The impact of molecular medicine on health services

Injudicious application of genetic testing may have unwanted effects on health-care-seeking behavior and health services.

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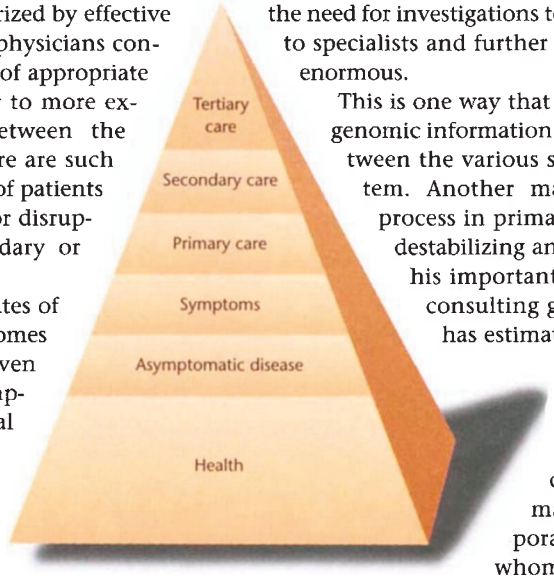
The creation of a new category of patients by the injudicious application of genetic testing has been described by Jonsen and colleagues, who have sounded a timely warning about the ethical dilemmas that molecular medicine may pose for patients and their physicians[1]. Through the unmasking of quantifiable risk or, more generally of hazard, genomic information concerning asymptomatic individuals may lead to the emergence of geneticized "tribes," at uncertain risk of disease in the future, distorting health-care-seeking behavior and posing unanswerable questions about surveillance and intervention. Beyond these ethical difficulties, however, may lie profound and unwanted effects on health services, through the destabilization of relationships between self-care, primary care and secondary care.

There is reasonable evidence that western health care systems with the lowest health care costs are characterized by effective primary care services, in which first-contact physicians contain resource utilization by the employment of appropriate technology and by acting as a referral filter to more expensive specialist care[2]. The relations between the community, primary care and secondary care are such that relatively small changes in the numbers of patients in any one of these sectors could cause major disruptions in the resources available for secondary or tertiary specialty care (see figure).

In the United Kingdom and the United States of America only one in forty symptoms ever becomes the subject of a medical consultation[3,4]. Even among individuals with more striking symptoms, such as abdominal pain or rectal bleeding, only one-quarter to one-third of them will seek medical attention, with the remainder using self-care to deal with their problems[5,6]. It is also clear that the physical nature of symptoms, such as their severity and frequency, are poor predictors of individuals' propensity to seek medical advice. In the case of dyspepsia, for example, most of the variance between consulting and nonconsulting individuals can be explained by their concerns and anxieties about the possible seriousness of their symptoms, particularly in relation to fears about cancer and heart disease[7]. Although we do not have the evidence on which to base a judgment about the appropriateness of the distribution of consulting and nonconsulting behaviors in the general population, it is clear, by reference to the figure, that a small shift in the proportion of patients deciding to seek medical advice may result in a substantially increased load at the primary care level and beyond. As Jonsen and colleagues point out, many patients "will be put into the class of those who must wait and watch for a sign of the disease, advised to organize their lives around colonoscopies and mammograms, the way we are all advised to visit the dental hygienist regularly. Some others will take on the sick role and may develop psychosomatic symptoms of all sorts. Perhaps some may even live as invalids." Those who are found to carry genetic susceptibility will, Jonsen *et al.* argue, constitute a new class of individuals for medicine, a class that might be designated "unpatients," neither patients in the usual sense of being under treatment nor nonpatients, in the sense of being free of medically relevant conditions. The implications for increased rates of consultation with primary care physicians, the need for investigations to provide reassurance, referrals to specialists and further investigations are potentially enormous.



Health and medical care: health and asymptomatic individuals are represented at the base of this pyramid. Most symptomatic individuals do not consult primary care physicians, who themselves act as gatekeepers to expensive secondary and tertiary care.

This is one way that the injudicious availability of genomic information might affect the interfaces between the various sectors of the health care system. Another may relate to the diagnostic process in primary care, also with potentially destabilizing and expensive consequences. In his important series of studies on patients consulting general practitioners, Thomas has estimated that some 40% of patients seen in primary care in the United Kingdom not only consult for conditions for which a precise physical diagnosis cannot be made, but may also be regarded as "temporarily dependent patients," for whom drug or nondrug intervention at the primary care level is unlikely to significantly influence the course of self-limiting symptoms and disorders[8,9]. Primary care physicians are faced with the attempt to make safe diagnoses in conditions of uncertainty when faced by patients whose symptoms are not yet organized into formal illness. Under these conditions, the role of the generalist is to marginalize danger (whereas that of the specialist is to marginalize uncertainty)[10]. To do so, general practitioners employ decision-making strategies with a concentrated version of the hypothetico-deductive method, utilizing relatively small numbers of questions with high negative predictive values, enabling them to decide whether patients can safely be treated by watchful waiting or reassurance or whether more urgent intervention is required[11]. Indeed, the use of time as an alternative to investigation is central to the task of the primary care physician; the specialist, confronted with an undiagnosed patient in the clinic

is expected to make a definitive diagnosis or, at least, to arrange investigation so that one can be made as speedily as possible. Having marginalized danger, the generalist is under no such pressure and may employ the technique of review over time, utilizing an already extensive knowledge of an individual's personal background and medical and social history.

There are at least two major ways in which developments in molecular medicine and genetics may adversely affect this process. The first is, once again, through the beguilingly increasing availability of genomic information, whose introduction into the consultation could distort the diagnostic method and could lead to amplification of the need of investigation and referral in many patients whose symptoms, in reality, merely betoken a self-limiting episode of minor illness. The second is the increasing availability of near-patient (office) diagnostic tests, frequently depending on identification of proteins expressed by a range of genes, associated with the presence of specific diseases. In this context the distinction between wanted and unwanted knowledge may be thrown into sharp focus. Instead of making judicious use of time and appropriate technology, primary care physicians may increasingly find themselves under pressure to undertake investigations that may have more significance for the need for further referral and investigation than for the management of self-limiting disorders.

The gatekeeper role of the primary care physician, acting as a referral filter between relatively inexpensive primary care and potentially expensive secondary care, is likely to be of critical importance in sustaining a cost-effective health care system. The characteristic diagnostic methods of the primary care physician, coupled with the appropriate use of time and technology, are important ways in which medical care is contained within the primary care sector. The escape into this sector of seductive technology that has not been properly evaluated may have serious consequences, resulting in escalation of the demand for expensive secondary care referrals and investigations.

It is possible to think of other ways in which an increasing appreciation of both risk and hazard in the general population and of diagnostic information that is neither needed nor wanted in both primary and secondary care sectors could lead to a general lowering of thresholds for consultation and referral. As well as welcoming the immensely important diagnostic and therapeutic advances promised by molecular medicine, health policy-makers and physicians alike will do well to sustain a keen awareness of the potential for disbenefits and adverse effects on precarious systems of health care.

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HIV-1 Tat protein as a potential AIDS vaccine

Intracellular traffic of the HIV-1 transactivator protein Tat appears essential for pathogenesis, and interdiction by immunization-induced antibodies to Tat should prevent AIDS.

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The Tat transactivator of HIV-1 is essential for the massive initial output of virus that is thought to enable HIV mutational variants to outpace and overwhelm the immune system[1,2], leading to chronic infection, eventual destruction of the immune system, and progression to AIDS. Tat protein release and cellular uptake are necessary for this process; it is thus proposed here that immunologic interdiction of extracellular Tat protein by prophylactic active immunization should critically reduce explosive replication of the virus and permit effective immune control.

Acute infection with HIV-1 is characterized by early high levels of plasma viremia, which decline as the immune response develops, but then persist through the long period of clinical latency[3]. The early relative sequence homogeneity of the virus, indicative of a single dominant strain, is soon changed by the rapid appearance of viral variants, presumably due to selective pressure of the developing immune response[1,2]. HIV-1 reverse transcriptase is highly error-prone, leading to high mutation rates and corresponding viral diversity, even within a single host[4]. This propensity to multiply rapidly, and to mutate frequently, has confounded conventional therapeutic and vaccine approaches to the treatment and prophylaxis of HIV-1 infection. Thus the developing immune response following acute infection is already exerting selective pressure for variant strains that can evade immune control.

Vaccination has been successful in control of various viral diseases and induces specific cytotoxic T-cell elimination of infected cells displaying viral proteins in association with HLA molecules and/or specific antibody blocking and clearing of free virus. This approach is effective for viruses with stable phenotypes, such as smallpox and measles, and for viruses with limited variation in their antigenic epitopes, such as poliomyelitis. But this mode of vaccination becomes more problematic with viruses such as influenza, for which the predominant epitopes may change from year to year, necessitating the preparation of an annual vaccine for use before the winter flu season.

For HIV-1, the huge diversity in immunogenic viral epitopes and the rapid mutational variations that occur within and between individuals[5,6] have so far prevented successful application of these conventional approaches[6].