Precision Nutrition for Low- and Middle-Income Countries: *Hype* or *Hope*?

sightandlife | Special Report

Imprint

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Why? This is the question we love to explore at *Sight and Life*.

We ask 'why' at the sight of a malnourished mother in a refugee camp in Jordan, a young boy in rural Malawi suffering from severe acute malnutrition or an adolescent girl in urban Nairobi with malaria and anemia. Keeping the 'why' at the forefront of our thought leadership approach to tackle malnutrition ensures people and impact remain at the center of our work. It was this viewpoint that inspired our exploration into the potential for precision nutrition (PN) within low- and middle-income countries (LMIC).

In addition to 'why,' we asked ourselves: Is PN a credible field of scientific research? Can we define the approach? Is PN a solution primarily for high-income countries (HIC) with limited relevance in other settings, or does it have value in resource-poor locations? Can we apply PN to target groups as well as the individual? With a deep dive into the literature and expert insight from key opinion leaders and practitioners in the field, we seek to answer these questions in this Special Report.

> **"Precision nutrition starts from the premise that each individual responds uniquely to specific foods and nutrients"**

The concept of PN calls into question the 'one-size-fits-all' approach, a common practice in public health nutrition. It starts from the premise that each individual responds uniquely to specific foods and nutrients. PN centers around the idea that one's characteristics such as genetic makeup, microbiome and metabolic response to specific nutrients or diets can inform the most effective selection of health and nutrition interventions.[1,2]

A dilemma for public health

This highly specific approach seems not only plausible and logical, but also cost-effective with regard to developing successful nutrition solutions to reduce associated disease burdens and improve health outcomes. However, this practice creates a dilemma for public health; how can we apply PN approaches to benefit more people, and which approaches provide the best opportunity for successful implementation? What resources are required to scale up PN, and is there even support and interest in bringing PN approaches to LMIC?

To date, there is no universally agreed definition of PN. Thus, there was ample scope to adapt the many existing ones and apply it to an LMIC context. In the article 'Surveying the Relevance of Precision Nutrition for Low- and Middle-Income Countries' on page 57 of this Special Report, we and others put forward a definition of PN for LMIC (see **Box 1**).

BOX 1: Definition of precision nutrition (PN) for low- and middle-income countries (LMIC) reported in this Special Report as Bedsaul et al. 2022

> "Precision nutrition is an approach that uses rigorous scientific information about an individual's characteristics and environment. This information is used to develop targeted, accessible, affordable, desirable nutrition solutions that offer measurable individualized benefit. Such targeted solutions address the most pressing nutrition challenges faced in LMIC."

We then wanted to categorize the various tools and methods that fall under PN and determine how they are employed but, more importantly, how accessible and realistic they are from an LMIC perspective. This resulted in our infographic 'Precision Nutrition Approaches' on pages 14–15.

What tools and methods are most and least widely applied globally?

As we considered the various methods and tools that fall under the PN umbrella, we identified a wide range of approaches that offer diverse levels of accessibility and specificity. The infographic on pages 14–15 delineates the various tools and methods of PN.[3] The tools and methods at the top of the pyramid are depicted in orange, and represent the less accessible, yet more specific, approaches. These include genetic and microbiota testing and counselling, as well as metabolic indicator assessments such as glucose monitors and energy intake sensors. As the pyramid becomes wider toward the bottom, the tools listed in blue represent the more widely accessible and less specific approaches. These include phenotype measurements, such as anthropometrics and nutritional indicators, as well as demographic survey information.

Importantly, both the more specific and more widely available tools play fundamental roles in the generation of a precise, targeted nutritional solution, and fall under the umbrella of PN. To reach the ultimate endpoint of PN, several of these tools likely must be implemented together within a healthcare plan for optimal outcomes.

> **"A focus on targeted groups is key when we talk about PN in resource-poor settings"**

This pyramid of PN tools and approaches is a helpful illustration of the stark reality that many methods at the top of the pyramid are not currently available for individuals in LMIC and instead are confined to HIC and certain research settings. Through our analysis of the literature, discussion with opinion leaders and review of the contributions in this report, we soon realized that a focus on targeted groups is key when we talk about PN in resource-poor settings. Not only is it more affordable to focus on stratified groups, but it can also help tackle some of the most pressing, overlapping nutritional challenges faced by vulnerable individuals, such as pregnant women with anemia or young children who are stunted.

A closer look into this Special Report

This Special Report includes three sections: the evidence base, experience from the field and resources for scale-up. We learned of several initiatives aimed at targeting specific groups more precisely from a nutritional health perspective, and we are pleased to share these examples in this report.

The evidence base for PN is growing, and new technologies are emerging that allow the identification of factors that are needed to fine-tune nutritional interventions and outcomes for individuals and specific groups in need. Ranging from point-of-care devices through certain foods or macro- and micronutrient supplements to the targeting of metabolism, genetics or microbiota, PN approaches have the power to improve diagnostics and help people achieve a healthy nutritional status. Thus, PN carries the promise to improve and save lives worldwide. While many less accessible tools such as omics- and microbiota-based approaches are still in the research stage, the evidence and applications are increasing. The reality of implementing precise nutrition-targeted solutions for more groups may transpire in the not-so-distant future, given continued research and investment. The evidence base section details the cutting-edge PN technologies, point-of-care diagnostics, important biomarkers and more.

> **"PN carries the promise to improve and save lives worldwide"**

In addition, we also include specific examples of current applications of PN in the field. As precise, affordable and machine-learning technology improves for field-friendly applications, we will likely continue to see greater desirability and application of these tools. The most crucial aspect of PN following the solid scientific evidence base, including studies in the field, is to bring these approaches and innovations to scale in order to deliver a wider, stronger impact. The final section in this report reviews the elements of an enabling environment and policies required for scale-up of PN.

We hope that through this *Sight and Life* Special Report we provide a suitable definition and build the narrative around precision nutrition for LMIC. We aim to shed light on its relevance and potential for impact in public health nutrition. Lastly, at the core of this report was our desire to answer 'Why PN?' for the most vulnerable populations. While we may not have answered this conclusively, we hope that it will stimulate further discussion and galvanize action within the scientific community and beyond to strive for impactful solutions for those who need them most.

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Glossary

Artificial intelligence

Artificial intelligence leverages computers and machines to mimic the problem-solving and decision-making capabilities of the human mind.

Source: *What is Artificial Intelligence (AI)? 7 July 2022. Internet: https://www.ibm.com/cloud/learn/what-is-artificial-intelligence (accessed 24 September 2022).*

Biomarker

Measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction. Refers to a broad subcategory of medical signs which can be measured accurately and reproducibly.

Source: *WHO International Programme on Chemical Safety – Biomarkers and Risk Assessment: Concepts and Principles. 1993. Internet: http://www.inchem.org/documents/ehc/ehc/ehc155.htm (accessed 30 September 2022); Strimbu K, Tavel JA. What are Biomarkers? Curr Opin HIV AIDS. 2010;5(6):463–6.*

Double burden of malnutrition

The double burden of malnutrition is characterized by the coexistence of undernutrition along with overweight, obesity or diet-related noncommunicable diseases (NCDs), within individuals, households and populations, and across the life course. This double burden of malnutrition can exist at the individual level (for example, obesity with deficiency of one or various vitamins and minerals, or overweight in an adult who was stunted during childhood), at the household level (when a mother may be overweight or anemic, and a child or grandparent is underweight) and at the population level (where there is a prevalence of both undernutrition and overweight in the same community, nation or region).

Source: *WHO. The double burden of malnutrition: policy brief. Geneva: WHO; 2017.*

Epigenomics

The study of all the epigenetic changes in a cell. Epigenetic changes are changes in the way genes are switched on and off without changing the actual DNA sequence. They may be caused by age and exposure to environmental factors, such as diet, exercise, drugs and chemicals. Epigenetic changes can affect a person's risk of disease and may be passed from parents to their children.

Source: *National Cancer Institute's Dictionary of Cancer Terms. Definition of epigenomics. 2 February 2011. Internet: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/epigenomics (accessed 24 September 2022).*

Fluorescence spectroscopy

Fluorescence is the light emission subsequent to absorption of ultraviolet or visible light of a fluorescent molecule or substructure, called a fluorophore. Fluorescence spectroscopy is a rapid, sensitive analytical method that can be used to monitor and characterize the molecular environments of food products, biomarkers, urinary metabolomics, nutrient deficiencies, etc.

Source: *Karoui R. Quality Control in Food Processing. In: Caballero B, Finglas PM, Toldrá F, eds. Encyclopedia of Food and Health. Academic Press; 2016:567–72; Tebani A, Bekri S. Paving the Way to Precision Nutrition Through Metabolomics. Front Nutr. 2019;6:41.*

Genomics

The study of the complete set of DNA (including all its genes) in a person or other organism. Almost every cell in a person's body contains a complete copy of the genome. The genome contains all the information needed for a person to develop and grow. Studying the genome may help researchers understand how genes interact with each other and with the environment and how certain diseases, such as cancer, diabetes and heart disease, form. This may lead to new ways to diagnose, treat and prevent disease.

Source: *National Cancer Institute's Dictionary of Cancer Terms. Definition of genomics. 2 February 2011. Internet: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/genomics (accessed 24 September 2022).*

Human microbiota and microbiome

The human microbiota consists of the 10–100 trillion symbiotic microbial cells harbored by each person, primarily bacteria in the gut; the human microbiome consists of the genes these cells harbor.

Source: *Ursell LK, Metcalf JL, Parfrey LW, Knight R. Defining the Human Microbiome. Nutr Rev. 2012;70(Suppl 1):S38–S44.*

Liquid chromatography

This technique has been used for most perfluorinated compounds (PFC) separations and has been applied to analyze per- and polyfluoroalkyl substances (PFSAs), perfluorocarboxylic acids (PFCAs), perfluorinated sulfonamide and their analogs in environmental water, animal tissue, human serum, blood, breast milk, nutrients in food such as vitamins, amino acids, carotenoids and other secondary plant ingredients.

Source: *ScienceDirect Topics. Liquid Chromatography – an overview. Internet: https://www.sciencedirect.com/topics earth-and-planetary-sciences/liquid-chromatography (accessed 29 September 2022).*

Machine learning
An evolving branch of computational algorithms that are designed to emulate human intelligence by learning from the surrounding environment. Techniques based on machine learning have been applied successfully in diverse fields ranging from pattern recognition, computer vision, spacecraft engineering, finance, entertainment and computational biology to biomedical and medical applications.
Source: *El Naqa I, Murphy MJ. What Is Machine Learning? In: El Naqa I, Li R, Murphy MJ, eds. Machine Learning in Radiation Oncology: Theory and Applications. Springer International Publishing; 2015:3–11.*

Metabolomics
The study of substances called metabolites in cells and tissues. Metabolites are small molecules that are made when the body breaks down food, drugs, chemicals or its own tissue. They can be measured in blood, urine and other body fluids. Disease and environmental factors, such as diet, drugs and chemicals, can affect how metabolites are made and used in the body.
Source: *National Cancer Institute's Dictionary of Cancer Terms. Definition of metabolomics. 2 February 2011. Internet: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/metabolomics (accessed 24 September 2022).*

Metabotyping
The classification of individuals in subgroups according to their metabolic profile. This approach has been employed to identify differential responses to dietary interventions..
Source: *Hillesheim E, Brennan L. Metabotyping and its role in nutrition research. Nutr Res Rev. 2020;33(1):33–42.*

Microfluidics
The technology of fluid manipulation in channels with dimensions of tens of micrometers. It has emerged in recent years as a distinct new area of research thanks to its application in many diverse fields, such as chemistry, biology, medicine and physical sciences. A strong motivation in microfluidic research comes from the development of lab-on-chip (LOC) devices, which are expected to bring a revolution in the field of chemistry and biology as integrated circuits did in computation capabilities.
Source: *Bragheri F, Martínez Vázquez R, Osellame R. Chapter 12.3 - Microfluidics. In: Baldacchini T, ed. Three-Dimensional Microfabrication Using Two-Photon Polymerization (Second Edition). Micro and Nano Technologies. William Andrew Publishing; 2020:493–526.*

Mycotoxins
Mycotoxins are naturally occurring toxins produced by certain molds (fungi) and can be found in different crops and foodstuffs, often under warm and humid conditions. Mycotoxins can cause a variety of adverse health effects and pose a serious health threat to both humans and livestock including acute poisoning to long-term effects such as immune deficiency and cancer.
Source: *WHO. Mycotoxins. Internet: https://www.who.int/news-room/fact-sheets/detail/mycotoxins (accessed 29 September 2022).*

Nutrigenomics and nutrigenetics
Comprise the science to understand human genomic/genetic variability in preferences, requirements and responses to diet, and may become the future tools for personalized nutrition, health maintenance and disease prevention.
Source: *Kussmann M. Nutriproteomics – Linking Proteomics Variation with Personalized Nutrition. Current Pharmacogenomics and Personalized Medicine. 2010;8(4):245–56.*

Nutrition ecology
An innovative concept to deal with complexity and multidimensionality in nutrition science and practice. Along the food supply chain, the dimensions of health, environment, society and economy are taken into account simultaneously and coequally. Nutrition ecology offers a concept to develop approaches to solving complex nutrition-related problems by combining special disciplinary knowledge with methods and principles of research on complexity and knowledge integration.
Source: *Schneider K, Hoffmann I. Nutrition Ecology–A Concept for Systemic Nutrition Research and Integrative Problem Solving. Ecol Food Nutr. 2011;50(1):1–17.*

Omics
Field of study in biological sciences that ends with -omics. The trademark characteristic of omics technologies is their holistic capability in the context of the cell, tissue or organism. They are aimed primarily at the universal detection of genes (genomics), mRNA (transcriptomics), proteins (proteomics) and metabolites (metabolomics) in a specific biological sample in a non-targeted and non-biased manner.

Source: *Vailati-Riboni M, Palombo V, Loor JJ. What Are Omics Sciences? In: Ametaj BN, ed. Periparturient Diseases of Dairy Cows: A Systems Biology Approach. Springer International Publishing; 2017:1–7.*

Point-of-care testing (POCT)

Involves the use of diagnostic tests with a fast turnaround time to identify pathogens at the site of patient care or nutrient testing across the food value chain. Such tests facilitate the immediate implementation of appropriate health management changes.
Source: *Hansen S, Abd El Wahed A. Point-Of-Care or Point-Of-Need Diagnostic Tests: Time to Change Outbreak Investigation and Pathogen Detection. Trop Med Infect Dis. 2020;5(4):E151.*

Point-of-need tests (PONT)

Rely on genomic identification of pathogens or track their immunological fingerprint. PONT include on-site testing of the environment, animals and food samples, although this term is not yet clearly defined.
Source: *Hansen S, Abd El Wahed A. Point-Of-Care or Point-Of-Need Diagnostic Tests: Time to Change Outbreak Investigation and Pathogen Detection. Trop Med Infect Dis. 2020;5(4):E151.*

Precision nutrition

Emerging research area that aims to use personal information about individuals or groups of individuals to deliver evidence-based and targeted nutritional advice.
Source: *Kirk D, Catal C, Tekinerdogan B. Precision nutrition: A systematic literature review. Comput Biol Med. 2021;133:104365.*

Proteomics

The study of the structure and function of proteins, including the way they work and interact with each other inside cells.
Source: *National Cancer Institute's Dictionary of Cancer Terms. Definition of proteomics. 2 February 2011. Internet: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/proteomics (accessed 24 September 2022).*

Ready-to-use therapeutic food (RUTF)

An energy-dense, micronutrient paste made using peanuts, sugar, milk powder, oil, vitamins and minerals that has helped treat millions of children threatened by severe wasting – the most dangerous form of malnutrition.
Source: *UNICEF. A wonder 'food' for the world's children. Internet: https://www.unicef.org/nutrition/RUTF (accessed 24 September 2022).*

Stable isotopes

Refer to non-radioactive isotopes occurring naturally, but elements or compounds can be synthesized that are enriched compared with the naturally occurring amount. Stable isotope techniques are noninvasive, or minimally invasive (blood draw), and can be used in nutrition to measure the amount of water or other nutrients in the body or the amount of an ingested nutrient that is absorbed and metabolized or excreted. They can be applied to determine the rate of absorption, utilization or synthesis of proteins, fats or carbohydrates.
Source: *Owino VO, Slater C, Loechl CU. Using stable isotope techniques in nutrition assessments and tracking of global targets post-2015. Proc Nutr Soc. 2017;76(4):495–503.*

Systems biology

A holistic approach to deciphering the complexity of biological systems that starts from the understanding that the networks that form the whole of living organisms are more than the sum of their parts. It is collaborative, integrating many scientific disciplines – biology, computer science, engineering, bioinformatics, physics and others – to predict how these systems change over time and under varying conditions, and to develop solutions to the world's most pressing health and environmental issues.
Source: *Institute for Systems Biology. What is Systems Biology. Internet: https://isbscience.org/about/what-is-systems-biology/ (accessed 30 September 2022).*

Transcriptomics

The study of all RNA molecules in a cell. RNA is copied from pieces of DNA and contains information to make proteins and perform other important functions in the cell. Transcriptomics is used to learn more about how genes are turned on in different types of cells and how this may help cause certain diseases, such as cancer.
Source: *National Cancer Institute's Dictionary of Cancer Terms. Definition of transcriptomics. 2 February 2011. Internet: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/transcriptomics (accessed 24 September 2022).*

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Precision Nutrition for Public Health

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Nutrition challenges

Good nutrition remains a global public health challenge, affecting both high- and low-resource communities. Lack of access to affordable nutrient-rich food, juxtaposed with increasing access to high-calorie processed food with low nutrient density, is partly to blame for the rise of the triple burden of malnutrition.[1–4] To our dismay, we are sadly on course to having nearly 670 million people undernourished by 2030.[1] It's imperative that we act to change this projection and reduce death and suffering by hunger and malnutrition, but *how?*

We have had success with reducing mortality using a one-size-fits-all approach in public health nutrition, and one such example is high-dose vitamin A supplementation for children under 5 years of age in developing countries.[5,6] Yet, we have also seen failures with the one-size-fits-all approach, which warrants rigor and careful consideration for its use going forwards.[7,8] Universal iron supplementation held potential to reduce anemia and improve health outcomes; however, the Pemba trial exposed that unintended harm can ensue for certain risk groups or contexts when approaches are not tailored.[7,8] In this trial, children in Pemba (Zanzibar, Tanzania) who received supplements containing iron and folic acid were more likely to die or experience adverse outcomes, probably due to increased infectious diseases such as malaria. This provided food for thought for investigators on safety monitoring and prompted the need for more precise solutions that address the etiology of conditions.[7,8]

Nutritional status and response to interventions are impacted by a variety of factors.[1,9] Without adequate clinical and nutritional data, which are often sparse in low- and middle-income countries (LMIC), it is challenging to determine which individuals, even which communities, need interventions and which interventions they may need most. So, while the example of iron and folic acid supplementation illustrates the substantial need to move away from a one-size-fits-all default in public health to reduce unintended harm,[7,8] this leads us back to *'how.'*

How do we overcome global malnutrition in a precise, safe, quick, yet inclusive manner? It is our view that in addition to improved access to affordable and nutritious food, access to affordable, easy-to-use precision nutrition (PN)[9] approaches will be essential to combat malnutrition.

> **"We are sadly on course to having nearly 670 million people undernourished by 2030"**

Precision nutrition for public health

There has been a rise in precision medicine approaches to tackle medical challenges such as cancer in high-income countries (HIC).[10] While PN has been described in the research sector, it remains an understudied and underimplemented approach to reduce malnutrition and improve health outcomes, especially in LMIC. In its basic form, PN takes into consideration personal and environmental characteristics to inform specific nutritional options and solutions.[9,11–15] PN for public health, however, focuses on tailored nutritional interventions for vulnerable groups that account for many similar biological and socioeconomic factors to achieve improved health outcomes and impact.

The key to designing these precise nutritional solutions lies in the use of simplified, accurate tools and methods that can assess the biology of stratified groups and their environment. Technologies, diagnostics and research into tailored interventions have proliferated in recent years, making the reality of PN for public health not only possible, but indispensable for better human and planetary health.[11–15]

> **"The apex of PN includes the targeting of each individual within a community with tailored, optimized nutritional solutions"**

Is it ethical?

Widespread problems exist within LMIC communities with regard to healthcare and food systems. We must not forget that many clinics in low-resource settings struggle to measure basic parameters of health and lack the means to treat patients accordingly.[16] As a result, undue death and suffering sweep these communities. While clinics struggle to provide care, research entities – including those in these same regions – receive funds to perform expensive experiments that may not provide foreseeable impact on the community.[16] We often ask ourselves: is this *just?* As scientists, public health and medical professionals, policymakers and others, do we have a moral obligation to prioritize solutions with high potential for scale-up and impact? With this in mind, we must ask ourselves whether PN is an ethical strategy for improving health with significant potential for impact.

The apex of PN includes the targeting of each individual within a community with tailored, optimized nutritional solutions. However, in LMIC, diagnostics and treatments at the individual level are expensive, and capacity is often limited. Targeting the individual may be rather preconceived, or 'pie in the sky,' for many regions around the world. Nevertheless, a movement towards targeting risk groups with precise, easy-to-use point-of-care methods may be a cost-effective approach to better inform nutritional interventions and improve the health of vulnerable groups.

PN is likely to succeed as a public health approach only if we keep impact at the forefront. To achieve impact, we need a framework that involves bringing together leaders in this space and policymakers, combined with local community expertise, viable business models and partnerships for scale-up.

Is it feasible?

PN for public health will require significant time, resources and workforces devoted to the cause. But we have seen in recent years that movements such as these are indeed possible.

Early on during the COVID-19 pandemic, great effort was seen around the world to rapidly identify the SARS-CoV-2 viral sequence, develop methods for its detection, elucidate the molecular mechanisms of infection and disease progression, design pharmaceutical treatments including multiple vaccines to prevent further death and suffering, and implement vaccination and awareness campaigns.[17,18] This was a truly astounding scientific movement that brought together diverse actors from many different sectors, generating robust public health impact. Groups raced to set up genomic sequencing units, and vaccines were made, tested, approved and distributed globally in less than a year, albeit delayed in LMIC.[17,18] This raises an important question: why can we not generate similar momentum and perform similar tasks to rapidly tackle death and suffering from malnutrition? The answer is: we can.

> **"PN is likely to succeed as a public health approach only if we keep impact at the forefront"**

We have the capability to further implement PN methods. The technology has advanced over the past decade and opportunities exist now that didn't exist before. If we do not act and use these technologies, we are hindering the speed of implementation of more precise interventions to improve public health.

Accelerating precision nutrition for public health

While some research groups and companies currently pursue work in PN, further collaboration and coordination are needed to propel PN forwards globally. To accelerate PN for public health, we need more research, data and tailored nutritional solutions that take into account specific factors.[9,11–15] Rigorous research is needed to discover and validate biomarkers as well as field-friendly tools to measure health and nutritional indicators in an affordable, accessible way. For PN to advance more readily, we need accurate data on food cost and consumption, nutritional status, socioeconomic situation and overall health status of risk groups that will be available for multiple sectors to build upon. With this additional information along with other environmental considerations, it is possible to generate refined nutritional solutions based on specific health and nutritional needs. These precise solutions are likely to be more successful at improving health outcomes and, thus, more cost-effective and impactful.

> **"PN could be the missing link to advance our efforts towards a world free from malnutrition"**

To do this, we need more proof-of-concept studies, organized data-collection and data-sharing methods, collaborations to take the approaches to scale, and policies at the local and national level for successful implementation. Performing rigorous research, turning the research into policies and policies into action will require multiple stakeholders to work together. Advancing PN for public health will also require the transfer of PN knowledge and technology from HIC to LMIC. We firmly believe that basic research to build capacity in LMIC has the potential to catalyze transformative change in food and health systems for health and wellbeing.

This report represents a leap towards expanding PN knowledge and creating an international coalition of thought leaders to support PN for public health as a solution with potential for great impact in both high- and low-resource settings. PN need not be inaccessible or only for an elite group, it's rather an equity issue. It could be the missing link to advance our efforts towards a world free from malnutrition.

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Precision Nutrition Approaches

Adapted from Sean H Adams et al. 2020.

AND METHODS

METABOLIC INDICATORS

(e.g., energy intake sensors, challenge testing such as oral glucose tolerance tests, gut microbiota and immune system)

PHENOTYPE MEASUREMENTS

(e.g., anthropometrics, clinical and nutritional biomarkers)

AND METHODS

Announcing *Sight and Life's* New Future-Ready Strategy

The Leadership Team
Sight and Life, Basel, Switzerland

Introduction

Sight and Life officially adopted a new strategy at the meeting of its board of trustees and leadership team in June 2022. Rooted in the goal of closing the micronutrient, lipid and protein gaps in low- and middle-income countries (LMIC), Strategy 2022–2025 outlines an ambitious new scope of work. In the course of the past 35 years, *Sight and Life* has established itself as a center of expertise in bringing out new scientific knowledge and research innovations for nutrition. It was time to take stock and see how we could become more effective. We will continue to build on our core expertise in generating scientific evidence but will now apply greater emphasis on how this knowledge leads to impact on the ground.

The three-stage testing of solutions

For making direct impact on the ground, three stages are required:

- **Stage 1: From Science to Solution**
  Generating scientific knowledge and converting this into evidence-based solutions for what needs to be done, which is a think tank's core area of work.

- **Stage 2: From Solution to Sustainable Business Model**
  The knowledge of how to deliver the Stage 1 solutions in a sustainable, locally led, efficient way, following the 'helping people help themselves' model.

- **Stage 3: From Sustainable Business Model to Scale-Up**
  Amplifying Stage 2 to achieve high levels of coverage, positively impacting lives and successfully addressing public health problems.

> **"It was time to take stock and see how we could become more effective"**

Strategy 2022–2025 will see a significant expansion as *Sight and Life* goes from being a think tank to becoming a major player in Stage 2 – developing sustainable social business solutions for malnutrition in LMIC (**Box 1**).

BOX 1: Strategy 2022–2025: Goals at a glance

Closing micronutrient, lipid and protein gaps in low- and middle-income countries

- Continue work on essential nutrient science; expand significantly on product innovation.
- Become the go-to agency for testing local sustainable business models. Achieve impact, directly, with partners and entrepreneurs on the ground.
- Transfer skills and knowledge to more established players for scale-up by entering into strategic partnerships.

A change for a changing world

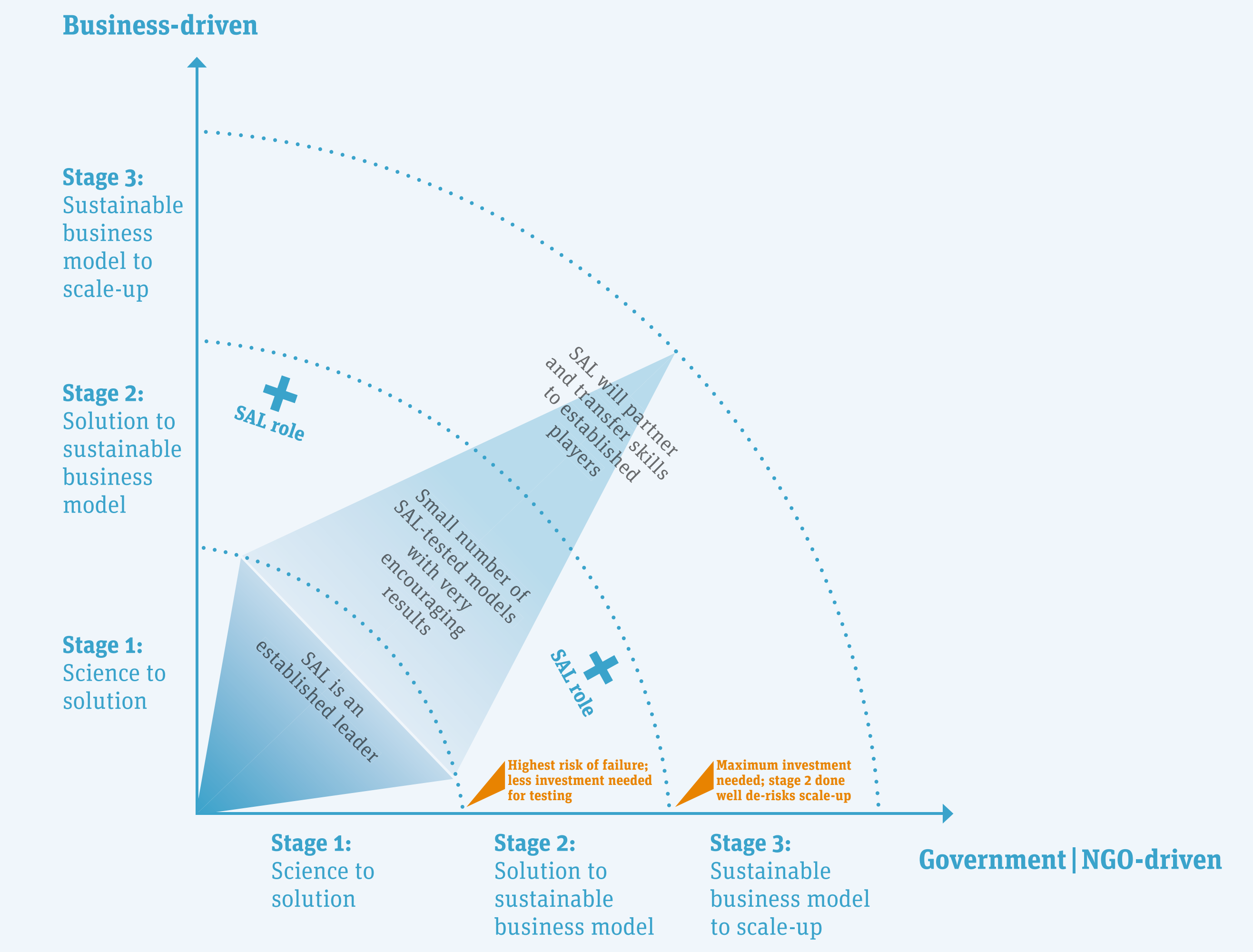
More people are hungry than ever before, with an additional 50 million people affected in 2021.[1] The climate emergency, COVID-19 and now war have disrupted food systems and supply chains, causing further damage to an already fractured and unequal food infrastructure across the world. Malnutrition is more relevant than ever today, as good nutrition is a prerequisite for nearly 50 percent of the Sustainable Development Goals set by the United Nations, while forming the supportive base for every single one of them.[2]

Over the past 5 years, we have been taking small steps towards developing products and business models, and the results are very encouraging. Business model thinking ensures that programs in countries become self-sustaining, and local entrepreneurs are key to this success. We can do more, and we want to: we have the capability.

Stage 1 requires the expertise and credibility that *Sight and Life* has successfully developed over the past three decades. The transition from Stage 1 to Stage 2 – a practical model for delivering the solution, locally, sustainably and in an efficient and impactful way – is where the highest risk of failure lies. This work requires different capabilities but is doable. It calls for less money, and results can be achieved in a short period. Building on the initial successes, *Sight and Life* will expand its work significantly in this area.

The good news is that Stage 2 done well will significantly reduce the risk involved in Stage 3, or the stage of scale-up. This

FIGURE 1: The *Sight and Life* (SAL) Innovation Funnel. The delivery of the three stages is shown through a public delivery system (x-axis) and through a market-driven approach (y-axis). High coverage and sustainability require both delivery systems



is critical, as Stage 3 is where most money is spent. There are many established players in Stage 3 with global teams who can achieve scale. *Sight and Life* will transfer skills and knowledge to such partners. The world around us is changing and if we want to make a difference, this is the time to raise our ambition level. The nutrition funding landscape has changed, with more philanthropies and private-sector actors stepping up. With this, the risk appetite of investors has increased. There is an opportunity to do something truly transformative, and the nutrition sector needs this today more than ever.

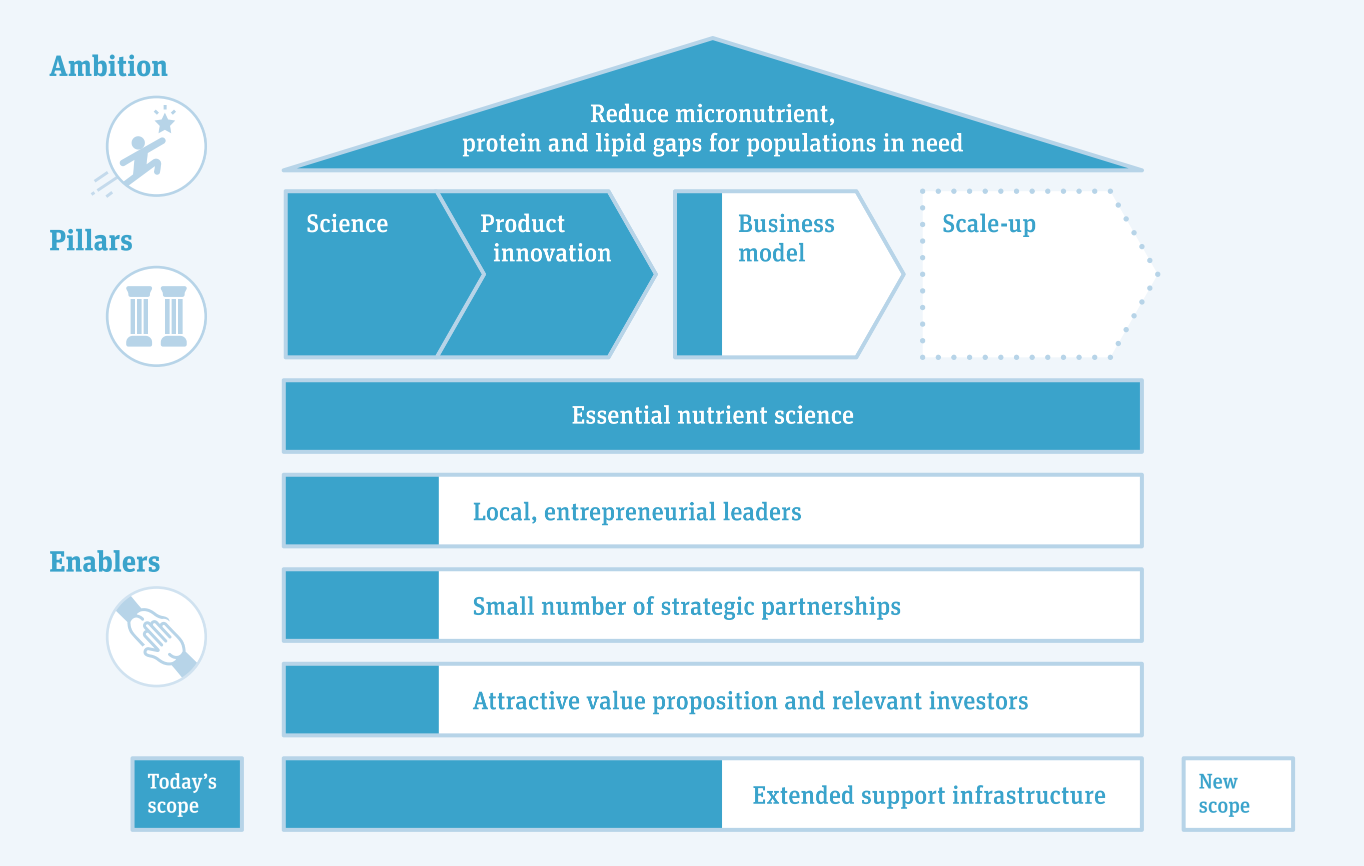
What will change?

- We will specialize in local social business model development and validation for scale.
- We will carry out relevant, real-world testing of the entire business model for significant risk mitigation ahead of scale-up.
- We will implement with a business mindset to bring impact with efficiency.
- We will build country-specific value chains for production, distribution and marketing of these products.
- We will partner with the right organization or entrepreneur in each country to scale up these solutions.
- We will become a better partner ourselves and help our partners become more impactful.

What will not change?

- We still discover science-based solutions for malnutrition.
- We still continue our knowledge management work.
- We still do not scale up ourselves: we will transfer the skills and knowledge for stage 3 scale-up by established partners.

FIGURE 2: The new *Sight and Life* strategy house aims to deliver locally led impact on the ground



"There is an opportunity to do something truly transformative"

Ambition

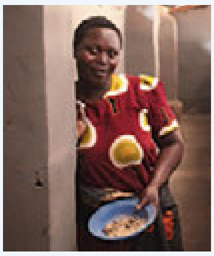
When *Sight and Life's* leadership team studied the ecosystem, it became apparent that the biggest area of need was the transition from Stage 1 to Stage 2. By becoming a specialist in this area, we can become better partners and accelerate impact.

In the next 3 years, *Sight and Life's* new strategy has the potential to reduce micronutrient, protein and lipid gaps for millions of people across the world and to support the livelihoods of nearly half a million farmers.

We are excited about this new journey and look forward to collaborating with existing and new partners to work towards a better, more equitable, world. If you are a partner who is interested in discovering science-based solutions, or pioneering a new product innovation, or testing sustainable social business models for the scale-up of impactful nutrition solutions, please contact us to collaborate. If you are an investor who wants to see real sustainable impact on the ground through science-based solutions, please contact us.

As an investor, you will enjoy the satisfaction of working with a lean, agile, entrepreneurial and dedicated team who are keen to deliver measurable results. It is our vision to see *Sight and Life* at the forefront of translating science to truly impact lives on the ground.

Meet Grace Nyirongo: One of *Sight and Life's* farmer partners in Malawi



Prosperous farmers drive out hunger and malnutrition from their communities.

Grace * joined us 4 years ago with a flock of 300 birds, and is today a proud owner of 1,200 birds. She now earns three times the minimum wage in Malawi, can put her daughter through school and supplies up to 1,000 eggs a day to her community.

Empowering smallholder farmers is at the core of our work. When their produce improves, they can pull themselves out of poverty and, in turn, also nourish their communities, thus improving the malnutrition status of entire populations.

* Name changed in accordance with our privacy policy

Here's to a malnutrition-free future.

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The Evidence Base

Examining the Nutrition Ecology: An approach to achieving precision in public health

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Precision in public health nutrition

The motivation of this *Sight and Life* initiative is to explore ways by which we may improve precision in how we address public health nutrition. This is an aspirational goal, but what exactly do we mean by precision? Is it the accuracy of measurement (i.e., the accuracy of a device to measure to a given decimal point)? Or is it more broadly "the quality, condition or fact of being exact and accurate" (i.e., more inclusive of the sources of variability that might affect a given outcome of interest)?

An important goal of biomedical research is to achieve a level of precision in health promotion, disease prevention and treatment. According to the Precision Medicine Initiative at the National Institutes of Health (NIH), precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[1] The core premise is that context matters, and that one size does not fit all. The question here is how to apply such an approach to address the role of nutrition in public health.

> **"In precision medicine, context matters"**

Defining the nutrition ecology

The term 'nutrition ecology' has been used with some frequency over the years with the focus on the impact of nutrition on food systems and the environment.[2] Herein we will make the case for taking an 'ecological' approach to the study of nutrition based on the definition of an ecology as the extent and nature of the interactions of a complex system and its (internal and external) environments. The underlying principle of this approach to nutrition is that nutrition is a biological variable reflecting an array of internal and external influences.[3] Consequently, we suggest the need to refocus the view of nutrition from a collection of independent indicators of nutrient status, to an array which itself comprises a biological variable or system. This view goes beyond considerations of food systems, food supply and dietary exposure to involve all aspects of human health. Furthermore, it highlights nutritional status as both an input to and an outcome of health and disease. **Figure 1** is a representation of the nutrition ecology and its interactive components.

Nutritional assessment

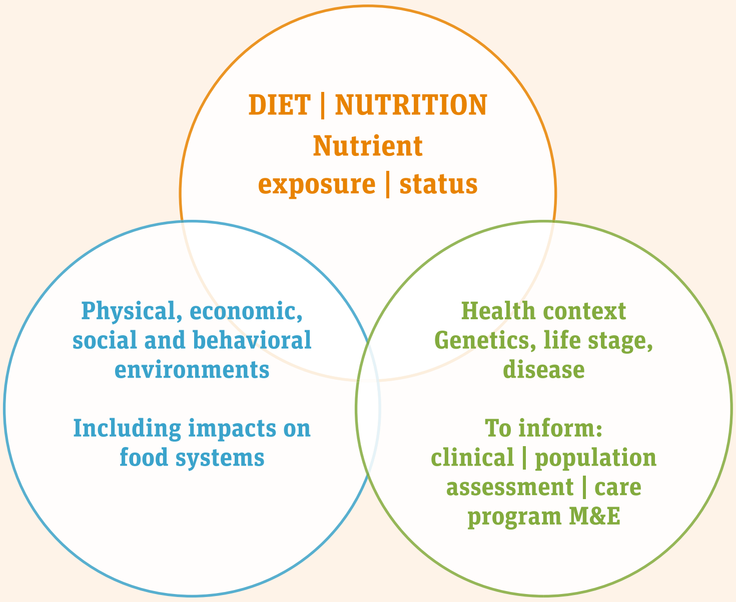
Our ability to understand the role of nutrition in health is driven by our capacity to address three fundamental questions:

1. Where do normal nutrient requirements end and needs relating specifically to health/physiological condition begin?
2. What is the role of diet/nutrition in those conditions that would require special consideration above and beyond the provision of a balanced diet providing all essential nutrients needed for growth, development and health?
3. What are the best types and amounts of evidence to support the establishment of standards of care and the development of programs to address the role of nutrition in health promotion and disease prevention?

> **"Each of the processes of nutrition affect and are affected by nutrition and, more broadly, health and disease"**

These questions are based on the principle that nutrition is involved in all aspects of human biology. Nutritional status, which is the operational measure of the adequacy of the diet and the integration of dietary components to support health, is achieved as a result of a series of behavioral, physiological and metabolic processes involved in the taking in, and the utilization of, dietary substances/nutrients that must be present to support growth, repair and maintenance of the body as a whole or in any of its parts. This definition illustrates the complexity of the nutrition ecology, as each of the processes of nutrition affect and are affected by

FIGURE 1: The nutrition ecology



nutrition and, more broadly, health and disease. Thus, the assumption that we can answer questions about diet, nutrition and health by limiting our focus to exposure (i.e., merely focusing on the first step in achieving nutritional status) is flawed.

If we accept this premise, then where does that leave us in terms of both nutritional assessment and determining the precise role of nutrition in such multifactorial conditions as anemia, stunting and nutrition-related noncommunicable diseases (e.g., obesity, diabetes, cancer)?

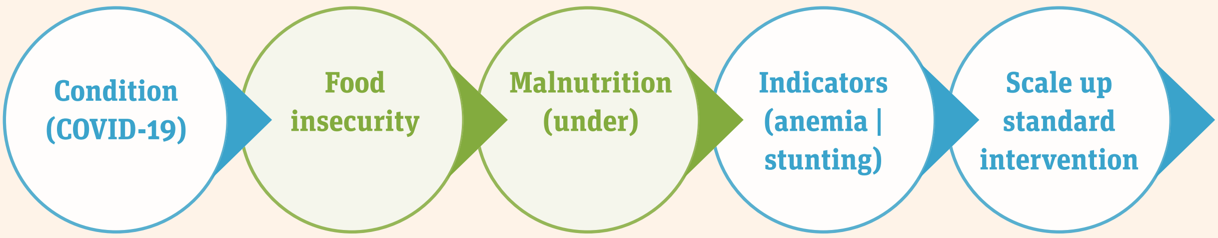
An ecological approach to nutritional assessment

With specific regard to the 'usual' approaches to nutritional assessment, which include dietary intake assessment, anthropometry, biochemical assessments (i.e., the use of biomarkers of specific nutritional status) and responses to interventions, it is clear that the use of one of these approaches to the exclusion of others is problematic; rather, an ecological approach to nutritional assessment is warranted for the following reasons:

- **Exposures:** In the absence of biochemical indices/biomarkers, intake data alone are insufficient to determine functional status or the effect of nutrients on an individual's health, as intake data informs us only about exposure with no indication of whether/how the dietary constituents of interest are being used. In the current global context, the dual burden of overnutrition (overweight and obesity) and undernutrition (underweight and micronutrient deficiency), stunting and anemia all represent multifactorial conditions that exist at both the population and individual levels. Furthermore, these conditions coexist with an increasingly complex global health context including pandemic infections, noncommunicable diseases and the increasing impact of climate change. This all presents as a complex biological milieu that cannot be understood as simply a 'too much or too little' scenario.

- **Anthropometry:** We cannot rely on anthropometry alone

FIGURE 2: Linear logic applied to attempts to understand the impact of COVID-19 on nutrition



to make a judgment about nutrition and health, as anthropometric measurements lack the sensitivity and specificity to allow precise attribution in terms of etiology.

- **Biochemical assessments:** With regard to nutrition and health relationships, it is difficult to make any inferences about biochemical indices without knowing an individual's dietary intake or health context. Is the measure the result of dietary insufficiency or some other inherent aspect of biology, begging the question: "Is the observed measurement the result of physiology versus exposure?" For example, abnormal circulating levels of a particular nutrient may be due to many factors (i.e., inadequate intake, inflammation, inherent biochemical abnormalities, genetics, pathologies or problems associated directly or indirectly [via interactions with therapeutics/interventions] with a given condition).

- **Response to interventions:** Without knowing the pre-intervention status of an individual, it is difficult to distinguish between the effects of correcting a primary nutrient deficiency and those of correcting a secondary nutritional anomaly associated with disease, medicines, etc. The ability to determine optimal nutrient doses for interventions is also contingent on an appreciation of dietary intake, physiological need, nutritional status and the impact of the condition on the processes of nutrition.

For examples of how these challenges play out in real time, we need look no further than the challenges presented by the COVID-19 pandemic. As with many other such global health crises, a linear logic (**Figure 2**) has been applied to attempts to understand the impact of COVID-19 on nutrition.[4]

While there is no question that the COVID-19 pandemic has had significant impacts on the access and availability of food and necessitates the mobilization of all the tools in the global food security toolkit, this linear and limited view of the intersection of the biology of nutrition and SARS-CoV-2 infection has stymied our ability to answer the three core questions posed above (What about SARS-CoV-2 infection would require a nutritional intervention beyond the provision of an adequate diet? What about SARS-CoV-2 infection and its prevention [vaccines] and treatment might warrant a different approach to nutrition? What role does nutritional status play in susceptibility to and response to interventions for SARS-CoV-2 infection?).

A more integrated approach

To close, our ability to be more integrated and 'ecological' in our approach to nutritional assessment will improve the value and precision of surveillance, interpretation and decision-making in terms of both the development and the deployment of context-specific, safe and efficacious interventions.

The next contribution in this Special Report – entitled 'Understanding the Anemia Ecology: An approach to address the global anemia challenge' – is a summary of an application of the principles of the nutrition ecology to a high-priority global challenge, anemia.

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Disclaimer

The contents of this article represent the authors' views and do not constitute an official position of the National Institutes of Health or the United States Government.

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Case Study

Application to Improve Precision: Understanding the anemia ecology

An approach to address the global anemia challenge

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As highlighted in the contribution to this Special Report entitled 'Examining the Nutrition Ecology,' our ability to improve precision will be contingent on a fuller appreciation of the elements contributing to the internal and external ecology of a given condition. The complex systems represented by human biology demand an ecological approach to improve the assessment and the development and implementation of context-specific, equitable interventions. The following is a description of the application of such an ecological approach to address an ongoing global health challenge: anemia.

Introduction

Anemia remains a critical global health problem that contributes to increased morbidity and mortality, particularly in women of reproductive age and preschool-age children.[1] To address this challenge, the US Agency for International Development (USAID), through its project USAID-Advancing Nutrition, constituted the USAID-Advancing Nutrition Anemia Task Force (ATF). Since 2021, the ATF, a group of leading experts in anemia research and programming, advises USAID Advancing Nutrition in areas of anemia reduction that are relevant to public health. The ATF serves as a research advisory body to support the translation of state-of-the-art evidence into specific interventions. To accomplish its tasks, the ATF created three working groups, described in **Table 1**.

TABLE 1: Anemia Task Force working groups and their foci

Working group	Focus
Biology	Mechanisms of action of primary anemia causes, largely from a public health perspective
Assessment	Different approaches for assessing anemia, its prevalence and primary etiologies
Translation and implementation	Approaches to address anemia based on a framework for translating available evidence on biology and assessment

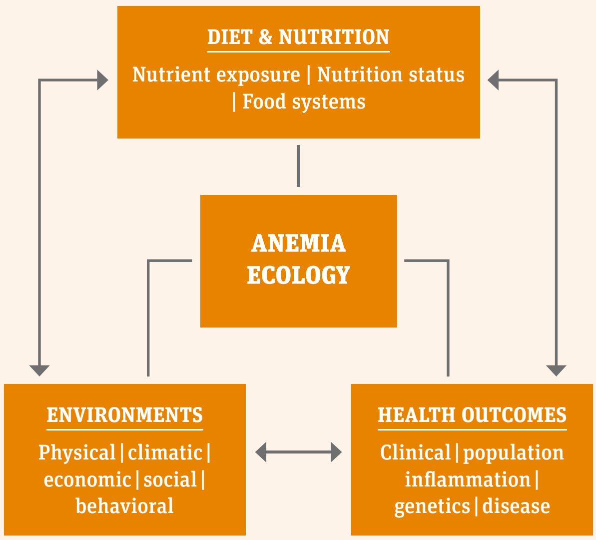
The following is a synopsis of a larger report created by the ATF for USAID Advancing Nutrition with the goal of providing an overview of anemia causes, available assessment methods, and intervention strategies to identify, prevent and treat anemia.

> **"The complex systems represented by human biology demand an ecological approach"**

Conceptual approach

- Anemia coexists with pandemics of food/nutrition insecurity, malnutrition, and infectious and noncommunicable diseases. The manifestations of anemia are most severe in women, infants and young children.[2] Our ability to improve the precision of the assessment and interventions for anemia demands an approach that appreciates its complex 'ecology.'

FIGURE 1: Highlights of the components of the 'ecology of anemia'



The components of the 'ecology of anemia,' which intertwines biological and non-biological factors such as health conditions and nutritional status, as well as other underlying factors – demographic, social/behavioral, economic and physical.

Source: Authors

The following operating assumptions guide us in understanding the components of the ecology of anemia in an effort to identify and treat it with precision at both individual and population levels.

- Anemia – the result of decreased production or increased loss of red blood cells (RBCs) – has multiple determinants (i.e., an ecology involving nutrition, genetics, infection, disease, populations, economics, life cycle and the environment).
- Ecology considers the relationships of complex systems with their environments. The ecology of anemia includes both internal and external environments (**Figure 1** and **Table 2**).

Biology

Understanding the ecology of anemia requires a comprehensive view of its underlying biological mechanisms from a clinical and public health perspective. The body regulates RBC oxygen-carrying capacity to meet its physiological needs.[1] Newly produced RBCs replace circulating RBCs at the end of their ~120-day life span.[1] Anemia develops when the RBC oxygen-carrying capacity can no longer be maintained because of:

- inadequate RBC production,
- a decreased RBC life span,
- an increased blood loss or
- combinations of these causes.[3]

Anemia presents when the circulating hemoglobin concentration falls below a certain threshold.

Although there are multiple causes of anemia, iron deficiency (ID) remains a primary cause.[4] However, it is important to point

TABLE 2: Key elements of the assessment, analysis and action framework

Elements	Components
Biology and BASIC science	To help guide assessment:
	• Potential etiologies
	• Relevant aspects of the health of potential target populations including sex,
	stage of development and genetic background
	• Potential implications of clinical care/pre-existing public health interventions
Assessment	Includes consideration of target:
	• Diet/nutrition versus other etiologies/health
	• Clinical management goals versus public health surveillance
Analysis	Context including:
	• Internal environment: biology, health, therapeutics, toxins, other relevant exposures
	• External: food security, sanitation, prevalence of relevant conditions in the setting of interest
	including health systems (equity, sex/gender) and other social/behavioral factors
	• Physical environment including climate
Translation and Monitoring & Evaluation	Will rely on:
	• Translation of research and evidence to support both clinical and public health
	interventions/programs
	• Implementation science
	Continuous efforts to improve the deployment, sustainability, resilience and implementation
	of new, and improvement of existing, programs based on:
	• Data from other elements listed above
	• Particular focus on potential unintended consequences

out that ID not only refers to inadequate iron intake, but can also be due to impairment of iron metabolism.[5] **Table 3** highlights key aspects of our understanding of the anemia etiology.

From a public health perspective, each setting has distinctive components defining the common causes of anemia, its pattern of severity, the ages and populations most affected, and more broadly the health context in which these factors exist.[6] To improve precision both clinically and at scale and to inform context-specific decisions, the ecological approach acknowledges the need to distinguish between populations with a high prevalence of anemia attributed to ID (both absolute and functional) and those with widespread genetic conditions affecting RBCs, especially in sub-Saharan Africa and regions in Asia and Oceania.

Assessment

One of the key challenges of reducing the global anemia burden is the variability of prevalence estimates and anemia trends resulting from the different assessment techniques that are used to develop these data.[7] To progress on global goals for anemia reduction and to determine the effectiveness of interventions with precision, the availability of appropriate assessment tools is imperative for assessing not only hemoglobin concentration but also the underlying anemia causes in both clinical and population-based settings.[8]

In the ATF report, we considered appropriate methodologies and procedures for assessing anemia, based on low hemoglobin or hematocrit concentrations, followed by an evaluation of the likely causes of anemia in different settings. The causes of anemia are broadly classified as:

- non-nutritional: due to infection, inflammation, blood loss or genetic disorders,[3] or
- nutrition-specific: the ATF focused on anemia due to deficiencies in iron, vitamin A, riboflavin, vitamin B_{12}, folate or zinc, while recognizing that other nutrients may rarely be implicated.[7]

The ATF report introduces a decision-making framework for anemia assessment in populations based on the global burden of disease cause-specific prevalence estimates. This approach specifies data on anemia causes that need to be evaluated and the means to collect these data. The report also proposes an approach to interpret anemia risk factors from population-based surveys to facilitate decision-making when designing context-specific interventions.

> **"The ATF report emphasizes the importance of a systematic determination of the anemia etiology in populations"**

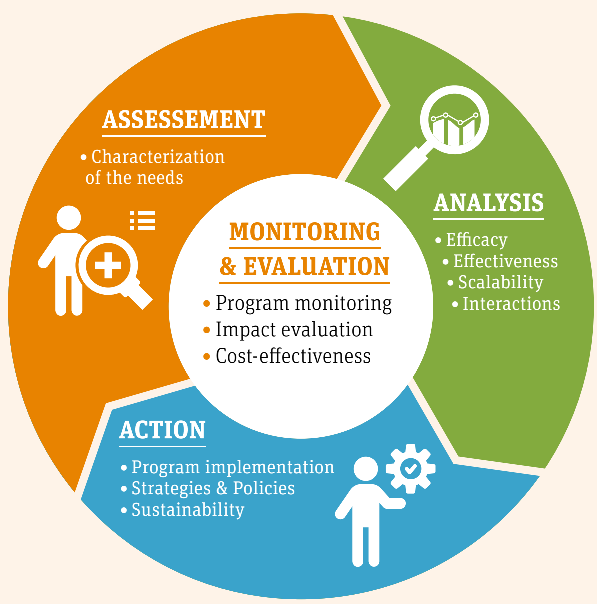
Translation, intervention and implementation

Based on the biology and assessment of anemia, the ATF report presents context-specific considerations to inform choices about interventions to address anemia. The ATF report emphasizes the importance of a systematic determination of the anemia etiology in populations. Consistent with the overarching ecological approach, we address interventions for anemia using three main categories: interventions addressing (**1**) nutrients alone, (**2**) non-nutritional causes of anemia, and (**3**) both nutritional and non-nutritional causes. The emphasis is on interventions of public health relevance, such as food-based approaches to enhance iron intake and absorption, supplementation, and also delayed cord clamping and deworming, but the clinical context is also considered.

Specifically, the report focuses on:

- iron and other nutrients (vitamin A, B vitamins and zinc), especially their role in hemoglobin synthesis or cell replication with an emphasis on the importance for anemia prevention;
- interventions at different stages of the life course – with a focus on women of reproductive age and preschool-age children;
- the impact of inflammation and infection on the applicability and utility of the interventions, as well as genetic mutations, nutrient delivery, bioavailability and safety for selecting interventions; and
- considerations of interventions within the broader context of external environments, including sustainability, social and cultural factors, and climate change.

FIGURE 2: Triple A framework for selecting interventions: assessment, analysis and action



Source: Adapted from UNICEF 1997[9]

TABLE 3: Key understandings of anemia etiology

Definition	Characteristics
Iron deficiency (ID) anemia	• Circulating iron within the blood supply is insufficient for red blood cell (RBC) production and tissue needs. • Iron-limited RBC production fails to maintain the circulating hemoglobin concentration above the threshold used to identify anemia.
'Absolute' ID	• Body iron stores are absent/reduced and do not meet an individual's physiological need. • Affected individuals may be responsive to oral iron supplementation, as in nutritional or dietary ID. • Responsible in many instances for anemia cases globally.
'Functional' ID	• Body iron stores are adequate but unavailable for use because of the effects of infection or inflammation. • Unresponsive to oral iron supplementation, and is a common cause of anemia in low- and middle-income countries.
Genetic disorders	• The importance of genetic conditions as causes of anemia depends on the specific inherited hemoglobinopathy (e.g., sickle cell disease, thalassemia), abnormalities, the pattern of inheritance, and the examined populations and geographic areas.
Infection / inflammation	• Infection may be responsible for either functional or absolute ID, or both. • Inflammation is associated with functional ID primarily via the action of hepcidin. • Inflammation is also a critical factor affecting the interpretation of available biomarkers of relevant nutrients (e.g., ferritin, retinol binding protein) via stimulation of the acute phase response.

The ATF framework for the translation and implementation of interventions

Because we live in a resource-constrained global environment, an effective, efficient and sustainable approach to reducing anemia requires multisectoral collaborative efforts where the motivations and mandates of different stakeholders might be disparate. In this context, we can use tools for selecting interventions that allow for harmonizing a multifaceted approach. A nutrition-specific framework offers a useful starting point for a broadly applicable approach to combat anemia (**Figure 2**).

The framework is based on UNICEF's Triple A approach[9] and highlights the sequence and components of assessment, analysis and action. This iterative cycle and continuous feedback loop lends itself to a sector-independent approach that can be overseen by, and provide input to, a cost-effective monitoring and evaluation plan.

The components of this framework reflect action based on evidence, which must consider key elements as outlined in **Table 2**.

Conclusion

The aim of the ATF is to refocus our view of anemia to improve the precision of diagnosis and interventions by emphasizing its complex ecology and multiple determinants. The suggested approach covers key components of that ecology, and includes a review of assessment and intervention strategies to support more precise, context-specific solutions for addressing anemia in all its forms – both clinically and from a public health perspective. The Triple A framework reflects an integrated strategy that fully incorporates the essential elements of the anemia ecology. The ATF offers these concepts in the hope that this more integrated and context-specific approach will provide the direction needed to support the global efforts to positively change the course of this public health challenge.

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Introducing Precision Nutrition for Vulnerable Children in Low-Resource Settings

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Current nutritional interventional approaches for vulnerable children

Considerable effort has been made to improve nutrition among vulnerable children, including those who are stunted and/or wasted. Between 2000 and 2015, child growth deficits in Africa fell, albeit with striking subnational heterogeneity. However, in 2020, globally 149 million children under 5 years of age were stunted and 45 million were wasted.[1] Current programmatic approaches are mostly generic, and not tailored to regional, communal, household or personal characteristics. For example, while vitamin A or zinc deficiency varies considerably in low- and middle-income countries,[2] this is not usually considered in designing interventions such as the composition of ready-to-use therapeutic foods used to treat children with severe malnutrition. Such public health approaches have been effective at scale where resources are limited; however, there is likely to be a ceiling for the gains attainable from a 'one size fits all' approach.

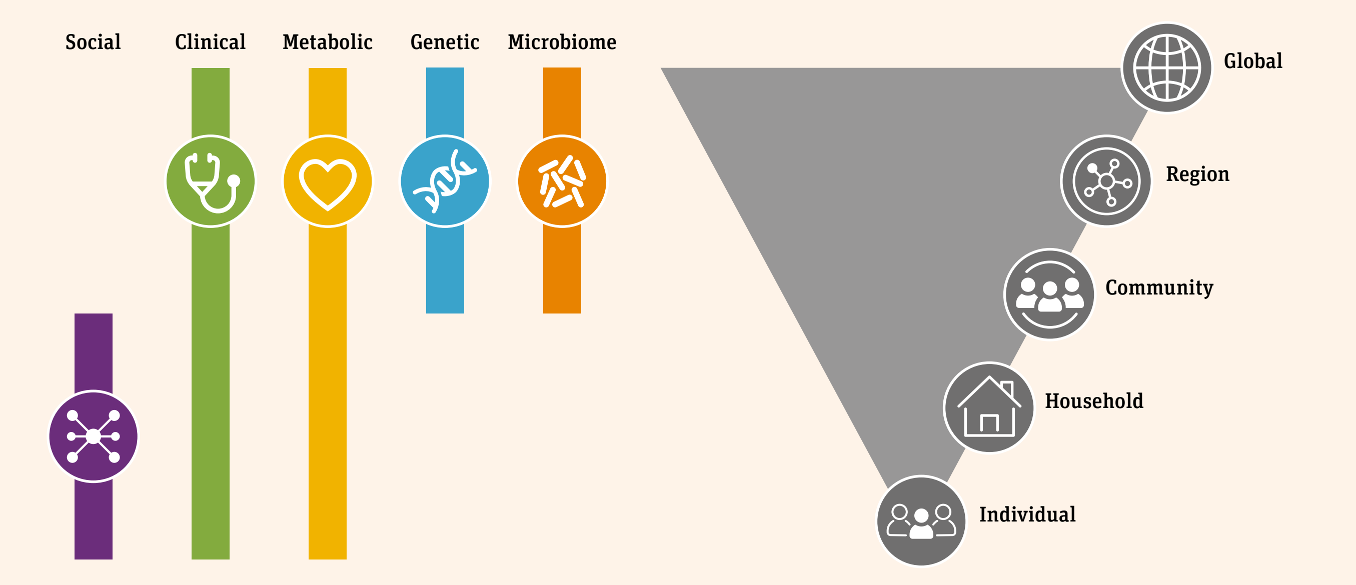
> **"Precision nutrition could help the target populations of interventions where resources are limited"**

Appropriate nutrition is essential for growth, development and resilience, preventing diseases and their impacts. Ingested nutrients transit through metabolic pathways influenced by genetics, epigenetics, the microbiome and environmental factors, contributing to heterogeneity in individual needs and responses. These factors also underlie differences in disease susceptibility and response to therapy. Thus, they have the potential to inform recommendations for different segments of populations (**Figure 1**) in precision nutrition approaches. Precision nutrition combined with spatially resolved data could help the target populations of interventions where resources are limited.[3] Integration of big data related to genetic, epigenetic, microbiome, lifestyle and environmental factors is required to expand our understanding of the diversity of human metabolism in response to diet.

The emerging role of precision nutrition

Precision nutrition encompasses utilizing a group or an individual's characteristics to optimize interventions. It is rapidly gaining traction, largely because of new 'omics' tools and consequent insights into the roles of the intestinal microbiome in metabolic and hormonal processes, and their association with diet. Differential responses to diet due to genetic and epigenetic factors ('nutrige-

FIGURE 1: The multilevel role of precision nutrition to prevent and manage disease



netics') are increasingly recognized. For example, malnutrition in all its forms (undernutrition, micronutrient deficiencies, overweight or obesity)[1] influences DNA methylation, affecting host metabolism.[4] Metabolites of the microbiota, such as short-chain fatty acids, can also alter DNA methylation and histone acetylation, potentially affecting epigenetic regulation of metabolic processes.[5] Clinical status and social factors also offer the potential to target approaches. For example, integrating anthropometry, diet, physical activity and microbiome can accurately predict glycemic response to a meal.[6]

> **"Identifying food components that improve beneficial functions of the microbiota is a potential dietary approach to enhancing precision"**

Feeds for severe malnutrition

Two milk-based formulae – F-75 (lower protein, lower energy) and F-100 (higher protein and higher energy) – are used to treat children with severe malnutrition in the stabilization and rehabilitation phases of inpatient treatment, respectively. The World Health Organization recommends ready-to-use therapeutic foods that have a similar nutritional composition to F-100 for community-based management of severe malnutrition in a single rehabilitation phase. While these feeds are critical, their composition, amounts and duration have not been customized to meet the individualized needs. Variability in energy requirements may need to be addressed, and proteomics and metabolomics studies have demonstrated that HIV-infected children with severe malnutrition potentially require feeds with a different lipid composition.[7] However, in general, local preferences have informed the composition of therapeutic feeds in some countries including Bangladesh, Vietnam and India to increase acceptability.[8–10]

Intestinal microbiota

The intestinal microbiota lives symbiotically within the host, harboring ~100-fold more genes than the host. Its composition and function are shaped by gestational age, birth mode, genetics, epigenetics, feeding, antimicrobials and the environment. Diet is a key driver of variation in constituent organisms and their functional gene content.[11–16] The intestinal microbiota influences human development and homeostasis by modulating immune regulation, gut integrity,[17,18] metabolism[19,20] and energy homeostasis, brain function and pathogen colonization resistance.[21] Thus, the microbiota is an intermediary between nutrition and health, and an important target for precision nutrition-based interventions.

Undernutrition has been associated with an 'immature' microbiota phenotype that is largely refractory to current nutritional interventions.[22,23] Dysbiosis[24,25] (altered microbiota composition or function) likely interferes with processes essential for host health and wellbeing. Identifying food components that improve beneficial functions of the microbiota is a potential dietary approach to enhancing precision. Microbiota-directed feeds using readily available foods such as chickpea, soy, peanut and banana can alter the microbiome, promoting weight gain.[26,27] Since both composition and targets may vary regionally, such precision nutrition approaches have the potential to radically change strategies and may optimize benefits, given resource limitations.

Functional readouts of the microbiome can assess the effects of nutritional approaches. For example, short-chain fatty acids are bacterial fermentation compounds of dietary fibers that play a role in immune regulation.[28] Poorly digested fibers can lead to the accumulation of pro-inflammatory metabolites.[29] Therefore, assessing an individual's fiber digestive capacity could lead to differential nutritional recommendations for poor versus high fiber-digesters. Microbiome-dependent metabolism of pharmaceutical compounds can also be assessed to optimize treatment responses.[30,31] For example, the relationship between metformin and the microbiome is partially responsible for its beneficial effects on lifespan.[32] Thus, reshaping host–microbiota interactions through precision nutrition is a new therapeutic avenue for both disease control and prevention, and could be harnessed to affect functional/clinical outcomes including immune function, cognition and growth.

Risk prediction for precision nutrition

Clinical parameters that are collected routinely in nutritionally and clinically vulnerable children can be harnessed to guide more precise nutritional management (**Figure 2**). Studies in intensive care units in high-resource settings demonstrate that limiting caloric intake during critical illness can improve outcomes.[33] Ideally, nutritional intake should be based on individual basic energy needs, but stratified approaches may be feasible with improved knowledge of energy requirements for malnourished children with different levels of clinical illness severity. Clinical warning signs provide an opportunity to identify changes which occur daily that can be used to stratify children to alternative nutritional and medical treatments (**Figure 2**).[34–36] Specific metabolic biomarkers and volatile organic compounds are associated with poor outcomes in severe malnutrition.[37–40] Both are a proxy for systemic inflammation and altered microbiota, and could be developed as a near-bedside point-of-care tool.

Tools for precision nutrition

Longitudinal growth analyses

Longitudinal growth monitoring is essential for the evaluation of children's nutritional and health status.[41] Thus, growth pathways constructed using longitudinal measurements are an important tool for assessing growth longitudinally at both individual child level and population level.[42,43] The shapes of growth trajectories have been associated with health outcomes such as cardiometabolic health.[44] Thus, it is possible to predict growth and therefore to design targeted interventions for individual children through precision nutrition.

Systems thinking

The role of nutrition in vulnerable children is multifaceted. Systems thinking provides the framework to study the interrelationships between elements of the system and the function of the system as a whole.[45] Potential advantages of system-based approaches include reducing inequities in health research and policymaking. This can be achieved by modeling complex social interactions between different communities[46,47] and bridging the gap between research and practice by the potential impact of implementing an intervention.[48] **Figure 3** shows an application of systems thinking.

FIGURE 2: Biomarkers and clinical warning signs can be used to stratify patients and to monitor and evaluate a treatment plan, resulting in treatment more tailored to the individual's needs

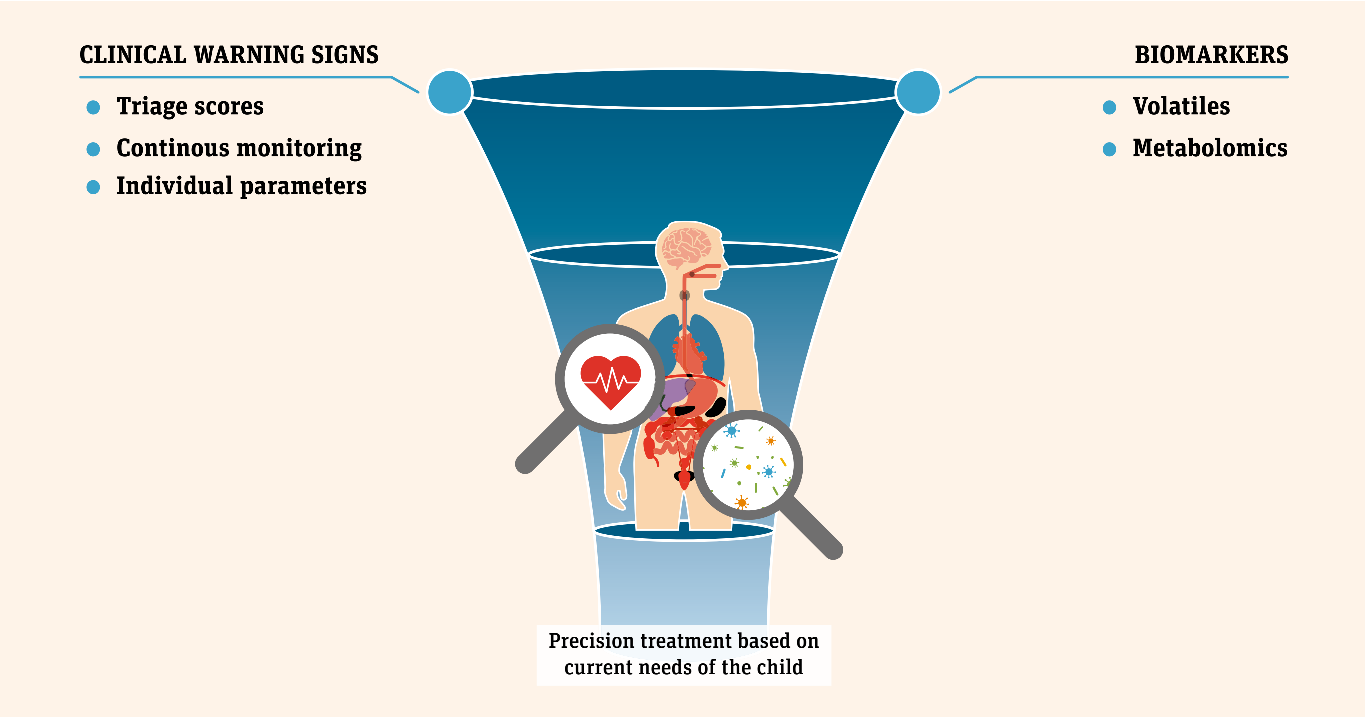
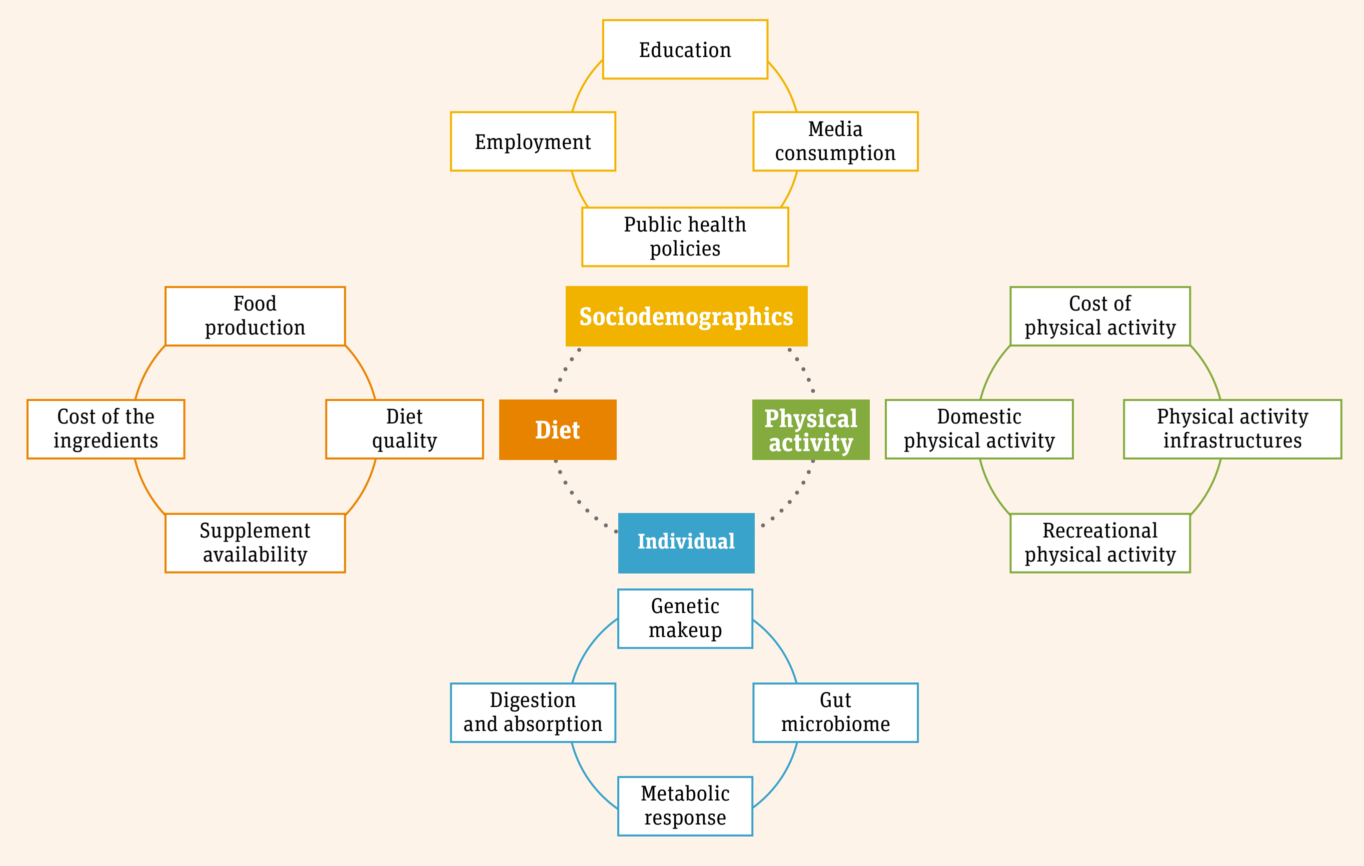


FIGURE 3: Precision nutrition for vulnerable children in low-resource settings from the systems thinking perspective



> **“Tailoring interventions to actual needs may be cost-effective”**

In summary, new tools and approaches allow us to identify groups in whom interventions can be targeted to optimize benefit, thus introducing a precision nutrition approach to public health nutrition. Resource limitations in low- and middle-income countries are a major factor dictating programs and policy; however, tailoring interventions to actual needs may be cost-effective, and this needs to be assessed in robust clinical trials.

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Precision Nutrition: A Solution for the global community? Learnings from ZOE PREDICT

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Dietary factors play a critical role in the etiology of noncommunicable diseases (NCDs).[1–3] It is estimated that 8 million deaths were attributable to dietary risk factors in 2019.[4] NCDs disproportionately afflict people living in low- and middle-income countries (LMIC), accounting for 80 percent of the global burden of disease.[5]

At the public health level, mitigations for NCDs such as cardiovascular disease, type 2 diabetes, obesity and some cancers focus on population averages, applying a one-size-fits-all approach to reducing disease risk. However, with increasing rates of diet-related NCDs in LMIC,[6–8] it must be argued that these mitigations are coming up short. What is more, the need to 'look beyond the mean' is well established, with multiple studies demonstrating large inter-individual variation in how humans respond to food and entire dietary patterns.[9–12] Research in precision nutrition (PN), based on the idea that personalizing nutritional advice, products or services will be more effective than generic population-wide approaches, has demonstrated early potential.

> **"We are in an exciting era of big data opportunities"**

Precision nutrition at present

Today, PN exists in a diverse array of commercial direct-to-consumer products claiming to provide health-promoting services. The PN industry is projected to reach US$15.6 billion in value by the end of 2022.[13] PN research is also gaining considerable momentum. The National Institutes of Health (NIH, USA) recently awarded US$170 million to the Nutrition for Precision Health program, which aims to develop algorithms predicting personalized responses to food consumption.[14]

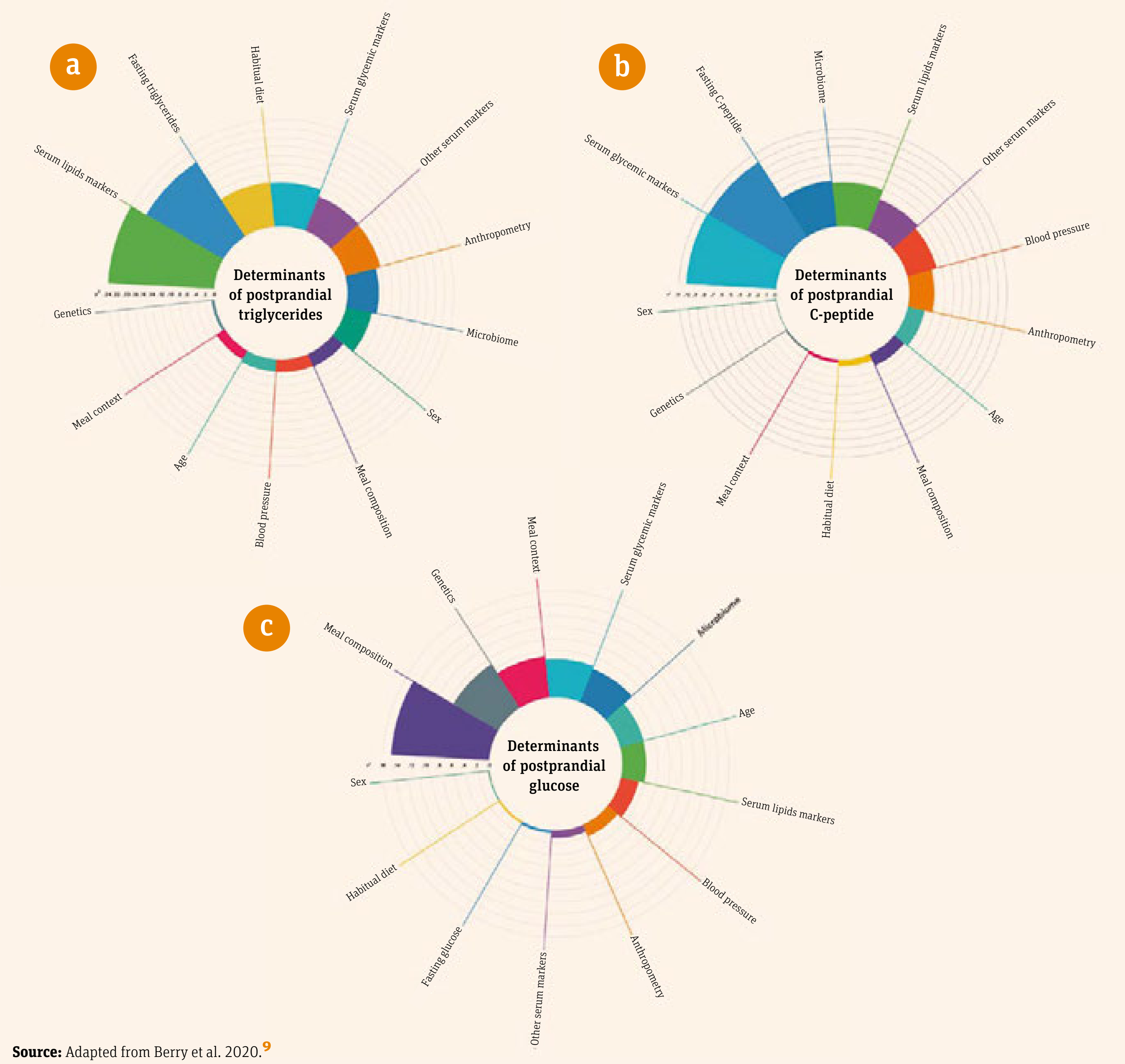
A recent systematic review of PN identified 11 studies in healthy adults that showed dietary quality improved to a greater extent in participants randomly assigned to receive personalized nutrition advice, based on a combination of dietary information, phenotype, genotype and/or lifestyle factors, compared with generalized advice.[15] At the dietary level, the Food4Me study demonstrated that adults randomized to a personalized dietary behavior intervention for 6 months had more healthful dietary changes than those receiving standard, non-personalized advice, through greater reductions in discretionary food and beverage intakes (high in added sugars, fat and salt).[16] On a metabolic level, multiple groups have shown that machine learning algorithms can use individual postprandial metabolic responses to dietary interventions as inputs to predict future metabolic responses to other foods.[9,17–19] Efficacy of these algorithms in improving metabolic markers of nutritional response has also been demonstrated in small, controlled settings; individuals following the recommendations generated by their tailored algorithm showed improved glycemia (glucose time in range and HbA1c) and lipemia (triglycerides and cholesterol).[17,18]

Precision nutrition opportunities

We are in an exciting era of big data opportunities. The development of new biological measurement technologies, advances in big data analytics and growing interest in citizen science have enabled research to leave behind the traditional trade-off between high-precision and large-scale studies. PN research is currently being performed at incredible depth, breadth and scale. This has enabled investigators to pose questions about how our responses to foods are impacted by who we are, what we eat, where and how we eat it.

This perfect storm of opportunity has fueled the ZOE PREDICT Program, of which the ZOE PREDICT 1 Study will be described here. This landmark study aimed to derive algorithms that predict an individual's postprandial metabolic responses to foods and sought to identify the relative importance of response determinants. Multiple exposure variables, ranging from personal characteristics (anthropometry, glycemic and lipemic responses, gut microbiome variables, habitual diet, genetics) through meal composition to meal context, were integrated using machine learning to understand inter-individual variations in responses (**Figure 1**).[9] Non-food factors, including meal-timing, sleep and activity, were highly informative of these person-specific responses. Compared with a clinically measured response to dietary intervention, personalized prediction algorithms predicted glycemic responses with strong accuracy (Pearson's R, 0.77; $p<0.001$).

FIGURE 1: The relative contribution of multiple exposure variables relating to the individual, meal composition and meal context in predicting the individual response to: (a) serum triglycerides; (b) serum C-peptide, a pseudo-measure of insulin; (c) plasma glucose



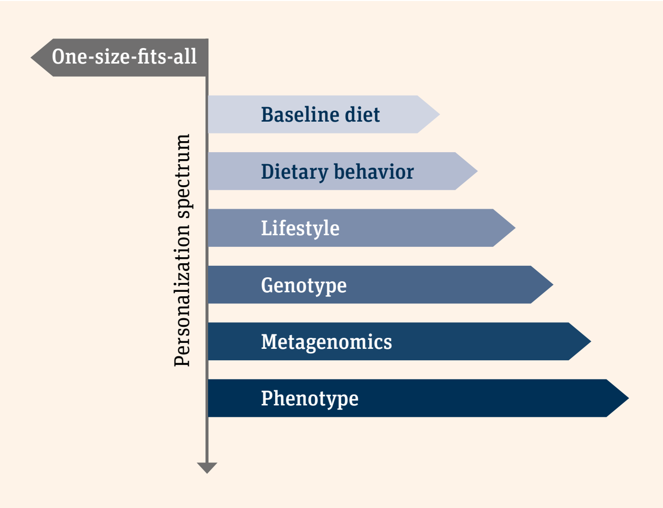
Source: Adapted from Berry et al. 2020.[9]

ZOE PREDICT 1 has uncovered a wealth of knowledge about the association between the gut microbiome and human health shared diet–metabolic health microbial signatures that segregate favorable and unfavorable bacterial taxa based on their association with health markers.[20] Where post-menopausal women were found to have worse glycemic control than men and pre-menopausal women, the association of menopausal state and metabolic health was partially mediated by the microbiome.[21] Such work advances the application of the modifiable gut microbiome as a cardiometabolic risk marker and could lead to development of microbiome-reshaping strategies that improve personalized dietary health.

PN research remains a high-cost and high-resource effort. However, while a significant health disparity exists between populations of different socioeconomic backgrounds, recent findings and developments in PN research and big data have highlighted multiple targets for application in resource-poor contexts.

> **"ZOE PREDICT 1 has uncovered a wealth of knowledge about the association between the gut microbiome and human health"**

FIGURE 2: Personalization of nutritional advice can be tailored to the individual by considering different parameters of personalization. While a one-size-fits-all approach represents no personalization, progressively deeper personalization can be achieved by measuring and incorporating various individual and environmental descriptive parameters into prediction algorithms



Bridging the gap

With 80 percent of NCD cases occurring in LMIC, there is an urgent need to reform traditional nutritional interventions and identify components of the PN process that can be adapted to low-resource users. PN can promote healthful metabolic and dietary behavior by means of different tiers of exposure measurement and personalization of advice, ranging from using baseline dietary assessment to deep clinical phenotyping.[17–19]

A spectrum of personalization exists, such that nutritional advice can be tailored to an individual to different degrees (**Figure 2**). Previous PN interventions have demonstrated the efficacy of a remote intervention across levels of personalization. The Food4Me study[19] aimed to explore different levels of personalized nutrition advice; although a personalized intervention was more successful than standard dietary advice, the group found that greater personalization of the advice using nutrigenomics and individual phenotyping did not further improve health outcomes. This highlights the fact that the efficacy of PN approaches should be evaluated at multiple levels of personalization, to identify potential benefits that are suitable to low-resource contexts where not all exposures can be measured or integrated into PN.

With technological advances in research methodology, biological assessment tools are becoming more accessible. One such example is the reduced costs for metagenomic analysis of the human gut microbiome. Moreover, as smartphones and internet connections become ever more accessible, the potential for remote data collection and targeted advice increases.

The ZOE PREDICT Program has leveraged the remote setting using a specially built smartphone application, thus reducing research costs and encouraging free-living compliance and real-world data collection. It has also utilized newly emerging remote methodologies for collecting individual biological data; such technology has been shown to be both accurate and of high potential for furthering the field of personalized nutrition research.[22] Using research publications and social media platforms, the ZOE group has also been able to leverage citizen science for contributions to PN research. To date, PN findings suggest that this application has the scalable potential to remotely produce prediction algorithms for the reduction and prevention of disease risk.

Concluding remarks

Research to date has been confined to high-income contexts with largely cost-prohibitive research methodologies and output applications. While the biological rationale for adopting PN approaches is clear, this field remains in its infancy and further understanding of response determinants and the practicality of PN intervention is necessary before LMIC and large-scale implementation. Moving forward, further evidence from well-designed intervention studies demonstrating the efficacy, cost-effectiveness and long-term sustainability of PN is required. In striving to minimize health disparities both within and between socioeconomic communities, PN approaches should be designed, built and tested using a tiered approach that enables greater access to them by all health professionals and those seeking health interventions.

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Beyond Conventional Iron Status Biomarkers
Stable isotopes as a precise tool for generating evidence to tackle anemia

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Anemia as a global health problem

Anemia remains a global public health problem, affecting one-third of women of reproductive age and four out of 10 children below 5 years of age.[1,2] It is associated with a high risk of cognitive impairment, decreased work capacity and, in severe cases, an increased risk of death during pregnancy, infancy and childhood.[3] One of the World Health Assembly (WHA) targets is to reduce anemia by 50 percent in women of reproductive age by 2025. The COVID-19 pandemic disrupted health and food systems, limiting access to nutritious foods and antenatal care programs. It has already led to increased deficiency of some micronutrients even though it is not clear how this has impacted the prevalence of anemia.[4–6]

Iron deficiency anemia (IDA) is a common form of anemia found in low- and middle-income countries (LMIC), and occurs when dietary iron intake fails to meet physiological requirements or when there is increased iron loss.[3] Food-based approaches such as dietary diversification including animal-source foods, and enhancement of iron intake through supplementation, food fortification and biofortification are being implemented to address IDA. However, information on the nutritional impact of these approaches is limited, partly because of challenges in the assessment of iron status and absorption. Precise methods such as stable isotope techniques have great potential to advance the evidence base to help inform actions needed to reach the WHA target on anemia reduction.

> **"Precise methods such as stable isotope techniques have great potential to advance the evidence base"**

Measurement of iron status

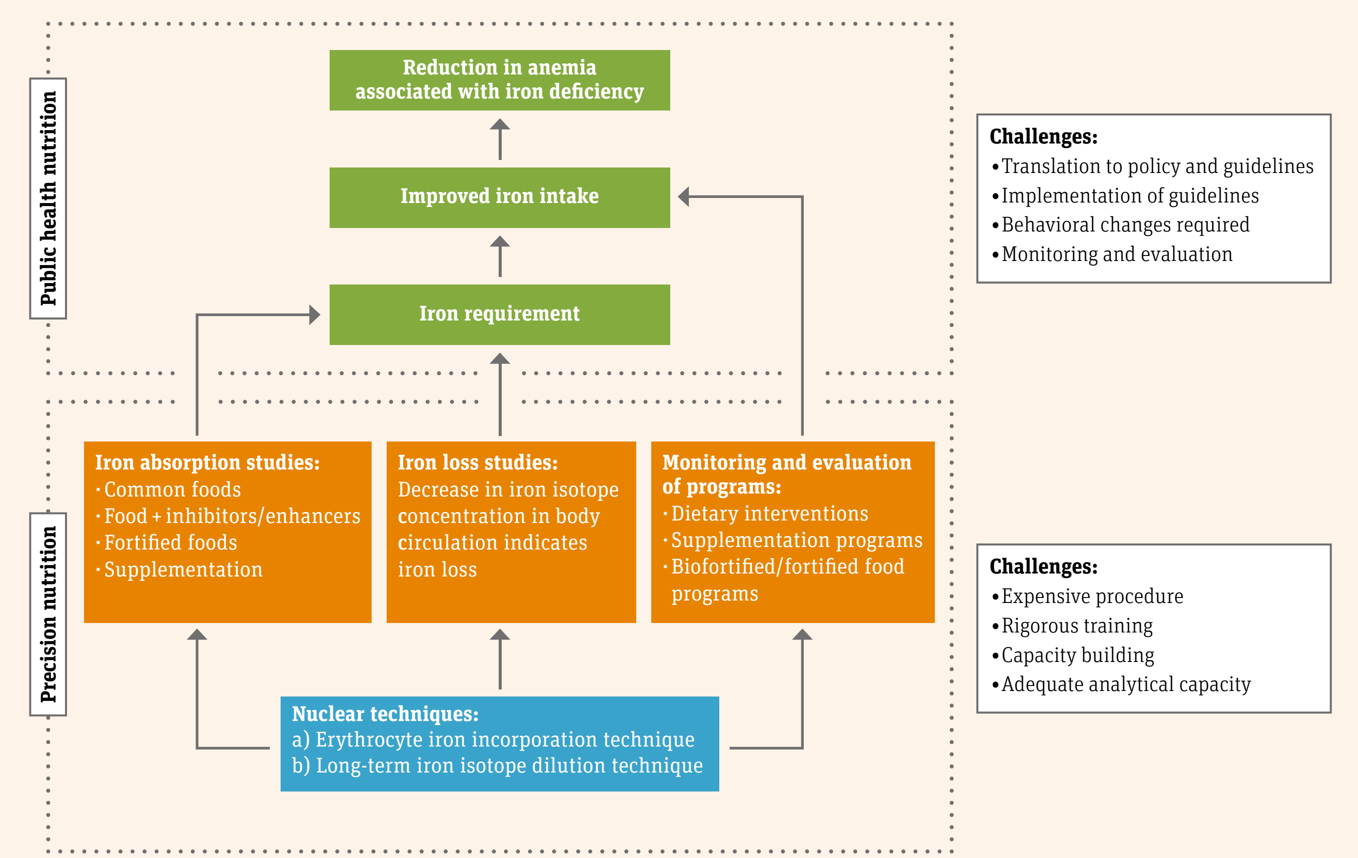
Iron status can be measured using conventional biomarkers such as serum ferritin, soluble transferrin receptor or hemoglobin, a commonly used proxy for iron status. However, these biomarkers are influenced by factors such as inflammation or infection. Moreover, they do not provide information on iron absorption and iron loss, the two most important factors related to iron status and requirements.[7] Iron absorption and loss can be accurately assessed using stable iron isotopes (**Figure 1**). There are four iron isotopes, of which the most abundant is ^{56}Fe. The rarer iron isotopes, ^{54}Fe, ^{57}Fe and ^{58}Fe, are commonly applied in iron studies,[8] using two different approaches: (**a**) the erythrocyte iron incorporation technique to measure iron absorption; and (**b**) the long-term iron isotope dilution technique to measure both iron absorption and iron loss.

Iron bioavailability studies to inform targeted interventions

The erythrocyte iron incorporation technique (**a**) is premised on the fact that iron metabolism is tightly regulated and 80 percent of absorbed iron is incorporated into red blood cells (RBCs) within 10–12 days. The enrichment stays stable over the lifespan of RBCs (~120 days). In a typical study, single or multiple test meals labeled with iron isotopes are administered (**Figure 2a**).

In the case of a single test meal, a blood sample is collected at baseline, before a study participant consumes the test meal extrinsically labeled with an iron isotope (^{57}Fe), followed by a second blood sample 14 days later (to allow enough time for incorporation into the RBCs). When multiple test meals are administered, these are extrinsically labeled separately with either ^{57}Fe or ^{58}Fe and are administered on different days, followed by blood collection after 14 days. The ratio between the enrichment of the administered tracer and that of the naturally abundant isotope (^{56}Fe) is then measured to calculate iron bioavailability. The bioavailability of nonheme iron from plant-based foods is lower than that of heme iron from animal-source foods.[9–11] The presence of inhibitors (e.g., phytates, polyphenols) and enhancers (e.g., ascorbic acid) in the meal also influences iron bioavailability. For example, concurrent consumption of tea with an iron-containing meal has been associated with a reduction in iron absorption by up to 15 percent; conversely, the presence of ascorbic acid was associated

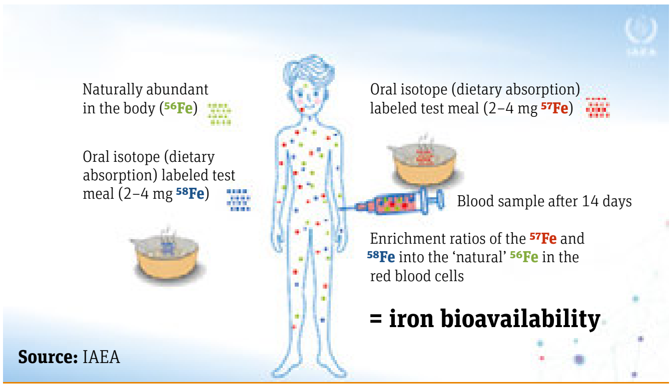
FIGURE 1: Framework to address iron deficiency anemia at the population level using a precision nutrition approach



The figure provides an overview of the possible linkages between precision nutrition and public health. Stable iron isotopes are used based on two approaches – erythrocyte iron incorporation or long-term iron isotope dilution – to measure iron absorption and iron loss, the two parameters necessary to define iron requirements at the population level. Further, stable iron isotopes are also used to monitor and evaluate national interventions or prophylaxis programs aimed at improving iron intake in order to reduce iron deficiency anemia. Despite being relatively expensive to conduct on a routine basis and the need for rigorous training and capacity building, isotope-based iron status assessment offers a precise evidence base to address anemia as a public health issue.

with a 10 percent increase in iron absorption.[12–14] Iron bioavailability is also influenced by physiological factors such as iron status, inflammation, infection and hypoxia. Studies on iron-deplete and iron-replete women showed twofold higher iron absorption in iron-deplete women.[12,13] These studies indicate the importance of targeted approaches to address issues such as different dietary patterns, diet quality and iron status.

FIGURE 2A: Stable iron isotope method to measure iron absorption using the erythrocyte iron incorporation technique



Source: IAEA

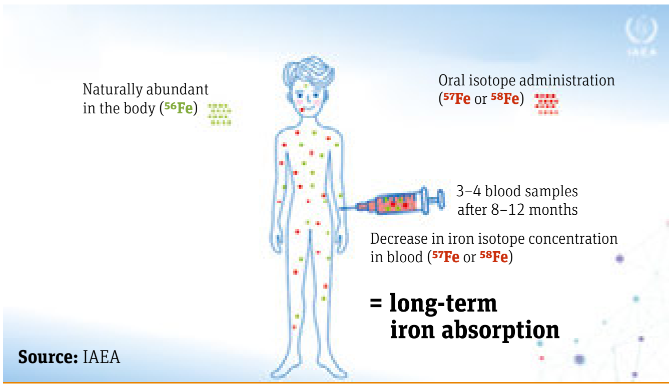
> **"Studies indicate the importance of targeted approaches"**

Defining iron requirements for specific populations and contexts

Long-term iron absorption in a real-life situation is measured using the iron isotope dilution technique (b). Previously, the assessment of long-term iron absorption and basal iron loss were founded on more invasive techniques using radioactive iron isotopes. These techniques formed the basis for reference iron intakes issued by the World Health Organization (WHO) and the US Institute of Medicine. More recently, the method was advanced to allow the safer assessment of long-term iron absorption using stable isotopes.

In this technique, an iron isotope is administered 8–12 months before the start of the study. This period allows for iron isotope equilibration in the body, thereby altering the iron isotopic signature (Figure 2b). Further dilution occurs with naturally abun-

FIGURE 2B: Stable iron isotope method to measure iron absorption using the long-term iron isotope dilution technique



Source: IAEA

dant iron from the diet, leading to a decrease in the enrichment of administered iron isotope, which represents iron absorption. The decrease in the quantity of iron isotope in circulation indicates iron loss and can be used to assess iron balance.

This technique was used on Gambian toddlers who were supplemented daily with 12 mg of iron for 12 weeks, followed by a 12-week control period. Results showed that the daily iron absorption was 3.8 times higher and the iron loss was unexpectedly higher (~72 percent) during the supplementation period compared with the control period.[15] The long-term isotope dilution technique using stable iron isotopes has successfully been used among women, children and adolescents to define iron loss and balance,[16–18] and the International Atomic Energy Agency (IAEA) plans to support the further use of this technique to address problems of nutritional anemia through Coordinated Research Activities.

Informing food fortification programs from stable isotope-derived data

Stable iron isotopes continue to be used to assess the effectiveness of national food fortification programs and the efficacy of community interventions providing iron supplementation (**Figure 1**). The IAEA has supported research to evaluate the impact of various food-based approaches to improve iron status in LMIC through its Technical Cooperation Program or Coordinated Research Activities. For example, researchers in Thailand, Haiti and Morocco evaluated iron absorption from various forms of iron in iron-fortified rice and wheat flour. The bioavailability of different forms of iron fortificants – including ferrous sulphate, ferric ammonium citrate, and a combination of ferrous sulphate and ferric sodium ethylenediaminetetraacetic acid (NaFeEDTA) in 2:1 molar ratio added to a rice dessert – was studied in Thai children (8–24 months), and showed that iron absorption was significantly higher when provided in combination with other forms of iron, as opposed to separately.[19]

Another study among Haitian women and children showed about 40 percent increase in iron absorption with NaFeEDTA compared with ferrous fumarate when added to wheat flour.[20] This study provided the evidence base for the Haitian Government to define the level and type of fortificants to add to wheat flour as part of their national fortification program.[21] Similarly in Morocco, using the precise erythrocyte iron incorporation technique, iron bioavailability from wheat flour was found to be higher with NaFeEDTA compared with elemental iron; this led to a redefinition of the wheat flour fortification policy, with a shift to NaFeEDTA as the preferred fortificant.[22]

Currently, the IAEA supports researchers in Benin to evaluate the impact of a school canteen food program on iron status. In Botswana too, researchers are receiving support from the IAEA to evaluate the impact on iron absorption and anemia prevalence of a sorghum–soy porridge blend fortified with multiple micronutrients. This dietary intervention is part of the national food program targeting children aged 6–36 months. Stable iron isotopes have also been used to evaluate projects on biofortification. For example, a study from India showed that iron absorption from biofortified pearl millet was 3 percent higher compared with control pearl millet in young children.[23] These studies can help to shape programs to reduce IDA.

> **"Stable isotope techniques provide accurate and precise information on iron absorption"**

Conclusion

Stable isotope techniques are safe and applicable across all age groups, and provide accurate and precise information on iron absorption. It is important to note that these techniques are relatively expensive to conduct routinely because they rely on specialized analytical procedures and high-grade chemicals. In addition, they require rigorous training and capacity building of resource personnel along with adequate institutional facilities and equipment. However, the use of stable iron isotope techniques has helped inform context-specific dietary recommendations and national food-based policies. Further, it is now possible to accurately measure long-term iron absorption, loss and balance in real-life conditions, offering the potential to inform the debate on context- and population-specific recommendations on iron requirements.

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Settling the Protein Quality and Requirements Debate: How isotopes can help

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The case for additional research on protein requirements

Is protein still considered a nutrient of global public health significance? This question was well articulated under the theme 'the protein gap' by Semba in 2016.[1] The Food and Agriculture Organization of the United Nations (FAO) has led discussions on protein requirements and protein quality evaluation since 1955.[2]

This discussion is more imperative than ever now, with a rapidly increasing global population and dynamic food systems driven by varying externalities such as elevated emissions of atmospheric CO_2 that are projected to lead to a significant reduction in the food protein content of major food crops by 2050.[3] In order to reduce the diet-related environmental footprint, a shift to more plant-based protein sources has been proposed.[4] However, such diets are limiting in indispensable amino acids (IAA) and the risk of protein deficiency is increased, especially in low- and middle-income countries, where diets are predominantly plant-based; therefore dietary recommendations to enhance protein quality need to be context- and population-specific.

This review summarizes isotope-derived evidence on protein quality, and argues the case for additional research on protein requirements. Stable isotopes can provide precise and accurate information about protein quality and requirements with the potential to help improve protein intake recommendations for different age groups and physiological states in specific populations.

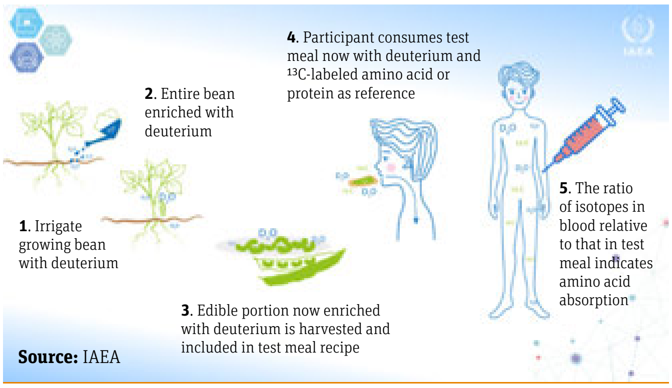
> **"Dietary recommendations to enhance protein quality need to be context- and population-specific"**

Isotopic techniques in the assessment of protein quality

The protein quality of a given food connotes a combination of the concentration of IAA and their respective bioavailability. Protein digestibility has conventionally been based on oro-ileal balance studies that require either naso-ileal intubation or terminal ileum fistulation, which are invasive.[5] In 2013, an FAO Expert Consultative Group report[6] recommended a shift from the use of the protein digestibility corrected amino acid score (PDCAAS) to the digestible indispensable amino acid score (DIAAS). The PDCAAS is based on the amino acid score of a crude dietary protein multiplied by its respective true fecal nitrogen digestibility; it is prone to errors associated with microbiota protein synthesis.[7] By contrast, the DIAAS is based on ileal digestibility and reflects a percentage of the total daily requirements of the most limiting essential amino acid in a given protein.[8] A 2014 FAO Expert Consultative meeting[9] recommended various methods, including isotopic techniques, to be used for DIAAS assessment.

A dual isotope tracer technique (DSIT) developed under a coordinated research project[10] on the digestibility of protein from plant-based diets supported by the IAEA involved intrinsic labeling of growing legumes with deuterium oxide (**Figure 1**).

FIGURE 1: Dual isotope tracer technique involving intrinsic labeling of growing legumes with deuterium oxide



Source: IAEA

Upon harvest, the edible portion was incorporated into habitual local recipes to prepare a test meal to which a second isotope-labeled reference protein (e.g., ^{13}C-spirulina) or crystalline amino acid (e.g., ^{13}C-phenylalanine) was added before it was consumed. Isotopic enrichment in blood relative to that in the test meal represents the IAA absorption that is used to calculate the DIAAS based on the reference amino acid pattern.[8] The DSIT has been applied to generate the first data of its kind on the true ileal digestibility of amino acids from various foods in human studies.[11–14]

Shivakumar and colleagues[11] showed that the absorption of amino acids from staple plant-based foods (mung bean, finger millet and rice) commonly used in preparing complementary foods for children below 2 years of age was much lower than that of egg protein, and that there is an inverse relationship between the risk of stunting and measured DIAAS. Another study[12] showed that the absorption of amino acids (especially methionine, lysine and threonine) from legumes was very low among healthy Indian adults. A study from Mexico[13] showed that threonine was the most limiting IAA in pinto beans.

These three studies reinforce the need for the inclusion of animal-source foods in diets, especially for growing children. However, consuming more animal-source foods will not suffice if general dietary patterns are poor. Another study[14] demonstrated that IAA absorption from hen's egg was much reduced if black tea was consumed simultaneously with the meal. This confirms the need for population-specific dietary guidelines and educational programs to ensure the intake of adequate quality protein to meet requirements across different age groups and physiological needs. To enable this, as a first step, a global database on protein quality based on the DIAAS will be developed.

> **"Consuming more animal-source foods will not suffice if general dietary patterns are poor"**

Isotopic techniques in the assessment of protein requirements

Protein requirements can be defined as the minimum average daily intake of protein from diverse foods to prevent deficiency and to meet physiological and developmental needs,[15] and are derived as an estimated average requirement to meet the needs of half the population. However, the requirements are often set as recommended dietary allowance to satisfy about 98 percent of the population, taking into account inter-individual variability.[16] Hitherto, human protein requirement recommendations have been set based on nitrogen balance studies.[17] Nevertheless, the nitrogen balance approach is known to underestimate protein requirements.[18] With recent advances in isotopic techniques, such as the indicator amino acid oxidation (IAAO) method, ^{15}N end-product method, whole-body potassium counting (WBKC) and $^{2}H_2O$-creatinine, it is now possible to accurately assess protein and amino acid requirements in different population groups.[15] Current adult data on protein requirements from the joint FAO/WHO report of 2007[19] were derived using either IAAO or a combined 24-hour IAAO and indicator amino acid balance method (24h-IAAO/IAAB).[18] The IAAO method is based on a short-term protocol (~8 hours) that enables adaptation to a feed with a range of test amino acid intakes and assessment of the oxidation of another amino acid referred to as the indicator amino acid, typically ^{13}C-phenylalanine. In IAAO, it is assumed that if one IAA is deficient, all other IAAs including the limiting indicator amino acid will be oxidized. The oxidation of the indicator amino acid decreases with increasing amounts of the limiting test amino acid and plateaus once the minimum requirement of the test IAA is met.[16,18] Using the IAAO method, Elango and colleagues[20] demonstrated that the mean and population safe protein requirements for children (aged 6–11 years) are much higher (71 percent and 63 percent, respectively) compared with previous recommendations for US children of similar age. Another study,[21] showed that current recommendations for total aromatic amino acid intake for pregnant women represent an underestimation of true requirements by 22 percent and 39 percent in early and late pregnancy, respectively. In contrast, a study using WBKC,[22] based on naturally occurring radioactive potassium isotope, showed that additional protein requirements in the second and third trimesters of pregnancy were comparable with the 2007 WHO/UNU/FAO recommendations.

Summary and looking ahead

The intake of adequate and quality protein is important across the life course and varying physiological states. Isotopic techniques are being used to generate data on protein and amino acid digestibility based on the DIAAS and new evidence to better estimate population-specific protein requirements. However, a few considerations are worthy of note here. The various isotopic techniques need validation against the oro-ileal intubation method. Additionally, controlled feeding protocols with repeated measurements are required, but this approach is associated with a high participant burden, limiting the potential for wide application. Nevertheless, isotopic approaches remain the only precise and accurate tools available to generate new information on protein quality and protein and amino acid requirements. Stable isotopes are safe and have been used for decades across all age and physiological groups, with no adverse health effects.[23] More studies are required to generate true protein digestibility and DIAAS data from a variety of foods to inform guidelines on the protein quality of locally available foods and the adequacy of meeting protein requirements. To this end, the IAEA and FAO will continue working to update evidence on protein quality assessment, develop a protein quality database and advance dialogue on protein requirements.

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Harnessing the Plasma Proteome to Reveal Hidden Hunger

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Micronutrient deficiencies represent a substantial public health burden in low- and middle-income countries, where a widely quoted number of 2 billion affected, first reported at the World Health Assembly in 1991,[1,2] has recently been updated to suggest 1.6 billion women and preschool-aged children *alone* are deficient in at least one of three often surveyed micronutrients. The exercise suggests that the global number deficient across all age groups, and additional micronutrients, is far higher.[3] Periodic surveys have affirmed the number is large, if variable, by nutrient, life stage and region.[4]

It is a concern that micronutrient surveys have been infrequent, or not performed at all, in most countries where risks of deficiencies are widespread and, thus, remain *hidden*. Reasons lie with high operational costs at reference laboratories, given the sophisticated instrumentation and technical expertise required to conduct biochemical assays that vary in methodology by biological matrix and properties of the analytes of interest.[5]

As a result, few standardized methods for individual nutrients exist on a broad scale. When performed, surveys typically still assess the status of only a few of the essential nine trace minerals and the 13 fat- and water-soluble vitamins.[6] At times, an inflammatory biomarker may be included, but rarely are nonessential nutrients, lipids, or other metabolic and functional biomarkers of health, dietary intake or development measured. Further, while dietary, food security and anthropometric findings typically accompanying micronutrient surveys are usually rapidly available, biochemical results on micronutrient status and deficiencies often take 2 years or longer to disseminate, and are rarely repeated within a decade. Consequently, governments and public health agencies are often left to interpret outdated and incomplete data on prevalence, trends and intervention responses.

Assays evaluating one to a few nutrient and inflammation biomarkers have largely been aimed at facilitating field surveys.[7,8] However, low-resource countries with persistent undernutrition would be well served to have a single, reliable and efficient meth-

Rural Bangladeshi children and women, illustrating demographic groups in low- and middle-income societies intended to benefit most from a future low-cost, in-country, high-throughput, multiple micronutrient assay.

TABLE 1: Summary of proteins correlated in relative abundance with concentrations of micronutrient and other plasma indicators[a] in a population sample of 500 6- to 8-year-old children in southern Nepal

Plasma constituents		Correlated proteins[b]			
Target molecule	**Biochemical indicator**	**Positive**	**Negative**	**No. of predictors (lead protein)[c]**	**$R^{2,c}$**
Vitamins					
Fat-soluble					
Vitamin A[10]	Retinol	81[d]	61[d]	2 (RBP4)[e]	0.79
Vitamin D[10]	25(OH)D2	4	2	2 (GC)[e]	0.48
Vitamin E[25]	α-Tocopherol	61	58	6 (APOC3)[e]	0.71
	γ-Tocopherol[f]	8	4	2 (APOC3)[e]	0.20
Vitamin K[28]	PIVKA-II[f]	2	3	1 (F2)[e]	0.29
Water-soluble					
Vitamin B_6[d]	Pyridoxal 5-phosphate[f]	39	49	6 (C9)[e]	0.65
Folate (B_9)[a]	Folate	0	0	0	–
Vitamin B_{12}[d]	Cyanocobalamin	0	0	0	–
Carotenoids[29]					
	α-Carotene[f]	0	0	0	–
	β-Carotene[f]	1	3	0	–
	β-Cryptoxanthin[f]	31	20	3 (APOA1)[e]	0.50
	Lutein/zeaxanthin[f]	7	4	1 (APOC3)[e]	0.34
	Lycopene[f]	0	0	0	–
Trace elements					
Copper[27]	Copper	103	129	6 (CP)[e]	0.76
Iron[a]	Ferritin[f]	19	16	3 (TF)[e]	0.44
Selenium[26]	Selenium	3	0	2 (SEPP1)[e]	0.63
Iodine	Thyroglobulin[f]	0	0	0	–
Cholesterol[30]					
	LDL-C[f,g]	13	2	1 (APOB)[e]	0.48
	HDL-C[f,g]	39	23	1 (APOA1)[e]	0.62
	Triglycerides[f,g]	10	14	1 (APOC2)[e]	0.28
Inflammation[31]					
	α1-acid glycoprotein[f]	84	122	1 (ORM1)[e]	0.77
	C-reactive protein[f,h]	85	109	1 (CRP)[e]	0.85

a Relative abundance of plasma proteins were quantified by isobaric tags for relative and absolute quantitation (iTRAQ);[9,10] nutrient and acute phase reactant concentrations were measured by conventional biochemical assays.[23] Proteins were log_2-transformed per convention, and linear mixed effects (LME) models were employed to derive best linear unbiased predictions on which nutrient and inflammation biomarker concentrations were regressed and correlations derived.[10]

b Nutrient: protein correlates for which individual LME regression slopes (b) were statistically significantly different (q = chance-adjusted p < 0.1, except for inflammation proteins for which q < 0.01) from a null hypothesis of b = 0.

c Variance in nutrient or inflammation biomarker concentration explained by predictor proteins modeled by a forward stepwise multiple regression procedure. Proteins in parentheses were lead proteins in models; where no models have been reported to date, the lead protein listed is a most strongly associated protein with its R^2 value reported.

d Unpublished summaries from manuscripts in preparation.

e Protein Entrez Gene symbol, in alphabetical order: APOA1, APOB, APOC2 and APOC3, Apolipoproteins A-1, B, C-II and C-III; CP, ceruloplasmin; CRP, C-reactive protein; C9, complement 9; F2, prothrombin or coagulation factor II; GC, Group Component (vitamin D binding protein); ORM1, orosomucoid 1, or α1-acid glycoprotein (AGP); RBP4, retinol-binding protein 4; SEPP1 (selenium protein P1); TF, transferrin.

f Distribution was normalized by log_2 transformation before analysis.

g Low- (LDL-C) and high- (HDL-C) density lipoprotein cholesterol.

odological platform capable of locally evaluating population status with respect to a more comprehensive panel of micronutrient, inflammation and other health biomarkers. This ability would allow governments to make timely decisions about appropriate interventions for entire populations or targeted at vulnerable subgroups, and to monitor their effects. While not 'precision' nutrition at the individual level, this potentially fills a current gap in thoroughly describing context-specific nutritional needs, given that diets, morbidity burdens and other health risks can vary between countries and, thus, require country-specific solutions.

> **"Few standardized methods for individual nutrients exist on a broad scale"**

Discovering the plasma nutriproteome

A one-stop assay for revealing hidden hunger does not yet exist. However, building on advances in the field of proteomics, and inspired by opportunities to apply omics to understand nutrition, there has been progress in profiling the plasma proteome for clusters of proteins that may prove to reliably co-vary with plasma nutrient concentrations (*nutriproteomes*). From these clusters, predictors can be modeled to mimic distributions and estimate prevalences of multiple nutrient deficiencies, guided by statistical criteria of model quality.[9,10] Further, from the overall sample of detected proteins, which can range from hundreds to thousands, depending on the proteomics assay, additional biomarkers of metabolic, nutritional and health status may emerge meeting thresholds for false discovery.

Notwithstanding biological complexity (reflected in a 10-billion-fold range in protein concentrations),[11] extensive post-translation modifications, and methodological challenges for quantification and analysis,[12–14] there are two compelling reasons to probe the plasma proteome to assess a population's micronutrient status.

The first is that, as master controllers of all cell processes,[13] proteins mediate virtually all direct and systemic biological functions of micronutrients. The *plasma proteome*, or the sum of all circulating proteins, offers the most comprehensive array of proteins of any tissue in the body from which to detect correlates of nutrients. Originating from the liver and peripheral tissue, plasma proteins include those that function in the blood such as albumin, apolipoproteins, acute and chronic phase reactants, and molecules of the complement and coagulation cascades. They also comprise cellular content leaked into the bloodstream from catabolic processes that may nonetheless be correlated with nutrient concentrations, and also be markers of disease. Finally, broadly, low-abundance proteins exist that function in cell-signaling cascades, such as hormones and cytokines, among numerous other intra- and extracellular actors.[12]

A second motivation to probe the plasma proteome is that once detected, a selection of predictive proteins could ultimately all be quantified on a common methodological platform. Currently, detection of the plasma proteome requires sophisticated laboratories, capable of performing and supporting high-throughput tandem mass spectrometry,[13] or more recent methods such as multiplexed, slow off-rate modified aptamer (SOMAmer)-based protein quantification[15–17] or methods based on nanoparticle detection technology.[18] Combining proteomics with nutrient status data similarly requires state-of-the-art nutritional biochemistry to provide 'gold standard' distributions of micronutrient biomarkers and other analytes. Thus, for the time being, discovering the *plasma nutriproteome*, clusters of plasma proteins associated with nutrient status with a low false discovery rate (FDR), necessarily remains an expensive and time-consuming pursuit, while advances in biochip microarray[19] and microfluidics[20,21] technologies offer future promise of candidate predictor concentrations being quantitated on resource-adaptable, benchtop platforms.[22]

> **"Proteins mediate virtually all direct and systemic biological functions of micronutrients"**

Initial proof of concept

In recent years, proof of concept has been demonstrated through state-of-the-art biochemical and proteomics methodology to reveal clusters of plasma proteins (*nutriproteomes*) that co-vary across nutrient concentrations with a low FDR (a chance-adjusted p-value < 0.1 or < 0.05), from which provisional models predicting status have been developed for some nutrients. This work has also revealed value in mining the plasma proteome for other biomarkers of health and development.

Briefly, among 500 6- to 8-year-old children living in the southern plains of Nepal, where undernutrition is endemic, plasma micronutrient concentrations were estimated by conventional biochemical assays.[23] Samples were depleted of six highly abundant proteins, to enable detection of low-abundance proteins, and relative abundance was estimated for nearly 1,000 proteins by isobaric tags for relative and absolute quantitation (iTRAQ) tandem mass spectrometry.[9,10] Missing values were imputed, distributions $\log_2$-transformed as needed to normalize, and each nutrient : protein pair was evaluated across the 500 samples employing linear mixed effects models, providing the opportunity to evaluate the slope and statistical significance of association and reveal membership in certain plasma nutriproteomes.

Protein expression was also evaluated against other analytes (i.e., lipids and acute phase proteins), anthropometric measurements and scores on a subsequently administered cognition test. Plasma proteomes (meeting an FDR < 0.1) were observed for 12 of 17 examined nutrients and dietary carotenoids, ranging in size from three proteins for selenium to 232 for copper[24] (**Table 1**). Forward stepwise regression analysis created models that, with two to six protein co-variates, could explain high proportions of variance (coefficient of determination, or R^2) in plasma concentrations of retinol (0.79),[9] α-tocopherol (0.71),[25] vitamin B_6 (0.65) (unpublished, 2022), selenium (0.63)[26] and copper (0.76).[27] Presently, R^2 values of ~0.6 and higher have been found to adequately predict in-sample distributions and prevalences of deficiency for vitamin E[25] and selenium.[26] Notably, prediction was found to rely more on a strongly associated binding protein first entering a model, rather than the overall number of proteins associated with a nutrient. Plausible, if not predictive, proteomes have been observed for vitamins D[10] and K (PIVKA-II)[28] and three of five carotenoids, particularly β-cryptoxanthin.[29] Proteomes were not observed in this study for either folate or vitamin B_{12}, possibly reflecting nonalignment of detected dynamic ranges required for these two nutrients. However, large and plausible proteomes were revealed for other systems regulating lipid homeostasis (i.e., low-/high-density cholesterol and triglycerides)[30] and inflammation ($α_1$-acid glycoprotein and C-reactive protein).[31] Beyond emerging promise in micronutrient assessment, the plasma proteome may offer biomarkers of other functional aspects of health and nutrition. For example, in the Nepal study, clusters of proteins were associated with anthropometric indicators of childhood including height-for-age, weight-for-age and upper arm muscle area.[32] The relative abundance of a network of cytoskeletal proteins was found to be depressed in children who were born with a small head circumference, a proteomic footprint of gestational growth not observed with other birth measurements.[33] Finally, Universal Nonverbal Intelligence Test (UNIT) scores, evaluated a year later, were negatively correlated with pro-inflammatory proteins (e.g., complement components), possibly revealing depressive effects of prolonged, subclinical inflammation on cognition.[34]

"The plasma proteome may offer biomarkers of other functional aspects of health and nutrition"

Generalizability of a plasma proteomics approach to micronutrient assessment rests on reliable prediction by proteins across populations, signaling a need to expand discovery, validation and application by state-of-the-art methods. For example, a study is under way to detect proteins associated with nutrient, lipid and inflammation status in plasma samples of first-trimester pregnant women in Bangladesh,[35] in which ~6,500 plasma proteins are being assessed by SOMAmer scanning,[17] a methodology that has proven valuable in systems medicine and modeling chronic disease risks.[15,16] A reliable, predictive plasma proteome, assayed on a single platform, has the potential to reveal hidden hunger more broadly, create additional biomarkers of public health value, and contribute to the advancement and integration of multiple omics assessment strategies in the future.[36]

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Experience from the Field

Point-of-Need Diagnostics Across the Nutrition Value Chain

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The potential of point-of-need diagnostic tools

Miniaturization of traditional laboratory tests to develop field-friendly diagnostic testing tools, broadly referred to as point-of-need (PON) diagnostics (Dx) in this article, can be used by anyone, anywhere. Such PON Dx are a critical component of a precision nutrition[1–4] technology ecosystem that can be implemented across the food value chain from farm to fork to optimize food quality, safety and health. Portable quantitative and semiquantitative devices or test kits have the potential to overcome some of the limitations of traditional methods of testing,[5] such as the need for sending test samples to a centralized laboratory, expensive equipment and specially trained staff. PON Dx can potentially bridge major healthcare, research, monitoring and implementation gaps for precision nutrition by making testing easily accessible to a large proportion of the global population. **Figure 1** shows a schematic of the farm-to-fork food value chain and points at which PON Dx testing could be applied.

Nutrient quality

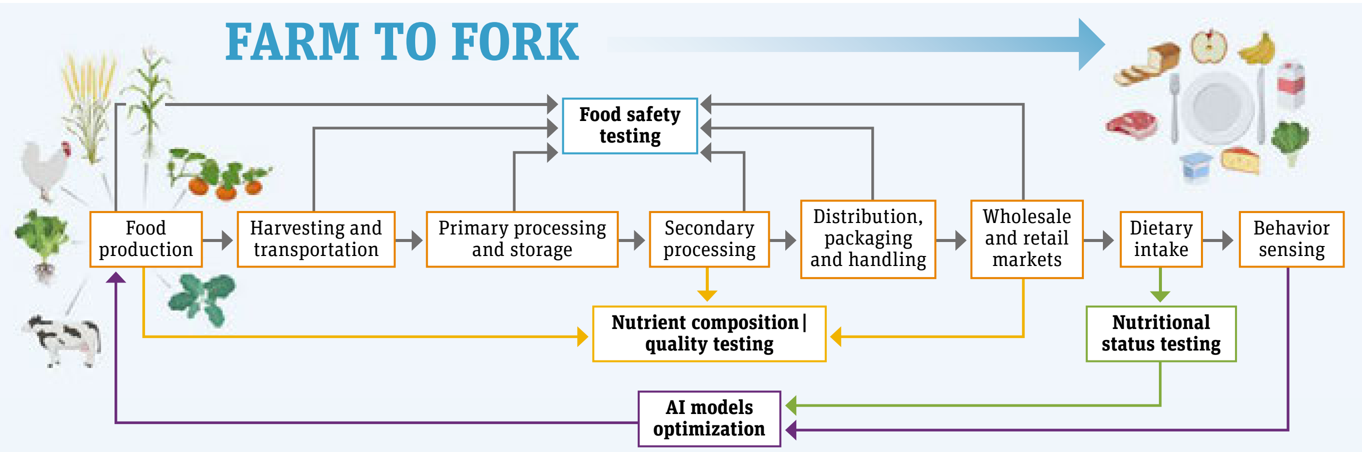
Recent advances in PON Dx have the potential to strengthen quality control in food fortification programs by enabling improved monitoring of nutrient composition at every stage, from production to consumption. This can include monitoring to ensure optimal dosing during processes such as fortification, and assessment of fortification levels of food sourced from market. Examples of commercially available devices for micronutrient analysis in food products include BioAnalyt's iCheck series for vitamin A, vitamin E and carotene, and the Strategic Alliance for the Fortification of Vegetable Oils (SAFO) Test Kit by BASF.

> **"Point-of-need diagnostics can potentially bridge major healthcare, research, monitoring and implementation gaps"**

Food safety testing such as for mycotoxins in crops and foods

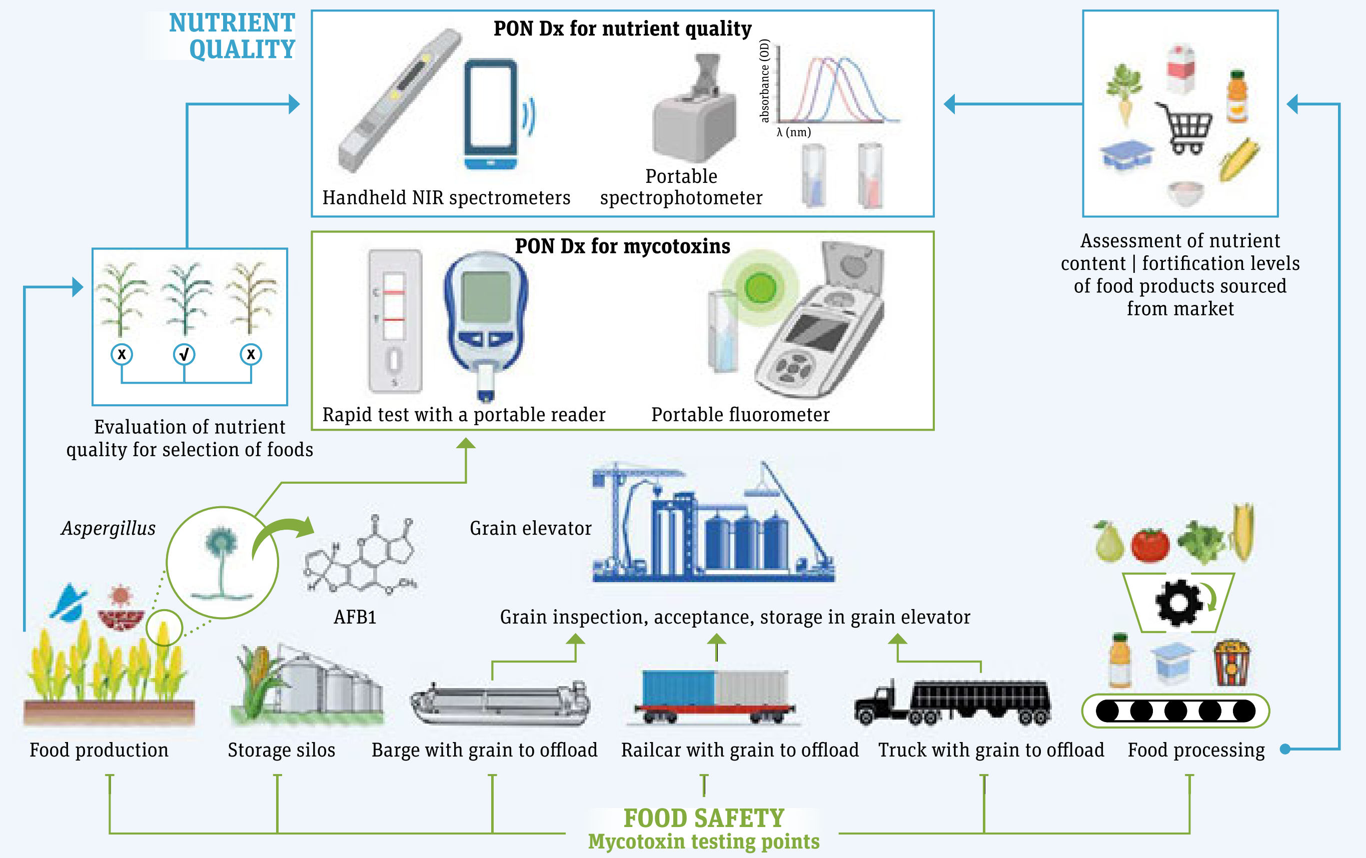
For the purposes of this paper, we use mycotoxins as an illustrative example for the multiple domains of food safety. Mycotoxins are toxins produced by certain fungi that are harmful to humans and domestic animals. Mycotoxins may contaminate staple foods and feeds worldwide, posing several significant food safety concerns. Portable testing methods to detect mycotoxins at various stages of the food value chain are critical to prevent adverse outcomes of consumption of contaminated food or feed. Numerous commercial mycotoxin testing kits are commercially available

FIGURE 1: Opportunities for point-of-need diagnostics across the food value chain



Source: Created with BioRender.com

FIGURE 2: Nutrient quality and mycotoxin testing points in the food value chain



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from Charm Sciences, Neogen, Romer Labs and VICAM that include lateral flow assays and portable fluorometers for various types of mycotoxins. **Figure 2** summarizes the nutrient quality and mycotoxin testing points in the food value chain.

Assessment of nutritional status

The lack of accurate methods for evaluating nutrition status at the PON hampers our ability to enable precision nutrition and target interventions to those who need it most, thereby limiting major improvements in public health. Mobile-device-based diagnostics based on lateral flow immunoassays developed by our research team and others, similar to the rapid antigen tests for infection or pregnancy tests, have been shown to meet WHO's ASSURED[6] criteria for quantification of a wide range of biomarkers of nutritional status. PON screening for biomarkers of nutritional status and inflammation including ferritin,[7] soluble transferrin receptor,[8] C-reactive protein,[9] alpha-1-acid glycoprotein,[10] folate,[11] retinol-binding protein,[12] vitamin D_3[13] and procalcitonin[9] from a drop of finger-prick blood within a few minutes have been described. PON Dx for nutritional status assessment can be applied for monitoring during intervention and surveillance programs in home, community and clinical settings. **Figure 3** shows a schematic of the iterative process for nutritional intervention[14] and monitoring, along with nutrient composition and quality. Such nutritional assessment can be useful to identify individuals likely to benefit from an intervention, provide tailored recommendations, and help determine the efficacy and effectiveness of a nutrition program.

Challenges and limitations

There are unmet research and technological needs for improving PON diagnostics across the nutrition value chain, including better sampling techniques for large-volume samples, multiplexed tests, and simpler sample preparation for both food and human specimens. The cost per test can also be prohibitive when large numbers of samples are to be tested in surveillance studies. Furthermore, the cost of the reader and reagents used in some of the commercially available test kits can sometimes be a limiting factor for implementation in low-resource settings.

> **"PON Dx can help transform multiple points of the food and nutritional value chain"**

Future directions

The ongoing development framework for precision nutrition is expected to drive a major demand for advancements in portable diagnostics and decision support systems that enable regular assessment of nutritional status in individuals and populations as well as the nutrient quality and safety of food. Investments in last-mile translational efforts for existing technologies to transition out of academia and funding to enable new entrants in the market, particularly in low-resource settings, can lower costs and increase both the range of potential tests offered and their availability for wider use and greater impact.

Developers of PON Dx would benefit from evaluating implementation barriers and how technology adopters perceive its value from the very early stage of development, rather than focusing on technical considerations alone.[15] Given the multidisciplinary nature of nutrition research, this requires collaboration among researchers with a broad range of expertise, including nutritionists, clinicians, bioinformaticians, social scientists and other stakeholders.

Overall, PON Dx can help transform multiple points of the food and nutritional value chain to improve food quality, enable targeting of resources and help optimize overall health. Internet of Things (IoT) devices across the value chain can further enable feedback to producers, fortifiers, food aid program providers, policy planners and end users on how to best meet the needs of consumers.

Conflict of interest

Saurabh Mehta and David Erickson hold equity in VitaScan, a startup commercializing point-of-care assays for micronutrient status based partially on the technology developed in their research laboratories at Cornell University.

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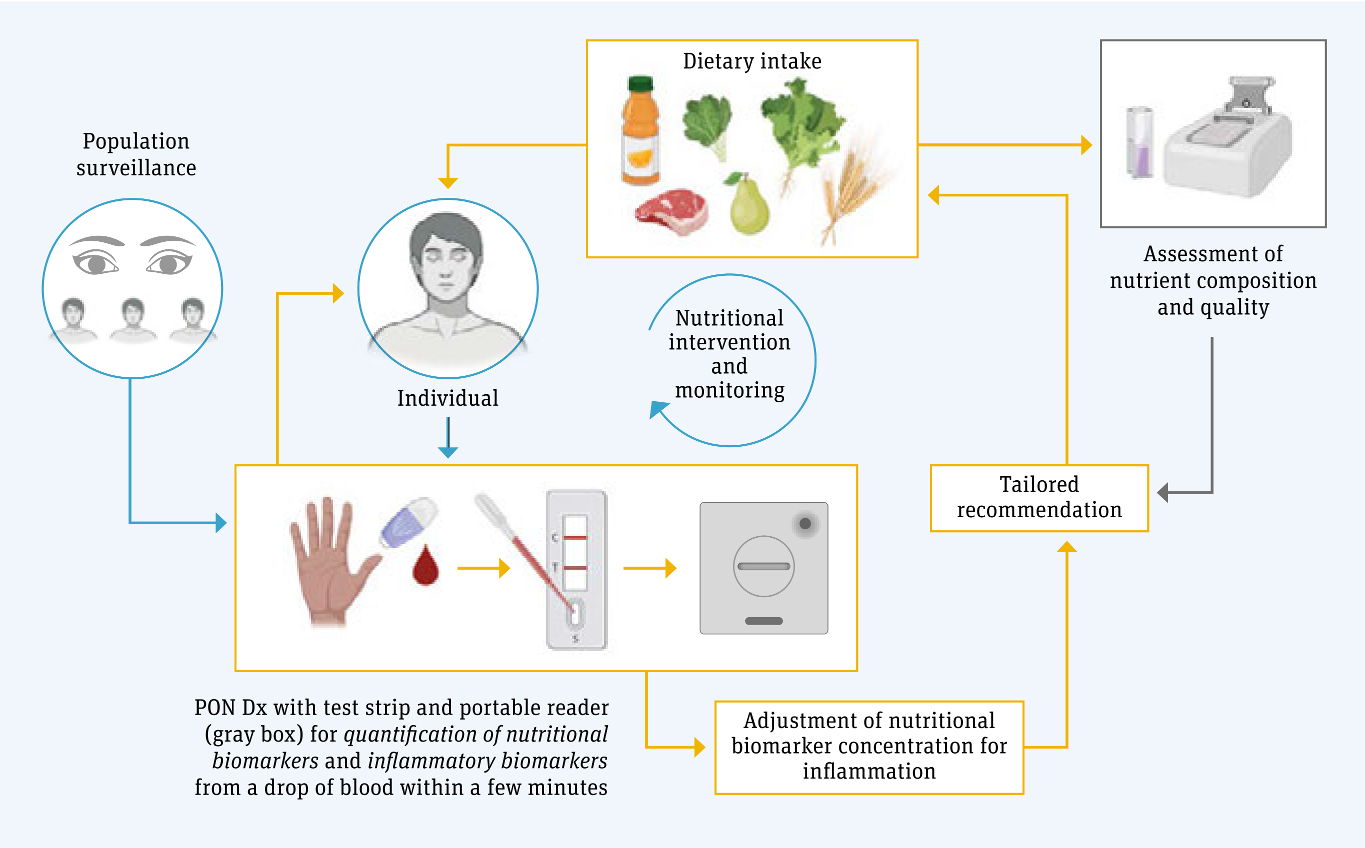
FIGURE 3: Intervention and point-of-need diagnostics for monitoring nutritional status and assessment of nutrient composition and quality



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Surveying the Relevance of Precision Nutrition for Low- and Middle-Income Countries

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The definition of precision nutrition

The Precision Nutrition (PN) for Low- and Middle-Income Countries (LMIC) project is supported by the Swiss Food & Nutrition Valley (SFNV), a not-for-profit association aiming to innovate the food ecosystem for better planetary and human health through collaboration with a variety of entities including *Sight and Life*.

The mission of the PN for LMIC project is to make the use of PN more accessible, affordable and desirable to LMIC as an approach to tackle the most pressing nutrition challenges. The first key project objective was to conduct a joint needs assessment with nutrition experts working in these settings, to identify geographic-specific nutritional challenges, current solutions and the relevance of PN for LMIC. The aim of the assessment is to gain a better and deeper understanding of the relevance, needs, challenges and opportunities that PN approaches can address for the benefit of LMIC populations.

The PN for LMIC working group found that the terms 'personalized nutrition,' 'targeted nutrition' and 'PN' were largely used interchangeably and were confined to high-income countries. The three terms, however, had common core elements, including tailoring nutritional recommendations and solutions to account for individual variation in relation to phenotype, genotype, lifestyle behavior, goals and preferences.[1–15] To help build understanding, the working group developed its own definition (see **Box 1**).

BOX 1: The Precision Nutrition (PN) for Low- and Middle-Income Countries (LMIC) project working definition of PN for LMIC

"Precision nutrition is an approach that uses rigorous scientific information on an individual's characteristics and environment. This information is used to develop targeted, accessible, affordable, desirable nutrition solutions that offer measurable individualized benefit. Such targeted solutions address the most pressing nutrition challenges faced in LMIC."

The PN for LMIC working group

PN approaches include tools with varied accessibility, ranging from anthropometric and other measures of nutritional status that are more widely accessible for LMIC, to gene- and 'omics'-based types of information that are less accessible.[1–15] One example of a successful application of PN in LMIC incorporates a proteomics approach.[16] HIV-infected children with severe acute malnutrition were found to exhibit metabolic stress, including pathways enriched for inflammation and lipid anabolism.[16] Because HIV is a chronic infection,[17] this likely represents a sustained altered lipid metabolism. Current treatments include ready-to-use therapeutic foods, which are high in fat and could potentially cause unintended harm to these children; therefore, children in this risk group could benefit from precisely formulated ready-to-use therapeutic foods.[16]

To assess whether PN approaches could find further relevance in LMIC, we distributed a 24-question survey to 13 key opinion leaders in nutrition who work in LMIC, and we conducted an inter-

TABLE 1: The opinion leaders interviewed as part of the PN for LMIC project and their affiliations and regions of work (ordered by first name alphabetization)

PN for LMIC nutritional expert	Academic and organization affiliations	Regions of work
Andrea Henze	University of Potsdam; Martin Luther University, Halle-Wittenberg	Germany; Ghana; Thailand
Andrew Prentice	MRC Unit The Gambia at LSHTM[a]	The Gambia
Anuraj Shankar	University of Oxford; Oxford University Clinical Research Unit – Indonesia	Indonesia; Vietnam; India; Brazil; sub-Saharan Africa; LMIC global
Audrey Essilfie	Nestlé R&D Center, Abidjan	Sub-Saharan Africa
Florian Schweigert	BioAnalyt	Germany; LMIC global
Georgette Konan	Université Félix Houphouët-Boigny; Centre Suisse de Recherches Scientifiques en Côte d'Ivoire	Côte d'Ivoire
Jay Berkley	University of Oxford	Africa; South Asia
Lucia Meko	University of the Free State	South Africa; sub-Saharan Africa
Matilda Steiner-Asiedu	University of Ghana	Ghana
Pascale Vonaesch	University of Lausanne	Africa; Southeast Asia
Robert Bandsma	University of Toronto, SickKids	Canada; Malawi
Saurabh Mehta	Center for Precision Nutrition and Health, Cornell University	USA; India; Ecuador; LMIC global
Tahmeed Ahmed	ICDDR[b], University of Washington	Bangladesh

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view with each of them. The principal learnings from the needs assessment are summarized below in four categories: The Problem, Current Solutions, PN Relevance and Collaboration.

> **"The mission of the PN for LMIC project is to make the use of PN more accessible, affordable and desirable to LMIC"**

Part I. The Problem: current food and nutrition-related challenges and target population

The interviewees shared insights on PN for LMIC, specifically in regions in which they work (see **Table 1**). They first discussed several nutrition-related challenges in their areas. Undernutrition, including stunting, wasting, protein energy malnutrition and micronutrient deficiencies, was more commonly reported as a nutrition-related challenge than overnutrition, which includes overweight, obesity and nutrition-related noncommunicable diseases. Importantly, most participants reported both under- and overnutrition, also referred to as the 'double burden' of malnutrition.

Several key barriers to addressing these nutrition challenges were mentioned by the interviewees (see **Table 2**). The top barrier discussed by participants was nutrition awareness, education and training among individuals and the workforce. One participant mentioned, "Communities do not know much about nutrition and the impact that it has on overall development. That's a really big challenge for us." Other highly reported barriers included available tools and diagnostics, research and data, and data analysis and management, as well as organization, collaboration and engagement among the sectors.

The interviewees were asked to choose one priority target population for intervention in their regions, and most chose children, which includes the first month of age up to school-age children. Adolescents and young adults were reported as the next highest priority group. The elderly group was reported as well. Of note, the preference to not separate preconceptional mothers, pregnancy and early infancy was highly encouraged by some interviewees and was therefore considered its own target population for this analysis. Nevertheless, the need for integrated PN approaches that are accessible within the healthcare system to benefit all groups in need was emphasized.

Part II. Current Solutions: the primary approaches being considered

Most interviewees stated that they were not satisfied with current solutions to nutritional problems in their regions, although some expressed optimism about current methods. One interviewee stated, "I am rather satisfied with the methods and impressed by the progress that has been made by the community in the last 10 years." The issues raised with current approaches include consistent funding and sufficient trained people coordinating efforts; thus, progress is slow, and data lacking.

TABLE 2: Reported barriers to addressing the key nutritional challenges in LMIC

Barriers to addressing nutrition-related challenges	Number of participants
Nutrition awareness, education and training of individuals and workforce	10
Research, diagnostics and tools, data, data analysis and management	8
Organization and coordination of systems, collaboration and engagement	7
Funding	6
Affordability, accessibility, food insecurity, food systems and poverty	6
Guidelines, policy and necessary communications	4
Targeting and intervention coverage	3
Infections, gut health and hygiene	3
Media and other influences	2
Ethics	1
Habit and psychology	1

"The most-cited PN tools were 'omics'- and microbiota-based approaches as well as noninvasive parameter monitoring and point-of-care devices"

Part III. PN Relevance: understanding PN and its perceived relevance for LMIC

We surveyed the participants on whether they thought PN could be part of the solution for the nutrition challenges in their respective regions and, if so, to name a few approaches. Considering that PN approaches consist of both widely and less widely accessible tools, all the participants believed that PN could be at least part of the solution. Two participants made the following powerful statements:

"PN has the potential to address all the problems I've mentioned."

*"It's more than part of the solution. It **is** the solution, but it is all about how you get there."*

There are factors that must be considered, including ethics and culture as well as linking the data collection with recommendations. As stated by another participant, "PN is not only the collection of data; it's the translation into an application." We were also reminded by one participant that: "Most clinics and hospitals cannot even measure basic clinical biochemical indices crucial to clinical care." Therefore, the most helpful solutions for certain regions may involve directing efforts towards ensuring that widely accessible PN tools and field-friendly point-of-care devices are available.

The most-cited PN tools that could address the key nutritional challenges mentioned were 'omics'- and microbiota-based approaches as well as noninvasive parameter monitoring and point-

TABLE 3: Reported barriers to implementing PN approaches in LMIC

Barriers to implementing PN approaches	Number of participants
Funding, affordability of approaches, resources and resource allocation	10
PN knowledge and trained workforce	6
Research and development of noninvasive tools and suitable technology	3
Collaboration	3
Acceptability in population	2
Government, guidelines and policy	2
Data privacy, protection and standardization	1
Food producers	1
Commercialization focus	1
Health coverage	1
Ethical issues	1

of-care devices. Notably, the top barriers to implementing PN approaches were adequate funding, affordability, resources and resource allocation, as well as PN knowledge and trained workforce (see **Table 3**).

Part IV. Collaboration: interest in collaborating with SFNV on PN for LMIC

It was clear after speaking with interviewees that collaboration will be crucial for implementing PN approaches in LMIC. All opinion leaders were open to collaborating with SFNV, with the overarching goal of piloting a few PN approaches to accelerate solutions to pressing nutritional challenges. One participant emphasized the importance of collaboration, saying, "A product by itself isn't going to have much impact, but a product tied to a trial and tied to improved outcomes in a large trial would make a difference." Bringing together multiple stakeholders will be essential to seeing impactful PN approaches in LMIC.

> **"Funding and training will be key to implementation"**

Summary

The survey results indicated that PN approaches are interesting and relevant for LMIC. While several nutritional challenges were reported in the different geographical regions by the interviewees, the double burden of malnutrition affects most of the communities in which they work. Apart from access to healthy foods, nutrition awareness and trained workers, the reported barriers to addressing nutrition challenges were acquisition of data, data management and collaboration. Progress with existing solutions is slow and unsatisfying to many interviewees, although the methods themselves are viewed as promising. Most participants selected children as the highest priority subgroup to target for interventions. They believed 'omics'- and microbiota-based PN approaches as well as noninvasive, point-of-care tools could help address specific reported nutritional challenges, although funding and training will be key to implementation. Collaboration with other organizations, including SFNV, was well supported and considered essential to move the PN for LMIC project forward. We are therefore optimistic about the relevance of PN to provide solutions to specific nutrition-related health challenges in LMIC.

Acknowledgments

We kindly thank the nutrition experts for their participation in our needs assessment survey and for their time and valuable inputs on the relevance of PN for LMIC.

Limitations

Due to limited network and time constraints, other opinion leaders in the fields of nutrition, PN and, more broadly, precision medicine were not included in this needs assessment.

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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 things (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.

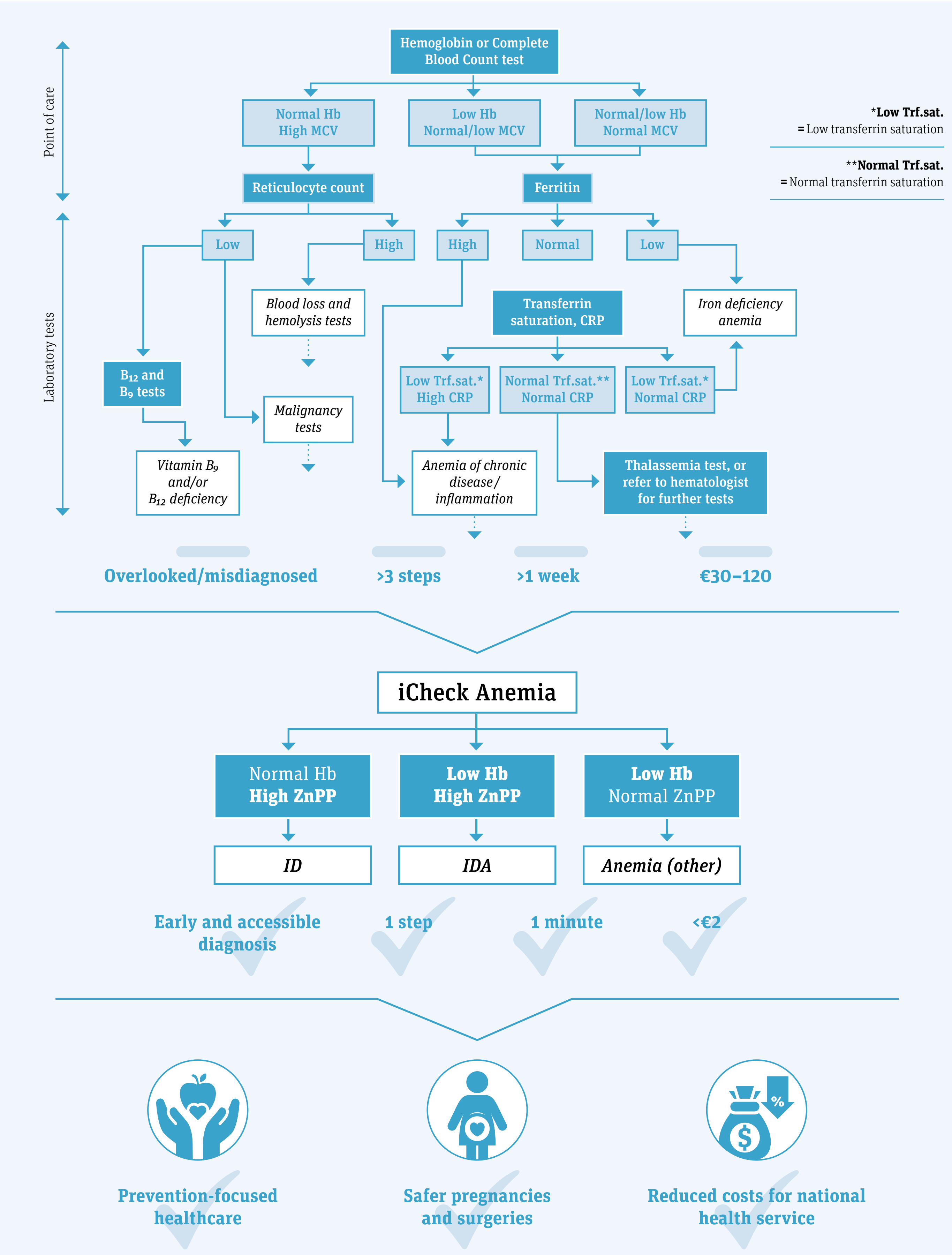
Innovative approach to iron deficiency diagnostics in precision nutrition

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 omission of lab

FIGURE 1: Complexity of laboratory analyses compared with iCheck Anemia



CRP, C-reactive protein; **Hb,** hemoglobin; **ID,** iron deficiency; **IDA,** 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

testing altogether, resulting in misdiagnosis and delays in timely treatment.

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]

> **"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"**

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 for iron deficiency 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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Potential Contributions of Precision Nutrition to Micronutrient Deficiency Control Programs

Definitions, opportunities and challenges in low- and middle-income countries

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Tailoring nutrition interventions to the individual

Micronutrient deficiencies (MNDs) and their consequences remain an important subset of the myriad nutrition challenges currently faced in low- and middle-income countries (LMIC). Micronutrient intervention programs operate primarily at the public health level through 'universal' approaches (e.g., large-scale food fortification) or with target groups that are broadly defined by age, physiological status (e.g., pregnancy) and classification as experiencing a public health problem (e.g., micronutrient powders, or iron or vitamin A supplementation).[1] On the other hand, increasing knowledge on individual-level differences in response to dietary patterns and nutrition interventions has led to interest in the potential for tailoring nutrition interventions to the individual, as well as interest in the data and analytical tools required to do so. Here we consider the question: What does precision nutrition mean for the design and management of MND control programs in LMIC? More specifically, what should be measured, at what level of precision, at what time intervals, and for what actor and purpose? We draw parallels to recent advances in precision agriculture, and pay particular attention to potential for policymakers, program managers and resource-poor households to act upon the new information that precision nutrition might provide.

What can and should be measured?

As new technologies accelerate the amount and quality of data that can be collected and managed, questions arise regarding what is feasible to measure (now and into the future), the costs of enhanced measurements and their analyses, and to what purposes improved data might be put by decision-makers. Key information needs for the design and management of micronutrient intervention programs include: (**1**) micronutrient intake and status, by important subgroups, (**2**) reach and impact of current programs, (**3**) the potential impacts of hypothetical new or improved programs, and (**4**) program costs, by stakeholder group (including program beneficiaries).

> **"Habitual dietary intake is difficult to measure at the individual level"**

In theory, with sufficient information on individual micronutrient status and its determinants, interventions could be targeted only at those who are deficient, and intervention products (e.g., different doses or forms of micronutrient) or messages could be tailored based on individual characteristics, such as genetic variation in micronutrient metabolism or individual dietary preferences. Data collection might also include information on non-nutritional determinants (e.g., infections or inherited blood disorders) of micronutrient status or related conditions such as anemia. Prioritization must also consider what level of precision is attainable. For example, biomarkers such as serum ferritin may provide reasonably reliable information on individual iron status in the absence of inflammation, whereas others, such as serum retinol, are best interpreted at the population level. Similarly, habitual dietary intake is difficult to measure at the individual level; doing so may require new tools and/or data collection platforms (e.g., to conduct short-term assessments with sufficient frequency to approximate habitual intake).

What level of precision is 'actionable'?

Perhaps the most important consideration is what level of precision is actionable by policymakers and households. To justify the collection of more or different data, there must be a clear path-way for whose behavior will change, e.g., individuals or program managers. Literature on personalized nutrition demonstrates the potential for novel analytical tools and technologies to provide comprehensive information to guide individual food choice.[2] With regard to micronutrient nutrition, individual-level assessment of deficiency is now feasible with point-of-care diagnostic technology.[3] However, in the context of LMIC (and, indeed, among resource-constrained subgroups in high-income countries), many interrelated constraints limit the capacity for individual behavior change. Physical, social and economic barriers to accessing nutritious foods and healthcare are well documented,[4,5] and these must be mitigated in order for individuals to be in a position to act on new information about their individual nutritional status or health. Hence, more precise data may come with additional policy action and/or programmatic costs.

> **"Micronutrient intervention programs may be informed by the concept of 'precision public health'"**

Targeting at individual versus subgroup level

Assessment and action at the subnational level is an intermediate option to increase precision without overreliance on individual behavior change capacity or the resources to screen and target the individual level. Previous modeling demonstrated that subnational data on vitamin A intake, and program reach and cost, could be used to identify more cost-effective portfolios of vitamin A intervention programs.[6] Micronutrient surveys designed with appropriate (targetable) strata could inform the development of subnationally targeted interventions that could improve the impact and, potentially, the cost-effectiveness of micronutrient interventions without the need for individual data. Micronutrient intervention programs may, thus, be informed by the concept of 'precision public health,' emphasizing multidisciplinary action, prevention over treatment, and modernizing surveillance systems[7] and maintaining a focus on social determinants of health.[8]

Parallels with precision agriculture

Other disciplines, such as precision agriculture, have made progress in leveraging measurement technology and analytical systems for identifying how 'precision' might be defined in time and space, and how increasing the precision of measurements of status, processes and outcomes might lead to cost-effective and sustainable improvements in production systems.[9] Examples from agriculture include the use of groundwater sensing instruments and laser planes to more efficiently manage irrigation systems, tractor-mounted GPS data systems that collect site-specific data on yields that can later be used to improve the efficiency of fertilizer application, and remote sensing images to detect and manage pests. Many data collection tools exist, but all require analytical systems to 'translate' precise data into information that can be used by farmers and/or policymakers,[10–12] and may also require trained and equipped intermediaries (e.g., extension agents).

> **"The public sector will have key roles to play in the evolution of impactful, sustainable and, especially, equitable systems"**

Developing and managing impactful, efficient and equitable data systems

As one might expect, there are often a temporal and other disconnects between the availability of more precise data, the analytical systems available to translate data into information that is useful to decision-makers, and the ability of decision-makers to weave this new information into decision-making processes and act upon the new information. This is especially true in the context of LMIC, although progress can be quick for tools and information that generate short-term private benefits, even when collective action is required.[13] Recent reviews[9,14] highlight these challenges and suggest a path forward including the steps outlined in **Table 1**.

TABLE 1: Steps to designing and managing precision nutrition systems for micronutrient deficiency control programs in low- and middle-income countries

1.	Identify the key policy issues to be addressed by more precise data
2.	Co-design data collection and analytical systems
3.	Pre-establish digital infrastructure
4.	Make the needed up-front and continual investments in digital literacy
5.	Establish, train and equip key intermediaries
6.	Formally address issues of data ownership, use and privacy
7.	Think forward regarding the interoperability and openness of systems
8.	Estimate costs, and identify who will be called upon to pay them

The private sector can be expected to take the lead in tool and data system development, with a focus on economically better-off, agile and trained actors, but the public sector will have key roles to play in the evolution of impactful, sustainable and, especially, equitable systems.

Summary

New approaches to individually tailor micronutrient intervention programs and recommendations could provide greater benefits to individuals, and could potentially improve the efficiency of existing programs, for example by delivering products and services only to those in need. However, careful attention is needed regarding what to measureand when, how to turn data into information, and how the information will be used (and by whom). Reacting to more precise data may be more feasible for program managers than for individuals because of constraints on individual behavior change in LMIC. Regional subgroup targeting may offer an alternative to individual targeting where it is not feasible or cost-effective to target individuals. Modeling of the costs and benefits of different targeting scenarios could help guide priorities for precision-nutrition-informed approaches to improve MND control programs in LMIC.

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"We Are Living in a Microbial World"

Interview with Wilbert Sybesma

Wilbert Sybesma is the founder and owner of Swiss-based Microbiome Solutions GmbH, and also the co-founder of the Yoba for Life Foundation. He explains the potential of probiotics in supporting better nutrition and improved health.

***Sight and Life* (SAL):** *Wilbert, you have been active in the human nutrition and health industry for more than 20 years. How did your interest in nutrition originate, and how did it develop in the early stages of your career?*

Wilbert Sybesma (WS): I think it's important to do things that are meaningful, that have a purpose, and this certainly applies to the subject of food and nutrition. My PhD, which I completed at Wageningen University in the Netherlands in 2003, was in food biotechnology – specifically, the metabolism of lactic acid bacteria. I was interested in how the production of vitamins by good bacteria can be increased during fermentation, an example being the production of yoghurt within which extra folic acid (vitamin B_9) is generated.

This interest in functional foods and probiotics took me to Nestlé, where I worked for 14 years in fermentation technology, initially in R&D and then in production. I also did an MBA at Rochester-Bern Executive Programs in Bern, Switzerland, during that time, where I worked out a business plan around probiotics for people living at the bottom of the pyramid, the Yoba for Life concept. The probiotics I developed for Nestlé were predominantly destined for the Western world, for inclusion in baby food, adult food and also supplements, and the main focus of my work was the question of how to keep probiotic bacteria bioactive. My interest in nutrition further evolved by lecturing in Food Biotechnology at EPFL *(École polytechnique fédérale de Lausanne)*, which I still do alongside my work for Microbiome Solutions GmbH.

© Jeroen van Loon, for the Yoba for Life Foundation

Yoba school feeding program at Happy Times Nursery School, Mbarara, Uganda.

'Women's group producing Yoba in Mwanza, Tanzania.

> **"I think it's important to do things that are meaningful, that have a purpose"**

SAL: *Could you tell us something about Yoba for Life?*

WS: My work at Nestlé strengthened my belief that for innovation to be successful, it should be both simple and scalable. In 2009, while still at Nestlé, together with a friend I set up the Yoba for Life Foundation, whose aim is to improve the quality of life in resource-poor countries by means of local production of an affordable probiotic yoghurt with proven health benefits. This yoghurt is called Yoba. The Foundation developed an innovative starter culture containing the probiotic bacterium *Lactobacillus rhamnosus yoba 2012*. One gram of starter culture permits the production of 100 liters of probiotic yoghurt from the locally sourced milk. There are now 300 small units in Africa producing Yoba.

SAL: *You also worked for DSM, Wilbert. How did you come to move from Nestlé to DSM?*

WS: My activities at Nestlé were exclusively in the business-to-consumer sector. I was aware that companies like Nestlé could also profit from the products that innovation-driven companies such as DSM can deliver, and so it was a logical step for me to move on to DSM, where I took up the position of Innovation Manager – Gut Health. I joined at an interesting time, because although DSM was the world leader in vitamin production, the company was not yet very active in pre- or probiotics. Interestingly, the trillions of microbes present in our body produce vitamins, not only for themselves, but also for their hosts. However, if the microbiome is disturbed, this vitamin production is hampered. I therefore led a project focused on delivering bioactive vitamins to the gut microbiome.

> **"Fermented foods have an important role to play in supporting immune function"**

SAL: *There has been a notable revival of interest in fermented foods in recent years. How do you view this trend?*

WS: I see this as a natural reaction to processed foods, which often have reduced nutritional value. In fermentation, the nutritional value of foods is actually increased, the taste and texture are enhanced, and preservation is assured, while at the same time the naturalness of the food is maintained. The relevant scientific literature shows that fermented foods have an important role to play in supporting immune function and thus making the metabolism more resilient. A good analogy would be a forest containing thousands of different species, which is bound to be much more resistant to natural shocks than a monoculture: the bacteria in fermented foods actively increase the presence of beneficial bacteria in the gut. I very much hope that the relevant authorities will start including fermented foods in their guides to good nutrition. Kimchee, for instance, is probably the healthiest food on Earth, offering all the benefits of fiber and fermentation, together with great taste. As I often say, we're living in a microbial world!

SAL: *How did you come to set up Microbiome Solutions GmbH?*

WS: At DSM, I was leading the Gut Health R&D team, but the Sales & Marketing teams frequently approached me, asking me to create messages for consumers about the solutions we were developing. This experience made me realize that I was good at explaining complex material and formulating marketing communications. Eventually I decided to set up my own business, Microbiome Solutions, which is predicated on the creation of end-to-end value in the microbiome space. I advise companies about innovation in microbiome-related health and also about the future of research in this field. It was a big step in life, which involved lengthy discussions with my family, but I don't regret it. One of the disadvantages of working in a corporate setting is that one has to spend a lot of time on internal stakeholder management. That's not the case when you're working in your own company: you can fully concentrate on your real purpose and direct needs of your customers.

> **"Big nutrition companies have to take responsibility for their impact on society"**

SAL: *Precision nutrition is often associated with high-income countries. Do you think it can be effectively deployed in middle- and low-income settings too?*

WS: I think it's excellent to generate awareness of the potential benefits of precision nutrition in LMIC, but we must also be aware of the crisis of malnutrition that is currently occurring in both urban and rural contexts in Africa. Nutrition education is key here, but the requirements of urban environments in Africa are very different than those of rural ones. We should address the gap in nutrition information and education in LMIC first and then turn our attention to the potential of precision nutrition in these countries. I believe that big nutrition companies have to take responsibility for their impact on society. I myself would like to see import taxes applied to unhealthy processed foods, and I'd also like to see the provision of health insurance and pension plans, connected to purchases of nutritious food, to disadvantaged populations in these countries.

SAL: *How do you see the role of food fortification in Africa?*

WS: Food fortification is extremely important in Africa, but I'm of the opinion that the foods we eat should be so healthy in themselves that supplementation is superfluous. To improve nutrition in low-resource settings, I think we should apply four principles: tailor local solutions to local needs; encourage the aspiration to a more nutritious diet; improve access to better nutrition; and create the necessary purchasing power to allow people to avail themselves of nutritious, affordable foods. The traditional fermented foods that were made 3,000 years ago were extremely nutritious. I'd love to see them on modern menus. The local communities of the past were characterized by a strong sense of purpose, and they had no option but to develop local nutritional solutions. I'd like to see more people in nutrition taking responsibility for the communities in which they live – and fermented foods, feeding us and the beneficial gut microbes that live within us, have an important role to play here. As I like to say, in gut we trust!

SAL: *Thank you, Wilbert.*

WS: Thank you too.

Wilbert Sybesma was interviewed by Jonathan Steffen.

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Resources for Scale-up

MyFoodRepo: Artificial intelligence for precision nutrition tracking

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The complexity of nutrition

At first sight, it appears remarkable that, a quarter of the way into the 21st century, our understanding about the effects of nutrition on health remains limited. By now, shouldn't we know which foods are healthy, for whom, when and why? Looking closer, however, it becomes clear that the task at hand is much more difficult than one might think. To begin with, the causal effects of nutrition on health are notoriously hard to pin down. More than this, however, nutrition poses a particular problem because of its staggering complexity. The chemical input in the form of food dwarfs everything else to which our bodies are exposed on a daily basis. We continually ingest hundreds of different food types, composed of thousands of different chemical compounds. This chemical complexity is matched only by the ecological complexity in the body, the gut microbiota, digesting the food and making further nutrients available to us.

> **"The Digital Epidemiology Lab at EPFL in Geneva is focusing on making sure that capturing food intake is done correctly"**

We are now beginning to break through the surface of this complex interplay. Personalized nutrition is the idea that diets can be adjusted to the individual – based on a plethora of personal data capturing some of the complexity – in order to maximize the positive effect on personal health outcomes.[1] This is a multidisciplinary challenge in its truest form: from capturing the complexity of nutritional uptake, through understanding its journey through the body, to identifying the causal effects on health outcomes. My group, the Digital Epidemiology Lab at EPFL in Geneva, is focusing on making sure that the first part, capturing food intake, is done correctly. Because if we don't get this part right, what hope do we have of understanding anything downstream of nutritional uptake?

The challenge of tracking food

Tracking food is notoriously hard. The field has invented a number of different methods to measure what people are eating. The two most common approaches are food frequency questionnaires and food recalls. The questionnaire method usually focuses on long-term food patterns over months or even years. The recall method focuses more on short-term patterns over days, with the 24-hour recall being the most common version. Both methods have shortcomings that are broadly understood and accepted.[2] In particular, if we want to understand in more detail what people are eating, and when – over an extended period of time, rather than just 1 day – both of these methods are problematic. Put simply, food frequency questionnaires provide a good overview of long-term diet patterns, but lack precision; 24-hour recalls, on the other hand, provide good short-term precision, but are limited to 1 day. In addition, both methods depend on the ability of a person to accurately remember their food intake. Finally, they can be cumbersome to do (**Table 1**).

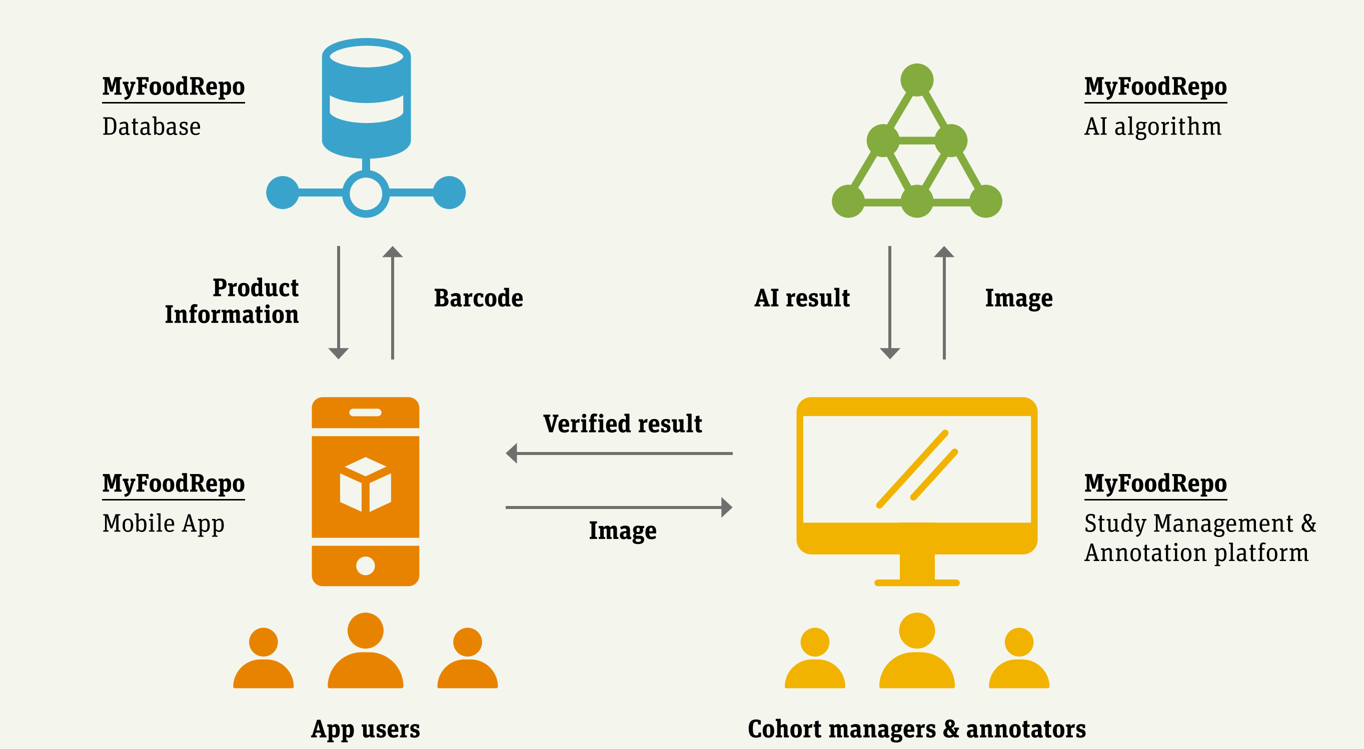
Mobile apps

In the past few years, mobile apps have started to emerge to address these issues. The key advantage of mobile apps is that they are – usually – present at the moment of food intake. However, because entering data on a small mobile screen is burdensome, this advantage is not sufficient in itself, and early apps have suffered from severe adherence problems. What is needed is a smart user interface that allows food intake to be captured in a minimally bur-

TABLE 1: Food tracking methods

Method	Tracking duration	Precision	Burden on user
Food frequency questionnaire	Long term	Low	Low
24-hour recall	Short term	High	Medium
Mobile app without artificial intelligence (AI)	Medium term	High	High
Mobile app with AI (MyFoodRepo)	Medium term	High	Low

FIGURE 1: The MyFoodRepo deep learning model



Source: Author

densome way. Arguably the fastest way to enter data is to simply press a button to take a photo. This is the philosophy behind the latest generation of mobile apps for food tracking. However, the image then needs to be transformed into meaningful food intake data for analysis. This is where artificial intelligence (AI) comes in.

Deep learning

In recent years, automatic recognition of images has made tremendous progress, thanks to deep learning, a type of machine learning approach that uses very large models of neural nets. Image recognition based on deep learning now approaches – or even surpasses – human performance for certain tasks.[3] The key factor for the increasing performance in image recognition is the availability of labeled data. Put simply, the more labeled data there is (i.e., food images with correct annotations about the nutritional content on the image), the better a deep learning model can perform. The task is thus twofold: first, to make sure that there is a continual stream of high-quality, annotated data; and second, to make sure that the best model architecture is chosen.

Given the potential value of such models, a growing field of applications are implementing such deep learning models for food image recognition. Almost without exception, these models are privately owned black boxes. Researchers may suggest to their study participants to use such apps for data collection, but the data often disappears behind closed walls, and the resulting analytical output has to be taken at face value. Moreover, while the app owner may benefit from having more data, the research community will not. The reason for this dynamic is typically found in the financing model: collecting and annotating data, and training machine learning models, takes time and expertise, and is thus expensive. Giving away the key assets (data and model) therefore makes little economic sense. On the other hand, academia, which is more used to sharing data and models openly, generally lacks the type of long-term technology infrastructure funding needed, which is why many such attempts to build apps ultimately fail.

> **"MyFoodRepo aims to build a world-class food tracking system through an open data and open model approach"**

MyFoodRepo

The MyFoodRepo approach is a hybrid one. It aims to build a world-class food tracking system through an open data and open model approach, while remaining financially sustainable through a 'cohorts pay per use' research platform model. It works as follows. Cohort participants track their nutrition with the MyFoodRepo mobile app, typically simply by taking pictures, with the alternatives of barcode scanning and manual entry. These images are then sent to the MyFoodRepo server, where they are analyzed by a deep learning model (**Figure 1**). Since no model is perfectly accurate, the resulting data is verified, and if necessary corrected, by a human annotator, either from the MyFoodRepo team or the cohort team. The end result is high-resolution food intake data with high – i.e., human-verified – accuracy, something that has recently been independently validated.[4] Critically, this data belongs to the cohort and its participants.

> **"We hope to establish this system as a transparent gold standard for fully reproducible, high-precision food tracking"**

The biggest differentiator, however, is that MyFoodRepo users are asked to share their image data with the public. If they agree, their annotated data becomes part of an open machine learning benchmark, whereby developers around the world compete to improve the accuracy of the deep learning model. This MyFoodRepo food benchmark has already been running for six rounds, and the resulting models are openly accessible. Because the top-performing models are then used by the MyFoodRepo system, a virtuous circle of transparent model development is established. Notably, every additional cohort using the system not only has full access to their data and the models (ensuring full transparency and reproducibility), but the system gets better for everyone, and thus the entire field benefits. We have recently shown how this approach results in continually better models.[5] Originally developed for Switzerland, the MyFoodRepo system is now being internationalized for the USA, Germany, France, Canada and other countries. As more countries are onboarded, we hope to establish this system as a transparent gold standard for fully reproducible, high-precision food tracking.

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Enabling Precision Nutrition: An ecosystem approach

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A glimpse into the future

The year is 2035 and precision nutrition has become the norm. The number of people affected by obesity and type 2 diabetes has dropped. Consumers in higher-income countries use implants and wearable devices paired with apps – and their fridges – to identify what they should eat and avoid. More affordable models are increasing access in emerging markets, with some governments subsidizing precision nutrition plans, while manufacturers have adapted their products to tune into the main metabo-types.

This was the thought-provoking, futuristic scenario set out in an article in *The Economist* last year.[1] It may well be fiction, but the content is founded on real science and the trajectory of this fascinating field is certainly looking promising. The global precision nutrition market is projected to grow from USD8.2 billion in 2020 to USD16.4 billion by 2025, and countless startups have become active in this space in the last few years.[2]

The seeds needed to grow this future have been planted. But how do we water them? To explore solutions, I would first like to take a step back and examine the challenges that this ambitious agenda sets out to address.

> **"Countless startups have become active in this space in the last few years"**

Tackling food system challenges

Our global food system today is peppered with contradictions: 1.9 billion adults are overweight or obese, while 750 million are undernourished.[3,4] We need to find new solutions to ensure that nearly 10 billion people on Earth by 2050 have access to affordable, nutritious meals. At the same time, we waste around one-third of all food produced.[5] Solutions must support people to make healthier choices and, at the same time, make sure that our planetary resources go further.

In recent years, government and industry have started to acknowledge the benefits of more personalized and collaborative approaches. Following acceptance of the limitations of national nutritional guidelines, population health has come to the fore.[6] These approaches recognize that many aspects of an individual's health lie beyond the reach of healthcare services and that multiple actors – including consumers themselves – need to be actively involved in delivering health outcomes. Precision nutrition provides the tools to take this a step further.

As we know, self-optimization is already becoming the norm for some consumer groups. Many of us measure the steps we take, count our calories or track how well we have slept. This data is becoming central to how we live our lives, and it can play a vital role in driving and maintaining positive health behaviors.

What we choose to eat every day is arguably one of the most personal health decisions we make and is inextricably linked with our own perception of culture and identity. Rather than consumers being told to adhere to externally imposed guidelines, precision nutrition empowers consumers by putting the information they need about their own bodies in the palm of their hands, thereby enabling them to make more informed decisions. These subtle shifts can have a significant impact when it comes to tackling the 'last-mile' behavior change in the context of managing noncommunicable diseases.[7] To drive this agenda forward, however, all food system actors need to understand and engage with this opportunity.

> **"Precision nutrition empowers consumers by putting the information they need about their own bodies in the palm of their hands"**

Collaborating for impact

Swiss Food & Nutrition Valley, a purpose-driven, not-for-profit association, was created in 2020 to drive collaboration between Swiss ecosystem actors and strengthen Switzerland's contribution to more future-proof food systems. The Valley network has since grown to encompass over 100 partners – from global corporations, retailers and governments to leading universities, innovation facilitators, small and medium enterprises, and startups.

After mapping the Swiss FoodTech Ecosystem 2021, we recognized that Switzerland was well placed to play a key role in

FIGURE 1: Overview of the concept of metabotyping, after Hillesheim and Brennan

Sources: [a] https://www.hsph.harvard.edu/nutritionsource/precision-nutrition
[b] https://academic.oup.com/advances/article/11/1/25/5556010

shaping the precision nutrition agenda.[8] The country is home to countless global nutrition players, such as Nestlé, Givaudan, Firmenich, DSM and ADM, as well as a dynamic startup scene, and many of its leading universities were also conducting groundbreaking research in this space. We therefore took the decision to focus our first Impact Platform – the Valley's methodology to develop and deliver ecosystem-owned collaborative projects – on this promising topic.

Spotting the hurdles

From autumn 2021 to summer 2022, we held a series of events to bring actors together to discuss the state of play, identify challenges and opportunities, and kick off collaborative projects.

Colleagues from all sectors shared the belief that precision nutrition could make a significant contribution to tackling the global health crisis. Many barriers to implementation remained, however. Firstly, there was no established definition of 'precision nutrition' or 'personalized nutrition,' and in practice the terms are often used interchangeably (**Figure 1**). Then there was the issue of managing consumers' personal data effectively.

There was also a common perception that due to the pricing of current solutions, precision nutrition was not scalable and would only be accessible for a small slice of global populations. We were consequently eager to investigate how we could leverage the expertise within the Swiss innovation ecosystem to explore how an early focus on lower- and middle-income countries could influence scientific and technological developments, ensuring that solutions would also be transferable to other economic and cultural contexts.

Ecosystem-owned projects

In parallel, Valley partners were invited to submit ideas to take forward collaborative projects, and seven proposals were received. Some partners saw value in mapping out the Swiss precision nutrition landscape and technologies in more detail, with a view to identifying synergies. Others were interested in creating an algorithm to support companies in developing precision nutrition approaches or zooming out to better understand the link between diet and noncommunicable diseases more broadly.

To address partners' concerns in relation to potential health inequalities, we also scoped out a project together with them to examine the role that precision nutrition can play in lower- and middle-income countries. The findings of this project so far are summarized on pages 57–61 of this report.

Our Impact Platform projects are still in development, but our learnings are clear. The topics that will shape the future of food are too broad to be tackled by any single actor. By harnessing the power of the ecosystem, we create powerful synergies and can move the needle much faster.

> **"Precision nutrition allows us to make the most of the food we have"**

Realizing the vision

When you look beyond the science and the tech, precision nutrition is simple. It's all about identifying the needs of the individual or a targeted group and empowering them to make the food choices that are most suitable for them. This ultimately allows us to make the most of the food we have.

As an expert at one of our Impact Platform events put it, precision nutrition is no longer an 'if' or a 'maybe.' It's the future. But to get there, we need universities to continue their groundbreaking research and startups to develop innovative solutions so that we can remove barriers to access and increase availability for the most vulnerable populations. Manufacturers need to continue to work alongside consumers to develop the nutritionally- and context-tailored products that are likely to fill our shelves in the future. Governments and policymakers, medical schools, health insurers and the pharmaceutical industry will also need to figure out how they fit into this rapidly evolving picture.

The stage is set. Now it's over to the ecosystem to come together and create solutions that are easy to use, accessible and affordable – so that everyone can benefit, and no-one is left behind.

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Precision Nutrition Approaches to Health Challenges in Low- and Middle-Income Countries

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Food and nutrition are recognized to play a vital role in health promotion and disease prevention, yet globally the number of people living with food insecurity is on the rise, and the burden of malnutrition (over- and undernutrition together with micronutrient deficiencies) remains a significant challenge.[1–6] Preventing and correcting suboptimal nutrient intake are particularly important during critical developmental life stages such as the pre- and perinatal period and during infancy and early childhood.[7] However, accurately defining the nutritional problems and applying corrective measures, with regular monitoring of progress, remains a daunting task, particularly in low and middle-income countries (LMIC) and rural environments.[8]

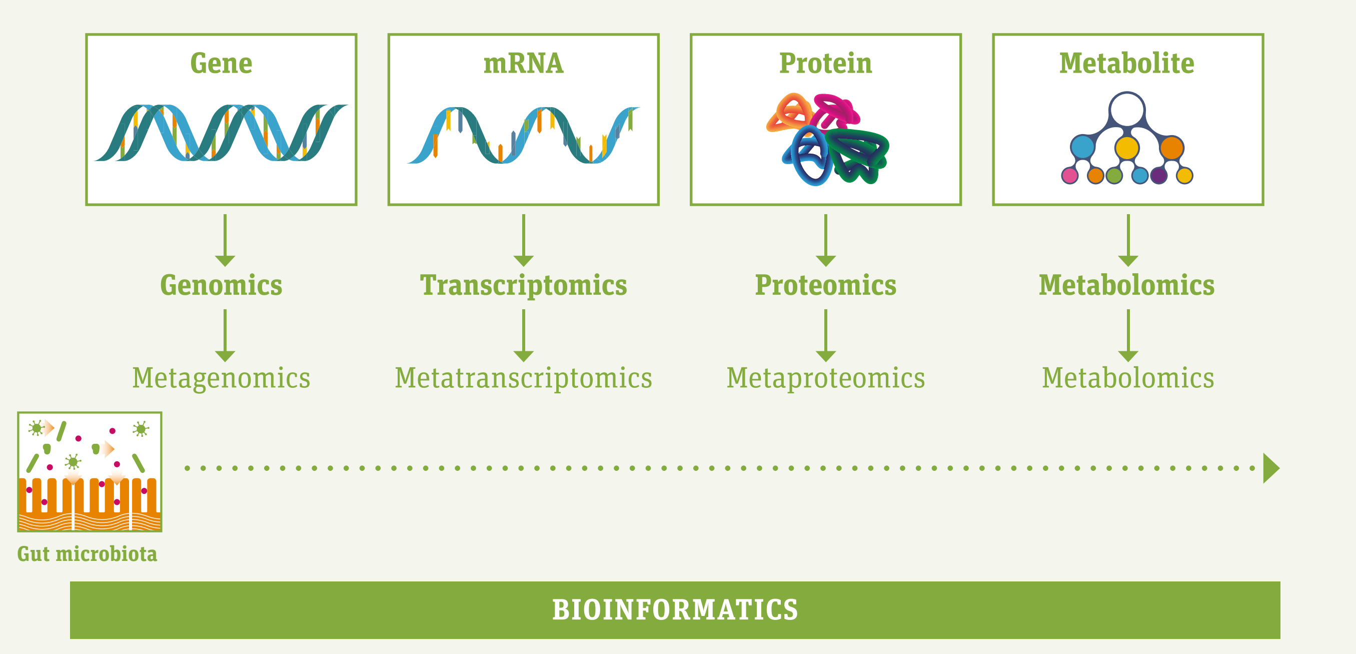
Today, new precision nutrition (PN) technologies and integrated approaches are transforming nutrition research and the understanding of chronic diseases, particularly in high-income countries.[9–11] It is anticipated that some of the learnings from PN approaches such as 'omics' technologies may help accelerate solutions to health challenges in LMIC (**Figure 1**).

> **"'Omics' technologies may help accelerate solutions to health challenges in LMIC"**

Precision in biomarker detection for point-of-care (POC) applications (Table 1)

Correcting for nutrient inadequacies and deficiencies in a measured and targeted manner requires accurate measurement of validated nutrition and health biomarkers that reflect nutrient exposure, status and functional effects.[14–16] Since the Biomarkers of Nutrition for Development (BOND) initiative began in 2009, biomarkers for key micronutrients (iron, zinc, iodine, vitamin A, folate and vitamin B_{12}) have been validated, and multiple micronutrient supplementation (MMS) strategies have been successfully implemented.[14–18] However, clinicians and researchers are

FIGURE 1: The four major 'omics' technologies and their application to gut microbiota studies – meta-omics



Source: Raupach et al.[12] Daliri et al.[13] – simplified and adapted by the author

TABLE 1: Promising PN tools and their approaches and advantages for use in LMIC

Purpose	Tools or approaches and advantages
Precision biomarker detection (nutrient physiological status, inflammation and infection status monitoring) at point of care[19–37]	• **Microfluidic systems/lab-on-a-chip (LOC)** · Convenient and affordable · Ultrasensitive – enables less-invasive sampling · Potential for other biofluids (saliva, extracellular vesicles, tears)
Precision in assessing diet quality, diversity and health benefits[14–16,33–35,38]	• **Metabolomics** · Urinary metabolites for objective assessment of food intake and diet patterns · Validation of biomarkers of nutrient functional status
Precision in tackling obesity and noncommunicable diseases[35,39–41]	• **Metabotyping (Figure 2)** · Apply to a local cohort using simplest approach – anthropometrics, clinical biochemistry and, optionally, metabolic response and genomics
Precision in assessing gut health[42–47]	• **Integrated omics/microbiomics/meta-omics (Figure 1)** · Facilitates understanding of microbiota and host–microbiome interactions • **Breathomics** – breath volatile metabolome · Less invasive and more convenient than stool sampling

now more acutely aware of the need to understand the underlying pathologies of malnutrition, such as infection and inflammation, and there is a desire to move to multiple nutrient biomarker assessment panels at the point of care.[8]

The recent global pandemic has highlighted the shortcomings of traditional diagnostic methods at the POC, and research efforts to develop rapid and affordable tests have intensified.[19,20] A range of POC devices and applications are playing an increasingly important role in both disease prevention and health promotion and many are suitable for use in resource-limited settings.[19–21] According to the ASSURED criteria of the World Health Organization (WHO), ideally POC tests are affordable, sensitive, specific, user-friendly, rapid, equipment-free and deliverable to end users.[22]

Microfluidics and lab-on-a-chip (LOC) platforms

Microfluidic systems are miniaturized, fully portable analytical laboratories that have proven applications across the life sciences sector.[23, 24] These integrated platforms bring numerous benefits for bioanalysis and the rapid and highly sensitive detection of biomarkers in POC or decentralized applications, ideally suited to field studies in low-resource settings.[25,26] Promising systems for POC assays involve inexpensive materials such as paper-based microfluidic devices coupled with portable and accessible detectors such as smartphones.[20,27] The cost of such devices may also be reduced by chip manufacturing technologies such as 3D printing.[24,25,28] Developments in 'multiplexing' (simultaneous detection of several biomarkers) could potentially improve the relevance for nutritional approaches.[18,23] However, there needs to be a concerted effort to finance and encourage the successful scale-up of these highly relevant devices and systems.[25,26,29]

Biomarkers in biological fluids

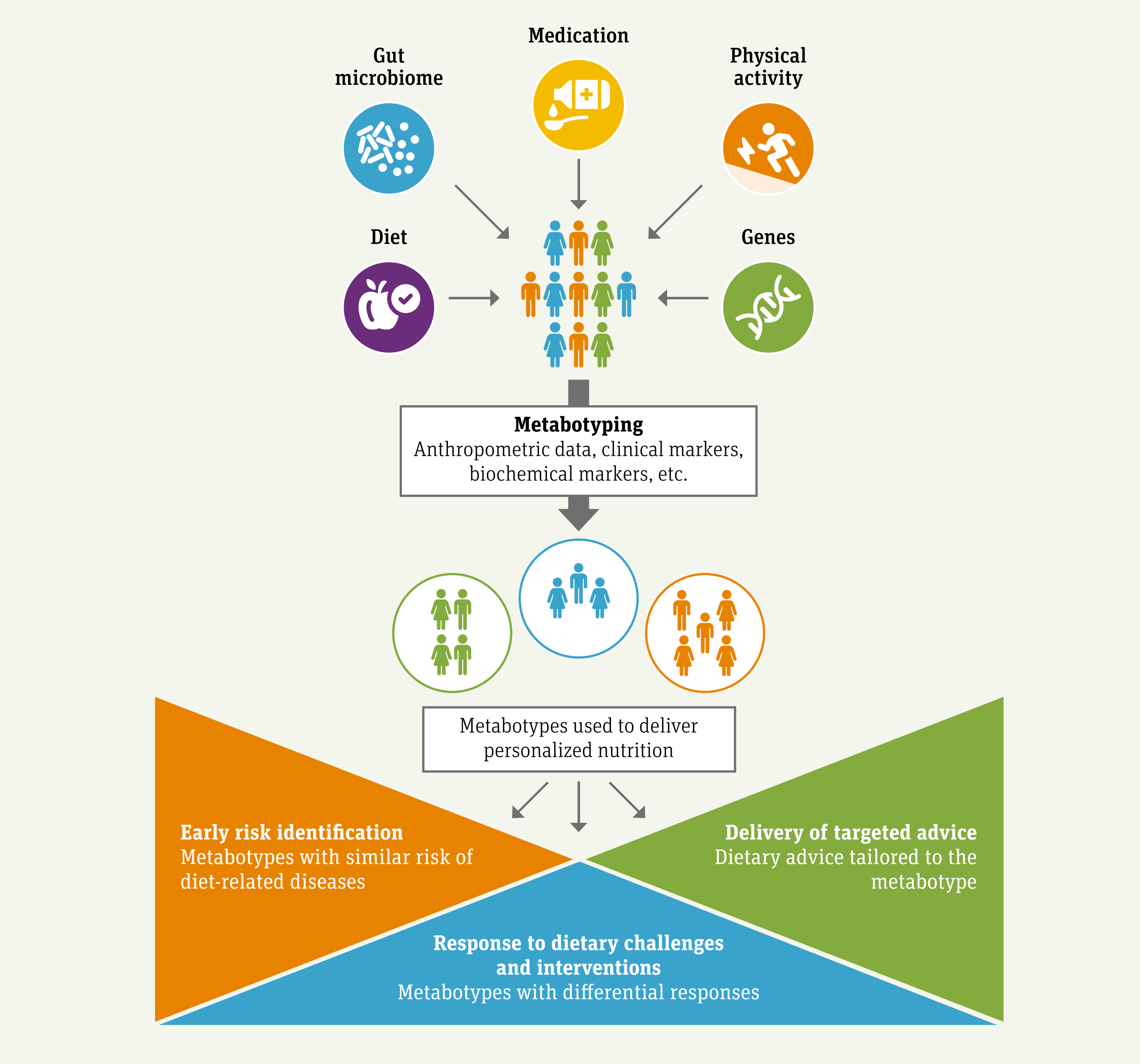
Thanks to the superior detection levels of microfluidic systems, it has become possible to measure biomarkers in biofluids other than blood or serum.[30,31] Saliva is easily sampled in a rapid, low-cost and relatively noninvasive manner. Saliva is now increasingly being used for POC tests to assess a range of biomarkers, such as proteins, hormones and viral or bacterial infectious agents,[30–32] and is validated as a source of biomarkers to assess selected vitamins and minerals.[8] Urine has many advantages over blood and serum, and is increasingly used as a source of biomarkers for metabolomics studies (see next section).[33–35] Precision approaches at the POC may allow the rapid assessment of inflammatory biomarkers such as C-reactive protein (CRP) and α-1-acid glycoprotein (AGP) in saliva or urine, to allow the correct interpretation of macro- and micronutrient physiological status.[36]

Other noteworthy future approaches involve the measurement of biomarkers contained in extracellular vesicles, which are present in biofluids including saliva and urine, and are detectable using sensitive microfluidic technologies.[23,37]

Precision in assessing diet quality and diversity: Biomarkers and urinary metabolomics

Dietary and food intake biomarkers can substantially improve the accuracy of dietary assessment by self-reported methods such as 24-hour food recall and food frequency questionnaires. Assessing the impact of a particular dietary pattern or food group on health or disease can be facilitated using urinary metabolomic approaches.[33,34,38] Intake biomarkers are single or multiple metabolites that reflect the consumption of a specific food, food group or dietary pattern.[14–16] In the research environment, metabolites can be monitored in readily accessible fluids such as urine, by detection methods such as mass spectroscopy or nuclear magnetic

FIGURE 2: Overview of the concept of metabotyping



Source: Adapted from Hillesheim and Brennan[40]

resonance spectroscopy.[35,38] In the future, validated multi-biomarker panels will continue to add objectivity and accuracy to nutrition research studies and may prove to be particularly valuable when assessing the health benefits of regional and local foods in LMIC. Fortification and biofortification programs or supplementation strategies to correct nutrient inadequacies or deficiencies are also likely to benefit tremendously from the validation of a range of nutritional biomarkers.[17,18]

Precision in the approach to tackle obesity and noncommunicable diseases

Obesity and chronic diseases are on the rise globally, but the increases in LMIC are particularly concerning.[3–5] To attempt to combat obesity and associated cardiometabolic diseases, a few research studies in Europe have used a 'metabotype' approach, which characterizes individuals or groups of individuals according to similar phenotypes to improve the quality of dietary recommendations (**Figure 2**).[35,39–41] Typically, three or four metabolic phenotypes are established, and these are based upon anthropometric data, basic blood biochemistry, metabolic response to foods and, optionally, also genetic data and gut microbiota enterotype.[39] Although clearly not fully reproducible in the LMIC setting, some elements of the metabotype approach could perhaps be adopted in the future. This approach would allow for stratification of groups within the population to enable the delivery of more targeted advice.

Precision in assessing gut health

Techniques such as metagenomics and culturomics are today increasingly being used in pilot studies to explore the relationship between poor nutrition, immune deficits and gut health.[42] Analyses of the fecal DNA from malnourished children in various regions have revealed differences in the maturity and composition of intestinal microbiota, in a direction which favors enteropathogen infection, impairs barrier function, and promotes inflammation and a 'dysbiotic' state.[42–45] The associations between changes to the microbiota and stunting is an area of intense research.[45] Future studies with larger subject numbers and with various integrated omics approaches are likely to enhance the understanding of the compositional and functional aspects of the gut microbiome of the malnourished child.[43]

Techniques mentioned above are primarily suited to the clinical research setting and require invasive and problematic sampling. On the horizon are alternative noninvasive techniques such as breath volatile metabolome (breathomics), which may provide an insight into gut microbiota function.[15,46,47]

> **"The increased use of metabolomics and metabotyping will allow for the design of more effective fortification and biofortification, nutritional supplementation and dietary advice strategies"**

Future perspectives

Applying selected tools and techniques of PN may accelerate progress towards the understanding of the various underlying pathologies associated with malnutrition and chronic diseases in LMIC. Diagnosis and treatment protocols that involve simultaneous monitoring of nutritional and inflammatory state biomarkers, as well as the presence of intestinal pathogens, could be facilitated by affordable and convenient microfluidic POC mobile applications. Furthermore, with the increased use of PN methods such as metabolomics and metabotyping, a far deeper knowledge of the impact of the food environment on host physiology will be gained, allowing for the design of more effective biofortification, nutritional supplementation and dietary advice strategies.

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Precision Nutrition to Fight Acute Malnutrition: Country- and patient-specific solutions

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Adapted food products for acute malnutrition

Acute malnutrition is still a major public health problem in many countries, affecting 45.4 million children under 5 years of age worldwide.[1] This situation is expected to worsen in many low- and middle-income countries (LMIC), given the new global challenges that have fueled the international nutrition crisis. With rising food prices, access to healthy diets is especially difficult for the most vulnerable groups, such as women and children, making food and nutritional security more precarious worldwide. The impact of the global crisis could lead to an increase of 13.6 million more children being affected by wasting.[1] In this context, the prevention and treatment of severe acute malnutrition (SAM) are more relevant than ever. Here, we argue how precision nutrition could help improve both the treatment and prevention of SAM.

The introduction of ready-to-use therapeutic foods (RUTFs) in the early 2000s[2,3] as a treatment for SAM was revolutionary in that it provided a successful home-based product that does not require preparation before consumption, making it safe even in unhygienic conditions. RUTFs are lipid-based, energy-dense foods (> 520 kcal/100 g) that contain both macro- and micronutrients. The most-used RUTF in the world, Plumpy'Nut, is made from peanuts, sugar, milk powder, vegetable oil and a vitamin–mineral premix.[4] However, its general one-size-fits-all formulation makes global acceptability difficult, due to different cultural and organoleptic preferences (taste, consistency, texture) and cost (milk powder being expensive). Moreover, peanuts are an allergen and can be contaminated with aflatoxin.

> **"The prevention and treatment of severe acute malnutrition (SAM) is more relevant than ever"**

RUTFs developed in the 1990s were formulated as a life-saving treatment, focusing primarily on weight gain, in an era when precision nutrition did not yet exist. Indeed, factors such as changes in body composition during treatment, the risk of noncommunicable diseases in later life, and the impact on local food systems or on the host intestinal microbiome were either unknown or not considered.[5,6] Children affected by SAM have a more immature gut flora, even after fully recovering,[7,8] which could significantly affect the relapse risk of SAM after treatment. Several studies have shown that a healthier microbiome composition and metabolic function could contribute to improved body composition.[9–11]

Therefore, reformulation of RUTFs is needed, not only to address country-specific organoleptic preferences and to make better use of local ingredients to increase sustainability, but also to take into account the latest understanding of the pathology of SAM, thereby addressing questions concerning the intestinal microbiome and the long-term consequences of acute malnutrition.

The beginning: nutrient profiling for RUTF in Vietnam

One pioneer experience in developing a country-specific product to address SAM was carried out in 2009 in Vietnam, where the National Institute of Nutrition (NIN), UNICEF and the French


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A child testing four different types of RUTF during an acceptability trial in Attapeu, Laos (January 2022).

Testing acceptability is important, as different RUTFs are appreciated differently around the world. Acceptability testing in Attapeu, Laos (January 2022).

National Research Institute for Sustainable Development (IRD) worked on the development of a locally produced RUTF called HEBI, with ingredients common in the local diet: rice, mung beans and soya. HEBI's formulation met international RUTF standards,[12] and its form was made to resemble green bean cake, a popular Vietnamese snack. An acceptability trial allowed us to adapt the texture of HEBI to population demand, and an effectiveness trial showed its non-inferiority to Plumpy'Nut.[13] HEBI was further developed and improved and it is now used by the Vietnamese Government for the management of SAM.

The need to adapt RUTF to local context: Cambodia's experience

Based on HEBI's high acceptability and effectiveness in Vietnam, IRD developed a similar approach for Cambodia in partnership with UNICEF, Cambodian ministries, Vissot/DCF (a social enterprise) and Copenhagen University. The product was conceived to suit local organoleptic preferences, and to make it less costly and more sustainable, milk powder was replaced by a locally produced dried fish powder. Two products were developed: an RUTF, now called Nutrix, with high energy, lipids and micronutrient density, matching the nutrient requirements for RUTF products,[3] and a ready-to-use supplementary food called NumTrey.

An acceptability study[14] allowed us to improve the texture and presentation of the products by filling the paste into a crispy wafer, a popular snack in Cambodia. An effectiveness study[15] showed no differences in mean weight gain between children treated for SAM with Nutrix or BP-100, an imported milk-based RUTF, while NumTrey had modest effects on preventing the development of moderate acute malnutrition.[16] Nutrix and NumTrey production was recently scaled up, and these products are currently used for the prevention and treatment of acute malnutrition in Cambodia.

> **"HEBI is now used by the Vietnamese Government for the management of SAM"**

The present and future of RUTF development

These recent developments in Southeast Asia demonstrate the potential of using more precise nutritional solutions by incorporating local ingredients to reformulate RUTFs in order to make them low-cost, country-specific and well-accepted, facilitating integration into programs to fight acute malnutrition. Obviously, more research is needed to increase our knowledge about replacing or reducing milk powder with other protein sources in RUTFs, as current recommendations still stipulate that more than 50 percent of protein must come from dairy sources, and milk powder easily contributes to more than 30 percent of overall production costs. Nevertheless, other research questions – such as the long-term impact of RUTFs on the nutrition and health of children recovered from SAM, the optimal essential fatty acid composition, and the short- and long-term impact of SAM treatment on the intestinal microbiome – demand answers urgently. In Indonesia, IRD, Colorado University, IPB (Bogor Agriculture University) and Savica

Testing of different RUTFs for acceptability in Cambodia (2014).

Using the mid-upper arm circumference (MUAC) to screen for acute malnutrition in Cambodia.

are developing an RUTF including rice bran. This locally available ingredient has prebiotic properties and demonstrated potential in reducing gut inflammation and improving the absorption of micro- and macronutrients,[17,18] boosting microbiome recuperation[19] and thus potentially decreasing the risk of relapse in SAM children.[20]

> **"By applying precision nutrition to RUTF formulation, we could enhance the impact on the long-term consequences of malnutrition"**

The above examples illustrate more general adaptations of RUTFs, but precision nutrition methods for SAM treatment could be developed by making better use of the indicators that are used to diagnose SAM, weight-for-height Z-score (WHZ) and the mid-upper arm circumference (MUAC).[21]

Using either of these indicators independently implies that an individual loses weight and arm tissues proportionally. However, studies have shown that WHZ and MUAC identify different subgroups of children with SAM;[22] in some countries, more than 80 percent of children are diagnosed as severely malnourished by one indicator[23] but are not considered to be malnourished by the other indicator. This poses problems for health policies, as WHZ is at least as strongly associated with the risk of death in children as MUAC. Hence, one cannot ignore WHZ as an indicator for SAM,[24] even though some argue that WHZ is too difficult to measure.

But using both indicators for SAM also offers opportunities for precision nutrition, as WHZ and MUAC have different associations with body composition. For example, children identified as having SAM based on a low WHZ tend to have less lean body mass than children identified as having SAM based on a low MUAC, and perhaps they might benefit from an RUTF with a (slightly) different composition than children with a low MUAC.[25] Thus, in the near future, we can aspire to give a personalized RUTF to children based on gender and nutritional status, with a low MUAC, a low WHZ, or both.

By applying precision nutrition to RUTF formulation, we could adapt to organoleptic preferences and enhance the impact on the long-term consequences of malnutrition.

Using specific components, such as prebiotics, could ameliorate the gut microbiome and metabolic function, ultimately improving body composition – a proxy indicator for the risk of noncommunicable diseases.

In any case, the development of sustainable, low-cost RUTFs will stimulate local food systems and economies. It will also boost equitable access to diet quality and diversity as well as to malnutrition prevention and treatment, thereby contributing to building resilience for LMIC in this global food crisis.

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Measuring skinfold in Cambodia to estimate body fat.

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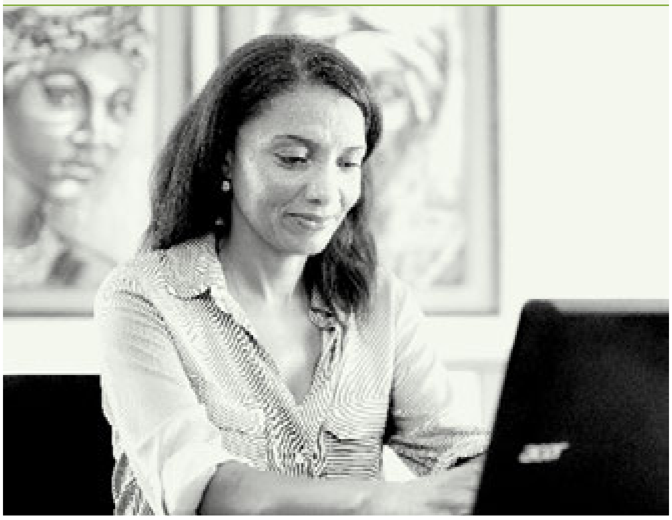
"The Future of Health is Personalized Nutrition, and It Is Already Here"

Interview with Mariette Abrahams



Mariette Abrahams is the CEO & Founder of Qina, the first-ever hub for data and insights about personalized nutrition. She explains the genesis of Qina and the potential of precision nutrition for LIMC.

***Sight and Life* (SAL):** *Mariette, what attracted you to the field of nutrition?*

Mariette Abrahams (MA): I was interested in nutrition and cooking from a young age, and was also very sporty. One of my teachers therefore suggested I might follow a course in dietetics and nutrition, which led to me completing a 4-year degree at Stellenbosch University, South Africa.

After graduating, I had roles in the food service sector and at a retail pharmacy, after which I went into clinical dietetics specializing in gastroenterology (inflammatory bowel disease) in the UK National Health Service (NHS). I worked in the NHS for 8 years, managing patients who required nutritional support, while studying towards an MBA and managing a team of specialist dietitians.

Having always been interested in new technologies and approaches within my field and beyond it, I left the NHS for a job as scientific and medical affairs manager at Nestlé Health Sciences UK, where I focused on specialist medical food products. The advent of genotyping and nutrigenetics was opening up many interesting new avenues for research at the time, which piqued my interest. But in 2009, my husband (who is Portuguese) and I moved to Portugal, where we still live. I decided to combine my interest in nutrition with my business skills and set up as a consultant. Despite my first client's business folding, I continued consulting, believing in the promise and potential of personalized nutrition, and also embarked on a PhD. Eventually, Qina was founded in 2019.

SAL: *What informed the concept of Qina?*

MA: I had observed that many recently established personalized nutrition companies had no background in nutrition; they really had a need for people with specifically clinical expertise. The idea of Qina was to help make these companies more transparent, rooted in the science and accountable by offering them a checking- and challenging-point provided by nutrition experts in the field. So the value we brought to companies was not just in nutrition per se but also in the ethical issues and behavioral science that go along with it. We operate at the intersection of food, technology, health and society.

SAL: *How does Qina work, Mariette?*

MA: Qina is a platform that tracks the personalized nutrition industry, which means that we aggregate and analyze market data and provide expert insight into what shifts are happening and why. Essentially, we combine nutrition knowledge with market data, so that any company, practitioner or organization can easily find accurate information about the industry in one place. We also provide consultancy services for companies who are interested in conducting research or would like to innovate using the latest in digital tools and agile approaches.

SAL: *And what is a Qina score?*

MA: It's a benchmark score for nutrition companies – not for nutritional products. The Qina score is designed to help the nutrition industry set its own technology-driven benchmarks. To develop the scoring system, we looked at a wide range of criteria to evaluate companies active in the field of personalized nutrition. There's still no universally accepted definition of personalized nutrition, but the Qina score helps new players in this field orientate themselves.

> **"The idea of Qina was to help make nutrition companies more transparent, rooted in the science and accountable"**

SAL: *Could you clarify the distinction between personalized nutrition and precision nutrition?*

MA: Personalized nutrition is based on consumer lifestyle, tastes and needs at the lower level, whereas precision nutrition involves using more advanced (omics) technologies at the higher level to deliver more precise nutritional advice and recommendations. These two terms are often used interchangeably. Personalized nutrition is the overarching term, however.

SAL: *And what services does Qina provide?*

MA: We offer four distinct services: the Qina Hub helps our clients understand and explore the competitive landscape through our comprehensive database, which uses advanced filters and a unique taxonomy, our expert-created content, and a market data dashboard.

Secondly, we provide insights into the evolving landscape through our advanced text analytics tool QinaVer, which allows easy searching through all content by timeframe, keyword or category.

Then we have the Qina score, which permits easy benchmarking of personalized nutrition solutions in the industry.

Finally, our consultancy services support companies with their innovation projects, from new product development through providing strategic advice to conducting mixed-methods research.

We are currently also working on a new tool (Qina FML), which is particularly applicable to LMIC, as it will help our clients to design and deliver nutrient-dense, affordable foods that are based on locally sourced ingredients as well as local production capabilities, and tailored to specific local needs.

SAL: *Has your thinking about personalized nutrition changed as a result of your experiences to date with Qina?*

MA: I certainly appreciate the importance of the consumer perspective a lot better. If we are going to support individuals to change their behavior, we need to involve them in designing new solutions from the start. We don't actually need more tools to help consumers: we simply need to combine them better so that we can answer the all-important question, "How can I help you to be healthier today?"

SAL: *What barriers currently exist to the implementation of precision nutrition in LMIC, and what would be the preconditions for creating an effective enabling environment in these countries?*

MA: There are multiple barriers. Firstly, many consumers can have unrealistic expectations of what precision nutrition can deliver today, as the research is only emerging. This factor is often compounded by a lack of basic understanding of nutrition itself. Then comes the issue of costs and funding: not everyone is in a position to invest financially in their health. Next come old ways of thinking: the farming lobby has been very influential for many years, but governments today need to understand that investments are required not just in the production of food but also in the prevention of nutrition-related diseases. On top of these factors, any successful implementation of precision nutrition has to be data-driven, and it should also take into account the various ethnic, racial and national groups specific to the contexts in which it is applied. These groups are often under-represented in the relevant clinical literature, and they need to have a voice if precision nutrition is to be equitable. This is where we believe Qina has a huge role to play.

> **"How can I help you to be healthier today?"**

SAL: *You're passionate about bridging the gap between academia, consumers, industry and frontline healthcare professionals. How can these disparate groups collaborate most effectively?*

MA: I think that this collaboration is starting to happen already. There's no dominant discipline at present; everyone is in the same room and talking with each other. This is progress! I'm on the Board of the University of Illinois, working on this subject right now, and the conversation is centering on the question of what we should do first and who has to be included in order to advance the field as a whole.

SAL: *Precision nutrition has so far been generally confined to high-income countries. What might be its potential benefits for LMIC?*

MA: Precision nutrition can have a huge impact on population health in LMIC. However, this will require multiple stakeholders to share data and collaborate from farm to fork. Without a solid technology infrastructure this will be a challenge, and therefore governments and the private sector will need to collaborate in order to develop and deliver services where they are most needed. There are many great examples in Uganda, Rwanda, Kenya and Nigeria that are leveraging digital tools to deliver healthcare, but we need to do a better job at connecting the use of digital tools for nutrition. Adoption of mobile phones, for instance, is high, yet the use of (smart) phones to drive behavior change in nutrition and health is lagging. Currently we are part of an ecosystem that aims to develop nutritious products using local and sustainable ingredients that improve health, but where the local communities will benefit as well. We believe this is the future for LMIC, where preventable lifestyle diseases are contributing to high rates of obesity, cardiometabolic conditions and cancer. With a precision nutrition approach, one could then develop specific nutritional formulations where a specific nutritional need exists, based on solid data.

We must also address the current skills gap and a global shortage in healthcare workers by leveraging technologies, but users need to be involved in the design and execution in order to increase motivation and adherence. My biggest worry at present is the inequities brought about by the effects of climate change and the current pressure on global food systems. The West can and should step up now to ensure that no-one is left behind. At Qina, we believe that the future of health is personalized nutrition, but the ideal of global health will not be achieved unless everyone has access to affordable and healthy food.

SAL: *Thank you, Mariette.*

MA: Thank you.

Mariette Abrahams was interviewed by Jonathan Steffen.

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"Precision Nutrition Has to Be Democratized"

Interview with Lu Ann Williams and Kamel Chida

Lu Ann Williams is Co-Founder and Insights Director at Innova Market Insights; Kamel Chida is a Business Advisor at Nucleus Capital, a venture capital firm supporting purpose-driven founders. They discuss the requirements for making the benefits of precision nutrition available to a greater proportion of the global population.

***Sight and Life* (SAL):** *Let's talk briefly about personalized nutrition before we discuss precision nutrition. The trend toward personalized nutrition is on the rise. What are the main drivers behind this trend, and what are its potential benefits for consumers?*

Lu Ann Williams (LAW): I think there are four main trends. The first concerns the growing awareness of the role that nutrition has to play in wellness; COVID-19 was a masterclass in this! Then come the ever-expanding possibilities of product customization. Thirdly, we have the development of precision medicine, which makes use of recent advances in the field of genotypes and biomarkers, for example. Lastly, we have rapid advances in capabilities for tracking and testing – for instance, with the aid of smartphones. For general consumers in the United States and Europe, these developments have the potential to support healthy ageing, meaning that individuals may expect more healthy years of life accompanied by the sense of being in active control of their health.

Kamel Chida (KC): Indeed – we should also recognize that there are plenty of lower-income consumers in the United States and Europe as well as in LMIC who could benefit from personalized nutrition solutions. And there's also the divide between the global north and the global south to consider. Consumers in the global north may be concerned about how to use nutrition to support improved health, but many consumers in the global south have much more basic concerns about how to put food on the table. In the global south, nutritional standards overall need to be raised. Poor nutritional status in these regions is accompanied by a significant increase in the incidence of noncommunicable diseases (NCDs). A one-system approach is required to address this development.

> **"COVID-19 was a masterclass"**

SAL: *What is the relationship between personalized nutrition and precision nutrition, and what benefits does precision nutrition offer, in your view?*

LAW: There's no universally accepted definition as yet, but if we think of traditional attempts to describe good nutrition in terms of a pyramid or plate comprising all the essential elements, personalized nutrition takes this further by providing significantly more detail concerning the dietary requirements of individuals. Precision nutrition goes further still, by addressing interactions between diet and the metabolism in far more detail – exploring, for instance, the relationship between diet and the biome of the individual.

KC: We can see this as development that will become more refined in the course of time. Some 15 years ago, people started talking about food as medicine – although this concept was entirely familiar to the Ancient Chinese. And recent years have seen considerable focus on the nutritional benefits of the Mediterranean diet. Precision nutrition goes much deeper than this, using the insights of genetics and metabolics to enable the creation of foods that can be customized to meet individual nutritional needs. The possibilities of artificial intelligence (AI) will greatly enhance the potential impact of precision nutrition, but, as with any significant new scientific development, this calls for some form of regulation.

> **"In the global south, nutritional standards overall need to be raised"**

SAL: *How much traction has the concept of precision nutrition gained thus far? Is it already informing the thinking of policymakers and the buying patterns of consumers?*

KC: The USA has been a beacon for the rest of the world in many ways: it has fostered the spread of pop culture and fast food for example, with the latter generating a rise in the incidence of diet-related NCDs. By the same token, it has the potential to play an important role in spreading the benefits of precision nutrition around the world, reaching places where it has the greatest potential to improve human nutrition and health. The question is whether the global south has the capability of availing itself of these benefits and integrating them into its own systems.

LAW: A good point. The US market is a far simpler one in which to operate, because it's a very large single entity.

SAL: *What are the key technology enablers supporting the development of precision nutrition?*

LAW: Modeling is absolutely key, because we're faced with vast quantities of extremely complex data. The extraction of robust and credible models from this wealth of information is only just now becoming practicable and, indeed, affordable. AI has a crucial role to play in this.
KC: The dynamics of supply and demand are also significant. Consumers in the USA, Europe and also Asia are changing their attitudes and accompanying behaviors more rapidly than in the rest of the world, but the issue of trust is critical. People trust companies more than they do governments. For this reason, early adopters of precision nutrition are looking on it as a means to help control their own destinies. Above and beyond this, there's a huge north–south divide in terms of AI capabilities. The data gap in the global south needs to be addressed, and the role of governments is critical here.

SAL: *What are the key priorities of consumers in LMIC when buying and preparing food?*

KC: Well, it wasn't easy before, it's become harder and it will get worse in the future in view of what is currently happening on the world stage. Of course, all countries have a rich class, a middle class and a poor class, but at the base of the pyramid there are hundreds of millions who are living on less than a dollar a day, and that dollar has to be earned, day in day out. In Nigeria a few years ago, for example, the cost of an egg was 40 percent of the daily wage of a laborer in the fourth income quintile. Precision nutrition has the potential to fill vital nutrition gaps through population-level interventions such as the fortification of staple foods. Governments in the global south have a pivotal role to play in this. In the USA, by contrast, the drive towards precision nutrition is more of a market-based, grassroots phenomenon.

SAL: *What would be the requirements for successfully introducing precision nutrition into LMIC?*

KC: The necessary functionalities and tools already exist, but a critical factor is who will pay to fill the data gap and whether governments will permit collection of the necessary data. In terms of implementation, the requirements will vary enormously country to country, dependent on the availability of budgets, the local regulatory framework and also the situation on the ground. The problem of diet-related NCDs is more pressing in some countries than others. It's acute in Mexico and the Philippines, for instance.

"Precision nutrition has the potential to fill vital nutrition gaps"

SAL: *Should a uniform approach to the introduction of precision nutrition be adopted in all LMIC, or do different countries call for different solutions?*

KC: It won't be an organic development. Some form of trigger is needed. In the global north, people are in the habit of buying nutritional supplements. It's therefore a relatively easy step to go from this to precision nutrition. The case is different in the global south. There, governments are traditionally in the lead in such developments. I'd like to see the creation of partnership-based solutions involving collaboration between government, the private sector and consumers. Such initiatives would make it possible to demonstrate the impact of precision nutrition among the populations of the global south.
LAW: Indeed. We should also bear in mind that most functional food products fail due to lack of consumer compliance. In the global south, however, people might be more acutely aware of their nutritional needs and be consequently more compliant. Under no circumstances, however, do they want to eat food that has been developed for 'poor people'. Precision nutrition has to be democratized.

SAL: *Thank you, Lu Ann; thank you, Kamel.*

LAW: Thank you.
KC: Thank you too.

Lu Ann Williams and **Kamel Chida** were interviewed by Jonathan Steffen.

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"The Power to Redesign the Global Food System Lies with Us"

A Day in the Life of Michelle Grant

Michelle Grant is the founder of The Great Full, a "place to explore how we can improve personal and planetary wellbeing by leading change from the inside out." She discusses her work to help bring about a more sustainable world.

***Sight and Life* (SAL):** *Michelle, your first degree was in chemical and environmental engineering. Nine years after graduating, you became Executive Director of the World Food System Center at ETH Zurich. Could you tell us about that evolution?*

Michelle Grant (MG): My first degree gave me a solid technical foundation, but I realized I was interested in addressing environmental challenges in a broader way. I participated in a summer school at the end of my degree that introduced me to the concept of sustainable development. As I started working in that field, I realized how central food is to all the global challenges we were trying to tackle. I later learned of a new opportunity at the World Food System Center at ETH Zurich, where I'd previously worked and done my master's studies, and applied for it. I was appointed Executive Director in December of 2011 and stayed in that role for the following 6 years.

SAL: *You're still connected with ETH Zurich, as a lecturer and adviser on sustainable food systems. Do you think we will ever see a world in which all food systems are genuinely sustainable? And what would it take for this to happen?*

MG: That's a very good question. I have no objective answer, but I must believe that it's possible. I'd describe myself as urgently optimistic. It's essential to realize that we ourselves have designed a global food system which is not serving everyone equally and that the power to redesign it consequently lies with us. This involves various areas of focus: making significant changes to our diets; understanding the true cost of the current agricultural and food system; introducing more diversity in food production and consumption; and eliminating food loss and waste. Most important of all, however, is the factor of human agency. These are problems that we as humans have created for ourselves, and we need the right sort of leadership to rectify them. This also means building skills to 'manage the overwhelm' that is inevitable when working in such a complex system.

SAL: *In 2020, you published a work entitled 'The Great Full: Sustainable Eating with Purpose and Joy.' Can you tell us something about that publication – how you came to write it, and what the book sets out to achieve?*

MG: The title comes from the idea of what it means to lead a great and full life, and the role of food in that. I had the privilege to work in an academic environment, which gave me the opportunity to be exposed to a wider range of cross-disciplinary thinking about food systems and sustainability. I felt a responsibility to spread this message to a broader audience and thought a cookbook format would help people engage with the content in a different, and practical, way. Through this approach, I enjoyed connecting with a wide range of people, helping them explore their role in building both personal and planetary wellbeing through food.

"I'd describe myself as urgently optimistic"

SAL: *The Great Full is more than a book, however; it's a platform that shapes a new approach to leadership in the cause of sustainable change. What is the philosophy behind your work, and how is it being received?*

MG: The Great Full aims to help us make our contribution to a more sustainable food system, and world, in a way that is both purposeful and joyful. It's informed by my profound conviction that the necessary change must be led from the inside out. Many people who operate in the sustainability space are driven by altruism, but I see them burning out because they feel that nothing they do can ever be sufficient to address the problems with which they are confronted.

We need to understand the deeper drivers of our actions in order to be able to define what is enough and live and work in a more sustainable way. This also means finding a way to combine both purpose and joy, to work driven not only by fear but also by love for what we want to build. We want to treat both ourselves and the world better, and there's much joy to be gained from that endeavor. I work on these topics by offering coaching and training programs, a podcast and a professional community. There seems to be a strong resonance with these topics at the moment, and I'm enjoying working with really inspiring changemakers.

SAL: *You're a certified leadership coach. Could you tell us a little about your training, and about why leadership as a topic is so important to you?*

MG: I graduated as a Professional Certified Coach in Integral Leadership Coaching from the Graduate School of Business of the University of Cape Town, South Africa. My interest in coaching stems from the realization that people tend to overlook the role of leadership when trying to drive food systems transformation. I also noticed that more and more people were coming into my office looking for support to find their role in creating change, and it was their questions that encouraged me to acquire a formal qualification in coaching. The course was extremely holistic, considering all the different aspects of being human we need to integrate to create change. As Warren Bennis says, "Becoming a leader is synonymous with becoming yourself, it is precisely that simple and it is also that difficult." I think that's extremely true.

> **"Becoming a leader is synonymous with becoming yourself"**

SAL: *What role do you think that women specifically have to play in leading the world towards a more sustainable way of living?*

MG: At present, fewer than 10 percent of countries and companies worldwide are led by women. Yet research has shown, and the pandemic highlighted, that women perform better than men in a crisis, demonstrating more empathy, humility and compassion. We are facing multiple crises right now, so we all need to think about how we can integrate these values that were traditionally considered feminine into our lives and work. I'd say that our current society is too focused on competition, performance and productivity right now. We need to re-examine what we are doing, how we are doing it and who is leading.

SAL: *The title of this feature is 'A Day in the Life.' With a such a wide range of interests and activities, do you actually have such a thing as a 'normal' working day?*

MG: Well, my work always involves emails and Zoom meetings, but there's plenty of variety, with a podcast, training programs, one-to-one coaching, facilitation and other activities. This week I moderated an event at the 2022 World Economic Forum, hosted some podcast interviews and ran a leadership program for women working in food systems that focused on understanding our deeper motivators and drivers as leaders. I found that mix very fulfilling.

SAL: *What do you enjoy most about your work, Michelle?*

MG: The people I get to interact with – individuals who have the courage to lead change. I love seeing what happens when people have the chance to show up as full human beings and make their contribution to a better world from that place.

SAL: *If you could change one thing about your working life, what would that be?*

MG: I'd like to create more spaces for collaboration. I've been working on my own much more in recent times, partly because of the decision to set up my own organization and partly because of the effects of the pandemic.

> **"You can't stop the waves, but you can learn to surf"**

SAL: *How about your interests outside of work?*

MG: I think less about work–life balance and more about work–life integration. For instance, I do yoga and meditation and I integrate that into my daily work. Outside of that, I am currently learning Italian, as well as exploring lino-cutting and painting. I think it's very important to create space for one's own creativity; it is so easy to become disconnected from it, yet it can be a major source of inspiration in our professional lives.

SAL: *Is there anyone who has ever particularly inspired you in your career?*

MG: I'm very inspired by many of the young people I come across in the course of my work – for instance, two 17-year-olds whom I interviewed for my podcast. They are on the Youth Board of the Bite Back movement, fighting to make healthy food accessible for children in the UK. They're trying to fix the mess that another generation has got them into, and I really admire how they are showing up to do that.

SAL: *Do you have a favorite motto or quotation?*

MG: Coming from Australia, I'd have to say, "You can't stop the waves, but you can learn to surf." I love surfing myself, and I see the agency of the surfer as a metaphor for how to work with change.

SAL: *If people reading this article are interested in contributing to a more sustainable world, what would you recommend them to do?*

MG: I think we could each spend a lifetime exploring that question! In brief, though, I'd make five observations. One: Start from wherever you are, as small as necessary. Two: No single human can do everything, so ask yourself what you personally can do. Three: Find something to do that provides fulfilment and joy; anger can be an important catalyst, but it's not a sustainable fuel. Four: Find kindred spirits and connect with them in order to build a community around what you care about. And five: Try to understand the deeper drivers behind your own wish to make a positive contribution and understand how that might be contributing to unsustainable patterns.

SAL: *Many thanks, Michelle.*

MG: Thank you too.

Michelle Grant was interviewed by Jonathan Steffen.

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