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New clues to prevalence and penetrance of Mendelian disorders in the general population

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A fresh look at exome data from a large aggregated database reveals that more people may harbor variants in genes associated with rare Mendelian disorders than previously understood. In this issue, Tarailo-Graovac *et al.* report that just shy of 3% of exomes in the Exome Aggregation Consortium database (ExAC) had a disease-associated genotype for a rare Mendelian disorder. The ExAC database includes sequencing data on 60,706 unrelated individuals from 17 disease-specific and population genetic studies, but, importantly, excludes individuals affected by a severe pediatric disease. Yet these adult subjects, who were presumably healthy individuals, were found to harbor 113 variants with genotypes implicated in pediatric disease. The finding raises interesting questions about disease variability and penetrance and suggests that excavation of large unselected data sets for information about variants could lead to more accurate variant classification, as well as hold surprises for our notions of penetrance. The research team points out that the lack of certain data within the data set (e.g., age and clinical phenotype) places limits on its utility. The findings also highlight the need for continued data-aggregation efforts that combine clinical and genetic data for diverse populations. Such efforts "will play a crucial role in better understanding of variability and penetrance of both known and novel rare disease variants in the context of different genetic and nongenetic backgrounds," the authors suggest. *—Karyn Hede, News Editor*

Invasive prenatal testing rate plummets in Australia

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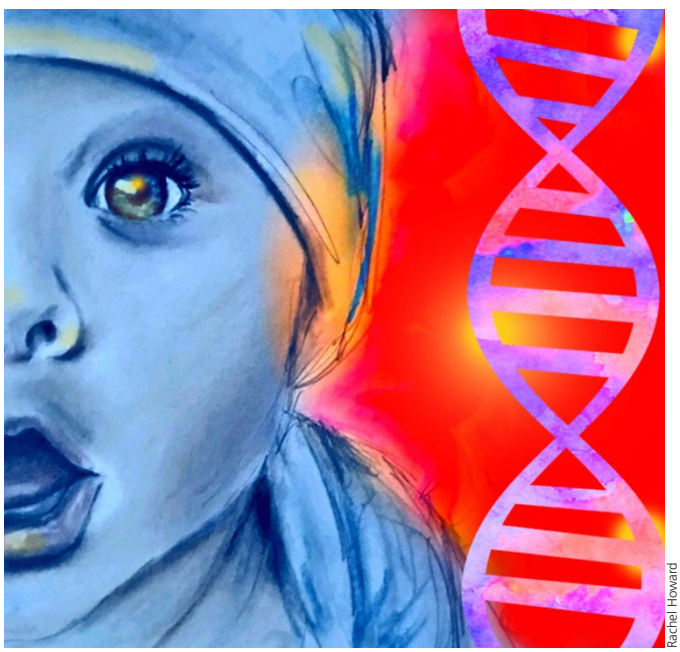
The first population-based study of noninvasive prenatal screening (NIPS) shows a dramatic downshift in the use of invasive testing in Australia. A unique, long-standing collaboration among all laboratories performing prenatal tests in the Australian state of Victoria allowed Hui *et al.* to track the use of prenatal care from 2000 to 2015, permitting comparison before and after the introduction of NIPS. The Australian government fully funds amniocentesis and chorionic villus sampling, but the total cost of NIPS is borne by the patient. During the study period, the out-of-pocket cost of NIPS dropped in half, from more than AUD 1,000 (US$746) to AUD 500 (US$373). Invasive testing dropped 40%. While it was not possible to determine how many women opted for NIPS, its impact on other testing services was dramatic. For instance, 204 confirmed cases of trisomy 21 were recorded in Victoria in 2015, the most ever detected. Of these, half (105) had received a high-risk NIPS result that precipitated further diagnostic testing. In addition, use of chromosome microarrays (CMAs) for prenatal diagnostic testing increased significantly. The percentage of all tests that were submitted for CMA analysis increased from 14.2% in 2012 to 85.3% in 2015. The researchers concluded that women have paid out-of-pocket for NIPS at a high enough rate to cause a dramatic reduction in invasive testing over a narrow (3-year) window. Over that same period, NIPS became the single biggest contributor to fetal trisomy 21 diagnosis in the study population. *—Karyn Hede, News Editor*



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