COMPANION DIAGNOSTICS: Challenges for developing, regulating and coverage decision making at the beginning of the era of personalised medicine

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WORKSHOP REPORT
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Section 1: Executive Summary

Background to the Workshop

It has been suggested that improved knowledge of complex biological systems combined with the convergence of new technologies will lead to a “P4” medicine model: predictive, personalised, preventative and participatory. Indeed, this convergence of biomedical technology is key to improving the safety, efficacy and effectiveness of medicines and provides new approaches to prevention, screening, diagnosis, therapy, monitoring and management of disease.

The advent of advanced genomic, proteomic and metabolomic technologies are enabling diseases to be interrogated with increasing sophistication, leading to the sub-setting of both diseases and patient populations. In addition, in response to the rising challenge of finding safe, affordable drugs of ever-increasing effectiveness distributed widely across the general patient populations, the pharmaceutical industry has shifted from a “blockbuster” to “niche-buster” model. The development of companion diagnostics to define the populations who are most appropriate for these “precision” medicines would seem to be logical and in the best interests of regulators, coverage bodies and clinicians. These diagnostics should help in patient selection, reduce safety risks and aid in value-based pricing. However, despite their promise, industry incentives for the development of companion diagnostics may have been lacking and in practice there are a relatively small number in use. This is expected to change in the near future, as many companies have announced a focus on developing companion genomic diagnostics for patient characterisation, heralding an upcoming wave of precision therapies in the future.

In order for a shift to occur in the development and clinical utilisation of companion diagnostics, clarity must be achieved regarding methodologies for their regulation as well as for the demonstration of their value in the health technology assessment setting. This Workshop sought to identify both the opportunities and the barriers to the use of companion diagnostic treatments by looking at key issues surrounding their development, regulation, reimbursement and clinical uptake.

Workshop Objectives

- **Identify both the opportunities and the barriers** to the integration of companion diagnostic evaluations into patient care decision-making by looking at key issues surrounding their development, regulation, reimbursement and clinical uptake.
- **Discuss the effect of different scenarios** for utilisation of companion diagnostics on patient access to new medicines of agreed high medical and economic value.
- **Make recommendations on appropriate pathways** for enhancing the opportunities and overcoming barriers to facilitate the appropriate and effective use of companion diagnostics in patient care decision making.

Introduction

Challenges abound in the development, regulation and reimbursement of medicines, including lengthy and expensive product development cycles, relatively low success yields in screening compounds and clinical trials and struggles to identify likely safety issues from signals in early development. Centre for Innovation in Regulatory Science (CIRS) Executive Director Lawrence Liberti invited Workshop participants to examine the growing role for companion diagnostics in addressing these issues and in contributing to the efficient use of society’s investment in healthcare. Topics proposed for discussion included the refinement and optimisation of regulatory pathways, clinician training and decision-making paradigms for the reimbursement of stratified medicine.

Key points from presentations

Presenting regulators with robust benefit-risk and value propositions, companion diagnostics can expedite market access for important new medicines; however, unexpected challenges to their use have emerged. Using the examples of the 2011 FDA approvals for XALKORI (crizotinib) for ALK+ advanced non-small cell lung cancer NSCLC in five months and ZELBORAF (vemurafenib) for BRAFV600E+ metastatic melanoma in three and one half months, Day 1 Chairman, Dr Peter Honig, Head, Global Regulatory Affairs and Patient Safety, AstraZeneca,
USA explained that the uptake for these new medicines has faced issues that were among those to be considered at this Workshop, ranging from tissue biopsy availability to emerging competition and the lack of platform diagnostics.

**SESSION: SETTING THE SCENE**

The use of companion devices should be based on transparent, reasonable, evidentiary, analytical standards by which to evaluate their relevance, validity, feasibility and timeliness. **Dr Ansgar Hebborn**, Head – Global Market Access Policy, **F. Hoffmann-La Roche Ltd, Switzerland** opined that a properly functioning pricing and reimbursement system could be used to guide research and development activities, providing financial incentives to develop a level of evidence for companion diagnostics appropriate to satisfy all stakeholders. But currently, poorly valued tests are poorly reimbursed, with little incentive to develop appropriate supportive studies, resulting in a lower level of evidence and poorly characterised utility and ultimately reinforcing the low value.

**SESSION: BARRIERS AND OPPORTUNITIES IN DRUG-DEVICE COMBINATIONS**

Developing companion diagnostic products with demonstrated analytic and clinical validity and clinical utility at launch in line with the stages of pharmaceutical development remains a challenging and iterative process. **Dr Greg Rossi**, Vice President, Payer and Real World Evidence, AstraZeneca, UK outlined the critical next steps in this process as the alignment of processes for health technology assessment, coverage and reimbursement, the design of assessment standards that encourage the adoption of emerging technologies, the demonstration of the clinical utility of co-dependent technologies, the development of linked databases to allow for real-world effectiveness and coverage with evidence development to address evidence uncertainty and stimulate primary healthcare adoption and the consideration of the value of rewarding innovation to maximise potential health outcomes for patients.

Companion diagnostics are associated with the potential for improved efficacy for medicines in patients selected as most likely to benefit while excluding those least likely to benefit. There is also the potential to test out risk and exclude those most likely to be harmed, with the result that testing has a critical effect on the safety and effectiveness of targeted therapies, altering the benefit-risk model. Because the US FDA understood that the benefit-risk assessment for a targeted therapy requires an accurate and reliable companion diagnostic, the *Draft Guidance for Industry and FDA Staff; In Vitro Companion Diagnostic Devices* was published in July 2011. **Dr Elisabeth Mansfield**, Director, Personalized Medicine Staff, Office of In Vitro Diagnostic Devices, Center for Devices, Food and Drug Administration, USA reported that a final version of this document will be available soon.

According to **Kimby Barton**, Director of the Bureau of Cardiology, Allergy and Neurological Sciences, Health Canada, biomarkers reflect a physiological or pathological process and their validation is generally based on correlation with real-world experience. Therefore, translating a positive outcome into a clinical benefit can take some time to demonstrate and reviewers are not always comfortable with accepting the biomarker in the absence of such real-world data. Relevant questions that arise among Canadian reviewers include the level of validation achieved for biomarkers; when and where the information concerning the biomarker should be included in the product monograph; if the test or kit is readily available in Canada and whether patient access to the medicine will be inappropriately restricted based on patient sub-typing.

**Dr Naomi Aronson**, Executive Director, Technology Evaluation Center, Blue Cross and Blue Shield Association, USA reported on the pilot programme of Premera Blue Cross of Washington and Alaska in which drugs were assigned to one of four flexible formulary tiers by a multidisciplinary Value Assessment Committee based on the therapy’s cost-effectiveness. Although Dr Aronson agreed that providing incentives for innovation in companion diagnostics may be needed, she cautioned that health plans are likely to regard this funding as a business matter between partners and to be sceptical of higher payment based on an industry-proposed assessment of a companion diagnostic’s value.

Common issues in the design of many controlled clinical efficacy trials include their failure to capture endpoints that may be relevant to a broad user population and to address clinically relevant heterogeneity. **Jean Slutsky**, Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, Dept of Health and Human Services, USA, stated that although...
nonrandomised studies will never supplant the need for well-designed randomised clinical trials; they can enrich understanding of how patients treated in real-world practice differ in characteristics from those in trials; examine whether trials results are replicable in community settings; explore sources of differences in safety or effectiveness arising from variation among patients, clinicians and settings and produce a more complete picture of the potential benefits and harms of a clinical decision for individual patients or health systems.

Numerous factors will dictate payer participation in value-based pricing for combination diagnostic therapies including the nature of real-world evidence of improved quality of outcomes and their effect on total cost of care. Brian Kelly, Group President, Product Value Strategy, OptumInsight, United Health Care Group, USA said that value pricing will be dependent on a variety of factors including acquisition costs, testing specificity and sensitivity, subpopulation size and the rate of adoption and appropriate use of the test.

In the United States, coverage decisions for the diagnostic in drug-diagnostic combinations with regulatory approval are not usually problematic as the drug-test combination faces the hurdles of comparative effectiveness and cost effectiveness as a pair. Left to itself, however, Dr Bruce Quinn, Senior Health Policy Specialist, Foley Hoag LLP, USA explained that the diagnostic test faces both longstanding biases that tests are overused and automated level-of-evidence hurdles in HTAs that are sometimes disproportionate to established scientific facts.

SESSION: PRACTICAL CONSIDERATIONS FOR DEVELOPING COMPANION DIAGNOSTICS

The Centre for Medical Technology Policy (CMTP) has organised a technical working group to develop an effectiveness guidance document to provide specific recommendations on the design of prospective studies of molecular diagnostics to inform decisions by patients, clinicians and payers. Dr Patricia Deverka, Senior Research Director, Centre for Medical Technology Policy (CMTP), USA said that more informative studies for clinical and policy decision making, including meaningful outcomes for patient decision making and the development of practice guidelines and coverage and reimbursement decisions were among the outcomes envisioned for this guidance document.

SESSION: HORIZON SCANNING: AS WE MOVE INTO A WORLD OF PERSONALISED MEDICINE WILL COMPANION DIAGNOSTICS BECOME THE NORM?

After outlining some of the multiple pharmacoeconomic methodological challenges in personalised medicine, Dr Lou Garrison, Professor, Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy; Adjunct Professor, Departments of Global Health and Health Services, University of Washington explained that changes in public policy to be considered from a values-creation perspective include flexible and value-based pricing and reimbursement; incentive-oriented reforms linking pricing and reimbursement for drugs and diagnostics to value creation; a strong, consistent, predictable intellectual protection environment and a change from a narrow focus on pharmacogenomics technologies to a broader consideration of biomarkers.

Discussing the possibility of a combined post-licensing pathway for medicines and companion diagnostics, Prof Hans-Georg Eichler, Senior Medical Officer, European Medicines Agency remarked that after licensing, both regulators and health technology assessment (HTA) assessors continue to need evidence to support treatment decisions using the approved medicine and companion diagnostic as well as evidence for the performance and utility of the test-drug combination. Unlike payers, however, regulators do not require additional information that supports stratification of recipients to maximise efficacy or its comparative or relative effectiveness.

When a treatment and a diagnostic are used in combination to target a subgroup of patients, the total value created depends on the combination. Some portion of the value needs to be attributed to one or the other but current attribution is essentially arbitrary, presenting a challenge to the concept and operation of valued-based reward for both diagnostics and treatments. Prof Adrian Towe, Director, Office of Health Economics, UK, explained that it is essential that both diagnostic-dedicated and drug HTA processes use a common, consistent and comprehensive approach to assessing value. This will provide a clear incentive to companies to invest in evidence collection to raise the standard of clinical utility data available to support the case for using a test.
Recommendations from across the Syndicates

1. Employ a broad approach in diagnostic strategies, understanding the value of what remains unknown internally while developing external capabilities.

2. Understand the economics of external diagnostic partnerships; the relatively low investment costs of employing external expertise should be considered in the cost of a pharmaceutical development plan.

3. There should be the option to develop plans to retrospectively analyse clinical trial data including pro-actively addressing informed consent issues; these analyses may mitigate downstream safety issues.

4. Support post-approval companion diagnostics that may have a significant positive impact on a product lifecycle.

5. Consider joint HTA-regulatory consultations and include representatives from both of these stakeholders in advice sessions and review processes for the drug-diagnostic combination.

6. Align development timelines (which will differ for the drug and the diagnostic) and key consultation points.

7. Balance evidence uncertainty versus the need for timely access to new combination therapies through the use of post-launch commitments.

8. CIRS should continue to monitor the regulatory-HTA pathways for these combinations and revisit issues following the publication of anticipated new EU regulations on devices and clinical trials.

9. Investigators should proactively raise the issue of ongoing patient consent for analysis of clinical trial biosamples with Investigational Review Boards, Ethics Committees, regulators, Data Safety Monitoring Boards and other relevant parties, including privacy officers.

10. Explore the opportunity to provide appropriate incentives for companion diagnostic development and innovation.

11. Align quality standards and guidance for laboratory-developed (home-brew) tests among regulators and payers.

12. All appropriate stakeholders should engage in a concerted effort to change the infrastructures, organisations and behaviours surrounding the use of companion diagnostics through the use of incentives.
## Workshop Programme

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<td>Industry perspective</td>
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<td>HTA perspectives</td>
<td>Dr Naomi Aronson, Executive Director, Technology Evaluation Center, Blue Cross and Blue Shield Association, USA</td>
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<td>Technology assessment needs for the USA</td>
<td>Jean Slutsky, Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, Dept of Health and Human Services, USA</td>
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<td>Coverage decision-perspective</td>
<td>Brian Kelly, Group President, Product Value Strategy, OptumInsight, United Health Care Group, USA</td>
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<td>US coverage decision-maker perspective</td>
<td>Dr Bruce Quinn, Senior Health Policy Specialist, Foley Hoag LLP, USA</td>
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## Session: Syndicates

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### Syndicate A: What strategies should companies employ for the effective development of drug-diagnostic combinations?

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<td>Dr Anant Murthy, Executive Director, Global Market Access and Pricing, Celgene Corporation, USA</td>
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### Syndicate B: Can regulatory and coverage clinical requirements, in particular, trial design and validation, be aligned?

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### Syndicate C: Companion diagnostics are challenging existing review processes. Are the regulatory and reimbursement processes for assessment fit for purpose? How can these be improved?

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<td>Rapporteur</td>
<td>Dr Rizwana Sproule, Executive Director, Therapeutic Area Head, Global Regulatory Affairs and Safety, Amgen Inc, USA</td>
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## Day 2: Wednesday 19 September 2012

### Chairman’s introduction

**Prof Sir Alasdair Breckenridge**, Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), UK

### Session: Horizon scanning: as we move into a world of personalised medicine will companion diagnostics become the norm?

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### Session: Feedback from Syndicates

| Panel discussion | Dr Lucinda Orsini, Group Director, GHEOR Oncology and Pharmacodiagnostics, Bristol-Myers Squibb, USA  
Kimby Barton, Director of the Bureau of Cardiology, Allergy and Neurological Sciences, Health Canada  
Dr Naomi Aronson, Executive Director, Technology Evaluation Center, Blue Cross and Blue Shield Association, USA |
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Section 2: Syndicate Discussions

Three Syndicate Discussion Groups were asked to discuss aspects of companion diagnostics and provide strategies and recommendations for change.

Syndicate Discussion A

What strategies should companies employ for the effective development of drug-diagnostic combinations?

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Background

Drug-diagnostic combinations are growing in importance. Companion diagnostics may become an essential piece of the pharmaceutical development tool kit as they represent a way of identifying patients who can be helped by particular drugs (and patients who cannot) as well as a method of aiding regulatory and HTA agencies and companies in decisions regarding the efficacy, safety and effectiveness of a new therapy.

The combination of the diagnostics and pharmaceutical businesses should also improve R&D effectiveness and the clinical outcomes of disease treatment. However, the use of diagnostics also has challenges for companies, including the fact that there are a number of potential routes for their development, that is, they may be developed as a proprietary endeavour linked to a specific medicine or as a commodity readily available from multiple third parties. For the former option to occur, it will be essential for major pharmaceutical companies to develop advanced diagnostics capabilities. Although this will be primarily an internal strategic decision by companies, it may be worthwhile to consider the implications, issues and opportunities and to decide if partnering with a speciality diagnostic company is a more efficient development route.

The objectives of this Syndicate group were to discuss each of the following options in terms of the different strategies and the regulatory and coverage pathway implications, issues and opportunities:

- Novel drug and novel diagnostic, both being developed by the same company
- Novel drug and novel diagnostic, separate companies developing the drug and diagnostic
- Diagnostic development that occurs in the post-approval period, independent of the initial drug development plan.

Questions for consideration

- What are the challenges, benefits and implications for companies developing diagnostics in parallel with new drugs prior to registration?
  - What are the implications for diagnostics developed in-house alongside new drugs?
- How can the collaboration between the drug and speciality device/diagnostic company be managed when there are different regulatory pathways, mindsets and business strategies?
- Are there other approaches that can facilitate the co-development of diagnostics and therapeutics and if so, what are the implications of this approach?
  - Are there roles for pre-competitive consortia, public-private partnerships or a “virtual” R&D approach?
- Regarding development of companion diagnostics for drugs that are already on the market
  - What are the drivers for such development to be conducted?
  - What are the implications for intellectual protection, marketing and regulatory and reimbursement issues?
What are the next steps that should be undertaken to facilitate more efficient development of drug-diagnostics combinations?

Critical issues

It was not clear to this Syndicate that industry fully understands the regulatory perspective on companion diagnostics. Members expressed a desire for greater clarity regarding the different regulatory review divisions and their roles and responsibilities as well as the diversity in pathways for submission/review.

The commercial sustainability of the low-margin, high-volume diagnostic business within industry is questionable, particularly with existing health system constraints such as those imposed by diagnostic-related group (DRG) codes. However, challenges also exist for manufacturer/diagnostic partnerships such as a lack of alignment on incentives and the necessity to develop often complicated contracts. Pharmaceutical manufacturers must develop internal alignment on issues such as when and how to bring diagnostic science into the product development stream and the goal of the diagnostic: is it to enable regulatory approval, to add to the commercial viability or ethical nature of a product by showing enhanced efficacy in certain populations etc? In addition, there are built-in biases and financial ramifications against adding complexity or delay to clinical trials imposed by the use of a diagnostic test.

Strategies

After discussing whether diagnostics should be an internal or external part of pharmaceutical development, the Syndicate suggested that both possibilities should be considered. Although it was recognised that in-house diagnostic capability can spur innovation, the need for highly specialised developers and the often unfavourable economic realities could necessitate external partnerships.

An ongoing assessment of viability is required as a product moves throughout its lifecycle, including potential commercial success with and without a companion diagnostic. Although the use of companion diagnostics after regulatory approval has not been traditionally welcomed by industry because of the potential for market segmentation and the potential to limit revenue, there has been recent recognition of the potential for scientific innovation that results from academic interest and investigator-initiated trials, including advancing the management of downstream safety signals. In order to deal with the uncertainty that surrounds the future need for retrospective diagnostic analysis beyond the original clinical trial design, informed consent for sampling and banking of tissue from patients is critical. However, the costs and operational and legal complexities may be prohibitive factors in many cases, particularly in large international clinical trials for which the necessary informed consent language developed with ethics committees may vary greatly.

Recommendations

1. Employ a broad approach in diagnostic strategies, understanding the value of what remains unknown internally while developing external capabilities.
2. Understand the economics of external diagnostic partnerships; the relatively low investment costs of employing external expertise should be considered in the cost of a pharmaceutical development plan.
3. There should be the option to develop plans to retrospectively analyse clinical trial data including pro-actively addressing informed consent issues; these analyses may mitigate downstream safety issues.
4. Support post-approval companion diagnostics that may have a significant positive impact on a product lifecycle.
Syndicate Discussion B

**Can regulatory and coverage clinical requirements, in particular trial design and validation, be aligned?**

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**Background**

The addition of molecular diagnostic technology to the development of new medicines should enhance the outcomes of both pharmaceutical research and the treatment of disease but industry is challenged to undertake a development plan that will meet the requirements of licensing bodies as well as those of reimbursers or payers of the new drug-diagnostic combinations.

The objective of this syndicate group was to discuss whether regulatory and coverage clinical trial requirements can be aligned, in particular requirements for trial design and validation of the diagnostic.

**Questions for consideration**

- **What study designs are most appropriate to demonstrate the value of both the diagnostic and the therapy?**
  - What are the implications of such designs on the development burden?
- **Should there be validation of new diagnostics or of new drug-diagnostic combinations?**
  - Are current regulatory and HTA requirements fit-for-purpose or does there need to be a more refined approach that simultaneously addresses the needs of both regulators and HTA?
  - Is the validation of biomarkers a key area of concern and how can it be addressed?
- **Can the clinical study of the diagnostic and the therapy be designed such that it will be acceptable from both a regulatory and coverage body perspective?**
  - Are issues such as regional demographics, pharmacogenetic profiles and standards of care key and how should they be overcome?
  - What would companies ideally like as an efficient pathway? If this is not the state of the art, what needs to be changed?
- What aspects are non-negotiable from a regulatory or coverage body perspective?
- What are the next steps that should be undertaken to align regulatory and reimbursement requirements?

**Critical issues**

Although acknowledging this is an evolving and complex area, Syndicate B regarded pharmacogenetics as the future of medicine that will better define and enhance the therapeutic index for patients. The implementation of this paradigm, however, requires accelerated thinking around ways to implement this approach by maintaining momentum through dialogue among all stakeholders, including patients, whose perspective should be actively solicited.

Although not identical, there is significant overlap in regulatory and HTA requirements for diagnostics. In fact, regulatory approval can be considered a necessary but not sufficient condition of reimbursement recommendation. Sponsors should seek advice regarding specific requirements early in clinical development and the early identification and validation of biomarkers is critical for their successful HTA review, with particular attention paid to the size of the potential treatment population compared with the size of the therapeutic effect. Post-approval commitments and adaptive licensing may be part of the approval and reimbursement process for molecular diagnostic and therapeutic combinations. Finally, the cost of diagnostic combinations matters globally and will affect implementation, local access and use in clinical practice.

Although the syndicate briefly discussed situations in which a new diagnostic was developed for a previously approved (old) drug such as those in oncology, hepatitis C and cardiology, they decided to focus on those instances in which a diagnostic and drug were developed in tandem (Figure 1). It was the
consensus of the group that both regulators and payers would be concerned with the validity of the test, the size of the population versus the size of the effect, the clinical utility and the unmet need covered by the new combination as well as identifying a need for broader supportive evidence. Additionally, payers would likely request evidence submitted for the regulatory approval, evidence of comparative effectiveness and alignment with standards of care and guidelines, including local and regional guidelines, patient perspectives and a reasonable cost.

Strategies
When developing the evidence packages for regulatory approval and for reimbursement, industry should be guided to balance practical and methodological considerations in trial design and supporting information. Futility analyses and analyses of pre-specified subgroups should be included in trial assessments. A role for contextual and non-randomised evidence should be considered as well as the applicability of the combination to care settings. It must be recognised that solutions for unmet medical needs are highly desired by both regulators and payers. Finally, implementation guidance is critical for all stakeholders.

Recommendations
1. Consider joint HTA-regulatory consultations and include representatives from both of these stakeholders in advice sessions and review processes for the drug-diagnostic combination.
2. Align development timelines (which will differ for the drug and the diagnostic) and key consultation points.
3. Balance evidence uncertainty versus the need for timely access to new combination therapies through the use of post-launch commitments.
4. CIRS should continue to monitor the regulatory-HTA pathways for these combinations and revisit issues following the publication of anticipated new EU regulations on devices and clinical trials.

Background
In addition to the challenges that companies face with regard to the development of companion diagnostics, they also face challenges in understanding the regulatory and coverage decision pathways for these types of products. The objective of this Syndicate was to discuss whether the regulatory and reimbursement processes for assessment of companion diagnostics are fit for purpose and if they are not, decide how they can be improved.

Questions for consideration
- What are the challenges for companies and
regulators with regard to the regulatory approval of companion diagnostics?

- How should drug–diagnostics be classified and reviewed, that is, as one or separately and what is the appropriate regulatory pathway? What are the pros and cons to each approach?

- What would companies ideally like as an efficient pathway? If this is not the state of the art, what needs to be changed?

- What do regulators find to be the most challenging aspects of reviewing companion diagnostic submissions? How can these difficulties be overcome?

• What are the HTA and coverage decision-making challenges with respect to companion diagnostics?

• What do HTAs and payers find to be the most challenging aspects of reviewing companion diagnostic submissions? How can these difficulties be overcome?

• Are the regulatory and HTA guidelines for these types of products fit for purpose? If not, what would be an ideal approach?

• What are the label implications for a product:

  - For which the diagnostic is developed simultaneously with the therapeutic

  - For which the diagnostic is developed independently from the therapeutic

• What are the next steps that should be undertaken to facilitate regulatory and reimbursement reviews?

Critical issues

Syndicate C identified four critical issues with associated strategies and recommendations for change.

1. Future investigations of molecular diagnostics may be challenged if the appropriate consent to use biosamples obtained from clinical trials have not been obtained.

2. There is often a disconnect between reimbursement of companion diagnostics and their companion drugs.

3. There is a lack of regulatory oversight or approval of the clinical utility for follow-on laboratory-developed tests or so-called “home brews” thereby providing a disincentive to innovation.

4. Appropriate real-life utilisation of and compliance with the appropriate use of companion diagnostics is an issue for all stakeholders.

Strategies

For critical issue 1: When designing informed consent forms for clinical trial participants, investigators should determine the benefits of including appropriate provisions regarding potential future research that may rely on biomarker assessment. Investigators should engage with Investigational Review Boards or Ethics Committees and regulatory agencies to obtain approval to proceed with testing of biomarkers in collected and stored samples.

For critical issue 2: Lawmakers should consider providing patent exclusivity or other incentives for innovation for the developers of molecular diagnostics to allow the recoup of investment.

For critical issue 3: A regulatory agency or agencies should assume responsibility for oversight of the quality for follow-on (home-brew) laboratory-developed tests. This action would require collaboration among industry, regulators and payers to ensure the aligned process is balanced and appropriate for the development and marketing of such companion diagnostics.

For critical issue 4: Effective education programmes should be designed for physicians on the appropriate use of approved diagnostics with metrics to incentivise appropriate behaviours and payer involvement to ensure compliance.

Recommendations

1. Investigators should proactively raise the issue of ongoing patient consent for analysis of clinical trial biosamples with Investigational Review Boards, Ethics Committees, regulators, Data Safety Monitoring Boards and other relevant parties, including privacy officers.

2. Explore the opportunity to provide appropriate incentives for companion diagnostic development and innovation.

3. Align quality standards and guidance for laboratory-developed (home-brew) tests among regulators and payers.

4. All appropriate stakeholders should engage in a concerted effort to change the infrastructures, organisations and behaviours surrounding the use of companion diagnostics through the use of incentives.
Panel Discussion of Syndicate Results: Key points

Discussion Panel

- **Dr Lucinda Orsini**, Group Director, GHEOR Oncology and Pharmacodiagnostics, Bristol-Myers Squibb, USA
- **Kimby Barton**, Director of the Bureau of Cardiology, Allergy and Neurological Sciences, Health Canada
- **Dr Naomi Aronson**, Executive Director, Technology Evaluation Center, Blue Cross and Blue Shield Association, USA
- **Michael Pacanowski**, Office of Clinical Pharmacology, US Food & Drug Administration

The Panel and Workshop attendees discussed the results of the Syndicate presentations.

**Key Points**

**Clinical utility and comparative effectiveness**

- Although companion diagnostics promise to bring new efficiencies to the healthcare system, they also add an additional layer of complexity. For example, evaluating the clinical utility of a combination diagnostic does not only entail an evaluation of its effectiveness in defined subgroups, but also its level of informed, appropriate use by pathologists and other laboratory personnel as well as by prescribing clinicians and patients.

- Other complexities include making choices among multiple diagnostics, understanding the observations that many diseases are characterised by changes in multiple markers therefore, focusing on a single biomarker may provide an incomplete assessment of a patient's disease state and the provision of informed consent and additional biosamples for future testing for patients among whom biomarker expression may change over time.

- As the use of molecular diagnostics is evolving, it is currently unknown whether they actually are expediting the development of therapies and reducing the cost of therapy and ultimately benefitting society. These questions might be answered through economic analysis and research among patients and clinicians as to their likely use of these tests in specific contexts as well as such topics as the societal impact of identifying novel uses for therapies that seemed to have limited efficacy.

- The benefit-risk profiles for companion diagnostics will need to be monitored and adjusted based on actual clinical use and utility. It is not clear which stakeholder is responsible to provide the necessary education or training that may be needed to ensure their proper use. Moreover, today there is heightened sensitivity to the potential for inappropriate promotion of the test through communications provided to patients.

- Measurements of comparative effectiveness that take into account all factors that mediate outcomes are key to the effective use of financial resources to cover the cost of drug-test combinations. These factors include structural incentives, preferences, organisational settings and individual behaviours.

- Perceptions of health technology assessors and regulators regarding the clinical utility and clinical validity of drug-test combinations will vary on a case-by-case basis, depending on the pre-marketing or post-approval time frames of the products and the need in the specific therapeutic area. Retrofitting a diagnostic to identify best-use of an existing drug is inherently different than the development of a new combination because the benefit for an approved drug has already in part been established in the absence of the test.

**Timing**

- The incremental benefits of the use of a new medication in various subgroups identified with a new diagnostic may take a considerable time to accrue. However, because of the need to expedite access to new therapeutics, the co-development of a molecular diagnostic in the same timeframe as a new drug may result in a suboptimal understanding of the full implications of the real-world predictability of the biomarker.

**North American-specific issues**

- In Canada, the federal government would prefer to be involved with fewer rather than more regulations and the regulation of laboratory-developed tests could be considered a provincial rather than federal responsibility. Canada has implemented the International Conference on Harmonisation E2 guidelines on post-approval risk management but the mechanisms and regulations for post-license data collection are also dependent on individual province requirements.
• In the United States, clinical cardiology guidelines have not been changed to recommend genetic testing to aid in warfarin therapy administration because the clinical trials performed thus far have not been judged as providing adequate controlled evidence with consistent results.

• The United States Food and Drug Administration is committed to personalised medicine and the development of companion diagnostics. Many recent new drug applications contain genetic and pharmacogenetic data in the submissions and the agency is working to employ more reviewers with the appropriate expertise to review these types of submissions and increase the capability to provide appropriate advice in earlier development phases. Although much work in this area has been in oncology, work in other therapeutic areas such as cystic fibrosis is increasing and familiarity and comfort levels in these therapeutic areas in the agency and in the clinical community continues to grow.

• The US FDA has recently released a Guidance document for the use of pharmacogenomics in early drug development1 and had previously published Guidance on pharmacogenetic data submission.2 The agency currently is conducting collaborative reviews of INDs and NDAs that deal with co-development of companion diagnostics and gives consolidated advice from its Drug and Device Centers and is drafting a Guidance in this area as well.

**HTA and payers**

• The HTA community has taken responsibility to work with patient and clinical groups to translate scientific clinical knowledge about combination diagnostics to patient-level information.

• Medical innovation has been an important driver for the US economy, but we have entered a time period during which the current model for the financial sustainability of medicines’ development is at issue. To fully appreciate the payer’s role in disbursing public resources to support innovation in companion diagnostics, it is necessary to contextualise the notion of value. In the United States health insurance system, what is ultimately available for coverage for reimbursement is based on contributions from workers’ wages and employer contributions.

**Education and training**

• Regulators are encouraged to prioritise the issue of educating patients and healthcare professionals regarding the role of diagnostics in disease management by consulting their international colleagues regarding education approaches. The US FDA in particular is developing a wide-ranging effort to solicit patient perspective regarding new therapies.

• While some Workshop participants expressed a need for patient education in companion diagnostics and that it is within the purview of regulators to administer these programmes, a lack of regulatory resources and the complexity of management is problematic and industry efforts in this area need to be conducted with guidance from regulators and payers.

• The European Patients’ Academy on Therapeutic Innovation (EUPATI) funded by the Innovative Medicines Initiative (IMI) was cited as an excellent example of a path to patient education.

**Laboratory-developed tests**

• When considering the integrity of a laboratory-developed (home-brew) test, it is important to realise that the attributes of individual laboratories and their ability to optimise the performance of tests is more important than the actual attributes of the test. For example, regardless of the method of measurement selected for the measurement of bone density, there is currently a huge error variance across testing facilities that can dissipate the clinical utility of the test.

• While the lower costs and unregulated nature of laboratory-developed tests may be attractive to payers these erode intellectual property protection for approved diagnostics and may be a disincentive to innovation.

**References**


Section 3: Presentations

**Putting the puzzle together: How do companion diagnostics fit into the whole healthcare system landscape?**

**Dr Ansgar Hebborn**  
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**Definition**

According to the US Food and Drug Administration (FDA) Draft Guidance, an in vitro companion diagnostic device is defined as an “in vitro device that is a determining factor in the safe and effective use of a corresponding therapeutic product to identify patients who are most likely to benefit from a particular therapeutic product; identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product and to monitor response to treatment for the purpose of adjusting treatment (eg, schedule, dose, discontinuation) to achieve improved safety or effectiveness.”

This definition should be expanded, however, to include a basis on a set of transparent, reasonable, evidentiary, analytical standards by which to evaluate the relevance, validity, feasibility and timeliness of the device. Furthermore, to increase the value of personalised medicines, these standards should be established through a collaborative process involving all stakeholders. For patients, the expected standards are for the best treatment at the right time that results in predictable outcomes. Physicians and other healthcare providers also expect to realise predictable outcomes with maximum benefit and minimum toxicity. Payers and reimbursers meanwhile, look toward the efficient use of healthcare resources whilst regulators and policy makers expect improved healthcare outcomes. However, not all stakeholders may gain equal benefits from every personalised medicine. For instance, it may not be possible to provide the most efficient use of healthcare resources for payers and reimbursers that also represents the “best” treatment to patients.

**Partnerships**

The growing trend toward partnerships is expanding the value proposition of companion diagnostics. For example, the number of partnerships between pharmaceutical and diagnostic companies continues to increase, particularly in the field of oncology. This concentration may be explained both by an enhanced understanding of the molecular mechanism of cancer as well as by the financial attractiveness of launching co-dependent technologies in this therapeutic area. Within Roche, where there is a unique opportunity for collaboration across the divisions of a single company, a well-organised programme of biomarker research has emerged and there are currently more than 15 compounds with companion diagnostics in phase 2 and 3 development.

Some public agencies have also initiated measures toward policy and procedure development for companion diagnostics. Draft Guidance documents for the development and use of these technologies are being finalised in both the United States and Europe, which are expected to provide clarified understanding of regulatory positioning relative to emerging technologies as well as relevant guidance.

The involvement of Health Technology Assessment (HTA) agencies in the evaluation of personalised medicines and companion diagnostics is also increasing. In the United States, the US Patient Protection and Affordable Care Act requires that the agenda of The Patient Centered Outcomes Research Institute (PCORI) strongly emphasises the personalisation and targeting of care in the comparative assessment of technologies, explicitly highlighting the need to identify patient subpopulations whose genetic and molecular markers may indicate their potential for enhanced outcomes. In Australia, the Department of Health and Ageing has aligned with diagnostic and pharmaceutical developers to ensure that access is granted in a technologically appropriate manner.

**Challenges in development**

Ideally, there would be parallel development for pharmaceuticals and their companion diagnostics, with pharmacogenomics-based clinical trials dramatically reducing the cost for development and increasing the success
rate associated with traditional clinical trials. Considerable uncertainty, however, still surrounds the requirements for these developing technologies and more guidance is needed from regulatory and HTA authorities to create a level playing field for all developers. This guidance would serve to move the new technologies toward the concept of target engineering in which a solid, scientific basis is used to target engineer a desired product with a specific outcome. In addition, because pharmaceutical drug development is a global endeavour, some degree of consistent, coherent requirements and evidentiary and analytical standards is also needed.

A well-designed pricing and reimbursement system could be used to guide research and development activities, providing financial incentives to develop a level of evidence for companion diagnostics appropriate to satisfy all stakeholders. But currently, poorly valued tests are poorly reimbursed, with little incentive to develop appropriate studies, resulting in a lower level of evidence and poorly characterised utility, ultimately reinforcing the low value.4

Unfortunately, healthcare budget management measures, particularly those in resource-constrained economies, are often short sighted, focusing on easy targets and aimed at short-term relief. Although it can be extremely challenging for payers, politicians and policy makers to adopt policies of value-based pricing, reimbursement and funding, use of these systems would ultimately reward added value and incentivise meaningful product and service differentiation sending reliable signals to guide innovation (Figure 2).

Pricing, reimbursement and funding pathways for companion diagnostics and pharmaceuticals are frequently misaligned thereby impeding the development of personalised medicines, with heterogeneity in diagnostic reimbursement within and among national economies leading to differences in patients’ access to innovative medicines. In addition, the reimbursement system for companion diagnostics is less transparent than that of their therapeutic counterparts, making it more challenging for smaller companies to navigate.

A targeted pricing approach would ensure that new products are optimally developed and utilised, providing increased incentives for manufacturers to develop innovative therapies to their full clinical potential in more indications and allowing more patients to benefit from these novel therapies (Figure 3).

Conclusions
The fulfilment of certain requirements will ensure the development of a better future for diagnostic technologies and ultimately, enhance patients’ access to innovation in the personalised healthcare environment.

• A common language and a consistent set of definitions will allow stakeholders to engage on common ground.

• Reasonable evidentiary and analytical development standards will balance relevance, validity, feasibility and timeliness, provided they are based on a thorough understanding of the real world of technology development and its challenges and established in close collaboration between all stakeholders, particularly patients to understand their preferences in benefit-risk evaluations.

• Value-based pricing, reimbursement and funding as the result of transparent pricing and reimbursement processes and aligned therapeutic and diagnostic pricing, reimbursement and funding pathways and transparency in the process of decision making will provide necessary incentives for innovation.
Putting the puzzle together: Barriers and opportunities in drug-device combinations — An industry perspective

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The pharmaceutical industry continues to be challenged to create better stakeholder value for its research and development programmes. Despite the trend that more products are being approved, the value of those products as measured by forecasted sales is actually decreasing. In an effort to counter this trend and in response to emerging science and changes in policy legislation, the pharmaceutical industry has made significant investment in a number of approaches over the past several years including value-based decisions, biomarker adoption and comparative effectiveness trials. In addition, many clinical programs are being evaluated as to the relevance of associated co-dependent diagnostic technologies. However, developing companion diagnostic products with demonstrated analytic and clinical validity and clinical utility at launch in line with the stages of pharmaceutical development remains a challenging and iterative process.

Levels of evidence and emerging science
In a 2010 publication in the Journal of Clinical Therapeutics, Dr Woodcock of the Center for Drug Evaluation and Research, US Food and Drug Administration identified the three possible scenarios for drug-diagnostic development as co-development, rescue and retrofit.¹ The idealised approach to develop evidence for one of these scenarios, the co-development of companion diagnostic technology, as specified by the Australian government publication Co-dependent and hybrid technologies includes Level 1 evidence resulting from a complex, double randomised trial of six treatment groups:

Groups 1-2: patients with a tested positive sensitivity to a biomarker who receive drug A or drug B;
Groups 3-4: patients with a tested negative sensitivity to a biomarker who receive drug A or drug B;
Groups 5-6: patients whose biomarker sensitivity has not been tested who receive drug A or drug B²

Although the trials that result in this Level 1 evidence can clearly provide a significant amount of information about the diagnostic

References
technology as well as the molecule and its potential applications, this evidence may be too costly and complex to develop and Level 3 evidence is more typically accrued. Level 3 evidence is derived through a trial of patients who have been identified through testing as positive for sensitivity to a biomarker and whose treatment is randomised to drug A or drug B. This level of evidence was used for the approval of vemurafenib (Hoffman-La Roche) in patients with unresectable metastatic melanoma positive for the BRAF V600E mutation. Patients who participated in the vemurafenib trials had tested positive for the mutation through use of a companion diagnostic (Roche Diagnostics) that was approved by the US FDA at the same time as vemurafenib and were randomised to groups being treated with that drug or dacarbazine.

The context and the relevance of data developed within an emerging science should be approached with a pragmatic view that should incorporate the consideration and management of several issues. The development of linked electronic health record and tissue databases should be stimulated to understand the incidence, natural history and prognostic impact of biomarkers in high-impact diseases such as cancer. Informed consent processes should be managed to protect patient data but also to facilitate the optimal use of emerging diagnostic techniques. Clear standards for post hoc observations should be developed and value of perfect information concepts should be adopted (in which additional research is undertaken only when the expected value of perfect information exceeds the financial and societal cost of that information) to minimise patient exposure to repetitive or low-value trials and to aid access to innovative new technologies.

Standards for post hoc analysis have been proposed. Original studies of cetuximab and panitumumab in refractory metastatic colorectal cancer were based on testing of patients with proven expression of the epidermal growth factor antibody. As the science evolved, however, it became clear that the drugs were not effective in a subset of these patients and in fact, post hoc analyses consistently indicated that there was no effect in patients with tumours harbouring KRas mutations in codons 12 or 13. This evidence was regarded by both US and European regulatory agencies as sufficient to impact labelling for the therapies. During the Oncologic Drug Advisory Committee Meeting in December 2008, the FDA indicated important characteristics that would allow retrospective analyses to inform labelling:

1. The trial must be adequate, well conducted and well controlled
2. The sample size must be sufficiently large to be likely to ensure random allocation
3. Tumour tissue must be evaluable for ≥ 90% of the registered and randomised study subjects
4. Before analysis, the FDA must have reviewed the assay methodology and determined that it has acceptable analytical performance characteristics
5. Genetic analysis must be performed according to the qualified assay method by individuals who are masked to treatment assignment and clinical outcome results
6. Before conducting the analysis of clinical outcomes, agreement with the FDA must be reached on the analytical plan for hypothesis testing for the proposed labelling and promotional claims.

Bloom and colleagues reported an instance in which access to innovative technologies created a significant impact on research and ultimately on health outcomes: approximately 20% of appropriate patients may have been excluded from the study of vemurafenib if the Sanger method, which had been considered the gold standard, rather than the newer Cobas method was used for screening. Use of the Sanger method produced a number of discordant results that could have resulted in patients being denied access to a therapy that was actually appropriate for their disease (Figure 4). The coordination of reimbursement and payment for co-dependent technologies is challenging because of heterogeneous processes and timelines, but progress has been made in some jurisdictions. In 2006, the French Ministry of Health and the Institut National du Cancer organised twenty-eight regional platforms through which high-quality
molecular testing is performed for all patients with cancer as soon as a new targeted therapy becomes available. This successful programme has demonstrated that providing easy access to innovative diagnostic tools for treatment stratification is cost effective, optimising health outcomes while sparing the cost of inappropriate treatment.5

Beginning in 2000, the US Center for Disease Control and Prevention established the ACCE model for evaluating genetic tests. ACCE is named for the four main criteria for genetic testing: analytic validity, clinical validity, clinical utility and ethical, legal and social implications. The ACCE definition of clinical utility is "the balance of benefits and harms associated with the use of a test in practice, including improvement in relevant outcomes and the usefulness of added value in decision making compared with not using the test."6 This definition implies need for real-world evidence similar to that derived from the Italian managed entry schemes, which have managed utilisation, provided evidence on use patterns and outcomes and driven timely access of high-cost oncology therapeutics.7

Moving forward, it is critical that stakeholders align processes for health technology assessment, coverage and reimbursement and design assessment standards that encourage the adoption of emerging technologies such as next-generation sequencing or multiplex assays. They must allow the demonstration of the clinical utility of a test to take advantage of existing evidence to form an indirect evidence chain and stimulate the development of linked databases to allow for real-world effectiveness and coverage with evidence development to address evidence uncertainty and stimulate primary healthcare adoption. Finally, all stakeholders should consider the value of rewarding innovation as part of the willingness-to-pay thresholds for co-dependent technologies and maximising the potential health outcomes for patients.

References
Companion diagnostics: What’s in it for all of us?

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FDA companion diagnostic guidance

In the past, not everyone would benefit from newly discovered therapies and some may even have been harmed because of undiscovered differences between responders and non-responders to treatment. In addition, when diagnostics were present, they were often phenotypic or organ-specific and could not distinguish who would or would not benefit or who would be harmed.

Today, therapies are being developed for subpopulations, targeting molecular pathways and simple or complex markers can divide populations into different molecular categories. There is the potential for improved efficacy in patients selected as most likely to benefit while excluding those least likely to benefit. There is also the potential to test out risk and exclude those most likely to be harmed, with the result that testing has a critical effect on the safety and effectiveness of targeted therapies, altering the benefit-risk model. However, the effectiveness and safety of these therapies depend on accurate, reliable companion tests.

Because the FDA understood that the benefit-risk assessment for a targeted therapy may require an accurate and reliable companion diagnostic, the Draft Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices was published 14 July 2011.1 In addition to describing FDA policies for approval and labelling of a therapeutic diagnostic product pair, this document defines a companion diagnostic as “an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labelling of both the diagnostic device and the corresponding therapeutic product, as well as in the labelling of any generic equivalents of the therapeutic product.” Purposes for devices can be predictive, prognostic, monitoring, dosing or selection (Figure 5).

Generally, companion diagnostics are not used for the diagnosis of disease, although this may be the source of confusion as some diseases are sub-classified by their molecular characteristics. They are also not used to check the status or the response or lack of response of patients under treatment and they must be tied to a specific drug.

Premarket review and clearance or approval of a companion diagnostic will typically be required by the FDA contemporaneously with approval of the therapeutic product and this evaluation will include an assurance that the diagnostic has been appropriately validated for its intended use. Although there are some exceptions, the companion diagnostic and the therapeutic product depend on each other and co-approval is required and failure or lack of approval for the test means that there will be no therapeutic product approval. In addition, post-market and quality system controls for companion diagnostics must be in place to help to assure continuing performance at the level specified to support the safety and effectiveness of the therapeutic product.

Labelling

If a drug or biological product has been shown to be safe and effective only in a certain patient population identified by a diagnostic test, the Indications and Usage sections of the product label must clearly define the patient population in whom the drug is approved. Additionally, if a diagnostic test is essential for monitoring either therapeutic or toxic effects, the type of

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**Figure 5. Potential uses and types of companion diagnostics.**

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test should be identified under Warnings and Precautions sections. The therapeutic label should refer to the companion diagnostic as an “FDA approved test” unless there is compelling reason to name a specific test. This lack of a specific test name allows new tests to be used without changes to the drug label. However, the FDA may consider a specific test label if safety and effectiveness questions necessitate. The Intended use within the companion diagnostic label should refer to specific use with a specific therapeutic product. If the test is applicable to more than one therapeutic product, it must be determined if there is a class effect. New indications for the diagnostic will require submission of a new pre-marketing application or a pre-marketing application supplement. Because performance is critical to the companion diagnostic, appropriate labelling is required and the FDA expects to require compliance with device regulation whether the test is laboratory developed or distributed as a kit.

FDA requirements
Investigational approval will usually be needed for tests used to make critical decisions in clinical trials, for tests used without confirmation by another medically established diagnostic and for tests with the potential for serious risk to the patient. This approval requires submission of information about the test and its use.

A premarket submission must address all applicable validation parameters. The analytical validation of a companion diagnostic must be sufficient to assure the test is safe under investigational conditions in terms of its accuracy or precision, cut-off points, limit of detection of quantitation and other factors as necessary. Clinical validation of a companion diagnostic (or its prototype) is required through its use within a pivotal therapeutic trial. No systematic difference in validation will occur whether the associated therapy is undergoing normal or accelerated approval.

The analysis of the diagnostic device performance will be related to the therapeutic trial outcome; that is, if the therapeutic trial fails, the diagnostic will be judged as not informative and if it succeeds, the diagnostic will be considered generally informative. The companion diagnostic label will reflect its use in the pivotal trial and generally, no additional clinical validation of the diagnostic will be required. For predictive claims, the clinical study should be powered to detect differences in response by diagnostically defined strata.

Challenges
The decision to test a companion diagnostic is a business risk for industry as it is not always certain that a companion diagnostic will be necessary for the optimal use of a therapy. In addition, a drug might fail or might only work in a limited population and the predictive value of the test cannot be determined in advance.

Timing will continue to present an additional challenge for developers and reviewers. Drug and companion diagnostic reviews function according to different timelines and although important new drugs may be accorded an accelerated review, diagnostic review timing may be more challenging to expedite. Furthermore, as was discussed by Dr Rossi (p 18) evolving science can support retrospective testing or the addition of claims or required warnings to companion diagnostic combinations that have already been approved or are in the process of being tested.

Finally, laboratory-developed diagnostic tests can represent another obstacle to industry and agencies. Although these may be available more quickly, their performance is an unknown factor and multicentre clinical trial enrolment may be compromised when diagnostic tests used for inclusion are not comparable and multiple platforms are used for different tests.

Despite these challenges, the US FDA believes that the use of approved tests is critical when drug safety and efficacy are dependent on test results. The review process that has been developed by the agency for companion diagnostics has worked successfully for several products and enhancements and refinements are currently underway.

Reference
Companion diagnostics in Canada: Regulatory challenges

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Although the use of biomarkers and surrogate endpoints can expedite drug development, it can also enhance both the benefits and risks for patients. Pharmacogenomics may have utility for the determination of drug disposition, the surveillance or monitoring of disease-based expression, the identification of target patient populations and the investigation of the genetic basis of adverse drug reactions. However, validated endpoints and an established link to clinical outcomes are required.

Status of regulation of companion diagnostics in Canada

Biomarkers are not defined in Canada's Food and Drugs Act and regulations but the regulations do allow for flexibility in approval with sufficient evidence of safety, efficacy and quality. Therefore, Health Canada does not need to specifically legislate or regulate around the use of pharmacogenomics, but rather can rely on guidance already in force. Biomarkers, pharmacogenomics and personalised medicines may be associated with a clinical trial application, as a medical device licence, with a drug submission or as part of a special access programme request. However, laboratory-developed tests and direct-to-consumer genetic testing are outside of scope of the Food and Drugs Act and Regulations.

Health Canada has posted a guidance document on pharmacogenomics on its website (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/pharmacog/pharmacog_guid_1d-eng.php), which provides guidance on how and when to submit pharmacogenomic information to the agency. In addition, Health Canada participated in drafting the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E-15 Guideline, Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories and E-16 Guideline, Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions. The agency has also adopted those guidelines and is currently training staff on their use. Finally, Health Canada has examined the short- and long-term implications of biomarkers and personalised medicines to agency policy and has participated in international collaborations and scientific approaches to the analysis and evaluation of these regulatory submissions.

Health Canada encourages requests for pre-submission meetings for pharmacogenomic submissions and although the agency does not maintain a list of acceptable biomarkers, it has authorised up to 40 active ingredients where a biomarker plays a role in the use of the products

Challenges

Biomarkers reflect a physiological or pathological process and validation is often based on experience. Translating a positive outcome into a clinical benefit can take some time to accept and reviewers are not always comfortable with such a leap of faith. Questions that arise include the level of validation achieved for this biomarker; whether the information concerning the biomarker should be included in the Indications, Warnings and Precautions or Special Subpopulations sections of the product monograph; if the test or kit is readily available in Canada and whether patient access will be restricted based on patient subtyping.

Although it seems apparent that diagnostic testing data should be contained in product monographs, it can be difficult to generalise this information to make it appropriate for inclusion.
An examination of representative monographs demonstrates that information relevant to a new medicine’s efficacy and safety is listed in diverse sections (Figures 6 and 7). For example, because of the tragic death of an infant nursed by a woman who was a rapid metaboliser of codeine, safety information regarding rapid metabolism is included in the Special Populations: Nursing Mothers section of the product monograph for the drug, even though rapid metabolism is not limited to this subpopulation.

Pharmacogenomic information should also be included in labelling under certain conditions such as when subgroups of patients experience higher or lower clinical efficacy or are at increased risk for adverse drug reactions, or require special dosage considerations or simply when testing is recommended or required to optimise the use of the drug.

**Government responsibility**

In the Canadian Federal Government, stewardship for pharmacogenomics lies at the Health Portfolio level with the Canadian Institutes of Health Research (CIHR). CIHR is a research organisation that funds academic networks engaged in discovery, development and validation of biomarkers. The Health Products and Food Branch within the government applies pharmacogenetics information to regulatory submissions and the Health Product Directorate sets policy in this area.

Manufacturers apply to receive medical device licences, investigational testing authorisation or access to a special programme. Companion diagnostics regulated by the Health Products and Food branch and are primarily in-vitro tests regulated as class III medical devices. Devices and drugs or biologics are reviewed by separate groups, requiring separate applications and there is currently no process for a joint application. In fact, with a 90-day review window, medical device applications are reviewed more quickly than the review cycle for new drugs. A list of medical devices approved by this division can be found at [www.mdai.ca](http://www.mdai.ca).

In summary, although Canada has the regulatory flexibility to receive submissions for companion diagnostic products, it needs to develop consistency in approach and comfort with inclusion of information. More experience will provide clarification as to whether process changes for companion diagnostics are required.
COMPANION DIAGNOSTICS; 18-19 September 2012; Washington, DC

Companion diagnostics:
Clinical utility and value

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Blue Cross and Blue Shield Technology Evaluation Center

The Blue Cross and Blue Shield (BCBS) organisation consists of 38 independent plans, which act as a core system guided by principles and standards of membership. Collectively, the group contracts with 90% of US hospitals and 80% of doctors and insures 100 million beneficiaries, which represents almost one third of the US population.

Since 1985, BCBS has supported the Technology Evaluation Center (TEC) as an independent organisation for clinical evidence development. The TEC mission consists of the systematic rigorous assessment of the clinical evidence for a new technology to answer the ultimate question: Does this technology improve health? The dedicated professional TEC staff includes physicians, pharmacists, epidemiologists, statisticians and librarians. Since 1997, TEC has also been one of the evidence-based practice centres of the Agency for Healthcare Research and Quality (AHRQ), most recently focusing on comparative effectiveness reviews in cancer and infectious disease.

Technology assessment supports health plans and other stakeholders in developing evidence-based policies such as medical policies, which are based on scientific evidence without consideration of costs or coverage. Coverage policies, on the other hand, are determined by purchasers of health plan products and the cost-effectiveness of those products is an important consideration. Finally, payment policies are based on contracts between health plans and medical professionals and providers.

Assessments are reviewed by an independent, expert medical advisory panel who are identified on the TEC website along with a three-year inventory of completed TEC assessments (www.bcbs.com/tec). In addition to these assessments, TEC provides informational evidence reports to maintain and update approximately 400 BCBS medical reference policies each year, with around 15 reports also provided to clinical pharmacist decision makers.

Clinical utility and patient heterogeneity

For the past several decades, health technology assessors have struggled with issues surrounding the progress of diagnostic medicine along the continuum of efficacy from accuracy of diagnosis to improvements in health and societal outcomes.1 Using the analytic validity, clinical validity, clinical utility and ethical, legal and social implications (ACCE) framework for evaluation of genetic evidence2 shows the complexity of demonstrating the clinical ability of a test and the impact that it may exert on health outcomes for individuals.

For example, the history of diagnostic imaging has been one of many great successes but also great cost, as many unnecessary procedures and treatment practices have been driven by FDA approval and by reimbursement policies.3 So while the medical diagnostic system successfully generates costs and revenues, its use is stimulated by capacity and the health outcomes it delivers are less certain.

The evaluation of companion diagnostics are relevant to recent discussions surrounding the harmonisation of regulatory and health technology assessment. In the recent TEC Special Report, Companion diagnostics: Example of BRAF gene mutation testing to select patients with melanoma for treatment with BRAF kinase inhibitors, the Center found that the targeted drug-companion diagnostic co-development process ensured sufficient validation; that is, clinical utility, of the companion diagnostic.
test, such that an independent evaluation of the test was not necessary. In this instance, using the test to select patients for treatment resulted in improved outcomes compared to the usual standard of care. Additional specific examples, however, will be required to determine whether the co-development process will ensure sufficient evidence of clinical utility for all companion diagnostics approved via this regulatory review pathway.

Furthermore, the report raised questions regarding response in patients with other V600 variants as there were no data on tumour tissue heterogeneity or homogeneity for the BRAFV600E mutation and correlation with response. It was unclear whether the co-development review process allowed for the later development of improved companion tests.

Healthcare should be driven by patient-centred rather than technology-centred assessments with a focus on the clinical decision rather than the test or diagnosis. In addition to the heterogeneity of patients, clinical management strategies are also mediated by the conditions of clinical practice such as the nature of the organisation and interventions of healthcare providers and the behaviours of individuals within the healthcare system including their knowledge, technical skill and adherence to guidelines.

Value: Can we afford it?
A consensus is emerging that the level of healthcare spending in the US is not sustainable. For example, when thalidomide was approved for multiple myeloma after having been used to treat erythema nodosum leprosum (leprosy), treatment costs, which increased more than 10-fold per year were characterised by the manufacturer as good value since they were approximately half the cost of other innovative advanced cancer treatments.

In 2010, in an attempt to come to grips with the escalating cost of drugs such as these for their members, Premier BCBS of Washington and Alaska developed a pilot programme for use with their employees that included value-based formulary tiering. In the pilot, in addition to an evaluation of a new drug’s safety, efficacy and effectiveness by the traditional Pharmacy and Therapeutics Committee, drugs were assigned to one of four flexible tiers by a multidisciplinary Value Assessment Committee based on the therapy’s cost-effectiveness. Assignments ranged from tier 1, for drugs which were considered very cost effective to tier 4 drugs, which were judged to be minimally cost effective. Committee members used a template devised through previous work by the American Academy of Managed Care Physicians (AMCP) and by the National Institute for Clinical Excellence (NICE) for their assessments and also considered ethical issues, rare diseases and unmet needs (Figure 8).

In general, under this new value-based system, many expensive drugs shifted from upper to lower tiers as they became less costly to employers, while some drugs shifted to higher tiers for certain patients based on genetic stratification (Figure 9).

Summary
Diagnostic tests and treatments are components of clinical management strategies, but the clinical utility of diagnostics and the heterogeneity of response, harms and net health outcome or treatment have been key evidence gaps. Starting with clinical decisions, patient-centred rather than technology-centred evidence should be developed. The co-development of drug and diagnostics adheres to this principle and bridges key evidence gaps of utility and heterogeneity. There are foreseeable limitations to companion diagnostics, however, including variability in laboratory practice, sampling issues and open issues of future test development.

The value and affordability of companion diagnostics are intertwined. Health plans are likely to regard funding for companion
diagnostics as a business matter between partners and to be sceptical of higher payment based on an industry concept of value. Although cost is the “third rail” of healthcare decision-making to be approached with caution, sustainable healthcare requires stewardship by all stakeholders.

A US coverage decision-maker perspective

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Improved outcomes and lowered cost of care

What are the potential benefits of using diagnostics in disease and patient sub-settings from a reimbursement perspective? At OptumInsight the future is focused on achieving the benefits of improved patient outcomes and satisfaction while reducing the total cost of care with real-world evidence (Figure 10).

These goals can be met though achieving healthcare quality and efficiency, which are functions of decisions made in the examination room, where stakeholders can achieve affordable effectiveness and ultimately patient satisfaction through intelligent clinical decisions by physician and patient. However, the quality of healthcare decisions is dependent on the availability of patient information and access to evidence-based science and benefit information as well as the ability to track the progress of therapy which often can be monitored by the use of companion diagnostics.

In addition to positive impacts on outcome quality and patient satisfaction, the total cost of care can be improved by the use of companion diagnostics. Even though the costs of these technologies must be added to the total cost of disease therapy, identifying the target group of patients most likely to benefit from the therapy ultimately lowers the total cost of care by eliminating the treatment’s overuse, underuse and inappropriate use while increasing its effectiveness.

In at least one instance, however, treatment guidelines have not encouraged the use of a diagnostic for a validated biomarker. Although a black box label outlines the strong evidence that patients with a cytochrome P450 2C19 polymorphism will not respond adequately to the anti-platelet agent clopidogrel (Plavix) and payers have agreed to reimburse the diagnostic test for the mutation, interventional cardiology guidelines specify that the diagnostic be “considered but not compelled”.

Value-based cost and reimbursement

The potential for companion diagnostics is clear, but realisation of that potential is conditional. Evidence drives coverage under two rules: 1)
Numerous factors will dictate payer participation in value-based pricing for combination diagnostic therapies including real-world evidence of improved quality of outcomes and total cost of care.

The focus should be on informing decisions rather than restricting them and 2) evidence informs risk and risk informs coverage and administration. Therefore, substantial evidence of improved outcomes and improved cost of care will open coverage alternatives.

Adoption and appropriate use of therapies drive their value, but these goals can be elusive. The methods by which the diagnostic therapeutic alternative is efficiently integrated into an episode of care must be considered including potential provider and patient impact. Additionally, the method of dispersal of the diagnostic across provider types, regions and systems must be determined as well as a method for the control of its appropriate use.

In fact, the control of use seems a vital component of value. Despite research demonstrating the link between the over-expression of human epidermal growth factor receptor 2 (HER2) and the effectiveness of the oncology drug trastuzumab (Herceptin), records for one recent five-year period show considerable prescribing of trastuzumab to patients without HER2 over-expression as well as a considerable lack of use by those who have tested positive.

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Numerous factors will dictate payer participation in value-based pricing for combination diagnostic therapies including real-world evidence of improved quality of outcomes and a favourable impact on the total cost of care. Pricing will be dependent on acquisition costs, testing specificity and sensitivity, subpopulation size and the rate of adoption and appropriate use. The time interval between disease detection and its consequence can also confer value. Precisely correct treatments can be most cost effective or most appealing to patients after failing alternative regimens or after a substantial delay in treatment but this may not be the most cost-effective approach to their use.

There are reimbursement plans that support the use of companion diagnostics:

**Episodic or bundled payments** feature clinical alignment on optimal treatment pathways and on the best few therapies and diagnostic therapy combinations. There is standard payment across each pathway and premium payment for outcomes, quality measures and pathway compliance. This represents an effective method to raise the level of assurance of the tight coupling of diagnostic therapy combinations.

**Accountable care organisations (ACOs)** align incentives across payer and provider in the best interest of patient and population. Treatment decisions are bounded by ACOs but left proximal to the specific patient episode rather than to the rigid orthodoxy of guideline, creating a fast and effective method of the diffusion of appropriate use.

**Coverage with evidence development** is coverage with a strong initial evidence of value, with a commitment to generate ultimate evidence of value in a real-world setting. This type of reimbursement allows risk and reward to be shared between the innovator and payer communities, at least in theory leading to earlier coverage opportunities.

**Summary**

Affordable effectiveness guides payer reimbursement and payers recognise the intrinsic value of diagnostic therapeutic combinations in achieving this goal. There is a strong desire among healthcare stakeholders to achieve affordable effectiveness with these combination approaches but the strength of the real-world evidence remains key to their success. Value-based pricing can emerge, but it will be based on healthcare system conditions that are largely not determined by payer such as evidence, adoption, appropriate use, the strength of investment efficiency and a delay in the precise intervention to maximise patient satisfaction.
Coverage decision: A legal perspective

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Rising healthcare costs

Americans pay more for healthcare than any other people in the world and the cost is continuing to increase at a rate in excess of the growth of the economy and the rate of inflation. Not surprisingly, at a time when belief in market forces has achieved near religious status, many have seen changing the structure of health services as a route to cost containment. Unfortunately, all this spending does not buy better healthcare and these issues dominate the national dialogue.

In 2001, the Institute of Medicine report, *Crossing the Quality Chasm,* documented high rates of defects in American health care: “In its current form…American healthcare is incapable of providing the public with quality care…”¹ and more recently, Donald Berwick called accountable care organisations (ACOs), which are one of the proposed solutions to healthcare cost issues, “a promise not a panacea.”²

Payer models

Unlike personalised medicine, which is driven by science, the new payer models are driven by economics, which also drive politics and policies. These models have evolved, starting with the original self-pay system, moving through the early days of indemnity insurance and emerging several decades later with physician capitation and preauthorisation. Finally, current payer systems are represented by the ACO model, health technology assessment and integrated payer providers (Figure 11).

ACOs are plans for shared savings that are realised for stakeholders if per capita costs are reduced per member per year. The plans only include hospital- and physician-administered drugs and not over-the-counter or pharmacy benefit manager drugs; private models vary and evolve. HTA coverage favours technology assessment-based coverage rather than utilisation review and ad hoc preauthorisation. Ideally, this form of coverage represents an objective view of the medical science surrounding new technologies. Traditional models of an integrated payer provider such as the Veterans Administration and Kaiser Permanente are well known in the United State. Some are very large health plans, continually venturing toward acquiring additional providers.

Under ACO and integrated systems, choices and purchases are pushed down to the hospital or integrated system level where healthcare decisions are based on guidelines and standards of care as they emerge. Under the HTA coverage decision model, extremely granular decisions are required. Challenges include problems of top-down management and difficulties in transmitting and enforcing decisions in real time in non-integrated environments. In addition, the results of HTA standards of operation and medical coverage decisions are frequently divergent owing to the fact that diagnostic tests work on the principle of correlation rather than causation. Furthermore, despite the demands of the hierarchy of evidence, it is not possible to conduct double blinded studies of diagnostic tests.

Medicare

In the 1980s, Medicare did not yet have a coverage system to implement early federal health technology assessment. By the 2010s, Medicare had developed an increasingly centrifugal delivery processes including ACOs and integrated systems, suggesting again that HTAs will not be implemented in a federal coverage system.

The US Medicare system must deal with separate laws, regulations and benefits for
hospitals, physicians, ambulances, oral drugs and diagnostic tests. For example, there are different rules for imaging versus cardiology versus laboratory tests. Laboratory tests themselves go into two different legal channels, one for physician-mediated tests, others for clinical chemistry tests and each with separate coding systems and pricing structures. Payment rules for these services are completely insensitive to pharmacoeconomic value and the same payment of $500 is issued for a $50 laboratory-developed test and the $500 FDA-approved test created through rigorous research and development.

The value and coverage of diagnostic testing

Coverage decisions for the diagnostic in drug-diagnostic combinations with regulatory approval are not usually problematic. The drug-test combination faces the hurdles of comparative effectiveness and cost effectiveness as a pair. Left to itself, however, the diagnostic test faces both longstanding biases that tests are overused and automated level-of-evidence hurdles in HTAs that are sometimes disproportionate to established scientific facts. Despite a century-old bias that diagnostic tests are overused, testing can be of significant value in personalised medicine although it is possible to misframe that value. For example, significant chemotherapy regimen changes are prescribed for 20% to 30% of patients who receive gene panel "tumour of unknown origin" tests. However, the benefits of increased survival associated with the tests are computed for all people who receive the tests, rather than the percentage whose therapy was changed as a consequence of the test, resulting in a misleadingly small value.

In clinical or evidence-based decision making, brute facts lead to warrants or rules that are backed by data or evidence. For example, if the brute facts are that a male, 58-year-old patient has advanced metastatic pancreatic cancer, the warrants are that the average survival is one year, a rate which does not improve with chemotherapy and that the best treatment for patients with pancreatic cancer is palliative. These warrants are backed by randomised clinical trials of four chemotherapies. The medical decision, therefore is for palliative care.

Similarly, in critical reasoning medicine, if a female, 57-year-old patient has a 1-cm grade 2 breast cancer, the warrants are for the performance of a diagnostic test for the genetic markers of the BRCA gene that correlate well with disease recurrence. For the woman in this example, diagnostic testing results in additional brute fact data of tumour gene expression that does not signify tumour recurrence (an algorithm result <8%). Both the need for diagnostic testing and the gene expression correlation are backed by multiple large studies and unequivocal reasoning. This medical decision, therefore, for the performance of the diagnostic test and for the withholding of chemotherapy are backed by scientific evidence as is the payer coverage of the diagnostic test (Figure 12).

References

Collaborative development of evidentiary standards for the clinical utility of molecular diagnostics

Dr Patricia Deverka
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Molecular diagnostics and clinical utility

There is a widespread recognition that molecular diagnostics may have transformational impact on the management of patients across a variety of conditions over the next several decades. In particular, the use of molecular diagnostic tests to guide the management of oncology patients is an area of both rapid growth and unmet clinical need. There is a great deal of optimism that this technology will be used to not only improve survival of patients with cancer but also to improve their quality of life, functional status and productivity. But also there’s a hope that that molecular diagnostics may also provide the opportunity to better manage the cost of new cancer therapies particularly combination treatments and expensive biologics by identifying those who will not respond to a therapy and starting or switching their treatment to one that will be more effective.

Payers have developed evidence requirements for evaluating molecular diagnostics for coverage decision making. The diagnostics must do what they are purported to do, with accuracy, reliability and reproducibility. They must exert impacts on both medical decision making and patient outcomes (clinical utility). However, one of the major stumbling blocks to reimbursement and coverage is inadequate evidence of clinical utility. Evidence may be inadequate for a myriad of reasons. Technology changes rapidly and the availability of evidence of effectiveness often takes time to catch up. The diagnostic business model does not generate adequate return on investment to justify investment in prospective studies to evaluate the impact of the test on patient outcomes. Finally, there is a lack of clarity about how to design studies that will meet the evidentiary requirements of payers and clinical guidelines committees and the lack of evidence of clinical utility has consequences for patients and healthcare systems.

In recognition of the need to establish context-specific evidentiary thresholds for clinical utility, in 2008, the Secretary’s Advisory Committee on Genetics, Health, and Society wrote “Information on clinical utility is critical for managing patients, developing professional guidelines and making coverage decisions,” recommending that the Department of Health and Human Services develop “a public-private entity of stakeholders to . . . establish evidentiary standards and levels of certainty required for different situations.”

CMTP Effective Guidance Document

The Centre for Medical Technology Policy (CMTP) is a non-profit organisation that seeks solutions to improve the quality, relevance and efficiency of health care research. Creating balanced forums, CMTP engages in robust communication and dialogue among stakeholders that represent a broad array of perspectives and experiences. All stakeholders are given an equal voice in CMTP projects and stakeholder engagement is viewed as an ongoing relationship, rather than a single activity.

Funded by WellPoint, Kaiser Permanente and industry partners, CMTP has taken on the charge to develop an effectiveness guidance document to provide specific recommendations on the design of prospective studies of molecular diagnostics to inform decisions by patients, clinicians and payers. The document aims to strike a balance between internal validity, relevance and feasibility to provide decision makers with a reasonable level of confidence that the intervention improves net health outcomes. The target audience is clinical researchers working in industry or academic settings. This guidance is analogous and complementary to FDA’s guidance and is focussed on design elements particularly relevant to clinical and payer decision making.

Because multiple social objectives require dialogue and collaboration from a number of stakeholder categories, CMTP invited an expert technical working group to provide advice on the content of the recommendations, utilising a legitimate accountable process so that the perspectives of all stakeholders were heard. The US-focussed group consisted of academic researchers, industry representatives from large companies and a small start-up, payers, a research funder, a policy maker and a patient advocate.

Actionable tests in all types of cancer were considered. Actionable tests were defined as tests that would lead to a change in the clinical management strategy of a patient with cancer.
Because analytic validity is being studied by other investigators, this group concentrated on clinical validity and utility. Existing guidelines were referenced whenever possible. The focus of the work included stand-alone tests and new tests for old drugs.

During the two-year process, the group reviewed the literature, conducted key informant interviews and identified evidence gaps. A molecular diagnostics advisory group was constituted to ensure that studies designed using these recommendations are going to meet the evidence needs of payers making them more likely to be covered and reimbursed. A draft was prepared outlining issues and recommendations and a Delphi survey was conducted among group members and meetings and workshops held. A draft version of the recommendations was completed at the end of 2012. There is currently targeted outreach to ensure additional stakeholders have the opportunity to weigh in on the draft document, before posting it on the CMTP website for a 60-day public comment period (Figure 13).

It is anticipated that the document will be finalised by mid 2013 after which formal publication and dissemination will be initiated.

In addition, a pilot clinical trial is planned that will be developed with industry partners using the recommendations, potentially in a setting of coverage with evidence development.

**Recommendations**

Among its ten recommendations, the document specifies that clinical utility studies should include the assessment of proven outcomes that measure both benefits and harms, recognising that these outcomes may occur at different time points and are the result of management decisions guided by the test results. For example, measures of benefits and harms could include avoiding an ineffective therapy; switching more quickly to an effective therapy; helping to choose among seemingly equal treatment options. Patient-reported outcomes, survival and progression-free survival and avoidance of high-cost and lengthy treatments are other important determinations of clinical utility. The document also indicates that in vitro diagnostic companion diagnostic tests approved or cleared by the FDA have undergone a development process which is likely to produce sufficient evidence of clinical utility. This conclusion was based on review of early cases, draft FDA guidance and will probably need to be revisited.

Unresolved post-regulatory evidence needs in companion diagnostics included the fact that true co-development may not occur. In addition technology, knowledge of tumour biology and clinical management are evolving rapidly. As Dr Aronson reported, the Blue Cross Blue Shield Association Technology Assessment Group uncovered unresolved issues of tissue heterogeneity in the approved molecular testing of BRAF<sup>V600E</sup> mutations (see page 26).

**Companion diagnostics managed entry**

CMTP recognises that environmental barriers may exist to the performance of clinical utility studies; that is, not all companies will be in a position to produce evidence of clinical utility at the time of product launch. Accordingly, the working group developed a position statement regarding the topic of managed entry for diagnostics:

- We support the development and use of novel policy approaches to promote clinical utility evidence generation for molecular diagnostic tests and other medical devices and drugs. Managed entry schemes encompass a broad range of policy tools that provide the flexibility to payers to cover...
innovative, emerging molecular diagnostic tests while generating valid evidence on the relative benefits and risks of these tests while these are in use in clinical practice.

- Among the possible tools to be considered on a case-by-case basis are FDA-CMS parallel review and adaptive licensing (for companion diagnostics and in vitro diagnostic tests undergoing FDA review) and performance-based risk-sharing arrangements (potentially applicable to both laboratory-developed tests and in vitro diagnostic tests undergoing FDA review), including the provision of coverage for patients in well-designed clinical trials to gather clinical utility evidence for clinically promising molecular diagnostic tests.

Coverage with evidence development provides coverage contingent on participation in a clinical study. For diagnostic tests, evidence of impact on health outcomes may not be feasible for initial coverage; however, unconditional coverage significantly reduces incentives to assess health impacts. Optimal public health benefits from genomic diagnostics may be achieved through coverage with evidence development: initial coverage based on clinical validity and subsequent studies of clinical utility.

Conclusions
There are numerous advantages to the use of the effective guidance document. It will be possible to develop more informative studies for clinical and policy decision making, including meaningful outcomes for patient decision-making and the development of practice guidelines and coverage and reimbursement decisions.

Test developers will gain greater certainty regarding evidence requirements and an opportunity to conduct studies that meet both FDA and post-regulatory information needs while determining whether their business models make sense. Research funders will benefit from increased consistency of study designs within specific clinical conditions or related treatments enabling higher quality meta-analyses and systematic reviews.

Reference
and conditions that affect the interaction of the DNA with the environment are only recently beginning to be understood.5 Although progress in personalised medicine has been slower than many expected, there have been achievements in this area with a direct impact on health, primarily in oncology. For example, the treatment of breast cancer was revolutionised when the effectiveness of Herceptin (trastuzumab) in patients identified as positive for her2 expression was recognised and other breakthroughs followed. the identification of patients with relevant genetic markers facilitated the development of Gleevec (imatinib), Sprycel (dasatinib) and Tasigna (nilotinib) in chronic myelogenous leukaemia; Tarceva (erlotinib), Iressa (gefitinib) and Xalkori (crizotinib) in lung cancer; erbitux (cetuximab) and Vectibex (panitumumab) in colorectal cancer; and Zelboraf (vemurafenib) in melanoma.

The value of and barriers to personalised medicine
Value can be defined as what fully informed patients would be willing to pay for a new diagnostic or therapy, based on any cost savings, life years gained, improvements in quality of life or morbidity or a reduction in uncertainty. Personalised medicine can add value through multiple mechanisms. For example, as non-responders or poor responders to medicines are removed from the pool of users, their monetary and negative utility costs are avoided. In addition, better targeting of new therapies can lead to a greater volume of adoption by good responders, some of whom would not have used the medicine previously and improved compliance with good responders resulting in greater net benefits, especially for long-term therapies. Finally, the improvement of predictability of outcome creates additional value for patients as they face less uncertainty.

However, there are challenges that must be addressed before the value of personalised medicine can be realised:

1. Science: As previously mentioned, the complexities of personalised medicine are only beginning to be understood. Developing, testing and validating a biomarker strategy can compound the intricacies of drug development and add further timing pressures to those associated with developing an innovative therapy with a fixed patent life.

2. Regulatory issues: Regulatory pathways for diagnostics have yet to be defined and include the resolution of issues surrounding laboratory-developed tests versus approved in vitro diagnostics.

3. Evidence: Diagnostics typically come to market with limited evidence as to their clinical utility and intellectual property incentives for developers of evidence of this utility are lacking.

4. Economic evaluation: Although as Taylor and Iglesias wrote “The cost per quality of life in many settings has become that gold standard metric, regardless of whether a policy maker is evaluating a drug, medical device, or any other health-care technology”6 the cost-per-quality-of-life year metric does not consider the value of reducing uncertainty. Furthermore, a linked diagnostic-drug combination is a joint product—the attribution of value to either aspect of this product is arbitrary.

5. Reimbursement: Companion diagnostics are reimbursed under a cost-based, administered pricing system that does not reward value creation or incentivise evidence generation to support value demonstration.

Dr Garrison presented the results of an analysis of the economic value and distribution of that value for a hypothetical diagnostic test that predicted the response to a therapy based on a readily detectable biomarker with 100% accuracy.7 In this analysis, 100 patients received a medicine without pre-therapy diagnostic
testing and 20 patients responded. As each of the patients was willing to spend $1,000 each on this therapy for which the benefit was uncertain, its total value was $100,000. This valuation was compared with a situation in which 100 patients were pre-screened and only those 20 patients likely to respond to the medicine received it. Those 20 patients, however, were willing to pay $6,000 each for the medicine, because the uncertainty of benefit was removed, resulting in a value of this therapy of $120,000.

To answer the question of whether the manufacturer of the therapy, the developer of the diagnostic, the insurer or the patient would capture the additional value generated by the diagnostic test, five scenarios were examined. An analysis of the scenarios revealed that the value would be captured according to whether the therapy and the diagnostic pricing reimbursement were value based or cost based and how flexible the reimbursements were over time. It also depended on whether the therapy was already on the market when the diagnostic was developed, whether there was intellectual property protection and the level of the competitiveness of the insurance market in the short and long term (Figures 14 and 15).

Conclusions

There are multiple pharmacoeconomic methodological challenges in personalised medicine including taking the costs and performance of testing and the valuation of reduction of uncertainty into consideration in cost-effectiveness models and assessing the impact of uptake on aggregate value and the greater predictability of response on compliance and consequent health outcomes.

Changes in public policy required from a values-creation perspective include flexible and value-based pricing and reimbursement; incentive-oriented reforms linking pricing and reimbursement for drugs and diagnostics to value creation; a strong, consistent, predictable intellectual protection environment and a change from a narrow focus on pharmacogenomics technologies to a broader consideration of biomarkers.

References


Issues in post-marketing and clinical practice

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Limitations of companion diagnostics

Despite the well-known advantages of personalised medicine, the diagnostic tests that identify candidates for therapy are bound with some limitations and do not yet predict the best responders with complete accuracy. That is, in addition to false positive and negative results, diagnostic tests may not present a complete profile of the most appropriate patients. For example, although clinical trials have demonstrated that trastuzumab (Herceptin) is effective against tumours that over-express human epidermal growth factor 2 (HER2), not all HER2+ tumours respond to the medication and more research is required to identify additional biomarkers present in HER2+ tumours that are affected by this therapy.

In addition, the stratification of patients according to level of treatment response can present complex issues for assessors and payers of health technology. Donnelly and colleagues identified a single nucleotide polymorphism in the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) gene that affects response to statins in patients with diabetes. In this study, retrospective analysis identified two strata of patients, one of whom reached the total cholesterol target level in 72% of the cases, versus 49% in the other group. At appropriate dosages, statins have a relatively benign safety profile and the benefit-risk ratio is positive for both groups of patients. Therefore, those who assess or reimburse health technology must decide if there is justification for restricting the reimbursement of the statins to the stratum achieving the higher response.

Goals of post-marketing requirements for companion diagnostics

The goals of regulatory and HTA post-marketing information requirements include obtaining data to determine the utilisation, real-life performance, clinical utility and comparative effectiveness of the test-drug combination as well the impact of new tests or methodologies as they emerge.

The utilisation of companion diagnostics was studied in 2009 by Barron and associates who examined the degree of physician adherence to 2001 guidelines recommending testing for HER2 expression in patients who are newly diagnosed with breast cancer. The researchers found that HER2 testing occurred in 88% of all newly diagnosed patients for whom testing was recommended. Among those in whom HER2 testing was performed, 22% were positive for over-expression, 77% were negative and the HER2 status of 1% was unknown. Of the 52 patients who used trastuzumab in this study, only 1 patient did not have documented HER2 over-expression. Of the 45 HER2+ women who had stage 2 or higher breast cancer, 13% did not receive trastuzumab.

Compared with the 22% patients with HER2+ tumours in this investigation, the percentage of patients whose tumours were found to over-express HER2 in clinical trials conducted for the registration of trastuzumab was approximately 80%, indicating that the clinical trial patients were not representative of the real-life population and that the benefit-risk ratio may need to be reassessed on the basis of post-marketing trials. As the study also shows that not all patients who tested positive for HER2 over-expression received trastuzumab, companion diagnostic utilisation testing would also yield useful data for the regulator and the assessor of health technology.

Test performance in real-life situations can vary according to the skills and performance...
of individual laboratories and the positive and negative predictive and cut-off values that are employed can depend on the tested populations.

Once approved, companion diagnostics will compete with alternative proprietary test or ‘in house’ tests. In diagnostic testing in which competing tests may be used, a potential patient may be screened in or out, depending on the test administered such as was the case with immunohistochemistry (IHC), fluorescence in situ hybridization (FISH) and chromogenic in situ hybridization (CISH) in trastuzumab testing. These differences would obviously exert an impact on both the benefit-risk balance and cost-effectiveness of a medicine.

In a 2010 publication, Dr Janet Woodcock, Director of the Center for Drug Evaluation and Research at the US FDA wrote that the clinical utility of a companion diagnostic can be determined by asking a simple question: “is the test worth doing?” Clinical utility, however, should be viewed in the context of the life cycle approach to medicine development and a post-licensing research plan will depend on its licensing pathway.

Cystic fibrosis, a childhood disease with serious unmet treatment needs is caused by the dysregulation of the cystic fibrosis transmembrane conductance regulator (CFTR) resulting from one of 1,800 different possible mutations. Kalydeco (ivacaftor) is effective in cystic fibrosis caused by 551D mutation, but not that associated with the F508del mutation, which is the most prevalent subtype. Its effectiveness in the many other mutations is not yet known and is a highly appropriate avenue for post-licensing research.

The fundamental information needs to determine comparative or relative effectiveness are relatively similar for companion diagnostic-guided and non-stratified therapies, although some specifics may differ such as the impact on cost effectiveness of a positive to negative test results ratio in a given population.

**Combined post-licensing pathway**

After licensing, both regulators and HTA assessors continue to need evidence to support treatment decisions using the approved medicine and companion diagnostic as well as evidence for the performance and utility of the test-drug combination. Unlike payers, however, regulators do not require additional information that supports stratification of recipients to maximise efficacy or its comparative or relative effectiveness (Figure 16). There is considerable overlap despite these divergences, however and a combined post-approval pathway could be developed by industry, regulators and health technology assessors that serves the information requirements of both communities.

**References**


Who will pay?

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Value of diagnostic-drug combinations

Traditionally, the key elements of value for therapeutic interventions are the health effects experienced by patients, that is, the therapy’s clinical efficacy or effectiveness measured by the quality-adjusted life year gained indicator (QALY) and the cost offsets, that is, the savings to the healthcare system. There are value dimensions not considered in this equation, however, such as society preferences for giving priority to certain patients or diseases; health-related quality of life aspects not reflected in generic measures used in comparative effectiveness analyses and healthcare process-related aspects such as dignity, time and location of treatment. Additionally, information provided to the patient may not be acted upon and lead to any change in health.

Pathways toward value for molecular diagnostics encompass their ability to reduce or avoid adverse drug reactions, reduce or avoid delay in selecting optimal treatment, increase patient adherence or willingness to start preventive interventions, enable the availability of therapies with a small proportion of responders and reduce uncertainty about value.

Attribution of value

When a treatment and a diagnostic are used in combination to target a subgroup of patients the total value created depends on the combination and the attribution of some portion of the value to one or the other is essentially arbitrary. This presents a challenge to the concept and operationalisation of valued-based reward for both diagnostics and treatments.

Consider an extreme situation in which a treatment cannot be used without a diagnostic test, there are significant adverse effects for the “wrong” patients who use the drug and the test currently has no other application. Assuming that the drug and test combined have a value of 100, if the test is taken away, the treatment has zero value and if the treatment is taken away the test has zero value. However, in other less extreme situations the test may increase the value of the drug by enabling it to be targeted. That is, assuming the net benefit to the health system of the drug on its own is 60 and with the test the net benefit increases to 100. Therefore the test adds value of 40. The test also has some value in the absence of the drug as it can be used to help target treatments that are much less effective. If the value of the test without the drug is 20, the drug increases the value to 100, adding 80 to the value of the test on its own. Thus it can be observed that there is no “correct” way of dividing the joint value of 100 between a test and drug. Benefit can be allocated using a rule similar to these, but the allocation is essentially arbitrary.

Diagnostics reimbursement is based on expected cost rather than on the delivered value. First-in-class diagnostics have to show clinical validity and payers are increasingly looking for evidence of clinical utility, but prices are usually still linked via an administered reimbursement system to a perceived cost, rather than to value. For the same reason, follow on tests with better predictive value cannot get higher prices. It is essential that both diagnostic-dedicated and drug health technology assessment (HTA) processes use a common, consistent and comprehensive approach to assessing value. This will provide a clear incentive to companies to invest in evidence collection to raise the standard of clinical utility data available to support the case for using a test. There is an emerging tendency among countries such as the UK and Australia to extend HTA arrangements to diagnostic tests.

Institutional processes affect the valuation
of a molecular diagnostic (Figure 17). In the United States, the Oncotype diagnostic was not developed as a companion diagnostic but was rather launched independently of a chemotherapy treatment. Under the current procedure-based code stacking approach in the United States, the 21-gene assay cost would have totalled approximately $580 with a Medicare fee schedule basis. Instead, however, the manufacturer pursued a value-based pricing model utilising diagnostic clinical trial and patient outcome studies to demonstrate clinical differentiation and cost-effectiveness. The main focus of the cost-effectiveness argument was the cost-offset obtained by not undertaking expensive chemotherapy treatments for women at low risk of disease recurrence. Thus the manufacturers were able to achieve reimbursement for the assay at roughly seven times the code-stacking reimbursement, that is, approximately $3,500. It took about four years to obtain nearly 90% payer coverage. However, in the United Kingdom the National Institute for Health and Clinical Excellence (NICE) Oncotype was evaluated based on the adverse effects avoided from chemotherapy use without expected benefit, that is, the quality-adjusted life year gained indicator, arriving at a £29,000 to £40,000 cost per QUALY and the technology was rejected.2

Pricing flexibility
Reimbursement systems for innovative medicines are currently not generally set up to cope with a drug that previously had a broad indication, but has now narrowed, albeit with greater benefit, since drug prices cannot go up after launch in most countries. Drug developers are under pressure to ensure that any targeting is reflected in the initial price at launch, thereby discouraging post-market investment in better targeting. There is a need for payers and pricing and reimbursement authorities to allow for flexible pricing (both up and down) for drugs after launch should evidence suggest they can be targeted in a narrower patient group or used in a number of different indications or subgroups of different value.

Drug developers bringing drug-test combinations to market are currently under pressure to keep the companion test as simple as possible because the ability to take that test through a regulatory, commercialisation and market access programme is infinitely more straightforward than taking a complex test through. Yet, in the next eight to ten years, this model of co-development of drugs and diagnostics may be seen as a transient phase where, for a range of mechanisms, a new diagnostic will initially be a companion diagnostic, but there will come a time as the molecular classification of disease becomes better understood, when all drugs targeting a particular pathway will use existing established tests.

Flexible development and regulatory and reimbursement routes are needed to make stratified drug development a viable business model in current circumstances. In the case of drug-test companion developments it is important initially that the delivery of a prototype assay for use in phase 3 development does not call for significant investment in advance of being in position to recognise the efficacy of the drug itself in phase 2. This flexibility may require the payer and pricing and reimbursement arrangements for drug-test combinations to concentrate on the evidence from the phase 3 drug development trial and not require a patient randomisation of a double randomised trial to use the test.

When clinical utility is demonstrated by a first-in-class test, others can “piggyback” on the evidence charging lower prices. A method is required to better manage intellectual protection for first-in-class tests but to also allow for innovation. Data exclusivity, such as used for medicines, is a regulatory tool to consider and could be given to evidence for diagnostics requiring follow-on tests to replicate the evidence generated by the first-in-class test.

In addition to the data exclusivity requirement, there must be an expectation that payers will pay more for the test with the stronger evidence base. There is also a need for greater flexibility in acceptance of diagnostic test evidence demonstrating clinical utility to payers, which returns consideration to the necessary evidence base for a diagnostic. Is the randomised clinical trial the right level of evidence? A pragmatic approach is required through which the clinical utility of diagnostics is assessed, but perhaps in small randomised studies, if they are not already built into phase 3, plus real-world data collection. Forms of coverage with evidence development...
can be used, but in order to facilitate real-world data collection we need increased investment in post-approval data collection mechanisms such as electronic health records.

References


### Appendix: Workshop Attendees

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<th>Regulatory and government agencies</th>
<th>Pharmaceutical and legal industry and consultancies</th>
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