FDA's Role and Tools for ID-NGS Diagnostics

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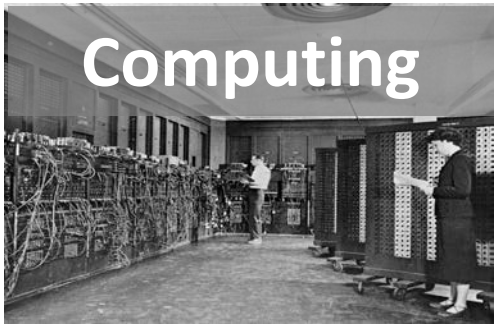
Opinions are my own



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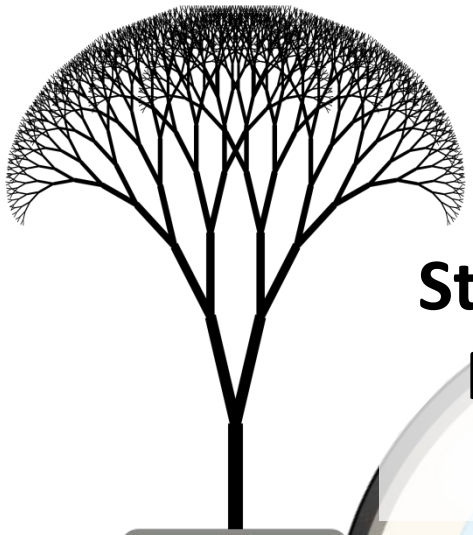
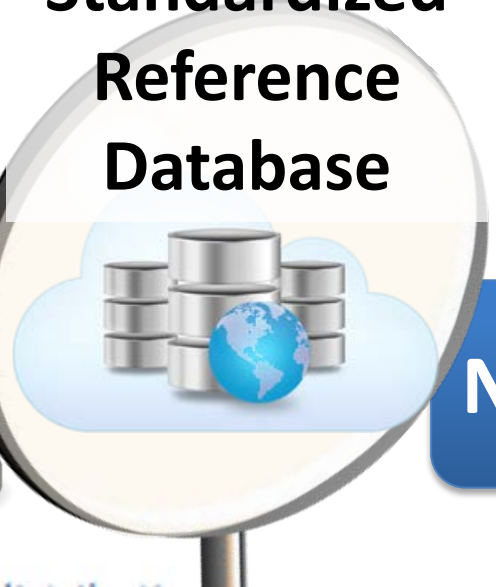


Progress

Standardized
Reference
Database



NGS Dx

ISO

IEEE

ISO

NIST

First FDA Clearances of NGS

NGS Sequencing Platform

- **Tool Claim**

De novo for the Illumina MiSeqDx instrument and the Illumina Universal Kit reagents, two devices that make up the first FDA-regulated test system that allows laboratories to develop and validate sequencing of any part of a patient's genome. The Universal Kit reagents isolate and create copies of genes of interest from patient blood samples; the MiSeqDx platform analyzes the genes. The software compares the patient's genomic sequence to a reference sequence and reports back any differences.

NGS Assays with Specific Indications

- **139 Variant Claim**

The Illumina MiSeqDx Cystic Fibrosis 139-Variant Assay: Detects known CFTR variants (based on the Clinical and Functional Translation of CFTR database information).

- **CFTR Gene Claim**

The Illumina MiSeqDx Cystic Fibrosis Clinical Sequencing Assay: Sequences a large portion of the CFTR gene.

Press Announcement:
http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm375742.htm

The MiSeqDx Platform is not intended for whole genome or de novo sequencing.

Infectious Disease (ID) NGS Dx

There is no FDA cleared NGS instrument for sequencing of microbial genomic DNA for identification of microbial targets or detection of virulence or resistance genes.

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FEDERAL REGISTER
The Daily Journal of the United States Government

Notice

Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers; Draft Guidance for Industry and Food and Drug Administration Staff; Availability

A Notice by the Food and Drug Administration on 05/13/2016

Comments on this document are being accepted at Regulations.gov SUBMIT A FORMAL COMMENT

ACTION Notice.

SUMMARY The Food and Drug Administration (FDA) is announcing the availability of a draft guidance entitled "Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers." This draft guidance provides recommendations to assist industry in designing studies to establish the analytical and

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PDF DEV PRINT PUBLIC INSPECTION

FDA Current Thinking

NGS Technologies

Targeted (*amplicon*)

- Scope limited to defined regions that target a specific organism(s), gene(s) or marker(s).
- Targets are selected *apriori* by any lab or bioinformatics method (e.g., amplicon sequencing or a k-mer signature database) based on the diagnostic devices intended use.

Agnostic (*whole genome, shotgun*)

- No *apriori* knowledge of targets.
- Generally can identify all constituents (e.g., organism(s), gene(s) or marker(s), microbiota, human background, and contaminants) in a sample.

Sample Applications

Single Target (Pathogen, Gene, Marker)

Pathogen/Marker Panel

Gene Panel (16S)

Metagenomics

Novel and Emerging Pathogens

FDA Tools for ID NGS Dx

FDA-ARGOS Database

:microbial reference genomes for regulatory use

- ✓ **New and flexible regulatory pathway**
  - **Enable In-silico validation**
  - **Reduce testing burden**
- ✓ **Reference database**

Interagency ID NGS Working Group

: team of agency-wide NGS subject matter experts

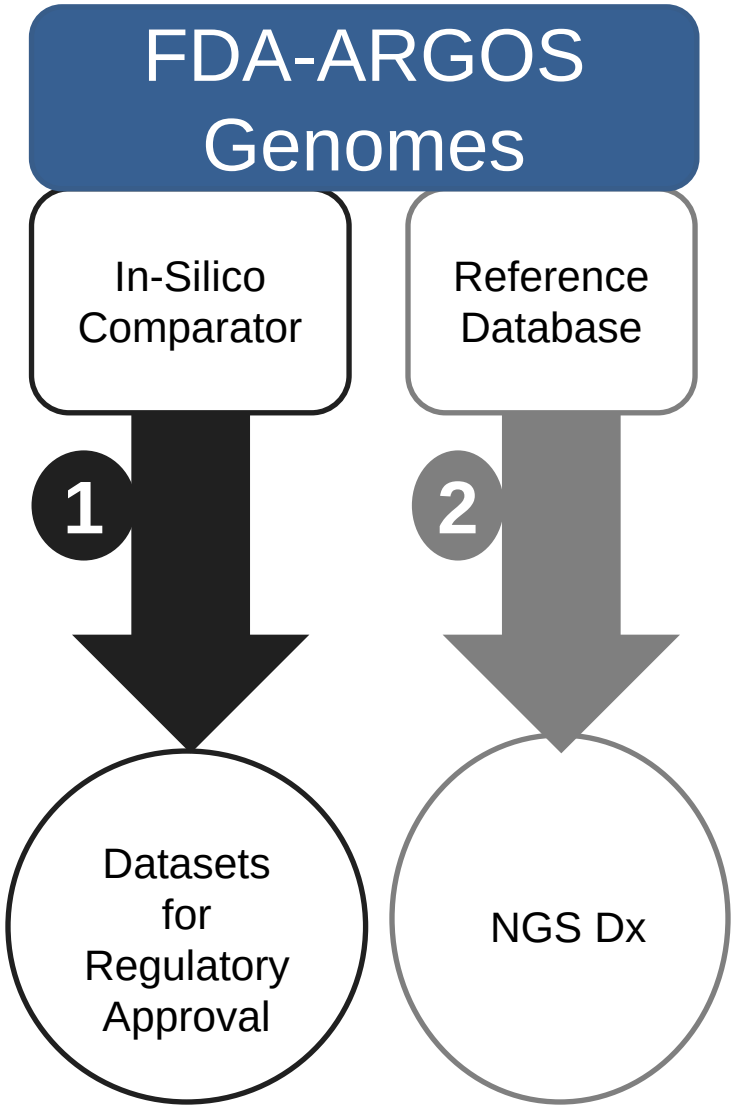
- ✓ **ID NGS Dx Advisory Board**
- ✓ **Consensus FDA-ARGOS genome vetting**
- ✓ **Keep current on state of the art**
- ✓ **Tackle open questions (i.e. sens/spec)**

FDA-ARGOS: Goal and Use

- Public Resource
- Regulatory-Grade Genomes
- US-Initiated
- Medical Countermeasures
- Common clinical
- Near neighbors

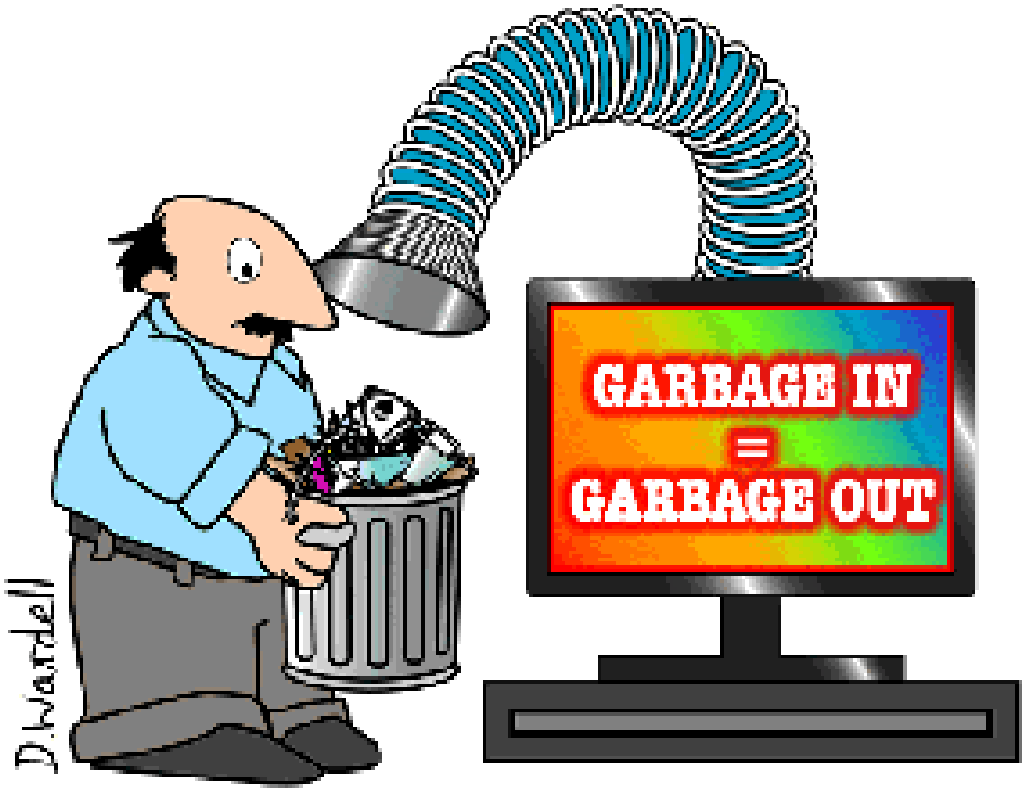
- **Coverage for US Interest**
- **Does NOT reflect *Needs for Developing World* and associated *Global Standards***

NCBI Project **PRJNA231221**

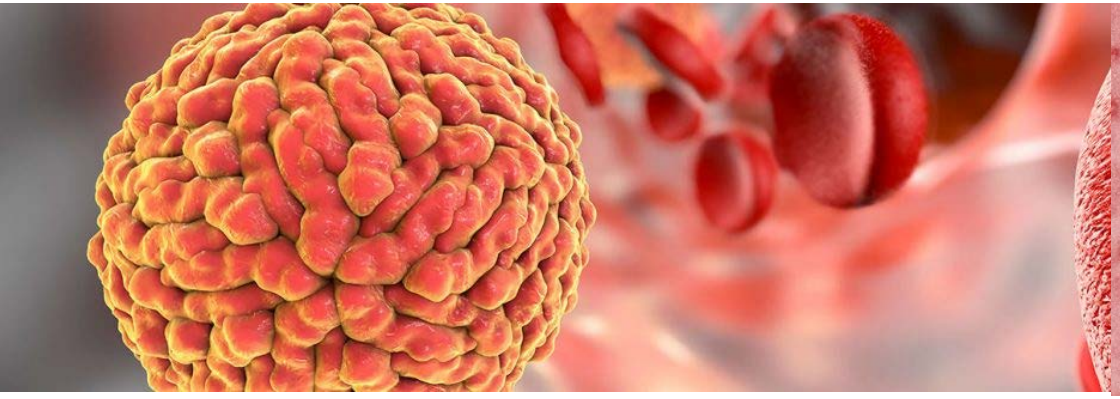


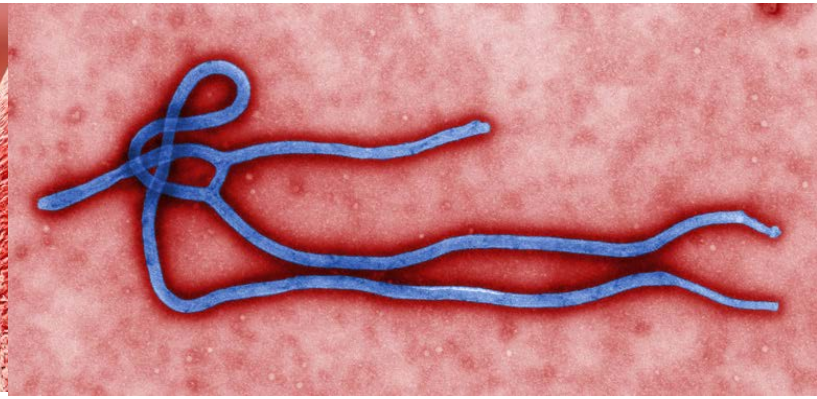

FDA-ARGOS
Global-ARGOS
COMPREHENSIVE
ACCURACY
EMERGING THREATS
Coverage
Precision
Inclusivity
VERACITY
Rigor
Temporal
Timeliness
Robustness
Specificity
Geography
Sustainability
Spatial

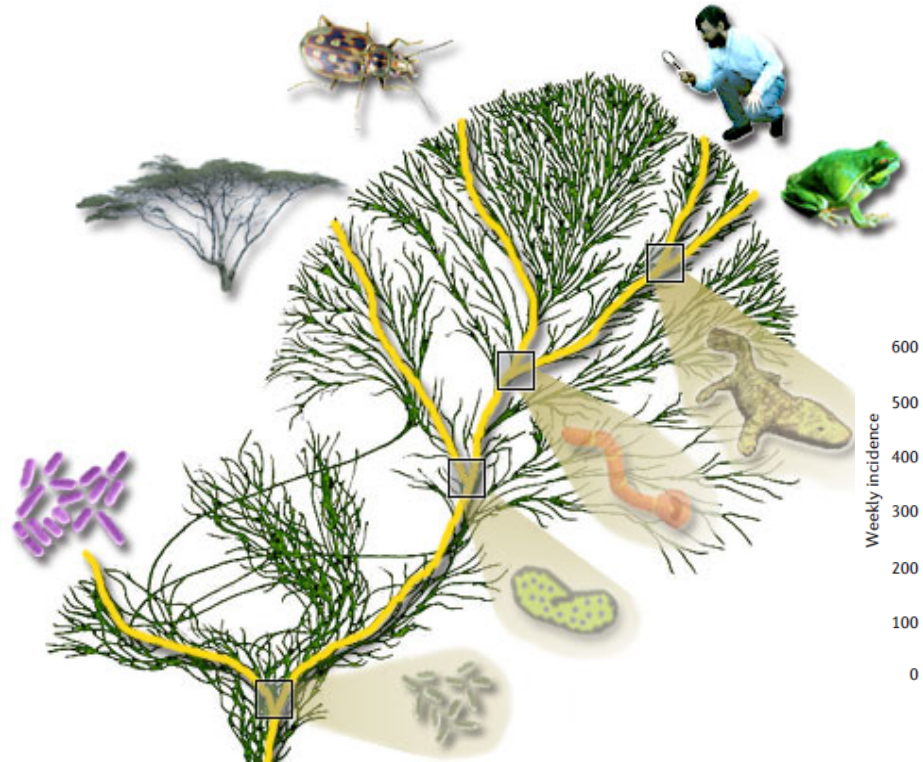
Accuracy



Coverage: Spatial/Temporal







Aquificae (hyperthermophilic chemolithoautotrophs)

Thermotogae (hyperthermophilic, obligately anaerobic

Thermodesulfobacteria (thermophilic, sulfate-reducin

Chrysiogenetes (a chemolithoaut n)

Nitrospira (includes nitrite-oxidize ulf

cte

bac

oph opl

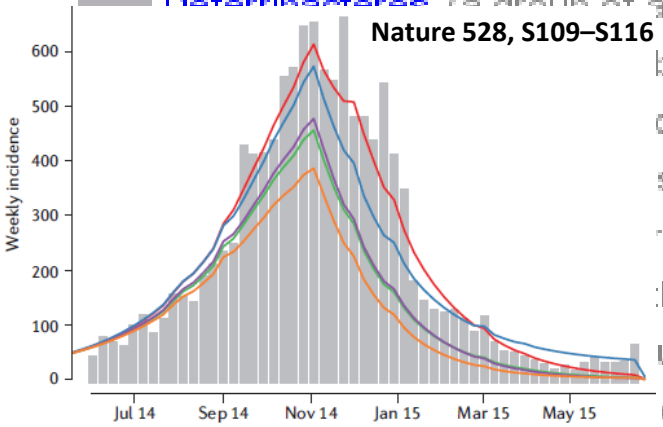
stin

ia and relatives)

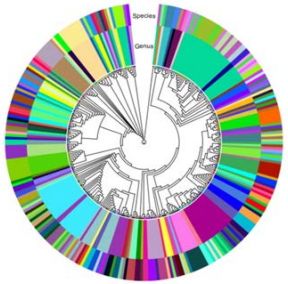
h peptidoglycan-less ce

ular parasites of eukary

chemoheterotrophs)



Nature 528, S109–S116

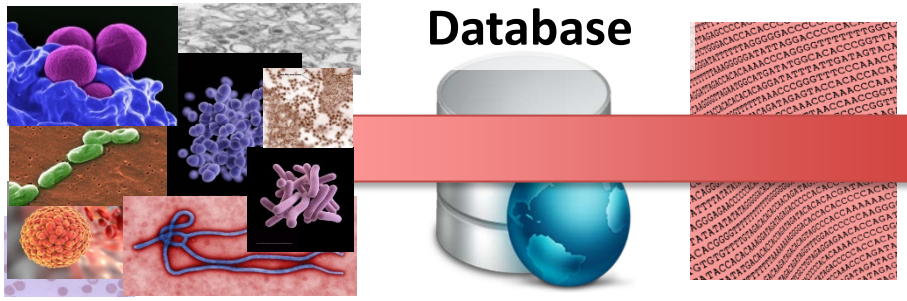


FDA-ARGOS

Reference Genome Gap: Ebola

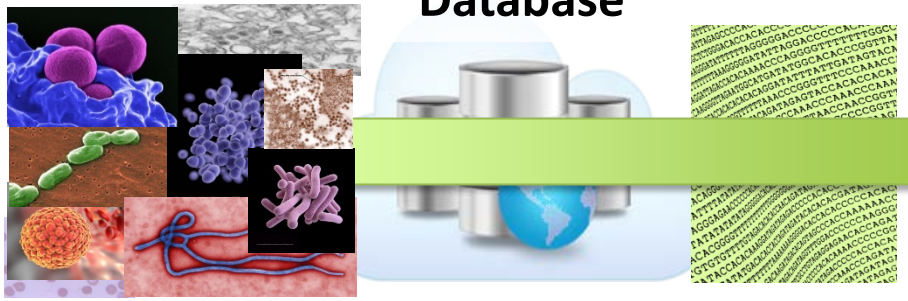
Endemic African Diseases
Chikungunya virus
Crimean-Congo Hemorrhagic Fever virus
Dengue virus serotype 1
Dengue virus serotype 2
Dengue virus serotype 3
Dengue virus serotype 4
Ebola virus
Lassa virus
Marburg virus (Angola)
Marburg virus (Ci67)
Plasmodium falciparum
Rift Valley fever virus
West Nile virus
Yellow fever virus
Zika virus

Non-Curated Database



Misdiagnosis:
- ❑ False Positives
- ❑ False Negatives

Standardized Reference Database



Correct Diagnosis:
- ❑ True Positives
- ❑ True Negatives

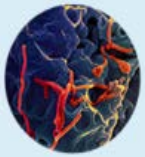
✓ ***Minimize Misdiagnosis***

✓ ***Evolutionary Change***

✓ ***Rapid*** **Diagnostics**

FDA----------
---dAtabase for
-----Reference-
----Grade------
micrObial--------
-----Sequences

- ✓Coverage of circulating strain in reference database first step to catch the bug



Decoding Ebola: Next-Generation Sequencing of the Ebola Genome for the FDA ARGOS Database

When you need a test to confirm disease in an outbreak, you need it fast. Global

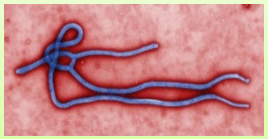
THE FUTURE

Infections Disease NGS Dx

Platform?

Global ARGOS

Prevent Outbreak



Viral Immunol 28(1): 19-31

Sustainable Solution