Regulatory Science through NGS and beyond

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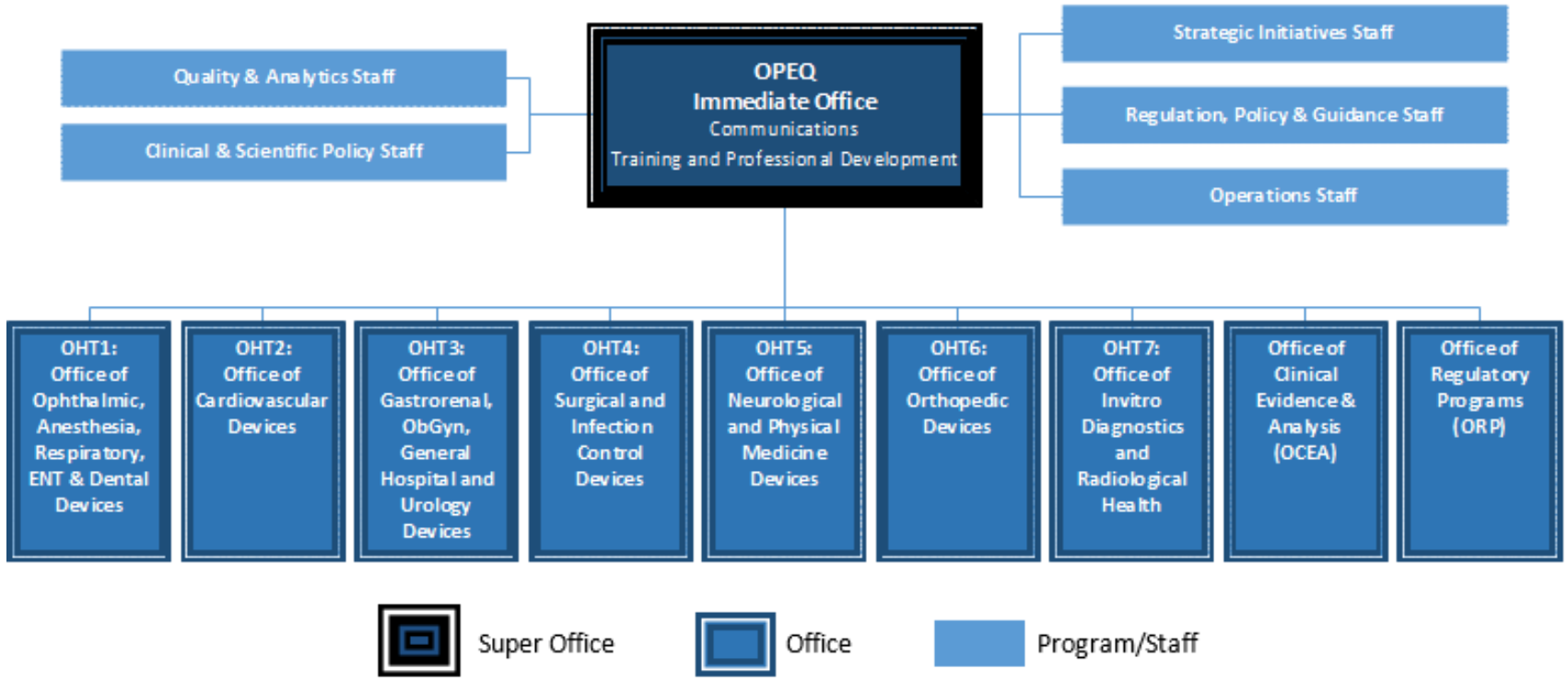
Outline

- Introduction to CDx Regulation
- FDA Organizational Introduction (Office of Product Evaluation & Quality)
- Diagnostic update



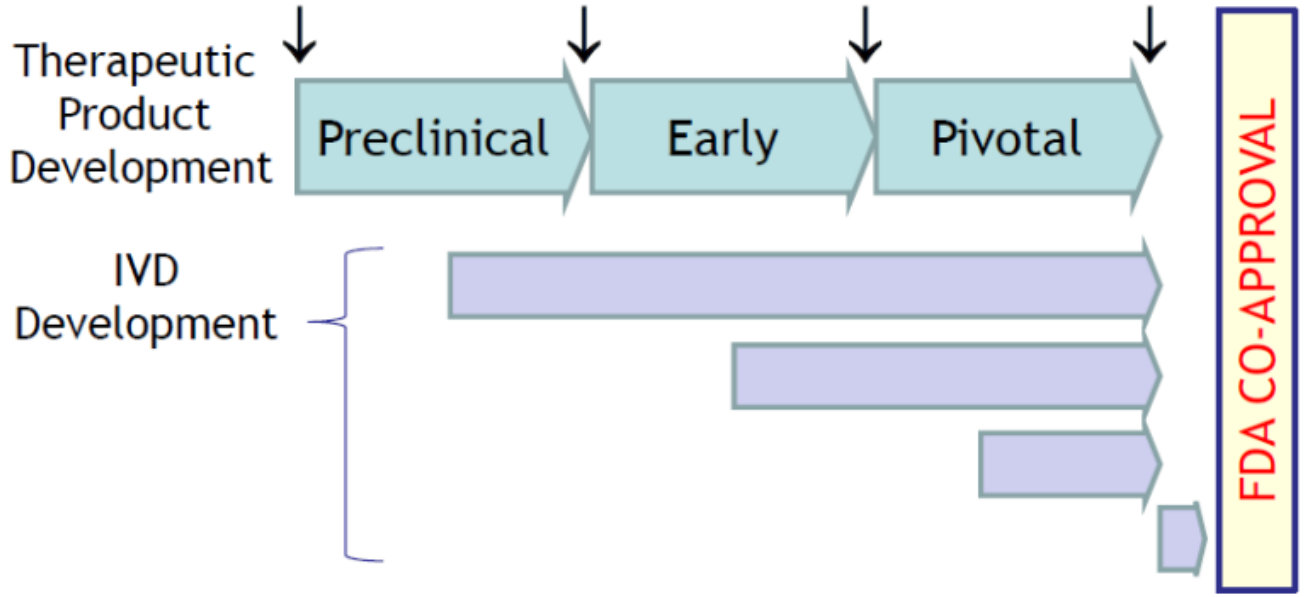
FDA Classifies Medical Devices into One of Three Classes

DRIVEN BY LEVEL OF RISK AND INTENDED USE

Risk Category	Definition	Risk Controls	Examples
Class I	Low-risk; subject to the least regulatory control	General controls including facility registration, product listing with FDA, record keeping, premarket notification, and adherence to quality systems regulation (QSR)	• Elastic bandages • Examination gloves • Hand-held surgical instruments
Class II	Higher risk; general controls alone are insufficient to ensure safety and effectiveness	• All Class I controls • Performance standards, post-market surveillance, patient registries, and FDA guidelines • 510(K) clearance • (Ask me what is *de novo?*)	• Powered wheelchairs • Infusion pumps • Surgical drapes • **Most Diagnostic Tests**
Class III	Highest risk; life-sustaining, life-supporting, and implantable devices, or new devices not substantially equivalent to legally marketed devices	• All Class I and II controls • Must receive premarket approval (PMA) to ensure safety and effectiveness	• Heart valve replacements • Implanted stimulators • Breast implants • **CDX**

Co-development of Drug-Diagnostic

- Codevelopment does not require simultaneous development of CoDx and therapeutic product from beginning to end.
- Biomarker discovery (↓) and test development can occur at any point during the therapeutic product development process.



- Whether initiated at the outset of development or at a later point, codevelopment should generally be conducted in a way that will facilitate obtaining contemporaneous marketing authorizations for the therapeutic product and the associated IVD companion diagnostic.

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So what do I need …

- FDA recommends that the IVD is analytically validated prior to use in clinical trials, **particularly around the clinical decision points**
  - Analytically validate prior to use, preferably use a fully-specified "market-ready" test for enrollment of patients into a trial
- **Bank specimens** for future AV studies, bridging studies
- Consider **informed consent** policies for all uses of samples (e.g., retesting)
- Consider lability issues when storing specimen; for example, store BLOCKS and not SLIDES if possible, for SLIDES are more labile
- Bonus question: TRAINING vs VALIDATION!

List of Approved CDx (not exhaustive)

Table 5. List of FDA approved CDx assays for genes targeted by F1CDx

	Device	Company	Technology	Therapy	Indication
HER2-Amplification	PathVysion HER-2 DNA Probe Kit	Abbott Molecular, Inc.	FISH	Herceptin (trastuzumab)	Breast cancer
	Pathway Anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody	Ventana Medical Systems, Inc.	IHC	Herceptin (trastuzumab)	Breast cancer
	Insite HER-2/neu Kit	Biogenex Laboratories, Inc.	IHC	Herceptin (trastuzumab)	Breast cancer
	Spot-Light HER2 CISH Kit	Life Technologies, Inc.	CISH	Herceptin (trastuzumab)	Breast cancer
	Bond Oracle Her2 IHC System	Leica Biosystems	IHC	Herceptin (trastuzumab)	Breast cancer
	HER2 CISH pharmDx Kit	Dako Denmark A/S	CISH	Herceptin (trastuzumab)	Breast cancer
	INFORM HER2 DUAL ISH DNA Probe Cocktail	Ventana Medical Systems, Inc.	Dual ISH	Herceptin (trastuzumab)	Breast cancer
	HercepTest	Dako Denmark A/S	IHC	Herceptin (trastuzumab) Perjeta (pertuzumab) Kadcyla (ado-trastuzumab emtansine)	Breast cancer Gastric or Gastroesophageal junction adenocarcinoma
	HER2 FISH pharmDx Kit	Dako Denmark A/S	FISH	Herceptin (trastuzumab) Perjeta (pertuzumab) Kadcyla (ado-trastuzumab emtansine)	Breast cancer Gastric or Gastroesophageal junction adenocarcinoma
BRAF-V600	THxID BRAF Kit	bioMerieux	PCR	Mekinist (tramatenib)	Melanoma
	cobas BRAF V600 Mutation Test	Roche Molecular Systems, Inc.	PCR	Zelboraf (vemurafenib)	Melanoma
BRAF-600E	THxID BRAF Kit	bioMerieux	PCR	Tafinlar (dabrafemib)	Melanoma
	Oncomine Dx Target Test	Life Technologies, Inc.	NGS	Tafinlar (dabrafemib) Mekinist (trametinib)	Non-small cell lung cancer
NRAS	Praxis Extended Ras Panel	Illumina	NGS	Vectibix (panitumumab)	Colorectal cancer
KRAS	**cobas** KRAS Mutation Test	Roche Molecular Systems, Inc.	PCR	Erbitux (cetuximab) Vectibix (panitumumab)	Colorectal cancer
	therascreen KRAS RGQ PCR Kit	QIAGEN	PCR	Erbitux (cetuximab) Vectibix (panitumumab)	Colorectal cancer
	Praxis Extended Ras Panel	Illumina	NGS	Vectibix (panitumumab)	Colorectal cancer
***ALK* - fusion**	Vysis ALK Break Apart FISH Probe Kit	Abbott Molecular, Inc.	FISH	Xalkori (crizotinib)	Non-small cell lung cancer
	ALK (D5F3) CDx Assay	Ventana Medical Systems, Inc.	IHC	Xalkori (crizotinib)	Non-small cell lung cancer
***EGFR* – Exon 19 deletions & L858R**	**cobas** EGFR Mutation Test v2	Roche Molecular Systems, Inc.	PCR	Tarceva (erlotinib)	Non-small cell lung cancer
	therascreen EGFR RGQ PCR Kit	QIAGEN	PCR	Gilotrif (afatinib) Iressa (gefitinib)	Non-small cell lung cancer
	Oncomine Dx Target Test	Life Technologies, Inc.	NGS	Iressa (gefitinib	Non-small cell lung cancer
***EGFR* T790M**	**cobas** EGFR Mutation Test v2	Roche Molecular Systems, Inc.	PCR	Tagrisso (osimertinib)	Non-small cell lung cancer
BRCA1/2	FoundationFocus CDx$_{BRCA}$	Foundation Medicine, Inc.	NGS	Rubraca (rucaparib)	Advanced Ovarian

Abbreviations: FISH – fluorescence *in situ* hybridization; IHC – immunohistochemistry; CISH – chromogenic *in situ* hybridization; ISH – in situ hybridization; PCR – polymerase chain reaction; NGS – next generation sequencing.

Follow-On CDx

Follow-on Companion Diagnostics

- Test 1: FDA-approved companion diagnostic for a therapeutic product; select a subset for a drug
- Test 1 approved with a therapeutic clinical trial; drug efficacy (e.g. HR) for outcome Y available

- Test 2 (follow-on): New manufacture intended for the same therapeutic indication

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What is a Follow-on CDx?

- A follow-on companion diagnostic (FCD) is intended to be used with the therapeutic product in the indicated patient population, as in the labeling of the comparator companion diagnostic. (CCD)

- However, the manufacturer of a follow-on companion diagnostic device may not have a therapeutic partner to conduct a new clinical trial or may lack the patient samples from the original clinical trial, where the comparator and therapeutic product were evaluated.

- As such, an external concordance study is conducted to assess the concordance between the comparator and the follow-on device. Difficulty and challenges arise on how to evaluate the follow-on devices clinical performance based the agreements from an external concordance study.

Follow-On Companion Diagnostic

Types of fCDx

Scenarios of Follow-on Companion Diagnostic Test

- Samples available from clinical trial for Test 1 to test with follow-on Test 2:
  - (1) All (Scenario I)
  - (2) Some (Scenario II)
  - (3) None (Scenario III)

	Test 1	Follow-on Test 2	Outcome Y
Clinical Study	✓†	(1), (2)	✓†
Concordance study	✓	(3)	

†Only for (3), sponsor of follow-on may have only access to summary level data in clinical study.

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From Gene Pennello's presentation

Key Principles of FCD/CCD Analysis

- The FCD Manufacturer will retest the patient samples from the original clinical trial using FCD to determine patient biomarker status defined by FCD. For example, if FCD is intended to select marker positive patients for the treatment, then the primary analysis for FCD clinical validation is the therapeutic efficacy in FCD positive patients.

- Therefore, if a patient enrolled in the original clinical trial has FCD negative result, the patient should be excluded in the primary analysis. Using the agreements between FCD and CCD and the clinical data from the original clinical trial, the therapeutic efficacy in FCD IU population can be estimated directly using the same statistical method as the bridging studies (Li 2015).

- If only CCD positive patients are enrolled in the original trial, all available enrolled patient samples from the original trial should be retested by FCD to determine their FCD results.

- In addition, sufficient number of CCD negative patient samples should be retested by FCD so that both positive (PPA) and negative percentage agreements (NPA) between CCD and FCD can be assessed. Note that PPA and NPA are needed to assess the therapeutic efficacy in FCD IU population (Li 2015).

FDA Approved device as comparator for concordance studies

Table 25. FDA Approved CDx devices used as comparator method for concordance studies

Biomarker	Comparator Method
EGFR exon 19 deletions and L858R	**cobas®** *EGFR* Mutation Test v2
EGFR T790M	**cobas®** EGFR Mutation Test v1 **cobas®** EGFR Mutation Test v2
ALK rearrangements	Ventana *ALK* (D5F3) CDx Assay Vysis *ALK* Break-Apart FISH Probe Kit
KRAS	*therascreen®* KRAS RGQ PCR Kit
ERBB2 (HER2) Amplifications	Dako HER2 FISH pharmDx® Kit
BRAF V600	**cobas®** *BRAF* V600 Mutation Test THxID™ *BRAF* kit
BRCA1 and *BRCA2*	FoundationFocus CDx_{BRCA}

CDx claims were based on a non-inferiority (NI) statistical testing approach using the enrichment design presented in the paper by Li (2016)[9], when the concordance study sample is not a random sample from the companion diagnostic (F1CDx) intended use population and a reference standard is not available. F1CDx was compared to FDA-approved CDxs. The agreements were calculated based on the methods described in the paper by Li (2016)[9]. All studies based on NI passed the acceptance criteria specified in each study protocol. The clinical concordance studies, with the exception of *ALK* and *EGFR* T790M, were subject to pre-screening bias, therefore the concordance results may be overestimated and the failure rate may be underestimated. Details regarding the pre-screening method(s) are included in the study summaries below.

FDA works in a creative and collaborative manner in seeking performance studies…

- Analytical Validation was demonstrated both for specific calls as well as at platform level
- For example, Precision was evaluated for specific alterations associated with CDx claims as required for a follow-on CDx claim but representative alterations were chosen to support platform level performance including MSI, TIM and MAF of short variants,

Table 15. Sample set with CDx variants

Gene	# of Unique Samples	Alteration	Tumor Type
EGFR	3	Exon 19 Deletion	NSCLC
	2	Exon 21 L858R	
	2	Exon 20 T790M	
KRAS	3	Codons 12/13 substitution	CRC
ALK	3	Fusion	NSCLC
BRAF	3	V600E/V600K	Melanoma
ERBB2 (HER2)	3	Amplification	Breast

Table 16. Sample set for platform validation

Alterations Type	# of Unique Samples	Alteration Size	Genomic Context
Substitution	3	-	-
Short Insertion	2	1-2bp	Homopolymer Repeats
Short Insertion	2	1-2bp	Dinucleotide Repeats
Short Insertion	2	3-5bp	-
Short Insertion	2	> 5bp	-
Short Deletion	2	1-2bp	Homopolymer Repeats
Short Deletion	2	1-2bp	Dinucleotide

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P170019

Extensive interrogation of the system was performed

- DNA Extraction
- DNA Amplification
- Guard banding robustness on the steps – library construction, hybrid capture and sequencing
  - Including robustness in detection INDELs and Re-arrangements
- A large Tissue comparability study was performed since we were seeking a pan-tumor claim

Table 24. Summary of tissue types included in the tissue comparability study

Tissue Group	Number of Samples in Tissue Group	Biopsy Sites Included	% Passing DNA Extraction Yield QC	% Passing LC Yield QC	% Passing HC Yield QC	% Passing Median Exon Coverage QC
Abdomen	1161	Abdomen, Abdominal wall	91.2	99.8	99.1	98.3
Adrenal Gland	689	Adrenal Gland	90.9	99.8	99.8	98.7
Anus	115	Anus	97.3	99.1	99.1	99.1
Appendix	177	Appendix	97.3	99.3	100.0	100.0
Bladder	974	Bladder	98.1	99.8	99.6	99.3
Brain	5840	Brain, Pituitary gland, Pituitary, Central nervous system (CNS), Pineal, Pineal Gland	96.1	99.8	99.6	99.2
Breast	3304	Breast	96.0	99.7	99.4	98.7
Cervix	346	Cervix	96.3	99.3	100.0	99.3
Chest Wall	820	Chest Wall	92.0	99.6	99.4	99.3
Colon	5560	Colon, Rectum	97.4	99.9	99.6	99.2
Diaphragm	112	Diaphragm	94.8	100.0	99.0	97.8
Esophagus	902	Esophagus	96.1	100.0	99.7	98.6
Fallopian Tube	211	Fallopian Tube	99.0	100.0	100.0	100.0
Gallbladder	373	Gallbladder	96.6	100.0	100.0	99.7
Gastro-esophageal junction	301	Gastro-esophageal junction	93.8	100.0	99.2	98.8
Head and Neck	1777	Head and neck, Tongue, Trachea, Mouth, Nasal Cavity, Nasopharynx and Paranasal Sinuses, Tonsil, Eye, Larynx, Head or Neck, Ear, Lacrimal Gland	93.4	99.7	99.4	99.1
Kidney	945	Kidney	96.5	99.8	98.8	99.2
Liver	12112	Liver	90.4	99.6	99.6	98.7
Lung	15700	Lung, Pleura	89.6	99.6	99.3	98.8
Lymph Node	7785	Lymph Node	93.0	99.7	99.5	98.9
Malignant effusions	1587	Pleural Fluid, Peritoneal Fluid, Pericardial Fluid	94.4	99.8	99.4	98.8
Mediastinum	493	Mediastinum	91.0	99.8	99.5	99.5
Omentum	1761	Omentum	94.6	99.9	99.7	98.9

EGFR follow-on study results

EGFR mutations exon 19del/L858R in NSCLC patients inform treatment with Gilotrif, Iressa or Tarceva. CCD = cobas EGFR mutation test (replicates 1, 2), F = F1CDx

Table 26. Concordance Table with CCD1, CCD2 and F1CDX results with eligible samples

	CCD1+				CCD1-			
	CCD2+	CCD2-	CCD2 missing	Total	CCD2+	CCD2-	CCD2 missing	Total
F1CDx+	106	0	0	106	1	1*	0	2
F1CDx-	2**	1	0	3	3	153	0	156
F1CDx Missing	3	0	0	3	1	9	2	12
Total	111	1	0	112	5	163	2	170

Looking at Percent agreements

Example: F1CDx was compared with Roche Cobas EGFR test

Table 27A. PPA and NPA for *EGFR* Exon 19del /L858R Unadjusted for Prevalence

	% Agreement
PPA_{C1C2}	99.1%
PPA_{C1F}	97.2%
NPA_{C1C2}	97.5%
NPA_{C1F}	98.7%
PPA_{C2C1}	96.4%
PPA_{C2F}	95.5%
NPA_{C2C1}	99.4%
NPA_{C2F}	99.4%

Table 27B. PPA and NPA for *EGFR* Exon 19 del/L858R Adjusted for Prevalence (22.1%)

	% Agreement
PPA_{C1C2}	99.1%
PPA_{C1F}	97.2%
NPA_{C1C2}	97.5%
NPA_{C1F}	98.7%
PPA_{C2C1}	91.7%
PPA_{C2F}	92.1%
NPA_{C2C1}	99.7%
NPA_{C2F}	99.4%

PPA_{C1C2} is the PPA between CCD1 and CCD2 conditional on CCD1.
PPA_{C1F} is the PPA between CCD1 and F1CDx conditional on CCD1.
PPA_{C2C1} is the PPA between CCD1 and CCD2 conditional on CCD2.
PPA_{C2F} is the PPA between CCD2 and F1CDx conditional on CCD2.
NPA_{C1C2} is the NPA between CCD1 and CCD2 conditional on CCD1.
NPA_{C1F} is the NPA between CCD1 and F1CDx conditional on CCD1.
NPA_{C2C1} is the NPA between CCD1 and CCD2 conditional on CCD2.
NPA_{C2F} is the NPA between CCD2 and F1CDx conditional on CCD2.

Follow-on Studies

- Similar concordance studies were performed for
  - EGFR T790M
  - ERRB2
  - ALK
  - KRAS
  - BRAF

Table 39A. PPA and NPA for ALK Unadjusted for Prevalence

	% Agreement
PPA_{C1C2}	91.3%
PPA_{C1F}	85.9%
NPA_{C1C2}	90.4%
NPA_{C1F}	96.4%
PPA_{C2C1}	91.3%
PPA_{C2F}	88.0%
NPA_{C2C1}	90.4%
NPA_{C2F}	98.8%

Table 45A. PPA and NPA for *KRAS*, Unadjusted for Prevalence

	% Agreement
PPA_{C1C2}	98.9%
PPA_{C1F}	98.9%
NPA_{C1C2}	99.4%
NPA_{C1F}	100.0%
PPA_{C2C1}	99.4%
PPA_{C2F}	99.4%
NPA_{C2C1}	98.7%
NPA_{C2F}	100.0%

Table 51. Concordance of *BRAF* dinucleotide samples

Dinucleotide Samples	THxID+	THxID-	THxID Missing	Total
F1CDx+	26	0	3	29
F1CDx-	1	24	4	29
Total	27	24	7	58

Regulatory Strategy for a WSI-based AI/ML algorithm

- There are two main regulatory concepts that I would focus on for this device:
  - The whole slide image scanner and the regulatory considerations thereof;
  - The processing of the captured images – creating an algorithm based on the images captured – and based on that providing a predictive/prognostic score for the slide in question - IVDMIA
- Precedents exist for both of these activities individually, but have not been approved/cleared yet in a joint context (thus far)
- Let's look at each of the component regulatory concepts one after the other

Companion Dx v/s Clinical Decision Support

- Are we pursuing a CDx or a CDS?
- CDS definition – Most software to date have been in the CDS category

> A software function is considered CDS, for the purposes of this guidance, if it meets the following:
>
> - Not intended to acquire, process, or analyze [criterion (1)];
> - Intended for the purpose of displaying, analyzing, or printing medical information [criterion (2)]; and
> - Intended for the purpose of supporting or providing recommendations [part of criterion (3)].

- Clearly, this talk assumes we are pursuing a CDx.

Whole Slide Imaging Scanners

Aperio – Leica Biosystems – cleared October 2008

21 CFR 807.92(a)(2):

Trade Name of Device:	ScanScope® XT System
Regulatory Section:	21 CFR 864.1860 Immunhistochemistery reagents and kits
Classification:	Class II
Product Code:	OEO (automated digital image manual interpretation microscope)

System: The system comprises a ScanScope® XT digital slide scanner instrument and a computer system executing Spectrum™ software. The system capabilities include digitizing microscope slides at diagnostic resolution, storing and managing the resulting digital slide images, retrieving and displaying digital slides, including support for remote access over wide-area networks, providing facilities for annotating digital slides and entering and editing metadata associated with digital slides, and facilities for image analysis of digital slides, including the ability to quantify characteristics useful to Pathologists, such as measuring and scoring immunohistochemical stains applied to histology specimens, such as Dako PR, which reveal the presence of PR (Progesterone Receptor) protein expression, which may be used to determine patient treatment for breast cancer.

Whole Slide Imaging Scanners

Aperio – Leica Biosystems – cleared October 2008 – INTENDED USE

Indications for Use:

The ScanScope® System is an automated digital slide creation, management, viewing and analysis system. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape.

The ScanScope® system is intended for use as an aid to the pathologist in the detection and quantitative measurement of PR (Progesterone Receptor) by manual examination of the digital slide of formalin-fixed, paraffin-embedded normal and neoplastic tissue immunohistochemically stained for PR on a computer monitor.

It is indicated for use as an aid in the management, prognosis, and prediction of therapy outcomes of breast cancer.

Whole Slide Imaging Scanners

Aperio – Leica Biosystems – cleared October 2008 – STUDY DESIGN

Two Clinical Laboratory Improvement Amendments (CLIA) qualified clinical sites participated in the study. Prior to their participation in the study each clinical site obtained exemption status from an Institutional Review Board (IRB).

A total set of 180 formalin-fixed, paraffin-embedded breast tissue specimens from both clinical sites were used for the PR study; 80 slides from the first clinical site and 100 slides from the second clinical site.

The specimens at the first clinical site were selected based on their clinical scores on file to provide an equal distribution of PR slides in the percentage of positive nuclei ranges 0%, 1% to 4%, 5% to 9%, 10% to 49%, and 50% to 100%. The specimens at the second clinical site were routine specimens taken from their clinical operation, representing the true target population of cases in a typical clinical setting.

All specimens for the PR study were immunohistochemically stained at the clinical sites using Dako in vitro diagnostic (IVD) FDA cleared Monoclonal Mouse Anti-Human Progesterone Receptor (Clone PgR 636) (K020023).

Please Note: The antibody used to stain was FDA-cleared

Whole Slide Imaging Scanners

Philips Intellisite Pathology Solution –cleared October 2017

1. Indications for use:

The Philips IntelliSite Pathology Solution (PIPS) is an automated digital slide creation, viewing, and management system. The PIPS is intended for in vitro diagnostic use as an aid to the pathologist to review and interpret digital images of surgical pathology slides prepared from formalin-fixed paraffin embedded (FFPE) tissue. The PIPS is not intended for use with frozen section, cytology, or non-FFPE hematopathology specimens.

The PIPS comprises the Image Management System (IMS), the Ultra Fast Scanner (UFS) and Display. The PIPS is for creation and viewing of digital images of scanned glass slides that would otherwise be appropriate for manual visualization by conventional light microscopy. It is the responsibility of a qualified pathologist to employ appropriate procedures and safeguards to assure the validity of the interpretation of images obtained using PIPS.

IVDMIA – In Vitro Diagnostic Multivariate Index Assay

Definition and Regulatory Status of IVDMIAs

Definition

- An IVDMIA is a device that:
- Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a “classification,” “score,” “index,” etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and
- Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user.

What’s out there…

Scratching the surface – lot of activity, we will need to focus our approach

Path AI collaboration with BMS on PD-L1

To develop its algorithms, PathAI collected whole-slide images of PD-L1-stained cells from cancer patients, generated thousands of frames of sections of these slides, and brought them into its cloud-based software platform. Pathologists from PathAI's network of board-certified pathologists around the country then annotated the different features of the cells in each frame, such as PD-L1-positive and negative cells, areas of invasive cancer and necrosis, and normal tissue. These frames were then analyzed using deep learning algorithms to create models, which can be used to score unlabeled slide images and compared against the manual annotations of pathologists.

Concentriq Dx (CE-mark) enables pathologists to make a primary diagnosis of diseases like cancer from digitized images of patients' tissue biopsies, helping laboratories to deliver more timely, higher quality diagnoses. By centering the practice of pathology around images instead of physical glass slides, Concentriq Dx automates time-consuming and error-prone manual tasks and streamlines access to specialized expertise.

UT Southwestern’s new AI-software tool

The ConvPath algorithm can "look" at cells and identify their types based on their appearance in the pathology images using an AI algorithm that learns from human pathologists. This algorithm effectively converts a pathology image into a "map" that displays the spatial distributions and interactions of tumor cells, stromal cells (i.e., the connective tissue cells), and lymphocytes (i.e., the white blood cells) in tumor tissue.
Whether tumor cells cluster well together or spread into stromal lymph nodes is a factor revealing the body's immune response. So knowing that information can help doctors customize treatment plans and pinpoint the right immunotherapy.
Ultimately, the algorithm helps pathologists obtain the most accurate cancer cell analysis - in a much faster way.

Core Concepts of FDA's thinking on AI/ML devices

Using the 510(k) paradigm

Types of AI/ML devices – Let's discuss formative principles

510(k) cleared SaMD

- Framework refers to 510(k) software modification guidance's focus

(Note: keep in mind that 510(k) is about iterative changes to a device; where a legally marketed predicate exists)

- A change that introduces a new risk or modifies an existing risk that could result in a significant harm
- A change to risk controls to prevent significant harm
- A change that significantly affects critical functionality or performance specifications of the device

PMA-approved SaMD

- *Not all AI/ML-based SaMD are locked; some algorithms can adapt over time*.
- The power of these AI/ML-based SaMD lies within the ability to continuously learn, where the adaptation or change to the algorithm is realized after the SaMD is distributed for use and has "learned" from real-world experience. Following distribution, these types of continuously learning and adaptive AI/ML algorithms may provide a different output in comparison to the output initially cleared for a given set of inputs.

Core Concepts of FDA's thinking on AI/ML devices

Using the 510(k) paradigm

Types of AI/ML devices – Let's discuss formative principles

- **Modifications related to performance, with no change to the intended use or new input type:** This type of modification includes improvements to analytical and clinical performance that can result from a number of changes. This may include re-training with new data sets within the intended use population from the same type of input signal, a change in the AI/ML architecture, or other means

- **Modifications related to inputs, with no change to the intended use:** These types of modifications are those that change the inputs used by the AI/ML algorithm. These modifications may involve changes to the algorithm for use with new types of input signals, but do not change the product use claims.

- **Modifications related to the SaMD's intended use:** These types of modifications include those that result in a change in the significance of information provided by the SaMD (e.g., from a confidence score that is 'an aid in diagnosis' (drive clinical management) to a 'definitive diagnosis' (diagnose)).

Foundation One CDx

Intended Use

INDICATIONS FOR USE

FoundationOne CDx™ (F1CDx) is a next generation sequencing based in vitro diagnostic device 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. 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. The F1CDx test is a single-site assay performed at Foundation Medicine, Inc.

21 CFR 807.92(a)(5): Intended use and labeled indications for use: Aperio Scanner

The ScanScope® System is an automated digital slide creation, management, viewing and analysis system. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape.

AV Issues to consider

Analytical Validation Issues

- Slide quality
- Fails Normalization
- Insufficient Tumor
- Tumor region not specified
- Tumor region not in focus
- Fixation not uniform
- Staining not uniform
- Slide expiration
- Robustness of slides
- Staining too old
- Partial Fixation
- Slide cut non-uniform
- Types of Fixative used (demonstrate robustness regardless of fixative?)
- Operator variability
- Scanner variability

Learning from the experts

Here's what I have been reading

Journal of Pathology
J Pathol 2019; **249:** 286–294
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(wileyonlinelibrary.com) DOI: 10.1002/path.5331

REVIEW

Computational pathology definitions, best practices, and recommendations for regulatory guidance: a white paper from the Digital Pathology Association

Esther Abels[1], Liron Pantanowitz[2], Famke Aeffner[3], Mark D Zarella[4], Jeroen van der Laak[5,6], Marilyn M Bui[7], Venkata NP Vemuri[8], Anil V Parwani[9], Jeff Gibbs[10], Emmanuel Agosto-Arroyo[7], Andrew H Beck[11] and Cleopatra Kozlowski[12]*

JAMA | Original Investigation

Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer

Babak Ehteshami Bejnordi, MS; Mitko Veta, PhD; Paul Johannes van Diest, MD, PhD; Bram van Ginneken, PhD; Nico Karssemeijer, PhD; Geert Litjens, PhD; Jeroen A. W. M. van der Laak, PhD; and the CAMELYON16 Consortium