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LETTERS

Genetic Testing

The excellent News & Comment article by Rachel Nowak "Genetic testing set for takeoff" (22 July, p. 464) clearly documents the problems of the use of genetic tests as general screening tools to identify those predisposed to inherited disease in adult life: the current costs are too high, there are too many genes to test with too many mutations in each gene, and there are not enough genetic counselors to interpret the results of the tests to those who have them. Furthermore, the predictive value of these tests is unknown when used in a general screening. In an earlier letter to the editor (1 April, p. 13), David Danks of the Royal Children's Hospital in Melbourne, Australia, examined the mathematics of a case finding by general screening and pointed out that confining such studies to members of families at risk had a far greater yield (and a better predictive value for the interpretation of the test result). He was considering testing as a public health measure; not, as Nowak's article implies, as a response to market demand.

Nowak contemplates legislative controls on discriminatory uses of genetic testing and refers to the ever-quoted 41 cases described by Paul Billings some years ago. She points out that "all the time people are turned down for life and health insurance" on the basis of test results for the Huntington mutation. As an ex-geneticist, now working in the insurance business, I would like to put the case for our industry into perspective in this discussion.

The predictive value of any laboratory test is a function of sensitivity, specificity, and prevalence of the disease in the test group. Most genetic mutations are rare in the general population and provide low predictive value. The genes *MSH2* and *MLH1* are thought to be mutated in 18% of 5% of the population (thus predisposing them to hereditary nonpolyposis colon cancer), or less than 1 out of 1000 individuals. At this time, no one is quite sure what the mortality risk for these mutations will be. In contrast, serum cholesterol, for which a test is performed on most insurance applicants, is elevated in 40% of them, and the insurer, the applicant, and his family doctor all believe they have some understanding of the risk the elevation represents.

The discriminatory function of genetic tests will be prone to error unless the tests are done in the extended families of identified probands. Insurance testing is not structured on a random access basis, but uses only general screening tools. The cost, for example, of separating those who should have *MSH2* or *MLH1* tests from those that should have a test for the *APC* gene (so as to detect proneness to familial adenomatous polyposis, another cause of colon cancer) would be prohibitive in this industry. That situation is unlikely to change.

Insurers today do not do any genetic testing. They clearly recognize the problems as being excellent reasons to avoid DNA screening tests. On the other hand, insurers do want to know the results of tests that have been done by others, for cause, on individuals who are applying for insurance. Insurance is sold to provide financial protection against unanticipated loss. If people who know they will die at an early age are allowed by law to purchase insurance, then they are at an advantage not only over the insurer but over all the other policyholders covered by that company. As a basic principle, insurance is priced so that those at equal assumed risk pay equally for their protection. If that is not the case, the price of all insurance must change. It is true that people are denied insurance on the basis of family history alone (because, for example, their parent died with Huntington's disease), but they are also turned down if they had cancer surgery 6 months ago—even though they may appear otherwise healthy. They are turned down because their risk of early death is expected to be extremely high and appropriate premiums cannot be calculated. In those instances both the applicant and the insurer know the nature of the risk.

If, however, only the applicant is privileged to know his or her risk and may legally conceal it from the insurer, then insurance will become too expensive for all but those who know they will succumb at an early age. When "everyone" has been tested and all their lifetime genetic risks identified, only those like Billings' unfortunate 41 will be buying insurance while the rest of us, who by definition will have perfect genes, need not bother. In reality, the complete genome test, with interpretation, is a long way in the future. Competitive market forces continue to drive the insurance industry to sell as much insurance as possible and to determine individual risks on the basis of information that is already known to the applicant. If legislation is enacted today to limit the use of test results done by others, it will only provide a new

complexity to an overregulated industry, it will have been written before anyone fully understands the impact it will have in the next decade, and it will add to the cost of a product that should be available to all.

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Nowak's article about genetic testing for human diseases raises several questions regarding the optimal approach for diagnosis, liability, regulation, and fees, especially for the rare genetic diseases. In my laboratory we have addressed the efficacy of DNA-based tests by using polymerase chain reaction and restriction fragment length polymorphism procedures for identifying specific mutations in disease-related genes, as opposed to functional tests for the gene products. This was alluded to in Richard Fishel's remarks about developing tests for the mismatch repair genes *MSH2* and *MLH1*. We have been involved in developing functional tests for the rare repair-deficient diseases xeroderma pigmentosum (XP) and Cockayne syndrome (CS) (*1*).

When there is clear phenotypic expression, functional tests are simpler than DNA tests, especially for multigenic and multiallelic diseases such as XP and CS. But functional tests for rare diseases have the disadvantage that they are often specialized, tailored to the specific disease, and difficult to transfer to a clinical testing laboratory. They require specialized knowledge, and clinicians are unlikely to raise enough money to justify their use. Such tests, therefore, may best be administered in a research laboratory specializing in the particular disease. But this raises other problems, among which insurance and liability are major concerns.

Although we have been able to produce consistent patient and prenatal diagnoses, the financial and administrative burden has become excessive. In addition, and more important, the introduction of the Clinical Laboratory Impovements Act (CLIA88) and other regulations have made it difficult if not impossible for a research laboratory to carry out the diagnostic tests it is equipped to do because the licensing procedures are burdensome and unrelated to the reliable execution of the diagnostic tests.

The development of both DNA-based and functional tests, therefore, needs to be fostered in a regulatory climate that permits research-based laboratories to develop tests for rare disorders on a patient-specific basis, and even to continue when functional specialized tests cannot be economically carried out by a clinical testing laboratory. Because of the current regulatory environment, we are already in the position of declining to carry out tests that we know to be predictive, something that is disappointing to ourselves and to patients.

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Mechanism of Scrapie Replication

The Perspective "Structural clues to prion replication" by Fred E. Cohen *et al.* (22 April, p. 530) indicates that the elucidation of the mechanism of scrapie replication is within reach. It is therefore important to acknowledge those individuals who have contributed significantly to the development of the mechanistic scheme presented therein by Stanley Prusiner and his co-workers. All of the mechanisms for the replication of a protein-only scrapie agent that have been debated over the years were first proposed by J. S. Griffith in 1967 (*1*). Since that time, Carleton Gadjusek (*2*) and others have discussed the possibility of a crystallization mechanism, and models that involve the modification of host protein by the infectious agent have also been suggested (*3*).

Two detailed and mutually exclusive chemical mechanisms have been proposed, the heterodimer model of Stanley Prusiner and co-workers (*4*) and our seeded polymerization model (*5*). The Perspective presents a general scheme which embraces our specific proposal. Despite their recent statements to the contrary (*6*), Prusiner and co-workers now seem to concede the possibility that prion formation involves a polymerization. They also seem to agree with our proposal (*5*) that unfolding of the cellular prion protein is required for its conversion into the infectious form and that pathogenic mutations may act by influencing the unfolding equilibrium. On the basis of our work on peptide models of the prion protein, we proposed that prion replication occurs via a nucleation-dependent polymerization process which resembles a crystallization and that the scrapie infectious agent is a seed for the polymerization process (*5*). According to this scenario, formation of the nucleus is the rate-determining step in in vivo aggregation, while the conformational change that Prusiner and others have studied is a consequence of the aggregation process (*5*). I look forward to the experimental elucidation of this fascinating process.

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Biodiversity Questions

The role of biodiversity in controlling pest outbreaks (Y. Baskin, News & Comment, 8 Apr., p. 202) receives little attention. In Southern Africa, altered biodiversity as a result of interannual climate variability helps explain a "rodent plague" that is reducing grain supplies.

Rodents annually reduce Southern African cereal harvests and stores by an average of 1.3 million tons (out of 10 million tons). Major infestations in Zimbabwe (1974–76, 1983–85, 1993–94) have often followed El Niño–Southern Oscillation warm events, data complementing the findings of Cane *et al.* (*1*). This year's infestation in Zimbabwe and western Mozambique—involving the multimammate rat [*Praomys* (*Mastomys*) *natalensis*], the house mouse (*Mus musculus*), and the giant rat (*Cricetomys gambianus*)—has been particularly severe, and seeds, maize cobs (in milky and mature stages), and some stored grain are being consumed. Once again food security in the region is threatened.

We believe the severe drought of 1991–92 reduced predators of field rodents (for example, snakes and raptors) and draft animals, which thwarted tillage and preserved burrows. With plentiful rains and grains in 1992–93, and short rains and scant predation this year, well-nourished rodents have flourished. Rodents transport many pathogens including hantaviruses (News & Comment, 5 Nov. 1993, p. 832) (*2*) and five emerging arenaviruses in Latin America that cause hemorrhagic fevers (*3*), Lyme disease, and plague.

We submit that (i) top predators (competitors and insurance species) provide resistance against the selection and emergence of opportunistic pests and pathogens; (ii) climate can impact biodiversity directly or indirectly through cumulative cascades that involve species' synchronies and time lags; and (iii) rodent (and insect herbivore) abundance and distribution are sensitive biological indicators, integrating global signals with local conditions. Meteorological forecasting and eco-