Title: Towards Universal Health Coverage with Low-cost Noninvasive Health Monitoring with Smartphones

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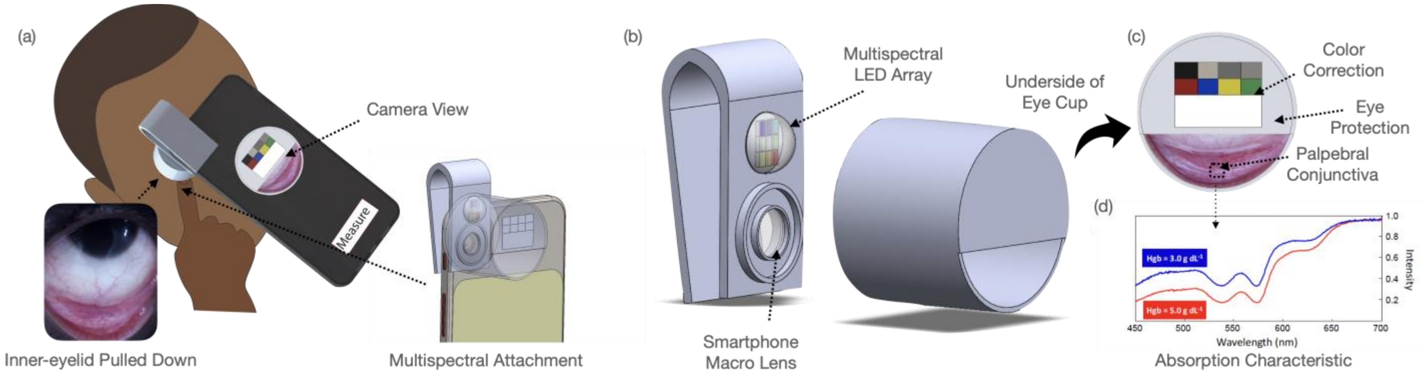
Universal Health Coverage (UHC) is an aim to ensure that all people can get the health services they need without suffering financial hardship. In 2012, UHC received global support when the United Nations General Assembly unanimously adopted a resolution that emphasizes health as an essential element in sustainable development. One of the key elements that cuts across the vast diversity of needs of differing economic and geographical regions is providing basic primary care to everyone to prevent diseases from ever starting and to diagnose diseases early when they are much more treatable. In this proposal, we aim to develop a low-cost smartphone attachment for noninvasive blood analysis that can perform hemoglobin measurements for anemia screening. Although recent data reveal a lower global prevalence of anemia in 2010 when compared to 1990, nearly one third of the world's population are estimated to be anemic and it remains a "severe public health problem" by the World Health Organization (WHO). Unfortunately, anemia – which assumes a disproportionate burden in resource-limited areas including sub-Saharan Africa (SSA) – is under diagnosed due to a sub-optimal laboratory infrastructure. The detrimental effects of anemia include health consequences related to inadequate oxygen delivery to tissues (e.g. fatigue, impaired concentration), economic consequences secondary to school and work absenteeism, as well as an increase in disability-adjusted life years. The toll of anemia is particularly severe among cancer patients and children. Our system will attach on to average smartphones, converting the phone camera into a multi-spectral imager suitable for imaging hemoglobin concentrations noninvasively from the subject's inner eyelid. The system will support the operator with an on-screen guidance interface that reduces operator error through AI-supported decision support.

Why are the current solutions not good enough? Despite this recognition of the need for UHC, survey by the World Bank and WHO showed in 2017 that half the world lacks access to essential health services. 800 million people spend at least 10% of their household budgets on health expenses alone, with 100 million people being driven into extreme poverty because of the high cost, forcing them to live on just USD$1.90 or less a day. There are high levels of health service access inequalities, with only 17 percent of mothers and children in the poorest fifth of households in low- and lower-middle income countries (LMICs) receiving at least six of seven basic maternal and child health interventions, compared to 74 percent for the wealthiest fifth of households. Cost of healthcare services is at the core of the issue. Point of care medical devices are costly to manufacture. Often the complexity of their operation requires training of health workers to operate them. The current solutions do not lend itself to empower local communities to care for their own health service needs and develop competencies towards long-term financially sustainable health coverage. For anemia screening, rural populations in LMIC depend on visiting community health workers from urban areas to host community hemoglobin measurements using point-of-care finger prick devices. To use these devices, a trained health worker is required for handling a specialized blood analyzer, biohazardous materials, and disposing of single-use needles and cuvettes.

How will smartphones facilitate the goal for UHC? To achieve UHC, a key element is to lower the cost of health care facilities and workforce that can deliver the necessary health services wherever people live. Smartphone adoption around the world have dramatically increased the access for computing, sensors, and connectivity for the global community. These devices, even the cheapest ones for under USD$50, have computing capabilities more powerful than those in many medical devices, at a fraction of the cost, due to economies of scale. These devices not only can perform complex data analysis, but also include basic sensors such as cameras and microphones. Furthermore, the user interfaces of smartphones are designed for ease of use for everyone and not just trained specialists. In recent years, researchers, including myself, have begun tapping into this new sensorized computing infrastructure as a mechanism to deliver health monitoring capabilities without manufacturing totally new devices. Smartphone apps have shown feasibility in analyzing a diversity of primary care needs including blood analysis, respiratory function, cardiovascular age, infections, skin lesions, and more.

Limitations for smartphone as a medical device? The function of a device, as its design is intended for, ultimately determines its form. A smartphone is designed with the use of consuming and interacting with visual information from the screen, taking photos of subjects away from the user or at the user themselves, and, of course, taking a phone call held up to the ear. The phone, on the hand, was never designed to be held up to someone's eyes without ambient light interference to get accurate color reflections, direct sound waves into the ear canal to capture fluid, and pressed against the chest to capture subtle crackle and wheezes of the lung. In engineering terms, we call this an impedance mismatch. Where there is an inherent mismatch at the interface causing the signal to be poorly transferred. Medical devices on the other hand are designed with how the sensor will couple to the body contour, surface, and orifice such that the measured signal is accessible, isolated, and consistent, leading to repeatable and robust measurements that can be trusted for clinical decision making.

Research Vision and Proposal Contribution towards Tenure. A core research direction in my early career as a jointly appointed tenure-track professor in both the Jacobs School of Engineering and The Design Lab is to develop solutions that can dramatically reduce the cost of medical devices by leveraging the sensorized computing infrastructure afforded by smartphone technology while bridging the impedance mismatch that inhibits current smartphone health sensing solutions to truly work for real-world use. As a research topic, my group is working on developing an array of medical monitoring solutions that uses the smartphone's complex sensors/computing/connectivity at its core and augmenting it with ultra-low-cost attachments that transforms the phone's sensors into a fully competent medical device at a fraction of the cost. One may argue that this solution still requires a smartphone, however, our goal is to develop attachments that cost ~USD$1-5 each. In this way, a kit of 10 such attachments + a phone may cost around USD$100, capturing important metrics of blood pressure (Hypertension/Preeclampsia), hemoglobin (Anemia/Blood Loss), lung capacity (Ashthma/COPD), bilirubin (Jaundice/Liver Disease), pupillary response (Concussion/Cognitive Function), pulse transit time (Arteriosclerosis). With current technologies, to enable all the metrics listed would require a full clinic costing far north of $100, with multiple point of care devices, phlebotomy equipment, lab testing facility, as well as highly trained clinician/nurse who can operate them all. My vision is that such a low-cost kit would be affordable to be distributed into any village/community center no matter how remote, with operation that is no more complicated than a typical blood pressure monitor, performs all measurements noninvasively with the support of a well-designed guidance system shown on screen. In this way, communities themselves could gain training on how to operate this kit for themselves instead of relying on external support, building their own competencies in community health services.



Innovation: Smartphone Multispectral Imaging Attachment for Noninvasive Hemoglobinometry. This proposal focuses on the development of a blood analysis imager attachment that is designed to leverage the complex computing and hardware of smartphone cameras with a set of low-cost lens and LED to enable the smartphone to image blood from the inner-eyelid of a patient. Our system relies on the phenomenon where the inner lining of the eyelid, the palpebral conjunctiva, is transparent and exposes the capillary to direct imaging. In fact, observed pallor of the conjunctiva is a clinically used indication that a patient is anemic. Prior work has indeed shown that by taking a photo of the inner-eyelid color does have correlation with blood test of hemoglobin concentration, however the accuracy is not high enough for clinical decision making. Our solution takes these as foundations to our concept but extends it by combining an additional imaging unit that incorporates low-cost LEDs spread from 400-700nm, a macro lens, and an eye cup. The use of a multi-spectral

LED setup provides additional spectral information that will provide more accurate estimation of the exact color of the conjunctiva, the macro lens increases the resolution of the image, and the eye cup helps to interface the phone camera with the eye to reduce ambient light effects and usability.

Approach. Our proposed research aims to develop the described low-cost attachment to smartphones with the associated algorithms to perform noninvasive hemoglobinometry from the inner-eyelid. To successfully develop this system, the research effort is divided into three specific aim tasks. In Aim 1, we will design and develop the multi-spectral imaging attachment. In Aim 2, we will conduct a small-scale clinical data collection study to perform measurements of inner-eyelid color of multiple individuals at different hemoglobin concentration levels. In Aim 3, we will develop the supporting algorithms to recognize the palpebral conjunctiva and estimate the hemoglobin concentration from the multi-spectral image.

<u>Related Experience</u> Dr. Wang has extensive experience with developing mobile health technologies using smartphones. His dissertation work was an early instantiation of the proposed idea around a smartphone-based hemoglobin monitor. In this prior work, Dr. Wang demonstrated the use of the smartphone camera for capturing hemoglobin through the finger in a similar way as a finger clip used in pulse oximeter. In addition, he has worked on deploying this technology in a variety of contexts including a clinical setting as well as in the field in villages in Peru. Through this experience, Dr. Wang built extensive knowledge regarding developing smartphone-based health sensing solutions, methods around their validation, and most importantly their limitations. The prior work, although demonstrated feasibility for estimating hemoglobin struggled in a few ways that the new solution aims to address. First, to measure hemoglobin at the finger, the finger needs to be placed over the camera and LED for at least 10-15 seconds to capture enough information to perform a hemoglobin estimation. This introduces a number of issues. First, with the use case focused on children under 5 years old, many young children have fingers much too small to cover the camera and flash completely. In addition, through the deployment in Peru, Dr. Wang learned first-hand how difficult it is to have children that age, in a fast moving environment of a community health screening, to stay still enough for 10-15 seconds for a quality measurement. Lastly, and most importantly, the skintone of the patient can at times significantly affect the measurement. With these limitations in mind, the proposed solution eliminates these issues by performing the measurement where the blood is much more exposed such that the measurement only takes a second and is much less dependent on the physiological characteristics of the patient.

Aim 1: Development of low-cost multispectral imaging smartphone attachment for hemoglobin monitoring. The attachment will be designed with three key components. (1) An LED array that evenly samples the spectrum between 400nm to 700nm, (2) eye cup interface that creates a light seal from the phone to the eye, and (3) macro lens attachment integration. We will design a custom printed circuit board to test different LED wavelengths. We will initially start by placing 9 surface mount LEDs. The LEDs will be packed tightly into a tight 3x4 grid and covered by a cheap convex lens to produce more even distribution of light. The choice of LED wavelengths will aim to cover key absorption points of hemoglobin as shown in literature, as shown in Figure1d. These specific wavelength measurements provide the necessary reconstruction of the absorption profile of the inner-eyelid to infer the hemoglobin concentration. The eye cup interface will be designed using rapid prototyping with 3D printing to quickly iterate multiple designs. Using a multi-material printer, we will prototype with different flexible material to investigate light sealing appropriateness of different designs. An important function that the eye cup serves, in addition to removing ambient light, is to act as a color calibration. Because every smartphone has slightly different camera settings, the camera sensor may have different sensitivity to different wavelengths. This calibration will be provided using a color correction grid placed at the end of the eye cup, allowing each image to be captured with a color correction. Finally, the macro lens attachment will be built around commercially available macro lens attachment to smartphones, where a macro lens is mounted on a clip that clips directly onto a smartphone. Figure1b shows a exploded view of the fully integrated attachment.

Aim 2: Hemodilution Study for Data Collection and Validation. In order to develop the system fully, it is necessary to collect a dataset of images with the attachment system on multiple people at different hemoglobin concentrations. One method to accomplish this is to conduct a data collection with a population that has a high prevalence of anemia to capture individuals who are in the lower spectrum of hemoglobin concentration. However, based on prior experience, such datasets often contain many confounds that are difficult to control along with the difficulty in accessing such a population in United States due to the low prevalence of severe anemia except in highly immunocompromised patients such as leukemia patients or sickle cell disease patients recovering from a sequestration crisis. Instead, we have devised a study with a partner Consulting Research Organization (CRO) capable of performing a controlled Hemodilution Study. A Hemodilution Study is a clinical study procedure where a subject's blood is diluted to induce anemia between 1 to 3 g/dL. This dilution procedure is fully IRB approved and is performed by removing 0.5L of whole blood from the subject and replacing it with 0.5L of saline. This methodology is performed by the CRO, Clinimark LLC, located in Louisville, CO, a clinical research facility located in Avista Adventist Hospital. Dr. Wang has previously collaborated with Clinimark in an oxygen desaturation study and has received a preliminary quote regarding the proposed study.

Each procedure will last about 1 hour. A fleet of 3 different smartphones will each be outfitted with the same attachment system. In 5-minute intervals, a blood draw is performed, and the subject's hemoglobin will be referenced by a complete blood count (CBC). At the time of each measurement, each eye will then be measured by taking a photo with each phone in alternation. The initial study is slated for 6 subjects to provide pilot data for the development of the system. At the conclusion of the study, we will have a dataset of multispectral images of the palpebral conjunctiva at a variety of hemoglobin levels captured by different smartphones. This dataset will be a one-time investment towards a highly valuable dataset for Dr. Wang's lab for future developments in machine learning algorithms intended to improve palpebral-based hemoglobin sensing. No prior work has captured such highly controlled dataset and will lead to high-impact journal publications based on this work.

Aim 3: Development of Machine Learning Algorithm for Hemoglobin Tracking. Within scope of this proposal, the images will be manually segmented for the palpebral conjunctiva region. In future work, our goal will be to develop the computer vision algorithm to automatically segment the conjunctiva in order to demonstrate an end-to-end system. Once the region of interest is segmented for each image, the absorption spectrum is calculated for each image by taking the mean intensity of four equidistant regions of the conjunctiva. The absorption intensity at each wavelength will be used as features to train a machine learning algorithm where the training data are labeled by the CBC reference values of hemoglobin. To minimize impact of overfitting, we will employ best practice machine learning methods such as leave-one-subject-out cross validation and utilize classical machine learning techniques which are more suitable for small N datasets.

Broader Impact and Future Funding Opportunities. My group aims to tackle a number of the key metrics that will have some of the biggest impacts towards UHC, starting with blood pressure and hemoglobin. Dr. Wang has currently received seed funding towards exploring an ultra-low-cost blood pressure monitor development which have successfully been completed and is now in the process of applying for funding in the NIH. Through the generous support of the Hellman Foundation, Dr. Wang hopes to develop the initial feasibility of the hemoglobin monitoring system and apply for further R01 funding from NIH/NIBIB, combining the blood pressure and hemoglobin as the basis of a kit for prenatal/neonatal care for preventing maternal mortality due to preeclampsia, screening of iron-deficiency anemia, and early detection of splenic sequestration crisis of sickle-cell disease. As a joint faculty between School of Engineering and The Design Lab, this type of contribution blending technological ingenuity and major real-world impact is crucial for Dr. Wang's promotion.

Study Timeline and Budget Justification. The proposed feasibility study will be conducted over 9 months. The device development of Aim 1 will be conducted between Months 1-6. The hemodilution study of Aim 2 will aim to be scheduled for Month 7, with the study taking two days to complete. Finally, once data collection is complete, the data will be analyzed under Aim 3 between Months 8-9. The support from the grant will involve two primary expenditures: (1) Funding of a PhD graduate student from the ECE department at 24.99% and (2) contract for the hemodilution study. The PhD student will be funded at an additional 24.99% through Dr. Wang's Startup Funding to dedicate fulltime on this project as well as travel funding to oversee the study.