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Precision nutrition — review of methods for point-of-care assessment of nutritional status

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Precision nutrition encompasses prevention and treatment strategies for optimizing health that consider individual variability in diet, lifestyle, environment and genes by accurately determining an individual's nutritional status. This is particularly important as malnutrition now affects a third of the global population, with most of those affected or their care providers having limited means of determining their nutritional status. Similarly, program implementers often have no way of determining the impact or success of their interventions, thus hindering their scale-up. Exciting new developments in the area of point-of-care diagnostics promise to provide improved access to nutritional status assessment, as a first step towards enabling precision nutrition and tailored interventions at both the individual and community levels. In this review, we focus on the current advances in developing portable diagnostics for assessment of nutritional status at point-of-care, along with the numerous design challenges in this process and potential solutions.

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Introduction

As per the 2016 Global Nutrition report [1], one in three people is malnourished in one form or another and monitoring nutritional status is becoming increasingly more vital both at the population and the individual level. In resource-rich settings, with increasing awareness of the importance of nutrition, dietary fads and supplements often become popular with unknown efficacy. In resource-poor settings on the other hand, many programmatic approaches such as food fortification [2], micronutrient supplementation [3] and dietary diversification [4] are being deployed to overcome nutritional deficiencies, sometimes with limited knowledge of their effectiveness. The lack of accurate methods for evaluating nutrition status at the point-of-care hampers our ability to enable precision nutrition and target interventions to those who need or respond to them, thereby limiting major improvements in public health. With advances in technology, it is now becoming possible to meet some of these diagnostic challenges to revolutionize health care at point-of-care and this is the focus of this review.

Precision nutrition

The recommended approaches [5] for nutritional screening include anthropometric indices based on body measurements, biochemical indicators (biomarkers), examination of clinical symptoms, and dietary assessment. Technology is changing our capacity to assess each of these; however, the focus of this review is on measurement of biomarkers, which often enables early diagnosis of deficiency or risk of certain diseases and provides potential opportunities for relatively simple interventions before the emergence of clinical symptoms. The Biomarkers of Nutrition for Development (BOND) program [6–8] is working to identify and harmonize the decision making process about the best uses of biomarkers in specific scenarios. A summary of various micronutrients, corresponding biomarkers and their physiological levels for determining deficiency/insufficiency, and health consequences have been summarized elsewhere [9••]. The ability to assess the health impacts of nutritional status depends on the availability of accurate and reliable biomarkers that truly reflect nutrient exposure, status and effect [10]. Precisely measuring nutritional biomarkers [11,12•,13] in biological samples can be useful to predict future events, identify individuals likely to benefit from an intervention, and help determine the efficacy and effectiveness of a nutrition program.

Conventional diagnostics for nutritional biomarkers

Numerous commercially available analyzers can be applied for quantification of nutritional biomarkers. Some examples include ADVIA Centaur XP Immunoassay System (Siemens Healthcare GmbH), IMMULITE 2000 XPi Immunoassay System (Siemens Healthcare

GmbH), ACCESS 2 Immunoassay System (Beckman Coulter, Inc.). But these analyzers are not suitable for point-of-care applications, are expensive, not portable, require cold chain, and require skilled technicians to operate them.

Microfluidics/lab-on-a-chip for nutritional biomarkers

Microfluidics-based [14] lab-on-a-chip (LOC) platforms [15,16•] handle very small volumes of test samples and can be designed to perform diagnosis and real-time monitoring of nutritional biomarkers at the point-of-care. Numerous microfluidics based analytical techniques for quantification of nutritional biomarkers have been reported in recent years, and interested readers are encouraged to refer to a summary [9••] elsewhere. LOC platforms can be designed to be disposable and also handle a wide range of clinical samples that includes blood, saliva, and urine. LOC devices can be made cost-effective by mass production, quality control, and miniaturization [17••,18]. Table 1 lists a few examples of LOC platforms applied to detection of nutritional biomarkers. Table 2 lists some of the diagnostics related considerations for nutritional biomarkers in terms of selection of appropriate biomarkers [19], type of biological samples and their storage/handling.

Real-time nutritional screening in traditional lab settings is expensive, is time-consuming and can be even more challenging with issues such as fluctuating power supply in economically poor settings with the highest burden of malnutrition. Most of these disadvantages can be overcome by applying LOC technology to develop cost-effective, portable, rapid, high-sensitivity point-of-care testing (POCT) [29–32] for nutritional biomarkers. In diagnostics, time is of the essence and POCT can provide results much faster, typically less than an hour, compared to the traditional laboratory approach. However, there is a trade-off between speed, range of parameters tested for, and portability. It is desirable for POCT to be suitable for use by minimally trained operators and reducing user error is critical to achieve the most benefit.

Table 1

Examples of lab-on-a-chip (LOC) platforms applied in detection of nutritional biomarkers

Nutritional Biomarker	Sample	Sensor	Sensitivity	Specificity	Characteristics	References
Retinol-binding protein (RBP)	Artificial serum	Impedimetric	n/a	n/a	Impedance spectroscopy to detect the binding between RBP and anti-RBP on an indium tin oxide surface.	[20]
RBP	Serum	Enzyme immunoassay	n/a	n/a	A competitive assay uses RBP adsorbed to microtest strip wells to compete with RBP in serum.	[21]
RBP4	Serum	ssDNA aptamer-based Surface plasmon resonance (SPR)	n/a	n/a	RBP4-specific aptamer immobilized on a gold chip for a label-free RBP4 detection using SPR.	[22]
Ferritin	Serum ferritin controls	Photonic crystal (PC) optical biosensor	n/a	n/a	Iron-oxide nanoparticles (IONPs) combined with a photonic crystal (PC) optical biosensor.	[23]
25-OH vitamin D (25OH-D)	Standard 25OHD solutions	SPR and electrochemical	SPR — 4.8 m ml/μg DPV — 0.020 μA ml/ng	n/a	Comparison of SPR and electrochemical methods for 25OHD detection.	[24]
Soluble transferrin receptor (sTfR)	Standard sTfR solutions	Photonic crystal (PC) optical biosensor	n/a	n/a	Iron-oxide nanoparticles (IONPs) combined with a photonic crystal (PC) optical biosensor.	[25]
Soluble transferrin receptor (sTfR)	Whole blood	Immunofluorometric assay	n/a	n/a	Immunoassay for sTfR based on the all-in-one dry-reagent assay concept and time-resolved fluorescence detection.	[26]
Ferritin, RBP and C-reactive protein (CRP)	Whole blood	Optoelectronics/lateral flow assay	Ferritin — 80.6% RBP — 75.0% CRP — 100%	Ferritin — 84.1% RBP — 62.3% CRP — 80.7%	Electronics enabled microfluidic paper-based analytical device (EE-μPAD).	[27•]
Vitamin B12	Whole blood	Lateral flow assay	87%	100%	Lateral flow assay coupled to a mobile platform.	[28•]

Table 2

Nutritional biomarker considerations for developing new diagnostic platforms

- Type of specimen: Selecting the most appropriate specimen type (such as plasma, serum, urine, saliva) for the biomarker of interest that accurately and reliably reflects the nutrient exposure, status and effect is critical. Specimen type also affects the sample preprocessing steps (if required) of the diagnostic technique and should be taken into consideration during the design phase.
- Specimen collection/storage: Recommended specimen collection method (such as finger prick, venipuncture, midstream urine) and sample volume considerations will have to be compatible with the diagnostic technique. Integrity of the storage container (leaks, exposure to light and oxygen), optimal storage temperatures and specimen stability under extreme weather are important, especially in field conditions when specimens are to be collected and stored for future testing.
- Effect of infection/inflammation: The impact of disease on nutritional biomarkers has been long documented. Owing to the possible effects of disease on biomarker levels, researchers should determine whether inflammation markers such as C-reactive protein (CRP) should be measured simultaneously to allow better interpretation of the nutritional biomarker data.
- Temporal relation with dietary intake: Biomarkers can be classified as short term (representing dietary intake or exposure over past hours/days), medium-term (over weeks/months) and long-term markers (over months/years). Knowledge of nutrient intake, as well as acute/chronic exposure should be considered to decide the timing and frequency at which the diagnostic test is performed.
- Gold standard methods/reference values: Diagnostics performance should be compared with established gold standard methods for the quantification of the nutritional biomarker. Some of the performance metrics of interest include sensitivity/specificity, working range within established physiological reference ranges of the biomarker within the population of study.

Additional advantages include the fact that an investment in diagnostics followed by subsequent tailored interventions (if required) can be more cost-effective than long-term universal treatment [33]. LOC platforms can also be a valuable tool for collecting epidemiological surveillance [34] data and can also be really useful for expanding the reach of conventional labs in resource-limited settings. However, there are numerous challenges that have to be overcome for these diagnostic platforms to be adapted to such settings. Table 3 lists some of the design challenges in resource-limited settings for LOC platforms for detection of nutritional biomarkers.

Data management

Most of the POCT devices require external readers/accessories and do not have the data management capabilities to transfer the data to a local server that can be accessed by the physician. Many POCT devices have instrument-specific data management systems, but the challenge [35] lies in integrating them with the laboratory information system (LIS) and hospital information system (HIS). The true success of LOC platforms relies on making the test results available for making clinical decisions. One of the approaches to overcome this limitation is to couple a smartphone with the LOC platforms. One of the main factors for meeting information needs of POCT implementations is connectivity, which is the ability to transfer POCT data including patient data into the LIS/HIS [36]. Connectivity should be bidirectional and provide access to complete laboratory information with full data handling capability. The American Association for Clinical Chemistry has been a driving force behind the establishment of a connectivity industry consortium [37]. The connectivity consortium is represented from both industry and health care providers and will be mandated to develop industry-wide POCT connectivity

Table 3

Design challenges and potential solutions in resource-limited settings

Challenges in resource-limited setting	LOC platform design adaptation
Limited or no power supply	Ideally, require no external power supply. Device should require low operating power and be able to function for the required operation time by utilizing battery power.
No external supporting instrumentation	Device should be self-sufficient without the need for other external instrumentation.
Lack of refrigeration/temperature controlled environment/harsh environments	Device should be able to withstand and function under a wide range of temperatures (up to 40°C) without affecting its functionality. The protocol to handle sample storage and transportation should not rely on refrigeration. Sensitivity of test sample to light, oxygen or temperature has to be considered to avoid deterioration of test sample, and also possible measurement errors resulting from these conditions should be determined.
Lack of skilled staff	Device should be user-friendly and provide results that are easy to interpret.
Unavailability of basic lab supplies and reagents	Design should incorporate all the required test reagents and supplies within the device.
Biosafety and waste management	Device design should take into consideration the safe containment and transportation of bio-waste to nearest waste management facility or design sustainable means of sterilizing the biohazardous waste.
Affordability	The cost of the POC platform, and any additional equipment required has to be low. The cost of the disposables has to be kept very low by suitably selecting the fabrication material and the fabrication process.

standards. The focus is on 'open' standards, which will provide the ability to mix and match instruments from various suppliers and enable POCT results to be easily integrated into the LIS/HIS. The end goal is to establish automated data acquisition techniques by applying POCT coupled with telecommunications links to provide integrated and electronic health records.

Your smartphone will see you now

The major advantage of a smartphone-coupled diagnostics [38–41] is that all the required computing power for data processing, hardware such as camera, display for test results, a power source, and most of the auxiliary support required for diagnostics are already available within a smartphone owned by the end users worldwide. In 2015, an estimated 64% of American adults owned a smartphone of some kind, an increase in number from just 35% in the spring of 2011. The central challenge in exploiting this ubiquitous resource for diagnostics is to craft smart interfaces between the diagnostic components and smartphones [42]. Initiatives such as the Phonebloks [43] and Project Ara [44] that are focused on developing modular smartphones that can be assembled by combining individual plug-n-play hardware modules will only further complement LOC diagnostics in the future. The existing familiarity of these smartphones can make them easily acceptable among new users without much hesitation, reduce the training requirements, and minimize user interpretation errors during testing. Recently, numerous diagnostics coupled with smartphones for various applications such as dermatology [45], clinical microscopy [46], assessment of vitamin D status [47], food allergen testing [48] and ovarian cancer biomarker detection [49] have been demonstrated. Besides providing cost–benefits, this also allows the developers to focus on developing the assays, disposables, accessories and the software apps, without having to engineer the entire standalone hardware. The use of smartphone-coupled monitoring of nutritional status can provide a rapid and personalized awareness of deficiencies through direct physiological feedback. Many nutritional deficiencies can be overcome by proper changes in diet, intake of supplements or behavior modification. The availability of at-home diagnostics can provide an instant feedback on the success of these interventions since physiological ranges of most of the biomarkers for nutritional status have been well established. Also, the test results can be made more specific by providing quantitative results on biomarkers, instead of mere low/good/high type of qualitative feedback. In resource-limited settings, these smartphone-coupled diagnostics can enable POCT with minimal instrumentation and increased portability. Often patients come from far away locations to a central primary health care center and may not be able to visit frequently or sometimes not return for a follow-up test. In such cases, LOC platform that can be used at home directly by the patients may be more suitable.

Outlook

Malnutrition is a major worldwide public health concern and assessment of nutritional status through precise measurement of physiologically relevant biomarkers is a vital tool to make appropriate interventions at an early stage, sometimes even before the symptoms become visible in individuals. Initiatives to address the need for cost-effective and point-of-care measurement of nutritional biomarkers in resource-limited settings are still in their early stages. There are several design challenges in developing portable diagnostics for resource-limited settings and the ever-burgeoning field of microfluidics has the potential to meet some of these challenges. For example, technologies such as lateral flow immunoassays continue to evolve from just providing binary test results to giving quantitative output when coupled with new reader technologies. Coupling these advances with smartphones and with advanced data-management technology can potentially transform individual health behavior and may make people more proactive about their health by providing them with necessary tools and information to maintain a healthy life style. Even though numerous benefits are possible, addressing ethical issues regarding privacy and data security will also become important.

At the population level, such LOC devices can be a critical tool for international nutritional surveillance programs and monitoring of intervention programs. The WHO has estimated that there is global shortage [50] of approximately 4.3 million doctors and nurses, which makes telemedicine and personalized POCT more crucial in regions where there is such shortage. This shortage is much worse in regions such as sub-Saharan Africa with low density of doctors and nurses, but have high disease and malnutrition burden. In summary, current point-of-care technologies can potentially bridge a major healthcare, research, monitoring, and implementation gap by making testing for nutritional status accessible to a large proportion of the global population.

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