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

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| 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

The Royal College of Pathologists of Australasia (the College) offers a number of certification modules for Fellows of the Royal College of Pathologists of Australasia who have completed Fellowship in the discipline of Haematology.

The development of these certification modules has been required to satisfy the recent NPAAC requirements (http://health.gov.au/internet/main/publishing.nsf/Content/health-npaac-docs-supervision.htm), particularly as applicable to supervision of testing involving molecular diagnostics and genomics.

To adequately medically supervise a molecular/genomic service, 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 increasingly become integral to the work of pathology laboratories. These modules are designed to provide all haematologists with the opportunity to participate in accordance with NPAAC requirements.

# GENERAL AIMS OF THE TRAINING PROGAM

The genetics/genomics certification modules build on discipline-specific Fellowship training. As well as gaining additional competencies in genetics/genomics relevant to haematology, candidates are expected to extend further their skills in management, research and scholarship, as well as the professional qualities they have been developing during their pre- and post-Fellowship years and will continue to develop during their professional life.

This Handbook outlines requirements for the Haematology Certification Modules. It is based on a common approach for Fellows in all pathology disciplines to develop/demonstrate the minimum professional competencies required for safe clinical service provision of genetic/ genomic testing. As such, the certification modules and associated competency standards outlined within this handbook have shared features with the modules outlined in the equivalent handbooks for other disciplines.

The purpose of the modules outlined in this Handbook is to offer Fellows the opportunity to gain certification of expertise for a graduated range of genetic/ genomic testing categories specifically for clinical applications within their pathology discipline.

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, investigation of intellectual disability or prenatal diagnostic testing.

An essential part of sub-specialty genetics/genomics training is for practitioners to gain sufficient understanding of the breadth of the field; are aware of the limits of their own knowledge and appreciate when it is in the best interests of patients to refer onto, or formally consult with, genetic pathologists or other appropriately credentialed colleagues.

 

# SECTION 2

# LEARNING OUTCOMES AND RECOMMENDED TRAINING ACTIVITIES



 

# Module 1 – Targeted testing for presence/ absence of predefined genomic variation associated with malignancy, by molecular methods.

*Rescinded in November 2018*

The Curriculum Development Working Group met in late November 2018, and it was agreed upon that Module 1 content and professional competency was now covered with the standard Trainee Curriculum for the discipline of Haematology.

Applicants for the Recognition of Prior Learning pathway are not required to address the contents of this module in their application.

 

# Module 2 – Targeted testing for presence/ absence of predefined genomic rearrangements associated with haematological/ 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. Practical challenges associated with this type of work include:

- Technical challenges (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 (*e.g. detection of trisomy 9 when looking for BCR- ABL1 in myeloproliferative disorders, trisomy 15 when looking for PML-RARA in APL etc.)*

**Knowledge and practical skills**

*Required practical skills:*

- 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

*Analytical considerations:*

- Demonstrated competency in interphase FISH analysis

*Post-analytic considerations*

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

 

## Professional Competency

- **Log book** - summarising all laboratory-based experiences, which includes analysis and reporting of at least 50 disease-associated variants, with no more than 10 of the same category. *Log book to include test name; assay type; number of assays/ runs; test failures requiring review.*
- **Portfolio Requirements** - should also include:
    - *Fifteen (15) technically challenging or unusual cases/consultations involving lab. data. * See below for a list of examples of technical considerations/ challenges.*
    - *Five (5) MDT attendances*
    - *Eight (8) quality assurance activities (including two (2) compulsory), and*
    - *One (1) significant/critical laboratory incident report relevant to the module*
- **Case-based Discussions** - *write up (2-page limit) of case in addition to CbD cover sheet) on five (5) "challenging" cases that required use of multiple skills, including consideration of lab. data. At least one (1) CbD should be on further workup/management of findings.*
- **Supervisor sign-off**
    - 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
- **Dry Practical** (practical cases)
- **Structured Oral**

### * Examples of technical considerations/challenges:

- 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

 

# Module 3 – Targeted screening for undefined variants in genes associated with specified clinical phenotypes.

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.

## Methodologies covered

- Sanger sequencing
- Multiplex-ligation primer amplification (MLPA)
- Massive parallel sequencing with a range of library preparation/ bio-informatic filtering
    - Targeted amplicon enrichment
    - Hybridisation-based enrichment

## Knowledge and practical skills

*General considerations*

- This is complex and specialised training, which builds upon the sound genomic basics in Module 1.
- 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, National Pathology Accreditation Advisory Council, 2017*)
- Knowledge of potential sources of error arising from massively parallel sequencing assays designed for formalin-fixed, paraffin-embedded tissues.

*Wet lab considerations*

- General practical skills understanding of nucleic acid preparation method(s), quantification/purity/intactness, storage/archiving (as per core module 1)
- 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.

 

*Dry lab considerations*

- 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.

*Analysis considerations*

- Detailed working knowledge of HGVS/ISCN nomenclature and its practical application
- 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 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)
- 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
- 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
- Knowledge of ethical, clinical and regulatory structures/framework around germline testing for inherited disease/predictive testing.

*Post-Analytic Considerations*

- 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.

 

## Professional Competency

- **Log book** - summarising all laboratory-based experiences, which includes analysis and reporting of at least 200 cases with at least 100 disease-associated variants. *Log book to include test name; assay type; number of assays/ runs; test failures requiring review*
- **Portfolio Requirements** - should also include:
    - *Fifteen (15) technically challenging or unusual cases/consultations involving laboratory data. * See below for a list of examples of technical considerations/ challenges. NOTE: evaluation of variants of uncertain significance MUST be included.*
    - *Five (5) MDT attendances,*
    - *Eight (8) quality assurance activities (including two (2) compulsory), and*
    - *One (1) significant/critical laboratory incident report relevant to the module*
- **Case-based Discussions** - d*etailed discussion (at least one (1) page description of case in addition to CbD cover sheet) on five (5) "challenging" cases that required use of multiple skills, including consideration of laboratory data. At least one (1) CbD should be on further workup/management of unusual such as "off target" findings. (note: discipline-specific discussion topics to be defined).*
- **Supervisor sign-off**
    - 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
- **Dry Practical** (practical cases)
- **Structured Oral**

### * Examples of technical considerations/challenges:

- 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.

 

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

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.

### Methods and approaches

- G-banded karyotyping
- Sequential G-banding to FISH
- M-FISH and mBAND analysis
- CGH array
- SNP-array

### Knowledge and practical skills

*General considerations*

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, National Pathology Accreditation Advisory Council, 2013).

 

*Wet lab considerations*

- 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
- Refer to items applying to microarray, which are listed in Module 1 (*Generic knowledge and practical skills)*

*Dry lab considerations*

- 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

*Analytic considerations*

- Competence in monitoring data quality and result verification
- Competence in the assessment of chimerism and somatic and germline mosaicism
- Detailed working knowledge of ISCN/HGVS nomenclature and its application
- 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 of major genome browsers and databases required to interpret karyotyping and CGH and SNP array findings
- Knowledge and application of pathogenicity classification systems for somatic and constitutional variants.

*Post-analytic considerations*

- 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
- Guidance regarding follow-up testing including result validation and testing of other family members
- Knowledge of the relevant regulatory framework(s)
- Knowledge of ethical, clinical and regulatory structures/framework around germline testing for inherited disease/predictive testing
- 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 e.g. a genetic pathologist.

 

## Professional Competency

- **Log book** - 200 cases with 100 unique variants. If array technology is also being assessed, the total of 250 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 250 should also include at least 50 FISH with 50% abnormal variants. For both FISH and array, a total of 250 cases would be sufficient as long as at least 50 microarrays and 50 FISH cases have been completed.
- **Portfolio Requirements** - should also include:
    - *Fifteen (15) difficult or unusual cases/consultations,*
    - *Five (5) MDT attendances,*
    - *Eight (8) quality assurance activities (including two (2) compulsory), and*
    - *One (1) significant/critical laboratory incident report relevant to the module*
- **Case-based Discussions** ***(note:*** *discipline-specific discussion topics to be defined) - detailed discussion (at least one (1) page description of case in addition to CbD cover sheet) on five (5) "challenging" cases that required use of multiple skills, including consideration of laboratory data. At least one (1) CbD should be on further workup/management of unusual findings.*
- **Supervisor sign-off**
    - 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
- **Dry Practical** (array-detected variant curation, cytogenetic- and array- based practical cases, etc)
- **Structured Oral**

### * Examples of technical considerations/challenges:

- Investigations/actions when karyotype 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.

 

# 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.

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.

**Methodologies covered**

Massive parallel sequencing using amplicon-based and hybridisation capture-based assays.

**Knowledge and practical skills**

*General considerations*

- This is complex and specialised training and builds upon modules 1 and 3.

 

- Sound working fluency in dealing with the range of expected challenging outcomes and additional, "off-target" findings.
- Knowledge of specific quality issues, validation and requirements of supervision of massive parallel sequencing (i.e *Requirements for human medical genome testing utilising massively parallel sequencing technologies, National Pathology Accreditation Advisory Council, 2017*)

*Wet lab considerations*

- Refer to module 3.

*Dry lab considerations*

- Refer to module 3.

Additionally:

- 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

*Analysis considerations*

- Refer to module 3.

*Post-Analytic Considerations*

- Refer to module 3.

Additionally:

- Close link with a clinical genomics service, particularly for whole genome /exome services.

 

## Professional Competency

- **Log book** – summarising all laboratory-based experiences, which includes analysis and reporting of at least 200 cases with 100 unique variants. *Log book to include test name; assay type; number of assays/ runs; test failures requiring review*
- If module 3 and module 5 are both being undertaken, then a minimum of 400 cases with 50% unique variants with 30% of cases specific to each module should be completed as part of case mix.
- **Portfolio Requirements** - should also include:
    - *Fifteen (15) technically challenging or unusual cases/consultations involving lab. data. * See below for a list of examples of technical considerations/ challenges.*
    - *Five (5) MDT attendances,*
    - *Eight (8) quality assurance activities (including two (2) compulsory), and*
    - *One (1) significant/critical laboratory incident report relevant to the module*
- **Case-based Discussions** *(**note:** discipline-specific discussion topics to be defined) - detailed discussion (at least one (1) page description of case in addition to CbD cover sheet) on five (5) "challenging" cases that required use of multiple skills, including consideration of lab. data. At least one (1) CbD should be on management of "off target" findings.*
- **Supervisor sign-off**
    - 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
- **Dry Practical** (variant curation, practical cases)
- **Structured Oral**

### * Examples of technical considerations/challenge:

- 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.

 