
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.

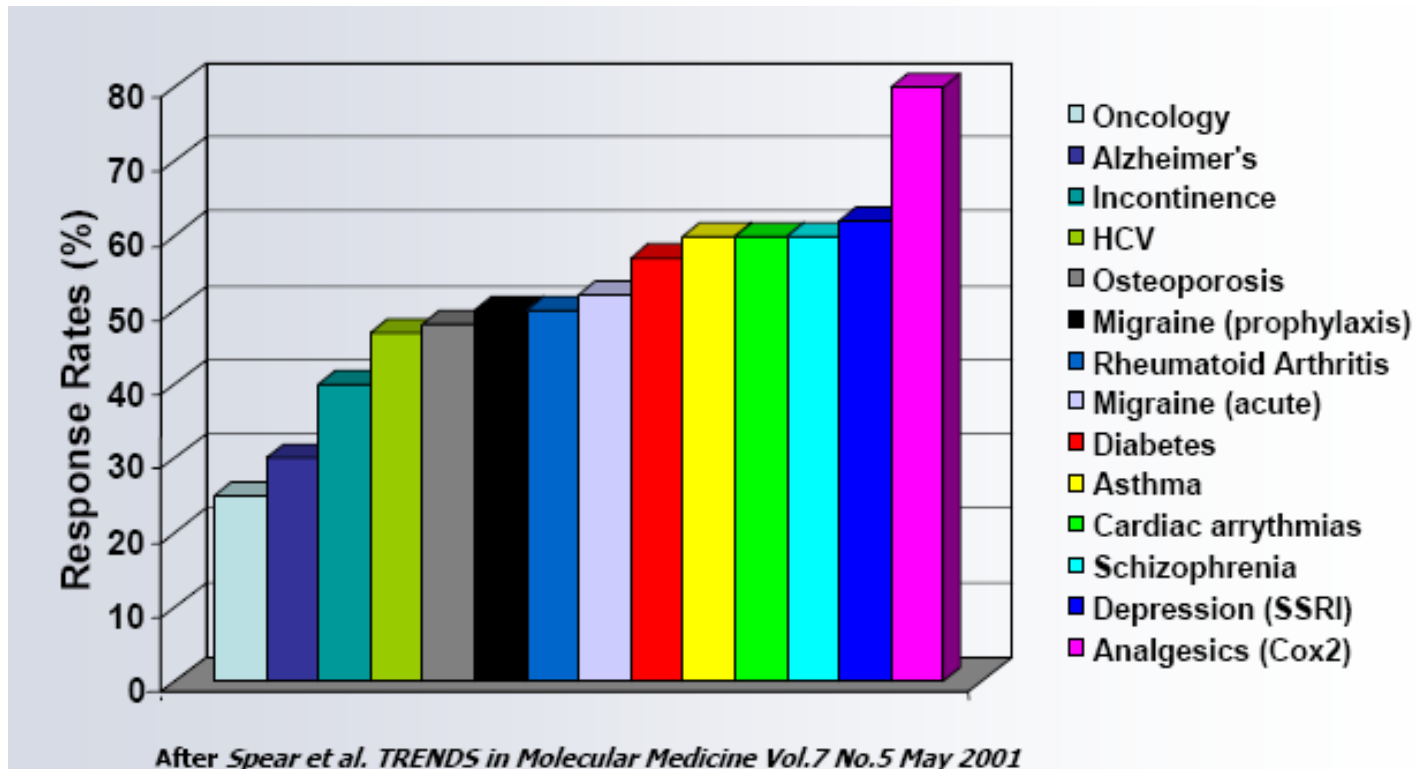
An Ongoing Medical Revolution

- 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?

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
 - <http://www.hhs.gov/myhealthcare/news/personalized-healthcare-9-2007.html>

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”
 - http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

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

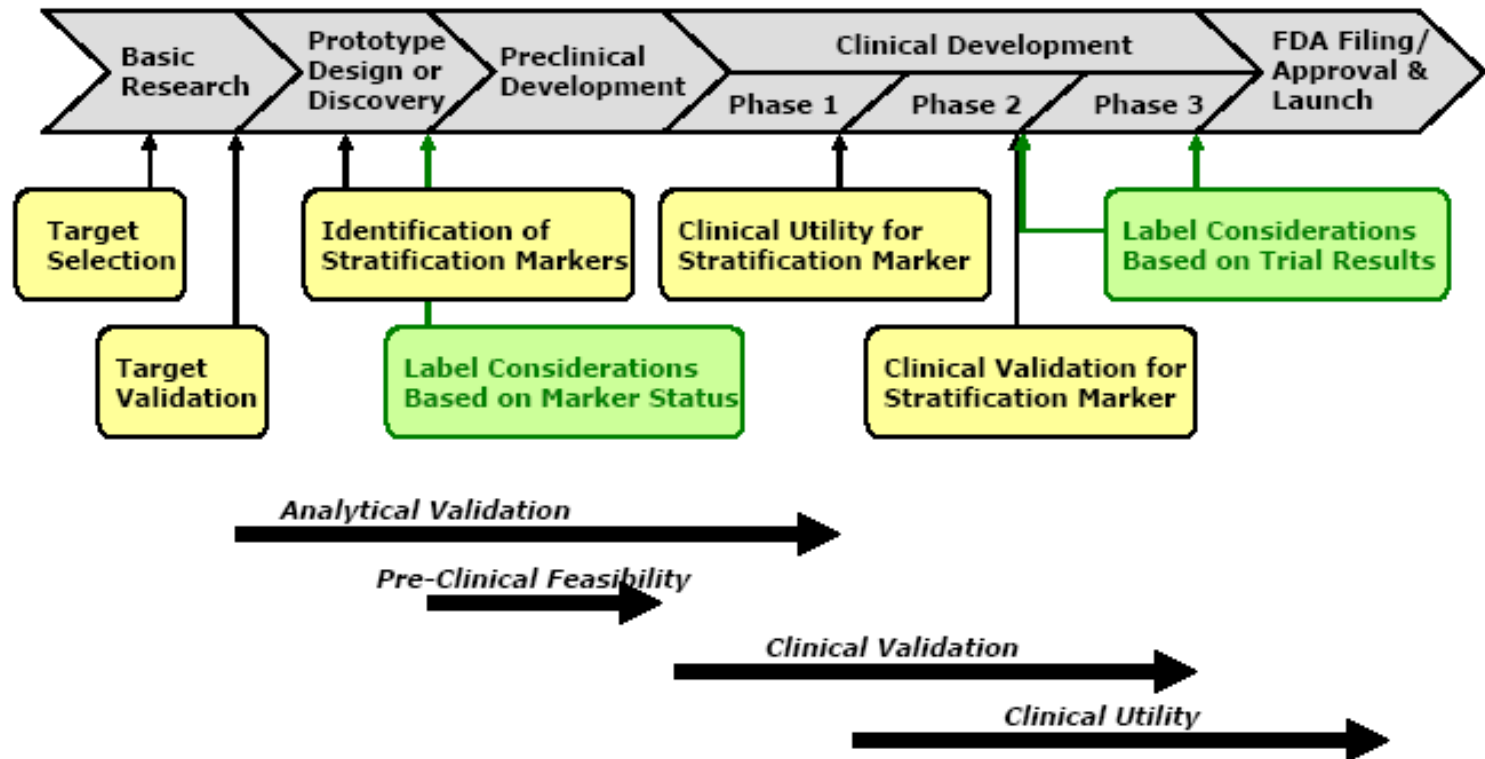


Leverage FDA Process For ...

- 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

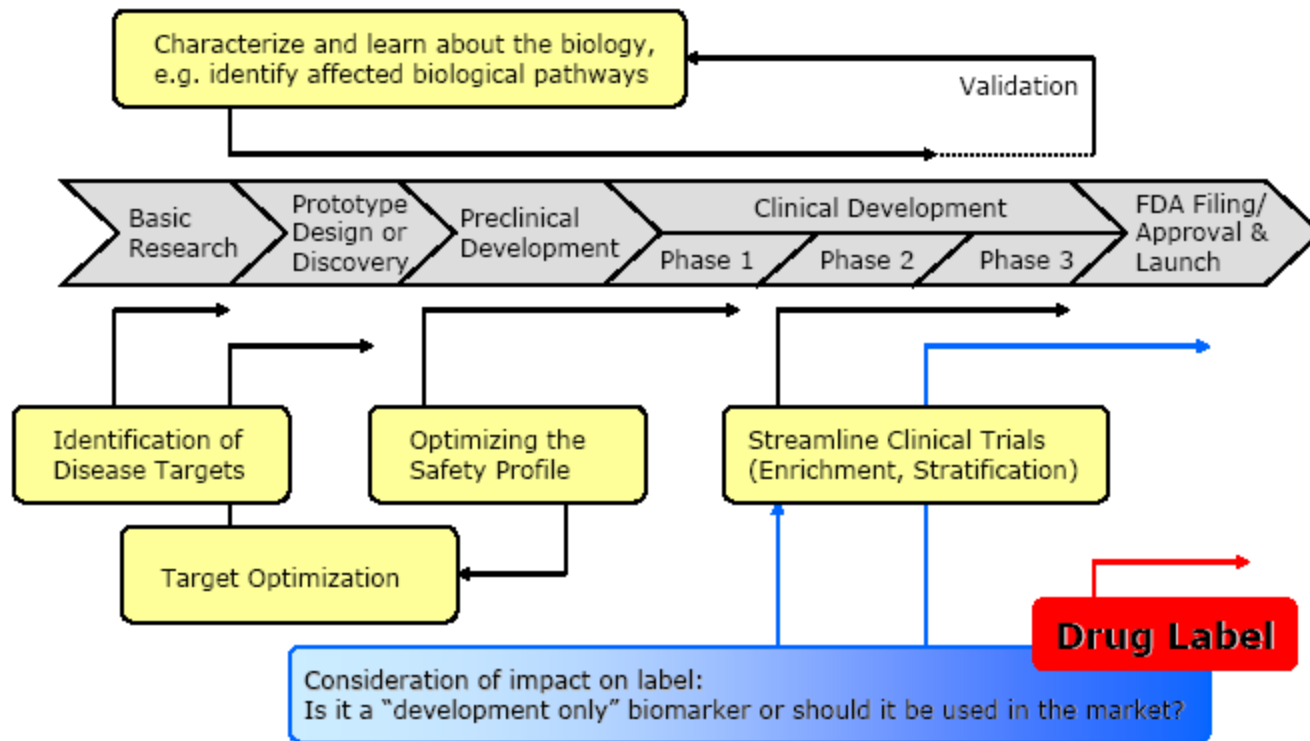
FDA Process Design (1)

Biomarker Development



FDA Process Design (2)

Dx-Rx Co-Development



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

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