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Standardized Classification of Infants With Robin Sequence Using MicroNAPS: The Impact of Syndromes and Comorbidities

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Background: MicroNAPS, a classification for infants with Robin sequence (RS) intended to guide treatment decisions, consists of 5 elements: micrognathia, nutrition, airway, palatal clefting, and syndromes/comorbidities. Scoring of the first 4 elements is well defined, but the assignment of the syndromes/comorbidities score (S score) introduces subjectivity by necessitating judgment regarding the clinical impact of the diagnosis. A database of comorbid diagnoses associated with RS and consensus-based S scores for each is needed for the MicroNAPS system to be reproducible.

Methods: Diagnoses known to be associated with RS were identified from existing literature, and preliminary severity grades were applied. A series of electronic surveys were distributed to RS experts seeking agreement or recommendation and explanation for updated scoring, according to the Delphi technique, until at least 75% consensus was achieved for each item. A previously published series of 100 infants was rescored according to the resulting grades, and changes from initial scoring were assessed.

Results: A total of 170 associated syndromes and comorbidities were identified. Complete responses were received from 20 of the 35 experts (57.1%) surveyed. Consensus on S scores was achieved for all but 3 diagnoses (98.2%) after 4 rounds of surveys. Rescoring of the published series found 25 (25%) changes in S scores resulting in 5 modifications to R stages.

Conclusions: We have compiled a comprehensive list of syndromes and comorbid diagnoses associated with RS and achieved expert consensus regarding the impact on early treatment decision-making for most. This list, assigned S scores, and a complete MicroNAPS calculator are publicly available at www.prscalculator.com.
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INTRODUCTION

Extreme heterogeneity within the phenotypic triad of micrognathia, glossoptosis, and upper airway obstruction (UAO) known as Robin sequence (RS) has hindered the fabrication of accepted management pathways.[1–3] The magnitude of micrognathia, severity of UAO, and degree of

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feeding impairment observed in an infant with RS are highly variable. Moreover, the amplitude of any 1 deficit does not correlate in a linear fashion with the impact of any other.[4]

The most diverse factor affecting the presentation, treatment, and prognosis of infants with RS is the presence/absence of genetic syndromes and comorbid diagnoses.[5] More than 40 syndromes have been associated with RS, and nearly 70% of patients with RS carry at least 1 comorbid diagnosis.[6–8] The impacts of these conditions on UAO, feeding dysfunction, and early treatment decisions are diverse; classical stratification into "syndromic" and "nonsyndromic" categories is woefully insufficient. Variable access to neonatal genetic testing has further confounded stratification.

Resnick et al[9,10] recently introduced the MicroNAPS classification system for infants with micrognathia, RS, and tongue-based airway obstruction. This system is intended to standardize communication and treatment for infants with RS and facilitate stratification for research studies. A stage (R0–R4) is assigned based on the grading of the 5 elements in the acronym MicroNAPS: micrognathia, nutrition, airway, palatal clefting, and syndromes/comorbidities. The scoring of the first 4 variables is well defined in the classification rubric.[9] Assignment of the syndromes and comorbidities score (S score), however, requires the clinician to consider the expected impact of that diagnosis on early management, which may be subjective. Early anecdotal application of MicroNAPS has demonstrated reliability for all but the S element.

For MicroNAPS to be broadly used and to serve as the basis for the development of valid, severity-based clinical treatment pathways, it must be simple and reproducible. The primary purpose of this study, therefore, was to catalog diagnoses known to be associated with RS and assign S scores to each via a Delphi process of consensus-building among experts in the field. A secondary aim was to rescore a previously published series of infants using the resulting database of S scores to assess the impact of grading changes.

MATERIAL AND METHODS

Study Design

A comprehensive literature review was performed using PubMed queries for articles containing "Robin sequence" or "Pierre Robin sequence" and "comorbidity," "comorbidities," "syndromes," and/or "syndromic diagnosis." These searches generated 67 articles containing 170 independent diagnoses known to be associated with RS. These diagnoses were compiled into a REDCap (Vanderbilt University, Nashville, TN) electronic database. A surgeon with extensive experience managing infants with RS (C.M.R.) and a neonatal intensive care unit (NICU) nurse practitioner with 10 years' experience in a level IV NICU (J.E.H.) assigned a preliminary S score of 0–3 to each diagnosis as follows:

0 = No impact on neonatal management
1 = Minor impact on neonatal management
2 = Moderate impact on neonatal management
3 = Severe impact on neonatal management

Takeaways

Question: More than 70% of children with Robin sequence have at least 1 comorbidity that may influence management. Can stratification of these heterogeneous diagnoses facilitate creation of treatment guidelines?

Findings: A total of 170 associated diagnoses were identified. Consensus on categorization of their impact on neonatal management utilizing the existing MicroNAPS classification structure was reached for all but 3 conditions by 27 experts via a series of electronic surveys utilizing Delphi methodology.

Meaning: Standardization of the syndromes and comorbidities score of the MicroNAPS classification system will increase reproducibility of the system and facilitate the development of clinical pathways.

An electronic survey was then created in REDCap with the compiled scores.

Study Sample

The electronic survey was sent via email to all members of the micrognathia focus group of the Children's Hospitals Neonatal Consortium (CHNC), which represents multiple specialties that provide multidisciplinary management for infants with micrognathia. The survey provided the list of diagnoses with assigned preliminary S scores and prompted either agreement with the score assignment or disagreement with a suggestion for an updated score. Feedback was solicited through free-text boxes. Respondents were provided with the following instructions:

> For the MicroNAPS classification, the impact to early RS management is weighted more heavily than other repercussions of the diagnosis. "Impact" refers to upper airway obstruction and feeding management decisions. To assess *impact to early RS management*, consider: Does the diagnosis imply diminished… (1) respiratory drive? (e.g., neurologic disease); (2) respiratory efficiency? (e.g., hypotonia, extreme prematurity); (3) cardiopulmonary reserve? (e.g., congenital cardiac disease); (4) craniofacial growth capacity? (e.g., Treacher Collins, Nager syndromes); (5) response to interventions for UAO? (e.g., laryngomalacia). **To assign a score, complete the thought exercise: "Compared to an otherwise healthy infant with RS, I would alter early airway and feeding management decisions __*minorly/moderately/severely*__ because of this diagnosis.**

Disclosure statements are at the end of this article, following the correspondence information.

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

The CHNC is a network of children's hospitals in the United States and Canada that prospectively contribute neonatal outcomes data to the Children's Hospitals Neonatal Database. At the time of this study, there were 45 centers in the CHNC. The micrognathia focus group of the CHNC was established in 2022 and includes 35 experts in micrognathia and RS from the fields of pediatrics, neonatology, genetics, pulmonology, oral and maxillofacial surgery, plastic surgery, and otolaryngology practicing at level IV NICUs.

Delphi Process

Standard Delphi methodology was applied, including predetermination of a minimum threshold for consensus (75%), anonymity of respondents, solicitation of feedback, transparent incorporation of feedback into future survey iterations, and serial surveying to reach consensus.[11,12] Diagnoses that met or exceeded the 75% consensus threshold were excluded from subsequent surveys.

After completion of the Delphi process, the resulting scoring database was used to regrade all S scores from the series of 100 infants evaluated in the original MicroNAPS publication.[9] Changes in S scores from the original assessment and the impact of these changes on the R stage were calculated.

Ethical Approval

This study was approved by the Boston Children's Hospital institutional review board (no. P00047220).

RESULTS

Complete responses to at least 1 survey iteration were returned by 27 participants (77.1% of the distribution). Of the respondents, 18 (66.7%) were men and 9 (33.3%) were women (Table 1). The mean years in practice was 15.2 ± 9.8. Respondents represented all 5 regions of the United States and included 10 (37%) pediatricians or neonatologists, 2 (7.4%) geneticists, 1 (3.7%) practitioner boarded in both neonatology and genetics, 3 (11.1%) pulmonary sleep medicine physicians, and 11 (40.7%) craniofacial surgeons (plastic surgeons, n = 6; otolaryngologists, n = 4; oral and maxillofacial surgeons, n = 1).

Table 1. Characteristics of Survey Respondents

n	27
Males, n (%)	18 (66.7)
Years in practice	15.2 ± 9.8
Specialty, n (%)	
Pediatrics/neonatology	11 (40.7)*
Plastic surgery	6 (22.2)
Otolaryngology	4 (14.8)
Genetics	3 (11.1)*
Pulmonology/sleep medicine	3 (11.1)
Oral and maxillofacial surgery	1 (3.7)
US region, n (%)	
West	8 (29.6)
Southeast	7 (25.9)
Midwest	6 (22.2)
Northeast	4 (14.8)
Southwest	2 (7.4)

*One respondent boarded in both neonatology and genetics.

Twenty experts responded to the first survey (57.1% of distribution). More than the minimum threshold 75% agreed with the initial score assignments for 149 of the 170 diagnoses (87.6%, Fig. 1). Feedback regarding the remaining 21 diagnoses was incorporated into the next survey, including such changes as the merging of 2 diseases into 1 category (facial femoral syndrome and bilateral femoral dysgenesis syndrome) and further qualification of 3 conditions: choanal atresia, qualified as unilateral or bilateral; vocal cord paralysis, qualified as unilateral or bilateral; and laryngeal cleft, qualified as type I versus type II–III.

The second survey was distributed to the entire focus group (n = 35) and yielded 15 responses (42.9%). Of these, 9 overlapped with the first group, yielding a total of 27 respondents between rounds 1 and 2. Ten additional diagnoses reached consensus on this survey. Feedback was applied to a third iteration, which was distributed to the 27 prior respondents. Consensus was achieved for 6 additional diagnoses from 13 participants (65% of the distribution). A final, fourth survey with the remaining 5 comorbidities lacking consensus received a response rate of 100% from the distribution of the 27 respondents from rounds 1 and 2. Following this round, 3 diagnoses failed to gain consensus agreement: Beckwith–Wiedemann syndrome, congenital central hypoventilation syndrome (CCHS), and umbilical hernia. As there were no significant changes from prior surveys in the percentage of respondent agreement for these 3 conditions, it was decided to conclude the study at this time.

A complete list of diagnoses and "S" scores is shown in Supplemental Digital Content 1. (**See figure, Supplemental Digital Content 1**, which shows a list of diagnoses and "S" scores, **http://links.lww.com/PRSGO/D994**.) For the final list, no syndromes/comorbidities received an "S" score of 0 (no impact). A score of 1 (minor impact) was assigned to 92 (54.1%) conditions, a score of 2 (moderate impact) was associated with 53 (31.2%) diagnoses, and a score of 3 (major impact) was attributed to 25 (14.7%) syndromes or comorbidities.

When the 100 infants evaluated in the original MicroNAPS study[9] were rescored based on the results of this Delphi study, there were 25 (25%) changes to their "S" scores (Table 2). Of these, the R stage was altered for 5 patients (5% of the sample, 20% of those with modified "S" scores). The most common change was in the score for gastroesophageal reflux disease, which was assigned a 1 in the original assessment but was upgraded to a 2 by the expert panel. This affected 13 patients (13%), but did not affect the R stage for those patients. The next most frequent change was in the downgrading of hemifacial (craniofacial) microsomia from a 3 to a 2, which affected 3 patients (3%) in the original series. This change led to downgrades in the R stage for all 3 patients. All other changes were single occurrences.

DISCUSSION

Stratification of the heterogenous group of infants with RS is critical to facilitate the development of treatment

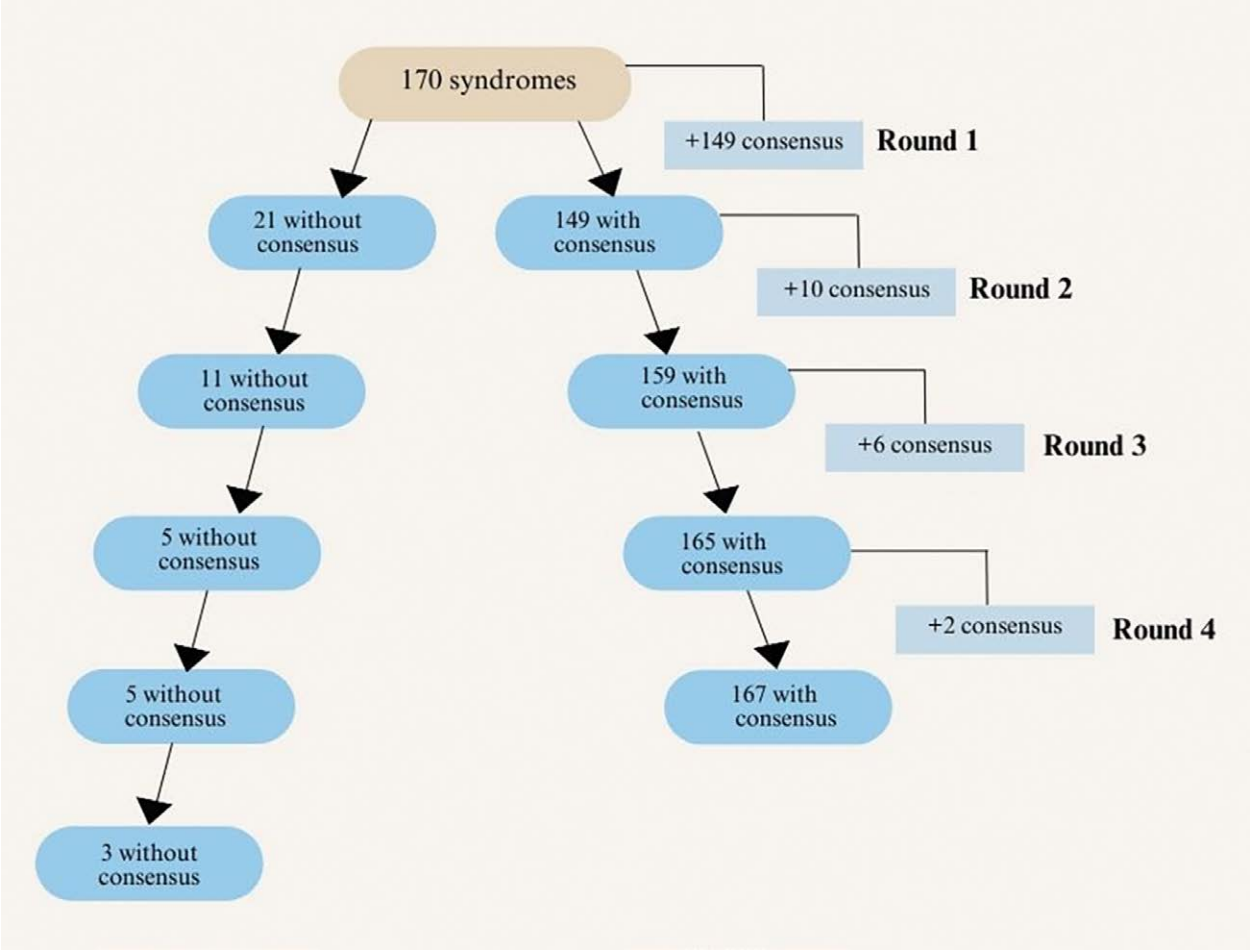

Fig. 1. Flowchart of the study process.

guidelines and to standardize research methodology. Although the MicroNAPS classification system has paved the way toward effective subgrouping, the application of the "S" syndrome/comorbidity score has proven inconsistent in clinical practice. To bolster the strength and reproducibility of MicroNAPS, we compiled a comprehensive list of diagnoses associated with RS and solicited consensus on "S" scores from a series of experts in the field utilizing a rigorous Delphi methodology. The resulting database of diagnoses and scores, as well as a complete online MicroNAPS calculator tool, are publicly available at www.prscalculator.com.

The expert panel agreed with 149 of the 170 scores (87.6%) initially assigned at study onset. The Delphi technique proved an efficient method to reach a wide range of experts and to incorporate iterative feedback with minimal attrition. Ultimately, consensus was achieved for all but 3 conditions (98.3%). The majority of diagnoses (53.5%) were assigned a score of 1, indicating a minor impact on neonatal management. The remaining 46.5% received higher impact scores of 2–3 and tended to include diagnoses that either directly affected respiration or cardiovascular function or were complex syndromes impacting multiple body systems.

Differences in "S" scores from those assigned in the original MicroNAPS publication[9] to those achieved by Delphi consensus affected 25% of the original infant sample. The majority (80%) of these changes, however, did not affect R stages. This demonstrates moderate concordance in ultimate severity staging for these infants but belies the importance of consistency in this classification system. The availability of prevetted scores for the cornucopia of syndromes and comorbidities associated with RS will enhance uniformity and support the use of the MicroNAPS classification system for outcomes assessment and treatment guidelines.

Three diagnoses failed to reach a consensus. For BWS, a majority of respondents (58.3%) assigned a minor impact score of 1, and the remainder (41.7%) chose a moderate "S" score of 2. This disagreement may reflect the unique influence of the macroglossia seen in BWS on the RS phenotype. The etiopathogenetic sequence of RS is thought to be initiated by micrognathia, which induces glossoptosis of an otherwise normal tongue, which, in turn, creates UAO. In BWS, however, primary macroglossia is the more likely direct cause of the UAO.[13] It, therefore, stands to reason that patients with BWS may present with UAO that does not fit the RS model and

Table 2. Comparison of Original MicroNAPS Grading and Updated Scoring Based on Delphi Results

Study ID	Original "S"	New "S"	Diagnosis	Original Stage	New Stage	Change in Stage
3	3	2	Laryngomalacia, severe	4	2	Yes
13	0	1	Laryngomalacia, mild	3	3	No
14	1	2	GERD	3	3	No
16	1	2	GERD	3	3	No
17	1	2	GERD	2	2	No
18	1	2	GERD	3	3	No
24	1	2	GERD	3	3	No
26	2	3	Aortic coarctation	0	0	No
33	1	2	GERD	2	2	No
36	1	3	Catel–Manzke syndrome	1	3	Yes
50	1	2	GERD	3	3	No
52	1	2	GERD	3	3	No
56	0	1	ASD and VSD (congenital cardiac disease, mild)	3	3	No
59	3	1	Cornelia de Lange syndrome	0	0	No
60	1	2	GERD	3	3	No
61	1	2	GERD	3	3	No
71	1	2	GERD	2	2	No
72	1	2	GERD	2	2	No
80	2	1	Cerebellar hemorrhage	3	3	No
88	3	2	Hemifacial (craniofacial) microsomia	4	2	Yes
91	1	2	Kabuki syndrome	3	3	No
95	1	2	GERD	0	0	No
97	3	2	Hemifacial (craniofacial) microsomia	4	3	Yes
98	2	1	Shprintzen–Goldberg syndrome	0	0	No
99	3	2	Hemifacial (craniofacial) microsomia	4	2	Yes

ASD, atrial septal defect; GERD, gastroesophageal reflux disease; VSD, ventricular septal defect.

may respond differently to management. Further, there is extreme heterogeneity in BWS, with several distinct molecular etiologies and medical comorbidities (eg, the chance of associated malignancies ranges from <3% to 29% depending on molecular etiology, and variable presence of hyperinsulinism, macroglossia, and omphalocele). Additionally, as most infants with BWS are never admitted to an NICU, experience with this diagnosis among the CHNC group may be limited.

CCHS received an "S" score of 2 from 54.5% of respondents and a score of 1 from 45.5%. CCHS is a rare condition caused by global autonomic dysfunction and alveolar hypoventilation. Although previously life-threatening, modern treatment strategies may be effective.[14] Like BWS, however, CCHS directly affects respiratory efficacy via a pathway independent of the RS phenomenon. The majority of individuals with molecularly confirmed *PHOX2B*-related CCHS do not have micrognathia or RS. As such, management of the primary neonatal concerns of RS (breathing and feeding) will be highly influenced by the presence and severity of this diagnosis. The co-occurrence of CCHS and RS is extremely rare, so the scoring of the diagnosis for this study was likely influenced by a small number of individual cases.

Disagreement for the diagnosis of umbilical hernia is more curious: 58.3% of the respondents chose a score of 1 and 41.7% assigned a score of 2. Umbilical hernias are very common in neonates and are typically asymptomatic. Intervention is deferred for asymptomatic hernias, and about 90% spontaneously close by age 5 years.[15] Those that incarcerate may require urgent intervention, and perhaps it is the possibility for this variant that led to disagreement in severity scoring. Additionally, umbilical hernias may occur as a component of a genetic syndrome such as BWS, which also failed to reach consensus. Practitioners responding to this survey may have been influenced by these heterogeneous presentations.

This study has several limitations. First, the methodology relies on expert opinion and consensus, which provides a limited level of evidence and inherently includes subjectivity. There exists a possibility of anchoring bias by respondents to the score assigned in the initial survey iteration, which is inherent to the Delphi technique. Nonetheless, the Delphi methodology is a robust and validated method for consensus-building from large datasets. This approach differs from other methods of agreement, such as the use of the Cohen kappa analysis for agreement testing between expert panel scores and clinicians, as was used for studies of the index of orthognathic functional treatment need.[16,17] There is also the possibility of subjectivity bias in score assignments. We attempted to mitigate this by surveying geographically diverse experts from multiple medical and surgical specialties. Additionally, as many of these diseases are rare, it is likely that respondents had limited knowledge or experience with some and may have relied on secondhand information to provide selected responses.

CONCLUSIONS

We herein present a comprehensive database of syndromes and comorbid diagnoses associated with RS,

and consensus-based MicroNAPS "S" scores to denote the impact of each on neonatal management. We expect that these scores will further bolster the existing MicroNAPS classification system for infants with micrognathia, RS, and tongue-based airway obstruction.[9,10] Future studies will seek to validate the MicroNAPS classification system and its association to treatment outcomes.

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DISCLOSURES

Following the PRS Conflict of Interest Disclosure Guidelines, the authors have the following to disclose: (1) Dr. Resnick served as a consultant for AbbVie Pharmaceuticals from 2021 to 2023. (2) Dr. Wenger was a coinvestigator for a study to improve access to care for critically ill newborns funded by GeneDx. (3) Dr. Swanson received educational grants from DePuy Synthes and KLS Martin to develop educational content. The other authors have no financial interest to declare in relation to the content of this article.

REFERENCES

1. Mackay DR. Controversies in the diagnosis and management of the Robin sequence. *J Craniofac Surg*. 2011;22:415–420.
2. Gangopadhyay N, Mendonca DA, Woo AS. Pierre Robin sequence. *Semin Plast Surg*. 2012;26:76–82.
3. Padula MA, Naing K, Wenger TL, et al. Spectrum of disease in hospitalized newborns with congenital micrognathia: a cohort of 3,236 infants at North American tertiary-care intensive care units. *J Pediatr*. 2024;265:113799.
4. Lee VS, Evans KN, Perez FA, et al. Upper airway computed tomography measures and receipt of tracheotomy in infants with Robin sequence. *JAMA Otolaryngol Head Neck Surg*. 2016;142:750–757.
5. Resnick CM, Calabrese CE. Is obstructive apnea more severe in syndromic than nonsyndromic patients with Robin sequence? *J Oral Maxillofac Surg*. 2019;77:2529–2533.
6. Cohen MM, Jr. The Robin anomalad—its nonspecificity and associated syndromes. *J Oral Surg*. 1976;34:587–593.
7. Shprintzen RJ. The implications of the diagnosis of Robin sequence. *Cleft Palate Craniofac J*. 1992;29:205–209.
8. Costa MA, Tu MM, Murage KP, et al. Robin sequence: mortality, causes of death, and clinical outcomes. *Plast Reconstr Surg*. 2014;134:738–745.
9. Resnick CM, Katz E, Varidel A. MicroNAPS: a novel classification for infants with micrognathia, Robin sequence, and tongue-based airway obstruction. *Plast Reconstr Surg Glob Open*. 2023;11:e5283.
10. Resnick CM, Katz E, Varidel A. Application of the MicroNAPS classification for Robin sequence. *Cleft Palate Craniofac J*. 2024;Feb 1:10556656241229892.
11. Shang Z. Use of Delphi in health sciences research: a narrative review. *Medicine (Baltim)*. 2023;102:e32829.
12. Thangaratinam S, Redman CW. The Delphi technique. *Obstet Gynaecol*. 2005;7:120–125.
13. Cielo CM, Duffy KA, Taylor JA, et al. Obstructive sleep apnea in children with Beckwith-Wiedemann syndrome. *J Clin Sleep Med*. 2019;15:375–381.
14. Trang H, Samuels M, Ceccherini I, et al. Guidelines for diagnosis and management of congenital central hypoventilation syndrome. *Orphanet J Rare Dis*. 2020;15:252.
15. Hansen EA, Gallagher S, Ryckman JG. Timing of surgical intervention of uncomplicated pediatric umbilical hernias. *S D Med*. 2023;76:542–544.
16. Borzabadi-Farahani A. Systematic review and meta-analysis of the index of orthognathic functional treatment need for detecting subjects with great need for orthognathic surgery. *Cleft Palate Craniofac J*. 2023:10556656231216833.
17. Ireland AJ, Cunningham SJ, Petrie A, et al. An index of orthognathic functional treatment need (IOFTN). *J Orthod*. 2014;41:77–83.