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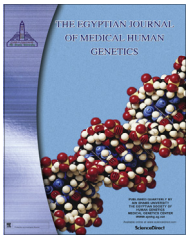

ORIGINAL ARTICLE

Assessment of respiratory involvement in children with mucoplysaccharidosis using pulmonary function tests

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KEYWORDS

Mucopolysaccharidosis;
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Abstract *Background:* Mucopolysaccharidosis (MPS) are classified into seven clinical types based on eleven known lysosomal enzyme deficiencies of glycosaminoglycan (GAG) metabolism. Respiratory involvement seen in most MPS types includes recurrent respiratory infections, upper and lower airway obstruction, tracheomalacia, restrictive lung disease, and sleep disturbances.

Aim of the study: To delineate the pattern of respiratory compromise and pulmonary function abnormalities in MPS patients.

Methods: This is a cross section observational study conducted on 30 patients recruited from the Neurometabolic Clinic, Children's Hospital, Cairo University over a period of 18 months. All patients were screened first by the quantitative determination of GAGs in urine, and diagnosis was confirmed by unidimensional electrophoresis for GAGs in urine and/or specific enzymatic assay in blood leucocytes. Infant pulmonary functions (IPFT) were done in twenty-two patients (< 3 years of age), while 8 cases performed impulse oscillometry (IOS) test (3–6 years of age).

Results: Ages at diagnosis ranged from 1 to 9 years with a median of 2.3 years. Male to female ratio was 4:1. Consanguinity was observed in 53.3% whereas similar family condition was present in 40% of cases. Lumbar kyphosis was detected in 60% of cases, while scoliosis was detected in 46.7%. Results of pulmonary functions were mainly obstructive in 20 (66.6%) cases; however, combined obstructive and restrictive were detected in only 6 (20%) of cases. Data showed no association

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between the presence of scoliosis or the presence of organomegaly and the pattern of pulmonary function abnormalities.

Conclusions: Evaluation and follow up of patients with MPS using pulmonary function tests are essential to detect early involvement of respiratory system and hence start treatment for respiratory complications early in the course of the disease.

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1. Introduction

The mucopolysaccharidosis (MPS) are lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs), also known as mucopolysaccharides. These conditions are differentiated by their clinical features and age of presentation. MPS are rare conditions; with an estimated total incidence of approximately 1/20,000 live births [1].

Respiratory complications affect patients with all types of MPS and contribute to death and disability as their disease progresses. Respiratory abnormalities result from airway obstruction, excessive secretions, skeletal restriction and frequent infections. Progressive deposition of GAGs in the soft tissue of the throat and trachea is thought to be responsible for the airway obstruction and dysfunction. These problems can lead to progressive respiratory insufficiency, severe sleep apnea, and sudden death from central apnea [2].

Few studies were published about respiratory functional assessment in MPS patients. The availability of new measurement systems specifically tailored to pediatric patients now allows clinicians to diagnose and follow up deterioration of lung function, which was previously challenging in this population [3].

2. Aim of the present study

The aim of the study is to assess the pattern of respiratory compromise and pulmonary function abnormalities in MPS patients.

3. Subjects and methods

3.1. Study design and sampling

This cross section observational study was conducted on 30 cases diagnosed as MPS and was followed up in the Neurometabolic Clinic at Children's Hospital, Cairo University over a period of 18 months (from March 2011 till September 2012). This work was carried out in accordance with The Code of Ethics of The World Medical Association (Declaration of Helsinki) and was approved by the Faculty of Medicine, Cairo University Ethics Committee. Informed consents were received from the families of all participants in Arabic before being enrolled in this study.

3.2. Methods

MPS patients were screened first by the quantitative determination of GAGs in urine, and diagnosis was confirmed by unidimensional electrophoresis for GAGs in urine and/or specific enzymatic assay in blood leucocytes. Quantitative GAG analysis was performed using the dimethyl-methylene blue (DMMB) method [4]. Cellulose acetate was used to differentiate and identify different types of sulfated glycans extracted from urine in electrophoresis using Barium acetate solution (12%) as a buffer medium and DMMB as a colorant [5]. The resulting bands were compared with the bands of GAG standard mix solution in every run. Specific enzymatic activities using fluorescent substrates α-L-iduronidase for Hurler-Scheie [6], iduronate-sulfatase for Hunter [7], heparin-sulfamidase for Sanfilippo type A [8] and galactose 6-sulfate sulfatase for Morquio type A [9] were performed in the homogenates of patients' leucocytes and referred to the total protein content of the sample.

All selected MPS patients were subjected to comprehensive clinical evaluation including general, respiratory, cardiac and neurological clinical history and examinations. Magnetic Resonance Imaging (MRI brain), electrocardiography (ECHO) as well as ear nose and throat (ENT) examinations were done to all recruited cases.

Pulmonary functions using infant lung functions (IPFT) for infants < 3 years old, while impulse oscillometry (IOS) was used for preschool children aged 3–6 years. Infant pulmonary functions tests were performed using Master screen Babybody (V.4.53 Erich Jaeger GmbH, Wurzburg, Germany) [10]. Routine safety measures in pulmonary function test laboratory were taken including full resuscitation equipment, two trained personnel during testing, continuous monitoring using pulse oximetry, use of transparent face mask and adherence to a specific protocol for sedation. Patients with any contraindication to perform pulmonary functions as severe upper respiratory obstruction were excluded from the study. Patients with history of upper respiratory tract infections were deferred for 3 weeks following attack. Length and weight were measured on each occasion together with proper posturing to avoid flexion or rotation of the neck. Fasting was not indicated. Reference values for the supine position were available [11,12].

The following IPFT parameters were measured:

(1). Tidal breathing parameters were measured by a pneumotachograph attached to a face mask, tidal breathing was recorded in epochs of 30 s. Each epoch contains at least 20 breaths. The mean of five trials was reported [13].
(2). The single occlusion technique was used for measuring passive respiratory mechanics in this study. The equipment used for the occlusion techniques included a shutter, flowmeter, and transducers [14]. The length of the occlusion was set at 400 ms. The occlusion was automatically stopped once an adequate plateau had been reached. The occlusion was also automatically stopped if the infant inspires against the closed valve, and the maximum length of the occlusion was set at 1000 ms.

(3). Infant whole body plethysmography was used for measuring airway resistance and functional residual capacity according to the recommendations of the European Respiratory Society/American Thoracic Society (ERS/ATS) task force on standards for infant respiratory function testing [15].
(4). The tidal rapid thoracoabdominal compression (RTC) technique was used to measure the maximal flow at functional residual capacity (V'_{maxFRC}) that can be produced by forced expiration from end-tidal inspiration. Measurements of lung function with the RTC techniques were performed according to the recommendations for infant respiratory function testing [16].

The oscillometry system (Masterscreen pediatric-IOS digital-Jaeger, Germany) was used for measuring lung functions in preschool children 3–6 years old. IOS is a variant of the forced oscillation technique (FOT). It is a rapid, non-invasive technique, allowing the evaluation of total respiratory impedance (Zrs) and providing values of its two components: total respiratory resistance (Rrs) and total respiratory reactance (Xrs).

3.3. Data management and statistical analysis

Results are expressed as median (minimum–maximum) or number (%). Association between categorical data was performed using Chi square test. SPSS computer program (version 16 windows) was used for data analysis. P value $\leqslant 0.05$ was considered significant and $\leqslant 0.01$ was considered highly significant.

4. Results

4.1. Descriptive data of the studied patients

Thirty cases with MPS were recruited from the Neurometabolic Unit, Children's Hospital, Cairo University. Their ages ranged from 1 to 9 years with a median of 2.3 years and a mean ± SD of 3.26 ± 2.28 years. Sex predilection was higher for males (24 (80%)) in comparison to females (6 (20%)). Positive consanguinity was observed in 16/30 (53.3%) of selected cases, while the presence of a similar condition in the family was detected in 12 cases (40%).

MPS Patients were classified into subtypes using qualitative GAG's and specific enzymatic analysis; Hurler syndrome in 12 (40%), Hunter in 4 cases (13.3%), Sanfillipo in 8 (26.6%) and Morquio in 6 cases (20%).

4.2. Clinical features

Regarding the clinical characteristics of the study group, mean height measured was 83.7 ± 11.9 cm; where all patients had short stature. Dysmorphic features were detected in 86.7% of cases and included thick lips, large tongue, flat nasal bridge and abundant coarse hair texture. Abnormal shape of chest included pectus carinatum in 4 cases and pectus excavatum in 4 cases. Abnormal chest auscultatory findings were detected in 60% of patients and included harsh vesicular breathing with prolonged expiration ± wheezes or crepitations. Adenoid enlargement was detected in 18 cases and 10 of them reported sleep disturbances (obstructive sleep apnea). Abnormal cardiac examination included muffled first heart sound in 4 cases, accentuated second heart sound in 2 cases and audible murmurs in 2 cases (Table 1).

4.3. Radiological data (imaging studies)

Radiological studies including skeletal survey, MRI brain and Echocardiography were done to all patients and are represented in Table 2. Patients with narrow foramen magnum were all diagnosed as Morquio disease. Dysostosis multiplex included spatulate ribs, large skull, hypoplastic epiphyses, thickened diaphyses and bullet shaped metacarpals. White matter change in MRI brain included areas of periventricular incomplete myelination for age and others with areas of dysmyelination.

4.4. Pulmonary functions

Results of pulmonary functions in the study group were mainly obstructive in 20 (66.6%) cases, however combined obstructive and restrictive was detected in 20% of cases only (Table 3).

The values of the infant pulmonary function test parameters of the study population and the normal reference ranges in infancy are shown in (Table 4). The median tidal breathing ratio (t_{PTEF}/t_E) and the median maximal expiratory flow of the study population (V'_{maxFRC}) were lower than the normal reference ranges in infancy, while the median respiratory system resistance (Rrs) was higher than the normal reference range.

Out of a total of 22 patients who performed infant lung function tests, 10 (45.5%) had abnormal infant lung function parameters. Most of them had abnormal tidal breathing ratio (t_{PTEF}/t_E) (63.6%), and total respiratory system resistance (Rrs) (63.6%); followed by abnormality in respiratory system compliance (Crs) (36.4%) and functional residual capacity (FRC) (36.4%); followed by abnormality of tidal volume (V_T) (27.3%), effective airway resistance (R_{eff}) (27.3%) and maximal expiratory flow at functional residual capacity (V'_{maxFRC}) (27.3%) (Table 5).

Eight patients performed impulse oscillometry. Four of them had abnormal total respiratory resistance (Rrs5), four had abnormal proximal respiratory resistance (Rrs20), while all had abnormal distal capacitive reactance (Xrs5) (Table 6). The values of Rrs5, Rrs20 and Xrs5 by IOS of the study population are shown in (Table 7).

Table 1 Clinical characteristics of the study group.

Characteristics	Patient group (n = 30)
Dysmorphism	26 (86.67%)
Short stature	30 (100%)
Short stature associated with kyphosis	18 (60%)
Abnormal chest shape	8 (26.7%)
Abnormal chest auscultation	18 (60%)
Abnormal heart examination	8 (26.7%)
Hepatomegaly alone	4 (13.3%)
Hepatosplenomegaly(HSM)	20 (66.6%)
Corneal clouding	2 (6.67%)
Adenoid enlargement	18 (60%)

Data are expressed as number (%).

Table 2 Radiological studies done to the studied patients.

Test	Number	Percent
X-ray		
Dysostosis multiplex	24	80
Kyphoscoliotic angle (Cobb's angle)	14	46.6
MRI brain		
Normal	20	66.67
Brain atrophy	2	6.67
Narrow foramen magnum	4	13.33
White matter changes	4	13.33
Echo heart		
Normal	20	66.67
Chamber enlargement and valve affection	6	20.00
Valve affection	4	13.33

Table 3 Results of pulmonary functions of the studied group.

	Number	Percent
Normal pulmonary functions	4	13.33
Obstructive airway disease	20	66.67
Combined obstructive and restrictive disease	6	20.0

4.5. Association between PFT and other features

Regarding the association between the presence of scoliosis and type of pulmonary function abnormalities, all patients with normal PFT did not have scoliosis however obstructive and mixed patterns in PFT were observed in patients with and without scoliosis. (Table 8 and Fig. 1).

No association could be demonstrated between the presence of organomegaly and pattern of PFT as 20 (66.6%) patients who did not suffer from any organomegaly had obstructive pattern in PFT (Table 9).

5. Discussion

MPS encompasses a group of rare lysosomal storage disorders that are associated with the accumulation of GAGs in organs and tissues. This accumulation can lead to the progressive development of a variety of clinical manifestations. ENT and respiratory problems are very common in patients with MPS and are often among the first symptoms to appear. Typical features of MPS include upper and lower airway obstruction and restrictive pulmonary disease, in addition to chronic rhinosinusitis, chronic ear infections, recurrent upper and lower respiratory tract infections, obstructive sleep apnea, impaired exercise tolerance, and respiratory failure [17].

The present study included 30 patients diagnosed as MPS, 12 as Hurler, 8 as Sanfillipo, 6 as Morquio and 4 as Hunter disease. Their ages at diagnosis ranged from 1 to 9 years, with a mean ± SD 3.26 ± 2.28 years. A study done by Wraith et al. reported that the mean age of MPS patients at diagnosis was 9 months. It is difficult to reduce this age without consideration of newborn screening for MPS. An earlier age at diagnosis is likely to lead to better results following therapy such as bone marrow transplantation and enzyme replacement therapy. Clinical features which should arouse suspicion of MPS

Table 5 Number and percentage of patients with normal and abnormal parameters of IPFT ($n = 22$).

Parameters of infant pulmonary function tests	No. of normal (%)	No. of abnormal (%)
Respiratory rate (RR)	12 (54.5%)	10 (45.5%)
Tidal volume (V_T)	16 (72.7%)	6 (27.3%)
Tidal breathing ratio (t_{PTEF}/t_E)	8 (36.4%)	14 (63.6%)
Respiratory system compliance (Crs)	14 (63.3%)	8 (36.4%)
Respiratory system resistance (Rrs)	8 (36.4%)	14 (63.6%)
Functional residual capacity (FRC_{pleth})	14 (63.6%)	8 (36.4%)
Effective airway resistance (R_{eff})	16 (72.4%)	6 (27.3%)
V'_{maxFRC} maximal expiratory flow	16 (72.2%)	6 (27.3%)

Table 6 Numbers and percentages of normal and abnormal cases according to parameters of IOS ($n = 8$).

Parameters of IOS	No. and % of normal cases	No. and % of abnormal cases
Total respiratory resistance (Rrs5)	4 (50%)	4 (50%)
Proximal respiratory resistance (Rrs20)	4(50%)	4 (50%)
Distal capacitive reactance (Xrs5)	0	8 (100%)

Table 4 Parameters of infant pulmonary function test.

Infant pulmonary function test parameter	Mean ± SD	Median	Range (minimum–maximum)	Reference range
Respiratory rate (breaths/min)	30.7 ± 7.3	27.1	23.2 (21.1–44.3)	26–31
Tidal volume (V_T) (ml/kg)	9 ± 1.4	9.4	4.5 (6.1–10.6)	8.3–10.6
Tidal breathing ratio (t_{PTEF}/t_E) (s)[a]	0.26 ± 0.10	0.24	0.28 (0.15–0.43)	0.26
Respiratory system compliance (Crs) (ml/kpa/kg)	12.08 ± 3.86	13.10	12.1 (6.60–18.70)	11–15
Respiratory system resistance (Rrs) (kpa/s/L)	3.12 ± 0.77	3.20	2.46 (1.60–4.06)	2–3
Functional residual capacity (FRC_{pleth}) (ml)[b]	240 ± 73	241	266 (126–392)	217–377
Effective airway resistance (R_{eff})	4 ± 3	3	10 (0–10)	2.6–6.6
V'_{maxFRC} (ml/s)[c]	133 ± 45	140	169 (34–203)	Girls: 192–614 Boys: 179–648

[a] (t_{PTEF}/t_E): ratio of time to peak total expiratory flow to total expiratory time.
[b] (FRC_{pleth}): plethysmography functional residual capacity.
[c] V'_{maxFRC}: maximum flow at functional residual capacity.

Table 7 Values of IOS parameters in the studied patients ($n = 8$).

IOS Parameter	Value (kPa/l/s)		% Predicted	
	Mean ± SD	Range (minimum–maximum)	Mean ± SD	Range (minimum–maximum)
Rrs5	1.59 ± 0.41	0.86 (1.23–2.09)	141.68 ± 58.12	116.30 (81.90–98.20)
Rrs20	1.05 ± 0.04	0.07 (1.01–1.08)	137.68 ± 44.54	100.50 (75.00–175.50)
Xrs5	−0.57 ± 0.42	1.00 (−1.14–−0.14)	133.10 ± 112.50	255.10 (40.30–295.40)

Table 8 Comparison of PFT between patients with and without scoliosis.

PFT	Scoliosis		*P* value
	No $n = 16$ (%)	Yes $n = 14$(%)	
Normal IPFT ($n = 4$)	4 (25%)	0 (0%)	0.103
Obstructive pattern ($n = 20$)	10 (62.5%)	10 (71.43%)	
Both obstructive and restrictive disease ($n = 6$)	2 (12.5%)	4 (28.57%)	

Data are expressed as number (%).
$P > 0.05$ = not significant.

type 1 include frequent ENT surgery and recurrent hernia. Clinical vigilance is needed for early diagnosis [18].

One of the commonest clinical presentations which should alert the physician to the possibility of MPS is recurrent and chronic rhinitis, enlargement of the tonsils and adenoids. Nashed et al. conducted a study on eleven MPS patients using polysomnography, results showed that seven of 11 (64%) had evidence of OSA and 3/7 children were classified as having severe OSA [19]. The present study showed that 18 patients (60%) had adenoid enlargement; out of them, 10 had a history suggestive of obstructive sleep apnea, however, this was not documented by polysomnograpy.

The measurement of urinary GAG levels is a useful screening test for the MPS disorders. The current study revealed that 10 cases had normal GAGs. A positive result is very suggestive of an MPS, but false-negative results are very common [20]. Urine testing may be falsely negative in MPS III and IV. In MPS III, this is due to lower urinary GAG levels and smaller heparan sulfate fragments than in the other MPS diseases. In MPS IV, analysis of urine may be unreliable because keratan sulfate levels decline with age in this condition [21]. Thus, enzyme analysis should be performed when MPS disease is strongly suspected, even when urinary GAG excretion appears to be normal.

Consanguinity was observed in 53.3% whereas a similar family condition was present in 40% of our cases. Khadhiri

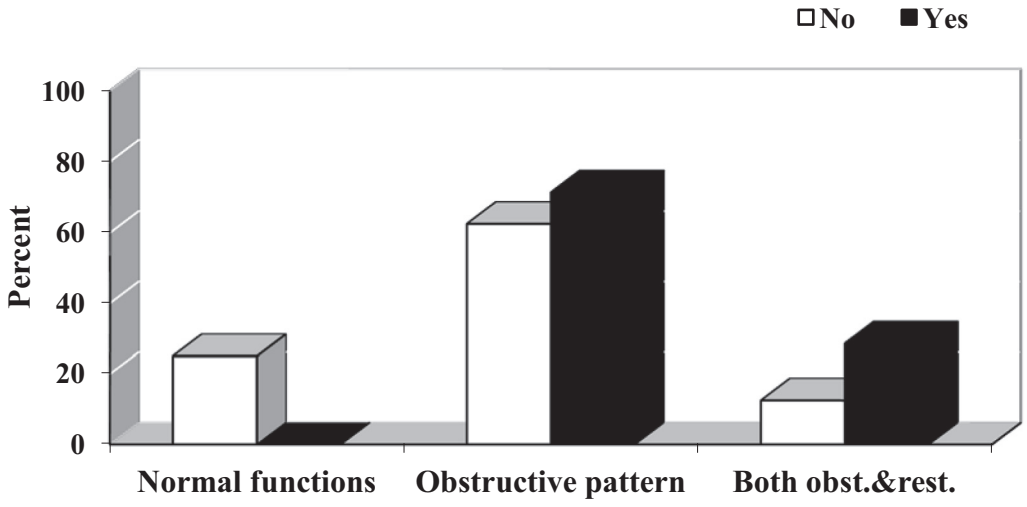

Figure 1 Type of PFT in relation to the presence or absence of scoliosis.

Table 9 Comparison of PFT between the patients according to the presence of organomegaly.

PFT	Organomegaly			*P* value
	Hepatomegaly $n = 4$(%)	HSM $n = 20$(%)	No organomegaly $n = 6$(%)	
Normal IPFT($n = 4$)	0 (0%)	2 (10%)	2 (33.33%)	0.178
Obstructive pattern ($n = 20$)	4 (100%)	12 (60%)	4 (66.67%)	
Both obstructive and restrictive disease ($n = 6$)	0 (0%)	6 (30%)	0 (0%)	

Data are expressed as number (%).
P value $\leqslant 0.5$ is significant.

et al. carried out a study on MPS type I and MPS type IVA unrelated families recruited from many regions of Tunisia. A consanguinity rate of 77.1% with first degree cousins was detected in all families except one Hurler family and one Morquio A family where the consanguinity was third cousin degree [22].

The present study showed that the most common pattern of PFT was the obstructive pattern in 20 cases (66.7%), however 6 cases (20%) had mixed pattern (both obstructive and restrictive). This could be attributed to the fact that most of our patients had upper airway obstruction. Kamin et al. monitored a 17-year-old male with Hunter syndrome over the course of a 9-month period and observed very rapid progression of respiratory dysfunction as the patient lost 22% of his functional lung capacity and there was a 25% decrease in the volume of air he could expire in 1 s i.e. the forced expiratory volume in 1 s (FEV1). A similar rapid deterioration in lung function in other patients was observed [3].

Similarly, 36.4% of the patients in our study had abnormal functional residual capacity.

Leboulanger et al. reported that patients with MPS have a significant reduction of the minimal cross-sectional area of the upper airways and an increase of the airways resistance, as compared to a matched control group [23]. Recognition of respiratory disease and early intervention improve their survival and quality of life [24].

In the current study, vertebral column affection in the form of lumbar kyphosis was detected in 18 cases (60%), while scoliosis was detected in 14 cases (46.7%). In a study done by Dalvie et al. on seven MPS children who underwent anterior instrumentation for correction of a thoracolumbar gibbus not arrested by brace treatment, preoperative kyphosis ranged from 42° to 64° (average, 52.5°). The authors declared that kyphosis was the commonest vertebral column deformity (45.9%), while scoliosis was found in only 4.9% [25].

The clinical disorders of the thoracic cage affect the thoracic motion and modify the mechanical properties of the lung and chest wall. Restriction of chest wall reduces the total lung capacity and results in an increase in respiratory frequency and decreased tidal volume (V_T) [26]. Rodriguez et al. demonstrated that patients with Morquio syndrome exhibited a decrease in Xrs5 ($P < 0.05$) and an increase in Rrs ($P = 0.05$), independent of the frequency by impulse oscillometry [27].

Similarly 50% of MPS patients included in the current study had an increase in Rrs5 and Rrs20, while all had a decrease in Xrs5, reflecting a reduction of elasticity or elastic recoil in the peripheral lung.

This study revealed that ten out of 14 patients (71.4%) with scoliosis had obstructive airway disease, however combined obstructive and restrictive patterns were observed in 4/14 (28.5%) cases. However no statistically significant association was found between the presence of scoliosis and the parameters of infant lung functions ($P > 0.05$). Rodriguez et al. declared that the metabolic defects in Morquio disease lead to cellular accumulation of GAGs causing skeletal, respiratory and neurologic sequelae. If the deposition is in the lung parenchyma, worsening of lung compliance occurs and restrictive lung disease can be seen [27].

A systematic review on publications over past 50 years demonstrated that scoliosis impairs growth and development of lungs, limits chest wall movement, and results in restrictive ventilation defect and gas exchange dysfunction [28]. However most of our patients with scoliosis ($n = 14$) had associated upper airway obstruction, that's why obstructive pattern was the most commonly observed pattern in PFT.

6. Conclusion

We concluded that evaluation and follow up of patients with MPS using PFT is essential to detect early involvement of respiratory system and hence start treatment for respiratory complications early in the course of the disease, as a significant amount of morbidity and mortality is attributable to respiratory complications.

Conflict of Interest

The authors declare no conflict of interest. There is no financial or personal relationship with other people or organizations that would inappropriately influence their work.

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