HANDBOOK

RCPA
The Royal College of Pathologists of Australasia

Extension of Scope of Practice in Molecular Genetics

(NPAAC Supervision Certification Modules)

Haematology

Table of Contents

Glossary

CPDP	RCPA Continuing Professional Development Program
(F)RCPA	(Fellow of the) Royal College of Pathologists of Australasia
IANZ	International Accreditation New Zealand
MDT	Multi-disciplinary team
NATA	National Association of Testing Authorities
NPAAC	National Pathology Accreditation Advisory Council
PPD	Personal Professional Development
RCPAQAP	RCPA Quality Assurance Programs Pty Ltd
SOP	Standard Operating Procedure
WHS	Workplace Health and Safety

SECTION 1

Introduction

1.1 Introduction

The Royal College of Pathologists of Australasia (the College) offers four certification modules in genetic/genomic pathology for those who have attained FRCPA.

These modules have been designed to satisfy the recent NPAAC Requirements, particularly as applicable to supervision of testing involving molecular diagnostics and genomics.

To competently supervise a molecular/genomic service, medically qualified haematologists need to have adequate and detailed knowledge of the wet and dry laboratory aspects of the technology and bioinformatics analysis. It is recognised that this knowledge may not be the same as the hands-on experience of the scientist in the genomics laboratory, however, supervising pathologists should be familiar with the limitations and strengths of the methodology, the ethical considerations of data use and reporting, and the clinical relevance for assessing appropriate requesting and reporting.

It is anticipated that in the next few years, genomic analysis will be integral to the work of pathology laboratories and thus the general Fellowship training program. These modules are designed to provide currently practising haematologists with the opportunity to participate in accordance with NPAAC requirements if applicable to their practice.

1.2 General aims

The genetics/genomic certification modules build on discipline-specific Fellowship training. They are designed to build base knowledge, analytical and interpretive skills, quality assurance and communication capabilities relevant to genetics/genomic testing in Haematology.

Certification aims to ensure a level of competence required to supervise testing and ensure safe clinical service provision in the relevant field.

Completion of one or more modules will result in the extension of scope of practice within Haematology to the limits defined for each module. The scope of practice would not extend into other discipline areas, for example the investigation of intellectual disability or prenatal diagnostic testing.

While candidates will gain understanding of the breadth of the field, they must remain aware of the limits of their own knowledge and appreciate when it is in the best interests of patients to refer to, or formally consult with, genetic pathologists or other appropriately credentialed colleagues.

1.3 Registration

Applicants must complete a registration form, obtainable from the RCPA website and submit this with the application fee. The form must clearly state the modules(s) being applied for. Applications for partial exemption from assessments (recognition of prior learning) must be submitted with supporting documentation at the time of registration.

1.4 Training structure and requirements

The modules are outcomes-based, with no fixed time requirements for completion. Candidates must participate in a range of laboratory-based experiences to achieve the listed outcomes. All specified assessment tasks must be completed satisfactorily to achieve certification.

1.5 Supervision

All training must be supervised by an approved Fellow of the RCPA with the required expertise. Supervisors are expected to monitor and provide regular feedback on the candidate's developing competence. Formal meetings with the candidate are expected to occur at least every three months.

The supervisor will complete a Supervisor Report at the end of the training period, along with a completed and signed portfolio summary sheet. If the training period exceeds twelve months, an additional annual Supervisor report will be required.

The supervisor will carry out workplace-based assessments or may delegate this responsibility to another suitably qualified pathologist or senior scientist.

1.6 Assessment

Assessment consists of a range of activities and workplace-based assessments to be documented in a portfolio, and formal examinations as prescribed for each module.

Portfolios may be maintained in paper-based and/or electronic format with back-up. Portfolios do not need to be submitted to the College. The supervisor will verify that all entries and assessment tasks have been completed on the portfolio summary sheet to be submitted with the final Supervisor Report for the module.

1.7 Continuing professional development

Activities carried out and documentation associated with the modules may be included, along with general haematology activities, in the relevant categories of the RCPA Continuing Professional Development Program (Professional Performance Framework). Following certification, specialists are expected to undertake ongoing professional development relevant to the modules for which they are certified.

1.8 Note

Module 1 (Targeted testing for presence/ absence of predefined genomic variation associated with malignancy, by molecular methods) has been rescinded since it has been deemed that the content is now covered in the standard Fellowship program for Haematology. This module is not required or available but numbering of subsequent modules has been retained for consistency with previously circulated documents.

SECTION 2

Learning outcomes and recommended training activities

Module 2: Targeted testing for presence/absence of predefined genomic rearrangements associated with haematological and related solid tumours by FISH microscopy

FISH is mostly used to assess cancer samples for particular translocations known to be associated with the cancer type in question, such leukemias and lymphomas.

2.1 Learning outcomes

2.1.1 Theoretical and Technical Knowledge

- Working familiarity with the techniques associated with processing samples for conventional cytogenetic- and FISH-based analysis of bone marrow, peripheral blood and paraffin embedded tissues, including both direct and cultured samples
- Demonstrated competency in interphase FISH analysis
- Addressing technical challenges such as:
  - Poor quality hybridisations, differentiating technical/artefactual false positive results from true positive results etc.
  - Mosaicism/clonality and establishing relevant assay performance characteristics (measurement uncertainty, limit of detection)
  - "Unintended" detection of copy number changes (eg. detection of trisomy 9 when looking for BCR- ABL1 in myeloproliferative disorders, trisomy 15 when looking for PML-RARA in APL etc.)

2.1.2 Analytical and interpretive skills

- Synthesis and clinical interpretation of laboratory data taking account of the clinical presentation, morphology, immunophenotype and other relevant non-genomic and genomic investigations.

2.1.3 Quality assurance

- Knowledge of technical performance, limitations and quality issues
- Knowledge of specific quality issues, validation and requirements of supervision
- Knowledge of potential sources of error
- Recognition and troubleshooting of challenges
- Competence in monitoring data quality and result verification
- Knowledge of ethical, clinical and regulatory structures/framework

2.1.4 Communication and Consultation

- Ability to provide clinically appropriate advice regarding contents of reports including diagnostic, prognostic and therapeutic implications of the results

- Ability to communicate results and provide interpretative discussion to referring specialists and in multidisciplinary meetings
- Ability to recognise when complex test results mean that patient safety is best served by consultation with an expert colleague eg. a genetic pathologist

2.2 Specific considerations/challenges to be addressed in assessment

- Identification of a poor-quality sample preparation, and actions taken (e.g. re-processing sample, re-hybdridisation, analysing cultured cells rather than a direct preparation, re-sampling patient)
- Correlation of FISH results with other tests (e.g. molecular testing, immunohistochemistry), particularly for discrepant results
- Investigations/ actions when sex discrepancy, discordant result, sample mix up identified
- Investigations/actions when results are not consistent with standard targeted variant or with wildtype (i.e. may suggest a different variant at that locus)
- Investigations/actions when testing performed at another laboratory does not match with the result in your laboratory
- Validation process for a TGA-accredited targeted assay
- Validation process for a non-accredited targeted assay (i.e. an in-house IVD, including establishing qualitative and quantitative performance characteristics)
- Investigations/actions when an external QA program does not award full marks for genotyping
- Investigations/actions when an external QA program does not award full marks for result interpretation/reporting.

2.3. Assessment

2.3.1 Portfolio requirements

Item	Requirements (number/type)	Documentation
Case Log	Summaries of all laboratory-based experiences, including analysis and reporting of at least 50 disease-associated variants (no more than 10 of the same category).	Log book to include test name; assay type; number of assays/ runs; test failures requiring review. (See Appendix 2)
Clinical Consultations	Fifteen (15) technically challenging or unusual cases/consultations involving lab data. Should address challenges as listed in paragraph 2.2.	Clinical Consultations Sign-Off Form (Appendix 2)
Process-based Discussions (PdD)	• Write up (2-page limit) of case in addition to PbD cover sheet) on five (5) “challenging” cases that required use of multiple skills, including consideration of lab data. • At least one (1) PbD should be on further workup/management of findings.	PbD Assessment Form (Appendix 2)
MDT Participation	Five (5) MDT attendances	Multidisciplinary Meeting Sign-Off Form (Appendix 2)

Quality Assurance (QA) Activities Log	Eight (8) quality assurance activities (including two (2) compulsory). (**note**: You may include a significant/critical laboratory incident relevant to the module as a QA Audit)	Quality Assurance Activities Log (Appendix 2)
QA Reflection	Reflection on each of above	QA Reflection Form (Appendix 2)
Supervisor Report	One final report, plus additional annual report if module not completed in <12 months.	With sign-off indicating: • successful fluorescent-labelling of slides, at a quality level sufficient for reporting; • strong understanding of QC procedures for the methods, including internal and external QA; • working knowledge of method anomalies and associated trouble-shooting requirements. (Supervisor Report, Appendix 2)
Portfolio Summary sheet	To accompany final Supervisor Report	Portfolio Summary Form

2.3.2 Formal examinations

See Appendix 1

2.3.3 Assessment matrix

See Appendix 3

Module 3: Targeted screening for undefined variants in genes associated with specified clinical phenotypes

This is complex and specialised training, which builds upon the sound genomic basics covered in the Haemalogy fellowship training program.

Examples of typical clinical applications for this module would include:

- Targeted gene panels for cancer diagnosis, prognostication and targeted therapy selection (e.g. myeloid/ lymphoid malignancies; etc)
- Targeted gene panels for diagnosis/predictive testing for pre-defined inherited haematological conditions (e.g. thalassemia/haemoglobinopathy, rare inherited platelet disorders, bone marrow failures, etc)

The unifying concept of this module is the detection of unknown genomic variation within a pre-defined list of genes for analysis (focused on a specific haematological phenotype/clinical context) which allows for the practice and development of discipline-specific expertise.

Typically, these assays are 20-30 gene amplicon panels, which are run for disease diagnosis or stratification. They may also include single gene- or single exon-sequencing for specific diseases.

Types of genomic variation covered
Targeted panels and associated bioinformatic pipelines may be designed to detect sequence variants, copy number changes and structural variants/fusions involving pre-defined genes/regions on the targeted panel, depending on the nature of the genomic variations contributing to the defined clinical phenotype.

3.1 Learning outcomes

3.1.1 Theoretical and Technical Knowledge

- Methods covered
  - Sanger sequencing
  - Multiplex-ligation primer amplification (MLPA)
  - Massively parallel sequencing with a range of library preparation/ bio-informatic filtering
    - Targeted amplicon enrichment
    - Hybridisation-based enrichment
- Knowledge of theory and processes relating to Wet Lab:
  - General practical skills and understanding of nucleic acid preparation method(s), quantification/purity/intactness, storage/archiving
  - Knowledge of technical performance, limitations and quality issues associated with different library preparation methodologies (amplicon, hybridisation based, use of unique molecular identifiers (UMI), etc.)
  - Knowledge of technical performance, limitations and quality issues associated with different sequencing technologies
- Knowledge of theory and processes relating to Dry Lab:
  - Knowledge of primary, secondary and tertiary analysis, variables and limitations
  - Knowledge of relevant bioinformatics issues including performance and limitations of demultiplexing/alignment tools/variant callers, variant annotation strategies, bioinformatic methods of structural variant detection, reference generation strategies for copy number assessment, performance and validation of copy number calling algorithms
  - Knowledge of data architecture, computing/processing/capacity issues and data security/privacy
  - Knowledge of cloud based secondary and tertiary analysis systems

- Knowledge of somatic variant curation strategy including understanding of variant annotation, advantages and limitations of cancer (e.g. COSMIC) and healthy population databases (e.g. gnomAD), curation of literature with regard to diagnostic, prognostic and targeted therapies, advantages and limitations of *in silico* prediction tools and splice prediction tools, current somatic reporting guidelines
- Knowledge of constitutional/germline variant curation strategy including understanding of variant annotation, advantages and limitations of cancer (e.g. COSMIC) and healthy population databases (e.g. gnomAD), locus specific databases/Clinvar, segregation analysis, modes of inheritance, curation of constitutional literature, mosaicism, appropriate germline samples, advantages and limitations of in silico prediction tools and splice prediction tools.

3.1.2 Analytical and interpretive skills

- Detailed working knowledge of HGVS/ISCN nomenclature and its practical application
- Knowledge and application of pathogenicity classification systems for somatic and germline variants
- Management of incidental genomic findings (e.g. germline variants of significance detected during somatic testing; more generally, and variant associated with significant clinical outcomes unrelated to the purpose of testing)
- Integration of the genomic variations detected with accompanying morphological, immunophenotypic, cytogenetic and clinical context of the patient in order to provide a clinically appropriate genomic report
- Synthesis and clinical interpretation of laboratory data taking account of the clinical presentation, morphology, immunophenotype and other relevant non-genomic and genomic investigations.

3.1.3 Quality assurance

- Knowledge of specific quality issues, validation and requirements of supervision of massively parallel sequencing (i.e *Requirements for Human Medical Genome Testing Utilising Massively Parallel Sequencing Technologies, NPAAC, 2017*)
- Knowledge of potential sources of error arising from massively parallel sequencing assays designed for formalin-fixed, paraffin-embedded tissues
- Knowledge of ethical, clinical and regulatory structures/framework around germline testing for inherited disease/predictive testing
- Recognition and troubleshooting of challenges
- Competence in monitoring data quality and result verification
- Knowledge of technical performance, limitations and quality issues

3.1.4 Communication and Consultation

- Ability to provide clinically appropriate advice regarding contents of genomic reports including diagnostic implications, prognostic implications and therapeutic implications of detected genomic variations
- Advice on appropriate follow-up genomic testing/other modalities as required (including testing of family members)
- Involvement and ability to communicate in multidisciplinary meetings with pathologists, haematologists, scientists and other referring specialists.

3.2 Specific considerations/challenges to be addressed in assessment

- Investigations/actions when DNA is of inadequate quantity for testing
- Sanger sequencing primer design
- Sequence with poor quality Phred score
- Trouble-shooting poor quality sequence
- Challenges associated with homopolymer runs
- Challenges with assay controls – positive and negative
- Trouble-shooting a massively parallel sequencing run with poor quality control metrics – wet lab and/or dry lab
- MPLA probe design
- Issues with sample depurination
- Trouble-shooting MLPA results – quantitation, standard deviation, abnormal marker patterns, low probe signals, apparent single exon deletion etc.
- Investigations/actions when control samples perform adequately but one or more samples does not pass QC metrics
- Investigations/actions when testing performed at another laboratory does not match with the result in your laboratory
- Validation process for Sanger sequencing/ MLPA
- Validation process for massively parallel sequencing, including validation of bioinformatic pipeline
- Maintenance of bioinformatic pipeline, including version control, verification of new versions
- Assessment of variants of uncertain clinical significance (MUST be included)
- Consultation with colleagues regarding an incidental/secondary finding
- Investigations/actions when an external QA program does not award full marks for genotyping
- Investigations/actions when an external QA program does not award full marks for result interpretation/reporting

3.3 Assessment

3.3.1 Portfolio requirements

Item	Requirements (number/type)	Documentation
Case Log	Summaries of all laboratory-based experiences, including analysis and reporting of at least 150 cases with at least 100 disease-associated variants.	Log book to include test name; assay type; number of assays/ runs; test failures requiring review (See Appendix 2)
Clinical Consultations	Fifteen (15) technically challenging or unusual cases/consultations involving laboratory data. Should address challenges as listed in paragraph 3.2.	Clinical Consultations Sign-Off Form (Appendix 2)
Process-based Discussions (PdD)	• Detailed discussion (at least one (1) page description of case in addition to PbD cover sheet) on five (5) "challenging" cases that required use of multiple skills, including consideration of laboratory data. • At least one (1) PbD should be on further workup/management of unusual such as "off target" findings. (*note:* discipline-specific discussion topics to be defined)	PbD Assessment Form (Appendix 2)

MDT Participation	Five (5) MDT attendances.	Multidisciplinary Meeting Sign Off Form (Appendix 2)
Quality Assurance (QA) Activities Log	Eight (8) quality assurance activities (including two (2) compulsory). (**note**: You may include a significant/critical laboratory incident relevant to the module as a QA Audit)	Quality Assurance Activities Log (Appendix 2)
QA Reflection	Reflection on each of above	QA Reflection Form (Appendix 2)
Supervisor Report	One final report, plus additional annual report if module not completed in <12 months.	With sign-off indicating: • the principles of the method are understood; • working knowledge of instrument processes and maintenance requirements; • successful generation of results from each method, at a quality level sufficient for reporting; • strong understanding of QC procedures for the method, including internal and external QA; • working knowledge of method anomalies and associated trouble-shooting requirements. (Supervisor Report, Appendix 2)
Portfolio Summary sheet	To accompany final Supervisor Report	Portfolio Summary Form

3.3.2 Formal examinations

See Appendix 1

3.3.3 Assessment Matrix

See Appendix 3

Module 4: Untargeted screening for known and unknown variants across the genome by microscopy/ karyotyping or DNA microarray analysis

This is complex and specialised training and builds on the sound genomic basics in Module 2. Knowledge of specific quality issues, validation and requirements of supervision of cytogenetics testing are well summarised elsewhere (see Requirements for Cytogenetic Testing, NPAAC, 2013)

Examples of typical clinical applications for this module would include:

- G-banded karyotyping of haematologic and solid malignancy
- Sequential G-banding to FISH analysis of haematologic and solid malignancy
- Multicolour (M)-FISH and multicolour (m)-BAND analysis of haematologic and solid malignancy
- CGH-array analysis of haematologic and solid malignancy
- SNP-array analysis of haematologic and solid malignancy

As the module involves untargeted screening for disease-linked genomic variants the following outcomes may occur:

- False positive results
- False negative results
- Detection of variants of uncertain clinical significance
- Detection of variants with partial penetrance or expressivity
- Findings that may allow reproductive choices

Additionally, other additional or “off-target” findings may also be detected:

- Medically treatable disorders
- Serious, incurable conditions
- Variants conferring susceptibility to disease
- Mis-attributed paternity
- Close consanguinity

Types of genomic variation that will be identified

Autosomal and sex chromosome aneuploidy, polysomies, structural anomalies, translocations and other balanced rearrangements, copy number changes, absence/loss of heterozygosity and uniparental disomy, identify-by-descent (distant and close) and chimerism.

4.1 Learning outcomes

4.1.1 Theoretical and Technical Knowledge

- Methods and approaches covered
  - G-banded karyotyping
  - Sequential G-banding to FISH
  - M-FISH and mBAND analysis
  - CGH array
  - SNP-array
- Knowledge of theory and processes relating to Wet Lab:
  - Cell culture, selection and processing for whole cell-based genetic analysis
  - Processing of samples referred for cytogenetic and molecular analysis: whole blood, bone marrow, lymph node (and solid tumour biopsies)
  - Cell culture and selection
  - Culture, synchronisation, mitogens, harvest and fixing of metaphase cells for cytogenetic analysis
  - Slide-making and banding Microarray

- Knowledge of theory and processes relating to Dry Lab:
  - Bright-field and fluorescence microscopy
  - Karyotypic analysis
  - Metaphase and interphase FISH
  - Image capture and analysis systems for G-banding and FISH
  - Array technologies and analysis
- Detailed working knowledge of ISCN/HGVS nomenclature and its application
- Knowledge of major genome browsers and databases required to interpret karyotyping and CGH and SNP array findings

4.1.2 Analytical and interpretive skills

- Competence in the assessment of chimerism and somatic and germline mosaicism
- Clinical evaluation of mosaic somatic genomic anomalies detected by karyotyping and array
- Clinical evaluation of mosaic and non-mosaic constitutional genomic anomalies detected by karyotyping and array
- Knowledge and application of pathogenicity classification systems for somatic and constitutional variants
- Synthesis and clinical interpretation of laboratory data taking account of the clinical presentation, morphology, immunophenotype and other relevant non-genomic and genomic investigations
- Assessment of familial recurrence risks arising from chromosomal anomalies

4.1.3 Quality assurance

- Knowledge of ethical, clinical and regulatory structures/framework around germline testing for inherited disease/predictive testing
- Competence in monitoring data quality and result verification
- Knowledge of ethical, clinical and regulatory structures/framework around germline testing for inherited disease/predictive testing
- Knowledge of potential sources of error
- Recognition and troubleshooting of challenges
- Knowledge of technical performance, limitations and quality issues
- Knowledge of specific quality issues, validation and requirements of supervision

4.1.4 Communication and Consultation

- Guidance regarding follow-up testing including result validation and testing of other family members
- Ability to provide clinically appropriate advice regarding contents of reports including diagnostic, prognostic and therapeutic implications of the results
- Ability to communicate results and provide interpretative discussion to referring specialists and in multidisciplinary meetings
- Ability to recognise when complex test results mean that patient safety is best served by consultation with an expert colleague eg. a genetic pathologist

4.2 Specific considerations/challenges to be addressed in assessment

- Investigations/actions when Microarray data is not fit for clinical purpose (e.g. poor banding resolution)
- Investigations/actions when microarray data is not fit for clinical purpose (e.g. microarray quality control metrics indicate increased risk of false negative or positive results)
- Further investigation of an abnormality detected using microarray by application of microscopy-based methods (FISH, karyotype) to further elucidate the clinical significance of a finding (and vice versa)
- Approach to a germline secondary finding, detected when testing for somatic variants (e.g. evidence of consanguinity; detection of a sex chromosome abnormality; detection of a pathogenic variant in a dominant disease gene unrelated to the purpose of testing)
- Approach to assessment and reporting of variants of uncertain significance in the somatic and germline context
- Approach to assessment and reporting of 'susceptibility variants' or risk alleles in the somatic and germline context
- Investigations/actions when testing performed at another laboratory does not match with the result in your laboratory
- Validation process for microarray testing
- Consultation with expert colleagues regarding an incidental/secondary finding, or other complex finding
- Investigations/actions when an external QA program does not award full marks for genotyping
- Investigations/actions when an external QA program does not award full marks for result interpretation/reporting.

4.3 Assessments

4.3.1 Portfolio requirements

Item	Requirements (number/type)	Documentation
Case Log	150 cases with 100 unique variants. If array technology is also being assessed, the total of 200 should also include at least 50 microarrays with 50% abnormal variants (including variants of uncertain significance). If FISH technology is also being assessed, the total of 200 should also include at least 50 FISH with 50% abnormal variants. For both FISH and array, a total of 200 cases would be sufficient as long as at least 50 microarrays and 50 FISH cases have been completed.	Log book to include test name; assay type; number of assays/ runs; test failures requiring review. (See Appendix 2)
Clinical Consultations	Fifteen (15) difficult or unusual cases/consultations. Should address challenges as listed in paragraph 4.2.	Clinical Consultations Sign-Off Form (Appendix 2)

Process-based Discussions (PdD)	• Detailed discussion (at least one (1) page description of case in addition to PbD cover sheet) on five (5) "challenging" cases that required use of multiple skills, including consideration of laboratory data. • At least one (1) PbD should be on further workup/management of unusual findings. (**note:** discipline-specific discussion topics to be defined)	PbD Assessment Form (Appendix 2)
MDT Participation	Five (5) MDT attendances	Multidisciplinary Meeting Sign Off Form (Appendix 2)
Quality Assurance (QA) Activities Log	Eight (8) quality assurance activities (including two (2) compulsory). (**note**: You may include a significant/critical laboratory incident relevant to the module as a QA Audit)	Quality Assurance Activities Log (Appendix 2)
QA Reflection	Reflection on each of above	QA Reflection Form
Supervisor Report	One final report, plus additional annual report if module not completed in <12 months.	With sign-off indicating: • the principles of the method are understood; • working knowledge of instrument processes and maintenance requirements; • successful generation of results from each method, at a quality level sufficient for reporting; • strong understanding of QC procedures for the method, including internal and external QA; • working knowledge of method anomalies and associated trouble-shooting requirements. (Supervisor Report, Appendix 2)
Portfolio Summary sheet	To accompany final Supervisor Report	Portfolio Summary Form

4.3.2 Formal examinations

See Appendix 1

4.3.3 Assessment Matrix

See Appendix 3

Module 5: Sequence-based screening for known and unknown variants in multiple genes, including genes potentially linked to clinical phenotypes that have not been previously diagnosed in the patient

This is complex and specialised training and builds upon Module 3

Examples of typical clinical applications include:
- Diagnosis of diseases with diverse genetic etiologies
- Whole genome/ exome sequencing for inherited haematological disorders
- Whole exome/genome sequencing for common and rare haematologial cancer types

The unifying concept of this module is the application of massively parallel methodologies to screen for disease-causing and disease-associated genomic variants in multiple genes, including genes which can be linked to clinical phenotypes that have not been previously diagnosed in the patient.

The purpose of genome-wide testing would be to bioinformatically extract panels of genes relevant to haematological phenotypes, or for genome-wide analysis of haematological malignancies.

The approach used to detect disease-linked variants will also yield the following outcomes:
- False positive results
- False negative results
- Detection of variants of uncertain clinical significance
- Detection of variants with partial penetrance or expressivity
- Findings that may allow reproductive choices

Wide scope sequencing may also yield other additional or “off-target” findings:
- Medically treatable disorders
- Serious, incurable conditions
- Variants conferring susceptibility to disease
- Variants with pharmacogenetic implications
- Mis-attributed paternity
- Close consanguinity

Types of genomic variation covered
Bioinformatic “pipelines” can be targeted to screen massively parallel sequencing output for nucleotide variants, copy number changes and structural variants/fusions across a large number of specified genes up to the level of all exons of all known genes, or even the whole genome.

5.1 Learning outcomes

5.1.1 Theoretical and Technical Knowledge

- Methodologies covered
  - Massively parallel sequencing using amplicon-based and hybridisation capture-based assays
- Knowledge of theory and processes relating to Wet Lab:
  - General practical skills and understanding of nucleic acid preparation method(s), quantification/purity/intactness, storage/archiving
  - Knowledge of technical performance, limitations and quality issues associated with different library preparation methodologies (amplicon, hybridisation based, use of unique molecular identifiers (UMI), etc.)
  - Knowledge of technical performance, limitations and quality issues associated with different sequencing technologies
- Knowledge of theory and processes relating to Dry Lab:
  - Knowledge of primary, secondary and tertiary analysis, variables and limitations
  - Knowledge of relevant bioinformatics issues including performance and limitations of demultiplexing/alignment tools/variant callers, variant annotation strategies, bioinformatic methods of structural variant detection, reference generation strategies for copy number assessment, performance and validation of copy number calling algorithms
  - Knowledge of data architecture, computing/processing/capacity issues and data security/privacy
  - Knowledge of cloud based secondary and tertiary analysis systems
- Knowledge of read depth and coverage issues whilst using whole exome or genome techniques for somatic variant analysis in cancer and /or in rare phenotypes/inherited conditions
- Knowledge of somatic variant curation strategy including understanding of variant annotation, advantages and limitations of cancer (e.g. COSMIC) and healthy population databases (e.g. gnomAD), curation of literature with regard to diagnostic, prognostic and targeted therapies, advantages and limitations of in silico prediction tools and splice prediction tools, current somatic reporting guidelines

5.1.2 Analytical and interpretive skills

- Detailed working knowledge of HGVS/ISCN nomenclature and its practical application
- Knowledge and application of pathogenicity classification systems for somatic and germline variants
- Integration of the genomic variations detected with accompanying morphological, immunophenotypic, cytogenetic and clinical context of the patient in order to provide a clinically appropriate genomic report
- Management of incidental genomic findings (e.g. germline variants of significance detected during somatic testing; more generally, and variant associated with significant clinical outcomes unrelated to the purpose of testing)
- Knowledge of constitutional/germline variant curation strategy including understanding of variant annotation, advantages and limitations of cancer (e.g. COSMIC) and healthy population databases (e.g. gnomAD), locus specific databases/Clinvar, segregation analysis, modes of inheritance, curation of constitutional literature, mosaicism, appropriate germline samples, advantages and limitations of in silico prediction tools and splice prediction tools
- Sound working fluency in dealing with the range of expected challenging outcomes and additional, “off-target” findings
- Synthesis and clinical interpretation of laboratory data taking account of the clinical presentation, morphology, immunophenotype and other relevant non-genomic and genomic investigations

5.1.3 Quality assurance

- Knowledge of specific quality issues, validation and requirements of supervision of massively parallel sequencing (i.e *Requirements for Human Medical Genome Testing Utilising Massively Parallel Sequencing Technologies, NPAAC, 2017*) Knowledge of technical performance, limitations and quality issues
- Knowledge of potential sources of error
- Recognition and troubleshooting of challenges
- Competence in monitoring data quality and result verification
- Knowledge of ethical, clinical and regulatory structures/framework

5.1.4 Communication and Consultation

- Maintain a close link with a clinical genomics service, particularly for whole genome /exome services
- Ability to provide clinically appropriate advice regarding contents of genomic reports including diagnostic implications, prognostic implications and therapeutic implications of detected genomic variations
- Advice on appropriate follow-up genomic testing/other modalities as required (including testing of family members)
- Involvement and ability to communicate in multidisciplinary meetings with pathologists, haematologists, scientists and other referring specialists.

5.2 Specific considerations/challenges to be addressed in assessment

- Evaluating primary specimen for suitability for molecular testing
- Normal cell contamination
- Investigations/actions when signal is detected in a no-template control
- Investigations/actions when DNA is of inadequate quantity for testing
- Investigations/actions when DNA is of inadequate quality/amplifiability for testing
- Investigations/ actions when sex discrepancy, discordant result, sample mix up identified
- Investigations/actions when results may be confounded by repetitive DNA sequences/ pseudogenes
- Investigations/actions when testing performed at another laboratory does not match with the result in your laboratory
- Trouble-shooting a whole exome/genome sample/run with poor quality control metrics – wet lab and/or dry lab metrics
- Validation process for a targeted assay based on bioinformatic filtering of whole genome/exome sequencing data
- Panel selection from WES/WGS data, including technical and clinical considerations
- Approach to targeted genes which are not adequately covered for clinical reporting
- Investigations/actions when an external QA program does not award full marks for genotyping
- Investigations/actions when an external QA program does not award full marks for result interpretation/reporting
- Approach to assessment and reporting of variants of uncertain significance in the somatic and germline context
- Approach to assessment and reporting of ‘susceptibility variants’ or risk alleles in the somatic and germline context
- Consultation with expert colleagues regarding an incidental/secondary finding, or other complex finding

5.3 Assessments

5.3.1 Portfolio requirements

Item	Requirements (number/type)	Documentation
Case Log	Summarising all laboratory-based experiences, which includes analysis and reporting of at least 150 cases with 100 unique variants. If module 3 and module 5 are both being undertaken, then a minimum of 200 cases with 50% unique variants with 30% of cases specific to each module should be completed as part of case mix.	Log book to include test name; assay type; number of assays/ runs; test failures requiring review. (See Appendix 2)
Clinical Consultations	Fifteen (15) technically challenging or unusual cases/consultations involving lab. data. Should address challenges as listed in paragraph 5.2.	Clinical Consultations Sign-Off Form (Appendix 2)
Process-based Discussions (PdD)	• Detailed discussion (at least one (1) page description of case in addition to PbD cover sheet) on five (5) "challenging" cases that required use of multiple skills, including consideration of lab. data. • At least one (1) PbD should be on management of "off target" findings (**note:** discipline-specific discussion topics to be defined)	PbD Assessment Form (Appendix 2)
MDT Participation	Five (5) MDT attendances	Multidisciplinary Meeting Sign-Off Form (Appendix 2)
Quality Assurance (QA) Activities Log	Eight (8) quality assurance activities (including two (2) compulsory). (**note**: You may include a significant/critical laboratory incident relevant to the module as a QA Audit)	Quality Assurance Activities Log (Appendix 2)
QA Reflection	Reflection on each of above	QA Reflection Form
Supervisor Report	One final report, plus additional annual report if module not completed in <12 months.	With sign-off indicating • the principles of the method are understood; • working knowledge of instrument processes and maintenance requirements; • successful generation of results from each method, at a quality level sufficient for reporting; • strong understanding of QC procedures for the method,

		including internal and external QA; • working knowledge of method anomalies and associated trouble-shooting requirements. (Supervisor Report, Appendix 2)
Portfolio Summary sheet	To accompany final Supervisor Report	Portfolio Summary Form

5.3.2 Formal examinations

See Appendix 1

5.3.3 Assessment Matrix

See Appendix 3

SECTION 3

Appendices

Assessment

Assessment is by

- Formal examinations (see Appendix 1)
- A portfolio of evidence of having participated in a sufficient number and type of work activities (see Appendix 2)
- Satisfactory progress (supervisor reports) (see Appendix 2)

An assessment matrix is provided in Appendix 3

Portfolio requirements

Portfolio activities are carried out in the workplace provides evidence that fellows have engaged in the appropriate number and type of work-based activities to build base knowledge, analytical and interpretive skills, quality assurance and communication capabilities relevant to genetics/genomic testing in Haematology. Requirements or each module are summarised in a table at the end of the module in Section 2.

Appendix 2 contains the forms and logbook pages for recording the portfolio activities. Please file the hard copy forms in a **portfolio folder** with separate sections as in the table provided in each module.

A soft copy **portfolio summary** (Excel spreadsheet) should also be compiled so that the fellow can keep track of what has been completed. The spreadsheet can be downloaded from the RCPA website. It is the fellow's responsibility to keep both hard and soft copy records up-to-date.

The portfolio summary spreadsheet should be apprehended to the annual supervisor reports and will be reviewed by the Registrar, Board of Education and Assessment and the Chief Examiner. Signatories and fellows may be contacted to confirm evidence of satisfactory completion.

Appendix 1: Examinations

There will be a multi-station examination consisting of three stations, each of twenty minutes, with two examiners for each. This will include stations focussing on practical cases, for example:

- Array-detected variant curation, cytogenetic- and array- based practical cases (Module 4)
- Practical cases for variant curation (Module 5)

Candidates will be allowed 1 hour pre-reading time, during which they may review data and reports, making notes where applicable, prior to discussion with the examiners.

The examination will focus on ability to:

- Analyse and interpret findings
- Explain principles of the test methods used, identifying any limitations
- Apply quality management principles and troubleshooting methods to explain and prevent possible sources of error
- Communicate clinically relevant conclusions and advice to referring doctors, including discussion of uncertainties
- Discuss broader health implications and/or ethical considerations relevant to the testing performed

Appendix 2: Forms and log pages for portfolio

Medical Genomics Haematology
Routine Case Log

How to use this form

From the beginning of training, Fellows should log all laboratory-based experiences, including analysis and reporting. Only runs that the Fellow has been directly involved with should be logged.

Module 2: A minimum of 50 disease-associated variants should be recorded during the Module.

Modules 3,4 &5: A minimum of 150 cases with at least 100 disease-associated variants

The log book should include:

- Test name
- Assay type
- Number of assays/ runs
- Test failures requiring review

At the end of each Module, the log should be sighted and signed off on the Supervisor Report.

Fellow Name	**Fellow ID**	**Module of Training (**please tick) ☐ Module 2 ☐ Module 3 ☐ Module 4 ☐ Module 5

	Date	***Test name***	***Assay type***	***Number of assays/ runs***	***Test failures requiring review***
1					
2					
3					
4					
5					
6					
7					

8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
Final Outcome (please tick) ☐ Competent ☐ Not Competent					
Signature of Assessor			**Signature of Fellow**		
Name of Laboratory					

Medical Genomics Haematology
Clinical Consultations Sign-Off Form

How to use this form

From the beginning of training, Fellows should log consultations with clinical colleagues that involve significant, difficult or unusual cases.
A minimum of (fifteen) 15 consultations should be recorded during the Module.

Consultation type **should be noted on the form as:** ***ORAL:****Telephone Outpatient* ***(TOP) OR*** *Telephone Inpatient* ***(TIP)***
WRITTEN: *Outpatient* ***(OP) OR*** *Inpatient* ***(IP)***

Each logged entry must be sighted and signed off by supervising consultant(s) on the day of the consultation.
At the end of each Module, this form and appended case lists should be sighted by the supervisor and signed off.

Fellow Name	**Fellow ID**	**Module of Training (**please tick) ☐ Module 2 ☐ Module 3 ☐ Module 4 ☐ Module 5

	Date	***Headline summary of case***	***Issue(s) raised by the case***	***Consult type***	***Fellow's role in the case***
	example	***e.g.TP53 mutation or deletion***	***Clinician seeking guidance on diagnostic possibilities and investigations***	***TOP / TIP OP / IP***	***Advice offered; review of results; follow-up discussion with referring clinician***
1					
2					
3					
4					
5					
6					
7					
8					

9					
10					
11					
12					
13					
14					
15					
Final Outcome (please tick) ☐ Competent ☐ Not Competent					
Signature of Assessor			**Signature of Fellow**		
Name of Laboratory					

Medical Genomics Haematology PbD Assessment Form

Process based Discussion

Fellow Name	**Fellow ID**	**Module of Training (**please tick) ☐ Module 2 ☐ Module 3 ☐ Module 4 ☐ Module 5
Assessor Name	**Assessor position** ☐ Pathologist ☐ Other (please specify)	

Techniques/methods (tick the box that applies).

1. ☐ Nucleic acid preparation method(s), quantification/purity/intactness, storage/archiving
2. ☐ Banding and Karyotype
3. ☐ Microarray
4. ☐ FISH analysis
5. ☐ PCR-based assays (end point, quantitative and real-time)
6. ☐ Next generation sequencing based procedures and analysis

Please comment on whether these aspects of the Fellow's performance	**Yes**	**No**	**N/A**
Understands the principles of the method			
Understands and complies with the laboratory documentation, package inserts, manuals, etc.			
Has observed all phases of an assay successfully and been involved in the production of a valid result that can be reported			
Able to explain the Quality Controls procedures for this method, including internal and external Quality Assurance.			
Able to discuss anomalies and resolve uncertainties for the method			
Able to explain maintenance and trouble-shooting requirements for the method			

Please comment on other relevant aspects, especially on aspects for improvement (use the reverse side if insufficient room)

Final Outcome (please tick)

☐ Competent ☐ Not Competent

Signature of Assessor	**Signature of Fellow**

Name of Laboratory

Medical Genomics Haematology
Clinical/Multidisciplinary Meeting Sign Off Form

How to use this form

This form is to be used to record that the Fellow has fulfilled the following requirements:

Present cases at a minimum of five (5) clinical or laboratory meetings throughout the module.

Fellows should retain a list of the cases/entities presented at each meeting in the portfolio.

At the end of the module, this form and appended case lists should be sighted by the supervisor and signed off.

Fellow Name:	**Fellow ID:**	**Module of Training (**please tick) ☐ Module 2 ☐ Module 3 ☐ Module 4 ☐ Module 5

	Meeting date	**Brief description of meeting; subject(s) of discussion**	**Did Fellow present cases? Y/N**
1			
2			
3			
4			
5			
6			
7			
8			
9			

Final Outcome (please tick) ☐ Competent ☐ Not Competent

Signature of Assessor	**Signature of Fellow**

Name of Laboratory

Medical Genomics Haematology
Quality Assurance Activities Log

How to use this form

Eight (8) activities should be selected from the list. Items 9 and 10 are compulsory.

Use the Reflection Form in this handbook to write a brief reflection on what you learned from doing each activity (photocopy as many copies of the form as you need).

Keep the forms in your portfolio along with other specified documents if required

At the end of each rotation, the log should be sighted and signed off by the supervisor.

Fellow Name	**Fellow ID**	**Module of Training (**please tick) ☐ Module 2 ☐ Module 3 ☐ Module 4 ☐ Module 5

	Quality activity	***Summary of Fellow's role in the activity or comment (where applicable)***	***Date***
1	Analyse the design and operating characteristics of a particular instrument or platform		
2	Work through the development of a new in vitro diagnostic test and the associated IQA processes		
3	Review relevant AS ISO standards (list documents reviewed)		
4	Review relevant NPAAC standards and guidelines (list documents reviewed)		
5	Review the laboratory's quality policy, including policy guiding response to unsatisfactory QAP results		
6	External QAP (particularly involvement with the HGSA/QAP, EMQN, ASoC programs)		
7	Active involvement in preparations for laboratory accreditation		

Medical Genomics Haematology
Quality Assurance Activities Log

How to use this form
Eight (8) activities should be selected from the list. Items 9 and 10 are compulsory.
Use the Reflection Form in this handbook to write a brief reflection on what you learned from doing each activity (photocopy as many copies of the form as you need).
Keep the forms in your portfolio along with other specified documents if required
At the end of each rotation, the log should be sighted and signed off by the supervisor.

Fellow Name	**Fellow ID**	**Module of Training (**please tick) ☐ Module 2 ☐ Module 3 ☐ Module 4 ☐ Module 5

	Quality activity	***Summary of Fellow's role in the activity or comment (where applicable)***	***Date***
8	Participate in a workflow check of effective/ efficient laboratory function		
9	**MANDATORY ACTIVITY** Review and update laboratory internal QC procedures. **Minimum of two (2) prior to examinations.** Include reports in portfolio.		
10	**MANDATORY ACTIVITY** Significant incident: Involvement in assessment, reporting and review, focussing particularly on the quality issues that were identified and addressed. **Minimum of one**. OR Quality audits: Conduct. Where possible, include comparison with relevant national/international guidelines. **Minimum of one**. Include documentation in portfolio. Use the reporting form in supplied in this Handbook		

Supervisor name……..... Signature…….....…… Date…….....

Medical Genomics Haematology Quality Assurance Reflection Form

Fellow Name	**Fellow ID**	**Module of Training (**please tick) ☐ Module 2 ☐ Module 3 ☐ Module 4 ☐ Module 5

Nature of activity

Your role in the activity

Your reflection on what you learned from your involvement in this activity

Points to consider: -

- *Type of Activity*
- *Actions undertaken*
- *Findings*
- *Resource considerations*
- *Ethical considerations*

Fellow signature	**Date**
Supervisor name (please print) and signature	**Date**

Name of Laboratory

Medical Genomics Supervisor Report Haematology

Please review the Fellow's portfolio and logbook before completing this report

Fellow Name (please print)	**Fellow ID**	**Module of Training (**please tick) ☐ Module 2 ☐ Module 3 ☐ Module 4 ☐ Module 5

Name of Organisation

Training period:

_____/_____/_____ to ___/_____/_____

Name of supervisor (please print) **Supervisor RCPA ID no.**

Please inspect the forms in the Fellow's portfolio and use the Table below to record evidence of completion

Portfolio items for which there is a minimum requirement				
	Previous total (if applicable)	Number in current year/ module	Cumulative Total	Minimum for completion of module
Case Log				Module 2: 50 Module 3, 4, 5: 150
Clinical Consultations				15
Process-based discussion (PbD)				5
MDT Participation				5
QA Activities				8
QA Reflection				1 per each QA activity
Previous Supervisor's reports				1 report/ 12months
Portfolio Summary				

Does the print-out of the portfolio summary spreadsheet accurately record the contents of the portfolio?

☐ Yes ☐ No

Please score the Fellow's performance using this scale

1 = Performance currently falls far short of expected standards for level of training.
There is a serious problem that may have implications for accreditation of the current training period. The problem must be stated clearly on the final page.

2 = Performance currently falls short of expected standards for level of training.
There is an area of lower than expected performance. The problem must be stated clearly on the final page.

3 = Performance is consistent with the expected level of training.
About 80% of fellows will merit this grade.

4 = Performance is better than expected for level of training.
About 10% of fellows will merit this grade.

5 = Performance is exceptional.
Very few fellows will merit this grade.

N/A = Not Applicable to this training period

	Score
The principles of all methods are understood	
Working knowledge of method anomalies and associated trouble-shooting requirements	
Working knowledge of instrument processes and maintenance requirements	
Successful generation of results from each method, at a quality level sufficient for reporting	
Working knowledge of method anomalies and associated trouble-shooting requirements	
Strong understanding of QC procedures for the methods, including internal and external QA	
Clinically appropriate advice regarding contents of reports including diagnostic, prognostic and therapeutic implications of the results	
Follow-up genomic testing/other modalities as required (including testing of family members)	
Communication with pathologists, haematologists, scientists and other referring specialists	
Recognise when patient safety is best served by consultation with an expert colleague eg. a genetic pathologist	

Overall evaluation

Have the outcomes of this module been satisfactorily achieved?

☐Yes ☐No

Is specific further professional development required? If yes, please outline process

☐Yes ☐No

Signatures

Fellow (please PRINT name and sign)	Date
Supervisor name (please PRINT name and sign)	Date
Other senior staff member/second supervisor (if applicable) (please PRINT name and sign)	Date
Head of Department (please PRINT name and sign)	Date

Comments by Fellow:

_____

_____

_____

_____

Please return this Supervisor's Report to:

The Royal College of Pathologists of Australasia
207 Albion Street
Surry Hills NSW 2010 AUSTRALIA

Faxed reports will not be accepted.

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA USE ONLY

Signature

Registrar/Deputy Registrar, Board of Education and Assessment (please PRINT name and sign)	Date

Appendix 3: Assessment matrix

	Portfolio of workbased activities					Supervisor report	Oral exam
	Case Log	Consul tations	PbD	MDT	QA Activity		
Theoretical & technical knowledge	Y	Y	Y	Y		Y	Y
Analytical and interpretive skills		Y	Y	Y	Y	Y	Y
Quality assurance			Y	Y	Y	Y	Y
Communication & consultation		Y	Y	Y	Y	Y	Y