

# PYIR

Pediatric Year  
in Review



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# Pediatric Year in Review Bibliography

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## Advances in Cystic Fibrosis

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### DAILY TREATMENT REGIMEN IN CYSTIC FIBROSIS

Mayer-Hamblett N, Ratjen F, Russell R, Donaldson SH, Rieker KA, Sawicki GS, Odem-Davis K, Young JK, Rosenbluth D, Taylor-Cousar JL, Goss CH, et al.

**Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials.** *Lancet Respir Med.* 2023 Apr 1;11(4):329-40.

#### Summary

In this new era of CFTR modulators, lung health for many people with CF is greatly improved. Many have questioned whether the daily time-intensive mucus clearance regimen is still necessary. To answer this question, these 2 parallel clinical trials examined the health effects of people with cystic fibrosis on elexacaftor tezacaftor ivacaftor (ETI) discontinuing either dornase alfa or hypertonic saline. The outcome was change in FEV<sub>1</sub> percent predicted over 6 weeks. These were non-inferiority trials, so they compared that the change in FEV<sub>1</sub> percent predicted was not worse in those that discontinued a medication compared to those that continued the medication. The clinical trials enrolled 595 teenagers or adults with cystic fibrosis on ETI with normal or mild lung disease. There were no significant differences in change in FEV<sub>1</sub> percent predicted over 6 weeks between those who continued or discontinued therapy for both the dornase alfa and the hypertonic saline studies.

#### Comments

1. Short-term discontinuation of either hypertonic saline or dornase alfa did not change FEV<sub>1</sub> over 6 weeks, but the long-term effect of discontinuation on pulmonary function decline and exacerbations remains unknown.
2. In the era of highly effective CFTR modulators, the need for daily preventative treatments and therapies must be investigated and balanced with the burden on daily life.

3. It is not known if daily medications can be reduced in those with moderate or severe lung disease from cystic fibrosis on ETI.
4. Future studies are needed to follow long-term outcomes and if people with more severe lung disease can also discontinue therapies safely.
5. Unique trial designs such as non-inferiority clinical trials may be necessary in the era of CFTR modulator therapy.

### PREGNANCY IN CYSTIC FIBROSIS

Peng G, Taylor-Cousar JL, Lee M, Keller A, West NE, Kazmerski TM, Goralski JL, Aitken ML, Roe AH, Hadjiliadis D, Uluer A, et al. **Association between unplanned pregnancies and maternal exacerbations in cystic fibrosis.** *J Cyst Fibros.* 2023 Apr 5.

#### Summary

Pregnancies in people with CF have greatly increased in the past few years with CFTR modulators. This multi-center, retrospective study compared the health effects of pregnancy in people with CF who had planned pregnancies compared to unplanned pregnancies. They found that 40% of the pregnancies were unplanned. Compared to those with planned pregnancies, people with CF with unplanned pregnancies were 3 years younger, less likely to have college education, had lower FEV<sub>1</sub> % predicted pre-pregnancy, and lower BMI pre-pregnancy. There was a similar drop in FEV<sub>1</sub> % predicted in those with planned and unplanned pregnancies. In those with a planned pregnancy, the number of pulmonary exacerbations was 16% lower after pregnancy compared to prior to becoming pregnant. However, in the unplanned pregnancy group, the number of pulmonary exacerbations was 26% higher after pregnancy compared to before pregnancy. Planned pregnancies had a higher rate of Cesarean sections, a lower rate of preterm birth, lower rate of NICU stays, and higher rate of breastfeeding.

#### Comments

1. Pregnancy in people with CF is increasing as health outcomes have improved with CFTR modulators.

2. Unplanned pregnancy is common in people with CF.
3. This study found that people with CF with unplanned pregnancies had a 26% increase in number of pulmonary exacerbations, while planned pregnancies had fewer exacerbations, even though there was no difference in lung function decline between groups.
4. People with unplanned pregnancies had worse baseline health and had higher rate of birth or neonatal complications.
5. This study highlights the need for discussion of highly effective contraception and family planning with people with CF.

### INTERNATIONAL DISPARITIES IN CYSTIC FIBROSIS

Zampoli M, Sykes J, Verstraete J, Cheng SY, Morrow B, Pepper MS, Stewart C, Zar HJ, Stephenson AL. **Global disparities in cystic fibrosis outcomes prior to CFTR modulators: A CF registries cohort study in South Africa and Canada.** *J Cyst Fibro.* 2023 Sep 12.

#### Summary

Mortality in CF varies greatly between countries across the globe, but differences in disease characteristics or care are not described. This cross-sectional study compared lung function and nutritional outcomes in people with CF in the Canadian CF registry and in the South African CF registry in 2018. The study only compared people not on CFTR modulators and those without lung transplants. People with CF in South Africa has lower pulmonary function (FEV<sub>1</sub> -8.9%) than people with CF in Canada at all ages and in a multivariate analysis adjusted for confounders such as *Pseudomonas*, poor nutrition, and pulmonary therapies. Compared to Canada, poor nutrition was 1.7 higher in South Africa in multivariate analysis. There were many differences in the health of people between countries. A higher proportion of people with CF in South Africa had *Pseudomonas*, used hypertonic saline and azithromycin, and had 1 or more courses of IV antibiotics than in Canada. There was a large disparity in diagnosis by newborn screening as there was no newborn screening in South Africa in 2018, while 13% of people in Canada were diagnosed via newborn screening.

#### Comments

1. Even with adjustment of CF disease characteristics, people with CF living in South Africa had worse health outcomes than in Canada.
2. Socioeconomic status, access to care, quality of healthcare and public health are likely contribute

to the observed disparities, although were not measured in this study

3. Health disparities between high-income and low-income countries are likely much worse than this study described due to lack of access to CFTR modulators and lung transplant.
4. There is an urgent need for advocacy for equitable access to all CF-specific medications, including pancreatic enzymes and CFTR modulators, for people with CF in all countries.
5. CF registries are needed for other low-income or middle-income countries to identify areas for interventions to improve patient outcomes.

### EFFECT OF CFTR MODULATORS ON SPUTUM

Schaupp L, Addante A, Völler M, Fentker K, Kuppe A, Bardua M, Duerr J, Piehler L, Röhm J, Thee S, Kirchner M, et al. **Longitudinal effects of ellexacaftor/tezacaftor/ivacaftor on sputum viscoelastic properties, airway infection and inflammation in patients with cystic fibrosis.** *Eur Resp J.* 2023 Aug 1;62(2).

#### Summary

Ellexacaftor/tezacaftor/ivacaftor (ETI) improves pulmonary disease but the pathways and effects have not been well-described. This prospective study of 79 people with CF investigated the downstream effects of ETI by comparing changes in airway mucus characteristics (including microbiome, inflammation, proteases, viscoelasticity) before and after ellexacaftor/tezacaftor/ivacaftor. People with CF were also compared to normal controls. The total bacterial load of the airway mucus microbiome did not change but there was an increase in  $\alpha$ -diversity with ETI. The relative abundance of *Pseudomonas aeruginosa* decreased in the sputum with ETI. No aspect of the airway mucus microbiome normalized on ETI. Of the airway inflammation markers, only IL-1 $\beta$  improved over time with ETI. Airway inflammation remained higher than normal controls. Free and membrane-bound neutrophil elastase significantly improved with ETI, but were higher than normal controls. The sputum viscoelastic properties significantly improved by 3 months of ETI, but did not normalize.

#### Comments

1. Airway mucus from people with CF on ETI improved in multiple aspects, such as microbiome diversity, abundance of *Pseudomonas*, and neutrophil elastase, but did not normalize.
2. Airway sputum inflammation remained elevated on ETI, which is concerning for ongoing lung damage.

3. The impact of ETI on airway mucus environment may be different in infants and children with CF, as their baseline respiratory disease is not as advanced as adults, but needs further investigation.
4. While ETI has led to significant improvements in the health of people with CF, this study highlights that ETI does not normalize the respiratory environment and is not a cure for CF.
4. Many pathways to lung disease severity in cystic fibrosis had significant loci identified including inflammation, infection, and lung development.
5. The study's results are biased as almost all the samples were from people of European background and thus not applicable to people with CF of other backgrounds, races, or ethnicities.

### GENETIC MODIFIERS IN CYSTIC FIBROSIS

Zhou YH, Gallins PJ, Pace RG, Dang H, Aksit MA, Blue EE, Buckingham KJ, Collaco JM, Faino AV, Gordon WW, Hetrick KN, et al. **Genetic modifiers of cystic fibrosis lung disease severity: whole-genome analysis of 7,840 patients.** *Am J Resp Crit Care Med* 2023 May 15;207(10):1324-33.

#### Summary

Lung disease severity is highly variable and the variability is thought to be partially due to non-CFTR modifier genes. This is the largest study in people with CF to examine for possible modifier genes. This study combined whole genome sequencing (WGS) data from 4,238 people with CF from prior CF studies with genome-wide genotype data from 3,592 people with CF. All samples had lung function data prior to CFTR modulator therapy. Lung function was transformed into a quantitative measure, Kulich normal residual mortality-adjusted (KNoRMA) lung phenotype, allowing for comparisons across ages or cohort effects. The study examined for genetic loci that were associated with KNoRMA lung phenotype. There were six genome-wide significant loci and four suggestive loci were identified, all of which were genes that were likely biologically relevant to CF lung physiology. The identified loci were involved in inflammation, bacterial infection and host responses, immunity, endomembrane and microtubular function, and lung development. Of note, approximately 95% of the samples were from people of European ancestry.

#### Comments

1. It is still unknown why lung severity varies in people with CF and non-CFTR modifier genes may contribute to the variability.
2. Non-CFTR modifier genes are a potential target for therapeutic intervention, particularly in people with CFTR variants non-responsive to CFTR modulators.
3. This study identified ten genetic loci that were associated with lung disease severity.

### LUNG TRANSPLANT IN CYSTIC FIBROSIS

Hayes Jr D, Dani A, Guzman-Gomez A, Zafar F, Morales DL, Ziady AG. **Changing racial and ethnic differences for lung transplantation in cystic fibrosis.** *Ped Transpl* 2023 Feb;27(1):e1

#### Summary

Lung transplant has changed in cystic fibrosis with the health of many people with CF dramatically improving with CFTR modulators, but people who are Asian, Black, or Hispanic are less likely to qualify for or be prescribed CFTR modulators. This study used the United Network for Organ Sharing (UNOS) database to examine lung transplant frequency in people with CF. Lung transplants in children and adults with CF dramatically decreased after 2019 with the advent of elexacaftor/tezacaftor/ivacaftor. The average per year in adults with CF prior to 2019 was 145 but significantly decreased to 73 in 2020 and 45 in 2021. The proportion of adults receiving lung transplants having cystic fibrosis also significantly decreased from about half of transplants to 16% after 2019. Similar trends were seen in the pediatric CF population with only 2 transplants in 2021. The authors compared changes in the proportion of lung transplants with CF, comparing those who were non-Hispanic white to those of another race/ethnicity. The proportion of lung transplants in non-Hispanic white children decreased from 49.5% before 2019 to 8.3% after 2019. However, children of other races and ethnicities had a smaller decrease: 33.5% before 2019 to 22.5% after 2019.

#### Comments

1. The frequency of lung transplants significantly decreased in both children and adults with cystic fibrosis since the approval of elexacaftor/tezacaftor/ivacaftor in 2019.
2. People with cystic fibrosis who are a race or ethnicity other than non-Hispanic white did not have as much of an improvement in lung transplant frequency.
3. This is the first study to describe differences in lung transplant trends by race and ethnicity in cystic fibrosis.

4. As there is an ongoing need for lung transplantation in people with CF who are Asian, Black, or Hispanic, further work and/or resources are needed to ensure transplantation is accessible to those who need it.

#### OTHER ARTICLES OF INTEREST

Nichols DP, Morgan SJ, Skalland M, Vo AT, Van Daltsen JM, Singh SB, Ni W, Hoffman LR, McGeer K, Heltshe SL, Clancy JP, et al. **Pharmacologic improvement of CFTR function rapidly decreases sputum pathogen density, but lung infections generally persist.** *J Clin Invest.* 2023 May 15;133(10).

Hayes Jr D, Dani A, Guzman-Gomez A, Zafar F, Morales DL, Ziady AG. **Changing racial and ethnic differences for lung transplantation in cystic fibrosis.** *Ped Transpl* 2023 Feb;27(1):e1

McGarry ME, Ren CL, Wu R, Farrell PM, McColley SA. **Detection of disease-causing CFTR variants in state newborn screening programs.** *Ped Pulm.* 2023 Feb;58(2):465-74.

Martiniano SL, Wu R, Farrell PM, Ren CL, Sontag MK, Elbert A, McColley SA. **Late Diagnosis in the Era of Universal Newborn Screening Negatively Affects Short- and Long-Term Growth and Health Outcomes in Infants with Cystic Fibrosis.** *J Peds.* 2023 Nov 1;262:113595.

Palipana AK, Vancil A, Gecili E, Rasnick E, Ehrlich D, Pestian T, Andrinopoulou ER, Afonso PM, Keogh RH, Ni Y, Dexheimer JW, et al. **Social-environmental phenotypes of rapid cystic fibrosis lung disease progression in adolescents and young adults living in the United States.** *Enviro Adv.* 2023 Dec 1;14:100449.

Goetz DM, Frederick CK, Perez G, Borowitz D. **Airway clearance after highly effective CFTR modulators: normalizing life and reducing treatment burden.** *Ped Pulm.* 2023 Aug;58(8):2375-80.

Gómez-Montes E, Salcedo Lobato E, Galindo Izquierdo A, García Alcázar D, Villalain González C, Moral-Pumarega MT, Bustos Lozano G, Luna-Paredes C. **Prenatal cystic fibrosis transmembrane conductance regulator modulator therapy: a promising way to change the impact of cystic fibrosis.** *Fetal Diagnosis and Therapy.* 2023 Jul 11;50(2):136-42.

Patel P, Yeley J, Brown C, Wesson M, Lesko BG, Slaven JE, Chmiel JF, Jain R, Sanders DB. **Immunoreactive trypsinogen in infants born to women with cystic fibrosis taking elexacaftor-tezacaftor-ivacaftor.** *International Journal of Neonatal Screening.* 2023 Feb 21;9(1):10.

Flatt AJ, Sheikh S, Peleckis AJ, Alvarado P, Hadjiliadis D, Stefanovski D, Gallop RJ, Rubenstein RC, Kelly A, Rickels MR. **Preservation of  $\beta$ -cell function in pancreatic insufficient cystic fibrosis with highly effective CFTR modulator therapy.** *J Clin Endo Meta.* 2024 Jan;109(1):151-60.

## Precision Medicine in Asthma: Omics and Biologics

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Namjou B, Lape M, Malolepsza E, DeVore SB, Weirauch MT, DiKilitas O, Jarvik GP, Kiryluk K, Kullo IJ, Liu C, Luo Y, Satterfield BA, Smoller JW, Walunas TL, Connolly J, Sleiman P, Mersha TB, Mentch FD, Hakonarson H, Prows CA, Biagini JM, Khurana Hershey GK, Martin LJ, Kottyan L; eMERGE Network. **Multiancestral polygenic risk score for pediatric asthma.** *J Allergy Clin Immunol.* 2022 Nov;150(5):1086-1096. doi: 10.1016/j.jaci.2022.03.035.

### Summary

The objective of this study was to train and validate a polygenic risk score based on asthma genetic determinants to predict disease occurrence in children of diverse ancestries. The investigators applied a Bayesian regression framework method using the Trans-National Asthma Genetic Consortium genome-wide association study summary statistics to derive a multiancestral PRS score, used an electronic medical record cohort as a training set, and then used 2 independent cohorts to validate and replicate the findings. The multiancestral asthma polygenic risk score was associated with asthma in the 2 pediatric validation datasets. The investigators found significant discrimination across pediatric subcohorts of European, African admixed American, Southeast Asian, and East Asian ancestry. Children with the top 5% polygenic risk scores had 2.80 to 5.82 increased odds of asthma compared to the bottom 5% across the training and 2 validation cohorts when adjusted for ancestry. A phenome-wide association study analysis confirmed the strong association of the identified polygenic risk score with asthma and related phenotypes.

### Comments

1. The investigators developed an asthma polygenic risk score had good discriminatory performance in children of diverse ancestries, demonstrated increased performance compared to other scores, and showed potential pleiotropic effects.
2. The asthma polygenic risk score performed better in children that is similar to previous genetic studies suggesting a larger genetic contribution in children compared to adults.

3. One limitation of the study was the investigators were unable to identify individuals with adult-onset asthma.
4. This polygenic risk score may have future potential to help families of children at high risk for asthma take preventive steps to avoid disease.

Granell R, Curtin JA, Haider S, Kitaba NT, Mathie SA, Gregory LG, Yates LL, Tutino M, Hankinson J, Perretti M, Vonk JM, Arshad HS, Cullinan P, Fontanella S, Roberts GC, Koppelman GH, Simpson A, Turner SW, Murray CS, Lloyd CM, Holloway JW, Custovic A; UNICORN and Breathing Together investigators. **A meta-analysis of genome-wide association studies of childhood wheezing phenotypes identifies ANXA1 as a susceptibility locus for persistent wheezing.** *Elife.* 2023 May 25;12:e84315. doi: 10.7554/eLife.84315.

### Summary

The investigators conducted a novel multivariate GWAS meta-analysis to identify genetic associates of childhood wheezing phenotypes using an unbiased analysis of data collected from birth to 18 years in 9568 individuals from five UK birth cohorts. The investigators identified subsets of SNPs differentially associated across four wheezing phenotypes: early-onset persistent (44 SNPs, 19 loci), early-onset pre-school remitting (25 SNPs, 10 loci), early-onset mid-childhood remitting (33 SNPs, 9 loci), and late-onset (32 SNPs, 20 loci). The analysis demonstrated variation in a novel locus on chr9q21.13 (ANXA1; rs75260654) was associated solely with early-onset persistent wheeze.

### Comments

1. The investigators identified a novel locus in chr9q21 nearby ANXA1 exclusively associated with the early-onset persistent wheeze phenotype. Previous studies have demonstrated that genetic variation in ORMDL3 and GSDMB (17q12 locus) are associated with childhood-onset asthma but also have associations with additional preschool wheezing phenotypes (both early- and intermediate-onset persistent wheeze).

2. There was a lack of genetic associations spanning across different phenotypes suggesting that the genetic architecture of each preschool wheeze phenotype may be characterized by unique phenotype-specific genetic associations.
3. By GWAS standards, the study was relatively small and potentially underpowered. This may be less of an issue in this study as the children had detailed phenotyping over more than two decades in five independent birth cohorts.
4. Another limitation was that the study population was largely of European descent, and the results may not be generalizable to other populations.
5. The ANXA1 pathway in persistent disease may be a future therapeutic target.

Dapas M, Thompson EE, Wentworth-Sheilds W, Clay S, Visness CM, Calatroni A, Sordillo JE, Gold DR, Wood RA, Makhija M, Khurana Hershey GK, Sherenian MG, Gruchalla RS, Gill MA, Liu AH, Kim H, Kattan M, Bacharier LB, Rastogi D, Altman MC, Busse WW, Becker PM, Nicolae D, O'Connor GT, Gern JE, Jackson DJ, Ober C. **Multi-omic association study identifies DNA methylation-mediated genotype and smoking exposure effects on lung function in children living in urban settings.** *PLoS Genet.* 2023 Jan 13;19(1):e1010594. doi: 10.1371/journal.pgen.1010594.

### Summary

The objective of this study was to perform GWAS analyses of lung function in a multiethnic cohort of 1,035 children from two clinical trials living in low-income urban neighborhoods. One novel locus at the TDRD9 gene in chromosome 14q32.33 was significantly associated with percent predicted forced expiratory volume in one second (FEV1). Using mendelian randomization and mediation analyses, the investigators demonstrated that this genetic effect on FEV1 was partially mediated by DNA methylation levels at this locus in airway epithelial cells and was also significantly associated with environmental tobacco smoke exposure. In addition, the investigators also identified a nearby gene, PPP1R13B, which promotes the deactivation of damaged cells and the expression of this gene in airway cells supported these genetic and epigenetic effects.

### Comments

1. The investigators found a common genetic variant associated with lower lung function in multiethnic children living in low-income urban neighborhoods and this association was mediated by epigenetic changes in DNA

methylation, which also correlated with smoke exposure.

2. The methods used, Mendelian randomization and mediation analyses, rely on assumptions that are challenging to verify. The investigators performed a secondary analysis which combined the instrumental variants into a single, unweighted score and systematically tested for confounding associations with additional environmental measures available in the two urban studies. However, unmeasured confounding factors are still possible.
3. Another limitation was the relatively small sample size for a GWAS. This likely contributed to the lack of statistically significant replication for previously identified lung function loci in prior GWAS. However, the two urban cohorts represent unique pediatric populations that likely harbor distinct genetic and environmental risk factors compared to older, primarily European ancestry cohorts included in previous GWAS of lung function.
4. The findings of this study have yet to be replicated in an independent cohort and are thus preliminary but future studies would need to be repeated in similar populations.
5. These findings may lead to future interventions to decrease the burden of asthma in socioeconomically disadvantaged children.

Jackson DJ, Bacharier LB, Gergen PJ, Gagalis L, Calatroni A, Wellford S, et al. **Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): a randomised, double-blind, placebo-controlled, parallel-group trial.** *Lancet* 2022;400:502-11.

### Summary

The objective of this study was to examine the efficacy of mepolizumab compared to placebo in 290 urban 6–17-year-old children and adolescents living in disadvantaged neighborhoods with a history of 2 or more exacerbations in previous year and blood eosinophils  $\geq 150$  cells/mm<sup>3</sup>. Phenotype-directed therapy with mepolizumab in urban children was demonstrated to reduce exacerbations, annualized rate of asthma exacerbations was 0.96 (95% confidence interval [CI] 0.78–1.17) with mepolizumab and 1.30 (95% CI, 1.08–1.57) with placebo (rate ratio 0.73; 95% CI, 0.56–0.96;  $p=0.027$ ). Airway transcriptomic analyses identified eosinophil and epithelial airway inflammatory pathways associated with differential clinical responses to mepolizumab. There were no significant differences in secondary outcomes, including time to first exacerbation, lung function, or composite asthma



severity index (CASI). Importantly, significant improvements in asthma control were observed in both mepolizumab- and placebo-treated participants, emphasizing the importance of adherence to guideline-based care in high-risk children.

### Comments

1. This study demonstrates how children may have different responsiveness to biologic therapy compared to adults. In contrast to studies in adults, the use of mepolizumab in urban children aged 6–17 years revealed only a small reduction in asthma exacerbations and did not show the larger benefits predicted from adult studies.
2. A strength of this study was the inclusion of a diverse, high-risk cohort of predominantly Black and Hispanic children living in disadvantaged urban communities which is an understudied population.
3. Nasal airway samples were used as a proxy for lower airway disease; however, this is assuaged by the relevance of these inflammatory pathways to asthma outcomes.

McDowell PJ, McDowell R, Busby J, Eastwood MC, Patel PH, Jackson DJ, et al. **Clinical remission in severe asthma with Biologic Therapy: an analysis from the UK Severe Asthma Registry.** *Eur Respir J* 2023; 10.1183/13993003.00819-2023.

### Summary

The objective of this study was to define clinical characteristics associated with on-treatment clinical remission in patients treated with biologic therapy. This study was a retrospective analysis of a large cohort of severe asthma patients registered in the UK Severe Asthma Registry (UKSAR) who met strict national access criteria for biologic therapy. Patients had a baseline assessment prior to biologic initiation and annual review. The primary definition of on-treatment clinical remission included Asthma Control Questionnaire (ACQ)-5 <1.5, no oral corticosteroids for disease control, and forced expiratory volume in 1 s above lower limit of normal or no more than 100 mL less than baseline. In patients with severe asthma treated with biologic therapies, 18.3% of patients achieved the primary definition of on-treatment remission. Those patients who were composite T2-biomarker high (Blood eosinophil count  $\geq 150$  cells/ $\mu$ L and fractional exhaled nitric oxide level  $\geq 20$  ppb) were 7.44-fold more likely to achieve clinical remission than those who were composite T2-biomarker low (Blood eosinophil count <150 cells/ $\mu$ L and fractional exhaled nitric oxide level < 20 ppb) (95% CI: 1.73–31.95,  $P = .007$ ). The adjusted

odds of on-treatment remission were lower in patients who were female (OR 0.61, 95% CI 0.45–0.93), obese (OR 0.49, 95% CI 0.24–0.65) or had ACQ-5  $\geq 1.5$  (OR 0.19, 95% CI 0.12–0.31) at baseline prior to biologic therapy. On-treatment remission was more likely in T2-high biomarker patients with shorter duration of disease and less comorbidities.

### Comments

1. In this analysis of patients with severe asthma from a large national registry, 18% met the primary definition of on-treatment remission.
2. On-treatment clinical remission was more likely in males, never-smokers and non-obese individuals with higher T2 biomarkers. These patients had a shorter disease duration, were older at disease onset, and had lower symptoms burden and fewer exacerbations at biologic therapy initiation.
3. As with all registry based observational studies, it is possible that the proportion of patients achieving on-treatment remission may be overestimated due to regression to the mean.
4. These study results demonstrate the need for future research on the optimal time to start biologics therapy in severe asthma and if on-treatment clinical remission is maintained over time.

Bacharier LB, Maspero JF, Katelaris CH, Fiocchi AG, Gagnon R, de Mir I, Guilbert TW, Jackson DJ, Staudinger HW, Laws E, Mannent LP, Akinlade B, Maloney J, Tawo K, Khokhar FA, Li N, Hardin M, Abdulai RM, Lederer DJ, Robinson LB; Liberty Asthma EXCURSION Investigators.

**Assessment of long-term safety and efficacy of dupilumab in children with asthma (LIBERTY ASTHMA EXCURSION): an open-label extension study.** *Lancet Respir Med.* 2024 Jan;12(1):45–54. doi: 10.1016/S2213-2600(23)00303-X.

### Summary

The initial study of more than 400 children showed that dupilumab reduced asthma attacks and improved spirometry and disease control over 52 weeks compared with placebo. This 52-week open-label extension study of 365 6–11-year-old children with moderate-to-severe asthma assessed the long-term effects of add-on dupilumab therapy on safety and efficacy. The study results showed that long-term, treatment benefits were maintained. 91% of patients did not experience asthma exacerbations, and had improved spirometry and decreased serum IgE over 52 weeks. Dupilumab treatment was well tolerated with a

safety profile similar to that observed in the parent study with nasopharyngitis and respiratory tract infections being the most frequently reported. Serious adverse events occurred in seven patients and treatment discontinuation due to treatment emergent adverse events occurred in three patients (1%; one each of allergic conjunctivitis, ascariasis, and pulmonary tuberculosis). Hypersensitivity was reported in 10 children, eosinophilia in 15 children.

### Comments

1. This is the first study to examine both the safety and efficacy of add-on biological therapy over a two-year time period in children 6–11 years old with moderate-to-severe asthma.
2. The study demonstrated that dupilumab resulted in continued reduction in annualized severe exacerbation rates and consistent improvements in lung function.
3. This was a single-arm, open-label extension study and it was not designed for comparisons between treatment groups and the results are limited to descriptive summaries. Children were enrolled after completing the parent trial which may have introduced bias; however, approximately 90% of patients participating in the parent study enrolled in the extension study with similar proportions between treatment groups.
4. The number of patients enrolled from the U.S. was low compared to the overall trial population. This should be considered before generalizing these findings to under-represented populations in the U.S.
5. A portion of the study was conducted during the pandemic timeline but compliance with dupilumab treatment was high and the treatment benefits of dupilumab were consistent across both time periods (before and during the pandemic).

### OTHER ARTICLES OF INTEREST

#### OMICS

Hallmark B, Wegienka G, Havstad S, Billheimer D, Ownby D, Mendonca EA, Gress L, Stern DA, Myers JB, Khurana Hershey GK, Hoepner L, Miller RL, Lemanske RF, Jackson DJ, Gold DR, O'Connor GT, Nicolae DL, Gern JE, Ober C, Wright AL, Martinez FD. **Chromosome 17q12-21 Variants Are Associated with Multiple Wheezing Phenotypes in Childhood.** *Am J Respir Crit Care Med.* 2021 Apr 1;203(7):864-870. doi: 10.1164/rccm.202003-0820OC.

Altman MC, Calatroni A, Ramratnam S, Jackson DJ, Presnell S, Rosasco MG, Gergen PJ, Bacharier LB,

O'Connor GT, Sandel MT, Kattan M, Wood RA, Visness CM, Gern JE; Inner City Asthma Consortium. **Endotype of allergic asthma with airway obstruction in urban children.** *J Allergy Clin Immunol.* 2021 Nov;148(5):1198-1209. doi: 10.1016/j.jaci.2021.02.040.

Tsuo K, Zhou W, Wang Y, Kanai M, Namba S, Gupta R, Majara L, Nkambule LL, Morisaki T, Okada Y, Neale BM; Global Biobank Meta-analysis Initiative; Daly MJ, Martin AR. **Multi-ancestry meta-analysis of asthma identifies novel associations and highlights the value of increased power and diversity.** *Cell Genom.* 2022 Nov 8;2(12):100212. doi: 10.1016/j.xgen.2022.100212.

Sordillo JE, Lutz SM, Jorgenson E, Iribarren C, McGeachie M, Dahlin A, Tantisira K, Kelly R, Lasky-Su J, Sakornsakolpat P, Moll M, Cho MH, Wu AC. **A polygenic risk score for asthma in a large racially diverse population.** *Clin Exp Allergy.* 2021 Nov;51(11):1410-1420. doi: 10.1111/cea.14007.

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#### BIOLOGICS

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# Management of Neuromuscular Disorders in Children

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## RESPIRATORY INSUFFICIENCY IN NEUROMUSCULAR DISEASE

Mayer OH, Amin R, Sawnani H, Shell R, Katz SL; RIND Study Group. **Respiratory Insufficiency in Neuromuscular Disease (RIND): A Delphi Study to Establish Consensus Criteria to Define and Diagnose Hypoventilation in Pediatric Neuromuscular Disease.** *J Neuromuscul Dis.* 2023;10(6):1075-1082.

### Summary

Chronic respiratory failure, often hypoventilation, is a common endpoint in progressive neuromuscular disease (NMD). Early detection and timely intervention are associated with increased survival, quality of life and well being. Polysomnography is the gold standard for hypoventilation assessment, yet challenges such as limited testing availability and inconsistent use of CO<sub>2</sub> monitoring can delay detection. Additionally, the American Academy of Sleep Medicine specifies different hypoventilation criteria for children versus adults and considers the diagnosis in the context of sleep disordered breathing. This study involved an international expert panel (15 pediatric pulmonologists from 13 hospitals across 5 countries) conducting a two-round Delphi process to identify critical items related to pediatric neuromuscular disease, using item generation from guidelines, literature reviews, and current clinical practices. The group summarized six domains pertinent to hypoventilation in neuromuscular disease, ultimately defining a new paradigm: Respiratory Insufficiency in Neuromuscular Disease (RIND) which proposes new criteria for hypoventilation: TcCO<sub>2</sub> > 45 mm Hg for > 25% of sleep, TcCO<sub>2</sub> > 50 mmHg for > 2% sleep or 5 minutes continuously, and TcCO<sub>2</sub> increase 10 mmHg above baseline for > 2% sleep. And proposed criteria for hypoxemic respiratory failure: mean SpO<sub>2</sub> < 94%, SpO<sub>2</sub> < 90% for > 2% sleep, and SpO<sub>2</sub> < 90% for > 5 minutes continuously.

### Comments

1. A history of morning headache, FVC <50 percent predicted or awake TcCO<sub>2</sub> >45 mmHg suggests high concern for hypoventilation and may indicate the need for polysomnography

2. This new criteria for hypoventilation and hypoxemia respiratory failure offer the paradigm that respiratory insufficiency can present in a variety of different ways, allowing more opportunities for early detection and treatment.
3. Assessing the patient's respiratory effort, looking for persistent tachypnea and thoracoabdominal asynchrony, can help anticipate pending respiratory failure.
4. The new RIND paradigm would benefit from further validation and investigation with specific sub-types of NMDs.
5. At this time, ambulatory/home testing, notable home CO<sub>2</sub> monitoring, is still being developed to reliably offer data on par with polysomnography

## MICRO-DYSTROPHIN THERAPY FOR DUCHENNE MUSCULAR DYSTROPHY

Mendell JR, Shieh PB, McDonald CM, Sahenk Z, Lehman KJ, Lowes LP, Reash NF, Iammarino MA, Alfano LN, Sabo B, Woods JD, Skura CL, Mao HC, Staudt LA, Griffin DA, Lewis S, Wang S, Potter RA, Singh T, Rodino-Klapac LR. **Expression of SRP-9001 dystrophin and stabilization of motor function up to 2 years post-treatment with delandistrogene moxeparvovec gene therapy in individuals with Duchenne muscular dystrophy.** *Front Cell Dev Biol.* 2023 Jul 11;11:1167762. doi: 10.3389/fcell.2023.1167762. PMID: 37497476; PMCID: PMC10366687.

### Summary

Duchenne muscular dystrophy (DMD) is a progressive NMD caused by the absence of functional dystrophin protein. Delandistrogene moxeparvovec, the first gene therapy approved for DMD in the US, delivers a functional fraction of the gene (micro-dystrophin attached to an adeno associated virus vector) via one time intravenous infusion. This Phase 2, double blinded, two part (48 weeks per part) cross over study evaluated longitudinal effectiveness of delandistrogene moxeparvovec (SRP-9001). Primary outcomes included detection of dystrophin in the muscle and change from baseline (CFBL) on the North Star Ambulatory Assessment (NSAA) scale. In total, 41 patients were recruited and randomized into 2 groups. All patients

treated with delandistrogene moxeparvovec had robust expression of SRP-9001 in the muscle. A comparative analysis of the drug's impact on motor function showed no significant difference between the treatment and placebo groups, likely due to disparity in baseline motor functions, especially in the 6-7 year-old subgroup. Subgroup analyses did demonstrate significant improvement in motor scores. Adverse events included vomiting, nausea and liver injury that resolved. There were 5 serious events with 3 instances of rhabdomyolysis that resolved (1 patient had received placebo). In all, the findings suggest that SRP-9001 is well tolerated and effective. Phase 3 trials are underway.

### Comments

1. More analysis might be needed to understand the differing impacts of the treatment in different age groups as observed in the subgroup analysis.
2. Delandistrogene moxeparvovec, the first gene therapy for DMD appears effective and safe and is indicated for patients 4-5 years old.
3. Further long-term studies are needed to ascertain the durability and sustainability of the treatment's efficacy.
4. Potential confounders like baseline motor function differences between treatment and placebo groups need to be controlled in future studies for more accurate insights.

### ONASEMNOGENE ABEPARVOVEC EFFECT ON BULBAR FUNCTION

McGrattan KE, Shell RD, Hurst-Davis R, Young SD, O'Brien E, Lavrov A, Wallach S, LaMarca N, Reyna SP, Darras BT. **Patients with Spinal Muscular Atrophy Type 1 Achieve and Maintain Bulbar Function Following Onasemnogene Apeparvovec Treatment.** *J Neuromuscul Dis.* 2023;10(4):531-540

### Summary

The study evaluated onasemnogene abeparvovec's on bulbar function in Spinal Muscular Atrophy type 1 (SMA). Bulbar function was determined by SMA experts and measured using four specific endpoints: unimpaired swallowing, complete oral nutrition, lacking pulmonary instability-related adverse events, and expressive communication abilities. The post-hoc analyses incorporated data from three studies (START, STR1VE-US, and STR1VE-EU), focusing on those receiving the treatment while under 6 months of age. Assessments included the ability to swallow, meet nutritional needs orally, maintain pulmonary stability, and establish early verbal communication skills. The analysis was descriptive, using the last evaluated time point to

assess individual and the composite outcomes of bulbar function.

The analysis covered 65 patients across the 3 clinical trials; but only 20 had evaluations on all 4 composite endpoints. Of these, 75% of patients treated with onasemnogene abeparvovec (OA) achieved the composite endpoint of having a normal swallow, achieving full oral nutrition, demonstrating no pulmonary instability and demonstrating expressive communication abilities. The retrospective nature of these investigations limits the ability to utilize age-based standardized assessments for deglutition and communication. Direct comparisons between studies are challenging due to differing designs, populations, and outcomes. These findings suggest that OA can effectively enhance bulbar function in SMA patients, potentially improving quality of life by addressing critical aspects of feeding and communication.

### Comments

1. The findings underscore a critical advancement in treating SMA type 1, moving beyond survival and motor function improvement, to enhancing quality of life through the restoration of functions like eating and speaking.
2. The lack of standardized, objective measures for bulbar function highlights a significant gap in SMA management.
3. Ongoing and future real-world studies, along with START, STR1VE-US, and STR1VE-EU follow-ups, will help clarify the long-term benefits of onasemnogene abeparvovec.
4. Unlike nusinersen and risdiplam, onasemnogene abeparvovec uniquely has been shown to improve bulbar outcomes in SMA type 1 patients.

### SLEEP DISORDERED BREATHING IN SPINAL MUSCULAR ATROPHY AFTER GENE THERAPY

Chiang J, Xiao L, Nigro E, St-Laurent A, Weinstock L, Law E, et al. **Sleep disordered breathing in infants identified through newborn screening with spinal muscular atrophy.** *Sleep Med.* 2023 Nov;111:161-9.

### Summary

Spinal Muscular Atrophy (SMA) is a genetic disorder characterized by neuromuscular weakness and sleep disordered breathing. This retrospective review of infants with SMA at a single institution highlights longitudinal polysomnography (PSG) data for infants with SMA after receiving gene therapy onasemnogene abeparvovec (OA). The study included 11 infants, diagnosed with SMA by newborn screen. All patients received OA in addition to a weaning course of systemic

steroids. This study cohort exhibited a diverse SMN2 gene copy number and 5 infants received nusinersen while awaiting OA. The age of the treatment varied with the median age of 3.6 weeks old. Motor skills were assessed using Alberta Infant Motor Scale (AIMS). These PSGs were conducted at the time of diagnosis and subsequently at intervals of roughly 3, 6, 12, 18, and 24 months of age. All infants met criteria for sleep disordered breathing at time of diagnosis, with 3 patients using respiratory support at some point (1 used supplemental oxygen for central apnea and 2 clinically weak infants used noninvasive ventilation for obstructive apnea). There was no significant correlation between motor scores and polysomnography parameters. All patients had improvement in sleep disordered breathing by 12 months of age, which is in sharp contrast to previous natural history studies.

### Comments

1. The apnea hypopnea index in newborns with SMA was elevated in the first 3 months of life, even in asymptomatic newborns, suggesting there may be subtle presence of disease not easily detectable.
2. A longitudinal comparison between PSG findings in healthy infants and infants with SMA treated with OA would help to understand the significance of the PSG findings.
3. Infants who are asymptomatic for SMA or sleep disordered breathing may not require aggressive sleep testing as their sleep disordered breathing may improve by 12 months of age with monitoring.
4. The lack of correlation between PSG indices and motor strength scores suggests the need to evaluate these independently for a holistic assessment of the infant's clinical status.
5. Longitudinal studies are needed to better characterize sleep disordered breathing in older children with SMA type 1 after treatment with OA

### GENETICS OF NEUROMUSCULAR DISEASE IN UNDER-REPRESENTED POPULATIONS

Wilson LA, Macken WL, Perry LD, Record CJ, Schon KR, Frezatti RSS, Raga S, Naidu K, Köken ÖY, Polat I, Kapapa MM, Dominik N, Efthymiou S, Morsy H, Nel M, Fassad MR, Gao F, Patel K, Schoonen M, Bisschoff M, Vorster A, Jonvik H, Human R, Lubbe E, Nonyane M, Vengalil S, Nashi S, Srivastava K, Lemmers RJLF, Reyaz A, Mishra R, Töpf A, Trainor CI, Steyn EC, Mahungu AC, van der Vliet PJ, Ceylan AC, Hiz AS, Çavdarlı B, Semerci Gündüz CN, Ceylan GG, Nagappa M, Tallapaka KB, Govindaraj P, van der Maarel SM, Narayanappa G, Nandeesh BN, Wa Somwe S, Bearden DR, Kvalsund MP, Ramdharry GM, Oktay Y, Yiş U, Topaloğlu H, Sarkozy A, Bugiardini E,

Henning F, Wilmshurst JM, Heckmann JM, McFarland R, Taylor RW, Smuts I, van der Westhuizen FH, Sobreira CFDR, Tomaselli PJ, Marques W Jr, Bhatia R, Dalal A, Srivastava MVP, Yareeda S, Nalini A, Vishnu VY, Thangaraj K, Straub V, Horvath R, Chinnery PF, Pitceathly RDS, Muntoni F, Houlden H, Vandrovцова J, Reilly MM, Hanna MG. **Neuromuscular disease genetics in under-represented populations: increasing data diversity.** *Brain.* 2023 Dec 1;146(12):5098-5109. doi: 10.1093/brain/awad254. PMID: 37516995; PMCID: PMC10690022.

### Summary

Neuromuscular disease is believed to affect about 15 million people worldwide; however, with most of the testing now DNA based, low/middle income countries may struggle to gain access to timely and accurate diagnostic testing. Additionally, a significant 86% of published genomic studies are derived from European ancestry, highlighting the need for increased representation. This study developed a cloud-based transcontinental partnership to enhance understanding of genetic diversity and improve diagnostic strategies in neuromuscular diseases. The partnership included trained fellows across 18 centers, spanning 7 countries, with an emphasis on cohorts from low-to-middle income populations. These fellows helped recruit participants with a suspected neuromuscular disorder (or close relatives of someone with a confirmed or suspected disorder). Of the 3631 probands (individuals), 60% were based in India, and 82% were of non-European ancestry. The most common diagnoses were Limb girdle muscular dystrophy. Over half of tested participants received a research-based genetic diagnosis. The study demonstrates the feasibility and benefits of virtual transcontinental partnerships and the use of big data for genetic diagnoses in under-represented populations, paving the way for broader testing capacity and tailored care guidelines.

### Comments

1. The project demonstrated the feasibility of cloud based, transcontinental partnership and can be a model for efficient data sharing across different disciplines.
2. Broad international collaboration can be mutually beneficial, bringing knowledge and therapies to low/middle income countries and deepening wider understanding of variants of unknown significance.
3. Expanded genetic testing may make emerging gene therapies more available to a wider patient base, potential reducing disparities.

### OTHER ARTICLES OF INTEREST

**MONITORING AND MANAGEMENT OF NEUROMUSCULAR DISEASE**

Yu MKL, Chiu AYY, Chau SK, Rosa Duque JS, Wong WHS, Chan SHS. **A pilot study of an integrated, personalized, respiratory and motor telerehabilitation program for pediatric patients with hereditary neuromuscular disorders.** *Muscle Nerve.* 2023 Nov;68(6):857-864.

Shi J, Chiang J, Ambreen M, Snow N, Mocanu C, McAdam L, Goldstein RS, Rose L, Amin R. **Ambulatory transcutaneous carbon dioxide monitoring for children with neuromuscular disease.** *Sleep Med.* 2023 Jan;101:221-227.

Khan A, Frazer-Green L, Amin R, Wolfe L, Faulkner G, Casey K, Sharma G, Selim B, Zielinski D, Aboussouan LS, McKim D, Gay P. **Respiratory Management of Patients With Neuromuscular Weakness: An American College of Chest Physicians Clinical Practice Guideline and Expert Panel Report.** *Chest.* 2023 Aug;164(2):394-413. doi: 10.1016/j.chest.2023.03.011. Epub 2023 Mar 13. PMID: 36921894.

Ronco L, Khirani S, Vedrenne-Cloquet M, Barrois R, Barnerias C, Desguerre I, Bignamini E, Fauroux B. **Limitations of the apnea-hypopnea index in children and young adults with neuromuscular disorders.** *Neuromuscul Disord.* 2023 Jun;33(6):468-473. doi: 10.1016/j.nmd.2023.05.001. Epub 2023 May 5. PMID: 37196510.

**SPINAL MUSCULAR ATROPHY**

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Pechmann A, Behrens M, Dörnbrack K, Tassoni A, Stein S, Vogt S, Zöllner D, Bernert G, Hagenacker T, Schara-Schmidt U, Schwersenz I, Walter MC, Baumann M, Baumgartner M, Deschauer M, Eisenkölbl A, Flotats-Bastardas M, Hahn A, Horber V, Husain RA, Illsinger S, Johannsen J, Köhler C, Kölbl H, Müller M, von Moers A, Schlachter K, Schreiber G, Schwartz O, Smitka M, Steiner E, Stögmann E, Trollmann R, Vill K, Weiß C, Wiegand G, Ziegler A, Lochmüller H, Kirschner J; SMARTCARE study group. **Effect of nusinersen on motor, respiratory and**

**bulbar function in early-onset spinal muscular atrophy.** *Brain.* 2023 Feb 13;146(2):668-677. doi: 10.1093/brain/awac252. PMID: 35857854.

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Dunaway Young S, Montes J, Glanzman AM, Gee R, Day JW, Finkel RS, Darras BT, De Vivo DC, Gambino G, Foster R, Wong J, Garafalo S, Berger Z; SHINE Study Group. **Nusinersen Treatment of Children with Later-Onset Spinal Muscular Atrophy and Scoliosis Is Associated with Improvements or Stabilization of Motor Function.** *J Clin Med.* 2023 Jul 26;12(15):4901. doi: 10.3390/jcm12154901. PMID: 37568304; PMCID: PMC10419863.

**DUCHENNE MUSCULAR DYSTROPHY**

D'Ambrosio ES, Mendell JR. **Evolving Therapeutic Options for the Treatment of Duchenne Muscular Dystrophy.** *Neurotherapeutics.* 2023 Oct;20(6):1669-1681. doi: 10.1007/s13311-023-01423-y. Epub 2023 Sep 6. PMID: 37673849; PMCID: PMC10684843.

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Hnaini M, Downs M, Miller MR, Campbell C, St-Laurent A. **Duchenne muscular dystrophy respiratory profiles from**

real world registry data. *Pediatr Pulmonol.* 2023 Oct;58(10):2725-2732. doi: 10.1002/ppul.26554. Epub 2023 Aug 4. PMID: 37539841.

#### INHIBITION OF MYOSTATIN INCREASES MUSCLE SIZE IN MOUSE MODEL FOR NEMALINE MYOPATHY

Lindqvist J, Granzier H. **Pharmacological Inhibition of Myostatin in a Mouse Model of Typical Nemaline Myopathy Increases Muscle Size and Force.** *Int J Mol Sci.* 2023 Oct 12;24(20):15124. doi: 10.3390/ijms242015124. PMID: 37894805; PMCID: PMC10606666.

#### CURRENT PERSPECTIVES IN POMPE DISEASE

El Haddad L, Khan M, Soufny R, Mummy D, Driehuys B, Mansour W, Kishnani PS, ElMallah MK. **Monitoring and Management of Respiratory Function in Pompe Disease: Current Perspectives.** *Ther Clin Risk Manag.* 2023 Sep 1;19:713-729. doi: 10.2147/TCRM.S362871. PMID: 37680303; PMCID: PMC10480292.

El Haddad L, Lai E, Murthy PKL, Biswas DD, Soufny R, Roger AL, Tata PR, ElMallah MK. **GAA deficiency disrupts distal airway cells in Pompe disease.** *Am J Physiol Lung Cell Mol Physiol.* 2023 Sep 1;325(3):L288-L298. doi: 10.1152/ajplung.00032.2023. Epub 2023 Jun 27. PMID: 37366541; PMCID: PMC10625827.



# Updates in Primary Ciliary Dyskinesia and Non-CF Bronchiectasis

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## OUTCOME MEASURES IN NON-CF BRONCHIECTASIS

Chang AB, Boyd J, Bush A, Hill AT, et al. **A core outcome set for bronchiectasis in children and adolescents for use in clinical research: an international consensus study.** *Lancet Respir Med.* 2024 Jan; 12: 78-88.

### Summary

The authors set out to define important outcome measures for future studies in children and adolescents with non-CF bronchiectasis. They established an international panel of experts who utilized systematic review to generate a list of 21 outcome measures, then surveyed 562 individuals (including patients, parents, and health-care professionals from across the world) to define a 10-item *core outcome set (COS)*, five of which were defined as essential. The COS includes quality of life, symptoms, exacerbation frequency, non-scheduled health-care visits, and hospitalizations (all essential), as well as time to next exacerbation, lost days of work, school, or day care, adverse events, lung function, and burden of therapy. The panel also defined intervention-specific and discovery outcomes including sputum microbiology, characteristics and biomarkers, cross-sectional imaging (magnetic resonance imaging (MRI) or computed tomography (CT)), cost-effectiveness, anthropometrics, and breath and blood biomarkers (largely related to inflammation).

### Comments

1. This article presents consensus guidance from patients, families, and providers on outcome measures most important to patients with non-CF bronchiectasis in future studies.
2. There is a clear emphasis on overall quality of life and ability to participate in daily life without interruption, as all essential outcomes deemed essential related directly to quality of life.

## OUTCOME MEASURES FOR INTERVENTIONAL STUDIES IN PRIMARY CILIARY DYSKINESIA

Kos R, Goutaki M, Kobbernagel HE, Rubbo B, et al. **A BEAT-PCD consensus statement: a core outcome set for pulmonary disease interventions in primary ciliary dyskinesia.** *ERJ Open Res.* 2024; 10: 00115-2023.

### Summary

The objective of this consensus statement was to define important and reliable outcome measures for future studies in patients with primary ciliary dyskinesia (PCD). An international, multidisciplinary panel of experts was convened to generate a list of outcomes based on literature review; they then utilized a modified e-Delphi technique to determine the most relevant endpoints specifically for interventions targeting pulmonary disease, as well as how these outcomes should best be reported. The authors defined four outcomes important for all studies, with five additional measures for specific settings. The *core outcome set (COS)* for clinical trials evaluating pulmonary disease interventions in patients with PCD includes spirometry, health-related quality of life scores, exacerbations, and microbiology. Other measures that are recommended but lack consensus either for utilization or implementation include anthropometric measures, physical activity, dyspnea scores, and cross-sectional imaging (CT or high-resolution CT (HRCT)).

### Comments

1. This consensus document presents a core outcome set for clinical trials in patients with PCD that aims to maximize the impact and relevance of future clinical trials of pulmonary interventions.
2. Much like recent guidelines for outcome measures in studies of patients with non-CF bronchiectasis (see Article 1), quality of life and impact on daily life is heavily emphasized, represented in half of the measures in the COS.

## CILIARY DEFECT/GENOTYPE AND DISEASE SEVERITY IN CHILDREN WITH PRIMARY CILIARY DYSKINESIA

Kinghorn B, Rosenfled M, Sullivan E, Onchiri F, Ferkol TW, et al. **Airway Disease in Children with Primary Ciliary Dyskinesia: Impact of Ciliary Ultrastructure Defect and Genotype.** *Ann Am Thorac Soc.* 2023 Apr; 20(4): 539-547

### Summary

This is a cross-sectional analysis of 141 children with PCD (mean age 8.5 years) enrolled in a prospective

observational study. Subjects were grouped by ciliary ultrastructural defect type - outer dynein arm (ODA), ODA/inner dynein arm (IDA), IDA/microtubular disorganization (MTD), and normal/near-normal ultrastructure by ciliary electron microscopy and genotype. The authors investigated associations between ultrastructural defect and both lung function (by spirometry) and structural lung disease (by chest CT using a novel, PCD-specific scoring system). Higher percentage of disease on chest CT was associated with older age, lower body mass index, and lower forced expiratory volume in 1 second (FEV<sub>1</sub>) by spirometry. Subjects with IDA/MTD defects had a higher percentage of disease on CT than children with ODA defects, largely driven by increased mucus plugging.

### Comments

1. This study employed a novel CT scoring system specific for patients with PCD (MERAGMA-PCD), as opposed to utilizing scoring systems developed for patients with CF.
2. Mean FEV<sub>1</sub> in this cohort of children with PCD was at the lower end of normal (82.4% predicted), emphasizing the significant disease burden of PCD.
3. A clear association was seen between structural disease and lung function measures, with a lower FEV<sub>1</sub> associated with increased atelectasis and increased mucus plugging.

### RACIAL DISPARITIES IN DIAGNOSIS AND STUDY OF PCD

Carr KA, O'Connor MG, Shapiro AJ, Machogu EM. **Racial disparities in primary ciliary dyskinesia: Defining the problem and potential solutions.** *Pediatr Pulmonol.* 2023; 58: 2687 – 2690.

### Summary

In this letter to the editor, the authors highlight discrepancies between expected (based on mutation prevalence by country/region of ancestral origin) and observed racial/ethnic makeup of subject populations in North American studies and registries involving patients with PCD. Within the estimated global prevalence of PCD (1 in 7554 individuals), individuals of African descent have the highest prevalence of predicted PCD-causing genetic variants, followed by non-Finnish European, East Asian, and Latino populations, yet white, non-Hispanic patients make up the majority of patients with PCD in North American literature. Diagnostic bias may contribute, based largely on the racial composition of current studies – genetic testing for PCD, in particular, is likely to be more sensitive in patients of white European ancestry as that population comprises the majority of subjects in

published research. Referral bias may also play a role, as lower provider suspicion of PCD in BIPOC (Black, Indigenous, and People of Color) patients leads to lower rates of diagnosis. Structural/systemic racism limiting access to care, particularly evaluation/diagnosis at research centers, may also be a driving factor.

### Comments

1. The authors highlight the significant impact of provider bias in the diagnosis of rare diseases such as PCD, as a lower rate of suspicion of PCD in BIPOC patients may contribute to discrepancies between actual and expected rates of diagnosis in BIPOC populations.
2. Lack of BIPOC representation in research studies in PCD, particularly those involving genetics, then contributes to diagnostic bias, as subsequent genetic testing for PCD may be more sensitive for patients of white European ancestry.

### GENOTYPIC AND PHENOTYPIC DIAGNOSIS OF PCD IN PALESTINIAN PATIENTS

Rumman N, Fassad MR, Driessens C, Goggin P, Abdelrahman N, et al. **The Palestinian primary ciliary dyskinesia population: first results of the diagnostic and genetic spectrum.** *ERJ Open Res.* 2023; 9: 00714-2022.

### Summary

The authors present the results of a collaborative effort between Dr. Rumman (the only provider testing individuals in Palestine) and experts in the UK to evaluate and diagnose Palestinian children and adults with symptoms consistent with PCD. Four hundred sixty-four patients were identified based on clinical history, with 350 undergoing nasal nitric oxide (nNO) testing, 183 transmission electron microscopy for ciliary ultrastructural analysis, and 82 genetic screening. Sixty-eight subjects met diagnostic criteria established by the European respiratory society, with another 57 having high suspicion for PCD based on symptoms, situs status, and /or low nNO measures. Mean age of diagnosis was 10 years (range 3 months to 40 years); 43% had situs inversus and most patients were from consanguineous backgrounds. Clinical symptoms were consistent with previous reports from Europe and North America, including neonatal respiratory distress, persistent wet cough, persistent rhinosinusitis, and middle ear disease; however, digital clubbing was noted at a higher prevalence (19.4%) than reported in other literature. Despite being from a small geographical area, there was marked genetic heterogeneity of PCD mutations, however, all genetic diagnoses involved homozygous variants.

### Comments

1. The authors present a remarkably successful, international, collaborative effort to establish a diagnostic process for evaluation of patients for PCD in Palestine, representing 8 years of work.
2. Clinical characteristics of PCD in this Palestinian population were similar to those reported in other (largely North American and European) literature, though this may represent selection bias as screening/evaluation was based on previously published symptoms.
3. The authors highlight the barriers to care faced by patients with PCD in Palestine, making both diagnosis and management of chronic disease more challenging.

### **SURGICAL MANAGEMENT OF CHILDREN WITH NON-CF BRONCHIECTASIS**

Mocelin HT, Fischer GB, Piccini JD, Bau R, Andrade CF, Lukrafka JL. **Surgical treatment of non-cystic fibrosis bronchiectasis in children and adolescents: A review.** *Pediatr Res Rev.* 2023; 46: 57 - 62

### Summary

This non-systematic literature review discusses the role of surgical management in the clinical care of children with non-CF bronchiectasis in low- and middle-income countries (LMIC). The authors emphasize an overall lack of data regarding diagnosis and management of children with bronchiectasis, particularly in LMIC. They highlight the significant symptom burden of bronchiectasis in children and adults, and the added

complications and worse prognosis that can be associated with barriers to care, including increased mortality. Surgical intervention is presented as a treatment option when clinical management has failed to relieve symptoms or slow disease progression, particularly with localized and/or non-recurring disease, though the authors acknowledge a lack of consensus around indications for surgery. Pre-operative considerations include quality of life, growth/nutrition, and adequate definition of diagnosis by CT. The goal of surgery is to remove non-functioning pulmonary tissue that is most contributing to symptoms and exacerbations. Overall, surgeries were well-tolerated, with the majority of patients in most studies reporting clinical improvement. The most common complications being air leak, bleeding, and atelectasis.

### Comments

1. Surgical intervention (lobectomy) is a consideration for children with symptomatic bronchiectasis not responsive to aggressive clinical management, particularly in areas or situations with marked barriers to care.
2. Surgical intervention is more likely to be successful in improving symptoms and course of disease in children with localized disease and those with non-recurring etiologies (e.g. tuberculosis, foreign body).
3. Chest physiotherapy and other clinical treatment measures are still recommended post-operatively.