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Companion Diagnostics: Oncology Technologies and Pathways

Host: Derrick Gingery
Speakers: Bridget Silverman and David Filmore

Agenda / moderator intro slide

- Companion Diagnostic Development: Technology and Regulatory Drivers
- Pharma Perspective: Trends, Strategies and Future Directions

Companion Diagnostics: Technology and Regulatory Drivers

David Filmore,
Editor in Chief, US, Medtech Insight

Agenda

- Market Overview
- Technology Drivers
- Regulatory Context
- Advancements and Collaboration

Companion Diagnostics: Growing Market

- $2bn-plus market, growing upwards to $6bn in the next several years
- Dominated by oncology space
- Driving partnerships: Companion diagnostics deals, as a % of all Dx partnerships have held relatively steady over the past five years, despite an overall decrease in the number of diagnostics deals.
- 40 Companion Diagnostic approvals listed by FDA

Key Factors

Dx Technology

- Increasing accuracy, speed and throughput of assay technology
- Supporting more creative clinical trials and indication options

Regulation

- Growing library of guidelines and best-practices
- Outside-of-the-box thinking on IVD regulation
- Work in Progress
- Seeking speed and predictability
- Some uncertainties and challenges

Technology Catalysts

Next-Gen Sequencing

- Allows more flexibility in assessing molecular subsets
- Helps address challenges from limited tissue availability
- Supports innovative clinical trial
- Move toward comprehensive diagnostics

Liquid Biopsy

- More convenient and less invasive
- Serial testing/treatment tracking
- First FDA approved cDx: Roche cobas (Tarceva)
- Breakthrough status: Foundation and Guardant

US Regulatory Context –Guidance Development

Key Guidance Documents

Co-development/co-review

2014 IVD Companion Dx Guidance:

- Basics for FDA review and simultaneous drug/Dx approval.

2016 Codevelopment draft guidance:

- Regulatory landscape for clinical codevelopment
- Trial design, timing, IDE/IND considerations

US Regulatory Context –Guidance Development

Key Guidance Documents

IVDs in drug trials

- Two draft guidances:
  - *December 2017: Is an IDE needed or no?*
  - *April 2018: Streamlined approach for IVDs in Oncology Trials: Single IND*

Targeted therapeutics/Tissue-agnostic

- 2017 Targeted therapies draft guidance: Low-frequency molecular alterations
  - *Builds on 2017 Keytruda approval: Tissue-agnostic*
  - *Significance of NGS-based biomarkers: finding relevant molecular alterations*
- Coming soon: More focused guidance on tissue-agnostic approvals and Orphan designation based on molecular targeting

Regulatory Context – Innovative IVD Regulation

- Goal to accelerate Dx part of co-development/review
- Novel pathways: Breakthrough, De Novo, 3rd Party
- New paradigm for next-gen sequencing
- Laboratory-developed test questions

Innovative IVD Regulation

New paradigm for NGS

Two guidance docs finalized in April:

- **Use of Public Human Genetic Variant Databases:** Shared databases to support arguments of clinical validity
- **Considerations for Design, Development, and Analytical Validation:** Encourages development and use of consensus standards **(Germline only)**

Novel Pathways

- **Breakthrough Program:** Leveraged for NGS and Liquid Biopsy
- **De Novo:** Established pathway that is growing in use
- **Pre-certification?**

Innovative IVD Regulation

Laboratory-developed tests

- **Unsettled policy area**
  - Companion Dx require FDA approval
  - Outside-of-the-box thinking:
    - *Third-party review: MSK-IMPACT tumor-profiling Example*
    - *Lab pre-certification (hybrid FDA/CLIA)*
  - Congress could weigh in: New regulatory system for IVDs/LDTs?

Regulatory Context – Europe

Key EU Developments

- **EU IVD Regulation: Adopted: 2017; Applied: 2022**
  - Defines “Companion Diagnostics” for the first time in EU rules
  - Envisions cooperation between notified bodies and medicines regulators (competent authorities or EMA)
  - More clarity, but more requirements

- **EMA Concept Paper on Companion Dx (2017)**
  - Enhance true co-development, rather than “coming together superficially towards the end.”
  - Preliminary step toward more formal guidance

Evolving Reimbursement Landscape For Molecular Dx

Payment Challenges

- Congress enacted “market-based” payment reforms (PAMA/2014)
- Enactment has not been what Dx/lab space had hoped for on rates and predictability

Coverage Progress:

March 2018 Medicare coverage policy for NGS Companion Dx

- Resulted from FDA/CMS Parallel Review for FoundationOne
- National coverage for FDA-approved Companion Dx
- Flexibility: Up to local contractors for non-FDA-approved tests

Complexity And Collaboration

As complexity grows, partnerships will evolve

- **Oncomine**
  - Thermo Fisher partnered with both Pfizer and Novartis for three-drug decision matrix in lung cancer
  - Included joint meetings and with the regulatory authorities on a regular basis
  - **Challenge:** Complicated confidentiality arrangements
  - **Advantage:** Allows use of one platform for simultaneous development

- **PD-1/PD-L1 Blueprint Project**
  - Collaboration between 4 drug and 2 Dx firms
  - Address the “matrix” of individual cDx for different drugs
  - **2017 study**: several assays interchangeable

Companion Diagnostics: The Pharma Perspective

Bridget Silverman,
Managing Editor, Pharma US Regulatory Analysis

Agenda

- Key trends
- Three strategic points to consider in developing drugs with companion diagnostics
- Future directions

Precision Medicine's Quick Uptake

Almost **one-quarter** of novel FDA approvals are precision medicine

- 33 of the 151 novel agents approved 2013-2017

Oncology is most common therapy area

- 48% of PM novel approvals are for cancer, vs. 21% of non-precision approvals

Faster development and review

- Novel precision approvals took 5.8 years; non-precision took 7.5

(Source: Health Affairs, May 2018. "Precision Medicines Have Faster Approvals Based On Fewer And Smaller Trials Than Other Medicines")

Uptake Benefits From FDA Incentives

Regulatory Designation	Precision Medicines	Non-Precision Medicines
Breakthrough Therapy	48%	19%
Accelerated Approval	30%	13%
Priority Review	85%	48%
Orphan Drug	64%	36%

…but **regulatory uncertainty** remains.

Terminology Is Imprecise

General terminology

- Precision medicine, personalized medicine, targeted therapy
- Theme: biomarker-informed drug development

In US drug labeling

- Companion diagnostic vs. ‘complementary’ diagnostic have different implications.

Cross Disciplinary Thinking

Regulatory

FDA Oncology Center of Excellence

Big Pharma

- Roche/Foundation Health
- Bristol/Illumina

Three Strategic Themes In FDA Review Rx/Dx Products

- Biomarkers should correlate with a clinically relevant characteristic and not exclude patients who could benefit from treatment
- FDA prefers prospective to retrospective analysis. (If you have to go retrospective, look for a lot of supporting evidence)
- Postmarketing studies are an integral component of regulatory framework and should be considered early in a development program

Biomarkers: Justify and Validate

- Combination product model: CDx needs to demonstrate contribution to Rx therapy
- Trial design to support approval of both Rx and CDx
- Unmet need unlocks regulatory flexibility

Example: Celgene and Agios' Idhifa (enasidenib) for IDH2 mutation+ r/r AML

FDA Likes Specificity In Biomarkers

- Evolution of EGFR inhibitors in lung cancer
  - *acquired resistance mutations*
- Outside oncology: cystic fibrosis labeling

Example: Celgene and Agios' Idhifa (enasidenib) for IDH2 mutation+ r/r AML

FDA Prefers Prospective Analyses

Lynparza – Retrospective CDx analysis was key to FDA's discomfort with indication first sought

AstraZeneca's original olaparib NDA relied on retrospective identification of ovarian cancer patients with germline BRCA mutations in study that had enrolled patients without regard to BRCA status. FDA's views:

- Post hoc analyses entail loss of randomization
- Convenience sample (patients with whole blood samples available for retrospective testing) not sufficient to support approval

> *"The small sample size of gBRCAm patients and the retrospective identification of this patient population calls into the reliability of the estimation of treatment effect."*
>
> ***-- FDA review materials for the original 2014 Lynparza NDA***

Post-Marketing Is Integral To FDA Perspective

Precision medicine approvals are more likely to be based on surrogate endpoints than non-precision

- FDA can require post-marketing studies for accelerated approval and safety issues

Post-marketing studies should be factored in when first designing a research program, and could be viewed as an opportunity, not hurdle

- Lynparza illustrates how confirmatory trials are being woven into trials that also serve to extend the indication footprint

FDA Can Be Flexible

- FDA is aware of flux in science
- Regulation gives reviewers latitude when addressing serious unmet needs

Example: Agreement with Celgene/Agios to incorporate updated Idhifa data when it became available instead of delaying submission

What's Next: Complementary Diagnostics

Companion diagnostic: Labeled indication incorporates use of CDx

Complementary diagnostic: Indication does not define population by biomarker, but clinical trials section of label presents results for biomarker-defined subgroup as well as unselected patients

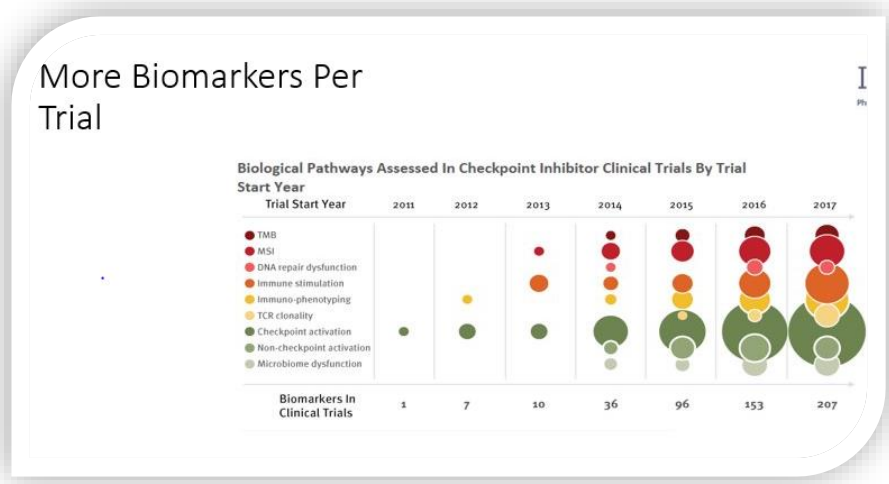
- Concern about excluding patients who could benefit
- FDA trusts doctors to weigh evidence

"It would not be appropriate to separate out a subgroup from an overall positive trial unless there was a clear detriment to that subgroup."

-- FDA review comments on inclusion of non-gBRCAm patients in Lynparza indication

What's Next: Regulatory framework will need to accommodate more complex combinations of biomarkers

- Current FDA framework: Limited number of biomarkers/CDx per indication
- Next-generation sequencing can look for hundreds of biomarkers
- Liquid biopsy can make sample collection easier for clinical trials and in clinical practice
- How will the current regulatory approach evolve?
  - Tumor mutation burden as a potential model for future Rx/Dx co-development



Thank you.