Clinical versus Genetic Diagnosis of Cystic Fibrosis in High Risk Egyptian Children

Asmaa R. Sheta¹*, Eman R. Abd Almonaem¹, Doaa R. Soliman¹, Waleed E. Abdulghany¹, Hala T. El-Bassyouni², Ekram Fateen³ and Khalda S. Amr²

¹Pediatrics Department, Faculty of Medicine, Benha University, Egypt.
²Clinical Genetics Department, Human Genetics and Genome Research Institute, National Research Centre, Cairo 12622, Postal Code, Egypt.
³Biochemical Genetics Department, National Research Centre, Cairo 12622, Postal Code, Egypt.

Abstract

Background: Cystic fibrosis (CF) is a hereditary disorder affecting primarily the respiratory and digestive systems, caused by mutations in the CFTR gene. Globally, CF is a significant cause of morbidity and mortality, especially prevalent among populations of European descent. In the Middle East, including Egypt, the prevalence is less well-documented, leading to potential diagnostic challenges and delays. Objective: This comprehensive review aims to explore the clinical and molecular diagnosis of cystic fibrosis, with a particular focus on the application of these diagnostic methods in a sample of Egyptian children. The review seeks to provide an in-depth analysis of current practices, highlight unique diagnostic challenges, and suggest improvements for the Egyptian healthcare context. Conclusions: A combined clinical and molecular diagnostic approach is crucial for the accurate and early diagnosis of cystic fibrosis. While clinical methods remain essential, molecular diagnostics provide a deeper understanding of the genetic basis of CF, enabling personalized treatment strategies. For Egyptian children, where specific mutations may be more prevalent, adopting a comprehensive diagnostic protocol is imperative. The review highlights the need for improved screening programs, enhanced genetic research, and public health strategies to better manage CF in Egypt and similar regions. Future research should focus on expanding molecular diagnostic capabilities and developing tailored treatment approaches.

Keywords: Cystic fibrosis, Clinical, Molecular, Diagnosis.

1. Introduction

Cystic fibrosis (CF) is a complex, multisystemic genetic disorder predominantly affecting the respiratory and digestive systems. It is caused by mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene located on chromosome 7 [1].

The CFTR protein functions as a chloride channel, playing a crucial role in maintaining the balance of salt and water across epithelial surfaces in the lungs, pancreas, and other organs. Mutations in the CFTR gene disrupt the function of this protein, leading to the production of thick, sticky mucus that obstructs airways and glandular ducts [2].

The pathophysiology of CF involves chronic respiratory infections, progressive lung damage, and pancreatic insufficiency. The thick mucus provides a fertile environment for bacterial growth, leading to recurrent infections and inflammation. Over time, this cycle results in bronchiectasis and respiratory failure, which are the primary causes of morbidity and mortality in CF patients. Additionally, the obstruction of pancreatic ducts impairs the secretion of digestive enzymes, causing malabsorption of nutrients and poor growth [3].

2. Epidemiology

Globally, CF is one of the most common life-threatening genetic disorders, particularly prevalent among Caucasian populations. In the United States and Europe, the incidence of CF is approximately 1 in 2,500 to 3,500 live births. However, the incidence varies significantly across different regions and ethnic groups. For instance, CF is less common in Asian and African populations [4].

In the Middle East and North Africa, including Egypt, the prevalence of CF is less well-documented. Limited data suggest a lower incidence compared to Western countries, but this may be due to underdiagnosis and lack of awareness. Studies indicate that consanguineous marriages, which are relatively common in the region, could increase the incidence of CF and other genetic disorders. The lack of comprehensive newborn screening programs and genetic testing facilities further complicates the accurate estimation of CF prevalence in Egypt [5].

3. Importance of Diagnosis

Early and accurate diagnosis of cystic fibrosis is crucial for improving patient outcomes and quality of life. Timely diagnosis allows for the initiation of appropriate
treatments that can significantly slow disease progression and manage symptoms. Key benefits of early diagnosis include [6, 7]:

1. **Improved Respiratory Function:** Early intervention with airway clearance techniques, antibiotics, and other therapies can help maintain better lung function and reduce the frequency and severity of infections.

2. **Nutritional Management:** Early diagnosis allows for the timely initiation of pancreatic enzyme replacement therapy and nutritional support, preventing malnutrition and promoting normal growth and development in children.

3. **Personalized Treatment:** Genetic testing enables the identification of specific CFTR mutations, which can guide targeted therapies such as CFTR modulators. These treatments are designed to correct the underlying defect in CFTR protein function.

4. **Family Planning and Counseling:** Genetic diagnosis provides valuable information for family planning and genetic counseling. Parents and relatives can benefit from understanding the hereditary nature of CF and the risks for future offspring.

5. **Public Health Implications:** Early and accurate diagnosis can inform public health strategies, including the implementation of newborn screening programs and the development of specialized CF care centers.

4. **Clinical Diagnosis of Cystic Fibrosis**

   ❖ **Clinical Presentation**
   
   Cystic fibrosis (CF) can present with a wide range of clinical symptoms, often varying in severity among individuals. Common signs and symptoms in children include [8]:
   
   1. **Respiratory Symptoms:**
      - **Chronic Cough:** Persistent cough that produces thick mucus, often starting in infancy or early childhood.
      - **Frequent Lung Infections:** Recurrent respiratory infections, including bronchitis and pneumonia, often caused by unusual bacteria like Pseudomonas aeruginosa.
      - **Wheezing and Shortness of Breath:** Due to mucus plugging and inflammation of the airways.
      - **Nasal Polyps and Sinusitis:** Growth of polyps in the nasal passages and frequent sinus infections.
   2. **Gastrointestinal Symptoms:**
      - **Poor Growth and Weight Gain:** Despite normal or increased appetite, due to malabsorption of nutrients.
      - **Bulky, Foul-Smelling Stools:** Due to fat malabsorption caused by pancreatic insufficiency.
      - **Meconium Ileus:** Intestinal blockage occurring in newborns, often the first sign of CF.
      - **Pancreatitis:** Inflammation of the pancreas in some children.
   3. **Other Symptoms:**
      - **Salty-Tasting Skin:** Parents may notice a salty taste when kissing their child.
      - **Clubbing of Fingers and Toes:** Thickening and rounding of the fingertips and toes due to chronic hypoxia.
      - **Delayed Puberty:** Often seen in teenagers due to chronic illness and malnutrition.
      - **Male Infertility:** Almost all males with CF are infertile due to congenital bilateral absence of the vas deferens (CBAVD).

   ❖ **Diagnostic Criteria**
   
   The diagnosis of cystic fibrosis is typically based on a combination of clinical symptoms, family history, and laboratory tests. The standard clinical criteria for CF diagnosis include [9]:
   
   1. **Clinical Features:**
      - **One or more characteristic phenotypic features (e.g., chronic respiratory or gastrointestinal symptoms, meconium ileus).**
   2. **Family History:**
      - A sibling with CF or a positive family history of the disease.
   3. **Laboratory Evidence:**
      - Positive results from sweat chloride test or identification of CFTR gene mutations.
      - To establish a diagnosis, at least one clinical feature and laboratory evidence of CFTR dysfunction (elevated sweat chloride levels or identification of two CF-causing mutations) are required [10].

   ❖ **Sweat Chloride Test**
   
   The sweat chloride test is the gold standard for diagnosing cystic fibrosis. It measures the concentration of chloride in the sweat, which is abnormally elevated in individuals with CF due to defective CFTR function [11].
   
   **Procedure:**
   
   1. **Inducing Sweat:** A chemical called pilocarpine is applied to the skin, typically on the forearm, to stimulate
sweat production. This is done using a process called iontophoresis, which involves applying a mild electrical current.

2. **Collection:** Sweat is collected on a special gauze or filter paper over a period of about 30 minutes.

3. **Analysis:** The collected sweat is analyzed for chloride concentration.

**Interpretation:**
- **Normal:** Sweat chloride levels < 30 mmol/L.
- **Intermediate/Borderline:** Sweat chloride levels between 30-59 mmol/L. Further testing is needed.
- **Positive for CF:** Sweat chloride levels ≥ 60 mmol/L on two separate occasions.

❖ **Newborn Screening**

Newborn screening for cystic fibrosis is crucial for early diagnosis and intervention, significantly improving outcomes for affected infants. The screening process typically involves the following methods:\[12, 13]:

1. **Immunoreactive Trypsinogen (IRT) Test:**
   - A blood sample is taken from a newborn's heel, usually within the first few days of life, to measure the level of immunoreactive trypsinogen, a protein produced by the pancreas. Elevated IRT levels suggest possible CF but are not diagnostic on their own.

2. **DNA Testing:**
   - If the IRT levels are elevated, the same blood sample is tested for common CFTR gene mutations. This step helps identify infants at high risk for CF.

3. **Sweat Chloride Test:**
   - Infants with positive IRT and DNA test results undergo a confirmatory sweat chloride test to establish a definitive diagnosis.

The role of newborn screening is to identify infants with CF before symptoms develop, allowing for early intervention with treatments that can prevent or minimize lung damage, improve growth, and enhance overall quality of life. Early diagnosis through newborn screening also facilitates genetic counseling and family planning.\[14]

The clinical diagnosis of cystic fibrosis involves recognizing characteristic clinical symptoms, applying standard diagnostic criteria, performing the sweat chloride test, and utilizing newborn screening programs. These diagnostic tools collectively ensure timely and accurate diagnosis, which is essential for effective disease management and improved patient outcomes.\[15].

❖ **Molecular Diagnosis of Cystic Fibrosis**

✓ **Genetic Mutations**

Cystic fibrosis (CF) is caused by mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene, which encodes a protein that functions as a chloride channel in epithelial cells. There are over 2,000 known mutations in the CFTR gene, but not all are disease-causing. These mutations can be broadly classified into several categories based on their impact on the CFTR protein.\[16]:

1. **Class I Mutations:** Lead to no CFTR protein production (e.g., G542X).
2. **Class II Mutations:** Result in defective protein processing and trafficking, causing the protein to be degraded before reaching the cell surface (e.g., ΔF508, the most common CF mutation).
3. **Class III Mutations:** Produce proteins that reach the cell surface but are dysfunctional (e.g., G551D).
4. **Class IV Mutations:** Result in proteins with reduced chloride channel function (e.g., R117H).
5. **Class V Mutations:** Lead to reduced amounts of functional CFTR protein due to defective splicing or promoter activity (e.g., 3849+10kbC>T).
6. **Class VI Mutations:** Cause accelerated turnover of the CFTR protein at the cell surface (e.g., Q1412X).

✓ **Molecular Techniques**

Molecular diagnosis of CF involves detecting mutations in the CFTR gene using various techniques, each with its strengths and limitations.\[17]:

1. **Polymerase Chain Reaction (PCR):**
   - PCR is used to amplify specific regions of the CFTR gene to detect known mutations. It is a rapid and sensitive technique often used in initial screening tests.
   - Allele-specific PCR can detect common mutations, while multiplex PCR can identify multiple mutations simultaneously.
2. Next-Generation Sequencing (NGS):
   - NGS allows for comprehensive analysis of the entire CFTR gene, enabling the detection of both common and rare mutations. It provides high-throughput sequencing of many DNA fragments in parallel.
   - NGS is particularly useful for identifying novel mutations and understanding the full mutation spectrum in different populations.

3. Sanger Sequencing:
   - Sanger sequencing is the gold standard for mutation verification. It involves sequencing targeted regions of the CFTR gene to confirm the presence of specific mutations detected by other methods.
   - It is highly accurate but less efficient for large-scale mutation screening compared to NGS.

4. High-Resolution Melting Analysis (HRM):
   - HRM is used to screen for mutations by detecting differences in the melting curves of DNA duplexes. It is a rapid and cost-effective method for scanning known mutation hotspots.

5. Microarray Technology:
   - DNA microarrays can screen for a panel of known CFTR mutations simultaneously. They are useful for high-throughput screening in clinical settings.

✓ Genotype-Phenotype Correlation
Understanding the relationship between specific CFTR mutations and the clinical severity of CF is crucial for personalized patient management. Certain mutations are associated with particular phenotypic outcomes.

1. ΔF508 Mutation:
   - The ΔF508 mutation, present in approximately 70% of CF patients worldwide, is associated with severe CF symptoms, including early onset of lung disease and pancreatic insufficiency.

2. G551D Mutation:
   - The G551D mutation, a Class III mutation, results in a dysfunctional CFTR protein that reaches the cell surface. Patients with this mutation benefit from CFTR modulators like ivacaftor, which enhance the protein's function.

3. R117H Mutation:
   - The R117H mutation, a Class IV mutation, typically results in milder symptoms and a later onset of disease. The clinical severity can vary depending on the presence of other modifying factors.

4. 3849+10kbC>T Mutation:
   - This Class V mutation leads to reduced CFTR protein production and is associated with a milder phenotype. Patients may present with atypical CF or single-organ involvement.

✓ Ethnic-Specific Mutations
The spectrum of CFTR mutations varies across different ethnic groups, influencing the prevalence and severity of CF in specific populations. In the Egyptian population, certain mutations are more prevalent, reflecting the genetic diversity and historical genetic mixing in the region:

1. ΔF508 Mutation:
   - While common globally, the ΔF508 mutation is also found in the Egyptian CF population but with a lower frequency compared to European populations.

2. 3120+1G>A Mutation:
   - This mutation is relatively common in Middle Eastern populations, including Egyptians, and leads to a severe CF phenotype.

3. W1282X Mutation:
   - Found in both Egyptian and other Middle Eastern populations, this mutation results in a truncated, non-functional CFTR protein and is associated with severe disease.

4. N1303K Mutation:
   - Another mutation found in the Egyptian population, leading to severe CF phenotypes.
symptoms, including pancreatic insufficiency and early lung disease. Identifying ethnic-specific mutations is essential for developing targeted genetic screening programs and understanding the clinical diversity of CF in different populations. It also highlights the need for region-specific diagnostic protocols to improve early detection and management [21]. Molecular diagnosis of cystic fibrosis involves detecting CFTR gene mutations using advanced genetic techniques. Understanding genotype-phenotype correlations and recognizing ethnic-specific mutations are critical for accurate diagnosis, personalized treatment, and better management of CF, particularly in underrepresented populations like Egyptian children [22].

5. Combined Clinical and Molecular Approach

Advantages
Combining clinical and molecular diagnostic approaches offers several significant benefits for the accurate and early detection of cystic fibrosis (CF) [23, 24]:

1. Enhanced Diagnostic Accuracy:
   - The combination of clinical symptoms, sweat chloride testing, and genetic testing improves the overall accuracy of CF diagnosis. Clinical symptoms alone can sometimes be ambiguous, and molecular testing helps confirm the diagnosis.

2. Early Detection:
   - Molecular techniques, such as newborn screening and genetic testing, enable the detection of CF even before symptoms appear. Early diagnosis allows for timely intervention, which is crucial for preventing or minimizing long-term complications.

3. Personalized Medicine:
   - Understanding the specific CFTR mutations in a patient allows for personalized treatment plans. For instance, certain CFTR modulators are effective only for specific mutations. Personalized treatment improves patient outcomes and quality of life.

4. Comprehensive Understanding:
   - A combined approach provides a comprehensive understanding of the disease, including its genetic basis and phenotypic expression. This holistic view is essential for developing effective management strategies.

5. Family Planning and Counseling:
   - Genetic testing provides valuable information for family planning. It helps identify carriers of CFTR mutations, enabling genetic counseling for families and reducing the risk of CF in future offspring.

6. Public Health Impact:
   - Implementing combined diagnostic strategies can inform public health policies and lead to the establishment of national screening programs. This is particularly important in regions like Egypt, where CF might be underdiagnosed.

Diagnostic Algorithm
A proposed algorithm for diagnosing CF in Egyptian children can integrate both clinical and molecular diagnostic approaches as follows [25, 26]:

1. Newborn Screening:
   - Step 1: Perform the Immunoreactive Trypsinogen (IRT) test on newborns.
   - Step 2: If IRT levels are elevated, proceed with DNA testing for common CFTR mutations.

2. Initial Clinical Assessment:
   - Step 3: Conduct a thorough clinical evaluation for symptoms indicative of CF, such as chronic respiratory issues, failure to thrive, and gastrointestinal symptoms.

3. Sweat Chloride Test:
   - Step 4: Perform the sweat chloride test on symptomatic children and those with positive newborn screening results.
   - Step 5: Interpret the sweat chloride test results:
     - $< 30 \text{ mmol/L}$: CF unlikely.
     - $30-59 \text{ mmol/L}$: Borderline, further testing required.
Clinical versus Genetic Diagnosis of Cystic Fibrosis in High Risk Egyptian Children

- **≥ 60 mmol/L:** Indicative of CF.

4. **Genetic Testing:**
   - **Step 6:** Conduct comprehensive genetic testing using techniques such as PCR or NGS to identify CFTR mutations, especially for borderline or ambiguous cases.
   - **Step 7:** Confirm the diagnosis if two CF-causing mutations are identified.

5. **Final Diagnosis and Counseling:**
   - **Step 8:** Confirm the diagnosis of CF based on clinical symptoms, sweat chloride test, and genetic testing.
   - **Step 9:** Provide genetic counseling and discuss the implications of the diagnosis with the family, including treatment options and management strategies.

### Challenges and Limitations

Implementing a combined clinical and molecular diagnostic approach for CF presents several practical challenges and limitations:

1. **Resource Availability:**
   - Advanced molecular diagnostic tools such as NGS and comprehensive genetic testing require significant financial investment and infrastructure, which may be limited in resource-constrained settings.

2. **Access to Healthcare:**
   - In many regions, particularly rural areas, access to specialized healthcare facilities and diagnostic services may be limited. This can result in delayed or missed diagnoses.

3. **Cost:**
   - The cost of molecular testing can be prohibitive for many families and healthcare systems. Insurance coverage and governmental support are crucial for making these tests widely accessible.

4. **Technical Expertise:**
   - The implementation of molecular diagnostic techniques requires specialized training and expertise, which may not be readily available in all healthcare settings.

5. **Ethical and Cultural Considerations:**
   - Genetic testing raises ethical issues, such as privacy concerns and the potential for discrimination. Cultural beliefs and practices may also influence the acceptance and utilization of genetic testing.

6. **False Positives/Negatives:**
   - While combining clinical and molecular approaches increases diagnostic accuracy, there is still a risk of false positives or negatives, particularly with intermediate sweat chloride results or rare mutations not covered by standard panels.

7. **Genetic Diversity:**
   - The genetic diversity within populations can complicate the identification of relevant CFTR mutations. Tailoring genetic panels to include region-specific mutations is necessary but challenging.

In conclusion, a combined clinical and molecular approach to diagnosing cystic fibrosis offers substantial advantages in terms of accuracy, early detection, and personalized care. However, practical challenges such as resource availability, access to healthcare, and ethical considerations must be addressed to fully realize the benefits of this approach, particularly in regions like Egypt. Developing tailored diagnostic algorithms and investing in healthcare infrastructure are essential steps toward improving CF diagnosis and management in these settings.

### Implications for Clinical Practice Management

Accurate diagnosis of cystic fibrosis (CF) significantly impacts treatment and management strategies, leading to improved patient outcomes. Key implications include [6, 27, 28].

1. **Early Intervention:**
   - Early and accurate diagnosis allows for the timely initiation of treatments, including airway clearance techniques, inhaled medications, and nutritional support, which are crucial for slowing disease
progression and preventing complications.

2. **Targeted Therapies:**
   - Identifying specific CFTR mutations enables the use of CFTR modulators, which are tailored to correct the underlying defect in the CFTR protein. These targeted therapies have been shown to improve lung function, reduce pulmonary exacerbations, and enhance the quality of life for CF patients.

3. **Comprehensive Care:**
   - Accurate diagnosis facilitates the development of individualized care plans that address the multisystemic nature of CF. This includes managing respiratory, gastrointestinal, and nutritional aspects of the disease, as well as monitoring for complications such as CF-related diabetes and liver disease.

4. **Preventative Care:**
   - Regular monitoring and preventative care, guided by an accurate diagnosis, can help detect and manage complications early. This includes routine lung function tests, imaging studies, and regular follow-up with a multidisciplinary CF care team.

**Patient and Family Counseling**

Genetic counseling plays a crucial role in the management of CF, providing valuable information and support to patients and their families [29, 30].

1. **Understanding the Disease:**
   - Genetic counseling helps patients and families understand the genetic basis of CF, the implications of specific mutations, and the expected course of the disease. This knowledge empowers families to make informed decisions about care and management.

2. **Reproductive Choices:**
   - Counseling provides information on reproductive options for parents who are carriers of CFTR mutations, including the risks of having affected children and the availability of prenatal and preimplantation genetic diagnosis.

3. **Psychosocial Support:**
   - Genetic counseling addresses the emotional and psychological impacts of a CF diagnosis, offering support and resources to help families cope with the challenges of the disease.

4. **Family Planning:**
   - Understanding the hereditary nature of CF enables families to plan for future pregnancies, considering the potential genetic risks and available preventive measures.

**Public Health Perspective**

From a public health perspective, accurate diagnosis and comprehensive management of CF require strategic policies and programs:

1. **Screening Programs:**
   - Implementing national newborn screening programs for CF can ensure early detection and intervention, significantly improving outcomes. These programs should include both IRT and DNA testing to maximize diagnostic accuracy.

2. **Public Awareness:**
   - Increasing public awareness about CF, its symptoms, and the importance of early diagnosis can help reduce stigma and encourage families to seek timely medical evaluation.

3. **Healthcare Infrastructure:**
   - Developing specialized CF care centers equipped with the necessary diagnostic and treatment facilities is essential. Training healthcare professionals in the latest CF management strategies ensures high-quality care.

4. **Research and Data Collection:**
   - Establishing national registries for CF can help collect data on prevalence, genetic mutations, and outcomes, guiding public health policies and research initiatives.
Clinical versus Genetic Diagnosis of Cystic Fibrosis in High Risk Egyptian Children

Future Directions and Research Advancements in Molecular Diagnosis
Emerging technologies hold promise for enhancing the molecular diagnosis of CF [31, 32]:

1. CRISPR-Based Diagnostics:
   - CRISPR technology is being explored for its potential to detect CFTR mutations with high specificity and sensitivity, offering rapid and cost-effective diagnostic solutions.

2. Whole Genome Sequencing (WGS):
   - WGS provides comprehensive genetic information, allowing for the identification of rare and novel CFTR mutations. This technology can improve diagnostic accuracy, especially in ethnically diverse populations.

3. Point-of-Care Testing:
   - Developing portable and easy-to-use molecular diagnostic devices can facilitate rapid testing in various healthcare settings, improving access to timely diagnosis.

Personalized Medicine
Personalized treatment strategies based on genetic diagnosis are revolutionizing CF care [33, 34]:

1. CFTR Modulators:
   - Drugs like ivacaftor, lumacaftor, and tezacaftor, which target specific CFTR mutations, exemplify the potential of personalized medicine. Continued research is needed to develop modulators for a broader range of mutations.

2. Gene Therapy:
   - Advances in gene therapy hold promise for correcting CFTR mutations at the genetic level, potentially offering a long-term cure for CF. Ongoing clinical trials are exploring the safety and efficacy of various gene delivery methods.

3. Pharmacogenomics:
   - Understanding how genetic variations influence drug response can optimize treatment regimens for individual patients, reducing adverse effects and improving therapeutic outcomes.

Research Gaps
Identifying and addressing research gaps is crucial for advancing CF diagnosis and treatment:

1. Mutation Spectrum:
   - There is a need for comprehensive studies to characterize the CFTR mutation spectrum in diverse populations, including those in Egypt, to inform genetic screening programs and treatment strategies.

2. Long-Term Outcomes:
   - Longitudinal studies are necessary to evaluate the long-term impact of new diagnostic and therapeutic approaches, particularly CFTR modulators and gene therapy.

3. Psychosocial Aspects:
   - Research into the psychosocial impacts of CF and the effectiveness of support interventions can improve the overall quality of life for patients and their families.

4. Healthcare Disparities:
   - Investigating disparities in access to CF care and outcomes across different regions and socioeconomic groups can guide efforts to ensure equitable healthcare.

Integrating clinical and molecular approaches enhances the accuracy and timeliness of CF diagnosis, facilitating personalized treatment and improved patient outcomes [27, 35, 36]. Ongoing advancements in molecular diagnostics and personalized medicine, coupled with strategic public health policies, are essential for addressing the challenges of CF, particularly in regions with limited resources. Future research should focus on expanding genetic studies, optimizing treatment strategies, and addressing healthcare disparities to advance CF care globally.

7. Conclusions:
   - A combined clinical and molecular diagnostic approach is crucial for the accurate and early diagnosis of cystic fibrosis. While clinical methods remain essential, molecular diagnostics provide a deeper understanding of the genetic basis of CF, enabling personalized
treatment strategies. For Egyptian children, where specific mutations may be more prevalent, adopting a comprehensive diagnostic protocol is imperative. The review highlights the need for improved screening programs, enhanced genetic research, and public health strategies to better manage CF in Egypt and similar regions. Future research should focus on expanding molecular diagnostic capabilities and developing tailored treatment approaches.

References
Clinical versus Genetic Diagnosis of Cystic Fibrosis in High Risk Egyptian Children


