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Rosacea

Number: 0547

Policy

Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers medical treatment of rosacea medically necessary. However, surgical treatment of disfigurement from rosacea (e.g., scarring and telangiectasias) is considered cosmetic.

Aetna considers excision or shaving of rhinophyma medically necessary for the treatment of bleeding or infection refractory to medical therapy (i.e., the need for repeated cautery of bleeding telangiectasias or frequent courses of antibiotics for pustular eruptions),

Aetna considers topical oxymetazoline (Rhofade) medically necessary for the treatment of persistent facial erythema associated with rosacea in adults.

Aetna considers the following procedures experimental and investigational because their effectiveness has not been established:

- Measurement of serum bilirubin, uric acid and zonulin levels in rosacea

Policy History

Last Review

08/18/2020

Effective: 06/29/2001

Next

Review: 06/10/2021

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

- Reflectance confocal microscopy and spectrometry for rosacea assessment and monitoring of therapy

Aetna considers the following treatments of rosacea experimental and investigational because their effectiveness for this condition has not been established:

- Botulinum toxin
- Helicobacter pylori therapy
- Hydroxychloroquine
- Phytochemical and botanical therapies
- Intense pulsed light (for ocular rosacea)
- Nano-emulsion of pioglitazone
- Polyphenols
- Recombinant bovine basic fibroblast growth factor gel
- Topical calcineurin inhibitors (e.g., pimecrolimus and tacrolimus)
- Topical minocycline.

Also
see CPB 0559 - Pulsed Dye Laser Treatment (0559.html).

Note: Cosmetic surgery is excluded from coverage under Aetna standard benefit plans. Please check benefit plan descriptions for details.
See CPB 0031 - Cosmetic Surgery (../1_99/0031.html).

Background

Rosacea, also called acne rosacea, is a multi-factorial skin disorder that usually affects middle-aged individuals and is characterized by persistent erythema, telangiectasias and acute episodes of edema, papules, and pustules. Patients may have a tendency to flush easily. Chronic inflammation is involves especially the skin of the nose, forehead, and cheeks that is characterized by congestion, flushing,

telangiectasia and marked nodular swelling of tissues especially of the nose. Treatment is difficult and is dependent on the severity of disease. Avoidance of excessive sunlight and extreme temperatures is typically recommended. Medical management is aimed only at the inflammatory papules and pustules and the erythema that surrounds them. Topical preparations of metronidazole, clindamycin and erythromycin have been shown to be helpful for mild cases. Oral tetracycline and erythromycin are often prescribed for moderate cases, and Accutane (isotretinoin) has been found to be effective in severe refractory cases. Oral metronidazole has also been used in severe refractory cases.

Laser, dermabrasion and chemical peels are used to eliminate erythema, telangiectasias and other cosmetic effects of rosacea. Laser skin resurfacing involves removal of the upper layer of skin that triggers the body's natural production of new collagen and skin cells. Chemical peels involve the controlled removal of the outer layer of facial skin with specific chemicals such as phenol and trichloroacetic acid (TCA) to smooth out the skin. Dermabrasion is a procedure that abrades the facial skin to remove the upper layer resulting in smoother skin.

Accepted guidelines indicate that laser surgery and electrocautery are the only satisfactory treatments for the telangiectasias. Treatment is directed toward obliteration of ectatic vessels. Rhinophyma (soft tissue and sebaceous hyperplasia of the nose) is considered the culmination of acne rosacea. Rhinophyma responds to electrosurgery, laser excision, and surgical debulking. Because telangiectasias and rhinophyma do not cause functional limitations, their treatment is considered cosmetic.

Goldberg (2005) stated that pharmacological agents remain the mainstay for initial and maintenance treatment of rosacea. However, monochromatic (i.e., laser) and polychromatic light-based therapies are increasingly being used for the treatment of certain signs of rosacea. The author noted that despite the

increased use of lasers and other light-based therapies, few well-controlled studies have been conducted on their use for the treatment of rosacea. Furthermore, a Cochrane review on interventions for rosacea (van Zuuren et al, 2005) concluded that the quality of studies evaluating rosacea treatments was generally poor. There is evidence that topical metronidazole and azelaic acid are effective. There is some evidence that oral metronidazole and tetracycline are effective. There is insufficient evidence concerning the effectiveness of other treatments. Good randomized controlled trials looking at these treatments are urgently needed.

Parodi et al (2011) stated that a range of treatment options are available in rosacea, which include several topical (mainly metronidazole, azelaic acid, other antibiotics, sulfur, retinoids) and oral drugs (mainly tetracyclines, metronidazole, macrolides). In some cases, the first choice is a systemic therapy because patients may have sensitive skin and topical medications can be irritant. Isotretinoin can be used in resistant cases of rosacea. Unfortunately, the majority of studies on rosacea treatments are at high or unclear risk of bias. A recent Cochrane review (van Zuuren et al, 2011) found that only topical metronidazole, azelaic acid, and oral doxycycline (40 mg) had some evidence to support their effectiveness in moderate-to-severe rosacea and concluded that further well-designed, adequately-powered randomized controlled trials are needed. In the authors' practice, they evaluated their patients for the presence of 2 possible triggers, Helicobacter pylori infection and small intestinal bacterial over-growth. When they are present, these clinicians use adapted antibiotic protocols. If not, they use oral metronidazole or oral tetracycline to treat papulopustolar rosacea. They also look for Demodex folliculorum infestation. When Demodex concentration is higher than 5/cm(2), they use topical crotamiton 10 % or metronidazole.

Bamford et al (2012) noted that a 2006 article published in the International Journal of Dermatology reported that oral zinc sulfate 100 mg thrice-daily was associated with improvement in the severity of facial rosacea. The current study was undertaken to further evaluate the role of zinc in the management of rosacea. This was a randomized, double-blind trial of 220 mg of zinc sulfate twice-daily for 90 days in patients with moderately severe facial rosacea at baseline. Subjects were recruited in the Upper Midwest USA between August 2006 and April 2008, and followed until July 2008. A total of 44 subjects completed the trial (22 in each arm). Rosacea improved in both groups. There were no differences in magnitude of improvement based on rosacea severity scores between subjects receiving zinc sulfate and subjects receiving placebo ($p = 0.284$). Serum zinc levels were higher in subjects receiving zinc ($p < 0.001$). Oral zinc sulfate was not associated with greater improvement in rosacea severity compared with placebo in this study. The authors stated that additional studies are needed to determine what role oral zinc may have in the management of rosacea.

Chang et al (2012) stated that papulopustular acne rosacea is a chronic inflammatory condition that can be difficult to treat. Many patients are unwilling to use systemic medications, and single topical agents alone may not address all the symptoms of rosacea. A combination topical clindamycin phosphate 1.2 % and tretinoin 0.025 % gel is efficacious for acne vulgaris, and may be helpful for rosacea, since acne vulgaris and rosacea shares many similar clinical and histologic features. In a randomized, double-blind, placebo-controlled, 2-site pilot study, these investigators examined the safety and effectiveness of a combination gel consisting of clindamycin phosphate 1.2 % and tretinoin 0.025 % on papulopustular rosacea after 12 weeks of usage. A total of 79 subjects with moderate-to-severe papulopustular acne rosacea using both physician and subjects' validated assessment tools wer included in this study. Primary endpoint consisted of statistically significant reduction in absolute papule or pustule

count after 12 weeks of usage. There was no significant difference in papule/pustule count between placebo and treated groups after 12 weeks (p = 0.10). However, there was nearly significant improvement in physicians' assessments of the telangiectasia component of rosacea (p = 0.06) and erythemato-telangiectatic rosacea subtype (p = 0.05) in treated versus placebo group after 12 weeks. The only significant adverse event difference was facial scaling, which was significantly increased in treated group (p = 0.01), but this did not result in discontinuation of study drug. The authors concluded that a combination gel of clindamycin phosphate 1.2 % and tretinoin 0.025 % may improve the telangiectatic component of rosacea and appears to better treat the erythemato-telangiectatic subtype of rosacea rather than papulopustular subtype. They stated that these future studies with much larger sample size might confirm these preliminary findings.

Sadick et al (2011) rhinophyma is a benign dermatological disease of the nose that affects primarily Caucasian men in their 5h decade of life. Its main characteristic is a slowly progressive hyperplasia of the sebaceous glands and the adjacent tissue with irregular thickening of the nasal skin and nodular deformation. It is defined as the end stage of acne rosacea. The main reasons for patients to seek medical help are cosmetic problems and functional impairments (e.g., nasal airway obstruction, difficulty in eating). Surgery is indisputably the treatment of choice for rhinophyma.

Macdonald and Nguyen (2012) presented the case of a 42-year old man with a 10-year history of rosacea, and who exhibited impaired nasal breathing and a mass on the tip of his nose that began growing 9 months earlier. Examination revealed a multi-lobulated sebaceous nodule (4 cm by 3 cm) protruding from the nasal tip. The histopathological findings of marked sebaceous hyperplasia, follicular rupture, an absence of granulomas, and prominent fibrosis confirmed the clinical suspicion of rhinophyma. A biopsy specimen was obtained,

and staining did not reveal infectious organisms. Phyma is the result of hyperplasia and fibrosis of the sebaceous glands in the presence of rosacea. Although rhinophyma is by far the most common pattern in cases of phyma, metophyma (swelling of the forehead), otophyma (swelling of the ear), and gnathophyma (swelling of the chin) can also be observed. The lesions can become large, causing significant social stigmatization and posing a challenge in the management of patient care. Re-contouring with the use of electrosurgery or CO2 laser resurfacing is common. This patient underwent staged procedures, with shave-debulking surgery followed by contouring with electrosurgery. His breathing was restored to normal.

Little et al (2012) stated that rhinophyma is a cosmetically disfiguring disease of the external nose that most frequently affects elderly Caucasian males. Frequently, there is associated derangement of nasal airway patency. Although the true incidence of rhinophyma and its exact etiology remain unknown, it is widely believed to represent the final stage in a continuum of acne rosacea. Medical therapy has not been effective in reversing the disease process, and surgery remains the most accepted method of treating rhinophyma. A wide variety of surgical techniques have been developed and modified over the years in an effort to treat this disorder safely and without significant sequelae. Despite many advances in fundamental understanding, surgical techniques, and related technologies, no single method has been universally embraced and employed as the "gold standard". These investigators described the most commonly employed modern surgical techniques and methods used throughout the world to treat rhinophyma. There was special emphasis on the authors' preferred method of excision and post-operative management (tumescent anesthesia, Weck blade excision, and argon beam coagulation), which has been demonstrated to be effective and expeditious.

Husein-Elahmed and Armijo-Lozano (2013) noted that early stages of rhinophyma can be managed with medical treatment using isotretinoin or oral antibiotics (metronidazole). However, severe cases usually are refractory to medical approaches. Surgical therapies to treat these severe refractory cases have been described. These investigators described a simple, safe, efficient, and cost-effective approach to the treatment of severe rhinophyma using a scalpel and the electroscalpel, instruments readily available in every operating room.

An UpToDate review on "Management of rosacea" (Maier, 2013) states that "Tissue hypertrophy, dilated follicles, and irregular nodular overgrowths are characteristic features of the phymatous subtype of rosacea. These changes most commonly affect the nose (rhinophyma), but may also affect other areas such as the chin, cheeks, and ears …. Laser ablation and surgical techniques can be used to debulk and recontour tissue distorted by phymatous changes. Ablative carbon dioxide lasers and infrared diode lasers have been used for this purpose. Surgical debulking can be performed through dermabrasion, scalpel excision, electrosurgery, or cryosurgery".

Moustafa et al (2014) reviewed important aspects of the pathogenesis of rosacea and the role of new treatment options in its management. New, emerging treatments show promise; however, quality randomized controlled trials (RCTs) for many of these drugs are lacking. Brimonidine tartrate (Mirvaso) is an effective newly approved treatment for erythemato-telangiectatic rosacea. Topical oxymetazoline has potential for the treatment of erythemato-telangiectatic rosacea, with efficacy described in case reports and RCTs currently underway.

In a Cochrane review, van Zuuren et al (2015) evaluated the safety and effectiveness of treatments for rosacea. The authors concluded that there was low quality evidence for low dose minocycline, laser and intense pulsed light therapy and

cyclosporine ophthalmic emulsion for ocular rosacea. Time needed to response and response duration should be addressed more completely, with more rigorous reporting of adverse events. They stated that further studies on treatment of ocular rosacea are needed.

An UpToDate review on “Management of rosacea” (Maier, 2015) states that “The role of topical calcineurin inhibitors (tacrolimus and pimecrolimus) in erythematotelangiectatic rosacea is uncertain. Improvement with topical tacrolimus has been reported in small numbers of patients …. Topical calcineurin inhibitors do not appear to be beneficial for papulopustular rosacea …. The US Food and Drug Administration approved topical ivermectin 1 % cream for the treatment of inflammatory lesions of rosacea in December 2014. The drug is not yet commercially available …. Ivermectin 1 % cream is applied once daily. Apea-sized amount is applied to each affected area of the face (e.g., forehead, chin, nose, each cheek) and spread into a thin layer”.

In a phase III, investigator-blinded, randomized, parallel-group study, Taieb and colleagues (2015) demonstrated superiority of once-daily ivermectin 1 % cream (IVM 1 %) once-daily versus twice-daily metronidazole (MTZ 0.75 %) cream, regarding percentage reduction of inflammatory lesions in subjects with moderate to severe papulo-pustular rosacea (PPR). Subjects received IVM 1 % once-daily, or MTZ 0.75 % twice-daily over 16 weeks. Efficacy assessments were inflammatory lesion counts and Investigator's Global Assessment (IGA). Safety assessments included incidence of adverse events (AEs) and local tolerance parameters. Subjects evaluated their disease following a 5-grade scale and completed questionnaires. A total of 962 subjects were randomized to receive IVM 1 % (n = 478) or MTZ 0.75% (n = 484). At week 16, IVM 1 % was significantly superior to MTZ 0.75 % in terms of reduction from baseline in inflammatory lesions (83.0 % versus 73.7 %; $p < 0.001$), observed as early

as week 3 (Last Observation Carried Forward, LOCF). Investigator's Global Assessment results (subjects 'clear' or 'almost clear') also favored IVM 1 %: 84.9 % versus 75.4 %, respectively ($p < 0.001$). Incidence of AEs was comparable between groups and local tolerability was better for IVM 1 %. More subjects receiving IVM rated their global improvement as 'excellent' or 'good'. The authors concluded that Ivermectin 1 % cream was significantly superior to MTZ 0.75 % cream and achieved high patient satisfaction.

Phytochemical and Botanical Therapies

In a systematic review, Fisk and colleagues (2015) evaluated clinical studies on the use of botanical agents for the treatment of rosacea. Medline and Embase databases were searched for clinical studies evaluating botanical therapies for rosacea. Major results were summarized, and study methodology was analyzed. Several botanical therapies may be promising for rosacea symptoms, but few studies were methodologically rigorous. Several plant extract and phytochemicals effectively improved facial erythema and papule/pustule counts caused by rosacea. Many studies were not methodologically rigorous. The authors stated that further research is critical, as many botanicals have been evaluated in only 1 study. These investigators noted that botanical agents may reduce facial erythema and effectively improve papule/pustule counts associated with rosacea; although promising, further research in the area is imperative.

Botulinum Toxin

Dayan and colleagues (2012) noted that there are many different treatment modalities for each of the physical findings associated with rosacea, and all have varying results. As the use of onabotulinumtoxinA (BoNT-A) rises, its benefit in the treatment of a growing number of medical diseases increases. The authors reported anecdotal evidence of patients with rosacea experiencing improved symptoms of erythema and

flushing after treatment with intradermal, microdroplets of onabotulinumtoxinA. There were no AEs reported for any of the treatments. The mechanism of action through a likely neurogenic component to vascular dysfunction, inflammation, and hyper-sebaceous activity was reviewed. The effectiveness of BoNT-A in the treatment of rosacea needs to be examined in well-designed studies.

Bloom et al (2015) evaluated the safety and effectiveness of intradermal BoNT-A on facial erythema of rosacea. A total of 25 subjects aged 35 to 70 years with Fitzpatrick skin types I to IV and facial erythema of erythemato-telangiectatic rosacea were enrolled in the trial. Subjects received 15 to 45 units of intradermal injections of BoNT-A to the nasal tip, nasal bridge, and nasal alae. A non-treating investigator assessed the facial erythema of rosacea using a standardized grading system (0 = absent, 1 = mild erythema, 2 = moderate erythema, and 3 = severe erythema) to evaluate digital photographs at baseline, 1, 2, and 3 months after treatment. Statistical analysis of erythema grade included 1-way repeated-measures analysis of variance and pairwise comparisons using SPSS (IBM Corporation) software; 15 of the 25 enrolled subjects completed all the appropriate follow-up visits. Only the 15 subjects with complete data were included in analysis. The subjects were of Fitzpatrick skin types I to III, a mean age of 54 years, and 80 % women. The mean baseline erythema grade was 1.80 (± 0.56), and the mean erythema grade at 3 months after treatment was 1.00 (± 0.38). The treatment resulted in statistically significant improvement in erythema grade at 1, 2, and 3 months after treatment when compared with baseline ($p < 0.05$, $p < 0.001$, and $p < 0.05$, respectively). Pair-wise comparison to baseline showed a mean erythema grade improvement of 0.80 ($p < 0.001$) at 3-month follow-up. The authors concluded that intradermal injection of botulinum toxin for the treatment of facial erythema of rosacea appeared both safe and effective. Moreover, they stated that larger, randomized, blinded, placebo-controlled studies are needed;

additionally, further investigation is needed to elucidate the mechanism of action by which botulinum toxin improves facial flushing of rosacea.

Schlessinger and colleagues (2017) stated that BoNT-A is now widely established for the main approved indication of reducing glabellar lines, and is also widely used off-label to improve the appearance of wrinkles and lines in other parts of the face. The number of aesthetic procedures continues to increase as the patient population becomes more diverse, in particular with increasing numbers of people of color and men. Further developments in treatment may continue to expand the audience for BoNT-A by making procedures more comfortable and by delivering a more natural, less static appearance. These may be achieved through use of combinations of BoNT-A with other aesthetic procedures, tailoring the dose of toxin to the patient's muscle mass or by using novel injection and application techniques. Beyond amelioration of facial lines, encouraging results have been seen with the use of BoNT-A to improve the appearance of hypertrophic and keloid scars and even to prevent them. Studies have been conducted with scars in various parts of the body and further research is ongoing. Dermatological and other medical uses for BoNT-A are also active areas of research. Injections of BoNT-A have been shown to reduce signs and symptoms of acne, rosacea, and psoriasis, to reduce neuromuscular pain, and to bring about significant improvements in a number of rare diseases that are caused or exacerbated by hyperhidrosis. The authors reviewed these new uses for BoNT-A, looking at the rationale for their use and discussing the results of published case studies and clinical trials. These areas have shown great promise to-date, but more and larger clinical studies are needed before these treatments become a clinical reality.

Topical Oxymetazoline

In a phase-II clinical trial, DuBois and co-workers (2018) evaluated the optimal oxymetazoline (an alpha 1A-adrenoceptor agonist) dosing regimen in patients with moderate-to-severe persistent facial erythema of rosacea. Patients were randomly assigned to oxymetazoline cream, 0.5 %, 1.0 %, or 1.5 %, or vehicle, administered once-daily (QD) or twice-daily (BID) for 28 consecutive days. The primary efficacy end-point was the proportion of patients with greater than or equal to 2-grade improvement from baseline on the Clinician Erythema Assessment (CEA) and the Subject Self-Assessment of erythema (SSA-1) on day 28. Safety assessments included treatment-emergent AEs (TEAEs) and dermal tolerability. A total of 356 patients were treated (mean age of 50.0 years; 80.1 % women). The proportions of patients achieving the primary end-point were significantly higher with oxymetazoline 0.5 % QD ($p = 0.049$), 1.0 % QD ($p = 0.006$), 1.5 % QD ($p = 0.012$), 1.0 % BID ($p = 0.021$), and 1.5 % BID ($p = 0.006$) versus their respective vehicles. For both QD and BID dosing, the efficacy of oxymetazoline 1.0 % was greater than the 0.5 % dose and comparable to the 1.5 % dose. Safety and application-site tolerability were similar across groups. The authors concluded that oxymetazoline 1.0 % QD provided the optimal dosing regimen and was selected for evaluation in phase-III clinical trials.

In a phase-III, multi-center, double-blind clinical trial, Kircik and associates (2018) evaluated the safety and efficacy of topical oxymetazoline in patients with facial erythema associated with moderate-to-severe rosacea. Patients were randomly assigned to treatment with oxymetazoline hydrochloride cream 1.0 % or vehicle applied QD for 29 days, and were followed for 28 days post-treatment. The primary efficacy outcome was having at least a 2-grade decrease from baseline on both the CEA and the Subject Self-Assessment for rosacea facial redness (SSA) scales (composite success) at 3, 6, 9, and 12 hours post-dose on day 29. Safety assessments included TEAEs and post-treatment worsening of erythema (composite CEA/SSA increase of 1-grade severity from baseline; rebound

effect). A total of 440 patients (mean age of 49.5 years; 78.9 % women) were randomized (oxymetazoline, n = 222; vehicle, n = 218); most had moderate erythema. On day 29, significantly greater proportions of oxymetazoline recipients achieved the primary efficacy outcome at each time-point ($p < 0.02$) and overall ($p < 0.001$) compared with vehicle recipients. The incidence of discontinuation due to TEAEs was low in both groups (oxymetazoline group, 1.8 %; vehicle group, 0.5 %). The most common TEAEs reported during the entire study period were application-site dermatitis, application-site erythema, and headache in the oxymetazoline group (1.4 % each), and headache (0.9 %) in the vehicle group. Following cessation of treatment, low proportions of patients experienced rebound effect (oxymetazoline group, 2.2 %; vehicle group, 1.1 %). The authors concluded that oxymetazoline applied to the face once-daily for 29 days was safe, effective, and well-tolerated in patients with moderate-to-severe persistent facial erythema of rosacea.

In a phase-III clinical trial, Baumann and colleagues (2018) evaluated oxymetazoline for the treatment of moderate-to-severe persistent erythema of rosacea. Eligible patients were randomly assigned 1:1 to receive oxymetazoline cream 1.0 % or vehicle applied topically to the face QD for 29 days. The primary efficacy outcome was greater than or equal to 2-grade improvement from baseline on both CEA and SSA (composite success) at 3, 6, 9, and 12 hours post-dose on day 29. Digital image analysis of rosacea facial erythema was evaluated as a secondary efficacy outcome measure. Safety assessments TEAEs and dermal tolerability. Patients were followed for 28 days post-treatment to assess worsening of erythema (1-grade increase in severity from baseline on composite CEA/SSA in patients with moderate erythema at baseline; rebound effect). The study included 445 patients (mean age of 50.3 years; 78.7 % women); most had moderate erythema at baseline (84.0 % on CEA; 91.5 % on SSA). The proportion of patients achieving the primary efficacy outcome was significantly greater with oxymetazoline versus vehicle ($p = 0.001$). Similar

results favoring oxymetazoline over vehicle were observed for the individual CEA and SSA scores ($p < 0.001$ and $p = 0.011$, respectively). Median reduction in rosacea facial erythema on day 29 as assessed by digital image analysis also favored oxymetazoline over vehicle ($p < 0.001$). Safety results were similar between oxymetazoline and vehicle; discontinuations due to TEAEs were low (2.7 % versus 0.5 %). Following cessation of treatment, 2 (1.2 %) patients in the oxymetazoline group and no patient in the vehicle group had rebound effect compared with their day 1 baseline score. The authors concluded that topical oxymetazoline applied to the face once-daily for 29 days was safe, effective, and well-tolerated in the treatment of moderate-to-severe persistent facial erythema of rosacea.

Draelos and colleagues (2018) examined the long-term safety and efficacy of oxymetazoline cream 1.0 % in patients with rosacea with moderate-to-severe persistent erythema. Patients applied oxymetazoline QD for 52 weeks. Safety assessments included TEAEs, skin blanching, inflammatory lesion counts, telangiectasia, disease severity, and rebound effect. Efficacy was assessed by the CEA and SSA composite score at 3 and 6 hours after the dose on day 1 and at weeks 4, 26, and 52. Among 440 patients, 8.2 % reported treatment-related TEAEs; the most common were application-site dermatitis, paresthesia, pain, and pruritus. The rate of discontinuation due to AEs (mostly application-site TEAEs) was 3.2 %. No clinically meaningful changes were observed in skin blanching, inflammatory lesions, or telangiectasia. At week 52, 36.7 %, and 43.4 % of patients achieved a 2-grade or greater composite improvement from baseline in both CEA and SSA 3 and 6 hours after a dose, respectively. Less than 1 % of patients experienced a rebound effect following treatment cessation. The authors concluded that this long-term study demonstrated sustained safety, tolerability, and efficacy of oxymetazoline for moderate-to-severe persistent erythema of rosacea.

According to the Prescribing Information, Oxymetazoline hydrochloride cream (Rhofade) is indicated for the topical treatment of persistent facial erythema associated with rosacea in adults.

Helicobacter Pylori Therapy

Jorgensen and associates (2017) stated that rosacea is a common skin disease characterized by facial erythema, telangiectasia, papules and pustules. Helicobacter pylori infection has been suggested to play a role in the etiopathogenesis of rosacea. These investigators systematically reviewed and meta-analyzed the relationship between rosacea and infection with Helicobacter pylori. A literature search was performed using PubMed, Embase and Web of Science. Data extraction and analyses were performed on descriptive data. Study quality was assessed using the Newcastle-Ottawa Scale. Random-effects models with DerSimonian-Laird methods were utilized to estimate pooled odds ratios (ORs), with 95 % confidence intervals (95 % CIs). Heterogeneity of results was assessed using I^2 statistics. A total of 454 articles were identified and 42 full-text articles were chosen for further review; 14 studies were included in the quantitative meta-analysis, comprising a total of 928 rosacea patients and 1,527 controls. The overall association between Helicobacter pylori infection and rosacea was non-significant (OR 1.68, 95 % CI: 1.00 to 2.84, p = 0.052), but analysis restricted to C-urea breath test showed a significant association (OR 3.12, 95 % CI: 1.92 to 5.07, p < 0.0001). Effect of eradication treatment on rosacea symptoms was assessed in 7 studies, but without significant effect (RR 1.28, 95 % CI: 0.98 to 1.67, p = 0.069). The authors concluded this meta-analysis found weak associations between rosacea and Helicobacter pylori infection as well as an effect of Helicobacter pylori therapy on rosacea symptoms, albeit that these did not reach statistical significance.

Moreover, they stated that whether a pathogenic link between the 2 conditions exists, or whether Helicobacter pylori infection represents a proxy for other factors remains unknown.

Intense Pulsed Light (for Ocular Rosacea)

In a review on “Topical, systemic and light-based therapies”, Kennedy Carney and colleagues (2009) reported that rosacea is a common chronic inflammatory disorder of the facial skin characterized by periods of exacerbation, remission and possible progression. The principle subtypes include erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea and ocular rosacea. Although the pathogenesis is unknown, rosacea is largely recognized as an inflammatory disorder. Individual subtypes are likely a result of different pathogenic factors and respond best to different therapeutic regimens. The non-pharmacologic approach to therapy is adequate skin care, trigger avoidance and photo-protection; in addition, there are several topical, herbal, systemic and light based therapies available. Standard Food and Drug Administration

(FDA)-approved treatments included topical sodium sulfacetamide, metronidazole, and azelaic acid. Anti-inflammatory dose doxycycline, a controlled-release 40-mg formulation offered a non-antibiotic, anti-inflammatory therapeutic option. Combination of azelaic acid or topical metronidazole with anti-inflammatory doxycycline appeared to have a synergistic effect. Oral isotretinoin may be effective for phymatous rosacea and treatment resistant rosacea. Light based therapies with pulsed dye laser and intense pulsed light (IPL) are effective in treatment of erythema and telangiectasias.

In a systematic review, Wat and associates (2014) reported that the FDA has approved IPL devices for the treatment of a variety of benign pigmentary and vascular lesions, but the range of disease amenable to IPL treatment continues to

expand, and there are no evidence-based clinical guidelines for its use in FDA-approved and off-label indications. These investigators provided evidence-based recommendations to guide physicians in the application of IPL for the treatment of dermatologic disease. They performed a literature search of the CENTRAL (1991 to May 6, 2013), Embase (1974 to May 6, 2013), and Medline in-process and non-indexed citations and Medline (1964 to present) databases. Studies that examined the role of IPL in primary dermatologic disease were identified, and multiple independent investigators extracted and synthesized data. Recommendations were based on the highest level of evidence available. Level 1 evidence was found for the use of IPL for the treatment of melasma, acne vulgaris, and telangiectasia. Level 2 evidence was found for the treatment of lentiginous disease, rosacea, capillary malformations, actinic keratoses, and sebaceous gland hyperplasia. Level 3 or lower evidence was found for the treatment of poikiloderma of Civatte, venous malformations, infantile hemangioma, hypertrophic scars, superficial basal cell carcinoma, and Bowen's disease. The authors concluded that IPL is an effective treatment modality for a growing range of dermatologic disease and in some cases may represent a treatment of choice. It is typically well-tolerated; further high-quality studies are needed.

Furthermore, an UpToDate review on “Management of rosacea” (Maier, 2018) states that “Improvement in both facial erythema and telangiectasias can occur after treatment with pulsed dye lasers, KTP lasers, or intense pulsed light. Most data on the efficacy of these modalities are derived from uncontrolled studies. One split-face randomized trial compared treatment with a pulsed dye laser with non-purpuragenic settings to intense pulsed light and no treatment in 29 patients with rosacea. The two therapies were similarly beneficial for facial erythema and telangiectasias”.

Polyphenols

Saric and colleagues (2017) noted that various therapeutic options are available for the management of rosacea symptoms such as facial erythema, telangiectasia, papules and pustules, burning, stinging, and itching. Botanical therapies are commonly used to treat the symptoms. These researchers evaluated the use of polyphenols in rosacea treatment. PubMed, Embase, Biosis, Web of Knowledge, and Scopus databases were systematically searched for clinical studies evaluating polyphenols in the management of rosacea. Of 814 citations, 6 met the inclusion criteria. The studies evaluated licochalcone (n = 2), silymarin (n = 2), Crysanthellum indicum extract (n = 1), and quassia extract (n = 1). The studies only evaluated topical formations of stated polyphenols. Main results were summarized. The authors concluded that there is evidence that polyphenols may be beneficial for the treatment of rosacea symptoms.
Polyphenols appeared to be most effective at reducing facial erythema and papule and pustule counts. However, available studies had significant methodological limitations; thus, large-scale, randomized, placebo-controlled trials are needed to further evaluate the safety and efficacy of polyphenols in the treatment of rosacea.

Topical Minocycline

In a phase-II, randomized, double-blind clinical trial, Mrowietz and colleagues (2018) examined the safety, tolerability, and efficacy of a minocycline foam, FMX103, in the treatment of moderate-to-severe facial papulo-pustular rosacea. Healthy subjects aged greater than or equal to 18 years with moderate-to-severe rosacea that had been diagnosed greater than or equal to 6 months previously and with greater than or equal 12 inflammatory facial lesions were randomized (1:1:1) to receive once-daily 1.5 % FMX103, 3 % FMX103, or vehicle for 12 weeks. The primary end-point was the absolute change in inflammatory lesion count at week 12. Other assessments included grade 2 or higher Investigator's Global Assessment (IGA) improvement, IGA "clear" or "almost clear" (IGA 0/1),

clinical erythema, and safety/tolerability. Safety and efficacy were evaluated at weeks 2, 4, 8, and 12, with a safety follow-up at week 16. A total of 232 subjects were randomized; 213 completed the study. At week 12, inflammatory lesion count reduction was significantly greater for the 1.5 and 3 % FMX103 doses than for vehicle (21.1 and 19.1 versus 7.8, respectively; both $p < 0.001$). Both doses were significantly better than vehicle for achieving grade 2 or higher IGA improvement and assessment of "clear" or "almost clear". Both doses appeared generally safe and well-tolerated. In total, 11 (4.7 %) subjects reported TEAEs; all but 1 (eye discharge) were dermal related, and all resolved by study end. No treatment-related systemic TEAEs were reported; 4 subjects discontinued the study because of TEAEs (3 % FMX103, n = 3; vehicle, n = 1). The authors concluded that topical minocycline foam, FMX103, appeared to be a safe, effective and well tolerated treatment for moderate-to-severe papulo-pustular rosacea. These findings need to be validated in phase-III studies.

Nano-Emulsion of Pioglitazone

Espinoza and colleagues (2019) noted that pioglitazone (PGZ) is a peroxisome proliferator-activated receptor agonist . Its role in the inflammatory response modulation opens the door for additional therapeutic applications. These researchers developed a PGZ nano-emulsion (PGZ-NE) to examine its anti-inflammatory efficacy on the skin. For that a NE vehicle aimed for skin delivery was optimized and characterized. The resulting PGZ-NE showed a good anti-inflammatory efficacy by decreasing the expression of adipose inflammatory cytokines IL-6, IL-1β and TNF-α. The properties of the developed nano-carrier allowed achieving a high permeation flux of PGZ through the skin as well as high retained amount in the skin, probably due to the depot effect of ingredients, which assured a prolonged local action, with good skin tolerability among participating individuals. The authors concluded that these

findings suggested that PGZ-NE may be used as an alternative treatment for inflammatory skin diseases such as rosacea, atopic dermatitis or psoriasis.

Recombinant Bovine Basic Fibroblast Growth Factor Gel

In a randomized, single-blind, and vehicle-controlled study, Luo and colleagues (2019) examined the effect of topical use of recombinant bovine basic fibroblast growth factor (rbFGF) gel on the repair of facial skin lesions in patients with rosacea. A total of 1,287 patients with Demodex mite-induced rosacea who received treatment with ornidazole tablets were randomized to rbFGF gel treatment group (n = 651) or control group (n = 636) without revealing the group identity. Patients in the treatment group were treated with topical application of rbFGF gel over the skin lesions (0.2 g/cm2) for up to 8 weeks, whereas patients in the control group received gel vehicle treatment unless ulceration occurred. Skin lesions of all patients were scored before and after treatment with rbFGF gel and subjected to histological analysis. All patients were followed-up for 6 months. Significant improvement in the total effective rates for erythema, papules, desquamation and dryness were observed in the rbFGF treatment group. At the end of the 2, 4 and 6 months of follow-up, the total effective rates for patients in the treatment group were significantly higher than those in the control group (81.67 versus 28.84 %; 85.11 versus 40.81 %, and 96.56 versus 55.82 %, respectively). Following treatment for 6 months, none of the patients in the rbFGF group exhibited ulceration or scar formation. In the control group, 61 % of patients experienced exacerbation of skin lesions, of which, 12 % exhibited ulceration and were treated with rbFGF gel to prevent scar formation. Histological analysis revealed gradual reduction in epidermal hyperplasia and resolution of dermal edema in skin lesions treated with rbFGF gel. The authors concluded that rbFGF gel may improve the repair of facial rosacea skin lesions in patients treated with anti-Demodex.

The authors stated that in the present study, the effective rate was lower than that in their previous study, which may be attributable to several causes: The higher efficacy rate in the previous study may have been due to the relatively small sample size (n = 14), compared with the larger sample size in the present study (n = 1,204). Difference in the sample size may result in variable effective rate. Furthermore, the patients enrolled in the present study had symptoms of erythema, papules, desquamation, dryness and telangiectasia, which suggested a more severe state of disease; this may also explain the relatively lower effective rate. Unfortunately, there was no internal control due to the disapproval of the Ethics Committee of Lanzhou General Hospital. As an alternative, an rbFGF gel vehicle control was used as an external control, in accordance with previous studies. Most importantly, the effectiveness of rbFGF treatment was evaluated by the pathological changes in the patients before and after the treatment. This single-blind study focused on Demodex mite-induced rosacea manifested with papules and pustule. All patients included in the study were classified as moderate-t-severe rosacea with primary features including transient and non-transient erythema, papules and pustules and telangiectasia. As such, patients were not further divided into subtypes. In the patients' interest, doctors were allowed to decide whether the patients from the control group should be allowed to cross-over to the treatment group. The disadvantages of the single-blind study were similar to those of double-blind studies and included potential influence on data collection, analysis by investigators and the cross-over effect. The cause of rosacea was unknown, but it may be due to a variety of hereditary and environmental factors. These researchers stated that their future studies will examine the effect of rbFGF on the Demodex-mite negative rosacea induced skin lesions and its underlying mechanisms. The sample size may also be increased for pathological analysis. They stated that a further double-blind study with longer duration of follow-up and independent evaluators will be carried out in the near future to validate the present findings.

Hydroxychloroquine for the Treatment of Rosacea

Li and colleagues (2020) stated that rosacea is a chronic inflammatory disease in face. Hydroxychloroquine (HCQ), an anti-malaria drug, was reported to have anti-inflammation activities. However, the role of HCQ on rosacea remains unclear. These researchers examined the potential molecular mechanism by which HCQ improved rosacea in rosacea-like mice and mast cells (MCs). Moreover, the effects of HCQ treatment for rosacea patients were investigated. They found HCQ ameliorated the rosacea-like phenotype and MCs infiltration. The elevated pro-inflammatory factors and mast cell protease were significantly inhibited by HCQ treatment in rosacea-like mice. In-vitro, HCQ suppresses LL37-induced MCs activation in-vitro, including the release of inflammatory factors, chemotaxis, degranulation and calcium influx. Moreover, HCQ attenuated LL37-mediated MCs activation partly via inhibiting KCa3.1-mediated calcium signaling. Therefore, these evidences suggested that HCQ may ameliorate rosacea-like dermatitis by regulating immune response of MCs. The authors also noted that the 8-week HCQ treatment exerted satisfactory therapeutic effects on erythema and inflammatory lesions of patients with rosacea, indicating that it is a promising drug for the treatment of rosacea. Moreover, these researchers stated that large scale clinical trial is needed to further verify the safety and effectiveness of HCQ in the treatment of rosacea.

Measurement of Serum Bilirubin, Uric Acid and Zonulin Levels in Rosacea

Karaosmanoglu and colleagues (2020) noted that rosacea is an inflammatory skin disease with a chronic course. Although the pathogenesis of rosacea is not completely understood, it is regarded as an inflammatory process. These investigators examined serum uric acid (UA) levels in patients with rosacea and investigated the correlation of UA levels with disease activity. A total of 61 patients with rosacea and 64 sex- and

age-matched controls were included in the study. Demographic characteristics, medical history, and dermatological examination of the patient and control groups were recorded. Concentrations of serum UA and C-reactive protein (CRP) were evaluated and compared in both groups. This study included 61 patients with rosacea (39 females, 22 males, median age = 30 years) and 64 age- and sex-matched controls. Metabolic syndrome was significantly more common in patients with rosacea than in the control group. Patients with rosacea had significantly higher body mass index (BMI) values compared with those of controls. Serum UA and CRP values were significantly higher in the rosacea group than values in the control group. There was no statistically significant correlation between serum UA level and clinical rosacea severity. The authors concluded that the findings of this study suggested that rosacea is not only a skin-related disease but also an inflammatory disease that could be related to higher UA levels, BMI values, and metabolic syndrome. These researchers stated that it may be recommended that clinicians pay careful attention to the clinical follow-up of these patients to avoid missed associated co-morbidities.

Turkmen (2020) stated that rosacea is a common chronic inflammatory skin disease that the pathogenesis is not fully understood. Although the significant role of oxidative stress in rosacea pathophysiology has been shown in recent studies, there is no study addressing the potential roles of bilirubin and UA in rosacea. In this study, serum bilirubin and UA antioxidant levels were measured in rosacea patients. A total of 87 rosacea patients and 81 healthy controls (HCs) of similar age and gender were included in this trial. From all subjects, blood samples were drawn and the values of total bilirubin (Tbil), direct bilirubin (Dbil), indirect bilirubin (Ibil), and UA were analyzed. The type of rosacea was erythemato-telangiectatic in 51.7 % of the patients, papulo-pustular in 43.7 %, and phymatous in 4.6 %. In rosacea group serum, Tbil, Dbil, Ibil, and UA values were found to be significantly lower than in the HCs. Male rosacea patients were found to have lower Tbil,

Dbil, Ibil, and UA levels when compared with the males in the HCs. There was also the same significant difference in female patients. The authors concluded that the principal finding of this study was that when compared with the control group, serum bilirubin and UA levels were significantly lower in rosacea patients. These levels sustained the hypothesis that antioxidant status and oxidative stress are important in the pathogenesis of rosacea.

Yuksel and Ulfer (2020) noted that although the etiopathogenesis of acne rosacea has not yet been clearly elucidated, it has been discussed over the years that autoimmunity may play a role. Genetic and environmental factors are known to have combined effects in the background of autoimmunity, but it has recently been emphasized that an impaired intestinal barrier system is also involved in the development of the disease. Zonulin is a protein that reversibly increases intestinal permeability. These researchers examined serum zonulin levels in acne rosacea. A total of 61 subjects (30 diagnosed with acne rosacea and 31 healthy controls) were included in this trial. There was no difference between the 2 groups in terms of age, gender, and BMI. Serum zonulin was examined using the enzyme-linked immunosorbent assay (ELISA). Serum zonulin levels were found to be significantly higher in the patient group than in the control group (18.5 ± 2.9 ng/ml versus 13.2 ± 2.7 ng/ml, respectively; $p < 0.001$). The authors concluded that this was the 1st study in the literature to show that the serum zonulin levels were increased in patients with acne rosacea. This was a small (n = 30 for acne rosacea); these preliminary findings need to be validated by well-designed studies.

Furthermore, UpToDate reviews on “Rosacea: Pathogenesis, clinical features, and diagnosis” (Dahl, 2020) and “Management of rosacea” (Maier, 2020) do not mention measurements of serum bilirubin, uric acid and zonulin as management tools.

Reflectance Confocal Microscopy / Spectrometry for Assessment and Monitoring of Therapy

Logger and associates (2020b) stated that reflectance confocal microscopy (RCM) enables non-invasive Demodex mite detection in rosacea. Objective scoring of rosacea severity is currently lacking. These researchers examined the value of RCM for monitoring Demodex, inflammation and vascular parameters in rosacea during treatment. In 20 rosacea patients, clinical and RCM examination were performed before, during, and 12 weeks after a 16-week treatment course with topical ivermectin. Using RCM, number of mites and inflammatory cells, epidermal thickness, and vascular density and diameter were measured; RCM features were correlated with clinical assessment. Treatment resulted in clinical reduction of inflammatory lesions. Mites were detected in 80 % of patients at baseline, 30 % at week 16, and 63 % at week 28. The number of mites reduced significantly during treatment, but no changes in inflammatory cells, epidermal thickness or vascular parameters were observed. Correlation between number of inflammatory lesions and mites was low. None of the RCM variables was significant predictors for clinical success. The authors concluded that RCM enabled anti-inflammatory effect monitoring of topical ivermectin by determining mite presence. Quantifying exact mite number, and inflammatory and vascular characteristics is challenging due to device limitations. These researchers stated that in its current form, RCM appeared to be of limited value for non-invasive follow-up of rosacea in clinical practice.

Logger and colleagues (2020a) noted that rosacea assessment and therapy monitoring can be challenging to standardize, as most clinical evaluation systems are prone to inter-observer variability and not always validated. Thus, objective, reliable and preferably non-invasive measurement tools are needed. In a systematic review, these investigators examined available non-invasive imaging techniques and biophysical methods in rosacea. PubMed, Embase, Cochrane

and Web of Science databases were searched until September 1, 2018 in accordance with PRISMA guidelines, to identify studies providing original data about objective non-invasive imaging and/or biophysical skin measurement techniques for diagnosis, assessing severity or therapy monitoring of adult patients with cutaneous facial rosacea. Risk of bias of included articles was assessed with the Cochrane Risk of Bias tool, Quality in Prognosis Studies tool, and the Newcastle-Ottawa Scale. A total of 78 studies were included, describing 14 imaging and biophysical methods. Widespread information about (sub)surface cutaneous morphology and functionality was obtained. Methodological study quality was relatively low and inter-study outcome variability was large. Several tools showed promising value in research settings: for treatment follow-up Demodex mites are countable with RCM, spectrometry can quantify erythema, and rosacea severity could be objectified with skin hydration- and trans-epidermal water loss measurements. The authors concluded that the findings of this systematic review described the spectrum of non-invasive imaging and biophysical methods in rosacea assessment, giving multi-faceted information regarding structure and properties of rosacea skin, especially useful for research purposes. These researchers stated that larger studies with good methodological quality are needed to create validated protocols for further implementation into research. They noted that RCM and spectrometry are especially promising in therapy monitoring and skin barrier measurements for rosacea severity assessment; larger studies with better methodological quality are needed to create validated protocols for implementation into research.

Furthermore, UpToDate reviews on “Rosacea: Pathogenesis, clinical features, and diagnosis” (Dahl, 2020) and “Management of rosacea” (Maier, 2020) do not mention reflectance confocal microscopy and spectrometry as management tools.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
CPT codes covered if selection criteria are met:	
10040	Acne surgery (e.g., marsupialization, opening or removal of multiple milia, comedones, cysts, pustules) **[for acute rosacea]**
30120	Excision or surgical planing of skin of nose for rhinophyma [for the treatment of bleeding or infection refractory to medical therapy (i.e., the need for repeated cautery of bleeding telangiectasias or frequent courses of antibiotics for pustular eruptions)]
CPT codes not covered for indications listed in the CPB:	
Helicobacter pylori therapy, measurement of serum zonulin levels - no specific code:	
15780	Dermabrasion; total face (e.g., for acne scarring, fine wrinkling, rhytids, general keratosis)
15781	segmental, face
15782	regional other than face
15783	superficial, any site (e.g., tattoo removal)
15788	Chemical peel, facial; epidermal
15789	dermal
15792	Chemical peel, nonfacial; epidermal
15793	dermal

Code	Code Description
17000	Destruction (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), premalignant lesions (e.g., actinic keratoses); first lesion
+17003	second through 14 lesions, each (List separately in addition to code for first lesion)
17004	Destruction (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), pre-malignant lesions (e.g., actinic keratoses); 15 or more lesions
17106	Destruction of cutaneous vascular proliferative lesions (e.g., laser techniques); less than 10 sq cm
17107	10.0 to 50.0 sq cm
17108	over 50.0 sq cm
17110	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; up to 14 lesions
17111	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; 15 or more lesions
17340	Cryotherapy (CO_2 slush, liquid N_2) for acne
17360	Chemical exfoliation for acne (e.g., acne paste, acid)
82247	Bilirubin; total
82248	Bilirubin; direct

Code	Code Description
84550	Uric acid; blood
96931	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition and interpretation and report, first lesion
96932	image acquisition only, first lesion
96933	interpretation and report only, first lesion
+96934	image acquisition and interpretation and report, each additional lesion (List separately in addition to code for primary procedure)
+96935	image acquisition only, each additional lesion (List separately in addition to code for primary procedure)
+96936	interpretation and report only, each additional lesion (List separately in addition to code for primary procedure)
HCPCS codes covered if selection criteria are met:	
Topical oxymetazoline (Rhofade) - no specific code:	
HCPCS codes not covered for indications listed in the CPB:	
Topical calcineurin inhibitors, topical oxymetazoline, polyphenols, topical minocycline, nano-emulsion of pioglitazone, recombinant bovine basic fibroblast growth factor gel, hydroxychloroquine - no specific code :	
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit
ICD-10 codes covered if selection criteria are met:	

Code	Code Description
L53.9	Erythematous condition, unspecified [persistent facial erythema]
L71.0 - L71.9	Rosacea
ICD-10 codes not covered for indications listed in the CPB:	
I78.0 - I78.9	Disease of capillaries [telangiectasias and scarring from rosacea]
L90.5	Scar conditions and fibrosis of skin [from rosacea]

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Amendment to
Aetna Clinical Policy Bulletin Number: 0547 Rosacea

For the Pennsylvania Medical Assistance plan, effective January 1, 2020 all medications included on the Pennsylvania Statewide Preferred Drug List be reviewed using the guidelines for determination of medical necessity developed by the Pennsylvania Department of Human Services.

revised 08/18/2020