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Dr. Gregory Downing
United States Department of Health and Human Services
Room 434-E, Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

RE: Request for Information (RFI): Improving Health and Accelerating Personalized Health Care Through Health Information Technology and Genomic Information in Population and Community-based Health Care Delivery Systems

Dear Dr. Downing,

On behalf of the Johnson & Johnson Family of Companies (J&J), I am providing the following comments and recommendations in response to the Request for Information (RFI): Improving Health and Accelerating Personalized Health Care Through Health Information Technology and Genomic Information in Population and Community-based Health Care Delivery Systems, put forth by the U.S. Department of Health and Human Services (DHHS) (71 FR 64282).

J&J is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical and medical devices and diagnostics markets. J&J has more than 200 operating companies in 57 countries around the world employing more than 109,000 employees and selling products in more than 175 countries. The fundamental objective of J&J is to provide scientifically sound, high quality products and services to help heal, cure disease, and improve the quality of life.

The November 1 Notice discusses the activities of the American Health Information Community (AHIC) toward advancing the development of electronic health records and a nationwide interoperable health information technology (HIT) system. J&J fully shares the Administration's goal for every American to have access to secure electronic health records by 2014. Our comments below outline the many ways that using HIT to populate data repositories containing information from personal health records can facilitate: translational and clinical research (including the use of biomarkers); product safety surveillance; personalized health care; and health outcomes monitoring. We would encourage DHHS to pursue ways to facilitate the contribution of HIT to these important public health objectives.

<u>Clinical Research and Development: Importance of Healthcare Information Networks</u>

Access to detailed clinical data in a standardized, interoperable format could revolutionize how clinical research and product development is conducted, providing patients with quicker access to more effective treatments that are developed at less cost. In developing a

product to meet an unmet clinical need, J&J first ensures that a clinical trial protocol has the optimal design and that patients and physicians are available for the trial. Trial design is often based upon published information about disease prevalence and progression characteristics and the experience of the lead investigator. Often this information is not readily available for certain subgroups of populations (e.g. women, children, the elderly, and other special populations), or may be incomplete for any number of reasons. Access to detailed, longitudinal clinical data could address these concerns.

At present, clinical researchers do not have access to reliable first-hand information to determine whether appropriate patients are available to participate in a clinical trial, or even where such subjects might be found. Rather, researchers rely on a variety of second-hand sources, such as published literature and questionnaires to potential investigators about likely potential recruits. Frequently, the result is that the potential patient population is recruited very slowly, or the clinical trial cannot be completed. Again, access to detailed, longitudinal clinical data would permit a quicker assessment of the availability and geographic location of appropriate patients.

In addition, researchers must fully understand the usual patterns of clinical care associated with a disease state or specific patient population they are attempting to study. To address gaps in care, it is important to develop a thorough understanding of the clinical reasons for decisions by physicians and patients to choose one therapy over another, or to switch therapies. For example, if decisions are based primarily on the basis of side effects, that would lead to a potentially different course of drug development than if decisions are based on lack of effect.

Disease state analyses assess both the disease and condition characteristics (etiology and risk factors, prevalence and incidence of the disease and associated morbidity and mortality) as well as the typical clinical care (drugs, diagnoses, etc). They analyze modes of treatment, identify potential gaps and needs in the market, and increase insight into off-label uses of products. Currently, these studies are performed using claims and existing clinical trial data that are limited in breadth and scope.

Large clinical data repositories can provide the ability to answer questions important to protocol design in real-time and virtually “simulate” a protocol’s recruitment potential by querying a database (i.e., in silico clinical trial design). An example of such a database currently available is the General Practice Research Database (GPRD) in the United Kingdom. According to its web site (http://www.gprd.com/home/), GPRD is the “world’s largest computerised database of anonymised longitudinal medical records for primary care.” The data are used to support a variety of medical and public health research activities, including: clinical research, drug utilization, analyzing treatment patterns, health outcome analysis, and drug safety monitoring. However, even the GPRD currently has information gaps. For example, detailed information on what happens to patients in the hospital is missing, although the fact of the hospitalization and any major diagnoses are generally captured.

Broader access to detailed, longitudinal clinical data sources could allow investigators to quickly select inclusion and exclusion criteria that balance study recruitment in terms of clinical heterogeneity of the study population. This allows for more refined and personalized criteria selection, which will help prevent inefficient trials and ensure comprehensive understanding of a product’s impact on various subpopulations of patients. These data sources can also enable epidemiological analyses based on clinically detailed patient data to provide insight into all elements of care associated with a specific diagnosis. These analyses increase efficiency and understanding of a disease/condition in order to improve decision-making and clinical study

design. The result would be more effective and safer treatments developed more efficiently (at lower cost).

Biospecimen And Genomic/Proteomic/Metabolic Biomarker -Based Clinical Testing In Pharmaceutical Research The November 1 Notice requested information about the use of biospecimen resources in research applications. Recent strides in human genome mapping and molecular characterizations of a wide array of disease states, as well as advances in molecular medicine, create a revolutionary opportunity to incorporate biospecimens and genomic information into the development of potential therapeutics and diagnostics. Integration of biomarkers into clinical research enables more focused development and earlier confirmation of the efficacy of potential therapeutic agents.

This concept of biomarkers is closely related to the notion of "surrogate endpoints" in clinical trials. Such surrogate endpoints, or biomarkers, require validation against clinical endpoints of interest, but conceptually, the goal of exploring pharmacodynamic effects as well as toxicity, on a short-term measurement, is appealing. In addition, molecular and genomic biomarkers can be utilized to determine appropriate dosing ranges and predict potential toxicities before Phase II trials. In addition, there is a potential to better understand susceptibility and resistances in specific subpopulations of patients. Overall, the widespread establishment of such 'theranostic' biomarkers will lay the foundation to understand the subtle molecular distinctions in divergent classes of disease pathways and also in patient responses, leading to more targeted and controlled therapeutic interventions.

The collaborative development of large biospecimen repositories, or "biobanks," could enable faster development of effective and safe medicines and better biomarkers. In order for this to occur, researchers must have access to large collections of high-quality biospecimens that are well managed and well annotated on multiple dimensions. Access to appropriate biospecimens for biomarker analysis in patients allows for early assessment of whether the drug is working by real-time measurements of the pharmacodynamic effects of the drug on a target well before the onset of Phase II clinical trials. Drug efficacy biomarkers help companies focus only on the most promising drugs, saving tremendous time and resources, ultimately bringing life-saving treatments to market more rapidly and cost-effectively.

The value of biospecimens is intricately tied to the quality of the associated heath care information. In order to assess the potential of new drug targets or biomarkers identified by probing biospecimens, access to specific clinical data regarding disease diagnosis, progression, treatment response, demographics, lifestyle, and social history can reveal complex gene-environment linkages to the disease. This knowledge is critical to screen for the best targets. Biospecimens are only as good as the clinical data linked to them. HIT is essential for high quality biorepositories and for translational medicine.

Disease-Specific Biomarkers In addition to facilitating the discovery of markers for pharmacodynamic evaluations in early development, biospecimen repositories and 'omic' data can be valuable for the identification of markers that characterize specific disease states and subtypes within the diseases.[1] In the past decade, tremendous innovations have occurred in the methodologies and technologies for classification of disease taxonomies at a molecular level. Many complex diseases such as diabetes and HIV are due to a combination of multi-factorial causative agents which result in 'unique' clinical courses for individuals. Major improvements in

[1] The term 'omics' refers to any molecule that can be detected and measured in a living organism to include genes (genomics - DNA/RNA), proteins (proteomics), sugars (glycomics), metabolites (metabolomics), etc.

healthcare will happen if treatment can be tailored to an individual's disease subtype. These types of biomarkers can be employed to evaluate physiologic or phenotypic impacts of targeted therapies on a disease process for routine assessments of efficacy during Phase II and III clinical trials, and also in the delivery of care.

Gaining a deeper understanding of the most complex disease states in this way could lead to potential highly effective preventative or treatment strategies that would not otherwise have been possible. In short, these biomarkers for different underlying *biological* variants of the same general *clinical* presentation, could lead to more individualized treatment decisions. More specifically, the goal of these activities would be to target therapies to those patients most likely to benefit and/or least likely to experience adverse effects. By greatly facilitating and expanding researchers' access to clinically relevant biospecimens through computerized biobanks, HIT will accelerate the pace of these advances.

Product Safety Surveillance

Today, detection of safety issues relies primarily on traditional, spontaneous reporting systems. For example, the Food and Drug Administration (FDA) requires physicians to report adverse events to regulatory agencies and to the manufacturer, but it has been estimated that fewer than 10 percent of serious adverse events are reported. In addition, adverse events can occur long after the treating physician has prescribed the drug, meaning adverse events may escape detection for years after a drug or device enters the market.

Large, HIT-enabled, clinical data sets would dramatically improve safety surveillance by tracking the outcomes of many more patients treated with a therapeutic agent. This would allow researchers to monitor the long-term safety of drugs and medical devices in both diverse and specific patient populations. Sophisticated analyses of these data can drastically reduce the time needed to detect safety issues. This ultimately would reduce the severity and number of adverse events by providing physicians and patients with early warnings of clinical signals that often foreshadow such incidents in specific patient populations.

Outcomes & Health Economics

Increasing attention is being focused on measuring and evaluating the effectiveness of alternative therapies. Medicare and other payors are seeking to ensure the value of the health care they are financing. Recognizing the important role of HIT in enabling the evaluation of health outcomes, AHIC established a Quality Workgroup charged with recommending ways to use HIT to improve the ability to collect and measure quality outcomes. In the November 1 Notice, DHHS requested input from interested parties on "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."

Outcomes measures provide payors, providers, and patient with an assessment of the clinical and quality of life outcomes associated with specific care pathways, medications and medical devices. Current outcomes analyses using claims data may provide an incomplete picture of the outcome of care delivered to a patient for some conditions and populations. While these data can be used to identify differences in certain outcomes such as rehospitalizations, they may not contain sufficient clinical information necessary to track or assess the outcomes of different treatment options among distinct patient populations.

Longitudinal clinical and financial data from real-world practice settings can be used to assess the effectiveness of medications and medical devices in the real world. For example, while manufacturers are prohibited from promoting off-label use of their products, physicians are not restricted from using these products for new indications. This promotes innovation in health care but limits the ability of manufacturers to monitor the use of their products. HIT-enabled longitudinal data repositories can bring a new kind of transparency into the health care realm, enabling manufacturers to monitor and assess the types of patients receiving their products, the methods of prescribing and utilizing products, and their associated outcomes. This wealth of information is likely to reduce the risk to patients by identifying patterns of inappropriate usage and to facilitate the discovery of new indications or treatment regimes for specific patient populations (that can be validated through further clinical trials).

Medical Decision-Making Using Personalized Health Care

Despite recent advances in biomarker and epidemiological research, as well as pharmaceutical and diagnostic development paving the way for personalized healthcare, the translation of these advances into practical medicine is still poorly supported. The advancement of this approach to delivering care requires strong collaborations between all healthcare stakeholders, especially between researchers, providers and patients. Therefore, J&J applauds AHIC's recent creation of the Personalized Healthcare Workgroup charged with making recommendations to foster the use of HIT in support of clinical decision-making for the health care provider and the patient. We are particularly pleased that the Workgroup includes representatives of the pharmaceutical industry. As demonstrated by these comments, manufacturers have a keen interest in the development of HIT in ways that facilitate the development of therapies and companion diagnostics that improve patient outcomes.

A fully functional and interoperable HIT environment will facilitate the practice of high-quality and evidence-based medicine that delivers greater value to the individual patient and the health care system. An example is the potential to link evidence-based medicine with patients' molecular disease classifications and genetic predispositions. Repositories of biospecimens and 'omic' information linked to medical records and outcomes data can provide the basis for vastly extending the knowledge base used for clinical pathway decision-making. Another example is the development of diagnostic products in conjunction with drugs to profile the disease, to predict progression and response, to evaluate treatment regimens given a patient's medical history and genotypic makeup, and to quickly adjust treatment strategies in cases of resistance, relapse, or toxicity.

Stratification of patients into response categories will lay a foundation for highly effective individualized care options with fewer adverse effects. Screening and selection of the most informative biomarkers to use as companion diagnostics will allow doctors to identify the right patient with the right disease for treatment with the right drug. Using linkages with electronic health records, longitudinal clinical patient data can be integrated with large correlative studies to more comprehensively understand the combination of factors (e.g., genetic, lifestyle, and environmental) that is at the root of many complex diseases. Having access to a bigger picture allows clinicians to identify the many complex decision points and unmet needs in the process of treating different, overlapping, and complex medical conditions.

Furthermore, continual incorporation of the latest research findings from biomarker and other initiatives into HIT portals can provide an educational resource for both providers and patients, leading to enhanced quality improvement.

Data Confidentiality

J&J fully understands and supports the importance of ensuring the confidentiality of any information in such a large data repository made up of personal health and demographic information. We applaud AHIC for also establishing a workgroup to address this critical issue and ensure the public's trust that the maintenance and exchange of personal health records will not compromise individual privacy.

With the baseline that individual privacy must be maintained, there are some issues from a data user's perspective that need to be considered. Overly-narrow or poorly-defined patient consent protocols could prevent researchers from investigating unanticipated yet critical questions that arise as their research progresses. Therefore, broad consent to the use of biosamples in a variety of different research initiatives and therapeutic development efforts is important in order to maximize the usefulness of these data to researchers.

Furthermore, in order to make the direct connection between clinical outcomes and biomarkers, researchers need to be able to link the clinical data to the biomarker data. Many specimen banks are now completely anonymized, which protects data privacy but may not allow the assessment of the statistical connection between biomarker status and patient outcomes. Without the ability to link biosamples to clinical outcomes, both types of data would be of limited utility. We encourage DHHS to explore ways to maintain appropriate data confidentiality in a way that does not unduly hinder important research.

Additional Issues

Although the following issues were not directly raised in the November 1 Notice, we believe they merit consideration as DHHS and AHIC consider ways that HIT can foster personalized health care, particularly involving genomic research.

Standardization and Automation Many biobanks and data repositories suffer from the lack of a standard nomenclature that can affect the utility of the data asset, thereby preventing interoperability with other data resources and severely limiting the prospect of generalized and reproducible research. Development and application of uniform data standards and procedures across all biobanking and clinical data repository initiatives will lead to vast interconnectivity between resources, enhancing efficient sharing and synthesis of information. Standardization and automation will also allow more efficient use of researchers' energies, as they will have to spend less time on manual tasks and can depend on the integrity of the data.

Informatics and Analytic Applications Researchers require analytic applications that will allow complex and systematic evaluation of large volumes of clinical and genomic data. In addition, advances in informatics can further elucidate the quantitative aspect of risk management to more precisely characterize the patient population based on their particular data characteristics.

Sample Acquisition There is great difficulty in gaining access to standardized, well-annotated and appropriately preserved biospecimens to enable molecular probing for disease markers, drug targets, and therapeutic pharmacodynamic and toxicity indicators. Intact, carefully preserved specimens are the *critical reagents* for the drug and therapeutic industries. Clinical specimens provide the foundation for discoveries and validation of targets and biomarkers that are crucial for the advancement of translation and clinical research. Without biorepositories, progress in healthcare will be slowed to a crawl.

Biobanking must adhere to rigorous protocols that ensure the preservation of clinically useful macro-molecular markers. However, currently there are few universal standards and no authorized regulatory organization to manage biobanking. For example, in many biobanks, there is limited, if any, documentation of how and when samples were collected; and unclear and narrow specifications of patient consent. In addition, very few biospecimen resources integrate longitudinal health information and treatment outcomes that are necessary for a comprehensive understanding of disease progression. Properly preserved samples accompanied by well-documented clinical information and clear patient consent can foster intensive research applications leading to advances in personalized healthcare.

Summary

As we indicated above, J&J is supportive of the efforts of AHIC to advance the adoption of HIT, and we appreciate this opportunity to provide our views on the questions raised in the November 1 Notice. We would, however, encourage AHIC and DHHS to give particular consideration to the potential impact HIT can have on: clinical research and the development of new treatments; product safety surveillance; personalized health care; and health outcomes monitoring..

Sincerely,

Kathleen A. Buto