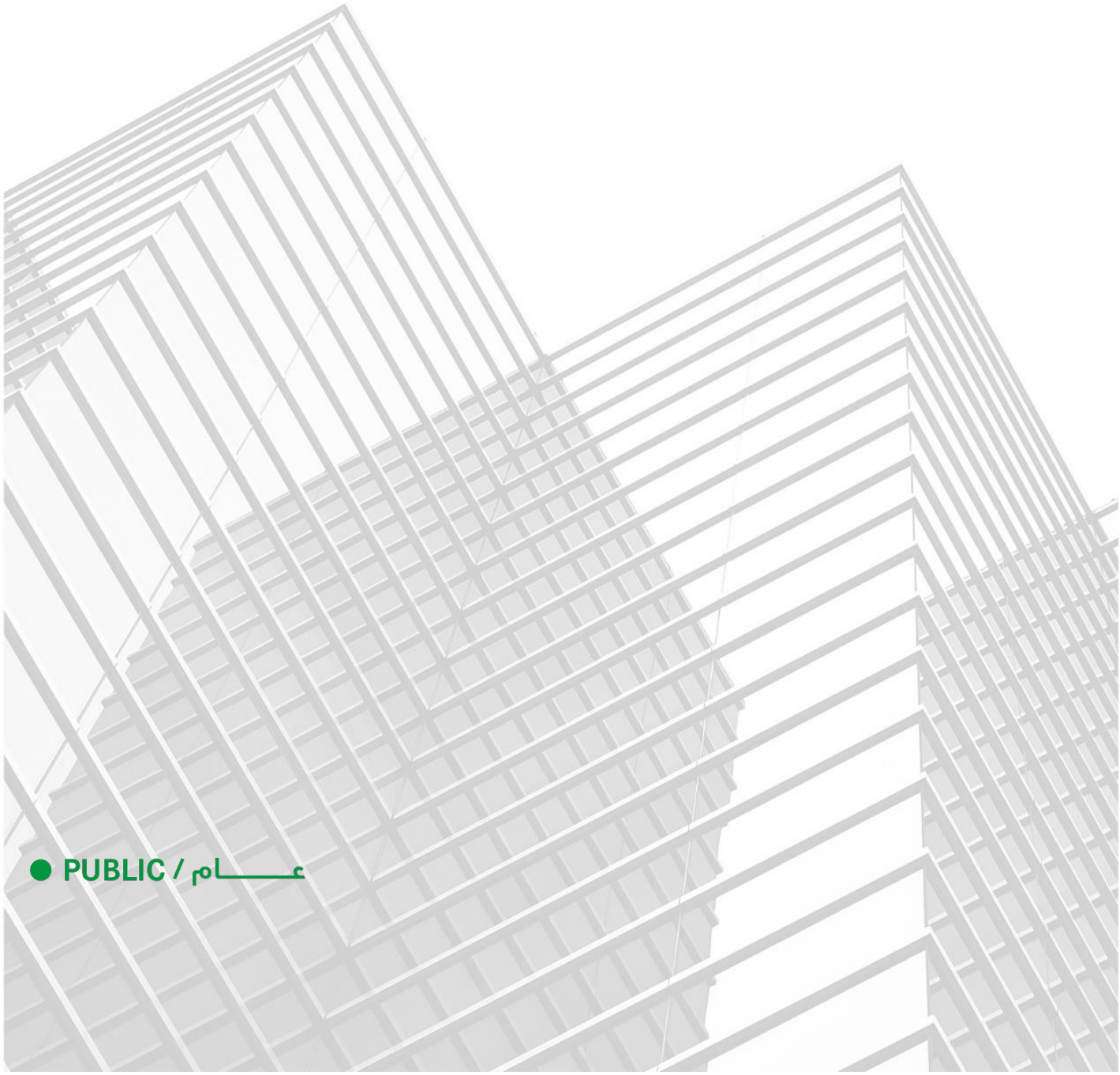
دائـــــرة الـصـــحـــة
DEPARTMENT OF HEALTH

Guidelines for Genetic Testing in rare diseases: Benefits, Diagnostics and Ethical Considerations



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Contents

1. Guideline Purpose and Brief

This clinical guideline is intended to provide healthcare professionals with a comprehensive framework for the diagnosis and management of rare diseases through genetic testing. The goal is to enable prompt and accurate diagnosis and offer tailored, precision-medicine-based treatment options in accordance with UAE federal law. The guideline emphasizes the importance of genetic and genomic testing in rare diseases and outlines the processes, including obtaining consent, managing samples, and addressing challenges when parental samples are unavailable.

This guideline aims to establish clear recommendations for rare disease diagnosis and management. Recommendations are based on international guidelines that are referenced at the end, and on the basis of the opinion and consensus of the convened subject matter experts.

The guidelines are designed to offer recommendations and guidance for healthcare professionals licensed by DoH in their practice areas within the health sector of Abu Dhabi. These guidelines should not be interpreted as comprehensive or exclusive of other valid approaches or methods. They do not guarantee specific outcomes. Treatment decisions for individual patients shall be made based on the independent judgment of healthcare providers, considering each patient's unique circumstances.

2. Definitions and Abbreviations

No.	Term / Abbreviation	Definition
2.1	Cascade Testing	Cascade screening is a strategy that systematically tests relatives of a person diagnosed with a genetic condition, identifying those at risk and enabling early intervention.
2.2	Chromosomes	Bundles of tightly coiled DNA located in the nucleus of almost every cell in the human body, and carry genes that transmit Genetic Data
2.3	Clinical geneticists	Clinical geneticists are health care professionals who specialize in diagnosis and managing patients and families with or at risk of a genetic condition. They must meet the qualifications outlined by the Department of Health (DoH) in the Professional Qualification Requirements (PQR).
2.4	CNVs	Copy Number Variations
2.5	Duo Testing	Testing two related individuals, such as a parent and child
2.6	Common Aneuploidy Testing	This screens for abnormal numbers of chromosomes. It is often applied in prenatal testing to detect conditions like Down syndrome (Trisomy 21). Copy Number Variations
2.7	DNA (deoxyribonucleic acid)	DNA (deoxyribonucleic acid) contains the information for making and maintaining all living things, including people
2.8	DNA Repair Testing	This analyzes genes involved in DNA repair mechanisms to detect inherited mutations that may increase cancer risk.
2.9	EGP	Emirati Genome Program

2.10	FISH (Fluorescence in Situ Hybridization)	FISH uses fluorescent probes to detect specific DNA sequences on chromosomes, identifying structural rearrangements, deletions, or duplications.
2.11	GDPR	General Data Protection Regulation
2.12	Genes	Basic unit for the transmission of genetic traits from parents to children. It consists of a DNA Sequence that occupies a specific position in the chromosome.
2.13	Genome	All the genetic material in a living organism, including (genes) that contain all the biological data it needs to build and sustain another organism similar to it and distinct from its type. The human Genetic balance is composed of (46) compact molecules of DNA called Chromosomes, in addition to mitochondrial genes.
2.14	Genetic condition	A condition or disease caused by an abnormality in a gene or chromosome
2.15	Genetic counselling	A health service that provides data and support to people with or at risk of genetic diseases
2.16	HCP	Health Care Professional
2.17	Hereditary condition	A condition that is inherited or passed down through families.
2.18	HIPAA	Health Insurance Portability and Accountability Act
2.19	Karyotype	Karyotyping visualizes whole chromosomes under a microscope to identify large genetic changes, such as extra or missing chromosomes.
2.20	Large, Medium, Small Panels	These panels analyze selected sets of genes, chosen based on their known association with certain diseases or traits. "Large" panels cover more genes, while "small" panels are more targeted.
2.21	Methylation Testing	Methylation tests analyze epigenetic changes in DNA that can turn genes on or off, providing insight into conditions related to gene expression without changing the DNA sequence.
2.22	Microarray	A microarray is a type of genetic test methodology that checks many DNA segments simultaneously for specific genetic variants to assess the quantity of genetic material and can detect structural copy number variants such as micro deletion or micro duplications as well as inform regarding presence of areas of loss of heterozygosity and presence of unilateral disomy and mosaicsm. It's commonly used for large-scale screening and detecting copy number changes.
2.23	Microsatellite Instability (MSI) Testing	MSI testing looks for instability in microsatellite regions, which is common in certain cancers and can indicate DNA mismatch repair deficiency.
2.24	MLPA (Multiplex Ligation-dependent Probe Amplification)	This technique assesses copy number variations (CNVs) in genes, helping detect duplications or deletions. It is often used in cancer and genetic disorder testing.
2.25	NIPD (Non-Invasive Prenatal Diagnosis)	Similar to NIPT, NIPD is used to diagnose specific genetic conditions in the fetus by analyzing fetal DNA from a maternal blood sample.
2.26	NIPT (Non-Invasive Prenatal Testing):	NIPT screens fetal DNA in maternal blood to detect chromosomal abnormalities like Down syndrome, reducing the need for invasive testing.
2.27	Optimal testing	Optimal testing in genetic diagnostics refers to the ideal set of tests that should be conducted to confirm a diagnosis based on the clinical indication.

2.28	PLWRD	People living with rare disease
2.29	Predictive Testing	A genetic test for a condition that may or will occur later in life. This testing is available to healthy individuals who are pre-symptomatic (no signs and symptoms of condition) but who are at risk of the condition due to their family history.
2.30	Rare Diseases	A rare disease is a medical condition characterized by a specific pattern of clinical signs, symptoms, and findings that affect fewer than or equal to 65 in 100000 individuals.
2.31	Single Cell RNA sequencing	Single-cell RNA sequencing (scRNA-seq) is a cutting-edge technique that allows the study of gene expression at the resolution of individual cells. It involves isolating RNA from individual cells, converting it to complementary DNA (cDNA), and sequencing to understand cellular function, heterogeneity, and dynamic processes within tissues or organisms.
2.32	Single Gene Sequencing	This test sequences only one specific gene, usually when there's a strong suspicion of a mutation in that particular gene based on clinical signs and symptoms.
2.33	Singleton Testing	Testing a single individual
2.34	STR Testing (Short Tandem Repeat Testing)	STR testing examines repeating sequences in DNA. It's often used for forensic analysis, genetic fingerprinting, and detecting genetic disorders with repeat expansions.
2.35	Targeted Variant Testing	This focuses on specific, known variants (mutations) in the DNA rather than a full gene or the whole genome. It is often used when a particular mutation is suspected and known.
2.36	Trio Testing	Testing three individuals, usually both parents and the child.
2.37	UAEGDA	UAE Genetic Diseases Association
2.38	Uniparental Disomy (UPD) Testing	UPD testing checks if both copies of a chromosome come from one parent, which can affect gene function and lead to genetic disorders.
2.39	VUS	Variants of Unknown Significance
2.40	WES (Whole Exome Sequencing)	WES (Whole Exome Sequencing): WES targets only the exons (coding regions) of genes, which make up about 1-2% of the genome but contain around 85% of known disease-causing mutations. It's used to detect variants in the genes responsible for producing proteins.
2.41	WGS (Whole Genome Sequencing)	This method sequences the entire DNA of an individual, covering all genes and non-coding regions. It's comprehensive and helps identify almost any variant across the genome
2.42	X-Inactivation Testing	This evaluates the process in females where one of the two X chromosomes is randomly silenced, which can impact the expression of X-linked genes.

3. Guideline Content

3.1. Rare diseases

3.1.1. Rare diseases encompass a wide range of conditions, including rare genetic disorders, rare cancers, rare infectious diseases, rare poisonings, rare immune-related diseases, rare idiopathic diseases, and/or rare undetermined conditions.

3.1.2. Due to their uncommon nature, people living with rare diseases (PLWRD) face distinct and significant challenges. Often, these individuals experience prolonged diagnostic odysseys, which may involve delays or even the absence of a proper diagnosis. Misdiagnoses are frequent, leading to inappropriate treatments and potential exacerbation of the disease. Furthermore, clinical management is often inadequate, stemming from limited knowledge about rare diseases among healthcare providers.

3.1.3. The scarcity of effective treatment options is compounded by clinicians' lack of awareness of existing therapies. Additionally, research and investment in rare diseases remain insufficient, resulting in a lack of available treatments. The burden of rare diseases extends beyond the individuals affected; it impacts caregivers, families, healthcare systems, and society, necessitating greater visibility and recognition.

3.2. Indications for Genetic Testing for Rare Diseases

Genetic testing for rare diseases is crucial for diagnosis, management, and family planning. Individuals who shall be referred for rare genetic testing include:

3.2.1. Individuals with Symptoms: Those exhibiting symptoms characteristic of a rare disease or multiple rare diseases.

3.2.2. Family History: Individuals with multiple family members affected by similar symptoms, indicating a potential hereditary condition.

3.2.3. Newborn and Infant: Those showing early onset symptoms, such as seizures or congenital anomalies (congenital disorders), warranting prompt evaluation.

3.2.4. Family Planning: Prospective parents may consider testing to assess the risk of inherited conditions in future children.

3.2.5. Consanguinity: Individuals married to blood relatives may be at higher risk to have children with certain inherited conditions and could benefit from genetic testing.

3.2.6. Unconfirmed diagnosis: Standard diagnostic approaches have not been able to confirm the diagnosis.

3.3. Benefits of Genetic Testing for Rare Diseases

3.3.1. Diagnostic Yield:

Certain genetic tests, such as whole genome sequencing, can achieve a positive diagnosis rate of up to 50%. This rapid identification can expedite the diagnostic process, allowing individuals or their families to receive critical health information sooner, informing treatment decisions.

3.3.2. Enhanced Health Information:

Even if a definitive diagnosis is not achieved, genetic testing can provide valuable insights into the symptoms experienced. It can help rule out suspected genetic conditions and guide further diagnostic approaches, reducing uncertainty in the diagnostic journey.

3.3.3. Personalized Treatment:

Genetic testing can identify specific biomarkers, which can inform precision medicine strategies. This means treatments can be tailored to the individual's genetic profile, helping to predict which therapies may be most or least effective.

3.3.4. Family Planning:

Genetic testing can offer insights into potential hereditary risks for individuals with a rare genetic disease who are considering starting a family. This information can assist in making informed decisions about family planning and understanding the likelihood of passing on genetic variants that may lead to rare diseases in children.

3.4. Legal and Ethical Aspects of Genetic Testing in UAE

3.4.1. Adherence to UAE Federal Law

3.4.1.1. Genetic or genomic testing must follow local UAE regulations including DoH Genetic and Genomic Testing Standards and DoH guidelines related to genomic testing. It must also be carried out in an accredited facility. Healthcare professionals are responsible for ensuring the testing labs are certified and compliant with local and international standards.

3.4.1.2. Federal Law by Decree No. (49) of 2023 regulates the use of the human genome in the UAE, focusing on ethical practices and responsible research. The law emphasizes the importance of safeguarding individuals' rights and privacy regarding genetic data and research participation. By establishing clear guidelines for genomic research, the law aims to improve public health initiatives and support the development of personalized medical treatments for various diseases.

3.4.2. Ethical aspects of rare disease testing

3.4.2.1. Genomic testing has revolutionized healthcare by enhancing diagnostic accuracy, enabling personalized treatments, assessing disease risk, and improving preventive care strategies. However, it's essential that this testing and research respects human dignity, freedom, and human rights. Additionally, it must avoid any form of discrimination based on genetic traits.

3.4.2.2. Informed Consent: Patients or their legal guardians should be fully informed about the purpose, risks, and benefits of testing so that they can make informed decisions.

3.4.2.3. Privacy and Confidentiality: Genetic testing information is highly sensitive, and safeguarding patients' privacy is crucial to protect personal and family details.

3.4.2.4. Support for Vulnerable Patients: Patients with rare diseases are especially vulnerable and require support that includes medical care and attention to their psychological and social needs.

3.4.2.5. Societal Responsibility: Society has an ethical duty to ensure patients with rare diseases are not overlooked and receive adequate health care, treatment, and social support.

3.4.2.6. Encouraging Research: Since pharmaceutical companies may not focus on rare diseases, healthcare systems, and governments must support research and development of treatments.

3.4.3. Informed Consent

Informed consent should be unambiguous, ensuring individuals fully understand the purpose, process, risks, and benefits of genetic testing, particularly in rare disease screening and diagnosis. It guarantees that the decision to participate is freely given and voluntary. For genetic testing, the informed consent process shall:

3.4.3.1. Clearly explain the purpose of the test, including why it is needed and what rare diseases are being screened.

3.4.3.2. Provide detailed information about the process, ensuring participants understand how the test will be performed.

3.4.3.3. Communicate the potential risks and benefits, including emotional, ethical, and medical implications.

3.4.3.4. Respect cultural and linguistic differences, that the consent form is written clearly, accessible, and understandable to individuals of different educational backgrounds or languages.

3.4.3.5. Ensure individuals understand the privacy and confidentiality aspects of their genetic data, and how it will be stored, shared, processed and used.

3.4.3.6. Highlight voluntary participation, ensuring the individual knows they can withdraw at any time and how and where to do so.

3.4.3.7. Include a discussion about the alternatives to testing and possible outcomes and ensure ongoing support if genetic conditions are detected.

3.4.3.8. State the obligations of the institution and the rights of the participant in the event of complications or wrongdoings during the procedure.

3.4.3.9. For minors or incapacitated individuals, consent is obtained from a parent or legal guardian who is fully informed of the test's purpose, risks, benefits, and alternatives.

3.4.3.10. If the minor is considered mature enough (typically 7-18 years old), they should be asked to provide assent, meaning they agree to the procedure after it has been explained to them in an understandable way.

3.4.3.11. For conditions affecting future autonomy, it is crucial to reassess consent over time as the patient grows or regains the capacity to participate in decision-making.

3.4.3.12. Clearly outline the necessary actions following receipt of genetic test results:

3.4.3.12.1. Positive (Abnormal) Result: If genetic changes associated with a suspected condition are identified, this may confirm a diagnosis or predisposition to the disease. If needed, additional confirmatory or diagnostic testing will be recommended to refine the findings and guide further medical care.

3.4.3.12.2. Negative Result: A lack of detected genetic changes does not entirely rule out the possibility of genetic condition, as this result may be influenced by technical limitations or incomplete scientific understanding of certain genes. Periodic re-evaluation and consultation with a healthcare provider may be needed.

3.4.3.12.3. Inconclusive Result: If genetic changes are found but their connection to disease risk is uncertain such as VUS, the results are categorized as inconclusive and referred to clinical geneticists/ genomics trained HCPs for further decision. Further testing, expert genetic counselling, or advancements in genetic research may eventually help clarify these findings.

3.4.3.13. The consent should be obtained by the treating physician /HCP who is ordering the test

3.4.3.14. The consent process shall adhere to local laws governing healthcare decisions for minors or incapacitated individuals as well as data protection laws.

3.4.3.14. The process must be handled ethically, ensuring full comprehension and voluntary agreement before proceeding with any clinical or diagnostic testing.

3.4.3.15. Consent must be documented and securely stored in a manner that allows it to be easily retrieved in case of regulatory or legal requests. The record should include details of when and where the consent was provided. Furthermore, a clear and efficient mechanism should be in place to allow individuals to withdraw their consent at any time, ensuring it is promptly removed from the system in accordance with their request.

3.5. Clinical Applications of Genetic Testing in Rare Diseases

3.5.1. Accreditation of testing facilities

Accredited laboratories must follow quality standards such as those set by the Clinical Laboratory Improvement Amendments (CLIA), DoH Standard for Laboratory Accreditation for Genomic-Related Services and Products, the International Organization for Standardization (ISO), or other recognized regulatory bodies.

3.5.2. Testing methods and Target Types:

3.5.2.1. In genetic and genomic testing, the term **"target type"** refers to the specific type of genetic material or variation that a test aims to identify. The target type guides the testing process by focusing on specific areas of the DNA or RNA that are most relevant to the suspected condition. Selecting the right target type is essential because it determines the scope, precision, and suitability of the test for particular genetic findings. The sequencing methods can include:

3.5.2.1.1. Whole Genome Sequencing (WGS)

3.5.2.2.1. Whole Exome Sequencing (WES)

3.5.2.2. Available Panels:

3.5.2.2.1. Large, Medium, Small Panels

3.5.2.2.2. Single Gene Sequencing

3.5.2.2.3. Single Cell RNA sequencing

3.5.2.2.4. Targeted Variant Testing

3.5.2.2.5. Short Tandem Repeat Testing (STR Testing)

3.5.2.2.6. Multiplex Ligation-dependent Probe Amplification (MLPA)

3.5.2.2.7. Microarray

3.5.2.2.8. Common Aneuploidy Testing

3.5.2.2.9. Karyotype

3.5.2.2.10. Fluorescence in Situ Hybridization (FISH)

3.5.2.2.11.DNA Repair Testing

3.5.2.2.12. Methylation Testing

3.5.2.2.13. Uniparental Disomy (UPD) Testing

3.5.2.2.14. X-Inactivation Testing

3.5.2.2.15. Microsatellite Instability (MSI) Testing

3.5.2.2.16. Non-Invasive Prenatal Testing (NIPT)

3.5.2.2.17. Non-Invasive Prenatal Diagnosis (NIPD)

3.5.2.3. Optimal testing

3.5.2.3.1. The aim of optimal testing is to perform the most relevant tests to maximize diagnostic accuracy. All tests suggested for a specific clinical indication are generally performed unless there is a clinical or scientific reason not to, such as patient-specific factors or a lack of benefit in a particular case.

3.5.2.3.2. Consider optimal family structure testing which refers to the different strategies used to test individuals within a family based on their relationship to the person diagnosed with a genetic condition. The common testing structures include:

3.5.2.3.2.1. Singleton

3.5.2.3.2.2. Duo Testing

3.5.2.3.2.3. Trio Testing

3.5.2.3.2.4. Singleton or Trio

3.5.2.3.2.5. Parents Only Testing

3.5.2.3.3. Other: Any other relevant family structure, depending on specific needs

3.5.3. Recommendations/ instructions for ordering tests

Clinicians requesting genomic tests are recommended to follow the below practices that can improve the efficiency and effectiveness of genomic testing, ultimately benefiting patient care.

3.5.3.1. Personnel

Personnel requirements for all HCPs involved in testing and diagnosis of rare disease:

3.5.3.1.1. All HCPs must be qualified to perform their duties with appropriate education, training, experience and skill. Evidence of these qualifications must be provided.

3.5.3.1.2. All HCPs personnel must be licensed by DoH and perform their activities in compliance with DoH Clinical Laboratory standards, DoH standard for Clinical Privileging Framework, DoH Healthcare Professionals Manual and Unified Healthcare Professional Qualification requirements (PQR).

3.5.3.2. Selective Testing:

3.5.3.2.1. For EGP participants genetic testing is available through Biogenix Lab, M42. HCP can specify target tests (refer above in section 3.5.2 for types of target tests) which are required, and which one should be excluded. This helps streamline the testing process and reduces unnecessary costs. Genomic testing should primarily target individuals where a genetic or genomic diagnosis would influence treatment or care for the patient or their family

3.5.3.3. Clinical Indication:

3.5.3.2.2. Request the specific clinical indication by providing the disease name and ICD-10 code associated with it, if known. This ensures the laboratory understands the context of the test.

3.5.3.4. Relevant Clinical Information:

3.5.3.4.1. Provide as much pertinent clinical information as possible to aid in the interpretation of results. This may include patient history, symptoms, symptoms onset dates (age at which the symptom started), marital status for adults, consanguinity, family history, and any previous test results. Comprehensive information enhances the laboratory's ability to provide accurate and meaningful interpretations. The testing laboratory will evaluate the test request, review the relevant clinical details, and determine the most suitable constituent test(s) to support the request.

3.5.3.5. Laboratory sample process:

3.5.3.5.1. For Emirati patients participating in the Emirati Genome Program (EGP), sample collection and reporting are streamlined through the program, allowing them direct access to their genomic data and results. Lab might ask for additional sample if it was insufficient or had quality issues. However, for non-Emirati patients or Emiratis who choose not to participate in the EGP, new sample collection is required for genomic testing and analysis.

3.5.3.6. Sample collection and Storage:

3.5.3.6.1. Provide sample collection guide which includes sample volume and type, container required to use, storage and transportation conditions.

3.5.3.7. Consent form:

3.5.3.7.1. Attach the signed consent form with test requisition form.

3.5.4. Individuals right to report disclosure

To integrate the norms for results communication outlined in the UAE's Federal Law by Decree No. (49) of 2023, the following points provide guidance on how to handle genetic or genomic test results:

3.5.4.1. Right to Results: Every individual (or their legal representative, if incapacitated) has the right to access their genetic or genomic analysis results, whether participation in the screening is voluntary or mandated.

3.5.4.2. Option to Decline Results: Individuals may choose not to receive their results. This choice must be documented in writing, as specified in the law’s procedural forms.

3.5.4.3. Mandatory Disclosure of Life-Threatening Results: Results that indicate a life-threatening risk to the individual or fetus must be disclosed to the individual or their legal representative.

3.5.4.4. Genetic Counselling Requirement: A qualified physician or specialist must provide genetic counselling to the individual upon receiving their results. This counselling includes explaining potential health effects, preventive measures, and necessary therapeutic interventions.

3.5.4.5. Confidentiality of Sensitive Information: Testing and disclosure of information related to DNA profiling to prove lineage or kinship, will not be performed, except based on an order or ruling from the Competent Court in accordance with the legislation in force.

3.5.4.6. Consent for Additional Results: Any additional findings from the genomic screening that were not the primary target of testing require the individual's consent before disclosure.

3.5.4.7. Confidentiality: All diagnoses, results, data and information related to the human genome and genes, which were carried out or arrived at within the framework of scientific or clinical research or study, shall be kept completely confidential, and shall not be disclosed in cases permitted by the legislation in force in the Emirate and in line with the prevailing applicable laws and regulations.

3.6. Genetic Counselling

Genetic counsellors are experts in understanding how genetic factors can influence health and well-being. Clinical geneticists, genetic counsellors or HCP trained in genomics and genetic counselling can provide genetic counselling. For further scope of a genetic counselor, please refer to the DoH document on "Scope of Practice for Genetic Counsellor"

These counsellors can assist with the following:

3.6.1. Adapting to Implications: They help individuals and families cope with the medical, psychological, and familial implications of genetic and inherited diseases.

3.6.2. Informed Decision-Making: Counsellors support the individual and their family in making informed decisions regarding health and disease management, ensuring that they understand the available options.

3.6.3. Specialized Information: They provide detailed information about medical genetics and the clinical findings of the test to the healthcare provider, facilitating better communication and care.

3.6.4. Education on Human Genetics: Counsellors educate affected individuals and their family about human genetics and its relevance to their family history, helping them understand potential risks and implications.

3.6.5. Next Steps in Health Journey: They offer recommendations for appropriate next steps based on the genetic results, guiding affected individuals toward resources and actions that can enhance the health outcomes.

3.7. Screening Recommendations

Screening and genetic testing are crucial for the early identification of rare diseases, often before symptoms manifest. These tests are particularly significant for conditions present at birth due to genetic abnormalities or prenatal factors, such as sickle cell disease and spina bifida, which can be linked to folic acid deficiency around conception and early pregnancy. Early diagnosis aids in preventing complications and effectively managing the condition. However, screening programs raise complex ethical, legal, and social issues for individuals—whether adults seeking information for themselves or parents acting on behalf of their children.

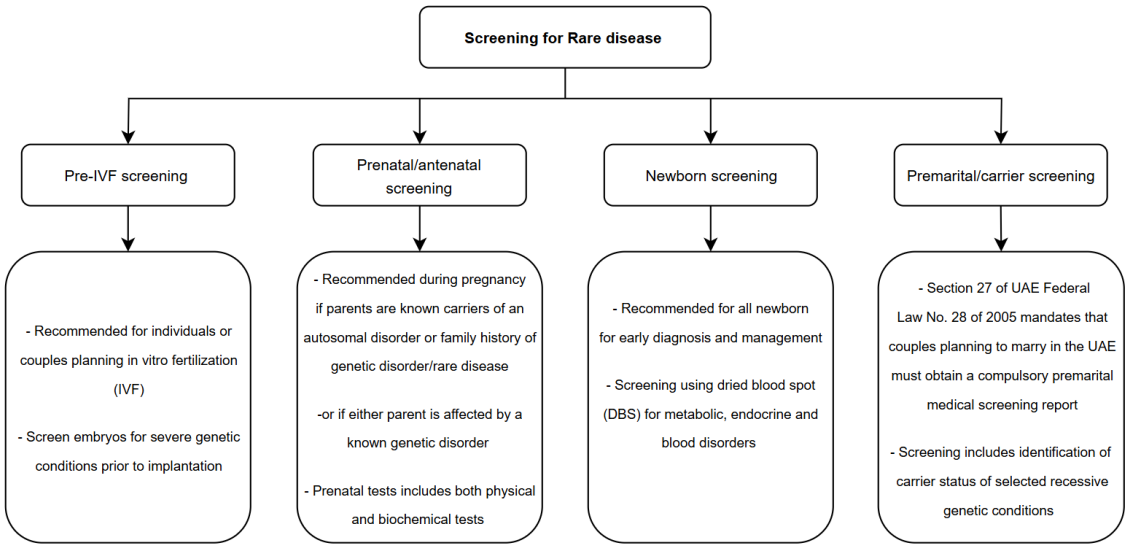

Figure 1: Screening for Rare diseases

For more information on screening, refer to Federal Law by Decree No. (49) of 2023 on use of the human genome, Standard for Newborn Screening Requirements, HAAD Standard Well Child visits (0-6 years), DoH Premarital Screening Standard.

3.7.1. Screenings Recommended:

3.7.1.1. Pre-IVF Screening: For couples planning IVF, genetic testing is recommended to detect potential genetic risks, especially for rare diseases, to prevent passing on congenital disorders. If results show risks, embryos can be screened, and only healthy embryos are preserved for implantation.

3.7.1.2. Prenatal Screening: Recommended for parents who are known carriers of autosomal or X/Y-linked disorders, have a family history of genetic disorders; or if either parent is affected by a known genetic disorder. Tests like ultrasounds, biochemical markers, and amniocentesis can identify abnormalities early, enabling informed decisions about pregnancy continuation and early intervention for certain conditions.

3.7.1.3. Newborn Screening: Screening includes dried blood spots to detect metabolic, endocrine and blood disorders, shortly after birth, allowing for timely treatment.

3.7.1.4. Premarital Screening: For couples it is mandatory to undergo premarital screening if one of the partners is a UAE national to identify potential genetic risks before marriage, allowing for informed decision making and family planning.

3.7.2 Screening for carriers of rare diseases

Carrier testing is recommended in the following scenarios:

3.7.2.1. High-Risk population: It is recommended for individuals at an increased risk of carrying specific inherited disorders, such as Tay-Sachs or thalassemia. It is advised for individuals from high-risk ethnic backgrounds to undergo carrier testing to facilitate informed reproductive decisions.

3.7.2.2. Affected families and individuals with known family history of rare disorder: Testing for carrier status of abnormal genes is particularly important in families with known

genetic disorders and among high-risk populations to identify potential risks for future offspring.

3.7.3. Cascade screening

3.7.3.1. Cascade screening helps in

3.7.3.1.1. Detecting carriers in selected families or high-risk groups.

3.7.3.1.2. Public health initiatives to identify individuals at risk.

3.7.3.2. Ethical Considerations for Minors:

3.7.3.2.1. Testing minors at risk for certain rare diseases raises ethical concerns:

3.7.3.2.1.1. Minors may not fully understand the risks and benefits.

3.7.3.2.1.2. They may lack the capacity to make independent decisions about testing.

3.7.3.3. Receiving a carrier diagnosis during childhood can be overwhelming.

3.7.3.4. It is strongly advisable to defer predictive testing for minors until adulthood unless they exhibit symptoms of a rare disease.

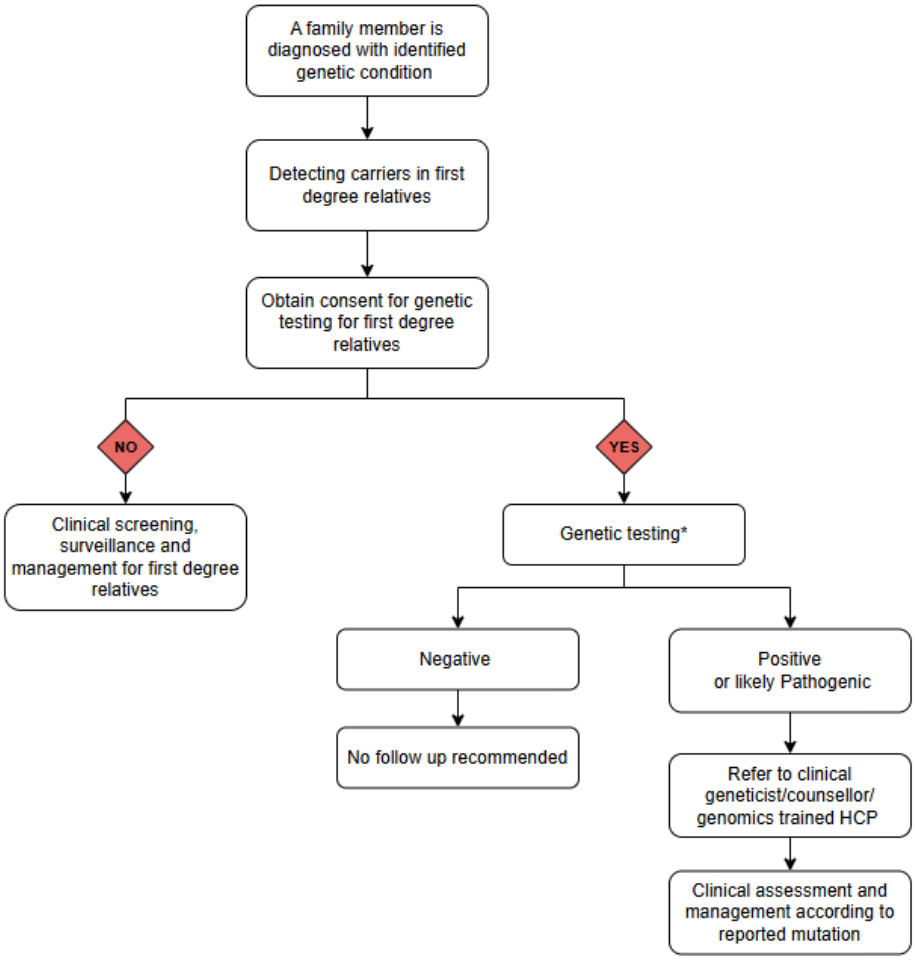

Figure 2: Familial Cascade Testing

*The workflow for sending samples for EGP participants is illustrated in the section on diagnostic pathway (Section 3.9)

3.8. Adult rare diseases

3.8.1. Adult rare disease (ARD) patients can be categorized into two main groups:

3.8.1.1 The first category includes individuals diagnosed with RDs during childhood who continue to face the challenges of their conditions into adulthood.

3.8.1.2 The second category comprises patients with adult-onset RDs, who typically experience longer diagnostic challenges compared to those with pediatric-onset conditions.

3.8.2. Challenges:

3.8.2.1. Delayed Diagnosis: Adult-onset RDs present with a broad range of symptoms that are often variable and nonspecific, leading to diagnostic delays as they can resemble more common conditions.

3.8.2.2. Gradual Symptom Onset: Symptoms may worsen slowly over time, with complex interactions between genetic, environmental, and other factors, making accurate diagnosis challenging.

3.82.3. Higher Rate of Non-Genetic Causes: Environmental exposures, lifestyle choices, and immune conditions contribute more significantly to adult RDs than pediatric cases, requiring consideration beyond genetics alone.

3.8.2.4. Psychosocial and Diagnostic Complexity: The emotional burden of living with a rare disease, combined with the uncertainty in diagnosis and prognosis, requires a comprehensive approach.

3.8.3. Recommendations:

3.8.3.1. Holistic Diagnostic Approach: Incorporate both genetic and non-genetic assessments to accurately identify and diagnose ARD.

3.8.3.2. Interdisciplinary Collaboration: Ensure access to specialists and collaborative care to address complex and varied symptoms.

3.8.3.3. Comprehensive Patient Support: Provide resources for psychosocial support alongside medical care to help manage the impact of living with a rare disease.

3.9. Diagnostic pathway

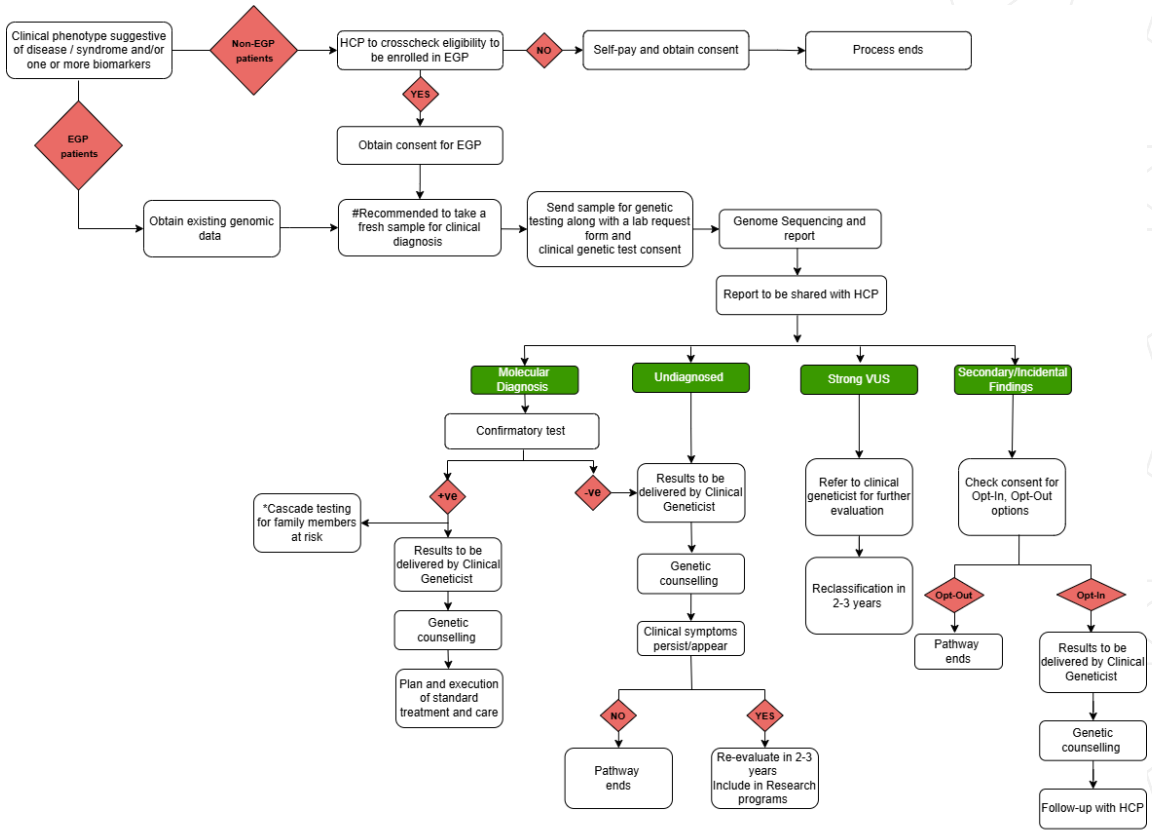

Figure 3: Clinical diagnostic pathway for Rare Diseases

#EGP participants are recommended to provide fresh sample for clinical genetic test

*Refer to the section on Cascade testing (Section 3.7.3)Abbreviations: EGP- Emirati Genome Program, VUS- Variants of Unknown Significance

3.10. Rare Disease Research

3.10.1. Diagnosing rare diseases presents a significant challenge, with successful outcomes depending on the implementation of innovative strategies, robust data-sharing practices, rigorous tracking of precision treatment outcomes, and strong partnerships with patient advocacy organizations. To improve the diagnosis and management of rare diseases, ongoing research is essential. This research process encompasses multiple stages, from the generation of data to its clinical application, ensuring that genetic insights are translated into improved diagnostic tools and therapeutic interventions. Key components of this research include:

3.10.1.1. Data generation: Includes sequencing data and clinical/ phenotypic data

3.10.1.2. Data storage: Cloud computing platforms for data storage

3.10.1.3. Data analysis: Variant calling - identifying variants in DNA between samples and reference genome.

3.10.1.4. Variant interpretation: Analysing identified variants through Annotations, population databases and phenotype driven prioritization

3.10.1.5. Collaborative Research efforts: Includes development of data sharing platforms and framework for data privacy. Collaboration across disciplines and sharing of data is crucial for advancing understanding and treatment of rare diseases.

3.10.1.6. Clinical application: Precision medicine strategies including gene therapy, protein targeted therapy and regenerative medicine.

3.10.2. Data protection

3.10.2.1. Data protection is a critical concern in rare disease research, as it ensures patient privacy, complies with regulatory standards, and upholds ethical standards in the handling of sensitive information.

3.10.2.2. Essential measures to safeguard data include obtaining informed consent, employing anonymization or de-identification techniques, utilizing encryption, and ensuring compliance with regulatory frameworks such as the General Data Protection Regulation (GDPR) and the Health Insurance Portability and Accountability Act (HIPAA).

3.10.2.3. Long-term research necessitates secure storage and auditing of data, with appropriate mechanisms for ensuring ongoing compliance and accountability.

3.10.2.4. Safely store and audit data for long-term research needs and keep patients informed about data usage and offer control over their data rights.

3.11. Recommendation for HealthCare Professionals

3.11.1. Empower Shared Decision-Making: Involve patients and families in treatment decisions to respect their expertise about their condition, fostering trust and partnership.

3.11.2. Enhance Communication and Follow-Up: Maintain regular, clear communication with patients, including consistent updates and check-ins to ease anxiety.

3.11.3. Timely Diagnosis and Referrals: Use specialized tools like ORPHANET to recognize symptoms early and make prompt referrals to genetic specialists or rare disease centers.

3.11.4. Integrate Telemedicine and Flexible Models: Offer telehealth and multi-professional meetings to enhance care accessibility, especially for remote patients.

3.11.5. Personalized, Multidisciplinary Models: Promote tailored, holistic care plans involving various specialties.

3.11.6. Culturally Sensitive and Accessible Care: Provide culturally appropriate, accessible information to support diverse populations, including indigenous and multilingual patients.

3.11.7. Promote awareness: Healthcare professionals should raise awareness among patients and families about the benefits of genetic testing for rare diseases.

3.11.8. Genomics and Data Sharing: Leveraging data for better diagnostics and treatments.

3.11.9. Follow-up and treatment: Clinicians should provide long-term follow-up to monitor treatment response and adapt care plans based on new genetic information.

3.11.10 Family communication: Genetic results should be communicated to the patient's family, particularly in cases of hereditary diseases, to facilitate early screening or preventive care for relatives.

3.12. Organizations and society

Support groups for rare disease patients and their families in the UAE provide essential resources, community support, and education. Here's a brief overview on UAE support groups which HCPs can guide patients to get support:

3.12.1. UAE Rare Disease Society:

3.12.1.1. This society actively advocates rare disease awareness in the UAE, connecting patients and families with medical professionals and offering educational resources to help them navigate their healthcare journey.

3.12.1.2. It provides platforms for sharing experiences and organizing awareness events.

3.12.2. UAE Genetic Diseases Association (UAEGDA):

3.12.2.1. Focused on preventing genetic disorders, UAEGDA provides genetic counseling, screening services, and public education initiatives.

3.12.2.2. Their efforts emphasize early diagnosis and family support to manage genetic conditions. Families can contact UAEGDA for personalized guidance and resources.

4.Relevant References Documents

No.	Reference Date	Reference Name	Relation Explanation / Coding / Publication Links
1	Oct 2023	**Federal Law by Decree No. (49) of 2023 Regulating the Use of the Human Genome**	https://uaelegislation.gov.ae/en/legislations/2195/download
2	Sep 2024	**Premarital Screening Standard.**	https://www.doh.gov.ae/-/media/6CFDB715D9B84AD1B309B20736CC357B.ashx
3	Dec 2023	**Standard for Laboratory Accreditation for Genomic-Related Services and**	https://www.doh.gov.ae/-/media/7E35F99573FD488DBD6F6AC3F8835465.ashx
4	2024	**Scope of Practice for Genetic Counselor - Department of Health**	https://www.doh.gov.ae/-/media/B0E5C7242C444DCD8C217A106F832DD2.ashx
5	2022	**Unified Healthcare Professional Qualification**	https://www.doh.gov.ae/en/pqr
6	2009	**Standard for Newborn Screening Requirements**	https://www.doh.gov.ae/-/media/00146134553F4236B9574DEBB8B642E1.ashx
7	2012	**HAAD Standard Well Child visits (0-6 years)**	https://www.doh.gov.ae/-/media/D4F6760CCEBF4A5AAA4140FA25E11373.ashx
8	2022	**DoH Policy in Genomics**	https://www.doh.gov.ae/-/media/1C68EF54799945839198F0FF27C04016.ashx

9	2025	**Patient Consent Standard**	https://www.doh.gov.ae/-/media/FE9E5EF1961D4F719319668B9234D667.ashx
10	NA	**EMA**	https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-
11	NA	**UAE Rare Disease Society**	https://uaerds.ae/
12	NA	**UAE Genetic Disease Association**	https://www.citysearch.ae/uae-genetics-diseases-association-dubai
13	Aug2023	**NIH**	https://pmc.ncbi.nlm.nih.gov/articles/PMC10468408/
14	Jul2024	**NHS- UK**	https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-national-genomics-test-directory-official-V7.1.xlsx
15	2019	**The UK Strategy for Rare Diseases**	https://assets.publishing.service.gov.uk/media/5c751152e5274a0ec6ed95f0/2019-update-to-the-rare-diseases-implementation-plan-for-england.pdf
17	2024	**Rare disease genomics and precision medicine**	https://genomicsinform.biomedcentral.com/articles/10.1186/s44342-024-00032-1
18	2024	**Inherited Retinal Disorders Genetic Testing and Management Guideline**	https://www.doh.gov.ae/-/media/DADBA67413B7493382B2E5A02C74ED26.ashx

19	2024	**Spinal Muscular Atrophy Clinical Guideline**	https://www.doh.gov.ae/-/media/00CC0A4E147C4835987A3ADBB362EAE9.ashx
20	2024	**Guidelines for Clinical & Translational Research in Genomics**	https://www.doh.gov.ae/-/media/6B13929E9036440093845DB2FB66A55D.ashx