Development of Companion Diagnostics
– An FDA Perspective

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Presentation Topics

• Co-development of drugs and companion diagnostics (CoDx)
• Investigational device exemption (IDE)
• Complementary diagnostics
• Follow-on CoDx (“me too”)
• Next generation sequencing (NGS)-based oncology panel (oncopanel)
• Liquid biopsy
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Companion Diagnostics

• The FDA issued final guidance titled “In Vitro Companion Diagnostic Devices” (Aug. 2014)

• Defined companion diagnostics (CDx) as IVD that provides information that is essential for the safe and effective use of a corresponding therapeutic product

• Described CDx uses
  - Identify population most likely to benefit or most at risk of adverse reaction
  - Monitor response to adjust treatment
  - Identify population for whom product is known to be safe and effective

• Clarified that, in general, the FDA expects contemporaneous regulatory approvals of the CDx and therapeutic product
## FDA Approved CDx

<table>
<thead>
<tr>
<th></th>
<th>Companion Diagnostics in Oncology (as of 06/24/2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>Approved Paired CDx-Therapeutic Indications</td>
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<td>32</td>
<td>Approved IVD Companion Diagnostics</td>
</tr>
<tr>
<td>27</td>
<td>Approved Cancer Therapeutic Products</td>
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<tr>
<td>17</td>
<td>Molecular markers</td>
</tr>
<tr>
<td></td>
<td>ALK, BCR/ABL, BRCA1, BRCA2, BRAF, C-KIT, EGFR, FLT3, HER-2/NEU, IDH2, KIT, KRAS, NRAS, PDGFRB, PD-L1, ROS1, 17p deletion</td>
</tr>
</tbody>
</table>

- **CDx are a subset of IVD; Drugs and their companion tests refer to each other in their labels**
- [https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm](https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm)
Ideal Co-Development Processes

Basic Res.
- Tractable Hit
- Lead Candidate

Preclinical
- Preclinical Evaluation
- Analytical Validation

Clinical
- Investigational New Drug
- Phase I
- Phase II

Biomarker Discovery
- “IDE level” Validation
  - For use in Phase I/II exploratory trials

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• Does your test measure the analyte you think it does?
• How accurately and reliably does it work in the hands of intended users?

Analytical performance: Sensitivity, accuracy, precision/reproducibility etc
Ideal Co-Development Processes

Basic Res.  Preclinical  Regulatory  Market

Tractable Hit  Preclinical Evaluation  Investigational New Drug  NDA
Lead Candidate

Preclinical Evaluation  Phase I  Phase II  Phase III

Investigational New Drug

Biomarker Discovery  Analytical Validation  Investigational Device  PMA
Assay Prototype

Analytical Validation  Exploratory  Clinical Validation

Investigational Device

Clinical Validation

Rx  Dx
CoDx Development Challenges

In reality...

- Business issues
  - Device manufacturers: CoDx development, validation, testing, submission, compliance with device regulations
  - Drug manufacturers: Assuring availability of a CoDx essential for the safe and effective use of their drug
    - Uncertainty of the CoDx needs (e.g., adaptive trials)
    - Underestimate of CoDx development efforts
    - Common use of lab developed tests

- Use of one or more clinical trial assays (CTAs) for patient enrollment (partly or completely)
Common Co-Development Processes

- Basic Res.
  - Tractable Hit
  - Lead Candidate

- Preclinical
  - Preclinical Evaluation

- Clinical
  - Investigational New Drug
    - Phase I
    - Phase II
    - Phase III

- Regulatory
  - NDA
  - BLA

- Market
  - Rx

- Biomarker Discovery
  - Analytical Validation

- Assay Prototype
  - Exploratory

- Investigational Device
  - Clinical Trial Assays

- Companion Diagnostics Development
  - Analytical Validation

- Bridging Study
  - PMA (510(k))

- Market
  - Dx
Challenges for Bridging Studies

• Unavailability or inadequacy of CTA- samples
  ➢ CTA- patients not sampled or consented for retesting
  ➢ Minimum or no demographics, clinicopathological info to verify representativeness of re-test population

• Unavailability or inadequacy of CTA+ samples
  ➢ Missing samples
  ➢ Unstable analytes

• Use of multiple clinical trial assays (CTAs) for patient enrollment (partly or completely)

• Training set vs test set
Plan for Bridging Studies

• Use a well-characterized CTA for enrollment in pivotal trial(s) of the therapeutic product
• Ensure informed consent allows retesting
• Archive CTA+ and CTA- patient specimens
  ➢ Annotation (e.g., demographics, clinicopathological info)
  ➢ Re-test population representative of trial population
• Address potential discordance, missing data, biases (selection, spectrum) in statistical analysis plan
• Consult CDRH via pre-submissions early and often
Plan for No Bridging Studies

- Establish biomarker strategy early during drug development program
  - Trial design as determinant of CoDx vs complementary claims
- Use an analytically validated CoDx for enrollment
  - A specified specimen type and collection method
  - A defined test platform/technology/regent
  - A validated test protocol
  - A selected clinical decision point (cut-off)
- Comply with QSR and IDE regulations
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Is the Test Investigational?

- Investigational device means a device...that is the object of an investigation
- An investigational IVD is not legally marketed for the intended use or indication for use identified in that study, whether or not it has been previously cleared or approved for a separate intended use
- You can find the IVDs that have been cleared or approved on FDA’s website
  - https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm
- Investigational Device Exemption (IDE) regulation
Does the Study Need an IDE?

All Device Investigations

- Studies Subject to the IDE Regulation
  - Significant Risk (SR)
    - Full Requirements
  - Non-Significant Risk (NSR)
    - Abbreviated Requirements
- Studies Exempt from the IDE Regulation
Study Risk Determination Questions

- Will any trial subjects forego or delay a treatment that is known to be effective?
- Will trial subjects be exposed to excessive safety risks (vs control therapies or non-trial SoC)?
- Will subjects who are NOT supposed to be enrolled do worse on the investigational therapy if enrolled?
- Will there be an invasive biopsy for investigational testing outside SoC that presents significant risk?
Study Risk of Oncology Trials

Context and effect of an incorrect test result

Cancer is a serious disease. Any effect on a treatment decision arising from IVD use poses significant risk.

More Risk

Less Risk

Cancer is a serious disease. Large and unmet medical need makes any IVD risk minor.

Accrual by test result
- Rx assignment
- Safety signal for Rx
- Targeted biomarker
- Invasive sampling

All-comers accrual
- Stratification
- No “known effective” Rx
- Convenience biomarker
- Non-invasive sampling
Streamlined Study Risk Determination (SRD)*

- IND sponsor may choose to submit SRD request in an IND
  - Alternatively (as current practice), submit a SRD Q-sub to CDRH
- CDRH/CDER/CBER make SRD at an IND safety meeting
  - Safe-to-proceed letter will include study risk determination
- IND sponsor ensures that
  - Analytically validated tests for enrollment
  - Informed consent covers risks associated with the investigational drug as well as an incorrect test result
  - IRB approvals of the trial and testing
  - Safety monitoring in all phases of the trial

*FDA draft guidance on Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry (April 2018)
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Investigational device exemption (IDE)

Complementary diagnostics

Follow-on CoDx ("me too")

Next generation sequencing (NGS)-based oncology panel (oncopanel)

Liquid biopsy
Emerging Paradigm – Complementary Diagnostics

• A **companion diagnostics** is an IVD that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

• A **complementary diagnostics** is an IVD that identifies a biomarker-defined subset of patients with a different benefit-risk profile than the broader population for which a therapeutic product is indicated, but that is not a prerequisite for receiving the therapeutic product.
### Companion vs Complementary

#### **KEYTRUDA® (pembrolizumab)**
- Studied only in PD-L1-positive patients with NSCLC, gastric or GEJ adenocarcinoma or cervical cancer
- CDx required/part of drug indication
- PD-L1 IHC 22C3 pharmDx
  - IU (excerpt): indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA®
  - NSCLC: TPS ≥ 50% (1st Line)
  - TPS ≥ 1% (2nd Line)
  - Gastric/Cervical: CPS>1%

#### **OPDIVO® (nivolumab)**
- No specific PD-L1 eligibility requirement; Prespecified analysis suggests better response when PD-L1 present
- No CDx/not in drug indication
- PD-L1 IHC 28-8 pharmDx
  - IU (excerpt): PD-L1 expression as detected by PD-L1 IHC 28-8 pharmDx in non-squamous NSCLC may be associated with enhanced survival from Opdivo®.
  - TPS ≥1% staining
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<tr>
<td><strong>Ventana PD-L1 (SP142) CDx ASSAY</strong></td>
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Follow-on CoDx – Opportunities

• To date: >20 different approved drug/diagnostic combinations
  – Current list of approved CoDx
    www.fda.gov/CompanionDiagnostics

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)

A companion diagnostic device can be an in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

The list of FDA cleared or approved nucleic acid based tests is maintained on a separate page at Nucleic Acid Based Tests.
## FDA-Approved HER2 CoDx

<table>
<thead>
<tr>
<th>Target</th>
<th>Diseases</th>
<th>Therapeutics</th>
<th>Approved CoDx</th>
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<tr>
<td>HER2</td>
<td>Breast</td>
<td>Herceptin (trastuzumab)</td>
<td>Abbott PATHVYSION HER-2 DNA Probe Kit&lt;br&gt;Biogenex InSite Her-2/neu mAb (CB11) kit&lt;br&gt;Dako Herceptest&lt;br&gt;Dako HER2 CISH pharmDx Kit&lt;br&gt;Dako HER2 IQFISH pharmDx&lt;br&gt;Leica Bond Oracle HER2 IHC System&lt;br&gt;Life Tech SPOT-LIGHT HER2 CISH Kit&lt;br&gt;Ventana PATHWAY Anti-HER2 Ab (4B5, CB11)&lt;br&gt;Ventana INFORM HER-2/NEU Dual ISH</td>
</tr>
<tr>
<td>HER2</td>
<td>Gastric</td>
<td>Herceptin (trastuzumab)</td>
<td>Dako Herceptest&lt;br&gt;Dako HER2 IQFISH pharmDx</td>
</tr>
<tr>
<td>HER2</td>
<td>Breast</td>
<td>PERJETA (pertuzumab)&lt;br&gt;KADCYLA (ado-trastuzumab emtansine)</td>
<td>Dako Herceptest&lt;br&gt;Dako HER2 IQFISH pharmDx</td>
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**HER2 Follow-on:**
See published SSED (Summary of Safety and Effectiveness Data) for required studies

[www.fda.gov](http://www.fda.gov)
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<tr>
<td>BRAF</td>
<td>Melanoma</td>
<td>Mekinist (tramatenib) Tafinlar (dabrafenib)</td>
<td>bioMérieux THxID BRAF kit</td>
</tr>
<tr>
<td>BRAF</td>
<td>Melanoma</td>
<td>Zelboraf (vemurafenib)</td>
<td>Roche COBAS 4800 BRAF V600 Mutation Test</td>
</tr>
<tr>
<td>EGFR</td>
<td>NSCLC</td>
<td>GILOTRIF® (afatinib) IRESSA® (gefitinib)</td>
<td>Qiagen therascreen® EGFR RGQ PCR Kit</td>
</tr>
<tr>
<td>EGFR</td>
<td>NSCLC</td>
<td>Tarceva® (erlotinib) Tagrisso® (osimertinib)</td>
<td>Roche cobas® EGFR Mutation Test v2 Roche cobas® EGFR Plasma Test</td>
</tr>
<tr>
<td>ALK</td>
<td>NSCLC</td>
<td>XALKORI® (crizotinib)</td>
<td>Abbott VYSIS ALK Break Apart FISH Probe Kit VENTANA ALK (D5F3) CDx Assay</td>
</tr>
<tr>
<td>PD-L1</td>
<td>NSCLC</td>
<td>KEYTRUDA® (pembrolizumab)</td>
<td>Dako PD-L1 IHC 22C3 pharmDx</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>Ovarian</td>
<td>Lynparza™ (olaparib)</td>
<td>Myriad BRACAnalysis CDx™</td>
</tr>
<tr>
<td>KRAS</td>
<td>CRC</td>
<td>Erbitux® (cetuximab) Vectibix® (panitumumab)</td>
<td>Roche cobas® KRAS Mutation Test Qiagen therascreen KRAS RGQ PCR Kit DAKO EGFR PharmDx Kit</td>
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</tr>
<tr>
<td>PDGFRB</td>
<td>MDS/MPD</td>
<td>Gleevec® (imatinib mesylate)</td>
<td>Arup PDGFRB FISH</td>
</tr>
<tr>
<td>KIT</td>
<td>SMCD</td>
<td>Gleevec® (imatinib mesylate)</td>
<td>Arup KIT D816V Mutation Detection</td>
</tr>
<tr>
<td>TP53</td>
<td>CLL</td>
<td>VENCLEXTA® (venetoclax)</td>
<td>Abbott VYSIS CLL FISH PROBE KIT</td>
</tr>
<tr>
<td>IDH1</td>
<td>AML</td>
<td>TIBSOVO® (ivosidenib)</td>
<td>Abbott RealTime IDH1</td>
</tr>
<tr>
<td>FLT3</td>
<td>AML</td>
<td>RYDAPT® (midostaurin)</td>
<td>Invivoscribe LeukoStrat® CDx FLT3 Mutation Assay</td>
</tr>
</tbody>
</table>
Follow-on CoDx – Challenges

• No direct estimate of drug efficacy
  ➢ Device not used in original clinical trial
  ➢ Samples from original trial unavailable for retesting
  ➢ Repeat of drug trial impractical or unethical

• Preservation of drug efficacy
  ➢ Effect size
  ➢ Covariates representative of intended use population
  ➢ Analytical sensitivity vs clinical effectiveness
  ➢ Analytical “accuracy” vs clinical effectiveness
Follow-on CoDx – Path Forward

- Analytical validation
  - Same gene/variant level validation as original CoDx
  - Published SSED as reference
- Method comparison with approved CoDx
  - No drug trial required
  - Banked samples from intended use population
- Requirement for preservation of drug efficacy
  - Variability between the follow-on CoDx and the originally approved CoDx be within the variability of the originally approved CoDx
- Consult CDRH via pre-submissions early and often
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• Liquid biopsy
NGS-Based Oncology Panel

- Multi-variants/multi-genomes in a single oncopanel
  - Unprecedented ability to detect rare and novel variants
- Rapidly evolving technology
  - Whole genome, exome, targeted-sequencing, RNA-Seq, methylation sequencing
  - High throughput, complex, evolving, big data, software standardization, etc
- Sensitivity, throughout, reduced cost
  - Increasingly employed in the clinical setting
  - Solution to limited sample availability
Oncopanel Validation Challenges

• Analytical Validation
  ➢ Multiple genes/variants/variant types (SNVs/indels/CNVs/fusions/undefined/novel variants)
  ➢ Multiple analyte types (DNA, RNA, methylation)
  ➢ Multiple specimen types (Blood, FFPE)
  ➢ Germline vs. somatic
  ➢ Comparator methods and reference materials
  ➢ Big data, software standardization

• Clinical Validation
  ➢ Single test, multiple biomarkers, multiple indications
Oncopanel Validation Requirements

• Analytical Validation
  - Established QC metrics at each step of the NGS processes
  - Representative subsets of variants covering the range of variant types, sizes and genomic regions/contexts
    - Variant level representativeness for SNVs and indels
    - Gene level representativeness for fusions and CNVs
  - Well-validated orthogonal methods for accuracy study
  - Representative/difficult and challenging tumor types (e.g., bone, brain, pancreas, thyroid) for ‘pan-cancer’ claim

• Clinical Validation
  - Prospective trial for CoDx
  - Method comparison study for follow-on CoDx claim
# FDA-Approved NGS CoDx

<table>
<thead>
<tr>
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<tr>
<td><strong>FoundationFocus™ CDxBRCA</strong></td>
</tr>
<tr>
<td>1st NGS CDx</td>
</tr>
<tr>
<td>Next generation sequencing based in vitro diagnostic device for qualitative detection of BRCA1 and BRCA2 alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue. Results of the assay are used as an aid in identifying ovarian cancer patients for whom treatment with Rubraca™ (rucaparib) is being considered.</td>
</tr>
<tr>
<td><strong>Oncomine™ Dx Target Test</strong></td>
</tr>
<tr>
<td>1st CDx for multiple indications</td>
</tr>
<tr>
<td>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. Aid in selecting NSCLC patients for treatment with Tafinlar, Iressa, and Xalkori.</td>
</tr>
<tr>
<td><strong>Praxis™ Extended RAS Panel</strong></td>
</tr>
<tr>
<td>1st CDx based on negative mutation status</td>
</tr>
<tr>
<td>Qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples. Aid in the identification of patients with colorectal cancer for treatment with Vectibix® (panitumumab) based on a no mutation detected test result.</td>
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Liquid Biopsy – Challenges

- Preanalytical
  - Analyte stability and sample process control
- Analytical sensitivity and specificity
- Biological variability/Tissue heterogeneity
  - Tumor type/stage, meds
  - Temporal, spatial
- Clinical
  - Follow-on claim
  - Use with conjunctive tests?
- Consult CDRH via pre-submissions early and often
Take Home Message

• Plan for co-development
  ➢ Trial design as determinant of CoDx claim
  ➢ SR determination for IDE

• What is “hot”
  ➢ NGS Based Oncopanel
  ➢ Liquid biopsy – cfDNA/ctDNA
  ➢ CoDx follow-on (“me too”)
  ➢ Complementary diagnostics

• Consult CDRH via pre-sub early & often
Thank you!

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Backup slides
Key Oncopanel Authorizations

• ThermoFisher’s Oncomine™ Dx Target Test
  – Lung cancer panel
  – 3 CDx claims
  – 23 genes

• MSK-IMPACT
  – Solid tumor panel for tumor profiling
  – 468 genes + MSI
  – De Novo set up Class II pathway, potential 3rd party review

• Foundation Medicine’s F1CDx
  – Solid tumor panel
  – 15 CDx claims in 5 cancer types plus tumor profiling
  – 324 genes + MSI & TMB
Three Tiered Approach for Reporting Biomarkers in Oncopanels

**Level 1 companion diagnostics:** Analytical validation for each biomarker; Clinical validity established by clinical study or clinical concordance with a previous CDx.

**Level 2 biomarkers:** Analytical validation either per biomarker or representative; Clinical validation established in professional guidelines, but **NOT** demonstrated with the test.

**Level 3 biomarkers:** Analytical validation by representative approach; Clinical validity not demonstrated either in professional guidelines or with the test, but suggestive based on clinical/biological evidence.
A Fluid Approach to Reporting within Levels 2 and 3

- Clinical evidence regarding mutations accumulates rapidly and may differ based on tumor type
- Test developers need flexibility in how they report mutations
- As clinical evidence develops, level 3 mutations can move to level 2 provided the analytical validation of the markers reviewed and established via a submission
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):
  - For tumor profiling tests making Level 2/3 claims only
  - Can choose to submit 510(k) to FDA directly or elect to use an FDA-accredited third-party reviewer (e.g., NYSDOH)
  - Test developers that want to submit their oncopanels for federal clearance through NYSDOH can request to have their NYSDOH package and review memo forwarded along to FDA
  - For 3rd party review, FDA has 30 days to make a determination upon receipt of package
  - For direct submission, FDA has 90 days to make determination
Regulatory Process

Class II (moderate risk)
- Traditional 510(k)
  - FDA Clearance
    - Device shows substantial equivalence to a legally marketed predicate
  - De novo 510(k)
    - No Predicate
    - Special Controls
    - S&E

Class III (high risk)
- Pre-market Approval Application (PMA)
  - FDA Approval
    - Device demonstrates safety and effectiveness (S&E)