Clinical Screening and Genetic Testing

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• Genetic architecture

Clinical screening lies at the heart of preventive medicine, because identification of a disease in its earliest form offers an opportunity to intervene and disrupt its expected deleterious course. In cardiovascular medicine, clinical screening is most effective in diseases such as hypercholesterolemia, where the disease in its earliest form may not have symptoms or signs but can be readily diagnosed with an inexpensive, noninvasive test. Other aspects of a disease like hypercholesterolemia also make a systematic screening program successful: it is relatively common, it has serious consequences such as myocardial infarction, and it is treatable, with the likelihood of adverse sequelae being reduced significantly by treatment. These and other criteria are used by groups, such as the US Preventive Task Force, to develop recommendations for screening programs (http://www.ahrq.gov/clinic/USpstfix.htm).

Genetic screening is a form of screening used for diseases with a significant heritable component. It involves searching for a one or more DNA variants in individuals believed to be at risk for a disease, where the DNA variant is believed to contribute to disease incidence or progression. Before comparing genetic and clinical screening, it would be helpful to review some aspects of the genetic basis of disease.

Genetic diseases lie along a continuum ranging from mendelian disorders to complex diseases, which arise from the interaction of a number of genetic and environmental factors. Mendelian disorders typically arise from a mutation in a single gene and have a sufficiently dramatic effect in that those who inherit the genetic mutation typically inherit the disease. The concept of penetrance captures the distinction between genetic variants contributing to Mendelian disorders and complex disease traits. Penetrance for a genetic mutation is defined as the proportion of individuals carrying a particular genetic mutation who also demonstrate the disease phenotype. The mutations that lead to Mendelian disorders have very high penetrances

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(approaching 100%); whereas, for most variants contributing to complex disease, the penetrance is quite low. This concept has significant relevance in the discussion of the utility of genetic screening.

The concept of genetic architecture describes the number of genes contributing to a disease trait, the number of variants per gene, and the magnitude of effect that each variant has on development of the trait. Although Mendelian disorders usually arise from inheritance of a single genetic mutation, many different individual genes may, when mutated, lead to a common disease phenotype (genetic heterogeneity). Furthermore, for any gene, many different mutations may also lead to the same disease phenotype (allelic heterogeneity). Both genetic and allelic heterogeneity introduce complexity when one goes about designing a genetic screening program for cardiomyopathies. Furthermore, although the penetrance of a disorder may be high, the exact manifestation of disease may vary from individual to individual, despite inheriting the same mutation (variable expressivity). A final level of complexity arises from the fact that multiple distinct diseases may share a common "low-resolution" phenotype, but in fact have a different pathologic basis (termed phenocopies), with potentially different disease course and treatment.

Genetic screening differs from clinical screening in several regards. Rather than serving as a way of diagnosing disease in asymptomatic individuals, the identification of a risk variant in an individual can give the probability of disease risk in individuals who may not yet have disease. Acting on this information may not only allow prevention of disease progression, but also the prevention of disease incidence, the "holy grail" of medicine. A second difference is that discovering that individuals with subclinical disease have a genetic risk variant may provide insight into the biologic basis of disease for that individual. For clinically heterogeneous diseases, such as atherosclerosis or hypertension, understanding the driving pathophysiologic progress may allow targeted therapy that may surpass the efficacy of the "one treatment fits all" approach commonly used. Moreover, with some limitations, knowledge of the causal process may permit a more accurate prognosis of catastrophic outcomes, such as sudden cardiac death or stroke, and allow the focused implementation of screening or preventive therapeutic procedures that may be too costly or risky for the general population, but have high likelihood of benefit for a limited number of high-risk individuals.

When should genetic screening used? An example may help illustrate the approach used for potentially heritable disorders. Consider an individual with a disease that does not appear to be arising from any known environmental cause—in genetic studies, this individual is called the proband. An initial step should be to establish whether the disease is familial, as this has relevance to pursuing a genetic diagnosis for the individual and on managing risk within family members. In addressing familiality, one must construct a careful family pedigree, asking about the health and manner of death of every relative. One needs to be careful to distinguish two apparently similar situations with considerably different ramifications: one where detailed pedigree information is available and no disease is apparent versus another where there does not appear to be any other relative with the disorder but inadequate family history is obtained. Only in the former case could one conclude that the disease is not familial but, instead, sporadic or attributable to environmental factors. If the proband has multiple relatives with the disorder, one would consider it to be familial and consider genetic screening.

The next considerations are related to the likelihood of identifying a causal variant in the proband. If the genetic architecture of the disease is such that there are a relatively small number of genes (low genetic heterogeneity) involved and there are causal genetic variants of moderate-to-high penetrance, genetic screening can be