GeneDx announces testing for **CHD7** in **CHARGE** syndrome

(April 8, 2005) Gaithersburg, Maryland
GeneDx, Inc., a worldwide leader in specialized genetic testing for rare genetic disorders, announced at the annual ACMG clinical genetics meeting in March that it has expanded its extensive test menu by adding **CHD7** testing in **CHARGE** syndrome. GeneDx offers complete sequence analysis of the coding region and splice junctions of the **CHD7** gene. This test will identify disease-causing mutations in more than 50% of individuals with **CHARGE** syndrome who do not have microdeletions of the gene locus. The availability of molecular diagnosis of **CHARGE** syndrome will aid physicians in differentiating this syndrome from 22q11 deletion syndrome (VCFS/DiGeorge syndrome), VACTERL association, retinoic embryopathy and other disorders, help in developing a targeted evaluation and management plan, and provides information for more accurate genetic family counseling.

CHARGE syndrome, also known as **CHARGE** association, comprises a cluster of birth defects, including coloboma of the eye, heart defects, choanal atresia, mental and growth retardation, genital hypoplasia, ear anomalies and/or hearing loss. It has a prevalence of 1 in 8,500 to 1 in 15,000 births and a high mortality rate of over 10% in the first 2 years of life, mostly attributable to congenital heart and choanal malformations. The clinical presentation of **CHARGE** syndrome is very complex and highly variable between patients, which can result in diagnostic difficulties.

In 2004, research studies revealed that **CHARGE** syndrome is an autosomal dominant disorder due to haploin-

sufficiency of the **CHD7** gene on chromosome 8q12. Most mutations in affected individuals, however, arise de novo. **CHD7** encodes for a member of the chromodomain helicase DNA-binding protein family, which plays a putative role in the general control of gene expression during embryological development as well as in mesodermal patterning. The spectrum of pathogenic mutations identified to date includes missense, nonsense, and splice-site mutations scattered throughout the gene, which can be detected by the test offered at GeneDx. Large deletions and other gross rearrangements of the **CHD7** gene, which would not be identified using sequence analysis, have been observed using cytogenetic and microarray methods in patients with **CHARGE** syndrome.

GeneDx celebrates its 5th birthday with expanded test menu

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GeneDx, Inc. is a worldwide leader in specialized genetic testing for rare genetic disorders. Established in March 2000 with the purpose of making the results of biomedical research accessible to the general public and starting with 14 tests, the company has now developed an unprecedented wide array of genetic assays for diagnosis, carrier detection, and prenatal testing.

GeneDx has become synonymous in the medical community with genetic testing in rare and "ultra rare" hereditary disorders, and now offers clinical diagnostic testing for almost 100 different hereditary conditions/genes. As Dr. Sherri Bale, President and Clinical Director of GeneDx, put it: "If you have never heard of a disorder or cannot pronounce its name—there is a good chance we will offer testing". The tests offered at GeneDx are based predominantly on DNA sequencing and are capable of identifying more than 99% of the most common types of DNA mutations in the coding regions and splice junctions of selected genes.

In marking their 5th anniversary, GeneDx has added several new tests to its extensive menu. Mutation analysis is

now available for the **RAI1** gene in patients with Smith-Magenis syndrome. This is an important milestone for the diagnosis in the 5% of patients, who do not have detectable microdeletions in chromosome 17p11.2. An assay for autoimmune lymphoproliferative syndrome scrutinizes the **TNFRSF6** gene for mutations, while testing of the **CASR** gene provides molecular diagnosis for at least four calcium sensing receptor-associated disorders.

Striving to make available the first comprehensive set of genetic tests for congenital ichthyoses and other skin disorders, GeneDx has enlisted Gabriele Richard, M.D., F.A.C.M.G., as Associate Scientific Director. Dr. Richard is an accomplished researcher in this field who discovered many of the known genes associated with ichthyosis and abnormal cornification. GeneDx now provides clinical testing for a total of 25 different genes important in epidermal differentiation, newly including **SPINK5** and **ABHD5**, which are associated with the autosomal recessive congenital ichthyoses Netherton syndrome and Chanarin-Dorfman syndrome, respectively.

In addition to the accurate and cost effective methods employed by GeneDx for clinical services, GeneDx also continues to serve the research community with genotyping services, assistance in study design and analysis, and in clinical confirmation of mutations identified in research laboratories. Projects are continuously in progress to develop assays for other genes involved in rare genetic disorders. Feedback and suggestions for new tests are invited from physicians, other health care professionals and researchers.

Additional information on GeneDx, Inc., the entire test menu offered and molecular testing in **CHARGE** syndrome can be found on www.genedx.com.

Diagnostic Nucleic Acid Microarrays Guideline to Serve as Laboratory, Educational Resource

Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) guideline *Diagnostic Nucleic Acid Microarrays; Proposed Guideline* (MM12-P)

The "New Products" page is designed to offer you news and information from businesses serving the genetics community. We welcome your submissions. All submissions are subject to review by the Editor. For more information, contact Al Lucchesi, National Accounts Manager, Lippincott Williams & Wilkins, 530 Walnut Street, Philadelphia, PA 19106; phone 215-521-8409; fax 215-521-8411; email alucchesi@lww.com

DOI: 10.1097/01.gim.0000181069.39618.35

will define the most favorable conditions and principles for the provision of accurate molecular information.

Intended as a reference for laboratories that perform molecular diagnostic tests, MM12-P provides recommendations for aspects of the array process including: nucleic acid extraction preparation, handling, and assessment of genetic material quality control analytic validation result interpretation and reporting.

Also addressed are array-based detection of variations in DNA sequence and gene expression analysis as it relates to: heritable variations somatic changes methylation profiling pathogen profiling, including antibiotic resistance analysis expression profiling gene dosage/comparative genomic hybridization.

MM12-P, written in partnership with the International Federation for Clinical Chemistry, is intended by its authoring subcommittee to become an educational resource for molecular genetics.

Clinical and Laboratory Standards Institute is a global, nonprofit organization dedicated to developing medical standards and guidelines through a consensus process that balances the

perspectives of industry, government, and the health care professions.

MM12-P is now available for purchase through Clinical and Laboratory Standards Institute, at + 610.688.0100 or www.clsi.org.

CLSI Responds to Need for Industry-Recognized Microarray Controls

Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) document *Use of External RNA Controls in Gene Expression Assays; Proposed Guideline* (MM16-P) has been developed to provide useful recommendations and protocols for: quality requirements for external assay controls statement of control characteristics and performance metrics explanation of performance specifications and acceptable performance preparation of individual transcripts pooling of transcripts design of primers and amplicons quality control.

The changes that have taken place in the research and clinical communities over the past two decades—in the scope and breadth of the designs, practices, analyses, and very imaginations of clinical and laboratory researchers—owe

largely to the introduction of polymerase chain reaction (PCR) and microarray technology.

The result has been an increased emphasis in the laboratory on collaboration and teamwork, including focus on well-defined clinical database structures, data management, and data access issues. The ability to report reliable gene expression results of known quality has become key to the successful employment of microarrays and quantitative reverse transcriptase real-time (QRT)-PCR as tools in toxicogenomics, pharmacogenetics, and pharmacogenomics, and as diagnostic devices in clinical medicine.

This guideline presents protocols supporting the use of external RNA controls in microarray and QRT-PCR-based gene expression experiments. The protocols enable research and clinical laboratories, regulatory agencies, accrediting agencies, reference laboratories, as well as test, microarray, and reagent manufacturers, to assess the performance of these expression assays.

MM16-P is now available for purchase through Clinical and Laboratory Standards Institute, at + 610.688.0100, or www.clsi.org.