**Promoting Quality Laboratory Testing for Rare Diseases:**
**Keys to Ensuring Quality Genetic Testing**

**May 20-21, 2004**
**Atlanta, GA**

## Summary of Major Recommendations

### I. Premises

- Clinically available genetic tests and efforts to translate research to clinical testing are woefully behind the pace of basic discoveries in genetics and genomics.
- High quality testing is the goal of all phases of the translation process, from the research phase to clinical laboratories.
- In considering efforts to improve the availability of rare disease testing, the inherent challenges of translational research and development of clinical services need to be recognized to avoid setting unrealistic expectations. Appropriate strategies and approaches should be developed.

### II. Recommended Major Areas of Activities

At the conference, participants developed both broad and specific recommendations on actions needed and issues to be further addressed to assure the quality of rare disease testing, improve test availability, enhance translation of gene findings to clinical testing, advance public knowledge and understanding, and improve access to quality testing. The recommendations can be summarized into the following 6 major areas:

1) Educational efforts to assure and promote quality for all patient testing and throughout the translation process;
2) Guidance, strategies, and criteria for evaluating the clinical readiness of potential tests;
3) Quality assurance strategies for rare disease testing;
4) Data collection;
5) Partnership and networks to improve research translation and data sharing; and
6) Infrastructure building to provide momentum and enable development of activities needed.

### 1. Education

Educational efforts are recommended to assure quality translation of research findings into clinical testing and appropriate use of testing services in practice. It will be important to have strategies in place and consensus on the teaching materials before initiating the educational activities, to minimize adverse impact on access to testing. Recommended activities include:

1) For the research community:
    a. Educational efforts regarding CLIA issues and other requirements that need to be considered in releasing individual-specific results in clinical research.

b. Guidance regarding the role of the research community in ensuring quality of the translation process (including test quality and data quality) from research discoveries to clinical use.

Suggested Lead: Professional organizations (e.g., ASHG) and funding agencies (e.g., NIH) to develop educational programs, materials, and guidance books, with assistance from CMS and CDC in developing teaching aids and disseminating information.

2) For IRBs: Education is needed for IRBs regarding CLIA and the role they should have in safeguarding the research and clinical interface, particularly the release of individual test results in clinical research.

Suggested Lead: OHRP should lead this activity, with assistance from CMS, CDC, funding agencies, and professional organizations to develop educational strategies, materials, and process.

3) For providers, including laboratory directors, clinicians, pathologists, other users of laboratory services, and payers: Provide education and information on test availability and appropriate use.

Suggested Lead: CDC, ASHG, ACMG, AMP, CAP

4) For research participants, patients and families, and advocacy groups: Education and information should be provided regarding quality and efficacy of testing, setting appropriate expectations for potential or available testing, and the public's role in ensuring and promoting quality testing for rare diseases.

Suggested Lead: Genetic Alliance, CDC, NIH(ORD)

1) Activities are needed to make the currently available educational resources more visible.

Suggested Lead: CDC, NIH, GeneTests, ASHG, ACMG

**2. Guidance for Clinical Readiness (or Transition Point)**

Participants recommended that mechanisms, guidance, and criteria be developed for determining if and when a test is ready for clinical use. It was recognized that the transition point is when individual-specific test information is released; currently, this decision is made by individual laboratories. Therefore, issues needing further exploration include how newly developed rare disease tests should be validated, and how analytic validity, clinical validity, and clinical utility should be established for rare disease tests. Suggested activities include the following:

1) Set forth guidelines for transferring potential tests from research to clinical use. Input will be needed from different professional organizations, including ASHG, ACMG, and organizations representing pathologists, to address the needs and issues specific for their members.
2) Develop a transition model for moving potential tests from research phase to clinical use, to demonstrate how newly developed rare disease tests should be validated, and how analytic validity, clinical validity, and clinical utility should be

established for rare disease tests with limited patient populations. (CAP, ACMG, AMP)

3) Form expert groups to set guidelines and criteria for test readiness and data/information needed. Strategies and options need to be developed to recognize the obligation to provide patients with access to testing that can generate helpful information, even if limited information is available regarding penetrance and sensitivity due to the rarity of the disease. Examples that can be considered include:
    a. For tests to be used for diagnostic purposes: Prader Willi and Angelman syndromes, genetic testing for colorectal cancer, and the experience of the Ataxia Molecular Diagnostic Testing Group.
    b. For determining readiness of a test for use in population screening: newborn screening, prenatal maternal serum screening, and the Tay-Sachs screening programs.
4) Develop strategies to monitor research development and public needs for rare disease tests. For each potential test, it will be important to bring together the needs and interests in a potential test with the expertise and resources for test development, to facilitate determination of the clinical readiness and to move the transition process forward. It was suggested that patient advocacy groups can play a significant role during this process.
5) Federal research funding agencies need to develop the expectation and the process for translation, by encouraging collaboration among research laboratories, clinical laboratories, patient support groups, and other needed parties.

Suggested Lead: Professional organizations, funding agencies, patient groups.

**3. Quality Assurance Strategies**

It was agreed that CLIA standards should apply to all patient testing and all steps of the testing process. Because CLIA requirements are minimum laboratory standards, participants recommended that more specific measures be developed to assure the quality of rare disease tests.

1) Define achievable and reasonable guidance and quality indicators for all phases of rare disease testing through the following actions:
    a. Establish specific requirements for genetic testing under CLIA. HHS should accelerate its current pace in developing the proposed CLIA regulation for genetic testing.

    Suggested Lead: HHS

    b. Establish quality indicators appropriate for rare disease testing, recognizing the limited availability of disease information, laboratories performing testing, quality control materials, and external quality assessment programs. The group agreed that this is an especially challenging area that needs support and input from multiple groups.

    Suggested Lead: ACMG, in collaboration with CDC

    c. Develop mechanisms to ensure accuracy of both positive and negative test results in light of the growing clinical laboratory services to confirm

mutations identified by non CLIA-certified laboratories. It was recognized that CLIA requires that all steps of patient testing process be performed by CLIA-certified laboratories and that pertinent performance characteristics must be established before reporting of patient test results. Therefore, the responsibilities of the partnering research and clinical laboratories in test development and validation need to be further addressed, with help from the CMS CLIA program to clarify related regulatory requirements. In addition, incentives should be explored for research laboratories to form the partnership with clinical laboratories. The following models need to be evaluated:

- Research laboratories attaining CLIA certification,
- Partnering between research and CLIA laboratories, and
- Partnering between clinical laboratories.

Suggested Lead: CDC, CMS, professional organizations, NIH

d. Establish validation guidance for rare disease genetic tests and criteria for evaluating their analytical and clinical validity. It was agreed that this is also an especially difficult issue, and can be addressed in concert with (c) above.

e. Establish standardized *generic* (i.e., not disease-specific) protocols for results reporting and for pre-analytic issues.

Suggested Lead: ACMG, in partnership with other standard-setting organizations, such as CAP, AMP, and NCCLS, with help from the Clinical Laboratory Improvement Advisory Committee (CLIAC).

2) Further explore cross-border testing issues (including out-of-country test referral and sharing of patient information for clinical and research purposes) with international partners. Issues including CLIA certification, international and US privacy regulations, and overarching issues regarding assuring quality of global rare disease testing should be addressed. CDC should convene international colleagues to discuss these issues and to develop strategies for moving forward.
Suggested Lead: CDC

3) Explore models of "equivalency" determination by CLIA for foreign laboratories, with regard to §493.1242(c) "The laboratory must refer a specimen for testing only to a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by CMS."

4) A pilot generic or methodology-based proficiency testing project should be considered for rare disease tests not included in available PT/EQA programs.

5) In developing quality assurance strategies, non-DNA-based rare disease genetic testing should be considered in addition to molecular tests.

6) The following issues need to be further discussed:

a. How should practical mechanisms be established to balance quality and access/availability – to ensure quality without imposing undue burden or restrictions on testing access, and to enhance availability and access without compromising quality? The group felt this is a critical issue that needs to be further discussed in conjunction with the recommendation on CLIA compliance for all patient testing.

b. To what extent quality assurance strategies should focus on the laboratory and to what extent the testing methodologies? The group felt a two-pronged approach would be needed and recognized the need to have further discussion on how the two aspects could complement each other in assuring quality testing.

c. How should guidance be developed to assure appropriate interpretation of results and patient counseling without excluding qualified professionals or specialists? It was agreed that both the Johns Hopkins University model and the New York State approach are valuable. It was suggested that if guidance is set forth by professional organizations or government agencies, appropriate expertise should be recognized to avoid disruption of quality service.

d. Should there be a mechanism for monitoring the announcements and advertisements laboratories make regarding their testing services? It was suggested that further discussion is needed on responsibilities of laboratories for truth in advertising and for informing their clients and the public regarding the quality, reliability, and validity of the tests being advertised.

**4. Data Collection**

Participants recommended that mechanisms and strategies be established to promote quality data collection during each step of test development through clinical application. This will help to 1) facilitate translation of potential tests to the clinical setting, 2) improve interpretation of results and subsequent use in patient management, 3) assess impact and benefits of testing on health outcomes, and 4) improve access to quality testing. Suggested activities include:

1) Collect data and information in the following areas to aid development of more specific and practical recommendations for improving quality, availability, and access to testing:
    a. The current rare disease testing landscape;
    b. Research laboratories releasing patient-specific test information and their concerns (to help develop practical educational means for CLIA compliance, to understand the impact on access associated with enforcing CLIA, and to minimize adverse impact without compromising quality);
    c. Practices and problems in the pre- and post-analytic phases, including informed consent and information provided in test reports;
    d. Personnel qualifications in laboratories performing rare disease testing;
    e. Tests for rare inherited conditions and laboratories offering rare genetic disease testing that are not listed on GeneTests;

f. Practices within academic centers in tracking laboratories doing rare disease testing and encouraging them to have quality assurance measures in place (to assist in exploration of funding needs and mechanisms).
g. Clinical impact and outcomes of genetic tests for rare disease diseases, to facilitate the process of bringing a test to market and the access to testing. Focused discussion on this issue is recommended at the next meeting

2) Enhance the data collection and analysis process, by establishing coordinating facilities to facilitate data sharing and genotype-phenotype correlation. Initiatives from major mutation databases, such as those affiliated with the Human Genome Variation Society (HGVS), should be supported. CDC and NIH should work closely to expand current efforts to develop evaluation and monitoring systems, including developing general or specific data formats to aid in evaluation of genotype-phenotype correlation with limited patient population.
3) Establish incentives for data sharing. It was recognized that incentives need to be established to encourage data sharing between and among research and clinical laboratories. Incentives could include authorship on publications but the scope and options need to be more broadly considered. This issue could be addressed in conjunction with discussion related to "Networks and Partnership" and "Infrastructure".

## 5. Partnership and Networks

1) Establish Rare Disease Testing Networks to include both DNA-based and biochemical genetic testing. A steering committee should be formed to include representatives from government agencies, professional organizations, and patient advocacy groups. Stakeholders of the networks should include laboratorians, clinicians, researchers, advocacy groups, payers, and other users of laboratory services. A $5,000 contribution was proposed for each member laboratory to initiate the network activities. The following initial activities are proposed:

   a. Communication and coordination – members of the network and the steering committee should convene discussions on steps needed to move tests from the research phase to clinical testing. Efforts should be considered to encourage coordination and convergence to limit duplicative efforts.

   b. Engage researchers – establish a web-based resource to provide information on how to contact and make requests to the network and to serve as an educational mechanism.

   c. "Match making" among clinical laboratories, research laboratories, and advocacy groups regarding test needs and stage of development

   d. Test selection by monitoring information from mutation databases and clinical correlation studies, to determine test readiness for clinical use and compile data needed for research translation and test validation.

e. Develop appropriate quality assurance mechanisms within the network for confirmation or backup services and for quality control/quality improvement purposes.

f. Seek additional support for continuation, enhancement, and formalization of the network, through grant applications, response to RFAs, and other mechanisms.

2) Partnerships need to be established between or among research investigators, clinical laboratories, patient groups, clinicians and payers, to facilitate data sharing, dissemination of information, and integration of new tests into practice. Mechanisms for developing partnerships could include:

   a. Establish resources to provide possible contacts and a list of laboratories that could serve as a resource for research translation, test validation, quality assurance, and special services for particular tests.
   b. Consider models of linking research laboratories with clinical laboratories in the same or other institutions, to help promote a shift from all-service laboratories to niche laboratories specializing in specific rare disease tests.

It was suggested that funding agencies encourage and eventually require such partnerships in funded projects. Professional organizations could create a pool of willing groups to participate in pilot projects.

3) Federal support of the effort to develop partnerships and networks is recommended.

**6. Infrastructure**

Participants recommended that the current infrastructure should be enhanced to facilitate the rare disease translational process, assure the quality of testing services, and improve access to testing. The following needs were identified:

1) Establish more obvious support mechanisms for translational research in order to move potential tests to the clinical setting. Both intramural and extramural approaches should be considered:
   a. Intramural approach to providing resources and funding mechanisms in response to requests from research laboratories. The NIH model presented by Dr. Gahl could be considered as a practical approach in support of the needs of the NIH clinical research programs as well as individual laboratories.
   b. Extramural approach to developing networks and partnerships among clinical and research laboratories, advocacy groups, and other stakeholders.

Suggested Lead: ORD and other NIH programs, HRSA, other funding organizations.

2) Enhance infrastructure to improve access to rare disease testing by addressing pre-market, market, post-market, and overarching factors affecting access:
   a. Pre-market phase needs:

- Funding agencies should consider including data collection on clinical validity and utility as an important goal in supporting research associated with development of new tests.
- Biobanks and repositories of patient samples need to be encouraged to promote test development, test validation and data collection.

b. Market phase needs:
- Gatekeeper-consultant systems need to be strengthened to direct healthcare providers to the appropriate test performed by qualified and experienced laboratories.
- Develop mechanisms for providing test information, including test availability and appropriate use, to healthcare providers. It was agreed that MD Consult or similar resources used by clinicians should be considered as possible mechanisms to tap into. In addition, guidelines could be developed by professional organizations, particularly the American College of Physicians, the American Academy of Pediatricians, the Society of General Internal Medicine, and other professional groups representing healthcare users of laboratory services.
- Education outreach should be considered for provider representatives and case managers from the insurance industry on rare disease test availability and use.

c. Post Market phase needs:
- Develop a process involving primary care and other healthcare providers in collecting data on evidence-based outcomes associated with quality testing.
- Create an expectation that healthcare providers should provide adequate clinical information with each test request to enable appropriate interpretation and utilization of test results in patient management.

d. Overarching factors:
- Develop infrastructure for improving the availability of quality rare disease genetic testing, both in terms of the number of testable conditions for which genetic testing is available and in terms of the number of laboratories offering the testing.
- In moving forward with the recommended activities and educational efforts on quality testing and CLIA compliance issues, establish a practical system for ensuring continued availability of rare disease testing so that the patient community will not lose access to the testing services they need.

3) Develop mechanisms for determining how test results influence patient care and health outcome.

4) Evaluate adequacy of current strategies for monitoring test quality and laboratory quality, and collecting data on current practices and outcomes to help identify problems and suggest possible solutions, forecasting and

tracking the impact of solutions on test quality and access to testing. Such assessment studies are critical for quality improvement. Key organizations need to be identified to lead in this area.

5) Develop strategies to address cost issues.
    a. The cost of test development needs to be subsidized and business models showing how this can be accomplished need to be publicized.
    b. Since costs of clinical tests are highly influenced by liability concerns, federal legislation similar to that for adverse outcomes of childhood and adolescent immunization might be needed to provide cost relief.
    c. Explore a proposal to reduce liability costs, particularly for prenatal diagnosis, by forming a network of laboratories to enable inter-laboratory comparison, service back-up, and other quality assurance measures.

6) Develop strategies to improve reimbursement schedule. Because development of and reimbursement for a new test can be influenced by public pressure, standards of care, and available data on clinical validity and utility, these strategies should be used when possible. Other strategies, if applicable, should also be utilized to stimulate development and reimbursement of testing for rare inherited diseases and conditions. It was agreed that while redefining billing codes to replace the current one-size-fits-all system is a long term goal; there is urgent and current need for the value of rare disease genetic testing and associated clinical services to be reflected accurately through billing codes. Education efforts should be directed towards payers about rare disease testing and why costs may be higher, with subsequent refinement of the existing standards of care as payers start providing coverage and their understanding of the tests improves.

7) To promote quality patient testing in clinical research, develop a checkbox on NIH grant applications to ensure test performance in CLIA-certified laboratories if results are to be released to research participants or their healthcare providers.