However, we believe this is erroneous for two reasons. First, rs2269475 has previously been described as a non-coding SNP in exon 4. Second, it is very unlikely that amino acid 15 will be found in the 4th exon of any gene. In addition to this, the authors reported they looked into another SNP, rs4711274. This SNP is located in intron 1 of the gene not intron 2 as stated. The association study may still be valid but rs2269475 does not represent an important functional change in AIF1 as the authors claimed.

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Comment on: An allograft inflammatory factor 1 (AIF1) single nucleotide polymorphism (SNP) is associated with anticentromere antibody positive systemic sclerosis: reply

Sir, AIF1 rs2269475 polymorphism is a non-synonymous coding polymorphism in NCBI database (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2269475). The rs2269475 polymorphism causes a tryptophan to arginine amino acid substitution that is predicted to be damaging by Polyphen (http://genetics.bwh. harvard.edu/cgi-bin/pph/pph4dbSNP.cgi). We regret the oversight in reporting the location of polymorphisms rs2269475 and rs4711274, which are in fact located on exon 3 and intron 1, respectively, of the AIF1 gene.

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Comment on: The pharmacogenetics of methotrexate

Sir, With interest, we have read the review by Hider and colleagues [1] on the pharmacogenetics of methotrexate (MTX) in patients with RA. In this letter, we would like to address an additional point of interest that is not discussed in their article.

We agree with the authors that the currently available pharmacogenetic data from association studies are inconclusive and do not allow us to draw definite conclusions about the relationship between genotype and treatment outcome in RA. Therefore, pharmacogenetic information has not yet established value with respect to the choice of drugs in RA treatment for the individual patient.

The authors report various single nucleotide polymorphisms (SNPs) related to the MTX mechanisms of action, which may influence the response to treatment. Their hypothesis that a combination of genotypes may be necessary to predict the individual response to MTX is of special importance. In addition, they emphasize that the effect of demographic and disease characteristics on treatment response should be investigated.

Recently, important progress has been made to predict the individual response to MTX treatment by our group, indeed combining multiple genes as well as non-genetic determinants of MTX response [2]. A clinical pharmacogenetic predictive model has been developed including eight genetic and non-genetic factors to categorize patients with early RA (n = 205) who started MTX monotherapy into three groups: non-responders with a low probability of response, patients with an intermediate probability of response and responders with a high probability of response to MTX monotherapy. The model for MTX efficacy consisted of the variables gender, RF and smoking status, the Disease Activity Score (DAS) at baseline and four polymorphisms in the adenosine monophosphate deaminase (AMPD1), 5-aminomimidazole-4-carboxamide ribonucleotide transformylase (ATIC), inosine triphosphate pyrophosphatase (ITPA) and methylenetetrahydrofolate dehydrogenase (MTHFD1) genes. The true positive and negative response rates were 95 and 86%, respectively. Sixty per cent of the patients were categorized into responders and non-responders with the use of this model.

This pharmacogenetic model has been validated in a small cohort, and will be further validated in an independent large cohort of early RA patients. Following validation, refinement and further improvement of the prediction model may be warranted.

In summary, personalized medicine using pharmacogenetic predictive models in common complex traits such as RA is becoming available and may have the potential to prove beneficial for individual RA patients.

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Comment on: The pharmacogenetics of methotrexate: reply

Sir, We thank Dr van der Kooij et al. [1] for their interest in our review and for highlighting their recently published study [2] examining the utility of a clinical pharmacogenetic model in