Horizon Scanning Series
The Future of Precision Medicine in Australia

Precision medicine to become standard practice, not a specialty

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1. Definitions

- Precision Medicine: An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. *https://ghr.nlm.nih.gov/primer/precisionmedicine/definition (accessed 2017)*

- Precision Medicine: The correlation of innate and external factors at an individual level, to better understand the pattern of disease and its impact on that individual and thus to tailor prevention, intervention and treatment. *Winship I. Med J Aust. 2015. 203(3):132-3.* "4P Medicine - predictive, personalised, preventive and participatory." *Hood, L & Friend S. Nature Reviews Clinical Oncology 2011. 8: 184-187*

An understanding of the role of genetics and genomics in disease can help to reduce the burden of disease through prevention, early detection and optimisation of management and, thereafter, monitoring. This is well illustrated for cancer; knowledge that underpins genomics in heritable predisposition, tumorigenesis, progression of disease and response to management will provide the basis for the implementation of personalised or precision management. Genomic variation contributes to risk estimation, allowing for risk stratification and consequent optimisation of cancer prevention through rational screening, ideally starting in a community health setting. Combining knowledge of biology with surveillance and therapeutics, including individual drug responses, will gather the evidence required for precision health care. Furthermore, molecular interrogation of individual tumours (somatic genomics) will guide medical oncologists and immune-therapists in the treatment of cancers.

The role of precision medicine in prevention extends beyond cancer. It is of value to individuals and their families to identify mutations in predisposition genes in multiple adult onset disease disorders such as cardiomyopathy, dementia or renal failure. Early intervention may have markedly improved outcomes. Polygenic risk scores will allow better risk estimation in the community as well as for individuals, with the allocation of resources to the areas of greatest need. The effective application of pharmacogenomics will reduce adverse events of medication, while efficacy will increase, using the right drug at the right dose for the right genotype. It is important to note that, while the analysis may be genetic and genomic, the intervention may be environmental, lifestyle change or medical.

2. Why precision medicine in public health?

The potential exists to create a sustainable health care ecosystem utilizing existing multidisciplinary expertise in every state, discipline and demographic. The current standard of care is often not good enough; we need to improve upon "one size fits all" model of care and prevention. Furthermore, it is evident that the cost of the "trial and error" approach in healthcare is more than financial.

2.1. Exemplars

2.2. Colorectal cancer

Colorectal cancer (CRC) a significant cause of morbidity and mortality, is the third most common cancer worldwide (1). CRC is potentially preventable- the identification of those at increased risk allows targeted

risk management strategies to prevent cancers, including risk-reducing medication, colonoscopy screening and polypectomy (2). There has been a rise in the incidence in young onset CRC (3). It is likely that to a third of CRCs have a heritable component, of which 5-10% of attributable to mutations in known susceptibility genes, in particular, Lynch Syndrome. The practice of clinical genetics is currently transitioning from phenotype-directed single gene testing to multigene panels comprising a range of known or potential CRC susceptibility genes or SNPs (4).

In Australia, more than 95 % of individuals are at population risk of CRC. While we have a National Bowel Screening programme for over the age of 50 years (Faecal Occult Blood testing), which is effective and well validated, only a third of those offered this screen complete the test. Furthermore, research shows significant inequities in access and uptake of colonoscopy for higher risk individuals (5). A precision approach will allow for the identification of the small proportion (5%) of individuals with a high risk, for whom more intensive risk management is required, thus improving efficacy and reducing existing disparities.

Once genomic tests that can identify circulating free DNA in the blood of persons with cancer before cancer detection can be combined with assessment of genome predisposition to CRC, this combination could lead to an approach that is both person-specific and precise.

2.3. Pharmacogenomics

This is the effective use of medications to reduce potentially adverse events/ toxicity, and to increase clinical efficacy, to reduce the amount of ineffective medical care.

Pharmacogenomic testing is therefore increasingly used to customise treatments with a wide range of medications in primary health and specialist care. The list of drugs which guide prescription is increasing but clinical practice in the implementation of pharmacogenomics lags behind the technology. In Australia this is amplified by the inconsistent use of electronic medical records, one of the key enablers.

Medical waste and inequity of care are major problems at a time of increasing demand on health services; with increasing cost, expectations and an ageing population, critical evaluation is required. In many clinical cases, drugs do not perform as expected or toxic effects may occur, irrespective of dose. This may be explained by genetic variants which impact on the individual response to drugs and therefore genetic pathways are becoming standard of care in a number of drugs. Candidate variants can be evaluated for clinical significance through clinical trials and cost effectiveness studies.

Safety outcomes determined by relevant pharmaco-genetics/genomic testing can be illustrated in cardiology, where an individual may need a cholesterol lowering drug, blood pressure control and anticoagulation. The *SLCO1B1* gene which encodes the OATP1B1 protein affects the hepatic uptake of a class of drugs called statins. A particular polymorphism SLCO1B1-c.521T>C is well recognised to change the pharmacokinetics of simvastatin particular, increasing the likelihood of a drug induced myopathy *SLCO1B1* genotyping is thus advised prior to high dose therapy with simvastatin (6). There are multiple other alleles not yet in routine practice. Clopidogrel is widely used as anti-coagulant drug used in ischaemic heart disease. A number of variant alleles result in poor metabolism and, therefore, little function or clinical effect. Likewise, prescribing for Warfarin is recommended to be modified on the basis of two genotypes, *CYP2C9* and *VK0RC1*. Similarly, if the patient also had renal failure and a B blocker was required, *CYP2D6* gene testing may be useful in predicting response and reducing risk of side effects (6). The combination of these genotypes along with the body mass index age, other comorbidities and other medications epitomise the potential for precision in healthcare.

Population consideration:
There are also target populations where testing is required. For instance, in Han Chinese individuals, HLA-

B genotyping is recommended before the use of the anti-epileptic drug, Carbamazepine. The HLA-B*1502 allele predisposes carriers using Carbamazepine to Steven Johnson Syndrome, an adverse response with high morbidity and mortality.

USE CASE:
A 59-year old female with metastatic hormone receptor positive breast cancer was treated with capecitabine. Within a few days she developed the symptoms of toxicity which necessitated 50 days in intensive care. Life-threatening toxicity may be caused by genetic susceptibility on the basis of dihydropyrimidine dehydrogenase (DPD) deficiency. Genomic sequencing revealed a pathogenic mutation in the DPYD gene, which explained her clinical course. Cascade testing to her extended family will facilitate a precision approach to relatives who may yet develop cancer, prior to commencement of potentially toxic and avoidable drug reaction

2.4. Enablers

Precision medicine in population health will be enabled by a recognition of the complete health ecosystem; genomics combined with existing multidisciplinary expertise and skills, and cognisance of co-morbidities and lifestyle factors in the community. Whether provided by private sector or public hospitals, community advocacy, general practice or national screening programmes, convergence of all the elements will form the basis of a respectful and efficient improved approach to health and well-being.

Genomic data curated to international standards, with standardised nomenclature and interoperability of data standards can then be correlated with phenotypic/ clinical data. This will be predicated upon good collaboration nationally and internationally.

Community engagement and ethical considerations cannot be understated; winning and retaining the public trust is central to precision medicine's progress.

3. What will precision medicine achieve?

3.1. Systemically for the Community

The goal is wellness through prevention. With a focus on equity and the reduction of health disparities, it is hoped that by reducing inefficiencies, as well as very costly side effects, better health outcomes with less adverse events will be achieved, with less clinical waste. Furthermore, translation and implementation of research into practice, can also lead to more innovation and the commercialisation of inventive contributions

3.2. Individual or family

This approach will underpin risk assessment, which allows risk management. In this way, early detection, early intervention and targeted therapy become a reality. Precision medicine to the individual aims to prevent predictable disease, to prevent predictable complications of disease and indeed, to prevent predictable complications of treatment

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