Putting genomics into practice
A new analysis casts doubt on the clinical utility of \textit{CYP2C19} genotype testing to help guide antiplatelet prescribing

Michael V Holmes \textit{Medical Research Council population health scientist fellow}\textsuperscript{1}, Juan P Casas \textit{senior lecturer in epidemiology}\textsuperscript{2}, Aroon D Hingorani \textit{professor of genetic epidemiology}\textsuperscript{1}

\textsuperscript{1}Genetic Epidemiology Research Group, Department of Epidemiology and Public Health, University College London, London WC1E 6BT, UK; \textsuperscript{2}Faculty of Epidemiology and Public Health, London School of Hygiene and Tropical Medicine, London, UK

Variation in the human genome has long been considered to contribute to individual differences in disease susceptibility and drug response. But a key question for clinical practice is whether knowledge of a patient’s genotype could be useful for stratifying disease risk or guiding treatment. In the linked systematic review (doi:10.1136/bmj.d4588) Bauer and colleagues report a systematic review and meta-analysis of studies examining the association of variation in the \textit{CYP2C19} gene and atherothrombotic events during treatment with clopidogrel.\textsuperscript{1}

The sequence of the human genome is now known,\textsuperscript{2} as are the positions of the several million nucleotides that differ most commonly from one person to the next and their inheritance patterns in different human populations. Laboratory and analytical techniques now permit rapid cost effective direct (and indirect) genotyping of many single nucleotide polymorphisms (SNPs) in the genomes of many thousands of people to gain insight into the regions that influence disease related biomarkers, susceptibility to common diseases, or the response to widely prescribed drugs.

By 2011, nearly 1000 such genome-wide association studies had reported their findings (figure).\textsuperscript{3} Genome-wide association studies of disease risk are typically large and collaborative, and the results have usually been replicated in independent samples before publication. This means that the findings are not only among the most novel but also the most secure in any field of biomedicine. Although the precise causal genetic variants have yet to be defined with certainty in most cases, these studies have already provided early insights into disease pathogenesis that will probably yield future dividends in the form of new treatments.\textsuperscript{4}

Unfortunately, information on common SNPs is proving less helpful for predicting disease risk than had been hoped \textsuperscript{5}: the common genetic variants that have been studied so far have too weak an effect. A panel of disease-associated SNPs may be more helpful for estimating risk at a group level, but only a minority of people in any population possess genomes with a large number of common risk variants. They are outnumbered by those with an intermediate number of common risk variants, who account for more of the cases, so even panels of SNPs associated with common diseases tend to perform poorly in distinguishing between those who will and will not become affected by a common disease.\textsuperscript{6} Rare genetic variants that are now being sought by high throughput DNA sequencing are predicted to have a larger effect on disease risk than common alleles.\textsuperscript{7} However, by their nature, few people in the population would harbour such variants, which reduces their usefulness for population-wide screening. Nevertheless, there is hope that rare,
highly penetrant disease associated variants might provide an effective means of family based screening for certain disorders. The area of personalised (or stratified) medicine, which is currently attracting substantial interest from industry, funders, and scientists, represents another potential application of the emerging genomic advances. Already, several established cancer treatments target cellular alterations caused by mutations or rearrangements in the genome of cancer cells.1 9 But, could inherited differences in drug response (pharmacogenetics)—mediated through alterations in the level or activity of proteins involved in absorption, metabolism, and elimination of drugs (pharmacokinetic-pharmacogenetics)—or the protein targets of drug action (pharmacodynamic-pharmacogenetics), help to predict treatment benefits and harms?

A few high profile examples illustrate the potential of pharmacogenomics (table; see bmj.com), but recommendations on the use of pharmacogenetic tests in clinical practice are often inconsistent. Moreover, a recent overview (covering pharmacogenetic studies between 1967 and 2008) highlighted several problems in this field.10 These include a preponderance of reviews over primary research articles, under-representation of certain disease areas and ethnic groups, small sample sizes, a relative dearth of genome-wide association studies (figure); widespread use of surrogate outcome measures; and evidence of small study bias, of which publication bias is one cause. Poor study quality could delay the clinical development of valuable pharmacogenomic tests but also lead to premature adoption of poorly validated tests.

In their systematic review and meta-analysis, Bauer and colleagues evaluated the strength of evidence on the association between the variation in the CYP2C19 gene and atherothrombotic events during treatment with clopidogrel.1 Clopidogrel, a widely prescribed, now off-patent, antiplatelet agent (originally licensed as Plavix), requires metabolism for its activation. Several hepatic cytochrome enzymes contribute to this, including CYP2C19. There is an emerging view that people who carry reduced activity CYP2C19 gene variants are less well protected from cardiovascular events during clopidogrel treatment and that genotype based tests could help inform decisions on the dose of clopidogrel, or whether to opt for newer more expensive (patented) antiplatelet drugs such as prasugrel or ticagrelor, which are considered less dependent on metabolism for their activation.

After several research articles on the association between CYP2C19 genotype and response to clopidogrel, the US Food and Drug Administration (FDA) issued a boxed warning,11 which notified clinicians “about reduced effectiveness in patients who are poor metabolizers of Plavix” and “that tests are available to identify genetic differences in CYP2C19 function;” it also advised them “to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.”

The analysis by Bauer and colleagues has now unearthed evidence of small study bias in the literature relating to this area, with weakening of the overall association when more recent larger studies are added. The authors also identified inconsistencies between studies in relation to genotyping, study outcomes, and effect estimates that collectively question the validity of CYP2C19 genotype testing to help guide antiplatelet treatment decisions.

The problems identified by Bauer and colleagues may not be unique to CYP2C19 genotyping and clopidogrel response.12 Efforts to strengthen the design, analysis, reporting, and appraisal of pharmacogenetic studies, drawing on experience from observational studies, gene-disease association studies, cancer biomarker studies, genetic tests as predictors of disease risk, and randomised trials, may now be needed to enable more efficient clinical translation of the emerging genomic discoveries.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; the authors have completed their own systematic review examining the CYP2C19 genotype association with clopidogrel response which is currently under review with another journal. Provenance and peer review: Commissioned; not externally peer reviewed.