Noninvasive Optical, Electrical, and Acoustic Methods of Total Hemoglobin Determination

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BACKGROUND: Anemia is an underdiagnosed, significant public health concern afflicting >2 billion people worldwide. The detrimental effects of tissue oxygen deficiency on the cardiovascular system and concurrent appearance of anemia with numerous high-risk disorders highlight the importance of clinical screening. Currently there is no universally accepted, clinically applicable, noninvasive hemoglobin/hematocrit screening tool. The need for such a device has prompted an investigation into a breadth of techniques.

METHODS: A synopsis of the literature and current directions of research in noninvasive total hemoglobin measurement was collected. Contributions highlighted in this review are limited to those studies conducted with a clinical aspect, and most include in vivo patient studies.

RESULTS: The review of potential techniques presented here includes optoacoustic spectroscopy, spectrophotometric imaging, diffuse reflectance spectroscopy, transcutaneous illumination, electrical admittance plethysmography, and photoplethysmography. The technological performance, relative benefits of each approach, potential instrumentation design considerations, and future directions are discussed in each subcategory.

CONCLUSIONS: Many techniques reviewed here have shown excellent accuracy, sensitivity, and specificity in measuring hemoglobin/hematocrit, thus in the near future a new clinically viable tool for noninvasive hemoglobin/hematocrit monitoring will likely be widely used for patient care. Limiting factors in clinical adoption will likely involve technology integration into the current standard of care in each field routinely dealing with anemia.

Although anemia is often perceived by the general population as a minor medical condition, it is a significant ailment that healthcare professionals have recognized as negatively affecting mortality and morbidity (1, 2). According to the WHO, anemia is the largest global illness adversely affecting mortality and worker capacity. The US Department of Health and Human Services has deemed anemia a significant public health concern, and the National Anemia Action Council has reported the estimate that although anemia has been diagnosed in 3.5 million people in the US, millions more cases go undiagnosed. In developing countries where nutritional inadequacies and infectious disease are more prevalent, the situation effects of anemia are thought to be amplified, severely hindering children from reaching their full genetically determined potential (3, 4). The WHO estimates that as many as 2 billion people worldwide are afflicted with anemia (5).

Anemia is the lack of healthy red blood cells (RBC)4 circulating in the vascular system. Medically, anemia is defined by the WHO as a hemoglobin (Hgb) concentration below 12 g/dL for females and below 13 g/dL for males (5, 6). Even in its mild forms, anemia can influence physical function through fatigue and weakness; it also decreases myocardial function, causes peripheral arterial vasodilation, and activates the sympathetic and renin-angiotensin-aldosterone system. These effects influence the progression of diseases such as cardiac and renal failure (7, 8). In addition, anemia is associated with a myriad of other diseases. For example, anemia affects at least 33% of all patients with cancer, an estimated 65%–95% of all patients with HIV/AIDS, and 70% of all patients with rheumatoid arthritis (9).

To screen for anemia, physicians currently perform a visual inspection of the palpebral conjunctiva, conduct a complete blood count (CBC) test, spin a hematocrit (Hct), or use a small blood volume Hgb meter. Visual inspection of the conjunctiva by a physician is, at best, 70% accurate independent of the phy-

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4 Nonstandard abbreviations: RBC, red blood cells; Hgb, hemoglobin; Hct, hematocrit; CBC, complete blood count; NIR, near-infrared; OPS, orthogonal polarization spectral; SpO2, pulse saturation.
physician’s experience and training; it has also been shown that physicians today are less accurate than those of the past (10). The CBC test is very accurate but is invasive and painful to the patient, associated with a significant cost, time-consuming in waiting for laboratory analysis, and often not part of a routine physical exam. Spinning an Hct or using a small blood volume Hgb monitor provides a mode of quick anemia detection, but it is painful to the patient while creating biohazards and the need for associated disposal procedures. A device that can quickly and accurately measure Hgb has many healthcare applications, such as in physical examinations, emergency departments, prehospital care providers, medical specialists, in situ measurement of bleeding during surgery for determining transfusion triggers, and in home healthcare for the chronically ill and aging population. A noninvasive portable tool for anemia screening can make a difference at emergency department triage points, in field treatment centers during large-scale disasters (11), and in austere environments where rapid triage and treatment decisions are based on few data points. The use of devices that require blood may not be suitable in these settings. We present a review of noninvasive techniques to measure Hct/Hgb, either of which provides a quantification of anemia. It is important to note that although correlation coefficients are given for most multipatient trials, the correlation methods and reference techniques vary with each study and these numbers are meant only to be a rough guide.

CONDUCTANCE METHODS

In 1980, Yamakoshi et al. reported on the potential of monitoring Hct using electrical admittance plethysmography (12). During pulsation, the change in blood volume in the finger translates to a change in electrical admittance (conductivity) of the finger. Submerging the finger in an electrolyte solution whose admittance is equal to that of the finger compensates for pulsatile variation in conductivity, after which the conductivity of the electrolyte solution can be related to the conductivity of arterial vessels and then correlated to the Hct. This technique was reported with a correlation to linear regression line of \( r = 0.98 \) (\( n = 16 \)), determined by calibration established from in vitro blood conductance measurements and compared to a capillary-centrifuged reference sample. This group further disclosed a more simplistic and potentially viable clinical method to implement this technique using an electrical admittance finger cuff (13). Electrodes are placed in the interior of an annular cuff, which is then filled with an electrolyte solution. With the finger inserted through the cuff, electrical admittance measurements are taken and related to the electrolyte solution conductance in a similar fashion to the submersion technique, translating to a cleaner and more portable device.

Although the accuracy reported for the conductance method is promising, albeit in a limited patient population, little recent work has been disclosed on this technique. Difficulties associated with probing conductivity include variations with temperature, intra- and extracellular water/ion content, and other blood constituents. Because conductance monitors only a single value, rejection sodium ion concentration variation becomes a limiting factor, particularly in a noninvasive setting where varying whole blood ion content cannot be measured and thus cannot be normalized, hindering the potential overall efficacy of this technique. This topic is not explicitly discussed in this contribution.

IMAGING AND SPECTROPHOTOMETRIC IMAGING

Because Hgb (both oxy- and deoxy- forms) is one of the primary chromophores in blood, an assortment of optical techniques has been evaluated in noninvasive Hgb screening devices. One subcategory of device includes combination near-infrared (NIR) vascular imagers/spectrophotometers that can target blood vessels and subsequently estimate Hgb concentration. Explicitly, photometric absorbance measurements from the vascular portions of the image are coupled with an estimation of the optical pathlength using the imaged vascular diameter (and assuming circular vessel cross sections). This group reported diagnostic sensitivity and specificity of 78.3% and 69%, respectively, for clinically defined anemia, with a correlation to linear regression line of \( r = 0.53 \) for anemic patients (\( n = 174 \)), \( r = 0.34 \) (\( n = 135 \)) for patients with normal Hgb levels, and \( r = 0.59 \) (\( n = 309 \)) for all patients, using predefined device calibrations and comparing results to an automated hematology analyzer. Although this group notes the device is poorly suited for Hgb determination from a single measurement owing to variability in efficacy with finger position, its precision lends to its suitability for tracking of Hgb levels in perioperative anemia, gastrointestinal bleeding, and other situations requiring dynamic blood monitoring. As a more accurate solution, numerous groups have examined spectrophotometric imaging at other physiological access points.

Nadeau and Groner have disclosed an alternative method of image collection to probe microvascular networks and measure Hgb noninvasively using polar-
ization modulation (16). Orthogonal polarization spectral (OPS) imaging was implemented in a commercial instrument (Hemoscan, Cytomtricsoft) to analyze the vascular network of the sublingual mucosa. Illuminating with a polarized source at a discrete spectral band of high Hgb absorbance (approximately 550 nm), a crossed polarizer is placed at the detection focal plane array that transmits only light that has been depolarized through scattering from deep penetration into tissue. Hgb concentration is determined on the basis of a computational estimation of the vascular network density from collected images and the intensity of reflectance signal from each vessel area. This group has reported a linear regression correlation of \( r = 0.93 \) (n = 71) for predefined instrument calibrations compared to an automated hematology analyzer. Beyond Hgb measurement, this mode of imaging also provides insight into underlying vascular disorders. Genzel-Boroviczeny et al. present a similar imaging technique using OPS to measure Hgb noninvasively in neonates (17), and a report by Winkelman discusses the technology and further clinical implications/ viability of this microcirculation imaging technique (18).

Rice et al. have reported on the potential of standardized retinal imaging as an indicator for Hgb, serum bilirubin, and glucose (19). The retina is illuminated through the pupil, preferably at isosbestic points for oxy- and deoxyhemoglobin, using several discrete visible/NIR light bands while the reflected light from vessels overlying the optic disk is analyzed. This technique yields a cross-validation correlation of \( r = 0.89 \) (n = 24) based on calibrated reflected intensities compared with a small volume in vitro Hgb analyzer (HemoCue B, HemoCue AB). Winkelman et al. describe a similar image analysis technique for Hgb concentration estimation that focuses on the bulbar conjunctiva capillaries rather than the retinal vessels (20). This method analyzes high-magnification images of the capillary vessels in the mucosal surface to estimate blood cell parameters, including Hgb.

Ifitima et al. present an alternative imaging mode of Hct determination using spectral-domain low coherence interferometry, (21, 22), an alternative configuration of optical coherence tomography for retinal imaging that enables faster data collection. In this configuration, the penetration depth of optical signals through a blood vessel is dependent on the amount of scatter, which in turn is correlated to Hct. Fig. 1 shows an image of retinal vessels obtained with tracking laser-scanning ophthalmoscopy and the correlated optical coherence tomography depth profiles. To maintain collection from a single retinal vessel in the presence of rapid eye movements, an active eye tracking system is integrated to maintain image fixation on a single blood vessel (21). Faubert et al. report a similar technique using reflectance measurements from the retinal vessels to correlate to Hgb concentration (23, 24).

The physiological structures discussed in the above studies, such as the retina, conjunctiva, and sublingual mucosa, are mucosal surfaces, and as such are excellent locations to noninvasively monitor blood analytes compared to thick tissue regions such as the finger or forearm. In these regions (1), the transparency of overlying mucous membrane allows for clear observation and imaging of underlying vessels, (2), and low melanin concentrations in these areas leads to high uniformity between patients with different skin pigments (3). Analysis of capillary beds in a mucosal surface yields stable optical pathlengths during pulsation and thus does not require acquisition during predetermined timeframes of systole and diastole. Although capillary beds provide a stable optical pathlength, they are sites of active metabolism, so determining total Hgb concentration requires technique tolerances for large variations in oxygen saturation. Fortunately, techniques such as those disclosed above can overcome this limitation because oxy- and deoxyhemoglobin have numerous isosbestic points in the visible spectral range, allowing blood vessels to be imaged with visible light.

Although many imaging studies have shown excellent performance in monitoring blood components, one potential clinical limitation of this class of device is the associated imaging instrumentation. High-resolution microvascular imaging requires focal plane arrays that may be expensive and have considerable associated electronics, making these devices cost-ineffective compared to standard invasive blood testing procedures. Still, with advancement in detector size, speed, and cost, rapid anemia screening tools using microvascular imaging can be implemented. This class of device may have maximum usefulness as a bedside stand-alone device rather than a mobile device.

**NIR TRANSMISSION SPECTROSCOPY**

NIR transmission spectroscopy is the embodiment of choice in the majority of studies of total Hgb detection, particularly methods of transcutaneous illumination of the fingertip. The primary emphasis for investigating transcutaneous Hgb monitoring techniques is the potential for integration into existing pulse oximeters, making these devices fully functional to measure pulse Hgb saturation (SpO\(_2\)) as well as total Hgb concentration. Challenges of measuring total Hgb concentration, compared to relative measurements such as SpO\(_2\), lie in the contributions of other skin chromophores, variations in blood vessel location and density, variation in spectral signatures of oxy- and deoxyhemoglobin in the NIR regime, and changes in vessel diameter and subsequent optical pathlength during pulsation.
Nevertheless, investigators have overcome these challenges and fabricated noninvasive Hgb screening devices utilizing transcutaneous illumination.

Aldrich et al. have reported on the ability to use NIR transmission through the fingertip at a single pseudoisosbestic wavelength (905 nm) coupled with a sonomicrometer to monitor pulsatile changes in the optical pathlength through the finger as well as correct for interpatient variation in finger diameter (25). Sonomicrometers were positioned at opposite sides of the finger to monitor the pathlength fluctuations during systolic pulsation, and subsequently used to normalize transmission of NIR irradiation, as shown in Fig. 2. Using a linear regression model, this group obtained a cross-validation correlation $r = 0.84$ (n = 24) for Hgb compared with a Coulter cell counter, with a sensitivity and specificity of 94% and 78%, respectively, for detecting anemia, and a mean error of prediction of 1.1 g/dL for Hgb. While providing accurate estimations of the pulsatile pathlength change, transducer-mediated monitoring makes integration into a pulse oximeter less straightforward, especially considering the need to secure the transducers on the skin using adhesives or other fluids.

A wholly optical method for direct measurement of Hgb noninvasively was reported by Jeon et al., who used a 5-wavelength diode-emitting array (26). In diffuse photon propagation through the fingertip, a segment of irradiation photons will interact with the arte-

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**Fig. 1. Retinal imaging for Hct determination.**
(A) Scanning image of retinal vessels using a laser tracking imager. (B), OCT image along the horizontal line in (A). (C), OCT image along the vertical line in (A). Hct is correlated based on depth profiles of individual blood vessels. Reproduced with permission from (21).

**Fig. 2. Setup of transcutaneous illumination coupled with pathlength modulation detection using sonomicrometer transducers (A) and the detected variation in light intensity corresponding to the sonomicrometer detected variation in optical pathlength (B).** Adapted and reproduced with permission from (25).
Volumetric restriction of blood flow to the finger and monitoring of changes in transmission is an attractive method for differentiating the absorption contributions of Hgb/blood from those of surrounding tissue chromophores and therefore improving accuracies over purely optical methods. Rendell et al. have explored NIR transmission through the fingertip as a marker of total Hgb concentration (as well as blood markers of total Hgb concentration) while stabilizing the finger and modulating blood flow using constrictive finger inserts (27). Applying a linear regression algorithm to multiple discrete spectral points taken both with and without the constrictive insert, this group obtained an optimum non-linear regression correlation of $r = 0.862$ ($n = 121$) between radiation intensity values of multiple wavelengths and Hgb reference determined by the potassium cyanide method.

Geva et al. examined a similar technique termed occlusion spectroscopy, which also uses fingertip NIR transmission and blood flow modulation in a commercial instrument (NBM-100, Orsense) (28). The transmission signal is varied by occluding blood flow with a restrictive finger cuff (similar to a blood pressure cuff), accelerating ischemia-driven RBC aggregation. The occluding cuff is later released, allowing RBC to disaggregate while the change in optical transmission at multiple NIR/visible wavelengths is monitored (28). Clinical evaluation of this commercial technology has shown average error values of 0.78 g/dL ($n = 110$) using predefined calibrations for Hgb compared to an undisclosed in vitro method (29). Powell et al. report on the accuracy of a similar device (Critscan, Hemametrics) that also uses a finger cuff to modulate the volume of blood flow into the finger and measures transcutaneous optical absorptions to infer Hct, with a correlation of $r = 0.88$ ($n = 121$), again using predefined calibrations for Hct compared to capillary-centrifuged in vitro tests (30).

Although NIR transcutaneous methods of Hgb measurement have been thoroughly studied, they have yet to gain widespread clinical adoption. This situation may be partly a function of the technology adoption barrier for medical devices, and underlying technological barriers may also be prohibiting clinical use. As highlighted earlier, limitations in this method can include interference from the many other chromophores in skin and large variations in photon interaction lengths from varying tissue thicknesses. Of the reported methods discussed above, the flow modulation technique should be the most tolerant of these variations, because the only parameter being modulated during occlusion and release is Hct/Hgb, allowing for normalization and removal of interference artifacts. Consequently, this class of device has appeared in commercially manufactured instruments and has the potential for more widespread clinical adoption in the future.

**Reflectance Spectroscopy**

Several studies have investigated the use of reflectance spectroscopy as an alternative method to measure Hgb/Hct. An advantage of reflectance spectroscopy is that features close to the surface are probed, so deep transmission through highly scattering turbid tissue is not necessary. Because the required optical penetration depths are considerably lower, shorter wavelength light can be used, eliminating much of the variation between oxy and deoxyhemoglobin.

In one such study, Wu et al. examined steady-state visible and NIR diffuse reflectance spectroscopy from the dorsal side of the arm and its correlation to Hgb and Hct (31). A linear regression analysis of the absorbance data resulted in cross-validation correlation $r = 0.8$ and an SE of cross validation of 0.9 g/dL for Hgb compared to a photometric reference instrument. Furthermore, this group used an in-house fabricated fiber-based temperature controlled reflectance spectrophotometer with six 10-nm bandpass filters and associated photodiodes for data collection. Temperature control over a small depth in the tissue is attractive because absorption/scattering coefficients and cutaneous blood flow have been shown to vary with local temperature variation (32), contributing to an unwanted variability in noninvasive Hgb measurement. Using a Monte Carlo simulation and partial least squares analysis, Wu et al. obtained a cross-validation correlation of $r = 0.8$ and an SE of cross validation of 0.8 g/dL for Hgb (again compared to photometric reference method) in a patient set with 10 light-skinned patients tested multiple times ($n = 26$).

Zhang et al. reported on the utility of a similar visible/NIR diffuse reflectance spectroscopy technique
A fiber optic probe was attached against the patient’s forearm, and NIR reflectance spectra were collected during cardiopulmonary bypass surgery. Because blood is diluted through heart-lung machines during cardiopulmonary bypass, dynamic intrapatient Hct concentrations can be evaluated over the course of the procedure. Using partial least squares regression, this group reported obtained an intrapatient cross-validation correlation of $r = 0.844$ (n = 10) between optical methods and a reference capillary centrifuge method, and an interpatient cross-validation correlation of $r = 0.509$ assessed by comparing cross-patient data using a single partial least squares regression model. This group has reported variations of this technology in additional human patient studies as well as animal models.

The studies listed above examine visible/NIR reflectance spectra from thick tissue regions and are consequently susceptible to variability in patients of different ethnicity as a result of melanin fluctuation, particularly in the short-wave visible regime. To minimize this error, a calibration should be built into the technique to normalize contributions from melanin, or the use of mucosal surfaces should be explored. McMurry et al. reported on the use of visible reflectance spectroscopy to analyze the mucosal palpebral conjunctiva (inner lining of the eyelid) as a method of non-invasively monitoring Hgb. In a nonlinear regression model from diffuse reflectance spectra from the palpebral conjunctiva, a cross-validation correlation of $r = 0.92$ (n = 30) was obtained for Hgb compared to CBC testing across an ethnically diverse population. Two additional studies have shown that the use of either a standardized color chart or photographs of the conjunctiva as a comparative tool for the patient’s palpebral conjunctiva hue improved the sensitivity and specificity of observational methods.

Although reflectance techniques may be more difficult to implement in existing medical devices, their comparable if not improved accuracy over transmission methods may enable their adoption as a new, stand-alone clinical screening tool. Like transcutaneous methods, devices using reflectance spectroscopy may be fabricated inexpensively and compactly, giving this class of device the same point-of-care capability across a wide scope.

ULTRASOUND AND OPTOACOUSTIC SPECTROSCOPY

The dependence of ultrasonic wave generation and propagation through tissue on blood constituents leads to a completely different set of technologies to noninvasively monitor Hct/Hgb, including optoacoustics and pulse-echo ultrasound.

Optoacoustic spectroscopy has been explored as a modality for noninvasive Hgb measurement in multiple in vitro and in vivo studies. The rapid thermal expansion of the tissue through laser absorption creates an optoacoustic (pressure) wave, the characteristics of which depend on the characteristics of the absorbing analyte(s). In the NIR regime, Hgb has a higher absorption coefficient than surrounding tissue, enhancing optically induced thermal modulation. Fig. 3A shows the variation in optoacoustic signal with Hgb concentration in a tissue phantom. The superficial radial artery is an effective location for optoacoustic stimulation in the NIR because the vessel is close to the surface and the saturation is approximately 100%, eliminating errors caused from the variation in absorption spectra from oxy- and deoxyhemoglobin. Opto-
Acoustic waves generated from the melanin layers in skin can be distinguished from those generated from the radial artery based on the phase delay in the pressure wave (41). Fig. 3B shows the optoacoustic signals coming from the melanin layers vs radial artery and the variation in this signal with saline infusion. The peak-to-peak intensity from the optoacoustic waves measured during in vivo dilution closely follows those found by measuring Hgb concentration directly in the in vitro dilution experiment, although no interor intrapatient predictive correlation was reported (42).

Along similar lines, Secomski et al. have discussed the use of pulse echo ultrasound in determining Hct (43). Specifically, Hct is determined by monitoring the ultrasonic wave attenuation in blood, calculated from the Doppler power spectrum. Investigation of both a multigate Doppler system (44) and a single transducer pulse echo device verified the predictive ability of this method for Hct in an in vitro animal blood model and in an in vivo human patient set. Secomski reported an optimal correlation coefficient of \( r = 0.90 \) (\( n = 168 \)) for an in vitro study using the pulse echo method and an optimal correlation coefficient of \( r = 0.96 \) (\( n = 14 \)) for an in vitro study using a Doppler gating system (43). In the 6-patient in vivo study, again using the gated Doppler method, Hct determined from the brachial artery was within 5% of the value obtained with capillary centrifugation but Hct determined from the carotid artery was only within 20%.

Although these studies of these methods are interesting, it is not clear how they will compare to optical methods. In their current configurations, optoacoustic and ultrasonic methods of Hgb/Hct determination are more difficult to implement in a clinical setting than spectroscopic or imaging methods, inhibiting their application in numerous settings discussed above. Further evaluation and clinical trials of these techniques will indicate the potential of commercially viable technologies.

**Conclusions**

Among the new methods described, the best have shown accuracy of 95% relative to in vitro measured Hgb/Hct. Although it is difficult at this point to compare the overall performance of each class of technique, general comments on the results of these studies seem to show that (a) more complex techniques using conductance and optoacoustics can have excellent performance if suitable for the particular environment, (b) transcutaneous optical measurements yield better results with blood flow modification to reject interfer-

### Table 1. Correlation coefficients for the multipatient studies evaluated in this review. Correlation coefficients were determined with cross-validation, calibration and measurement of a prediction set, or correlation to a defined parameter.

<table>
<thead>
<tr>
<th>Author</th>
<th>Technique</th>
<th>Sample size</th>
<th>( r ) value</th>
<th>Calibration method</th>
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<tbody>
<tr>
<td>Yamakoshi</td>
<td>Electrical admittance plethysmography of finger</td>
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<td>0.98 (Hct)</td>
<td>In vitro calibration</td>
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<tr>
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<td>Orthogonal polarization imaging</td>
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<td>0.93 (Hgb)</td>
<td>Prediction set</td>
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<tr>
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<td>Retinal spectral imaging</td>
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<td>0.89 (Hgb)</td>
<td>Cross validation</td>
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<tr>
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<td>Retinal tracking and low-coherence interferometry</td>
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<td>Not reported</td>
<td>Not applicable</td>
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<tr>
<td>Aldrich</td>
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<td>0.84 (Hgb)</td>
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<td>0.92 (Hgb)</td>
<td>Cross validation</td>
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ence from background tissue properties, (c) for the same tissue interference reasons, optical reflectance measurements do not perform as well, and (d) exploration of mucosal surfaces through imaging and spectroscopy is an additional way to reject tissue interference. Table 1 shows correlations in multipatient trials. Although reports reviewing techniques were first published more than 2 decades ago, a truly noninvasive device has yet to be adopted as a standard of care. The likely reasons for the lack of physician adoption include the complicated nature of data collection, necessary instrumentation, and inaccuracy/repeatability issues. These difficulties have not prevented numerous commercial devices from appearing in clinical studies, such as those used and evaluated in the preceding text. Efficient penetration of this technology hinges on the simplification and miniaturization of these devices so they can be implemented easily into patient care while maintaining clinically acceptable performance.

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