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Editorial

Do We Need to Check Our Genes for a Correct Estimate of GFR?

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Creatinine-based glomerular filtration rate (GFR) estimation shows significant imprecision in the normal range of GFR even when the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula is used, and this frequently leads to some individuals being classified in an incorrect CKD category.[1] Precise GFR estimation is important for correct classification into CKD categories because this classification potentially has critical consequences on an individual level regarding, for example, a patient's referral to specialist (nephrology) care, correct medication dosing, and cardiovascular and CKD progression risk assessment.[2,3] Thus, alternative glomerular filtration biomarkers are being evaluated, and current guidelines now are recommending serum cystatin C level as a possible alternative to serum creatinine level for classifying CKD.[2] Adding cystatin C to creatinine level in GFR estimation equations improves the precision of estimated GFR (eGFR), but this is far from perfect.[4] An important contributor to the imprecision in GFR estimation equations is the variability of glomerular filtration biomarkers due to factors unrelated to kidney function. GFR estimation equations thus contain age, sex, and race as variables, characteristics that are imperfect proxies for muscle mass. For cystatin C–based eGFR ($eGFR_{cys}$) prediction, independent contributors to imprecision include diabetes, inflammation, and steroid therapy.[5]

A further reason for the imprecision may be effects of genetic factors that add variability to cystatin C and creatinine concentrations by affecting production and metabolism unrelated to kidney function. Genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms (SNPs) that are associated with creatinine and cystatin C concentrations but not with kidney function per se.[6-8] Similar findings have been shown for 2 other glomerular filtration markers, beta-trace protein and β_2-microglobulin.[9,10]

In this issue of *AJKD*, O'Seaghdha et al[11] provide a meticulous step-by-step assessment of the role of genetic variation in GFR-independent cystatin C level variability and its importance at the population level for classifying CKD and assessing cardiovascular outcome. In the first step, O'Seaghdha et al[11] analyzed the association of one SNP (rs13038305) with cystatin C concentrations in 4 general population cohorts of European descent that together totaled 14,645 individuals. The association between this SNP and $eGFR_{cys}$ previously had been identified and confirmed with a very high level of significance in several GWAS.[6-8] According to the same GWAS, this SNP is not associated with creatinine-based GFR estimation. Therefore, one can safely conclude that it affects cystatin C blood concentrations without an effect on GFR. In the present study, the difference in cystatin C concentrations, and thus in unadjusted $eGFR_{cys}$ values, between genotype groups was highly significant: in individuals with the CC genotype, average $eGFR_{cys}$ was 76.9 mL/min/1.73 m^2, whereas in individuals with at least one copy of the minor T allele, it was 82.0 (heterozygotes) and 88.7 mL/min/1.73 m^2 (TT homozygotes). On first glance, this overestimation of $eGFR_{cys}$ by almost 12 mL/min/1.73 m^2 due to genetic variation appears especially important on a population level given the 20% prevalence of the SNP's minor allele. Similarly, CKD prevalence (defined as $eGFR_{cys} < 60$ mL/min/1.73 m^2) was significantly overestimated before adjustment for SNP genotype: CKD prevalence ranged from 8.4% in individuals homozygous for the minor T allele to 17% in those homozygous for the major C allele. As these large differences were not due to differences in kidney function in the genotype groups, they were not present after adjusting $eGFR_{cys}$ for the SNP genotype.

Next, the authors analyzed how many individuals were reclassified to another CKD category when using genotype-adjusted $eGFR_{cys}$ compared to non-adjusted $eGFR_{cys}$. Again, the results were striking: 7.7% of participants were reclassified to a worse $eGFR_{cys}$ category after adjusting for rs13038305 genotype. However, more than half of these reclassifications occurred in individuals with unadjusted $eGFR_{cys} \geq 90$ mL/min/1.73 m^2.

Finally, the authors analyzed whether genotype-adjusted $eGFR_{cys}$, and thus corrected CKD classification, would improve the prediction of 2 clinically important end points: incident cardiovascular disease (CVD) events and mortality. This was not the case when analyzing the overall population, which is disappointing given the genotype's apparently large effect on $eGFR_{cys}$. However, the lack of significant improvement in risk prediction may be because most reclassifications occurred in individuals with eGFR ≥ 90 mL/min/1.73 m^2 and thus in a range

Address correspondence to Carsten A. Böger, MD, Department of Internal Medicine II, Nephrology, University Hospital Regensburg, 93042 Regensburg, Germany. E-mail: carsten.boeger@klinik.uni-regensburg.de

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in which there is not a strong association between eGFR and CVD. In individuals with CKD, being reclassified was associated with a significantly higher CVD incidence rate. For example, whereas incidence rates for all-cause mortality and incident CVD disease hardly changed for participants who were reclassified from ≥90 to <90 mL/min/1.73 m^2, these rates doubled for those reclassified from 60-89 to <60 mL/min/1.73m^2, with similar observations in the next lowest CKD category.

The authors correctly conclude that this SNP's effects on reclassification are "modest" in the overall population. However, because this is a study in general population cohorts, this conclusion should not be generalized to populations enriched for CKD. In the general population, in which ~90% of individuals have normal kidney function, the large SNP-attributable differences in $eGFR_{cys}$ between genotypes are simply not large enough to significantly affect risk prediction for incident CVD and mortality, considering that they are found mainly in the normal GFR range.

What should we expect from this field in the future? First, a more comprehensive workup of the cystatin gene cluster's genetic variation and its role in biasing GFR_{cys} estimations could yield more SNPs with stronger effects. SNPs imputed from the 1000 Genomes backbone (www.1000genomes.org) and SNP genotypes from whole-exome genotyping may provide novel insights. A caveat here is that SNPs with stronger effects also may be less prevalent and thus lack a major clinical impact on a population level. Second, analogous analyses to those in the study by O'Seaghdha et al[11] should be performed in major cohorts enriched for CKD or those at risk for CKD.[12-17] It is possible that such analyses could show clinically relevant reclassifications that were not observable in general population cohorts. Third, the role of cystatin C SNPs in cohorts of individuals older than 70 years that apply the newly derived BIS (Berlin Initiative Study) formulas may provide important insights in this understudied segment of the population.[18] Fourth, the loci associated with creatinine-estimated GFR in GWAS that are not related to kidney function (especially the *GATM* [glycine amidinotransferase] and *SLC22A2* [organic cation transporter 2] loci[6]) should be analyzed for their role in biasing creatinine-based GFR estimations and CKD classification, analogous to the work on $eGFR_{cys}$ presented here by O'Seaghdha et al.[11] Fifth, there should be discussion about whether the insights gained from the studies proposed should be considered in the workup of potential living kidney donors, especially if the evaluating center does not measure GFR routinely. If a living kidney donor with borderline but overestimated eGFR (based on creatinine or cystatin C level) is accepted, the postdonation GFR may be unacceptably low. Finally, these analyses will provide the evidence base needed to determine the optimal setting in which SNP genotyping can be used for GFR estimation and CKD classification in routine clinical care.

In conclusion, genetic variation at loci that do not affect GFR but rather affect the production, secretion, and metabolism of glomerular filtration biomarkers, such as creatinine and cystatin C, increasingly is being recognized as a potentially clinically relevant factor affecting the precision of GFR estimation equations. Clinical nephrologists should follow this field as it develops because it may spawn relevant clinical applications of "genetic individualized medicine" in the not-so-distant future.

Carsten A. Böger, MD
University Hospital Regensburg
Regensburg, Germany

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