

SWIR camera as a novel solution to allergy skin testing

To the Editor,

For more than a century, allergy skin testing has remained an essential tool to diagnose allergic diseases.¹ When good technique is employed, skin testing can be both sensitive and specific¹ and offers some advantages over serum IgE testing.² The primary disadvantage of skin testing is that each individual wheal must be measured manually by a trained technician. Interpretation of skin test responses is time-consuming and often difficult to visualize leading to inconsistencies,^{3,4} particularly among those with dark skin pigmentation where skin colour may obscure both wheal and flare responses.⁵

Over the last few decades, researchers have attempted to improve skin test reliability by automating measurements using thermal IR imaging,^{6,51} computer algorithms⁵², 3D surface topography⁷ and visible range images.^{3,8} However, these methods are unreliable and suffer from technological limitations.⁹

Newly available short-wave infrared (SWIR) cameras allow passive imaging in the range of 1000 nm–2000 nm. SWIR is quite different than IR sensors (7500–14 000 nm) used extensively for thermal detection. SWIR technology has a unique ability to discriminate water as an inherent feature that allowed us to test our hypothesis that oedematous skin test wheals could be resolved effectively in this wavelength range.

We initially explored skin testing using several readily available camera technologies and then, based on the preliminary results, selected SWIR for specific interrogation. Exploratory technologies included visible range (380–740 nm), near infrared (NIR) (700–1000), thermal IR (7500–14 000 nm) and SWIR (1000–1700 nm). A total of 60 adults participated in the study of which 38% were males, 57% had a history of allergic rhinitis and 40% identified as African American. More detailed methodologies are provided in the online supplement.

Consistent with previously published studies, wheal measurements using a visible range camera were unreadable 22% of the time (78% sensitivity) and 43% of the time with NIR (57% sensitivity). Skin test reactions were often grossly visualized by thermal IR imaging but not measurable 62% of time, because of indistinct borders (38% sensitivity). Visible range camera wheal detection was often dependent on skin colour and the ability of the light source to cast shadows. Figure S1 demonstrates skin testing on individuals with both light and dark colour skin.

Thermal IR imaging was sometimes able to detect an enhanced area coinciding with the erythematous flare response (Figure S2A highlighted in red); however, a pattern could not easily be localized in most subjects. Figure S2B provides an example of the difficulties associated with thermal imaging.

SWIR technology does not detect the flare at all. However, Figure 1A, from a Caucasian subject, shows the superiority of SWIR for the detection of the wheal compared to other cameras. Figure 1B demonstrates skin testing on the forearm of eight subjects using only SWIR. To the right of each native, SWIR image is a processed image generated by a wheal finding software algorithm. Two subjects are African American; however, SWIR sensors are agnostic to skin colour making differentiation by race impossible.

Following pilot studies where a broad range of frequencies were explored, we then placed a 1400 ± 100 nm filter in the SWIR camera to capture skin tests in 24 individuals and compared this to standard of care measurements. Overall, the sensitivity of SWIR for the detection of the wheal was 100%. As shown in Figure 1A, wheals measured by SWIR using a digital calliper were not statistically different compared to standard methods ($R_s = 0.960$, $P < .00005$, mean of 5.1 ± 0.4 vs 5.2 ± 0.4 mm). Table S1 in the online supplement summarizes this series of measurements. The difference in wheal size between saline negative control and histamine measured by the standard method vs. SWIR was well correlated ($R_s = 0.849$, $P = .0001$).

Variability of standard skin test measurements has been evaluated extensively by others and generally varies by 1–2 mm.^{3–5} To further compare standard measurements with SWIR, we generated a precision profile comparing these methods in a series of 24 individual skin test measurements. In this analysis, standard measurements were highly correlated with the SWIR captured images measured by callipers ($P < .00005$, $R_s = 0.986$), by semi-automated software ($P < .00005$, $R_s = 0.887$) and by an automated wheal finding algorithm described in the online supplement ($P < .00005$, $R_s = 0.785$) as seen in Figure 2B.

All SWIR images were easily processed using a wheal finding algorithm so that the data could be transferred to analysis software for automated reading. Images could be analysed in real-time, off-site and/or at a later time point. On average, wheal measurements were generated 13× faster using SWIR derived images and automated software as compared to traditional methods (1.3 vs 16.5 seconds, $P < .001$).

Once the general utility of SWIR for the detection of skin tests was identified, we then applied hyperspectral imaging (HIS) technology to scan skin tests across the entire SWIR range in 12 individuals so that we could pinpoint which specific wavelength offers the best resolution. Image intensity along each wavelength (1 nm increments) was compared between the wheal and normal skin. Two spectral regions were identified at approximately 1380 nm and 1620 nm that produce

(A)

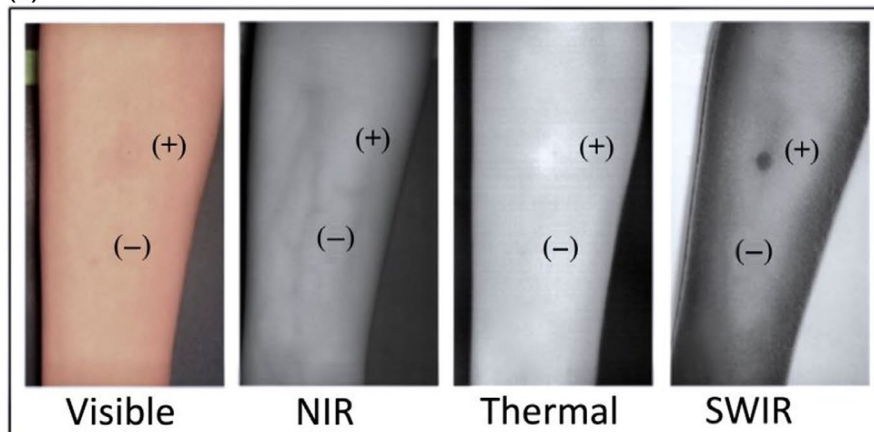
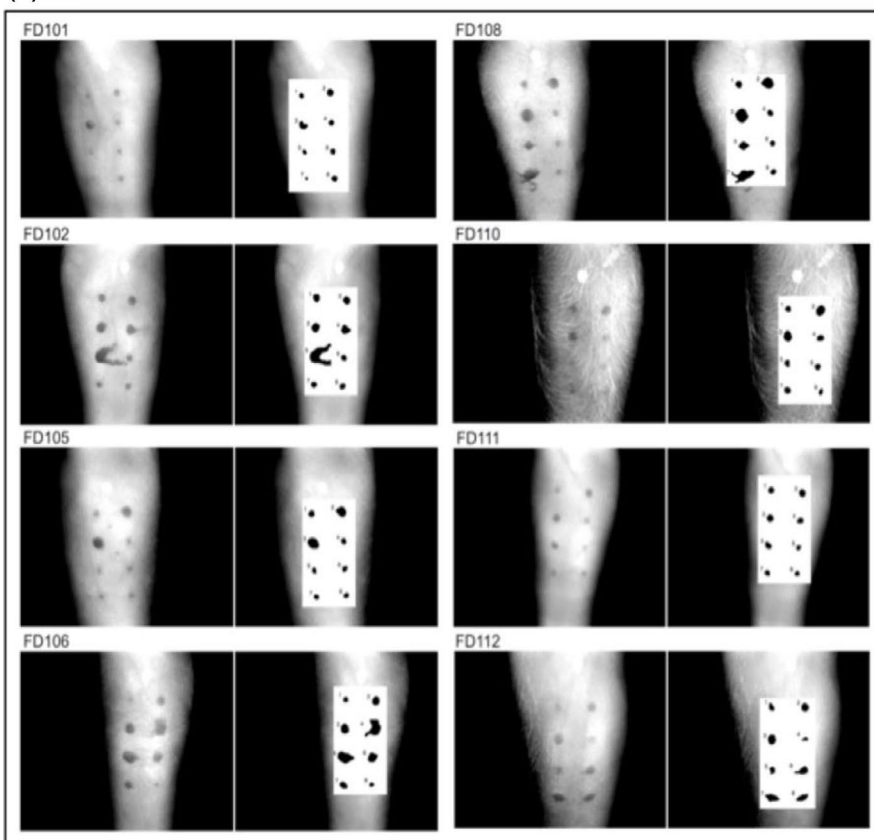


FIGURE 1 A, Images of skin test in a Caucasian individual 15 min after the placement of histamine (upper half of image) and saline (lower half) using four camera technologies. The wheals are more readily seen with SWIR imaging as compared to visible, NIR and thermal IR sensors. B, SWIR (1400 ± 100 nm) imaging in 8 subjects including two African Americans. To the right of each native, SWIR image is a software processed image

(B)



the greatest contrast between wheal and normal tissue. Figure S3 shows a HIS plot averaged from four representative subjects.

The purpose of this study was to scrutinize SWIR-based technology specifically. We did not explore all conceivable imaging technologies across the entire electromagnetic spectrum. We found unique information about skin test reactions using SWIR including wheal area and intensity, and wheal evolution through video time-lapse sequence. Of the 24 individuals we tested with dark skin colour, we found no limitations using SWIR. As such, patients with dark skin colour might particularly benefit from SWIR imaging through better detection.

In summary, we have discovered SWIR-based technology as a novel and important advancement for skin testing. This report

represents the first attempt to show that SWIR is a reliable and reproducible method for detecting allergic skin reactions in both light- and dark-skinned individuals. Cost analysis and efficiency studies, as well as the application of SWIR for remote telemedicine, and digital interpretation of the data by local or cloud-based machine learning need to be determined.

CONFLICTS OF INTEREST

Dr Tversky has received payment for educational presentations and consulting from AstraZeneca and Lincoln Diagnostics. Drs Tversky

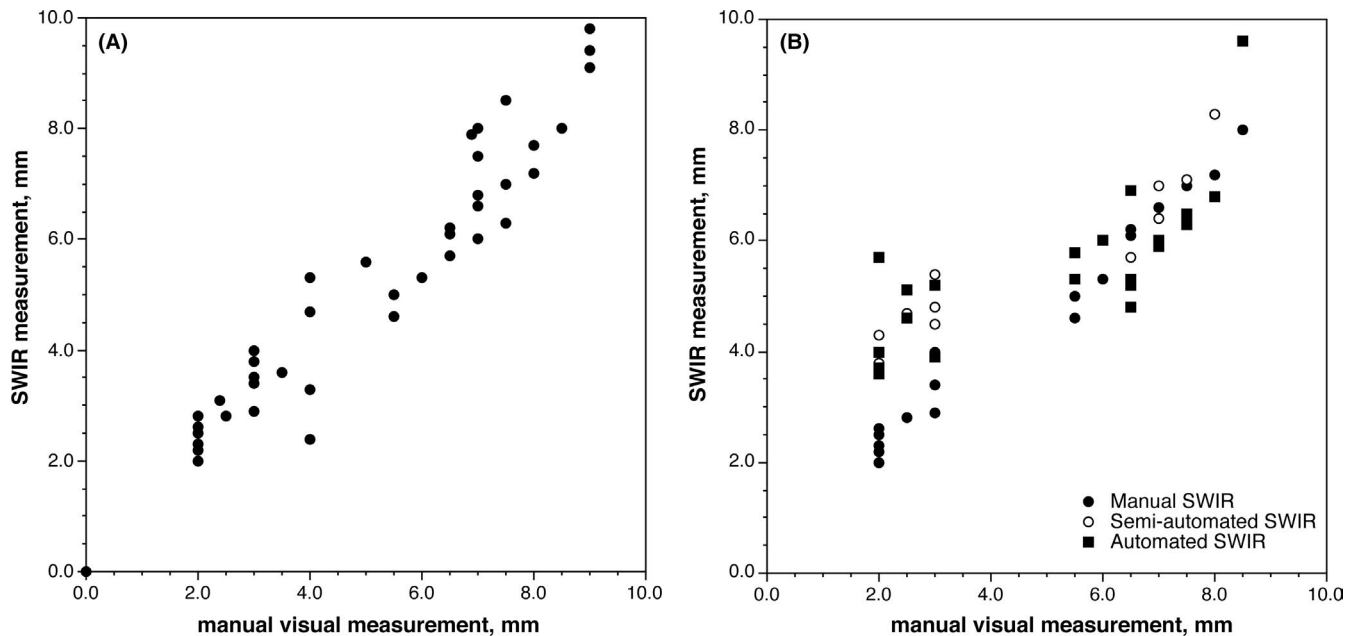


FIGURE 2 A, Precision profile comparing 48 standard visual wheal measurements to SWIR generated measurements. B, Standard measurements were also correlated with both semi-automated and fully automated software evaluation of SWIR images

and MacGlashan co-founded Flare Diagnostics that provided additional funding for the project.

KEYWORDS

Allergy, infrared camera, short-wave infrared, skin test, telemedicine

Jody Tversky 
Donald MacGlashan

Division of Allergy and Clinical Immunology, Department of
Medicine, Johns Hopkins University, Baltimore, MD, USA

Correspondence

Jody Tversky, Division of Allergy and Clinical Immunology, The Johns
Hopkins University School of Medicine, 5501 Hopkins Bayview
Circle, Baltimore, MD 21224, USA.
Email: jodytversky@jhmi.edu

ORCID

Jody Tversky  <https://orcid.org/0000-0003-3674-4143>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

SUPPLEMENTAL MATERIAL

TITLE

SWIR Camera as a Novel Solution to Allergy Skin Testing

AUTHORS

Jody Tversky, MD and Donald MacGlashan, MD, PhD; Division of Allergy and Clinical Immunology, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA

CONCLUSIONS

SWIR imaging may allow for construction of more reliable and automated skin test analysis tools and has the advantage of documenting wheal responses equally well in both light and dark skinned individuals.

MATERIALS AND METHODS

Participants

Sixty volunteer subjects aged 18 to 65 years, with or without a history of allergic disease, underwent skin testing followed by digital imaging with various technologies according to a Johns Hopkins University IRB approved protocol. Twenty-four subjects, were selected for more specific SWIR imaging analysis. 40% of all study subjects had dark colour skin. The primary exclusion criteria included the use of antihistamines within the last 10 days, dermatographism, severe atopic dermatitis, or the use of omalizumab. Consenting participants were recruited from the Johns Hopkins University Asthma and Allergy Center, USA from June 2014 to July 2018.

Skin test protocol

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Two commercially available skin test devices were used for testing; UniTest PC, and Multi-Test PC (Lincoln Diagnostics, Decatur, Ill). Manufacturer recommendations were followed in the application of each device using 1 mg/mL or 6mg/ml base histamine or glycerol-saline (both from Hollister-Stier). Several aeroallergens such as D. farinae, D. pteronyssinus, ragweed, oak, timothy grass, cat (Greer Laboratories, Lenoir, NC) were also included in the 24 subjects undergoing SWIR imaging. At 15 minutes, a single technician captured a digital image (described below), then carefully measured the wheal and flare reactions using a ruler. Maximum and orthogonal measurements were used to calculate the mean diameter. A true positive reaction was defined in the present study as a mean diameter of the wheal greater than or equal to 3 mm and at least 2 mm greater than that of the diluent control. A negative reaction was defined as a wheal diameter of less than 3 mm and/or less than 2 mm more than that with the diluent control.

Imaging

Illumination was provided by an incandescent light source with diffusers (Flare Diagnostics, Baltimore, MD) to create a soft and uniform surface without shadows. Visible range images were obtained using a 10-megapixel digital SLR (Canon USA, Melville, NY) or an iPhone 8 with 7-megapixel camera (Apple Inc, Cupertino, CA). NIR images were obtained with a 2-megapixel CMOS sensor with and without the use of 700nm bandpass filter (IDS Imaging, Obersulm, Germany). Thermal infrared imaging was obtained with a Tamarisk high-resolution microbolometer sensor (DRS technologies, Dallas, TX). Ambient room temperature was kept uniform at approximately 21 degrees Celsius while the microbolometer was allowed to equilibrate for one hour before calibrating. High-speed hyperspectral imaging was obtained using an FX series SWIR range sensor without a bandpass filter (Specim, Oulu, Finland). SWIR imaging was performed with a 320x240 pixel Bobcat series camera with an InGaAs sensor (Xenics USA, Beverly, MA) using

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either a 1380nm, 1400nm, 1608nm or 1625nm bandpass filter (Spectrogon, Mountain Lakes, NJ) although primary testing used a 1400±100 nm filter.

When possible, all cameras were set to manual gain, manual aperture, with a fixed exposure time and no flash. A steel washer, or star shaped or circular sticker was used as a reference point for scale and so that the location of the wheal could be identified in the images in 2-dimensions. In the case of hyperspectral imaging, the raw data points were extracted in the x and y plane so that the location of the wheal and normal surrounding tissue could be identified along each wavelength of the full 900-1700nm captured range.

Images procured by the SWIR camera were loaded into a customized software algorithm so that wheals could be analyzed by both a software-assisted approach and a fully-automated process and then compared to standard methods. The algorithm employed image smoothing, difference of Gaussian (DOG) convolution, and thresholding methods to produce high contrast images of the wheals. The time required to measure wheals using the automated software was compared to the time needed to measure wheals by traditional means using a ruler.

Statistical analysis

Based on previous studies, an *a priori* two-tailed power analysis determined that at least 12 subjects were needed to determine a 1-mm difference in the mean wheal responses ($\alpha= 0.05$; 85% power). 24 subjects were recruited for the primary aim to account for potential differences in imaging techniques and other potential unknown variables. A two-tailed t-test was used to compare mean wheal responses using SWIR versus standard methods. To determine sensitivity of SWIR a false negative was counted if the standard method yielded a positive wheal but the SWIR method was negative.

Exploratory methodologies for preliminarily determining superiority of SWIR to detect wheals compared to other technologies was based on the ability to visualize and measure the skin test reaction and then process the image by a software algorithm. When visualization of the wheal was not possible and the software algorithm was unable to locate a wheal, then the reaction was counted as unreadable such as the case with many of the visible, NIR, or thermal images.

RESULTS

A total of 60 adults participated in the study of which 38% were males, 57% had a history of seasonal or perennial allergic rhinitis and, 40% identified as African American. 36 participants engaged in the exploratory period comparing visible, NIR, thermal, SWIR and hyperspectral imaging. 24 subjects were then recruited to evaluate the accuracy of SWIR imaging in more detail.

Exploratory comparison of imaging technologies

As noted in the report, figure 1 demonstrates an example set of images on a single patient showing the superiority of SWIR for the detection of the wheal using a 1400nm bandpass filter. Similar results were derived using 1380nm, 1608nm and 1625nm bandpass filters (data not shown).

Consistent with prior studies, visible range cameras could sometimes detect wheals but this was highly dependant on skin colour and the ability of the light source to cast shadows. Figure S1 demonstrates skin testing on an individual with light colour skin (A), and dark colour skin (B). Positive wheals are more apparent on some individuals with light colour skin (note that the difference in apparent exposure is not due to lighting but the

darker skin colour). In either case, we were unable to reliably process digital images obtained from visible range cameras using automated software algorithms.

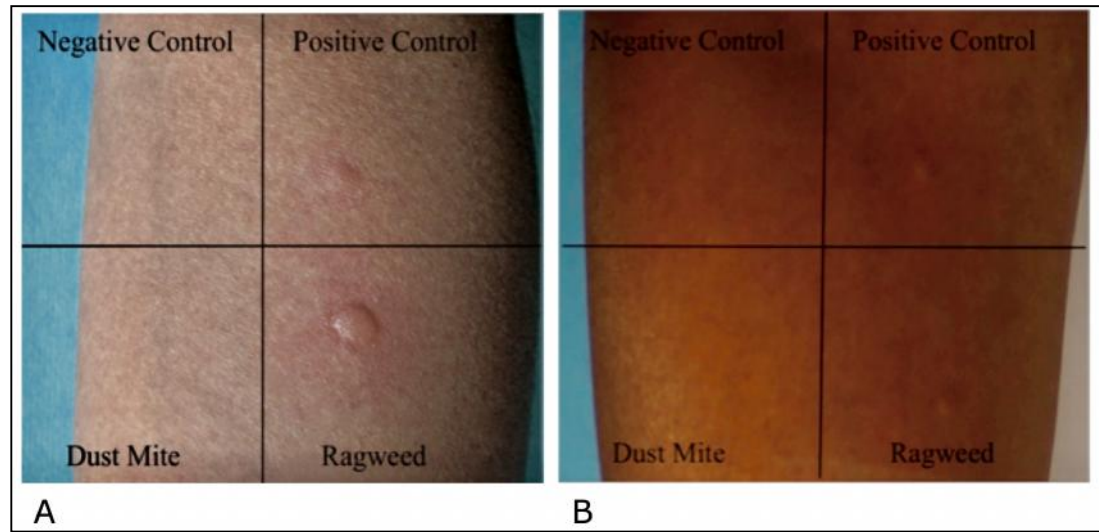


Figure S1. Representative visible range (380-740nm) images of skin prick testing in a Caucasian female (A) and an African American female (B). Skin test wheals, while apparent in some light skin colour individuals are often difficult to see in those with dark skin colour.

Similar to what was found with visible range images, thermal imaging was sometimes able to detect skin prick testing although there was much greater variability using this modality. In all subjects who underwent thermal imaging, there were few where the wheal could reliably be visualized or specifically localized. In some instances, an area of increased thermal energy was detected around the wheal consistent with the erythematous flare response (see Figure S2.A highlighted in red). However, most subjects did not reveal a pattern that could be easily identified, localized or measured. Thermal images were also complicated by the presence of vasculature, mottling and other dermal variations. Figure S2.B provides one example of the difficulties associated with thermal imaging. Various

regions of thermal intensity can be seen as white spots scattered throughout the skin of the forearm in a male Caucasian subject.

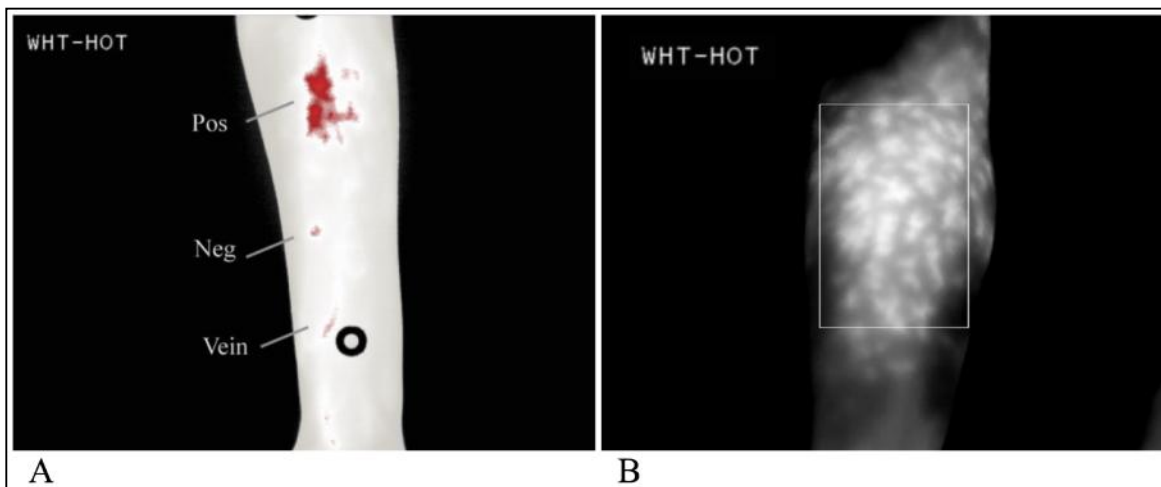


Figure S2. Thermal imaging of the skin prick test response can sometimes yield elevated temperature regions (white areas) likely corresponding to the flare in this example that is enhanced in red pseudo-colour (A). Another subject with a positive skin test response showed multiple enhanced white areas of colouration indicating scattered temperature variability and poor delineation of wheal versus normal tissue (B).

Hyperspectral imaging

4 individuals underwent skin prick testing followed by hyperspectral line scanning in the SWIR range (900-1700nm). The image intensity (contrast) along each wavelength was compared between the wheal and a nearby location on the skin where no wheal or flare was present. There are two spectral regions identified at approximately 1380nm and 1620nm that produce the greatest contrast between wheal and normal tissue. Figure S3 shows a plot averaged from the subjects.

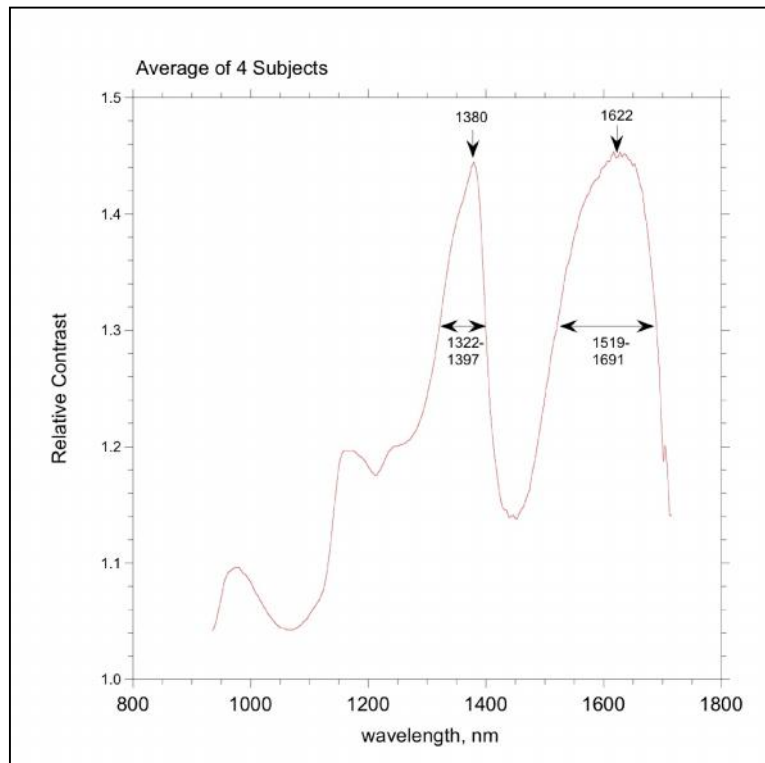


Figure S3. Hyperspectral images of allergy skin test wheal and surrounding area in the 1000-1700nm range. Absorption of light from an incandescent source is plotted as relative contrast intensity of the wheal vs non-wheal for an average of four subjects. Two spectral regions of interest (approx. 1380nm and 1620nm) show the greatest difference in relative absorption.

SWIR versus standard of care measurements

Overall, the sensitivity of SWIR for the detection of the wheal was 100% when measured with digital callipers or by software assisted methods. SWIR imaging did not detect the erythematous flare reaction that often surrounds skin test wheals. As shown in Table SI, mean SWIR measured wheal diameters using a digital calliper were not statistically different compared to standard methods that employ a ruler to the skin ($P=0.934$) and were highly correlated overall ($P<.00005$). All SWIR generated images were easily imported into automated software.

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Reagent Tested	Standard (Manual ruler)	SWIR (Calipers)	SWIR (Software Edit)	SWIR (Software Auto)
Overall (n=24)	4.8	4.6	5.5	5.5
Correlation <i>P</i> -value	N/A	<0.00005	<0.00005	=0.00005
Correlation <i>r</i> -value	N/A	0.986	0.887	0.785
Histamine (n=12)	6.9	6.3	6.7	6.3
Correlation <i>P</i> -value	N/A	<0.00005	=0.006	=0.0096
Correlation <i>r</i> -value	N/A	0.949	0.832	0.704
Saline Control (n=12)	2.6	2.9	4.4	4.5
Correlation <i>P</i> -value	N/A	<0.00005	=0.0037	=0.117
Correlation <i>r</i> -value	N/A	0.899	0.758	0.480

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153 **Table SI.** Comparison of standard versus SWIR measurement of wheal reactions in mm.

154 SWIR measurements were obtained with manual ruler, by wheal finding software along
 155 with user editing, and by a fully automated software algorithm without user editing.

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157 **ABBREVIATIONS**

158 HIS – hyperspectral imaging

159 NASA – National Aeronautics and Space Administration

160 NIR – near infrared

161 SPT - skin prick test

162 SWIR - short wave infrared

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164 **SUPPLEMENTAL REFERENCES**

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