



Defining Disease in the Genomics Era

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The human genome sequence will dramatically alter how we define, prevent, and treat disease. As more and more genetic variations among individuals are discovered, there will be a rush to label many of these variations as disease-associated. We need to define the term disease so that it incorporates our expanding genetic knowledge, taking into account the possible risks and adverse consequences associated with certain genetic variations, while acknowledging that a definition of disease cannot be based solely on one genetic abnormality.

Disease is a fluid concept influenced by societal and cultural attitudes that change with time and in response to new scientific and medical discoveries. Historically, doctors defined a disease according to a cluster of symptoms. As their clinical descriptions became more sophisticated, they started to classify diseases into separate groups, and from this medical taxonomy came new insights into disease etiology. For example, before the 20th century, schizophrenia and syphilitic insanity were treated as the same disease. But by early 1900, it became evident that psychoses without associated dementia represented a separate disease for which the term schizophrenia was then coined. The definition of schizophrenia continues to evolve: from the psychiatric disease of the 1960s to an illness with a suspected genetic etiology. While the hunt is still on for the genes involved, we contin-

ue to define schizophrenia in terms of the presence or absence of “positive” and “negative” symptoms.

Diagnosis is the act of labeling someone as diseased through clinical, laboratory, and pathological findings, combined with clinical knowledge and judgment. Disease is generally considered to be an

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attribute of a patient, whereas diagnosis is the belief that the patient has a disease, a belief that may or may not be true. In using a single phrase to describe a set of clinical findings, important information can be effectively communicated to other clinicians and care providers. Diagnoses are intended to inform patients and to tell clinicians who and how to treat.

Labeling someone as “diseased,” however, has enormous individual, social, financial, and physical implications. Irrespective of disease symptoms, the label itself may lead to significant distress. Individuals with asymptomatic conditions, including genetic variations, may be perceived by themselves or others as having a disease. Such labeling has severe ramifications, affecting decisions to have children or resulting in unjust treatment by life, medical, and disability insurers. Sometimes, however, labeling someone as diseased can be beneficial, legitimiz-

ing symptoms, clarifying issues of personal responsibility, and improving accessibility to health care.

Human genome sequencing will reveal thousands of genetic variations among individuals that many will assume are associated with disease. But translating such genotypic differences (genetic characteristics) into phenotypic states (visible characteristics) is prone to pitfalls. For example, genetic abnormalities differ in their penetrance (that is, not everyone carrying a genetic abnormality will suffer from adverse consequences); environmental effects have not been taken into consideration; and many diseases have complex etiologies that depend on a number of different genes. There are very few diseases that are caused by a single gene mutation. Automated genomic sequencing is becoming increasingly sophisticated, but distinguishing between normal variations in genes (polymorphisms) and alterations that are detrimental (mutations) remains extremely difficult. This difficulty will have direct consequences for genetic counselors, who must advise individuals about the presence of genetic abnormalities, what they mean, and which treatment or prophylaxis to follow.

Scant attention has been paid to defining disease in clinical medicine. Heslow has argued against the need for a definition of disease, stating that patients can be treated without one.* However, the importance of the term disease to patients, clinicians, and society cannot be disputed. Boorse defines disease as “a type of internal state which is either an impairment of normal functional ability—that is, a reduction of one or more functional abilities below typical efficiency—or a limitation on functional ability caused by environmental agents.”† This type of philosophical definition is impractical clinically and, more important, is unlikely to make the interpretation of genetic variations any simpler.

In thinking about how clinicians use the term disease, we think that three elements should be considered: disease is a *state* that places individuals at *increased risk of adverse consequences*. Treatment is given to those with a disease to prevent or ameliorate adverse consequences. The key element in this definition is risk: deviations from normal that are not associated with risk should not be considered synonymous with disease. Our definition has three definable elements and should serve clinicians well. Of course, its success will depend on whether it becomes clinically useful.

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*G. Heslow, *Theor. Med.* **14**, 1 (1993).

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Two schools—nominalist and essentialist (reductionist)—have debated the clinical criteria used to label a patient as diseased. Nominalists label symptoms with a disease name, such as schizophrenia, and do not offer an explanation of the underlying etiology. Essentialists argue that for every disease there is an underlying pathological etiology and that the disease state should be defined by the essential lesion. With recent dramatic advances in genetics and genomics, essentialists could argue that the essential lesion defining the disease state is a genetic abnormality.

Scadding suggests that diseases defined according to the essentialist tradition may be “precisely wrong,” whereas those defined in the nominalist traditional may be “roughly accurate.”[‡] We would argue that labeling the disease state according to only the phenotype (symptoms) or the genotype (genetic abnormality) is unsatisfactory. The genotype or phenotype describes a state that places individuals at some definable risk of adverse consequences and so either could be used as a criterion for disease. For example, in the cancer predisposition syndrome hereditary nonpolyposis colorectal cancer (HNPCC), members of HNPCC families have a 50% risk of developing colorectal and other cancers at a very young age. HNPCC has been defined according to both genetic mutations and clinical criteria. Clinical criteria for HNPCC can be used to define the disease state and to advise patients and family members about the need for cancer screening. In contrast, when considering specific genetic or pharmacologic therapies, the disease state may be better defined according to the type of genetic abnormality. Thus, both clinical criteria and genetic abnormalities can be used to define a disease state, and the choice of definition will vary according to what one wishes to achieve (in this case, genetic counseling of family members versus treating the patient).

To be considered a disease, the genotypic or phenotypic state of the patient must have the potential for adverse consequences. In Gilbert's syndrome, there is an asymptomatic elevation of liver enzymes in response to stress, but this condition is not considered a disease because it does not lead to adverse consequences. The World Health Organization's valuable classification of adverse consequences includes physical or psychological impairment, activity restrictions, and/or role limitations. The inclusion of role limitations is particularly important because it acknowledges the sociological consequences of disease in terms of shortening the quantity of life or disturbing its quality. When determining

states that are associated with disease, the challenge is to describe potential adverse outcomes comprehensively and explicitly. Because an adverse consequence in one culture may not be viewed as such in another, this consideration must take into account different ethnic and cultural beliefs. For example, whereas menopause is considered a medical condition in North America, in other cultures it is viewed as a normal aspect of aging.

Although a few diseases are universally and prematurely fatal, most diseases place patients at an increased but variable risk for morbidity or mortality. For example, some patients with high blood pressure will be asymptomatic throughout life, about 30% will suffer adverse consequences such as heart disease, and 5 to 10% will die from a stroke. Here, the “cutoff” between the categories of diseased and nondiseased could be based on many factors, including an im-

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PLICIT understanding of risk and potential for treatment. Criteria defining which individuals are diseased are important because abnormalities, such as genetic variations or elevated blood pressure, may occur in otherwise asymptomatic patients. Criteria for certain diseases, such as diabetes, have improved, owing to more accurate definitions of risk and better treatments. The risk of adverse consequences for some genetic abnormalities may be so low that the state is better described as a risk factor rather than being viewed as synonymous with disease. Defining the level of risk is important because, given the high societal expectations of human genetics, any trait, condition, or behavior associated with a genetic abnormality is in danger of being construed as disease-associated. This will not only overemphasize the genetic contribution to disease etiology, but will also blur the difference between ameliorating disease symptoms and enhancing human attributes.[§]

Patients with a genetic variation who are at minimal or no increased risk for adverse consequences should not be labeled as diseased. If the definition of disease is based solely on a genetic abnormality

rather than on a clear specification of the risk, the label may harm the patient. For example, treating genetic variations in the elderly may not only be unnecessary (because of the low risk of an adverse outcome), but may actually lead to deleterious side effects.

The continuing discovery of new genes, their sequences, and variations has led to confusion among clinicians and patients. First, not all patients with genetic mutations or abnormalities develop adverse outcomes. When a genetic mutation is initially identified, the likelihood of developing a disease is unknown, and so the importance of the mutation cannot be gauged. For example, it was originally estimated that 80% of Ashkenazi women with mutations in the breast cancer susceptibility genes *BRCA1* and *BRCA2* would develop breast cancer; subsequent studies revealed that the risk was closer to 50%. Thus, genetic mutations are not sufficient in themselves to lead to adverse consequences. Furthermore, individuals lacking an identifiable genetic mutation are not necessarily “disease-free.” For example, among non-Ashkenazi women who develop breast cancer, only 5% have a *BRCA1* or *BRCA2* mutation. Mutations in other genes or environmental factors may predispose these women to breast cancer, and so they may have the same or even an increased risk of adverse consequences compared with women carrying an identified genetic mutation. Thus, a genetic mutation is not an absolute prerequisite for a disease and cannot be used as the sole defining feature of that disease.

The human genome sequence is likely to reveal many harmless genetic variations that will turn out not to be associated with disease. Until we resolve questions about polymorphisms, incomplete penetrance of genetic mutations, and the contribution of environmental factors to disease etiology, we will not be able to assess the probability of adverse consequences associated with a particular gene abnormality. There is little doubt that many genetic variations will have no consequences and, like those in individuals with Gilbert's syndrome, will be interesting but inconsequential polymorphisms. Until a mutation is shown to demonstrate a defined risk of developing adverse consequences, individuals carrying that mutation should not be considered diseased. Defining adverse consequences and determining the risk of myriad small genetic variations is a mammoth task. But it is only with this information that clinicians can accurately define the term disease in the genomics era, and in so doing, be able to advise their patients appropriately.

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