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EELS (Ethical, Economic, Legal & Social) ARTICLE

# The current clinical practice of pharmacogenetic testing in Europe: TPMT and HER2 as case studies

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## Introduction

The many expectations surrounding the clinical application of pharmacogenetics remain mostly unfulfilled.[1–3] Only a limited number of applications have actually reached clinical practice.[4] To gain insight into the reasons behind the low level of implementation of pharmacogenetic testing in the clinical world we have carried out a survey on the clinical practice of two pharmacogenetic tests in four different European healthcare systems (the United Kingdom, Ireland, Germany and The Netherlands). These were testing for Human Epidermal Growth Factor Receptor 2 (HER2)-overexpression and tests for determining Thiopurine Methyltransferase (TPMT)-activity.

HER2 was identified as a potential monoclonal-antibody target in the early 1980s thereafter the humanized IgG1 monoclonal antibody 'trastuzumab' entered clinical trials in 1992.[5] In 1998 it was approved by the FDA as 'Herceptin', an anticancer therapy for use in breast cancer in patients who are HER2 positive. Commercial tests based on immunohistochemistry (IHC) testing and cytogenetic Fluorescent In-Situ Hybridization (FISH) testing have also been approved by the FDA for detection of HER2 overexpression. Herceptin was approved in Europe in the year 2000 by the EMEA's centralized procedure. The availability of commercial kits has coincided with or even preceded the launch of Herceptin in the countries studied. HER2 testing received a substantial boost when Roche, who market Herceptin in Europe, began to fund laboratories to provide HER2-testing services in large markets such as the UK and Germany. These services made HER2 testing available free of charge for physicians over a period of several years while the market for Herceptin became established.[6]

Thiopurine drugs such as 6-mercaptopurine (6MP) and Azothioprine have been used since the 1950s as immunosuppressants for a range of autoimmune conditions as well as Leukaemia. Thiopurine drug use is associated with potentially fatal myelosuppression in individuals who poorly metabolize the drug. An enzyme associated with thiopurine metabolism, named TPMT was isolated in 1980.[7] TPMT testing for patients with acute lymphoblastic leukaemia (ALL) has been provided in the UK, Germany, The Netherlands and Ireland as part of research programmes, often with financial support from national cancer charities. Owing to the small market for thiopurine drugs and generic competition there has been little commercial interest in TPMT testing.

The tests were selected because they were present in all countries studied and are among the first clinical examples of pharmacogenetic testing. Furthermore, they cover two important applications of pharmacogenetics, that is, the identification of good responders to reduce inefficacious use (HER2 test) and the prevention of adverse effects by identification of poor metabolizers (TPMT test).[8–10]

The study of clinical use of pharmacogenetics in these four countries is part of a wider ongoing project to assess the current European 'state-of-the-art' in pharmacogenetics being carried out by one of the institutes of the European Commission's Joint Research Centre.[11]

In order to understand the range and extent of factors influencing the implementation of HER2 and TPMT testing, our survey targeted relevant sites (e.g. Oncology and Haematology departments, Breast Cancer clinics and Paediatric hospitals) to request information addressing several dimensions of the clinical practice of these tests. This includes possible infrastructural, financial, perceptional, educational, social and legal barriers for implementation. The measure of the level of implementation within the responder-group was based upon the consistency of use, measured as the percentage of patients actually tested before they receive treatment.

## Results

### *Rate of response to the survey*

The sample surveyed consisted of 407 physicians in four countries. We attempted to include as many relevant hospitals and clinics as possible in each country, by means of contacting local networks. A total of 111 responses were obtained from physicians including both those that completed the questionnaire and those that responded saying they do not perform the test (Table 1).

This gives a total response rate of 27% (Germany 24%, UK 31%, Netherlands 33% and Ireland 7%). In total, we obtained 71 completed questionnaires for HER2 and 16 for TPMT

**Table 1 The response to the survey on the implementation of HER2 and TPMT testing**

| *Country* | *Number responded* | *Using test* | *Not using test at present* |
|---|---|---|---|
| *HER2* | | | |
| UK | 17 | 15 | 2 |
| D | 36 | 36 | 0 |
| NL | 23 | 19 | 4 |
| IR | 1 | 1 | 0 |
| Total | 77 | 71 | 6 |
| *TPMT* | | | |
| UK | 20 | 6 | 14 |
| D | 12 | 9 | 3 |
| NL | 2 | 1 | 1 |
| IR | 0 | 0 | 0 |
| Total | 34 | 16 | 18 |
| Total | 111 | 87 | 24 |

A significantly higher number of MDs responded to the HER2 questionnaire compared to the TPMT questionnaire. More than half of the TPMT response comes from departments where the testing could potentially be done, though indicating that they do not test at present. From this, the higher degree of implementation of HER2 above TPMT can be seen.

testing; this lower number is consistent with the lower usage of TPMT testing overall. Only one response was obtained from Ireland so this country has been excluded from further analysis.

*Levels of implementation*

Of the 77 HER2 respondents, 8% give treatment with trastuzumab without any testing, and another 8% use the test, but do not test *all* patients who receive the treatment.

Of all 34 respondents who treat with thiopurine drugs, 53% give treatment without prior use of a pharmacogenetic test and a further 35% do use the test, but do not test *all* patients who receive the treatment.

The actual levels of committed, consistent use (implementation) are 84% for HER2 testing and 12% for TPMT testing according to our survey. Significant differences in implementation between countries were not observed.

*Infrastructural barriers*

In the delivery of pharmacogenetic testing to the patient, communication with the laboratory undertaking the testing procedures is important for transferring of information.[12] Other possible barriers to consider are the sending and storage of the sample, the so-called physical infrastructure aspects. As shown in Table 2, problems with laboratory communication vary by country. The UK respondents using HER2 tests have significantly more problems with their laboratory communication, whereas Dutch hospitals perceived the least problems in HER2 testing.

*Financial barriers*

Cost is a common barrier to the application of novel medical technologies, and indeed in our survey, costs were seen as a problem for both HER2 and TPMT tests (Table 2).

A physician could perceive a test as cost-beneficial, but it is also important to see whether calculations have actually been made. For this reason, both perceived and calculated cost/benefit ratio were included in the survey. Subjects were not asked about the methodology used to make their calculations. The survey shows that HER2 testing is perceived as having more benefits than costs (Figure 1). UK has the most positive perception on HER2 testing and the Netherlands the least positive. Out of all respondents, 13% for HER2 and 20% for TPMT had made calculations about the cost/benefit ratio. The outcome led to a slightly more negative cost–benefit than the perceived cost/benefit ratio (Figure 1). Larger hospitals and departments with a higher percentage of doctors with recent education have made calculations more often (data not shown).

Reimbursement of the costs is extremely important: one laboratory in the Netherlands pointed towards the fact that they do not carry out TPMT testing routinely because reimbursement has not been arranged yet. Similarly in the UK no NHS reimbursement is available and testing is currently provided with research funding. The respondents were not consistent in answering the questions with disagreement in responses over whether or not reimbursement was available.

The highest consensus was reached among the HER2 respondents from UK, of whom the majority (73% for public and 80% for private insurance) answered that the test is fully reimbursed. Furthermore, 80% of these UK respondents agreed that HER2 testing is a requirement for reimbursement of trastuzumab. In Germany and The Netherlands, the consensus about full reimbursement and requirement (for public and private insurance) was between 50 and 60% for these topics and thus less clear. For TPMT, the number of cases was too low to draw conclusions.

*Perception barriers*

The therapeutic advantage, that is, the clinical utility, is probably one of the most important aspects in ensuring the success of a medical innovation. As can be seen in Figure 2, the clinical utility is perceived by the majority of respondents as quite high or very high for HER2 testing. For TPMT testing, the clinical utility is perceived by the majority of respondents as quite high (50%), but certain proportions also perceive these as quite or very low (12 and 13%). There seems to be a larger consensus on the clinical utility of HER2 testing when compared with TPMT testing. An obvious reason for this could be the presence of the Red blood cell counting (RBC) alternative for TPMT testing. Several respondents explained that they do not use the genetic test, because research is ongoing to determine whether genotypic or phenotypic methodologies should be used and which is the more suitable. As

**Table 2 Occurrence of possible barriers for HER2 and TPMT testing is investigated, though the response for the TPMT case was too low to draw conclusions**

| *Possible barrier* | *Hospitals in which a barrier has been perceived (number and %)* | |
|---|---|---|
| | *For HER2* | *For TPMT* |
| *Costs* | | |
| UK | 9 (60 %) | 0 (0 %) |
| D | 19 (54 %) | 5 (55 %) |
| NL | 9 (47 %) | ND[a] |
| *Storage of the sample* | | |
| UK | 3 (20 %) | 0 (0 %) |
| D | 8 (23%) | 2 (22 %) |
| NL | 1 (5 %) | ND |
| *Sending of the sample* | | |
| UK | 9 (60 %) | 1 (17 %) |
| D | 6 (17 %) | 2 (22 %) |
| NL | 2 (11 %) | ND |
| *Communication with laboratory* | | |
| UK | 8 (53 %) | 1 (17 %) |
| D | 11 (31 %) | 3 (33 %) |
| NL | 3 (16 %) | ND |
| *Testing capacity of the laboratory* | | |
| UK | 7 (47 %) | 0 (0 %) |
| D | 7 (20 %) | 2 (22 %) |
| NL | 3 (16 %) | ND |
| *Reluctance of employees* | | |
| UK | 2 (13 %) | 1 (17 %) |
| D | 3 (9 %) | 1 (11 %) |
| NL | 2 (11 %) | ND |
| *Asking for informed consent* | | |
| UK | 1 (7 %) | 0 (0 %) |
| D | 2 (6 %) | 2 (22 %) |
| NL | 0 (0 %) | ND |

The left-hand column, however, shows how the technical infrastructure is often problematic as regards means of communication, sending of samples to laboratories and the storage of these samples. These are most problematic in the UK. Cost is also reported as being a barrier for the use of testing.
[a]ND = not determined, owing to low representation in the sample.

a consequence, the monitoring of the RBCs is often done anyway, which lowers the relevance of the genetic test.

*Knowledge barriers*

An appropriate level of education is necessary for users to adequately use a new medical technology, and genetics is no exception.[13] Whether or not the MDs have difficulties interpreting the results of the tests can be a good indicator of a further need for specific education.[12] In each country, between 16 and 20% of respondents consider the interpretation of HER2 results to be 'difficult', and less than 11% consider the interpretation of TPMT results difficult.

Knowledge about the existence of the tests is not always sufficient either. Roche held an intensive campaign to promote the use of the HER2-test with trastuzumab treatment.[6] Such a campaign has never been held for TPMT. As one of the Dutch respondents mentioned: 'I am not sure what to do with TPMT testing. We receive thiopurines from our pharmacy, and if any testing would be necessary we assume that our pharmacy will tell us'.

*Social barriers*

Public acceptance is not the strongest determinant of implementation effectiveness, but the absence of it could certainly lead to failure. Although the use of genetic tests in medicine is broadly accepted by the public in Europe,[14] we have tried to investigate whether there is public/patient resistance to pharmacogenetic test use.

According to the respondents, patients are sometimes a bit worried about the test results but this could be because of its implications for their treatment and they hardly ever refuse a test.

Owing to the nature of genetic tests gaining proper informed consent is of great importance. However, survey results indicate that informed consent is not always requested by physicians using pharmacogenetics in practice and very few departments reported informed consent as a significant burden (Table 2).

Most of the physicians believed that patient organizations have a positive attitude towards HER2 testing. In the case of TPMT, most physicians think that patient organizations have a neutral attitude. From this information, no specific social issues appear, but patient interviews are needed to gain more insight in the situation.

*Legal barriers*

There is no regulatory framework imposing consistency of testing. One legal aspect that is often mentioned in literature is the prevention of liability issues by means of pharmacogenetic testing.[15] Fear of liability is likely to increase uptake of a pharmacogenetic test as a technology that helps to protect doctors from litigation.[16] One respondent from Germany had a clear opinion on the liability issue: Most clinicians prescribing azathioprine are getting more and more aware of the fact that if they prescribe thiopurines to a TPMT non-metabolizer and that patient develops a severe adverse reaction, the clinician will be held responsible.

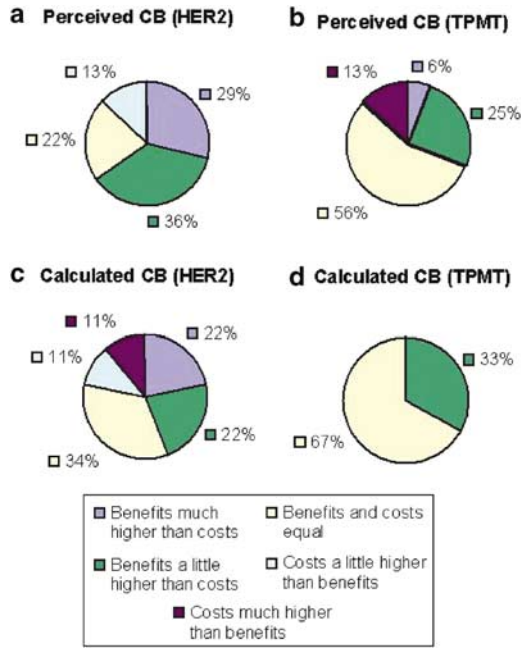


**Figure 1** The way in which the HER2 test users perceive the cost/benefits ratio is clearly more positive than for TPMT users. A significant part of the latter even considers the costs of TPMT testing much higher than the benefits. As appears from the lower part of the figure, the outcomes of calculated cost/benefit ratios vary strongly, which stresses the need for standardized calculation methods.

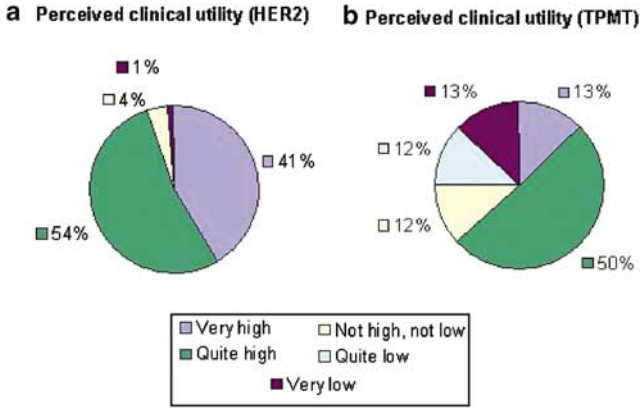


**Figure 2** The perceived clinical utility is clearly lower for TPMT than for HER2, which could be one of the explanations for the lower implementation of TPMT testing.

In our survey, 38% of the HER2 respondents think that pharmacogenetic testing prevents liability issues and 11% think this is not the case. A higher percentage (50%) of TPMT respondents believe that pharmacogenetic testing prevents liability issues whereas 12% believe this is not the case. The remaining respondents do not express a specific opinion on this.

Another legal factor that may support implementation of pharmacogenetic testing is regulatory requirement of the test.

## Conclusions

The clinical implementation of the two tests studied is incomplete. HER2 reaches much higher levels (84%) than TPMT testing (12%). This difference is reflected in a proportionally lower response rate for the TPMT case as well. Although most TPMT respondents perceive fewer barriers than HER2 respondents, the requirement in the drug label for HER2 and the presence of a phenotypic alternative for TPMT testing (monitoring with RBC count) could be reasons for the difference in implementation degree.

The quality of technical infrastructure aspects influences the clinical uptake. Respondents reported that sending of samples can sometimes be problematic in testing and that communication with the laboratory and the capacity of the testing laboratory are not always sufficient. Indeed, failure to have a protocol for the processing of samples for genetic tests has been reported elsewhere as a significant implementation problem.[17]

Costs are perceived as high and test users report costs as remaining problematic. This is an interesting finding considering that both HER2 and TPMT testing are reported as cost-effective in a number of cost–benefit exercises.[18,19] Certainly, this highlights a problem in that costs and benefits may be accruing to different parts of the healthcare system, thus it might be that policies are needed to incentivise physicians to use pharmacogenetics where this is rational for the health system as a whole, even when this may be more expensive for the individual departments that request tests. Positive cost–benefit studies are not sufficient for pharmacogenetic tests to become widely used.

Clear utility of the tests is obviously important. The majority of respondents perceive the clinical utility of HER2 and TPMT testing as high or quite high, although only the HER2 respondents think that the benefits clearly outweigh the costs. This could be an explanation for the higher level of implementation of HER2 testing, and implies that lower awareness of the cost benefits of using TPMT testing may form a barrier for TPMT testing. The use of RBC may also provide a disincentive for physicians to use TPMT testing.

Lack of specialized education of the physicians could be interfering with

the clinical use of pharmacogenetics. About one-fifth of the respondents consider the interpretation of HER2 test results as difficult. This is a worrisome result, as two-third of the respondents claim to have had additional courses or training and indeed the company distributing the test held an intensive informative campaign. TPMT respondents however appear to have fewer difficulties with the interpretation and less courses or training, though, at the same time, a number of respondents were not aware of the existence of the test.

No social barriers have been reported, and HER2 testing is even reported as being encouraged by patient organizations. Issues related to insurance, on the other hand, are seen as possibly inhibiting. There were great inconsistencies in the answers related to reimbursement procedures. This could either mean that it is unclear to them or that there are large differences between insurance companies. In any case, lack or difficulty of reimbursement becomes a strong barrier for implementation, as some of the responders admitted. On the other hand, reimbursement could be used to positively influence the clinical uptake if its use becomes a requirement for reimbursement, as with HER2 testing.

The consequences for a patient who is not tested before treatment with thiopurine drugs could be life threatening, and that might be why half of the people surveyed pinpointed to liability issues in TPMT testing. A higher percentage of TPMT users think that testing helps in preventing liability issues. Even though this should have a driving influence, the possibility of phenotypic monitoring through RBC count may reduce the drive to implement TPMT pharmacogenetic testing.

## Materials and methods

The survey was sent out by e-mail. A mailing list of physicians and heads of departments who were possibly involved in HER2-or TPMT-testing was compiled for the countries targeted by the survey: UK, Ireland, Germany and The Netherlands. The aim was to reach as many involved physicians as possible, as no data on pharmacogenetic test use is publicly available. The questionnaire covered the level of implementation and possible barriers in the implementation: economic barriers and reimbursement, technical barriers, educational, social and legal barriers.

Subjects were asked to complete the questionnaire in their own language or give their view on the topic. Subjects were given 2 weeks for submission and two reminders were sent afterwards.

## Duality of interest

None declared.

## Disclaimer

The views expressed in this study do not necessarily reflect those of the European Commission (EC).

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