The genome era begins…

doi:10.1038/ng1110

Looking back on the last decade, the progress in the field of genetics stands out as a monumental achievement. The acceleration of the Human Genome Project and the public availability of the human genome sequence did not provide instant knowledge regarding all things genetic, as much of the lay press might have insinuated. Rather, the technical and information explosions of the past decade are providing the tools to interrogate biology. The next decade will lead to major acquisitions of knowledge, much of it predicted in the reviews published in this issue. But what is not published in this issue?

In the past decade, many of the biological applications of genetic and genomic information to the problems of medicine development and delivery were not possible. These applications required the tools provided by the Human Genome Project. The next decade will see three new applications of genetics to medicine: (i) identification of disease-associated genes in target classes that are amenable to high-throughput drug screening; (ii) inexpensive high-throughput genotyping technologies and new statistical algorithms for rapidly defining multiple gene variants associated with a defined phenotype; and (iii) a pharmacogenetic system approved by regulatory authorities that facilitates delivery of safe and effective medicines. There are no reviews discussing these topics in this issue.

Time is a key variable that is frequently misunderstood. Identification of disease-specific drug targets is now possible, but the wave of new and approved medicines resulting from these findings will take years to pass through the drug discovery and regulatory processes. Expensive methods for whole-genome genotyping already exist in 2003. However, the collection of human DNA samples and the critical definition of clinical phenotypes that is necessary for high-quality association analyses have yet to be appreciated (and supported properly) as the rate-limiting steps in phenotype–genotype associations. A systematic method for regulators and industry to deal with adverse events is needed to maintain availability of effective medicines. This is particularly the case when dealing with the uncommon complications recognized only when a drug becomes available to large numbers of patients. Using current tools, it is possible to develop inexpensive tests that can predict an individual's susceptibility to an adverse event. Application and availability depend on a societal commitment to safety and new surveillance systems.

Recently, new technologies have been used to test for association between candidate genes and an uncommon adverse response to treatment with the anti-retroviral drug abacavir. Approximately 4% of individuals with human immunodeficiency virus (HIV) treated with abacavir develop a specific hypersensitivity reaction (HSR; *Lancet* **359**, 1121–1122 (2002)). We identified a 250,000-bp region of extended linkage disequilibrium that was associated with the HSR. Several HSR-associated single-nucleotide polymorphisms (SNPs) were predictive (individuals with the SNPs taking the drug had a 97% chance of experiencing the adverse event), but only half the individuals who experienced the adverse event carried the variants (97% specificity, 50% sensitivity; *Nat. Genet.* **32**, 353 (2002)). If we test the same patients with many thousands of mapped SNPs to define a small set of adverse event susceptibility variants, will we improve the specificity and the sensitivity significantly? If so, then what does this mean for the practice of medicine?

The SNP Consortium had published more than 2 million SNPs by the summer of 2001. To use the SNPs in a practical experiment, a sufficient number and density of SNPs necessary to detect linkage disequilibrium needed to be selected, primer sets to be generated and validated, and high-throughput analytical methods to be developed. These tools became available in December 2001 and were used in 2002 and early 2003 to test the proof of principle for this methodology in previously collected samples (*Nat. Rev. Drug Discov.* **1**, 541 (2002)). However, because the data are derived from individuals using a currently marketed drug, the data must first be submitted and considered by regulatory authorities. When the data are released, it will become apparent that the tools already exist to generate highly predictive SNP panels in 2003. Once it is clear that safety predictive profiles can be easily identified, there will be increased demand for using these tools for all drugs–including non-prescription medicines with known adverse events.

As stated above, identifying the individuals and their drug history and obtaining DNA for analysis are the rate-limiting steps. The time from availability of sufficient DNA samples to data analysis currently spans only weeks to months. Until a standardized Phase IV surveillance program for individuals taking newly marketed drugs is put in place, collecting DNA samples from these individuals will slow progress considerably. Over-the-counter drug safety will become a major opportunity for academic and commercial research.

Pharmacogenetics is about making effective medicines that extend quality of life and, indeed, save lives. Once proof-of-principle data from adverse events from several medicines are available for analysis, ethics will demand a better drug surveillance system for all medicines. That is the next decade.

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