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Cystic Fibrosis (CF) in the 21st Century: An Overview of Its Impact on Diverse Populations and Age Groups

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Introduction

Cystic fibrosis (CF) is a life-threatening genetic condition that primarily affects the lungs and digestive tract. It results from mutations in the CFTR gene and presents with a spectrum of severity depending on the specific mutations at hand and individual patient characteristics. Though common signs and symptoms include recurrent lung infections, mucus build-up in the lungs, and gastrointestinal issues, the disease's presentation and progression can vary greatly and may mimic other diseases, complicating clinicians' diagnosis.

Diagnosis of CF is typically confirmed through a sweat test and/or genetic testing. Despite advancements in treatment, there is no true cure for cystic fibrosis. Patients often face recurrent lung infections and other complications, leading to a shortened life expectancy with a median of 61.[1] Most commonly, patients with CF succumb to lung-related complications.[2]

While neonatal screening has significantly improved early detection, diagnosing cystic fibrosis in adults presents unique challenges. Misdiagnoses or delayed diagnoses can lead to prolonged periods without appropriate treatment, underscoring the importance of heightened awareness and improved diagnostic techniques for adult patients.

This poster explores the challenges in diagnosing adults with CF, the limitations of neonatal genetic screening, advances in genetic testing, and the misinformation surrounding ethnicity and genetic components of CF. It addresses the mental health impacts of living with CF, particularly in the context of emerging CF modulators, and highlights the importance of studying patients with late diagnoses. Understanding the presentations of CF beyond childhood is crucial for improving outcomes and quality of life for adult patients.

Neonatal Genetic Screening, Limitations, and Advances in Genetic Testing

Cystic fibrosis (CF) screening in Arizona typically involves testing for 46 common CFTR mutations, which are believed to capture approximately 92% of CF cases. [3] In addition to genetic testing, serum trypsinogen levels may also be used in the CF screening process. However, over 1,400 known mutations exist, and while current methods are generally effective, individuals with rarer mutations or milder forms of the disease may be missed. [4]

Screening practices have evolved significantly over the years as advancements in medical knowledge and genetic testing have been made. With such improvements to CF screening, more individuals are being diagnosed with the disease than ever before, and a push should be made towards improving screening and testing for individuals with rarer mutations or who were missed with previous methods and are presenting with symptoms later in life. [5] Of significance, neonatal screening methods may not always catch heterozygotes, and such individuals may be at risk for unknowingly passing on mutations to their children. [6] The variability in screening practices across different states also leads to inequities. Differences in the mutations tested and

the set cutoffs for 'positives' mean that the likelihood of an early and accurate CF diagnosis can depend significantly on geographic location. [7]

Advances in genetic testing are crucial in addressing these challenges. As our understanding of CFTR mutations expands and testing technology improves, more accurate and equitable screening programs can be developed, ensuring that individuals with CF are identified and treated as early as possible, regardless of where they live.

Challenges in Diagnosing Adults with CF

In Arizona, there is relatively widespread genetic screening of children for CF, leading to most cases being diagnosed early in life, which allows for prompt medical intervention, leading to improved health outcomes. However, such screening did not become widespread in Arizona until Oct 2007, [8] and those individuals born prior to it may not receive their CF diagnosis until later in life. In one study in the UK, 14.7% of those in the CF registry were diagnosed after their 16th birthday. [9] This delay is a slippery slope: the farther you are from the state given screening test, the worse the phenotype of CF is, and the more difficult it is to diagnose. Providers may be less inclined to consider CF as a diagnosis for a non-infant patient, as a heuristic in their head may assume the diagnosis would have been caught by the screening test or assume as the presentation is not “textbook” that it is not in their wheelhouse to make a diagnosis.

The presentation of CF in adulthood may be different and more varied from that of infancy or childhood. In one Italian study, the most common presentation in adults was lower FEV1 than expected, with 90.8% of patients having this finding. [10] They also noted 45.9% of patients with male infertility. However, another study in the UK showed the most common presentation as male infertility, with 90% of patients with this finding and only 60.8% of patients with lower FEV1. [11] This discrepancy highlights a key point we want to convey in this poster: adult presentations are varied, and thus, clinicians must be aware of the range of presentations in order to avoid missing a diagnosis and missing an opportunity to treat a CF patient as early as possible. This will be discussed later.

Misinformation Surrounding Ethnicity and Genetic Components of CF

Cystic Fibrosis historically has a perception of being a disease affecting those from Caucasian backgrounds, but such misconceptions can lead to underdiagnosis in individuals from other backgrounds. According to the Census Bureau, Arizona has a diversity index of 61.1%, with high percentages of Hispanic and Native American populations. [12] As these are already populations who are vulnerable to medical mistreatment, it is crucial that misinformation be addressed in order to ensure that all individuals, regardless of ethnicity or background, receive care and appropriate testing.

Cystic fibrosis is a disease associated with white people. This can lead to a lack of proper diagnoses for BIPOC peoples. Recent data also shows that the type of mutation of the CFTR gene varies with ancestral background. Type 1 mutations, or those with a premature stop codon that results in a truncated protein, are more common in non-white peoples. These mutations are not only less likely to be detected by current screening panels, but they are also the least treatable with current CF modulators, leading to an overall poor health story for those impacted. [13,14] Finally, just as with many chronic illnesses, BIPOC people are very underrepresented in clinical trials regarding CF, leading to an even poorer understanding of their disease process and how treatments will affect them. [15]

A study earlier this year profiled a Gambian individual born in Washington state who had two class I CFTR variants: c.2353C>T and c.1970delG – the latter of which is a novel mutation.[16] Both of these mutations also are not listed for treatment with modulators. For the first 15 years of this individual's life, they faced frequent infections with five acute pulmonary exacerbations, colonization with P. Aeruginosa and B. Cepacia, chronic constipation, and weight loss, uncontrolled dysglycemia with an A1C of 13.1%, scoliosis, and sinusitis with nasal polyps. Their current treatment regimen includes laxatives, intranasal steroids, sinus rinses, antihistamines, iron, pancreatic enzyme replacement, insulin, and chest physiotherapy with nebulized albuterol, 7% hypertonic saline, and dornase alfa. Azithromycin is given thrice a week and Vitamin D one a week. They have issues adhering to the medication regimen due to barriers.

Summary of the Cystic Fibrosis Foundation Patient Registry ALD Individuals, 2019–2022

Demographics	2019	2020	2021	2022
Individuals with ALD (n)[A]	1,787	1,950	2,087	2,126
Newly enrolled individuals with ALD (n)[B]	847	263	236	133
Mean age (years)	34.5	35.6	36.5	37.4
Median age (years)	32.1	33.1	34.0	34.8
Adults ≥18 years (%)	93.7	94.8	95.4	96.0
Race (mutually exclusive)[C]				
White (%)	91.2	91.1	90.5	90.8
African American (%)	4.5	4.6	5.1	5.0
Other race (%)	4.3	4.3	4.4	4.2
Hispanic (any race) (%)	8.8	8.8	8.7	9.1
Males (%)	54.9	54.7	54.6	54.3

Figure 1. *Cystic Fibrosis Foundation Patient Registry, 2022 Annual Data Report*, Bethesda, Maryland.

Advances in Genetic Testing

Newborn screening includes a cystic fibrosis genetic test, the earliest and most common CF genetic test, which detects the level of a pancreatic enzyme called immunoreactive trypsinogen (IRT) as the primary marker for CF diagnosis in neonates. This initial lab finding is usually

followed by a CFTR mutation test to confirm the diagnosis. Despite the precision and efficacy of this test, many individuals are not diagnosed with cystic fibrosis until beyond infancy. According to the Cystic Fibrosis Foundation, 59.8% of all new diagnoses and 91.6% of patients diagnosed under six months of age were identified through newborn screening in 2022.

The Cystic Fibrosis Patient Registry in 2022 reviewed the prevalence of the 25 most common phenotypes, finding that 85.4% of individuals had at least one copy of the F508del gene, while the remaining 14.6% had at least one copy of other common phenotypes. Considering there are over 2,000 variants of CF and not all are symptomatic, there is a crucial need for broader variant representation in genetic and newborn screening tests. Current testing standards predominantly cater to individuals of European ancestry, yet rare variants often present in Non-European patients.

Johns Hopkins DNA Diagnostic Laboratory offers the most comprehensive genetic test available, known as the Mutation Analysis Program (MAP). This test analyzes the entire CFTR gene, including introns, exons, 10kb upstream, 5kb downstream, and includes deletion/duplication analysis. The Cystic Fibrosis Foundation covers the cost of this test, excluding sample collection and shipping costs. MAP has increased sensitivity for detecting rare CF-causing variants. Additionally, the MAP team collects data on de-identified variants to better understand CF pathophysiology, CFTR function, and the efficacy of variant-specific FDA-approved modulators. The progress of MAP actively addresses the limitations of previous CF genetic testing and has the potential to set new standards for CF genetic testing modalities. [17, 18, 19]

	Mutation Analysis Program	*CFTR* Sequencing	*CFTR* Panel Genotyping
***CFTR* Exons**	100% at >50x coverage	100%	Selected variants only
***CFTR* Introns**	>96% at >50x coverage	10-20 nucleotides flanking each exon	No
Upstream & Downstream Regions	100% at >50x coverage	No	No
5' and 3' UTRs	100% at >50x coverage	Partial	No
Deletion/Duplication Analysis	Yes	Yes	Selected variants only
Number of Nucleotides Analyzed	205001	5166	1-165

Figure 2. *Mutation Analysis Program*. Johns Hopkins Medicine, www.hopkinsmedicine.org/dnadiagnostic/mutation-analysis-program. Accessed 17 Sept. 2024.

Mental Health Impacts and Cystic Fibrosis Modulators

Modulators cause clinically significant symptom worsening in adults w CF.[20] Individuals with cystic fibrosis (CF) and their caregivers experience higher rates of anxiety and depression compared to the general population, a trend also seen in other chronic illnesses. Depression in those with CF is linked to poorer adherence to treatments and negative health effects, such as reduced lung function, more frequent pulmonary exacerbations, lower health-related quality of life, and increased healthcare use and costs. The International Depression Epidemiological Study of 154 CF centers in 9 countries saw that of their 1005 included patients, close to a quarter of patients screened positive for depression and a third screened positive for anxiety. [21]

Since the introduction of Cystic Fibrosis Modulators there have been some case studies which report seeing an increase in symptoms associated with depression and anxiety. (Tindell et al., 2020; Ladores and Polen, 2021; Heo et al., 2022; Arslan et al., 2023). However, a one wider study of 70 patients based in Europe saw that starting modular therapy overall improves depression symptoms but does not affect anxiety symptoms at the group level in adult CF patients.[22] Despite this finding, the study recommends regular mental health screenings, including neurocognitive and neuropsychiatric assessments, for all CF patients as individual reactions vary greatly. Another systematic review, saw similar findings that most people with CF tolerate modulators well, a minority experience severe neuropsychiatric adverse effect (AEs). The review called for further research in understanding the biological mechanisms behind these effects to identify which individuals are likely to experience AEs and for developing evidence-based strategies to mitigate them while maintaining the effectiveness of the modulator. [23]

Importance of Studying Patients with Late Diagnosis of CF

Even though newborn screening for cystic fibrosis was completely implemented in the US by 2010, there are still delays in promptly evaluating newborns who have positive screening findings. One study discovered that delayed initiation of cystic fibrosis treatment is associated with worse long-term nutritional results by using data from the national patient registry.[24] Despite the common belief that cystic fibrosis (CF) is almost always diagnosed in childhood through newborn screening or early clinical presentation, diagnosing CF in adulthood is not rare for CF centers. One UK-based study showed that consistently, 30 to 50 new diagnoses per year are made after being missed by newborn screening. Notably, 14.7% (926 individuals) of adults in the CF registry were diagnosed at or after age 16, including 20 new diagnoses in that age group in 2021.[25] Data such as this has prompted research which indicates that adults diagnosed with CF often present with a different clinical phenotype, which likely contributes to the later age at diagnosis.[26]

An analysis of the adult-diagnosed CF population in the Canadian CF Registry indicated that a more timely diagnosis could positively impact prognosis. Older age at diagnosis was identified as an independent risk factor for death or transplantation in a multivariate model.[27]

Additionally, a large study using data from the U.S. CF Foundation Patient Registry demonstrated significant health improvements when adults diagnosed with CF over the age of 40 received CF-specific healthcare interventions.[28] Additionally, as many CFTR approved modulator therapies require certain mutations for a patient to be eligible, recognizing and formally diagnosing adults with CF can provide patients with life-saving therapies. [29]

It is crucial for both pulmonary and other specialists to recognize the potential for late presentation of cystic fibrosis, as advances in treatment over the years have significantly improved the prognosis for those with the condition. Ambiguous diagnostic results and late diagnoses in adulthood can lead to emotional distress and negative psychological impacts.[30] Patients diagnosed later in life need the same proactive and consistent treatment protocols as those diagnosed early, along with mental health follow-up to support their emotional and physical well-being. There is a clear need for the healthcare field to acknowledge that newborn screening is not foolproof and for further investigation into those patients with late diagnosis of CF to identify their needs and how to best support them.

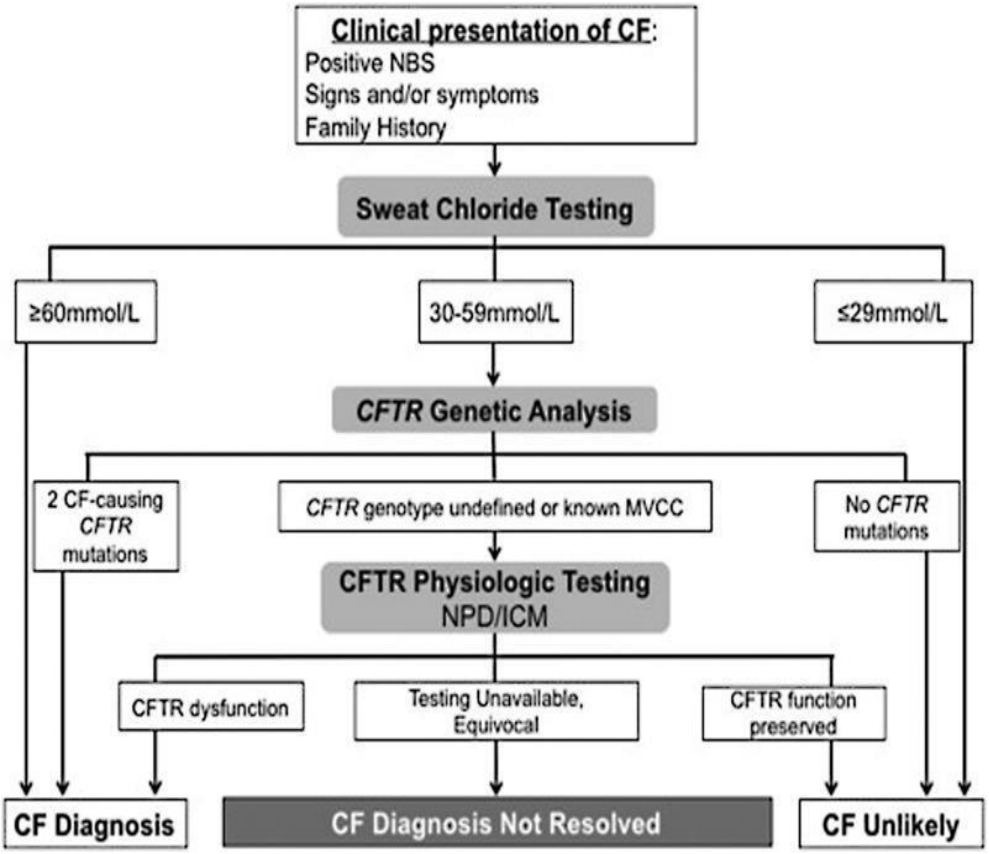

Figure 3. Current diagnostic algorithm for cystic fibrosis (CF). CFTR, cystic fibrosis transmembrane conductance regulator; ICM, intestinal current measurement; NBS, newborn screening; NPD, nasal potential difference. Reprinted from Farrell, Philip M. et al. *The Journal of Pediatrics*, Volume 181, S4 - S15.e1 [31]

Presentations of CF After Childhood

Cystic fibrosis (CF) is caused by the dysfunctional transport of chloride and other ions, such as sodium and bicarbonate, resulting in the production of thick, viscous secretions (e.g., mucus) in the lungs, pancreas, liver, intestine, and reproductive tract, and increased salt content in sweat gland secretions. Progressive lung disease is the primary cause of CF complications and patient mortality. The disease course varies widely, starting anywhere from a few months to several decades after birth, with many patients showing mild or atypical symptoms. Therefore, clinicians should be cautious not to exclude CF as a diagnosis, even if only a few typical signs and symptoms are present. [32]

A history of recurrent or chronic pancreatitis, persistent respiratory symptoms, or infertility in males should prompt consideration of a systemic issue.[33] Diagnosing CF in adulthood often stems from not identifying these patterns earlier, which can lead to higher patient morbidity, frustration, and diminished trust in medical professionals. Numerous case studies across the years have demonstrated the large heterogeneity in the presentation of CF, ranging from a 60-year-old male who presents with liver cirrhosis, chronic pancreatitis, and infertility to a 16-year-old male misdiagnosed with celiac disease who lived with nonspecific GI issues and weight loss.[34, 35] Even when patients present with classic respiratory symptoms such as a 63-year-old female with bronchiectasis since her teenage years, a CF diagnosis was missed due to a borderline sweat chloride test, which was followed up with only limited genetic testing. Only in-depth genetic testing and a nasal potential difference test confirmed the diagnosis.[36] Clinicians should recognize the wider array of potential presentations of CF and keep clinical awareness of CF given its broad symptom pool.

Social Determinants of Health

Social determinants of health (SDOH) are nonmedical factors that wield a profound influence on health outcomes, encompassing the conditions in which people are born, grow, work, live, and age. Research has unequivocally demonstrated that SDOH exerts a far greater impact on health than genetic factors or access to healthcare services.[37]

There has been a growing recognition of the profound impact of SDOH on the cystic fibrosis (CF) population. This group, in recent years, has been increasingly facing numerous challenges. A recent survey found that 64% of individuals with CF experience financial burdens, with 55% dealing with debt, 26% facing housing insecurity, and 33% struggling with food insecurity. Additionally, one-third of respondents reported unmet medical needs: 24% had unmet prescription needs, 12% delayed or shortened hospitalizations, and 10% postponed or skipped care center visits due to costs.[38]

These challenges are often linked to socioeconomic factors. An individual’s socioeconomic status (SES)—assessed by income, education, and occupation—is a critical component of

SDOH. According to the Cystic Fibrosis Foundation Patient Registry Annual Data Report 2022, less than half of the CF population is employed full-time, with 31.6% being college graduates and 9.2% attaining Master's or Doctoral-level degrees. Across all age groups, about half of the individuals in the Registry receive at least some component of their health insurance through federal or state-funded programs.[39]

Notably, Medicaid beneficiaries in the CF population, who tend to have lower SES, face a significant disparity in healthcare outcomes. Research by Schechter et al. found that the adjusted risk of death for people with CF on Medicaid was 3.65 times higher than for those not on Medicaid, underscoring the urgent need for targeted interventions.[40]

Conclusion

Our research highlights significant disparities in cystic fibrosis awareness, including limitations in early diagnosis, genetic testing, and timely treatment. It also addresses the increased risk of mental health disorders and variations in the presentation of cystic fibrosis. These findings underscore the importance of heightened awareness among the population and healthcare providers, which can support more timely diagnoses and more optimistic outcomes for cystic fibrosis patients.

Demystifying the archetype of what symptomatic and ancestral qualifications define a patient with cystic fibrosis enhances the diagnostic algorithms used by physicians and healthcare providers. Current genetic testing predominantly screens for the most common variants, excluding heterozygous and rare variants that primarily affect historically underrepresented populations. The Mutation Analysis Program offered at John Hopkins is the only comprehensive cystic fibrosis genetic test in the United States. Nationwide biomedical research institutions must broaden their cystic fibrosis genetic testing capabilities to offer equitable care to patients across the country.

In Arizona, newborn screening currently includes only 46 genetic variations out of the 2,000 known to exist. Expanding the range of genetic variants analyzed could improve numerous lives and reduce long-term healthcare costs, particularly in our increasingly diverse population.

Management of cystic fibrosis is further complicated by the side effects of modulator treatments, which can increase anxiety and depression. While studies present opposing views, continued investigation is necessary to determine the definitive causes of mental health disorders in cystic fibrosis patients.

Delayed or ambiguous diagnoses threaten the overall well-being of cystic fibrosis patients, making them more susceptible to nutrient deficiencies and emotional and psychological distress. Atypical presentations of cystic fibrosis can lead to missed or delayed diagnoses, as not all

patients present with the same symptoms. We recommend that healthcare providers consider cystic fibrosis as a potential diagnosis in patients with persistent or unexplained symptoms.

In conclusion, our research underscores the crucial gap in public awareness and clinical resources available for all patients living with cystic fibrosis. To bridge these knowledge gaps, we suggest targeted awareness campaigns and updated educational programs. Stakeholders should lead these efforts by integrating cystic fibrosis education into broader health initiatives, fostering collaborations with advocacy groups, and providing platforms for diverse cystic fibrosis patients to share their stories with all communities.

Future Direction

The future of cystic fibrosis (CF) care and research should involve several key initiatives aimed at improving diagnosis, management, and outcomes for patients, particularly those diagnosed in adulthood. By focusing on these future directions, we can significantly improve the identification and management of cystic fibrosis in adults, ultimately leading to better health outcomes and quality of life for the CF patient population.

There is a critical need to expand research on patients who receive their CF diagnosis later in life. Longitudinal studies are essential to understand better the long-term health outcomes and unique challenges faced by this population. These studies could help identify specific needs and inform more effective treatment strategies. In conjunction with such studies, developing comprehensive guidelines for the management of CF in adults is crucial. These guidelines should consider the disease progression in the adult CF population, ensuring that adults with CF receive tailored and effective care. When combined with effective screening, such advancements and efforts would ultimately work to improve patient outcomes and quality of life.

The development of a comprehensive application for individuals with CF could also help to improve patient care. Such an application could allow patients to keep all their medical information in one place, making it easier for clinicians to track disease progression, treatments, and outcomes. Improved information management would lead to better-coordinated care and enhanced patient outcomes.

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