IN THIS ISSUE

Challenges to the real-world use of NIPT

see page 681

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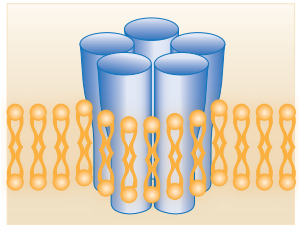
The rapid uptake of non-invasive prenatal testing (NIPT) has changed patterns of prenatal testing and created complicated genetic counseling scenarios at at least one university-based prenatal diagnosis unit. In a descriptive assessment of the changes brought on by routine use of NIPT in high-risk pregnancies, researchers from the University of North Carolina at Chapel Hill report an unanticipated number of "unclassified" results and higher-than-expected numbers of both false-positive and false-negative results in fetal aneuploidy testing. The sensitivity for detection of aneuploidy in chromosomes 21, 18, and 13 in this clinical setting was lower than that achieved in previous published studies performed in controlled research settings. The current team evaluated results obtained from NIPT aneuploidy tests performed beginning in January 2012, when the test was first offered to pregnant women of advanced maternal age or who had additional risk factors for chromosomal abnormalities. The center tested 208 women over the study period, which ended in September 2012. NIPT detected eight cases of aneuploidy and an additional five cases of "unclassified" abnormal results—an unclassified rate of 11.1%, as compared with 2.8% in prior studies. In three morbidly obese patients, NIPT yielded no result, due to insufficient fetal DNA sample. A false-positive result was obtained in a patient subsequently diagnosed with cancer. Several patients with abnormal ultrasound findings declined invasive testing, opting instead for NIPT. In two of these patients, the NIPT result was normal, yet they delivered neonates diagnosed with aneuploidy. The authors conclude that their findings highlight the importance of counseling patients that NIPT is merely a screening test that does not replace diagnostic testing with amniocentesis or chorionic villus sampling, and that normal NIPT results do not necessarily mean that no other genetic abnormalities are present. *—Karyn Hede, News Editor*

Defective nicotinic receptors involved in many genetic diseases

see page 649



In an Invited Review, Christian Schaaf, a medical geneticist at Baylor College of Medicine, Houston, Texas, covers the current understanding of disorders involving nicotinic acetylcholine receptors and the outlook for treatment. Schaaf, winner of the 2013 William K. Bowes Jr Award in Medical Genetics given annually to a promising early-career medical geneticist, explains the relationship between the role of these receptors in rare genetic syndromes and the increasing recognition of the importance of nicotinic acetylcholine receptors in common neurological, behavioral, psychiatric, and neurodegenerative disorders. These pliant and adaptable receptors generally mediate fast (in millisecond time frames) synaptic neurotransmission, and they have been shown to be involved in learning, memory, and attention. Schaaf was among the first to describe the effect of deletions and duplications of the *CHRNA7* gene, which encodes for a nicotinic receptor in the brain. Here, he discusses a variety of rare, single-gene disorders involving 1 of the 16 distinct subunits that constitute these receptors, as well as the increasing knowledge of what the genetic mutations and alterations do physiologically. He also discusses their role in relatively common disorders such as depression, attention-deficit hyperactivity disorder, schizophrenia, Alzheimer disease, and Parkinson disease, and he speculates that the development of targeted therapies for common disorders may also benefit those with rare Mendelian disorders. *—Karyn Hede, News Editor*

NEWS BRIEFS

Building a better human genome

Today we take for granted that the entire human genome is available at a mouse click, thanks to the Genome Reference Consortium (http://www.ncbi.nlm.nih.gov/projects/genome/assembly/grc), which maintains the most complete publicly available sequence information. The human genome reference is, by definition, the standard against which all other genomic information is compared. But even with constant correction and updating, the

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reference genome contains artifacts of its origin in the Human Genome Project. It is, contrary to myth, not the sequence of genome pioneer Craig Venter but an amalgam from several sources. There is now a move to create a reference genome from a single source, a so-called "platinum genome." Its origin and evolution are described in a long feature in *Bio-IT World* (30 June 2014). The Genome Institute at Washington University in St. Louis is assembling the platinum genome from a haploid cell line called CHM1, which is already an industry standard. CHM1 clones have never been assembled into a complete genome, but recent progress in producing longer and longer stretches of unbroken sequence from a single sequencing read is enabling researchers to come closer to complete assembly. When finished, the sequence

NEWS BRIEFS *(continued)*

will have advantages over the current reference genome in that it will be from a single individual and will have been assembled from longer fragments with fewer gaps than the current reference genome. The Genome Institute plans to deposit the full sequence in GenBank for public use as soon as it is ready. Researchers involved in the project say that it will be particularly useful in haplotype studies, where it is important to know which variants are often inherited together. In the longer term, a second publicly available reference genome should be an invaluable resource for everyone involved in genomic research.
—Karyn Hede, News Editor

As genome sequencing enters the clinic, insurers opt out

A recent investigation by Reuters News Service revealed that insurance companies are beginning to refuse to pay for whole-genome and whole-exome sequencing just as these technologies begin to enter clinical use. Reporter Julie Steenhuysen followed the medical odyssey of one family seeking an explanation for their infant son's baffling and debilitating symptoms. Standard single-gene tests revealed nothing useful, and the family had exhausted its resources. Like many families dealing with an undiagnosed condition, they pursued whole-exome sequencing, but their insurance company refused to pay for the test. Additional reporting revealed that many of the largest insurers in the United States are now routinely refusing to pay for whole-genome or whole-exome sequencing absent definitive evidence of clinical benefit. The Reuters report noted that Cigna, Blue Cross, Aetna, and other providers are demanding proof of clinical benefit in terms of improved outcomes, a standard of evidence that is often difficult to meet. The consensus among insurers seems to be, as James Cross, vice president of national medical policy and operations at Aetna, told Reuters, that the ability to sequence has gotten ahead of the evidence. He said coverage decisions are based on an individual test and whether it affects patient outcomes. At this point, it is going to be up to the clinical sequencing industry to prove to insurers that the tests provide value to patients and save money in the long run. Until then, as far as insurers are concerned, the tests may remain "investigational," i.e., not covered.
—Karyn Hede, News Editor

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