Disease risks derived from genetic variants need clinical context

To the Editor:

The recent article by Mihaescu et al.[1] makes important points regarding the impact of updates to risk factors and the limitations of disease risk estimates derived from genetic variants during a time of active discovery. However, there is a fundamental assumption made, both in this work and in the presentations of disease risk from commercial companies offering genome-wide scans, that is worthy of challenge. The threshold used is the population average. By presenting risks in relationship to the average in the overall population, clinical utility of the population average is implied, though this assumption most often is not supported.

In the Rotterdam Study population used by Mihaescu et al., the average risk of type 2 diabetes, calculated using both incident and prevalent cases, is reported as 20%. Based on the single *TCF7L2* variant, predicted risks were 17.6%, 20.8%, and 28.0% in the CC, CT, and TT genotype groups, respectively. So, consistent with the risk reporting used by direct-to-consumer companies offering full genome scans, risk of type 2 diabetes is deemed "below average" for CC individuals and "above average" for CT and TT individuals. However, what is the meaning of "above average" risk, particularly for the CT individuals, who make up about 40% of the population,[2] and in whom the predicted risk is 20.8%? In addition, what are the implications of comparing the risk in one subgroup of a population to the risk in the full population, when variants are common and subgroups make up a substantial portion of the total population (in this case 40%)?

Some well-studied, clinically developed risk scores have corresponding thresholds used in clinical care. The Framingham risk score, for example, provides estimates of the 10-year risk of heart attack or dying from coronary heart disease, based on a patient's age, gender, smoking status, diabetes status, blood pressure, and cholesterol.[3] Current guidelines for prescribing cholesterol lowering therapy from the National Cholesterol Education Program-(ACT III) incorporate ranges of Framingham 10-year risk ($<$10%, 10–20%, and $>$20%),[4] and physicians may use the threshold of 20% when making treatment decisions. Hence, in this setting, a threshold of 20% for Framingham 10-year risk has utility, and classifications and reclassifications based on this cutoff are consequential.

Returning to the example of type 2 diabetes, one might attempt to put the risks of disease based on genetic variants within clinical context by referring to comparable risk estimates in the clinical literature. The relationship between body mass index (BMI) and risk of diabetes has been established. Also, Narayan et al.[5] estimated the remaining life-time risk of type 2 diabetes at age 18 years to be 19.8% for men of average weight ($18.5 \leq$ BMI <25 kg/m^2), 29.7% for overweight men ($25 \leq$ BMI <30 kg/m^2), and 57.0% for obese men ($30 \leq$ BMI <35 kg/m^2). Similar estimates of remaining life-time risk of type 2 diabetes at age 18 years in women were 17.1%, 35.4%, and 54.6%, respectively. Based on these estimates, remaining life-time risks at age 18 years of 30–35% (overweight) and greater (55–57%, obese) provide a clinical framework, and possible thresholds, for reported risks. (To apply these cutoffs to the predicted risks presented by Mihaescu et al., however, one would have to demonstrate that the predicted risks, which might be interpreted as life-time risks of developing disease from birth to an average age of 69.5 years, are comparable with remaining life-time risk at age 18 years.)

Another approach to presenting risk estimates within a clinical context is to present risk of disease due to genetic and nongenetic factors side-by-side. This option, which our research team is currently pursuing, requires knowledge of an individual's medical, lifestyle, and family history. Granted for some diseases, risks due to lifestyle behaviors or other nongenetic factors that are relevant for all demographic groups are not available. However, presenting genetic risk alone and applying a threshold of the population average most often does not place reported risks within a meaningful clinical context.

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Disclosure: The author declares no conflict of interest.

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Reply to "Disease risks derived from genetic variants need clinical context"

To the Editor:

Dr. Stack correctly points out two limitations of genome-wide scans used for predicting common diseases: the clinical context is lacking, and there is limited utility in comparing individual risks with the average risk. To evaluate the utility of tests, defining the clinical context is crucial. A genetic test usually is intended for a specific population and useful only if it changes health decisions, for example, if test results lead to different recommendations or different interventions. In some instances, testing can be beneficial also in the absence of interventions because people may value the information gained from learning about their health risks. This benefit is proven for monogenic diseases, such as Huntington disease, but unclear for complex diseases.[1]

The question arises what is the clinical context in predictive genetic testing for type 2 diabetes, which we used as an example in our analysis?[2] Currently, there are no guidelines on risk thresholds for type 2 diabetes prevention,[3] similar to the thresholds of the Framingham risk score for cardiovascular disease.[4] Furthermore, the only available preventive strategy is adoption of a healthy lifestyle, which is recommended to all and should not need a genetic test to justify it. However, many companies promote that genetic tests will motivate preventive behavior. They argue that motivation increases when people learn that they are at higher risk than average. Whether their tests can

provide this benefit, without encouraging careless behavior among those at lower than average risk, remains to be proven.

We agree with Dr. Stack that it is doubtful to consider 20.8% as increased risk when the average is 20%. Although many companies initially did present the results in this way, several have changed their layout and now consider an additional average category. This evidently reduces the probability that people directly change from increased to decreased risk categories or vice versa. However, most likely, more people will move between risk categories, because the percentage of reclassification increases with the number of cutoff values.[5] Individuals may move from the average risk category to increased or decreased risks and vice versa. An interesting question then would be to investigate whether individuals prefer to be "below average risk" or "not above average," in other words, whether individuals put more value on one cut-off value than on the other.

Finally, Dr. Stack puts forward the question which average risk to consider. Although this is an important question when one is interested in the absolute risk of type 2 diabetes, it is not an issue for the mere fact of being higher or lower than average risk. All companies calculate an individual's risk starting from some average risk, which is then multiplied with the odds ratios of the genotypes of the variants carried by the individual. The companies then compare the individual's risk with the average risk they used as a starting point for the calculation. This deviation from average, i.e., whether someone has a higher or lower risk than average, is determined by the cumulative effect of the multiple variants, and this is the same whichever average is taken. Thus, whether a general average risk is taken, as we did in our study, or whether an age- and sex-specific risk is taken, the results with respect to the percentage of reclassification, our main measure, remain the same. The absolute risk of disease for an individual may be entirely wrong, as Dr. Stack points out, when other important risk factors are not included in the calculation as well. In our case, if body mass index is not taken into account, even age- and sex-specific average risks are incorrect. Given these observations and the fact that currently there are no preventive or therapeutic benefits associated with the results of these genome-wide DNA scans, these tests should only be bought to learn how one's DNA sequence compares with others but not for medical reasons.

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Disclosure: The authors declare no conflict of interest.

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