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Veterans opt into a large genetic study

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Research teams planning large, prospective cohort genetic studies may benefit from the experience of the Veterans Affairs (VA) healthcare system, which reports in this issue that more veterans prefer to be explicitly asked to participate. The survey of 451 veterans found that half had no preference between opting in or opting out of the planned Genomic Medicine Program, an ambitious project aiming to enroll 1 million veterans in a database that will include genetic, clinical, and environmental-exposure data. Of those who did express a preference, 29% chose the opt-in model and 14% chose the opt-out model. The researchers report that preference for the opt-in model seemed to be related to a desire simply to be asked rather than to have more control over their blood and tissue samples. When the authors looked specifically at the answers from various ethnic groups, they found that the opt-out model could result in underrepresentation of certain demographic groups, including Hispanics and younger veterans. The VA began recruiting veterans in January 2011 using an opt-in model and plans to compare its recruitment results with those expected based on the survey data. *—Karyn Hede, News Editor*

Long-term infantile Pompe disease survivors face new health challenges

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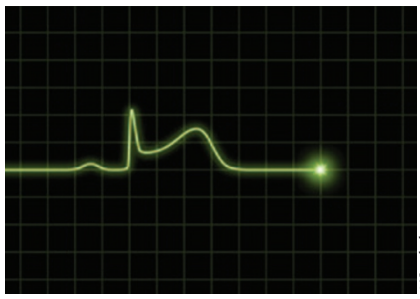


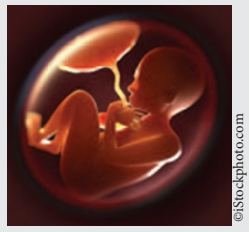
The Hollywood movie *Extraordinary Measures* brought to a mass audience the search for lifesaving enzyme replacement therapy (ERT) to treat the autosomal recessive lysosomal storage disorder Pompe disease (glycogen storage disease type II). In practice, recombinant alglucosidase alfa (Myozyme), available commercially since 2006, has extended life for most infantile Pompe disease patients, who would otherwise die before age 2 from glycogen accumulation in tissues. But no study has evaluated secondary health implications of long-term treatment. Prater et al. examined medical records for 17 infantile Pompe disease patients, ages 5 to 12, all of whom are free of invasive ventilation. The findings showed that, although treatment is effective in maintaining left ventricular function, it does not prevent arrhythmia, which can arise unpredictably despite regular treatment. The results underscore the importance of long-term follow-up, as the constellation of symptoms encountered in patients undergoing enzyme replacement therapies is likely to differ from that in patients with late-onset disease. The Pompe Disease Registry (http://www.registrynxt.com/Pompe/Pages/Home.aspx) is likely to contribute further to the findings of this and other studies. *—Karyn Hede, News Editor*

NEWS BRIEFS

High-throughput genome sequencing poised to impact cancer care

Sequencing tumor DNA in time to match patients with targeted therapy is quickly becoming a viable possibility for genomic medicine. The combination of relatively inexpensive high-throughput sequencing and increasing evidence of the potential inherent in understanding patterns of somatic mutation in individual cancer cases is being reported not only in journals but also in the public square. Beginning on July 7, the *New York Times* ran a series on personal genomics in cancer care, bringing genomic analysis of cancer to a large audience. The series raises a number of ethical issues about who should receive genomic tests and whether patients would even want to know results that offer no treatment options. The Washington University genomic team featured in the *Times* series published a paper in the June 10 issue of *Nature* showing in a retrospective analysis of estrogen receptor–positive breast cancer tumors that whole-genome analysis could predict responders to aromatase inhibitor therapy. Buried in Supplementary Table 18 of the paper, the authors match tumor mutations with existing targeted drugs, none of which are approved for treatment of breast cancer. The table highlights the problem of research findings getting ahead of approved uses of drugs, a dilemma poignantly laid out in the struggles of patients followed in the *Times* series. Perhaps the answer can be found in the *Nature* authors' call for prospective clinical trials that include comprehensive genome sequencing to guide treatment. *—Karyn Hede, News Editor*

Whole-genome sequencing of fetal DNA



In a technical tour de force, Kitzman et al. (*Sci Transl Med* 2012;4:137ra76) recently carried out noninvasive whole-genome sequencing (WGS) of a human fetus. In one sense this represents the next logical extension of the application of massively parallel sequencing to clinical medicine. However, for several reasons, such application remains firmly in the research realm. As the authors acknowledge, major issues remain to

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be tackled before WGS can be implemented clinically in the prenatal setting.

The reality is that we, of course, don't know how to interpret the vast majority of variants found in any given WGS. Given this lack of knowledge, coupled with the highly constrained timeline when dealing with analysis of fetal DNA, it is clear that WGS of fetal DNA for clinical purposes is a long way off. Not only is the timeline difficult, but the stakes are high with regard to interpreting fetal variants. Many individuals who seek fetal genetic analysis are doing so to help them decide about termination of pregnancy. Therefore, the implications of both false-negative and false-positive results (of which there were many in this experiment) loom large, and we will need to get much better at interpretation before we can offer parents reliable guidance through the use of this type of analysis.

The *targeted* application of such technology, though, is already finding its way into the clinic. At least three labs in the United States are offering noninvasive fetal DNA analysis via next-generation sequencing for the detection of trisomies, and there is no reason why, in principle, targeted noninvasive mutational analysis of fetal DNA for any given target gene could not be performed in this way. But, as always, the application of any such technology in the prenatal setting will require navigating a host of less tangible issues related to reproductive and fetal rights. —*James P. Evans, Editor-in-Chief*