

Regulatory update: Next Generation Sequencing (NGS)- Based oncopanels

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Risk Based Regulation/Review

- Considers what are the risks to patients if results are wrong
- Generally based on the indications for use
 - Screening
 - Monitoring
 - Prognosis/risk
 - Aid in the diagnosis
 - Companion diagnostic
- **Risk Mitigations – “Controls”** (a set of requirements or guidances that are in place and intended to help assure that a device performs in a safe and effective manner)
 - General Controls - e.g., design controls, labeling
 - Special Controls – e.g., provide evidence of validation in a submission
 - Postmarket Controls

Risk Based Regulation - General

Risk	Classification	Submission Type	Risk Mitigations	Examples
Low	Class 1 Exempt	None	General Controls	-Prealbumin -Extraction Kits
Low	Class 2 exempt	None or one*	General Controls Special Controls	-Autosomal recessive carrier screening gene mutation detection -Genetic Health Risk Assessment System*
Moderate	Class 2 (“Cleared tests”)	510(k) (or ‘De novo’ for first of a kind moderate risk)	General Controls Special Controls	-Gene expression for risk of breast cancer recurrence - NGS based tumor profiling tests
High	Class 3 (“Approved tests”)	PMA	General/Special/ Valid scientific evidence GMP inspection/ Postmarket	-Colon cancer screening - Companion diagnostics

Risk Based Regulation/Review

- Class II
 - General controls alone are insufficient to provide a reasonable assurance of safety and effectiveness.
 - There is sufficient information to establish special controls, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents
 - Special controls are existing methods that are enumerated by the sponsor and the FDA, including guidance documents, with performance specifications and labeling recommendations, mandatory performance standards
 - Notify the FDA prior to marketing those devices via a 510(k) submission (premarket notification)

Risk Based Regulation/Review

- Class III
 - Is reserved for devices deemed High Risk
 - Subject to Premarket approval (PMA)
 - a more complete demonstration of safety and efficacy
 - By statute, the PMA process is reserved for medical devices that “support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.”

Risk Based Regulation - General

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Companion Diagnostics (CDx)

- Medical device, often an in vitro diagnostic device, which provides information that is essential for the safe and effective use of a corresponding therapeutic product
- “Essential” determined by CDER/CBER
- Prescriptive for a specific therapeutic
- Pharma identifies the target population for the drug. The target population must be identifiable after drug approval
- CDx clinical validation is by the success of the trial
- “Bridging studies” validate a CDx test not used as the clinical trial assay (an analysis of efficacy based on CDx test results)
- Origin of class 3 decision: CDx results impact decisions that may be life prolonging, have serious toxicity

Overview of Companion Diagnostic Validation

- **Analytical validation**
 - Conducted with clinical specimens from the intended use population (exception for rare mutations)
 - Analytical validation (e.g., accuracy, reproducibility, specificity, stability) obtained with attention to the clinical decision point
 - Studies are aligned with the assay technology such as accuracy for molecular assays, inter-reader agreement for IHC assays
- **Clinical validation** of the device is supported by the results of the drug trial when a companion diagnostic is used to test specimens and identify patients eligible for the trial.
- www.fda.gov

NGS-based oncopanels

- Single Test, Multiple Biomarkers, Multiple Indications
 - Increasingly employed in the clinical setting
 - One panel can be used for multiple indications
 - Potential to detect rare and novel variants
 - Challenges the regulatory paradigm
 - Burdensome to demonstrate analytical validity for each variant.
 - FDA held a Public Workshop on Feb 25, 2016
 - <https://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm480046.htm>
- www.fda.gov

Evolution of NGS Regulation



Class 3 NGS Oncopanel – One biomarker/one tissue/one drug

- **FoundationFocus CDx_{BRCA} Assay (Foundation Medicine, Dec 2016): First NGS CDx**
 - qualitative detection of *BRCA1* and *BRCA2* alterations in FFPE ovarian tumor tissue
 - aid in identifying ovarian cancer patients for Rubraca™ (rucaparib)
- **Praxis Extended RAS Panel (Illumina, June 2017):**
 - qualitative detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in FFPE colorectal cancer tissue
 - aid in the identification of patients with colorectal cancer for treatment with Vectibix® (panitumumab) based on a no mutation detected test result

Multiple biomarkers/Drugs

Thermo Fisher Oncomine™ Dx Target Test (June 2017)



The Oncomine™ Dx Target Test is a qualitative *in vitro* diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in ROS1 from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM™ Dx System.

The test is indicated to aid in selecting NSCLC patients for treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

CDx indications based on clinical data with Oncomine and Rx

Table 1 - List of variants for therapeutic use

Gene	Variant	Targeted therapy
BRAF	BRAF V600E	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
ROS1	ROS1 fusions	XALKORI® (crizotinib)
EGFR	L858R, Exon 19 deletions	IRESSA® (gefitinib)

Safe and effective use of this test has not been established in tissue types other than NSCLC.

Results other than those listed in Table 1 are indicated for use only in patients who have already been considered for all appropriate therapies (including those listed in Table 1).

Analytical performance using NSCLC specimens has been established for the variants listed in Table 2.

Not CDx because no clinical data with Oncomine and Rx

Table 2 - List of variants with established analytical performance only

Gene	Variant ID	Nucleotide change
KRAS	COSM512	c.34_35delGGinsTT
KRAS	COSM516	c.34G>T

Evolution of NGS Regulation

Establishing a Class 2 regulatory path: NGS-Based Tumor Profiling Tests

- Recognize the significance of tumor testing in optimizing cancer patient treatment
- Reduce burden on test developers
- Streamline the regulatory assessment
- Modernize the approach for innovative products
- Partnered with NYSDOH and MSK to determine least burdensome strategy

MSK IMPACT

(De novo authorization: Nov 15, 2017)

De novo authorization of MSK-IMPACT assay established a new class II regulatory pathway for NGS-based tumor profiling tests. This designation makes these tests eligible for the 510(k) clearance process, either by applying to the FDA directly or through an accredited third-party reviewer like NYSDOH.



Nov 15, 2017 | [staff reporter](#)

"The goal of allowing NGS-based tumor profiling tests to undergo review by accredited third parties is to reduce the burden on test developers and streamline the regulatory assessment of these types of innovative products," said FDA Commissioner Scott Gottlieb in a statement. "As the field advances, we are modernizing the FDA's approach to the efficient authorization of laboratory tests from developers that voluntarily seek 510(k) clearance," he said.

Jeff Shuren, director of the FDA's Center for Devices and Radiological Health, said that the FDA recognized the significance of a patient's tumor mutations for the planning of their care and their outcome, and that FDA worked closely with NYSDOH and Memorial Sloan Kettering to assess the MSK-IMPACT test. "This collaboration is an excellent example of how the FDA can partner with the medical and development communities to review innovative tests as quickly as possible," he said.

Three Tiered Approach for Somatic NGS Tests Based on Level of Evidence

FDA

Level 1: Companion Diagnostics

- Prescriptive for a specific therapeutic

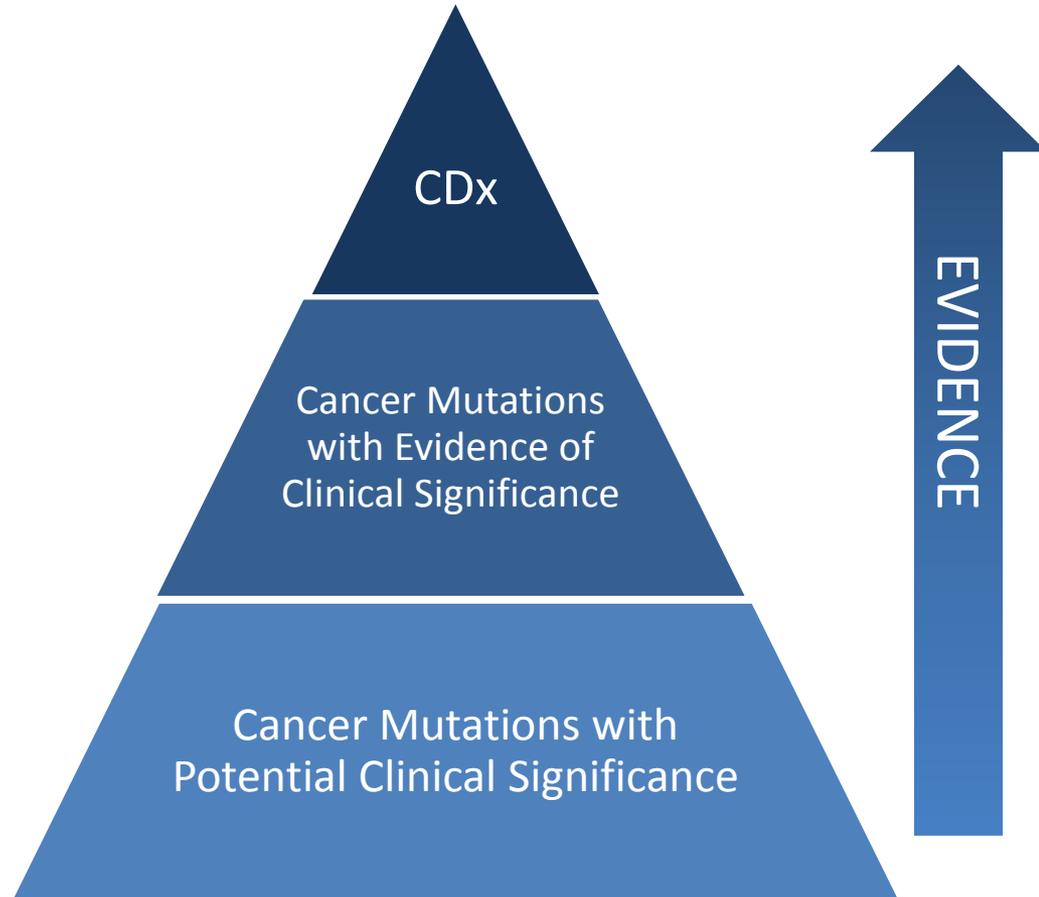
Tumor Profiling:

Level 2: Cancer Mutations with Evidence of Clinical Significance

- Based on professional guidelines

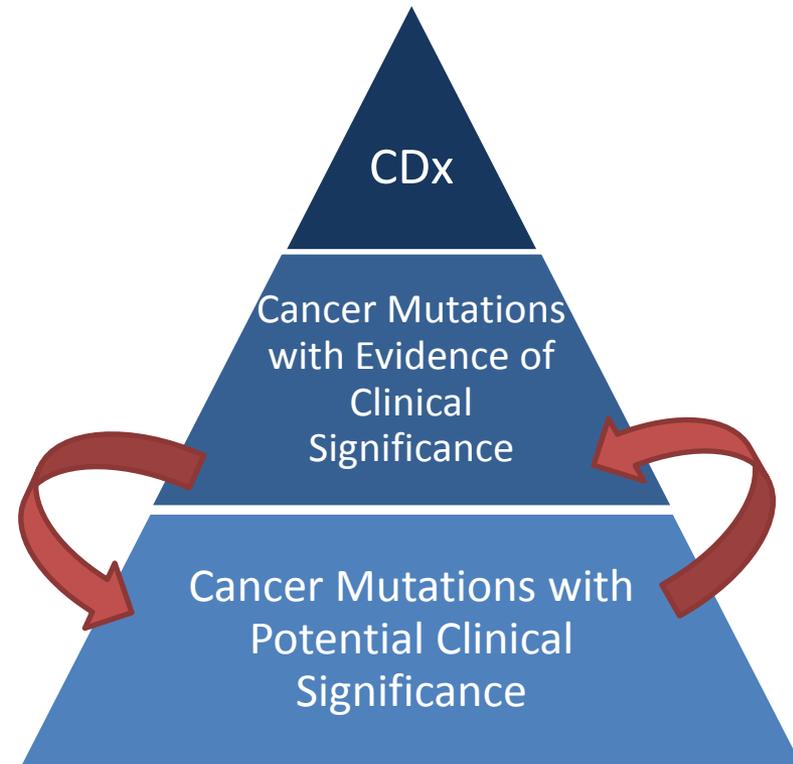
Level 3: Cancer Mutations with Potential Clinical Significance

- Literature or mechanistic rationale for inclusion in panel



A Fluid Approach to Reporting within Levels 2 and 3

- Clinical evidence may differ based on tumor type.
- Flexibility to report mutations based on current knowledge.
- Labeling/Results report does not include prescriptive uses, describes limitations of the information
- Separately, labs continue to provide “practice of medicine” page with select/annotated information



Leverage more from each sample (minimize clinical specimen testing)

- Wildtype from other variant positions to support negative call accuracy
- Panel-wide precision analysis (“incidental” variant precision and QC metrics across panel)

Use of real-world evidence

- Historical performance data to support assay specificity (interference) and tumor type comparability

Least Burdensome

Fluid reporting

- Updates between “Level 2” and “Level 3” reporting without new submission

Future modifications

- Postmarket (minor) modifications can be done without new submission. Submit protocols and pre-specified acceptance criteria

Quality metrics as surrogates

- Use run/sample/variant QC to support the claim

MSK-IMPACT Tumor Profiling Intended Use



Qualitative,
Targeted NGS



The MSK-IMPACT assay is a **qualitative** in vitro diagnostic test that uses **targeted** next generation sequencing of

Specimen type(s)



formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from

Target population:
patients previously diagnosed



patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel.

Variant types



The test is intended to provide information on **somatic mutations (point mutations and small insertions and deletions)** and **microsatellite instability**

Indication
(must include this statement)



for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product.

Single site and name



MSK-IMPACT is a **single-site assay performed at Memorial Sloan Kettering Cancer Center.**

www.fda.gov



NGS Tumor Profiling Assay –What documents and validation data needs to be submitted in a NGS tumor profiling 510(k)?

Aligned largely with NYSDOH

Follow the “Special Controls” described at the end of the Decision Summary:

https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170058.pdf

General:

- Device Description – platform, reagents, software, genes, rationale, specimen processing
- Description of how the test was optimized, metrics, thresholds, filters
- Pan tumor claim –report out the invalid rates across specimen types
- Focus is on Accuracy, limit of detection, precision
- Software/cybersecurity documentation
- Identify how results will be categorized into the two categories

www.fda.gov

Successful Collaboration

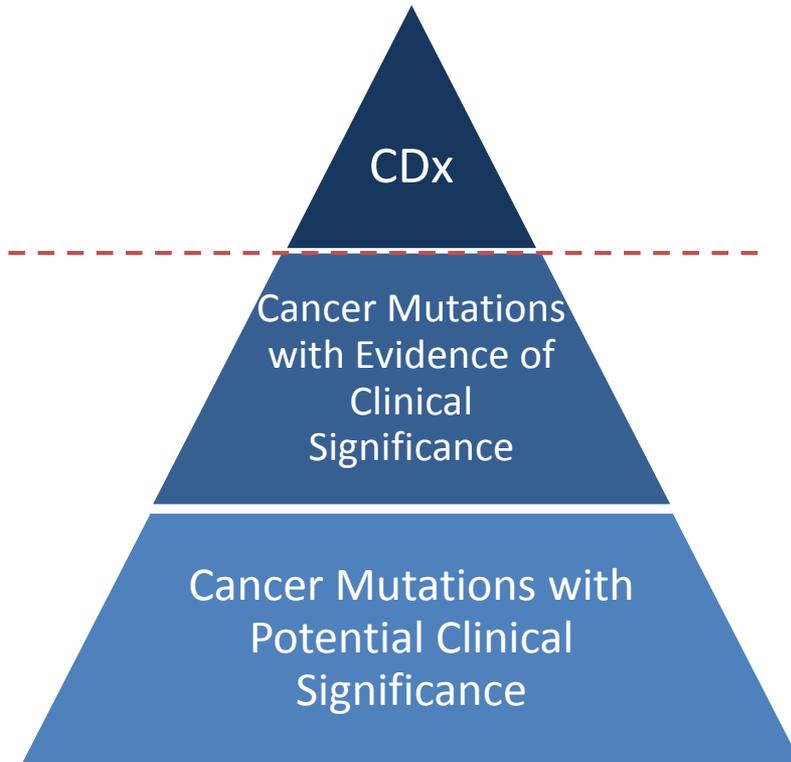
Advancing NGS in this Clinical Setting



- *First time - enabled a tissue agnostic path forward*
- *First time – focus on consideration for quality metrics as surrogates*
- *First time - Representative approach for analytical validation of SNVs and Indels*
- *First time - Enabled leveraging of database for professional guidelines and literature to support oncopanel claim*
 - (conventional regulatory approach required submission of **valid scientific evidence** to support the claim)
- *First time - Postmarket Modifications can largely be done without a new submission.*
 - - Submit protocols and pre-specified acceptance criteria
- Labs can use Research Use Only (RUO) instruments and reagents – assume responsibility for the test
- FDA committed to leveraging a robust third party program

Pathways for FDA Clearance or Approval

- Premarket Application (FDA):
 - Appropriate for oncopanels with companion diagnostic claims
 - Can also make Level 2/3 claims
- 510(k) Pathway (FDA or 3rd Party):
 - Level 2/3 claims only
 - 510(k) to FDA directly **or elect to use an accredited FDA third-party reviewer (e.g., NYSDOH)**
 - can request to have submitter's NYSDOH package and review memo forwarded along to FDA



Third Party Review Program

- FDA accredited NYS Department of Health as the first 3rd party reviewer for NGS tumor profiling assay.
- NGS tumor profiling assays can be submitted directly to FDA or through NYSDOH to obtain 510(k) clearance from FDA. Review elements and criteria are identical for both pathways.
 - For 3rd party review, FDA has 30 days to make a determination follow receipt of package
 - For direct submission, FDA has 90 days to make determination
- A few differences: See special controls established in MSK-IMPACT *De Novo*.

NGS Oncopanel

Companion Diagnostics “Follow-On”



- Follow-on tests = New tests for already approved companion diagnostic indications
- Should consistently and accurately select the same intended use patient population as the originally-approved companion diagnostic devices for the indicated therapeutic drug
- Demonstrate comparable analytical and clinical performance.
- Procured clinical sample set same as the target population
 - determine concordance to original CDx,
 - measure non-inferiority based on discordance

FoundationOne CDx™ (F1CDx)

(November 30, 2017)



- Broad-panel follow-on companion diagnostic test for 5 tumor indications
- Genomic profiling of 324 genes, MSI & TMB in all solid tumors
- Breakthrough
- Parallel Review

Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)

<https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290&ExpandComments=n&bc=ACAAAAAAQAAA&>

www.fda.gov

FDA News Release

FDA announces approval, CMS proposes coverage of first breakthrough-designated test to detect extensive number of cancer biomarkers

Agencies' parallel review process makes test for efficient identification of multiple targeted therapy options available to health care professionals, patients and eligible Medicare beneficiaries sooner

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For Immediate Release

November 30, 2017

Summary

FDA approves test to detect mutations in 324 genes, two genomic signatures. Second to be approved with proposed coverage under FDA/CMS Parallel Review Program.

FoundationOne CDx™ (F1CDx) (November 30, 2017)

-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 from FFPE tumor tissue specimens. The test is intended as a **companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed Table 1** in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide **tumor mutation profiling** to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms.

www.fda.gov

Table 1. Companion diagnostic indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	<i>EGFR</i> exon 19 deletions and <i>EGFR</i> exon 21 L858R alterations	Gilotrif [®] (afatinib), Iressa [®] (gefitinib), or Tarceva [®] (erlotinib)
	<i>EGFR</i> exon 20 T790M alterations	Tagrisso [®] (osimertinib)
	<i>ALK</i> rearrangements	Alecensa [®] (alectinib), Xalkori [®] (crizotinib), or Zykadia [®] (ceritinib)
	<i>BRAF</i> V600E	Tafinlar [®] (dabrafenib) in combination with Mekinist [®] (trametinib)
Melanoma	<i>BRAF</i> V600E	Tafinlar [®] (dabrafenib) or Zelboraf [®] (vemurafenib)
	<i>BRAF</i> V600E and V600K	Mekinist [®] (trametinib) or Cotellic [®] (cobimetinib) in combination with Zelboraf [®] (vemurafenib)
Breast cancer	<i>ERBB2</i> (HER2) amplification	Herceptin [®] (trastuzumab), Kadcyla [®] (ado-trastuzumab-emtansine), or Perjeta [®] (pertuzumab)
Colorectal cancer	<i>KRAS</i> wild-type (absence of mutations in codons 12 and 13)	Erbix [®] (cetuximab)
	<i>KRAS</i> (exons 2, 3, and 4) and <i>NRAS</i> (exons 2, 3, and 4)	Vectibix [®] (panitumumab)
Ovarian cancer	<i>BRCAl/2</i> alterations	Rubraca [®] (rucaparib)

NGS Oncopanel: Tumor Profiling vs. CDx



Difference between CDx and Tumor Profiling Assays		CDx	Tumor Profiling
IU	Conclusive/Prescriptive use for specific therapeutics?	Yes (IU specifies CDx biomarker and approved drug indications)	No
Clinical	Clinical validity (for selecting treatment) established using the test?	Yes (clinical efficacy or clinical concordance)	No
Analytical	Variant level validation data provided?	Yes	Not always
Regulatory Pathway	Currently eligible for 510(k) clearance?	No (PMA)	Yes

Is the Test Investigational?

- An investigational device is a device that is **used in a clinical investigation** or research involving one or more subjects that will **generate data** about the safety and effectiveness of the IVD as used in the study (i.e., for the clinical indication), and,
the device is not cleared or approved for that clinical indication
- NGS tests **may be investigational for a sponsor** when using the test to select patients to obtain specific therapeutic product safety and efficacy information.
- If the test is authorized though to report the specific biomarker, then, FDA does not need to conduct analytical review.

Draft Guidance: Investigational IVDs Used in Clinical Investigations of Therapeutic Products



-
- Released Dec 15, 2017
 - <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM589083.pdf>
 - Outlines how to comply with the IDE regulation when including IVDs in drug trials
 - Recommendations are applicable to other types of studies
 - Current study types
 - Oncology
 - Rare disease
 - Genomics

Draft Guidance: Investigational IVDs Used in Clinical Investigations of Therapeutic Products



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When an approved IVD is used to guide the therapeutic management of subjects in a clinical trial of a new therapeutic product (e.g., a HER2 test that is approved for use with trastuzumab in breast cancer is used to guide the therapeutic management of subjects in a clinical trial of a new breast cancer drug for the same analyte HER2), generally the use of the IVD would be considered investigational (see section III.A). However, for such IVDs, FDA does not intend to examine whether they comply with the requirement for IDE approval under the FD&C Act and 21 CFR Part 812

Draft Guidance: Investigational IVDs Used in Clinical Investigations of Therapeutic Products



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- Page 17 continued.....
 - when IRB approval is obtained and maintained for the investigation using such IVD,
 - the investigation meets the abbreviated requirements under 21 CFR 812.2(b)(1)(i), (iii)-(vii),
 - and assurance is provided to the IND that the IVD is used with the new therapeutic product in accordance with the instructions for use (IFU) that are provided in the device's approved labeling. Assurance of adherence to the IFU should minimally address the intent-to test criteria (e.g., disease type [such as lung cancer, colon cancer], specimen type [such as plasma, serum, tissue], and specimen adequacy), the test methodology, and the classification criteria (i.e., cutoff, if used).

FDA finalizes guidances to accelerate the development of reliable, beneficial next generation sequencing-based tests



April 12, 2018

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based *In Vitro* Diagnostics

Guidance for Stakeholders and Food and Drug Administration Staff

Document issued on April 13, 2018.

The draft of this document was issued on July 8, 2016.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0850 (expires 03-31-2021).

See additional PRA statement in Section 7 of the guidance.

For questions about this document concerning devices regulated by CDRH, contact Laura Koontz at 301-796-7561 or OIRPMGroup@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 240-402-8010 or by email at ocod@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

Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases

Guidance for Stakeholders and Food and Drug Administration Staff

Document issued on April 13, 2018.

The draft of this document was issued on July 8, 2016.

For questions about this document concerning devices regulated by CDRH, contact Zivana Tezak at 301-796-6206 or Adam Berger at 240-402-1592 or by email at OIRPMGroup@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 240-402-8010 or by email at ocod@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

NGS – New guidances

“Considerations for Design, Development, and **Analytical Validation** of Next Generation Sequencing (NGS)– Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases”

- Can form the basis for future FDA-recognized consensus standard(s) and/or special controls.
- Standards would be developed with the scientific community, and can be updated as science and technology advance.

“Use of **Public** Human Genetic Variant **Databases** to Support **Clinical Validity** for Genetic and Genomic-Based In Vitro Diagnostics”

- Use of curated databased to provide clinical evidence
- Voluntary process for publicly available databases to obtain recognition as information sources to support the link between genetic variation and health/disease.
- Test developers may be able to use such databases in lieu of traditional clinical studies.

NGS submission information

CDRH FACT SHEET - Tumor Profiling NGS Tests:

<https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM584603.pdf>

MSK-IMPACT Decision summary:

https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170058.pdf

Oncomine™ Dx Target Test SSED:

https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160045B.pdf

F1CDx SSED:

https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf

FDA Companion Diagnostic Decision Summaries

<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm?source=govdelivery>

Guidance Documents

- *In Vitro Diagnostic (IVD) Device Studies- Frequently Asked Questions*
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf>
- *Guidance on In Vitro Companion Diagnostic Devices*
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>
- *Draft Guidance on Principles of Co-development of Companion Diagnostic Devices with Therapeutic Product*
<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM510824.pdf>
- *Use of Public Human Genetic Variant Databases to Support **Clinical Validity** for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics*
<https://www.federalregister.gov/articles/2016/07/08/2016-16200/use-of-public-human-genetic-variant-databases-to-support-clinical-validity-for-next-generation>
- *Considerations for Design, Development, and **Analytical Validation** of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected *Germline Diseases**
<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm509838.pdf>

Software Guidance

- *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices - Guidance for Industry and FDA Staff (2005)*
<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf>
- *General Principles of Software Validation; Final Guidance for Industry and FDA Staff (2002)*
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM085371.pdf>
- *Guidance for Off-the-Shelf Software Use in Medical Devices; Final (2002)*
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073779.pdf>
- *Guidance for Industry - Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software (2005)*
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077823.pdf>
- *Content of Premarket Submissions for Management of Cybersecurity in Medical Devices – Guidance for Industry and Food and Drug Administration Staff (2014)*
<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm356190.pdf>
- *Postmarket Management of Cybersecurity in Medical Devices - Guidance for Industry and Food and Drug Administration Staff (2016)*
<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm482022.pdf>

Want to discuss your test?

CDRH Pre-Submission Program:

<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>

Questions?

Reena.Philip@fda.hhs.gov

Thank you

