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Impact of elexacaftor/tezacaftor/ivacaftor therapy on older adults with cystic fibrosis

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Background: Survival of people with cystic fibrosis (CF) has increased over the past few decades and is projected to rise further with the use of effective CF transmembrane conductance regulator (CFTR) modulator therapy. We aimed to assess clinical response of individuals with CF aged 40 and older to elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) therapy, and explore the impact of ELX/TEZ/IVA therapy on liver function tests (LFTs) and cardiovascular risk factors, including serum markers of inflammation, lipid profiles, blood pressure (BP), and noninvasive measurements of central arterial stiffness, including pulse wave velocity (PWV) and augmentation index (AI).
Methods: We conducted a single-center, prospective, observational study between August 2020 and December 2021 of people with CF aged 40 and older prescribed ELX/TEZ/IVA after licensing of this CFTR modulator in the United Kingdom. C-reactive protein (CRP), liver function, serum iron, lipid profile, spirometry, sweat, BP, PWV, and AI were tested at times of clinical stability before commencing ELX/TEZ/IVA therapy and 3 to 6 months thereafter. All permanent and temporary discontinuations of ELX/TEZ/IVA were recorded.
Results: Sixty-five of 73 adults aged 40 and older who commenced ELX/TEZ/IVA (including 31 *phe508del* homozygotes) were studied. Mean percentage predicted forced expiratory volume in 1 scone improved from 54.6 ± 22.9% to 61.0 ± 22.8% ($p < 0.001$), mean weight increased by 1.9 kg ($p < 0.001$), and sweat chloride decreased by 41.4 mmol/L ($p < 0.001$), with the greatest decrease seen in the minimal function group. There was an increase in serum iron levels from 11.9 ± 6.1 mmol/L to 15.7 ± 7 mmol/L ($p = 0.009$). CRP decreased from a median of 3 mg/L (interquartile range 1.0–59) to 1 mg/L (interquartile range 1.0–11.0) ($p = 0.001$). A change in lipid profiles was observed with increases in triglycerides ($p = 0.006$) and apolipoprotein A1 ($p = 0.006$). No statistically significant change was found in serum total cholesterol, high-density lipoprotein, low-density lipoprotein, cholesterol/high-density lipoprotein ratio, or apolipoprotein B or apolipoprotein B/A1 ratio. There were also no significant changes in BP or AI, although PWV increased from 8.6 ± 1.2 m/s to 9.3 ± 2.4 m/s ($p = 0.02$). LFTs showed increases in aspartate aminotransferase (22.6 ± 8.8 IU/L to 23.8 ± 10.7 IU/L; $p = 0.006$) and bilirubin 7.5 ± 6.0 µmol/L to 9.3 ± 5.8 µmol/L ($p < 0.001$).
Conclusions: Individuals with CF aged 40 and older had a response to ELX/TEZ/IVA therapy, measured according to sweat chloride, spirometry, and weight, similar to that of younger individuals with CF in phase III trials. Further research is required to establish the longer-term impact of CFTR modulation on comorbidities including dyslipidemia and other potential risk factors for cardiovascular disease.

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Feasibility of using a modified menstrual tracking app to correlate menstrual cycles and cystic fibrosis symptoms in women with CF: Early findings of the MENSTRUAL study

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Background: The MENstrual Symptom Tracking to Understand and Assess (women) Living with CF (MENSTRUAL) study explores the feasibility of using a modified menstrual tracking smartphone application to track disease-specific symptoms during the menstrual cycle in women with cystic fibrosis (CF).
Methods: In this prospective cohort study, participants were recruited using social media and listservs and through referrals from CF care centers. After completing a virtual training session, participants used a modified period tracking app daily to report whether they had menstrual bleeding and the presence and severity of CF symptoms, such as lung congestion, coughing, and hemoptysis. These symptoms were considered equal and were selected from a preset list developed by women with CF and a multidisciplinary patient-centered team of family practice, ob/gyn, and CF care clinicians. Participants tracked their daily symptoms for 3 consecutive months using the smartphone application. We received institutional review board approval, and all participants provided informed consent.
Results: We were able to modify a smartphone application to track each participant's menstrual cycles and CF symptoms. Seventy-four women with CF participated in this study. Participants were age 18 to 45 and from every region of the United States. Eighty percent of participants reported that it was very easy to track CF symptoms using the application. Participants reported that it took them less than 1 minute to complete the daily track. Only two participants (2.7%) needed additional technical support to use the application. The application allowed us to determine where each participant was in her menstrual cycle and whether she had frequent or severe CF symptoms. Preliminary analysis of the data suggests that, during the luteal phase of the menstrual cycle, there is an increase in the overall number and severity of CF symptoms.
Conclusions: A modified menstrual tracking smartphone application is feasible to study the intersection of menstrual and CF-related symptoms. Although larger studies are needed, these results may inform CF clinical practice by demonstrating that women can use a smartphone application to anticipate menstrual cycle–related changes in CF symptomatology and share this tracking with their CF care clinicians. These results may also help focus future interventions to alleviate symptoms in menstruating women with CF. A menstrual tracking smartphone application could be used to identify trends in menstrual cycles and disease-specific symptoms to promote a personalized approach to CF care and research.
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Characteristics of late diagnosis through newborn screening and effects on growth and pulmonary health outcomes in infants with cystic fibrosis

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Background: Newborn screening (NBS) for cystic fibrosis (CF) was fully implemented in the United States in 2010, but delays in timeliness of evaluation for infants with positive NBS tests persist. We aimed to determine characteristics and effects of late CF care on health outcomes in infants with CF.
Methods: We studied infants enrolled in the Cystic Fibrosis Foundation Patient Registry born from 2010 to 2018 and diagnosed before the age of 1. Exclusions were meconium ileus, prematurity, sweat chloride less than 30 mEq/L, CF transmembrane conductance regulator (CFTR) modulator use before age 1, missing gestational age, and missing ZIP code. Age at first evaluation (AFE) was defined as the earliest age of one (or more) of the following CF events: sweat test, CF center clinical encounter, or care episode lasting longer than 24 hours (hospitalization). We compared initial CF event characteristics and nutritional and pulmonary health outcomes of infants from the youngest (early) to the oldest (late) AFE quartile, matching for covariates chosen a priori of sex, median income according to ZIP code, race, ethnicity, genotype (McKone class), and pancreatic status.
Results: Of 6,879 infants, 3,607 met inclusion criteria. After quartile assignment and matching, 551 infants were in each cohort. Median AFE was

10 days (interquartile range 8–12) in the early cohort and 47d (interquartile range 37–72) in the late cohort ($p < .001$). Late infants were more likely to have only one CFTR variant detected on commercial 23-variant panels (28%, vs 22% for early, $p = 0.01$) and 39-variant panels (26%, vs 17% for early, $p < 0.001$). Late infants were also more likely to have a sweat test as a first CF event (70%, vs 50% for early, $p < 0.001$) and less likely to have a clinical encounter as a first CF event (49%, vs 61% for early, $p < 0.001$). Breastfeeding rates were significantly lower at 2 and 6 months of age in the late infants. Late infants were less likely to have parents with reported college or graduate school education. Despite no differences in birth weight or length, late infants had lower median weight-for-age and height-for-age Z-scores at first encounter and 1 year. At 3 and 5 years, weight-for-age Z-scores were similar, but late infants had persistently lower height-for-age. There were no differences in *Pseudomonas aeruginosa* infection, pulmonary function at age 7, or hospitalization rates between cohorts.

Conclusions: Use of limited CFTR variant panels may result in later evaluation at a CF center. Although groups were matched for income, parent education may also contribute to later diagnosis, potentially because of difficulties navigating the health care system and confirmatory testing. Late diagnosis was associated with less likelihood of breastfeeding, lower weight and height at presentation and 1 year, and lower height through 5 years of age. This study highlights ongoing delays in timely NBS in the United States, with resultant long-term consequences. Qualitative studies and improvement work that evaluate more specific system factors in NBS follow-up programs are essential to ensure equitable, timely evaluation at CF care centers for all infants (MCCOLL19QI10).

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Outcomes of children with cystic fibrosis transmembrane conductance regulator–related metabolic syndrome

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Background: Newborn screening (NBS) evaluation for high immunoreactive trypsinogen level (IRT) associated with a cystic fibrosis (CF) transmembrane conductance regulator (CFTR) mutation (IRT+/DNA+) has led to early identification and treatment of children with severe CF, although it has also identified children with genetic and biochemical findings indicating risk of CF but without symptoms or conclusive diagnostic results (CFTR-related metabolic syndrome (CRMS)). Some of these children transition to CF, but the effect of early diagnosis and treatment is unclear. This study evaluated outcomes of children designated with CRMS after NBS referral.

Methods: Children with IRT+/DNA+ on NBS referred to our CF Center from 2008 to 2020 had their charts reviewed and data collected for results of IRT, genotype, sweat chloride test (SCT) values, stool elastase, and sputum swab cultures. Children were categorized according to the most recent Cystic Fibrosis Foundation diagnostic guidelines as CFTR mutation carrier, CF, or CRMS. CRMS group was further subcategorized according to the child's final diagnosis in 2020 as CRMS transitioned to CF (CRMS-CF), CRMS transitioned to carrier (CRMS-carrier), or CRMS persistent (CRMS-P).

Results: Of 1,346 children referred for IRT+/DNA+ with a SCT, 86% were initially designated as carriers, 10% as CF, and 5% as CRMS. Mean first SCT was significantly higher for CRMS than for carriers ($p < 0.001$). Of those initially designated as CRMS (n = 63), 17.5% transitioned to CF because repeat SCT reaching diagnostic threshold, clinical symptoms, expanded genetics, or re-classification of their CFTR mutation. Of CRMS-CF, 36% had initial SCT between 30 mEq/L and 39 mEq/L, 36% between 40 mEq/L and 49 mEq/L, and 27% between 50 mEq/L and 59 mEq/L. Age of transition for this group ranged from 2.2 months to 8.4 years. Mean first SCT value was significantly higher for CRMS-CF (45 mEq/L) than CRMS-P (30.27 mEq/L) ($p < 0.001$) and CRMS-carrier (35 mEq/L) ($p = 0.003$). CRMS-CF had significantly higher values at all repeat SCTs than CRMS-P ($p < 0.001$). No association between IRT and first SCT or difference in stool elastase levels was noted for CRMS subgroups. CRMS-CF cultured more bacterial species than CRMS-carrier ($p < 0.001$) or CRMS-P ($p = 0.01$). Of children with CRMS that cultured *Pseudomonas aeruginosa,* 50% transitioned to CRMS-CF. *Pseudomonas* was cultured at least once in 19% of CRMS-CF, 7.7% of CRMS-P, and 0% of CRMS-carrier.

Conclusions: Expanded genetics and repeat SCT were helpful in diagnosing children at our CF center initially designated as CRMS who eventually transitioned to CF. Thirty-six percent of the CRMS-CF group had a first SCT of less than 40 mEq/L, in contrast to prior studies finding no children with an initial SCT ofless than 40 mEq/L transitioning to CF. Most of the CRMS-CF group had increasing SCT values before transitioning to CF, but not all reached the diagnostic threshold before genotype or clinical symptoms confirmed diagnosis. Thirty-seven percent of CRMS-CF transitioned after 6 years of age. Annual sputum culture appears warranted in children designated with CRMS given known deleterious effects of certain pathogens on the lungs of children at risk of CF. Prospective evidence-based monitoring will provide greater insight into the risk of CF in this population.

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Making cystic fibrosis community insights more accessible: An overview of the Cystic Fibrosis Foundation Community Data Repository

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Background: Community Voice is a program that enables the Cystic Fibrosis Foundation (CFF) and cystic fibrosis (CF) researchers and clinicians to tap into the lived experiences and insights of the CF community. Since it began in 2014, Community Voice has provided volunteer opportunities for community members and has shaped CF research, care, and CFF programmatic efforts. To ensure that gathering insights and lessons learned from community members is efficient and not duplicative of past research, the CFF created the Community Data Repository in 2018 to house past research on insights of the CF community, organize the research, and tag it for future use.

Methods: Previous community research and methodologies were identified and organized in chronological order. These included notes from interviews with community members, focus group reports, survey result reports, and other community data collected. Software was identified to assist in tagging efforts, and QSR International NVivo 11 for Windows was chosen to create hierarchical tagging. Two reviewers reviewed, tagged, and sorted the projects by chronological order. Tags were then categorized, consolidated, and cleaned up. More than 100 projects were tagged, most of them surveys or focus group notes. Nearly half were Community Voice projects completed from 2017 to 2022). All raw data were then organized separate from NVivo to allow open access and use for users.

Results: About one-third of tags were categorized into life with CF, more than 600 total tags. This includes research and data related to connecting with others, mental health, perceptions of CF, aging, nutrition, and reproductive health. The remaining two-thirds were sorted into four other major categories: CF complications (400+), research (300+), access (300+), and delivery of care (300+). CF complications tags included community data on complications that people living with CF face, such as pulmonary complications, gastrointestinal problems, endocrine complications, sinus complications, and aging-related problems. Research tags mostly comprised the community's perceptions of clinical trials, modulators, research prioritization, and drug discovery. Access tags included access to health insurance, health care expenses, and policy tags. Delivery of care includes community data on treatment and therapies, treatment burden, care centers, diagnosis of CF, and other complications. These five major categories make up most of the tags in the Community Data Repository. Tags related to the CFF were also created, which allows flexibility in tagging programmatic and CFF-related efforts within community data collected. An admin tag was also created to denote certain characteristics of projects, such as available segmentation or potential data cuts.

Conclusions: The Community Data Repository provides a robust look into past community research involving people living with CF and their family members. This resource is available, upon request, to CF researchers and clinicians who want to partner with the community in future projects and is also available to facilitate future engagement efforts.