

Written Testimony Submitted by the Public on the Health Research Priorities for 2012-2013

The Pennsylvania Department of Health solicited written testimony on health research priorities for state fiscal year (SFY) 2012-2013 using the form contained on pages 2-7. This document provides a copy of all of the written testimony submitted to the Department by June 15, 2011. 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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* Testimony was submitted by more than one person. This table shows only the name of the first person listed on the form. See form for the names of other persons.



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 2012-2013. Please use the form below 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 June 15, 2011, 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. After you submit written testimony, if you want to request a revision to your testimony, that request for revision must be submitted no later than June 15, 2011.

Questions? Contact: 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.

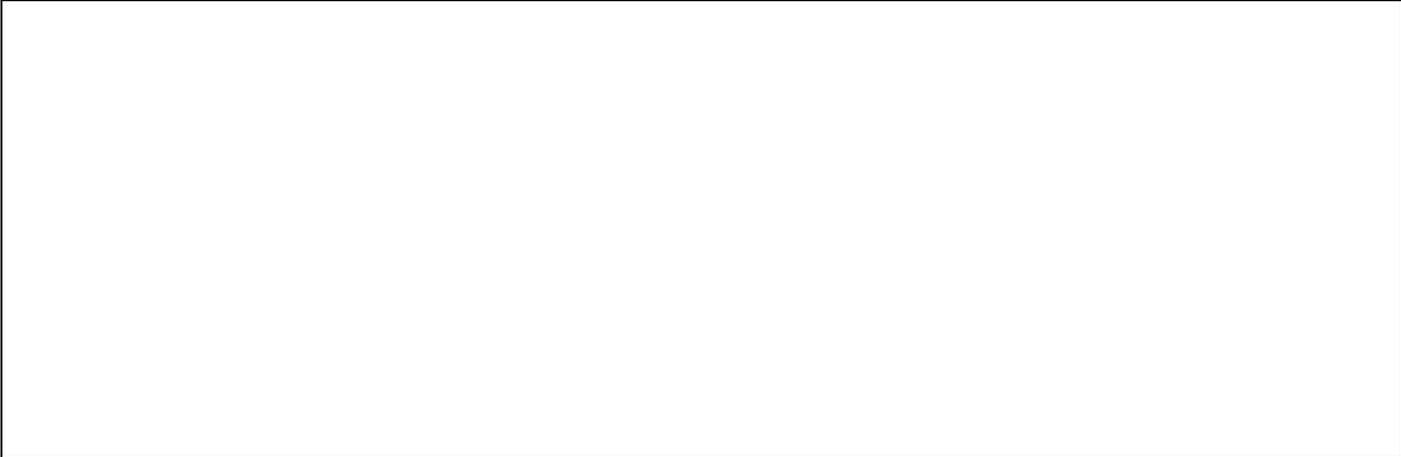
TITLE (IN 60 CHARACTERS OR LESS, INDICATE THE HEALTH ISSUE THAT THE PROPOSED RESEARCH PRIORITY WILL ADDRESS):
DESCRIPTION OF THE PROPOSED HEALTH RESEARCH PRIORITY:

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 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. **If there are no questions or hypotheses that need to be investigated for a particular type of research, enter "none" in the appropriate box.** 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 whether persons should be invited to attend the Committee’s fall meeting. During the Committee meeting those persons who are invited to testify will be asked to summarize the critical research questions related to their written testimony and then answer Committee members’ questions. If invited by the Department to do so, would you or your representative be willing to present testimony and answer questions about your proposed research priority at the Committee meeting in the fall of 2011?

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 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), autism spectrum disorders and antibiotic resistance (2008-09), cancer vaccines and blindness and visual impairment (2009-10), substance abuse (2010-2011), and translational genomics and commercialization of cancer diagnostics and therapeutics (2011-2012). 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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Health Research Priority Title and Description

Environmental Chemical Exposures in the Development of Metabolic Syndrome

The prevalence of obesity has risen dramatically in the United States and in other regions of the world over the past two decades. In the United States, 30% of adults have been defined as clinically obese and 65% defined as overweight. Perhaps more important is that obesity and related diseases, such as diabetes, are rising dramatically in our children. More than sixty percent of children 10 years and older either are or will become obese later in life. There is considerable evidence that obesity risk may begin early in life, during pregnancy, and early childhood. There are numerous studies showing that rapid weight gain in the first few months of life is associated with obesity later in life.

There is an emerging hypothesis, based on data from several chemicals in animal studies that the obesity epidemic could be due to chemical exposures during vulnerable windows of development, mainly in utero and the first few years of life. Indeed in animal models there are data showing that developmental exposure to endocrine disrupting chemicals such as tributyl tin, bisphenol A, organochlorine pesticides, air pollution, lead, Diethylstilbestrol, perfluorooctanoic acid, monosodium glutamate and nicotine can lead to increased weight gain later in life. An outstanding challenge is that the molecular mechanism by which environmental chemicals promote obesity and diabetes remains largely unknown.

Biomedical Research Questions and Hypotheses

We hypothesize that nuclear hormone receptors play an important role in the effect of environmental chemical on obesity and type 2 diabetes. Specifically, we the previously known xenobiotic receptor PXR plays an important role in metabolic disease. Specifically, we hypothesize that loss of PXR prevents obesity and type 2 diabetes, whereas activation of PXR by bisphenol A (BPA) may have mediated the pro-obesity and diabetic effect of this environmental endocrine disruptor.

To our knowledge, the current study represents the first attempt to determine the function of the “xenobiotic receptor” PXR in metabolic disease in vivo and the role of PXR in mediating the pro-obesity and diabetic effect of environmental endocrine disruptors. Results from this study will increase our understanding of the role and the underlying mechanism of environmental chemical exposures in the development of obesity, type 2 diabetes and metabolic syndrome.

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

According to the Department of Health, the burden of diabetes in Pennsylvania is great and diabetes incidence rates continue to increase. In 2008, the national BRFSS indicated that Pennsylvania ranked eighteenth in the nation (out of the 50 States) for the percent of adults who had ever been told by a doctor that they had diabetes (8.8 percent). Diabetes affects people of all ages and racial and ethnic groups. However, some groups are disparately burdened by the disease. For example, Non-Hispanic blacks have higher diabetes prevalence rates than both Hispanics and non-Hispanic whites.

For the 2006-2008 period, the rate of diabetes increases dramatically with age and becomes significantly higher for older adult groups (45+) compared to their younger counterparts. Those in the 65+ age range were disparately affected and had the highest diabetes prevalence of all the age groups.

Among school children, reviewing data from the five prior school years available indicates that the rate of diabetes has increased steadily in each year. However, it is important to note that these increases may be due to better reporting—not increasing incidence.

In 2006-2008, black, non-Hispanic Pennsylvania adults had significantly higher diabetes prevalence (13, CI 11-16) compared to white, non-Hispanic (8, CI 7-8) and Hispanic (7, CI 5-11) Pennsylvania adults. This data supports the claim that diabetes affects racial and ethnic groups differently.

Estimated diabetes prevalence decreases with increases in education level. In 2006-2008, each education level had a significantly lower diabetes prevalence compared to each lesser education level.

In 2006-2008, Pennsylvania adults with annual income levels less than \$25,000 had significantly higher diabetes prevalence compared to all other income groups. In 2006-2008, Pennsylvania adults with annual income levels greater than \$50,000 had significantly lower diabetes prevalence compared to all other income groups.

Contact Information

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Health Research Priority Title and Description

Towards a better understanding and treatment of diabetes

The prevalence of diabetes and obesity is increasing. Currently, it is estimated that 25.8 million people in the United States has diabetes. Another 79 million Americans are at greater risk for developing diabetes in the next few years. The rate is higher among the elderly and Hispanics, Native Americans, and African-Americans. The cost of diabetes reached \$174 billion for 2007 in the U.S. The Centers for Disease Control has projected that one out of three children born in the United States in the year 2000 will develop diabetes in their lifetime. Much of this is type 2 diabetes, which represents 90-95% of the epidemic, though type 1 diabetes is also on the rise, and the complications both type 1 and type 2 diabetes are devastating, including heart attack, stroke, blindness, infection, and kidney disease. Although progress has been made, there is still much to be learned about diabetes and its complications. For example, recent large randomized controlled studies disappointingly did not observe improved cardiovascular outcomes with better control of blood sugar. This raises fundamental questions about our current approach to the treatment of diabetes.

Biomedical Research Questions and Hypotheses

1) Why does insulin resistance result from obesity?

- We hypothesize that this is due to factors related to fat cells, as well as to inflammation, which are found in man as well as other mammals. Moreover, we hypothesize that excessive caloric intake leads to defined abnormalities in metabolic pathways in liver and adipose tissue.

2) What are the effects of different diabetes therapies on cardiovascular risk factors?

- We hypothesize that different therapies, including bariatric surgical procedures, have different effects.

3) Can personalization of disease understanding guide therapy?

- We hypothesize that genetic differences, including Single Nucleotide Polymorphisms (SNPs) in the human genome, underly the variation in outcome and complications, and that linkage of particular SNPs to outcome would personalize care for diabetes, leading to improved outcomes.

Clinical Research Questions and Hypotheses

1) Why does insulin resistance result from obesity?

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Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

The epidemics of diabetes and obesity are a major threat to health of Pennsylvanians and Americans in general. The problem is global, with 250 million people worldwide having diabetes, yet these individuals receive only a fraction of the attention as the 33 million living with HIV/AIDS. To quote the 2010 Pennsylvania Department of Health report *The Burden of Diabetes in Pennsylvania*, "the burden of diabetes in Pennsylvania is great and diabetes incidence rates continue to increase. In 2008, Pennsylvania ranked eighteenth in the nation (out of the 50 States) for the percent of adults who had ever been told by a doctor that they had diabetes (8.8 percent, or approximately 872,000 people). Diabetes is a disease that affects groups disparately. In Pennsylvania during 2006-2008, an estimated 13% of non-Hispanic African Americans and 7 percent of Hispanics are affected compared to 8 percent of non-Hispanic whites. Those individuals in lower income brackets and with limited amounts of education are affected more than those in higher income brackets and with more education. Those in the older age brackets are affected more than their younger counterparts. Diabetes affects people of all ages and racial and ethnic groups. However, some groups are disparately burdened by the disease. In 2007, diabetes was listed as the underlying cause of death for 3,420 residents of Pennsylvania for a death rate of 201.3 per 10,000. Because diabetes is likely to be underreported as an underlying cause of death, with only about 10 to 15 percent of decedents having diabetes listed as such, this number is likely much higher. In fact, diabetes was listed as a contributing cause of death for an additional 8,403 Pennsylvania residents who died in 2007." In addition, based on statistics accumulated in 2008, "approximately 36 percent of Pennsylvania adults were considered overweight and 28 percent of Pennsylvania adults were considered obese."

Contact Information

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Health Research Priority Title and Description

Damage and Impaired Healing in Musculoskeletal Tissues Due to Tobacco/Nicotine

Bioengineering approaches to musculoskeletal diseases have yielded many important findings and understanding concerning development, normal tissue homeostasis, structure-function relationships, and the repair response to injury. It has long been known that smoking is a comorbidity which results in impaired tissue healing in tissue culture experiments, in animal models, and in clinical studies. Recently, it has also been shown, in animal models, that smoking is detrimental to native tissue properties, making these tissues susceptible to injury (in addition the known poor healing capacity). These findings are present in essentially all musculoskeletal tissues including bone, cartilage, ligament, meniscus, and tendon. This is truly problematic and must be addressed with research toward understanding the mechanisms of these processes as well as in development and evaluation of potential treatment modalities.

Biomedical Research Questions and Hypotheses

What are the fundamental mechanisms resulting in inferior native tissue properties due to smoking/nicotine?
What are the structure-function relationships governing native tissue properties due to smoking/nicotine?
What are the fundamental mechanisms underlying poor healing in musculoskeletal tissues?
What bioengineering approaches can be used to aid in understanding these disease and injury processes.

Clinical Research Questions and Hypotheses

What are the relationships between smoking/nicotine use and poor musculoskeletal tissue healing?
How can bioengineering be used to develop novel treatment modalities.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Healthy People 2010 has an explicit goal to increase the amount of physical activity of Pennsylvania's population. While this is certainly an important goal and is important for cardiovascular and other fitness, with increasing physical activity comes increasing tendon, ligament, and joint injuries. There is a clear and direct correlation between increased physical activity and increased musculoskeletal injuries. In fact, recent data shows that musculoskeletal symptoms were the number 2 reason for physician visits. Further, more than one in

four Americans has a musculoskeletal impairment which is likely consistent with the data for Pennsylvanians. Putting added stresses on tissues already predisposed to injury due to inferior native tissue properties will further increase the frequencies of injuries. And, once injured these tissues will have impaired healing resulting in an increased cost to society due to lost work days, increasing need for medical attention, and inability to perform ones recreational sports, and a wide range of activities of daily living. Both basic biomedical and clinical research is necessary to understand the causes for poor musculoskeletal tissue properties and to design and evaluate modalities to help prevent injuries and to help treat and cure injuries once present. Successful accomplishment will keep people working at their jobs, participating in their recreational or competitive sports, exercising as they prefer, and further, keep them with the ability to live independently without the need for nursing or assistive care.

Contact Information

PERSON SUBMITTING TESTIMONY		
NAME (First Name MI Last Name) Sean P. Hennessy	DEGREE(S) PharmD, PhD	<input type="checkbox"/> Ms. <input type="checkbox"/> Mr. <input checked="" type="checkbox"/> Dr.
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Health Research Priority Title and Description

Preventing Harmful Drug-Drug Interactions

Pennsylvania is home to the second-highest number of senior citizens in the US. Because many seniors take multiple medications, they are at greatest risk for harmful drug-drug interactions. Although several medical compendia provide doctors, pharmacists, and patients with advice about which drug-drug pairs to avoid, these compendia disagree with one another to a surprising and dramatic degree. This disturbing disagreement is because most of the information contained in the compendia are based on are anecdotes rather than controlled scientific data. Not surprisingly, electronic prescribing software based on these compendia also disagree markedly. This leaves patients at risk for receiving harmful drug-drug interactions, and also prevents co-administration of medicines that would actually benefit patients if given together, but are avoided because of unnecessary fear of harmful interactions.

Biomedical Research Questions and Hypotheses

We will test how well mechanistic hypotheses about adverse drug-drug interactions are reflected in real-life patient populations. Further, observations made in populations will lead to biological hypotheses that will be fed back to laboratory researchers. Thus, this is an optimal model for translational research in drug-drug interactions.

Clinical Research Questions and Hypotheses

We propose to use known and hypothesized pharmacologic mechanisms to predict which drug-drug pairs will result in clinically important harmful drug-drug interactions, and test these predictions in very large, epidemiologic, population-based studies using administrative (i.e., health insurance) databases. We have used such databases for many years and are well acquainted with their advantages and limitations. Such studies will provide crucial mechanistic insight into interactions between drugs and provide crucial evidence to physicians, pharmacists, and patients. Potential research to be examined could include: 1) Does discontinuation of statins in patients receiving warfarin results in an increased risk of stroke; 2) Does initiation of colchicine in patients receiving statins result in a higher risk of colchicine toxicity than when colchicine is administered to colchicine non-recipients? and 3) Does initiation of diltiazem or verapamil in patients receiving pioglitazone result in an increased risk of serious hypoglycemia?

Health Services Research Questions and Hypotheses

Using the results of these large, population-based epidemiologic studies, we will then design, implement, and evaluate evidence-based health care interventions, for example, using information technology (e.g., computerized physician order entry programs) to reduce the risk of harmful drug-drug interactions while at the same time permitting co-administration of drug combinations that have been shown to be safe. Such interventions can be implemented on a widespread basis throughout the Commonwealth of Pennsylvania and beyond. We will further rigorously evaluate the effectiveness of such interventions, including looking for potential unintended consequences of such interventions.

Impact on Health of Pennsylvanians

Pennsylvania is home to 1.9 million senior citizens (over 15% of the Commonwealth's population), second in percent only to Florida. Not surprisingly, the elderly population, and in particularly the frail elderly population, is both at highest risk of receiving multiple interacting medications and experiencing adverse effects of those medications. In addition, Medicaid beneficiaries, who include low-income and disabled persons and a disproportionate number of minorities, are also among the highest risk individuals for harmful drug-drug interactions. Another high-risk population is the low-income senior population served by the Pharmaceutical Assistance Contract for the Elderly (PACE) program, which is administered by the Pennsylvania Department of Aging. Among community-dwelling elderly individuals, harmful drug-drug interactions account for 13% of all adverse drug reactions, and are responsible for nearly 3% of all hospitalizations. Harmful drug-drug interactions are the source of a great deal of concern among health professionals and the general public alike. A public opinion poll conducted in 2002 found that fully 70% of respondents indicated that, if hospitalized, they would be "concerned about receiving two or more medicine that interact in a negative way."

Thus, a rigorous, science-based program to reduce harmful drug-drug interactions would have enormous impact within the Commonwealth of Pennsylvania and beyond.

Contact Information

PERSON SUBMITTING TESTIMONY		
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Health Research Priority Title and Description

Pathophysiology and treatment of abdominal aortic aneurysms

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. This is a major health disparity with the adverse impact on the older 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.

This project when funded would lead to a better understanding of the basic mechanisms of abdominal aortic aneurysms which will lead directly to better testing and prevention of aneurysmal degeneration. The discovery at the basic science level would lead to better screening procedures to identify aneurysms and in the future ideally limit the number of patients that require surgical treatment.

Contact Information

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Health Research Priority Title and Description

Interventional pathways to disrupt the progression from obesity to diabetes

The health research priority is interventional mechanisms that disrupt the disease transformation from the health risk obesity to the disease state diabetes. Stated this way, biomedical, clinical, or health services research projects can be included. Obesity has been characterized as 'the public health challenge of our time.' Incidence and prevalence are epidemic, and show no sign of slacking, despite nearly twenty years of heightened awareness (obesity was designated in 2005). Populations of color and low socioeconomics are affected disparately, more severely. From the PA Dept. of Health website: 60% of adult Pennsylvanians are overweight or obese (BMI>25), and 25% are physically inactive. Nearly 18% of Pennsylvania youth are overweight, more than the national average. Meanwhile, diabetes grows equally unchecked, presenting similar confounders (ethnicity, socioeconomics, education, age). State, national prevalence is ~10 percent. Diabetes is accompanied by significant concomitant medical conditions and is an under-reported cause of death, yet still among the top ten. Obesity increases risk of diabetes 10x. Diabetes, like alcoholism, affects the way the pancreas processes insulin and glucose, suggesting that glucose utilization might be the metabolic missing link between health and disease. From the oral health perspective, periodontitis is the BIDIRECTIONAL sixth major complication of diabetes, and periodontitis-induced changes in immune cell function cause metabolic dysregulation of lipid metabolism involving pro-inflammatory cytokines.

Biomedical Research Questions and Hypotheses

(1) What is the role of inflammation in the pathophysiology of the two conditions, obesity and diabetes? Given that inflammatory cytokines induce insulin resistance, and that circulating inflammatory cytokines in adipose tissue further aggravate metabolic control, what are the effects of weight loss? (2) What is the nature of adipose tissue? (3) What is the precise pathophysiology of glucose metabolism? (4) What are the effects of various vitamins, minerals, and supplements on glucose metabolism? This includes popular diet-myth-or not products (acai, chromium, bariatrics). What is the role of cortisol, ACTH, and in general the adrenal glands and hypothalamus? (5) Improved insulin sensitivity and endothelial function will result in overall reduction of inflammatory mediators TNF-alpha, IL-6, and C-reactive protein, with increased levels of adiponectin. What are the effects of (the general interactions of inflammatory mediators) on the body's major organ systems, in isolation and systemically? on the world's medical and disease challenges? (6) What is the specific elucidation

of the pathways of insulin resistance, glucose metabolism, and the metabolic syndrome cascade? (7) What are the precise inflammatory pathways and mediators in obesity?

Clinical Research Questions and Hypotheses

(1) Obesity is an established risk for Type II diabetes and periodontal disease is an established complication of diabetes (Löe 1993). The relationships are interdependent and may be bidirectional (Grossi 1998). Diabetes related to periodontal infection is an example of systemic disease predisposing to oral infection and inflammation, which in turn exacerbates the systemic disease. What are the clinical interventions available to dentistry to interrupt the disease transformation from obesity to diabetes? (2) What are the clinical relationships between periodontal disease, obesity, overweight, body mass, and diabetes? (3) What are the effects of the control of periodontal disease, diet, and body mass reduction on the improvement of metabolic control in people with diabetes, in the clinical parameters of diabetes, and in the general systemic health of diabetic adults? (4) Control of the infection and inflammatory process in the oral cavity will not only improve oral health but will diminish negative diabetic symptoms. (5) Weight loss will improve periodontal health, as it reduces diabetic symptoms.

Health Services Research Questions and Hypotheses

(1) The Diabetes Prevention Program is a proven effective tool to interrupt the progression from obesity to diabetes. The Diabetes Prevention Program, in development, has been established by endocrinologists and nutrition scientists from the University of Pittsburgh. How can the breadth and depth of that knowledge and expertise base be successfully exploited and partnerships made with stakeholders in the community (churches, community groups, health insurance providers) to disseminate that knowledge to the individuals in the community who need it? The national YMCA organization announced last month that it will be rolling out community programs derived from the model at 150 sites operated by 50 different YMCAs.

(2) How can oral health specialists partner with community stakeholders to create and disseminate interventions that successfully disrupt the progression from obesity to diabetes?

(3) What are the most effective mechanisms to disseminate information about the significant health risk of obesity that would successfully disrupt the disease transformation from obesity to diabetes?

Impact on Health of Pennsylvanians

The impact of the disease transformation from obesity to diabetes is both ENORMOUS and ALARMING. SIXTY PERCENT of adult Pennsylvanians are overweight or obese, and 25% of adults are physically inactive. Nearly 18% of Pennsylvania youth are overweight, a figure higher than the national average (from the PA Dept. of Health website). Increasing obesity rates will result in higher health care spending for states and individuals. Using even a low estimate for Pennsylvania obesity (42 percent), the Americas Health Rankings report (2009) estimated that obesity-associated health care costs will surpass \$13.5 billion by 2018. NO STATE, including least-fat Colorado (18.5 percent) meets the Healthy People 2010 obesity target of 15 percent. Obesity tops the multi-risk factor cluster of conditions predisposing to other significant chronic medical conditions. Populations of color, low socioeconomics, and the less-better educated are affected disparately and more severely. Oxford University research (900,000 subjects, 2009) found that common moderate obesity (BMI 30-35) shortened the lifespan by three years. Severe obesity (BMI 40-50, still uncommon) reduced life expectancy by about 10 years; similar to the effect of lifelong smoking. Unchecked obesity WILL RESULT in the disease transformation to diabetes, the seventh leading cause of death in the United States and a significantly UNDER-reported cause of death. Like obesity, diabetes presents similar confounders (race and ethnicity, low socioeconomic status, poor education. Also significantly: age). Diabetes is accompanied by significant concomitant medical conditions - kidney disease resulting from damage over time because of high blood glucose levels, necessitating the expense and human capital loss of dialysis; retinopathy and glaucoma in the eyes; numbness in the extremities

commonly caused by peripheral nerve damage in severe diabetes (diabetic neuropathy) leading to foot ulcers, gangrene and amputations in the elderly and advanced diabetics (more than 60 percent of nontraumatic lower-limb amputations are in diabetics); heart and blood vessel disease (the leading cause of death for diagnosed diabetics), heart attacks, strokes, high blood pressure and atherosclerosis. On the basis of prevalence and incidence among diabetics, and of special significance to dental health providers, the sixth major complication of diabetes is periodontal disease. Among young adults, those with diabetes have about twice the risk of periodontal disease. Adults ages 45 years or older with poorly controlled diabetes (A1C above 9 percent) were 2.9 times more likely to have severe periodontitis than those without diabetes. The likelihood was even greater (4.6x) among smokers with poorly controlled diabetes. One-third of people with diabetes have severe periodontal disease, which may cause tooth loss and malnutrition. Good oral hygiene and regular visits to the dentist can make a real difference in managing this complication. Pregnancy in a diabetic woman, controlled or not, automatically becomes high-risk. People with diabetes are twice as likely to have depression, which can complicate diabetes management, and depression is associated with a 60 percent increased risk of developing Type 2 diabetes. Unfortunately many diabetic complications will present themselves whether the diabetic has exercised good and consistent metabolic control, or not. Estimated diabetes costs across the United States (2007) were \$174 billion (total costs, direct and indirect). Direct medical costs were \$116 billion, and after adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than what expenditures would be in the absence of diabetes. The indirect costs (disability, work loss, premature mortality 2007) of diabetes were \$58 billion. Medical expenses for people with diabetes are more than twice that for people without diabetes [SOURCE for all: National Diabetes Information Clearinghouse, accessed May 2011].

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Health Research Priority Title and Description

Personalization of medicine

Nonsteroidal antiinflammatory drugs (NSAIDs) are amongst the most commonly consumed drugs and relieve pain and inflammation. However, association with cardiovascular (CV) risk has limited their use in conventional and emerging indications, such as the chemoprevention of cancer. We first predicted and then mechanistically explained this risk, combining studies in patients, healthy volunteers and in model systems. Now we wish to perform translational studies to identify factors that predict CV risk or detect its emergence at the individual level. As only 1-2% of patients taking NSAIDs chronically develop CV events, such as myocardial infarction, stroke or heart failure, our objective is to combine clinical, metabolomic and genomic information together with measures of drug exposure to predict those patients at greatest risk and to detect emerging risk during chronic drug treatment. We will combine information from our basic and clinical research using systems biology to generate novel hypotheses relating to predictive signatures of CV risk that can then be tested at scale. The identification of a personalized signature of risk - or its emergence- based on clinical examination and collection of blood and urine for analysis would be a major public health advance for these effective drugs. It would also re-open their potential utility in the chemoprevention of cancer where NSAIDs prevent precancerous lesions in the colon, but further investigation has been deterred because of the CV risk.

Biomedical Research Questions and Hypotheses

Hypothesis 1. That variation in modifier genes conditions the CV response to NSAID administration. We will utilize the blood pressure (BP) response to NSAIDs as a quantitative surrogate for CV risk. In mice this is highly influenced by genetic background and the response is similarly highly variable in humans. Our studies will use two NSAIDs that differ in their relative propensity for inhibiting cyclooxygenase (COX) - 2 (celecoxib) and COX-1 (naproxen) and next gen sequencing in inbred strains of mice to identify modifier genes that influence this response. We will also seek metabolomic and epigenomic signatures of response and adjust for variation in drug exposure. Analogous strategies will be utilized in zebrafish. These studies will inform the search for variation in candidate genes in our studies of extreme phenotypes of the BP response in humans.

Hypothesis 2. Variation in COX expression modulates the response to COX inhibitors. Expression of both COXs by volunteers in B lymphocytes varies by orders of magnitude. Using more than 30 unique mouse lines in which the magnitude and location of the COX pathways are altered we will assess the BP and prostaglandin inhibitory effects of the target NSAIDs.

Clinical Research Questions and Hypotheses

Hypothesis 1. That patients who exhibit extreme BP phenotypic responses to acute and chronic exposure to our target NSAIDs are characterized by distinct genomic, epigenomic and /or metabolomic signatures. Normotensive patients exhibit, on average an increase in systolic BP of 2-3mmHG to NSAIDs, varying with the selectivity for inhibition of COX-2. Under controlled conditions of acute and chronic dosing and ambulatory monitoring of BP we will segregate those with extreme responses and seek unbiased signatures that distinguish the groups. Systems biological integration of data from model systems and these human data will be assembled in an iterative manner to generate novel hypotheses for CV risk prediction that can then be tested at scale. Hypothesis 2. Patients with extreme variability in COX expression in their immortalized lymphocytes ex vivo will exhibit variability in their response to NSAID administration in vivo. Volunteers selected based on extremes of COX expression will be administered the two NSAIDs and differences sought in prostaglandin inhibition, BP response and metabolomic signatures, adjusting for drug exposure. Results will be integrated with those from analogous basic studies in a systems analysis.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

NSAIDs are amongst the commonest drugs consumed world wide and their safety and efficacy is of particular relevance to the aging population of Pennsylvania. Presently although patients often insist that particular NSAIDs work best for them there is no scientific evidence that addresses this possibility and consequently no knowledge of what might underlie such individual variability in drug response. Previously, our group was the first to predict the possibility of CV toxicity from NSAIDs designed specifically to inhibit COX-2. Translational integration of our studies in mice and other model systems with detailed studies in humans demonstrated that the increased risk of heart attack, stroke and heart failure were attributable to suppression of COX-2 dependent formation of a cardioprotective prostaglandin, prostacyclin. However many factors determine whether an individual taking an NSAID suffers such an event. It is estimated that this afflicts only 1-2 % of patients exposed but there are few means extant to predict individual risk. On average, risk is increased in patients at CV risk for other reasons, is likely increased in more COX-2 selective, potent and long lived NSAIDs and is attenuated to some degree by low dose aspirin. However, while this last strategy has appeal it erodes the one advantage of COX-2 inhibitors over older drugs that inhibit COX-1 and COX-2, their more gentle impact on the gastrointestinal tract. In this proposal we would like to address the issue of predicting CV risk or detecting its emergence - this is of relevance as several trials of NSAIDs and studies in mice are consistent with risk transformation during chronic treatment.

Here we wish to deploy a similar translational approach - integrating studies in cells, model systems and humans - as we previously applied to predict and elucidate the core mechanism underlying CV risk - to move towards a personalized approach to risk prediction and detection. By using changes in BP in response to NSAIDs as a quantitative surrogate for CV risk and integrating data from cells, mice and humans, using the tools of systems biology, we wish to develop novel hypotheses based on genomic, epigenomic and metabolomic signatures that can be tested in outcome studies at scale. Should such predictive paradigms be supported, they will enable a practitioner to decide whether to use or continue an NSAID, if so which one and if so for how long. A science based approach to managing risk would permit not only the safer use of NSAIDs for conventional purposes but also would reinvigorate the investigation of the utility of NSAIDs for cancer chemoprevention. Presently, despite the marked effectiveness of NSAIDs in preventing precancerous colonic polyps in predisposed individuals, their broader application in cancer has not been pursued and many trials discontinued because of the CV risk, particularly given the independent predisposition of some patients with cancer to blood clotting.

These studies are of particular relevance to the aging population of the state, many of whom have arthritis and coexistent CV disease. A rational basis for NSAID selection would be of particular relevance to such patients. Furthermore, we noted that COX-2 expression ex vivo in immortalized lymphocytes is significantly lower in African Americans than in Caucasians. Interestingly, in overview analysis of the NSAID COX-2 inhibitor celecoxib that the incidence of myocardial infarction is higher in African Americans (Hazard ratio 3.7 [95% CI 0.8, 17.8]) than in Caucasians (1.6 [1.1, 2.2]). Our studies in humans and mice will determine whether such variance in enzyme expression modulates CV drug response and whether African Americans are at particular risk.

Finally, our studies offer the possibility of a new approach to the personalization of medicine of relevance to the stabilization of the large presence of Pharma in Pennsylvania at a time of change for that industry and also for the population health as the approach extends to other classes of drugs.

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Health Research Priority Title and Description

Concussions in Youth: Neurobiology and Interventions

Traumatic Brain Injury (TBI) is a leading cause of death and disability in the young. TBI from contact sports is one potentially preventable and treatable cause of TBI in adolescents. Because adolescence is a time of rapid neurocognitive maturation, even mild TBI has more serious implications in this age group and is often not recognized. In addition, the management of common sequelae, such as difficulties with attention, mood lability, sleep, and headaches are based on clinical experience, rather than empirical data. Estimates from adults who have experienced TBI show markedly elevated levels of depression, anxiety, PTSD, substance abuse, and suicidal behavior post-injury. To better understand the predictors of sequelae and recovery from TBI in adolescents, it is crucial to compare the impact of TBI over time in youth who participate in contact sports to similar participants who have not experienced TBI, supplementing a standard neuropsychological battery with baseline and follow-up structural and functional MRI, DTI, and MRS spectroscopy, genetic and other biomarkers, postural evaluation, and assessment of current and previous psychiatric disorders. Treatment studies to evaluate the best clinical management of problems of sleep, pain, motivation, concentration, and mood lability are also needed in this age group. In addition, it is important to raise the standard of care for TBI among practitioners in Pennsylvania and to address disparities in the assessment and treatment of TBI among minority adolescents.

Biomedical Research Questions and Hypotheses

What are the neural, genetic, and biomarker predictors and indicators of onset and course of adverse sequelae to TBI? Hypotheses: a) Genetic polymorphisms in the APOE, COMT, and ACE genes will predict short-term recovery; genetic polymorphisms in the serotonin transporter and related genes will predict depression and anxiety, and polymorphisms, in the dopamine system will predict difficulties with sustained attention and motivation; b) fMRI early post-injury performance in working memory, attention-control, reward response (in the striatum), cortical activation during decision-making, and amygdala activation to emotional stimuli will predict memory problems, impulsivity, depression and low motivation, impulsive risky behavior, and anxiety and mood lability, respectively. Moreover, these findings will be more common in those with TBI, and will predict onset and persistence of the above-noted sequelae; c) DTI imaging will show that reduced functional anisotropy post-injury and will predict lower processing speed and slower recovery and; d) MRS will show that post-injury changes in n-acetyl aspartate, choline, and creatine will predict onset and prolonged recovery from cognitive and psychiatric sequelae.

Clinical Research Questions and Hypotheses

1) What constellation of the above predictors of adverse outcomes best predict persistence of impairment and conversely, recovery? 2) How efficacious are currently employed symptomatic treatments for headache, sleep difficulties, concentration, and mood lability? Hypotheses: a) Youth with a history of maltreatment, personal, or family history of psychiatric disorder, or previous concussions will be more likely to have adverse sequelae; b) Specifically, individuals with a history of ADHD will be more likely to develop cognitive difficulties, those with a history of anxiety or depression will be more likely to develop low motivation, mood lability, and/ or sleep difficulties, and those with a history of aggression will be more likely to develop difficulties with impulse control; c) Low-dose amitriptyline will be superior to placebo for management of headache; d) Amantadine will be superior to placebo for attentional and memory difficulties; e) Melatonin will be superior to placebo for management of sleep difficulties; and f) Burpropion will be superior to placebo for the treatment of depression, fatigue, and low motivation.

Health Services Research Questions and Hypotheses

1) Can testing and referral reduce the known disparities in diagnosis and treatment of TBI among African American youth? 2) What is the current practice among primary care practitioners and specialists (e.g., neurologists, psychiatrists, rehabilitation medicine) for the management of the sequelae of TBI? 3) What is the best way to get evidence-based care to those who need it? Hypotheses: a) Compared to current practice, providing screening and referral for athletes in schools with high minority demographic composition will reduce the disparity for diagnosis and treatment of TBI among African American athletes; b) Current practitioners, aside from a small number of those engaged in specialized practice, have low knowledge about the assessment, diagnosis, and clinical management of the sequelae of TBI; c) Participation in targeted CME trainings can improve practitioners' knowledge and practice with respect to the diagnosis and management of TBI; and d) access to care, particularly among minority youth, can be improved by providing evidence-based treatment in primary care and in school-based clinics.

Impact on Health of Pennsylvanians

Traumatic brain injury (TBI) is a major public problem in the United States and in Pennsylvania. Up to 3.8 million Americans and 245,000 Pennsylvanians experience TBI each year. TBI is most common in children and adolescents, with 65% or 160,000 of these injuries occurring in Pennsylvanians under the age of 21. Between 5-12% of athletes in contact sports will have at least one concussion, with at least 3,000 hospitalizations and 400 deaths annually. Even mild TBI, which is the most commonly occurring form of TBI in young athletes, is associated a very high rate of morbidity, since a significant minority of those who experience mild TBI will have adverse sequelae requiring additional educational, psychosocial, and medical attention. Although 1.5 times as many people die of TBI as HIV/AIDS each year, there are \$9,000 spent on HIV/AIDS treatment and research for every \$1 spent on comparable activities for individuals with TBI. Therefore, there is a need for investment in research in order to improve outcomes of TBI and reduce the burden of disability among Pennsylvanians. Moreover, there are significant healthcare disparities in the diagnosis and treatment of TBI, with two-fold higher rates of TBI in African American adolescents, but lower rates of referral and treatment. Research on adolescent TBI will: help to identify those youth most vulnerable to adverse health outcomes, identify mechanisms by which youth develop these sequelae, and test interventions to attenuate these sequelae and restore function. Additionally, research can help to address racial and ethnic disparities in the diagnosis and management of TBI in high school athletes and develop curricula to improve the assessment and management of TBI among primary care practitioners.

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Health Research Priority Title and Description

Reducing Asthma Disparities using a Racially -Specific Approach

African American children and adults have higher prevalence, morbidity and mortality from asthma than White or non-Puerto Rican Hispanics. According to the U.S. National health Interview Survey, the prevalence of childhood asthma in African Americans (15.5%) is more than twice as high as that of Whites (7.4%). Compared to Whites, African Americans are diagnosed at an earlier age, have more severe asthma and more frequent severe exacerbations, and worse quality of life, even after accounting for socio-economic status. Although inadequate healthcare access/treatment certainly contributes to the increased asthma burden in African Americans, other racially-specific factors including genetic/epigenetic determinants of asthma pathogenesis and the specific role of IgE remain to be explored. Our three goals to reduce unacceptably high levels of asthma morbidity in the African American community (in both children and adults) of Pennsylvania are to: 1) identify novel asthma epigenetic biomarkers while concomitantly addressing exposure to levels of modifiable environmental/lifestyle risk factors for asthma 2) determine whether treatment with anti-IgE therapy reduces asthma morbidity to a greater degree in African Americans and 3) promote increased disease understanding and management through school and primary care outreach approaches. This unique opportunity to integrate international expertise in adult and pediatric asthma with cutting edge translational and basic research will make these goals possible.

Biomedical Research Questions and Hypotheses

Recent evidence strongly suggests that heritable and/or de novo changes in gene expression that occur without changes in DNA sequence (epigenetic) mediate environmental effects on asthma. Very few studies have examined asthma epigenetics, and none has been conducted in African Americans. The best studied epigenetic

mechanism is DNA methylation, the covalent addition of a methyl group to a cytosine residue occurring mostly in a CpG site (i.e., a cytosine next to a guanine). We hypothesize that DNA methylation of CpG sites in genes relevant to immune response influence asthma in African American children. We will test this hypothesis in school-age children by: 1) conducting a genome-wide study of methylation and asthma, lung function and allergy markers using DNA from white blood cells and nasal epithelium, and 2) testing whether relevant environmental/lifestyle factors (tobacco smoke, obesity, air pollution, allergens, and psychosocial stress) influence asthma through DNA methylation. The proposed study should yield new (epigenetic) biomarkers of environmentally-induced asthma, which should in turn lead to novel insights into the prevention, diagnosis and treatment of asthma in general and in African Americans in particular.

Clinical Research Questions and Hypotheses

While asthma rates are high (>13%) in Pennsylvania, even higher percentages of Blacks are diagnosed with asthma (~16%). Blacks are diagnosed at younger age and in western PA have 43% of the total emergency room visit compared to Whites. Data from Univ of Pitt report that the serum IgE is a strong predictor of severe asthma in Blacks, while having no impact in Whites (JACI 2010). In addition, a recent NIH study of predominantly Black inner-city children reported a robust improvement in asthma following treatment with an antibody which blocks IgE (NEJM 2010). The response appeared greater than earlier studies of predominantly White asthmatics. We hypothesize that asthma in Blacks is more predominantly a Th2/IgE mediated disease than asthma in Whites. Because of this, Blacks will respond better to anti-IgE (omalizumab) treatment than Whites. To address this, we propose a 12 month parallel study of omalizumab in asthmatics >12 yrs of age stratified by self identified race in poorly controlled asthmatics with the primary endpoint being asthma exacerbations. This clinical trial will integrate with the proposed epigenetic and genetic research studies above and recruit using the outreach identified below.

Health Services Research Questions and Hypotheses

Asthma is under-diagnosed and undertreated in African Americans. We hypothesize that intervening at the community level, in the school or in the primary care provider (PCP) office will improve diagnosis and management of asthma in minority communities. A school-based asthma screening program will identify children with or at risk for asthma, who will be referred to our Pediatric Environmental Medicine Center (PEMC) caremobile unit, for care at no cost. PEMC staff will then send a letter to the child's PCP with spirometry results and a management plan. Children will also be enrolled in the Open Airways for Schools Program, which improves asthma literacy, thereby reducing school absences and improving academic performance. In addition, the Asthma Institute has forged alliances with PCPs in underserved communities. Adult and pediatric asthma specialists/nurses see patients in partnership with the PCP, at his/her office. Lung function testing is performed and educational efforts undertaken, both with the patient and the physician. Outcomes are asthma control, quality of life and reduction in exacerbations, as captured in the electronic medical record. Results are compared to those not seen in partnership.

Impact on Health of Pennsylvanians

Asthma is a major public health problem in the United States and worldwide. While often identified as a disease of childhood, this chronic disease impacts the lives of both children and adults. Asthma is associated with enormous social and economical expenses. Beyond traditional hospitalizations and emergency room (ER) visits, asthma leads to loss of work productivity/absenteeism in adults, as well as high rates of school absenteeism in children and the associated work absenteeism in their parents. Pennsylvania is one of the states most burdened by asthma, with one of the highest rates nationally (13.4% of the population) for asthma in both children and adults. Prevalence rates are even higher in children and young adults (23% in 18-24 yr olds). One of the biggest health issues facing the U.S. and Pennsylvania relate to disparities in disease-specific outcomes

by racial, ethnic and socioeconomic background. Asthma is no exception, with asthma mortality (death) rates reported to be 7-10 fold higher in African Americans and Caribbean Hispanics (i.e. Puerto Ricans) than in Whites. Some of the disparity relates to the overall increased prevalence in these groups (16% of African Americans have been diagnosed with asthma). However, beyond the higher prevalence, data support unacceptable disparities in asthma morbidity as well. Of the 9,633 ER visits for asthma at six hospitals affiliated with the University of Pittsburgh Medical Center in 2009-2010, 4,142 (43%) corresponded to visits by African American children and adults, despite those groups making up only 10-12% of the population. In a recent survey of 579 random households across seven neighborhoods in Allegheny County (conducted by Children's Hospital of Pittsburgh of UPMC), there was also an uneven distribution in the prevalence rates of asthma hospitalizations across communities. As an example, in the past year, 19% of asthmatic children were hospitalized for an asthma exacerbation in Braddock. This rate is substantially higher than the national average for children (~2.9%). Braddock is a community outside of Pittsburgh with lower than average socioeconomic status and a higher than average percentage of African American citizens. Like many post-industrial communities, Braddock has higher poverty, crime and unemployment rates. There is greater exposure to personal and 2nd hand tobacco smoke. In addition, Braddock still has a working steel mill in the community where air quality remains poor by national standards. All these factors impact daily asthma symptoms, exacerbations (both ER visits and hospitalizations) and overall severity. These statistics for Braddock are repeated across other similar areas around Pittsburgh (and other Pennsylvania communities), including Wilksburg, Mt Oliver and the Hill District. In addition, general access to health care, in particular specialty health care related to asthma, is often limited, such that most children and adults if they are seen at all, are seen in busy primary care practices where appropriate attention to the education required for the care of severe chronic diseases is often overlooked. Finally, there is a growing realization that individual susceptibility to environmental factors (i.e. the interactions among genetic variants with the environment for a given person) are likely to influence asthma and response to therapy. African Americans are often overlooked in clinical trials and published data now strongly suggest that what works best for Whites, in general, may not work best for African Americans. Being sensitive to and understanding the genetic, epigenetic, environmental, social and therapeutic differences among asthmatic patients from different backgrounds should improve the health of Pennsylvania's 1.3 million asthma sufferers, while decreasing the economic burden on the state. Thus, the proposed studies, which integrate a range of expertise from internationally recognized social, clinical, translational and basic researchers, should improve outreach to medically underserved communities, advance the understanding of asthma pathogenesis in racially mixed groups, and open up new avenues for treatment, thereby improving the existing health disparities in asthma.

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Health Research Priority Title and Description

Health Disparities in Older Pennsylvanians

According to the National Institute on Aging, there are approximately 35 million Americans 65 and over in the US and it is anticipated that the number will double in the next 25 years. In fact Americans 85 and older represent the fastest growing group of the US population. However, despite increases in life expectancy, sex/gender and race/ethnic disparities in health persist in older Americans. Cardiovascular disease, cancer, diabetes and osteoporosis are among the diseases widespread in this population. Moreover, poor health literacy, comorbidities, multiple and often contradictory health messages in media pose several challenges to health promotion in older Pennsylvanians. Research is needed on the prevention and reduction of disease in older Pennsylvanians with emphasis on disparate groups. Research on effective health promotion efforts for older adults and their care takers is often needed as well as models to promote the translation of science to community. Community Based Participatory efforts have been used to effectively accomplish this goal. Therefore, community based participatory research on the prevention (primary, secondary and tertiary) of disease, promotion of health and advocacy in the health care encounter are needed to better address the health needs of older Pennsylvanians and the disparities that currently exist.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

Behavioral studies include addressing barriers to care by incorporating a sex/gender analysis framework and taking into consideration racial and ethnic disparities. Sample research questions include: If men did not delay in regular health screening exams, would health outcomes including longevity and overall quality of life be improved?; How can systems of care delivery be changed to support gender based needs of geriatric men and women? Although osteoporosis impacts women at much higher rates than men, what factors need to be included in regular geriatric screening to identify men before fracture? Although men are at higher risk for heart disease, more women die of disease - how can we better identify impact of cardiovascular risk factors; earlier screening and better intervention to reduce heart deaths in women? Menopause results in muscle mass loss in women. This loss can contribute to decrease in core strength and overall stability. What kind of strength training should occur to decrease the incidence of falls in the elderly? We hypothesize that a mixed qualitative and quantitative methodology that engages both clinicians and patients in a CBPR model can inform and improve health outcomes.

Health Services Research Questions and Hypotheses

This research would build upon initiatives exploring sex/gender and race/ethnic health disparities in older adults. Examples of research questions include: What is the role of gender and culture in disparate health outcomes for older adults; Can the prevalence of disability and disease be decreased by better health promotion efforts targeting older adults and their caregivers; Can barriers to health including poor health literacy, comorbidities, poor communication and advocacy in the healthcare encounter be modified through effective community based participatory research health interventions for older adults and their care takers? What health toll exists for grandparents who serve as parents? We hypothesize that health interventions grounded in CBPR principles will effectively address barriers to screening and adherence, health practices and behaviors in older adults.

Impact on Health of Pennsylvanians

Approximately 15% of Pennsylvanians are 65 and over, representing about 2 million people. About 1 in 5 Pennsylvanians are 60 or over. Pennsylvania ranks third in the US for population over 65 and 4th for population 85 and older. It is estimated that by 2020 Pennsylvania's population of residents 60 and over will represent 25% of the population. Therefore it is imperative that we address the persisting disparate health outcomes for older adults. With a growing population of adults in the state these issues will only continue to grow and pose a worse threat to the health and wellbeing of residents if left unabated.

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Health Research Priority Title and Description

Study and therapy of disorders identified through newborn screening

Genetic and metabolic disorders were once believed to be rare. However, 2-3% of all babies born in the United States suffer from a genetic disorder. Newborn screening (NBS) in the state of Pennsylvania (PA) has recently expanded from a handful of disorders to nearly 50 as per recommendations from the US Health Resources Services Administration (HRSA). NBS now identifies genetic or metabolic disorders in about one in every greater than 1 in every 1000 babies born, an incidence comparable to colorectal cancer. Inborn errors of metabolism are the most frequent of the disorders identified through NBS. In aggregate, they represent the largest preventable cause of mental retardation in newborns. Dealing with follow up of screenable disorders places a huge burden on the health care system, but unfortunately our understanding and treatment of these disorders now lags behind our ability to identify them. The purpose of this proposal is to provide additional support in the state for biomedical research into inborn errors of metabolism and other disorders identified through newborn screen. This would include longitudinal outcome studies to better understand the natural history and effects of interventions in these disorders, support to join national efforts to establish patient registries and databases, clinical trials to optimize treatment, and development of better educational resources for community physicians, patients and families (including expanding telemedicine diagnosis and treatment options) regarding these disorders.

Biomedical Research Questions and Hypotheses

Early detection of inborn errors of metabolism has identified an entire new cohort of presymptomatic patients with these disorders, however, the specific nature of the genetic mutations and their impact on overall cellular metabolism in patients remains uncharacterized. 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 projects are proposed. First, we propose to collect gene mutation data on patients with screenable disorders identified in Pennsylvania through expanded newborn screening. Second, we propose to examine the metabolic effects of mutations in these genes on cellular metabolism and function through a genomics and metabolomics approaches. Third, we propose to develop treatment consortia for disorders identified through newborn screening to plan and evaluate efficacy of therapy. Development of telemedicine and rural outreach programs will improve our ability to treat these patients.

Clinical Research Questions and Hypotheses

Early identification of screenable disorders 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 to develop a comprehensive clinical database to collect ongoing information on these patients. 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 metabolomics studies in the biomedical research component will allow identification of new biomarkers of disease outcome and therapeutic efficacy and will study this through the patient database information collected.

Health Services Research Questions and Hypotheses

An increase in disorders identified through newborn screening from 6 to >30 places enormous new stresses on the 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 developed 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 novel educational resources will allow primary care providers to feel more comfortable in participating in the care of patients with screenable disorders and ease the burden of caring for these patients on the tertiary care centers. We propose to develop education materials as well as a telemedicine program and rural out reach program, and to study the impact on primary care practitioners in Pennsylvania. The economic impact of treatment of screenable disorders is also considerable and often poorly covered by insurance. We propose to examine this issue 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 >1,000 who have one of the screenable disorders. This number will increase dramatically in the next 5-10 years as more disorders are added to the HRSA standard newborn screening panel. Prior to newborn screening many of these 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 half of 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 most of the screenable disorders significantly reduces 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 newborn screening follow up clinics in the State, one each in Pittsburgh and Philadelphia. One other each in Philadelphia and Hershey offer partial services. 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 with the need 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. Improving access to care by telemedicine, outreach clinics, physician education, and expanded screening follow up programs will provide all residents of Pennsylvania improved access to services to vulnerable newborns. Development of optimal treatment protocols through clinical trials and long term follow up programs will insure that patients receive the best possible therapy for their disorders.

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Health Research Priority Title and Description

Mental Health Disparities Among Racial Minorities

Disparities in health outcomes are widely known to be present among racial minorities. Disparities in mental health outcomes among racial minorities with a psychiatric disability are particularly prominent. Decades of research has shown that racial minorities receive fewer ambulatory services, poorer quality of care, and are less likely to seek services until an emergency arises. A growing body of evidence also indicates, however, that racial minorities rely on non-traditional methods of addressing mental health problems, including broad family and community supports. Despite the large evidence base that has accumulated documenting the presence of disparities among mental health outcomes among racial minorities in Pennsylvania and the broader United States, surprisingly little is known about how to improve mental health outcomes and reduce disparities in services among minorities. Addressing disparities in mental health services and outcomes among Pennsylvania's nearly 2 million minorities is a key public health concern for the Commonwealth and the country.

Biomedical Research Questions and Hypotheses

Research Question #1: Do biological signatures of mental disorders differ among racial minorities, and do these differences contribute to disparities in mental health outcomes?

Research Question #2: Can biomarkers be used to personalized mental health treatments, and thus provide improved and more appropriate care to racial minorities?

Clinical Research Questions and Hypotheses

Research Question #1: What treatments for mental disorders do racial minorities find most acceptable?

Research Question #2: What treatments for mental disorders are most effective among racial minorities?

Research Question #3: What is the comparative effectiveness of pharmacotherapies and psychotherapies in minority populations?

Health Services Research Questions and Hypotheses

Research Question #1: What are the contributors to disparities in mental health services among racial minorities?

Research Question #2: What workforce and organizational interventions can effectively address racial bias and prejudice in the mental health care of minorities?

Research Question #3: What organizational changes are needed to community mental health systems that would improve the acceptability of mental health care among racial minorities?

Impact on Health of Pennsylvanians

There are nearly 2 million minorities living and working in Pennsylvania. Approximately 900,000 of these individuals will develop a significant mental disorder. The toll of psychiatric disabilities on all individuals and families who suffer from them is considerable, frequently leading to loss of work productivity, social disability, and a poorer quality of life. Racial minorities are among some of the most vulnerable of Pennsylvania's residents, with a significantly greater proportion living in poverty and struggling daily to support their family and future. Despite the adversity that many minorities face, prevalence of mental disorders is not appreciably higher in most minority groups. However, the quality and effectiveness of mental health services provided to racial minorities is exceedingly disparate, even among those who have private insurance. Closely linked with these service disparities, is an extremely concerning disparity in the outcome of mental health conditions among minorities. Fewer minorities respond well to mental health treatments compared to their non-minority counterparts, and many have found the mental health system ill-equipped to meet their needs. This disparity has persisted and been documented in Pennsylvania for nearly four decades, and is among the strongest contributors to poor health and quality of life among minorities living in the Commonwealth. It is now essential to move beyond documenting the disparities in mental health outcomes among racial minorities in Pennsylvania, and begin systematically identifying methods to improve the care of this population. Such an initiative would have profound effects on the quality of life of many residents of Pennsylvania, and would generate knowledge to support better mental health care for minorities throughout the United States.

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Health Research Priority Title and Description

Diabetes Prevention and Treatment

Diabetes incidence is rising exponentially, with most experts indicating that diabetes has reached epidemic proportions. In 2011, there are >24 million people in the US with diabetes(1), with some 1.2 million in PA(2). This accounts for some 8% of the PA population(2). The complications of diabetes are extensive and expensive. These include coronary artery disease, dialysis, stroke, and blindness. According to a recent report, diabetes cost the nation \$174 billion in both direct cost and productivity losses (3). The report also showed that approximately half the people with diabetes are covered by publicly funded health care and that routine diabetes care is relatively low cost, with most of the cost as a result of poor chronic management of the disease (3). Although diabetes is one of the most pressing state health care priorities, our clinicians trail behind the rest of the US in care. PA ranked 47th out of 50 states in accomplishing adequate glycemic control (4). In the Commonwealth, 70.9% of Pennsylvanians with diabetes had a hemoglobin A1c (HbA1c) of greater than 6.5%, only 0.2% above the State of Mississippi. Very troubling is the economic impact where in PA there are four times the rate of diabetes hospital admissions as the best-performing states (5). There are recent attempts to address chronic disease with improved health systems approaches being delivered across the Commonwealth (6). Despite these good efforts, the associated escalating health care costs continue to stress state employers and health systems.

Biomedical Research Questions and Hypotheses

Customized treatment of type 2 diabetes: Development of tailored treatment strategies. Research Question: 1) How do the age of the patient and length of diabetes duration affect diabetes treatment response to lifestyle intervention or pharmacologic therapy? Lifestyle modification with diet and exercise is accepted to be a cornerstone in the first-line treatment of type 2 diabetes. Likewise, the benefits of specific anti-diabetic drugs to improve insulin sensitivity or insulin secretion are generally well described. Little objective data exists, however, regarding how the age of the patient, ranging from adolescents to the elderly, as well as the duration of disease may influence response to treatment. For example, little data is available to suggest whether or not those patients respond as well to diet and exercise due to their dwindling pancreatic reserve to secrete insulin, i.e., whether increasing insulin sensitivity is sufficient to treat their diabetes. We hypothesize that diabetes in old age and long-standing diabetes are both more likely to be more resilient to lifestyle and pharmacologic treatment of insulin resistance. This research could directly translate objective data into better evidence-based medicine in the treatment of diabetes.

Clinical Research Questions and Hypotheses

Rural and Minority Outreach. Research Question: 1) What are the specific determinants that affect diabetes care in high risk rural dwelling and minority populations? 2) What culturally sensitive and behavioral approaches are most effective in improving outcomes in underserved populations with diabetes?

Implementing and evaluating diabetes interventions with comprehensive approaches is particularly critical in rural and minority communities, since this population experiences particularly increased rates of diabetes and its complications. Rural residents and minorities have a poorer perception of overall health, lower income, and do not receive the same number and type of chronic care services, such as annual HbA1c measures, eye exams, cholesterol and blood glucose measurements. Investigators at the University of Pittsburgh have extensive experience in deploying programs for underserved rural and minority communities. Thus, we propose to support research to elucidate the determinants of gender, social, and disparities in diabetes care and treatment outcome, and to develop culturally sensitive interventions and behavioral approaches that are tailored to the needs of these under-served populations.

Health Services Research Questions and Hypotheses

Alternate Care Delivery and Telehealth. Research Question: 1) What alternative systems are most effective in providing access to team based care and improved patient outcomes? Team care is shown to be the most positive predictor of improved diabetes outcomes. However, there is a severe shortage of endocrinologists and primary care physicians (PCP) in the US. In the face of the epidemic, innovative alternate ways to support team care are imperative. 90% of diabetes care is provided by PCPs. They are overwhelmed and often unprepared to provide comprehensive care for optimal management, resulting poor outcomes. Thus, examining alternative strategies are essential, like engaging nurse practitioners, pharmacists, educators, etc. Several diabetes technology programs that improve access to team-based care have been designed by Pitt investigators. Exciting new advances include internet technology to enhance team communication and ongoing behavioral support. Specialists visits can be facilitated through teleconsultation where patients in outlying communities have access to a specialist miles away. Expansion and evaluation of these alternative and telehealth efforts are needed.

Impact on Health of Pennsylvanians

Diabetes in the US, and particularly Pennsylvania, has reached epidemic proportions. As further hard evidence, the Centers for Disease Control has recently acquired the topic of Diabetes as one of its central themes; and one in three children born will develop diabetes during his/her lifetime. The CDC also recently reported that the incidence of diabetes has increased by 70% in the 30-40 yr age group, the group most likely to lose time and productivity in the workforce. Recent statistics suggest that the prevalence of diabetes will double between 2000 and 2030 with the most important demographic change in those >65 y.o.

Pennsylvania will experience at least a doubling in diabetes prevalence given its high rates of obesity and old age. Given the overwhelming increase in the prevalence, it is inevitable that an increase in the complications associated with diabetes will follow. Unless efforts are initiated to take evidence-based treatment strategies into high risk communities, this path will lead to enormous health care costs and decreased quality of life. PA has the 3rd largest rural population of any state. 42 of its 67 counties are classified as rural, accounting for 30% of PA's population. Remarkably, Fayette County has one of the highest amputation rates in the US. Fortunately, PA is beginning to recognize the magnitude of the diabetes problem, and to formulate health policy reforms directed against diabetes. Stakeholders from across the Commonwealth have joined forces to address the very deficiencies described above with a PA Diabetes Action Plan and through work on PA Chronic Care Commission.

Extensive evidence shows that both diabetes and its complications - blindness, cardiovascular disease, kidney failure/dialysis, and neurological disease - can be substantially delayed, or even prevented by tight glycemic control and other interventions. As national examples, the Diabetes Control and Complications Trial (DCCT) and the Diabetes Prevention Program (DPP), (facilitated at the University of Pittsburgh DPP Lifestyle Resource Core that developed the successful Intensive Lifestyle Intervention) showed that if people at risk for developing diabetes make lifestyle changes, they can decrease their chance of progressing to diabetes and for those with diabetes, complications can be prevented with proper treatment and education. To date, however, findings from these national trials have not been effectively translated into real-world communities, particularly in underserved communities far from academic hub sites.

The University of Pittsburgh and its health system the University of Pittsburgh Medical Center (UPMC) have a long tradition of excellence in diabetes care and prevention. At present, over 180,000 people with diabetes in western Pennsylvania receive care annually at UPMC facilities, and 30% of patients hospitalized at UPMC facilities annually have diabetes. With its network of academic, community hospital, and primary care practices, UPMC affords the opportunity to translate the findings from trials into diverse communities and practices. There is extensive evidence that both diabetes and its complications can be substantially delayed or even prevented, yet translating findings from the major trials has not been done.

Pitt has been very active in these areas on a local as well as a national level. We have already joined forces with other renowned PA academic institutions and communities. To translate the programs described above from the research to community setting, novel methods for testing the effectiveness of these programs need to be put into place.

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Health Research Priority Title and Description

"Junk DNA" in the Onset, Progression, and Treatment of Disease

The term "Junk DNA" was coined in the early 1970's to refer to the part of the human genome that does not code for proteins. Junk DNA represents nearly 98% of the human genome's total real estate and is virtually completely uncharted. Research during the last decade has revealed that the Central Dogma of Biology ("DNA is transcribed into RNA; RNA is translated into Protein") cannot adequately describe the full spectrum of a cell's key players. Indeed, there is now abundant evidence that a large fraction of an organism's genome (DNA) will generate RNA transcripts that will never be translated into proteins: these non-translated transcripts are summarily referred to as "non-coding RNAs" (ncRNAs). For the subset of ncRNAs known as microRNAs, an exceedingly small fraction of the ncRNA universe, it has been shown that their dysregulation (whether it is by deletion, duplication or regulation-driven change of abundance) is intimately linked to important cellular processes and, thus, to the disruption of homeostasis and the onset and progression of many human conditions and diseases. In the last few years, orthogonal discoveries by us and others have provided compelling evidence along three important dimensions: a) many additional uncharacterized regions in the Junk DNA portion of the genome are linked to important diseases b) these regions can be present in one organism (e.g. human) and absent in another (e.g. mouse); c) these regions hold tremendous potential for transformative impact and the creation of a new field of research.

Biomedical Research Questions and Hypotheses

"Pyknons" are DNA motifs that were discovered computationally and span ~16% of the Junk DNA portion of the human genome. Earlier analytical work: a) posited that pyknons capture novel classes of RNAs; b) predicted new roles for messenger RNAs; c) demonstrated that the pyknon motifs capture widespread functional conservation between human and mouse in the absence of sequence conservation; d) posited novel regulatory interactions between introns and exons that are effected by pyknons. Preliminary published work by other laboratories in the US and abroad have generated first evidence supporting many of my earlier predictions. Additionally, recent evidence indicates that pyknons are functionally relevant in leukemia and colon cancer, thus establishing a first, very important link between pyknons and two human diseases. The following biomedical research questions emerge naturally: 1) what is the gamut of these new molecules (both precursor molecules and processed products)? 2) what are the rules governing the biogenesis of these new molecules and their processing into mature shorter products? 3) what are the rules governing the targeting preferences of these new molecules?

Clinical Research Questions and Hypotheses

For one pyknon that we have cloned we have shown (currently unpublished) that it is prognostic of disease progression in colon cancer patients. In parallel, compelling evidence (also unpublished) that we have generated using "next generation sequencing" type of analysis on carefully selected RNA samples (both normal and disease) from platelets, and breast and pancreas tissues, suggests that the pyknon motifs are true molecules whose relative abundance is characteristic of tissue, and, importantly, of tissue state. The evidence and the diversity of contexts of the pyknons suggests a mechanistic and deep link between pyknons, homeostasis and the onset and progression of disease. The following clinical research questions emerge naturally: 1) For a given tissue, determine exhaustively the group of pyknons that are most characteristically present in it and are absent from other tissues. 2) Among the tissue-specific pyknons, identify those whose abundance increases or decreases with disease progression; also, determine how standard methods of care impact and modulate this abundance. 3) For the molecules found in step 2) identify candidates to pursue as new therapeutic agents, e.g. by attempting to restore their 'normal' levels.

Health Services Research Questions and Hypotheses

The novel category of ncRNAs that is emerging from analytical and experimental work holds tremendous potential for developing new prognostic tests, new diagnostic tests and new therapeutic agents. The novelty of the findings, their unanticipated location ("Junk DNA"), lack of knowledge of the regulatory interactions in which these molecules participate, etc will require a multi-faceted, multi-disciplinary effort in order to bring the findings to the bedside. Several of the technologies that will be required in that regard are already in place; nonetheless, it is virtually certain that there will also be need to develop novel technologies as well.

Through an iterative process, the basic, applied, clinical and translational research components will need to inform one another as they advance towards determining the best strategy for identifying, inspecting, quantifying and countering the culprit molecule(s) in each case and how to best implement that strategy at the point-of-care sites.

Impact on Health of Pennsylvanians

This written testimony proposes to focus our basic, applied, clinical and translational activities to a previously unexplored part of the human genome that is currently referred to as "Junk DNA". The endeavors we propose transcend geographical, social, racial and economical boundaries. The anticipated benefits will thus be of relevance to the population of the state of Pennsylvania and beyond.

Characteristically, for many decades, activities by the research community and the pharmaceutical industry in the US and elsewhere have taken a protein-centric view of the cell and of cellular processes. Without a doubt this has been a very fruitful and extremely successful endeavor. Indeed, not only has it augmented our understanding of proteins as important biological molecules and the roles proteins play in the context of health and disease, but it has also allowed us to translate that knowledge to life-saving substances and health practices. These successes notwithstanding, numerous important questions continue to remain unanswered in the context of many human conditions and diseases.

The advent of novel experimental methods and the technological advances during the last decade have helped establish that there is a diverse universe of molecules that far outnumbers the classical protein-coding transcripts mentioned in and captured by the Central Dogma of Biology. Despite tremendous progress in the last several years, a whole lot remains to be discovered, including the full complement of these non-protein-

coding transcripts, their functional involvement in the regulation of cellular processes, their role in the onset and progression of human disorders, etc.

Two key observations have emerged from these recent research activities. First, it is now clear that as a community we need to liberate ourselves from the confines of the 2% of the human genome that corresponds to protein-coding transcripts. Indeed, it is increasingly evident that the Junk DNA portion of the human and other genomes holds valuable and arguably crucial information: understanding Junk DNA will help us better understand the kinds of things that matter the most, namely the prevention and therapy of disease. Second, the rapid unfolding of what could be called the “RNA revolution” has revealed that some of the RNAs that do not code for proteins (i.e. ncRNAs) are among the cell’s key regulatory players. The current ncRNA universe is very diverse vis-à-vis biogenesis, composition and function, and has been expanding rapidly. Our earlier computational work has uncovered within that universe what appears to be a very sizeable subset of novel RNAs that emanate from ~16% of the Junk DNA portion. Importantly, our initial experimental work has already revealed that these RNAs are important in several diseases; the specifics of that importance remains to be uncovered and is currently part of our ongoing efforts.

The area proposed here as a Health Research Priority is at the forefront of ncRNA research and human disease and aims to map the uncharted territory of a previously unknown regulation layer effected by molecules that we did not know, until recently, existed and matter. It is important to keep in mind that Junk DNA, in general, and pyknons, in particular, capture genomic regions that are generally not conserved across organisms e.g. between human and mouse. Since, based on the current evidence, Junk DNA matters the resulting corrolary is that there must exist aspects of human diseases that cannot be captured by animal models as they do not correspond to their "common biology." Approaching the problem from the standpoint of Junk DNA will open up new vistas of exploration and lead to truly innovative thinking and research and, eventually, treatments.

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Health Research Priority Title and Description

Cervical Cancer Education, Monitoring, and Therapies for PA.

Even though there are two vaccines against HPV, many questions still remain concerning its uptake, HPV infection and HPV carcinogenesis. The health research priority we are proposing is focused on human papillomaviruses (HPVs) associated cancers. This priority covers all three areas of research, Biomedical, Clinical, and Health Services. Health Services Research will seek to understand barriers to vaccine uptake and test strategies to overcome the barriers. Clinical Research will seek to understand the appropriate and effective use of the vaccine with Pap testing in a clinical setting for specific populations based on comorbidities, age, sexual practices, and geographic location. Biomedical Research will seek to describe epidemiological markers for high-risk HPV infection. Additionally, studies to monitor HPV type- and variant-specific persistent infection and vaccine failure by population group. Biomedical Research will also develop laboratory-based monitoring system of type- and variant-specific infection proclivities, vaccine efficacy and waning, and population type-specific pathogenesis for specific population groups. Biomedical and clinical research will develop and test cross-protective prophylactic and therapeutic vaccines.

Biomedical Research Questions and Hypotheses

Biomedical research hypotheses focusing on asking what types and variants of HPV are infecting vaccinated and unvaccinated Pennsylvanians and the potential for 2nd generation vaccine interventions. A) We hypothesize that Pennsylvanians, particularly ethnic populations and those of specific geographical regions have a predilection for specific HPV types and variants, especially types and variants not protected by the vaccine. B) We hypothesize that the types and variants identified in A differ in their basic biology specifically replication and infectivity properties, and these differences relate to host factors and behaviors including ethnicity and geography. C) We hypothesize that the vaccine will wane in effectiveness over time and that the kinetics can differ by population. D) We hypothesize that cross-protective vaccines can be developed for types and variants not in the present in the available vaccines. E) We hypothesize that cell-mediated CD8 T-cell responses to HPV epitopes can be exploited for the development of therapeutic vaccines for HPV-associated cancers.

Clinical Research Questions and Hypotheses

Clinical research hypotheses focusing on epidemiological and behavioral questions to understand at a population-specific level programs and policies that can lead to the prevention of high-risk HPV infection,

persistent infections, and waning of vaccine efficacy in some of Pennsylvanian's most vulnerable populations. Population being defined both as an age, ethnicity, sexual practices and geographical region. A) We hypothesize that risks for infection with specific types and variants of HPV are not the same for all groups of Pennsylvanians and vary by age, sexual practices, and geographic location. B) We hypothesize that risk of infection and persistent infection in specific populations in Pennsylvania can be monitored prospectively through active surveillance methods. C) We hypothesize that clinical protocols for vaccine administration, both the initial series and possible booster injections, can be developed and monitored for public health and school and other public sites.

Health Services Research Questions and Hypotheses

Health services research hypotheses focusing on increasing uptake of the HPV vaccine through education, services and policies. A) We hypothesize that population-based needs can determine a more efficient and effective structure and design for providing support, resources and materials to Pennsylvanians seeking guidance concerning cervical cancer, HPV, the vaccine options, and other HPV-associated cancers. B) We hypothesize that increasing women's and healthcare provider's awareness in Pennsylvania of HPV and its co-factors through community education programs moderated by physician and nurse leaders from each community using population-specific materials can improve awareness of HPV, its associated cancers, and its prevention. C) We hypothesize that partnering with the PA Department of Health to develop cervical screening population-specific programs in each community to increase knowledge of the prevention, screening and treatment for cervical cancer will raise awareness, improve life choices, and lower cancer rates. D) We hypothesize that ethnic and geographical specific knowledge, attitudes and behaviors is related to cervical cancer rates.

Impact on Health of Pennsylvanians

Impact on Health of Pennsylvanians

Human papillomaviruses (HPVs) are associated with over 99.7% of all cervical cancers and are the most important risk factor. Consequently, there is the potential to eliminate cervical cancer from Pennsylvania. Pennsylvanians living in rural or inner city areas, and ethnic minorities have elevated cervical cancer rates. There are four general areas of research need that will have a major impact on the health of Pennsylvanians as it concerns HPV associated infection and cancer progression.

1) Education Awareness: Awareness of HPV associated cancer is still low, there is a lack of knowledge of life choices that influence infection and cancer progression, there is a strong need for increased education for Pennsylvanians. Presently Pennsylvanian women in rural areas, inner cities, and of ethnic minorities are less likely to get any available information or to have proper screening and follow-up medical care.

2) Education Vaccine: Two vaccines are now available but proper education, for the patient or the healthcare worker, has not correlated with the availability of the vaccines leading to improperly informed choices. Population-specific educational tools would be developed increasing the likelihood for properly informed choices.

3) Vaccine Effectiveness: There are still conflicting messages and many unknowns as to the long-term effectiveness of the vaccine. Both Gardasil and Cervarix were reported from their clinical trial data to be 100% effective against the risk of developing HPV16 and 18 associated high-grade cervical lesions. However, the vaccines have not shown to protect against all variants of HPV16 and 18. Ethnic minority women have shown a proclivity to infection and persistence of infection with variants of HPV16 and 18. Additionally, the vaccine does not cover all HPV types known to be associated with cervical cancer. These HPV types, which presently are not as common as HPV16 and 18, could eventually increase their presence once HPV16 and 18 are removed by vaccination. The vaccine is recommended for young girls, 9-12 years of age, before they become sexually active. Screening programs to monitor continued efficacy of the HPV vaccines are generally centered on Pap diagnoses and histological examination for precursor lesions. While the vaccines protect against the

development of cancer this is indirect. Vaccination protects against infection by HPV not cancer progression. Monitoring for the presence of disease does not provide a true measure of continued efficacy of the vaccine. Because disease can lag behind infection by years and even decades the presence or absence of disease will not tell when infection occurred. To monitor long-term effectiveness of vaccines in Pennsylvania, techniques and protocols need to be developed and evaluated, including surveying HPV type and variant incidence in vaccinated and unvaccinated populations and correlating this to ethnicity and geography. Additionally, proper laboratory-based surrogate measurements of long-term effectiveness of vaccines are needed. Monitoring for the presence of disease alone can miss the beginning of loss of protection from infection by years and even decades.

4) Vaccine 2nd Generation: Because more than 15 HPV types are associated with cervical cancer, there is a need to develop 2nd-generation vaccines that are more broadly cross-protective. The need for more cross-protective 2nd-generation vaccines is especially important for Pennsylvanians of diverse ethnic backgrounds who have a higher risk of having persistent infections with variants or types not represented in the vaccines. In addition, many Pennsylvanians are already infected with HPV and it is well recognized that the current particle vaccine will not produce immunity to existing HPV infections. Therefore, development of effective therapeutic vaccines is needed.

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Health Research Priority Title and Description

The Potential Health Impact of Marcellus Shale Drilling

The Nature Conservancy of Pennsylvania projects that by 2030, 40,000 hydrofracturing (fracking) wells will have been drilled throughout the Commonwealth to collect natural gas from Marcellus Shale. There is a critical need to study the potential public health impact of this relatively new industry. Available information suggests that members of the Pennsylvania Marcellus Shale Advisory Commission agree on the need for consideration of stricter regulation of wastewater from drilling and updates to the Oil and Gas Act to improve safety and collect data. Anecdotal reports have led to public concern for safety in a number of fronts, including human, veterinary and ecological health effects of water quality (due to the composition, distribution and disposal or purification of fracking solutions) and air quality (shown to be a concern with other natural gas wells). Socio-economic and quality of life impacts on communities, including public safety, traffic, and tourism (resulting from demographic changes and stress on existing infrastructure) seem also to be of concern. Analysis of environmental impact of wells and chemicals used in the gas extraction strongly suggest a potential for adverse impact on health exists. It is therefore urgent that baseline metrics be established in each of these areas of potential concern. Baseline assessment studies undertaken now will enable appropriate follow-up studies of the Marcellus Shale well regions to analyze the effect of drilling on the public health of the residents of the Commonwealth.

Biomedical Research Questions and Hypotheses

We hypothesize that exploration of Marcellus Shale for natural gas results in changes in quality of water and air, as well as alterations in socioeconomic dynamics that may place the health of the residents of Pennsylvania in the communities surrounding the drilling sites at risk. This is a testable set of general but important hypotheses that do not presuppose that public health is compromised as a result of gas extraction from Marcellus Shale. Instead, the hypotheses reflect our belief in an urgent need to establish baseline metrics of public health and environmental contamination through ongoing comprehensive health and exposure surveillance. This will ensure that going forward, real effects of the hydrofracturing and gas collection, if any, can be quantified and mitigation measures can be proposed in a timely manner.

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Different locales have adopted different approaches prompted by public concerns. For example, the state of Maryland recently created the Marcellus Shale Safe Drilling Initiative, and New York State stopped issuing drilling permits so that impact studies on fracking could be conducted (Fruskin, 2010). The Commonwealth has convened a Marcellus Shale Advisory Commission, which has identified areas of concern such as potential toxicological effects associated with water and compromises in air quality. There is scant research literature on the public health effects related to fracking. In a thorough review of 81 papers on Marcellus Shale Research collected by Bucknell University, no more than three of the reports address health consequences; none in a satisfactory manner that can best inform policy makers, industry, public health experts and community members about the extent of health risk. In 2009, the Pennsylvania Department of Environmental Protection and the Susquehanna River Basin Commission examined Material Safety Data sheets for 41 products using in fracking, determining that 73% of the products had between six and fourteen different adverse health effects. A recent study (Osborn, 2011) showed increased methane levels in drinking water within 1000 meters of active drilling areas in Pennsylvania and New York. Despite credible concerns about threats to public health on this issue, there is an acute shortage of relevant research data and conclusions. Such an “information vacuum” can result in frustration and mistrust in affected communities, creating adverse effects associated with living with uncertainty about the future health of one’s community as well as social and economic prosperity.

The Commonwealth has an opportunity now to link a health surveillance effort to exposure surveillance and evolution of hydrofracturing technology. This will allow policy makers and other stakeholders to respond to emerging threats by recommending and/or implementing technological and policy innovations to safeguard public health. This will help mitigate public health threats that have potential to be discovered years or even generations after the drilling was begun in these regions. Baseline public health metrics should be established today and metrics monitored well into the future, while maintaining concurrent and proactive research aimed at reducing the environmental impact of hydrofracturing and natural gas extraction. Ideally baseline data will be collected via a baseline health survey in affected (e.g. living with 30 miles of a well) and comparison communities. Once a baseline is established, researchers and policy makers can “return” in the future to gauge impact. As part of this effort, the Commonwealth should consider creating a comprehensive underground water monitoring system and plans to collect comprehensive data on spills (Finkel, 2011).

A report from the state of Colorado (R. Witter et al., 2008) articulated the types of health indicators that can be readily examined to detect large trends in the health of communities in response to analysis of potential emissions from hydrofracturing drilling. Much can be learned about health threats in the short term by focusing on readily available metrics such as adverse pregnancy outcomes, childhood cancers, emergency room admissions for injuries, aggravated respiratory diseases and police records. If the health surveillance effort is linked to exposure surveillance and evolution of hydrofracturing technology, we will be in an excellent position to respond to emerging threats by recommending technological and policy innovations that will both protect health of public and ensure continued economic benefits to the Commonwealth.

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Health Research Priority Title and Description

Extremity war trauma treatment and recovery

Operation Iraqi Freedom and Operation Enduring Freedom have resulted in approximately 3000 deaths to soldiers engaged in military operations during the Global War on Terror, yet survivability due to injury is approximately 90%. Of those soldiers who have survived blast-related injuries, approximately 75% suffered major limb extremity trauma. The number of individuals who have suffered limb-loss due to combat related injuries has steadily risen since the beginning of Operations Enduring Freedom and Iraqi Freedom and the U.S Army has established dedicated facilities for individuals who have suffered traumatic injury in order to provide the necessary care for both the primary and secondary medical complications resulting from injury. The cost of direct care for these injuries has been estimated at \$65 million and \$169 million in disability costs with extremity injured soldiers accounting for nearly 65% of both direct costs and disability. The opportunity to fund traumatic orthopaedic research related to the war is invaluable as promising treatments can be developed to enhance recovery and return to active duty or civilian life, while ultimately reducing the fiscal implications of long term care and rehabilitation due to primary or secondary pathology.

Biomedical Research Questions and Hypotheses

Non-drug-based metal-organic surface treatments, which have shown promise in vitro and in small animal models, can be optimized to reduce post operative infection following intramedullary nailing in large species models without inhibiting fracture repair.

Load bearing, osteoinductive and anti-infective composite synthetic long bone graft can allow for earlier weight bearing, accelerate bone regeneration, and reduce the risk of infect to better repair segmental bone defects.

Identify effective techniques of wound debridement and treatments of segmental bone defects.

Identify antibiotic treatment and infection control during wound debridement and management of open fractures.

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Unique to terrorism conflict is a new type of patient, a warfighter with multiple and severely injured extremities due to blasts involving several musculoskeletal structures. Enhanced orthopaedic research is critical to the long-term care of today's warfighter in order to either return to active duty following a blast-related injury or to improve the quality of life after the military. Military personnel suffering blast-related traumatic amputation have been reported to demonstrate poor long term physical and psychological health outcomes. Cardiovascular disease, with risk factors of hypertension, hyperlipidemia, excess body weight/fat, and diabetes often develop in this military population. The insidious onset of hypokinetic-related risk factors for cardiovascular disease is likely a function of diminished physical function, general health, and psychological well-being, which has been demonstrated in several long term follow-up studies. Previous research indicated nearly 20% of Soldiers with an amputation will develop cardiovascular disease, but the rate of cardiovascular disease increases to 78% when ambulation is severely restricted. Further, Soldiers who suffer from blast-related injuries and traumatic amputations have a higher incidence of deadly chronic diseases such as cardiovascular disease. During WWII the relative risk for cardiac-related death was 1.58 greater in unilateral above-knee amputees and 3.5 greater in bilateral above knee amputees compared to other injured soldiers. Prosthetic ambulation requires greater energy expenditure than in normal ambulation and as such often results in a more sedentary lifestyle. Given the increasing number of individuals with blast-related amputations, there is an increasing need to develop effective strategies to treat and rehabilitate the primary orthopaedic injury, which will ultimately ameliorate the secondary health issues (overweight/obesity, cardiovascular diseases). In addition to the costs associated with the primary injury, concomitant pathologies increase the costs to the military, in terms of both direct costs for increased health care and disability payments and indirect costs for lost workdays since military personnel are unable to continue with their current occupational demands. Early intervention to treat and rehabilitate the primary orthopaedic trauma and prevention of the secondary co-morbidities is critical to avoid developing a cascading series of risk factors that will result in a diminished quality of life after the military and corresponding costs due to necessary treatment.

To date, 1690 military personnel from Pennsylvania have been wounded in action in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) representing approximately 4% of hostile injuries reported from all military personnel across all states. Pennsylvanian military personnel are ranked in the top 5 for total magnitude of wounded in action personnel for OIF and OEF. Of all injuries sustained across all military personnel and all states during OIF and OEF, 76% are under the age of 30 suggesting the need for early intervention to improve the treatment and rehabilitation and restore pre-injury activities to return to active duty. The Pennsylvania National Guard is one of the largest in the country and since 2001 has had over 25,000 deployments to support the Global War on Terror. In 2001 the Army converted a Brigade within the 28th Infantry Division to a Stryker Brigade Combat Team (SBCT) demonstrating the strength and readiness of the 28th Infantry Division as it parallels the activities of the other six SBCT, which are active Army. The magnitude and frequency of deployed military personnel within Pennsylvania and quality of life impact underscores the importance of research to support the treatment and rehabilitation of military personnel from blast-related injuries.

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Health Research Priority Title and Description

Motor coordination in patients with central nervous system (CNS) injury

Injury to the CNS affect a large proportion of the general population. Their incidence increases with age, but younger persons can also demonstrate such disorders. Most commonly, CNS disorders are associated with stroke, spinal cord injury, and neurodegenerative disorders (for example, Parkinson's disease). One of the most common consequences of such disorders is loss of movement coordination, which makes people unable to work productively and dependent in their everyday life on help from caregivers. The current understanding of the neural mechanisms of disordered coordination is very poor. It creates a major obstacle for the development of novel, effective rehabilitation strategies. The recent progress in studies of unimpaired motor coordination allows to apply the developed methods to study the mechanisms of disordered coordination.

Biomedical Research Questions and Hypotheses

We plan to use the method of analysis of motor synergies to quantify disordered digit coordination in multi-digit tasks such as pressing, holding, and manipulating a hand-held object, and disordered muscle coordination in whole-body tasks such as standing, swaying, and making a step. We plan to document atypical patterns of coordination that will correlate with the clinical status of the patients. We also plan to develop simple tests that can be used to quantify improvement or deterioration of motor coordination with therapy and/or progression of the disease.

We hypothesize that patients with CNS injuries will show reduced indices of motor synergies and this reduction will correlate with the clinically assessed severity of the disorder. We also plan to show that therapy is able to reverse the reduction in the synergy indices and bring them close to those in healthy persons.

Clinical Research Questions and Hypotheses

We plan to focus primarily on patients with Parkinson's disease treated in the Hershey Medical Center. The patients will be tested on and off their prescribed medications to demonstrate that motor synergies can be modified with therapy. We also plan to use the indices of synergies to demonstrate and quantify impaired feed-forward control of movements by those patients. This is an important issue because feed-forward control is essential for the production of voluntary actions, particularly fast ones. We plan to show that the quantified impairments in the feed-forward control correlate with the classical cardinal sign of Parkinson's disease, namely bradykinesia. Further, we plan to expand this line of research to include persons with spinal cord injury with and without spasticity and stroke survivors.

Health Services Research Questions and Hypotheses

Currently, assessment of patients with CNS injury does not involve quantitative measures of motor coordination. We plan to demonstrate that such measures are essential for adequate assessment of the patient's clinical state and recovery of the motor function. Incorporation of such tests and measures into the established health service practice would be beneficial for treatment of such disorders and accelerated recovery of independence by the patients.

Impact on Health of Pennsylvanians

CNS trauma and disorders affect a large number of people in the state of Pennsylvania. Parkinson's disease is the most prevalent degenerative neural disorder with over 0.1% of the population affected (about 20,000 in Pennsylvania). Stroke is the leading cause of disability in the US with over 5.5 million Americans affected (about 50,000 in Pennsylvanians). Spinal cord injuries affect around 290,000 people in the US every year (about 1,000 in Pennsylvania). Overall, disorders of the CNS are a major health problem, and the cost of medical care, rehabilitation, and lost workforce is astronomical. For example, the cost to society associated with SCI is estimated to be over \$30 billion per year. The costs associated with Parkinson's disease and strokes are proportionally higher.

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Health Research Priority Title and Description

Tissue engineering approaches to musculoskeletal disease and injury

We are suggesting that tissue engineering and regenerative medicine approaches to musculoskeletal diseases and injury be considered a health research priority. Musculoskeletal diseases and injuries can be defined as those that affect bones, muscles, tendons, ligaments, joints, cartilage, and other connective tissue. These include back and neck pain, spinal deformities such as scoliosis, osteo and rheumatoid arthritis, osteoporosis and other metabolic bone diseases, developmental problems, bone and connective tissue cancer and injuries to the musculoskeletal system including military injuries. Tissue engineering and regenerative medicine hold a unique promise to alleviate the pain and suffering associated with musculoskeletal disease and injury. The goals of tissue engineering and regenerative medicine are to restore cells, tissues and structures lost to disease injury and aging. Tissue engineering and regenerative medicine research necessitates the collaboration of cell and developmental biologists, stem cell biologists, engineers, material scientists, computational scientists and clinician scientists. It is by nature translational research the outcome of which is will directly benefit the patient. Making tissue engineering and regenerative medicine approaches to musculoskeletal diseases and injuries a priority for the competitive non formula health research grants will lead to the development of new therapies to ease the suffering of many patients in the commonwealth.

Biomedical Research Questions and Hypotheses

- Novel biomaterials can activate stem cell recruitment to sites of bone injury.
- Induced pluripotent stem cells can enhance osteogenesis in a murine model of osteoporosis.
- Fracture healing in aged mice can be enhanced by activation of gap junctional intercellular communication.
- Novel scaffold and adult stem cell composites can enhance both osteogenesis and chondrogenesis in an animal model.
- Resurfacing processed allografts with nanotopographic biomaterials enhance allograft osteointegration.

Clinical Research Questions and Hypotheses

- Individuals with delayed fracture healing possess a unique genotype.
- Induced pluripotent stem cells can regenerate bone and enhance fractures in patients with delayed fracture healing.
- Biomemetic scaffolds combined with adult human mesenchymal stem cells increase bone healing in patients with critical size defects.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Musculoskeletal diseases and injuries comprise a set of afflictions for which there has been relatively little research and funding. Research funding for musculoskeletal diseases and injury is only 2% of the National Institutes of Health Budget, yet musculoskeletal conditions represent some of the top health concerns for citizens in the United States and the commonwealth. According to the American Academy of Orthopaedic Surgeons (AAOS), in 2005, musculoskeletal conditions were reported by 107.67 million adults in the United States, representing nearly one in two persons age 18 and older. The cost of these conditions is \$849 billion annually in the United States alone and musculoskeletal diseases and injuries are the leading cause of physical disability in this country resulting in more visits to physicians' offices than any other condition.

The health impact to the Commonwealth of musculoskeletal disease and injury cannot be overstated. This is partly because of the positive correlation between the incidence of musculoskeletal disease and aging. The aging population of Pennsylvania continues to increase dramatically. According to the Pennsylvania Department of Aging, from 1990 to 2000 the total number of people age 60 and over remained at about 2.4 million. However, those age 75 to 84 increased by 21 percent and those age 85 and older increased by 38 percent. Furthermore, the percentage of minorities, including African Americans, Hispanics and Asians, that are elderly is increasing faster than the percentage of whites.

Musculoskeletal disease and injury are especially prominent in the elderly population. For instance, 14% of all individuals over 50 and 23% of women over 50 in Pennsylvania have been diagnosed with osteoporosis. Additionally, in Pennsylvania in 2003, 32 percent of the adult population, representing over 3 million Pennsylvania adults, was diagnosed with arthritis. Groups disproportionately burdened by arthritis include adults age 65 and older (63 percent), adults with less than a high school education (46 percent), and adults with an income of less than \$20,000 (42 percent)(from the Center for Disease Control: http://www.cdc.gov/arthritis/state_programs/programs/pennsylvania.htm). Since individuals with arthritis are at higher risk for osteoporosis these individuals are also at increased risk for fractures. Discharge rates for vertebral fractures, which are often a result of osteoporosis, were significantly higher in Hispanic residents of Pennsylvania relative to white residents. Thus, there are health disparities as regards musculoskeletal disease, in that sub populations of Pennsylvanians, including the elderly, Hispanics and low income individuals, are disproportionately affected. Fortunately, fractures that result from osteoporosis, cartilage degradation that results from arthritis, spinal deformities, developmental diseases and most other musculoskeletal conditions, have a strong potential to be successfully treated by tissue engineering and regenerative medicine approaches.

Another group of Pennsylvanians greatly affected by musculoskeletal disease and injuries are veterans. As the AAOS points out, the majority of trauma that occurred in Operation Iraqi Freedom and Operation Enduring Freedom is orthopaedic-related, particularly involving the upper and lower extremities. Because soldiers are better protected with high tech gear, they come home with devastating injuries, especially to their arms and legs, that might well have killed them in earlier wars. These musculoskeletal injuries can best be treated by developing novel tissue engineering and regenerative medicine strategies (J Am Acad Orthop Surg, Vol 16, No 11, November 2008, 628-634).

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Health Research Priority Title and Description

Developmental etiology of pediatric airway and lung diseases

Human health and survival are critically dependent on adequate oxygen intake, a process mediated by the airway and lung, and thus children born with developmental abnormalities involving the airway and lung are particularly vulnerable. These congenital lung defects can include conditions arising from deficient lung growth referred to as pulmonary hypoplasia or other congenital broncho-airway malformations, as well as cystic conditions associated with airway and lung maldevelopment, and other conditions referred to as bronchopulmonary dysplasia. Such infants and children often have poor prognosis and in the absence of insights into the developmental etiology of these developmental disorders, therapeutic options are very limited. At present, the cellular and molecular mechanism and developmental etiology for such congenital airway and lung disorders remain unknown and are largely unexplored. Therefore, investigations to elucidate the etiology of such airway and lung developmental disorders and their pathological mechanisms are needed to facilitate development of more effective therapeutic options for these devastating pediatric lung diseases. It is only with insights into the underlying cellular and molecular mechanisms for such developmental airway and lung diseases that personalized medicine may be applied with targeted therapies to treat these life threatening pediatric diseases.

Biomedical Research Questions and Hypotheses

Children born with developmental disorders involving the airway and lung often have poor prognosis, as there are few effective therapeutic options in the absence of mechanistic insights into the etiology of these airway and lung defects. Therefore, investigations into the mechanisms regulating airway and lung development and the causes of airway/lung developmental disorders are important research areas that can help improve the survival and health of children born with these devastating airway/lung conditions.

This important area of research investigation can be framed in terms of several hypotheses:

Hypothesis 1: Developmental disorders of the airway and lung can arise from genetic defects that disrupt developmental pathways required for formation and patterning of the airway and lung.

Hypothesis 2: Defects involving stem cell and stem cell progenitors required for growth and development of the airway and lung can give rise to developmental disorders of the airway and lung.

Hypothesis 3: Disruption of cell signaling pathways and cell-cell interactions required for airway and lung development can give rise to pediatric airway and lung diseases.

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Developmental disorders of the airway and lung are serious medical conditions that affect the viability and health of newborn infants and children. At present, there is no state-wide statistics gathered on such pediatric diseases for Pennsylvania. While the prevalence of such pediatric airway and lung disorders has not been established, such disorders affect the most vulnerable citizens of Pennsylvania, our newborn infants and children. Moreover, such diseases cause disproportionately more morbidity and mortality due to the severity of the conditions and the lack of medical treatment options. Therefore, research in this medical area is compelling and much needed to help accelerate the development of better therapeutic options for improving the health and welfare of our most vulnerable citizens.

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Health Research Priority Title and Description

Improving Quality of Life For People With Diabetes Complications

According to Healthy People 2020, almost 24 million people currently have diabetes and it is the 7th leading cause of death in the United States. Diabetes can lower life expectancy up to 15 years, increase the risk of heart disease and depression, and is the leading cause of adult-onset blindness, kidney failure, and lower limb amputation. According to Centers for Disease Control and Prevention, diabetes is also a major cause of stroke. Approximately 60-70% of people with diabetes are affected with some form of nervous system damage. New studies show that diabetes is associated with cognitive impairment (Saczynski et al. 2008) while other studies have shown that people with diabetes and comorbid major depression have clinically significant microvascular and macrovascular complications (Lin et al. 2010). New biomedical studies are attempting to link type 2 diabetes with Alzheimer's Disease by examining their overlapping pathologies (Zhao & Townsend 2009). Another study has found an association between number of prescription medications and falls among patients with diabetes (Huang et al. 2009). The aforementioned data and research studies illustrate that the complications due to diabetes are widespread and varied, including both physical and cognitive detriments. Diabetes and its complications reduces the quality of life for Pennsylvania residents. Improving the quality of life for people with diabetes complications should be a research priority considering that the prevalence of diabetes is projected to increase in Pennsylvania.

Biomedical Research Questions and Hypotheses

- Examine the pathophysiology of cognitive impairment in people with diabetes complications.
- Examine the mechanism by which hyperglycemia alters cerebral structure and function.
- Examine the mechanism by which diabetes causes eye complications other than diabetic retinopathy.

Clinical Research Questions and Hypotheses

- Develop community intervention techniques to increase the proportion of people with diabetes who obtain yearly foot examinations, yearly dilated eye exams, annual dental examinations, etc.
- Develop interventions to combat depression in people with diabetes in an effort to reduce future diabetes complications.
- Develop interventions to improve the quality of life in people with diabetes with visual impairment due to diabetic retinopathy.

Health Services Research Questions and Hypotheses

- Test the efficiency of a program that provides A1C testing at faith-based organizations in order to diagnose people with diabetes whose condition is undiagnosed.
- Examine doctor-patient education initiatives to improve glycemic control, blood pressure, and cholesterol.
- Show the cost-effectiveness of widespread diabetic testing for undiagnosed, high-risk individuals in faith-based organizations.
- Develop culturally appropriate intervention strategies to motivate people with diabetes to improve self-care.

Impact on Health of Pennsylvanians

In a recent study conducted by the Institute for Alternative Futures, researchers predict Pennsylvania will be one of the 10 states that will carry the burden of diabetes in the United States, defined by the predicted prevalence and cost in 2025. These are troubling statistics considering that in 2008, Pennsylvania ranked 18th in the nation for the percentage of adults told they have diabetes while ranking 47th in accomplishing glycemic control ('The Burden of Diabetes in Pennsylvania 2010', Department of Health). In 2010, 1.3 million people in Pennsylvania had diabetes (both diagnosed and undiagnosed). Additionally, there are 3.2 million people in Pennsylvania who have pre-diabetes. In 2025 the number of people with diabetes in Pennsylvania (diagnosed and undiagnosed) is predicted to increase to 1.9 million, a 30% increase (Institute for Alternative Futures and the CDC) despite stable predicted population levels.

The statistics become more troubling when taking diabetic complications into account. Hospitalizations due to diabetes increased 11% between 2000 to 2007 ('The Burden of Diabetes in Pennsylvania 2010, Department of Health). In 2010, more than 150,000 people were visually impaired or blind due to diabetes. (Institute for Alternative Futures and the CDC). This number is predicted to increase 35% by 2025. Additionally, there were approximately 2500 leg amputations due to complications of diabetes in Pennsylvania in 2010 alone. This number is expected to increase by 15% by 2025. Diabetes complications, such as visual impairment and leg amputations are common causes of disability in Pennsylvania and contribute greatly to the indirect costs of diabetes, a national \$58 billion dollar burden in 2007 (National Diabetes Fact Sheet 2011, CDC). These increases in the aforementioned diabetes complications are predicted despite the fact that Pennsylvania's overall population is expected to remain constant.

The Department of Health Report, 'The Burden of Diabetes 2010' shows how diabetes disproportionately impacts particular segments of the population. For example, the prevalence of diabetes is also statistically much higher for black residents in Pennsylvania compared to Hispanics and whites. Disparities also exist with regards to income and education level. Reported incidence of diabetes decreases with increases in education and income level. Diabetes is a widespread problem in Pennsylvania and its prevalence and cost are only projected to get worse. Diabetes should be a research priority for the state and research initiatives should reduce the disease and economic burden of diabetes while improving the quality of life for people who have diabetes or are at risk for developing diabetes and its associated complications, such as visual impairment, over the next decade.

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Health Research Priority Title and Description

Improving Health Literacy in PA

Healthy People 2020 defines a health disparity as a particular type of health difference that is linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their race, religion, socioeconomic status, gender, age, etc. One factor that contributes to health disparities is low health literacy. A 2004 report from the Institute of Medicine describes health literacy as the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. People with low literacy have less health knowledge, worse self management of chronic disease, lower use of preventative services, and overall worse health (Bennett et al., 2009; Chew et al., 2008; Peterson et al., 2011). While many studies have linked low health literacy as a contributing factor to numerous health disparities, there have been few studies that seek to improve health literacy in order to reduce health disparities. Conversely, there are many research initiatives that seek to reduce health disparities directly through interventions targeting prevention and self-care behaviors. By making health literacy a research priority, researchers would be able to address patient health literacy for a wide range of medical conditions while ultimately reducing many health disparities that exist in Pennsylvania today.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

- Development of educational tools to improve comprehension of prevention behaviors like dilated eye exam adherence, mammograms, etc.
- Examine the impact of social and cultural factors and health literacy on health disparities.
- Examine the skills and abilities (reading, cognition, oral language, mathematical) needed to be health literate.
- Targeting relevant communication technologies, using tailored information systems, to support health education efforts (i.e. computer interventions, text message interventions, etc).
- Examine the influence of social, contextual, and environmental factors on health literacy outcomes

Health Services Research Questions and Hypotheses

- Development of easy to read instructions for medications to improve medication adherence.

- Medical practitioners use of tailored interventions, using patient familiar language and concepts while reducing cognitive demands to improve medical adherence.
- Develop communication tools to help health care professionals identify, and communicate with patients with different levels of health literacy, including those from different cultural backgrounds.
- Show cost/effectiveness of health literacy interventions to reduce health disparities.
- Test current health care practices and policies and whether the effect on health literacy varies due to age, race, disease, etc.

Impact on Health of Pennsylvanians

According to the PA Department of Health, black, non-Hispanic adults in PA are significantly more likely than White, non-Hispanic adults to be obese, to report fair or poor general health, to have cancer, and to not have a personal health care provider. Black, non-Hispanic adults compared to white, non-Hispanic adults have higher mortality rates overall as well as higher mortality rates due to cardiovascular disease, heart disease, total cancers, renal failure, diabetes, HIV/AIDS, hypertension (hypertension renal disease), and asthma. Hispanics, a growing population in PA, are more likely than whites to be hospitalized due to asthma, uncontrolled diabetes, and preventable pneumonia.

In a systematic review of health literacy research, analysis revealed that about 25% of subjects had low health literacy and another 20% had marginal health literacy (Paasche-Orlow et al., 2004). In another study, researchers found that health literacy mediated race disparities in self-rated health status and that health literacy mediated educational disparities in preventative health behaviors such as getting a mammogram or flu vaccine (Bennett et al., 2009). Another study has found that those with marginal or inadequate health literacy have higher mortality rates compared to those with adequate health literacy (Baker et al., 2007). This same study found that 25% of a national sample of Medicare enrollees have inadequate health literacy. Another study found that African Americans were 2.40 times more likely to be non-adherent to taking HIV medications (Osborn et al., 2007). However, when the researchers controlled for health literacy in their analysis, the effect of race on medicine adherence was no longer statistically significant. In another study assessing health literacy among people with type 2 diabetes, researchers found that those with limited health literacy were significantly more likely to experience hypoglycemia (Sarkar et al., 2010). In an analysis of patient education materials from the American Diabetes Association and the American Heart Association, researchers found that these materials met few criteria for usability by patients with low health literacy (Hill Briggs & Smith, 2008).

Health disparities due to race, age, gender, education, socioeconomic status have been well-documented in the literature. Additionally, many studies have found that health literacy is a large and widespread problem and the aforementioned studies have shown that low health literacy is a contributing factor to many health disparities. While there have been studies and public health initiatives to reduce health disparities in PA and nationally, there have been few studies that have aimed to improve health literacy in order to reduce health disparities.

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Health Research Priority Title and Description

Comparative effectiveness of organizational strategies for quality improvement

In recent years, there has been considerable attention to the gap between scientifically proven optimal practices in medicine and implementation of those practices into medical care settings. Implementation research within healthcare evaluates methods to promote the uptake of evidence-based practices into routine practice, resulting in improvement in healthcare, including improved effectiveness, reliability, safety, equity and efficiency. Healthcare systems have invested in the infrastructure and personnel needed to implement industry models of quality improvement. However, these individual efforts are poorly coordinated and not tied to scientific methods in order to accelerate our understanding of the basis for healthcare system improvement. This research priority will stimulate collaboration across the State to accelerate the advancement of knowledge in implementation sciences. To advance science in this area requires linking the clinical operations of a network of community and academic medical centers with a team of scientists conducting innovative work in operations research and implementation sciences to improve quality. Already, we have established a partnership with the Geisinger Health System to conduct this work and additional partnerships across the State will be created. This priority will emphasize the creation of a common electronic platform for sharing health system data and support studies to identify best processes for translating evidence into clinical practice across diverse health care delivery settings.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

The increasing complexity and specialization of the healthcare system has led to substantial fragmentation of care, especially during the course of an acute care hospitalization and during transitions from inpatient back to outpatient care. Fragmentation creates measurable drops in the quality and efficiency of health care, that result in poor patient outcomes and escalating healthcare costs. Operational sciences, especially as applied in non healthcare industries, provide a series of testable strategies for improving the quality and efficiency of healthcare delivery, especially across points of discontinuity. Research questions include:

1. Can a team based management strategy incorporating community health workers improve care coordination for low income patients discharged from the hospital. Hypothesis: A transition program incorporating community health workers can improve patient outcomes and reduce overall health costs.

2. Can process standardization and feedback create a reliable process that reduces hospital-acquired catheter associated infections compared to standard practice Hypothesis: Hospital-acquired infections can be minimized using industry approaches to process standardization.

Health Services Research Questions and Hypotheses

While the operational strategies utilized by other industries (e.g., continuous quality improvement (QI), lean production systems) could be implemented in healthcare settings to improve the safety and quality and efficiency of medical care, there are significant questions regarding the unique features of healthcare settings that will modify the effectiveness of these strategies. Specific health services research questions in this area address issues of implementation of programs and scalability across diverse health care delivery settings.

Research questions include:

1. Do the organizational structures currently used for hospital QI programs impact the success of these programs? Hypothesis: QI structures that incorporate bottom-up strategies and rapid cycles are associated with more successful QI programs, including discharge coordination and medication safety programs.
2. What organizational factors modify the effectiveness of interventions that are successfully implemented at one site and then disseminated to other sites. Hypothesis: Measurable attributes of local champions are associated with the ability of QI interventions to be successfully implemented at additional sites.

Impact on Health of Pennsylvanians

Taken together, preventable medical errors and the failure to delivery evidence-based high quality care account for substantial morbidity and mortality in our medical system at tremendous increased cost. Medical errors account for a minimum of 44,000 deaths annually, which is more than motor vehicle accidents, breast cancer, or HIV.(1) In the Institute of Medicine's report, "To Err is Human: Building a Safer Health System," the important research questions ask about the conditions under which people make errors, the types of errors being made, and the types of systems that can be put into place to prevent errors altogether when possible.

Analogously, the IOM report "Crossing the Quality Chasm: A New Health System for the 21st Century" highlights the gap between our understanding of evidence-based effective treatments and the delivery of those treatments, even in our most elite medical institutions. For example, in a recent national study, only 22.8% of patients received recommended care (prophylactic antibiotics and anticoagulation) during acute hospitalizations for hip fracture.

In Pennsylvania, there is abundant evidence that all Pennsylvanian's do not receive the highest quality of care available and preventable medical errors occur at an alarming rate. For example, according to data from the Pennsylvania Health Care Cost Containment Council (PHC4), in 2007, 27,949 patients experienced hospital-acquired infections in Pennsylvania, a rate of 17.7 per 1,000 admissions. These largely preventable infections (including catheter associated urinary tract and blood stream infections and ventilator associated pneumonia) resulted in substantial morbidity, mortality and cost: patients with infections experienced 12.2% mortality, 15 day median length of hospitalization, and \$87,655 median hospital charges compared to 2% mortality, 3 day median length of hospitalization, and \$19,748 median charges for patients without infections.(3) Similarly, evidence suggests that there are many opportunities for raising the quality of care delivered in PA hospitals. For example, according to PHC4 data, 57,360 patients discharged from PA hospitals with selected conditions were readmitted within 30 days, accounting for 18.7% of all admissions. These data also highlight substantial variability across PA hospitals in risk adjusted length of stay and total charges for many clinical diagnoses, including cardiovascular and pulmonary diseases and pneumonia.(4) Standardization of evidence based procedures for these common conditions can improve clinical outcomes and reduce readmissions at substantial cost savings. Yet, our understanding of organizational barriers to implementing these evidence based guidelines is limited and has resulted in a substantial gap between what we know and what we deliver.

Disparities in the occurrence of medical errors and the delivery of high quality, evidence-based care are prevalent. In a study of hospitalized patients in New York, rates of adverse events rose with age, and the

percentage of adverse events due to negligence was markedly higher among the elderly.(5) Advanced age is also consistently cited as a risk factor for medication errors. Racial and ethnic disparities in the delivery of high quality, evidence-based care are also prevalent, with multiple national studies demonstrating that African Americans consistently receive lower quality of hospital care than whites. Central to efforts to improve quality of care and patient safety is a focus on improving equity across the health system in PA.

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Health Research Priority Title and Description

Concussion in Children: Prevention to Treatment

It is estimated that 2-4 million sports concussions occur in the U.S. each year. Children are at particular risk for concussion due to their developing brains and high rate of participation in at-risk sports such as football, hockey, and soccer. Researchers have identified risk factors, symptoms, neurocognitive, and neuromotor effects of concussion. Most research has focused on assessment and management of concussion. Researchers have paid little attention to prevention and active treatments and therapies; and prospective, multidisciplinary studies are generally lacking. As such, we advocate for research on preventative initiatives to reduce the risk; and controlled studies of pharmaceutical, vestibular, physical, and other therapies on concussion in children. In addition, emerging symptom, genetic, and biomarker risk factors need to be studied. Research is also needed in the area of diagnosis using new imaging techniques in conjunction with established clinical, symptom, and neurocognitive protocols. We also believe that researchers must address the growing disparity in concussion awareness and care in underrepresented groups. Finally, we think that it is important for Pennsylvania to continue to be at the forefront in concussion policy and care. Hence, we believe that Pennsylvania should set the standard for concussion education, care, and surveillance via state-wide, technologically-driven initiatives to increase concussion knowledge and care, and decrease concussion risk among children.

Biomedical Research Questions and Hypotheses

1. What are the medical history, symptom, neurocognitive, vestibular, genetic and biomarker predictors of concussion severity and recovery? Hypotheses- Each of the following will predict concussion severity and recovery: A. History of migraine and previous concussion; B. Migraine and vestibular symptom clusters; B. Clinically significant neurocognitive declines in the acute phase of injury; C. Positive vestibulo-ocular, somatosensory, and posturography findings; D. Specific alleles of 5HTT, ACE, APOE, BDNF, COMT; E. Elevated AMPA receptor peptide/GluR antibody assay. 2. Can imaging techniques assess neurometabolic changes in the brain following concussion? Hypotheses- Concussion will result in: A. DTI- axonal damage (reduction in anisotropy); B. fMRI- increased temporal and parietal, and decreased frontal lobe activation during working memory tasks; C. MEG/EEG- less elevated intra-parietal and intra-occipital cortices and abnormal dipolar wave activity during memory tasks; D. NIRS- dysregulated cerebral blood flow during cognitive processing; E. BNA/ERP – changes in connectivity and ERPs in the dorsal lateral prefrontal, anterior cingulate, orbitofrontal, and infraparietal cortices during Go-No Go, N-back, and odd ball tasks.

Clinical Research Questions and Hypotheses

1. Can emerging pediatric neuropsychological concussion tests assess and manage concussion in young (<12 years) children? Hypothesis: Emerging pediatric neuropsychological tests will be effective in assessment and determining recovery from concussion in young children. 2. What are the effects of vestibular and physical therapies on recovery following concussion? Hypothesis: Vestibular and physical therapies will decrease recovery time. 3. Which pharmaceuticals will be efficacious in treating concussion? Hypotheses: A. Amantadine will be more effective than placebo control in treating post-concussive symptoms and improve reaction time, processing speed, and memory. B. Melatonin will be more effective than placebo control in treating acute post-concussive insomnias. 4. What is the role of comorbid conditions (e.g., ADHD, LD, depression, anxiety) on concussion outcomes? Hypotheses: A. Pre-existing ADHD and LD will predict increased concussion severity and prolonged recovery; B. Pre-existing depression and anxiety will predict emotional symptom clusters, lower neurocognitive scores, and prolonged recovery.

Health Services Research Questions and Hypotheses

1. Which strategies might reduce the risk of concussion for children? Hypothesis: Increased awareness, concussion-related rule changes, proper use of equipment, and identification of at-risk children will decrease the risk among children in Pennsylvania. 2. Can we address health disparities in concussion among underrepresented communities (e.g., African Americans)? Hypothesis: Awareness programs and community-based concussion clinics developed in partnership with these communities will decrease health disparities. 3. Can we implement a state-wide evidence-based, concussion training and CEU/CME program for healthcare and educational professionals, and coaches? Hypothesis: A training/CEU program will increase awareness, identification, referrals, and care. 4. Can we implement a state-wide online, baseline neurocognitive concussion testing protocol? Hypothesis: A baseline testing protocol will result in better concussion management for children in Pennsylvania. 5. Can we implement a state-wide, online concussion reporting system? Hypothesis: An online concussion reporting system will provide data on the prevalence, outcomes, and direct/indirect costs of concussion in Pennsylvania.

Impact on Health of Pennsylvanians

Pennsylvania accounts for approximately 156,000 of the 2-4 million sport-related concussions that occur each year in the U.S. This figure represents nearly 64% of the estimated 245,000 brain injuries that occur each year in Pennsylvania. It is estimated that concussions affect over 20,000 children in Pennsylvania each year. More than half of the 502,000 emergency department visits for concussion in children in the U.S. each year are a result of sports participation. With regard to morbidity and mortality 287,000 Pennsylvanians have a lifelong disability due to brain injury, and 2,300 die from brain injuries each year. Concussions involve considerable morbidity, and if mismanaged, may lead to chronic and even catastrophic effects. For example, a second blow to the head that occurs before a child's brain recovers from a concussion can result in Second Impact Syndrome involving rapid brain edema, permanent brain damage, and even death. Concussions in sport are particularly problematic for children, as their brains are not yet fully developed, and they are less likely to receive the standard of care afforded to collegiate and professional athletes. Moreover, the average recovery time from concussion in children is 10-14 days compared to 5-7 days for college age adults. Additionally, 20% of children take longer than 21 days to recover from concussion, and some require months or longer to recover, and must withdraw from school and other activities as result of their injury. Researchers have also reported that there exists a significant health disparity with regard to brain injury awareness and access to care among underrepresented groups (e.g., African Americans) in the U.S. In conclusion, research on concussion in children with a comprehensive focus from prevention through treatment and emphasis on health disparities will improve the health and safety of children in Pennsylvania. Therefore, because concussion has a significant and

potentially far-reaching impact on the health of children in Pennsylvania we believe that it warrants consideration as a health research priority for the Commonwealth Universal Research Enhancement Program.

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Health Research Priority Title and Description

Enhancing Motor Function after CNS Injury

Most central nervous system (CNS) injuries results in loss of voluntary motor function. The corticospinal tract is a main contributor to the control of voluntary movements in humans. Observations throughout the years have demonstrated that corticospinal axons have the intrinsic capacity for reorganization and contribute to motor recovery after CNS injury. Although this descending motor tract has a critical role in a large number of human functions, there is little experimental evidence about how to improve the efficacy of corticospinal projections after injury. To study this question the scientific effort of our team will employ human and animal models of spinal cord injury (SCI) to enhance our understanding in the following important areas: corticospinal axon guidance and synaptogenesis (Dr. Meriney), corticospinal axon regeneration (Dr. Oudega), physiological plasticity in corticospinal pathway (Dr. Perez), and characterization of the corticospinal pathway using neuroimaging techniques (Dr. Kim). By combining these multiple disciplines our approach will provide fundamental knowledge for SCI research and may impact current therapies in a large number of patients who suffered from CNS disorders. The lack of effective treatments to regenerate corticospinal axons and to recover motor functions in patients with corticospinal damage highlights the relevance of these investigations. This effort may help more than 200,000 Pensylvanians that are affected by some form of paralysis due to corticospinal involvement.

Biomedical Research Questions and Hypotheses

The biomedical aspect of the research in this proposal are: 1) the use of molecular techniques in an in vitro motor neuron culture model system to study axon growth and synaptogenesis, and 2) the use of an in vivo spinal cord injury model system to study corticospinal axon regeneration. The interplay between the in vitro and in vivo model systems may result in novel targets for corticospinal axon regeneration with the potential for clinical translation. To facilitate clinical translation, we will employ a model system of SCI involving a contusive injury, which is the injury mechanism in over 75 % of spinal cord injuries in humans. Selective injuries to descending tract and spinal cord zones will be completed to understand their cellular effects on mechanisms of sprouting and repair.

We hypothesize that:

Promoting corticospinal axon regeneration and synaptogenesis after SCI increases functional restoration.

Clinical Research Questions and Hypotheses

The following clinically relevant aspects will be examined in humans with chronic SCI: 1) examine the physiology and plasticity in the corticospinal pathway targeting partially paralyzed muscles to study corticospinal reorganization after injury, and 2) detect neurodegenerative process and anatomical reorganization in the spinal cord by using structural magnetic resonance imaging (MRI). Transcranial magnetic stimulation is a powerful non-invasive brain stimulation technique that will be used to study corticospinal reorganization after injury. MRI will focus on estimating changes in spinal cord atrophy and differential tract imaging (DTI) of the spinal cord. The combination of physiological and imaging techniques will allow us to acquire patient-specific anatomical and physiological information and may open the possibility of understanding parameters that will contribute to specific functional deficits. We hypothesized that: (a) Human physiological outcomes can be combined with imaging markers to characterize the site and extent of the lesion in a functionally relevant manner, (b) Aspects of physiological and imaging outcomes can be used to predict and quantify system reorganization after SCI.

Health Services Research Questions and Hypotheses

The healthy services aspect of the research aim at incorporating outcomes from our molecular, cellular, neurophysiological, and imaging approaches with current clinical outcomes used in diagnostic procedures after human SCI.

We hypothesized that:

Basic research outcomes obtained by our different disciplines will be sensitive to distinguish aspects associated with axonal repair, plasticity and rehabilitation strategies.

Impact on Health of Pennsylvanians

SCI affects approximately 12,000 people in the U.S. each year. Around 7-8% of these injuries occur in the state of Pennsylvania (PA). These injuries involve the cervical, thoracic, and lumbar spinal cord resulting in large impairments in overall motor function (www.nscisc.uab.edu 2010). The National cost to society associated with SCI is estimated to be over \$30 billion per year. In the first year after injury, spinal cord injured people will incur annual costs between \$209,000 and \$710,000. Every year thereafter, people with SCI will incur annual costs between \$14,000 and \$127,000.

In the U.S. there are 14 Model SCI System Programs and 7 Form II Centers sponsored by the National Institutes of Disability and Rehabilitation Research, Office of Special Education and Rehabilitation Services, and U.S. Departments of Education. These Center Models provide assistance to establish innovative projects for the delivery, demonstration, and evaluation of comprehensive medical, vocational, and other rehabilitation services to meet the needs of individuals affected by SCI. Two of these Model Centers for SCI Research are located in the State of PA. This includes the Regional SCI System of Delaware Valley in Philadelphia and the University of Pittsburgh Model System on SCI in Pittsburgh. Spinal cord injury care at the University of Pittsburgh Model System is at the new UPMC Rehabilitation Institute. UPMC Mercy, the oldest teaching hospital in Pittsburgh, has over a 150-year history of caring for all types of patients and, in 1967, was acquired into the UPMC health system in 2007 as a second Level 1 trauma center within our system. Having two Level 1 trauma centers, UPMC Presbyterian and UPMC Mercy, expand our services and increasing the volume that are seen by our services. This makes the University of Pittsburgh a unique and qualified environment to study initiatives that will enhance the quality of lives of individuals who suffered from SCI.

Because thousands of individuals suffer from motor disabilities due to deficits in corticospinal transmission related to stroke, amyotrophic lateral sclerosis, traumatic brain injury, multiple sclerosis, and other CNS disorders, our work may also be relevant for a large number of patients. For example, in the state of PA over 8,000 people each year sustain traumatic brain injury that results in life-long disability. There are also over 12,000 people each year that sustain a stroke resulting in a large number of physical disabilities affecting daily-life motor functions. Understanding changes in the corticospinal pathway by using an interdisciplinary approach from cellular, molecular, physiological and imaging techniques as proposed here will not only provide fundamental knowledge for SCI research but our contribution may impact current therapies in a large number of patients who suffered from CNS disorders that involve the corticospinal pathway.

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Health Research Priority Title and Description

Impact of Inadequate Sleep

Data from the CDC suggest that about 30% of Americans are obtaining inadequate sleep. Consequences of inadequate sleep include excessive sleepiness, lapses in performance, and increased risk of vehicular crashes. There are also consequences for metabolism and the cardiovascular system, including appetite changes, increased risk of obesity, insulin resistance and hypertension. While this is likely true in general, there are marked individual differences in response to sleep loss that are likely in large part genetic. Some individuals who sleep less than 6 hours/night do not suffer any consequences; they seem to need less sleep. Currently, we do not know what proportion of short sleepers are in this category. We also do not know whether individuals without performance impairment do suffer from the metabolic consequences of sleep loss -- are performance impairment and metabolic consequences related or are they dissociated? Finally, we do not know the gene variants that determine response to sleep loss. Knowing this would provide prediction information about who is particularly sensitive to inadequate sleep and identify novel pathways for therapeutic intervention. There are now a large number of model systems, including mice and fruit flies, in which sleep can be studied. This will facilitate genetic research.

Biomedical Research Questions and Hypotheses

Hypothesis 1: Inadequate sleep leads to performance impairment, metabolic dysregulation, and cardiovascular consequences in individuals living in Pennsylvania who have reduced amounts of sleep. The magnitude of the effect of inadequate sleep on these domains (behavior, metabolic and cardiovascular) varies among individuals. Moreover, the different effects of inadequate sleep have different "dose-response" relationships, i.e., a greater decrease in sleep may be required for cardiovascular and metabolic effects than for behavioral and performance effects.

Hypothesis 2: There are genetic variants that determine the magnitude of behavioral impairment as a result of inadequate sleep. Different gene variants determine the metabolic and cardiovascular consequences of insufficient sleep.

Hypothesis 3: The effect of these gene variants are conserved across species [Drosophila (fruit flies) and mice]. Studies in these species can be used to assess functional significance of gene variants found in human studies as well as identify novel gene variants whose effects can be assessed in humans.

Clinical Research Questions and Hypotheses

Hypothesis 1: Inadequate sleep, defined as sleeping less than 6 hours/day on average, is highly prevalent in Pennsylvania as assessed not only by self-report but also by objective means of sleep measurement (i.e., actigraphy).

Hypothesis 2: Short sleep in the community as assessed by actigraphy is independently associated with an increased number of episodes of falling asleep driving, fall-asleep crashes, insulin resistance, obesity and hypertension after controlling for confounding variables.

Hypothesis 3: Short sleepers, as assessed by actigraphy, are a heterogeneous group based on the following: some will show no performance impairments or metabolic consequences, others will show performance impairment only or metabolic consequences only, and while some will show both.

Hypothesis 4: The major risk factors for short sleep in Pennsylvania are societal issues related to work (number of jobs, commute time, work schedule), family (childcare responsibilities, sleep schedule of spouse), and technology (online activity, television viewing, mobile technology).

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Sleep loss represents a major health issue for Pennsylvania. Reduced sleep is an important contributor to risk for 4 of the 7 leading causes of death in Pennsylvania: Heart Disease, Stroke, Diabetes, and Accidents. Sleep loss may causally contribute to weight gain and obesity, depression, alterations of the neuroendocrine stress system, pain, maternal and fetal complications, and higher use of alcohol and other drugs. Because of this, the Institute of Medicine recently published a report entitled, "Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem," and Healthy Sleep has been added as a national health goal in Healthy People 2020.

Sleep loss is an important factor in public safety. Nearly 20% of all auto accidents resulting in serious injury or death are caused by driver sleepiness, independent of alcohol effects. Fatigued workers are 70% more likely to cause accidents at work and are 89% more likely to die as a result of a job-related accident.

The negative effects of sleep loss are particularly relevant for Pennsylvanians. Recent CDC data show that the average Pennsylvanian reports insufficient sleep on about 30% of nights. This same study showed that after adjusting for age, sex, race, socioeconomic status and overall health, individuals who obtained <5 hours of sleep on a regular basis (compared to 7 hours) were 42% more likely to be obese, 40% more likely to have diabetes, 69% more likely to have hypertension, 36% more likely to have high cholesterol, 62% more likely to have had a stroke, and 152% more likely to have experienced a heart attack.

Our Commonwealth is home to one of the nation's largest populations of older adults (second per capita only to Florida). These older adults are at higher risk for sleep disorders such as sleep apnea and insomnia and they are more likely to experience chronic health conditions which worsen sleep. Lack of sleep in this group is associated with a 50% increase in fall risk. Also, Pennsylvania is home to one of the largest concentrations of African-Americans in the nation. The Philadelphia metro region (the most populous in the state) represents the sixth-largest concentration in the USA, with over 1.2 million (the Pittsburgh region also ranks highly at #40 nationally). African-Americans, even after adjusting for economics, are more likely to experience sleep loss. A recent study from the Philadelphia region found that African-American women were about 5-10 times more likely to report not getting as much sleep as they needed, relative to White women of a similar age and income.

In the current economic climate, the societal costs of sleep loss become even more apparent. Not only do reductions in sleep time result in slower performance on the job, more errors, poorer judgments when taking risks, and decreased cognitive performance, but sleep loss is an important predictor of missed days at work, extended leave, and unemployment. Every worker who experiences insufficient sleep on a regular basis costs his/her employer approximately \$3,000 per year. This will cost businesses in the Commonwealth an estimated \$3.5 billion dollars in 2011. Further, sleep loss is associated with increased costs to the healthcare system. This is particularly troubling, as poor sleep is disproportionately experienced by those who are economically disadvantaged. A recent study of individuals in the Philadelphia region found that those in poverty (representing >10% of Pennsylvanians) are 184% more likely to experience poor sleep, irrespective of racial group. In summary, not only is sleep an important health concern for the people of Pennsylvania, but it is also bad for our economy.

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Health Research Priority Title and Description

Strategies for Repair and Rehabilitation after Spinal Cord Injury

Traumatic insults to the spinal cord induce both immediate mechanical damage and subsequent tissue degeneration leading to a substantial physiological, biochemical and functional reorganization of the spinal cord. Spinal cord injury (SCI) is a significant cause of permanent disability with over 11,000 new injuries occurring every year in the United States (The University of Alabama National Spinal Cord Injury Statistical Center), with upwards of 1,000 occurring in Pennsylvania. This does not take into account individuals with disabilities due to other neurological disorder such as amyotrophic lateral sclerosis (Lou Gehrig's Disease), multiple sclerosis or spinal stenosis. Interestingly individuals with SCI have a near normal life expectancy, meaning that the number of chronically injured individuals is steadily increasing. It is estimated that over 5 million individuals in the US suffer from some sort of paralysis. Various SCI models and therapeutic interventions have shown the adaptive potential of the spinal cord and its limitations in the case of total or partial absence of input from the brain. Meaningful recovery of function after SCI will most likely result from a combination of therapies, comprised of regenerative/neuroprotective transplants and neurotrophic factors, elimination of inhibitory molecules, functional training, and/or electrical stimulation of paralyzed muscles or spinal circuits. Our long-term goal is to develop treatments for acute and chronic spinal cord injury that can be translated into clinical care.

Biomedical Research Questions and Hypotheses

Most investigators agree that while limited recovery can be brought about by a variety of treatments that target different aspects of SCI, combinations of these treatments promise greater recovery. We know that long distance axon growth that is needed to reconnect across a lesion is difficult to achieve. We also know that spinal cord circuitry is altered when isolated from descending pathways by the injury and that it can be modified by specific training protocols. The Drexel Spinal Cord Research Center focuses on mechanisms that can account for and promote functional recovery after SCI. We concentrate on two issues: 1) re-establishing communication across a spinal cord lesion site through transplantation approaches to promote long distance regenerative axonal growth, the formation of novel relays, and/or sprouting by spared systems, and 2) sculpting intrinsic spinal cord circuitry through transplantation, delivery of neurotrophic factors and/or activity specific training/exercise. Because these two strategies target mechanisms that are largely distinct, we hypothesize that the combination of transplantation and physical training will act synergistically to generate greater recovery than either alone.

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

In the commonwealth of Pennsylvania (PA) there are approximately 1000 individuals who suffer a spinal cord injury (SCI) each year. There are many more individuals afflicted with some other form of neurological disorder leading to paralysis, but accurate figures about incidence are difficult to confirm. Regardless, with a near normal life expectancy for SCI patients the population of chronically injured individuals is steadily increasing in PA. There are many causes of SCI but the highest incidence involves motor vehicle accidents, violence and sport-related accidents. There is a disproportionate incidence of SCI in young, male individuals (82% male vs 18% female; median age at injury is 31), although the average age at time of injury is increasing steadily as the incidence of falls (~21%) is increasing in our ever aging population.

Survivors of spinal cord injury require a lifetime of treatment and rehabilitation at an estimated cost of 150,000 - 400,000 per year. The percentage of SCI individuals who are unemployed eight years after injury is nearly 65% (2002 statistics), so the burden of care falls to private insurance, Medicare or Worker's Compensation. It is important to appreciate the fact that every year between 33-50% of SCI patients are re-admitted to the hospital for respiratory care, bowel or bladder problems, bedsores or renal failure. These figures emphasize the need for study of the chronic injury condition with the goal of improving functional capabilities long after the initial injury.

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Health Research Priority Title and Description

Bioengineering research in improved biomaterials for cardiovascular applications

The proposed health research priority is to support bioengineering research in the areas of cardiovascular biomaterials. Cardiovascular biomaterials include metallic and polymeric materials and coatings used in devices such as stents, heart valves, prosthetic grafts, cardiopulmonary bypass (heart-lung) machines and mechanical blood pumps. The technical challenges include resistance to clot formation, inflammation, and infection. In the longer term, tissue engineered approaches may replace conventional prosthetic devices. This approach will enable biohybrid organs for treating diabetes and liver failure, and stem-cell/biomaterial constructs for replacing damaged myocardium, heart valves, and small bore blood vessels.

It is generally understood that blood-material interactions involve three primary components: materials, fluid flow, and blood. Therefore, successful research in cardiovascular biomaterials includes the fields of materials science, fluid dynamics, and hematology. Future materials will include tissue-engineered approaches which are hybrids of artificial substrates and biological materials or cells. Materials may also be designed to release drugs to inhibit undesired responses (such as inflammation or clot formation) or to promote desired responses (such as angiogenesis). Expertise and collaboration will also be required in the biological sciences (including stem cell biology) and pharmacology.

Biomedical Research Questions and Hypotheses

Improvements in biomaterials for blood contact applications (e.g. prosthetic vascular grafts, heart valves, catheters, blood pumps, dialysis machines, oxygenators) require basic research into the mechanisms of protein adsorption and conformation, platelet adhesion and activation, and blood coagulation on artificial materials.

The rational design of new cardiovascular biomaterials can be achieved by manipulation of surface chemistry and structure at the nano, micro, and macro scales. To support cell growth and function in tissue-engineered applications, the inclusion of growth factors and extracellular matrix proteins will be important.

Computational models which include fluid flow, molecular transport, and cellular models can provide meaningful predictions of biocompatibility, thereby reducing the need for expensive and time-consuming animal testing.

Clinical Research Questions and Hypotheses

Cardiovascular biomaterials impact the treatment of a broad range of diseases. Current biomedical devices that are in contact with blood, such as artificial vascular grafts, heart pumps, oxygenators, dialysis machines, stents, and catheters, are limited in their duration of use, and are associated with complications such as thrombus formation and stroke. Further advances in these therapies will require basic and applied bioengineering research.

Although a significant aspect of this health priority falls under basic bioengineering research, clinical studies will be appropriate in order to investigate the biological response in patients to current devices, and to investigate new devices through clinical trials.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Bioengineering research in improved cardiovascular biomaterials impacts a wide range of health issues in Pennsylvania. Cardiovascular disease (CVD) includes heart disease and cerebrovascular disease. Heart disease is the leading cause of death in Pennsylvania, accounting for 25.9% of deaths in 2009, while cerebrovascular disease is the third leading cause of death with 5.5% of deaths in 2009. The rate of CVD is higher in African Americans, higher in males than in females, and increases significantly with age.

Medical devices that contact blood range from short-term devices like catheters to long-term devices such as heart valves and vascular grafts. When blood contacts artificial materials, clots are formed via the adhesion and activation of platelets and a cascade of reactions in the coagulation and inflammatory pathways. The resulting blood clots can cause occlusions, or embolize to cause strokes or peripheral ischemia. Current approaches to minimize this thrombogenic response include modification of the surface chemistry to preferentially affect protein adsorption and/or the conformation and exposure of functional groups to coagulation factors and platelet receptors. In current practice, patients are often required to take anticoagulants and platelet inhibitors, which are only marginally effective and increase the risk of bleeding.

The proposed research priority applies bioengineering methods to develop improved biomaterials and apply them to devices. For example, the risk of thromboembolism and bloodstream infection associated with central catheters can be reduced by developing materials which resist platelet and bacterial adhesion. Peripheral vascular disease is a leading cause of disability among people older than 50 years and in those with diabetes. About 10 million people in the United States have peripheral vascular disease, or 5% of people older than 50 years. In the most severe cases, prosthetic vascular grafts are needed to bypass blocked vessels. However, synthetic grafts have significantly lower patency rates (freedom from occlusion) than native vessel grafts. Tissue-engineered approaches will be required in the future, which will likely require advanced biomaterial scaffolds. Improved small bore vascular grafts will also be applied as coronary artery bypass grafts to treat ischemic heart disease, and as dialysis shunts.

Prosthetic heart valve replacements are already in routine use. However, the need for anticoagulants (for long term use mechanical valves) and the lack of pediatric-sized valves also require biomaterial solutions. In severe cases of chronic heart disease, mechanical blood pumps are being used increasingly to support the heart as a bridge to heart transplantation or as destination therapy. The rate of thromboembolism in current devices of 5-10%, as well as infection risk, limits widespread use in less sick patients. The epidemiological impact of heart transplantation is limited by the availability of donor organs (approximately 2500 annually in the U.S.). Further

reductions in thromboembolic rates will require improved materials for blood contact and improved modeling of blood flow, molecular transport, and platelet function. Future applications of this research will also include long-term implantable sensors (e.g. glucose, blood pressure), and miniaturized intravascular blood pumps.

In addition to the impact on health in Pennsylvania, this health research priority involving bioengineering, materials science, and medical device development, provides a positive economic impact to the state in terms of new job and business creation.

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Health Research Priority Title and Description

The Ethics of Behavioral Healthcare

Bioethics is a field of study and practice that seeks to expose, examine and resolve ethical issues in biomedical research, clinical medicine and the delivery of healthcare. One subfield of bioethics-- the ethics of behavioral (mental) healthcare-- has been an oft overlooked but increasingly fraught area of clinical practice and research. Over the past decade ethical issues in behavioral healthcare have increased significantly. These issues include but are not limited to: research involving mentally ill subjects (i.e. how can we ensure the safety of mentally ill persons in clinical research?); the extent to which mental disorders have been overdiagnosed or underdiagnosed in a particular patient population and the dynamics of so-called 'medicalization' of abnormal behavior (e.g. debates within pediatric psychiatry about bipolar disorder and ADHD); the (over)use of psychotropic drugs in juvenile detention facilities; questions pertaining to the appropriate use of 'vaccines' currently in development to treat addiction (e.g. TA-NIC nicotine vaccine and TA-CD cocaine vaccine); the way in which shifts in the official nosology of psychiatry (the DSM) will affect diagnosis, treatment, and the economics of behavioral healthcare. Each of these areas require systematic interdisciplinary study, education and outreach. I therefore propose funding that would allow for a state-wide initiative to build a robust program to address several key areas of behavioral healthcare ethics.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

A statewide behavioral healthcare ethics program will create a foundation for both conceptual research (bioethical, philosophical, and policy-based examinations of ethical issues) and empirical studies (including assessments about how ethical issues manifest and outcomes research related to educational interventions). Specific questions will include: (1) What are the ethical issues related to the use of addiction vaccines and will such interventions be used in compulsory (mandated) treatment regimes? If so, what are the ethical limits of such treatment? (2) How will diagnostic shifts in the DSM-5 for personality disorders, Asperger's syndrome, nonchemical addictions (gambling, sex, internet), and neurocognitive disorders affect the treatment, stigma-dynamics, and accessibility to care for patient populations across the Commonwealth? (3) What kinds of ethics

educational interventions are needed for behavioral healthcare trainees and providers? How can these interventions be developed, deployed and evaluated across the Commonwealth? (4) What are the theoretical and clinical limitations of the current concept of informed consent as it relates to addicts and other mentally ill research subjects?

Impact on Health of Pennsylvanians

The ethical issues of behavioral healthcare such as those described above create both obstacles and frictions within the mental healthcare research and delivery infrastructure. It has been convincingly demonstrated that a strong interdisciplinary bioethics research program can complement clinical and biomedical training, aiding and enhancing research and improving patient care outcomes. Federal departments have long recognized the need and value of bioethics research programs through grant programs such as the Ethical, Legal and Social Implications (ELSI) Research Program at the National Human Genome Research Institute and Ethics Education in Science and Engineering (EASE) at NSF. I thus propose that a focus on ethics of behavioral healthcare will serve the Commonwealth well as we face a number of challenges related to mental healthcare.

Elderly Pennsylvanians will need increasingly higher levels of behavioral healthcare; children and adolescents of the Commonwealth will need assistance with learning, behavioral, and cognitive disorders that are increasingly recognized and diagnosed; adults receiving medical assistance will continue to place strains on the Commonwealth's healthcare resources; and addiction and recovery services will continue to increase as both substance and nonchemical addictions increasingly become subject to medical treatment.

Meeting each of these challenges will require both empirical investigations into best treatments and resource allocation. Studies conducted by clinicians, social scientists and health policy specialists will provide these data. But there are moral and ethical questions about how to allocate limited resources fairly, how to set statewide research priorities in behavioral healthcare (such as through this CURE application process itself), and, more fundamentally, how to understand the ways in which mental illnesses affect our view of ourselves and of our fellow Pennsylvanians. These are normative questions that require sustained ethical analysis and reflection.

A key objective in building a robust program in behavioral healthcare ethics will be to create a statewide consortium of psychiatric and behavioral healthcare ethics centers with its hub at the Center for Bioethics at the University of Pennsylvania, where a nascent program on behavioral healthcare ethics now exists. With the support of the Commonwealth this consortium can lead sustained research and education well beyond the CURE funding years and serve as a national model.

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Health Research Priority Title and Description

Orphan Drug Development

A rare disease is a disease that effects only a small patient population. Drugs are often “orphaned”, or never are produced and sold on the market, even when a compound is thought to be useful for the treatment of a rare disease. Due to the small number of patients suffering, and the resultant lack of revenue they provide, pharmaceutical companies do not have any incentives to develop drugs and treatments for rare diseases.

Pharmaceutical companies are faced by restrictions in where time and money can actually be invested into. They often have limited resources available to them for research and development (“R&D”), so research must be prioritized. The drugs or treatments that will bring in the largest amount of revenue will be ranked highly and be of most importance, while developing treatments for rare diseases will fall very low.

Financial assistance from organizations outside of industry such as the Commonwealth of Pennsylvania, can result in incredible advances in orphan drug development as the funding dollars are not just "another drop in the bucket" but instead a resource that otherwise does not exist.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

Apogee Biotechnology has a very promising lead compound, ABC294640, that has shown great promise in several orphan diseases such as lupus and various small market cancers such as liver, kidney and pancreatic cancer. We would like to test the hypothesis that we can make significant advances for such Orphan Drug diseases in clinical trials with ABC294640.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

According to the 2009 Pennsylvania Bio MedTRACK Patient Impact Report on Orphan Drugs, there are currently over 20 Pennsylvania companies trying to make advances in over 40 orphan drug diseases. This is

clearly an important industry for the Commonwealth that could have a great impact on Pennsylvanians suffering from these rare afflictions.

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Health Research Priority Title and Description

Neurodegeneration: diet, environment & genetic interactions

Age-related neurodegenerative disorders [e.g., Alzheimer's (AD) and Parkinson's diseases (PD)] affect millions of Americans, of particular relevance to Pennsylvania with one of the highest populations of elderly. Although rare genetic mutations can cause young-onset familial AD and PD, most neurodegenerative disorders are sporadic, and the lack of clear genetic etiology underscores the importance of environmental influences. Recent research has shown that environmental toxicants ranging from pesticides to industrial and mining by-products are important risk factors for neurodegeneration. New data also suggest that diet (fatty acid and caffeine intake) and our behavior (i.e. smoking, exercise) can also have a marked influence on the incidences of PD. Citizens of the Commonwealth have a particular risk associated with environmental exposures resulting from the agricultural (e.g., pesticides) and industrial (e.g., welding; mining) sectors. Understanding how genetic makeup, diet, and environmental factors interact in the causation of these and related neurodegenerative diseases is an increasingly important health issue for Pennsylvania, especially because it may lead to practical interventions (diet and behavioral) that result in human health benefits. There now are opportunities to study the involved biological mechanisms using both laboratory animals and model molecular systems, while simultaneously studying some of the same key mechanisms in humans using state-of-the-art imaging methodologies and biochemical analyses.'

Biomedical Research Questions and Hypotheses

Advances in the past decade have provided tools that allow exploration of the complexity of genetic, environment, and dietary interactions in cell culture, animal models and human subjects. There should be a focus of such biologically relevant basic research on factors for which there is a high likelihood of human health impact based on available epidemiological, prospective, and case-control human data. Some of the important specific hypotheses might include: 1) Wide, genetically-based differences in sensitivity to the toxicity of pesticides reflect individual differences in human sensitivity to these toxicants; 2) Proteomic profiles predict the degree of toxicity pesticides have in causing neuronal cell death; 3) Genomic and proteomic regulatory elements and networks influence differential sensitivity to environmental toxicants such as pesticides; 4) Specific, controllable dietary factors have marked effects on the toxicity of different pesticides, and may be detrimental or protective depending on the dietary agent; 5) Iron biology is a critical factor both in the toxicity and response to insult of pesticides and other toxicants. 6) Animal models can test the concepts of gene-environment interaction and directly inform about human susceptibility.

Clinical Research Questions and Hypotheses

The clinical research questions both influence the biological questions, and in turn, are educated by them. As such, the clinical hypotheses should be highly informed by the wealth of data resulting from recent epidemiological, prospective, and case-control human studies. Some of the important specific and testable hypotheses that would seem of particular importance to citizens of the Commonwealth include:

- 1) Farmers who use pesticides will show changes in iron homeostasis and altered neuronal structure compared to the non-exposed; this can be detected in vivo using state-of-the-art magnetic resonance imaging.
- 2) Welders and other industrial workers will show changes in iron and manganese homeostasis and altered neuronal structure compared to non-exposed population that can be detected in vivo using state-of-the-art magnetic resonance imaging.
- 3) Changes in brain will be correlated with surrogate markers of toxicant exposure (e.g., pesticide metabolites in urine or metal accumulation in brain and other tissues) and human behavioral outcome in high exposure subjects (such as exposed farmers and welders).

Health Services Research Questions and Hypotheses

The outcome of this research will have direct influence on public, occupation policies and services for high exposure groups to

- 1) Identifying protective methods through diet and behavioral modifications for high risk populations
- 2) Provide screening methods for early diagnosis of neurodegenerative disorder in high risk groups
- 3) Provide early intervention strategies for already diagnosed populations
- 4) Prescribe educational opportunities for subjects with increased susceptibility or those who developed neurodegenerative disease due to exposure--such as long term care and how to minimize risk or disease progression through behavioral modifications.

Impact on Health of Pennsylvanians

Pennsylvania has more than 60,000 farm families who are the stewards of more than 7.7 million acres of farmland. With \$6.1 billion in cash receipts annually from production agriculture, Pennsylvania farmers and agribusinesses are the leading economic driver in our state. In addition to production agriculture, the industry also raises revenue and supplies jobs through support services such as food processing, marketing, transportation, and farm equipment. In total, production agriculture and agribusiness contributes nearly \$61 billion to Pennsylvania's economy.

There are about 16,000 welders in the Commonwealth. . Eighty percent of welding-related job are in five industries: specialty trade contractors; transportation equipment; fabricated metal production; manufacturing; and machinery manufacturing, repair and maintenance. All of these represent important cogs of the Pennsylvania economy: all are ranked in the top 35 industries and all employ at least 30,000 people. It is forecasted that the greatest number of job openings in South-central Pennsylvania will be welding-related in the coming years (Cater 2009). Yet while this workforce is swelling, it is also aging rapidly (Cater 2009).

Thus, the agricultural and industrial sectors are both major employers in Pennsylvania, and citizens of the Commonwealth. Both sectors have direct and indirect potential exposure to agents that are hypothesized to play a role in the occurrence of neurodegenerative diseases. Because such disorders are chronic and long-term, and because cause an increasing burden on the resources of both families and the Commonwealth, increased understanding of the factors that are described above can have a large impact on the health and welfare of Pennsylvania and its citizens. Similar issues arise in the mining sector that is having a renewed impact on the Pennsylvania economy. A major hypothesis that is ripe for testing is that the biological and clinical studies described above may lead to what could be termed as "personalized protection", that is, allowing individuals involved in higher risk professions to modify diet or exposure to decrease particular risk that they may have. A

second hypothesis is that some specific interactions may be particularly dangerous, and may be attenuated by targeted (rather than global) public health interventions. A third hypothesis that is that we may develop screening methods for early detection of neuron-injury before full blown neurodegenerative disease was formally diagnosed and implement early intervention and treatment stratigest. Last, but not least, the research outcomes may prime the public policy changes in high risk occupation and health related issues are predicted earlier in terms of healthy insurance and longterm care for workers in these sectors.

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Health Research Priority Title and Description

The Application of Bioengineering to Minimally-Invasive Therapeutics for Gastrointestinal Disease.

Many disorders of the gastrointestinal (GI) system are diagnosed and treated using endoscopic and minimally invasive surgical therapies, which we collectively refer to as Minimally Invasive Therapy (MIT). Whether performed through small incisions or via natural body openings such as the mouth, there is the potential for much more advanced treatment using these techniques that will ultimately be less painful, less costly, and allow faster return to productivity. The instruments required for these procedures must be very small but also allow for great dexterity within the body. The major factor limiting progress in these fields is the difficulty in the design and manufacture of advanced instruments that can be introduced through small openings and can work at long distances. The instruments must be small in diameter (often 1mm diameter or less), work at distances (2 meters) and still be able to maneuver, cut, and dissect in the same way as our traditional instruments. The goal of the long-term collaboration between Dr. Randy Haluck and Dr. Mary Frecker in Penn State Mechanical Engineering is to develop a new class of surgical instruments that provide multiple functions and multiple modes of movement at the instrument tip. These instruments require advanced materials and advanced design and manufacturing processes. Our design approach and fabrication methods will allow microsurgical instruments to perform major gastrointestinal procedures via flexible endoscopic surgical procedures.

Biomedical Research Questions and Hypotheses

Will the development of advanced design processes, materials, and manufacturing process yield instruments that are suitable for Minimally Invasive Therapies (MIT) such as Natural Orifice Surgery (NOTES)?

Clinical Research Questions and Hypotheses

As the instrumentation enables critical surgical functions for MIT, will that ultimately enable the success of procedures such as NOTES?

Health Services Research Questions and Hypotheses

As MIT procedures such as NOTES become commonplace in medical practice, will these procedures ultimately create a true benefit to patients in terms of outcomes as well as an economic advantage in terms of procedural cost reduction and faster return to productivity?

Impact on Health of Pennsylvanians

In a one year period from 2008-2009, Pennsylvanians underwent more than 1.6 million surgical operations and almost 450,000 endoscopies. Certainly, not all of the operations were Gastrointestinal related however more and more specialties and procedures are moving toward Minimally Invasive Therapy (MIT) techniques and would likely benefit from advanced miniaturized instrumentation. Likewise, of all of the endoscopies, some would not require advanced instrumentation. However for an intervention as simple as a biopsy, instruments that can reach around corners, get better tissue samples, result in less bleeding, and increase diagnostic accuracy would be of great benefit.

With specific reference to gastrointestinal disorders, MIT hold great promise. MIT when done through natural orifices such as the mouth, to remove a gallbladder for example, holds the promise of truly scarless surgery. Surgery without scars has the potential for far more than an improved cosmetic result. The major component of morbidity for many elective traditional "open" operations is related to the incision itself. The skin is the site for the majority of pain receptors. Healing from surgery usually means healing from the large incision and large incision surgery carries significant long-term consequences such as adhesion formation and risk of bowel obstruction and hernia formation(in the case of abdominal surgery).

The development of these new procedures requires much more than taking our scalpels, forceps, and scissors and shrinking them to tiny size. At the required sizes the physics and materials of blades, hinges, and scissors do not function at all in the same way that they do for traditional surgery. The first hurdle is the design of these instruments. Completely new mechanisms are required. Dr. Mary Frecker has already developed a unique software algorithm for designing new instruments that will allow for force calculations. The next requirement is for new materials. Conventional materials such as stainless steel and titanium do not have the strength to perform on such a small scale. Finally, new modes of manufacturing are required. Again, traditional instrument manufacturing technologies such as casting, stamping, grinding, and polishing will not suffice for the creation of very small instruments. The development of the instruments needed requires a highly specialized multidisciplinary team of doctors, engineers, and materials specialists.

What does this mean for Pennsylvanians? Pennsylvanians already have access to some of the best healthcare via our community programs as well as several leading university hospitals. Pennsylvanians also have the benefit of several leading research universities in materials, engineering, and micro- to nano-fabrication research and manufacturing. There is tremendous potential for Pennsylvania to lead the world in these new types of MIT and to provide Pennsylvanians truly cutting-edge health care.

By receiving the latest in operative and diagnostic procedures, Pennsylvanians will also be the first to realize the true benefit of these technologies via lower healthcare costs especially in terms of return to productivity after MIT. Further economic impact can be realized through the enhancement of robust research and development university programs, the spin out of high-tech small businesses, and the creation of jobs in high-tech areas for Pennsylvanians.

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Health Research Priority Title and Description

Orphan Drug Advancement

A rare disease is a disease that affects only a small patient population yet they affect between ten to twenty million people in the United States alone. Challenges associated with having a rare disease include delay in getting an accurate diagnosis, few treatment options, and difficulty finding medical experts. Many rare diseases have no approved treatment, and insurance may not cover treatments that aren't approved. Medical and social services may be denied because those making the decisions are not familiar with the diseases.

The federal Orphan Drug Act has made great stridse in raising awareness of orphan diseases and the hurdles they face for getting funding toward research and resultant pharmaceuticals to treat the diseases. There still remains a significant gap in the actual funding to develop these drugs toward the market, giving people with rare diseases a treatment and hope.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

We plan to test the hypothesis that GB-13 is an effective new treatment for brain cancer in patients with high grade glioma and glioblastoma.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

According to the PA Dept of Health Website, there were 1,013 invasive cases of brain and other central nervous system cancers reported to the Pennsylvania in 2008. There were 581 resident deaths due to cancer of the brain/other nervous system in 2008. According to the National Cancer Institute, Pennsylvania ranked 8th among the 50 states with an incidence rate of 7.4 cases per 100,000 of its citizens.

High grade glioma and glioblastoma multiform continue to be in serious need of new and effective treatments. These cancers still have historical life expectancies of under a year, even with the best possible care and treatment options. We believe that GB-13 will make a significant difference is this indication.

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Health Research Priority Title and Description

Identifying prognostic & predictive biomarkers of fracture healing

The health research priority is the development of RNA expression profiling for the early identification of prognostic and predictive biomarkers of orthopaedic organ failure and treatment response respectively. The health problem of interest is fracture nonunion. Fracture nonunion, a musculoskeletal organ, failure occurs, consistently, in about 5% of all fractures and as frequently as 19% in lower extremity fractures. Nonunions significantly impact psychological and economic outcomes in adults. Global nonunion risk factors, such as obesity, diabetes, advanced age, smoking, and polytrauma, are unreliable predictors of treatment response. Traditional protein-based biomarkers of bone turnover also fail to identify patients at risk. Genomics and RNA expression profiling is under developed in non-neoplastic conditions. Microarray technology and bioinformatics make high throughput analysis a realistic approach to the debilitating and costly clinical problem of fracture nonunion. We propose a prospective observational study of the circulating RNA expression profiles of fracture patients from the time of injury through healing/nonunion and follow up. The body of evidence to support the role of circulating RNAs as systemic biomarkers in disease processes has grown rapidly. The proposed research applies this reliable technology to the dynamic process of fracture healing to identify opportunities for early treatment intervention that would reduce the morbidity and cost of this widespread health problem.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

Does RNA profiling of peripheral blood, either individually or as a panel, serve as a prognostic biomarker of the natural course of fracture healing? Can sub-panels or individual RNA species serve to alert physicians to patients who are likely to not experience complete and timely healing (nonunion)? Does RNA profiling of peripheral blood, either individually or as a panel, serve as a predictive biomarker of treatment response among patients who form nonunions?

Hypothesis 1: RNA isolated from the peripheral blood of acutely injured fracture patients will be significantly different from RNA isolated from the peripheral blood of either healthy volunteers or of subjects with diagnosed nonunion.

Hypothesis 2: RNA profiles at regular intervals from peripheral blood of acutely injured fracture patients from the time of injury to 9 months post-injury (approximately 100 subjects) will reveal a consistent pattern of RNA expression within the subpopulations of normal healers, slow healers, and nonunions.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

The health research priority is the development of RNA expression profiling for the early identification of prognostic and predictive biomarkers of orthopaedic organ failure and treatment response respectively. The health problem of interest is fracture nonunion. Fracture nonunion, a musculoskeletal organ failure, occurs consistently in about 5% of all fractures and as frequently as 19% in non-pathologic lower extremity fractures. Known risk factors associated with fracture nonunion include advanced age at the time of injury, obesity, diabetes, and smoking. Pennsylvania is currently the 4th oldest state in the union with 15% of the population age 65 or older. In 2008, a report by the Pennsylvania State University Department of Public Health estimated that Pennsylvanians smoked 309 packs of cigarettes per person per year. Despite the emphasis on smoking cessation in Pennsylvania, a January 6, 2011 story in the Standard Speaker, reported that 1 in 4 residents in the Wilkes-Barre/Scranton/Hazleton metro area smoke an average of 17 cigarettes per day. According to the Center for Disease Control's Division of Diabetes Translation National Diabetes Surveillance System 2009 data, $\geq 26\%$ of Pennsylvania residents are obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) (up from 18-21.9% in 2000) and 7.5-8.9% of the population has been diagnosed with Diabetes (up from 6.0-7.4% in 2000). The concentration of global health and behavioral risk factors for nonunions are highly concentrated among Pennsylvania residents. To put this into numerical perspective, the population of Pennsylvania is approximately 12.6M with about 15% of them being over age 65. Assuming half the population is female, there are about 945,358 females over the age of 65. For a white woman at age 40 with no other risk factors the risk of getting a major osteoporotic fracture is about 1.7%. That same woman's risk would be 9.5% at age 65. The population at risk is about 80,020 (white women only). There is a 5–10% bone density deficit in patients who smoked compared with patients who were non-smokers. If smoking estimations are accurate, and 23% of the Pennsylvania population smokes, then the increased risk of fracture due to smoking is increased in a subpopulation of about 20,000 women. Further, the aged population of Pennsylvania have an increased risk for fragility fracture and other disorders of the musculoskeletal system. The rate of nonunion among fragility fracture patients is 20%. Nonunion treatment can be complex and included multiple revision surgeries with or without the implantation of bone stimulating material. The cost of nonunion management can be astronomical. In 2008, more than \$1.6 billion was spent on bone grafts and substitutes in the United States. The cost of other treatments, including antibiotics, hardware revisions, electrical stimulation, and ultrasound treatments are not included in the above estimation. Unfortunately for the patient and the surgeon, there is no reliable algorithm to determine which patients are most likely to develop nonunion or, among these, which will respond to which treatment. The diagnosis of nonunion is not made until >6 months have passed from the time of initial injury. The major complications of nonunions include infection, compartment syndrome, and deep venous thromboembolism. The risks of these complications are further exasperated by smoking, obesity, and diabetes, all of which are prevalent in the Pennsylvania population. Ultimately, the contributions of behaviors or disease states to the risk of fracture or to the formation of nonunions after fracture are poorly quantified and are not useful for guiding clinical care. The biological processes directing fracture healing are undeniably tied to well regulated expression profiles of multiple markers over the timecourse of healing. The value of any one or more RNA molecules as a prognostic indicator of nonunion formation or as a predictive biomarker of treatment response is currently unknown, though interest in this area is growing. We have identified a number of circulating RNAs that may be suitable biomarkers for nonunion formation and treatment response. Further work is required to confirm these findings.