National Heart, Lung, and Blood Institute Clinical Proteomics Working Group Report

Christopher B. Granger, MD; Jennifer E. Van Eyk, PhD; Stephen C. Mockrin, PhD; N. Leigh Anderson, PhD; on behalf of the Working Group Members*

Abstract—The National Heart, Lung, and Blood Institute (NHLBI) Clinical Proteomics Working Group was charged with identifying opportunities and challenges in clinical proteomics and using these as a basis for recommendations aimed at directly improving patient care. The group included representatives of clinical and translational research, proteomic technologies, laboratory medicine, bioinformatics, and 2 of the NHLBI Proteomics Centers, which form part of a program focused on innovative technology development. This report represents the results from a one-and-a-half-day meeting on May 8 and 9, 2003. For the purposes of this report, clinical proteomics is defined as the systematic, comprehensive, large-scale identification of protein patterns (“fingerprints”) of disease and the application of this knowledge to improve patient care and public health through better assessment of disease susceptibility, prevention of disease, selection of therapy for the individual, and monitoring of treatment response. (Circulation. 2004;109:1697-1703.)

Key Words: proteins diagnosis prognosis genetics plasma

The practice of medicine is based on defining disease by patient history, physical examination, and various clinical laboratory parameters that enable selection and guidance of effective treatments. The use of more sophisticated markers of disease, both in imaging and in the laboratory, has enabled more targeted therapy. Improvements in proteomic technologies that allow characterization of protein gene products, coupled with carefully constructed clinical databases and sophisticated analytic techniques, will serve as an important bridge to connect our nascent appreciation of biological complexity with our ultimate goal of understanding and treating disease. Furthermore, thorough understanding of early protein abnormalities associated with major diseases will result in a revolution in preventive medicine by greatly enhancing our ability to identify patients at risk and those with preclinical disease. Such is the promise of clinical proteomics.

Clinical proteomics aims to link expertise in a number of disparate scientific and clinical domains to achieve very practical ends. These domains include separating, identifying, and characterizing proteins; defining and constructing clinical databases and sample collections; and testing clinically relevant hypotheses against complex data sets derived from high-throughput measurement techniques and well-phenotyped human populations. Optimal exploitation of the relationships between protein patterns and disease further depends on careful integration with information about genetic variation and gene expression. The resulting knowledge of the molecular processes and mechanisms underlying disease will lead to novel therapeutic strategies, both through more targeted application of existing therapies and through identification of novel therapeutic targets.

Diseases and disorders of the heart, lungs, blood, and sleep constitute many of the major causes of morbidity and mortality. Chronic obstructive pulmonary disease causes more than 500 000 hospitalizations and more than 100 000 deaths a year in the United States, which places an enormous burden on our healthcare system. Sleep-related problems occur very frequently in adults and children and are estimated to affect 50 to 70 million Americans. Sleep disturbances reduce productivity and quality of life; increase the likelihood of workplace, home, and vehicular accidents; and are associated with a markedly higher risk of morbidity and mortality. Although blood diseases may be relatively uncommon, sickle cell disease is a major health problem in the black and Hispanic populations, affecting 72 000 Americans, and hemophilia affects ≈20 000 Americans.

The good news is that major progress has been made in treating some of these diseases. For example, a number of therapies have been proven in large clinical trials to reduce mortality in coronary heart disease and sepsis. The cost, complexity, and side effects of these therapies, however, can
limit their availability and use. Improving public health during the next 5 to 10 years will depend in large part on better application of these existing treatments to individual patients. To do this, we will need a much deeper understanding of disease classification, staging, and response to therapy in the context of the complexity of the individual. Such unprecedented, detailed characterizations of human disease will emerge primarily from efforts in clinical proteomics, which justifies an aggressive strategy for research investment in this field.

Improved patient care through the use of protein markers is a well-proven paradigm. For example, use of novel protein markers has become an integral part of clinical cardiology in the past 10 years. Blood measurements of C-reactive protein, troponin, and B-type natriuretic peptide (BNP) are becoming routine measures to determine risk, diagnose, prognosticate, and guide treatment of coronary heart disease, acute coronary syndromes, and heart failure. In fact, the very definition of heart attack, as well as determination of the relative benefit of more potent antithrombotic treatments, currently rests on serum troponin measurement. Even detection of minute levels of this protein identifies patients at high risk of adverse outcomes and identifies which patients will derive greater benefit from antithrombotic and other aggressive interventional strategies.

BNP provides a recent example of the relatively rapid discovery and clinical validation of a novel marker for managing congestive heart failure. First reported to be found in human hearts in the early 1990s, BNP levels in the blood were found to correlate with existing heart failure in a number of small studies. A study of 1586 patients showed that a point-of-care BNP assay added substantially to standard clinical information in the diagnosis of congestive heart failure, and the test has been approved by the US Food and Drug Administration (FDA). BNP has also been shown to risk-stratify patients with heart failure and with acute coronary syndromes, and it has become a common candidate marker to define populations of patients who may derive particular benefit from a variety of new (and often more expensive) treatments, including implantable cardioverter defibrillators. Yet an obvious hypothesis is that definition of patterns of disease-related changes, including novel disease marker proteins, would provide substantially more useful clinical information than a single marker.

Observational studies have shown that the combination of protein markers (for example, troponin and C-reactive protein) into panels can provide valuable additional information in stratifying risk in acute coronary syndromes. Yet the use of protein markers is limited by the lack of information about how patterns of change (“disease fingerprints”) in panels of proteins may provide more useful information than individual measures. Moreover, the study of protein markers has been focused on “candidate” protein approaches, whereas technologies now allow unbiased assessment of how patterns of proteins differ in various disease states. So far, there are only a few examples of the systematic approach to defining such protein fingerprints, but these appear very promising (eg, the use of protein mass spectra to provide a powerful diagnostic tool for ovarian cancer). This, then, is the opportunity for clinical proteomics: to define patterns of proteins that provide clinically useful information about susceptibility to disease, diagnosis, prognosis, and guided therapy.

Figure 1. Three stages required for clinical proteomics to affect delivery of health care.

Opportunities

General

The foundation laid by the Human Genome Project, providing the basic blueprint for molecular medicine, is now ready to support construction of a large practical structure, one that can be used to ascertain the detailed medical status of an individual patient and to select the best therapy. The National Heart, Lung, and Blood Institute (NHLBI) has invested in a broad portfolio of programs aimed at genomics in medicine, and now is an appropriate time to reexamine how these investments will be translated into tangible improvements in public health. We, a group of experts representing various relevant disciplines, believe that there is now a unique opportunity, through clinical proteomics, to focus thinking and resources at the intersection of proteomic technologies and clinical research.

The opportunity for clinical proteomics to impact the delivery of health care will require coordination of 3 stages (Figure 1): discovery and selection of protein patterns, validation in large clinical data sets, and translation into clinical practice. Although the investment in technology and discovery that has been made to date is a requisite, the major opportunity now is to enhance the validation stage, as well as integration of discovery and validation as a bridge to translation into the clinic.

Advancing Technologies

Technology development has been a major driver of opportunities in proteomics, as it has been in genomics. These technologies are aimed at improving our ability to separate, identify, quantify, and characterize the complexity of proteins and protein systems for the discovery and selection of biomarkers, targets, and disease fingerprints, followed by validation with large clinical databases. In addition, the NHLBI Proteomics Initiative, which has funded 10 Proteomics Centers, will accelerate development of important new technologies that can be applied in clinical proteomics for discovery and validation of proteins for clinical application. These NHLBI Proteomics Centers offer exciting opportunities for leveraging this investment for improved application of novel technologies to broader clinical proteomic applications. In parallel with the development of novel technologies...
for discovery proteomics, there are major efforts to apply and adapt the existing, more robust technologies of the clinical laboratory, including widely used and very sensitive immunoassay platforms, to the problems of high-throughput marker validation.

Bioinformatics
As advanced technologies and carefully defined patient populations permit generation of higher-quality clinical proteomic data sets, the opportunity provided by advanced informatics, bioinformatics, and other analytic approaches will become increasingly important. Improved data visualization technologies and multivariate statistical algorithms, for example, provide key tools for finding disease fingerprints in proteomic and microarray data sets. Because large-scale application of these methods is still in its infancy, there is so far no general agreement on which resulting pattern is “right” or which mathematical method is most appropriate in a given clinical study design. Significant and rapid maturation of this field is necessary to support FDA acceptance of multiparameter tests, including a well-developed understanding of both biological and measurement errors. With the opportunity to leverage complementary genetic and gene-expression information along with clinical data, bioinformatics will also provide the means for effective integration of multiple biological levels, thereby supporting discovery and evaluation of candidate disease patterns in large clinical data sets. Expansion of existing information technology infrastructure (bioinformatics and statistics) and training efforts (among clinicians and scientists) will be required to support effective progress toward these goals.

Clinical Samples
Completed and ongoing clinical trials and epidemiological studies, sponsored by the National Institutes of Health (NIH) and by industry, have commonly included patient sample collection in their protocols. Whereas modest numbers of very-well-characterized clinical samples are critical for protein marker discovery, large numbers of equally high-quality samples are required to validate these markers and progress them toward routine clinical use. Extensive sample sets could be obtained from existing sample banks and ongoing studies if the sponsoring groups can be assured that many important candidate markers will be tested in small volumes of precious samples. The NHLBI can play a key role in fostering access to such samples for clinical proteomics, leveraging the investment in previous studies and enhancing the value of future work through incorporation of optimized proteomics sample collection protocols.

Although the most commonly collected sample is blood (the focus of most clinical proteomic study to date), other body fluids may provide additional important opportunities. Urine has advantages of easy accessibility and stability, and its contents reflect a wide variety of blood vessel and other pathophysiology. Moreover, even total urine protein content contains highly significant independent prognostic information in vascular and metabolic disease. Bronchoalveolar lavage fluid provides important information about lung function that may be useful for study of a variety of pulmonary diseases. For all of these sample types, collection and long-term storage methods can be improved substantially with reference to the requirements of discovery clinical proteomics, especially through prevention of protein modification (eg, proteolysis). Because there is currently no reason to assume that many newly discovered protein markers will be more labile than the proteins currently used in clinical diagnostics, retrospective sample collections should play a major role in validation.

Disease Focus
The NHLBI has the opportunity to guide clinical proteomics resources toward diseases that have both high impact and high likelihood of rapid progression to clinical application. In diseases of the heart, lungs, blood, and sleep, one common theme for diagnosis and prognosis is inflammation, and the advance provided by the C-reactive protein, a nonspecific measure of inflammation, suggests that there may be further opportunity to impact clinical practice with refined inflammatory protein marker patterns. Likewise, care of patients with heart failure and with acute myocardial infarction already depends on protein marker guidance, and clinicians might readily embrace further development. Sleep disorders represent an excellent opportunity for the discovery of biomarkers with proteomic approaches. The current diagnostic “gold standard” is polysomnography, the monitoring of physiological data during sleep. This costly approach consistently underestimates the incidence of sleep disorders. Like coronary artery disease, sleep disorders are accompanied by an inflammatory response that is amenable to proteomic analysis. Diseases of coagulation factor abnormalities are also well suited for clinical proteomic characterization. Ultimately, insights into mechanism and novel targets will generate new therapies.

Challenges
Dealing With Complexity in Clinical Proteomics
Proteomics is inherently challenging because of the complexity of the molecules with which it deals, the protein working parts of biological systems. Their varied functional roles require proteins to be made, modified, and often quickly remodeled under the control of numerous multilevel systems. Clinical proteomics is further complicated by the fact that proteins manifest genetic differences among patients at both the structural and quantitative levels. Compared with nucleic acids, proteins show much wider variations in physical properties (which leads to greater difficulties in global separation and detection) and in abundance (protein concentrations vary by more than 10^10 in plasma, which generates additional technical challenges for detection of minor components). Despite these difficulties, proteins offer the best general picture of what is working in a cell or tissue, and what is not. Thus, although proteomics is currently far from comprehensive, it can point to numerous proteins with intriguing, if unproven, clinical utility.

Translational Infrastructure
The major shortfall of clinical proteomics exists in the infrastructure required to translate new protein knowledge.
into practical products and practices that have an impact on medicine. The rate of FDA approvals of tests for new protein markers in blood has actually declined over the last decade to a level near zero today (almost no new tests being offered to supplement the existing protein diagnostic portfolio). Similarly, the introduction of fundamentally new classes of therapeutic drugs, aimed at novel protein targets, has also slowed in recent years. This lack of progress is counterintuitive in the face of an expanding understanding of biology at the protein level and results, at least in part, from shortfalls and bottlenecks in translational research.

The requirement for translation arises because, like most biological discoveries, the connection of a certain protein fingerprint with a disease usually emerges from experimental studies using small sets of patient samples and the advanced but laborious analytical methods of “discovery” proteomics. Even with optimal proteomics technology and analysis, failure to carefully characterize the most relevant patient populations may limit the discovery process. And then investigators who make these discoveries are not generally equipped to take them to the next crucial stage: the “validation” of the protein fingerprint. Validation is necessary to confirm the relationship of the fingerprint to the target disease in large numbers (often thousands) of patient samples. Validation studies require highly standardized “factory-scale” protein measurement systems and access to large sets of very carefully selected samples with associated clinical information. In other words, they require different expertise and greater clinical resources than does the discovery step. The validation process provides the critical evidence necessary for the adoption of a protein test as a commercial product by the in vitro diagnostics industry. Combined with clinical efficacy studies, it provides the evidence of the clinical value of a protein fingerprint and justifies its ultimate use in nationwide medical practice.

Important components of the required validation infrastructure are not effectively accessible to the clinical proteomics community today. Missing elements include the following: (1) technology for measuring numerous candidate markers accurately in small volumes of many samples at reasonable cost (validation assay technology); (2) large, well-characterized clinical data and sample sets; and (3) funding for the performance of validation studies. The integration of these resources into a functioning pipeline and their combination with clinical genomics data remain to be accomplished.

**Patent and Regulatory Barriers**

Additional public policy challenges arise in the areas of intellectual property and government regulation. Given the large number of gene and protein patents that have been filed, the assembly of diagnostic panels of proteins used in fingerprint diagnostic tests could be seriously constrained by the difficulty of assembling the necessary bundles of rights from multiple patent holders. At the same time, the FDA has not yet approved any multiprotein panel or fingerprint as a diagnostic test; the regulatory approach the agency will take in this area has not yet been made clear, and no clinically significant bodies of data have been made available to the FDA in support of any indication for their review. These issues point to the fact that a successful effort to obtain the clinical benefits of protein fingerprints must incorporate substantial communication and outreach to other interested communities in the public policy arena.

**Public-Private Partnerships**

The current paradigm for clinical technology innovation focuses primarily on the pharmaceutical model, in which a highly profitable industry with large research budgets leverages NIH-supported basic science into effective drugs. This industry supports extensive validation efforts to confirm the value of drug targets (generally proteins) and supports a complete pipeline to discover drugs and test them in animals and ultimately humans. By comparison, the worldwide diagnostics industry (the primary commercial vehicle by which many of the early benefits of clinical proteomics will be conveyed to patients) is roughly 1/20th the size of the pharmaceutical business and operates under rigorous cost containment; this industry does not have the financial resources (in the form of research budgets) to undertake extensive validation efforts for more than a handful of candidate protein disease markers on its own. Protein markers may provide intermediate phenotypes for guiding drug monitoring and development, as well as elucidation of novel pathways and targets that may be useful to the pharmaceutical industry. However, this type of marker development is focused on internal uses that cover a limited spectrum of therapeutic opportunities and is thus unlikely to contribute to a significant expansion of the generally accessible diagnostic portfolio. For these reasons, public resources are necessary to bridge the “validation gap” and bring new protein tests to commercial feasibility and clinical use.

**Multidisciplinary Research**

Clinical proteomics involves a very broad mix of disciplines, including clinical medicine, proteomics, study design, clinical diagnostics, and several areas of bioinformatics. Developing working relationships among such a diverse set of investigators is challenging, particularly when the main goal is development of a coherent pipeline to ensure successful progression of protein markers through a series of stages. In addition, the best team of investigators must pull together various disciplines across institutional and geographic boundaries.

**Education and Skills Development**

A major related challenge is the paucity of skilled investigators available to apply their efforts to clinical proteomics. Many investigators skilled in proteomics technology have yet to focus their attention on heart, lung, blood, and sleep research, whereas heart, lung, blood, and sleep researchers face significant hurdles in choosing among proteomics approaches and acquiring the associated instrumentation and expertise. Some components of the skills base are concentrated in commercial organizations (biotechnology, pharmaceutical, and diagnostic industries), and it will be especially challenging to bring them into the public research arena.
Recommendations
The emergence of clinical proteomics promises major advances in disease management, provided that a complete pipeline exists for translating protein discoveries into tangible medical products. The protein marker pipeline is currently limited by a major bottleneck at the level of candidate marker validation: the systematic testing of proposed protein markers and their patterns to establish value in clinical practice. An opportunity thus exists to construct an effective public-private partnership (Figure 2) in which the NHLBI can leverage open the protein marker pipeline to generate near-term clinical benefit through creation of clinical proteomics networks.

Recommendation 1: Establish Clinical Proteomics Networks
These clinical proteomics networks should function as integrated umbrella entities to perform 2 principal activities critical to improving diagnosis and treatment of NHLBI diseases. These activities, detailed below, require cross-disciplinary collaboration and effective coordination and are thus envisioned as activities of integrated components within each clinical proteomics network.

Discovery and Selection: Identifying Candidate Disease Markers
The discovery and selection process should be focused on the design of sets of protein markers that are most useful in clinical situations with unmet needs. Initial priority should be given to markers measurable in plasma or serum, with selected expansion to include bronchoalveolar lavage samples, urine, and other body fluids. An “open source” model and culture should be developed to accelerate progress toward the networks’ goals: operations of the networks should be as transparent as possible; the data generated should be openly accessible in the public domain; and the networks should solicit broad collaborative effort in data analysis.

Validation of Protein Patterns in Large Clinical Data Sets
To implement validation testing of the selected candidate markers and patterns and to deliver the desired diagnostic capability, support should be provided for quantitative measurement of hundreds of candidate markers in large sets (thousands) of carefully selected clinical samples (see below). A validation component of the clinical proteomics network, with membership partially or fully overlapping the selection component described above and with a similar combination
of disciplines, should be responsible for selecting sample sets and setting validation criteria for candidates.

- Several technology platforms already exist for measuring some proteins (eg, cardiac troponins, coagulation proteins, and cytokines), and additional conventional tests to provide high sensitivity, specificity, and accuracy at high through-put will be developed over time. These should be used where possible to assess the potential contributions of commercially assayable proteins to more effective multivariate panels.

- We suspect that in the majority of cases, new assays will be required for the accurate measurement of novel protein candidates, and support should be provided for the development and implementation of new assays and low-cost, high-sensitivity, high-precision measurement platforms that provide measurements of multiple proteins. Special emphasis should be placed on minimizing sample consumption per protein analyzed, to maximize the number of candidates than can be validation tested in available volumes of highly characterized clinical specimens.

- An ongoing validation effort, comprising 1 or more laboratories dedicated to providing protein measurement data of clinical laboratory quality, should be fostered to make accurate measurements of the prioritized protein candidates from the discovery and selection component in the appropriate clinical samples.

- These networks should develop and operate with an “open” database of validation data, together with statistical and bioinformatics tools to support their analysis. All validation data should be placed in the public domain, and all interested parties should be encouraged to assist in its analysis to achieve maximum diagnostic utility.

- The networks should develop and test innovative mathematical methods for selecting protein marker sets and for increasing the diagnostic sensitivity and specificity achievable by combining their measurements.

- These networks should develop and implement mechanisms for training clinical and scientific investigators in the multidisciplinary approaches of clinical proteomics.

**Recommendation 2: Create a Clinical Sample Repository to Support Clinical Proteomics**

Effective validation of protein diagnostics requires measurement of the candidates in large numbers of patient samples selected according to appropriate statistical designs. Such samples are expensive and time-consuming to acquire, and the lack of sample sets constitutes a major barrier to validation activities. Compared with the cost of creating an entire new study to collect data, a sample repository would leverage already existing sample sets, clinical trials, and epidemiological studies to establish a library of clinical and sample data that would overcome a major barrier to advances in clinical proteomics.

Demonstration of diagnostic specificity is particularly challenging, because the candidate diagnostic pattern must be shown to be absent in sets of samples from controls that include a broad range of other diseases. A repository of clinical specimens should therefore be created in which well-characterized samples from well-designed clinical studies (including controls) can be collected, stored, and made available to support clinical proteomics activities. This resource could also provide sample availability for genetic and gene-expression studies. The repository should assist validation and research efforts of a cross section of investigators through a peer review–access mechanism.

- The sample repository should be managed by a sample steering committee that includes representation from clinical trialists, the clinical proteomics networks, clinical chemists, and NHLBI staff.

- Sample acquisition efforts initially should focus on obtaining existing relevant sample sets through collaboration with existing NHLBI trials and epidemiological studies.

- Criteria should be developed to identify and prioritize samples for inclusion and minimal standards should be developed. Factors would include sample processing, disease, type, and quality of clinical database.

- Efforts to standardize sample collection methods and to develop advanced methods specifically suited to clinical proteomics should be supported.

- Acquisition efforts should concentrate initially on human plasma and serum and later expand to include bronchoalveolar lavage fluid, cerebrospinal fluid, urine, and other body fluid samples.

- Disease and demographic gaps should be identified and filled through collaboration with future studies.

- Longitudinal studies should be emphasized where possible because of their unique value in evaluating candidate disease markers, especially for identifying disease susceptibility and prognosis.

- NIH should recommend that all relevant future NIH-funded trials contribute samples to the repository.

- All relevant, available clinical data should be obtained on each specimen and incorporated into a database and methods and policies developed to permit effective use of the clinical data in collaborative proteomic efforts.

- Ethical, legal, and social issues and intellectual property support must be addressed to enable the repository collection to be used to greatest benefit in an open data environment.

- Privacy issues, including compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), must be ensured to avoid jeopardizing intended use of samples. This includes systematic approaches toward institutional review board approval, consent, appropriate security safeguards, and procedures to incorporate anonymity.

**Recommendation 3: Create a Mechanism to Support Ancillary Studies**

Large numbers of completed clinical trials and studies have already collected samples and clinical data that provide excellent opportunities for clinical proteomics research. However, lack of funding to assay and analyze these data sets may limit their usefulness. An effective way to increase the pace and output of clinical proteomics would be to provide supplemental funding to investigators to leverage these existing resources. For example, short-term, limited funding programs with expedited review could be used to stimulate
ancillary studies of such existing databases and clinical samples specifically for clinical proteomics study. Likewise, for industry or NIH studies that lack funding to collect samples for subsequent proteomics research, a supplemental grant program with expedited review should prove effective.

**Recommendation 4: Leverage Existing NHLBI Proteomics Centers**

The NHLBI’s investment in advancement of proteomics technologies can benefit clinical proteomics through shared access to improved marker-discovery technology, candidate disease markers, advanced bioinformatics platforms useful in annotation and validation of candidate protein markers, and proteomics expertise. Cross access and interaction between the Clinical Proteomics Networks and the existing Proteomics Centers should be facilitated. Collaboration could be enhanced through a joint clinical proteomics steering committee with representatives from Proteomics Centers, Clinical Proteomics Networks, Sample Repository, and Clinical Proteomics Education Program.

**Recommendation 5: Leverage Existing NIH Biomarker Networks**

Investment in advancement of proteomics technologies can benefit clinical proteomics through access to and interaction with the existing NCI Early Detection Research Network. Collaboration could be enhanced through a joint clinical proteomics steering committee with representatives from each institute and other NIH institutes developing proteomics initiatives.

**Recommendation 6: Promote Clinical Proteomics Education and Communication**

Progress in clinical proteomics should be encouraged through a variety of communication/education mechanisms in addition to the programs detailed above. Specific examples include the following:

- Encourage an emphasis on proteomics for study section reviewers, including K-award and F32 committees.
- Convene symposia/workshops to bring clinical proteomics researchers together with diagnostics industry and data analysis experts.
- Develop a “road show” to provide condensed education for clinicians on clinical proteomics and solicit sample sets and disease expertise.
- Develop ways to modify the reward system in the academic sphere to motivate the best researchers in each field to engage in multidisciplinary large-scale efforts like the clinical proteomics network.
- Highlight clinical proteomics progress at annual meetings of the American Heart Association, American Thoracic Society, American Society for Hematology, and Association for Patient-Oriented Research.

**Appendix**

**Members of the Working Group**

Dr Leigh Anderson, Plasma Proteome Institute, Cochair; Dr Christopher Granger, Duke Clinical Research Institute, Cochair; Dr Richard Boucher, University of North Carolina at Chapel Hill; Dr Joseph Garcia, Johns Hopkins Asthma and Allergy Center; Dr Jacek Hawiger, Vanderbilt University; Dr Jon Klein, University of Louisville; Dr Mark Knepper, National Heart, Lung, and Blood Institute; Dr Larry J. Kricka, University of Pennsylvania Medical Center; Dr Alexander Kurosky, University of Texas Medical Branch; Dr Kenneth Mann, University of Vermont; Dr Aleksandar Milosavljevic, Baylor College of Medicine; Dr Emanuel Petricoin, Food & Drug Administration; Dr Pei Pei Ping, University of California at Los Angeles; and Dr Jennifer Van Eyk, Johns Hopkins University. NHLBI representatives: Drs David Balshaw, Ebony Bookman, Santhi Ganesh, Stephen Mockrin, Pankaj Qasba, Susan Banks-Schlegel, and Pothur Srinivas.

**References**

National Heart, Lung, and Blood Institute Clinical Proteomics Working Group Report
Christopher B. Granger, Jennifer E. Van Eyk, Stephen C. Mockrin and N. Leigh Anderson
on behalf of the Working Group Members

doi: 10.1161/01.CIR.0000121563.47232.2A
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/109/14/1697

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/