Usense internal report #1

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Design and validation of a point-of-care device for the detection of multiple urinary biomarkers

Introduction

The usability of the urinary matrix for screening, diagnosis and monitoring of pathologies

Urine analysis plays a pivotal role in healthcare and clinical settings, providing valuable insights into an individual's health status, disease progression, and treatment efficacy. Often overshadowed by blood as a more esteemed and crucial fluid in emergency situations, urine holds immense value as an incredibly rich matrix abundant in biologically significant markers. Emerging evidence has revealed that urine can harbor an impressive range of detectable metabolites, around 3,000, including inorganic ions, organic metabolites, hormones, and disease markers (3). Physiologically, urine is produced by the kidneys and serves two major functions: excretion of solute waste and regulation of fluid volumes, generating a specific imprint representative of the organism's physiology and metabolism. Urine volume can vary widely, from approximately 500 mL to several liters per day (4), while the presence of biomarkers is influenced by energy and nutrient intake, body and cellular metabolism, environmental factors, and the presence of pathology.

The comprehensive examination of urine offers a non-invasive and easily obtainable means to assess various physiological and metabolic parameters. As mentioned earlier, urine contains a vast array of detectable metabolites, including hormones, organic compounds, inorganic ions, and disease-specific markers (5).
This wealth of data in urine holds immense importance in several aspects of medical practice. Firstly, urinalysis aids in the early detection of diseases and conditions. Due to its non-invasive nature and the potential presence of early disease markers, urine analysis can enable the identification of pathologies, such as kidney diseases, long before they manifest observable symptoms (3). This early detection allows for timely interventions, significantly improving patient outcomes and potentially saving lives.

Furthermore, urine analysis provides valuable information for monitoring the progression of diseases and evaluating treatment effectiveness. By regularly examining specific biomarkers in urine, healthcare professionals can assess the response to therapies, make informed adjustments to treatment plans, and detect any disease relapse or progression (6).

Urinalysis serves as a vital tool in providing essential data for diagnosing various renal and extrarenal disorders (7). These tests examine several aspects:

- Physical characteristics of urine, such as clarity, color, and specific gravity. Normal fresh urine is clear, pale yellow, with a density ranging from 1.005 to 1.030. However, pathological conditions, such as urinary tract infections, can alter these characteristics, with the presence of bacteria (cloudiness), erythrocytes (red color), hemoglobin (reddish-brown color), or bilirubin (dark yellow to brown), which may indicate serious medical conditions such as bladder infections, pyelonephritis, kidney stones, or kidney diseases.
- Chemical examination is vital for assessing both normal and pathological compounds in urine, including minerals, fluid balance, markers of renal function, metabolism, prediabetes, liver diseases, brain diseases, and infections. Unlike blood, urine can reflect multiple changes occurring in the body.
- Another significant advantage of urine analysis is the ease and cost-effectiveness of sample collection.

Routine urine analyses can be used to rapidly and easily monitor the health status of patients and, in some cases, detect pathologies at an early stage (such as prediabetes, kidney stones, cancer). The utilization of urine in biological analysis offers invaluable insights into an individual's health and disease state, providing a non-invasive and readily available sample for comprehensive monitoring and early detection of various conditions. Its rich composition and ease of collection make urine an invaluable resource in understanding human physiology and improving diagnostic approaches (8) (9).
As an example biological data from urinalysis is a key element in the:

- Detection of urinary tract infections, with a faster screening allowing faster antibiotic treatment (10) (11).
- In the management of lithiasic disease and relapse with a key biological monitoring of the urines (12).
- In the screening of complex genetic diseases, such as porphyrias, producing specific biomarkers that will be detected in urine, allowing a reduced diagnosis wandering and a quicker time-to-treatment (13).
- In the follow-up of nutritional and hydration status to monitor overall health status (4).

Utilization of spectroscopy and electroanalytical methods for the characterization of biological fluids

Spectrometry and electroanalytical methods have played a crucial role in the field of biology for several decades, facilitating the qualitative and quantitative analysis of biological samples. These techniques have been widely employed in various scientific disciplines, including biochemistry, molecular biology, pharmacology, and clinical diagnostics (14) (15).

Spectrometry, with its ability to measure the interaction of molecules with light, has been extensively utilized to explore the intricate molecular composition of biological systems. It has proven instrumental in identifying and characterizing individual components within complex biological matrices such as proteins, nucleic acids, metabolites, and other biomolecules. The utilization of spectrometry in biological liquids is an emerging approach referred to as "liquid biopsy," which is increasingly referenced in the literature (16).

By measuring the absorption or emission of light at different wavelengths, spectrometry allows scientists to gain insights into the structure, concentration, and dynamics of these molecules. This information is invaluable for understanding their roles in biological processes, disease mechanisms, and drug interactions (14).

In parallel, electroanalytical methods have provided invaluable tools for studying the electrical properties of biological samples. By measuring electrical signals and conductive properties, electroanalytical techniques enable the determination of ions, charged molecules, and their concentrations in biological fluids. This information is crucial for assessing electrolyte balance, detecting metabolic abnormalities, and monitoring the physiological and pathological conditions of an organism. Furthermore, these methods have been extensively employed in clinical settings for the analysis of urine, which serves as a valuable source of diagnostic information due to its composition and accessibility (15).

The integration of spectrometry and electroanalytical methods offers a comprehensive approach to characterize biological fluids. By combining these techniques, we can obtain a wealth of information regarding the chemical, molecular, and electrical aspects of biological samples. This integrated approach enables a more holistic understanding of the complex interactions and processes occurring within living organisms, paving the way for advancements in diagnostics, disease monitoring, and personalized medicine.

With recent advancements in instrumentation, data analysis, and artificial intelligence, the application of spectrometry and electroanalytical methods has become even more powerful. These technologies offer enhanced sensitivity, resolution, and automation, enabling healthcare professionals to go deeper into the complexities of biological systems. The integration of these techniques with computational approaches and machine learning algorithms holds tremendous potential for extracting valuable insights from complex biological data, facilitating early disease detection, personalized treatment strategies, and improved patient outcomes.

Utilization of machine learning in spectrometry and electroanalytical methods

Association of optical technology with machine learning has demonstrated success in predicting biomarker concentrations in blood (17) or urine (18) (19) (20) with significant results, however it is essential to consider the context in which these predictions are made. Many studies in the literature have relied on relatively small datasets (20), which may limit the generalizability and robustness of the models. These small datasets often consist of a few hundred samples, which can pose challenges in achieving optimal model performance and reliability. To address the limitations posed by small datasets, researchers have employed techniques such as partial least squares regression (PLS) and specific pre-processing methods. These approaches aim to enhance the performance of machine learning models by extracting relevant features and reducing noise in the data. However, despite these efforts, the performance of traditional machine learning algorithms may still be constrained by the limited dataset size.
Recently, there has been growing interest in exploring the potential of deep learning methods, such as convolutional neural networks (21) and Transformers (22), in biomarker prediction. Deep learning architectures have shown remarkable success in various domains by effectively

capturing complex patterns and relationships in large datasets. However, their application to biomarker prediction, particularly in the context of spectra analysis in the urinary matrix, is still in its early stages. (23)

By leveraging larger and more diverse datasets, deep learning techniques have the potential to unlock new insights and improve the accuracy of biomarker predictions. The integration of machine learning and deep learning in biomarker prediction holds great promise for advancing personalized medicine, accelerating disease diagnosis, and improving patient outcomes. The continued exploration of these methodologies, along with the accumulation of larger and more diverse datasets, will propel the field of biomarker analysis and pave the way for more accurate and clinically relevant predictions in the future.

Description of the the point-of-care device

Description of the hardware and technologies

Our JIMINI medical device represents an innovative breakthrough in the field of urinalysis. The device utilizes a computer-implemented method for measuring biomarkers in urine samples, offering a rapid and cost-effective solution for assessing various health parameters.
The hardware incorporates:

- State-of-the-art optical spectrometers and fluorimeters that acquire high-resolution optical spectra of urine samples over a broad range of wavelengths (ranging from infrared to ultraviolet spectrum);
- Electroanalysis measurement tools that allow the acquisition of electro-analytical data with values ranging from 0 Hz to 1 Hz.

These technologies (**Figure 1**) are embedded in a small and portable device as displayed in **Figure 2**.

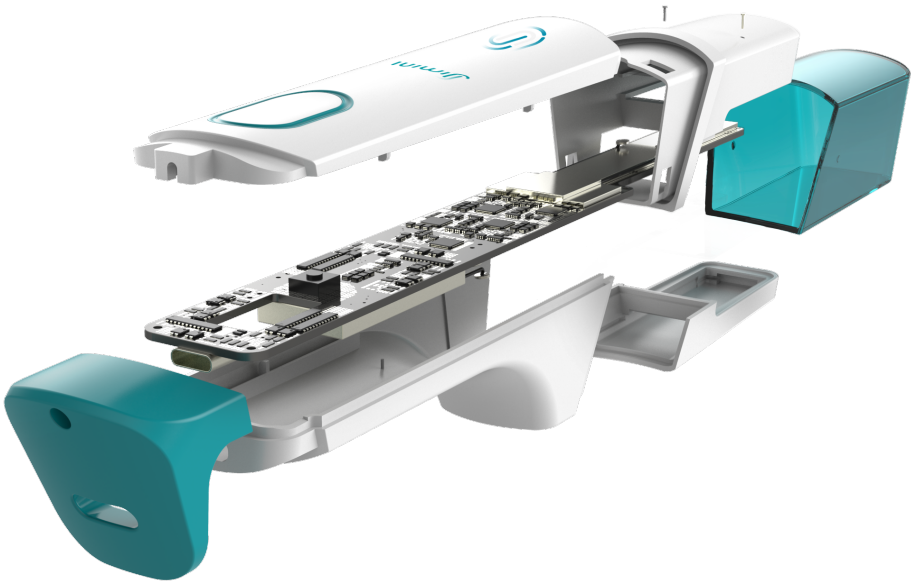

Figure 1: View of the Jimini's technologies

Figure 2: View of the Jimini medical device

The data collected by JIMINI are then processed using advanced algorithms and biomarker models trained on reference data to estimate the values of specific biomarkers. The device provides accurate and real-time results, enabling healthcare professionals to quickly assess the health status of patients. Its portable and user-friendly design allows for point-of-care testing, making it suitable for various healthcare settings. By streamlining the measurement process and eliminating the need for expensive laboratory equipment, JIMINI device offers a cost-effective and efficient alternative to traditional methods. With its potential to enhance early diagnosis and facilitate timely interventions, JIMINI medical device holds significant promise in improving patient outcomes and revolutionizing urinalysis practices.

Description of the biomarker estimation models

Providing that the number of samples is still limited for more complex methods, we opted for a combination of signal processing and plain statistical modeling.

Total porphyrin estimation

In the case of the total porphyrin estimation, we expect the molecule to fluoresce at a specific frequency, provided a photic stimulation with a wavelength around 405nm. The current model uses the Beer-Lambert law, under which, for a specific wavelength, in an homogenous matrix, the logarithm of the electromagnetic radiation attenuation is linearly related to the compound concentration.

For this model, the absorption spectrum is first normalized by its value at the stimulation frequency, followed by a double derivative Savitzky-Golay filter. The value at 620 nm is then extracted from the spectrum.

Finally, this estimation of the attenuation is fit to the gold standard porphyrin concentration using a k-fold cross validated linear regression.

Porphobilinogen estimation

To estimate the porphobilinogen concentration, we rely on the spectral difference observed in a urine sample before and after a heating procedure. This model follows a procedure similar to the total porphyrin estimation, except that the model is applied on the difference between the two spectra, and the frequency at which we observed the attenuation (490 nm).

Our approach

We have developed a medical device that takes a comprehensive and innovative approach to urine analysis, combining advanced technological components with machine learning algorithms. With its ability to analyze a wide range of biomarkers relevant to major health conditions, our device empowers healthcare professionals to make informed decisions, improve patient outcomes, and potentially reduce healthcare costs.
In terms of development, we have had a 2-step approach. The current research was designed:

1. As a feasibility study to evaluate the simultaneous measurement of 9 urinary biomarker using standard optical and electro-analysis technologies
2. As a validation study to compare results obtained with JIMINI point-of-care technology to Laboratory gold-standard methods used in routine.

Methods and results

Biomarkers analyzed with the JIMINI point-of-care technology

We have performed a validation study of the performance of the JIMINI for 2 biomarkers, Total Urinary Porphyrins and Porphobilinogen (PBG).

Table 1: List of biomarker measured by the JIMINI point-of-care technology and associated Lab gold standard methods

List of biomarker	Biomarker of	Lab gold-standard methods
Porphobilinogen (PBG)	Acute Hepatic Porphyria	Liquid chromatography with mass spectrometry
Total Urinary Porphyrins	Porphyria	Spectrophotometry

Total Urinary Porphyrins

Total urinary porphyrins refer to the collective measurement of various porphyrin molecules excreted in urine. Porphyrins are organic compounds involved in the synthesis of heme.
The assessment of total urinary porphyrins provides valuable information for the diagnosis and monitoring of porphyria, a group of inherited disorders characterized by abnormal porphyrin metabolism. These disorders are caused by deficiencies in specific enzymes involved in heme production, leading to the accumulation of porphyrin precursors. (24)

Total urinary porphyrin measurement involves quantifying the concentration of various porphyrin species in urine samples. The most common porphyrins analyzed include uroporphyrin, coproporphyrin, and protoporphyrin.
Elevated levels of total urinary porphyrins can indicate:

- The presence of a porphyric disorder, as these accumulated porphyrins are excreted in the urine. Total urinary porphyrin testing is particularly useful in diagnosing specific types of porphyria, such as porphyria cutanea tarda and erythropoietic protoporphyria

(13). Additionally, total urinary porphyrin analysis can guide treatment decisions and assess the effectiveness of therapeutic interventions aimed at reducing porphyrin accumulation.

- An elevated level of porphyrins can also be symptomatic of lead or heavy metal poisoning, sometimes mimicking acute porphyrias (25) (26).
- Some links are even being explored between the presence of elevated levels of total urinary porphyrins and autistic spectrum disorders (27).

Porphobilinogen

Porphobilinogen is a chemical compound that plays a crucial role in the biosynthesis of heme, a vital component of hemoglobin and other heme-containing proteins.
It is an intermediate molecule in the porphyrin pathway, which is responsible for the production of heme. Porphobilinogen is formed through a series of enzymatic reactions in the body, involving the condensation of two molecules of 5-aminolevulinic acid (ALA). This process occurs primarily in the liver and bone marrow, where the enzymes involved in heme synthesis are predominantly expressed (28).

Abnormal levels of porphobilinogen can be indicative of certain inherited disorders known as porphyrias. These disorders are characterized by defects in the enzymes responsible for heme synthesis, leading to the accumulation of porphyrin precursors such as porphobilinogen. One specific porphyria related to porphobilinogen is Acute Hepatic Porphyria. The measurement of porphobilinogen levels in urine or blood is crucial for diagnosing and monitoring porphyrias, including Acute Hepatic Porphyria. Increased levels of porphobilinogen can indicate an acute porphyria attack (29).
Urinary porphobilinogen testing is commonly used as a diagnostic tool for acute porphyrias. A positive result indicates the presence of excess porphobilinogen, suggesting an active attack of the disease. This information is crucial for guiding treatment decisions and monitoring disease progression.

Validation study: Results obtained with the JIMINI device against Laboratory gold-standard methods.

In current clinical practice, the measurement of Total Urinary Porphyrins and Porphobilinogen in urine is generally time consuming because very few laboratories and hospitals are able to perform the measurement. In general, there is only 1 expert center per country receiving and treating all urine samples. Thus, the development of simple screening tools that can be deployed everywhere would represent a major advance in the democratization of the measurement of these two biomarkers. **Figure 3** represents the results on continuous estimation of the two biomarkers of interest by JIMINI vs Laboratory gold-standard methods. Results showed a linearity vs. laboratory machines and a high sensitivity and specificity from a threshold of 350nMol for porphyrins and 50µMol for PBG. With the current algorithm, we obtain a mean absolute error of 140.8nMol for porphyrin estimation, and 23.2uMol for porphobilinogen estimation respectively. Those results are promising, however, the estimation is hindered for high concentrations or dense matrices. We are currently working on normalization mechanisms to increase performance for those samples.

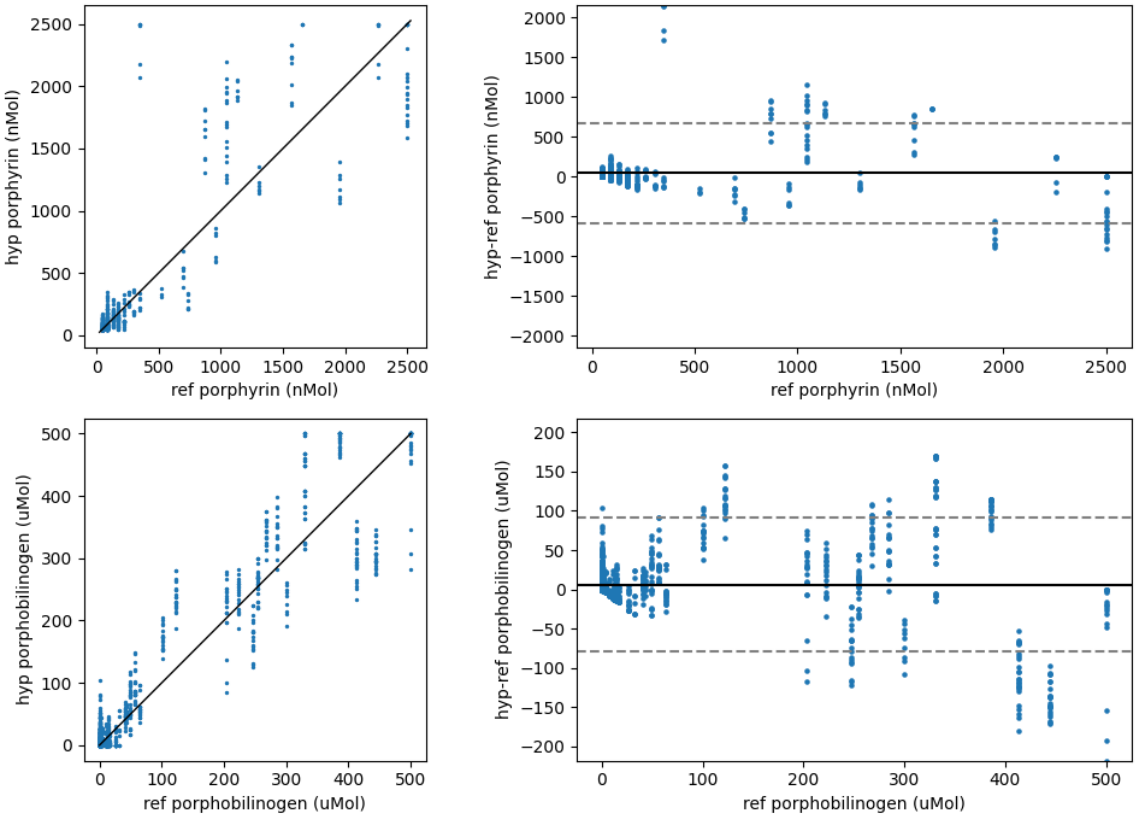

Figure 3: Scatter plot of estimation vs reference (left) and bland-altman plot (right) for the porphyrin (top) and porphobilinogen (bottom) estimation.

Biomarkers measurable with optical and electroanalysis technologies

In order to increase the number of analytes measured with the Jimini, we have performed a feasibility study to evaluate accessibility of 9 other urinary biomarkers using optical and electroanalysis technologies. This feasibility study represented a first step before biomarker integration into JIMINI device and the launch of a validation study of method comparison.

Table 2: List of urinary biomarker of interest and associated Lab gold standard methods

Indication	**List of biomarker**	**Biomarker of**	**Lab gold-standard methods**
Nutrition	Urea	Protein Intake	Enzymatic absorption spectrophotometry
	Urine Specific Gravity (USG)	Hydration	Reflectometry
	Osmolality	Hydration	Freezing Point Osmometer
	Sodium	Sodium intake	Potentiometry

	Chlorine	Kidney function	Potentiometry
Infection	Nitrites	Urinary Tract Infection (Gram -)	Urine dipstick
	Leucocytes	Infection	Flow Cytometry
	Hematia	Hematuria	Flow Cytometry
	Bacteria	Urinary Tract Infection	Bacteria Culture Test

Many urinary markers are of major interest in the detection or monitoring of pathologies. Among the most important medical indications, we can find urinary infections. Urinary tract infection (UTI) is a very common bacterial infection in all age groups, associated with significant morbidity. Establishing the severity and extent of infection (i.e. lower UTI vs. pyelonephritis) is clinically important to determine further management. Urinary biological markers may have the potential to diagnose UTI. Urinary Tract Infection is biologically defined as the presence of bacteria in the urinary tract. Thus, direct measurement of bacteria or other conventional markers, in addition to clinical evaluation, may indicate the presence of UTI. As an example, infected urine may contain considerable amounts of nitrite as a result of bacterial nitrate reductase activity, and detection of nitrite in urine is routinely used in the diagnosis of bacterial cystitis. Similarly, a high number of leukocytes in the urine indicates inflammation or infection along the urinary tract, often in the bladder or kidney. And bloody urine may also indicate a problem in any part of the urinary tract.

The second indication of interest is the monitoring of nutrition markers. Indeed, the monitoring of these biomarkers can be useful in the evaluation of the risk of development of pathologies (for example, sodium in the context of arterial hypertension) but also in the daily monitoring of sick patients (for example, hydration for patients suffering from renal diseases). Urine is a biological fluid, not subject to homeostasis, that represents an ideal candidate for monitoring protein consumption (urea), hydration (osmolality, USG), sodium consumption (sodium) or renal health (chlorine)

Feasibility study: Results obtained with optical technologies against Laboratory gold-standard methods

A feasibility study was carried out to assess the accessibility of measuring several urinary biomarkers in parallel using optical technologies. Indeed, even if the optical spectrum of biological samples contains a wealth of information, it is necessary to be able to extract, analyze and use it in a clinical context with a precision level that is useful to the practitioner.

The present study compared the results obtained on the measurement of 5 nutritional biomarkers (urea, USG, osmolality, sodium and chlorine) and 4 infection biomarkers (nitrites, leucocytes, hematia, bacteria) by spectrophotometry vs. gold standard laboratory technique.

To this end, 4,000 urine samples were collected and tested on spectrophotometers and standard automated assay systems. Overall, the results show that the 9 biomarkers studied have an optical fingerprint that can be analyzed spectrophotometrically.

Table 3: Results obtained with optical reference technology on biomarker of nutrition

	Urinary biomarkers				
	Urea	USG	Osmolality	Sodium	Chlore
Coefficient of correlation *vs* Lab Results measured with gold standard measure (r2)	0.99	0.95	0.81	0.71	0.88
Mean Absolute Error	0.63 mmol/L	0.001	168 mOsm/L	20.7 mmol/L	14.1 mmol/L

For nutrition, the results obtained for urea and urinary density (USG), respectively markers of protein consumption and hydration, showed results comparable to those obtained on standard automated laboratory systems, with reduced mean absolute errors of 0.63 mmol/L and 0.001 respectively. These results could be of great interest if they were reproduced with the JIMINI. First, because there is no existing technology providing instantaneous measurement of urinary urea. Secondly, because it would enable us to offer more accurate results than the urine dipstick currently used routinely for the measurement of USG.
The results obtained from continuous optical measurement of sodium, chlorine and osmolality are still insufficient for routine clinical use. However, proposing categorical measurement of concentration ranges could significantly improve clinical interest, and would be useful in daily practice to facilitate patient referral. As an example, the cut-off used in clinical research for urinary osmolality is 500 mOsm/L. This target value, easily achievable with optical technologies, could be used to assess the risk of recurrence of kidney stones or other renal pathologies. We are currently in the process of defining optimal thresholds for each of these biomarkers.

Table 4: Results obtained with optical reference technology on biomarker of infection

	Nitrites	Leucocytes	Haematia	Bacteria
Sensitivity	0.90	0.70	0.69	0.78
Specificity	0.88	0.75	0.74	0.88
AUC	0.94	0.79	0.79	0.88

For infection, the results are presented directly in categorical form, as the measurement scales are particularly wide (from <1000 cells/mL and up to 10^6 cells/mL). Moreover, the most important indicator remains the presence or absence of these biomarkers. For the detection of nitrites or bacteria, the results showed a precision level similar to the urine dipstick, already used in current practice. These 2 biomarkers are the most important for diagnosing urinary tract infection, based on the total quantity of bacteria. The presence of nitrite indicates the presence of gram-negative bacteria.

The results obtained for detecting the presence of leukocytes or red blood cells are promising, even if they still need to be improved, particularly for low values. On these two last markers, the results obtained are very similar to those of the urine dipstick.

All the biomarkers tested showed an optical signature enabling their concentration and/or presence/absence to be estimated in a urine sample. The next step will therefore be to validate the measurement of these markers using a miniaturized medical device such as the JIMINI, to offer a unique solution enabling precise parallel measurement of multiple urinary biomarkers. For integration into the JIMINI, we'll also be relying on a combination of several technologies, which we haven't been able to test here.

Discussion and conclusion

The use of urine in biological analysis offers invaluable insights into an individual's health and disease state, providing a non-invasive and readily available sample for comprehensive monitoring and early detection of various conditions. Yet, due to limited resources and absence of miniaturized point-of-care technologies available, some analyses are often restricted to a few central hospitals and health centers. In the present project, we iteratively developed a portable, miniaturized medical device and optimized it to analyze, in parallel, multiple urine parameters in a few seconds. We integrated custom optical and electroanalysis technologies associated with machine learning algorithms to establish a biological measure. To date, a first set of biomarkers were tested, integrated and validated for Acute Hepatic Porphyria detection. In parallel, a set of 5 biomarkers on nutrition and 4 biomarkers on infection were tested with optical reference technologies (spectrophotometers) to evaluate accessibility of these measures with the JIMINI. The results obtained showed that the 9 biomarkers have an optical signature that can be detected by the Jimini device. A validation study is therefore underway to integrate their measurement into the device.

The device described in this paper brings a pioneering and innovative approach to urinalysis. By combining the convenience of urine dipsticks with the precision of laboratory automation, we have created a breakthrough device that brings biology directly into the hands of practitioners and at the bedside of patients. This cutting-edge technology has the potential to transform the way healthcare is delivered and improve patient outcomes on a global scale. One of the key advantages of our device is its ability to bridge the gap between biological data and clinical decisions. By bringing the power of biology to areas with limited resources, including third-world countries, we aim to provide equal access to high-quality diagnostics and enable early detection of diseases that were previously challenging to diagnose accurately. This breakthrough is a significant step towards achieving equitable healthcare worldwide.

Our platform device is designed to provide real-time, quantitative results for multiple biomarkers in urine, it empowers healthcare professionals to perform comprehensive health assessments, track treatment effectiveness, and monitor disease progression over time. This proactive approach to healthcare management can lead to early intervention, personalized treatment plans, and improved overall patient well-being.

This device is integrated in a 360° solution environment to combine innovation of the JIMINI hardware with the power of our artificial intelligence algorithms. In order to give out instant and precise results.

Figure 4: The JIMINI product environment

The benefits of the parallel measurement of multiple urine biomarker would be multiple:
1°) Urinary tract infection tests are among the most common, and require a rapid response in order to manage patients as quickly as possible. Simultaneous measurement of nitrites, bacteria, red blood cells and leukocytes, with results superior to those of the urine dipstick, could enable better patient orientation. Moreover, no dipstick, to date, allows direct measurement of bacteria.
2°) Routine use of the presence of infection could make it possible to systematize the measurement of AHP biomarkers, which are too infrequently tested. This would make it possible to calculate more accurately the prevalence of this still poorly understood disease and, perhaps, to realize that, as with other long-ignored pathologies (e.g. endometriosis), the number of carrier patients is higher than previously imagined.
3°) Integrating the measurement of nutritional markers with diagnostic markers means that the devices can be deployed in patients' homes in the future, to enable regular monitoring and personalized nutritional advice.

This approach enhances diagnostic accuracy and provides valuable insights into various health conditions, including genetic disease, urinary tract health, kidney & liver function, and metabolic disorders. The device's versatility and broad range of applications make it an valuable tool for a quick, user-friendly, and routine use.

In conclusion, our device aims at breaking barriers to improve accessibility of health for early diagnosis and empowering healthcare professionals to deliver better care through urinalysis. The current system is a first-generation platform that we intend to improve. Possible and planned upgrades and enhancements include addition of new biomarker detection, implementing higher optical resolutions sensors and combining multiple sensors for biomarker estimation. These changes should improve detection accuracies and precisions.

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