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# Intrusive and Non-Intrusive Techniques for Blood Sugar Measurement: A Practical Review

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***Abstract* – Measurement of sugar levels in blood is the main means of diagnosing for diabetes and other complications of blood sugar levels. The established principle of the methodology for this is the extraction of blood from the subject and submission of the blood sample to chemical tests that determine the presence of substances, such as glucose, that indicate blood sugar levels. This principle is inherently intrusive; R&D into methods with this principle has the goal of improving convenience and minimizing amount of sampling needed, while maintaining reliable accuracy. There is also R&D into developing non-intrusive methods that estimate blood sugar levels without blood sampling, with the aim of producing results that can be comparable with intrusive methods. The common goal of either approach is making blood sugar measurement more convenient for as many people as possible. At this time of writing, non-intrusive methods have yet to replace the gold standard. A breakthrough in this matter can facilitate the implementation of machine learning in interpreting blood sugar levels.**

***Keywords*— *Diabetes Diagnosis, Blood Sugar Level, Blood Sugar Measurement, Intrusive Method, Non-Intrusive Method.***

## I. Introduction

*Diabetes melitus*, otherwise known as “diabetes”, is a common disease with harmful consequences, including in Malaysia [1]. Therefore, there is significant effort invested into the detection and diagnosis of diabetes; this continues to the present-day [2].

Among medical professionals, the established diagnosis for diabetes is levels of blood sugar that are persistently elevated above what is normal for the patient [3]. Various factors have been considered to avoid diagnosing other complications to be diabetes, if these complications are also related to blood sugar [3]. Nevertheless, the diagnostic processes, whether they lead to confirmation of diabetes or not, still involve the measurement of blood sugar levels.

Thus, there is research and development (R&D) into methods for the measurement of blood sugar levels. This article is about the review of these methods in the present era.

## II. Methodology of Review

### *A. Background Research*

The topical matter involves a known disease, i.e., diabetes. Thus, the review begins with a brief background study of the pervasiveness of diabetes and its consequences to health, followed by a brief mention of the need for quick and convenient detection and diagnosis of diabetes. The comorbidities and complications of diabetes are mentioned when describing the detection and diagnosis of diabetes via the presence and confirmation of these. There is also the mention of the need to set what are “normal” blood sugar levels before making measurements.

For consistent use of terminology, the word “intrusive” will be used throughout this text to refer to any intrusive or invasive methods, unless there is nomenclature that is specifically attributed to the

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publications of others. The list of references is an exception.

### *B. Curating, Citing References and Data Comparison*

The topical matter of this article is the measurement of blood sugar and its practicalities. Therefore, other matters such as the harm of diabetes and pervasiveness of diabetes are briefly mentioned, followed by citations of relevant references, e.g., journal articles authored by people that have studied such matters in depth.

There are more references on the technical factors and specifics of measuring blood sugar. These include citations of procedures for both intrusive and non-intrusive methods; the sequence of the citations follows the pacing of the explanation of these procedures. Incidentally, these references also have empirical data for use in the sections about comparisons.

More recent references are favoured over the older ones, unless the latter can provide a prefacing statement for a dissertation.

### *C. Explanation of Procedures*

The bases and/or principles of the procedures to measure blood sugar are mentioned first, followed by mentions of their complications and setbacks. Where relevant, the attempts to solve or otherwise address these are mentioned too. These explanations are split into sections in this article, where there are overarching principles that are followed by different methods.

### *D. Accuracy Comparisons*

The scope of this article does not include in-depth examination of the definitions of accuracy. Instead, the mentions of accuracy will depend on citations of the principles that original authors have used for their own work. This article is also not an in-depth study of the merits of the principles of accuracy that are used; such a study is best reserved for another article that is specifically about this instead, e.g., the merits of the empirical quantities that are used as measurements of accuracy.

Comparisons between intrusive and non-intrusive methods are made according to each category of methods for coherent pace and layout of writing. The factors of comparisons, such as 95% confidence interval, are used for both sets of comparisons, so that there is still empirical parity to compare intrusive methods to non-intrusive ones.

Another reason for the separate comparisons for intrusive methods and non-intrusive methods is that the different categories of methods have significantly different techniques and procedures such that there are few common denominators for parity analyses. For example, the non-intrusive methods do not draw blood for chemical tests [4].

The section about accuracy comparisons begins with intrusive methods first, before transitioning to non-intrusive methods. The accuracy measurements that are cited are the most generally cited in studies about reliability of measurements, e.g. 95% confidence interval for blood sugar measurements such as in the work of Raoufi et al. [5]. Other types of measurements such as the levels of markers are not included in the accuracy comparisons because these are associated with the comorbidities of blood sugar complication and thus would diverge from the focus on blood sugar measurements [6].

For the literature research on non-intrusive methods, there were few if any studies that involve people with low blood sugar complications; most studies on these methods involve diabetic and hyperglycemic people.

### *E. Practicality Comparisons*

There is a section on the feasibility of the methods for wide-spread use. The scope of feasibility includes cost citations and time for or frequency of delivery of results.

### *F. Review of AI Analytics*

Blood sugar measurements involve accumulation of empiric data, so there is potential for interpretations through machine learning and predictions by artificial intelligence (A.I.). There is description of the basis for such A.I. work, followed by commentary on their complications.

## III. Principle of Blood Sugar Levels

Persistently high blood sugar levels beyond normal are the main criterion for diagnosis of diabetes. There are also health complications that are characterized by blood sugar levels below normal, such as hypoglycemia. Therefore, the normal level of blood sugar must be determined before the diagnoses for these complications. The following dissertations expand further on this statement.

### *A. Range of Normal Blood Sugar Levels*

In medical studies, normal blood sugar levels are generally represented as a range [7]. The definitions of this range can differ from one medical community to another, and can also change over the years, to reflect discoveries in studies about diabetes [7]. This is because the factors that affect blood sugar levels are significantly dependent on the choices and circumstances of the individuals whose levels are being measured [8]. This implies that the diagnosis of diabetes is dependent on the opinion of the medical examiner(s), instead of any supposedly established range that can be read from any source of information about diabetes [9].

### *B. Individual Circumstances*

As mentioned already, the circumstances of individual persons are significant factors in diagnosing diabetes. For example, there is the metabolism of a person, such as the secretion of glucagon-like peptide-1 that is thought to affect the reliability of diabetes diagnoses that rely on fasting [10]. The individual may also have other health complications, such as heart conditions, which may affect blood sugar levels [11].

Thus, medical examiners who are diagnosing diabetes must determine if an individual's circumstances can affect the results of the tests [10]. They must adjust the definition of a normal blood sugar level according to the lifestyles of the subjects and any medical issues that they have [12].

### C. Comorbidities

Among the circumstances that can affect blood sugar levels, comorbidities are notably significant. Comorbidities, especially those that need treatment with drugs and enzymes, can cause variations in blood sugar levels, which in turn can lead to higher risk of diabetes [11]. Medical examiners must adjust what is considered “normal” blood sugar level for persons that have comorbidities to account for the effects of the treatments [12].

### D. Other Symptoms

Physiological and psychological responses to changing blood sugar levels can differ from person to person [13]. Depending on the severity of their symptoms, the blood sugar levels at which these symptoms emerge would be the basis for deciding which levels are normal and which are not [13]. Such data would also not be readily available to medical examiners who do not have the means to monitor their patients around the clock, so diabetes diagnoses must include questionnaires about their patients’ lives [14].

The main takeaway of utilizing blood sugar level as a factor of diagnosis is that medical examiners must consider other related factors, such as those described in this section, before deciding what is the normal blood sugar level for the person that is being examined. Measurements that are reliable for diagnosis can only be had after these have been determined.

## IV. Blood Sugar Level Measurement Methodologies

Established methods to measure blood sugar levels must involve extraction of blood samples. Therefore, such methodologies are inherently intrusive and will pose issues such as risks of infection from the infliction of any wound. However, there are attempts to develop non-intrusive means [15]. The following dissertations describe these two approaches further.

### A. Bodily Fluid Extraction and Sampling

Intrusive methods involve extracting bodily fluids or tissues from people suspected of diabetes and subjecting these samples to tests and examinations [16].

The current gold standard for intrusive methods is the extraction of a droplet of blood, followed by submission of the droplet to an electrochemistry test; this method is considered the least intrusive and the quickest [12][15]. However, certain procedures in this method, especially the infliction of the wound that is necessary to draw blood, are still not comfortable to every individual [18]. Figure 1 is an illustration of the gold standard, specifically the extraction of a blood droplet from a fingertip [19].

Alternatives to the gold standard will be described later in Section V.

### B. Non-intrusive Measurements

The discomfort from and concerns about extracting fluid or tissue examples are the main reason for developing non-intrusive methods of measuring blood sugar levels [15]; these discomforts and concerns will be explained further in Section V. That said, non-intrusive methods must produce outcomes that are comparable and commensurate with the results of testing fluid or tissue samples, to be considered reliable [20].

These methods rely on the effects of changes in blood sugar levels on other aspects of a person’s physiology. Figure 2 shows an example of a non-intrusive measurement; notice that blood is not extracted [19].

Figure 2 illustrates the utilization of pulse rates. Non-normal blood sugar levels are thought to alter pulse rates, so pulse measurements could be used as supplementary data for diabetes monitoring [21]. These relations between blood sugar levels and other aspects of physiology will be described further later in Section VII.

The main obstacle in non-intrusive methods is the correlation between the estimates of blood sugar levels from these methods and the levels as measured through intrusive methods [20]. This obstacle will be elaborated further later when specific methods are described in Section VII.

## V. Intrusive Methods

The main procedure of every intrusive method of blood sugar measurement is the extraction of bodily fluids for sampling [16]. In the case of in-depth pathological tests, tissues may be extracted too [16]. These samples contain substances that are associated with blood sugar levels.

### A. Extraction of Bodily Samples, in General

Intrusive methods require the extraction of bodily samples. The first historically noted symptom of diabetes is abnormal sugar content in urine, so the first bodily sample to be considered was urine [22]. Due to concerns of hygiene and reliability, this was eventually replaced with the testing of blood samples [22]. Other bodily samples will be described in Section VI.

### B. Chemistry Tests on Bodily Samples, in General

Abnormal blood sugar levels change the composition of bodily samples that are affected by, dependent on, or otherwise associated with blood sugar [9]. Intrusive tests check for components of blood that have glucose, residues of glucose metabolization, e.g. enzymes, or substances that otherwise are associated with management of blood sugar [10].

In the case of tests on blood samples, the amount of blood glucose and its residues in the sample is the main indicator that is used; the median amount for healthy individuals is established first, before being compared with the amount from the results of testing [12]. Deviations would suggest the presence of diabetes, but further observations such as investigation of risk factors are necessary before any diagnosis can be confirmed [23].

The chemical tests for alternative samples will be described in Section VI.

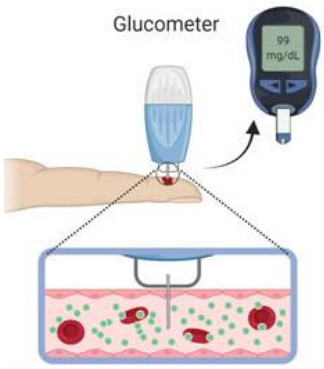


**FIGURE 1. Example application of the gold standard for blood sugar level measurement, via a device known as "glucometer"; this method involves pricking fingertips with a lancet [19].**

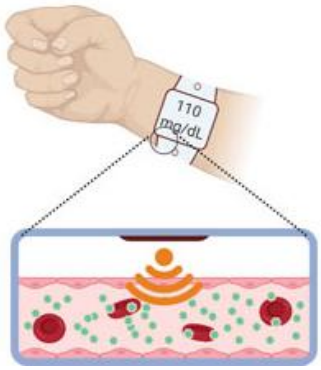


**FIGURE 2. Example of a non-intrusive method of estimating blood sugar levels; in this case, a photoplethysmography (PPG) device is used to estimate blood sugar levels from the volumetric properties of blood underneath the skin [19].**

### *C. Capillary Blood Sampling, a.k.a. Self-Monitoring of Blood Glucose*

The current gold standard of blood sugar level measurement is the technique that is labelled "self-monitoring of blood glucose", or "SMBG", in medical communities that are dedicated to the study of blood sugar complications [4].

SMBG requires the user to prepare one's fingertip for the procedure, usually by applying pressure on the fingertip to temporarily increase blood flow and sterilizing the fingertip with disinfectant [24]. This is followed by the shallow puncturing, or "pricking", of one's finger with a device called a "lancet"; this wound should pierce blood capillaries beneath the fingertip [24]. A globule of blood is then eased out of the wound to form a drop of blood; this is also used for other blood sampling procedures that require capillary blood [25]. This drop of blood is then collected and subjected to the electrochemistry test that checks blood sugar; this test will be described further later in the subsection for tests on blood.

The main setback of SMBG is the collection of the blood drop. Although this has been described as "minimally invasive" due to only the person's extremities being wounded, the procedure is still not comfortable to everyone [24]; incidentally, this complaint also extends to other tests involving the extraction of capillary blood [25]. R&D into SMBG involves efforts such as reducing the discomfort of finger-pricking [18], but this does not address the requirement of having to draw blood from a wound.

Still, SMBG will continue to see use, because this procedure has been developed into the use of convenient and commercially viable self-testing kits, as its name suggests [26].

### *D. Venous Blood Monitoring, a.k.a. Continuous Monitoring of Blood Glucose*

Venous blood monitoring is a real-time monitoring blood sugar levels; this method is also called "Continuous Glucose Monitoring" (CGM) [27]. CGM requires the insertion of intravenous devices, thus limiting this method to scenarios of hospitalization or ward stays [28]. There are devices that are more portable, but they are bulky due to the use of mounts or harnesses on the patient's body, and they require regular maintenance, e.g., removing accumulated blood samples [29].

CGM devices extract venous blood into components that check for blood sugar levels, like capillary blood sampling [27]. However, CGM necessarily samples blood more frequently than SMBG, and the blood samples are not returned to the patient for hygienic reasons; thus, there is the concern of blood loss over time [28].

The main reason for using CGM over SMBG is real-time data, e.g., the fluctuations of blood sugar levels in the patient after ingestion of food or water. This data ostensibly provides more accuracy in identifying the details of a patient's complications [29].

### *E. Testing of Blood Sample*

Intrusive methods that involve sampling of blood require chemical testing of the blood sample. The tests must include measurements of glucose levels in the blood sample [12]. The threshold for what is considered normal levels must also be determined, depending on the patients' circumstances [12] [13].

The main complexity of testing blood samples is the method that is used to determine the blood sugar levels [29]. The current gold standard uses sampling of capillary blood, which has response times in terms of a few seconds [29]. However, this method does not account for every possible component of blood; there are multiple components of blood that can be affected by diabetes or other blood sugar complications [12]. These components must be tested in laboratory conditions, which in turn means longer times for delivery of test results [12].

The current trend of R&D in testing blood samples focuses on decreasing response time and reducing the needed amount of blood or other bodily fluids [30] [31].

## VI. Upcoming Intrusive Methods

The following passages are for innovations and R&D efforts into alternatives for measuring blood sugar through intrusive methods. The goals of these efforts are generally the improvement of the reliability of measurements or the minimization of complications.

**TABLE 1. Example of chemical markers that are associated with blood sugar levels.**

| Established sourcing from these samples: | Chemical Markers | | | |
|---|---|---|---|---|
| | Blood Glucose | Insulin | Lactate | Pancreatic Enzymes |
| ***Capillary Blood*** | ✓ [12] | ✓ [12] | | |
| ***Venous Blood*** | ✓ [12] | ✓ [12] | ✓ [32] | ✓ [12] |

Thresholds for these markers for the diagnosis of diabetes and blood sugar complications can differ from individual to individual, depending on their circumstances [10][11][12].

### *A. Additional Chemical Tests*

Established chemical tests mainly use blood samples because this has significant presence of sugar and sugar residues [31].

Additionally, lactates, lactic acids and related substances are formed from the metabolization of glucose sources and the products of the metabolization, so they could be used as chemical markers if they are available in the blood sample [32].

The chemical markers that are used for these tests are shown in Table 1; urine, sweat and saliva are omitted from Table 1 due to current experimental issues of reliability in correlation with results from other sample types.

However, comorbidities, other health complications and other somatic factors, e.g. the physiological conditions of individual patients, could alter the levels of these markers, including the additional ones [32][33]. Thus, there are still concerns about the technical and procedural reliability of the methodologies that are being developed with additional markers [32][33].

Due to their importance in the metabolization of sugars, pancreatic enzymes are also markers for diabetes and blood sugar complications. However, due to their involvement in the metabolization of substances other than sugars, these are complementary information for investigation into comorbidities of diabetes [34].

### *B. Spectroscopy of Blood Samples*

All blood sugar estimations that utilize chemical or electrochemical tests do not return the bodily samples to the subject, for reasons of hygiene and safety; this loss of blood is a significant setback to any such method [28]. Spectroscopy is a method with the potential to return blood to the patient [35].

Dialysis machines have space for the inclusion of machinery for dialysis treatment; more space can be allocated for the incorporation of spectroscopy equipment [35]. Spectroscopy has been used in dialysis to estimate blood volume and ease of flow, generally by examining the composition of blood and its flow rate [36]. Thus, there is the opportunity to detect and measure blood sugar in blood that is flowing through dialysis machines [35].

Spectroscopy is also considered in non-intrusive methods. This version will be described later in Section VII because it has different workings.

## VII. NON-INTRUSIVE METHODS

The principle of non-intrusive methods is that they do not require samples of bodily fluids to be extracted from the subject. However, the main concern of these methods is their reliability when compared to intrusive methods, such as the gold standard of SMBG; they also happen to be still in R&D at this time of writing.

### *A. Examination of Subdermal Blood Vessels*

Established methods estimate blood sugar levels from data that is obtained from examination of blood or somatic factors that are associated with blood [20]. This poses a significant obstacle for non-intrusive methods, which must not extract blood for sampling [20]. Therefore, these methods must examine body regions with significant density of blood vessels so that close examination of blood or blood-related somatic factors is feasible; the subdermal, i.e., beneath the surface of skin, is such a region [20]. Examples of this type of region include fingertips and soles of feet [37].

### *B. Subdermal Photoplethysmography*

Photoplethysmography (PPG) is a method that illuminates and examines blood vessels below the surface of the skin [37]. (This should not be confused with “postprandial glucose”, which is a metric for blood sugar levels that also uses the same acronym.) The working hypothesis of using PPG for estimating blood sugar levels is that changes in blood sugar levels will also change the visual properties of blood vessels, e.g. changing their opacity and reflectivity [37].

However, this method is still being developed, due to lack of a solution for the main obstacle of isolating the effects of blood sugar levels on the visual properties of blood vessels from the effects of other factors, such as proximity to other tissues. For example, PPG checks on the blood vessels of the ear lobe could reach accuracies of up to 90% on the Clarke error grid, enough to avoid clinical misdiagnosis but not enough for confidently reliable confirmation of blood sugar complications [38].

### *C. Subdermal Spectroscopy*

Spectroscopy has been described earlier as a method to examine extracted blood without preventing it from being returned to the body. Figure 3 shows an example.

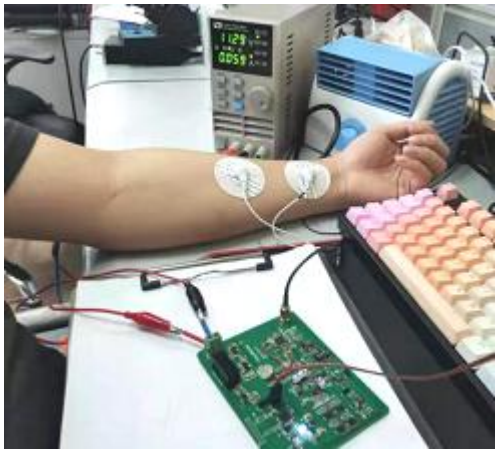

**FIGURE 3. Image of the experimental equipment that has been developed by Gong et al. for utilizing spectroscopy in non-intrusive blood sugar estimation [39].**

Spectroscopy can also examine subdermal blood vessels where the sensing probes can detect them, like near-infrared [39] and infrared sensors [40]. The working hypothesis for this is that changes in blood sugar levels would change the impedance of blood to the electromagnetic sensing that is used in spectroscopy, e.g., altering the frequencies of emissions from blood vessels [39].

However, like PPG, isolating the effects of blood sugar levels from the effects of other factors on the results is an obstacle; in the case of the work of Gong et al., the correlation value between the results of their methodology and those of chemical tests on extracted blood can reach above 0.85, which is potentially feasible but not enough for reliable confirmation [39].

## VIII. Upcoming Non-Intrusive Methods

The following passages are for innovations and R&D efforts into alternatives for measuring blood sugar through non-intrusive methods. Incidentally, such methods avoid interaction with blood vessels, with the intention of avoiding the discomfort that arises from this.

### *A. Estimation from Voice Quality*

Changes in blood sugar levels can lead to observable consequences, such as numbness and weakness of limbs; these consequences are categorized as diabetic peripheral neuropathy [41]. Therefore, there is the hypothesis that blood sugar levels could be estimated by quantifying and measuring these observations and correlating them to blood sugar levels.

Changes in one's voice have been proposed as one of the means from estimating blood sugar levels from peripheral factors [42]. One of the hypotheses for this is that changes in blood sugar levels can alter the vocal emanations of the larynx by changing its suppleness [42]. Another hypothesis is that significantly abnormal blood sugar levels can cause changes in speech, e.g. greater urgency or anxiety in one's voice when affected by hyperglycemia [42].

However, like PPG and spectroscopy, isolating the effects of blood sugar levels from those of other factors on voice qualities is an obstacle; Kaufman et al. discovered that high intraclass correlation due to individual personalities meant that any results of testing and calibration may be applicable only to individuals who have been tested [43].

### *B. Estimation from Electrocardiography*

Another peripheral neuropathic factor is the effect of changes in blood sugar levels on physiological signals. Electrocardiography (ECG), having been used for neuropathic tests in studies about other health complications like heart diseases, is a potential method for studying this factor [44]. ECG also offers the convenience of portable wrist-worn devices [44].

However, like the other non-intrusive methods, ECG has results that can be affected by factors that are not related to blood sugar levels; for example, height and age can introduce bias [44]. Tas et al. highlighted this issue in their study about using ECG, which involved non-diabetic people [45].

## IX. Accuracy Comparisons

As mentioned in Section II, this article is not an in-depth study of the merits of the principles of accuracy that are used in estimating blood sugar levels. However, there will be commentary about the overarching issues of accuracy.

The 95% confidence interval methodology involves the repeatability and consistency of measurements within a range. This is the statistical measurement that is used for the accuracy comparisons in this section. Furthermore, the lowest densities of blood sugar in samples that can be reliably and repeatably measurable is used for the comparisons; smaller is better, in theory, due to the need for sensitivity to small changes [46]. This measurement is also the only common denominator in the types of statistics that are used to demonstrate sensitivity in both studies of intrusive and non-intrusive methods [46] [47].

The factor of confidence interval is closely associated with the factor of the frequency of measurement. To briefly describe this association, the measurements must have regular timing so that there is consistency for reliable confirmation of confidence levels. For this factor, lower frequency is theoretically better because less sampling is needed, especially for intrusive methods [12]. Non-intrusive methods would not be subjected to this factor, but due to the need for reliability testing that in turn requires the results of intrusive methods, they occur at the same frequency as intrusive methods during their R&D [46] [47].

### *A. Brief Comparisons of Accuracies of Intrusive Methods*

Table 2 shows the comparison of the accuracy of intrusive methods. Lab tests are the first column in this table; these tests directly measure the presence of sugar in blood samples; the cited numbers are from A1C blood plasma tests, which are the most common lab tests for blood sugar [48]. The numbers given are recommended by the authors in the cited articles. However, the circumstances of different individual persons may result in different amounts; Eichenlaub et al. suggested a median amount for CGM in their study, but they have implied that there can be variations between healthy individuals [49].

### *B. Caveat for Intrusive Methods Due to Individual Circumstances*

Despite the mentions of the factors for comparisons, such comparisons could not account for the different circumstances between these methods. For example, lab testing is performed on extracted blood samples, i.e., any results from such testing cannot be considered real-time data on the blood sugar levels of the subjects [50]. This means that lab testing will not be suitable for patients who have blood sugar complications involving rapid fluctuations [50].

Collation of data on blood sugar measurements depends on samples taken from individuals, who may have different circumstances that affect blood sugar levels. Statistical comparisons may already be biased by factors within the sample population, e.g. their lifestyles and cultural diets that can affect blood sugar levels [12].

**TABLE 2. Summarized comparison of accuracy factors between intrusive methodologies.**

| Factors | Intrusive methodologies: | | |
|---|---|---|---|
| | ***Lab Tests*** | ***CGM*** | ***SMBG*** |
| **95% Confidence Interval** | 1.2 mmol/L [46] | 2.22 mmol/L [49] | 3.3 mmol/L [52] |
| **Measurement Frequency** | 4 times per day [12] | 3 times per day [51] | 2 times per day [52] |

Readings of mmol/L are for lowest blood sugar levels that can be consistently and reliably measured.

**TABLE 3. Summarized comparison of accuracy factors between non-intrusive methodologies.**

| Factors | Non-intrusive methodologies: | | |
|---|---|---|---|
| | ***PPG*** | ***Spectroscopy*** | ***ECG*** |
| **95% Confidence Interval** | 3.9 mmol/L [55] | 5.8 mmol/l [56] | 2.3 mmol/l [57] |
| **Root mean-square error** | 1.129 mmol/L [58] | 0.29 mmol/L [56] | 1.49 mmol/l [59] |

Readings of mmol/L for 95% confidence internal are for lowest blood sugar levels that can be consistently and reliably measured; the works cited for spectroscopy do not have data that include people with low blood sugar complications [56].

Therefore, any medical consultation about blood sugar complications should be made against any statistical data that is localized [12]. Moreover, the data for these comparisons comes from people who have subjected themselves to fasting, among other practices to regulate their blood sugar levels before extraction of blood [51].

The lowest reliably measurable levels of blood sugar, such as those in Table 2, are obtained from individuals with low blood sugar complications [52] [53]. Therefore, there will be a limited availability of data for statistical comparisons that utilize ranges of blood sugar levels; this problem is further compounded upon by privacy concerns [54].

### *C. Brief Comparisons of Accuracies of Non-Intrusive Methods*

Table 3 shows an accuracy comparison of non-intrusive methods of blood sugar measurement; as a reminder, these do not involve extraction of blood and chemical tests. The reliability tests of these methods compare the measurement results against those of established intrusive methods, i.e., individual people are subjected to both methods so that there is data for the comparison [47]. Therefore, their measurement results are in the form of blood sugar levels, e.g., units of mmol/l, though the measurements are derived from electrical signals [55].

In the case of entries for spectroscopy in Table 3, the works cited used data from individuals that are diabetic or hyperglycemic [56]; they did not have sensing data from people with low blood sugar complications at this time of writing. This gap in data might be addressed in future studies when non-intrusive methodologies are further developed and tested.

However, authors like Shi et al. and Li et al. also include dissertations on the potential of these methods, e.g., tracking real-time changes in blood sugar levels [55] [56]. Therefore, Table 3 also includes a row for root mean square error (RMSE), which is a metric that is significant to real-time sensing [58].

### *D. Caveats for Non-Intrusive Methods*

Despite the mentions of the factors for comparisons, such comparisons could not account for the significant differences between the techniques and logistics that are needed for intrusive methods and those for non-intrusive methods.

For example, the factor of measurement frequency is shown in Table 2 but not in Table 3. In practice, the frequency at which non-intrusive methods are used is not a major concern because there is no need to draw blood [56]. Furthermore, due to inherent advantages such as not needing blood samples, they are not affected by the accuracies of chemical tests, which further complicate any parity analysis between intrusive and non-intrusive methods.

Yet, non-intrusive methods are still being developed and compared against intrusive ones for calibration and reliability tests; thus, their frequency of testing must match those of intrusive methods during their R&D [47] [56] [60].

## X. PRACTICALITY COMPARISONS

Matters of cost, time per test and frequency of testing can determine the practicality of a method and how it can remain or become the next gold standard. (For this section, a “test” is defined as the yielding of an individual number for blood sugar level estimation.)

The following subsections provide statistical comparisons with parity, in terms of cost per test, and time per test. There can be other factors, but these depend on the specific health complications of individual persons [47].

### *A. Brief Cost Comparisons*

Table 4 shows a brief cost comparison between intrusive methods, whereas Table 5 shows that for non-intrusive ones. This separation is due to lack of parity in the practical circumstances of the methods, such as their logistics.

**TABLE 4. Summarized comparison of cost and time factors between intrusive methodologies.**

| Methodology | Factors | |
|---|---|---|
| | **Cost per test, USD** | **Time per test** |
| ***Lab Tests*** | 6.48 [61] | 6 minutes [61] |
| ***CGM*** | 397.517 [62] | 5 minutes [64] |
| ***SMBG*** | 0.50 [63] | 15 minutes [64] |

Lab tests involve batch testing; the time and cost for batch testing have been divided by the number of samples taken to provide the numbers for lab tests in this table.

**TABLE 5. Summarized comparison of cost and time factors between non-intrusive methodologies.**

| Methodology | Factors | |
|---|---|---|
| | **Cost per device, USD** | **Sampling Frequency, Hz** |
| ***PPG*** | N/A [65] | 100 [37] |
| ***Spectroscopy*** | 25 [66] | 50 [40] |
| ***ECG*** | N/A [59] | 1000 [44] |

For example, the need for blood samples for chemical testing means that intrusive methods would incur the cost of managing organic samples and the associated risks of health and safety. Therefore, non-intrusive methods already have an inherent advantage from this viewpoint. Furthermore, due to their relative novelty, non-intrusive methods may pose concerns that are unique to themselves, such as the cost of the bindings needed to secure portable device [47]. In-depth analysis involving parity of comparison is beyond the scope of this review article.

Table 4 has an entry for the cost of each test with an intrusive method. This is because testing must be done on submitted samples, so there can be costs that can be associated with each turnover of results.

In the case of lab tests, the costs include the labor for the lab worker and the maintenance of lab equipment, among other things concerning facility operation [61]. In the case of CGM, the cost includes the cost of warding the subject for monitoring and the distributed cost of maintenance that is associated with each test, because the equipment for CGM is not portable and cannot be readily used on other persons due to reasons of hygiene [62]. These circumstances do not contribute to the parity of cost comparisons with intrusive methods that are more disposable.

In the case of SMBG, the cited numbers have taken into consideration the typical lifespan of the portable devices used in SMBG; the costs of consumables, such as glucose strips, are also included [63]. SMBG also benefited from R&D as consumer products, in contrast to the other intrusive methods that do not have circumstances that are conducive to such R&D; thus, SMBG has an advantage in cost comparisons and will likely continue to, despite R&D of the other intrusive methods [64].

Table 5 describes the typical cost of devices that are used for non-intrusive methods; the cost per test factor of Table 4 is not suitable for these, because the lifespans of the devices have not been exhaustively tested such that there are measurable lifespans to distribute costs across time of use [36] [37] [44].

There is no available and clear data on the cost of PPG devices that are designed for blood sugar measurement. This is despite studies of PPG for this purpose often citing their low cost compared to other methods [65].

The cost that is cited for spectroscopy is the typical cost for a device that utilizes near-infrared sensors, which are the least expensive category of sensors that can be used for spectroscopic sensing [66]. More complex devices such as higher-band infrared sensors, such as those for thermal imaging could be used, but at higher costs that would be impractical for commercial devices [66].

In the case of ECG, R&D of this method uses ECG equipment that is meant for cardiograms [59]; there are no available studies on portable ECG devices for blood sugar measurement at this time of writing. Thus, there is no sufficient data for parity comparisons of the costs for non-intrusive methods.

### *B. Brief Time Comparisons*

Like the cost factor of lab tests, the time factor for lab tests has been divided by the number of test samples in each batch [61]. The comparison of time per test is for statistical parity; the ease of convenience of getting results from lab tests is realistically different from that for portable methods.

The factor of time per test is inherent for CGM. To elaborate, CGM involves constant monitoring, so it yields a blood sugar estimate every 5 minutes [64]. This contrasts with SMBG, the frequency of which is voluntary, and the time taken also depends on the skill of the user. Therefore, the statistical parity of time per test does not consider emergent factors such as the habits of the patient.

In the case of SMBG, the cited time per test is inclusive of the time for preparatory measures prior to the extraction of blood; this is to account for psychosomatic and hygiene influences that might affect the results [65]. Without addressing this concern, the time for the extraction and testing of blood could vary significantly, depending on individual skill [66].

There is no suitable factor that has empirical parity between intrusive and non-intrusive methods in the matter of time for testing. One of the reasons for this is that non-intrusive methods hypothetically do not need time for turning over results; they can ostensibly make measurements in real-time [36] [37] [44].

The R&D of intrusive methods has measurements occurring alongside measurements with intrusive methods, e.g., CGM alongside PPG in the work of Zeynali et al. [37]. However, this is for estimating the reliability of the non-intrusive methods, and not for parity comparisons about the factor of time.

Therefore, Table 5 has entries for sampling frequencies instead of the time per test in Table 4. This factor also accounts for their ability to give estimates in real-time. The highest frequencies are cited, if ranges are mentioned in the cited sources, e.g., near-infrared sensors could sample up to 50 Hz for consistent readings [40].

In the case of ECG, the sampling frequency is much higher than the other non-intrusive methods. This happens to give ECG an advantage in AI-assisted R&D of prediction methods, which will be described next.

## XI. Data Analytics and A.I.

There is a trend of implementing data analytics and A.I. assistance in matters of health and medicine; the measurement of blood sugar has been subjected to this too [67] [68].

A.I. is also used in the real-time monitoring of blood sugar and the control of blood regulating machines [69]. (However, control of blood regulating machines is beyond the scope of this article, so this will not be described further.)

### *A. Risk Prediction*

The implementation of data analytics in blood sugar measurement is the prediction of a person's risk of having blood sugar complications [70] [71].

A person's own personal history of blood sugar measurements is the most appropriate data-set for such analytics [70]. The procedures will still need to be supervised by a medical professional as per medical practice on diagnosis of blood sugar complications, but data analytics is expected to save time on data interpretation [72].

Where personal data is not available, community-based data-sets could be used to train models for risk estimation, i.e., using big data to predict the potential occurrence of blood sugar complications in people who live within a region [73]. This is expected to be of more use to doctors who practice within a locale than for individual persons, especially in helping doctors to prepare for possible cases of blood sugar problems [73]. This is not so useful for predicting risks for an individual, because the individual could not be assumed to follow the same lifestyle as others [12].

### *B. Availability of Data for Interpretation*

As mentioned already, a person's own personal history of blood sugar measurements is the most appropriate data-set for training A.I. on assisting the confirmation of any blood sugar complications [70]. However, such training is only practical if there is substantial amount of data for A.I. to learn to interpret changes in blood sugar levels [71].

Incidentally, training A.I. for assistance in interpretation is more convenient for methods that can generate substantial amounts of data, such as the non-intrusive methods [71]. However, those methods must be confirmed as comparable with intrusive methods, which means that there must be a comparable amount of data from intrusive methods for the R&D of A.I. trained for this purpose [72].

## XII. Conclusion

Current R&D efforts generally do not seek to improve upon SMBG, which is the gold standard of blood sugar measurement. Instead, they focus on developing alternatives that work around the main issue of SMBG, which is finger-pricking for the extraction of blood [20].

In the case of intrusive methods, the alternatives for blood samples are other bodily samples. However, they are not complete substitutes for blood samples. Instead, they complement the diagnosis of diabetes by determining the presence of any comorbidities; on their own, factors that are not related to blood composition can affect the reliability of diagnoses [30].

Non-intrusive methods use present-day technology, which allows for examination of somatic factors that are close to the surface of the skin, e.g. subdermal blood vessels [20]. Development of these methods must include comparisons with the results of intrusive methods, e.g. SMBG, so that correlation studies are possible. This also means that established intrusive methods must be used at the same time as the non-intrusive methods that are being developed. There has yet to be a non-intrusive method that can become the next gold standard.

In summary, there are no comparable substitutes for the gold standard of SMBG, which remains the most economically and logistically practical method of measuring blood sugar levels [47]. Any alternatives are developed with the intention of addressing issues of discomfort and hygiene concerns of SMBG [47]. There are promising non-intrusive alternatives that can be quick and painless, but correlation between their results and actual blood sugar levels has yet to reach levels that are enough for reliable diagnoses [20]. Furthermore, a successful correlation may only be applicable to the persons that have participated in the R&D [45] [47].

There is a need for in-depth statistical studies of the methodologies for blood sugar measurement. Yet, this need is complicated by the fact that the data for these studies must be obtained from individual people. This means that there is a scarcity of data for certain comparisons, e.g., the lowest reliably measurable levels of blood sugar must come from data obtained from people with low blood sugar complications [52].

The drafting of this article prior to the final version had considered factors for objective comparisons between intrusive and non-intrusive methods. However, due to significant differences in their techniques and procedures, among other factors like logistics, parity comparisons between them are complicated by the lack of factors that are common to both categories of methods. Consequently, Tables 2, 3, 4 and 5 are brief and have factors that are associated with one category or the other.

Present-day R&D methods for blood sugar estimation emphasize ease of use and yielding of results as soon as possible. This means that the convenient ones, like SMBG, do not involve collecting and returning samples to facilities, such as for lab tests. Thus, practical differences between conveniently deployable methods and those that require facilities are not so readily apparent in brief parity comparisons such as those in Table 4.

Therefore, future review articles that focus on comparisons between methods must consider the holistic and emergent concerns about the parity of the factors that will be used for the comparisons. If this can be achieved, the implementation of machine learning and A.I. in blood sugar measurement and diagnosis of blood sugar complications can be reliably performed with the significant amount of data from non-intrusive methods that could be proven reliable.

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## ETHICS STATEMENTS

This work did not involve human subjects, animals or social media platforms.

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