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Precision Medicine: Priority Initiatives and What It Means for Diagnostics Now and Into the Future

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Areas of Recent Interest

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1. Precision Medicine: Recognition of increasing Companion Diagnostic (CoDx) complexity
2. Clinical Trials
3. Next Gen Sequencing (NGS)

Diagnostics and Precision (Personalized) Medicine

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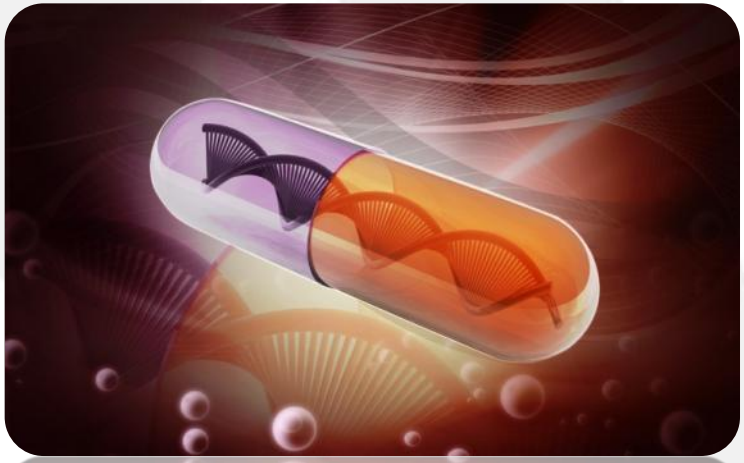
***Diagnostics** and…*

Utilizing available information to make decisions…

…Precision Drug



…that deliver individualized patient outcomes and value in the real world

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Precision medicine isn't the future.

Precision medicine: Stratification of a patient population to identify and engineer better solutions for illness and wellness that demonstrates improved real-world outcomes.

Targeted Therapies in the 1990's in ~ 5% of new drug approvals and increasing to 45% in 2013

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PD-L1 Blueprint Proposal Overview

FDA-AACR-ASCO Public Workshop
24 March 2015

Candidate CoDx Complexities – The Case of PD-L1

- 4-8 drugs in development
- Parallel development programs
- Various trial designs
- Multiple anti-PD-L1 immunohistochemistry (IHC) companion diagnostics
  - Different test for each drug

At the March 24, 2015 Public Workshop “Complexities in Personalized Medicine: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies“, a blueprint proposal for Companion Diagnostic Comparability was presented by an industry working group.

Has FDA held any further meetings with this working group to continue discussion on this blueprint proposal?

Is there a revised blueprint proposal anticipated?

New Paradigm

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Recently, a new evidence-based guideline for Colorectal Cancer Molecular Testing was jointly issued by the American Society for Clinical Pathology, the College of American Pathologists, the Association for Molecular Pathology, and the American Society of Clinical Oncology. This guideline recommends an "expanded KRAS panel", which includes mutations that are not available in the FDA-approved version of the test. The expanded KRAS panel is presently only available as a Laboratory Developed Test.

How might such dilemma be addressed?

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Clinical Trials

Comparison of Dx and Rx Regulations

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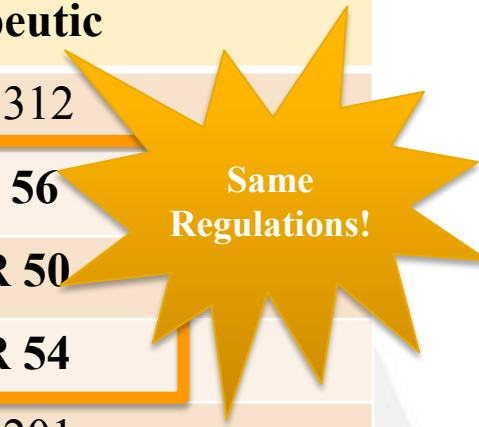
Topic	Diagnostic Device	Therapeutic
Clinical Trial Application	21CFR 812	21CFR 312
IRB / Ethics Review	**21CFR 56**	**21CFR 56**
Informed Consent	**21 CFR 50**	**21 CFR 50**
Financial Disclosure	**21 CFR 54**	**21 CFR 54**
Labeling	21 CFR 801, 809.10	21CFR 201
PMA/510(k)/BLA/NDA	21 CFR 814, 807 Subpart E, 809	21 CFR 314, 316, 315, 601



Device Clinical Investigations - What is an Investigational Device Exemption (IDE)?

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An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data to support PMA or 510(k) submission.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations without complying with requirements of the FD&C Act that apply to devices in commercial distribution. Investigational use labeling is required (§812.5(a)).

Clinical investigations for IVDs are exempt from most IDE investigation requirements unless they pose certain risks (§812.2(c)(3)).

Clinical Trials

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IDE applications were previously primarily associated with medical devices and only a small number for IVDs. Companion Diagnostics are different since Companion Diagnostics are directly connected to the Drug clinical trial under the purview of FDA. The drug clinical trial is covering clinical trial information such as the clinical investigational sites, clinical investigators, addresses of the investigators, etc.

For significant risk IVDs, how could the IND cover the companion diagnostics instead of requiring an IDE?

Companion Diagnostic Labeling Example

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Drug Label - Indications and Usage

"Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of: Head and Neck Cancer and Colorectal Cancer
Erbitux is indicated for the treatment of K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use……
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125084s262lbl.pdf

- Drug label specifies that an FDA approved test is required.
- Drug label does not specify IVD test by brand name.
- Dx label Specifies the analyte and the drugs

Diagnostic Label - Intended Use

2012: "**-Qiagen therascreen KRAS RGQ PCR Kit,** real-time qualitative PCR assay used on Rotor-Gene Q MDx instrument for detection of seven somatic mutations in the human KRAS oncogene, using DNA extracted from FFPE, colorectal cancer (CRC) issue. Therascreen KRAS RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with Erbitux (cetuximab) and Vectibix (panitumumab) based on a KRAS no mutation detected test result."

2015 " **Roche Molecular Systems cobas® KRAS Mutation Test**, used with the cobas® 4800 System, is a real-time PCR test for the detection of seven somatic mutations in codons 12 and 13 of the KRAS gene in DNA derived from FFPE human colorectal cancer (CRC) tumor tissue. The test is intended to be used as an aid in the identification of CRC patients for whom treatment with Erbitux® (cetuximab) or with Vectibix® (panitumumab) may be indicated based on a no mutation detected result. "
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Access at Time of Approval

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Having only FDA approved tests in Rx label can limit access to Diagnostic testing at time of original approval.

How can FDA assure access to patients at the time of first approval?

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Next Gen Sequencing (NGS)

Sanger Sequencing

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- A method of **DNA sequencing** based on the selective incorporation of chain-terminating dideoxynucleotides by DNA polymerase during in vitro DNA replication.
- Most widely used sequencing method for approximately 25 years.
- Supplanted by "Next-Gen" sequencing methods, especially for large-scale, automated genome analyses.
- However, the Sanger method remains in wide use, for smaller-scale projects, validation of Next-Gen results and for obtaining especially long contiguous DNA sequence reads (>500 nucleotides).

Next Generation Sequencing

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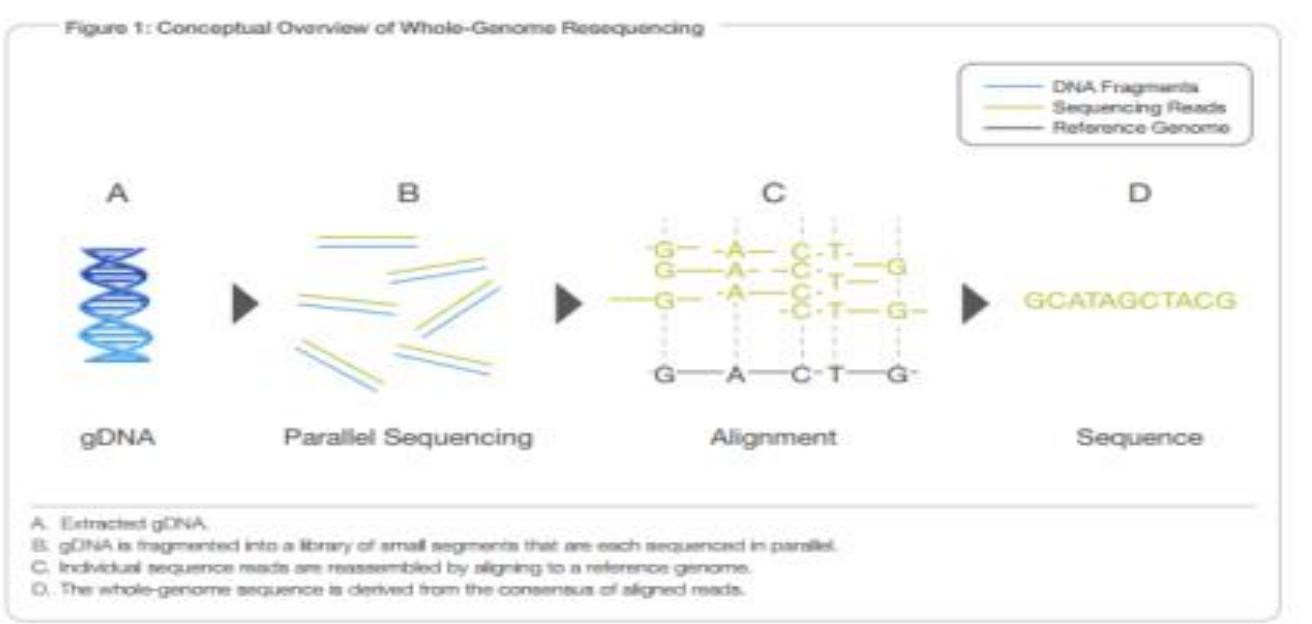
- Non-Sanger-based high-throughput DNA sequencing technologies. Millions or billions of DNA strands can be sequenced in parallel.
- Turnaround time reduced from months to days



Next Generation Sequencing (NGS)

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With regard to NGS – tools used in NGS tests, e.g., DNA bar codes, library prep instruments/reagents, cell sorters, what is the Agency's view with regard to their regulatory classification?

510(k) exempt?

What is the process to get classification and 510(k) or not decided – pre-sub?

Next Generation Sequencing (NGS)

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An IVD test consists of kits developed by company A and sequencer developed by company B.

What is company A's responsibility in terms of ensuring that the kit still functions when the sequencer from company B is changed?

Precision Medicine – a Paradigm Shift in the US towards Companion Diagnostics*

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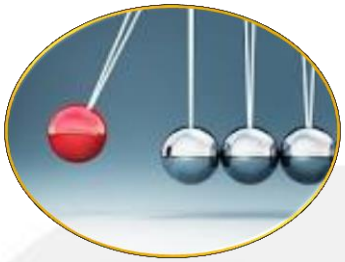

**FDA is the first health authority to define companion diagnostic tests as a subset of IVDs*

- A companion diagnostic is a medical device, often an in vitro device, which provides information that is **essential** for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether a particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks
- The FDA requires a companion diagnostic test if a new drug works on a specific genetic or biological target that is present in some, but not all, patients with a certain disease
- With the advent of more drugs that target particular genetic mutations, there has been increasing acceptance from drug manufacturers that these diagnostic tests can greatly increase the clinical success of certain medications

FDA Consumer Health Information/U.S. FDA; July 2014

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