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.

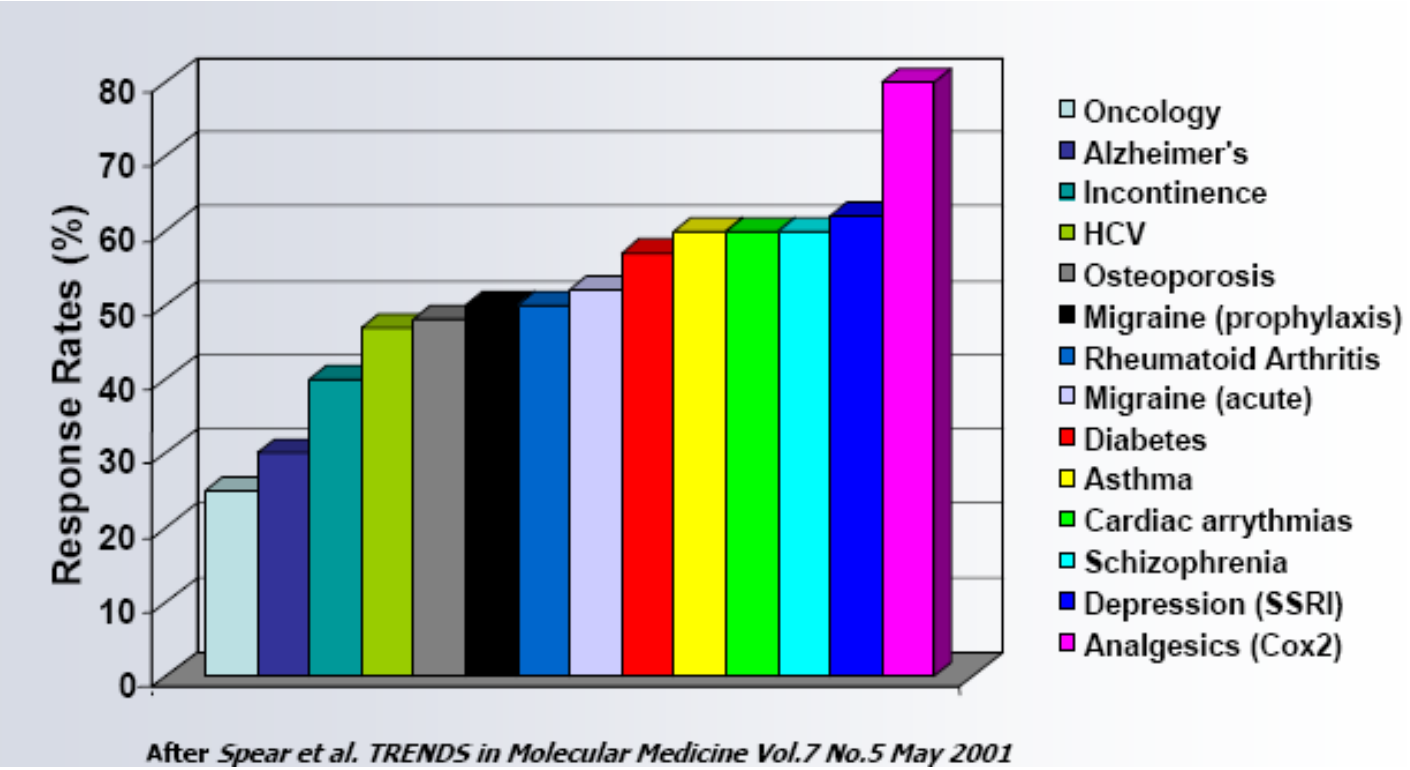
An Ongoing Medical Revolution

- 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



After *Spear et al. TRENDS in Molecular Medicine Vol.7 No.5 May 2001*

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/presonalized-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

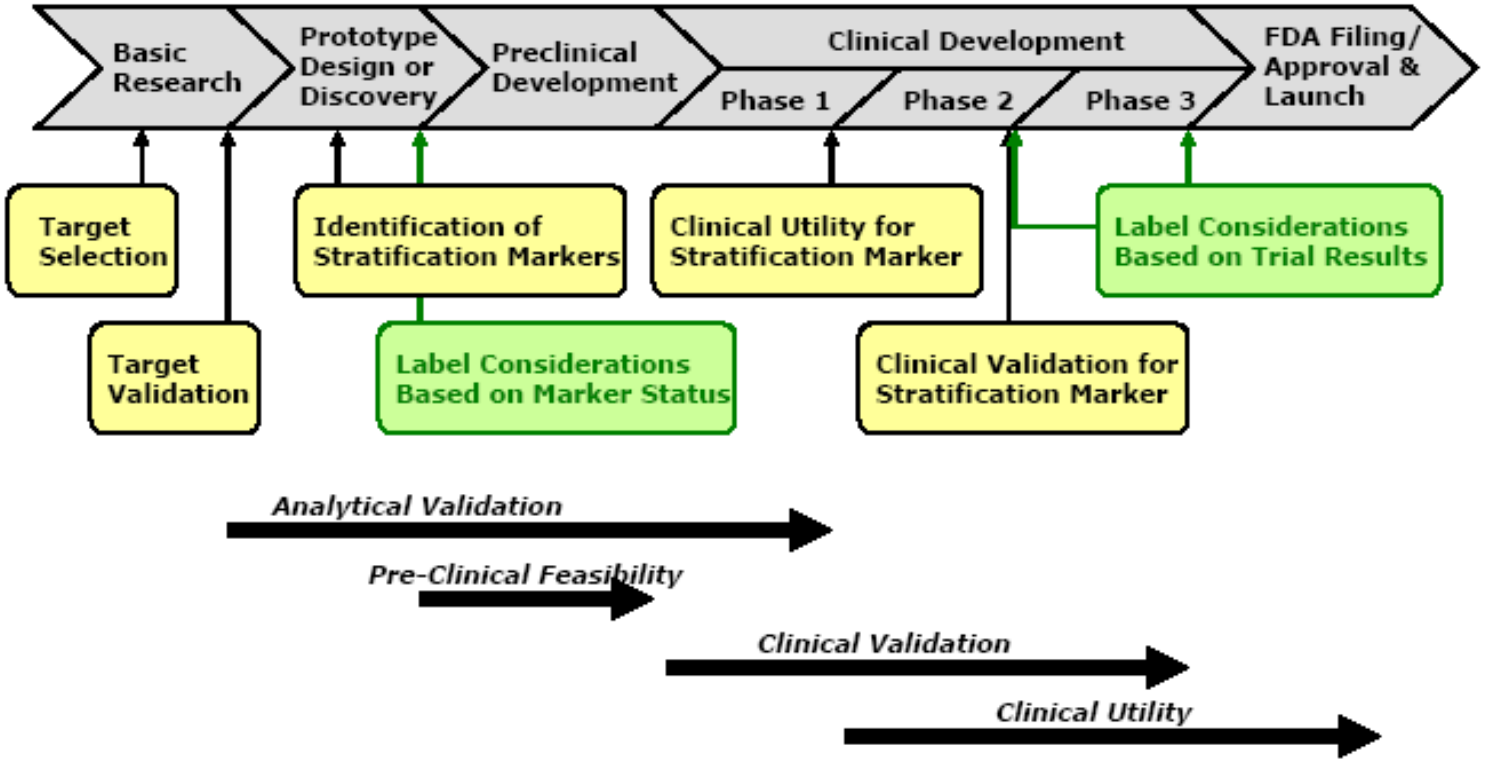
- Staff analyses
- Contracted analyses
- External technology assessments
  - E.g. TEC, ECRI,
- Position statements by relevant groups
- Expert opinion
- Public comments

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

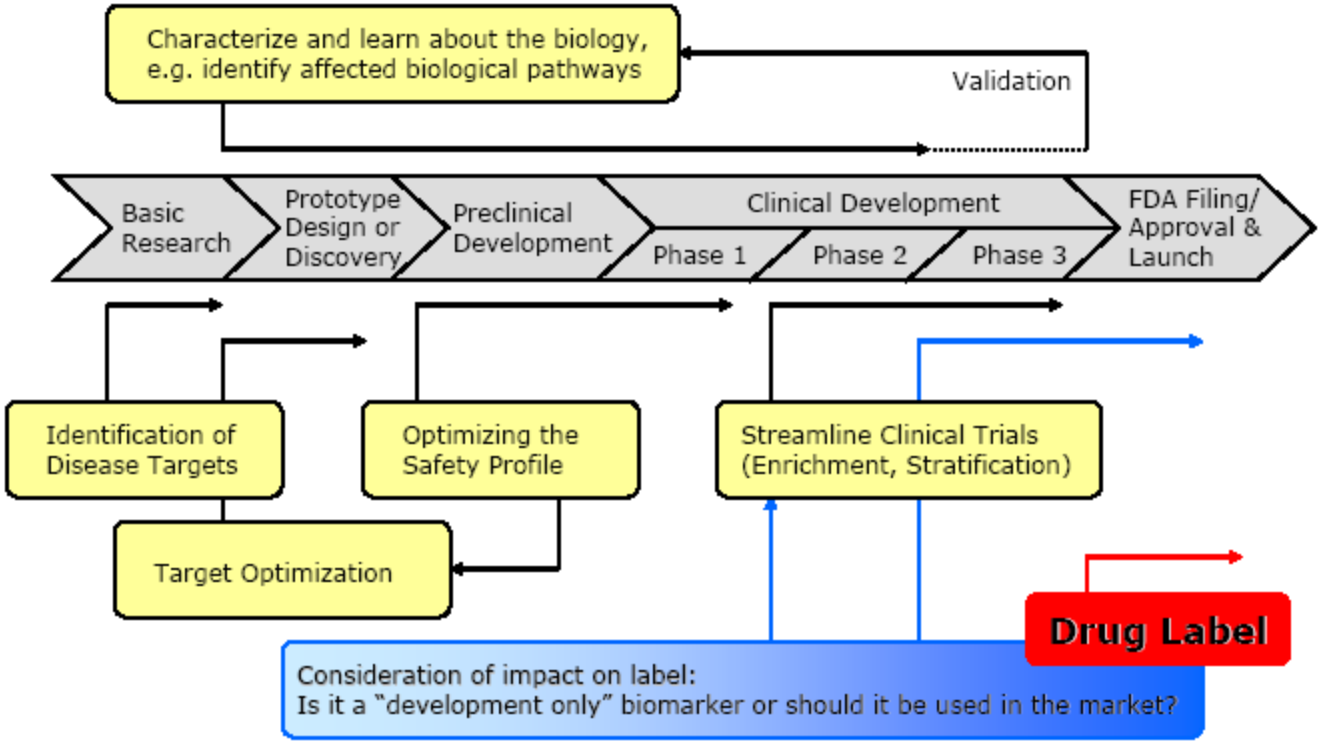
FDA Process Design (1)

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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