Complex Regional Pain Syndrome (CRPS)/Reflex Sympathetic Dystrophy (RSD): Diagnosis

Aetna considers the following tests experimental and investigational for the diagnosis of reflex sympathetic dystrophy (RSD), also known as complex regional pain syndrome (CRPS), because there is insufficient scientific evidence to support the effectiveness of these approaches.

- Antioxidant profile (e.g., enzymatic activities consisting of serum glutathion peroxidase (GPX), glutathione S-transferase (GST), and superoxide dismutase (SOD))
- Biomarkers of inflammation (e.g., autoantibodies, calcitonin gene-related peptide [CGRP], CD8+ T lymphocytes, CD14+CD16+ monocytes, interleukin-6 [IL-6], mast cell numbers, microRNA [miRNA], soluble interleukin-2 receptor [sIL-2R], substance P [SP], and tumor necrosis factor-alpha [TNF-α])
- Bone SPECT/CT
- Computed tomography (CT)
- Determination of highly unsaturated fatty acids and trans fatty acid status
- DNA methylation profiles (for predicting the development of CRPS after traumatic injury)
- Electronic nose (Aeonose) for diagnosis of CRPS
- Gene expression profiling (e.g., CREB-binding protein (CREBBP), early region 1A binding protein p300 (EP300), human leukocyte antigen (HLA) family genes such as HLA-DQB1 and HLA-DRB1, integrin alpha M, signal transducer and activator of transcription (STAT)3, and STAT5A)
- Intravenous phentolamine (Regitine)
- Laser Doppler flowmetry
- Magnetic resonance imaging (MRI)
- Magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) of brain metabolites and peripheral biomarkers of inflammation
- Measurement of dermal nerve fiber and mast cell density, and proximity of mast cells to nerve fibers
- Measurement of serum anti-neuronal antibodies/autoantibodies
- Musculoskeletal ultrasonography
- Plain film radiography
- Positron emission tomography (PET)
- Small non-coding RNAs (microRNAs) as diagnostic and prognostic biomarkers for CRPS
- Thermography

For autonomic testing for reflex sympathetic dystrophy (e.g., quantitative sudomotor axon reflex test (QSART), resting sweat output (RSO), and resting skin temperature (RST)), see CPB 0485 - Autonomic Testing/Sudomotor Tests

https://aetnet.aetna.com/mpa/cpb/400_499/0485.html
Background

Reflex sympathetic dystrophy (RSD), one of the major causes of disability, is a general descriptive term for a set of symptoms and signs without any implication of pathophysiology or etiology. It is characterized by diffused burning pain, allodynia (pain on light touch), and autonomic dysfunction with sweating, temperature change, and redness or cyanotic mottling. Reflex sympathetic dystrophy occurs in adults and children, and usually develops in a limb after a relatively minor injury. It can be temporary, permanent, episodic, or migratory, and may occur in one area or more. In an attempt to clarify the subject, the International Association for the Study of Pain listed 4 diagnostic criteria for RSD. All 4 of the following criteria must be met for the diagnosis of RSD to be established: (i) the presence of an initiating noxious event, or a cause of immobilization; (ii) continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to the initiating event; (iii) confirmation at some time of edema, changes in blood flow, or abnormal sudomotor activity in the area of the pain such as changes in skin temperature, skin color, or sweating; and (iv) the absence of other conditions that would account for the pain and dysfunction. Despite intensive clinical investigations in the past 5 decades, the diagnostic and therapeutic approaches for RSD remain controversial. In this regard, some researchers have advocated the use of systemic sympathetic blockade with phentolamine as a diagnostic test for this condition. Phentolamine mesylate (Regitine) is a short-acting alpha-adrenergic blocking agent that acts at both alpha-1 and alpha-2 adrenergic receptor sites. As a test to diagnose RSD,
patients are usually given an intravenous infusion of 25 to 75 mg phentolamine for 20 mins. Pain relief following phentolamine administration is then taken as a confirmation of RSD. However, the value of the phentolamine test in diagnosing RSD has been challenged by many investigators.

In a recent review on complex regional pain syndrome (CRPS) (Wasner et al, 2003), the phentolamine test is not listed as a diagnostic test for this syndrome. Furthermore, Atkins (2003) stated that CRPS is a clinical diagnosis and there is no single diagnostic test. Laser Doppler flowmetry has been used to evaluate blood flow in patients with CRPS because it has been suggested that CRPS may be associated with vascular disturbances (e.g., a loss of cutaneous sympathetic vasoconstrictor activity). Vital capillaroscopy is a technique using Doppler flowmetry to gauge anatomical vascular mapping and capillary blood flow in the affected extremity.

Wasner et al (1999) examined cutaneous sympathetic vasoconstrictor innervation by laser Doppler flowmetry in 2 patients with CRPS and 1 normal control subject. This study was designed to investigate the pathophysiology of CRPS. However, the study did not demonstrate how well laser Doppler flowmetry would perform in establishing or excluding the diagnosis of CRPS. Nor did this study show how management is influenced and clinical outcomes are improved in patients with symptoms of CRPS. Baron and Maier (1996) assessed the role of the sympathetic nervous system in patients with RSD of the hand using laser Doppler flowmetry. Cutaneous blood flow, skin resistance and skin temperature were measured at the affected and contralateral hands. These investigators found that (i) side differences in skin temperature and blood flow are no static descriptors in RSD. They are dynamic values depending critically on environmental temperature. Thus, they have to be interpreted with care when defining reliable diagnostic criteria, and (ii) vascular disturbances in RSD are not due to
constant over-activity of sympathetic vasoconstrictor neurons. Changes in vascular sensitivity to cold temperature and circulating catecholamines may be responsible for vascular abnormalities. Alternatively, RSD may be associated with an abnormal (side different) reflex pattern of sympathetic vasoconstrictor neurons due to thermoregulatory and emotional stimuli generated in the central nervous system.

Gorodkin et al (2004) assessed microvascular endothelial function in patients with CRPS compared with healthy controls, as measured by iontophoresis of vasoactive chemicals and laser Doppler imaging. These researchers found that CRPS was not associated with impairment of microvascular endothelial function.

Laser Doppler flowmetry has been used as a research tool in quantifying blood perfusion in persons with microvascular disease due to diabetes and other vascular conditions. However, there is insufficient evidence of the clinical value of this study in improving the management of patients with diabetes such that clinical outcomes are improved.

Thermography involves the use of an infrared thermometer to measure several symmetrical points on the affected and contralateral extremity, making comparisons between the 2 extremities. In general, a difference of 0.5 degrees C is considered mildly asymmetrical, and a difference of 1.0 degrees C is considered significant. Although asymmetries in temperature have been found in persons with CRPS, it has been reported that a lack of asymmetry does not exclude the diagnosis (Rho et al, 2002).

Niehof et al (2007) found that, although observer assessment of thermographic images may distinguish between CRPS1 patients and healthy controls, the reliability and repeatability of this assessment was "rather low." This study aimed at evaluating the sensitivity, specificity, reliability and repeatability
of observer assessment of thermographic images taken from CRPS 1. A computer program was developed to let observers rate the difference between randomly presented thermographic images of pairs of hands of individuals. The investigators reported that the sensitivity was 71 % and the specificity 85 %. The repeatability was 0.5267 and the reliability was 0.4967.

Gradl and colleagues (2003) reported that thermography had poor sensitivity and specificity for CRPS1. The investigators studied the value of clinical evaluation, radiography and thermography in the early diagnosis of traumatic CRPS1. A total of 158 patients with distal radial fractures were followed-up for 16 weeks after trauma. Apart from a detailed clinical examination 8 and 16 weeks after trauma, thermography and bilateral radiographs of both hands were carried out. At the end of the observation period 18 patients (11 %) were clinically identified as CRPS1. Sixteen weeks after trauma easy differentiation between normal fracture patients and CRPS1 patients was possible. The investigators reported that, 8 weeks after distal radial fracture, clinical evaluation showed a sensitivity of 78 % and a specificity of 94 %. On the other hand, thermography (58 %) and bilateral radiography (33 %) revealed poor sensitivities. The specificity was high for radiography (91 %) and again poor for thermography (66 %).

Schürmann et al (2007) compared several imaging studies in diagnosing post-traumatic CRPS. A total of 158 consecutive patients with distal radial fracture were followed-up for 16 weeks after trauma. A detailed clinical examination was carried out 2, 8, and 16 weeks after trauma in conjunction with bilateral thermography, plain radiographs of the hand skeleton, 3-phase bone scans (TPBSs), and contrast-enhanced magnetic resonance imaging (MRI). All imaging procedures were assessed blinded. At the end of the observation period 18 patients (11 %) were clinically identified as having CRPS I and 13 patients (8 %) revealed an incomplete clinical picture which were defined as CRPS borderline cases. The sensitivity
of all diagnostic procedures used was poor and decreased between the 1st and the last examinations (thermography: 45 % to 29 %; TPBS: 19 % to 14 %; MRI: 43 % to 13 %; bilateral radiographs: 36 %). In contrast a high specificity was observed in the TPBS and MRI at the 8th and 16th-week examinations (TPBS: 96 %, 100 %; MRI: 78 %, 98 %) and for bilateral radiographs 8 weeks after trauma (94 %). Thermography presented a fair specificity that improved from the 2nd to the 16th week (50 % to 89 %). The authors concluded that the poor sensitivity of all tested procedures combined with a reasonable specificity produced a low positive predictive value (17 % to 60 %) and a moderate negative predictive value (79 % to 86 %). These results suggested that those procedures can not be used as screening tests.

Imaging methods are not able to reliably differentiate between normal post-traumatic changes and changes due to CRPS I. Clinical findings remain the gold standard for the diagnosis of CRPS I and the procedures described above may serve as additional tools to establish the diagnosis in doubtful cases.

Niehof et al (2008) evaluated the validity of skin surface temperature recordings, based on various calculation methods applied to the thermographic data, to diagnose acute CRPS1 fracture patients. Thermographic recordings of the palmar/plantar side and dorsal side of both hands or feet were made on CRPS1 patients and in control fracture patients with/without and without complaints similar to CRPS1 (total in the 3 subgroups = 120) just after removal of plaster. Various calculation methods applied to the thermographic data were compared using receiver operating characteristics analysis to obtain indicators of diagnostic value. There were no significant differences in demographic data and characteristics among the 3 subgroups. The most pronounced differences among the subgroups were vasomotor signs in the CRPS1 patients. The involved side in CRPS1 patients was often warmer compared with the non-involved extremity. The difference in temperature between the involved site and the non-involved extremity in CRPS1 patients significantly differed.
from the difference in temperature between the contralateral extremities of the 2 control groups. The largest temperature difference between extremities was found in CRPS1 patients. The difference in temperature recordings comparing the palmar/plantar and dorsal recording was not significant in any group. The sensitivity and specificity varied considerably between the various calculation methods used to calculate temperature difference between extremities. The highest level of sensitivity was 71% and the highest specificity was 64%; the highest positive predictive value reached a value of 35% and the highest negative predictive 84%, with a moderate 0.60 greater than or equal to area under the curve less than or equal to 0.65. The authors concluded that the validity of skin surface temperature recordings under resting conditions to discriminate between acute CRPS1 fracture patients and control fracture patients with/without complaints is limited. Furthermore, in a review on CRPS, Albazaz and colleagues (2008) stated that no specific diagnostic test is available. Thus, diagnosis is based mainly on history, clinical examination, and supportive laboratory findings.

Krumova et al (2008) evaluated long-term skin temperature changes under everyday circumstances in 22 patients with CRPS, 18 patients with limb pain of other origin and 23 healthy controls. The asymmetries in skin temperature and oscillation number (Q Oscill), the percentage of assessed time with a-synchron temperature changes on both body sides and the determination coefficient of the individual regression (r² id) were compared between the groups. Patients with CRPS differed significantly from healthy controls in nearly all parameters. Minor differences between both patient groups were found regarding the percentage of assessed time with side difference greater than 2 degrees C (DeltaT2). However, both patient groups differed significantly in parameters characterizing the skin temperature dynamics. A sum score (2 *Q Oscill + r² id + DeltaT2) allowed diagnosing CRPS with a specificity of 67% versus patients with other painful diseases and 79% versus healthy controls (sensitivity: 73%, and 94%,

https://aetnet.aetna.com/mpa/cpb/100_199/0147.html
respectively) and reflected the severity of the dysfunction in CRPS better than the mean skin temperature side differences alone.

Cohen and Raja (2009) stated that measurement of skin temperature dynamics differentiated between CRPS and arm pain secondary to other etiologies with a sensitivity of 73% and a specificity of 67%. Although the technique Krumova and colleagues (2008) used is more practical than those previously described, it is still too onerous for patients and physicians to routinely employ. These researchers anticipate that improved identification of pain mechanisms will translate into better treatment outcomes, but this hypothesis remains to be tested.

In a pilot study, Ramsden and colleagues (2010) compared the omega-6 (n-6) and omega-3 (n-3) highly unsaturated fatty acids (HUFA), and trans fatty acid (trans FA) status of CRPS patients to pain-free controls. A total of 20 patients that met the Budapest research diagnostic criteria for CRPS and 15 pain-free control subjects were included in this study. Fasting plasma fatty acids were collected from all participants. In CRPS patients, pain was assessed using the McGill Pain Questionnaire-Short Form. In addition, results from the perceived disability (Pain Disability Index), pain-related anxiety (Pain Anxiety Symptom Scale Short Form), depression (Center for Epidemiologic Studies Depression Scale Short Form), and quality of life (Short Form-36 [SF-36]) were evaluated.

Compared with controls, CRPS patients reported elevated concentrations of n-6 HUFA and trans FA. No differences in n-3 HUFA concentrations were observed. Plasma concentrations of the n-6 HUFA docosatetraenoic acid were inversely correlated with the "vitality" section of the SF-36. Trans FA concentrations positively correlated with pain-related disability and anxiety. The authors concluded that these preliminary data suggest that elevated n-6 HUFA and trans FA may play a role in CRPS pathogenesis. They stated that these findings should be replicated, and more research is needed to
explore the clinical significance of low n-6 and trans FA diets with or without concurrent n-3 HUFA supplementation, for the management of CRPS.

Ringer and colleagues (2012) stated that to date, no attempt has been made to investigate the agreement between qualitative bone scintigraphy (BS) and the presence of CRPS 1 and the agreement between a negative BS in the absence of CRPS 1. These investigators summarized the existing evidence quantifying the concordance of qualitative BS in the presence or absence of clinical CRPS 1. They searched Medline, Embase, Dare and the Cochrane Library and screened bibliographies of all included studies; and selected diagnostic studies investigating the association between qualitative BS results and the clinical diagnosis of CRPS 1. The minimum requirement for inclusion was enough information to fill the 2-by-2 tables. A total of 12 studies met inclusion criteria and were included in the meta-analysis. The pooled mean sensitivity of twelve 2-by-2 tables was 0.87 (95% confidence interval [CI]: 0.68 to 0.97) and specificity was 0.69 (95% CI: 0.47 to 0.85). The pooled mean sensitivity for the subgroup with clearly defined diagnostic criteria (seven 2-by-2 tables) was 0.80 (95% CI: 0.44 to 0.95) and specificity was 0.73 (95% CI: 0.40 to 0.91). The authors concluded that based on the findings of this study, clinicians must be advised that a positive BS is not necessarily concordant with presence or absence of CRPS 1. Moreover, they noted that given the moderate level of concordance between a positive BS in the absence of clinical CRPS 1, discordant results potentially impede the diagnosis of CRPS 1.

**Antioxidant Profile**

Baykal et al (2014) stated that the mechanism and pathogenesis of CRPS still remains unknown. Some findings indicating oxidative stress have been reported. These researchers examined the role of oxidative stress in patients with CRPS. A total of 20 patients (13 women and 7 men) with
CRPS and 20 age- and sex-matched healthy controls were enrolled in this study. Complex regional pain syndrome was diagnosed according to the modified International Association for the Study of Pain (IASP) criteria. These investigators evaluated demographic, clinical and laboratory characteristics of the patients. Antioxidant enzymatic activities consisting of serum glutathion peroxidase (GPX), glutathione S-transferase (GST) and superoxide dismutase (SOD) activities were measured using appropriate methods and compared with healthy controls. The mean age of the patients was 39.5 years and the mean duration of symptoms was 5.5 months. Complex regional pain syndrome developed after a traumatic event in 90% of patients. In 10% of patients there were no traumatic events; GPX, GST and SOD levels were significantly higher in patients with CRPS than healthy controls (p = 0.036, p = 0.016, and p = 0.012, respectively). The authors concluded that their findings suggested a possible role of oxidative stress in the pathogenesis of CRPS. The role of antioxidant profile in the diagnosis of CRPS has yet to be established.

**Musculoskeletal Ultrasonography**

Vas and Pai (2016) noted that musculoskeletal ultrasonography (MSK-US) can identify myofascial structural lesions. In a retrospective study, these investigators described the observational findings of US data of muscles from limbs affected with neuropathic pain in 7 patients and compared them with muscles affected with CRPS-1 in 7 patients. These researchers highlighted findings that distinguish between the 2 conditions. Musculoskeletal US of muscles in CRPS was characterized by a variable or/and global intramuscular structural disruption with loss of muscle bulk. Adjacent muscles coalesced with one another to present an uniform hyper-echogenic mass of tissue. Muscle edema was found in some patients. In comparison, MSK-US in muscles affected by neuropathic pain exhibited structural normalcy, but also showed considerable reduction in muscle bulk. The authors
concluded that MSK-US showed promise as a diagnostic modality to distinguish between these 2 conditions that currently have only clinical diagnostic criteria to aid diagnosis.

**Other Experimental and Investigational Procedures**

An UpToDate review on “Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis” (Abdi, 2015) states that “Plain radiographs often demonstrate patchy osteoporosis but the sensitivity of this finding for CRPS is very low .... Autonomic tests that have been used to evaluate patients with suspected CRPS include the resting sweat output (RSO), the resting skin temperature (RST), and the quantitative sudomotor axon reflex test (QSART). Some experts advocate serial measurement of skin temperatures, based upon evidence from one small study that a 2°C difference for the affected versus unaffected side was supportive of the diagnosis of CRPS. However, this method requires monitoring for five to eight hours with recording of skin temperature at one minute intervals using temperature sensors applied to the index fingers. Thus, it is not practical as a routine clinical test .... There is no clear role for MRI or CT scanning in the evaluation of suspected CRPS, nor is there any role for the response to sympatholysis to confirm the diagnosis of CRPS”.

**Anti-Neuronal antibodies/Autoantibodies**

Dirckx et al (2015) noted that autoimmunity has been suggested as one of the pathophysiologic mechanisms that may underlie CRPS. Screening for anti-nuclear antibodies (ANA) is one of the diagnostic tests, which is usually performed if a person is suspected to have a systemic autoimmune disease. Anti-neuronal antibodies are autoantibodies directed against antigens in the central and/or peripheral nervous system. These researchers compared the prevalence of these antibodies in CRPS patients with the normal values of those antibodies in the healthy population; 27
(33 %) of the 82 CRPS patients of whom serum was available showed a positive ANA test. This prevalence was significantly higher than in the general population; 6 patients (7.3 %) showed a positive result for typical anti-neuronal antibodies. This proportion, however, did not deviate from that in the general population. The authors concluded that these findings suggested that autoantibodies may be associated with the pathophysiology of CRPS, at least in a subset of patients. Moreover, they stated that further research is needed into defining this subset and into the role of autoantibodies in the pathogenesis of CRPS.

Response to Systemic Chemical Sympatholysis

An UpToDate review on “Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis” (Abdi, 2016) states that “Other tests and interventions -- There is no clear role for MRI or CT scanning in the evaluation of suspected CRPS, nor is there any role for the response to sympatholysis to confirm the diagnosis of CRPS. MRI may be useful for excluding some conditions in the differential diagnosis; but is not useful for confirming the diagnosis of CRPS. Limited data suggest that CT scanning can show focal areas of osteoporosis in a Swiss cheese-like appearance. However, weighing the cost, radiation dose, and limited experience with use of CT scanning in evaluation of patients with CRPS, we suggest not using CT as a diagnostic test. Historically, abrupt transient relief from pain and dysesthesia with a systemic chemical sympatholysis (i.e., intravenous regional anesthesia, also termed a Bier block, and/or a regional sympathetic nerve block such as stellate ganglion or lumbar sympathetic nerve blocks) was considered necessary to make the diagnosis of CRPS. However, as the role of the sympathetic nervous system in the pathogenesis of CRPS remains unclear and contradictory, it is now widely accepted that a positive response to sympathetic block is not diagnostic of CRPS. Rather, such a response is an important indicator of sympathetically maintained pain".
Bone Scintigraphy

Wertli and colleagues (2017) noted that since 2007, the Budapest criteria are recommended for the diagnosis of CRPS 1. The usefulness of bone scintigraphy (BS, index test) for the diagnosis of CRPS 1 remains controversial. Imperfect reference tests (RT) result in under-estimation of the diagnostic accuracy of BS. Further, biased results can occur when a dependency between the RT and BS exists. These researchers evaluated the impact of different RTs, specifically the Budapest criteria, and the assumed imperfect nature of the RT on the diagnostic accuracy of BS. Further, these investigators analyzed the association between baseline characteristics and positive BS in patients with CRPS 1. The authors performed a systematic literature review and Bayesian meta-analysis to assess the test accuracy of BS with and without accounting for the imperfect nature of the RT. They examined correlations (Spearman correlation coefficients / Wilcoxon tests) between baseline characteristics and the proportion of positive BS in patients with CRPS 1. The pooled sensitivity was 0.804 (95 % CI: 0.225 to 1.0, 21 studies) and specificity 0.853 (95 % CI: 0.278 to 1.00). Sensitivity and specificity of BS increased when accounting for the imperfect nature of the RT. However, in studies using Budapest criteria as reference, the sensitivity decreased (0.551; 95 % CI: 0.046 to 1) and the specificity increased (0.935; 95 % CI: 0.306 to 1).

Shorter disease duration and a higher proportion of males were associated with a higher proportion of positive BS (27 studies, disease duration less than 52 weeks; Wilcoxon test p = 0.047, female proportion Spearman correlation -0.63, p = 0.009). The authors concluded that compared to the accepted Budapest diagnostic criteria, BS cannot be used to rule-in the diagnosis of CRPS 1. In patients with negative BS, CRPS 1 is less likely the underlying illness. They stated that studies using older or no diagnostic criteria should not be used to evaluate the diagnostic accuracy of BS in CRPS 1. These
investigators stated that based on the results of this study, BS did not add any value to the clinical diagnosis of CRPS 1, and cannot be used to confirm the diagnosis.

The study was limited by the small number of studies using a reference test for the diagnosis of CRPS 1. Furthermore, many studies were only of moderate or low quality and some of small sample size. Small studies on diagnostic accuracy were often imprecise, with wide CIs. The lack of a gold standard reference test is another drawback, which the authors addressed within the Bayesian model formulation; however, the resulting posterior CIs for overall sensitivity and specificity of the index test were wider than they would be with a perfect reference test. Only few studies reported factors that influence sensitivity and therefore, the findings need to be interpreted with caution and addressed in future studies.

**Gene Expression Profiling**

Tan and colleagues (2017) predicted key genes and proteins associated with CRPS using bioinformatics analysis. The gene expression profiling microarray data, GSE47603, which included peripheral blood samples from 4 patients with CRPS and 5 healthy controls, was obtained from the Gene Expression Omnibus (GEO) database. The differentially expressed genes (DEGs) in CRPS patients compared with healthy controls were identified using the GEO2R online tool. Functional enrichment analysis was then performed using the Database for Annotation Visualization and Integrated Discovery online tool. Protein-protein interaction (PPI) network analysis was subsequently performed using Search Tool for the Retrieval of Interaction Genes database and analyzed with Cytoscape software. A total of 257 DEGs were identified, including 243 up-regulated genes and 14 down-regulated ones. Genes in the human leukocyte antigen (HLA) family were most significantly differentially expressed. Enrichment analysis demonstrated that signaling pathways, including immune response, cell motion, adhesion and angiogenesis.
were associated with CRPS. Protein-protein interaction network analysis revealed that key genes, including early region 1A binding protein p300 (EP300), CREB-binding protein (CREBBP), signal transducer and activator of transcription (STAT)3, STAT5A and integrin α M were associated with CRPS. The authors concluded that the results suggested that the immune response may therefore serve an important role in CRPS development. Also, genes in the HLA family, such as HLA-DQB1 and HLA-DRB1, may present potential biomarkers for the diagnosis of CRPS. Furthermore, EP300, its paralog CREBBP, and the STAT family genes, STAT3 and STAT5 may be important in the development of CRPS.

**Positron Emission Tomography**

Jeon and colleagues (2017) noted that CRPS is characterized by chronic, severe pain, but its pathophysiology is not clearly understood. In a pilot study, these researchers examined neuro-inflammation in patients with CRPS using positron emission tomography (PET), with an 18-kDa translocator protein specific radio-ligand [C]-([R])-PK11195. [C]-([R])-PK11195 PET scans were acquired for 11 patients with CRPS (aged 30 to 55 years) and 12 control subjects (aged 30 to 52 years). Parametric image of distribution volume ratio (DVR) for each participant was generated by applying a relative equilibrium-based graphical analysis. The DVR of [C]-([R])-PK11195 in the caudate nucleus (t(21)=-3.209, p=0.004), putamen (t(21)=-2.492, p=0.022), nucleus accumbens (t(21)=-2.218, p=0.040), and thalamus (t(21)=-2.395, p=0.026) were significantly higher in CRPS patients than in healthy controls. Those of globus pallidus (t(21)=-2.045, p=0.054) tended to be higher in CRPS patients than in healthy controls. In patients with CRPS, there was a positive correlation between the DVR of [C]-([R])-PK11195 in the caudate nucleus and the pain score, the visual analog scale (VAS; r=0.661, p=0.026, R=0.408) and affective subscales of McGill Pain Questionnaire (r=0.604, p=0.049, R=0.364). These investigators demonstrated neuro-inflammation in basal ganglia of CRPS.
patients. The authors concluded that these findings suggested that microglial pathology can be an important pathophysiology of CRPS; association between the level of caudate nucleus and pain severity indicated that neuro-inflammation in this region might play a key role in the central sensitization in CRPS highlighting a fascinating area for future research.

This study had 2 main drawbacks: (i) this study only examined a small number of CRPS type I patients (n = 11). Thus, future studies with larger sample size are needed to generalize this finding to CRPS patients as a whole, and (ii) CRPS patients included in this study were taking analgesic agents, including opioids, during the study period, and these researchers were therefore unable to exclude this analgesic effect in the results. However, they did examine subjects who were not taking benzodiazepine drugs, which directly affects 18-kDa translocator protein (TSPO)-binding affinities, for at least 2 weeks before the [11C]-(R)-PK11195 PET examination to minimize medication effect.

**Bone SPECT/CT**

Narimatsu and colleagues (2017) reported on the case of a 64-year old man with lung cancer with a history of revascularization of the occluded right femoral artery who underwent bone scintigraphy, which showed intense uptake in the distal side of the right leg. The additional SPECT/CT clarified that the uptake was predominantly increased in the epiphyses of the right ankle and foot with possible osteopenia. One month later, follow-up SPECT/CT showed the manifestation of periosteal resorption in the hyper-metabolic sites with slight decrease in bone metabolism. The authors concluded that radiological correlation between bone metabolism and subsequent bone resorption in addition to clinical symptoms in this patient suggested the diagnosis of RSD.
An UpToDate review on “Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis” (Abdi, 2018) states “There is no clear role for magnetic resonance imaging (MRI) or computed tomography (CT) scanning in the evaluation of suspected CRPS, nor is there any role for the response to sympatholysis to confirm the diagnosis of CRPS. MRI may be useful for excluding some conditions in the differential diagnosis but is not useful for confirming the diagnosis of CRPS. Limited data suggest that CT scanning can show focal areas of osteoporosis in a Swiss cheese-like appearance. However, weighing the cost, radiation dose, and limited experience with use of CT scanning in evaluation of patients with CRPS, we suggest not using CT as a diagnostic test”.

**Measurements of Dermal Nerve Fiber and Mast Cell Density, and Proximity of Mast Cells to Nerve Fibers**

Morellini and colleagues (2018) noted that an interaction between cutaneous nerves and mast cells may contribute to pain in CRPS. To explore this, these investigators examined the density of dermal nerve fibers, and the density and proximity of mast cells to nerve fibers, in skin biopsies obtained from the affected and unaffected limbs of 57 patients with CRPS and 28 site-matched healthy controls. The percentage of the dermis stained by the pan-neuronal marker protein gene-product 9.5 was lower in the affected limb of patients than in controls (0.12 ± 0.01 % versus 0.22 ± 0.04 %, p < 0.05), indicating a reduction in dermal nerve fiber density. This parameter did not correlate with CRPS duration. However, it was lower in the affected than unaffected limb of patients with warm CRPS. Dermal mast cell numbers were similar in patients and controls, but the percentage of mast cells less than 5 µm from nerve fibers was significantly lower in the affected and unaffected limbs of patients than in controls (16.8 ± 1.7 %, 16.5 ± 1.7 %, and 31.4 ± 2.3 % respectively, p < 0.05). The authors confirmed previous findings of a mild neuropathy in CRPS. They stated that these findings
suggested that this either developed very early after injury or preceded CRPS onset; and loss of dermal nerve fibers in CRPS might result in loss of chemotactic signals, thus halting mast cell migration toward surviving nerve fibers. Failure of normal nerve fiber-mast cell interactions could contribute to the pathophysiology of CRPS. Further investigation is needed to establish the clinical value, if any, of measurement of dermal nerve fiber and mast cell density, and proximity of mast cells to nerve fibers as a diagnostic tool for CRPS.

**Small Non-Coding RNAs (microRNAs) as Diagnostic and Prognostic Biomarkers for CRPS**

Konig and co-workers (2017) stated that CRPS is a rare, but often painful and disabling, disease. Biomarkers are lacking, but several inflammatory substances have been associated with the pathophysiology. These researchers outlined the current knowledge with respect to target biomolecules and the analytical tools available to measure them. Targets include cytokines, neuropeptides and resolvins; analysis strategies are thus needed for different classes of substances such as proteins, peptides, lipids and small molecules. Traditional methods like immunoassays are of importance next to state-of-the art high-resolution mass spectrometry techniques and "omics" approaches. The authors concluded that future biomarker studies need larger cohorts, which improve sub-grouping of patients due to their presumed pathophysiology, and highly standardized work-flows from sampling to analysis.

Birklein and colleagues (2018) CRPS is a pain condition that usually affects a single limb, often following an injury. The underlying pathophysiology appeared to be complex and probably varies between patients. Clinical diagnosis is based on internationally agreed-upon criteria, which consider the reported symptoms, presence of signs and exclusion of alternative causes. Research into CRPS biomarkers to support patient stratification and improve diagnostic certainty is an important scientific focus, and recent progress in this
area provides an opportunity for an up-to-date topical review of measurable disease-predictive, diagnostic and prognostic parameters. Clinical and biochemical attributes of CRPS that may aid diagnosis and determination of appropriate treatment are delineated. Findings that predict the development of CRPS and support the diagnosis include trauma-related factors, neurocognitive peculiarities, psychological markers, and local and systemic changes that indicate activation of the immune system. The authors concluded that analysis of signatures of non-coding microRNAs that could predict the treatment response represents a new line of research; and results from the past 5 years of CRPS research indicated that a single marker for CRPS would probably never be found; however, a range of biomarkers might assist in clinical diagnosis and guide prognosis and treatment. These researchers noted that small non-coding RNAs (microRNAs) are emerging as diagnostic and prognostic biomarkers for CRPS.

**Magnetic Resonance Spectroscopy (MRS) and Positron Emission Tomography (PET) of Brain Metabolites and Peripheral Biomarkers of Inflammation in Diagnosis and Management of CRPS**

In a pilot study, Jung and colleagues (2019a) examined peripheral biomarkers and central metabolites affecting neuroinflammation in CRPS patients using [11C]-(R)-PK11195 PET and magnetic resonance spectroscopy (MRS). These researchers measured associations between neuro-metabolites and neuroinflammation in 12 CRPS patients and 11 healthy controls. Furthermore, these investigators examined various peripheral parameters that may affect neuroinflammation in CRPS. They found positive correlations of Lipid (Lip)13a/total creatine (tCr) and Lip09/tCr with neuroinflammation, the distribution volume ratio (DVR) of [11C]-(R)-PK11195 in the right and left insula in CRPS patients. However, these correlations were not found in controls. High hemoglobin levels correlated with decreased
neuroinflammation (the DVR of [11C]-(R)-PK11195) in the right thalamus and left insula in healthy controls. These researchers found that high levels of glucose and pH correlated with increased neuroinflammation, but high levels of CO2, basophil, and creatinine were associated with decreased neuroinflammation in the left thalamus and the right and left insula in CRPS patients. The authors concluded that this was the first report indicating that elevated neuroinflammation levels were associated primarily with lipids in the brain and pH, glucose, CO2, basophil, and creatinine in the peripheral parameters in CRPS patients. These researchers stated that these findings suggested that characterizing the peripheral biomarkers and central metabolites affecting neuroinflammation is essential to understanding the pathophysiology of CRPS.

In a pilot study, Jung and associates (2019b) examined distinct neuro-metabolites in the right and left thalamus and insula of patients with CRPS compared with healthy controls using proton MRS. Levels of N-acetyl-aspartate (NAA), N-acetyl-aspartyl-glutamate (NAAG), myo-inositol (mi), glutamine (Gln), glycerol-phospho-choline (GPC), glutathione (GSH), and alanine (Ala) relative to tCr levels, including creatine and phosphocreatine, were determined in the right and left thalamus and insula in 12 patients with CRPS compared with 11 healthy controls using MRS. Levels of NAAG/tCr and Ala/tCr were higher in patients with CRPS than in controls in the left thalamus; NAAG/tCr, mi/tCr, and Gln/tCr levels were higher but NAA/tCr levels were lower in the right insula of patients with CRPS compared with controls. There were negative correlations between GSH/tCr and pain score (McGill Pain Questionnaire) in the left thalamus. These findings were paramount to understand and determine all aspects of the complex pathophysiological mechanisms that underlie CRPS, including involvement of the central and para-sympathetic nervous systems as well as oxidative stress and antioxidants. The authors concluded that the distinct
metabolites presented herein may be essential to understand a strong diagnostic and prognostic potential for CRPS and to develop effective medical treatments.

**Biomarkers of Inflammation in the Diagnosis and Management of CRPS**

Bharwani and colleagues (2019) stated that CRPS is characterized by continuous pain that is often accompanied by sensory, motor, vasomotor, sudomotor, and trophic disturbances. If left untreated, it could have a significant impact on the quality of life (QOL) of patients. The diagnosis of CRPS is currently based on a set of relatively subjective clinical criteria: the New International Association for the Study of Pain clinical diagnostic criteria for CRPS. There are still no objective laboratory tests to diagnose CRPS and there is a great need for simple, objective, and easily measurable biomarkers in the diagnosis and management of this disease. These investigators discussed the role of inflammation in the multi-mechanism pathophysiology of CRPS and highlighted the application of potential biomarkers of inflammation (e.g., autoantibodies, calcitonin gene-related peptide [CGRP], CD8+ T lymphocytes, CD14+CD16+ monocytes, interleukin-6 [IL-6], mast cell numbers, microRNA [miRNA], soluble interleukin-2 receptor [sIL-2R], substance P [SP], and tumor necrosis factor-alpha [TNF-α]) in the diagnosis and management of this disease. The authors concluded that although there are a number of promising biomarkers of inflammation described in CRPS, it is still difficult to determine the place of these biomarkers in the diagnosis and management of CRPS based on the current literature. These researchers stated that future studies should focus on finding correlations between clinical symptoms and signs and these biomarkers.

**DNA Methylation Profiles and CRPS After Traumatic Injury**

https://aetnet.aetna.com/mpa/cpb/100_199/0147.html
Bruehl and colleagues (2019) noted that factors contributing to development of CRPS are not fully understood. These researchers examined possible epigenetic mechanisms that may contribute to CRPS following traumatic injury. DNA methylation profiles were compared between individuals developing CRPS (n = 9) and those developing non-CRPS neuropathic pain (n = 38) after undergoing amputation following military trauma. Linear Models for Microarray (LIMMA) analyses revealed 48 differentially methylated cytosine-phosphate-guanine dinucleotide (CpG) sites between groups (unadjusted p's < 0.005), with the top gene COL11A1 meeting Bonferroni-adjusted p < 0.05. The 2nd largest differential methylation was observed for the HLA-DRB6 gene, an immune-related gene linked previously to CRPS in a small gene expression study. For all but 7 of the significant CpG sites, the CRPS group was hypo-methylated. Numerous functional Gene Ontology-Biological Process categories were significantly enriched (false discovery rate-adjusted q value < 0.15), including multiple immune-related categories (e.g., activation of immune response, immune system development, regulation of immune system processes, and antigen processing and presentation). Differentially methylated genes were more highly connected in human protein-protein networks than expected by chance (p < 0.05), supporting the biological relevance of the findings. Results were validated in an independent sample linking a DNA biobank with electronic health records (n = 126 for CRPS phenotype, n = 19,768 for non-CRPS chronic pain phenotype). Analyses using PrediXcan methodology indicated differences in the genetically determined component of gene expression in 7 of 48 genes identified in methylation analyses (p's < 0.02). The authors concluded that these findings suggested that immune- and inflammatory-related factors might confer risk of developing CRPS following traumatic injury.

**Electronic Nose (Aeonose) for Diagnosis of CRPS**
Bijl and colleagues (2019) noted that CRPS is a complication after surgery or trauma and is characterized by a continuing regional pain in a distal extremity. The pain is disproportionate in severity and duration in relation to the preceding trauma. Currently, the diagnosis is based on the patients’ signs and symptoms. There is no objective clinically applicable test available to confirm the diagnosis of CRPS, however this could contribute to a more reliable and valid diagnosis. Since the treatment of CRPS differs from that of other types of pain this could thereby lead to earlier and (more) appropriate treatment and possibly to lower medical costs. The Aeonose is a diagnostic test device that detects volatile organic profiles in exhaled air. Exhaled breath analysis using an electronic nose has been successfully applied to differentiate between sick and healthy individuals for various indications. In a prospective, observational, feasibility/pilot study, these investigators examined if the Aeonose is able to measure a difference in the volatome of CRPS patients compared to the volatome of healthy controls. Subjects were adult patients diagnosed with CRPS according to the latest IASP criteria (n = 36) and matched healthy controls (n = 36). Breath profiles were sampled by breathing in and out through the Aeonose. Data were compressed using a Tucker3-like solution and subsequently used for training an artificial neural network together with the classification “CRPS: Yes” or “CRPS: No”. Cross-validation was applied using the leave-10 %-out method. Data of the 72 subjects were analyzed, resulting in a sensitivity of 83 % (95 % CI: 67 % to 93 %), specificity of 78 % (95 % CI: 60 % to 89 %), and an overall accuracy of 81 %. The authors concluded that the findings of this study suggested that the Aeonose could distinguish patients with CRPS from healthy controls based on analysis of their volatome. Moreover, these researchers stated that further validation steps are needed to establish the value of the Aeonose in the differential diagnostic process of CRPS.
The authors stated that drawbacks of this study were that these researchers did not correct for lifestyle, physiological status and genetic background, that the percentage of cardiac, pulmonary and gastro-intestinal co-morbidities were significantly different between the patients and healthy controls and that although patients were asked to refrain from drinking alcohol, coffee and smoking 1 hour before the breath sample was taken, there was no period of refrainment on eating and drinking in general.

### CPT Codes / HCPCS Codes / ICD-10 Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</strong></td>
<td></td>
</tr>
<tr>
<td>CPT codes not covered for indications listed in the CPB:</td>
<td></td>
</tr>
<tr>
<td>No specific code:</td>
<td></td>
</tr>
<tr>
<td><strong>CREB-binding protein (CREBBP), Measurement of serum anti-neuronal antibodies/ autoantibodies, Gene expression profiling of early region 1A binding protein p300 (EP300), Signal transducer and activator of transcription (STAT)3, Signal transducer and activator of transcription of (STAT5A), Measurement of dermal nerve fiber and mast cell density, Proximity of mast cells to nerve fibers, Small non-coding RNAs (microRNAs) as diagnostic and prognostic biomarkers, inflammation biomarkers, DNA methylation profiles, electronic nose (Aeonose)</strong></td>
<td></td>
</tr>
<tr>
<td>72170</td>
<td>Radiologic examination, pelvis</td>
</tr>
<tr>
<td>72190</td>
<td><strong>+</strong></td>
</tr>
<tr>
<td>73000</td>
<td>Radiologic examination, upper extremities</td>
</tr>
<tr>
<td>73140</td>
<td><strong>+</strong></td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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</tr>
<tr>
<td>73501 - 73660</td>
<td>Radiologic examination, lower extremities</td>
</tr>
<tr>
<td>73218 - 73222</td>
<td>Magnetic resonance imaging, upper extremities</td>
</tr>
<tr>
<td>73718 - 73723</td>
<td>Magnetic resonance imaging, lower extremities</td>
</tr>
<tr>
<td>76390</td>
<td>Magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>76808</td>
<td>Brain imaging, positron emission tomography (PET); metabolic evaluation</td>
</tr>
<tr>
<td>76809</td>
<td>perfusion evaluation</td>
</tr>
<tr>
<td>76881 - 76882</td>
<td>Ultrasound, extremity, nonvascular, real-time with image documentation; complete or limited, anatomic specific</td>
</tr>
<tr>
<td>77078</td>
<td>Computed tomography, bone mineral density study, 1 or more sites, axial skeleton (eg, hips, pelvis, spine)</td>
</tr>
<tr>
<td>78320</td>
<td>Bone and/or joint imaging; tomographic (SPECT)</td>
</tr>
<tr>
<td>78811</td>
<td>Positron emission tomography (PET) imaging, limited area (eg, chest, head/neck)</td>
</tr>
<tr>
<td>78812</td>
<td>skull base to mid-thigh</td>
</tr>
<tr>
<td>78813</td>
<td>whole body</td>
</tr>
<tr>
<td>81111</td>
<td>Human Platelet Antigen 9 genotyping (HPA-9w0, ITGA2B (integrin, alpha 2b (platelet glycoprotein llb of llb/llla complex, antigen CD41) [GPIIb]) (eg neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpural), gene analysis, common variant, HPA-9a/b (V837M)</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
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</tr>
<tr>
<td>81370 - 81377</td>
<td>HLA Class I and II typing, low resolution (eg, antigen equivalents)</td>
</tr>
<tr>
<td>81378 - 81383</td>
<td>HLA Class I typing, high resolution (ie, alleles or allele groups)</td>
</tr>
<tr>
<td>82725</td>
<td>Fatty acids, nonesterified</td>
</tr>
<tr>
<td>82726</td>
<td>Very long chain fatty acids</td>
</tr>
<tr>
<td>82978</td>
<td>Glutathione</td>
</tr>
<tr>
<td>93740</td>
<td>Temperature gradient studies</td>
</tr>
<tr>
<td>93922</td>
<td>Limited bilateral non-invasive physiologic studies of upper or lower extremity arteries, (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus bidirectional, Doppler waveform recording and analysis at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus volume plethysmography at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries with transcutaneous oxygen tension measurements at 1-2 levels)</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>93923</td>
<td>Complete bilateral non-invasive physiologic studies of upper or lower extremity arteries, 3 or more levels (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental blood pressure measurements with bidirectional Doppler waveform recording and analysis at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental volume plethysmography at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental transcutaneous oxygen tension measurements at 3 or more level(s), or single level study with provocative functional maneuvers (eg, measurements with postural provocative tests or measurements with reactive hyperemia))</td>
</tr>
<tr>
<td>93925</td>
<td>Duplex scan of lower extremity arteries or arterial bypass grafts; complete bilateral study</td>
</tr>
<tr>
<td>93926</td>
<td>unilateral or limited study</td>
</tr>
<tr>
<td>93931</td>
<td>Duplex scan of upper extremity arteries or arterial bypass grafts; unilateral or limited study</td>
</tr>
</tbody>
</table>

**HCPCS codes not covered for indications listed in the CPB:**

| J2760    | Injection, phentolamine mesylate, [Regitine], up to 5 mg                                                                                                                                                                                                            |

**ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):**

| G90.50 - G90.9 | Complex regional pain syndrome I (CRPS I)                                                                                           |
The above policy is based on the following references:


27. Martin CW; WCB Evidence Based Practice Group. CRPS (Complex Regional Pain Syndrome): Towards the development of diagnostic criteria and treatment guidelines. Richmond, BC: Workers Compensation Board of British Columbia (WorkSafe BC), Compensation and Rehabilitation Services Division; January 2004.


44. Verdugo RJ, Campero M, Ochoa JL. Phentolamine sympathetic block in painful polyneuropathies. II.


Amendment to Aetna Clinical Policy Bulletin

Number: 0147

Complex Regional Pain Syndrome (CRPS)/Reflex Sympathetic Dystrophy (RSD):

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania

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