Molina Clinical Policy
Prescription Digital Therapeutics: MEDICARE
Policy No. 412b

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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 the Federal government or CMS for Medicare. 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

To increase patient participation and healthcare delivery, digital health technology has rapidly advanced to fill the need of bringing health and wellness directly to individuals. Digital health technology is a wide umbrella that encompasses technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes. This technology includes mobile health (mHealth), telehealth (telemedicine), smart devices, sensors and wearables, mobile medical or wellness applications, health information technology, and personalized medicine.

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.

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. PDTs are authorized by the US Food and Drug Administration 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):

- 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
- 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 and have approved directions for use
- Developed to deliver evidence-based and high-quality software-driven therapeutic interventions that diagnose, prevent, manage, or treat a medical disorder or disease independently or in combination with medications, devices, or other treatments to optimize patient care and health outcomes
- Prescribed by a licensed healthcare provider

Regulatory Status

As the number of digital therapeutics and mobile health applications rapidly evolve, the US FDA Center for Devices and Radiologic Health continues to develop a framework and guidelines for evaluating new and existing software. The International Medical Device Regulators Forum distinguishes between software *in a* medical device and software *as a* medical device (FDA 2017). The FDA is not enforcing compliance for lower risk mobile apps, such as those that address general wellness, nor are they addressing technologies that are purposed to receive, transmit, store, or display data from established medical devices.

The FDA status of each PDT is listed under the individual section in the Summary of Medical Evidence.

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):

- AspyreRx (Better Therapeutics Inc.)
- BlueStar Rx (WellDoc)
- Canvas Dx (Cognoa)
- CureSight (NovaSight)
- d-Nav Insulin Guidance System (Hygieia, Inc.)
- Endeavor Rx (Akili Interactive Labs, Inc.)
- FibriCheck
- Freespira (PaloAlto Health Sciences, Inc.)
- Halo AF Detection System (LIVMOR, Inc.)
- Home Vision Monitor (HVM) (Vital Art and Science, LLC)
- Leva Pelvic Health System (Renovia, Inc.)
- Insulia Diabetes Management Companion (Voluntis)
- INVU (Nuvo)
- Luminopia One (Luminopia Inc.)
- Mahana (Mahana Therapeutics, Inc.)
- MamaLift (Curio)
- MindMotion GO (MindMaze S.A.)
- My Dose Coach (Sanofi, Inc.)
- myVisionTrack (Vital Art and Science, LLC)
- Nerivio
- NightWare (Apple, Inc.)
- RelieVRx (AppliedVR, Inc.)
- Rejoyn (Otsuka Precision Health, Inc.)
- reSET (Pear Therapeutics, Inc.)
- reSET-O (Pear Therapeutics, Inc.)
- Somryst (Pear Therapeutics, Inc.)

REGULATORY STATUS and SUMMARY OF MEDICAL EVIDENCE

The Prescription Digital Therapeutics (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. The evidence remains insufficient to conclude that the technology improves health outcomes overall.

Prescription Digital Therapeutics for Diabetes Mellitus

Non-Randomized Studies, Retrospective Reviews, and Other Evidence
Hayes (2024) conducted a Health Technology Assessment on the use of PDTs in the management of Type 1 Diabetes Mellitus (T1DM) and concluded the overall body of evidence was of very low quality and insufficient to form 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 quality of life and diabetes-related morbidity. The assessment rated the technology for this indication a D[2].

Hayes (2024) conducted a Health Technology Assessment on the use of PDTs in the management of Type 2 Diabetes Mellitus (T2DM) and 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. 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. It is also noted that the current evidence is insufficient in establishing definitive patient selection criteria for the use of PDTs for the management of T2DM.The assessment rated the technology for this indication a C.

National and Specialty Organizations

The **American Diabetes Association** (ADA) and the European Association for the Study of Diabetes (EASD) published a joint consensus report on diabetes digital application technology. The report stipulated that PDTs were in are an addition to blood glucose monitoring applications that log BG data and include insulin titration capabilities. The report emphasized that regardless of the clearance status of PDTs, any technology that is used in patient care should be backed by clinical evidence and real-world performance/outcomes, of which is currently extremely limited in quantity and quality. Overall, the report concluded that while PDTs and diabetes technology is showing promise in improving short-term outcomes, quality rigorous RCTs with larger sample sizes and longer follow ups are needed to distinguish the effect of these applications from possible concomitant effects. The authors strongly emphasized that technology's role is to aid in the management of diabetes and should never replace a health care provider (Fleming et al. 2020).

The **American Association of Clinical Endocrinology** (AACE) published a guideline on the use of advanced technologies in the management of diabetes mellitus. The guideline strongly recommends 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. The guideline also suggested that people with diabetes use clinically validated smartphone apps to teach/reinforce DM self-management skills, and to encourage engagement and offer support to achieve desired health behaviors (e.g., healthy eating instruction, physical activity tracking). PDTs specifically are not mentioned in this guideline (Grunberger et al. 2021).

AspyreRx (Better Therapeutics Inc.) for Type 2 Diabetes Mellitus
AspyreRx is a PDT designed to treat cardiometabolic disease via a cognitive behavioral therapy app. The device is currently approved for adults with T2DM. AspyreRx was created on the foundation that behavior is learned and can be transformed through therapeutic techniques and interventions. The app provides an experience tailored to each individual patient and is prescribed as a 90-day treatment (Better Therapeutics 2023).

Regulatory Status
AspyreRx was granted FDA approval on July 7, 2023, through the De Novo clearance process under the name BT-001. The product code is QXC, and de novo number is DEN220058. The product is classified as a Diabetes Digital Therapeutic Device.

Hsia et al. (2022) conducted a RCT to evaluate the safety and efficacy of a PDT app (AspyreRx) delivering cognitive behavior therapy designed to improve glycemic control in adults with T2DM. Adults with T2DM and an HbA1c of 7 to <11% were randomly assigned to receive access to a digital therapeutic app delivering CBT or a control app. Both groups received standard of care management. The primary study end point was treatment group difference in mean HbA1c change from baseline to 90 days. Six hundred and sixty-nine patients were randomly assigned to either the PDT group or control group. Baseline HbA1c was 8.2 and 8.1% in the PDT and control groups, respectively. After 90 days of app access, change in HbA1c was -0.28% (95% CI -0.41, -0.15) in the PDT group and +0.11% (95% CI -0.02, 0.23) in the control group (treatment group difference 0.39%; P < 0.0001). HbA1c reduction paralleled exposure to the therapeutic intervention, assessed as the number of modules completed on the app (P for trend <0.0001). No adverse events in either group were attributed to app use and no adverse device effects reported. The

authors concluded that the PDT may provide a scalable treatment option for patients with T2DM.

BlueStar Rx (WellDoc) for Type 1 and Type 2 Diabetes Mellitus

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 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.

Only the BlueStar Rx of the two WellDoc BlueStar apps currently requires a prescription; the BlueStar app is available without a prescription but does not come with an insulin calculator. BlueStar Rx products' functionalities have changed over time, thus research relating to the original BlueStar product are included below for historical purposes.

Regulatory Status

The BlueStar Rx device was granted FDA approval on January 12, 2017, through the 510(k) premarket clearance process under the device name WellDoc BlueStar, WellDoc BlueStar Rx. The device has had multiple updates and indication expansions, resulting in subsequent approvals. The device can be found under the product codes MRZ, LNX, and NDC. 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.

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 HbA1c 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 HbA1c 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 HbA1c 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.

Quinn et al. (2011) conducted a cluster-RCT to assess whether the addition of mobile application coaching and 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.

d-Nav Insulin Guidance System (Hygieia) for Type 2 Diabetes Mellitus
d-Nav Insulin Guidance System is an insulin-titration app 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 everyone 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.

Regulatory Status
d-Nav Insulin Guidance System received FDA approval on February 4. 2019 through the 510(k) premarket clearance process under the product code NDC and 510(k) number K181916. It is classified as a drug dose calculator.

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) for Type 2 Diabetes Mellitus
Insulia Diabetes Management Companion 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.

Regulatory Status
Insulia Diabetes Management Companion was granted FDA approval on June 19, 2017, through 510(k) premarket clearance process under the product code NDC and original 510(k) number K170669. The device has had multiple updates and indication expansions, resulting in subsequent approvals. 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.

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 HbA1c from baseline. In the short-term (4 months), PDTs use resulted in a statistically significant greater reduction in HbA1c 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.

My Dose Coach (Sanofi Inc.) for Type 2 Diabetes Mellitus
My Dose Coach is intended for use by a 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
My Dose Coach received FDA approval on March 22, 2017, through the 510(k) premarket clearance process under the product code NDC and 510(k) number K163099. It is classified as a drug dose calculator.

Hermanns et al. (2023) conducted a multicenter, randomized trial to determine if a smartphone application (My Dose Coach) could improve blood sugar control in patients with type 2 diabetes. Participants with type 2 diabetes, BMI ≥25 kg/m², and HbA1c >7.5% were randomized into two groups: a smartphone-guided titration group (n = 128) and a control group using a written titration chart (n = 123). After 12 weeks, the intervention group showed a greater reduction in HbA1c (-0.31%, p = 0.0388) and higher insulin dose increases (5.5 IU more than controls, p = 0.0011). There were 30 adverse events reported, including three hypoglycemic episodes in the intervention group. Study limitations included the short follow-up period, variable HbA1c measurement methods, and a post-recruitment change in analysis, potentially introducing bias. Overall, the smartphone applicated showed potential for better glycemic control without compromising safety, although longer-term effects are unknown.

Tamez-Perez et al. (2022) 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 HbA1c 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.

Prescription Digital Therapeutics for Other Conditions or Disease Processes

CureSight (NovaSight, Ltd.) for Pediatric Amblyopia
CureSight is a digital eye tracking system indicated to treat lazy eye using a special device and red-blue treatment glasses. The system tracks the gaze of each eye and blurs the vision of the dominant eye when it senses the lazy eye gaze diverting, by providing the lazy eye with a clear picture it stimulates the visual system to use the information coming from the lazy eye to process the fine details, improving its acuity and developing stereoacuity as the eyes learn to work together. It is intended amblyopia patients aged 4 to 9 years, to use at home while working with an eye health care professional. 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.

Regulatory Status
CureSight received FDA approval on September 29, 2022, through the 510(k) premarket clearance process under the product code QQU and 510(k) number K221375. It is classified as digital therapy device for amblyopia.

Wygnanski-Jaffe et al. (2022) conducted an RCT involving 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.

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.

Leva Pelvic Health System (Renovia Inc.) for Urinary Incontinence
The Leva Pelvic Health System is a motion-sensing intravaginal device with an app-based software program is intended to strengthen pelvic floor muscles (PFM) and rehab weak PFM for the treatment of stress and mild to moderate urgency urinary incontinence (including overactive bladder) in women (FDA, 2021). The Leva system consists of a probe, storage case, associated batteries, and the Renovia Digital Health App; and wirelessly facilitates PFM training with real-time performance data transmitted through the dedicated mobile application.

Regulatory Status
Leva Pelvic Health System received FDA approval on September 8, 2021, through the 510(k) premarket clearance process under the product code HIR and 510(k) number K212495. It is classified as a perineometer.

Weinstein et al. (2022) evaluated whether the use of an intravaginal motion-based PDT 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 (Hayes 2024) on the use of the leva 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 Leva Pelvic Health System (Renovia Inc.) has minimal support for the treatment of urinary incontinence in female patients.

The **American College of Obstetricians** (ACOG) / **American Urogynecologic Society** (AUGS): Urinary Incontinence in Women (ACOG/AUGS 2015; reaffirmed 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).

INVU (Nuvo) for Fetal Heart Rate and Uterine Activity Monitoring

Invu by Nuvo (Nuvo Inc.) is a wearable noninvasive device designed to continuously monitor fetal heart rate, maternal heart rate, and uterine activity. The Invu system utilizes a sensor band to wirelessly transmit data to the Invu app installed on the user's mobile phone. The Invu sensor band acquires the fetal heart electrocardiogram and maternal heart electrocardiogram signals from abdominal surface electrodes and the fetal phonocardiogram and the maternal phonocardiogram signals from surface acoustic sensors to generate tracings (Nuvo 2024).

Regulatory Status

INVU by Nuvo received FDA approval on May 28, 2021, through the 510(k) premarket clearance process under the product code LQK and 510(k) number K210025. It is classified as a home uterine activity monitor.

Schwartz et al. (2022) conducted a prospective, open-label, 2-center study to validate a novel algorithm (INVU System) that uses biopotential and acoustic signals to noninvasively detect uterine contractions via a wireless pregnancy monitor. Participants had tracings recorded via tocodynamometry, intrauterine pressure, and the wireless monitor. Eligible women were those carrying singleton pregnancies at ≥32 0/7 weeks' gestation who were in the first stage of labor. The study consisted of a training phase and a validation phase. Simultaneous recordings from each device were passively acquired for 30 to 60 minutes. Three maternal-fetal medicine specialists, blinded to the data source, identified and marked contractions in all modalities. The positive agreement and false-positive rates of both the wireless monitor and tocodynamometry were calculated and compared with that of the intrauterine pressure catheter. One hundred and eighteen participants were enrolled, 40 in the training phase and 78 in the validation phase (of which 39 of 78 participants were monitored simultaneously by all 3 devices) at a mean gestational age of 38.6 weeks. In the training phase, the positive agreement for the wireless monitor was 88.4% (1440 of 1692 contractions), with a false-positive rate of 15.3% (260/1700). In the validation phase, using the refined and finalized algorithm, the positive agreement for the wireless pregnancy monitor was 84.8% (2722/3210), with a false-positive rate of 24.8% (897/3619). For the subgroup who were monitored only with the wireless monitor and intrauterine pressure catheter, the positive agreement was 89.0% (1191/1338), with a similar false-positive rate of 25.4% (406/1597). For the subgroup monitored by all 3 devices, the positive agreement for the wireless monitor was significantly better than for tocodynamometry (P<.0001), whereas the false-positive rate was significantly higher (P<.0001). Unlike tocodynamometry, whose positive agreement was significantly reduced in the group with obesity compared with the group with normal weight (P=.024), the positive agreement of the wireless monitor did not vary across the body mass index groups. The authors concluded the novel method to noninvasively monitor uterine activity, via a wireless pregnancy monitoring device designed for self-administration at home, was more accurate than the commonly used tocodynamometry and unaffected by body mass index. Together with the previously reported remote fetal heart rate monitoring capabilities, this added ability to detect uterine contractions has created a complete telehealth solution for remote administration of nonstress tests.

Luminopia One (Luminopia, Inc.) for Pediatric Amblyopia

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 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. 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.

Regulatory Status
Luminopia One received FDA approval on October 20, 2021, through the De Novo clearance process under the product code QQU and De Novo number DEN210005. It is classified as a digital therapy device for amblyopia.

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 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.

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.

Nerivio (Theranica Bio-Electronics Ltd.) for Migraine
Nerivio is a non-pharmacological, non- invasive, wearable, wireless, battery-operated stimulation unit remote electrical neuromodulation (REN) stimulation device self-administered by the patient via a smartphone application. REN is a recently developed nonpharmacological acute migraine treatment which noninvasively stimulates upper arm peripheral nerves. 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 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
Nerivio Migra received FDA approval on May 20, 2019, through the De Novo clearance process under the product code QGT and De Novo number DEN180059. It is classified as a distal transcutaneous electrical stimulator for treatment of acute migraine.

Yarnitsky et al. (2019) conducted an RCT to assess the efficacy and safety of a remote electrical neuromodulation (REN) device for the acute treatment of migraine. Two hundred and fifty-two adults meeting the International Classification of Headache Disorders criteria for migraine with 2-8 migraine headaches per month were randomized in a 1:1 ratio to active or sham stimulation. Treatment consisted of a smartphone-controlled wireless device applied for 30-45 minutes on the upper arm within one hour of migraine onset. The electrical stimulation was at a perceptible but non-painful intensity level. Migraine pain levels were recorded at baseline, two-, and forty-eight-hours post-treatment. The primary efficacy endpoint was the proportion of participants achieving pain relief at 2 hours post-treatment. Active stimulation was more effective than sham stimulation in achieving pain relief (66.7% [66/99] vs 38.8% [40/103]; therapeutic gain of 27.9% [CI95%, 15.6-40.2]; P < .0001), pain-free (37.4% vs 18.4%, P = .003), and MBS relief (46.3% vs 22.2%, P = .0008) at 2 hours post-treatment. The pain relief and pain-free superiority of the active treatment was sustained 48 hours post-treatment. The incidence of device-related adverse events was low and similar between treatment groups (4.8% [6/126] vs 2.4% [3/126], P = .499). The authors concluded that REN provides superior clinically meaningful relief of migraine pain compared to placebo, offering a safe and effective non-pharmacological alternative for acute migraine treatment.

In an Evolving Evidence Review (Hayes 2023) it was concluded there is minimal support for using Nerivio Migra for acute episodic migraines for pain management. The report stated “Two RCTs showed more effective pain management with Nerivio than a sham device and 3 case series (i.e., without a comparison group) reported benefits in pain management, functional improvement, and other symptoms (e.g., nausea) in many patients. However,

evidence comparing Nerivio with standard migraine care is needed to inform its real-world value as a treatment option. Adoption of this novel device into practice may be hampered due to a lack of support by third-party payers; further, it has not been addressed in clinical practice guidelines."

The **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. 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 neuromodulatory 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. (Ailani et al. 2021).

Cognitive Behavioral Therapy (CBT) PDTs for a Variety of Conditions

RelieVRx (AppliedVR, Inc.) for Chronic Low Back Pain
RelieVRx (formerly EaseVRx) is a prescription-use immersive virtual reality 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 low back pain (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.

Regulatory Status
EaseVRx (currently branded RelieVRx) received FDA approval on November 16, 2021, through the De Novo clearance process under the product code QRA and De Novo number DEN210014. It is classified as a virtual reality behavioral therapy device for pain relief.

The FDA assessed the safety and effectiveness of EaseVRx in a randomized, double-blind clinical study of 179 participants (n=179) with chronic low back pain 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).

reSET® (Pear Therapeutics, Inc) for Substance Use Disorder (SUD)
reSET is intended to provide CBT 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, 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. 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.

Regulatory Status
ReSET received FDA approval on September 14, 2017, through the De Novo clearance process under the product code PWE and De Novo number DEN160018. It is classified as a computerized behavioral therapy device for substance use disorders.

Luderer et al. (2022) conducted a clinical trial to evaluate the engagement rates for 206 participants enrolled in a treatment program for SUD. Participants were randomized to receive treatment as usual (TAU) or reduced TAU plus the prescription digital therapeutic (PDT) education system for 12 weeks. Participants were eligible for contingency management incentives for module completion (modules cover Community Reinforcement Approach topic areas) and negative urine drug screens. Analyses examined the association of module completion with end-of-treatment abstinence. Participants completed a mean of 38.8 (range 0-72) TES modules over 12 weeks of treatment. Study completers (n = 157) completed a mean of 45.5 (range 9-72) TES modules, whereas study noncompleters (n = 49) completed a mean of 17.4 (range 0-45) TES modules. The study observed a strong positive correlation between TES engagement (i.e., total number of modules completed) and the probability of abstinence during weeks 9-12 of treatment among 157 study completers (OR = 1.11; 95% CI 1.08-1.14). Each module completed increased the odds of abstinence during weeks 9-12 by approximately 11% for study completers and 9% for the full sample. The study observed a similar, but weaker, association between engagement and abstinence among 49 patients who did not complete the study (OR = 1.02; 95% CI 0.98-1.07). The authors concluded greater engagement with a digital therapeutic was strongly associated with the probability of abstinence in the last four weeks of treatment.

reSET-O® (Pear Therapeutics, Inc) for Opioid Use Disorder (OUD)
reSET-O is intended to increase retention of patients with OUD in outpatient treatment by providing a 12-week 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 which are sequentially unlocked as patients progress through the therapeutic. 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
reSET-O received FDA approval on December 10, 2018, through the 510(k) premarket clearance process under the product code PWE and 510(k) number K173681. It is classified as a computerized behavioral therapy device for substance use disorders.

[1]Maricich et al. (2021) conducted a secondary analysis of the pivotal study data (Christensen et al. 2014) 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).

[2]Maricich et al. (2021) 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.

Christensen et al. (2014) conducted a randomized, unblinded, trial to evaluate the effectiveness of adding internet-delivered behavior therapy to buprenorphine medication program for opioid dependence. Participants, aged 20 to 63, met DSM-IV criteria for opioid dependence and FDA qualifications for buprenorphine treatment. Exclusion criteria included pregnancy, incarceration, and active psychiatric or significant medical conditions. The trial compared two groups: one receiving an internet-based community reinforcement approach with contingency management (CRA+) alongside buprenorphine, and another receiving contingency management alone (CM-alone) with buprenorphine. Key outcomes were longest continuous abstinence (LCA), total abstinence (TA), and days retained in treatment. CRA+ participants achieved a mean LCA of 55.0 days compared to 49.5 days for CM-alone (p=.214). For TA, the CRA+ group had a mean of 67.1 days versus 57.3 days for CM-alone (p=.011). The study noted limitations, including the absence of a standard care comparison group, a sample size potentially underpowered for detecting smaller differences, lack of post-treatment follow-up data, and constraints of the controlled trial design. Despite these limitations, the findings suggest that internet-based CRA+ treatment is effective and enhances outcomes in buprenorphine-based opioid treatment programs.

Somryst® (Pear Therapeutics, Inc.) for Chronic Insomnia
Somryst is a 9-week PDT that provides a neurobehavioral intervention that focuses on addressing the maladaptive behaviors, routines, and dysfunctional thoughts that perpetuate sleep problems. It is intended for patients 22 years of age and older with chronic insomnia. There are 6 therapeutic cores focused on CBT concepts, 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.

Regulatory Status
Somryst received FDA approval on March 23, 2020, through the 510(k) premarket clearance process under the product code QVO and 510(k) number K191716. It is classified as a computerized behavioral therapy device for insomnia.

Vedaa et al. (2020) conducted a large scale randomized controlled trial investigating the effect of a fully automated digital cognitive behavioral therapy for insomnia (dCBT-I) program on insomnia severity, sleep-wake patterns, sleep medication use, and daytime impairment. The study design was comprised of a parallel-group superiority randomized controlled trial comparing dCBT-I with online patient education about sleep. The interventions were available through a free-to-access website, publicized throughout Norway, which incorporated automated screening, informed consent, and randomization procedures, as well as outcome assessments. Adults (age ≥18 years) who had regular internet access and scored 12 or higher on the Insomnia Severity Index (ISI) were eligible for inclusion and were allocated (1:1) to receive dCBT-I (consisting of six core interactive sessions to be completed over 9 weeks) or patient education (control group). Participants were masked to group assignment and had no contact with researchers during the intervention period. The primary outcome was the change in ISI score from baseline to 9-week follow-up, assessed in the intention-to-treat population. After screening, a total of 1721 participants were randomly allocated (868 to receive dCBT-I and 853 to receive patient education). At 9-week follow-up, 584 (67%) participants in the dCBT-I group and 534 (63%) in the patient education group completed the ISI assessment. The

latent growth model showed that participants in the dCBT-I group had a significantly greater reduction in ISI scores from baseline (mean score 19·2 [SD 3·9]) to 9-week follow-up (10·4 [6·2]) than those in the patient education group (from 19·6 [4·0] to 15·2 [5·3]; estimated mean difference -4·7 (95% CI -5·4 to -4·1; Cohen's d -1·21; p<0·001). Compared with patient education, the number needed to treat with dCBT-I was 2·7 (95% CI 2·4 to 3·2) for treatment response (ISI score reduction ≥8) and 3·2 (2·8 to 3·8) for insomnia remission (ISI score <8). No adverse events were reported to the trial team. The authors concluded that dCBT-I is effective in reducing the severity of symptoms associated with the insomnia disorder, and the study findings support the widespread dissemination of dCBT-I.

In an Evolving Evidence Review (Hayes 2023) on Somryst concluded there is moderate evidence supporting Somryst in the treatment of insomnia and stated "Clinical studies showed greater reduction in symptoms of chronic insomnia with Somryst than sham (1 RCT) and online patient education (3 RCTs). These studies used an online version of the program rather than the currently available smartphone/tablet application. Current evidence does not compare Somryst with conventional cognitive behavioral therapy (CBT). However, when administered under the supervision of a qualified clinician, Somryst may present a convenient alternative to conventional CBT for patients who prefer its format. No guidelines recommending for or against the use of Somryst were identified. A large number of potentially relevant ongoing studies were identified, indicating frequent monitoring of the literature for new studies is warranted."

Prescription Digital Therapeutics for Psychiatric, Behavioral, and/or Cognitive Conditions

EndeavorRx™ (Akili Interactive Labs, Inc.) for Attention-deficit/hyperactivity disorder (ADHD)
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. Delivered through an action video game experience, EndeavorRx 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. 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
EndeavorRx received FDA approval on June 15, 2020, through the De Novo clearance process under the product code QFT and De Novo number DEN200026. It is classified as a digital therapeutic software for attention deficit hyperactivity disorder.

Kollins et al. (2020) evaluated the PDT 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) for Post-traumatic stress disorder (PTSD) and Panic Disorder (PD)
Freespira is an adjunctive treatment to reduce panic symptoms in patients with PD or PTSD. The treatment

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. The treatment measures respiration rate and exhaled CO2 levels in real time, graphically displaying physiological data, and then 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.

Regulatory Status
Freespira received FDA approval on August 23, 2018, through the 510(k)-clearance process under the product codes: HCC, CCK and 510(k) number: K180173. It is classified as a biofeedback device.

Cuyler et al. (2022) reported real world outcomes of Capnometry Guided Respiratory Intervention (CGRI), of which Freespira is based, in a series of patients treated with the intervention in clinical practice. A total of 1,395 patients met symptom criteria for PD, and 174 met criteria for PTSD. Participants were assessed by a healthcare professional and then treated using the 28-day intervention in their homes, supported by telehealth coaching. The metrics measured were pre- and post-treatment self-reported symptom reduction via Panic Disorder Severity Scale (PDSS) and the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) scores, measures of respiratory rate and end-tidal carbon dioxide levels, drop-out and adherence rates drawn from an automatic data repository in a large real-world series of patients receiving CGRI for panic disorder and PTSD. PD patients showed a mean pre-to-post-treatment reduction in total PDSS scores of 50.2% ($P < 0.001$, $d = 1.31$). Treatment response rates for PD (defined as a 40% or greater reduction in PDSS total scores) were observed in 65.3% of the PD patients. PTSD patients showed a pre-to-post-treatment reduction in total PCL-5 scores of 41.1% ($P < 0.001$, $d = 1.16$). The treatment response rate for PTSD (defined as a ≥10-point reduction in PCL-5 scores) was 72.4%. In an additional analysis of response at the individual level, 55.7% of panic disorder patients and 53.5% of PTSD patients were classified as treatment responders using the Reliable Change Index. Patients with both normal and below-normal baseline exhaled CO2 levels experienced comparable benefit. Across the 28-day treatment period, mean adherence rates of 74.8% (PD) and 74.9% (PTSD) were recorded during the 28-day treatment. Dropout rates were 10% (PD) and 11% (PTSD) respectively. The authors concluded the results from this cohort of 1,569 patients treated with the CGRI intervention demonstrate significant rates of symptom reduction and adherence consistent with prior published clinical trials. The brief duration of treatment, high adherence rates, and clinical benefit suggests that CGRI provides an important addition to treatment options for panic disorder and PTSD.

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.

An Evolving Evidence Review (Hayes 2024) concluded the research support for Freespira was minimal and stated "Evidence from 1 poor-quality and 1 very poor-quality single-arm study suggests that the Freespira is associated with clinically significant benefits in panic symptom severity and reduction of number of panic attacks per week for adults with panic disorder. These benefits reflect changes from baseline; no comparison with alternative therapies was made. High patient satisfaction was reported in both studies. While 1 study documented several self-resolving mild and moderate complications, neither reported any serious adverse events associated with Freespira. Although multiple practice guidelines outline recommendations for panic disorder in general, none specifically address the use of Freespira. Clinical studies with larger sample sizes that compare the Freespira device with standard treatment options, such as cognitive behavioral therapy, exposure therapy, or drug therapy, are necessary before its effectiveness can be verified and to inform selection of Freespira among competing alternatives."

NightWare (Apple Watch®) for PTSD-driven Traumatic Nightmares
NightWare, exclusively for Apple Watch, monitors heart rate and body movement using a gyroscope and accelerometer. The data is 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 PTSD. NightWare is intended for home use under the supervision of a health care provider as an adjunct to prescribed medications and other recommended therapies for PTSD associated nightmares.

Regulatory Status
NightWare received FDA approval on November 6, 2020, through the De Novo clearance process under the product code QMZ and De Novo number DEN200033. It is classified as a digital therapy device to reduce sleep disturbances for psychiatric conditions.

Davenport and Werner (2023) conducted a randomized sham-controlled clinical trial to determine the efficacy of a novel wearable device-based application (NightWare) in 65 veterans with impaired sleep secondary to trauma-related nightmares. Changes in measures of sleep quality, posttraumatic stress disorder/depression symptoms, and quality of life across the 30-day trial were compared between the Active and Sham systems. The results revealed that while the effects associated with the Active condition were consistently of greater magnitude than those associated with Sham, no difference between conditions reached statistical significance, indicating that the effects of the intervention could not be distinguished from those of other contributions to treatment response (e.g., expectations, motivation, individual differences) with the current sample size. The authors repeated the analyses excluding the 17 participants (9 Active, 8 Sham) who used the device fewer than 50% of nights (median usage: Active 33%, Sham 39%) to determine whether under-utilization contributed to under-estimation of effects. Within this "high usage" subsample (median usage: Active 74%, Sham 75%), the Active condition was associated with significantly greater improvement, compared to Sham, on the PSQI (4.1 vs 1.9; P = .016, d = 0.72) and NWL (6.1 vs 2.7; P = .002, d = 0.94). Overall, these results provide preliminary evidence that a wearable device may improve self-reported sleep quality for veterans reporting frequent trauma-related nightmares, especially in compliant users.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
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 (Healthcare Common Procedure Coding System)

Code	Description
A9291	Prescription digital cognitive and/or behavioral therapy, FDA cleared, per course of treatment
A9292	Prescription digital visual therapy, software-only, 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 (CBT), including pre-programmed therapy software

	(e.g., RelieVRx)
S9002	Intravaginal motion sensor system, provides biofeedback for pelvic floor muscle rehabilitation device (e.g., Leva Pelvic Health System)
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

12/11/2024 Policy reviewed. No change in coverage criteria. Updated Summary of Medical Evidence and References.
04/10/2024 Policy reviewed. No change in coverage criteria. IRO Peer Reviewed on March 20, 2024, by a practicing physician board certified in Internal Medicine.
04/13/2023 Policy reviewed. No changes to coverage criteria.
02/08/2023 Policy updated with multiple new PDTs.
04/13/2022 New policy.

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