PRMA Insights:
Market Access Success for Companion Diagnostic–Drug Pairings in Oncology

This PRMA Insights provides in-depth understanding of the evolving market access environment for therapeutic–diagnostic combinations, and the challenges and opportunities that it presents. Critical analysis developed by industry-experienced experts with comprehensive cross-functional knowledge is supported by actionable strategic insights, providing a cornerstone on which to build an innovative and integrated market access strategy.

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Companion diagnostic–drug pairings require a more innovative approach to market access than for a targeted therapeutic alone. This requires in-depth understanding of the unique challenges and obstacles faced from both regulatory and reimbursement perspectives. Such challenges include different and often disconnected reimbursement pathways for the test and drug, appropriate clinical trial design, and payors’ and clinicians’ attitudes to the value of such tests. It is imperative that the requirement for a test does not become a barrier to use of the drug – through lack of or delayed reimbursement, access to the test, or at the prescribing level.

With critical analysis of the current and evolving market access environment, supported by actionable strategic insights, this is a key resource that provides a solid basis for planning the market access strategy for your therapeutic–diagnostic combination.

Whilst focusing on oncology, where the importance of companion diagnostic testing is growing rapidly, this strategic resource is also applicable to addressing challenges in other therapeutic arenas.

“This is the most insightful assessment of market access issues for companion diagnostics that I have seen”

Diagnostic manufacturer comment to their biotech partner
Introduction

The pairing of a targeted drug with a companion diagnostic test may be considered favorably by payors looking to limit access to subpopulations of patients in whom the drug is most cost-effective or where unmet need is greatest. However, the requirement for the test introduces a host of challenges in terms of market access. Both the drug and diagnostic manufacturers must fully understand the issues in order to develop an integrated market access strategy.

Both partners must be fully cognizant of the data requirements to support reimbursement of the test as well as the therapeutic — where these overlap and where they differ. This in turn informs the clinical trial strategy, data analysis, and health economics strategy, and any additional studies that may be needed to generate data to support the value proposition of the pairing. Clearly, this requires a highly coordinated approach.

The issue of who pays for the test is not resolved in many jurisdictions. Both partners need to understand the mechanisms for reimbursement of the test in different markets, and how this relates to reimbursement of the drug — if indeed it does. It is also imperative that both parties understand the potential post-marketing challenges, to ensure that the requirement for a test does not become a hurdle to prescription of the drug.
About this resource

PRMA Insights: Market Access Success for Companion Diagnostic–Drug Pairings in Oncology is an invaluable resource for manufacturers faced with developing an innovative and integrated market access strategy. The framework set out below is used to analyze the current dynamics of the oncology market for targeted products with companion diagnostics and how this is evolving, with actionable strategic insights to inform the clinical development pathway and market access strategy.

**Development and validation of companion diagnostic tests**

Chapters 1–3 provide essential background relating to biomarkers as the basis for companion diagnostic tests, development and validation of the test, and regulatory issues.

**Key issues in developing the market access strategy for drug–test pairings**

Chapter 4 provides a bridge between the technical aspects of the first three chapters and the more specific and detailed discussion of the processes in individual countries and how targeted drug–test pairings have been evaluated. This chapter discusses the key issues that manufacturers face and themes that resonate with multiple stakeholders on three broad themes: clinical development and regulatory considerations, HTA and reimbursement, and post-marketing considerations.

**Evaluation and reimbursement of tests and pairings in the major markets**

Chapters 5–11 explain the reimbursement pathways for tests and therapeutics in each of the scope countries (Australia, US, EU major 5), and the evidentiary requirements. These chapters also draw together the key issues from the HTAs of the scope products in each jurisdiction and other factors that influence reimbursement and delivery of diagnostic tests. Each chapter includes actionable strategic insights that can be incorporated into development of the market access strategy.

**Case studies**

The case studies in Chapters 12–15 provide a detailed analysis of the development of the drug and test, and their evaluation by HTA and P&R agencies. Each chapter includes key learnings that will help manufacturers to anticipate and plan for issues that arise during clinical development and in considering the market access strategy.

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**Key learnings**

Issues that are critical to consider in developing the market access strategy are highlighted in Chapter 2 and the case studies and are summarized in the Chapter summaries and Executive summary.

**PRMA Strategic Insights**

Developed by our in-house experts, PRMA Strategic Insights provide critical advice to manufacturers in planning their market access strategy in the key markets. These are listed in the Chapter summary and Executive summary, as well as being presented in context at relevant places in the text.
Case studies

- **EGFR and ALK testing in NSCLC**  
  (Chapter 12)  
The role of EGFR as a biomarker, and the importance of EGFR mutation status (rather than EGFR expression level or gene copy number) as a predictor of response to Iressa and Tarceva, emerged after regulatory approval. This chapter illustrates the “catch-up” approach required in terms of further trials and subsequent label changes. This contrasts with the coordinated – and rapid – development of Xalkori and ALK testing, which supported simultaneous approval of the drug and test.

- **BRAF mutation testing in melanoma**  
  (Chapter 14)  
The therapeutic (Zelboraf) and the diagnostic (BRAF V600 mutation test) were co-developed; this chapter illustrates how incorporation of the test into pivotal trials can support rapid regulatory approval – of both the test and the drug. The FDA label for Zelboraf includes the requirement for use of an FDA-approved test, essentially meaning the Roche cobas test, as this is the only approved test. This chapter also illustrates how the HTA of a co-developed drug contrasts with the evaluation of drugs when the test has been developed separately.

- **KRAS mutation testing in colorectal cancer**  
  (Chapter 13)  
KRAS mutation status emerged as a stronger predictor of response than EGFR expression status during trials of Erbitux and Vectibix. This was possible through retrospective analysis of tumor samples, but also required post hoc analysis and thus presented a greater challenge in terms of regulatory and payor scrutiny. This chapter illustrates some of the difficulties of this “retrospective” approach – and what can be learnt in terms of being prepared for a similar scenario emerging during trials.

- **HER2 testing in gastric cancer**  
  (Chapter 15)  
This chapter illustrates a fourth scenario in which an established drug and companion diagnostic test are developed for a new indication; in this case HER2 testing, originally developed to inform use of Herceptin in breast cancer, was developed to inform use of Herceptin in gastric cancer. This required modification and validation of the established test for a different tumor type with different characteristics, which presents some similar and some different challenges from the scenarios above.

**Example issues**

This resource had been written by a core team of in-house experts with in-depth knowledge and hands-on experience of the market access and pricing and reimbursement of oncology products across the scope countries. This is supported by input from payors, health economists, pathologists, and international and national opinion leaders, giving a truly cross-functional perspective.

- What is the reimbursement pathway for the diagnostic?
- What are realistic price expectations for the test within the current reimbursement frameworks?
- How will the test be considered by HTA agencies, if at all? When is this connected or disconnected from HTA of the drug?
- How do the evidence requirements for the drug and test differ between countries?
- How will use of the therapeutic be affected if the diagnostic test is not reimbursed, or reimbursement is delayed?

- Will inclusion of a companion diagnostic in the product label be perceived as an additional barrier to prescription of the therapeutic, leading clinicians towards other products? How can this be addressed proactively?
- How should the cost of testing be incorporated into cost-effectiveness and budget impact models?
- Can the manufacturer of the therapeutic circumvent potential problems by paying for the test themselves? Has this precedent already been set in some markets?
- How can manufacturers “protect” the commercial test from being replaced by “home brew” tests that may perform inadequately? How do other commercial tests perform in selecting eligible patients?
- What are the trade-offs between a better chance of market access in a small targeted population versus slower or more limited approval but in a larger population?
- How should the companion diagnostic be incorporated into risk-sharing schemes?
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References
Author profiles

This resource has been written a core team of in-house experts with in-depth knowledge and hands-on experience of the market access and the P&R of oncology products across the scope countries. This is supported by extensive secondary and primary research, and input from payors, health economists, pathologists, and international and national opinion leaders.

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Clare has more than 10 years’ experience in R&D and marketing of biotechnology and medical devices, particularly diagnostics and personalized medicine, and leads applied research on market access for products with companion diagnostics. Clare has worked in a number of therapy areas including oncology, respiratory disease, and allergy. Clare holds a PhD in Molecular Biology from the University of Warwick, an MBA from the University of Oxford, and a Diploma in Health Economics from the University of York.

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Dr Helen Barham
Helen has led the content development of multiple PRMA Insights titles, working closely with authors and contributors. She has broad knowledge of market access and P&R, combined with expertise in a wide range of therapeutic areas and over 15 years’ experience in medical publishing. Helen has a PhD in Pharmacology from the University of Sheffield, which included work on pharmacogenetics, and conducted postdoctoral research in oncology at the former MRC Radiobiology Unit near Oxford.

Michael Aristides
Michael is based in Australia and has more than 20 years’ experience in HEOR. He specializes in demonstrating the value of health technologies and in the assessment of cost-effectiveness, planning research activities and data collection, and designing and reviewing models and submission dossiers. He has served as deputy director of the Pharmaceutical Evaluation Section in the Australian Federal Health Department, and was part of a multidisciplinary team responsible for implementing the Australian Pharmacoeconomic Guidelines.
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Monika has more than 15 years’ experience in the pharmaceutical industry and statutory health insurance in Germany and was formerly responsible for market access strategy at GlaxoSmithKline in Germany, the UK, and Europe for a broad range of disease areas, including oncology, neurology, urology, and vaccines. Monika has in-depth knowledge of the German healthcare system, the benefit assessment system, and the AMNOG legislation. She holds an MSc in Health Economics from the University of York.

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The development of a drug with a companion diagnostic is more complex than that for a targeted drug alone, and a multitude of issues need to be considered across stages of development, from clinical and regulatory, through KIB and reimbursement, to post-commercialization. Manufacturers used to developing value propositions for targeted drugs face several additional complexities around the development, validation, regulatory, and reimbursement of the test. Regulators and health technology agencies are beginning to develop their thinking and methodologies to support the development of these co-dependent technologies; manufacturers need to mobilize the actions and decisions of the agencies to understand how they are evolving. Achieving reimbursement of the therapeutic but not the test could have commercially disastrous consequences. We believe that achieving coordinated reimbursement of the two elements represents a new market access model that manufacturers need to address proactively if physicians and patients are to gain access to their products.

The first three chapters have discussed the process of identifying biomarkers and development of the companion diagnostic test, the structure of clinical trials, and the regulatory requirements for the test. This chapter draws together the key challenges that manufacturers need to consider in the development of drug-diagnostic pairings. It is written from the market access perspective but includes issues at various points of the development and marketing process, based on the framework set out in Figure 4.6. None of the issues can be considered in isolation and the issues considered under clinical development will necessarily be impacted by success of reimbursement and market access. Thus, the aim of this chapter is to provide a comprehensive picture across the development life cycle and to identify critical decision points between the various relevant stakeholders.

4.1 Case studies for development of companion diagnostic tests

In an “ideal” companion diagnostic, the biomarker is identified early in clinical development, and the test is developed in parallel with the drug and validated alongside it. The recent examples of Erbitux and Herceptin are illustrative. Erbitux is an antibody that targets the epidermal growth factor receptor (EGFR), and was approved for the treatment of colorectal cancer for patients with specific somatic alterations in the KRAS gene.

Adaptive clinical trial design is increasingly recognized as a valid method for improving the efficiency of studies (e.g., shorter duration, fewer patients) and is more likely to demonstrate any effect of the drug in a more efficient and cost-effective manner, for patients who have either identified or unselected (or uncharacterized) subgroups. The DNA reflection paper on pharmacogenomic biomarkers in clinical development and patient selection acknowledges that adaptive design may be applicable to trials of drugs with potential companion diagnostic (WMA, 2010). The FDA (2010) issued a draft guidance on adaptive designs in February 2010, to provide guidance to manufacturers in planning and conducting studies, and to ensure efficient FDA review (FDA, 2010). This document gives advice on aspects of adaptive design for clinical, statistical, regulatory, and pharmaceutical reasons, and is intended to: (1) assist researchers in the design and development of adaptive clinical trials to improve efficiency in clinical research; (2) provide general advice on adaptive design; and (3) discuss the regulatory considerations of adaptive trials. The goal of the FDA is to achieve an efficient procedure for obtaining and reviewing data in the context of drug development.

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The first three chapters have discussed the process of identifying biomarkers and development of the companion diagnostic test, the structure of clinical trials, and the regulatory requirements for the test. This chapter draws together the key challenges that manufacturers need to consider in the development of drug-diagnostic pairings. It is written from the market access perspective but includes issues at various points of the development and marketing process, based on the framework set out in Figure 4.6. None of the issues can be considered in isolation and the issues considered under clinical development will necessarily be impacted by success of reimbursement and market access. Thus, the aim of this chapter is to provide a comprehensive picture across the development life cycle and to identify critical decision points between the various relevant stakeholders.

4.1 Case studies for development of companion diagnostic tests

In an “ideal” companion diagnostic, the biomarker is identified early in clinical development, and the test is developed in parallel with the drug and validated alongside it. The recent examples of Erbitux and Herceptin are illustrative. Erbitux is an antibody that targets the epidermal growth factor receptor (EGFR), and was approved for the treatment of colorectal cancer for patients with specific somatic alterations in the KRAS gene.

Adaptive clinical trial design is increasingly recognized as a valid method for improving the efficiency of studies (e.g., shorter duration, fewer patients) and is more likely to demonstrate any effect of the drug in a more efficient and cost-effective manner, for patients who have either identified or unselected (or uncharacterized) subgroups. The DNA reflection paper on pharmacogenomic biomarkers in clinical development and patient selection acknowledges that adaptive design may be applicable to trials of drugs with potential companion diagnostic (WMA, 2010). The FDA (2010) issued a draft guidance on adaptive designs in February 2010, to provide guidance to manufacturers in planning and conducting studies, and to ensure efficient FDA review (FDA, 2010). This document gives advice on aspects of adaptive design for clinical, statistical, regulatory, and pharmaceutical reasons, and is intended to: (1) assist researchers in the design and development of adaptive clinical trials to improve efficiency in clinical research; (2) provide general advice on adaptive design; and (3) discuss the regulatory considerations of adaptive trials. The goal of the FDA is to achieve an efficient procedure for obtaining and reviewing data in the context of drug development.

PRMA Insights: Market Access Success for Companion Diagnostic–Drug Pairings in Oncology
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12.2 Treatment

Radiation platinum-based chemotherapy for advanced disease provides response rates of 30–40%, but median survival of 8–11 months without compromising HRQoL (Villaruz and Socinski, 2011). However, the use of the lapatinib and trastuzumab combination in patients with high HER2 levels has improved outcomes for patients with breast cancer (Section 15.4.6.3). The addition of bevacizumab to the standard platinum-based chemotherapy regimen improved tumor response rates, time to progression, and survival (Jenkins et al., 2016; Nish et al., 2016; Sandler et al., 2006). In all trials, HER2 status was determined by IHC and/or FISH, using predefined cutoffs for clinical trial eligibility (Sections 15.4.6.3 and 15.6.3). The HER2 test was not revalidated by the IHC and/or FISH assays and not linked to the trial arm during the trial period (Wék et al., 2010). HER2 status was determined by IHC and/or FISH, using predefined cutoffs for clinical trial eligibility (Sections 15.4.6.3 and 15.6.3). The HER2 test was not revalidated by the IHC and/or FISH assays and not linked to the trial arm during the trial period (Wék et al., 2010). HER2 status was determined by IHC and/or FISH, using predefined cutoffs for clinical trial eligibility (Sections 15.4.6.3 and 15.6.3). The HER2 test was not revalidated by the IHC and/or FISH assays and not linked to the trial arm during the trial period (Wék et al., 2010).

12.3 Molecular alterations in NSCLC

It is estimated that more than half of NSCLC tumors have a known oncogenic driver (e.g., EGFR, BRAF, ALK, MET, ROS1, ALK, ROS1, etc.; et al., 2010). Figure 12.3 illustrates molecular alterations in NSCLC.

Key learnings: gastric cancer

The case of Herceptin illustrates a key trend in the development of companion diagnostic tests that a biomarker and test must be validated and approved in individual tumor types. Many of the key learnings are discussed more generally in Chapter 5.

- The FDA stated that, because of the differences between gastric and breast tumor tissues, tests had to be approved separately for use in each tumor type. Similar, CE-marking is also required for each tumor type (Section 15.5).
- The degree of heterogeneity of tumors is to be considered in the case of gastric cancer, heterogeneity is greater than in breast cancer. Thus, biopsies samples need to be taken from multiple sites within the tumor, to ensure that all eligible patients are identified (Sections 15.4.5 and 15.4.6).
- Measurement should be replaced in early trials, to determine whether gene amplification translates into protein overexpression, and thus which is the better biomarker or whether both tests are required (Sections 15.4.6.3 and 15.6.3). The markers are the most relevant for clinical use. The biomarkers of choice are the HER2 IHC assay (Section 15.5). The core of the companion diagnostic test is the HER2 assay, which should be performed on the tumor tissue. The HER2 assay should be performed on the tumor tissue. The HER2 assay should be performed on the tumor tissue. The HER2 assay should be performed on the tumor tissue. The HER2 assay should be performed on the tumor tissue. The HER2 assay should be performed on the tumor tissue.
**How to use this resource**

The diagram illustrates just a few ways in which this resource can support your planning.

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<th>Understand how companion diagnostic tests are considered, used, and reimbursed</th>
<th>All chapters</th>
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<tr>
<td>Inform the clinical development program (subgroups, comparators, test strategy)</td>
<td>Chapters 2–4, Country chapters (particularly Australia [Ch 5] and UK [Ch 7]); case studies</td>
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<tr>
<td>Develop a testing strategy for the clinical trial that will translate into the real-world setting</td>
<td>Chapter 2, Country chapters (particularly Australia [Ch 5] and UK [Ch 7]); case studies</td>
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<td>Understand how to work with your diagnostic partner to develop a relevant and appropriate evidence base that meets payors' expectations</td>
<td>Chapters 4, 12 (Xalkori case study), 14 (Zelboraf case study)</td>
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<tr>
<td>Integrate the cost of testing into economic models</td>
<td>Chapters 4, 5–11 (particularly Chapters 5 [Australia] and 7 [UK])</td>
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<td>Competitor approaches</td>
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<td>Develop and inform value propositions</td>
<td>Chapters 4–15</td>
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<td>Internal education</td>
<td>All chapters</td>
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<tr>
<td>Cross-functional collaboration</td>
<td>All chapters</td>
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**Understand:**

- The need for an integrated market access strategy for the drug and test
- How diagnostic tests are evaluated in different jurisdictions
- How tests are reimbursed and the implication for pricing
- Driving factors behind adoption of branded versus “home brew” tests
- Practical barriers to use of tests (availability, clinicians’ prescribing behavior)

**Understand:**

- FDA and EMA expectations in terms of clinical trial design, subgroup analysis, and efficacy, safety, and post-marketing studies
- Reimbursement/HTA agencies’ evidentiary requirements to support the test or drug–test pairing, and how these differ between markets
- Key learnings from the strategies used for establishing pairings – what worked, what didn’t, and why
- Importance of subgroup analysis (both *a priori* and potentially *post hoc*) and how this is best conducted and powered to meet agencies’ expectations whilst retaining flexibility should the biomarker strategy change

**Understand:**

- Sample handling, storage, archiving, retrieval, and consent
- Key issues to consider when transferring an established test into a different tumor type
- How testing used in clinical trials transfers into clinical practice
- How different strategies were considered by payors in terms of:
  - number and type of test
  - sequencing of tests
  - parallel vs sequential testing

**Understand:**

- How evolving requirements are changing the market access paradigm
- The data requirements to support both the test and the drug
- Where the two development pathways are integrated and coordinated and where they are disconnected, and the implications for evidence generation
- How the test supports the drug in HTA
- The reimbursement framework for each element
- Realistic pricing expectations for the test

**Understand:**

- How test performance needs to be factored into cost-effectiveness analysis
- Which costs should be included in cost-effectiveness and budget impact models
- How requirements for cost-effectiveness analysis may differ when the drug and test have been developed separately or co-developed
- Requirements for market-relevant estimates of biomarker prevalence

**Understand:**

- The impact of the companion diagnostic on economic models
- HTA feedback on eligible populations
- Development and evolution of strategies for subgroup analysis and reimbursement positioning

**Understand:**

- Understand the value propositions for established drug–test pairings and their acceptance by payors
- Develop an integrated drug–test value proposition that proactively addresses the market access paradigm

**Use as educational materials to enable colleagues to become familiar with the evidentiary requirements for the test and drug–test pairings and the market access challenges**

**Understand trade-offs and implications for market access when designing the clinical trial program for the drug–test pairing**

- Ensure common understanding across the organization in order to develop a single integrated strategy that meets various stakeholders’ needs in terms of:
  - Market access challenges and opportunities
  - HEOR strategy development
  - Regulatory expectations: indication, trial design
  - A consistent value proposition that supports both market access and marketing
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