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Internally Validated Independent Results for Noninvasive, Cuff-less Blood Pressure Estimation Utilizing Valencell's Deep-PPG Technology

EXECUTIVE SUMMARY

The purpose of this study was to demonstrate the accuracy of a cuff-less BP monitoring technology, based upon photoplethysmography (PPG), embedded within a popular audio earbud form-factor. A training dataset was collected via BP measurements collected from thousands of participants in 3 sequential readings: a manual auscultatory reading, an automated oscillometric cuff reading, and a PPG reading from a commercial PPG sensor embedded within a wireless audio earbud. With the manual readings serving as “ground truth”, a machine learning model for ear-PPG BP (EPBP) was trained to predict both systolic and diastolic BP based solely on ear-PPG sensor data and subject meta data (age, weight, height, and gender).The resulting EPBP model comprised both an automated qualifier and BP estimator, such that data into the model is automatically qualified (deemed “suitable”) for accurate processing by the BP estimator. An unbiased accuracy assessment of the trained EPBP model was generated by statistical analysis of the model’s BP predictions for a “qualified test dataset”, collected via the ISO 81060-2(2018) standard for noninvasive sphygmomanometers, comprising 654 measurements from 147 unique individuals. This qualified test dataset, comprising all collected data meeting the ISO acceptance criteria and also deemed suitable for accurate processing by the automated qualifier, was collected completely independently of the training dataset and was never used to train the model, thus serving as a truly unbiased test dataset.

For the qualified test dataset, the EPBP model was able to predict manual BP measurements with an accuracy comparable to that of the automated cuff. Moreover, the ability of the EPBP model to determine hypertension status was equivalent to that of automated cuff. The results prove than an ear-worn PPG sensor can generate accurate BP estimates without a BP cuff. Because this PPG solution can be embedded within commercially popular audio earbuds used by hundreds of millions of consumers, the solution is expected to encourage a much broader-scale compliance of daily blood pressure monitoring, widely viewed as a promising means of improving health outcomes and reducing medical costs.

OUTLINE

1) INTRODUCTION

This report summarizes work performed by Valencell in developing and validating the world's first cuff-less, calibration-free, all-PPG solution for accurately assessing BP in a general population. The key goal of this R&D effort was to demonstrate a commercially viable cuff-less, calibration-free, all-PPG BP monitoring solution that could ultimately:

1) Provide demonstrable public health value
2) Provide cuff-like accuracy in a general population

At the heart of this solution is a highly integrated PPG sensor module with embedded software employing a highly sophisticated machine learning model. Though many form-factors were investigated in this study, the ear region has shown the most promise in terms of accuracy and generalizability. The PPG-BP model developed for the ear, referred to herein as the EPBP (ear PPG BP) model, has been integrated into an embedded solution enabling biometric earbuds and eventually hearing aids to accurately estimate blood pressure, enabling a wealth of general wellness and medical use cases – such as stress management, diet and exercise planning, hypertension management, diabetes management, vital status monitoring, ambulatory monitoring, stroke prediction, peripheral artery disease management, angina monitoring, kidney disease management, and more [1].

The public health value of routine daily blood pressure (BP) monitoring has been the subject of much discussion in recent years [2-6]. According to the Center for Disease Control (CDC), hypertension (the "silent killer") was a primary or contributing cause of death for more than 410,000 Americans in 2014 [7]. Moreover, roughly 1/3rd of American adults have hypertension, and only half of them know they have the disease [7]. The alarming rate of hypertension in the United States, combined with supporting data showing the positive impact of regular BP monitoring, has led to the American College of Cardiology updating their guidelines for blood pressure monitoring, targeting lower blood pressure values than traditionally advised [8]. Broader than the U.S. alone, the "silent killer" is estimated to cause ~7.5 million deaths each year worldwide (roughly 12.8% of all total deaths) [9].

The "silent" aspect of hypertension is due to the fact that the condition is largely asymptomatic its early, yet very damaging, stages [10], perhaps due to the protracted etiology between hypertension and cardiovascular disease, which remains the subject of much debate [11-13]. Namely, it is believed that high BP damages the delicate tissues of the heart and blood vessels over time [14]. In turn, LDL (so-called "bad cholesterol") forms plaque along these damaged regions of tissue, leading to the onset of atherosclerosis [14]. Once this process begins, a vicious cycle escalates damage over time – as the arteries narrow, the average blood pressure continues to increase, which causes more damage, which thereby accelerates atherosclerosis, and they cycle progressively escalates [14]. Changes in cardiovascular performance may also change over this period, but these changes may be so gradual that the symptoms may not be observable. In such case, the detection of hypertension may be the only warning sign, making regular monitoring of blood pressure critical in detecting a long-term trend towards

hypertension. This can be extremely valuable for individuals and public health at large. Because diet and lifestyle changes have been shown to be extremely effective at reducing high blood pressure, combining general wellness with regular BP monitoring can be a powerful combination towards improved health and reduced risk of heart attack or stroke [15].

Indeed, many people want to monitor their health on a regular basis, as do their physicians, but a key challenge is that the workhorse of BP monitoring – the BP cuff – has proven to be to inconvenient for regular public use. There are numerous challenges associated with taking BP cuff readings: 1) the device form-factor is odd and not part of what people already wear, making it inconvenient to carry and don, 2) the process of measuring BP with a cuff requires a tedious set of steps that are difficult to reproduce with each measurement (i.e., choosing cuff sizes, keeping body positioning consistent, positioning the cuff correctly, etc.), 3) the pressure sensors require calibration on a routine basis to maintain accuracy, and 4) many of the measurement errors are inconsistent and unpredictable [16-20]. For these reasons, a convenient method of measuring blood pressure with sufficient accuracy, via a socially acceptable form-factor that people already use each day, is of high market value.

Valencell realized the importance of cuff-less BP monitoring since foundation in 2006. At the time, it was well-known that BP information exists within the photoplethysmography (PPG) waveform [21]. Because Valencell had developed great expertise in the area of wearable PPG, it ultimately was worth the risk for the company to investigate the potential of employing PPG towards BP monitoring in wearable devices. PPG enables cuff-less blood flow readings at virtually any location on the body, and it is currently the workhorse of wearable heart rate monitoring in the consumer marketplace, as evinced by tens of millions of heart rate wristbands and earbuds sold each year worldwide [22]. However, Valencell discovered that the transfer function between the PPG signal and BP is complex and nonlinear; thus, the company determined that developing a PPG technology with cuff-like accuracy without a cuff would benefit from a machine learning approach. The results of this initial study were promising (see Valencell US patents# 9,788,794 and 10,206,627) [23, 24], and it was determined that additional data collection would be necessary to generate a machine learning BP model that could provide even greater accuracy across a broad population. This began the construction of a framework for Valencell's "Deep-PPG" methodology, which applies machine learning to raw PPG signals and contextual data, yielding numerous accurate assessments and use cases for PPG-enabled wearables.

A data collection effort began in 2009 and ramped up substantially in 2016 and 2018. By 2019, a substantial dataset of more than 3000 world-wide human subjects had been generated, comprising raw PPG data, meta data, and labels (such as manual and auto-cuff BP values) for both finger and ear form-factors. Moreover, the data collection process became automated to facilitate scalable and reproducible data collection in the field, and sufficient data collection was attained to enable the development of a cuff-less, generalizable, all-PPG machine learning model for estimating BP. The key inputs to this model are PPG and static biometrics, as well as accelerometry data for contextual analysis [23, 24].

To prove the generalizability of the machine learning model, it was important to validate the accuracy of the model – without bias -- using a test dataset collected completely separately from the training data and never used to train the model. It was decided that this test dataset would ideally be generated using the ISO 81060-2(2018) protocol, as the formalism for data collection is widely accepted for validating calibration-free automated noninvasive BP cuffs. While certainly not ideal, as it was designed for measuring blood pressure cuffs and not PPG earpieces, the ISO protocol was found the be the most suitable for generating an overall assessment of a PPG-BP solution.

Following ISO data collection, the accuracy of Valencell's EPBP model was statistically analyzed according to the ISO 81060-2(2018) protocol and assessed for the ability of the model to categorize whether a subject were hypertensive or not hypertensive. The results and analysis are summarized herein.

2) METHODS

2.1) Study Design

The study design followed the International Standard for Non-invasive Sphygmomanometers, Third Edition 2018-11 (ISO 81060-2) [25], herein referred to as the ISO Standard. Target enrollment to meet the requirements for the ISO standard included a minimum of 85 participants with at least 255 measures, meeting the following guidelines:

i. At least 30% males and females
ii. At least 5% with systolic blood pressure ≤100
iii. At least 5% with systolic blood pressure ≥160
iv. At least 20% with systolic blood pressure ≥140
v. At least 5% with diastolic blood pressure ≤60
vi. At least 5% with diastolic blood pressure ≥100
vii. At least 20% with diastolic blood pressure ≥85

Participant Recruitment

In order to meet the target enrollment, Volunteers were recruited from previous blood pressure and heart rate study participants, as well as Valencell's extended test subject network. Recruitment emails were sent to these individuals offering Amazon gift cards to participate in this blood pressure study. All study visits took place at Valencell's Headquarters in Raleigh, NC.

Participants were required to be at least 18 years of age and not have any form of irregular heart rhythm (i.e. - Bigeminy, trigeminy, isolated ventricular premature beat (VPB), atrial fibrillation). They were asked to wear a short sleeve shirt and empty their bladder prior to testing. No other requirements were made as far as fasting and/or refraining from alcohol. Participants were not allowed to eat or drink during the testing session and were asked to remain seated throughout. The entire testing session took less than one hour.

Instrumentation

Samsung S8 phones were used for data collection to record the PPG measures (one phone was paired to each device), and a Valencell mobile application on the phone was used to enter all data so that it could be stored in the electronic database. The four PPG sensors under were the Benchmark Earbud 5.0 (BE5.0), Benchmark Earbud 1.2 (BE1.2), Benchmark Wristband 1.2 (BW1.2), and the finger sensors on the Samsung S8. An OMRON Intellisense Digital Blood Pressure Monitor was used as the automatic cuff. The reference manual sphygmomanometer used complied with the requirements of ISO 81060-1, with maximum permissible error of ±1 mmHg (0,13 kPa). the reference. This report includes the results of the BE5.0, BE1.2 and the automatic cuff in comparison to the reference manual sphygmomanometer.

2.2) Testing Procedures

After reviewing and signing the informed consent, participants were asked a few demographic questions (date of birth, gender, skin type, smoking status, BP medication) and had several measurements taken (height, weight, upper-arm circumference, and arm length).

Participants were then fitted with the Valencell PPG sensors. The BE5.0 and BE1.2 earbuds were worn with a medium gel unless a different size was required for the sensor to stay on the ear. The BW1.2 was worn snuggly, but not overly tight, approximately one finger proximal to the ulnar styloid process. Participants were shown how to hold the S8 with their palm up and with the PPG sensor resting on their middle finger.

Data collection procedures followed the ISO standard with the goal of comparing both the automatic cuff and the PPG sensors to the manual reference sphygmomanometer. Because the goal has been to perform analysis on both the automatic blood pressure cuff and the PPG sensors, procedures followed a hybrid of the “same arm sequential method” (5.2.4.1) and the “opposite limb simultaneous method” (5.2.4.2). Namely, it was simultaneous for the automatic cuff, but sequential for the PPG sensors. The only difference for the PPG sensors from the “same arm sequential method” according to the ISO standard was that the arm used for the manual cuff was alternated. The unique nature of this study justified this compromise, so that the automatic cuff could be compared during the same session following simultaneous method, and since none of the PPG sensors were located at the arm.

Data Collection

Three trained observers were required to run all data collection. Two observers were assigned to “data collector” roles while the third was the “recorder.” Prior to any measures, the participant rested quietly for five minutes with their back and arms supported.

After the rest, a practice round of measures was performed for each subject. Appropriate cuff sizes were selected for the manual and automatic cuffs based on the ranges noted on the inside of cuffs. The data collectors took the manual measurement first using a dual-headed stethoscope and listening for the Korotkoff sounds. The first sound indicated the systolic blood pressure (SBP) and the last sound indicated the diastolic blood pressure (DBP). Each data collector wrote down the blood pressure they heard and passed it to the recorder. The recorder started the automatic cuff at the same time as the manual cuff began to inflate and recorded all results. For the practice round, the recorder told the data collectors if the measures did not match and they could discuss any discrepancies. For all measures, it was ensured that the participant:

- was comfortably seated with legs uncrossed and feet flat on the floor;
- had their back, elbows and forearms supported;
- had the measurement site at the level of the left ventricle of the heart;
- avoided talking during the entire procedure; and
- had the cuff applied on the bare arm with no arm compression proximal to the cuff.

The recorder started a timer after the cuffs were deflated and after a one-minute break, the official measures began. The data collectors repeated the manual measure with the automatic measure being taken simultaneously on the opposite arm. This time, only the recorder saw the blood pressure measures and recorded the results on the data collection sheet and entered them into the phone.

After this, the cuffs were taken off and switched arms, and the Samsung phone was placed in the participant's hand with their middle finger on the sensor. As long as one minute had passed since the manual and automatic measures and the PPG waves all looked smooth, the data collectors started the PPG measures on all four devices simultaneously. Data was recorded for one minute. After another one-minute break, these steps were repeated seven more times (for a total of eight official measures).

If participants had cold hands, thereby precluding the ability to generate a smooth PPG signal at the finger, a hand warmer was used during the breaks. At the completion of testing, participants were provided with the approximate average of their SBP and DBP along with the ranges they fall into based on the AHA categories. If the participant's resting SBP and/or DBP was above the optimal range, the nurses explained what factors can contribute to high blood pressure (diet, stress, white coat syndrome, lifestyle, smoking, weight, etc.) and that follow-up with their primary care physician is recommended.

2.3) Data Analysis & Qualified Test Dataset Generation

Following data collection, data clean-up was performed. The handwritten data collection sheets were compared to the electronic database and corrections were made as necessary. The data was then analyzed to determine what could be included in the analysis.

According to the ISO Standard, the following requirements (ISO Standard Dataset Requirements) must be met to include the collected data within the official ISO dataset:

- The paired DBP and SBP values for each manual measure must be within 4mmHg
- There must be a valid pair of measures before and after the device undertest
    - The valid pair before and after are averaged to determine the reference value
- Any two of the reference DBP values cannot differ by more than 8 mmHg*
- Any two of the reference SBP values cannot differ by more than 12 mmHg*

**Note that the difference of 8 and 12 mmHg is a requirement for the sequential method where the reference manual measurements are all taken on the same arm. For the opposite-limb simultaneous method, the requirement is for the difference in opposite limbs to be no more than 10 mmHg for DBP and no more than 15 mmHg for SBP (with the 8 and 12 mmHg still required for measures on the same arm). Since testing procedure followed a hybrid of the two methods, the more stringent cut-offs of 8 and 12 mmHg were used for all measures.*

Data Exclusion & Qualified Test Dataset

Data was excluded if it did not meet the criteria above, with the goal of having three reference blood pressure values for each participant. According to the ISO Standard, up to 10% of the measures could be used with only two reference values. Additional reasons for excluding data included:

- The Korotkoff sound was inaudible
- The BP cuff was unable to be used on both arms (for example: the participant had a diabetic needle in the arm, the participant recently had surgery on one arm, etc.)
- The automated data qualifier deemed the PPG data to be unsuitable for accurately estimating blood pressure

It is important to note that data exclusions came from 3 key categories: 1) the data was required to be removed by the ISO protocol (as described below), 2) the manual BP cuff reference was unable to generate a BP reading, and 3) the automatic data qualifier deemed the PPG data to be unsuitable for accurately estimating BP. For all 3 cases, there was no measurement bias whatsoever. Namely, for all 3 categories, these datasets were removed at the outset before the BP model was used to estimate BP. And for the 3rd category, the qualifier software was autonomous and required no human input to make the determination that the PPG data would likely be unsuitable for accurately estimating BP.

The resulting qualified test dataset is presented below (Table 2.3.1 & Table 2.3.2) for both the BE1.2 and BE5.0 biometric earpiece sensors. This test dataset was collected completely independently of the training dataset and was never used to train the BP model. Thus, the BP model estimation results for this test dataset can be viewed as truly unbiased.

Table 2.3.1 – Summary of Qualified Test Dataset

	BE1.2	**BE5.0**
Total # of Measures	654	622
Total # of Participants	147	137
Percent Only Two Measures	4.6%	4.8%
Percent on BP Medication	16.5%	16.6%
Percent Male/Female	39% / 61%	41% / 59%
Number of SBP ≤ 100	57	44
Number of SBP ≥ 160	2	0
Number of SBP ≥ 140	46	32
Number of DBP ≤ 60	60	58
Number of DBP ≥ 100	0	0
Number of DBP ≥ 85	160	106

3) BP MODEL

3.1) Goals

Valencell's blood pressure estimation subsystem is the culmination of an iterative development process spanning several years. The model builds upon a history of BP R&D funded by Valencell, going back as far as 2009, as summarized in several Valencell patents and patent applications [23, 24]. The purpose of this effort has been to overcome the wearability and usability limitations of blood pressure cuffs with a noninvasive, cuff-less biometric solution. Because of the functionality, utility, and wearability of PPG, and due to Valencell's unique experience in wearable PPG monitoring, an "all-PPG" approach to BP monitoring was explored. Early data exploration and model development aimed to determine the extent of correlation that existed between the PPG waveform and measured blood pressure readings. Given that a sufficient correlation existed, a development goal was set to improve BP estimate accuracy and precision over a general population to ultimately provide cuff-like accuracy without the need for a BP cuff. Namely, the goal was to generate a noninvasive, cuff-less, calibration-free PPG solution that would be as "cuff-like" as possible in terms of accuracy and precision while also being substantially more convenient to wear and use on a regular basis.

3.2) Scope of the Problem

Measuring BP non-intrusively results in measurement variance no matter the methodology used. Ground truth BP measurements (the reference measurements used to validate DUT estimates) are difficult to obtain and face fundamental limits of resolution. Even when using an invasive arterial blood pressure methodology (i.e., the arterial line) in a highly controlled and stationary environment, the measurement variance associated with the coupling of blood pressure information to the pressure transducer will lead to imprecise measurements. Similarly, with noninvasive blood pressure cuffs, the pressure coupling between the pressure transducer, the cuff, and the body of the subject can be a source of substantial error, and thus well-established rules have been in place to determine which cuff sizes should be used for various arm circumferences [25]. Moreover, the vertical displacement of the pressure transducer with respect to the heart of the subject can cause considerable error, as well as transient changes in blood pressure following physical activity [25]. Some of these errors are reducible by following key procedures, but other errors may be effectively irreducible due to the nature of measurement modality. These well-known sources of error are largely why the ISO exclusion criteria have been designed to be so strict (see **Section 2: Methods**).

The good news is that there exists a transfer function between the PPG measurement and blood pressure. However, this transfer function is complex and nonlinear, involving multiple latent biometrics signals, all of which are statistically non-stationary. Namely, these latent signals and the blood pressure values are changing over time, many of their relationships are changing over time, and many of these relationships are different from subject-to-subject. More specifically, the time-varying PPG signal, even with the subject at complete rest, is affected by numerous time-dependent variables, including blood oxygenation, venous congestion,

sympathetic tone, blood pressure, heart rate, breathing rate, and various cardiorespiratory dynamics [21]. Given that the subject is rarely at complete rest, motion artifacts can also greatly impact the PPG signal. Additionally, relatively static biometric parameters, such as vascular elasticity and vascular structure, can also impact the relationship between the PPG waveform and BP from person-to-person. Thus, not only is the ground truth difficult to nail-down in building a PPG-based BP monitor, but so is the relationship between PPG and BP. In order to build a model that can account for the variance in ground truth and the complex transfer function, a substantial amount of labeled data must be collected. To summarize (as shown in (**Fig. 3.2.1**), developing a PPG-based model for BP estimation is faced with the challenges of limited data, relatively high variance in both the reference and estimated data sets, and a transfer function that is stochastic and non-stationary not only between subjects but even within a single subject over time, with the existence of competing signals within the estimation space to boot!

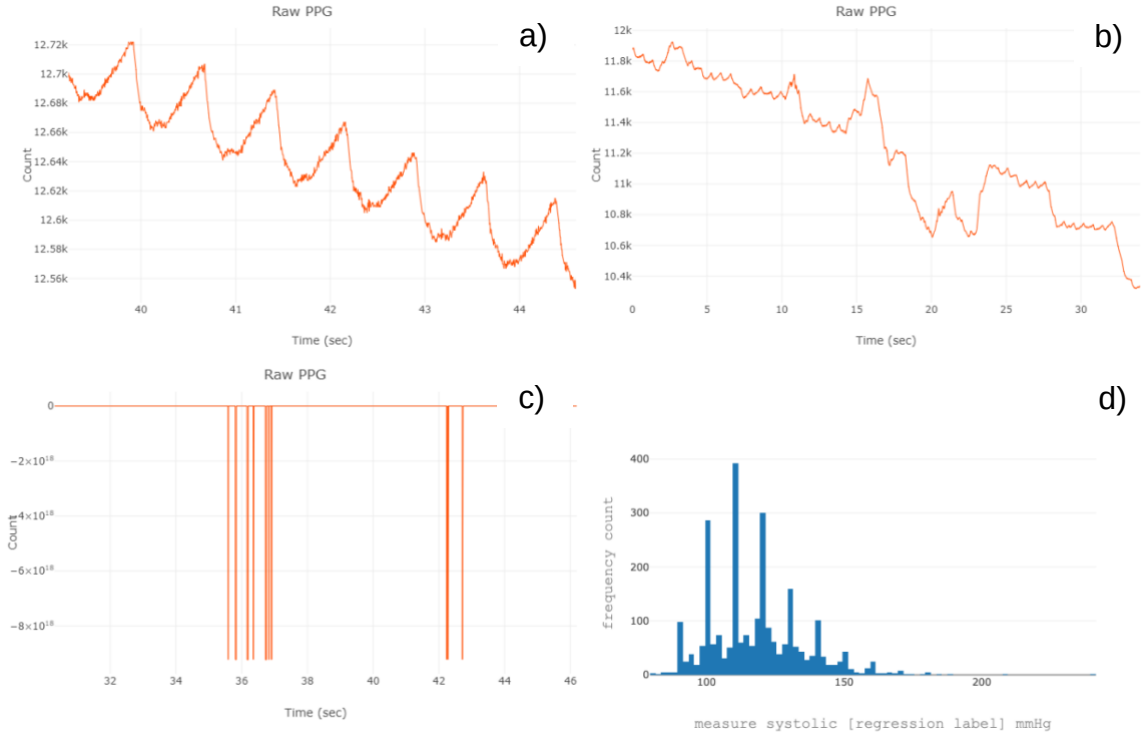

Figure 3.2.1: Examples of noise in measured signal: a) high frequency noise, b) interference signal from motion artifacts, c) electronic communication noise, and d) noise in BP manual (sphygmomanometer based) estimations, as evinced by grossly disproportionate BP estimations at multiples of 10 mmHg.

3.3) BP Estimation via Machine Learning

At the core of the blood pressure estimation subsystem is a machine learning model which generates meta-transfer function from the available data. The BP estimation model utilized herein utilizes numerous parameters; by comparison, current neural networks for detecting single-class biometrics, such as arrythmia, employ models that are roughly 200,000 parameters large [26-29].

Training Data

The training data used to estimate the desired meta-transfer function consists of disparate sources in an effort to increase data support and generalization. Thus, data has been collected from three different geographic locations: the United States, the Philippines, and Vietnam. The crux of the issue in data collection is a trade-off between the ease of data collection versus noise in the data, and thus methods have been developed to improve label accuracy and ease of measurement simultaneously. A summary of how the training data was collected is presented in **Appendix A**.

Herein, the optimization method currently used in training employs Valencell PPG-BP datasets collected internally by Valencell and externally in the Philippines and Vietnam. However, the ISO qualified test dataset collected for this report is a key exception in that it was not used in model training. Thus, the qualified test dataset collected for this report may be viewed as a pure and pristine, unbiased test dataset, and all of the analysis therefrom may be considered truly unbiased. It should be noted that, to the best of Valencell's knowledge, no such massive unbiased testing dataset for BP PPG has ever been reported in the literature.

Training Data Metrics

As outlined in previous sections, data collection is quite challenging for blood pressure. There is an optimization involving cost of collection, ease of collection, accuracy of measurements, and data coverage. A summary of training data is provided in the table and graphs below. Data from more than 3000 subjects was collected, and following a rejection of poor-quality PPG datasets and missing labels, a total of 1691 unique participants (see **Table 3.3.1**) were utilized to train the machine learning PPG-BP model utilized in this report. As stated earlier, the geographic location of these data collection efforts spanned across the globe. In all, there were 2620 unique tests, more male participants (61%), very few smokers (5%), and a reasonable fraction of participants taking BP medication (16%). As shown in **Figure 3.3.1**, the training dataset is skewed towards younger participants and average BMI values.

Table 3.3.1 – BP Estimator Training Data Statistics

# of unique tests:	2620			**Mean ± SD**	**Range**	**Units**
# of unique participants:	1691		**Age**	46 ± 18	18 - 82	Years
			BMI	28 ± 7	18 - 57	N/A
Gender:	Count	Percentage	**Systolic BP**	119 ± 16	86 - 218	mmHg
Male	1610	61%	**Diastolic BP**	74 ± 12	48 - 132	mmHg
Female	1010	39%				
Smoker:	Count	Percentage				
No	2489	95%				
Yes	131	5%				
BP Medication:	Count	Percentage				
No	2191	84%				
Yes	429	16%				

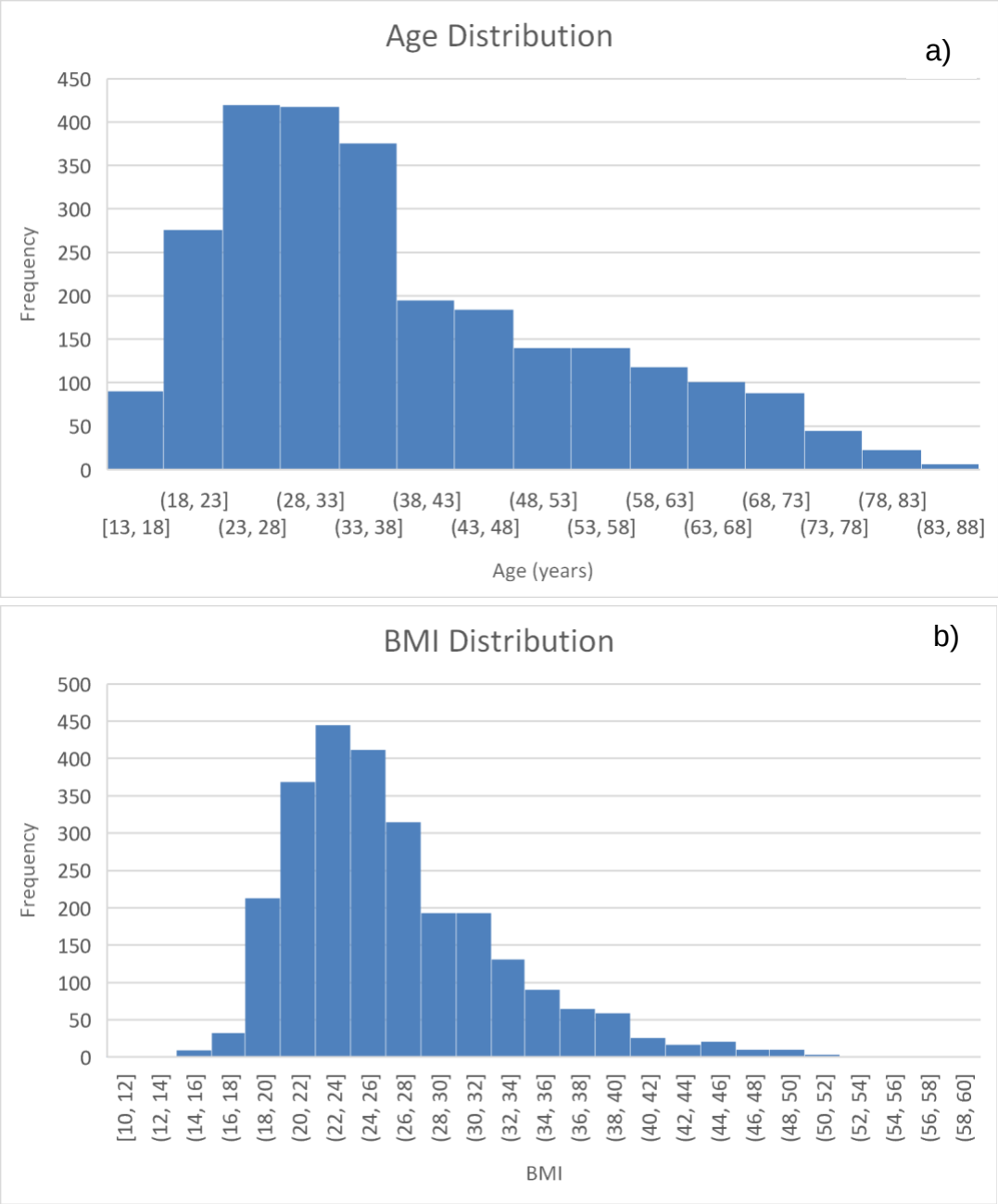

***Figure 3.3.1*: Histogram of the training data for the BP estimator: a) age of subjects and b) BMI of subjects. There is a skew towards younger participants and average BMI.**

3.4) Data Qualifier

Valencell has developed an autonomous (patented [23-24, 30, 33] and patent-pending) data qualifier that assesses the likelihood that PPG data can yield an accurate BP estimation via the BP estimator. Valencell's data qualifier has the benefit of not only reducing false positive and false negatives in hypertension categorization but also in providing an assessment of the accuracy of the BP estimate. This enables a solution which can tell the end user their

estimated BP as well as the range of estimation error associate with their measurement. The BP estimator and BP qualifier work together to provide accurate BP estimates, preventing false positives and false negatives when assessing hypertension. The results of the EPBP model presented herein (see **Section 5: RESULTS**) are based on the combined outputs of the BP qualifier and estimator.

4) EMBEDDED SOLUTION

The EPBP model was developed offline, and from the beginning of the BP R&D program it was appreciated that the structure of the model would need to facilitate an embedded solution using conventional consumer electronics. To this end, the BP software has been architected to ensure cross-platform functionality and scalability to a variety of platforms. In this fashion, the same BP algorithm code can be embedded within micro-controllers, mobile phones, servers, and a variety of other “targets”.

Valencell’s data qualifier has also been ported to target code. It is expected that the recommending interface will consist of a reported accuracy estimate given the input data, as explained in Valencell’s US patent# 10,441,224 [30]. If the reported accuracy is not within a target accuracy (ISO-8, ISO-10 or customer), then host software may then choose not to output a measurement. Alternatively, the host may choose to output the estimated BP along with a metric statistic showing the probability distribution surrounding the estimated BP value. Thus, the end user not only gets the best estimate for BP but also an indication (via the metric statistic) of where the actual BP value may be within a statistical spread.

The firmware resource requirements for the EPBP solution are suitable for an embedded solution using common commercially available consumer-grade microprocessors, including the microprocessors currently used in Valencell’s existing reference designs for the BW and BE product line. A summary of resource requirements will be provided to partners interested in integrating Valencell’s BP monitoring technology into their products.

5) RESULTS

Fig. 5.1 presents the comparative plots of all EPBP estimates (using the BE1.2 sensor) and all auto-cuff measurements versus the manual auscultatory reference, for all measurements in the qualified test dataset (summarized in **Table 2.3.1**). After applying the formulas outlined in Section 5.2.4.1.2 of the ISO 81060-2:1998 protocol to the BP estimations of **Fig. 5.1**, the resulting accuracy statistics (mean ± STDEV) are summarized in **Table 5.1**. It is clear from both the figure and the corresponding table that the accuracy of the PPG earpiece sensor is essentially identical to that of the automated cuff. Of further note, the accuracy statistics (mean ± SDTEV) of the EPBP model are within the 5 ± 8mmHg requirement outlined in the ISO protocol, for both systolic and diastolic estimates.

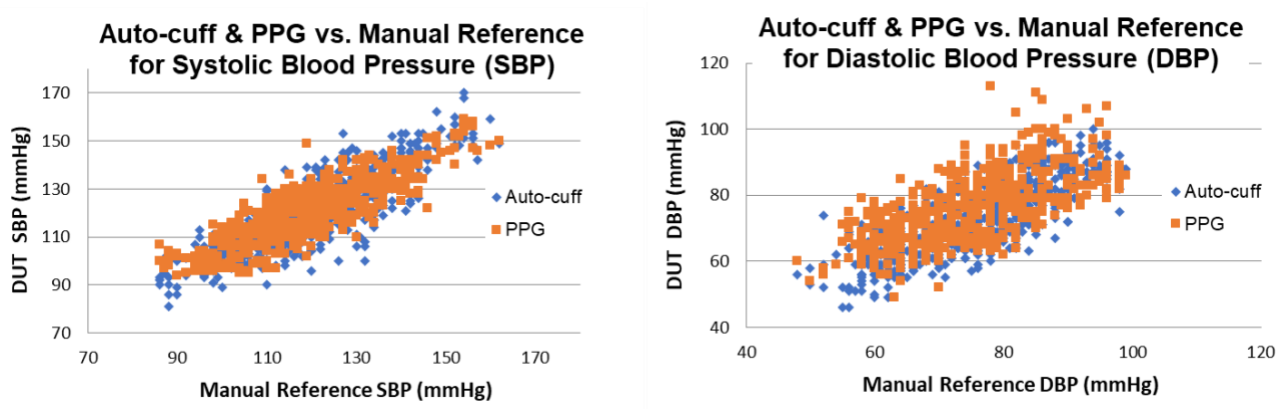

***Figure 5.1*: EPBP (ear-PPG) estimates and auto-cuff BP estimates vs. the manual reference measurements for each of the 654 measurements summarized Table 2.3.1.**

Table 5.1 – EPBP Model Accuracy Results for Qualified Test Dataset

	BE1.2/BE5.0		**Automatic Cuff**	
	Mean Diff. (mmHg)	*St. Dev. (mmHg)*	*Mean Diff. (mmHg)*	*St. Dev. (mmHg)*
SBP – 8 mmHg cutoff	1.7	7.7	0.9	8.0
DBP – 8 mmHg cutoff	-1.1	8.0	-2.3	6.8

It should be noted that the accuracy statistics (mean ± SDTEV) for the BE1.2 and BE5.0 sensor were found to be essentially identical (within less than ±0.1 mmHg of each other). Namely, the same EPBP model as applied to both sensors generated the same results. Considering that the BP model was trained on BE1.2 data, these results suggest that the EPBP model is robust enough to translate between completely different types of silicon (see **Section 7: Appendix A**).

6) DISCUSSION

The ultimate purpose of this R&D program was to develop and validate the world's first cuff-less, calibration-free, all-PPG solution for accurately assessing BP in a general population. To this end, the two key goals were to demonstrate a commercially viable cuff-less, calibration-free, all-PPG BP monitoring solution that could ultimately:

1) Provide demonstrable public health value
2) Provide cuff-like accuracy in a general population

Both objectives were achieved for the qualified test dataset, as summarized in **Table 6.1**. Of particular note, the 3rd row, which presents the results of a hypothetical hypertension classifier, is particularly useful for public health purposes. This hypertension classifier simply implements the systolic BP (SBP) threshold recommended by American College of Cardiology, where hypertension is determined to exist for SBP ≥ 130 mmHg [8]. The classifier results were generated by processing the BE1.2 PPG-derived systolic BP data of **Table 2.3.1** using the formalism presented in **Table 6.2**. The resulting classification accuracy is significantly higher than can currently be attained by estimating hypertension status from heart rate and step rate alone [32]. Moreover, hypertension status may be generated from a single measurement, rather than via processing a period of long-term subject data collection, as reported by other researchers [32]. Moreover, as shown in **Table. 6.1**, the EPBP model and auto-cuff share essentially the same accuracy in categorizing hypertension.

Table 6.1: Achievement of Performance on Goals

<table>
<tr><th>Goal</th><th>Auto Cuff</th><th>EPBP (Valencell)</th><th>Notes</th></tr>
<tr><td>80-85% of datapoints within ± 10 mmHg</td><td>Yes</td><td>Yes</td><td>Ideally both devices would hit 85% [31]</td></tr>
<tr><td>Mean ± STDEV (5 ± 8 mmHg)</td><td>Yes</td><td>Yes</td><td>Roughly 60% of PPG datasets were qualified for EPBP measurements</td></tr>
<tr><td>Ability to predict hypertension in a general population</td><td>Yes</td><td>Yes</td><td>
<table>
<tr><th></th><th>PPG</th><th>Auto-cuff</th></tr>
<tr><td>Accuracy</td><td>89%</td><td>88%</td></tr>
<tr><td>Precision</td><td>73%</td><td>69%</td></tr>
<tr><td>Sensitivity</td><td>77%</td><td>75%</td></tr>
<tr><td>Specificity</td><td>93%</td><td>92%</td></tr>
</table>
</td></tr>
</table>

Table 6.2: Hypertension Identification via EPBP Model Applied to BE1.2 Dataset Summarized in Table 5.3

TP = 102, TN = 483, FN = 31, FP = 38
Accuracy = (TP + TN) / (TP + TN + FP + FN) = 89%
Precision = TP / (TP + FP) = 73%

Sensitivity = TP / (TP + FN) = 77%
Specificity = TN / (TN + FP) = 93%

The statement that the EPBP model enables “cuff-like performance” is further supported by a comparative error analysis with the manual BP reference. **Figure 6.1** presents the PPG error overlaid against the auto cuff error versus the manual reference readings (for both SBP and DBP). Note that the patterns and trends are nearly identical. Thus, not only does the EPBP model track BP similarly to the auto cuff (see **Fig. 5.1**), but the respective error trends are also quite similar.

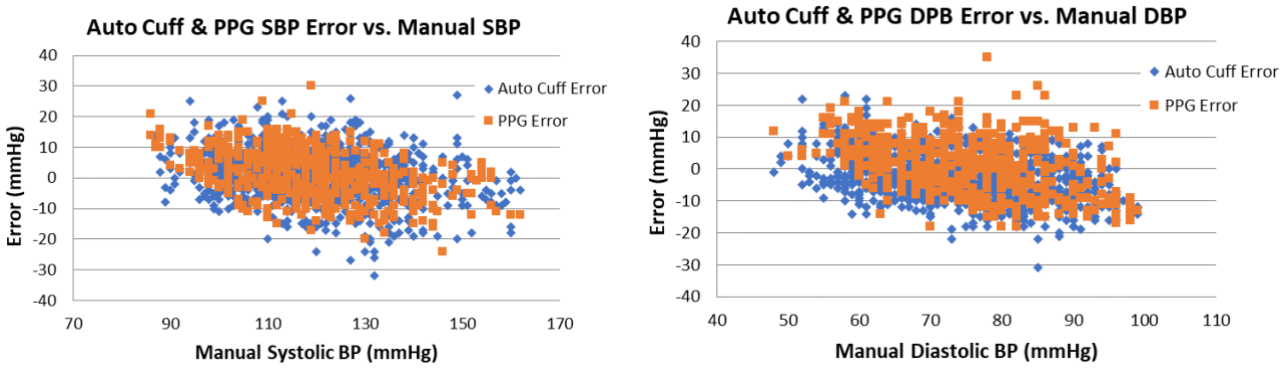

***Figure 6.1*: A comparative error analysis for the auto-cuff and EPBP (ear PPG-BP) model versus the manual reference; the trend in errors is nearly identical between the auto-cuff and ear PPG measurements.**

7) APPENDIX

Appendix A – Training Pool Methods

Data collection for the training pool (the training dataset used to train the EPBP machine learning model) took place at four locations around the world: two malls in the United States and two Sonion offices in Vietnam the Philippines. The two malls included Crabtree Valley Mall in Raleigh, NC and The Streets at Southpoint mall in Durham, NC. At the two Sonion offices, employees were recruited to participate with the goal of measuring at least 100 people five different times across several weeks.

After receiving an explanation of the testing procedures, interested volunteers gave verbal consent to participate. They were asked to provide an email address in order to receive compensation for participating, and they also had the option to provide a phone number or remain anonymous if desired. They were then asked date of birth, age, gender, height and weight, smoking status and whether they are on blood pressure medication. A scale and stadiometer were available and recommended, if the participant was willing. Otherwise, reported measures were accepted.

Blood pressure was then assessed by the manual cuff, an automatic cuff, and the Valencell sensors. The two sensors used were the BE1.2 and the finger sensor on the Samsung S8. Results were recorded in a hand-written log book as well as entered into a mobile application on the S8 where the data was synced with the database.

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