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October 2015

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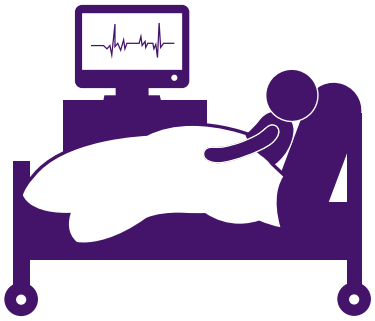
Protecting patients from healthcare associated infections: a role for genomics



Whole genome sequencing and other genomic technologies could have a significant impact on infection control efforts in hospitals, by more accurately determining transmission and sources of infection in situations where the use of conventional technologies has not been successful.

Stringent infection control practices in hospitals are vital to reduce the prevalence of healthcare associated infections and the related burden of morbidity and mortality. For example, improved infection control practices have had a significant impact on the number of blood stream infections caused by the methicillin-resistant *Staphylococcus aureus* (MRSA) bacterium in UK hospitals. Numbers of these life-threatening infections have reduced by 80% since 2004. Despite these efforts, lapses in hygiene practices such as hand washing or transmission of infection from an unexpected source mean infection outbreaks do still occur.

Conventional methods of identifying pathogens and outbreak investigation can lack the resolution needed to determine the source and transmission of infections, information which is vital for the health system to appropriately manage a suspected outbreak. Once an infection source has been accurately identified, targeted infection control measures will minimise the chances of infection recurring via this route.

Conventional methods of identifying pathogens and outbreak investigation can lack the resolution needed to determine the source and direction of transmission of infections.

In this briefing note we outline how genomic technologies could complement and improve control of infection, particularly those threats that have not or cannot easily be brought under control by existing infection control measures.

Identifying and characterising pathogens: what are the limitations of conventional methods?

A variety of techniques are available to identify and characterise pathogens, which can be divided into one of two categories:

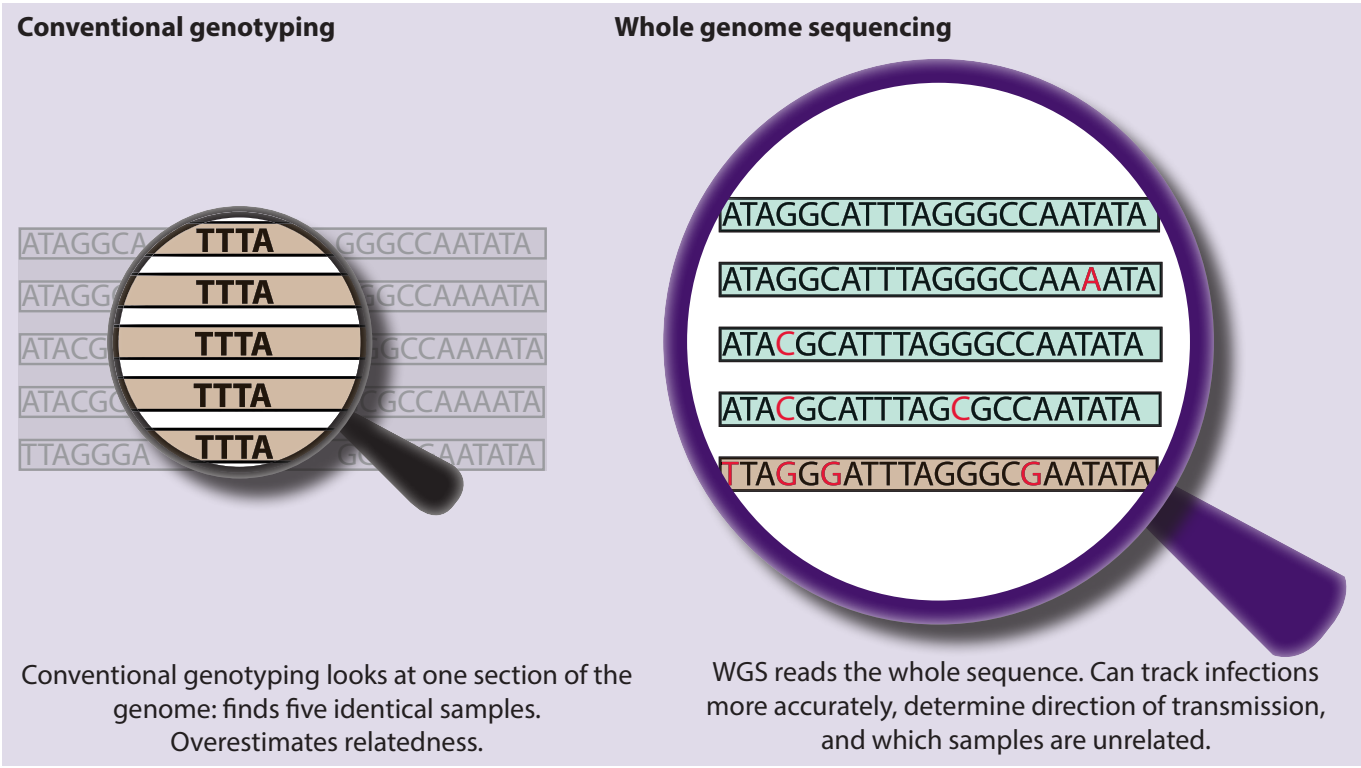
1. **Phenotyping methods:** these techniques include examining the physical characteristics of pathogens or measuring their growth in response to antibiotics. Although many are quick and cheap, to perform these tests vary in their resolution and some can take weeks to carry out, or require expensive reagents.

2. **Genotyping methods:** these tests examine only a select portion of the genome, for example to count the number of repeats of short sections of DNA at specific locations. Eighty percent of MRSA infections in the UK belong to the same sub-group according to genotyping methods, so are effectively indistinguishable from one another (Figure 1).

Whole genome sequencing – greater resolution

Whole genome sequencing (WGS) determines the sequence of all an organism's genetic information, highlighting differences to single nucleotide resolution. This adds value in terms of greater resolution and more detailed information than standard tests, including inferring direction of transmission. In cases of MRSA, WGS can differentiate infections belonging to the same sub-group genotype.

Figure 1 Conventional genotyping *vs.* whole genome sequencing



How could WGS improve the management of outbreaks?

When implemented correctly many infection control practices are highly effective in controlling infections. Whole genome sequencing can, however, have an impact in areas where current practice does not provide enough information and / or is not sufficient to prevent the spread of infection.

- **Responsive use:** this would be triggered by a suspected outbreak, for example cases that have clustered in time and space, where conventional methods have not determined the cause. The use of WGS in this context can rule an outbreak in or out, and identify the source and route of transmission, allowing targeting of effective interventions.

A recent study in a Birmingham hospital burns unit used WGS to confirm that patients were becoming infected with *Pseudomonas aeruginosa* when receiving hydrotherapy, and could then trace the source to specific items of plumbing[1].

- **Prospective surveillance:** the improved resolution of WGS can be useful for outbreak detection, compliance monitoring and refinement of infection control policy. This can include sequencing all diagnosed cases of pathogens of particular concern, either continuously or at regular intervals, to: monitor the numbers of cases; determine resistance to drugs (for some pathogens); understand transmission between patients and / or the environment; confirm how current infection control practices are working.

A WGS study of *Clostridium difficile* infections in Oxfordshire hospitals over a 3.6 year period showed that only 35% of infections were transmitted from symptomatic patients. Great genetic diversity between the cases suggested many diverse sources of infection such as strains circulating in the community, or asymptomatic patients who developed infections once in hospital[2].

What are the benefits of implementing WGS?

- **Excluding outbreaks:** clearer and more detailed genetic information allows clinicians to determine whether or not cases are related. If not, outbreaks can be excluded, for example where cases have been imported from the community. This has financial benefits such as reduction in patient bed days, and more focused targeting of infection control resources.

- **Swifter resolution of outbreaks:** WGS can determine the source of outbreaks in cases where conventional methods cannot.

An outbreak of MRSA in a neonatal unit was proving difficult to resolve. WGS led the investigating team to suspect a member of staff, one of whom turned out to be asymptomatic, and was spreading the infection. Once the staff member was decolonised, no further cases occurred[3].

Benefits of implementing WGS

- **Potentially earlier detection of 'cryptic' outbreaks:** if used in a prospective surveillance setting in situations where cases do not appear to be linked according to conventional methods, but can be linked by WGS. This means that infections are less likely to circulate unchecked.
- **Better targeting of infection control measures:** due to more accurate identification of the source and transmission of infections leading to targeted response measures *e.g.* cleaning focussed on particular areas or equipment. In response to the Birmingham *P. aeruginosa* outbreak, the hospital initiated extra deep-cleaning measures in the hydrotherapy rooms, including replacing sections of plumbing, and installing water filter units in highest-risk water outlets in the ward[2].
- **Better informed infection control policy:** knowing when there has not been a failure of infection control, thereby avoiding unnecessary follow-up measures.

Implementing WGS for infection management: policy issues

To ensure that genomics is used optimally, users should consider what their needs are and the situations in which genomics can make a significant contribution to control of infection[4]:

- **Knowledge development:** are the services (or knowledge to establish a service) available in each healthcare setting – *i.e.* is there access to genomics expertise and can results be interpreted and acted upon fully?
- **Impact of genomics:** can genomics make a significant impact in the hospital, for example are conventional methods not determining accurately where infections are coming from, and how they are spreading? Is this having an impact on patient well-being?
- **Cost effectiveness:** is there evidence that the use of genomics is likely to be cost effective, given the cost of services?
- **Cost of interventions:** are there resources available to manage potentially expensive infection control interventions suggested by WGS?
- **Optimised care and infection control pathways:** are these pathways optimised and resourced to take advantage of genomic information, *e.g.* can infected patients be isolated or items of equipment replaced?

References

1. Quick J. *et al.* BMJ Open, 4(11): p. e006278. (2014). 2. Eyre D.W. *et al.* N Engl J Med, 369(13): p. 1195-205. (2013) 3. Harris S.R. *et al.* Lancet Infect Dis, 13(2): p. 130-6 (2013). 4. Luheshi L. *et al.* Pathogen Genomics Into Practice (2015).

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