Horizon Scanning Series
The Future of Precision Medicine in Australia

Pathology and Imaging

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1. Introduction

Introduction to the future of diagnostic tests/pathology/advanced imaging including 'omics.
Precision medicine is by implication a more precise approach to the patient. Since the days of Hippocrates, the patient has long been observed carefully by doctors and in doing so, these observable traits, or phenotype, determine a basis upon which the doctor acts. As advances occur in medicine, the detail of this phenotype expands as does the need to continue to build an evidence base upon which the doctor can act. Whilst the phenotype is an expression of the genotype (or genetic code) other environmental interactions (epigenetics) are also important.

Patient care should be central to the agenda. Genomic information, which in fact typically includes a substantial number of changes irrelevant to the outcome of the patient, needs to be interpreted in the context of the patient. It is not just about generation of huge amounts of genetic data but how the data is used to effect actual patient care. Health service–wide multi-disciplinary interactions with treating physicians, pathologists, scientists and signalling experts should be established to exactly interpret and predict the functional consequences of the genetic data in order to link in with known targeted therapies. Molecular tumour boards should be established in each major hospital and this is where investment needs to go. There is no more need to invest in super genomic facilities. There is a lot of genomic data sitting on servers around the world not being used or not able to be used for patient care as the downstream capacity is limited. We need to concentrate on integration and patient care and resourcing the downstream processes for the benefit of patients which is a clear deficiency in the health services.

Precision medicine is based on an accurate diagnosis. As an example of precision medicine, the accurate pathological diagnosis and classification of tumours underpins routine clinical care (and translational research) in cancer. In the future, the characterisation of any tumour will most likely be via a multi-pronged approach to include; morphology, immunohistochemistry (outlining the proteins expressed and location in the tissue biopsies received), in-situ hybridization (detailing tumour gene expression in-situ in biopsy material) and 'omic studies such as; genomic studies (defining the gene mutations present in the tumour), methylomic studies (methylation data detailing epigenetic changes), proteomic studies (viewing all the proteins expressed in the tumour), and transcriptomic data (viewing the gene read outs present in the tumour). Whilst morphology and immunohistochemistry are routine in pathology laboratories, in-situ hybridisation, genomic and methylation studies are either recently present or being developed in many NATA accredited clinical laboratories and will continue to develop in the near future. Centralisation of some of the tests that are rarely required would seem a sensible future approach. Proteomic and transcriptomic studies are not yet in the main arena of routine diagnostic care but it is highly likely they will be in the near future. The process of pathology laboratory test development is a continuum and dependent on; availability of skills and equipment, need and volume of tests requested, budget available, NATA accreditation and an evidence base for the value of the test.

Service provision, with immediate patient impact, is central to precision medicine and requires adequate funding. Diagnostic testing using any technology including genomics (whether the information is derived as part of a 'research' program or as service), must be subjected to rigorous quality assurance and quality control procedures (NATA accreditation and participation in ongoing performance evaluation programs) so that the end user understands the performance characteristics of the test (for genomics, the error rate in the primary genotypic data, and the precision in calling the phenotype based on the correctly assessed genotype).

2. Current diagnostic Molecular Pathology actions, alliances and initiatives

2.1. Australia

The RCPA is involved in;

- Development of Standards for clinical databases of genetic variants
- Development of Standards for sequence variation interpretation
- Establishing guidelines for implementation of Massive Parallel sequencing in Laboratories
- Development of a genetic testing website available on-line
- Development of a National Molecular Pathology Curriculum (in – development)
- Conducting surveys on Genetic Testing use in Australia through DoHA

Appendix 1 provides an overview of the existing resources of NATA/RCPA accredited Molecular laboratories in Australia currently performing molecular testing.

Advances in diagnostic Pathology (in brief)

Recent advances in Pathology and Imaging technologies highlight the role increased detail regarding the phenotype can play in improving patient care on a day-to-day level. Some key advances, that have been recently introduced and are likely to become more common place in hospital medicine over the next 5-10 years are discussed below and include advances in; techniques that improve the accuracy of the details of a tumour in tissue removed from patients (anatomic pathology), detection of circulating tumour DNA (pathology) and imaging patients in-vivo (nuclear medicine imaging for cancer and for dementia).

Molecular testing of humans samples in NATA/RCPA accredited Pathology laboratories has shown an increase in the breadth and range of testing over the past decade with over 50 accredited testing laboratories now operating Nationwide (see lists below). Molecular tests are many, with over 500,000 tests performed each year. The tests are varied and include; single gene analysis, gene panels, cytogenetics, microarray, genomic sequencing and SNP analysis. The volume of somatic molecular tests has increased significantly recently as they now include tests for; BCRABL1, JAK2, KRAS, BRAF, NRAS, cKIT, NRAS and EGFR (and others), reflecting advances in knowledge in the field of targeted therapies for cancer (precision medicine).

Assessment of targetable sites (i.e. drug targets for cancer treatment) has been a main focus of much recent development in laboratory testing (BRAF, KRAS, NRAS, cKIT, EGFR) done by genomic testing performed on carefully selected tumour tissue by the pathologist and interpreted in conjunction with the pathological diagnosis. More recently, accurate predictions of mutations by immunohistochemistry testing has become a cheaper and quicker alternative to genomic testing in some circumstances, so the wheel is turning on from genomics and Australia needs to have the capacity to meet this next wheel turn in the near future in the field of pathology (with advances in tumour immmunoprofiling) and development of tumour molecular boards based in major hospitals in which the patient care is centre. Tests that more accurately determine the primary tumour type are also either recent mainstream or an area of test development i.e. HER2 status in breast carcinoma, 1p19q co-deletion in-situ hybridisation and detection of IDH1 gene mutations using immunoperoxidase studies for brain tumours. Analysis of programmed cell death-1 (PD-1) pathways in relation to the assessment of the new immune check point inhibitors is also a major field of recent advance in pathology testing requiring continued validation of both tests and outcomes as is analysis of nuclear transcription factors in tumour tissues.

The most recent WHO classification system of tumour diagnoses are now incorporating such combined molecular data into the diagnostic criteria. It is Pathologists that take all the data and put the molecular findings into context with the morphology. Single data points from any of the 'omics cannot be interpreted in isolation of the basic morphology if the best outcomes are the desired endpoint (c.f. (Louis *et al.*, 2014; Pajtler *et al.*, 2017; Sturm *et al.*, 2017)). The diagnoses made are then used by the oncologists to determine the treatment and management of the patients, based on evidence.

Whilst the specificity of diagnostic criteria continues to change over the next 5-10 years, there will be a need to continually re-evaluate the evidence provided by specific treatments (clinical trials) and updated tumour classifications. Pathology departments in the next 5-10 years will have to continue to improve their NATA accredited functionality in this multi-modal approach within a stringent quality controlled environment management system. As such, precision medicine will be continually evolving into the next decade.

The continued development of tests in cancer medicine is impeded by the requirement for;

- an MBS schedule for the new tests to avoid pressure on departmental budgets
- continued advancement in knowledge by pathologists interpreting tests, scientists performing the tests and NATA validating the test use in the clinical setting, hence continued education at the cutting edge of technologies with the abilities to implement this new knowledge in to the healthcare sector.
- a targetable drug being available for the specific new diagnostic test and hence the process of new diagnostic test development is dependent upon drug development and clinical trials validating each drugs use in cancer treatment
- new instruments and engineering that in themselves have to have been validated.

Hence the process of development of new tests has requirements at multiple levels including new knowledge, new science, new instruments, new engineering, new money, new preclinical studies, new validation within a laboratory setting and new clinical studies validating the worth of the test after continued use.

Advances in Ct DNA detection

Further advances in precision medicine techniques as applicable to cancer medicine, are likely to come through the use of detection of small amounts of DNA ('circulating tumour DNA' or ctDNA) into the patient's bloodstream (Wan *et al.*, 2017). Recent advances in genomic technologies now allow levels of ctDNA to be accurately measured in the blood and used as a highly sensitive and specific biomarker in various aspects of cancer management. The use of ctDNA for clinical applications has several key advantages as it can be studied from a simple blood test that is easy to perform, safe, minimally invasive and can be repeated frequently during patient follow-up. Importantly, ctDNA analysis can provide a 'liquid biopsy' alternative to tissue biopsies to follow tumour specific genomic changes over time. The most immediate clinical application of this strategy is in the identification of specific genomic alterations to guide the selection of targeted therapies. The ability to perform blood-based tumour genotyping assays from ctDNA facilitates the ease with which therapeutic targets can be identified in individual patients and importantly, allows these targets to be monitored in real-time during therapy. Clinical applications in this arena are likely to expand in coming years with the development of future genotype-driven targeted therapies. Secondly, the development of treatment resistance is a major problem currently faced in the care of cancer patients, and represents another key area where ctDNA analysis is likely to play an important role. ctDNA analysis can allow the early emergence of mutations associated with treatment resistance to be assessed noninvasively across a range of cancer types, and this information can then be used to guide treatment decisions. Finally, ctDNA analysis can also be used after curative treatment for cancer, to identify minimal residual disease and individuals at risk of relapse. Recent studies across several cancer types have shown that monitoring ctDNA levels following surgical resection can identify individuals with residual or recurrent disease. The early diagnosis of relapse may allow effective treatment strategies to be introduced at a time when disease burden is still minimal and likely to be most effective. Current clinical trials are aimed at understanding the clinical utility of ctDNA testing for a variety of clinical applications across a wide range of malignancies.

As far as is known, currently there are very few Australian hospital facilities (n=3), all based in Victoria, with the capacity and expertise to perform and interpret ctDNA.

Advances in Patient Imaging

Nuclear medicine is a powerful imaging modality and plays a vital role in the diagnosis and management of a wide range of medical conditions. In particular, nuclear medicine plays a key role in precision cancer diagnosis and cancer treatment. Major technical developments in the field over the last 15 years, including the combination of position emission tomography with computed tomography (PET/CT), have led to superior diagnostic accuracy compared with more conventional techniques. These advances have proven to translate into high management impact consistent across cancer types resulting in improved patient outcomes (Hillner *et al.*, 2008). Nuclear medicine also has an established role in the treatment of a variety of cancer types through the targeted delivery of radiation directly to cancer cells.

More recently, several ground-breaking advances in the field of nuclear medicine are redefining diagnostic and management pathways of patients with cancer, dementia and other medical conditions. These advances include new molecular imaging techniques for prostate cancer, neuroendocrine tumours and neurodegenerative disorders which are proving to be "game changers" in the field (Alby, Woodward and Rowe, 2014; Afshar-Oromieh *et al.*, 2015; Sabri *et al.*, 2015; Deppen *et al.*, 2016). Along with these diagnostic tools, recently developed nuclear medicine treatments are also proving to be highly effective offering hope to many patients with advanced cancer (Kulkarni *et al.*, 2016; Rahbar *et al.*, 2016; Emmett *et al.*, 2017; Strosberg *et al.*, 2017).

In the current age of rapidly developing targeted and personalised treatments, precise characterisation of disease processes using nuclear medicine techniques is becoming ever more central to individualised patient care. With an expanding number of clinical applications and the increasing use of established techniques, the field of nuclear medicine is expected to grow significantly over the next 5-10 years.

A list of all PET scanning sites in Australia can be found at
http://www.health.gov.au/internet/main/publishing.nsf/Content/pet-nuclear-medicine-imaging

Impediments for PET scanning into the future is the current lack of a funding with a very restricted range of Medicare item numbers and a lack of regulatory agencies that are keeping up to date with current practices. TGA approvals for tracers in clinical use lags behind the best current practice.

Appendix 1: Existing resources

The following is a list of the Existing Resources of NATA/RPCA accredited Molecular laboratories in Australia currently doing Molecular testing (of any type). These are the accredited laboratories actively doing molecular diagnostic tests on (non-research) patient samples in 2017 (see table 1).

LABORATORY NAME	HOSPITAL	SUBURB	STATE
Sullivan Nicolaides Pathology		Bowen Hills	Qld
Pathology North	Royal North Shore	St Leonards	NSW
NSW Health Pathology	Concord Hospital	Concord	NSW
St Vincent's Pathology (SydPath)	St Vincent's Hospital	Darlinghurst	NSW
NSW Health Pathology	RPA Hospital	Camperdown	NSW
Douglass Hanly Moir		Macquarie Park	NSW
QML Pathology		Murarrie	Qld
NSW Health Pathology	SEALS	Randwick	NSW
The Children's Hospital at Westmead	Westmead	Westmead	NSW
SA Pathology	Flinders Medical Centre	Bedford Park	SA
SA Pathology	Royal Adelaide Hospital	Adelaide	SA
SA Pathology	Women's and Children's Hospital	North Adelaide	SA
Alfred Pathology Service	Alfred Hospital	Melbourne	Vic
PathWest Laboratory Medicine WA	Royal Perth Hospital	Perth	WA
PathWest Laboratory Medicine WA	Fiona Stanley Hospital	Murdoch	WA
PathWest Laboratory Medicine WA	QEII Medical Centre	Nedlands	WA
Melbourne Health Shared Pathology Service	Royal Melbourne	Parkville	Vic
Peter MacCallum Cancer Centre		Melbourne	Vic
ACT Pathology	The Canberra Hospital	Garran	ACT
St Vincent's Pathology	St Vincent's Hospital	Fitzroy	Vic
Victorian Infectious Diseases Reference Lab	Doherty Institute	Melbourne	Vic
Mater Pathology	Mater Hospital	Brisbane	Qld
Pathology Queensland	Royal Brisbane and Women's Hospital	Herston	Qld
Austin Pathology	Austin Hospital	Heidelberg	Vic
Monash Pathology	Monash Hospital	Clayton	Vic
Adelaide Fertility Centre Pty Ltd		Dulwich	SA
NSW Health Pathology	Liverpool Hospital	Liverpool	NSW
Royal Hobart Hospital		Hobart	Tas
Genea Ltd		Sydney	NSW
Western Diagnostic Pathology		Myaree	WA
Victorian Clinical Genetics Services Ltd	Royal Children's Hospital	Parkville	Vic
Australian Clinical Labs		Clayton	Vic
Pathology North	John Hunter Hospital	New Lambton Heights	NSW
St Vincent's Hospital Melbourne Limited		Fitzroy	Vic
Griffith University		Nathan	Qld
Genomics Research Centre Diagnostic Clinic		Kelvin Grove	Qld
The Garvan Institute of Medical Research		Darlinghurst	NSW
Australian Red Cross Blood Service		West Melbourne	Vic
Genomics for Life Pty Ltd		Newmarket	Qld
Hudson Institute of Medical Research		Clayton	Vic
Genomic Diagnostics		Heidelberg	Vic
Cancer Genetics Diagnostic Laboratory	Royal North Shore	St Leonards	NSW
VIAFET		Penrith	NSW

Genome.One Pty Ltd	Darlinghurst	NSW
Virtus Health Specialist Diagnostics	Spring Hill	Qld
GenSeq Labs Pty Ltd	South Yarra	Vic
Clinical Laboratories (WA) Pty Ltd	Subiaco	WA
Monash Reproductive Pathology and Genetics	Clayton	Vic

The following is a list of the Existing Resources of NATA/RPCA accredited Molecular laboratories in Australia currently doing Molecular testing (of any type) using Next-generation sequencing methods.

ACREDITED FOR MPS

Sullivan Nicolaides Pathology	BOWEN HILLS
South Eastern Area Laboratory Services (SEALS)	RANDWICK
The Sydney Children's Hospitals Network	WESTMEAD
SA Pathology	ADELAIDE
SA Pathology	BEDFORD PARK
SA Pathology	NORTH ADELAIDE
PathWest Laboratory Medicine WA	NEDLANDS
PathWest Laboratory Medicine WA	MURDOCH
Peter MacCallum Cancer Centre	MELBOURNE
SA Pathology	NORTH ADELAIDE
St Vincent's Pathology	FITZROY
Mater Pathology	SOUTH BRISBANE
Pathology Queensland	Herston
Austin Pathology	HEIDELBERG
Victorian Clinical Genetics Services Limited	PARKVILLE
Australian Clinical Labs	CLAYTON
Pathology North	NEW LAMBTON HEIGHTS
Prince of Wales Hospital	SHATIN N.T.
Genomics Research Centre Diagnostic Clinic	KELVIN GROVE
Genomics for Life Pty Ltd	NEWMARKET
Genomic Diagnostics	Heidelberg
Genome.One Pty Ltd	Darlinghurst
St John of God Pathology	SUBIACO

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