The past 3 months have seen the publication of a series of studies examining the inherited genetic underpinnings of common diseases such as prostate cancer, breast cancer, diabetes, and in this issue of the *Journal*, coronary artery disease (reported by Samani et al., pages 443–453). These genomewide association studies have been able to examine interpatient differences in inherited genetic variability at an unprecedented level of resolution, thanks to the development of microarrays, or chips, capable of assessing more than 500,000 single-nucleotide polymorphisms (SNPs) in a single sample. This “SNP-chip” technology capitalizes on a catalogue of common human genetic variations that is provided by the HapMap Project, which was made possible by the completion of the consensus human-genome sequence.¹

The amount of data in these studies is four to five orders of magnitude greater than that in the previous generation of case–control studies, which tested only a handful of variants, often in a specific candidate gene. This unprecedented volume poses unusual statistical challenges for the analysis, display, and interpretation of the data.

The chief strength of the new approach also contains its chief problem: with more than 500,000 comparisons per study, the potential for false positive results is unprecedented. One proposed solution is to adopt the approach conventionally used in much medical research — choosing a stringent P value at which statistical significance will be declared. To address the 500,000 or more comparisons, a Bonferroni approach can be used; for example, one can divide the commonly used P value of 0.05 by 500,000 to obtain a cutoff P value of 0.0000001 (10⁻⁷), which is sometimes referred to as the threshold of “genomewide significance.”

Even with access to all the available primary-association data (see sidebar), it will probably still be desirable to select a subgroup of SNPs with the strongest associa-
The unprecedented number of comparisons being made in genomewide association studies using “SNP chips” has led to the recognition that no initially identified association can be relied on until it has been replicated in one or more studies of adequate size.4 The process usually involves a multistage design, in which replication is attempted for a number of the SNPs that were found in the original study to have the most significant associations with the disease in question. Since genotyping a small number of SNPs is less expensive than using a SNP chip, such a design results in lower overall costs than using SNP chips for all studies. The main drawback is that if the P value for association for a given SNP in the initial study is not sufficiently small, the SNP will not be carried forward to the second stage of analysis — yet the association thus dismissed may actually be falsely negative.

If more than one genomewide association study has been conducted for a specific disease, an obvious alternative process of replication is to use one study to assess all the SNP associations found in the other study. In this issue of the Journal, Samani et al. compare a genomewide association study for coronary artery disease conducted in the United Kingdom with one conducted in Germany. Another use of two or more studies is to combine their data to provide increased statistical power for selecting the SNPs for smaller-scale replication in future studies. Again, Samani et al. provide an example of this approach, although by limiting their joint analysis to SNPs for which associations had P values of less than 0.001 in at least one scan, presumably to limit the number of false positive results, they have probably missed an opportunity to “resurrect” false negative results in either scan that did not meet their P value cutoff.

The benefits of these approaches suggest that if groups conducting genomewide association studies agree to share data — or better still, to make their data public in a format that permits other groups to obtain the results easily — progress in identifying causal loci will be accelerated. Although many groups conducting such studies have not declared their intentions regarding data availability, there are some encouraging examples. The National Cancer Institute’s Cancer Genetic Markers of Susceptibility project has made the P values, relative risks, and confidence intervals from its genomewide association study of breast and prostate cancers available before publication (at http://cgems.cancer.gov), and investigators from the Diabetes Genetics Initiative have done the same (www.broad.mit.edu/diabetes). Samani et al. have committed to making the primary data from their two genomewide association studies available through a registration procedure (see the Data Access section of their article). The National Institutes of Health is finalizing a policy that may oblige grantees to make such data available through sites such as its Genotype and Phenotype database (dbGaP; www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gap), again through a registration procedure. This level of access to the full results from human studies is novel and should speed the identification of genetic variants associated with the diseases and other phenotypes that are the subject of genomewide association studies. We hope that many more examples of the benefits of data sharing will be forthcoming.
frequently used in the reporting of results from genomewide association studies is the population attributable fraction, often called the population attributable risk — an estimate of the percentage of cases of disease that would be avoided if the exposure were removed. This statistic combines information about the strength of the association, or relative risk, with information on the prevalence of the exposure (in this case, the genotype). Thus, mutations that convey very high relative risks of disease (such as mutations associated with familial hypercholesterolemia) but that are rare in the population are estimated to have low population attributable risks. Common polymorphisms imparting much smaller increases in risk may be estimated to have substantial population attributable risks.

For example, Samani et al. estimate that the variants they identified have population attributable risks of 10%, 11%, and 22%, with a combined estimate of 38%. Although this value suggests that they have discovered the causes of an impressively high percentage of cases of coronary heart disease, readers should be aware of some awkward properties of this measure. Individual population attributable risks cannot simply be summed to give the combined value; the sum of 10%, 11%, and 22% is 43%, as compared with the combined estimate of 38%. This fact complicates the combining of the estimates across studies, since their sums can exceed 100% — and clearly, we cannot prevent more than 100% of cases of a disease. Nor can we factor in the contribution of the additional, yet undiscovered, gene variants that researchers are confident they will find as they continue to comb through data from genomewide association studies. Thus, the population attributable risk provides a rough guide to the relative contribution of a gene variant to disease but should not be interpreted too literally, not least because its literal interpretation — which involves the hypothetical removal of the relevant exposure — does not apply as readily to gene variants as it does to modifiable environmental exposures.

The avalanche of recent data provided by genomewide association studies represents a quantum leap in information about the inherited component of certain diseases. However, a few caveats should be noted. Although SNP chips provide a vast quantity of information on common genetic variation, there is a substantial proportion of the known common variation that they do not capture. Manufacturers are producing newer chips, with probes for as many as 1 million SNPs, that will increase coverage, particularly for persons of African ancestry, suggesting that the rescanning of samples would uncover some loci missed by earlier generations of chips. Non-SNP gene variants, such as small deletions and insertions, are not formally represented on the SNP chips (although some of them may have SNP surrogates). Gains and losses of larger chromosomal segments, including variation in the number of copies of genes, have recently been found to be more common than previously appreciated. Identifying such variants will require special analysis of the chips, which has not been performed by most researchers to date.

This first wave of genomewide association studies is producing
an impressive list of unexpected associations between genes or chromosomal regions and a broad range of diseases. There have been few, if any, similar bursts of discovery in the history of medical research. Relatively conventional statistical techniques are adequate for the analysis and interpretation of these initial studies. But as we delve further into the genome in the search for networks of interacting gene variants and interactions between these networks and environmental factors, much more sophisticated methods of statistical analysis are likely to be required.

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O nly 30 or 40 years ago, rheumatic fever was a common topic in the Journal. A PubMed search for articles on rheumatic fever published between 1967 and 1976 returned 55 New England Journal of Medicine articles — fewer than for endocarditis (77) but more than for stroke and syphilis (24 entries each). A similar PubMed search for the decade 1997 through 2006 yielded just eight entries for rheumatic fever. This trend holds for all Medline-indexed journals: an average of 516 articles on rheumatic fever per year from 1967 through 1976, but only 172 per year from 1997 through 2006. Most observers would probably consider this decrease to be a reasonable reflection of the waning incidence of the disease. After all, in the mid-20th century, children with rheumatic fever occupied many of the beds in pediatric wards in industrialized countries — indeed, entire hospitals were dedicated to the treatment of, and rehabilitation from, rheumatic fever. But in the latter half of the 20th century, rheumatic fever receded as an important health problem in almost all wealthy countries. Today, most physicians in these countries are unlikely ever to see a case of acute rheumatic fever, and their experience with rheumatic heart disease will be limited to heart-valve lesions in older patients who had rheumatic fever in their youth.

The reality, however, is that the decrease in publications reflects only the waning burden of disease among the less than 20% of the world’s population living in high-income countries. For everyone else, rheumatic fever and rheumatic heart disease are bigger problems than ever. It was estimated recently that worldwide 15.6 million people have rheumatic heart disease and that there are 470,000 new cases of rheumatic fever and 233,000 deaths attributable to rheumatic fever or rheumatic heart disease each year. These are conservative estimates — the actual figures are likely to be substantially higher. Almost all these cases and deaths occur in developing countries.

How did rheumatic fever become rare in wealthy countries? Medical science can take some of the credit, thanks largely to the use of penicillin for primary prevention, but most of the reduction is attributable to improved living conditions, which have resulted in less overcrowding and better hygiene, with consequent reductions in transmission of group A streptococci. In other words, rheumatic fever is a disease of poverty. That it is in many ways the epitome of diseases of poverty and social injustice is exemplified by the situations in Australia and New Zealand. In these countries, which boast living standards that are among the best in the world, there are indigenous populations,