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NGS superior to genotyping for carrier screening in an Ashkenai Jewish population

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Next-generation sequencing (NGS) is poised to take over from traditional genotype-based screening as economical NGS tests become available. As reported in this issue, a recent carrier screening study of 506 Ashkenazi Jews living in Chicago suggests that commercially available NGS in this population performs better than traditional screening methodologies. Researchers at the Center for Jewish Genetics identified 288 carriers and two carrier couples at risk for recessive disorders that would have been missed through traditional screening methods. Genetic testing in this heavily screened population typically employs targeted mutation analysis (genotyping) for founder mutations in Tay–Sachs disease and a handful of other disorders, typically a total of 19. In contrast, the commercial NGS panel reported here encompassed 85 genetic disorders. The research team reports that 288 (57%) people were carriers of at least one genetic condition, with a smaller number carrying two or more mutations, for a total of 434 pathogenic variants revealed. The findings showed that only 312 (72.5%) would have been detected using a targeted mutation analysis panel. The researchers point out that this is a narrowly defined, high-risk, and self-selecting population. Nonetheless, the results raise questions about best practices for patient education and how best to describe the nature and limitations of various forms of genetic testing. *—Karyn Hede, News Editor*

Newborn screeing for Krabbe disease raises ethical considerations

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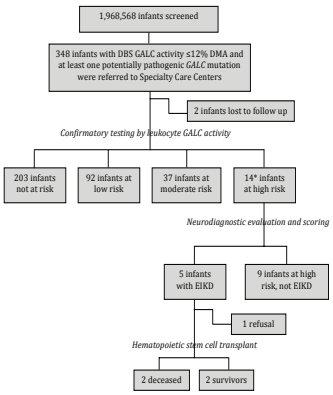
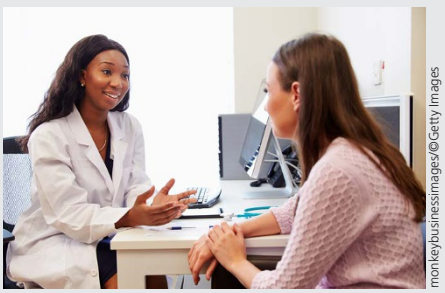


Newborn screening programs that include testing for lysosomal storage diseases such as Pompe disease have been essential in identifying infants who could benefit from available early treatment, for example, enzyme replacement therapy . But for some disorders, treatments are not as well established. In this issue, Wasserstein *et al.* and the New York State Krabbe Consortium discuss the outcomes for New York State's newborn screening for Krabbe disease, a rare lysosomal storage disorder affecting the central and peripheral nervous systems. There is no enzyme replacement for galactocerebrosidase (GALC), the missing enzyme, which is responsible for myelin turnover. Early hematopoietic stem cell transplantation (HSCT) is thought to improve outcomes if performed soon after birth. However, in New York State's experience, the risks may outweigh the benefits of screening, according to the authors. Of the nearly 2 million infants screened during the study, five were diagnosed with early infantile Krabbe disease. Three of them died—two from HSCT-related complications and one from untreated disease. The two remaining children, who both received HSCT, have moderate to severe developmental delays. The authors suggest that in the case of Krabbe disease, the risk-versus-outcome analysis of newborn screening may need to be reassessed from an ethics standpoint. *—Karyn Hede, News Editor*

NEWS BRIEFS

A simmering turf war: who can provide genetic counseling?

A September 2016 report by Kaiser Health News (KHN) is raising questions about a relatively new requirement by some insurers that women receive counseling by a certified genetic counselor before getting tested for cancer-predisposing mutations. Two insurers, United Healthcare and Cigna, have insisted for some time now that genetic counseling should take place prior to insurance approval for *BRCA1/2* testing. Earlier this year, Cigna's Genetic Testing and Counseling Program went further, making genetic counseling



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mandatory prior to testing for all forms of hereditary cancers. But that stance is not sitting well with some physician groups. In a statement released a year ago, the American College of Obstetricians and Gynecologists and the American Congress of Obstetricians and Gynecologists (collectively ACOG) released a formal statement opposing such restrictions and suggesting that the requirement would limit access to care. The statement implies that such restrictions only make it harder for patients to obtain care at a time "when delays may lead to worse outcomes." The group states, "ACOG opposes such attempts to restrict the scope of practice of obstetrician-gynecologists, who are fully qualified to provide pre-test counseling to their patients." Requiring women to receive genetic counseling from certified genetic counselors could particularly impact patients in underserved areas where fewer certified genetic counselors are available. In a conciliatory gesture, Cigna

NEWS BRIEFS *(continued)*

then stated that it had not ruled out counseling by physicians. Jeffrey F. Hankoff, medical officer for performance and quality at Cigna, told KHN that physicians who get additional training in cancer genetics could fill the genetic counseling role. —*Karyn Hede, News Editor*

A nail in the coffin of the thrifty gene hypothesis?

Escalating rates of obesity and diabetes among ethnic groups introduced to modern diet patterns have for decades inspired geneticists to try to explain the phenomena. The "thrifty gene" hypothesis, first posited in 1962, states that among early humans a genetic predisposition to store fat in times of famine would have been an evolutionary advantage. The concept has enjoyed great intuitive resonance and support, but the search for genes contributing to thrift has largely been unfruitful. Indeed, in recent years some evidence suggests that the hypothesis should be discounted. Now, a fresh genetic analysis published in *Cell Metabolism* in September 2016 that looked for positive selection pressure found that only 9 of 115 genes known to be associated with obesity might have been under positive selection. Of these nine, only four favored obesity while five favored leanness. The analysis utilized public databases such as the HapMap Consortium and the 1000 Genomes Project. "This is probably the hardest evidence so far against the thrifty gene hypothesis—our ambition here is for people to entertain a wider range of ideas about where the genetic basis of complex diseases, like obesity, comes from," said John Speakman, a biologist at the Chinese Academy of Sciences Institute of Genetics and Developmental Biology in Beijing, who coauthored the piece with Guanlin Wang, one of his PhD students at the Chinese Academy of Sciences. "The process of evolution is a lot more complex than just the spread of favorable traits by natural selection and the thrifty gene is like an emblem of this older way of thinking about evolutionary aspects of medicine." —*Karyn Hede, News Editor*

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