Personalized Medicine: Current and Future Realities

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What is Personalized Medicine?

- Customizing therapy toward the individual patient and disease.
- Nothing new!
- The laboratory has always played a central role.
- Tests to identify the presence or absence of specific drug targets.
Why all the hype?

- Catchy tag is a good way to attract the attention of Wall Street.
- Brings the clinical laboratory to the forefront of medicine.
- Molecular techniques have fostered rapid progress in many areas.
A Few Examples

- Molecular oncology – therapies that target signaling pathways
  - HER-2 over-expression in breast and gastric cancer
  - BRAF mutation in melanoma
  - ALK mutation in NSCLC

- Toxicity
  - CYP2C9 mutations and warfarin

- Efficacy
  - CYP2C19 mutations and Plavix
Signaling Pathways

2011 ASCP Annual Meeting
But does that test really do anything?

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<th>Response</th>
<th>Biomarker Positive</th>
<th>Biomarker Negative</th>
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Would you do a drug study without a control?

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And so the needed design is…

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Don’t let the perfect get in the way of the very good

- Other considerations in designing pivotal trials:
  - Expense
  - Time
  - Recruitment

- There are always compromises
  - Which tumor type do you go after?

- Ethical standards
  - Should subjects be exposed to toxic, investigational treatments if we believe there is no chance that the subject will benefit from that treatment?
Food for Thought

- Is it necessary to demonstrate that drug response is higher in the biomarker positive population than it is in the biomarker negative population before using that biomarker for patient selection?
- Is it necessary to demonstrate that drug response is higher for Tumor A than it is for Tumor B before using that drug to treat Tumor A?
Possible Test Descriptions

- Measurand only
  - “HER-2 positive”

- Measurand and methodology
  - “3+ positive by IHC for HER-2”
  - “positive by FISH for HER-2”

- “FDA approved” for measurand
- Lot’s of other possibilities and combinations
Pitfalls of Analytical Validation

Clinical Data

Test A

Test B

Test C
Multiple Indications

Indication 1

Test X

Indication 2

Test Y
CDER and OIVD need to get on the same page!

- **Plavix label**
  - CYP2C19*1 allele corresponds to fully functional metabolism
  - CYP2C19*2 and *3 alleles are nonfunctional
  - Other alleles associated with absent or reduced metabolism are ... CYP2C19*4, *5, *6, *7, and *8

- No FDA-cleared device to assay for CYP2C19*4, *5, *6, *7, and *8
Open Questions

- What evidence is needed to validate a test for patient selection?
  + Clinical epidemiology
  + Pragmatics of doing the study
  + Shifting ethical standards of such a study

- What validation is needed to substitute a new test for the one that was actually used to select patients in the pivotal trial?

- How will drug label and diagnostic device labels be coordinated?
By the way…

- Neither vemurafenib nor crizotinib was tested in biomarker-negative group in pivotal trial
- Crizotinib was approved without a control group
- Some have questioned the ethics of depriving subjects of the benefit of vemurafenib during the conduct of pivotal clinical trials
- Labels for vemurafenib and crizotinib both refer to an “FDA approved” test
Regulatory Considerations for Personalized Medicine and Companion Diagnostics

2011 ASCP Annual Meeting

Katherine Serrano
OIVD/CDRH/FDA

October 21, 2011
What is Personalized Medicine?

• For FDA: a model for taking into account a patient’s particular genetic, genomic, or proteomic constitution to deliver treatments that are as safe and effective for that patient as possible

– “The right therapy for the right patient at the right dose….”
What’s Different about Regulation for Personalized Medicine?

- Diagnostic test to determine therapy/dose
- Test and therapy must work together for optimal safety and effectiveness

- Regulatory process and scientific approach: must account for both products
Companion Diagnostics

- Companion Diagnostic
  - A medical device that identifies/determines a condition of use for a therapeutic product and is important to ensure the safe and effective use of that product
Risk-Based Classification of IVDs

- The risk of an IVD is based on the consequences of a false result.

- 3 Classification levels:
  - Class I: common, low risk devices
  - Class II: more complex, moderate risk
  - Class III: most complex, high risk and novel intended uses
Risk of Companion Diagnostics

• Healthcare practitioners rely on information from companion diagnostic devices to help make critical treatment decisions.

• Companion diagnostics
  – Provide benefit in optimizing treatment
  – Bring risk if test result is incorrect
FDA Companion Diagnostics Policy

• Draft guidance entitled *Draft Guidance for Industry and FDA Staff; In Vitro Companion Diagnostic Devices* published July 14, 2011
  – Docket FDA-2011-D-0215
Focus of the draft guidance

• Defines “IVD companion diagnostic”
• Describes FDA’s policies for approval and labeling of a therapeutic/diagnostic product pair
• Does not provide details regarding how therapeutic/diagnostic product pair should be co-developed
IVD Companion Diagnostics

• IVD Companion Diagnostic:
  – In vitro diagnostic device that provides information essential for the safe and effective use of a corresponding therapeutic product

• Use of an IVD Companion Diagnostic:
  – Use is stipulated in the instructions for use in the labeling of the diagnostic device and the corresponding therapeutic product/labeling of generic equivalents of the therapeutic product
What Types of Dx Could Be IVD Companion Dx?

• Identify patients likely to respond or not respond to a particular medical product
  – *Predictive* test that can select either a population that is likely to respond, or a population that is not likely to respond

• Generally validated in Ph 3 trials, although could be a postapproval addition, e.g., K-RAS
What Types of Dx Could Be Companion Dx? (2)

- Identify subgroups of the larger population with *poor prognosis* who are likely to benefit from a particular therapeutic product
  - Test selects those who might benefit from treatment with a therapeutic product due simply to otherwise poor prognosis
What Types of Dx Could Be Companion Dx? (3)

- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product (predictive)
  - Validation design can be tricky
  - Consideration of whether other therapies are available, seriousness of disease to be treated
What Types of Dx Could Be Companion Dx? (4)

- *Monitor* response to treatment for the purpose of *adjusting treatment* (schedule, dose, etc) to achieve improved safety or efficacy
  - Specific test performance needed, specific test values critical
  - Not generally accepted biomarkers for status
What Types of Dx Could Be Companion Dx? (5)

- **Individualize the dose** of particular therapeutic product
  - Predicts safe/effective dose based on specific test result
What Types of Dx Could Be Companion Dx? (6)

• Use as integral part of therapeutic clinical trials conducted to support market approval of a therapeutic product
  • selection of trial participants
• primary trial analysis performed using diagnostic device data to demonstrate therapeutic performance
  • If test was used in any way to define trial success, it will need to be available to select the same population when therapeutic is approved
Regulatory Concept: Premarket Review

• Premarket review and clearance or approval of the companion diagnostic will typically be required contemporaneously with approval of the therapeutic product
  – Assurance that the diagnostic has been appropriately validated for its intended use
  – Risk-based regulation
Regulatory Concept: Co-approval

- Companion Dx and therapeutic product depend on each other
- Co-approval required*
- Failure/lack of test approval = no therapeutic product approval

* Exceptions will exist
Investigational Use

• Tests used in clinical trials to make critical clinical decisions
  – Investigational approval will usually be needed
    • Tests used without confirmation by another medically established diagnostic
    • Potential for serious risk to patient
    • Can be IDE or within therapeutic IND
Therapeutic Product Labeling

• If a drug or biological product has been shown to be safe and effective only in a certain patient population identified by a diagnostic test, the Indications and Usage section must clearly define the patient population in whom the drug is approved.

• If a diagnostic test is essential for monitoring either therapeutic or toxic effects, the type of test should be identified under Warnings and Precautions.

• Therapeutic label will likely refer to “FDA approved test” (unless compelling reason to name specific test)
  – Allows new tests to be used without drug label change
  – When safety and effectiveness questions necessitate, may consider specific test label
Therapeutic Product Labeling
(Example)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XALKORI® safely and effectively. See full prescribing information for XALKORI.

XALKORI® (crizotinib) Capsules, oral
Initial U.S. Approval: August 2011

----------------------------------INDICATIONS AND USAGE----------------------------------
XALKORI is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. (1) This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.
Companion Dx Labeling

- Intended use to refer to specific use with specific therapeutic product
- If test is applicable to more than one therapeutic product
  – *Class effect?*
  – *New indications = new premarket submission*
Companion Diagnostic Labeling (Example)

INTENDED USE
The Vysis ALK Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue specimens to aid in identifying those patients eligible for treatment with XALKORI® (crizotinib). The test is for prescription use only.
Enforcement

• When a diagnostic is brought forward as a companion diagnostic to support a therapeutic product, FDA expects to require compliance with device regs whether the test is laboratory developed or distributed as a kit
  – Performance is critical, no matter who the manufacturer
  – Appropriate labeling is needed
Helpful Information that is NOT in the Guidance
Issues observed in Codevelopment

- Test analytical performance not validated prior to use in clinical trial
- Multiple tests (with different performance?) used to enroll subjects in clinical trial
- No way to determine test performance if only marker + samples available
  - Results in selection, but not predictive, claim
- Bridging studies from CTA to companion Dx need high sample ascertainment (> 90% recommended)
Analytical Validation

• Use a test for patient selection/stratification that has been as completely analytically validated as possible, and has acceptable performance characteristics for your purposes.

• For tests that detect multiple possible genetic changes, e.g., multiple mutations within a gene, should be analytically validated for each change to be detected.

• When performing analytical validation, consideration should be made of the ultimate specimen source to be used once drug is on the market, i.e., FFPE tissue, blood, CSF
Enrollment Issues

• If test is part of inclusion/exclusion criteria for therapeutic trial
  – Use a central site to do ALL testing (not confirmation of local test)
Or:
  – Use SAME test (same demonstrated performance characteristics) at ALL sites
AND:
  – Assure any test used has adequately validated measurement characteristics (analytical validation)
Testing Protocol/Samples

- Neither the test nor the testing protocol should be altered once the pivotal trial is begun.
- Sponsors should save samples from all patients enrolled in the trial.
- When only test-positive patients are enrolled:
  - do not prescreen for eligibility with a different test
  - save samples from patients who are test-negative and are thus not enrolled in the trial.
- If a change in specimen type is anticipated for future testing, obtain paired samples on initial testing.
- For any samples that have been stored prior to testing, perform validations to assure that analyte is stable under storage conditions.
Marker Positive Only Trials

• “Marker positive” = choice of only one stratum, based on marker status, to study

• Benefits:
  – May be more efficient, if justified
  – May be more palatable when safety is an issue

• Issues:
  – No marker information by treatment is generated
  – Difficult/impossible to assess diagnostic PV
  – Without good mechanistic data, may be misled
Clinical Validation of Companion Dx

• Companion Dx (or its prototype or CTA) used within pivotal therapeutic trial
  – No systematic difference whether normal or accelerated approval of therapeutic

• Analysis of diagnostic device performance related to therapeutic trial outcome
  – Therapeutic trial fails = diagnostic not informative
  – Therapeutic trial succeeds = diagnostic (generally) informative
    • Diagnostic label will reflect use in pivotal trial
  – Generally, no additional clinical validation of diagnostic needed
    • For predictive claims, therapeutic trial should be powered to detect differences in response by diagnostically defined strata.
Guidance

• If you are involved in co-developed products, seek FDA input early and often
• Use common sense in considering approach
• Plan ahead (a lot)
• Don’t rely on short-cuts/post-hoc fixes
• Get to know your pharma or diagnostic partner
• Ask FDA if you are confused
Current Success Stories

• 2 Recent Therapeutic/Dx Co-Approvals

  – August 17, 2011
    • Cobas® 4800 BRAF V600 Mutation Test
      – Qualitative detection of the BRAF V600E mutation in DNA
      – Aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib
    • Zelboraf® (vemurafenib)
      – kinase inhibitor
      – Indicated for use in patients with BRAF V600 E mutation

  – August 26, 2011
    • Vysis ALK Break apart FISH Probe Kit
      – Qualitative test detecting rearrangements in the ALK gene via FISH in NSCLC tissue specimens
      – Aid in identifying patients eligible for treatment with crizotinib
    • Xalkori® (crizotinib)
      – Kinase inhibitor
      – Indicated for treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive
Current Success Stories: What Went Well

• Both approvals made before statutory deadlines
  – BRAF/Vemurafenib: 2 months early
  – Vysis/crizotinib: 1 month early

• Early Interaction with FDA

• Good communication/coordination among all parties

• Information provided to FDA by Therapeutic/Diagnostic Sponsors in a timely manner
Looking Forward

• FDA’s process is evolving

• Each new submission raises different regulatory and scientific issues

• Contact the Agency early and often!
Thanks!

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