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NIH Undiagnosed Diseases Program documents two-year pilot as clinic of last resort

Genomic tools prove integral to solving medical mysteries

After its first two years of work, the Undiagnosed Diseases Program (UDP) of the National Institutes of Health is citing successes in patients whose cases have stumped specialists at leading medical institutions around the country. The researchers published the program's first retrospective analysis in the Sept. 26, 2011 early online issue of *Genetics in Medicine*.

The successes include the diagnoses of siblings whose calcium-riddled blood vessels made it excruciatingly painful to walk, a woman with life-threatening protein deposits in her muscles and a 20-year-old whose diagnosis makes him the oldest survivor of his previously undiagnosed muscle and lung disorder.

"The UDP responds to a critical unmet need, with compassion, clinical expertise and state of the art genomic technologies," said Daniel Kastner, M.D., Ph.D., scientific director at the National Human Genome Research Institute (NHGRI). "A patient who cannot be diagnosed may cycle through the medical system with no satisfactory treatment plan or be abandoned by the medical system. Through the UDP, NIH provides a glimmer of hope to patients and their families, while at the same time gaining remarkable medical insights."

The UDP is supported by the NIH Office of the Director, NHGRI, the NIH Office of Rare Diseases Research (ORDR) and the NIH Clinical Center.

The report focuses on 160 patients of the total 326 cases accepted into the program. More than half of the accepted patients had undiagnosed neurological problems. Other prominent disorder categories include gastrointestinal disease; fibromyalgia and chronic fatigue syndrome; immune-mediated and rheumatic illnesses; psychiatric conditions; pain; dermatologic disorders; and cardiovascular disease.

So far, most of the solved cases — 37 of 39 cases for which the UDP team arrived at a diagnosis — involved diseases previously encountered in the world of medicine, according to

UDP authors. In general, about 500 diseases are common enough to be in any physician's repertoire for diagnosis, while another 6,500 are known but are exceptionally rare, according to ORDR data.

UDP researchers reviewed, evaluated and diagnosed 23 patients with rare diseases, of which 15 cases reflect extremely rare diseases affecting fewer than 10,000 people. The authors note that while these are known disorders, some lack diagnostic tests or medical definitions to describe them. Rare diseases are defined as those affecting fewer than 200,000 people in the United States.

The program has also delved into the realm of unknown maladies. In February, the UDP announced the program's first discovery of a new disease, called ACDC, or arterial calcification due to deficiency of CD73, in the *New England Journal of Medicine*. CD73 is a protein that produces a small molecule, adenosine, which protects arteries from calcifying. A report on one additional new disorder is pending publication.

The siblings whose cases led to discovery of ACDC continue to experience pain while walking more than a short distance. The NIH researchers, however, have obtained approval to start a drug treatment protocol that could improve their condition, which will be initiated within months.

The patient who UDP researchers encountered with an unexplained muscle condition was diagnosed with a rare form of amyloidosis, a condition in which bone marrow produces excess immunoglobulin proteins, which had accumulated in the patient's muscle tissue. The NIH team referred the patient for a stem-cell, bone marrow transplant, using healthy donor stem cells. The patient has subsequently experienced progressive improvement in her condition.

The UDP team also succeeded in diagnosing the 20-year-old patient with a condition called spinal muscular atrophy with respiratory distress. The condition causes damage to muscles, including respiratory muscles. The patient remains dependent on a respirator for much of his day but last year achieved the significant personal milestone of high school graduation. The diagnosis has allayed the patient's concern that the condition might at any point impair his learning.

UDP's novel approach

A typical UDP patient visits the NIH Clinical Center for one week. The case is evaluated by specialists from several of NIH's 27 institutes and centers, with expertise in areas such as neurology, radiology, dentistry and rheumatology. A key component of the program is genetics, so researchers collect DNA from blood or tissue samples from all participating patients, and often from family members to support the genomic analyses.

Most of the patients accepted in the first two years of the UDP had their DNA analyzed for known single nucleotide polymorphisms (SNPs), which reflect differences in the single chemical subunits of DNA that could indicate a genetic disorder. Their tool in the SNP analysis process is called a million-SNP array, which can be used to find potentially important differences between the genome of an affected individual and an unaffected family member, pointing to the genetic cause of a disorder. This approach resulted in three successful diagnoses.

The researchers performed both whole-genome sequencing, deciphering all of an individual's DNA code, and whole-exome sequencing, an approach that decodes the 1-2 percent of the

genome that contains protein-coding genes. They analyzed DNA from 32 patients, along with DNA from 78 unaffected family members. This approach proved critical for the diagnoses of six patients' disorders.

NIH is evaluating use of these advanced genomic analyses for broader utility. The UDP diagnostic successes have proven the usefulness of SNP detection techniques and genome sequencing tools – both whole genome and whole exome sequencing – in the clinical evaluation of patients, according to the study. But UDP researchers also know that genome sequencing does not provide the whole answer. In addition to genomic analyses, clinical findings — from specialty consults to radiological tests — led to one third of the 39 diagnoses, according to the study.

A flood of applications

Doctors from around the country responded to the May 2008 call for UDP applications, summarizing, documenting and sending the UDP 1,191 cases for review within the subsequent two years alone. Each application includes a referring health care provider summary letter and complete medical records.

"The applications may represent years of evaluation by multiple doctors at more than one medical facility—but with no conclusive diagnosis," said William Gahl, M.D., Ph.D., NHGRI clinical director and UDP director. "We look for some clue in the medical record—from an abnormal lab test to a collection of symptoms that don't usually occur together. If we can establish a direction for further follow up, we may invite that patient to be seen by our team at NIH."

NIH clinicians participating in UDP — up to 60 health care providers at the nation's largest research hospital — screen the applications and accept patients based on the availability of clinical and research resources. The program currently has a backlog of applications and since July 2011 has suspended acceptance of new applications until November 2011.

"In addition to our discovery of new disorders, the UDP work has expanded the clinical description — or phenotype — of numerous disorders," Dr. Gahl said. "The limited rate of diagnosis during the program is sobering. While we wish we could arrive at a conclusive diagnosis for each patient, the reality is that many of their conditions are likely new diseases and we continue to pursue clues long after patients depart the hospital here at NIH." To increase the success rates, the UDP plans to make case descriptions available to designated expert researchers, to both validate findings and enhance understanding of disorders.

NHGRI is one of the 27 institutes and centers at the NIH, an agency of the Department of Health and Human Services. The NHGRI Division of Intramural Research develops and implements technology to understand, diagnose and treat genomic and genetic diseases. Additional information about NHGRI can be found at its website, www.genome.gov.

The NIH Clinical Center (CC) is the clinical research hospital for the National Institutes of Health. Through clinical research, physician-investigators translate laboratory discoveries into better treatments, therapies and interventions to improve the nation's health. For more information, visit <http://clinicalcenter.nih.gov>.

The NIH Office of Rare Diseases Research stimulates and coordinates research on rare diseases and supports research to respond to the needs of patients, healthcare providers and the research communities involved in the care, treatment, and evaluation of products for the prevention, diagnosis, or treatment of these conditions. For more information about ORDR and its programs, visit <http://rarediseases.info.nih.gov>.

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About the National Institutes of Health (NIH): NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov.