AMRrules

Interpretive Standards for AMR Genotypes

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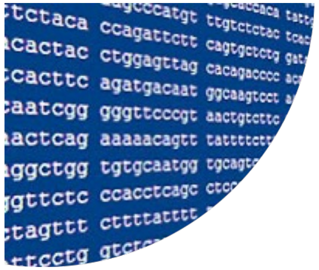
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

ESCMID ESGEM-AMR

amrrules.org

MONASH University



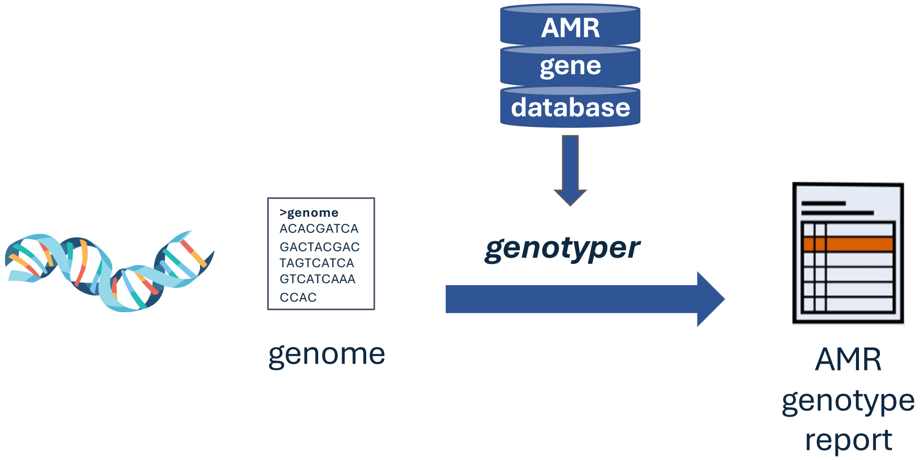
Genomics for AMR

- AMR evolution & spread at different scales
- Epidemiology and transmission of AMR infections
- Outbreak investigation
- Hospital infection prevention & control (IPC)
- Sequence-based detection and diagnostics
- Public health disease surveillance
- Enviro detection & One Health AMR surveillance

Assay: Genotyping AMR determinants in bacterial genomes

Ecosystem of bioinformatics tools and resources

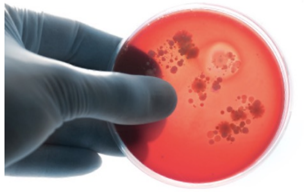
- ✓ **Databases** of AMR determinants - *NCBI, CARD, ResFinder*
- ✓ **Genotypers** to identify these in genomes – *AMRFinderPlus, CARD RGI, species-specific tools*



Missing rules for interpretation

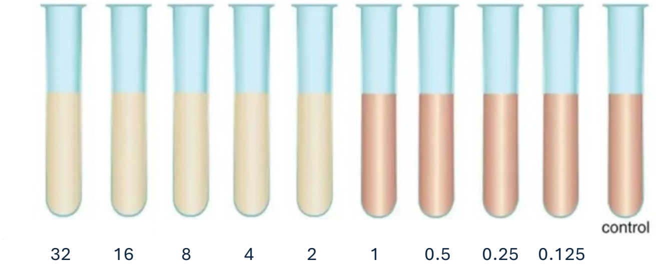
What does **variant X** in **species Y** mean for **drug Z?**

Interpretive standards for phenotypes



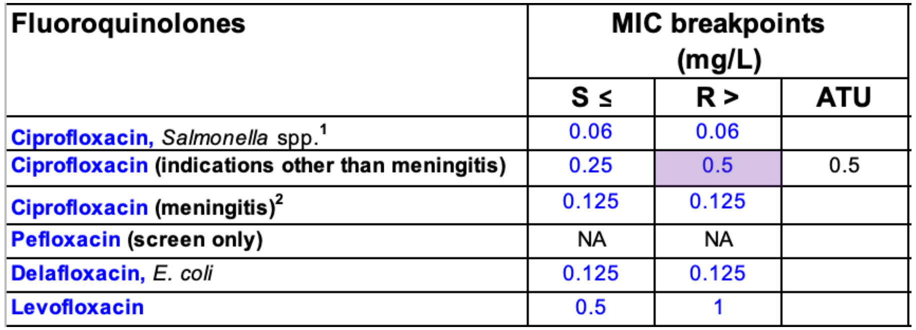
K. pneumoniae

Assay (microbroth dilution)



Ciprofloxacin concentration

EUCAST BreakpointTables

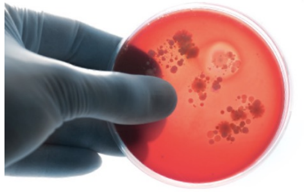


Fluoroquinolones	MIC breakpoints (mg/L)		
	S ≤	R >	ATU
Ciprofloxacin, *Salmonella* spp.[1]	0.06	0.06	
Ciprofloxacin (indications other than meningitis)	0.25	0.5	0.5
Ciprofloxacin (meningitis)[2]	0.125	0.125	
Pefloxacin (screen only)	NA	NA	
Delafloxacin, *E. coli*	0.125	0.125	
Levofloxacin	0.5	1	

Assay Result: MIC=2 mg/L

Interpretation: Ciprofloxacin resistant

Interpretive standards for genotypes



K. pneumoniae

Assay (WGS +AMRFinderPlus)

“expert rules”

Genotype result: *qnrS1*, *gyrA* p.Ser83Tyr

Interpretation: Ciprofloxacin resistant

Interpretation vs prediction

EUCAST interpretations (eucast.org)

S - high likelihood of therapeutic success (using standard dosing regimen)

I - high likelihood of therapeutic success (when exposure is increased)

R - high likelihood of therapeutic failure even with increased exposure

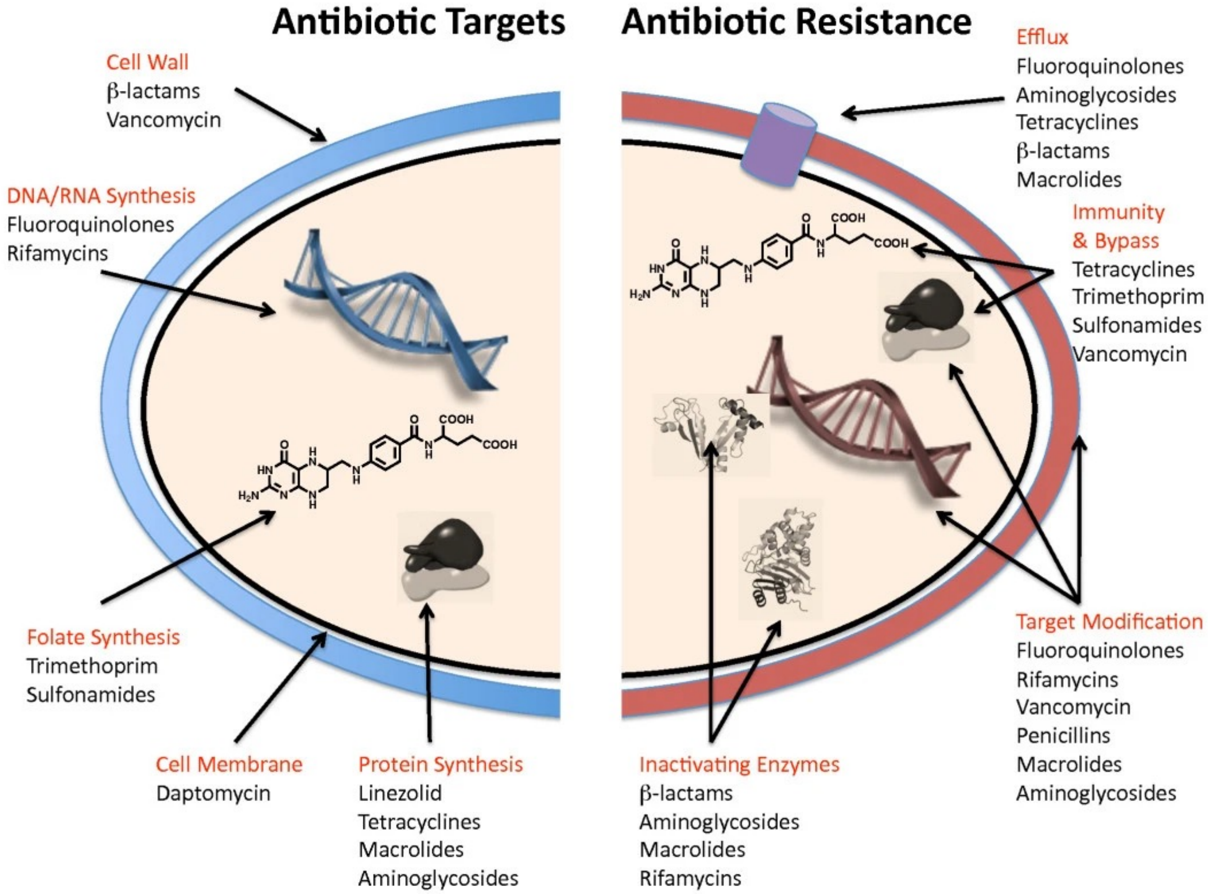
Interpretation…
understand assay data, including what it means for treatment

Prediction…
anticipate outcome for a given treatment, for a specific patient and context

AMR genotypes often interpreted *alongside* phenotypic assay measures, the goal is not to predict those assay measures

Collective knowledge of AMR genetics

Biological complexity of AMR



Antibiotic Targets

Cell Wall
β-lactams
Vancomycin

DNA/RNA Synthesis
Fluoroquinolones
Rifamycins

Folate Synthesis
Trimethoprim
Sulfonamides

Cell Membrane
Daptomycin

Protein Synthesis
Linezolid
Tetracyclines
Macrolides
Aminoglycosides

Antibiotic Resistance

Efflux
Fluoroquinolones
Aminoglycosides
Tetracyclines
β-lactams
Macrolides

Immunity
& Bypass
Tetracyclines
Trimethoprim
Sulfonamides
Vancomycin

Target Modification
Fluoroquinolones
Rifamycins
Vancomycin
Penicillins
Macrolides
Aminoglycosides

Inactivating Enzymes
β-lactams
Aminoglycosides
Macrolides
Rifamycins

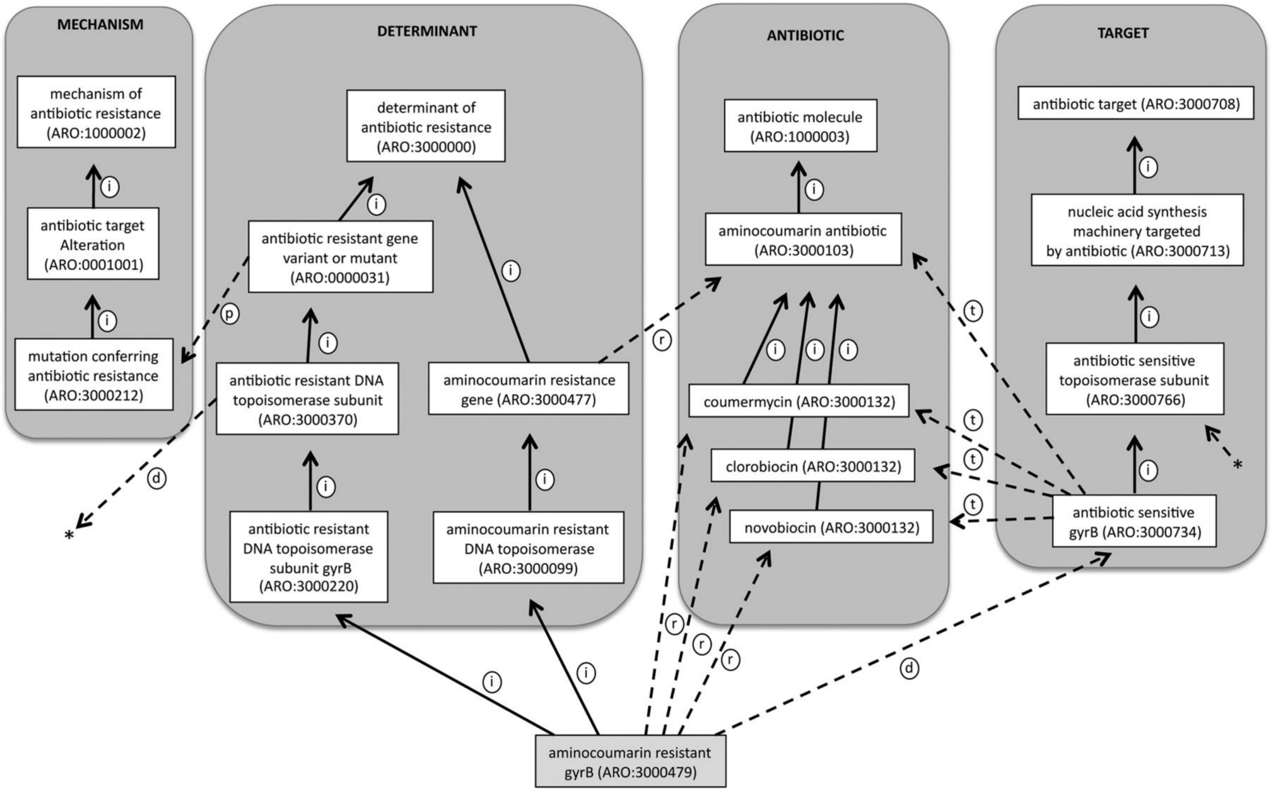
Wright GD, *BMC Biology* 2010

The Comprehensive Antibiotic Resistance Database

A bioinformatic database of resistance genes, their products and associated phenotypes.

7253 Ontology Terms, 5230 Reference Sequences, 1960 SNPs, 3310 Publications, 5278 AMR Detection Models

Resistome predictions: 413 pathogens, 24291 chromosomes, 2662 genomic islands, 48212 plasmids, 172216 WGS assemblies, 276270 alleles



card.mcmaster.ca

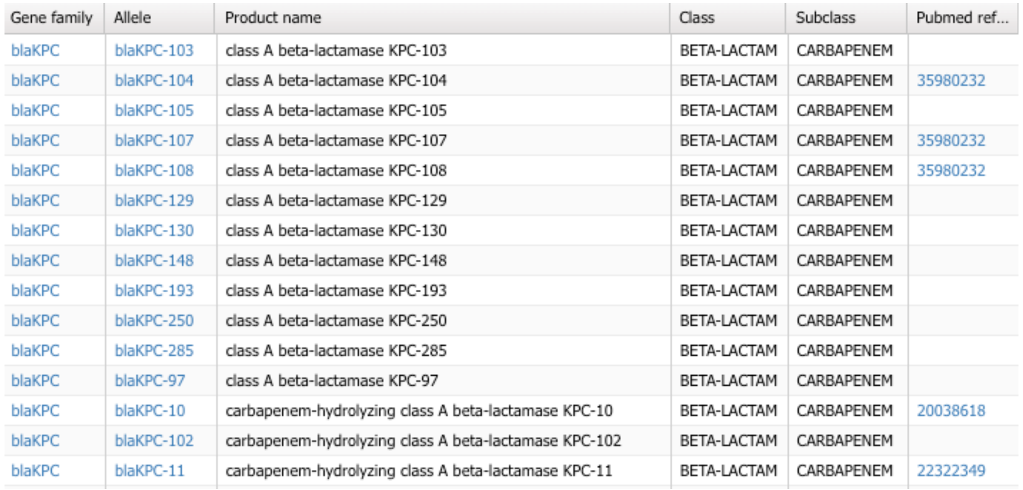
refgene

Reference sequences:

- 8,302 AMR-associated genes
- 1,528 AMR-associated mutations

Linked PubMed IDs:

- 42% of genes
- 27% of mutations



Gene family	Allele	Product name	Class	Subclass	Pubmed ref...
blaKPC	blaKPC-103	class A beta-lactamase KPC-103	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-104	class A beta-lactamase KPC-104	BETA-LACTAM	CARBAPENEM	35980232
blaKPC	blaKPC-105	class A beta-lactamase KPC-105	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-107	class A beta-lactamase KPC-107	BETA-LACTAM	CARBAPENEM	35980232
blaKPC	blaKPC-108	class A beta-lactamase KPC-108	BETA-LACTAM	CARBAPENEM	35980232
blaKPC	blaKPC-129	class A beta-lactamase KPC-129	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-130	class A beta-lactamase KPC-130	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-148	class A beta-lactamase KPC-148	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-193	class A beta-lactamase KPC-193	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-250	class A beta-lactamase KPC-250	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-285	class A beta-lactamase KPC-285	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-97	class A beta-lactamase KPC-97	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-10	carbapenem-hydrolyzing class A beta-lactamase KPC-10	BETA-LACTAM	CARBAPENEM	20038618
blaKPC	blaKPC-102	carbapenem-hydrolyzing class A beta-lactamase KPC-102	BETA-LACTAM	CARBAPENEM	
blaKPC	blaKPC-11	carbapenem-hydrolyzing class A beta-lactamase KPC-11	BETA-LACTAM	CARBAPENEM	22322349

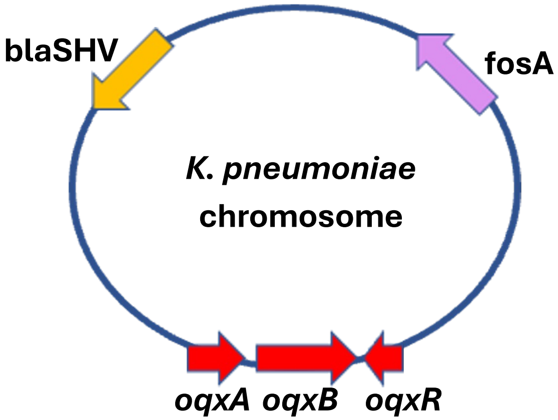
ncbi.nlm.nih.gov/pathogens/refgene/

AMRFinderPlus output for wildtype *Klebsiella pneumoniae*

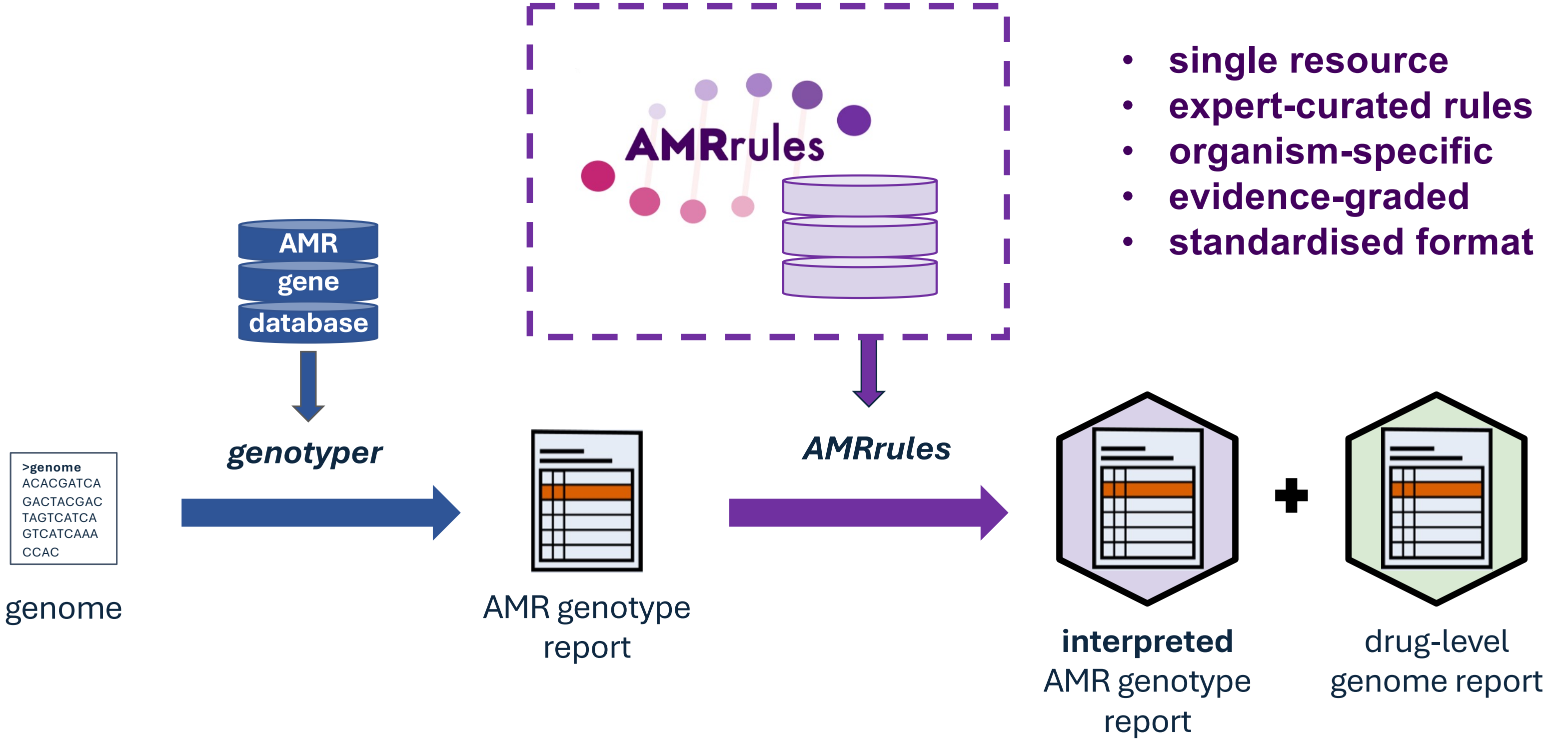
***K. pneumoniae* str. SGH10**

Gene symbol	Class	Subclass
blaSHV-11	BETA-LACTAM	BETA-LACTAM
fosA	FOSFOMYCIN	FOSFOMYCIN
oqxA	PHENICOL/QUINOLONE	PHENICOL/QUINOLONE
oqxB19	PHENICOL/QUINOLONE	PHENICOL/QUINOLONE

all are **core genes** in this species



Concept: expert “rules” for interpreting genotypes



- single resource
- expert-curated rules
- organism-specific
- evidence-graded
- standardised format

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Implementation: Phase 1

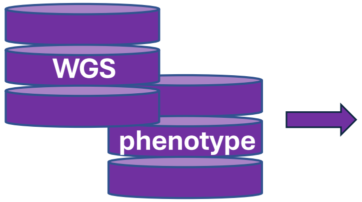
- ✓ **Establish working group**
  esgem-amr.amrrules.org

- ✓ **Develop rule specification and interpretation engine**
  spec.amrrules.org

- ✓ **Expert subgroups define rules**
  browse.amrrules.org

Working Group: ESCMID Study Group on Epidemiological Markers (ESGEM)-AMR

esgem-amr.amrrules.org



ESCMID | ESGEM-AMR

- Expert curation
- Matched genome/phenotype data
- Link to phenotype rules

ESKAPEE / WHO AMR Priority Pathogens
Acinetobacter baumannii
Enterococcus
Enterobacter cloacae complex
E. coli/Shigella
Klebsiella pneumoniae
Staphylococcus
Pseudomonas aeruginosa
Neisseria gonorrhoeae
Salmonella
Serratia
Campylobacter spp.
Mycobacterium tuberculosis
Bordetella
Burkholderia pseudomallei
Legionella
Neisseria meningitidis
Proteus mirabilis
Shewanella
Yersinia
...more in progress

~200 members

Rule specification

spec.amrrules.org

Specify the variant to which a rule applies

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gene	nodeID	protein accession	nucleotide accession	mutation	variation type
16S	-	-	NZ_AP019853.2: 1155759-1157299	c.1191C>T	Nucleotide variant detected
23S	-	-	NC_002946.2: 1119158-1116249	c.[2059A>G][4]	Nucleotide variant detected in multi-copy gene
blaTEM-1	blaTEM-1	WP_000027057.1	-	-	Gene presence detected
gyrA	gyrA	WP_033785346.1	-	p.Ser91Phe	Protein variant detected
mtrC	mtrC	-	NZ_CP012026.1: 1110850-1110550	c.-120C>T	Promoter variant detected
mtrD	mtrD	WP_003695678.1	-	-	Inactivating mutation detected
NG1 & NG2	-	-	-	-	Combination

RefSeq

at least ONE required to uniquely identify a reference seq

HGVS

hAMRonization

Specify the phenotypic interpretation

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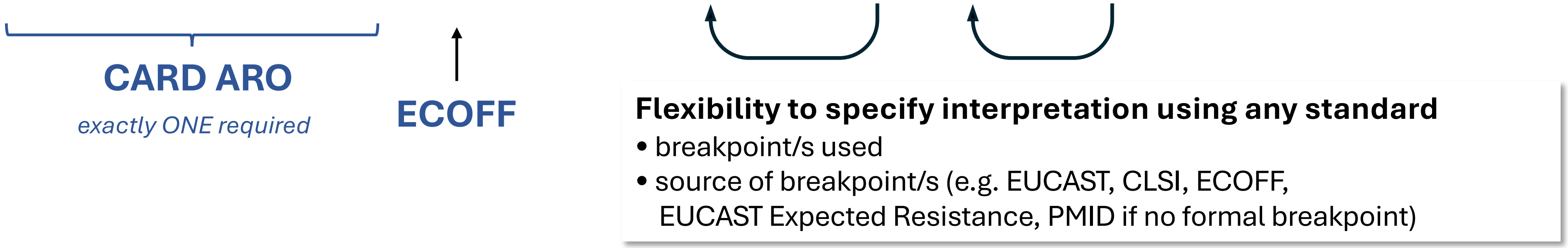
drug	drug class	phenotype	clinical category	breakpoint	breakpoint standard
spectinomycin	-	nonwildtype	R	MIC >64 mg/L	EUCAST v14.0 (2024)
azithromycin	-	nonwildtype	R	MIC >1 mg/L	ECOFF (January 2024)
benzylpenicillin	-	nonwildtype	R	MIC >1 mg/L	EUCAST v14.0 (2024)
ciprofloxacin	-	nonwildtype	R	MIC >0.06 mg/L	EUCAST v14.0 (2024)
azithromycin	-	nonwildtype	S	MIC <=1 mg/L	ECOFF (January 2024)
azithromycin	-	wildtype	S	MIC <=1 mg/L	ECOFF (January 2024)



CARD ARO

exactly ONE required

ECOFF

Flexibility to specify interpretation using any standard

- breakpoint/s used
- source of breakpoint/s (e.g. EUCAST, CLSI, ECOFF, EUCAST Expected Resistance, PMID if no formal breakpoint)

Specify the evidence supporting a rule

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PMID	evidence code	evidence grade	evidence limitations	curation note
2138078, 10770780	ECO:0001103 natural variation mutant evidence, ECO:0001113 point mutation phenotypic evidence	moderate	statistical geno/pheno evidence but no experimental evidence	...
20585125	ECO:0001103 natural variation mutant evidence	high	-	...
11585791, 25149062	ECO:0000005 enzymatic activity assay evidence	high	-	...
7830580, 11181352	ECO:0005027 genetic transformation evidence, ECO:0001103 natural variation mutant evidence	high	-	...
18761689	ECO:0005027 genetic transformation evidence	moderate	low clinical relevance	...
9534233	ECO:0005027 genetic transformation evidence	moderate	lacks evidence of the degree to which MIC is affected	...

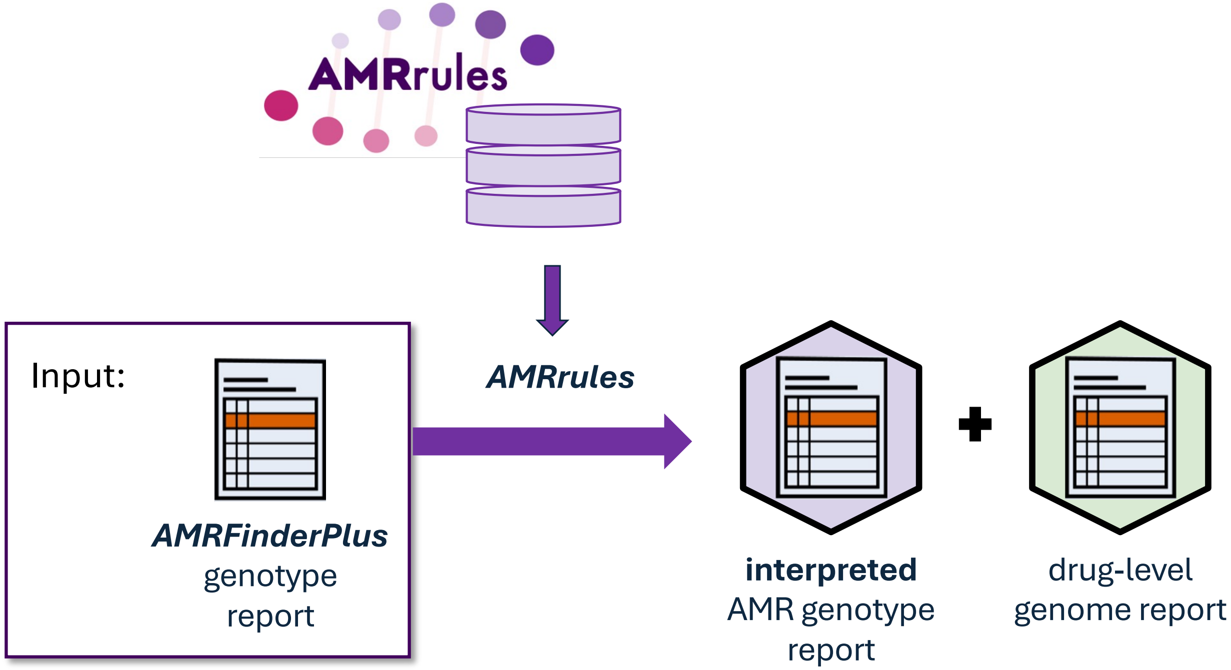
PubMed

Evidence & Conclusion Ontology

AMRrules (GRADE)

AMRrules (controlled terms)

Interpretation engine: AMRrules (Python package)



Input:

AMRFinderPlus genotype report

AMRrules

interpreted AMR genotype report

drug-level genome report

Jane Hawkey
Monash University
Bioinformatics Lead, AMRrules

docs.amrrules.org

amrrules.org

Output 1: Annotated genotype report

Example interpreted summary output for wildtype *Klebsiella pneumoniae* str. SGH10

Name	Gene symbol	Class	Subclass	Hierarchy node
SGH10	emrD	EFFLUX	EFFLUX	emrD
SGH10	oqxB19	PHENICOL/ QUINOLONE	PHENICOL/ QUINOLONE	oqxB19
SGH10	oqxA	PHENICOL/ QUINOLONE	PHENICOL/ QUINOLONE	oqxA
SGH10	blaSHV-11	BETA-LACTAM	BETA-LACTAM	blaSHV-11
SGH10	fosA	FOSFOMYCIN	FOSFOMYCIN	fosA5_fam

AMRFinderPlus output

(abbreviated example)

Output 1: Annotated genotype report

Example interpreted summary output for wildtype *Klebsiella pneumoniae* str. SGH10

Name	Gene symbol	Class	Subclass	Hierarchy node	ruleID	context	drug	drug class	phenotype	clinical category	evidence grade	version	organism
SGH10	emrD	EFFLUX	EFFLUX	emrD	-	-	-	-	-	-	-	1.0	-
SGH10	oqxB19	PHENICOL/ QUINOLONE	PHENICOL/ QUINOLONE	oqxB19	KPN0003	core	ciprofloxacin	-	wildtype	S	moderate	1.0	s__Klebsiella pneumoniae
SGH10	oqxA	PHENICOL/ QUINOLONE	PHENICOL/ QUINOLONE	oqxA	KPN0002	core	ciprofloxacin	-	wildtype	S	moderate	1.0	s__Klebsiella pneumoniae
SGH10	blaSHV-11	BETA-LACTAM	BETA-LACTAM	blaSHV-11	KPN0001	core	-	**penicillin beta-lactam**	**wildtype**	**R**	high	1.0	s__Klebsiella pneumoniae
SGH10	fosA	FOSFOMYCIN	FOSFOMYCIN	fosA5_fam	KPN0004	core	fosfomycin	-	wildtype	S	moderate	1.0	s__Klebsiella pneumoniae

NCBI **AMRFinderPlus output**

AMRrules **genotype interpretation**

(abbreviated example)

Output 2: Drug-level genome summary

Example genome summary output for wildtype *Klebsiella pneumoniae* str. SGH10

drug	drug class	clinical category	phenotype	evidence grade	markers (non-S)	markers (no rule)	markers (S)	ruleIDs	combo rules	organism
ciprofloxacin	fluoroquinolone antibiotic	S	wildtype	moderate	-	-	oqxB19 (core); oqxA (core)	KPN0002; KPN0003	-	s__Klebsiella pneumoniae
(all)	**penicillin beta-lactam**	**R**	**wildtype**	high	blaSHV-11 (core)	-	-	KPN0001	-	s__Klebsiella pneumoniae
fosfomycin	phosphonic acid antibiotic	S	wildtype	moderate	-	-	fosA (core)	KPN0004	-	s__Klebsiella pneumoniae
(n/a)	antibiotic efflux	-	-	none	-	emrD	-	-	-	s__Klebsiella pneumoniae

interpretation

basis for it

Rule curation

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AMRrules v1.0 1,272 rules defined in 32 species

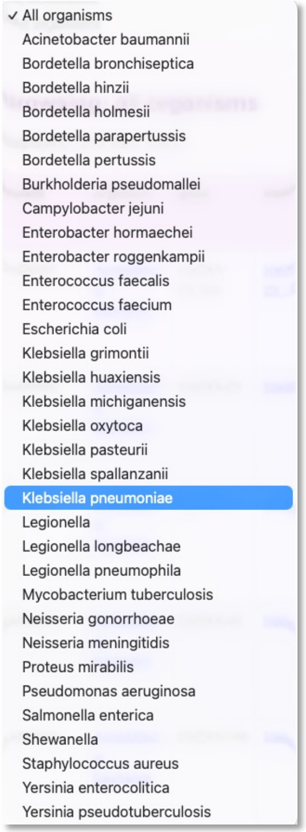
Priorities

- ✓ Core genes in key AMR pathogens (ESKAPEE + WHO priority list)
- ✓ Phenotypes defined by EUCAST
- ✓ Compatible with AMRFinderPlus & NCBI databases

Browsing: Klebsiella pneumoniae

Displaying 7 row(s).

ruleID	organism	gene	mutation	variation type	gene context	drug	drug class	phenotype	clinical category	breakpoint standard	PMID	evidence gr…	evidence limitations
KPN0001	Klebsiella pneumoniae	blaSHV	-	Gene presence detected	core	-	penicillin beta-lactam	wildtype	R	EUCAST Expected resistant phenotypes v1.2 (2023)	32284385	high	-
KPN0002	Klebsiella pneumoniae	oqxA	-	Gene presence detected	core	ciprofloxacin	-	wildtype	S	EUCAST v15.0 (2025)	30834112	moderate	low clinical relevance, lacks evidence for this allele
KPN0003	Klebsiella pneumoniae	oqxB	-	Gene presence detected	core	ciprofloxacin	-	wildtype	S	EUCAST v15.0 (2025)	30834112	moderate	lacks evidence for this species
KPN0004	Klebsiella pneumoniae	fosA5_fam	-	Gene presence detected	core	fosfomycin	-	wildtype	S	ECOFF (May 2025)	33128341	moderate	lacks evidence for this species
KPN0005	Klebsiella	fosA5	-	Gene	core	fosfomycin	-	wildtype	S	ECOFF (May	25441705	moderate	lacks evidence for



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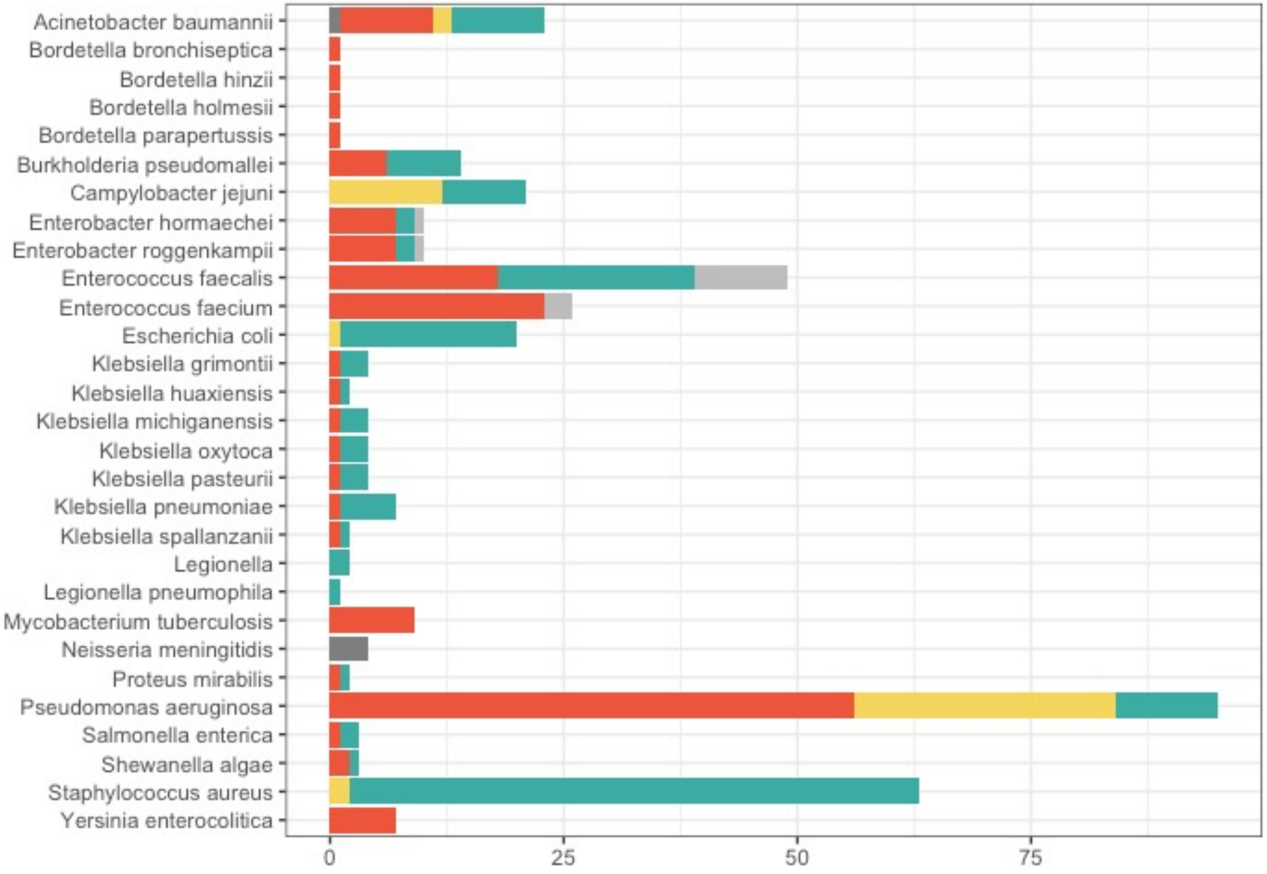
Rules to interpret *presence* of core genes



393 rules

🟩 **WT S (43%)**

🟨 **WT I (11%)**

🟥 **WT R (40%)**

135 unique genes

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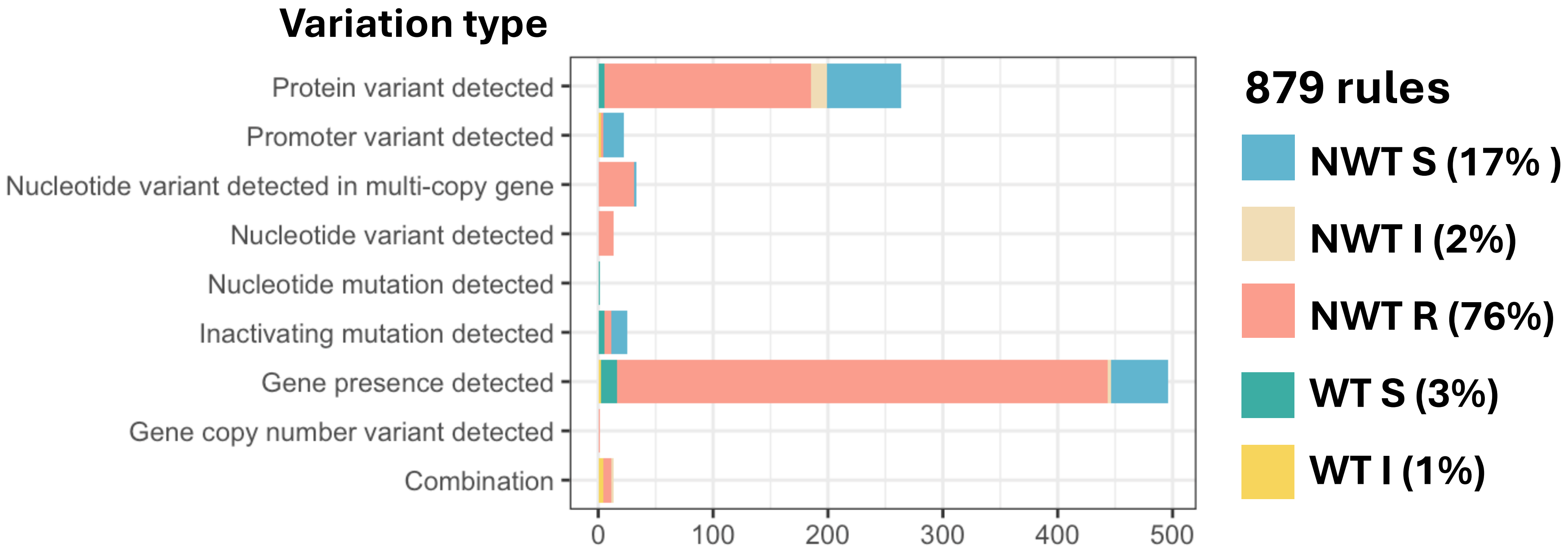
Rules for acquired variants

(i.e. rules other than detection of core gene presence)



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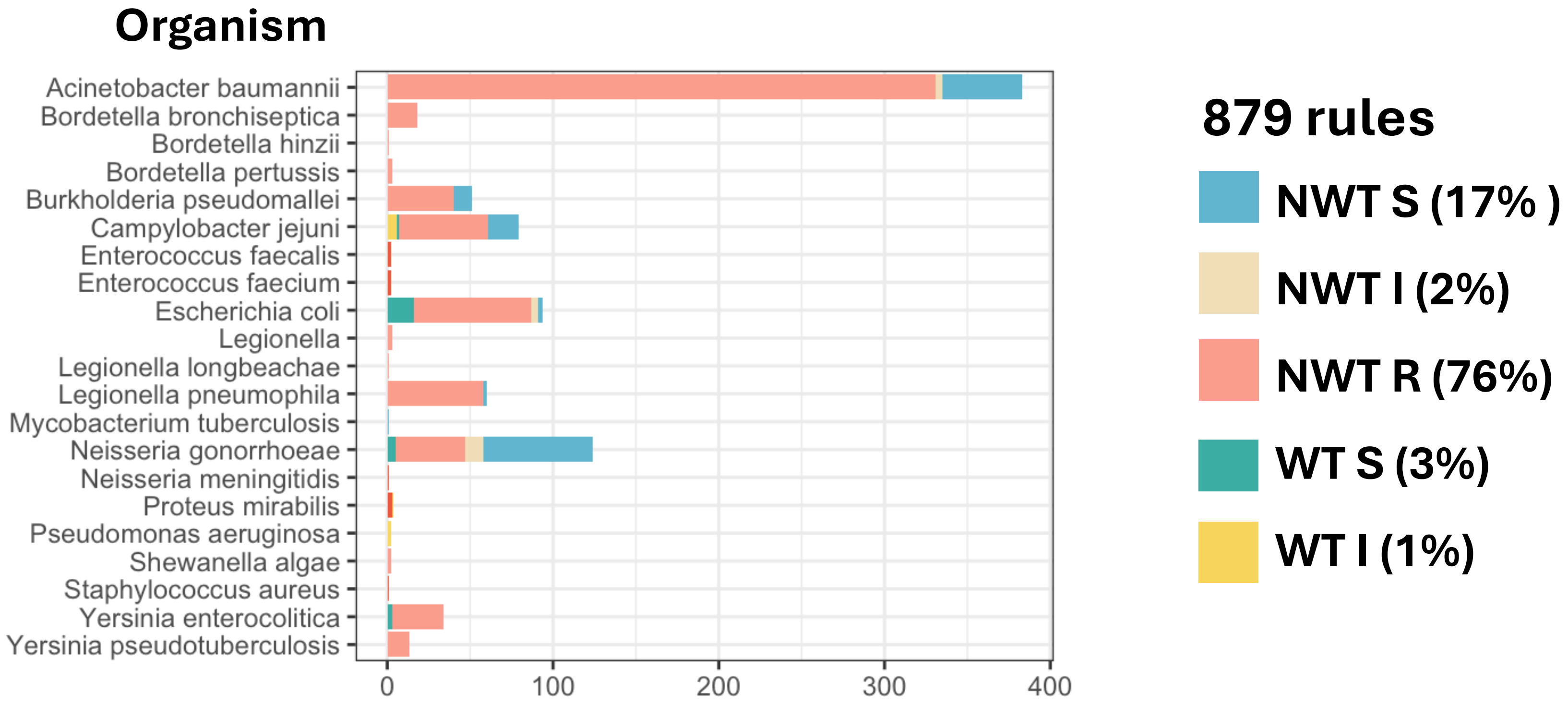
Rules for acquired variants

(i.e. rules other than detection of core gene presence)



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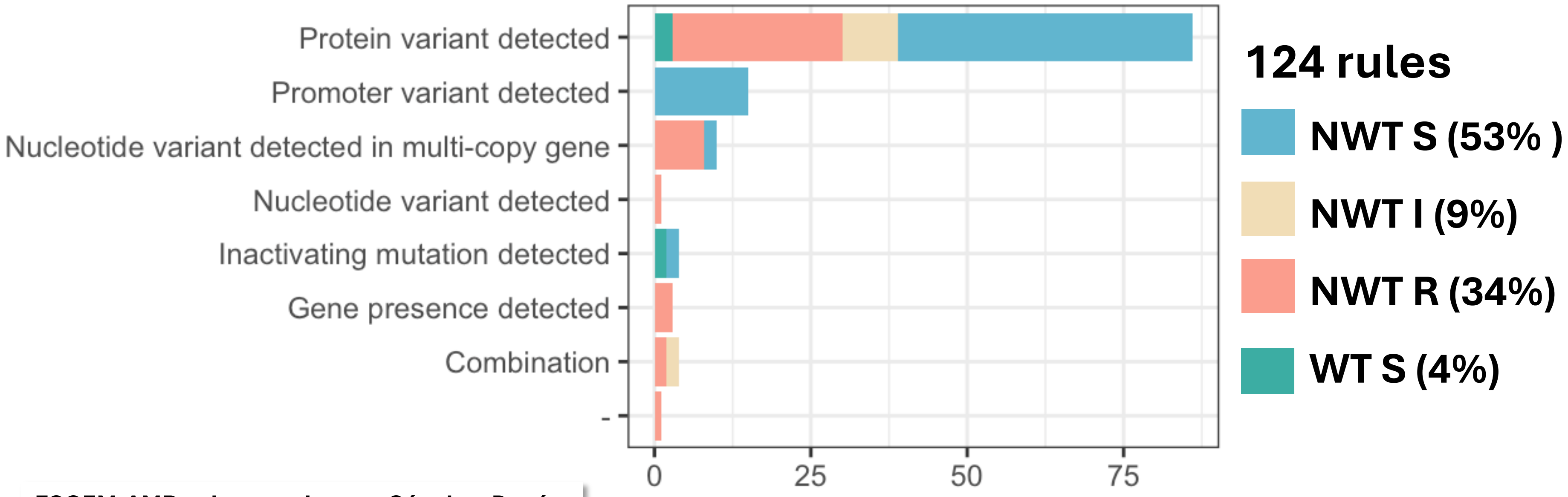
Acquired variants in *N. gonorrhoeae*



ESGEM-AMR subgroup: Leonor Sánchez Busó, Yonatan Grad, Sheeba Manoharan-Basil, Martin McHugh, Tatum Mortimer, Anna Roditscheff, Faina Wehrli, Adam Witney, Raffael Frei, Daniel Golparian, Magnus Unemo

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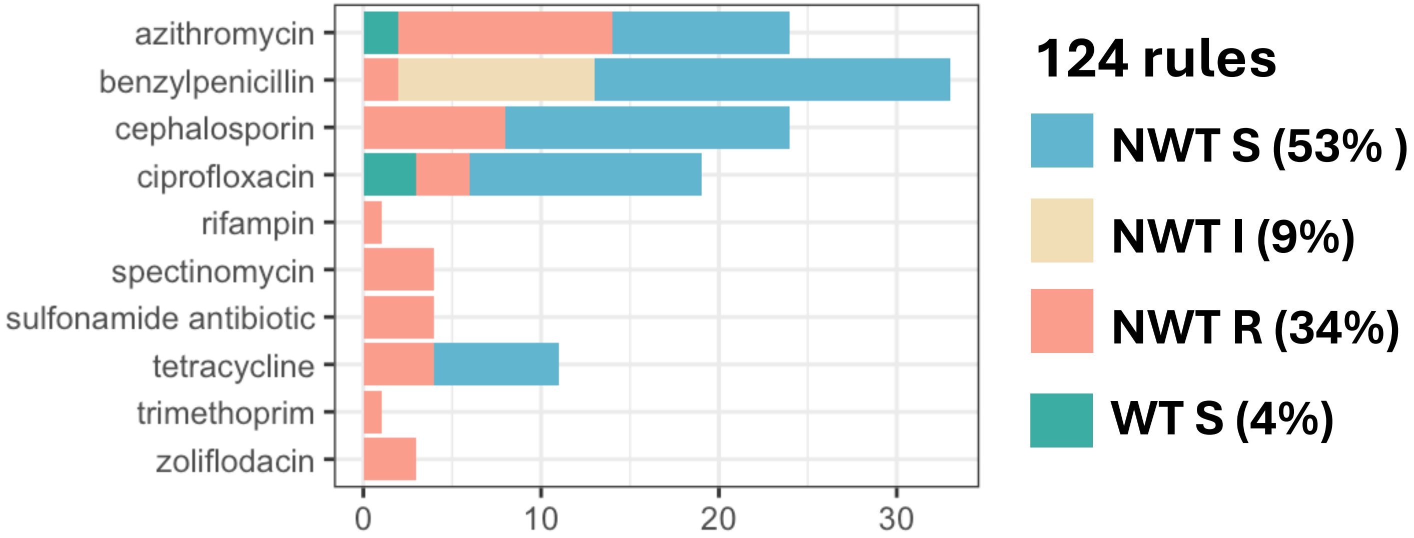
Acquired variants in *N. gonorrhoeae*



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AMRrules interpretations for CIP in *N. gono*

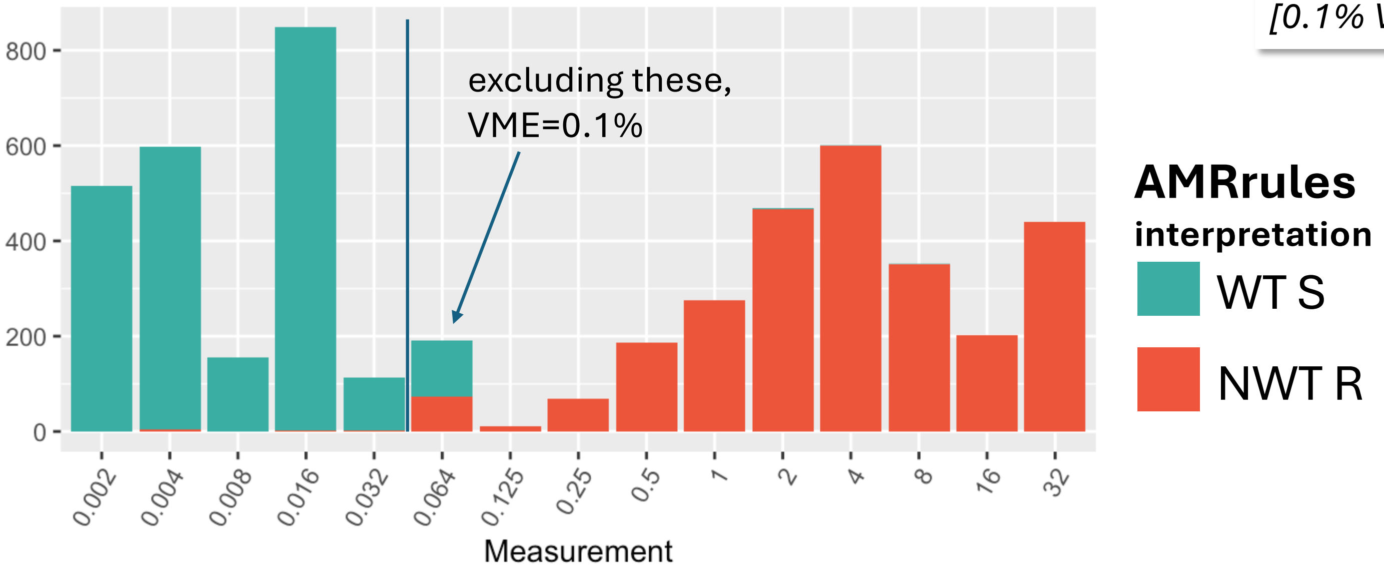
Public data from EURO-GASP

<u>Categorical concordance</u>
95.7% Sensitivity
99.6% Specificity

0.3% Major error (S predicted R)
4.2% Very major error (R predicted S)
[0.1% VME excluding MIC=0.64]

Observed ciprofloxacin MIC distribution

5,025 isolates



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AMRrules interpretations for *A. baumannii*

Public data from EBI/CABBAGE

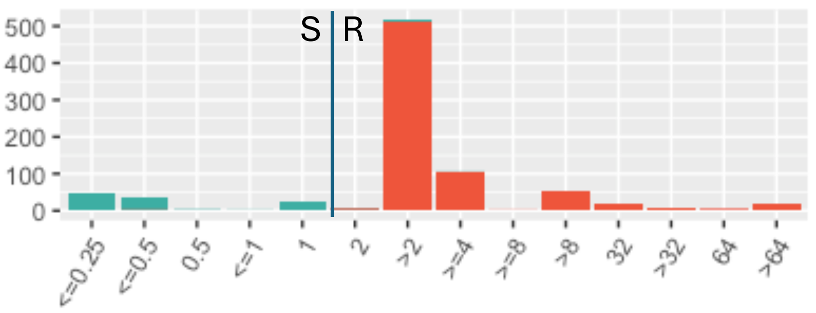
AMRrules interpretation

🟩 WT S

🟥 NWT R

Ciprofloxacin MIC

(n=852)

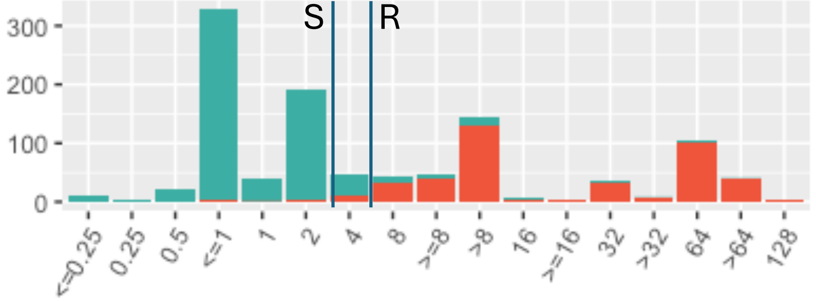


Categorical concordance
98.1% Sensitivity
99.1% Specificity

ESGEM-AMR subgroup:
Paul Higgins, Bogdan Iorga, Rahul Garg, Mehrad Hamidian, Priyanka Khopkar-Kale, Margaret Lam, Bruno Silvester Lopes, Ignasi Roca, Varun Shamanna, Clement Tsui, David Wareham, Valeria Bortolaia, Adrian Egli, Lucie Amoureux, Vera Manageiro, Antoine Abou Fayad, Beverly Egyir

Imipenem MIC

(n=1,067)



Categorical concordance
90.6% Sensitivity
97.0% Specificity

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AMRrules

Phase 2: Quantitative rule generation

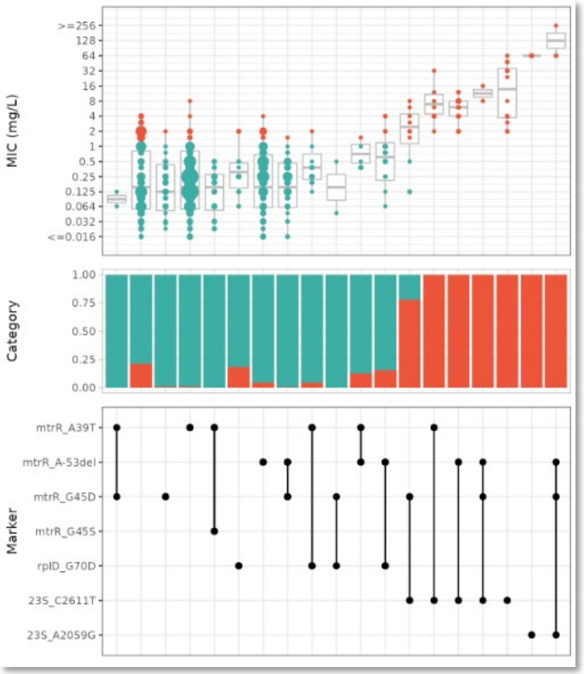
Priorities for AMRrules v2

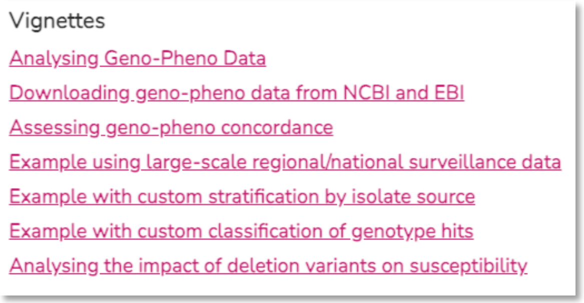
- Rules for <u>all</u> markers reported by AMRFinderPlus in each organism
  - ✓ Propose addition of new markers where needed
- EUCAST and CLSI phenotypic standards
- Expand AMRrules Specification to include quantitative fields
- Add support for CARD, ResFinder

Quantitative approach implemented by ESGEM-AMR

R package for AMR geno/pheno analysis

- **Import AST phenotypes**
  - NCBI, EBI, Sensititre, Phoenix, Vitek, Microscan, WHOnet
  - Re-interpret with latest breakpoints/ECOFF via AMR R pkg
- **Import AMR genotypes**
  - AMRFinderPlus, CARD RGI, ABRicate, Kleborate
- **Retrieve public data**
  - Genotypes and phenotypes from NCBI & EBI
  - Reference MIC/disk zone distributions from EUCAST
- **Format phenotype data for submission**
  - To NCBI & EBI
- **Analyse and visualise geno/pheno data**
  - Logistic regression
  - Positive predictive value
  - Assay distributions
  - Upset plots
  - Concordance metrics





Vignettes

- Analysing Geno-Pheno Data
- Downloading geno-pheno data from NCBI and EBI
- Assessing geno-pheno concordance
- Example using large-scale regional/national surveillance data
- Example with custom stratification by isolate source
- Example with custom classification of genotype hits
- Analysing the impact of deletion variants on susceptibility

Developers

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Richard N. Goodman
Author

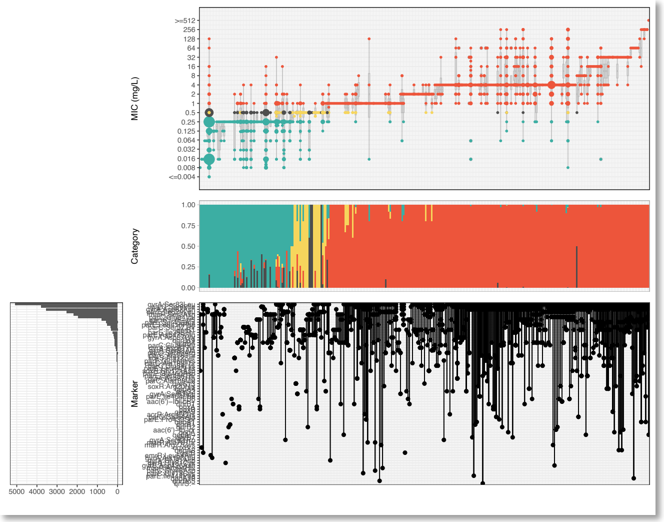
AMRgen.org

AMRrulemakeR

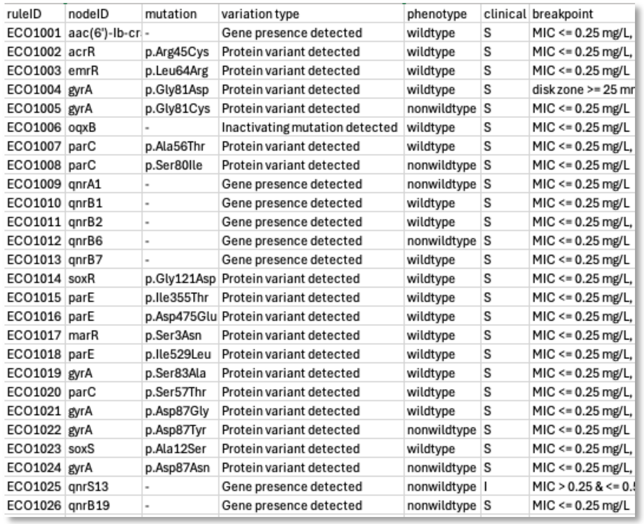
R package to define and test AMRrules

Input: geno + pheno data for a given species

Analyse geno/pheno

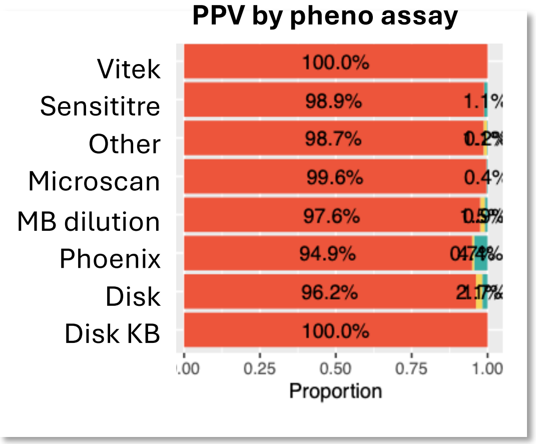


Propose AMRrules



ruleID	nodeID	mutation	variation type	phenotype	clinical	breakpoint
ECO1001	aac(6')-Ib-cr	-	Gene presence detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1002	acrR	p.Arg45Cys	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1003	emrR	p.Leu64Arg	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L
ECO1004	gyrA	p.Gly81Asp	Protein variant detected	wildtype	S	disk zone >= 25 mr
ECO1005	gyrA	p.Gly81Cys	Protein variant detected	nonwildtype	S	MIC <= 0.25 mg/L
ECO1006	oqxB	-	Inactivating mutation detected	wildtype	S	MIC <= 0.25 mg/L
ECO1007	parC	p.Ala56Thr	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1008	parC	p.Ser80Ile	Protein variant detected	nonwildtype	S	MIC <= 0.25 mg/L
ECO1009	qnrA1	-	Gene presence detected	nonwildtype	S	MIC <= 0.25 mg/L
ECO1010	qnrB1	-	Gene presence detected	wildtype	S	MIC <= 0.25 mg/L
ECO1011	qnrB2	-	Gene presence detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1012	qnrB6	-	Gene presence detected	nonwildtype	S	MIC <= 0.25 mg/L
ECO1013	qnrB7	-	Gene presence detected	wildtype	S	MIC <= 0.25 mg/L
ECO1014	soxR	p.Gly121Asp	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1015	parE	p.Ile355Thr	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1016	parE	p.Asp475Glu	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1017	marR	p.Ser3Asn	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1018	parE	p.Ile529Leu	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1019	gyrA	p.Ser83Ala	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1020	parC	p.Ser57Thr	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1021	gyrA	p.Asp87Gly	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1022	gyrA	p.Asp87Tyr	Protein variant detected	nonwildtype	S	MIC <= 0.25 mg/L
ECO1023	soxS	p.Ala12Ser	Protein variant detected	wildtype	S	MIC <= 0.25 mg/L,
ECO1024	gyrA	p.Asp87Asn	Protein variant detected	nonwildtype	S	MIC <= 0.25 mg/L,
ECO1025	qnrS13	-	Gene presence detected	nonwildtype	I	MIC > 0.25 & <= 0.
ECO1026	qnrB19	-	Gene presence detected	nonwildtype	S	MIC <= 0.25 mg/L

Internal validation



Automated ciprofloxacin resistance rules for E. coli

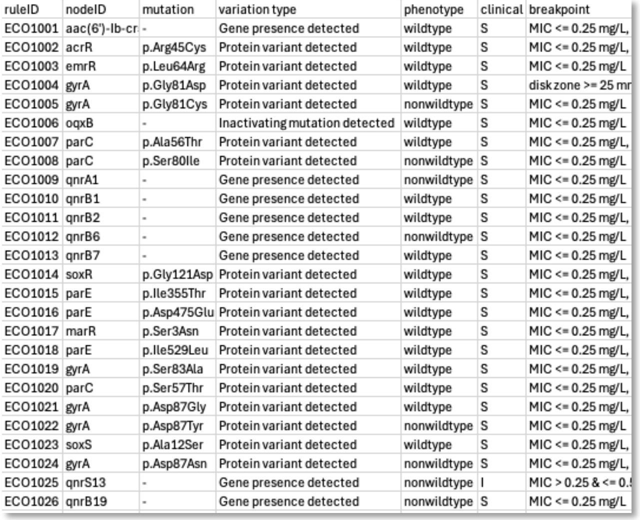
make.amrrules.org

AMRrulemakeR

R package to define and test AMRrules

Input: geno + pheno data for a given species

Propose AMRrules



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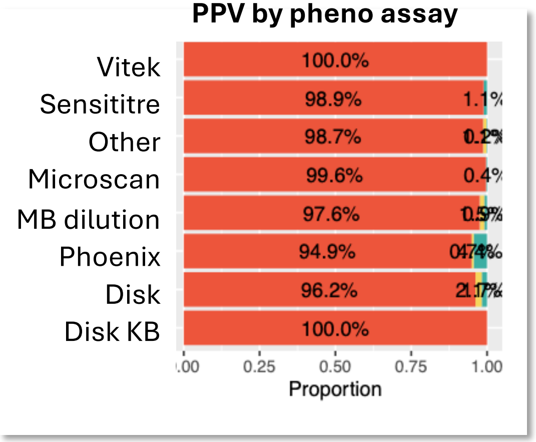
Automated ciprofloxacin resistance rules for E. coli

Internal validation



ESCMID | ESGEM-AMR

Outputs curated by organism experts

- ✓ Biological and clinical sense check
- ✓ Add experimental evidence & review evidence grades
- ✓ Exploring AI-assisted biocuration

make.amrrules.org

Phase 3: Routine update and review cycle

Automate updating reviews based on new data

- ➢ Link to public (EBI/NCBI) and/or private (WHO/regional) geno/pheno DBs
  - EBI/NCBI, WHO/regional/national
- ➢ Expert committee for review and oversight

Interoperability

- ➢ Maintain/extend compatibility with relevant tools and standards
- ➢ Contribute to standardised approaches to AMR genomics
  - E.g. Facilitate converting AMRrules generic output into dynamic formats, applying local reporting rules, etc

AMRrules

ESCMID | ESGEM-AMR

Organism subgroup leads contributing rules to v1.0
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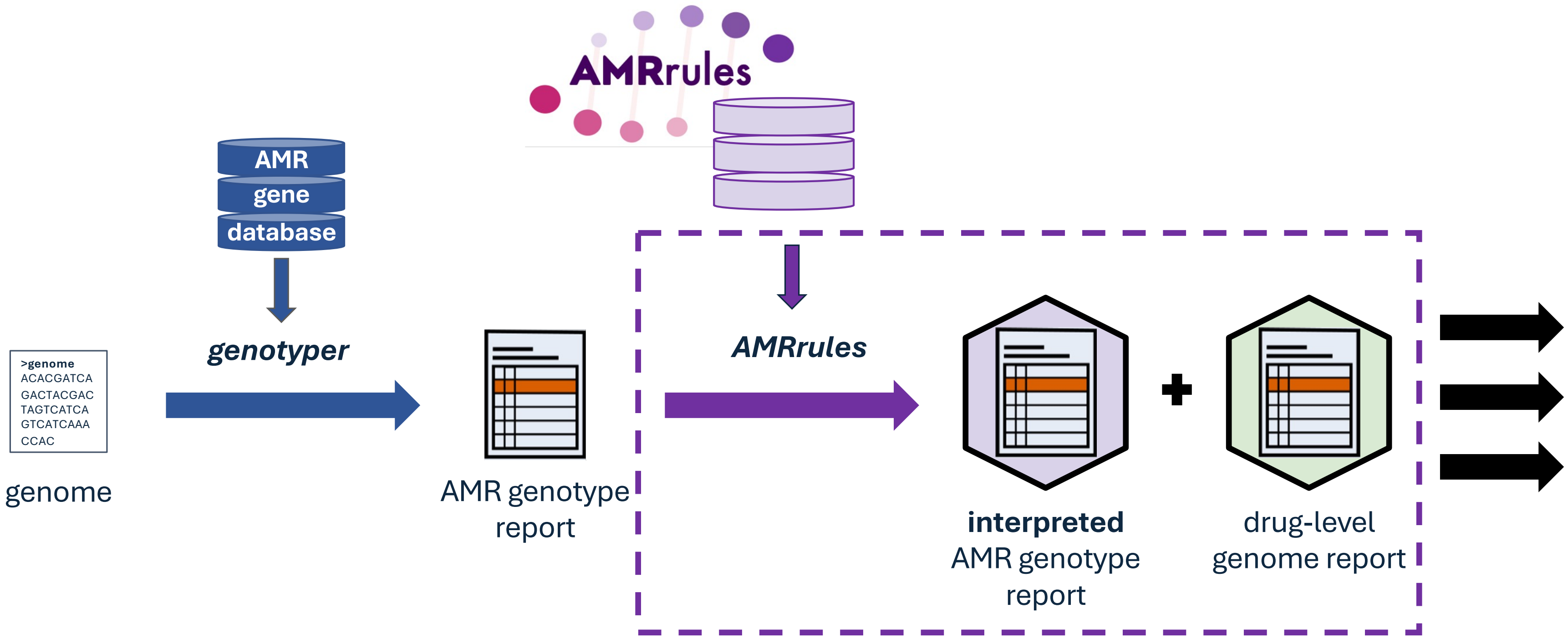
Where does AMRrules fit in the ecosystem & workflows?



AMRrules

AMR gene database

genotyper

AMRrules

>genome
ACACGATCA
GACTACGAC
TAGTCATCA
GTCATCAAA
CCAC

genome

AMR genotype report

interpreted AMR genotype report

drug-level genome report

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