Evolving paradigm for companion diagnostics and other diagnostic tests at FDA

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DISCLAIMER

- Thoughts presented here are preliminary and do not represent finalized FDA policy.

THE EVOLUTION OF IVDs

CLASSIC	DAWN OF THE MODERN ERA	LIFE IN THE 21st CENTURY	TO THE FUTURE AND BEYOND…
Blood chemistry ELISAs	HER2 Single PCR assays FISH	Microarrays IVDMIA Multiplex tests Array CGH	NGS Proteomics Epigenetics Microbiome
Medical Device Amendments (1976)	Concept of companion diagnostics	Guidance on CDx, IVDMIA, etc.	?

In Vitro Diagnostics (IVDs)

- In vitro diagnostic devices include "…those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act " (21 CFR § 809.3)

- Intended use: How will the device will be used in the therapeutic product trial? Encompasses:
  - Analyte to be detected
  - Type of result (quantitative, semi-quantitative, qualitative)
  - Specimen type(s)
  - Disease to be screened, monitored, treated, or diagnosed
  - Target subject population
  - etc.

Scientific Review : IVD Performance

- Analytical Performance Characteristics

  Reliability and accuracy of analyte measurements

- Clinical Performance Characteristics

  Clinical sensitivity and specificity

  Positive and negative predictive values

- Labeling

  Intended use, device design, directions for use, warnings/limitations, result interpretation, performance

- NOTE: FDA does not review for clinical utility. However, IVDs that are not sufficient analytically or clinically valid won't have clinical utility.

Clinical validity and FDA submissions

- Clinical studies
  - For many IVDs, these are usually retrospective studies using banked samples
  - For companion diagnostics, a “locked-down” IVD is used in a drug trial
  - Bridging studies are often necessary
- “Big data” approach
  - Databases
  - Literature
  - Case studies

Companion Diagnostics

- Draft guidance 2011
- Final guidance 2014
- Historically, one analyte-one test-one drug
- www.fda.gov/companiondiagnostics

Unique Challenges of Next Generation Sequencing

- High information content
  - Over 3 billion bases in the human genome
  - Every individual may have millions of variants
  - Many of the variants will be rare within the general population
- Often no pre-defined intended use
  - NGS can be used to diagnose a large number of diseases
  - Incidental findings
- NGS tests are frequently modified (run parameters, software, etc.)
  - Innovation
  - Accommodate specific testing needs
- NGS tests use a variety of “mix-and-match” components for specific uses
  - Not every test result will be generated in the same way
- Often difficult to establish connection between variants and specific disease or condition because of rarity and multiple variants, so traditional clinical trials may not be feasible.

Lessons from the Illumina Clearances

Separation of tool and clinical claims

Tool: MiSeqDx instrument
Use: Sequences DNA

Analytical validation
- Cell-line samples (“normals”)
- Performance demonstrated on a representative set of variants

Clinical validation not needed

Clinical: CF 139 variant and whole gene tests
Use: Sequences 139 variants or whole CFTR gene

Analytical validation
- Specific validation of 139 variants, plus validation of CFTR normal sequence

Clinical validation
- Use of the CFTR2 database (JHU) for evidence

Use of the CFTR2 database

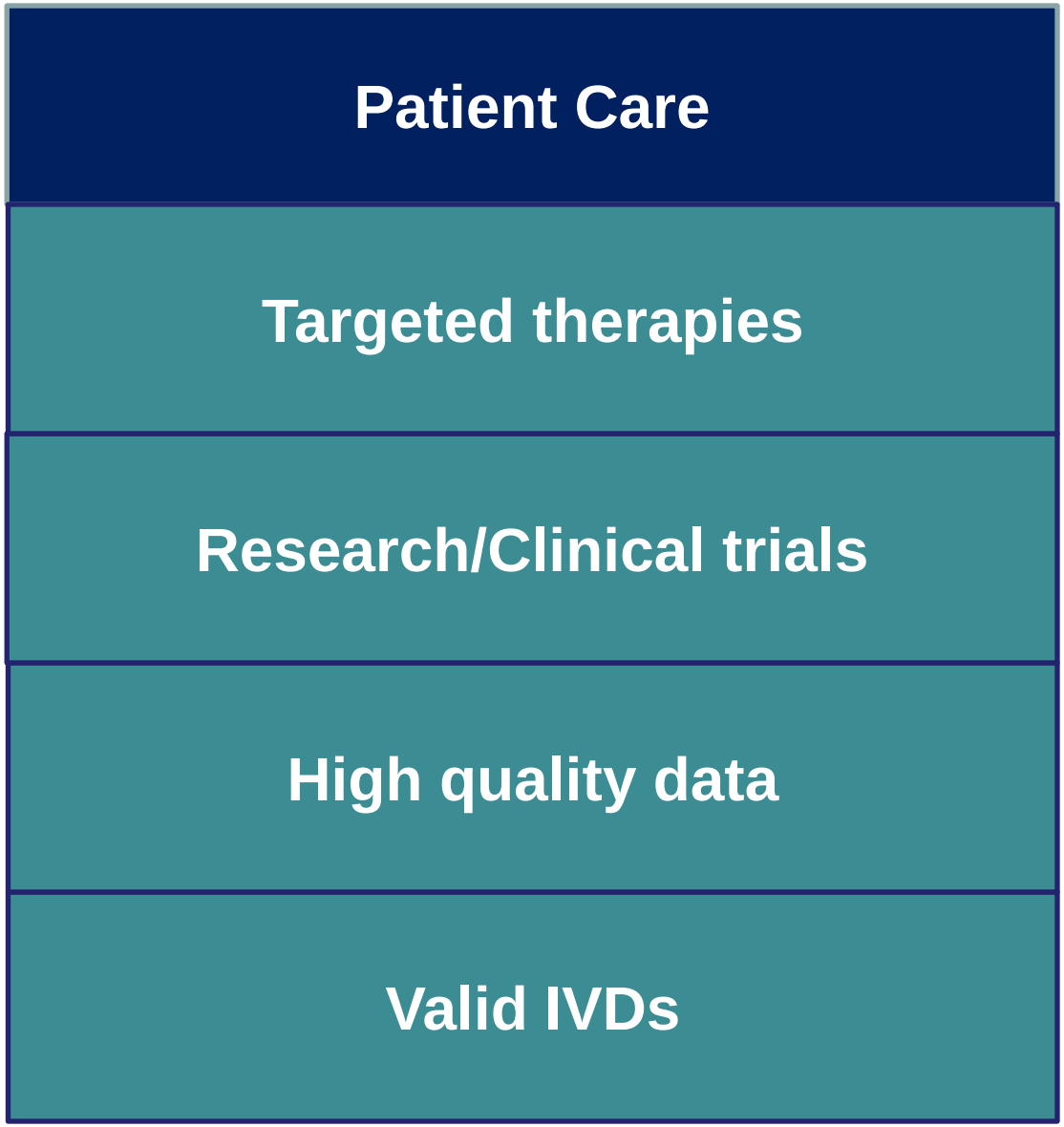
- Illumina MiSeqDx Cystic Fibrosis 139-variant assay
- Used to demonstrate clinical validity of CFTR variants
- Features of the CFTR2 database
  - Curated
  - Contains preclinical and clinical data
  - Functional assays for CFTR function available
  - Cooperation of patient community
  - Required versioning

CFTR2 Database (http://www.cftr2.org/)

Datatype	Information Captured
Mutation name/Associated Nomenclature	Provides a standardized mutation name and mutation by amino acid and nucleotide number (relative to the CFTR gene)
Associated Clinical Characteristics/Validation	Provides the following relevant clinical characteristics: • Average sweat chloride value at time of diagnosis • Range of FEV1 percent predicted value based on age group • Percentage of patients with positive Pseudomonas aeruginosa culture • Percentage of pancreatic insufficient individuals
Functional testing/Validation of Mutation	Notes the results in vitro laboratory tests performed for applicable mutations. Specifically, assesses protein processing and maturation, CFTR dependent chloride current, and gene splicing.
Literature Review	Notes research previously completed on this particular mutation.
Annotation History	Provides a history of changes and timestamps of any revisions to the annotation.

Concept of a "Regulatory Grade" Database

- What constitutes a high quality database?
- Need to consider
  - Annotation (patient, diagnostic, etc.)
  - Versioning
  - Source of testing results
  - Procedures and practices
  - Sustainability


Patient Care
Targeted therapies
Research/Clinical trials
High quality data
Valid IVDs

Local Testing and Quality of Data

- Test results from local testing are often used in clinical trials for accrual, subgroup analysis, etc.
- Local tests for the same thing may be performed using tests with different technologies and/or performance.
- When results aren't comparable, patient population is more heterogeneous, and analysis of CT results may be affected.
- Local testing reflects practice of medicine

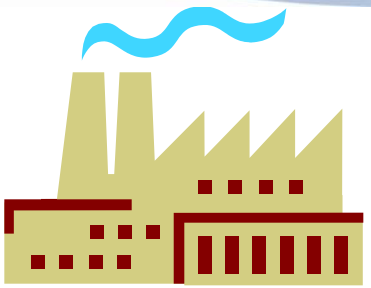
Possible Solutions

- Confirmation of local results with central testing
  - Selection bias
- Purely central testing may address selection bias, but does not always reflect practice of medicine
- May have same problem in genetic databases, where central testing is not possible
- Need to capture test information in EHRs and other systems

What the future holds

- Liquid biopsies
- Cancer panels
  - Combination of CDx and novel markers
- Whole exome/Whole genome sequencing
- Other omics
- Consideration of new regulatory approaches (e.g., centralized databases)

Today's LDTs are marketed under enforcement discretion by FDA.



"test kit" manufacturer

Performed in CLIA-certified lab

CLIA-certified lab

FDA "Enforcement Discretion"

Performed within same lab that developed test

FDA's Current Proposal for LDTs

www.fda.gov/LDTs

1. Collect basic information on all LDTs through new notification process (i.e., no-fee alternative to R&L)
2. Use public process (i.e., advisory committees) to obtain input on risk and priority for regulation
3. Phase-in regulatory framework over ~9 years based on risk
4. Continue some enforcement discretion for specific categories determined by FDA to be in the best interest of public health

Interacting with FDA…

…For Applicants

PRESUBMISSION

- You can meet with the FDA for nonbinding discussions and advice:
  - *before* conducting studies, including clinical trials
  - *before* submitting a marketing application
- This is an opportunity to address new scientific and regulatory issues.
- Particularly important when developing new technologies.
- Guidance on the pre-submission process http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf\

DURING REVIEW OF A SUBMISSION

- Acceptance Review Communication
- Substantive Interaction
- Interactive Review

Resources

- Guidance
- Device Advice
  - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm
- CDRH Learn (including information about sponsor responsibilities, investigator responsibilities, IRBs, and the Bioresearch Monitoring Program)
  - http://www.fda.gov/Training/CDRHLearn/default.htm

…On LDT Policy

- Webinar
- Solicitation of Public Input via FR Notice announcing:
  - 120 day public comment period
  - Public Workshop

  Goal: to work with all stakeholders to determine a framework for regulation that is in the best interest of public health
- Analysis of public input and edits to guidances
- Stakeholder calls

…and other issues

- FDA outreach
  - Presentations and presence at meetings
  - Webinars
  - Guidance, etc.
- FDA participation in internal and external working groups
- Workshops
- Other opportunities

Thank you!

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