Computerized Digital Dermoscopy: Sensitivity And Specificity Aren’t Enough

To the Editor:

The proliferation of new diagnostic technology requires that dermatologists become familiar with test characteristics, such as sensitivity, specificity, positive predictive value, and false negativity, when caring for patients. A recent article by Rubegni et al (2002) investigating computerized melanoma digital dermoscopy exemplifies the increasing value of these test characteristics in the dermatology literature. In this study, the authors report a sensitivity of 93% and a specificity of 92.75% for their diagnostic test, and suggest that it is superior to other forms of dermoscopy. We would like to take the opportunity to demonstrate how clinicians can apply these test characteristics to evaluate the usefulness of this new technology for their patient population.

Although sensitivity and specificity are informative measures of test performance, they cannot inform clinicians of the probability that an individual patient has melanoma. This limitation results from the fact that these test characteristics are determined from patient groups known a priori to have or to not have the disease (Giard and Hermans, 1996). Sensitivity refers to the probability of a positive test result in a person who has the disease. Specificity refers to the probability of a negative test in a person who does not have the disease. When seeking a diagnosis, clinicians do not know their patients’ true disease state. Thus, the property of interest to clinicians is not the test’s sensitivity or specificity, but its predictive value: the probability that a patient has the disease given a positive test result, or, alternatively, the probability that a patient does not have the disease given a negative test result. These concepts refer to a test’s positive predictive value (PPV) and negative predictive value (NPV), respectively. The PPV may be calculated using Bayes’ theorem, which combines three estimates: (1) test sensitivity; (2) test specificity; and (3) the patient’s pre-test probability (Smith et al, 2000). The negative predictive value may be calculated similarly, but is described elsewhere (Hagen, 1995). Under Bayes’ theorem, PPV is the fraction of the patients who truly have the disease among all patients with a positive test result (Smith et al, 2000). Mathematically, this expression is

$$\text{PPV} = \frac{\text{pre-test probability} \times \text{sensitivity}}{\text{pre-test probability} \times \text{sensitivity} + (1-\text{pre-test probability}) \times (1-\text{specificity})}$$

Pre-test probability refers to the probability that the patient under investigation has the disease of interest. In the case of melanoma, pre-test probability may be estimated using history (i.e., family history of melanoma, number of blistering sunburns in youth), physical examination (i.e., lesion morphology, number of nevi, skin phototype), as well as knowledge of the approximate prevalence of melanoma in the population being tested. An African-American child with no significant historical or physical findings other than a clinically atypical pigmented lesion on the palm, for example, may have a pre-test probability of 0.01 for melanoma. By contrast, a 68 y old Caucasian man with a previous history of melanoma and a clinically atypical and changing pigmented lesion on the back may have a pre-test probability of 0.60 for a new melanoma. Because even an excellent test, as defined by its sensitivity and specificity, may have poor predictive value when used in patients with a low pre-test probability, clinicians must consider a patient’s pre-test probability when assessing the clinical relevance of new diagnostic technology (Grimes and Schultz, 2002).

Another test measure of interest to clinicians is the probability that a patient has the disease of interest given a negative test result, that is, the probability of a false negative result. As NPV captures the probability that a patient does not have the disease given a negative test result (i.e., the probability of a true negative result), the probability of a false negative result is the complement of NPV, that is, 1-NPV.

Applying the reported sensitivity (93%) and specificity (92.75%) of Rubegni et al’s test to Bayes’ theorem, we determined the PPV and 1-NPV for a range of clinically reasonable pre-test probabilities. 0.01 (a very low-risk melanoma patient) to 0.95 (a very high-risk melanoma patient) by increments of 0.05 using SAS statistical software. Results are presented in Table I. Based on its PPV, Rubegni et al’s test appears to be a powerful diagnostic aid. A positive test result increases the probability that a particular patient may have melanoma even for patients with very low pre-test probabilities (for a patient with pre-test probability of 0.01, it yields a 10-fold increase for a PPV of 0.11). It is further associated with an acceptable 1-NPV, or false negative probability (given a negative test result, a patient with a 0.15 pre-test probability for melanoma only has a 0.01 probability of having the disease). These results are clinically important because some dermatologists may opt to observe a lesion with only a 1% probability of being melanoma, whereas a lesion with >10% probability of being melanoma would receive more aggressive management. Tests with PPV and 1-NPV that change patient management are thus clinically important.

Even with good PPV and 1-NPV, however, new diagnostic technology may still not be practical, particularly in settings where the clinician has a very low threshold to act upon a suspicion. In the case of melanoma, clinicians confront a disease that is eminently and easily curable in its early stages, but associated with a high degree of therapy-related morbidity and almost universal fatality in its advanced stages. Melanoma thus represents a lesion for which the biopsy threshold for most dermatologists is quite low. As biopsy would obviate the need for digital dermoscopy, it is crucial for clinicians to ask under which pre-test probabilities would digital dermoscopy alter their decision and benefit their patient. Given the severity of melanoma, it may be reasonable to assume that many dermatologists would biopsy pigmented lesions with a pre-test probability for melanoma ≥0.01 (1 in 100 chance, or greater), and may observe those with a lesser pre-test probability. If this assumption is accurate, a positive test result using digital dermoscopy would be clinically informative solely in the subset of patients with a pre-test probability less than 0.01, as the remainder of patients would receive a biopsy irrespective of the test result (Table I). Similarly, a negative test result would be meaningful solely in the subset of patients with pre-test probabilities less than 0.05, as the probability for a false negative becomes unacceptably high once pre-test probability ≥0.10 (Table I). Rubegni et al’s test may only be useful in low-risk pigmented lesions (pre-test probability: 0.01~0.05). Further, if the clinician’s patient population has a very low prevalence of melanoma, the digital dermoscopy will not be put to use often.

Particular clinical scenarios, however, may warrant use of digital dermoscopy. For example, a clinician may be hesitant to biopsy a pigmented lesion located at the lateral canthus of a 7 y old child if this lesion is associated with a low pre-test probability (for instance, 0.05). Use of Rubegni et al’s test in this context may
Active Human Herpesvirus 6 Infection in a Patient with Drug Rash with Eosinophilia and Systemic Symptoms

To the Editor:

Clinical and biologic manifestations of drug rash with eosinophilia and systemic symptoms (DRESS) are well characterized and mimic viral infection: high fever, facial edema, erythroderma followed by an exfoliative dermatitis, diffuse lymphadenopathy, hyperesinophilia, atypical circulating lymphocytes, abnormal results of liver function tests. Other systemic manifestations may occur (e.g., pneumonitis, pancreatitis, neurologic symptoms). This drug adverse reaction was first described with anticonvulsants but minocycline is also well known to induce this kind of reaction (Disdier et al, 2001). The role of viral infection in the development of this drug adverse reaction is suspected. We implicated for the first time human herpesvirus 6 (HHV-6) infection in a patient with phenobarbital-induced DRESS complicated by a fulminant hemophagocytic syndrome (Descamps et al, 1997). In a small prospective series of seven consecutive patients hospitalized with DRESS we demonstrated serologic evidence of HHV6 active infection (Descamps et al, 2001). But evidence of viremia, which is the main criterion for confirmation of active infection, was not demonstrated in these cases (Descamps and Mahe, 2002; Tohyama and Hashimoto, 2002). Recently, we and others reported HHV-6 encephalitis associated with DRESS (Descamps et al, 2003). We report here a typical case of DRESS associated with minocycline and bring evidence of viremia by quantification of HHV-6 DNA in serum samples.

A 25-25-year-old patient was prescribed minocycline for the treatment of folliculitis on the scalp on the 16 May 2000. Seven weeks later on the 7 July 2000 he developed an erythroderma and systemic symptoms (DRESS) are well characterized and mimic viral infection: high fever, facial edema, erythroderma followed by an exfoliative dermatitis, diffuse lymphadenopathy, hyperesinophilia, atypical circulating lymphocytes, abnormal results of liver function tests. Other systemic manifestations may occur (e.g., pneumonitis, pancreatitis, neurologic symptoms). This drug adverse reaction was first described with anticonvulsants but minocycline is also well known to induce this kind of reaction (Disdier et al, 2001). The role of viral infection in the development of this drug adverse reaction is suspected. We implicated for the first time human herpesvirus 6 (HHV-6) infection in a patient with phenobarbital-induced DRESS complicated by a fulminant hemophagocytic syndrome (Descamps et al, 1997). In a small prospective series of seven consecutive patients hospitalized with DRESS we demonstrated serologic evidence of HHV6 active infection (Descamps et al, 2001). But evidence of viremia, which is the main criterion for confirmation of active infection, was not demonstrated in these cases (Descamps and Mahe, 2002; Tohyama and Hashimoto, 2002). Recently, we and others reported HHV-6 encephalitis associated with DRESS (Descamps et al, 2003). We report here a typical case of DRESS associated with minocycline and bring evidence of viremia by quantification of HHV-6 DNA in serum samples.

A 25-25-year-old patient was prescribed minocycline for the treatment of folliculitis on the scalp on the 16 May 2000. Seven weeks later on the 7 July 2000 he developed an erythroderma and increasing fever. The rash was itchy and associated with generalized lymphadenopathy. On the 22 May 2000, a skin biopsy of the right leg was performed, which showed a subacute dermatitis with dense infiltrate of eosinophils. A biopsy of the scalp was also performed, showing a folliculitis on the 16 May 2000. Seven weeks later on the 7 July 2000 he developed an erythroderma and increasing fever. The rash was itchy and associated with generalized lymphadenopathy. On the 22 May 2000, a skin biopsy of the right leg was performed, which showed a subacute dermatitis with dense infiltrate of eosinophils. A biopsy of the scalp was also performed, showing a folliculitis.