



Dear Francis:

I received a note that you were seeking input for NIH in the new administration.

As a member of the HHS Secretary's Advisory Committee on Genetics Health and Society, I remember well your contributions to our discussions of the proposed large-scale study of genetics and environmental contributions to common and complex diseases. Those discussions emerged in part from your earlier proposal for a large US prospective cohort study of genes and environment (Nature 2004;429:475-477).

As editor in chief of two Nature Publishing Group journals (Molecular Psychiatry, IF=11 and The Pharmacogenomics Journal, IF=5) that publish cutting edge research on the genetics of common and complex disorders, I completely agree with that strategy and think that the start of a new administration would be an ideal time to set up that major and important initiative, which would be ideally suited to be part of a domestic spending stimulus package.

I believe that in medical research we have been excessively focused on identifying causes and collecting treatment evidence for single diseases. That is a scientific reduction that is dissociated from the reality of clinical medicine. Most people suffer from multiple disorders. As an example in my NIGMS-funded study on the pharmacogenomics of depression (GM061394) we had to screen over 4,000 people to randomize approximately 400 to the study. The majority of exclusions were due to multiple diagnoses.

The emerging genetic basis for common and complex disorders that is being revealed through whole genomic association studies points out to multiple risk alleles, each of small effect. It is unlikely that each risk allele will turn out to be disease specific. It is more likely that combinations of risk alleles may predispose to specific diseases, with overlaps among risk factors for different medical entities. The co-morbidity of common and complex disorders such as depression and obesity might therefore be explained by shared risk alleles that in an individual - in the presence of other genetic and environment factors - may result in multiple diseases.

The proposed large-scale study, discussed by the HHS Secretary's Advisory Committee on Genetics Health and Society, would be an ideal approach to dissect the genetic and environmental bases of common and complex diseases and it would be highly suited to permit the identification of genetic risk alleles that are shared in co-occurring diseases. This would for the first time enable us to understand not only the basis of individual diseases, but the shared (and non-shared) fundamental biology of common co-morbid diseases. This may give us new insights into combined treatment approaches that would be far more efficacious than our current, piecemeal, disease-by-disease approach to therapeutics. Because that study, as you initially proposed, and others have agreed to, would include large numbers of minorities and currently under-represented groups throughout the United States, this would be ideally suited to be included in the new administration's domestic stimulus package. An additional possibility would be to tie that large US prospective cohort study of genes and environment to other domestic spending priorities such as implementation of fully electronic medical records in public hospitals, which would be an ideal setting for the proposed large population study.

With best regards,  
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