Thank you for the opportunity to provide the American Health Information Community (AHIC) with information on "Improving Health and Accelerating Personalized Health Care Through Health Information Technology and Genomic Information in Population- and Community-based Health Care Delivery Systems." We commend you on the creation of the working group on Personalized Health Care and very much look forward to our continued involvement and collaboration with the members of the AHIC and your colleagues at HHS. This working group provides the coordination and centralization needed to integrate multiple facets of our health care system to effectively develop and hopefully implement policy initiatives that will not only expand the adoption of electronic medical records, but recognize the crucial and synergistic role health IT plays in advancing personalized medicine.

Affymetrix, Inc. manufactures GeneChip ® Microarrays, and is considered to be a leader in the development of microarray products for the collection and analysis of complex genetic and genomic information. GeneChip® microarrays are used by hundreds of pharmaceutical, biotechnology, agrichemical, diagnostics and consumer products companies as well as academic, government and other non-profit research institutes to study and develop products based on the relationship between genes and human health. Over the years, Affymetrix has actively engaged in dialogues shaping policy surrounding personalized health care through our Government Relations and Public Policy office in Washington and direct participation in the Personalized Medicine Coalition, the Coalition for Genetic Fairness, agency hosted roundtable discussions, the OECD, CLSI, international standards development consortia, our own annual Genetic Age Symposium, and more.

Definition of Personalized Health Care

In early December, we held our most recent Genetic Age Symposium to foster dialogue on genomics policy issues. This year, we partnered with Northwestern University and hosted three panel discussions highlighting the Path to Personalized Medicine, addressing the climate and infrastructure needed to usher in this new era in medicine and the role of the individual. A theme that emerged from these discussions was the notion that many healthcare providers feel that they are currently practicing personalized health care and that they take offense when people say otherwise. During the October AHIC meeting, one of your panelists, Dr. Alfred Berg, raised this same concern. This is greatly tied to the definition of personalized health care, which should indicate more than the individualized interactions, but the use of genomic information to guide healthcare decisions. In their white paper called "The Case for Personalized Medicine," the Personalized Medicine Coalition summarizes personalized medicine as incorporation of molecular analysis to achieve optimum medical outcomes in the management of a patient's disease.[1] This is a subtle distinction, but one that the working group should acknowledge as they carry out their charge.

[1] http://www.personalizedmedicinecoalition.org/communications/TheCaseforPersonalizedMedicine_11_13.pdf

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Privacy

With the incorporation of genomic data and samples into healthcare records, the privacy of patients is crucial. HIPAA provides Federal protections and privacy of sensitive health information and includes genetic information within its scope. However, these protections only apply to those in group health insurance plans leaving those with individual coverage vulnerable to discrimination based on genetic information in their health records. Many states have laws that vary in strength offering protections to people, but this patchwork quilt of laws does not offer equal protections for all Americans. The Genetic Information Nondiscrimination Act (GINA) will provide the same necessary protections to genetic information that already exist for other types of health information. We have been actively involved in the grassroots efforts to pass GINA and are on the executive committee of the Coalition for Genetic Fairness, a group of hundreds of organizations supporting GINA. President Bush has twice endorsed GINA and we are extremely grateful for the Administration's recognition of and support for these significant protections. As you move forward with your working group, we encourage you to include genetic information in your discussions about privacy and the integrity of data collection sets and electronic health records.

Intellectual Property

Affymetrix believes that a strong system of protection for intellectual property is essential for the advancement of science and technology. In both the private and public sectors, innovation must be coupled with incentive for researchers to perform the kinds of work that will lead to breakthroughs in understanding, treating and preventing disease. Affymetrix holds over 190 non-gene sequence patents, with another some 360 patents pending, and the company supports steps that would modernize the US Patent and Trademark Office and would bring uniformity to the patent system worldwide. However, Affymetrix does not believe that the patenting of naturally occurring gene sequences is in the best interest of scientific research, innovation or competition. The plethora of gene and SNP patents being issued today carries the potential to stymie rather than encourage research. While the company supports patenting innovative ways of exploring and monitoring genes and gene activity and the products and processes, such as therapeutics, that result from invention, research, and development, Affymetrix believes that allowing the patenting of the sequences themselves is contrary to our belief that genes are naturally occurring entities and that unencumbered genetic information should be in the public domain to encourage innovation and the quality and quantity of research. More recently, Affymetrix has worked in scientific, legal and public policy arenas to encourage innovative approaches to the IP challenges inherent in modern genomics. Specifically the company has urged that serious consideration be given to the formation of patent pools or clearing houses, as has historically been done with other developing technologies like computers and DVDs, to both foster innovation and create clear rules and procedures about the use of existing intellectual property.

Lack of Economic Evidence as a Barrier

A common criticism for personalized health care is that there is limited data available to support the economic benefit of incorporating genomic information into health care

decisions. Diagnostics are poorly reimbursed and when linked to a treatment decision, their coverage will be crucial to its uptake. As a companion diagnostic, a genetic test could significantly reduce adverse events, improve patient compliance, and increase drug response by appropriately indicating the correct drug and dose administered. This is a new emerging discipline and approach in medicine. The lags in data supporting the partnering of test and drug creates a significant barrier to its advancement. Moreover, the time to complete these studies is contingent on the availability of subjects which can be limited by low disease prevalence and hence, would further hinder the adoption of personalized health care. There is no reason to believe that genetic tests will not provide the same level of health economic outcomes that have been enabled through dozens of protein based assays introduced over the last two decades. We encourage the working group to focus on the currently available data as well as identify mechanisms supporting the collection of data that will help remove this barrier to reimbursement by recognizing the potential health care cost savings from the incorporation of personalized health care technologies.

Workforce Shortage

There is currently a shortage of health professionals with genetics training and/or the expertise required to incorporate genomic information in the practice of medicine. This situation will be exacerbated as increasingly complex genomic information and advances are further incorporated into the practice of healthcare. In fact, in the US, there are only approximately 3.5 MD clinical geneticists per million people and the majority of these specialists are clustered around academic centers. This limits access in rural areas and many parts of the country.[2] Seventeen states have an inadequate supply of medical geneticists. Moreover, about 70% of geneticists report that their practices are full and they cannot accept new patients. There are fewer than 1000 advanced nurse practitioners specializing in genetics nationwide and just over 2000 genetic counselors registered with the National Society of Genetic Counselors. [34]

Similar worrisome statistics are seen in the laboratory community, where in the past six years, there were only approximately 33 new clinical laboratory geneticists certified each year.[5] This shortage is occurring while laboratory services are increasing in volume, complexity, and scale.[6] The number of certified medical technologists who staff clinical laboratories is also declining. The number of training programs for this profession has decreased by almost two thirds and the number of graduates has decreased by about half in the past twenty years.[7]

The reality is that genetic testing will become more commonplace and move from the specialist setting and the hands of the specialist to the generalist. This is especially true as personalized healthcare advances and becomes integrated into our healthcare system. However, it will be these specialists aiding this transition, serving educational and advisory

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[2] Cooksey JA, Forte G, Benkendorf J, and MG Blitzer. "The State of the Medical Geneticist Workforce: Findings of the 2003 Survey of American Board of Medical Genetics Certified Geneticists." *Genetics in Medicine*, Vol. 7, No. 6, July/August, 2005.
[3] International Society of Nurses in Genetics, "Advanced Practice Nurses in Genetics: A survey of ISONG Members, April 12, 2005.
[4] National Society of Genetic Counselors, www.nsgc.org
[5] Cooksey et al.
[6] Cooksey et al.
[7] Pinkerton, FH. "Diagnostic & Research Supplies." Banc of American Securities

roles, and continuing to deal with complex cases. People will rely on those clinical laboratories providing services that include help in ordering and interpreting tests. The number of tests requested will continue to increase. We need to invest in our genomics health professions now to ensure adequately trained professionals to facilitate personalized healthcare at the patient care settings and in the clinical laboratories.

Additional References

We also encourage you to review the following documents.

Collins CD et al. "The Application of Genomic and Proteomic Technologies in Predictive, Preventive and Personalized Medicine." *Vascular Pharmacology*, Vol 45 (2006): 258-267.

Louie B et al. "Data Integration and Genomic Medicine." *Journal of Biomedical Informatics*, Vol 40 (2007): 5-16.

Guttmacher AE et al. "Educating Health-Care Professionals About Genetics and Genomics." *Nature Reviews: Genetics*, Vol 8 (2007): 151-157.

Hoffman MA. "The Genome-Enabled Electronic Medical Record." *Journal of Bioinformatics*, Vol 40 (2007): 44-46.

Sander C et al. "Genomic Medicine and the Future of Health Care." *Science*, Vol. 287 (2000): 1977-1978.

Garrison LP and MJ Finley Austin. "Linking Pharmacogenetics-Based Diagnostic and Drugs for Personalized Medicine." *Health Affairs* Vol 25, No 5 (2006): 1281-1980.

Phillips KA et al. "Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions." *JAMA* Vol 286 No 18 (2001): 2270-2279.

We have chosen to directly comment on six of the specific points outlined in your request for information as well as providing the above broader context for you to consider.

1. Anticipated applications of genomic-based clinical testing in medical decision-making, safety assessment, and risk management

In Dr. Janet Warrington's presentation at the October 31st meeting of the AHIC, she presented data on already available applications of personalized medicine, including treatments for cancer, mental health, cardiac disease, and blood thinning medications. Additional assays are currently in development using genomic technologies in the areas of cancer, cardiovascular disease, metabolic disorders, pharmacogenetics, inflammatory disorders, transplantation medicine, infectious disease, childhood health and development, and newborn screening.

Additionally, in October 2006, The Foundation for the National Institutes of Health (FNIH), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and the Pharmaceutical Research and Manufacturers of America (PhRMA) announced the launch of a major public-private biomedical research partnership, ***The Biomarkers***

Consortium. The goal of this partnership is to identify and validate new biological markers to accelerate dramatically the delivery of successful new technologies and medicines for prevention, early diagnosis, and treatment of disease. This consortium will greatly advance and contribute to the expanding field of personalized medicine.

2. Organizational or institutional practices to address ethical, legal, and social implications regarding the use of patient information, including genetic data, to support personalized healthcare.

The Affymetrix Ethics Advisory Committee (EAC) was formed in 1997 in order to understand how our technology can best be used to help scientists alleviate human suffering and improve the quality of life. EAC members act in an advisory role; we do not ask for their specific approval or veto on issues brought before the committee. The Affymetrix Ethics Advisory Committee meets about 4 times per year with the possibility of adding additional meetings at the advisors request.

Our committee currently has 6 external advisors. They are:

- Biochemist (Nobel Laureate)
- Ethics Center Director Biomedical Ethics
- Law School Professor
- Sociology Professor
- Physician, formerly on National Bioethics Advisory Commission
- Genetic Counselor

In addition, a number of Affymetrix employees attend each meeting depending on the topic at hand. Regular attendees include Dr. Stephen Fodor (Chairman and CEO), Dr. Thane Kreiner (SVP, Corporate Affairs), Barbara Caulfield (Chief Counsel and former Federal Judge), Dr. Rob Lipshutz (SVP, Corporate Development), Dr. Janet Warrington (VP, Research and Development), Katie Buck (Corporate Affairs and Ethics), as well as various scientists and product developers.

Topics can be brought to the committee from any department within the corporation. In general, discussions tend to fall into two categories: 1) broad topics including ethics positions, company responsibility and informed consent, and 2) specific topics including contract language, product development and collaborations. Recent topics include:

- Corporate vs. social responsibility – how responsible should we be for our customers' research using our products? What can we control? With whom should we collaborate?
- Moving genomics to the clinic – what issues do we have to consider as our products move into the diagnostics realm? What do we expect of our collaborators?

In order to facilitate discussions, we often use hypothetical case studies to examine where our corporate responsibilities lie. This provides us an opportunity to preemptively discuss situations that may come to pass. It also allows us to make business decisions that will help avoid the challenging situation all together. Affymetrix believes that informed public discussion and meaningful application of ethical principles will foster the constructive uses of genetic information, while precluding inadvertent or intentional misuse. Affymetrix'

philanthropic giving actively supports organizations that help foster an ongoing public dialogue about genetic-related ethics.

In addition, Affymetrix has a long-term commitment to promoting the public discussion about genetics, ethics and related public policy. To this end, we have a program of events on The Genetic Age in which we have examined issues such as the sequencing of the human genome and its implications for health and society, and the patenting of naturally occurring gene sequences. In addition, we have an active educational outreach program in the communities in which we are based coupled with a philanthropic emphasis on educational programs focused on math and science education.

In order to promote awareness of the Ethics Advisory Committee and the corporate value of integrity, we have developed a number of internal ethics initiatives.
In 2001, Affymetrix participated in the development of a bioethics training program for the biotechnology industry. Funded by the Greenwall Foundation and organized through the Georgetown Law Center, the Kennedy Institute of Ethics, the Johns Hopkins Bioethics Center and the University of Virginia Institute of Ethics, this pilot program was designed to help biotechnology managers evaluate ethical decisions. Managers, scientists and the Executive Committee all participated in these training courses.

Affymetrix created an Ethics Speaker Series in 2001 in order to bring ethicists to Affymetrix for discussions about various bioethics topics. These seminars draw a wide variety of employees and the Q&A portion of the discussion is usually very energetic.

3. Examples of utilizing large clinical data repositories for practical clinical research to discover effective technologies, therapeutics, diagnostics, and prevention strategies for different populations.

A recent example of an initiative directed at addressing fundamental questions of reproducibility of microarray data is the MicroArray Quality Control (MAQC) project (Nature Biotechnology Sept 2006). The goal of the initial MAQC project was to determine intra-lab and inter-lab reproducibility of assay results. Currently in the planning phase, is a subsequent study (phase 2) that will utilize large clinical data sets generated in a variety of laboratories, focused in a number of different diseases areas to evaluate the impact of algorithm selection, data handling and statistical methods on gene expression signature identification and to develop recommendations and best practice guidelines for the research, diagnostic, pharmaceutical and regulatory communities. This project is a public-private initiative involving six FDA centers, NIST, EPA, academic centers, microarray tools providers, and other stakeholders. The results of the first phase were published in September 2006 in Nature Biotechnology.[8] In September, the data sets and samples were also released to the public. Phase 2 is just beginning and aims to develop recommendations by December 2007. For additional information, we also refer you to the FDA website: http://www.fda.gov/nctr/science/centers/toxicoinformatics/maqc/ and to our website: http://web1-dev.neomorphic.com:9100/community/standards/maqc.affx

4. Issues and challenges associated with incorporating genomic information as a part of a broad longitudinal data collection.

Clinical, molecular and genomic information as it exists today is not perfect or complete. The complexity of the content will change, the context will change. Better tools for

[8] The focus of the September 2006 issue of Nature Biotechnology is on the MAQC and includes 11 articles.

integrating clinical and molecular data will evolve. Medical records data needs to be in a format that will not inhibit the evolution of clinical knowledge and the tools developed to more efficiently and effectively realize the benefits of technological and medical progress, e.g. xml.

Perhaps the most important factor to consider when creating longitudinal data collections that will contain medical information is the manner in which the samples were initially collected with a special focus on the consent process. The ultimate ownership of these samples belongs to the donors and they should have the right to consent to the use of their samples in a database with broad access by researchers for use to study any area of biomedical research. Appropriate drafting of consent forms and a thorough informed consent process will enable participants to donate samples and avoid misunderstandings in the future. This drafting will require a delicate balance to allow the consent to be broad enough to anticipate every possible use, but not too broad so that it is meaningless.

Additionally, before genotyping studies begin, it is important to fully address the complex intellectual property issues regarding the genotyping data. An example of a data collection that resolved both consent and intellectual property concerns is our partnership with GlaxoSmithKline and academic researchers to compile a control cohort database which is housed at the National Center for Biotechnology Information (NCBI). The goal of this database is to create a large set of mapping genotype data from "normal" individuals from a variety of ethnic backgrounds. To be eligible for the database, the samples must either be a random selection of a population without respect to phenotype or unaffected individuals from a case control study. All studies must have proper consent and IRB approval prior to the release of the samples to any researcher. Genotype data must be made public within one month of completion and all intellectual property generated must be dedicated to the public domain.

Affymetrix has also contributed to the Genetic Association Information Network (GAIN), a public-private partnership to identify genetic factors associated with complex diseases, which took a different approach to address intellectual property concerns.[9] While the institutions that collected the original samples do not have intellectual property rights over the samples and the genotyping data will be accessible by researchers at other institutions, they do have a grace period where they are the only researchers allowed to publish papers based on the data. Addressing issues of access to and use of databases up front, can avoid conflict later on in the process.

Unlike other health information, genotypic information is relatively static over time. It is more stable and easier to store than other medical history such as prescription use or liver function tests. Aside from the ownership issues addressed above, the main concern is that the information is stored in a consistent and useful manner. Standards for collection, processing, reporting, and storage should be established prior to embarking on the development of a longitudinal data collection.

Often times, people tag a sense of exceptionalism to genetic information. In the end, the main concern will remain the challenges associated with storing large volumes of data. As stated earlier, it will be crucial to develop standards for the storage of genetic samples, and identify ways to accommodate large amounts of data, especially as these samples are genotyped.

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[9] http://www.fnih.org/GAIN/GAIN_home.shtml

All health related information should have the highest safeguards in place to protect confidentiality and privacy, regardless of whether or not it is genetic information. Due to the gaps of covering genetic information in HIPAA and other federal protections for the privacy of health information, Affymetrix has actively participated in the grass roots efforts to pass the Genetic Information Nondiscrimination Act. This bill failed to become law in the 109th Congress, and it will remain on the top of our legislative priorities in the new Congress.

5. Needs for community-wide standards or best practices that will facilitate large-scale data integration and exchange to benefit personalized healthcare.

The development of widely adopted standards can be a challenging consensus building process, but one with achievable goals and a worthwhile endeavor that will greatly benefit personalized healthcare. To embark on this activity, we encourage you to learn from other success stories of standards development. A recent example involving genomic information is the External RNA Controls Consortium (ERCC) made up of over 175 members from 14 different countries. The aim is the creation of well-characterized and tested RNA spike-in controls useful for evaluating sample and system performance, to facilitate development work and regulatory evaluation of expression profiling data. The ERCC is developing RNA controls for which there will be consensus on utility and acceptance in the community. The need for an international standard for working with RNA products in testing situations is a necessary component to ensure high quality tests. The consortium consists of volunteers donating their time and expertise and decision making is consensus based. Meetings are open to the public and the first deliverable of the ERCC was published by the CLSI in August 2006 titled, "Use of External RNA Controls in Gene Expression Assays; Approved Guideline," and information about it can be found at www.clsi.org. The consortium has collected over 150 external controls which are in preparation for testing on microarray and QRT-PCR platforms this winter. A progress report of the ERCC was published in Nature Methods October 2005.

Other initiatives underway in this community include the Clinical and Laboratory Genetics ands Genomics Standards Group. This is a voluntary international effort to bring together the stakeholder community to leverage existing clinical genetic testing lab and development expertise to create a recommendation paper on the selection and qualification of controls for microarray based DNA tests. More information about this effort can be found at www.IFCC.org

6. Opportunities and challenges for the development of electronic tools to aid in the integration and analysis of large datasets of clinical parameters to assist in outcomes evaluations.

Business and financial incentives are a necessary component of innovation, including the development of an electronic medical record keeping database designed to advance personalized healthcare. A number of healthcare centers have implemented such systems at considerable cost. Many other institutions simply cannot take on the burden of that cost. The Palo Alto Medical Foundation, The Mayo Clinic, and Partners Healthcare are examples of pioneering efforts in this area. Standardization of content, terminology, and metrics with the intention of facilitating interoperability between systems and centers is critical to the advancement of integrated healthcare and more efficient and effective realization of the

benefits of personalized healthcare dollars spent. The PHW and the AHIC are uniquely positioned to facilitate the development of those standards.

Another challenge with the adoption of electronic medical records is the protection of privacy and secure information systems. Fortunately, with growing familiarity with the internet, electronic banking and shopping online, people are becoming more comfortable with the electronic management of personal and sensitive information. For years, people feared misuse of information derived from financial transactions over the Internet, and today, few people hesitate to complete bank transactions electronically. Protecting the privacy of an individual's medical information while promoting interoperability across systems and medical centers will remain an interesting and important challenge.