Economic evaluations of whole-genome sequencing for pathogen identification in public health surveillance and health-care-associated infections: a systematic review

My Tran, Kayla S Smurthwaite*, Son Nghiem, Danielle M Cribb, Alireza Zahedi, Angeline D Ferdinand, Patiyan Andersson, Martyn D Kirk, Kathryn Glass, Emily Lancsar, on behalf of AusPathoGen Program partners*

Whole-genome sequencing (WGS) has resulted in improvements to pathogen characterisation for the rapid investigation and management of disease outbreaks and surveillance. We conducted a systematic review to synthesise the economic evidence of WGS implementation for pathogen identification and surveillance. Of the 2285 unique publications identified through online database searches, 19 studies met the inclusion criteria. The economic evidence to support the broader application of WGS as a front-line pathogen characterisation and surveillance tool is insufficient and of low quality. WGS has been evaluated in various clinical settings, but these evaluations are predominantly investigations of a single pathogen. There are also considerable variations in the evaluation approach. Economic evaluations of costs, effectiveness, and cost-effectiveness are needed to support the implementation of WGS in public health settings.

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*Joint first authors

National Centre for Epidemiology and Population Health, Australian National University, Canberra ACT, Australia (M Tran PhD, K S Smurthwaite PhD, S Nghiem PhD, D M Cribb BSc, Prof M D Kirk PhD, Prof K Glass PhD, Prof E Lancsar PhD)**; Public Health Microbiology, Forensic and Scientific Services, Queensland Health, Brisbane QLD, Australia** (A Zahedi PhD)**; Microbiological Diagnostic Unit, Peter Doherty Institute, University of Melbourne, Melbourne VIC, Australia** (A D Ferdinand PhD, P Andersson PhD)

Correspondence to: Dr My Tran, National Centre for Epidemiology and Population Health, Australian National University, Canberra, ACT 2601, Australia
my.tran@anu.edu.au

Introduction

Infectious diseases continue to pose a substantial threat to public health globally. The rise of whole-genome sequencing (WGS) technologies, including next-generation sequencing, has facilitated the rapid investigation and management of disease outbreaks and routine infections compared with conventional pathogen typing methods.[1–3] There is global interest in implementing WGS for public health surveillance, with established systems across Europe, the UK, Canada, and the USA.[3–8] In Australia, WGS is progressively being introduced to public health laboratories for outbreak investigation and routine surveillance activities.[9] Globally, the use of WGS has been applied to foodborne, antimicrobial-resistant, vaccine-preventable, and nosocomial pathogens.[3,5,10–12] International public health events, including COVID-19 and mpox (formerly known as monkeypox), have further shown the value of genomics for pathogens of public health importance.[13–18]

Conventional typing includes well-established, culture-dependent methods, such as pulsed-field gel electrophoresis (PFGE), multi-locus variable number of tandem repeats analysis (MLVA), and multi-locus sequence typing (MLST).[2,3,10,19,20] Although these methods provide discriminatory data for pathogen detection and analysis, they do not have adequate resolution as stand-alone methods and often require resource-intensive and species-specific protocols.[2] PCR, a component of MLVA and MLST, has developed over the past two decades as a culture-independent testing method, allowing quick and inexpensive pathogen detection.[10,21] However, none of these methods provide sufficient detail on pathogen relatedness for many public health surveillance activities (eg, antimicrobial susceptibility testing and subtyping).[10,21]

WGS technology provides a high-throughput process, high-resolution results to the single nucleotide level, and information on species identity, serotype, virulence, and antimicrobial resistance genotypes through a single approach.[1,2] The public health applications of the high-resolution data derived from WGS for pathogen identification and surveillance can increase precision for source attribution, reduce the size and burden of outbreaks, and detect and quantify antimicrobial resistance in pathogen strains.[11,12,22–28] Decreases in the cost of WGS, improvements in the speed and accuracy of the technology, and advancements in bioinformatics tools potentially make large-scale implementation feasible for public health surveillance.[29] However, WGS is more expensive than some conventional phenotypic and molecular detection methods, and adopting the technology requires substantial financial and workforce investment due to high equipment costs and workforce upskilling.[2,3,12]

Economic evaluations of WGS implementation, compared with conventional typing methods or conducting primary diagnostic testing only, can elucidate the economic and societal value of WGS for the surveillance and management of infectious diseases in public health settings. Although systematic reviews in this area are scarce, a study has summarised the economic implications of WGS use on bacterial pathogen surveillance.[30] Our study addresses additional key gaps within the literature on the economic evidence of WGS in public health and infection control settings, specifically the methodological quality of existing economic evaluations. We conducted a comprehensive systematic review of published literature, including all pathogen types, to identify which pathogens have been studied in an economic evaluation of WGS in a public health setting, identify which economic questions have been addressed, identify which methods have been used in economic evaluations of WGS, and synthesise the evidence regarding the costs, effectiveness, and cost-effectiveness of WGS in a public health setting. Based on the review findings, we provide

Key messages

- Implementation of whole-genome sequencing for pathogen identification is an emerging alternative to conventional pathogen typing methods
- Current economic evidence of whole-genome sequencing for infectious disease surveillance is setting-specific and pathogen-specific, with a broad range of costs and effectiveness estimates globally
- Economic evaluations are limited to high-income countries and centred on health-care-associated infections and foodborne pathogens
- Estimates of the costs and benefits of whole-genome sequencing largely exclude indirect impacts on the health-care system
- Access to national-scale longitudinal epidemiology data is vital for a more rigorous economic evaluation
- A consistent economic evaluation framework would allow the comparison of evidence across public health settings

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recommendations for the future economic evaluation of WGS for pathogen identification and surveillance.

Methods

We designed a systematic review according to the PRISMA guidelines.[31] The original protocol is registered with the International Prospective Register of Systematic Reviews (CRD42022313658).

Search strategy and selection criteria

See Online for appendix

We considered articles reporting an economic evaluation of WGS for pathogen surveillance for inclusion in this systematic review. Only full-text articles available in English were considered. The inclusion and exclusion criteria for the systematic review are in the appendix (p 2).

We developed the search terms for the online database using an iterative method. First, we compiled keywords using the Medical Subject Headings (MeSH) associated with the review question using filters for English language and human participants. Next, we used the key terms and MeSH to search one database (PubMed) to test the sensitivity of the draft search strategy. Following agreement on the search strategy, we applied the search strategy to additional online scientific journal databases, including Web of Science, Ovid MEDLINE, EconLit, Cochrane, and the Centre for Reviews and Dissemination Database. The search syntax for each database is in the appendix (p 3).

We conducted searches of relevant grey literature sources, including reports, guidelines, and frameworks from the US Food and Drug Administration, WHO, US Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control, UK Health Security Agency, and the Australian Government Department of Health. We applied the same search syntax when advanced searching was available on grey literature websites. When searching was limited to keywords, we conducted a search using keywords associated with "whole genome sequencing" and "economic evaluation".

Two reviewers (KSS and MT) conducted database searches and screening in duplicate. After compiling the articles from the online databases, the reviewers extracted the articles to EndNote X9 and, subsequently, Rayyan.[32] The reviewers independently screened the articles in a three-step process at the title, abstract, and full-text levels. Following each stage, the reviewers compared screening decisions to reach a consensus on the articles included at each screening stage. A third reviewer (KG) assessed the remaining articles for which there was no consensus for inclusion in the review at the full-text stage.

We conducted forward and backward citation searches of articles included in the final review using an online tool called connected papers. Identification of articles from the forward and backward citation searches followed the same inclusion and exclusion criteria and three-step screening process.

Data extraction

Two reviewers extracted data from the articles based on their areas of expertise. The first reviewer (epidemiologist; KSS) extracted data for study design, study population, public health setting, and pathogen surveillance, and the second reviewer (economist; MT) extracted data related to the economic evaluation, including statistical analysis and outcomes. We extracted information from the included publications using a bespoke proforma (appendix p 4).

Quality assurance

Two reviewers (MT and SN) assessed the risk of bias for each study using the Consensus Health Economic Criteria (CHEC; scores can range from 0 to 100, with higher scores indicating a lower risk of bias),[33] which includes 19 questions on the economic evaluation design and the key components of the economic evaluation (eg, perspectives, costs, and outcomes; appendix p 5). The percentage of positive answers of the total number of valid answers was used as a score to synthesise the risk of bias score. We further classified studies into four groups: low risk (score 90–100%), lower moderate risk (80–89%), higher moderate risk (70–79%), and high risk (<70%).

Classifications of publications

We categorised publications into two groups: full or partial economic evaluations, following definitions proposed by Drummond and colleagues.[34] Publications were defined as full economic evaluations if data on both costs and outcomes were presented and data included a comparison of at least two alternative typing or testing methods. Publications that only included data on either costs or outcomes or considered costs and outcomes but

only for a single intervention were categorised as partial economic evaluations.[34]

Following Drummond and colleagues,[34] partial evaluations were further categorised into five types of studies, as follows: (1) studies that examined only the costs of a single intervention or programme and ignored outcomes were classified as cost description studies; (2) studies that compared the costs of at least two alternative interventions or programmes and ignored outcomes were classified as cost analysis studies; (3) studies that examined only the outcomes of a single intervention or programme and ignored costs were classified as outcome description studies; (4) studies that compared the outcomes of at least two alternative interventions or programmes and ignored costs were classified as outcome analysis studies; and (5) studies that described both costs and outcomes of a single intervention or programme were classified as cost–outcome description studies.

Full economic evaluations were categorised into five approaches, again following Drummond and colleagues.[34] All five approaches measured costs in monetary terms but differed in the measurement of outcomes or effectiveness. In a cost-consequence analysis, disaggregated incremental costs and a range of incremental outcomes are presented to allow readers to form their own opinion on the relevance and relative importance to their decision making context. Cost–minimisation analysis compares the costs of alternatives, assuming or knowing that the outcomes of competing alternatives are equivalent. In cost-effectiveness analysis, outcomes are measured in natural units (eg, cases detected producing an incremental cost per case detected). Cost–utility analysis defines outcomes in terms of quality-adjusted life-years (QALYs), which captures both quality of life and longevity, and produces an incremental cost per QALY gain. In both cost-effectiveness analysis and cost-utility analysis, results are expressed as incremental cost-effectiveness ratios (ICERs), which are compared with a threshold (in terms of decision makers' willingness to pay per QALY) to determine whether an intervention is cost-effective. Finally, in cost-benefit analysis, outcomes are valued in monetary terms, with such monetary values elicited with approaches such as contingent valuation or discrete choice experiments. Cost–benefit analysis results are commonly expressed as cost–benefit ratios or net benefits, in which a positive net benefit implies cost-effectiveness.

Data analysis

Counts were calculated for study characteristics with STATA 17.[35] All costs estimated for WGS and other typing methods were extracted from the included studies and converted to 2022 US$ on the basis of purchasing power parities with an online converter tool.[36] Purchasing power parities reflect the costs of purchasing a common basket of goods and services in different countries and are subject to fewer fluctuations than exchange rates. Minimum and maximum costs were calculated for each typing method. Finally, we calculated the ICER for studies that reported costs and effectiveness for all alternatives but did not report cost-effectiveness by dividing the incremental cost by incremental effectiveness.

Results

Of the 2285 unique publications identified through online database searches, 19 satisfied the inclusion criteria (figure 1). The review of grey literature sources provided no additional publications for inclusion. Forward and backward search added one additional publication.

Study characteristics

Studies were published between May, 2014 and Dec 13, 2021, with over half published in 2021. This pattern was consistent with the introduction of WGS to the public health setting in 2014 and its increased use since 2020.[21–23] Studies were primarily concentrated in high-income countries such as Australia (six studies), the USA (three studies), the UK (two studies), Denmark (two studies), Germany (one study), Spain (one study), and Canada (one study). The study sample size varied from 106 patients to a cohort of more than 400 000 patients. In total, eight studies reported the

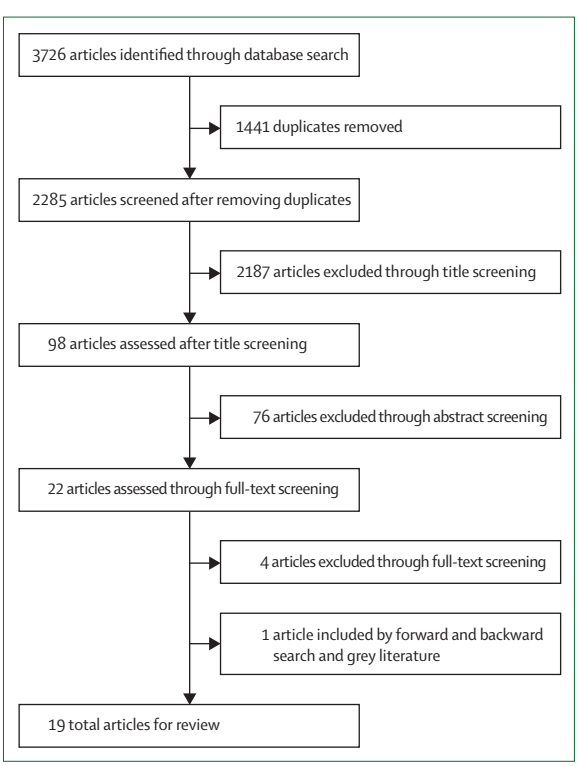

Figure 1: **Study selection**

number of isolates (range 22–645), number of samples (26–15 791), and number of specimens (37–345), and one study reported number of sequences (174). All articles considered a time horizon (ie, the duration over which health outcomes and costs are calculated) for their analyses, ranging from 7 days to 10 years.

We identified 19 economic evaluations of WGS used for pathogen identification and surveillance (appendix pp 6–7), of which seven were partial economic evaluations,[22,37–42] and 12 were full economic evaluations.[12,24,43–52] Of the full economic evaluations, six were cost–consequence analyses,[12,44,46,48,50,52] three were cost–benefit analyses,[24,45,49] two were cost-effectiveness analyses,[47,51] and one was a cost–utility analysis.[44] Of seven partial economic evaluations, two were cost analyses,[22,37] two were cost descriptions,[39,41] two were cost–outcome description studies,[38,40] and one was a budget impact analysis.[42]

Quality scoring varied from 27 to 100 points on the CHEC list (appendix pp 6–7).[33] Figure 2 illustrates the frequency of the 19 reviewed papers on four quality categories, determined by the inclusion of cost analysis, outcomes analysis, a comparator, and a sensitivity analysis. On the basis of these categories, more than 80% of the economic evaluations were assessed to be at high or moderate risk of bias (appendix pp 6–7). Of the seven partial evaluations, we classified five as high risk[22,38–41] and two as low moderate risk.[37,42] Of the 12 full evaluations, three were high risk,[12,46,50] four were high moderate risk,[24,43,44,52] two were low moderate risk,[45,48] and three were low risk.[47,49,51]

Types of pathogens

Of the 19 publications, ten studied health-care-associated infections,[39,40,42–44,46–48,51,52] four studied foodborne pathogens,[12,22,24,45] four studied *Mycobacterium tuberculosis*,[38,41,49,50] and one studied both foodborne and respiratory pathogens.[37]

Of the health-care-associated infection studies, we identified four cost–consequence analyses,[44,46,48,52] two cost-effectiveness analyses,[47,51] one cost–utility analysis,[43] one budget impact analysis,[42] one cost description,[39] and one cost–outcome description.[40] Of the foodborne studies, two were cost–benefit analyses,[24,45] one was a cost-consequence analysis,[12] and one was a cost analysis.[22] Of the *M tuberculosis* studies,

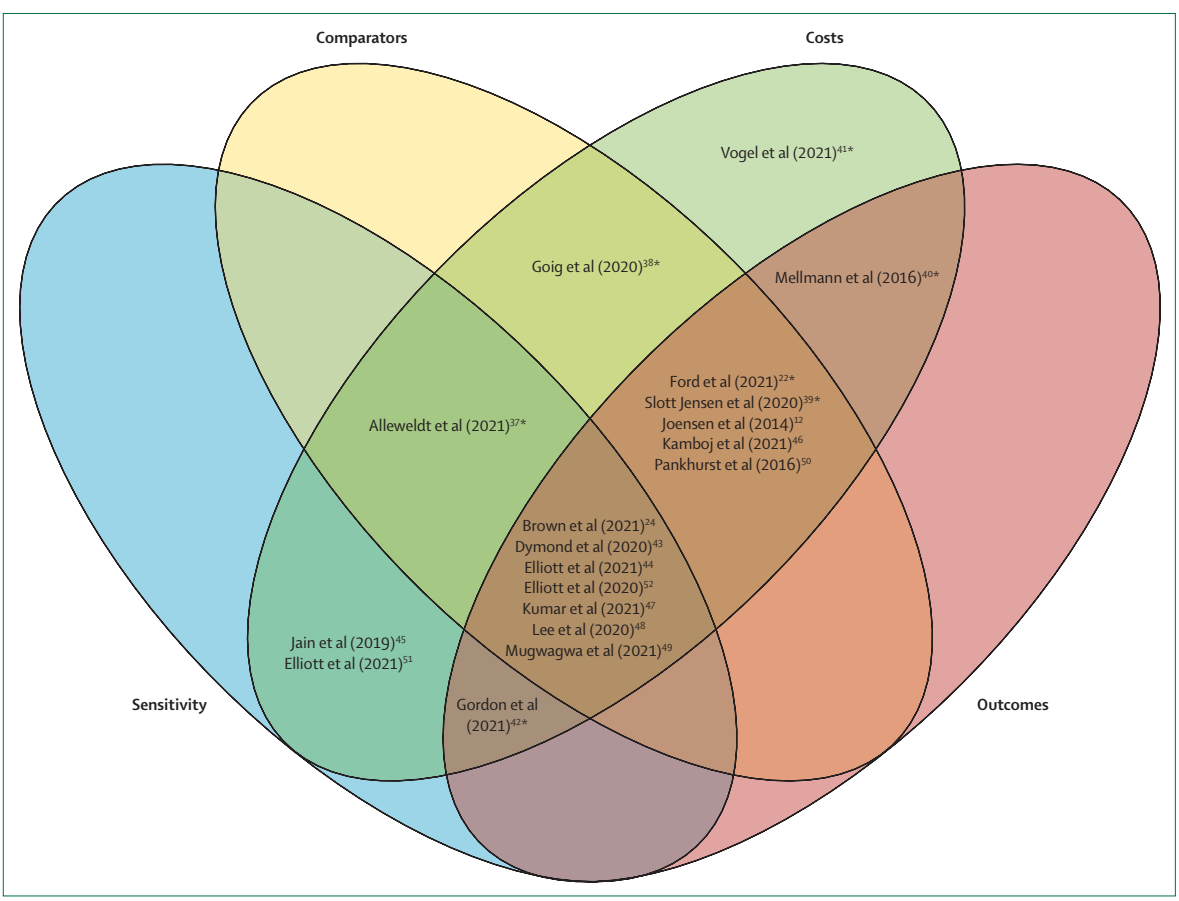

Figure 2: **Venn diagram of the overlap of four quality categories, determined by the inclusion of: cost analysis (costs), outcome analysis (outcomes), a comparator (comparators), and a sensitivity analysis (sensitivity) in the reviewed article**
*Indicates partial evaluations.

one was a cost–benefit analysis,[49] one was a cost–consequence analysis,[50] one was a cost–outcome description,[38] and one was a cost description study.[41] The study by Alleweldt and colleagues[37] was the only study that examined the use of WGS for both foodborne and respiratory pathogens, but it was limited to a cost analysis only.

Economics questions

There were substantial variations in the research questions addressed in the publications. In terms of population, ten studies investigated the use of WGS for hospitalised patients to identify transmission and control of hospital outbreaks.[39,40,42–44,46–48,51,52] The other nine studies examined the use of WGS for public health purposes in the general population—eg, to identify community clusters and enable contact tracing.[12,22,24,37,38,41,45,49,50]

The majority of the publications studied WGS alone or as a substitute for other typing and testing protocols.[12,22,24,37–42,44–48,49,50,52] Only two studies assessed WGS as a complementary investigation in infection control practice and hospital outbreak investigation.[43,51]

Four of the 19 studies were not a comparative analysis.[38–41] Of the 15 publications that stated the comparators, three studies compared WGS with a do-nothing option;[48,52] one study compared WGS and metagenomics with a do-nothing option;[51] two studies compared WGS with PFGE;[24,45] one study compared WGS with drug sensitivity and molecular tests;[49] one study compared a one-step protocol (ie, WGS alone) with a two-step protocol (ie, WGS and MLST together);[46] one study compared WGS with PCR, serotyping, and MLVA;[22] and seven studies compared WGS-based practice with current practice.[12,37,42–44,47,50] Current practice refers to alternative typing or testing methods and standard infection control protocols.

Costs included the cost of WGS, health-care costs, indirect costs (eg, productivity loss, premature mortality, and closed bed days), and intangible losses. Seven studies reported only costs of WGS,[12,37,38,40,41,46,50] nine reported both WGS and health-care costs,[39,42–44,47–49,51,52] and three included the cost of WGS, health-care costs, and indirect costs.[22,24,45]

Effectiveness can be measured using technical outcomes (eg, accuracy and turnaround times), clinical outcomes (eg, number of people infected or isolated cases and number of avoided deaths), and economic outcomes (eg, QALYs and disability-adjusted life-years). Five studies examined only technical outcomes,[12,38,40,46,50] seven reported only clinical outcomes,[22,24,42,44,47,48,52] and four assessed both clinical and economic outcomes.[43,45,49,51] Three studies reported cost-effectiveness as an ICER,[42,43,47] and three studies reported cost-effectiveness as net benefits.[24,45,49]

Methods of economic evaluation

The perspective of economic evaluation is important, as this determines which costs and effects should be incorporated into the study. Five studies, which were all partial economic evaluations, did not state the perspective of their articles clearly.[12,38–41,46] Of the 14 studies that stated their perspective, five adopted laboratory and hospital perspectives,[12,44,47,50,51] four adopted health system perspectives,[37,48,49,52] two adopted a government perspective,[42,43] and three adopted a societal perspective.[22,24,45]

We identified three sources of epidemiological data from the literature: outbreak data, clinical data, and national surveillance data. Six studies used historical outbreak data to simulate an outbreak.[37,39,44,47,51,52] Nine studies used clinical data collected from administrative records or trials.[12,38,40–43,46,48,50] Only four studies used data from national surveillance programmes.[22,24,45,49] Clinical data or trial data were more common in partial evaluations.

Of the reviewed papers, there were no studies that did both trial-based and model-based evaluations. Instead, there were seven trial-based evaluations.[12,38–41,46,50] Three trials used the same isolates or specimens to compare WGS with other typing methods.[12,46,50] In addition, we identified eight model-based evaluations, in which a model was developed to estimate the incremental costs and benefits of WGS compared with other methods. A hybrid model, combining agent-based and discrete events, was the most common decision analysis model approach.[44,48,51,52] Dynamic transmission network models were used in two studies.[47,49] Two studies used decision tree analysis.[43,45] Other evaluation approaches included break-even analysis,[22,37] budget impact analysis,[42] and regression analysis.[24]

Since most studies were completed within a year, discounting was not included. However, of the five studies that used a time horizon of more than a year, three did not discount future costs or benefits.[24,41,42] Moreover, eight studies did not conduct sensitivity analyses to account for uncertainty in important parameters.[12,22,38–41,46,50]

Synthesis of economic evidence

Table 1 summarises the cost estimates for WGS and other typing methods. All 19 studies reported costs. However, six studies did not identify all relevant costs of each alternative[12,38–41,46] and three papers did not measure costs in physical units (ie, per unit cost or price).[12,22,38] 13 papers did not explain how their costs were estimated, including information on the physical units of resources used and their unit costs and prices.[12,22,37,38,40–46,52]

Cost per isolate, cost per sample, and cost per test were the most frequently reported costs (n=16). Some cost estimates overlapped, particularly in the six papers

	Minimum cost, US$	Maximum cost, US$
Per isolate		
WGS (n=7)	66·53	513·07
PFGE (n=2)	15·47	243·53
MLST (n=1)	13·52	..
Per sample		
WGS (n=4)	196·57	358·02
Sanger sequencing (haemagglutinin and neuraminidase analysis; n=1)	459·11*	..
Sanger sequencing (whole genome; n=1)	1185·27*	..
PCR; Sanger sequencing (haemagglutinin or neuraminidase); virus isolation; haemagglutination inhibition; virus neutralisation; NA-Star (n=1)	111·36*	..
Serotyping; PFGE; PCR; MLVA (n=1)	137·00*	..
Biochemical analysis; serotyping; PCR; MALDI-TOF; PFGE (n=1)	57·90*	..
PFGE; PCR; MALDI-TOF (n=1)	100·81*	..
PFGE; biochemical testing; serotyping (n=1)	128·86*	..
PCR; MLVA: MLST; fluorophore membrane; serotyping; phage typing; PFGE; D-tartrate; glucose gas; aminoglycoside-modifying enzymes; biochemistry (n=1)	228·63*	..
Per test		
WGS (n=6)	73·93	267·01
Metagenomics (n=1)	174·69	..
MLVA (n=1)	57·01	..
PCR (n=1)	37·57	..
Serotyping (n=1)	48·57	..
Microbiology tests (unspecified methods; n=2)	59·64	..

All costs are in 2022 US$. WGS=whole-genome sequencing. PFGE=pulsed-field gel electrophoresis. MLST=multi-locus sequence typing. MLVA=multi-locus variable number of tandem repeats analysis. MALDI-TOF=matrix-assisted laser desorption ionisation-time of flight. *Costs reflect all methods used when there is more than one method.

Table 1: **Summary of number of studies, and minimum and maximum of cost estimates for WGS and alternative typing method**

	Minimum	Maximum
Hands-on time		
WGS (n=1)	6·5–8 h	..
Serotyping, PCR, and PFGE (n=1)	14·5 h	..
Turnaround time		
WGS (n=3)	5 days	9 days
WGS and multi-locus sequence typing (n=1)	1 day	11 days
Genotyping (n=1)	31 days	..
Concordance rates	..	..
WGS (n=2)	93%	100%
Number of foodborne cases		
WGS (n=2)	32 957	47 082
PFGE (n=2)	46 902	..
Number of HAI cases (including asymptotic cases)		
With WGS (n=5)	3	709
Without WGS (n=5)	30	863
Number of HAI-related deaths		
With WGS (n=2)	3	5
Without WGS (n=2)	6	7
Number of HAI transmissions		
With WGS (n=1)	48	..
Without WGS (n=1)	89	..
Number of closed bed days		
With WGS (n=1)	268	..
Without WGS (n=1)	2176	..
Annual quality-adjusted life-years per person		
With WGS (n=2)	23·48	35·21
Without WGS (n=2)	23·27	35·20

WGS=whole-genome sequencing. PFGE=pulsed-field gel electrophoresis. HAI=health-care-associated infection.

Table 2: **Summary of number of studies, minimum, and maximum for outcome estimates for WGS and alternative typing methods**

that applied cost estimates from other studies.[42–44,47,49,51] For example, per isolate cost estimates ranged from US$66·53 for sequencing with the IonTorrent in Denmark[12] to $513·07 for an unspecified platform in the USA.[24] Per sample, costs ranged from $196·57 with MiSeq in the UK[51] to $358·02 with MiSeq in Spain.[38] Per test, costs ranged from $73·93 with NextSeq52 to $267·01 with an unspecified platform in Australia.[44,52] Such wide ranging costs are due to variations in the costing models—eg, cost components or costing approach. Cost estimates are shown in the appendix (pp 8–11).

Various outcomes were assessed in the publications, including technical outcomes (eg, turnaround times and concordant rates), clinical outcomes (eg, numbers of cases, numbers of deaths, and numbers of bed days), and economic outcomes (eg, QALYs). Two studies did not report any outcome estimates,[39,41] and six studies did not identify all relevant outcomes separately for each alternative.[12,22,38,40,46,50] The most reported outcomes were turnaround times and number of cases. Table 2 summarises the effectiveness estimates for WGS, other typing approaches, and do-nothing alternatives. Detailed effectiveness estimates are shown in the appendix (pp 12–14).

Turnaround times of WGS (including library preparation, quality control checks, and sequencing) ranged from 5 to 9 days in the USA.[46] Hands-on time, or time spent manually completing a task, was lower for WGS (6·5–8 h) compared with routine typing (eg, serotyping, PCR, and PFGE), which took 14·5 h.[12] However, there is inadequate evidence quantifying the interval between the time of sequencing and the time of public health or infection control responses.

The number of cases was reported to reduce by 70% when WGS was used instead of PFGE to monitor foodborne diseases in Canada.[45] In addition, Elliott and colleagues[52] found that use of WGS along with existing standard protocols can improve clinical decisions, resulting in better control and management of outbreaks in hospitals.

Studies that assessed WGS reported three to five deaths, which was lower than the number of deaths reported when WGS was not used (six to seven deaths).[43,47] The numbers of health-care-associated infection transmissions and closed bed days were lower

	Country	Interventions	Comparator	Pathogens	Incremental cost, US$	Incremental effectiveness estimate (units)	ICER or net benefit
Jain et al (2019)[45]	Canada	WGS	PFGE	*Salmonella* sp	2 million	$83 million (monetary value)	$85 million
Dymond et al (2020)[43]	UK	WGS and current practice	Current practice	MRSA	–1·1 million	14 (QALYs gained)	–$80 800 per QALY gained*
Elliott et al (2020)[52]	Australia	Delayed WGS	No WGS	OXA-181 *Escherichia coli*	–159 932	77 (avoided colonisations)	–$2077 per avoided colonisation*
Elliott et al (2020)[52]	Australia	Early WGS	No WGS	OXA-181 *E coli*	–365 728	151 (avoided colonisations)	–$2422 per avoided colonisation*
Lee et al (2020)[48]	Australia	Delayed WGS	No WGS	OXA-181 *E coli*	–30 941	77* (avoided colonisations)	–$2999 per avoided colonisation*
Lee et al (2020)[48]	Australia	Early WGS	No WGS	OXA-181 *E coli*	–528 111	151* (avoided colonisations)	–$3497 per avoided colonisation*
Brown et al (2021)[24]	USA	WGS	PFGE	*Listeria, E coli, Salmonella* sp	22·6 million	$528 million (monetary value)	$505 million
Elliott et al (2021)[44]	Australia	WGS	Current practice	Non-multiresistant MRSA	–520 069	306 (avoided isolations)	–$1699 per avoided isolation*
Elliott et al (2021)[44]	Australia	WGS	Current practice	Non-multiresistant MRSA	–520 069	1899 (avoided closed bed days)	$273 per closed bed day*
Elliott et al (2021)[51]	Australia	WGS	No WGS	CRAB	–54 436	59 (QALYs gained)	–$922 per QALY gained
Elliott et al (2021)[51]	Australia	WGS and metagenomics	No WGS	CRAB	–68 007	74 (QALYs gained)	–$919 per QALY gained
Elliott et al (2021)[51]	Australia	WGS and metagenomics	WGS	CRAB	–13 571	15 (QALYs gained)	–$904 per QALY gained
Gordon et al (2021)[42]	Australia	WGS	Current practice	MRSA, ESBL *E coli*, VRE, ESBL *Klebsiella pneumoniae*, CPE, CRAB	–22·7 million	2085 (avoided infections)	–$10 902 per avoided infection
Gordon et al (2021)[42]	Australia	WGS	Current practice	MRSA, ESBL *E coli*, VRE, ESBL *K pneumoniae*, CPE, CRAB	–22·7 million	34 641 (avoided colonisations)	–$656 per avoided colonisation
Kumar et al (2021)[47]	USA	WGS	Current practice	*K pneumoniae, Acinetobacter baumannii, Clostridioides difficile, Pseudomonas aeruginosa, Pseudomonas putida*	–9822	37·9 (averted transmission)	–$259 per transmission averted
Mugwagwa et al (2021)[49]	UK	WGS	DST	*Mycobacterium tuberculosis*	–11·72 million	$170 000 (QALYs gained, at £20 000 per QALY)	$11·89 million
Mugwagwa et al (2021)[49]	UK	Xpert and DST	DST	*M tuberculosis*	–0·06 million	$13·94 million (QALYs gained, at £20 000 per QALY)	$14 million
Mugwagwa et al (2021)[49]	UK	Xpert-Ultra and DST	DST	*M tuberculosis*	–0·08 million	$18·41 million (QALYs gained, at £20 000 per QALY)	$18·49 million
Mugwagwa et al (2021)[49]	UK	Xpert and WGS	DST	*M tuberculosis*	–9·41 million	$14·36 million (QALYs gained, at £20 000 per QALY)	$23·77 million
Mugwagwa et al (2021)[49]	UK	Xpert-Ultra and WGS	DST	*M tuberculosis*	–8·91 million	$18·5 million (QALYs gained, at £20 000 per QALY)	$27·41 million

All costs and cost-effectiveness estimates are in 2022 US$. CPE=carbapenem-resistant Enterobacterales sp. CRAB=carbapenem-resistant *Acinetobacter baumannii*. DST=drug susceptibility testing. ESBL=extended-spectrum beta-lactamases. ICER=incremental cost-effectiveness ratio. MRSA=meticillin-resistant *Staphylococcus aureus*. PFGE=pulsed-field gel electrophoresis. QALY=quality-adjusted life-year. VRE=vancomycin-resistant Enterococcus sp. WGS=whole-genome sequencing. *Authors' calculations.

Table 3: **Summary of the cost-effectiveness estimates of WGS**

when WGS was used than when WGS was not used.[44] Finally, QALYs per person ranged from 23·48 when WGS was used during a carbapenem-resistant *Acinetobacter baumannii* outbreak[46] to 35·21 when WGS was used along with Xpert-Ultra for tuberculosis diagnosis in a low-burden setting.[49]

Ten studies[24,42–45,47–49,51,52] did an incremental analysis for costs and outcomes for each alternative, of which four did not report ICER or net benefits.[43,44,48,52] Table 3 summarises the cost-effectiveness estimates of these 11 studies.

Three studies reported net benefit and incremental net benefit.[24,45,49] All three studies found a positive net benefit and incremental net benefit when WGS was used, indicating that WGS is likely to be cost-effective. Net benefit ranged from $85 million in Canada[45] to $505 million in the USA when WGS was used to replace PFGE in foodborne pathogen surveillance.[24] Incremental net benefit ranged from $11·89 million for WGS alone to $27·41 million for WGS with Xpert-Ultra when used to replace drug sensitivity tests in tuberculosis diagnosis in England.[49]

Two studies reported cost per QALY gained.[43,51] The estimates ranged from $922 when WGS was used in hospital carbapenem-resistant *A baumannii* outbreak management in Australia[51] to $80 800 when WGS was

used in hospital meticillin-resistant *Staphylococcus aureus* surveillance in England.[43] Both studies found that WGS is likely to be cost-effective at the thresholds of £20 000 in the UK and AU$50 000 in Australia.

Three studies[42,48,52] reported cost per avoided colonisation, of which two distinguished the benefits by early and delayed uses of WGS.[48,52] Delayed use of WGS was associated with US$2077–2999 per avoided colonisation, and early use of WGS was associated with $2422–3497 per avoided colonisation. Both studies compared the scenario when WGS was used against the scenario when WGS was not used in managing an OXA-181 *Escherichia coli* outbreak at an Australian hospital. Compared with current practice, WGS surveillance of six common multidrug-resistant organisms (ie, *S aureus, E coli, Enterococcus faecium, Klebsiella pneumoniae, Enterobacter* sp, and *A baumannii*) also saved the hospital $656 per avoided colonisation and $10 902 per avoided infection.[42] However, none of the studies reached a conclusion on the cost-effectiveness of WGS in these settings.

Elliott and colleagues[44] compared the costs and numbers of isolated patients of a WGS-based hospital protocol with current practice, to allow the discontinuation of contact precautions for patients with non-multiresistant meticillin-resistant *S aureus*. The authors found that the WGS protocol saved $273 per closed bed day. Finally, Kumar and colleagues[47] compared a WGS surveillance-based infection prevention programme with the standard of care and found that WGS was cost-saving and cost-effective at $259 per transmission averted.

Discussion

From our systematic review of 19 relevant studies, the economic evidence to support the broader application of WGS as a front-line pathogen characterisation and surveillance tool is inadequate and of low quality, despite WGS showing utility for public health surveillance and infection prevention.[24,42–45,47–49,51,52] There is a need to standardise approaches for future studies and broaden the scope of investigations, as only specific pathogens have been studied in the existing literature. Primarily, the full economic evaluations of WGS assessed cost-effectiveness in outbreak control for health-care-associated infections in clinical settings. Of the 12 full economic evaluations, only two assessed the use of WGS in tracking foodborne (eg, salmonella) and respiratory (eg, tuberculosis) pathogens. Notably, the cost-effectiveness evidence of WGS in influenza surveillance was not investigated. Furthermore, the available economic evidence is both context-specific and pathogen-specific. Although the specificity reflects the diversity of WGS applications in real life, the results are not generalisable to other pathogens or across settings, meaning these findings should be interpreted with caution for further policy and practice.

Studies predominantly took a laboratory and hospital perspective, reflecting the most common application of WGS in public health.[28] Therefore, analyses did not account for societal costs (eg, productivity loss and premature death). Clinical or outbreak data were used in most analyses, with national surveillance data only used in three publications. Although clinical and outbreak data provide more detailed information at the patient level, national surveillance data provide practitioners and decision makers with the potential to generalise the results. National surveillance data also allows researchers to conduct subgroup analyses, which have not been explored extensively in the existing literature. Thus, the post-COVID-19 establishment of national surveillance data presents a valuable opportunity for these crucial variables to be systematically captured and enable future economic evaluations. More than 60% of the studies were model-based evaluations, with several applying cost estimates from early studies to new clinical contexts. Moreover, none of the studies considered economic spillover effects, in which the introduction of WGS in one jurisdiction has a ripple effect on the outcomes of nearby jurisdictions (eg, food recall in international trade). In addition, most studies considered a short time horizon (ie, <1 year). Since WGS requires a higher initial level of investment, its cost-effectiveness might not be realised in a short timeframe.

Although evidence suggests that WGS is more expensive than most conventional typing methods, except for metagenomics, the method yields more information crucial to effective pathogen surveillance.[51,52] Furthermore, WGS is more convenient and quicker than conventional typing methods to identify and categorise pathogens, such as *M tuberculosis*, verotoxigenic *E coli*, and *Clostridioides difficile*, while retaining the same level of accuracy.[12,38,46,50] The most common outcome measure considered was the number of cases detected, with few studies using outcome measures recommended for economics evaluations, such as survival or quality of life. Of 19 publications, only five studies produced evidence of cost-effectiveness. Due to the methodological variability in the examined publications and as cost-effectiveness considerations depend on the clinical context, study timing, population, and other health system factors, we cannot make conclusive statements about the cost-effectiveness of WGS.

Overall, this systematic review indicates that there is an inadequate health economics evidence base to support the broader adoption of WGS in bacterial typing.[53] More economic evidence of WGS in public health and infection control settings is required to support researchers, practitioners, and policy makers in making evidence-based recommendations on incorporating WGS into the existing workflow. A consistent economic evaluation framework across

countries and pathogens is imperative to enabling comparisons and gaining insights into the overall value of WGS for pathogen surveillance. Future economic evaluations should be built on widely recognised guidelines, as recommended in the Consolidated Health Economic Evaluation Reporting Standards statement and by Drummond and colleagues[34] and Husereau and colleagues.[54] Consultations with national and international stakeholders are crucial to reaching a consensus on the most suitable evaluation methodologies. To maintain relevancy, the framework should be updated through continuing liaison between industry, policy makers, practitioners, and researchers. The collection of economic outcomes (eg, QALYs) in the data would enable future economics evaluations to compare across interventions when health-care resource allocation decisions are being considered.

In addition, economic evaluation design should involve randomisation, through randomised controlled trials or natural experiments. If possible, WGS should be done geographically, allowing large-scale data collection of costs and outcomes to be compared between areas with WGS and areas without WGS. The indirect costs and benefits to society should be included in the evaluation to account for any effect that WGS might have on the health system. Thus, including economic evaluation at the design phase is crucial to facilitate such data collection for analysis. Finally, future research should evaluate WGS over a longer period and for more than one type of pathogen to capture the overall long-term benefits of WGS.

Economic evaluations of WGS implementation, compared with conventional typing methods or conducting primary diagnostic testing only, showed inadequate evidence for the surveillance and management of infectious diseases in public health settings. Although economic evaluations of WGS have investigated various clinical settings, evidence is context-specific and pathogen-specific, and there is considerable variation in evaluation approaches, limiting the generalisability of findings. This systematic review highlights the potential cost-effectiveness of WGS in the identification and surveillance of pathogens that are foodborne (eg, salmonella, listeria, and *E coli*) or cause health-care-associated infections (eg, meticillin-resistant *S aureus* and carbapenem-resistant *A baumannii*). We also emphasise the opportunity for future economic evaluations based on newly developed national-scale longitudinal epidemiology data. A consistent economic evaluation framework is crucial to ensure future research can compare evidence across clinical settings and countries.

Contributors

MT and KSS contributed towards the conceptualisation, methodology, validation, formal analysis, investigation, data curation, writing of the original draft, visualisation, and project administration. SN contributed towards the investigation, data curation, validation, review and editing of the manuscript, and visualisation. DMC contributed to the data interpretation, writing of the original draft, visualisation, and project administration. AZ, ADF, and PA contributed towards the data interpretation and review and editing of the manuscript. MDK, KG, and EL contributed towards the conceptualisation, methodology, data interpretation, review and editing of the manuscript, and funding acquisition. MDK and EL were responsible for supervision. All authors had full access to all the data in the study and accept responsibility for the final decision to submit the paper for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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