

# PHARMACOGENETICS: Better, Safer Medicines?



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People vary in how they respond to medicines and some of this variation is known to be due to genetic differences between individuals. Sometimes, people suffer 'Adverse Drug Reactions' (ADRs), which can be mild or serious and even deadly. Other medicines simply do not work for many people taking them. If genetic tests could be used to identify such people before they take a medicine, they could be prescribed a different drug or a higher or lower dose. Lives and money might be saved. However, there are reasons to be sceptical about some of the claims made for what is known as 'pharmacogenetics'.

Some important questions are:

- How good are genetic tests at predicting the safety or efficacy of a medicine?
- How important is genetic variation in determining and/or preventing Adverse Drug Reactions?
- What are the implications for medicines development and health inequalities?

## What is pharmacogenetics?

Pharmacogenetics is the study of how genetic variations affect an individual's response to medicines.

There are two types of genetic test that might be used to try to predict medicines response<sup>1</sup>:

- tests of genetic changes that occur during a patient's lifetime, such as the mutations in a cancer cell;
- tests of the genetic make-up individuals are born with.

Both types of test can be used to try to predict either the efficacy or the safety of a medicine.

One example of the first type of test is currently used in clinical practice. This is the

HER2 genetic test for women with breast cancer (see Box 1). This type of test involves classifying a *disease* into different genetic types and then finding the 'right medicine for the right disease'.

### Box 1: Trastuzumab (Herceptin)

The breast cancer treatment, trastuzumab (brand name: Herceptin), can only be used to treat breast cancer in women whose tumours have particular genetic mutations. These mutations, which occur in 15-20% of breast cancers, mean the tumour over-expresses a protein called HER2. This type of tumour is harder to treat and is also thought to result in a lower life expectancy. Herceptin's effectiveness in this relatively small patient population has enabled the biotech and pharmaceutical companies, Genentech and Roche, to sell the product at a premium compared to other cancer therapies<sup>2</sup>.

Although clearly important to those women who benefit from it, Herceptin normally increases survival time only by a matter of months, and its high cost has been controversial<sup>3</sup>. Not everyone who is identified as suitable to take Herceptin benefits from it. Some serious side-effects have been found and there has also been some controversy about the reliability of the HER2 tests<sup>4</sup>.

The second type of genetic test involves classifying *people*, rather than diseases, into different genetic types. It is this approach that is often referred to as the 'right medicine for the right patient'. A few US clinics are already using this type of test for children with leukaemia (see Box 2) and many similar tests are being developed which look for more common genetic variations (see Box 3 for an example). Many different genes are being studied, particularly those which make enzymes involved in the metabolism of medicines or the response of the immune system.

The former head of the BioIndustry Association has argued that everyone should be tested at birth for this type of genetic variation, and the information stored and used whenever they are treated for an illness in the future<sup>5</sup>. An alternative is to use specific tests only when someone is being treated and the test has been demonstrated to be useful and cost effective.

The growing understanding of the influence of genetic factors on response to drugs can also be used to try to make better, safer medicines, which do not necessarily need a genetic test when they are given to a patient.

#### **Box 2: TPMT**

A few US clinics test for genetic mutations in an enzyme called TPMT in children with leukaemia<sup>6</sup>. About 1 in 300 patients have a nonfunctional form of this gene (although this varies in different ethnic groups). Their bodies cannot break down some of the drugs (known as thiopurine drugs) used to treat leukaemia, making an Adverse Drug Reaction more likely. These patients can usually be safely treated with doses 10 to 15 times lower than normal. However, a recent study of 23 patients with thiopurine intolerance found that only 6 had nonfunctional TPMT genes, emphasising the importance of monitoring all patients carefully, whatever their genetic test results<sup>7</sup>.

***Most reactions to medicines are complex, there are difficulties in reproducing findings, and many tests have limited predictive value***

#### **Box 3: CYP2D6**

The enzyme CYP2D6 is thought to be involved in the metabolism of more than 40 medicines<sup>8</sup>. However, the original division of patients into 'poor metabolisers' and 'extensive metabolisers' is now known to be over-simplistic. There appears to be a spectrum, rather than a clear-cut division, of metabolic rates. Some 75 different mutations have now been identified<sup>8</sup> and an 'ultra-rapid metaboliser' phenotype has also been discovered.

One study has found that psychiatric patients with no CYP2D6 activity who are taking medicines metabolised by CYP2D6 tend to suffer more adverse drug events, stay longer in hospital and cost more to treat<sup>9</sup>. However, the study concludes that hundreds of thousands of patients would need to be studied to find out if these differences are significant. The predictive value for drug efficacy and safety of testing patients for genetic variations in CYP2D6 therefore remains unclear.

### **Predicting efficacy or safety?**

The idea that genetic testing can identify 'the right drug for the right patient' even before they become ill is an attractive one. But how accurate will these genetic predictions be?

Genes clearly play an important role in the metabolism of some medicines and a few cases will be relatively clear-cut. However, most reactions to medicines are complex, there are difficulties in reproducing findings, and many tests have limited predictive value<sup>10,11,12</sup>.

Although patients certainly vary in their response to many medicines, and part of this variation is genetic, many other factors are also important. These include exposure to other medicines, supplements, toxins, allergens and infections; the patient's diet, smoking and drinking habits; and their age, size and sex. An individual's reaction to a particular drug may also involve many different genes.

There is no doubt that genetic variations can make a significant difference to the concentration of a medicine in a patient's blood, but a wide variation is only likely to be important if the drug has a 'narrow therapeutic range'<sup>13</sup>. Such drugs are only safe and effective at a particular concentration and can be dangerous or ineffective if the concentration is unexpectedly higher or lower, even by a small amount. However, even in such cases, it is unlikely that correct doses could be calculated in advance using genetic test results because of the many different factors involved.

In many cases, better monitoring of drug concentrations in individual patients may be better than trying to predict response. However, even monitoring has its limitations and it has proved difficult to establish the best concentrations for many psychiatric and cancer drugs<sup>14</sup>. Better recording of Adverse Drug Reactions (ADRs), and particularly listening to patients and sharing decisions with them, may be more likely to identify the treatment that best suits each individual<sup>15</sup>. Genetic testing is unlikely to remove the need for monitoring because, at best, it will only indicate which patients are more or less likely to respond well to a drug. Relying on genetic tests alone could do more harm than good if it means that signs of a dangerous drug reaction are ignored (see Box 4).

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#### **Box 4: Abacavir (Ziagen)**

About 5% of HIV patients treated with abacavir (brand name: Ziagen) develop a severe reaction to it, which usually takes a few weeks to develop. Patients usually improve within 24 hours of discontinuing the drug, although if they take the medicine again it can rapidly prove fatal. One year after abacavir's approval, its manufacturer, Glaxo Wellcome (now GlaxoSmithKline) issued a warning to doctors. 11 reported deaths had occurred – 5 in people who had been given the drug a second time despite an earlier reaction to it, 4 in people who had continued taking the drug despite an adverse reaction, and 2 in circumstances that are unclear<sup>16</sup>.

One study has found a strong association between a combination of three genetic variations in the HLA-B gene, which is involved in the body's immune response, and this ADR<sup>17</sup>. However, many more different genes and other non-genetic factors are likely to be involved in influencing sensitivity to abacavir, as well as the progression of the disease itself<sup>18</sup>. Another study, by researchers at GlaxoSmithKline, has confirmed the statistical link between genetic variations in HLA-B and hypersensitivity to abacavir, but found a much lower predictive value for this genetic test<sup>19</sup>. In addition, very few men of African descent or women were included in the study.

The authors concluded that the genetic test should not be used to diagnose the ADR because it could not identify everyone who would have it. There would be a danger that some of those not identified by the genetic test could be given the drug a second time, when it might rapidly prove fatal.

Others have argued that the test should be used because it would be worth identifying the white male patients with these genes, around half of whom might be expected to have the ADR (assuming the study can be replicated)<sup>20</sup>. However, it is clear that careful monitoring and record keeping of any reaction to the drug is more useful and important than the genetic test.

***Relying on genetic tests alone could do more harm than good if it means that signs of a dangerous drug reaction are ignored***

## **Reducing Adverse Drug Reactions?**

*"The Genetics Knowledge Parks...will develop pharmacogenetic tests for the targeted treatment of patients, not only getting the right medicine to the right patient but also reducing the incidence of unwanted side effects."*  
The Rt Hon Alan Milburn MP, former Secretary of State for Health<sup>21</sup>.

*“The utility and clinical application of pharmacogenetic approaches towards improving safety, in particular with regard to serious adverse events, will meet with much greater hurdles and is therefore expected as much less likely to become reality...”*

Klaus Lindpaintner, Roche Genetics<sup>22</sup>.

ADRs are caused by the inherent properties of medicines, many of which can be toxic or cause allergic reactions in some people, even when taken correctly. ADRs do not include medical errors - taking the wrong medicine or being given the wrong dose by a doctor. Assessing the true extent of ADRs is difficult. This is partly because only around 50% of people with chronic disease take their medicines as prescribed and partly because most ADRs are not recorded or reported<sup>23,24</sup>.

Many proponents of pharmacogenetics argue that genetic testing will significantly reduce the incidence of ADRs. They frequently cite a study of patients hospitalised between 1966 and 1996 that ranked ADRs as between the fourth and sixth leading cause of death in the US, killing around 110,000 people a year<sup>25</sup>. But would genetic testing significantly reduce these figures?

To answer this question, we would need to know how many of these ADRs might have been prevented by genetic testing or by other measures, such as better monitoring of patients. One US study has found that adverse reactions to drugs known to be affected by genetic variability in metabolism seem to occur more often than reactions to other drugs<sup>26</sup>. This suggests that genetic differences between patients could be important. However, the study could not determine to what extent these ADRs could be reduced by basing the choice and dose of drug on genetic test results.

The Audit Commission has found that reported deaths in England and Wales from the adverse effects of medicines rose nearly five-fold between 1990 and 2000<sup>27</sup>. The reasons for this increase are poorly understood, but cannot include an increase in ‘genes for adverse drug reactions’. Some relevant factors could include:

- the increasing toxicity of some new medicines<sup>27</sup>;
- the limitations of safety testing and monitoring of new medicines<sup>28</sup>;
- the increasing use of medicines, including multiple medicines and more ‘over the counter’ sales<sup>29,30</sup>.

There is a danger that these factors will be given less attention than pharmacogenetics, even though they may be more important. Tackling some of them implies imposing tighter restrictions on the use of some medicines, meaning lower profits for the companies selling them. Other methods, such as better monitoring of ADRs and improving packaging, are less exciting than genetic science and require political will and government investment to make them happen.

In the current commercial context, where innovation has slowed, pharmaceutical companies are seeking to expand the market for their existing products. There is growing concern that this might lead to inappropriate medicalisation, including the increasing use of ‘lifestyle’ and ‘preventive’ medicines by healthy people<sup>31</sup>. Claims that pharmacogenetics will deliver ‘the right drug to the right patient’ are often accompanied by claims that genetics will also deliver *“individualised preventive medicine based on genetic risk”*<sup>32</sup>. This promotion of genetic testing for disease susceptibility (not just drug response) is another factor that could lead to more ‘pills for the healthy ill’ and increase, rather than reduce, the number of people who suffer side-effects<sup>33</sup>.

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## Improving efficacy?

It has been estimated that as few as one third of patients taking prescription medicines actually derive the intended benefit. Sir George Poste, former chief science and technology officer at GlaxoSmithKline, has estimated that up to 30% of patients do not respond to statins (used to lower cholesterol), up to 35% do not respond to beta-blockers (used to lower blood pressure), and up to 50% do not respond to some older (tricyclic) antidepressants<sup>34</sup>.

Genetic testing might improve the efficacy of some medicines by finding the 'right medicine for the right disease', particularly in different types of cancer (see Box 1). HIV treatment may also be improved by switching to a different medicine as soon as mutations associated with drug resistance are found<sup>35</sup>.

Some companies are now investigating the alternative approach - testing the genetic make-up of the patient - to try to predict which medicine will work. There are no tests of this kind yet in use, although predicting efficacy should in theory be easier than predicting safety<sup>22</sup>. The US biotech company, Genaissance, is trying to correlate genetic variations with patients' response to statins so that they can be given the most suitable of four available drugs to reduce their risk of heart disease<sup>36</sup>. However, even if this does make statins more effective, they are likely to remain expensive compared to alternatives such as smoking cessation programmes<sup>37</sup>.

The pharmaceutical industry is unlikely to promote genetic testing as a means to *reduce* the use of ineffective medicines since this would be against its own financial interests. However, a failed drug might be rescued if it can be shown to work in a minority of patients with a particular genetic make-up. For example, Roche is studying genetic variations in patients treated with a new drug for anxiety or depression<sup>38</sup>. This type of drug (known as 'Substance P') failed earlier tests by another company because it did not work<sup>39</sup>.

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## Medicines development, racism and inequalities

The pharmaceutical industry has started to discontinue the development of some drugs at an early stage if it finds that they are affected by genetic variations in metabolism<sup>40</sup>. An alternative is to continue to develop such medicines but market them only with a genetic test. There are differences of opinion within the industry about whether such 'genetically-tailored' drugs are a good idea. Some fear that the drug market will become fragmented into small groups, limiting the profit to be made from each different medicine<sup>41</sup>.

One possible advantage of pharmacogenetics to pharmaceutical companies is the 'streamlining' of the clinical trials used to test a drug before it is marketed<sup>42</sup>. Patients with the wrong genetic make-up would be excluded from the final, large-scale trials of a medicine (known as Phase III trials) either because they are thought to be at higher risk of reacting badly to the drug or because the treatment is only expected to work in certain people. Once the drug was marketed, doctors or pharmacists would then be required to check that any patient treated with it had the right genetic test results.

***No genetic test will be perfect at identifying those who can take a drug safely***

The danger is that this approach could reduce the chance of detecting ADRs in the trial without preventing them from happening later<sup>43</sup>. No genetic test will be perfect at identifying those who can take a drug safely and no system can ensure that only those with certain genes take the drug. People at increased risk might then include those who:

- have the 'right genes' but still react badly to the drug;

- have the ‘wrong genes’ but have no other treatment options so take the medicine anyway;
- are given the medicine by mistake because the test result is wrong or has been misinterpreted;
- refuse to take a pharmacogenetic test;
- do not have access to genetic tests (people living in poor countries, for example).

***By ‘streamlining’ clinical trials, increased fatalities or other serious harm to people’s health might occur before an Adverse Drug Reaction is identified***

Initially, ‘streamlining’ trials is likely to be applied to existing drugs that have failed to gain approval (or had to be withdrawn) because they have not been shown to be beneficial or safe enough<sup>3</sup>. In these cases, there may at least be some (limited) data on what happens when these medicines are given to people with the ‘wrong’ genetic make-up. ‘Streamlining’ trials becomes more dangerous if the drug is never tested at all on people with the ‘wrong’ genes. Increased fatalities or other serious harm to people’s health might occur before an ADR is identified.

There are already problems with people at higher risk of ADRs being excluded from clinical trials<sup>28</sup>. Children and the elderly are often given medicines that have never been tested in the most vulnerable people<sup>44,45</sup>.

In the longer term, medicines might not be developed for people with certain genes because there are too few of them or they are too poor to be a highly profitable market.

There is particular concern that some ethnic groups might be excluded from drug development or treatment. Ethnic labels, such as ‘black’, ‘white’ or ‘Asian’, are insufficient and inaccurate representations of the genetic structure of human populations, which varies much more within different ethnic groups than between them. However, ethnicity is likely to remain as a stand-in for genetic difference for the foreseeable future<sup>46</sup>. Being ‘black’ or ‘white’ could be associated with a particular drug response even though other factors may be much more important. A recent study concluded that a type of heart disease drug is more effective in white than black patients and it has been suggested that this difference may be genetically determined. This reportedly led to some physicians arguing that black race should be a reason not to prescribe this drug<sup>47</sup>.

An individual’s response to a drug depends on many factors, such as socio-economic status, which may be affected by their ethnicity or gender<sup>48</sup>. This means that the predictive value of a gene, not just how many people have it, also varies between different populations. Most research is focused on white males (see Box 4) and the results may simply not apply to others.

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## **Conclusions**

Pharmacogenetics is already improving understanding of drug metabolism and this may lead to better medicines in the long term. However, the prospects for improving the effectiveness of medicines (particularly finding the ‘right medicine for the right disease’) are probably more realistic than improvements in safety. Plans to expand the drug market to more healthy people – including the ‘genetically susceptible’ – could increase the side-effects of medicines way beyond any reductions brought about by pharmacogenetics. Other strategies to reduce the incidence of side-effects - including listening to patients - should not be neglected.

Proposals to exclude some people from clinical trials on the basis of genetic test results could be dangerous if medicines are only tested in the minority of people expected to respond best to them.

It is critically important that doctors and their patients understand the limitations of pharmacogenetic tests and do not assume that they give a simple answer to who should get which medicine. Too much reliance on genetic test results could mean that warning signs of Adverse Drug Reactions are ignored. Pharmacogenetic tests can reveal information that is not limited to drug response, but may also be relevant to risk of future illness<sup>49</sup>. Genetic counselling should therefore be provided.

Pharmacogenetic tests require independent regulation so that their validity and usefulness can be assessed<sup>43</sup>. Many such tests will be more useful for research than in a doctor's surgery and none are likely to replace the need for monitoring the use of dangerous medicines. Screening the whole population for genetic variations is unlikely to bring significant benefits to health and would be needlessly expensive. It would also increase concerns about access to genetic test results by insurers, employers, the police or the government<sup>50</sup>.

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