The current series of Genomic Medicine review articles concludes in this issue of the Journal with the publication of an article on cognitive impairment and autism by Mefford and colleagues. The topic of this article is an appropriate capstone for the Genomic Medicine series: it highlights the clinical advances in genomics regarding the care of patients with neurologic conditions, and it shows the potential of genomic science to further accelerate the pace of discovery in the neurosciences.

The power of genomic technologies — in particular, DNA sequencing — is extraordinary. These techniques have led to a precipitous plunge in the cost of generating sequence data (Fig. 1). Remarkably, best estimates suggest that by the end of 2012, the National Institutes of Health will have funded whole-exome or whole-genome sequencing of samples from approximately 70,000 subjects involved in research protocols. This number would have seemed pure fantasy to most observers a decade ago. The advent of the $1,000 genome promises to have a profound effect on biomedical science by effectively democratizing genome-scale sequencing for research and clinical purposes. Low-cost sequencing has also brought us to a point at which the cost of interpreting, manipulating, and storing data from genomic research is the barrier to use of the data.

The ability to sequence human genomes inexpensively raises complex issues concerning the rights and responsibilities of scientists, health care providers, policymakers, and the public. Although the Health Insurance Portability and Accountability Act (HIPAA), the Americans with Disabilities Act (ADA), and the Genetic Information Nondiscrimination Act (GINA) have addressed some of these issues, many issues remain unresolved. Their resolution will be critical to realizing the full benefit of genomic advances. Central to some of these issues is the boundary between research and clinical care, as defined in the Belmont Report produced by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and the “Common Rule” that governs much of federally funded biomedical research in the United States.

Making clinical use of the vast complexity of human genomic variation will require the ability to determine correlations among clinical attributes, including treatment outcomes, for large numbers of subjects and their genomes. The high cost of developing and following large series and cohorts of well-phenotyped and well-genotyped subjects for prospective research curbs the advancement of genomic science, although it is not prohibitive, as evidenced by the creation of the U.K. Biobank and the National Children’s Study in the United States. National efforts to develop a robust, interoperable infrastructure for clinical health-information technology in the United States have created the possibility of marrying subjects’ genomics data to vast quantities of clinical information. However, in most health care institutions, bright and often inflexible lines are drawn between research and clinical infrastructures, effectively blocking the ability to achieve maximal synergy among existing resources. The potential consequences of blurring clinical and research infrastructures are considerable, and such a merger should not be undertaken without extensive public debate.

Dwindling public and private dollars for biomedical research may suggest a reassessment of the acceptable ratio of benefits to harm of such
a blended approach to genomics research and health care delivery.

The current distinction between research and clinical infrastructure can have immediate and profound consequences for subjects who participate in research protocols. In a hypothetical yet increasingly common scenario involving the "incidentalome," a research scientist who is studying autism incidentally discovers that a child's genome contains a variant in the mismatch-repair gene MLH1, which predisposes the research subject to colorectal cancer. Because her research laboratory is not certified under the Clinical Laboratory Improvements Amendments (CLIA) of 1988, she may not divulge this information to the parents without first having the sample retested in a CLIA laboratory. Worse, the subject's family members cannot be contacted because of the terms of the informed consent obtained at the time of recruitment. Thus, the subject is at risk for real harm. The complexity of the byzantine patchwork of approaches governing return of results often does not serve the research subjects, and we endorse efforts to make the process less convoluted.

Clearly, further research is needed to identify which of the gene products and molecular mechanisms that are implicated by sequencing and genomewide association studies make good targets for experimental interventions. We have before us several thousand susceptibility variants, mainly identified by such studies. Although each of these variants typically has a small effect and thus is not helpful in predicting risk, the identification of such variants expands our understanding of the biology of human health and disease and implicates specific genes, loci, and pathways in disease susceptibility or progression. Although the translation of knowledge about genes associated with mendelian diseases to interventions has proved more difficult than many observers anticipated, there have been and continue to be many notable successes. These successes are founded on studies such as that during the past 4 years, the rate of decline in the cost of sequencing a human genome has dramatically exceeded that of Moore's law, which states that the number of transistors on a computer chip doubles every 24 months, allowing scale to become proportionately smaller. The cost is for sequencing the human genome at 6x coverage until October 2007, at 10x coverage in the quarter ending in January 2008, and at 30x coverage in the quarter ending in April 2008. Data are from the National Human Genome Research Institute.
Colorectal cancer is the third most common cancer worldwide. The lifetime risk of colorectal cancer in the United States is approximately 5%. Clinical symptoms develop late in the course of the disease, and precursor lesions (adenomas) can be easily detected and removed. The disease is a candidate for early detection and prevention by screening. This issue of the *Journal* features two important studies that shed light on a number of interesting features in screening for colorectal cancer.

**Colonoscopy as a Triage Screening Test**

Michael Brethauer, M.D., Ph.D., and Mette Kalager, M.D.

Zauber and colleagues present long-term follow-up data on mortality from colorectal cancer from the National Polyp Study. After a mean period of 15.8 years, mortality from colorectal cancer was 53% lower among patients who had undergone colonoscopy and had adenomas removed than in a reference group from the Surveillance, Epidemiology, and End Results (SEER) Program (absolute risk, 0.8% vs. 1.5%). Interestingly, the risk of death from colorectal cancer was similarly low in the adenoma cohort and a concurrent nonadenoma cohort during the first 10 years of follow-up, when a strict surveillance strategy was applied for patients with adenomas, but the risk increased for patients with adenomas thereafter, when surveillance was not organized by the investigators. This highlights the importance of long-term surveillance for patients after the initial removal of adenomas.

The observed 50% reduction in mortality from colorectal cancer seems reasonable, although it has to be recognized that the National Polyp Study is not a screening study and that the SEER comparison group had higher mortality from all causes, which may bias the results. Also, the study mimics a situation in which 100% of the population complies with screening, which is not a real-life scenario. Randomized, population-based trials are needed to obtain valid estimates of the effectiveness of screening on a population level. The article by MacKenzie in this issue of the *Journal*, which establishes an experimental approach to the treatment of spinal muscular atrophy. The funding of similar research in the context of both rare and complex diseases is critical.