FDA's Role In Building the ID NGS Diagnostic Toolkit

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Disclaimer

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Opinions are my own

Organizational Chart

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Approved by the FDA Reorganization Coordinator & Principal Delegation Control Officer 25 September 2017

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Legend:
- - - - Direct report to DHHS General Counsel
. . . . Indirect reporting relationship to the Office of Chief Scientist

FDA White Oak Campus

Resources For You

Medical Devices

- **Emergency Use Authorizations**
  - https://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm
- **Device Advice: Comprehensive Regulatory Assistance**
  - https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm
- **Recently-Approved Devices (PMA, 510(k), HDE, De novo)**
  - https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/default.htm
- **Classify Your Medical Device**
  - https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm
- **Science and Research (FDA-ARGOS Database)**
  - https://www.fda.gov/MedicalDevices/ScienceandResearch/DatabaseforReferenceGradeMicrobialSequences/default.htm

In Vitro Diagnostic Devices

Definition:

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. … for use in the collection, preparation, and examination of specimens from the human body. [21 CFR 809.3]

US FDA Regulated Uses:

- Detection and Diagnosis
- Screening
- First Response

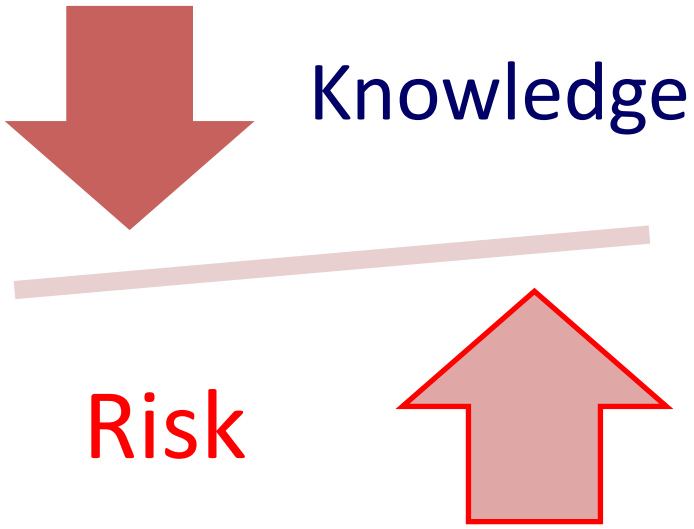
- **Not** Environmental Screening

Device Classification

A device should be placed in the lowest class whose level of control will provide reasonable assurance of safety and effectiveness.

Risk Based Regulation of IVDs

Class I most 510(k) exempt



Knowledge Mitigates Risk

Class I - Low likelihood of harm
register & list (21CFR §807)
General Controls

Class II - Moderate likelihood of harm or risk can be mitigated
Special Controls

Class III - High or unknown likelihood of harm
Significant Risk
Pre-market Approval

Risk Dependent on Intended Use

Different Use, Same Test

- A CFTR genotyping multiplex assay on the same instrument with the indication
  - ✓for aid in diagnosis →***510(k)***
  - ✓for fetal screening →***PMA***

- A breast cancer assay to be used
  - ✓for screening, diagnosis →***PMA***
  - ✓for prognosis in already diagnosed patients →***510(k)***

ID NGS Draft Guidance

There is no FDA cleared NGS system 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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Next Document

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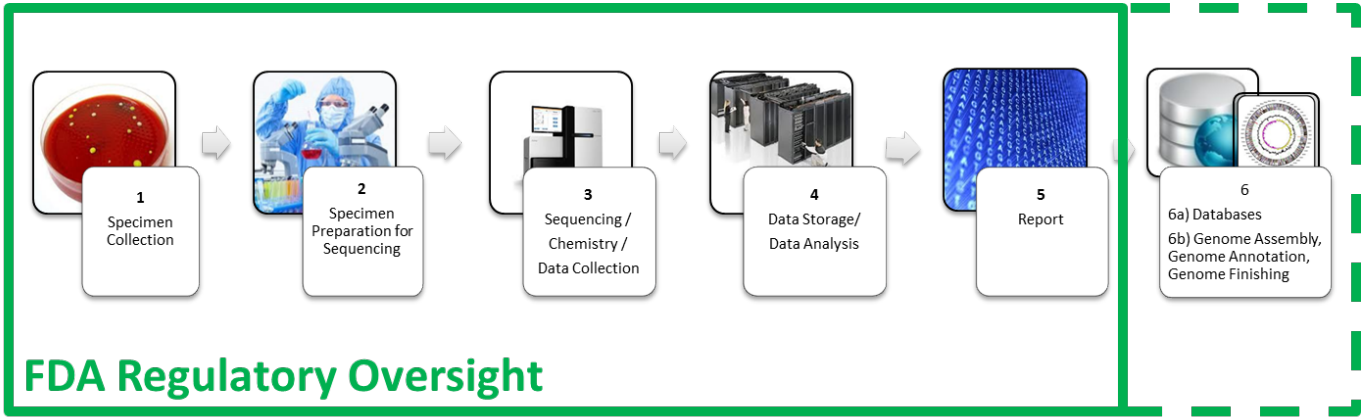
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM500441.pdf

FDA Current Thinking



NGS Technologies

Targeted (*amplicon, bioinformatics*)

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

Hypothesis-Free (*whole genome, shotgun*)

- No *a priori* 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

De Novo Regulatory Pathway

The De Novo process provides a pathway to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device. De Novo classification is a risk-based classification process.

There are two options for when a sponsor can submit a De Novo request for the FDA to make a **risk-based evaluation for classification of the device into class I or II.**

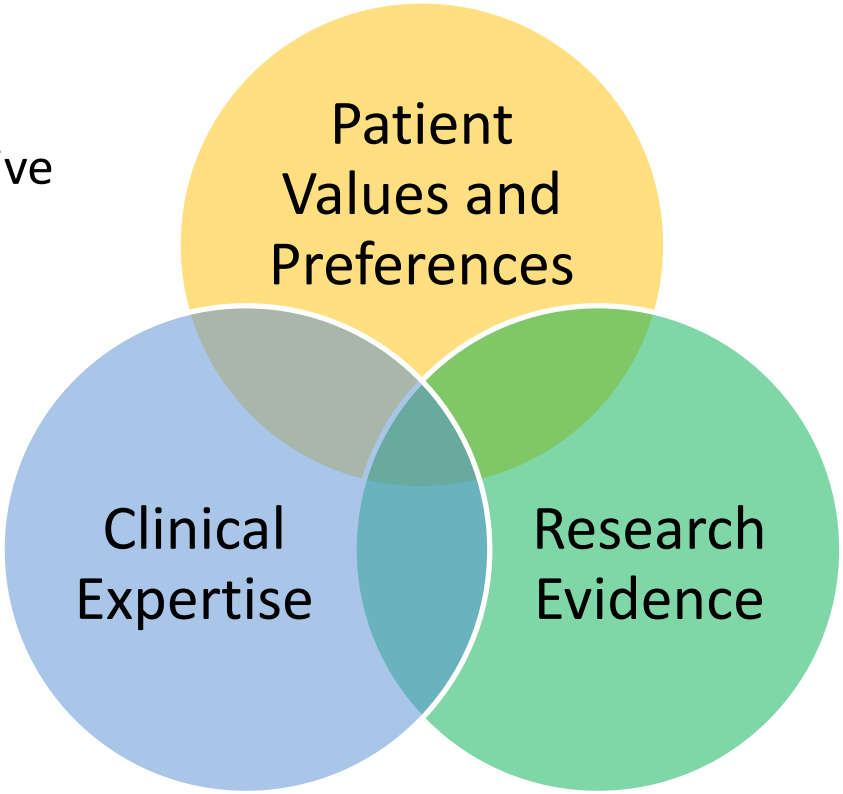
- Option 1: After receiving a high-level not substantially equivalent (NSE) determination (i.e., new intended use and/or different technological characteristics that raise different questions of safety and effectiveness) in response to a 510(k) submission.
- Option 2: Upon the sponsor's determination that there is no legally marketed device upon which to base a determination of substantial equivalence (therefore without first submitting a 510(k) and receiving a high-level NSE determination).

Prior to submitting a De Novo request, it is recommended that you consider submitting a pre-submission (pre-sub)to obtain feedback from the appropriate premarket review division.

De Novo Classification Process (Evaluation of Automatic Class III Designation) - Guidance for Industry and Food and Drug Administration Staff (PDF - 139KB)

Risk-Based Evaluation

- Real clinical samples where feasible
  - Prevalence of analyte is low? Consult with FDA about alternative sample types
- Prospective or retrospective evaluation
  - Comparison to a reference method
  - Comparison to a predicate device
  - Comparison to a clinical outcome
- In-Silico evaluation
  - FDA-ARGOS Reference-Grade Genomes (Bioproject 231221)
  - Mixed Microbial Reference Material



ID NGS Diagnostic Toolkit Needs

- ID NGS Diagnostic Assay
- Tools to support regulatory review
  - **FDA-ARGOS Reference-Grade Genomes** for regulatory use to enable sponsor to perform in-silico validation of claims
  - **Mixed Microbial Reference Materials** that sufficiently challenge the entire ID NGS Diagnostic Assay workflow
    - Ideally cell-based
    - Performance for assay's intended use

FDA Tools for ID NGS Dx

FDA-ARGOS Database

:microbial reference genomes for regulatory use

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

Interagency ID NGS SME Working Group

: team of NGS agency-wide 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)**
- ✓ **NGS Reference Material**

Reference Genomes For Regulatory Use

Support in-silico analytical and clinical validation

A. Identified by orthogonal reference method
B. Sequenced and de-novo assembled using 2 sequencing methodologies
C. High depth of sequencing coverage
D. Minimum of 20X over 95 percent of the assembled and polished core genome
E. Taxonomy-specific ANI thresholds that are sufficient for identification
F. Placed within a pre-established phylogenetic tree
G. Sample specific metadata, raw reads, assemblies, annotation and details of the bioinformatics pipeline are available

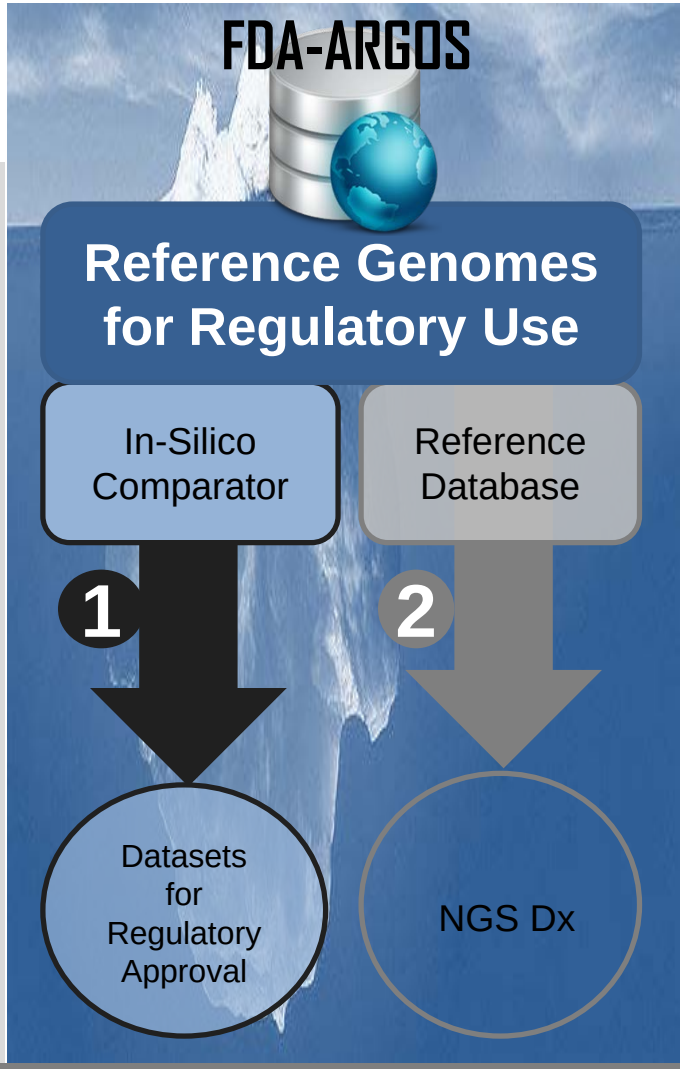
FDA dAtabase for Reference Grade micrObial Sequences (FDA-ARGOS)

NCBI

UNIVERSITY of MARYLAND SCHOOL OF MEDICINE INSTITUTE FOR GENOME SCIENCES

Government-Academic-Clinical Partnership

- In May 2014, the FDA and collaborators established FDA-ARGOS (**www.fda.gov/argos**)
- With funding support from FDA's Office of Counterterrorism and Emerging Threats (**OCET**) and **DoD**, the FDA-ARGOS team are initially collecting and sequencing 2000 microbes that include biothreat microorganisms, common clinical pathogens and closely related species.
- Currently, FDA-ARGOS microbial genomes are generated in 3 phases.
  - Phase 1 entails collection of a previously identified microbe and nucleic acid extraction from government, academic and clinical collaborators (>30).
  - Phase 2, the microbial nucleic acids are sequenced and de novo assembled using Illumina and Pac Bio sequencing platforms at the **Institute for Genome Sciences at the University of Maryland (UMD-IGS).**
  - Phase 3, the assembled genomes are vetted by an ID-NGS subject matter expert working group consisting of FDA personnel and collaborators and the data are deposited in **NCBI** databases.



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FDA dAtabase for Reference Grade microbial Sequences (FDA-ARGOS)

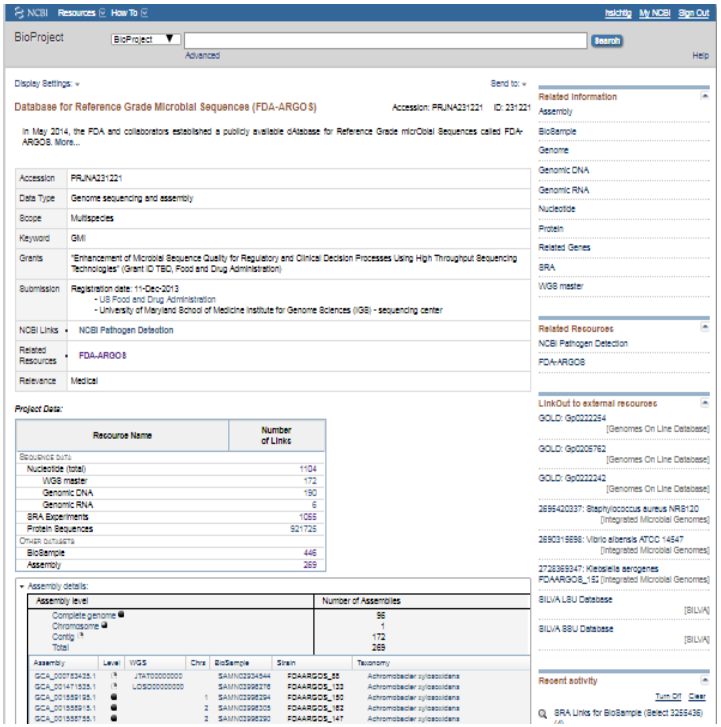
Landing page for FDA-ARGOS information directly from GenBank and also linked to from our FDA website. https://www.ncbi.nlm.nih.gov/bioproject/?term=FDA-ARGOS (NCBI BioProject **231221**)
>> To get all associated genbank entries, select the Nucleotide database and enter this search term: '231221[BioProject]'

GenBank records (annotations, not RefSeq):
https://www.ncbi.nlm.nih.gov/nuccore?term=231221%5BBioProject%5D

BioSamples:
https://www.ncbi.nlm.nih.gov/biosample?Db=biosample&DbFrom=bioproject&Cmd=Link&LinkName=bioproject_biosample&LinkReadableName=BioSample&ordinalpos=1&IdsFromResult=231221

Assemblies:
https://www.ncbi.nlm.nih.gov/assembly?LinkName=bioproject_assembly_all&from_uid=231221

Raw reads:
https://www.ncbi.nlm.nih.gov/sra?linkname=bioproject_sra_all&from_uid=231221



- ❑ American Type Culture Collection/ BEI
- ❑ Bernard Nocht Institute for Tropical Medicine, Germany
- ❑ Biodefense and Emerging Infections Research Repository
- ❑ British Columbia Centre for Disease Control (BCCDC)
- ❑ Children's National Medical Center
- ❑ Defense Threat Reduction Agency (DTRA)
- ❑ George Washington University
- ❑ Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD)
- ❑ Lawrence Livermore National Lab (LLNL)
- ❑ Los Alamos National Lab (LANL)
- ❑ Mayo Clinic
- ❑ National Biodefense Analysis and Countermeasures Center
- ❑ National Institute of Allergy and Infectious Diseases (NIH-NIAID)
- ❑ New York State Wadsworth Laboratories
- ❑ Public Health Agency Canada (PHAC)
- ❑ Public Health England (PHE)
- ❑ Rockefeller University
- ❑ Rutgers University
- ❑ Stanford University Medical Center
- ❑ University of California, San Francisco (UCSF)
- ❑ University of Colorado Denver
- ❑ University of Ibadan, Nigeria
- ❑ University of Louisville
- ❑ University of Michigan
- ❑ University of North Carolina at Chapel Hill
- ❑ University of Texas Medical Branch (UTMB)
- ❑ University of Washington School of Medicine
- ❑ U.S. Army Edgewood Chemical Biological Center (ECBC)
- ❑ U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID)
- ❑ U.S. Food and Drug Administration
- ❑ Weill Cornell Medicine

In-Silico Comparator Example

DoD/USAMRIID Collaboration

- Sequencing-based diagnostic device
- Generate FDA-ARGOS Reference Genomes
- Datasets for Regulatory Approval

> Enable In-Silico Data Analysis

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

FDA-ARGOS Pipeline

FDA-ARGOS microbial genomes are generated in 3 phases:

Phase 1- collection of a previously identified microbe and nucleic acid extraction

Phase 2- sequencing and de novo assembly at UMD

Phase 3- Vetting and data deposit in NCBI databases

FDA-ARGOS Reference Genome Characteristics:

A. Identified by orthogonal reference method
B. Sequenced and de-novo assembled using 2 sequencing methodologies
C. High depth of sequencing coverage
D. Minimum of 20X over 95 percent of the assembled and polished core genome
E. Taxonomy-specific ANI thresholds that are sufficient for identification
F. Placed within a pre-established phylogenetic tree.
G. Sample specific metadata, raw reads, assemblies, annotation and details of the bioinformatics pipeline are available.

Bacteria/Fungi/Eukaryote Pipeline

- Collect samples /grow samples
- Extract samples
- Q/C extractions at IGS (>10ug cutoff)
- Batch and library prep/sequence on Illumina –Megablast QC
- Library prep/sequence on PacBio –Megablast QC
- Assemble long/short raw reads
- Annotate with in-house pipeline for Q/C
- Data Analytics Q/C Pipeline at FDA
- Register BioSamples and submit raw reads to SRA DB and assemblies to Assembly DB
- NCBI annotates genomes

Viral Pipeline

Q/C extracted genomic material at IGS (25ng)

Library Prep/sequence on Illumina

- Shotgun
- Amplicon (may require primer set design –Ebola, Zika)
  - Looking into WNV, Dengue –Broad Institute
- RACE

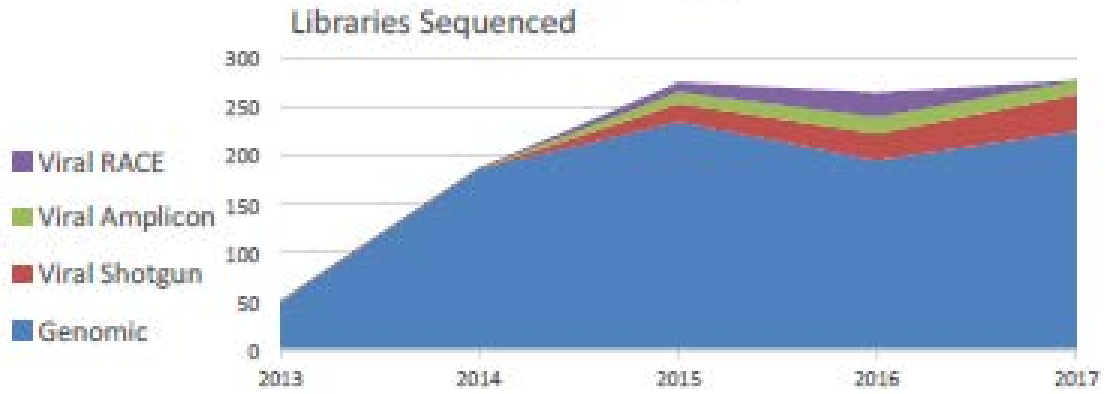
Assemble raw reads

Data Analytics Q/C Pipeline at FDA

Register BioSamples and submit raw reads to SRA DB and assemblies to Assembly DB

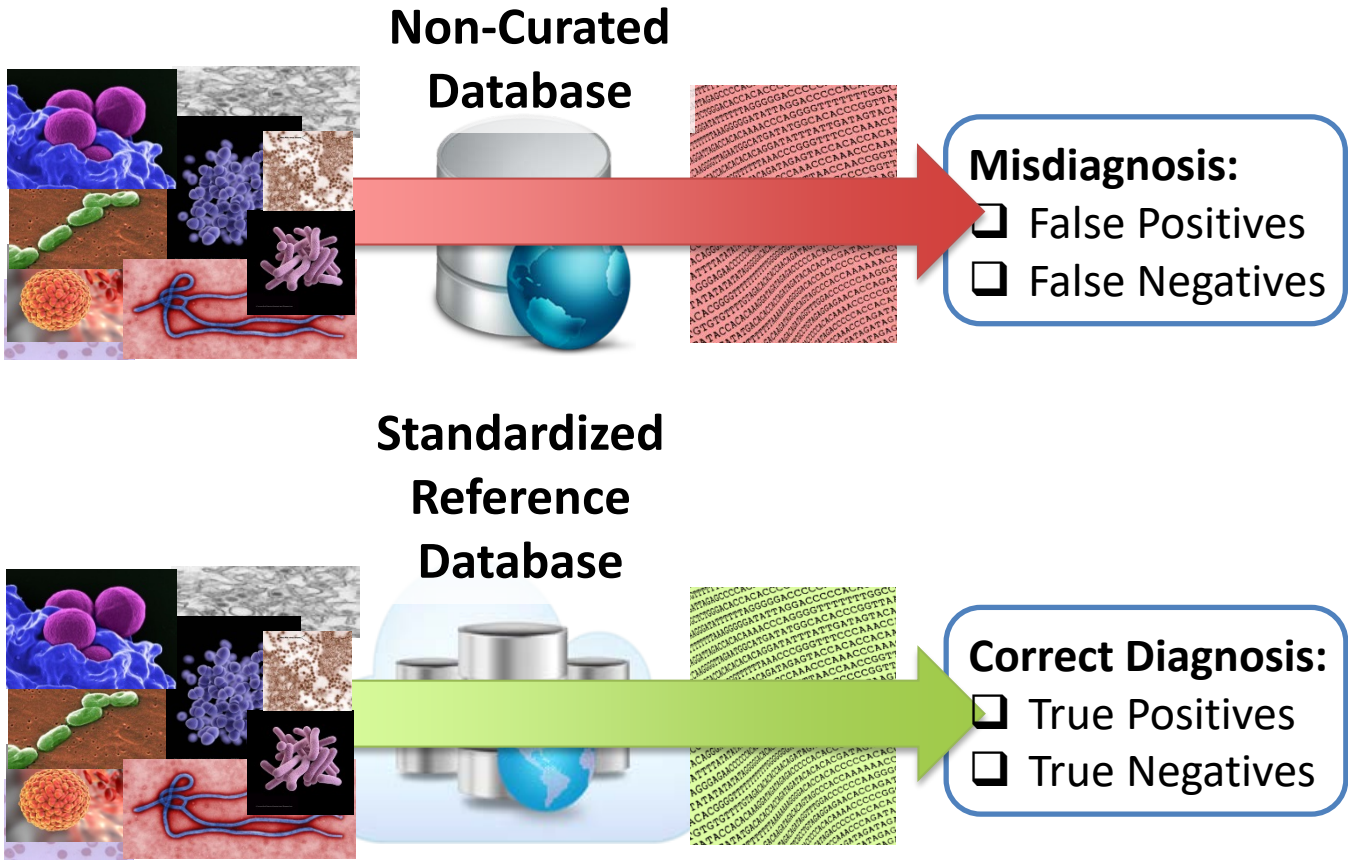
FDA-ARGOS Sample Progress

- 970 Genomes sequenced
  - 872 bacterial
    - 95 genera
  - 85 viral
    - 9 viral types
    - Ebola, Zika, Dengue, WNV, etc.
  - 13 fungal/parasite
- 30+ collaborators



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



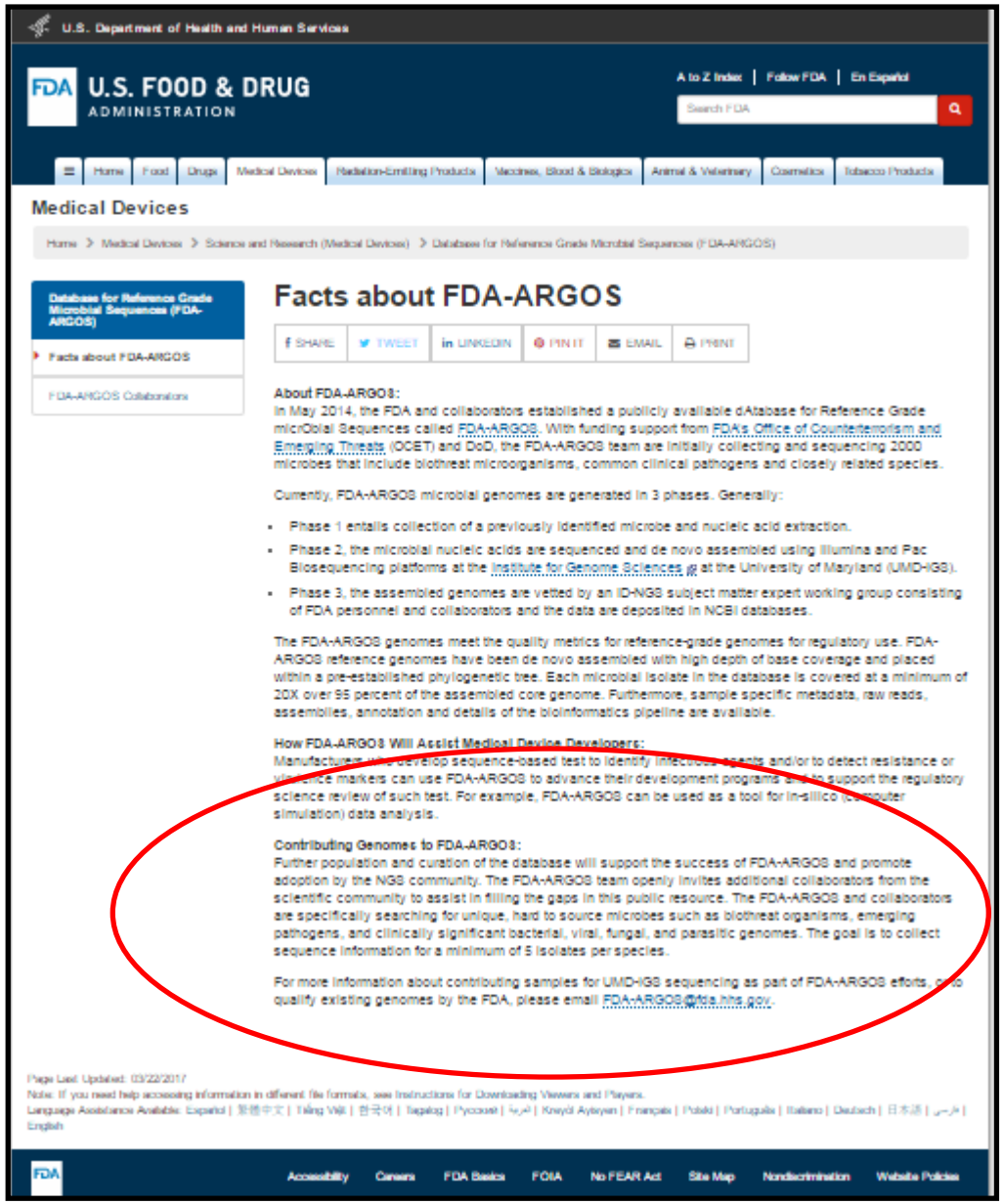
✓ ***Minimize Misdiagnosis***

✓ ***Evolutionary Change***

✓ ***Rapid*** **Diagnostics**

Sustainable Solution

https://www.fda.gov/argos



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Medical Devices

Home > Medical Devices > Science and Research (Medical Devices) > Database for Reference Grade Microbial Sequences (FDA-ARGOS)

Database for Reference Grade Microbial Sequences (FDA-ARGOS)

- Facts about FDA-ARGOS
- FDA-ARGOS Collaborators

Facts about FDA-ARGOS

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About FDA-ARGOS:
In May 2014, the FDA and collaborators established a publicly available dAtabase for Reference Grade microbial Sequences called FDA-ARGOS. With funding support from FDA's Office of Counterterrorism and Emerging Threats (OCET) and DoD, the FDA-ARGOS team are initially collecting and sequencing 2000 microbes that include biothreat microorganisms, common clinical pathogens and closely related species.

Currently, FDA-ARGOS microbial genomes are generated in 3 phases. Generally:

- Phase 1 entails collection of a previously identified microbe and nucleic acid extraction.
- Phase 2, the microbial nucleic acids are sequenced and de novo assembled using Illumina and Pac Biosequencing platforms at the Institute for Genome Sciences @ at the University of Maryland (UMD-IGS).
- Phase 3, the assembled genomes are vetted by an ID-NGS subject matter expert working group consisting of FDA personnel and collaborators and the data are deposited in NCBI databases.

The FDA-ARGOS genomes meet the quality metrics for reference-grade genomes for regulatory use. FDA-ARGOS reference genomes have been de novo assembled with high depth of base coverage and placed within a pre-established phylogenetic tree. Each microbial isolate in the database is covered at a minimum of 20X over 95 percent of the assembled core genome. Furthermore, sample specific metadata, raw reads, assemblies, annotation and details of the bioinformatics pipeline are available.

How FDA-ARGOS Will Assist Medical Device Developers:
Manufacturers who develop sequence-based test to identify infectious agents and/or to detect resistance or virulence markers can use FDA-ARGOS to advance their development programs and to support the regulatory science review of such test. For example, FDA-ARGOS can be used as a tool for in-silico (computer simulation) data analysis.

Contributing Genomes to FDA-ARGOS:
Further population and curation of the database will support the success of FDA-ARGOS and promote adoption by the NGS community. The FDA-ARGOS team openly invites additional collaborators from the scientific community to assist in filling the gaps in this public resource. The FDA-ARGOS and collaborators are specifically searching for unique, hard to source microbes such as biothreat organisms, emerging pathogens, and clinically significant bacterial, viral, fungal, and parasitic genomes. The goal is to collect sequence information for a minimum of 5 isolates per species.

For more information about contributing samples for UMD-IGS sequencing as part of FDA-ARGOS efforts, or to qualify existing genomes by the FDA, please email FDA-ARGOS@fda.hhs.gov.

Page Last Updated: 03/22/2017

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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Contributing Genomes to FDA-ARGOS

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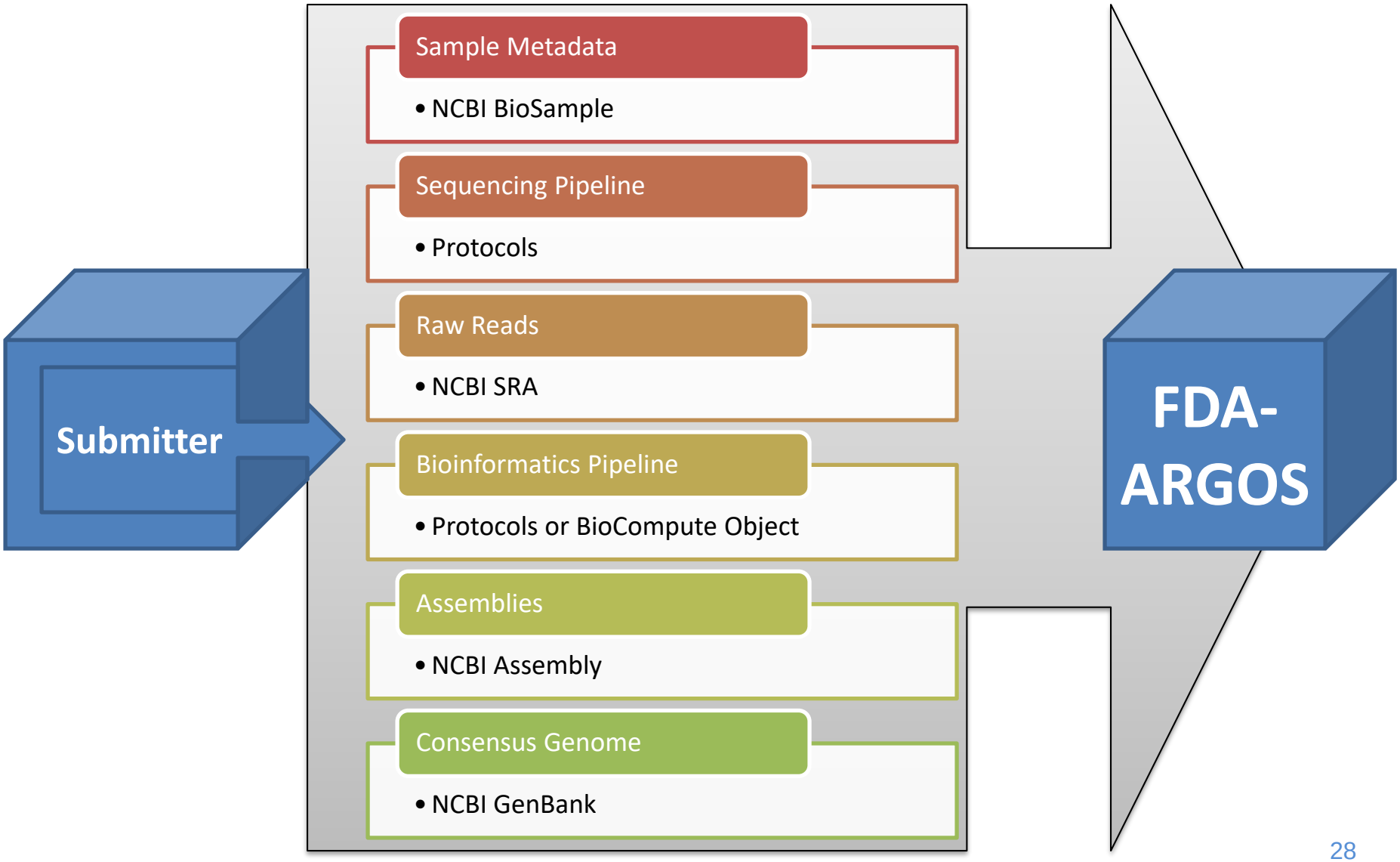
External Genome Submission



Reference Materials

- Support analytical validation of entire ID NGS Diagnostic assay workflow
  1. Cell-based in clinical matrix (blood, urine, stool) to test from specimen collection to result
  2. Reference material organism panel should sufficiently capture ID NGS assay's claimed target characteristics (intended use)
     - Size of the genome, G/C content, DNA/RNA, Near neighbors, Repetitive content, Commensal, Extremes
- Cross-platform comparison

NIST/FDA Reference Material Efforts

- Microbial Genomic DNA Reference Material
  - RM 8375 - Microbial genomic DNA standards for sequencing performance assessment
  - 2 FDA-ARGOS strains/ 2 FDA-CFSAN strains
- Mixed Pathogen DNA Research Material
  - A mixture of genomic DNA from 25 clinically-relevant pathogens plus human genomic DNA.

Build Reference Genomes:

- PacBio/Illumina sequencing of microbial constituents as part of FDA-ARGOS project

Other Reference Material Efforts

- ZymoBIOMICS™ Microbial Community Standards by Zymo Research
  - A mock microbial community consisting of eight bacterial and two fungal strains
- UCSF Control Material

Build Reference Genomes:

- PacBio/Illumina sequencing of microbial constituents as part of FDA-ARGOS project

Which of the following are characteristics of Reference-Grade Genomes for Regulatory Use?

- HMW genomic material from unknown organism
- Sequenced and de-novo assembled using 2 sequencing methodologies
- High depth of sequencing coverage
- Minimum of 1X over 95 percent of the assembled and polished core genome
- Generalized ANI threshold
- Placed within a pre-established phylogenetic tree
- Sample specific metadata, raw reads, assemblies, annotation and details of the bioinformatics pipeline are available.

Which of the following are characteristics of Reference-Grade Genomes for Regulatory Use?

- ~~HMW genomic material from unknown organism~~
- ✓ Sequenced and de-novo assembled using 2 sequencing methodologies
- ✓ High depth of sequencing coverage
- ~~Minimum of 1X over 95 percent of the assembled and polished core genome~~
- ~~Generalized ANI threshold~~
- ✓ Placed within a pre-established phylogenetic tree
- ✓ Sample specific metadata, raw reads, assemblies, annotation and details of the bioinformatics pipeline are available.

REVIEW
Characteristics of
Reference-Grade Genomes for Regulatory Use

A. Identified by orthogonal reference method
B. Sequenced and de-novo assembled using 2 sequencing methodologies
C. High depth of sequencing coverage
D. Minimum of 20X over 95 percent of the assembled and polished core genome
E. Taxonomy-specific ANI thresholds that are sufficient for microbial organism identification
F. Placed within a pre-established phylogenetic tree
G. Sample specific metadata, raw reads, assemblies, annotation and details of the bioinformatics pipeline are available

Acknowledgements

FDA-ARGOS team members include representatives from the:

- U.S. Food and Drug Administration
- U.S. Department of Defense
- National Institutes of Health
- Institute for Genome Sciences at University of Maryland

Funding Agencies

FDA's Office of Counterterrorism and Emerging Threats

Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD)

American Type Culture Collection/ BEI
Bernard Nocht Institute for Tropical Medicine, Germany
Biodefense and Emerging Infections Research Resources Repository
British Columbia Centre for Disease Control (BCCDC)
Children's National Medical Center
Defense Threat Reduction Agency (DTRA)
George Washington University
Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD)
Lawrence Livermore National Lab (LLNL)
Los Alamos National Lab (LANL)
Mayo Clinic
National Biodefense Analysis and Countermeasures Center
National Institute of Allergy and Infectious Diseases (NIH-NIAID)
New York State Wadsworth Laboratories
Public Health Agency Canada (PHAC)
Public Health England (PHE)
Rockefeller University
Rutgers University
Stanford University Medical Center
University of California, San Francisco (UCSF)
University of Colorado Denver
University of Ibadan, Nigeria
University of Louisville
University of Michigan
University of North Carolina at Chapel Hill
University of Texas Medical Branch (UTMB)
University of Washington School of Medicine
U.S. Army Edgewood Chemical Biological Center (ECBC)
U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID)
U.S. Food and Drug Administration
Weill Cornell Medicine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