

# New Medical Device and Therapeutic Approvals in Otolaryngology: State of the Art Review of 2021

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## Abstract

**Objective.** To evaluate new medical devices and drugs pertinent to otolaryngology–head and neck surgery that were approved by the Food and Drug Administration (FDA) in 2021.

**Data Sources.** Publicly available FDA device and drug approvals from ENT (ear, nose, and throat), anesthesia, neurosurgery, plastic surgery, and general surgery FDA committees.

**Review Methods.** FDA device and therapeutic approvals were identified and reviewed by members of the American Academy of Otolaryngology–Head and Neck Surgery’s Medical Devices and Drugs Committee. Two independent reviewers assessed the relevance of devices and drugs to otolaryngologists. Medical devices and drugs were then allocated to their respective subspecialty fields for critical review based on available scientific literature.

**Conclusions.** The Medical Devices and Drugs Committee reviewed 1153 devices and 52 novel drugs that received FDA approval in 2021 (67 ENT, 106 anesthesia, 618 general surgery and plastic surgery, 362 neurosurgery). Twenty-three devices and 1 therapeutic agent relevant to otolaryngology were included in the state of the art review. Advances spanned all subspecialties, including over-the-counter hearing aid options in otology, expanding treatment options for rhinitis in rhinology, innovative laser-safe endotracheal tubes in laryngology, novel facial rejuvenation and implant technology in facial plastic surgery, and advances in noninvasive and surgical treatment options for obstructive sleep apnea.

**Implications for Practice.** FDA approvals for new technology and pharmaceuticals present new opportunities across subspecialties in otolaryngology. Clinicians’ nuanced understanding of the safety, advantages, and limitations of these innovations ensures ongoing progress in patient care.

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medical devices, drugs, FDA, therapeutic

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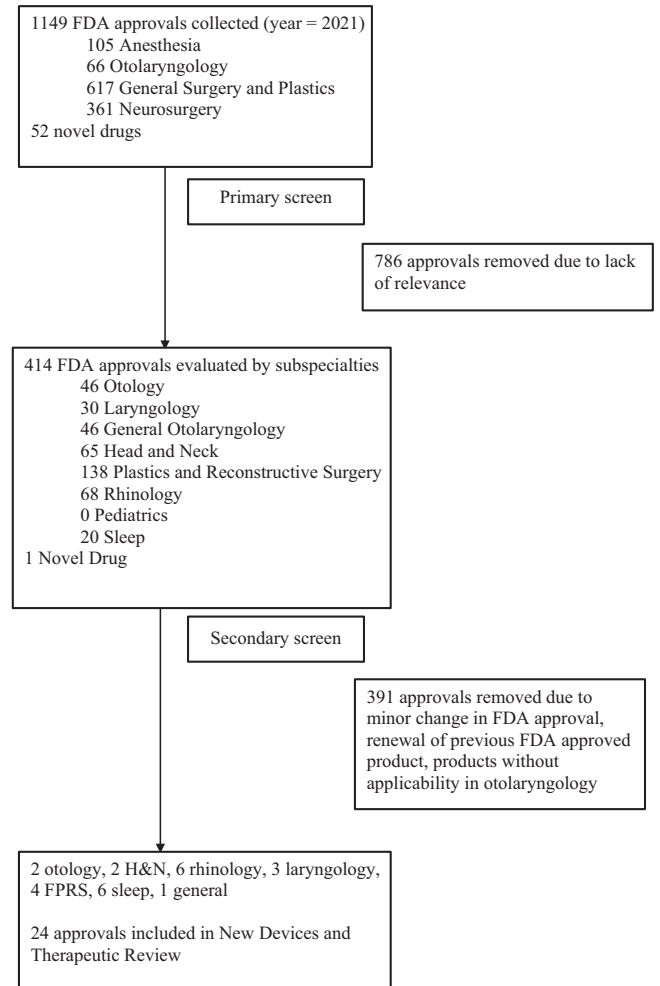
Medical technology is in constant advancement, ranging from incremental improvements to disruptive innovation. Otolaryngologists are at the forefront of developing and bringing these innovations to patients. Being new does not necessarily mean being useful, and so each new technology requires careful evaluation during the adoption process. The role of the Food and Drug Administration (FDA) is to ensure safety and efficacy, serving as a gatekeeper for approval of new drugs and devices. The Medical Devices and Drugs Committee of the American Academy of Otolaryngology–Head and Neck Surgery annually reviews new FDA approvals with the objective of critical evaluation and to highlight novel drugs or devices that may affect our field.<sup>1,2</sup> As compared with 2019 and 2020, the committee has reviewed an increasing number of new FDA-approved devices and drugs. Understanding the innovation behind new developments in medical technology allows otolaryngologists to provide novel, safe, and effective treatment to patients.

## Methods

All medical devices and drugs that received FDA approval from January 1 to December 31, 2021, were eligible for inclusion in the review. Publicly available records from the FDA were reviewed for each drug or device. These records included de novo devices, premarket approvals, and 510(k) submissions. Drugs and devices cleared by the otolaryngology, neurosurgery, anesthesia, plastic surgery, and general surgery committees of the FDA were assessed. Two independent reviewers assessed novelty, relevance, and overall impact to the specialty, with approvals allocated by subspecialty expertise of the reviewers. Companies were contacted for clarification of product details and for permission to reproduce images of products in accordance to manuscript guidelines.

## Results

The FDA database included 82 anesthesia, 39 ENT (ear, nose, and throat), 199 neurosurgical, and 475 plastic and general surgery 510(k) clearances. In addition, 23 anesthesia, 25 ENT, 156 neurosurgical, and 140 plastic and general surgery premarket approval devices were reviewed in addition to 2 ENT, 2 plastic and general surgery, and 6 neurosurgical de novo devices. Fifty-two novel drugs were approved in the 2021 calendar year. Renewals of previously established products, minor changes to existing FDA approvals, and products not applicable to otolaryngology were excluded. This yielded 1 therapeutic and 23 device approvals relevant to otolaryngology (**Figure 1**, **Table I**). The level of scientific evidence supporting these novel therapies varied,



**Figure 1.** Flowchart of review process of otolaryngology-pertinent Food and Drug Administration (FDA) approvals in 2021. FPRS, facial plastic and reconstructive surgery; H&N, head and neck.

ranging from retrospective case-control studies to prospective randomized clinical trials.

## Discussion

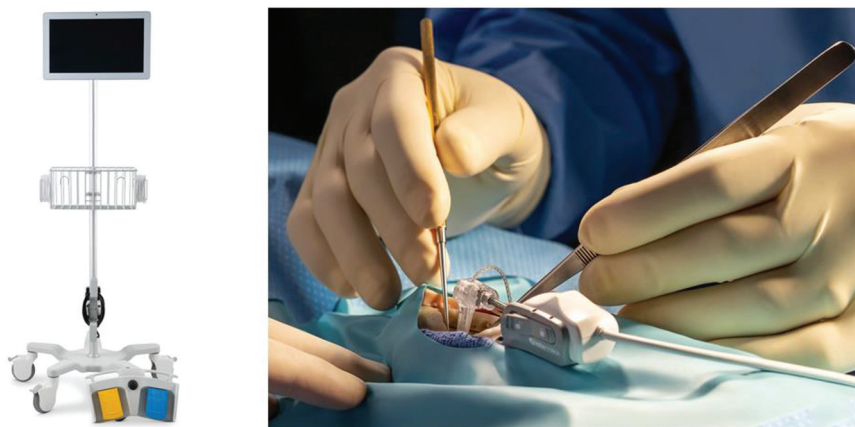
### Otology

*IotaSOFT Insertion System for Robotic-Assisted Cochlear Implantation.* This device was approved through the relatively new de novo pathway. So-called atraumatic cochlear implant (CI) electrode array insertion techniques aim to maximize preservation of residual hearing. Traditionally, atraumatic electrode array insertion involved manual control by the surgeon using the soft surgical technique.<sup>3,4</sup> The IotaSOFT Insertion System (IotaMotion, Inc) controls the speed of electrode array insertion, reducing overall electrode array insertion forces and insertion force variability when compared with manual insertions.<sup>5,6</sup> The thumb-sized, robotic-assisted system consists of a single-use sterile electrode insertion drive unit (**Figure 2B**) connected to a reusable control console and foot pedal (**Figure 2A**). Prior to electrode array insertion into the cochlea, the surgeon

**Table 1.** Otolaryngology-Relevant Devices and Drugs Approved by the Food and Drug Administration in 2021 by Subspecialty.<sup>a</sup>

	Devices (n = 23)	Drugs (n = 1)
Otology	iotaSOFT Insertion System Bose SoundControl Hearing Aids	None
Rhinology	Neuromark system I688 Advanced Imaging Modalities 4K Platform Cube Navigation System Allerblock Junior Peregrine Drivable ENT Scope Rebellion/Phantom Bone Removal System	None
Plastic and reconstructive surgery	Kerecis Reconstruct Meticuly Patient-Specific Titanium Mesh Implant Sofwave System Ellacor Dermal Micro-Coring System	None
Laryngology	Tracoe Vario Tracheostomy Tubes Tenax Endotracheal Tube Trachealator	Avacopan
Head and neck/endocrine	Single-Port robotics system	None
Sleep	Inspire Hypoglossal Nerve Stimulation 2-incision technique Noninvasive ventilation face masks (4) AcuPebble SA100	None
Pediatrics	None	None
General	None	None

<sup>a</sup>Refer to the text for details about each product.



**Figure 2.** (A) iotaSOFT Insertion System Controller and Accessories Kit. (B) iotaSOFT Drive Unit.

secures the unit to the patient with self-drilling bone screws, couples the iotaSOFT onto the CI lead, and then positions and aligns the array in the target insertion trajectory outside the facial recess via an adjustable stabilizing arm. During insertion, the surgeon selects an insertion rate from 100 to 1000  $\mu\text{m/s}$  on the console and controls the electrode array insertion via a foot pedal and standard manual instrumentation to guide as needed. The device works with select implants from each of the 3 CI companies. Clinical testing on 21 patients were performed by 3 surgeons using the iotaSOFT insertion system. CIs from all 3 companies were inserted. Results revealed normal impedance and neural

response telemetry measurements in patients with normal cochlear anatomy at 1 month postoperation. Postinsertion x-ray outcome was satisfactory with all insertions with normal cochlear anatomy. Hearing preservation was not evaluated in this study.<sup>7</sup> Despite a strong theoretical basis, there are limited data on clinically relevant hearing preservation with use of this device.

**Bose SoundControl Hearing Aids.** The Bose SoundControl Hearing Aid (Bose Corporation) is one of a newer-generation over-the-counter (OTC) hearing aids. With the recent proposed rule in October 2021 by the FDA to



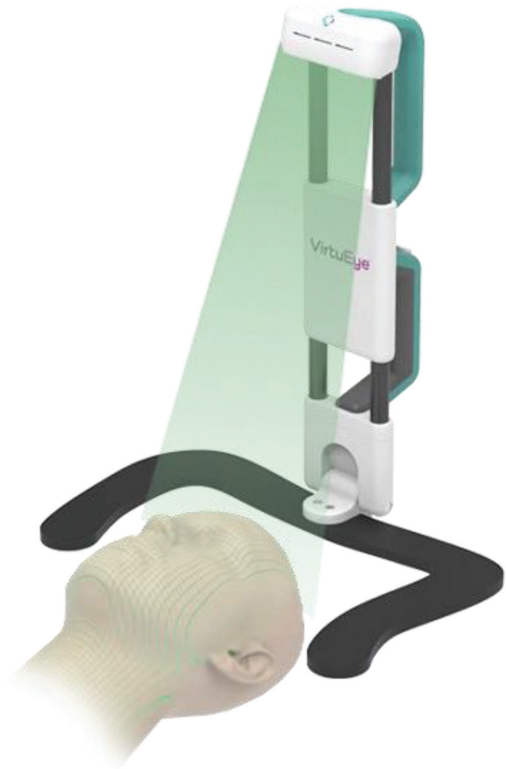
**Figure 3.** Neuromark Bipolar Radiofrequency Console With Deployed Leaflets.

establish a new category of OTC hearing aids, this product was one of the first OTC hearing aids seeking FDA approval for the marketplace. It is a self-fitting wireless air conduction hearing aid that can be self-adjusted. No preprogramming or professional programming of the device is needed. A clinical study demonstrated that the Bose Self-Fitting method results in hearing outcomes similar to those achieved with professional fitting.<sup>8</sup> Additionally, subjects reported satisfaction with their hearing using the self-fitting method as well as a preference for their self-adjusted settings over the professionally selected settings. Despite recent restructuring within the company, Bose continues to sell the device at the time of submission.

### Rhinology

**Neuromark System.** The Neuromark system (Neurent Medical) utilizes a bipolar radiofrequency console to disrupt parasympathetic input from the posterior nasal nerves in patients with chronic rhinitis. This product has similarities to RhinAer (Aerin Medical) and Clarifix (Stryker) in direct ablative targeting of the posterior nasal nerve.<sup>9,10</sup> The primary differences relate to the geometry of the electrode array. The device is operated via a slider and an activation switch on the handle. Once the desired position is achieved, the outer sheath is retracted, and therapy is deployed via leaflets targeting 20 microlesion ablation sites (**Figure 3**). This smart console gives feedback via audio and visual cues on treatment location and duration by constantly monitoring bioimpedance parameters. The RELIEVE study was a prospective single-arm (nonrandomized) feasibility and safety study that consisted of 10 adults with chronic rhinitis (not specified allergic vs nonallergic). At 1-month follow-up, there was an 80% positive responder rate and an overall reduction in total nasal symptom scores of  $3.5 \pm 0.4$  (out of 15;  $P < .001$ ).<sup>11,12</sup> The advantage of this device in comparison with its predecessors is the larger area of treatment, which is useful given the variability of the location of posterior nasal nerves and other accessory parasympathetic branches in the nasal cavity.

**1688 AIM 4K Platform.** The 1688 AIM 4K camera system (Advanced Imaging Modalities; Stryker) includes many enhancements as compared with its predecessor, the 1588 AIM HD system, in terms of resolution, light sensitivity,



**Figure 4.** VirtuEye Infrared Camera Facial Image Capture for Calibration of Cube Navigation System Image Guidance.

image clarity, and advanced imaging functionality. The 4K upgrade from a  $1920 \times 1080$  HD camera offers 4 times the resolution of a 1080p image alongside a more accurate color gamut. A proprietary chip within the camera head allows 4K image registration and output on a 32-inch 4K screen. The sinuscope retains a reverse post configuration but has improved optics with a larger depth of field, increased durability, and improved polyether ether ketone insulation surrounding the light post for decreased heat output and ergonomics for surgeons. The light source has automatic light adjustment technology that senses image oversaturation at 60 frames per second and adjusts the light output throughout the case to provide optimal visualization. To further streamline the intraoperative experience, voice control compatibility via a headset has been introduced to facilitate photo and video capture, white balance, and other intraoperative functions. This upgrade is part of an ongoing trend in improving visual quality in endoscopic sinus and skull base surgery.

**Cube Navigation System.** The Cube Navigation System (Intersect ENT) is an image guidance system that utilizes automated facial recognition technology captured via a camera to generate a model of the patient's sinus anatomy in endoscopic sinus and skull base surgery. The Cube Navigation software collects  $>50,000$  registration points using 1 photograph and potentially reduces image guidance preparatory time and user error in tactile registration (**Figure 4**). In a prospective study evaluating this technology



**Figure 5.** Rebellion/Phantom Bone Removal System.

as compared with its conventional surface registration, there was a statistically significant improvement in accuracy at the head of the middle turbinate, axilla, and face of the sphenoid of 0.45 mm ( $P = .002$ ), 0.4 mm ( $P < .001$ ), and 0.4 mm ( $P < .001$ ), respectively. The registration time (40 seconds) was equivalent to conventional surface registration.<sup>13</sup> The navigation system is also compatible with multiple navigating malleable pointers and suction tubes as well as single-use probes, suction, and navigating balloons. This upgrade improves and streamlines the registration process for image guidance in endoscopic sinus procedures and surgery.

**Allerblock Junior.** Allerblock Junior (Nasaleze International Ltd) is an OTC nasal spray that delivers an inert barrier powder, HPMC (hydroxypropyl methylcellulose), with mint or strawberry scent flavoring. The powder reacts with the natural moisture within the nose to form a protective gel barrier that traps allergens, preventing them from reaching the nasal mucosa and eliciting an allergic reaction. This medication is now approved for use in children aged  $>8$  years. A single-blinded randomized study including 64 patients (32 patients in each treatment arm) with allergic rhinitis was conducted comparing Nasaleze HPMC powder and intranasal mometasone spray. Both groups had statistically significant and comparable improvement in symptoms of sneezing, runny nose, nasal congestion, itchy eyes, and itchy throat, suggesting similar efficacy between the interventions at 14 and 28 days.<sup>14</sup> This form of barrier-protective therapy provides an alternative option to intranasal and oral antihistamine and corticosteroid therapy for patients with allergic rhinitis, particularly in patients who cannot tolerate first- and second-line treatments. Larger, well-designed studies are needed to evaluate long-term efficacy.

**Peregrine Drivable ENT Scope.** 3NT Medical Ltd received 510(k) clearance for modifications in size, shape, and electronics for the Peregrine Endoscopy System, also known as the Peregrine Drivable ENT Scope, which initially received FDA approval in 2017. Software updates to support these changes and a new integrated tablet-based video display and user interface received clearance, as well as packaging changes. The device is a single-use sinus endoscope with an advanceable 2.3-mm tip. Embedded in the end is a distal chip providing a 120° field of view diagonally and an LED

(light-emitting diode) for illumination. The endoscope can turn from its tip at angles of 0° to 125° and be further advanced. This scope allows for better visualization during functional endoscopic sinus surgery and has the potential for evaluation and treatment of disease affecting the far lateral frontal sinus, such as a mucocele or allergic fungal sinusitis.<sup>15,16</sup>

**Rebellion/Phantom Bone Removal System.** The Kerrison rongeur is used commonly in endoscopic sinus and skull base surgery to remove or harvest bone. Several modifications of the Kerrison rongeur have improved its function.<sup>17,18</sup> The Rebellion/Phantom device (Morpheus AG) improves upon the traditional Kerrison rongeur in a number of ways (**Figure 5**). The blade advances across a 14-mm opening, which cuts through bone without compressing it, preserving the cancellous structure when needed for autografts. Suction and irrigation ports are integrated into the hand piece, and a compatible trap can be attached to collect bony pieces for grafting or for pathology specimen collection. The continuous removal of bone via suction or multibite capability saves time by eliminating the need to remove the instrument each time to clear bony debris from the tip. The Rebellion/Phantom Bone Removal System is a single-use instrument and is available in 2 lengths (200 and 250 mm) and 3 sizes (2, 3, and 4 mm). Although approved for use in skull base surgery per 510(k) approval, futures clinical studies are needed to compare the effectiveness of this device with the traditional Kerrison rongeur.

### Plastic and Reconstructive Surgery

**Kerecis Reconstruct.** The Kerecis Reconstruct (Kerecis Limited) is an acellular biologic dermal matrix. This device was deemed substantially equivalent to the Cook Biodesign Plastic Surgery Matrix. Kerecis uses wild Atlantic cod as the initial raw material, as opposed to the Cook Biodesign product, which is sourced from porcine small intestinal submucosa. The Reconstruct synthetic mesh is derived from decellularized cod fish skin. Potential applications within otolaryngology include treatment of burns, oral cavity defects, coverage of open wounds, and dural repair. The proposed advantages of fish skin as a dermal matrix xenograft is reduced risk of disease transfer between cold-water fish and humans. Kerecis grafts retain native proteins and lipids, such as omega-3 polyunsaturated fatty acids, collagens, elastin, and glycan. Preservation of these components is conducive to wound healing, neovascularization, and cell repopulation. Additionally, there are no cultural or religious constraints on usage. Recent studies using acellular fish skin grafts demonstrate faster and more efficacious wound healing than traditional wound dressings, bovine collagen grafts, or dehydrated human amnion/chorion membrane allograft.<sup>19-22</sup>

**Meticuly Patient-Specific Titanium Mesh Implant.** The Meticuly Patient-Specific Titanium Mesh Implant (Meticuly Co, Ltd) is a custom titanium implant indicated for use in selective

trauma of the cranial and craniofacial skeleton (eg, frontal bone, temporal bone, occipital bone, parietal bone, sphenoid bone, supraorbital process, vomer), cranial and craniofacial surgery, and reconstructive procedures. The Meticuly implant is custom designed to replace each patient's bony void. It uses computed tomography data before 3-dimensional printing with laser-based powder bed fusion as additive manufacturing. The titanium mesh is thin, at 0.5 mm, improving on aesthetics, weight, and x-ray artifact. Concurrently, the implant retains sufficient strength despite maintaining a low profile. Titanium has also been shown to have a lower infection rate than other prosthetic materials, such as autogenous free bone grafts, PMMA-based grafts, and ceramics.<sup>23</sup> Applications include cranial reconstruction after tumor resection, traumatic brain injury, craniotomy, and craniofacial trauma including complex orbital fractures.<sup>24</sup>

**Sofwave System.** Ultrasound tightening of the skin was first approved in 2009.<sup>25</sup> This technology utilizes microfocused ultrasound emitted through an applicator to heat the dermis and create thermal damage. This therapy induces deposition of collagen and elastic fibers, tightening the skin. Sofwave Medical Ltd first received FDA approval in 2019 for noninvasive improvement of facial lines and wrinkles by way of the Sofacia System.<sup>26</sup> This approval supported microfocused ultrasound technology applied to tightening the skin of the face and neck. The device held similar application to the Ulthera System (Merz Pharmaceuticals); however, the treatment depth of the Sofwave is more superficial (<3 mm). The Sofwave also consists of a thermoelectric cooler that maintains the epidermis at a cool temperature. In 2021, the Sofwave System received additional approval for lifting the eyebrow and tightening lax submental/neck tissue.<sup>27</sup> A total of 80 subjects received treatments at 5 investigational sites in the United States.<sup>28</sup> Each subject was treated on 3 face and neck zones: the forehead/temples, cheeks, and submentum/neck. Improvements were reported in the eyebrow and submentum. Objective measurement of eyebrows revealed an average lift of 0.78 mm for maximal eyebrow height and 0.69 mm for average eyebrow height. Overall, 80% of subjects were improved per physician assessment. Objective measurement of lax submental and neck tissue revealed an average lift of 38 mm<sup>2</sup>. Eighty-five percent (61/72) of subjects were improved per physician assessment. Fifty-five percent had subjective improvement and satisfaction for the eyebrow lift and submentum lift. One device-related adverse event of a blister was reported, which was moderate and transient and resolved completely with topical cream only. This device offers advancements in treating the aging face with improvement in technology and broader indications of use.

**Ellacor Dermal Micro-Coring System.** Ellacor (Cytrellis Biosystems, Inc) is a minimally invasive device that removes microsized areas of excess skin without surgery, thermal energy, or scarring. The microcoring technology is FDA approved for the treatment of moderate to severe wrinkles in the mid- to lower face. The system uses a modified

hollow hypodermic needle for fractional removal of skin and achieves closure along the relaxed skin tension lines. Preclinical studies conducted in porcine subjects demonstrated favorable skin healing at 1 week and resolution of erythema within 2 weeks. Collagen content increased by 89% and was accompanied by an increase in epidermal and papillary dermal thickness.<sup>29,30</sup>

Three prospective clinical trials subsequently evaluated outcomes of dermal microcoring. Short- and long-term data were collected for facial skin by using 22- to 25G needles. As in preclinical studies, microcoring resulted in skin tightening and an increase in skin thickness with few side effects.<sup>31</sup> On postprocedure day 30, the facial skin surface area decreased 9.4% ± 4.3% with a 10% treatment density, corresponding to significant improvement relative to controls. However, most subjects had light skin, and patients were excluded who had a history of smoking, keloid formation, hypertrophic scarring, bleeding disorder, use of anticoagulation, and other skin disorders.

The procedure is performed with local anesthetic and can be repeated to reduce the skin surface area. A potential advantage over energy-based devices such as fractional laser or radiofrequency ablation is avoidance of cellular necrosis from thermal injury, which can delay healing. The microcoring procedure is well tolerated by patients, and the discomfort is comparable to that of microneedling. Findings of skin tightening and increased skin thickness without complications suggest promise for skin rejuvenation, although long-term studies investigating a wider range of anatomic sites will help define optimal use.

## Laryngology

**Avacopan.** Avacopan (Tavneos; ChemoCentryx, Inc) is the first oral medication specifically classified as a complement inhibitor approved for use for granulomatosis with polyangiitis (GPA; formerly known as Wegener's granulomatosis). ENT manifestations of GPA include rhinitis, epistaxis, septal perforation, collapse of nasal cartilaginous support (eg, saddle nose deformity), serous otitis media, gingival hyperplasia, and tracheal/subglottic granulomatous masses.<sup>32</sup> Avacopan is a complement 5a receptor (C5aR) antagonist that blocks C5a-mediated neutrophil activation and migration. Avacopan is indicated as an adjunctive treatment of severe GPA in combination with glucocorticoids. It has been shown to be noninferior but not superior to prednisone taper with respect to remission at week 26 and was superior to prednisone taper with respect to sustained remission at week 52. Adverse events were hepatic-related adverse reactions (13.3%), dizziness (6.6%), and angioedema (1.2%).<sup>33</sup> Its main advantage is overall reduction of daily glucocorticoid use.

**Tracoe Vario Tracheostomy Tubes.** Tracoe Vario Tracheostomy Tubes (TRACOE Medical) were improved in 2021. They continue to have an adjustable neck flange with a locking mechanism that allows the length of the tube to be adapted to an individual patient. The neck flange includes 2 flexible/



**Figure 6.** Tenax Endotracheal Tube.

rotatable wings that permit secure fastening of the tracheostomy strap around the patient's neck. Recent changes approved by the FDA include a fenestrated model, additional XL models, use of the subglottic suction line for above-cuff vocalization, and a minimally traumatic insertion system in some models.

Phonation has been shown to assist the medical and psychological improvement of some patients with chronic tracheostomy tubes.<sup>34</sup> Phonation is also possible with the Blom Tracheostomy Tube and Speech Cannula (Pulmonary), and length adjustments are available in LP Cuff Adjustable Neck Flange Tracheostomy Tubes (Arcadia Medical).

**Tenax Endotracheal Tube.** Bryan Medical released the Tenax Endotracheal Tube, a new addition to the laser-safe endotracheal tube market designed for laser endolaryngeal procedures. The product contains many of the desirable attributes of a laser-safe tube, as defined by survey of members of the American Broncho-Esophagological Association and American Head and Neck Society.<sup>35</sup> The tube is encased in a silicone sheath to allow for smooth outer contour to reduce potential for inadvertent tissue trauma. It contains depth markings that aid in proper depth of placement, another potential advantage over existing market products (**Figure 6**). The tube is aluminum wrapped, reinforced, and latex-free. The dual cuff is tight-to-shaft to reduce trauma on insertion and is preloaded with blue dye to aid in detection of inadvertent cuff rupture and to reduce risk of accidental laser ignition. Sizes range from an inner diameter of 5.0 mm (7.9-mm outer diameter) to 7.5 mm



**Figure 7.** Trachealator for nonocclusive airway balloon dilation.

(11.0-mm outer diameter) and come with or without a disposable stylet.

**Trachealator.** The Trachealator (DISA Medinotec) device allows ventilation during tracheal dilation. It consists of a series of parallel balloons on a catheter that, when deployed, provide an outward radial force while creating an interballoon space or passage for airflow (**Figure 7**). Dilation is recommended for 3 minutes with tracheal stenosis. Balloon inflation diameters range from 6 to 18 mm, making it useful in pediatric and adult patients. These ranges are comparable to the CRE Pulmonary Balloon Dilatation Catheter (Boston Scientific) and INSPIRA AIR Balloon System (Acclarent) airway balloon dilators.<sup>36</sup> Traditional airway balloons entail transient airway occlusion during dilatation, which limit concurrent oxygenation/ventilation, reduce safe duration of dilatation, and potentially increase risk of hypoxic injury or barotrauma. The nonocclusive Trachealator design, wherein oxygenation/ventilation can be maintained, is particularly useful for individuals with limited pulmonary reserve.<sup>37</sup> Future comparative studies are needed to evaluate efficacy in balloon dilation for tracheal and subglottic stenosis.

## Head and Neck/Endocrine

**Head and Neck Robotics.** Beginning with FDA approval in March 2019, Intuitive Surgical gained approval for the Single-Port robotic system for transoral lateral oropharyngeal and tongue base procedures. The Single-Port platform is a single-cannula system conducive to narrow-field procedures, allowing surgeons to negotiate the anatomic constraints of the oropharyngeal and hypopharyngeal cavities. The system accommodates narrow flexible 6-mm instruments, and a novel flexible endoscope with cobra-style articulating function mitigates the need for angled endoscope exchanges. The most recent authorization via the FDA 510(k) pathway has substantial equivalence to the Firefly Imaging System for endoscopic near-infrared visualization. This near-infrared capability will likely add fully integrated and easily toggled endoscopic filters for tumor margin assessments and neurovascular identification, as available on prior models of the Intuitive robotic systems.<sup>38</sup> This will also apply to fluorescent-guided surgical applications with the Single-Port system. Initial experience with

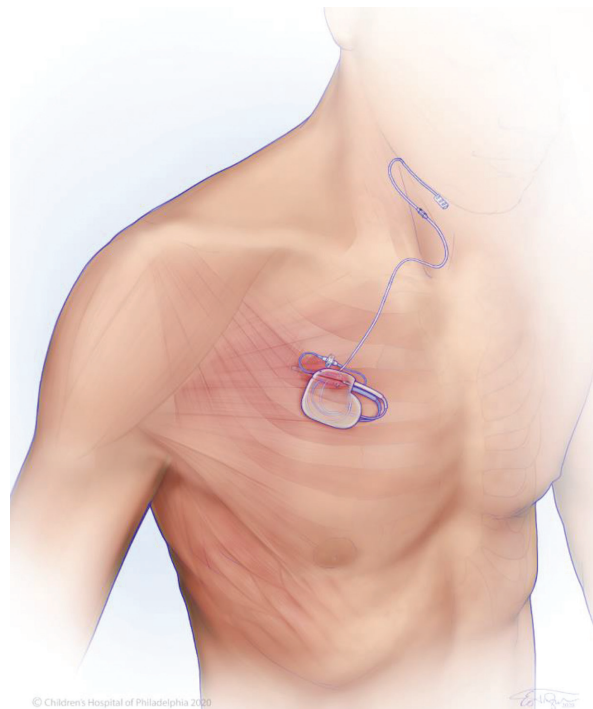
the Single-Port robotic system in head and neck surgery documents safe operation and potential opportunities for expanded clinical use.<sup>39-41</sup>

## Sleep

**Improvements in Inspire Hypoglossal Nerve Stimulation Implantation.** FDA approved in 2021, the implantation technique has advanced from a 3-incision to a 2-incision technique, which has greatly facilitated implantation (**Figure 8**). The Inspire hypoglossal nerve stimulator (Inspire Medical Systems) was the first and currently only FDA-approved hypoglossal nerve stimulator for treatment of moderate to severe obstructive sleep apnea since 2014. This system is aimed at patients with anterior-posterior upper airway collapse as determined by preoperative drug-induced sleep endoscopy.<sup>42-45</sup> With the 2-incision technique, the sensor lead can now be placed in the second rib space. A recent retrospective review comparing the 2 techniques showed similar complication rates but a statistically significant decrease in average operation time from 143 to 129 minutes ( $P < .001$ ).<sup>46</sup> Upcoming improvements are focused on having the inspiration sensor incorporated within the implantable pulse generator, further decreasing procedure time and risk of complication for the device.

**Noninvasive Ventilation Face Masks.** In June 2021, Philips Respironics (a major respiratory sleep and respiratory care device manufacturer and distributor) voluntarily recalled certain ventilators and BiPAP/CPAP machines (bilevel/continuous positive airway pressure). These devices contained polyester-based polyurethane foam, which was originally utilized to lessen sound and vibration generated from the medical devices. However, with prolonged use, the foam material was noted to break down resulting in unintended inhalation or deglutition. This recall has increased the importance and demand for non-CPAP treatments, as well as safe noninvasive ventilation face masks that have incorporated design elements that optimize comfort and care to the patient. These devices include the Innova Nasal NVM (Sleepnet Corp), Sleep Apnea Breathing Therapy Full Face Mask (YUWELL), Dreamwear Silicone Pillows Cushion Mask (Phillips Respironics), and F&P Visairo Nov Mask (Fisher & Paykel Healthcare), which were all FDA approved in 2021.<sup>47-51</sup>

**AcuPebble SA100.** Sleep diagnostic devices continue to be developed with the aim of being less invasive and intrusive. The AcuPebble SA100 (Acurable) is an automated base of neck sensor that can be utilized to obtain measurements such as apnea-hypopnea index and oxygen desaturation index, as well as apnea event classification and respiratory/cardiac feature analysis for diagnosis of obstructive sleep apnea (**Figure 9**). It records respiratory- and cardiac-related sounds. Sophisticated signal-processing algorithms are applied to automatically extract the parameters used for sleep apnea diagnosis, and data are then uploaded to a secure cloud platform. Study results validated the efficacy



**Figure 8.** Inspire 2-incision technique for obstructive sleep apnea. Previously, a third incision was required for sensor lead placement over the fifth rib space. Now, the same incision of the implantable pulse generator can be used to place the sensor in the second rib space.



**Figure 9.** AcuPebble SA100 automated base of neck sensor for obstructive sleep apnea diagnosis.

of the AcuPebble SA100 as an automated diagnosis alternative to cardiorespiratory polygraphy. In addition, the results demonstrate that the AcuPebble SA100 can be used by patients without requiring human training or assistance. A reported 90% apnea detection agreement with a sleep specialist was noted vs polysomnography software at 12% agreement (7 times more accurate). The AcuPebble correctly diagnosed 100% of cases of moderate and severe sleep apnea.<sup>52,53</sup>



## Limitations

This review encapsulates FDA approvals of devices and drugs in otolaryngology over the past year but does not characterize the long-term effects of these technologies. Postmarket surveillance is imperative for novel technologies. Furthermore, subjectivity in determining clinical relevance of the products is inherent in device selection. Some devices or drugs excluded from the analysis may prove relevant to the otolaryngology community in the future. Last, despite efforts to be comprehensive, technological advancements come in multiple forms that may not require direct FDA oversight but may be impactful, although outside the scope of our review (eg, improvement in software).

## Implications for Practice

Medical advances and innovation within otolaryngology continue to develop at a rapid pace. While only some advances will shift clinical practice or supplant current standards of care, it is important that otolaryngologists be cognizant of what technologies are at their disposal to provide the highest-quality and safest care possible.

## Author Contributions

**Alexander M. Choi**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Michael J. Brenner**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Daniel Gorelik**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Isaac D. Erbele**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Matthew G. Crowson**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Prajoy Kaddake**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Masayoshi Takashima**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Peter L. Santa Maria**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Robert S. Hong**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Austin S. Rose**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Benjamin T. Ostrander**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Cyrus C. Rabbani**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Robert J. Morrison**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Philip A. Weissbrod**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Alan D. Tate**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Joshua J. Kain**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Ioan A. Lina**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Scott R. Shaffer**, contributed to data acquisition and assessment; editing, writing, and revision of the review; **Omar G. Ahmed**, contributed to the formulation of the project, development of the study design, data acquisition and assessment; editing, writing, and revision of the review. All authors contributed to the development of the study design, procurement and analysis of data, composition, and revision of the manuscript

pertinent to their subspecialty devices or therapeutic agents and approve of the final manuscript.


## Disclosures

**Competing interests:** Peter L. Santa Maria—Auration Biotech, Flotherm, Audience; Scott R. Shaffer—HealthyNose LLC. Omar G. Ahmed: Aerin Medical, Medtronic, Optinose. Masayoshi Takashima—Aerin Medical, Medtronic, Lyra Therapeutics, Acclarent.

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## References

1. Rameau A, Hong RS, Djalilian H, et al. New medical device and therapeutic approvals in otolaryngology: state of the art review of 2019. *OTO Open*. 2020;4(2):2473974X20932506. doi:10.1177/2473974X20932506
2. Brenner MJ, Shenson JA, Rose AS, et al. New medical device and therapeutic approvals in otolaryngology: state of the art review 2020. *OTO Open*. 2021;5(4):2473974X211057035. doi:10.1177/2473974X211057035
3. Gstoettner W, Kiefer J, Baumgartner WD, Pok S, Peters S, Adunka O. Hearing preservation in cochlear implantation for electric acoustic stimulation. *Acta Otolaryngol*. 2004;124(4):348-352. doi:10.1080/00016480410016432
4. Mirsalehi M, Rau TS, Harbach L, et al. Insertion forces and intracochlear trauma in temporal bone specimens implanted with a straight atraumatic electrode array. *Eur Arch Otorhinolaryngol*. 2017;274(5):2131-2140. doi:10.1007/s00405-017-4485-z
5. IotaSOFT™ Insertion System Instructions for Use. Published October 26, 2021. <https://iotamotion.com/wp-content/uploads/IotaSOFT-Insertion-System-Instructions-for-Use-403-036-2000-v6-1.pdf>
6. Kaufmann CR, Henslee AM, Claussen A, Hansen MR. Evaluation of insertion forces and cochlea trauma following robotics-assisted cochlear implant electrode array insertion. *Otol Neurotol*. 2020;41(5):631-638. doi:10.1097/mao.0000000000002608
7. De novo classification request for IotaSOFT Insertion System—drive unit, controller, and accessories. Published October 1, 2021. [https://www.accessdata.fda.gov/cdrh\\_docs/reviews/DEN190055.pdf](https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN190055.pdf)
8. Sabin AT, Van Tasell DJ, Rabinowitz B, Dhar S. Validation of a self-fitting method for over-the-counter hearing aids. *Trends Hear*. 2020;24:2331216519900589. doi:10.1177/2331216519900589
9. Hwang PH, Lin B, Weiss R, Atkins J, Johnson J. Cryosurgical posterior nasal tissue ablation for the treatment of rhinitis. *Int Forum Allergy Rhinol*. 2017;7(10):952-956. doi:10.1002/alr.21991
10. Stolovitzky JP, Ow RA, Silvers SL, Bikhazi NB, Johnson CD, Takashima M. Effect of radiofrequency neurolysis on the

- symptoms of chronic rhinitis: a randomized controlled trial. *OTO Open*. 2021;5(3):2473974X211041124. doi:10.1177/2473974X211041124
11. Douglas Reh, Dubin M, Kern R. Evaluation of the NEUROMARK system (Rhinitis Neurolysis Therapy) in patients with chronic rhinitis [conference presentation]. Published September 10, 2020. [https://www.american-rhinologic.org/assets/docs/Meetings/2020\\_Annual/2020%20ARS%20Annual%20-%20Full%20Program.pdf](https://www.american-rhinologic.org/assets/docs/Meetings/2020_Annual/2020%20ARS%20Annual%20-%20Full%20Program.pdf)
  12. Peng S. 510(k) summary: Neurent Medical's Neuromark System. Published October 22, 2021. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf21/K212666.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf21/K212666.pdf)
  13. Glicksman JT, Reger C, Parasher AK, Kennedy DW. Accuracy of computer-assisted navigation: significant augmentation by facial recognition software. *Int Forum Allergy Rhinol*. 2017;7(9):884-888. doi:10.1002/alr.21982
  14. Mahmoodi NS, Reza Okhovat SA, Reza Abtahi SH, Moslehi A. The comparison of Nasaleze and Mometasone nasal spray to control the symptoms of allergic rhinitis. *Adv Biomed Res*. 2018;7:27. doi:10.4103/2277-9175.225590
  15. Van Zele T, Soudry E, Landsberg R, Gevaert P. A prospective, feasibility study to evaluate the efficacy and usability of a novel drivable endoscope in patients with chronic rhinosinusitis. *Eur Arch Otorhinolaryngol*. 2019;276(9):2499-2505. doi:10.1007/s00405-019-05535-0
  16. Carniol ET, Vázquez A, Patel TD, Liu JK, Eloy JA. Utility of intraoperative flexible endoscopy in frontal sinus surgery. *Allergy Rhinol (Providence)*. 2017;8(2):e81-e84. doi:10.2500/ar.2017.8.0205
  17. Sim E. A useful modification of the Kerrison rongeur. *Spine (Phila Pa 1976)*. 2002;27(1):E9-E10. doi:10.1097/00007632-200201010-00025
  18. Maroon JC, El-Kadi M, Bost J. Pneumatic Kerrison rongeur: technical note. *Surg Neurol*. 2009;71(4):466-468. doi:10.1016/j.surneu.2008.10.008
  19. Kirsner RS, Margolis DJ, Balduresson BT, et al. Fish skin grafts compared to human amnion/chorion membrane allografts: a double-blind, prospective, randomized clinical trial of acute wound healing. *Wound Repair Regen*. 2020;28(1):75-80. doi:10.1111/wrr.12761
  20. Lullove EJ, Liden B, Winters C, McEaney P, Raphael A, Lantis Ii JC. A multicenter, blinded, randomized controlled clinical trial evaluating the effect of omega-3-rich fish skin in the treatment of chronic, nonresponsive diabetic foot ulcers. *Wounds*. 2021;33(7):169-177. doi:10.25270/wnds/2021.169177
  21. Kim TH, Park JH, Jeong HG, Wee SY. The utility of novel fish-skin derived acellular dermal matrix (Kerecis) as a wound dressing material. *J Wound Manag Res*. 2021;17(1):39-47. doi:10.22467/jwmr.2020.01228
  22. Yoon J, Yoon D, Lee H, et al. Wound healing ability of acellular fish skin and bovine collagen grafts for split-thickness donor sites in burn patients: characterization of acellular grafts and clinical application. *Int J Biol Macromol*. 2022;205:452-461. doi:10.1016/j.ijbiomac.2022.02.055
  23. Matsuno A, Tanaka H, Iwamuro H, et al. Analyses of the factors influencing bone graft infection after delayed cranioplasty. *Acta Neurochir (Wien)*. 2006;148(5):535-540. doi:10.1007/s00701-006-0740-6
  24. Kittichokechai P, Sirichatchai K, Puncreobutr C, Lohwongwatana B, Saonanon P. A novel patient-specific titanium mesh implant design for reconstruction of complex orbital fracture. *Plast Reconstr Surg Glob Open*. 2022;10(1):e4081. doi:10.1097/GOX.0000000000004081
  25. Fabi SG. Noninvasive skin tightening: focus on new ultrasound techniques. *Clin Cosmet Investig Dermatol*. 2015;8:47-52. doi:10.2147/CCID.S69118
  26. Chen L. 510(k) summary: Sofwave Medical's Sofacia System. Published September 9, 2019. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf19/K191421.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf19/K191421.pdf)
  27. Chen L. 510(k) summary: Sofwave Medical's Sofwave System. Published November 15, 2021. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf21/K211483.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf21/K211483.pdf)
  28. Kauvar A, Friedman P, Geronemus R, Kilmer S, Munavalli G. Synchronous ultrasound parallel beam technology for lifting lax submental and neck skin [conference presentation]. Published November 19, 2021. <https://www.asds.net/portals/0/PDF/am21-abstracts.pdf>
  29. Fernandes JR, Samayoa JC, Broelsch GF, et al. Micro-mechanical fractional skin rejuvenation. *Plast Reconstr Surg*. 2013;131(2):216-223. doi:10.1097/PRS.0b013e3182789afa
  30. Russe E, Purschke M, Farinelli WA, et al. Micro-fractional, directional skin tightening: a porcine model. *Lasers Surg Med*. 2016;48(3):264-269. doi:10.1002/lsm.22444
  31. Pozner JN, Kilmer SL, Geronemus RG, Jack M, Burns JA, Kaminer MS. Cytrellis: a novel microcoring technology for scarless skin removal—summary of three prospective clinical trials. *Plast Reconstr Surg Glob Open*. 2021;9(10):e3905. doi:10.1097/GOX.0000000000003905
  32. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers*. 2020;6(1):71. doi:10.1038/s41572-020-0204-y
  33. Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021;384(7):599-609. doi:10.1056/NEJMoa2023386
  34. Husain T, Gatward JJ, Harris RD. Use of subglottic suction port to enable verbal communication in ventilator-dependent patients. *Am J Respir Crit Care Med*. 2011;184(3):384. doi:10.1164/ajrccm.184.3.384
  35. Friedman AD, Gerber ME, Bhayani MK, et al. Ideal characteristics of a laser-protected endotracheal tube: ABEA and AHNS member survey and biomechanical testing. *Ann Otol Rhinol Laryngol*. 2018;127(4):258-265. doi:10.1177/0003489418757549
  36. Peng S. 510(k) summary: DISA Medinotec's Trachealator. Published December 9, 2021. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf21/K211894.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf21/K211894.pdf)
  37. Peer S, Brooks A, McGuire J. "How I do it": novel non-occlusive balloon dilation in paediatric airway stenosis—a paradigm shift (with video). *Eur Ann Otorhinolaryngol Head Neck Dis*. 2021;138(suppl 1):21-22. doi:10.1016/j.anorl.2021.05.020
  38. Scott-Wittenborn N, Jackson RS. Intraoperative imaging during minimally invasive transoral robotic surgery using near-infrared

- light. *Am J Otolaryngol*. 2018;39(2):220-222. doi:10.1016/j.amjoto.2017.09.001
39. Van Abel KM, Yin LX, Price DL, Janus JR, Kasperbauer JL, Moore EJ. One-year outcomes for da Vinci single port robot for transoral robotic surgery. *Head Neck*. 2020;42(8):2077-2087. doi:10.1002/hed.26143
40. Mendelsohn AH, Lawson G. Single-port transoral robotic surgery hypopharyngectomy. *Head Neck*. 2021;43(10):3234-3237. doi:10.1002/hed.26794
41. Chan JYK, Tsang RK, Holsinger FC, et al. Prospective clinical trial to evaluate safety and feasibility of using a single port flexible robotic system for transoral head and neck surgery. *Oral Oncol*. 2019;94:101-105. doi:10.1016/j.oraloncology.2019.05.018
42. Johnson MD, Dweiri YM, Cornelius J, et al. Model-based analysis of implanted hypoglossal nerve stimulation for the treatment of obstructive sleep apnea. *Sleep*. 2021;44(44, suppl 1):S11-S19. doi:10.1093/sleep/zsaa269
43. Yu JL, Younes M. Relation between arousability and outcome of upper airway stimulation in the Stimulation for Apnea Reduction (STAR) Trial. *J Clin Sleep Med*. 2021;17(4):797-801. doi:10.5664/jcsm.9050
44. Op de Beeck S, Wellman A, Dieltjens M, et al. Endotypic mechanisms of successful hypoglossal nerve stimulation for obstructive sleep apnea. *Am J Respir Crit Care Med*. 2021; 203(6):746-755. doi:10.1164/rccm.202006-2176OC
45. Strollo PJ, Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med*. 2014;370(2):139-149. doi:10.1056/NEJMoa1308659
46. Sagalow ES, Rodin J, Estephan L, et al. Two-incision approach for hypoglossal nerve stimulator placement: a single institution assessment. *Laryngoscope*. Published online February 11, 2022. doi:10.1002/lary.30050
47. Philips. DreamWear silicone cushion. <https://www.usa.philips.com/healthcare/product/HC1146469/philips-dreamwear-silicone-pillows-mask>
48. Costanzo MR, Javaheri S, Ponikowski P, et al. Transvenous phrenic nerve stimulation for treatment of central sleep apnea: five-year safety and efficacy outcomes. *Nat Sci Sleep*. 2021;13: 515-526. doi:10.2147/NSS.S300713
49. Clay P, Cruz C, Ayotte K, Jones J, Fowler SB. Device related pressure ulcers pre and post identification and intervention. *J Pediatr Nurs*. 2018;41:77-79. doi:10.1016/j.pedn.2018.01.018
50. Agency for Healthcare Research and Quality. Preventing pressure ulcers in hospitals: a toolkit for improving quality of care. Published 2012. <https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/systems/long-term-care/resources/pressure-ulcers/pressureulcertoolkit/putoolkit.pdf>
51. Carron M, Freo U, BaHamam AS, et al. Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials. *Br J Anaesth*. 2013;110(6):896-914. doi:10.1093/bja/aet070
52. Devani N, Pramono RXA, Imtiaz SA, Bowyer S, Rodriguez-Villegas E, Mandal S. Accuracy and usability of AcuPebble SA100 for automated diagnosis of obstructive sleep apnoea in the home environment setting: an evaluation study. *BMJ Open*. 2021;11(12):e046803. doi:10.1136/bmjopen-2020-046803
53. Rodriguez-Villegas E, Chen G, Radcliffe J, Duncan J. A pilot study of a wearable apnoea detection device. *BMJ Open*. 2014; 4(10):e005299. doi:10.1136/bmjopen-2014-005299