Blood self-sampling devices: innovation, interpretation and implementation in total lab automation

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Review

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Abstract: The introduction of the vacuum tube in 1949 revolutionized blood collection, significantly improving sample quality and patient comfort. Over the past 75 years, laboratory diagnostics have evolved drastically, from manual to automated processes, reducing required test volumes by over 1,000 times. Despite these advancements, venous blood collection presents logistical challenges, including centralized scheduling and a large volume of biological waste due to the imbalance between the needed blood volume (often very little) and the collected volume (often in excess). The COVID-19 pandemic further emphasized the need for decentralized healthcare solutions and patient empowerment. Capillary blood collection, widely used in point-of-care testing, offers a promising alternative, particularly for patients facing frequently, or difficulties with, venous sampling. The Leiden University Medical Center in the Netherlands experienced a 15 % reduction in volume of laboratory tests during and after the pandemic, attributed to patient preference for local blood collection and testing. To address these challenges, self-sampling devices are emerging, empowering patients and streamlining sample logistics. However, challenges such as cost, transportation regulations, and sample volume adequacy persists. Robust devices tailored for total lab automation and sustainable practices are crucial for widespread adoption. Despite hurdles, the integration of self-sampling into diagnostic processes is inevitable, heralding a shift towards patient-centered, proactive healthcare. Practical recommendations include robust device design, ease of use, affordability, sustainability, sufficient quality and acceptability by seamless integration into laboratory workflows. Although obstacles remain, self-sampling represents the future of laboratory diagnostics, offering convenience, cost-effectiveness, interoperability and patient empowerment.

Keywords: blood self sampling; total lab automation; patient empowerment; total testing process; dry blood spot; dry serum spot

Introduction

In 1949, Becton Dickinson registered the intellectual property of the vacuum tube with the patent “Blood Collecting Apparatus” (US Patent 24660641). The introduction of the vacuum tube was a huge improvement for both the quality of the blood sample and patient well-being. Before the introduction of the vacuum tube, blood collection was performed with a glass syringe that transferred blood from a vein into a tube with a pre-added additive. The appropriate volume on the tube with additive was indicated by an etched line in the glass. For patients requiring different tests, e.g., chemistry, hematology and coagulation, multiple blood draws were required. After the blood was transferred from the syringe into the tube with additive, the tubes were sealed with a rubber cap. For a blood gas measurement, mineral oil was added to the blood to prevent loss of CO_2. If serum was needed, a wooden stick was used to remove the clot from the tube. After use, the syringes and needles were cleaned and, if necessary, the needles were sharpened using a whetstone [1].

The blood volume collected in the 1950s was necessary for the required test volume (see Table 1) [2–9]. The past 75 years have seen a tremendous evolution in laboratory diagnostics: from manual pipetting to automated analysis, from single-test batch analyzers to multi-test random access analyzers, from milliliter to microliter test volume, miniaturization of equipment and from hours to minutes of analysis time. Nowadays, the required test volume is 100–1,000 times lower compared with the 1950s. According

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to our calculations, more than 90 % of the collected blood volume in the Leiden University Medical Center (LUMC) is disposed as medical waste. In addition to the high cost of medical waste, venous blood collection has a number of other challenges. Both centralized and decentralized venous blood collections are time- and location-dependent and require a specific appointment at a phlebotomy unit. The logistics of decentralized venous blood collection tubes to a central lab can lead to crowding of patients and to peak loads in test production. In addition, the availability of trained phlebotomy personnel can also be a challenge for the laboratory. Patient challenges include fear of needles [10] and blood sampling specific in case of children/babies, elderly, obese patients and people with venous insufficiency. Moreover, in ICU patients, hospital acquired anemia may be partly caused by insufficiently managing venous blood sampling volumes [11, 12].

If microliters rather than milliliters are needed for laboratory diagnostics and venous blood collection has its disadvantages, would not capillary blood collection of a few hundred microliters be sufficient? After all, the use of capillary blood from a finger prick for point-of-care (POC) testing is already widely used in practice for the analysis for example of glucose, hemoglobin, D-dimer, INR or CRP. Another well-known clinical laboratory application of capillary blood is the newborn screening and therapeutic drug monitoring [13]. Capillary blood collection for clinical chemistry parameters is currently used only for infants, children and individuals in which venous blood collection is a challenge.

The LUMC is one out of eight academic centers of expertise acknowledged by the Dutch Ministry of Health. Patients from all over of the Netherlands are treated for specific and rare diseases such as rare liver diseases, rare solid tumors, cutaneous lymphoma's, endocrine bone disorders, Marfan syndrome, rare neuromuscular diseases, inherited heart diseases, rare genetic neurodegenerative diseases and organ transplantation of kidney, pancreas, liver and islets of Langerhans. For the follow-up of treatment, these patients have frequent blood draws for laboratory diagnostics. For example, the annual post-operation check-up of kidney transplant patients consists of the analysis of lipids, liver parameters, PTH, HbA_{1c}, magnesium, ferritin, uric acid and leucocyte differentiation.

Since the COVID-19 pandemic a reduction of 15 % was seen in the volume of laboratory tests in the clinical chemistry department of the LUMC. This decrease arose from patients who preferred a blood collection and analysis near home instead of travelling to the LUMC. The distance between the patients' home and the LUMC can be as much as 250 km (155 miles) which can be a challenge due to high population density and daily traffic jams in the Netherlands. Decentralized blood collection and analysis can lead to exchange of test results that are unharmonized and therefore not comparable and suitable for follow-up [14].

This article reviews the various decentralized capillary blood self-sampling options (Figure 1 and Table 2) that may empower patients and solve sample logistics with remote monitoring. Blood self-sampling devices that allow equivalence with central lab tests and enable interoperability and interfacing with the current total lab automation (TLA) concept are preferred. TLA refers to a comprehensive strategy aimed at maximizing the potential of laboratory technologies to enhance and streamline the execution of repetitive tasks, thereby facilitating the development of novel and enhanced processes within the laboratory setting [15].

Table 1: Evolution in sample volumes of routine clinical chemistry serum tests in the past 75 years.

Test	Sample volume, µL Roche Cobas 8000 (2024)	Test volume, µL	Year	Reference
Glucose	2	1,000	1947	2
Creatinine	4	5,000	1957	3
Cholesterol	2	500	1964	4
Albumin	3.5	500	1935	5
ASAT	3.5	100	1956	6
Iron	8.5	200	1960	7
Magnesium	3	2,000	1955	8
Uric acid	5	300	1965	9

Blood self-sampling devices (BSSD)

The best-known sites for capillary blood sampling are the fingertips of the middle and ring finger and the heel. In the last few years, products using the upper arm for capillary sampling have also become available. Based on the various BSSD available, capillary blood sampling can be divided into sampling where the blood remains fluid and sampling where blood is collected on a layer such as filter paper (Figure 2). Liquid blood has the advantage that it can be analyzed immediately once arrived in the lab and testing of hematological parameters is possible. The disadvantage of liquid blood is that its usability is time and temperature dependent. In contrast, the usability of dried blood/serum is suggested to be more stable than liquid blood for some analytes [16–18]. Other advantages of DBS are the low transportation costs and ease of collection. However, dried blood spots (DBS) need first to be reprocessed into liquid

Figure 1: An overview of the different blood self-sampling devices, see Table 2 for additional information. Devices for collecting liquid blood: Ezdraw blood sampler (1), Onflow (2), TAP micro (3), Tasso^{+} (4), Redrop (5), Microtainer/MiniCollect (6) and Hem-Col (7). Dry blood spot devices: OneDraw (8), DB10 (9), Mitra (10) and Capitainer B (11). Dry serum/plasma spot devices: Ser-Col (12), Velvet (13) and plasma separation card (14).

material before analysis. Hematological tests based on cell counting cannot be analyzed in DBS.

Liquid capillary blood collection

Ezdraw blood sampler – PreciHealth

PreciHealth has developed the Ezdraw blood sampler which is sticked to the upper arm and after activation, a lancet cuts the skin superficially. Vacuum from a standard vacuum tube (13 × 75 mm) draws milliliters of blood from the skin and collects the blood in the tube. An unique feature of the Ezdraw blood sampler is it's seamlessly connection to TLA due to the use of a standard vacuum tube. To the best of our knowledge, no study has been published investigating the performance of the Ezdraw blood sampler.

Onflow device – Loop Medical

The Onflow device is placed on the upper arm. After activation, a lancet cuts the skin and blood is collected in a small tube under the influence of a vacuum. Onflow is available in the following varieties: EDTA, serum, serum-gel, heparin plasma and heparin plasma gel. Upon arrival at the laboratory, the microtube can be placed on an adapter in order to be processed via TLA. Noble et al. examined the analytical performance of ASAT, ALAT, LDH, potassium and creatinine determined in blood collected with the Onflow device and compared with blood obtained by venipuncture from 100 participants [19]. ALAT and ASAT show an almost 100 % agreement, creatinine shows a negative bias of −5.6 µmol/L and LDH and potassium show a positive bias 6.7 and 3.6 % probably due to a mild degree of hemolysis (0.5–3.0 g/L) in 35 % of the withdrawals. The biases found in this study were not considered clinically relevant and similar to the biases generally found between venous and capillary blood results.

TAP micro – YourBio Health

The TAP Micro is placed on the upper arm. The device is activated by pressing a button which forces a microneedle array into the skin. A negative pressure is created causing blood to be drawn from the skin and collected in the tube. TAP Micro is available in the following varieties: EDTA, serum, serum gel, heparin plasma and heparin plasma gel. The blood collection tube cannot be integrated into a TLA solution as the blood needs to be transferred to another suitable tube before analysis. Multiple studies on SARS-CoV-2

Table 2: An overview of the different blood self-sampling devices.

	Blood self-sampling device	Collected volume, µL	State of blood	Matrix	Internal standard	TLA proof	Manufacturer	Country	List price 2024, €	Certification for use as BSSD	URL (accessed June 2024)
1	Ezdraw blood sampler	500–3,000	Liquid	Native	–	YES	PreciHealth	Switzerland	Unknown	–	precihealth.com
2	Onflow	1,500–3,000	Liquid	Native	–	YES	Loop medical	Switzerland	Unknown	FDA submission	Loop-medical.com
3	TAP micro	280–800	Liquid	Native	–	NO[a]	YourBio Health	USA	20	CE IVDD	yourbiohealth.com
4	Tasso^{+}	400–600	Liquid	Native	–	YES	Tasso Inc.	USA	20	CE IVDD/FDA Class II lancet 510(k)	tassoinc.com
5	RedDrop	500–800	Liquid	Native	–	YES	RedDrop Dx	USA	17	FDA Class II lancet 510(k)	reddropdx.com
6	Microtainer/MiniCollect	200–500	Liquid	Native	–	YES	BD/Greiner	USA/Austria	<1	CE[b] IVDD/FDA Class II 510(k)	bd.com/gbo.com
7	Hem-Col	200	Liquid + conservation	Diluted	Lithium	YES	Labonovum	Netherlands	1–2	CE IVDD	labonovum.com
8	OneDraw	150	DBS	Diluted	–	NO	Drawbridge	USA	Unknown	CE IVDD/FDA Class II 510(k)	drawbridgehealth.com
9	DB10	40	DBS	Diluted	Ht	NO	Hemaxis	Switzerland	10	CE IVDD/FDA Class I 510(k)	hemaxis.com
10	Mitra	30	DBS	Diluted	–	NO	Neoteryx	USA	12	CE IVDD	neoteryx.com
11	Capitainer B	10	DBS	Diluted	–	NO	Capitainer	Sweden	8	CE IVDD/FDA Class I 510(k)	www.capitainer.com
12	Ser-Col	200	DSS	Diluted	Na/Cl	NO	Labonovum	Netherlands	5–10	CE IVDD	labonovum.com
13	Velvet	180	DSS	Diluted	Cl	NO	Weavr Health	USA	20	CE IVDD/FDA Class I 510(k)	nightingalehealth.com
14	Plasma separation card	70–140	DSS	Diluted	–	NO	Roche	Switzerland	3.50	CE IVDD	roche.com

DBS, dry blood spot; DSS, dry serum spot. [a]Tube is not compatible with TLA due to an attached cap, [b]CE marked for professional use only, not for self-sampling.

Figure 2: Different forms of capillary blood collection. Blood collected in a tube can remain liquid or blood can be collected on a paper carrier as whole blood (dry blood spot) or can be first separated into cells and serum/plasma (dry serum/plasma spot).

antibody formation after vaccination have been performed with the TAP Micro [20, 21]. A study by Silliman et al. showed that Anti-Müllerian Hormone (AMH) determined in blood collected with the TAP Micro was comparable to blood collected with venipuncture with a correlation of 0.99. The AMH test results from the TAP device showed a R-squared of 0.99 compared to venous blood and demonstrated 100 % sensitivity and 100 % specificity [22].

Tasso^{+} – Tasso Inc.

The Tasso+ device is also to be placed on the upper arm. After activation of a lancet, a negative pressure is created, causing blood to be collected from the skin into a BD microtainer. The BD microtainer can be fitted with an adapter resulting in the TLA required 13 × 75 mm tube size. The Tasso+ has been frequently used in studies of SARS-CoV-2 antibody formation [23]. The study by Wickremsinhe et al. shows that the Tasso+ has a very good correlation (>0.99) for ALAT, ASAT, alkaline phosphatase and total bilirubin compared to venous blood. A correlation >0.95 was found for albumin, chloride, enzymatic creatinine, glucose, magnesium and phosphate. The venous concordance across these analytes support the use of the Tasso+ device as an alternative blood collection method to monitor these specific analytes [24].

RedDrop – RedDropDx

After activation, the RedDrop device makes two incisions in the skin of the upper arm and a vacuum is created. Blood is

collected in a standard BD microtainer tube that can be fitted with an adapter required for TLA-accepted tube dimensions. To the best of our knowledge, no study has been published investigating the performance of the RedDrop device.

Microtainer – BD/MiniCollect – Greiner

BD's Microtainer and Greiner's MiniCollect series can both be used for self-sampling although both tubes are CE-marked for professional use only. With clear instructions and a lancet, blood can be collected from a finger prick. Both microtubes are available with an adapter to get the TLA required 13 × 75 mm tube size. Ansari et al. show that blood collected in a microtube and analyzed after several days passed clinical acceptability for cholesterol, triglycerides, HDL, LDL, bilirubin, ALAT, ASAT, gamma-GT, alkaline phosphatase and HbA_{1c}. Clinical acceptability was determined by two criteria, the maximum permitted difference based on biological and analytical fluctuations as described by McCormack et al. [25] and the anticipated clinical need. The anticipated need was included because observed differences in test results between venous and capillary results that exceed the maximum permitted difference may not be clinically significant. Also fingerprick capillary blood collection is influenced by preanalytical variables that are not accounted for by analytical and biological variation such as patient preparation to collect a sufficient volume of capillary blood and the method of collection. Albumin, urea, creatinine, magnesium and calcium failed comparability assessment because the mean difference between venous and capillary results was greater than the maximum permitted difference [26]. The study by Doeleman et al. shows that complete blood counts determined in capillary blood stored at room temperature up to even 72 h after collection remained within a desirable total allowable error. However, the feasibility and clinical validity of delayed blood sample analysis depends also on the clinical situation and required precision of the result [27].

Hem-Col – Labonovum

Blood is collected in the Hem-Col tube via a finger prick. The Hem-Col tube is available as a no-additive tube or with a conservation fluid based on the following anti-coagulants: lithium heparin, EDTA and sodium fluoride. The Hem-Col LiHep, EDTA and NaF contain 200 µL of buffer. The advantage of this buffer, besides anti-coagulation, is increasing the sample volume and stabilizing the blood for 5 days between 5 and 25 °C. The disadvantage could be the dilution of the blood (3–5 times) for the limit of detection of some analytes. Dilution of the blood is determined by measuring the dilution of the internal standard lithium with a concentration 16 mmol/L in the preservation fluid. This lithium concentration is outside the detection limit of the current generation lithium assays and any modification to the lithium assay needs to be validated according to the IVDR guidelines. The study by Voigt et al. shows the stability of CEA for 4 days collected in the Hem-Col LiHep tube [28]. The stability of clozapine in the Hem-Col LiHep tube was demonstrated for 5 days at 2–25 C° [29]. In a recent study by Kurstjens et al. it was demonstrated that only 4 (total cholesterol, LDL-cholesterol, TSH and HbA_{1c}) out of 30 frequently requested clinical chemistry and hematology parameters met the pre-defined acceptance criteria. Predefined acceptance criteria were met when the 95 % confidence interval of the slope contained 1, the intercept contained 0, and the R^2 was above 0.9. It was suggested that the total analytical error of the analyte in these tests encompasses the analytical error of the lithium measurement and the analytical error of the analyte of interest [30].

Dried blood spots

OneDraw – Drawbridge

The OneDraw device is stuck to the upper arm, after activation, a lancet makes an incision in the skin. Under slight negative pressure, blood from the skin is transferred to a piece of filter paper placed in a plastic frame in the device. Afterwards, the frame is pulled out of the device and sent to the laboratory by regular postal services. Koulman et al. show that DBS can be collected at home by patients themselves using the OneDraw device and that the results for SARS-CoV-2 antibodies are comparable to venous blood with a R-squared of 0.97. Applying the established manufacturer cut-offs for defining seropositivity, complete agreement was found in the classification of definitive positive and negative results between the OneDraw device and venipuncture [31].

DB-10 – Hemaxis

The principle of the DB-10 is based on 4 capillaries that allows the collection of 10 µL of fingerprick blood per capillary. When the device is closed, the content of a capillary is transferred to filter paper. The DBS are eluted from the paper and the Ht (v/v) is used as an internal standard to calculate the dilution factor. Canil et al. describe the use of DBS collected with the DB-10 in the determination of the

anti-oncolytics Olaparib, Rucaparib and Niraparib with LC-MS/MS. Linearity was demonstrated by a correlation coefficient of respectively 0.995 and 0.960 for respectively Olaparib and Niraparib, both anti-oncolytics showing an intercept close to zero and the slope was near 1. Due to a limited dataset for Rucaparib the correlation coefficient was 0.935 [32].

Mitra – Neoteryx

Mitra, developed with volumetric absorptive micro sampling (VAMS), consists of a plastic rod with an adsorbent hydrophilic polymeric probe that can be used to collect blood from a finger prick. Using the Mitra 96-Autorack, elution of the Mitra can be automated by an ELISA pipetting robot.

The utilization of VAMS in the analysis of endogenous metabolites has emerged very recently, aiming towards either disease diagnosis and monitoring, nutritional deficiency assessments, drug monitoring, alcohol abuse, sports doping, or metabolomics research. The use of VAMS for the analysis of endogenous analytes such as tacrolimus, ciclosporin, everolimus and sirolimus in biological samples shows large interlaboratory variation compared to whole blood methods due to the lack of standardization. The variation is of such magnitude that it will affect clinical decisions [33].

Capitainer B – Capitainer

Capitainer B, also known as Capitainer qDBS, is a blood collection device that collects 2 fixed volumes of 10 µL of blood from a fingerprick whereas the Capitainer B50 collects 2 fixed volumes of 50 µL of blood. During collection the blood is transferred within the device from either a 10 µL or a 50 µL capillary to a layer of paper. Capitainer is a hematocrit independent alternative for dried blood spot collection. Liu et al. developed an ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) method to simultaneously quantify eight antibiotics in support of pharmacokinetic studies in neonates [34]. Vethe et al. demonstrated the performance of Capitainer for the monitoring of tacrolimus, creatinine and hemoglobin in kidney transplant recipients. Capitainer showed a consistent sampling success and analytical quality defined by the proportion within ±20 % difference compared to venous sampling: 79–96 % for tacrolimus and the proportion within ±15 % were 92–100 % for creatinine and 93–100 % for hemoglobin [35]. A study by Wikström et al. focuses on improving lithium treatment monitoring, which typically involves frequent serum concentration measurements due to its narrow therapeutic window and toxicity risk. In this study, dried blood spots collected by Capitainer, were used for lithium concentration determination. Capitainer and serum lithium concentrations were strongly correlated in a linear way with a Pearson's R of 0.95 [36].

Dried serum/plasma spots

Ser-Col – Labonovum

The Ser-Col allows blood from a finger prick to be transferred to lateral flow (LF) paper. LF paper has the property of "capturing" blood cells in a network of glass fibers. The serum diffuses through the paper. When the separation of serum and cells is complete and the paper dries, the result is a dry serum spot. In the laboratory, the dried serum spot can be eluted with elution buffer. The dilution of the plasma can be calculated by the dilution of sodium and chloride where the expected sodium concentration was defined as 140 mmol/L and the expected chloride concentration was defined as 102 mmol/L [37]. Two studies have shown that Ser-Col has comparable results with venous plasma for antibodies to SARS-CoV-2 and HIV. The specificity of antibodies to HCV, HBsAg and Syphilis in serum eluted from Ser-Col were 100 %, whereas the sensitivity was respectively 0 , 83 and 87 % [38, 39].

Velvet – Weavr Health Corp.

The Velvet collects blood from a finger prick into three 60 µL heparinized capillaries. Once the capillaries are filled and the device is closed, the blood is transferred to a strip of LF paper to separate the blood cells from the plasma. The dried plasma spot can be eluted with an elution buffer. The dilution of the plasma can be calculated by the formula $Cl^-_{expected}/Cl^-_{measured}$. The expected chloride concentration was defined as 100.3 mmol/L, derived from the patient mean of chloride measurements of 62.648 venous serum and plasma samples. Chloride normalization was performed for all lipid measurements in eluted dried plasma samples. HbA_{1c} is reported as a ratio of hemoglobin and glycated hemoglobin, and did not require chloride normalization. The study by Crawford et al. shows a correlation of >0.95 for cholesterol, HDLC, LDLC and triglycerides in blood collected with the Velvet compared to venous blood [40].

Cobas plasma separation card – Roche

The use of dry blood spots is recommended by the World Health Organization in self-care interventions as an additional strategy to increase human immunodeficiency virus (HIV) and *Treponema pallidum* (Tp) testing uptake. Dry blood spots can also be used to monitor antiretroviral treatment of HIV by measuring the HIV-1 viral load. However, cellular components in DBS may result in low specificity i.e., overestimation of viral loads compared to plasma.

The Cobas plasma separation card (PSC) collects 70–140 µL of capillary heparinized blood from a finger prick. The PSC consists of a filter that allows the plasma to elute through and retain the blood cells. Below this filter is a membrane that absorbs the plasma. The plasma membrane is eluted with phosphate-buffered saline with 0.05 % Tween 80 overnight at 4 °C.

In a study from Hans et al., the PSC showed a sensitivity of 96.9 % and specificity of 97.4 % for the HIV viral load using plasma as the reference [41]. Vubil et al. showed the stability of the HIV-1 viral load in blood collected with the PSC exposed to high temperatures (25–42 °C) for up to 28 days [42]. Vanroye et al. evaluated the performance of HIV and Tp antibody detection on PSCs. For HIV antibody detection, the PSCs showed a sensitivity of 99 % and a specificity 68 % and for Tp antibody testing 90 % sensitivity and 100 % specificity was found [43].

Discussion

Rationale for remote blood self-sampling devices

The COVID-19 pandemic resulted in a reduction of 15 % in the volume of laboratory tests in the clinical chemistry department of Leiden University Medical Center in the Netherlands, due to decentralized blood collection and analysis. Remote pre-analytical services that strengthen patient empowerment and BSSD could be one of the solutions for this sample logistics problem. To enable the pre-analytical part of the total testing process (TTP) to be done by patients in their habitat and to keep care accessible and affordable now and in the long term, blood self-sampling innovations are needed. In recent years, there has been a tremendous growth in medical devices that allow patients to collect themselves their own blood for diagnostic purposes. Blood self-sampling can maintain the laboratory testing of patients who live far away from the hospital and keep the patient records complete and data comparable. Lingervelder et al. showed that self-collection of blood by a finger prick in chronic ill patients is likely cost-saving compared to phlebotomy as it is expected to reduce societal cost [44]. The amount of blood collected by self-sampling is often less than 5–10 % of the blood volume obtained by venipuncture. This blood waste reduction has a positive impact on reducing CO_2 emissions and is in line with the EFLM guidelines for green and sustainable medical laboratories [45].

Similar to self-testing, blood self-sampling involves a balance between convenience, accuracy, and comprehensive health monitoring. Blood self-sampling only comprises the pre-analysis performed by the patient, whereas blood self-testing comprises both the pre-analysis and the analysis by the patient. While both methods offer undeniable benefits in terms of accessibility and privacy, it is essential for individuals to approach them with caution, seeking guidance from healthcare professionals and understanding the limitations of both methods. We strongly believe in the added value of blood self-sampling in order to have the test results generated in a state-of-the-art laboratory and reported in the electronic patient file. Ultimately, an integrated solution is needed, where blood from BSSD or from venipuncture can be used interchangeable.

Limitations of blood self-sampling

However, there are also disadvantages to the use of self-sampling devices. Some of the current generation of self-sampling devices are more expensive than the average costs for phlebotomy (Table 2). According to the norm 7.2.5 “Sample Transportation” of the ISO 15189:2022, registration of the temperature during transport should take place. An example of an inexpensive and automated temperature registration system is the Varcode SmartTag™ (www.varcode.com) which is a barcode made of thermolabile ink. The barcode changes with temperature rise and duration and can be read with a scanner upon arrival at the laboratory.

Another challenge can be the sample volume collected that, despite the low required test volume, may not be sufficient due to the contribution of the dead volume which may vary from analyzer to analyzer (40–300 µL). The acceptance of a BSSD tube at the level of TLA and analyzer determines the degree of automation. It is not desirable to first manually transfer a BSSD sample into a tube that does meet TLA and analyzer requirements [15].

A significant pillar of success of self-sampling are the instructions for use that can be provided in different ways. Prior to self-sampling, a physical instruction/training can be given by a healthcare professional. In addition, it is also

possible to provide this instruction on paper, by video or animation or even through an App [13, 46, 47].

Accurate and unique identification of patients along the care process is essential for patient care and safety and enhancing data sharing and interoperability [48]. According to the norm 3.24 "pre-examination processes" of the ISO 15189:2022, the patient needs to be unequivocally identified. In the case of self-sampling, it is not possible to make a positive patient identification during blood collection at home.

Product-market combination

An important consideration is which device is used for which laboratory diagnostics, the so-called product-market combination. The requested test panel can differ per caregiver. Primary care by the general practitioner includes prevention, screening and follow-up of chronic diseases. Secondary care by a specialist such as an oncologist, cardiologist and endocrinologist differs from laboratory testing in academic care.

For hematological parameters, blood should remain liquid in the presence of EDTA in contrast to therapeutic drug monitoring (TDM) which can also be determined in dry blood spots [13]. Before considering blood self-sampling, the differences between venous and capillary blood should be well identified [49], as well as the influence of time and temperature between blood collection and analysis.

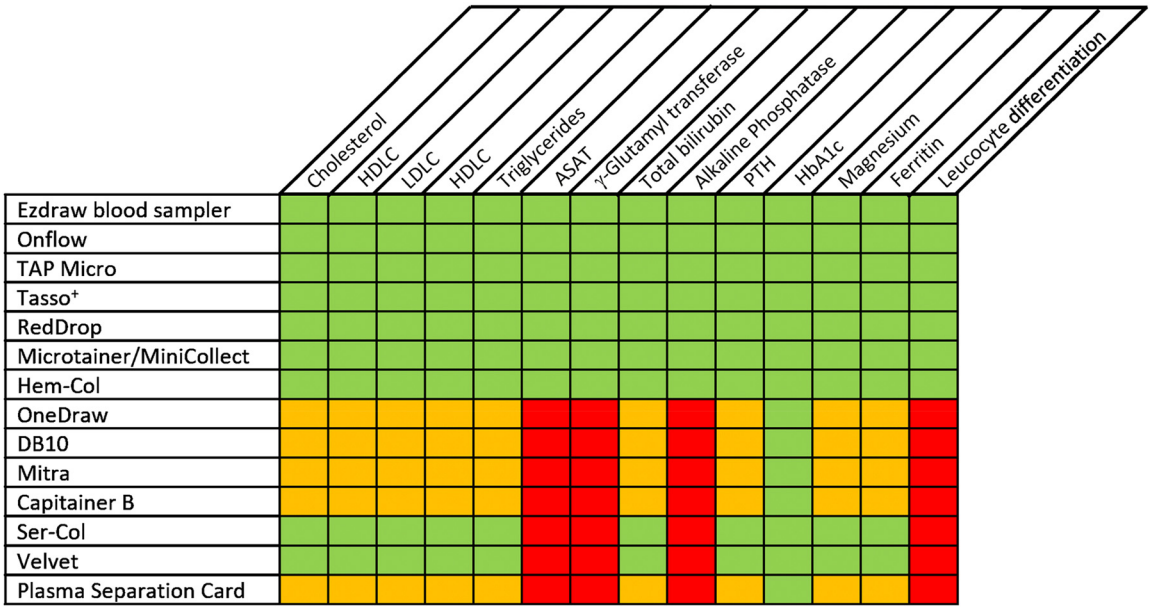
In case of the periodic post operative check-up parameters of kidney transplantation patients from the LUMC, only the BSSD based on liquid collection are suitable for laboratory testing. Most of the BSSD based on dry blood or plasma/serum spot have either a low volume or high dilution for the complete set of parameters (Table 3).

Integration of BSSD in the total testing process

Laboratories and diagnostic institutions are facing pressure to do more with less, from scarce resources and reduced budgets, to faster turnaround requirements and the need to grow in an increasingly competitive environment. At the same time, the tendency to empower patients with BSSD and the trend to new diagnostic analyzers and decentralized diagnostics are challenging labs to securely merge data from various sources and streamline complex workflows.

IVD-companies like Roche developed digital portals that fill the gaps and support the entire TTP, including BSSD and home monitoring. In case of Roche the Navify Diagnostic portfolio was developed which provides a wide range of digital solutions to answer these challenges: total solutions including the entire pre-preanalytical and pre-analytical

Table 3: Periodic post operative check-up parameters of kidney transplantation patients.



Green, collection method is suitable for analysis and the amount of blood volume collected is sufficient for analysis; orange, collection method is suitable for analysis and the amount of blood volume collected is partly sufficient for analysis due to small volume and/or large dilution; red, collection method is not suitable for analysis.

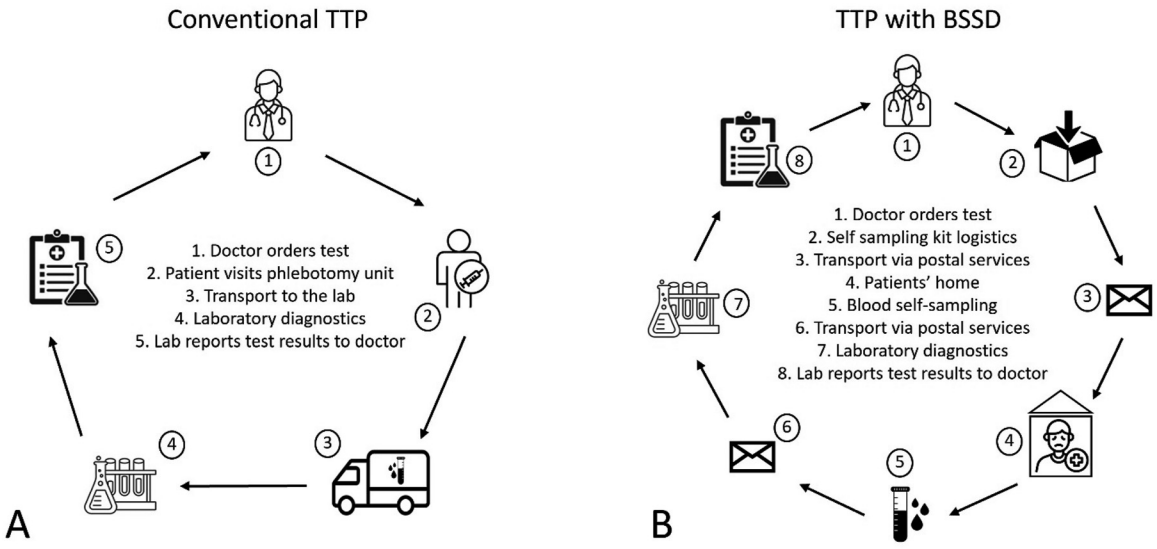


Figure 3: Brain-to-brain loop in case of centralized medical testing in hospital controlled settings (A) compared to decentralized approaches with patients being responsible for the pre-analytical phase of the TTP (B).

phase, the digital infrastructure that integrates data streams across the central lab and POC or home operation; operational excellence to improve diagnostic services of the central lab and added value by empowering patients with remote sampling. This kind of total solutions are needed to guarantee a complete integration of BSSD within the TTP and will be considered by the authors for the Leiden setup (Figure 3).

Table 4: Ideal characteristics of blood self-sampling devices to be eligible in TLA-concepts.

Fail-safe, easy to use and painless
Letterbox fit and temperature monitored
Tube and label tailored for TLA
Sustainable and recyclable (circular economy)
Affordable/"break even" compared to current blood sampling solutions
Integration of a digital portal for test ordering, reporting and integration data in electronic patient file
BSSD samples should produce equivalent results in central labs as compared to venous blood samples

Practical recommendations

In summary, before a BSSD is considered to be technology ready and useful in patient care, it needs to comply with the following requirements (Table 4): (A) the BSSD device should be robust, fail-safe and preferably painless. Usability testing by non-healthcare professionals during the design process helps the manufacturer to track down user-challenges in an early stage. (B) If transport of the blood sample to the laboratory is taken care of by regular medical postal services, the package should be letterbox fit and temperature monitoring during transport is essential. In general, the postal service costs for letterbox-fit packages are much lower than for parcels. (C) In order to be tailored for TLA, the choice for the blood collection tube should be made by the laboratory. Both tube manufacturer, tube dimension, tube volume, the use of serum or plasma as well as tube label size cannot be changed easily by the lab. The involvement of laboratory professionals is essential and of added value to overcome the hurdles of connecting the BSSD to the TLA and to fit the pre-analytical trajectory in the TTP of ISO certified labs. (D) Another very important point of interest is sustainability and circularity. Although less blood is collected compared to venipuncture, some of the BSSD produce more plastic waste than venipuncture does. The use of circular materials can also contribute to the reduction of the CO_2 footprint. (E) Taking into account the rising healthcare costs, BSSD use needs to be cost effective. (F) The integration of blood self-sampling in the diagnostic TTP requires complete digital portals in order to streamline this complex workflow. (G) Remote TTP lab results need to be equivalent with the central TTP lab results and therefore fit for purpose.

There are still a number of hurdles to overcome before BSSD will be adopted and implemented by all stakeholders such as patients, laboratories and insurance companies. However, it is no longer the question if, but when BSSD will become sufficiently robust and digitizable state-of-the-art solution that empowers patients and reduces societal costs.

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