DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Summary from the Molecular & Clinical Genetics Panel Meeting – March 8 & 9, 2011

Summary

A meeting of the Molecular and Clinical Genetics Panel was held on March 8 & 9, 2011. The Panel met to discuss and make recommendations on scientific issues concerning direct to consumer (DTC) genetic tests that make medical claims. The scientific issues discussed included:

(1) The risks and benefits of making clinical genetic tests available for direct access by a consumer without the involvement of a clinician (i.e., without a prescription). The discussion considered the benefits and risks of direct access for different tests or categories of tests that would support differences in the regulatory approach. Clinical genetic test categories that have been proposed to be offered directly to consumers include:
   (a) Genetic carrier screening for hereditary diseases (e.g., cystic fibrosis carrier screening);
   (b) Genetic tests to predict risk for future development of disease, in currently healthy persons (e.g., tests to predict risk of developing breast or ovarian cancer); and
   (c) Genetic tests for treatment response prediction (e.g., tests to predict whether individual will respond to a specific drug).

(2) The risks of and possible mitigations for incorrect, miscommunicated, or misunderstood test results for clinical genetic tests that might be beneficial if offered through direct access testing.

(3) The level and type of scientific evidence appropriate for supporting direct-to-consumer genetic testing claims including whether it should be different than that required to support similar claims for prescription use clinical genetic tests.

This was a non-voting Panel meeting.

FDA Presentations:

FDA opened the meeting with Dr. Elizabeth Mansfield's extensive overview of the history and landscape of DTC clinical genetic tests. On the second day the FDA presented the current evidence requirements for determining the safety and effectiveness for prescription clinical genetic tests and home use tests. Reena Philip, PhD, Deputy Director, Division of Immunology and Hematology Devices, presented on the FDA's evaluation process of prescription genetic tests including pre-analytical, analytical and clinical validation requirements. Carol Benson, Deputy Director, Division of Chemistry and Toxicology Devices, presented the FDA's regulation of at-home testing, including the risk and benefits of home use, device performance, interpretation of results and the role of human factors. Dr. Marina Kondratovich, Associate Director for Clinical Studies in the Personalized Medicine Staff, presented on DTC risk assessment tests providing high-level background on the calculations of absolute risks, relative risks, likelihood ratios and odds ratios; description of the calculations of outputs by a typical DTC risk assessment test and clinical validation.

Guest Speakers:

There were six invited guest speakers that presented to the panel on Day One:

Teri Manolio, MD, PhD, Director, Office of Population Genomics, NHGRI, presented background information about genome wide association (GWA) research studies in a presentation titled *Genome-wide association studies and clinical application*. Dr. Manolio gave an overview of GWA studies and their unique aspects, and what GWA studies have to do with DTC testing. She explained mapping the relationships among SNPs, mentioned 1000 Genomes project cataloging human genetic variation in much greater depth than has been

done in GWA studies to date, and showed chronology of the continued progress in genotyping technology. She provided examples and the list of traits with published GWA studies (199 on 3/4/11), with the web link to NHGRI catalog of GWA studies. Dr. Manolio also discussed the proportion of familial risk explained by GWA studies to date. She listed the limitations of genetic markers in risk assessment for disease, as well as clinical questions that GWA-defined associations may help answer.

Stuart Hogarth, PhD, from the Global Biopolitics Research Group in the Department of Political Economy at King's College, London gave an overview of global trends in DTC genetic test regulation; (*Regulating DTC genetics: an overview of global trends*). He outlined the range of regulatory options, from a completely unregulated market through to a total ban, and a middle ground involving some type of regulation. Dr. Hogarth described a range of national and transnational regulatory initiatives including international treaties/standards, national legislation on genetic technologies, reform of IVD regulations, and codes of practice. Common themes which emerged were restrictions on who could perform or order genetic tests and attempts to establish standards for genetic services, often with particular sensitivities about certain types of genetic tests such as predictive and prenatal tests. He pointed out that the applicability of some national legislation to cross-border trade was unclear and that while the number of countries imposing legal restrictions on consumer genetics was growing, in general, rule-making activity was more apparent than actual enforcement.

Nancy S. Wexler, PhD, President, Hereditary Disease Foundation and Higgins Professor of Neuropsychology, Columbia University presented a talk titled *Toxic Information: Handle With Care*. Dr. Wexler gave an overview of research studies she has led on helping to identify the Huntington's Disease (HD) gene. She described the genetic defect in HD, how the CAG repeat length relates to age of disease onset, presented 1994 guidelines for the molecular genetics predictive test in HD, and discussed how prenatal genetic diagnosis may be potentially helpful, but cautioned that predictive testing in genetic disease such as HD has led to a number of catastrophic events, according to 1998 survey data as well as her personal experience. Dr. Wexler quoted the 2010 Genetics and Public Policy Center data listing 31 DTC genetic testing companies existing at the time, and discussed an example of a problematic DTC company. Dr. Wexler also reported on the work of Ethical, Legal and Social Implications (ELSI) of Human Genome Research Task Force on promoting Safe and Effective Genetic Testing in the USA.

Daniel B. Vorhaus, JD, Robinson, Bradshaw & Hinson, P.A., Editor, Genomics Law Report presented on *Clearing a Path for DTC Oversight*. Mr. Vorhaus presented on the factors precipitating the meeting, starting with the declining cost of DNA sequencing. He provided some context and focus for questions the FDA is considering, including the meaning of "DTC," questions that are and are not being discussed, and relevant ELSI issues. Mr. Vorhaus described what he perceives to be several areas of common ground in DTC oversight (including, a need for clearer scientific evidentiary standards, consumer access to raw data, and greater DTC industry transparency), as well as several areas of disagreement regarding the appropriate oversight of DTC genetic testing, particularly whether DTC tests should or should not be routed through a clinician. He cited and analyzed some of the written public comments provided to the FDA docket for the ongoing Advisory Panel meeting, and listed studies that did not find indications of harms as a consequence of DTC testing. Mr. Vorhaus suggested additional issues the FDA should consider, such as mechanisms for education of clinicians and consumers, the approaching transition to multiplex and whole genome sequencing (WGS) testing, and FDA coordination with external personal genomics policy and regulatory efforts. Mr. Vorhaus also offered a number of questions to consider in reviewing potential next steps.

Colleen McBride, PhD, Chief & Senior Investigator, Social and Behavioral Research Branch, Head, Public Health Genomics Section, NHGRI, gave a talk on *Direct Access Genetic Testing: Lessons Learned from The Multiplex Initiative*. Dr. McBride gave an overview of the Multiplex Initiative, including study aims, design, sampling strategy, and recruitment. She listed eight conditions that were tested by the Multiplex prototype test, and described test feedback/results provided. Dr. McBride described the study population and noted that the study oversampled for several categories that had higher likelihood for opting out. The main messages Dr. McBride cited were considerable self-selection in who seeks testing, use of effective communication strategies provides adequate decision support, and testers can understand the limits of test feedback. She highlighted data to support each message. She provided recommendations (deploying direct access testing may be okay) and considerations (differences between Multiplex study vs. DTC milieu).

Cinnamon S. Bloss, PhD, Assistant Professor, Scripps Translational Science Institute, Scripps Health & The Scripps Research Institute presenting on the *Impact of Consumer Genome-wide Disease Risk Profiling: The Scripps Genomic Health Initiative.* The Scripps Genomic Health Initiative (SGHI) was a longitudinal cohort study of behavioral response to genome-wide risk testing for common diseases. The aim was to assess the impact of consumer genome-wide risk assessment (psychological, behavioral and clinical impact). Dr. Bloss described study methods, procedures, behavioral measures, test used, enrollment, cohort and demographics. She presented results on the overall impact of genome-wide testing by outcome measure, finding no significant difference in anxiety level, and listing the relationship between: genetic risk and intended health screening; genetic risk and psychological impact; genetic risk and test related distress; genetic risk and behavioral impact. The study found: no measurable adverse psychological changes, no improvements in diet/exercise, and no increases in actual health screening behaviors; however it is possible that health screening may increase in the future; a large proportion of study subjects shared their genomic information with a physician. Limitations of the study: sample of convenience, and study was based on single follow-up assessment.

Open Public Hearing:

The panel heard different perspectives on value and benefits vs. risks of direct access to clinical genetic tests from the following speakers:

Jeff Gulcher, MD, PhD, CSO, DeCODE

Ashley Gould, General Counsel, 23andMe, Inc.

Lewis H. Bender, CEO, Interleukin Genetics, Inc.

Jeremy Gruber, President, Council for Responsible Genomics

David Kaufman, PhD, Director of Research and Statistics, Genetics and Public Policy Center

Ann Maradiegue, PhD, MSN, RN, FNP -B.C, FAANP, American Nurses Association (ANA)

Adele Schneider, MD, Director, Clinical Genetics, Director, Victor Center for Jewish Genetic Diseases

Destry Sulkes, MD, Co-founder, Medivo Inc.

Mary K. Pendergast, JD, LL.M, Pendergast Consulting

Diana Zuckerman, PhD, President, National Research Center for Women & Families/Cancer Prevention and Treatment Fund

Chantal Hemens-Davis, VP Operations, Quality & Regulatory Affairs, DNA Genotek

Ed MacBean, VP, Product Development, Pathway Genomics Corporation

Rose Romeo, Senior Director Regulatory Affairs/Quality Assurance, 23andMe, Inc.

David A. Mongillo, V.P. Policy and Medical Affairs, ACLA

David Dunn, Regulatory consultant to 23andMe (among other companies)

Panel Deliberations/FDA Questions:

FDA opened the meeting with the presentation outlining the history and landscape of DTC clinical genetic tests. FDA ended its introductory presentation by providing the current challenges and the rationale for the meeting: to hear perspectives from broad panels of experts, invited speakers and public commenters on difficult issues in oversight of DTC

clinical genetic testing; to consider appropriate approaches to new technology and science; and ultimately help to improve public benefit from scientific discovery.

The first question discussed by the Panel was related to risks and benefits of making clinical genetic tests available for direct access by a consumer without the involvement of a clinician. A question on the value, considering likely benefits and risks, in offering clinical genetic tests directly to consumers (DTC) rather than through more traditional means, was discussed for each of five test categories: carrier tests, pre-symptomatic tests, susceptibility/pre-dispositional tests (risk assessment), pharmacogenetic tests, and nutrigenetic tests:

- The Panel felt that carrier testing encompasses a very complex class of diseases. The panel could not generalize a recommendation for this whole category of devices, in part due to differences between individual tests in this category, and different interpretations of results. There was a range of different opinions expressed by panel members on whether or not with the current level of knowledge risks outweigh the benefits of offering this category of tests DTC.
- The Panel generally agreed on the recommendation that several categories or specific genetic tests should be offered solely upon prescription; these categories include pre-symptomatic tests with high predictor for a disease, with potentially severe consequences, and pharmacogenetic tests.
- The Panel expressed concerns that the current state of scientific knowledge may not warrant the risk assessment claims being made by DTC companies.
- The nutrigenetic test category was assessed as being lower level of risk if test is analytically and clinically valid, and the panel stated they may not see as problematic offering many of these tests DTC, with certain caveats, unless there was a potential risk to the patient pertinent to a specific test.
- There was some discussion of potentially offering some of the test categories DTC if results are routed through a qualified health care professional, and potential caveats.

The discussions on the second day summarized below (on questions 2 and 3) were based on the hypothetical availability of different categories of clinical genetic tests discussed above as DTC.

The Panel discussed Question 2 - possible mitigations against incorrect, misinterpreted, miscommunicated, or misunderstood test results for clinical genetic tests offered through DTC testing, without live counseling. Following are some points from the discussion:

- Some tests lack established performance characteristics for certain populations, and that there are differences in the absolute risks for these tests between ethnic and geographic groups; this would need to be transparent and clear in the labeling, but would not preclude test offering to other non-specified ethnic groups.
- Other essential risk mitigation tools for providing DTC test results include patient training and education, clear labeling, health provider input into the results, online videos and training. Panel members suggested using a type of knowledge test prior to providing the DTC clinical genetic test to assess whether the consumer understands the meaning or consequences of test results.
- In testing general populations for rare conditions/markers, the false positive rate can be significant, warranting the need for confirmatory tests to confirm the initial result. Confirmatory test may need to be different from the original test in order to confirm the condition, and not performed by the DTC test offerer.
- Whether medically actionable results for certain DTC tests would need to be always routed through a clinician or specialist is a complex question due to the number of different genetic tests and disease states. The definition of "medically actionable" may vary depending on the disease state; some of the rarer and more complex test results should be routed through the consumer's primary care doctor.
- The Panel discussed the need for involvement of a genetic counselor when ordering the test or providing DTC genetic test results, citing the potentially inadequate number of genetic counselors. The companies should be required to provide qualified genetic counselors (or other appropriately licensed genetic professionals) for the consumers that purchase DTC clinical genetic tests. Overlap between clinical counseling and genetic counseling was discussed; each adds different value and should be considered separately.
- The Panel deliberated on the measures of risk and which are easier to understand; absolute risk is used as the bench mark for treatment in cardiovascular testing and is easily understood by patients; Panel members who have seen and interpreted results from DTC genetic tests in their daily practice felt that individuals tested understood absolute better than relative risk; Panel felt that absolute risk is in general much easier to understand. However, relative risks do play a part in the overall health of patients and should not be ignored. Short term risk vs. long term risk should be presented in a clear manner.

The Panel discussed Question 3 - the requirements of valid scientific evidence in order to determine that medical devices, including home-use and over-the-counter (OTC) tests, are safe and effective.

- The panel felt that different DTC, OTC, and prescription tests do not suggest different evidence requirements or performance level for supporting DTC genetic test claims. All tests should be held to the same quality, and transparent standards, in order to market the device.
- Tests should incorporate the available science, including family histories, environmental factors, personal history. Although there may be no way to incorporate this information completely or rigorously, available non-genetic information is important to consider in presenting genetic test results. In some cases the environmental and phenotypic characteristics may trump genetic contributions and that should be clearly stated.
- Several panel members expressed the opinion that there is no need to restrict what genetic claims can be bundled in the same device; this can be left to companies to decide.
- Panel felt that proposed "cytogenetic array approach" to validation - to select and validate an appropriate subset of genetic markers, with an inference that the platform/test as a whole is analytically valid and is an appropriate approach for analytical validation of highly multiplexed genetic tests. The subset should be chosen so that it is both enriched with markers that pose analytical challenges and with markers from each of relevant disorders tested, representing the most commonly found variations, plus additional statistical considerations. Adoption of this approach would require performing confirmatory testing of the results of highly multiplexed clinical DTC genetic tests.
- DTC companies may validate tests using results and information from current customers; important characteristics of this population may differ from the characteristics of the general population to whom the test is offered. The Panel agreed that unless there is validation from an independent population it is hard to expand upon the population tested; this needs to be labeled accordingly - if the consumer does not fit into that population, it should be clear that test results may not apply to them.
- The panel discussed the appropriate study design for a DTC tests (case-control vs. cohort studies, and differences between results obtained). Judging from historical examples for other disease markers, the panel felt that cohort studies are the best to understand the clinical performance of the DTC clinical genetics tests reporting absolute risks. The Panel felt that forming a separate group of experts who can summarize information from existing literature would be extremely useful to move the field forward.
- Web-based studies would select a certain subpopulations, limiting the study. The regular standard of peer review is essential.

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