1st FWD AMR – RefLabCap workshop

Multidisciplinary training for public health microbiologists and epidemiologists

Added value of whole-genome sequencing

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Provision of EU networking and support for public health reference laboratory functions for antimicrobial resistance in *Salmonella* species and *Campylobacter* species in human samples

Whole-genome sequencing in clinical settings

Main advantages

- Higher resolution for typing and cluster analysis
- Simplicity of storing and sharing data

Main concerns

- Acceptance by healthcare professionals
- Cost of implementation and routine use → Cost-analysis studies

Cost-analysis studies

Summary of publications

- Eight studies selected: WGS-based diagnostics and/or surveillance
- Very recent analyses: 2019 - 2021
- Similar type of socioeconomic settings: United Kingdom, Australia, Canada, United States of America
- Catchment sizes: hospital-wide up to country-wide
- Timeframes for conclusions: mainly yearly

Savings of million Euros per year

[Decrease in number of infections, hospitalizations and deaths]

Cost-analysis studies

Publications

- Three analysed in-depth as examples
- Rest summarized in the end

Cost-analysis studies

Colman RE, Mace A, Seifert M, Hetzel J, Mshaiel H, Suresh A, et al. Whole-genome and targeted sequencing of drug-resistant Mycobacterium tuberculosis on the iSeq100 and MiSeq: A performance, ease-of-use, and cost evaluation. PLoS Med 2019;16:e1002794. https://doi.org/10.1371/journal.pmed.1002794.

Methods and findings

In this study, we evaluated WGS and targeted NGS for TB on both the new iSeq100 and the widely used MiSeq (both manufactured by Illumina) and compared sequencing performance, costs, and usability. We utilized DNA libraries produced from *Mycobacterium tuberculosis* clinical isolates for the evaluation. We conducted WGS on three strains and observed equivalent uniform genome coverage with both platforms and found the depth of coverage obtained was consistent with the expected data output. Utilizing the standardized, cloud-based ReSeqTB bioinformatics pipeline for

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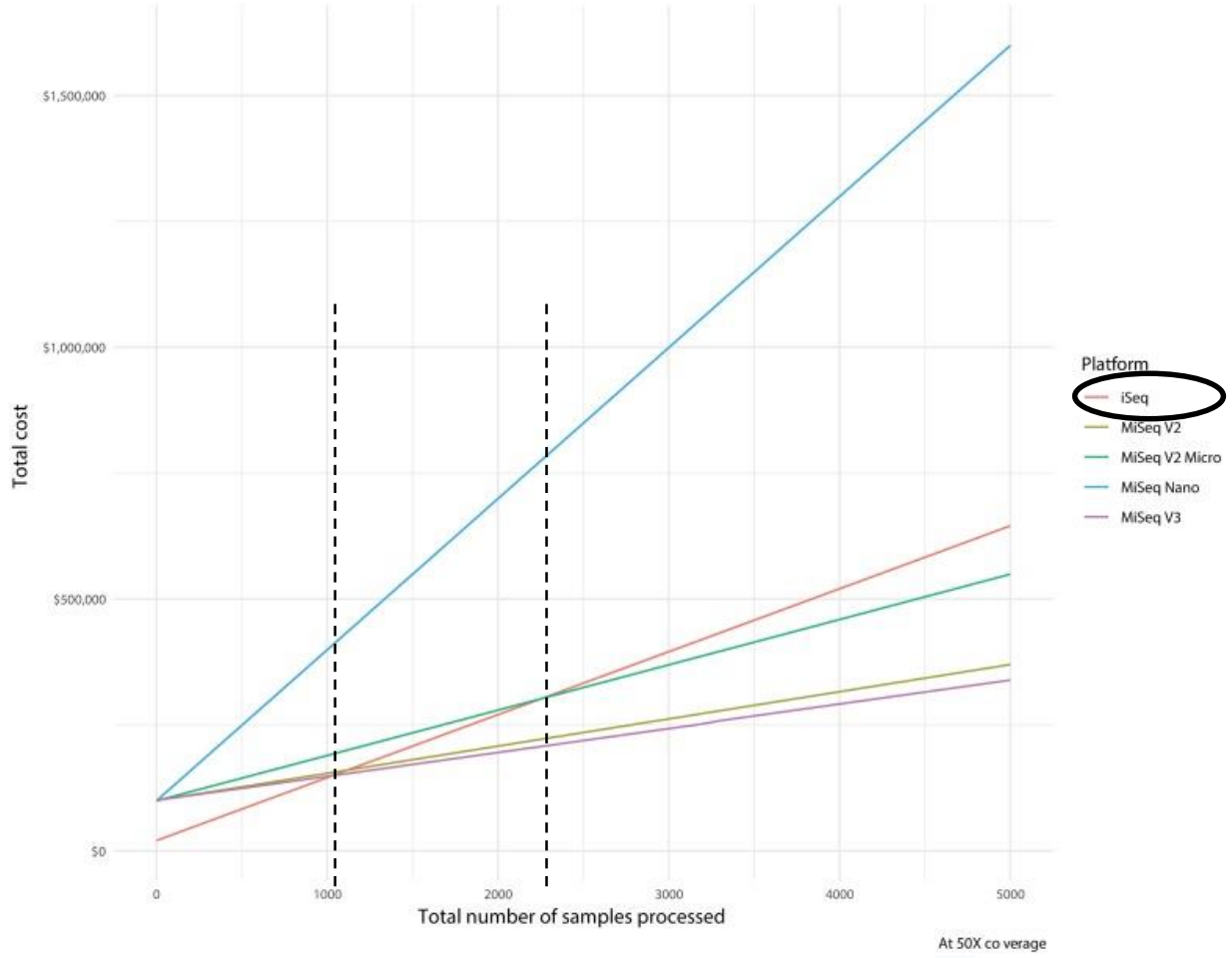
The upfront capital costs are almost 5-fold lower for the iSeq100 ($19,900 USD) platform in comparison to the MiSeq ($99,000 USD); however, because of difference in the batching capabilities, the price per sample for WGS was higher on the iSeq100. For WGS of *M. tuberculosis* at the minimum depth of coverage of 30x, the cost per sample on the iSeq100 was $69.44 USD versus $28.21 USD on the MiSeq, assuming a 2 × 150 bp run on a v3 kit. In terms of ease of use, the sequencing workflow

USA, 2018

Cost-analysis studies



Cost trajectories with total numbers of samples processed. Cost per sample was calculated for average depth of 50× coverage using 2 × 150 bp runs. Total cost includes capital cost of sequencer and sequencing cost per sample.

Cost-analysis studies

Conclusions

The iSeq100 instrument is capable of running existing TB WGS and targeted NGS library preparations with comparable accuracy to the MiSeq. The iSeq100 has reduced sequencing workflow hands-on time and is able to deliver sequencing results in <24 hours. Reduced capital and maintenance costs and lower-throughput capabilities also give the iSeq100 an advantage over MiSeq in settings of individualized care but not in high-throughput settings such as reference laboratories, where sample batching can be optimized to minimize cost at the expense of workflow complexity and time.

Cost-analysis studies

Table 3

Instrumentation comparison of MiSeq and iSeq100 platforms.

Characteristic	MiSeq	iSeq100
Footprint (cm) W × H × D	68.6 × 52.3 × 56.6	42.5 × 30.5 × 33
Number of steps to start sequencing[a]	74	59
Number of steps after sequencing run[a]	27	6
Maintenance	Washes monthly, standby wash after idle mode (idle for 7 days)	Air filters every 6 months
Hands-on time[b]	Approximately 53 minutes	Approximately 27 minutes
Time to completion (2 × 150 bp run)	24 hours	17.5 hours

Open in a separate window

[a]Calculated from the system guides.

[b]Calculated including both setup and post-run steps.

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	Benchtop Sequencers			Production-Scale Sequencers	
	 iSeq 100	 MiniSeq	 MiSeq Series	 NextSeq 550 Series	 NextSeq 1000 & 2000
Popular Applications & Methods	Key Application	Key Application	Key Application	Key Application	Key Application
Large Whole-Genome Sequencing (human, plant, animal)					
Small Whole-Genome Sequencing (microbe, virus)	●	●	●	●	●
Exome & Large Panel Sequencing (enrichment-based)				●	●
Targeted Gene Sequencing (amplicon-based, gene panel)	●	●	●	●	●
			(...)		
Run Time	9.5–19 hrs	4–24 hours	4–55 hours	12–30 hours	11-48 hours
Maximum Output	1.2 Gb	7.5 Gb	15 Gb	120 Gb	360 Gb *
Maximum Reads Per Run	4 million	25 million	25 million †	400 million	1.2 billion *
Maximum Read Length	2 × 150 bp	2 × 150 bp	2 × 300 bp	2 × 150 bp	2 × 150 bp

https://www.illumina.com/systems/sequencing-platforms.html

Cost-analysis studies

What does this mean for us?

- It’s not enough to consider the initial cost of the machine
- Person-work hours must be taken into account
- Throughput needs must be evaluated

Cost-analysis studies

Gordon LG, Elliott TM, Forde B, Mitchell B, Russo PL, Paterson DL, et al. Budget impact analysis of routinely using whole-genomic sequencing of six multidrug-resistant bacterial pathogens in Queensland, Australia. BMJ Open 2021;11:e041968. https://doi.org/10.1136/bmjopen-2020-041968.

Design Budget impact analysis was performed over the following 5 years. Data were primarily from sequencing results on clusters of multidrug-resistant organisms across 27 hospitals. Model inputs were derived from hospitalisation and sequencing data, and epidemiological and costing reports, and included multidrug resistance rates and their trends.

Setting Queensland, Australia.
Participants Hospitalised patients.

2021

Approx. 1.6 M hospitalizations/year

and accounted for 95% of all sequenced isolates. A review of Australian hospital infection data, government reports and published studies provided the estimates for the analysis. Sequencing data to identify clusters were examined over 2 years. Costs were aggregated for the state of Queensland based on the expected number of MRO isolates arising in Queensland hospital patients. Costs were calculated annually across 5 years from the base year 2020. The International Society for Pharmacoeconomics and Outcomes Research good practice guidelines for

Cost-analysis studies

Table 1 Parameter values used in estimating the number of hospitalised patients affected by MROs

Variable	Estimate (95% CI)	Source
Number of Queensland hospital admissions per quarter	409 972 (348 476 to 462 243)	Queensland Health[9]
Prevalence of all hospitalisations with HAI (%)	9.9 (8.8 to 11.0)	Russo *et al*[10]
Species of all HAIs* (%)		
Staphylococcus aureus	13.8 (10.2 to 17.3)	Russo *et al*[10]
Escherichia coli	8.8 (5.9 to 11.7)	
Enterococcus faecium	5.8 (3.4 to 8.2)	
Klebsiella pneumoniae	4.4 (2.3 to 6.5)	
Enterobacter cloacae	1.9 (0.5 to 3.3)	
Acinetobacter baumannii	1.1 (0.0 to 2.2)	
Multidrug-resistant† (%)		

Table 2 Variables used in estimating the cost of MRO screening and treatments

Variable	Estimate (95% CI)	Comment/source
Cost of screening for pathogens		
Usual screening: microbiology test and PCR	$82 ($58 to $107)	Elliott *et al*[5]
WGS: microbiology test, PCR and WGS	$437 ($309 to $565)	Elliott *et al*[5]
Cleaning and extra nurse time per detection*	$122 ($90 to $155)	Elliott *et al*[5]
PPE per day in isolation	$50 ($35 to $65)	Otter *et al*[18]
Closed-bed day	$246 ($151 to $342)	Page *et al*[25]†
Cost of antibiotic treatment per infected patient		
MRSA		

Cost-analysis studies

Interventions WGS surveillance of six common multidrug-resistant organisms (*Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Enterobacter* sp and *Acinetobacter baumannii*) compared with standard of care or routine microbiology testing.

Hospital and Princess Alexandra Hospital. Genetic relatedness was determined by examining the number of core genome single nucleotide polymorphisms (SNP) that differ between any two isolates (pair-wise core genome SNP distance). Genetically related isolates were subdivided into clusters when the SNP distance between them was under a predefined threshold, adjusted for genome size (5 SNPs/Mb).[14 15] Clustering was evident in all six pathogens, and isolates within these clusters demonstrate

The number of patients in whom infection or colonisation could have been prevented was calculated after WGS identified a cluster (two or three patients) and began control measures. The turnaround time for WGS testing was 7 days; this is the time required for WGS to be processed and the results made available to the physicians. For example, if the cluster was identified after two

Cost-analysis studies

Primary and secondary outcomes Expected hospital costs, counts of patient infections and colonisations, and deaths from bloodstream infections.

Results In 2021, 97 539 patients in Queensland are expected to be infected or colonised with one of six multidrug-resistant organisms with standard of care testing. WGS surveillance strategy and earlier infection control measures could avoid 36 726 infected or colonised patients and avoid 650 deaths. The total cost under standard of care was $A170.8 million in 2021. WGS surveillance costs an additional $A26.8 million but was offset by fewer costs for cleaning, nursing, personal protective equipment, shorter hospital stays and antimicrobials to produce an overall cost savings of $30.9 million in 2021. Sensitivity analyses showed cost savings remained when input values were varied at 95% confidence limits.

38%

0.7%

20 M EUR

Cost-analysis studies

What does this mean for us?

- It’s important to have a strong overview of national epidemiological situation
- Costs are pathogen-dependent
- Clear advantage of WGS-based surveillance compared to other methods

Cost-analysis studies

Kumar P, Sundermann AJ, Martin EM, Snyder GM, Marsh JW, Harrison LH, et al. Method for Economic Evaluation of Bacterial Whole Genome Sequencing Surveillance Compared to Standard of Care in Detecting Hospital Outbreaks. Clin Infect Dis 2021;73:E9–18. https://doi.org/10.1093/cid/ciaa512.

Methods. The economic value of a WGS surveillance-based IP program was assessed from a hospital's perspective using historical outbreaks from 2011–2016. We used transmission network of outbreaks to estimate incremental cost per transmission averted. The number of transmissions averted depended on the effectiveness of intervening against transmission routes, time from transmission to positive culture results and time taken to obtain WGS results and intervene on the transmission route identified. The total cost of an IP program included cost of staffing, WGS, and treating infections.

U.S.A.

Table 1. Outbreak-specific Inputs

Variable	Value
Number of outbreaks by organism	11
Klebsiella pneumoniae	3
Acinetobacter baumannii	2
Clostridioides difficile	4
Pseudomonas aeruginosa	1
Pseudomonas putida	1
Total number of patients, N	89
Number of patients in each outbreak, median (range)	4 (2–32)

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” *The number of transmissions averted (…)*

(…) total number of days taken to obtain WGS results and intervene (…)

(…) assumed 8 days
(5 days to take the culture since transmission + 3 days to receive culture results) ”

Table 2. Data Inputs for Variables in the Model

Variable
Effectiveness related parameters
Time from transmission to positive culture results under WGS surveillance-based IP program
Response time under WGS surveillance-based IP program[b]
Effectiveness (relative risk) of intervening against transmission routes
Instrument
Inpatient unit
Unknown
% colonized respiratory cultures[c]
Attributable mortality risk due to infection
Pneumonia
Wound
Urinary tract
Bacteremia
Clostridioides difficile
Cost-related parameters[d]

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Table 3. Results: Number of Transmissions Averted Under WGS Surveillance-based infection prevention (IP) Program

No.	Outbreak	SoC	WGS Surveillance	Transmissions averted
1	*Klebsiella pneumoniae* – A	21.0	10.2	10.8
2	*K. pneumoniae* – B	32.0	7.0	25.0
3	*K. pneumoniae* – C	7.0	5.0	2.0
4	*Acinetobacter* – A	3.0	3.0	0.0
5	*Acinetobacter* – B	5.0	4.4	0.6
6	*Clostridioides difficile - A*	2.0	2.0	0.0
7	*C. difficile - B*	2.0	2.0	0.0
8	*C. difficile - C*	2.0	2.0	0.0
9	*C. difficile - D*	4.0	3.7	0.3
10	*Pseudomonas aeruginosa*	8.0	6.0	2.0
11	*Pseudomonas putida*	3.0	3.0	0.0
	Total	89.0	48.3	40.7

Abbreviations: SoC, standard of care; WGS, whole genome sequencing.

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Base Case Results

The 11 outbreaks included 89 patients and each outbreak had 2–32 patients. Had WGS surveillance for outbreak detection been in place during the study period, there would have been approximately 41 fewer transmissions (including both colonization and infection) and 3.1 fewer deaths (Table 3 and Table 4).

Had WGS surveillance been in place at the time of each outbreak and assuming the same number of outbreaks, it would have resulted in saving of $487 747 in infection treatment costs (~$11 900 per transmission averted) over the study period. However, the net savings would have been $11 817 because the cost of doing WGS surveillance increased by $475 930. The cost-effectiveness results indicated that the WGS surveillance-based IP program resulted in net saving of $9073 (discounted) and approximately 38 fewer transmissions (discounted), thereby making WGS surveillance-based IP program a less costly and more effective strategy than SoC (Table 4).

Cost-analysis studies

What does this mean for us?

- It’s possible to perform more ”simple” retroactive analyses of cost-effectiveness
- More modest savings this way, but still clear advantage of WGS-based surveillance

Cost-analysis studies

Hospitalar

Reference	Settings	Conclusions
Dymond A, Davies H, Mealing S, Pollit V, Coll F, Brown NM, et al. Genomic Surveillance of Methicillin-resistant Staphylococcus aureus: A Mathematical Early Modeling Study of Cost-effectiveness. Clin Infect Dis 2020;70:1613–9. https://doi.org/10.1093/cid/ciz480.	United Kingdom, one hospital with catchment of 5 M people (65.000 patients), during one year	290 cases avoided 2 deaths prevented Savings of 800,000 EUR per year (only considering MRSA)
Elliott TM, Lee XJ, Foeglein A, Harris PN, Gordon LG. A hybrid simulation model approach to examine bacterial genome sequencing during a hospital outbreak. BMC Infect Dis 2020;20:72. https://doi.org/10.1186/s12879-019-4743-3.	U.S.A., one nosocomial outbreak of *E. coli* within a cohort of ca. 550 patients	Early WGS: 151 colonizations avoided 40 infections prevented Savings of 500.000 EUR per one outbreak
Sundermann AJ, Chen J, Kumar P, Ayres AM, Cho S-T, Ezeonwuka C, et al. Whole-Genome Sequencing Surveillance and Machine Learning of the Electronic Health Record for Enhanced Healthcare Outbreak Detection. Clin Infect Dis 2021;ciab946. https://doi.org/10.1093/cid/ciab946.	U.S.A., surveillance of HAI during two years in one hospital	25 to 63 transmissions avoided 8.000 to 11.000 EUR saved per transmission Total savings of 197.000 to 710.000 EUR

Cost-analysis studies

Food

Reference	Settings	Conclusions
Jain S, Mukhopadhyay K, Thomassin PJ. An economic analysis of salmonella detection in fresh produce, poultry, and eggs using whole genome sequencing technology in Canada. Food Res Int 2019;116:802–9. https://doi.org/10.1016/j.foodres.2018.09.014.	Nontyphoidal Salmonellosis from fresh produce, poultry and eggs in Canada	Savings of 4 - 66 M Euro per year
Brown B, Allard M, Bazaco MC, Blankenship J, Minor T. An economic evaluation of the Whole Genome Sequencing source tracking program in the U.S. PLoS One 2021;16:e0258262. https://doi.org/10.1371/journal.pone.0258262.	GenomeTrakr network on the U.S.A. (foodborne *E. coli*, *Listeria*, and *Salmonella*)	Savings of > 450 M Euro per year

To consider…

Limitations

- Cost-analysis studies are generally restricted to the place where they are conducted
- Most of these are predictive

Applicability

- Framework to conduct local analysis
- Evidence to include in business cases

Thank you on behalf of the FWD AMR-RefLabCap team

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