Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
August 23-24, 2006

Cardiovascular Program – Theme # 10: Personalized Medicine Planning

Introduction:

Personalized medicine (PM) is the single most likely avenue by which application of genomic and other "omic" technologies will move from bench-to-bedside-to-community. Personalized medicine will improve the efficacy and safety of existing therapies and facilitate introduction of new therapies into routine clinical practice. The first applications are likely to be in the area of biomarkers of inter-individual variation in response to currently prescribed medications, but the long-term goal should be to compliment primary prevention and life-style modification. Application of high throughput molecular analyses to NHLBI's resource of extensively phenotyped individuals in clinical trials and population-based cohorts should rapidly lead to the development of novel biomarkers of disease and therapeutic response that will be the basis of PM for heart, lung and blood (and sleep) disorders. This committee has identified and prioritized strategic recommendations in five areas: biomarker discovery, research structure, clinical decision making, bioinformatics and data analysis, and training. We summarize below the recommendations with the goal of realizing PM's promise in a timely manner to improve quality of life and reduce the cost of health care delivery for society.

Recommendations:

1. Biomarker Discovery: Biomarkers include quantitative biological measures, imaging, genetic and other data that are in the causal pathway of disease or have utility for risk stratification. They are critical to PM from four perspectives: risk assessment, diagnosis, prognosis, and predicting response to therapy. Discovery and validation initiatives:

- Identify the clinical settings where focused and rapid biomarker discovery and validation can yield significant short term gains in clinical decision making. This goal will best be realized by using existing and ongoing clinical trials and population studies and partnering with the private sector.
- Apply existing high throughput technologies for the discovery of key genomic and other biomarkers and invest in the development of novel technologies for increasing the scope of applications.
- Leverage existing experimental paradigms (e.g. cell culture and animal models) to define pathways influencing response to defined stimulations relevant to specific therapies or prevention strategies.

2. Research Structure: Taking full advantage of the opportunities for personalized medicine will require changes in the structure and design of research studies and collaborations.

- Create more comprehensive NHLBI-supported biobanks and registries by:
    - Using the tremendous resource of existing NHLBI cohorts and other studies to create a useable "data enclave" available to biomedical researchers;
    - Creating registries that focus on adverse drug reactions in the post-approval setting to accrue events and develop novel predictors aimed at drug safety;

    - Standardizing phenotypes, markers, methods of evaluation for adverse events and major health outcomes;
    - Providing vital infrastructure to help all investigators better utilize these data and to integrate new investigator-initiated research (e.g. evaluation of novel markers and secondary data analyses).
- Leverage existing and future multi-center trials to validate the utility of proposed tools in clinical practice for efficient use of existing study data and to harmonize future phenotypic, environmental and genotypic data collection.

3. Training: PM affords great medical opportunities but realization will require the creation of uniquely trained researchers and physicians in contemporary "omics" technologies, the quantitative sciences, medicine and biology to alter the burden of heart, lung and blood (and sleep) diseases. We recognize the importance of training not only those in the fields of biomedical research and clinical medicine, but also other stakeholders (patients, legislators, healthcare agencies, consumers, etc.). Specifically, we recommend that NHLBI:

- Integrate educational activities in common with other NIH institutes in the area of the "omics" and quantitative sciences for new investigators, existing investigators coupled with individuals from other areas with relevant expertise.
- Target all grants for the expansion of the training of investigators with a NHLBI-related focus at various levels of their training and career paths, emphasize team research.
- Create a compelling story for "omics" related to cardiovascular medicine that is broadly understandable and compelling to all stakeholders. Fund thought-leaders, in partnership with industry, for the targeted dissemination of the importance of PM in CVD information to all healthcare stakeholders from patients to citizen groups to community physicians.
- Make PM one of the central principles of medical education but with a greater emphasis on concepts and predictive models than solely on case studies.

4. Data Analysis and Bioinformatics: Biomedical research in general and PM in particular, is encountering enormous data volumes from advances in "omic" technologies and biomedical imaging. However, the current "flood" is a mere "drop in the bucket" compared to what is on the horizon from affordable individual genome sequencing, real-time metabolomics and electronic medical records. Realizing the rich utility of these data will require a significant partnership between biomedical researchers, statisticians and computer scientists, and involvement from the IT industry. Specifically, we recommend:

- Development, validation and dissemination of analytic methods to predict an individual's response to treatment or life-style modification that are tailored for very large numbers of inter-related yet disparate variables (e.g. genomic variation and clinical data).
    - Appropriate methods from other data analysis intensive fields (e.g. energy and finance).
    - *De novo* development of novel analytical methodologies.
- Creation and dissemination of data enclaves facilitating large-scale analysis of existing data, especially "omic" data and outcome data from integrated health care networks.
    - Analysis of response to treatment and safety studies in NHLBI's clinical trials;
    - Gene by environment interaction studies in NHLBI's large cohort studies;
    - Outcomes and gene-by-environment interaction studies of electronic medical record data from large health care networks (e.g. Kaiser).

5. Clinical Decision Making: PM programs need to leverage novel genomic findings and combine them with traditional clinical and molecular markers to provide diagnostic and prognostic information and to evaluate biologically relevant pathways that guide therapeutics. Furthermore, PM will define and validate previously unrecognized subgroups within large patient populations. To make PM a clinical reality, we recommend that NHLBI:

- Expand collaborative efforts with other stakeholders (e.g., Payers, industry, VA, CMS, FDA) to validate the impact of markers on clinical outcomes and clinical decision making, specifically to:
    - Evaluate efficacy, cost-effectiveness and safety outcomes;
    - Optimize personalized medication dosing as well as disease prevention;
    - Identify high priority areas, including clinical settings with high cost, serious disease outcomes, or interventions with a narrow therapeutic index and higher complication rate (e.g. anticoagulants)
- Partner with the Roadmap translational initiatives (e.g. CTSA) to include community practitioners in extramural multidisciplinary teams so that diagnostic tests, interventions and screening can more rapidly translate into practice and improve quality of life and public health.

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Business Operations
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Recommendations:

	High	Medium	Low	Priority Rank
1. Create streamlined procedures for renewing grants for established investigators, including a briefer application and greater emphasis on prior productivity	7	8	5	5
2. Funding and Award Mechanisms	5	11	3	4
3. Create incentives and mechanisms for cross-Institute and interagency funding of large projects	15	3	1	2
4. Review the NHLBI pre-approval process for investigator-initiated grants with direct costs >$500K in any year and the process for Institute-initiated programs (RFAs, RFPs):	6	6	7	6
5. Create a mechanism to provide infrastructure support for large observational studies to facilitate addition of ancillary studies. Create mechanisms to assure that the data and samples from the core studies are made available to the wider scientific community as a resource for further research	16	4		1
6. Issues related to CSR and study sections	3	5	12	7
7. Dissemination and communication of advances and discoveries and resources made by NHLBI-Supported Investigators	10	6	4	3

a. Improving NHLBI Grant Efficiency

- Translate known markers by emphasizing technologies that NHLBI has already invested in (e.g., imaging and genomic variation) before investing in new technology (e.g., proteomics) (even if a $1000 genome scan were available it is unclear how this will be helpful clinically)
- Mining/Dissemination of existing data is crucial for the future of Personalized Medicine.
- Encourage cost effective methods for validation of genetic variants' risk prediction.

b. Expanding Cross NIH Partnerships

- Expand #5 to assure that the sample/data dissemination include other NIH institutes.
- Collaborate with NIMH; develop behavioral interventions targeting psychological risk factors.
- Catalog efforts among all NIH institutes and pool resources to decrease redundancy.
- Individualized medicine needs to be a pan-institute initiative.

c. Reaching out to Non-NIH Partners

- Develop partnerships with industry, insurers, CMS, VA to fund and evolve new approaches.

- Streamline funding mechanisms for collaboration with industry.
- Engage public and private partners to assist with collection of blood from patients enrolled in trials during the last 10 years.

d. NIH Grant Administration or Review

- Streamline the revision process for borderline applications.
- Streamline procedures for applying for a supplement to pursue a new finding that has emerged from ongoing currently funded work.
- Enhance collaboration by making subcontracting issues easier in multi-investigator/multi-institutional grants.
- Speed up recognition of Co-PI status and giving "credit" to multiple institutions

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