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MODERN DIAGNOSTICS OF CYSTIC FIBROSIS

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Introduction. Cystic fibrosis (CF) is the most common life-threatening autosomal recessive monogenic disorder in the Caucasian population. The disorder is caused by mutations in the cystic fibrosis transmembrane regulator gene. (CFTR), which disrupts the transport of chloride and sodium ions through epithelial cells. This results in the production of abnormally viscous secretions from the exocrine glands, which causes progressive damage to the respiratory system, gastrointestinal tract, and other organs. The current era of CF diagnostics is characterized by a shift from the recognition of clinical symptoms to an active search for the disease at preclinical stages using high-tech molecular genetic, biochemical, and functional methods. This approach fundamentally changes the patient care paradigm, paving the way for early intervention and personalized targeted therapy that directly impacts the molecular pathogenesis of the disease. This review systematizes key modern strategies and innovative methods for cystic fibrosis diagnostics , forming the basis for highly effective treatment standardized in the latest international and national guidelines.

1. Multi-level diagnostic system: from screening to verification

Modern diagnostics of CF is a multi-stage algorithm that begins before a child is born and continues throughout the patient's life for monitoring and treatment adjustments.

1.1. Prenatal and preimplantation diagnostics prenatal diagnostic methods (amniocentesis , chorionic villus sampling) are associated with the risk of pregnancy complications. A modern breakthrough is associated with the development of non-invasive Prenatal testing (NIPT). In 2025, the results of a large study of the Unity test , which analyzes circulating fetal DNA in the mother's blood as early as the first trimester of pregnancy, were presented. This method allows for the detection of mutations in the CFTR gene without the use of paternal biomaterial and demonstrated 100% accuracy in detecting CF in the study cohort. The key practical value of this method lies in the ability to plan treatment strategies as early as possible—in utero— including the initiation of therapy immediately after birth, which dramatically improves the prognosis . In families with a known high risk of having a child with CF, preimplantation genetic diagnosis is used as part of IVF programs.

1.2. Neonatal screening

Mass newborn screening for CF is mandatory in most developed countries, including Russia, and serves as the cornerstone of early diagnosis. The algorithm typically includes two stages:

1. Biochemical stage: Determination of the level of immunoreactive trypsinogen (IRT) in a dried blood spot from a newborn. Elevated IRT levels are a marker of pancreatic insufficiency, which often accompanies CF.

2. Genetic stage (DNA-IST): If the IRT test result is positive, the same blood sample is searched for the most common mutations of the CFTR gene. This allows for confirmation of the diagnosis in most patients at the preclinical stage, before the onset of significant symptoms.

1.3. Postnatal diagnosis in case of clinical suspicion

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In patients with late manifestation or not covered by screening, the diagnosis is established on the basis of the clinical picture and confirmed by a number of mandatory tests regulated by national and European standards :

Sweat test: Remains the "gold standard" for diagnosis. Determining the chloride concentration in sweat (≥60 mmol /L with a positive result) is a key diagnostic criterion.

Molecular genetic testing: Comprehensive analysis of the CFTR gene to identify mutations in the proband.

2. High-tech molecular genetic diagnostics as the basis for personalized medicine

Advanced genetic diagnostics has ceased to be merely a confirmatory tool and has become a guide for choosing treatment. The modern algorithm includes several levels.

2.1. Advanced genetic analysis

Panel Next-generation sequencing (NGS): Allows for simultaneous analysis of all exons and adjacent intronic regions of the CFTR gene to identify both common and rare mutations. This is the most effective first-line method for patients who screen negative for common mutations. Studies such as the one conducted in the Republic of Bashkortostan demonstrate that NGS can achieve a high mutation identification rate (up to 97.3% of chromosomes) and verify the diagnosis even in complex cases.

Search for large deletions /duplications: Methods such as multiplex ligase -dependent probe amplification (MLPA) are used to identify large rearrangements in the CFTR gene that are not detected by sequencing .

Functional analysis of mutations in in vitro : For rare, unclassified, or controversial genetic variants (variants of unknown Functional tests are crucial for the diagnosis of CFTR (VUS) significance . The forskolin test on rectal organoids (mini-organs grown from the patient's cells) allows for a direct assessment of residual CFTR protein function and predicts the response to modulator therapy.

2.2. From diagnosis to therapy: personalizing treatment

Identifying a specific pair of mutations allows us to assign a patient to a specific molecular class and, accordingly, select a targeted drug. European standards place particular emphasis on a personalized approach based on genetic profiling .

For patients with the F508del mutation (the most common), combination therapy with CFTR correctors and potentiators (e.g., tezacaftor / ivacaftor or new combinations) has become the standard.

The innovative drug Alifetrek (vanzacaftor / tezacaftor / deutivacaftor) , approved in 2025, demonstrates comparable efficacy with a simplified dosing regimen (once a day), offering an alternative for patients intolerant to other regimens.

For patients with mutations that do not respond to available modulators (approximately 10-15%), fundamentally new approaches are being developed, such as an mRNA -based therapy (RCT2100), which promotes the production of functional CFTR protein in lung cells. The FDA approved the next phase of clinical trials for this drug in 2025 .

3. National and international standards: unification of the diagnostic process

Standardization is a crucial element of modern care. In 2023-2024, the European Cystic Fibrosis Society (ECFS) completely updated its standards of care, which were translated into Russian with the support of the Ostrova Foundation . These documents cover all aspects: from diagnostic criteria and genetic counseling to complication monitoring and the organization of multidisciplinary care. In Russia, National Clinical Guidelines, which are also regularly updated and serve as a reference for physicians, play a similar role.

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4. Current challenges and prospects in the diagnosis of CF in Russia
Despite significant progress, the Russian healthcare system faces certain challenges:
1. Increasing the availability of high-tech DNA diagnostics: It is necessary to widely implement NGS and functional testing methods for a complete genetic characterization of all patients with CF, which is a prerequisite for the appointment of targeted therapy.
2. Integration of new methods: Russian studies have shown that patients are successfully transitioning to generic triple-action medications, maintaining efficacy and safety . However, careful monitoring and inclusion in regulatory documents are required.
3. Development of our own developments: Research in the field of gene therapy for CF is being actively conducted in Russian scientific centers (Bochkov Moscow State Medical Research Center, etc.), which is considered a strategic task for reducing dependence on foreign drugs.
4. Ensuring continuity and multidisciplinarity : The key theme of modern conferences, such as the V All-Russian Conference "ORPHADA", remains the need for interaction between geneticists, pulmonologists, gastroenterologists, nutritionists and psychologists for the comprehensive management of patients throughout their lives .
Conclusion. Modern cystic fibrosis diagnostics is a dynamically developing field, where revolutionary breakthroughs in genomics (NIPT, NGS, organoid technologies) are being integrated into clinical practice through strict international and national standards. The diagnostic process has evolved from simple disease confirmation to a complex system that includes prenatal screening, neonatal screening, and in-depth genetic and functional characterization. This detailed molecular diagnostics is the cornerstone of a new era of personalized medicine for CF, enabling the prescription of highly effective targeted drugs, such as CFTR modulators and promising mRNA - based therapies . Further efforts should be aimed at ensuring equal access to the most advanced diagnostic technologies for all patients, which is key to improving their quality of life and life expectancy.

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