

UNIVERSITY OF WASHINGTON
CENTER FOR GENOMICS AND PUBLIC HEALTH

**ASTHMA GENOMICS:
IMPLICATIONS FOR PUBLIC HEALTH**

A REPORT COMMISSIONED BY THE
CENTERS FOR DISEASE CONTROL AND PREVENTION

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EXECUTIVE SUMMARY

With support from the Centers for Disease Control and Prevention (CDC), the University of Washington Center for Genomics and Public Health convened an Asthma Working Group to evaluate the implications of genomics for public health efforts related to asthma. Between January and October of 2003, the Working Group gathered information from the medical literature, held discussions among working group members, and consulted with a diverse group of experts to address this question. A preliminary report of the Group's findings was presented at a meeting held in Seattle, WA on September 22nd and 23rd, 2003. This report summarizes these findings, incorporating discussions at the Sept 22-23 meeting.

Asthma is a chronic lung condition characterized by airway inflammation, hyperreactivity, and reversible airway obstruction. The disease is found disproportionately among children and minorities, and prevalence has increased significantly since the early 1980s. There is strong evidence for both genetic and environmental contributors to the development of asthma. Genomics research has identified numerous genes and gene loci associated with asthma; further studies of genes, protein functions, and biological pathways associated with asthma are likely to yield new information about disease biology and innovative therapeutic and preventive approaches. The earliest clinical applications of this research effort will be in pharmacogenomics. Genomic strategies will aid in the identification of new drug targets, and may lead to drugs designed for use in specific subsets of asthmatic patients, defined by genotype. In addition, pharmacogenomics research will produce genetic tests designed to predict drug responses and adverse side effects. In the long term, genomics research may also produce genetic tests that aid in disease classification and prognosis, or identify unaffected children who are at increased risk to develop asthma. One possible application of the latter capability would be testing of newborns to identify infants who might benefit from environmental modifications or immunotherapy for prevention.

While such research holds promise for improved treatment and prevention, this outcome will not be achieved without careful attention to the interaction between genetic and non-genetic contributors to asthma and assurance of adequate access to health care services for all patients seeking care. Actions on the part of public health can help to ensure that genomics research supports public health goals to reduce asthma morbidity and mortality. These include:

- Facilitating analysis of, and communication about, research in asthma genomics and relevant practice applications
 - On-going critical evaluation of research on genomic contributors to asthma, to guard against overly simplistic interpretation of data addressing genomic hypotheses.
 - Participation in the development of appropriate methods for evidence-based review of pharmacogenomics and genetic testing, including rigorous assessment of the utility and cost-effectiveness of drugs requiring prior testing to determine candidacy for treatment, and of genetic tests proposed as a means to tailor drug regimens or predict future disease.
 - Utilization of the convening power of public health, to foster multidisciplinary collaboration in research and broad stakeholder participation in the development of research, clinical, and public health practice policies.
- Promoting population-based research that incorporates consideration of both genetic and environmental risk factors
 - Funding and advocacy, to ensure that evidence gaps are addressed with appropriate research strategies. In particular, public health input will help to ensure adequate selection and definition of study populations, meaningful measures of environmental exposure, and identification of appropriate clinical outcomes.

- Participation in design of recruitment and data management strategies for population-based genomics research. CDC and state public health agencies could play an important role in crafting public messages and recruitment strategies to ensure adequate participation in population-based studies, and in developing policies for data collection and management that reduce fears about inappropriate uses of genomic information.
- Conducting advocacy and outreach
 - Promotion of efforts to ensure access to genomics-based therapies for the medically underserved, when they have been found to have clinical utility.
 - Support for community-based participatory research methods to assess attitudes toward genomics, need for genomics education, and the social outcomes associated with genomic applications in health care.

A partnership between federal, state, and local public health agencies, professional organizations, and academic institutions could provide mechanisms to accomplish these goals. We recommend the formation of a national group, with participation from each of these sectors, to provide leadership for this effort. With appropriate support, this group, or designated subcommittees, could monitor research progress, interface with practice guideline committees and major research groups, and provide periodic uptakes to the public health community on implications of asthma genomics for public health practice.

PURPOSE OF REPORT

The University of Washington (UW) Center for Genomics and Public Health (CGPH) convened an Asthma Working Group to evaluate the potential contribution of genomics research to the reduction of asthma-related morbidity and mortality. The Working Group utilized information derived from review of the medical literature, discussion among working group members, and consultation with a diverse group of experts. The purpose of this report is to summarize findings of the consultation process and consider their implications for public health action.

ASTHMA AS A PUBLIC HEALTH CONCERN

Asthma is a chronic lung condition characterized by airway inflammation, hyperreactivity and reversible airway obstruction. Asthma rates in the US have risen since the early 1980s (Mannino DM *et al.*, 1998). According to statistics from the Centers for Disease Control and Prevention (CDC) (National Center for Health Statistics; MMWR, 2001; MMWR, 2004; Mannino DM *et al.*, 2002):

- In 2001, approximately 14 million (69/1,000) US adults had current asthma and an estimated 22.2 million (109/1,000) US adults had been diagnosed with asthma during their lifetime.
- In 2001, an estimated 6.3 million (87/1,000) US children (0-17 yrs) had current asthma and roughly 9.2 million (126/1,000) US children had a lifetime asthma diagnosis.
- In 2000, approximately 10.4 million hospital outpatient visits, nearly 2 million emergency department visits, approximately 465,000 hospitalizations, and close to 4,500 deaths were attributed to asthma.
- Asthma prevalence is elevated in low-income populations as well as many minority populations (non-Hispanic multiracial, American Indian/Alaska Native, Puerto Rican, and black populations). In addition, many minority and low-income populations experience substantially higher rates of fatalities, hospital admissions, and emergency department visits when compared to non-Hispanic whites.
- The combined direct and indirect costs for asthma in United States rose from approximately \$10.7 billion in 1994 to approximately \$12.7 in 1998 (KB Weiss and SD Sullivan, 2001).

No single factor is responsible for the development of asthma. Environmental risk factors, such as poor diet and exposure to house dust mites, fungal spores, cockroaches, tobacco smoke, animal dander, and ozone have been identified as contributors. Socioeconomic factors appear to be important, as evidenced by the higher burden of disease in minority and low-income groups. This effect could reflect increased exposure to environmental risk factors (for example, as a result of substandard housing), poorer quality of care, or lack of access to care in economically disadvantaged populations. In addition, as early as the 1920s, studies demonstrated the existence of a familial predisposition to asthma. Mapping and candidate gene studies have provided evidence for an association between asthma and specific genes and gene loci. The majority of people with asthma are atopic (i.e., individuals with an increased tendency to mount immediate hypersensitivity reactions against substances such as mites, animal proteins, and fungi). The likelihood of developing asthma appears correlated with the relative ratio of cell-mediated immunity to endogenous and exogenous antigens, and thus to the balance of different classes of thymus derived lymphocytes (T cells) that mediate these immune responses. However, asthma course, severity, and precipitating factors vary markedly among different patients, indicating heterogeneous pathways to this disease state.

Today, experts believe that asthma results from a combination of environmental triggers and genetic predisposition. Gene variants associated with T cell differentiation and related biological processes, including cytokine function and immunoglobulin E (IgE) production, are likely related factors. Many gene variants

related to these functions are under investigation for their role in asthma. Other gene variants are being investigated for their role in modifying response to drug therapies. In addition, genomic techniques such as gene expression profiling and linkage studies are being used to identify new gene loci or functions not previously known to be associated with asthma. Although the study of asthma genomics is still in its early stages, understanding the interaction between gene variants and environmental exposures holds great promise for the development of new strategies for diagnosing, managing, and perhaps ultimately preventing or curing asthma.

GENOMICS AND PUBLIC HEALTH

This project was undertaken in the context of high expectations for health benefits from the Human Genome Project, an international collaborative effort to define the DNA sequence and identify all human genes. Rapid advances in human genomics and accompanying technologies (such as “gene chips,” which are used to identify properties of multiple genes simultaneously) are expected to bring about a revolution in medicine and public health, forming the basis for new approaches to preventive care and drug treatment, and leading to discovery of new therapies (Collins F *et al.*, 1999; Roses A, 2000).

Although these predictions suggest a dramatic impact on health outcomes in the long term, the implications for action now are uncertain. What do the many gene discoveries – seemingly announced almost daily – mean for public health? Until recently, the use of genetic information in health care has been confined largely to the realm of rare disorders caused by mutations in single genes (Burke W, 2002). Even so, the public health community has included components related to genetics in some of its work, experiencing noteworthy successes in birth defects prevention, newborn screening for inborn errors of metabolism, and development of genetic services capacity (Khoury M *et al.*, 2003; Piper MA *et al.*, 2001). Virtually all human disease results from the interaction between genetic susceptibility factors and the environment, broadly defined to include any exogenous factor – chemical, physical, infectious, nutritional, social, or behavioral. This concept of “gene-environment interaction” may help explain why some health conscious individuals suffer illnesses such as heart disease or cancer in the absence of known risk factors, while others seem immune despite obvious risk exposures. Asthma is a prime example of a disease with both genetic and environmental contributors. Genomics research offers the hope that an understanding of the complex interplay of genes and the environment will lead to new avenues for reducing the morbidity and mortality of asthma.

There is a gap, however, between the scientific products of the Human Genome Project and our ability to use genomic information to benefit health. This gap is particularly apparent in the field of public health, in which conversations regarding genomics and chronic disease have only just begun (Beskow LM *et al.*, 2001). The findings of the UW Asthma Working Group

THE LANGUAGE OF HUMAN GENETICS: A WORD ABOUT DEFINITIONS

Many people tend to associate the term “genetics” with the study of single genes and classic Mendelian principles of inheritance. Now that there are powerful new tools for sequencing DNA, scientists are sequencing the genetic material of entire organisms, including humans. These advances allow an expanded approach to understanding how multiple genes and gene products act within the context of a whole system of genes and environmental factors. We use the term genomics here to denote this more complex model of health and disease – what others sometimes call the “new genetics.”

Genetics: The study of the patterns of inheritance of specific traits.

Genome: All of the genetic material (DNA) belonging to a particular organism.

Genomics: The study of the structure and function of an entire genome (e.g., the human genome), including its sequences, structures, regulation, interactions, and products.

reported here suggest that public health can play a central role in bridging the gap between genomics research and the application of research findings in public health and clinical care.

METHODS

DEFINING THE QUESTION

In initial literature review and discussions, the UW Asthma Working Group identified four areas of potential action in which genomics research or information might contribute to public health efforts to reduce asthma morbidity and mortality: population-based prevention; targeted prevention based on risk status; diagnosis; and management. Population-based prevention was defined as intervention or detection efforts in the general population to avoid or delay asthma onset, and risk-based prevention was defined as intervention efforts targeted to those with identified susceptibilities to asthma, to avoid or delay asthma onset. The term diagnosis was defined as identification of individuals with asthma, including distinguishing asthma from other respiratory diseases and identification of asthma subtypes. Management efforts were defined as interventions to reduce disease burden of asthma, including pharmaceutical and other therapeutics, environmental modifications, and behavioral mechanisms. The Working Group also defined five key perspectives from which to evaluate potential interventions: patient and family, community, researcher, health care professional, and public health practitioner. The Working Group then developed a plan for expert consultation, seeking feedback on these potential areas of intervention and considerations from each of the identified perspectives. See Appendix A for list of group members and a timeline of the Asthma Working Group process. A sixth perspective, that of the commercial developer, was identified during the consultation process, although no consultants represented commercial developers.

This document focuses on public health practice and research, and thus on specific actions that might be taken by public health professionals in light of genomics research. Some public health opportunities – e.g., for defining research questions, developing public health messages, crafting policies, and implementing educational efforts – require an understanding of the needs of clinicians and families. In addition, public health research represents one part of a larger research effort that includes basic study of biological mechanisms and disease pathways, for the ultimate purpose of developing new strategies for treatment and prevention. To ensure a comprehensive evaluation of potential contributions from genomics research, we asked the experts we consulted to consider a range of perspectives, including:

- **Patient/family:** Can genomics contribute to better health care for asthma patients, reduced burdens for their families, or methods for prevention? Does genomic information pose risks?
- **Community:** What are the implications of asthma in communities and components of communities? What are the concerns and interests regarding genomics in various communities?
- **Researcher:** How can genomics research contribute to a better understanding of asthma and to the development of new therapeutic approaches? If a role for genomics is identified, what questions must be answered before public health action can be taken? What are the specific research questions to be addressed by public health?
- **Health care professional:** Can genomics contribute to improved diagnosis or treatment of asthma, or to innovative preventive strategies? Does the introduction of genomics into the clinical care of asthma pose risks? What educational needs will clinicians have?
- **Commercial developer:** What is the potential for commercial development of products related to asthma genomics? Will commercial interests promote research or influence the research agenda?

- **Public health practitioner:** How might genomics contribute to efforts by local, state, and federal agencies to reduce the morbidity and mortality of asthma? What is the role of public health in ensuring that appropriate policies are enacted related to genomics? Will the introduction of genetic tests or genome-based therapies pose new risks that will require public health action? What training/education or technical assistance will be needed by the public health workforce?

SOURCE OF EXPERTS FOR CONSULTATION

The initial round of consultation utilized the asthma expertise available in the Seattle community and within Washington State. Subsequent rounds of consultation sought advice from experts at the University of Michigan Center for Genomics and Public Health and the University of North Carolina Center for Genomics and Public Health; from national experts identified through consultation with local and federal advisors; and from experts attending the American Thoracic Society meeting (Seattle, May 2003) and the National Conference on Asthma 2003 (Washington DC, June 2003). See Appendix B for a listing of consultant-affiliated institutions.

PROCESS FOR EXPERT CONSULTATION

Experts were interviewed individually or in small groups. Most consultations began with a brief presentation of the framework developed by the UW Asthma Working Group. Consultants were then asked to comment on the framework and to address a set of open-ended questions on the implications of genomics for asthma prevention (see Appendix C for consultation guide). At the end of the interview or small group discussion, consultants were asked to identify other experts who might provide additional consultation. Most consultants also identified additional literature pertinent to the questions posed in the consultation process, which were subsequently reviewed and discussed by the UW Asthma Working Group. Consultations were recorded with a tape recorder or hand-written notes and summaries of each consultation were drafted. Over the course of the consultation and literature review process, specific questions emerged and became the focus of further discussion with experts representing appropriate expertise. These included the potential role of genetic profiling as a means for identifying individuals with increased asthma risk; the implications of commercial incentives for technology development; the relevance of current data on behavioral interventions, treatment adherence, and clinical outcomes for potential genome-based interventions; and the significance of current data related to differences in asthma prevalence across demographic groups for public health research and action.

PROCESS FOR COMMUNITY CONSULTATION

Additional information about the needs of patients, families, and communities was pursued through discussions with representatives of community-based organizations concerned either with asthma or with childhood health issues. Appropriate organizations in the Seattle area were identified and a two-step process to elicit feedback was implemented. In the first step, an initial phone contact was used to determine the organization's level of awareness and interest in genomics. Feedback was also sought on the community consultation process. If there was sufficient interest, a group meeting was scheduled to discuss the implications of asthma genomics, utilizing three scenarios illustrating potential asthma-related uses of genomic information, as identified by scientific experts. These scenarios included genetic testing to determine appropriate asthma medications, newborn screening to identify individuals susceptible to asthma, and the use of genetic susceptibility information in setting clean air standards. A total of three meetings were conducted with community groups in the Seattle area.

FINDINGS

THE SHORT-TERM VIEW: THE IMPORTANCE OF PHARMACOGENOMICS

Consultants consistently identified pharmacogenomics as the area of genomics research most likely to change asthma care in the near future. This term refers to the use of genomic techniques to enhance drug development and define drug responses. Genetic factors have been estimated to account for up to 60% to 80% of the variability in asthmatic patients' response to medications (Drazen JM *et al.*, 2000). Pharmacogenomics research could change asthma care through two main pathways.

Development of new therapies

Genomic techniques, incorporating the study of both gene variation and protein products, create an opportunity to define biological pathways and their functions at a new level of molecular detail, resulting in the identification of a range of potential new drug targets and pharmaceutical strategies (A Pahl and I Szelenyi, 2002). Many different genomics research strategies are likely to contribute to this process. Linkage studies and gene expression profiling can be used to identify genes associated with asthmatic responses (Susman E, 2003; Dolgonov GM *et al.*, 2001; DJ Erie and YH Yang, 2003). Molecular studies of pathways and physiological processes known to be involved in asthma, such as T cell differentiation and other immune response functions (Yazdanbakhsh M *et al.*, 2002), can be used to better define protein functions and interactions, including the use of small molecule probes to systematically manipulate discrete pathways in order to identify the clinical effect of small changes in function (Nguyen C *et al.*, 2003). Animal models of asthma are likely to play an important role in this research effort. Ultimately, however, the desired result will be new drugs to treat asthma more effectively.

It can be hoped that this research will lead to effective drugs with wide applicability to asthma patients. However, pharmacogenomics research is also likely to result in the production of "designer drugs" targeted to specific clinical sub-types of asthma or to individuals with specific genotypes. A possible analogue for such drugs is the IgE monoclonal antibody Xolair recently released by Genentech and Novartis. This drug is targeted to asthmatic individuals with high IgE levels; thus, IgE level must be measured prior to drug use to determine candidates for treatment. The estimated annual cost of the treatment is \$10,000 per year (Pollack A, 2003). These two features – a pre-test to determine candidacy for treatment and high cost, are potential features of new pharmacogenomic drugs.

Genomics as the basis for understanding responses to existing therapies

Adverse drug reactions are an important cause of iatrogenic complications, resulting in discontinued use of some effective drugs – for example, theophylline – and efforts to define the lowest effective dose for others, such as steroids. In addition, monitoring for non-response is an important element of asthma care (National Asthma Education and Prevention Program, 1997, 2002). A person's genotype – in particular, variants in enzymes involved in drug metabolism – is an important factor in drug response (JC Dewar and IP Hall, 2003; Drazen JM *et al.*, 2000; Weinshilboum R, 2003). It is likely that pharmacogenomics research will create the potential for genetic profiling to determine the safest and most effective drugs for a particular patient. Further understanding of the genomic contributors to the immune functions involved in atopic and asthmatic responses might also help to determine which patients will benefit most from different asthma drugs. A prominent example in asthma research is the association of polymorphisms in the beta-adrenergic receptor with response to beta-adrenergic drugs (RP Erickson and PE Graves, 2001; Israel E *et al.*, 2000; Taylor DR *et al.*, 2000; Lima JJ *et al.*, 1999; Martinez FD *et al.*, 1997). Gene variants affecting steroid response and efficacy of leukotriene antagonists are also under study (JC Dewar and IP Hall, 2003), as well as other

potential applications of pharmacogenomics. For example, a recent study reported that oral antioxidant supplementation with vitamins C and E reduced the ozone-related decline in pulmonary function among a group of children with asthma in Mexico City (Romieu I *et al.*, 2002). When the study population was stratified by *GSTM1* genotype (because *GSTM1* codes for an enzyme involved in response to oxidative stress), the effect was limited to children with the *GSTM1* null genotype (Romieu I *et al.*, 2004). Conversely, the Pro187Ser polymorphism of the *NQO1* gene – which codes for another enzyme involved in response to oxidative stress – had a protective effect on asthma severity in children with *GSTM1* null genotype (David GI *et al.*, 2003), illustrating the potential complexity of the genotype-phenotype relationship.

It is likely that pharmaceutical research currently in process includes the collection of genotype data that could be used to identify non-responders or individuals with increased risk for side effects to a range of asthma drugs. Using genetic testing for this purpose could reduce adverse drug reactions and avoid the cost and potential side effects of drugs to which the individual is unlikely to respond.

Issues in pharmacogenomics

In summary, pharmacogenomics research offers the possibility for several therapeutic innovations:

- New drugs for general use in asthma care, based on a better understanding of the molecular pathways leading to asthma. This innovation in drug development will not pose challenges that are new or unique to genomics.
- New drugs targeted to subsets of patients with particular genotypes. These drugs will require genotype testing prior to drug use.
- Genetic profiling tests, marketed independently from specific drugs, to provide information about an individual's potential response to one or several drugs. Tests of this kind are already on the market, although none is specifically marketed as a tool for asthma care. For example, two companies, Roche and Tm Bioscience, have recently launched tests utilizing gene microarray techniques to test for multiple gene variants in drug metabolizing enzymes (Tm Bioscience; Roche Diagnostics). Such tests could potentially have a role in selecting therapeutic regimens or medication doses for patients with asthma.

Pharmacogenomics research offers great promise for improving asthma therapies, but raises questions about allocation of health care resources and adverse labeling of patients. If new drugs require genetic testing prior to use to determine which patients should receive the drug, this process will add to the initial cost of care (although the cost may be compensated by reduced use of ineffective drugs). This practice strategy will require development of new practice guidelines and health provider education. Perhaps more importantly, genetic profiles that predict drug response may also provide other predictive information unrelated to asthma, such as information about other disease risks or susceptibility to occupational exposures (Their R *et al.*, 2003). Practice guidelines will need to address the obligations of health care providers to address such ancillary information, and the potential risks to patients of unsought predictive information.

Commercial incentives are an important factor in pharmacogenomics, with a potential for both positive and negative effects on patient care. Commercial investment is critical to drug research and development, but is likely to result in high prices for new drugs. Commercial incentives (or the lack of them) may also limit some pharmacogenomic opportunities. Potentially promising drugs might not be pursued if the market for them is perceived to be too small or non-remunerative. In addition, some important research findings will be proprietary and might not be publicly disclosed for market reasons. For example, a company might choose

not to disclose data on genotypes predicting non-response to medications it manufactures because such data might lead to tests that reduce market share.

These issues suggest that careful consideration should be given to the process by which clinical practice guidelines are developed related to new asthma drugs, with particular attention to the standards for use of genetic profiling to determine drug regimens. If new drugs like Xolair are very expensive, access to these drugs by the medically underserved is a potential concern. Expensive drugs that are recommended for use in a particular clinically defined subset of asthma patients or that require prior genotype testing will represent a challenge for publicly funded health care programs. Careful consideration will be needed to construct drug formularies that ensure appropriate access to such treatments, in the context of cost-effectiveness. Efforts to address this problem will be aided by public health efforts to ensure adequate outcome data comparing new and established therapeutic strategies.

It may also be important to invite collaborative discussion among representatives of commercial, public health, and academic research sectors to consider guidelines for disclosure of information that has been gained in drug trials and is of high public interest – such as data concerning genotypes that predict non-response to commonly used asthma drugs.

THE LONG-TERM VIEW: OTHER POTENTIAL APPLICATIONS OF ASTHMA GENOMICS

Although pharmacogenomics represents the application of genomics research most likely to affect asthma care in the near future, several experts predicted that genomics research will make an important contribution to asthma care in the long term through genetic testing, and may potentially usher in a new era of prevention. A key element in this scenario is the assumption that genomics research will contribute to an increasing understanding of gene-environment interactions. This understanding will allow for a more precise identification of environmental changes that could reduce asthma risk or morbidity and for tailoring of specific environmental or medical interventions to high-risk patients. In addition, as the underlying biological processes are clarified by genomics research that incorporates a sophisticated understanding of environmental risk factors, explanations for the wide variation seen in asthma phenotypes are likely to emerge. This research effort could lead to better ways to classify asthma patients, with implications for prevention and treatment, and to the identification of candidates for innovative prevention strategies. The practical application of such knowledge could, for example, take the form of:

- Genetic testing for **diagnosis and classification** of asthma. In addition to identifying individuals who might benefit from specific drug regimens, genetic testing might allow for earlier diagnosis of asthma in individuals with suggestive symptoms – for example, young children with wheezing, or adults with persistent cough after a respiratory infection. Early identification might allow for more rapid institution of effective care, leading to improved outcomes. Genetic testing might also enable clinicians to determine which patients with newly diagnosed asthma are at greatest risk for developing severe disease and who, therefore, might benefit from intensive case management. While research on the genomics of asthma is not yet at a point where such tests could be developed, consultants suggested that this is a likely outcome of current research and should be anticipated. A particular application that has important policy implications is the potential for genetic testing to predict workplace asthma risk. For example, gene variants in *HLA DQB1* appear to be associated with susceptibility to isocyanate-induced asthma, and variants in other genes may also contribute to the development of this work-related asthma syndrome (Mapp *et al.*, 2000; Mapp *et al.*, 2002; Wikman H *et al.*, 2002; Piirila P *et al.*, 2001).

- **Population-based prevention.** In an ideal scenario, the study of gene-environment interactions leading to asthma might also lead to the use of genomic data as a means to define optimal safety standards for environmental exposures. For example, clean air standards could be based on research defining the level of safe exposure for the most genetically susceptible individuals. Such approaches are unlikely, however, and might be difficult to justify if the prevalence of the most susceptible genotypes were very low.

However, data on gene-environment interactions, family history, or genetic classification of specific asthma subtypes, could lead to population-based interventions that utilize family history information or genetic testing. Belanger et al. reported a difference in risk factors associated with respiratory symptoms (wheeze and persistent cough) in children whose mothers had a physician diagnosis of asthma and children whose mothers had not been diagnosed with the disease (Belanger K *et al.*, 2003); suggesting that individuals with a positive family

history of disease and those without may have different susceptibilities to environmental exposures. In addition, several consultants predicted that newborn screening would be possible at some point in the future, to identify children who would benefit from specific environmental modifications, preventive drug treatment, or immunizations (or other immunotherapy) designed to reduce their likelihood of developing asthma or other atopic diseases. As an example of the potential feasibility of this approach, Smart *et al.* recently reported on inhibition of experimental asthma in mice using an orally administered plant-based allergy vaccine (Smart V *et al.*, 2003). Genetic testing as a means to institute targeted prevention would not necessarily be limited to the newborn period, if preventive interventions appropriate to older children or adults were developed.

To determine the potential role of genomic information in clinical practice and public health, the following questions must be assessed in different populations:

- The **prevalence** of gene variants
- The **magnitude** of disease risk associated with gene variants (relative and absolute risks)
- The **contribution** of gene variants to the occurrence of disease (attributable risks)
- The magnitude of disease risk associated with **gene-gene and gene-environment interaction**
- The **clinical validity** of genetic tests (sensitivity, specificity and positive and negative predictive values for specific disease outcomes)
- The **clinical utility of genetic tests** (outcomes associated with the use of testing and associated interventions)
- **The clinical utility of interventions based on genomic information** (outcomes associated with genetic tests or genome-based interventions)

THE IMPORTANCE OF GENOMICS RESEARCH FOR THE PUBLIC HEALTH AGENDA

The potential uses of genomic information underscore the significance of the research agenda for the public health community. Genomic information is now an integral part of health sciences research, and innovative approaches to disease prevention and management are possible throughout the pathway by which basic research findings are developed into potential methods to prevent disease and reduce morbidity and mortality; systematically evaluated; and then implemented. At each step in this pathway, public health has a potential funding role and a strong interest in the research process, particularly in ensuring that research relevant to achieving public health goals is undertaken. In addition, public health can act as a catalyst for interdisciplinary discussion among the diverse groups of professionals working at various points along this translational pathway. Public health can also play a significant role in determining when genomics findings have applications in healthcare, formulating appropriate public policies and guidelines, assessing genomics information and applications, and assuring that genomic applications and information meet the needs of populations.

As noted earlier, pharmacogenomic testing is an important potential development in asthma care, foreshadowed by the recent release of Xolair and by the potential for microarray-based tests to assess individual drug responses to a wide array of commonly used drugs. In addition, a future role can be envisioned for genetic testing, either to identify individuals at risk for disease or exposure to specific triggers, or to define prognosis in people with asthma. Yet genetic test development is currently largely unregulated (Secretary's Advisory Committee on Genetic Testing, 2000) and, in other disease areas, genetic tests with poorly characterized sensitivity, specificity, and predictive value are already in clinical use and are promoted through direct-to-consumer marketing.

Several core questions must be addressed when determining the potential role of genomic information in clinical practice and public health. These core questions point to elements of research methodology that are of particular importance to public health in the study of asthma genomics: appropriate selection and definition of study populations; careful consideration of alternative case definitions; the potential pitfalls in association studies; strategies for concurrent assessment of genetic and non-genetic risk factors; appropriate methods for assessing clinical interventions; and additional social or economic factors that influence the effectiveness of interventions with proven benefit.

Epidemiology has often been defined as the core discipline of public health, and epidemiological principles will play an increasingly important role in asthma genomics as gene variants with putative roles in the development of asthma are identified. Gene variants will need to be studied in adequately powered population-based studies, with attention to environmental contributors to risk, before their implications for the disease burden of asthma can be fully understood. Good measures of clinical phenotype and environmental risk will be needed. Public health has an important role to play in assuring the quality of research in this area, through critical evaluation of existing data according to objective criteria (Khoury M, 2002; Little *et al.*, 2002; Burke *et al.*, 2002), and through participation in new studies. For each of these critical areas, we have identified issues of particular importance in asthma genomics.

Appropriate selection and definition of study populations in studies of genetic risk

Often, initial identification of gene variants associated with specific disease outcomes is easiest in isolated, relatively homogenous populations. The public health implications of gene-disease associations also must be assessed in larger and more representative populations, with due attention to variation in environmental exposures. In addition, the prevalence and distribution of gene variants may differ by racial or ethnic group. Observations of this kind may lead to important but largely untested hypotheses that differences in rates of disease among populations might be caused by different population-specific gene variants or by differences in the prevalence of specific gene variants (Collins FS, 2003; Lester LA, 2001). In evaluation of such hypotheses, definitions of race/ethnicity and sample sizes are critical considerations. For example, the Collaborative Study on the Genetics of Asthma has provided data suggesting that differences in genetic susceptibility to asthma may occur among Hispanic, African-American, and white populations (CGSA, 1997; Xu J *et al.*, 2001; Blumenthal *et al.*, 2004). However, these data used a small Hispanic population of Mexican Americans. Thus, the study could not address differences seen between Puerto Ricans and Mexican Americans in asthma prevalence, mortality, and responsiveness to bronchodilators (OD Carter-Pokras and PJ Gergen, 1993; Mendoza FR *et al.*, 1991; Homa DM *et al.*, 2000; Burchard EG *et al.*, 2004), which were hypothesized by several of the consultants to be due to genetic differences. Careful attention to population sampling and study design is needed to investigate such hypotheses, including consideration of competing explanations – e.g., that group differences are due to environmental or social differences. Yet, definitions of race/ethnicity and geographic origin are often limited or inconsistent, and sometimes absent, in studies reporting genomic data. Further, data for minority populations is often far less robust than data on white populations. These problems point to the need for epidemiological rigor in assessing genomic contributors to disease.

As with all asthma research, problems related to case definition are also important in genomic studies. Case-definition measures currently in use include reports of symptoms; physician diagnosis; bronchial hyperreactiveness; elevated IgE levels; and other clinical or physiological data (National Asthma Education and Prevention Program, 1997). The variety of measures used to diagnose asthma underscores the need for standardized definitions both of asthma phenotypes and of population characteristics (Postma DS *et al.*, 1998; Koppelman GH *et al.*, 1999; Ayres J, 2001). While genomic characterization may ultimately contribute to better definitions of different asthma sub-types, research studies addressing the genomic characterization of asthma must be carefully scrutinized for biases that over-simplify or obscure important relationships.

Pitfalls of linkage and association studies

In particular, gene-disease association studies must be rigorously assessed. Recent studies have documented the poor reproducibility of most published gene-disease association studies (Hirschorn JN *et al.*, 2002; Ioannidis JP *et al.*, 2001). Some conflicting results are undoubtedly the result of genetic differences and/or variation in modifying factors that affect disease outcome among different populations. However, a recent study of published literature suggested that inadequate sample sizes, over-interpretation of data, and publication bias are the leading causes of conflicting results in published studies of genetic contributors to disease risk (Calhoun HM *et al.*, 2003).

Evaluation of the association between asthma and variants of the gene *ADAM-33* offers an example of the complexities of gene-disease association studies. Just over a year ago, a group of researchers led by Genome Therapeutics, reported an association between asthma and *ADAM-33*, a member of a family of genes that encode membrane-anchored proteins with a disintegrin and a metalloproteinase (ADAM) domain (van Eerdewegh P *et al.*, 2002). In this study, a positive linkage to a region on the short arm of chromosome 20 (20p13) was found using the phenotype definition of asthma only or asthma and bronchial hyperresponsiveness (BHR). No linkage was found when defining the phenotype as asthma and elevated levels of immunoglobulin E (IgE). To identify genes linked with asthma the researchers utilized single nucleotide polymorphisms (SNPs) of genes spanning the chromosomal region in which linkage to asthma was greatest and found that the majority of positive associations occurred in *ADAM-33*. Although not clear, it is thought that this gene may play a role in small-airway remodeling in asthma patients (S Shapiro and C Owen, 2002).

The association of asthma with *ADAM-33*, the first major novel gene to be identified from a whole genome scan, led to much excitement about the prospect of asthma genomics. The findings excited hopes in scientists "...that unraveling the genetics of common diseases may not be quite as hard as had been feared" (KR Ahmadi and DB Goldstein, 2002). However, the findings of Van Eerdewegh and colleagues have yet to be replicated in other linkage studies (Lind DL *et al.*, 2003; Haagerup A *et al.*, 2002; Ober C *et al.*, 2000) and there is uncertainty as to the biologic function of *ADAM-33*, and how it might relate to asthma pathophysiology. Cookson suggests that the ADAM-33 study may be difficult to replicate for various reasons, including: a false positive finding in the initial report, population-specific differences in studies, methodological differences in studies, or small sample sizes (Cookson W, 2003). Before *ADAM-33* can be confirmed to be an important factor in asthma development, it is likely that studies will need to focus on studies of gene function rather than "hard-to-replicate" association studies, and may require further attention to differences in asthma phenotypes and the effect of other contributing risk factors. The ADAM-33 example underscores that discovery of an apparent gene-disease association should be considered a preliminary, hypothesis-generating result, rather than a definitive finding; its significance may only be known after additional epidemiological, physiological and clinical studies are completed.

Strategies for concurrent assessment of genetic and non-genetic risk factors

Multiple gene variants and non-genetic risk factors contribute to asthma outcomes. Research strategies are needed to address this complexity. In addition to unbiased study populations with sufficient power to detect small effects (LJ Palmer and WO Cookson, 2001; Weiss ST, 2001; Little J *et al.*, 2002), innovative study designs are needed. An example is the proposal by Martinez, von Mutius, and co-workers to pursue genetic studies in populations selected for a well-defined environment relative to asthma risk – such as children living in farm environments where exposure to elevated endotoxin levels may be protective early in life (von Mutius E, 2002; Eder W *et al.*, 2004). This approach would invoke the environmental equivalent of a genetically homogenous population. Another example is the use of environmental exposure as a stratifier in gene linkage studies (Colilla *et al.*, 2003). Because of the many different environmental risk factors described for asthma, and genetic studies suggesting the potential contribution of hundreds of different genes (Susman E, 2003), potential research opportunities are immense. A critical part of determining appropriate study design – and efficient use of research resources – will be a careful evaluation of current data to develop credible hypotheses of gene-environment interactions that warrant further study. Careful secondary analysis of existing studies is likely to provide a useful contribution to this effort. This effort is most likely to be successful if it is multidisciplinary; that is, if effective ways can be found to share the insights of molecular genetics, epidemiology, cell physiology, environmental sciences, social and behavioral sciences and clinical medicine in developing a research agenda.

Appropriate methods for assessing clinical interventions

The risks and benefits of new interventions can be understood only after systematic observation in the form of well-designed controlled trials, cohort or case-control studies. New drugs based on pharmacogenomic studies will be required to undergo clinical trial evaluation according to the regulatory requirements of the Food and Drug Administration (FDA). However, regulatory oversight of genetic tests, including pharmacogenetic tests, is limited (Secretary's Advisory Committee on Genetic Testing, 2000). Because most genetic risk factors, even for common diseases, occur in a relatively small subset of the population, sample sizes of genetically susceptible subjects are often small. Initial use of many genetic tests has been based on intermediate biological endpoints and limited clinical observations (Burke W *et al.*, 2002), in part because of the difficulty in performing large randomized studies for rare conditions, and because there may be ethical arguments against delaying treatment when pathophysiological studies argue for benefit in a rare, clinically serious condition (Wilcken B, 1999). As genetic testing is considered for the identification of risk related to common diseases such as asthma, it will be important to consider the appropriate evidentiary standards to be used in developing clinical practice guidelines. Any deviation from the rigorous standards already adopted for clinical practice guidelines in asthma care (National Asthma Education and Prevention Program, 1997; 2002) would need to be carefully justified.

Additional social or economic factors that influence the effectiveness of interventions with proven benefit

Even when randomized controlled trials suggest an intervention has benefit, additional questions remain. Is it ethical to target certain asthma interventions based on genomic factors? Are the interventions acceptable to the target population? Adherence, already identified as an important factor in asthma care (Ho J *et al.*, 2003), may involve additional factors when genetic testing is introduced. In addition, interventions with efficacy may not be cost-effective. The introduction of new therapeutic approaches will require attention to the resources required to introduce and maintain them, as well as the social or opportunity costs involved. Testing as a means to identify individuals with an increased risk to environmental pollutants or workplace exposure could, for example, have implications for public policies related to environmental protection or workplace safety. Addressing these questions represents a significant challenge from both research and policy perspectives. These issues may be of particular concern when new therapies involve genetic testing, and when the disease condition under consideration is thought to be more prevalent among minority and economically disadvantaged groups.

Investigation of these questions will require acceptance and endorsement from affected communities. Innovative study designs that combine qualitative and quantitative methods may be necessary to evaluate the potential impact of new interventions. Genetic testing must be evaluated in terms of clinical, economic, and social outcomes. Thus, in order to examine the potential for genomics to improve asthma outcomes, public health must begin to understand the concerns, interests, and requirements of the larger community. Promoting a dialogue about public health genomics with community representatives and advocacy groups is one way to engage communities, and to identify their priorities, willingness to participate in research, receptivity to care based on the use of genetic tests, and other relevant needs and concerns.

Public health dialogue with communities

The interaction of public health with communities is an important component of public health practice (Institute of Medicine 1988, 1996, 2003). As knowledge about asthma etiology and pathogenesis changes with new discoveries in asthma genomics, public health activities involving the general public and subgroups of the public are also likely to change. To bridge the gap between genomics research and public health practice, public health activities will need to adjust to newly identified needs and priorities of people concerned about interventions that utilize genomic information.

While findings from the Asthma Working Group community consultations do not represent a comprehensive analysis of public needs and priorities with regards to genomics, they can serve as a starting point for gauging knowledge about asthma genomics and for identifying key topics of interest in genomics. Three groups consulted with us, including a group of citizens volunteering in asthma prevention and management activities, and representatives of Latino and Cambodian neighborhood groups with an interest in asthma. Overall, potential public concerns about the use of genomic information, as assessed through the consultations, were: increased health costs, stigmatization, breach of confidentiality, misinformation, and discrimination in insurance coverage, employment, and government benefits. Central themes that arose in conversations with these groups included the need for acknowledgement of the prior history of relationships between communities and researchers, cultural competency, and public education in genomics.

For public health researchers and practitioners to interact successfully with people affected by or concerned with asthma, it will be important to acknowledge the prior history of relationships between communities and researchers (e.g., the distrust generated by US Public Health Service study of syphilis in black males, which was mentioned in one of the community consultations). Recommendations made by some community consultants for building successful relationships with communities included creating transparency – that is, open disclosure of research or intervention methods, goals, and uses of data – and attempting to understand the needs and culture of communities by working with community leaders and/or trusted “community agents”. When interfacing with the general public, public health practitioners and researchers will also have to ensure that programs and research studies are culturally competent. As one community representative stated, people may, “hear your words, but not feel your words,” if a message is not tailored appropriately.

Consultants also expressed a need for public education and information about current genomics activities. Genomics is a topic with widespread coverage in the media, but one that is not necessarily well understood by the public. While media may provide some useful information about genomic discoveries, coverage of genomics and other health issues may be misleading (Burke W *et al.*, 2001; Geller G *et al.*, 2002). Public education is an important component of public health activities and incorporation of genomics concepts into these education efforts will be necessary. The addition of genomic information to public discussions about asthma, the environmental component of which is difficult enough to describe, may make education of the general population a much more complicated task. It will be important for educators to have a good grasp of genomic information and to be able to gauge the level of comprehension within the population. It is likely that there will be varying levels of understanding among different populations and that

an individual's level of knowledge will differ by topic. For example, an individual may have a proficient understanding of what it means for a condition or trait to be genetic, but may or may not have a deeper level of understanding about terms often appearing in the media, such as gene therapy, genetic code, and the "Human Genome Project". Unless resources with more detailed information are made available, there is the potential for misunderstanding (i.e., that there is a single gene for asthma or that people carrying mutations associated with asthma are "fated" to get the disease).

The rapid rate of advances in genomics and the uncertainty about genomic applications in healthcare bring into question how and when public health practitioners should provide information to the public. It was suggested during consultations that public health practitioners could potentially serve as a filter of information, communicating information to appropriate audiences (i.e., the general public, asthma advocacy groups, community organizations, patients, etc.) when it has relevance and when it is desired. However, the effectiveness of various methods, timing, and content of genomics education for different individuals in asthma communities has yet to be examined. Opinions may vary as to the appropriate point in time that information about asthma genomics should be dispersed (i.e., before or after there is scientific certainty and whether or not the information is associated with a definitive action that results in a positive health outcome) and the appropriate venue for information dispersal (i.e., physician's office, community groups, mass media etc.).

While researchers, public health practitioners, and healthcare professionals have important roles in decreasing asthma related morbidity and mortality, they cannot be successful without the support and perspective of asthma patients and involved communities. The findings reported here may serve as a starting point for considering the public in the context of public health genomics by shedding light on potential public concerns and informing readers about potential issues that may arise if genomics findings are integrated into public health and healthcare practice. Additional efforts will need to be made if we are to have adequate knowledge and capacity to undertake future genomics activities with public involvement. Further efforts are also needed if public health is to ensure that genomic information is used appropriately and effectively, and that the potential benefits of its use outweigh the potential harms.

PROMOTING DIALOGUE AND CONSENSUS

As research on the genomic contributors to asthma progresses, there will be an increasing need for cross-disciplinary collaboration in research and policy development. Public health goals are likely to be advanced by the effective use of dialogue and consensus development in both these areas.

Research

Research utilizing study participants that are representative of the general population, with robust measures of clinical phenotype and environmental risk factors, is essential to ensuring that genomics research supports public health goals. Cross-disciplinary efforts are needed, including the contributions of, among others, clinicians, epidemiologists, social and behavioral scientists, industrial hygienists, cell biologists, immunologists, and geneticists to study design. Similarly, an on-going effort to pool research data and identify evidence gaps will be needed. It is very likely that studies of gene-environment interactions will require iterative efforts to define different genetic and environmental risk factors and to evaluate interactions systematically. Innovative approaches will be needed to accomplish this task efficiently. Dialogue among different interested groups, including communities in which research participation is needed, can help to move this ambitious research agenda forward.

Policy

Research in asthma genomics has implications for several aspects of health policy. The first is research funding. Public health practitioners have an interest in a research agenda and funding decisions that favor the strategies most likely to yield information relevant to the reduction of asthma morbidity and mortality. As with other complex biological questions, accumulating knowledge and technical innovation will change research opportunities over time. Public health leadership could play an important role in advocating for a research agenda that takes advantage of efficient strategies for assessing the dual contributions of genes and environment to asthma outcomes.

Research policy discussions might also include strategies to increase the availability of research data collected in drug trials. For example, it might be possible to consider strategies to encourage or require proprietary data collected in drug trials to be published or made available to other researchers without compromising the commercial opportunities of the sponsoring company. Public health leadership might be able to assist in exploratory discussions of this issue.

Clinical practice guidelines represent another important policy area, particularly as the potential for diagnostic or predictive genetic tests related to asthma approaches feasibility. Two new aspects of clinical practice guidelines can be anticipated. The first will be the consideration of pharmacogenomic tests and new drugs, likely to be costly, targeted at specific clinical subtypes of asthma. Evaluation of new drugs will often involve evidentiary questions similar to those already addressed in clinical practice guidelines for asthma. However, the potential involvement of genotype testing to determine candidacy for treatment will require genetics expertise and consideration of the evidentiary standards to be used for determining when the use of a genetic test/drug pathway is appropriate for clinical practice.

The second issue to be addressed in clinical practice guidelines will be the appropriate clinical use of freestanding genetic tests, for specific gene variants or “genetic profiles” measuring multiple gene variants in a single test. Although genomics research is likely to produce tests with sufficient predictive value to be considered for clinical use, they will certainly not be as predictive as genetic tests for single gene diseases. Rather, genetic tests will identify a significantly increased likelihood of asthma, or other clinically relevant risks, such as sensitivity to specific environmental exposures, or increased risk for chronic persistent asthma. Ultimate outcomes will vary among different people with the same genotype, and it is likely that variation will be only partially explained by identifiable environmental exposures. At what level of risk is a test suitable for use, and to what extent should test results determine the interventions to be used? Will some form of genetic counseling be needed if such tests are to be used? If so, how can these resources be made available? If not, what are the implications for genetic education of primary care clinicians?

Need for an informed public health workforce

Public health expertise can make important contributions toward assuring effective research study design, appropriate research goals, rational practice guidelines and strategies for assuring access to new technologies to the medically underserved. Yet there is skepticism: most public health practitioners can legitimately ask, “Where’s the beef?” (Wulfsberg EA, 2000), because concrete applications of genomics in public health remain, for the most part, distant and uncertain. Realistically, the lack of immediate public health applications in asthma and other common chronic diseases means that learning about genomics is not a high priority for most public health practitioners right now. Nevertheless, the likely impact of genomics in the future calls for a strategy to develop a public health workforce that is adequately prepared. Thus, the goal should be to create an infrastructure that supports evaluation, dissemination of information, and education. This infrastructure would most likely take the form of a small national group with multidisciplinary expertise, interacting with state and academic partners, to serve as a source of expertise on an as-needed basis for local and state public health agencies and their partners. Providing support for this infrastructure could be an important federal function. One role for the public health participants in this process would be to engage in a variety of cross-

disciplinary dialogues – contributing to study design and setting of research agendas, critical evaluation of research, and discussion of potential practice applications.

IMPLICATIONS FOR PUBLIC HEALTH: REVISITING OTHER PERSPECTIVES

This consultation considered a range of perspectives, as a background for considering potential public health actions. Given the possible outcomes of genomics research for the care of asthma patients, implications for different groups can be summarized as follows:

- **Patient/family:** In the short term, genomics research may result in the development of new drug treatments, and of genetic tests that predict drug response. These developments will apply to people with diagnosed asthma and are not likely to result in dramatic changes in how people receive care. However, some new drugs may be very expensive, making access a crucial issue for the medically underserved. If genetic testing prior to prescribing drugs becomes a routine practice, testing implications will become an important consideration: tests that predict medical outcomes beyond drug response will have the potential to generate worry, unnecessary or unproven treatment, or discrimination. In the long term, genetic testing may become a means to prevent asthma and improve its management. Patients and families will have an interest in how the potential risks of genetic testing – including unwanted information, the potential for discrimination, and individual or group stigma – are addressed. They are also likely to play an important role as participants in research, and need to be assured that research agendas are appropriately focused on health care improvements.
- **Community:** Research into the genetic contributors to asthma carries with it the potential for promoting genetic determinism; that is, the idea that gene variants *cause* asthma, rather than contributing as one of many factors to it. Study designs that focus exclusively on genetic differences may provide apparent support to this concept. If the prevalence of gene variants associated with asthma differ among different populations, this approach could lead to an overly simplistic conclusion that genetics is the cause of disparities in asthma burden among different populations, underestimating the importance of environmental factors. Similarly, a focus on the genetic contributors to workplace asthma could turn attention away from remediable workplace exposures.
- **Researcher:** Because the etiology of asthma is complex, research across many disciplines is needed, and with it, support for and access to multidisciplinary collaboration. Collaboration across disciplines can be difficult however – often researchers from different disciplinary backgrounds use terminology differently and have a limited understanding of the components of scientific rigor outside their area. For example, an epidemiologist may have limited knowledge about the technical demands of genotyping studies and, conversely, a geneticist may construct a case-control study with little attention to the comparability of the populations from which the two groups are drawn. There is a need for experts who are fluent in multiple scientific languages to facilitate such collaboration. Alternatively, teams of experts can be established and supported; however, this approach requires commitment from all involved. In addition, resources for large, well-designed studies that offer sufficient power will be needed, with a commitment to using such expensive resources ethically and efficiently.
- **Health care professional:** As new treatments or prevention strategies emerge from genomics research, health care professionals will need data to support evidence-based practice guidelines. To the extent that genetic testing becomes a part of asthma care, they will need access to appropriate education and referral sources to ensure appropriate use of testing. New pharmaceuticals are typically marketed heavily to physicians, and at least one pharmacogenetic test (not related to asthma) is already being actively

marketed (OtoDx, Athena Diagnostics). As genomics based clinical care is proposed, physicians will need trusted sources to separate hype from genuine opportunities.

- **Commercial developer:** New drugs and genetic tests will not be developed without commercial incentives, and commercial developers have a legitimate interest in preserving the value of proprietary data and products. The convening power of public health may play an important role in fostering discussion among different stakeholders, on issues such as the release of data from drug trials and the evidentiary standards by which new drugs and genetic tests will be evaluated.

IMPLICATIONS FOR PUBLIC HEALTH ACTION

We identified several areas where actions on the part of public health can help to ensure that genomics research provides support for public health goals to reduce asthma morbidity and mortality.

RESEARCH

Critical evaluation of genomics research related to asthma

Intense interest in genomics research for health care tends to promote what one of the consultants referred to as a “genocentric” view of complex clinical problems. Headlines proclaim the discovery of “the gene for disease X”, without much attention to the complex etiology of diseases such as asthma (Khoury M *et al.*, 2000). Researchers and practitioners concerned about the public health implications of asthma research need to be vigilant against the over-interpretation of genetic data, or an overly ready assumption of genetic causes for observed differences. We encountered several experts who considered a genetic explanation likely for the difference in asthma prevalence observed between Mexican Americans and Puerto Ricans, because these populations differ considerably in geographic origin. However, all agreed that potential environmental factors that have not yet been systematically studied might explain or contribute to the difference. Public health has an important role to play in assuring that such systematic assessment occurs. This evaluative process could occur at CDC, through collaboration between the National Center for Environmental Health and the Office of Genomics and Disease Prevention, or could become a core task of designated academic groups, such as the Centers for Genomics and Public Health or other academic partners.

Ensuring that needed research gets done

As critical evaluation reveals evidence gaps, funding and advocacy will be needed to ensure that the gaps are addressed with appropriate research strategies (United States Department of Health and Human Services, 2004).

There are likely to be productive opportunities in existing studies. For example, funding and appropriate expertise might help to improve collection of concurrent environmental measures in existing linkage studies and other gene discovery studies, and to add genetic measures to epidemiological studies focused on environmental exposure. Large population-based studies will be needed in the foreseeable future to assess key hypotheses (such as gene-environment interactions that might form the basis for innovative immunotherapy or other new therapeutic approaches). CDC could play an important role in contributing to the design and implementation of such studies.

CDC and state public health agencies could also play an important role in crafting public messages to ensure adequate participation in population-based studies. Some of the consultants involved in this project expressed concern about the possibility that fear of genetics might make people reluctant to participate in research involving genetic testing. Consultants voiced the belief that public health leadership, especially from

CDC as a trusted agency, could help to ensure that effective and informed recruitment for large-scale genetic studies occurs. An important starting point is to understand the concerns of various communities with regard to participating in studies that involve the collection of genetic material. Knowledge and attitudes about genetic information and the organizations conducting genetic research may affect recruitment and participation in research studies. Thus, an effort should be made to engage communities, particularly those at increased risk and likely to be approached for such studies, early in this process rather than at the point when recruitment begins. Such dialogue is likely to ensure that community needs are addressed and contribute to the definition of appropriate research policies for collection and management of genetic data, to guard against inappropriate uses or disclosures.

CLINICAL PRACTICE GUIDELINES

Public health leadership plays a central role in the development of evidence-based practice guidelines for asthma care (Williams SG *et al.*, 2003). Clinical guidelines for interventions to reduce environmental exposures may be influenced in the future by genetic tests that identify populations with a high susceptibility to specific environmental exposures. The most immediate application likely to affect clinical practice guidelines, however, is pharmacogenomics. Participants in this policy-making process should be prepared for critical evaluation of pharmacogenomic-based therapy. This process will require a careful assessment of the utility of drugs requiring prior testing to determine candidacy for treatment, and of genetic tests proposed as a means to tailor drug regimens.

Currently genetic tests – even those proposed as a guide to drug therapy – are not subject to regulatory oversight prior to marketing, unless they are sold as kits (Secretary’s Advisory Committee on Genetic Testing, 2000). Post-market oversight is through the Clinical Laboratory Improvement Amendments (CLIA, <http://www.cms.hhs.gov/clia/>), and focuses primarily on analytic validity – that is, on whether the test accurately identifies the genotype or other analyte in question. As a result, policy-makers cannot assume that the kind of outcome data mandated for drug treatment – randomized clinical trials – will be available for pharmacogenetic tests. Public health leadership could be critical in defining acceptable evidence thresholds for the use of such tests, and in assuring that the research is done to gather the needed evidence.

In addition, policy-makers will need to consider how access to effective treatments can be assured for the medically underserved. If new drugs, like Xolair, are very expensive, a careful assessment of cost-effectiveness in comparison with other therapeutic regimens will be needed.

In the future, policy makers will face questions about the use of genetic tests to predict asthma risk or prognosis. As with pharmacogenetic tests, evidentiary standards for the clinical use of predictive genetic tests are not defined. It is most likely that decisions regarding the use of genetic tests in asthma care will follow a process of expert consensus and practice guideline development, rather than a regulatory model. The CDC could use its convening power to initiate discussions on this issue, involving all stakeholders, in order to lay the groundwork for development of clinical practice guidelines in the future.

CREATING AN EFFICIENT INFRASTRUCTURE FOR TECHNICAL SUPPORT, CONSULTATION, AND EDUCATION

A well-informed workforce needs to be developed if public health professionals are to make meaningful contributions to genomics research; incorporate genomics measures into epidemiological and health services research; and participate in development of practice guidelines involving pharmacogenetics and predictive genetic testing. Realistically, given the lack of current practical applications of genomics to asthma care, this should be done incrementally, with the initial emphasis on a small group of well-informed public health personnel who can provide a public health presence in collaborative discussions and serve as a resource to colleagues on an as-needed basis.

It is likely that the most efficient way to accomplish this task will be to develop an infrastructure comprising three components:

- A national committee, with representation from federal, state and local public health agencies, professional organizations, and academic institutions, could provide leadership for this effort. The group, or designated subcommittees could, with appropriate support, monitor research progress, interface with practice guideline committees and major research groups, and provide periodic uptakes to the public health community on implications of asthma genomics for public health practice.
- Public health personnel in state or local agencies with asthma expertise, who would be willing to serve as the “genetics point person” in their region. These personnel would represent a reserve workforce, expending relatively little effort on genetics issues at the present time, but willing to become informed about genetics so that they are able to respond quickly when genetic initiatives, related either to research or service development, are needed. Some might participate as members of the national committee.
- Academic groups with an interest in public health genomics, which could provide a link between asthma genomics activities and other public health genomics activities. These groups could contribute to the critical assessment of current genetic research activities and development of new research ideas, could implement research, and could provide technical assistance on an as-needed basis to states in their region. The Centers for Genomics and Public Health that have been established in Washington, Michigan and North Carolina represent one model for this type of resource.

With this kind of infrastructure, the public health system could move quickly to assess opportunities for new genomics programs – e.g., routine use of pharmacogenomic testing prior to prescribing asthma drugs or newborn screening to identify children at risk – without involving the entire workforce in an area of genomics that does not yet have public health applications. When genomic applications reach a point of potential feasibility, these groups could work together to develop appropriate education and practice guidance for the public health workforce.

While genomics research holds promise for improved treatment and prevention, these outcomes will not be achieved without careful attention to the interaction between genetic and non-genetic contributors to asthma, and assurance of adequate access to health care services for all patients with asthma. Actions on the part of public health can help to ensure that genomics research supports public health goals to reduce asthma. Public health can be instrumental in facilitating analysis of, and communication about, research in asthma genomics and relevant practice applications. Public health can achieve this role through ongoing critical evaluation of research on genomic contributors to asthma, participation in the development of appropriate methods for evidence-based review of pharmacogenomics and genetic testing, and utilization of the convening power of public health to foster multidisciplinary collaboration. Public health can also play a role in endorsing population-based research that incorporates consideration of both genetic and environmental risk factors by funding and advocating to ensure that evidence gaps are addressed with appropriate research strategies, and participating in design of recruitment and data management strategies for population-based genomics research. Lastly, public health can play a role in advocacy and outreach. This role can be realized through promotion of efforts to ensure access to genomics-based therapies for the medically underserved and support for community-based participatory research methods to assess attitudes toward genomics, needs for genomics education, and the potential for genomic application in health care to result in adverse social consequences.

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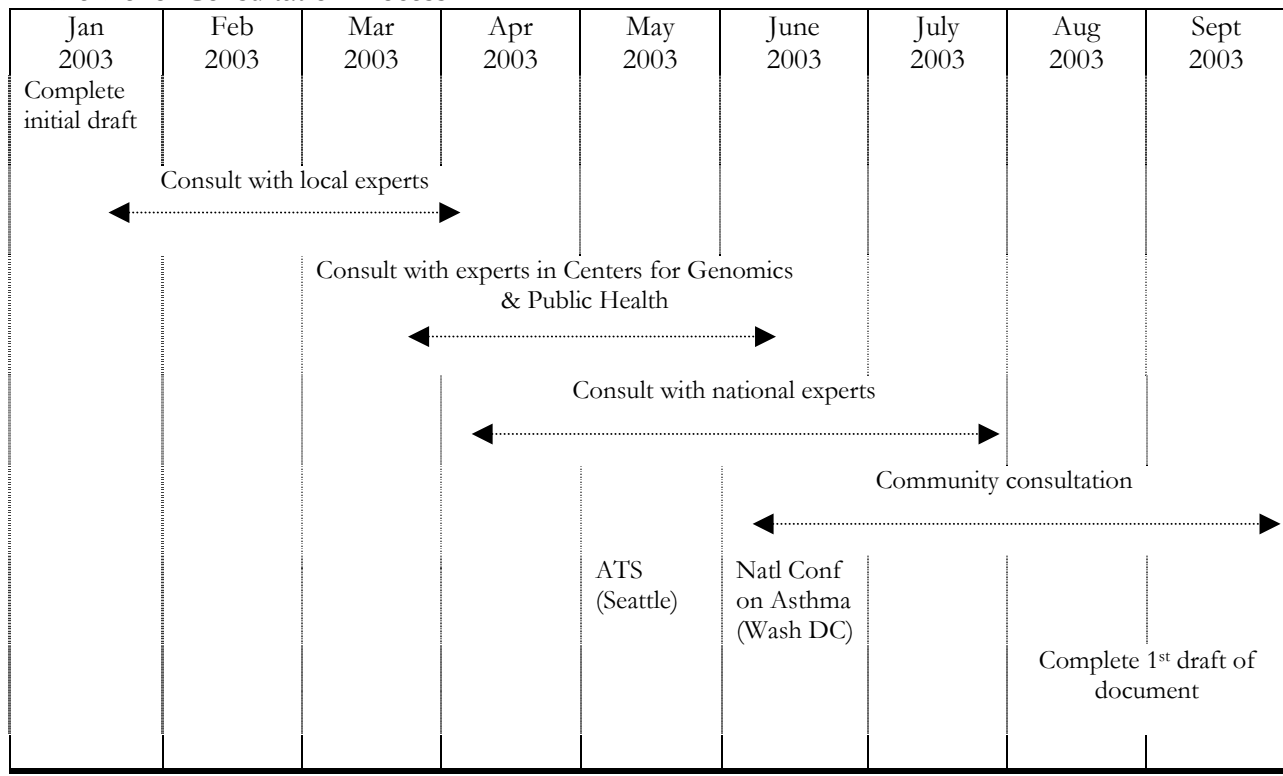
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Timeline for Consultation Process



APPENDIX B: ACKNOWLEDGEMENTS¹

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APPENDIX C: CONSULTATION GUIDE

1. How would you define genomics?
2. Does the framework provided by the translational pathway and the table provide a useful way of framing the discussion of the implications of genomics for asthma disease prevention?
 - Are there missing perspectives? What different groups/agencies do you see represented in each perspective?
 - Are there alternative ways to approach the problem?
 - What perspective(s) do you feel you represent?
3. From your perspective, is genomics currently a factor in asthma care? If yes, does it affect:
 - Universal prevention measures
 - Risk-based prevention measures
 - Diagnosis
 - Management
 - Public health effortsIf no, why not and what would make it applicable? Are there barriers?
4. Is genomics likely to have an impact on asthma care in the future? If yes, will it affect:
 - Universal prevention measures
 - Risk-based prevention measures
 - Diagnosis
 - Management
 - Public health effortsIf no, why not and what would make it applicable? Are there barriers?
5. What research is most important in the area of asthma genomics? Why is this research most important?
 - What are the barriers to accomplishing this research?
 - What could be done to encourage this research?
 - How could this research contribute to improved asthma outcomes?
6. Are there potential harms related to asthma genomics?
 - If yes:
 - What are they?
 - Are there potential mechanisms/solutions to prevent or control these harms?
 - If no, why not?
7. Does your own work involve genomics?
 - If yes, how?
 - If no, do you expect it to do so in the future?
8. Do state agencies and the CDC have a role in the application of genomic information or research to asthma disease prevention?
 - If yes, how?
 - If no, why and do you expect it to do so in the future?

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