Molina Clinical Policy
Prescription Digital Therapeutics: Policy No. 412
Last Approval: 4/13/2022
Next Review Due By: April 2023

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 includes technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes, including concepts such as mobile health (mHealth), telehealth (i.e., telemedicine), smart devices, sensors, and wearable's, health information technology, and personalized medicine. **Digital therapeutics (DTx)** is a class of digital health solutions that provide “evidence-based therapeutic interventions driven by high-quality software programs to prevent, manage, or treat a medical disorder or disease,” (Digital Therapeutics Alliance). Similar to pharmacological agents and medical devices, DTx is reviewed and cleared or approved by the U.S. Food and Drug Administration (FDA) and available over the counter (OTC) or by prescription.

Prescription Digital Therapeutics (PDT) 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). PDT is authorized by the U.S. FDA to treat diseases through an approved label and 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; and
  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 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, 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 general public for download including over-the-counter or direct-to-consumer applications, promote general wellness or operated by a healthcare practitioner in a clinical setting for remote health monitoring are not addressed in this policy.

COVERAGE POLICY

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 include, but are not limited to, the following (list is not all inclusive):

- BlueStar Rx
- Canvas Dx
- d-Nav Insulin Guidance System
- Endeavor Rx
- Freespira
- Halo AF Detection System
- Ieva Pelvic Health System
- Insulia
- My Dose Coach
- Nerivio
- NightWare
- reset
- reSET-O
- Somryst

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

REGULATORY STATUS and SUMMARY OF MEDICAL EVIDENCE

The PDTs outlined below are not inclusive of all PDTs *available on the market but include those with relatively more available data, clinical trials, published peer-reviewed literature, or systematic reviews. However, the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

*22 PDTs are on-market / available as of Jan 31, 2022, with 14 PDTs authorized by FDA and 8 launched under FDA's COVID Emergency Use Authorization (EUA).

Device (Software Developer)	**Summary of Supporting Evidence**
Type 2 Diabetes Mellitus Published peer-reviewed evidence was identified for 4 PDTs, including Insulia Diabetes Management Companion (predicate name, the DIABEO System), the d-Nav Diabetes Insulin Guidance System, BlueStar, and My Dose Coach (discussed below).	
BlueStar Rx (WellDoc) BlueStar Rx is a digital health platform for Type 1 (T1) and Type 2 (T2) diabetes 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	*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-randomized clinical trial (RCT) to assess whether the addition of mobile application coaching and patient/provider web portals to community primary care compared to standard diabetes

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 over-the-counter (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. On the basis of 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)

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 log-ins 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) 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 hemoglobin A1c 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. FDA Product Code: NDC. February 4, 2019	Current data is limited to a single study of small sample size, and long-term data on net health outcomes are currently lacking. 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) [predecessor, DIABEO system] 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* 510(k) marketing clearance: K202596 (June 2021); K172177 (Nov 2017); K170669 (June 2017); K161433 (Sep 2016). FDA Product Code: NDC	Clinical outcomes have not been reviewed by the FDA; therefore, the cited clinical study below does not establish any efficacy claim for Insulia in the United States (DTxAlliance 2022; accessed March 2022). 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 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.)

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-mo 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.

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	Pending	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

Hayes. A Health Technology Assessment (HTA, Mar 14, 2022) concluded that there is low-quality of evidence suggesting that PDTs are safe and may be associated with clinically significant reductions in hemoglobin A1c (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 in regard to 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.

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 (EASD), 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): The AACE, in its guidelines on the use of advanced technologies in the management of DM published in 2021, strongly recommended the use of telemedicine, including smartphone-web interactions, periodic supervision by healthcare professional/provider interactions to educate, to remotely monitor glucose and/or insulin data for therapeutic adjustments, and to improve outcomes (Grunberger et al., 2021). The guideline also recommended the use of clinically validated smartphone apps by persons with DM 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 exercise tracking) (Grunberger et al., 2021). However, there is no mention of PDTs in this report.

National Institute for Health and Care Excellence (NICE): The NICE has 2 evidence-based practice guidelines related to the management of both type 1 DM (T1DM) (Type 1 Diabetes in Adults: Diagnosis and Management [NG17], updated July 2021) and T2DM (Type 2 Diabetes in Adults: Management [NG28], updated November 2021). No specific recommendations for PDTs were mentioned in either guideline; however, cell-based therapies for achieving HbA_{1c} targets are included as a key recommendation for future research (NICE, 2021a; NICE, 2021b).

Canvas Dx™ (Cognoa, Inc.)

Canvas Dx is a diagnostic tool indicated as an aid in the diagnosis of Autism Spectrum Disorder (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 in evaluating a child's 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.

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,

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.	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.) EndeavorRx is software 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. One prescription will provide 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 through the De Novo pathway (DEN200026) under 21 CFR 882.5803. It is defined by FDA as "a software intended to provide therapy for ADHD or any of its individual symptoms as an adjunct to clinical supervised treatment." It is indicated to improve attention function as measured by computer-based testing in children ages 8-12 years old with primarily inattentive or combined-type ADHD, who have a demonstrated attention issue. FDA Product Code: QFT (2020)	Kollins et al. (2020) evaluated the DTx for improved attentional performance in pediatric patients with attention-deficit hyperactivity disorder (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 Test of Variables of Attention (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 commensurate to generally accepted standards of medical practice.

Freespira (PaloAlto Health Sciences, Inc) Freespira is an adjunctive treatment to reduce panic symptoms in patients with panic disorder or posttraumatic stress disorder (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. *Regulatory Status* 510(k) marketing clearance (K180173) as substantially equivalent to a marketed predicate device. FDA states it is for the intended use as a relaxation treatment for the reduction of stress by leading the user through guided and monitored breathing exercises. The device is indicated as an adjunctive treatment of symptoms associated with panic disorder and/or PTSD to be used under the direction of a healthcare professional, together with other pharmacological and/or nonpharmacological interventions. (2018) The initial 510 (k) clearance was in 2013 (K131586) under the name Canary Breathing System. FDA Product code: HCC, CCK (2013)	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 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. The currently available evidence assessment for Freespira lacks comparisons with generally accepted standards of medical practice and is limited by the small sample size and bias due to loss at follow-up.
Halo AF Detection System™ (LIVMOR, Inc) The Halo AF Detection System is a wearable smartwatch device that provides continuous monitoring of pulse rhythm to detect atrial fibrillation (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.	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.

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)	
Ieva Pelvic Health System (Renovia Inc.) 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.	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. **Hayes** published an Evidence Analysis Research Brief, Ieva Pelvic Health System Digital Therapeutic for Female Urinary Incontinence, in which a review of abstracts suggests that there is currently insufficient published, peer-reviewed literature to assess the evidence related to the Ieva Pelvic Health System for treatment of female UI in a comprehensive assessment. **National and Specialty Organizations** Guidelines addressing the female urinary incontinence did not mention PDTs or have specific recommendations for DTx for female urinary incontinence. **American College of Obstetricians (ACOG).** A search for clinical guidance on ACOG Clinical Search did not yield any results (searched terms: *Digital therapeutic, Digital training, incontinence,* or *Ieva Pelvic Health System*). **American Urological Association (AUA)** Surgical treatment of female stress urinary incontinence (SUI): AUA/SUFU guideline (2017) did not mention digital training or the Ieva Pelvic Health System are not mentioned in this guideline. **National Institute for Health and Care Excellence (NICE)** The NICE guidelines do not specifically reference Ieva PHS: • Pelvic floor dysfunction: prevention and nonsurgical management [NG210] (2021) guideline suggests that women with pelvic floor dysfunction consider digital information sources as support. • Urinary incontinence and pelvic organ prolapse in women: management [NG123] (2019) guideline advises against utilizing perineometry or pelvic floor electromyography as biofeedback in PFM training.
Nerivio (Theranica Bio-Electronics Ltd.) 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 wireless device, self-applied to the upper arm, delivers transcutaneous electrical nerve stimulation, which is thought to disrupt pain soas they travel to the brain. 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	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

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

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.

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 over-the-counter 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 (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®) 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) 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 substance use disorder (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 substance abuse disorder (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	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

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. *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 device for psychiatric disorders*	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 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) reSET-O is intended to increase retention of patients with opioid use disorder (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 device 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-O. 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.)

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, 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 (Cognitive Behavioral Therapy for Insomnia) in patients 22 years of age and older with chronic insomnia. FDA Product Code: PWE. (2020)

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-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 [Insomnia Severity Index (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's Emergency Use Authorization. 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]
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 behavioral therapy, FDA cleared, per course of treatment Effective date: April 1, 2022
A9999	Miscellaneous DME supply or accessory, not otherwise specified
E1399	Durable medical equipment, miscellaneous [when specified as a mobile-based health management software application]
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

4/13/2022 New policy. IRO Peer Review. 3/20/2022. Practicing Physician.

REFERENCES

Government Agency

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database (search: "digital therapeutic"). Accessed from CMS.

U.S. Food and Drug Administration (FDA)

2. Center for Devices and Radiological Health 510(k) Premarket notification database: Summary of safety and effectiveness. Rockville, MD: FDA. Available from FDA. Accessed February 2022.
3. Digital Health Center of Excellence. Available from FDA. Accessed February 2022.
4. Developing the software precertification program: Summary of learnings and ongoing activities: 2020 update. Available from FDA.
5. Policy for device software function and mobile medical applications: guidance for industry and Food and Drug Administration staff. Available from FDA. Published September 27, 2019. Accessed February 2022.
6. Software as a Medical Device (SAMD): Clinical evaluation. Guidance for Industry and Food and Drug Administration Staff. Available from FDA. Published December 8, 2017. Accessed February 2022.
7. Digital health innovation action plan. Available from FDA. Accessed February 2022.
8. Guidance document. Enforcement policy for digital health devices for treating psychiatric disorders during the Coronavirus disease 2019 (COVID-19) public health emergency. Available from FDA. Published April 14, 2020. Accessed February 2022.

Center for Devices and Radiological Health (CDRH)
510(k) Premarket Notification Summary
9. BlueStar®Rx, (WellDoc, Inc.; Columbia, MD). No. K162532. 2017. Silver Spring, MD. Available from FDA. Accessed February 2022.
10. BlueStar®Rx, (WellDoc, Inc.; Columbia, MD). No. K190013. 2019. Silver Spring, MD. Available from FDA. Accessed February 2022.
11. BlueStar®Rx, (WellDoc, Inc.; Columbia, MD). No. K193654. 2020. Silver Spring, MD. Available from FDA. Accessed February 2022.
12. d-Nav System®. (Hygieia, Inc.; Livonia, MI). No. k181916. Available from FDA. Published February 4, 2019. Accessed February 2022.
13. DrowzleTM. (Resonea, Inc.; St. Louis, MO). No. KI73974. Available from FDA. Published July 14, 2019. Accessed February 2022.
14. EndeavorRx™. (Akili Interactive Labs Inc.; Philadelphia, PA). No. 21 CFR 882.5803. Available from FDA. Accessed on Feb 2022
15. Freespira, (Palo Alto Health Sciences, Inc.; Kirkland, WA). No. K180173. 2018. Silver Spring, MD. Available from FDA. Accessed February 2022.
16. Halo™ AF Detection System. (LIVMOR, Inc., Frisco, Tx). No. K201208. Available from FDA. Published September 23, 2020. Accessed February 2022.
17. Insulia®. (Voluntis S.A. Suresnes, France). No. K161433. Available from FDA. Published November 9, 2016. Accessed February 2022.
18. LIVMOR Halo AF Detection System™. (LIVMOR Inc; Irvine, CA). No. K201208 .2020. Silver Spring, MD. Available from FDA. Accessed February 2022.
19. NightWare™. (NightWare, Inc., Minneapolis, MN). No. DEN200033. Available from FDA. Published November 6, 2020. Accessed February 2022.
20. reSET-O®. (Pear Therapeutics, Inc.; Boston, MA). No. K173681. Available from FDA. Published May 23, 2019. Accessed February 2022.
21. Somryst®, (Pear Therapeutics, Inc; San Francisco, CA). No. K191716. 2020. Silver Spring, MD. Available from FDA. Accessed Feb 2022.

De Novo Classification
22. De Novo Classification Order for Cognoa ASD Diagnosis Aid, (Cognoa, Inc.; Palo Alto, CA) De Novo Number: DEN200069. Available from FDA. Accessed February 2022.
23. De Novo Classification Order for NightWare Kit (Apple iPhone, Apple Watch, Apple iPhone Charging Cable, Apple Watch Charging Cable). (NightWare, Inc.; Minneapolis, MI). De Novo Number: DEN200033. 2020. Silver Spring, MD. Available from FDA. Accessed February 2022.
24. De Novo Classification Decision Summary for EndeavorRx, (Akili Interactive Labs, Inc.; Boston, MA) De Novo Number: DEN200026. 2020. Silver Spring, MD. Available from FDA. Accessed February 2022.
25. Device Classification Under Section 513(f)(2)(De Novo). ReSet (Pear Therapeutics; Boston, MA). De Novo Number: DEN160018. Available from FDA. Accessed February 2022.

Prescribing Information and Compendia
1. BlueStar Rx. WellDoc. Available from WellDoc. Accessed February 2022.
2. EndeavorRx (Akili Interactive Labs, Inc.). Indications, safety and cautions. Available here. Accessed February 2022.
3. EndeavorRx (Akili Interactive Labs, Inc.). Products. Available here. Accessed February 2022.
4. Halo AF Detection System (LIVMOR, Inc.). Available here. Accessed February 2022.
5. Hygieia (The d-Nav way). Available from Hygieia. Accessed February 2022.
6. NightWare (Nightware, Inc.) Available from NightWare. Accessed February 2022.
7. Renovia Inc. Ieva Pelvic Health System: Digital therapeutic. Available from Renovia. Accessed February 2022.
8. Somryst (Pear Therapeutics, Inc.). Available from PearTherapeutics. Accessed February 2022.

Peer Reviewed Publications
BlueStar Rx
1. Agarwal P, Mukerji G, Desveaux L, et al. Mobile app for improved self-management of type 2 diabetes: Multicenter pragmatic randomized controlled trial. JMIR Mhealth Uhealth. 2019. Available here.
2. Cui L, Schroeder PR, Sack PA. Inpatient and outpatient technologies to assist in the management of insulin dosing. Clin Diabetes. 2020;38(5):462-473. doi:10.2337/cd20-0054.
3. Quinn CC, Shardell MD, Terrin ML, et al. Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. Diabetes Care. 2011;34(9):1934-1942.

CanvasDx
1. Abbas H, Garberson F, Glover E, Wall DP. Machine learning approach for early detection of autism by combining questionnaire and home video screening. J Am Med Inform Assoc. 2018; 25(8):1000-1007. https://doi.org/10.1093/jamia/ocy039.
2. Abbas H, Garberson F, Liu-Mayo S, et al. Multi-modular AI approach to streamline autism diagnosis in young children. Sci Rep. 2020; 10(1):5014. https://doi.org/10.1038/s41598-020-61213-w.
3. Kanne SM, Carpenter LA, Warren Z. Screening in toddlers and preschoolers at risk for autism spectrum disorder: evaluating a novel mobile-health screening tool. Autism Res. 2018;11(7):1038-1049. doi:10.1002/aur.1959.

Endeavor Rx
1. Akili Interactive Labs, Inc. EndeavorRx. Akili Interactive Labs. Available from Akili.

Freespira
1. Kaplan A, Mannarino AP et al. Evaluating the impact of Freespira on panic disorder patients' health outcomes and healthcare costs within the Allegheny Health Network. Appl Psychophysiol Biofeedback. 2020;45(3):175-181. https://doi.org/10.1007/s10484-020-09465-0.
2. Tolin DF, McGrath PB, Hale LR, et al. A multisite benchmarking trial of capnometry guided respiratory intervention for panic disorder in naturalistic treatment settings. Appl Psychophysiol Biofeedback. 2017;42(1):51-58.

Ieva Pelvic Health System
1. Rosenblatt P, McKinney J, Rosenberg RA, et al. Evaluation of an accelerometer-based digital health system for the treatment of female urinary incontinence: A pilot study. Neurourol Urodyn. 2019 Sep;38(7):1944-1952. doi: 10.1002/nau.24097. Epub 2019 Jul 16. PMID: 31310369; PMCID: PMC6852391.

2. Weinstein MM, Collins S, Quiroz L, et al. Multicenter Randomized controlled trial of pelvic floor muscle training with a motion-based digital therapeutic device versus pelvic floor muscle training alone for treatment of stress-predominant urinary incontinence. Female Pelvic Med Reconstr Surg. 2022 Jan 1;28(1):1-6. doi: 10.1097/SPV.0000000000001052. PMID: 33787561.

Nerivio
1. Ailani J, et al. The American Headache Society consensus statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039. doi: 10.1111/head.14153. Epub 2021 Jun 23. PMID: 34160823.
2. Grosberg B, Rabany L, Lin T, et al. Safety and efficacy of remote electrical neuromodulation for the acute treatment of chronic migraine: An open-label study. Pain Rep. 2021;6(4):e966.
3. Hershey AD, Irwin S, Rabany L, et al. Comparison of remote electrical neuromodulation (REN) and standard-care medications for acute treatment of migraine in adolescents: A post-hoc analysis [published online ahead of print, 2021 Jun 29]. Pain Med. 2021;pnab197.
4. Moisset X, Pereira B, et al. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. J Headache Pain. 2020;21(1):142. Published 2020 Dec 10. doi:10.1186/s10194-020-01204-4.
5. Yarnitsky D, Dodick DW, Grosberg BM, et al. Remote electrical neuromodulation (REN) relieves acute migraine: a randomized, double-blind, placebo-controlled, multicenter trial. *Headache*. 2019;59(8):1240-1252. doi:10.1111/head.13551.
6. Yarnitsky D, Volokh L, Ironi A, et al. Nonpainful remote electrical stimulation alleviates episodic migraine pain. Neurology. 2017;88(13):1250-1255. doi:10.1212/WNL.0000000000003760.

reSET
1. Campbell AN, Nunes EV, Matthews AG, et al. Internet-delivered treatment for substance abuse: A multisite randomized controlled trial [published correction appears in Am J Psychiatry. 2014 Dec 1;171(12):1338]. Am J Psychiatry. 2014;171(6):683-690.

reSET-O
1. Christensen DR, Landes RD, Jackson L, et al. Adding an internet-delivered treatment to an efficacious treatment package for opioid dependence. J Consult Clin Psychol. 2014; 82(6):964-972. doi: 10.1037/a0037496.
2. Institute for Clinical and Economic Review (ICER). Digital health technologies as an adjunct to medication assisted therapy for opioid use disorder. December 11, 2020. Available here.
3. Maricich YA, Bickel WK, Marsch LA, Gatchalian K, Botbyl J, Luderer HF. Safety and efficacy of a prescription digital therapeutic as an adjunct to buprenorphine for treatment of opioid use disorder. Curr Med Res Opin. 2021 Feb;37(2):167-173. doi: 10.1080/03007995.2020.1846022. Epub 2020 Dec 7. PMID: 33140994; PMCID: PMC8666102.
4. Maricich YA, Xiong X, Gerwien R, et al. Real-world evidence for a prescription digital therapeutic to treat opioid use disorder. Curr Med Res Opin. 2020b. Dec 7.
5. Velez FF, Colman S, Kauffman L, et al. Real-world reduction in healthcare resource utilization following treatment of opioid use disorder with reSET-O, a novel prescription digital therapeutic. Expert Rev Pharmacoecon Outcomes Res. 2020 Nov 4.

Somryst
1. Hagatun, S, Vedaa, Ø, Nordgreen, T, et al. The short-term efficacy of an unguided internet-based cognitive-behavioral therapy for insomnia: A randomized controlled trial with a six-month nonrandomized follow-up. Behav Sleep Med. 2019;17(2):137-155. https://doi.org/10.1080/15402002.2017.1301941. Accessed February 2022.
2. Ritterband LM, Thorndike FP, and Ingersoll Karen S. Effect of a web-based cognitive behavior therapy for insomnia intervention with 1-year follow-up. JAMA Psychiatry. 2017; 74(1):68-75. doi: 10.1001/jamapsychiatry.2016.3249.
3. Ritterband LM, Thorndike FP, Gonder-Frederick LA, et al. Efficacy of an internet-based behavioral intervention for adults with insomnia [published correction appears in Arch Gen Psychiatry. 2010 Mar;67(3):311]. Arch Gen Psychiatry. 2009;66(7):692-698. doi:10.1001/archgenpsychiatry.2009.66.
4. Shaffer, KM, Hedeker, D, Morin, CM, et al. Intra-individual variability in sleep schedule: Effects of an internet-based cognitive- behavioral therapy for insomnia program and its relation with symptom remission. Sleep. 2020; 43(12). https://doi.org/10.1093/sleep/zsaa115. Accessed February 2022.
5. Vedaa Ø, Kallestad H, Scott J. et al. Effects of digital cognitive behavioural therapy for insomnia on insomnia severity: a large-scale randomized controlled trial. Lancet Digit Health. 2020 Aug;2(8):e397-e406. doi: 10.1016/S2589-7500(20)30135-7. PMID: 33328044.
6. Vedaa, Ø, Hagatun, S, Kallestad, H, et al. Long-term effects of an unguided online cognitive behavioral therapy for chronic insomnia. J Clin Sleep Med. 2019;15(1):101-110. PMID: 30621837.

National and Specialty Organizations

1. Ailani J, et al. The American Headache Society consensus statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039. doi: 10.1111/head.14153. PMID: 34160823.
2. American Medical Association. Proposed guidelines aim for safe, effective mobile health apps. Published January 22, 2018. Available from AMA. Accessed February 2022.
3. Digital Therapeutics Alliance. Available from DTxAlliance. Accessed February 2022.
   - Understanding DTx / product library. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile BlueStar. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile d-Nav. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile EndeavorRx. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile Freespira. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile Insulia. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile Ieva. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile Nerivio. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile reSET. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile reSET-O. Available from DTxAlliance. Accessed February 2022.
   - DTx product profile Somryst. Available from DTxAlliance. Accessed February 2022.

Opioid Use Disorder (OUD)
4. Institute for Clinical and Economic Review (ICER). Digital health technologies as an adjunct to medication assisted therapy for opioid use disorder. December 11, 2020. Available from ICER. Accessed February 2022.

Diabetes Mellitus
5. Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology clinical practice guideline: The use of advanced technology in the management of persons with diabetes mellitus. Endocr Pract. 2021;27(6):505-537. doi:10.1016/j.eprac.2021.04.008.
6. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [published correction appears in Diabetologia. May 2019;62(5):873]. Diabetologia. 2018;61(12):2461-2498. doi:10.1007/s00125-018-4729-5.
7. Draznin B, Aroda VR, Bakris G, American Diabetes Association (ADA), et al. Diabetes technology: Standards of medical care in diabetes-2022. Diabetes Care. 2022;45(Supplement_1):S97-S112. doi:10.2337/dc22-S007.
8. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: Diagnosis and management [NG17]. Updated July 21, 2021b. Available from NICE. Accessed February 2022.
9. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: Management [NG28]. Updated November 24, 2021a. Available from NICE. Accessed February 2022.

Other Peer Reviewed Publications
1. Hayes. Available from Hayes. Accessed February 2022. Registration and login required.
   - Health technology assessment. Prescription digital therapeutics for management of type 2 diabetes mellitus. Mar 14, 2022.
   - Evidence analysis research brief: Ieva Pelvic Health System Digital Therapeutic for female urinary incontinence. Feb 17, 2022.
   - Evolving evidence review: Nerivio (Theranica Bio-Electronics Ltd.) for treatment of acute migraine episodes. Jul 23, 2021.
   - Evidence analysis research brief: EndeavorRx (Akili Interactive Labs, Inc.) interactive digital therapy for treatment of ADD/ADHD. July 2020.
   - Evidence analysis research brief: Freespira Digital Therapeutic (Freespira, Inc.) for treatment of panic disorder. Sep 15, 2021.
   - Health technology assessment: Mobile Medical Applications for substance use disorder – mobile medical applications for substance use disorder. May 7, 2021.

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. **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).

2. **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.

3. **Ieva Pelvic Health System:** An NCD for biofeedback therapy for urinary incontinence was identified (searched keywords *incontinence* and *Ieva Pelvic* in all documents on the CMS Advanced Search Database). Although the Ieva Pelvic Health System was not named specifically, the NCD states that home biofeedback therapy is not covered. The policy applies to biofeedback therapy provided by a practitioner in an office or other facility setting, according to the NCD. Biofeedback therapy for the treatment of urinary incontinence (30.1.1) is not covered as an appropriate use at home (Biofeedback Therapy for the Treatment of Urinary Incontinence (30.1.1), 2001).

4. **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).

5. **Type 2 Diabetes Mellitus:** No NCD on PDTs for T2DM was identified on March 2022 (searched keywords *diabetes OR mobile* in all documents on the CMS Advanced Search Database).

6. **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.