



HỘI NGHỊ KHOA HỌC QUỐC TẾ LẦN 1 NĂM 2024 THÀNH PHỐ THỦ ĐỨC

Unleashing the combined power of second and third generation sequencing and AI in the battle Against Antimicrobial Resistance (AMR)

10/08/2024

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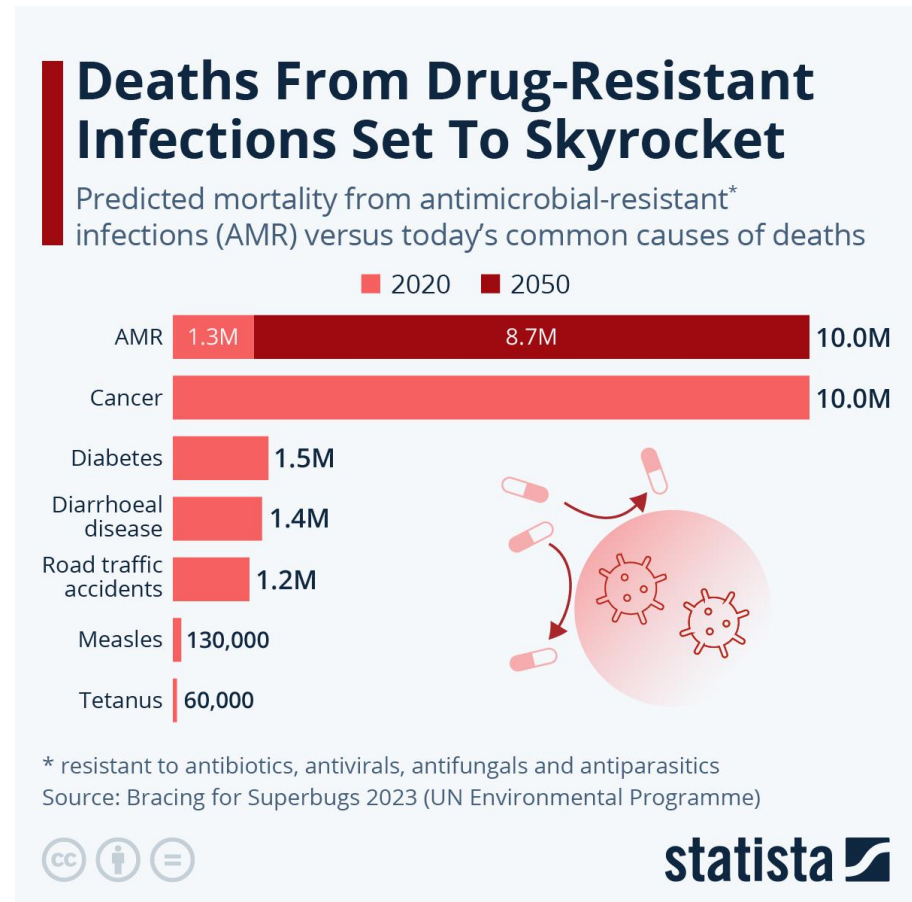
Content

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- Traditional Challenges in Combating AMR
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- The Role of Artificial Intelligence (AI)
- Combining Sequencing and AI for AMR Combat
 - Overcome Traditional Challenges for fighting AMR
 - Challenges and Future Directions

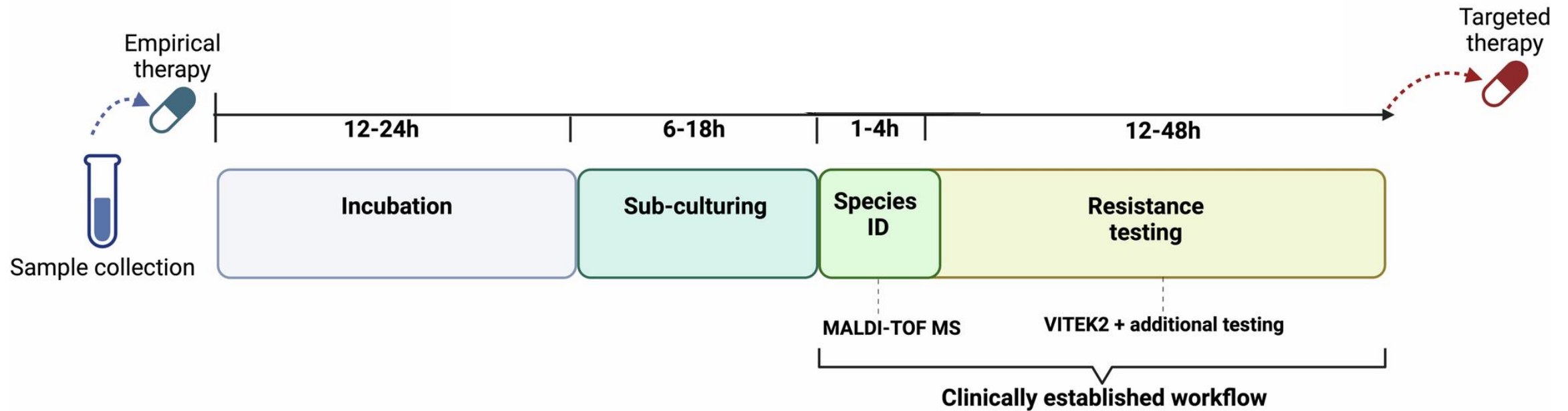
AMR is one of the ten most severe global health threats

- Resistant infections leading to higher mortality and morbidity due to delayed or inappropriate therapy
 - 2019: ~1.27M deaths specifically attributed to bacterial AMR
 - The highest all-age death rate in Western sub-Saharan Africa, 27.3/100K individuals (20.9–35.3)

=> Rapid and accurate identification of resistant bacterial pathogens could facilitate the earlier administration of appropriate therapy



Traditional Challenges in Combating AMR



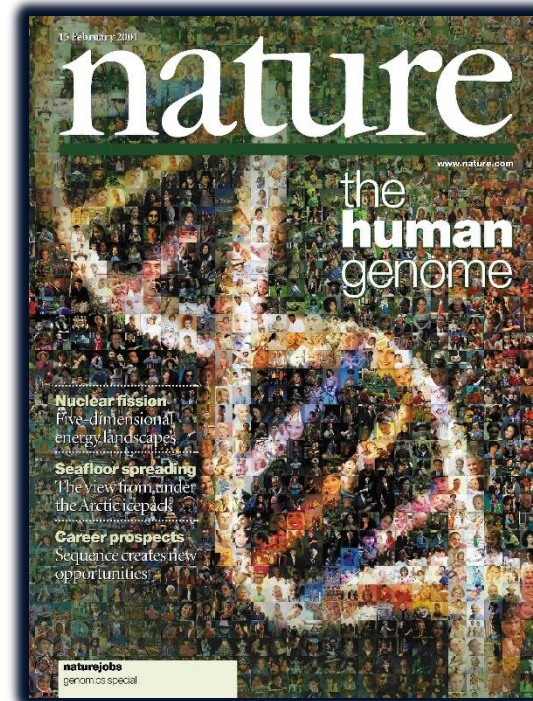
Workflow comparing a culture-based and a nanopore-based approach.

ID: Identification, AST: antibiotic susceptibility testing, MALDI-TOF MS: Matrix-assisted laser desorption ionization time-of-flight mass spectrometry.

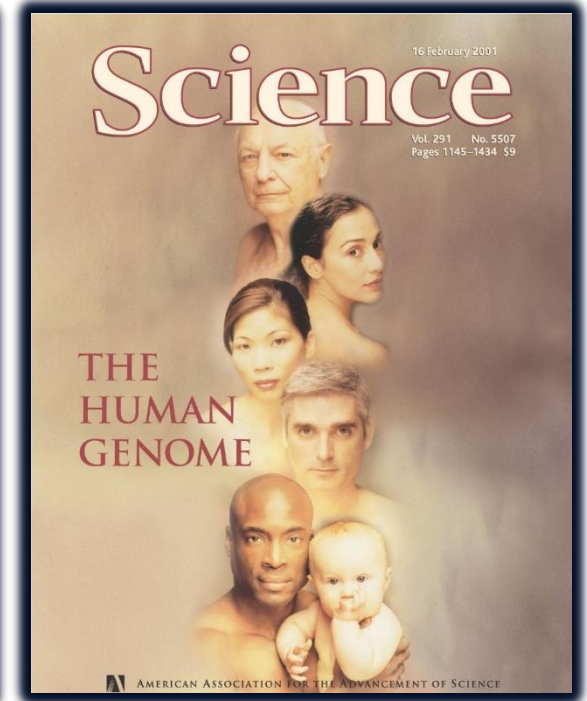
Sauerborn, E. et al. Detection of hidden antibiotic resistance through real-time genomics. Nat Commun (2024).

Human Genome Project - HGP (Oct 1990 - April 2003)

1. In 2003, the Human Genome Project produced a genome sequence that accounted for over 90% of the human genome (~3 GB).
 2. It was as close to complete as the technologies for sequencing DNA allowed at the time.
 3. Cost ~3 billion US\$
- => Facilitating advancements in **next-generation sequencing (NGS)** technologies



HGP Paper



Venter/Celera Paper

<https://www.genome.gov/human-genome-project>

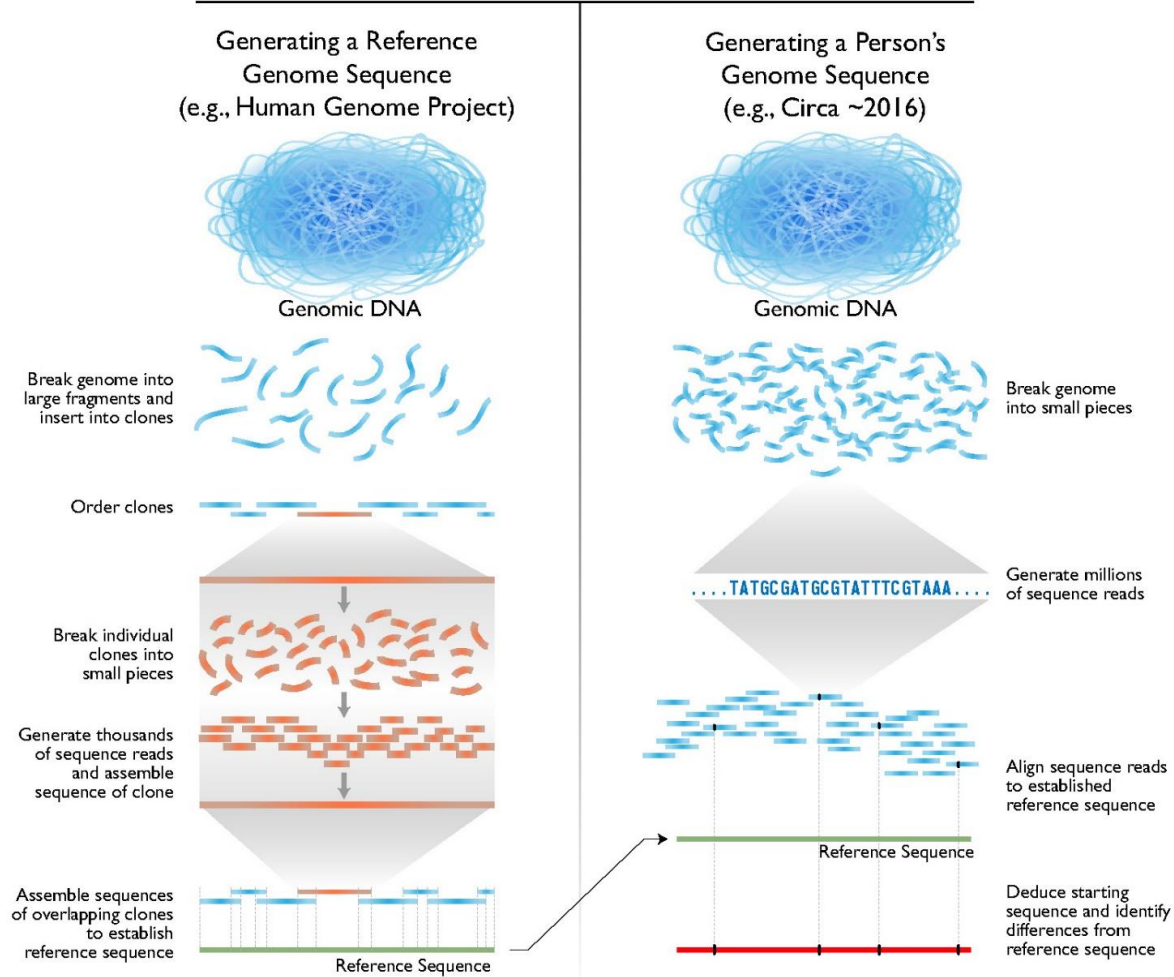


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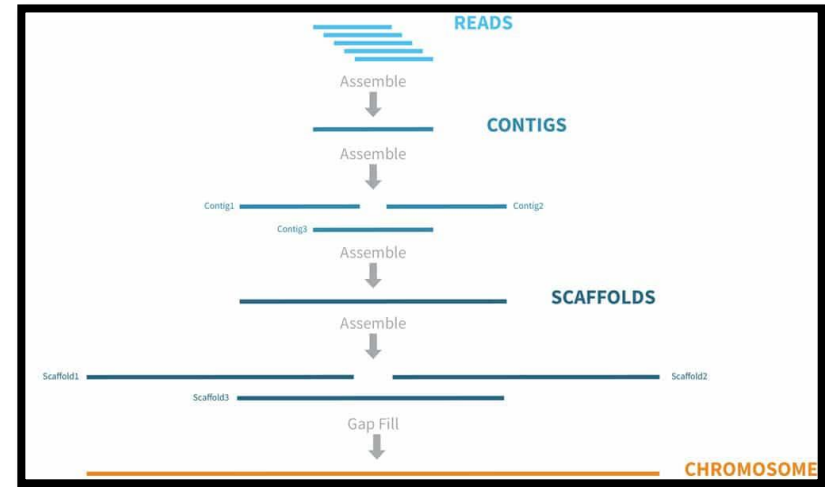
<https://www.ncbi.nlm.nih.gov/nuccore/806904736>

Next-Generation Sequencing (NGS)

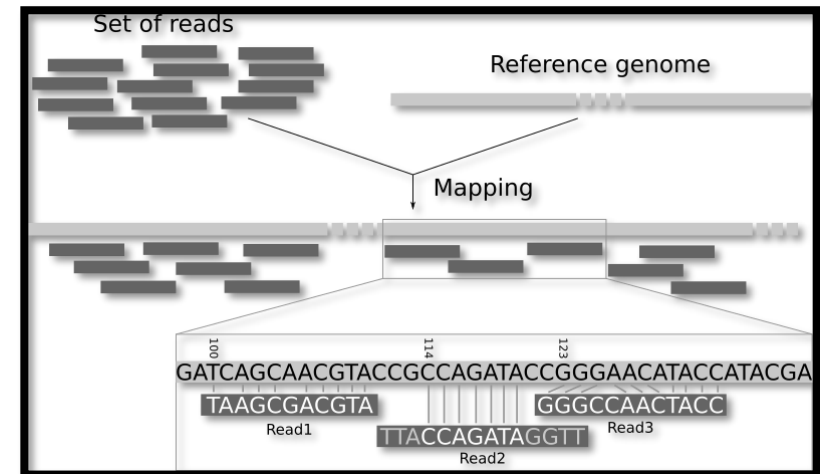
Human Genome Sequencing



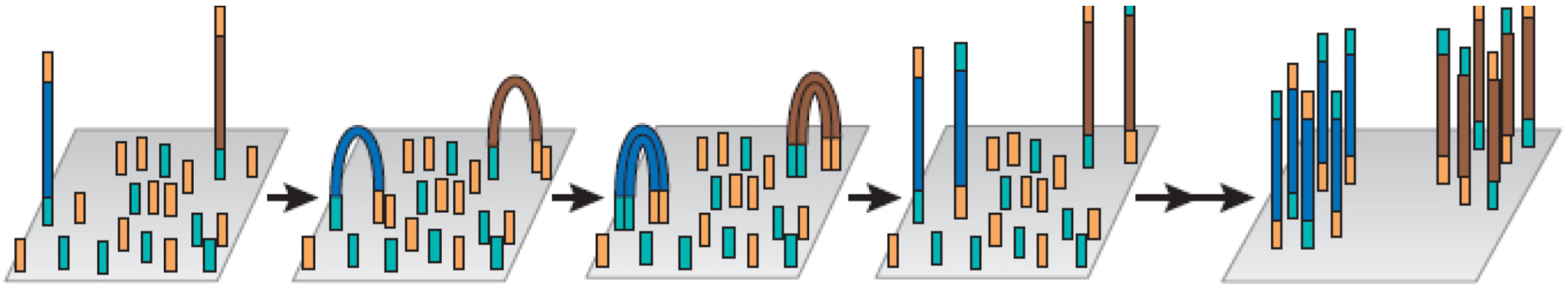
De novo assembly



Mapping to reference



NGS: 1) Parallel Sequencing



NGS: 2) Reference Genome

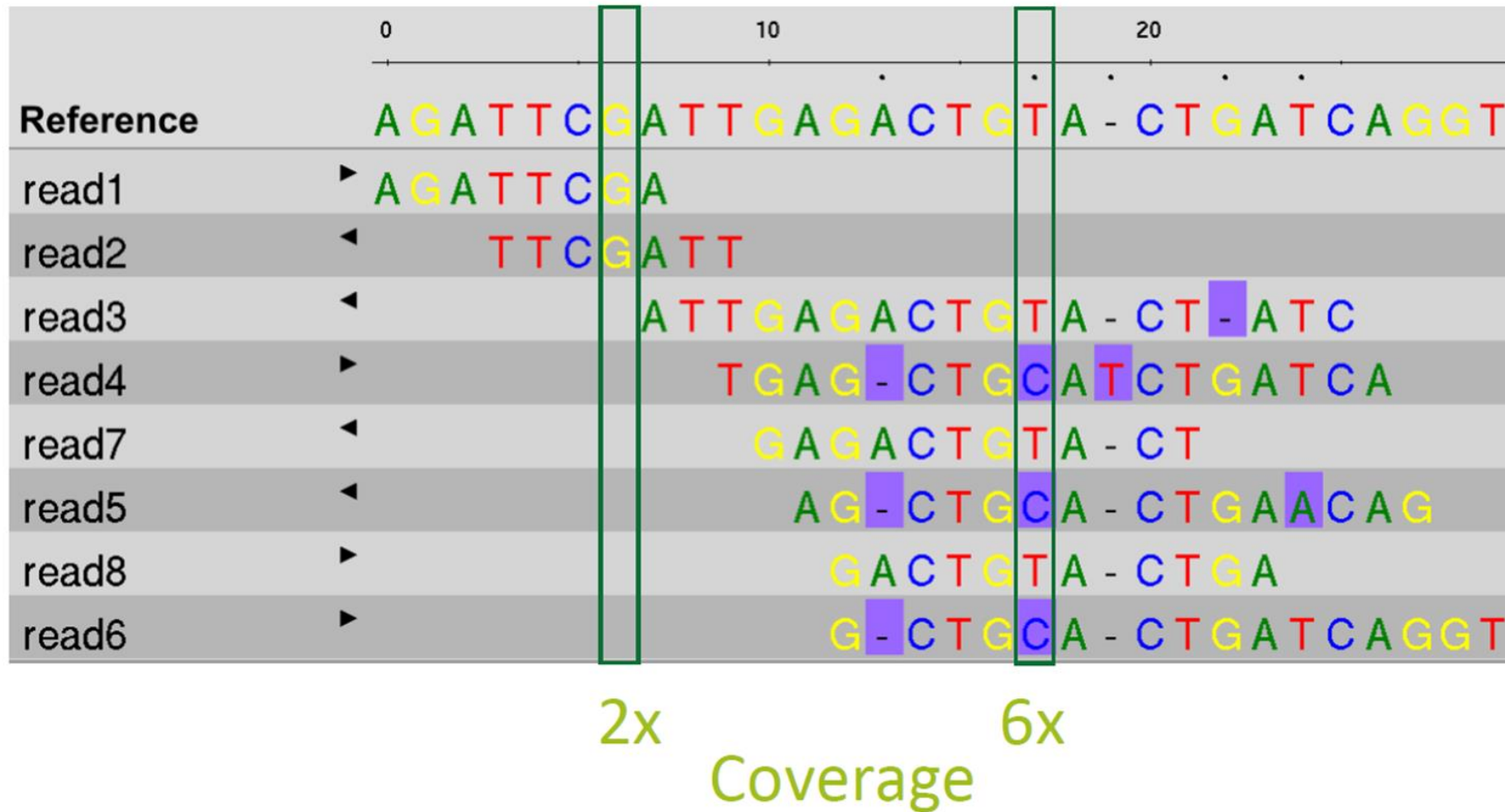
De novo assembly



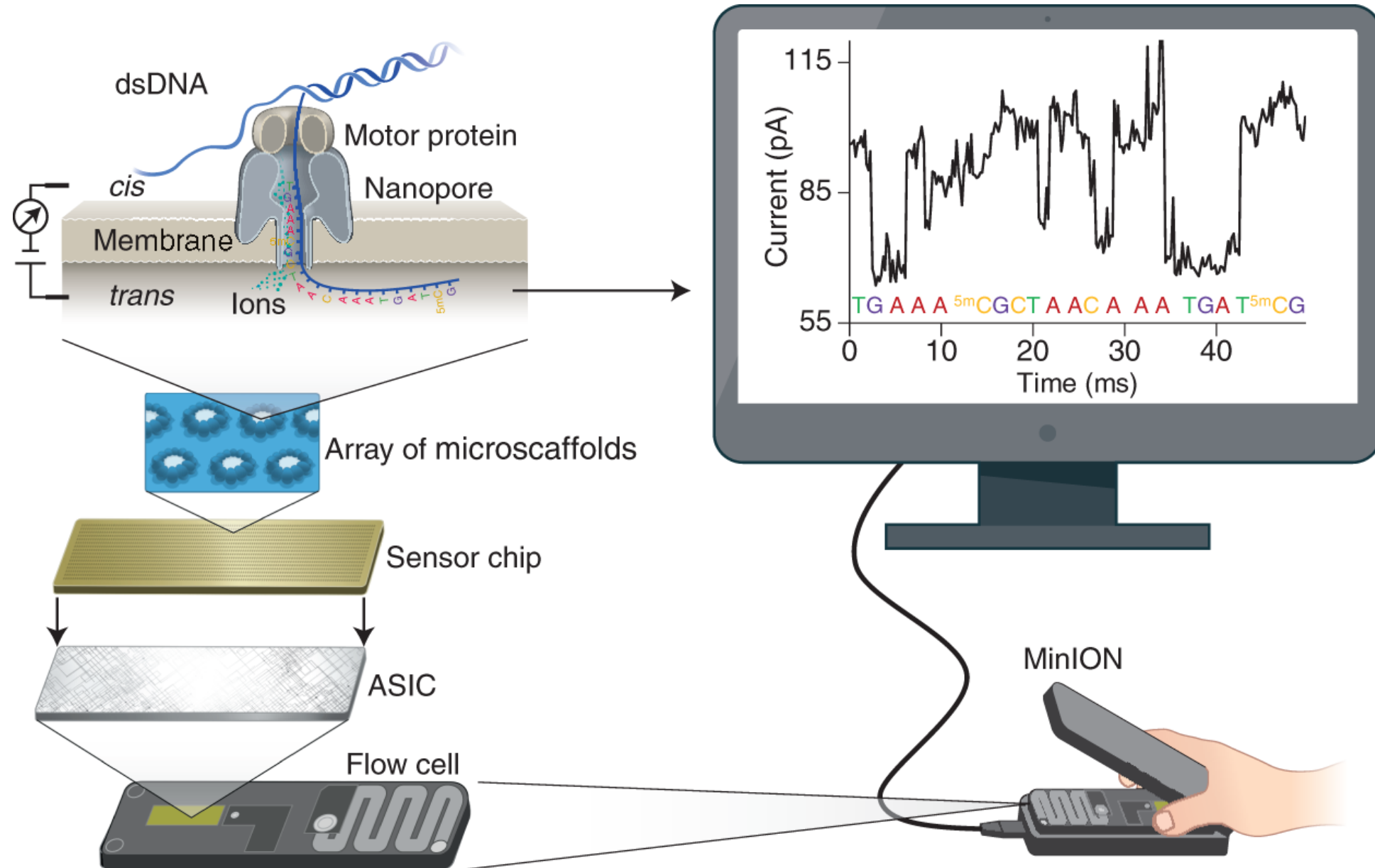
Mapping to reference



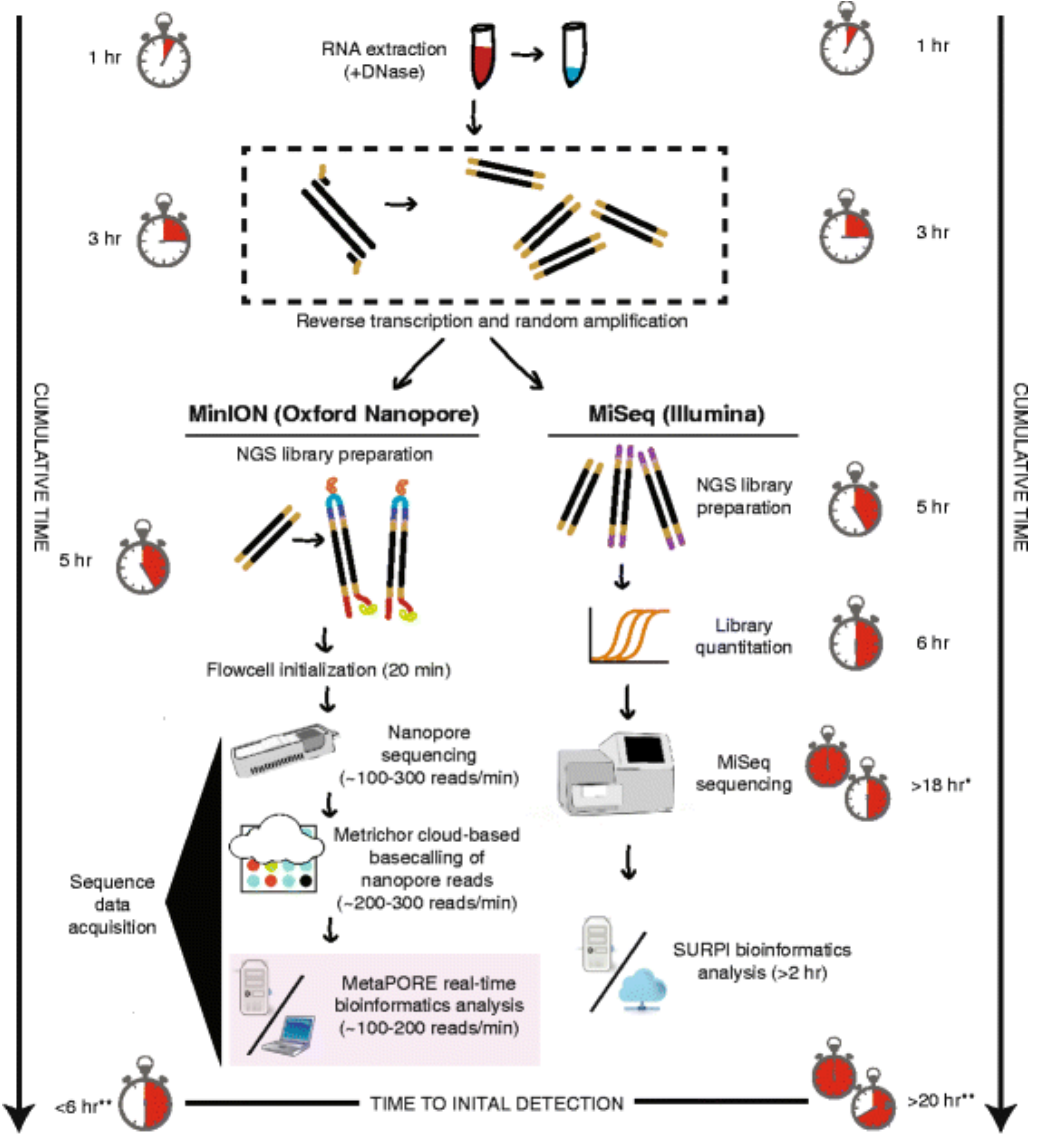
Alignment of short read to Reference Genome



Third Generation Sequencing (TGS): Oxford Nanopore Technologies



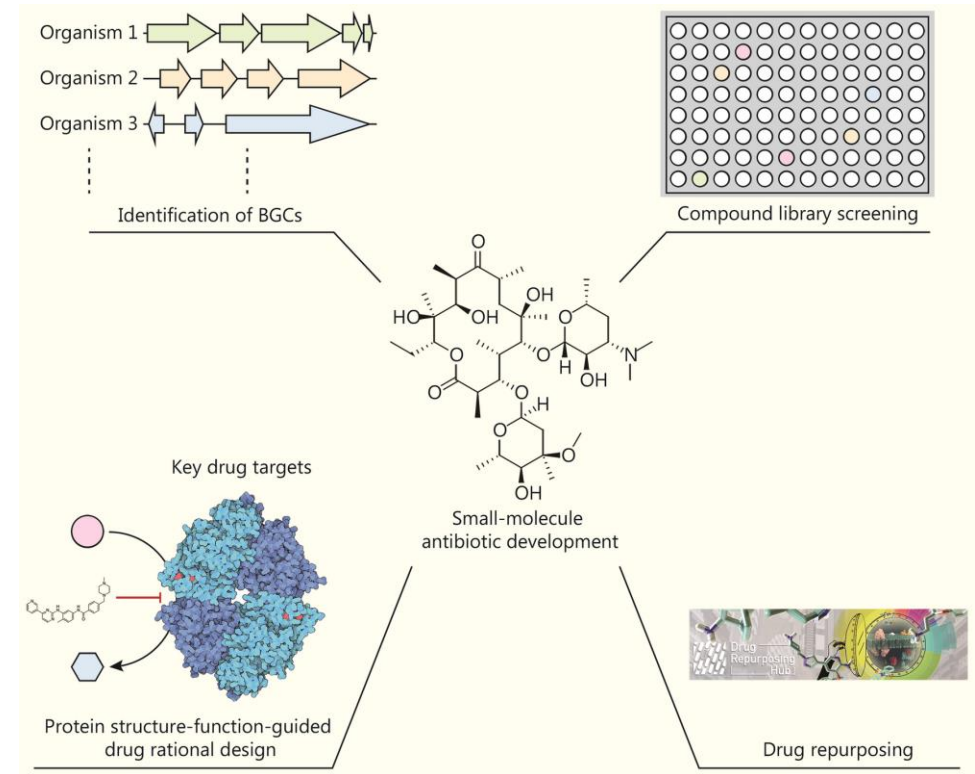
Metagenomic sequencing workflow: MinION vs MiSeq



Greninger, A.L. et al. Rapid metagenomic identification of viral pathogens in clinical samples by real-time nanopore sequencing analysis. *Genome Med* (2015)

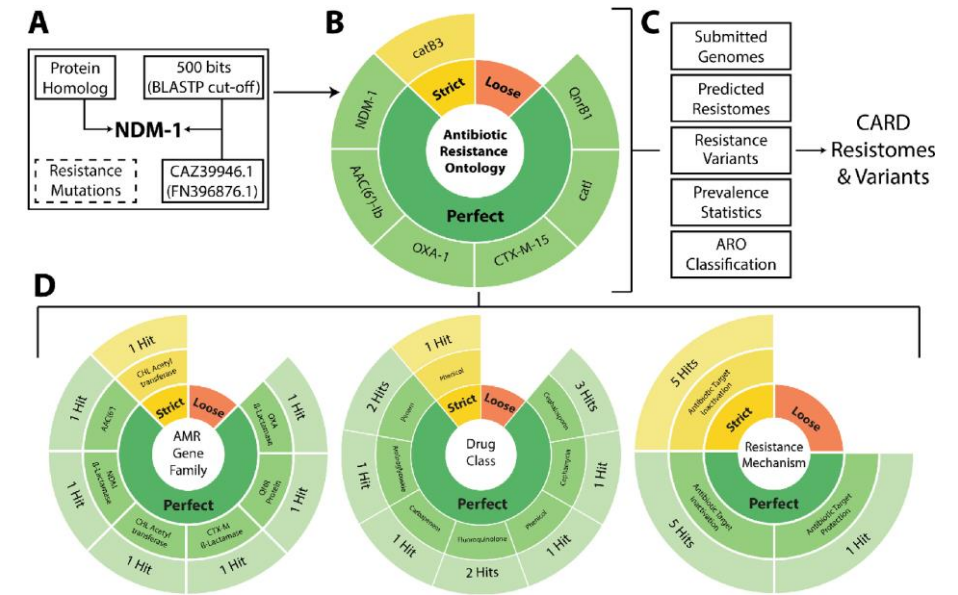
Artificial Intelligence (AI): a powerful tool to fight AMR

- Leverage known data, such as genomic data, to predict potential resistance sites, corresponding resistant antibiotics and related enzymatic functions for better targeted treatment and designing better antibiotics
- Image-based methods can help identify resistant bacteria
- Compound library screening or new compound structure design for antibiotic compounds
- Predict novel antibiotic compounds with current abundance of databases
- Facilitated target identification and dynamic modeling, peptide design and synthesis, and drug repurposing

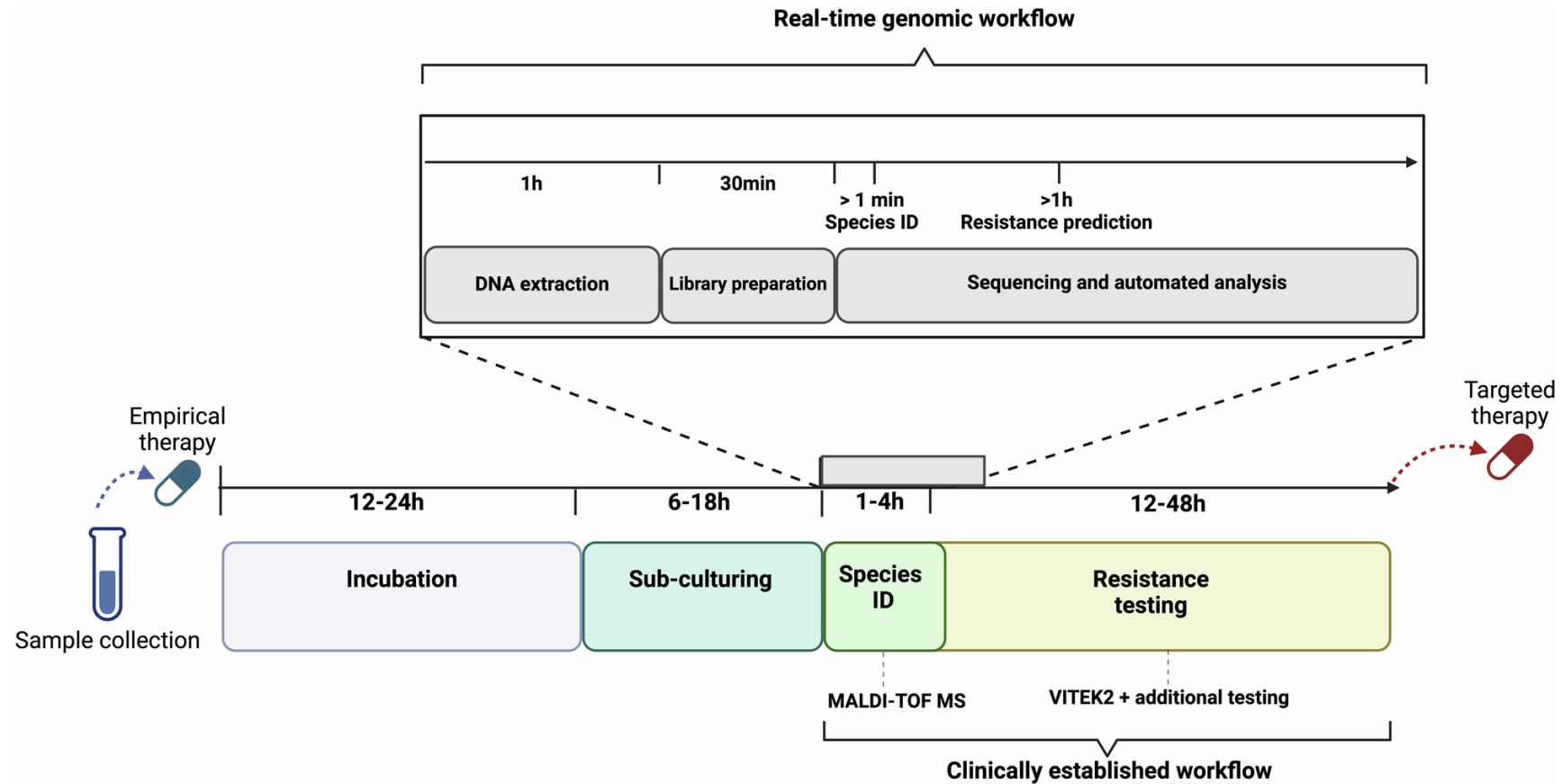


Public databases for resistance development prediction

- **BacMet** (<http://bacmet.biomedicine.gu.se>): bacterial resistance gene database (753 bacterial resistance genes confirmed by experiments, and it contains 155,512 potential predicted resistance genes)
- **The Comprehensive Antibiotic Resistance Database** (<https://card.mcmaster.ca/>): curated bioinformatic database of resistance genes, their products, and associated phenotypes (6627 ontology terms, 5010 reference sequences, 1933 single nucleotide polymorphisms, 3004 publications, and 5057 AMR detection models)
- **The Bacterial Diversity Metadatabase** (<https://bacdiverse.dsmz.de/about>) is currently the largest database with standardized bacterial phenotypic information (81,827 bacterial and archaeal strains, including 14,091 strains which covers approximately 90% of species)
- **Plasmid ATLAS**: plasmid-borne genetic factors
- **Virulence Factor Database**: virulence factors

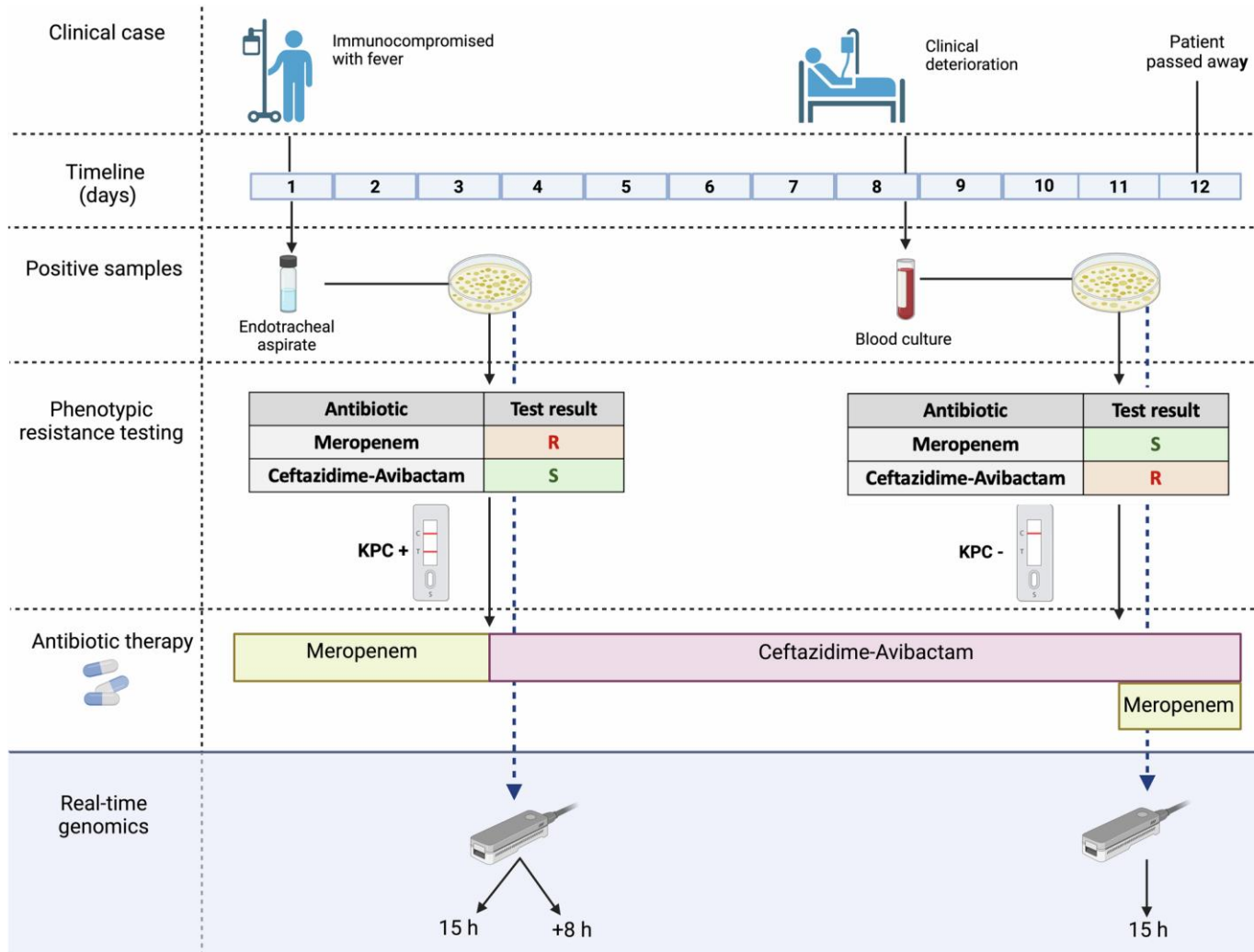


Overcome Traditional Challenges for fighting AMR (1)



Workflow comparing a culture-based and a nanopore-based approach.
ID: Identification, AST: antibiotic susceptibility testing, MALDI-TOF MS: Matrix-assisted laser desorption ionization time-of-flight mass spectrometry.

Overcome Traditional Challenges for fighting AMR (2)



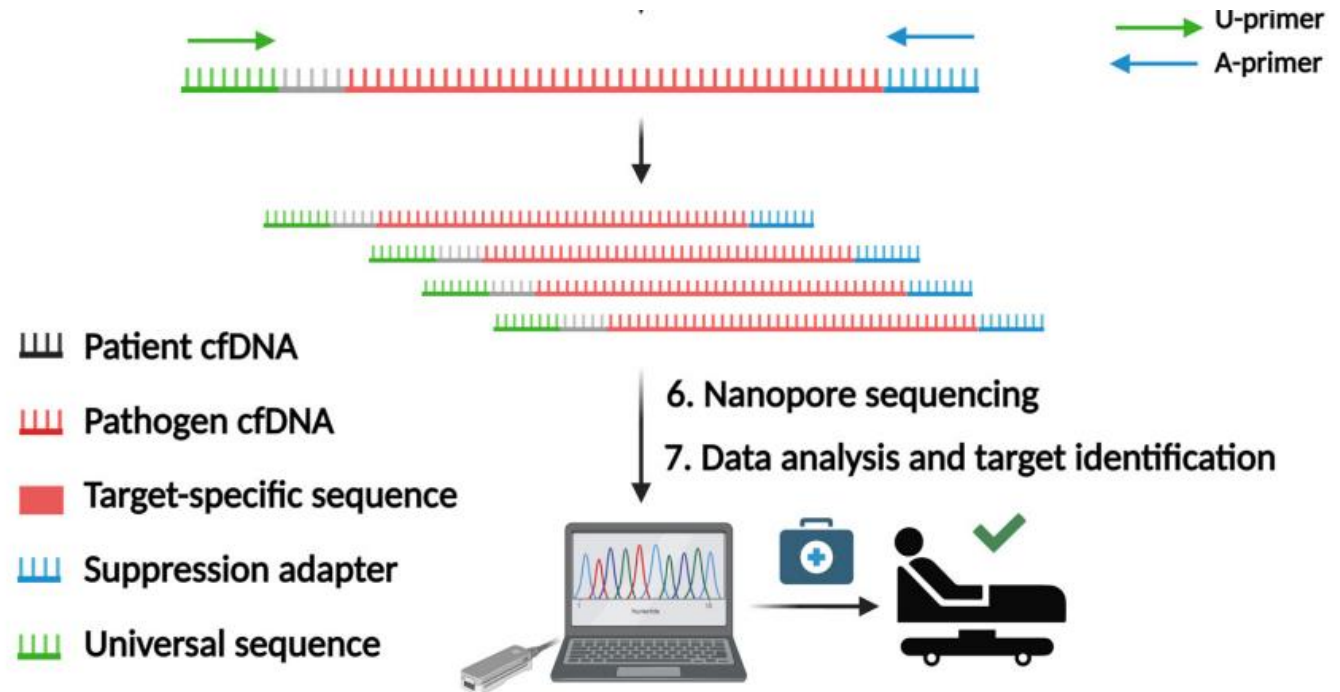
The patient was firstly treated with Meropenem. *K. pneumoniae* bacterial isolates of the first positive patient sample (endotracheal aspirate) were subjected to VITEK2 for general resistance testing and additional tests for CAZ-AVI resistance and KPC detection (R resistant, S susceptible; KPC +/-: absence or presence of KPC; Methods); the diagnostics led to a change in the antibiotic treatment to CAZ-AVI after three days. After clinical deterioration, the second isolate (from blood culture) showed reversed antibiotic resistance test results. While Meropenem was subsequently administered, the patient passed away shortly after. After completion of the routine diagnostics, we used real-time genomics to sequence DNA from the pre- and post-CAZ-AVI treatment bacterial isolates using the portable nanopore sequencing device Mk1b (Methods). Both isolates were sequenced for 15 h, and the first isolate was sequenced for another 8 h to simulate the potential of adaptive sequencing in the clinical setting (Methods).

Overcome Traditional Challenges for fighting AMR (3)

Article

Suppression PCR-Based Selective Enrichment Sequencing for Pathogen and Antimicrobial Resistance Detection on Cell-Free DNA in Sepsis—A Targeted, Blood Culture-Independent Approach for Rapid Pathogen and Resistance Diagnostics in Septic Patients

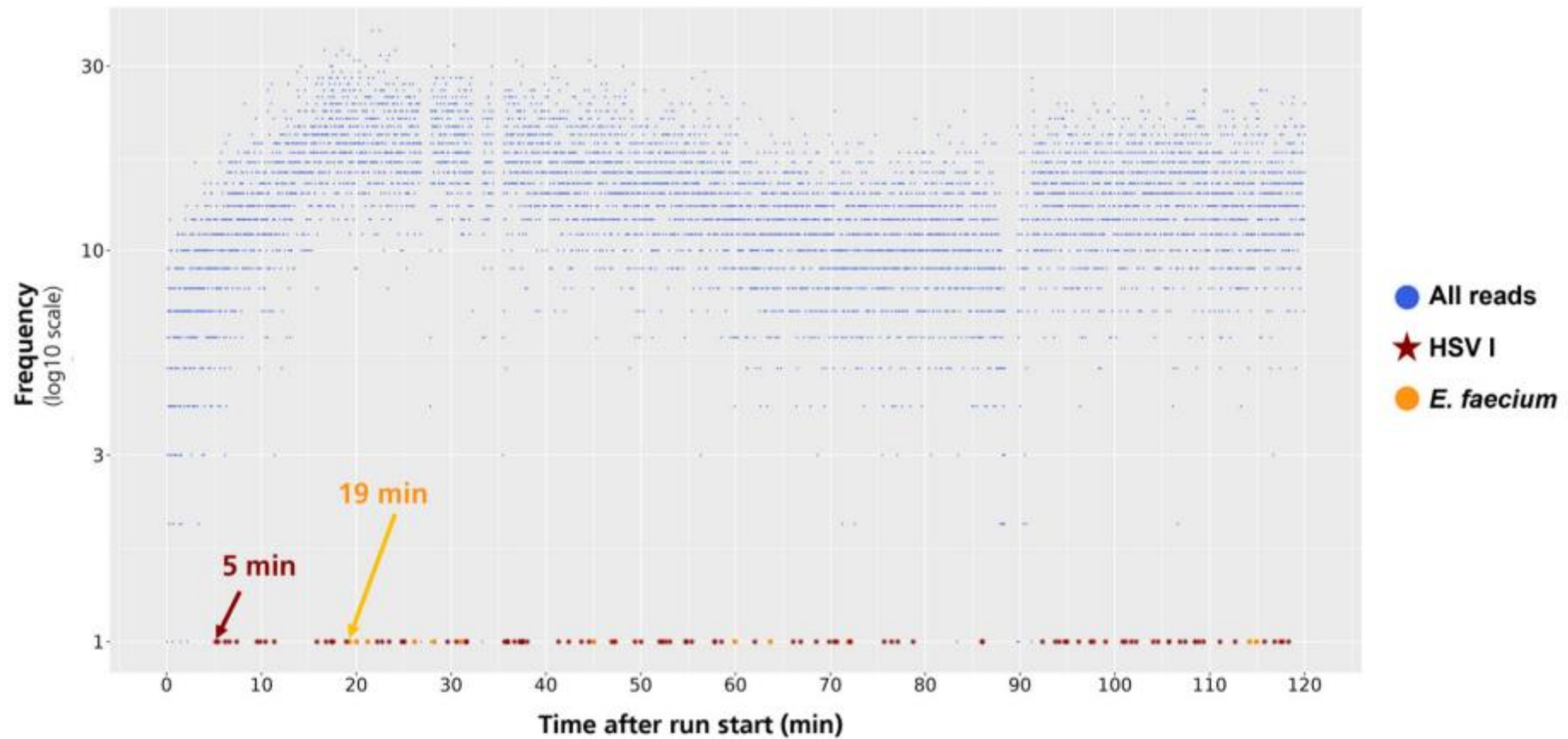
Mirko Sonntag ^{1,2,†}, Vanessa K. Elgeti ^{1,3,†}, Yevhen Vainshtein ¹, Lucca Jenner ¹, Jan Mueller ^{1,4,5,6}, Thorsten Brenner ⁷, Sebastian O. Decker ⁸ and Kai Sohn ^{1,*}



Overcome Traditional Challenges for fighting AMR (4)

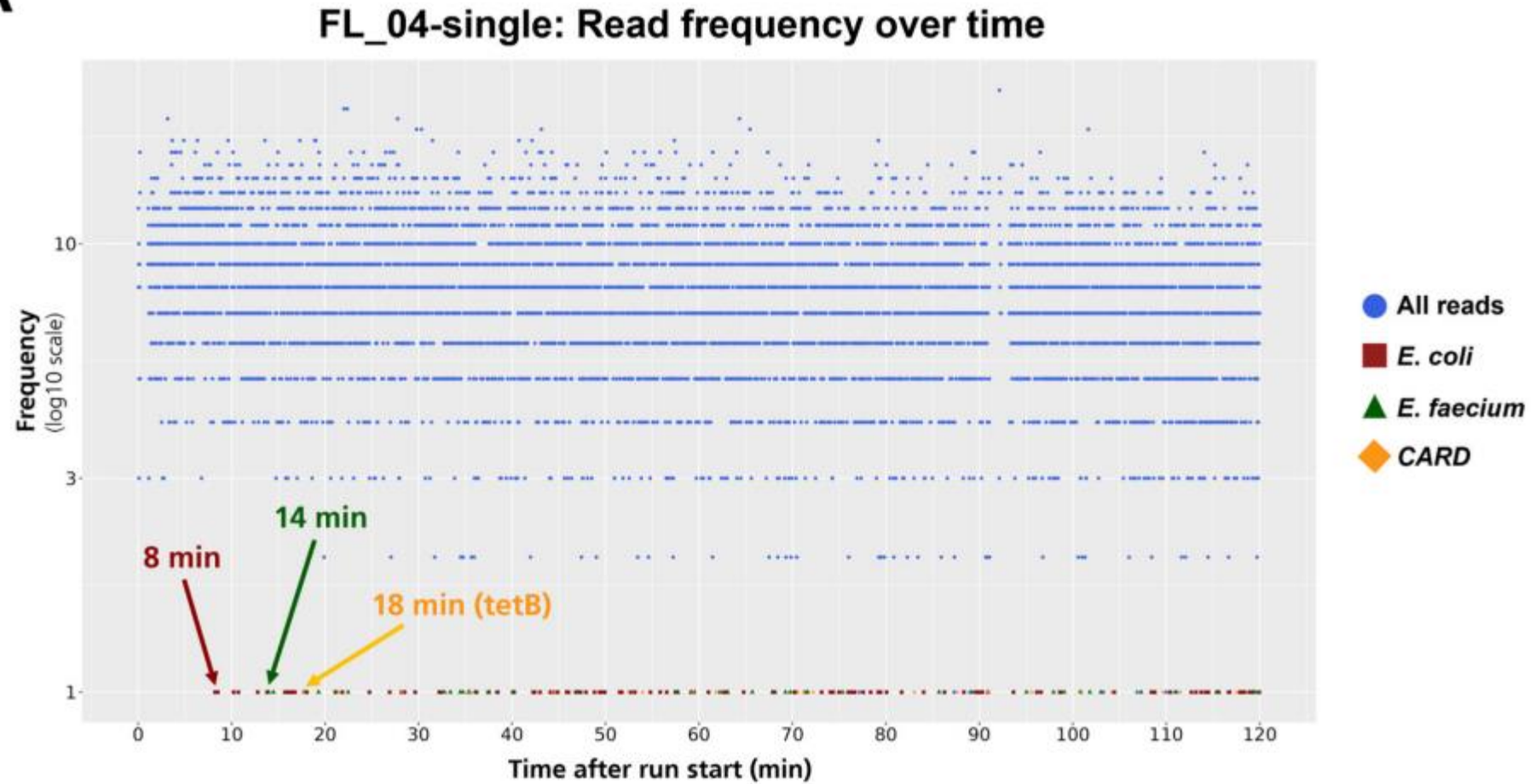
B

FC_01: Read frequency over time



Overcome Traditional Challenges for fighting AMR (5)

A



Precision microbiome testing: STI, HPV and AMR

Women's Health Test

Page 1 of 4

Patient Name:	nan	Provider:	Mony Sary, Yap Chew, Wendy Ullmer	Patient ID:	VS8
Gender:	nan	Provider NPI:	nan	Specimen ID:	KH20.45474
DOB:	nan	Order Date:	nan	Specimen Type:	nan
Age:	nan	Health Status Reported:	nan	Collection Date:	nan

Sexually Transmitted Infections

Name	Associated Condition	Result
<i>Neisseria gonorrhoeae</i>	Gonorrhea, urethritis, pelvic inflammatory disease, gonococemia, gonococcal ophthalmia neonatorum	Detected
<i>Chlamydia trachomatis</i>	Chlamydia, cervicitis, urethritis, pelvic inflammatory disease	Not Detected
<i>Mycoplasma genitalium</i>	Urethritis, cervicitis, pelvic inflammatory disease	Not Detected
<i>Treponema pallidum</i>	Syphilis	Not Detected
<i>Haemophilus ducreyi</i>	Chancroid	Not Detected
<i>Trichomonas vaginalis</i>	Trichomoniasis	Not Detected
<i>Human papillomavirus</i>	Cervical and anogenital cancers, genital warts	Detected
<i>Herpes simplex virus</i>	Genital herpes, oral herpes	Not Detected

Viruses Detected

Name	Associated Condition
<i>Human papillomavirus 62 (HPV 62)</i>	Unknown risk for cervical cancer

Note: Human papillomavirus (HPV) 16, 18, 31, 33, 35, 39, 45, 51, 56, 58, 59, and 68 are considered high-risk or probable high-risk due to their association with cervical cancer. HPV 6, 11, 42, 43, and 44 are considered low-risk for cervical cancer but may cause genital warts. Other HPV genotypes found in the sample may have intermediate or unknown risk for cervical cancer.

Antimicrobial Resistance Genes Detected

AMR Gene Name	Function	Drug Class
<i>Neisseria.gonorrhoeae.folP</i>	Dihydropteroate synthase (mutated)	Sulfonamide

Women's Health Test

Page 1 of 4

Patient Name:	nan	Provider:	Yap Chew	Patient ID:	nan
Gender:	nan	Provider NPI:	nan	Specimen ID:	202122865
DOB:	nan	Order Date:	nan	Specimen Type:	nan
Age:	nan	Health Status Reported:	nan	Collection Date:	nan

Sexually Transmitted Infections

Name	Associated Condition	Result
<i>Neisseria gonorrhoeae</i>	Gonorrhea, urethritis, pelvic inflammatory disease, gonococemia, gonococcal ophthalmia neonatorum	Not Detected
<i>Chlamydia trachomatis</i>	Chlamydia, cervicitis, urethritis, pelvic inflammatory disease	Not Detected
<i>Mycoplasma genitalium</i>	Urethritis, cervicitis, pelvic inflammatory disease	Not Detected
<i>Treponema pallidum</i>	Syphilis	Not Detected
<i>Haemophilus ducreyi</i>	Chancroid	Not Detected
<i>Trichomonas vaginalis</i>	Trichomoniasis	Not Detected
<i>Human papillomavirus</i>	Cervical and anogenital cancers, genital warts	Detected
<i>Herpes simplex virus</i>	Genital herpes, oral herpes	Not Detected

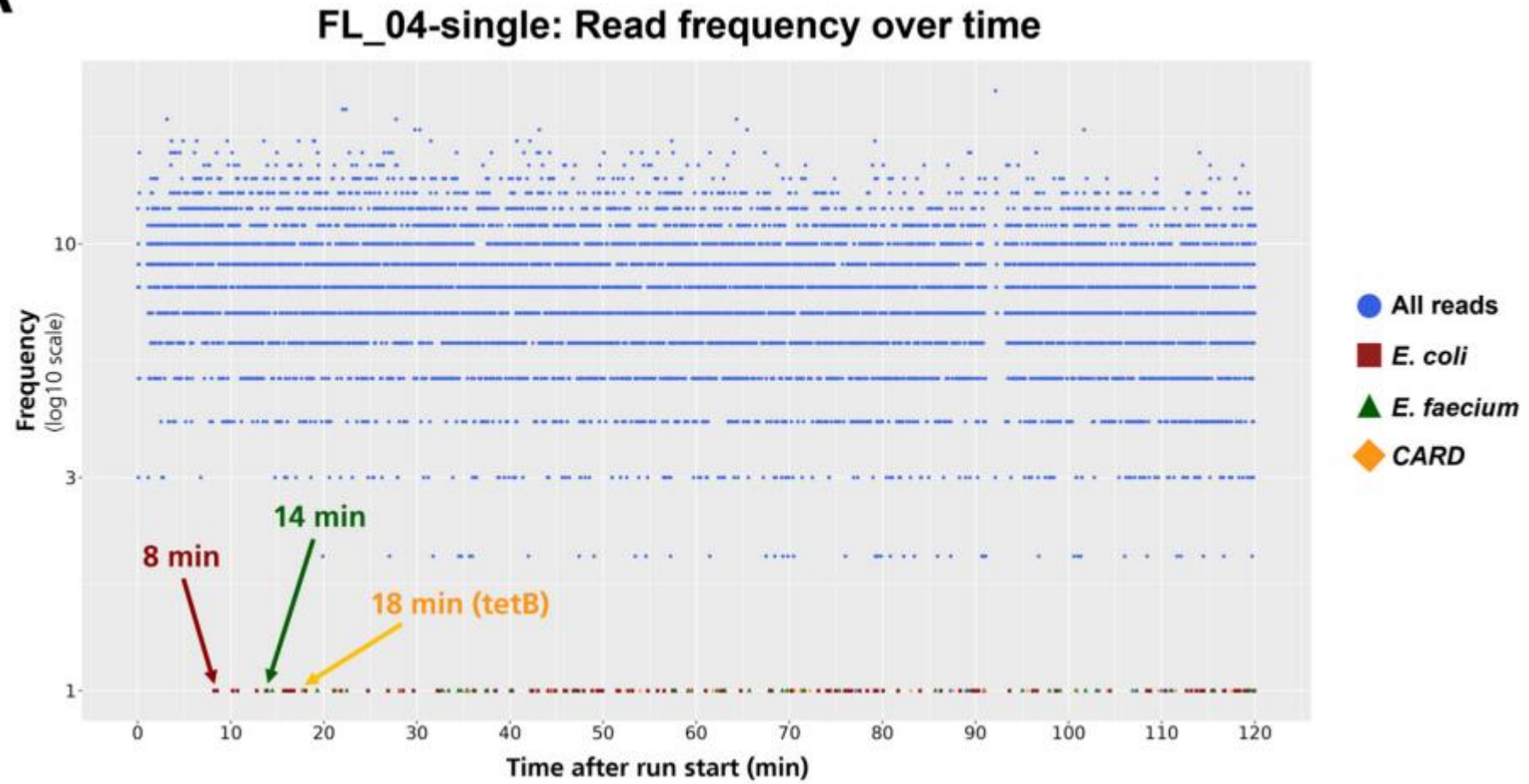
Viruses Detected

Name	Associated Condition
<i>Human papillomavirus 52 (HPV 52)</i>	High-risk for cervical cancer
<i>Human papillomavirus 68 (HPV 68)</i>	High-risk for cervical cancer

Note: Human papillomavirus (HPV) 16, 18, 31, 33, 35, 39, 45, 51, 56, 58, 59, and 68 are considered high-risk or probable high-risk due to their association with cervical cancer. HPV 6, 11, 42, 43, and 44 are considered low-risk for cervical cancer but may cause genital warts. Other HPV genotypes found in the sample may have intermediate or unknown risk for cervical cancer.

Challenges and Future Directions

A



Acknowledgement

A/Prof Phạm Lê An
Dr. Nguyễn Việt Hậu
Dr. Nguyễn Thị Kim Nhi



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Thank you for your attention!