How will patients, families and doctors handle the coming flood of personalized genetic data?

December 6 2011

Sequencing the entire human genome took more than a decade before leaders of the Human Genome Project announced their completion of a rough draft in a 2000 White House ceremony. Finished in 2003, sequencing that first genome cost nearly $3 billion. Today, with advances in technology, an individual's whole genome can be sequenced in a few months for about $4,000.

But knowing just what to do with this knowledge has not kept pace with the gusher of genetic data. People can now have their own genome analyzed—all 3 billion pairs of DNA letters per person—offering clues to their current and future risks of genetic diseases. But what will individuals do with this flood of information? Is some of it information that they prefer not to know? How will knowledge of a child's possible future risks affect the parents' decisions now?

These are just a few of the near-future issues being explored in a new four-year grant from the National Human Genome Research Institute (NHGRI), the federal agency that sponsored the Human Genome Project . The Children's Hospital of Philadelphia is one of five U.S. centers, and the only one focusing on pediatrics, to receive a new four-year Clinical Sequencing Exploratory Research Project award. Children's Hospital will receive $2.2 million per year for four years.

The NHGHI announced the grant today as part of an intensified focus on

the medical applications of its flagship Genome Sequencing Program.

The grant recipients are forming a consortium to define social and ethical issues associated with clinical sequencing, and to propose guidelines on sharing, interpreting and using this genetic information. Much of the consortium's work will focus on guiding physicians and genetic counselors in interpreting data for families and patients.

"Currently, when gene analysis helps us arrive at a diagnosis of a child's disorder, we can then counsel a family, providing information about what to expect and what options may be available for therapy and medical intervention," said clinical geneticist Ian D. Krantz, M.D. "But among the thousands of gene variants in someone's genome, only a handful will be clinically significant or actionable—lending themselves to doing something medically—while most will either not be actionable or will of unclear significance."

Krantz is the principal investigator (PI) of the project at The Children's Hospital of Philadelphia, along with co-PI Nancy B. Spinner, Ph.D., director of the Clinical Cytogenomics Laboratory at Children's Hospital. Both researchers also are faculty members at the Perelman School of Medicine of the University of Pennsylvania, which is partnering with Children's Hospital on three projects comprising the grant.

In addition to pinpointing gene variations that are the likely causes of a condition for which a patient is being studied, say the researchers, whole-genome sequencing will also uncover so-called "incidental findings." These findings are gene variants not related to a current condition, but having a bearing on an individual's future health. "We will investigate which of these incidental findings should be disclosed to a patient's family," said Spinner. "This is a complex issue that will benefit from the insights and contributions of the multidisciplinary team we have assembled for this program."

The first project under the grant, Clinical Genomics Studies, is co-led by Krantz and Spinner, and will enroll four cohorts of children in these disease groups: bilateral sensorineural hearing impairment, nuclear encoded mitochondrial respiratory chain disorders, sudden cardiac arrest and intellectual disability. "Each of these groups of disorders cannot be easily diagnosed with a gene-by-gene approach, so experts from several disciplines will develop tools for sequencing the patients' whole genomes and then interpreting the vast amounts of data," said Krantz. "Not all the gene mutations we find will be clinically useful, and we will work with families to understand what information they desire, and how clinicians should present it."

Project 2, Sequencing, Analysis and Interpretation of Sequencing Data, is led by Peter White, Ph.D., director of the Center for Biomedical Informatics at Children's Hospital. "This project," said White, "aims to build a framework for systematically assessing the gene sequence data we collect, to integrate the data with medical care. We envision Children's Hospital as a working lab to combine genomic analysis with our clinicians' observations and diagnostic expertise to support physicians and families in their decision-making." Members of this project will develop tools and processes for delivering information directly into a patient's electronic health record in ways that are most informative for clinicians and families acting on this information.

Ethical and Psychological Implications of Genome Sequencing is the title of Project 3, led by principal investigator Barbara Bernhardt, M.S. C.G.C., a genetic counselor and Clinical Professor of Medicine at the Perelman School of Medicine of the University of Pennsylvania. She and her co-investigators will conduct focus groups, interviews and surveys with parents, adolescents and healthcare providers to understand the impact and outcomes of genetic testing in children. The researchers will address questions such as what people prefer to receive in genetic sequencing results, what are barriers to informed consent when many

findings have uncertain implications, and how parents, patients and clinicians understand and use genomic results. Ultimately, the project scientists will make recommendations on the best ways to introduce genomic sequencing into pediatric practice.

"By the end of this decade, we anticipate that genomic sequencing will be ready to be offered for the diagnosis of pediatric disorders," said Krantz. He added, "Parents may elect to have sequencing done early in a child's life, and the child's disease risk will be assessed. Over the years, the child's medical information can be refreshed and reassessed. Our goal in this research is to help make that information-sharing process systematic, thoughtful and sensitive to the needs and desires of patients and families."

The four other centers receiving this NHGRI award are Baylor College of Medicine; Brigham and Women's Hospital; the University of Washington, Seattle; and the University of North Carolina, Chapel Hill. Together with Children's Hospital and Penn, they will form a Clinical Sequencing Exploratory Research Consortium.

Provided by Children's Hospital of Philadelphia