Corresponding Author:
Dr Andrew W. George
Data61, CSIRO
Ecosciences Precinct
41 Boggo Road, Qld 4102, Australia
Email: andrew.george@csiro.au

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Dear Editors,

Thank you for this opportunity to present our case for why our paper entitled "Eagle: making multi-locus association mapping on a genome-wide scale routine" is suitable for publication in *Nature Methods*, one of the world's top methods journals. We have structured our reasoning around your *Aims & Scope* page on the *Nature Methods* website.

Novelty: Our association mapping method is very different to our multi-locus counterparts. **It is relatively simple.** It is only a little more complicated than fitting a standard linear mixed model for association mapping. Yet, we are able to measure the association between all SNPs and a trait, simultaneously. **Our method is easy to run**. There are no significance thresholds to be set. There are no parameters to be fine-tuned. Our method produces **easy to interpret results.** Each SNP finding identifies a separate genomic region of interest. Our method is computationally efficient, sometimes by orders of magnitude than competing multi-locus methods. We achieve this via a novel dimension reduction step. Our method is **statistically superior to single-locus methods**, the methods-of-choice. It finds more true associations while rejecting the false associations.

Significance: Any piece of work with **the capacity to shift a community's methods-of-choice** to a better, more statistically powerful position is of great significance. Our paper is such a piece of work. **Previous attempts at shifting the community to multi-locus association mapping have failed**. This is because their underlying methods are shrouded in statistical complexity and they are implemented in prototype packages/programs with poor computational performance. Our paper presents a method that solves these problems.

Potential Audience: Our work will have **broad appeal to anyone from the animal, plant, and human genetic domains** interested in gaining greater insight from their GWASs. Also, there are an increasing number of GWASs collecting whole-genome sequence data. There is a growing hunger from the genetics community for association mapping methods that can better harness these new data.

Validation: We evaluate the performance of our method, statistically and computationally, against five other multi-locus methods and two state-of-the-art single-locus methods. We did this through the analysis of simulated data and real data collected from a large study in outbred mice.

Application: We understood the value of implementing our method in **easy-to-use production-level computer code.** To this end, we have not only developed a new package for multi-locus association mapping, but also developed an extensive support structure. The

package is **fully documented** and comes with its own **easy-to-use GUI**. We have develop a **website** (http://eagle.r-forge.r-project.org**)** for the package, containing tutorials, videos, How To guides, FAQs, and demos. We have also set up a dedicated email for user problems/questions.

We appreciate your time and the role you play in the dissemination of high-quality methods to the scientific community. Thank you for considering our paper for publication in *Nature Methods*.

On behalf of the authors,

Dr Andrew George

CSIRO