Reimbursement Strategy for Companion Diagnostics: Emerging Models and Requirements

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Definition

*Companion diagnostic* – A diagnostic test used to predict the likely clinical effectiveness and/or safety of a particular therapeutic intervention for a specific individual; the term is most often used to describe a molecular diagnostic test that stratifies a patient population with regard to the likelihood of response to, or the safety of, a pharmacologic therapy.
An Ongoing Medical Revolution

• Personalized medicine
  – The right Tx
  – For the right patient
  – In the right amount
  – At the right time
• Proteomics and Pharmacogenomics are critical enabling technologies
• Dx is the key to success
Limits of Traditional Medicine

- Tx success is frequently probabilistic
  - Protocols based on population-wide data
  - Non-response rates are high
  - Complication rates are high
  - Determinants of success are poorly known

- Informed guessing yields
  - Delays in identifying effective Tx
  - Exposure to unnecessary risks
  - Enormous financial, time and opportunity costs
Low Response Rates to Rx

Do higher response rates yield more complications?

After Spear et al. TRENDS in Molecular Medicine Vol. 7 No. 5 May 2001
Drug Developers Have A Parallel Problem

• Lengthy and expensive product development process
  – Size and duration of clinical trials is a major factor
• Painfully low yield rate on compounds screened
• High failure rate in clinical trials
• Phase IV (and beyond) safety issues
Companion Diagnostics

- Can yield substantial improvements in clinical care
- Promise major efficiencies and savings in drug development
- Contribute to more effective and efficient use of society’s investment in health care
In the Clinic …

• Stratify patient population on the basis of validated indicators of Tx/Rx effectiveness and/or safety
  – Increase Rx response rates
  – Decrease Tx complication rates
• Better and safer Tx targeted to the individual patient
• Less time and money wasted
In Drug Development …

• Targeted screening of compounds allows better choices for clinical development
• Ability to recruit patients who are likely responders yields smaller clinical trials with higher probability of success
• Economics of drug development transformed
  – Development time and cost reduced
  – Blockbuster model severely threatened
For Society …

• Targeted Tx selection means higher return on health care investment
  – Less ineffective or unnecessary care
  – Fewer complications and adverse events
  – Healthier population
  – Lower health insurance costs?
  – Reduced opportunity costs
  – Control of health care share of GDP?
Success Ought to Follow

• All affected parties seem to benefit
• No obvious major structural impediments
• No powerful adversaries
Many Positive Signs

• Technology platform is real and rapidly developing
• Drug and diagnostics companies are deeply engaged
• Venture capital is being invested (Dx)
• Various business models are being tried
• Regulatory agency (FDA) is on board
• “Buzz” is positive and growing
DHHS Is Supportive

• Secretary’s Advisory Committee on Genetics, Health and Society
  – http://www4.od.nih.gov/oba/SACGHS.HTM

• Dedicated website
  – http://www.hhs.gov/myhealthcare/

• “Personalized Health Care: Opportunities, Pathways, Resources”, Sept. 2007
FDA Programmatic Activities

- Critical path initiative
- Adaptive clinical trials
- Guidance for industry
  - Pharmacogenomic Data Submissions, 2005
  - Drug-Diagnostic Co-Development Concept Paper, 2005
- “Table of Valid Genomic Biomarkers”
Significant Rate-Limiting Factors

• Regulatory pathway and standards need to be refined, optimized
• Clinicians and regulators need to be educated and recruited into a new model of Tx and Rx selection
• Payers need to provide coverage and adequate payment for stratifying Dx
  – New decision making paradigms needed?
CHICKEN / EGG PROBLEM

• Industry blames slow progress on lack of clearly defined regulatory pathway, criteria and guidance
• FDA typically develops guidance documents through case accretion
  – generalizing from and codifying early experience
• Industry is stepping up demands for clearer FDA leadership
Private Payer Coverage Status

• Generally aware of pharmacogenomic developments
  – Coverage for Dx/Rx pairs is case-by-case
  – Traditional decision criteria have worked so far
  – Limited experience → no commitment to a model
  – Critical mass not yet reached

• Some PBMs understand the issues well
  – Uniquely positioned to evaluate and manage the financial benefits of companions
  – Report more receptivity from self-insured employers than from third party insurers
Critical Mass Not Yet Achieved

- Small # of established Dx/Rx pairs in clinic
  - HER2 → Herceptin
  - CYP2C9/VKORC1 → Warfarin
  - CYP2D6 → Tamoxifen
  - EGFR → Erbitux
  - And just a few more
- More in pipeline, but accretion rate is disappointing to many
Where is Medicare?

- Little knowledge and no planned action
  - Full plate re: traditional therapies
  - Staff and other resource constraints
- General perception of a looming issue
  - Open to education process
- Lagging private insurers in issuing case-specific coverage policies
  - Need a compelling first move (Warfarin?)
  - Will use traditional criteria by default
Priorities for Gaining Coverage

• Understand the traditional coverage criteria

• Integrate reimbursement planning into clinical development plan
  – Leverage FDA process and outcome

• Recognize the primacy of the therapeutic goal
  – Focus on clinical utility of Dx
  – Lock utilization into labeling
TEC* Coverage Criteria

• Final regulatory body approval
• Scientific evidence permits conclusions re: effect on health outcomes
• Improves net health outcomes
• As beneficial as any established alternatives
• Improvement attainable outside the investigational setting

*Blue Cross Blue Shield Technology Evaluation Center
TEC Review is Rigorous

- Requires peer-reviewed journal publications
- High premium on randomized double-blinded trial design
- Results are advisory to regional Blue Cross Blue Shield plans
  - Formal agreement with Kaiser Permanente
- Availability via Website means smaller insurers have free access
  - http://www.bcbs.com/betterknowledge/tec
CMS Coverage Criteria

• Reasonable and necessary standard
• Based on review of the relevant clinical evidence
  – Quality of individual studies
  – Generalizability of findings to the Medicare population
  – Overarching conclusions re: direction and magnitude of potential risks and benefits
CMS Hierarchy of Trial Designs

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case-control studies
- Cross-sectional studies
- Surveillance studies
- Consecutive case series
- Single case reports
CMS Considers Multiple Inputs

• Staff analyses
• Contracted analyses
• External technology assessments
  – E.g. TEC, ECRI,
• Position statements by relevant groups
• Expert opinion
• Public comments
Leverage FDA Process For …

• Unequivocal confirmation of biomarker validity – both analytic and clinical
• Demonstration of objective basis for stratification of patient population
• Empirical evidence of clinical utility
  – link between Dx status and Tx success
  – Minimization of probabilistic element
• Dx/Rx tied by label indications
FDA Process Design (1)

Biomarker Development

[Diagram showing the process of biomarker development, including stages such as Basic Research, Prototype Design or Discovery, Preclinical Development, Clinical Development, and FDA Filing/Approval & Launch, with sub-stages like Target Selection, Identification of Stratification Markers, Clinical Utility for Stratification Marker, and Label Considerations Based on Trial Results.]

Analytical Validation
Pre-Clinical Feasibility
Clinical Validation
Clinical Utility
FDA Process Design (2)

Dx-Rx Co-Development

- Characterize and learn about the biology, e.g. identify affected biological pathways
- Validation
- Basic Research
- Prototype Design or Discovery
- Preclinical Development
- Clinical Development
  - Phase 1
  - Phase 2
  - Phase 3
- FDA Filing/Approval & Launch
- Identification of Disease Targets
- Optimizing the Safety Profile
- Streamline Clinical Trials (Enrichment, Stratification)
- Target Optimization
- Consideration of impact on label: Is it a "development only" biomarker or should it be used in the market?
Co-Development Works Best

• Dx and Rx tied intimately from first step
  – Increased likelihood of Rx success
  – Success linked empirically to Dx status
    • Single unified clinical plan
  – Coverage decision for Rx is straightforward
    • Demonstrated clinical utility in population defined by Dx
  – Coverage of Rx demands coverage of Dx
Other Scenarios Raise Problems

• Dx development w/out Rx
  – Payers will not cover a biomarker test until there is demonstrated clinical utility
  – Development is for drug discovery market only

• Dx development for established Rx
  – Needs clinical demonstration that stratification improves therapeutic response rate
    • Expensive and lengthy clinical trial
    • Payers perceive unresolved methodological issues
    • Investment may not be justified by potential gains
Payment is Uneven

• Private insurer payment levels generally perceived as good by genetic testing labs
  – Low financial impact due to volume restraint
  – Expect price sensitivity as more tests are covered and volumes increase

• Medicare payment is inadequate
  – Clinical lab fee schedule frozen until 2010
    • A fraction of 1983 median charges
  – Bizarre state-to-state variation for molecular tests
Lab Coding System is Broken

- Most payments based upon CPT codes
- Molecular diagnostic tests are coded by processes, not by analyte
  - A single test may require multiple processes and process repetitions
  - Payers are hard-pressed to know what they are paying for
  - Ability to perform retrospective analyses is severely limited
Need To Pay For Value

- Will require agreement and coordination by many independent parties
  - AMA controls the CPT coding system
  - Congress mandates Medicare Clinical Lab payment methodology
  - CMS implements policy, integrates new test codes
    - Prescribed rules allow little flexibility
- Can only code a finite number of analytes
If Payment is Inadequate…

- Dx development cost is a fraction of Rx
- Dx charge is a fraction of Rx charge
  - One time vs. long-lasting
- Consider alternatives to Dx fee for service
  - If insurer pays for Dx, no charge for Rx nonresponders
  - Dx provided w/out charge by pharmaceutical company (absorbed as an overhead)
  - Etc.
Conclusions (1)

- No easy fix for molecular Dx coding system
  - Process-based coding for years to come
- No short-term prospect for rational Medicare payment
- Standard coverage analysis principles will apply for now … and for a while more
  - Focus on clinical utility
  - Quality of clinical data is key
Conclusions (2)

• Integrate Dx coverage analysis requirements into Rx clinical development plan
  – Collect all necessary Dx clinical utility data as part of your Rx clinical trial

• Co-Developed Dx/Rx pairings increase probability of success and reduce total costs
  – Other Dx development models are financially problematic