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Infectious Disease Practice

Understanding the potential role of whole genome sequencing (WGS) in managing patients with gonorrhoea: A systematic review of WGS use on human pathogens in individual patient care

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SUMMARY

Objectives: The utility of whole genome sequencing (WGS) to inform sexually transmitted infection (STI) patient management is unclear. Timely WGS data might support clinical management of STIs by characterising epidemiological links and antimicrobial resistance profiles. We conducted a systematic review of clinical application of WGS to any human pathogen that may be transposable to gonorrhoea.
Methods: We searched six databases for articles published between 01/01/2010–06/02/2023 that reported on real/near real-time human pathogen WGS to inform clinical intervention. All article types from all settings were included. Findings were analysed using narrative synthesis.
Results: We identified 12,179 articles, of which eight reported applications to inform tuberculosis (n = 7) and gonorrhoea (n = 1) clinical patient management. WGS data were successfully used as an adjunct to clinical and epidemiological data to enhance contact-tracing (n = 2), inform antimicrobial therapy (n = 5) and identify cross-contamination (n = 1). WGS identified gonorrhoea transmission chains that were not established via partner notification. Future applications could include insights into pathogen exposure detected within sexual networks for targeted patient management.
Conclusions: While there was some evidence of WGS use to provide individualised tuberculosis and gonorrhoea treatment, the eight identified studies contained few participants. Future research should focus on testing WGS intervention effectiveness and examining ethical considerations of STI WGS use.

Introduction

Sexually transmitted infections (STIs), such as gonorrhoea, represent a significant public health concern, given their profound impact on sexual and reproductive health. According to the World Health Organization, there are over one million STIs acquired daily.[1] In 2020, an estimated 82.4 million gonococcal infections were acquired annually.[2] STI control and mitigation of harm relies on multifaceted approach: successful prevention strategies, timely detection, and appropriate management of detected cases. Therefore, the integration of new technologies could provide an opportunity to supplement existing endeavours to curb STI-related harm.

The technologies available to sequence pathogen genomes such as STIs have evolved rapidly over recent years to become quicker and more affordable.[3] Next generation sequencing now allows nearly complete sequencing of the genome, i.e., whole genome sequencing (WGS), which can be used to compare genetic variation over time and to identify different strains within a population. Together with time, person and place data, the degree of genetic similarity can be used to reveal epidemiological dynamics. The use of bioinformatics pipelines facilitates the analytical process and interpretation of sequencing data. However, translation of complex WGS results into

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meaningful and actionable insights necessitates clear reporting and communication strategies. This ensures that findings are accessible to diverse stakeholders who may not possess bioinformatical expertise.

WGS applications for STIs include monitoring antimicrobial resistance (AMR) and surveillance and outbreak investigation.[4–7] As such, WGS has greatly improved understanding of STI networks and has been used successfully to enhance surveillance for gonorrhoea, shigella and syphilis. WGS has also provided insights into gonorrhoea transmission within high-risk sexual networks[6,8–15] and genotype-phenotype relationships,[16] including AMR prediction.[17] However, most of these applications occur retrospectively or with a significant time-lag such that results cannot be used for direct patient management.

A systematic scoping review that explored applications of WGS to bacterial pathogens to support public health functions, such as AMR surveillance and outbreak detection, between 2015–2018[18] identified two articles reporting STI applications. WGS has also been used to inform real-time outbreak management,[19–22] although, none of these were for STIs. It is unclear whether WGS can inform real-time clinical risk assessment and patient management during STI-related care episodes, such as tailoring interventions or treatment, or whether this would add value over existing standards of care. We conducted a systematic review to identify how WGS has been used to inform patient management and care for human pathogens. Our search encompassed all pathogens rather than restricting to STIs, to allow us to survey practice in other fields that may be relevant to the care and management of individuals with gonorrhoea.

Methods

A systematic literature review was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (CRD42021285498).

Search strategy and selection criteria

We systematically searched six electronic databases (MEDLINE, Web of Science, Scopus, Embase, PsycINFO and The Cochrane Library) to identify full text English articles published between 01/01/2010 and 06/02/2023 that reported on use of real- or near real-time human pathogen WGS as a clinical intervention. Real- or near real-time was defined as occurring where WGS directly affected clinical decision making, for example treatment and management. In light of the challenges in defining real-time and near real-time, which, depending on the infection, could span days (e.g., gonorrhoea) to months (e.g., tuberculosis), this was considered according to the pathogen and associated diagnosis and treatment durations. A start year of 2010 was selected to precede WGS use for surveillance purposes in the UK and USA.[24,25] No geographical restrictions were applied, and qualitative, quantitative, and mixed method articles reporting empirical research were included alongside case studies.

Three broad concepts were used to construct the search strategy: “whole genome sequencing”, “healthcare settings”, and “applications of whole genome sequencing” (Supp. Table A). The search strategy was developed iteratively and was refined for each database using a combination of Medical Subject Headings (MeSH), subject headings and free text searches. Published conference abstracts from The International Society for Sexually Transmitted Diseases Research, The International Union against Sexually Transmitted Infections, British Association for Sexual Health and HIV and European Society of Clinical Microbiology and Infectious Diseases were also screened. References of included articles were hand searched. All identified references were imported into EndNote 20 and deduplicated. Deduplicated references were imported into Rayyan[26] to facilitate and streamline the review process.

Screening and data extraction

The first reviewer (RO) screened all titles, abstracts, and full texts of articles. Authors of articles of interest were contacted to check whether additional detail could be provided prior to their inclusion. Two second reviewers (ED and AD) screened 15 % of all articles during the screening process and the results were compared between reviewers to assess agreement. Data was extracted by the first reviewer. ED independently extracted information from 50 % of included articles to assess extraction accuracy and minimise reviewer bias.

Strategy for data synthesis

Findings were analysed using narrative synthesis.[27]

Assessment of methodological quality

The first reviewer assessed the quality of all included articles. AD independently assessed the quality of 50 % of included articles to assess reviewer accuracy and minimise reviewer bias. Original research articles were assessed for completeness of reporting against the strengthening the reporting of molecular epidemiology for infectious diseases (STROME-ID) framework checklist for reporting of infectious-disease molecular data in epidemiological research.[28] This tool was not applied to the case reports. The Joanna Briggs Institute (JBI) Critical Appraisal Checklists for studies reporting prevalence data and JBI Critical Appraisal Checklist for Case Reports were used to assess study quality of research articles and case reports, respectively.[29]

Results

A total of 12,179 articles were identified, and 6755 remained following de-duplication. Full-text review was conducted for 231 articles, leading to eight meeting eligibility for inclusion (Fig. 1). Agreement between the first and second reviewers was high (k = 0.96). Reasons for exclusion included that articles were surveillance or outbreak studies, included outcomes that were not relevant to the research question, were animal studies, or explored pathogen biological mechanisms (Supp. Tables B and C).

Eight quantitative articles reported real- or near real-time applications to inform *Mycobacterium tuberculosis* (MTB) (n = 7) and *Neisseria gonorrhoeae* (NG) (n = 1) clinical management (Table 1).

Six articles[30–35] were cross-sectional studies, and two[36,37] were case reports. Publication dates ranged from 2015 to 2022, with the fieldwork or data collection conducted between 2008 to 2020 (one article did not report this[36]). Six studies[30,31,33,35–37] were conducted in hospital settings, of which one[30] involved community recruitment, one study[32] was in a specialist sexual health clinic, and no setting was reported for one study.[34] All studies were conducted in high-income countries; five[30,32,34,35,37] in the UK, one each in France,[31] South Korea[33] and the USA.[36] Sample sizes ranged from case studies of one participant to a study of 377 participants. Two articles[31,34] reported financial costs associated with WGS.

All articles used WGS data as an adjunct to clinical, microbiological, and epidemiological data for clinical applications. These included: antimicrobial susceptibility testing (n = 6) which was used to inform MTB treatment choices, contact-tracing (n = 2) which was used to confirm or disprove suspected transmission links for MTB and NG, or identifying cross-contamination (n = 1) which was used to distinguish between true and false positive MTB cases.

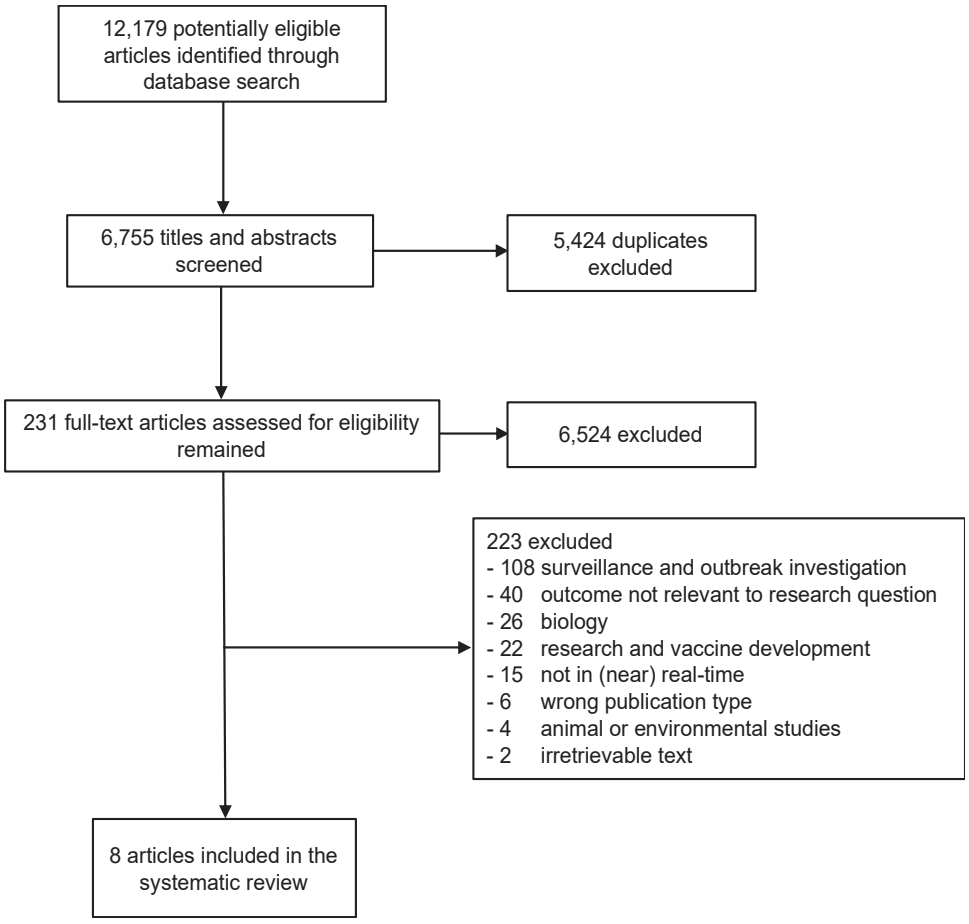

Fig. 1. A PRISMA flow diagram outlining the reasons and numbers of articles excluded at the various stages of the systematic review.

Reporting completeness

Incomplete study reporting may impact subsequent interpretation and inference of study findings. Regarding STROME-ID, no articles fully reported according to the checklist items (Supp. Table D & Supp. Text A). Most articles fully reported sequencing and bioinformatic pipelines used (Supp. Table E & Supp. Text B).

Study quality

The study design, quality methodology and the sampling used for specimen collection may affect reliability of article findings, generalisability, and subsequent interpretation. Regarding the JBI Critical Appraisal Checklists (Supp. Tables F and G) study design limitations were mainly due to potential selection bias, missing data, and small sample sizes (n = 1–377). Most articles used convenience sampling from a single clinic or hospital setting. Overall, none of the articles sought to examine the effectiveness or cost effectiveness of a WGS intervention.

Contact tracing

Two articles reported using WGS to assist with contact tracing or partner notification (PN) efforts.[30,32] Kong et al. piloted WGS to test feasibility of providing enhanced PN for individuals diagnosed with gonorrhoea in sexual health clinics.[32] The authors reported that WGS was used to identify cases with plausible direct (sampled individual to sampled individual) or indirect (via one or more intermediate unsampled individuals) transmission partners that were not identified using traditional PN. The authors theorised that either partner details were unknown by index cases, or they were reluctant to divulge identities. Similarly, Arnold et al. reported that traditional contact-tracing failed to identify two cases of extensively resistant TB, however, these were detected two years after the index case via WGS.[30] WGS results were consistent with transmission having occurred between the index and contact cases, which led to clinicians continuing treatment for drug resistant infections. Epidemiological contact-tracing, although an effective infection control tool, is known to possess limitations such as being prone to reporter bias. Both articles demonstrated the effectiveness of WGS in identifying putative transmission links between sequenced isolates in a clinically relevant time frame.

Antimicrobial susceptibility testing

Six articles (four primary research studies; two case reports) reported use of WGS to determine antimicrobial susceptibility.[30,31,34–37] The purpose of use and the timeliness of WGS data varied across these articles. Several studies reported that WGS results were available faster than phenotypic drugs susceptibility testing (pDST) results for TB,[30,34,35,37] and WGS was used following pDST to resolve possible erroneous results associated with testing for susceptibility to particular TB drugs, or to validate pDST findings by confirming drug susceptibility results.[31,35,36]

Arnold et al. used WGS to confirm genetic similarity of two isolates to a previous TB case where the drug susceptibility was known, which allowed for prompt treatment with appropriate therapy.[30] WGS results were available 21 to 50 days earlier than pDST results; it was not reported whether pDST results confirmed genotypic findings. Similarly, Pankhurst et al. reported that WGS results were used

Table 1
Summary of eight included articles in the systematic review.

Author	Pathogen & application	Aim	Study year	Study design, population, & study setting	Sample size & sampling strategy	Findings	Timeliness	WGS successes & challenges	Visualisation, communication, & reporting
Arnold et al.[30]	MTB Susceptibility testing/ resistance detection & contact-tracing	Describe a contact tracing investigation for an adult with XDR-TB and inform TB treatment	2013 (index case identified) – 2015	Cross-sectional contact tracing investigation. Identified people with TB who had resistance mutations in the rpoB gene and follow-up of their household, social and work contacts. Hospital and community follow-up (London, UK).	One acute index case led to 33 contacts being screened. Sputum and pleural samples of house, social and work contacts identified through concentric circle approach (used to assess risk of transmission).	Two patients presented two years after the index case and WGS results indicated direct, or indirect transmission despite weak epidemiological links to the index case. WGS were available prior to second-line pDST results, which led to prompt drug treatment decisions.	WGS results were available 21 - 50 days before second-line pDST results.	Superior discriminating power compared to other commonly used typing methods. Real-time use informed prompt treatment decisions. Not reported	Not reported
Genestet et al.[31]	MTB Susceptibility testing/ resistance detection	Performance of WGS in predicting MTB DST compared to pDST and LPA	2016 – 2019	Cross-sectional. TB patients in routine care (pulmonary and extrapulmonary isolates). Lyon University Hospital (Lyon, France).	250 patients with 274 isolates. Prospective sampling of routine samples.	Nearly 100 % agreement between WGS and pDST, superior to LPA, to predict susceptibility profile for 4 first line TB drugs.	Not reported	WGS had high sensitivity. WGS ruled out false-positive PZA resistance, which is a problem with pDST. Replacing LPA/ pDST with WGS would be less costly. WGS resistance prediction can produce discordant results compared to pDST.	Not reported
Kong et al.[32]	NG Contact tracing	Use WGS to measure performance of PN and improve control of NG infections	2016 – 2018	Cross-sectional. Patients with NG attending a SH clinic. Leeds Sexual Health Clinic (Leeds, UK).	377 cases, and 380 isolates. Consecutive sampling of patients with NG.	PN identified 18 % (69/380) of potential transmission partners. Concordant PN and WGS links were identified in 47 partner pairs. Of 308 cases with no transmission partner by PN, 60 % (185/308) had a case within 6 SNPs or less. WGS enabled identification of linked gonorrhoea cases that could not be verified through PN. This could facilitate appropriate and targeted management for WGS-identified partners. Future applications could also include directing interventions to key gaps in partner finding.	319 (84 %) isolates were sequenced within 14 days. 246 (65 %) had WGS reports sent within 14 days of sample receipt.	Shows feasibility of sequencing in SH clinic, as majority of isolates were successfully sequenced with reports generated within 14 days of sample reception. WGS could facilitate outreach to groups in emerging transmission chains (e.g., sex workers). The SNP threshold selected was arbitrary. Ethical issues around consent and deductive disclosure.	Isolate reports contained a sample identifier, sequencing quality, and sequences within 20 SNPs difference. Measured genetic distance between known partners. Identified clusters and PN networks within 6 SNPs for direct transmission events.

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Table 1 (*continued*)

Author	Pathogen & application	Aim	Study year	Study design, population, & study setting	Sample size & sampling strategy	Findings	Timeliness	WGS successes & challenges	Visualisation, communication, & reporting
Oh et al.[33]	MTB Identifying cross-contamination	Use WGS and clinical information to distinguish true positives from lab cross contamination for a suspected nosocomial TB outbreak	2020	Cross-sectional. Pre-XDR TB patients suspected of being part of a TB outbreak. Korea University Ansan Hospital (Seoul, South Korea).	6 cases, 7 isolates. Sputum samples of suspected TB patients.	WGS aided in ruling out a TB outbreak, revealing it to be a case of laboratory cross-contamination. By combining WGS results and clinical findings, authors concluded that the strains isolated from the second to fifth patients were contaminated with the strain infecting the first patient, and the sixth patient was another real TB patient infected with a different strain. Identical isolate pairs must not be confirmed as a case of recent transmission without supporting epidemiological and clinical Information.	Not reported	Used SNP analysis with WGS to determine drug resistance and facilitate rapid drug decision making. WGS results ruled out a hospital outbreak. Not reported	Not reported
Pankhurst et al.[34]	MTB Susceptibility testing/ resistance detection	Use WGS data to expedite treatment selection	2014	Cross-sectional. Smear-positive pulmonary tuberculosis patients. UK.	2 cases, 2 isolates. Not reported	WGS allowed patients to be treated promptly and appropriately. Two patients were linked to a previously sequenced drug-resistant TB case from 2010. Subsequent epidemiological investigation showed that both patients originated from the same European country as the case from 2010.	24 days for case 1. Not reported for case 2. WGS results were generated a median of 15-21 days faster than standard diagnostic tools.	WGS results provided the first diagnosis and outbreak alert for drug-resistant TB. Not reported	Not reported
Witney et al.[35]	MTB Susceptibility testing/ resistance detection	Use WGS in a clinical setting to inform timely treatment, and evaluate practical issues	2008 – 2014	Cross-sectional. Patients with suspected XDR-TB. St George's Teaching Hospital (London, UK).	6 cases, 16 isolates. Sputum/ non-sputum samples from suspected TB patients.	WGS detected resistance mutations associated with AMR. Concordant WGS results with prior pDST results increased confidence in the clinical decision. WGS results can provide DST results several weeks earlier than full pDST. The implementation of WGS involved a team with clinical, microbiology, and genomics expertise.	Authors reported that WGS results for 5 patients were delivered in a "clinically relevant timeframe".	WGS results generally demonstrated concordance with pDST results. Where results were discordant, these were often associated with TB drugs that have known issues with pDST. This article demonstrated a useful case study for the application of WGS. Discrepancies occurred between pDST and WGS.	Short report prepared for clinical colleagues, included a summary of isolates, predicted resistance profiles, isolates compared to others in the hospital.

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Table 1 (*continued*)

Author	Pathogen & application	Aim	Study year	Study design, population, & study setting	Sample size & sampling strategy	Findings	Timeliness	WGS successes & challenges	Visualisation, communication, & reporting
Realegeno et al.[36]	MTB Susceptibility testing/ resistance detection	Use WGS to resolve discordant results following two separate drug susceptibility tests	Not reported	Case report. Cancer patient with disseminated TB. Unknown hospital (Los Angeles, USA).	1 case, 2 isolates. Not applicable	WGS predicted susceptibility despite evidence of drug resistance from a previous drug susceptibility test.	Not reported	WGS resulted in a less toxic treatment regimen after resolving discordant DST results. Not reported	Not reported
Hopmeier et al.[37]	MTB Susceptibility testing/ resistance detection	Investigated whether mutations in the rpoB gene can predict fully susceptible TB	2020	Case report. Smear-positive pulmonary TB patient. Royal London Hospital (London, UK).	1 case, 2 isolates. Not applicable	WGS predicted TB drug resistance to rifampicin despite a negative result from a rifampicin susceptibility testing NAAT.	WGS results were available after 22 days following diagnosis. Resistance was later confirmed following pDST at later date (not reported).	WGS predicted evidence of drug resistance in TB isolate resulting in a change in management. Not reported	Not reported

Abbreviations: MTB: *Mycobacterium tuberculosis*; XDR-TB: extensively drug resistant tuberculosis; TB: tuberculosis; UK: United Kingdom; WGS: whole genome sequencing; pDST: phenotypic drug susceptibility testing, DST: drug susceptibility testing; LPA: line probe assay, PZA: pyrazinamide; NG: Neisseria gonorrhoeae; PN: partner notification; SH: sexual health; SNP: single nucleotide polymorphism; AMR: antimicrobial resistance; USA: United States of America; NAAT: nucleic acid amplification test.

to confirm the genetic similarity of two isolates to a previously identified drug-resistant TB case.[34] WGS results at 24 days from diagnosis for drug susceptibility diagnostics indicated multi-drug resistance to first line therapies, which prompted additional testing and enabled initiation of appropriate therapy. Genotypic resistance predictions were later confirmed by pDST at an unreported date. Hopmeier et al. reported that WGS could be used to improve prediction of drug resistance for TB isolates with a negative result from a rifampicin resistance nucleic acid amplification test (NAAT), a test used to detect markers of drug resistance.[37] WGS results were available 22 days after diagnosis which resulted in clinicians selecting different TB management; resistance to first-line TB drugs was later confirmed using pDST at an unreported date. Witney et al. reported WGS results for suspected extended drug-resistant TB isolates.[35] Early WGS results did not detect resistance genes which enabled treatment to be initiated earlier than the availability of pDST results. Subsequent pDST fundings later confirmed genotypic results at an undisclosed date. Compared to standard culture and drug sensitivity diagnostics, WGS results allowed more rapid and targeted treatment of TB cases, where availability of genotypic drug susceptibility results ranged from 21 to 50 days prior pDST.

On the other hand, Genestet et al. reported use of WGS in ruling out false positive resistance to specific TB drugs which can occur with pDST.[31] WGS was to validate all pDST findings and informed clinical management through change to regimen where WGS results indicated genotypic resistance or susceptibility. Realegeno et al. reported use of WGS results to resolve discrepant findings in pDST between blood and sputum isolates: WGS results successfully predicted susceptibility to first-line therapies.[36] WGS data resulted in a change to clinical management via a simplified drug regimen. Witney et al. also reported that WGS results were compared to pDST findings where resistance or susceptibility was detected.[35] Studies commented on discordant results between pDST and WGS results.[31,35] In some cases, WGS results did not detect mutations in genes responsible for resistance, where pDST results suggested resistance was, which might be due to errors in pDST, culture specimens containing heterogeneous populations, unknown mutations causing resistance observed with pDST, or new mutations evolving.

Identifying cross-contamination

Oh et al. reported use of WGS to identify laboratory cross-contamination of TB specimens to distinguish between true and false positive TB cases in a suspected outbreak involving inpatient and outpatient hospital attendees.[33] Clinical, epidemiological, and pDST results were combined with WGS data to differentiate laboratory contamination from true infection. The authors reported that WGS results differed to pDST, and standard culture findings later confirmed that these patients were not infected with TB. Four patients' samples were contaminated by a true positive due to testing in the same laboratory. The authors reported that these findings prevented delays in treating a TB case and avoided uninfected individuals being exposed to TB therapy unnecessarily.

Communication of WGS results

Three articles[32,34,35] published example reports displaying WGS results for clinicians (Fig. 2). Witney et al. provided results based on identified mutations and phenotypic implications.[35] Kong et al. issued a report containing all clustering gonococcal sequences within a 20 SNP-threshold from the last three months indicating possible transmission sources for the sequenced case.[32] Pankhurst et al. published a WGS drug susceptibility report.[34] No articles discussed how WGS results might be reported to patients.

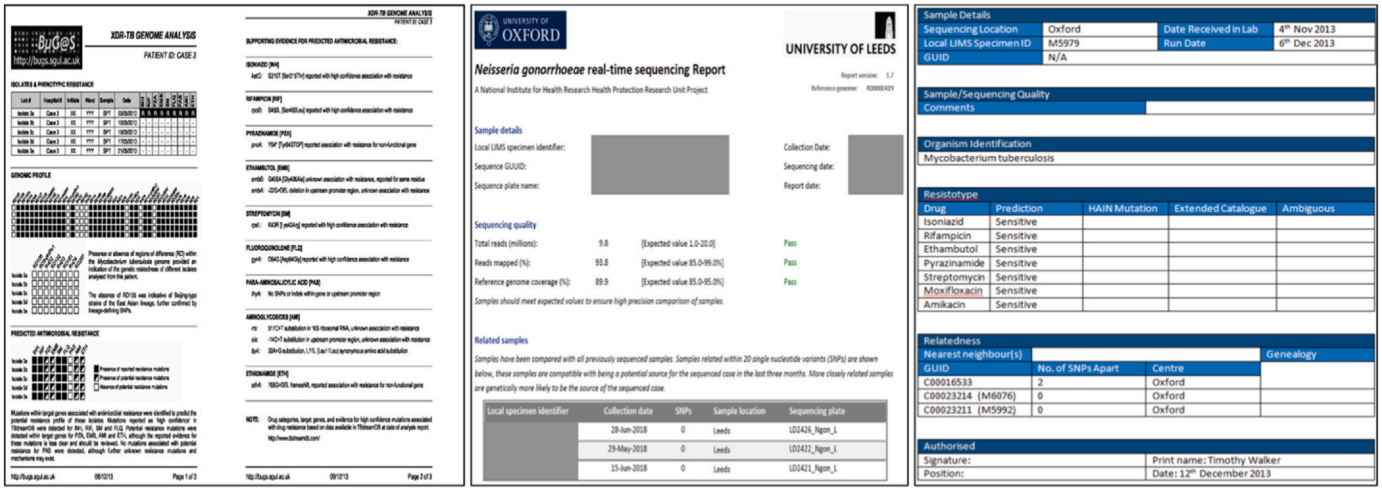

Fig. 2. Example reports displaying genomic results (left to right: Witney et al.,[35] Kong et al.,[32] Pankhurst et al.,[34]).

Discussion

In this systematic review we found very little published evidence on how WGS has been used to inform real- or near-real time clinical management of patients. Eight articles reported use of WGS results alongside clinical and epidemiological data to inform TB and gonorrhoea case-management through contact-tracing, identifying cross-contamination or antimicrobial susceptibility testing.

Most of the papers identified (n = 7) used WGS in the context of TB, which has several important biological characteristics that make WGS a potentially useful tool for clinical applications. First, MTB cannot acquire genetic material horizontally and is considered a strictly clonal species, which means that related isolates contain a high proportion of identical nucleotides.[38] Second, MTB possesses a limited accessory genome content and slow-mutation rate, which means that the degree of variation between related isolates is small.[38] Third, culture and thus traditional phenotypic testing can take up to 60 days, which leaves clinicians with the choice to delay treatment, use empirical treatment (aided by NAAT testing for rifampicin resistance), or start second line therapies in the case that the index case has a drug resistance infection. In contrast, WGS can be conducted after just a few weeks of growth in culture. Taken together, this means WGS-based prediction of antimicrobial susceptibility works well and can be used to expedite treatment decision-making by reducing the time needed to decide about treatment. Infection control for TB and STIs both use PN or contact tracing and antimicrobial susceptibility testing, and so instances where WGS applications are used for TB may be relevant to inform decisions about uses in controlling STIs. The review findings demonstrated that WGS can successfully inform contact tracing for TB. However, diagnostics and antimicrobial susceptibility testing for TB are typically much longer than for STIs. There are also differences in the severity and potentially life-threatening nature of TB infection when left untreated, which is not the case for most STIs, and treatment duration for TB is considerably longer (typically six to nine months), and sometimes causes significant adverse effects. Therefore, some caution is needed when applying learning from use of WGS for TB to STIs.

Kong et al. reported use of WGS for patients with NG to enhance PN, where WGS was used to identify linked individuals who were not identified using traditional PN.[32] Although WGS data were consistent with isolates being from individuals within the same sexual network, linked patients were already receiving gonorrhoea clinical management. One possible explanation is that index cases may have successfully notified their partners and not informed the clinic. Thus, WGS application may be used to close PN loops and avoid repeated contact of the index patient to enquire about PN efforts. The authors successfully demonstrated the feasibility of returning WGS results in a clinically relevant time frame, but WGS results did not ultimately change index or partner management. Future applications could therefore include insights into patient exposure to other pathogens that are more commonly detected within particular networks, or early detection of resistance mutations or absence of resistance markers to allow targeted gonorrhoea treatment. This could result in enhanced patient management using anonymous sexual network data which could facilitate prompt and appropriate management.

However, the bacterial properties of NG pose challenges for interpretation of WGS data for several reasons. First, NG is a non-clonal species, which is highly competent at homologous recombination and acquiring genetic material via horizontal gene transfer from other Neisseria species.[39,40] Recombination increases antigenic diversity and introduces more variation than would be expected from point mutation alone.[41] Second, NG possesses mobile genetic elements containing repetitive regions, which complicates sequence assembly.[42,43] Third, incomplete sampling of sexual networks due to some intermediate cases being unknown (i.e., not presenting to healthcare) means that reconstruction of these networks is done with incomplete information.[44] Finally, NG can be difficult to culture in vitro, leading to a relatively high proportion of diagnoses where NAATs are positive but culture is negative (or not done). In the absence of culture independent sequencing, reliance on sequencing from cultured isolates is also likely to result in incomplete characterisation of sexual networks. Collectively, these challenges hinder interpretation of WGS data and their use in inferring transmission dynamics, which may have implications for clinical applications, such as contact tracing.[9] To mitigate, alternative approaches, such as metagenomics and target enrichment to allow culture independent sequencing, could be used, although these approaches are currently more costly and technically more challenging. Target enrichment is currently the most viable option for other STIs that are extremely difficult to culture in *vitro*, such as *Treponema pallidum* and *Mycoplama genitalium*.

There are already several examples of WGS data being used for STI surveillance purposes, but this review found only one example of WGS being employed in a clinic setting for individual patient use. Real-time WGS has the potential to inform treatment choice in a clinically relevant time frame, in the absence of rapid diagnostics. For example, gonorrhoea AMR is a major public health concern due to increased detection of isolates with reduced susceptibility to

antimicrobial therapy. Therefore, WGS could be used to augment clinical decisions about antibiotic treatment for gonorrhoea, which might become more important given the shift towards culture independent testing.

However, using STI WGS to inform individual management by identifying possible transmission links between individuals raises ethical considerations due to the risk of deductive disclosure. The risk of deductive disclosure when communicating WGS results to patients' is present, even when using anonymised data, and caution is therefore needed in how these results are communicated to ensure confidentiality.[45] WGS use in this manner presents risks which must be addressed in study design and ethical protocols alongside applications in real life scenarios. The reviewed articles rarely discussed the ethical implications of using WGS results to inform individual care. One article[32] considered the ethics of using WGS in clinical management of gonorrhoea, particularly about the absence of patient informed consent mechanisms and the potential for deductive disclosure of direct or indirect sexual partners. For example, WGS data might impact social relationships due to stigmatising findings, affect future engagement with sexual health services, or even result in criminal consequences to individuals if transmission can be demonstrated and might be deemed a criminal exposure to an infectious agent.[46,47]

Thus, care must be taken to realise the possible harms from WGS findings and develop communication tools and ethical frameworks collaboratively with affected populations. In the field of human genetics, communication of WGS results to patients and clinicians has been considered in detail.[48–50] Frameworks and policies have been developed in collaboration with stakeholders to maximise the knowledge, skills and behaviours required for disseminating and understanding genetic results. However, little research has examined how pathogen WGS results might be visualised and communicated to patients. This is important because interpretation of WGS data is complex and requires care, particularly where misreporting or misinterpreting WGS findings might occur with significant social consequences for patients and their partners. Despite inherent difference, the field of infectious diseases could glean insights from human genetics concerning the co-production of frameworks.

Using WGS data to inform clinical management relies on high-quality sequencing and a representative reference dataset from which to infer genetic similarity. Indeed, the heterogeneity in methodologies within infectious disease genomics research can pose notable challenges. Currently, the absence of universally accepted gold standards exacerbates these challenges[51]; nevertheless, various organisations, such as the Genomics Standards Consortium, have devised standards and guidelines for analysis and quality control when undertaking bacterial genomics research.[52] Using standardised and quality-assured protocols throughout the process – sample collection and processing, library preparation, sequencing, and bioinformatics analysis – can help minimise variability and ensure consistency across research and clinical studies. Moreover, integrating genomic data alongside clinical and epidemiological metadata, such as patient demographics and risk factors, can aid the interpretation of WGS data, for example, distinguishing true positive links from false positives. Furthermore, contextualising sequencing results within a broader representative dataset containing known reference sequences can mitigate WGS data interpretation errors. Reference databases and genomes can also facilitate the implementation of quality-assured pipelines, as well as collaboration and cross-study comparisons, thereby enhancing the reproducibility and reliability of WGS research findings.[53,54]

The strengths of this systematic review were the robust and systematic methods employed for screening and appraising the literature. Combined MeSH and free text searches and piloting of the search strategy prior to conducting the main search helped to optimise the sensitivity and specificity of the search terms. The second reviewers independently screened the data to attenuate the impact of observer bias. Despite the comprehensive approach to the search strategy, some articles may have been missed. The search terms elected may not have captured all relevant articles which may have reduced the number that could have been potentially included. The second reviewers screened and reviewed a proportion of the data, which may minimise the robustness of findings and introduce bias. The effect of this impact was considered small due to the high-agreement with the second reviewers. A further limitation was the exclusion of non-English articles. Despite applying temporal limits to the search, it is unlikely that any articles published pre-2010 would have any relevance given the rapid advancement of WGS. Overall, study sample sizes were not large enough or designed to examine WGS as a clinical intervention. Additionally, included studies were either case reports or observational in design and likely to include sources of bias, caution should thus be exercised in interpreting and generalising findings.

Conclusion

Despite great promise suggested for WGS, there was little published literature on how WGS might be used to inform individual patient management for gonorrhoea. While there was some evidence of WGS informing TB treatment decisions, more research is needed on the potential role of WGS for gonorrhoea management. Future research should focus on testing the effectiveness of WGS interventions, as well as examining the ethical considerations of STI WGS use.

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CRediT authorship contribution statement

RO, JS, GH, NF, MC, and XD conceptualised and designed the study. RO designed the search strategy. RO, ED, and AD contributed to the screening, data extraction and quality assessment. RO synthesised the data with help from JS, GH, NF, MC, and XD. All authors contributed to the interpretation of data. RO wrote the first draft of the paper, and all authors read, commented on, and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106168.

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