Southern African Society for Human Genetics

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HPCSA INTERNSHIP TRAINING FOR MEDICAL BIOLOGICAL SCIENTISTS IN HUMAN GENETICS: RECOMMENATIONS FOR MINIMUM TRAINING OUTCOMES

The following recommendations for minimum outcomes of the HPCSA internship training for Medical Biological Scientists were compiled by the Medical Scientists' Working Group within the South African Society of Human Genetics (SASHG). These recommendations were guided by the role and professional scope of a Medical Biological Scientist in the discipline of Human Genetics, with its unique requirements in terms of exposures, skills and competencies, relevant to the diagnostic laboratory environment. The document is intended to guide the training process with regards to the minimum, discipline-specific outcomes, rather than serve as a training programme, which must align with the National Curriculum (CMS 01 MBS) and is currently specifically tailored to each training unit.

1 TRAINING ENVIRONMENT

The greater part of the HPCSA internship should be conducted in an HPCSA-accredited diagnostic laboratory setting, where the intern scientist will gain exposure to the systems, workflows and service-focused ethos of the healthcare environment. The research component may be conducted in an affiliated research laboratory but should, ideally, have a translational nature. Certain technological platforms or investigations may not be available in every training laboratory. For example, some laboratories do not offer chromosomal microarray or paternity testing, hence cannot provide this type of training/exposure. Such limitations should be overcome by setting up collaborations and exchange programmes between training facilities to ensure that interns gain the necessary exposure and training.

2 INSIGHTS AND EXPOSURES

In addition to the technical competencies, internship training should incorporate a theoretical component relating to the analytical and clinical validity of each investigation, as well as its clinical and personal utility. This includes knowledge of the genetic mechanisms of the disorder tested, as well as the principles, capabilities and limitations of the methods and platforms used. Such insights are important not only for confidence in test analysis and reporting but also for research translation, new test design and validation and troubleshooting of the existing assays, all of which lie within the professional scope of a medical biological scientist.

It is important that the training of an intern scientist in Human Genetics includes interaction with clinicians, especially medical geneticists and genetic counsellors, as understanding the clinical context and family history of the patient is essential for appropriate result interpretation and compilation of informative, correctly phrased test reports.

3 METHODS AND PLATFORMS (technical skills).

At the end of the 24-month training period, the intern should have gained practical competencies and theoretical insights pertaining to a range of methods and platforms used for diagnostic testing in each of the following categories:

3.1 Molecular analysis

Technical proficiency and understanding of the principles behind the following methods and platforms (as a minimum), within the context of Mandelian disorders and detection of known and unknown DNA variants:

- Nucleic acid isolation (manual and automated methods)
- PCR: (various: end-point, multiplex, real-time etc.)
- Sanger sequencing
- Restriction endonuclease analysis
- Fragment analysis using agarose and capillary electrophoresis
- Multiple ligase-dependent Probe Amplification (MLPA)
- Short Tandem Repeat (STR) analysis (e.g., linkage, microsatellite instability etc.)
- *Next Generation Sequencing (NGS).

3.2 Chromosome analysis (karyotyping)

Karyotyping in the diagnostic setting is traditionally, though not exclusively, part of the professional scope of the medical laboratory technologist/scientist, with the relevant competencies and HPCSA registration in the discipline of Cytogenetics. It is addressed to a limited extent in the university Honours programmes, which mainly focus on molecular genetics/genomics and bioinformatics. However, correct interpretation of chromosomal microarray results, which have superseded karyotyping in many instances, requires molecular as well cytogenetic insights. It is therefore important to incorporate a level of practical cytogenetics into the internship training for medical biological scientists in Human Genetics:

- *Blood and/ amniocyte culture
- *Cell harvest
- *Slide preparation
- *Staining and Chromosome analysis (manual or partially/automated).

3.3 Molecular Cytogenetics

Molecular methods/platforms for detection of genomic copy number variants (CNVs):

- *Fluorescent In-situ hybridisation (FISH)
- *Quantitative Fluorescent PCR for aneuploidy (QF-PCR)
- *MLPA (for genomic CNV detection e.g., microdeletion syndromes)
- *DNA microarray.

3.4 Somatic Cell Genetics

- DNA extraction from paraffin embedded material
- Somatic variant detection using molecular and/or cytogenetic techniques.

3.5 Kinship Analysis

In principle, kinship analysis (parentage testing etc.) exists within the realm of human identification (genetic fingerprinting) and forensic science. It is however offered as a service in many medical genetics laboratories and is frequently requested by hospital/medical authorities in situations such as suspected baby swaps, disability grant applications, etc. Therefore, exposure to the analysis, result interpretation and reporting of kinship testing should be included in the training for scientists in genetics:

- *Paternity and/or kinship testing of family trios/relatives using STR analysis.
- *Statistical calculations for inclusion/exclusion of relationship (probability and likelihood ratios).

3.6 Basic Bioinformatics and in-silico Analysis

Bioinformatic skills gained in the research setting are mainly dictated by the requirements of the specific project and may be quite different from those used for diagnostic applications. Therefore, internship training should ensure that the scientist is capable of:

- Designing primers and optimising PCR
- Accessing and using the content of population and variation/mutation databases such as: Ensembl; gnomAD, NCBI, Decipher, Database of Genomic variants (DGV), Human Genetic Mutation Database (HGMD), Leiden Open Variation Database LOVDs, STRbase etc.
- Using analysis software for:
  - Fragment analysis e.g., GeneMapper, PeakScanner or similar.
  - Sanger sequencing (visualisation and alignment): BioEdit or similar, NCBI Blast, Mutation Surveyor or similar.
  - *NGS output files: Integrated Genome Viewer (IGV), Ion Reporter etc.
  - *DNA microarray: Agilent CytoGenomics, Affymetrix Chromosome Analysis Suite (ChAS) or similar.

- *Kinship analysis (e.g., Converge, GeneMarker etc.).

- Using software aiding in variant nomenclature and interpretation: Mutalyser, Variant Effect Predictor (VEP), Mutation Taster, various other in-silico tools e.g., SIFT, Polyphen, CADD scoring, missense tolerance ratios, Human Splice Finder (HSF) etc.

*** Exposure to these methods should be mandatory, though full technical competency may not be required as part of the internship, depending on the individual facility and training programme. Exposure my involve observation or partial competency (training to perform certain aspects of the process).**

4 RESULT ANALYSIS AND INTERPRETATION

At the end of the training period, an intern should be capable of independent analysis of raw test data using the appropriate tools and methods. He/she should be able to interpret test results based on the genetic mechanism of the disorder tested, the specific clinical and familial context of the individual, as well as the informativity and limitations of the assay employed.

4.1 Independent analysis of raw data outputs obtained through testing with the techniques listed in Section 3, for quality assessment, visualisation and identification of:

- Chromosomal numerical and structural aberrations (microscopy)
- PCR fragments (sizing and semi/quantitation, where relevant (use of software))
- Genomic CNVs (use of software)
- DNA sequence variants (cycle sequencing)
- DNA variant detection (NGS: variant filtering and prioritisation, visual scrutiny on IGV).

4.2 Variant nomenclature

- Correct description of sequence alterations according to the Human Genome Variation Society (HGVS)(1).
- Annotation of copy number and chromosomal aberrations using the International System for Human Cytogenetic Nomenclature (ISCN)(2).

4.3 Variant Interpretation

Understanding and application of the ACMG guidelines for sequence and copy number variant interpretation(3,4).

5 REPORTING OF GENETIC TEST RESULTS

Training should incorporate skills related to writing informative, clear test reports, with the appropriate headings and content, in keeping with international and local guidelines/recommendations (example: Claustres et al. 2014(5)), for each of the main test request categories:

- Diagnostic
- Carrier
- Prenatal
- Predictive
- Paternity/kinship

6 LABORATORY ACCREDITATION AND MANAGEMENT

Internship training should include involvement in setting up and maintaining quality management systems (QMS):

- Understanding of SANAS accreditation and the ISO15189 and/or 17025 standards including:
  - Internal and external quality assurance (IQA and EQA: Continuous Method Verifications, IPT schemes, EQA Schemes)
  - Sample acceptance/rejection criteria
  - Test reporting and turn-around-times (TAT)
  - Stock Management

- Equipment maintenance
- Internal test validation/verification (addressed in Section 8)
- Performing a vertical audit
- Raising and closing non-conforming events (NCs)
- Writing standard operating procedures (SOPs)
- Laboratory Health and Safety
- Staff competencies, qualifications and scope of practice
- Confidentiality and ethical conduct in the laboratory

7 TROUBLE-SHOOTING AND INVESTIGATION OF ERRONEOUS RESULTS/FAILED ASSAYS

The intern should demonstrate the ability to analyse, investigate and trouble-shoot erroneous or unusual test results, and to propose corrective measures or confirmatory tests. This may overlap with handling a non-conforming event (Section 8). The errors or inaccuracies may stem from:

- Incorrect/inconsistent EQA/IQA results
- Failed runs and/or controls
- Poor quality of outputs (such as Sanger sequencing results with high background)
- Human induced errors vs method/systems errors.

8 RESEARCH AND TRANSLATION

Whilst research forms part of the National Curriculum (CMS 01 MBS), most interns have previous experience of research gained through their Honours, Masters or PhD degrees. This, depending on the project and discipline, is usually incorporated into the Portfolio of Evidence, to show experience/exposures to aspects such as writing a research or grant proposal, obtaining ethical approval, etc.

However, internship training in Human Genetics, as a dynamic discipline with a high rate of translatable research and new test/method implementation, should provide insights into the complexities of research translation into clinical laboratory practice. This understanding may be conveyed through designing a new test validation or a translational mini-project, with special attention given to:

- Analytical and clinical validity
- Clinical and personal utility
- Ethical considerations and approval

9 INTERNAL VALIDATION AND VERIFICATION OF NEW TESTS

The validation and verification of laboratory methods and procedures before implementation in the diagnostic laboratory is essential for providing a safe and reliable service to clinicians and patients. Interns should demonstrate understanding of the requirements and processes involved in the validation and verification of new assays, commercial kits and platforms:

- Validation vs verification
- Validation of commercial kits vs in-house developed assays (“home-brews”)
- Validation of quantitative vs qualitative assays
- Validation and verification process planning and design: compliance with in-house and international standards (ISO, CLSI), acceptance criteria etc.
- Validation terminology and measurements, such as sensitivity, specificity, robustness, precision, accuracy and limit of detection
- Writing of validation plans and reports.

10 ASSESSMENTS: CRITERIA AND ASSESSMENT METHODS

Evidence-based continuous assessments must be performed over the full internship period, covering all components of the training programme. Evidence of assessments should be included in the Portfolio of Evidence, as stipulated in the HPCSA guidelines. The types of continuous assessment are at the discretion of the training facility, but may include the following:

- Exams/tests (essays, multiple choice, short answer questions, open book, oral etc.)
- Oral and/or poster presentations (journal clubs, seminars, conferences)
- Patient laboratory reports
- SOPs
- Validation reports
- Simulated or actual non-conforming events: report, root cause analysis, corrective action.

Relevant HPCSA documentation:

CMS A	POLICY REGARDING THE TRAINING OF INTERN MEDICAL SCIENTISTS
CMS 01 MBS	THE NATIONAL CURRICULUM: MEDICAL BIOLOGICAL SCIENTISTS
CMS 02 MBS	GUIDELINE FOR SUBMISSION AND ASSESSMENT OF PORTFOLIO OF EVIDENCE: MEDICAL BIOLOGICAL SCIENTISTS

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