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# PRINCIPLES FOR THE TRANSLATION OF ‘OMICS’- BASED TESTS FROM DISCOVERY TO HEALTH CARE

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## Abbreviations and acronyms

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AAO	American Academy of Ophthalmology
ACMG	American College of Medical Genetics and Genomics
AHEC	Australian Health Ethics Committee (a Principal Committee of NHMRC)
AMD	Age-related Macular Degeneration
ARTG	Australian Register of Therapeutic Goods
ASD	Autism Spectrum Disorder
CNV	Copy Number Variant
EGFR	Epidermal Growth Factor Receptor
GA4GH	Global Alliance for Genomics and Health
GWAS	Genome-Wide Association Study
HGAC	Human Genetics Advisory Committee (a Principal Committee of NHMRC)
HREC	Human Research Ethics Committee
ICGC	International Cancer Genome Consortium
IOM	Institute of Medicine (part of the US National Academy of Sciences)
ISO	International Organisation for Standardisation
IVD	In-Vitro Diagnostic medical device
MPS	Massive Parallel Sequencing
NATA	National Association of Testing Authorities, Australia
NHMRC	National Health and Medical Research Council
NIH	US National Institutes of Health
NPAAC	National Pathology Accreditation Advisory Council
NSCLC	Non-Small Cell Lung Cancer
OA	Optometry Australia
PDD-NOS	Pervasive Developmental Disorder Not Otherwise Specified
PICF	Patient Information and Consent Form
RCPA	Royal College of Pathologists of Australasia
SNP	Single Nucleotide Polymorphism
TGA	Therapeutic Goods Administration
TKI	Tyrosine Kinase Inhibitor
VUS	Variants of Unknown Significance

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# Introduction

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An ‘*omics*’ test is an assay composed of or derived from many molecular measurements that is interpreted by a fully specified computational model to produce a clinically actionable result (Institute of Medicine 2012). *Omics* technologies include assays of the genome, transcriptome, metabolome, epigenome or proteome. The focus of this document is on genomics because most activity is currently in this field.

*Omics* tests differ from genetic tests in that the latter characterises one or a few genes at a time whereas *omics* tests are capable of contemporaneously analysing all molecules (DNA, RNA, or protein) in a cell or tissue. *Omics* analysis therefore generates large and complex (high-dimensional) data sets that can be prone to ‘overfitting’<sup>1</sup>. Current *omics* research is typified by retrospective studies that apply genomic assays to stored human tissues samples. While many such studies have been published, only a small number have been successfully translated into clinically useful tests (McShane *et al.* 2013).

The dramatic reduction in cost and speed of massively parallel sequencing (MPS) technologies makes it cost effective to replace some monogenic assays with gene panel, exome or whole genome analysis, even if the sequence of only a single gene is required. Despite the availability of MPS, monogenic assays will remain the preferred method of gene analysis in many medical circumstances.

*Omics*-based tests can potentially improve patient outcomes by providing information about risk or diagnosis of disease, by guiding clinical management decisions, or by enabling public health measures. This promise of *omics*, coupled with the availability of new instrumentation, has primed the research and medical community for early adoption of this type of testing. The current challenge confronting *omics* technologies is no longer the development of equipment, but rather the interpretation and analysis of data and ultimately the demonstration of improved health outcomes (clinical utility).

With this background, the NHMRC (see strategic priority 3 for action, NHMRC Strategic Plan 2013-2015<sup>2</sup>) has recognised the need to develop Australian evidential standards or principles for the translation of *omics*-based discoveries into research-grade *omics* assays and clinical grade *omics* tests. The principles are based on accepted methodologies for evaluating genetic tests, such as the ACCE framework<sup>3</sup>, but add considerations to facilitate the appropriate development and evaluation of mathematical algorithms for high-dimensional data.

The document employs principles over other more detailed types of guidance to maintain currency given that the field of *omics* is developing rapidly. It also emphasises genomics over other *omics*-based technologies because genomics is the focus of current research efforts with a more immediate health care delivery focus. Over time the emphasis will shift from genomics to other *omics* technologies that are time and tissue dependent, such as transcriptomics. This increases the uncertainty and variability associated with *omics*-based analyses.

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1 Overfitting (of data) usually occurs when a model is excessively complex and has too many parameters relative to the number of observations. Computational models based on over-fitted data may perform well on the samples used for the discovery research; however they can have poor predictive performance for other samples (IOM 2012).

2 <http://www.nhmrc.gov.au/guidelines/publications/nh160>

3 The ACCE framework was developed by the US Centers for Disease Control and Prevention. ACCE takes its name from the four main evaluation criteria it uses — analytical validity, clinical validity, clinical utility and ethical legal and social issues ([www.cdc.gov/genomics/gtesting/ACCE/](http://www.cdc.gov/genomics/gtesting/ACCE/)).

The principles should be read in conjunction with the *National Statement on Ethical Conduct in Human Research (2007)*<sup>4</sup> (the National Statement), the *Australian Code for the Responsible Conduct of Research (2007)*<sup>5</sup> (the Code), and other more specific standards and guidance documents outlined in **Appendix A**. It is expected that research conducted in Australia should comply with the Code. Where the research involves human participants, human tissue samples or human data, it is also expected that the research should comply with the National Statement.

The principles recognise that the current preference is to apply MPS equipment as a more efficient and cost effective means to generate results for a single or defined number of genes in a single test. The full potential of *omics* will only be realised when big data can be synthesised into a usable format by automated or less labour intensive means. The document makes it clear that translation of *omics* into clinical research and practice will only occur if all individuals and institutions adhere to principles which ensure research integrity and evidence-based health care.

While many expert *omics* scientists and clinicians will be familiar with and already observing the principles outlined below, these concepts are brought together here in this document in order to provide a single point of reference. Moreover, the principles will assist anyone who wishes to enter or broaden their involvement in the field of *omics* testing such as health professionals wanting to integrate *omics*-based applications into their research or clinical trials.

The first section of the document outlines the governing ethical and operational principles that apply to the translation of *omics*-based discoveries into health care. The document is then divided into two parts – the framework for the translation of *omics*-based discoveries (Part A), and the specific principles that apply to each of the domains<sup>6</sup> identified in the framework (Part B). Each principle includes a rationale to explain why it has been included and/or additional information. Scenarios at the end of the document demonstrate how the principles can be applied in practice to resolve clinical and technical dilemmas. They are designed to be illustrative in nature only.

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4 <http://www.nhmrc.gov.au/guidelines/publications/e72>

5 <http://www.nhmrc.gov.au/guidelines/publications/r39>

6 For the purposes of this document domains are defined as spheres of activity with common procedures (e.g. clinical validation), whereas the principles refer to the functional activities that apply to each domain.

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# Governing principles for the translation of *omics*-based discoveries into health care

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## Ethical principles

As for other scientific and medical disciplines, the ethical principles that apply in *omics* are grounded in the values set out in the National Statement (research) and the various codes of conduct for health professionals delivering *omics*-based health care. These principles should therefore be applied where *omics* applications and results are utilised in discovery and translation. In particular, Chapter 3.5 of the National Statement deals with research involving Human Genetics.

## Operational principles

- **Reproducibility** – scientific method involves observations from which hypotheses can be made and then tested. The complexity and number of steps involved in *omics*-based analysis, coupled with the large number of measurements, means that reproducibility must be a key governing principle.
- **Collaboration** – the complexity and multi-disciplinary nature of *omics* research necessitates integration and data sharing to support analysis and interpretation. The sharing of data must respect the privacy and autonomy of individuals and where relevant, their communities.
- **Education** – the potential of *omics* to transform medicine from symptom-oriented diagnosis and treatment of disease to disease prevention and early diagnosis will necessitate comprehensive and ongoing education for health professionals, patients and the public.
- **Interoperability** – the complexity and multi-disciplinary nature of *omics* data requires compliance to data standards, including minimal information, use of structured vocabularies and ontologies to enable efficient data integration and data interoperability.

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## Part A: Framework for considering the principles

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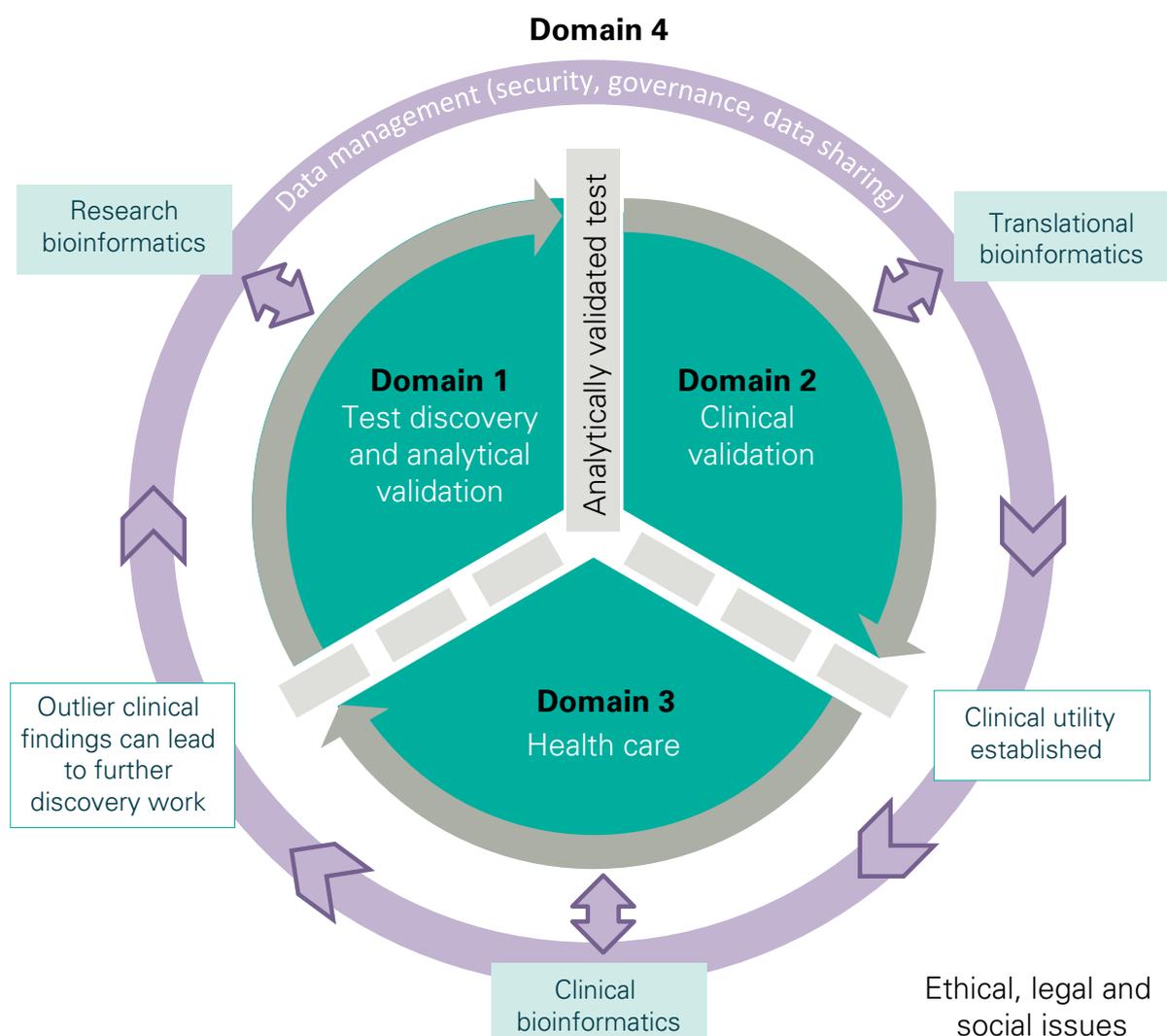
An Australian framework for the translation of *omics*-based discoveries into clinical research and health care is presented in **Figure 1**. Importantly, the key domains of the model (Test Discovery and Analytical Validation, Clinical Validation, Health Care, and Data Management) are those that comprise the established ethical and regulatory paradigm for the translation of research discoveries into clinical care and population health. Ethical, Legal and Social Issues (ELSI) underpin each of these domains.

Although clinical research and health care are often viewed as fundamentally different activities, they are inextricably linked. The blurring of the boundary between research and health care (shown as a broken line in **Figure 1**) creates the opportunities for continuous improvement in medical practice. Quality improvement and comparative effectiveness research help bridge the gap between research and clinical care. Undoubtedly *omics* tests and datasets introduce a new level of complexity to all the domains and interstices shown in **Figure 1**.

In **Figure 1**, a solid line is shown between test discovery and clinical validation to reflect the need for *omics*-based tests to be properly analytically validated before they are tested for clinical validation in trials. This validation step is similar to the 'bright-line' advocated by the Institute of Medicine (IOM 2012) in that it requires a clinical test to be fully defined and validated prior to it being used in a clinical trial. As with the Institute of Medicine approach, changes to the test after the bright-line has been crossed require the test to be revalidated.

At first glance there appears to be tension between the need to fully verify the *omics* test prior to use in clinical research and the use of data generated through clinical testing to further understand and refine the test. However, quality improvement is only made possible by the generation of validated clinical data which can be used to further refine the *omics*-based algorithms or to generate new hypotheses. This is very much an iterative process and is demonstrated by the continuous cycle in **Figure 1**.

Many of the central issues in the translation of *omic* tests are the same as those that arise in single gene testing: autonomy, privacy, confidentiality, and ownership. In essence, this means that people offered a test should be able to exercise choice in what they learn about themselves, decide within the provisions of the law who else will have access to these data (or the information), and be protected from the misuse of test results by others.



**Figure 1 – Translation of *omics*-based discoveries into health care**

*Omic*s, however, gives rise to specific ethical, legal and social issues, in large part due to the continuing evolution of knowledge, volume of data generated, and the scale of uncertainty in interpretation. The nature of these issues calls for specific consideration in dealing with consent, autonomy, privacy, confidentiality and custodianship. The potency of these issues comes into play because an *omics* test, unlike a single genetic test, can provide information (possibly predictive) about an unrelated health condition. *Omic*s tests are also more likely to provide predictive information that relates to health conditions that may or may not manifest in later life and may or may not be heritable. Because of this, particular care is required in dealing not only with consent, privacy and custodianship issues but also with the return of incidental results (see **Appendix B**). Guidance on how to deal with this in practice can be found in **Domain 3** of this document.

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## Part B: Domain specific principles

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### Domain 1 – Test discovery and analytical validation

#### Test discovery

Principle	Rationale/Additional information
1.1 Candidate <i>omics</i> tests should be fully defined.	During the test development phase, the biological rationale, the molecular measurements, the computational procedures and the proposed clinical use should be defined for each candidate <i>omics</i> test.
1.2 Candidate <i>omics</i> tests should be appropriate for the patient population.	The samples used to develop a candidate <i>omics</i> test may be sourced from a comparatively homogenous set of patients, whereas the intended patient population could be far more heterogeneous. Ideally the test should be independently confirmed using specimens sourced from a different patient population and collected and processed by a different laboratory.
1.3 Computational procedures used should be evaluated by independent experts.	Given the complexity of the data and the analyses involved in developing an <i>omics</i> test, the candidate test, the computer code and computational procedures used to develop the test, should be subject to scientific and statistical verification.
1.4 Research laboratories using <i>omics</i> should have standards in place for data quality control and data reporting.	Data quality control is crucial in <i>omics</i> . Laboratories should disclose their data quality standards in publications so that conclusions can be verified. Reporting standards are also crucial in <i>omics</i> to ensure data interoperability.

#### Analytical validation

The purpose of analytical validation is to establish whether the candidate test can accurately detect whether the full range of specific *omics* variants are present.

Principle	Rationale/Additional information
1.5 Analytical validation of <i>omics</i> tests for clinical use should be performed in a laboratory accredited for laboratory medical testing.	National Association of Testing Authorities, Australia (NATA) accreditation should be required for laboratories validating <i>omics</i> tests ( <a href="http://www.nata.com.au">www.nata.com.au</a> ).
1.6 Parameters for analytical validation of an <i>omics</i> test should be clearly defined.	Minimal characteristics for an <i>omics</i> test include specificity, sensitivity and reproducibility.

## Domain 2 – Clinical validation

As for other analytical tests, clinical research is conducted to establish the clinical validity and utility of a candidate *omics* test; or in other words, to establish whether the test aligns with the presence, absence, or risk of a disease and to ascertain whether the test enables an effective diagnosis (or prediction in the case of screening) to be made.

Principle	Rationale/Additional information
2.1 <i>Omics</i> -based research should be compliant with the National Statement.	The National Statement sets out Australian standards for the ethical design, review and conduct of human research <sup>7</sup> .
2.2 Institutions conducting research should ensure that the appropriate support is provided for <i>omics</i> -based clinical trials.	Given the complexity and multidisciplinary nature of <i>omics</i> -based research, administering institutions should provide appropriate oversight and promote a culture of scientific integrity and transparency.
2.3 Only <i>omics</i> tests that have been validated analytically should be used for clinical validation studies.	Empirical, statistical and computational reproducibility is critical to clinical research. Hence, before an <i>omics</i> test is used in clinical validation studies it should be defined and validated analytically. Any subsequent change to the candidate <i>omics</i> test requires the test to be revalidated before it is utilised.  In the interests of reproducibility and interoperability, computer code used to generate <i>omics</i> -based tests should be made accessible where possible.
2.4 The most appropriate evidence should be applied to clinical validation.	As for analytical validation, candidate <i>omics</i> tests should be evaluated for clinical validity using an independent set of specimens that are consistent with the intended use for the test. Whenever possible, experiments should be replicated in multiple settings to ensure reproducibility and longitudinal studies should be employed to refine <i>omics</i> -based algorithms. Consistency of phenotype classification is essential for clinical validation.
2.5 Where the goal of the clinical study is to develop an <i>omics</i> test for clinical care, the Therapeutic Goods Administration (TGA) should be consulted for guidance on the appropriate requirements to prepare for regulatory approval as an in-vitro diagnostic medical device (IVD) <sup>8</sup> .	<a href="http://www.tga.gov.au">www.tga.gov.au</a>
2.6 A data management plan that includes data standards should be an essential component of all clinical research involving <i>omics</i> tests.	Whenever possible the data management plan should allow for a continuum of data collection from research to clinical practice. Researchers should be conscious of specific data repository standards for data sharing. For instance, databases may apply different specifications or standards to the collection and transmission of data.
2.7 <i>Omics</i> -based clinical trials should be registered with an appropriate clinical trials registry.	Benefits of clinical trial registries are well documented and include reducing unnecessary duplication of research effort, improving the availability of evidence to inform health care, and providing a reliable and unbiased source of information about trials for systematic reviews and evidence based guidelines.

7 For example, where proposed research involving the use of human biospecimens may reveal important information for the health of donors, their relatives, or the community, whether anticipated or incidental to the scope of the research, the National Statement requires that researchers should prepare a plan that sets out the parameters by which results and findings will be returned; including how, by whom and to whom.

8 Note that most *omics* tests are likely to be in-house tests. While such tests are expected to be exempt from inclusion in the Australian Register of Therapeutic Goods (ARTG), the laboratory is required to notify the TGA of the in-house IVDs held by the laboratory and the laboratory must be accredited by NATA. See **Appendix B** for further details.

Principle	Rationale/Additional information
<p>2.8 Individuals participating in research should be able to exercise their autonomy in making decisions on the return of incidental findings.</p>	<p>Incidental findings are usually unrelated to the person's condition (or the topic of research), but may suggest a future risk of disease. Where the return of incidental findings is feasible, and the results are adequately validated, informed individuals participating in research should have autonomy to decide whether or not to request return of incidental findings<sup>9</sup>. Further guidance for managing findings from <i>omics</i> research and health care is provided in the 'decision tree' at <b>Appendix B</b>.</p> <p>Incidental findings should only be returned after retesting (using a new sample) in an accredited laboratory and, if indicated, should be accompanied by genetic counselling (counselling may not be required for somatic, some constitutional, and pharmacogenetic testing).</p> <p>There is no requirement for research laboratories to be NATA accredited. However if <i>omics</i> test results are to be used for clinical decision making then the sample must be retested in a NATA accredited laboratory. Moreover, it is not appropriate for researchers to reanalyse or reinterpret outside the parameters of their Human Research Ethics Committee (HREC) approved research or after the completion of a study.</p>

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<sup>9</sup> For research involving Aboriginal and Torres Strait Islander peoples, the community may take a collective view of DNA ownership. This should be reflected in the research protocol.

## Domain 3 – Health care

The use of *omics* tests in health care is governed by the principles that apply to clinical medicine in general, including where health professionals deal with uncertain and evolving clinical evidence. Under this model, validated clinical data can be fed back to further refine the algorithms upon which treatment options are based (**Figure 1**). Note: Each time a change is made to an *omics* test, the test needs to be revalidated.

Principle	Rationale/Additional information
3.1 Clinical use of <i>omics</i> tests needs to be informed by the best available evidence.	The evidence base for <i>omics</i> tests is not static; hence clinical guidance for such tests should be easily updateable and include advice on which clinicians can request the test and advice on suitable subpopulations for testing.
3.2 Only laboratory and clinically validated <i>omics</i> tests should be provided in clinical care.	There should be a clear distinction between ‘clinically validated’ tests and those that are ‘research only’, which should be reflected in clinical reports. Testing should only be provided if it is of clinical benefit in terms of clinical decision making or intervention. National Pathology Accreditation Advisory Council (NPAAC) requirements for in-house IVDs stipulate that an IVD “must not be used in the provision of a service by a laboratory unless its validity has been established” <sup>10</sup> .
3.3 <i>Omics</i> test and pharmaceutical combinations (co-dependent technologies) should be developed in an environment that encourages competition to improve tests and therapy over time.	A drug/test combination is where a pathology test (an <i>omics</i> test in this situation) helps to determine the population group for using that drug. Improvements can continue to be made to the associated <i>omics</i> test using validated clinical data.
3.4 Uniform interpretive reporting standards should be developed and utilised.	This is especially in relation to reporting variants of unknown significance (VUS). NPAAC has relevant standards for good medical practice in pathology laboratories, including for medical testing of human nucleic acids <sup>11</sup> .
3.5 Only NATA accredited diagnostic laboratories whose certification includes <i>omics</i> -based testing as part of their scope of practice should conduct such testing.	<a href="http://www.nata.com.au/nata/">www.nata.com.au/nata/</a>
3.6 Clinical laboratories should encourage multidisciplinary interpretation and application of <i>omics</i> tests.	Genetic pathologists are responsible for writing clinical reports to treating clinicians. They should liaise with bioinformaticians and statisticians in developing each report.
3.7 Expectations relating to reanalysis and reinterpretation of data should be tempered against diagnostic laboratory resources and priorities.	New knowledge can lead to clinical diagnostic laboratories being asked to reanalyse and reinterpretation past test results. This will be done by an appropriate test request from the requesting clinician.
3.8 Test referrals to international providers should be arranged through an accredited Australian diagnostic provider.	By observing this process, health practitioners can help to ensure that the quality and validity of testing and analysis provided by overseas laboratories meets agreed Australian standards.

10 NPAAC *Requirements for the Development and Use of In-House In Vitro Diagnostic Medical Devices* (3rd Ed. 2014). See **Appendix A** for further details.

11 NPAAC *Requirements for medical testing of human nucleic acids* (2nd Ed., 2012). See **Appendix A** for further details.

## Domain 4: Data management

The key data challenges are shifting from data generation to data quality control, storage, analysis, interpretation and sharing, possibly drawn from large numbers of individuals stored in multiple databases. Linking of *omics*-based data and clinical characteristics has the potential to accelerate medical research into clinical practice and lead to better patient outcomes. Data sharing will facilitate this<sup>12</sup>.

Although there are currently many online mutation databases available, few meet the standards required for medical practice. Current generations of *omics* databanks have variable data quality. This situation represents a risk to patient care.

Principle	Rationale/Additional information
4.1 Databanks should have suitable standards in place to address ethical considerations, including consent, data identifiability and privacy.	Governance standards for databanks are required to protect the privacy and autonomy of individuals. These should allow for the traceability of patient data <sup>13</sup> . Databanks with an intended clinical use must assure secure sharing, quality, accuracy and potential clinical utility. Issues associated with consent are complex <sup>14</sup> , but must be fully addressed.
4.2 Access to <i>omics</i> data should be open and treated in a respectful and responsible manner.	The benefits of sharing <i>omics</i> data in public databanks are well documented and include accelerating discovery and knowledge, and better data quality control <sup>15</sup> . However, such sharing must be done under defined circumstances, particularly in relation to the protection of individuals. Research that has been publicly funded should make its resultant data accessible, with appropriate protection and consideration of privacy issues.
4.3 Databanks should observe defined standards for data content, including for data quality and data provenance.	Current submissions to databanks tend to be highly variable in quality, content and accuracy, which limits their clinical utility. Databanks require a defined scope, custodianship, curation, and minimum set of specifications that should include (for example): file formats, data quality, variant call quality, and information that will allow for interpretation of clinical significance (such as phenotypic information associated with variants). Databanks must also provide a provenance/audit trail regarding the source of the data, with provision for quality audits. These data standards are currently being developed by professional societies and will align globally <sup>16</sup> .

12 Frequently cited examples of well organised international biomedical research projects generating big data include the 1000 Genomes Project and the International Cancer Genome Consortium (ICGC).

13 Example: the American College of Medical Genetics and Genomics (ACMG) clinical laboratory standards for next-generation sequencing require that methods used to store data (whether it be in house, offsite, or cloud supported) are compliant with the *US Health Insurance Portability and Accountability Act 1996*.

14 Example: consent processes might permit access to all non-identifiable data, but restrict access to identified data. Note that the National Statement avoids the term 'de-identified data', as its meaning is unclear. While this term is sometimes used to refer to a record that cannot be linked to an individual (non-identifiable), it is also used to refer to a record in which identifying information has been removed but the means still exist to re-identify the individual. When the term 'de-identified data' is used, researchers and those reviewing research need to establish precisely which of these possible meanings is intended.

15 International advice on genomic data sharing includes the US National Institutes of Health (NIH) *Genomic Data Sharing Policy* (2014) (<http://gds.nih.gov/03policy2.html>) and the Global Alliance for Genomics and Health (GA4GH) *Framework for the Responsible Sharing of Genomic and Health Related Data* (<http://genomicsandhealth.org/files/public/Responsible%20Data%20Sharing%20Framework%20-Arabic-29-09-14.pdf>).

16 In 2013 the ACMG published Clinical Laboratory Standards for Next-Generation Sequencing and in 2014 the Royal College of Pathologists of Australasia (RCPA) published Standards for Clinical Databases of Genetic Variants (<http://www.rcpa.edu.au/getattachment/0f8737df-49d9-4b8e-a31e-196831044d25/RCPA-Standards-for-Clinical-Databases-of-Genetic-V.aspx>).

Principle	Rationale/Additional information
4.4 Databanks should have standards for data storage and security.	<p><i>Omic</i>s data security requires ethical responsibility and accountability from all those who handle such data, and needs to be supported by policies and infrastructure to protect storage and safe data sharing (both for active data storage and backup data storage). Design of storage and security for data repositories requires appropriate IT expertise. Databank design should define the access, lifespan, and contingency for a provision of continuity of access to data in the case of demise<sup>17</sup> of a databank. Superseded or less frequently used databases may be suitable for archiving, possibly with a 'hierarchy of access' for those involved. Access to all <i>omic</i>s databanks, and particularly to whole genome sequence data, must be guided by professional ethical standards. The rationale should specifically mention data backups and the need to ensure that the same policies apply to these as they do to the active/production data.</p>

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<sup>17</sup> Consideration should be given to premature termination of database life due to (for example) loss of funding, loss or change of custodianship, or force majeure.

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# Scenarios to demonstrate use of the principles

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## Scenario 1: Targeting actionable mutations in cancer treatment

A middle-aged, non-smoking woman of Asian descent was diagnosed with liver metastases secondary to adenocarcinoma of the lung. Activating mutations in the epidermal growth factor receptor (EGFR) were not detected using a registered IVD in a NATA accredited pathology laboratory. Following receipt of the negative EGFR results, the oncologist arranged for MPS of the tumour to be undertaken in a research laboratory. The research laboratory detected a rare mutation in EGFR and also identified a case study suggesting the mutation may be “actionable”.

*EGFR mutations are almost exclusively confined to lung cancers which exhibit a non-squamous histology (which account for 80% of non-small cell lung cancer, NSCLC). Tumour EGFR mutations are found in 10% of Western patients and almost 50% of Asian patients with NSCLC. Within non-squamous NSCLC, the prevalence of EGFR mutations is also much higher in females (~40%), in never smokers (~35%), and in tumours with adenocarcinoma histology (>50%). The anti-tumour activity of the EGFR-tyrosine kinase inhibitors (EGFR-TKIs) including afatinib, gefitinib, and erlotinib is restricted to non-squamous NSCLCs which have mutations in the EGFR gene.*

The referral of sample from a NATA accredited laboratory to a research laboratory for the purposes of providing a test result for clinical use violates a number of principles in **Domain 1B** (most notably **1.5**), **Domain 2 (2.2, 2.4, 2.6)** and **Domain 3 (3.2, 3.4, 3.5)**. Testing was transferred from a diagnostic to research setting for the purpose of obtaining information which was potentially clinically actionable. This occurred without obtaining patient consent or approval from a human research or clinical ethics committee. The premise on which the diagnostic laboratory sent the sample and the research laboratory receipted the sample was not pre-specified. The research result was likely provided to the referring clinician without appropriate disclaimers<sup>18</sup>. By instigating steps which blurred the boundary between testing in a research and diagnostic laboratory the oncologist violated the principle of *Non-maleficence*. The patient should have consented for participation in a research study which included testing in the research laboratory. The research results should have been validated and interpreted by a NATA laboratory before release to the treating clinician.

The oncologist informed the patient that treatment with EGFR-TKIs delays the progression of cancer by 9 months compared with only 6 months for chemotherapy. He/she mentions that clinical trials have examined the efficacy of EGFR-TKIs in patients with the common EGFR mutations and that the effectiveness of these drugs in patients with rare EGFR mutations is unknown. On balance the oncologist recommends the patient proceed with EGFR-TKI treatment.

*Approximately 30% of patients with NSCLC have rare EGFR activating mutations. The responsiveness of these tumours to TKI therapy has not been evaluated. The EGFR-TKIs are funded on the Pharmaceutical Benefits Scheme for treatment of patients with activating EGFR mutations known to confer sensitivity to treatment with EGFR-TKIs.*

The patient was not provided with a fair and balanced view of her situation. She was not told that the progression free survival of patients with EGFR wild-type tumours treated with EGFR-TKIs is 1.5 months compared to 6 months for treatment with chemotherapy. The governing principle of *Collaboration* and the domain **Principle 3.6** were also violated. The interpretation of the test results and risk benefit of treatment required multi-disciplinary peer input prior to the clinician recommending treatment. The patient should have been afforded the opportunity to receive professionally administered pre-treatment counselling.

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<sup>18</sup> Apart from the ethical considerations, in providing a patient result the research laboratory is considered to have an IVD and would be required to comply with regulatory requirements (or have an exemption to provide access to an unapproved IVD).

Six days after commencing treatment with the TKI the patient developed rapidly progressive interstitial lung disease and died of respiratory failure despite cessation of the EGFR-TKI. A review of the case was instigated. Repeat molecular testing in a NATA accredited laboratory failed to identify the mutation reported in the research laboratory. The error was attributed to a sample mix-up.

*Treatment with EGFR-TKIs is associated with a significantly increased risk of developing interstitial lung disease, although this side effect is rare (incidence 1.6%), the mortality is 13%. The patient has forgone the opportunity for an effective treatment on the basis of an erroneous molecular test result.*

**Principles 4.3** and **4.4** highlight the importance of standards for data collection and transmission. It is not clear how the outcome of the case review was conveyed to the researchers to avoid the use and potential deposition of inaccurate data into research repositories. Non-validated research findings should not be deposited into data repositories. In testing this patient's sample, the research laboratories violated **Principle 2.1** which relates to compliance with the National Statement. Finally all aspects of this case reinforce the importance of the governing operational principle of *Education*.

## Scenario 2: Incidental finding of cancer predisposition in a research participant

A child with severe intellectual disability participates in a longitudinal research project which aims to identify the causes of intellectual disability. As part of this study, the research group conducts whole exome sequencing of the affected child and their parents. This research testing identifies two disease-causing variants in the PMS2 gene of the affected child; each parent carries one of these changes.

*PMS2 is not a known cause of intellectual disability. PMS2 is a known cause of the hereditary cancer predisposition syndrome, Lynch Syndrome. People with a single mutation in PMS2 have a 20% lifetime risk of developing colorectal cancer and women also have an increased risk of gynaecological cancer (endometrial and ovarian cancer). The presence of biallelic mutations (i.e. a disease causing mutation inherited from each parent) combines to cause a childhood cancer syndrome, with an increased risk of haematological malignancies and tumours of the brain and bowel. PMS2 testing is available in some NATA accredited diagnostic laboratories.*

The discovery of mutations in *PMS2* are 'incidental' to the goals of the research, namely the causes of intellectual disability. Nonetheless, the finding is of proven clinical significance, a validated test to confirm the research result exists and there is evidence that surveillance will improve outcomes. The overarching principle of *Collaboration* is applicable in seeking expert opinion on the findings.

The child is now 10 years old and the parents are in their thirties.

The overarching ethical principles outlined in the National Statement of *Beneficence* and *Harm Minimisation* apply. The presence of biallelic *PMS2* mutations is of significance in childhood, while single mutations are relevant only in adulthood. In this case, this finding has immediate relevance for all three people tested and they therefore could benefit from this knowledge which can be used to optimise medical management and minimize the impact of the gene mutations. The outcome of applying these principles would be reversed for the child if there was no immediate benefit; that is if the mutations found only had an impact on health during adulthood.

At the time of its establishment, the study did not anticipate incidental findings for the child or parents and they were not specifically mentioned in the Patient Information and Consent Form (PICF).

**Principle 2.8** states that 'Individuals participating in research should be able to exercise their autonomy in making decisions on the return of incidental findings'. In anticipation of this possibility, researchers should ensure that the consent process addresses participant's preferences for return of incidental findings of clinical relevance to them.

Based on clinical opinion, the family were referred by the researchers to a specialist cancer genetic service to discuss the research findings. The multidisciplinary team discussed the implications of the research findings with the family and provided the option of confirming the findings through testing in a NATA accredited diagnostic laboratory. After genetic counselling, the parents gave informed consent for clinical testing of themselves and their child. A new sample was collected and tested following protocols that complied with the standards required for pathology testing.

The governing principle relating to *Reproducibility* of results (empirical, statistical and computational) is critical to clinical research. Pathology standards for sample collection, identification, tracking and testing ensure that the highest degree of confidence possible.

Results of the testing were returned to the family in the multidisciplinary clinic with further counselling and surveillance advice for each person according to their confirmed result.

### Scenario 3: Genetic diagnostic tool for autism/autism spectrum disorder (ASD)

ASD represents a highly heterogeneous group of neurodevelopmental disorders characterised by impaired social functioning. It is reasonably common - incidence is around 1/200. Diagnosis is generally not made until three or four years of age and is based purely on behaviour. Early diagnosis and optimization of health care is likely to have a positive effect on functional outcome and quality of life of both the child and the family (Myers *et al.* 2007).

Concordance in monozygotic twins is ~80% and in dizygotic twins is ~5%. Recent progress has been made in identifying underlying genetic risk factors, which can involve amplification/deletion of specific genes or rare de novo copy number variants (CNVs) at one or more of over one hundred separate genes/regions. Our ability to predict based on genetic information alone is still poor. Approximately 20% of individuals with ASD have genetic changes that can be detected by CNV or whole exome sequencing but it remains difficult to be certain these are causative. This percentage is likely to increase as we develop better detection of small amplifications and analyse more cases.

Because of the large number of different loci that might be involved and because some of these appear to be unique to one family/ individual, the argument for genome wide analysis is reasonably strong.

#### **Situation One:**

*A family with one ASD child requests genetic/genomic testing of family members to predict risk in younger sibling/ fetus. While no genetic test for risk of autism currently exists, it is possible that such a test might emerge in the near future and that commercial availability will precede an adequate understanding of the test characteristics. The risk of over interpretation (in either direction) is high. The inability to predict the phenotypic severity (incomplete penetrance; see glossary) of the disease is also a problem – a problem that will crop up often during translation of omics into clinical practice. Some clinicians might decide to test for some known causative mutations based on published papers reporting tight associations in one or two families.*

Is genetic testing appropriate?

Principles to be considered:

**Principle 3.1:** 'Clinical use of *omics* tests needs to be informed by the best available evidence'.

**Principle 3.2:** 'Only laboratory and clinically validated *omics* tests should be provided in clinical care'. The issue of what determines clinical validation is not straightforward. Is publication of a test used for a small family study sufficient?

### **Situation Two:**

A “normal” individual discovers that they have an abnormality in one of these regions as a result of having their genome sequenced for other reasons, possibly as part of an unrelated research study. This raises the general problem that discoveries “not-yet-made” could affect a person’s view of themselves at some later date if they have retained access to the data. There is mild form of the syndrome (PDD-NOS; pervasive developmental disorder not otherwise specified).

Principles to be considered:

**Principle 2.8:** ‘Individuals participating in research should be able to exercise their autonomy in making decisions on the return of incidental findings’.

**Principle 4.4:** ‘Databanks should have standards for data storage and security’.

## Scenario 4: Genomic-based diagnosis of Rett syndrome

The parents of a two-year old girl with developmental delay and autistic-like features consult with a clinical geneticist to explore whether there may be a genetic basis for their daughter’s problems. Further history and examination raises the possibility of a disorder called Rett syndrome, for which genetic testing is potentially available. The parents are keen for a precise diagnosis in case there may be therapeutic implications for the child and genetic implications for the family.

*Rett syndrome is a rare (incidence around 1 in 10,000) neurodevelopmental disorder affecting primarily girls, and has its onset usually within the first year of life. The clinical picture evolves over time, and as there is no specific biomarker for the disorder, diagnosis is often delayed until 3 years or even later. About 95% of typical and 40 – 60% of variant cases (based on clinical consensus criteria) have mutations in the X-linked gene, Methyl CpG-binding Protein 2 (MECP2), and mutations in several other genes (CDKL5, FOXP1, TCF4) have been associated with clinical phenotypes which overlap to some degree with Rett syndrome. Whereas sequencing for the individual genes is possible, a more efficient and cost effective genetic screening approach would be to use MPS technologies to screen this panel of genes. However, current MPS approaches cannot guarantee a 100% mutation identification rate.*

Utilisation of an *omics* based approach to screening the genes in question in a diagnostic setting mandates that the laboratory offering this testing conforms to **Principles 1.5, 1.6** and **2.3**. NATA accredited laboratories offering such testing would benefit from working in partnership with relevant clinical experts to ensure that the interpretation of test results is of maximal clinical utility.

A known pathogenic MECP2 gene mutation is identified, confirming the clinical diagnosis of Rett syndrome. Appropriate genetic counselling is given, predicting a low recurrence risk, and relevant cascade testing is consistent with this prediction.

A therapy for MECP2 mutation-positive individuals is subsequently developed, and available evidence suggests that the earlier that treatment is instituted the better the therapeutic outcome, leading to a push to apply MPS technologies to newborn screening cards to facilitate pre-symptomatic diagnosis.

*It remains to be established whether MPS technologies could be applied to DNA extracted from dried blood spots, the key issue being whether there is sufficient high quality DNA for MPS. Assuming such technologies could be validated for analysis of the four genes associated with Rett syndrome and overlapping clinical phenotypes, it is unlikely that a clinical utility and health economic argument could be demonstrated for an MPS approach to a mass-screening program of newborns for only a small number of genes. An alternate approach would be to apply whole exome or whole genome sequencing on samples collected in the newborn period, with an iterative process of interrogating the sequencing data at key periods during the life of an individual to answer specific health related questions.*

With regard to the implementation of a clinical trial, it would be important that the trial complies with **Principles 2.1** and **2.2** so that patients are not potentially at risk of harm, and so that clinical research funding is not wasted. In order to gain maximal benefit from the MPS data over the life of the individual, it would be critical for the MPS data to be delivered to and accessible from a suitably configured data repository, which complies with **Principles 4.1**, **4.3** and **4.4**.

There are many ethical, legal and social implications to such an approach, including education of the general public, informed consent, and access to life insurance. Newborn screening is currently not mandatory in any Australian jurisdiction. An “opt in” system may prove appropriate, particularly if an extra blood sample is required because it proves technically difficult to use dried blood spots for MPS approaches.

## Scenario 5: Genetic testing for age-related macular degeneration (AMD) in a clinical trial and in allied health practice

There is evidence that some vitamins delay the development of AMD and this response is related to genetic risk markers. An Australian research consortium now wishes to run a multi-centered trial of “AREDS”<sup>19</sup> vitamins (Aronow 2014) to prevent AMD in people with (1) a family history of AMD and, (2) a high genetic risk profile based on at least 19 loci identified in a recent international Genome-Wide Association Study (GWAS) meta-analysis (Fritsche 2013). Not all these risk Single Nucleotide Polymorphisms (SNPs) have been identified in Australian populations and the relative risk for SNPs continue to change with further research. Without enrolling over 3,000 very high risk individuals (40% risk of developing AMD, who are in the top 10% genetic risk profile), the study is likely to be underpowered (or too expensive) to show effect of the vitamin supplementation.

The HREC is assessing the consortium’s proposal to test potential participants by running a GWAS using a single research laboratory and analysing selected SNPs based on international studies. Individuals being screened for enrolment in the study will be told if they are in the highest 10% genetic risk, as only that group will be enrolled to be given the vitamins or placebo. The HREC are unsure if the study complies with the *omics* principles.

The HREC will be directed by the National Statement and consider the principle of *Beneficence*, which for the use of the vitamin treatment is minimal. However, confirming participants have a high genetic risk of AMD may distress participants and other family members. The proposed genetic risk profiling is based on many SNPs that have been reproduced across multiple studies and meta-analyses. Collaboration for AMD genetics has been undertaken with the International AMD genetics consortium continuing to identify and refine the genetic risk profile for this blinding disease. Equitable and timely access to technology of proven benefit may not be followed but the ethics committee accepts that people from ethnic minorities, for whom the genetic AMD-risk profile is not accurately known, would not be enrolled in the study.

The HREC accepts that the majority of people recruited into the AMD Genetics Consortium are of Northern European ancestry and thus many people in Australia would fit the profile having Northern European ancestry. **Principle 1.2** states that ‘Candidate *omics* tests should be appropriate for the patient population’. Although compliant with other **Domain 1** principles, there is debate about **Principle 1.5**, which states that ‘Analytical validation of *omics* tests for clinical use should be performed in an accredited laboratory’. This is a research study and the proposed analysis is to be conducted in a high quality research laboratory with appropriate quality control and does not need to be NATA accredited (**Principle 2.8**). However, if *omics* test results are to be used for clinical decision making then the sample must be retested in a NATA accredited laboratory (**Principle 3.5**).

19 AREDS – Age-Related Eye Disease Study

**Principle 2.4** states that 'The most appropriate evidence should be applied to clinical validation'. The study is using data from multiple international studies and meta-analyses to stratify risk prediction. AMD has one of the best SNP predictors for a complex genetic disease with almost half the genetic risk explained by identified risk alleles. There will however, be local variation in disease specific prevalence and SNP allele frequency in the Australian population.

Although the *omics*-based test is currently established on international risk data, this is being continually refined as larger cohorts, broader imputation and whole genome sequencing data is added. The study will require a defined and locked-down risk profile for the entry into the study (**Principle 2.3**). Post hoc risk re-evaluation may be used but the study SNP entry profile cannot be changed once the study has commenced and enrollment completed. As the study test will hopefully be used in a future IVD, the researchers should discuss with the TGA (per **Principle 2.5**) and the results of this study will help to validate the *omics* test for future clinical use (**Principle 3.2**). This is an example of an *omics* test/drug combination that is in an open environment that encourages competition to improve testing (**Principle 3.3**). Vitamins are being promoted by certain companies but the genetics research is independent of these companies.

At the same time Optometry Australia wishes to know if they can allow members to refer their patients to have 'online' DNA testing for a similar panel of SNPs and provide vitamins to patients at higher risk based on the current published data of high risk SNPs, in effect pre-empting the results of the proposed research study.

There is only clinical trials evidence that vitamins delay AMD in individuals who have already developed the disease. This proposal is in violation of **Principle 3.2** which states that 'Only laboratory and clinically validated *omics* tests should be provided in clinical care', as the clinical application of this *omics* test has not yet been clinically validated. Although the *omics* test may show an increased risk for AMD, there is currently no clinical intervention that has been proven to prevent disease development. Vitamin usage is only proven for people who have developed AMD to stop progression. There is currently no evidence to support clinical use of genetic testing in AMD management. The American Academy of Ophthalmology Task Force on Genetic Testing currently recommends against genetic testing for AMD outside the research environment.

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## Glossary

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**Analytical validation:** refers to the range of conditions under which the assay will give reproducible and accurate data. With respect to *omics*, this definition needs to be extended so that the data are also representative of the population of interest (Teutsch *et al.* 2009).

**Beneficence:** a concept in research ethics whereby the welfare of research participants should take precedence over other considerations.

**Clinical genetics:** is a medical specialty with close laboratory links that provides diagnostic services, genetic counselling and increasingly, interventional management for individuals or families with, or at risk of, conditions which may have an inherited basis. Genetic services aim to help those affected by, or at risk of, a genetic disorder or predisposition to live and reproduce as normally as possible<sup>20</sup>.

**Clinical validation:** refers to the ability of an *omics*-based test to accurately and reliably predict the clinically defined disorder or phenotype of interest (IOM 2012).

**Clinical utility:** refers to the ability of a test to lead to an improved health outcome (Burke *et al.* 2007).

**Genetics:** is the study of inheritance. It attempts to explain the similarities and differences between related individuals and the way that characteristics are passed on from one generation to the next. More recently the term has come to refer to the DNA sequence.

**Genomics:** is the application of specific technologies to analyse information about the entire genome of an organism (UK Dept of Health 2012). **Genetics** scrutinises the functioning / composition of a single gene whereas **genomics** addresses all genes and their inter-relationships.

**Genomic medicine:** is patient diagnosis and treatment based on information about a person's entire DNA sequence, or 'genome'. It covers a wide spectrum of disciplines and potential applications; all linked using the same underlying technologies. It incorporates clinical genetics and molecular pathology.

**Incidental findings:** refers to findings of potential clinical significance unexpectedly discovered during research or through medical genetic testing. While the terms 'incidental findings' and 'secondary findings' are sometimes used interchangeably, the latter refers to findings that are sought after rather than being discovered unexpectedly.

**In-vitro diagnostic medical devices (IVDs):** refers to any instrument, equipment or apparatus, reagent (alone or in combination) or control/calibrator, which is intended to be used in-vitro for the examination of a specimen derived from the human body. (Details of the TGA regulatory framework for IVDs are provided in **Appendix B**.)

**Omics:** includes genomics which investigates interactions between all of the DNA sequences in a cell or tissue, proteomics (all the proteins), transcriptomics (all the RNA molecules), epigenomics (all the epigenetic modifications) and metabolomics (all the metabolites).

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<sup>20</sup> <http://www.rcplondon.ac.uk/specialty/clinical-genetics>

**Omics-based test:** an assay composed of or derived from many molecular measurements and interpreted by a fully specified computational model to produce a clinically actionable result (IOM 2012).

**Penetrance:** describes the clinical expression of a mutant gene in terms of its presence or absence at a particular stage (Trent 2012). For example, if six out of 10 people show a clinical phenotype at a particular age, the phenotype is described as 60% penetrant. Any penetrance value less than 100% can be referred to as incomplete.

**Variant of unknown significance:** describes a DNA change found in an individual that has not yet been reliably characterised as benign or pathogenic.

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## Appendix A

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### Alignment with existing guidance documents and requirements

The principles outlined in this document should be used in conjunction with the following guidance and requirement documents<sup>21</sup>.

#### a) Guidance and requirements for research

Title	Link	Précis
<i>National Statement on Ethical Conduct in Human Research (2007)</i>	<a href="https://www.nhmrc.gov.au/guidelines/publications/e72">https://www.nhmrc.gov.au/guidelines/publications/e72</a>	Intended for use by investigators conducting research with human participants, members of ethical review bodies reviewing that research, those involved in research governance, and potential research participants. The National Statement is designed to be used in conjunction with other guidelines and codes of practice that are relevant to particular fields of research.
<i>Australian Code for the Responsible Conduct of Research (2007)</i>	<a href="https://www.nhmrc.gov.au/guidelines/publications/r39">https://www.nhmrc.gov.au/guidelines/publications/r39</a>	Guides institutions and researchers in responsible research practices and promotes research integrity. It assists institutions in developing their own employee codes of conduct and procedures for the investigation of allegations of research misconduct by providing a comprehensive framework of acceptable academic standards.
<i>NPAAC Requirements for the Development and Use of In-House In Vitro Diagnostic Medical Devices (3rd Ed. 2014)</i>	<a href="http://www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-dhaivd.htm">http://www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-dhaivd.htm</a>	Outlines the principles and assessment criteria by which <i>in house</i> IVD's must be designed, developed, produced and monitored for use by medical laboratories in Australia.

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<sup>21</sup> Note that individual codes of conduct for individual professions that could be involved in *omics* (e.g. *Medical board of Australia – Good medical practice: a code of conduct for doctors in Australia 2014*) are not included.

## b) Guidance and requirements for health care

Title	Link	Précis
<i>NPAAC Requirements for medical testing of human nucleic acids (2nd Ed., 2012)</i>	<a href="http://www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-docs-nad2.htm">http://www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-docs-nad2.htm</a>	Sets out the minimum requirements for the accreditation of laboratories performing human nucleic acid testing.
<i>NATA Guidelines for Laboratory Accreditation of Massively Parallel Sequencing (Next Generation Sequencing). Technical Note 37 – 2014 (Issued June 2014, reissued October 2014)</i>	<a href="http://www.nata.com.au/nata/phocadownload/publications/Guidance_information/tech-notes-information-papers/technical-note-37.pdf">http://www.nata.com.au/nata/phocadownload/publications/Guidance_information/tech-notes-information-papers/technical-note-37.pdf</a>	Applicable to accredited facilities and those seeking accreditation. The guidelines are based on the RCPA <i>Requirements for Implementation of Massively Parallel Sequencing (2014)</i> ( <a href="http://www.rcpa.edu.au/getattachment/7d264a73-938f-45b5-912f-272872661aaa/implementation-of-massively-parallel-sequencing.aspx">http://www.rcpa.edu.au/getattachment/7d264a73-938f-45b5-912f-272872661aaa/implementation-of-massively-parallel-sequencing.aspx</a> ). To achieve the desired confidence limits, the accreditation process overseen by NATA is iterative.
<i>Australian Regulatory Guidelines for Medical Devices (ARGMD), V1.1, 2011</i>	<a href="http://www.tga.gov.au/industry/devices-argmd.htm">http://www.tga.gov.au/industry/devices-argmd.htm</a>	Developed by TGA and industry as a consolidated reference document detailing the Australian regulatory requirements for medical devices in Australia.

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## Appendix B

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### **Omics tools<sup>22</sup> – Decision tree for the management of findings in research and health care**

Traditionally, clinical tests (including genetic tests) are performed for a defined purpose, and the scope of a test result is confined to what has been requested. However, by their very nature, *omics* tests yield large quantities of analysable information and have the potential to generate incidental or secondary findings with varying degrees of validity, reliability or clinical significance. The guidance provided in Figure 2 aims to assist clinicians and researchers with determining when it may be appropriate to return findings. This material is intended as a supplement to the guidance available for return of results contained in the National Statement.

Although there is some blurring of the boundaries between research and clinical practice, there are important differences in the duties of clinicians and researchers with respect to the management of findings. These differences are reflected in the divergent guidance provided to health professionals or researchers below. In particular, health professionals have a duty to provide care in the best interest of the patient and to allow patients the right to access all clinical information. In contrast, researchers do not have a provider-patient relationship or an obligation to provide participants with access to research information, although they are required to comply with the conditions of consent, to respect privacy and confidentiality and to minimise any risk of harm that applies in the research setting.

Despite the different obligations of health professionals and researchers with respect to management of findings, there are a number of governing principles that should underlie decision making in both settings. The first threshold issue is to establish the scientific validity<sup>23</sup> of any test that is used and the consequent integrity of the analysis and interpretation of the test findings. Once the validity and integrity of a test is established, then the questions of whether the finding is clinically significant or actionable<sup>24</sup> follow. The seriousness of the health condition and its potential impact on the patient or their family is also a highly relevant factor, as is whether the finding relates to the presence of a condition or disease or only to risk factors associated with a condition or disease.

The above requirements minimise the potential for harm caused by returning findings that may be misunderstood with respect to their reliability or significance and that may result in anxiety in patients/participants or induce actions that may not be supported by the reliability or significance of the findings.

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22 NHMRC is developing several tools to assist with the development and use of *omics*. The first of these is the Decision Tree outlined here.

23 Scientific validity refers to the accuracy and reproducibility of the test (i.e. that it actually does detect the targeted mutation(s) with high specificity and sensitivity).

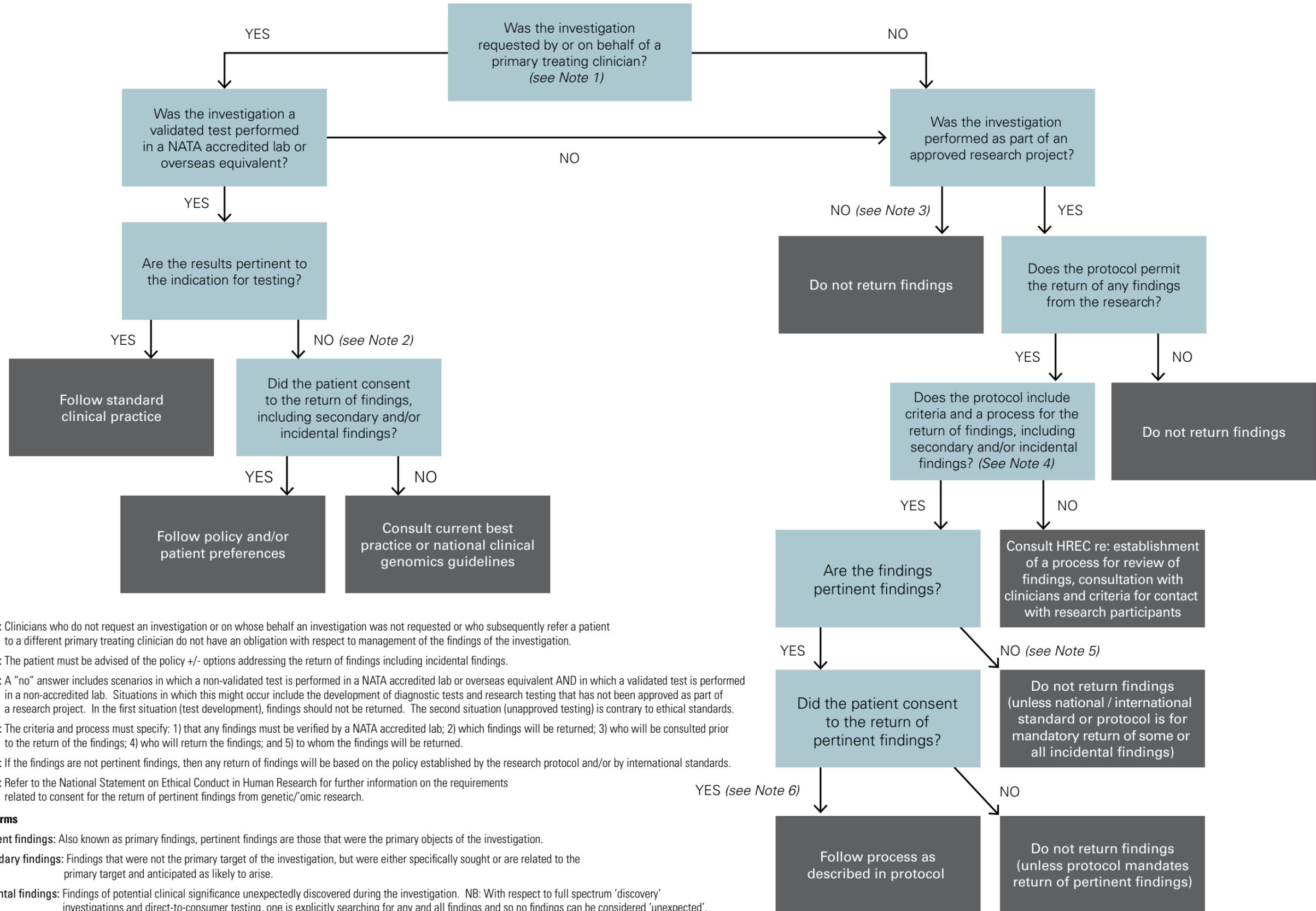
24 Actionable findings are those which have a positive value in diagnosing, treating or managing the condition or disease in question.

Decision makers should also recognise the role of patient/participant preference as a critical factor determining whether and which findings are returned. Prior to any clinical or research investigations from which findings may be made available, patients/participants can be advised that there are likely, foreseeable and possible findings that might arise. Thus informed, they can provide consent as to what information they wish to be disclosed to them. In accordance with their prior agreement, they would then be provided with the information that falls into the class of findings specified for disclosure, provided that findings meet the aforementioned requirements for validity and clinical significance.

Clinicians and researchers should also be aware that national and international guidelines on the management of incidental findings (also referred to as or categorised along with anticipated or secondary findings) are in early stages of development and subject to change, as is the field of *omics* research and the use of *omics* investigations in clinical practice. As a consequence, professional and institutional standards and policies are likely to evolve over time. This guidance document reflects the potential for these changes.

This guidance represents general principles for the management of findings and does not purport to address all possible scenarios which may arise. It should also be noted that the guidance has been developed with adult participants / patients in mind, and that there may be additional ethical considerations where clinical or research investigations involve children.

Figure 2 – Decision tree for the management of findings in research and health care



**Note 1:** Clinicians who do not request an investigation or on whose behalf an investigation was not requested or who subsequently refer a patient to a different primary treating clinician do not have an obligation with respect to management of the findings of the investigation.

**Note 2:** The patient must be advised of the policy +/- options addressing the return of findings including incidental findings.

**Note 3:** A “no” answer includes scenarios in which a non-validated test is performed in a NATA accredited lab or overseas equivalent AND in which a validated test is performed in a non-accredited lab. Situations in which this might occur include the development of diagnostic tests and research testing that has not been approved as part of a research project. In the first situation (test development), findings should not be returned. The second situation (unapproved testing) is contrary to ethical standards.

**Note 4:** The criteria and process must specify: 1) that any findings must be verified by a NATA accredited lab; 2) which findings will be returned; 3) who will be consulted prior to the return of the findings; 4) who will return the findings; and 5) to whom the findings will be returned.

**Note 5:** If the findings are not pertinent findings, then any return of findings will be based on the policy established by the research protocol and/or by international standards.

**Note 6:** Refer to the National Statement on Ethical Conduct in Human Research for further information on the requirements related to consent for the return of pertinent findings from genetic/omic research.

**Key Terms**

**Pertinent findings:** Also known as primary findings, pertinent findings are those that were the primary objects of the investigation.

**Secondary findings:** Findings that were not the primary target of the investigation, but were either specifically sought or are related to the primary target and anticipated as likely to arise.

**Incidental findings:** Findings of potential clinical significance unexpectedly discovered during the investigation. NB: With respect to full spectrum ‘discovery’ investigations and direct-to-consumer testing, one is explicitly searching for any and all findings and so no findings can be considered ‘unexpected’.

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## Appendix C

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### Regulation of *omics*-based tests in Australia

In Australia the Therapeutic Goods Administration (TGA) is responsible for regulating therapeutic goods including medicines, medical devices, blood and blood products. This includes genetic tests which are regulated under the medical devices regulatory framework using a separate classification system for in-vitro diagnostic medical devices (IVDs). Under this system IVD medical devices are classified according to the risk posed to the health of the public or an individual, and relates to the risk of an incorrect result arising from the use of the IVD. Genetic tests, including microarray tests, fall into risk Class 3 (the second highest risk class of four), which means that they carry a “moderate public health risk or high personal risk”. It is presumed that *omics*-based tests will also fall into Class 3.

The IVD framework encompasses both commercial and in-house IVDs – currently most *omics*-based tests are in-house IVDs. All commercial IVDs are required to be included in the Australian Register of Therapeutic Goods (ARTG) (by 30 June 2015). Laboratories that develop Class 1-3 in-house IVDs are exempt from inclusion in the ARTG however they are required to notify the TGA of the in-house IVDs held by the laboratory and the laboratory must be accredited by the National Association of Testing Authorities (NATA) to ISO 15189<sup>25</sup> and comply with the National Pathology Accreditation Advisory Council (NPAAC) standard for the development and use of in-house IVDs. Laboratories with Class 1-3 in-house IVDs are required to comply with these requirements by 30 June 2017.

Accreditation of pathology laboratories in Australia is overseen by the NPAAC. NPAAC is managed by the Australian Government Department of Health. The medical testing accreditation program is administered by NATA in conjunction with the Royal College of Pathologists of Australasia (RCPA). NATA/RCPA accreditation to the Requirements specified by NPAAC (which includes compliance with ISO 15189) is available to facilities performing tests in various fields of human pathology including molecular biology. The program also offers accreditation for a limited range of samples of non-human origin. NATA also offers accreditation programs for non-medical testing.

In addition to Commonwealth oversight of clinical laboratories and clinical tests, several professional societies, such as the RCPA and the Human Genetics Society of Australasia, also develop guidance for clinical genetics laboratories.

#### TGA Regulatory Framework for IVDs

IVDs are classified according to the risks posed to public or individual health in the event of an incorrect or misleading result arising from the use of the IVD.

Levels of risk by IVD class:

- Class 1 IVD - No public health risk or low personal risk
- Class 2 IVD - Low public health risk or moderate personal risk
- Class 3 IVD - Moderate public health risk or high personal risk
- Class 4 IVD - High public health risk

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<sup>25</sup> ISO 15189 specifies the quality management system requirements particular to medical laboratories.

A laboratory (or medical laboratory network) that manufactures Class 1-3 in-house IVDs must:

- be accredited as a medical testing laboratory to ISO 15189 by NATA;
- meet the NPAAC performance standard - Requirements for the development and use of in-house in-vitro diagnostic devices (IVDs); and
- notify the TGA by 30 June 2017 (and thereafter annually) of their Class 1-3 in-house IVDs.

A laboratory is considered to have manufactured an in-house IVD if it is developed:

- from first principles; or
- from a published source (includes scientific literature or design specifications from another laboratory); or
- from a research use only (RUO) kit or analyte specific reagents (ASRs); or
- from a commercially supplied IVD where the commercially supplied IVD is:
  - used for a purpose other than that originally intended by the manufacturer; or
  - not used in accordance with the manufacturer's instructions for use.

Laboratories that manufacture Class 4 in-house IVDs are subject to the same conformity assessment procedures as commercial Class 4 IVDs and are required to:

- apply to the TGA for conformity assessment certification (includes an assessment of the quality management system to ISO 13485 and product evaluation for each Class 4 in-house IVD); and
- include all Class 4 in-house IVDs in the ARTG (note: TGA conformity assessment certification is required prior to inclusion in the ARTG).

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## Appendix D

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### Regulation of *omics*-based clinical trials in Australia

Clinical trials of medicines and medical devices conducted in Australia are subject to Commonwealth Government regulation administered by the TGA. There are two schemes under which clinical trials involving therapeutic goods may be conducted, the Clinical Trial Exemption (CTX) Scheme and the Clinical Trial Notification (CTN) Scheme.

#### The CTN Scheme

Under the CTN scheme, all material relating to the proposed trial, including the trial protocol is submitted directly to the Human Research Ethics Committee (HREC) by the researcher at the request of the sponsor. The TGA does not review any data relating to the clinical trial. The HREC is responsible for assessing the scientific validity of the trial design, the safety and efficacy of the medicine or device and the ethical acceptability of the trial process, and for approval of the trial protocol. In some institutions a scientific review or drug subcommittee may review the proposal before consideration by the HREC. The institution or organisation at which the trial will be conducted, referred to as the 'Approving Authority', gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.

#### The CTX Scheme

Under the CTX Scheme, a sponsor submits an application to conduct clinical trials to the TGA for evaluation and comment. In the case of clinical trials of medicines, the TGA reviews the information about the product provided by the sponsor, including the overseas status of the medicine, proposed Usage Guidelines, a pharmaceutical data sheet, a summary of the preclinical data and clinical data. For medical device trials the TGA examines the design specifications and preclinical data.

#### Other relevant guidance and legislation

Before granting approval to conduct a clinical trial, all parties must be satisfied that the conduct of the proposed trial is in accordance with:

- the National Statement;
- the CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) or the ISO 14155 Clinical Investigation of Medical Devices, whichever is applicable;
- TGA requirements as outlined in this document; and
- any requirements of relevant Commonwealth and/or State/Territory laws.