

Additional, independent SNPs on 4q25 have been associated with AF, and a polymorphism on chromosome 1q21 was recently associated with lone AF. Although these polymorphisms with smaller effects are unlikely to improve predictive accuracy, future studies will be needed to evaluate the predictive information content of genome-wide SNP data. Furthermore, recent studies have demonstrated that asymptomatic episodes of AF may not be uncommon and may confer increased stroke risk. Characterization of populations for such episodes might reveal that genotypic risks based on clinical AF are underestimates.

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INVITED COMMENTARY

Genetic Prediction for Common Diseases: Will Personal Genomics Ever Work?

A major promise of human genetics has been the use of genetic information to predict the risk of common diseases in order to prevent and treat these conditions more effectively. Most common diseases have a complex etiology, and genes are expected to explain much of their risk. However, even though PubMed already retrieves more than 2 million articles with “gene OR genetic” (n=2 015 109 as of February 10, 2011) and half (n=1 040 434) are tagged as “Human,” there are formidable difficulties in materializing this promise.¹

Genome-wide association studies have now successfully identified thousands of common genetic variants that influence the risk of complex diseases. Large-scale evidence, agnostic testing with stringent statistical criteria, and rigorous replication standards guarantee that this literature has high credibility. Nevertheless, the discovered gene variants do not markedly expand our predictive ability compared with what can be achieved by using only information from long-known traditional risk factors. In this issue of the *Archives*, Smith et al² add another example for

in which genetic information does not materially improve prediction. Genotyping for 3 robustly replicated gene variants for atrial fibrillation enhanced the area under the curve (AUC) by only 0.009 and 0.005 for prevalent and incident atrial fibrillation, respectively.

This failure is not surprising. The risks conferred by the identified common gene variants are almost ubiquitously small; therefore, they are unlikely to change predictive discrimination perceptibly. Simulations show that new risk factors with small odds ratios cannot change the AUC by more than 1% when there are already other traditional risk factors available that can already achieve modest predictive discrimination.³ Much larger effect sizes and/or a very large number of genetic variants are needed to start making substantial improvements in predictive discrimination. One disease for which we have been closest to such a success is probably age-related macular degeneration. With close to 20 gene variants identified to date, and with some of them having an odds ratio of greater than 2 per risk allele, consideration of traditional plus genetic risk factors for age-related macular degeneration can generate an AUC above 0.90.⁴ Such predictive discrimination has not yet been achieved for other common diseases, even when we have discovered many dozens of genetic variants with small effects. Apparently, for some common diseases such as type 2 diabetes mellitus or coronary heart disease, the genetic variants that are implicated are probably in the range of many hundreds. Knowing several dozens or even 100 of them is still too few.

In theory, even minor changes in discrimination may have clinical importance if they achieve marked improvements in reclassification.⁵ Reclassification metrics, such as the net reclassification index,⁵ examine the extent to which the addition of information from new risk factors allows patients to be recategorized into more (rather than less) appropriate risk categories. Optimal management and best-indicated interventions differ in these categories. Several highly visible articles have claimed highly promising reclassification metrics for some common diseases, eg, 1 article claimed that information on just 9 cholesterol-related variants can markedly improve the categorization of patients with intermediate predicted risk of cardiovascular disease.⁶ However, simulations show that the net reclassification index estimate is extremely volatile and highly influenced by minor changes in the selection of thresholds to separate the risk categories.⁷ For almost all diseases, we have no consensus or good evidence on what the ideal cutoffs of risk are that should define categories with different management plans. Even when we do, eg, the categories proposed by the Framingham Risk Score for cardiovascular disease, in practice the selection of cutoffs frequently deviates from the proposed thresholds.⁸ Therefore, the most extravagant net reclassification index results may simply be examples of how a metric that is susceptible to the choice of assumptions and selective reporting can fuel spurious expectations.

Eventually, we have to prove with pragmatic patient outcomes that genetic or other predictive information works in real life. While discrimination and reclassification exercises provide some initial screening, the proof of principle requires demonstration of benefits in randomized controlled trials. Predictive discrimination or reclassification metrics are unable to fully foretell the results of

such trials. For example, an ongoing randomized trial is allocating participants who consider initiation of statins to 2 strategies: either learn their 10-year risk estimate for coronary heart disease with information added from their genomic profile on 19 relevant gene variants or get this genomic information after the end of the trial (clinicaltrials.gov Identifier: NCT01406808). A similar concept is also being tested in another randomized trial using genomic information on diabetic risk.⁹ Studies on Mendelian disorders, eg, familial hyperlipidemia, suggest that individuals may be responsive to genetic information and may increase adherence to treatment.¹⁰ By extrapolation, genetic profiling of common variants may also motivate individuals to modify their behavior, lifestyle choices, and adherence to drug treatment. Preliminary observational data offer some reassuring evidence that provision of such genetic information does not increase the levels of anxiety in individuals¹¹ but also show no major impact on exercise or dietary habits.¹¹ The results of randomized trials will give us some more rigorous evidence on what we can expect to achieve with genetic risk information.

In designing this generation of personal genomics randomized trials, there are hundreds of diseases and genetic variants that one can choose to study. It is probable that priority should be given to common diseases with a high burden of disease as well as to those diseases for which (1) risk information seems most predictive, (2) effective interventions are available, and (3) intervention is likely to be effective and/or cost-effective only when prescribed to patients above a given risk threshold. There is probably a window of opportunity for performing such studies now that a wide segment of the general public is excited, fascinated, or at least intrigued by the prospects of personal genomics. In the next few years, we should be able to find out whether genetic information offers only the joy of learning about the complexity of our genes (an otherwise splendid educational or recreational activity) or whether we can also make some real use of this information for the betterment of health and health care.

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COMMENTS AND OPINIONS

To Sleep or Not To Sleep: Do We Forget Our Patient's Sleep?

In the January issue of the *Archives*, we read with great interest the article by Yoder et al.¹ In this study, the authors demonstrated that patients' sleep suffers significantly from hospital noise in that they slept significantly less in the hospital relative to home conditions. Furthermore, sleeping in a hospital setting was associated with poorer sleep efficiency (ie, the ratio of time spent asleep to the amount of time spent in bed). These findings are significant in light of previous research indicating that impaired sleep influences measures of general health. For instance, compared with regular sleep, recurrent partial sleep deprivation for 6 days after first exposure to an influenza antigen has been found to impair the early phase of the subsequent adaptive immune response.² The fact that the detrimental impact of hospital noise on sleep quality may in turn adversely affect recovery from disease underlines the importance of this research, both from a clinical and an economic point of view. However, some important questions require more detailed discussion. Sleep consists of cycles of slow-wave sleep (SWS, also known as deep sleep) and rapid eye movement sleep, alternating in periods of approximately 90 minutes.³ Previous research has shown that beneficial effects of sleep on general health are specifically related to SWS. For instance, a previous study has shown that the amount of SWS predicts insulin sensitivity in response to an intravenous glucose tolerance test the next morning,⁴ highlighting a critical role of this sleep stage in daytime glucose regulation. Furthermore, the production of antigen-specific antibodies after vaccination against hepatitis A has recently been associated with the amount of SWS activity during the postvaccination night.⁵ Thus, future research should not only address the influence of hospital noise on sleep quantity (the time spent asleep) but also on sleep architecture (the time spent in each sleep stage).

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In reply

We certainly agree with our colleagues that studying the effect of noise disruption in the hospital setting on sleep architecture, particularly on the level of slow-wave sleep (SWS) is critical. Because our study used actigraphy and not polysomnography, we are unable to ascertain the association between hospital noise and sleep architecture in our sample. In future studies, quantifying the SWS loss due to hospitalization may help understand adverse health consequences hospitalized patients face. This is especially the case, as our colleagues at the University of Chicago and others have demonstrated that selective deprivation of SWS is associated with a variety of adverse health consequences that could affect the recovery process from acute illness, including impaired blood glucose tolerance, higher blood pressure, and decreased pain tolerance.¹⁻³ Given the typical compensatory increase of SWS in response to acute sleep deprivation, another interesting question is whether a corresponding "rebound" of SWS occurs in recently hospitalized patients.

While studies examining the relationship between noise and sleep architecture, such as percentage of SWS, in hospitalized ward patients are lacking, it is worth examining the more extensive literature in the intensive care unit (ICU) setting, which could inform hypotheses to test in hospitalized ward patients. For example, studies show that ICU patients experience sleep fragmentation with a predominance of stage 1 sleep and a lack of SWS.⁴ Moreover, at least 1 study has shown that a simple intervention, ear plugs, for ICU patients can result in a greater amount of rapid eye movement sleep.⁵ These studies highlight that it is reasonable to suggest that noise in the hospital setting disrupts sleep architecture. Although using polysomnography may present challenges in studying hospitalized ward patients, future work should attempt to ascertain whether hospitalized patients face selective SWS deprivation due to nighttime noise and what the potential impact may be on health and recovery for these patients.

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