

Written Testimony Submitted by the Public on the Health Research Priorities for 2010-2011

The Pennsylvania Department of Health solicited written testimony on health research priorities for state fiscal year (SFY) 2010-2011 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, 2009. To conserve space, instructions for each item on the form and the responses to item 5 were removed from the individual testimonies. See table below for the list of persons who submitted testimony. Note that testimony is ordered by date and time submitted to the Department.

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

The Pennsylvania Department of Health is inviting the public to submit written testimony to recommend health research priorities for the CURE Program for state fiscal year 2010-2011. 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, 2009, to: ra-healthresearch@state.pa.us. Only testimony that is submitted to the ra-healthresearch mailbox by the deadline will be accepted. All testimony submitted by the deadline will be posted on the Department’s CURE Web site under the *CURE Health Priorities* link. The Department will not correct the testimony for spelling, grammatical or other errors. Any text that exceeds the page and size limitations specified on this form will be deleted, including any appendices. The Health Research Advisory Committee will review the testimony that has been submitted and then recommend persons who will be invited by the Department to make presentations to the Committee and answer Committee members’ questions. The Committee is not interested in receiving proposals for specific research projects.

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

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

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

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

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

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

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 which persons should be invited to attend the Committee’s fall meeting. During the Committee meeting those persons who were invited to testify will be asked to summarize the critical research questions related to their written testimony and then answer Committee members’ questions. If invited by the Department to do so, would you be willing to present testimony and answer questions about your proposed research priority at the Committee meeting to be held in Philadelphia on October 8th?

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), and cancer vaccines and blindness and visual impairment (2009-10). 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

Geriatric Trauma

The state of Pennsylvania has one of the oldest populations of all of the U.S. Of the preventable causes of disability, loss of independence and death in this group of people, trauma ranks as number one. The type of trauma most common within this age group is injury due to falls from standing due to loss of balance, overmedication, gait disturbances, fatigue, joint failure, etc. Falls that might be innocuous in a younger person can result in catastrophic injury in the elderly.

Means of preventing falls or abrogating their effect should be a health care priority in Pennsylvania. By stressing prevention and intervention, we would not only elevate the quality of life for our seniors but save millions of dollars in extended hospitalizations that arise due to these accidents.

Falls in the elderly should be attacked in a number of ways:

1. technological advances in secure living environments, 2. smart drug dispensation systems to avoid senior polypharmacy, 3. advances in assistive gait technology, 4. frequent gait analysis to predict impeding posture or gait failure.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

1. Development of a "falls archiving device" to monitor interventions in posture and gait in the elderly.
2. Develop inexpensive balance measuring devices that can be installed in personal care residences, nursing homes, and group homes that can detect worsening balance or gait disturbances.

Health Services Research Questions and Hypotheses

1. How can polypharmacy gait deterioration be detected early and does it decrease the incidence of falls in the elderly?
2. Can frequent (or regular) gait analysis in the elderly diminish the incidence of falls in the elderly?
3. Analysis of medications frequently used in the elderly for the unintended effect of causing gait abnormalities or balance degradation. Balance the benefit of the medication with that risk of that effect

Impact on Health of Pennsylvanians

The elderly population of Pennsylvania is large and growing. Out of the 12 million people in Pennsylvania, 1.5 million are over the age of 65. Although the percentages of elderly people with disabilities is known, the numbers of people over 65 with preventable disabilities is not.

The elderly are hospitalized at a rate of three times that of the population as a whole. What is not known is the rate at which the elderly are hospitalized for preventable injuries. Preventable injuries cost the elderly and the taxpayer too much money when a smaller investment in prevention could alleviate them.

Gait and balance testing for the elderly is not currently compensated and, hence, is not performed. A pilot program to prove the value of such interventions should be undertaken.

Contact Information

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Health Research Priority Title and Description

Chronic Virus Infection: Detection, Pathology, and Treatment Strategies

Chronic virus infections are responsible for at ~17% of all human cancer, and contribute to a variety of immunological disorders including rheumatoid arthritis, lupus erythematosus, and multiple sclerosis. New viruses continuously emerge through rapid evolution and by facilitated modes of transmission. In addition, previously unknown viruses are being discovered and linked to human disease through improved methods of detection, sequencing, and genomic analysis. Advances in human health will require improvements in methods for detection, prevention and treatment of chronic viral infections, as well as a more complete understanding of the viral pathogenesis and host-immune response. We propose a new State Initiative to focus on the role of chronic and latent infections in human disease. This initiative would support the identification of novel viruses in cancer and autoimmune diseases in clinical samples and support basic research aimed at understanding the mechanisms of long-term viral persistence, latency, and reactivation, including the role of life-related stress in the viral reactivation process and the host-immune response. Finally, the initiative would support efforts directed at the eradication of latent infection either through development of small molecule inhibitors or novel vaccine strategies. The overall goal will be to reduce the burden of persistent viral infection on human health.

Biomedical Research Questions and Hypotheses

Chronic viral infections, such as hepatitis B/C, human papillomavirus, and Epstein-Barr virus lead to a number of cancers that are highly elevated in ageing and immunocompromised populations. Evidence suggests that immune cell function is compromised in viral-associated cancers due to environmental cofactors, genetic predisposition, T-cell exhaustion, or viral-induced immune dysfunction. We propose a study of virus biology, immunological responses to viral infection, and tumor-microenvironment interactions in the context of chronic infection. The hypotheses to be tested include (1) whether chronic exposure to viral antigens induces exhaustion of viral-specific T-cells response, (2) whether virus encoded factors promote immune tolerance through negative T-cell regulatory pathways including Tregs, HVEM, and PD1, and (3) whether environmental cofactors associated with local inflammatory response alter immune regulation of viral infected pre-cancerous cells. We also propose to develop antiviral strategies, including small molecule inhibitors of key viral and cellular regulatory pathways, and the development of anti-viral therapeutic vaccines designed to overcome the negative regulatory arms of the immune response.

Clinical Research Questions and Hypotheses

Chronic viral infections are known to cause several human cancers and are suspected of causing a variety of immunological disorders. New methods of virus identification, detection, and characterization have enhanced our ability to connect viruses to specific disease states. We hypothesize that previously uncharacterized virus-associated diseases exist and will be identified using high-throughput sequencing methods. We propose to

establish a network of clinical and basic researchers who will use human tissue samples to identify viral markers associated with specific diseases using the most sophisticated gene sequencing and genomic technologies.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Chronic viral infections are responsible for a large number of cancers in humans, including cervical and head and neck cancers (HPV); liver cancer (Hepatitis B and C); central nervous system lymphoma, non-Hodgkins lymphoma, and Hodgkins lymphoma (Epstein-Barr virus). In addition, chronic viral infections are suspected of causing immunological disorders such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. As with many diseases, minorities are disproportionately affected by these diseases. Although a vaccine against HPV is now available, there are many women who were exposed to the virus prior to the development of the vaccine; and it will be many decades before HPV infection will be largely eliminated in the population. It is essential that we continue to search for therapies to treat HPV.

Evidence suggests that normal immune cell function is compromised in viral-associated cancers due to genetic predisposition (e.g., X-linked lymphoproliferative diseases), environmental cofactors (e.g., chronic inflammation, alcohol, tobacco), T-cell exhaustion (e.g., HIV/AIDS), or viral-induced immune dysfunction (e.g., Castleman's disease). Elucidating the molecular mechanisms by which latent viral infections induce cancer and compromise the human immune system will lead to the development of new therapies, including small molecules (drugs) and immune-based therapies (vaccines and antibodies), for the treatment of chronic viral infections.

The development of new therapies to eradicate latent viral infection in humans will serve the needs of all Pennsylvanians; these infections strike regardless of socio-economic status.

Contact Information

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Health Research Priority Title and Description

Reducing Drug Use and Crime through Drug Courts

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

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

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

effects. If supported this could serve as a core set of elements to improve and tailor the drug court model throughout the State.

Impact on Health of Pennsylvanians

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

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

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

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

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

Contact Information

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Health Research Priority Title and Description

Prescription drug-abuse by children and adolescents is on the rise (Monitoring the Future, 2006) and their abuse of prescription painkillers has ranked second only to marijuana since 2002 (U.S. Department of Justice, 2005). This rise in prescription drug abuse comes at a time when prescription drugs and pro-drug propaganda are increasingly available on the Internet. The Internet has been cited by various organizations as a reliable source of prescription drugs such as narcotics, sedatives, and anabolic steroids (GAO, 2004; United Nations, 2005). Research conducted by our group and others has identified an alarming number of Internet-based no-prescription pharmacies that offer to sell medications, including controlled narcotics such as hydrocodone and oxycodone, without a prescription or even a medical consultation. In addition, this research has identified numerous websites that promote illicit drug use, provide information on how to cultivate or manufacture illicit substances, and outline ways to presumably use these substances safely and/or to avoid detection. Given that 87% of children age 12 to 17 use the Internet (Lenhart, Madden, & Hitlin, 2005), there is a clear need for prevention and intervention programs to protect our youth from these online threats.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

In response to internet drug threats, TRI developed and pilot-tested a parent workshop to 1) increase awareness of the availability of illicit drugs and drug propaganda on the internet, 2) provide parents with practical prevention strategies to monitor their children's computer use, and 3) teach parents how to intervene with their children if problems occur. Findings showed that the workshop increased parents' awareness of internet drug threats and use of the monitoring and prevention strategies; parents reported high satisfaction with the workshop. Advances in online learning offer advantages, and reviews/studies (e.g., Cook et al., 2008) have found these methods to be superior in transferring information and increasing access/utilization. The aims are: to develop and conduct surveys of adolescents to determine the extent of internet drug acquisition; to enhance the parent awareness and action workshop to mitigate internet drug threats; and to develop and test an online interactive version of the workshop. We hypothesize that we will document meaningful rates of adolescent internet drug acquisition, and that a targeted parent workshop will be widely accessed, particularly online, and can reduce adolescent internet drug searches.

Impact on Health of Pennsylvanians

Drug abuse affects all Pennsylvanians especially the young, under-privileged and minorities. While PA has developed several Healthy People 2010 targets for reduced mortality and morbidity from drugs, performance indicates that these markers have not gotten better. Drug abuse affects our young disproportionately more than 50,000 Pennsylvania adolescents and young adults have died from alcohol or drug related causes since 2002. These rates are again, disproportionately higher among African and Hispanic Pennsylvanians.

Young adults between the ages of 15 and 24 dying from drug overdoses has nearly tripled between 1999 and 2005; from 849 to 2,355 as reported by the CDC. Mortality is the worst and final outcome of alcohol and drug addiction - there are other widespread and costly health and social effects as well. High rates of auto accidents and emergency room visits due to alcohol or drug involvement are well known. Drug-related crimes account for over 65% of all incarcerations in state prisons in Pennsylvania; and over 50% of all re-incarcerations due to parole violations. The UN WHO-commissioned study of chronic illnesses showed that addiction to alcohol was the 2nd and addiction to other drugs the 4th most disabling conditions. These ranked as so disabling because of their greater prevalence, early origins (i.e., adolescence and early adulthood), and because untreated addiction reduces productivity and quality of life for the addict and those around him/her.

These figures suggest that effective prevention strategies are crucial. Also, given the recalcitrant nature of addiction once established, primary prevention strategies have the potential for the greatest impact.

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Health Research Priority Title and Description

How Do Financing Arrangements Affect Adoption of EBP's in Addiction Treatment Settings

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

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

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

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

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

Impact on Health of Pennsylvanians

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

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

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

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

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Health Research Priority Title and Description

Sickle Cell Disease (SCD)

Sickle cell disease (SCD) affects approximately 72,000 primarily African Americans and Hispanics, including an estimated 5,000 persons in the Commonwealth. While sickle cell disease is caused by a genetic abnormality in hemoglobin that results in hemoglobin polymerization and red blood cell "sickling," the major cause of death is a progressive vasculopathy (damage to blood vessels). This vasculopathy can lead to an elevation of the pressure in the blood vessels of the lungs in a full 1/3 of adults with sickle cell disease. These patients are at 10 times greater risk of death than the general population of SCD patients (Gladwin; New England Journal of Medicine 2005). In fact, 40% of these patients will die within 40 months if not identified and treated. Advances in our understanding of vascular biology have revealed that imbalances in vasodilator molecules and vasoconstrictor molecules in the endothelium (the cells lining the blood vessel) lead to abnormal constriction of the blood vessel, abnormal growth of the endothelium and smooth muscle, and blood vessel inflammation and thrombosis (clot development). The development of new treatments that target this at-risk and underserved population requires advances in our understanding of fundamental vascular biology using novel transgenic animal models and translational research tools, coupled with comprehensive outreach and screening protocols to identify the at-risk pediatric and adult sickle cell population of Pennsylvania.

Biomedical Research Questions and Hypotheses

A central molecule that regulates normal vascular health is nitric oxide (NO), which is normally produced by the endothelium and regulates basal vasodilator tone; inhibits platelet activation; inhibits NF-kB-dependent adhesion molecules, such as VCAM-1, ICAM-1 and the selectins; and reduces superoxide levels by radical-radical scavenging. A central biomedical research question is how this important NO signaling pathway is impaired in SCD? Two vascular injury paradigms are hypothesized to contribute to the low NO levels and vascular injury: 1) During SCD related hemolysis, hemoglobin is released from the red blood cell into plasma, where it generates reactive oxygen species and directly reacts with and scavenges NO. 2) Microvascular entrapment of sickle erythrocytes and leukocytes acutely obstructs blood flow, producing cycles of ischemia and reperfusion, activating vascular oxidases and leading to inflammatory stress, increased expression of endothelial cell adhesion molecules and inflammatory cytokines, and leukocytosis. Studies using transgenic mouse models of sickle cell disease and human blood flow studies will provide insights into the mechanisms of disease and facilitate the identification of novel molecular therapeutics.

Clinical Research Questions and Hypotheses

The development of vascular disease, and specifically high blood pressure in the lungs in patients with SCD, is associated with heart failure, reduced exercise tolerance, and increased risk of sudden death. Well-designed population screening and therapeutics research projects can increase the diagnosis, access to care, and therapies available for this complication. Aim 1. Develop a community-based screening program that will identify sickle cell patients at high risk of developing pulmonary hypertension. For example, plasma samples can be screened using a novel biomarker called N-terminal brain natriuretic peptide (NT-BNP), which is released by the heart during pressure overload. Patients with NT-BNP levels greater than the 75th percentile can be screened for renal dysfunction and undergo cardiac ultrasound testing. Patients identified with pulmonary hypertension can then be referred to clinical research centers for right heart catheterization for definitive diagnosis. These studies will define a novel population based-screening and risk assessment paradigm. Aim 2. Population-based studies and trials can be used to evaluate novel vasodilator agents (NO, phosphodiesterase 5 inhibitors, eNOS recoupling agents).

Health Services Research Questions and Hypotheses

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

Impact on Health of Pennsylvanians

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

Despite considerable advances in the treatment of SCD, most patients have poorly controlled pain and require recurrent hospitalization. The mean age of death of SCD patients is 38 years.

There exists a statewide and national failure to transition care of the aging pediatric population to comprehensive adult care programs. This transition gap pushes large populations to the emergency room setting and dramatically reduces access to drugs, such as hydroxyurea, that are necessary to reduce end-organ injury. As a result, adult patients begin to develop end-organ complications such as pulmonary hypertension and kidney failure. End-organ complications that develop in the absence of comprehensive therapy include: 1) Stroke: 10% of children develop stroke and 22% have silent strokes on MRI, which are associated with neurocognitive sequelae and increased risk of overt clinical stroke. This complication is preventable with transfusion and hydroxyurea therapy. 2) Pulmonary hypertension is a deadly complication that affects over 30% of adolescents and adults, and 40% of all patients by the age of 40. Pulmonary hypertension is associated with a 10-fold increase in risk of premature mortality and accounts for over 35% of all deaths in patients with SCD. Transfusion therapy and hydroxyurea can prevent this complication, and more than seven FDA approved medications to treat this complication are now available. 3) Kidney and liver failure: With increased age there is an accumulation of sickle cell-related organ damage, with more than 50% of patients developing irreversible organ damage by the time they enter the fifth decade of life. 4) The first decade after transition to adult care represents a very high risk period for patients with SCD: approximately 6-20% of young adults die of complications related to SCD between age 20 and 30 years.

The proposed initiatives to understand the biological underpinnings of vasculopathy in sickle cell disease linked to community screening and referral for novel treatment studies will have a great impact on these devastating complications of the most common genetic disease affecting African Americans.

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Health Research Priority Title and Description

Arthritis: Osteoarthritis and Rheumatoid Arthritis

The Centers for Disease Control (CDC) has determined that more than 21% (over 46 million) of U.S. adults report doctor-diagnosed arthritis. Over 40% of these individuals report arthritis-attributable activity limitation and over 30% report arthritis-attributable work limitation. These numbers are only expected to increase with the aging of the US population. In addition, arthritis is the single greatest cause of chronic pain and disability. Although there are over 100 types of arthritis, the most common ones, osteoarthritis (OA) and rheumatoid arthritis (RA), mainly account for the increased morbidity and health care costs. OA is the most prevalent form of arthritis and is among the most prevalent chronic conditions in the US. OA of the hip and knee is the most common cause of difficulty in walking or climbing stairs. The challenge in osteoarthritis is to identify patients earlier in the disease course to facilitate prevention and treatment of the disease. RA is the most common type of inflammatory arthritis and affects 1% of the adult population. The cause of RA is unknown, but most likely there are various subsets of rheumatoid arthritis defined by abnormalities in the immune response. A major challenge in RA is to determine which subsets of patients with RA will benefit the most from the newer, specific targeted, expensive biologic therapies. There are now 8 biological therapies on the market. Research is urgently needed that addresses the comparative and cost effectiveness of these expensive agents compared to costs of traditional less expensive drugs.

Biomedical Research Questions and Hypotheses

Although targeted expensive biologic therapy has revolutionized the treatment of rheumatoid arthritis (RA), only 50% of patients have a reasonable response. Urgent research is needed to determine the specific immune/inflammatory abnormalities that characterize the RA phenotype/genotype and treatment response. We hypothesize that specific biomarkers (i.e., DNA, RNA, serum and imaging biomarkers) will differ among subsets of patients with RA and will determine individual responses to different therapies. To address this question and fulfill the promise of “personalized medicine,” prospective, longitudinal cohort studies with extensive biospecimen assessment, combined with detailed clinical information, will be necessary. Advances in imaging have allowed the detailed morphologic characterization of the abnormalities present in osteoarthritis (OA) before the end-stage manifestations seen on x-ray. To better understand the pathophysiology of OA, studies are needed to examine changes in cartilage and meniscus composition as well as morphologic changes. We hypothesize that newer imaging techniques will identify changes in collagen/proteoglycans that precede loss of cartilage and meniscal degeneration in OA.

Clinical Research Questions and Hypotheses

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

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

Health Services Research Questions and Hypotheses

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

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

Impact on Health of Pennsylvanians

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

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

Total joint replacement of the knee or hip is an effective therapy for end-stage osteoarthritis, relieving pain, reversing joint deformity and improving quality of life. Between 2000 to 2002, over 80,000 knee and hip

replacements were performed for osteoarthritis in Pennsylvania hospitals. Indeed, the rate of total joint replacements for osteoarthritis increased by 15% over this three-year period. With the aging of the population and the growing obesity epidemic, the rate of total joint replacement is expected to increase dramatically in the coming years.

Unfortunately, despite the well-documented efficacy of total joint replacement, not all segments of the population have benefited from these procedures. Numerous reports have documented racial/ethnic disparities in the utilization of total knee or hip replacement. African-Americans are much less likely than whites to undergo total joint replacement and recent investigations suggest that this disparity is increasing. Furthermore, recent studies suggest that African-Americans may be at risk of worse outcomes after total joint replacement as compared to whites.

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

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

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Health Research Priority Title and Description

Early Intervention to Prevent Obesity

The childhood obesity epidemic elevates risk for adult obesity and its co-morbidities, and has the potential to overwhelm our healthcare system. The fetal and infant periods play critical roles in the development of obesity, but there has been little focus on preventing obesity during these periods. The need for early intervention is obvious: 24.4% of US children aged 2-5 years are already overweight, while the prevalence of obesity among infants 6 to 23 months has increased 60% in the last 3 decades. Early intervention is critical because overweight infants and toddlers have elevated risk for obesity, diabetes, and cardiovascular disease later in life when attempts to prevent and treat obesity have had limited success. In contrast, the prenatal period and infancy are opportune times to begin obesity prevention; they are periods of rapid growth, developmental plasticity, and learning, which can have both immediate and long-lasting metabolic and behavioral consequences. Recognizing that early obesity increases risk for obesity and the metabolic syndrome later in life, the Institute of Medicine's expert committee wrote "the prenatal period, infancy, and early childhood may be stages of particular vulnerability to obesity development because they are unique periods for cellular differentiation and development. This unique vulnerability might make it possible for actions taken at these stages to determine the future course of adiposity." Fortunately, basic research findings suggest numerous perinatal interventions with great potential for providing lifelong benefit.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

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

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

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

We hypothesize that various aspects of an infant's life are ripe for interventions that can prevent obesity in the long term. Such areas include promoting breastfeeding, promoting healthy sleep habits, promoting other

methods to soothe infants instead of feeding, establishing healthy food preferences early in life, and improving parental understanding of healthy growth patterns when their children are infants. Each of these can be improved by evidence-based interventions shown to improve parent-infant interactions surrounding feeding and weight gain early in life.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

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

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

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

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

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

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Health Research Priority Title and Description

Drug and Alcohol Abuse and Addiction

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

Biomedical Research Questions and Hypotheses

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

Hypothesis: That a new class of small proteins, called chemokines, first discovered in the immune system, and now shown to be present and to have a functional role in the brain, are important in inhibiting drug craving, reducing development of drug dependence, and reducing symptoms of withdrawal. It is proposed that altering brain chemokine levels can modulate pathways that lead to addiction.

Question II: How do multiple drugs interact in regard to drug craving and dependency?

Hypothesis: That neuronal circuits, cells and mediators are differentially altered in subjects addicted to a single drug (e.g., alcohol, opioids or cocaine) as compared to those addicted to or abusing multiple drugs in addition to their drug of primary dependence.

Clinical Research Questions and Hypotheses

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

Hypotheses:

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

Health Services Research Questions and Hypotheses

Questions:

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

Impact on Health of Pennsylvanians

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

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

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

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

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

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

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

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

Clearly substance abuse is an all-pervasive problem for our state. Yet, of the \$3 billion states spent on prevention, treatment, and research nationally in 1998, only 0.1% was on research. The vast majority,

approximately \$2.5 billion, was spent on treatment. Given the magnitude of the substance abuse problem, and its global impact on society, the lack of spending on research into how drugs hijack the brain is difficult to justify. With other biomedical problems, like heart disease and cancer, funds directed to unraveling the biological basis for the disease have led to enormous strides in treatment and prevention. It is anticipated that research into the biology of substance abuse will identify novel targets leading to new pharmaceuticals to treat the user and the addict, and possibly to prevent addiction. Investment in substance abuse research is important for the State of Pennsylvania. It will allow partnerships with biotech and pharmaceutical industries, which are prominent in the state. It will hold out the promise of new and better treatments for citizens whose lives are driven by cravings for drugs, which they cannot control.

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Health Research Priority Title and Description

PAIN, ACUTE AND CHRONIC

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

Biomedical Research Questions and Hypotheses

Our overarching hypothesis is that pain is so fundamental a process in adaptation, physiological regulation, development, and motor function that an integrated study of pain on the molecular, physiological, and clinical levels can significantly improve our ability to treat most diseases; favorably influence the development of children and adolescents with pain; and improve the adaptation, cognition, mood and disability of any individual with pain once these insights are disseminated into practice. Pain is an opportune target for therapeutic attack because the first few cells signaling pain from the periphery are highly specialized for pain and grouped with other pain cells in nerve ganglia and spinal cord. Further, most types of pain share many of the same molecular mediators. We hypothesize that researchers can discover new therapeutic target molecules whose manipulation will have fewer side effects than current pain treatments (opioids, NSAIDs, anticonvulsants, antidepressants) by approaches combining physiological, expression, and proteomic studies in these specialized pain-mediating neural cells with genome-wide genetic association studies in animals and humans.

Clinical Research Questions and Hypotheses

We have accumulated evidence that chronic nonmalignant pain in cognitively intact older adults impairs brain function (i.e., neuropsychological performance) and that this impaired function may be a key link between pain and physical disability. As an extension of these findings, we hypothesize that chronic pain may accelerate the

rate of decline in cognitive function among cognitively intact older adults as well as those with Alzheimer's disease. We predict that intensive pain treatment with safe modalities (e.g., acupuncture, meditation, acetaminophen) may ameliorate physical and cognitive decline.

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

Health Services Research Questions and Hypotheses

We hypothesize that undertreatment of pain in African-Americans, well-documented in ambulatory, inpatient and long-term care settings, is caused by (1) clinicians' biases that these patients are at higher risk of addiction and (2) patients' overestimate of the risk of opioid addiction (even when used appropriately). Comprehensive interventions that address both of these factors will reduce the undertreatment of pain. We predict that documented high-yield interventions to reduce the costs and disability in pain patients can be translated to health systems in Pennsylvania, including: (a) a back-to-work cognitive-behavioral intervention in individuals with back pain that reduced disability costs across Nova Scotia; (b) a post-operative anesthesiological intervention in older patients with severe pain after limb trauma that reduced disability, pain levels, and analgesic use 6 months later in a New York City hospital system. We hypothesize that the dissemination of individualized management plans for Pennsylvania's 4,000 sickle cell patients will lead to decreased hospitalization for uncomplicated pain crises, decreased length of hospital stay, and improved school attendance and psychosocial development.

Impact on Health of Pennsylvanians

Pain is the reason for more than 20% of visits to physicians and pain drugs make up about 10% of prescriptions, so we can estimate that the medical costs of treating pain are 10-20% of health care costs, or \$200-400 billion/year in the US. In addition, lost/reduced productivity at work and disability payments cost the US another \$100 billion/year. Prorated to the size of the Pennsylvania population, 4% of the US total, the cost estimate of pain in Pennsylvania is \$12 – 20 billion/year.

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

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

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

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Health Research Priority Title and Description

The effects of atherosclerosis and its risk factors on autonomic regulation in response to physical activity

Atherosclerosis is an important disease process leading to stroke, heart attack, and peripheral vascular disease. We believe an important and as yet understudied area of investigation is the effect atherosclerosis has on the ability of the autonomic nervous system to regulate heart rate, blood pressure and organ blood flow. It is clear that altered autonomic regulation can raise heart rate, blood pressure and reduce organ blood flow. These effects can worsen the impact of disease. We believe a better understanding of the impact of the atherosclerosis on autonomic control will lead to new therapies and approaches to disease. In turn, this knowledge will have a major impact on the health of Pennsylvania residents.

Biomedical Research Questions and Hypotheses

1. What are the effects of atherosclerosis on the autonomic responses to physical activity?
2. What are the effects of smoking on the autonomic responses to physical activity?
3. What are the effects of hypertension on the autonomic responses to physical activity?
4. What are the effects of diabetes mellitus on the autonomic responses to physical activity?
5. What are the effects of obesity on the autonomic responses to physical activity?

Clinical Research Questions and Hypotheses

1. Will treatments for atherosclerosis such as stenting procedures, medication, and exercise therapy reverse the alterations in autonomic responses seen with physical activity?
2. Will smoking cessation reverse the alterations in autonomic responses to physical activity?
3. If treatment is successful in controlling hypertension, will it reverse the alterations in hemodynamic responses to physical activity?
4. If diabetes mellitus is controlled, will it reverse the alterations in autonomic responses to physical activity?
5. Will a treatment with antioxidants (such as dark chocolate), inhibit the oxidative stress caused by smoking, hypertension or diabetes, and reverse the alterations in the autonomic responses to physical activity?
6. Will significant weight loss reverse the alterations in the autonomic responses to physical activity?

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Atherosclerosis and its modifiable risk factors have a profound impact both directly and indirectly on the health of Pennsylvanians. From 2002-2006, close to 4% of deaths in Pennsylvania were attributed directly to atherosclerosis, diabetes, and hypertension. This excludes deaths directly attributed to diseases of the heart (~28%), that is exacerbated by all three stressors. In addition, smoking is implicated in those disease states as well, and the estimated percentage of smoking-related deaths in Pennsylvania in 2002-2003 was 16%. These are sobering statistics, especially when treatments and interventions are available to treat these conditions.

In addition to mortality, health care costs for treatment related to atherosclerosis, diabetes, hypertension obesity, and smoking are staggering. In 2007, 7.8% of adults in Pennsylvania had been diagnosed with diabetes and 29% of adults had been told they had high blood pressure. Both of these risk factors can be reduced by proper diet and exercise, however, only about a fourth of the adults consumed the recommended daily servings of fruit and vegetables and only about half engaged in moderate to vigorous physical activity. As a result, only about a third of the population maintains a healthy weight. Despite the extensive education programs on the effects of smoking, approximately 23% of adults in Pennsylvania continue to smoke.

It is likely that a high percentage of Pennsylvanians will continue to be at risk for atherosclerosis, diabetes, obesity and hypertension in the future, and their ability to perform physical activity will be affected by these diseases. Therefore, we feel it is important to not only study these diseases from a treatment standpoint, but also from the standpoint of the changes in normal reflex responses that lead to disease.

We need to plan for an ever increasing elderly population as more live into their 8th and 9th decade of life. Focusing on modifiable risks factors of atherosclerosis may improve the quality of life for the patients and decrease health care costs.

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Health Research Priority Title and Description

An integrated forensic and monitoring system supporting the response to microbial pathogens and antibiotic resistance

Infectious diseases pose a continuous grave threat to the health of Pennsylvanians. Due to the frequent travels and trades, microbial pathogens (both novel and variants of known pathogens) rapidly migrate from one region to another. Rapid evolution of resistance to antimicrobials limits our options for control. After the September 11 attacks and the subsequent anthrax release, it also became apparent that threats from deliberate releases of microbial agents cannot be overlooked. Thus, an effective and rapid response system should be in place to prevent and quickly respond to microbial disease outbreaks and to mitigate the economic and social impacts resulting from such outbreaks. Considering the diversity and rapid evolution of pathogens and their frequent genetic changes, it is critical to base our countermeasures based on an accurate and rapid diagnosis and a clear understanding of their biology and ecology. We also need a well-established mechanism that supports the communication among experts and policy makers and with the general public to rapidly implement intervention strategies based on best available scientific knowledge. We should also archive biological materials, lessons, and experiences from past and current outbreaks in a format that can help us better manage similar outbreaks in the future. We propose to develop a system that addresses these needs via a combined use of molecular tools, genomics and informatics using zoonotic microbial agents as a model.

Biomedical Research Questions and Hypotheses

Within each of infectious agents, disease is often caused by a specific subset of strains, referred to as epidemic clones. In order to develop effective intervention strategies that reduce disease burden, new methods for accurately identifying and tracking both existing and newly emerged epidemic clones must be developed. A combination of recent advances in the field of genomics and informatics will permit the development of a comprehensive genetic forensic database that supports the identification and tracking the spread of epidemic clones and antibiotic-resistant populations of diverse microbial pathogens and the archiving of key pathogen isolates and associated information. This genetic information also supports the development and validation of diagnosis tools that allow the rapid detection of multiple pathogen species and their variants simultaneously.

Clinical Research Questions and Hypotheses

One problem in our current preparedness against infectious agents is that the main focus is on detecting and responding to specific known and anticipated agents. Accordingly, we are ill prepared for dealing with the resulting unanticipated threats. Pathogens that are presently unknown to us can be devastating, as exemplified by Severe Acute Respiratory Syndrome (SARS) and H1N1 influenza. Variants of known pathogens, through genetic changes, with enhanced virulence and antibiotic resistance are constantly emerging too. Advances in genomics and molecular biology facilitate high-resolution genetic fingerprinting of historic and contemporary

clinic isolates to build a comprehensive forensic database. A pathogen monitoring system should be based on such a forensic database so that we can monitor how pathogen communities are structured and have changed. This database accompanied by a state-wide monitoring network will help define the routes of transmission of microbial pathogens, which will permit the implementation of intervention strategies that prevent further spread and future outbreaks.

Health Services Research Questions and Hypotheses

The exponential increase of scientific knowledge presents vast opportunities for advancing fundamental knowledge about biological, environmental, and ecological factors affecting infectious disease outbreaks and translating the resulting knowledge into enhancing public health. However, at the same time, the information overload slows down the integration of existing knowledge to build big pictures. Because of the need for multifaceted approaches to understand and manage infectious diseases and antibiotic resistance, the need for proactively creating mechanisms supporting knowledge sharing and integration is greater than many other areas of science. To effectively support coordination of intervention strategies in cases of disease outbreaks by novel pathogens, a communication mechanism that closely network major stakeholders in decision making is also needed. Information technology can effectively address these needs.

Impact on Health of Pennsylvanians

All Pennsylvanians are increasingly exposed to dangerous zoonotic microbial agents, which are defined as those disease-causing microbial agents that are transmitted from animals to humans. Zoonotic microbial agents include bacteria such as *E. coli* O157:H7, *Salmonella*, *Campylobacter*, *Bordetella*, and *Listeria*, and also viruses such as Avian Influenza and West Nile. Spread of these microbial agents to the human population can result anywhere in the entire food system when food and water come in contact with infected animals or animal products. Spread also occurs by direct contact of humans with animals and the farm environment. Examples of bacterial zoonotic diseases are: i) *E. coli* O157:H7 outbreaks in 2006 that had a huge economic impact within the California produce industry, ii) a large outbreak in 2002 that was traced to *Listeria monocytogenes* contamination in a large turkey processing plant in Pennsylvania, and iii) ongoing outbreaks due to *Salmonella enteritidis* in eggs produced in Pennsylvania. Avian Influenza and West Nile viruses are also of great concern in Pennsylvania, which has a large population of wild birds and poultry and a history of contamination with these microbial agents.

The Pennsylvania Department of Health website reports statistics for only a small subset of zoonoses, and indicates that approximately 1500 cases of *Campylobacter*, 70 cases of *E. coli* O157:H7, and 2000 cases of *Salmonella* illness were reported from foodborne contamination in 2004. These specific agents are of great concern to Pennsylvania's pediatric and minority populations. For example, *E. coli* O157:H7 is the leading cause of kidney failure among the United State's pediatric population. *Campylobacter* is a leading bacterial cause of diarrhea among infants, and the incidence of *Salmonella* illness is approximately 30% higher for Pennsylvania's Black population than it is for the White population. Additionally *Listeria*, for which data concerning the incidence of disease is not present on the Department of Health's website, primarily attacks infants and children and also causes spontaneous abortion in pregnant women.

These statistics highlight a number of areas of concern. First, because experts generally agree that the actual incidence of foodborne diseases is 30-fold higher than reported statistics, these three (*E. coli* O157:H7, *Campylobacter*, and *Salmonella*) microbial agents likely sickened about 100,000 Pennsylvania citizens per year. Secondly, statistics for other foodborne infectious agents such as *Listeria* are lacking, even though this microbe causes severe disease in infants and pregnant women. Third, data are lacking for the spread of zoonoses to humans through routes other than food products. Lastly, statistics are lacking for "evolving" microbial agents, which are defined as newly recognized zoonoses that are increasing isolated from farm and food sources. The importance of recognizing and tracking these evolving agents is illustrated by the example of *E. coli* O157:H7, which has progressed from being an unrecognized cause of human disease in 1982, to an organism that today is carried by approximately 10% of cattle within the United States, and causes nearly 3,000 cases of reported human illness yearly in this country.

In order to develop effective intervention strategies that reduce the disease burden of zoonoses, new mechanisms for accurately identifying and tracking both existing and newly emerged zoonotic microbial agents and coordinating our intervention strategies must be developed. We propose that the development of such mechanisms would ultimately have a great impact on the health of Pennsylvania's populations especially pediatric and minority. In addition to contributing to the public health burden of Pennsylvania citizens, zoonotic agents also threaten the huge economy of Pennsylvania. Animal husbandry is a large portion of the Commonwealth's agricultural infrastructure. Also at stake is the Pennsylvania food processing industry, which ranks 4th nationally, employs hundreds of thousands of workers, and contributes \$20 billion annually to the Pennsylvania economy.

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Health Research Priority Title and Description

Adaptive Aging in Place

Aging of the American population is the most dramatic demographic trend of our time, bringing with it a host of challenges including runaway health care costs and pressures on geographically dispersed families to monitor and care for their elders. The situation is particularly severe in Pennsylvania, where, by the year 2020, an estimated 25% of PA's population will be age 60 or over. The situation will be exacerbated as members of the 'baby boom generation' become seniors and as nuclear families shrink in size. Most seniors prefer to remain in their own homes and avoid placement in assisted living facilities for as long as possible. Devising effective interventions that allow seniors to 'age in place' would also reduce the substantial health care costs associated with building, staffing, and overseeing assisted living facilities in PA. Challenges related to physical frailty, cognitive decline, health behaviors and geographic isolation can make independent living risky and insecure for seniors. Overcoming these challenges requires interdisciplinary and translational research to optimize existing home environments to enable adaptive aging in place for PA residents from all economic brackets. It will be necessary, at a minimum, to coordinate research efforts in architecture, business, engineering, geriatric medicine, gerontology, health and human development, information sciences and technology, psychology, and sociology. Adaptive aging in place is a preventive medicine challenge of unprecedented proportion for our commonwealth.

Biomedical Research Questions and Hypotheses

(1) How can interventions that modify (a) home living environments and (b) the roles of professionals such as visiting nurses and health care technicians promote important health behaviors and minimize risk factors associated with loss of functional independence?

The hypothesis is that a coordinated set of low cost environmental, educational and behavioral interventions can promote important health behaviors that enhance and prolong aging in place. Targeted health behaviors will include sleep hygiene, healthy eating, physical activity, social engagement and intellectual engagement, all of which contribute to functional independence in seniors. This hypothesis can be evaluated effectively in a two step approach: first, examine proximal biobehavioral outcomes, including cholesterol, weight, blood pressure, well-being and cognitive function; second, examine how changes to these proximal measures of biobehavioral health predict longer-term outcomes, such as postponement of disability and maintenance of functional independence.

Clinical Research Questions and Hypotheses

(1) Can aging in place be improved or extended by cost-effective interventions or modifications in the home living environments of PA seniors?

The hypothesis is that low-cost interventions in indoor environmental attributes such as lighting, acoustics, indoor air quality, energy efficiency, thermal comfort and interior design can have significant, measurable effects on enhanced and prolonged aging in place. Such effects include mental health, immune system health, accident rate, medication management, emergency room visit rate, etc. While ultimately targeted to aging citizens who remain functionally independent, these hypotheses can be tested initially in more controlled elder populations residing in continuing care retirement communities in PA, prior to translating proven successes to the broader PA elder population.

Health Services Research Questions and Hypotheses

(1) Can aging in place be improved or extended by training and expanding the roles of emergency medical technicians and visiting nurses to perform in-home assessments, using mobile data acquisition devices, of elderly persons in rural settings with respect to accident risk, neurocognition, immunization, and home energy use?

Hypotheses related to the above research question can be tested with elderly subjects residing in selected rural PA communities, where appropriate emphases can be placed on addressing the needs of low- to middle-income PA seniors who are at risk of isolation and poor access to enabling services. This research will address preservation of independent living status, improved delivery of health care services to rural elders, and direct transfer of research pilot study results to rural elders in PA. Pilot studies are now addressing these questions on a small scale.

Impact on Health of Pennsylvanians

The so-called "Senior Tsunami" of baby boomers who are just now starting to reach retirement age and draw social security benefits is beginning to wash upon the shores of the U.S. health care system. Pennsylvania is particularly vulnerable: it is one of nine states to have more than 1 million elderly, and has the second highest proportion of elderly living in the state (2000 census), many living in rural PA. Managing the geriatric health care of these elders in the 'business as usual' mode will surely not be affordable. In fact, the health care costs of the Senior Tsunami could make some of the serious economic problems of 2008 - 2009 look modest by contrast. Constructing enough assisted living facilities to accommodate the burgeoning number of baby boom elders is neither economically feasible nor desired by the vast number of our elders who wish to remain in their

own homes. Thus, enabling our elder population to age in place with an acceptable quality of life for as long as possible is a major preventive health care challenge now facing Pennsylvania, the United States and many countries throughout the world.

For the small proportion of the general population who can afford to purchase quality health care in continuing care retirement communities and the like, adaptive aging in place is less of a concern. However, for the vast majority of our population who cannot afford such continuing care, they must be able to age in place adaptively for as long as possible. The obstacles are particularly strong for elders in rural PA, where logistics and infrastructure issues are challenging and personal incomes are relatively low.

The increasing number of elders who require strategies and services to keep them safe in their own homes, living with an optimal quality of life will require sustained and widespread interventions. Understanding the needs of elders, particularly those living in rural areas with less access to services, will be necessary in determining appropriate interventions and allowing assessment of these interventions. The creation of systematic methods for evaluating health issues such as home safety, appropriate use of medications, vaccinations, assistive devices, health care follow-up and nutrition will lead to diminished overall health care costs, delayed or avoided transfer to long term care institutions, and improved quality of life for elders. Many elders who are at risk may not request available services that could potentially allow them to successfully remain independent in their homes. Often the result is avoidable injury or illness that requires acute intervention and often leads to loss of independence through institutionalization. The cost implications are enormous and will be non-sustainable. Loss of independence turns out to be an expensive outcome that often could be prevented by earlier intervention. Accompanying this scenario is the rapid spend-down of personal resources since institutionalization is expensive compared to independent living in one's home, which often results in the need for Medicaid services.

Elders are an extremely heterogeneous population, which creates additional need for careful evaluation and individualized interventions. Specific needs may relate to cognitive decline, mobility issues, substance abuse, depression, polypharmacy, pain management or frailty. Many, if not most, elders will have multiple chronic conditions that could interact with each other, increasing the complexity of their management.

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Health Research Priority Title and Description

Hereditary Gastrointestinal Cancer Risk in Minority and Underserved Populations

A substantial number of incident cancers of the gastrointestinal tract have an identifiable genetic risk or strong hereditary component. Diagnosis of cancer at a young age remains one of the most powerful markers of hereditary cancer risk. Early-onset cancers (< 50 years) of the upper gastrointestinal tract (pancreas, stomach, liver and bile duct) are rapidly increasing across Pennsylvania, with young black men and women bearing the greatest burden of these increases. Knowledge of genetic/hereditary cancer risk is remarkably poor among physician and minority/underserved populations. Equally, cancer risk assessment services are underutilized, and large racial/ethnic disparities in access and uptake have been documented. Improved identification of individuals and families with a hereditary risk of cancer allows early targeting of appropriate and often costly screening and prevention services to the highest risk groups. Improved awareness and access to cancer risk assessment services for minority/underserved men and women in Pennsylvania at risk for gastrointestinal cancers is desperately needed.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

1) Providing tailored education and low-cost community-based access to cancer risk assessment services among young men and women from minority and underserved populations will improve awareness and identification of individuals at high-risk for hereditary gastrointestinal cancers.

Hypothesis: Knowledge, access (geographic, lack of primary care physician, poor knowledge among community physicians) and cost represent the most important barriers to awareness of cancer risk, genetic testing, and screening efforts in the minority and underserved populations of Pennsylvania.

2) The prevalence of common hereditary gastrointestinal cancer syndromes is largely unknown in underserved and minority populations.

Hypotheses: A) Hereditary gastrointestinal cancer syndromes explain a significant portion of the early-onset cancers of the gastrointestinal tract in Pennsylvania. B) Community-based cancer risk assessment (pedigree analysis, low-cost counseling and genetic testing) can improve identification of high-risk individuals.

Health Services Research Questions and Hypotheses

Individual and community-wide barriers to gastrointestinal cancer risk assessment, risk factor management, and prevention services exist among minority and underserved populations.

Hypotheses: A) Perceived cancer risk, perceived benefits and barriers to cancer risk assessment services, preferences for genetic testing, access/cost, and fears of discrimination significantly impact utilization of gastrointestinal cancer risk assessment services. B) Individual and community-wide barriers are surmountable through tailored education and low-cost, community-based cancer risk assessment services. C) Widening disparities in gastrointestinal cancer incidence may be reduced through education, gastrointestinal cancer risk assessment, and risk factor modification.

Impact on Health of Pennsylvanians

Recent data from the National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) Program and the American Cancer Society demonstrate that Pennsylvania (PA) is experiencing a crisis of upper and lower gastrointestinal (GI) cancers of remarkable proportions. Updated SEER (2001-2005) data demonstrate a dramatic rise in the incidence of upper gastrointestinal (GI) tumors in PA (pancreas, stomach, and hepatobiliary cancers). Incidence rates surpass national figures as well as those recorded in neighboring, demographically and socioeconomically comparable states (e.g., New York, New Jersey, Ohio). These changes are highlighted by a striking 25.2 (p<0.05) annual percentage change (APC) increase in the rate of stomach cancer among young (<50) black men, a 48.1 (p<0.05) APC INCREASE in the rate of hepatobiliary cancers among young black women, and a 14.1 APC increase for pancreatic cancer among young black men and women (compared to a 0.9 APC DECREASE in pancreatic cancer among young black men and women nationwide). Compounding this crisis, the incidence of lower gastrointestinal cancer (colorectal) in Pennsylvania is the fifth highest in the nation for both men (68.4 cases/100,000) and women (49.6 cases/100,000) (American Cancer Society, 2009).

Individuals with early-onset cancer are at markedly increased risk of having an underlying hereditary cancer risk. Through cancer risk assessment services and cancer predisposition genetic testing technology, high-risk individuals may be identified, counseled about cancer risks and risk reduction strategies (e.g., screening, prophylactic surgery, chemoprevention), and offered genetic testing to better quantify cancer risks for themselves and family members. Disparities in knowledge of hereditary cancer risk and awareness of genetic testing have been well documented, as have access to and utilization of cancer risk assessment services (Hall 2005, Hall 2006). Furthermore, striking racial disparities in modifiable environmental and behavioral risk factors (e.g., obesity rates, physical activity levels, smoking rates) exist nationally and in the state of Pennsylvania. Barriers to cancer risk assessment services and genetic testing include awareness, access to general healthcare, cost, and fears of social stigma and discrimination (Armstrong 2005). Pilot programs have shown low-cost, community-based cancer risk assessment services can lead to reduced racial and socioeconomic disparities in services access, high follow-up/return rates among underserved and minority individuals, and improved identification of high-risk individuals and family members through genetic testing (Ricker 2006). Strategies to reduce barriers to cancer risk assessment services through targeted education and outreach programs, low-cost community-based services, and low-cost genetic testing will benefit all Pennsylvania residents by reducing the incidence of and improving the early diagnosis of gastrointestinal cancers, especially in the young black population.

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Health Research Priority Title and Description

Addiction and Violence

Addiction research, and specifically research into the relationship between addiction and violence, should be the priority of the CURE program. Recent brain imaging studies have revealed that the same reward centers of the brain activated by drugs, alcohol, gambling and sex also activate when people are wronged by others and crave revenge. That is, when perceived wrongdoers are punished, reward centers in the brains of punishers significantly activate, producing physiological and psychological effects similar to those associated with powerful drugs of abuse. This brain vulnerability is now suspected of being a root cause of destructive anti-social behaviors including violent crime, which is epidemic across Pennsylvania in the form of high rates of child abuse, school violence, domestic violence, workplace conflicts, gang violence, interpersonal violence and murder, prison incarceration and recidivism.

Public health research aimed at addiction now promises to yield valuable insights not only into substance abuse--which also has become a major intractable public health problem in Pennsylvania--but also violence and criminality. With these insights comes the potential for developing tools to identify those most vulnerable and interventions and treatments to control these addictive behaviors and impulses and improve public health and welfare.

Biomedical Research Questions and Hypotheses

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

Clinical Research Questions and Hypotheses

1) Can revenge-gratification (inflicting punishments on others) manifest for some individuals into an addictive/impulse control disorder ("justice addiction") with a neurobiological substrate, highlighted by an uncontrollable urge to inflict pain and suffering upon those perceived as wrongdoers (compulsive anti-social/destructive behavior)? 2) If so, what are the risk factors for these individuals? 3) Is "justice addiction" a root cause of destructive, anti-social behavior, including violent crime? 4) Is there a brain-behavioral connection between drug addiction and "justice addiction"? Hypotheses: Yes to all. Rationale: The U.S. Department of Justice NDIC (2007) has found that violent crime is the principal threat to public health and safety in the Philadelphia area and that most violent crime and murder is the result of interpersonal disputes (revenge gratification). FBI 2002-2006 crime statistics confirm that arguments are the primary cause of murder nationwide. Yet homicide perpetration and victimization across Pennsylvania is distributed unequally by race and gender (CDC WISQARS), with incidence significantly higher among black males, coincident with drug abuse, suggesting a co-existent justice-addicted population.

Health Services Research Questions and Hypotheses

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

Impact on Health of Pennsylvanians

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

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

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

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

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

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

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

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

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

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Health Research Priority Title and Description

ADDICTION and associated crime, violence, HIV/AIDS

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

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

Biomedical Research Questions and Hypotheses

What are the brain vulnerabilities that increase

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

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

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

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

Clinical Research Questions and Hypotheses

Our guiding hypothesis -- that similar frontal deficits/genetic variation may confer vulnerability to relapse, to addiction, to violence, and to HIV risk -- will be used to predict outcome/treatment response in the following

target populations: 1) For drug court clients with cocaine-related crime, can we predict which clients are at greatest risk for relapse AND for violence -- while offering behavioral treatment addressing both problems? 2) For underserved minority females with nicotine dependence, stratified on dopamine transporter genetics: Can a novel medication impact the brain response to drug cues, improving treatment outcomes? 3) For Veteran (Afghanistan; Iraq) and non-veterans with alcohol dependence and prior trauma: Can brain and genetic measures predict treatment response to a novel medication that may benefit both alcohol and PTSD? 4) For opiate-addicted individuals receiving depot naltrexone treatment: Can imaging of brain opiate receptor occupancy predict medication efficacy and clinical outcome? 5) For ADHD adolescent smokers at-risk for illicit drug use: Will brain/genetic measures predict progression to illicit drug use? Can brain measures be used to create more effective anti-drug/pro-health messages?

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

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

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

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

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

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

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

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

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Health Research Priority Title and Description

Generating New Evidence Using Comparative Effectiveness Research

Comparative effectiveness research compares different interventions and strategies to prevent, diagnose, treat, and monitor health conditions. Typically, most drugs and other new medical strategies are studied in randomized clinical trials including homogeneous populations, compared to a placebo. This is sufficient to show the drug or device works. It does not show whether it works better or worse than alternative approaches to the same medical problems, nor does it show that it works and is safe for use in the real world, as opposed to the ideal world of that clinical trial. It also does not identify subgroups in whom the approach is most likely to be effective, or most likely to do harm. All this information is badly needed for practical clinical decisions by clinicians or patients, to determine which interventions are most effective for which patients. Further, at a time of concern over health care costs, it behooves us to apply the treatments which are most effective, and only those. Yet, this evidence is usually missing.

Comparative effectiveness research is typically performed by: 1) synthesizing evidence already available, 2) generating new evidence, and 3) disseminating the available evidence to be certain it is applied clinically. There is especially a need for an increase in #2, and for an increase in human and data infrastructure to conduct it.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

Many comparative effectiveness studies are conducted using patient-oriented research methods, in particular using clinical trials. Their primary goal, however, is not to study disease mechanisms, but rather to compare patient outcomes when given alternative treatments. The types of questions are therefore the same as those addressed by health services research, and are discussed below.

Health Services Research Questions and Hypotheses

The techniques used to generate new evidence for comparative effectiveness research are typically large simple clinical trials, and epidemiologic analyses of large compilations of existing clinical (e.g., electronic health records) and claims (e.g., Medicaid and PACE) databases. The former are very expensive, but are the only valid approach, when there is substantial channeling of the different alternative interventions into different populations. The latter require adequate databases to be available and the absence of such channeling. A wide

range of questions can be addressed using these techniques, e.g., comparison among alternative treatments for methicillin-resistant staphylococcal infections; comparison among different frequencies for use of colonoscopy in the elderly; comparison among treatments for the prevention of amputation in diabetics; comparative risk of hepatotoxicity among different treatments for hepatitis C; comparison of different approaches to computerized provider order entry, in modifying provider practice; comparison of different approaches to the regionalization of critical care delivery; and comparative risks of injuries resulting from use in the elderly of different sedatives and hypnotics.

Impact on Health of Pennsylvanians

The leading causes of mortality in Pennsylvania (2004-2006 data) are heart disease (age-adjusted death rate 229/100,000/year), cancer (195/100,000/year), stroke (49/100,000/year), chronic lower respiratory disease (39/100,000/year), accidents (39/100,000/year), and diabetes (23/100,000/year). Yet, these vary substantially in different subpopulations. The infant death rate was 7/1000 live births/year, but ranged from 5/1000 live births/year for Asians and Pacific Islanders, to 17/1000 live births/year for blacks. 15.2% of Pennsylvania's population is 65 years of age or older, the third-largest percentage in the nation. 7.2% of Pennsylvanians over age 5 have one type of disability and 9 percent have two or more types of disability. The resources expended in Pennsylvania to address this disease burden are vast. Based on data from the Medical Expenditure Panel Survey conducted by the Agency for Healthcare Research and Quality, Pennsylvanians spent about \$4 billion on healthcare in 2006.

Yet, strikingly, despite these huge resources, in very many clinical situations we do not even know some of the most basic information we need, i.e., do our treatments really work, and in whom should they be used? In the past, we have seen treatments that were expected to save lives, actually increase mortality. We have recently found out that some thrombolytics are better than others in certain circumstances. Among antipsychotics, the newer and more expensive drugs appear like they may have the same effectiveness as the older ones, and perhaps not large differences in safety. Thioridazine and haloperidol appear to have similar overall rates of life threatening sudden death and ventricular arrhythmia, but thioridazine is worse at high dose. When should angina be treated medically, when with angioplasty, and when surgically? We now have antidiabetic agents of many types, given in part to decrease myocardial infarction, but there are accusations that at least one may increase the risk of myocardial infarction. Is this true, and is it different for the other drugs for this condition? These are all questions of comparative effectiveness. Knowing the answers, will permit us to use the best approach for a given clinical setting. In the process, we would have better clinical outcomes, prevent unnecessary adverse reactions, and decrease the overuse of ineffective treatments and testing. The net impact would be decreased mortality and morbidity from many conditions. Further, there might be a decrease in healthcare costs, with more efficient use of the available technology. For certain, there should be an improvement in healthcare outcomes, which in turn should have beneficial societal and economic effects.

Further, could some of these drugs be better for some subpopulations, and other drugs be better for others? This study of heterogeneity of response is a central role of comparative effectiveness research, and is critically missing. This is especially important to minorities and the elderly. Not only are they vulnerable to many of the illnesses which would be studied, but if there are treatments which work particularly well in these subpopulations, or where they are at particularly high risk of the treatments' adverse events, it is critical that we learn this information so therapy can be steered accordingly.

Finally, the specialized techniques used to generate new evidence for comparative effectiveness research, described above, each requires special expertise, and special facilities. The research team needs to be multidisciplinary, and special training is needed for researchers in this field. Pennsylvania has the opportunity to be a major leader in developing this infrastructure. Indeed, it has a number of individuals already serving as leaders in this new field, and databases which can be useful for this research, e.g., PACE, so it is well poised to accomplish this. This is also a major new focus of federal funding. If Pennsylvania develops the infrastructure to be a leader in conducting these studies, it will be positioned to attract substantial federal funding into the state, and in the process continue these efforts long-term.

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Health Research Priority Title and Description

Gastrointestinal cancers and diseases

The digestive tract comprises the esophagus, stomach, small intestine, colon, liver and pancreas. All play vital roles in basic nutrition, physiology and pharmacology. Disorders and diseases of the digestive tract are amongst the most common human conditions in the United States and the state of Pennsylvania, as highlighted by the NIH in their burden of digestive diseases report (Gastroenterology 136:376-386, 2009, 136:741-754, 2009 and 1134-1144, 2009; see also, www3.nidk.nih.gov/Burden_of_Digestive_Diseases), costing society hundreds and hundreds of millions dollars. The US Congress and the NIH commissioned experts and members of the lay public to address the burden of digestive diseases and develop a long-range plan. The recommendations of the National Commission on Digestive Diseases, outlines a broad and ambitious agenda aimed at improving the health of the nation for digestive diseases through research (<http://NCDD.nidk.nih.gov>). These diseases and disorders include, but are not limited to the following: (1) gastroesophageal acid reflux, Barrett's esophagus and esophageal cancer; (2) Chronic pancreatitis and pancreatic cancer; (3) Polyps and colon cancer; (4) Inflammatory bowel disease and colon cancer; and (5) Viral hepatitis, liver cirrhosis and liver cancer. They share common themes of the interplay of environmental and dietary exposures with genetic factors. The goals of this proposal are to impact the biological understanding, clinical management and health care delivery of these diseases.

Biomedical Research Questions and Hypotheses

1. How does Barrett's esophagus lead to esophageal cancer?

Hypothesis: Transdifferentiation of the normal esophageal epithelium involves the interplay of developmental pathways to induce Barrett's esophagus, a widely prevalent condition associated with acid-reflux and the main precursor to esophageal adenocarcinoma, which has the fastest rate of increase of any cancer.

2. How do colon polyps give rise to colon cancer?

Hypothesis: The progression of polyps to cancer involves newly identified pathways, apart from chromosomal instability and microsatellite instability. These new pathways involve hypermethylation, B-raf mutation, microRNAs, and other genomic alterations.

3. How does the gut microbiome influence the development of inflammatory bowel disease?

Hypothesis: Changes in the bacterial flora in the gut influences the initiation and progression of inflammatory bowel disease, reminiscent of associations in diabetes mellitus and obesity.

Clinical Research Questions and Hypotheses

1. How is diabetes mellitus related to colon cancer development and progression?

Hypothesis: Insulin, both endogenous and exogenous, leads to a greater prevalence and incidence of colon cancer.

2. Do the inherited and familial forms of pancreatic cancer inform about the sporadic form of pancreatic cancer?

Hypothesis: The inherited (known genes) and familial forms (unknown genes) can help in the early detection and therapy of pancreatic cancer.

3. Do the use of probiotics and antibiotics improve the clinical outcomes in inflammatory bowel diseases?

Hypothesis: Changes in the gut bacterial flora will help in the clinical management of inflammatory bowel disease through the use of probiotics and antibiotics.

4. Does liver cancer respond to immunotherapy?

Hypothesis: Changes in the immune response to liver cancer antigens will improve survival in liver cancer.

Health Services Research Questions and Hypotheses

1. Can we improve the access to colon cancer screening in traditionally underserved populations in Pennsylvania, including African-Americans, Asian-Americans and Hispanic Americans?

Hypothesis: Access to colon cancer screening can be improved through the overcoming of cultural, social and language barriers. This will lead to decreased colon cancer incidence.

2. Can we improve screening and surveillance of liver cancer in Pennsylvania?

Hypothesis: Targeting of at-risk population groups (those with hepatitis B, hepatitis C) will impact upon decreasing liver cancer incidence.

3. Can we improve screening of pancreatic cancer in Pennsylvania?

Hypothesis: Through the instruction and implementation of fixed clinical protocols in the general population, at-risk population groups can be identified so that pancreatic cancer can be detected as a precancerous stage or at an early stage.

Impact on Health of Pennsylvanians

Digestive tract cancers and diseases are common in the Commonwealth of Pennsylvania. These cancers arise in the colon/rectum, pancreas, stomach, esophagus, and liver. They are in aggregate amongst the most common cancers in Pennsylvania. Some of these cancers arise in counties where there has been exposure to industrial waste; all are associated with cigarette-smoking; and all are associated with increasing incidence in traditionally under-represented minority groups--African-Americans, Hispanic-Americans and Asian-Americans. Through research--biomedical, clinical and health services--using state of the art laboratory based approaches, clinical trials, and population based studies and strategies, Pennsylvania has the unique opportunity to impact upon these otherwise devastating cancers (as each one is associated with poor outcomes) and take the lead in the United States. The benefits relate to the residents of Pennsylvania, those who relocate to Pennsylvania, and for attracting new partnerships with biotechnology and pharmaceutical companies as well as the NIH/NCI.

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Health Research Priority Title and Description

Acute Exacerbations of chronic obstructive pulmonary disease (AECOPD)

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are to COPD what myocardial infarctions are to coronary artery disease. They are the acute and sometimes deadly manifestations of a chronic disease. AECOPD have been reported to: (1) be the primary cause for frequent hospital admissions and relapses/readmissions; {{430 Roberts,C.M. 2002;280 Garcia-Aymerich,J. 2003; }}2) contribute directly to the death of many patients, either during hospitalization or shortly thereafter; {{280 Garcia-Aymerich,J. 2003;289 Groenewegen,K.H. 2003; 229 Connors,A.F.,Jr 1996; 88 Ai-Ping,C. 2005; }} {{534 Zvezdin,B. 2009; }} 3) cause patients significant stress, prolonged physical discomfort, and dramatically reduced quality of life; {{452 Seemungal,T.A. 1998;259 Domingo-Salvany,A. 2002; 228 Connors,A.F.,Jr 1996; }} 4) consume the majority of the resources available to manage this chronic condition; {{294 Halpern,M.T. 2003;378 Miravitlles,M. 2002; 465 Sin,D.D. 2002; 473 Sullivan,S.D. 2000; 229 Connors,A.F.,Jr 1996; }} 5) frequently are allowed to progress to a severe stage warranting hospitalization before any abortive treatment changes are instituted, {{535 Chandra,D. 2009; }} and ; 6) may hasten the progressive loss of lung function {{260 Donaldson,G.C. 2005; }}, a steady decline that is a cardinal feature of COPD.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

1. Explore the demographics of Pennsylvania residents hospitalized for AECOPD
2. Understand the impact of geographic location in Pennsylvania (e.g., rural and urban regions) for hospitalized AECOPD
3. Explore the impact of gender and race on hospitalized AECOPD
4. Investigate the pathogenesis of hospitalized AECOPD on lung and systemic inflammation and procoagulant mechanisms
5. Study the high rate of cardiac events (e.g., arrhythmias, acute myocardial infarction, and unstable angina) and venous thromboembolism (VTE, deep venous thrombosis and pulmonary embolism) that are major causes of morbidity and mortality in COPD in those hospitalized for AECOPD
6. Study new treatments or approaches to prevent hospitalized AECOPD
7. Explore new therapies and approaches to treatment in Pennsylvania residents hospitalized for AECOPD
8. Examine the cost-effectiveness of new approaches to the treatment of hospitalized AECOPD

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

AECOPD that require hospitalization are the most severe manifestation of a worsening of the course of the patient with COPD. 50% of patients are readmitted to the hospital within 6 months of the initial hospitalization and patients overall experience an approximately 15% 6- month mortality. Hospitalization for AECOPD is a major problem for Pennsylvania residents and continues to afflict 28,000 to 30,000 patients annually (Figure 1)

No decrease has occurred in AECOPD hospitalizations in Pennsylvania in contrast to admission for acute myocardial infarctions in Pennsylvania residents over the past 6 years. Based on PHC4 data, hospitalization in FY 2007 incurred annual total charges of \$593 million, approximately 200 million dollars more than the cost of care for Pennsylvanians admitted for care of acute myocardial infarction (Figure 2).

Clearly, AECOPD that require hospitalization is a major problem that requires attention for Pennsylvanian residents.

Despite the obvious great clinical need and high morbidity and mortality of hospitalized AECOPD, there have been no new major approaches to the pharmacologic treatment of hospitalized AECOPD in over 3 decades. I believe that a new focus into the epidemiology, prevention and potential treatments that either prevent or lessen the impact of AECOPD that require hospitalization could make major impact into the morbidity, mortality and high costs of care of hospitalized AECOPD.

Hopefully putting acute exacerbations of chronic obstructive pulmonary disease (AECOPD) that require hospitalization as a research funding priority topic will garner the appropriate resources to investigate and hopefully eventually treat this very common and important clinical problem in Pennsylvania residents

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Health Research Priority Title and Description

Research in Biomarkers to Improve Cancer Screening

Biomarker signatures that distinguish cancer patients from individuals without cancer have been reported, but few are in clinical use. The major limitation has been lack of sufficient sensitivity (presence of false negatives) or specificity (presence of false positives). This was demonstrated most recently by the failure of the serum biomarker prostate specific antigen (PSA) to increase survival for men diagnosed with prostate cancer. The performance of a biomarker in screening the general population must be extremely high, on the order of 99% overall accuracy (99% specificity and 99% sensitivity), which PSA never achieved. Newer methods using proteomic approaches to examine proteins in blood have a much greater potential to find combinations of biomarkers that can more accurately discriminate between individuals who do and do not have cancer. This approach could potentially also detect cancer at an early stage. Further, in a clinical context using a high-risk population, great improvement in clinical work-up of suspicious screening findings for a specific cancer can be achieved with tests that discriminate at much lower stringency, such as 80% sensitivity/85-90% specificity. Examples of high-risk populations are: those screened for lung cancer with abnormal computed tomography findings, women with changes in breast density seen on mammogram (possible breast cancer), those with colon polyps found at colonoscopy (possible colon cancer), and men with abnormal digital rectal exams (possible prostate cancer).

Biomedical Research Questions and Hypotheses

The hypothesis is that proteomic analysis of blood-borne proteins can distinguish in a high-risk population between individuals who do and do not have cancer.

The second hypothesis is that proteomic biomarkers can detect cancer at an early stage in high-risk populations.

Proteomic tests will be most readily applicable to those with suspicious, but inconclusive, findings on screening for lung cancer, breast cancer, colon cancer, or prostate cancer.

Clinical Research Questions and Hypotheses

In high risk patients screened for lung, breast, colon, or prostate cancer who have pre-cancerous findings or have findings that are suspicious of cancer, biomarker profiles found by proteomic analysis will be able to correctly predict or detect cancer at a sensitivity of at least 80% and a specificity of over 90%. Proteomic tests will be able to correctly rule out cancer in over 90% of high-risk patients who are cancer-free, while correctly identifying cancer in over 80% of those who do have the disease. The correct identification of those with cancer will also find cancer at an early stage where it is still curable. Use of proteomic tests will lessen the health costs and anxiety of cancer screening.

Health Services Research Questions and Hypotheses

Incorporating validated cancer biomarkers into a screening protocol will reduce the number of medical procedures in screened individuals who end up with a negative cancer diagnosis as a result of screening.

Incorporating validated cancer biomarkers into a screening protocol will reduce the anxiety level of individuals who undergo cancer screening and have a suspicious finding.

Impact on Health of Pennsylvanians

Most recent statistics available from the Pennsylvania Department of Health show that the following number of new cases of cancer were diagnosed in Pennsylvania in 2006: prostate (10,770); lung and bronchus (10,455); female breast (9,739); colon and rectum (8,004). These are the top 4 types of cancer diagnosed. The number of cancer deaths was also high for these 4 types of cancer: lung and bronchus (7,892); colon and rectum (2,884); female breast (2,096); and prostate (1,453). These cancer types represent more than 50 percent of all of the cancer deaths reported in the state.

Although improvements in cancer therapy are being made, the best way to avoid cancer death is early detection. Screening is an important part of early detection but can also lead to many false positive findings (suspicious changes that may resemble cancer but are actually benign). False positive results not only increase patient anxiety and health costs due to extra procedures performed to confirm or rule out cancer, they also lead in many cases to unnecessary surgery. These occurrences make cancer screening less efficient and, in some cases, cause at-risk individuals to avoid cancer screening. Blood tests that could complement screening will greatly improve the reliability of screening tests. This improvement will, in turn, lead to greater use of screening and higher probability of early cancer detection.

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Health Research Priority Title and Description

Improving survival of breast cancer patients

Breast cancer is a significant health issue, affecting nearly 2.5 million Americans and approximately 40,000 women and men are expected to have died from breast cancer in 2007, Although surgical and pharmacological regimens have significantly improved patient survival and quality-of-life, breast cancer remains one of the leading cause of death in the United States. The economic cost of breast cancer in the US for 2001 was estimated to be \$157 billion.

Approximately 25% of breast cancer patients overexpress the Her2 receptor (Her2-positive) and exhibit higher recurrence rates and decreased survival. Although many of these patients are well-treated with the monoclonal antibody trastuzumab, as many as 66% of those treated develop resistance to this chemotherapy. Recent work indicates that the efficacy of trastuzumab will likely be improved by combination with inhibitors of the Ras/MAPK and/or Akt pathway in populations of breast cancer patients. Selective inhibitors of protein tyrosine phosphatase 1B (PTP1B) inhibit activation of both the Akt and Ras/MAPK pathways and decrease the growth of breast cancer tumors. The proposed health research priority is to assess the clinical benefit of combining selective PTP1B inhibitors with existing chemotherapies to improve survival and quality of life for breast cancer patients.

Biomedical Research Questions and Hypotheses

The overarching hypothesis is that specific combinations of selective inhibitors can improve the course of breast cancer (BC) chemotherapy. Selective inhibitors of protein tyrosine phosphatase 1B (PTP1B) inhibit activation of both the PTEN/Akt and Ras/MAPK pathways and decrease the growth of breast cancer tumors. We hypothesize that more effective treatment regimens for breast cancer can be developed by the identification of synergistic chemotherapy regimens of a selective PTP1B inhibitor with existing therapeutic regimens. This hypothesis will be assessed by (1) studying the effect of isobolic combinations of trastuzumab with a selective PTP1B inhibitor on genomic and proteomic patterns of breast tumor cell apoptosis in physiologic and cell models, (2) assessing the efficacy of selected combination regimens of trastuzumab with a selective PTP1B inhibitor for inhibiting tumor growth in xenograft models, (3) evaluating the efficacy of a synergistic regimen of trastuzumab and a selective PTP1B inhibitor to reduce tumor volume and improve quality of life in breast cancer patients.

Clinical Research Questions and Hypotheses

Large numbers of breast cancer patients have benefited from newer therapies but of these, up to two-thirds become resistant to the treatment and undergo relapse. Will aggressive treatment of patients early in the disease course lead to improved patient outcomes and reduced disease activity? Will newer diagnostic techniques which

guide therapeutic regimens lead to clinical responses to chemotherapies? Are there specific biomarkers of breast cancer patients who develop resistance to trastuzumab and other chemotherapies? We hypothesize that newer assessments of resistance biomarkers in concert with combination therapies will lead to better health-related quality of life and a longer-lasting clinical effect.

Health Services Research Questions and Hypotheses

Resistance to existing chemotherapies is unquestionably complex and, to some extent, idiosyncratic with individual differences in sensitivity and in the impact on daily living. A major hypothesis is whether it will be possible to decrease resistance and improve response to existing therapeutic modalities by combining them with new agents which inhibit the activity of resistance markers, such as PTEN/Akt. With this hypothesis demonstrated, it will be important to identify patients likely to benefit from this novel regimen through the use of reliable biomarkers and/or pharmacogenomic analyses. This would permit the delivery of enhanced treatment modalities for breast cancer with a minimum of side effects. The ability to deliver more effective breast cancer therapeutics with reduced side effects has countless benefits to the individual citizens of the State, to their families, and to the overall impact wherein recurrent breast cancer severely compromises productivity and is a continuing and costly burden on the health care system.

Impact on Health of Pennsylvanians

Breast cancer is a significant health issue, affecting nearly 48,000 Pennsylvanians every year and approximately 2,096 women and men are expected to have died from breast cancer in 2006. Although surgical and pharmacological regimens have significantly improved patient survival and quality-of-life, breast cancer remains the third leading causes of death in the Pennsylvania, following lung and colon cancer (Pennsylvania Department of Health). The impact of novel treatment modalities for breast cancer would be a decrease in the mortality of Pennsylvania citizens from breast cancer.

A major objective of the proposed studies would be the development of new treatment modalities for breast cancer through the work of new and established Centers of Excellence within the state of Pennsylvania which will lead to new investigators and grant applications. Importantly, this effort will yield new partnerships and entrepreneurial opportunities that will help build the State's workforce as well as alleviate a serious debilitating impediment to comfort and productivity.

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Health Research Priority Title and Description

Monocytes and macrophages in lupus nephritis

Systemic lupus erythematosus (lupus) affects predominantly women in their peak wage-earning years. African American women are affected more than Caucasian women but in all cases the peak age of onset is 20-35 years of age. Ten percent of cases begin in childhood and a similar number of cases develop after menopause. Only 10% of cases occur in males and it tends to be older males. Therefore, the majority of cases arise in women at a time when they could be starting a family and initiating a career. Lupus can begin insidiously and is typically associated with fatigue and joint pain. Interventions for early or mild lupus include nonsteroidal anti-inflammatories. More aggressive treatments are typically reserved for significant renal disease, life threatening hematologic disease, or CNS disease. These treatments involve cyclophosphamide or other high level immune suppressive agents and these interventions are typically associated with a risk of infection and additional fatigue. Because of the risks associated with high level immune suppression, these treatments are not initiated for mild to moderate disease. Renal involvement is one of the most feared complications as it contributes to approximately half the mortality seen in lupus. The renal inflammations seen in lupus ranges from mild to severe and a macrophage dominance has been found in one study to predict poor outcome. Additional interventions are needed for lupus nephritis and understanding the role of the renal macrophage could lead to improved, targeted interventions.

Biomedical Research Questions and Hypotheses

We wish to define alterations to gene expression at two levels. Other gene expression studies in SLE have defined altered gene expression in peripheral blood mononuclear cell samples. One of the difficulties in the array studies of SLE patients has been the mixed cell population. An innovative aspect of the current application is that the monocyte has been specifically targeted. Although the monocyte has not received much attention with respect to lupus, it clearly plays an important role in atherosclerosis, which is accelerated in SLE and in renal disease, which continues to be the major source of morbidity on SLE. The second innovation of this application is that our study will pair expression arrays and histone ChIP arrays to define both the set of genes with altered expression and the set of genes with the potential for altered expression. This latter set will be identified by having altered histone modifications but RNA levels at baseline. The long term goal of this type of research is to identify novel pathways which could potentially be targeted therapeutically. By targeting the pathways which drive the histone modifications, the potential exists to re-regulate gene expression.

Clinical Research Questions and Hypotheses

The hypothesis that aberrant gene expression could be re-set to baseline is, at this point, untested. Our approach is to define the pathologic pathways which led to the altered histone modifications and target those

therapeutically in future studies. Epigenetic contributions to lupus could explain the twin discordance seen as well as the epidemiologically-defined effects of diet. Current therapeutics target immune dysregulation but are unable to re-establish a durable remission. Addressing the source of aberrant gene expression has the potential to induce a sustained disease remission. Importantly, by addressing the cause of the pathologic gene expression, this approach has the potential to cure renal disease not just temporarily tame the effects.

Health Services Research Questions and Hypotheses

Lupus nephritis represents a tractable system to investigate the epigenetic alterations to macrophages. It is anticipated that this style or approach could be beneficial in many chronic autoimmune syndromes. The concept of identifying a cure seems heretical but it may be possible once the aberrant pathways leading to dysregulated gene expression have been identified.

Impact on Health of Pennsylvanians

Lupus has unusual demographics, affecting predominantly women in their peak wage-earning years. African American women are affected more than Caucasian women. Ten percent of cases begin in childhood and a similar number of cases develop after menopause. Only 10% of cases occur in males and it tends to be older males. Therefore, the majority of cases arise at a time when the patient could be starting a family or a career. With a prevalence of approximately 1:1000, between 500,000 and 2 million people are affected, leading a significant lost number of work days and a significant burden on the health care system. SLE is one of the most common autoimmune diseases and its effects on joints, kidney, heart, and skin limit patients' ability to function in the work place.

This application proposes to identify pathways that could be therapeutically targeted in the future to reverse renal disease. The targets are pathways involved in histone modifications and these interventions have already been piloted in oncology. The concept that SLE could be treated in ways to prevent progression is new. The focus has been on improving renal outcome and mortality but now that patients are living longer, it is clear that smoldering inflammation is associated with an increased risk of atherosclerosis and quality of life studies have demonstrated that chronic symptoms are limiting job performance. For these reasons, the study of lupus is very important for CURE funding.

The goal of the research in my laboratory is to improve the health of patients with SLE. To do this will take a new strategy. The medications used today are no different than the medications used twenty years ago. There are new agents being developed recently which allow a targeted resetting of the gene expression. These agents have thus far been used primarily to treat malignancies, but the concept of utilizing the strategy of re-setting gene expression could be very powerful for autoimmune diseases in general, and for SLE specifically.

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Health Research Priority Title and Description

Food Allergy

Approximately 25% of the United States population believes that they have an allergic reaction to foods. The 2008 CDC report from Branum and Luckas indicated 1 out of 4 children have food allergies with nearly 3 million children reporting a food reaction in 2007. The prevalence of food allergies have increased 18% in the last 10 years and over 9500 hospital admission for food allergies were noted from 2004-06 making it an urgent medical need. Food allergies are the leading cause of pediatric Emergency Department Visits for acute allergic reactions. In addition, many food allergies are life-long and are potentially life-threatening making them a significant risk factor for adults. However, food reactions can vary and include life-threatening, wheezing, prolonged vomiting, or a mildly localized rash. The current diagnostic tests (prick skin tests and blood tests) have an acceptable rate of false positive and negatives and do not predict which patients. The treatment for food allergies is avoidance and preliminary trials for alternative treatments have mixed success. Therefore, there are no cure for food allergies and only avoidance. These large gaps in scientific knowledge show the strong need for an emphasis on research for food allergy.

Biomedical Research Questions and Hypotheses

Hypothesis: Genome-Wide Association analysis has the power to unveil genes and genetic factors that predispose to Food Allergies. Genome-wide association studies (GWAS) have been used to identify new genes in many other diseases including autism, diabetes, asthma and inflammatory bowel disease. It has not been used for food allergy, but provides a novel and important tool to discover new protein and protein interactions.

Question #1: Can a whole genome scan identify novel proteins or interactions that associate with Food Allergy including life threatening allergic reactions. Question #2: Will these novel proteins or protein interactions identify new pathways for diagnosis of food allergy. Question #3: Can GWAS identify novel protein or protein interactions that should be studied to develop a potential cure for food allergy?

Clinical Research Questions and Hypotheses

Hypothesis: Proteins or protein interactions identified by GWAS will lead to improved diagnostic techniques for food allergy and identify patients at risk for severe life-threatening reactions.

Question #1: Is there a way to predict which patients are at risk for different types of allergic reactions. Will the novel proteins identified by GWAS identify which patients are at risk for urticaria reactions, reactions of emesis only or the patients with acute life-threatening reaction with closure of the airway. Question #2. Will the novel proteins or their interactions identified by GWAS provide improved diagnostic techniques to allow better and improved diagnosis to prevent unnecessary food avoidance and allergic reactions. Question #3: Can GWAS

and analysis of protein interaction develop an improved approach to prevent the current increase in food allergy?

This area of research will be approximately 70% of the effort.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Food allergy affect upto 1 in 4 of children have food allergies affecting races and gender equally according to 2008 CDC data. There has been over 9500 hospital admission and 50,000 emergency department visits due to food allergies in the United States, but local Pennsylvania rates are unknown. It is a major issue in school and avoidance of food allergens in school create significant social and emotional barriers for the children with food allergies.

Children with food allergy also have a significant higher rate of asthma compared to general population (29% vs 12%) according to 2008 statistics from the CDC. This comorbidity has significant impact on pateints and health care cost in United States and Pennsylvania.

The impact on the school system is enourmous. Data from 2006 School Health Policy and Program Study indicate: over 50% of states required information on severe food or other allergies be obtained and kept in student records; over 95% of schools obtained and kept information on severe food or other allergies in student records and 45% of states provided model policies to districts or schools on severe food or other allergies. These statistics indicate the high prevalence of food allergies.

Food allergies are part of the Commonwealth of Pennsylvania Healthy People 2010 Program with objective 10-04. However, no data is available for this area indicating a need for further emphasis and research.

In conclusion, food allergies affect a large proportion of Pennsylvania residents including all races and gender. There is an increased rate in children; however, the exact numbers are unknown despite being one of the focal areas for Healthy People 2010.

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Health Research Priority Title and Description

Emerging healthcare challenges for children in foster care

Several decades of research document the increased medical and mental health needs of children in foster care. Such evidence has led to national guidelines endorsing universal screening for health and mental health conditions for these children, and the recent Fostering Connections Act now requires states to demonstrate that they are meeting the health and well-being needs of children under their supervision. As Pennsylvania seeks to confront the requirements to improve the healthcare delivery system for children in foster care, there are many challenges that will stand before them. Coordinating the care for children who frequently disrupt placements continues to be a great challenge, and uncertainty about who consents for treatment of children in foster care has led to an emerging crisis around the use of psychiatric medications by these children. This research topic area would endorse applications that seek to:

- 1) Study the impact of new healthcare delivery designs to improve the access to and quality of healthcare delivered to children in foster care;
- 2) Use existing data (and potentially data linked across systems) to evaluate emerging concerns about medication use by children; and
- 3) Through community-based participation, develop guidelines for safe and effective practice.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

Research question 1: Can coordination across public health and child welfare systems improve health and placement outcomes for children in foster care? [Hypothesis: implementing a system where the health departments assists child welfare to coordinate general medical and behavioral healthcare for children will improve access to care for children in foster care]

Research Question 2: What is the magnitude in growth of the use of psychiatric medications (and particularly antipsychotic medications) over time among children in foster care, and which children and placement settings are at greatest risk? [Hypothesis: there will be excessive variation in the use of medications by children across placement setting that can help systems identify outliers that require oversight and investigation.]

Research Question 3: Can a standardized approach to consent for treatment and oversight of medication use by children influence medication patterns among children? [Hypothesis: Guidelines will reduce overall frequency of polypharmacy and antipsychotic use among children in foster care.]

Impact on Health of Pennsylvanians

Children in foster care are among the most vulnerable of Pennsylvania's citizens. In Philadelphia alone, over 6,000 children remain in foster care, representing only 5% of the annual reports to child welfare for maltreatment each year. The challenges to coordinating the healthcare for these children have been well documented. National statistics illustrate that while 40%-80% of these children have serious behavioral problems, only about a quarter of them will receive care. For those that receive care, it remains unclear of how informed consent is obtained for treatment, particularly at a time when children are increasingly using psychiatric medications to treat disruptive symptoms. Analysis by the PolicyLab at the Children's Hospital of Philadelphia reveals, for example, that in 2004, 18% of children in foster care with Attention Deficit Disorder (1/2 of all children in foster care diagnosed with a behavioral disorder) were using three or more psychiatric medications in combination at the same time; 37% of these children were using antipsychotics.

The implication of these data is that for children in foster care, the challenges for delivering effective and safe healthcare are a double-edged sword. For many children, the issue of access to care, sharing of information with their caregivers, and principally the coordination of their healthcare with their experiences in foster care, remain a paramount issue. But, for those children who are able to access care, the issue then becomes how systems of care can ensure that treatments are safe and effective, and that the goals of treatment are aligned systemically to long-term goals for well-being.

With foster care on the national agenda following the Fostering Connections Act of 2008, this research topic area is particularly timely, as Pennsylvania will be asked to demonstrate how it is meeting the needs of these children. Aligning a research program with these requirements would be a great opportunity to inform the program improvement that will be required of Pennsylvania's public health and child welfare systems.

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Health Research Priority Title and Description

Infection, Immunity, and Cancer

Clinical and epidemiological studies suggest that infectious agents are responsible for over 15% of all malignancies worldwide, most of them being caused by viruses. Human papillomavirus (HPV)-induced cervical carcinoma is widespread amongst the general population, but the majority of virus-induced neoplasms affect smaller subpopulations. These are often immunocompromised, such as human immuno-deficiency virus (HIV)-positive individuals and elderly patients. Tumor viruses that are most prominently involved in these subpopulations are Kaposi's sarcoma-associated herpes virus (KSHV) and the newly identified Merkel cell carcinoma virus (MCV). Moreover, infection with high-risk HPV is intimately associated with anal carcinoma in HIV-positive patients. The population of Pennsylvania not only comprises of a very high proportion of residents over the age of 50, ranking number six in the nation, but also ranks sixth in the rate of HIV-positive individuals with the implication that virus-induced malignancies are a major health problem in Pennsylvania. The Molecular Virology Program at the University of Pittsburgh Cancer Institute has extensive experience in this field of research and is exceptionally well-suited to address this health research priority. Our main goals are (i) to better define how viruses cause cancer focusing on mechanisms of transformation, the host immune response and genomic instability, (ii) to develop biomarkers for diagnostic and prognostic purposes and (iii) to define novel therapeutic targets.

Biomedical Research Questions and Hypotheses

Our main goal is to address the question of how viruses cause cancer and to exploit this knowledge for novel preventive and therapeutic approaches. We will focus on several research areas to address this question. (i) What are the exact mechanisms of transformation? The identification of viral oncogenes and their mechanism of transformation will be essential to understand virus-induced carcinogenesis and the identification of therapeutic targets. (ii) What is the role of the host immune response? Because the above-mentioned virus-induced malignancies predominantly occur in the immunocompromised host, it will be imperative to dissect the host cell immune response after infection and during tumor progression. (iii) What pathways contribute to genomic instability? As most malignant tumors, virus-induced carcinomas are genomically unstable. We will therefore analyze mitotic defects as well as changes in the DNA damage response in these tumors. (iv) Which signaling pathways contribute to carcinogenesis? Tumor viruses are known to hijack the cellular signaling machinery. Hence, it will be crucial to map pathways that are aberrantly activated in virus-induced malignancies.

Clinical Research Questions and Hypotheses

Our main clinical objective is to improve patient management. Here, we will concentrate on two major areas: (i) the development of biomarkers for diagnostic and prognostic purposes and (ii) the identification of novel targets for prevention and therapeutic purposes. Diagnostic and predictive biomarkers will be instrumental to improve risk assessment and quality of life. Candidates will include molecules that have a major role in virus-induced carcinogenesis, such as viral oncogenes, members of the host immune response, regulators of the mitotic machinery or members of cellular signaling pathways (see above). Their respective value will be tested in blood or tissue samples obtained from patients. For prevention and therapy, we will focus on vaccine development and the identification of novel drug targets employing siRNA-based screens that were recently developed in the Molecular Virology Program. These will encompass libraries of genes that are pharmacologically targetable, such as kinases, phosphatases and members of the ubiquitin-proteasome system.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

The state of Pennsylvania has an exceptionally high number of older residents. 34.4% of all residents in Pennsylvania are of age 50 or older. This means that Pennsylvania ranks sixth of all states in the U.S. with a population over age 50 (Census 2007 Estimates; www.census.gov/popest/datasets.html). Moreover, Pennsylvania comprises an unproportionally high percentage of inhabitants that are seropositive for HIV and therefore likely to be immunocompromised. The total incidence of AIDS in Pennsylvania from 1980 to 2004 was 30,368 cases as reported by the HIV/AIDS Surveillance - Bureau of Epidemiology of the Pennsylvania Department of Health (www.dsf.health.state.pa.us/health/cwp/view.asp?A=171&Q=237037), and Pennsylvania ranked sixth in the United States for both cumulative AIDS cases (all ages) and new AIDS cases in 2007 (all ages; www.statehealthfacts.org, Kaiser Family Foundation).

These above-mentioned subpopulations have a significantly higher incidence for certain virus-induced malignancies, such as Kaposi's sarcoma, HPV-associated anal carcinomas and anal intraepithelial neoplasms (AIN) as well as Merkel cell carcinoma. Most importantly, because the advent of highly active antiretroviral therapy (HAART) has led to a significant increase in lifespan for HIV-infected patients, it has also led to an increase in tumor burden from AIDS-related malignancies in these individuals.

Although much progress has been made in the field of viral carcinogenesis in the recent past, many of these findings pertain to the etiology of virus-induced malignancies. It is clear that a number of major obstacles still need to be overcome. The main problems that need to be addressed involve the improvement of diagnosis and risk assessment, treatment options and quality of life. In elucidating the mechanisms of tumor formation as well as defining biomarkers and novel therapeutic targets, our research will have a major impact on patient management and quality of life especially for Pennsylvanians but also for elderly and immunocompromised patients in general.

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Health Research Priority Title and Description

Cancer Stem Cells, Drug Resistance, and Biomarker Discovery

Many of the most deadly cancers are resistant to cure with available therapies because the underlying cancer stem cells are either not eradicated or are resistant to the therapy. Greater understanding of cancer stem cells in lung, breast, prostate, colorectal, pancreas and other deadly forms of cancer can be achieved by deciphering their cancer stem cells. Genes which mark such stem cells provide robust biomarkers for more precise diagnosis and individualized therapy. This is particularly important to the diverse populations in the Commonwealth of Pennsylvania, as studies have shown disparate outcomes in cancer treatment based on gender, ethnicity, and socioeconomic status.

Biomedical Research Questions and Hypotheses

The hypotheses is that common deadly cancers are driven by cancer stem cells and that understanding the genetic and protein profiles of these stem cells will create better biomarkers and new targeted individualized therapies. Questions to be addressed include:

1. How are cancer stem cells best identified?
2. What are their genetic and protein profiles?
3. What are the best biomarkers of cancer stem cells?

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Robust biomarkers and individualized therapy based on the underlying cancer stem cells is particularly important to the diverse populations in the Commonwealth of Pennsylvania, as studies have shown disparate outcomes in cancer treatment based on gender, ethnicity, and socioeconomic status. For example, researchers at Jefferson recently indentified that the genetic profile of breast cancer in African-American women is distinct from that of Caucasian women. Furthermore, this distinction is associated with different stages at presentation and different responses to therapy.

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Health Research Priority Title and Description

The origins of adult diseases in childhood

Chronic conditions considered to be major health issues of middle age or later, such as hypertension, diabetes, dyslipidemia, and metabolic syndrome, originate in childhood. Early expression of these cardiovascular-metabolic disorders are accelerated by the childhood obesity epidemic. Little is known about 1) mechanisms underlying the early phase of these chronic conditions including gene-environmental interaction, 2) how to identify and quantify target organ injury, and 3) biomarkers of the pathogenic pathways. The Commonwealth's investment in 2005-2006 non-formula funding for obesity research was very timely and progressive. It is now clear that further progress must be made to build on this foundation. This work truly needs bench to bedside to community interactions, and impacts urban, suburban and rural citizens of the Commonwealth of Pennsylvania.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

Adult conditions originating in childhood must be studied across the health research spectrum, in biomedical labs, patient-oriented interventions, and community assessment and education. Thus there are biomedical, clinical and health services research questions. Chronic conditions considered to be major health issues of middle age or later, such as hypertension, diabetes, dyslipidemia, and metabolic syndrome can be detected in childhood. Early expression of these cardiovascular-metabolic disorders are accelerated by the childhood obesity epidemic. The hypothesis is that identifying at-risk children and adolescents will result in biomedical and behavioral interventions that reduce the likelihood of severe adult diseases. Questions are: 1) What are the underlying the early phase of these chronic conditions including gene-environmental interaction, 2) how do we identify and quantify target organ injury, and 3) What are the biomarkers of the pathogenic pathways?

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

All ethnic groups of both genders in the Commonwealth of Pennsylvania bear the burdens of hypertension, diabetes, dyslipidemia, and metabolic syndrome. Heart attacks, heart failure, strokes, kidney failure, blindness, limb ischemia and loss, and other major disorders follow. There is a major burden of productive work lost,

lives shortened, and cost to individuals and taxpayers. It is becoming clear that these conditions have their origins in childhood and adolescence in the obesity epidemic. More interdisciplinary studies are needed now to understand more about these conditions in order to prevent a tidal wave of adult chronic disease in the future. These studies have current benefits and long-term benefits for the health of Pennsylvanians.

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Health Research Priority Title and Description

Accelerating the translation of evidence into hospital practice

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. Within the “3 T’s of Translation”, this gap occurs at the third level of translation—translating clinical and epidemiological evidence into routine practice. 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. In response to regulatory and financial policies, individual 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 system change within healthcare delivery organizations. The purpose of this research priority is to stimulate collaborative research across the Commonwealth to rapidly accelerate the advancement of knowledge in implementation sciences. To advance science in this area requires the establishment of a sustainable, translational research infrastructure, coupling the clinical operations of a network of community and academic medical centers with a team of quantitative and qualitative scientists conducting innovative work in implementation sciences to improve quality and enhance patient safety.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

Research designed to improve patient safety and quality of care proceeds through three stages: describing the existing quality/safety gaps, identifying the system level factors associated with those gaps, and evaluating interventions to reduce gaps in safety and quality. Examples of questions to be addressed within each of these stages include:

- What is the frequency and clinical consequences of inadequate information exchange in the intra-hospital transfer of patients from ICU care to medical/surgical floor care? Hypothesis: inaccurate and incomplete information exchange is common and results in increased ICU readmissions, medication order errors, and increased length of hospitalization.
- What are the system-level factors associated with catheter associated infections? Hypothesis: lack of standardized catheter insertion and maintenance procedures are associated with increased risk of infection.
- Can an immediate feedback program improve quality of care for patients with in-hospital cardiac arrest? Hypothesis: Immediate (vs. delayed) feedback on cardiac arrest care can lead to improved outcomes.

Health Services Research Questions and Hypotheses

Substantial knowledge gaps currently underlie the inability of health care delivery systems to effectively and efficiently translate evidence into practice. This stands in stark contrast to models of quality improvement and system reengineering in many other industries, which have successfully linked operations with research and system-wide learning. As a result, key scientific areas of uncertainty exist in the areas of organizational behavior change, education and training, operations research, and communication. Examples of specific gaps in knowledge to be addressed include:

- The role and attributes of local physician and nurse champions in promoting organizational change to achieve quality improvement goals. Hypothesis: Local champions are critically important for implementation success.
- The tradeoffs between standardization vs. flexibility in communication tools between nurses and physicians. Hypothesis: Rigid standardization of communication tools reduces usability and reduces implementation of QI initiatives.

Impact on Health of Pennsylvanians

Taken together, preventable medical errors and the failure to deliver 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.

1. Kohn LT et al., eds. To Err Is Human. Building a Safer Health System. Washington, DC: National Academy Press, 2000.

2. McGlynn et al., The quality of health care delivered to adults in the United States. NEJM. 2003.
3. <http://www.phc4.org/reports/hai/07/reporthighlights.htm>
4. <http://www.phc4.org/reports/hpr/07/keyfindings.htm>
5. Brennan TA et al. Incidence of adverse events and negligence in hospitalized patients. NEJM 1991.

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Health Research Priority Title and Description

Substance Abuse and Addiction: Developing and Implementing Evidence-based Disease Management Treatment Models

The health research priority to be discussed is substance abuse and addiction. Over 34 million adults in this country meet diagnostic criteria for dependence on tobacco, alcohol, prescription medications and/or illicit drugs. While often thought of as a social problem, comparisons between addictions and chronic illnesses on key features such as etiology, genetic heritability, pathophysiology and response to treatment show substantial commonality. Like other chronic illnesses, the etiology and course of addictions are affected by genetic heritability, personal choice, family, and environmental factors. Many behavioral interventions and medications are effective in the treatment of addictions; though non-compliance and relapse rates are as high in addiction as in most other chronic illnesses. Like other chronic illnesses, there is presently no cure for addiction but medical treatments can provide cost-effective reductions in substance use and its attendant public health problems. This is important because according to the UN-WHO study of all chronic illnesses, addiction to alcohol was the second most disabling condition (after Major Depression) and addiction to other drugs ranked fourth. Addictions are more disabling than other chronic illnesses because of their greater prevalence and early onset (16 - 24) and because untreated addiction reduces productivity and quality of life not only for patients, but also for their loved ones. Studies show that the family members of substance abusers utilize four times more health services and typically have impaired daily functioning.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

Addiction is now widely accepted as a chronic medical illness, but it is not insured, treated or managed like other chronic illnesses. Standard addiction treatment typically involves 30 - 60 days of outpatient counseling with no medication and with relapse rates of 40 - 60% within six months. Imagine the relapse rates that would occur in diabetes or hypertension if those illnesses were treated in this acute care fashion. We hypothesize substantially better clinical outcomes among addicted individuals under a "disease management" approach that uses long-term monitoring with continuing treatment, medication adjustment, and family and other services (e.g., educational) as needed; similar to what is typically insured and provided in other chronic illnesses. Moreover, we hypothesize reduced costs of related health conditions (e.g. cirrhosis, HIV, HCV) and ER visits for addicted patients treated in a disease management approach. Some support for this hypothesis comes from a study of addicted physicians who received a disease management model of treatment (3 - 6 months of formal

treatment, followed by 3.5 years of monitoring and supports) and had 80% positive outcomes over five years (McLellan, DuPont & Skipper, 2008).

Health Services Research Questions and Hypotheses

There are numerous, research-derived, evidence-based treatments for most addictions and new evidence-based disease models of treatment are being developed; yet most programs do not use evidence-based treatments and the overall quality of available addiction treatment is suspect. Even when providers try to learn new evidence-based treatments, the level of training available usually does not teach them to provide a good quality evidence-based treatment. Worse yet, research shows that typical training methods may lead providers to believe they are implementing evidence-based treatments when they are not. Furthermore, payers, families, and affected individuals are not readily able to evaluate the quality of addiction treatment services. Can economical and effective training and certification programs be developed for evidence-based treatments? If consumers had information about treatment programs' use of and certification in these treatments would they select programs certified in them? Would programs that were certified in evidence-based treatments have better clinical outcomes? Based on treatment and training studies and on our own work with families and substance abusers, we hypothesize that the answer to all 3 questions is "yes."

Impact on Health of Pennsylvanians

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

And things are not getting better nationally. The CDC figures shown that young adults between the ages of 15 and 24 dying from drug overdoses has more than doubled between 1999 and 2005; from 849 to 2,355. While mortality is the most devastating effect of alcohol and drug abuse - there are substantially more prevalent and more costly health and social effects related to alcohol and drug abuse. Specifically, alcohol is implicated in over 60% of all emergency room and trauma center visits nationally (figures not available for PA). It is suspected that drug use is also implicated in a significant proportion of highway accidents and ER visits, but drug abuse is not as easily detected as alcohol nor as widely tested. Drug-related crimes account for over 65% of all incarcerations in state prisons in Pennsylvania; and over 50% of all re-incarcerations due to parole violations (personal accounts during Governor's Council Meeting with State Attorney General - April, 2008). Fully seventy percent of all foster children nationally (figures not available from Pennsylvania) have been placed into foster care due to drug and alcohol related parental rights restrictions. Finally, the UN-WHO commissioned a study of all chronic illnesses and found that addiction to alcohol was the second most disabling condition and addiction to other drugs ranked fourth. Addictions are more disabling than other common chronic illnesses because of its greater prevalence, because it begins in early life (16 - 24); and because untreated addiction reduces productivity and quality of life for patients and for those around them. Studies indicate that the family members of substance abusers utilize four times more health services (Langenbucher, 1994) and often have impaired daily functioning (Hudson et al., 2002).

As recently as June 18, 2008 a New York Times editorial commented on the lack of addiction treatment - particularly for young people "...fewer than 1 in 10 American adolescents who need drug treatment get it, according to the Substance Abuse and Mental Health Services Administration. This threatens their health and well being."

Family members are often distressed about the adolescent or young adult's substance use long before the substance user realizes they have a problem. Family members are usually desperate to find help to deal with the

young person and their problems, but little help is available. Several evidence-based family treatments have been developed to help families encourage substance abusers to enter treatment, to stay in treatment, and to improve treatment outcomes (e.g., Fals-Stewart et al., 2005; Kirby et al., 1999; Meyers et al., 2002; O'Farrell et al., 2008). These types of treatments could have positive health impacts on adolescent and young substance abusers and their families.

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Health Research Priority Title and Description

Chronic and Latent Virus Infection: Pathology and Treatment

Chronic virus infection is responsible for ~17% of all human cancer, and contributes to a variety of immunological disorders, including rheumatoid arthritis, lupus erythematosus, and multiple sclerosis. New viruses continue to emerge through rapid evolution or by facilitated modes of transmission. In addition, new viruses are being discovered and linked to human disease through improved methods of detection, sequencing, and genomic analysis. Significant advancements are needed in the methods of virus detection, as well as a better understanding of viral infection, pathogenesis, and host-immunity. This information is necessary for the development of novel anti-viral pharmaceuticals and biologicals, as well as traditional and non-traditional vaccine strategies. We propose a new State Initiative to focus on the role of chronic and latent infections in human disease. This initiative will support (a) research focused on the identification of novel or previously undetected virus agents in cancer and auto-immune disease settings; and (b) basic research aimed at understanding the mechanism of long-term viral persistence, latency, and reactivation, including the role of life-related stress in the reactivation process. This initiative will also promote a deeper understanding of the interaction of chronic viral infection on the immune system. This initiative will support efforts directed at the eradication of latent infection through either small molecule inhibitors or vaccine strategies. The overall goal of this will be to reduce the burden of viral infection on human health.

Biomedical Research Questions and Hypotheses

Chronic viral infections, such as hepatitis B/C, human papillomavirus, and Epstein-Barr virus lead to a number of cancers that are highly elevated in ageing and immunocompromised populations. Evidence suggests that immune cell function is compromised in viral-associated cancers due to environmental cofactors, genetic predisposition, T-cell exhaustion, or viral-induced immune dysfunction. We propose a study of virus biology, immunological responses to viral infection, and tumor-microenvironment interactions in the context of chronic infection. The hypotheses to be tested include (1) whether chronic exposure to viral antigens induces exhaustion of viral-specific T-cells response, (2) whether virus encoded factors promote immune tolerance through negative T-cell regulatory pathways including Tregs, HVEM, and PD1, and (3) whether environmental cofactors associated with local inflammatory response alter immune regulation of viral infected pre-cancerous cells. We also propose to develop antiviral strategies, including small molecule inhibitors of key viral and cellular regulatory pathways, and the development of anti-viral therapeutic vaccines designed to overcome the negative regulatory arms of the immune response.

Clinical Research Questions and Hypotheses

Chronic viral infections are known to cause several human cancers and are suspected of causing a variety of immunological disorders. New methods of virus identification, detection, and characterization have enhanced

our ability to connect viruses to specific disease states. We hypothesize that previously uncharacterized virus-associated diseases exist and will be identified using high-throughput sequencing methods. We propose to establish a network of clinical and basic researchers who will use human tissue samples to identify viral markers associated with specific diseases using the most sophisticated gene sequencing and genomic technologies.

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

Chronic viral infections are responsible for a large number of cancers in humans, including cervical and head and neck cancers (HPV); liver cancer (Hepatitis B and C); central nervous system lymphoma, non-Hodgkins lymphoma, and Hodgkins lymphoma (Epstein-Barr virus). In addition, chronic viral infections are suspected of causing immunological disorders such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. As with many diseases, minorities are disproportionately affected by these diseases. Although a vaccine against HPV is now available, there are many women who were exposed to the virus prior to the development of the vaccine; and it will be many decades before HPV infection will be largely eliminated in the population. It is essential that we continue to search for therapies to treat HPV.

Evidence suggests that normal immune cell function is compromised in viral-associated cancers due to genetic predisposition (e.g., X-linked lymphoproliferative diseases), environmental cofactors (e.g., chronic inflammation, alcohol, tobacco), T-cell exhaustion (e.g., HIV/AIDS), or viral-induced immune dysfunction (e.g., Castleman's disease). Elucidating the molecular mechanisms by which latent viral infections induce cancer and compromise the human immune system will lead to the development of new therapies, including small molecules (drugs) and immune-based therapies (vaccines and antibodies), for the treatment of chronic viral infections.

The development of new therapies to eradicate latent viral infection in humans will serve the needs of all Pennsylvanians; these infections strike regardless of socio-economic status.

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Health Research Priority Title and Description

Cancer Pain Management

Pain is one of the most frequent and often most feared symptoms in patients diagnosed with cancer. The prevalence of cancer pain remains unacceptably high and, in many cases, is unremitting and unresponsive to treatment with existing pharmacological therapies. Breast, lung and prostate cancers account for approximately 80% of all bone metastases and over half of all metastatic cancers will be associated with pain. Often, chemotherapeutic treatments produce neuropathic pain that persists once treatment has been discontinued. Chemotherapeutic-induced neuropathies are often limiting factors in cancer treatment and preclude a patient's ability to tolerate higher - and potentially more effective - doses. There is a need for systematic epidemiological studies incorporating the powerful tools of bioinformatics and health informatics to examine potential biomarkers and outcomes in patients with regard to the type of cancer pain, the type of treatment for the cancer, as well as the effectiveness and duration of treatment for the cancer-related pain. Additionally, there is a corresponding need for the development and integration of animal models of cancer pain to parallel this clinical assessment to evaluate of emerging novel drug targets that compare current treatments and evaluate the effectiveness of new drugs for cancer pain management. A combination of the powerful tools and expertise available within the Pennsylvania biomedical research community promises many novel opportunities for developing new treatment approaches to cancer pain.

Biomedical Research Questions and Hypotheses

The emphasis of this recommendation is to pursue a bold, comprehensive, and integrated approach to cancer pain management. The fundamental tenet behind this proposal is that there is a pressing need for multiple approaches within the biomedical community to be directed towards developing a better understanding of cancer pain syndromes, current treatment methods, and innovative model systems that will generate new hypotheses designed to discover and provide better treatments for this significant unmet need. The research would focus on the following questions: i) how closely aligned are the current animal models to the pathophysiology and progression of the disease in humans; ii) what animal models provide the opportunity to evaluate current therapeutic approaches to different types of cancer pain (e.g., metastatic bone cancer, chemotherapy-induced neuropathic pain); iii) what are the new targets to be evaluated for the treatment of cancer pain; iv) is there a relationship between cancer progression and pain therapy; and v) can newer animal models be used to identify and evaluate new molecular targets and compounds with a view to providing more effective treatments that are devoid of the side effects that occur with existing therapies?

Clinical Research Questions and Hypotheses

A major emphasis of this research would be to employ and align the powerful methods of clinical and epidemiological assessment of cancer pain and treatment with the pharmacological research efforts to better understand and treat cancer pain. Epidemiological studies will address the following questions: i) what are the current treatment approaches and outcomes assessments for different types of cancer pain, modalities and efficacy of treatment; ii) what are the major liabilities and shortcomings of current approaches to the management of cancer pain and where are there the greatest unmet needs; iii) are there valid and reliable biomarkers that can distinguish responders from non-responders to various pain therapy approaches among different cancer populations; iv) can these methods predict side-effect profiles, the development of tolerance, and other characteristics that might also inform basic research studies and be useful in the identification of new targets; and v) can these biomarkers be used as translational tools to inform the use of animal models to better predict efficacy and side-effect profiles that would permit more rapid introduction and assessment of new therapeutics into the clinic?

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

The Pennsylvania Department of Health has estimated that over 70,000 Pennsylvanians would be diagnosed with cancer in 2008, with over 28,000 patients expected to die in cancer-related deaths (Pennsylvania Cancer Registry, Bureau of Health Statistics and Research, Department of Health). This report also indicates that between 1995 and 2005, the annual age-adjusted cancer mortality rates in Pennsylvania were consistently higher than comparable U.S. mortality rates. It is estimated that on average, an estimated 97 male residents were expected to be diagnosed with invasive cancer each day during 2008; for females this figure is 96. The majority of these patients will have cancer-related pain that is directly related to the cancer or is associated with the chemotherapy used to treat the cancer. Pain is often most severe and intractable at the end of life for these patients.

A major objective of this proposed approach would consist of a systematic and careful epidemiological assessment of cancer pain within the State of Pennsylvania. The plan is to utilize the combined strengths of epidemiology, the tools of contemporary biomedical science, such as bioinformatics and health informatics, together with the discipline of pharmacology to develop a thorough characterization of cancer pain within the State and to integrate this information into a basic research program. The research program will be based within the Department of Pharmacology, College of Medicine at Drexel University and will be strongly aligned with the School of Public Health. This effort to address the impact of cancer pain on the health of Pennsylvanians will not only provide a rigorous evaluation of the current approaches to the treatment of cancer pain with a view towards delineation of optimal treatment strategies, but will also serve as a platform to identify newer, more effective treatments. A longer-term goal of this proposal is to seek partnership with pharmaceutical companies in the Philadelphia area and the State to establish the infrastructure for drug discovery and development to address this critical unmet need. These efforts will yield new discoveries, new tools for clinical assessment and prescribed therapies, as well as new investigators and grant applications. Importantly, it will provide a detailed analysis of cancer pain and treatment approaches within the State of Pennsylvania designed ultimately to provide more effective cancer pain management for its citizens. Furthermore, this effort will potentially yield new partnerships and entrepreneurial opportunities that will help build the State's workforce as well as alleviate a serious debilitating impediment to comfort at a time when the major focus should be on cancer treatment not associated pain.

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Health Research Priority Title and Description

Cancer & Nano-biotechnology Detection and Targeted Treatment

In Pennsylvania alone over 70,000 cases of invasive cancer are diagnosed each year and over 28,000 deaths are attributed to cancer, according to the American Cancer Society. The last 20 years has seen reduced mortality for cardiovascular disease, but similar advances have not been made with cancer. The relatively poor outcomes of several cancers illustrate a need for improved methods of early detection and of targeted treatments. Both the National Institute of Health Roadmap and the Alliance for Nanotechnology in Cancer have pointed to the important role that nano-biotechnology can play.

Nano-biotechnology holds the promise to advance cancer outcomes by enabling new strategies for examining basic mechanisms of protein and cellular function associated with disease, and developing novel diagnostic and therapeutic technologies. The state's universities and medical schools, in conjunction with nationally recognized nanotechnology centers position Pennsylvania as a leader with unique capabilities in this arena. As such, a multi-disciplinary collaborative program is required to address specific technical issues that limit implementation of these strategies to a broader range of cancers.

Biomedical Research Questions and Hypotheses

Biomolecular recognition is a process with two sided function. It is the basis of targeting and can be used for focused chemotherapy of cancer tumors and enhanced imaging for early detection. On the other hand it is the basis of sensing biomarkers for cancer diagnostics. Combining biomarker detection and microfluidic technology yields a device for early screening of oral cancer. What is the range of biomarkers that can be implemented in these strategies so that it can be applied to other cancers?

Nanoparticles can be functionalized to exhibit molecular recognition of specific protein targets leading to targeted drug delivery and imaging detection strategies. What are the limits to and guiding principles for extending this approach to include a wider range of biomarkers?

Protein interactions are prime disease indicators. New tools allow protein motility to be quantified and protein mapping and characterization on a scale necessary to direct biomarker development.

Clinical Research Questions and Hypotheses

As the number of medical and non medical devices that incorporate structures increases, the potential for exposure to the population in general increases. While some nanoparticles have been shown to be non toxic, for many cases the toxicological impact is not known. A recent study by the Wilson Center pointed to the need for much more research in this area. Critical research questions include:

Under what conditions do structures pose a toxicity hazard?
Are the outcomes of exposure cancer related disease?
Are manufacturers and/or clinicians at risk of exposure if current protocols are followed?
What strategies for exposure prevention should be implemented?

Health Services Research Questions and Hypotheses

None

Impact on Health of Pennsylvanians

As noted above cancer is a health issue that impacts a large number in Pennsylvania and the same is true nationally. In many cases the relatively poor outcomes in terms of survival would be mediated by improved methods of early detection and of targeted treatments.

Outcomes of this research initiative will include:

Enhanced understanding of the effect of disease on protein interactions

A strategy for automated, rapid detection and molecular analysis of cancers in a miniaturized format suitable for use in the clinic and/or the operating room.

A suite of functionalized nanostructures for molecular recognition at tumors.

Understanding of toxicology of nanostructure.

The application of these concepts to early detection and treatment will increase positive treatment outcomes and patient quality of life in Pennsylvania as well as the nation..

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Health Research Priority Title and Description

Improving Medicaid Retention: A Health Literacy Focus

As noted in Healthy People 2010, creating a stable child health insurance system has been one of the most intractable challenges in American health policy that contributes to persistent child health disparities. Despite recent efforts, one-quarter to one-third of Medicaid-eligible children are disenrolled in any given year. Furthermore, studies have shown that two-thirds of the nation's uninsured children are eligible for Medicaid or SCHIP and, in 2006, one-third of uninsured children had been enrolled in one of these programs during the previous 12 months. Continuous insurance coverage is particularly important for children because they require regular health supervision visits to attain optimal health and developmental outcomes. In adults, studies have shown that low health literacy results in inadequate engagement in, and benefit from, health care advances and that low health literacy is likely a major contributor to adverse health outcomes. Given that low health literacy affects more than 90 million American adults (~20% of the adult population), many children have caregivers with inadequate health literacy. As the wording used in many states' Medicaid applications and informational documents score well above a fifth grade level on literacy tests, caregivers with low health literacy may not fully understand renewal instructions for these programs and this may lead to lapses in insurance coverage for their children. These lapses may lead to delays in obtaining care, such as immunizations, health supervision visits, and developmental evaluations.

Biomedical Research Questions and Hypotheses

None

Clinical Research Questions and Hypotheses

None

Health Services Research Questions and Hypotheses

H1. Parents/caregivers with low levels of health literacy will express greater difficulties navigating the Medicaid application and renewal process than those with high levels of health literacy.

H2. Parents/caregivers with low levels of health literacy will have children with lower Medicaid retention rates than those with high levels of health literacy.

H3. Parents/caregivers from racial/ethnic minorities will have children with lower Medicaid retention rates than those from other groups.

Impact on Health of Pennsylvanians

As of May 2009, the Pennsylvania Department of Public Welfare reported approximately 933,000 Medicaid eligible children living in the state of Pennsylvania. There is clear evidence that participation in specific public programs, such as Medicaid, leads to positive child health outcomes. Many reports have documented that uninsured children are more likely to have adverse health outcomes, such as delayed immunizations, inadequate health care utilization, and increased risk of hospitalization for ambulatory care sensitive conditions. Recently, attention has been focused on the consequences of discontinuous coverage for children and there is evidence that gaps in coverage lead to delays in medical care for children, including preventive visits, and unfilled prescriptions. Dr. Pati's ongoing review of Medicaid retention rates among children in all 50 states found that 27.8% of children receiving Medicaid in Pennsylvania experienced at least one gap in coverage in the two year period from 2001-2002. Based on these results, we propose focusing research on improving Medicaid retention through literacy-related interventions.

We propose research focused on literacy because prior studies have identified literacy-related barriers as noteworthy contributors to low child retention rates in Medicaid. Despite the body of literature discussing this correlation and the existence of health literacy guidelines for Medicaid applications in 45 states, to our knowledge, no research has been done to assess the impact of health literacy focused interventions designed to improve retention in Medicaid. According to a survey administered by Health Literacy Innovations, Pennsylvania has a 4th grade reading level guideline for state Medicaid information. However, the current Medicaid application scores well above the 4th grade reading level on available literacy tests. This is particularly relevant in light of Dr. Pati's recent study involving 717 primarily African-American single mothers living in medically underserved areas of Philadelphia which found that ~20% of these mothers had inadequate or marginal health literacy as measured by administration of the S-TOFHLA.

Several overriding trends regarding participant characteristics and persistent under-enrollment in public health insurance programs have been documented in numerous reports. These reports have consistently demonstrated that low-income, racial and ethnic minorities, young and single mothers, and mothers who have not completed high school are more likely to participate in these programs than high-income, white, older, married mothers who completed high school. Similar characteristics have been identified in relation to patterns of retention. However, the likelihood of dropping out of Medicaid while remaining eligible for coverage has proven more difficult to predict. A review of the Survey of Income and Program Participation (SIPP) concluded that white children, children from two-parent families, children in families with incomes between 100-200% of poverty and children with a full-time working parent were proportionally more highly represented among the population of eligible uninsured children than in the population covered by Medicaid. Though under-enrollment is difficult to estimate, reports estimate that, nationally, approximately 24%-45% of uninsured children are eligible for Medicaid and that 65-83% of Medicaid-eligible children participate. Other reports have documented that approximately one-quarter to one-third of Medicaid-eligible children are disenrolled in any given year. The findings from this research may provide critical data for the implementation of sustainable interventions to improve child Medicaid retention and, ultimately, reduce disparities in child health outcomes for the approximately 25% of Pennsylvania's children who receive Medicaid.

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Health Research Priority Title and Description

Pediatric Advanced, Palliative, and Hospice Care

Each year in Pennsylvania, approximately 2000 infants and children die. While approximately half of these children die from acute or preventable conditions, the other half live with life-threatening complex chronic conditions for months or years before dying. While the parents and siblings of all of these children could benefit from bereavement services, those children in the second group may especially benefit from pediatric advanced care, including palliative and hospice care. As recently detailed in a PA taskforce report (sponsored by the Department of Public Welfare; www.dpw.state.pa.us/About/Secretary/PPHC/), these children and families face daunting challenges and vast unmet needs, ranging from support regarding medical decisionmaking through to pharmacological management of pain and symptoms. Pediatric advanced care for children with life-threatening complex chronic conditions, including palliative and hospice care, aims to improve quality of life for the child and help the family (including siblings) with the challenges they confront. As medical technology and advancements in health care enable more infants and children to survive what previously would have been quickly fatal conditions, the priority of meeting the needs of these children and their family steadily mounts, as does the need to assure access to high quality pediatric advanced care to all children, including those from different cultural backgrounds and with different languages.

Biomedical Research Questions and Hypotheses

1. What basic biologic difference account for differences among patients with regard to opioid effects and side effects? Patients exhibit different responses to opioid analgesics, with some patients having symptomatic relief on a dose that to another patient brings no relief, and to another comparable patient is a dose large enough to induce stupor. Our hypothesis is that this variation in response to opioids (and the associated opioid-related side effects) can be explained by 2 primary forms of genetic variation, specifically splice variant mu-opioid receptors or to single nucleotide genetic polymorphisms. Knowledge regarding the existance and size of this effect would enable us to tailor analgesic therapy to individual patients more effectively.

Clinical Research Questions and Hypotheses

1. How to best support medical decisionmaking by parents on behalf of an infant or child with a life-threatening complex chronic condition? The standard approach to date has emphasized the cognitive aspects of decisionmaking, specifically in terms of informed consent regarding the risks and benefits of proposed medical interventions. We hypothesize, based on preliminary data from a prospective cohort study, that parental emotion (positive and negative affect) are strong determinants of subsequent medical decisions, above and beyond the impact of clinical risk/benefit information. Knowledge regarding the impact of emotions on medical decisionmaking would enable better forms of decision support to be developed.

2. What are the best modes of support for siblings of pediatric patients living with life-threatening complex chronic conditions? We hypothesize that a "strengths-based" approach to helping siblings adapt to the challenges that they confront will result in lower levels of psycho-social-educational distress. Knowledge of best practices in this realm would help parents and teachers to better help these siblings.

Health Services Research Questions and Hypotheses

1. What are the impacts, medically and financially, of pediatric palliative and hospice care on children with life-threatening complex chronic conditions and their families? We hypothesize that children receiving these services live as long as matched patients (ie, with similar conditions and stages of illness) who do not, and experience less suffering and higher satisfaction with care, at reduced or comparable costs. Knowledge regarding these impacts would improve counseling provided to individual families as well as planning for the health care system and payers in terms of funding levels of various services.

2. What is the most effective method to teach health care providers to delivery "bad news" to parents and to partner with parents in the care of their children with life-threatening complex chronic conditions? We hypothesize that an approach built around principles of "collaborative communication" and "partnering leadership" will results in greater statisfaction of parents (and of health care providers as well). Knowledge regarding the most effective techniques would improve the education and training of healthcare professionals and benefit children and parents throughout the Commonwealth.

Impact on Health of Pennsylvanians

As mentioned above, 2000 pediatric patients die each year in Pennsylvania; countless more live on with life-threatening conditions (accurate population-level statistics regarding the prevalence of these conditions is lacking). For these infants and children, and their families, inadequate palliative and hospice care has at least 7 levels of negative repercussions (as was documented time and again in the taskforce report cited above):

1. Parents often face some of the most challenging decisions that one could ever imagine alone, without adequate support to think through what mode of care is in a child's best interest, and to sort out one's feelings about what is the best way to be a good parent for a child. Parents are often told 'bad news' about their children's diagnoses or prognoses in ways that are insensitive and hurtful. Parents too often feel that they must navigate through the medical system on their own, coordinating care as best they can, and advocating for the care of their child and not just the treatment of a disease.
2. Children often do not receive optimal management, and relief from, pain and other terrible symptoms (data from studies of children with cancer suggest that more than 2/3rd of patients were in excessive amounts of pain during the last week of their lives, along with a host of other symptoms).
3. Because decisionmaking is not adequately supported, some children receive extreme forms of medical intervention that can cause harm and suffering when unsuccessful.
4. The forementioned problems all result in depriving children and families from experiencing a higher qualitative of life for the weeks, months, or even years that they may live with the life-threatening condition (this point is worth underscoring: the average life-expectancy of pediatric patients who received a palliative care consultation in a study of 6 pediatric palliative care programs was in excess of a year).
5. Many families are tasked with providing home care that entail a vast amount of work, on a ceaseless 24/7/365 schedule, resulting in a parent devoting herself/himself entirely to the care of the child, leaving the employed workforce, and creating further financial hardships for the family, which likely also has to content with medical bills and out-of-pocket healthcare expenses.
6. Meanwhile, the siblings of these ill children (and more than half of the children receiving palliative care do have sisters or brothers) are often relegated to the status of an afterthought, as all the attention and time of the parents are poured into the care of the ill child, and no systematic attempt is made to address the psychological needs of the sibling.
7. At the same time as children and families are suffering for want of a better system of care, healthcare providers (the vast majority of whom want to do the right thing for these children) are also suffering, unsure of how to bring comfort to the child or sound and supportive counsel to the parents (an uncertainty that has been well documented among pediatricians, nurses, and others involved in the care of children repeatedly), in need of better education and wider dissemination of best clinical practices regarding the care of children with life-threatening complex chronic conditions and their families.

Pediatric advanced, palliative, and hospice care are not panaceas that will completely solve all of the above-mentioned problems, but they are necessary ingredients for any clinically effective and ethically sound solution. Two other attributes of the situation also need mention: First, we know from what limited research has been conducted regarding disparities in pediatric palliative care that cultural differences and language barriers are formidable challenges to providing outstanding care for children with life-threatening conditions. Second, while we do not want clinical decision-making for these children to be unduly influenced by financial considerations, we acknowledge the not only the deleterious repercussions on the families (as noted above), but also the economic impact on the Commonwealth of parents' who must leave the workforce, and on the system of public health insurance that underwrites much of the medical care.

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Health Research Priority Title and Description

Closed-Loop Controlled Breathing Assist Device Development and Application

Respiratory insufficiency may result from a variety of neurological and/or developmental conditions including spinal cord injury, central apnea, SIDS, and stroke. These conditions cause a loss of proper activation of the breathing muscles and reduce gas exchange. Treatment often includes mechanical ventilation, which causes an array of problems including pulmonary infections (e.g., pneumonia), and for this reason clinicians endeavor to wean patients off artificial ventilators. We propose to alleviate respiratory insufficiencies directly by developing a closed-loop (feedback controlled) system that will drive diaphragmatic muscle contraction via electrical stimulation of the phrenic nerves. In our initial construct, phrenic nerve stimulation parameters will be modified on-the-fly by blood oxygenation (measured transdermally), and eventually by pulmonary stretch receptor activity measured in the cervical vagus nerve. The device will be developed via a combination of basic science research and clinical application across four major biomedical institutions in Philadelphia, each with significant research and clinical investment in this area, where patient populations are readily available, and where an existing, rudimentary phrenic pacing device is in use. By leveraging the combined expertise of biomedical scientists/engineers, physicians and rehabilitation specialists, our goal is to quantifiably reduce both patient suffering and health care costs via re-training the key neuromuscular components of breathing.

Biomedical Research Questions and Hypotheses

Respiratory rhythm is produced primarily in the brain stem, which activates motor neuron pools in stereotypical patters. Respiratory arrhythmias/cessation (e.g., central apnea) or weakened motor drive (e.g., in SIDS, ALS, or from stroke or spinal cord injury) inevitably produce ventilatory insufficiencies, and hence the need for assist devices such as artificial positive-pressure ventilators. Recently, direct activation of the diaphragm via electrical pacing of the phrenic nerve has demonstrated that ventilatory insufficiencies can be markedly reduced without the use of artificial ventilation. However, existing phrenic pacemakers have no feedback control; the parameters are set and cannot respond to alterations in metabolic demand (e.g., sleep vs. waking, quiet rest vs. physical exertion). Thus, we ask, "Can an integrated phrenic stimulator that includes feedback control be created and control breathing in animals with diminished respiratory function?" Respiratory neuroengineers and neurophysiologists at Drexel University College of Medicine (Drs. Rogers, Rybak, Nissanov, Murray, Fischer) will develop a new generation of phrenic pacemakers in conjunction with a local manufacturer, and test this system in animals.

Clinical Research Questions and Hypotheses

Upon successful fabrication of a feedback-controlled phrenic stimulator, patient populations will be selected at Shriners Hospital for Children (Drs. Betz, Selzer), and at Thomas Jefferson University Hospital (Drs. Harrop, Sharan). Patients will be implanted with phrenic stimulator systems equipped with feedback control modules. Rehabilitation progress will be evaluated via standard physical (e.g., maximum inspiratory pressure, forced vital capacity) and physiological measures (e.g., nocturnal oxymetry, arterial blood gases), providing an answer to the central question, "Do patients with feedback-controlled pacemakers recover more completely and rapidly than those with standard phrenic stimulators and than those with no stimulators?" In two separate clinical trials, outcomes from multiple subgroups based on underlying causes of respiratory insufficiency including spinal cord injury, stroke, central apnea, and general autonomic dysfunction, will be evaluated in order to identify the groups most responsive to phrenic stimulation.

Health Services Research Questions and Hypotheses

Analyses of cost savings will be performed by administrators at the Shriner's and TJU health care systems. Recovery time and degree, need for additional therapies, and health care provider man-hours will be quantified in order to evaluate the hypothesis that "phrenic stimulation with feedback control reduces the burden of healthcare costs to the Commonwealth of Pennsylvania," in addition to improving health outcomes.

Impact on Health of Pennsylvanians

POPULATION: Respiratory insufficiencies or failures are caused by a multitude of diseases, injuries, and conditions, and therefore affect a diverse array of Pennsylvanians, and some more than others. For example, African-Americans are several times more likely to have traumatic spinal cord injuries than whites. The elderly, who represent a substantial fraction of Pennsylvanians, are more susceptible to stroke and post-polio syndrome. Neonates experience SIDS, central apnea, and respiratory distress syndrome, and among them poor and minority babies are affected at higher rates than other classes and races. A study conducted in 2001 reported that 18 of every 1,000 live births required mechanical ventilation, and the incidence was higher in boys than girls (20 vs. 15.6) and in African-Americans (29), with a fatality rate of 11.1% (higher in minority groups). Many spinal cord injured (SCI) patients experience respiratory insufficiencies. Ventilator-related diseases, specifically pneumonia, cause 19% of the deaths within the first year of injury, and 13% of those after the first year. In addition, SCI patients are 10 times more likely to experience sleep apnea than individuals without SCI. 67% of acute SCI patients experience respiratory complications (atelectasis 36%, pneumonia 31%, respiratory failure 22.6%), with an increased prevalence with age, level of injury, and completeness of injury.

COSTS: In neonates, the mean hospital stay and costs were 31.1 days and \$51,000 (2001 figures) for those requiring mechanical ventilation. In the US in 2001, there were 8500 deaths (of 80,000 hospitalizations), with total hospital costs of \$4.4 billion, and ventilator use in neonates is only approximately one-fifth that of adults. Other studies found that 55% of mechanical ventilation-dependent patients experience pulmonary complications requiring 22 days of hospitalization per year, with a 3-year mortality rate of 37%. First year expenses for paraplegics and quadriplegics were \$152,000 and \$417,000, while average lifetime costs for paraplegics and quadriplegics were \$428,000 and \$1.35 million, respectively (2002). 52% of SCI individuals were covered by private insurance, and 63% of them were unemployed.

APPROACH: Since the diaphragm produces 65% of vital capacity (air movement), its activation has the largest impact on restoration of normal breathing. Electrical activation of the phrenic nerves causes diaphragmatic contractions.

INSTITUTIONAL STRENGTHS: Drexel University College of Medicine has one of the premier groups of spinal cord injury research and the only center of its kind in the Commonwealth of Pennsylvania. This group, centered in the Department of Neurobiology and Anatomy, is in a unique position to provide the leadership required in developing an inter-disciplinary and inter-institutional approach that combines the needed basic respiratory neuroscience and clinical expertise required for phrenic stimulator development. The members of this group have acquired a broad expertise from 20 years of research that includes the use of cell

transplantation, gene therapy, pharmacological interventions, physiological analysis and behavioral assessment of functional recovery. The Spinal Cord Center has core facilities, primary and affiliated faculty members and a research portfolio of over \$10 million. In addition, Drexel University already has a joint Neuroengineering program between the School of Biomedical Engineering and the College of Medicine, which is directed at collaborative research projects and educational programs at both schools. Shriners Hospital has recently made significant investment in clinical research, and Dr. Selzer is leading an effort to treat SCI, and other mechanical ventilation-dependent, children. Thomas Jefferson University is the location of one of only 16 Spinal Cord Injury Centers in the United States, as designated by the National Institute on Disability and Rehabilitation Research. In addition, a manufacturer of phrenic stimulators (Synapse Biomedical, Inc.) operates centers in both TJU and Shriners.

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Health Research Priority Title and Description

Translation of genomics into clinical practice

Advances in genomics have the potential to improve the delivery of health care by targeting interventions to individuals who will receive the greatest benefit and experience the lowest risk of adverse events. The promise of this approach, often termed personalized medicine, for improving health outcomes is widely recognized. Perhaps less well recognized is that more effective targeting of interventions will also reduce health care costs, a critically important goal for the US economy today. Because of this promise, the nation has invested billions of dollars in the sequencing of the human genome and the identification of genetic markers for disease and disease outcomes. However, this investment is currently at risk because of a lack of information about how to translate these discoveries into clinical practice. The number of potential tests is overwhelming but knowledge about how to use these tests is almost non-existent. Without evidence to guide the use of these tests, genomics risks becoming another example of a new technology that increases health care costs without improving the health of the US population. We propose to develop a multidisciplinary initiative to generate the evidence needed to ensure the effective translation of genomic tests into improvements in disease prevention and treatment. This initiative will focus on the use of genomics in cancer because of the significant cancer burden in Pennsylvanians and the potential for genomics to transform cancer prevention, diagnosis and treatment in the immediate future.

Biomedical Research Questions and Hypotheses

This initiative builds upon basic science discoveries in genomics to answer research questions about how these discoveries should be used in clinical practice to improve health outcomes and increase health care value. However, the results of these studies will also increase understanding of the mechanisms linking genetic markers to outcomes, thereby informing the basic biomedical research in cancer. For example, one of the areas of investigation is the use of EGFR/KRAS testing to determine treatment for non small cell lung cancer (NSCLC). This testing has the potential to target treatment and improve outcomes in a disease where 5 year survival is currently under 20%. Studying the use of personalized therapy in NSCLC will provide important evidence about how to improve outcomes in this disease today but will also provide insight into the mechanisms by which EGFR and KRAS influence cancer initiation and progression, thereby supporting the development of new therapies that may improve disease outcomes in the future.

Clinical Research Questions and Hypotheses

The initiative will answer important clinical questions about the use of personalized and genomic strategies to improve outcomes of cancer prevention, treatment and survivorship. These questions fall into three main areas: (1) whether pharmacogenetic testing can improve treatment effectiveness and reduce treatment related side effects; (2) whether genomic risk panels (i.e. SNPs) can be used to improve the accuracy of cancer screening to

reduce the risk of false positive and false negative tests; (3) whether tests of somatic genetic changes in tumors can be used to tailor cancer treatment to improve treatment effectiveness and reduce treatment related side effects; and (4) whether genetic tests for cancer susceptibility can improve adherence to cancer prevention behaviors and interventions among high risk individuals. For each of these areas, there are novel genomic strategies that need to be tested in multiple different cancer types, including breast, colorectal, lung, melanoma, prostate and leukemia.

Health Services Research Questions and Hypotheses

This initiative will also address important health services research questions about the cost-effectiveness of personalized and genomic strategies. These questions include the relative value of different strategies (i.e. how much benefit is achieved at what cost) and whether the use of personalized and genomic strategies save health care dollars by reducing utilization of unnecessary and often highly expensive therapies (e.g. adjuvant chemotherapy in a patient who has an extremely low risk of recurrence). Given the current economic climate and the economic burden created by rising health care costs, understanding the value of these new technologies and how they impact the cost of prevention and treatment is necessary to inform effective health policy in Pennsylvania. Furthermore, by providing evidence to support the development of policy in these areas, these research questions help to reduce disparities in access created by uneven insurance coverage policies or inadequate investment in the delivery systems for high value interventions.

Impact on Health of Pennsylvanians

The potential impact of genomics on cancer prevention, diagnosis, treatment and survivorship in Pennsylvanians is staggering. In 2006, 73,895 Pennsylvanians were diagnosed with invasive cancer and 28,955 died from their disease. Cancer is the second leading cause of death among Pennsylvanians. The burden of cancer is particularly great among minority populations with African-American men being 37% more likely to die from cancer than white men and African-American women 17% more likely than white women. Furthermore, the adverse impact of cancer treatment is enormous, both for the long-term health consequences for cancer survivors and the costs for the population as a whole. The cost of cancer care in the US is estimated to be 219 billion dollars a year. It is difficult to overestimate the potential impact of improved strategies for the prevention, diagnosis and treatment of cancer on the health of Pennsylvanians.

While new genomic approaches to cancer are continually being developed in the laboratory, there are currently many examples that already have the potential to dramatically impact the burden of cancer in Pennsylvania. For each of these examples, investigators at the University of Pennsylvania and other institutions in Pennsylvania are poised to conduct the clinical studies necessary to move these discoveries into clinical practice. These include:

- (1) Pharmacogenetic tailoring of nicotine addiction treatment: Cigarette smoking causes 80-90% of all lung cancer deaths, and increases the risk of several other cancers. Current approaches to nicotine addiction treatment are limited because of variability in response to the FDA approved therapies (nicotine replacement, bupropion and varenicline), side effects and high rates of relapse. Use of information about individual variation in nicotine metabolism (based upon the nicotine metabolism ratio) to optimize therapy may result in greater rates of sustained abstinence with fewer side-effects and lower costs.
- (2) Genetic susceptibility and breast cancer screening and prevention: Breast cancer remains the most common cancer among women in Pennsylvania with 9,739 new cases in 2006. Breast cancer risk assessment has the potential to decrease morbidity and mortality from breast cancer through improved prevention and screening strategies but current risk prediction models are inadequate for use in clinical practice. Genome wide association studies have identified multiple genetic markers that may dramatically improve risk prediction and screening and prevention decisions. Tests using these markers are currently available and studies are needed to determine their effectiveness in breast cancer risk stratification.
- (3) Personalized treatment for NSCLC: In 2009, 45% of all newly diagnosed lung cancer cases will be advanced stage NSCLC. Standard treatment involves empiric, relatively toxic therapy given with little distinction between histologic subtypes and virtually no input based on molecular typing. However,

developments in cancer genomics over the last five years suggest that both pathologic analysis and molecular typing (particularly EGFR and KRAS mutation testing) may be important in determining appropriate therapy for patients with NSCLC and improving disease outcomes and reducing toxicity.

(4) Genetic testing in melanoma families: Adherence to sun protection behaviors remains one of the major challenges in cancer control, particularly for individuals with a personal or familial history of melanoma. The impact of genetic testing for p16 mutations on adherence is promising but currently unknown.

While the potential benefit of these genomic approaches to the health of Pennsylvanians is substantial, the development of evidence to support the translation into clinical practice is particularly important to ensure that these approaches are able to benefit all segments of the population, including traditionally disadvantaged groups. Disparities in the use of health care advances are an important problem and evidence based guidelines for these advances are an important step to addressing these disparities.

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Health Research Priority Title and Description

MOLECULAR IMAGING FOR EARLY DETECTION AND TAILORED THERAPY OF DISEASE

Exciting new opportunities to improve health have emerged in the post-genomic era. Strides in our understanding of the molecular foundations of disease have created the potential to diagnose diseases earlier and more precisely than heretofore possible. This era has also spawned novel treatments that target specific molecular aspects of disease and tailor therapy to individual patient phenotype. Advanced molecular imaging will be required to translate such opportunities into improved patient health. Molecular imaging is the science and practice of sensing specific molecular targets, biological processes, or cell types in living humans, distinct from traditional anatomic or functional imaging modes in current clinical use. Molecular imaging sits at the confluence of multiple disciplines, including chemistry, biology, physiology, engineering, imaging, medicine, epidemiology, and public health, with far reaching applications in medical diagnosis, risk stratification, and drug discovery, particularly within cardiovascular disease, diabetes, and oncology. The development of new drug, gene, or cellular therapeutics will ultimately be constrained by paucity of non-invasive imaging strategies to detect and monitor molecular-biological effects of such treatments. It is proposed that a health research priority be articulated to promote the multidisciplinary efforts required to clinically implement molecular imaging; this initiative will support critical yet unmet needs in the translation of our post-genomic insights into human disease into improved patient outcome.

Biomedical Research Questions and Hypotheses

Imaging modalities requiring research and development for molecular imaging include single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), and ultrasound (US), which each have unique advantages for molecular imaging across a spectrum of organ systems. Research effort will be required to identify suitable targets and to develop imaging agents and hardware platforms. A partial list of topics that can be addressed includes: **CARDIOVASCULAR:** (1) Identification of atherosclerotic plaques at greatest risk for rupture and causing infarction or stroke based on molecular characterization of plaque composition (e.g. PET imaging of plaque metabolism; MRI of plaque macrophages; US imaging of adhesion molecules); (2) Detection of acute thrombosis, angiogenesis, or an ischemic cause to chest pain by imaging molecular markers unique to these conditions; (3) In vivo tracking of therapeutically delivered cells (e.g. stem cells). **CANCER:** (1) Identification of tumors by imaging unique molecular markers (e.g. breast cancer screening with molecular US); (2) Assessment of malignant potential. **DIABETES:** Quantification of beta cell mass (pre-diabetes).

Clinical Research Questions and Hypotheses

Molecular imaging should be implemented in patient populations as part of research or clinical trials along the spectrum of disease states listed above, as well as others (e.g. Alzheimer's disease). A partial list includes: (1)

Longitudinal studies comparing molecular imaging endpoints vs. standard risk factors to predict future outcomes (e.g. conventional Framingham risk score vs. PET or MRI molecular imaging of plaques; endothelial function measurement by brachial reactivity vs. identification of endothelial adhesion molecules; mammography vs. ultrasound molecular imaging; beta cell mass quantification vs. serial glucose measurements in long term follow up of diabetes); (2) Diagnosis of cardiac chest pain in the emergency department by imaging molecules indicative of “ischemic memory;” (3) Evaluation of novel pharmaceuticals in clinical trials using intermediate molecular endpoints as surrogates for long term clinical endpoints (e.g. nanoparticle enhanced MRI, FDG-PET); (4) Evaluation of the effects of mental stress or mental health on molecular markers of endothelial dysfunction (e.g. adhesion molecules) or plaque inflammation, to establish a mechanistic connection between mental health and cardiovascular disease.

Health Services Research Questions and Hypotheses

Multimodality molecular imaging (i.e. combination of above modalities, e.g. PET, SPECT, etc.) can be implemented to improve screening for disease and monitoring treatment. Population screening can be performed, for example, in asymptomatic subjects with standard coronary risk factors, and those with “rupture prone plaque” based on molecular imaging criteria would undergo aggressive lifestyle and/or medical interventions vs. “standard of care.” In such studies, molecular surrogate intermediate endpoints (e.g. plaque inflammation) could be measured and used as timely feedback on treatment efficacy, in addition to conventional endpoints. Similar studies can be performed in obese patients: those with early “impending” diabetes based on imaging of beta cell mass could be more aggressively managed. Studies to evaluate risk/benefit ratios and cost effectiveness are required, with an emphasis on the financial and health consequences ensuing from the prevention of disease through application of molecular imaging, as well as the impact of image-guided therapies. For modalities that can be easily exported (e.g. US), research should pilot technology transfer to outpatient settings to further extend the capabilities to the community.

Impact on Health of Pennsylvanians

Successful realization of molecular imaging strategies can play a transformative role in health outcomes, particularly in the areas of cardiovascular disease, diabetes, and cancer. The power of imaging strategies that are based on an interrogation of molecular and cellular changes that accompany disease is that they can allow early diagnosis by identifying otherwise “invisible” markers that predate the clinical manifestations of illness. Furthermore, molecular imaging can enable novel therapeutics targeted at the molecular basis of the disease. In this regard, molecular imaging can provide meaningful surrogate endpoints for non-invasively measuring treatment efficacy more rapidly than traditional clinical outcomes, which can take years to detect. Treatments that fail to demonstrate an early effect on the molecular level can be triaged out, sparing the health and financial burdens of therapies that may ultimately prove to be ineffective years later using traditional clinical endpoints. Given that cardiovascular disease is the leading cause of mortality in Pennsylvania, accounting for 28% of deaths in the state in 2005, the impact of mature clinical molecular imaging programs on the health of Pennsylvania residents could be particularly significant. Also, disparities in the morbidity and mortality from stroke and heart disease exist along racial lines; while the etiology for these disparities is complex, their existence invites an examination of fundamental differences in mechanisms of disease which might be detected using molecular imaging approaches. The identification of patients at high risk for plaque rupture based on a molecular characterization of plaque composition can lead to pre-emptive mechanical or pharmacologic interventions that should reduce morbidity and mortality from stroke and acute coronary syndromes and their sequelae of congestive heart failure. The accurate diagnosis of cardiac chest pain in the emergency department using molecular imaging could spare thousands of patients from unnecessary hospitalization and save health dollars spent on admissions for low risk non-cardiac pain, while selecting patients in true need of hospitalization for acute cardiac care. Molecular imaging will enable regenerative cell therapies for heart disease by allowing in vivo tracking of the fate of delivered cells, ultimately improving outcomes in heart failure. Molecular imaging will benefit cancer patients as well: The annual age adjusted incidence rates for all cancers diagnosed between 1998-2005 show that Pennsylvania had higher rates than the rest of the United States, and annual age-

adjusted cancer mortality rates were consistently higher in Pennsylvania than in the rest of the country. There were 75,130 new cases of cancer diagnosed in Pennsylvania in 2007. The early diagnosis of cancer and evaluation of response to treatments stand to benefit from molecular imaging and quantification of cell-specific markers of malignancy. As such, given the burden of cancer to Pennsylvania, molecular imaging may exert a significant mitigating effect on the toll of cancer in terms of mortality, morbidity, health dollars, and loss of work productivity. The impact of molecular imaging on diabetes could also be significant: In 2007, the rate of diagnosis of diabetes among Pennsylvanians was 7.8%, compared to the Healthy People 2010 national goal of 2.5%. Only 34% of Pennsylvania's population is at "healthy weight," implying a major burden of future metabolic syndrome or diabetes. Serial molecular imaging of pancreatic beta islet cell mass would have tremendous value in risk stratifying patients and hence targeting interventions. To the extent that molecular imaging may provide a more sensitive index of responses to new treatments than traditional clinical endpoints, it can be used to refine therapies more quickly, and serve as a form of feedback for the effect of biobehavioral interventions in diabetes management. In sum, the unique "lens" provided by noninvasive imaging on a molecular scale, combined with the scope of organ systems amenable to this level of interrogation, position molecular imaging strategies to have a significant impact on the health outcomes of Pennsylvania denizens.