Longitudinal monitoring of metabolomic profiles with at-home dried blood sampling devices

Esther Wortmann, Gordian Adam, Alice Limonciel

biocrates life sciences gmbh, Innsbruck, Austria

1 Introduction

Many diseases are only diagnosed once clinical symptoms appear. While some countries offer regular medical assessments before clinical symptoms appear, blood analysis is often only carried out once a patient visits a medical professional or clinic because of a health problem.

In this context, health self-monitoring is becoming increasingly popular, for example using wearables. The potential benefits of combining microsampling with information collection through wearables for physiome profiling and precision health monitoring (Shen et al. 2024) are increasingly understood and accepted. Consequently, an growing number of companies offer tests for self-monitoring health-related parameters at home, an emerging form of participatory medicine.

Indeed, many diseases are associated with early warning signs that can be measured in biological samples before clinical symptoms appear. For example, plasma branched-chain amino acid concentrations have been identified as early markers of diabetes (Magnusson et al. 2013). However, tracking relevant markers in healthy individuals comes with difficulties.

A major challenge for the analysis of blood samples is the invasiveness of normal venipuncture, which requires medical personnel. While some consumer tests have thus focused on sampling of feces or urine, which is less invasive, analysis of blood samples provides unique information about systemic changes, enabling a comprehensive snapshot of a body's metabolic state.

Therefore, alternative methods have been developed for minimally invasive at-home collection of blood samples. Generation of dried blood spots (DBS) only requires a finger prick for a few drops of blood on filter paper (Reed et al. 2024). The use of traditional DBS is limited, but several derivatives like Capitainer devices (Deprez et al. 2023) have been developed that enable absolute metabolite quantification. Volumetric absorptive microsampling devices (VAMS), especially Mitra tips (Fuller et al. 2019), have emerged as a promising alternative to DBS. They absorb a constant volume of capillary blood, which dries faster than in DBS due to the large surface area, stopping biological processes quickly. These properties make Mitra tips suitable for reliable quantification of metabolites.

Metabolite stability at room temperature for several days is crucial for at-home sampling and subsequent shipment to the metabolomics service location, where robust and reliable measurement processes must be in place. To this end, we investigated the suitability of dried blood Mitra tips for standardized measurements with the biocrates MxP® Quant 500 and SMartIDQ alpha kits for metabolite measurements using dried blood Mitra tips.

We also compared Mitra tips and DBS regarding their suitability for quantitative metabolomics in a different application note (Application note - Metabolite stability in dried blood samples (v1-2024)). While these results have shown that technical challenges can be overcome, it has not

been established whether at-home blood sampling in combination with metabolomics leads to reliable and relevant results despite the biological variance.

The plasma metabolome of healthy individuals is influenced by many factors such as age, sex, diet, microbiome, body composition, and genetics (Chen et al. 2022; Wang et al. 2025). Indeed, most of these effects are rarely considered when interpreting single-timepoint measurements.

In this application note, we investigated whether regular longitudinal sampling using Mitra tips would enable the detection of relevant changes in metabolism on an individual basis.

2 Methods

Longitudinal study

A one-year study with longitudinal metabolomic measurements in 5 healthy volunteers using dried blood Mitra tip samples was performed. During the first 15 days, samples were taken daily. After the first two weeks, samples were taken bi-weekly for the rest of the year. Blood samples were taken in a fasted state in the morning and stored at room temperature for up to 5 days. Detailed metadata regarding food consumption, physical activity, illnesses, and sleep were recorded for 3 days before each sampling, using wearables and self-reporting questionnaires.

Reference ranges

In addition, Mitra tip samples from a cohort of individuals of various health status (252 samples from 157 individuals) were used to generate reference ranges. The generation of these matrix-specific reference ranges was necessary, as reference concentration in dried blood Mitra tips cannot be directly compared to concentrations in plasma or serum samples.

The measured concentrations in this matrix are more similar to whole blood (as for DBS). Based on this reference population, values of parameters assessed can be visualized on a scale ranging from critically low to critically high values or scores (Figure 1).

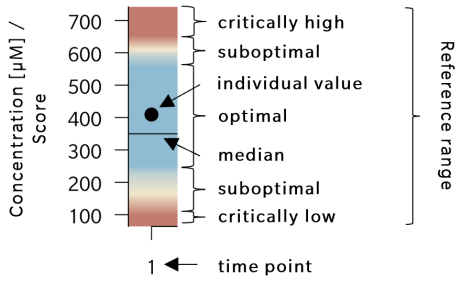

Figure 1. Reference range based on a reference population consisting of healthy and non-healthy individuals.

Specific goals of this study were to:

- investigate day-to-day variations,
- study fluctuations over a longer time span,
- determine if “normal ranges” as shown in Figure 1 are applicable to all individuals.

Furthermore, we assessed the suitability of metabolomics from Mitra tips for personalized tracking of metabolomic parameters related to nutrition, fitness, microbiome, wellbeing, and mental fitness (Figure 2).

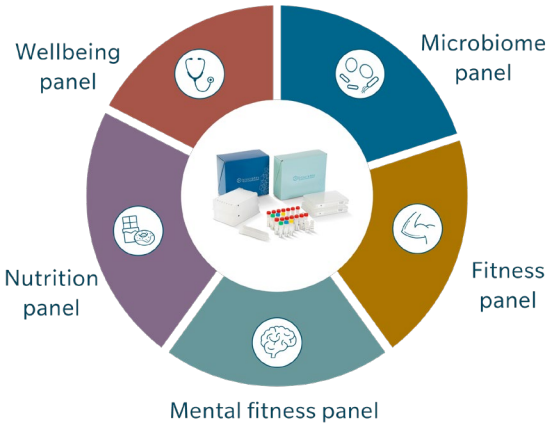

Figure 2. Overview of the biocrates metabolite panels.

3 Results

3.1 Day-to-day variability

Generally, the metabolites that were identified as stable in dried blood Mitra tips displayed consistent results and high traceability in this study, confirming the rationale that this matrix is suitable for such a setup. Typical gender-related metabolism differences (Tian et al. 2023) were observed, like higher levels of phosphatidylcholines and sphingomyelins in females and higher levels of spermine and DHEAS in males (Figure 3).

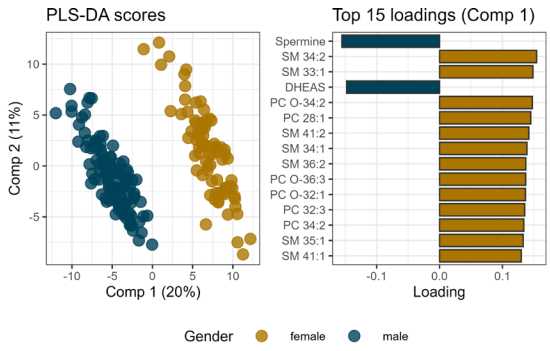

Figure 3. PLS-DA score plot by gender (left) and the corresponding 15 most important loadings for component 1 (right).

Some metabolites displayed comparably high day-to-day variability, while others remained within a small concentration window. High variance was observed in the same classes that are known to display high short-term fluctuations in other blood-based matrices like plasma (Fiamoncini et al. 2022; Lang et al. 2013). Bile acids were the metabolite class with the highest variance within each individual over the course of the study (Figure 4) - even though all samples were always taken in a fasted state in the morning.

While concentrations of bile acids depend on individual factors like microbiota composition, diet also has a substantial effect on the levels of bile acids that can be measured in blood.

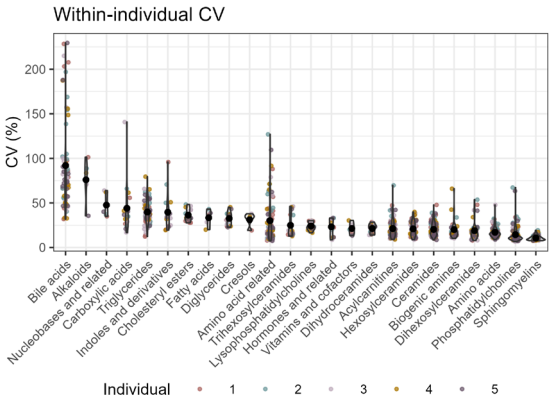

Figure 4. Coefficient of variation (CV) of all samples measured during the 1-year long-term study per individual and metabolite, grouped by class. The black dots represent the mean CV for each metabolite class across all individuals.

A high fat diet leads to the secretion of conjugated bile acids into the small intestine, where they undergo modifications due to bacterial metabolism, for example deconjugation, before most of them are reabsorbed and transported back to the liver.

Special events or unusual food intake recorded during the long-term study were also reflected in the metabolome. One individual recorded a day with a particularly fatty diet, which was followed by a day of fasting (Figure 5, left panel). This was directly reflected by a high concentration of deconjugated bile acids, followed by a drop on the following day (Figure 5, right panel). This example demonstrates the direct effect of diet on the measured bile acid concentrations in blood.

The influence of other lifestyle factors could be observed in the metabolome as well. For example, a mentally stressful week resulted in unusually high cortisol levels, while a party night with high alcohol consumption led to increased levels of a ketosis marker (hydroxybutyrylcarnitine) and lower levels of histidine, known consequences of alcohol intake (Hasken et al. 2022; Naik et al. 2022).

Many metabolites fluctuate on a daily basis, depending on factors like nutrition, stress, or other special events. Such factors are rarely controlled and can lead to over-

interpretation of certain results. Regular sampling to investigate longitudinal trajectories could circumvent these problems.

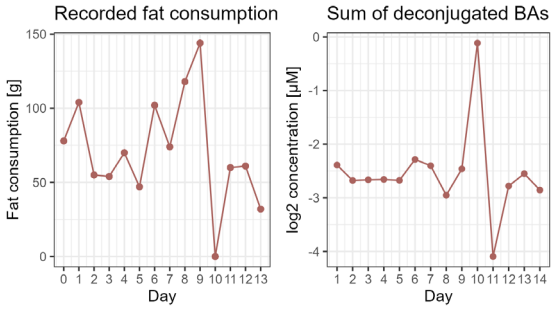

Figure 5. Recorded fat consumption (g) on the left and the sum of deconjugated bile acids (BAs) on the right during the first 15 days of the study.

3.2 Longitudinal trajectories

Some parameters displayed values in a consistent concentration range for all participants both short-term and long-term, independent of factors like age, gender or daily nutrition. Universal reference ranges for healthy concentrations can be applied well to such parameters. An example is the ratio of choline to betaine (Figure 6). Both metabolites play an important role in methyl group metabolism and in a healthy state, these two metabolites are balanced.

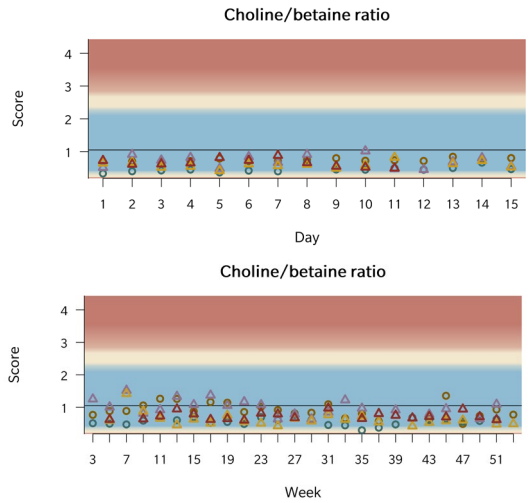

Figure 6. Ratio of choline to betaine. Triangles represent men, circles represent women. Top panel: the first 15 days of daily sampling, Bottom panel: the subsequent biweekly sampling.

A high value for their ratio can be an early indicator for development of metabolic syndrome and was found to correlate with related diseases (Guasch-Ferré et al. 2017; Dai et al. 2020). Tracking this ratio over time can help identify deterioration of metabolic health early and might therefore motivate the implementation of lifestyle changes before worsening of the physical state occurs. Longitudinal sampling can be used not only to catch early warning signs of morbidity, but it can also be used to track lifestyle changes or nutritional interventions in healthy individuals.

Important influential factors like sex or age are often ignored when applying general reference ranges. Our measurements of DHEAS (Figure 7) highlight that a single reference range for healthy adults does not make sense for parameters affected by such factors; more specific reference ranges are needed for defined subgroups.

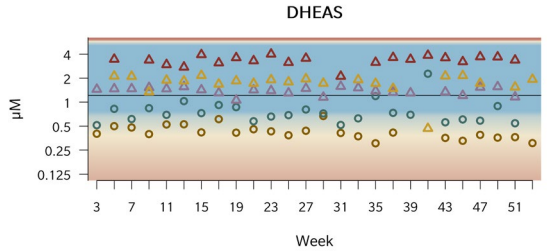

Figure 7. DHEAS levels in men (triangles) and women (circles).

Higher serum levels of secondary bile acids like deoxycholic acid (DCA), lithocholic acid (LCA) and their conjugated forms and lower levels of primary bile acids like cholic acid have been detected in patients with Alzheimer's disease (Mahmoudian Dehkordi et al. 2019). Calculating the ratio of these potentially neurotoxic bile acids to neuroprotective bile acids could be used as an early risk marker for neurodegenerative diseases. Figure 8 shows an example of an individual for which this ratio was close to the median of the normal population during the initial two weeks. However, long-term monitoring revealed a worrisome trend toward a higher ratio, despite some

measurements still being in the normal range.

This example highlights the benefits of longitudinal sampling, especially for variables that vary on a day-to-day basis. It is also an example where the combination of individual values and trends in addition to the reference range of the general population are beneficial to catch relevant changes in the metabolome early-on before physiological symptoms manifest.

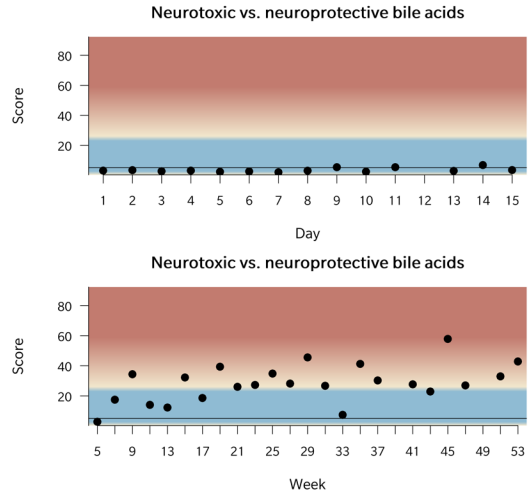

Figure 8. Mental fitness panel: Neurotoxic vs. neuroprotective bile acids in the first two weeks of daily sampling (top) and the subsequent biweekly sampling (bottom).

The mentioned examples emphasize that longitudinal sampling is crucial to spot deviations which could easily be missed in a single timepoint assessment and using general reference ranges. Conversely, deviations from normal ranges may occur occasionally without being the symptom of an underlying disease. Longitudinal measurements can prevent overinterpretation of such outliers and direct the focus to intensifying trends that deserve attention.

Naturally, many parameters displayed a higher fluctuation over the whole study period than during the first two weeks. As illustrated by the trend emerging for the parameter in Figure 8, repeated measurements every few months give a more accurate impression of the health status and potential trends than several samples within a short time frame.

3.3 Longitudinal sampling to monitor lifestyle and nutrition

Many metabolites or metabolite ratios are used as biomarkers informing about fitness status, balanced diet, or general wellbeing. While not all known plasma-based biomarkers work in dried blood Mitra tips, distinct markers for certain nutritional habits, specific food groups, stress, exercise, and microbiome composition could be confirmed and monitored.

Metabolomics can be used to track training success during different phases of a training cycle for athletes. Our study showed that assessment and comparison of fitness is possible with the metabolite set validated for at-home dried blood Mitra sampling. Hypoxanthine has been proposed as a universal metabolic indicator for training status (Zieliński et al. 2015). Its level is especially sensitive to high volume of anaerobic training (Włodarczyk et al. 2020). A lower hypoxanthine level at rest might indicate a better readiness for high intensity exercise (Zieliński et al. 2015).

In line with these findings, one individual with very little exercise at high intensity (Figure 9, individual A) had the highest hypoxanthine levels.

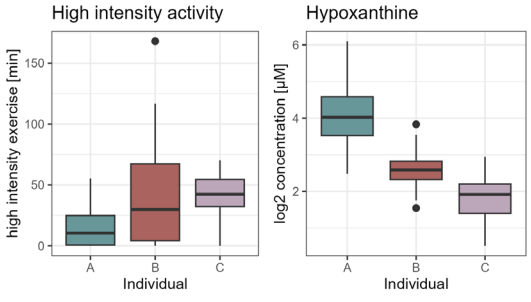

Figure 9. High intensity exercise [min] and the respective hypoxanthine levels in 3 individuals. Individual A: very little high intensity training. Individual B: unstructured training; Individual C: regular high intensity exercise. The boxplots represent values and measurements across the whole 1-year sampling period.

In contrast, an individual that did some high intensity training, but not consistently, had

lower levels of hypoxanthine, while the individual with the most consistent and longest exercise at high intensity had the lowest levels of hypoxanthine (Figure 9, individual C).

Self-reported food intake is often not very accurate (Bindels et al. 2025; Ravelli et al. 2020), meaning that perceived food intake might not match actual consumption. Therefore, monitoring the diet with metabolomics, or rather, monitoring the effect of the diet on the core metabolism, makes sense.

Precision nutrition is a concept that assumes each person reacts differently to specific food intake (Berry et al. 2020). This also means that an optimal diet might look different for each person. In addition, food processing like cooking and conservation or even food storage have a substantial impact on nutrients (Kramer 1977). Longitudinal blood sampling provides optimal monitoring of individual reactions to nutrition and an unbiased reflection of the nutritional status.

While current biocrates kits were not designed to directly target many diet-derived metabolites, many core metabolism and microbiome-related metabolites from these panels are relevant diet-related health indicators like polyunsaturated fatty acids.

Both omega-3 and omega-6 fatty acids are essential polyunsaturated fatty acids that the human body does not produce itself. Western diets are usually low in omega-3 and high in omega-6 fatty acids. A low ratio of omega-3 to omega-6 fatty acids promotes inflammation and cardiovascular disease (Simopoulos 2002).

Tracking this ratio over time helps assess if the intake of these fatty acids is adequate and balanced (Figure 10). Our study showed a comparatively good correlation between this ratio and fish consumption on an individual level (conditional r^2 = 0.463 with the individual as a random factor), as expected.

Of note, while the typical range of any parameter in the healthy reference population is usually considered optimal, the typical range for this parameter is still considered low, as the recommended omega-3 fatty acid intake exceeds the typical nutritional levels in the healthy population.

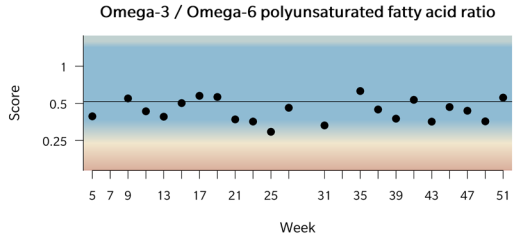

Figure 10. Ratio of omega-3 to omega-6 polyunsaturated fatty acids in one of the participants over time.

Individual dietary habits are also partly reflected in the metabolome. A ketogenic diet for example can be tracked with hydroxybutyrylcarnitine. A sustained ketogenic diet promotes the breakdown of fatty acids by beta-oxidation for energy production. Indeed, comparing an individual on a strictly ketogenic diet with an individual on a normal diet shows differences in both the ketosis marker and the metabolic indicator for beta-oxidation (Figure 11).

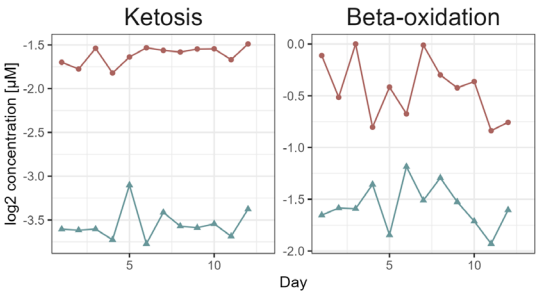

Figure 11. Markers for ketosis and beta-oxidation in two individuals, indicated by different colors and shapes, reflect the differences in diet composition.

3.4 Dried blood metabolomics as biomarkers of health and disease

While the participants in the longitudinal study were considered generally healthy, several incidences of infections were monitored, with distinct metabolic changes.

For example, a COVID infection - at a time before vaccinations were available - was reflected by lower levels of carnitine, taurine, and polyamines, especially spermidine. Carnitine is mainly taken up through the diet, and reduced food intake was directly reflected in lower carnitine levels. Taurine has antioxidant and anti-inflammatory activity and decreased concentrations were detected in COVID-19 patients (Atila et al. 2021). Spermidine and spermine have been shown to reduce COVID-19 propagation *in vitro* by autophagy-induction, resulting in lower levels of these polyamines (Gassen et al. 2021). Interestingly, these effects were not observed in individuals that got COVID-19 infections at later time points after having been vaccinated.

Metabolomics is not only an excellent measure of acute diseases such as infections. Metabolomic panels can also be used to track metabolites that are known risk markers for chronic disease.

Sphingomyelins were the most stable metabolite class over the course of study (Figure 4). While most sphingomyelins are influenced by factors like age, sex, smoking, or diabetes status (Mielke et al. 2015), these factors did not change drastically for the participants during the analyzed timeframe. However, studies show that sphingomyelin levels in diabetes patients are associated with comorbidities like retinopathy (Jadhav et al. 2025) or kidney disease (Mäkinen et al. 2012). Therefore, longitudinal monitoring could be used to catch warning signs for these morbidities early, while accounting for the many cofactors that affect sphingomyelin levels in blood.

Catching metabolic changes early would allow implementing preventive measures in time. As a first mover in Europe, the diagnostic laboratory BIOVIS offers the test "Prevent 360", which allows health monitoring based on dried blood Mitra tip metabolomics. They offer insights into health relevant aspects with a focus on intestinal health, cardiovascular health, inflammation, and other metabolic markers.

3.5 Influence of seasons

During the evaluation of dried blood Mitra tips for longitudinal metabolomics measurements, seasonal effects were observed for several metabolites. The list of affected metabolites, however, was mostly identical with those that exhibited stability issues when stored at room temperature for several days, as laid out in the application note on metabolite stability in dried blood samples.

This indicates that the seasonal effects observed do not have a biological cause but reflect the difference in room temperature during the time span between sampling at home and freezing in the laboratory (three days on average). This confirms that metabolites that are not stable at room temperature should not be considered for health monitoring combining at-home sampling with metabolomics.

Among the metabolites that were evaluated as stable in dried blood Mitra tips stored at room temperature for at least three days, a seasonal effect could be observed for very few specific metabolites in some individuals only, which were caused by nutritional differences between the seasons. For example, a high consumption of citrus fruits during certain months of the year was reflected by higher concentrations of the known citrus fruit intake marker proline betaine (Figure 12).

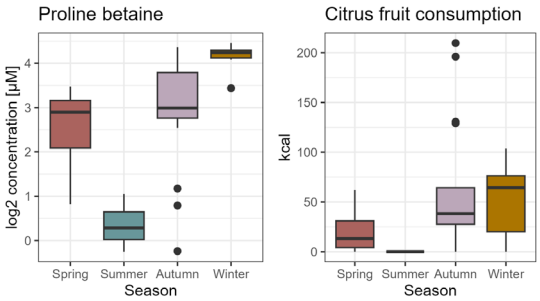

Figure 12. Proline betaine as a seasonal marker for citrus fruit consumption. Left plot: proline betaine concentrations in a representative individual, summarized by season. Right plot: average citrus fruit consumption of the 3 days before each sampling (same individual).

3.6 Limitations of the study

Metabolic profiling with Mitra tips has many advantages, as shown in the previous chapters. However, there are also some important limitations to be aware of, in order to make optimal use of Mitra tip sampling for longitudinal monitoring.

While certain metabolites remain stable throughout the day and even throughout the year, others react directly to specific nutritional or environmental factors. Longitudinal blood sampling enables tracking of metabolic shifts over time, offering a more reliable signal than single timepoint measurements. Over-interpretation of normal inter-individual differences and day-to-day variance can be avoided and deviations from an individual's normal level can be detected and followed up. Once individual normal ranges have been established, trends can be identified early even while still within the normal range of the general population and ideally counteracted by lifestyle adaptation. Such interventions, however, prompt a thorough understanding of the links between lifestyle, metabolism, and health. Therefore, even though devices suitable for at-home sampling abolish the need for medical personnel for blood draws, medical experts are still required for interpretation of the results and identification of suitable advisory measures.

A disadvantage of dried blood sampling is the lack of established normal concentration ranges for the healthy population. To this end, biocrates is offering the normal ranges established based on dried blood Mitra tip samples from self-declared healthy individuals as part of its Quantitative Metabolomics Database (QMDB). The QMDB is a commercially available database introduced originally to provide normal concentration ranges of plasma metabolites assessed with biocrates kits, because no reference ranges are available for many of these metabolites (Application note 35046-QMDB (v1-2022). It also contains metadata like gender and age for the generation of stratified reference ranges. Extending the database to include dried blood Mitra tip measurements provides the required reference ranges that facilitate interpretation of dried blood metabolomics results both for medical practitioners associated with diagnostic laboratories as well as academic researchers.

4 Conclusions

Personalized medicine and nutrition are becoming more relevant for individuals as well as healthcare providers. However, blood drawing by professional medical personnel on a regular basis is time consuming, expensive and not accessible to all individuals.

At-home sampling of blood for metabolomics measurements opens possibilities not only for monitoring clinical markers, but also to track individual lifestyle changes, such as training adaptation or the success of dietary interventions. The fact that longitudinal at-home sampling approaches can yield reliable results and enable drawing medically relevant conclusions also lowers the bar for pre-clinical and clinical studies, reducing both personnel costs and logistical effort.

In this study, we investigated the applicability of dried blood Mitra tips for longitudinal monitoring with metabolomics. The combination of these technologies is set out to be a great driver of participatory medicine, supporting a broader implementation of the other four pillars of 5P medicine – preventive, predictive, population-based and precision medicine.

In conclusion, longitudinal sampling of dried blood Mitra tips emerges as an extremely useful mode of sampling for individuals with an interest in their own health and lifestyle and as a powerful tool for researchers and medical professionals.

At-home blood sampling for 5P medicine

Longitudinal blood sampling using minimally invasive methods like Mitra tips or dried blood spots supports all five pillars of 5P medicine (5P medicine). It can be used as a **preventive** measure by monitoring proven risk parameters and starting interventions early. The possibility to sample at home is a milestone for **participatory** medicine. This also provides the possibility to create large, **population-based** data bases to identify new diagnostic or predictive markers on a larger scale. Such **predictive** markers can then be used to assess early markers for disease development or progression, or to predict drug response. Lastly, **precise** treatments or interventions can be defined by monitoring deviations from an individual's normal levels of metabolic markers.

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