such reversal to individual Pennsylvanians include enhanced quality of life; prevention of disability and disease; greater longevity; ability to offer volunteer service longer; and reduced health care costs. Benefits for the Commonwealth of Pennsylvania include: healthier communities around the state; reduced burden on health care delivery and funding systems; increased civic engagement of Pennsylvania residents through the creation of community health advocates/educators; more volunteerism and civic engagement possibilities due to healthier adults who are living longer; and Pennsylvania can become a national exemplar of cost effective ways to foster both healthy aging and civic engagement by tapping into the rich resource and wisdom of the age 65+ population.

Contact Information

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Health Research Priority

The current war on terror has caused significant distress in many soldiers and their families. Pennsylvania has sent large numbers of both National Guard and Armed Services Reservists to the wars in Iraq and Afghanistan. In total, there are more than 1.1 million veterans residing in Pennsylvania. Despite this, only 25% have sought health care within a Department of Veterans Affairs medical center. Veterans who don't seek care with the VA system likely use community services despite availability of VA services. This may be especially true for Pennsylvania National Guard troops. Optimizing access to care particularly mental health care for all veterans is a state priority but little is known about the best mechanisms for outreach and engagement. An additional area of concern facing veterans in Pennsylvania is the need for improved family services. Family members of veterans are not usually eligible for services in the VA despite significant suffering and having to cope with the distress of war. Military deployment and reintegration of the veteran in the post-deployment necessitates change and adaptation, and thus involves stress to all family members. Survey studies indicate that 9% of married service members cite that the deployment leads to an improved relationship with their spouse, but about 15% cite missing important family events while deployed and 11% report worsened marital relationships.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

Specific research questions for family members include:

- 1) Are psychiatric symptoms of the veteran related to poorer family functioning across a one-year time frame?
- 2) Do difficulties with family reintegration mediate the impact of psychiatric symptoms on overall family functioning over time?
- 3) What specific family reintegration problems are associated with PTSD and depression symptoms of recently returned military veterans?
- 4) In the perception of the veteran and his or her marital partner, how do psychiatric symptoms interfere with common reintegration tasks (i.e., renegotiating family roles, redeveloping/ normalizing routines, veteran re-developing close relationships with children and other family members)?

Health services research questions and hypotheses:

Research is needed to best understand integration of state resources with federal resources available from the department of veteran affairs. Specifically:

A. What are the most effective strategies for engaging veterans in available VA services or establishing links between community based resources and the VA.

It is hypothesized that partnerships between local community organizations and veteran support organizations and religious organizations will enhance engagement over and above direct outreach to the veteran.

B. Can alternative forms of treatment deliver be effective in reducing stress and mental health symptoms.

It is hypothesized that a web based positive affect program and/or a cognitive behavioral telephone based counseling program will enhance productivity (job and home) and reduce overall stress.

Impact on Health of Pennsylvanians

A well-functioning family is a key resource for veterans. Current evidence suggests, however, that veterans who return from war-time service with behavioral health symptoms have poorer individual and family functioning. A significant minority of veterans suffer from post-deployment behavioral health problems.

Interest in the family life of the military veteran has grown over the last several decades, but there are significant gaps in our knowledge. We know a great deal about the stresses of deployment on families due to the need for changing roles for the parents, increased operational tempo for the service member prior to deployment, unpredictability of deployment scheduling, and the effects of the absence of the service member on their children. Furthermore, the long-term negative impact of war trauma on the social and relationship functioning of military service members is well-documented. However, much less is known about the specific ways in which war trauma-related symptoms interfere with the family reintegration process during the post-deployment period.

Clinical models suggest that the circumstances surrounding a war-time deployment lead to greater challenges for service members and their families compared to peacetime deployments. The deployment schedules are more unpredictable, there is greater fear of death of the service member, and level of aggression that must be rechannelled upon return. The research findings support that greater levels of war trauma and resulting psychological symptoms result in proportionally greater the disruption in the functioning of the service member and his or her family. The results of the National Vietnam Veterans Readjustment Study (NVVRS) and other studies indicated that higher levels of war-related trauma and post-traumatic stress disorder (PTSD) symptomatology were associated with more marital problems, greater family violence, and greater child behavior problems than those without trauma.

Very few studies have examined this phenomenon among Iraqi/Afganistan (OEF/OIF) veterans, but these studies support the association between symptoms of war trauma and family problems. Work conducted at the Philadelphia VAMC found that among 86 OEF-OIF veterans, those with PTSD or depressive symptoms were more likely to have problems in family reintegration. In addition, among those with a current or former partner (N=134), OEF-OIF veterans with minor or major depression, or a generalized anxiety disorder, were more than twice as likely to exhibit at least mild levels of relationship abuse.

The rates of behavioral health problems of all returning OEF-OIF veterans are estimated in a RAND Corporation study at 5 – 15% for PTSD, 2 – 14% for Major Depression, and 19% for Traumatic Brain Injury (TBI). Population-based surveys of Army and Marine veterans, based on the post-deployment health assessments, reveal similar rates of psychiatric disturbance. There was a prevalence of 19.1% of reporting a mental health problem among those returning from Iraq, 11.3% among those returning from Afghanistan, and 8.5% among those deployed elsewhere.

As so many Pennsylvanians participate in the war on terror, it is our responsibility to provide adequate support for the veteran and their family members. New and innovative methods for engaging and delivering mental health care are vital to these soldiers leading productive and health lives.

Contact Information

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Health Research Priority

Serious mental disorders, especially psychotic illnesses, exact a major toll on affected individuals, families, communities and society. A growing body of literature indicates that these are neurodevelopmental disorders that are present already in childhood, but remain undiagnosed and untreated sometimes for years. There is evidence that earlier intervention leads to better clinical outcome and quality of life, and lowers the long-term costs to society of caring for the chronically impaired. Adolescence is a critical time in brain maturation, with vulnerability to the effects of stress and susceptibility to risk-taking behaviors such as substance use. Therefore, it is often difficult to recognize the initial onset of frank psychosis, or to identify those youths who have the greatest potential risk of becoming ill. The proposed initiative will apply state of the art basic and clinical neuroscience methods to identify teens at risk for schizophrenia and related psychotic disorders before the onset of psychosis or at the early prodromal phases of the illness. Advances in the field enable to predict progression to schizophrenia in 80% of teens at risk due to family history, cognitive, affective and functional deficits. Early identification of youth at risk will enable targeted interventions before the full syndrome is clinically present. This will curtail the derailment in functioning associated with the syndrome and permit better recovery and attainment of independence in adulthood.

Biomedical research questions and hypotheses:

Adolescence is a period of marked social, emotional, and physical development. The brain undergoes rapid changes throughout adolescence and, in vulnerable individuals, psychosis can emerge. While there are accumulating data on behavior, neuroanatomy and neurophysiology, there is a gap in understanding how these components relate to each other during adolescence. To elucidate the pathophysiology of psychosis we need to integrate basic and clinical neuroscience research in a systematic effort to identify and examine youth at risk for psychosis because of family history or presence of prodromal symptoms. We propose to apply cutting-edge methodologies in cognitive and affective neuroscience in conjunction with genomics to test the hypothesis that the development of cognitive and emotion processing is linked to volume and connectivity changes in specific nodes of brain circuitry. Aberrant brain development in psychosis prone individuals increases vulnerability during adolescence. Early indicators of psychosis - impaired thinking, problem solving, attention, memory, emotion processing, olfaction, brain structure and function - can serve as converging markers for identifying youths at greatest risk, allowing for early intervention.

Clinical research questions and hypotheses:

The recognition that psychotic disorders, such as schizophrenia and bipolar illness, emerge in adolescence has underscored the need to chart the developmental trajectory of psychotic disorders during this critical transition period. There is need to: 1. Establish the differences in neurodevelopmental trajectory between psychosis prone individuals and typically developing adolescents; 2. Relate clinically salient abnormalities in psychosis prone individuals to differences in brain structural and functional developmental trajectories; 3. Test the effects of

intervention in psychosis prone individuals who are randomized to active treatment with Cognitive and Social Training compared to those who continue with treatment as usual. We hypothesize that: a. Psychosis prone adolescents manifest impaired “growth chart” on neurobehavioral measures of executive function, affect processing and social cognition with corresponding aberrations in regional volume, connectivity and brain activity measures in pertinent circuits; b. The degree of delayed maturation relates to risk load and to symptoms severity; c. Intervention results in improved symptoms, brain function and social and adaptive behavior.

Health services research questions and hypotheses:

Schizophrenia and other psychotic disorders represent the most severe forms of mental illness, with limited clinical response and poor outcome, costing the nation in excess of \$317 billion annually by recent conservative estimates. Duration of untreated psychosis is associated adversely with clinical response and functioning. We need to merge state of the art measures of brain function associated with risk of psychosis (endophenotypes) and employ a multidisciplinary treatment approach within a regional network that specializes in early detection of youth with warning signs and first-onset of psychosis.

Specifically, the program will aim to

1. Delay or prevent progression of symptoms and emergence of psychosis
2. Improve clinical response to treatment
3. Preserve independent daily functioning, socialization, and academic and occupational skills
4. Within the Commonwealth of Pennsylvania, disseminate information about early detection and prevention of psychosis

Impact on Health of Pennsylvanians

According to a study by the World Health Organization in 2001, mental illness ranks first in terms of causing disability in the North America and Western Europe, and accounts for 25% of all disability in major industrialized countries. Schizophrenia presents as the most severe mental illness affecting about 1 percent of the population within the United States and with higher rates in minority groups, socially disadvantaged populations, and in urban areas.

Inadequately treated schizophrenia is commonly viewed as devastating in its consequences on symptoms, brain functioning and psychosocial functioning. Within the United States, schizophrenia care accounts for roughly 2.5% of all health care expenditures. The overall U.S. 2002 cost of schizophrenia was estimated to be \$62.7 billion, with \$22.7 billion excess direct health care cost and total indirect excess costs estimated at \$32.4 billion. The indirect excess cost due to unemployment (of the people who have schizophrenia) is the largest component of overall schizophrenia cost and the resulting economic burden is commonly carried by families. The national burden of serious mental illness, excluding incarceration (22% of prisoners), homelessness (about 1/3), comorbid conditions (e.g. people with schizophrenia consume 44% of all cigarettes in the US) and early mortality (loss of 13-32 years), has been recently estimated in excess of \$317 billion annually. It is generally estimated that today only 10-15% of people who have schizophrenia are able to maintain full-time employment of any type. Within Pennsylvania, the Department of Public Welfare (DPW) serves about 126,000 individuals with mental illness and in the 2007/08 the Mental Health Services budget included \$723 million in state funds and \$176 million in other funds.

The onset of schizophrenia, defined by acute psychosis (hallucinations, delusions, disorganization) and cognitive deficits, is commonly in adolescence or early adulthood and is almost always preceded by a period of subtle, but pervasive changes including cognitive impairment, affective symptoms, social withdrawal and odd thoughts, perceptions and beliefs, which produce social and occupational/scholastic dysfunction. This prodromal period portends to behavioral risk for schizophrenia and may last between several months to a few years. At that time many young people experiment with drugs which will further complicate early identification and treatment. Once psychosis emerges, effective treatment remains a vexing effort with respect to diagnostic certainty, insight into need for treatment, medication adherence and abstinence from drugs, and social supports.

Even though persons with first-onset schizophrenia respond remarkably well to antipsychotic treatment, about 80% relapse within the early years of treatment with marked consequences on subsequent treatment response and on psychosocial functioning, including academic and occupational achievement. As a result of repeated relapses and limited treatment response, many people with schizophrenia are unable to lead independent lives. Psychosocial functioning, including ability to work, are related to duration of untreated psychosis and this relationship underscores the importance of early identification and treatment.

It is obvious that the standard approach to illness, which typically centers on optimizing pharmacologic intervention, is plainly inadequate to the task of grappling with schizophrenia. Over the past decade, there have been increasing efforts in identifying young persons at behavioral risk for developing schizophrenia. More recent multidisciplinary treatment efforts within the US adapt approaches and findings of major recent studies from Australia and Europe. The novelty of this approach lies in the clinical outreach by teams of practitioners from different disciplines who focus on community and family education, and multidisciplinary assessment and treatment of persons at behavioral risk for schizophrenia with the goal of intervening at first signs of psychosis and maintaining psychosocial functioning.

Contact Information

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Health Research Priority

The mental disorders of late life constitute one of the most pressing global public health issues of the 21st Century. According to a major study by the World Health Organization, depression will be second only to heart disease as a cause of disability worldwide. Our work has shown that over a 2-year follow-up, depression contributed as much to mortality rates as did heart disease or diabetes, and we reported that providing depression management in the community (e.g., the primary care setting) may decrease mortality. Addressing the psychiatric and behavioral disturbances of older adults in the coming decades is all the more challenging when one considers demographic trends (aging of the population), patterns of service use and delivery (older adults have complex medical problems occurring together with depression), and the training and composition of the health care work force (training programs focusing on the care of older adults are underfunded). Because older adults, particularly ethnic minorities, often do not use specialty mental health services, may be reluctant to take medication for depression, and have accompanying medical co-morbidity that complicates identification and management of depression, new models of intervention development and service delivery are needed that account for medical conditions such as diabetes and cardiovascular disease and that are culturally relevant.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

Depression is associated with increased risk of dying from cardiovascular disease, diabetes, and cancer. Depression may result in poor health because medical regimens are not followed, depressed persons have excess functional impairment, and have stressed social networks. Non-adherence among older adults results in increased hospitalizations, health care costs, and mortality and is a major public health concern. On average one in three patients does not complete depression treatment, and depression is associated with non-adherence to medical treatment and poor control for conditions like diabetes and hypertension: (1) What system and practice interventions would facilitate identification and management of depression among persons with chronic conditions such as diabetes and heart disease? (2) What interventions can be developed to improve adherence to medical regimens for diabetes, heart disease, and other conditions? (3) How can primary care physicians work together better with mental health professionals to improve communication and coordinate care?

Health services research questions and hypotheses:

Despite decades of research focused on clinic-based interventions, disparities in health outcomes persist. A public mental health model emphasizes the development of interventions that are community-wide, congruent with existing community understandings of mental disorder, recognize the medical comorbidity of depression, highlight the importance of sustainability, and partner with natural helping networks, including communities of faith. Factors related to translation of research into practice are best addressed as components of the study and

intervention design rather than as an afterthought: (1) How do older adults manage depressive symptoms in their daily lives and in the context of medical conditions such as diabetes? (2) How can depression management be integrated into community-based care for diabetes, cardiovascular disease, and other chronic medical conditions? (3) How can we bolster the role of community organizations in the design and implementation of culturally-relevant and sustainable interventions to prevent or treat adverse consequences of depression on diabetes, cardiovascular disease, or other chronic conditions?

Impact on Health of Pennsylvanians

Diabetes, cardiovascular disease, smoking, and unhealthy behaviors remain significant challenges for improving the health of Pennsylvanians. Ample evidence from the Department of Health indicate that the number of persons with conditions such as diabetes and heart disease are growing, that rates increase with advancing age, and outcomes are associated with significant disparities across ethnic groups. Depression often accompanies medical illness but may be unrecognized and unaddressed -- contributing to poor adherence to medical treatment, poor control of diabetes and blood pressure, and excess disability, death, and costs associated with heart disease and diabetes. Rates of depression in persons with medical illness are around 40% of those with stroke, 35% of those with cancer, 25% of those with Parkinson's disease, 20% of those with cardiovascular disease or diabetes. Persons with medical illnesses such as arthritis are at greater risk for becoming disabled if also depressed. Most people with depression are seen in community settings and die from medical conditions such as heart disease. Depression may act to amplify or precipitate symptoms of medical disorders (e.g., pain), leading to increased use of health care services. Because medical co-morbidity can affect depression presentation, identification, outcomes, and mortality, the challenge is to develop methods and interventions that account for medical co-morbidity.

Results of our studies of medical co-morbidity and depression are directly relevant to Pennsylvanians since primary care practices in Pittsburgh and Philadelphia participated (as did 1226 older adults). Among persons aged 60 years and older who were seen by primary care doctors and followed for 2 years, depression contributed as much to mortality rates as did heart disease or diabetes. We found that providing depression care management -- integrated into the primary care of persons with medical conditions -- decreased the risk of dying by one-half over a 5-year follow-up, especially for persons with diabetes.

The primary health care setting is pivotal for the initial identification and management of depression among all older persons, but African American patients are more likely than white patients to obtain mental health care from a primary care provider. Once in care, African American patients appear to be less likely than white patients to have received care thought to be effective for depression. African American patients have been reported to be less likely than white patients to adhere to depression treatment once initiated, even though no difference in treatment response according to ethnicity among patients who accept and sustain treatment has been identified. Primary care physicians are less likely to identify older African American patients as depressed and once identified, are less likely to report having actively managed the patient's depression. This is a major public health issue that likely contributes to disparities observed in the outcomes and care for chronic medical conditions: incorporating and respecting community values and preferences may be the key to improving depression treatment in chronic illness.

The focus of depression treatment needs to integrate depression care into community-based and primary care-based management of conditions such as cardiovascular disease and diabetes, in order to have a population impact on the health of Pennsylvanians. Improving the community-based treatment of depression among persons with medical co-morbidity could have a significant public health impact, since most of the disability arising from depression among older adults occurs in the context of cardiovascular disease, diabetes, and other medical conditions -- health objectives for chronic diseases will not be adequately addressed without considering depression.

Contact Information

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Health Research Priority

Clinical/Health services. The research is designed to prevent or control all diseases related to tobacco smoking. Tobacco smoking is the single most important cause of cancer including lung, oral cavity, pharynx, larynx, esophagus, bladder, pancreas, liver, kidney, stomach, cervix, and some forms of leukemia. Tobacco is an important cause of cardiovascular disease, stroke, respiratory health and birth defects. Despite the success of nationwide smoking cessation efforts over the past several decades, the decline in adult smoking prevalence has levelled off in the past several years and millions of Americans continue to smoke. Emerging evidence indicates that the effects of smoking are not just a function of the number of cigarettes smoked, but on a host of other factors that affect how deeply smokers inhale cigarettes. These factors may include stress, socioeconomic status, racial/ethnic identity, price and access to cigarettes, indoor smoking bans, and the genetics of nicotine addiction. Advances in studies of smoking behaviors, genetics, and smoking biomarkers will allow researchers to better predict who is at risk for smoking-related illnesses among those who cannot quit, and to provide targeted interventions and more accurate risk assessments in smoking reduction programs among smokers who cannot quit but need to reduce their risk.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

1. Determine whether Pennsylvanians with lower levels of socioeconomic status (SES) or medically-underserved/rural areas have a higher risk of smoking-related disease. The hypothesis is that lower SES individuals, because of stress or other factors, smoke more intensely resulting in greater biological exposure to tobacco on a per cigarette basis.
2. Determine if other high risk groups such as African Americans and women also smoke more intensely.
3. Determine whether indoor smoking bans affect smoking inhalation behaviors and biomarkers of tobacco smoke exposure. Our hypothesis is non-intuitive in that smoking bans may actually increase smoking exposure in active smokers as restrictions increase cravings and the rapidity of smoking during employment or home smoking breaks.
4. Determine whether smoking reduction programs affect the biological exposure to tobacco smoke in these groups. Our hypothesis is that simply reducing cigarette consumption in smokers may not reduce biological exposure as social/behavioral/ economic factors may affect smoking intensity.

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Cigarette smoking is the leading cause of cancer mortality nationally and statewide and a major cause of heart and respiratory disease. The risk is directly related to the number of years smoked and number of cigarettes smoked per day. The harmful effects of smoking are greater in certain segments of the population than others. Numerous studies have shown higher incidence rates of lung and other tobacco-related cancers and higher risk of disease in lower income and disadvantaged neighborhoods, minority populations and in women. The higher rates/risks in these groups is not due to differences in smoking rates or cigarettes per day as demonstrated in large prospective studies such as the nationwide Cancer Prevention Studies conducted by the American Cancer Society and others (Haiman CA et al. *New Engl J Med* 2006;354:333-42. Steenland K et al. *Am J Epidemiol* 2002; 156: 11-21). The reasons for this are unclear but are hypothesized to be due to the way cigarettes are smoked. Social or economic stress may cause smokers to inhale more intensely or take more puffs per cigarette than smokers of higher affluence, resulting in a greater biological exposure to tobacco smoke carcinogens (Radi S, *Am J Ind Med* 2007;50:584-96). Therefore the way cigarettes are smoked may be just as important as the number of cigarettes smoked in terms of exposure to tobacco toxins. The implications of this are clearly significant, and especially for identifying high risk populations such as low SES groups and minorities. The implications are also critical for designing and targeting effective interventions at those who continue to smoke. Because smoking is behaviorally modifiable, effective smoking interventions now need to consider the factors that impact on how people smoke and not just reductions in the number of cigarettes. The greater hazard associated with tobacco smoke exposure on a per cigarette basis in lower income groups is especially relevant to Pennsylvania since a large percent of the state's population lives in Appalachian or low-income rural counties.

The higher risk of lung cancer on a per cigarette basis in African Americans than in white Americans may be due to social/cultural factors such as the preferred use of mentholated cigarettes which facilitate inhalation, or stressors in urban neighborhoods. This issue is also important to the state of Pennsylvania given the large minority populations in Philadelphia, Pittsburgh, and elsewhere. Similarly, the higher risks in women vs. men since lung cancer is the leading cause of cancer death in women in Pennsylvania.

Finally, the Commonwealth of Pennsylvania has recently enacted comprehensive smoking ban legislation that will decrease exposure to environmental tobacco smoke. While this is a significant public health measure, many Pennsylvanians will continue to smoke because of the strong addicting properties of nicotine. Consequently the health effects of the smoking bans on the smokers themselves need to be considered. If smoking bans increase cravings due to restricted access resulting in compensatory behaviors such as increasing the number or intensity of smoking during their smoking breaks, the bans could potentially have the unintended consequences of increasing their exposure. Research in this area will help to determine these effects and respond to smokers needs as well as nonsmokers.

The underlying theme behind all these studies is that the way people smoke and not just the numbers of cigarettes smoked may be a critical factor for future disease risk in Pennsylvania and nationwide. Identifying factors that cause increased smoke exposure and then determining how to reduce this exposure can have a huge impact on the tobacco-related mortality and health care costs in Pennsylvanians.

Contact Information

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Health Research Priority

2-3% of all babies born in the United States are affected with genetic disease. Testing in the newborn period for genetic disease has recently expanded from a handful of disorders in most states to 30 or more, bringing the identification rate to about one in every 2-3,000 babies. The State of Pennsylvania recently passed legislation to expand newborn screening to match the national average. Inborn errors of metabolism are the most frequent of the disorders identified through newborn screening. In aggregate, they represent the largest preventable cause of mental retardation in newborns. Thus, treatment of these disorders represents a huge potential impact on the health care system. Unfortunately, understanding and treatment of these disorders now lags behind our ability to identify them. This proposal is to provide additional support in the state for biomedical research into inborn errors of metabolism identified through newborn screen, clinical trials to optimize their treatment, and development of better educational resources for community physicians, patients and families regarding these disorders.

Biomedical research questions and hypotheses:

Early detection of inborn errors of metabolism has identified an entire new cohort of pre-symptomatic patients with these disorders, however, the specific nature of the genetic mutations and their impact on overall cellular metabolism in these patients remains uncharacteristic. We hypothesize that the spectrum of mutations in these patients will be different than those identified later in life through symptoms and that a better characterization of these mutations will lead to improved therapy. Three priorities are recognized.

The first priority is to collect gene mutation data on patients with inborn errors of metabolism identified in Pennsylvania through expanded newborn screening. The second priority is to examine the metabolic effects of mutations in these genes on cellular metabolism through advanced laboratory approaches such as proteomics and metabolomics. The third priority is to identify novel therapeutic agents to treat inborn errors of metabolism including pharmacogenomic approaches and random chemical library screening to develop new drugs for treatment.

Clinical research questions and hypotheses:

Early identification of inborn errors of metabolism offers the chance to identify patients with life threatening disorders before they become symptomatic. It also offers the opportunity to begin treatment before symptoms arise. However, screening also identifies a cohort of patients with mild symptoms or previously unrecognized biochemical findings that do not lead to disease. We hypothesize that long term follow up studies will allow us to identify those patients needing aggressive, immediate therapy vs. those that can be followed more conservatively. To examine this aim, we propose the need to develop a comprehensive clinical database to collect ongoing information on these patients and augment State data collection. We also hypothesize that early treatment will improve clinical outcome in patients identified through newborn screening vs. later with the development of symptoms. We propose to examine current treatments and test novel ones through formal

clinical trials in this population of patients. Finally, we hypothesize that the identification of new biomarkers of disease outcome and therapeutic efficacy will improve outcome in these patients.

Health services research questions and hypotheses:

An increase in disorders identified through newborn screening from 6 to >30 places enormous new stresses on the health care system designed to track and care for these patients. It also clearly impacts on primary care providers and metabolic treatment centers charged with the metabolic management of these patients. In recognition of this, the American College of Medical Genetics has begun development of ACT sheets, protocols for primary care providers, that outline the measures necessary in the initial response to an abnormal newborn screening results. We hypothesize that the development of similar educational resources will allow primary care providers to feel more comfortable in participating in the care of patients with inborn errors of metabolism and ease the burden of caring for these patients on the tertiary care centers. We propose the need to develop education materials to this end and study the impact on primary care practitioners in Pennsylvania. The economic impact of treatment is also considerable and poorly covered by insurance. We propose the need to examine current funding mechanisms for treatment of inborn errors with the goal of showing that better treatment translates into health care dollar savings.

Impact on Health of Pennsylvanians

Approximately 150,000 babies are born in the Pennsylvania each year. 4,500 of these have a genetic disorder including 400-600 who have an inborn error of metabolism. Prior to newborn screening many of these latter babies died as a result of their disease, often before it was recognized. Many also went on to exhibit chronic medical health care problems including mental retardation. Nearly one quarter of the hospitalizations in the pediatric population are related to genetic disorders including inborn errors of metabolism. Thus the impact on the health care system in Pennsylvania is enormous. Fortunately, early identification and treatment of inborn errors of metabolism can significantly reduce this impact. As the leading cause of preventable mental retardation in newborns, early identification and treatment of inborn errors of metabolism can reduce the burden of long term care costs for these patients, and more importantly, ensure them the opportunity to become normally functioning members of our population. There are only two full service inborn errors of metabolism clinics in the State, one each in Pittsburgh and Philadelphia. This leaves a significant portion of patients in the rest of the State with the need to travel long distance for specialty care. It also places primary care providers in a position to become more familiar with these disorders and their management. The economic impact on patients and families is also often devastating. Many of these disorders are treated by diet rather than more standard medications. The specialty formulas and foods necessary to manage inborn errors of metabolism are costly due to their limited market and are not covered by most prescription plans since they are not "drugs." This leaves families to cover tens of thousands of dollars in costs out of pocket. The composite result of travel for medical care and uncovered treatment expenses is a disproportionate burden on families with low incomes. Identification of new prognostic markers to predict outcome and new therapeutic interventions in these disorders will lead to improved public health for less health care dollars.

Contact Information

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Health Research Priority

The Centers for Disease Control (CDC) has determined that more than 21% (over 46 million) of U.S. adults report doctor- diagnosed arthritis. Over 40% of these individuals report arthritis-attributable activity limitation and over 30% report arthritis-attributable work limitation. These numbers are only expected to increase with the aging of the US population. In addition, arthritis is the single greatest cause of chronic pain and disability.

Although there are over 100 types of arthritis, the most common ones, osteoarthritis and rheumatoid arthritis, mainly account for the increased morbidity and health care costs. Osteoarthritis is the most prevalent form of arthritis and is among the most prevalent chronic conditions in the US. Osteoarthritis of the hip and knee is the most common cause of difficulty in walking or climbing stairs. The challenge in osteoarthritis is to identify patients earlier in the disease course to facilitate prevention and treatment of the disease. Rheumatoid arthritis is the most common type of inflammatory arthritis and affects 1% of the adult population. The cause of rheumatoid arthritis is unknown, but most likely there are various subsets of rheumatoid arthritis defined by abnormalities in the immune response. The challenge in rheumatoid arthritis is to determine which subsets of patients with RA will benefit the most from the newer, specific targeted, biologic therapies.

Biomedical research questions and hypotheses:

Although targeted biologic therapy has revolutionized the treatment of rheumatoid arthritis (RA), only 50% of patients have a reasonable response. More research is needed to determine the specific immune/ inflammatory abnormalities that characterize the RA phenotype/genotype and treatment response. We hypothesize that specific biomarkers (i.e., DNA, RNA, serum and imaging biomarkers) will differ among subsets of patients with RA and will determine individual responses to different therapies. To address this question and fulfill the promise of “personalized medicine,” prospective, longitudinal cohort studies with extensive biospecimen assessment, combined with detailed clinical information, will be necessary.

Advances in imaging have allowed the detailed morphologic characterization of the abnormalities present in osteoarthritis (OA) before the end-stage manifestations seen on x-ray. To better understand the pathophysiology of OA, studies are needed to examine changes in cartilage and meniscus composition as well as morphologic changes. We hypothesize that newer imaging techniques will identify changes in collagen/proteoglycans that precede loss of cartilage and meniscal degeneration in OA.

Clinical research questions and hypotheses:

Only a limited number of patients with RA have benefited from newer therapies. Will aggressive treatment of patients early in the disease course or those with more established disease lead to improved patient outcomes and reduced disease activity? Will newer imaging techniques lead to better assessment of disease activity? We hypothesize that frequent monitoring of disease activity with tailored combination anti-rheumatic and biologic drugs will lead to decreased pain, improved function, better health-related quality of life and more clinical remissions. Emerging data suggests that smoking may be a risk factor for developing at least one disease subset

of RA. Will smoking cessation decrease the risk of RA or improve outcomes in RA in this disease subset? Are there specific biomarkers that characterize this disease subset?

Because the cause of pain in osteoarthritis (OA) is unknown, studies are needed to better characterize OA-related pain and identify potential causes of pain in OA. We hypothesize that newer assessments of pain frequency, intensity, pattern and location in combination with state-of-the-art imaging techniques will help to identify the etiology of pain in OA.

Health services research questions and hypotheses:

Prior joint injury is a major risk factor for osteoarthritis and there is an epidemic of joint injuries among female athletes. Can individuals at high risk of injury be identified and will a targeted injury prevention program directed at these individuals be effective in preventing injury? We hypothesize that specific risk factors for joint injury in female athletes can be recognized and that a targeted injury prevention program will help to prevent joint injuries and their physical and psychological sequelae.

Racial disparities in total joint replacement (TJR) utilization have been demonstrated and prior research indicates that African-American patients' preferences related to TJR may underlie this disparity. Reduction or elimination of racial disparities has been designated as high priority by the National Institutes of Health (NIH). Investigations are needed to test interventions designed to reduce or eliminate disparities in TJR utilization. We hypothesize that biobehavioral interventions directed toward patients' willingness to consider TJR and patients' outcome expectations related to TJR will help increase African-American patients' willingness to consider TJR and ultimately, reduce racial disparities in TJR utilization.

Impact on Health of Pennsylvanians

Given the aging of the US population, the Centers for Disease Control (CDC) estimate that the number of Americans with arthritis is expected to increase from over 46 million in 2006 to over 67 million in 2030. Data from the 2005 Pennsylvania Behavioral Health Risk Factor Surveillance Survey (BRFSS) show that 32% of Pennsylvania adults (nearly three million) have been diagnosed with arthritis and that almost 60% of Pennsylvanians over age 65 have arthritis. According to the CDC, only two other states in the US have a higher percentage of the population affected by arthritis. The economic impact of arthritis in the US is significant, with a total cost of over \$65 billion that includes an estimated medical bill of \$15 billion per year, 35 million physician visits and more than 744,000 hospitalizations. Cost increases are projected to increase by 54% to \$100 billion by 2020. Specifically, arthritis accounts for over 4100 hospitalizations in Pennsylvania, with the median charges exceeding \$13,000 per hospitalization. Among Pennsylvanians of working age (18 to 64), twice as many of those with arthritis, 28% vs. 14%, reported they were not working. Pennsylvania vital statistics for 2000 indicated that diseases of the musculoskeletal system and connective tissue disease were responsible for 5.1 deaths per 100,000 population. Thus arthritis is major public health problem in the US, and particularly in Pennsylvania.

The most common type of arthritis is osteoarthritis (OA), a degenerative disease of cartilage and bone which causes changes in underlying bone and supporting tissue. OA most frequently occurs in weight-bearing joints such as the knees and hips. and knee and hip OA can result in significant loss of function with pain and suffering and work disability.

Total joint replacement of the knee or hip is an effective therapy for end-stage osteoarthritis, relieving pain, reversing joint deformity and improving quality of life. Between 2000 to 2002, over 80,000 knee and hip replacements were performed for osteoarthritis in Pennsylvania hospitals. Indeed, the rate of total joint replacements for osteoarthritis increased by 15% over this three-year period. With the aging of the population and the growing obesity epidemic, the rate of total joint replacement is expected to increase dramatically in the coming years.

Unfortunately, despite the well-documented efficacy of total joint replacement, not all segments of the population have benefited from these procedures. Numerous reports have documented racial/ethnic disparities

in the utilization of total knee or hip replacement. African-Americans are much less likely than whites to undergo total joint replacement and recent investigations suggest that this disparity is increasing. Furthermore, recent studies suggest that African-Americans may be at risk of worse outcomes after total joint replacement as compared to whites.

Rheumatoid arthritis (RA) is the most common type of inflammatory arthritis and affects 1% of the adult population. It is an autoimmune disease characterized by chronic pain, swelling and stiffness in multiple joints, most commonly the small joints of the hands and feet. There is inflammation of the joint lining that causes destruction of bone, cartilage and surrounding soft tissues. RA is associated with major activity limitations, and work disability, and may shorten the lifespan by 10 years. RA is accompanied by systemic inflammation and immune suppression. The major cause of death is premature atherosclerosis. Patients with RA are also at increased risk of developing serious infections and certain types of cancer.

In summary, the impact of arthritis on the health of Pennsylvanians is enormous. Not only is it highly prevalent, arthritis is also the leading cause of disability and is associated with major economic costs. In addition, rheumatoid arthritis is accompanied by premature mortality. Furthermore, there are racial disparities in the utilization of total joint replacement for OA.

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Health Research Priority

Trauma is the leading cause of death for individuals under age 45 in Pennsylvania, and a traumatic brain injury is the most common single cause for death from trauma. In 2004, 135,000 Pennsylvanians were hospitalized with a traumatic injury, 15,000 with a brain injury. The societal impact of trauma was profound, with \$4.68 billion in hospital charges alone that year, 64% of which was paid from government sources. Traumatic brain injury (TBI) also represents a major cause of disability, with 80 to 90,000 Americans each year acquiring a long-term cognitive, motor, behavioral or speech-language disability due to TBI. Trauma elicits an acute injury response that can lead to severe organ dysfunction and death. The complexity of the pathophysiology of TBI has stymied attempts at therapeutic modulation, resulting in a dearth of therapeutic options for persons suffering a brain injury. Recent successes in the application of computational simulation for the development of mathematical models for polytrauma have demonstrated the translational utility of computational simulation and modeling in the formulation of approaches to clinical trials and patient-specific diagnostics. Utilization of these translational systems biology approaches can substantially accelerate progress toward solutions to address the major societal problem of combined TBI/polytrauma.

Biomedical research questions and hypotheses:

Our overarching hypothesis is that mechanistic computational modeling, unlike statistical analyses, can yield novel, translational insights into traumatic brain injury, polytrauma, and combined TBI/polytrauma. All science heretofore in the field of TBI has failed to translate into meaningful clinical treatments. Thus, modern computational modeling techniques represent a particularly promising opportunity to make an impact on this devastating disease. The biomedical research questions to be addressed are the following:

- 1) Can computational modeling of cellular and molecular processes of polytrauma and traumatic brain injury lead to mechanistic insights as to the driving forces of damage in these complex diseases?
- 2) Can these computational simulations be used to reproduce the outcomes of failed clinical trials in TBI/polytrauma and/or for better utilization of existing therapeutic interventions?
- 3) Can the concept of nutritional modulation of the injury response be integrated into a clinical trial and patient-specific simulation?

Clinical research questions and hypotheses:

The overarching hypothesis is that the injury responses and sequelae in TBI create cognitive, communicative, and neurologic impairments, with lasting negative impact on functional outcomes among TBI survivors. The specific research questions to be explored are:

- 1) Can computational and agent-based models be used to predict the individual outcomes of patients after traumatic brain injury?

- 2) Can real-time computational modeling be employed clinically to identify patients at risk for further neurologic deterioration and/or death?
- 3) Can such models be used to formulate specific intervention strategies?

Health services research questions and hypotheses:

Our overarching hypotheses are the following: Long-term outcomes and societal/economic impact may be predicted by the severity of the spectrum of pathophysiology measured in the acute setting; Long-term functional outcomes and societal impact may be modulated by interventions initiated in the acute phase.

- 1) What impact do cognitive and related communicative impairments following head trauma have on psychosocial and employment outcomes post-injury?
- 2) Can early nutritional intervention improve outcomes following traumatic brain injury?
- 3) Can computational simulations of the trauma-related pathophysiologic responses at the cellular and molecular level shed insight into cognitive and neurologic impairments?

Impact on Health of Pennsylvanians

Trauma and traumatic brain injury are significant health issues for Pennsylvanians of all ages. In the period from 1995 to 1999, 74,565 Pennsylvanians sustained a TBI, an incidence rate of just over 124 per 100,000. These injuries were most likely to affect adults 25 to 44 years old (representing 19,127 cases). Trauma is the leading cause of death in Pennsylvania for persons under age 45, eclipsing death from heart disease, cancer, stroke, HIV, and lung disease, combined in this age group. While traumatic brain injury is disproportionately a disease of the young, Pennsylvania is unique from a national perspective in that traumatic brain injury is equally as likely to affect older adults age 75 and over (15,196 cases) as teenagers and young adults age 15 to 24 (14,157).

These injuries are costly: in 2004, injury-related hospitalizations in Pennsylvania accounted for \$4.68 billion in hospital costs to families, the state, and other third-party payers. Government sources were responsible for paying 46% of these charges. For traumatic brain injury, specifically, the Department of Health calculated hospital costs at \$1.85 billion for the period 1995-99.

Importantly, it is a subset of Pennsylvanians who bear a disproportionate part of this burden. For example, African-American males were 1.6 times more likely to experience a traumatic brain injury than Caucasian males. As a group, African-Americans, 10% of Pennsylvania's population in 2000, accounted for 11.6% of TBI hospitalizations and 13.4% of the costs related to those hospitalizations between 1995 and 1999. The incidence of trauma and traumatic brain injury among senior citizens of the Commonwealth is likewise on the rise. Falls are a particularly significant cause in the elder population, accounting for 45,000 hospitalizations in Pennsylvania in 2004, a 16% increase compared to 2000. Furthermore, traumatic brain injury in Pennsylvania is on the rise among certain segments of the population. A recent study reported that the rate of head injuries had increased by more than 30% since the repeal of Pennsylvania's motorcycle helmet law, with the associated hospitalization costs rising almost twice as fast as the costs for non-head-injuries from motorcycle accidents.

The social and economic burden of TBI survivors is quite substantial. Traumatic brain injury is disproportionately a disease of the young, which substantially magnifies the overall impact. Lifetime costs for treatment, rehabilitation, and social needs of severe brain injury survivors are estimated to exceed \$4 million per individual. The cumulative economic impact of traumatic brain injury is estimated at \$48 billion annually in the United States based on hospital costs of \$32 billion with \$16 billion attributed to fatal injuries. Because young

people who survive a brain injury face decades of disability, the potential to lessen the societal burden and enhance lives through improving treatment and rehabilitation is very substantial.

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Health Research Priority

Substance abuse has been deemed by public health experts and the Robert Wood Johnson Foundation as "the number one health problem in the country," yet there remain significant gaps in research on scientific treatment methods for combatting addiction, particularly among specialized populations. According to the Robert Wood Johnson Foundation Report, Substance Abuse: The Nation's Number One Health Problem, Key Indicators for Policy, "there are more deaths, illnesses and disabilities from substance abuse than from any other preventable health condition." Substance abuse poses a major strain on the nation's healthcare system, and although it affects all segments of society it disproportionately affects disadvantaged groups. Therefore, additional clinical research funding must be dedicated to evaluating the impact of addiction on special and disadvantaged populations, including studies on the effectiveness of therapeutic interventions focusing on: adolescents, families, the children of addicted women, trauma survivors, and victims of sexual abuse. Research on the effectiveness of various strategies for engaging individuals in substance abuse treatment and on the impact of 'aftercare programs' on long-term recovery rates is also warranted. Studies of the impact of substance abuse on the treatment of various other chronic health conditions, as well as strategies for addressing multiple disorders simultaneously, also is necessary.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

Clinical research questions to be investigated might include: 1) the impact of various substance abuse treatment interventions on special populations, including adolescents, families with inter-generational substance abuse problems, trauma survivors, women, minorities, and the children of addicted parents; 2) the effectiveness of various engagement strategies for encouraging individuals with substance abuse problems to enter into -- and remain in -- treatment; 3) the impact of aftercare programs on helping specific populations to remain clean and sober after a treatment episode; and 4) the impact of gender and culture-specific treatment interventions on long-term recovery.

Health services research questions and hypotheses:

Health services research questions to be investigated might include: 1) the effectiveness of co-locating brief treatment for substance abuse in alternative/non-behavioral healthcare settings (such as schools, primary care centers, and criminal or juvenile justice centers) and 2) the effectiveness of treatment models targeting behavioral health disorders and other chronic conditions simultaneously.

Impact on Health of Pennsylvanians

Healthy People 2010, the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Robert Wood Johnson Foundation have recognized substance abuse as a public health issue of constant and growing concern due to its influences on health outcomes, productivity, and costs across all communities but primarily affecting young adults/adolescents and African Americans. As the Robert Wood Johnson Foundation argues in its February 2001 Substance Abuse Report, this prominent public health problem underscores the growing need for attention.

As a main focus area of Healthy People 2010, substance abuse issues such as the drug-induced death rate, average age of first use of alcohol/marijuana, and other indicators have been shown either to remain stagnant or to move away from Healthy People 2010 goals for Pennsylvania. Healthy People 2010 aims to have only 1 per 100,000 persons fall victim to drug induced death. However, Health People data show a steady increase in the number of deaths (per 100,000) from 2001 to 2005. In 2005, it was reported that Pennsylvania's drug induced death rate reached 13.5 deaths, up from 8.3 in 2001. According to this data, Blacks experienced the highest mortality rate at 18.6 persons (per 100,000) compared with 13.5 for Whites and 12.6 for Hispanics. Each of these rates also has experienced increases - from 14.8, 8.0 and 11.0 respectively - since 2001. Although Blacks are shown to have the highest drug-induced death rate among Pennsylvanians, increases in the rate across all racial/ethnic groups demonstrate a problem that reaches across all communities in the Commonwealth.

For the average age of first use of alcohol among adolescents (12-17 years old), data remains steady from 2002 to 2005, at approximately 13 years old. No significant improvements were made to achieve the Healthy People 2010 goal of 16 years of age at first use. Similarly, the average age of first use of marijuana did not experience any change, remaining at approximately 13.8 years old for adolescents. Although Healthy People 2010 data show conditions not worsening over time for age of first use, SAMHSA reports that the overall conditions of illicit drug and marijuana use in Pennsylvania represents an increase in the gravity of the issue in the region. SAMHSA reports in its 2005-2006 National Survey on Drug Use and Health that 10.45% of Pennsylvanians ages 12 and older have used marijuana in the past year. Of that 10.45%, persons between the ages of 18 and 25 years represented the largest share of people who have used Marijuana in the past year, at 29.22%. Additionally, 7.65% of the Pennsylvania population (ages 12 and older) reports having used an illicit drug in the past month. Among this group, 19.51% of total respondents were between the ages of 18 and 25.

The Robert Wood Johnson Foundation states that alcohol abuse is a major cause for premature death and illness in the nation. More specifically, the Foundation reports that more than 100,000 deaths each year are attributable to excessive alcohol consumption. As reported by SAMHSA's 2005-2006 survey, 52.3% of Pennsylvanians have consumed alcohol in the past month, with persons between the ages of 18 and 25 representing the largest share at 63.44%. Compared with the states having larger populations than Pennsylvania (California, Texas, New York, Florida, and Illinois), Pennsylvania ranks 3rd, behind New York (54.75%), Florida (53.43%), and Illinois (52.47%), in percentage of persons consuming alcohol. Even with its smaller population, Pennsylvania reports higher past month use of alcohol than the nation's two largest states (California - 50.33% and Texas 49.49%).

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Health Research Priority

We propose that the Commonwealth of Pennsylvania select blindness and visual impairment as a health research priority, emphasizing 1) developmental disorders and diseases in children; and 2) major ocular diseases that affect the elderly. Visual disabilities have high impact on the quality of life, result in major medical expenses and can significantly limit economic productivity. In children, visual disabilities from conditions such as amblyopia, strabismus (crossed eyes) and retinal disease have lifelong impact. Refractive errors result from growth disorders of the eye; besides requiring spectacle correction, myopia (nearsightedness) predisposes to blinding eye diseases such as glaucoma, retinal detachment and other retinal disorders as people age. With the rapidly growing size of the elderly population, sight threatening diseases such as macular degeneration and glaucoma are having increasing impact. The medical community in Pennsylvania has great clinical and research strengths in these areas of eye disease; and we propose hypothesis-driven research that will exploit and enhance the strengths of the Pennsylvania eye research community, including the recruitment of new investigators. These proposals should stimulate basic, translational and clinical research initiatives, likely involving multi-investigator collaborations, and will lead to research aims that ultimately will improve the eye and vision health of Pennsylvanians.

Biomedical research questions and hypotheses:

For childhood eye disorders, we propose that combining advances in cell and molecular biology, bioengineering and molecular genetics can provide improved understanding of eye development, identify causes for childhood ocular disorders and provide new clinical therapies. Amblyopia, retinal disorders, including retinopathy of prematurity, strabismus and refractive errors will be emphasized. For eye diseases in the elderly, we propose that continuing application of genetics, molecular biology and cellular physiology can advance knowledge of the cause of these eye diseases, improve diagnosis and prevent blindness by developing new and improved diagnostic approaches. Macular degeneration and glaucoma will be emphasized. Like much medical research, eye research is becoming increasingly interdisciplinary. Distinctive interdisciplinary programs in the above areas are needed, will leverage the potential investment by the Commonwealth, impact with other clinical and research programs in the state and likely have a significant long-term clinical impact, especially because collaborative “program project grants” are not a funding mechanism presently supported by the National Eye Institute of NIH.

Clinical research questions and hypotheses:

Translational eye research, i.e., research designed to bridge basic laboratory investigations and the clinic, offers great promise for improving eye care for both children and the elderly. For childhood eye disorders, study of environmental, behavioural and genetic influences and their interactions can provide new insights into the cause of childhood eye disease and lead to the introduction of much needed new therapeutic approaches. Furthermore, the development and application of new diagnostic methods can make possible earlier diagnosis

and provide better methods to care for children with eye disease. For eye diseases in the elderly population, integrating laboratory investigations with clinical observations can provide needed insight into the cause of disease and novel therapies. In addition, the application of advanced imaging, computer and genetic methods can prevent blindness by providing earlier diagnosis and intervention by treatments known to be effective.

Health services research questions and hypotheses:

Establishing or strengthening existing Centers of Excellence in Eye Research will improve the diagnosis and therapy of eye disease for all citizens of the Commonwealth. Developing, validating and applying new diagnostic and screening methods can identify patients in populations that are underserved and/or at high risk for blinding eye diseases. Improving patient access to proven therapies and developing new therapeutic approaches can reduce the individual and societal burdens of blindness throughout the Commonwealth. Developing novel approaches and improving access to available visual aids and other services for patients with low vision will improve the quality of life for Pennsylvania's visually impaired citizens of all ages.

Impact on Health of Pennsylvanians

The chosen areas of concentration for reducing blindness and visual impairment each have very high impact on the health of Pennsylvanians. Vision disorders are the most frequently occurring handicapping conditions of childhood. These disorders include amblyopia (reduced visual acuity in one or both eyes or "lazy eye"; 2-5% prevalence), strabismus (misalignment of the eyes; 3-4% prevalence), significant refractive error (nearsightedness, farsightedness, and astigmatism; 15-20% prevalence), and retinopathy of prematurity (<1% prevalence). Early detection and treatment of these disorders can prevent vision loss and reduce their negative impact during childhood and later in life. The incidence of amblyopia, strabismus, and retinopathy of prematurity is higher among low income families. Despite the relatively high prevalence of these conditions, the mechanisms for their development are not understood clearly. There are effective treatments for amblyopia, strabismus, and retinopathy of prematurity but the timing of the treatments is critical so that screening of infants and young children is necessary. The immediate problem of providing clear vision to children with refractive errors is solved with spectacles, but affected people remain at higher risk of several serious eye conditions, such as retinal detachment and glaucoma, that do not manifest until much later in life. In addition, provision of glasses, contact lenses, and refractive laser correction can cost hundreds of dollars per year for the entire lifetime of the child.

The major causes of visual impairment and blindness in adults are age-related macular degeneration, glaucoma, cataract and diabetic retinopathy. The prevalence of each of these conditions increases dramatically with age. Pennsylvania currently has the 9th highest prevalence of visual impairment and blindness in the US. As the "baby boom" generation ages, the age distribution of the population is shifting; for example, the number of Americans age 85 and older will nearly double between 2000 and 2020. Because Pennsylvania's population already has a higher proportion of older adults, the rise in the numbers of blind and visually impaired people will be even more marked here than in other states. Vision loss at an older age has major negative effects on physical health, mental health, and health care spending. Compared to normally sighted people of the same age and general health, people with loss of vision have more falls and hip fractures, higher rates of nursing home entry, higher mortality, three times the rate of depression, and spend more than \$2000 per year extra for medical bills in addition to having to employ caregivers an extra week per year. Costs of treating patients are increasing; for example, new highly effective treatments for macular degeneration cost more than \$26,000 per year for a single patient.

There are marked racial differences in the causes of vision loss. Age-related macular degeneration is responsible for approximately 30% of blindness among Caucasians but less than 1% among African Americans. While relatively spared from macular degeneration, African Americans face an earlier age of onset of glaucoma, more rapid and more difficult-to-control disease progression and more blindness (25% of all blindness) than their Caucasian counterparts (10% of all blindness). The incidence of cataract is higher among

Caucasians, but because fewer Africans Americans receive sight-restoring surgery, they have a higher rate of blindness from cataract. Diabetes is 2.2 time more common in African Americans and can lead to retinopathy and cataract. Although effective treatment for diabetic retinopathy is available, annual examination is necessary to detect the advanced stages of the disease; and one-third of diabetic patients do not have regular examinations, a proportion that increases among both inner city and rural populations.

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Health Research Priority

Pain Management: Translational Medicine and Therapeutics - Over 34 million adults in the U.S. suffer some form of chronic pain. It is estimated that in the State of Pennsylvania 27% of all adults reported at least one or more days of pain that made usual activities difficult in the past 30 days (Bureau of Health Statistics & Research, 2006). In 2005, 40% of all adults in Pennsylvania experienced pain around the joint in the past 30 days (PA Behavioral Health Risk Factor Surveillance System), with over 3 million citizens of the State suffering from painful arthritis. Pain is often not well managed, as in cancer and in children suffering from terminal illness, and is frequently comorbidly expressed with other illnesses resulting in a severe impact on the quality of life and on the health care costs to the State. Current medications often have debilitating side effects and may also have abuse liability. A comprehensive interdisciplinary approach is needed to more adequately understand the molecular pathophysiology underlying various types of pain, to develop more suitable preclinical models of pain syndromes, and to then use this information to develop more effective pain medications. These approaches, coupled with the identification of appropriate biomarkers, bioinformatics and pharmacogenomics targeted to different types of pain and innovative clinical trial designs, promise to deliver more effective, safe therapies to citizens of the State.

Biomedical research questions and hypotheses:

The emphasis of this recommendation to pursue a bold, comprehensive and integrated translational approach to Pain Management is focused primarily on identifying new approaches to the investigation and treatment of chronic, unremitting pain. Although most of the debilitating pain that is experienced is chronic in nature, the preclinical focus has typically been on acute pain models. One major focus of the research would be to examine changes in the nervous system that occur under chronic pain conditions. This will be addressed at the molecular level using neuroanatomical imaging techniques, biochemical, as well as neurochemical techniques. A second major effort will include the development of more appropriate preclinical model systems. There is often a 'disconnect' between preclinical and clinical research whereby the assessment and evaluation of pain and its alleviation are not aligned. Models of neuropathic pain as well as cancer pain will be included. A major emphasis of this research will be to incorporate known and novel pain targets and compounds into this plan to identify more effective therapeutics devoid of potential side effects that can be rationally developed for patients.

Clinical research questions and hypotheses:

A major emphasis of this research is to more closely 'harmonize' the clinical assessment of pain with the often extensive preclinical studies conducted to provide a 'proof of concept' that justify the progression of compounds into clinical evaluation. It is often the case, however, that the methods used to determine efficacy in preclinical models are vastly different from those used in the clinic. There is, therefore, a critical need to more closely align preclinical and clinical studies of pain. There is a need for novel and innovative clinical trial designs (e.g., adaptive trials), the identification of suitable biomarkers, and the ability to identify patients and pain indications most likely to benefit from therapeutic intervention. A key aspect of this approach would include

pharmacogenomics and bioinformatics to help deliver high quality, safe and effective care and medical monitoring to patients in the State of Pennsylvania. A focus of this research will be to evaluate compounds in well controlled clinical trials in patient populations that suffer from chronic pain. This will include, for example, cancer patients as well as patients suffering from other types of pain that is chronic in nature such as diabetic neuropathies and complex regional pain syndromes.

Health services research questions and hypotheses:

Pain is unquestionably complex and, to some extent, idiosyncratic with individual differences in sensitivity and in the impact on daily living. Most approaches to pain management are limited to a few treatment options despite the diversity of the different types of pain. A major hypothesis is whether it will be possible to identify patients likely to benefit from a particular medication through the use of reliable biomarkers and/or pharmacogenomic analyses. This would permit the delivery of enhanced treatment modalities for the various types of pain with a minimum of side effects. The ability to deliver more effective pain therapeutics with reduced side effects has countless benefits to the individual citizens of the State, to their families, and to the overall impact wherein enduring pain severely compromises productivity and is a continuing and costly burden on the health care system.

Impact on Health of Pennsylvanians

The impact of chronic, unremitting pain on the health of Pennsylvanians is somewhat difficult to measure since pain is associated with many different illnesses such as cancer, rheumatoid arthritis, congestive heart failure, and diabetes. Pain is also often independent of these conditions as is the case with migraine and reflex sympathetic dystrophy or complex regional pain syndrome. However, it is estimated that in the State of Pennsylvania 27% of all adults reported at least one or more days of pain that made usual activities difficult in the past 30 days (2006 Bureau of Health Statistics and Research). In 2005, 40% of all adults in Pennsylvania experienced pain around the joint in the past 30 days (PA Behavioral Health Risk Factor Surveillance System), with over 3 millions citizens of the State suffering from arthritis. It is often the case that chronic pain is associated with depression and suicidal ideation and that, taken as a whole, pain cuts across a wide spectrum of disorders and is debilitating personally while also creating a severe burden to the family, to society, and to the healthcare system within the State of Pennsylvania.

A major objective of this proposed approach to Pain Management is to utilize the combined resources in the basic and clinical science departments at Drexel University College of Medicine and the School of Biomedical Engineering to develop and apply novel technologies for translational approaches to pain and to its management. This effort to address the impact of chronic pain on the health of Pennsylvanians would integrate this initiative within Drexel with other institutions and pharmaceutical companies in the Philadelphia area and the State to establish the infrastructure for drug discovery and development to address this critical unmet need. These efforts will yield new discoveries, new tools for clinical assessment and prescribed therapies, as well as new investigators and grant applications. Importantly, this effort will yield new partnerships and entrepreneurial opportunities that will help build the State's workforce as well as alleviate a serious debilitating impediment to comfort and productivity.

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Health Research Priority

The state of Pennsylvania ranks third in the nation in the percentage of people age 65 and older. By the year 2020, one in every four Pennsylvanians will be 60 or older, a concern addressed by Governor Rendell's Pennsylvania 2020 Vision Project (executive order #2006-04). As a result of this increase in older individuals, there has been a rise in the prevalence of diseases of aging. One of the major increases is seen in vision impairment and blindness (www.agingeye.net) which is also a target area for Healthy People 2010. The major eye conditions that increase with age include age-related macular degeneration (AMD), cataract, diabetic retinopathy and glaucoma. The reported prevalence for all forms of AMD and glaucoma among adults age 40 and above in the United States is 9% (Ophthalmology 1995;102:371-381) and 1.9% (Arch. Ophthalmol. 2004;122:532-538). Pennsylvania can take a leadership role in solving both AMD and glaucoma due to its large percentage of older individuals available for study. A multidisciplinary research center for gene discovery in AMD and glaucoma should be funded to focus on 1) obtaining subject material to perform Single Nucleotide Polymorphism genotyping on 500,000 to 1 million SNP chips, 2) identify environmental factors that influence disease, and 3) imaging technology to identify early phenotypic markers in the eye that could be used to predict drug response and long-term management.

Biomedical research questions and hypotheses:

To assure ourselves that novel treatments will be available for public health, there is a need to utilize the emerging technology available for studying complex diseases. Therefore, in this testimony I am calling for the funding of a multidisciplinary academic center that will focus on gene discovery, environmental interactions and advanced imaging technology. The Center will be a unique environment where experts in bioinformatics, statistical genetics, epidemiologists and imaging will work with clinicians to attack the leading causes of vision impairment in the elderly, AMD and glaucoma. To find the genes influencing complex diseases like AMD and glaucoma, Genome Wide Association Studies are necessary that require large cohorts. In the center, the following types of hypothesis will be tested:

Hypothesis 1: AMD and glaucoma are caused by multiple gene variants. To address this hypothesis cohorts of 2000 cases and 2000 controls should be collected for each disease to perform genome wide association studies (GWAS). Several replication groups of similar size or larger should be collected to replicate the findings in the discovery group.

Clinical research questions and hypotheses:

Hypothesis 2: Gene variants identified in the GWAS will have overlapping but distinct early ocular phenotypic changes that can be utilized for appropriate drug treatment as well as predictors of disease progression. To address this hypothesis, a large cohort of cases with early AMD or glaucoma will need to be evaluated by advanced imaging technologies, i.e. adaptive optics scanning laser ophthalmoscope and Fourier-domain optical coherence tomography.

Hypothesis 3: Environmental factors will act alone or in concert with gene variants to produce disease. For example smoking, sunlight exposure and diet are risk factors for AMD. Therefore, smoking history, sunlight exposure and dietary history should be evaluated in several defined cohorts across the state for their influence on AMD disease onset and progression. Questionnaires should be used to find environmental risk factors for glaucoma. The significant gene variants found on the GWAS should also be evaluated for gene-environment interactions that may lead to disease susceptibility.

Health services research questions and hypotheses:

Hypothesis 4: Changes in environment will lead to a lower prevalence of AMD and glaucoma. The success of this hypothesis can only be achieved in the case of AMD with a team of dieticians and behavioral specialists to alter diet, smoking habits, and sunlight exposure. Outreach programs will be utilized to educate the urban and rural populations how to reduce their chance of disease.

Hypothesis 5: Many Pennsylvania residents living in urban and rural areas are not aware of the available low vision aids used for endstage glaucoma and AMD. Stimulate the formation of focus groups to educate low vision patients about the new technology available that will allow them to see better.

Impact on Health of Pennsylvanians

Demographically, the Commonwealth of Pennsylvania ranks third in the nation in the percentage of people age 65 and older and by the year 2020 more than one in four Pennsylvanians will be age 60 or older. This spiraling upward in age distribution will result in the percentage of Pennsylvanians over 65 surpassing the percentage of young people under 15 in the year 2020 (2020 Pennsylvania Vision Report). This change in age distribution will have an enormous impact on the prevalence of AMD and glaucoma in Pennsylvania. Based on population data in 2004, Pennsylvania has the fourth highest prevalence rate for vision impairment and blindness (3.19% compared to overall national rate of 2.80%) behind Hawaii (1st), Rhode Island (2nd) and Florida (3rd) (Vision Problems in the U.S. 2008, Prevent Blindness America). Recent estimates on Pennsylvania from the 2004 report from Prevent Blindness America identify 121,472 cases of end-stage AMD (4th leading state) and 112,325 cases of glaucoma (5th leading state). This number will certainly grow as the aging population in the state increases over the next decade.

Pennsylvania also has a diverse representation of racial groups including Caucasian 85%, African American 10%, Hispanic 3% and Arian 2% (www.newpa.com). Both AMD and glaucoma have different prevalences among the racial groups. Nationally, the prevalence of AMD in the 45-85 year old age group is 5.4% in Caucasians, 2.4% in African Americans, 4.2% in Hispanics, and 4.6% in Chinese (Ophthalmology 2006, 113:373-380) while the glaucoma prevalence in subjects 40 years and older is 1.69% in Caucasians and 4.54% in African Americans (Arch. Ophthalmol. 2004, 122:532-38). Pennsylvania is also the home of a unique cohort, the Amish, that have been utilized over decades for genetic studies. Because of their excellent genealogical records, isolated groups such as the Amish are viewed favorably for studying complex disease (Clin. Genet. 61:233-47, 2002). According to the American Religion Data Archive, there were 25,340 Old Order Amish living in Pennsylvania in 2000 (www.State Health Improvement Plan 2006-2010, Chapter 6, page 6-1). The Amish live in a homogeneous environment and along with their excellent genealogical records make them ideal to identify new genes that often cannot be found due to genetic heterogeneity in outbred populations. My colleagues and I have been studying the Amish population for AMD. We have screened 2000 Amish subjects age 50 and over for AMD and found a prevalence of 21%. This population is particularly afflicted with this blinding disease and would benefit from advances made in AMD treatment. Importantly, the state of Pennsylvania is concerned about the cost and availability of health care in the Amish community because its members do not prescribe to conventional health insurance, live in rural areas and have limited transportation resources (State Health Improvement Plan 2006-2010, Chapter 6, page 6-1).

Additional gains to the Commonwealth and its citizens for supporting research on aging eye diseases like AMD and glaucoma include: 1) a decrease in the progression of early to late AMD reducing costs of healthcare and

increasing the quality of life experienced by Pennsylvania's seniors; 2) assisting Pennsylvania in keeping up with the other states that are investing in this field; 3) establishing Pennsylvania as a national leader in this growing field; 4) building an infrastructure useful to attract other funding into Pennsylvania, i.e. NIH; 5) developing new scientists in this growing field for Pennsylvania; 7) enhance education of preventive measures for the development of AMD and glaucoma; 8) make available new tools for improving vision in patients with endstage AMD or glaucoma; and 9) improved diagnostics through genetic testing and early phenotype classification leading to an eventual change in treatment commensurate with the developing field of personalized medicine.

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Health Research Priority

We request that chronic pain be proposed as a health research priority for 2009 - 2010 non-formula (competitive) tobacco grants. More than 50 million Americans experience chronic pain, and more than half of terminally-ill patients experience moderate to severe pain during the last days of their lives. Pain accounts for 20 percent of visits to physicians and 10 percent of all drug sales, costing the U.S. economy and estimated \$300-500 billion annually. In spite of the large burden chronic pain has on patients, their families, and society, the overall percentage of NIH grants focused on pain has been declining, to a current level of less than 1 percent of the NIH budget. NIH grants devoted to pain have declined from \$166 million in 2003 to \$142 million in 2007 - during a time when the total NIH budget rose by 7 percent. The Commonwealth of Pennsylvania is home to several institutions that house major pain research centers. The Penn Pain Medicine research program, which is an interdisciplinary program housed within Penn's Comprehensive Neurosciences Center, has made significant advances in our research infrastructure over the last year. Pain research funding through tobacco grants presents a unique opportunity for Pennsylvania-based pain research programs to make significant headway in our efforts to improve the care of patients with complex pain problems.

Biomedical research questions and hypotheses:

Pain affects millions of people every year, significantly degrading physical and emotional functioning, decreasing quality of life and causing lost work. This is especially true for those who are elderly, who frequently experience pain that interferes with normal functioning, and for those who do not receive adequate pain management.

We have an incomplete understanding of the underlying causes of abnormal pain states, and patients often have multiple contributing causes for their pain. Treatment is best accomplished using a biopsychosocial model for care, and often requires integrated care from multiple providers.

An improved understanding of nociceptive pathways would allow for the development of improved treatments. Likewise, early pharmacogenetic research has provided exciting results that may ultimately lead to the development of new, innovative therapy.

Clinical research questions and hypotheses:

There are several clinical research opportunities available that have a high likelihood of improving the care of patients with pain. This includes the conduct of clinical trials to evaluate the safety and efficacy of medications and other interventions for the prevention and treatment of acute, chronic, and cancer-related pain.

For example, researchers at the University of Pennsylvania are interested in the use of gabapentin for the prevention of pain following mastectomy and thoracotomy. While several investigators have described success using this method, no well-controlled clinical trial has clearly demonstrated the safety and efficacy of this

treatment. Unfortunately, gabapentin is not a branded drug, and as a result no pharmaceutical firm will pay the large cost to conduct such a study. Having said that, many people could be helped if a well-designed clinical trial demonstrated that short-term medical interventions at the time of surgery could lower the incidence of long-lasting chronic pain. The availability of funding for pain-related research could have immediate impact on the lives of people suffering from chronic pain.

Health services research questions and hypotheses:

Pain is a common problem, and one of the most common reasons patients obtain physician care. In spite of this, there is wide variability in the treatment methods used to treat acute and chronic pain. The development and implementation of disease-specific measures of health for the pain population may lead to improved outcomes for patients with pain.

Impact on Health of Pennsylvanians

As chronic pain is more prevalent with increasing age, the number of people with pain will continue to increase as the Pennsylvania population ages. In 2006, over 385,000 people over the age of 45 years were diagnosed with osteoarthritis in Pennsylvania. Pain and stiffness is often the presenting symptom of osteoarthritis, and this pain often becomes worse over time. Pain therapy may include the use of non-steroidal anti-inflammatory drugs, which are associated with numerous adverse effects, including alteration of platelet function, upper gastrointestinal bleeding, and alterations in hepatic and renal function. More severe pain may require the chronic use of potent opioids. Unfortunately, in spite of the widespread use of opioid analgesics, limited information is available regarding the long-term safety and efficacy of these drugs. Improved understanding of the risks associated with current pain therapy, as well as the development of new pain therapy may improve patient outcomes and quality of life.

Cancer continues to be a significant source of illness for Pennsylvanians. In 2007 is estimated that over 9,000 women were diagnosed with breast cancer. These individuals often undergo surgery as part of their treatment. Unfortunately, patients undergoing breast cancer surgery are at increased risk of chronic pain. Chronic symptoms in the breast and arm areas were found to be present in as many as 56% of breast cancer survivors. Likewise, in 2007 is estimated that over 10,000 people were diagnosed with pulmonary cancer, and persistent pain occurs in up to 80% of patients who undergo a thoracotomy. Of the 19,285 people estimated to be diagnosed with breast cancer or pulmonary cancer in 2007, over 13,000 may have developed chronic pain as a result of their treatment. There is evidence that the administration of gabapentin or pregabalin at the time of surgery may significantly lower the incidence of chronic pain following surgery. In addition, several other options have been studied to prevent pain following these types of surgery. Additional clinical research may allow for the development of novel treatments that may prevent chronic pain before it occurs.

Aggressive therapies for cancer have led to improved long-term survival. From 1996 to 2002, the 5-year survival rate for all cancers was 66%, which represents a significant increase from 51% from 1975 to 1977. It is estimated that there are 10 to 12 million cancer survivors alive in the United States. Life expectancies after a cancer diagnosis will likely continue to increase with new developments in cancer treatments.

Cancer survivors face residual problems that affect their ongoing level of functioning, quality of life, and need for health care. Pain among cancer survivors is a growing problem. The Institute of Medicine reported that pain in cancer survivors is a significant health care concern, and called for more research to better understand the magnitude of survivor pain syndromes and how they can be effectively managed. The non-formula tobacco grant program provides a unique opportunity to allow Pennsylvania researchers to accelerate their research efforts to improve therapy intended to prevent and treat chronic pain.

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Health Research Priority

PAIN, ACUTE AND CHRONIC

We propose that the topic include the epidemiology, mechanisms, prevention, and treatment of pain across all health disorders, as well as the mechanisms, prevention, and treatment of complications of pain, such as the pain-evoked components of anxiety, depression, cognitive impairment, and disability. Despite its vast public health impact, pain is an “orphan disease” with regard to NIH funding, accounting for over 20% of visits to physicians and 10% of prescriptions but less than 0.5% of NIH funds. The meager funding is even more anomalous in light of evidence that the specialized anatomy and chemistry of brain structures carrying pain make it straightforward to dissect. Scientists have made rapid progress in identifying pain mechanisms in animals, and with clinical scientists, have developed new treatments that are very effective in limited niches, such as migraine and major surgery. Pennsylvania health science institutions already have a large share of the leading pain researchers. Selection of pain research as a CURE topic could assure that the state’s health science schools and companies will be dominant in the expansion of pain research and products as the population ages and health care costs make treatment of symptoms more important than more expensive palliative treatments

Pain has an especially severe impact in the two million Pennsylvania residents who are age 65 or older. Half experience daily pain, most commonly from osteoarthritis and low back pain. Unfortunately, many older adults are unable to benefit from the most common pain drugs because of their toxicity in this group. When pain is chronic, many older adults develop depression and anxiety, loss of cognitive and physical function, social isolation, loss of appetite and impaired sleep. These complications may lead to loss of ability for self-care, with enormous financial costs. Despite these costs, there has been rather little study of painful disorders in older patients. Multiple lines of evidence indicate that older adults with chronic pain are not simply a chronologically older version of young chronic pain patients. For example, "chronic widespread pain" or "fibromyalgia" in younger patients appears to be a disorder in which the central nervous system amplifies painful inputs, and is associated with greatly elevated prevalence of mood and anxiety disorders. "Chronic widespread pain" is also common in older adults. Geriatric pain experts suggest that it is less influenced by emotional disorders, and may be caused by a greater burden of degenerative changes, but rigorous studies are needed to guide treatment

Pain also causes a disproportionate burden on ethnic minorities. Multiple studies show consistent undertreatment of African Americans and other minorities for cancer pain, acute postoperative pain, chest pain, acute pain in the emergency department, and low back pain. Elderly cancer patients in nursing homes were found to be particularly at risk. African American patients in nursing homes had a 63% greater probability of no pain treatment than non-Hispanic white patients. African Americans were less likely to have pain documented in their charts. African American children and adolescents are frequently undertreated for the pain of sickle cell disease, which affects 50,000 individuals in the US and 4,000 in Pennsylvania. There are no large clinical trials on the optimal management of painful vasoocclusive crisis, the hallmark of the disease. Poor management of this pain causes poor school attendance, loss of work, and abnormal psychosocial development. The distrust caused by poor pain management leads some patients to avoid follow-up care to prevent end organ damage, which may cause premature mortality.

Biomedical research questions and hypotheses:

Our overarching hypothesis is that pain is so fundamental a process in adaptation, physiological regulation, development, and motor function that an integrated study of pain on the molecular, physiological, and clinical level can significantly improve our ability to treat most diseases; favorably influence the development of children and adolescents with pain; and improve the adaptation, cognition, mood and disability of any individual with pain once these insights are disseminated into practice.

Pain is an opportune target for therapeutic attack because the first few cells signaling pain from the periphery are highly specialized for pain and grouped with other pain cells in nerve ganglia and spinal cord. Further, most types of pain share many of the same molecular mediators. We hypothesize that researchers can discover new therapeutic target molecules whose manipulation will have fewer side effects than current pain treatments (opioids, NSAIDs, anticonvulsants, antidepressants) by approaches combining physiological, expression and proteomic studies in these specialized pain-mediating neural cells with genome-wide genetic association studies in animals and humans.

Clinical research questions and hypotheses:

We have accumulated evidence that chronic nonmalignant pain in cognitively intact older adults impairs brain function (i.e., neuropsychological performance) and that this impaired function may be a key link between pain and physical disability. As an extension of these findings, we hypothesize that chronic pain may accelerate the rate of decline in cognitive function among cognitively intact older adults as well as those with Alzheimer's disease. We predict that intensive pain treatment with safe modalities (e.g., acupuncture, meditation, acetaminophen) may ameliorate physical and cognitive decline.

Methodological research can multiply the yield of pain clinical trials. We predict that standard methods of clinical epidemiology--an eclectic examination of contributors to variance in the outcome--can be applied to pain clinical trials in a way to at least halve the variance, or make their yield of information equivalent to a doubling of sample size. Plausible variables not yet thoroughly applied to pain trials include patient genotype, style of using pain scales, pain catastrophizing, use of "rescue" analgesic, and gender.

Health services research questions and hypotheses:

We hypothesize that undertreatment of pain in African-Americans, well-documented in ambulatory, inpatient, and long-term care settings is caused by (1) clinicians' biases that African-Americans at higher risk of addiction and (2) patients' overestimate of the risk of opioid addiction due to appropriate medical use. Comprehensive interventions that address both of these factors will reduce the undertreatment of pain. We also hypothesize that the dissemination of individualized management plans for Pennsylvania's 4000 sickle cell disease patients will lead to decreased hospitalization for uncomplicated pain crises, decreased length of hospital stay, and improved school attendance and psychosocial development.

We predict that documented high-yield interventions to reduce the costs and disability in pain patients can be translated to health systems in Pennsylvania, including: (a) a back-to-work cognitive-behavioral intervention in individuals with back pain that reduced disability costs across Nova Scotia; (b) an postoperative anesthesiological intervention in older patients with severe pain after limb trauma that reduced disability, pain levels, and analgesic use 6 months later in a New York City hospital system.

Impact on Health of Pennsylvanians

Pain is the reason for more than 20% of visits to physicians and pain drugs make up about 10% of prescriptions, so we can estimate that the medical costs of treating pain are 10-20% of health care costs, or \$200-400 billion/yr

in the US. In addition, reduced work capacity or disability payments cost the US another \$100 billion/yr. Prorated to the size of the Pennsylvania population, 4% of the US total, the cost estimate of pain in Pennsylvania is \$12 – 20 billion/yr.

Pain is the most common symptom of serious physical illness. In the SUPPORT study of 10,000 hospitalized patients with critical illnesses including cancer, heart, liver, lung, or multiorgan system failure, over 50% of patients reported pain and almost reported 20% persistent and severe pain.

Pain has an especially severe impact in the two million Pennsylvania residents who are age 65 or older. Half experience daily pain, most commonly from osteoarthritis and low back pain. Pennsylvania-wide Medicare expenditures on low back pain alone increased by 387% from 1991 to 2002, largely for CT scans, MRIs, spinal injections, and spine surgery that are not indicated by consensus guidelines. Twenty percent of pain-free individuals over 60 meet radiographic criteria for spinal stenosis, so pain and radiological findings alone often prompt unnecessary surgery. Conversely, great savings could be realized by adhering to more rigorous clinical diagnostic criteria.

Unfortunately, many older adults are unable to benefit from the most common pain drugs because of their toxicity in this group. When pain is chronic, many older adults develop depression and anxiety, loss of cognitive and physical function, social isolation, loss of appetite and impaired sleep. These debilitating complications may lead to loss of ability for self-care, with enormous financial costs. Despite these costs, there has been rather little study of painful disorders in older patients. Multiple lines of evidence indicate that older adults with chronic pain are not simply a chronologically older version of young chronic pain patients. For example, "chronic widespread pain" or "fibromyalgia" in younger patients appears to be a disorder in which the central nervous system amplifies painful inputs, and is associated with greatly elevated prevalence of mood and anxiety disorders. "Chronic widespread pain" is also common in older adults. Geriatric pain experts suggest that it is less influenced by emotional disorders, and may be caused by a greater burden of degenerative changes, but rigorous studies are needed to guide treatment

Pain also causes a disproportionate burden on ethnic minorities. Multiple studies show consistent undertreatment of African Americans and other minorities for cancer pain, acute postoperative pain, chest pain, acute pain in the emergency department, and low back pain. Elderly cancer patients in nursing homes were found to be particularly at risk. African American patients in nursing homes had a 63% greater probability of no pain treatment than non-Hispanic white patients. African Americans were less likely to have pain documented in their charts. African American children and adolescents are frequently undertreated for the pain of sickle cell disease, which affects 50,000 individuals in the US and 4,000 in Pennsylvania. There are no large clinical trials on the optimal management of painful vasoocclusive crisis, the hallmark of the disease. Poor management of this pain causes poor school attendance, loss of work, and abnormal psychosocial development. The distrust caused by poor pain management leads some patients to avoid followup care to prevent end organ damage, which may cause premature mortality.

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Health Research Priority

Sickle Cell Disease (SCD): Screening and therapy of lung complications that represent the most common cause of death in young adults. SCD affects approximately 72, 000 primarily African Americans and Hispanics, including an estimated 5000 persons in the Commonwealth. It has recently been discovered that a full 1/3 of young adults with SCD are developing pulmonary hypertension, an elevation of the pressure in the blood vessels of the lungs, and that these patients are at 10-times the risk of death as the general population with SCD (Gladwin; New England Journal of Medicine 2005). In fact 40% of these patients will die within 40 months if not identified and treated. There exist simple modalities to diagnose this complication using ultrasound, similar to that employed routinely in all pregnant women, yet this diagnostic modality is not available for the 5000 patients in Pennsylvania. There are now seven (7) FDA approved medications that can be used to treat this complication, in addition to proven sickle cell specific therapies such as hydroxyurea, which is a generic low cost and effective medication. We propose to initiate comprehensive outreach and screening protocols, linked to tertiary referral to comprehensive treatment programs, of the pediatric and adult sickle cell population of PA to identify and treat end-organ lung complications in an effort to improve the quality and quantity of life of this underserved population.

Biomedical research questions and hypotheses:

The development of high blood pressure in the lungs in young adults with sickle cell disease is associated with heart failure, shortness of breath, reduced exercise tolerance and increased risk of sudden death. We propose the following health service and screening research projects aimed at increasing the diagnosis, access to care, and therapies available for this complication. Aim 1. Develop a community based screening program that will identify sickle cell patients at high risk of developing pulmonary hypertension. Plasma samples will be screening using a biomarker called N-terminal brain natriuretic peptide (NT-BNP), which is released by the heart during pressure overload. Patients with NT-BNP levels greater than the 75th percentile will be screened for renal dysfunction and cardiac ultrasound. Patients identified with pulmonary hypertension will be referred to UPMC for right heart catheterization for definitive diagnosis. These studies will define a novel population based screening and risk assessment paradigm. Aim 2. Placebo controlled trials of sildenafil and hydroxyurea will be performed. Aim 3. Population based epidemiological studies will determine age dependent risk in both pediatric and adult patients.

Clinical research questions and hypotheses:

Aim 1. We hypothesize that patients with high levels of NT-BNP, and normal kidney and left heart function by cardiac ultrasound, will be at high risk for having pulmonary hypertension and right heart dysfunction. These patients will be at the highest risk of death and this risk assessment and diagnostic screening protocol can be

extrapolated to other populations at risk of pulmonary hypertension, such as obese patients with metabolic syndrome (diabetes) and patients with emphysema.

Aim 2. We hypothesize that the institution of hydroxyurea and sildenafil (viagra- a phosphodiesterase inhibitor that vasodilates the lung blood vessels) will improve clinical outcomes in this at-risk population.

We also hypothesize that systematic use of hydroxyurea in Pennsylvania can lead to decreased incidence of sickle cell related crises, decreased rate of organ damage and improved survival. Community based treatment trials will reduce state-wide morbidity associated with SCD.

Aim 3. We hypothesize that children and adolescents with SCD who have mild to moderate pulmonary hypertension will be at high risk of death in early adulthood (ages 17-25).

Health services research questions and hypotheses:

We hypothesize that community based screening and central referral to SCD treatment centers that use individualized pain management plans, dedicated areas within the hospital for the care of sickle cell related vasoocclusive pain crisis, and collaborative hematological, pulmonary and cardiology services will improve patient quality of life, outcomes and health care utilization. Endpoints to follow include patient pain scores and symptom diaries, a decrease in patients requiring hospitalization for pain management, a decreased average length of stay, a decrease in the rate of readmission, and ultimate increases in life expectancy. We hypothesize that the provision of quality multidisciplinary programs of designed to transition to pediatric patients (240 at UPMC alone) to adult health care will improve access to comprehensive care and decrease utilization of emergency room services, reduce rates of hospitalization, and ultimately improve survival. We hypothesize that a statewide web based secure sickle cell registry, linked to cardiopulmonary screening programs, will provide critical population data that can be used to benchmark state-wide health quality improvements, target populations and regions at risk, and improve regional health education.

Impact on Health of Pennsylvanians

Delivery of Health care services to patients with SCD is frequently fragmented and of poor quality. Examples of this systematic problem: 1) Many SCD patients receive episodic care in the emergency room as opposed to comprehensive care in the clinic outpatient setting. An emergency room treatment model limits access to trained experts in SCD and has been shown to limit access to proven therapies, such as hydroxyurea. This adversely impacts the quality of care, quality of life, health care costs and ultimately, patient survival. 2) Approximately 10% of children with SCD account for over 50% of total health care expenditures. 3) About a third of adult patients without access to central comprehensive care programs constitute more than 70 percent of visits to the emergency rooms and 40 percent of hospitalizations. 4) Approximately 50% of patients admitted for acute painful episodes are readmitted within 1 month after discharge, and 16% within one week after discharge. These rebound admissions occur secondary to premature discharge, drug withdrawal and recurrence of pain crises, and represent a major opportunity to reduce health care utilization and patient suffering. 5) Inadequate pain management results in a prolonged course of pain crises and prolonged duration of hospitalization. 6) Poor management of vasoocclusive pain crises is a major cause of patient distrust of the health care system and may adversely impact access to comprehensive or emergency care services, thus further increasing morbidity as well as utilization of health care resources.

Despite considerable advances in the treatment of SCD, most patients have poorly controlled pain, require recurrent hospitalization, and the median age of survival for men is 42 years and for women is 48 years.

There exists a statewide and National failure to transition care of the aging pediatric population to comprehensive adult care programs. This transition gap pushes large populations to the emergency room setting and dramatically reduces access to drugs, namely hydroxyurea, that are necessary to reduce end-organ injury. As a result, adult patients begin to develop end-organ complications such as pulmonary hypertension and kidney failure. End-organ complications that develop in the absence of comprehensive therapy include: 1)

Stroke: 10% of children develop stroke and 22% have silent strokes on MRI, which are associated with neurocognitive sequelae and increased risk of overt clinical stroke. This complication is preventable with transfusion and hydroxyurea therapy. 2) Pulmonary hypertension is a deadly complication that affects over 30% of adolescents and adults, and 40% of all patients by the age of 40. Pulmonary hypertension is associated with a 10-fold increase in risk of premature mortality and accounts for over 35% of all deaths in patients with SCD. Transfusion therapy and hydroxyurea can prevent this complication and more than seven (7) FDA approved medication to treat this complication are now available. 3) Kidney and liver failure: With increased age there is an accumulation of sickle cell related organ damage with more than 50% patients develop irreversible organ damage by the time they enter the fifth decade of life.

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Health Research Priority

Alzheimer's disease (AD) is growing concern in the health care as the population ages. Our previous studies revealed that glycosaminoglycans (GAGs) may play a pivotal role in the pathogenesis of AD, and may open an entirely new avenue in the treatment of neurodegenerative disorders including AD. However, these preliminary data require further studies.

Stress is not only one of the main causes of cardiovascular lesions, but it is associated with complex hypothalamic functions including growth, water balance and sexual regulation. Our previous data indicated juxtapositions between the neurons synthesizing stress-related neurotransmitters, and other hypothalamic neurotransmitter systems, indicating that the negative effects of stress may be blocked at hypothalamic level. These intricate neuronal networks require further studies.

The emergence of *Borrelia burgdorferi*, the causative agent of Lyme disease, in the tick population of Pennsylvania, has become a potential health hazard. Moreover, these ticks can also transmit babesiosis. Although preliminary studies revealed that a significant percentage of the tick population is infected with borrelia, many Lyme disease cases may go unnoticed. These diseases require studies regarding the frequency and distribution of the infected ticks.

Biomedical research questions and hypotheses:

Alzheimer's disease: Previous data indicate that glycosaminoglycans (GAGs) exert neuroprotective/neurorepair properties in the animal models simulating the lesions of neurodegenerative disorders. Are they beneficial in the treatment of AD? Which components of the GAG mixtures exert the most beneficial effects? Can AD be used as a therapeutic adjunct in other neurodegenerative diseases as well?

Stress: Hypothalamus is believed to be a coupling site between the stress signal and the stress response. Which of the neurotransmitter systems participate in the translation of the stress signal? What is the exact morphology and physiology of the neuronal circuits involved? What neurotransmitters/neurohormons may be used to influence the stress response? Can these signals be used to treat anxiety disorders, or help to understand the intricate circuitry associated with emotional and physical stress? Can cranial osteopathic manipulation be used to affect the neurotransmitter release of the hypothalamus?

Clinical research questions and hypotheses:

Lyme disease/babesiosis: Previous studies revealed that tick population in certain parts of Pennsylvania has been extensively infected with *borrelia burgdorferi* and *babesia* species. In contrast to these findings, relatively small numbers of Lyme disease cases are reported each year. Since the symptoms of Lyme disease often imitate the symptoms of other disorders, Lyme disease cases may go unnoticed. What is the prevalence of the infected

tick of different species in Pennsylvania? Which regions of the state propose the most significant health hazard? What is the most effective way to inform the local medical community of the health risk?

The majority of neurological deficits affecting children with autism are derived from a common neurodevelopmental injury. Do all autistic individuals share certain neurological deficits (e.g. nystagmus, elevated auditory thresholds)? How strongly can routinely observed neurological deficits predict a diagnosis of autism?

Once these deficits are clearly documented, it may allow physicians or other health care workers with a tool that can be utilized for early intervention or screening. In fact, a strong association with a certain neurological deficit may permit screening for autism shortly after birth.

Health services research questions and hypotheses:

What is the impact of innovative medical education programs (e.g. accelerated pathways) on the supply of physicians in PA, and on the quality of care delivered?

What is the impact of education in physician competency (e.g. professionalism, interpersonal skills, system-based practice, etc.) on the quality of care delivered to Pennsylvanians?

Impact on Health of Pennsylvanians

Alzheimer's disease (AD) is a progressive and irreversible brain disorder that is manifested in dementia, motor lesions and behavioral deficits. Since as many as 10% of the population is affected by AD above 65 years of age in the United States, AD is becoming a growing concern in the health care. Moreover, the extended and often ineffective treatment of the AD patients puts an enormous pressure on the health care budgets every year. Our previous studies revealed that glycosaminoglycans (GAGs) exert neuroprotective effects in several animal models simulating the lesions of AD. Since GAGs are relatively inexpensive to produce, these compounds may open an entirely new avenue in the treatment of neurodegenerative disorders including AD.

Stress is one of the leading factors in the cardiovascular diseases that are associated with high mortality. Moreover, stress affects complex hypothalamic functions including growth, water balance and sexual regulation. Our previous studies indicated that hypothalamus is one of the major sites where the stress signal translates into stress response. It is also conceivable, that the neurons responsible for the secretion of stress-related neurotransmitters/neuromodulators may contain estrogen receptors, and thus, may respond to estrogen treatment. These intricate neuronal networks, however, require further studies.

Lyme disease, and causative agent, the *Borrelia burgdorferi*, infecting the tick population of Pennsylvania, has become a potential health hazard in the recent years. Although preliminary studies revealed that a significant percentage of the tick population is infected with borrelia, many Lyme disease cases may go unnoticed. Moreover, these ticks can also transmit babesiosis. These diseases require studies regarding the frequency and distribution of the infected ticks.

Early diagnosis of autism is essential for early intervention that may improve the quality of life of individuals with autism.

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Health Research Priority

Poor oral health has profound effect on quality of life. Experience of pain, endurance of dental abscesses, problems with eating and chewing, or embarrassment about the shape of teeth or about missing, discolored or damaged teeth can adversely affect daily lives, well-being. Emerging research links periodontal status with overall systemic health: Untreated periodontitis complicates diabetes, rheumatoid arthritis, atherosclerosis, other cardiovascular conditions. Respiratory illness may be mediated by subgingival bacteria aspirated to the lungs, setting off chronic inflammatory response. In pregnancy, treatment of periodontal disease improves mother's health and may affect birth outcomes. Core modifiable, preventable, risk factors---and infection---are the common denominators. Diet and poor hygiene, smoking, alcohol consumption, risky behaviors causing injury, and stress---exacerbate infection, inciting the inflammatory cascade, which appears to compound systemically. Managing periodontal disease depends on the availability and accessibility of oral healthcare as much as novel treatment and detection modalities. Healthcare disparities are multivariate, complex, and sourced in a healthcare system with demonstrable social strikes against it. Reduction of risk to disease across the lifespan is possible when oral health services are oriented toward primary, systemic, healthcare and lifestyle disease prevention.

Biomedical research questions and hypotheses:

Medical and dental literatures show that destructive periodontal disease results---and worsens, or improves---by the interaction of factors related to the infectious agents (bacterial species, the nature of the biofilm); the host (systemic health and perhaps age; personal oral hygiene rigor, bad habits, or genetics), and the environment (access to and quality of oral healthcare). This extremely common source of chronic infection (dental disease) is linked to a variety of systemic conditions causing morbidity and mortality. Treatment of periodontal disease can put off or allay the development of these same diseases. Adverse implications for individuals affected by social factors like racial, ethnic, or age discrimination, lack of education, low income, or occupation loss, are real. Biomedical Research Questions: (1) What is the precise nature of the mediating, causal link(s) periodontal disease:chronic systemic disease? Essential is complete biochemical, microbiological, cognizance of the role of infection and inflammation in translating disease across the body's systems. (2) What are the relationships oral health: various systemic diseases; the pathways of the transmission of disease (or health); the plausible biologic causes for the relationships?

Clinical research questions and hypotheses:

Clinical Research Questions:

(1) How do novel treatment approaches (such as full-mouth disinfection, proposed by this periodontal investigator) improve the conditions of periodontal disease (as measured, for instance, by the periodontal disease indicators)? (2) Is it possible to deliver materials to the tissues that disinfect and stimulate healing at the same time? (3) How do novel periodontal treatment approaches improve general systemic health? (4) How does change in the systemic condition (improvement in health if diabetic, for instance) create change in the

periodontal condition? (5) Can the treatment of chronic periodontal disease put off the development of systemic disease? (6) If periodontal disease and systemic disease are linked by the common risk factors, what effect will controlling the risk factors have on both? [Examples of this are the periodontal:systemic health effects of smoking cessation programs, or nutrition counseling programs (as among WeightWatchers or Curves program attendees, or the effect of establishing a WeightWatchers or smoking-cessation program in a workplace)].

Health services research questions and hypotheses:

Health Services Research Questions:

(1) How does a concerted program of oral health promotion intervention (with/without application of novel treatment approaches) reduce or ameliorate oral health inequities [improving both periodontal and general systemic health] among disadvantaged citizens? This investigator has proposed this idea to colleagues on a Pennsylvania-wide basis: academic dental departments and dental hygiene programs in Allegheny, Erie, Westmoreland, Philadelphia counties (to begin) coordinate volunteerism via dental/dental hygiene professional societies and partner with faith-based organizations (like the Salvation Army), to reach deep into vulnerable regional populations to create mini-oral-health clinics to provide care within disadvantaged communities. (2) Assess the periodontal and oral health of the State's most underserved population(s), to determine unmet needs; utilization patterns of dental services; access to care barriers; and oral health behaviors, leading to (3) Establishing a 'dental healthcare home' at the University of Pittsburgh---accessible, culturally competent, coordinated---as means to reduce regional disparities in dental care.

Impact on Health of Pennsylvanians

Oral diseases are the most common of the chronic diseases and are important public health problems because of their prevalence, impact on individuals and society, and their expense of treatment---in some countries the fourth most expensive disease to treat. The determinants of oral diseases are the common risk factors---bacteria, smoking, alcohol, risky behaviors causing injuries, and stress. Effective public health methods are available to prevent oral diseases, and health policies should be reoriented to incorporate oral health, targeting the common risk factor approach for health promotion (Sheiham 2000; 2005).

Plaque and calculus cause dental caries, periodontal disease, tooth loss, and oral mucosal lesions. Oropharyngeal cancers, AIDS-related oral disease, and oral-dental trauma are global public health problems. Two-thirds of the U.S. population has subgingival calculus (bacterial biofilm requiring scaling/root-planing) and one-third have full-blown periodontal disease, periodontal pockets ≥ 4 mm. The young are not healthier: Among U.S adolescents, overt gingivitis and gingival bleeding is present in 82 percent. Periodontal disease is attributed to gram-negative bacteria and is an inflammatory process, which mounting research shows is linked similarly, if not causally, to major systemic illnesses like diabetes and obesity, cardiovascular diseases, and autoimmune disease, especially rheumatoid arthritis. It is well-known that diabetic control may be negatively influenced by the presence of chronic infection like periodontitis, and that treatment for periodontal condition improves diabetic status. Consider obesity: adipocytes in the adipose (fat) tissues produce quantities of active molecules regulating energy expenditure. Adipocytokines produce the proinflammatory tumor necrosis factor-alpha, elevated in the obese and declining with weight loss. TNF-alpha produced by adipose tissue is a risk for periodontal inflammation, and TNF-alpha produced by periodontal inflammation may be an important influence on insulin sensitivity. This interaction is the likely two-way mechanism between Type II diabetes and periodontal disease (Nishimura 2003). But as Time magazine pointed out, everybody---most dangerously physicians---hates to bring the subject of obesity up. But failing to state the diagnosis and forward a plan is to risk peoples' health.

NHANES data make clear that race and ethnicity, education, and neighborhood are associated with destructive periodontal disease. When socioeconomic status is applied to oral health, minority communities always come up short. Individuals with less than a high-school education and those living in poor neighborhoods are much more likely to have destructive periodontal disease than well-off others. Adult African-Americans (41 percent) show the highest prevalence of disease and the most loss of periodontal tissue, followed by Mexican-Americans (36 percent). White non-Hispanics (18 percent) show the least disease and tissue loss. The same pattern repeats for

each periodontal disease indicator. But when subjects share socioeconomics, differences in gum disease disappear. The state's Hispanic population grew by 118% in the past fifteen years, and the state's Black population by twenty. Both groups report that one of their current major behavioral health risk factors is needing to see a doctor but not being able to because of cost (PA Dept. of Health statistics 2007). Pressing need exists---people need to see a dentist but don't know where to turn, or how to pay. It is our experience that the first healthcare expense sacrificed is dental. The federal GAO admits, by Medicaid's own data and despite the known prevalence of tooth decay among subscribers, only about a third of Medicaid children received any dental service in fiscal 2005. In January 2007, that trouble finding a Medicaid dentist when a Baltimore family needed one cost them the life of their twelve-year-old son, who died after six weeks of suffering from the bacteria from a tooth infection that had spread to his brain. Cost to the taxpayers: over a quarter-million dollars. Poor people---especially kids---should not die because of the paperwork burden to get them a healthcare treatment.

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Health Research Priority

Cocaine abuse and dependence is a major health issue in Pennsylvania. Both powdered cocaine and crack cocaine are readily available throughout the state. Moreover, Pittsburgh is a distribution center for various locations in western Pennsylvania, eastern Ohio, and northwestern West Virginia. Despite the public health significance of cocaine abuse and dependence, little progress has been made on the development of evidence-based treatments for this disorder. With developments in understanding the neurobiology of addictive disorders including cocaine dependence, there is now the opportunity to conduct studies that help in understanding the addictive process and the road to recovery and abstinence.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

Can current psychosocial treatment methods for cocaine dependence be improved? In order to allocate services more efficiently, is it possible to determine the types of patients that respond to different forms (duration; format; setting) of treatment? What is the nature and amount of improvement in neurobiological disruptions that might occur over the course of cocaine treatment? Do certain neurobiological abnormalities predict treatment response for those with cocaine dependence? Is the degree of treatment-related improvement in neurobiological disruptions associated with lower risk of relapse following cocaine treatment? Can we use knowledge of neurobiological impairments associated with cocaine use to improve treatment?

We hypothesize that cocaine dependent patients with relatively higher dopamine transporter levels in certain areas of the brain (caudate and putamen) will have poorer response to treatment. Relatively higher dopamine transporter levels are also hypothesized to be related to the motivation to use again after initial abstinence (higher craving and anhedonia).

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Cocaine abuse is a major health issue throughout Pennsylvania. Of those aged 12 or older, 2.2% of Pennsylvanians have used cocaine in the past year (6.7% of those aged 18 to 25) and 12% have used cocaine in their lifetime. For many years now, cocaine has been the primary drug threat in Pennsylvania based on its high level of abuse, ready availability, widespread distribution, and association with violence. According to the

DEA, cocaine is the drug of choice in urban and suburban minority population centers. Cocaine abuse is high in Philadelphia, but there are also substantial levels of cocaine abuse in other parts of the state. The Pittsburgh Bureau of Police reports that crack cocaine is the drug of choice for both teens and adults in Pittsburgh. Cocaine, particularly crack cocaine, remains the principal drug of abuse in Erie, Harrisburg, and Johnstown.

Cocaine is the primary drug-related cause of deaths, emergency department visits, and treatment admissions to publicly funded facilities in Philadelphia. Many of those who have become addicted to cocaine have lost their jobs and rely on public assistance. Crack cocaine abuse and distribution often are associated with street violence and other crimes committed by drug abusers in need of money to buy drugs, including thefts, robberies, burglaries, shoplifting, and prostitution.

Certain segments of the Pennsylvania population are disproportionately involved with cocaine use. In Pennsylvania drug treatment programs, about half of the people admitted for treatment for cocaine are African-American. Moreover, cocaine appears to be particularly a problem for African-American women. Data from the last year available of the Arrestee Drug Abuse Monitoring Program indicate that, in Philadelphia, 45.4 % of female arrestees who were tested for drug use in Philadelphia tested positive for cocaine, more than for any other drug. Of African-American female arrestees tested for drugs, 53.0 % tested positive for cocaine. In comparison, 38.7 % of female white arrestees tested positive for cocaine. Among men, 48.6 % of male white arrestees who were tested for drugs tested positive for cocaine and 26.0% of African-American male arrestees tested positive for cocaine. Thus, more than twice as many female African-American arrestees tested positive for cocaine than male African-American arrestees.

Short-term health effects from cocaine include increased heart rate and blood pressure, as well as tremors, vertigo, muscle twitches, and paranoia. Other consequences of cocaine use include chaotic heart rhythms and seizures, and stroke. Studies have found that young drug abusers are over 6 times more likely to suffer a stroke than nondrug abusers, with cocaine identified as the drug used most often in drug-related strokes. Long-term use may lead to loss of sense of smell, throat irritation, and deterioration of the nasal septum. Prolonged ingestion of cocaine can cause bowel gangrene resulting from decreased blood flow. Long-term use also can cause aortic dissection (a tearing in the lining of, or rupturing of, the aorta), a condition that may result in death. About three quarters of cocaine dependent individuals have a co-occurring mental disorder. Crack cocaine has been identified as a significant factor in the transmission of sexually transmitted diseases and AIDS (through the promotion of high risk sexual behaviors and the exchange of sex for crack). Pregnant women who use crack cocaine expose their developing infants to the adverse health effects of cocaine, including constriction of blood vessels in the placenta and umbilical cord leading to a lack of oxygen and nutrients to the fetus, poor fetal growth, and impaired development. Overdose of cocaine can result in death.

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Health Research Priority

We propose that the Commonwealth of Pennsylvania consider blindness and visual impairment as a research priority. Blindness and visual impairment are major public health issues due to their effects on an individual's quality of life, morbidity, mortality, education, economic productivity and financial cost to society. Every year, 75,000 Americans become blind or visually impaired; and, according to data from the 2000 census statistics on Americans age 40 or higher, more than 1 million people are blind (~1%) and 3.4 million are visually impaired (~3%). Visual impairment and, ultimately, blindness usually cannot be cured. The leading causes of blindness in the United States are cataract, glaucoma, and macular degeneration. Glaucoma can be treated with medications, laser and conventional surgical techniques but cannot be cured and damage cannot be reversed. Age related macular degeneration (ARMD) can be treated with laser and, more recently, with retinal pharmacotherapy; the rate of progression may be slowed with vitamins and minerals, but again, there is no cure for ARMD. Finally, while cataract can be removed, it requires surgery (a solution that is not always available and carries risk). There exists no current medical treatment to slow or reverse cataract. Thus, research is needed to identify and develop new treatments and cures for eye diseases leading to blindness.

Biomedical research questions and hypotheses:

Hypothesis: Establishing a disease's biological foundation is critical to developing appropriate therapeutic and preventive interventions.

While many eye diseases can be treated, they cannot be cured, except through surgical procedures such as in the case of cataract. Understanding the biological underpinnings of disease has become an extraordinarily valuable tool in the quest to better prevent and treat diseases. Therefore, evaluating eye diseases using standard and state-of-the-art diagnostic techniques and technologies should assist in identifying the types of molecular abnormalities occurring in these diseases. The techniques and approaches available to address this hypothesis are many and include structural biology, computational biology, DNA microarray, protein analysis, and animal models to name a few. Establishing a disease's biological foundation is critical to developing appropriate therapeutic and preventive interventions. As the National Institutes of Health have established the roadmap for research, including a strong emphasis on translational research, so should the Commonwealth follow in this path.

Clinical research questions and hypotheses:

Hypothesis 1: Access to care is a major factor affecting the health of Pennsylvanians.

When refractive error accounts for 83% of visual impairment, we are facing a major problem in providing appropriate health care to the residents of this state. We hypothesize that this is only the tip of the iceberg, and that other blinding diseases, such as diabetes, glaucoma, macular degeneration and cataract are going

undetected and untreated as well, resulting in preventable visual impairment and blindness. We further hypothesize that care access issues are disproportionately prevalent among the poor and underprivileged, and perhaps among those living in rural areas as well.

Hypothesis 2: The environment has a major influence on diseases leading to visual impairment and blindness. We will identify correlations between environmental factors and differences in blindness and visual impairment rates, age of onset, and disease severity, as well as discern whether any Pennsylvania-specific conditions contribute to the incidence of visual disease. The large differences in urban versus rural areas and levels of pollution in PA are expected to result in differences in prevalence of eye diseases.

Health services research questions and hypotheses:

Hypothesis: The incidence and prevalence data required to plan for and meet the need for adequate eye care in the Commonwealth of Pennsylvania are lacking.

According to the 2004-2008 Commonwealth plan on aging, health and wellness are the highest priority to the elderly in Pennsylvania. Vision loss is the number one feared disability in aged individuals and the main contributor to them giving up an independent lifestyle. Pennsylvania houses the second largest proportion of elderly individuals in the United States. As the percent of aged individuals increases, which is likely as the nation's "baby boomers" reach 65, the PA health care system will face an inevitable and drastic increase in demand for resources due to blindness and visual impairment. Epidemiological surveys of blindness and visual impairment in Pennsylvania are necessary to determine the actual extent of eye disease in the Commonwealth. Knowledgeable health care policy and planning requires more information on the prevalence of eye disease in Pennsylvania than is currently available.

Impact on Health of Pennsylvanians

Pennsylvania has a greater than average burden of blindness. This primarily has to do with the burden of disease related to Pennsylvania's aging population. Pennsylvania had the 5th largest elderly population in the US in 2005 (~1,890,974) with 15.2% of its population 65 and older, behind only Florida, compared to 12.4% nationally. In Allegheny County, 17.1% of the population is over 65. In addition, there is racial disparity, as Pittsburgh's African American population is 27.1% (national 12.8% (2000, 2005 census)), and Pittsburgh's Hispanic growth is notable, at 33.4% since the 2000 census, compared to 25.3% growth nationally. Further, there is a national epidemic of obesity, resulting in a high rate of diabetes. Finally, there is the issue of access to care, given Pennsylvania's large rural population.

Advanced Age - The leading causes of blindness (cataract, glaucoma and macular degeneration) and some less prevalent eye diseases (diabetic retinopathy, retinitis pigmentosa, retinitis punctata albescens, retinal-, corneal-, macular- and foveomacular-dystrophies, and others) are highly associated with aging (Figure 1). Pennsylvania (PA), with 15.6% of the population aged 65 and older, is second only to Florida in its concentration of aged citizens. In 2006, the "baby boom" generation will began to turn 60, contributing to the rise in the number of older Pennsylvanians, which is estimated to reach 3 million by the year 2015. Based on its current age distribution, PA can expect to bear an inordinate and increasing burden of personal and economic cost due to blindness and visual impairment. Indeed, the 2000 US census shows that PA is ranked fifth in the number of individuals afflicted with cataracts and is second only to Florida (20.3%) in the proportion of individuals afflicted with cataract (19.1%). PA also ranks ninth overall in the percent prevalence of visual impairment and blindness. The health of the elderly is significantly affected by eye diseases and PA shoulders a large and growing share.

Race – The major blindness-causing diseases exhibit racial disparities. Glaucoma, for example, is twice as prevalent in the African-American population as in Caucasians according to both state and national figures. In addition, although cataracts are overall more prevalent in Caucasians, the incidence of cataract in the PA African-American population (14.9%) is higher than the national average (12.9%). This observation is startling

given that only 7.7% of PA's population is African-American compared to the national average of 9.9%. Both glaucoma and cataracts have been linked to diabetes, a condition reported on the national level to be as much as 2.2 times more prevalent in African-Americans than in Caucasians, and perhaps one source of the racial disparity in visual impairment.

Access to Care – Approximately 6.4% of persons are visually impaired. 83% could achieve good visual acuity with refractive correction, indicative of limitations on access to care and disease detection.

Other Factors – Most eye diseases are caused by a range of genetic events. The types and severity of symptoms, the age of onset, and the response to treatment are highly variable, suggesting a strong component of environmental factors in the development and progression of diseases that lead to visual impairment including exposure to light, radiation, pollutants, eye injury, medications, and stress.

The Financial Impact on the Health Care System of PA- The cost of providing medical service to a population afflicted with blindness extends beyond the burden of disease management. Compared to the general population, people with vision loss have been shown to require admission to nursing homes three years earlier, suffer twice the number of falls, three times the incidence of depression, and four times the occurrence of hip fractures. The percentage of persons 85 and over in PA is projected to increase by almost 50% in the next ten years, a rate significantly higher than the national rate of increase. In addition, visually impaired people are also less likely to be employed.

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Health Research Priority

Despite the wealth of knowledge on the dangers of illicit drug use, and stiff penalties for their manufacture, sale, and consumption, more people today than ever before abuse illicit drugs. This is a serious problem that strains the Pennsylvania healthcare system and burdens the State's economy. Substance abuse is a leading cause of death and serious physical injuries, acute and chronic health problems, criminal behavior and incarceration, and a host of other impairments. Regardless of its pervasiveness and deleterious effects, only a small percentage of substance abusers actually engage in treatment. Unfortunately, there are few opportunities to successfully encourage these individuals to enter treatment. One such occasion is when they enter the criminal justice system. Not only does this offer a "teachable moment" during which individuals may actually consider the negative consequences of their drug use, but it provides diversionary programs such as drug courts, through the promise of non-conviction or reduced sentences, with the leverage necessary to engage clients and facilitate compliance. Moreover, research indicates that nearly 60% of adult arrestees are either arrested on a drug-related offense, are intoxicated at the time of the offense, engage in regular use, or have a history of drug or alcohol treatment. As such, drug courts may serve as a perfect opportunity to address a large proportion of substance abuse throughout the State.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

None

Health services research questions and hypotheses:

Since its genesis in 1989, the drug court model has evolved as among the most effective models for reducing drug use and criminal recidivism, with unmatched empirical support from numerous evaluations, and experimental and meta-analytic studies. Nevertheless, there are still important issues that need to be addressed to improve drug court's efficacy and utility. Specifically, these issues include (1) reliably determining who is and who is not likely to benefit from this model, (2) providing standardized training to judges and court staff on empirically-based behavioral techniques, (3) increasing the acceptance and use of therapeutic medications (e.g., Naltrexone), (4) developing adaptive strategies for adjusting the intensity of judicial supervision and treatment in response to client progress throughout the program, and (5) developing a standard process and outcomes database to efficiently manage the above initiatives. We hypothesize that if drug courts were enhanced in this manner, they would lead to substantial decreases in drug use, criminal recidivism and other associated negative effects. If supported this could serve as a core set of elements to improve and tailor the drug court model throughout the State.

Impact on Health of Pennsylvanians

Between 1990 and 2006, drug violations increased by more than 100% in the Commonwealth, from 6% to 12% of all reported arrests (PCCD Center for Research, Evaluation and Statistical Analysis, 2006). Between 1990 and 2000, the number of reported sentences in the Commonwealth for driving under the influence of alcohol increased by 22% (Ibid 2003). Data from Healthy People 2010 show how alcohol related sentences translate into societal impacts in Pennsylvania: although injury rates for alcohol-related vehicular accidents improved between 2001 to 2005, death rates increased (4.31 to 4.68 per 100,000) over the same period (Healthy People 2010). In fact, in 1998, 14% of the Pennsylvania budget, (\$3.4 billion), was spent dealing with the consequences of substance abuse and addiction, and 4.7% (\$1.14 billion) was spent on criminal justice expenditures for drug-involved offenders (CASA, 2005).

Drug involvement and addiction also have substantial negative impacts on women, children, and families. Up to 80% of child abuse and neglect cases (Child Welfare League, 2001) and nearly 50% of domestic violence cases are substance-abuse related (Catalano, 2006). Moreover, drug and alcohol abuse contribute to higher rates of domestic violence and sexual violence (NIJ, 2007), and women who are drug addicts are more likely to be victims of abuse.

Drug treatment costs, hospitalization for long-term drug-related disease, and treatment resulting from family violence burden our already strapped health care system. In 2000, there were more than 600,000 hospital emergency department drug episodes in the United States. Health care costs for drug abuse alone were about \$15 billion. (DEA, 2005). To make matters worse, drug abuse has been shown to be inextricably linked with homelessness (exceeding 50% of the homeless population), chronic mental illness (in Philadelphia, nearly half of the VA's patients with psychiatric disorders also abuse drugs), and new HIV cases (with the CDC estimating that 36% of new HIV cases are linked to IV drug use).

The negative effects of substance abuse and addiction are not entirely equal opportunity problems, and have been shown to impact certain demographic groups more than others. Although national rates of illicit drug use and abuse do not appear to vary by gender or among racial sub-populations, serious health and social problems related to drug abuse and addiction have been shown to affect minority populations at substantially higher rates than whites. African-Americans accounted for 50% of total diagnosed AIDS cases in 2003. African-Americans account for 50% of HIV infected injecting drug users and Hispanics account for 23%; yet each of these groups represents an estimated 12% of the U.S. population. Minority drug abusers also have disproportionately higher rates of other illnesses associated with injection drug abuse, such as hepatitis B, hepatitis C, and tuberculosis, (NIDA, 2005).

The benefits of drug courts as a means for effectively reducing drug use and crime is exceptionally well documented and as such can go a long way toward reducing the negative impacts discussed above. Further, the drug court model has substantial economic benefits, over the ineffective, disproven alternatives such as incarceration. For example, the cost to incarcerate drug-using offenders is between \$20,000 and \$50,000 per person per year, and it can cost as much as \$80,000 to build a prison cell (NADCP, 2002). Conversely, it costs less than \$2,500 per person per year to sentence drug-using offenders to a comprehensive drug court program. Improving the effectiveness of drug courts by integrating and standardizing therapeutic processes and procedures can have far reaching benefits for the Commonwealth and serve as a national model.

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Health Research Priority

Cigarette smoking remains the leading cause of preventable morbidity and mortality in the United States overall and in Pennsylvania. Lung diseases associated with impaired mucociliary clearance and caused by smoking and secondhand smoke exposure including chronic sinusitis, bronchitis and asthma contribute significantly to this problem. Cigarette smoke damages cilia and increases mucus production and secretion by airway epithelial cells and submucous glands. Therefore, a smoke-exposed airway requires enhanced fluid secretion to maintain mucin hydration and normal mucus clearance. In human airway cells and submucosal glands, fluid secretion is increased by chloride secretion. However, data from our laboratory and others demonstrated that water-soluble cigarette smoke extract inhibited chloride secretion in airway epithelial cells, and data from others demonstrated that smokers have decreased chloride transport in nasal epithelial cells. Taken together, these data strongly suggest that smoke exposure further impairs mucus clearance by decreasing chloride secretion, and that therapies aimed at correcting this defect may be beneficial for treatment of smoking and secondhand smoke-related diseases. To date, however, the molecular mechanisms of inhibition of epithelial chloride secretion are unknown, thereby limiting our ability to propose novel, specific therapies for lung diseases caused by cigarette smoke.

Biomedical research questions and hypotheses:

Published and preliminary data demonstrate that cigarette smoke impairs salt and fluid secretion in human airway epithelial cells and lung submucosal glands. The first hypothesis that needs to be tested, therefore, is that cigarette smoke will impair fluid secretion in both airway epithelial cells and submucosal glands. Because the major pathways for chloride secretion by airway epithelial cells and submucosal glands are well-described, the broader hypothesis can be subdivided into individual hypotheses addressing the individual molecular mechanisms involved in chloride and fluid secretion.

Clinical research questions and hypotheses:

Although smoking and secondhand smoke exposure are significant causes of lung diseases related to impaired mucus clearance, there are clearly people who smoke or who are exposed to second-hand smoke who do not develop disease. Why does one person develop disease another not? One hypothesis to explain this is that people who develop disease are predisposed to inhibition of chloride and fluid secretion by cigarette smoke.

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Smoking and secondhand smoke exposure remain the leading cause of preventable morbidity and mortality among Pennsylvanians. According to the Pennsylvania Department of Health website, a recent Surgeon General's report "affirms the broad scientific consensus that secondhand smoke causes lung cancer, heart disease, sudden infant death syndrome, low-birth-weight, asthma, bronchitis and other serious illnesses and is responsible for tens of thousands of deaths each year in the United States." This same source reports that in 2002-2003 between 23 and 29% of Pennsylvanians smoked with smoking attributable personal health care expenditures over \$4,000,000,000. Notably, for that same period over 50,000 potential life years were lost due to respiratory diseases.

By percentages Black adults are more likely to smoke than non-Hispanic White adults (30% versus 22%). However, there are many more White adults (1,900,000) that smoke than Black adults (270,000). 30% of young adults reported smoking regularly, suggesting that smoking and secondhand smoke-related disease are likely to remain a problem for years to come.

Currently, acute and chronic lung diseases caused by smoking and secondhand smoke exposure are treated mainly with anti-inflammatory medications, antibiotics and bronchodilators. These therapies effectively treat the symptoms of smoke-induced lung disease, but do not address what we think is a major underlying cause of smoke-induced lung disease, namely impaired mucus clearance due to abnormal chloride and fluid secretion by lung airway epithelial cells and glands. We believe that understanding the mechanisms by which cigarette smoke inhibits fluid secretion in the lungs will lead to novel therapies directed at the specific cause and therefore will more effectively treat smoke-induced lung diseases.

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Health Research Priority

The research priority area of focus is the disease of addiction. The abuse of alcohol and/or drugs has had an increasingly significant adverse impact on the public health and public safety throughout the Commonwealth of Pennsylvania. While substance abuse treatment has been provided in Pennsylvania for more than 40 years, the science related to the understanding of addiction and the delivery of addiction services has improved substantially in the past 15 years. Research in the area of addiction has now evolved to the point where questions may be posed that can be answered in a way that can offer substantial improvements in both the reduction of health risks and in the delivery of services for individuals who can benefit from treatment and from risk reduction activities. In addition, there is currently a movement within the field of addiction treatment that has been focused on transforming the treatment system to a more recovery-oriented system of care. This shift to a holistic, person-centered approach has sought to build on the strengths of individuals seeking care by promoting resiliency, encouraging an awareness of cultural competency, and supporting the understanding of behavioral health disparities and the need for trauma-informed services. It also seeks to utilize endemic resources in the community to support the needs of individuals. Research on the efficacy of this movement will be invaluable in shaping services in the future.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

None

Health services research questions and hypotheses:

1. Does the shift in the delivery of substance abuse services from a treatment-focused system to a person-centered recovery oriented system of care result in the availability of a broader array of services, greater access to those services, and improved outcomes for those individuals being served in the transformed system?
2. Existing research findings have demonstrated that the longer individuals stay in treatment for substance abuse issues, the greater their likelihood of successful outcomes, i.e., longer periods of abstinence, increased involvement in the life of the community, etc. Do process improvement activities at service provider sites, such as earlier access to first appointments, facilitated transfers to different levels of care, etc. assist in improving patient retention and thus greater treatment success?
3. Can screening for substance abuse issues in primary health care settings for the purpose of prevention and/or early intervention help to prevent or reduce addictive behaviors?

Impact on Health of Pennsylvanians

Estimates of the number of individuals both in Philadelphia and across the Commonwealth with a substance use disorder, according to the National Survey on Drug Use and Health (NSDUH), have increased substantially in recent years. Research literature in the field of addiction suggests that only approximately 20% of individuals in need of some form of treatment for substance abuse are able to access the care they require annually.

According to the NSDUH, almost 9% of the population of Pennsylvania age 12 or older, or more than 945,000 people have a substance abuse disorder (2005 estimate). That would mean that in Pennsylvania, more than 750,000 people annually have a substance abuse disorder for which they are not receiving care. In Philadelphia, the estimate of the number of people with a substance abuse disorder is more than 116,000. For the most recent year, the number of individuals receiving substance abuse treatment services was approximately 25,000, consistent with the findings in the literature. While the supposition in some quarters may be that substance use and abuse is an urban problem, it is clear from these data that this is a problem throughout the Commonwealth of Pennsylvania.

Untreated substance abuse is a significant public health issue that costs tens of millions of dollars annually in lost productivity, public safety and in its impact on its deteriorating effect on other health conditions. It has a negative impact on the quality of life for hundreds of thousands of Pennsylvanians as it plays a critical role in violent crime, domestic violence, child abuse and neglect, and impaired driving, among other adverse effects. For a variety of reasons, federal funding for addiction research is being reduced. Increasing funds for addiction research can have the benefit of developing improved systems of care that can ultimately increase access for more individuals; identifying promising practices that can improve treatment and lead to better outcomes; and reducing the collateral costs of untreated substance abuse and addiction. Addiction research needs to be made a priority in Pennsylvania.

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Health Research Priority

Therapeutic Cancer Vaccines.

Cancer remains a notable unmet need and targeted therapies have emerged as a paradigm for improved outcomes and decreased toxicity. Therapeutic cancer vaccines target known factors involved in cancer causation and they have emerged as an attractive approach for the treatment of a variety of cancers that afflict Pennsylvanians. The recent commercialization of preventative cancer vaccines has provided a conceptual framework to overcome the obstacles that have prevented successful therapeutic cancer vaccination. Moreover, recent basic scientific studies have delivered key immunological insights that justify a major effort to test cancer vaccines in combination with novel immune modulatory agents. To do this, I propose the funding of an initiative to support translational and clinical research into therapeutic cancer vaccines. Specifically, funds would target research projects that would support novel combination approaches to enhance the efficacy of cancer vaccines, pilot clinical trials that would test applications of new discoveries in cancer biology and immunology, and new investigator awards to support and recruit young physician-scientists in this field.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

A central challenge in developing therapeutic cancer vaccines for common epithelial malignancies is overcoming tolerance and establishing immune memory to tumor antigens. A Therapeutic Cancer Vaccine Initiative would therefore test the hypotheses that (1) genetically enhanced bone marrow cells (e.g. T cells, NK cells, dendritic cells, etc) and strategies to decrease tumor immunosuppression (e.g. defeating regulatory T cells) can overcome tolerance and (2) that the efficacy of current cancer vaccines can be enhanced by testing vaccines in combination with other therapies to overcome tolerance and promote the establishment of long term memory cells. To test these hypothesis, the following clinical research efforts are needed: (1) Proof-of-concept (POC) clinical trials to test safety and efficacy of genetically enhanced cells and to determine whether enhanced lymphocytes and antigen presenting cells can overcome tolerance, (2) POC clinical trials that reduce immunosuppression at the tumor microenvironment, (3) POC that vaccines can target cancer stem cells, and (4) POC clinical trials that test combinations of agents that promote enhanced cancer immunity and promote the development of long term memory cells.

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Therapeutic cancer vaccines represent novel, potential treatment approaches for patients with common epithelial malignancies such as lung, breast, gastrointestinal, and prostate cancer. Although the ability of such tumors to create sites of immune privilege represents a significant obstacle to the efficacy of cancer vaccines, rapid progress has been made in understanding the immunobiological mechanisms of this barrier, and the opportunity is ripe to test novel approaches in proof-of-concept clinical trials that combine vaccines with immune modulatory agents. An emerging paradigm in cancer medicine -- and one that investigators in Pennsylvania have helped forge -- is that combination approaches will enable successful cancer vaccines. Examples include recent phase I clinical trials that targeted suppressive factors (e.g. anti-CTLA4 antagonistic antibodies combined with prostate cancer vaccines), and phase I trials indicating that transfusion strategies with adoptively transferred T cells can boost vaccine approaches in cancer patients.

Development of such novel combination immunotherapy approaches for the more common epithelial malignancies is a particularly urgent need, as these tumors are not only inherently poorly immunogenic but also greatly impact the health of citizens of the Pennsylvania. Statistical data indicate that residents in our Commonwealth have higher prevalence and mortality rates from such solid tumors. The Commonwealth ranks fourth in cancer incidence in the nation: 496 new cases per 100,000 population (NCI, SEER program), so that it has a disproportionate share of new cancer cases. This health disparity is especially prominent in urban areas of the state. For example, the death rates for lung cancer in Philadelphia are 317.3 per 100,000, while that of the Pennsylvania population as a whole is 252.9 (see www.statecancerprofiles.cancer.gov). These factors suggest that vaccine development for epithelial malignancies is a critical undertaking.

Unfortunately, unexpected barriers have emerged to conduct vaccine trials that employ combinations of biologic agents. Many such trials require business-to-business agreements that necessitate complex up front legal and business arrangements to test promising biologics in phase 1 clinical trials, and extensive negotiation required to test novel combination concepts has prevented rapid translation of new preclinical discoveries. These barriers were the subject of a recent joint FDA/NCI meeting on “Bringing therapeutic cancer vaccines and immunotherapies through development” held February 2007 (cms.palladianpartners.com/cms/1156354418/materials/agenda.htm). Infrastructure to promote academic based testing of promising biologic combinations would remove this barrier, and combinations that are deemed successful in academic-based testing could be easily handed off for biotechnology and pharmaceutical industry for advanced phase development.

Supporting translational medicine for cancer vaccines has potential to benefit The Commonwealth and its citizens at several levels:

- 1) Promote rapid and efficient testing of the most promising therapeutic cancer vaccine approaches.
- 2) Develop novel infrastructure to promote the development of novel cancer vaccine approaches at our medical research institutes and schools.
- 3) Bridge and unite the strong cancer vaccine work done across the Commonwealth from the University of Pennsylvania to the University of Pittsburgh
- 4) Recruit and train the best physician scientists, who will create the next generation of cancer vaccines.

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Health Research Priority

The medical, economic, and social impacts of untreated or poorly treated substance abuse are well-known and daunting at the state, community, and family levels. Although there are gaps in knowledge, research suggests that government practices (insurance, purchasing, regulatory, ie) may be inhibiting (or not fostering) widespread adoption of empirically proven approaches - in general health care settings, for example. Screening, Brief Intervention and Referral to Treatment (SBIRT) is a federally-sponsored program based on research indicating that identification of substance use in healthcare settings, early intervention and referral to treatment can improve outcomes for individuals with unhealthy use of alcohol and drugs, and for patients who need further treatment, yet more research is needed to understand and overcome organizational and financial barriers that impede its implementation. Ample research suggests that medication assisted treatment can improve recovery and lower recidivism rates among some types of patients (alcohol and opiod dependent, ie) yet use of pharmaceuticals in primary medical care is not widespread, possibly due to organizational, financing and other government barriers. Finally, findings from a study of a performance based contracting experiment suggest that paying financial incentives to substance abuse treatment providers may lead to improved quality of care (McLellan et al, 2008).

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

None

Health services research questions and hypotheses:

Do financial incentives built into contracts with treatment providers achieve the results desired by the purchaser at the client and the organizational level; do these incentives foster use of evidence-based clinical and/or administrative practices; how do different models of purchasing (i.e. bundling of services at a single rate, performance-based contracts, case rates) affect costs of treatment episodes?

What variables in medical settings associated with SBIRT correlate with entry into treatment; how does implementation of SBIRT differ by setting, e.g. primary care clinic, nurse managed settings, etc, and are there differential impacts on access, engagement or other variables?

How are patients assessed for potential medication-assisted treatments; what models are used to link primary care with specialty treatment providers; are models different for office-based medication-assisted treatment of opioid dependence (buprenorphine) and alcohol dependence (oral and depot naltrexone)?

Impact on Health of Pennsylvanians

Drug abuse and addiction are major public health challenges with ripple effects that are serious, sometimes devastating, and most certainly expensive - nationally and in Pennsylvania. In 2002, an estimated 22 million Americans aged 12 and older were classified as having a substance use disorder (9.4 percent of the population) yet only 3.5 million (1.5 percent of the population) received some kind of care for a problem related to the use of alcohol or illicit drugs (OAS, 2003). In 2001 estimates of the national costs of substance abuse were approximately \$484 million annually - in health care expenditures, lost earnings, costs for crime and accidents (CASA, 2001). In Pennsylvania, tracking data from Healthy People 2010 paint only a small snapshot of the pervasive and cross-cutting consequences of alcohol and drug abuse. Although rates of cirrhosis deaths and injuries from alcohol-related auto accidents have improved, the State is still far from attaining the 2010 goals on these objectives. There has been statistically insignificant change in the percentage of adults engaged in binge drinking the past month, and the State's rates for drug-induced death and alcohol-related auto fatalities have actually increased. (Healthy People 2010).

Drug abuse and addiction create health disparities among vulnerable populations. Nationally, while rates of illicit drug use and abuse do not vary by gender or among racial sub-populations, serious health and social problems related to drug abuse and addiction affect minority populations at far higher rates than whites. African-Americans accounted for 50 percent of total diagnosed AIDS cases in 2003, yet this group represents an estimated 12 percent of the U.S. population. Minority drug abusers also have disproportionately higher rates of other illnesses associated with injection drug abuse, such as hepatitis B, hepatitis C, and tuberculosis. (NIDA, 2005)

The burden of financing substance abuse treatment has shifted to the public sector. Recent estimates suggest that payment for roughly 77% of substance abuse treatment is made by public sources (Mark et al., 2007); estimates suggest that by 2014 payment by public sources will rise to 83% (Levit et al., 2008). While there are serious fiscal consequences of this shift, it also suggests governments have enormous potential to use their purchasing power and other administrative authorities to foster improvements in the quality of the treatment they fund. In Pennsylvania, of the facilities responding to SAMHSA's most recent N-SSATS survey (over a 96% response rate), the large majority of public sector funding came from the State: more than 79% reported receiving Medicaid funding and more than 30% other forms of State funding (SAMHSA, 2006). Like in most states, in the Commonwealth, grant- and contract-based financing arrangements that rarely change from year to year have tended to inhibit change. However, introducing performance incentives into an environment in which there are significant budget constraints (as there are in many States) may be possible with more study of the confounding policy, political, economic, organizational, and regulatory issues in the State.

There is evidence of a nascent movement toward SBIRT among Pennsylvania jurisdictions. Several Counties have experimented with SBIRT and the Philadelphia region continues to work on creating a system to support coordinated care between primary care and specialty substance abuse treatment. Similarly, pharmacotherapies have taken hold in Pennsylvania but more research is needed to nourish their use as part of comprehensive treatment strategy. Sixty-two of the N-SSATS respondents offer Naltrexone; 21 offer Subutex and 39 Suboxone (both Buprenorphine derivatives); and there are 63 Methadone clinics operating as of 2006 in Pennsylvania. (SAMHSA, 2006)

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Health Research Priority

Alcohol addiction is a major public health problem, affecting ~ 5% of American adults. Due to the nature of alcohol addiction, it plays a major role in automobile and occupational accidents. Alcohol addiction fragments families and is associated with many medical and psychiatric co-morbid conditions, leading to enormous social and economic costs. While some alcohol addicted individuals can remain abstinent through programs such as Alcoholics Anonymous, most have lifelong struggles with this addiction. There are two medications approved by the Food and Drug Administration for the pharmacotherapy of alcohol addiction, naltrexone and acamprosate. Both are characterized by limited efficacy, due in part to problems with compliance and side effects. Clearly, there is a need for improved medical treatment of alcohol addiction. In this clinical research priority, it is planned to conduct pharmacogenetic studies of naltrexone treatment of alcohol addicts, to determine whether DNA sequence variation in the mu opioid receptor gene (the main site of naltrexone's action) predicts outcome.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

Because alcohol addiction is a heterogeneous group of disorders, no one pharmacotherapy can be suitable for all alcoholics. If pharmacotherapy for alcohol addiction is to be maximally effective, the treatment must be matched to the individual patient. The working hypothesis for this clinical research is: sequence variation at the mu opioid receptor gene predicts outcome in naltrexone pharmacotherapy for alcohol addiction.

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Alcohol addiction is a common disorder among Pennsylvanians. According to the Behavioral Health Risks of Pennsylvania Adults (2006) web site (<http://www.health.state.pa.us/stats>), 5% of Pennsylvania adults consume more than 60 drinks monthly, and 2.4% admitted driving after having too much to drink in the past month! Further, 16% of Pennsylvania adults admitted to binge drinking (5 or more drinks for a man, 4 or more for a woman) in the past month. African-American Pennsylvanians are at somewhat decreased risk for alcohol addiction, compared to European-American Pennsylvanians, and all men are clearly at increased risk, compared to women. Thus, there is little doubt that alcohol addiction is a common disorder among Pennsylvanians.

This proposal is designed to improve pharmacotherapy of alcohol addiction. Although two medications (naltrexone and acamprosate) are FDA-approved for pharmacotherapy of alcohol addiction, these medications are under-utilized, in part due to compliance difficulties and due to a perception of limited efficacy. Given the

heterogeneity of alcohol addiction, it cannot be expected that one or two medications will be suitable and efficacious for all alcohol addicted persons. There is an opportunity, to reduce compliance difficulties through the use of a depot form of naltrexone (a product of a Pennsylvania pharmaceutical firm, Cephalon), which requires only once monthly administration.

There is also an opportunity to define DNA sequences which increase response rates. Two recent publications (Oslin et al, *Neuropsychopharmacology* 2003;28:1546-1552; Anton et al, *Arch Gen Psychiatry* 2008 65: 135) identified a DNA variant in the mu opioid receptor gene which predicts response of alcohol-addicted individuals to naltrexone. If this can be confirmed in a large patient population, using prospective identification of alleles and the depot form of naltrexone, then a real advance in pharmacotherapy of alcohol addiction will be brought to Pennsylvanians.

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Health Research Priority

Most cancer resources and services are designed and delivered in the specialty oncology setting during the treatment phase of the illness. However, patient and family physical, emotional, social, and financial concerns persist and evolve throughout the period of survivorship well beyond the period of initial treatment. Patients, families, their professional caregivers and the health care system are often ill-prepared to manage this important phase of the cancer trajectory. Resources are fragmented and patients and families are unsure about what questions to ask and where to turn for information, support and follow-up care. At a minimum, this can result in impaired quality of life for cancer survivors and their families. It may also affect whether and when survivors seek help for distressing post-treatment issues and symptoms and may ultimately be linked to worse outcomes. Because patient and family physical, emotional, social and financial concerns persist and evolve throughout the period of survivorship well beyond the initial clinical encounters, we need to think about survivorship care at the public health level. We need to ensure that policies, systems, and resources are strategically placed to support patients and families throughout the cancer trajectory and beyond.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

Clinical research questions: 1) What do cancer survivors need to do to maximize their physical and emotional health and quality of life? 2) How can we prepare survivors and their families to function as their own advocates as they return to their everyday lives following treatment? 3) What policies need to be put into place to advance the quality and quantity of life during and after cancer treatment?

Hypothesis 1: Cancer survivors who receive a treatment summary and a written plan for post treatment follow-up will have better physical and emotional health outcomes three and five years post treatment.

Health services research questions and hypotheses:

Health services research questions: 1) What do cancer survivors need to know post treatment? 2) How should the information be delivered? 3) How can we support primary and specialty care providers as they provide post treatment care? 4) Do survivors tend to return to their primary care provider or do they stay with their oncologist? 5) Are there subgroups of survivors (e.g. those with co-morbid chronic conditions) who follow different help seeking patterns post treatment?

Hypothesis 1: Cancer survivors who are educated about post treatment surveillance requirements, community resources, and post treatment sequelae will have fewer unmet needs than survivors who do not receive this education. Hypothesis 2: Survivors with co-morbid conditions will be more likely to seek follow-up care from their primary care provider than their oncologist. Hypothesis 3: Cancer survivors who seek follow-up care from

providers who are educated about survivorship needs and resources will have better physical and emotional health outcomes than survivors who seek care from providers who do not receive this education.

Impact on Health of Pennsylvanians

We conducted a study of unmet needs of people with cancer in Pennsylvania (n=614) in the survivorship period (the period post diagnosis and continuing after treatment) to determine whether existing resources and services in Pennsylvania are meeting patients' and families' needs (1). This study replicated a previous study in Pennsylvania reported by Houts et al. in 1986 (2). We found in our study that almost two-thirds of people with cancer in Pennsylvania report experiencing at least one unmet psychosocial need, particularly emotional, physical and treatment-related needs. In human terms, this means that in 2005, over 46,400 Pennsylvanians with cancer experienced at least one unmet need following their cancer diagnosis and over 34,000 Pennsylvanians experienced three or more unmet needs. People who are diagnosed at a later stage of disease, with younger age, multiple co-morbid conditions and lower income are most likely to experience unmet needs. When compared to Houts' findings in 1986, we find that it is likely that unmet needs in insurance, employment, information, and homecare increased during the 20 year interval between surveys, despite efforts to provide services in these areas.

That unmet needs have remained high since the Houts' et al. survey two decades ago may be due to a variety of factors. Patient expectations about the cancer experience, changes in the specific types of needs, and greater role disruptions resulting from the increased reliance on home-based care may account for some need. As well, changes in the ease with which survivors can access information without concomitant changes in the degree to which this information can be evaluated, weighed, and digested may result in greater levels of informational need now than in the recent past, and our data are at least consistent with this idea. In a similar manner, much has been accomplished in the past twenty years to improve the number and variety of resources available to cancer patients and survivors, but this increase in access may not be reflected in decreased need. Cancer care services that are rendered primarily to out-patients are frequently not covered by third party payors. Even when quality of life services are reimbursed, accessing services may be a difficult task given the competing demands of illness and role functions. Although numerous resources such as support groups, information services, patient education tools for symptom management, and home care programs exist, many gaps appear to persist. It remains unclear whether identified gaps between services and need is due to a mismatch between available services and perceived need, services that cannot keep pace with "new" needs, access issues related to resources, or a lack of information about resources. We need to understand the nature of physical, emotional, social, financial and education needs that cancer survivors face following the initial treatment period and we need to understand how to meet those needs with existing and new resources and services.

1. Barg FK, Cronholm PF, Straton JB, Keddem S, Knott K, Grater J, Houts, PS. Unmet psychosocial needs of Pennsylvanians with cancer: 1986-2005. *Cancer* 2007;110(3):631-639.
2. Houts P, Yasko JM, Kahn SB, Schelzel GW, Marconi K. Unmet psychological, social and economic needs of persons with cancer in Pennsylvania. *Cancer* 1986;58(10):2355-61.

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Health Research Priority

The health research priority would focus on the intersection between spirituality and religion on health. This topic relates to all three priorities. Understanding the effects of religious and spiritual practices requires better biomedical research to deeply understanding the actual physiological factors involved in this relationship with physical and mental health. Clinically, there is a great need for learning how to utilize interventions to improve and address psychospiritual problems as well as help address the spiritual needs of the patient. Finally, these issues need to be addressed in a health services setting to help identify the best methods for enabling patients to utilize spiritual beliefs as an aid for coping and improving health, to find the best ways of helping health care providers approach these issues with patients, and to better enhance the overall relationship between the health care provider and the patient.

Biomedical research questions and hypotheses:

What are the physiological mechanisms that underlie religious and spiritual practices and experiences and determine their relationship with psychological state and biological parameters of health. This includes measures of brain function, genetic predispositions, and immune and hormonal responses. Research can address the similar physiological correlates of the beneficial aspects of spirituality as well as when patients are involved in a personal religious struggle which has been shown to increase stress and anxiety. Also, research can determine whether or not there are physiological correlates to spirituality which includes formal religion and also a variety of spiritual practices and experiences. Hypotheses to be tested would focus on how changes in the religious or spiritual state of the person affect physiology. It will also be important to more systematically address the physiological relationship between spirituality and mental disorders such as mania, schizophrenia, and seizure disorders.

Clinical research questions and hypotheses:

Given the understanding of the physiology of the relationship between health and spirituality, and given the existing data on the positive effect of religion and spirituality on health, can we explore which type of practices, interventions, and beliefs, are most effective in strengthening an individual's health and well being? Can spiritual practices such as meditation or prayer be effective at reducing stress and improving health? Can this be useful in the prevention of various diseases such as cancer or heart disease? Can spiritual practices help to enhance response to traditional approaches to healthcare such as pharmacological or surgical? Positive mental states would presumably result in better medical and surgical outcomes.

Health services research questions and hypotheses:

Since religious and spiritual beliefs are held by approximately 90% of the population, it is critical on a global level to determine if there are specific factors or interventions that might be applicable to all types of patients with a particular emphasis on patients with chronic disease, cancer, or heart disease. It would also be important

to determine how religious institutions might help with the overall health care system via health outreach and the encouragement of maintaining healthy lifestyles. Finally, it will be important to find more effective ways of having the health care institutions engage in productive dialogue with religious individuals in order to better address potentially problematic issues such as abortion or stem cell research.

Impact on Health of Pennsylvanians

Religion and spirituality are virutally ubiquitous phenomena in our society. Many patients have religious and spiritual beliefs that they turn to when facing medical problems or with medical decision making. This is particularly the case with end of life decisions. Many patients eagerly want to discuss their religious or spiritual concerns in the context of their health and well being. However, too little is known about the relationship between religious and spiritual beliefs and health. It is important to address this topic on multiple levels. On the biological level, it is important to understand how different religious beliefs and practices may influence the body's physiology. Evidence suggests that practices such as prayer or meditation result in significant changes in the brain and body. However, the link between these changes and health have yet to be fully identified. Religion and spirituality have a significant impact on mental and physical health. Thus, clinically it will be valuable to understand which types of beliefs and practices may prove beneficial in the health care setting. On a system-wide perspective, religion and spirituality may be very important in helping many patients deal more effectively with illness, or help develop lifestyle approaches that lead to better health and well being. It may also be very relevant to determine the most effective ways of partnering health care and religious institutions in the overall health of the population. It could be very important to have religious institutions encourage their members to appropriate address and deal with their health. Thus, research on religious and spiritual beliefs can have an impact on many facets of health. This could have broad implications on improving healthcare across the state.

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Health Research Priority

Among diverse diseases that affect pregnant women, those that impact fetal growth or cause preterm delivery pose an enormous public health burden, because they leave a far-reaching imprint on the developing newborn. Children who survive the serious post-partum complications of inadequate intrauterine growth or prematurity are susceptible to cerebral palsy, developmental delay and neurobehavioral dysfunction. Moreover, substandard birth weight has been reproducibly associated with increased life-long risk of obesity, type-2 diabetes, hypertension, heart disease, and their sequelae, commonly clustered as the adult “metabolic syndrome”. Despite the broad implications of these illnesses, our understanding of the mechanisms, treatment, and prevention of these diseases remains rudimentary. Recent improvements in intensive care and neonatal survival led to an increase in the number of small-for-gestational-age and preterm babies, further escalating the problem. Because environmental, nutritional, and behavioral factors play a pivotal role in increasing the risk of substandard fetal growth or preterm delivery, and because of the long-term health impact of these diseases, we propose to make these factors a top health care priority for the CURE program in Pennsylvania for 2009-2010.

Biomedical research questions and hypotheses:

Our overarching hypothesis is that an adverse prenatal environment injures the placenta and fetal membranes, leading to placental dysfunction or generation of membrane signals that prematurely stimulate uterine contractions, culminating in low birth weight. We propose several questions that center on maternal and environmental influences on fetal growth and the timing of parturition. How does maternal inflammation affect fetal growth and organ development? What are the biological targets of the stress-induced cassette of placental transcripts that are regulated during uterine hypo-perfusion and hypoxia? What is the role of environmental toxins, such as TCDD (dioxin) or polychlorinated biphenyls (PCB), in perturbing placental function? What is the basis for the divergent effect of tobacco on fetal growth and preeclampsia? What are the molecular underpinnings of stress-induced preterm labor, and does maternal stress potentiate established stimulants of uterine contractions, such as inflammation and intrauterine bleeding? Can specific nutrients (e.g., folate, antioxidants, or omega-3 fatty acids) alter the response of placental trophoblasts to exogenous injuries, and reduce the expression of contractile proteins?

Clinical research questions and hypotheses:

We seek to translate our knowledge of environmental influences on fetoplacental development into diagnosis, treatment and prevention of suboptimal birth-weight that stems from substandard fetal growth or preterm delivery. Our overarching hypothesis is that environmental, nutritional, and behavioral factors predispose pregnant women to develop preterm labor or fetal growth restriction. We seek to address several cardinal clinical research questions: Can antibiotics or anti-inflammatory agents, when given prior to the onset of labor, mitigate inflammation and thereby delay preterm delivery? What is the effect of pre-pregnancy nutritional status on fetal growth? Does exposure to illicit drugs and tobacco during pregnancy exacerbate abnormal uterine blood flow and placental function, resulting in fetal growth restriction? Can diagnostic imaging (Doppler

ultrasound, MRI, or MR spectroscopy) detect acute or chronic changes in fetoplacental blood flow? Does physical stress during pregnancy, including exercise, redistribute maternal blood flow away from gravid uterus? How does psychosocial stress, reflecting the work place, a lack of spousal support, or intimate partner violence, impact fetal growth and the timing of delivery?

Health services research questions and hypotheses:

We hypothesize that a series of interventions during the preconceptional or prenatal period, particularly to those at risk for preterm delivery or fetal growth restriction, will effectively and safely improve measurable pregnancy outcomes. Specific questions include: What is the influence of interventions to reduce preterm birth on the frequency of NICU admission and the cost of postnatal care? Because recent retrospective studies suggested that folate administration one year prior to pregnancy reduces the incidence of preterm birth, can these data be extrapolated to include the initiation of folate during the first or second trimester of pregnancy to women at risk? Are interventions to reduce smoking during pregnancy effective in reducing the incidence of low birth weight? What is the cost-effectiveness and safety of treating of cervicovaginal infections, when intended to decrease the incidence of intrauterine inflammation, fetal injury and preterm birth? Can preconceptional health education and nutritional assessment to populations at risk improve pregnancy outcome? Which intervention to reduce psychosocial stress and intimate partner violence is effective in attenuating the risk of preterm birth or fetal growth restriction?

Impact on Health of Pennsylvanians

Children that are born at a lower than expected birth weight in the State of Pennsylvania, either because of fetal growth restriction or preterm delivery, are at a much greater risk for neonatal morbidity and mortality, as well as a host of serious physical and mental disabilities, such as cerebral palsy, mental retardation, and vision and hearing loss. Adults surviving these complications are predisposed to the metabolic syndrome, as well as psychiatric and behavioral dysfunction. Unfortunately, despite advances in medical care, the incidence of substandard birth weight has not decreased, and a large population of present and future Pennsylvanians remains at risk.

Over the past 10 years the number of births in the State of Pennsylvania has been relatively stable at 143,000-149,000. State statistics are available for 2006, indicating an annual total of 148,706 births (birth rate of 12/1000). The state statistics for 2006 also detail the incidence of major pregnancy-related indicators that highlight a significant health care challenge. The incidence of low birth weight neonates (<2500 grams) was 8.4%, or 12,491 children. Of these, 2,380 children were born at a very low birth weight (<1,500 grams), which entails a markedly greater health risk. Notably, the two most common reasons for low birth weight, which constitute the vast majority of cases, are preterm birth and fetal growth restriction, two diseases that are targeted by this proposal. The incidence of low birth weight is amplified when associated with other indicators of poor pregnancy outcome. For example, 3.8% of all pregnancies (5697 mothers) had late (third trimester) or no prenatal care. When compared to mothers who had prenatal care beginning in the first trimester of pregnancy, the incidence of low birth weight in mothers who had no prenatal care increased by more than 4-fold, from 7.8% to 33%. Compared to the general rate of low birth weight of 8.4%, the rate of low birth weight is 12% in teen mothers, which constitutes 9.2% of the population of pregnant mothers. This rate is increased to 14% in the African-American population, which constitutes 13% of all pregnant mothers. Lastly, the incidence of tobacco use during pregnancy, which is highly associated with preterm birth or fetal growth restriction, is 17.6%, affecting 26,172 pregnant mothers in the State of Pennsylvania. Together these grim statistics illuminate a leading health care challenge that calls for a conglomerated, multi-disciplinary approach to understand the underpinnings of exposure to diverse environmental injuries, clinical studies to define the scope and magnitude of injury, and health outcome research designed to identify effective ways to organize, manage, and deliver high quality care to pregnant mothers in our state.

We target environmental, nutritional, and behavioral factors because (a) they greatly impact the outcome of pregnancy, and (b) they are potentially accessible to intervention and risk-reduction. This basic, translational, clinical, and health care service priority harbors the inherent advantage of using a well-defined set of metrics for

programmatic success. Research performed as a part of the proposed priority will unveil previously unrecognized molecular and cellular links between the environment and injury to the feto-placental unit, paving the way to better understanding of events that culminate in fetal growth restriction or preterm delivery with their life-long sequelae. This has the potential to introduce novel approaches for intrauterine preventive care designed to avert the risk of future disease. We anticipate that a multidisciplinary team will address the deployment of medical technologies, social factors, and organizational processes to influence the quality and cost of care during pregnancy, designed to prevent low birth weight.

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Health Research Priority

Abdominal aortic aneurysm (AAA) is a common, late-onset and often fatal disease. The US Surgeon General has identified AAA and lung cancer as the only two diseases definitely caused and related to smoking. AAA rupture is a leading cause of death in the elderly, and is the thirteenth leading cause of death in the US (15,000 deaths annually). With the progressive aging of the US population the impact of AAA disease on public health will increase. The underlying causes of AAA formation are not known, but recent investigations suggest remodeling of the extracellular matrix and inflammation as important mechanisms. At the present time there are no simple laboratory tests to diagnose AAA and no non-surgical treatments. AAA is strongly associated with smoking. There is also a strong genetic risk for AAA.

Basic, translational and clinical research is needed to improve the diagnosis, treatment and long term outcomes of patients with AAA. Advances in these areas would have a substantial positive impact on both individual patients and overall public health.

Biomedical research questions and hypotheses:

What are the cellular and molecular mechanisms that cause AAA formation?

What are the genetic variants that affect inherited risk of AAA?

Are there common molecular mechanisms for all types of aneurysm (e.g. abdominal aortic aneurysm, thoracic aneurysm, intracranial aneurysm)?

Clinical research questions and hypotheses:

Discovery of AAA-associated biomarkers; development of novel ways to diagnose AAA-disease based on these biomarkers.

Identification of novel therapeutic targets based on knowledge of the molecular mechanism of AAA formation and/or AAA-associated biomarkers.

Clinical trials of non-surgical treatments for AAA.

Clinical trials of new devices to treat AAAs.

Screening programs to detect AAAs.

Health services research questions and hypotheses:

Can genetic AAA risk variants be used to identify at-risk patients and increase diagnosis and treatment?

Does population screening reduce mortality from AAA rupture?

Can new non-surgical or surgical treatments of AAA improve the health of the population of the Commonwealth of PA?

Impact on Health of Pennsylvanians

The incidence of AAA has been estimated between 30 and 66 cases per 1000 persons. More than 15,000 people die in the U.S. each year from aneurysm rupture, making AAAs the thirteenth leading cause of death in the U.S. overall. The frequency of AAA increases significantly with age. In persons between 65 and 84 years of age AAAs account for nearly 1% of all mortalities (CDC/NCHS National Vital Statistics System, 2002). Men are affected more than women by a ratio of approximately 4:1. The incidence of AAA has been increasing over the past several decades. This trend is likely to accelerate with the progressive aging of the U.S. population. The risk of aneurysm-related mortality is exacerbated by the fact that most AAAs are asymptomatic. Because there are no simple laboratory tests for AAA many aneurysms are undiagnosed. Many AAAs are detected incidentally from ultrasound, CT scan or other radiographic imaging of the abdomen during testing for other medical conditions. At the present time there are no medical treatments for AAA. Surgical or endovascular repair before aneurysm rupture is generally safe and effective, but not all patients are candidates for these procedures. In addition, undiagnosed patients will go untreated and at risk of death from AAA rupture. Earlier and more widespread identification of patients with AAA and the introduction of non-surgical therapies would lead to a significant decrease in AAA-related mortality.

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Health Research Priority

Human antibodies have shown remarkable safety and effectiveness in the treatment of cancer, auto-immune disease, and infectious disease. Academic Institutions have not had access to technology allowing development of native human antibodies into new therapeutics or diagnostics. To address this issue, Clinicians and Principal Investigators in Pennsylvania at Temple University, Salus University and Fox Chase Cancer Center have formed a consortium with the Lankenau Institute for Medical Research's Center for Human Antibody Technology (CHAT). The CHAT has optimized the generation of cell lines that secrete highly selective native human antibodies. Through the CHAT, this consortium intends to enable the translation of some of its most promising preclinical findings into potent therapeutics or diagnostics. This consortium will first focus on the production and clinical testing of novel and highly specific native human antibodies as therapeutics in lung, prostate, breast and colon cancer patients. In addition, a native antibody will be isolated and developed into a diagnostic test to screen for patients at risk for cancer-associated blindness. Native human antibodies isolation and production should become a Health Research Priority for the CURE program to enable the development of novel therapeutics and diagnostics in academic and nonprofit institutions across Pennsylvania.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

Four Pennsylvania academic and nonprofit research institutions formed a consortium to develop novel therapeutics or diagnostics. Through a novel cloning method available at the CHAT the isolation and production of native human antibodies has been optimized. This consortium proposes to initiate clinical research and test the hypotheses that:

- a native human antibody against the Epidermal Growth Factor Receptor (EGFP) possesses sufficient anti-tumor activity to be used as a therapeutic to treat lung cancer and colon cancer patients. In these cancers, the protein EGFP promotes the growth and survival of tumors.
- treatment with a native human antibody against Annexin II alone or in combination with a native human antibody against angiocidin can be successfully used in cancer patients. Annexin II and angiocidin are two proteins which are highly over-expressed in lung, breast, prostate and colon cancers.
- a native antibody against Recoverin, can be used as a positive control to create a reproducible clinical grade diagnostic test to screen for patients at risk for Cancer-Associated Retinopathy and blindness.

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Over 29,000 Pennsylvanians died of cancer in 2005 and more than 70,000 Pennsylvanians are diagnosed every year. In 2005, the cancer rate of Black residents (243.9 per 100,000) was 27 percent higher than the rate for White residents (192.0 per 100,000). As demonstrated through 2004 data, bronchus/lung (10108 deaths), Female breast (9568), prostate (9254) and colon/rectum cancers (8157) are by far the prominent forms of the disease. Current cancer treatments are clearly not satisfactory and a need for better therapeutics and diagnostics persists. Human antibodies comprise the most successful and rapidly growing sector of the field of biological pharmaceuticals, having shown remarkable safety and effectiveness in the treatment of cancer, auto-immune disease, and infectious disease. The development of novel human antibody therapeutics to target diseases such as these major cancers would certainly improve healthcare in Pennsylvania. Moreover, the development of such drugs would likely have other economical impacts on our State as some human antibody drugs, such as Herceptin and Avastin (cancer) and Synagis (infectious disease), qualify as "blockbuster drugs" with annual sales of over \$1 billion. In fact, the global market for monoclonal antibody therapeutics is projected to increase to \$16.7 billions in 2008. The pharmacokinetics of a human antibody drug can be closely predicted based on experience with existing drugs and the criteria for FDA approval of antibody drugs are clearly established. Thus, the clinical development process for a human antibody therapeutic can be more predictable, and less risky, than for a small molecule drug. The current global clinical antibody pipeline comprises almost 200 products in development. Despite these exciting results, the vast majority of diseases for which human antibodies are likely to be effective have no antibodies in clinical development. There are a number of reasons for this failure. First, the human antibody Intellectual Property (IP) landscape is focused on only two methods for making human antibodies i.e. transgenic mice and phage/yeast display methods. Anybody making human antibodies using these methods is likely to encounter substantial interfering IP that could carry significant royalties and thus impede commercialization. Second, the few genuine advances in the field of human antibody creation over the past 15 years have been owned by companies and therefore have not been readily available or affordable for academic researchers. Worsening this situation, three important biotechnology companies that own human antibody technologies are now controlled by single Big Pharma entities: Abgenix, bought by Amgen; Cambridge Antibody Technologies, bought by Astra-Zeneca and Medarex that formed an exclusive relationship with Novartis. Finally, the need for substantial technical expertise and infrastructure has set another barrier to human antibody production that has been difficult for even the most highly motivated and talented investigators to overcome. To address these problems a consortium of Pennsylvania academic and nonprofit research institutions was created. Through the Lankenau Institute for Medical Research's Center for Human Antibody Technology (CHAT), non profit institutions in Pennsylvania gain access to highly specific native human antibodies that could be developed into novel antibody-based therapeutics or diagnostics. CHAT uses a novel, highly efficient method for cloning native human antibodies. It offers an innovative platform that allows for the effective isolation of highly-specific native human antibodies that can readily be scaled up for current Good Manufacturing Practice (cGMP) production and are suitable for clinical use in humans without modification. The consortium will first focus on the development and clinical testing of novel native human antibodies as therapeutics or diagnostics in cancer. As a result, treatment of the four major classes of cancer that affect Pennsylvanians could be drastically improved. The creation of this consortium is in itself a testimony on the urgent and growing need for native human antibody production in Pennsylvania.

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Health Research Priority

Health Services Research

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the United States and the third most common cancer in men and women. Almost two-thirds of CRC deaths could be prevented with routine screening of individuals aged 50 or older. According to "A Study on Various Aspects of CRC Screening in Pennsylvania", Legislative Budget and Finance Committee of the Pennsylvania General Assembly, January 2007, Pennsylvania CRC incidence and mortality rates are higher than those expected in the nation. In 2005, a total of 14,614 cases were treated for CRC as a primary or secondary diagnosis, and the total in-patient costs for treating CRC were >\$205,000,000. CRC screening rates are low. In Pennsylvania, CRC screening rates in primary care practice settings are likely to average 50%. That is, only about half of those individuals who are 50 or more years of age and are eligible for CRC screening have had a screening test according to recommended guidelines. Minority populations have lower levels of CRC screening and experience higher CRC morbidity and mortality. Research is needed to determine how to increase CRC screening in primary care practices.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

None

Health services research questions and hypotheses:

Findings from randomized controlled trials reported in the literature suggest that interventions delivered to primary care physicians (e.g., education, training, support), and interventions delivered to patients eligible for screening (e.g., tailored education and patient navigation) can serve to increase CRC screening and the appropriate follow up of patients with abnormal screening test results.

It is hypothesized that the systematic application of provider and patient interventions in primary care settings can significantly increase provider and patient knowledge, provider-patient dialogue about CRC screening, and actual CRC screening use and the detection of preneoplastic disease and early CRC.

Impact on Health of Pennsylvanians

The Pennsylvania Comprehensive Cancer Control Plan (PA CCC Plan) calls for concerted efforts on a statewide basis to increase cancer screening among all citizens and to reduce disparities related to cancer awareness and screening use, particularly focusing on those cancer sites that have higher incidence and mortality levels. CRC is a priority cancer site in Pennsylvania where rates are higher than those expected on a national level and where several counties are disproportionately affected by the disease.

To facilitate achievement of the goals and objectives of the PA CCC Plan, it is imperative to (1) promote public awareness of colorectal cancer screening, (2) facilitate dialogue between primary care providers and patients related to colorectal cancer screening use, (3) make colorectal cancer screening services uniformly available to individuals at risk; and (4) reduce disparities related to colorectal cancer screening and follow-up. Health services research is needed to identify, implement, and evaluate the impact of best practices for achieving these outcomes.

The substantial burden and lifetime risk of colorectal cancer in Pennsylvania could be reduced through research that leads to the discovery and application of best practices that serve to increase CRC screening. Increased screening would help to prevent new cases of colorectal cancer from occurring and would reduce mortality from this disease. Survival from colorectal cancer would also be increased. Finally, the financial burden on individuals and families and the economic burden on the Commonwealth associated with this largely preventable disease would be substantially reduced.

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Health Research Priority

The health research priority to be discussed is substance abuse and addiction. Over 34 million adults in this country meet diagnostic criteria for dependence on tobacco, alcohol, prescription medications and/or street drugs. While often thought of as a social problem, comparisons between addictions and chronic illnesses on key features such as etiology, genetic heritability, pathophysiology and response to treatment show substantial commonality. Like other chronic illnesses, the etiology and course of addictions are affected by personal choice, family and environmental factors. But genetic heritability is also significant and quite comparable. Many medications are effective in the treatment of addictions; though non-compliance and relapse rates are as high in addiction as they are in most other chronic illnesses. Like other chronic illnesses, there is presently no cure for addiction but medical treatments can provide cost effective reductions in substance use, and its attendant public health problems. This is important because according to the UN-WHO study of all chronic illnesses, addiction to alcohol was the second most disabling condition (after Depression) and addiction to other drugs ranked number 4. Addictions are more disabling than other chronic illnesses because of their greater prevalence, because they begin in early life (16 - 24); and because untreated addiction reduces productivity and quality of life for patients and those around them.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

While addiction is now widely accepted as a chronic medical illness, it is not insured, treated or managed like other chronic illnesses. Standard addiction treatment is typically 30 - 60 days of outpatient counseling with no medications: relapse rates are 40 - 60% within six months. Imagine the relapse rates that would occur in diabetes or hypertension if those illnesses were treated in this acute care fashion. We hypothesize substantially better quality, patient satisfaction and clinical outcomes among addicted individuals under a "disease management" approach (long-term, continuing care with medication adjustment, educational, social and family services as necessary) that is common insured and provided in other chronic illnesses. Moreover, we hypothesize reduced costs of related health conditions (e.g. cirrhosis, infectious diseases such as HIV, HCV) and ER visits for addicted patients treated in a disease management approach. Indirect support for this hypothesis comes from a study of addicted physicians who do receive a form of disease management (3 - 6 months of formal treatment, followed by 3.5 years of monitoring and supports) and have 80% positive outcomes throughout five years (McLellan, DuPont & Skipper, 2008).

Health services research questions and hypotheses:

There are numerous, research-derived, evidence-based treatments for most addictions; and there are over 11,000 specialty programs purporting to treat addiction. Yet most programs do not use evidence based treatments and

the overall quality of available addiction treatment is suspect. Also, payers, families and affected individuals have more information about the important qualities of a washer or dryer, a restaurant, or a mutual fund - than an addiction treatment program. Without an informed consumer base it is simply not possible to have quality services. Thus, we have translated 15-20 well researched types of evidence-based clinical practices into easily answered, verifiable measures of program quality. It is possible to sum responses on these questions; and those programs that have more of the evidence-based components of care will have a higher quality score. Our questions are: 1) Will consumers and payers use the quality scores to make decisions on program selection? 2) Will programs that have higher quality scores also have better clinical outcomes? 3) Will the availability of a Consumer Guide to Quality Addiction Treatment increase the use of evidence-based clinical practices among programs?

Impact on Health of Pennsylvanians

Drug abuse and addiction affect all Pennsylvanians but particularly the young, the under-privileged and minorities. While the Commonwealth has appropriately developed several Healthy People 2010 targets for reduced mortality from alcohol related driving fatalities and from drug related deaths; as well as many targets for reduced morbidity (e.g. fewer young people binge drinking; initiating marijuana use, etc.) - an inspection of performance records on that website (2008) indicates that most of these markers have gotten worse instead of better since the goals were set in 2002! Recall that this disease affects our young disproportionately: more than 50,000 Pennsylvania teens and young adults have died from alcohol and/or drug related causes since 2002! Moreover, these already significant death rates are again, disproportionately higher among African and Hispanic Pennsylvanians. By contrast, the five year wars in Iraq and Afghanistan - significant worries to all parents of young service men and women - have killed fewer than 500 Pennsylvanians (NY Times, June, 2008).

And things are not getting better nationally. The CDC figures show that young adults between the ages of 15 and 24 dying from drug overdoses has more than doubled between 1999 and 2005; from 849 to 2,355. While mortality is the most devastating effect of alcohol and drug abuse - there are substantially more prevalent and more costly health and social effects related to alcohol and drug abuse. Specifically, alcohol is implicated in over 60% of all emergency room and trauma center visits nationally (figures not available for PA). It is suspected that drug use is also implicated in a significant proportion of highway accidents and ER visits but drug abuse is not as easily detected as alcohol nor widely tested. Drug-related crimes account for over 65% of all incarcerations in state prisons in Pennsylvania; and over 50% of all re-incarcerations due to parole violations (personal accounts during Governor's Council Meeting with State Attorney General - April, 2008). Fully seventy percent of all foster children nationally (figures not available from Pennsylvania) have been placed into foster care due to drug and alcohol related parental rights restrictions. Finally, the UN-WHO commissioned a study of all chronic illnesses. What was a surprise to many was that addiction to alcohol was the second most disabling condition (after Depression) and addiction to other drugs ranked number 4. Addictions are more disabling than other common chronic illnesses because of its greater prevalence, because it begins in early life (16 - 24); and because untreated addiction reduces productivity and quality of life for patients and those around them.

As recently as June 18, a NY Times editorial commented on the lack of addiction treatment - particularly for young people "fewer than 1 in 10 American adolescents who need drug treatment get it, according to the Substance Abuse and Mental Health Services Administration. This threatens their health and well being."

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Health Research Priority

The aorta is arguably the most significant artery in the body. It is a large, elastic artery, which receives all of the blood and tremendous pressure from each cardiac cycle, and then helps channel that blood to the rest of the arteries throughout the entire body, including arteries in the head, abdomen, arms, legs, and the heart itself. An abdominal aortic aneurysm-or AAA-is a vascular disease characterized by an enlargement in and weakening of the terminal aorta within the abdomen. This region of the diseased aorta usually enlarges and weakens silently, until it ruptures, spilling blood into the abdominal cavity. Because of the volume and pressure of blood transported, rupture is an extremely critical, medical emergency. AAAs are generally silent until rupture, at which time only 25% of affected individuals survive to hospital discharge following repair. Put differently, AAAs are 75% fatal. In the US, AAA is the 13th leading cause of death (10th leading cause of death in men over 55), with more than 15,000 deaths annually. Nearly 40,000 elective AAA repairs are performed each year, hoping to avoid rupture. It is not known what percentage of these patients would never have ruptured. To date, the exact pathology of AAA is not understood, and several disparities exist in the population. Smoking is a common element in patients with AAAs. More research is needed to better understand abdominal aortic aneurismal disease, screening, and surgical management.

Biomedical research questions and hypotheses:

To date, it is not known how an abdominal aortic aneurysm (AAA) develops or grows. Based upon work at the University of Pittsburgh and elsewhere, one central biomedical hypothesis is that the wall of an aneurysm, once formed, progressively weakens as a result of discordant repair mechanisms and/or increasing severity of protein breakdown, and these are both mediated by the local biophysical environment. Specifically, we hypothesize: 1) regions of concentrated mechanical wall stress lead to localized AAA degeneration by causing an alteration in the balance between protein synthesis and degradation in the surrounding tissue and 2) in regions of the AAA wall next to layers of blood clot (found in most aneurysms) decreased oxygen passage to the AAA wall results in additional alterations in the balance between surrounding protein synthesis and degradation. In addition to these basic, biological studies, the AAA must be mathematically modeled in order to better predict rupture non-invasively. Gender-based differences also occur in AAA which warrant investigation. Lastly, work must be done to determine a suitable animal model of this disease in order to study its very early stages.

Clinical research questions and hypotheses:

Currently, the decision of when to repair an aneurysm is largely based on size. Studies have shown that AAA greater than 5.5 cm have a higher probability of rupture, but this is an inexact measure, as clinicians have seen AAAs 5 cm or smaller rupture and AAAs 11 cm or larger not rupture. A better means to predict rupture is necessary in order to schedule intervention (which is not without risks) most appropriately. According to

principles of mechanics, the biomechanical stability of a AAA depends not only on the acting wall stress, but also on the wall strength. We hypothesize that a new Rupture Potential Index (RPI) - defined as the peak ratio of local wall stress to local wall strength - is a better predictor of AAA rupture than either the maximum aneurysm diameter or peak wall stress alone. In addition, there is a need for a robust vascular tissue database to catalog and record the discarded tissues from vascular surgical procedures, making human tissues available for study. Existing databases, like the Medicare database, are not suited for the many unanswered questions. Lastly, work must be done to determine blood markers of AAA disease. The combination of these areas could see the emergence of a real predictor of AAA rupture.

Health services research questions and hypotheses:

It has been recently shown that a woman's AAA ruptures at a smaller size than a man's. One research area would be to establish a new AAA diameter criterion for surgical intervention in the female that is lower than the current, general 5.5 cm diameter criterion. In addition, more vigorous screening procedures need to be developed for females. Further studies need done on endovascular approaches for females, so that more females may take advantage of the improved outcomes from endovascular techniques. We need to devise a better way to determine at-risk populations and to screen these people for AAA so they can be repaired before a rupture occurs. To do this we would create an epidemiological database and incorporate patient-specific details such as a complete medical history, smoking history, work history, toxic exposures, medications, and infections. We would then analyze these variables in light of the patient's RPI and wall-stress calculations to see if we could correlate aneurysmal behavior to human behavior. By doing this we would hope to both identify at-risk populations for screening patients with known AAA and use this knowledge to further our estimations of rupture potential on an individualized basis.

Impact on Health of Pennsylvanians

In the U.S., abdominal aortic aneurysm disease (AAA) is the 13th leading cause of death (10th leading cause of death in men over 55), with more than 15,000 deaths annually (2004 US Surgeon General's Report). Pennsylvania has a high rate of AAA disease, partially due to a large population of former and current smokers. Unfortunately this group may not have ready access to comprehensive medical care and may not have a AAA detected until rupture occurs. There are also segments of the general population who are more severely affected by AAA disease and do poorly after elective or emergent repair. These include women, current and former smokers, and people with renal dysfunction and diabetes.

Smokers are highly susceptible to abdominal aortic aneurysms. Although many diseases have been associated with smoking, AAA is one of only two diseases that the U.S. Surgeon General has said is caused by smoking. Smoking is associated with a 3- to 5-fold increase in the risk of developing a AAA, and AAA can afflict both current and former smokers. The risk for AAA has been associated with the number of years of smoking (Törnwall et al. 2001) and with the number of cigarettes smoked (Nilsson et al. 2001). The prevalence rates for AAA in the U.S. by smoking status were 6.8%, 11.5%, and 14.4% for never, former, and current smokers, respectively. According to the Center for Disease Control (CDC), Pennsylvania is the 33rd worst state in terms of smoking prevalence, and Pennsylvania's own Department of Health's 2008 statistics show 22% of the population are current smokers and 25% are former smokers. According to these statistics, within Pennsylvania's population of males and females aged 50 and older (4,176,623), there are 536,404 potential aneurysms. Unfortunately Pennsylvania is the 37th worst state in terms of youth smoking, so the prevalence of AAA is not expected to decrease.

Although men are at least 4 times more likely to have a AAA, women have poorer outcomes after AAA repair. At the University of Pittsburgh, Dr. Ellen Dillavou recently completed an analysis of the U.S. Medicare database to find that gender matters in AAA disease. For example, women die more frequently from ruptured AAA than do men, and over the last decade, men had a 30% decrease in AAA rupture surgery compared to only a 12% drop for women (Dillavou et al. 2004). Others have reported that female AAAs rupture at a significantly smaller size and may have increased rates of AAA enlargement compared to male AAA. Dr. David Vorp has

also published results of a study which showed female AAAs have decreased aortic wall strength-and therefore an increased Rupture Potential Index-compared to male AAAs. To date, no one knows why these gender differences exist within a female's AAA or in their medical outcomes, and more work is needed to correlate anatomic findings with clinical variables.

With Pennsylvania's aging population, we can expect to see more AAAs, as well as a larger population of renal failure and dialysis patients. Renal failure is consistently a risk factor for death after AAA repair (Sugawara et al. 1997). With an accurate RPI we could better predict which of these fragile patients could avoid surgery and the risks of morbidity and mortality.

Clearly, AAA disease has-and will continue to have-a large impact on the economy and life of Pennsylvanians. In the U.S., in 2003, AAA rupture took more than 15,000 loved ones from their families, with little notice or warning, and caused 50,000 others to have lengthy hospital stays. However, to date, the pathology of AAA is unknown. Much more research is needed on abdominal aortic aneurysms to help understand, control, and prevent this fatal disease.

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Health Research Priority

The National Institutes of Health (NIH) estimates up to 23.5 million Americans suffer from autoimmune disease and that the prevalence is rising. Researchers have identified 80-100 different autoimmune diseases and suspect at least 40 additional diseases of having an autoimmune basis. These diseases are chronic and can be life-threatening and include: Type 1 diabetes, rheumatoid arthritis, autoimmune thyroid diseases, Graves Disease, Hashimoto's Thyroiditis, Systemic Lupus Erythematosus, Multiple Sclerosis, Crohn's disease, ulcerative colitis, psoriasis, autoimmune neuropathies, scleroderma, and autoimmune eye diseases .

Autoimmune disease is one of the top 10 leading causes of death in female children and women in all age groups up to 64 years of age. The Institute of Medicine reports that the US is behind other countries in research into immune system self-recognition, the process involved in autoimmune disease. The NIH Autoimmune Diseases Research Plan states: "Research discoveries of the last decade have made autoimmune research one of the most promising areas of new discovery." Understanding how to modulate immune system activity will benefit transplant recipients, cancer patients, AIDS patients and infectious disease patients.

Biomedical research questions and hypotheses:

Hypothesis: Complementary and balancing signaling pathways governing the cellular mechanisms ensuring immune protection can, when imbalanced, lead aberrantly to development of life-threatening autoimmune conditions.

Research Questions:

1. How do cellular mechanisms of inflammation lead to autoimmune conditions?
2. By what chemical mechanism do environmental heavy metals induce autoimmune disease?
3. How do mechanisms of immune tolerance affect development and progression of autoimmune diseases?
4. What effects do opioids and cannabinoids have on immune responses?
5. Can neuropeptides and lipid mediators affect mechanisms leading to or exacerbating autoimmune conditions?

Clinical research questions and hypotheses:

Hypothesis: Mechanisms leading to autoimmune diseases can be controlled through pharmacologic manipulations of immune cell function and output.

Research Questions:

1. Can autoimmune responses be suppressed by delivery of dendritic cells transduced with self-inactivating lentiviral vectors coding for neuropeptides found to suppress autoimmune responses?
2. Will clinical investigations of Mer and other molecules involved in clearance of apoptotic cells result in discovery of targets for treatment of human autoimmune conditions?

3. Will B cell depletion prevent their loss of tolerance from contributing to or initiating autoimmune responses? Clinical models for investigations include: Multiple sclerosis, Inflammatory Bowel Disease, Rheumatoid Arthritis, Lupus erythematosus, and glomerular disease.

Health services research questions and hypotheses:

Hypothesis: Underserved populations suffering from autoimmune conditions can be better served to benefit from contemporary research and clinical advances in autoimmune diseases.

Research Questions:

1. Will a clinic dedicated specifically to treatment of lupus erythematosus allow underserved afflicted populations greater participation in clinical advances for treatment and patient services?
2. Will an effort to construct and maintain a central database of autoimmune patient information accelerate the process of clinical investigations leading to improved treatments?

Impact on Health of Pennsylvanians

In the USA:

- Prevalence of Autoimmune diseases: 9,189,519 people in the USA
- Prevalence Rate: approx 1 in 32 or 3.13% of the US population.
- 75% of cases of autoimmune diseases occur in women in the US (The National Women's Health Centre, 2004)
- Autoimmune disease is the fourth largest cause of disability among women in the US. (The National Women's Health Centre, 2004)
- NIH estimates annual direct health care costs for AD to be in the range of \$100 billion (source: NIH presentation by Dr. Fauci, NIAID). In comparison, cancer costs are \$57 billion (source: NIH, ACS), and heart and stroke costs are \$200 billion (source: NIH, AHA).

In PA:

- From the Survey of Behavioral Risk Factors among Elderly Pennsylvanians of 1996: 36% of respondents above age 65 were told by their physician that they had arthritis, with the highest proportion (41%) in females over 65.
- From statistics for 2006: Usual activities were curtailed for 31% of adults diagnosed with arthritis, and 22% were unemployed or unable to work.
- From Arthritis and Rheumatism, Volume 56, Issue 6, Pages 2092-2094: The prevalence of lupus erythematosus in PA was 149.5 of 100K total population, with 258 for women as compared with 38.7 for men, and with African-American women much more afflicted (693.7).

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Health Research Priority

SUBSTANCE ABUSE is one of the major afflictions of our modern era. It affects not only the individual, but that person's family, their community, and our state. Nicotine abuse is clearly causally linked to lung and other cancers as well as to compromised neonatal health. Alcohol abuse is linked to loss of judgment that has a major impact on society via increased violence and automobile accidents. Misuse of opioids, both heroin and prescription pain killers, can lead to addiction that has devastating consequences for life style, and frequently leads to criminal behavior. Similarly, use of cocaine, methamphetamines, and marijuana, as well as other abused substances, can lead to addiction and drug-seeking behaviors that compromise the capacity of the user to function at maximal capacity. We know very little about the biological basis for why people use drugs, the addictive state, and how to interrupt the cycle of drug craving. Current theory suggests that all of these drugs function by stimulating basic reward pathways in the brain. Further, addiction is thought to permanently alter brain chemistry, but the actual process is incompletely understood. Basic research is needed to illuminate the biological processes that lead to and sustain substance abuse in order to design interventions that will cure or prevent this affliction.

Biomedical research questions and hypotheses:

Question: What are the neural circuits, cells, and mediators in the brain that are involved in substance abuse and how can they be disrupted to break the cycle of addiction?

Hypotheses:

1. That a new class of small proteins, called chemokines, first discovered in the immune system, and now shown to be present and to have a functional role in the brain, are important in:
 - a. Inhibiting drug craving
 - b. Reducing development of drug dependence
 - c. Reducing symptoms of withdrawal
2. That chemokines alter neuronal function in the brain
3. That support cells in the brain, microglia and astrocytes, contribute to drug craving, drug dependence, and physical signs of withdrawal.
4. That altering levels of chemokines can modulate drug craving, drug dependence, and withdrawal signs.

Clinical research questions and hypotheses:

Questions: What are the neural circuits and brain regions activated during critical phases of drug abuse and addiction, including active drug use, drug craving and drug withdrawal? Can potential therapeutics for the management of addictive disorders be identified by their ability to alter these patterns of brain activation?

Hypotheses:

1. That specific brain regions and neural pathways are differentially activated during the critical phases of drug addiction and that these can be identified using fMRI in human drug abusers compared with appropriate control subjects
2. That therapeutics used to 1) reduce craving for drugs of abuse or 2) reduce drug withdrawal symptoms associated with discontinuation of drug use will normalize brain activity found to be dysregulated during drug addiction critical phases.

Health services research questions and hypotheses:

Questions:

- What are the barriers that prevent individuals from obtaining treatment for substance abuse disorders? --- How can access to appropriate health care for addictive disease be improved?
- What strategies should be employed at the elementary and high school levels to reduce or prevent drug abuse?
- How can treatment of medical professionals with addictive disease be improved?

Impact on Health of Pennsylvanians

The White House Office of National Drug Control Policy estimated that the national cost of drug abuse in 2002 was \$180.9 billion.

In ranking annual causes of death in the US in 2000, tobacco was #1, alcohol was #3, and all illicit drug use was #12.

In 2006 in Pennsylvania, the drug-induced death rate was 13,000/100,000 population.

In 2004-2005, in Pennsylvania, 36.4% of residents 12 or older reported using an illicit drug in their lifetimes, 10.6% reported use in the past year, and 7.9 % reported use in the past month (823,000 residents).

The National Center on Addiction and Substance Abuse estimates that Pennsylvania spent over \$3.5 billion in 1998 on substance abuse and addiction programs, which was 14.5% of the state budget.

Hospital admissions for all drug abuse in Pennsylvania in 2000 were close to 66,000. The Treatment Episode Data Set for 2005, which tracks admission to State-licensed or certified facilities for substance abuse treatment, shows that in Pennsylvania there were 15,830 total admissions, of which 5% were for opiates, 18.5% for cocaine, 14.4% for marijuana, and 0.7% for methamphetamine and other stimulants.

In 1999, statistics for arrests for drug abuse violations in the state totaled 46,632. Of those arrested and tested for drugs in one major city in the state, >70% tested positive. State money was spent for criminal justice, education, health, child-family assistance, mental health-development disabilities, public safety, and state work force programs, because substance abuse has myriad consequences impacting every aspect of our state.

Among the detrimental outcomes of substance abuse are infections such as HIV, hepatitis, and pneumonia; violence, motor-vehicle injury, suicide, homicide, and mental illness.

Clearly substance abuse is an all-pervasive problem for our state. Yet, of the \$3 billion states spent on prevention, treatment, and research nationally in 1998, only 0.1% was on research. The vast majority, approximately \$2.5 billion, was spent on treatment. Given the magnitude of the substance abuse problem, and its global impact on society, the lack of spending on research into how drugs hijack the brain is difficult to justify. With other biomedical problems, like heart disease and cancer, funds directed to unraveling the biological basis for the disease have led to enormous strides in treatment and prevention. It is anticipated that research into the biology of substance abuse will identify novel targets leading to new pharmaceuticals to treat the user and the addict, and possibly to prevent addiction. Investment in substance abuse research is important for the State of Pennsylvania. It will allow partnerships with the biotech and pharmaceutical industries, which

are prominent in the state. It will hold out the promise of new and better treatments for citizens whose lives are driven by cravings for drugs, which they cannot control.

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Health Research Priority

Addiction to revenge-gratification behaviors has reached epidemic proportions across Pennsylvania in the form of high rates of child abuse, school violence, domestic violence, workplace conflicts, gang violence, interpersonal violence and murder, prison incarceration and recidivism, road rage and litigation. Addiction research, and specifically revenge-gratification research, should be the priority of the CURE program.

Recent brain imaging studies have revealed that the same reward centers of the brain activated by drugs, alcohol, gambling and sex (e.g., dorsal striatum) also activate when people are wronged by others and crave justice in the form of revenge. That is, when perceived wrongdoers are punished, reward centers in the brains of punishers significantly activate, producing physiological and psychological effects similar to those associated with powerful drugs of abuse (gratification, tolerance, compulsion, etc.). This "justice addiction" is suspected of being a root cause of destructive anti-social behaviors, including violent crime.

Public health research must be aimed at "justice addiction" and the wide variety of addictive revenge-gratification behaviors traumatizing and destroying individuals, families and communities across Pennsylvania. Public health research must also be aimed at identifying and developing interventions and treatments to control these addictive behaviors and improve public health and welfare.

Biomedical research questions and hypotheses:

Do individuals with poor frontal brain function (as indexed by resting activity, gray matter density, and activity in inhibition paradigms), hyper-responsive amygdala (to threat and/or to reward probes), and hyper-responsive striatum/pallidum (to reward and to retaliation probes) have increased desire/likelihood of revenge-gratification behavior and aggression, as measured in laboratory paradigms, conviction history, and structured inventories? Hypothesis: Yes. Rationale: Singer, et al. 2006, showed that anticipated retaliation in males activates the same powerful brain reward circuitry (the striatum) as sex and powerful drugs of abuse. In these laboratory tasks, activation in the reward circuitry was proportionate to the desire to punish (deQuervain et al., 2004). Along with the desire to punish/increased activity in brain reward circuits, activation in empathy-related regions (anterior insula) is reduced in males but not females (Singer, et al.). Dreber et al. 2008, showed that inflicting costly punishments (revenge gratification) is maladaptive and against the punisher's interest, indicating compulsive behavior. Research in this area may offer powerful new insights into predicting and preventing destructive anti-social behaviors and violent crime.

Clinical research questions and hypotheses:

1) Can revenge-gratification (inflicting punishments on others) manifest for some individuals into an addictive/impulse control disorder ("justice addiction") with a neurobiological substrate, highlighted by an

uncontrollable urge to inflict pain and suffering upon those perceived as wrongdoers (compulsive anti-social/destructive behavior)?

2) If so, what are the risk factors for these individuals?

3) Is "justice addiction" a root cause of destructive, anti-social behavior, including violent crime?

4) Is there a brain-behavioral connection between drug addiction and "justice addiction"?

Hypotheses: Yes to all. Rationale: The U.S. Department of Justice NDIC (2007) has found that violent crime is the principal threat to public health and safety in the Philadelphia area and that most violent crime and murder is the result of interpersonal disputes (revenge gratification). FBI 2002-2006 crime statistics confirm that arguments are the primary cause of murder nationwide. Yet homicide perpetration and victimization across Pennsylvania is distributed unequally by race and gender (CDC WISQARS), with incidence significantly higher among black males, coincident with drug abuse, suggesting a co-existent justice-addicted population.

Health services research questions and hypotheses:

Can the characteristic fMRI "brain print" of justice seeking/revenge gratification be reversed or modified through the use of pharmacological and/or behavior modification interventions? In other words, can compulsive revenge-gratification/justice addiction be treated and/or prevented, and, if so, what intervention strategies would be useful? Hypothesis/rationale: The foregoing studies show that revenge gratification/justice addiction is physiologically similar to substance abuse and other addictive/impulse control disorders. It follows that interventions and treatments shown to be effective in combating substance abuse and other impulse control disorders could also be effective for revenge gratification/justice addiction. These interventions may include addiction treatment medications and/or addiction treatment behavioral modification therapies (counseling, 12 step programs, psychotherapy) tailored to justice addiction.

Impact on Health of Pennsylvanians

Medical research targeting justice addiction/revenge-gratification presents an unparalleled opportunity to make dramatic improvements in the health and welfare of all Pennsylvanians because the human and economic costs of justice addiction/revenge-gratification within the Commonwealth are widespread and enormous, preying upon vulnerable sections of the population and reflecting significant racial and gender disparities, demonstrated by the following statistics:

PRISON INCARCERATION: 44,450 people were incarcerated in Pennsylvania in 2006, a disproportionate 95% of whom were male and 61% of whom were black and Hispanic, as compared to 38% white (PA Dep't of Corrections, 2006). By contrast, the total prison population in Pennsylvania in 1980 was only 8,582, reflecting an increase of greater than 500% and costing Pennsylvania taxpayers \$1,500,000,000 annually--more than is spent by the Commonwealth on higher education.

RECIDIVISM: 46.3% of all inmates released from Pennsylvania prisons are re-incarcerated within three years (PA Dep't of Corrections, 2004).

VIOLENT CRIME: In 2006, 52,432 violent crime offenses were reported to Pennsylvania police departments, up 12% from 2002 (Pennsylvania State Police, 2006). Blacks constituted a disproportionate 38.1% of all violent crime victims. Males constituted a disproportionate 81.2% of all persons arrested for committing violent crimes, with blacks constituting a disproportionate 52% of all violent crime arrests..

MURDER: There were 721 murders in Pennsylvania in 2006 (Pennsylvania State Police, 2006). Of these, 235 known cases (32.6%) were the result of arguments and in 254 cases the victims knew their assailant (in 241 cases (33.4%), the circumstances of the murder and victim knowledge of the assailant was unknown, indicating that the proportion related to revenge-gratification/justice addiction could be significantly higher). Blacks constituted a disproportionate 66.4% of all murder victims in Pennsylvania and 64.9% of all murder suspects arrested. Males constituted a disproportionate 92.1% of all suspects arrested.

DOMESTIC VIOLENCE: 39,371 Protection From Abuse orders were filed in 2005 in Pennsylvania courts (National Coalition Against Domestic Violence). In that year, 64 women and 5 children were murdered in Pennsylvania as a result of domestic violence.

WORKPLACE VIOLENCE: In 2006, homicides (not accidents) were the most common fatal occupational injury in the Philadelphia metropolitan area, with workplace deaths attributable to homicides accounting for 24.7% of the city's fatality count--the highest percentage among the 12 largest metropolitan areas in the United States (U.S. Bureau of Labor Statistics, 2007). Fifty percent of all establishments with more than 1,000 employees, and 5% of total business and government establishments, reported at least one instance of work place violence in 2005 (U.S. Bureau of Labor Statistics, 2005).

CHILD ABUSE: 4,390 children were abused or neglected in Pennsylvania in 2005, producing 175 future violent criminals and costing Pennsylvania taxpayers \$1.7 billion (Fight Crime: Invest in Kids PA, 2006).

BULLYING: 3 out of 10 children are either bullies, victims, or both, leading to increased rates of depression, suicide, criminality and violence, including school shootings (Fight Crime: Invest in Kids, 2003; U.S. Secret Service, 2002).

CIVIL LITIGATION: In 2006, 131,230 civil cases were docketed in the Pennsylvania Court of Common Pleas (Administrative Office of Pennsylvania Courts, 2006) and 41,570 new civil cases were filed in the Pennsylvania federal courts (Administrative Office of U.S. Courts).

SUMMARY: Justice addiction is epidemic in Pennsylvania and research funding is needed.

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Health Research Priority

The American Cancer Society estimates that about 70,000 new cancer cases are expected to be diagnosed in the Commonwealth of Pennsylvania in 2008. Cancer affects both men and women and all minority groups. Effective therapies are now available for some cancers such as breast and colorectal, however, for many patients recurrence of cancer and metastasis lead to poor outcome. In 2008, 29,000 citizens of Pennsylvania are expected to die of cancer. A better understanding of the mechanisms of disease progression and an understanding of preventative potential of certain treatments such as vaccines, could lead to improvements in survival. Vaccines that prevent illnesses such as polio and small pox have had significant impacts on public health world wide and vaccines against Hepatitis B and Papilloma viruses have had a direct impact on cancer prevention. Studies into the mechanisms of cancer immunology has enabled us to introduce promising new therapies, such as monoclonal antibodies, into clinical practice. These antibodies could in fact function as vaccines when introduced into patients, by activating patients' own immune systems to fight their cancers. A better understanding of this process could lead to better treatment strategies.

Biomedical research questions and hypotheses:

The hypothesis to be explored is that use of antibodies can induce adaptive anti-tumor immune responses, thus linking the innate and adaptive (two arms of the immune system) immune responses. The induction of such immune response, by antibodies could in fact contribute to the efficacy of these agents. To explore this hypothesis, future attempts will be directed at selectively augmenting this adaptive immune response by improving the process of antigen presentation, host antibody production and expansion of tumor specific T cells.

Clinical research questions and hypotheses:

In the setting of a clinical trial, one could test the hypothesis that treatments with active antibody (i.e. cetuximab) could lead to the induction of adaptive immune responses. If detected, this will provide support for a novel mechanism of action for monoclonal antibody treatment responses. This immune response can then be augmented with the hopes of improving disease control and "immunizing" the patients against his/her own cancer.

Health services research questions and hypotheses:

The use of preventative or therapeutic cancer vaccines have very different challenges when introduced into large populations. While acceptance of therapeutic cancer vaccines will be directed to smaller populations, they will have unique issues which will require study.

For preventative vaccines, health services research questions such as optimal mechanism for dissemination, safety/efficacy criteria, educational strategies for public acceptance will provide fertile opportunities for research.

Impact on Health of Pennsylvanians

It is estimated that 70,000 Pennsylvanians will be diagnosed with cancer in 2008. Approximately 30,000 deaths are expected as a result of cancer in the Commonwealth. While advances have been made in the management and therapy of cancer, new treatments are required to substantially reduce the burden of this disease.

Immunotherapy, such as monoclonal antibodies, is a potentially widely applicable option for the cancer therapy. However, due to a lack of understanding of principals of cancer immunology, most immunotherapy strategies have not been as widely applicable or successful.

Use of antibodies as “In-Site” vaccines is a potentially attractive strategy as it addresses two issues. First, the antibody attacks the cancer cells with the hope of slowing its growth or destroying it and, second, it could activate the host immune system to help in the fight against the established cancer. Even if there is a subtle effect on immune control of cancer progression, the subsequent events may be amplified and, thus, could have a profound impact on the eventual irradiation of cancer.

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Health Research Priority

Active immunotherapy, or vaccination, represents a promising approach to harness the power of the human immune system to fight cancer. Our increasing knowledge of both cancer immunology and the molecular mechanisms driving cancer formation and progression provides us with promising strategies to immunize patients with a goal of both eliminating residual disease after initial treatments and preventing its recurrence. Strategies to prevent cancer in those at high risk for disease may also emerge. Cancer vaccine strategies can be applied to a wide range of cancers types and, thus, have the potential to make a major impact on the treatment of cancer patients in Pennsylvania.

Biomedical research questions and hypotheses:

It is hypothesized that the human immune system, when properly primed by vaccine strategies, can elicit efficacious anti-tumor responses. This hypothesis will be addressed by asking:

Can DNA and/or protein-based immunization strategies be developed that induce effective anti-tumor immune responses and under what setting are those immune responses most effective at fighting cancer?

A wide range of studies are now being undertaken by researchers across the Commonwealth to address such questions in vitro and in vivo such as the optimal volume of cancers controllable by cancer vaccines? The role of immune modifiers in enhancing vaccine strategies.

Clinical research questions and hypotheses:

Can safe and effective preventative vaccine strategies be developed that lower the risk of cancer for individuals at high risk for disease?

Are cancer vaccines most suitable in an adjuvant setting to eliminate residual disease and prevent recurrence?

Can immune system modifiers be combined with vaccination strategies to enhance the efficacy of cancer vaccines?

Health services research questions and hypotheses:

The use of preventative or therapeutic cancer vaccines have very different challenges when introduced into large populations. While acceptance of therapeutic cancer vaccines will be directed to smaller populations, they will have unique issues which will require study.

For preventative vaccines, health services research questions such as optimal mechanisms for dissemination, safety/efficacy criteria, educational strategies for public acceptance will provide fertile opportunities for research.

Impact on Health of Pennsylvanians

Based on statistics compiled by the American Cancer Society, individuals have between a 1:2 (men) and 1:3 (women) chance of developing cancer within their lifetime. In 2008, this translated into greater than 70,000 Pennsylvania residents being diagnosed with cancer and nearly 30,000 people dying of their disease. Despite the extensive advances that have been made in the types of treatments available, only modest improvement has been seen in the rate of age-adjusted cancer deaths over the last 50 years. In 1950, there were 194 cancer deaths per 100,000 population as compared to 184 deaths in 2005. By contrast, the death rate associated with heart disease fell from 587 to 211 per 100,000 over the same time frame. Obviously, new treatment options are required to reduce the burden of cancer.

It has long been hypothesized that the human immune system is capable of scanning for, and eradicating, tumors before they develop into clinically relevant disease. Such a role for the immune system is supported clinically both by the fact that tumor-reactive immune responses can be observed in patients with a variety of cancers and also by the observation that these responses can, in certain settings, correlate with increased patient survival. This has led to significant efforts to exploit the power and precision of the immune system for cancer therapy. Despite these past efforts little clinical success has been achieved. However, over the last decade preclinical, as well as clinical, research has led to a deeper understanding of cancer immunology. In turn, we are now poised to translate this knowledge into strategies that will potentially enhance the efficacy of cancer vaccines and better define the clinical settings most amenable to vaccine therapy.

Pennsylvania-based scientists and clinicians have made significant contributions to the fields of cancer immunology and cancer vaccines. We request that the Health Research Advisory Committee support initiatives to create Centers of Excellence focused on the development and testing of Cancer Vaccines. Allocation of funds for this purpose will help to support research that is absolutely necessary in order to validate if the promise of vaccines as cancer therapies can be fully realized.

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Health Research Priority

A collaborative research proposal is presented to solve major problems related to bone and craniofacial disorders, although the technologies being developed could be applicable to other diseases, in the context of “manufacturing implantable body parts”. However, this application will address only mineralized tissue related diseases. Orthopedic, dental and craniofacial diseases and disorders are among the most common health problems affecting people of the United States and around the world. The burden imposed by a variety of dental and craniofacial diseases and disorders range from simple and complex fractures of the bone to congenital defects such as cleft lip and palate, which occurs in every 1 in 525 to 714 live births, to injuries to the head and face, resulting in nearly 20 million emergency room visits per year, to devastating head and neck cancers, accounting for 8000 deaths and over 30,000 new cases. Several treatment strategies though researched extensively over the years have however failed to address the above issues adequately due to limitations in biomaterials, engineering and design, and the inability to bridge the gap between advances in health science and technology. We propose clinically relevant 3-D inkjet printing strategies leading to a revolutionary concept: "Customized Manufacturing for Medicine". This technology is applicable to several diseases wherever tissue grafting is needed.

Biomedical research questions and hypotheses:

There are several fundamental biomedical research questions that need to be addressed in order to achieve the milestones and overcome the hurdles currently facing myriad bone related diseases described above. These are: 1. lack of suitable engineered materials that can mimic the chemical, physical, biochemical and biological characteristics of mineralized tissue. 2. lack of a fundamental understanding of the biology of the mineral-tissue interface. 3. lack of comprehensive understanding of the biology of the signaling molecules and their interaction with host tissue, including stem cell interaction and the materials. 4. lack of proper correlation of engineering design principles with patients needs. In order to meet these challenges we propose the following hypotheses: 1. A 'customized medicine' concept utilizing CT scans of patient's osseous defect site combined with 3-D ink jet printing of novel functional hybrid biomaterials will meet the needs of patients. 2. Development of smart functional materials containing all the desired chemical, physical, mechanical, biological, and biochemical characteristics to heal and repair the osseous defect site. 3. Printed structures will provide ideal model systems to understand the materials/cell/tissue interface.

Clinical research questions and hypotheses:

Several clinical questions pertaining to the bone and craniofacial related diseases remain to be solved: 1. Can a multifunctional scaffold be generated representing the intricate micro and macro structure of the defective site that will form functional bone? Can we use CT scan data and deliver to the patient a custom made patient

specific therapy? 2. How can the scientific and technological gap between biomaterials, engineering, imaging, design and the biological response be met? Our hypotheses to address these questions are the following: 1. Generation of multifunctional smart scaffolds using novel 3-D inkjet printing techniques from CT scans of the defective osseous site of patients will replicate the intricate micro and macro structures of the site. 2. The multifunctional 3-D printed scaffolds will contain all the necessary biochemical, physical, chemical and mechanical attributes to induce proper healing and repair. 3. The CT scan derived 3-D inkjet printing of multifunctional novel biomimetic scaffolds will provide the ideal pathway to "Customized Manufacturing for Medicine". Although our focus is on mineralized tissues, these technologies are also applicable to other tissue types and diseases.

Health services research questions and hypotheses:

Following health service questions to current therapies for orthopedic and craniofacial diseases remain: 1. How can customized therapy be provided to patients to cure orthopedic and craniofacial diseases, currently non-existent? 2. Can patient cure be provided with minimal corrective reconstructive invasive surgeries? 3. Can we manufacture biomimetic body parts and harness the body's own ability to repair and regenerate itself? To address these questions, our hypotheses are the following: 1. Patient derived CT scans combined with novel 3-D inkjet printing under physiological conditions using novel biomimetic hybrid materials will provide the first ever revolutionary concept of "customized manufacturing therapies" for bone and other tissue healing. 2. The customized therapy from laboratory directly to patients will provide a cure that is tailor made for each individual patient unlike current generalized therapies. 3. Proposed therapy is extremely flexible and robust with the ability to incorporate cells (primary/stem cells), drugs, signaling molecules, proteins, DNA into a 'smart' functionalized structure mimicking the patient defect site thus providing patient specific customized therapeutic cure to orthopedic and craniofacial diseases.

Impact on Health of Pennsylvanians

Our proposed plan is to develop a revolutionary concept of "Customized Manufacturing for Medicine" and provide customized patient specific treatment options for myriad orthopedic and craniofacial defects and diseases. The proposed concept is unique and will provide treatment and cure for a number of orthopedic, dental and craniofacial problems related to bone disorders arising from debilitating conditions known to infants, adolescents, young and old Pennsylvanians such as arthritis, osteoporosis, birth defects such as cleft lip and cleft palate as well as oral cancers. Our treatment options is applicable indistinguishably to all sections of the population covering the new born to toddlers to teenage children, young and old adults irrespective of the gender. The concept is thus universal and offers tremendous opportunity for breakthrough in medical and engineering science and technology. The proposed concept will have a tremendous impact on resident Pennsylvanians who are afflicted with any of the following conditions:

1. Birth defects: This is a serious problem affecting 1 in 33 infants born in the United States. In Pennsylvania, approximately, 2% of the births or 2, 761 new borns had a birth defect reported in 2002. The most common bone related defect in new born infants is a structural defect such as Encephalocele, a condition resulting in abnormal closure of the skull where a portion of the brain is contained in a sac outside the skull. Another problem is craniosynostosis, cleft lip and cleft palate known to affect 1 in 700 babies.
2. Arthritis: This is a skeletal problem known to affect 35.5% of women in comparison to 27.2% males. This is a debilitating condition affecting both old and younger generation above the age of 40 severely limiting physical activity. Most of the arthritis afflicted male patients about 80% tend to be obese compared to 64% women.
3. Osteoporosis: Although this is a condition known to affect more women in post menopause years above 50, there is evidence of this condition affecting men as well. In fact osteoporosis is now recognized as an important public health issue because the number of men living above 70 is expected to double from 1993 to 2050.
4. Oral Health and Cancer: This is another serious problem affecting a number of Pennsylvania residents particularly those engaged in use of tobacco and excessive alcohol use. More than 90% of the oral cancers are found in people age 45 years of age and older, although oral cancer can develop at any age. Men develop oral

cancer twice as often as women, and it occurs more often in African Americans than in Whites. One of the common bone related cancers is that affecting the upper or lower jaw that causes dentures to fit poorly resulting in severe pain. The proposed novel approach of "Customized Manufacturing for Medicine" will provide a technology that has the potential to cure these debilitating conditions affecting Pennsylvanians outlined above. The technology that we propose using CT scans of patients enables the generation of a template matching the defect site of patients of all ages. Once the scan is obtained and translated to the 3-D printer, the internal and external structure can be monitored to match the overall geometry. We can monitor the type and nature of the porosity while using state-of-the-art compliant biomaterials/metals having the ability to heal and repair bone due to the excellent load bearing capability in addition to be able to deliver the desired growth factors, proteins and DNA if needed, all by varying the printing parameters completely under physiological conditions. In addition, the printer will enable the generation of spatial and temporal gradients of these factors to truly mimic the biological environment of the given patient's defect site irrespective of the type of bone and its location in the body or a defect in the craniofacial cavity or in the cranial socket. This approach is universal but patient specific.

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Health Research Priority

Blinding diseases are a huge and growing social and economic burden on the state. Together age-related Macular Degeneration, Diabetic Retinopathy and Glaucoma affect over one million people in the Commonwealth of Pennsylvania and create an economic burden of over \$3 billion per year. Although clinical management of these diseases has improved greatly in recent years we have no cures and we have no understanding of causes that would let us prevent their onset. We are proposing a broad program under the CURE program that encompasses basic biomedical research, clinical research and delivery of health information to the community.

At the basic biomedical research level we have identified a series of research priorities that will lead to identification of the causes of these diseases. We also propose a program to translate these findings into novel therapies. At the clinical level we propose a program leading to better diagnosis and outcomes measures of new treatments. Finally, we propose a program of community education to help the population understand these diseases and the new therapeutic options available.

Biomedical research questions and hypotheses:

We need to build upon the recent advances in the genetics of blinding eye disease. Specifically we need to identify additional risk factors for Macular Degeneration and carry out the same types of genetic screens for genes responsible for diabetic retinopathy and glaucoma.

It is essential that we use the information from genetic studies to identify the biochemical pathways leading to the loss of retinal cells and blindness. For example, our studies have shown a very strong associations of a form of Factor H, a protein of the immune system, and HTRA1, an enzyme, with Macular Degeneration. This has led to the hypothesis that Macular Degeneration involves inflammation and presents us with the challenge of explaining the link between inflammation and blindness. Diabetic retinopathy may also involve the inflammatory cascade suggesting that common biochemical pathways may underlie many blinding diseases.

Clinical research questions and hypotheses:

We need to test the ability of new drugs to block the biochemical changes that cause blindness. The Penn State JDRF Retinopathy Center serves as an excellent model for the translation of laboratory research into clinical practice. We need a focused collaborative effort of biologists, bioengineers and clinicians to turn candidate molecules into useful drugs, to develop ways of safely delivering them to the eye, and move them into clinical practice.

It is essential that we develop new ways of detecting early disease-related changes in vision and sensitive ways of measuring the effectiveness of new drugs. By the time a patient notices a significant loss of vision they can have lost up to 50% of key retinal cells. We must be able to screen for disease at an earlier stage. Sensitive imaging methods, electrical measurements and even blood tests are all showing promise and need to be

developed and tested rigorously. These tests will be critical in providing quantitative measures of the effectiveness of new drugs. By making the best of these tests part of clinical practice, early screening for blinding eye disease will be available, particularly for populations most at risk.

Health services research questions and hypotheses:

While the emphasis of this submission is on hypothesis driven research and the translation of the findings into new clinical tools, it is important that these efforts go in parallel with several forms of community education. The rural and urban poor, and inner city minority populations, too often leave visits to ophthalmologists until they have experienced serious vision loss. It is these groups that are most at risk for diabetic retinopathy and glaucoma. It is essential that as new early detection methods are developed they are made available to these seriously at risk groups. Although current treatments are as effective as we need, early detection and treatment can still slow the loss of vision.

Impact on Health of Pennsylvanians

To say that we are facing a social and economic crisis because of blinding diseases is a gross understatement. Figures from the National Eye Institute of the National Institutes of Health compiled in 2004 indicate that in the United States over 9 million people suffer from age-related macular degeneration, over 4 million from adult diabetic retinopathy and over 2 million from glaucoma. Because these are age-related diseases, the change in population structure predicts that these numbers will increase to a total of over 25 million by 2020. The Commonwealth of Pennsylvania will be disproportionately affected by these increases because the average age of its population is increasing more rapidly than that of most states. In addition, blinding diseases do not affect all groups equally. African-American and Hispanic groups have a higher incidence of glaucoma. Diabetes, and thus diabetic retinopathy, affects lower income groups at a much higher frequency.

The economic cost of blinding eye diseases is staggering. The National Eye Institute has put the 2003 direct costs of these diseases (medical care, drugs and rehabilitation services) at \$49 billion and the indirect costs (lost work days, people unable to work, caregiving) at \$19 billion. This suggests an economic cost to the Commonwealth of Pennsylvania of almost \$3 billion in 2003, with a substantially rising cost over the next decade.

If the program proposed below is adopted we would expect a number of substantial benefits for the statewide population.

First, additional biomedical research will identify the genetic risk factors for these diseases and the biochemical pathways by which the diseases progress. By telling us what causes these diseases ophthalmologists will be able to devise better programs to try and prevent or slow the progression of these diseases, which will also have a direct health impact.

Second, the definition of new “biomarkers” of these diseases would quickly translate into better diagnostic tools so that clinicians could identify patients at early stages of the diseases and clinical research teams could better assess the effectiveness of new therapies. Better diagnosis and better measures of treatment will have a direct impact on the health of Pennsylvanians.

Third, the most important long term health benefit will come from translating the basic biomedical findings into new and effective therapies for one or more of the blinding diseases. We are proposing an extensive translational medicine unit, modeled after the Penn State- JDRF Center for Mechanisms and Intervention of Diabetic Retinopathy based at the Penn State Milton S. Hershey Medical Center and Penn State College of Medicine.

Fourth, there is a need for a community education program through which people can be informed of the early signs of eye disease so that they can seek treatment and can learn adaptive mechanisms to help them cope with reduction in their vision.

Through all of these mechanisms we believe that the CURE program can play a major role in developing the new understanding of blinding eye diseases and in developing new therapies, both of which will have a direct and important beneficial impact on the health of a substantial percentage of Pennsylvanians.

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Health Research Priority

Brain injuries are a major cause of death and disability of children within the Commonwealth of PA. According to the Childhood Injury Report in 2006, traumatic injury was the leading cause of death of children in the State and national studies suggest the majority of these deaths are caused by brain injuries. However, there are many other acquired brain injuries (hypoxic/ischemic from cardiac arrest, meningitis, encephalitis, seizures, brain tumors, strokes, intracranial hemorrhages, and others) that are not tracked by these data systems. This lack of surveillance diminishes our capacity to determine the actual disease burden within the Commonwealth and limits potential novel treatment strategies for these conditions. Nevertheless, these injuries undoubtedly result in thousands of deaths and hundreds of millions of dollars in health care expenditures each year and a societal toll that is incalculable. Neurological outcomes after critical brain injury remain unacceptably poor. Therefore, we propose a clinical consortium to determine the incidence of brain injuries within the Commonwealth, establish contemporary and uniform treatment guidelines, and initiate therapeutic trials to treat these injuries or prevent their occurrence. The institutions within the consortium capture all critically-ill children in the Commonwealth, are international leaders within the field and will lead Pennsylvanian's children into improved neurological health into the future.

Biomedical research questions and hypotheses:

We will test the general hypothesis that goal-directed therapies in acute neurological injuries can improve mortality and neurological outcome in children. In 7 conditions that result in either death or permanent neurological damage to children (traumatic brain injury, hypoxic/ischemic encephalopathy from cardiac arrest, meningitis, encephalitis, excitotoxic injury following status epilepticus, stroke and cerebral hemorrhage), goal-directed therapies including resuscitative measures, advanced neurological monitoring, state-of-the-art neurological critical care and experimental new therapeutics will be employed at all institutions within the Commonwealth of PA Recovery from Brain Injury in Childhood Initiative (Children's Hospital of Pittsburgh, Children's Hospital of Philadelphia, St. Christopher's Hospital of Children, Hershey Medical Center and Geisinger Medical Center). With over 8000 annual admissions to the critical care units of these institutions, sufficient patient numbers for conditions will be available for randomized-controlled or interventional trials. Mortality and neurological outcome will be determined by neuropsychologists, psychiatrists and physical therapists by an established battery of testing after discharge.

Clinical research questions and hypotheses:

We will test the hypothesis that generation of guidelines for management of acute neurological injuries will improve overall neurocognitive outcome and mortality for children within the Commonwealth. To test this hypothesis, guidelines for the various diseases (traumatic brain injury, hypoxic/ischemic encephalopathy from cardiac arrest, meningitis, encephalitis, excitotoxic injury following status epilepticus, stroke and cerebral hemorrhage) will be established across centers within the Commonwealth of PA Recovery from Brain Injury in

Childhood Initiative. Protocols for acute care management of all aforementioned conditions will be generated from collaboration of experts from within all 5 institutions. Appropriate neurological, rehabilitative and psychological measures for these conditions will similarly be established from experts within the various institutions. Adherence to the protocols and patient outcomes will be tested and compared to cohorts of patients from previous years as well as national benchmarks. It is hypothesized that the generation of these protocols can decrease the mortality and neurological morbidity of each condition by at least 50% over a 10-year period.

Health services research questions and hypotheses:

The incidence of these 7 acute neurological injuries (traumatic brain injury, hypoxic/ischemic encephalopathy from cardiac arrest, meningitis, encephalitis, excitotoxic injury following status epilepticus, stroke, and cerebral hemorrhage) is not currently known. We will form a consortium of institutions (Pittsburgh Children's, Children's Hospital of Philadelphia, St. Christopher's Hospital for Children, Hershey Medical Center, Geisinger Medical Center) that encompass a vast majority of the critically-ill children in the state. These institutions will develop networks within their regions to track all children with these conditions from all hospitals within the Commonwealth to capture all potential patients. Within this population, we will determine the annual incidences of the above named conditions and track these incidences over a 3-5 year period. High-incidence areas will be identified. These regions will be targeted for unique training in neuroprotective strategies using pediatric simulation by Dr. Fiedor Hamilton at CHP (Director of Pediatric Simulation, Children's Hospital of Pittsburgh). Training of both professional and lay-persons regarding prevention, recognition and treatment for these conditions will be implemented.

Impact on Health of Pennsylvanians

The definition of “brain injury” in children is broadening within the community. Traditionally, brain injury referred to traumatic brain injury (TBI) specifically. Using only this limited definition, brain injury in children still constitutes a substantial public health problem for the Commonwealth. In the report “Childhood Injury in PA” (June 2006), the state estimates that (i) 55 children died each month from trauma-related injuries, (ii) 62% of the deaths of all children under 20 were related to trauma and (iii) 14,000 hospitalizations occur each year as a result of trauma for a total cost of \$258,000,000. In most national surveys, more than half of the mortality associated with trauma is a direct result of TBI and most survivors require substantial rehabilitative services for full recovery. In light of these facts, TBI alone is likely causing hundreds of deaths, thousands of permanent disabilities and costing the Commonwealth many millions of dollars in acute care, rehabilitative care and lack of future productivity each year to children.

However, a broader definition of brain injury in children has emerged in more recent years. Pediatric Critical Care Medicine, established as a subspecialty in 1987, has resulted in decreased mortality for a number of important diseases. This has been accomplished by supporting injured or failing organs during critical periods, thereby providing time for the organ to heal and opportunity for new therapies to take effect and restore organ function. Advances in respiratory care, including new ventilators, improved strategies for respiratory care and novel medications (such as surfactant and nitric oxide), have lowered the mortality from severe lung injury. Technological breakthroughs in cardiac care including extracorporeal techniques and assist-devices for cardiac support, new pharmaceutical agents to treat heart failure and improved operative techniques for structural heart disease have decreased mortality from heart disease in children. Renal dialysis with improved equipment and strategies for clearance of toxins has allowed children’s kidneys to recover from injuries or maintain some function while awaiting transplantation.

Strikingly, support for the brain during critical illnesses in general or during neurological emergencies is minimal. During critical illnesses, the effect of these supportive agents on neurological function is unknown, but likely adverse to normal brain development. We have recently found that neurological injury markers in serum are dramatically increased during septic shock, a prototypical critical illness. Neurological disability after corrective heart surgery is well known, with a decrease in IQ based on different operative strategies. Antibiotics have been used to kill bacteria in cases of meningitis, yet the inflammatory response to the infection is responsible for significant neurological damage and death in children. Hypothermia is being studied for

improved mortality and neurological function after cardiac arrest and TBI. Severe epilepsy is treated with a wide variety of drugs to diminish seizure frequency, yet, no conclusive studies have determined the superiority of agents or the long-term effects of these drugs on outcome or mortality.

The proposed consortium represents the largest institutions caring for critically-ill and injured children within the Commonwealth of PA (see below) and will likely capture the vast majority of children with these disorders. Combined, the institutions admit 8,000 critically-ill children each year and are the major trauma and transplantation centers in PA. By supporting these institutions toward the goal of improving neurological outcome and reducing mortality from neurological injuries, the Commonwealth will benefit significantly from these efforts. The “Tracking Healthy People 2010” initiative has stated many goals regarding the diminution of childhood mortality in the coming years. This consortium will seek to add “maximizing neurological outcome and improving quality of life” to these initiatives.

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Health Research Priority

Cardiac arrest, or the cessation of heart pumping activity to provide nutrients to the body, has profound effects on the body and is a public health problem within the Commonwealth. We have found that in a single year, there were 228 cardiac arrests admitted to an intensive care unit at one of 5 hospitals caring for children in Pennsylvania (Children's Hospital of Pittsburgh, Children's Hospital of Philadelphia, Hershey Medical Center, St. Christopher's Hospital for Children and Geisinger Medical Center). While the causes can be diverse, the ultimate outcome is usually the child's death (mortality 80 - 90%) or severe neurological impairment. Development of pharmacological strategies to combat disorders such as cardiac arrest require clinically-relevant animal models and putative agents that might mitigate against either mortality or neurological injury. To implement these strategies into clinical practice, a tracking system within the Commonwealth to identify regions of high incidence is also required. We propose that the priority of preventing cardiac arrest and effectively treating neurological injury after arrest within the Commonwealth is a critical public health goal. We believe that applying preventative strategies in our communities along with a pharmacological approach with neuroprotective agents to mitigate neurological damage in both pre-clinical models and humans could greatly improve the health of the Commonwealth.

Biomedical research questions and hypotheses:

Models of pediatric cardiac arrest are actively being developed within the Commonwealth. In particular, investigators at the Safar Center for Resuscitation Research at Pittsburgh (Drs. Kochanek, Fink and Clark) and those at the Center for Resuscitation Science at the University of Pennsylvania (Drs. Berg, Nadkarni and others) have been world leaders at developing clinically relevant animal models of pediatric cardiac arrest. This proposal will test whether the combination of erythropoietin, estrogen and granulocyte-colony stimulating factor (G-CSF) decreases neurological morbidity and mortality in rat and swine models of pediatric cardiac arrest. In particular, cell death within vulnerable regions (CA1 of hippocampus), infarct volume and activation of death cascades will be tested. Additionally, long-term behavioral studies testing memory and motor skills will be tested. The drug dosing regimens will be evaluated for maximization of effect and then these doses will inform decisions regarding the clinical trial outlined below. We believe that combination strategies such as this are the best pharmacological approach to achieve neuroprotection at this time and will be an invaluable aid to the clinical project.

Clinical research questions and hypotheses:

Since single drug therapies for neuroprotection have routinely failed in clinical trials, we hypothesize that a combination approach to target several mechanisms will improve 3 month survival and 12 month neurological

outcome in children after pediatric cardiac arrest. Specifically, we will test whether administration of 3 FDA-approved drugs (recombinant human erythropoietin - antioxidant, estrogen - anti-inflammatory and G-CSF - neurogenesis) in the acute period after pediatric cardiac arrest improves outcome. All agents have shown promise in pre-clinical trials of cerebral ischemia and will have undergone pre-clinical testing at our facilities. A consortium across the Commonwealth will be established encompassing the major centers for care of children after cardiac arrest. Dosing regimens will be determined for each agent as well as the combination in Phase II trials. Then, the combination therapy will be tested in a Phase III trial. A steering committee (Chairs: Drs. Bell (Pitt) and Nadkarni (Penn)), a data coordinating center (Hershey) and an outcomes center (Chair: Dr. Beers - Pitt) will be established. A Data Safety Monitoring Board will be appointed by Chairs at each of the Universities to monitor for the safety.

Health services research questions and hypotheses:

We hypothesize that the incidence of pediatric cardiac arrest varies greatly within different locations within the Commonwealth. Furthermore, we believe that there are identifiable risk factors for children within these locations, such as access to health care services, race and socio-economic status, that put them at increased risk for suffering a cardiac arrest. To test this hypothesis, a Pediatric Cardiac Arrest Registry will be created across the Commonwealth to determine incidence rates for children. Local resources (regional EMS centers and hospitals) will be questioned regarding the number of cardiac arrests in children observed and the patient outcomes. High-incidence and high-mortality regions will be identified and a protocol for individualized training of health care personnel and lay persons will be instituted by experts in pediatric simulation from Children's Hospital of Pittsburgh Simulation Center and the Peter M. Winter Institute for Simulation, Education, and Research of Pittsburgh (Dr. Fiedor Hamilton). The goal of this effort is to decrease the incidence of cardiac arrest by 30 - 50% in high-incidence regions and to train medical personnel at advances in neurological care of children after cardiac arrest.

Impact on Health of Pennsylvanians

Pediatric cardiac arrest is the cessation of all heart pumping activity, which results in loss of oxygen to tissues. The brain is a uniquely sensitive organ for nutrients and requires oxygen for any energy requiring process. Because of this unique vulnerability of the brain, any significant decrease in oxygen delivery causes cerebral dysfunction that quickly progresses to death of cells that cannot be replaced. The incidence of cardiac arrest in children in the Commonwealth is not known. However, we surveyed the major hospitals within the state last year and found that 228 children were admitted to one of our Pediatric Intensive Care Units with cardiac arrest in a 12-month period. We did not track survival of these children, but national estimates indicate that only 7 - 10% who suffer out-of-hospital cardiac arrest survive to hospital discharge with only slight improvement in those who have a cardiac arrest within the hospital. Chances of full neurological recovery after cardiac arrest remain extremely remote, with approximately 4% survival without neurological deficits in the out-of-hospital group. Assuming a 10% survival rate for these 228 children, a median age of cardiac arrest of 1 year and an average life-expectancy of 78 years, staggering statistics reveal themselves. An estimated 205 children died within our institutions in a single calendar year. These children will have lost an estimated 15,785 productive years of life if they lived to normal adulthood and avoided the cardiac arrest in infancy or adolescence. The amount of new disabilities for survivors and the costs of their life-long care have never been calculated but represent a tremendous burden to the families of the victims as well as the health system of the Commonwealth. The amount of health care resources spent on the care of these children is difficult to calculate, but likely represents tens or hundreds of millions of dollars when both acute and follow-up care is included. It is likely that these estimates could be doubled or tripled if children not reaching our intensive care units were included in the analysis. For these reasons, a substantial effort to detect, prevent and treat pediatric cardiac arrest in Pennsylvania is desperately required.

In our proposal, we plan on bridging the gap in knowledge about pediatric cardiac arrest within the Commonwealth. We plan on comprehensively defining the number of cardiac arrests that occurred to children within the Commonwealth so that this disorder can be better understood. In this process, we will liason with

primary care providers, hospitals and medical examiners of each county to determine the true incidence of cardiac arrest in the Commonwealth. We anticipate that "hot-spots" of cardiac arrest will be identified through this process with areas of high incidence and/or mortality. We will then use the internationally-renowned simulation center of Children's Hospital of Pittsburgh Children's Hospital of Pittsburgh Simulation Center and Peter M. Winter Institute for Simulation, Education, and Research (WISER) to assist in training care providers within those regions about the most effective techniques for resuscitation of children. For children who have suffered cardiac arrest, there are currently no definitive treatments for neuroprotection. Therefore, a clinical research program to determine pharmacological agents to produce neuroprotection in children will be designed. This approach will be used because multiple, single-agent strategies that showed promise in preclinical testing failed to show benefit to patients, probably because many mechanisms are responsible for neurological damage. We will focus on drugs with known safety profiles in children that have shown great promise in preclinical studies, including erythropoietin, estrogen and G-CSF. By acting on multiple mechanisms, we believe these agents show great promise in mitigating neurological injury. Lastly, this proposal will utilize the unprecedented talents of researchers in resuscitation to develop novel approaches to pediatric cardiac arrest using animal models. In total, these studies maximize care of children within the Commonwealth now and in the coming years.

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Health Research Priority

Cardiac arrest has a devastating effect on the neurological development of children within the Commonwealth. There are few statistics across the state, but we found that in 2006, there were 228 cardiac arrests at 5 Children's Hospitals in Pennsylvania (Children's Hospital of Pittsburgh, Children's Hospital of Philadelphia, Hershey Med. Center, St. Christopher's Hospital, and Geisinger Med. Center). Virtually all deaths from cardiac arrest are a result of severe neurological dysfunction from lack of blood flow and oxygen to the brain. While the mortality is extremely high for this condition (>80%), a greater burden may be borne by the survivors who frequently suffer life-long health impairment and require tremendous resources from the Commonwealth for ongoing care. We have developed a preclinical animal model to test potential pharmacological strategies and intend on pursuing translational trials that could be brought to the bedside concurrently. We propose that the priority of preventing cardiac arrest and effectively preventing and treating neurological injury after arrest within the Commonwealth is a critical public health initiative. We believe that applying preventative strategies in our communities through simulation-based training and from a comprehensive clinical registry, testing pharmacological agents in our pre-clinical model and advancing these agents into clinical trials, will improve the health of children in the Commonwealth.

Biomedical research questions and hypotheses:

Models of pediatric cardiac arrest are actively being developed within the Commonwealth. In particular, investigators at the Safar Center for Resuscitation Research at Pittsburgh (Drs. Clark, Bayir, Fink and Kochanek) have been world leaders at developing clinically relevant animal models of pediatric cardiac arrest. This proposal will test whether the combination of N-acetyl cysteine and probenecid (an anti-oxidant agent and one that helps other drugs remain across the blood-brain barrier) decreases neurological morbidity and mortality in rat and swine models of pediatric cardiac arrest. In particular, cell death in vulnerable regions of brain, functional outcome, and a number of biochemical methods for therapeutic drug monitoring (oxidative damage and anti-oxidant reserves) will be tested. Importantly, state-of-the-art behavioral studies of memory and motor skills reflecting the quality of neurological function will be tested. The dosing regimen will be established to maximize of effect and then these doses will inform decisions regarding the clinical trial outlined below. We believe this approach may represent a novel mechanism to achieve local brain delivery of potent anti-oxidants using agents that have been in clinical use for decades.

Clinical research questions and hypotheses:

Since single drug therapies for neuroprotection have routinely failed in clinical trials, we hypothesize that a targeted CNS anti-oxidant strategy will improve 3 month survival and 12 month neurological outcome in children after pediatric cardiac arrest. Specifically, we will test whether N-acetyl cysteine and probenecid in the acute period after pediatric cardiac arrest improves outcome. This approach may optimize the anti-oxidant

effects of the drug within the brain, has shown promise in pre-clinical trials of cerebral ischemia and will have undergone pre-clinical testing at our facilities. A consortium across the Commonwealth will be established encompassing the major centers for care of children after cardiac arrest. Dosing regimens will be determined for each agent as well as the combination in Phase II trials. Then, the combination therapy will be tested in a Phase III trial. A study planning committee (Chairs: Drs. Clark, Bayir and Bell (Pitt) and Nadkarni (Penn)), a data coordinating center and an outcomes center (Chair: Dr. Beers - Pitt) will be established. A Data Safety Monitoring Board will be appointed by Department Chairs at each of the Universities to monitor for the safety.

Health services research questions and hypotheses:

We hypothesize that the incidence of and the mortality after pediatric cardiac arrest varies within regions of the Commonwealth. Furthermore, we hypothesize that there are factors within various regions (race, socio-economic status, access to health care resources and others) that affect the incidence and mortality of pediatric cardiac arrest. To test this hypothesis, a Pediatric Cardiac Arrest Registry will be created to determine incidence rates for children of all ages. All EMS and hospitals within the Commonwealth will be contacted by principal investigators of the various participating sites and questioned regarding the number of cardiac arrests in children under 18 years of age. Where possible, the ultimate patient disposition and outcome will also be evaluated. High-incidence and high-mortality regions will be targeted for training by experts in Pediatric Simulation Center of Children's Hospital of Pittsburgh (Dr. Fiedor-Hamilton). In sessions for health-care providers, advanced life support skills for children will be taught and the result of this training will be tracked for improvement in patient outcomes. This will also serve as a foundation for future trials on pre-hospital studies to improve outcome after cardiac arrest in children.

Impact on Health of Pennsylvanians

Pediatric cardiac arrest can occur as a result of primary heart disease or, more commonly, as a result of progressive respiratory failure. Regardless of etiology, sequelae-free survival after cardiac arrest is very rare. National statistics indicate that < 10% survive to leave the hospital if the arrest occurs in the community, while only 1 in 5 children survive arrests that occur within the hospital and are witnessed. In this small percentage of survivors, those without neurological dysfunction after cardiac arrest approaches 5% in some of the most recent publications from the American Heart Association and the National Registry for Cardiopulmonary Resuscitation. Data from within the Commonwealth are currently not available primarily because cardiac arrest can result from a large number of disorders (congenital heart disease, pneumonia, sepsis, burns, trauma and others). This diversity of pre-existing or causative conditions is not conducive to routine monitoring of health in children that occurs for other diseases within the Department of Health's system. In preparing for testimony in 2007, we surveyed the 5 largest institutions caring for critically-ill children within the Commonwealth for information regarding neurological causes of injury or death (Children's Hospital of Pittsburgh, Children's Hospital of Philadelphia, Hershey Medical Center, St. Christopher's Hospital for Children and Geisinger Medical Center). In this survey, we found that 228 children were admitted to the PICU with cardiac arrest in 2006, meaning that 4 children suffered cardiac arrest every week of the year. A great majority undoubtedly did not survive their arrest, although we did not survey the ultimate outcome in this preliminary study. With the average age of such children likely near 1 year (based on the general age distribution of critically-ill children), these deaths mean a tremendous loss to the state of productive years of life for its residents. Moreover, it is likely that this represents a fraction of the children who suffered a cardiac arrest within the state, as children who were unsuccessfully resuscitated by EMS, in Emergency Departments or at other facilities would not have been collected based on our surveying methodology. Nevertheless, assuming a 10% survival rate, a median age of cardiac arrest of 1 year and an average life-expectancy of 78 years, a grim set of statistics emerge. Approximately 205 children died within our institutions and an estimated 15,785 productive life-years were lost. Saving these lives without neurological sequelae would be equivalent to allowing 1500 stroke victims to live an additional 10 years - which would be an incredible leap in care of adults with stroke. Moreover, the savings in health care dollars spent is virtually impossible to calculate at this time, but would undoubtedly be

substantial. For these reasons, a priority of preventing and treating pediatric cardiac arrest in Pennsylvania is desperately needed.

In our proposal, we plan on defining the incidence and mortality of cardiac arrest in children and developing pre-clinical and clinical treatment strategies to mitigate neurological injury. In the first aspect of our proposal, we intend to identify all children within the Commonwealth who suffer from a cardiac arrest and intervene in high-incidence areas to improve the response of the health system for this condition using the Simulation Center of Children's Hospital of Pittsburgh. Secondly, a clinical research program to determine if a novel anti-oxidant drug strategy can produce neuroprotection in children after cardiac arrest will be designed. This approach will use N-acetyl cysteine as an anti-oxidant agent and probenecid to aid in penetration into the brain. We will test these agents in established models of pediatric cardiac arrest in the lab and translate these findings to a series of clinical trials. Dosing (Phase I) and safety trials (Phase II) in humans will be performed based on the laboratory data and ultimately, a Phase III efficacy trial will be performed to test if this strategy can mitigate neurological damage after pediatric cardiac arrest. In total, these studies seek to maximize care of children within the Commonwealth now and in the coming years.

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Health Research Priority

Children suffer from cardiac arrest within the Commonwealth every day and currently there are no proven therapies to protect the brain once the arrest occurs. In 2006, we found that there were 228 cardiac arrests at the major 5 hospitals caring for children in Pennsylvania (Children's Hospital of Pittsburgh, Children's Hospital of Philadelphia, Hershey Medical Center, St. Christopher's Hospital for Children and Geisinger Medical Center). Over a 5-year period in our institution, we found that 200 children were admitted to our intensive care unit after cardiac arrest. While the causes are diverse, the most likely result is either death or severe neurological impairment. Hypothermia (the lowering of body temperature) is effective in adults after cardiac arrest but has not been fully tested in children. In this proposal, we will answer two fundamental questions regarding cardiac arrest in children. First, we will determine the incidence of cardiac arrest within the Commonwealth and develop an interventional strategy to train personnel in high-cardiac arrest areas on the newest techniques for restoration of blood flow and neuroprotection. Second, we will test if relatively prolonged hypothermia improves neurological outcome in pre-clinical and clinical trials compared to either normothermia or brief hypothermia. We propose that prevention and treatment of cardiac arrest within the Commonwealth is a critical public health goal that warrants investigation.

Biomedical research questions and hypotheses:

Hypothermia has been a focus of study within the Safar Center for Resuscitation Research for over 20 years and we are recognized experts within this emerging field of neuroprotection. Multiple models of human diseases have been developed including adult cardiac arrest, adult and pediatric traumatic brain injury and hemorrhagic shock. Recently, we developed a rat model of pediatric cardiac arrest in immature rats so that clinical strategies regarding pediatric cardiac arrest could be tested within our laboratory. In particular, prolonged hypothermia (12 h) will be tested against either brief hypothermia (3 h) or normal temperature in this established rat model of injury. Cell death in vulnerable regions (CA1 of hippocampus), infarct volume and activation of a number of inflammatory cascades (cytokines, oxidative stress) will be tested at various times after injury. State-of-the-art assessment of metabolites of neuronal damage and death in the brain will be measured by Magnetic Resonance Spectroscopy at Carnegie Mellon University MRI Center. Lastly, behavioral assessments of memory and motor skills will be performed. We believe that these studies will form the basis for the clinical trials of hypothermia that are desperately needed.

Clinical research questions and hypotheses:

Single drug therapies for neuroprotection have routinely failed in clinical trials. It has been theorized that this occurs because multiple pathological mechanisms interact to cause death and organ dysfunction. Hypothermia has been theorized as an ideal neuroprotectant because it acts via multiple mechanisms and may mitigate damage in multiple ways. We hypothesize that prolonged hypothermia (72 h of cooling to 32 - 34 degrees C) will provide greater neuroprotection than normal temperature or shorter hypothermia (24 h). We will assess outcomes by assessing MRSpectroscopy findings within the first week after arrest, mortality at 3 months and

neuropsychological function at 12 months. A research consortium across the Commonwealth will be established encompassing the major centers for care of children after cardiac arrest to allow for full recruitment of children within the Commonwealth. A research committee (Chairs: Drs. Fink and Bell (Pitt) and Nadkarni (Penn)), a data coordinating center (Hershey) and an outcomes center (Chair: Dr. Beers - Pitt) will be established. A Data Safety Monitoring Board will be appointed by Department Chairs at each of the Universities to monitor for the safety of the human subjects.

Health services research questions and hypotheses:

We hypothesize that the incidence of pediatric cardiac arrest varies within regions of the Commonwealth. Furthermore, we hypothesize that there are factors within various regions (race, socio-economic status, access to health care resources and others) that affect the incidence and mortality of pediatric cardiac arrest. To test this hypothesis, a Pediatric Cardiac Arrest Registry will be created across the Commonwealth to determine incidence rates for children of all ages. Regional emergency medical systems and hospitals within the Commonwealth will be queried regarding the number of cardiac arrests in children under 18 years of age and the patient outcomes. High-incidence and high-mortality regions will be identified and an intervention of training by experts in Pediatric Simulation from Children's Hospital of Pittsburgh (Dr. Fiedor-Hamilton) and Children's Hospital of Philadelphia (Dr. Nadkarni) will occur for health-care providers as well as sessions available for the lay public. The goal of this effort is to decrease the incidence of cardiac arrest by 30 - 50% in high-incidence regions and to train medical personnel at advances in neurological care of children after cardiac arrest.

Impact on Health of Pennsylvanians

Pediatric cardiac arrest is among the most lethal conditions of childhood. Survival statistics are grim, with between 7 - 10% survival to discharge in the case of out-of-hospital cardiac arrest and only 20 - 22% survival for children who suffer cardiac arrest in the hospital setting. Even worse, cardiac arrest after traumatic injury is almost uniformly lethal. Chances of full neurological recovery after cardiac arrest are slim, with approximately 4% survival without neurological deficits in the out-of-hospital group according to national studies. The actual number of pediatric cardiac arrests throughout the Commonwealth each year is currently unknown, but will be a focus of this proposal. At 5 large institutions caring for children (Children's Hospital of Pittsburgh, Children's Hospital of Philadelphia, Hershey Medical Center, St. Christopher's Hospital for Children and Geisinger Medical Center), 228 children were admitted to the PICU with cardiac arrest in 2006. This is likely a significant underestimation of the total burden on the Commonwealth because children who failed to survive to be admitted to one of our intensive care units or were admitted elsewhere would not have been captured in our methodology. It is therefore likely that up to 400 - 600 children suffer cardiac arrest within the Commonwealth each year. While this number may be small in comparison to conditions within the geriatric community (such as stroke or heart disease), the impact on health of the population is enormous. Assuming a 10% survival rate, a median age of cardiac arrest of 1 year and an average life-expectancy of 78 years, 600 cardiac arrests within the Commonwealth would likely lead to 540 deaths. This would be an estimated 40,500 life-years lost to the Commonwealth. If the Commonwealth could develop a program such as this in stroke that could extend the lives of 4,050 stroke victims by 10 years, we believe that program would be perceived as an paradigm shift in medical care. The program we are advocating for targets this type of medical advance to occur every year if arrests could be completely avoided or successfully treated. Moreover, this number of pediatric cardiac arrests in the Commonwealth implies that up to 60 survivors each year occur. The amount of health care resources these children require has never been calculated, but likely reaches tens to hundreds of millions of dollars each year if all acute and chronic care costs for these children were calculated. For these reasons, a substantial effort to detect, prevent and treat pediatric cardiac arrest in Pennsylvania is required.

In our proposal, we plan on both determining the extent of pediatric cardiac arrest within the Commonwealth and testing if prolonged hypothermia can mitigate against the dysfunction of the brain after the event. We will define the extent of the problem by gathering data from all EMS systems, hospitals and medical examiners within the Commonwealth. In this process, we anticipate that we will find areas within the Commonwealth

where health disparities are large (both incidence and mortality), likely in areas with poor access to primary health care. We will then use the internationally-renowned simulation center of Children's Hospital of Pittsburgh to assist in training care providers within those regions. There are currently no definitive treatments for neuroprotection for children after cardiac arrest, but hypothermia has been shown to be beneficial in adults and in neonates. Using both lab-based protocols for hypothermia after cardiac arrest in immature animals as well as a Phase III clinical trial in humans, we will determine if prolonged hypothermia improves neurological function and survival. By acting on multiple mechanisms, we believe hypothermia is well-suited to mitigate the anticipated neurological injury after cardiac arrest. The pre-clinical and clinical trials will use similar outcome measures (mortality, MR spectroscopy and neuropsychological in humans, mortality, MR spectroscopy and behavioral in animals) so benefits of hypothermia can be fully evaluated. In summation, these studies attempt to determine the optimal application of hypothermia in children within the Commonwealth with cardiac arrest.

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Health Research Priority

Cardiovascular disease is the No. 1 worldwide killer of men and women, including in the United States. It is responsible for 40 percent of all the deaths in the United States, more than all forms of cancer combined. The various diseases that fall under the umbrella of CV disease include coronary artery disease, heart attack, heart failure, aneurysms, high blood pressure and stroke. An aneurysm is a bulge or weakness in a blood vessel (artery or vein) wall, which usually increases in size over time, having the potential to rupture and cause life-threatening bleeding. Aneurysms can occur in arteries in any location in the body, but the most common sites include the abdominal aorta and the arteries at the base of the brain. The formation of an aneurysm represents the loss of structural integrity of the vessel wall. The abdominal aortic aneurysm (AAA) is a socially relevant cardiovascular health disease. The prevalence of AAA disease is 8.8% in the population above 65 years of age and men are affected more often than women by a ratio of 4:1. Intracranial aneurysms are lesions of the arterial wall commonly located at branching points of the major arteries coursing through the subarachnoid space, predominantly at the circle of Willis in the base of the brain. The incidence of reported ruptured aneurysm is about 10 in every 100,000 persons per year (about 27,000 patients per year in the U.S.), most commonly in people between ages 30 and 60 years.

Biomedical research questions and hypotheses:

What are the underlying mechanisms by which aneurysms (aortic and cerebral) rupture? How can rupture be predicted and prevented? How does the blood vessel expand and remodel over time leading to continuous aneurysm growth and eventual rupture? We hypothesize that (a) individual-specific geometry and shape of the diseased blood vessel influence the at-risk status of an aneurysm at any stage of the disease; (b) biomechanical determinants of aneurysm rupture include flow-induced elevated forces and strains on the blood vessel wall, which can be evaluated non-invasively by medical image-based and computational methods; (c) there is a positive correlation between subject-specific geometry and the biomechanical determinants of rupture potential, which places certain "categories" of aneurysm shape at a higher risk of rupture, regardless of the initial size of the aneurysm at the time of diagnosis. The assessment of rupture of aortic and cerebral aneurysms can be performed incorporating these geometry-based indices and biomechanical determinants in a non-invasive manner by means of computational (software) tools that can be used by the vascular surgeon or interventional radiologist in a clinical setting.

Clinical research questions and hypotheses:

The optimal strategy in the clinical management of cardiovascular disease as it relates to aneurysms is clear: prevention of aneurysm rupture is the primary goal. Currently, the assessment of aneurysm rupture is conducted on the basis of measuring the size (diameter) of the aneurysm. However, there are many large aneurysms that are detected at an advanced stage of the disease that have not ruptured at the time of diagnosis. Likewise, 10% to 24% of ruptured aneurysms are considered "small", typically less than 5 cm in maximum diameter in the case

of aortic aneurysms. There is need for a more reliable indicator of aneurysm rupture potential. Once an aneurysm is diagnosed, what is the at-risk status of this vascular disease and what quantitative parameters can be measured to evaluate the risk of rupture on an individual basis? We hypothesize that there are fundamental differences in the wall stress, size, tortuosity, asymmetry, wall thickness, aspect ratio, and thrombus content between ruptured and non-ruptured aneurysms. These and other factors must be evaluated accurately for subjects placed under surveillance to assess aneurysm rupture potential.

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Abdominal aortic aneurysm rupture kills about 15,000 Americans each year. This statistic is believed to be an underestimation as the disease is asymptomatic and many deaths related to aortic aneurysm rupture may be classified under a different cause. Cerebral aneurysm rupture occurs in about 27,000 Americans each year. The Commonwealth of Pennsylvania is no stranger to these statistics, given the elderly population residing here. The Pennsylvania Department of Health's EpiQMS online data system reveals out of the 379,509 deaths in the period 2004-2006 for Pennsylvania, 136,180 (36%) deaths were attributed to cardiovascular disease. Of these, 117,190 (86% of all CV disease related deaths) occurred in patients 65 years of age and older. The African-American population accounted for 9% of the death toll, well aligned with its statistical participation of the states' total population (10.5%). The major health concern with aneurysms is the high mortality and morbidity rates when the aneurysms rupture. For aortic aneurysms, mortality rates are reported up to 80%; for cerebral aneurysms, up to 60%. Given that risks factors for aneurysm disease include smoking, hypertension, chronic obstructive pulmonary disease, atherosclerosis, familial history, and advanced age, the Commonwealth of Pennsylvania, with its everly increasing elderly population, is particularly affected in a disproportionate manner for cardiovascular disease.

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Health Research Priority

The existence of health disparities affecting individuals and families in Pennsylvania coping with poverty, those living in isolated locales, and those minority individuals who have traditionally lacked access to culturally competent providers is made clear by all available statistical data. Chronic disease and obesity are more prevalent among minorities and persons living in poverty. Infant mortality rates are higher among these groups. Health outcomes are significantly poorer. Disparate health status and outcomes among vulnerable populations, particularly racial and ethnic minorities, reveals a health research priority in the Commonwealth. In establishing the Office of Health Equity, Pennsylvania has recognized that addressing the quality and competency of health care delivered to our most vulnerable residents is an urgent and unmet need in the Commonwealth. Further research aimed at simply quantifying the existence of health disparities across a spectrum of chronic diseases among vulnerable populations is not needed. Research is needed that seeks to clarify both the antecedents and the consequences of health disparities for individuals, for providers and for the overall healthcare system in the Commonwealth. The results would then be used to design targeted, specific interventions to address these disparities.

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

- Do individuals from vulnerable populations report reluctance to seek care because they fear discrimination or insensitivity? Are there identifiable subgroups who report greater reluctance or fear?
- What do health professionals believe about the need for culturally appropriate care? What attempts do they make to deliver culturally appropriate care? Do they perceive the care they deliver to be appropriate to persons from all economic groups, ethnic groups and ages and locations?
- What types of education about chronic disease and its management do health professionals provide to individuals from vulnerable populations? Do they perceive these educational materials or activities to be culturally appropriate?
- What do health professionals know about treatment adherence by individuals from vulnerable populations? How do they explain failure to adhere to treatment in these individuals? What strategies do they identify as necessary to improve adherence?
- Do health care providers perceive disparities in care for chronic disease and if so, how do they explain them? The primary hypothesis is that greater practitioner capacity to know, account for and integrate factors that affect patient behavior will improve chronic disease self management.

Health services research questions and hypotheses:

- Who provides medical and/or home care for chronic disease for individuals from vulnerable populations? Are there differences in where and how individuals obtain care related to geographical location, gender, age, race, sexual orientation, or economic status?
- What do individuals from vulnerable populations know about the causes, treatment, and management of chronic disease? Where do they obtain their information? What sources of information do they trust? Are there differences in health literacy related to geographical location, gender, age, race or economic status?
- What reasons do they give for failure to adhere? What factors do they identify as likely to increase adherence? What is the level of satisfaction with care is reported by individuals from vulnerable populations? What barriers to satisfactory care do individuals from vulnerable populations perceive? Primary hypotheses are that practitioner understanding of dynamics affecting vulnerable populations' attitudes toward and experience with health care will: lead to improvement in treatment adherence; and to improved outcomes of care.

Impact on Health of Pennsylvanians

The concerns regarding the impact on vulnerable populations are significant and far-reaching. Although over one in 10 (11%) white Pennsylvania residents over the age of 18 are uninsured the rates for both African Americans and Hispanics is about twice as high (21% and 22% respectively in 2006). The consequences of a lack of insurance are well documented: little or no preventive care and failure to seek any care at all until a health condition has become severe. In Pennsylvania, for example, 21% of Hispanics and 17% of blacks state they did not have a personal doctor, compared with 9% for whites. The impact of these consequences is particularly apparent in the diagnosis and treatment of chronic disease. Rates of chronic disease increase with age and are higher among minorities and those living in poverty. For example, 17% of individuals earning less than \$15,000 were told they have diabetes, compared with 6% of those earning over \$50,000. And according to state data, rates of diseases such as congestive heart failure, uncontrolled diabetes, and both pediatric and adult asthma are all significantly greater for both blacks and Hispanics in Pennsylvania. For some, such as pediatric asthma, the rates are 3 to 7 times greater for these populations (10.4/10,000 for whites, 31.7 for Hispanics and 75.9 for blacks). Health outcomes for minorities with chronic disease are poorer. For example, death rates for heart disease and stroke among black residents in 2003 (290.5 and 75.6 respectively) were substantially greater than white rates (238.9 and 49.9 respectively). Poor outcomes may result from lack of access to any type of care due to economic and/or geographic issues or from lack of access to culturally appropriate care including education about self care. Pennsylvania has high rates of hospitalizations resulting from the lack of early, ongoing care for chronic disease. It is estimated that the failure to deliver culturally appropriate, ongoing care for chronic disease results in over \$1.7 billion in potentially avoidable hospital charges for chronic disease sufferers. This economic cost is mirrored by human costs, both for those suffering from chronic disease and those providing care.

Descriptive/epidemiological research concerning the nature and sources of treatment received for chronic diseases by individuals from vulnerable populations is limited. At the same time we recognize that the term "vulnerable populations" includes but is not limited to racial and ethnic minorities as well as low income rural populations, inner city poor and others in the Commonwealth. Thus the scope of this initiative would consider residents representing a broader cross section of state vulnerability. Nonetheless, work to date on racially and ethnically diverse populations alone has suggested the potential benefits of such efforts. As seminal reports such as the Institute of Medicine's publication, "Unequal Treatment" have documented, research and interventions that increase practitioner knowledge of and capacity to respond to how the "cultures" of vulnerable groups affect understanding of and adherence to recommended treatment regimens for chronic conditions (including self management), have the potential to significantly improve health outcomes and reduce disparities. Similarly, practitioners throughout the state and their hospitals and other health care settings--as well as vulnerable

patients suffering from chronic illnesses--can benefit from the results of related initiatives through improved quality of care.

Contact Information

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Health Research Priority

The longterm complications of diabetes, including retinopathy, nephropathy, neuropathy and cardiovascular disease, are interrelated consequences of diabetes that cause disability and premature death on a massive scale. The rising incidence of diabetes calls for a comprehensive approach that includes ideal disease management, prevention, and, importantly, solutions for the large numbers of people who are already stricken with or at high risk for these devastating complications. The best approach to these problems requires combined biomedical, clinical and health services research efforts.

Biomedical research questions and hypotheses:

The risk of diabetes complications correlates closely with the degree of diabetes control and associated insulin resistance. Diabetes complications are characterized by vascular damage and low-grade inflammation. These facts suggest that impaired insulin action and nutrient excess causes diabetes complications. This hypothesis can be tested directly in animal models of diabetes in which insulin action and nutrient levels can be controlled, along with measures of the impact on the eye, heart, kidney, and nerves. These studies are vital because they can test the role of different variables in a short time and in both Type 1 and Type 2 diabetes models. Results will be directly applicable to human disease and will allow for investigation of genetic determinants of complications and pre-clinical testing of potential new treatments. we expect that Type 1 and Type 2 diabetes models will be found to have common metabolic pathways that lead to organ damage. These common pathways are most likely to be the critical points that require therapeutic control to reduce the progression of complications.

Clinical research questions and hypotheses:

The risk of diabetes complications correlates closely with the degree of diabetes control and associated insulin resistance. Diabetes complications are characterized by vascular damage and low-grade inflammation. These facts suggest that impaired insulin action and nutrient excess causes diabetes complications. This hypothesis can be tested clinically by studying patients with varying degrees of diabetes and complications, and can be approached in at least two ways. First, analysis of blood samples from subjects in the Diabetes Control and Complications Trial and other large studies in which the complications and metabolic control have been well characterized are important, and measurements of nutrient and other metabolite levels in these patients can be correlated with outcomes. A second approach is to investigate the abnormal metabolic regulation in rare patients who develop complications despite only modest increases in blood sugar. Results from these clinical studies can be correlated directly with findings in the animal models to determine which aspects of metabolic derangement most closely associate with complications. Again, these findings will have substantial therapeutic implications.

Health services research questions and hypotheses:

The risk of diabetes complications correlates closely with the degree of diabetes control and associated insulin resistance. Diabetes complications are characterized by vascular damage and low-grade inflammation. These facts suggest that impaired insulin action ("insulin resistance") and nutrient excess causes diabetes complications. In fact, the association between insulin resistance and complications has been demonstrated by the Dr. Trevor Orchard at the University of Pittsburgh. Large patient registries that have been developed in recent years, such as that at the Penn State College of Medicine, enable conduct of large population-based studies that could (1) reveal environmental and healthcare delivery variables that impact the development of diabetes complications, and (2) test new population-based treatments such as novel means of providing dietary and nutritional guidance to patients. For a high-incidence chronic disease such as diabetes having staggering costs when managed in traditional ways, development of these population-based interventions is essential.

Impact on Health of Pennsylvanians

"The Burden of Diabetes in Pennsylvania 2007" reports that persons with annual incomes less than \$15,000 have a significantly greater risk of having diabetic eye disease than those with incomes greater than \$75,000 (p. 47), and the risk of cardiovascular disease is 4-fold higher in persons with diabetes than those without (p. 46). Hispanics, African Americans and Caucasians in rural Pennsylvania are very likely to suffer the complications of diabetes. Effective medications are readily available to treat diabetes and associated conditions such as hypertension and high blood lipid levels. Control of blood pressure, blood glucose and lipids significantly reduces the risk of diabetes complications. Annual examinations for foot and eye problems substantially reduces the risk of impairment such as amputation or vision loss. Nevertheless, only 7% of persons reach target levels for blood pressure, glucose and lipids, and only 50% of persons at risk receive annual eye and foot examinations. The economic costs of diabetes complications are staggering, with national hospital costs of \$3.8 billion in 2001, of which two-thirds could be prevented. The costs of lost productivity and chronic disability add further to the costs, and the impact in Pennsylvania is consistent with national data.

The combined biomedical, clinical and health services research infrastructure in Pennsylvania is well positioned and motivated to make substantial impact on the impact of diabetes complications.

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Health Research Priority

Childhood obesity has reached epidemic proportions. Although evidence indicates that fetal and infant periods play critical roles in the development of obesity, there has been little focus on preventing obesity during pregnancy and infancy. Results of the recent National Health and Nutrition Examination Survey highlighted the need for very early intervention: A staggering 26.2% of children aged 2- to 5 years were already overweight, while the prevalence of obesity among infants 2- to 23 months had increased 60% in the last 3 decades. Recognizing the link between childhood obesity and later morbidity, the Institute of Medicine's expert committee wrote "the prenatal period, infancy, and early childhood may be stages of particular vulnerability to obesity development because they are unique periods for cellular differentiation and development. This unique vulnerability might make it possible for actions taken at these stages to determine the future course of adiposity." While interventions to prevent obesity among older children have generally been ineffective, there are numerous opportunities to interrupt the natural history of obesity very early in life. There is strong evidence that specific interventions in pregnant women and very young children could provide lifelong benefit. Clinical research to formally evaluate and further develop these interventions is needed."

Biomedical research questions and hypotheses:

None

Clinical research questions and hypotheses:

1) Can childhood obesity be prevented or moderated by delivering interventions to pregnant women?

We hypothesize that maternal characteristics that are associated with obesity in offspring are modifiable can be moderated through intervention. Such characteristics include maternal obesity, diabetes, pregnancy weight gain, and diet during pregnancy. Each of these can be positively influenced through evidence-based interventions that include education, healthy diet, and exercise.

2) Can childhood obesity be prevented through interventions delivered during infancy?

We hypothesize that various aspects of an infant's life are ripe for interventions that can prevent obesity in the long term. Such areas include promoting breastfeeding, promoting healthy sleep habits, promoting other methods to soothe infants instead of feeding, establishing healthy food preferences early in life, and improving parental understanding of healthy growth patterns when their children are infants. Each of these can be

improved by evidence-based interventions shown to improve parent-infant interactions surrounding feeding and weight gain early in life.

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Acknowledging the high prevalence of overweight and obesity in the United States, Healthy People 2010 sought to improve the proportion of Americans that have healthy weights. A target of 60% of Americans living at healthy weights was established, but unfortunately, as of 2006 only 37% of adults in Pennsylvania were not overweight or obese. Stated another way, 63% of Pennsylvanians are living at an unhealthy weight. This problem disproportionately affects minorities as 69% of Black adults and 73% of Hispanic adults in Pennsylvania are overweight or obese.

Because maternal health and weight status during pregnancy are key factors in determining the health and future weight status of their offspring, it is particularly concerning that nearly half (46%) of women between the ages of 20 and 39 are overweight. This fact puts the next generation of Pennsylvanians at risk for even worse health than our current generation where obesity has reached epidemic proportions.

Given the prevalence of overweight and obesity among adults, it is not surprising, but still quite concerning that 32% of children aged 2-19 are overweight or obese in the U.S. Minorities are again disproportionately affected with 35% of Black and 38% of Mexican American children characterized as overweight or obese.

These data are particularly troubling given the known associations of obesity with conditions such as heart disease, hypertension, and diabetes as well as poor emotional health. As a result, the Institute of Medicine has estimated that nearly 10% of all medical costs in the U.S. currently can be attributed to overweight and obesity. Further, between the late 1970s and the late 1990s, the costs related to obesity related hospital care for children tripled.

Since few strategies have proven effective in treating obese children, these troubling figures point toward an alternate solution - prevention. Prevention through early intervention to reduce weight gain and childhood obesity can make an essential contribution to addressing the health care problems arising from obesity by stemming the rising prevalence of childhood obesity, which tracks to from infancy to childhood to adulthood. Further, since there is evidence that becoming obese as a child leads to more serious complications during adulthood, probably due to longer exposure to obesity's adverse metabolic effects, the cumulative effect of obesity plus its comorbidities of diabetes, hypertension, hypercholesterolemia, and sedentary life style will likely overwhelm the healthcare system in Pennsylvania and across the United States in the near future. In fact, it is estimated now that one out of every three children born in the U.S. will have diabetes during their lifetime. Therefore, before another generation exceeds its predecessor and escalates the obesity epidemic, evidence-based prevention efforts must be developed, tested, and implemented.

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Health Research Priority

NANOMEDICINE for CANCERS

Nanomedical materials have the potential to dramatically impact healthcare delivery through the diagnosis and treatment of cancer and other diseases. This initiative would focus on the development and application of nanomaterials (sub-microscopic particles) to diagnose and treat cancers, including tumors that are particularly difficult to reach by conventional means. In the area of cancer treatment, nanoscale materials have the potential to radically improve cancer therapy and to increase the number of highly effective therapeutic agents. Nanoscale constructs can serve as delivery vehicles capable of carrying large doses of life-saving drugs directly into malignant cells while sparing healthy cells; greatly reducing or eliminating the undesirable side effects that accompany many current cancer therapies. This is particularly important in the brain - an organ that is not readily accessible for drugs and is associated with a particularly poor prognosis when cancer is involved.

Biomedical research questions and hypotheses:

We expect nanomedical materials to serve as platform technologies for enhanced drug delivery and diagnostic imaging, and recommend support for continued development of these materials and detailed study of their activity in the body. The ability of nanomedical modalities to efficiently deliver drugs to cancerous cells including precisely targeted areas of the central nervous system is based on documented crossing of the blood-brain barrier, sustained-release capabilities, targetability, and lack of toxicity of the nanoscale delivery systems themselves. The tailored optical or magnetic properties of certain nanomaterials also make them ideal candidates for cell-specific imaging. Important biomedical research questions include (1) range of therapeutic materials that can be packaged and stabilized in drug carriers; (2) influence of carrier materials and particle size on distribution and cell uptake; (3) novel means of targeting including novel receptor ligands, materials having cell type-specific absorption or intracellular destination, and use of externally applied signals to steer particles or initiate drug release. Solutions will be directly applicable to other diseases, including neurological disorders, in which therapeutic delivery is an issue.

Clinical research questions and hypotheses:

We expect that nanotechnology can be used for early diagnosis of diseases marked by significant changes in cell phenotype, especially cancer and neurological disease. Despite progress in the treatment of cancer, the majority of cases are still diagnosed after tumors have metastasized, leaving the patient with a grim prognosis. Similar nanotechnology platforms can be used to produce targeted therapeutics as well as cell-specific imaging to improve non-invasive diagnosis, biopsy analysis, and intra-operative guidance. Specific clinical research should include evaluation of constructs that are ready for clinical evaluation for each of these diagnostic and treatment modalities. Particularly in cancer care, nanotechnology offers an unprecedented opportunity to study cancer cells in real time, at the molecular and cellular scales, during the earliest stages of the cancer process. Studies of cells harvested from different regions around tumor margins will provide new understanding of cancer processes as well as improved guidance for therapy.

Health services research questions and hypotheses:

We further anticipate that nanomedical materials can be adapted for biosensor design and implementation. Making strides in these areas is critical to improving the effectiveness and lowering the cost of disease and disease risk screening processes. As disease markers are identified through basic science and clinical studies, Pennsylvania's existing strengths in material development, surface chemical patterning and material processing are directly applicable to the production of practical, low-cost diagnostic assays.

Impact on Health of Pennsylvanians

The prognosis for many cancers, including brain, lung and pancreatic cancers, continues to be incredibly poor. In Pennsylvania, cancer incidence rates have been rising since 1996 and now exceed comparable rates for the US. In Appalachian Pennsylvania, these rates are even higher. Thus, it is clear that paradigm-shifting modalities must be developed for the detection and treatment of cancers, particularly in underserved rural communities that may have limited access to medical care. The nexus of material sciences, bioengineering, pharmacology, oncology and neuroscience has recently generated several exciting nanoscale materials uniquely suited for in vitro and in vivo application. Both the National Institutes of Health Road Map and the National Alliance for Nanotechnology in Cancer have developed initiatives in the design and optimization of nanoscale materials suited for targeted or control-release drug delivery, enhanced in vivo bioimaging or automated analytical detection of biomarkers. Pennsylvania has a unique and immediate opportunity to exploit bionanotechnology to benefit the citizens of Pennsylvania through job creation (in research and high-tech manufacturing), economic development (through start-up companies and technology licensing), and leadership in medicine and healthcare. This will require multifaceted, interdisciplinary research teams of scientists, engineers, physicians and ethicists who can create new pathways of discovery. The Universities and Medical Schools in the Commonwealth of Pennsylvania, as well as several specialized research labs associated with Pennsylvania hospitals and health centers, are positioned to address the scale and complexity of emerging nanomedical research issues and problems. The Commonwealth has already recognized this opportunity by providing investment in nanotechnology. But with the infusion of more significant funds, our recent progress and success in the areas of nanomedicine and nanotechnology can be further leveraged to capture federal NIH programs and National visibility.

Where are we today? Carnegie Mellon University, Lehigh University, The Pennsylvania State University, the University of Pennsylvania, and University of Pittsburgh all hold prestigious and accomplished NSF Materials Research Science and Engineering Centers of Excellence or established nanotechnology institutes. It is in these academic centers where the fundamentals of nanoscale science and engineering are being discovered and developed into new technologies. We also possess several state-of-the-art facilities for nanotechnology research, and numerous centers and consortia that are positioned to address specific problems in life science, medicine and health care. The Pennsylvania State University currently houses an NSF National Nanofabrication Infrastructure Network site, while the University of Pennsylvania has a Nanotechnology Institute (NTI), where there are already several programs focused on biotechnology and medicine. Pennsylvania institutions currently

have many active translational medicine training initiatives in which courses will be focused on the nexus among material sciences, bioengineering and clinical sciences. These programs are designed to train a workforce for nanotechnology and bionanotechnology at all levels from associate science degree programs in Nanomaterials through graduate education programs such as the Biomaterials and Bionanotechnology Summer Institute. The existence of such expertise, facilities and training programs within Pennsylvania will entice corporations to remain or relocate to our Commonwealth.

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Health Research Priority

The disorders of addiction, and the associated public health problems of violence, crime, and HIV/AIDS, are health research priorities for the research efforts at the Addiction Treatment Research Center at the University of Pennsylvania School of Medicine. Annual costs to Pennsylvania of the addictions, in health care, in lost productivity, and in crime exceed 15 billion dollars.

The rates of relapse in addiction are very high -- despite our best current treatment options. And the number of youths who proceed to drug addiction is also unacceptably high -- despite conventional prevention efforts. We believe that addiction outcome -- and addiction prevention -- can be dramatically improved by application of research tools that have only become widely available in the past decade. These are the complementary tools of brain imaging and genetics. These new tools suggest that brains at greatest risk for addiction/relapse may be the "same brains" at great risk for violence and risk-taking (including HIV risk) -- helping to explain why these devastating public health problems often travel together in the same individuals. By applying state-of-the-art brain-behavioral tools to clinical populations (drug court clients; cocaine, opiate, nicotine and alcohol-addicted patients, and at-risk adolescents) we hope to impact not only addiction outcomes, but also the linked problems of violence and HIV risk.

Biomedical research questions and hypotheses:

What are the brain vulnerabilities that increase

- 1) the risk for relapse in those who are already addicted (to cocaine, opiates, nicotine and alcohol)?
- 2) the risk for addiction in those who are not yet addicted (adolescents at risk)?
- 3) the risk for aggression/violence and risk-taking behavior (including HIV risk), in all these groups?

Research in our lab, and in others', suggests that (structural and functional) deficits in the brain's frontal regions, responsible for modulating both reward and aggressive impulses, may be critical in explaining vulnerability to addiction, to relapse, and to the linked problems of violence/crime, and HIV risk.

What are the genetic variants associated with the above brain and behavioral vulnerabilities?

Our labs have already identified genetic variations that influence addiction medication response, risk for heavy smoking, and greater vulnerability to drug craving cues. Gene variants leading to frontal dysfunction (poor inhibition, poor impulse control, poor decision-making) are an important research focus.

Clinical research questions and hypotheses:

Our guiding hypothesis -- that similar frontal deficits/genetic variation may confer vulnerability to relapse, to addiction, to violence, and to HIV risk -- will be used to predict outcome/treatment response in the following target populations: 1) For drug court clients with cocaine-related crime, can we predict which clients are at

greatest risk for relapse AND for violence -- while offering behavioral treatment addressing both problems? 2) For underserved minority females with nicotine dependence, stratified on dopamine transporter genetics: Can a novel medication impact the brain response to drug cues, improving treatment outcomes? 3) For Veteran (Afghanistan; Iraq) and non-veterans with alcohol dependence and prior trauma: Can brain and genetic measures predict treatment response to a novel medication that may benefit both alcohol and PTSD? 4) For opiate-addicted individuals receiving depot naltrexone treatment: Can imaging of brain opiate receptor occupancy predict medication efficacy and clinical outcome? 5) For ADHD adolescent smokers at-risk for illicit drug use: Will brain/genetic measures predict progression to illicit drug use? Can brain measures be used to create more effective anti-drug/pro-health messages?

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Addictions -- and the closely-associated problems of violence, crime and HIV -- exact an extraordinary toll on the nation and on the health of Pennsylvanians. Addictions are extremely common psychiatric disorders, with the lifetime likelihood of 1 in 6 for meeting the diagnostic criteria for addiction.

Nationally, the estimated cost of illicit drug use exceeds 160 billion dollars annually, with the majority of the costs associated with loss of productivity -- but including the costs of addiction-related health care, auto accidents, and crime (Office of National Drug Control Policy, 2000). Alcoholism and drug abuse are the "number one cause of preventable illness and death and are the root cause of one in four deaths each year through infectious disease, cirrhosis, car accidents or overdoses (McLellan, testimony before Philadelphia City Council, May 2003)". Drug use is implicated in "40% of violent crime, 60% of domestic violence crime, 80% of child abuse and neglect cases, 50% of theft and property offenses, and 75% to 99% of crimes involving prostitution or drug dealing/manufacturing (ibid, 2003)".

Pennsylvania mirrors these alarming national statistics, with cocaine, opiates, and marijuana as the most commonly trafficked illicit drugs (US DEA, 2007). Cocaine led the list of problematic illicit drugs through the 1980's and 1990's (associated with a high rate of emergency room mentions), with a severe impact on African American communities. There is unfortunately still no FDA-approved medication for cocaine dependence. Heroin addiction has been on a sharp rise in past decade, fueled by increases in heroin purity: Philadelphia heroin is now up to 70% pure, nearly twice the national average (DEA Philadelphia Field Division). Abuse of prescription opiates (OxyContin, Vicodin) has risen steeply in Pennsylvania, with the youth involvement in these drugs of particular concern.

Addiction to the legal drugs of nicotine and alcohol have severe economic and health consequences for Pennsylvanians. Cigarette smoking is the leading cause of preventable death in the nation and in the state, with more than 20,000 Pennsylvania deaths annually due to smoking -- 7 times the number of deaths due to motor vehicle accidents, homicides and suicides combined (Pennsylvania Department of Health, Tobacco Facts 2008). Pennsylvania health care costs for smoking-related illnesses exceed 4 billion annually, and the additional costs for lost productivity are estimated at 4.5 billion. Though there are treatments for nicotine dependence, standard nicotine replacement does not work as well for females, and underserved minority females have high rates of smoking and smoking-related illnesses (as compared to non-minorities). Alcohol is associated with 39% of fatal Pennsylvania crashes, with billions in lost productivity and associated health care costs (e.g., cirrhosis). Underage drinking in Pennsylvania is associated with annual costs of 2 billion dollars. Half of this (nearly 1 billion dollars) is related to violence-associated costs, \$658 million is due to traffic crashes, and approximately \$152 million is related to high-risk sexual activity. Alcohol is the most prevalent problem drug for veterans returning from Afghanistan and Iraq, and is often co-morbid with the chronic, debilitating illness of post-traumatic stress disorder.

A final addiction-related health risk -- and high health cost -- for Pennsylvanians is exposure to the HIV virus. HIV risk among drug using populations derives not only from the risk behaviors of needle-sharing among

intravenous users, but also from high-risk, unprotected sexual behaviors while intoxicated by drugs and/or alcohol. HIV risk is particularly high in urban "hot spots"; in Philadelphia, HIV risk is over-represented among minorities.

Our hypothesis is that the epidemics of drug addiction, drug violence, crime, and HIV risk are linked not just by circumstance, but by a shared biologic vulnerability. We feel the combined tools of neuroimaging and neurogenetics can impact these intertwined problems, to great public health advantage.

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Health Research Priority

We propose that the CURE non-formula funds be used to support collaborative research efforts aimed at understanding the mechanisms of aging. Medical and public health improvements have greatly extended the human lifespan, but this expanded lifespan is associated with a greater burden of age-associated disease; and Pennsylvania has one of the oldest state populations in the country.

Fundamental research has begun to explain the mechanisms of aging. For example, cells grown in tissue culture will divide a limited number of times before they die. In cancer, this self-limiting mechanism fails and cells do not die. Biologists now understand important components of this process. In another example of fundamental research into aging it's been observed that a class of enzymes called sirtuins is linked to longevity. Defects in sirtuins have been linked to age-related diseases such as diabetes and cancer. Older people are also more susceptible to infectious diseases.

Thus, the time is right for a state funded effort into basic research applied to aging and age-related illnesses. A deeper understanding of the biochemical and genetic events underpinning the aging process will ultimately lead to treatments that will mitigate the effects of aging, leading to a better quality of life.

Biomedical research questions and hypotheses:

Research questions/goals:

Identification of genes, proteins and enzymes related to aging and age-related diseases.

Structural analysis of age-related genes and their protein products.

Systems biology and computational analysis of age-related gene networks.

Chemical biology approaches to identify biological target molecules related to aging and development of agents to perturb those targets.

A greater understanding in these areas will lead to better insight into aging and age-related diseases.

Clinical research questions and hypotheses:

None

Health services research questions and hypotheses:

None

Impact on Health of Pennsylvanians

Pennsylvania has one of the oldest populations in the country. The leading edge of the post-war Baby Boom has passed the age of 60, and that large cohort represents an impending wave of age-related diseases, such as

diabetes, Alzheimer's, cancer, and influenza, to name just a few. These diseases will put enormous social and economic burdens on society and the health care system.

Research to identify genes, proteins and enzymes related to aging and age-related diseases, structural analysis of age-related genes and their protein products, systems biology and computational analysis of age-related gene networks, and chemical biology approaches to identify biological target molecules related to aging and development of agents to perturb those targets, will be important steps in understanding and preventing age-related disease.

In summary, we believe the time is ripe for a comprehensive effort using a variety of biological systems to study the underlying mechanisms that govern the aging process. This will improve not only the health of our many older Pennsylvanians, but the health of individuals world-wide.