With the availability of increased information about the role of common genetic polymorphisms in disease susceptibility, response to therapy and toxicity of therapies, the prospect of increasingly personalized medicine is leading to the development of highly individualized, personal medicine. The prevention of cardiovascular complications of RA has assumed greater importance as our ability to treat the underlying joint disease has improved and it may be possible to predict which patients with RA are at greatest risk of developing cardiovascular disease.

Elevated homocysteine levels have long been associated with ASCVD (for example, [3]) and homocysteine is a direct toxin for the vascular endothelium. Low dose methotrexate therapy, by inhibiting MTHFR, diminishes recycling of homocysteine to methionine, leading to increases in plasma homocysteine, although folic acid supplementation abrogates the increase in homocysteine levels in methotrexate-treated patients with RA [4]. One potential contributor to homocysteine elevation is genetic alterations in MTHFR; two common polymorphisms in this enzyme have previously been reported to alter MTHFR activity (C677T and A1298C).

The A1298C polymorphism is quite common and is present in as many normal individuals (40% were AC heterozygotes and 10% were homozygous for the C allele). The striking finding by Palomino-Morales and colleagues was that RA patients with cardiovascular events were more likely to have the C allele of A1298C than those without (62% versus 50%, respectively) and the accumulated risk increased over time was strongly associated with the C allele of the A1298C polymorphism. It is interesting to note that the polymorphism associated with more marked declines in MTHFR activity, the C677T polymorphism, was not associated with a greater risk for cardiovascular disease. The numbers were probably too small to determine whether there was an interaction between these two common polymorphisms that further contributed to risk.

In some of the patients with RA the authors were able to directly probe the health of the endothelium by measuring the flow-dependent forearm vasodilatation and found that the RA patients with the minority A1298C allele in MTHFR had diminished vasodilatory responses, consistent with a less healthy vascular endothelium.

Patients with the C677T polymorphism, but not the A1298C polymorphism, are at greater risk for developing complications of methotrexate therapy and methotrexate therapy may ameliorate the risk of ASCVD in patients with RA [5,6]. Thus, it would be interesting to determine whether methotrexate therapy affected the frequency of cardiovascular events in this population and whether there was any interaction between methotrexate and genetic risk for cardiovascular disease in this population. Moreover, it would be important to know how many of these patients were taking folic acid supplements since folic acid supplementation has previously been shown to lower homocysteine levels in patients taking methotrexate [4,7-9], presumably by providing higher levels of folic acid.
substrate for the enzyme, and it is possible that folic acid supplementation in this group might have had a greater effect in the patients with the polymorphism on reducing risk of cardiovascular events.

More often than not, candidate genetic association studies, such as that described here, are not reproducible [10] and it is possible that this study may share the fate common to so many of these types of candidate gene studies. Nonetheless, Palmino-Morales and colleagues have made an interesting observation that may suggest a contributing factor to the development of cardiovascular disease in patients with RA. Moreover, this study provides an even greater rationale for the addition of folic acid to the therapy for RA, prevention of cardiovascular disease.

Abbreviations
ASCVD = atherosclerotic cardiovascular disease; MTHFR = methylene tetrahydrofolate reductase; RA = rheumatoid arthritis.

Competing interests
BNC holds or has filed applications for patents on the use of adenosine A2 receptor agonists to promote wound healing and use of A2A receptor antagonists to treat osteoporosis and other diseases of bone; the use of adenosine A1 and A2B receptor antagonists to treat fatty liver; and the use of adenosine A2A receptor agonists to prevent prosthesis loosening. Consultant (within the past 2 years) King Pharmaceutical (licensee of patents on wound healing and fibrosis above). CanFite Biopharmaceuticals, Savient Pharmaceuticals, Bristol-Myers Squibb, Roche Pharmaceuticals, Cellzome, Tap (Takeda) Pharmaceuticals, Prometheus Laboratories, Regeneron (Westat, DSMB), Sepacor, Amgen, Endocyt, Protalex, Allos, Inc., Combinatorx, Kyowa Hakka. Honoraria/Speakers’ Bureaus: Tap (Takeda) Pharmaceuticals. Stock: CanFite Biopharmaceuticals received for membership in Scientific Advisory Board.

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