The Health Technology Assessment of Companion Diagnostics: Experience of NICE

Sarah K. Byron¹, Nick Crabb¹, Elisabeth George³, Mirella Marlow¹, and Adrian Newland²

Abstract
Companion diagnostics are used to aid clinical decision making to identify patients who are most likely to respond to treatment. They are becoming increasingly important as more new pharmaceuticals receive licensed indications that require the use of a companion diagnostic to identify the appropriate patient subgroup for treatment. These pharmaceuticals have proven benefit in the treatment of some cancers and other diseases, and also have potential to precisely tailor treatments to the individual in the future. However, the increasing use of companion diagnostics could place a substantial burden on health system resources to provide potentially high volumes of testing. This situation, in part, has led policy makers and Health Technology Assessment (HTA) bodies to review the policies and methods used to make reimbursement decisions for pharmaceuticals requiring companion diagnostics. The assessment of a pharmaceutical alongside the companion diagnostic used in the clinical trials may be relatively straightforward, although there are a number of challenges associated with assessing pharmaceuticals where a range of alternative companion diagnostics are available for use in routine clinical practice. The UK HTA body, the National Institute for Health and Care Excellence (NICE), has developed policy for considering companion diagnostics using its Technology Appraisal and Diagnostics Assessment Programs. Some HTA bodies in other countries have also adapted their policies and methods to accommodate the assessment of companion diagnostics. Here, we provide insight into the HTA of companion diagnostics for reimbursement decisions and how the associated challenges are being addressed, in particular by NICE.

See all articles in this CCR Focus section, "The Precision Medicine Conundrum: Approaches to Companion Diagnostic Co-development."

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No potential conflicts of interest were disclosed.

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Learning Objectives
Upon completion of this activity, the participant should have a better understanding of the challenges associated with the health technology assessment of companion diagnostics. The participant should also gain insight into the policy and assessment approaches currently used at the UK National Institute for Health and Care Excellence to assess companion diagnostics.

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Introduction
Following the rapid advances in genomics and molecular biology over the last few decades, diseases that were traditionally thought of as a single disease are increasingly being stratified into subgroups of disease based on distinct molecular characteristics. Patient response to drug treatments is known to vary widely across the population, so this deeper understanding of disease has created the possibility that medicines can be tailored to the individual patient to improve response to treatment. Several of such stratified medicines are now on the market, and there is a great deal of interest and investment in generating more stratified medicines. As a consequence, companion diagnostic tests have also become increasingly important because the benefit of the stratified medicine is only realized if the patients with the appropriate subgroup of disease are correctly identified.

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Companion diagnostic tests are typically *in vitro* diagnostic assays that measure the levels of protein or gene expression or detect specific genetic mutations, which inform the clinician whether the stratified medicine is suitable for the patient.

The use of companion diagnostics in combination with stratified medicines is an important area for policy makers, payers, and industry because, increasingly, the licensed indications for new pharmaceuticals require the use of companion diagnostics. Fugel and colleagues (1) assessed the clinical pipelines of 21 leading pharmaceutical and biotechnology companies and reported that between 12% and 50% of products in development involve stratified medicine. This puts an increasing burden on health systems to absorb the additional cost of potentially high volumes of testing and to increase resources for testing services, thus ensuring patient access to both testing and subsequent treatment. In addressing this burden, Health Technology Assessment (HTA) bodies play an important role in ensuring that resources are appropriately allocated. However, their methods and processes for assessing the clinical- and cost-effectiveness of stratified medicines in combination with companion diagnostics may need to be adapted.

This article focuses on the challenges faced by HTA bodies and policy makers when making reimbursement decisions about companion diagnostics and discusses the experience of the UK HTA body, the National Institute for Health and Care Excellence (NICE, London and Manchester, UK), in assessing companion diagnostics.

Health Economic Considerations

The stratification of patient populations using companion diagnostics may allow improved clinical outcomes by focusing treatments in the patients who can benefit most and by avoiding adverse effects in patients who are unlikely to benefit (Fig. 1). Cost savings are also potentially achievable through avoiding treatments in patients who are unlikely to benefit. This may result in improved treatment cost-effectiveness, depending on the diagnostic testing costs associated with identifying the patient population for treatment. The companion diagnostic will be a particularly important factor in treatment cost-effectiveness where an expensive diagnostic test is required and/or where only a small proportion of patients tested are identified as eligible for treatment.

Challenges of Companion Diagnostic HTA

In some cases, the health technology assessment of a pharmaceutical requiring a companion diagnostic is relatively straightforward, with little additional complexity to that for a pharmaceutical alone. This applies where the tests to be used in clinical practice are the same as the test used in the pivotal clinical trials of the pharmaceutical. Here, health outcomes from the treatment, informed by the companion diagnostic, are used as the basis for the evaluation of the clinical effectiveness of the pharmaceutical/companion diagnostic "package." Health technology assessment in this situation is more straightforward than for other diagnostics, where studies following patients through diagnosis and treatment to outcomes are rarely available. In these cases, in the absence of such pivotal trials, a linked evidence approach and complex modeling are typically required to estimate patient outcome benefits.

The health technology assessment of companion diagnostics can become more complex where the companion diagnostic test used in the clinical trials is not widely adopted in routine clinical practice. The level of adoption is, in part, influenced by the current regulation of companion diagnostic tests.
diagnostics. Although regulation is evolving, to date in Europe, the licensed indication of a pharmaceutical may require the use of a companion diagnostic but the specific test for determining the mutation status is not normally stipulated (2). This permits the adoption of a diverse range of proprietary and “in-house” tests that are all consistent with the marketing authorization. These different tests can have varying levels of diagnostic accuracy, leading to different patient subpopulations being selected for treatment, with a resulting impact on treatment clinical- and cost-effectiveness.

For example, in a health technology assessment of EGFR receptor tyrosine kinase (EGFR-TK) mutation tests, one test seemed to have sensitivity and specificity estimates of 99% [95% confidence interval (CI), 94%–100%] and 69% (95% CI, 60%–77%), respectively, whereas the sensitivity and specificity estimates for other tests ranged from 60% to 84%, and 61% to 84%, respectively (3).

The regulation of companion diagnostics in the United States seems to be significantly different, with the requirement for companion diagnostics to be approved or cleared by the U.S. Food and Drug Administration (FDA; 2, 4). Here, the regulatory process examines the suitability of a specific test for selecting patients for treatment with the corresponding pharmaceutical, and this test is stipulated in the licensing. However, even in the United States, tests developed by laboratories operating under the Clinical Laboratory Improvement Amendments exemption (3) can be used as companion diagnostics, which means that in routine clinical practice, tests are sometimes used where their suitability for selecting patients for treatment with the pharmaceutical has not been demonstrated in a clinical trial.

There may be good reasons for adopting tests in clinical practice that are different from the ones used in the clinical trials of the corresponding pharmaceutical. It may be more efficient for laboratories to standardize as many tests as possible on a small number of instrument platforms, or there may be significant capital required to implement a companion diagnostic that was dependent on a specific proprietary platform. If the test used in clinical trials detected a limited set of mutations, a clinical research institute may wish to generate data on a broader range of mutations for research purposes in parallel with generating the information required for the immediate treatment decision. In addition, rapid advances in genomics and molecular biology can result in the mutation-specific tests used in clinical trials being quickly superseded and as stratified medicine becomes more established, the use of technology platforms applicable to a wide range of diseases (e.g., next-generation sequencing technologies) becomes increasingly attractive. For these reasons, there is perhaps an understandable reluctance from laboratories providing companion diagnostic testing to automatically deploy the test that was used in the clinical trials or an FDA-approved or -cleared test, even though these are the tests in which the evidence for the link between the use of the test and the respective patient outcome is likely to be strongest. Having a wide range of alternative companion diagnostics used in routine clinical practice for the same purpose presents challenges to payers because if an evidence-based approach to reimbursement is taken, an assessment of the clinical- and cost-effectiveness of all the companion diagnostic tests in addition to an assessment of the corresponding pharmaceutical needs to be undertaken. At NICE, an assessment of the companion diagnostic, EGFR-TK mutation testing for the treatment of adults with locally advanced or metastatic non–small cell lung cancer, resulted in ten tests being included in the assessment: three Conformité Européene (CE)-marked tests, five laboratory-developed tests, and two test strategies combining a CE-marked test and a laboratory-developed test.

In assessing the suitability of a test that was not used in the clinical trials of the corresponding pharmaceutical, HTA organizations may have to rely on a link to the trial data through comparative diagnostic accuracy studies. In these studies, the accuracy of an alternative test is compared with that of the test used in the clinical trial. Obtaining the accuracy data in these studies could involve the retrospective reanalysis of samples from the clinical trials using the alternative test or, where access to samples from the clinical trials is not possible, concordance studies may be useful. Concordance studies use both the alternative test and the test used in the clinical trials to analyze new samples, and then the results of each test are compared to determine whether they agree. This type of study focuses on whether the two tests produce the same result (positive or negative) for the same sample; the diagnostic interpretation of these results is rarely reported. Where equivalence (tests produce similar results) is established, it may be reasonable to extrapolate the trial data to the alternative test. Depending on the nature of the marker targeted by the companion diagnostic, it may also be possible to link to the trial data on the basis of analytical validation. Analytical validity refers to how well a test detects the presence or absence of a particular marker. Where the marker is very clearly defined (e.g., a specified single-point gene mutation), analytical validation of the alternative test alone may be sufficient to demonstrate equivalence to the test used in clinical trials. The link to outcomes evidence from analytical validation is much harder to establish for more complex markers. For example, the marker may be mutations in a gene with no specified point mutations. Here, the alternative test may not be designed to detect exactly the same mutations as the test used in the clinical trials so the tests could perform differently by design. In such cases, validation to ensure that the test is effective in detecting the mutations it was designed to detect, cannot be interpreted as the test also being suitable for selecting the patient population for treatment with the associated pharmaceutical. If, however, the alternative test detects a nonidentical but very similar set of mutations, it may select a broadly equivalent patient population for treatment compared with the population for the test used in the clinical trials. The extent to which the two tests will select different patient populations for treatment depends on the functional differences in the mutations targeted and the prevalence of these different mutations.

In light of the challenges outlined above, two potential strategies for companion diagnostics health technology
assessments have been developed. The first simply acknowledges the complexity of situations where there are potentially multiple companion diagnostic test options. In this strategy, only the evidence from the pharmaceutical clinical trials is considered and only the cost of companion diagnostic testing, based on the test used in the clinical trials, is included in the health technology assessment of cost-effectiveness. The issues associated with the potential use of alternative tests may be highlighted within the assessment without attempting to identify and consider specific evidence on the various alternatives. This model is considered a minimal and pragmatic approach, and can facilitate the rapid health technology assessment of new pharmaceuticals, where their use is dependent on companion diagnostics.

The second strategy includes a more in-depth consideration of the various companion diagnostic test options. Here, the main tests used in clinical practice are identified and searches for relevant evidence conducted. Separate cost-effectiveness analyses may be attempted for the pharmaceutical in combination with each of the alternative tests. This approach requires more resources and time, and if undertaken at the same time the pharmaceutical itself is being assessed, could potentially delay the assessment of the pharmaceutical. It may be appropriate in cases in which the companion diagnostic testing is technically complex and where it is possible that the alternative tests may deliver significantly different diagnostic accuracy to that used in the clinical trials. The approach may be applicable where the cost of the companion diagnostic test is a significant driver of the pharmaceutical’s cost-effectiveness.

Companion Diagnostics and NICE

Companion diagnostics topics may be considered in the NICE technology appraisal or diagnostics assessment programs. Both programs use the quality-adjusted life year (QALY) measurement to compare different interventions and capture their clinical effectiveness. Cost-effectiveness is expressed in £ per QALY and this measure is used to compare the cost-effectiveness of a new intervention with standard care. The two programs are briefly outlined below:

**NICE Technology Appraisal Program**

The NICE Technology Appraisal Program was the first activity of NICE and was established in 1999. The program provides recommendations to the National Health Service (NHS) and patients on the clinical- and cost-effectiveness of health technologies, with the majority being pharmaceuticals. Technologies recommended by NICE through the NICE Technology Appraisal Program are covered by the regulations underpinning the 2012 Health and Social Care Act that requires commissioners to ensure that funding and access for eligible patients are guaranteed in the NHS (6).

To date, NICE has published 11 pieces of technology appraisals guidance in instances when the pharmaceutical’s licensed indications require the use of companion diagnostics, as shown in Table 1. In these appraisals, there were varying levels of commentary on the companion diagnostic. In none of these appraisals was a specific companion diagnostic test recommended in the guidance.

In January 2013, NICE published an update to its guide to the methods of technology appraisal (7). Section 5.9 of the guide concerns companion diagnostics and is intended to provide a pragmatic approach for considering companion diagnostics while avoiding delaying the appraisal of the associated pharmaceutical. The costs of testing are incorporated into the assessment of cost-effectiveness where the test is used solely to support the treatment decision for the associated pharmaceutical. The guide also stipulates that a cost-effectiveness sensitivity analysis should be provided where the costs of testing are not included. This allows the impact of the companion diagnostic on the cost-effectiveness of the associated pharmaceutical to be readily understood. The guide also allows the issues associated with the potential use of alternative tests to be highlighted in the appraisal guidance without attempting to identify and consider evidence on any of the various alternative tests.

**NICE Diagnostics Assessment Program**

Established in 2010, the Diagnostics Assessment Program evaluates the clinical- and cost-effectiveness of diagnostic technologies, including genetic tests, other in vitro diagnostics, and imaging systems, and develops guidance on their use for the NHS. In assessing the clinical- and cost-effectiveness of a diagnostic, it is necessary to consider diagnostic accuracy, the impact of the test on clinical decisions, and the impact of these decisions on patient outcomes. For many diagnostics, there are no clinical studies that follow patients from diagnosis with the test to the downstream care pathway, yielding direct evidence of patient health outcomes (8). Linked evidence approaches and complex modeling are therefore used where diagnostic accuracy evidence is linked to existing relevant evidence on the downstream care pathway (e.g., randomized controlled trials on treatment effectiveness).

Following the publication of a NICE technology appraisal on a pharmaceutical requiring a companion diagnostic, it may become clear that in clinical practice, a range of different tests are being deployed. New tests may also be developed and marketed for use as companion diagnostics for the selection of patients for treatment with pharmaceuticals already approved in NICE technology appraisal guidance. Such tests may be notified to NICE by a commercial or clinical sponsor, and where appropriate, these are selected for guidance development in the diagnostics assessment program. In such assessments, the intention is not to revisit the cost-effectiveness of the pharmaceutical as determined in the NICE technology appraisal but to identify the test options that will support the clinical and cost-effective use of the pharmaceutical in clinical practice. To date, NICE has published guidance on one such topic—EGFR-TK mutation testing in adults with locally advanced or metastatic non–small cell lung cancer (9).

Before developing this diagnostics guidance, technology appraisal guidance had already been issued for the EGFR-TK inhibitor drugs, gefitinib (10) and erlotinib (11). Companion diagnostic testing to support the use of these drugs in
line with their marketing authorizations was also largely in place across the NHS in England. A wide variety of different test methods and strategies were being applied across the laboratories providing \textit{EGFR-TK} mutation testing services. The diagnostics topic was notified to NICE by a senior NHS clinician with the objective of identifying which of the tests were capable of supporting the clinical and cost-effective use of the \textit{EGFR-TK} inhibitor drugs based on a review of the available evidence. Following notification, the usual topic selection processes were applied (12) and the topic was referred to the Diagnostics Assessment Program.

During scoping, when the framework for the assessment was determined, it was considered desirable to include all of the main tests and test strategies in current NHS use within the scope. Stakeholders from the laboratories providing the testing services were keen that the eventual NICE guidance should not be unnecessarily restrictive on which tests should be used in clinical practice. The objective was not to identify a single "best test" but to identify all tests within the scope that would ensure the clinical and cost-effective use of the drugs. A further issue considered during scoping was that the assessment should not revisit the cost-effectiveness of the drugs, as these had already been appraised and recommended by NICE. The scope for this diagnostics assessment was published by NICE in August 2012 (13).

A diagnostics assessment report comprising a systematic review of the clinical evidence and cost-effectiveness analyses was produced by an independent external assessment group in line with the published diagnostics

<table>
<thead>
<tr>
<th>Appraisal title</th>
<th>Marker</th>
<th>Date published</th>
</tr>
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<tbody>
<tr>
<td>TA107 Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer</td>
<td>HER2 (protein marker)</td>
<td>March 2002</td>
</tr>
<tr>
<td>TA118 Bevacizumab and cetuximab for metastatic colorectal cancer</td>
<td>EGFR (protein marker)</td>
<td>January 2007</td>
</tr>
<tr>
<td>TA176 Cetuximab for the first-line treatment of metastatic colorectal cancer</td>
<td>KRAS (genetic marker)</td>
<td>August 2009</td>
</tr>
<tr>
<td>TA192 Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer</td>
<td>\textit{EGFR TK} mutations (genetic marker)</td>
<td>July 2010</td>
</tr>
<tr>
<td>TA208 Trastuzumab for the treatment of HER2-positive metastatic gastric cancer</td>
<td>HER2 (protein marker)</td>
<td>November 2010</td>
</tr>
<tr>
<td>TA241 Dasatinib, high-dose imatinib, and nilotinib for the treatment of imatinib-resistant chronic myeloid leukemia (CML), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance</td>
<td>Philadelphia chromosome (genetic marker)</td>
<td>January 2012</td>
</tr>
<tr>
<td>TA251 Dasatinib, nilotinib, and standard-dose imatinib for the first-line treatment of chronic myeloid leukemia</td>
<td>Philadelphia chromosome (genetic marker)</td>
<td>April 2012</td>
</tr>
<tr>
<td>TA258 Erlotinib for the first-line treatment of locally advanced or metastatic \textit{EGFR-TK} mutation-positive non-small cell lung cancer</td>
<td>\textit{EGFR TK} mutations (genetic marker)</td>
<td>June 2012</td>
</tr>
<tr>
<td>TA269 Vemurafenib for treating locally advanced or metastatic \textit{BRAF V600} mutation-positive malignant melanoma</td>
<td>\textit{BRAF V600} mutation (genetic marker)</td>
<td>December 2012</td>
</tr>
<tr>
<td>TA296 Crizotinib for treating adults with previously treated \textit{ALK}-positive advanced non-small cell lung cancer</td>
<td>Anaplastic-lymphoma-kinase (ALK) (genetic marker)</td>
<td>September 2013</td>
</tr>
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assess the cost-effectiveness of the EGFR-TK inhibitor drugs. The health economic models used in the appraisal of the drugs were carefully studied and used to inform model development for EGFR-TK mutation testing. During the assessment, it became clear that for several of the test strategies, there was very limited evidence on which to determine clinical- and cost-effectiveness. Three different analytic approaches were used to calculate cost effective-

Text Box 1. Analysis based on evidence of comparative effectiveness

Ideally, to determine the clinical effectiveness of the tests, their performance would be compared with a "gold standard" test for identifying EGFR-TK mutations. Currently, there is no "gold standard" test, in part, because the exact combination of mutations and level of mutation present in a tumor which will select the optimum population for treatment is unclear. In the absence of a "gold standard," an alternative method is to use studies that compare the treatment effect in patients with different mutation status as selected by the test. In this analysis, data were used from randomized controlled trials on the comparative effectiveness (progression-free survival and overall survival) of EGFR-TK inhibitor drugs and standard chemotherapy in patients with tumors of positive, negative, or unknown EGFR-TK mutation status. Two tests, one CE marked and one laboratory developed, were involved in these trials that provided evidence of how clinical outcomes from treatment with EGFR-TK inhibitors varied according to the test used to select the population of treatment. However, one major assumption underlying the use of these data is that the difference in comparative effectiveness between the EGFR-TK inhibitors and standard chemotherapy is solely due to the use of the different mutation tests.

Text Box 2. Analysis based on "linked evidence"

This analysis included data from studies on different EGFR-TK mutation tests which had data on the accuracy of the test for the prediction of response to treatment with EGFR-TK inhibitors but had no data on comparative effectiveness. Two other tests had this type of evidence, one laboratory-developed test and one test strategy. The two tests that had comparative effectiveness data were also included in this analysis so, in total, four tests were included. Evidence for the two tests with only accuracy data was "linked" to the comparative effectiveness data so it was assumed that progression-free survival and overall survival correlated between the tests. The assumption that the difference in comparative effectiveness is solely due to the use of the different mutation tests also applied in this analysis.

Text Box 3. Analysis based on equal prognostic value

For the remaining tests and test strategies, no data were available for the comparative effectiveness or the accuracy of the tests in predicting treatment response. Comparisons were therefore made based on differences in test failure rate and test cost, given the assumption of equal prognostic value equal to the test with clinical outcomes evidence. This assumption was not based on evidence but rather a lack of evidence on any difference in prognostic value between these tests. This approach is clearly limited because the cost-effectiveness estimates are essentially driven by cost given this assumption. The assessment included a survey of laboratories providing EGFR-TK mutation testing services that provided information on test technical performance characteristics and costs. Data from a national external quality assurance scheme study of EGFR-TK mutation testing was also considered. Two tests were not included in this analysis because there were no data on the test failure rate or test cost. Laboratories completing the survey reported that these two tests were not being used in clinical practice.

Consideration of Companion Diagnostics by Other HTA Agencies

Since the approval of the first therapeutic associated with a companion diagnostic test [Herceptin (Roche) and HercepTest (Dako)] in the United States in 1998 (15), an increasing number of companion diagnostic technologies...
have been developed. This has led policy makers to review not only their regulatory processes, but also the methods used to make reimbursement decisions for pharmaceuticals that are associated with a companion diagnostic. A review commissioned by the Australian government identified that an integrated approach was needed to evaluate pharmaceuticals associated with a companion diagnostic (16). The current methods for health technology assessment in Australia evaluate the drug and associated diagnostic test separately and therefore do not fully capture the benefits of using the therapeutic and test combined. In addition, the review also noted that diagnostic tests generally have a more limited evidence base than therapeutics, which can often make an evaluation of a diagnostic test more methodologically complex and time consuming. This poses a problem for policy makers who need to produce guidance simultaneously on the therapeutic and associated companion diagnostic to ensure patient access. These challenges are not unique to Australia but are faced by many other countries, including the United States, Canada, and many countries in Europe (17). Some countries have made more progress than others in adapting their methods to accommodate the growing number of therapeutics associated with a companion diagnostic entering the market. For instance, in response to the review of health technology assessment processes in Australia, the government created the Health Technology Assessment Access Point (HTAAP) to coordinate, manage, and monitor companion diagnostics through the Australian Government health technology assessment processes (18). The HTA body in Germany, Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWIG), is also trying to simplify the process of evaluating companion diagnostics but as yet, there is no standardized approach or published methodology. Although a number of countries may not have formal health technology assessment processes, many use a comparative analysis of efficacy of pharmaceuticals compared with alternatives for reimbursement decisions. Cost-effectiveness is also an established criterion for reimbursement in Australia, Canada, and the United Kingdom, and is increasingly used in other countries for decision making. A key issue for many countries is that the experience of evaluating diagnostic technologies is limited compared with that of pharmaceuticals. Payers of pharmaceuticals are often different from payers of diagnostics and the value of a diagnostic may be perceived differently from that of a pharmaceutical, leading to a need for coordinated decision making. The Australian HTAAP and NICE will provide a model to address these issues.

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Writing, review, and/or revision of the manuscript: S.K. Byron, N. Crabb, E. George, M. Marlow, A. Newland
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.K. Byron, M. Marlow

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