Phenotypic Flexibility as a Measure of Health Through the Life Cycle

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A healthy diet, within an overall healthy lifestyle, may maintain or improve cardiometabolic health and help prevent chronic diseases. However, showing that a specific dietary product, dietary pattern, or even a positive change such as losing weight, has a beneficial effect on cardiometabolic health in the general population is not easy. A next generation of biomarkers is needed that reflects optimal health rather than disease. Based on a proposed improved definition of health,[1] in which health is regarded as the resilience of the body to deal with daily stressors, Netherlands Organisation for applied scientific research (TNO) established new methodology, including biomarkers, which relates to the body's ability to adapt as a measure for health, which is referred to as phenotypic flexibility. In the literature, several human nutrition intervention studies indicated the added value of evaluating phenotypic flexibility in showing health modulation.[2–5] However, there was a need for a generic holistic standardized challenge test that would be able to identify the early signs of individual homeostatic disturbances as well as assessing individual health benefits from nutrition, by showing an optimized response to the challenge test.

Based on an extensive literature review,[6] the so called PhenFlex challenge test was developed. The PhenFlex challenge consists of a 400 mL oral dietary formulation (60 g palm olein, 75 g glucose, and 20 g casein). The idea was to collect a multitude of biomarker response profiles, reflecting defined and accepted biological processes followed by sophisticated multivariate statistical analyses, to more powerfully detect early changes than the limited set of individual biomarkers that is used traditionally by evaluating single blood markers after an overnight fast (Fig 1). In the example of vascular health, such a composite biomarker could be composed of flow-mediated dilation, a functional marker of endothelial function and blood pressure, resilience markers for endothelial damage after a metabolic challenge test such as vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and selectin E (SELE) responses, and total cholesterol or specific single nucleotide polymorphisms related to an increased risk for cardiometabolic disease development.[7] By combining this information into an integrated readout called "health space,"[8] a next generation flexibility marker for vascular health can be extrapolated.

To investigate if this phenotypic flexibility approach had potential, a number of human volunteer studies have been performed in patients with type 2 diabetes as well as in healthy individuals.[8,9] These studies showed that clear differences in individual health status could be determined in response to the PhenFlex challenge test. Lean younger active people processed the challenge test faster, and showed a better ability to adapt as compared to sedentary elderly. Furthermore, in the general population (age 30-60) it was shown that with increasing adiposity the individual's metabolic age increased, where subjects with high adiposity reacted similarly to the challenge test as compared to elderly subjects.[8] In addition, the PhenFlex response of patients with type 2 diabetes was clearly different from the healthy response.[9] These data indicate the ability of the PhenFlex challenge test to assess personal health.

As the PhenFlex challenge approach has been standardized it can now be used to scientifically demonstrate individual health effects and the effect of single food products on health. Following review of the relative contribution of each of the biomarkers in the initially broad panel in the previous studies, now a subset of biomarker responses can be used which are most important in measuring health in a certain domain of health or for a certain food product. Importantly, this indicates the possibility that recovery of homeostasis (eg, resilience) could be regarded as a new measure of individual health. In a first proof of concept case with whole grain wheat products, we showed a positive effect on

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resilience, as subjects' biomarkers moved toward the range of the younger group after 12 weeks of exchanging refined grains for whole grain wheat (Hoevenaars et al, submitted). Furthermore, the PhenFlex challenge test was able to discriminate between subjects that had a health benefit from 20% caloric restriction and those who did not (ie, responders vs non-responders). It appeared that only subjects with reduced phenotypic flexibility at baseline—indicated by multiple metabolites that showed a disturbed response to the PhenFlex challenge—could improve health, whereas subjects with already good flexibility, and therefore a good health status, could not further improve.[10] Finally, based on assessing flexibility in glucose metabolism by applying an oral glucose tolerance test (OGTT) in a cardiovascular patient population, we demonstrated that different insulin resistance (IR) subgroups could be distinguished (no IR, muscle IR, liver IR, or liver and muscle IR), and that these subgroups responded differently to two healthy diets. Patients with muscle IR benefit most from a Mediterranean diet, evidenced by increased beta-cell function (Disposition Index); patients with liver IR benefit most from a low fat diet; whereas, patients with combined liver and muscle IR benefit most from a Mediterranean diet, but to a lesser extent than patients with only muscle IR.[11] These data exemplify the potential for personalized nutrition.

Future perspectives It is envisioned that nutrition in the future will be personal. Nutrition intervention or dietary advice will be based on a diagnosis, by using personal health data including biological (eg, phenotypic flexibility) as well as behavioral measures. A science based model will be used to translate these data into personalized nutritional goals and foods. This model is then tailored to specific personal preferences and goals, to gain better adherence to diet. In addition, in the near future, information from large numbers of personal health databases will be available, which can be used to link diet, lifestyle and environment with health outcomes to fine-tune personalized lifestyle advice. Regular or even daily data from people will be available, which reflect long-term phenotypic flexibility; this has already been demonstrated by Snyder and colleagues.[12] Therefore, phenotypic flexibility may be a future standard measure of health through the life cycle. It is possible that a digital life companion will provide people with personalized lifestyle advice throughout life; starting even before conception, updated with the latest scientific evidence, tailored to your preferences, goals, culture, social and economic environment, thereby preventing even the developing fetus from chronic lifestyle related diseases.

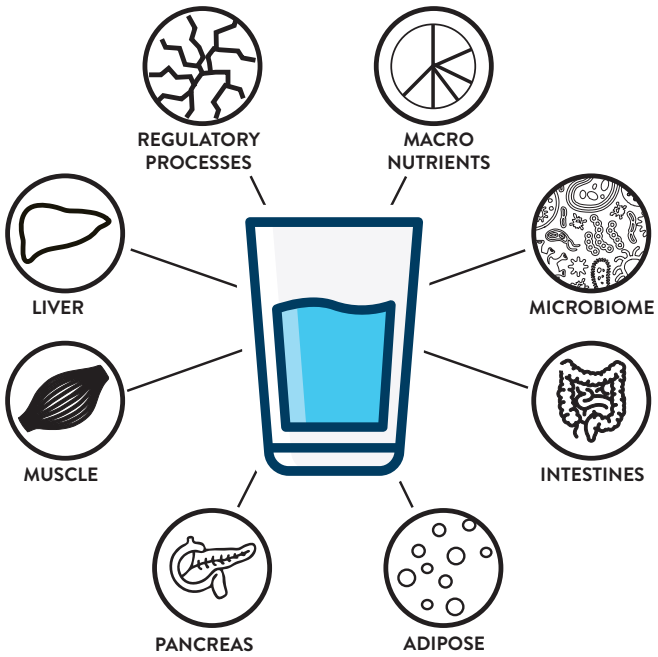

Fig 1. The PhenFlex challenge test.
The PhenFlex challenge test aspires to be a holistic standardized test that can measure health-related biological processes from key tissues and organs in the body impacted by nutrition and lifestyle.

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