Queensland Genomics

GENOMICS FOR INFECTION CONTROL

Genomics 101

Genomics is the study of genomes.

A genome is an organism's complete set of genetic information. Like us, bacteria have a genome which contains its genetic material.

Each bacterial cell's DNA is unique, and this can be revealed by using genomics.

What is whole genome sequencing?

Whole genome sequencing (WGS) is a technology used in a laboratory that can give us information on the complete genetic material, or genome, of bacteria.

Genomic sequencing can now help hospital infection control teams to improve how they respond to and manage infectious diseases within hospital and health care facilities.

Key terms

Bioinformatics: The use of algorithms and software to analyse sequencing data.

DNA: The chemical structure that makes up your genetic material.

Genome: The complete set of genetic information in an organism.

Genomic testing/sequencing: Involves the analysis of hundreds or even thousands of genes from a pathogen simultaneously using sophisticated computer-based algorithms.

Infection Control: Preventing and identifying the spread of infections in a healthcare environment to protect patients and staff.

Pathogen: A microorganism that can cause disease, such as bacteria, viruses, or fungi.

Whole genome sequencing: A laboratory process to determine the complete DNA sequence of an organism's genome.

Sequencing platforms

There are a number of different sequencing platforms available. All allow scientists to gain key insights into the genetics of a pathogen. However there are pros and cons with each platform. Each offer differences in:

- Accuracy
- Throughput (which effects processing time)
- Cost

Scientists can also take a hybrid approach and use a combination of two or more different sequencing platforms.

Bioinformatics

Bioinformatics is the use of algorithms and software to analyse sequencing data. Analysing the data helps to determine key information such as the strain of the pathogen, and any antibiotic resistant genes that exist.

Typical bioinformatics pipeline

Once a sample is sequenced a number of files (called fastq files) are produced that contain the DNA sequences (or reads).

Step 1: Quality Control – look at the quality of the sequences. This may involve removing individual bases from the start and end of a read, or the entire read, if the quality score is low.

Step 2: Taxonomic profiling – searching for matching sequences between reads and a large database of reference genomes, to determine the most likely species or strain.

Step 3: Species specific filtering (processes here will depend on the genome's strain):

- SNP profiling – align the reads to a reference genome and look for SNP's. This also allows scientists to go on to detect clusters by identifying how related different strains are to each other.
- MLST (multi-locus sequence typing) profiling
- Antibiotic resistance profiling
- *De novo* assembly – assemble reads together to perform further analysis

Step 4: Combine this information with patient clinical data to produce a report for the Infection Control Team.

* Many of the above steps carried out are based on existing databases. Results are dependent on the database you use, how well the data is curated, and how comprehensive the database is.

Phylogenomic trees

A phylogenomic tree is a representation of evolutionary relatedness of samples. Examples are below.

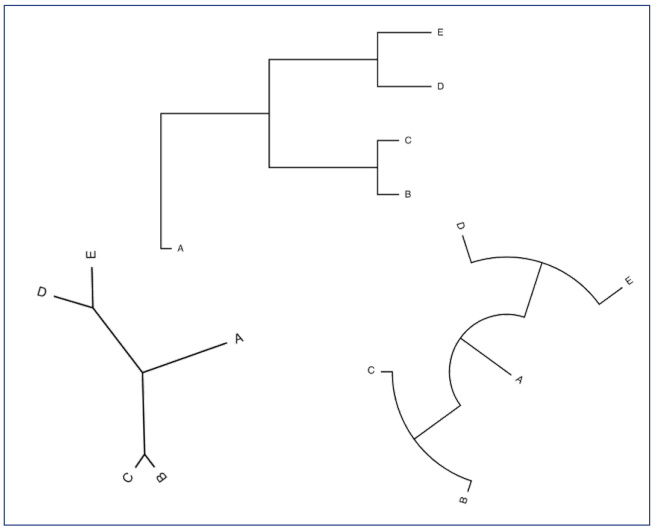

Image courtesy of The University of Queensland (Beatson and Forde groups)

Cluster analysis tool

A cluster analysis tool is an alternative method of looking at how related samples are, and is useful to help visualise an outbreak. .

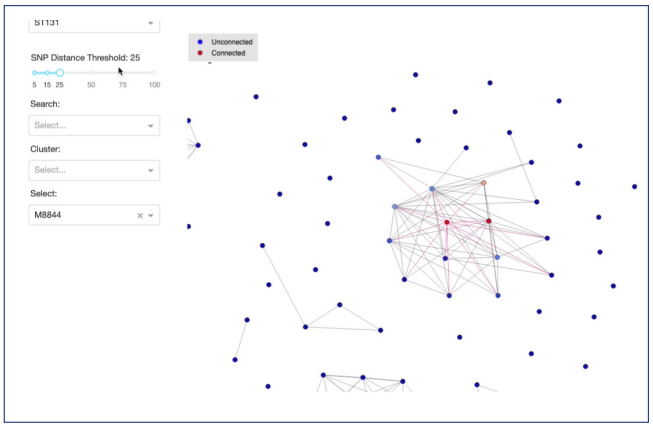

Image courtesy of The University of Queensland (Beatson and Forde groups)

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Infection control 101

Hospitals embody places of health, healing, and hygiene. They are places we go to when we need specialised medical care - where we expect to feel safe, cared for and protected.

Despite the best efforts it can also be a place where patients can pick up bacteria, causing infections. In fact, every year between 165,000 – 200,000 Australians contract a healthcare-associated infection because of their stay at an acute healthcare facility, causing significant ill health and costs to the health system. The most common types of hospital-acquired infections occur in the urinary tract, surgical wounds, respiratory system and blood stream.

Putting in place effective infection control measures is critical to reduce the spread of infection.

How do infections spread?

- Contact - person-to-person or via medical equipment
- Droplets - sprays or splashes
- Airborne - inhalation of tiny particles
- Sharps injuries which introduce a blood-borne pathogen

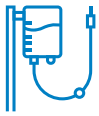
How to prevent the spread of infection

To minimise the risk and spread of infection healthcare workers maintain high infection control standards.

Standard precautions include:

Regular hand hygiene

Maintaining a clean environment



Disinfecting medical equipment after use

Wearing personal protective equipment like gloves, masks and eye shields

Handling and disposing of sharps and waste appropriately

Sometimes standard precautions are not sufficient, so additional measures called transmission-based precautions are introduced to help prevent the transmission of infectious agents.

Transmission precautions include:

- Contact precautions
- Droplet precautions
- Airborne precautions

For diseases that have multiple routes of transmission, more than one transmission-based precaution category may be used.

Antibiotic resistance

Antimicrobial resistance (AMR) occurs when microorganisms evolve and no longer respond to medicines such as antibiotics.

AMR limits treatment options making infections harder to treat, and can result in poorer outcomes for patients.

Ineffective infection prevention and control measures results in the increased use of antibiotics and increased opportunity for resistance.

To date, 1 in 10 hospitalised adults become colonised or infected with these organisms during their admission.

This is especially true for our most vulnerable patients, with weakened immune systems from cancer, chemotherapy or transplantation, or those undergoing complex surgical interventions or intensive care.

With the threat of drug resistant bacteria escalating, surveillance and prevention is more important than ever.

Examples of resistant organisms include:

- MRSA (Methicillin resistant *Staphylococcus aureus*)
- CA-MRSA (Community-acquired Methicillin resistant *Staphylococcus aureus*)
- VRE (Vancomycin resistant *enterococci*)
- ESBL (Extended spectrum beta lactamase producing organisms)
- CPE (Carbapenemase producing *Enterobacterales*)
- CRAB (Carbapenem resistant *Acinetobacter baumannii*)

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GENOMICS FOR INFECTION CONTROL

A day in the life of an infection control nurse

An Infection Control Nurse works to identify and prevent the spread of infections in a healthcare environment to protect patients and staff.

No two days are ever the same for an Infection Control Nurse, whose key areas of responsibility include:

- Clinical governance – Putting systems in place to support and promote the prevention and control of healthcare-associated infections, and improve antimicrobial stewardship.
- Custodianship of the Infection Control Management Plan – A health care facility's legislated plan to prevent or minimise infection risks.
- Risk management – Identifying and analysing risks that exist in a particular healthcare setting. Minimising risks by ensuring risk management is embedded into all policies, staff training is available, conducting monitoring and reporting activities.
- Education – Updating the skills and knowledge of all staff levels by providing education and training.
- Surveillance of hospital-acquired infection – Enable hospitals to monitor the outcomes of current practice and provide timely feedback to clinicians for continued practice improvement and better patient outcomes, through implementation of infection prevention and control activities.
- Outbreak and incident management – Identifying infectious disease outbreaks and putting necessary control and prevention measures in place.
- Screening and vaccination of the workforce and patients - Vaccination is important for the healthcare workforce to protect both patients and staff from vaccine preventable diseases.
- Coordinate hand hygiene program - Minimising healthcare associated infections by optimising hand hygiene practices among healthcare workers. This includes delivering education programs and regularly auditing practices.
- Coordinate aseptic technique program – Protecting patients during invasive clinical procedures by preventing and controlling healthcare-associated infections by measuring compliance through audit and review of surveillance data.
- Management of blood and body fluid exposures – Implementing guidelines and processes to protect healthcare workers from risk of blood born virus infection following occupational exposure to blood or body fluids.
- Environmental surveillance – Responding to pathogenic risks in the healthcare environment such as water sampling to detect *Legionella*, a bacterium which causes Legionnaires' disease.
- Evaluation of clinical consumables and equipment to ensure compliance with relevant standards.
- Leading National Standard and Quality Health Service Standards – Standard 3 to ensure hospitals implement and monitor systems to prevent, manage or control healthcare-associated infections and antimicrobial resistance, to reduce harm and achieve good health outcomes for patients.

The role of an Infection Control Nurse is not confined to the wards.

They are also involved in other hospital and health services, such as catering, waste management, and transportation - working with various teams to improve practices and support patient care.

Infection Control Nurses also play a key role in advising and educating staff, and advocating for both patients and healthcare workers.

Surveillance is an important part of their role and makes up a large part of the program. Infection control staff always need to have their eyes and ears open!

Typical surveillance plan will include:

- Surgical site surveillance
- Occupational exposures to blood and body substances
- Bloodstream infection surveillance
- Surveillance of significant organisms including multi-drug resistant organisms i.e VRE, CPE, MRSA and ESBL

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Microbiology 101

Microbiology is the study of microorganisms, or microbes, which include bacteria, viruses, fungi, protozoa and other parasites.

A microbiologist studies microorganisms that cause infections, with a focus on the structure, function and classification of these organisms; they also play a critical role in understanding how to design and interpret diagnostic tests to detect these pathogens and guide specific treatment.

Organisms are categorised into groups depending on their structure and characteristics. For example they may be grouped according to their species, strain, and the organism's antibiotic resistance profile.

A microbiologist provides key information to assist infection prevention and control teams in decision making and the implementation of interventions designed to minimise and prevent the transmission of infection.

Bacterial classification

Phenotypic description and genotyping are both essential to identify and classify a microorganism.

Phenotype

The phenotype refers to the type of features that can be seen. A microbiologist may examine an organism on a culture plate, observing what it looks like, its size, shape and microscopic or biochemical features. They will also look at the behaviour of the cells, whether it's growing in a certain way or if testing reveals it has any antibiotic resistance.

Genotype

The building blocks of the organism's phenotype is determined by the genotype or genetic makeup. Looking at the genes of bacteria requires different techniques to be used to define the genotype. These can be low-resolution methods where only small sections of the genome are characterised (e.g. multi-locus sequence typing) or the highest level of resolution, which can be provided by whole genome sequencing (WGS).

Screening specimens

Swabs often contain a diverse range of bacteria, including pathogenic organisms and "by-stander" commensal flora, so microbiologists use special media which only grows specific organisms, and will often have indicators in the media to tell these apart.

For example, chromogenic media helps to speed up the process of detecting common gram-negative bacteria (e.g. *E. coli, Klebsiella*). Further testing can determine whether resistance to antibiotics is observed.

This allows the laboratory to efficiently detect the most concerning pathogens in a short period of time.

Plasmids

Many resistance genes are carried on plasmids (mobile packets of DNA). Often there may be multiple antibiotic resistance genes on a single plasmid.

Carriage on plasmids allows for "horizontal" gene transfer to occur between cells, which can propagate resistance genes across different bacterial lineages, even across different species.

Piecing together the spread of these plasmids and the resistance genes they carry is challenging as you have to understand the evolution of the bacterial clones as well as the horizontal transfer of these mobile genetic elements.

Typical laboratory workflow

Culture - collect a clinical sample (e.g. blood culture, pus, sputum, etc) to look for organisms causing patient symptoms.

Grow the organism using specific media (e.g. agar plate), which may take 24-48 hours to grow or sometimes much longer (e.g. 4-6 weeks for some myobacteria or fungi).

Testing to define the species from the bacterial growth – using various methods (e.g. mass spectrometry, biochemical testing, phenotypic characterisation).

Additional testing to define resistance or susceptibility to antibiotics (e.g. automated broth microdilution, disk diffusion, gradient MIC strips).

Sometimes specific molecular tests are used to detect individual genes of concern (e.g. those causing carbapenem-resistance, or specific virulence factors).

Serious pathogens

- *Staphylococcus aureus* – a common cause of hospital and community-acquired infection and has increasingly developed resistance to antibiotics over recent decades.
- Vancomycin-resistant enterococci (VRE) - they are a type of bacteria which live in our intestines and on our skin, usually without causing problems. VRE has developed resistance to many antibiotics, especially vancomycin, which has traditionally been the standard treatment for certain types of enterococci. VRE endocarditis (infection of the heart) can occur and is almost untreatable.
- Gram-negative bacilli – they are a group of bacteria commonly found in the intestinal tract. They are essential for digestive processes, however, these bacteria can cause infection when introduced into normally sterile body sites, like the bladder, bloodstream or deep tissues. They can possess multiple mechanisms to resist antibiotics, so can be a challenge to treat.

Groups of gram-negative bacteria include:

- Enterobacteriaceae (now renamed as Enterobacterales) – live in the intestinal tract (*E. coli, Salmonella*).
- Non-fermenters – environmental opportunistic pathogens (e.g. *Acinetobacter* or *Pseudomonas aeruginosa*). You often find these bacteria in environmental reservoirs such as surfaces, sinks, taps or shower heads, and frequently colonise wounds, or artificial material in patients (such as venous lines, endotracheal tubes or catheters).

Genomics and antibiotic resistance

Antibiotic resistance is a major threat in modern healthcare, and the causes of the spread of antibiotic resistance are complex.

Whole-genome sequencing (WGS) is fast becoming an essential tool in the surveillance and control of antibiotic resistance. When you suspect you have a multi-resistant organism, WGS can be used to potentially tell you:

- What the organism is (i.e. which species or strain)
- Types of resistance mechanisms the organism has - known resistance genes can be compared to the genomic data to look for matching sequences
- How related the sample is to other organisms you've sequenced previously (i.e. is there evidence of transmission between patients, suggested by closely related or identical genome sequences?)
- Where the organism has come from (i.e. do the sequences share close similarity with samples from the environment?)

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How can genomics help infection control in your hospital?

Genome sequencing of pathogens can have a significant impact on infection control efforts in hospitals and improve patient care.

Genomic testing helps to track, treat and prevent hospital acquired infections. It is also overhauling the way we respond to and prevent outbreaks.

Confirmation or exclusion of outbreaks

Whole genome sequencing (WGS) takes a lot of the guess work out of managing an outbreak. Conventional testing can sometimes make samples look related when this is not the case. Because WGS looks at the entire genome, it's possible to determine whether an outbreak has actually occurred or if there is a series of unrelated cases.

More targeted infection control measures

WGS can be used to more accurately determine the direction of transmission and source of infection, so infection control teams can more accurately verify or refute transmission events.

Resolving outbreaks sooner

More detailed genetic information from WGS can uncover the source of infection where conventional testing has been unable to do so - minimising costs and in some cases saving lives.

How genomics can help improve infection control:

- Diagnose and identify pathogens
- Determine a pathogen's susceptibility to drugs and antibiotic resistance
- Confirm whether cases are linked
- Reveal the route of transmission
- Allowing a targeted infection control response

Whole genome sequencing has the biggest impact where current practice does not provide enough information to prevent the spread of infection.

Case Study: Outbreak in a special care nursery

A hospital in Queensland experienced an outbreak in their special care nursery. A baby born at 34 weeks had routine swabs taken and tested positive to ESBL producing *Klebsiella oxytoca* (a multi-drug resistant and potentially virulent pathogen in neonates). Despite an increase in screening, monitoring and cleaning in the nursery, one month down the track an additional three cases had been identified and it was declared an outbreak.

Epidemiologically the cases didn't overlap much, and infection control teams were at a loss as to what or whom could be the source of transmission.

Swab surveillance for patients was increased to every 48hrs, and a huge amount of environmental sampling was undertaken, which unfortunately did not reveal a source of transmission.

Initial genomic testing results suggested an environmental reservoir was the transmission source, which was a relief for nursing staff who had started to wonder if they themselves could be the source of transmission. Because genomic testing looks at all of the organism's genetic data, it allowed the laboratory to compare the samples with a level of detail that they could rule out patient-to-patient transmission. Knowing this, the infection control team expanded their monitoring and environmental sampling efforts to include the maternity and birth suite wards as well.

The first positive test result was taken from a drain in a multi-purpose room. After monitoring the room, infection control nurses noticed volunteers using the room to fill vases with flowers. They would carry a basket around the hospital to change and clean out vases, so the contents of the basket were also swabbed and tested.

Another positive swab was taken from a bottle of detergent in the basket. Other bottles of detergent around the hospital were then collected and tested, and an additional 12 bottles tested positive to *k. oxytoca*.

A recent study showed the use of whole genome sequencing as part of routine surveillance in Queensland hospitals could prevent a significant number of hospital acquired infections and related deaths every year. To learn more visit bit.ly/WGS-Qld

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Genomic data showed the strains isolated from the detergent bottles were either identical or closely related. This was important information for the infection control team as they were able to link these cases to the same outbreak.

One of the contaminated detergent bottles was in the milk room of the special care unit, and used by mothers to wash milk expressing equipment. The infection control team discovered the detergent bottles were being refilled from large drums, and cleaners were not completely using, washing and drying out the detergent bottles – which allowed the organism to reproduce and spread.

The source of transmission had been found, and no new cases emerged once these detergent bottles were removed. In this example, whole genome sequencing was instrumental in revealing the route of transmission and guiding the infection control response.

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