Guideline for Establishing a Private Genetic Laboratory

16 February 2023

Document Title	Guideline For Establishing A Private Genetic Laboratory
Document Type	Guideline
Directorate/Institution	Directorate General of Royal Hospital – National Genetic Centre Directorate General Of Private Health Establishment
Targeted Group	All Licensed Private Health Establishments
Document Author	Dr. Kamla Khalfan Al -Salmani Dr. Musallam Said Al- Araimi
Designation	Head of Genetic Laboratory Department Head Of Genetic Clinics & Counselling Department
Document Reviewer	Dr Munira Al Hashmi
Designation	Head Of Quality Control And Patient Safety
Release Date	March 2023
Review Frequency	Three Years

Validated By		**Approved By**	
Name	**Dr Munira Al Hashmi**	**Name**	**Dr Muhanna Al Muslahi**
Designation	**Head of Quality Control & Paitents Safety Department**	**Designation**	**Director General of Private Health Establishment**
Signature		**Signature**	
Date	**March 2023**	**Date**	**March 2023**

Table of Contents

Acronyms

aCGH	**Array-Based Comparative Genomic Hybridization**
DNA	**Deoxyribonucleic Acid**
DNAse	**Deoxyribonuclease**
FISH	**Fluorescence In Situ Hybridization**
GLP	**Good Laboratory Practice**
LIMS	**Laboratory Information Management System**
MD	**Doctor of Medicine**
MoH	**Ministry Of Health**
NGC	**National Genetic Centre**
PCR	**Polymerase Chain Reaction**
PhD	**Doctor of Philosophy**
PPE	**Personal Protective Equipment**
QC	**quality control**
RNA	**Ribonucleic Acid**
RNAse	**Ribonucleases**
SOPs	**Standard Operating Protocols**

Acknowledgments

Directorate General of Private Health Establishment (DGPHE) appreciates and acknowledges the effort of the team who participated in writing this document:

- Dr. Sami Sulaiman Al-Farsi (Director General of DGRH).
- Dr. Sulayma Nasser Al-Lamki (Director of the National Genetic Centre).
- Dr.Nishath Hamza (Senior Lab. Specialest-National Genetic Centre).

Definitions

Genetics: is the study of heredity, particularly the mechanisms of transmission through the different generations, each variation of inherited characteristics among similar or related families. This includes clinical genetics, cytogenetic and molecular genetics.

Cytogenetic: is a branch of biology focused on the study of chromosomes and their inheritance, especially as applied to medical genetics. Chromosomes are microscopic structures containing DNA that reside within the nucleus of a cell. During cell division, these structures become condensed and are visible with a microscope. Special staining techniques can be used to assess the number and structure of a person's chromosomes as part of diagnostic testing. The number and/or structure of chromosomes is known to be altered in certain genetic diseases.

Molecular genetics: it is a sub-fields are genomics(i.e. the study of all the nucleotide sequences, including structural genes, regulatory sequences, and non-coding DNA segments, in the chromosomes) where the study of heredity and variation at the molecular level. It is particularly focused in the function and regulations of genetic information's within the DNA, RNA, and protein levels.

Equipment's: The machines used for specific lab work.

Reagents: Solution used for specific protocols in the laboratory.

Patient Confidentiality: The security of patient information and results.

National Genetic Center: The Genetic Health Center of the Ministry of Health

Chapter One

Introduction

The technological advancements in the field of genomics have radically enhanced how genetic diseases are diagnosed, treated, managed and prevented. It has also proven to be beneficial in guiding prompt intervention for treating diseases when detected early in infancy through newborn screening. Aside from providing the precise etiology of underlying genetic disorders, genetic testing is vital for understanding the prevalence and healthcare burden from genetic diseases in Oman. Genetic tests are often very expensive and are generally carried out once in an individual's lifetime. Hence, it is important to ascertain high standards of quality in all aspects of medical genetic service provision.

Until a few years ago, medical genetic tests were provided only within governmental health institutions such as the National Genetic Centre (NGC) and Sultan Qaboos University Hospital. However, due to increasing demand for genetic tests in Oman and to balance the testing demand on governmental institutions, Ministry of Health (MoH) decided to permit the provision of medical genetic testing service by the Private Medical Sector for genetic tests. This document seeks to propose standards and guidelines for inspecting and licensing candidate laboratories within the private medical sector who wish to start offering genetic testing for the purpose of medical management and counselling.

Chapter Two

Private Medical Genetic Laboratory Evaluation

The MOH should nominate healthcare professionals with expertise in medical genetics from the NGC for inspection of candidate private laboratories. The nominated staff will inspect candidate labs in accordance with the standards and guidelines issued in this document. On passing MOH inspections successfully, the private labs should be mandated to subscribe to external quality assessment programs administered by national or international bodies to monitor accuracy and reporting standards of their genetic tests. Private genetic labs should be subject to periodic inspections by the MOH to ensure the requisite standards are met. In the event of any egregious lapses in testing accuracy or quality, the laboratory should be notified immediately and a report should be forwarded to the Technical and Administrative Violation Committee of the DGPHE.

Design and Requirements for A Genetics Laboratory

Genetic laboratories are generally divided into two sections; Cytogenetic and Molecular Genetics. Each section has a separate set of requirements for optimal design parameters, operational workflows and regulatory considerations, all of which are discussed below. At the same time, there are several standard requirements and practices which are common to both sections and critical for genetic laboratories to implement. Specific requirements for each section are discussed below.

Cytogenetic Section

Cytogenetics is a branch of biology focused on the study of chromosomes and their inheritance, especially as applied to medical genetics. Chromosomes are microscopic structures containing DNA that reside within the nucleus of a cell. During cell division, these structures become condensed and are visible using a microscope.

Special staining techniques are used to assess the number and structure of a person's chromosomes. The number and/or structure of chromosomes are known to be altered in certain genetic disorders.

The study of chromosomes using traditional cytogenetic techniques requires cells that are actively dividing. Chromosomes are individually distinguishable under the light microscope only during cell division and best examined during the metaphase stage of a cell's life cycle. Metaphase chromosomes are obtained from specimens that contain spontaneously dividing cells or from samples that are cultured and chemically induced to divide in vitro. These specimens include peripheral blood lymphocytes, bone

marrow, amniotic fluid and chorionic villi, etc. The specific choice of specimen and testing protocols used for cytogenetic analysis depend on clinical indications and whether the testing is to be performed on prenatal or postnatal samples.

Design of the Cytogenetic Laboratory

The cytogenetic section should have separate spaces for culturing, harvesting, slide preparation & banding, Fluorescence in situ hybridization (FISH), Array-based Comparative Genomic Hybridization (aCGH), image acquisition and karyotyping/data analysis. Cytogenetic sample processing is very sensitive as it incorporates induced cell culture protocols and requires a highly sterile workspace.

Accordingly, the following points should be considered while designing a cytogenetic laboratory:

1. Physical barriers to prevent contamination

2. The spatial separation of work areas for sample reception, cell culture, slide preparation & banding as well as data/image acquisition and analysis

3. The different types of spatial separation may include:

(a) Separate rooms (b) Class II biological safety cabinet (c) Dedicated bench space for each function

4. Reagent preparation should be carried out under sterile conditions within appropriate safety cabinets to avoid contamination and to ensure staff safety

5. Unidirectional spatial flow of sample processing (for eg: harvested samples/slides must not be brought to cell culture room)

6. Laboratory design must take into consideration:

a) Temperature and humidity requirements

b) Exhaust ventilation

c) Water quality

d) Electric outlet

e) Back-up power system

f) Eyewash

g) Ergonomic assessment

Molecular Genetics Laboratory

The molecular genetics section handles tests which identify disease etiology at theDeoxyribonucleic Acid(DNA), Ribonucleic Acid (RNA) or epigenetic level of the genome. Molecular genetic testing is used for the diagnosis of a particular inherited disease or condition, as well as predictive testing to assess risk for a clinical condition prior to presentation of disease symptoms. Molecular genetic tests can also detect heritable and non-inherited DNA variants that predict the response profile of an individual to a drug or course of therapy. These tests have significant implications for patient prognosis, counselling, treatment and family planning.

Molecular genetic tests require particular care since these tests may also be performed on asymptomatic individuals and results may have relevance to important lifetime decisions both for the individuals being tested, for their children and their extended families.

Design of Molecular Genetics Laboratory

One of the most important points that should be taken into consideration while designing a molecular pathology laboratory is to prevent contamination. Polymerase chain reaction (PCR)-based methods which form the foundation of all molecular genetic tests, are especially susceptible to contamination. Amplifying specimen DNA using the PCR method to enhance test accuracy provides an important diagnostic advantage; but this ability also leads to false results by increasing risk of contamination. False positive results due to PCR contamination often account for a large proportion of errors in the analytic phase of molecular genetic testing workflows. This mainly occur due to contamination from sample to sample, transport of amplified PCR products to pre-analytic spaces, cross-contamination of commonly-used reagents, etc. Hence, there should be adequate separation of the spaces allocated for preparation of reagents, sample preparation, PCR step and post-PCR steps within an ideal molecular pathology laboratory

Accordingly, the following points should be considered while designing a molecular genetic laboratory:

1. The laboratory should place mechanical barriers in the form of rooms, safety cabinets, etc; to prevent contamination

2. The material and spatial separation of pre-PCR and post-PCR work areas

3. Each area should be equipped with adequate technology required for specific processes.

4. Unidirectional flow of material transport through the steps of preparation of reagents, sample preparation, PCR step and post-PCR within every testing workflow

5. Only molecular biology grade reagents and water should be used

6. Only filter-pipette tips may be used for transfer of reagents and sample

7. Air pressure and exhaust ventilation must be adequately maintained to prevent air-borne contamination

8. Temperature and humidity conditions must be adequately maintained to prevent mould or fungal growth

General requirements for medical genetics laboratory

Material and spatial requirements:

1. Ensure that equipment in the laboratory perform optimally at all times through regular monitoring and maintenance
2. Use of an integrated Laboratory Information Management System (LIMS) which enables seamless and accurate record of patient, specimen and testing information
3. Adequate, safe and secure specimen storage facilities
4. Adequate data processing and secure data storage facilities to ensure data confidentiality and leverage in the event of unforeseen calamities, legal challenges, etc.
5. Mechanical barriers must be put in place to prevent contamination
6. The spatial separation of pre-analytic, analytic and post-analytic work spaces
7. Unidirectional flow of material and staff movement
8. Each work area must be adequately supplied with
    a) Refrigerator/freezer (manual defrost)
    b) Pipettes, filtered tips, tubes, and racks
    c) Centrifuge, timers, vortex
    d) Lab coat (color-coded), disposable gloves, safety glasses, and otherpersonal protective equipment(PPE)
    e) Cleaning supplies
    f) Office supplies
9. Adequate equipment (eg: autoclave, UV hood, etc) and/or reagents (eg:deoxyribonucleaseDNAse/ribonucleases RNAse reagents) for sterilization and/or decontamination procedures

10. Each laboratory should be ventilated separately and the air pressure must be adjusted separately. At positive pressure, the air pressure inside the room is higher than the air pressure outside the room, preventing the transport of unwanted substances from outside. Negative pressure, on the other hand, allows air to enter into the room and prevents the migration of the air to the surrounding rooms/ laboratories. The doors must be kept closed to maintain the negative pressure. Air pressure must be maintained as follows to avoid sample contamination:
    a) Reagent Prep – Positive
    b) Sample Prep – Negative
    c) Post amplification – Negative

Chapter Three

Staff and Personnel Requirements

1. Suitably qualified, trained and competency-assessed staff to ensure that service quality is not compromised
2. A clear distinction must be made between low, medium and high-complexity tasks within the laboratory to ensure that staff qualifications are consummate with day-to-day operational responsibilities within medical genetic laboratories. For example, only individuals with a Doctor of Medicine (MD) (or equivalent medical training in genetics) and/or a Doctor of Philosophy (PhD) in genetics or molecular biology (or similar field) may review and authorize the release of genetic test reports.
3. Adequate number of qualified staff must be available to carry out specific tasks
4. A clear chain of workflow and report authorization (eg. technician, supervisor, director, consultant, etc) must be stipulated within the laboratory operational procedures to ensure the accuracy of results with prompt and proficient performance

Quality Assessment

Quality management and monitoring are essential in all types of medical genetic evaluation procedures (i.e., pre-analytical, analytical and post-analytical). Accordingly, the following points should be considered:

1. Medical genetic tests must be validated using known controls and validation reports must be updated as and when required.
2. Monitoring for errors affecting the accuracy of the results should be conducted regularly under the supervision of a senior supervisor/scientist using well-characterized quality control (QC) samples
3. Continuous enrolment in periodic external assessment programs for specific tests to prevent erroneous reports and provide the confidence that quality requirements are fulfilled
4. Document all equipment maintenance and calibration
5. Document validation procedures and reports for all tests and equipment
6. Document all staff training and competency assessments
7. Seeking accreditation by a national or international organization (eg: ISO, CAP, etc) is highly recommended
8. Regular monitoring of turn-around time and test result statistics is highly recommended

Good Laboratory Practice (GLP)

Proper laboratory design and competent staffing must also be supported by good laboratory practices such as those discussed below:

1. Appropriate specimen handling, identifying and tracking procedures must be implemented

2. Ensure that each work-space contains the equipment and manuals with Standard Operating Protocols (SOPs) necessary to perform tasks designated for that specific site

3. Use positive displacement pipettes and disposable filtered pipette tips

4. Reagents used for amplification reactions should not be exposed to other work areas

5. Specimens for testing should not be exposed to post-amplification work areas

6. Minimize aerosolization while opening tubes to prevent sample contamination through the air

7. Use of sterilized single-use plastic ware

8. Use of clean room sticky floor mats

9. Ensure adequate decontamination and/or sterilization of workspaces and equipment

10. Use of nuclease-free or autoclaved water

11. Label all laboratory-prepared reagents with name of reagent and date of preparation

12. Use batched and labeled aliquots of reagents that are commonly used by different staff

13. Differentiate disposal of hazardous and non-hazardous waste

14. Ensure cleanliness of laboratory and appropriately label waste disposal

15. Implement an internal secure document management system

16. Ensure all worklists and worksheets are documented and stored securely

17. Minimize risk of sample carry-over on clothing, hair, and skin by using:

    a) Hairnet

b) Dedicated safety glasses

c) Disposable lab coat/gown, color-coded preferred

d) Gloves need to change periodically

e) Shoe covers

Patient Confidentiality

1. Patient genetic results are confidential and may be given to the patient or to the patient's guardian if the patient is below 18 years of age.
2. Exceptions to this policy have to be approved by the Laboratory Director
3. All paper records such as request forms, work forms, registers, related to patient testing must be maintained in designated locked cabinets only accessible by authorized members of staff.
4. All laboratory data and data storage units (paper, hardware or electronic) should be preserved from physical damage or deterioration.
5. Request for verbal reporting of results over phone or in-person must only be accepted from requesting doctor or authorized personnel of the referral medical center; but never to patients or their relatives.
6. Extreme care must be taken when using recycled paper so that patient information is not discernible.

Effective Contingency Planning

A contingency plan (also known as a Continuity of Operation Plan) is a strategy formulated to ensure uninterrupted organizational operation in the event of unfavorable situations, such as environmental disasters, disease epidemics, fire accidents, etc. A contingency plan is put in place to reduce operational risk, fasten disaster recovery, and to minimize cumulative loss.

A contingency plan for genetic laboratories must also include a strategy to accommodate external requests for testing or material/equipment/staff relocation in the event of national emergencies (for eg. the COVID-19 pandemic).

Chapter Four

Document History and Version Control

Version	Description	Review Date
1	**Initial Release**	**February 2023**
2		
3		
4		

References:

1) National Genetic center for Molecular and cytogenetic Guidelines and SOPs.
2) Franceschini N, Frick A, Kopp JB. Genetic Testing in Clinical Settings. Am J Kidney Dis. 2018 Oct;72(4):569-581. doi: 10.1053/j.ajkd.2018.02.351. Epub 2018 Apr 11. PMID: 29655499; PMCID: PMC6153053.
3) McPherson E. Genetic diagnosis and testing in clinical practice. Clin Med Res. 2006 Jun;4(2):123-9. doi: 10.3121/cmr.4.2.123. PMID: 16809405; PMCID: PMC1483893.

Annex one: **MoH/DGPHE/GUD/004/Vers.02**

Private Medical Genetic laboratory establishment inspection Request

A medical genetic laboratory is where genetic studies of individuals are carried out for diagnosis, management and/or genetic counseling with regards to a medical condition.

By applying to provide this service you take full responsibility for acceptance of appropriate test requests, sample processing and storage, reporting accuracy, patient confidentiality and referral to genetic counseling & management of the patient.

I/We are applying to establish genetic laboratory services including:

Cytogenetic Genetic laboratory	**Yes**	**No**
Molecular Genetic laboratory	**Yes**	**No**

1) To process:

Peripheral blood for postnatal studies	**Yes**	**No**
Bone marrow samples for onco-Heamatology diagnosis and management	**Yes**	**No**
Prenatal Samples for diagnosis and management	**Yes**	**No**
Tissue samples for diagnosis and monitoring	**Yes**	**No**

Checklist for provision of Cytogenetic services:

1	**Culture of patient samples to obtain metaphases used for karyotype of patient chromosomes**	**Yes**	**No**
2	**Apply specific florescent probes (Deletion, Break Apart & Fusion) probes to detect specific rearrangements using inerphases/metaphases of the patient sample**	**Yes**	**No**
3	**Extract DNA to apply for QF PCR or Real time PCR or micro array (CGH) to check for copy number variations (trisomies, deletion or duplications).**	**Yes**	**No**
4	**Genetic result reporting**	**Yes**	**No**
5	**Suitably qualified personnel for technical and scientific duties**	**Yes**	**No**

Checklist for provision of Molecular genetics services:

1	**DNA/RNA extraction manually**	**Yes**	**No**
2	**DNA/RNA extraction using automated machines**	**Yes**	**No**
3	**Molecular Hemoglobinopathy testing**	**Yes**	**No**
4	**HPLC (High performance liquid chromatography**		
5	**Flow-cytometer**	**Yes**	**No**
6	**Real time PCR (Polymerase chain reaction)**	**Yes**	**No**
7	**PCR (Polymerase chain reaction)**	**Yes**	**No**
8	**QF-PCR (Quantitative Fluorescence PCR)**	**Yes**	**No**
9	**MLPA (Multiplex ligation-dependent probe amplification**	**Yes**	**No**
10	**CE-IVD or FDA-IVD certified analysis**		
9	**Bio Genetic analyzers**	**Yes**	**No**
10	**Next Generation sequencing.**	**Yes**	**No**
11	**Gene expert**	**Yes**	**No**
12	**Genomic Data analysis**	**Yes**	**No**
13	**Sanger sequencing**	**Yes**	**No**
14	**Genetic result reporting**	**Yes**	**No**
15	**Suitably qualified personnel for technical and scientific duties**	**Yes**	**No**

Checklist for sample collection:

1	**Test request internally within the Center/Hospital.**	**Yes**	**No**
2	**Sample collection done within the lab/Center/hospital**	**Yes**	**No**
3	**Sample received from referring hospital in Oman**	**Yes**	**No**
4	**Samples will be received from outside Oman**	**Yes**	**No**
5	**Ethical approval for receiving samples from outside Oman is available**	**Yes**	**No**

Omani Patient samples will be processed locally within the country for diagnostic purpose only no research is allowed and no samples to be sent outside Oman without consent form and ethical approval. Omani Genetic data and DNA samples are not allowed to transfer outside Oman.

I have FULLY read and understood the contents of this application fully and I well make sure all required CONDITIONS are available before inspection.

Name …….. Signature …….. Date……

Stamp:

Annex Two:

Private Genetic Laboratory Inspection Report

Institution name	Nature of institution	Scope of work	Location

Inspection visiting team:

Name _____ **Signature** _____

Name _____ **Signature** _____

Name _____ **Signature** _____

Name _____ **Signature** _____

Name _____ **Signature** _____

Name _____ **Signature** _____

Cytogenetic Laboratories

Total number of Rooms available	Total number of Rooms
Culturing	
Harvesting-Slide preparation and banding	
Analysis	
Florescent in-situ hybridization (FISH)	
FISH preparation	
Microarray CGH	
QF PCR for aneuploidy for pre and postnatal testing	

Cytogenetic Laboratories requirements/ Equipment's	Total number	Comments
Culturing room		
Booking system		
Safety cabinet class II or III		
Incubators		
Co2 Incubators		
Dispenser		
Fridge		
Freezers		
Centrifuges (15-25ml)		

Sharpens		
Pipettes all (20-200ul)		
First aid kit		
Working SOP		
Harvesting-Slide preparation and banding		
Fume Cabinet		
Laminar flow		
Hot plat		
Oven		
Humidifier		
Balance		
Fridge (2-8°C)		
Freezers(-20°C)		
Centrifuges (for 15-25ml tubes)		
Dispenser		
West disposal containers		
Sharpen		
Water bath		
Slide trays		
Fume cupboard		

Working Benches		
Microscope		
Autoclave		
Pipettes all (50-200ul)		
Glass washing sink		
Water distillation system		
First aid kit		
Funnel and staining Jars		
Working SOP		
FISH preparation (Dark) Room		
Water bath		
Thermobrite		
hotplate		
microscope		
Incubator		
Micro-centrifuge		
Fridge (2-8°C)		
Freezers(-20°C)		
First aid kit		
Sharpen		

Slide trays		
Fume cupboard		
Working Benches		
Working SOP		
Pipettes all (20-200ul)		
Analysis Room		
Microscopes with Camera attached to them		
Computer softer wear like Isis and Ikaros or similar		
Working bench		
Reporting system Like ISCN and guidelines		
Microarray CGH		
Fridge (2-8°C)		
Freezers(-20°C)		
Centrifuge		
Refergrated Centrifuge		
vortex		
Pipettes all (20ul,200ul, 1000ul)		
Shaker (Foam)		
Thermo-cycler		
1.5ml centrifuge		

Oven		
Fluidexs		
Scanner		
Mini spin		
Analysis software eg Chas software		
Analysis Guideline		
Working SOP		
Working bench		
QF PCR (aneuploidy testing)		
Centrifuge for 25 ml		
Centrifuge for 1.5 ml		
Centrifuge for 0.2 ml		
Centrifuge for 96 well plate		
Thermo-cycler		
Vortex		
Genetic Bio-analyser		
Heat block (56°C) or Oven		
Nano-drop		
Safety Cabinet III		
Pipettes all (10ul,200ul, 1000ul)		

Molecular Genetics Laboratories

Total number of Rooms available	Total number of Rooms
Auto/manual DNA extraction room	
Auto/manual RNA extraction room	
Pre PCR Room	
Post PCR Room	
DNA Sequencing room	
PCR and Real-time PCR	

Molecular genetics Laboratories requirements/ Equipment's	Total number	Comments
Number of equipment depends on the work load of the lab		
Centrifuge for 1.5 ml and 0.2ml		
Centrifuge for 96 well plate		
Mini Centrifuge		
Thermo-cyclers		
Vortex		
Genetic Bio-analyser		
Heat block (56°C) or Oven		
Nano-drop		
Safety Cabinet III		

Pipettes all (1ul - 500ul)		
Pipettes all (1ul-200ul) (manual, multi-channel & electronic)		
Shaker		
Complete Electrophoresis unit or similar (caliper or lonza)		
incubator		
microwave		
Laminar flow hood		
PCR stations (for primer and library preparations		
DNA Extraction machine if Auto		
RNA Extraction machine if Auto		
Oven		
Fridge (2-8°C)		
Freezers(-20°C)		
Balance		
Next Generation Sequencing platform		

Final Report of the visit number

Genetic Laboratory approved ☐ **Genetic Laboratory not approved** ☐

Leading committee signature ..... Stamp