Introduction

In an analysis of 2013 claims data from private and governmental insurance providers, nearly 85 million Americans saw a physician for some form of skin disorder in 2013, exceeding current annual estimates for cardiovascular disease and diabetes, making skin disease an important public health concern.[1] According to this report, contact dermatitis was found to be the fifth most prevalent skin disease in the United States with a total population medical cost of $1.529 billion surpassing that of melanoma.[1] Contact dermatitis can occur at any age, and over 13 million Americans have sought some type of treatment for this chronic condition each year.[1] There are multiple types of dermatitis, and one of the most common causes of dermatitis is allergic contact dermatitis (ACD).[2,3] This must be differentiated from irritant contact dermatitis, atopic dermatitis, nummular dermatitis, and stasis dermatitis, among others.

ACD most commonly involves the hands and face, but can involve any region of the body. Not only does ACD lead to a cycle of persistent skin damage, pain, and inflammation, but it may also have a significant negative impact on patient's quality of life.[4–13] The chronic debilitating course of the disease can exact a substantial toll in terms of poor-quality sleep, physical and emotional distress, time lost from work, and a potentially inappropriate job change, all resulting in lower standard of living.[4–6,9] With incorrect or delay in diagnosis, many patients continue to suffer and undergo multiple specialist visits, using numerous inadequate therapies including topical, oral and parenteral corticosteroids, ultraviolet light therapy, and even various systemic immunosuppressants.[4,13] The burden of disease and treatment failures can lead to significant patient distress, morbidity and disability, and contribute greatly to increased health care expenditures.[4]

The "Cure" for Allergic Contact Dermatitis is Identification of the Offending Allergen

To properly treat ACD, it is important to accurately diagnose or define the particular substance or substances causing the reaction in the skin. It is noteworthy that once the clinically relevant allergen(s) is identified, allergic contact dermatitis can be cured by avoiding the responsible allergen(s).[13–15] In other words, the appropriate management of ACD is to perform a comprehensive test to suspect allergens and to provide alternative products, barriers and protection, or working conditions to avoid the specific agents responsible for the recurring problem. This means that if specific allergens are identified and appropriate strategies are implemented for allergen avoidance, there will be reduced medical costs from unnecessary physician visits and medications.

Contact Sensitization is Diagnosed by Patch Testing

ACD is definitively diagnosed by proper application, reading, and clinical correlation of the patch tested allergens (CPT code 95044). Studies have shown medical history alone is inadequate to diagnose ACD in the majority of cases.[16,17] Notably, epi-cutaneous patch testing is completely different from and unrelated to prick or intradermal allergy testing (CPT Code 95004). In addition to technical differences, these diagnostic tests evaluate completely different diseases with different pathophysiologic mechanisms. Patch testing is used to diagnose delayed, cell-mediated type-IV hypersensitivity reactions, such as ACD, whereas prick or intradermal testing is used to diagnose immediate, IgE-mediated type I hypersensitivity reactions such as rhinitis, asthma, conjunctivitis, urticaria, or food allergy.[18–20]

It has been repeatedly demonstrated that confirming a definitive diagnosis through patch testing has a positive impact on the quality of life of dermatitis patients and is cost effective.[4,8,21–24] Additionally, patch testing resulted in a larger decrease in the disease severity index and percentage disease activity from pre-diagnosis to post-diagnosis than in cases diagnosed without patch testing.[23,25] This also resulted in reduced pre- and post-diagnosis costs of prescriptions and office visits, and showed significant improvement in life quality indicators.[11,21] Despite the clearly demonstrated value of patch testing, a cross-sectional, ecologic study using data from the Centers for Medicare & Medicaid Services determined notable underutilization of this safe, effective tool.[26]

Patch Testing is Time-Consuming and Complicated

One of the main barriers to patch testing is that it is a time-consuming and labor-intensive procedure. The test requires three office visits over one week.[21,23] It necessitates significant investment of personal time by the patient and considerable clinic time by the physician and nursing staff to prepare and place the tests as well as properly interpret positive reactions. Briefly, individual allergens are applied to the patient's back, under occlusion, with hypoallergenic tape at the first visit. The allergens and tape remain in place for two days and then are removed, and an initial evaluation is performed. The final reading and evaluation is performed by the patch test provider 3-7 days post placement, and each site where an individual allergen was placed is assessed for erythema, edema, infiltration, scaling, and blisters. Based on these variables, the patient is determined to have contact sensitization, an irritant reaction, or no (negative) reaction to each allergen. The expert patch tester must then integrate the results of patch testing with the patient's history, exposures, and physical exam to determine if the positive

allergic reactions are clinically relevant. At this point, significant time is devoted to providing education and instructions to the patient, which is known to be critical for successful long-term prevention of a persistent disabling dermatitis.[27] It is not uncommon for this final visit to take 60-90 minutes and often involves reviewing ingredient lists of all of the patient's (and significant other's) personal care products as well as workplace materials.

Limited Patch Testing has Limited Value

"Targeted" patch testing utilizes a minimum number of allergens and may appear appropriate when a patient's history and physical exam suggests that only one or few allergens is likely to be causative (e.g. nickel sensitivity due to jewelry).[28,29] In contrast, "limited" patch testing typically involves testing with a commercially available screening panel of 36 allergens (36 units of CPT Code 95044).[2,17] Notably, many general dermatologists and allergists have received training in their residencies to perform limited patch testing, which can be an appropriate initial step for patients. That said, studies have shown that only about one third of the patients are fully evaluated by use of a limited patch test screening series.[17,30–34] The most recent NACDG data suggests that the commercially available T.R.U.E. TEST (35 allergens and one control) screening panel at most detects 66% of the clinically relevant reactions identified on the NACDG screening series of 70 allergens.[2] Notably, up to 50% of allergens causing occupational dermatitis are missed.[19] Table 1 summarizes other studies that have examined rates of detection of limited as well as extended series patch testing.

Furthermore, tertiary care referral patch test centers often see patients who have had limited patch testing and have little understanding of how to evaluate the results. Patients sometimes bring in current products listing the offending allergen which they continue to use

indicating limited post patch test counseling and education.[16,17] Limited patch testing may result in a confirmed diagnosis of contact sensitization; however, without clinically relevant determination of exposure and education regarding avoidance of those exposures, the clinical outcomes may not be impactful.

Of interest, patients with positive patch test reactions from limited testing have routinely been found to have additional allergens when more extensive testing is performed.[2,17,35] Setting a quota for a maximum number of allergens placed per patient or restricting testing only to certain arbitrary time intervals (i.e every 1-3 years) can interfere with the diagnostic process, delay effective treatment, and result in unnecessary increased costs.[36] Notably, each year new contact allergens are described in the literature – in the years 2008-2015, 172 new compounds were identified that would have been missed by limited patch testing. This underscores the significant clinical impact of appropriate comprehensive patch testing.[37] For these reasons, the American Contact Dermatitis Society (ACDS) endorses the concept of clinically appropriate patch testing as described in the Noridian Medicare Local Coverage Determination which states:

"The number of tests performed should be judicious and dependent upon the patient's history and physical finding and should be used in conjunction with sound clinical judgment. All patients should not necessarily receive the same tests nor the same number of sensitivity tests."

Diagnosis of Contact Dermatitis Requires Comprehensive Patch Testing

Other available standard screening tools include the ACDS Core 80 Allergen Series and the North American Contact Dermatitis Group (NACDG) Screening Series (Table 2).[15,38] The NACDG is a clinical group which has standardized patch testing methods and chemicals in the United States and Canada since 1970. The NACDG screens an evaluative standard of 70

allergens, which has been demonstrated to be substantially more effective than the commercially available limited screening kit because it is routinely updated.[2] Studies have determined that 21-34% of ACD diagnoses would be missed by the NACDG Screening Series without the use of supplemental allergens.[2,29,39] The NACDG group members routinely test supplemental substances alongside their Screening Series, as warranted by history and physical examination to improve diagnostic yield.[2,40]

In comprehensive patch testing, patients are tested to a large number of allergens, typically between 65 and 200 (65 to 200 units of CPT Code 95044).[3,16,41] When deciding which allergens to test, it is important to integrate the patient's medical history, examination findings, and environmental exposure history. The occupation of a patient can be helpful in narrowing the suspected exposure. With an appropriate history and examination, patch testing can lead to the proper diagnosis and management of ACD, but only if the patch test provider has access to additional causal allergens beyond those found in even an expanded screening series.[15] Multiple studies have repeatedly demonstrated that comprehensive patch testing carries a much higher probability of yielding a diagnosis of a specific allergy for a patient, compared to targeted or limited patch testing, thus leading to a much higher probability of a cure.[30–32,41–45] For these reasons, it is sometimes more appropriate to forgo limited and standard screening patch testing and proceed directly to comprehensive patch testing for many patients to correctly evaluate their dermatitis, especially in occupational settings.

There is a Shortage of Expert Patch Test Providers

Comprehensive patch testing should be performed by providers who have received adequate training in their residencies, fellowships, or post-doctoral training programs. In a

survey of 3,779 fellows and members of the American College of Allergy, Asthma, and Immunology, only 8.3% of the respondents reported an "expert" ability to perform patch testing.[20] Van der Valk *et al.* stress that proper pretest probability assessment can only be done in expert centers, because problem-based testing requires both a thorough knowledge of the patch-test procedure and knowledge about potential sensitizers in a specific environment.[46]

Not only is there a shortage of expert providers, there is also a maldistribution of patch test utilization in the United States. Analysis of 2014 data from the Centers for Medicare & Medicaid services revealed many hospital referral regions (HRRs, as defined by Dartmouth Atlas of Healthcare) were not associated with any patch testing. In HRRs associated with patch testing, utilization ranged from 0 to 41,626.5 tests per 100,000 Medicare beneficiaries. Hospital referral regions were divided into quartiles based on their utilization rates. Notably, quartile 1, representing areas of lowest utilization, was primarily comprised of areas in the Southwest and Northwest.[1] This is in accordance with a survey conducted in 1999 of the 322 ACDS members, which revealed a maldistribution of providers with a majority 23% practicing in the Northeast; 16% practicing in the Midwest; 14% in the South; 10% in the Southwest; and only 5% practicing in the Northwest.[39] Ultimately, restricting the number of allergens that can be placed per each test session results in more visits for the patient. This further aggravates the issues of maldistribution in overburdened and underserved areas.

Conclusion

The benefits of patch testing to patients are clear. An improvement in the diagnosis of ACD through appropriate use of patch testing can lessen both the morbidity and economic impact of this chronic skin disorder. Patch testing remains the gold standard objective scientific method

available to physicians to diagnose ACD. The likelihood of establishing an accurate diagnosis can be increased by use of comprehensive patch testing. In contrast to the limited patch test and screening series patch test, comprehensive patch test encompasses a broader range of available allergens, allowing for greater diagnostic potential and improved patient outcomes.

While a standard screening series may be an appropriate starting point for screening for potential allergens, it has significant limitations. With over 82,000 compounds in use in the U.S. and only 25% of them subjected to basic testing, how can it not? Notably, only 500 of these compounds (0.006%) have been characterized and standardized for patch testing. Remarkably, testing with the highest prevalent allergens is able to detect up to 70% of the clinically relevant sources of ACD (based on an 80 allergen panel of the 500 available compounds). That said, extending patch testing with supplemental allergens (selection based on medical, environmental, and occupational history) is critical for correct diagnosis, management, and cure of ACD.

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Table 1 Studies examining detection rates of limited and extended patch testing

Summary of findings	Reference
21% of tested patients had at least 1 relevant allergic reaction to an allergen not on the NACDG series; 14.6%of these were occupationally related. The T.R.U.E. TEST would have hypothetically missed one quarter to one third of reactions detected by the NACDG screening series.	DeKoven et al 2017 (2)
74.31% of patients had a positive reaction to either an NACDG patch-tested allergen or a supplemental allergen; 65.42% of patients testing positive for an allergen were positive to an NACDG allergen only, and 90.51% of the total positive reactors were positive for at least one NACDG test allergen.	Cohen et al 2008 (15)
Approximately a quarter of patients had at least 1 relevant allergic reaction to a non-NACDG allergen. In addition, approximately one-fourth to one-third of reactions detected by NACDG allergens would have been hypothetically missed by T.R.U.E. TEST	Warshaw et al 2015 (17)
Of the patients evaluated with T.R.U.E. TEST, 50.8% had at least one positive reaction, 31.7% had a diagnosis of ACD, and 24.0% were suspected to have ACD from other allergens	Militello et al 2006 (31)
Positive allergens would have been missed in 12.5% of patients when evaluating with T.R.U.E TEST allergens alone, whereas 25.6% would be partially evaluated	Camacho-Halili et al 2011 (33)
The T.R.U.E. test series of 23 allergens would have completely identified all allergens in only 25.5% of patients and clinically relevant allergens in 28% of patients	Saripalli et al 2003 (34)
Less than 40% of positive patch test reactions were detected by the NACDG screening series of 65 to 70 allergens.	Warshaw et al 2013 (40)

Abbreviations: T.R.U.E.-Thin-layer Rapid Use Epicutaneous, NACDG-North American Contact Dermatitis Group

Table 2. Available Patch Tests Based on Allergen Count

Targeted Patch Test	Limited Patch Test (T.R.U.E. TEST ®)	NACDG Screening Series	ACDS Core Series	Comprehensive Patch Test
<24 Allergens	24-36 Allergens	70 Allergens	80 Allergens	65-200 Allergens

Abbreviations: T.R.U.E.-Thin-layer Rapid Use Epicutaneous, NACDG-North American Contact Dermatitis Group, ACDS-American Contact Dermatitis