Author Reply

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We thank Professors Somogyi and Suthers¹ for their interest in our work and drawing attention to the pharmacogenetics of statin intolerance.

We agree that inherited genes influence drug pharmacokinetics and pharmacodynamics, including the risk of side effects. Using macrolide antibiotics as a practical example, we cited evidence to highlight the potential significance of variants in some cytochrome P450 enzymes in the pathogenesis of statin-associated rhabdomyolysis.² As the correspondents state, there is a significant association between the *SLCO1B1* gene T521C polymorphism and statin-related myopathy risk, but the polymorphism is not diagnostic for myopathy.³ The strongest evidence for the risk of statin-associated muscle symptoms (SAMS) related to this mutation is for simvastatin⁴ and is less well-studied for other statins. The risk appears to be dose-related, and may vary in frequency by ethnicity. While the *SLCO1B1* gene is by far the most robustly associated variant with SAMS, an increasing array of genetic variants are also reported to be associated with SAMS phenotypes.⁵

A predisposing genetic polymorphism will increase the risk of an event, such as SAMS, but the vast majority of people with a high-risk polymorphism will still not develop the event.⁶ Conversely, people without a high-risk polymorphism may still develop the condition. Hence, while it can be helpful to know an individual's pharmacogenetic profile, in clinical practice the diagnosis and management (with or without such genetic knowledge) still revolves around our suggested strategy of statin withdrawal and re-challenge, potentially at a lower dose or with a different statin and also careful consideration of alternate diagnoses.

Clinical pathology laboratories are already equipped with relevant instruments and skilled scientists to test for genetic markers, and already do so in cancer and some

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heritable disorders, such as coeliac disease and haemochromatosis, and genetic markers may play an important role in precision medicine. If knowledge of the statin response genetic risk factor status is desired, such screening tests have recently been included in a pharmacogenomics panel available from some private pathology laboratories in Australia, but such tests are not yet subsidised by Medicare. In the meantime, such statin-related genetic studies could be applied to clinical trials and databases of statin intolerant (and tolerant) subjects and could guide intervention trials in statin intolerant subjects.

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