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Genomics and the management of antimicrobial resistance: current successes and future challenges

The targeted use of genomics presents a valuable opportunity to support and enhance the ability of the health services to minimise ineffective use of antibiotics and antivirals, to combat the spread of resistance through improved infection control, and to ensure that these vital therapies continue to be effective in the years to come.



Antimicrobial resistance (AMR) is one of the great challenges facing 21st century medicine.

Antimicrobial resistance (AMR) is one of the great challenges facing 21st century medicine. The development of new antibiotics has slowed rapidly, with few new drugs in development. In addition, current antibiotics are becoming increasingly ineffective at treating some common infections. The emergence of bacterial infections, such as gonorrhoea, that are resistant to the antibiotics of last resort indicates that the number of untreatable infections could increase, leading to the return of a significant death toll from previously easy to treat infectious agents.

The continued rise in infections, such as multi-drug resistant tuberculosis, coupled with the emergence of new drug-resistant organisms such as carbapenem-resistant Enterobacteriaceae, suggests there is still significant room for improvement in managing AMR in both community and healthcare settings.

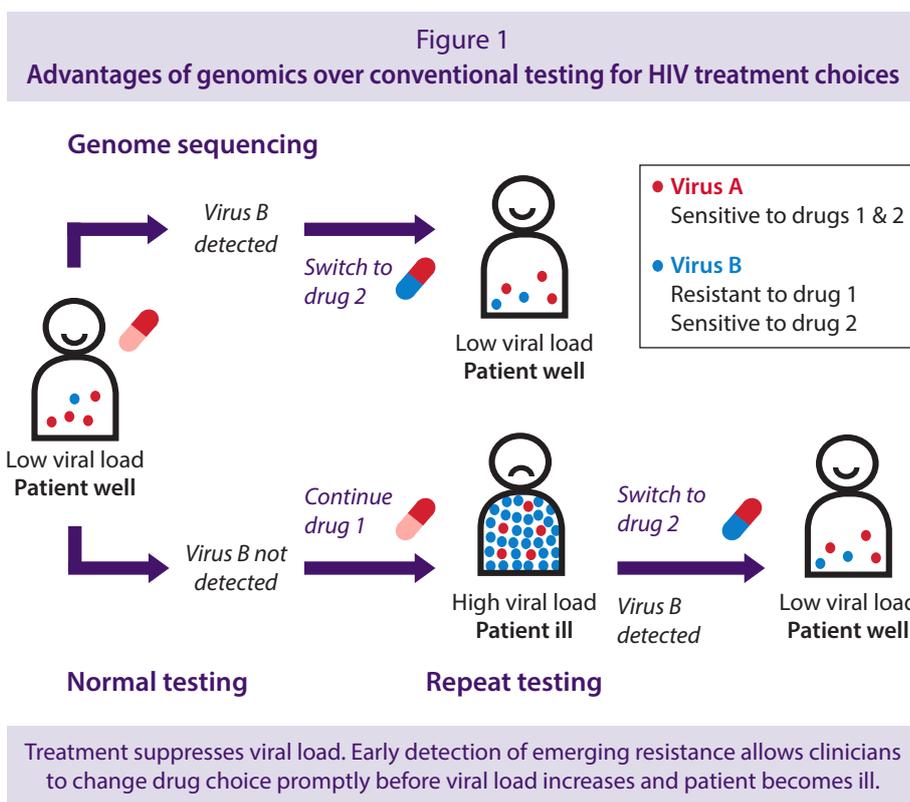
Antimicrobial resistance - responding to a growing threat

The UK government is adding antibiotic resistance to the National Risk Register of significant potential threats to the nation, and in 2013 launched a five-year strategy outlining how it plans to slow the development and spread of antimicrobial resistance. Measures central to achieving this aim include:

- **Prompt diagnosis of infections**
- **Rapid identification of pathogen susceptibility to drugs**
- **Appropriate prescribing practice**
- **Robust infection control**

Current strategies used to diagnose the presence of infectious pathogens and test their susceptibility to drugs, such as culture techniques or mass spectrometry, remain the quickest and most cost-effective approaches. Reductions in the incidence of infections caused by antibiotic resistant organisms, such as MRSA in healthcare settings, demonstrates that infection control in hospitals has improved significantly. However, the continued rise in other infections, such as multi-drug resistant tuberculosis (TB), coupled with the emergence of new drug-resistant organisms such as carbapenem-resistant Enterobacteriaceae, suggests there is still significant room for improvement in managing AMR in both community and healthcare settings.

In this briefing we explore ways in which the pathogen whole genome sequencing could underpin these improvements.



How can genomics contribute to tackling AMR?

Resistance of pathogens to drugs is determined by the presence of specific genes and / or mutations. There are several key areas where the use of whole genome sequencing (WGS) of pathogens could improve the understanding and management of antimicrobial resistance:

- **Rapid treatment decisions for slow growing pathogens**

WGS can be quicker than traditional methods for characterising pathogens, especially those that are very slow growing or difficult to culture.

For example, using genomics to detect antibiotic resistance in multi-drug resistant TB infections gives clinicians a diagnosis in one or two weeks, as opposed to at least six weeks using conventional methods. Earlier detection ensures that patients start receiving the correct treatments much sooner.

- **Pathogen spread and infection control**

One of the challenges when dealing with AMR is that resistance genes are easily transferred between some types of bacteria. Genomics can be used to track the spread of these genes through a pathogen population and to monitor the spread of susceptible and resistant pathogens within human populations, or between people and the environment or animals.

Genomics can also be used to determine whether cases of a resistant infectious disease are related (*i.e.* constitute an outbreak requiring investigation) and to help pinpoint human or environmental sources of infection. It can also inform public health measures that aim to minimise spread by eliminating the source of the resistant infection and its onward transmission.

- **Targeted treatment decisions**

Once the presence and nature of resistance are known, this information helps clinicians decide which drug might be the best choice to treat a patient.

- **Evolving drug resistance within individuals**

WGS can also be used for real-time tracking of how an infectious agent responds genetically to a course of treatment, potentially providing early warning of any emergence of resistance. For example, genomic analysis of the HIV virus in infected patients with rising viral levels alerts clinicians to the development of resistance to therapy and allows them to choose new combination therapies to which the virus remains susceptible (see figure 1).

- **Understanding genomic mechanisms of resistance**

WGS enables researchers to understand the different genomic mechanisms that lead to resistance, which can inform the development of new therapies and guide the development of new point-of-care diagnostic tests.



Rapid
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decisions



Pathogen
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Foundations are already in place for genomics to tackle antimicrobial resistance, but strategic oversight and a clear and consistent approach are urgently needed to maximise the benefits for patients and the health system.

Policy issues and actions

While genomics is already beginning to be introduced into some microbiology laboratories, the following issues should be considered to ensure available technology is put to the best use, integrated appropriately into existing workflows and applied to the areas of greatest need:

- **Effective data sharing**
Knowledge shared between laboratories will enhance the ability of the health system to respond swiftly to the emergence of antimicrobial resistance, and underpin comprehensive and rapid cataloguing of the genomic determinants of AMR, about which there is only limited knowledge.
- **Coordinated and consistent approach**
A coordinated and consistent national approach to how and when genomics are used as part of an antimicrobial resistance strategy is needed. This should include clear standards for the procedures used to assess and monitor antimicrobial resistance, so that information is easily transferable between different laboratories. Similarly, consistent and comprehensible computational and statistical techniques for data analysis should be implemented throughout the health system.
- **Resource availability and distribution**
While resources already exist to carry out sequencing in various parts of the health system, consideration must be given to how the workload should be distributed across national, regional and local services. There is also a need to balance the financial impact of using genomics to tackle AMR, likely to be felt in the short term at the local / regional level where the services are being delivered, against the expected health and financial benefits, which may predominantly be realised on a national scale, and over much longer periods.
- **Prioritisation for the use of genomic technologies**
Strategies must be developed to prioritise the application of genomics to those situations where it will have the greatest impact. Approaches could include constant monitoring of key pathogens where AMR presents a known threat, together with a reactive service that responds to outbreaks when they occur or to the emergence of resistance in previously susceptible species.
- **Clear communication**
Guidelines on how and when to use genomic technologies should be developed, including: clear standards of practice; where sequencing is to be carried out and by whom; which pathogens have priority for sequencing. These guidelines should be regularly updated to take into account developments in the technology and how any changes to practice will be implemented.

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