

Horizon Scanning Series

The Future of Precision Medicine in Australia

Infectious Disease

This input paper was prepared by Professor Mark Walker, Professor David Patterson, Professor Paul Young, Professor Mark Schembri, Associate Professor Scott Beatson, Professor Alexander Khromykh (The University of Queensland)

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Executive summary

The threat of infectious diseases is an important global issue confronting human health. Two major threats are the rise of antibiotic resistance, and emerging infectious disease outbreaks. The development of diagnostic, therapeutic and preventative strategies to combat these threats will only come from an improved understanding of the mechanisms by which microorganisms engage with individual patients and populations to cause disease. Australian indigenous populations and neighbouring populations of South-East Asia bear a disproportionate disease burden. Precision medicine, and in particular the deployment of genomic technologies, will allow the rapid identification of antibiotic resistant pathogens and outbreak agents, informing epidemiology, public health responses, and target identification for new therapeutics and vaccines. Gaps in the Australian system include the optimal resourcing of Centres of Research Excellence (critical mass or research scientists and physicians) in the infectious diseases research area (e.g. Australian Infectious Diseases Research Centre in Brisbane; Doherty Institute in Melbourne; Mary Bashir Institute in Sydney) and funding to enhance integration with State Health Authorities to support a concerted national approach to this problem.

Infectious Diseases Research Landscape in Australia

Infectious diseases are the second most important cause of death globally after heart disease, and kill more people than cancer.¹ Australia has a strong history of research excellence and contribution in the infectious diseases field.² Research groupings are dispersed nationally, usually embedded within Advanced Health Research and Translation Centres³ and based within Hospitals, Research Institutes and Universities. Three major Centres of Research Excellence are working on a broad range of pathogens and encompassing significant critical mass of research scientists and physicians:

- Australian Infectious Diseases Research Centre (UQ and QIMRB)⁴
- Doherty Institute for Immunity and Infection (U Melbourne)⁵
- Mary Bashir Institute for Emerging Infectious Disease and Biosecurity (U Sydney)⁶

Other research groupings with specific research expertise/skills, also dispersed nationally, include: Australian Animal Health Laboratories (AAHL), Geelong (CSIRO), Australian Institute of Tropical Health and Medicine (JCU), Menzies School of Health Research (Darwin), Glycomics Institute (Griffith University), WEHI (Melbourne), Burnett Institute (Melbourne), I3 Institute (UTS), Hudson Institute of Medical Research (Melbourne), Adelaide Research Centre for Infectious Diseases (U Adelaide) and the Marshall Centre (UWA).

Precision medicine is defined by the US National Institutes of Health as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes,

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environment, and lifestyle for each person."⁷ **For infectious diseases it is knowledge of precise genetic or phenotypic variability amongst the infecting pathogens themselves that enables a precision approach for the treatment or prevention of disease in an individual.** Precision medicine, and in particular the deployment of genomic technologies, is being rapidly taken up by several of the aforementioned Research Centres, given its utility for the rapid identification of antibiotic resistant pathogens and outbreak agents, informing epidemiology, public health responses, and target identification for new therapeutics and vaccines.⁸⁻¹⁰

The relationship between precision medicine and infectious disease in Australia

Precision medicine has significant impact on three major facets of infectious diseases research, including outbreak monitoring and pathogen emergence, genomic epidemiology and investigating antimicrobial resistance in the hospital setting, and the identification of novel infectious disease agents, vaccine development and therapeutic drug target identification.

Outbreak monitoring and pathogen emergence

The application of genome level phylogenetic and comparative analyses is a long established technology for monitoring viral outbreaks, facilitated by the reduced size of many viral genomes. Use of precision genomic technologies is exemplified in investigation of recent viral outbreaks such as SARS, MERS, Nipah, Zika, Ebola, Chikungunya and Influenza. The availability of accessible and established databases for virus genome information allows identification of new infectious agents, monitoring of changes in virulence, determination of new outbreak isolates and the transfer of known viral strains into new geographic settings. The power of applying genomics in real time to an emerging outbreak was particularly evident in the recent Ebola epidemic. Genomic sequencing technologies were deployed in the field to assess the specific point-to-point spread of the ongoing epidemic allowing appropriate health care intervention (e.g. appropriate ring vaccination late in the epidemic using an available experimental vaccine). Lessons learnt from that outbreak have been adopted by the WHO, who have initiated a more proactive program of research aimed at preparedness for the next emerging pathogen outbreak. A working group at WHO have identified about a dozen "exotic" agents that have the potential of causing an explosive outbreak. The Coalition for Epidemic Preparedness Innovations (CEPI) was born out of this initiative (funded by the Wellcome Trust, Gates Foundation, World Bank and partner countries) and have identified 3 agents, Lassa fever virus, MERS and Nipah virus for assessing the World's preparedness for a rapid response.¹¹ Genomics applications are at the heart of this program and Australian institutions named above are partners in this global effort. One of the first tangible local outcomes has been the establishment of the Australian Vaccine Pipeline consortium, aimed at piecing together the required infrastructure for the rapid development, testing and deployment of novel outbreak targeted vaccines.

Bacterial, fungal and parasite infectious agents have only more recently been subjected to genome level phylogenetic and comparative analyses due to the availability of next generation sequencing technologies capable of sequencing the larger genomes of these infectious pathogens. Nonetheless, the application of genomic technologies has revolutionized our capacity to monitor outbreaks and the spread of infectious clones such as carbapenem resistant *Enterobacteriaceae*, the extended spectrum beta-lactamase resistant *E. coli* ST131 clone, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* (MRSA), enterohaemorrhagic *E. coli*, *Legionella* spp., multiple drug-

resistant *Mycobacterium tuberculosis*, *Clostridium difficile*, and scarlet fever causing group A streptococci. Precise knowledge of outbreak strains guides the clinical and public health response at both local level (e.g. Wesley Hospital Legionella outbreak)¹², national level (e.g. vancomycin resistant VRE and VRSA)¹³ and globally (e.g. scarlet fever outbreaks in China¹⁴ and the UK).

Genomic epidemiology and investigating antimicrobial resistance

Genomic epidemiology, the application of high-throughput genome sequencing to microbial infectious disease isolates in the hospital, allows monitoring of infection transmission in the clinical setting and is set to revolutionize current practice in clinical microbiology. This genomic information provides unequivocal information on transmission pathways of infectious disease agents, and antimicrobial resistance profiles. Such information is able to be deployed to break transmission pathways, develop novel diagnostics and will inform precise antibiotic dosing against infectious disease pathogens in critical care environments. Routine genomic interrogation of infectious disease agents from the clinical setting will also allow monitoring of the spread of individual resistance genes (e.g. plasmid-encoded antibiotic resistance genes) at a resolution that has not been previously achievable. The identification of resistance mechanisms will no doubt form the basis for new approaches in combating the problem of antimicrobial resistance. For viral therapy (e.g. Hepatitis C, HIV, cytomegalovirus in transplant patients), genomic information on individual viral drug targets already allows the tailoring of individualized therapy for infected patients.

Identification of vaccine and therapeutic drug targets

The NCRIS funded Bioplatforms Australia Research Data Services (RDS) Sepsis Initiative (<http://www.bioplatforms.com/antibiotic-resistant-pathogens/>; <http://omics.data.edu.au/>)¹⁵ exemplifies the potential contribution that genomics in combination with other 'omics' technologies can make to the fight against infectious disease pathogens. A better understanding of sepsis (as exemplified by established bloodstream infection) is crucial to the development of new approaches to clinical management, including strategies such as virulence-attenuating approaches that do not necessarily select for more antimicrobial resistance. This strategy requires the coordinated action of multi-disciplinary teams to identify common pathogenic pathways that may be exploited for the early diagnosis, treatment and prevention of life-threatening bacterial infections. This national research data infrastructure will support the storage, integration, analysis, annotation, visualisation, sharing and publication of data generated from multi-omic research (i.e. genomics, transcriptomics, proteomics and metabolomics). Such nationally collaborative approaches are expected to facilitate the identification of new vaccine and therapeutic targets against important sepsis pathogens in the Australian context.

Recent advancements in infectious disease as related to precision medicine

Precision medicine in the hospital setting

Hospital-acquired infections are common and associated with significant morbidity and excess healthcare-related cost. Furthermore, the impact of these infections is exacerbated by rapidly increasing rates of antibiotic resistance. At present, we have limited laboratory capacity to track pathogens causing these infections in real time or detect patient-to-patient transmission. Genome sequencing promises to revolutionize modern clinical microbiology by capturing information within

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the entire pathogen genome, providing an unparalleled understanding of clinically relevant characteristics that are usually unknown. This will allow a detailed analysis of antibiotic resistance genes in pathogenic bacteria, identification of genetic elements associated with the ability of these pathogens to cause disease, strain typing and tracing of pathogen transmission. A dedicated national approach to pathogen sequencing in the hospital setting has the capacity to produce the following outcomes: (i) clinically-actionable, validated and timely genomic analysis of pathogens isolated from hospital-admitted patients, (ii) development of advanced bioinformatic pipelines to facilitate genomic analysis of pathogens, (iii) monitoring of pathogen transmission between patients to inform infection prevention and control responses, (iv) reduction in the overall burden of hospital-acquired infections and the early detection of new outbreaks, (v) establishment of databases to contextualize new pathogens with historical isolates, and (vi) nationwide tracking of pathogens in the hospital setting.

Metagenomic discovery of new human pathogens and the human microbiome

A growing number of chronic human diseases have an underlying basis of infection. Examples of such infectious disease agents include the Australian discovery of *Helicobacter pylori* as the cause of stomach ulcers and gastric cancer, the association of *Clostridium difficile* with ulcerative colitis and inflammatory bowel disease, and the identification of Human Papilloma Virus as the causative agent of cervical cancer. The increased use of genomic technologies, and in particular the use of metagenomic analysis, may allow the identification of new pathogens responsible for diseases not thought to have an underlying infectious trigger. Similarly, the microbiome is presently subject to intense metagenomic research, and the disruption of the human microbiome is associated with immune imbalance.

Gaps in Australia (and how this may compare internationally)

Each of the State-based health systems has procedures in place to respond to potential outbreaks in Australia, as evidenced by responses to a number of emerging pandemic pathogens (e.g. Ebola, Zika, H1N1, H5N1) and more localized epidemics (e.g. *Legionella*, meningococcus, invasive group A *Streptococcus* etc). The alternative to this federated model that has been adopted in a number of countries is the resourcing of a central Centre for Disease Control (e.g. US CDC, China CDC). This concept was addressed in detail as part of national discussions around a Federal Government commissioned white paper in 2013 (Towards a Communicable Disease Control Framework for Australia)¹⁶, and the need was again re-enforced by a call for an Australian CDC by the Australian Medical Association earlier this year. Whichever of the two different outbreak control systems that is favored in any national jurisdiction requires adequate resourcing to ensure seamless coordination across State boundaries.

The use of genomic technologies for the control of outbreaks, combating the rise of antimicrobial resistance and characterisation of infectious agents to ensure best practice response requires shared data analysis pipelines and secure databases that may be accessed across a national level. The advent of genomic technologies and the introduction of these technologies into lab pathology and public health would provide an opportunity to rationalize and harmonize platforms for data generation, data analysis, data access and secure data storage. In order to most effectively utilize genomic technologies in the best interest of the health of the entire Australian population and

enable real-time data generation and utilization, the sharing of secure datasets nationally needs to be realized.

The three major Centres of Research Excellence (Brisbane, Sydney and Melbourne) are working at the forefront of solutions for effective data generation, data analysis, data access and data storage. National infrastructure and coordination is provided through initiatives such as the Australian Biosciences Cloud¹⁷, Bioplatforms Australia¹⁵ and EMBL Australia Bioinformatics Resource¹⁸. Ensuring these efforts are adequately resourced and harmonized is an essential prerequisite for these efforts.

Where the field is heading and what opportunities and challenges the next 10 years may bring for Australia

Genomic technologies are starting to be transferred as pilot studies into public health and pathology labs in Australia. For example, a forthcoming Queensland Genomic Health Alliance demonstration project encompasses routine sequencing of multidrug resistant bacteria in the pathology laboratory.¹⁹ At the hospital level, precision medicine will enable detection of previously unrecognized transmission events and enable targeted patient management in response to knowledge of antimicrobial resistance carriage (for example, extended-spectrum beta-lactamases or carbapenemases). For sepsis or other intensive care patients, genomics will enable real-time identification of resistance gene profiles and resistance development facilitating more targeted antibiotic use. In the community, rapid genomic screening of urinary samples will not only enable resistance detection but will establish sexual health network tracking for common organisms such as gonorrhoea. The availability of personalised microbiomes also has the potential for targeted treatment of urinary tract or diarrheal infections with an antibiotic course that takes account of resistance genes carried by a patient. For this technology to be most effectively utilized for the national interest, this technology transfer should be coordinated and harmonized, rather than be undertaken *ad hoc*. This will allow outbreak and antimicrobial resistant pathogens to be monitored nationally, highlighting transmission pathways and disease impact. Furthermore, the national benefit of genome databases will be cumulative as the ability to link clusters, outbreaks and emerging resistance patterns increases over time.

To realize these ambitions, significant resourcing will need to be directed into coordinated training and infrastructure, allowing this new technology to run in parallel with existing procedures and then allowing existing procedures to be phased out where genomic analysis is superior. Training is required both for bioinformaticians to establish, validate and extend the pipelines for precision medicine, but also for clinical staff to ensure that they are fully informed to act appropriately upon the results. The harmonization of platforms for data generation, data analysis, data access and secure data storage will facilitate monitoring at the national level.

Efforts are already underway to bring about this precision medicine revolution in the area of infectious diseases research.²⁰ The main Centres of Research Excellence are conducting research together on various projects. Analysis pipelines are being built for research that can be adapted for standard public health and pathology utilization. Training modules are being formulated (e.g. RDS, EMBL Australian Bioinformatic Resource etc).

Conclusion

Precision medicine has the capacity to make a major impact in the monitoring, control and prevention of infectious diseases in Australia. To achieve this goal funding is required for resources, upskilling, technology development and increased integration between Centres of Research Excellence and State Health Authorities.

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- ⁷NIH Precision Medicine Definition: <https://ghr.nlm.nih.gov/primer/precisionmedicine/definition>
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This report can be found at www.acola.org.au Australian Council of Learned Academies

¹⁷Australian Science Clouds: <https://nectar.org.au/new-australian-science-clouds/>

¹⁸EMBL Australia Bioinformatic Resource: <https://www.embl-abr.org.au/>

¹⁹Queensland Genomics Health Alliance: <http://www.qgha.org/project-round1/>

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