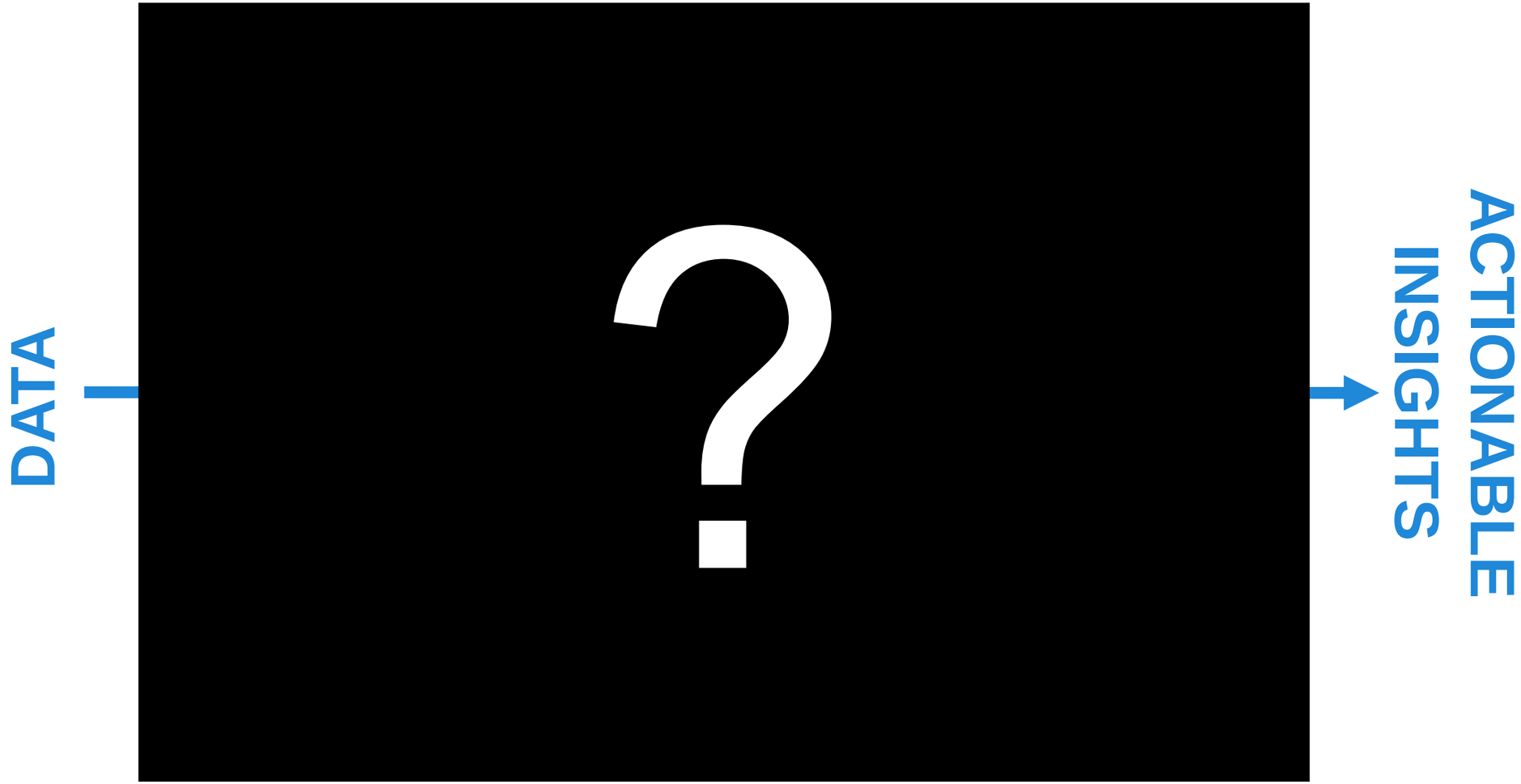
# Artificial Intelligence in AMR Diagnostics

**Advancing Data Technologies to corner AMR | Amsterdam | June 5th 2019**

**Dr. Andreas Posch | Managing Director & CEO | Ares Genetics**

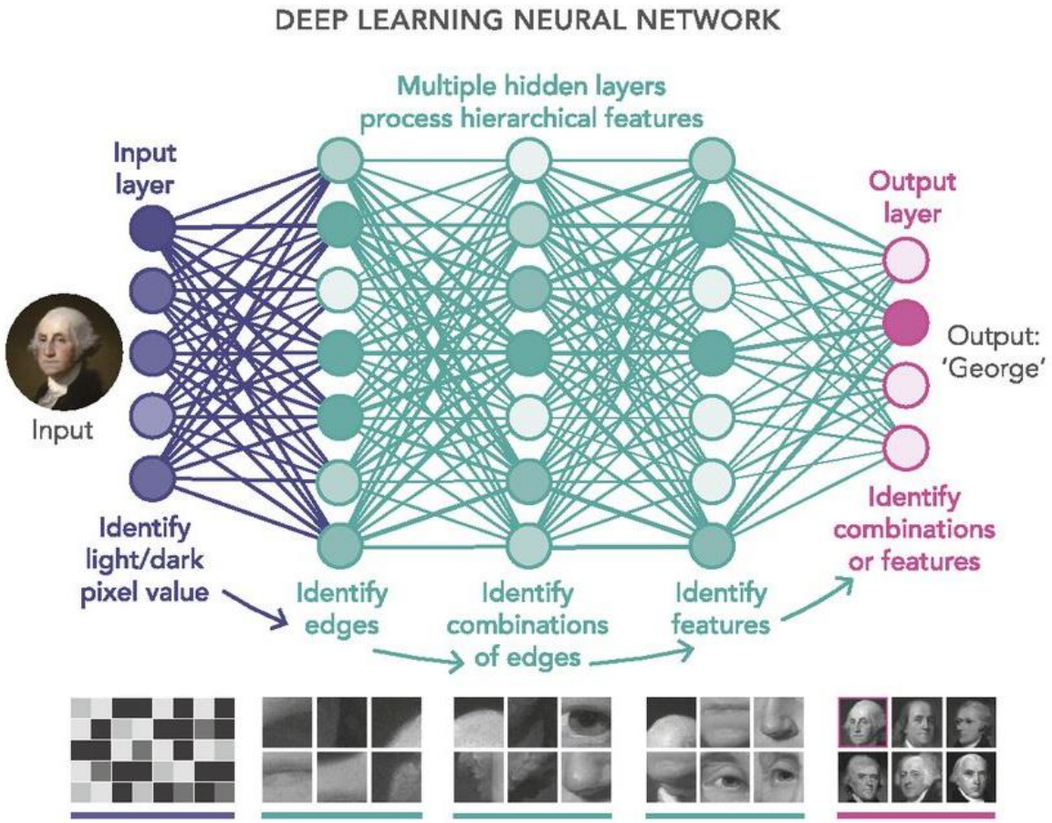
# WHAT WE ARE TALKING ABOUT WHEN WE TALK ABOUT AI

# WHAT WE ARE TALKING ABOUT WHEN WE TALK ABOUT AI



# WHAT WE ARE TALKING ABOUT WHEN WE TALK ABOUT AI

DATA




M. Mitchell Waldrop PNAS 2019;116:4:1074-1077

ACTIONABLE INSIGHTS

# WHAT WE ARE TALKING ABOUT WHEN WE TALK ABOUT AI

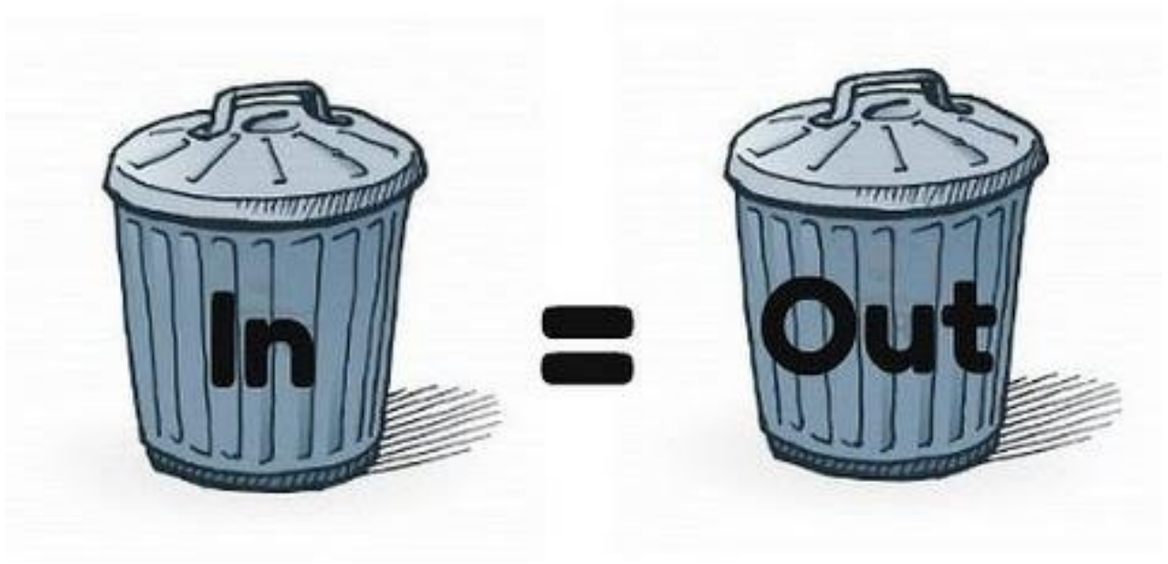
DATA


ACTIONABLE INSIGHTS

**https://www.explainxkcd.com/wiki/index.php/1838:_Machine_Learning**

# WHAT WE ARE TALKING ABOUT WHEN WE TALK ABOUT AI

DATA

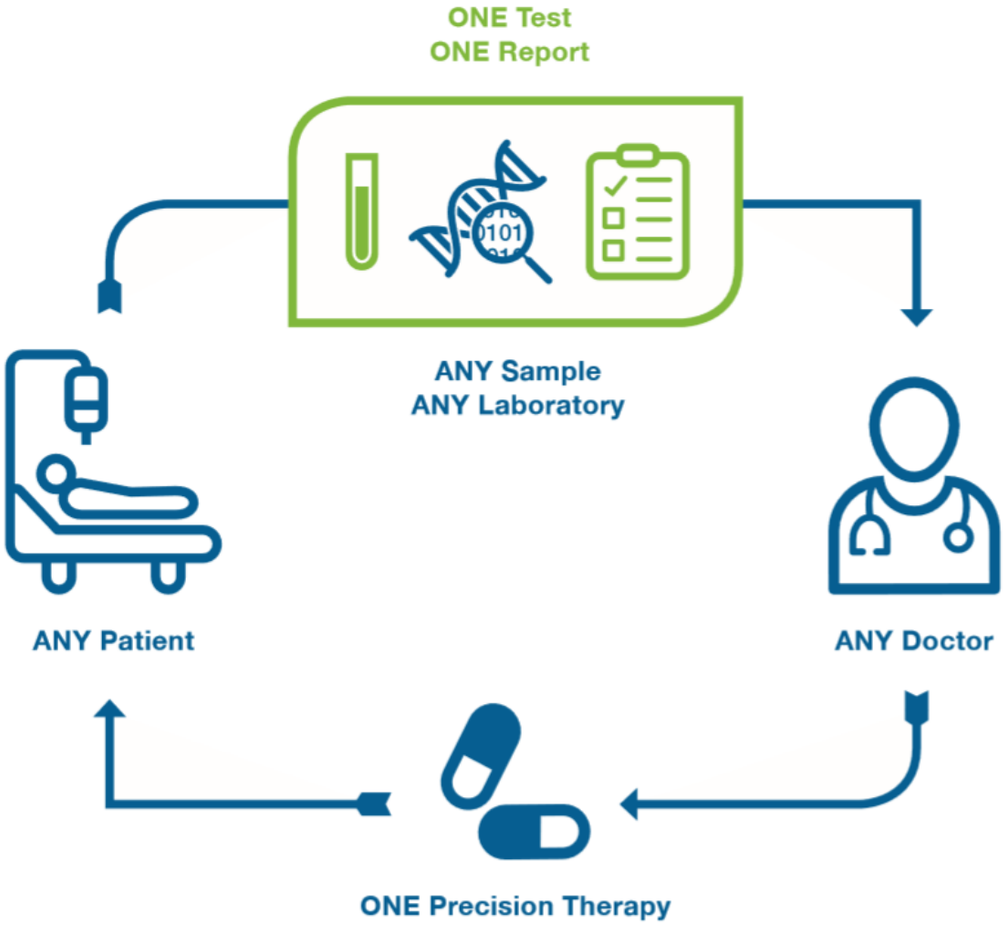



ACTIONABLE INSIGHTS

ares genetics

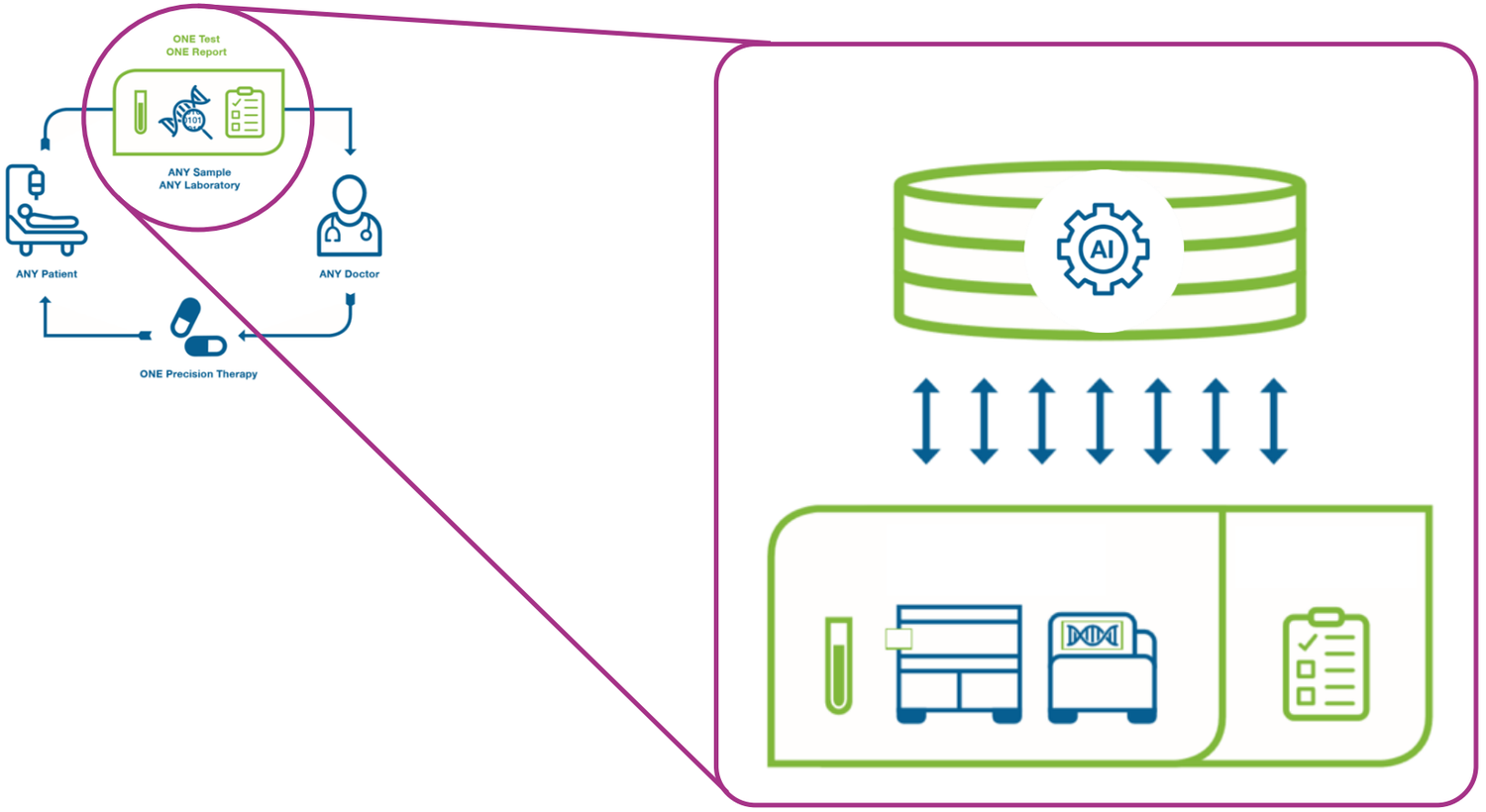
# Actionable Insights in AMR Diagnostics

# OUR VISION: ONE RAPID UNIVERSAL ASSAY FOR PATHOGEN ID AND PRECISE DRUG RESPONSE

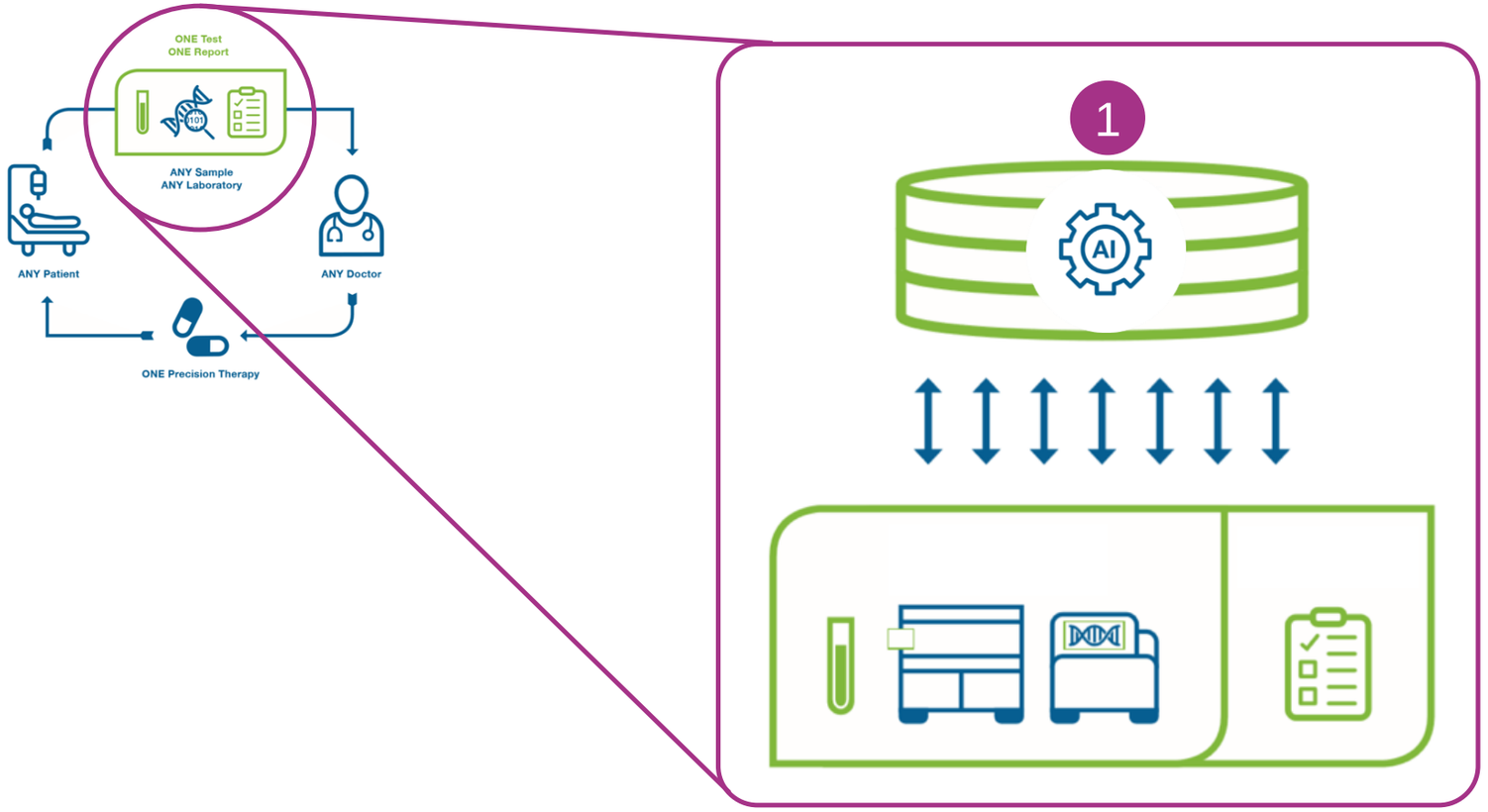



- Any Patient Sample
- Universal NGS-Sequencing Assay
- Actionable Insights
- Personalized Therapy

# OUR UNIVERSAL PATHOGENOME ASSAY:
# KEY ELEMENTS

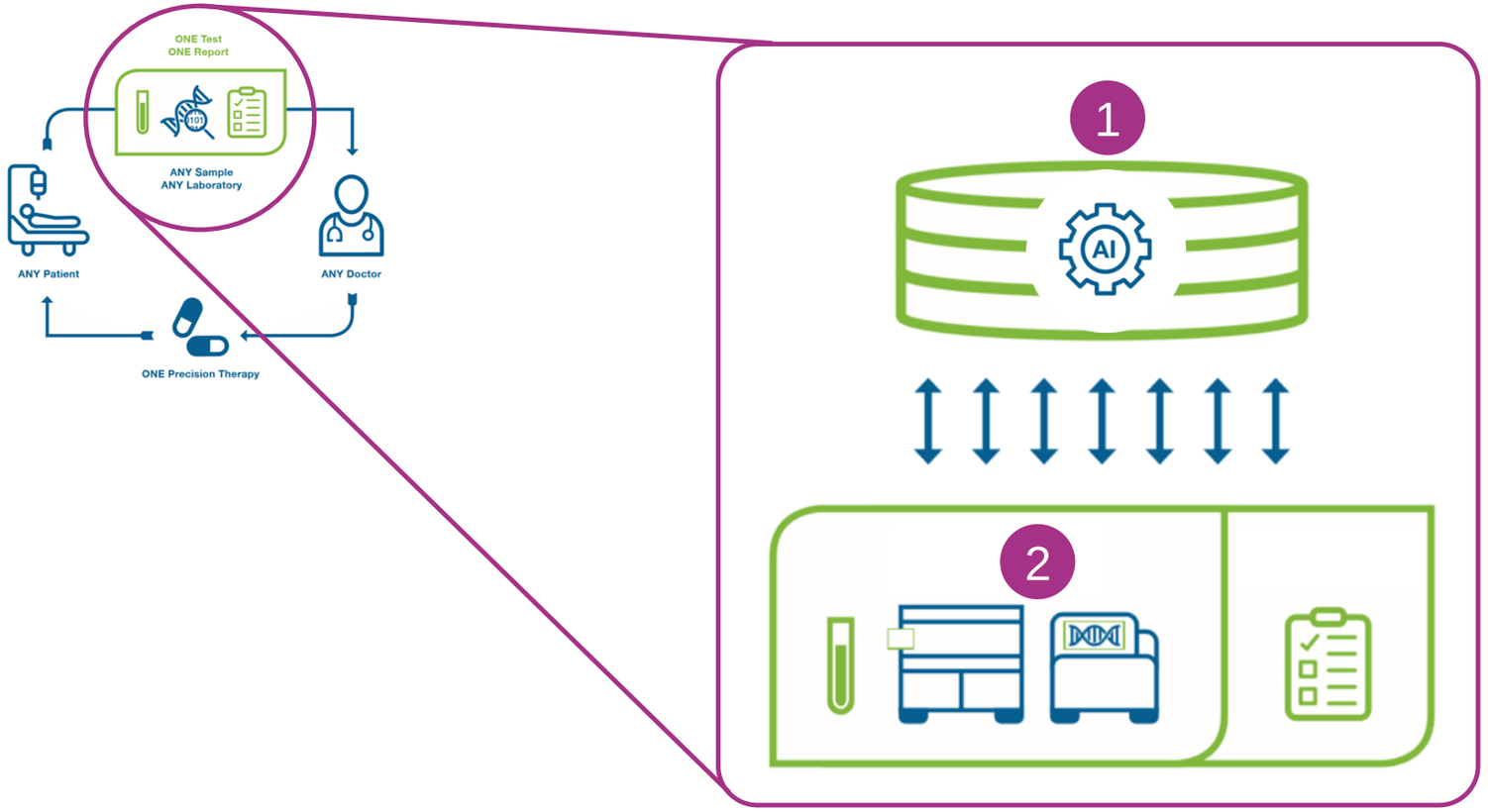


# OUR UNIVERSAL PATHOGENOME ASSAY:
# KEY ELEMENTS




1 A curated & validated, global reference database that is sustainably up-to-date with AMR evolution and epidemiology.

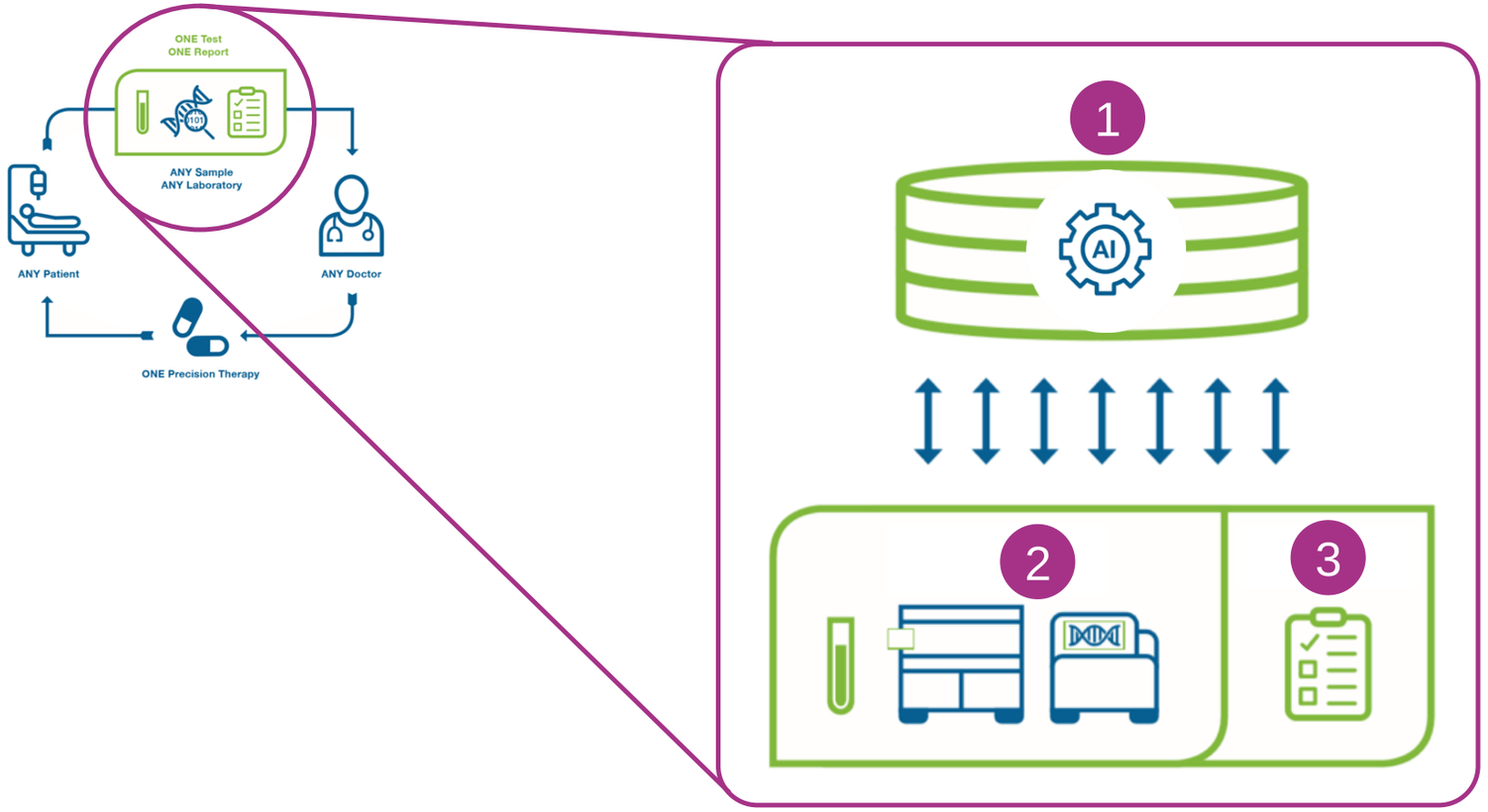
# OUR UNIVERSAL PATHOGENOME ASSAY: KEY ELEMENTS




1. A curated & validated, global reference database that is sustainably up-to-date with AMR evolution and epidemiology.

2. A universal, fully automated NGS lab workflow for generic local data generation.

# OUR UNIVERSAL PATHOGENOME ASSAY:
# KEY ELEMENTS

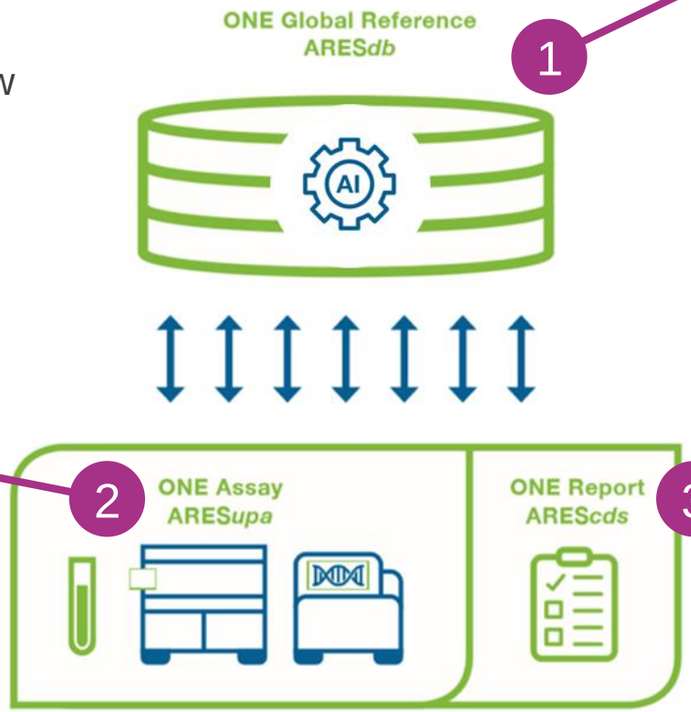



1. A curated & validated, global reference database that is sustainably up-to-date with AMR evolution and epidemiology.
2. A universal, fully automated NGS lab workflow for generic local data generation.
3. A HIPAA compliant, cloud-based data interpretation & clinical decision support system translating NGS data into actionable insights.

# OUR UNIVERSAL PATHOGENOME ASSAY: IMPLEMENTATION

**ARESupa**
Sample-to-Answer NGS Workflow

- Collaboration with BGI
- Feasibility demonstrated
- Data presented at ASM NGS 2018 | USA and ICG-13 2018 | China




**ARESdb**
Expert Curated & AI-Powered Reference Database


**ARESdb**
Clinical Decision Support Platform

# TURNING NGS INTO ACTIONABLE INSIGHTS: A CHALLENGE THAT CAN BUILD ON LEARNINGS IN HIV & CANCER

| | HIV | Cancer | AMR |
|---|---|---|---|
| **Annual Casualties** | ~1 Mio[1] | 8,8 Mio[1] | **> 10 Mio[2]** |
| **BioIT Complexity** | ~ 10 kb genome (low) | ~ 3 Gb genome (high) | **~ 5Mb genome 1000s of strains genetic plasticity** |
| **Reference Databases** | **Numerous public resources** | **Numerous public resources** | **Few public resources, but not suitable as diagnostic reference** |
| **Competitive Landscape** | **Saturated** (established Laboratory Diagnostics) | **Growing but Crowded** (Molecular Pathology & BioIT companies) | **Untapped Potential:** Next-Gen Molecular Microbiology |

**1000s of Strains**
**X**
**100s of Drugs**
**X**
**100s of MoRs**

[1] WHO Factsheets, 2017 [2] projected by 2050, The Review on Antimicrobial Resistance, 2014

# TURNING NGS INTO ACTIONABLE INSIGHTS IN AMR:
# A DATA INTEGRATION & CURATION CHALLENGE

# TURNING NGS INTO ACTIONABLE INSIGHTS IN AMR: A DATA INTEGRATION & CURATION CHALLENGE

!!! Fragmented public AMR databases

# TURNING NGS INTO ACTIONABLE INSIGHTS IN AMR: A DATA INTEGRATION & CURATION CHALLENGE

!!! Fragmented public AMR databases

!!! Lack of diagnostic performance parameters for AMR genes (i.e. PPV, NPV, etc.)

# TURNING NGS INTO ACTIONABLE INSIGHTS IN AMR: A DATA INTEGRATION & CURATION CHALLENGE

!!! Fragmented public AMR databases

!!! Lack of diagnostic performance parameters for AMR genes (i.e. PPV, NPV, etc.)

!!! Limited phenotypic information

# TURNING NGS INTO ACTIONABLE INSIGHTS IN AMR: A DATA INTEGRATION & CURATION CHALLENGE

!!! Fragmented public AMR databases

!!! Lack of diagnostic performance parameters for AMR genes (i.e. PPV, NPV, etc.)

!!! Limited phenotypic information

!!! Lack of standardization

# TURNING NGS INTO ACTIONABLE INSIGHTS IN AMR: A DATA INTEGRATION & CURATION CHALLENGE

!!! Fragmented public AMR databases

!!! Lack of diagnostic performance parameters for AMR genes (i.e. PPV, NPV, etc.)

!!! Limited phenotypic information

!!! Lack of standardization

!!! Lack of defined quality criteria

# TURNING NGS INTO ACTIONABLE INSIGHTS IN AMR: A DATA INTEGRATION & CURATION CHALLENGE

!!! Fragmented public AMR databases

!!! Lack of diagnostic performance parameters for AMR genes (i.e. PPV, NPV, etc.)

!!! Limited phenotypic information

!!! Lack of standardization

!!! Lack of defined quality criteria

!!! Lack of meta data

# TURNING NGS INTO ACTIONABLE INSIGHTS IN AMR: A DATA INTEGRATION & CURATION CHALLENGE

!!! Fragmented public AMR databases

!!! Lack of diagnostic performance parameters for AMR genes (i.e. PPV, NPV, etc.)

!!! Limited phenotypic information

!!! Lack of standardization

!!! Lack of defined quality criteria

!!! Lack of meta data

!!! Genomic & phenotypic data not always from identical & pure clones

# TURNING NGS INTO ACTIONABLE INSIGHTS IN AMR: A DATA INTEGRATION & CURATION CHALLENGE

!!! Fragmented public AMR databases

!!! Lack of diagnostic performance parameters for AMR genes (i.e. PPV, NPV, etc.)

!!! Limited phenotypic information

!!! Lack of standardization

!!! Lack of defined quality criteria

!!! Lack of meta data

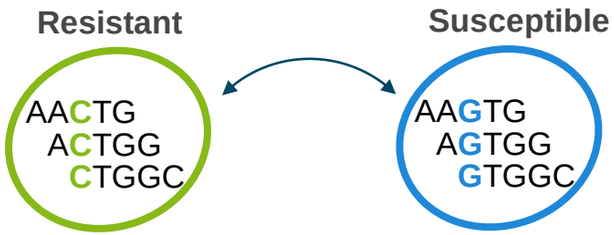
!!! Genomic & phenotypic data not always from identical & pure clones

!!! Limited information on AMR conferring mutations

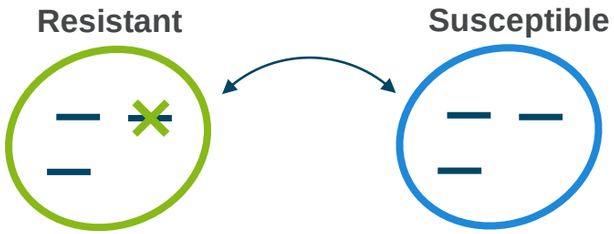
!!! …

# ARESdb: EXPERT CURATED REFERENCE DATABASE CATALOGUING AMR RESISTANCE GENES AND MUTATIONS

Gene **mutation** determines resistance



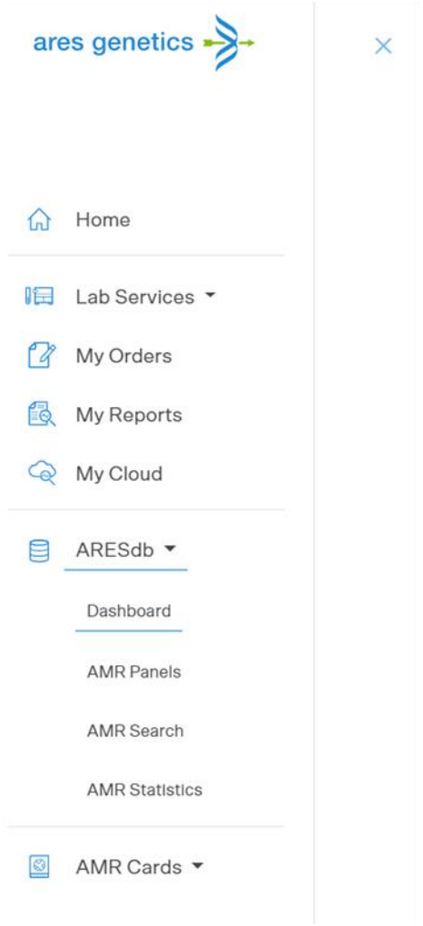

Gene **presence / absence** determines resistance

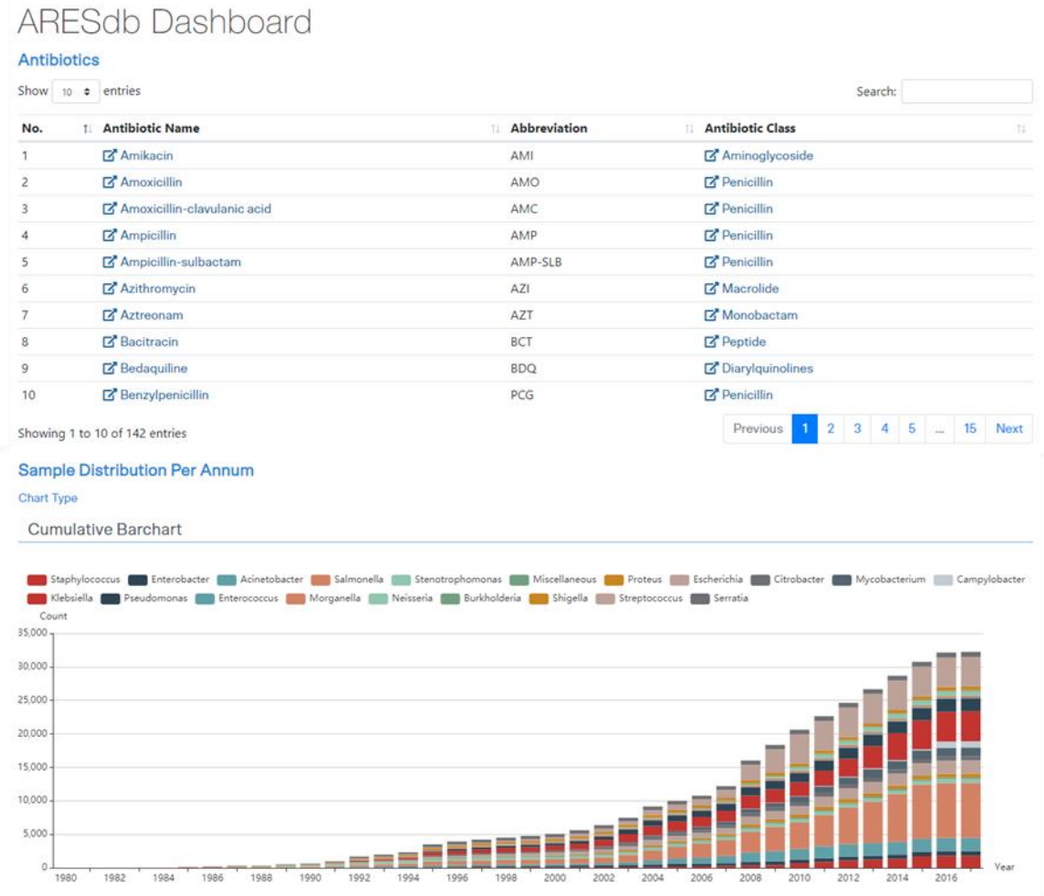



**ARESdb.** A highly **standardized**, **quality controlled** resource of **pathogen genomes**, **AMR phenotypes & AMR marker** building on **CLSI guidelines**

ONE Global Reference
ARES*db*

# ARESdb: GLOBALLY LEADING, CONTINUOSLY UPDATED AMR KNOWLEDGEBASE ESTABLISHED BY SIEMENS




SIEMENS Healthineers

**~ 40,000 whole-genome** sequenced bacterial strains collected globally from over 200 clinical centers.

Quantitative antibiotic susceptibility data for **more than 100 antibiotics.**

Originally established based on the **SIEMENS** Microbiology strain collection.

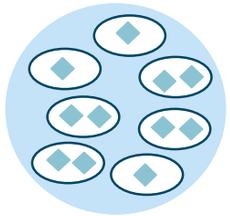
# ARESdb: ACTIONABLE GENETIC RESISTANCE MARKERS FOR AMR DIAGNOSTICS

## Adv. & Robust Biostatistics | Population Structure Correction | Decision Trees | Gradient Boosting

### Resistant Population

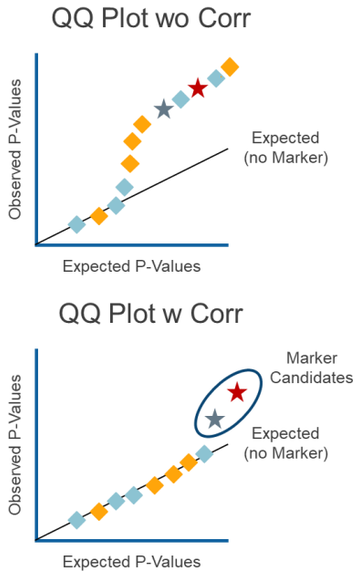
ARESdb Marker
(DNA Sequence
Features)

### Susceptible Population

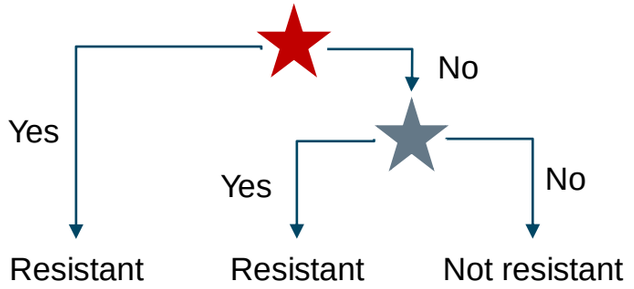


Population
Marker

### Filtering of False-Positive Population Marker




### Decision Tree Building for AMR Detection




**Combining week learners in ensemble model for optimal accuracy by gradient tree boosting (up to >98%)**

# ARESdb: BUILDS ON CURATION PRACTICE IN ONCOLOGY

## New marker are systematically classified based on predefined criteria and rules

- Public Resources, Clinical studies & Scientific papers all provide a wealth of unstructured AMR data
- There is a need for interpretative categories for clinical utilization of AMR markers
- A similar problem was faced (and solved) in the field of oncology via consensus guidelines for marker classification
- ARESdb is automating the process of AMR marker classification reducing manual curation needs

HHS Public Access

Author manuscript

*Genet Med*. Author manuscript; available in PMC 2015 November 01.

Published in final edited form as:

*Genet Med*. 2015 May ; 17(5): 405–424. doi:10.1038/gim.2015.30.

**Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology**

**Sue Richards [Chair, ACMG],**

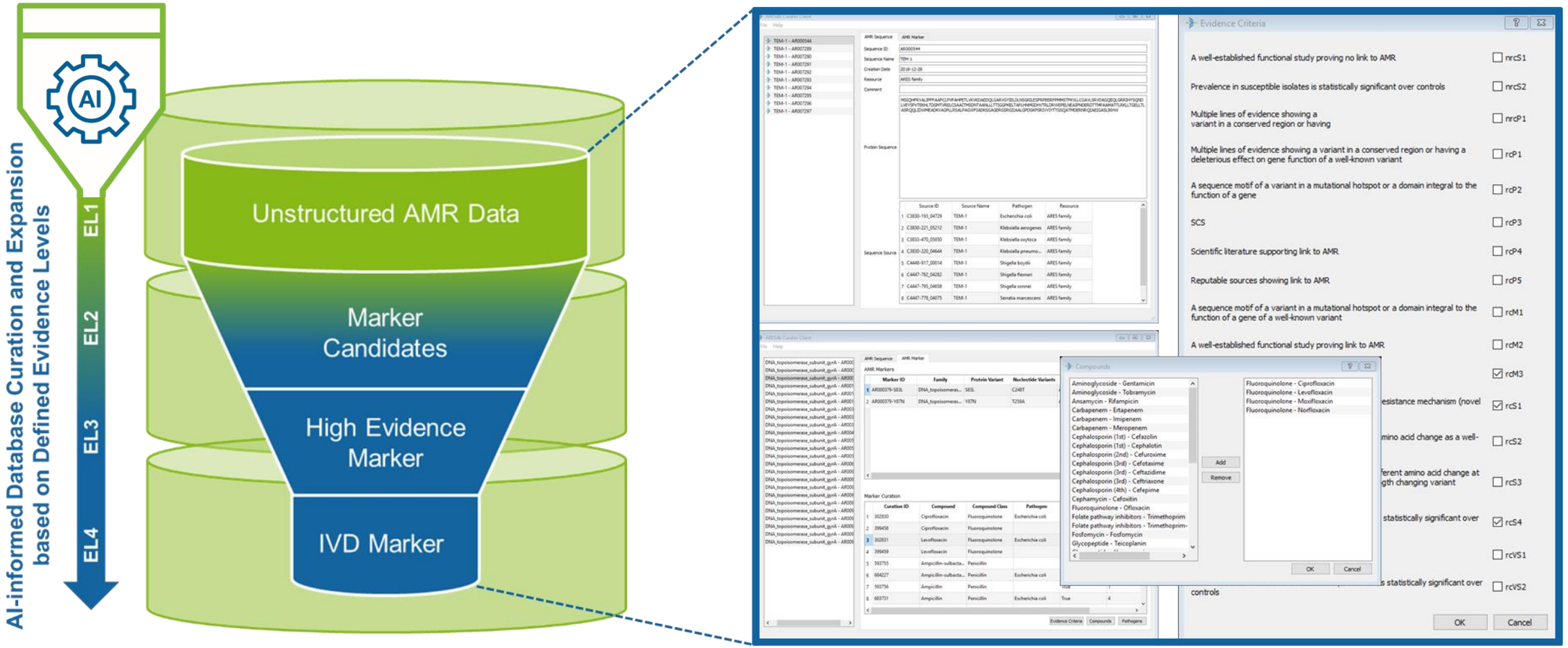
Knight Diagnostic Laboratories; Department of Molecular and Medical Genetics; Oregon Health & Science University, Portland, OR, USA

**Nazneen Aziz [CAP],**

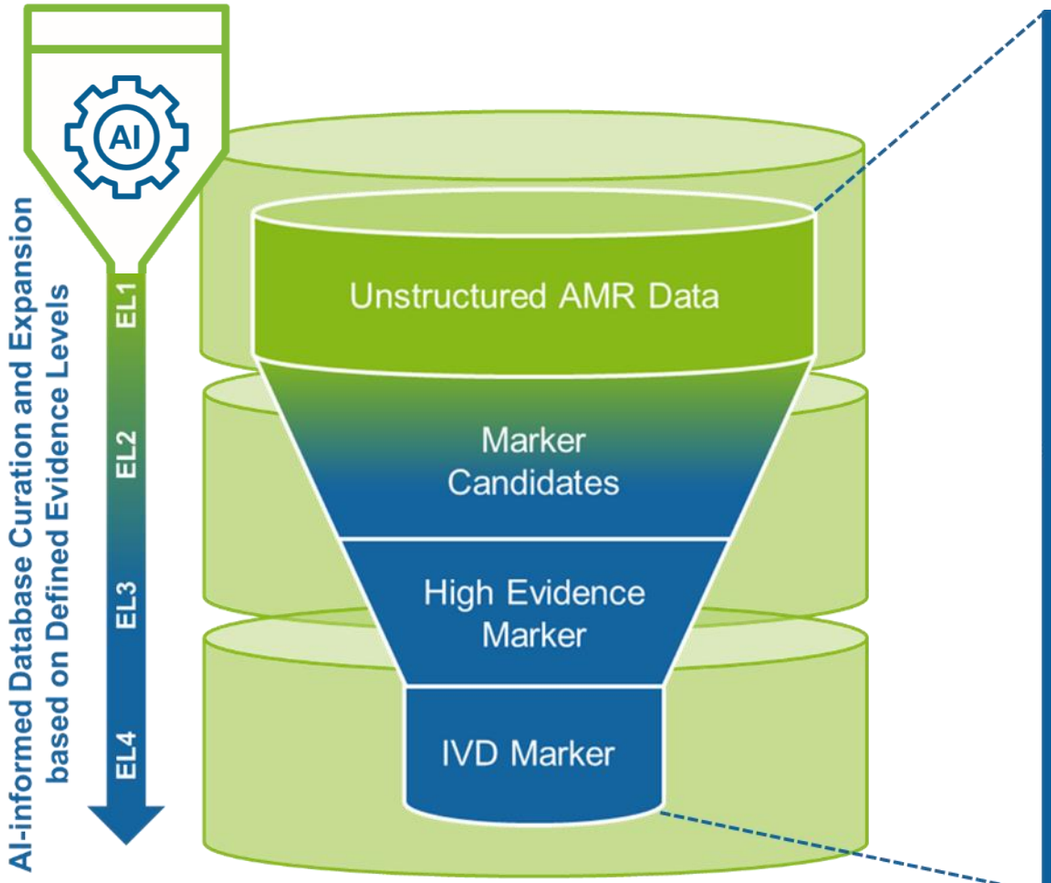
College of American Pathologists, Chicago, IL, USA

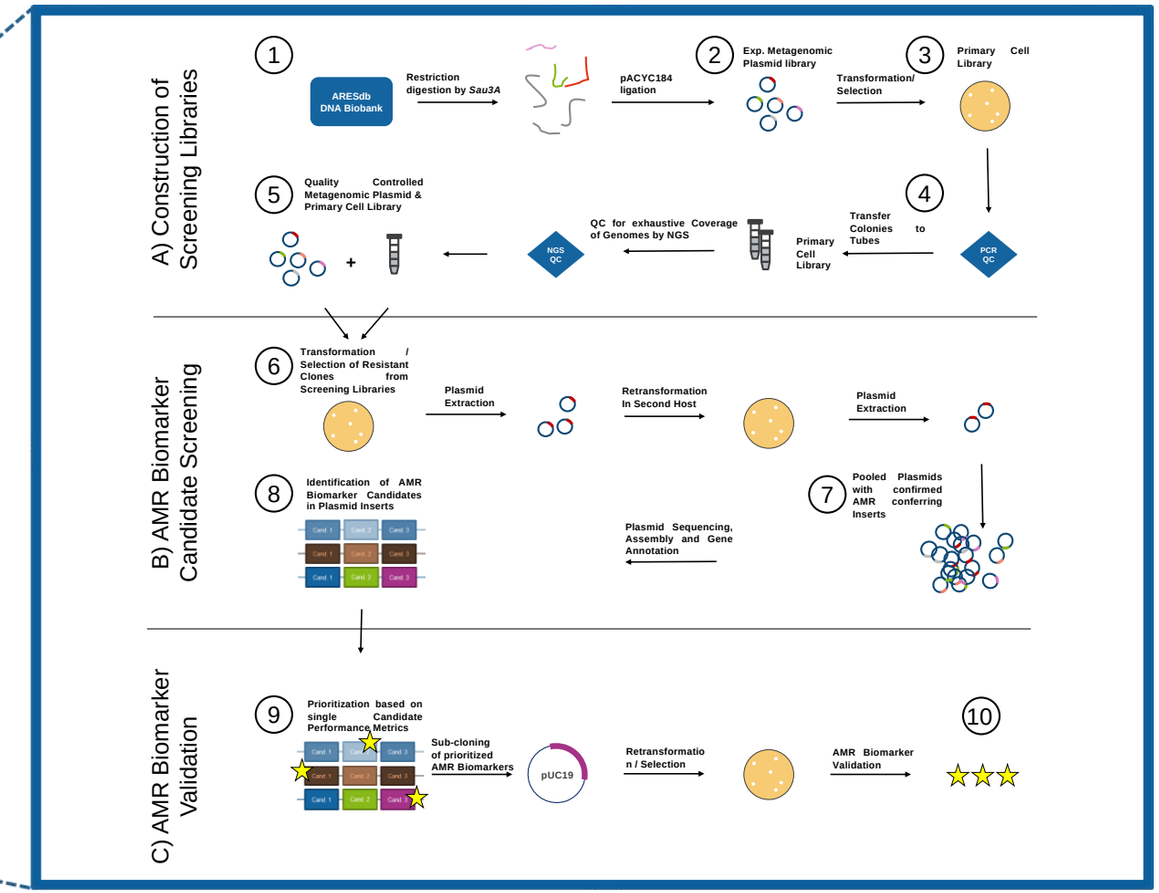
| | Benign | | Pathogenic | | | |
|---|---|---|---|---|---|---|
| | Strong | Supporting | Supporting | Moderate | Strong | Very Strong |
| **Population Data** | MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2* | | | Absent in population databases *PM2* | Prevalence in affecteds statistically increased over controls *PS4* | |
| **Computational And Predictive Data** | | Multiple lines of computational evidence suggest no impact on gene /gene product *BP4*<br>Missense in gene where only truncating cause disease *BP1*<br>Silent variant with non predicted splice impact *BP7* | Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3* | Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5*<br>Protein length changing variant *PM4* | Same amino acid change as an established pathogenic variant *PS1* | Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1* |
| **Functional Data** | Well-established functional studies show no deleterious effect *BS3* | | Missense in gene with low rate of benign missense variants and path. missenses common *PP2* | Mutational hot spot or well-studied functional domain without benign variation *PM1* | Well-established functional studies show a deleterious effect *PS3* | |
| **Segregation Data** | Non-segregation with disease *BS4* | | Co-segregation with disease in multiple affected family members *PP1* | Increased segregation data → | | |
| **De novo Data** | | | | *De novo* (without paternity & maternity confirmed) *PM6* | *De novo* (paternity & maternity confirmed) *PS2* | |
| **Allelic Data** | | Observed in *trans* with a dominant variant *BP2*<br>Observed in *cis* with a pathogenic variant *BP2* | | For recessive disorders, detected in *trans* with a pathogenic variant *PM3* | | |
| **Other Database** | | Reputable source w/out shared data = benign *BP6* | Reputable source = pathogenic *PP5* | | | |
| **Other Data** | | Found in case with an alternate cause *BP5* | Patient's phenotype or FH highly specific for gene *PP4* | | | |

# ARESdb: AI-POWERED AMR MARKER DISCOVERY, CLASSIFICATION, VALIDATION AND CURATION



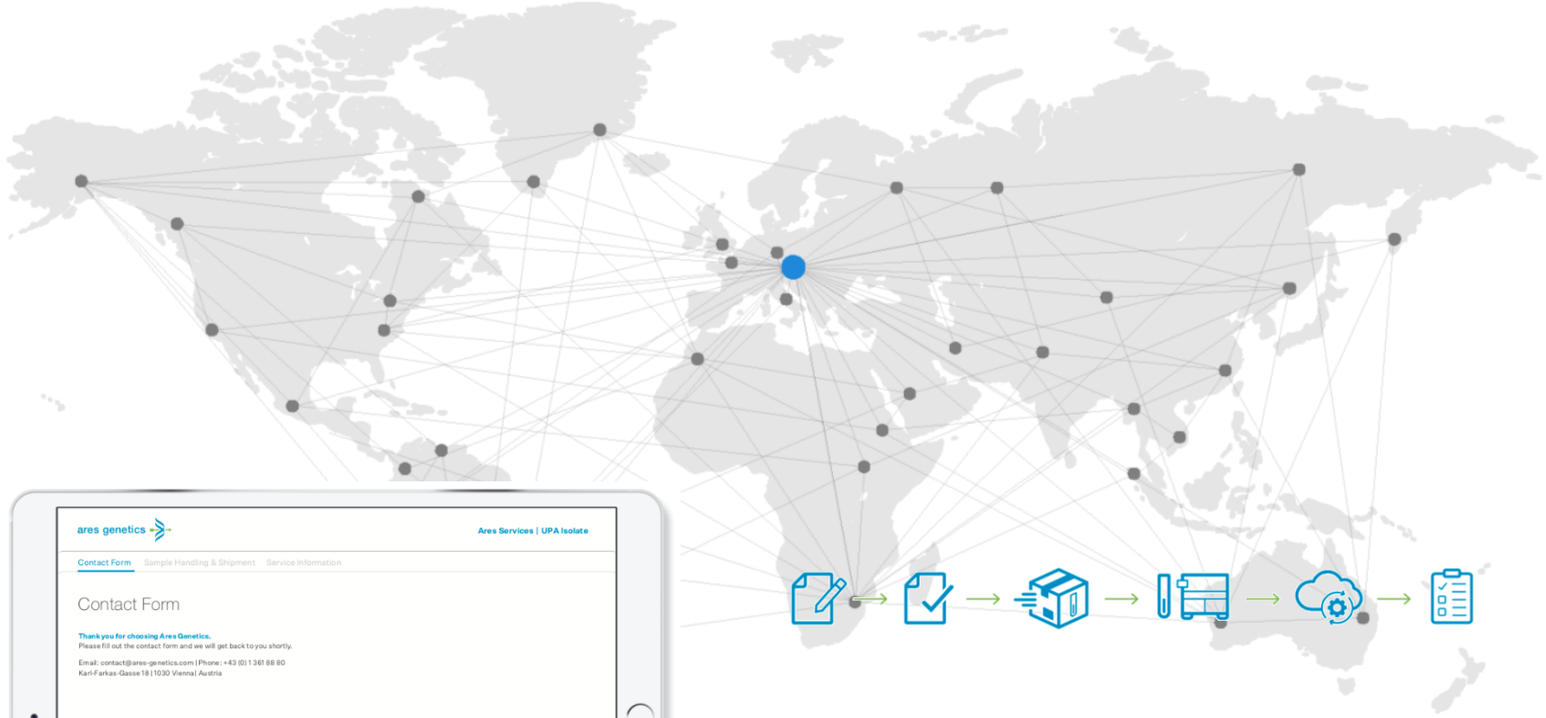
# ARESdb: PATENTED HIGH-THROUGHPUT FUNCTIONAL VALIDATION FOR HIGH-QUALITY IVD MARKER

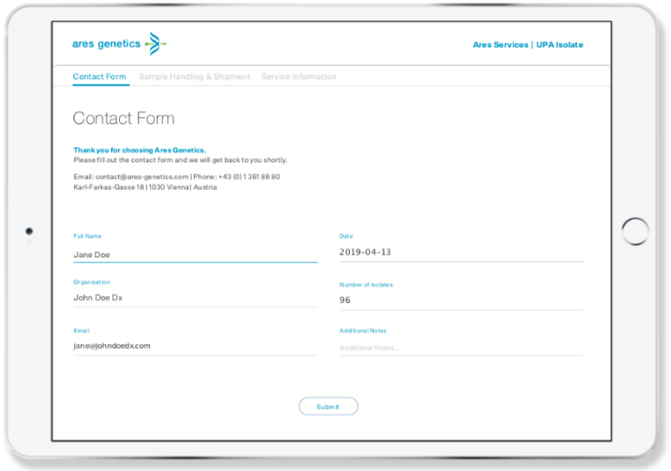



*Joint manuscript with HZI / Prof. Mueller in review*

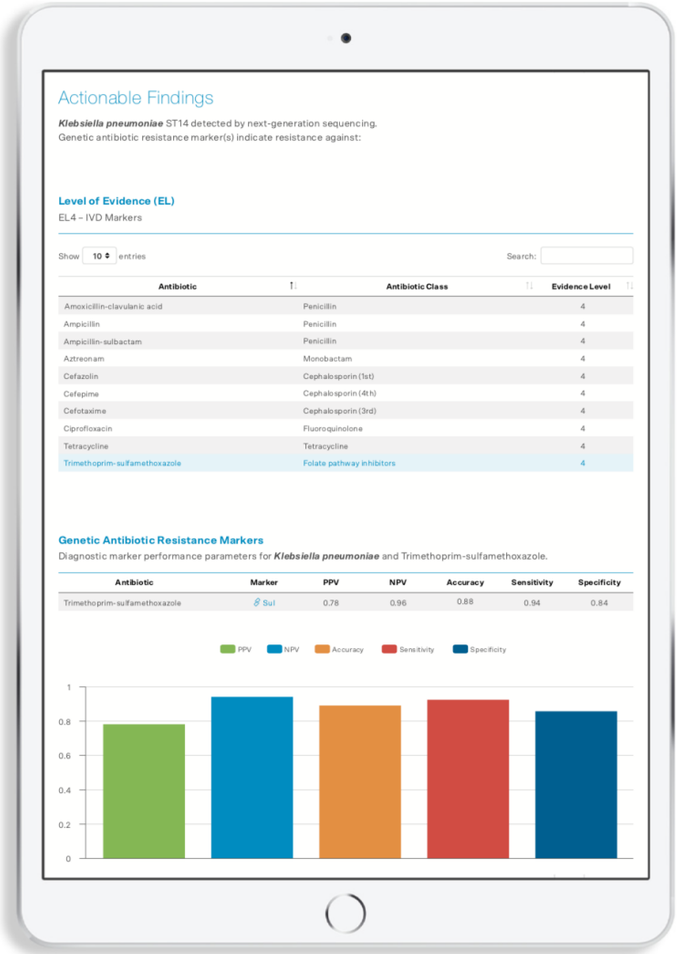
# AREScds: CLOUD-BASED DECISION SUPPORT SYSTEM TURNING NGS DATA INTO ACTIONABLE INSIGHTS








1. Register online at **ares-genetics.com**
2. Request a quote or order a test
3. Submit your isolates
4. Isolate profiling by next-generation sequencing via **ARESupa**
5. Strain identification and drug resistance detection by **ARESdb**
6. Interpret results, access and download reports via **ARESdb**



# OUR SOLUTIONS: FROM PUBLIC HEALTH AND PHARMA SERVICES TO DIAGNOSTIC SERVICES AND IVD PRODUCTS

| Offer | Customer | Need | Timeline |
|---|---|---|---|
| **IVD & SaaS Products** | **Healthcare Provider** | Early informed treatment by rapid near-patient testing for Hospital Acquired Infections | **tbd**<br>Under development |
| **Diagnostic Testing Services** | **Healthcare Provider** | Informed treatment in situations where current culture methods often fail and/or take > 3 days | **2020 (est.)**<br>Under development |
| **Public Health & Pharma Services** | **Healthcare Provider**<br>**Public Health Labs** | Infection control &<br>Outbreak monitoring | **Launched 2018** |
| | **Pharma Companies** | Accelerated drug development &<br>Improved drug positioning | |

ares-genetics.com

ares genetics

# ARESdb: ISOLATE SEQUENCING POWERED BY ARESdb

Contact | Service Information | Sample Handling & Shipment

## Contact Form

Thank you for visiting Ares Genetics.

Please fill out the form below and we will get back to you shortly.
We appreciate your interest and we look forward to working with you soon.

**Contact Details**

contact@ares-genetics.com
+43 (0) 1 361 8880

Karl-Farkas-Gasse 18
1030 Vienna
Austria

Service*
Clinical Isolate Sequencing

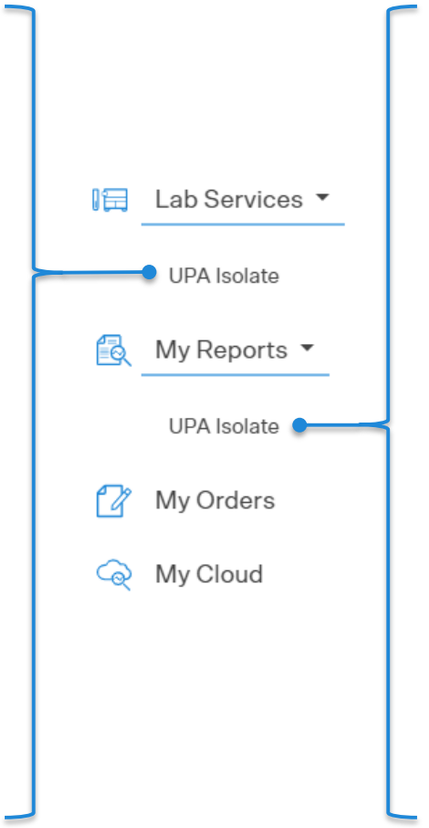
Full Name*
Stephan Beisken

Organisation*
Organisation

Email*
stephan.beisken@ares-genetics.com

Date*
2019-04-08

Number of Isolates*
96




## Isolate Listing

Isolates sequenced with the UPA Isolate service are listed by their tracking ID and isolate names.

For further information on a single isolate, please click on the isolate's row. This will bring up information on multiple locus sequence typing, antimicrobial resistance testing, assembly statistics and taxonomy identification.

Show 25 entries  Search:

| Isolate Name | Organism | ST | Origin | Date | Tracking ID | Report |
|---|---|---|---|---|---|---|
| AS012926 (DESF) | *Escherichia coli* | ST69 | | | | |
| AS012925 (R2746) | *Escherichia coli* | ST354 | | | | |
| AS012924 (R2745) | *Escherichia coli* | ST226 | | | | |
| AS012923 (R619) | *Serratia marcescens* | - | | | | |
| AS012922 (R208) | *Serratia marcescens* | - | | | | |
| AS012921 (R186) | *Pseudomonas aeruginosa* | ST1560 | | | | |
| AS012920 (R38) | *Providencia stuartii* | - | | | | |
| AS012919 (R494) | *Klebsiella pneumoniae* | ST70 | | | | |
| AS012918 (R179) | *Klebsiella pneumoniae* | ST14 | | | | |
| AS012917 (R24) | *Klebsiella pneumoniae* | ST14 | | | | |
| AS012239 (14C3) | *Klebsiella pneumoniae* | ST147 | | | | |
| AS012238 (13G2) | *Klebsiella pneumoniae* | ST307 | | | | |
| AS012237 (LANN) | *Escherichia coli* | ST12 | | | | |
| AS012236 (DESF) | *Escherichia coli* | ST69 | | | | |
| AS012235 (R2757) | *Escherichia coli* | ST5409 | | | | |
| AS012234 (R2752) | *Escherichia coli* | ST410 | | | | |
| AS012233 (R2746) | *Escherichia coli* | ST354 | | | | |

ares-genetics.com

| Isolate Name | Organism | ST | Origin | Date | Tracking ID | Report |
|---|---|---|---|---|---|---|
| AS012238 (13G2) | *Klebsiella pneumoniae* | ST307 | | | | |

ares genetics

# ARESdb: ISOLATE SEQUENCING POWERED BY ARESdb

## AS012238 (13G2)

Klebsiella pneumoniae

ares genetics

### Metadata

| Isolate Name | Organism | Taxonomy ID |
|---|---|---|
| AS012238 | *Klebsiella pneumoniae* | 573 |

| Country | Date | Tracking ID |
|---|---|---|
| | - | |

### Multilocus Sequence Typing

| Sequence Type | MLST Scheme |
|---|---|
| ST307 | kpneumoniae |

| gapA | infB | mdh | pgi | phoE | rpoB | tonB |
|---|---|---|---|---|---|---|
| 4 | 1 | 2 | 52 | 1 | 1 | 7 |

### Assembly Statistics

| Assembly | Quality Tier | GC Content |
|---|---|---|
| 13G2 | Tier 1 | 56.72% |

| Size | N50 | L50 |
|---|---|---|
| 5.9 Mbp | 104516 | 16 |

| Coding Sequences | tRNA Anticodons | rRNA Anticodons |
|---|---|---|
| 5491 | 19 | 3 |

## Actionable Findings

Genetic species identification detected ***Klebsiella pneumoniae***. Antibiotic resistance marker(s) indicate resistance against:

Level of Evidence (EL)

= EL4 - IVD Markers

Show 25 entries Search:

| Antibiotic | Antibiotic Class | Evidence Level |
|---|---|---|
| Amoxicillin-clavulanic acid | Penicillin | 4 |
| Ampicillin | Penicillin | 4 |
| Ampicillin-sulbactam | Penicillin | 4 |
| Aztreonam | Monobactam | 4 |
| Cefazolin | Cephalosporin (1st) | 4 |
| Cefepime | Cephalosporin (4th) | 4 |
| Cefotaxime | Cephalosporin (3rd) | 4 |
| Ciprofloxacin | Fluoroquinolone | 4 |
| Gentamicin | Aminoglycoside | 4 |
| Tetracycline | Tetracycline | 4 |
| Tobramycin | Aminoglycoside | 4 |
| Trimethoprim-sulfamethoxazole | Folate pathway inhibitors | 4 |

## Resistance Markers

Show 10 entries Search: sul2

| Antibiotic | Marker | Marker Family | PPV | NPV | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| Trimethoprim-sulfamethoxazole | Sul2 | Sul | 0.81 | 0.80 | 0.38 | 0.97 |

ares-genetics.com

| Isolate Name | Organism | ST | Origin | Date | Tracking ID | Report |
|---|---|---|---|---|---|---|
| AS012238 (13G2) | *Klebsiella pneumoniae* | ST307 | | | | |

ares genetics

# ARESdb: ISOLATE SEQUENCING POWERED BY ARESdb

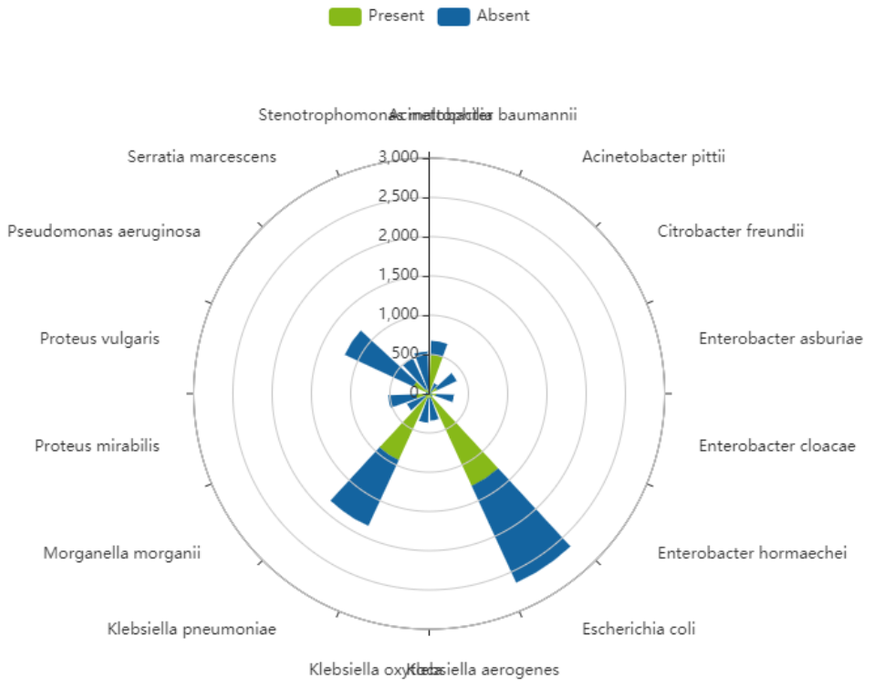
## Resistance Markers

Show 10 entries Search: sul2

| Antibiotic | Marker | Marker Family | PPV | NPV | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| Trimethoprim-sulfamethoxazole | Sul2 | Sul | 0.81 | 0.80 | 0.38 | 0.97 |

## Diagnostic Relevance

### Prevalence Among Affected Pathogens for family "Sul" (based on AREScdb)

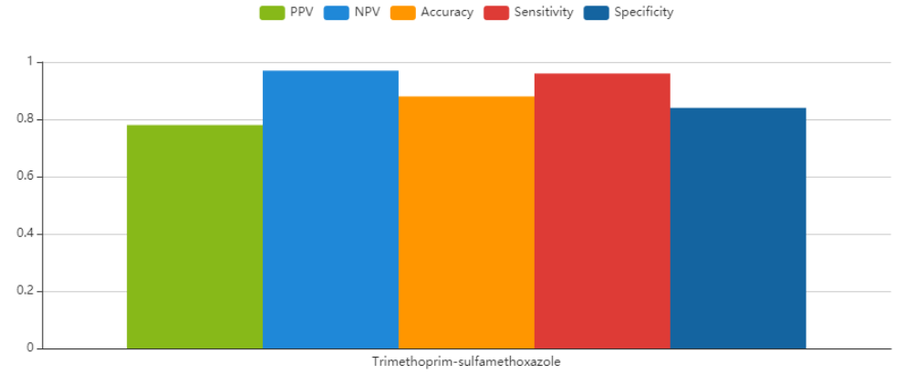


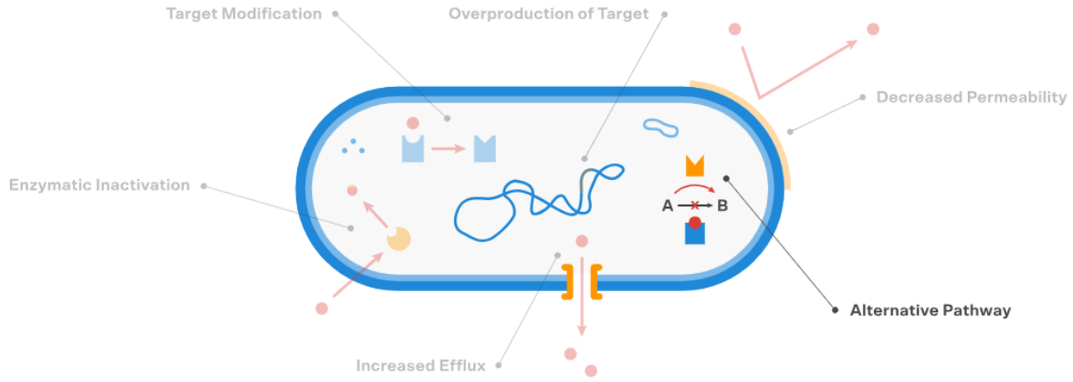

### Diagnostic Performance for family "Sul" (based on AREScdb)

Query Pathogen: Klebsiella pneumoniae

Query Antibiotic: Trimethoprim-sulfamethoxazole

Diagnostic marker performance parameters for *Klebsiella pneumoniae* and Trimethoprim-sulfamethoxazole

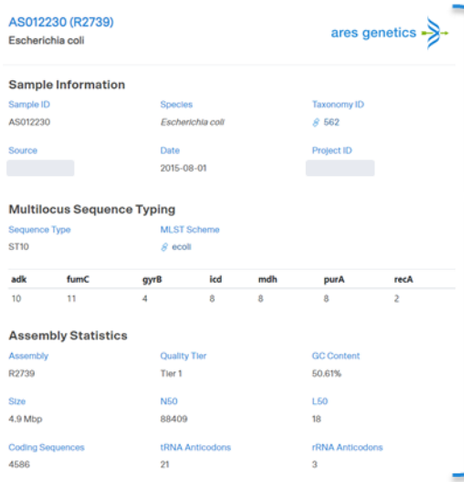


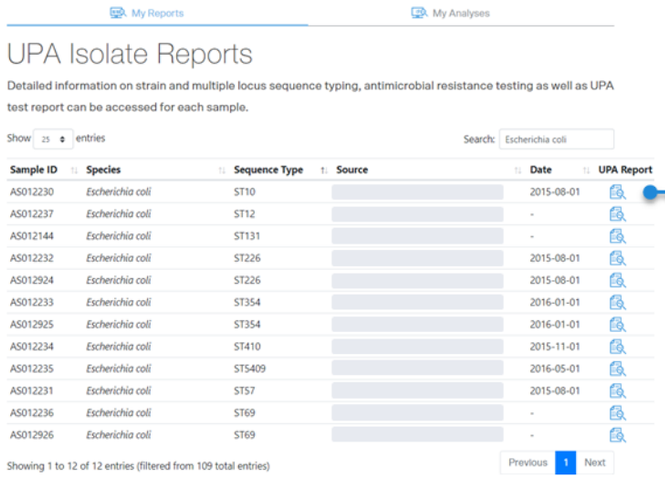



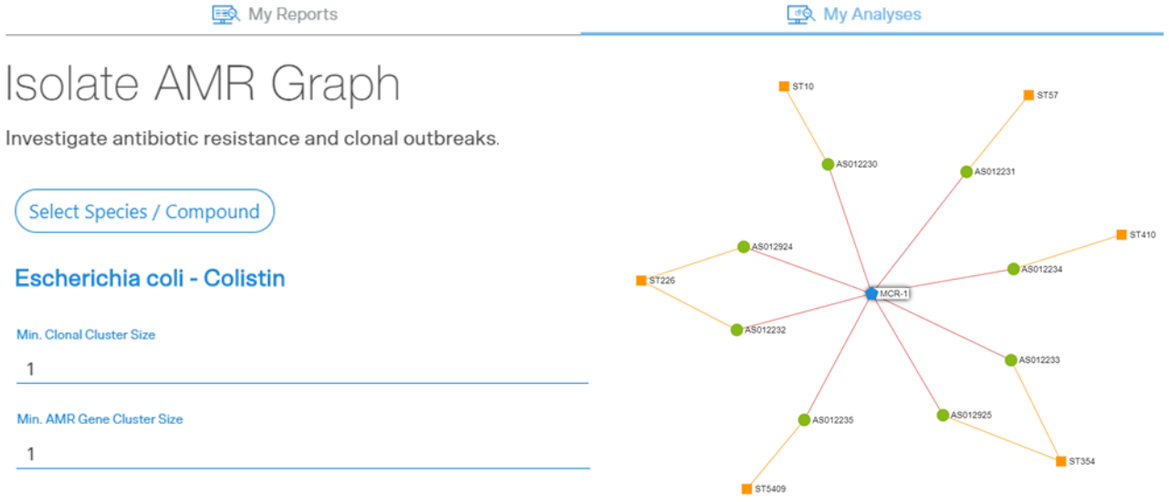
ares-genetics.com

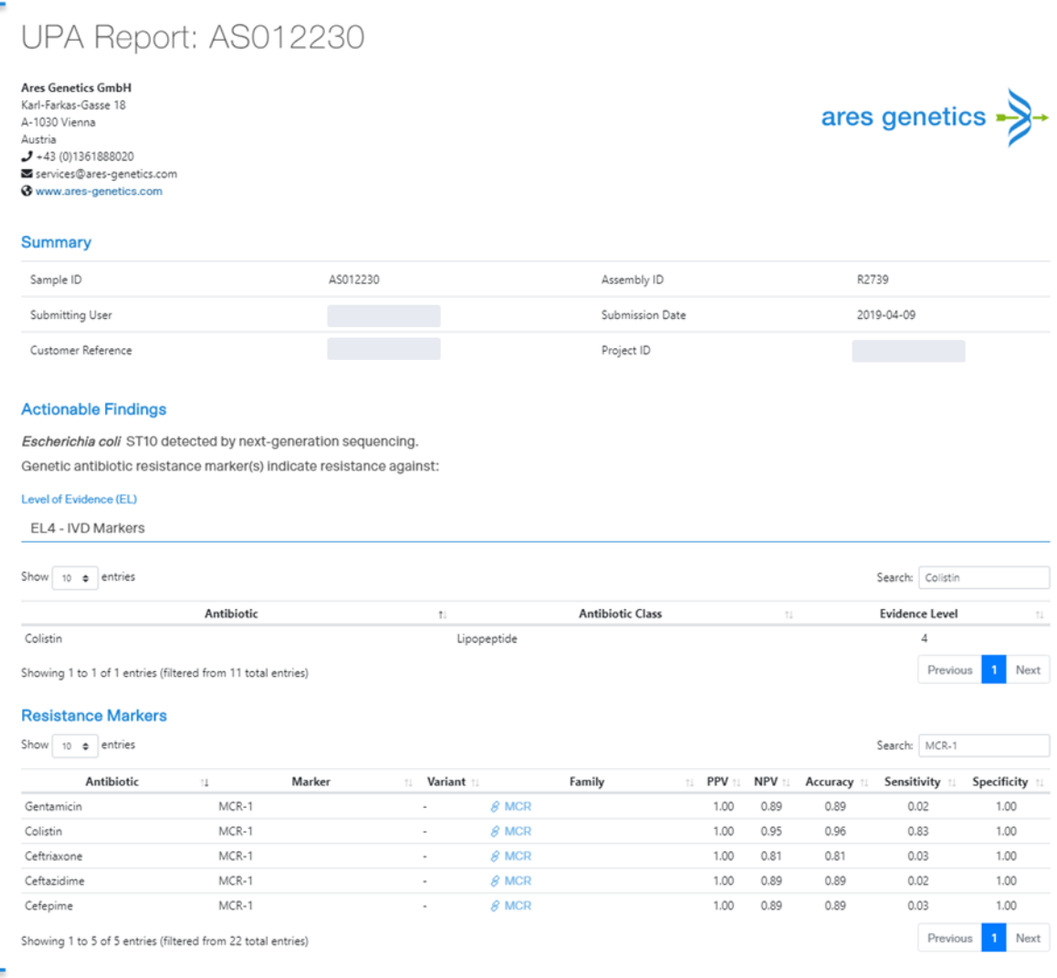
ares genetics

# ARESCds: DETAILED INTERACTIVE REPORTS PER STUDY & SAMPLE | MCR-1 CASE STUDY



Get in Contact for Early Access !

ares genetics

# ARESdb | DIAGNOSTIC PERFORMANCE: VERIFIED PANELS FOR >150 BUG / DRUG COMBINATIONS – GROWING FAST

ares genetics

- Home
- Lab Services
- My Orders
- My Reports
- My Cloud
- ARESdb
  - Dashboard
  - AMR Panels
  - AMR Search
  - AMR Statistics
- AMR Cards

## ARESdb AMR Marker Panels

### Summary

ARESdb enables molecular detection of antibiotic resistance for > 150 pathogen / drug combinations with up to 98% accuracy. More than 50 ARESdb AMR Marker Panels have already been optimized for *research use only* as part of ARESupa Universal Pathogenome Assay.

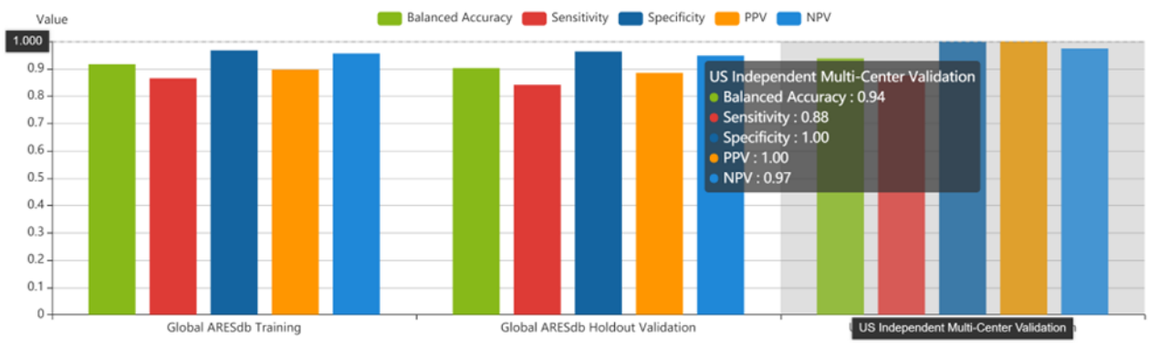
### Pathogen/Compound Panels

Select Pathogen: Klebsiella pneumoniae

Select Antibiotic: Gentamicin

Query

### Panel Performance



# ARES GENETICS: ACTIONABLE INSIGHTS FOR AMR DIAGNOSTICS AND DRUG DEVELOPMENT

QIAGEN

ABOUT US INVESTOR RELATIONS NEWSROOM CAREERS

HOME › NEWSROOM › PRESS RELEASES › QIAGEN PARTNERS WITH ARES GENETICS

FEB 18 2019

QIAGEN partners with Ares Genetics to advance global fight against antibiotic-resistant pathogens

Developing Sample to Insight solutions to accelerate research on growing public health threat

Hilden, Germany, Holzgerlingen, Germany, ar
2019 – QIAGEN N.V. (NYSE: QGEN; Frankfurt Pri
a broad agreement with Ares Genetics, a subsidiary
develop innovative bioinformatics and assay solution
growing global health challenges posed by antibioti

QIAGEN has acquired an exclusive license to levera
antimicrobial resistance database, ARESdb, as well
from the ARES Technology Platform, ARESTools, in Q
services for researchers. QIAGEN also obtained a n
develop and commercialize molecular research assa
QIAGEN next-generation sequencing (NGS) and pc
solutions. Powered by artificial intelligence, ARESdb
and continuously updated proprietary knowledge ba
markers and their diagnostic relevance.

**Sandoz teams up to drive cutting-edge digital solutions in global fight against antimicrobial resistance (AMR)**

Dec 18, 2018

- *Strategic collaboration agreement with Curetis subsidiary Ares Genetics to develop digital platform for development and life-cycle management of antibiotics*
- *Program will combine established microbiology laboratory techniques with advanced bioinformatics and AI methods*
- *Short-term focus on repurposing existing antibiotics to treat infections involving multi-drug-resistant pathogens*

**Holzkirchen, December 18, 2018 –** Sandoz today announces the signature of a strategic collaboration agreement with Ares Genetics GmbH, to jointly develop a digital platform for development and life-cycle management of antibiotics.

**QIAGEN and ARES** to develop BioIT AMR Community Platform. Preferred access to Ares Genetics‘ partners contributing to ARESdb.

**SANDOZ and ARES** build on ARESdb for development of combination therapies & optimal drug positioning.

**BGI and ARES** develop integrated NGS-based workflows for infectious disease diagnostics.

**ARES** listed by Forbes as **leading AI start-up**

…

## JOIN THE FIGHT!
## TALK TO US!

# LET'S TAKE INFECTIOUS DISEASE TESTING TO THE NEXT LEVEL. TOGETHER.

## ACKNOWLEDGEMENTS


CHAIR FOR CLINICAL BIOINFORMATICS
SAARLAND UNIVERSITY

Andreas Keller
Valentina Galata
Christina Backes
Cédric Christian Laczny

华大基因 BGI  MGI 华大智造

Yong Chen
Chunyang Zhang
Jing Zou
Jinjing Wang
Yongping Li
Roy Tan et al.

SIEMENS

SIEMENS Healthineers

Susanne Schmolke
Howard Li
Laura Smoot
Patrick Froese
Holger Quast
Cord Stähler

Helmholtz-Institut für Pharmazeutische Forschung Saarland
HELMHOLTZ ZENTRUM FÜR INFEKTIONSFORSCHUNG
UNIVERSITÄT DES SAARLANDES

Rolf Müller
Carsten Volz


## CONTACT


Dr. Andreas Posch
Managing Director & CEO
Ares Genetics GmbH
Karl-Farkas-Gasse 18
1030 Vienna
Austria
andreas.posch@ares-genetics.com
+43 664 4377 196


ares genetics

www.ares-genetics.com