Point-of-care Diagnostics Lead the Way to Precision Nutrition
The example of iron deficiency

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The concept of precision nutrition

In precision nutrition, personal information about individuals is collected to deliver nutritional advice that would be more suitable than generic advice. Precision nutrition can also address groups of individuals with similar key characteristics.[1–4] Precision nutrition is founded on the concept of biological variation between individuals in response to nutrition, and based on the extraction of data from multiple sources. These sources include dietary intake data, anthropometric data, personal data, genetics, metabolomics, and clinical and biochemical parameters, to name but a few.[5] Especially regarding 'omics' data – in which the output is vast, and analysis requires significant time, research and skill – it is crucial to identify new, accurate biomarkers that can be used in low-cost, rapid test systems at the point of care (PoC).[5–8] Based on individual data and/or 'omics' datasets, a machine learning algorithm learns specific patterns within the dataset and uses these patterns to make a maximum likelihood prediction about the outcome. In this setting, an internet of medical thing (IoMT) system links data sources to network resources via cloud computing.[9,10] This will enable remote monitoring and screening of health conditions anywhere and anytime, and is thus especially valuable in remote and low-resource settings.[11] An important challenge is the global uniformity of data and datasets for seamless integration into specific systems and/or exchange between systems.

> **"Precision nutrition is based on the extraction of data from multiple sources"**

Among the many available datasets that can be used to feed the machine learning systems are clinical and biochemical data. Different sources are available, such as health records from the data records of patients over time, blood samples, or other body fluids or tissue sampled for a specific diagnostic purpose. Blood parameters can be obtained invasively (venous blood sampling) or by using minimally invasive (finger prick sampling) or noninvasive methods. For example, glucose measurements are obtained either invasively or noninvasively, depending on the method or tool used.

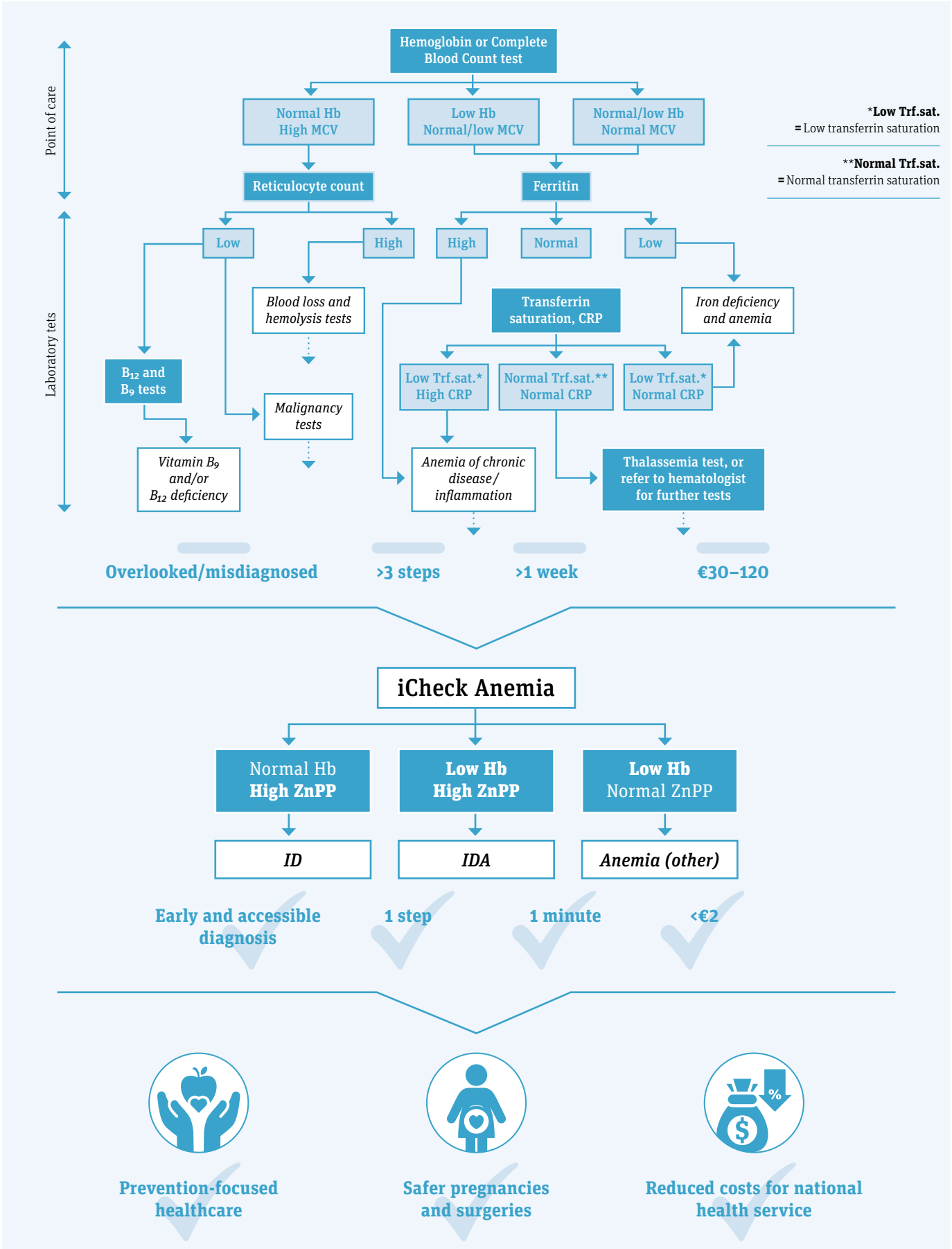
Innovative approach to iron deficiency diagnostics in precision nutrition

An analytical approach of a rapid PoC test system to diagnose iron deficiency can be used as an example to apply precision nutrition at the level of individuals and groups.

Anemia is a serious public health problem and the most prevalent chronic disease, affecting about 1.7 billion people globally.[12] Even mild cases have negative consequences on the cognitive and physical development of children, and lead to a loss of work productivity among adults.[13–17] Worldwide, productivity and cognitive losses due to anemia surpass US$45 billion annually, according to the World Bank.[18] The ethology of anemia is complex, as it includes nutrition, malaria, inflammation, heavy menstrual bleeding and genetic hemoglobin disorders such as thalassemia, sickle cell anemia or glucose-6-phosphate dehydrogenase deficiency (G6PD), to name just a few. However, approximately 50 percent of anemia cases are due to iron deficiency and termed iron deficiency anemia (IDA).[12] Risk groups include women of childbearing age, particularly pregnant women, children and the elderly population, as well as preoperative and gastrointestinal cancer patients. Anemia increases the post-surgery mortality risk and is directly responsible for up to 20 percent of maternal deaths.[19,20]

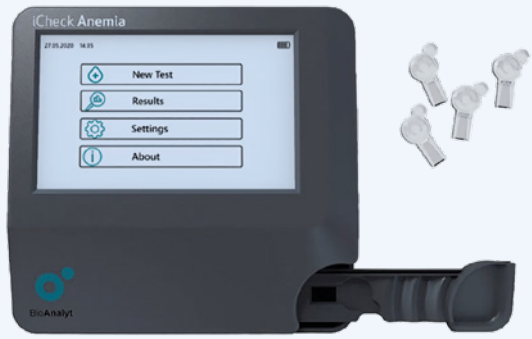
To identify the underlying causes of anemia, multiple and different invasive measurements are necessary. This is one of the reasons why many anemic patients are misdiagnosed or go undiagnosed. In a medical setup, such as a hospital or a clinic, anemia is first confirmed using a hemoglobin PoC testing device.[21,22] However, this provides no information whatsoever about what is the cause of anemia. Laboratory-bound analysis of blood is required for an accurate diagnosis and to inform as to the best treatment. However, laboratory analyses are not trivial procedures: (1) a blood draw from the vein is needed; (2) logistics services must be set up for sample transport to the lab; (3) the lab must have the equipment and trained personnel to run the complex methods; and (4) it can take several days to get the result (see **Figure 1**). These complications frequently lead to overall

FIGURE 1: Complexity of laboratory analyses compared with iCheck Anemia



CRP C-reactive protein; **Hb** hemoglobin; **ID** iron deficiency; **ID** iron deficiency anemia; **MCV** mean corpuscular volume**; ZnPP** zinc protoporphyrin

FIGURE 2: iCheck Anemia, a portable device for the point-of-care analytics of anemia and iron deficiency



omission of lab testing altogether, resulting in misdiagnosis and delays in timely treatment.

> **"To identify the underlying causes of anemia, multiple and different invasive measurements are necessary. This is one of the reasons why many anemic patients are misdiagnosed or go undiagnosed"**

Numerous analytical parameters are available for diagnosing the causes of anemia. Usually, the diagnosis of anemia indicated by reduced hemoglobin values can identify or exclude specific causes of anemia. Ferritin, transferrin saturation and zinc protoporphyrin (ZnPP) are generally valid markers of body iron stores. A decreased ferritin level below 30 µg/L and ZnPP levels above 40 µmol/mol heme indicate an absolute IDA.[23,24] Under co-conditions of an inflammation, decreased hemoglobin and iron levels are associated with a reduced transferrin saturation. Ferritin levels, however, are increased similar to acute-phase proteins such as C-reactive protein, for example.[25]

ZnPP has been widely used to characterize IDA in different target groups under different settings. Numerous studies have identified ZnPP as a biomarker of IDA, which is typically not, or only slightly, affected by co-occurring acute inflammations.[26,27] ZnPP has been shown to detect and quantify derangements of iron metabolism associated with chronic inflammatory disorders, and also helps to monitor the success of iron therapy for chronic inflammatory diseases.[24,28] Interestingly, it has also been shown that increased levels of ZnPP are associated with a negative outcome in COVID-19 patients.[29] The usability of ZnPP as a biomarker has been validated especially in low-resource settings, where IDA is frequently associated with a different cause of inflammation. It might be emphasized that ZnPP is a cost-effective and simple method to analyze biomarkers for iron deficiency if the direct measurement in a drop of capillary whole blood is used.

There are different approaches to analyze ZnPP either by blood extraction and fluorometric spectroscopy or by liquid chromatography with subsequent fluorometric detection.[30,31] The analysis of ZnPP in whole blood by front-face fluorescence has been applied for many years. The specific devices, however, are no longer commercially available.[32]

Based on the principle of front-face fluorescence, a portable device for the PoC analytics of anemia and iron deficiency has been developed by BioAnalyt, a German biotech company. This device simultaneously measures hemoglobin by absorption spectroscopy and ZnPP by front-face fluorescence (excitation at 405 nm; emission at 630 nm). The whole analytical process is performed without any sample pretreatment directly in a drop of blood taken minimally invasively from a finger prick sample. The blood is directly collected via capillary forces into a disposable microcuvette and inserted into the measuring device (see **Figure 2**). The analytical procedure takes less than a minute. Data for hemoglobin and ZnPP are comparable with standard methods. Ease of handling, low cost and robustness make this analytical approach suitable for both individual diagnostic and population-based screening.

The analytical device also reports data related to the patients, climate and geolocation, and enables the exchange of data via the cloud with network resources. It is thus an ideal integral analytical component for data generation and collection in precision nutrition or precision medicine, especially in remote and low-income settings.

Rapid developments in the field of optical and fluidic technology will also enable the integration of further analytical parameters such as erythrocyte number, size and stability to include additional information regarding inflammation and genetic hemoglobin disorders such as thalassemia. The integration of numerous diagnostic parameters into a single analytical device with a minimal requirement of blood is promising and will substantially contribute to providing more targeted nutrition advice to individuals or specific risk groups.

Disclosure

The author is also involved with BioAnalyt GmbH, which is active in this field.

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