Exhibit 14

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA
Civil Action No. 1:19-cv-00272

MAXWELL KADEL, et al.,)
)
Plaintiffs,)
)
vs.)
)
DALE FOLWELL, in his official)
capacity as State Treasurer of)
North Carolina, et al.,)
)
Defendants,)
_____)

DEPOSITION OF DAN H. KARASIC, M.D.

Remote
September 20, 2021
9:00 a.m. Pacific Time

Prepared by:
Vicki L. O'Ceallaigh Champion, CR
Certificate No. 50534

Prepared for:

(Certified copy)

way at least that I know of.
BY MR. KNEPPER:
Q. Did you discuss the changes in Finland in your expert report?
MR. HASKEL: Objection to form, mischaracterizes testimony --
A. No. I would say if, you know, that in different countries, different national health systems, they can come up with different protocols, and -- but I'm not aware in these countries of denying care broadly to transpeople, that there, you know, can be vigorous debate in different countries about, you know, how much psychotherapy might be provided or, you know, whatever services might be provided, but I'm not aware that they have said in these countries that they have, you know, prohibited people from getting hormones and surgery.
As a matter of fact, each of these countries have national health care systems where that care in some ways is more easily available, because it's paid 100 percent by the government through their national health service, and the patients themselves are not responsible, you know, as far as I'm aware, of any expenses in any of those European countries.
MR. KNEPPER: I'm going to show you

Exhibit 1

BlueCross BlueShield of Illinois

Medical Policies

Medical Policies - Administrative

Print

Experimental, Investigational and/or Unproven Procedures/Services

Number: ADM1001.032

Effective Date: 10-01-2021

Coverage:

CAREFULLY CHECK STATE REGULATIONS AND/OR THE MEMBER CONTRACT

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

When the requested chemotherapeutic agent is being utilized in a regimen in combination with other chemotherapeutic agents, the entire regimen (including dose, frequency, and duration) must be consistent with recommendations in at least one authoritative source, including but not limited to FDA labeling and nationally recognized compendia or clinical guidelines such as National Comprehensive Cancer Network (NCCN) and CMS coverage policy. HCSC may require a provider to submit documentation from nationally recognized compendia, clinical guidelines, or active Phase III clinical trials supporting the requested regimen.

The following list of procedures/services **are considered experimental, investigational and/or unproven** as there is insufficient evidence to support long-term safety and/or efficacy.

Service/Procedure	Code(s)
Eye movement analysis without spatial calibration for concussion (EyeBOX®)	0615T

Tibial or peroneal vein endovascular arterialization (LimFlow Stent Graft System)	0620T
Excimer laser trabeculostomy for glaucoma (ExTra ELT)	0621T; 0622T
Cleerly Coronary®	0623T; 0624T; 0625T; 0626T
Viable Allograft Supplemental Disc Regeneration (VAST)	0627T; 0628T; 0629T; 0630T
Visible light hyperspectral imaging (HyperView™)	0631T
Therapeutic IntraVascular UltraSound (TIVUS™)	0632T
Flowsense™	0639T
Noncontact near-infrared spectroscopy studies of flap or wound (e.g., SnapshotNIR)	0640T; 0641T; 0642T
Non-pneumatic compression garment/controller (e.g., Dayspring™ system)	K1024, K1025, K1031, K1032, K1033
Transcatheter left ventricular restoration device implantation	0643T
Transcatheter implantation of coronary sinus reduction device	0645T
Transcatheter tricuspid valve implantation/replacement	0646T
Hemospray® Endoscopic Hemostat	C1052
Intravascular lithotripsy (Shockwave Medical Intravascular Lithotripsy [IVL] System)	C1761, C9764; C9765; C9766; C9767; C9772, C9773, C9774, C9775
Transoral esophageal mucosal integrity testing by electrical impedance (e.g., MiVU)	C9777
External upper limb tremor stimulator of the wrist (e.g., Cala Trio™)	K1018; K1019

Description:

Refer to Rationale for descriptions of services/procedures.

Rationale:

This policy was developed based on literature review using the PubMed database.

Eye Movement Analysis (EyeBOX)

Effective Date: 05/15/2021

Review: N/A

Eye movement analysis without spatial calibration for concussion (EyeBOX)	0615T

The EyeBOX is intended to measure and analyze eye movement as an aid in the diagnosis of concussion within one week of head injury in patients 5 through 67 years of age in conjunction with a standard neurological assessment of concussion. Using a proprietary processing algorithm and machine learning technology that measures and analyses eye movement while the patient watches a 220 second video, the device then calculates a score on a 0-20 scale based on these measurements and displays an EyeBOX classification based upon whether the scale value is above 10 or not. Scale values of 10 or more yield a positive classification that may correspond to eye movement that may be present in both patients with or without a concussion, while scale values under 10 yield a negative classification that may correspond with eye movement that is consistent with a lack of concussion.

In a cross-sectional case-control study, Bin Zahid et al. (2020) evaluated an automated eye-tracking algorithm as a biomarker for concussion. Concussed children (n=56; mean age of 13 years) were compared with 83 uninjured controls at a mean of 22-weeks post-injury. Metrics comparing velocity and conjugacy of eye movements over time were obtained and were compared with the correlation between Acute Concussion Evaluation (ACE) scores, convergence, and accommodation dysfunction. The subjects' eye movement were recorded with an automated eye tracker while they watched a 22-second cartoon film clip played continuously while moving within an aperture. Twelve eye-tracking metrics were significantly different between concussed and non-concussed children. A model to classify concussion as diagnosed by its symptoms assessed using the ACE achieved an area under the curve (AUC) = 0.854 (71.9% sensitivity, 84.4% specificity, a cross-validated AUC = 0.789). An eye-tracking model built to identify near point of convergence (NPC) disability achieved 95.8% specificity and 57.1% sensitivity for an AUC = 0.810. Reduced binocular amplitude of accommodation had a Spearman correlation of 0.752 (P value <0.001) with NPC. Researchers concluded that eye tracking correlated with concussion symptoms and detected convergence and accommodative abnormalities associated with concussion in the pediatric population.

Samadani et al. (2015) conducted a single-center prospective study (n=322) to determine the sensitivity and specificity of a novel eye tracking metric as a biomarker for concussion. Brain injured (n=34) and control subjects (n=34) underwent both eye tracking performed while watching television or a video moving inside an aperture with a set trajectory for 220 seconds, and Sport Concussion Assessment Tool 3. The results of eye tracking biomarker-based classifier models were then validated against a dataset of individuals not used in building a model (n=254; adults with concussion [n=7] and uninjured adults [n=247]). Significant group differences between brain injured and concussed subjects versus negative controls were found for 28 eye tracking metrics that were not influenced by age or gender. These were used to develop the three

classifier functions. In a sample of 21 concussion cases versus age and gender balanced uninjured controls, the 'best subset' model selected four metrics and the resulting receiver operating characteristic of the classifier had an area under the curve (AUC) of 0.878, and a cross-validated AUC of 0.852. The LASSO model selected two metrics and resulted in an AUC of 0.880 and a cross-validated AUC of 0.826. In an external dataset of 254 subjects (247 controls and 7 concussions), 'best subset' had a misclassification rate of 14.2%, LASSO had a misclassification rate of 13.8% and random forest had a misclassification rate of 13.0%. Researchers concluded that although current results are promising, additional data on potential confounders of eye tracking still need to be investigated. These include alcohol and other intoxicants, fatigue and prior history of trauma and neurologic or ophthalmic disorders among others.

In a 2020 Clinical Evidence Assessment, ECRI found the evidence on EyeBOX for aiding in the diagnosis of concussion to be "inconclusive – too few data on outcomes", and indicated that randomized controlled trials comparing standard concussion workup with and without EyeBOX and assessing patients within the one week specified by the U. S. Food and Drug Administration (FDA) label are needed to determine the efficacy of EyeBox in the diagnosis of concussions.

References:

1. Bin Zahid A, Hubbard ME, Lockyer J, et al. Eye tracking as a biomarker for concussion in children. Clin J Sport Med. Sep 2020; 30(5):433-443. PMID 30095503
2. Samadani U, Li M, Qian M, et al. Sensitivity and specificity of an eye movement tracking-based biomarker for concussion. Concussion. Aug 2015; 1(1):CNC3. PMID 30202548
3. ECRI Institute. EyeBox (Oculogica, Inc.) for Aiding Diagnosis of Concussion; Jun 2020 (Clinical Evidence Assessment).

LimFlow Stent Graft System

Effective Date: 01/01/2021

Updates: N/A

Review: N/A

Tibial or peroneal vein endovascular arterialization (LimFlow Stent Graft System)	0620T

LimFlow is a minimally invasive technology designed to divert blood around diseased arteries in the leg and into the tibial veins that feed the foot. This technique would bring blood and oxygen to the starved tissues in the foot, relieving pain and promoting healing of chronic wounds.

Schmidt et al. conducted a retrospective study of 32 patients suffering from no-option chronic limb-threatening ischemia (CLTI) treated with a dedicated system for percutaneous deep venous arterialization (pDVA) using the LimFlow device between July 2014 and June 2018. Of all patients, 21 (66%) had diabetes, 8 (25%) were on immunosuppression, 4 (16%) had dialysis-dependent renal failure, 9 (28%) had Rutherford category 6 ischemia, and 25

(78%) were deemed at high risk of amputation. The primary outcome was amputation-free survival (AFS) at 6 months. Secondary outcomes were wound healing, limb salvage, and survival at 6, 12, and 24 months. Technical success was achieved in 31 patients (96.9%). The median follow-up was 34 months (range 16-63). At 6, 12, and 24 months, estimates were 83.9%, 71.0%, and 67.2% for AFS, 86.8%, 79.8% and 79.8% for limb salvage, and 36.6%, 68.2%, and 72.7% for complete wound healing, respectively. Median time to complete wound healing was 4.9 months (range 0.5-15). The DVA circuit occluded during follow-up in 21 patients; the median time to occlusion was 2.6 months. Reintervention for occlusion was performed in 17 patients: 16 because of unhealed wounds and 1 for a newly developed ulcer. The authors concluded percutaneous deep venous arterialization could be a recommended treatment to prevent amputation and heal wounds.

References:

1. LimFlow System. Available at: <https://limflow.com> (accessed Sept. 22, 2020).
2. Schmidt A, Schreve MA, Huizing E, et al. Midterm Outcomes of Percutaneous Deep Venous Arterialization With a Dedicated System for Patients with No-Option Chronic Limb-Threatening Ischemia: The ALPS Multicenter Study. J Endovasc Ther. 2020 Aug; 27(4):658-665. PMID 32419597

ExTra Excimer Laser Trabeculostomy (ELT)

Effective Date: 01/01/2021

Updates: N/A

Review: N/A

Excimer laser trabeculostomy for glaucoma (ExTra ELT)	0621T; 0622T

Excimer laser trabeculostomy (ELT) is a microinvasive glaucoma surgery (MIGS) that creates multiple laser channels through the trabecular meshwork using a cold laser system, which minimizes tissue fibrosis and aids in bypassing the main area of resistance to aqueous outflow.

Durr et al. published a review of studies (1 randomized controlled trial [RCT], 4 prospective case series and 5 retrospective studies) on the use of excimer laser trabeculostomy for glaucoma. The authors found that non-head-to-head prospective randomized study comparing standalone ELT to trabecular bypass MIGS or trabeculotomies had been conducted. The best evidence was from an RCT comparing ELT to 180-degree selective laser trabeculoplasty (SLT). ELT appeared to outperform SLT although it was not statistically significant likely due to an underpowered study. There is a question as to if SLT is the best comparator, as SLT is an incision-less procedure. The authors concluded their review by stating that current available evidence shows an intra-ocular pressure lowering effect from ELT alone or in combination with cataract surgery with encouraging results across different studies and patient populations. There was less scarring using ELT than from traditional thermal lasers, as well as repeatability in different quadrants, ease of use and lower hyphema risks compared to ablative

procedures. The procedure also appears to have a favorable safety profile with few intraoperative or postoperative risks. More studies are needed to better characterize ELT further substantiate promising results.

References:

1. Durr GM, Töteberg-Harms M, Lewis R, et al. Current review of Excimer Laser Trabeculostomy. Eye and Vision. 2020; 7:24. PMID 32391398

Cleerly Coronary®

Effective Date: 01/01/2021

Updates: N/A

Review: N/A

Cleerly Coronary®	0623T; 0624T; 0625T; 0626T

Cleerly Coronary® is a web-based service that provides analysis of data obtained with a coronary computed tomography (CT) angiography. It assesses for coronary heart disease by quantifying and characterizing arterial plaque buildup.

No published clinical trial was located.

References:

1. Cleerly Coronary®. Available at: <https://cleerlyhealth.com> (accessed Nov. 5, 2020).

Viable Allograft Supplemental Disc Regeneration (VAST)

Effective Date: 01/01/2021

Update: N/A

Review: N/A

Viable Allograft Supplemental Disc Regeneration (VAST)	0627T; 0628T; 0629T; 0630T

Viable allograft supplemental disc regeneration (VAST) or Via Disc is a therapeutic percutaneous injection of the lumbar spine using an allogeneic cellular or tissue-based product to replace or supplement the disc tissue. It repairs or reconstitutes a damaged intra-vertebral disc.

The Viable Allograft Supplemented Disc Regeneration in the Treatment of Patients with Low Back Pain With or Without Disc Herniation (VAST) Trial was a prospective, randomized parallel-arm multicenter study approved to enroll up to 220 subjects at up to 15 clinical sites. The aim of the trial was to investigate the clinical relevance of treating painful intervertebral disc tissue by a supplementary transplantation of viable cellular allograft disc matrix and compare the cellular allograft with a saline placebo or continued treatment with sustained conservative care.

This interim analysis enrolled 24 subjects who were randomized to receive allograft or saline at either 1 or 2 levels or continue nonsurgical management (NSM). Data were collected at baseline, 3, 6, and 12 months. Back pain with

a visual analog scale (VAS) and disability by the Oswestry Disability Index (ODI) were assessed, as were adverse events. At 6 and 12 months, the VAS improved from 54.81, 55.25, and 62.255 in the allograft, saline, and NSM subjects, respectively, to 16.0 and 41.0 in the allograft and saline groups at 6 months, and 12.27 and 19.67, respectively, at 12 months. All subjects in the NSM cohort crossed over to allograft treatment. At 6 and 12 months, ODI improved from 53.73, 49.25, and 55.75 in the allograft, saline, and NSM subjects, respectively, to 18.47 and 28.75 in the allograft and saline groups 1 and 2 at 6 months, and 15.67 and 9.33, respectively, at 12 months. At 3 months the ODI of the NSM group was 62.75 and subjects reached 19.0 and 11.0 at 6 and 12 months, respectively. Adverse events were transient and resolved in all cohorts.

References:

1. Beall DP, Wilson GL, Bishop D, et al. VAST Clinical Trial: Safely Supplementing Tissue Lost to Degenerative Disc Disease. International Journal of Spine Surgery. 2020; 14(s):239-253. PMID 32355632

Visible light hyperspectral imaging (HyperView™)

Effective Date: 01/01/2021

Updates: N/A

Review: N/A

Visible light hyperspectral imaging (HyperView™)	0631T

HyperView™ is a handheld battery-operated portable device that utilizes a proprietary form of hyperspectral imaging to assess oximetry in superficial tissue. According to the product brochure, it “uses visible light and an internal spectrometer to differentiate light absorption between oxygenated hemoglobin and deoxygenated hemoglobin. Results are presented as color-coded images containing quantitative data which depict levels of oxyhemoglobin and deoxyhemoglobin, as well as oxygen saturation values. Built-in software tools allow the clinician to analyze various areas within the image corresponding to locations on the skin surface. This allows the clinician to determine areas of ischemic tissue and visualize arterial and venous sufficiency in localized tissue, for example the boundary around a diabetic foot ulcer.”

The U.S. Food and Drug Administration (FDA) granted approval of the HyperView™ device based on a predicate device developed by the same company. It is indicated for use by physicians and healthcare professionals as a noninvasive tissue oxygenation measurement system that reports an approximate value of oxygen saturation, oxyhemoglobin level and deoxyhemoglobin levels in superficial tissue for patients with potential circulatory compromise.

In 2009, Nouvong et al. published results from a prospective single-arm blinded study of 66 patients with type 1 and type 2 diabetes. Transcutaneous oxygen tension was measured at the ankles. Superficial tissue oxyhemoglobin (oxy) and deoxyhemoglobin (deoxy) were measured with hyperspectral imaging from intact tissue bordering the ulcer. A healing index

derived from oxy and deoxy values was used to assess the potential for healing. Fifty-four patients with 73 ulcers completed the study; at 24 weeks, 54 ulcers healed while 19 ulcers did not heal. When using the healing index to predict healing, the sensitivity was 80% (43 of 54), the specificity was 74% (14 of 19), and the positive predictive value was 90% (43 of 48). The sensitivity, specificity, and positive predictive values increased to 86, 88, and 96%, respectively, when removing three false-positive osteomyelitis cases and four false-negative cases due to measurements on a callus. The results indicate that cutaneous tissue oxygenation correlates with wound healing in diabetic patients. Hyperspectral imaging of tissue oxy and deoxy may predict the healing of diabetic foot ulcers (DFU) with high sensitivity and specificity based on information obtained from a single visit.

Chin et al. sought to determine if hyperspectral imaging could accurately assess the presence or absence of peripheral artery disease (PAD) and accurately predict PAD severity. In their prospective study patients with lower extremity edema were excluded. Patients underwent hyperspectral imaging at nine angiosomes on each extremity. Additional sites were imaged when tissue loss was present. Patients were separated into no-PAD and PAD groups. Differences in hyperspectral values between the groups were evaluated using the two-tailed t test. Analysis for differences in values over varying severities of PAD, as defined by triphasic, biphasic, or monophasic Doppler waveforms, was conducted using one-way analysis of variance. Hyperspectral values were correlated with the ABI using a Pearson bivariate linear correlation test. The study enrolled 126 patients (252 limbs). After exclusion of 15 patients, 111 patients were left for analysis, including 46 (92 limbs) no-PAD patients and 65 (130 limbs) PAD patients. Groups differed in age, diabetes, coronary artery disease, congestive heart failure, tobacco use, and insulin use. Deoxyhemoglobin values for the plantar metatarsal, arch, and heel angiosomes were significantly different between patients with and without PAD ($P < .005$). Mean deoxyhemoglobin values for the same three angiosomes showed significant differences between patients with monophasic, biphasic, and triphasic waveforms ($P < .05$). In patients with PAD, there was also significant correlation between deoxyhemoglobin values and ABI for the same 3 angiosomes ($P = .001$). Oxyhemoglobin values did not predict the presence or absence of PAD, did not correlate with PAD severity, and did not correlate with the ABI. The authors concluded the results suggest the ability of hyperspectral imaging to detect the presence of PAD; and hyperspectral measurements can also evaluate different severities of PAD.

References:

1. HyperView™ Product Brochure. Available at: <https://hypermed.com> (accessed Nov. 5, 2020)
2. U.S. Food and Drug Administration. HyperView 510(k) Summary. Available at: <https://accessdata.fda.gov> (accessed Nov. 5, 2020).
3. Nouvong A, Hoogwerf B, Mohler E, et al. Evaluation of Diabetic Foot Ulcer Healing with Hyperspectral Imaging of Oxyhemoglobin and Deoxyhemoglobin. Diabetes Care. 2009 Nov; 32(11):2056-2061. PMID 19641161

4. Chin JA, Wang EC, Kibbe MR. Evaluation of hyperspectral technology for assessing the presence and severity of peripheral artery disease. J Vasc Surg. 2011 Dec; 54(6):1679-88. PMID 21803525

Therapeutic IntraVascular UltraSound (TIVUS™)

Effective Date: 01/01/2021

Updates: N/A

Review: N/A

Therapeutic IntraVascular UltraSound (TIVUS™)	0632T

Therapeutic intravascular ultrasound (TIVUS) is an investigational intravascular treatment that can be performed as part of a right heart catheterization for patients suffering from pulmonary arterial hypertension (PAH) according to the manufacturer website. (11) A catheter-based technology, it causes denervation of nerves surrounding blood vessels and other structures like the bronchus. Per information on the manufacturer website, “the catheter generates non-focused ultrasound waves that pass through the flowing blood and through the wall of the artery where the energy is taken up by the tissue outside of the blood vessel, specifically the nerve bundles. It results in the nerves being heated to the point of causing necrosis and the nerves effectively become ablated, losing their ability to pass signals. This results in a decrease in sympathetic hormones that are released from the nerves. This reduction in hormones results in the blood vessels relaxing, reducing the resistance in the vessels, reducing the pressure in the vessels and in pulmonary hypertension, reduces the resistance in the right side of the heart, potentially leading to improvements in exercise tolerance.”

Rothman et al. published the results of an early feasibility study on TIVUS in 2020. The aim of this study was to investigate whether therapeutic intravascular ultrasound pulmonary artery denervation (PDN) is safe and reduces pulmonary vascular resistance (PVR) in patients with PAH on a minimum of dual oral therapy. TROPHY1 (Treatment of Pulmonary Hypertension 1) was a multicenter, international, open-label trial undertaken at 8 specialist centers. Patients 18 to 75 years of age with PAH were eligible if taking dual oral or triple non-parenteral therapy and not responsive to acute vasodilator testing. Eligible patients underwent PDN (TIVUS System). The primary safety endpoint was procedure-related adverse events at 30 days. Secondary endpoints included procedure-related adverse events, disease worsening and death to 12 months, and efficacy endpoints that included change in pulmonary hemodynamic status, 6-min walk distance, and quality of life from baseline to 4 or 6 months. Patients were to remain on disease-specific medication for the duration of the study. Twenty-three patients underwent PDN, with no procedure-related serious adverse events reported. Pulmonary vascular resistance (PVR) was reduced 17.8% at 4- or 6-month follow-up which was associated with a 42-minute increase in 6-min walk distance as well as an increase in daily activity. In this multicenter early feasibility study, PDN with an intravascular ultrasound catheter was performed without procedure-related adverse events and was associated with a reduction in PVR and increases in 6-min walk distance and daily activity in patients with PAH on background dual or triple therapy. The authors

concluded further studies are required to evaluate the efficacy, durability, safety, and long-term clinical impact of PDN in patients with pulmonary hypertension of various forms.

References:

1. TIVUS™. Available at: <https://sonivie.com> (accessed Nov. 6, 2020).
2. Rothman AMK, Vachiery JL, Howard LS, et al. Intravascular Ultrasound Pulmonary Artery Denervation to Treat Pulmonary Artery Hypertension (TROPHY1). JACC Cardiovasc Interv. 2020 Apr 27; 13(8):989-999. PMID 32327095

Flowsense™

Effective Date: 01/01/2021

Updates: N/A

Review: N/A

Flowsense™	0639T

Flowsense™ is a wireless, noninvasive thermal flow sensor that can be mounted on a patient's neck overlying a ventricular shunt placed to treat hydrocephalus to detect the presence and magnitude of cerebrospinal fluid (CSF). Composed of soft silicone, there are no hard edges and is similar in size to a bandage. Data is wirelessly transmitted to a custom designed mobile app.

A development article published by Krishnan et al. in 2020 looked at the use of a wearable, wireless sensor placed on 7 hydrocephalus patients. According to the article, a Bluetooth Low-Energy System on a Chip (BLE-SoC) embedded system architecture allowed for robust, high quality data transfer during normal patient activities, where a miniaturized on-board, rechargeable battery supports continuous operation for several hours. On-body measurements and field trials on those patients revealed reliable operation during both spot-checks and extended measurements of flow during natural motions of the body as well as for different orientations. The authors state the results suggest broad applicability for monitoring of shunts in patients across age ranges, pathologies, and settings, including the home.

References:

1. Flowsense. Available at: <https://www.rhaeos.com> (accessed Nov. 6, 2020).
2. Krishnan SR, Arafa HM, Kwon K, et al. Continuous, noninvasive wireless monitoring of flow of cerebrospinal fluid through shuts in patients with hydrocephalus. NPJ Dig Med. 2020 Mar 6; 3:29. PMID 32195364

Noncontact Near-Infrared Spectroscopy Studies of Flap or Wound

Effective Date: 07/01/2021

Updates: N/A

Review: N/A

Noncontact near-infrared spectroscopy studies of flap or wound (e.g., SnapshotNIR™)	0640T, 0641T, 0642T

Oxygen plays an integral role in all phases of the wound healing process, with adequate tissue oxygenation being a key determinant of successful wound healing. The U.S. Food and Drug Administration (FDA) approved the SnapshotNIR™ under the 510(k) clearance process as a non-invasive tissue oxygenation measurement system. (1) Using a near-infrared (NIR) reflectance-based technology, SnapshotNIR™ measures relative amounts of oxygenated and deoxygenated hemoglobin in the microcirculation where oxygen exchange is happening, purportedly providing users with a tissue oxygenation map that can be used in medical decision making (i.e., for tracking and trending oxygenation, and for evaluating tissue viability). (2)

In a 2019 Product Brief, ECRI did not identify any relevant clinical studies published as full articles to inform decision about how well the SnapshotNIR™ non-invasive tissue oxygenation measurement system works for plastic surgery procedures or how it compares to similar products. (3) (Evidence is inconclusive)

Hill et al. (2020) undertook a pilot study to evaluate the capacity of NIR spectroscopy to detect clinically relevant differences is tissue perfusion intraoperatively. (4) Patients undergoing oncologic resection of breast cancer, sarcomas, and cutaneous tumors requiring flap reconstruction (local, regional, or free) between January 2018 and January 2019 were analyzed in this study. Clinicians were blinded to device tissue oxygen saturation (StO2) measurements taken intraoperatively after closure and at follow-up appointments in the first 30 days. Measurements were categorized as 1) control areas not affected by the procedure, 2) areas at risk, and 3) areas of necrosis. These areas were retrospectively demarcated by 2 blinded assessors on follow-up images and transposed onto anatomically correlated intraoperative StO2 measurements. Mean StO2 values were compared using a single-sample *t* test and analysis of variance (ANOVA) to determine differences in oxygenation. Forty-two patients were enrolled, and 51 images were included in the analysis. Oncologic procedures were predominantly breast (22), post-extirpative melanoma (13), and sarcoma (3) reconstructions. Flap reconstruction involved 30 regional skin flaps, 3 pedicled flaps, and 3 free flaps. Nine patients (20.9%) and 11 surgical sites developed skin flap necrosis (SFN). Mean intraoperative StO2 measurements for control areas, areas at risk, and areas of SFN were 74.9%, 71.1%, and 58.3%, respectively. Relative to control areas, mean intraoperative StO2 measurements were lower by 17.5% ($P = 0.01$) in ultimate areas of SFN and in areas at risk by 5.8% ($P = 0.003$). Relative to areas at risk, mean StO2 measurements from areas of ultimate SFN were lower by 8.3% ($P = 0.04$). These preliminary data suggest that measuring skin flap tissue oxygenation intraoperatively, with NIR spectroscopy, can differentiate objective variations in perfusion that are associated with clinical outcomes.

Serena et al. (2020) conducted a pilot study comparing measurement of tissue oxygenation of NIR spectroscopy with transcutaneous oxygen measurement (TCOM) in patients with acute and hard-to-heal wounds. (5) The Shapiro-Wilk test was used to evaluate the normality of the data. The

level of agreement between NIR spectroscopy and TCOM was determined using Bland-Altman analysis. The relationship between TCOM and NIRS was examined using Pearson correlation. A total of 24 observations were obtained from 10 patients using TCOM and NIR spectroscopy. The weighted mean partial pressure of oxygen (pO) in the study population was 39.54mmHg (8.96 standard deviation). Bland-Altman analysis showed that mean difference was positive (18.75), suggesting an overestimation of oxygen measurements using TCOM compared with NIR spectroscopy. The oxygen levels measured by TCOM and NIR spectroscopy showed a strong correlation (r=0.74). The wound and hyperbaric community would benefit from a simplified procedure for measuring tissue oxygenation. These findings suggest a strong trend toward correlation between NIR spectroscopy and TCOM. A further study in a larger population is recommended.

References:

1. FDA – Medical devices. 510(k) Summary: Kent Camera (K113507). Food and Drug Administration – Center for Devices and Radiologic Health. Available at <https://www.fda.gov> (accessed May 10, 2021).
2. Kent Imaging. SnapshotNIR. Available at <https://www.kentimaging.com> (accessed May 10, 2021).
3. ECRI Institute. SnapshotNIR Camera (Kent Imaging, Inc.) for Assessing Tissue Perfusion during Plastic Surgery; Aug 2019. (Product Brief).
4. Hill WF, Webb C, Monument M, et al. Intraoperative near-infrared spectroscopy correlates with skin flap necrosis: A prospective cohort study. Plast Reconstr Surg Glob Open. Apr 2020; 8(4):e2742. PMID 32440412
5. Serena TE, Yaakov R, Serena L, et al. Comparing near infrared spectroscopy and transcutaneous oxygen measurement in hard-to-heal wounds: a pilot study. J Wound Care. Jun 2020; 29(sup6):S4-S9. PMID 32530756

Non-Pneumatic Compression Garment/Controller

Effective Date: 10/01/2021

Updates: N/A

Review: N/A

Non-pneumatic compression garment/controller (e.g., Dayspring™ system)	K1024, K1025

The Dayspring™ system by Koya Medical is an FDA-cleared device that employs sequential gradient compression to treat and manage lymphedema and provides patients with mobility during treatment. It is also indicated for venous insufficiency and is used to promote wound healing. The device provides compression through segments that contract and relax flexible frames in a segmental appliance without the use of air. When a patient uses the compressor in conjunction with the appliance, the device creates the desired, calibrated, gradient pressures in the appliance and moves excess fluid in a rhythmic, distal to proximal manner.

In an open-label pilot study in 40 subjects, Rockson et al. (2021) evaluated the quality of life (QoL) and limb volume maintenance efficacy of a novel wearable compression system (Dayspring™). (1) Authors reported that after 28 days of use, subjects had a statistically significant 18% ($p < 0.001$) improvement in overall QoL as measured by the Lymphedema Quality-of-Life Questionnaire compared with baseline. Individual QoL domains, and limb volume improved with therapy. Adherence was 98% over the course of the study. Researchers concluded that results of the clinical evaluation suggest the Dayspring™ wearable compression device is safe and effective and improves QoL and limb volume.

Large, multicenter, randomized controlled trials comparing Dayspring™ with pneumatic compression and other lymphedema treatments, along with long-term patient-oriented outcomes are still needed. There are several ongoing clinical trials on this product that may partially address these evidence gaps.

References:

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Transcatheter Left Ventricular Restoration Device Implantation

Effective Date: 07/01/2021

Updates: N/A

Review: N/A

Transcatheter left ventricular restoration device implantation	0643T

The Less Invasive Ventricular Enhancement (LIVE) procedure is based on a law of physics which describes how the shape and pressure inside of the left ventricle can create stress on the heart. Heart failure symptoms worsen as the stress on the left ventricle increases, and the only way to stop the progression of heart failure is to reduce the stress on the left ventricle. The LIVE procedure is designed to reduce this wall stress by restoring the functionality of the left ventricle.

Performed by both an interventional cardiologist and cardiac surgeon, the LIVE procedure uses the Revivent TC™ Ventricular Enhancement System to implant micro-anchor pairs into the scar tissue of the heart. The internal anchor is placed inside the right ventricle" of the heart through the jugular vein in the neck. The external anchor is placed on the outside of the left ventricle through a small incision on the left side of the chest. Once the anchors are in position, they are pulled toward each other resulting in the anchor pairs excluding the scar tissue from the healthy tissue on the left ventricle. This isolates the nonfunctioning part of the heart muscle and allows the remaining healthy tissue to work more effectively. An average of 2-3 anchor pairs are typically implanted and remain in the heart once the procedure is finished. Currently, the LIVE procedure is performed in the U.S. at participating clinical trial centers as part of an investigational study. (1)

1. BioVentrix. ALIVE Patient Brochure. Available at <https://www.bioventrix.com> (accessed May 10, 2021)

Transcatheter Implantation of Coronary Sinus Reduction Device

Effective Date: 07/01/2021

Updates: N/A

Review: N/A

Transcatheter implantation of coronary sinus reduction device	0645T

Refractory angina is a debilitating condition that affects millions globally. Currently CE marked in Europe, the Neovasc Reducer™ is a wire mesh implanted into a vein in the heart. It provides relief of angina symptoms by altering blood flow within the myocardium of the heart and increasing the perfusion of oxygenated blood to ischemic area of the heart muscle. The device is placed using a minimally invasive transvenous procedure that is similar to implanting a coronary stent and is completed in approximately 20 minutes. (1) In January 2021, Neovasc Inc. announced that it had received a not-approvable letter from the FDA regarding its premarket approval submission for the Neovasc Reducer for the treatment of refractory angina. (2)

References:

1. Neovasc Inc. Neovasc Announces First Neovasc Reducer™ Implants in France. Available at <https://www.globenewswire.com> (accessed May 11, 2021).
2. Cardiac Interventions Today. FDA Does Not Approve Neovasc's Reducer. Available at <https://www.citoday.com> (accessed May 11, 2021).

Transcatheter Tricuspid Valve Implantation/Replacement

Effective Date: 07/01/2021

Updates: N/A

Review: N/A

Transcatheter tricuspid valve implantation/replacement	0646T

The tricuspid valve directs blood flow from the right atrium into the right ventricle. Tricuspid regurgitation (TR) occurs when the tricuspid valve does not close properly, allowing blood to flow backwards from the ventricle to the atrium. The gold standard for treating tricuspid valve disease is surgical annuloplasty. Presently there are no FDA-approved devices to be delivered in the tricuspid position. Devices for transcatheter tricuspid valve replacement are in the early stages of development.

Hahn et al. (2018) presented a single-site experience of 5 patients with severe TR who underwent implantation of a novel transcatheter tricuspid valve replacement (TTRV) device. (1) All patients had: 1) symptomatic,

massive and/or torrential TR at baseline, 2) computed tomography, transthoracic and transesophageal echocardiographic assessment of the tricuspid valve and right heart anatomy, and 3) a surgical transatrial approach performed with valve implantation guided by fluoroscopy and intraprocedural transesophageal echocardiography. Baseline characteristics of the patients showed a substantial burden of comorbidities. All patients had successful implantation of the transcatheter valve, with significant reduction of TR to ≤2+. Baseline poor right ventricular (RV) function measured by global longitudinal strain and RV change in pressure divided by change in time were associated with post-implantation RV failure and poor clinical outcomes in this small group. Four of the 5 patients were followed for 3 to 6 months following the initial implantation and showed evidence of RV remodeling, increased cardiac output, and reduction in New York Heart Association functional class. Researchers concluded that implantation of a first-generation TTVR device was technically feasible in patients with more than severe TR. Transcatheter tricuspid valve replacement was associated with RV remodeling, increased cardiac output, and improvement in New York Heart Association functional class in most patients. Further studies are needed to refine patient population selection for this device and to determine long-term outcomes.

References:

1. Hahn RT, George I, Kodali SK, et al. Early single-site experience with transcatheter tricuspid valve replacement. JACC Cardiovasc Imaging. Mar 2019; 12(3):416-429. PMID 30553658

Hemospray® Endoscopic Hemostat

Effective Date: 05/15/2021

Updates: N/A

Review: N/A

Hemospray® Endoscopic Hemostat	C1052

The Hemospray® Endoscopic Hemostat device is intended for hemostasis of non-variceal bleeds in the gastrointestinal (GI) tract. Hemospray is an inert, bentonite powder developed for endoscopic hemostasis. The powder is delivered by use of a carbon dioxide powered delivery system and through a catheter inserted through the working channel of an endoscope which provides access to the site of the bleed. (1)

In a September 2019 Product Brief, ECRI termed the evidence for treating intraluminal GI bleeding with Hemospray as “evidence raises concerns”. Although studies suggest that Hemospray may work as well as standard treatments, they were of low quality, were at high risk of bias, and findings need validation in larger, multicenter, controlled trials. Additionally, there have been reports to the FDA describing serious device-related adverse events, raising concerns on risk of malfunction and serious injury. (2)

Alzoubaidi et al. (2020) reported on patients’ outcomes after treatment with Hemospray from an international multicenter registry. Prospective data (Jan 2016-May 2018) from 12 centers across Europe were collected. Immediate hemostasis was defined as endoscopic cessation of bleeding within 5

minutes after application of Hemospray. Rebleeding was defined as subsequent drop in hemoglobin, hematemesis, persistent melena with hemodynamic compromise post-therapy. Three hundred and fourteen cases were recruited worldwide (231 males, 83 females). Median pretreatment Blatchford score was 11 (IQR: 8-14) and median complete Rockall score (RS) was 7 (IQR: 6-8) for all patients. Peptic ulcer disease (PUD) was the most common pathology (167/314 = 53%) and Forrest Ib the most common bleed type in PUD (100/167 = 60%). 281 patients (89.5%) achieved immediate hemostasis after successful endoscopic therapy with Hemospray. Rebleeding occurred in 29 (10.3%) of the 281 patients who achieved immediate hemostasis. Seven-day and 30-day all-cause mortality were 11.5% (36/314) and 20.1% (63/314), respectively (lower than the predicted rates as per the RS). Similar hemostasis rates were noted in the Hemospray monotherapy (92.4%), combination therapy (88.7%) and rescue therapy (85.5%) groups. Researchers concluded that these data show high rates of immediate hemostasis overall and in all subgroups. Rebleeding and mortality rates were in keeping/lower than predicted rates. (3)

In a 2020 systemic review, Aziz et al. assessed the efficacy of Hemospray in patients with non-variceal upper GI bleeding. A total of 20 studies with 1280 patients were included in the final analysis. Technical success of Hemospray was seen in 97% of cases (95% confidence interval [CI] 94-98%, *I* =52.89%) and a significant trend towards increasing technical success was seen during publication years 2011-2019. Clinical success of Hemospray was seen in 91% of cases (95%CI 88-94%, *I* =47.72%), compared to 87% (95%CI 75-94%, *I* =0.00%) for other hemostatic measures. The secondary outcomes of aggregate rebleeding, early rebleeding, delayed rebleeding, refractory rebleeding, mortality and treatment failure following the use of Hemospray were seen in 27%, 20%, 9%, 8%, 8%, and 31% of cases, respectively. The review had several limitations, including inclusion of only 2 randomized controlled trials (RCTs), inclusion of studies with a non-randomized designed which introduced possible selection bias, inability to identify the impact of Hemospray as monotherapy, in combination with other agents, or as a rescue agent, inconsistent identification of bleeding sources, and subjective self-reporting data from endoscopists of varying expertise. Future research, including RCTs and large cohort studies, are needed to specifically compare Hemospray to other hemostatic powders, as well as to other individual, mechanical modalities. (4)

Baracat et al. (2020) conducted a pilot RCT with patients that presented with an active non-variceal upper GI bleeding lesion. Patients were randomized either to the Hemospray or Hemoclip group. The randomization list was generated by a computer program and remained unknown throughout the entire trial. All patients underwent second-look endoscopy. Thirty-nine patients were enrolled. Peptic ulcer was the most frequent etiology. Primary hemostasis was achieved in all Hemospray cases and in 90% of Hemoclip group ($p = 0.487$). Five patients in Hemospray group underwent an additional hemostatic procedure during second-look endoscopy, while no patient in the Hemoclip group needed it ($p = 0.04$). Rebleeding, emergency surgery and mortality rates were similar in both groups. No toxicity, allergy events, or gastrointestinal obstruction signs were observed in Hemospray group. (5)

Chahal et al. (2020) conducted a retrospective cohort study of Hemospray use, analyzing outcomes of hemostasis, rebleeding, need for embolization or surgery, and death. Eighty-six applications of Hemospray were identified. The most common etiology of upper GI bleeds were ulcers (67.1%) whilst the etiology of lower GI bleeds varied. Hemospray was applied as monotherapy in 28 procedures (32.6%). Immediate hemostasis rate was 88.4%, but there was a high rate of re-bleeding (33.7%). Most re-bleeds occurred within 7 days (86.2%). Syncope was an independent predictive factor re-bleeding at 7 days for EGD (OR = 12.16, 95% CI = 1.51-97.75, P = 0.019). Bleeding refractory to endoscopic treatment with Hemospray required radiological embolization in 9 instances, and surgery in 9 instances. Hemospray therapy was protective against need for embolization ($p < 0.05$). Researchers concluded that Hemospray is effective in achieving immediate hemostasis but is plagued by high rates of rebleeding. (6)

Hussein et al. (2020) prospectively collected data on the use of Hemospray from 16 centers. Hemospray was used during the presence of progressive intraprocedural bleeding post-endoscopic therapy as a monotherapy, dual therapy with standard hemostatic techniques or rescue therapy once standard methods had failed. Hemostasis was defined as the cessation of bleeding within 5 minutes of the application of Hemospray. Re-bleeding was defined as a sustained drop in hemoglobin (>2 g/l), hematemesis or melaena with hemodynamic instability after the index endoscopy. A total of 73 patients were analyzed with bleeding post-endoscopic therapy. The median Blatchford score at baseline was five (interquartile range 0–9). The median Rockall score was six (interquartile range 5–7). Immediate hemostasis following the application of Hemospray was achieved in 73/73 (100%) of patients. Two out of 57 (4%) had a re-bleed post-Hemospray, one was following esophageal endoscopic mucosal resection and the other post-duodenal endoscopic mucosal resection. Both patients had a repeat endoscopy and therapy within 24 h. Re-bleeding data was missing for 16 patients, and mortality data was missing for 14 patients. There were no adverse events recorded in association with the use of Hemospray. However, this was not an RCT; the decision to use Hemospray as a treatment modality was at the discretion of the endoscopist which could have contributed to selection bias. Additionally, there can be interobserver variability in the definition of immediate hemostasis after the application of Hemospray to the site of bleeding. Although it has a potential role as first-line therapy for bleeding at the end of a procedure rather than as a rescue therapy, larger RCT are required to validate these findings. (7)

In a 2020 systematic review and meta-analysis, Mutneja et al. evaluated the efficacy of Hemospray in the management of upper GI bleeding. A total of 11 prospective studies, including 4 randomized trials were included for the analysis. The pooled immediate hemostasis rate with Hemospray was 93% (95% CI 90.3-95%, $p<0.001$). Rebleeding occurred in 14.4% (95% CI 8.8-22.8%, $p<0.001$) of patients. For the subgroup of tumor-related bleeding, the immediate hemostasis rate was 95.3% (95% CI 89.6-97.3%; $p <0.001$) and rebleeding rate was 21.9% (95% CI 13.9-32.7%, $p <0.001$). In patients with variceal bleeding, immediate hemostasis was achieved in 92.7% (95% CI 83.6-96.9%; $p<0.001$) of patients, with a rebleeding rate of 3.1% (95% CI 0.9-10.2%, $p <0.001$). Reviewers concluded that Hemospray shows high

immediate hemostasis and low bleeding percentages. The odds were in its favor compared to conventional endoscopic modalities, but not statistically significant. The results are undermined by the risk of bias in the studies. Nevertheless, it is an easy technique that should be further investigated with better studies. (8)

Practice Guidelines and Position Statements

In a 2020 update of the 2010 International Consensus Recommendation on the Management of Patients with Nonvariceal Upper Gastrointestinal Bleeding (9), the following statements were included:

- "In patients with actively bleeding ulcers, we suggest using TC-325 [hemostatic powder spray] as a temporizing therapy to stop bleeding when conventional endoscopic therapies are not available or fail (Grade: Conditional recommendation, very low-quality evidence)."
- "In patients with actively bleeding ulcers, we suggest against using TC-325 as a single therapeutic strategy versus conventional endoscopic therapy (clips alone, thermocoagulation alone, or combination therapy) (Grade: Conditional recommendation, very low-quality evidence)."

The American Gastroenterological Association issued a practice update on endoscopic therapies for non-variceal upper GI bleeding (2020) (10) which states: "Hemostatic power should be preferentially used as a rescue therapy and not for primary hemostasis, except in cases of malignant bleeding or massive bleeding with inability to perform thermal therapy or Hemoclip placement."

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1. U.S. Food and Drug Administration. Hemospray Endoscopic Hemostat 510(k) Summary. Available at: <https://accessdata.fda.gov> (accessed Jan. 14, 2021).
2. ECRI Institute. Hemospray Endoscopic Hemostat (Cook Medical, Inc.) for Controlling Gastrointestinal Bleeding. Plymouth Meeting (PA): ECRI Institute; 2019 Sep 05, (Custom Product Brief).
3. Alzoubaidi D, Hussein M, Rusu R, et al. Outcomes from an international multicenter registry of patients with acute gastrointestinal bleeding undergoing endoscopic treatment with Hemospary. Dig Endosc. Jan 2020; 32(1):96-105. PMID 31365756
4. Aziz M, Weissman S, Mehta T, et al. Efficacy of Hemospray in non-variceal upper gastrointestinal bleeding: a systematic review with meta-analysis. Ann Gastroenterol. Mar-Apr 2020; 33(2):145-154. PMID 32127735
5. Baracat FI, Hourneaux de Moura DT, Brunaldi VO, et al. Randomized controlled trial of hemostatic powder versus endoscopic clipping for non-variceal upper gastrointestinal bleeding. Surg Endosc. Jan 2020; 34(1):317-324. PMID 30927124
6. Chahal D, Lee JGH, Ali-Mohamad N, et al. High rate of re-bleeding after application of Hemospray for upper and lower gastrointestinal bleeds. Dig Liver Dis. Jul 2020; 52(7):768-772. PMID 32127325
7. Hussein M, Alzoubaidi D, de la Serna A, et al. Outcomes of Hemospray therapy in the treatment of intraprocedural upper gastrointestinal

bleeding post-endoscopic therapy. United European Gastroenterol J. Dec 2020; 8(10):1155-1162. PMID 32588788
8. Mutneja H, Bhurwal A, Go A, et al. Efficacy of Hemospray in upper gastrointestinal bleeding: A systematic review and meta-analysis. J Gastrointestin Liver Dis. Mar 13, 2020; 29(1):69-76. PMID 32176745
9. Barkun AN, Almadi M, Kuipers EJ, et al. Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations from the Internal Consensus Group. Ann Intern Med. Dec 3, 2019; 171(11):805-822. PMID 31634917
10. Mullady DK, Wang AY, Waschke KA. AGA Clinical Practice Update on Endoscopic Therapies for Non-Variceal Upper Gastrointestinal Bleeding: Expert Review. Gastroenterology. Sep 2020; 159(3):1120-1128. PMID 32574620

Intravascular Lithotripsy

Effective Date: 05/15/2021

Updates: N/A

Review: N/A

Intravascular lithotripsy (Shockwave Medical Intravascular Lithotripsy (IVL) System	C1761, C9764; C9765; C9766; C9767; C9772, C9773, C9774, C9775

The Shockwave Medical Intravascular Lithotripsy (IVL) System is intended for lithotripsy-enhanced balloon dilation of lesions, including calcified lesions, in the peripheral vascular. The device has integrated lithotripsy emitters and is designed to enhance percutaneous transluminal angioplasty by enabling delivery of the calcium-disrupting capability of lithotripsy prior to full balloon dilatation at low pressures. The application of lithotripsy mechanical pulse waves alters the structure of an occlusive vascular deposit (stenosis) prior to low-pressure balloon dilation of the stenosis and facilitates the passage of blood. (1)

In a July 2020 Clinical Evidence Assessment, ECRI termed the evidence for treating peripheral artery disease (PAD) with the Shockwave Peripheral Intravascular Lithotripsy System as “evidence is inconclusive: too few results on outcomes of interest”. Although the five small case series ECRI reviewed reported high procedural success rates, reduced stenosis, and few serious events, the evidence was deemed to be at too high a risk of bias to support conclusions on the safety and effectiveness of the Shockwave device for treating PAD. Multicenter, randomized controlled trials (RCTs) that compare Shockwave to conventional angioplasty and other treatments for calcified PAD with are needed to validate these findings. (2)

In a prospective, nonrandomized, multicenter, single-arm industry-sponsored, observational study, Adams et al. (2020) assessed the acute safety and effectiveness of the Shockwave Peripheral IVL System for the treatment of calcified, stenotic lower limb arteries. In the 220 target lesions, IVL was more commonly used in combination with other balloon-based technologies (53.8%) and less often with concomitant atherectomy or stenting (19.8% and

29.9%, respectively). There was a 3.4-mm average acute gain at the end of procedure; the final mean residual stenosis was 23.6%. Angiographic complications were rare, with only 2 type D dissections and a single perforation following drug-coated balloon inflation (unrelated to the IVL procedure). There was no abrupt closure, distal embolization, no reflow, or thrombotic event. Use of peripheral IVL to treat severely calcified, stenotic PAD in a real-world study demonstrated low residual stenosis, high acute gain, and a low rate of complications despite the complexity of disease. (3)

Armstrong et al. (2020) evaluated the safety and efficacy of peripheral IVL during endovascular treatment of iliac arterial PAD. The Disrupt PAD III Observational Study is a prospective, non-randomized, multi-center single-arm study to assess the 'real-world' safety and effectiveness of the Shockwave Peripheral IVL System for the treatment of de novo calcified lesions in the peripheral arteries, with a goal of treating 1500 patients. This is an analysis of consecutive patients enrolled for treatment of an iliac artery, a specified sub-group, with at least moderate calcification and a minimum length of 20 mm. Between December 2017 and July 2019, 118 patients with a total of 200 lesions were enrolled across 20 sites. 101 patients were treated primarily for claudication or critical limb ischemia, while 17 patients were treated to optimize the iliac vasculature for large-bore access. All 118 patients had successful IVL catheter delivery. The average reference vessel diameter was 7.3 mm ± 1.9 mm, with an average diameter stenosis of 83.1% ± 13.4% and an average lesion length of 58.3 mm ± 57.6 mm. Severe calcification was present in 82.0% of overall cases. Stent placement was performed in 72.9% of the overall cases. As expected, the access group received less adjunctive therapies including stents (41.2%, $p < 0.001$). Angiographic complications were minimal with no flow-limiting dissections and a final mean residual stenosis of 12.0% ± 12.1% with no differences between the groups. (4)

Madhavan et al. (2020) performed an individual patient-level data (IPD) pooled analysis to evaluate the efficacy and safety of IVL in the treatment of PAD. Researchers pooled IPD, including baseline and procedural variables, from five prospective studies which assessed IVL in the treatment of patients with extensive peripheral artery calcification. Final postprocedural percent diameter stenosis (%DS) and procedural angiographic complications were assessed by independent core laboratory. Efficacy endpoints were analyzed using linear mixed effects models and safety endpoints were tabulated overall and by vascular bed. Among 336 patients who underwent endovascular revascularization with use of IVL, there was a significant reduction between pre-procedural and final %DS of 55.1% (95% confidence interval 53.3–57.0%, $p < .0001$). Core-laboratory assessed lesion-level complications, including flow-limiting dissections (Types D–F), vessel perforation, distal embolization, thrombus, abrupt closure, and no reflow, occurred in 4/328 (1.22%) of treated lesions. Authors concluded that the present IPD of five prospective studies, marking the largest analysis to date evaluating the use of IVL in significantly calcified PAD lesions, demonstrates this treatment strategy to be both effective and safe. However, the trials included in the analysis were single-arm studies with no comparators, so there is an inability to effectively compare the efficacy and safety of IVL with other endovascular PAD treatment devices. (5)

1. U.S. Food and Drug Administration. Shockwave Medical Intravascular Lithotripsy (IVL) System 510(k) Summary. Available at: <https://accessdata.fda.gov> (accessed Feb. 12, 2021).
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Transoral Esophageal Mucosal Integrity Testing

Effective Date: 08/15/2021

Updates: N/A

Review: N/A

Transoral esophageal mucosal integrity testing by electrical impedance (e.g., MiVU™)	C9777

Historically, diagnostic testing for chronic esophageal disorders has relied on histopathology analysis of biopsies or uncomfortable transnasal catheters or wireless pH monitoring, to capture abnormal intraluminal reflux. (1) As an alternative, a balloon mucosal impedance (MI) catheter system called the MiVu™ Mucosal integrity Testing System that instantly detects changes in esophageal mucosal integrity during endoscopy, has been developed. (2)

In a prospective study, Patel et al. (2019) evaluated the ability of a balloon-incorporated MI catheter to detect and evaluate esophageal disorders, including gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE). (1) Sixty-nine patients undergoing esophagogastroduodenoscopy with or without wireless pH monitoring were classified as having GERD, EoE, or non-GERD. Receiver operating characteristic curves (ROC) and area under the ROC curve (AUC) were used to compare the accuracy of balloon MI in diagnosis. Probabilities of assignment to each group were estimated using multinomial logistic regression. MI pattern along the esophageal axis differed significantly ($p < 0.01$) among patients with GERD, EoE and non-GERD. Patients with non-GERD had higher MI values along all measured segments. The MI pattern for GERD was easily distinguished from that of EoE: in patients with GERD, MI values were low in the distal esophagus and normalized along the proximal

esophagus, whereas in patients with EoE, measurements were low in all segments of the esophagus. Intercept and rate of rise of MI value (slope) as distance increased from the squamo-columnar junction identified patients with GERD with an AUC = 0.69, patients with EoE with an AUC of 0.89, and patients with non-GERD with an AUC = 0.84 in the development cohort.

Study authors acknowledged that the study had some limitations. The prediction model assumed that subjects must belong to one of the three diagnosis groups, and uses an equal baseline prevalence of GERD, non-GERD, and EoE (35%, 35%, 30%) to estimate conditional (post-test) probability of the disease given MI intercept and slope. However, clinically, certain demographic and clinical symptoms can help augment the pre-test probability. For instance, studies have shown that clinical features that independently predicted EoE were younger age (<50 years), male, symptoms of dysphagia or history of food impaction, and documented food allergies/asthma. An ideal clinical prediction model would incorporate clinical characteristics to change the pre-test probability of a disease and then use balloon MI to provide more definitive post-test probability of the disease. However, this would require a very large sample size; investigators are now in the process of performing future studies using clinical characteristics in addition to balloon MI to augment the prediction model. It should also be noted that use of balloon MI should be avoided in patients with severe fibrostenotic disease that precludes safe expansion of the balloon catheter. The study also did not include patients with esophageal dysmotility. (1)

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External Upper Limb Tremor Stimulator of the Wrist

Effective Date: 08/15/2021

Updates: N/A

Review: N/A

External upper limb tremor stimulator of the wrist (e.g., Cala Trio™)	K1018; K1019

The most common cause of action tremor in adults, essential tremor (ET) classically involves the hands and is brought out by arm movement and sustained antigravity postures. ET is slowly progressive and can involve the head, voice, and sometimes the legs, in addition to the upper limbs. Disability from the tremor can be significant, and a variety of symptomatic therapies are available. (1)

The Cala Trio™ is a U.S. Food and Drug Administration approved non-invasive targeted therapy intended to reduce action tremors in the hands of adults with ET. Using a simple, wrist-worn device, the Cala Trio™ delivers

electrical stimulation to nerves in the wrist that project to central brain networks that are responsible for generating hand tremor in ET. This stimulation is thought to disrupt the network activity causing hand tremor, resulting in temporary tremor reduction in the treated hand. (2)

In a pilot study, Lin et al. (2018) evaluated the efficacy of median and radial nerve stimulation as a noninvasive, nonpharmacological treatment to aid in the symptomatic relief of hand tremor in individuals with ET. (3) Twenty-three blinded subjects were randomized to treatment or sham groups. For stimulation, hydrogel electrodes were positioned on the wrist over the median and radial nerves. Efficacy was measured as the change in the Tremor Research Group's Essential

Tremor Rating Assessment Scale (TETRAS) Archimedes spiral drawing task following stimulation compared with pre-stimulation. The response in the treatment group was significant compared with both baseline and sham. In the treatment group, blinded rater scores significantly improved following stimulation (1.77 ± 0.21) compared with pre-stimulation (2.77 ± 0.22; P = 0.01). In the sham group, scores did not change significantly following stimulation (2.37 ± 0.22) compared with pre-stimulation (2.62 ± 0.14; P = 0.37). The response to treatment corresponded to an estimated hand tremor amplitude reduction of 60% ± 8.4% and was significantly greater in the treatment than in the sham group (P = 0.02). Three subjects experienced transient redness and/or itchiness under the hydrogel electrodes that resolved without intervention. No unanticipated device effects occurred during the study. The study had too few subjects to allow for subanalyses of the effects of age, medication status, or medical history. Future studies should expand the subject count, investigate the response rate, repeatability, durability, and effects of chronic use, and add assessments of quality of life.

Pahwa et al. (2019) evaluated the safety and effectiveness of a wrist-worn peripheral nerve stimulation device in a randomized controlled study of 77 patients with ET in a single in-office session. (4) Patients received either treatment stimulation (N = 40) or sham stimulation (N = 37) on the wrist of the hand with more severe tremor. Tremor was evaluated before and immediately after the end of a single 40-minute stimulation session. The primary endpoint compared spiral drawing in the stimulated hand using the TETRAS Archimedes spiral scores in treatment and sham groups. Additional endpoints included TETRAS upper limb tremor scores, subject-rated tasks from the Bain and Findley activities of daily living (BF-ADL) scale before and after stimulation as well as clinical global impression-improvement (CGI-I) rating after stimulation.

Subjects who received peripheral nerve stimulation did not show significantly larger improvement in the Archimedes spiral task compared to sham but did show significantly greater improvement in upper limb TETRAS tremor scores (p = 0.017) compared to sham. Subject-rated improvements in ADLs were significantly greater with treatment (49% reduction) than with sham (27% reduction; p = 0.001). A greater percentage of ET patients (88%) reported improvement in the stimulation group as compared to the sham group (62%) according to CGI-I ratings (p = 0.019). No significant adverse events were

reported; 3% of subjects experienced mild adverse events. While results are encouraging, future studies are needed to confirm the effectiveness of this noninvasive therapy over time.

Isaacson et al. (2020) conducted a prospective, single-arm study with 263 patients. (5) Patients were instructed to use non-invasive neuromodulation therapy (called Transcutaneous Afferent Patterned Stimulation [TAPS]) twice daily for three months. Pre-specified co-primary endpoints were improvements on clinician-rated TETRAS and patient-rated BF-ADL dominant hand scores. Other endpoints included improvement in the tremor power detected by an accelerometer on the therapeutic device, CGI-I and Patient Global Impression (PG-I) scores and Quality of Life in Essential Tremor (QUEST) survey. Two hundred and five patients completed the study. The co-primary endpoints were met (p?0.0001), with 62% (TETRAS) and 68% (BF-ADL) of 'severe' or 'moderate' patients improving to 'mild' or 'slight'. Clinicians (CGI-I) reported improvement in 68% of patients, 60% (PGI-I) of patients reported improvement, and QUEST improved (p = 0.0019). Wrist-worn accelerometer recordings before and after 21,806 therapy sessions showed that 92% of patients improved, and 54% of patients experienced ≥50% improvement in tremor power. Device-related adverse events (e.g., wrist discomfort, skin irritation, pain) occurred in 18% of patients. No device-related serious adverse events were reported. Although the study suggests that TAPS therapy is safe and improves hand tremor and quality of life over three months of use, the study had several important limitations, including the open-label, single-arm design, lack of blinding of the clinical raters to the study's design, treatment response variability between tasks, and the primary and secondary end-points excluded the 58 patients who exited the study early, 14 of which were known to cite "lack of device benefit" as the reason for withdrawal.

In a comprehensive review, Pascual-Valdunciel et al. (2021) analyzed 27 studies that reported the use of peripheral electrical stimulation to reduce tremor and discussed various considerations regarding peripheral electrical stimulation: the stimulation strategies and parameters, electrodes, experimental designs, results, and mechanisms hypothesized to reduce tremor. (6) While studies demonstrate the potential and usability of peripheral electrical stimulation as an intervention to reduce tremor, results are highly variable across studies and patients, which points out the need for consensus and standardized procedures to allow more reproducibility and cross-comparisons.

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1. Deik A and Tarsy D. Essential tremor: Treatment and prognosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Available at <https://www.uptodate.com> (accessed May 10, 2021).
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6. Pascual-Valdunciel A, Hoo GW, Avrillon S, et al. Peripheral Electrical stimulation to reduce pathological tremor: a review. J Neuroeng Rehabil. Feb 2021; 18(1):33. PMID 33588841

Summary of Evidence

Based on the literature review for each of these products/services, the evidence is insufficient to determine the effects of the technology on health outcomes.

Contract:

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coding:

CODING:

Disclaimer for coding information on Medical Policies

Procedure and diagnosis codes on Medical Policy documents are included only as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, device or diagnosis codes in a Medical Policy document has **no** relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a medical policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT/HCPCS/ICD-9/ICD-10 Codes
The following codes may be applicable to this Medical policy and may not be all inclusive.
CPT Codes
0615T, 0620T, 0621T; 0622T, 0623T; 0624T; 0625T; 0626T, 0627T; 0628T; 0629T; 0630T, 0631T, 0632T, 0639T, 0640T; 0641T; 0642T, 0643T, 0645T, 0646T

HCPCS Codes
C1052, C1761, C9764; C9765; C9766; C9767; C9772, C9773, C9774, C9775, C9777, K1018; K1019, K1024, K1025, K1031, K1032, K1033
ICD-9 Diagnosis Codes
Refer to the ICD-9-CM manual
ICD-9 Procedure Codes
Refer to the ICD-9-CM manual
ICD-10 Diagnosis Codes
Refer to the ICD-10-CM manual
ICD-10 Procedure Codes
Refer to the ICD-10-CM manual

Medicare Coverage:

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

References:

References are included in the Rationale following each procedure/service.

Policy History:

Date	Reason
10/1/2021	Document updated. (See Rationale for effective, update, and review dates for each individual procedure/service.)
8/15/2021	Document updated. (See Rationale for effective, update, and review dates for each individual procedure/service.)
7/1/2021	Document updated. (See Rationale for effective, update, and review dates for each individual procedure/service.)
5/15/2021	Document updated. (See Rationale for effective, update, and review dates for each individual procedure/service.)

1/1/2021	New medical document. The list of procedures/services are considered experimental, investigational and/or unproven as they have not received approval from the U.S. Food and Drug Administration (FDA) and/or there is little to no evidence to prove efficacy.

Archived Document(s):

Title:	Effective Date:	End Date:
Experimental, Investigational and/or Unproven Procedures/Services	08-15-2021	09-30-2021
Experimental, Investigational and/or Unproven Procedures/Services	07-01-2021	08-14-2021
Experimental, Investigational and/or Unproven Procedures/Services	05-15-2021	06-30-2021
Experimental, Investigational and/or Unproven Procedures/Services	01-01-2021	05-14-2021

Exhibit 1

Transcript of the Testimony of

Frank G. Fox, Ph.D.

Date: 9/12/2022

C.P. vs BLUE CROSS BLUE SHIELD OF ILLINOIS

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IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF WASHINGTON
AT TACOMA

C.P., by and through his parents, PATRICIA PRITCHARD AND NOLLE PRITCHARD; and PATRICIA PRITCHARD, Plaintiffs, vs. BLUE CROSS BLUE SHIELD OF ILLINOIS, Defendant.	No. 3:20-cv-06145-RJB

REMOTE
VIDEOTAPED DEPOSITION UPON ORAL EXAMINATION OF
FRANK G. FOX, Ph.D.
September 12, 2022

Taken remotely
Witness location: Seattle, Washington

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ALSO PRESENT:

Bryan Gaver, Videographer

FRANK G. FOX, Ph.D. - September 12, 2022

I N D E X

Kaiser study's a medical record study. That wouldn't include the universe.

Q. Did you notice the statement in the Quinn study before right now that only two-thirds of the people in those numbers actually received care?

A. Absolutely.

ATTY. HAMBURGER: Object as to form; misrepresents the statement.

Q. (By Atty. Payton) But that didn't change your calculation?

A. Not at all.

Q. Okay. Turn with me, if you would, please, to Paragraph 12 of your report.

A. I'm there.

Q. Okay. Hold on for a minute. Because we've covered some of this stuff, so I'm trying not to duplicate it. Just a second.

Okay. Actually, I think we can move on to Paragraph 15, if you so would, in your report.

A. I'm there.

Q. Okay. I think we started talking about this issue a little earlier, but I want to finish the discussion. You use numbers from the state of Illinois, correct?

A. Bureau census data, yes.

Q. Why Illinois?

A. We didn't know where the insureds actually resided, and that figure was necessary to get the kind of age cohort specificity that the model would be best run with. We could have used US census data across the different age cohorts as identified in the Williams Institute, but we didn't.

And because we didn't have that specificity, counsel and I talked about this issue, and we determined that it would be reasonable -- it would be a reasonable assumption to use Illinois.

Q. Okay. The named plaintiff resided in Washington; is that right?

A. Correct. But that wasn't just about the plaintiff. It was about all the insureds under these gender affirming plan exclusions.

Q. Did you ask for the distribution of members geographically?

A. As I mentioned, counsel and I talked about it. I don't believe she was -- she indicated she was able to obtain it. But we did discuss it.

ATTY. HAMBURGER: Counsel, if you want to supply that information, we're happy to receive it.

Q. (By Atty. Payton) I'm going to ask you here about your tables. And I'll use the 2017 Williams report, because that's what you used, just so that it lines up. Is that fair?