

Genomics and Global Health: Time for a Reappraisal

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Although currently there are only a limited number of genomic technologies that are applicable to health care in the developing countries, this is unlikely to be the case in the near future. If, however, the full potential of genomics for health care is to be fulfilled, there will have to be a complete change of emphasis in education and research in the richer countries toward a more global view of disease and its consequences.

The announcements of the partial completion of the human and some of the pathogen genome projects were accompanied by promises that these remarkable achievements would lead to a complete revolution in medical practice over the next 20 years; many of our intractable killers would become preventable, and those that are not would be controlled by new families of medicines derived from knowledge of our genetic make-up, or those of our pathogens (1–3). Only 2 years later, and as we celebrate the 50th anniversary of the discovery of the structure of DNA, it is becoming clear that some of these promises were premature. Most of these pronouncements related to the common diseases of the richer countries, which are likely to be the result of variable susceptibility mediated through many different genes, the action of rapidly changing environmental agents, and the complex and ill-understood pathology of aging. As we enter the new millennium, even these complexities pale into insignificance compared with the health problems of the developing world: four million children lost each year from infectious diseases for which vaccines or other forms of prevention are already available; 70% of the 40 million people with HIV/AIDS infection concentrated in countries with completely dysfunctional health care systems; and millions dying each year because of poor sanitation, unsafe water, and air pollution, not to mention a lack of basic health care (4, 5). Nor are the problems of the poorer countries restricted to the effects of communicable disease and poverty. As social and environmental conditions improve, many countries pass through the epidemiological transition from infectious to noncommunicable disease. Globally, heart disease is now the commonest killer, and late-onset diabetes and obesity are emerging as a new pandemic; it is estimated that there are 150 million affected people worldwide, and that number is expected to double by 2025. In some poorer populations, the rate of stroke is al-

ready four to five times that in richer countries. To make matters worse, in many countries that are going through this epidemiological transition, infectious disease has not yet been controlled (6).

Considering the magnitude of these problems, it is not surprising that the major international health agencies have made the reduction of known or perceived risk factors for both communicable and noncommunicable disease their main priority for the immediate future (4). Genomics research and its immediate applications do not appear anywhere on their agenda.

Is There a Case for Introducing Genome-Based Technology into the Developing Countries Now?

In 2001, the Director General of the World Health Organization (WHO) called for a report on the role of genomics in world health (7). The central issue was not so much the long-term potentials of genomics for health care. These had been well aired; plans were already being developed for financing a major effort at genomics research relating to AIDS, tuberculosis, and malaria, and several poorer countries were creating the biotechnology base required to tackle communicable diseases peculiar to their populations. Rather, the question was whether there were already advances stemming from this field that could be applied in the developing countries for the benefit of their populations, or whether the international health community should wait for further progress in the richer countries' research programs on genomics and health care and instead focus all its efforts on public health and preventive medicine.

This was a difficult question to answer because, in truth, with a few exceptions research in the molecular medicine era has not yet led to many changes in day-to-day clinical practice for the benefit of patients. After the extensive consultations that preceded the writing of the WHO report and the feedback following its publication, it became clear that there is widespread support for the introduction of DNA technology into the developing countries now, at

least in the fields of monogenic and communicable disease.

The role of DNA technology for the control of the hemoglobin disorders, notably thalassemia and sickle cell anemia, offers a particularly valuable model system to explore the potential of molecular medicine in the developing world. Currently, it is estimated that about 7% of the world's population are carriers and that many thousands of babies with severe forms of these diseases are born each year (8). As rates of mortality in early childhood due to malnutrition and infection decline, most of these children survive long enough to present for treatment; hence, these conditions are producing an increasingly serious burden on their countries' health care resources. For example, in Thailand, it is estimated that there are ~10,000 new children with thalassemia born each year, that the total number of cases in the country is now between half and three quarters of a million, and that, if adequate treatment becomes available for many of them, this figure could double over the next 20 years. The situation is similar in many other countries in southeast Asia (9).

Although much remains to be learned about the genotype/phenotype relations of these diseases, there is already abundant evidence that they are amenable to control and better management with DNA diagnostics. Through development of North/South partnerships, the underlying mutations, which are different in each ethnic group, have been determined, and reliable methods have been developed for their prenatal detection (10). These advances have already led to a marked reduction in the frequency of these conditions in many Mediterranean populations, a trend which is gradually spreading to many parts of the Indian subcontinent and southeast Asia (11). However, there are still many countries in which these diseases have not yet been controlled; the huge problem of sickle cell anemia in sub-Saharan Africa is a prime example (8).

Another example of the value of transfer of DNA technology by North/South partnerships is the development of DNA-based diagnostic methods adapted for communicable diseases in individual developing countries. The Sustainable Science Institute in San Francisco has developed a program that involves training of technical staff, local mod-

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ification of equipment, recycling of reagents, and other technical developments directed at the rapid, cost-effective DNA diagnosis of infectious disease (12). This approach has been applied successfully in Nicaragua for the rapid diagnosis of leishmaniasis, dengue hemorrhagic fever, and leptospirosis. Similar programs have been developed between the Swiss Tropical Institute and Tanzania for the application of polymerase chain reaction technology to identifying drug resistance to malaria and for genotyping malarial parasites (12). Pilot studies carried out in Africa are showing the value of these approaches for typing patients for genetic resistance to drugs used in HIV/AIDS treatment (13) and for community studies of drug-resistant malarial

How Can North/South Interactions Be Encouraged and Expanded?

As exemplified by the recent report of the WHO Commission on Macroeconomics and Health (16), there is much current thinking about how to mobilize the skills and resources of the richer countries for the benefit of the health of the developing world. However, from an ethical, institutional, and practical perspective, it is far from clear how this international effort should be organized or, even more importantly, funded. On the basis of doubts about the efficiency and bureaucracy of large international bodies, it has been suggested that a virtual global network for health research be established in which the leading research agencies of the North and

tom-up approach to international health research has many attractions. The examples cited earlier emphasize the importance of developing North/South partnerships and the particular value of forming links of this type between universities or other academic institutions. These partnerships need to be long-standing, encompass research fields of genuine relevance to developing countries ranging from public health to genomics, and, ideally, form part of the teaching programs of both Northern and Southern partners. Programs along these lines would greatly augment anything that could be achieved by large international agencies and would have the added advantages of personal interaction and less bureaucracy.

A More Global Outlook on Health in the Universities of Richer Countries

Developments of this kind will, however, require a major change of attitude in the universities of richer countries, particularly in their science and medical faculties. It will entail a complete change of emphasis in teaching toward a much more global view of disease and the development of infrastructure for the organization of overseas programs. It will also require a much closer amalgamation of the fields of public health, clinical research, and the molecular sciences, a situation which is sadly lacking in many of the big international health agencies but which could be accomplished more readily within a university setting. In short, the time has come for our universities, funding bodies, and higher education as a whole to take a much more international view of their activities.

Enough is known already to allow us to be confident that the fruits of genomics research will augment our epidemiological and clinical approaches to medical research. Surely it is time for the research community of the richer countries to reorganize itself such that these benefits can be made available to the poorer countries of the world as they come to fruition in future years. Otherwise, the widely held fear that the fruits of genomics will simply widen the gap in health care between rich and poor (7) may become a reality.

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Thalassemia in Sri Lanka. Children receive their monthly blood transfusion, closely monitored by their mothers. DNA diagnostics have many potential roles in the control of this disease, including population screening, prenatal diagnosis, assessment of the potential severity of the disease, and, hopefully, in the future, the development of rapid and cost-effective methods for screening transfused blood for pathogens.

parasites (14). Furthermore, the remarkable advances of the last few years in relating genetic variation to individual susceptibility to malaria and other common infections (15) may have important practical applications, particularly if attenuating vaccines are to be tested in particular populations.

Clearly, therefore, it is already possible to transfer cost-effective DNA technology into the developing countries. The great advantage of this approach is that it provides a base whereon more sophisticated techniques can be added as more information about the value of genomics for world health becomes available in the future. In addition, it offers an incentive to develop the local ethical and regulatory bodies that will be required to monitor work of this type.

South take part, together with a coordinating council (17). In this scheme, or in a modified form (18), both government funding agencies and charitable bodies would retain their autonomy and mechanisms of funding, while at the same time their individual programs could be better integrated toward the problems of global health. Whether those agencies that rely on government funding would be able to convince their governments that more of their budgets should be spent on work in the developing world, and whether increased funding might be made available for this purpose, is another matter.

However, given the unwieldiness, political complexity, and other uncertainties of major international organizations, this bot-

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VIEWPOINT

Genomic Priorities and Public Health

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Given the continuing difficulty of identifying genes for complex disorders in a robust, replicable manner, and the extensive resources devoted to this effort, it is becoming increasingly important to analyze the relative benefits of genomics research for public health applications and for the understanding of disease pathogenesis. To establish priorities for genetics research, we review and evaluate several characteristics of selected exemplary complex diseases, including phenotypic accuracy, knowledge of specific and nonspecific genetic and environmental risk factors, and population prevalence and impact. We propose that complex diseases with the strongest evidence for genetic etiology, limited ability to modify exposure or risk factors, and high public health impact should have the highest priority for genetics research.

Advances in molecular genetics have generated substantial progress in identifying the genetic basis of Mendelian diseases; however, the pace of the discovery of genes for complex disorders has been slower (1). The limited progress has generated substantial debate regarding optimal strategies and priorities for genetic studies of complex human disorders, particularly in light of the copious resources devoted to identifying susceptibility genes. Although the importance and relevance to human biology of identifying and characterizing genes for complex disorders has been amply demonstrated, it is unlikely that the current level of resources devoted to basic and applied genetic research can be sustained indefinitely. With the continuing difficulty of identifying genes for complex disorders in a robust, replicable manner, questions regarding the cost and potential applications of this work to public health will become increasingly salient (2, 3). In Table 1, we describe disorder characteristics that may be evaluated in choosing appropriate strategies for genetic research. Rather than providing a comprehensive list, specific disorders were selected to illustrate variability in the key areas of phenotypic accuracy, knowledge regarding specific and nonspecific genetic

and environmental risk factors, and population prevalence and impact.

How Well Can We Define the Phenotype?

The reliability and validity of phenotypic characterization for complex diseases is highly variable. Whereas tumor biopsies, insulin levels, glucose reactivity, and immunoreactivity can be measured reliably, other diseases in the table (such as autism and schizophrenia) are based primarily on diagnostic criteria obtained from a clinical interview. Our limited ability to measure and characterize these phenotypes is often the rate-limiting step in etiologic research. Research designed to identify endophenotypes [phenotypic traits or markers that may represent intermediate forms of expression between the output of underlying genes and the broader dis-

ease phenotype (4)] may lead to more rapid success in identifying susceptibility genes for these disorders.

What Is Known Regarding the Etiologic Role of Genes?

Familial recurrence risks, measured by λ (i.e., the ratio of the risk of disease in relatives of affected cases to the population prevalence or to relatives of controls, based on controlled family studies of first degree relatives) are shown in the first column of Table 1 under the heading "Genes" (5). Successful identification of genes for several complex disorders resulted from the discrimination of disease subtypes based on clustering within families (such as type 1 versus type 2 diabetes and early versus late onset of breast cancer and Alzheimer's disease). Although the absolute risk of disease in first degree relatives of cases may be low, elevated risk with respect to the population prevalence (as measured by λ) can indicate the importance of genetic susceptibility. Genetic epidemiologic studies can provide information on the extent to which the familial recurrence risk is attributable to genes. For example, although the absolute risk to relatives of multiple sclerosis cases is only 4%, it is still 20 times as great as the general population risk. Twin, adoption, and half-sibling studies have shown that the familial clus-

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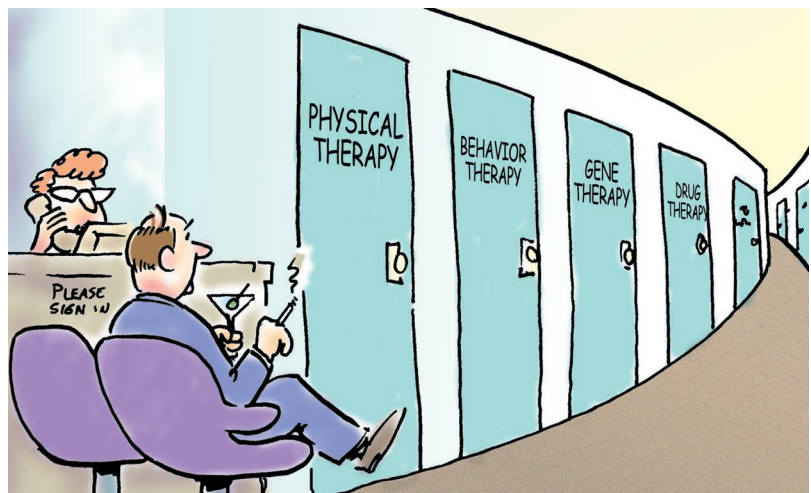


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