FDA's Role and Tools for ID-NGS Diagnostics

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DHS Sequencing Meeting 2017

Disclaimer

The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy.

Opinions are my own

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Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers; Draft Guidance for Industry and Food and Drug Administration Staff; Availability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SUMMARY The Food and Drug Administration (FDA) is announcing the availability of a draft guidance entitled "Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and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 This draft guidance provides recommendations to assist industry in designing studies to establish the analytical and

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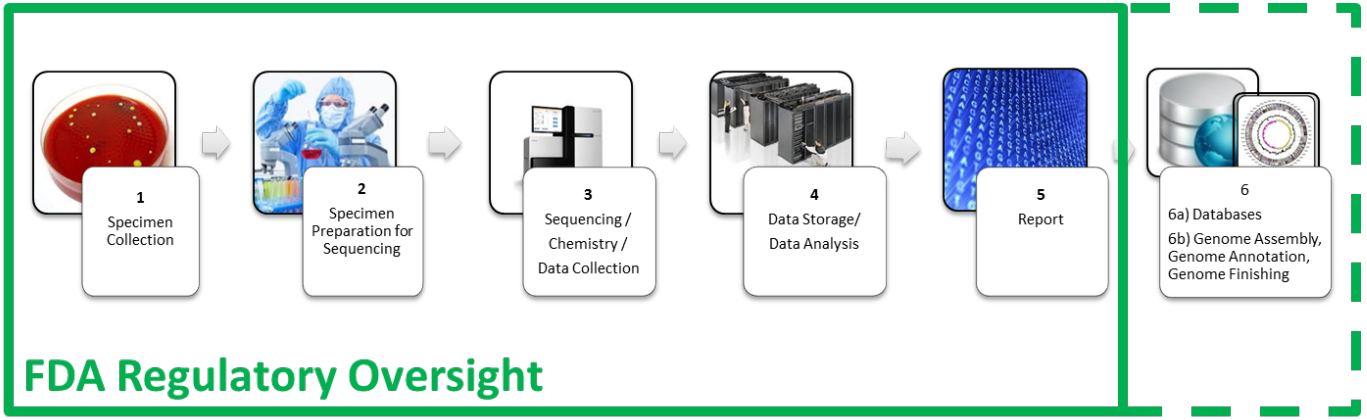
FDA Current Thinking



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

- ✓ 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

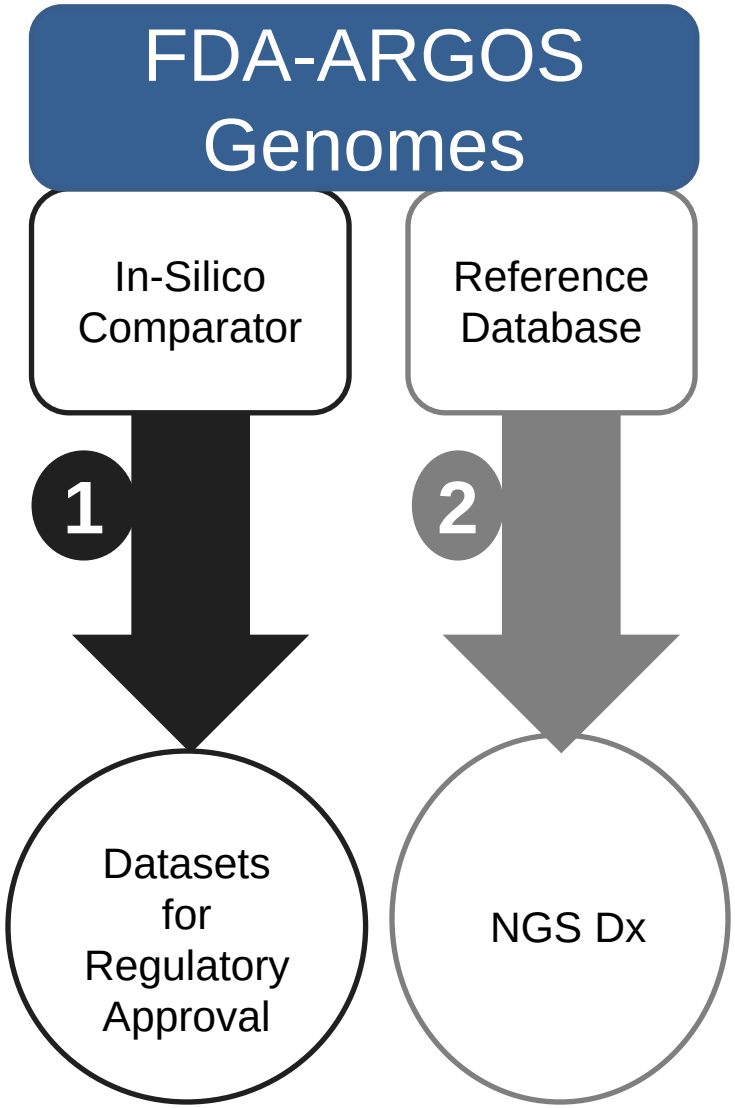
- ✓ ID NGS Dx Advisory Board
- ✓ Consensus FDA-ARGOS genome vetting
- ✓ Keep current on state of the art
- ✓ Tackle open questions (i.e. sens/spec)

FDA-ARGOS: Goal and Use

- Public Vetted Resource
- Microbial Reference-Grade Genomes for **Regulatory Use**
- US-Initiated
- Medical Countermeasures
- Common clinical
- Near neighbors

- **Coverage for US Needs**
- **Currently not funded to support *Needs for Developing World* and associated *Global Standards***

NCBI Project **PRJNA231221**



DoD Collaborations

- USAMRIID
  - PreEUA NGS data prep
  - Enable In Silico validation
- DBPAO
  - West Africa panel
  - Full assay characterization
    - Analytical
    - Clinical
    - Inclusivity/Exclusivity

Pathogen
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

USAMRIID Targeted NGS (environmental)

MTE NGS Pathogen Detection		
Borrelia burgdorferi	Human coronavirus 229E	Nipah virus
Bundibugyo virus	Human parainfluenza virus Type 1	Onyong-nyong virus
Bunyamwera virus	Human parainfluenza virus Type 2	Oropouche virus (TR9760)
Candiru virus	Human parainfluenza virus Type 4b	*Plasmodium falciparum*
Chikungunya virus	Human respiratory syncytial virus (RSV) A-2	Powassan virus
Cowpox virus	Human respiratory syncytial virus (RSV) 18537	Ravn virus
Coxiella burnetii	influenza B virus (B/Ohio/01/2005)	Reston virus
Crimean-Congo hemorrhagic fever virus	Junín virus	Rift Valley fever virus
dengue virus serotype 1	La Crosse virus	Ross River virus
dengue virus serotype 2	Lassa fever virus	SARS coronavirus
dengue virus serotype 3	Lujo virus	Semliki forest virus
dengue virus serotype 4	Lymphocytic choriomeningitis virus	Sindbis virus
eastern equine encephalitis virus	Machupo virus (Malele)	St. Louis encephalitis virus
Ebola virus (Zaire)	Machupo virus (Chicava)	Taï Forest virus
Ebola virus (Kikwit)	Marburg virus (Angola)	Toscana virus
Getah virus	Marburg virus (Ci67)	Venezuelan equine encephalitis virus
Guanarito virus	Marburg virus (Musoke)	Wesselbron virus
Hantaan virus	Mayaro fever virus	western equine encephalitis virus
Heartland virus	Monkeypox virus	yellow fever virus
Hendra virus	Naples virus	Zika virus
Highlands J virus	Ndumu virus	

Sequencing Approach

Bacteria

- **Hybrid sequencing** approach using Illumina HiSep2000 and the BacBio RSII platform to generate industry standard high quality sequences. Use of multiple assemblers. 3 sets of de novo genome assemblies will be produced 1) Illumina only, 2) BioPac only, and 3) Illumina/BioPac hybrid

Virus

- IGS will use existing and well-established laboratory and bioinformatics pipelines within the Genomic Resource Center. A **three-prong** Illumina sequencing approach followed by customized assembly

FDA-ARGOS Genome Status

- There are **827 (bacterial, viral)** samples currently at various stages within the FDA-ARGOS sequencing pipeline.
- **322 (bacterial, viral)** genomes from other efforts (i.e. TTC) to be qualified.
- Goal is to collect and sequence **2000** gap organisms

Overall pipeline

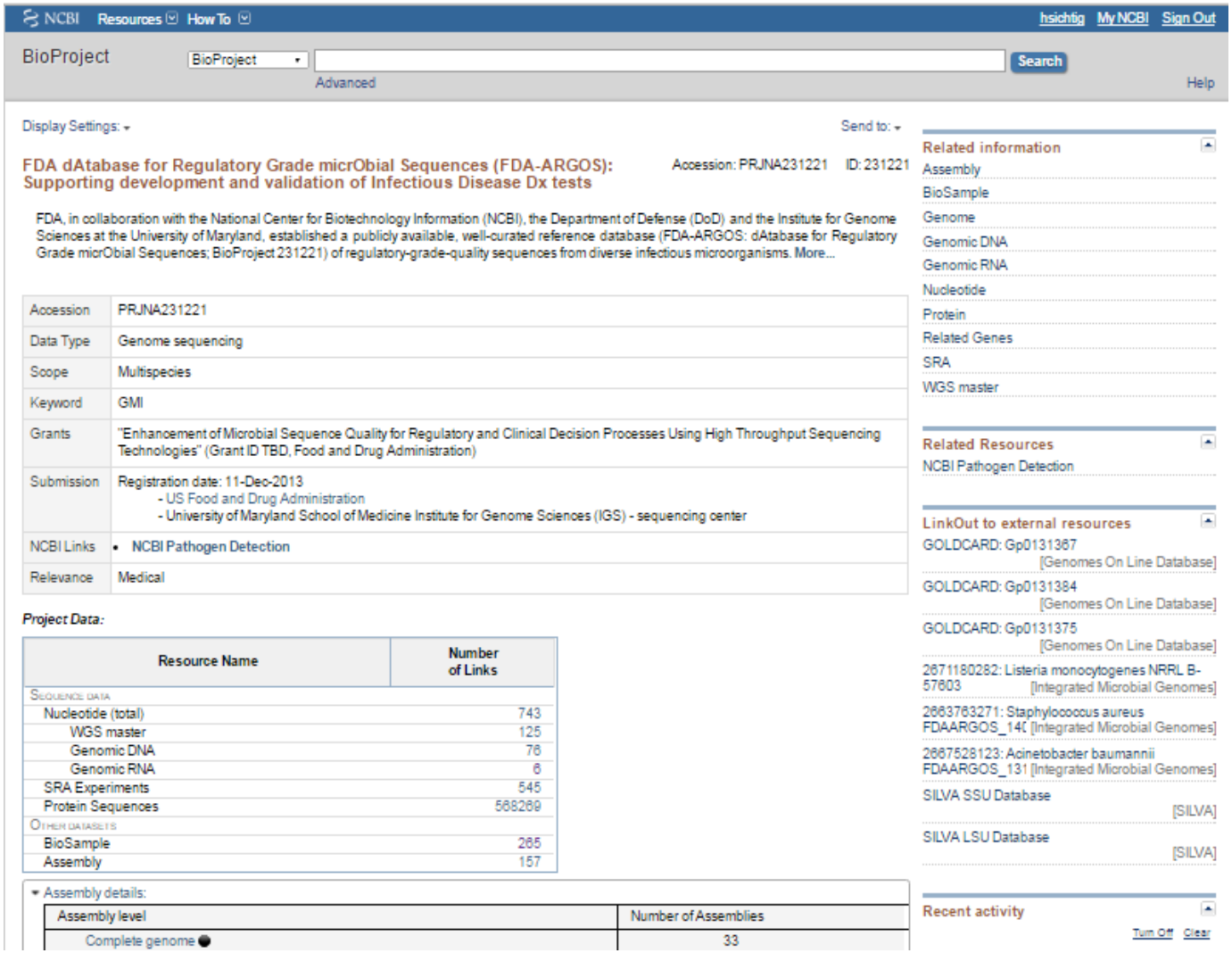
Collaborator -> FDA OSEL -> UMD/IGS -> NCBI/FDA

Collaborator -> USAMRIID -> UMD/IGS -> NCBI/FDA

*Stocks are archived at USAMRIID when available per agreement

NCBI BioProject 231221

:houses FDA-ARGOS genomes generated with the IGS-UMD Sequencing pipeline



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FDA dAtabase for Regulatory Grade micrObial Sequences (FDA-ARGOS): Supporting development and validation of Infectious Disease Dx tests

Accession: PRJNA231221 ID: 231221

FDA, in collaboration with the National Center for Biotechnology Information (NCBI), the Department of Defense (DoD) and the Institute for Genome Sciences at the University of Maryland, established a publicly available, well-curated reference database (FDA-ARGOS: dAtabase for Regulatory Grade micrObial Sequences; BioProject 231221) of regulatory-grade-quality sequences from diverse infectious microorganisms. More...

Accession	PRJNA231221
Data Type	Genome sequencing
Scope	Multispecies
Keyword	GMI
Grants	"Enhancement of Microbial Sequence Quality for Regulatory and Clinical Decision Processes Using High Throughput Sequencing Technologies" (Grant ID TBD, Food and Drug Administration)
Submission	Registration date: 11-Dec-2013 - US Food and Drug Administration - University of Maryland School of Medicine Institute for Genome Sciences (IGS) - sequencing center
NCBI Links	• NCBI Pathogen Detection
Relevance	Medical

Project Data:

Resource Name	Number of Links
SEQUENCE DATA	
Nucleotide (total)	743
WGS master	125
Genomic DNA	76
Genomic RNA	6
SRA Experiments	545
Protein Sequences	568269
OTHER DATASETS	
BioSample	265
Assembly	157

Assembly details:

Assembly level	Number of Assemblies
Complete genome	33

Related information
Assembly
BioSample
Genome
Genomic DNA
Genomic RNA
Nucleotide
Protein
Related Genes
SRA
WGS master

Related Resources
NCBI Pathogen Detection

LinkOut to external resources
GOLDCARD: Gp0131367 [Genomes On Line Database]
GOLDCARD: Gp0131384 [Genomes On Line Database]
GOLDCARD: Gp0131375 [Genomes On Line Database]
2671180282: Listeria monocytogenes NRRL B-57603 [Integrated Microbial Genomes]
2663763271: Staphylococcus aureus FDAARGOS_14([Integrated Microbial Genomes]
2667528123: Acinetobacter baumannii FDAARGOS_131 [Integrated Microbial Genomes]
SILVA SSU Database [SILVA]
SILVA LSU Database [SILVA]

Recent activity
Turn Off Clear

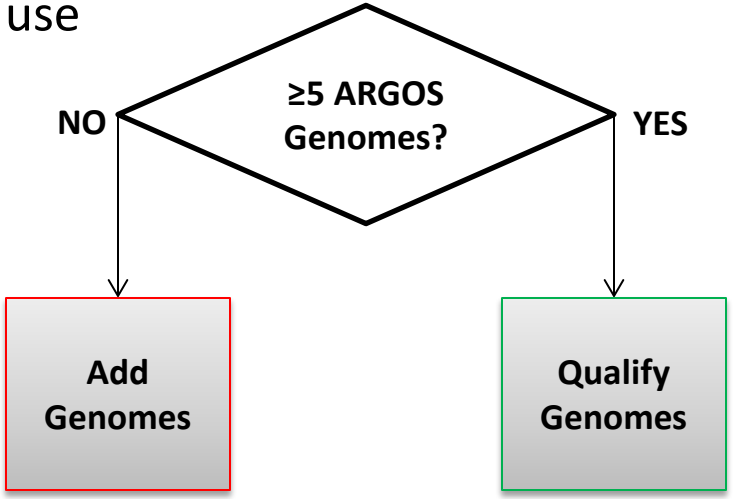
FDA-ARGOS
Global-ARGOS
COMPREHENSIVE
ACCURACY
EMERGING THREATS
Coverage
Precision
Inclusivity
VERACITY
Rigor
Temporal
Timeliness
Robustness
Specificity
Geography
Sustainability
Spatial

Accuracy

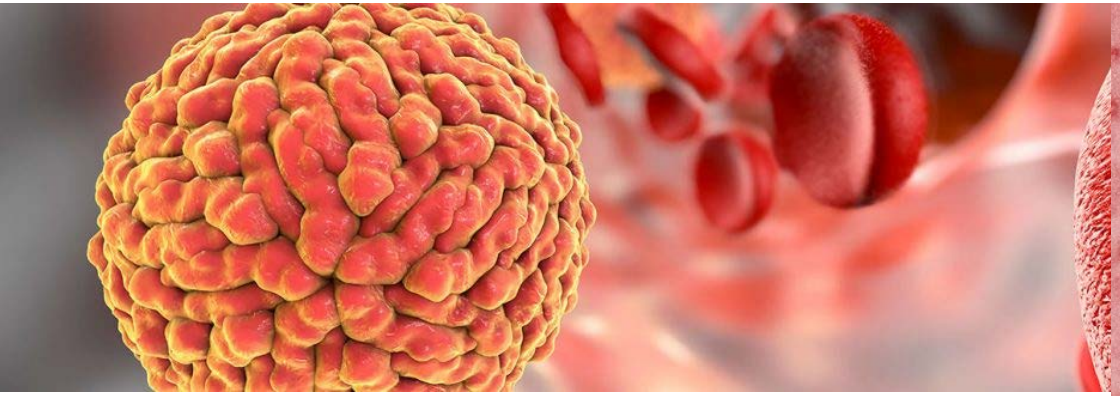
Why Reference Grade Genomes for Regulatory Use?

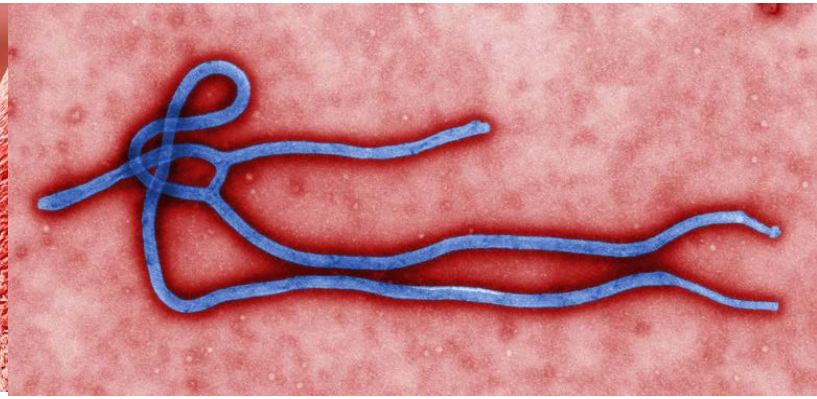
Species-specific Quality Metrics

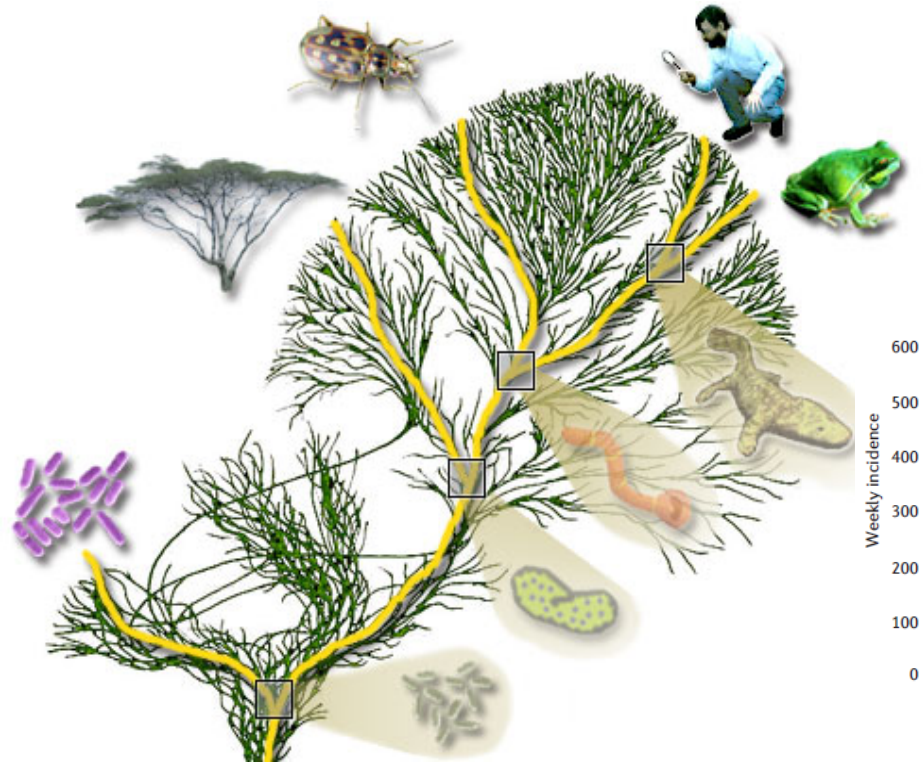
- Vetted by ID NGS SME Team for regulatory use
- Genome similarity measure and range
  - Based on at least 5 representatives
  - Nucleotide similarity (ANI)
  - Species core genome
    - Minimum 20X over 95%
- Sample-specific Metadata
- Raw reads, assemblies, annotations
- Pipeline
  - Sample Prep, Library , Platform, Assembler



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

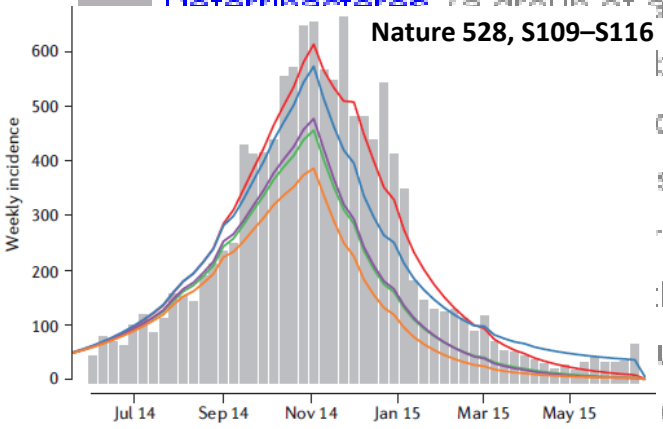
stin

ia and relatives)

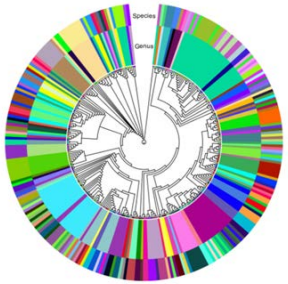
h peptidoglycan-less ce

ular parasites of eukary

chemoheterotrophs)



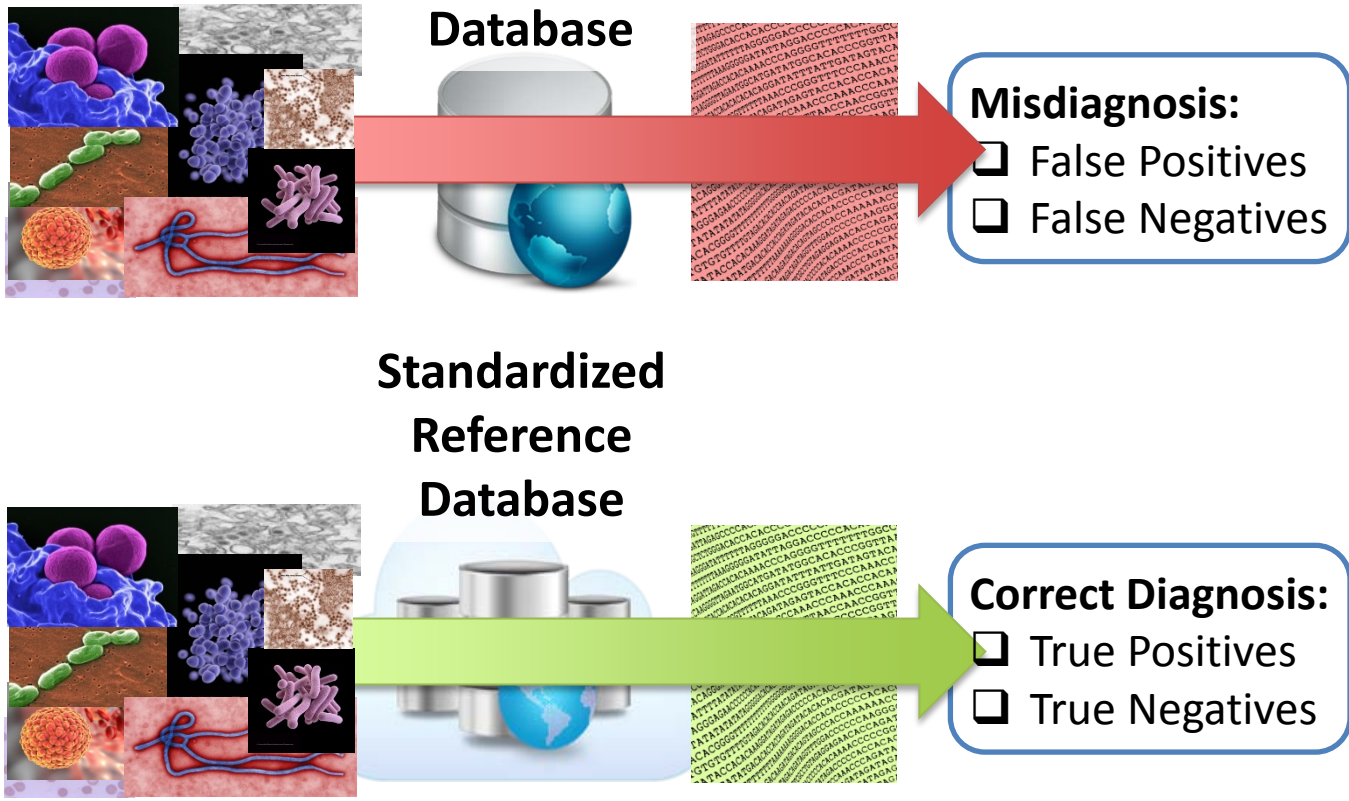
Nature 528, S109–S116



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



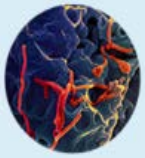
✓ *Minimize Misdiagnosis*

✓ *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

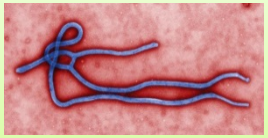
When you need a test to confirm disease in an outbreak, you need it fast. Global

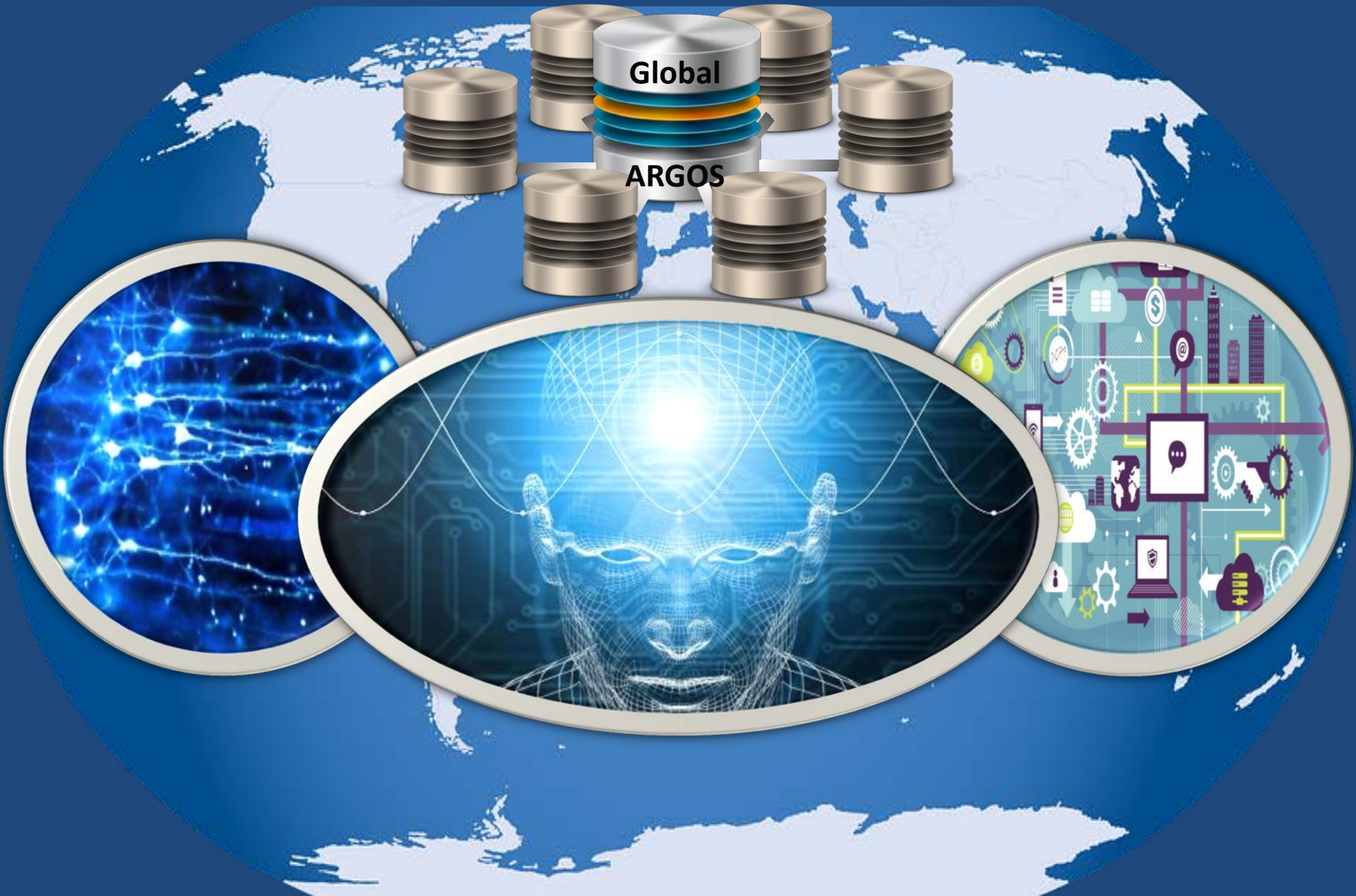
THE FUTURE

Platform?

Global ARGOS

Prevent Outbreak



Viral Immunol 28(1): 19-31

Sustainable Solution