nant women's choices for or against prenatal screening, it would be interesting to compare the rates of informed choice between different countries.

Third, this paper describes the findings of a cluster-randomized trial that was aimed to replicate the findings of earlier correlational studies. These studies did find higher rates of informed uptake in a routine visit setting as compared to a separate visit setting. The present study shows equal percentages of informed choice in both contexts. The authors discuss this discrepancy by questioning the quality and power of the trial. However, in correlational studies causality cannot be assumed, and the findings can be biased as a result of other underlying factors. The results of the trial support the fact that there may be possible alternative explanations of the previously found correlation between setting and informed choice. All in all, the question remains whether a separate visit entails unnecessary barriers, or prevents test acceptance without deliberation.

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Gene Expression Profiling to Monitor Therapeutic and Adverse Effects of Antisense Therapies for Duchenne Muscular Dystrophy

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Paving the Way towards Antisense Therapy against Duchenne Muscular Dystrophy

In May 2006, the Leiden University Medical Center (LUMC) and the biotech company Prosensa got approval for an exploratory study that involves 6 patients with Duchenne muscular dystrophy (DMD). The patients will be given an intramuscular dose of antisense oligonucleotides to restore the (local) production of the defective protein dystrophin. DMD is caused by frameshifting mutations in the *dystrophin* gene. The antisense oligonucleotides induce the specific skipping of a single exon, such that the reading frame is restored. This allows the synthesis of a largely

functional dystrophin, associated with a milder Becker muscular dystrophy phenotype.

In the research report reviewed here, the researchers of the LUMC describe an important step towards this very first clinical trial using antisense oligonucleotides. Taking this therapeutic approach as an example, they assessed the utility of the gene profiling technique for the preclinical evaluation of drug efficacy and safety. Two different treatment protocols with previously established efficacy were applied in muscles from dystrophin-deficient mice: injection of (1) synthetic antisense oligonucleotides with different uptake-enhancing carriers and (2) recombinant adeno-associated virus-expressed antisense sequences. Muscular gene expression microarrays provided a comprehensive picture of beneficial and negative effects of both treatments. The authors found that the synthetic oligonucleotides are essentially nontoxic, but that the effective uptake enhancer of the oligonucleotides, poly-ethylenimine, worsens the inflammation already present in dystrophin-deficient mice. The use of viral vectors resulted in efficiency-dependent normalization of muscular gene expression patterns: i.e. much higher dystrophin production and reductions in inflammation and fibrosis. An adverse effect of the treatments applied was the induction of an inflammatory reaction against the injections themselves. No evidence was found for other adverse effects like increased levels of apoptosis, necrosis, DNA repair or oxidative stress.

Comments

So far, few studies have made integrated use of microarrays in pharmacogenomics and even fewer reports show that therapy-induced disease regression is reflected by a normalization of gene expression patterns. Backed up by the results of their study, the authors foresee that expression profiling will be increasingly used for the preclinical and clinical evaluation of drug safety and efficacy, thereby reducing the number of different biological assays required. Specifically, expression profiling would be suited excellently to address the safety concerns associated with viral gene therapy.

This study is one of many steps towards the treatment of a devastating childhood disease. DMD, characterized by progressive muscle degeneration, typically leads to death in the second or third decade after birth due to heart or respiratory failure. No curative therapy, reestablishing the function of dystrophin, is yet available. For many parents of Duchenne patients it is a race against the clock to find ways of curing their child. In the Duchenne Parent Project, started in 1994, they combine their efforts in the fight against one of the most common deadly genetic diseases: 1 in 3,500 boys get the disease independent of race or geography. Duchenne parents in the Netherlands have collected and spent more than three million euros on research at 13 different universities across Europe, one of them being the LUMC in Leiden. After the promising results of the laboratory and animal experiments, there is a new and important role for patients with muscular dystrophy. This year the very first clinical study in Duchenne patients using antisense oligonucleotides will start. In this new phase, the development of safe and efficient ways of administering the antisense molecules is central. The next years will prove whether the combined efforts of scientists, Duchenne patients and their parents can further slow down the progression of the disease and perhaps even stop it.

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