Molina Clinical Policy
Prescription Digital Therapeutics: Policy No. 412
Last Approval: 4/13/2023
Next Review Due By: April 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Digital health encompasses technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes, such as mobile health (mHealth), telehealth (telemedicine), smart devices, sensors and wearables, health information technology, and personalized medicine. **Digital therapeutics (DTx)** is a class of digital health solutions that deliver “evidence-based therapeutic interventions driven by high-quality software programs to prevent, manage, or treat a medical disorder or disease” (Digital Therapeutics Alliance). Like pharmaceutical agents and medical devices, DTx are evaluated and approved by the U.S. Food and Drug Administration (FDA) and are available over the counter (OTC) or with a prescription.

Prescription Digital Therapeutics (PDTs) are software-based therapeutic interventions for the prevention, management, or treatment of medical illnesses or diseases that have been evaluated for safety and efficacy in randomized clinical trials (RCTs). PDTs are authorized by the U.S. FDA to treat diseases through an approved label and are differentiated from other digital health technologies (traditional health and wellness apps) by the following unique characteristics (Digital Therapeutics Alliance, 2021):

- Authorized by the FDA Center for Devices and Radiological Health through the 510(k) premarket notification or de novo classification for medical devices following the submission of superiority trial data;
  A 510(k) is a premarket submission demonstrating that the device to be marketed is at least as safe and effective as another legally marketed device. The de novo premarket review pathway is a regulatory pathway for low- to moderate-risk devices that are novel, and for products for which there is no legally marketed predicate device with which to claim substantial equivalence.
- Developed to treat specific medical disorders and diseases, defined by ICD-10 diagnosis codes; and
- Prescribed by a healthcare provider as a stand-alone treatment or in conjunction with an existing medication or therapy; and
- Required to demonstrate safety and clinical efficacy across target populations through controlled clinical trials, and appropriate reporting of outcomes, and publication of results in peer-reviewed journals.

This policy addresses the use of FDA-cleared or approved clinician-prescribed software applications when used on a mobile device (e.g., mobile phone, laptop, smartwatch, or tablet) for health management purposes with the intent to evaluate, diagnose, or treat an illness, injury, disease, or its symptoms.

This policy does not address mobile-based software applications that are not FDA cleared or approved and are accessible to the public for download, including OTC or direct-to-consumer applications that promote general wellness or are operated by a healthcare practitioner in a clinical setting for remote health monitoring.

COVERAGE POLICY

Please consult state-specific health plan rules and benefit contracts prior to applying this policy. Individual State and Federal Health Plan Medicaid regulations and benefit contracts that supersede this policy. All State and Federal Health Plan eligibility requirements, including any applicable consent forms, must be met, and completed.

PDTs are considered **experimental, investigational, and unproven** due to insufficient clinical evidence and peer-reviewed medical literature establishing long-term safety, efficacy, and effect on net health outcomes, including but not limited to the following (not an exhaustive list):

- BlueStar® Rx
- Canvas Dx™
- CureSight™
- d-Nav® Insulin Guidance System
- Drowzle™ Pro
- Endeavor Rx™
- Freespira®
- Halo™ AF Detection System
- Home Vision Monitor (HVM)®
- Ieva Pelvic Health System
- Insulia®
- Luminopia One™
- Mahana™
- MindMotion™ GO
- My Dose Coach™
- Nerivio®
- NightWare™
- RelieVRx
- reSET®
- reSET-O®
- Somryst®
- Tidepool Loop (Tidepool)

REGULATORY STATUS and SUMMARY OF MEDICAL EVIDENCE

The PDTs outlined below are not exhaustive of all *commercially available PDTs but include those with relatively higher-level evidence, such as clinical trials, published peer-reviewed literature, or systematic reviews. However, the evidence remains insufficient to conclude that the technology improves health outcomes overall.

Device (Software Developer)	Summary of Supporting Evidence
DIABETES MELLITUS	
BlueStar® Rx (WellDoc) *Type 1 (T1) and Type 2 (T2) DM* BlueStar Rx is a digital health platform for T1 and T2 DM that provides tailored guidance driven by artificial intelligence. It is indicated for use by healthcare providers (HCPs) and adult patients to aid in their diabetes self-management. BlueStar Rx comprises software for use in the home or in professional healthcare settings on mobile phones or personal PCs. Other	*Only the BlueStar Rx of the two WellDoc BlueStar apps currently requires a prescription; the BlueStar app is available without a prescription. BlueStar Rx products' functionalities have changed over time, thus research relating to the original BlueStar product are included below for historical purposes. Note: There were no studies that met the inclusion criteria for the BlueStar Rx PDT.* Quinn et al. (2011) conducted a cluster-RCT to assess whether the addition of mobile application coaching and

diabetes-related healthcare information and educational content can also be entered into the app. An insulin dose calculator is included in BlueStar Rx, allowing patients to utilize their recommended regimen to determine an insulin dose for a specific amount of carbohydrates and/or fat. BlueStar Rx connects via Bluetooth to many glucose meters (including OneTouch, Accu-Chek, and Contour, Dexcom CGM system) which allows users to transmit their glucose monitoring data to the app (Cui et al. 2020). The BlueStar Rx System is complementary to current therapies (e.g., pharmacologic, diet, exercise, and counseling) and is not intended to replace the care provided by a licensed HCP, including prescriptions, diagnosis, or treatment. *Note: The BlueStar System, available without a prescription, does not include the insulin calculator.*

Regulatory Status
The BlueStar Rx device was cleared in 2017, with a prescription required for use of the insulin dose calculator (K162532). According to the clearance document, using the BlueStar device without the insulin dose calculator does not require a prescription and therefore considered an OTC use of the software system:

- 510(k) marketing clearance (K162532) as substantially equivalent to a marketed predicate device.

  Indicated for use in patients 21 years of age or older who have T2DM. Based on real-time blood glucose readings, the software system captures, saves, and transmits coaching messages (motivational, behavioral, educational) to promote diabetes self-management. The software includes an insulin dose calculator that allows patients to determine their insulin dose based on their carbohydrate intake and/or blood glucose levels. FDA Product Code: LNX, NDC. (2017)

  FDA expanded the indications to patients 18 years of age or older who have T1 or T2 diabetes. (K190013). FDA Product Code: MRZ, NDC. (2019)

  FDA expanded the indications to basal insulin users with T2DM and now includes an Insulin Adjustment Program (IAP) (K193654) which calculates appropriate long-acting basal insulin doses for titrating insulin levels based on configuration by an HCP (the HCP must activate and configure the IAP for patient-specific parameters). FDA Product Code: MRZ, LNX, NDC. (2020)

patient/provider web portals to community primary care compared to standard diabetes management would decrease glycosylated hemoglobin (Hgb) levels in patients with T2DM. The study included 163 individuals with T2DM whose HbA_{1c} levels were poorly controlled or abnormal at the time of enrollment. Enrolled primary care practices (PCP) were randomized to a control (usual care) group (n=56) and 1 of 3 treatment groups. Maximal treatment included a mobile- and web-based self-management patient coaching system and provider decision support. The 3 stepped treatment groups include: coach-only (n=23), coach PCP portal (n=22), and coach PCP portal with decision support (n=62). The primary outcome was a change in glycated Hgb levels over a 1-year treatment duration and secondary outcomes included changes in patient-reported diabetes symptoms, diabetes distress, depression, and other clinical (blood pressure) and laboratory (lipid) values. Participants who were randomized to use an MSA to help manage their diabetes in addition to usual care, improved HbA_{1c} by an average 1.9%, compared with 0.7% improvement in those randomized to usual care alone, a difference of 1.2% over the 12-month study period. Significant differences were not noticeable between groups for patient-reported diabetes distress, depression, diabetes symptoms, or blood pressure and lipid levels. The authors concluded that the combination of behavioral mobile coaching with blood glucose data, lifestyle behaviors, and patient self-management data individually evaluated and presented with evidence-based guidelines to providers significantly decreased glycosylated Hgb levels over 1 year. Limitations of the study were its small sample size in the study arms.

Agarwal et al. (2019) conducted a multicenter, pragmatic RCT to determine whether BlueStar application usage leads to improved hemoglobin A1c (HbA1c) levels among diverse participants across diverse clinical scenarios. The study involved 223 participants (n=223); 110 participants (n=100) were randomized to the immediate treatment group (ITG) receiving the intervention for 6 months, and 113 (n=113) participants randomized to the wait-list control (WLC) group receiving usual care for the first 3 months and then receiving the intervention for 3 months. The primary outcome was HbA_{1c} levels at 3-month follow-up. Secondary outcomes assessed intervention impact on patient self-management, experience of care, and self-reported health utilization using validated scales (i.e., the Problem areas in Diabetes, the Summary of Diabetes Self-Care Activities, and the EuroQo1-5D). Intervention usage data was captured by the BlueStar mobile app. At 3 months, the mean difference in HbA_{1c} levels between the ITG and WLC groups was not statistically significant. Similarly, there was no effect on secondary outcomes. BlueStar usage was found to vary significantly across clinical sites (median of 9 versus 36 logins over 14 weeks at the lowest, versus highest usage sites, respectively). Results suggest that in the short-term, the PDTs app did not improve HbA_{1c} levels compared with conventional care. In addition, use of the PDTs app did not impact healthcare utilization or reduce the frequency of hypoglycemic episodes. The low patient adherence to the app warrants further study of patient and significant variation in implementation across sites may have impacted the study's ability to detect a clinical effect. Evidence of BlueStar's clinical efficacy remains to be established.

d-Nav® Insulin Guidance System (Hygieia) *T2DM* d-Nav is an insulin-titration app (available for both iOS and Android mobile phones) that titrates individualized doses for all types of insulin regimens, delivering recommendations directly to the patient. It is intended to significantly improve HbA1c along with a reduction in the frequency of hypoglycemia when used with outpatient therapy. The physician prescribes the initial regimen and dosage, and the d-Nav adjusts the dosage. Adjustments are typically made weekly by the device; however, if insulin requirements drop or hypoglycemia ensues, immediate adjustments are made. Patients use the device to monitor glucose levels before each injection and receives a personalized dose recommendation. By analyzing glucose patterns, the device automatically adjusts insulin dosage, as often as needed, to achieve and maintain optimal glycemic balance for each individual without provider supervision or user behavior changes. The system relies on cloud-based technology and virtual clinical support by a team of d-Nav Care Specialists who monitor individual patient data sent to the cloud to assist with proper patient use and address clinical concerns via in person and telephone communication. d-Nav adjusts most types of insulin regimens in T2DM (e.g., once-daily basal insulin, twice-daily premixed long- and short-acting insulin, and intensive insulin therapy involving long-acting and fast-acting insulin with or without carbohydrate counting. *Regulatory Status* 510(k) marketing clearance (K181916) as substantially equivalent to a marketed predicate device. Product Code: NDC. February 4, 2019	Current evidence is limited to a single study of small sample size, and long-term data on net health outcomes are currently lacking. These findings need to be validated with a larger sample size and with longer-term follow-up. Bergenstal et al. (2019) studied 181 patients with uncontrolled T2DM in a multicenter RCT. Patients were randomly assigned to one of two study groups: d-Nav with help from a healthcare professional (n=93) or HCP support alone (n=88). The primary outcome was to compare the average change in HbA1c from baseline to 6 months. Safety was evaluated by the frequency of hypoglycemic events. At 6 months, the group utilizing d-Nav had a significant reduction in HbA_{1c} of 1.0% compared to a reduction of 0.3%in the group not using d-Nav. The researchers noted that the difference between groups was statistically significant. The frequency of hypoglycemic events per month was similar between the groups. It was concluded that automated insulin titration guidance in combination with HCP support provides superior glycemic control compared with stand-alone HCP. However, there is additional need to perform an evaluation across large healthcare systems to validate these findings.
Insulia® Diabetes Management Companion (Voluntis) *T2DM* Insulia Diabetes Management Companion (Insulia) is intended for use by healthcare professionals and their T2DM adult patients treated with basal insulin analogues (e.g., Lantus, Levemir, Toujeo, Tresiba (U-100), and Basaglar) as an aid in the management of diabetes. Insulia provides automated insulin dose recommendations and coaching messages to T2DM patients while enabling the health care team to remotely monitor progress. The device includes a basal calculator intended to provide direction to the patient in response to blood glucose and health events, within the scope of a preplanned treatment program from an HCP for insulin adjustments, similar to the directions provided to pts as a part of routine clinical practice. Complementary to basal insulin therapy. *Regulatory Status* FDA 510(k) marketing clearance (K161433) as substantially equivalent to a marketed predicate device. Additional dosing modifications of these insulin analogs received FDA 510(k) marketing clearance in 2017 (K170669) and (K172177), and in 2020 (K202596) when it was modified	No clinical outcomes have been reviewed by the FDA; therefore, the cited clinical study does not establish any efficacy claim for Insulia in the United States (DTxAlliance, 2023; accessed January 2023). Insulia Diabetes Management Companion has no published studies. The following is a summary of its predecessor, the Diabeo® system, which is a class IIb CE marked device in Europe but lacks FDA approval. Voluntis and Sanofi of France partnered to develop the Diabeo® system; their partnership concluded in December 2020. Franc et al. (2019) reported mixed findings in the Telediab 2 study that evaluated the efficacy and safety of two telemonitoring systems to optimize basal insulin (BI) in 191 participants (n=191) with inadequately controlled T2DM in a 13-month RCT. The subjects were randomized into 3 groups: group 1 (standard care, n=63), group 2 (interactive voice response system, n=64) and group 3 (Diabeo-BI app software, n=64). All 3 treatment groups were followed up for an initial 4-month period to establish comparative effectiveness and subsequently followed for an additional 9-month extension period. All treatment groups experienced an overall reduction in HbA_{1c} from baseline. In the short-term (4 months), PDTs use resulted in a statistically significant

to be compatible with Semglee® long-acting insulin. FDA Product Code: NDC	greater reduction in HbA_{1c} compared with CC. In an extended follow-up (13 months), however, there was no statistically significant difference between the PDTs and CC treatment groups. No severe episodes of hypoglycemia were reported in the initial 4-month period mild hypoglycemia continued to be a rare event in the 9-month extension period. The current data is limited to a short duration of evaluation; sample sizes for the comparative arms were modest.
My Dose Coach™ (Sanofi Inc.) *T2DM* My Dose Coach is intended for use by a previously diagnosed T2DM patient who has been prescribed a once-daily long-acting basal insulin outside of the clinic setting. My Dose Coach is designed to assist patients by recommending doses based on the HCP's independent professional judgment. The HCP must adjust the dose instructions for the specific patient and activate the application using the specific patient instructions before My Dose Coach can be utilized. The program uses the dose plan instructions provided by the HCP to recommend once-daily long-acting basal insulin doses (basal insulin titration) based on the individual's fasting blood glucose and hypoglycemia occurrence. The app does not measure, interpret, or make decisions on the data it transmits, nor is it meant to give automated treatment decisions or be used as a substitute for professional judgment, according to HCP Portal User Guide. All medical diagnosis and treatment must be under the supervision and guidance of a qualified health care professional (HCP). *Regulatory Status* 510(k) marketing clearance: K163099 (March 22, 2017); K171230 (May 26, 2017). FDA Product Code: NDC	Tamez-Perez et al. (2021) conducted a noncomparative, prospective, single-arm study to evaluate the safety and effectiveness of a PDTs app for management of T2DM. A total of 158 patients with T2DM (n=158) enrolled given a PDT to help manage glycemic control. At 4-months follow-up, 141 pts completed the 4-month study period (14 patients dropped out of the study (n=14) and 3 patients discontinued insulin (n=3)]. Patients experienced a mean reduction in HbA_{1c} of 1.97% from baseline, which the investigators noted was statistically significant. The predefined glycemic target (90-130 milligrams per deciliter [mg/dL]) was achieved in over half (58.9%) of the patient population within 66 days. Results suggest that pts treated with the PDT experienced SS improvements from BL in HbA1c, and patient well-being. However, this study has notable limitations in that it is a single center study with a lack of control or comparator group and insufficient follow-up to establish long-term outcomes.
Tidepool Loop (Tidepool) *T1DM* Tidepool Loop, an automated insulin dosing app, is intended for use with compatible devices for automated insulin dosing to help manage T1DM in patients six years of age and older. The Loop is essentially an algorithm that will eventually be used with commercially available insulin pumps and continuous glucose monitors (CGMs). The goal of the interoperable design is to allow users and healthcare providers to choose the compatible components that work best for personalized care management. The Tidepool app is a prescription-only device for single patient use that works with integrated CGMs (iCGMs) and alternate controller enabled pumps to automatically increase, decrease, and suspend delivery of basal insulin based on iCGM readings and predicted glucose values. The app can also recommend, and with the user's confirmation, control the delivery of correction insulin amounts when glucose values are predicted to exceed user configurable thresholds. Tidepool Loop's algorithm technology is designed to be compatible with other individual interoperable devices that meet pre-specified acceptance criteria set forth in a validation	FDA clearance was based on data from an observational study (ClinicaTrials.gov Identifier: NCT03838900) that evaluated the safety and effectiveness of the app in adults and children with T1DM. Over 6 months of follow-up, findings showed that use of the app was associated with improved time in range.

and integration plan provided by the sponsor and cleared by the FDA as part of the premarket submission. It will be available as an app on iOS, to enable insulin delivery from a compatible Apple Watch.

At the time of FDA approval, Tidepool had not yet announced the anticipated launch date for the new AID system and its initial launch device partners (January 24, 2023). The company is currently working to finalize partnerships with CGM and pump manufacturers, as well as an official launch date.

Regulatory Status
510(k) marketing clearance: K203689 (January 23, 2023); FDA Product Code: *not available on FDA site on date of approval*

With FDA approval, Tidepool Loop can be used as a predicate device for future interoperable Automated Insulin Dosing submissions, providing a more defined regulatory pathway.

Comparison of PDTs for Outpatient Electronic Glycemic Management Systems

Product	Long-Acting Insulin Dosing	Rapid-Acting Insulin Dosing	Format	Type(s) of DM	Information Input	Other Functions
Insulia	Yes	No	Mobile app with Web-based portal	T2	Manually entered	Shares reports with providers; patients receive educational coaching messages; safety rules for hypoglycemia management
My Dose Coach	Yes	No	Mobile app with Web-based portal	T2	Manually entered	Shares reports with providers
BlueStar Rx	Yes	Yes	Mobile-app with Web-based portal	T1 and T2	Manually entered; automatically transmitted from OneTouch Verio Flex, Accu-Check Aviva, Accu-Check Guide, TrueMatrix, Relion Premier Blu, Contour Next One, and Dexcom CGM	Shares reports with providers; stores personal health record; sends educational coaching messages; reminds user to take medication; communicates with providers
d-Nav System	Yes	Yes	Mobile app with Web-based portal	T2	Manually entered; BioTel and iGlucose meters automatically upload data to the phone app; pending new Cloud-based glucose meter and CGM will also transmit data automatically	Shares reports with providers
Tidepool Loop	Yes	Yes	Mobile app with Web-based portal	T1	Hybrid closed loop algorithm that uses Bluetooth to communicate with interoperable pumps and compatible integrated CGMs	Shares reports with providers and patient data in hourly, daily, and weekly interactive graphs to identify trends and patterns.

Health Technology Assessment (HTA)
T1DM. An HTA concluded the overall body of evidence for the use of PDTs in the management of T1DM was of very low quality and insufficient to inform a conclusion regarding the effectiveness and safety of PDTs for management of T1DM. The report noted that substantial uncertainty remains regarding the extent of clinical benefit of reduced HbA1c levels, comparative effectiveness of different PDTs, long-term safety, patient adherence, patient selection criteria, and the long-term effects of PDT use on QOL and diabetes-related morbidity (Hayes, 2022).

T2DM. A HTA concluded that there is low-quality of evidence suggesting that PDTs are safe and may be associated with clinically significant reductions in HbA1c levels relative to baseline levels and compared with conventional care over the short term without increasing the risk of hypoglycemia. Furthermore, there is uncertainty as to the comparative effectiveness of different PDTs regarding patient adherence, patient selection criteria, and the long-term effects on quality of life and diabetes-related morbidity. The HTA also notes that the current evidence is insufficient in establishing definitive patient selection criteria for the use of PDTs for the management of T2DM (Hayes, 2022).

National and Specialty Organizations

National and specialty organizations with guidelines addressing the management of both type 1 DM (T1DM) did not mention PDTs or have specific recommendations for PDTs.

American Diabetes Association (ADA): PDTs were not mentioned in the section addressing diabetes technology in the Standards of Medical Care in Diabetes published by the ADA in 2022. The guidelines recognized the benefits of the use of systems that combine technology and online coaching for treating prediabetes and diabetes for some individuals and that technology should be individualized based on the patient's needs, desires, skill level, and availability of devices, however PDTs were not specifically mentioned (Draznin et al., 2022).

A consensus report, a collaboration between the ADA and European Association for the Study of Diabetes, published in 2018 on the management of hyperglycemia in patients with T2DM recognized the increasing need for technology and telemedicine to improve patient outcomes, however, specific PDTs were not mentioned (Davies et al., 2018).

American Association of Clinical Endocrinology (AACE): AACE strongly recommended the use of telemedicine, including smartphone-web interactions, periodic supervision by healthcare professional/provider interactions to educate, remotely monitor glucose and/or insulin data for therapeutic adjustments, and to improve outcomes, in its guidelines on the use of advanced technologies in the management of DM published in 2021. The guideline also suggested that people with diabetes use clinically validated smartphone apps to teach/reinforce DM self-management skills, encourage engagement (e.g., coaching), and support and encourage desired health behaviors (e.g., healthy eating instruction, physical activity tracking). However, PDTs are not mentioned in this report (Grunberger et al., 2021).

National Institute for Health and Care Excellence (NICE): NICE has two evidence-based practice guidelines for managing T1DM and T2DM. Both guidelines make no specific recommendations for PDTs; however, cell-based therapies for achieving HbA1c targets are included as a key recommendation for future research [Reference: Type 1 Diabetes in Adults: Diagnosis and Management [NG17], updated July 2021) and T2DM (Type 2 Diabetes in Adults: Management [NG28], updated November 2021)]. NICE, 2021a; NICE, 2021b).

AMBLYOPIA	
Luminopia One™ (Luminopia, Inc.) *Amblyopia; pediatric use* The Luminopia One is a software-only PDT for the treatment of amblyopia. It is defined as a dichoptic (binocular) therapy (i.e., using both eyes together) and comprises of proprietary software that therapeutically changes video content viewed using a compatible commercially available virtual reality (VR) headset. The purpose of the therapeutic video modification is to stimulate the use of the patient's weaker eye and to encourage the child's brain to combine visual input from both eyes. As the video plays, the Luminopia One software modifies the content in real time to provide therapeutic dichoptic (binocular) visual stimuli for the child.	A pivotal RCT (Xiao et al., 2022) and a pilot study (Xiao et al., 2021) evaluated the efficacy of Luminopia One for the treatment of amblyopia in children. Xiao et al., 2022 conducted a phase 3 RCT that evaluated the efficacy and safety of Luminopia One in 105 amblyopic children (n = 105) aged 4 to 7 years. Patients were randomized to receive either Luminopia One with glasses (treatment group) or glasses alone (control group) (Xiao et al., 2022). The primary outcome measure was the change in amblyopic eye visual acuity from baseline to 12 weeks. At 12 weeks, 90 patients (45 in each group) had outcomes data available for analysis. The Luminopia treatment group improved amblyopic eye visual acuity by 1.8 lines

Luminopia One is indicated for improvement in visual acuity in amblyopia patients, aged 4-7, associated with anisometropia and/or with mild strabismus, having received treatment instructions (frequency and duration) as prescribed by a trained eye-care professional. Luminopia One is intended for both previously treated and untreated patients; however, patients with more than 12 months of prior treatment (other than refractive correction) have not been studied. Luminopia One is intended to be used as an adjunct to full-time refractive correction, such as glasses, which should also be worn under the HMD during Luminopia One therapy. Luminopia One is intended for prescription use only, in an at-home environment (FDA, 2021). *Regulatory Status* De Novo classification (DEN210005) on February 26, 2021. FDA Product Code: QQU.	compared to the control group by 0.8 lines. As early as 4 weeks, a statistically significant difference in visual acuity improvement was reported across the groups. Furthermore, 62% of patients in the treatment group improved by two lines or more in the weak eye, compared to 33% in the control group. There were no major adverse events; 19.6% of children using Luminopia One and 13% of those wearing glasses reported relatively mild adverse events, such as headache, new heterotropias, and worsened VA. In accordance with the protocol and due to the positive results, the trial was terminated early. There were no position statements or guidelines addressing the use of Luminopia One or dTx for amblyopia. The American Academy of Ophthalmology (AAO) Amblyopia Preferred Practice Pattern (2018) stated that there was insufficient evidence to recommend vision therapy techniques or binocular therapy for treatment of amblyopia.
CureSight™ (NovaSight, Ltd.) *Amblyopia; pediatric use* CureSight is indicated for improvement in visual acuity and stereo acuity in amblyopia patients, aged 4 to 9 years, associated with anisometropia and/or with mild strabismus, having received treatment instructions (frequency and duration) as prescribed by a trained eye care professional. It is intended for home use and as an adjunct to full-time refractive correction (i.e., glasses). The child watches Disney, Netflix, Prime Video, Hulu, History Channel, and National Geographic streaming videos on a computer touchscreen while wearing red-blue glasses. The streaming video is displayed in different colors for each eye, and the software algorithm uses embedded eye-tracking and image-processing sensors to blur the images in the dominant eye's center of vision while providing normal, sharp images to the amblyopic eye, encouraging the visual system to integrate visual information from both eyes. The cloud technology monitors patient compliance and progress in real time and sends the prescribing eye care practitioner a treatment summary and progress report. This procedure is an alternative to patching the non-amblyopic eye. A total of 120 hours of treatment are provided in 90-minute sessions five days a week for 16 weeks. The CureSight Monitoring Center provides installation, setup, training, and technical assistance. CureSight is only available with a prescription. *Regulatory Status* FDA 510(K) marketing clearance (K221375) as substantially equivalent to a marketed predicate device (the Luminopia One). FDA Product Code: QQU.	One prospective, multicenter RCT (Wygnanski-Jaffe et al., 2022) randomized 103 children aged 4 to 9 years with anisometropic, small-angle strabismic, or mixed-mechanism amblyopia to CureSight, a digital binocular, eye-tracking-based home treatment delivered through watching passive video streaming content (n =51) or eye patching of the non-amblyopic eye (n=52). Investigators who completed primary outcome assessments were blinded to treatment group assignments at all follow-up visits. Over 16 weeks, the CureSight treatment group received 90 minutes of home treatment five days a week for 120 hours. For 224 hours, control group participants wore an adhesive patch over their dominant eye for 2 hours a day, 7 days a week for 16 weeks. Outcomes were assessed at weeks 4, 8, 12, and 16. Outcome measures included the Amblyopia Treatment Study (ATS) Diplopia assessment, a Symptom Survey (5-question ocular symptom survey from the ATS Miscellaneous Testing Procedures Manual), and masked examiners' distance visual acuity and stereoacuity testing based on participants' ages at enrollment. The primary efficacy endpoint in both trial groups was defined as the mean improvement in amblyopic eye visual acuity from baseline to week 16. The non-inferiority margin was set to 1 logMAR line. The results were based on data from 95 participants with 16-week outcomes. The mean amblyopic eye visual acuity in the CureSight treatment group was 0.37±0.15 logMAR at baseline, while it was 0.37±0.14 logMAR in the patching group. At 16 weeks, the mean improvement from baseline in the CureSight therapy group was 0.28±0.13 logMAR ($p<0.0001$) and 0.23±0.14 logMAR in the patching group ($p<0.0001$). As a result, the study met its primary efficacy endpoint of noninferiority of improvement in amblyopic eye visual acuity in the CureSight therapy group against patching. At 16 weeks, the CureSight treatment group's adherence to the allocated regimen was considerably higher than that of the patching group, with mean adherence of 91% vs 83%, a difference of 8%. Secondary outcomes stereoacuity

	improvement of 0.40 log-arcseconds (p<0.0001) and binocular visual acuity improvement (0.13 logMAR, p <0.0001) were similar in both groups and did not differ significantly. The percentage of patients in the treatment group who improved their amblyopic visual acuity by two lines or more from baseline was 79% (34/43) compared to 61% (30/49) in the patching group, which was not statistically significant. There were no severe side effects noted. There were certain limitations to the study, such as 90% of the subjects being anisometropic amblyopes, limiting generalizability to strabismic and mixed amblyope populations. A larger sample size and longer-term follow-up are required to determine whether the improvement in amblyopic eye visual acuity is sustained, as the improvement for both groups was similar until week 12 and was not sustained until week 16. All authors are affiliated with NovaSight, Ltd., and several have financial stock options and patent interests in the study sponsor or product, which may bias the study. There were no position statements or guidelines addressing the use of CureSight or digital therapies for amblyopia. The AAO 2018 Amblyopia Preferred Practice Pattern mentions binocular therapy provided via video game, stating that "research is ongoing, however there is inadequate evidence to support binocular therapy for treatment of amblyopia."
RelieVRx™ (formerly EaseVRx) (AppliedVR, Inc.) *Chronic Low Back Pain (LBP)* **CMS issued a benefit category determination of DME for RelieVRx,** the first virtual reality (VR) therapeutic device to receive a HCPCS code and Durable Medical Equipment, Prosthetics, Orthotics and Supplies (DMEPOS) designation as set forth in 42 C.F.R. § 414.202. Refer to 'Regulatory Status' below. RelieVRx is a prescription-use immersive VR system intended to provide adjunctive treatment based on cognitive behavioral therapy (CBT) skills and other evidence-based behavioral methods for adult patients with a diagnosis of chronic LBP (defined as moderate to severe pain lasting longer than 3 months). The device consists of a modified proprietary headset as well as a patented breathing amplifier allows integration of bio-enabled immersive experiences, and preloaded software. RelieVRx therapy is intended for in-home use and administered daily as a 3-to-16-minute module over the course of 56 days. It is intended to be used during an 8-week treatment program in the patient's home and involves a sequential set of immersive experiences with a mix of different components used in CBT, including pain education, diaphragmatic breathing practices, pain distraction, interceptive awareness, and mindfulness escapes. The device is locked such that it can only be used for treatment of the specified clinical indication. The device consists of preloaded software, a proprietary headset and a patented breathing amplifier which allows for integration of bio-enabled immersive experiences.	The FDA assessed the safety and effectiveness of EaseVRx in a randomized, double-blind clinical study of 179 participants (n=179) with chronic LBP who were randomly assigned to one of two 8-week VR programs: the EaseVRx immersive 3-D program or a control 2-D program that did not use skills-based CBT methods of treatment (Garcia et al. 2021). Participants were followed for a total of 8.5 months after enrollment in the trial, which included a two-week baseline assessment period, an eight-week VR program, a post-treatment assessment, and follow-up at 1, 2, 3, and 6 months after program completion. EaseVRx participants reported a higher than 30% reduction in pain after treatment, compared to 41% of control individuals. Forty-six percent of EaseVRx individuals experienced a better than 50% pain reduction, compared to 26% of control participants. At one-month follow-up, all EaseVRx participants reported a 30% reduction in pain, and at two- and three-month follow-up, all outcomes except pain intensity reported a 30% reduction in pain. At one-, two-, and three-month follow-up, the control group reported pain reductions below 30% for all outcomes. (ClinicalTrials.gov NCT04415177). Additional evidence in the form of well-designed trials is needed to confirm the characteristics of those who would benefit from this therapy system and the clinical significance and durability of the effects of this strategy on chronic LBP management. The study findings are limited by its short duration and additional evidence is needed to confirm the characteristics of those who would benefit from this therapy system and the clinical significance and durability of the effects of this strategy on chronic LBP management.

Regulatory Status EaseVRx (currently branded RelieVRx) was granted FDA breakthrough status as the first FDA-authorized immersive VR medical device for home use indicated for the treatment of chronic LBP on March 2021. De Novo classification (DEN210014) on November 16, 2021. FDA Product Code: QRA (VR behavioral therapy device for pain relief). RelieVRx (formerly EaseVRx) is classified as a Level II device and is the only device granted regulatory approval and clearance under product code QRA. Effective April 1, 2023, CMS is established a new HCPCS Level II code E1905, "Virtual reality cognitive behavior therapy device (cbt), including pre-programmed therapy software" for RelieVRx.	
Drowzle® Pro (Resonea) *Obstructive Sleep Apnea (OSA)* Drowzle Pro is an FDA-cleared, stand-alone software medical device that is indicated to record a patient's respiratory pattern during sleep for the purpose of prescreening patients for OSA. It currently operates on a mobile computing device with an Apple iPhone 7, iPhone 8 or iPhone X using iOS v10.0 or later. Drowzle is only available by prescription for adults 21 years of age and older. The device is designed for use in home-screening of adults with suspected possible sleep breathing disorders. Drowzle records sleep breathing patterns, sends them to secure cloud servers, and then analyzes and interprets the results, as well as the individual's profile data, to measure and track sleep-related health risks over time. Results are used to assist the healthcare professional in determining the need for further diagnosis and evaluation. Drowzle is not intended as a substitute for full polysomnography (PSG) when additional parameters such as sleep stages, limb movements, or EEG activity are required (FDA, 2022a; Resonea, 2022). *Regulatory Status* FDA 510(K) marketing clearance (KI73974) received March 24, 2013. Substantially equivalent to a marketed predicate device (SleepStrip II, S.L.P LTD; K112822) under 21 CFR 868.2375 in 2019). FDA Product Code: MNR.	Drowzle was assessed in a longitudinal cohort study of 59 individuals who received a clinically indicated PSG in a sleep laboratory, where researchers compared the Drowzle algorithm to PSG results. Compared to PSG scores, researchers observed that the algorithm had a sensitivity of 93.7%, a specificity of 63.0%, a negative predictive value of 89.5%, and a positive predictive value of 75% in detecting moderate and severe OSA in individuals. There is a lack of data addressing the impact of screening results on OSA diagnosis and management as compared to generally accepted medical practice standards, as well as studies evaluating real-world application.
Home Vision Monitor (HVM) (Vital Art and Science, LLC) *Degenerative Eye Diseases* (e.g., macular degeneration and diabetic retinopathy) HVM (previously myVisionTrack) is an FDA-approved, prescription-only medical device that is available as an app. It is intended to detect and characterize central 3 degrees metamorphopsia (visual distortion) in patients with maculopathy, including age-related macular degeneration (AMD) and diabetic retinopathy, and to aid in monitoring the progression of disease factors causing metamorphopsia. It is intended to be used by patients who have the capability to regularly perform a simple self-test at home. The myVisionTrack is not intended to diagnose; diagnosis is the responsibility of the prescribing eye-care professional. The	Korot et al. (2021) conducted a cohort survey study of 417 participants to analyze the uptake and engagement of the HVM application. Adult patients receiving intravitreal injections for retinal disease at Moorfields Eye Hospital between May 2020 and February 2021 were included in this cohort survey. Engagement was favorably correlated with to more comfort with technology, White British ethnicity, visual acuity, a diagnosis of neovascular AMD, and the number of intravitreal injections, and it was adversely associated with advancing age. Several limitations exist in this survey study. The definition of relevant metrics to measure human behavior, such as uptake and engagement, is difficult to define, and their relevance in various practice settings has not been

myVisionTrack performs a shape discrimination hyperacuity vision test and provides regular monitoring of disease progression for timely detection of significant changes in vision function. If a significant decline in vision function is observed, the physician will be informed and granted access to the patient's vision self-test results to determine if the patient needs to be seen sooner than their next scheduled appointment. It is not intended to diagnose (FDA, 2022). *Regulatory Status* FDA 510(K) marketing clearance (K121738) as substantially equivalent to a marketed predicate devices under 21 CFR 886.1330. FDA Product Code: HOQ.	evaluated. HVM app uptake failure includes receptive patients who cannot utilize the app but not unwilling patients. Only active users' compliance was surveyed. The survey cohort was well-educated and familiar with technology and does not include a range of participants with other levels of education or backgrounds. No published studies have assessed clinically meaningful outcomes and it is uncertain whether the treatment results in improvement in the net health outcome as compared to generally accepted standards of medical practice.
Mahana™ (Mahana Therapeutics, Inc.) *IBS* Mahana for IBS (formerly Parallel or Regul8) is a prescribed mobile application accessible on an iPhone or Android device that intended to provide cognitive behavioral therapy for adults aged 22 years of age and older diagnosed with IBS as a 3-month treatment to reduce the severity of symptoms of IBS. It is intended to be used together with other treatments for IBS by tracking symptoms, managing flare-ups, altering behaviors, and personalizing techniques for symptom relief (e.g., relaxation, improving eating habits, reducing stress, managing emotions differently, and reducing unhelpful thoughts). Mahana aims to teach CBT skills that are practiced outside of the app and a toolkit to support your daily lesson content. The program consists of 10 sessions and multiple lessons within each session. Patients are encouraged to use the DTx once a day to achieve optimal results. *Regulatory Status* FDA 510(K) marketing clearance (K211372) as substantially equivalent to a marketed predicate device (Parallel, De Novo pathway clearance DEN200029 under 21 CFR 801.109 in 2020). FDA Product Code: QMY.	One pilot RCT analyzes Regul8, an early web-based version of MahanaTM for IBS. Previous versions of Mahana for IBS (formerly Parallel) experienced technological modifications from the website to the mobile version, including technical optimization of some features and content modifications such as upgrading information to follow best practices. Due to the difference in mode of application, this study is therefore excluded from this assessment of the evidence. There is no published peer-reviewed evidence for Mahana for IBS.
MindMotion™ GO (MindMaze) *Telerehabilitation (Stroke)* MindMotion GO, an FDA-cleared medical device software, is a telerehabilitation program that uses a video game interface to encourage adherence to therapy protocols at home to aid in the restoration of motor function and maximize a patient's recovery potential. The video games. The video games, designed by neuroscientists, use software in conjunction with the Microsoft Kinect v2 and Leap Motion controller to assist adults with physical rehabilitation in acute inpatient settings, outpatient clinics, and at home. The software uses game-based digital therapies, such as rehabilitation exercises for the upper extremity, trunk, and lower extremity; audio-visual feedback and graphic movement representations for individuals; and individual performance metrics for healthcare professionals. Individual assessment, exercise guidance, and approval by a healthcare professional are required prior to using MindMotion GO (FDA, 2022c; MindMaze, 2022).	There is no published peer-reviewed evidence for MindMotion™GO. Telerehabilitation for stroke survivors appears to be an active area of research and publication in general; however, no clinical studies, systematic reviews, or guidelines addressing MindMotion GO were located. As a result, current evidence does not indicate whether MindMotion GO is more, less, or similarly effective or safe as other telerehabilitation programs, in-clinic programs, or traditional physical therapy. The program's information on the manufacturer's website and in regulatory documentation is extremely limited (Hayes, 2022). In addition, no guidelines pertaining to MindMotion GO were identified, which is to be expected given the lack of published clinical studies on MindMotion GO.

Regulatory Status MindMotion GO received FDA 510(k) marketing clearance (K173931) as substantially equivalent to previously marketed predicate devices. FDA states its indication for use is, "as a medical device software used in combination with the Microsoft Kinect v2 and Leap Motion controller that supports the physical rehabilitation of adults in the clinic and at home. The software includes rehabilitation exercises for the upper extremity, trunk, and lower extremity." Approval by a medical professional is required prior to use. FDA Product Code: LXJ (as an *interactive rehabilitation exercise device,* and the indications further stipulate it is intended for use in clinic or at home.) Note: MindMotion GO is not specifically indicated for stroke survivors, but it is marketed for stroke survivors.	
Canvas Dx™ (Cognoa, Inc.) *Autism Spectrum Disorder (ASD)* Canvas Dx is a diagnostic tool indicated as an aid in the diagnosis of ASD in pediatric patients ages 18 months through 72 months. The machine learning (ML)-based software uses an algorithm to analyze data submitted by parents and health care providers. The device is not intended for use as a stand-alone diagnostic device but as an adjunct to the diagnostic process and intended to be used along with other information, such as patient history, clinical evaluation, and observation. (Canvas Dx, 2021; Cognoa, 2021). Canvas Dx is designed to be completed in minutes (instead of hours for the traditional full assessment) (Abbas et al. 2018) and is readily accessible, whereas traditional assessments can require long waiting times and further delaying access to treatment (Kanne et al., 2018). CanvasDx utilizes a clinically validated AI technology that integrates 3 main components to evaluate symptoms: via a mobile app a parent or caregiver completes at home questionnaires regarding their child's behavior and can also upload video documenting their child's behavior as well, a physician inputs through a provider portal answers to preloaded questions about the child's behavior problems, and manufacturer-trained and certified specialists can view and analyze the uploaded videos via a video analysis portal. If there has been sufficient information provided for its algorithm to process, the software then generates a positive or negative diagnosis to help diagnose or rule out autism It is proposed that this will help in earlier diagnoses being made, which can lead to earlier interventions when they are the most effective. *Regulatory Status* FDA clearance through the De Novo pathway (DEN200069) under 21 CFR Part 801.109. It is indicated for use by HCP as an aid in the diagnosis of autism spectrum disorder (ASD) for patients ages 18 months through 72 months who are at risk for developmental delay based on concerns of a parent, caregiver, or HCP. FDA Product Code: QPF (pediatric ASD diagnosis aid) (2021). Breakthrough Device Designation by the FDA in October 2018.	Abbas et al. (2018) conducted a multi-center clinical study of 162 children (n=162) to determine the performance of these algorithms and their combination. Machine learning (ML) was applied to gold standard clinical data captured across thousands of children at-risk for ASD. Two algorithms for identifying autism, including one based on short, structured parent-report questionnaires and short semi-structured home videos of children, identify key behaviors, which are then combined in the algorithm to produce a more accurate single assessment. While demonstrating significant accuracy in measures of AUC, sensitivity, and specificity compared with standard screening tools, the authors discuss the myriad confounding factors in clinical analyses, noting that the results are statistically limited. Additional clinical studies are warranted to firmly support the findings of this study that a mobile, ML process can be a reliable method for detection of autism outside of clinical settings. Abbas et al. (2020) evaluated a multi-modular, ML-based assessment of ASD via a mobile app in a blinded, multi-site clinical study that included 375 children who were 18 to 72 months of age. The ML-based assessment of autism consisted of a multi-modular assessment system combined of three modules: a 4-minute parent questionnaire, a 2-minute clinician questionnaire, and a video assessment module questionnaire completed by a video analyst who reviews 2 videos of the child recorded by the parent/caregiver. The results demonstrated that the ML-based assessment outperformed baseline autism screening assessments (i.e., the Child Behavior Checklist, the Modified Checklist for Autism in Toddlers, Revised, and the Social Responsiveness Scale – Second Edition) administered to children by 0.35 in specificity when operating at 90% sensitivity. Additionally, in children less than 48 months of age, the researcher's ML-based assessment outperformed the most accurate baseline screening assessment by 0.18 in AUC and 0.30 in specificity when operating at 90% sensitivity. Limitations of the study include: its retrospective analysis design, the clinical validation was weighted towards an autism diagnosis since the participants were preselected as having a high risk of autism, the new clinician module was only tested at 3 academic tertiary care clinical centers so the ability to generalize its accuracy in a primary care setting

	cannot be made, and there is a potential for bias as the study authors were all affiliated with Cognoa. In addition, prospective, well-designed randomized studies with larger sample sizes from the general population are needed. There is insufficient evidence to determine that the technology results in an improvement in the net health outcome.
EndeavorRx™ (Akili Interactive Labs, Inc.) *Attention-deficit/hyperactivity disorder (ADHD)* EndeavorRx is DTx intended to provide therapy for ADHD or any of its individual symptoms as an adjunct to clinical supervised treatment. This DTx is delivered through an action video game experience and is designed to challenge a child's attention span during gameplay with the necessary focus and flexibility to perform multiple tasks at the same moment. EndeavorRx is a digital therapeutic indicated to improve attention function as measured by computer-based testing in children ages 8 to 12 years old with primarily inattentive or combined type ADHD, who have a demonstrated attention issue. Patients who engage with EndeavorRx demonstrate improvements in a digitally assessed measure Test of Variables of Attention (TOVA) of sustained and selective attention and may not display benefits in typical behavioral symptoms, such as hyperactivity. EndeavorRx should be considered for use as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder. One prescription provides 3 months of access to this treatment. The duration of daily treatments last approximately 25 minutes and should be completed by the patient without interruption. *Regulatory Status* FDA clearance for EndeavorRx was issued to Akili Interactive Labs Inc. on June 15, 2020, through the De Novo pathway (DEN200026). It is a Class II device, Product Code QFT (digital therapy device for attention deficit hyperactivity disorder), under 21 CFR 882.5803. FDA Product Code: QFT (digital therapy device for ADHD)	Kollins et al. (2020) evaluated the DTx for improved attentional performance in pediatric patients with ADHD in a randomized, double blind, parallel group, controlled trial. The Software Treatment for Actively Reducing Severity of ADHD (STARS-ADHD) study included 348 children (ages 8-12) diagnosed with ADHD to receive treatment with either EndeavorRx (n=108) or a digital control intervention (n=168). Enrolled children were ineligible if they were already receiving medical therapy for ADHD. EndeavorRx targets attention and cognitive control delivered through a video game-like interface through at-home play for 25 minutes per day, 5 days per week for 4 weeks. The primary outcome was a mean change in TOVA API from pre-intervention to post-intervention. Among children who received Akili, the mean change from baseline on the TOVA Attention Performance Index (API) was 0.93 in the EndeavorRx group and 0.03 in the control group; there were no differences between groups on secondary measures. No serious adverse events or discontinuations were reported. Treatment-related adverse events were mild and included frustration (3%) and headache (2%). Compliance averaged 83% of expected sessions played. The researchers concluded EndeavorRx might be used to improve objectively measured inattention in pediatric patients with ADHD with minimal adverse events. Study limitations include enrollment of only children with an objective baseline deficit in attentional function and those not currently receiving medical treatment for ADHD, thus representing a small subset of the ADHD population. In addition, the study-period was limited to just 28 days of follow-up. Finally, it is uncertain whether the treatment results in clinically significant outcome or benefits consistent with generally accepted standards of medical practice.
Freespira (PaloAlto Health Sciences, Inc) *Post-traumatic stress disorder (PTSD); panic disorder* Freespira is an adjunctive treatment to reduce panic symptoms in patients with panic disorder or PTSD. The DTx incorporates a proprietary sensor, physiological feedback display, and coaching to train patients over 28-days to normalize the respiratory irregularities underlying a key physiological driver of anxiety attacks and PTSD symptoms (carbon dioxide hypersensitivity). The Freespira platform combines a proprietary sensor, a nasal cannula, a connected tablet and proprietary software. The treatment measures respiration rate and exhaled CO2 levels in real time, graphically displaying physiological data. It guides patients to regulate exhaled CO2 levels and respiration. After a single training session, Freespira is used at home in two 17-minute breathing sessions a day over a four-week period, after which the treatment is complete.	Tolin et al. (2017) evaluated Freespira in a multicenter, single arm trial of 69 adults with panic disorder who received 4 weeks of Capnometry Guided Respiratory Intervention (CGRI), which provides feedback of end-tidal CO_2 ($P_{ET}CO_2$) and respiration rate via a custom sensor device. This intervention is delivered via home use following initial training by a clinician and provides remote monitoring of client adherence and progress by the clinician. Outcomes were assessed immediately post-treatment and at 2- and 12-month follow-up. CGRI was associated with a response rate of 83% and a remission rate of 54%, in addition to large decreases in panic severity. Additionally, large decreases in panic severity were noted as well as similar decreases in functional impairment and in global illness severity. The authors noted that gains were largely sustained at follow-up and PETCO2 moved from the slightly hypocapnic range to the normocapnic range. This study served as a benchmarking analysis against a prior

Freespira is indicated as an adjunctive treatment of symptoms associated with panic disorder, panic attacks and/or PTSD in patients 18 and older. In younger patients, Freespira has been evaluated and is being made available as permitted by FDA's COVID-19 Enforcement Discretion Guidance (Freespira Inc., 2022). *Regulatory Status* Freespira received 510(k) clearance through Palo Alto Health Sciences Inc. Palo Alto Health Sciences became Freespira Inc. on December 28, 2020. The Code of Federal Regulations 21 882.5050 applies product codes HCC and CCK to class II biofeedback devices. Freespira was cleared as substantially equal to the Canary Breathing System (Palo Alto Health Sciences Inc.) on December 10, 2013. Freespira's marketing notification (K180173) states that the device can be used while plugged into a power adapter and its indication was expanded to PTSD. FDA Product code: HCC, CCK (2013)	published controlled trial and confirmed prior clinical results and further supported the viability of CGRI in the treatment of PD. Kaplan et al. (2020) reported on impact of Freespira over a 12-month period in a cohort of 51 individuals enrolled at a single center. Freespira collaborated with Highmark Health and Allegheny Health Network on a study of patients diagnosed with panic disorder. Researchers measured clinical outcomes and cost reductions over a full year following treatment with Freespira and the results were notable. In total, 45 (87%) completed the 4-week, twice-daily Freespira home device treatments and at least 15 of the 56 protocol-specified therapy sessions. By the end of the study at 12 months, only 22 participants were available for complete analysis. Overall, 86% of patients were symptom-free immediately post-treatment and 73% were still symptom-free 12 months post treatment. No clinical practice guidelines or position statements specifically addressing Freespira were identified. The current evidence assessment for Freespira lacks comparisons with generally accepted standards of medical practice (cognitive behavioral therapy or pharmaceutical therapy) and is limited by small sample size and bias due to loss at follow-up before its efficacy can be established.
Halo AF Detection System™ (LIVMOR, Inc) *Detection of atrial fibrillation (AF)* The Halo AF Detection System is a wearable smartwatch device that provides continuous monitoring of pulse rhythm to detect AF, on-demand during the day and automatically at night. The system consists of a proprietary algorithm that filters and detects irregular pulse rhythms suggestive of AF from photoplethysmography (PPG) data, a patient user interface that informs patient data collection. When a signal is suggestive of AF, the rhythm is flagged for physician review through a cloud-based portal. The device software interfaces with the LIVMOR Halo+ home monitoring system and compatible Samsung Halo smartwatches to capture PPG data and sync to a server. *Regulatory Status* 510(k) marketing clearance (K201208) as substantially equivalent to a marketed predicate device (FibriCheck). It is indicated for use by patients who have been diagnosed with or are susceptible to developing AF and who would like to monitor and record their pulse rhythms on an intermittent basis and alert their physicians of any detected irregular heart rhythms. It is used in conjunction with the Halo + Home Monitoring System™ and is not validated for use with any other pulse monitoring system. FDA Product Code: DXH. (2020).	No published peer-reviewed evidence. A multi-center clinical trial was conducted with 269 enrolled patients, comparing the accuracy of the Halo System, in the processing of PPG signals recorded by the Samsung wearable, with a concurrently recorded electrocardiogram (ECG), currently the gold-standard for measuring heart rhythms. The ECG recordings were reviewed for accuracy by automated algorithms, ECG technicians, and cardiologists, and were subsequently compared to the concurrently recorded pulse rhythms from the Halo™ system. The Halo™ was 100% sensitive in identifying patients with AF and 93% specific in identifying patients without AF.

Ieva Pelvic Health System (Renovia Inc.)
Urinary Incontinence

The Ieva Pelvic Health System (Ivea) is a motion-sensing intravaginal device with an app-based software program is intended for: 1) strengthening of the pelvic floor muscles (PFM); and 2) rehabilitation and training of weak PFM for the treatment of stress, mixed and mild to moderate urgency urinary incontinence (including overactive bladder) in women (FDA, 2021). The Ieva system wirelessly facilitates PFM training and transmits real-time performance data through a dedicated mobile application that has been downloaded onto the patient's mobile device. The Ieva consist of a probe, storage case, associated batteries, and the Renovia Digital Health App (App). Thermoplastic elastomer was used as the material overlay for the electronics and 6 accelerometers are contained within the probe. Additional electronics are contained in the storage case to transmit data wirelessly between the device and the App." (FDA, 2021).

Regulatory Status
FDA clearance through the 510(k) marketing clearance (K212495) and is classified as a perineometer under FDA Product Code: HIR. The device is governed by 21 CFR 884.1425 of the Code of Federal Regulations (CFR) and has been given the product code HIR. On October 9, 2014, Remendium Labs LLC received the initial 510(k) clearance for the Ieva Rehabilitative Positional Device (K133990). On June 30, 2022, the most recent 510(k) clearance (K213913) was issued. In addition, the system received a Breakthrough Device designation in October 2021 as a treatment for fecal incontinence, which was added to the clearance indications on June 30, 2022.

Rosenblatt et al. (2019) assessed the efficacy and patient satisfaction of the Ieva, a PFM training system for the treatment of female urine incontinence that uses an accelerometer-based system. The patients in this prospective, single-center, open label trial were 23 premenopausal women with mild to moderate stress or mixed urinary incontinence who were monitored for 6 weeks. The study results were as follows: the Urogenital Distress Inventory (UDI) score decreased from 36.7 ± 4.7 to 1.45 ± 0.8 at 6 weeks, the Patient's Global Impression of Severity score decreased from 1.5 ± 0.1 to 0.2 ± 0.1 at study endpoint, the PFM contraction duration increased from 13 ± 2.6 at baseline to 187 ± 9.6 seconds, repeated contractions in 15 seconds increased from 5.9 ± 0.4 at enrollment to 9.6 ± 0.5 at 6 weeks, and maximum pelvic floor angle (a measure of lift) increased from 65.1 ± 2.0˚ to 81.1 ± 1.8˚. Additionally, increasing PFM contraction duration and maximum pelvic floor angle correlated with decreasing UDI-6 scores, r = -0.87; r = -0.97, respectively. Device-related adverse events were absent.

Weinstein et al. (2022) evaluated whether the use of an intravaginal motion-based DTx device for PFM training (intervention group) or PFM training alone (control group) in women with stress-predominant urinary incontinence (SUI). A total of 61 female volunteers (N=61) with SUI or SUI-predominant mixed urine incontinence took part in this multicenter, randomized-controlled trial. The intervention group (n=29) was treated PFM training with the device, while the control group (n=32) was treated PFM training alone. Change in the Urinary Distress Inventory, short-version, and improvement in the Patient Global Impression of Improvement were the primary objectives examined at 8 weeks. In addition, the Pelvic Organ Prolapse and Colorectal-anal Distress Inventories, the Pelvic-Floor-Impact Questionnaire, and a 3-day bladder diary were completed by the patients. The intervention group improved significantly more than the control group on the Pelvic Organ Prolapse and Colorectal-anal Distress Inventories and the Pelvic-Floor-Impact Questionnaire, and the median number of SUI episodes decreased from baseline to 8 weeks by -1.7 per day in the intervention group and -0.7 in the control group. This study was, however, prematurely halted due to device technical issues. From baseline through week 8, participants in the intervention group had 70% fewer SUI episodes than those in the control group, which was statistically significant. Only those in the intervention group showed statistically and clinically significant symptom alleviation as early as 4 weeks, implying quicker results than those in the control group.

An Evolving Evidence Review (2023) on the use of the Ieva Pelvic Health System for the treatment of urinary incontinence in female patients, including a review of full-text clinical studies and full-text systematic reviews, suggests that the Ieva Pelvic Health System (Renovia Inc.) has little support for the treatment of urinary incontinence in female patients. According to the findings, no clinical studies compared PFMT with Ieva to PFMT with other biofeedback devices. (Hayes, 2023).

National and Specialty Organizations
There were no relevant professional society position statements or clinical practice guidelines that specifically

	mentioned the leva Pelvic Digital Health System; however, there are numerous intravaginal PFM training systems on the market that are intended for the treatment of UI, and professional organizations are unlikely to specifically endorse any single device in this category. According to an evolving evidence review, 'Based on a review of full-text clinical practice guidelines and position statements, guidance appears to confer no/unclear support for the leva Pelvic Health System for treatment of UI in female patients.' (Hayes, 2023). **American College of Obstetricians (ACOG) / American Urogynecologic Society (AUGS)**: Urinary Incontinence in Women (ACOG/AUGS, 2015; reaffirmed in 2022) stated the following: "Pelvic floor muscle exercises [alone or augmented with biofeedback] can be effective as a first-line treatment for stress, urgency, or mixed [UI]. Numerous descriptions of specific [PFMT] programs exist; however, it is unclear which is most effective. Treatment efficiency decreases over time and is most effective when initiated under the supervision of a physician" (p. e72).
Nerivio® (Theranica Bio-Electronics Ltd.) *Migraine* Nerivio is a non-pharmacological, non- invasive, wearable, wireless, battery-operated stimulation unit remote electrical neuromodulation (REN) stimulation device controlled by the patient via a smartphone application. REN is a recently developed nonpharmacological acute migraine treatment which noninvasively stimulates upper arm peripheral nerves. The Nerivio system comprises of a power source and a pair of electrodes attached on an armband. The Nerivio system comprises of a power source and a pair of electrodes attached on an armband. The wireless, self-applied device delivers transcutaneous electrical nerve stimulation, which is thought to disrupt pain impulses traveling to the brain. The device's functionality is dependent on it being applied to the patient's upper arm during the onset of a migraine and adjusted at a non-painful intensity for a 45-minute period. Nerivio is self-administered by the patient, controlled by a smartphone app, and intended for acute treatment of migraine with or without aura in patients 12 years of age or older. Nerivio includes a secured, personal migraine diary, which patients can use to record their symptoms before treatment and 2 hours post-treatment. It can be used as a stand-alone treatment for migraines or in conjunction with other treatments. Nerivio is not recommended for individuals with congestive heart failure, severe cardiac disease, cerebrovascular disease, uncontrolled epilepsy, or active implantable medical devices, such as pacemakers or hearing aids. *Regulatory Status* The Nerivio Migra was granted De Novo clearance (DEN180059) on May 20, 2019. The *trunk and limb electrical stimulator to treat headache* class II device, Product Code QGT, is subject to 21 Code of Federal Regulations 882.5899	Grosberg et al. (2021) assessed the efficacy and safety of REN in an open-label, single-arm study of 91 persons (n=91) with chronic migraine (CM) according to the International Classification of Headache Disorders-3 criteria. The percentage of patients who experienced pain alleviation two hours after therapy was the primary outcome. Pain relief, as well as improvements in related symptoms and functional impairment, were secondary outcomes. Modified intent-to-treat patients obtained pain alleviation and pain removal in 59.3% (54/91) and 20.9% (19/91) of the time, respectively. 64.4% (29/45) of individuals who experienced pain reduction at 2 hours had sustained pain alleviation after 24 hours. REN reduced nausea, photophobia, and phonophobia, as well as improving functional abilities. There was only one device-related adverse event reported. The study limited as a single arm with no control or comparator group, thus the results of the REN treatment were not compared with those of sham stimulation, which may be considerable. Hershey et al. (2021) compared the efficacy of REN to that of standard-care medications for the acute treatment of migraines in 35 adolescent patients between ages 12 to 17 years (n=35) post hoc analysis of data from a clinical trial. The efficacy of a run-in phase in which attacks were treated with standard-care drugs (triptans or OTC medications) versus an intervention phase in which attacks were treated with REN was compared. The McNemar's test assessed efficacy at four endpoints (2 hours after treatment): single-treatment pain freedom and pain relief, consistency of pain freedom and pain relief, and consistency of pain freedom and pain relief (defined as response in at least 50% of the available first four treatments). Pain freedom was achieved by 37.1% of participants with REN, vs. 8.6% of participants with medications, pain relief by 71.4% with REN, vs. 57.1% with medications, consistency of pain freedom was achieved by 40% with REN, vs. 8.6% with medications, and consistency of pain relief was achieved by 80.0% with REN, vs. 8.6% with medications. Over a third of patients with REN

FDA clearance through the 510(k) marketing clearance (K203181) and is classified as a 'Distal Transcutaneous Electrical Stimulator for Treatment Of Acute Migraine' under FDA Product Code: QGT. Initially authorized for use in adults with acute migraine (≤ 12 headache days per month) who do not have chronic migraine, Nerivio was subsequently cleared for adults with chronic migraine in 2020 and expanded for use in adolescents with ≥ 2 migraines per month in 2021.	(37.1%) were pain-free, compared to 8.6% of individuals using medications. The authors concluded that REN may be more effective than several standard-of-care medicines in the acute treatment of migraine in adolescents; however, a larger-scale, blinded comparative-effectiveness and tolerability study is required. Moisset et al. (2020) conducted a systematic review and meta-analysis of RCTs focusing on the use of neurostimulation methods to treat migraine. There were 38 studies in total, only 2 of which included Nerivio Migra-based REN, Yarnitsky et al. (2017) and Yarnitsky et al. (2019). Both RCTs were conducted by the same group of researchers (Yarnitsky et al. 2017 and Yarnitsky et al. 2019). The meta-analysis of the 2 RCTs found Nerivio was associated with a greater likelihood of pain-free status at 2 hours post-treatment than sham. However, no other outcomes were analyzed, and no comparisons with other active treatment alternatives were made. The review noted that If the findings of these two studies are confirmed by a third party, REN will be a compelling therapy option for acute migraine. For the most part, larger, well-conducted trials with longer follow-up are still required to establish the benefits of neurostimulation. **Hayes.** The use of Nerivio Migra for acute episodic migraines for pain management is supported by current literature and consensus in an Evolving Evidence Review study published by Hayes in July 2021. The report addressed whether these full-text clinical studies, systematic reviews, and clinical practice guidelines and position statements support the use of Nerivio Migra for acute episodic migraines for pain relief. A full-text evaluation of clinical studies and systematic reviews concluded minimal support for the use of Nerivio Migra to treat acute migraine attacks. A full-text review of clinical practice guidelines and position statements identified one consensus statement supporting the use of neuomodulatory devices. The guidance appears to provide weak support for using Nerivio for the management of acute migraine episodes (AHS 2021, discussed below). **American Headache Society (AHS)** published an update to a consensus statement regarding the use of newly introduced treatments for adults with migraine based on the expanded evidence base and emerging expert consensus concerning post-approval usage (AHS 2021). The guideline mentions REN but does not include Nerivio or Nerivio Migra; however, evidence about Nerivio was evaluated to influence the suggestion. Furthermore, while the consensus in favor of using neuomodulatory devices included a literature review, it was not based on a systematic study. *'All patients with a confirmed diagnosis of migraine may be treated with a neuromodulatory device, which modulates pain mechanisms involved in headache by stimulating the nervous system centrally or peripherally with an electric current or a magnetic field... alone or in combination with pharmacotherapy for acute migraine*,' according to the consensus.

NightWare (Apple Watch®) *PTSD-driven Traumatic Nightmares* NightWare exclusively uses an Apple Watch and iPhone. The Apple Watch monitors body movement using a gyroscope and accelerometer, and measures heart rate. These data are sent to the NightWare server and using a proprietary algorithm, the device creates a unique sleep profile for the user during a learning period of up to 10 days. When NightWare detects the occurrence of nightmares based on its analysis of heart rate and body movement, it arouses the wearer by vibrating with the intention of interrupting the nightmare without waking the sleeper. Nightware is approved for adults who are at least 22 years old and have been diagnosed with nightmare disorder or have nightmares related to post-traumatic stress disorder (PTSD). NightWare is not a standalone therapy for PTSD and should be used in conjunction with prescribed medications for PTSD and other recommended therapies for PTSD-associated nightmares and nightmare disorder, according to relevant consensus guidelines. NightWare is intended for home use under the supervision of a health care provider. *Regulatory Status* FDA clearance through the De Novo pathway (DEN 200033) under 21 CFR Part 801.109. Received Breakthrough Device designation and indicated to provide vibrotactile feedback on an Apple Watch based on analysis of heart rate and motion during sleep for the temporary reduction of sleep disturbance related nightmares in adults 22 years or older who suffer from nightmare disorder or have nightmares from PTSD. FDA Product Code: QMZ.	No published peer-reviewed evidence. The approval was based on data from a 30-day randomized sham-controlled trial involving 70 patients who were randomly assigned to receive either the NightWare app or a placebo app with no vibrations. Patients in the sham group wore the device, but no vibratory stimulation was provided. Safety was assessed using validated measurements of suicidality and sleepiness, and there were no changes in either over the course of the study in either group. While both groups self-reported improved sleep quality, the benefit was greater for those provided with the Nightware product. Findings showed greater improvements on 2 versions of the Pittsburgh Sleep Quality Index scale (both the self-rated questionnaire for sleep quality and a version intended for PTSD patients) with NightWare compared with sham. Findings from the study showed no changes in either suicidality or sleepiness in either group, indicating that the evidence demonstrated the probable benefits outweighed the probable risks.
reSET® (Pear Therapeutics, Inc) *SUD* reSET is intended to provide cognitive behavioral therapy, as an adjunct to a contingency management system, for patients 18 years of age and older, who are currently enrolled in outpatient treatment under the supervision of a clinician. reSET is indicated as a 12-week treatment for patients with SUD, who are not currently on opioid replacement therapy, who do not abuse alcohol solely, or who do not abuse opioids as their primary substance of abuse. reSET delivers therapy based on the community reinforcement approach (CRA), an intensive form of validated neurobehavioral therapy for SUD, along with contingency management and fluency training to enhance learning. There are 62 interactive modules in reSET (32 core modules and 30 supplemental modules). The basic modules cover CRA fundamentals as well as skill development to help reinforce behavior change and avoid relapse. The additional modules cover a variety of topics (e.g., relationship skills, living with hepatitis C). It takes about 10 to 20 minutes to complete each module. A mobile operating system is required to use the reSET app (e.g., smartphone or tablet). reSET is not intended to be used as a stand-alone therapy for SUD, but as a supplement to outpatient treatment of buprenorphine drug therapy.	Campbell et al. (2014) investigated the Therapeutic Education System (TES), an internet-based behavioral intervention with motivational incentives, as a clinician-extender in the treatment of SUD. Adults (n=507) enrolled in 10 outpatient addiction treatment programs were randomized in a 1:1 ratio to receive 12 weeks of either treatment-as-usual (TAU) (n=252) or TAU plus TES (n=255), with the intervention replacing around 2 hours of regular therapy per week. TES had 62 interactive computer modules that included strategies for obtaining and sustaining abstinence, as well as prize-based motivational rewards tied to abstinence and treatment adherence. Individual and group counseling were part of the standard treatment at the participating institutions. Abstinence from drugs and excessive drinking (assessed by twice-weekly urine drug screenings and self-report) and time to treatment dropout were the primary endpoints. The TES group had a lower dropout rate and a higher abstinence rate, according to the study's findings. This effect was stronger in participants (n=228) who had a positive urine drug or breath alcohol screen at the start of the research. According to the results, combining TES with traditional treatment lengthens the time spent in treatment and increases the number of patients who have achieved 12-week substance abstinence. There was no statistically significant treatment effect for TES vs. standard care after 12 weeks. Patients

Regulatory Status FDA clearance through the De Novo pathway (DEN160018) 9/14/2017. FDA Product Code: PWE (9/14/2017) *FDA-cleared Class II Medical Device, 21 CFR 882.5801 Computerized behavioral therapy devices for psychiatric disorders*	who were non-abstinent at the start of the treatment had a greater chance of abstinence, but pts who were abstinent at the start of the treatment had no statistically significant effect on abstinence. Additional research is needed to assess effectiveness in non-specialty clinical settings and to differentiate the impacts of the community reinforcement approach and the contingency management aspects of TES, according to the authors. Because the intervention was mostly delivered via computer at a treatment center, it must be determined whether it is effective as a mobile medical application in any setting.
reSET-O® (Pear Therapeutics, Inc) *OUD* reSET-O is intended to increase retention of patients with OUD in outpatient treatment by providing a 12-week (84-day) cognitive behavioral therapy (CBT) application for use as adjunct to outpatient treatment that includes transmucosal buprenorphine and contingency management, for patients 18 years or older who are currently under the supervision of a clinician. The app combines contingency management (CM) with OUD-specific CBT known as the community reinforcement approach (CRA). CM gives small rewards (cash, gift cards) for desired behaviors (negative urine drug screen tests, completing CBT modules) and the size of the reward increases, on average, with consecutive desired behaviors. In the CRA, a form of CBT, patients and clinicians work together try to understand the function that drugs play in their lives and develop individual goals to promote drug-free living. ReSET-O content consists of a series of 67 interactive, on-demand audio, text, and video CRA modules (also called therapy lessons) which are sequentially unlocked as patients progress through the therapeutic. Modules are designed to deliver approximately 30 min of treatment. It is recommended that patients complete 4 modules per week. Participants can revisit already-completed modules but are required to complete the sequence of modules in the order prescribed. *Regulatory Status* FDA clearance through the 510(k)-marketing clearance (K173681) as substantially equivalent to a marketed predicate device (reSET, which is used to treat SUD other than OUD). FDA Product Code: PWE. (12/10/2018) *FDA-cleared Class II Medical Device, 21 CFR 882.5801 Computerized behavioral therapy devices for psychiatric disorders.*	reSET-O was authorized on data from a multisite, controlled, 12-week clinical trial of 170 opioid-dependent adults (n=170) who received supervised buprenorphine treatment paired with a behavioral therapy program, either with or without the addition of reSET-0. Christensen et al. (2014) assessed the benefit of adding an internet-delivered behavior therapy to a buprenorphine medication program and voucher-based motivational incentives. Participants received supervised administration of buprenorphine and urine screens 3 times per week in a contingency management system that rewarded negative urine tests. reSET-O was not shown to decrease illicit drug use any more than buprenorphine treatment and contingency management alone. However, the data from the same 12-week treatment program also showed a statistically significant increase in retention for the patients who used reSET-O (82.4% retention rate) compared with those who did not (68.4%). No adverse effects were found to be associated with reSET-O use. The researchers concluded that an internet-based treatment has efficacy and adds clinical benefits to a contingency management/medication-based program for opioid dependence. Additional research is required to evaluate whether the effect of the treatment seen in the trial may be replicated and whether an internet-based program would be effective outside the clinic (i.e., is attendance at a clinic a necessary component for encouraging clients to complete CRA modules). Maricich et al. (2020a) conducted a secondary analysis of the pivotal study data in 170 adult participants meeting DSM-IV criteria for OUD. Participants were randomized to 12 weeks of treatment-as-usual (TAU) or TAU plus a digital therapeutic occurred. TAU consisted of buprenorphine maintenance therapy, 30 min biweekly clinician interaction, and abstinence-based contingency management. The digital therapeutic consisted of 67 digital, interactive educational modules based on the Community Reinforcement Approach. Primary outcomes were treatment retention and abstinence (negative urine drug screen) during weeks 9-12 of treatment. Adverse events monitoring served as the safety parameter. The study results were as follows: recipients of TAU plus a digital therapeutic had significantly greater odds of opioid abstinence during weeks 9-12 compared to TAU: 77.3% vs. 62.1%, respectively, and the risk of participants leaving treatment was significantly lower in the digital therapeutic group. The difference in observed rate of adverse events between groups was not significant. The authors reported that TAU plus a digital therapeutic improves clinically

	significant patient outcomes, including abstinence from illicit opioids and retention in treatment compared with TAU. However, the study was had several limitations, such as a single study site, open label (all parties were aware of the treatment interventions), single study site and small study population (primarily Caucasian males). Maricich et al. (2020b) assessed 3144 individuals in a large, real-world addiction interventional dataset. This observational evaluation includes patients who redeemed a 12-week prescription for the reSET-O on their mobile devices (i.e., smartphones or tablets) in the routine course of their treatment in clinics across the US. This real-world analysis focused on patient engagement and product use data and clinical outcomes of opioid use and retention, including associations with other relevant variables. Substance use was assessed as a composite of self-reports recorded using reSET-O and Urine Drug Screening (UDS). The abstinent rate (defined as abstinent in the last 4 weeks of treatment) was observed to be 91% when excluding participants with missing data from analysis, or 66% abstinent using "missing data excluded (patients with no data as positive)." reSET-O was used appropriately and consistently (completed 4 or more modules per week) for the first 4 weeks by only 29% of the study population; thus adherence to reSET-O's proper use was low in this very large, real-world cohort. The results show that high engagement with therapy in the real world is positively associated with abstinence and retention in treatment. For patients with OUD, ReSET-O is a potentially valuable adjunct to buprenorphine MOUD therapy. However, findings relied on self-reports and lacked clinically meaningful measures beyond UDS, which were not routinely measured at study sites. *Institute for Clinical and Economic Review (ICER)* published an evidence report in 2020 which included published data evaluating the reSET-O. The report states that there is no direct, peer-reviewed evidence of the effectiveness of any digital health technology (DHT) in relevant populations. While the use of the DHTs is unlikely to be harmful to patients, there is moderate certainty in the outcome of medication-assisted therapy (MAT) plus DHT use are comparable to MAT alone. The report concludes that "no randomized trials, cohort studies or case series that evaluated the DHTs [digital health technologies] reviewed in this report until after the draft report was released. Recently, two uncontrolled studies suggested potential benefits with reSET-O, but there was a high risk of bias for both studies."
Somryst® (Pear Therapeutics, Inc.) *Chronic Insomnia* Somryst is a 9-week PDT that provides a neurobehavioral intervention for patients 22 years of age and older with chronic insomnia. Digital cognitive behavioral therapy for insomnia (CBT-I) is a neurobehavioral treatment that focuses on addressing the maladaptive behaviors, routines, and dysfunctional thoughts that perpetuate sleep problems. There are 6 therapeutic cores focused on CBT-I concepts,	Christensen et al. (2016) assessed whether an online self-help insomnia program reduces depression symptoms in a randomized controlled study of 1149 participants (n=1149) (18-64 years). Subjects had insomnia and depressive symptoms but did not meet the criteria for major depressive disorder (MDD). Study participants were randomly assigned to receive a 6-week, modular online insomnia program based on CBT-I, Sleep Healthy Using the Internet (SHUTi, is an earlier version of Somryst with equivalent content]) or HealthWatch (an interactive, attention-

each completed at a frequency of one core per week. Somryst has patient- and clinician-facing dashboards. The patient dashboard includes a daily sleep journal that is completed by the patient whereas the clinician-facing dashboard includes information about patient use of the device, the Insomnia Severity Index (ISI), the Patient Health Questionnaire, and sleep metrics derived from sleep diaries. Somryst is contraindicated in patients with conditions worsened by sleep restriction (e.g., bipolar disorder, schizophrenia, other psychotic spectrum disorders), untreated obstructive sleep apnea, parasomnias, epilepsy, high risk of falls, pregnancy, and unstable or degenerative illness that are exacerbated by the application of sleep restriction and consolidation delivered as a part of CBT-I.

Regulatory Status
510(k) marketing clearance (K191716) as substantially equivalent to a marketed predicate device (reSET®). It is indicated to provide a neurobehavioral intervention (CBT-I) in patients 22 years of age and older with chronic insomnia. FDA Product Code: PWE (2020)

matching, internet-based placebo-controlled program). The primary endpoint was depression symptoms at 6 months, as measured with the Patient Health Questionnaire (PHQ-9). Results were based on 581 (51%) participants completing the study program assessments at 6 weeks and 504 (44%) of participants that completed the 6-month follow-up. SHUTi recipients had significantly lower depression symptoms on the PHQ-9 at 6 weeks and at 6 months compared to HealthWatch. MDD was diagnosed in 22 (4%) participants at 6 months (n=9 in the SHUTi group and n=13 in the HealthWatch group), with no superior effect of SHUTi vs. HealthWatch. No adverse events were noted. The authors concluded that online CBT for insomnia treatment is a pragmatic and effective approach to reducing depressive symptoms and may have the ability to reduce depression at the population level.

Ritterband et al. (2017) conducted an RCT comparing the internet CBT-I with internet sleep hygiene education at baseline, 9 weeks, 6 months, and 1 year reported sustained benefits with SHUTi for those with insomnia compared to sleep hygiene education (n=151 and n=152, respectively) at 1 year follow-up.

The trial included 303 adults (n=303) with chronic insomnia of whom 151 (49.8%) reported at least 1 medical or psychiatric comorbidity. Participants either received the internet CBT-I (Sleep Healthy Using the Internet [SHUTi]) (n=151) or the online patient education program (n=152). SHUTi is a 6-week fully automated, interactive and customized web-based program that incorporates the key principles of face-to-face CBT-I, while the online patient education program includes non-customized and fixed online information on insomnia. The primary sleep outcomes were self-reported online ratings of insomnia severity ISI and online sleep diary-derived values for sleep-onset latency and wake after sleep onset, collected prospectively for 10 days at each assessment period. The secondary sleep outcomes included sleep efficiency, number of awakenings, sleep quality, and total sleep time. Results of the 3 primary sleep outcomes showed that the overall group × time interaction was significant for all variables, favoring the SHUTi group. Treatment effects were sustained at the 1-year follow-up, with 56.6% reaching remission status and 69.7% deemed treatment responders at 1 year based on ISI data. In addition to total sleep time, secondary sleep results showed a significant overall group x time interaction in favor of the SHUTi group. The study provides evidence that the web-based CBT-I intervention SHUTi can meaningfully improve insomnia symptoms and sleep variables; however, the authors noted the limitations of this study (such as primarily Caucasian participants and the full range of medical and psychiatric conditions that co-occur with insomnia is not represented in this study) and recommended that future studies to determine the most suitable patient population for CBT-I intervention.

Other evidence for adults with chronic insomnia who receive treatment with Somryst include the following RCTs:

- Vedaa et al. (2020) and Hagatun et al. (2019) conducted a double-blind RCTs performed to 9-week follow-up showed improvement in ISI scores from

	SHUTi (Somryst's web platform) compared to sleep hygiene education. – Veeda et al. (2020) reported that findings demonstrate that digital CBT-I is efficacious in reducing the severity of symptoms associated with the insomnia disorder but notes more research is needed to understand the key moderators and mediators of any therapeutic effect and to identify the moderators of response and improve targeting. – Hagatun et al. (2019) reported that improvements were maintained among the completing SHUTi participants in the 6-month nonrandomized follow-up, which suggests that Internet-based CBTi produced significant short-term improvements in sleep in patients with chronic insomnia; however, it is noted that the rate of dropout attrition in this trial limits the generalizability of the findings. • Shaffer et al. 2020, in a single-blind RCT, reported that bedtimes were 30% more regular in SHUTi recipients (n=151) compared to bedtime in sleep hygiene education recipients (n=152) after 1 year. • Ritterband (2009) reported on an open-label RCT that compared SHUTi to waitlist (no treatment) (n=22 and n=23, respectively). Significant improvements in ISI scores were noted in the Internet group, but not in the control group. The internet group also maintained their gains at the 6-month follow-up. Limitations of the reported trials include small sample sizes (fewer than 100 participants) and high attrition rates in several of the studies. In addition, it is unknown whether there are differences in the patient experience using the Somryst app on a mobile device because all of the studies were assessed via the web based SHUTi platform. A comparative study of Somryst versus face-to-face CBT-I as an alternative or adjunct to sleep medication would be beneficial. The evidence is insufficient to determine whether Somryst results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

FDA Emergency Use Authorization (EUA). The FDA relaxed regulatory requirements to increase access to digital health products for remote monitoring and the management of psychiatric conditions. According to the EUA, 'in the context of the COVID-19 public health emergency, the use of digital health technologies, including software as a medical device or other DTx solutions, may improve mental health and well-being of patients with psychiatric conditions during periods of shelter-in-place, isolation, and quarantine. In addition, the use of such technologies has the potential to facilitate "social distancing" by reducing patient contact with, and proximity to, health care providers, and can ease the burden on hospitals, other health care facilities, and health care professionals that are experiencing increased demand due to the COVID-19 public health emergency.' (EUA, April 2020).

Mobile Medical Apps (MMA) are medical devices that are mobile apps, meet the definition of a medical device, and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device (FDA, 2019).

Software as a Medical Device (SAMD) is defined by the International Medical Device Regulators Forum (IMDRF) as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device." (FDA, 2017).

CODING & BILLING INFORMATION

CPT Codes

CPT	Description [NOT COVERED]
0687T	Treatment of amblyopia using an online digital program; device supply, educational set-up, and initial session
0688T	Treatment of amblyopia using an online digital program; assessment of patient performance and program data by physician or other qualified health care professional, with report, per calendar month
0704T	Remote treatment of amblyopia using an eye tracking device; device supply with initial set-up and patient education on use of equipment
0705T	Remote treatment of amblyopia using an eye tracking device; surveillance center technical support including data transmission with analysis, with a minimum of 18 training hours, each 30 days
0706T	Remote treatment of amblyopia using an eye tracking device; interpretation and report by physician or other qualified health care professional, per calendar month
0740T	Remote autonomous algorithm-based recommendation system for insulin dose calculation and titration; initial set-up and patient education
0741T	Remote autonomous algorithm-based recommendation system for insulin dose calculation and titration; provision of software, data collection, transmission, and storage, each 30 days
99199	Unlisted special service, procedure or report [when specified as a mobile-based health management software application]

HCPCS Codes

HCPCS	Description [NOT COVERED]
A9291	Prescription digital cognitive and/or behavioral therapy, FDA cleared, per course of treatment
A9999	Miscellaneous DME supply or accessory, not otherwise specified
E1399	Durable medical equipment, miscellaneous [when specified as a mobile-based health management software application]
E1905	Virtual reality cognitive behavioral therapy device, including pre-programmed therapy software (e.g. RelieVRx) (new code effective 4/1/23)
T1505	Electronic medication compliance management device, includes all components and accessories, not otherwise classified [when specified as a mobile-based health management software application]

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

4/13/2023 Policy updated and revised. Added RelieVRx.
2/08/2023 Policy updated and revised. Added Luminopia One™ (Luminopia, Inc.) and CureSight (NovaSight, Ltd.) for amblyopia; Mahana™ for IBS (Mahana Therapeutics, Inc.); MindMotion™GO (MindMaze) for stroke telerehabilitation; Tidepool Loop (Tidepool) for T1DM; Drowzle® Pro (Resonea) for OSA; Home Vision Monitor™ (HVM) (Vital Art and Science) for degenerative eye diseases.
4/13/2022 New policy.

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5. Evidence analysis research brief: EndeavorRx (Akili Interactive Labs Inc.) for treatment of attention deficit hyperactivity disorder. Published June 13, 2022.
6. Evidence analysis research brief: RelieVRx (AppliedVR Inc) for management of low back pain. Published April 11, 2022.
7. Evolving evidence review: Nerivio (Theranica Bio-Electronics Ltd.) for treatment of acute migraine episodes. Published July 23, 2021.
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9. Evolving evidence review. MindMotion GO (MindMaze) for stroke telerehabilitation. Published April 1, 2022.

APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

Centers for Medicare & Medicaid Services (CMS)

1. **ADHD:** No NCD for DTx devices for patients with ADHD was identified on the Medicare Coverage Database on June 2, 2022 (searched keywords: *ADHD and digital therapeutic*).

2. **Canvas Dx:** No NCDs addressing coverage for Canvas Dx for the diagnosis of ASD was identified (searched keywords *autism spectrum disorder*, *cognoa*, and *canvas DX* in all documents on the CMS Advanced Search Database).

3. **Freespira:** An NCD for biofeedback therapy was identified on the CMS website. NCD 30.1 states that biofeedback therapy is not covered for treatment of psychosomatic conditions.

4. **Ieva Pelvic Health System:** A NCD was identified on the CMS website addressing coverage for biofeedback therapy for treatment of urinary incontinence in a search conducted on November 16, 2022 (searched CMS Advanced Search Database by keywords *leva*, *kegel*, *pelvic floor*, or *incontinence* [searched separately]). The leva Pelvic Health System is not specifically mentioned; however, the use of biofeedback-assisted pelvic muscle exercise training is only covered in an office or other facility setting, not in the home. See NCD Biofeedback Therapy for the Treatment of Urinary Incontinence (30.1.1).

5. **Nerivio:** No NCDs were identified on the CMS website addressing coverage for Nerivio for the treatment of migraine (searched keywords *migraine* and *Nerivio* in all documents on the CMS Advanced Search Database).

6. **Diabetes Mellitus:** No NCD on PDTs for diabetes was identified on January 2023 (searched keywords *diabetes OR mobile* in all documents on the CMS Advanced Search Database).

7. **Substance Use Disorder (SUDs) OR Opioid Use Disorder (OUD):** No NCD on MMAs for people with SUD was identified on April 19, 2021 (searched keywords *Substance Use Disorder (SUDs)* OR *Opioid Use Disorder (OUD)* in all documents on the CMS Advanced Search Database).

HCPCS Code

CMS established a new Level II HCPCS code for certain PDTs. The code will take effect on April 1, 2022.

The code, A9291, is described as “prescription digital behavioral therapy, FDA cleared, per course of treatment.” Based on the code description, it would appear this HCPCS code applies to all FDA-authorized PDT products that administer behavioral therapy, a very common mode of action in DTx products. The code would not apply to DTx products that administer behavioral therapy but do not require a prescription. The table lists FDA-authorized PDT products that work through behavioral therapy. Note that the list may not be comprehensive.

Product	Manufacturer	Indication	Course of Treatment
reSET	Pear Therapeutics	Substance use disorder	12 weeks
reSET-O	Pear Therapeutics	Opioid use disorder	12 weeks
Somryst	Pear Therapeutics	Insomnia	9 weeks
Ensemble[b]	Happify Health	Depression	10 weeks
Mahana IBS (Parallel)	Mahana Therapeutics	Irritable bowel syndrome	3 months

Abbreviations: IBS, irritable bowel syndrome; WAC, wholesale acquisition cost.
[a]According to third-party pricing database.
[b]Launched through FDA COVID-19 Enforcement Policy.
[c]According to the Happify Health website, Ensemble is only available through enrollment in a research study.

Some DTx products have a National Drug Code (NDC) or Universal Product Codes (UPC) which may allow reimbursement through the pharmacy benefit; however, the establishment of a HCPCS code allows reimbursement through medical benefits. Beginning on September 24, 2023, the FDA will object to the use of legacy FDA identification numbers (such as NDCs) on device labels and packages: FDA guidance.

Of note, in its decision to create this HCPCS code for PDT, CMS indicated it would help facilitate options for non-Medicare payers to provide access to this therapy in the home setting. It is unclear whether Medicare beneficiaries would be covered with this code at this time.

Since the FDA COVID-19 Enforcement Policy went into effect in April 2020, many DTx products have entered the U.S. market. The interim policy exempts several regulatory requirements for digital health products that use behavioral therapy from the FDA's requirement to submit premarket notifications under Section 510(k). This is one of the most common authorization/clearance pathways for DTx products.