Update on Regulation of Liquid Biopsy

AMDM 2016 Focus meeting
October 13-14, 2016

Reena Philip, Ph.D.
Division Director
Division of Molecular Genetics and Pathology
OIR/CDRH/FDA

Outline

- Background
  - Liquid Biopsy as Companion Diagnostics
  - Assay Performance Considerations
- Recent FDA Approval of a Liquid Biopsy Test
- NGS Oncology Panels

Liquid Biopsy

- Testing for tumor DNA using a blood sample
  - noninvasive method
  - shed from tumors into the blood
- Circulating tumor DNA (ctDNA) or cell-free tumor DNA (cfDNA) in plasma
- Incorporated into numerous drug development programs

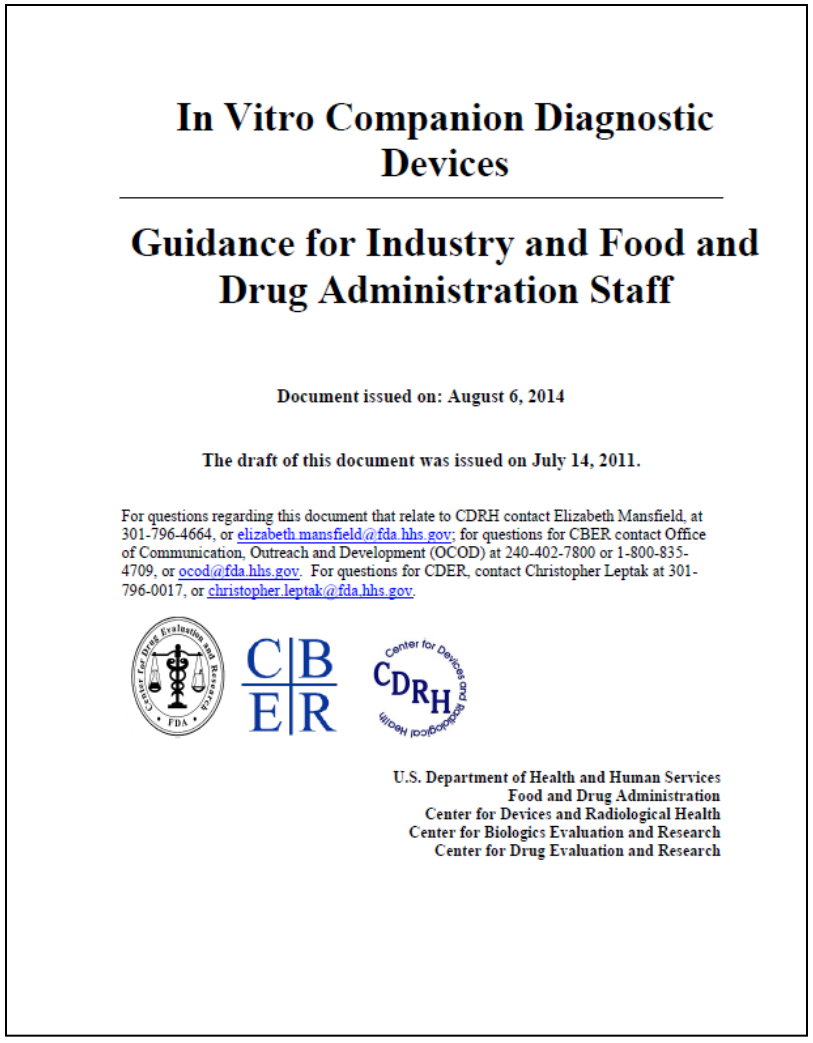
Liquid Biopsy
FDA-AACR Workshop

- FDA-AACR Liquid Biopsies in Oncology Drug and Device Development Public Workshop: July 19, 2016
  - http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/pages/fda-aacr-liquid-biopsies-in-oncology-drug-and-device-development.aspx#bypslides

Outline

- Background
  - Liquid Biopsy as Companion Diagnostics
  - Assay Performance Considerations
- Recent FDA Approval of a Liquid Biopsy Test
- NGS Oncology Panels

Companion Diagnostics



In Vitro Companion Diagnostic Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on: August 6, 2014

The draft of this document was issued on July 14, 2011.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 240-402-7800 or 1-800-835-4709, or ocod@fda.hhs.gov. For questions for CDER, contact Christopher Leptak at 301-796-0017, or christopher.leptak@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research

- Final Guidance issued on August 6, 2014
- CDx is defined as a test that provides information that is **essential** for the safe and effective use of a corresponding therapeutic
- FDA policies for approval and labeling are outlined
- Contemporaneous regulatory approvals

Validation of Companion Diagnostics

- Assay selects target population enrolled in the trial
  - A specific assay is identified for detecting the marker
  - A specific protocol is used with the assay
  - A clinical decision point (cut-off) is selected
  - A specific specimen type is identified for testing
- Analytical validation
- Clinical validation

Analytical Performance

- Test = Specimen to Result (validate all steps)
- Pre-analytic steps are part of assay
  - e.g., plasma processing, cfDNA isolation
- Validation with the intended specimen type, using clinical specimens from the intended population
- All studies should follow protocol in labeling
- Studies should demonstrate robustness at clinical cut-off, as needed

Clinical Performance

- Determine how the device will be used in clinical setting and ensure study design is appropriate
- Study design should support the Intended Use
- Pre-specified clinical and statistical analysis plan
- Establish clinical performance of device compared to an endpoint or appropriate surrogate
- Analytical validation precedes clinical validation

Practical Considerations for Liquid Biopsy (LB) Tests

- Analytical issues: Clinical specimens for analytical validation may be limiting
- Samples should represent the intended use patient population, not just available specimens
- Lack of reference method / standards
- LB to Tissue concordance: Relevance to clinical outcomes, not just analytical status, should be demonstrated

Procured LB ↔ Tissue?

- Key factors impacting circulating vs. tissue status (e.g., tumor type, stage) observed in cohorts outside of therapeutic trials
- Potential inflated concordance if “easier” distribution and/or frequency of analytes, in specimen cohort

Outline

- Background
  - Liquid Biopsy as Companion Diagnostics
  - Assay Performance Considerations
- Recent FDA Approval of a Liquid Biopsy Test
- NGS Oncology Panels

FDA Approval of a Liquid Biopsy Test

cobas EGFR Mutation Test v2 (using plasma specimens)

Roche Molecular Systems, Inc.

- First "liquid biopsy test" approved for NSCLC
- Approved on June 1, 2016, as a companion diagnostic to identify patients eligible for treatment with Tarceva (erlotinib).
- Approved on September 28, 2016, as a companion diagnostic to identify patients eligible for treatment with Tagrisso (osimertinib).
- Test was previously approved for same indication using FFPE tissue specimens.

Intended Use

The **cobas® EGFR Mutation Test v2** is a real-time PCR test for the qualitative detection of defined mutations of the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC) patients. **Defined EGFR mutations are detected using** DNA isolated from formalin-fixed paraffin-embedded tumor tissue (FFPET) or **circulating-free tumor DNA (cfDNA) from plasma derived from EDTA anti-coagulated peripheral whole blood.**

The test is indicated as a companion diagnostic to aid in selecting NSCLC patients for treatment with the targeted therapies listed in Table 1 below in accordance with the approved therapeutic product labeling:

Table 1

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	Exon 19 deletions and L858R	Exon 19 deletions and L858R
TAGRISSO™ (osimertinib)	T790M	

Patients with positive cobas® EGFR Mutation Test v2 test results using plasma specimens for the presence of EGFR exon 19 deletions or L858R mutations are eligible for treatment with TARCEVA® (erlotinib). **Patients who are negative for these mutations by this test should be reflexed to routine biopsy and testing for EGFR mutations with the FFPET sample type.**

Intended Use (cont'd) – Approval, June 1st

Drug safety and efficacy have not been established for the following EGFR mutations listed in Table 2 below that are also detected by the **cobas**® EGFR Mutation Test v2:

Table 2

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	G719X, exon 20 insertions, T790M, S768I and L861Q	G719X, exon 20 insertions, T790M, S768I and L861Q
TAGRISSO™ osimertinib)	G719X, exon 19 deletions, L858R, exon 20 insertions, S768I, and L861Q	G719X, exon 19 deletions, L858R, exon 20 insertions, T790M, S768I, and L861Q

For manual sample preparation, FFPET specimens are processed using the **cobas**® DNA Sample Preparation Kit and plasma specimens are processed using the **cobas**® cfDNA Sample Preparation Kit. The **cobas** z 480 analyzer is used for automated amplification and detection.

Intended Use – Approval Sep 28th

The **cobas® EGFR Mutation Test v2** is a real-time PCR test for the qualitative detection of defined mutations of the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC) patients. **Defined EGFR mutations are detected using** DNA isolated from formalin-fixed paraffin-embedded tumor tissue (FFPET) or **circulating-free tumor DNA (cfDNA) from plasma derived from EDTA anti-coagulated peripheral whole blood.**

The test is indicated as a companion diagnostic to aid in selecting NSCLC patients for treatment with the targeted therapies listed in Table 1 below in accordance with the approved therapeutic product labeling:

Table 1

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	Exon 19 deletions and L858R	Exon 19 deletions and L858R
TAGRISSO™ (osimertinib)	T790M	**T790M***

Patients with positive cobas® EGFR Mutation Test v2 test results using plasma specimens for the presence of EGFR exon 19 deletions or L858R mutations are eligible for treatment with TARCEVA® (erlotinib). **Patients who are negative for these mutations by this test should be reflexed to routine biopsy and testing for EGFR mutations with the FFPET sample type.**

Intended Use (cont'd) – Approval Sep 28th

*The efficacy of TAGRISSO™ (osimertinib) has not been established in the EGFR T790M plasma-positive, tissue-negative or unknown population and clinical data for T790M plasma-positive patients are limited; therefore **testing using plasma specimens is most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained**.

Drug safety and efficacy have not been established for the following EGFR mutations listed in Table 2 below that are also detected by the **cobas**® EGFR Mutation Test v2:

Table 2

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	G719X, exon 20 insertions, T790M, S768I and L861Q	G719X, exon 20 insertions, T790M, S768I and L861Q
TAGRISSO™ osimertinib)	G719X, exon 19 deletions, L858R, exon 20 insertions, S768I, and L861Q	G719X, exon 19 deletions, L858R, exon 20 insertions, S768I, and L861Q

Validation Studies

Analytical Performance Studies

- Limit of Detection
- Precision
- Accuracy
- Lot Interchangeability
- Interference
- Contrived Sample Commutability*
- Reproducibility
- Comparator Method Validation*
- Robustness
- Stability

Validation Studies

Analytical Performance Studies

- Limit of Detection
- Precision
- Accuracy
- Lot Interchangeability
- Interference
- Contrived Sample Commutability*
- Reproducibility
- Comparator Method Validation*
- Robustness
- Stability

- LoD established with contrived samples
- LoD confirmed using clinical samples from NSCLC patients.
- Commutability study conducted to demonstrate that contrived samples are equivalent to clinical specimens.

Validation Studies

Analytical Performance Studies

- Limit of Detection
- Precision
- Accuracy
- Lot Interchangeability
- Interference
- Contrived Sample Commutability*
- Reproducibility
- Comparator Method Validation*
- Robustness
- Stability

- An NGS method was used as a comparator
  - Validation for the comparator was provided
- Clinical specimens were evaluated
  - Plasma volumes from pivotal clinical study were lacking
  - Additional specimens from other clinical studies were included

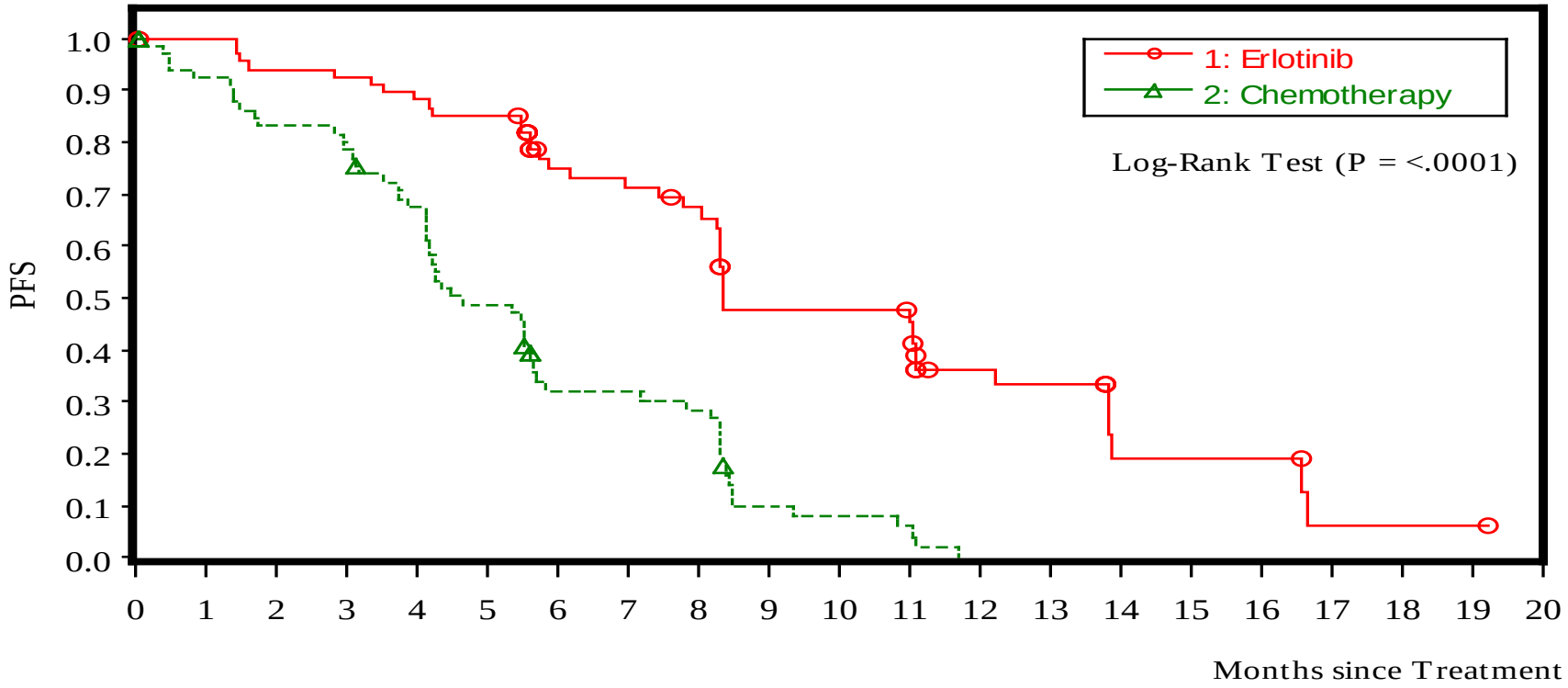
Clinical Validation

Cobas EGFR mutation test using plasma for Tarceva

Clinical Performance Studies

- Clinical Bridging Study
- Correlation between Plasma and Tissue
  - ENSURE Phase III study of erlotinib vs. cisplatin in combination with gemcitabine as first-line therapy for stage IIIb/IV NSCLC
  - Patients were enrolled based on detection of EGFR activating mutations (exon 19 deletions or L858R mutations) in FFPE tissue specimens by the cobas EGFR Tissue Test v1
  - Available plasma samples evaluated and bridged to FFPET

Clinical Bridging Study: Kaplan-Meier Plot of PFS by treatment for patients with mutation detected by the cobas® EGFR Test in both plasma and tissue



N at Risk

1	68	67	63	62	59	57	40	38	35	23	23	22	12	11	4	4	4	1	1	1	0
2	69	60	54	51	43	31	18	18	16	5	4	3	0								

Correlation between Plasma and Tissue: Agreement between Plasma Test & Tissue Test for Detection of EGFR Mutation (with 2.0 mL Plasma Sample)

		cobas® Tissue Test v1		
		EGFR+ (MD)	EGFR(-) (NMD)	Total
cobas® Plasma Test v2	EGFR+ (MD)	161	4	165
	EGFR(-) (NMD)	49	217	266
	Total	210	221	431
With only Valid Result	PPA (95% CI)	76.7% (70.5%, 81.9%)		
	NPA (95% CI)	98.2% (95.4%, 99.3%)		

Clinical Validation

Cobas EGFR mutation test using plasma for Tarceva

- Clinical Bridging Study
- PFS benefit in patients who are tissue positive whether plasma positive or negative
- Observed drug efficacy of tissue test: HR 0.34 (0.21, 0.54)
- Observed drug efficacy of plasma test: HR 0.29 (0.19, 0.45)
- Correlation between Plasma and Tissue
- High NPA for exon 19 deletions or L858R mutations in plasma compared to tissue
- "Reflex" companion diagnostic - Patients with positive test results are eligible for treatment with TARCEVA. Patients who are negative for these mutations by this test should be reflexed to routine biopsy and testing for EGFR mutations with the FFPET sample type.

Intended Use – Approval on June 1st

The **cobas® EGFR Mutation Test v2** is a real-time PCR test for the qualitative detection of defined mutations of the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC) patients. **Defined EGFR mutations are detected using** DNA isolated from formalin-fixed paraffin-embedded tumor tissue (FFPET) or **circulating-free tumor DNA (cfDNA) from plasma derived from EDTA anti-coagulated peripheral whole blood.**

The test is indicated as a companion diagnostic to aid in selecting NSCLC patients for treatment with the targeted therapies listed in Table 1 below in accordance with the approved therapeutic product labeling:

Table 1

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	Exon 19 deletions and L858R	Exon 19 deletions and L858R
TAGRISSO™ (osimertinib)	T790M	

Patients with positive cobas® EGFR Mutation Test v2 test results using plasma specimens for the presence of EGFR exon 19 deletions or L858R mutations are eligible for treatment with TARCEVA® (erlotinib). **Patients who are negative for these mutations by this test should be reflexed to routine biopsy and testing for EGFR mutations with the FFPET sample type.**

Clinical Validation

Cobas EGFR mutation test using plasma for Tagrisso

Clinical Performance Studies

- Clinical Bridging Study
- Correlation between Plasma and Tissue
  - Patient specimen cohorts from two AstraZeneca clinical studies: The AURA1 Ext Phase 1 study and the AURA2 Phase II study enrolled patients with advanced or metastatic NSCLC who had progressed following an EGFR-TKI
  - Patients were enrolled based on T790M substitution mutation result in FFPE tissue specimens by the cobas EGFR Tissue Test v1
  - Available plasma samples evaluated and bridged to FFPET

Clinical Validation

Cobas EGFR mutation test using plasma for Tagrisso

Clinical Performance Studies

- Clinical Bridging Study
  - The ORR as determined by the BICR in the AURA2 study was 61% (128/210).
  - Among the 207 patients with evidence of T790M mutation by the EGFR Plasma Test v2 who were enrolled in AURA2, the ORR was also 61% (127/207).
  - Since patients with a “tissue negative/plasma positive” result for T790M were not enrolled in AURA2, the response rate in this population is unknown.

Correlation between Plasma and Tissue: Agreement between Plasma Test & Tissue Test for Detection of EGFR T790M Mutation (with 2.0 mL Plasma Sample)

		cobas® Tissue Test v1		
		T790M+	**T790M(-)**	**Total**
cobas® Plasma Test v2	**T790M+**	131	22	153
	T790M(-)	92	89	181
	Total	223	111	334
With only Valid Result	**PPA (95% CI)**	58.7% (52.2%, 65.0%)		
	NPA (95% CI)	80.2% (71.8%, 86.5%)		

Correlation between Plasma and Tissue

Using archival plasma samples obtained from the population screened for enrollment in the AURA2 trial:
EGFR Plasma Test v2 has adequate accuracy as compared to NGS,
but has poor agreement with the results of the EGFR Tissue Test v1

	Screening Population with Valid Plasma test Results*vs NGS (n=320)	Screening Population with Valid Plasma test Results*vs EGFR Tissue Test v1 (n=334)
Positive Percent Agreement (PPA) (95% CI)	91.5% (85.7, 95.1)	58.7% (52.5, 65.0)
Negative Percent Agreement (NPA) (95% CI)	91.1% (86.0, 94.4)	80.2% (71.8, 86,5)
Positive Predictive Value (PPV) (95% CI)	89.0% (82.8, 93.1)	85.6% (79.2, 90.3)
Negative Predictive Value (NPV) (95% CI)	93.1% (88.4, 96.0)	49.2% (42.0, 56.4)

LB ↔ Tissue Discordance

- LB-/Tissue+ → reflex to tissue
- LB+/Tissue- → less likely to be referred, underestimated in tissue+ trials?
- Impact of selecting altered intended use population, especially LB+/tissue-

Clinical Validation

Cobas EGFR mutation test using plasma for Tagrisso

- Correlation between Plasma and Tissue
- Poor Agreement led to the following drug labeling implications:
- Confirm the presence of a T790M EGFR mutation in tumor or, in the absence of tumor, plasma specimens prior to initiation of treatment with TAGRISSO
- Testing for the presence of the mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained.
- If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing.

Intended Use (cont'd) – Approval Sep 28th

*The efficacy of TAGRISSO™ (osimertinib) has not been established in the EGFR T790M plasma-positive, tissue-negative or unknown population and clinical data for T790M plasma-positive patients are limited; therefore **testing using plasma specimens is most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained**.

Drug safety and efficacy have not been established for the following EGFR mutations listed in Table 2 below that are also detected by the **cobas**® EGFR Mutation Test v2:

Table 2

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	G719X, exon 20 insertions, T790M, S768I and L861Q	G719X, exon 20 insertions, T790M, S768I and L861Q
TAGRISSO™ osimertinib)	G719X, exon 19 deletions, L858R, exon 20 insertions, S768I, and L861Q	G719X, exon 19 deletions, L858R, exon 20 insertions, S768I, and L861Q

Recommendation for Postmarketing Commitments

- Since there is some uncertainty regarding the clinical outcomes in patients selected for osimertinib treatment solely using the EGFR Plasma Test v2
  - FDA requested that the data on overall response rate with osimertinib from one or more "real-world" cohorts who have been selected for treatment on the basis of an EGFR T790M mutation positive result from plasma (ctDNA) using the cobas® EGFR Mutation Test v2 be submitted and
  - potentially support further modification of the labeling regarding use of the EGFR Plasma Test

Summary of Practical Considerations

- Analytical issues: Clinical specimens for analytical validation may be limiting
  - Contrived samples used in some studies; demonstrated commutability
- Samples represented the intended use patient population, not just available specimens
- Lack of reference method / standards
  - Validated orthogonal comparator method used
- LB to Tissue concordance: Relevance to clinical outcomes, not just analytical status, should be demonstrated
  - Treatment outcomes based on tissue; bridging study conducted

Outline

- Background
  - Liquid Biopsy as Companion Diagnostics
  - Assay Performance Considerations
- Recent FDA Approval of a Liquid Biopsy Test
- NGS Oncology Panels

NGS Oncology Panels

Increasingly employed for use in oncology applications, and introduce challenges to the current companion diagnostic regulatory paradigm.

One Test, Multiple Variants/Allele Representation, Different Genes, Multiple Indications, Multiple Drugs

- Intended to be used as companion diagnostic devices for the clinical management of previously diagnosed oncology patients, and
- Alternative therapeutic management for patients who have already been considered for all appropriate therapies

NGS Oncology Panels (cont'd)

- Markers intended to guide therapy with a corresponding drug – analytical and clinical validation required.
- Markers not associated with therapeutic outcome – analytical validation required; no clinical claim until clinical trial data available.
- Markers intended as follow-on companion diagnostic – analytical method comparison study required; should be comparable to the originally approved test.

Follow-on Companion Diagnostic

- Follow-on companion diagnostic should consistently and accurately select the same intended use patient population as the originally-approved companion diagnostic device for the indicated therapeutic drug.

- Follow-on companion diagnostic should demonstrate the same or comparable level of analytical and clinical performance for specific mutations in the originally-approved companion diagnostic device.

Current Thinking

- Validation studies should be designed to demonstrate the performance characteristics of the device for its intended use
- Entire test system validation
  - From specimen collection & sample preparation to the steps in the sequencing pipeline and the generation of a result report
- Representative variant approach should cover all relevant variant types with consideration to size, genomic context, etc.
- If clinical validity of mutations from cell free DNA to select patients for therapy has not yet been demonstrated,
  - clinical outcome data to support the Companion Diagnostic claims for these mutations is needed.
- Validation for a follow-on claim should be comparable to that of the original companion diagnostic
- Appropriate validation for modifications to an approved panel

Resources

- FDA website on companion diagnostics: http://www.fda.gov/companiondiagnostics
- FDA companion diagnostic guidance: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf
- FDA-AACR: Liquid Biopsies in Oncology Drug and Device Development (7/19/2016): http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/pages/fda-aacr-liquid-biopsies-in-oncology-drug-and-device-development.aspx#bypslides
- FDA Public Workshop: NGS-Based Oncology Panels (2/25/2016): http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm480046.htm
- cobas EGFR Mutation Test v2 - SSED http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150047B.pdf

Acknowledgements

PMA P150044 & P150047 Review teams

Karen Bijwaard: Lead Reviewer
Eunice Lee
Abraham Tzou
Soma Ghosh
Nicholas Anderson
Yun-Fu Hu
Erny Satyadi
Joshua Levin
Lauretta Odogwu
Erin Larkins
Gideon Blumenthal
Patricia Keegan

Meijuan Li
Yuying Jin
Tinghui Yu
Charles Peterson
Hongying Helen Jiang
Marisa White
Janette Collins-Mitchell
Veronica Calvin
Rebecca Ward
Bhaskara Chikkaveeraiah

Questions?

Reena Philip

FDA/CDRH/OIR/DMGP

Reena.philip@fda.hhs.gov

Thank You

Reena Philip

FDA/CDRH/OIR/DMGP

Reena.philip@fda.hhs.gov