First NGS Group Claim

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Agenda

1. Introduction to Group Claims
2. First NGS Group Claim

   BRAF V600E and V600E/K Group Claim Indications in FoundationOne®CDx
3. Concluding Remarks

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Introduction to Group Claims

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Traditional Companion Diagnostic (CDx) Development and Labeling

Process

- One CDx for each therapeutic product
- CDx label may list out multiple, individual drugs per biomarker and cancer type

Problem

- Current model is not optimal for patient care. Clinician may need to:
  - Order a different CDx test
  - Obtain additional biopsies

CDx Device Labeling

Cancer type	**Biomarker**	**Therapeutic X**
		Therapeutic Y
		Therapeutic Z

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What is a group claim?

Definition:

A companion diagnostic claim indicated for a specific group of oncology therapeutic products

CDx Device Labeling

Cancer type	Biomarker	Group of FDA-approved therapies

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FDA Guidance

- In April 2020, FDA finalized the guidance, “Developing and Labeling *In Vitro* Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products”.
- The guidance suggested a framework and specific criteria needed to develop a CDx to support the indicated use for a group of therapeutics.
- CDx manufacturers can submit a new PMA supplement or new 510(k), as appropriate, to obtain a group claim for existing devices.

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FDA Considers the Following When Defining a Group:

- Whether a specific group of oncology therapeutic products can be defined for which a companion diagnostic will identify an appropriate patient population for potential treatment.
- Whether there is a detailed understanding of:
  a) the mechanism of action of the specific group of oncology therapeutic products being considered for use with the companion diagnostic and
  b) the interaction between the therapeutic products and the biomarker(s), at the molecular alteration level, detected by the companion diagnostic.
- Whether there is sufficient clinical experience with at least two therapeutic products for the same biomarker-informed indications.
- Whether analytical validity of the companion diagnostic has been demonstrated across the range of biomarkers that inform the indication.
- Whether clinical validity of the companion diagnostic has been demonstrated with the therapeutic products in the disease of interest.

1. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-and-labeling-vitro-companion-diagnostic-devices-specific-group-oncology-therapeutic

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Benefits to Stakeholders

Clinicians & Patients

- Group claims enable greater flexibility to choose the most appropriate therapeutic product based on a patient's biomarker status.
- Clinicians will not have to order multiple tests to select a different treatment option.

FDA

- Least burdensome approach for submissions and review.
- Recognition of therapeutics with the same mechanism of action.
- Encourages harmonized biomarker definitions across therapeutics in a group for a device.

Industry

- Device manufacturers can broaden the labeling of marketed CDx devices.
- Validation for cleared or approved devices may be leveraged to support a group claim.

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First NGS Group Claim

BRAF V600E and *BRAF* V600E/K in Melanoma for FoundationOne®CDx

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FOUNDATIONONE®CDx

FoundationOne®CDx is a qualitative next-generation sequencing (NGS) based *in vitro* diagnostic test that uses targeted high throughput hybridization-based capture technology for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens.

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Pre-Group Claim Melanoma Labeling for FoundationOne®CDx

Claims received as part of the original PMA approval in November 2017

Tumor Type	Biomarker(s) Detected	Therapy
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)

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Questions and Considerations

- How to define the group(s) of therapeutics?
- How to take the monotherapy indications into account?
- How would the BRAF and MEK inhibitor combinations fit into the overall group?
- Is the mechanism of action the same for each combination?

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Defining the Indications for Use

FoundationOne®CDx can identify patients with melanoma whose tumors have *BRAF* V600E or *BRAF* V600E and V600K mutations and are suitable for treatment with BRAF inhibitors or BRAF/MEK inhibitor combinations approved by FDA for that indication.

two separate group claims

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FDA-Approved BRAF/MEK inhibitors for Unresectable or Metastatic Melanoma and Approved Companion Diagnostic Tests

FDA-Approved Companion Diagnostics	FDA-Approved Therapeutic Products					
	dabrafenib	vemurafenib	trametinib	cobimetinib in combination with vemurafenib	encorafenib in combination with binimetinib	dabrafenib in combination with trametinib
FoundationOne® CDx	X	X	X	X	-	-
bioMérieux THxID™ BRAF Kit	X	-	X	-	X	-
Roche cobas® 4800 BRAF V600 Mutation Test	-	X	-	X	-	-

Note: none of the CDx labels were specifically indicated for treatment with dabrafenib in combination with trametinib. This was misaligned with the indication listed in the dabrafenib and trametinib drug labels, for which the combination therapy is approved for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations as detected by an FDA-approved test.

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Evidence for Group Claims

Biomarkers- *BRAF* V600E and *BRAF* V600E/K

Patient Population- unresectable or metastatic melanoma

Analytical Validation- limit of detection and precision studies

Clinical Validation- non-inferiority studies with the cobas® 4800 BRAF V600 Mutation Test and THxID™ BRAF Kit

Mechanism of Action- BRAF inhibitors and MEK inhibitors target two different kinase nodes in the RAS/RAF/MEK/ERK pathway to inhibit cell growth of various BRAF V600 mutation-positive tumors

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Post-Group Claim Melanoma Labeling for FoundationOne®CDx

Approved Nov 10, 2021

Tumor Type	Biomarker(s) Detected	Therapy
Melanoma	*BRAF* V600E	BRAF Inhibitors Approved by FDA*
	BRAF V600E and V600K	Mekinist (trametinib) or BRAF/MEK Inhibitor Combinations Approved by FDA*

*For the most current information about the therapeutic products in this group, go to: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

Note:

- Patient reports will continue to list out all associated therapeutics

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FDA Webpage for *BRAF* in Melanoma Group Claim

FoundationOne CDx (Foundation Medicine, Inc.)	Melanoma - Tissue	P170019/S025 (11/10/2021)	"Identifying patients with melanoma whose tumors have BRAF V600E and are suitable for treatment with BRAF Inhibitors approved by FDA for that indication" List of BRAF Inhibitors approved by FDA for this indication: • Tafinlar (dabrafenib) - NDA 202806 • Zelboraf (vemurafenib) - NDA 202429
			"Identifying patients with melanoma whose tumors have *BRAF* V600E and V600K and are suitable for treatment with BRAF/MEK Inhibitor Combinations approved by FDA for that indication" List of BRAF/MEK Inhibitor Combinations approved by FDA for this indication: • Cotellic (cobimetinib) - NDA 206192 in combination with Zelboraf (vemurafenib) - NDA 202429 • Braftovi (encorafenib) - NDA 210496 in combination with Mektovi (Binimetinib) - NDA 210498 • Tafinlar (dabrafenib) - NDA 202806in combination with Mekinist (trametinib) - NDA 204114

1. https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

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Concluding Remarks

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FMI’s Experience with Group Claim Approvals

- Consider the criteria in the guidance closely to evaluate the applicability of a group claim for a device
- Examine the existing analytical and clinical validation for cleared or approved CDx devices
- Define the group based on the intended use of the therapeutics, mechanism of action, and biomarker definition

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