

certain compounds increases ozone production. Importantly, certain groups may be acutely susceptible to the effects of air pollution, and clinicians should advise them accordingly.

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Tailoring access to high cost, genetically targeted drugs

Assessment of real cost effectiveness, with data linked to individual health outcomes while protecting patient privacy, is an essential challenge we need to meet

Pharmacogenetics and pharmacogenomics — the use of genetic and genomic information, respectively, to tailor drugs to the treatment of individual patients — make it possible to use information from the human genome in ways that will radically transform the prevention and treatment of human disease.^{1,2} Over the past several years, Australians have been given access to several drugs which can be prescribed under a taxpayer-funded scheme only if the patient has a specific molecular disease target that predicts a good treatment outcome.

The first such drug was trastuzumab for the treatment of breast cancer in women whose tumours over-express the HER2 protein. This drug was supplied by the government from December 2001 through a special program outside the Pharmaceutical Benefits Scheme (PBS). Another drug, imatinib, was also listed on the PBS in December 2001 for use in the accelerated and blast phases of chronic myeloid leukaemia, and in October 2002 for use in the chronic phase of that disease. In December 2004, gefitinib was listed for the treatment of non-small cell carcinoma of the lung in patients with evidence of an activating mutation in the epidermal growth factor receptor gene. These drugs are likely to be harbingers of a stream of drugs in which genetic information about individuals or their tumours (whether they result from DNA or RNA sequence changes, or protein alterations) will be used to maximise the efficacy of treatment.

Funding the provision of new biological agents under the PBS will present a major financial outlay. Though the number of eligible patients may be small, the costs per patient are high (eg, more than \$45 000 per patient per year for imatinib and more

than \$50 000 per year for gefitinib and trastuzumab). The high cost of providing these drugs to relatively small numbers of patients will add to the cost of the PBS when annual growth in government expenditure on pharmaceuticals averaged 10.5% between 1992–93 and 2002–03 (increasing from \$1.883 billion to \$5.121 billion).³

The Australian Pharmaceutical Benefits Advisory Committee (PBAC) makes recommendations to government on which drugs to list on the PBS on the basis of their comparative clinical efficacy, safety and cost-effectiveness.⁴ Given the high price of many of these new and existing biological agents, it has been argued that alternative models of access are needed, because they may only be cost-effective in a subgroup of patients with a disease.⁵

The PBAC has used a number of strategies that allow access to new biological agents while respecting the principle of cost-effectiveness. These options depend critically on identifying the subgroup of patients in whom the drug is cost-effective compared with the main available alternative treatment. Patient groups are defined by the presence of particular molecular markers of disease severity, underlying disease mechanism, or treatment prognosis.⁴

The PBAC has recently developed a collaborative model to enable the listing of the tumour necrosis factor-alpha inhibitor class of biological agents (including etanercept, adalimumab and infliximab) and anakinra, an interleukin-1 receptor antagonist, all of which are used in managing rheumatoid arthritis. Although molecular markers were not part of the restrictions for these drugs, the collaborative model that was developed can be

applied more broadly. This model involves working with key stakeholders in the relevant medical specialty, representatives from the pharmaceutical company producing the drug, and consumer organisations to develop restrictions that will ensure that the drugs are used in ways that are the most cost-effective.^{4,6}

These restrictions include detailed rules for initiation and continuation of therapy. The initiation rules may include a specified diagnostic test and/or evidence that the patient has failed to respond to existing treatments for the condition. Continuation of treatment requires evidence of adequate benefit on some appropriate clinical or biological test. Patients who start taking the drug are required to sign an agreement indicating that they understand and accept that PBS-subsidised treatment will cease if the criteria defining a satisfactory response to the drug are not achieved in the follow-up clinical assessment.⁶ An underlying difficulty (and additional cost) in listings with molecular targets is that the mechanism for identifying the target population is not coordinated with the drug development process.

We need to evaluate the effects of genetically or genomically targeted drugs that are listed on the PBS on patient outcomes to improve the existing regulatory arrangements for these new drugs. Ideally, such evaluations should use data that link information on drug use and individual health outcomes. Linked data are currently very difficult to obtain for reasons of patient privacy and confidentiality, but methods should be put in place at the time of drug listing, with appropriate privacy safeguards, that enable the impact of these drugs to be assessed.

The policy and economic challenges posed by these drugs also warrant wider public discussion. Increased public appreciation of the challenges that these drugs pose to the PBS is essential if we are to develop a broadly supported policy that will make these very expensive drugs available to patients who have the potential to benefit from them at a price that reflects their therapeutic value and at a cost that the government and the taxpayer are prepared to bear.

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