MARKET ACCESS CHALLENGES FOR IN VITRO DIAGNOSTICS: SIMILARITIES AND DIFFERENCES BETWEEN US AND EUROPEAN MARKET

Tuesday, May 21st, 2013

HTA Special Interest Group (SIG)
HTA of Medical Devices & Diagnostic Working Group (WG)

Moderator & Speakers

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Outline:

- Overview and Introduction: Diagnostic Reimbursement and HTA in the US and Europe
- The unintended consequences of addressing Molecular Pathology Stacking Codes.
- Real world examples of HTA and payer actions impacting diagnostics in Europe
- Payer perspectives and actions impacting diagnostics in the US and Europe
- Q&A

Introduction: Diagnostic Reimbursement and HTA in the US and Europe

Susan Garfield, DrPH, MSc, SM
Sr. Vice President
Gfk Bridgehead
GLOBALLY WE FACE CHALLENGES FUNDING HEALTH CARE

BUT WHY ARE OUR HEALTH CARE COSTS HIGHER THAN OTHER COUNTRIES?..

WHO SAID THAT?

USA

DIAGNOSTICS NEED TO DEMONSTRATE VALUE TO PAYERS AND HTAS WITHIN THIS COST CONSTRAINED ENVIRONMENT

EVERYONE AGREES TO HELP REDUCE HEALTH CARE COSTS!...

I CAN'T AFFORD THAT DIAGNOSIS. DO YOU HAVE A CHEAPER ONE?
EACH COUNTRY IS REACTING TO BUDGET CONSTRAINTS WITH MEASURES TO REIGN IN SPENDING AND GAIN VALUE FOR HEALTH-CARE INVESTMENT

RECENT ANALYSIS HELPED CHARACTERIZE CONDITIONS IN DIFFERENT MARKETS PREDICTIVE OF TECHNOLOGY RECEPTIVITY AND FUNDING (PRESENTED AT ISPOR 2012)

Key Findings:

• Entrants to markets without an official regulatory body face stiff competition from non-standard or counterfeit comparator products.

• At the other extreme, some countries require substantial country-specific clinical evidence for approval, making them cost-prohibitive for smaller manufacturers.

• High government debt ratios and a publically funded health system were found to be predictive of increased austerity measures, which broadly have a negative impact on market access for new technologies.
BASIC DRIVERS OF MARKET ACCESS CREATE BOTH INDEPENDENT AND INTERDEPENDENT MECHANISMS THAT SUPPORT REIMBURSEMENT OUTCOMES

• DRG-based systems were found to be more receptive than markets that reimbursed inpatient facilities through annual global payments.

• The likelihood of a medical device receiving a HTA in any country is dependent on (1) regulatory requirements for market entry, and (2) the existence of device- and diagnostic-focused HTAs.

• In countries where inpatient procedures are funded by global payments, hospital-level reviews are more likely than a national assessment.
HTAs
- Processes vary by country
- Evidence requirements may be varied and non-explicit
- Groups that review “diagnostics” often also review “imaging diagnostics”
- Few diagnostic reviews have occurred
- Where reviews exist (i.e., IQWiG HPV testing analysis in Germany), comparative assessment and evidence base are critical
- General test utility versus product specific analysis
CODING AND PAYMENT INFRASTRUCTURES NOT DESIGNED FOR DIAGNOSTICS IN MOST CASES

- Many countries have simple diagnostic coding systems that don’t adequately describe innovations
- System for novel payment based on method rather than value
- System not yet in place for combined review of companion diagnostics and drugs in many settings

“Payers in Europe understand that you cannot isolate a diagnostic. They must be educated about the entire story. Industry must get involved with payers, though this is difficult because this decision-making happens at different points.” - German Payer

THIS FORUM WILL DISCUSS REIMBURSEMENT AND MARKET ACCESS CHALLENGES FOR DIAGNOSTICS IN THE US AND EUROPE

- The process of securing reimbursement and funding for a diagnostic test on a global scale is extremely challenging
- Stakeholders need to recognize what evidence payers/purchasers are looking for
- International reimbursement structures vary, so strategies and tactics need to be tailored to each market
- Global landscape of cost-effectiveness & comparative effectiveness expanding
Molecular diagnostics (MDx) are transforming the way health care is practiced today. These breakthrough diagnostics are:

1. Providing precise information on disease states
2. Improving accuracy of therapies
3. Saving doctors from prescribing expensive drugs to patients who wouldn’t respond to them
4. Enabling physicians to help their patients avoid adverse events
5. Helping to manage health care costs
6. Lending themselves to quantified results
• There are over 3,000 molecular and genetic diagnostics marketed for clinical use, both LDTs and FDA cleared IVDs.

• According to Frost & Sullivan, MDx is the fastest growing sector of clinical pathology lab testing.

• National costs for MDx reached $6.2 billion in 2010, growing at 15 to 20% a year.

• In November 2010, the Chief Medical Office at CMS termed this growth as a “tsunami of tests” that could soon become unaffordable. Obviously this is not a positive forward looking statement for MDx.

Stacking Codes or methodology-based code stacks for molecular assays precludes identification of the assay actually performed. Use of such code stacks makes it impossible to evaluate the service rendered and the medical necessity for many molecular assays submitted for payment.
MOLECULAR PATHOLOGY STACKING CODES

Molecular Pathology Stacking Codes

- 83890 molecular isolation or extraction
- 83892 enzymatic digestion
- 83898 amplification
- 83903 mutation scanning
- 83904 mutation identification by sequencing
- 83907 lysis of cell

WHO ARE THE PLAYERS SOLVING THIS ISSUE?

- American Medical Association (AMA)
- Association for Molecular Pathology (AMP)
- Palmetto GBA
- McKesson
- CAP
- MolDx
- BlueCross BlueShield Association
- CMS
WHO ARE THE PLAYERS SOLVING THIS ISSUE?

- AMA
- Association for Molecular Pathology
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- PALMETTO GBA
- cap
- BlueCross BlueShield Association
- CMS
WHO ARE THE PLAYERS SOLVING THIS ISSUE?
December 2009 The CPT Editorial Panel Molecular Pathology Coding Workgroup (MPCW) was charged to construct new CPT codes to report molecular pathology.

In January 2013, stacking codes were replaced with 127 newly created molecular pathology CPT codes.

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>MAAA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Volume Tests</strong></td>
<td><strong>Low to mid volume tests</strong></td>
<td><strong>Multianalyte Assays with Algorithmic Analyses</strong></td>
</tr>
<tr>
<td>Code is assay specific</td>
<td>Levels of complexity</td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>1-9</td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td></td>
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<tr>
<td>BRCA</td>
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</tbody>
</table>
Given the limitations of the CPT process, these CPT codes still do not have the capacity to accurately identify the individually “proprietary” based LDTs nor the generated differential results.

Palmetto GBA developed the MolDx program to systematically catalog and determine coverage for genetic tests. For each genetic test, MolDx determines if Medicare coverage for the test is appropriate, and establishes rates of reimbursement.

MolDx performs a technical assessment (TA) to determine whether the test meets coverage requirements. A positive coverage decision is equivalent to subjugating the FDA regulatory process.

McKesson developed a comprehensive, industry-wide master catalog and began assigning unique IDs and gathering information for MDx.

**McKesson “Z-codes”** identify the test, laboratory, ordering physician, reason for ordering, and results — similar to the health plan-defined HCPCS S-codes.

*January 04, 2012*
AMA Threatens to File HIPAA Complaint Unless CMS Halts Program Requiring Z-Codes for MDx Tests

*February 26, 2013*
American Medical Association and McKesson Team Up to Bring Transparency and Clarity to Molecular Diagnostic Testing
In January 2013 CMS directed the Medicare Administrative Contractors (MACs) to individually determine (Gap-filling) a reimbursement amount for each molecular pathology code. A median reimbursement rate will be calculated from the individually produced reimbursement rates and become effective January 1, 2014.

Initial Gap-filling Results Are Chaotic!

- Initially Palmetto only published reimbursement rates for LDTs tests, not FDA cleared tests.
- Palmetto has differentiated reimbursement for LDTs from FDA Cleared test via Z-codes.
- Cahaba did not differentiate between LDTs and FDA cleared tests.
- Noridian did not differentiate between LDTs and FDA cleared tests.
- CGS did differentiate between LDTs and FDA cleared test to a greater degree than Palmetto and closely followed Palmetto’s pricing.

Overall there is a 20% discount over the previous stacking codes.
A coalition representing over 120,000 medical and laboratory professionals and institutions that perform the vast majority of clinical molecular pathology testing in the United States released a joint statement regarding new Medicare prices for those tests.

American Association for Clinical Chemistry (AACC)
American Clinical Laboratory Association (ACLA)
American College of Medical Genetics and Genomics (ACMG)
American Society for Clinical Pathology (ASCP)
American Society for Histocompatibility and Immunogenetics (ASHI)
Association for Molecular Pathology (AMP)
California Clinical Laboratory Association (CCLA)
College of American Pathologists (CAP)
Society for Inherited Metabolic Disorders (SIMD)

The coalition's concerns include:
- Cuts in reimbursement for molecular pathology tests,
- Denials of claims without publication of sufficient information on the basis for those decisions,
- Incorrect determinations that certain tests are investigational.

Their recommendations include:
- Removing coverage and payment restrictions,
- Providing greater transparency about the evidence for coverage decisions and basis for payment decisions,
- Extending the period for reconsideration of denials,
- Convening stakeholder meetings with CMS.
LDTs have gained a 4 year head start over manufacturer kit developed tests

<table>
<thead>
<tr>
<th></th>
<th>Manufacturer</th>
<th>LDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>1-2 YR</td>
<td>0.5 YR</td>
</tr>
<tr>
<td>FDA</td>
<td>1 YR</td>
<td>0.0 YR</td>
</tr>
<tr>
<td>CPT</td>
<td>2-3 YR</td>
<td>0.0 YR</td>
</tr>
<tr>
<td>Z-Code</td>
<td>0.0 YR</td>
<td>0.5 YR</td>
</tr>
<tr>
<td>Total</td>
<td>5-6 YRS</td>
<td>1 YR</td>
</tr>
</tbody>
</table>

Evidence: LDTs only need to provide data to support laboratory performance and quality results, FDA cleared tests need to present evidence to support intended use.

Is this good medical policy?

Do we really want to create an environment that would encourage manufacturers to by-pass the regulatory process given that most patient treatment decisions are based on clinical laboratory diagnostic tests?
CLFS VS PFS

Many of the procedures covered by the codes can be performed without physician involvement;
• Placing these new codes on the PFS would subject them to patient copay
• Placement on the CLFS maintains the fee schedule that had been in place through CLFS using various stacking codes
• Placing the new codes on the CLFS will provide consistency if NCDs or LCDs are proposed by CMS or local contractors in the future.

CMS created G0452 for the option of an add-on physician interpretation code for any procedures that must have physician interpretation to produce results.

BREAKING NEWS!

Selected Genetic Tests for Cancer Diagnosis, Medical Evidence Development and Coverage Advisory Committee (MEDCAC)
May 1, 2013

MEDCAC Question #4
Please discuss the evidence as presented; may be generalized based on each of the following factors:
 a. Regulatory status of test (e.g., FDA approved/cleared vs. Laboratory-developed test)?
 b. Site of testing (e.g., University Medical Center or commercial laboratories vs. community-based laboratories)?
 c. Patient sub-groups within the Medicare beneficiary population (e.g., age)?

The question was not addressed by either the technology assessments or the MEDCAC panel members!
OUTRAGE OVER NON-PAYMENT OF MOLPATH TESTS!
A CONSEQUENCE OF THE GAP-FILLING PROCESS.

Forbes Tells the World How Medicare Bollixed
Molecular Diagnostic Test Payments, Leaving Nation’s
Clinical Laboratories Unpaid for Months

April 22, 2013
At this time most clinical laboratories are not being paid for molecular tests. This is probably the most under-reported story in the medical laboratory industry. For that reason, our sister publication, The Dark Report, devoted its latest issue (dated April 15, 2013) entirely to this important topic.

CHRONOLOGY OF EVENTS

2005 CAP-chaired Genetic Testing Workgroup and approved by the CAP-chaired Pathology Coding Caucus before approval by the CPT Editorial Panel
2009 AMP Memorandum - The AMP committee worked independently of the AMA CPT process, but developed a detailed coding system framework which is very similar to that later approved in 2010 by the much larger Molecular Pathology Coding Workgroup that did report through the Pathology Coding Caucus to the AMA.
December 2009 The CPT Editorial Panel Molecular Pathology Coding Workgroup (MPCW) was charged to construct a new subsection of the CPT Pathology and Laboratory subsection, guidelines, definitions and new CPT codes to report molecular pathology.

September 1, 2010 Palmetto GBA launched the first phase of a new program that is intended to increase the Medicare administrative contractor’s (MAC) accuracy rate for determining reasonable and necessary laboratory and molecular diagnostic services
September 28, 2011 Palmetto GBA issued a local coverage decision. The draft LCDs represent Palmetto GBA’s efforts to identify the growing number of laboratory-developed molecular diagnostic assays and genetic tests.

December 28, 2012 In the 2013 Medicare Physician Fee Schedule (MPFS), CMS ruled that the new molecular pathology codes will be paid under the Clinical Laboratory Fee Schedule (CLFS) and CMS chose gap-filling which means that local Medicare contractors will set the fees for 2013 based on local pricing patterns, e.g. what labs currently charge for the tests including discounts, what other payors reimburse for the same test, and what contractors pay for similar tests.

January 04, 2013 AMA Threatens to File HIPAA Complaint Unless CMS Halts Program Requiring Z-Codes for MDx Tests
June 1, 2012 Under the MolDx program, all labs that perform molecular diagnostic testing and bill in Jurisdiction E must register each assay and be assigned a unique identifier (either a McKesson Z-Code or a Palmetto Test Identifier). The labs must then submit test information and supporting evidence in order to seek payment from Palmetto.

January 1, 2013 AMA publishes 127 newly created MDx CPT codes
February 26, 2013 American Medical Association and McKesson Team Up to Bring Transparency and Clarity to Molecular Diagnostic Testing
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Table II.3
Medicare Benefit Payments by Type of Benefit
Fiscal Years 2008 - 2010

<table>
<thead>
<tr>
<th>Benefit Payment</th>
<th>Amount in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hi 1</td>
<td>217,791 334,362 245,180 100.0%</td>
</tr>
<tr>
<td>Inpatient Hospital</td>
<td>128,853 132,768 137,834 56.2</td>
</tr>
<tr>
<td>Skilled Nursing Facility</td>
<td>24,117 25,826 27,047 11.0</td>
</tr>
<tr>
<td>Home Health Agency</td>
<td>8,833 8,043 7,138 2.5</td>
</tr>
<tr>
<td>Hospice</td>
<td>11,137 11,977 12,910 5.3</td>
</tr>
<tr>
<td>Managed Care</td>
<td>47,160 60,780 60,253 24.8</td>
</tr>
<tr>
<td>Total GMI 2</td>
<td>353,017 355,726 265,410 100.0</td>
</tr>
<tr>
<td>Physician/Other Suppliers</td>
<td>64,240 87,040 88,771 33.1</td>
</tr>
<tr>
<td>Outpatient Hospital/Other Providers</td>
<td>56,211 49,522 44,130 16.3</td>
</tr>
<tr>
<td>Home Health Agency</td>
<td>16,100 11,328 12,067 4.5</td>
</tr>
<tr>
<td>Laboratory</td>
<td>7,033 7,410 6,139 3.0</td>
</tr>
<tr>
<td>Managed Care</td>
<td>43,088 63,109 64,786 23.4</td>
</tr>
<tr>
<td>Prescription Drugs</td>
<td>46,726 58,580 63,828 23.7</td>
</tr>
</tbody>
</table>

1 Includes the effect of regulatory changes and recent legislation, but not proposed law.
2 Excludes QIO expenditures.
NOTES: Based on 2011 Medicare Trustees Report. Benefits by type of service are estimated and are subject to change. Totals do not necessarily equal the sum of rounded components.

SOURCES: CMS/ACT/OFP

December 2011

FORUM

Real world examples of HTA and payer actions impacting diagnostics in Europe

Nick Poullos, PhD, PhD
Head, Medical Outcomes – Reimbursement & Economics, Roche Molecular Systems, Pleasanton, CA, USA
INCREASED HTA ACTIVITY WORLDWIDE

INAHTA – International Network of Agencies for Health Technology Assessment has now grown to 53 member agencies from 29 countries.

Bodies performing HTA per country (TOTAL 105)*

CAN HTAS CONTROL HEALTH SPENDING?

• Recently Established HTA
  ✓ South Korea (ref – Australia)
  ✓ Taiwan (ref – Canada/US)
  ✓ Brazil (ref – Canada/UK)

• HTA Under Review
  ✓ Singapore (ref – UK/Australia)
  ✓ Hong Kong (ref – UK/Australia)
  ✓ Thailand (ref – UK/Australia)
  ✓ China (ref ?)
  ✓ Turkey (ref – UK)

• In Discussion
  ✓ India
  ✓ Japan
  ✓ Russia

Health Expenditures as % of GDP (2010)
1. Assessment topics chosen (EGFR & KRAS)

2. Stakeholders invited to register

3. Scope prepared by NICE tech team
   • Defines the disease(s), the patients and the technology/ies
   • NICE asks the manufacturer(s) for relevant data
   • Scope is drafted by the NICE technical team and a scoping workshop involving registered stakeholders is held

4. Specialist Committee members recruited
   • The DAC is an independent advisory committee. Specialist members with expert knowledge of the subject are recruited

5. Scope finalised
   • The scope is finalised by a subgroup of the Diagnostics Advisory Committee, the Assessment subgroup

6. Information provided by stakeholders
   • Data - published and unpublished

7. Diagnostic assessment report prepared
   • By independent academic centre

8. Diagnostics Advisory Committee meeting
   • the diagnostics assessment report
   • comments received from registered stakeholders
   • an overview prepared by NICE technical team

9. Draft recommendations issued for public consultation

10. Final guidance produced

11. Resolution

12. Guidance issued
DAP PROCESS TIMELINE: 12 MONTHS+

**NSCLC EXAMPLE: DAP ASSESSMENT CHALLENGES**

Set the stage:
1. NSCLC - most common lung cancer in England & Wales, around 72% of all lung cancer cases
2. NICE TA guidances 192 & 258 recommend Gefitinib & Erlotinib for the 1st-line treatment of locally advanced or metastatic NSCLC
3. Frequently used Dx Tests:
   - Therascreen, Sanger sequencing, cobas® EGFR, pyrosequencing

Provisional recommendations:
1. Decision on technologies evaluated & recommended (or not)
   - Defines the disease(s), the patients and the technology/ies
   - Limited peer-reviewed publications/data
2. Decision - Outcomes
   - Tests are similar: however, LDTs should be designed to detect the mutations that can be detected by one of the CE-marked tests as a minimum
   - Inconclusive evidence: although C-E of the different tests and test strategies for EGFR-TK mutation testing are likely to be similar, there is insufficient evidence to support this conclusion
WHERE ARE HTAS GOING NEXT?

2014: Value Base Pricing Replaces PPRS

VALUE-BASED PRICING

VBP provides an opportunity

1. Access to new technologies – based on social values & budget constrained NHS

2. Aspects of value:
   1. Premium for innovation
   2. Severity, burden & need
   3. Wider economic benefits
   4. Uncertainty, evidence and investment

Caveat: it is not enough to establish that a new technology offers benefits to patients, carers and the wider economy, but that these benefits exceed those likely to be forgone as a consequence of the additional costs of the technology.
Challenges & Opportunities

1. **Standard practice**: Clinicians doing more (EGFR, BRAF, KRAS – HER2)

2. **Moving on to sequencing**: ideal is complete mutation testing
   - Knowledge about mutations evolves
   - Tumours evolve in response to treatment

3. **Tissue samples & other challenges**: tissue size & quality
   - FDA requiring a single CDX for every therapy - problematic

**Issue**: we don’t have 500 drugs for lung cancer, but we can test > 500 genes … a lot of academic centers will switch to sequencing and more multiplex testing during the next couple of years

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**FORUM**

**Payer perspectives and actions impacting diagnostics in the US and Europe**

**Eric Faulkner, MPH**
Director, Quintiles Global Market Access Consulting; Executive Director, Genomics Biotech Emerging Medical Technology Institute, National Association of Managed Care Physicians; Assistant Professor, Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, Research Triangle Park, NC USA  
[eric.faulkner@quintiles.com]
GENERAL PAYER CONSIDERATIONS FOR NEW HEALTH TECHNOLOGIES (INCLUDING DIAGNOSTICS)

• How can we best ensure the right test or treatment solution is targeted to the right patients?

• Do we have the right strength and level of evidence to inform access and management decisions?

• Which technologies & procedures are better than others? What are the differentiating characteristics among them?

• Do coding or health information systems enable sufficiently granular health outcomes assessment and resource management?

GENERAL PAYER CONSIDERATIONS FOR NEW HEALTH TECHNOLOGIES (INCLUDING DIAGNOSTICS) (2)

• How do we manage the array of technologies that end up being “additive” in terms of budget impact when things don’t “fall off the conveyor belt”?

• Do any regulations, policies or perceptions prevent us from doing the “prudent thing”?

• What are the right incentives & levers to support innovation and appropriate access, while limiting marginal or ineffective technologies?
OTHER STAKEHOLDERS BEYOND THE PAYER ARE ALSO CRITICAL FOR TEST ACCEPTANCE & HAVE DIFFERENT DECISION DRIVERS & EVIDENCE NEEDS

Key Dx & CDx Stakeholders

- **Oncologist** suspects cancer and orders biopsy
- **Hospital Administrator** may influence acceptance based on cost factors
- **Sample procurer** collects tumor sample and sends to lab
- **Lab / Pathologist** tests tissue for malignancy and for biomarker with companion diagnostic
- **Patient** may have preferences on test acceptance (e.g., if invasive or surfaces information they’d rather not know
- **Payers** reimburse test and drug

Common Questions Related to Test Acceptance

- What testing platforms & laboratory contracts are in place?
- Would the new test disrupt operations?
- Would the lab conduct the test in-house or outsource to a reference lab?
- What are the economics associated with running the new Dx in terms of cost, sample flow & staff requirements?
- Is there sufficient tissue to support testing? Are there provisions for storing samples?
- Would the hospital support a "loss leader" test if there is sufficient cost offset related to treatment use?

PROMISE VS. PRACTICE DISCONNECT: US PAYERS VIEW DIAGNOSTICS AS ONE OF THE MOST IMPACTFUL TECHNOLOGIES BUT MOST HAVE NOT DEVELOPED HTA CRITERIA

On a scale from 1-10, please rank the following technology types in terms of greatest potential to impact quality & cost of care, where 1 = lowest impact and 10 = highest impact.

- **Molecular Dx**
- **Personalized Medicine**
- **Biologic**
- **Vaccine**
- **Medical Device**
- **Cell & Gene Therapy**
- **Nanotech**

- **Over 60%** of respondents indicated that molecular diagnostics had high potential to impact quality + cost of care
- **Molecular diagnostics and personalized medicines** ranked second only to vaccines (9-10) in terms of potential to impact quality + cost of care
- **BUT…only 44%** have evolved criteria or practices for Dx AND **52%** indicated limited understanding of Dx “issues”

Source: 2012 US commercial payer survey of National Association of Managed Care Physicians (NAMCP) membership, N = 56
US PAYER PERSPECTIVES ARE HIGHLY VARIABLE IN TERMS OF WHAT TYPES OF DIAGNOSTICS EVIDENCE IN MOST IMPORTANT

- Clinical utility, and change in patient management were view as most important by greatest proportion
- BUT...responses were mixed suggesting that perspectives remain highly heterogeneous in regards to payer perspectives on diagnostic tests and we are still in “learning curve” mode
- While Ex-US perspectives may be differently distributed, similar heterogeneity would not be unexpected

What evidence of test value is important in developing policies on molecular or companion diagnostics?

- Clinical utility
- Test use changes patient mgmt/care pathway
- Clinical validity
- Test application (e.g., screening, diagnosis, monitoring)
- Absolute test performance
- Cost-effectiveness of test vs. SOC
- Absolute test cost
- Incremental test performance

Source: 2012 US commercial payer survey of National Association of Managed Care Physicians (NAMCP) membership. N = 56

GRAPPLING WITH THE RELEVANT VERNACULAR: THE DEVIL IS IN THE DETAIL FOR MARKET ACCESS

How do you define clinical utility of a diagnostic test?

- Test is used to improve outcomes
- Test is used to inform patient mgmt
- Test performance (i.e., sensitivity, specificity, etc.)
- Test measures a clinically meaningful variable

- In 2007 an NAMCP survey showed that only 38% of payers correctly defined clinical utility...this improved to 49% in 2012 reflecting payer business emphasis on diagnostics
- Also...suggests that payers can learn new things given enough time! 😊
  [Direct evidence on health economists not available]

Source: 2012 US commercial payer survey of National Association of Managed Care Physicians (NAMCP) membership. N = 56
EVEN GIVEN HETEROGENEITY, A GLOBAL LOOK AT POINT OF CARE (POC) DIAGNOSTICS SHOWS SOME COMMONALITIES

- A November 2012 analysis of POC tests indicated that clinical utility & validity, comparative effectiveness vs. SOC tests, and characterization of unmet need were key HTA focal points
- For tests that were rejected, HTA agency reports reflected greater scrutiny of budget impact & comparative effectiveness
- Although CER has not been a key focus of Dx historically, if this emphasis increases it will influence the scope and nature of study designs that may be applicable

Table 1. Frequency of POCT HTA Recommendation Categories and Criteria Scrutinized

<table>
<thead>
<tr>
<th>Top Individual Criteria Scrutinized</th>
<th>Recommended as Alternative to SOC (%)</th>
<th>Recommended as Adjacent to SOC (%)</th>
<th>Recommended as Alternative OR Adjacent to SOC (%)</th>
<th>Rejected (%)</th>
<th>No Recommendation Mode (%)</th>
<th>All HTAs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Total HTAs Reviewed</td>
<td>23%</td>
<td>19%</td>
<td>38%</td>
<td>21%</td>
<td>41%</td>
<td>100%</td>
</tr>
<tr>
<td>First</td>
<td>• Disease Burden (91%)</td>
<td>• Agreement With SOC Test (80%)</td>
<td>• Comparative Effectiveness/ Clinical Utility (88%)</td>
<td>• Comparative Effectiveness/ Clinical Utility (93%)</td>
<td>• Disease Burden (93%)</td>
<td>• Disease Burden (93%)</td>
</tr>
<tr>
<td>Second</td>
<td>• Comparative Effectiveness/ Clinical Utility (87%)</td>
<td>• Comparative Effectiveness/ Clinical Utility (90%)</td>
<td>• Disease Burden (64%)</td>
<td>• Disease Burden (92%)</td>
<td>• Comparative Effectiveness/ Clinical Utility (85%)</td>
<td>• Comparative Effectiveness/ Clinical Utility (88%)</td>
</tr>
</tbody>
</table>


GETTING SPECIFIC: SOME HTA AGENCIES AND PAYERS ARE EVOLVING EXPLICIT AND DETAILED CRITERIA FOR DIAGNOSTICS AND COMPANION DIAGNOSTICS

PBAC MSAC Guidance on Assessing Codependent Technologies

Retains the prize for most organized & transparent approach...

Sample Qs cover multiple dimensions

Role of biomarker

Test performance

Epidemiology

Comparative effectiveness

Patient Management

Outcomes

Cost-effectiveness

Is there a clear definition of the biomarker(s)? What is the biological rationale for targeting that biomarker(s) with the drug?

What is the analytical test performance?

What is the prevalence of a true positive biomarker in the population likely to receive the test?

Is the test an additional test to other(s) currently defining the condition? Or a replacement test? Or both

Can the proposed drug be used with other specific tests for that biomarker, other than the test proposed? What methodologies are available to test for the marker?

Is there direct evidence of prognostic impact associated with different biomarker status?

Does the direct evidence provided show a clinically important and statistically significant impact on patient-relevant health outcomes?

Is there linked evidence available of the test’s impact on patient health outcomes?

Was the positive predictive value (PPV) of the test calculated and included in the model?

Was the incidence of drug-related adverse events for true positives and false positives included?
WHILE TEST PERFORMANCE IN INCREASINGLY INTEGRATED INTO PERSONALIZED MEDICINE HTA, IT IS OFTEN NOT THE DOMINANT FACTOR FOR REIMBURSEMENT REJECTION

While development for Crizotinib was superior, costing 30% less, requiring 2,000 fewer patients, and 3 years quicker for regulatory approval, the drug was initially rejected for reimbursement based on cost-effectiveness & mixed treatment comparison issues.

**Clinical Trial Development Costs**
- Xalkori: $26
- Iressa: $39
- Tarceva: $40

**Total Clinical Trial Enrollment**
- Xalkori: 960
- Iressa: 2850
- Tarceva: 3110

**Phase 1 Initiation to New Drug Application**
- Xalkori: 1.8 years
- Iressa: 7.0 years
- Tarceva: 5.3 years

**Core Outcomes**
- Median PFS increased by 4.7 months compared with chemotherapy, non-significant OS difference.

Source: Quintiles analysis

**Initial HTA Rejection**

**Core Rationale:**
- Insufficiently cost-effective (£181K/QALY)
- No comparative effectiveness data; PFS with no mixed treatment analysis, QoL assumptions

**Key Considerations:**
- Test information played a minor role in terms of key rationale
- Is there a pricing threshold for personalized medicine irrespective of responder size?
- What are the implications for personalized medicine business models?

**Core Rationale:**
- Insufficient comparative effectiveness evidence vs. best supportive care
- Methodological issues making interpretation difficult

**Getting Real? Are Evolving Real World Evidence Study Methodologies Relevant for Dx...The Jury is Still Out**

Existing system for rewarding value for Dx makes it difficult for test manufacturers to develop evidence to explore every “nook & cranny” in developing a comprehensive evidence base.

**Key RWE Considerations**
- How clear is evidence characterizing the association between the biomarker & target disease state?
- How to characterize differential value & outcomes given that most IVD tests (for now) have nondescript coding?
- How and to what extent is do studies characterize the role and use of the test in patient management?
- What evidence around clinical utility for standalone tests may need to be filled outside of a pivotal validation study? What about CER?
- How to address evidence gaps for lab developed tests vs. FDA approved tests? How will pressure mount for this and what are the rules of the road?
- How to balance additional evidence “asks” given lack of value-based reimbursement?

Source: Faulkner E. Real world evidence and implications for emerging technologies. NAMCP Spring Managed Care Forum 2013.
A variety of additional factors complicate development, launch, and market access planning for diagnostics. Each of these can be curveballs influencing evidence development, willingness to innovate, and evolution of testing technology.

### Technological
- Next generation sequencing
- Circulating tumor cell
- Decision analytic tools & algorithms
- Health information technology & data resource development

### Clinical & Value-based
- Clinical pathways & more rigid guidelines
- Comparative effectiveness
- Value-based reimbursement models
- Evolution of test evidence standards & development models

### Economic
- Market economy collapse & “belt tightening”
- Regulatory & reimbursement reform
- Cost-effectiveness
- ACO models (US)
- Conditional coverage/CED