Do We Need Personalized Recommendations for Infants at Risk of Developing Disease?

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Abstract

Current nutrition recommendations, directed towards populations, are based on estimated average nutrient requirements for a target population and intend to meet the needs of most individuals within that population. They also aim at preventing common diseases such as obesity, diabetes and cardiovascular disease. For infants with specific genetic polymorphisms, e.g. some inborn errors of metabolism, adherence to current recommendations will cause disease symptoms and they need personalized nutrition recommendations. Some other monogenic polymorphisms, e.g. adult hypolactasia, are common but with varying prevalence between ethnic groups and within populations. Ages at onset as well as the degree of the resulting lactose intolerance also vary, making population-based as well as personalized recommendations difficult. The tolerable intake is best set by each individual based on symptoms. For polygenetic diseases such as celiac disease, type-1 diabetes and allergic disease, current knowledge is insufficient to suggest personalized recommendations aiming at primary prevention for all high-risk infants, although it may be justified to provide such recommendations on an individual level should the parents ask for them. New technologies such as nutrigenetics and nutrigenomics are promising tools with which current nutrition recommendations can possibly be refined and the potential of individualized nutrition be explored. It seems likely that in the future it will be possible to offer more subgroups within a population personalized recommendations.

Introduction

Historically, the main objective of nutrition recommendations was to prevent deficiency disorders. Today nutrition recommendations have shifted their main focus from prevention of deficiency disorders to maintaining good
health and preventing major chronic diseases, e.g. coronary heart disease (CHD), obesity, diabetes, cancer and osteoporosis. Our recent understanding that early nutrition may impact on morbidity in these diseases in adult life [1] has turned nutrient recommendations for pregnant women and infants into an even more challenging task. So far, dietary recommendations target populations, or subgroups of populations, e.g. infants, children, pregnant and lactating women and elderly, but not individuals. Below we discuss whether there is a need to make nutrition recommendations more personalized, in particular for infants with an increased risk of certain diseases, and if we have sufficient scientific basis for such a change.

**Nutrient Requirements and Dietary Recommendations**

Nutrient recommendations are based on scientific knowledge taking into account food habits and health conditions within the target population. Generally, observational and experimental studies are the basis for decisions on nutrient requirements, for associations of diet and health, and for food-based recommendations. The requirement for a nutrient in a population can be described as a cumulated dose-response relationship. In the Nordic Nutrition Recommendations [2] as well as in the European Union Scientific Committee for Food Recommendations [3], the average requirement denotes the intake of a nutrient that represents the average requirement for a group of individuals. This corresponds to the estimated average intake recommendations used in the UK [4] and USA [5]. Studies using biochemical indicators on ‘status’ after feeding diets with different amounts of a nutrient exceeding what is required to elicit clinical deficiency symptoms are often used to define the average requirements of a population. Nutrient balance studies and/or factorial methods are also used to assess average requirements and make decisions on recommendations, particularly for minerals. Hence, current nutrient recommendations are not for individuals, but variations in requirements between individuals of the same age and sex are taken care of by adding a margin of safety, e.g. +2 SD to the calculated average requirement. The reference intake in the Nordic Nutrition Recommendations [2], the reference nutrient intake in the European Union [3], recommended daily allowance in the USA [4] and population reference intake in the UK [5] refer to the amount of a nutrient that, based on current knowledge, can meet the known requirement and maintain good nutritional status among practically all healthy individuals in the target population.

**Geographic Differences in Nutrition-Related Disease Patterns**

Epidemiological studies have shown striking differences between populations and countries in the prevalence of many diseases. For instance, there is a
strong association between the incidence of CHD and the level of serum cholesterol in a population as well as between the death rate from CHD and the median serum cholesterol concentration, which also mirrors the correlation between CHD deaths and the percentage of fat derived from saturated fatty acids. It is now generally accepted that diet plays a role in the etiology of many multifactorial diseases such as cancer, CHD and diabetes [6]. Hence, besides the basic requirements to maintain body stores and functions, most dietary recommendations are also based on correlations, or at least associations between nutrient intakes and food composition on the one hand and the risk of developing various diseases on the other [2]. Thus, the importance of considering not only recommended intakes based on the average requirement and a safety margin but also maximum intakes or upper limits has caught increasingly more attention [7]. This has generally been adopted for the energy-yielding nutrients, i.e. fat, fatty acids and carbohydrate, but also for some other nutrients. Several controlled intervention studies have shown that a diet in agreement with, for instance, the Nordic Nutrition Recommendations [2], i.e. fat constituting around 30% of the energy (E%) of which no more than 10 E% should be saturated fatty acids (from 2 years of age), rich in dietary fiber, an adequate amount of n-3 fatty acids, and frequent consumption of fruit, vegetables, whole grain products, and regular consumption of fish and regular physical activity, can reduce the risk of or, alternatively, have a beneficial influence on several risk factors for overweight, diabetes and CHD including serum lipids, blood pressure and insulin resistance. The age from which the same recommendations should be applied for children as for adults is however controversial [8]. Although, these recommendations aim at reducing the risk of contracting common diseases on the population level, they do not take into account all possible individual risk factors such as extreme susceptibility due to genetic polymorphisms or to the feeding pattern in infancy.

**Nutrigenetics and Nutrigenomics**

Genetic variation is known to affect food tolerances among human subpopulations. There are many examples on how nutrients are directly involved in gene regulation, which may have both short- and long-term consequences, as well as on how genetic variation caused by single nucleotide polymorphisms (SNPs) within a gene may affect digestion, absorption, excretion, storage or transport of a nutrient, which in turn may contribute to variation in the requirement for that nutrient and also the risk of disease symptoms. One example is the Ala222Val polymorphism in the methylene tetrahydrofolate reductase gene, which substantially alters folate metabolism increasing the risk of neural tube defects and cardiovascular disease but possibly decreasing the risk of colon cancer [9]. This illustrates that merely increasing the reference intake for the whole population to cover the requirement for folate for this
phenotype may at the same time have negative health consequences for the target population. This is important to take into account when decisions on general supplementation programs are made, but also when considering personalized recommendations. All potential consequences need to be known before recommendations are given. Other known polymorphisms, for instance in apolipoprotein E can explain why some individuals respond differently than others to dietary modifications, e.g. aiming at normalizing elevated plasma cholesterol levels [6, 10]. Seemingly healthy individuals have different SNPs of a particular gene. In fact such polymorphisms are normal and only a minority of them causes disease, or may cause symptoms only when a nutrient is consumed in excess [9].

In the area of gene–diet interactions, nutrigenetics and nutrigenomics are two emerging concepts. The former addresses the importance of genotype (mainly SNPs) on the risk of nutritionally related disease. It has developed from the assumption that certain genetic polymorphisms measurably alter nutritional deficiency. Genetic polymorphisms are identified and studied to see if they modulate the relationships between nutritional exposure and risk. The aim of nutrigenetics is thus to generate recommendations on an individual basis regarding the risk and benefit of specific dietary components.

Nutrigenomics addresses the inverse relationship. It focuses on the effect of food-borne components on gene transcription, proteomics and metabolomics, and involves the characterization of gene products and the physiological function and interaction of these products, promoting an increased understanding of how nutrition influences metabolic pathways and homeostatic control. The premise in this case is that diet influences disease through mechanisms regulating gene expression. Nutritional genomics aims to identify the genetic variation that accounts for individual reactions to dietary components. It is obvious that nutrigenomics is much more difficult to use in nutritional research than nutrigenetics [10, 11]. The question is whether such individual differences impact on dietary recommendations to the extent that they become individualized for each genetic makeup. In this context it should however be noted that if the data used to set the reference intake (recommended daily allowance) and upper limits are based on a diverse population, these should encompass most of the genetic variation in that population.

**Some Examples from Monogenic Disorders**

*Phenylketonuria*

Phenylketonuria (PKU) is a classical autosomal recessive inherited deficiency of the enzyme phenylalanine hydroxylase, resulting in a lost or reduced capacity to convert phenylalanine to tyrosine, a substantial increase in phenylalanine in serum, and severe mental retardation unless dietary phenylalanine is restricted [12]. The prevalence varies between populations
but in Caucasians 1 infant per 12,000 born is diagnosed with PKU. Large
numbers of SNPs within the gene have been described. Because of the sever-
ity of the disease and the profound preventive effect of early dietary treat-
ment, many countries now screen all newborn infants for raised levels of
phenylalanine (the Guthrie test). Patients diagnosed with PKU are subject to
personalized dietary recommendations, illustrating that for a few genotypes
this already exists. So far neonatal screening is carried out for a few mono-
genic diseases but, with technical developments in recent years, the possibil-
ity of screening for many more inherited metabolic diseases has emerged [13].

**Familial Hypercholesterolemia**

Familial hypercholesterolemia (FH) is a co-dominant inherited disorder
classified by very high concentrations of low-density lipoprotein cholest-
terol (LDL-C) and a severely increased risk of premature CHD. The clinical
phenotype and, hence, premature death from CHD is much more pronounced
for homozygotes than for heterozygotes. While homozygous individuals are
rare (1 per million), the heterozygous condition, typically referred to as FH, is
relatively common (1 per 300 to 1 per 500 in most countries). The underlying
reason is a mutation in the LDL-receptor gene [14] with severely reduced
clearance of LDL particles from the circulation. More than 800 different
mutations have been identified and, as for PKU, the phenotypic expression
varies considerably. Obviously, some mutations result in more severe clinical
phenotypes than others depending on what exact function of the protein is
affected. However, also individuals who share the same SNP in the LDL-
receptor gene may differ substantially in clinical presentation of the disease.
It seems that additional factors influence the clinical course of FH, e.g. modi-
fying genes. Several factors, including various lipases and apolipoproteins,
e.g. apolipoprotein E polymorphisms, seem to have such a modifying effect
on LDL-C for several common polymorphisms of FH [10]. Another modifier is
of course diet, which is used in the treatment of hypercholesterolemia. It is
interesting to note that while FH is a much more prevalent disease than PKU,
and it is well established that the atherosclerotic process starts early in life
and that FH results in severe risk for premature morbidity and mortality [14],
there is no general screening for FH and most countries do not recommend
general pre-symptomatic diagnosis and early preventive dietary intervention
[15]. In fact, most countries do not screen children of parents diagnosed with
FH due to early CHD, which may seem doubtful from an ethical point of view.

**Adult Hypolactasia**

Geographic variation in disease patterns results from both dietary and
genetic differences. An example on how genetic variation may affect food tol-
erance is adult hypolactasia, a normal condition among mammals including
man, encompassing around 70% of the world’s population. After weaning
there is a gradual reduction in the activity of the lactase-phlorizin hydrolase
enzyme, which hydrolyzes lactose to absorbable glucose and galactose. Lactase persistence can be regarded as a mutant phenotype (autosomal dominant trait), which arose 5,000–10,000 years ago coinciding with the domestication of cattle. 95% of people of Asian origin carry the adult hypolactasia genotype, compared to 80% of African-Americans and less than 5% of Caucasians of northern European and Scandinavian descent [16]. Recently Ennath et al. [17] ascribed adult hypolactasia in caucasians to one major mutation (C13910T) located approximately 14 kb upstream from the LCT locus, the gene coding for lactase-phlorizin hydrolase. Interestingly, different mutations seem to have appeared around the same time among Africans and Caucasians [18]. The sensitivity to lactose differs considerably between individuals with the same genetic polymorphism, and symptoms may appear already in early childhood in Asian populations while they rarely occur before teenage or adolescence in Finns [16]. Therefore, it must be pointed out that while adult hypolactasia is a laboratory diagnosis, lactose intolerance is a clinical diagnosis. Thus confirming that the adult hypolactasia genotype is not sufficient for personalized dietary recommendations. The capacity to digest lactose varies between individuals, with age and a number of other factors, again illustrating that gene–diet interactions are indeed complex. The tolerable intake is best decided on by each individual based on symptoms.

Some Examples from Polygenic Disorders

Celiac Disease

Celiac disease (CD) is a chronic inflammatory disease of the small intestine, affecting genetically susceptible individuals. Virtually all CD patients express the HLA-DQ2 and/or HLA-DQ8 alleles. Other as yet not identified genes account for at least half of the genetic risk. CD is caused by failure to establish and/or maintain tolerance to dietary prolamins in wheat, barley and rye, and particularly to wheat gliadin. Active disease is associated with an intestinal lesion, typically showing villous atrophy, crypt hyperplasia, and increased numbers of lymphocytes within both the epithelium and the lamina propria [19]. Clinical and histological improvements are seen upon withdrawal of wheat, barley, and rye from the diet, which is the only current treatment of CD. Most likely each separate genetic risk factor is fairly frequent in the general population, suggesting that a combination of some of these genes and their interaction with the environment induce CD, making it a chronic disease of multifactorial etiology.

In the mid 1980s, Sweden experienced a unique epidemic of symptomatic CD in children below 2 years of age. The incidence reached levels higher than ever reported at that time. It decreased as quickly as it had increased to the level seen before the epidemic [20]. The most plausible cause of the epidemic was a variation over time of some causal factors affecting a large fraction of
the Swedish infant population as only children below 2 years of age were affected. Changes in infant feeding practices were suspected to be the culprit. In a case-referent study we could indeed demonstrate that early infant feeding practices contributed to the epidemic. If gluten is introduced slowly while the mother is still breastfeeding, the risk for the child to contract CD before 2 years of age is reduced (odds ratio (OR) 0.59; 95% confidence interval (CI) 0.42–0.83) [21] compared to if gluten is introduced after breastfeeding has been discontinued. The longer the mother continues to breastfeed after gluten has been introduced into the diet, the greater the protective effect seems to be. Moreover, the amount of gluten given during the first 2 weeks after the first exposure also was found to be an independent risk factor. Based on the distribution of flour consumption of the referents we found that consuming large amounts (corresponding to the upper third of the distribution) as compared to small or medium amounts (lower and middle third of the distribution) increased the risk (adjusted OR 1.5, 95% CI 1.1–2.1) [21]. These observations led to new national recommendations on gluten introduction in 1997, i.e. to change the age at introduction from 6 months to between 4 and 6 months as for other complementary foods, and to introduce small amounts of gluten gradually, preferentially while the mother is still breastfeeding. The new recommendations coincided with the observed rapid decline at the end of the epidemic [20], suggesting that primary prevention of CD may be possible by dietary recommendations. However, Sweden as most other European countries has adopted the WHO recommendation on exclusive breastfeeding for 6 months, i.e. again to postpone gluten introduction to 6 months of age, a change that preceded the abrupt increase in the epidemic in 1983 [20]. Thus, these two recommendations may be in conflict unless mothers continue to breastfeed beyond 6 months of age. Would it therefore be justified to adopt personalized dietary recommendations to reduce the risk for children below 2 years of age to contract CD? One possibility would be to test infants with first-degree relatives who have CD for the HLA-DQ2 and DQ8 haplotype. Should they carry one of them, their parents could be advised to introduce gluten between 4 and 6 months and encourage the mothers to continue breastfeeding well beyond the introduction. However, it is not yet known if cohorts born after as compared to during the epidemic carry less life-time risk of contracting CD. An ongoing Swedish screening study will answer if primary prevention by dietary guidelines is at all possible [22].

**Type-1 Diabetes**

There are indications that the pathogenic process leading to type-1 diabetes (T1D) starts very early in life and during childhood the incidence has shifted towards lower age in many countries. As for CD the early feeding pattern may modulate the risk of developing T1D in genetically susceptible individuals. Moreover, patients with T1D are at increased risk of developing CD. Not only are breastfed infants at less risk than formula-fed infants of developing
T1D but also the timing of the introduction of both gluten-containing solids and cow's milk as well as the amount of cow's milk consumed at 1 year of age have been suggested to affect the risk. It is possible that introduction before 3 months confers a greater risk than between 4 and 6 months of age [23, 24]. However, exactly how weaning habits affect the risk for T1D is still not clear. The ongoing Trial to Reduce IDDM in Genetically at Risk, which tests the hypothesis that weaning to an extensively hydrolyzed infant formula will decrease the incidence of T1D, as demonstrated in animal models, will hopefully solve the question on the role of cow's milk protein in the pathogenesis. Until then and until more is known about which genes besides HLA are crucial, it seems premature to give personalized advice for high-risk infants besides encouraging breastfeeding; although besides the introduction of milk as a potential risk factor, it seems that the same strategy suggested for CD could also be applied to the prevention of T1D.

**Allergic Diseases**

The prevalence of allergy and asthma is increasing and approximately 20% of the world population suffers from IgE-mediated allergic diseases. Individuals with a family history of atopy have an increased risk of developing IgE sensitization and typical symptoms of eczema, allergic asthma, allergic rhinitis and/or allergic conjunctivitis. Immune programming starts early in life and several approaches to prevent IgE sensitization have been implemented over the years. However, there are no reliable genetic and immunologic markers to identify an infant at risk, which complicates primary prevention of IgE sensitization. A positive family history is the most reliable predictor of allergy in infants [25]. Dietary measures in the prevention of allergy have included avoidance of dietary antigens during pregnancy and breastfeeding with no evidence of long-term prevention of allergy. Rather, such a diet could be harmful by adversely affecting maternal as well as fetal nutrition [26]. Studies exploring the effects of breastfeeding in the prevention of allergy have produced conflicting results, and an obvious shortcoming is the lack of randomized studies for ethical reasons. However, in a Cochrane review, exclusive breastfeeding for 6 vs. 3–4 months did not significantly reduce the risk of allergic disease [27]. The Section of Pediatrics of the European Academy of Allergy and Clinical Immunology recommends breastfeeding combined with avoidance of solid foods and cow's milk for the first 4–6 months of life in the prevention of allergic disease in high-risk infants. When breastfeeding is not possible, feeding of a hypoallergenic formula is recommended [28]. However, it is recognized that studies underlying these recommendations have methodological shortcomings [28, 29], and elimination diets in the long-term prevention of allergy have been inconclusive.

The decline in microbial exposure during early childhood is one of the most probable reasons for the increasing incidence of allergic disease in the Western world. Both epidemiological studies and gnotobiotic animal models have been
supportive of such a hypothesis [30]. Gut microbiota is a major stimulus of the immune system and is suggested to act by inducing T-cell immune regulation. This has driven the idea of using probiotics, mainly bifidobacteria and lactobacilli, for the treatment and prevention of allergic disease. Today, dietary preventive strategies are moving from allergen avoidance towards controlled dietary antigen exposure and stimulation of the gut microbiota via pre- or probiotics. Some studies have demonstrated a positive effect of probiotics in the treatment and prevention of eczema while other studies do not support these findings, and no clear preventive effect has been demonstrated on sensitization or any allergic disease other than eczema [for review see, 30].

Prebiotics, non-digestible fermentable oligosaccharides stimulating the growth and/or activity of a limited number of bacteria in the colon, can influence gut microbial composition and activity. Including prebiotics in the infant diet in the prevention of allergy is a promising approach, but so far data from clinical studies are limited. Data on pre- and probiotics in the treatment and prevention of eczema are still preliminary and inconclusive, and at this stage it is too early to recommend such treatment for all infants at risk. However, if parents still wish to try probiotic supplements in addition to standard treatment of eczema, personalized recommendations could be considered provided well-documented probiotic strains are used.

**Conclusion**

In conclusion, current nutrition recommendations are directed towards populations and are based on estimated nutrient requirements for these populations. Hence, these recommendations should cover most of the existing genotypes within a population. For certain infants with specific genetic polymorphisms, e.g. some inborn errors of metabolism, adherence to current nutrition recommendations or food-based recommendations will cause disease symptoms and they already need personalized nutrition recommendations. It can be foreseen that modern nutrigenetics will allow more diagnoses to be included in this group within a near future. Other SNPs, e.g. adult hypolactasia causing lactose intolerance, vary considerably between ethnic groups and within populations. Age at onset and sensitivity also vary making population-based as well as personalized recommendations difficult. For polygenic diseases such as CD, T1D and allergic disease, current knowledge is too limited to suggest personalized recommendations for all high-risk infants, although it may be justified to provide such recommendations should the parents ask for them. With refined methodology and a growing understanding of nutrigenomics, our capacity to identify larger groups of the population who would benefit from personalized nutrition- and food-based recommendations will increase. However, who will pay the cost and who will have the competence to make these recommendations?
References

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Discussion

Dr. Vaarala: In diabetes research we have seen that there are high-risk and moderate-risk genotypes. Nowadays there is a very high incidence of diabetes in Sweden and Finland, and the proportion of patients carrying the so-called moderate-risk genotype is increasing all the time, therefore the environmental pressure for type-1 diabetes is increasing so that even with a low genetic risk the diabetic phenotype develops. When the incidence of celiac disease was increasing in Sweden, did you find that there were more patients with the DQ8 genotype which is usually quite rare in patients with celiac disease?

Dr. Hernell: I can’t answer that because we didn’t do genotyping, but I think that it is a very interesting question. However, based on our studies recently I don’t think that this is the explanation. There are also other aspects of this epidemi. Our best estimate is that an unfavorable gluten introduction accounted for at most 50% of the increase during the epidemic, which means that there is still 50% to be explained. One factor that also seems to have contributed is if a child had more than 3 infections during the first 6 months, that is actually before the introduction of gluten, compared to fewer infections. Thus, it seems as if infections actually have something to do with the epidemic and indeed recently rotavirus has been implicated as a trigger. It could also be as simple as if you have more infections you probably have an increased gut permeability which results in an increased risk of an untoward reaction when gluten is introduced.

Dr. Szajewska: In addition to what you said, it may be interesting for the audience that there is a randomized control trial financed by the European Union in which we are trying to find out whether or not it is possible to induce tolerance to gluten in genetically predisposed children by introducing small amounts of gluten during breastfeeding between the ages of 4 and 6 months (www.preventcd.com). I know that there are slightly different recommendations compared to other parts of Europe when it comes to the introduction of gluten in Sweden. Can you please comment? My understanding is that gluten is introduced in small amounts and gradually and, as I already asked some time ago, what is a small amount? You said you didn’t know, but perhaps you know now.

Dr. Hernell: No, I don’t know what it is because in the study we had to define it one way or the other. What we did was actually to calculate at 7 months of age the intake of gluten in cases and controls. We used the controls, the reference group, and graded their intake into the upper one third, the middle one third and the lower one third, and then we took the upper one third of that intake and defined that as a large
amount. That was the best we could do. If you want me to give you an exact amount in grams per day, I can’t do that.

**Dr. Brandzæg:** Regarding these Swedish experiments; when you have the epidemiology ready and it turns out that you have only delayed the presentation of celiac disease, would that be an advantage or not? There has been a heated discussion on this aspect. Even with the EU project, early induction of tolerance may turn out to be broken later, so this is really an uncertain long-term investigation.

**Dr. Hernell:** It is, and I don’t think there is a simple answer to that question. Probably it was quite naïve to say that if a child is going to have celiac disease it is better to get the diagnosis early and be correctly treated. However, now it seems that celiac disease is a spectrum and we see more and more cases that are diagnosed at an older age and many of them have only vague symptoms and not the typical subtotal villus atrophy. Perhaps they only have an increased number of intraepithelial lymphocytes in the mucosa. Do these children benefit from the treatment to the same extent as infants with severe malabsorption? We really don’t know. Moreover, a gluten-free diet is said to reduce the risk of other associated diseases like diabetes, but again I think we don’t really know if the preventive effect is the same for all celiacs. There is also the question of transient disease and I think in Finland they have found that it is not uncommon with an increase in transglutaminase antibodies during late infancy that spontaneously normalizes with time. So what does this actually mean? Is it part of developing oral tolerance in those individuals? We really do not know.

**Dr. Salminen:** The last slide nicely summarizes future opportunities. It is really trying to use modern technology, you see on the top that the diaper is full so you need to do something. On the first line it gives you the urine analysis, the hydration level of the baby and tells you to add vitamin C. In the stool analysis I am still worried about the extra serving of cereals and the figs indicating that the bowel movements are regular, but at least I like the approach to combine high technology with very simple individual recommendations on what to do next.

**Dr. Lau:** I agree with some of your concerns regarding providing personal recommendations on nutrition requirements, but on the other hand some of the obstacles that you listed are not insurmountable. For example it is true that at the current stage some should probably not be used for routine profiling and then followed by recommendations. We are at a stage where discoveries are being made, and these discoveries can be translated to something even more simple that can be given to the general public and not necessarily using very high profiling as the final step. As far as having a lot of genotype subgroups, it is true that the more homogenous the groupings you can define, the more likely you will be able to actually find the gene step associated with certain types of phenotypes. But that is the reason why these studies need to be done as an international consortium where you would be able to acquire that type of study population. As far as the cost of genotyping, it is expensive but on the other hand there are now resources available that are willing to pay for such studies. For example, the Wellcome Trust actually has an open competition for people to propose studies, and as long as the sample size is large enough to power it, they are willing to take it into consideration and actually underwrite the cost of the genotyping. So there are ways to get around some of these obstacles, including the one that says that nutritional effects may take a long time to manifest. It is very similar to what we are doing in oncology as well, we cannot wait for the tumors to progress before we say this doesn’t work. So the effort is to try to find surrogate markers that can correlate with these long-term effects such that you can actually carry out your study in a more realistic timeframe. Plus if you can find the surrogate markers in the blood or plasma that would make it even more feasible because it won’t involve any invasive procedure to sample the patient. Yes, these are real concerns but perhaps there are
creative ways of getting around these concerns that I hope the community will be willing to take on.

**Dr. Hernell:** I completely agree with you that we will use these tools, no doubt about that, and they will become simpler and, hopefully, be integrated in the recommendations in the future. But I wanted to point out the problem of extrapolating a future perspective from experiences in specific pharmacological treatments of defined malignant diseases within oncology. I think that when it comes to nutrition the situation is far more complex. When we consider nutrition and particularly individualized nutrition recommendations for healthy populations, the question is whether it is worth doing gene chips on such individuals to start to try to define an optimal diet. My understanding is that it depends on what we actually mean with personalized nutrition recommendations. Does personalized mean strictly individual or does it mean dividing current recommendations into more subpopulations of healthy individuals? As I mentioned, presently we can't even agree on whether we should increase the intake of folic acid for a subpopulation of healthy individuals (pre-pregnant and pregnant women) or for the entire population, so I think we are quite far from individualizing recommendations.

**Dr. Walker:** I do think there is a role for personalized nutrition in the context of intrauterine nutrition, but I rather disagree with you on the folic acid story. It is a tragedy to have a child with a neural tube defect (NTD), and if we know that 25% of the population has a SNP that requires more folic acid, then I think that is a reason to raise the dose. The same thing has been shown in choline and vitamin D is also in question. So I think these are areas where malnutrition or undernutrition have a profound impact on the patient. I think we really need to concentrate on that and look at genomics, but also move those recommendations along.

**Dr. Hernell:** I agree with you to some extent but, looking at folic acid fortification, I don't think we have enough information. Every infant born with a NTD is a tragedy and of course we should do everything we can to reduce the risk. However, we must bear in mind the possible risk of increasing the number of cancer cases in the entire population. How many infants born with NTDs could be spared by fortification in a country like Sweden, given that women today are screened and when NTD is diagnosed there is a parental choice to have an abortion? It has been estimated that the figure would be 5–10 cases/year. This needs to be balanced against the incidence of colon cancer in the population. If that incidence increases just a few percent, this would concern many more individuals.

**Dr. Walker:** But in that instance you could increase folic acid during the pregnancy and then you could reduce it thereafter. I don't think a single increase in folic acid during pregnancy is going to enhance the likelihood of colon cancer that much. So I think in this particular situation 5 cases is 5 cases too many and I think you really need to look at it.

**Dr. Hernell:** The problem, when I was discussing the Swedish or the European cases, is the question of increasing the intake for the whole population by fortifying flour. But if the recommendation is to increase folic acid intake for women before they become pregnant and then reduce the intake to normal after the first trimester or after pregnancy, that is fine. But the problem is that there is a substantial fraction of those you want to reach who will not be reached by such an approach. So it is very complicated.

**Dr. Bier:** I wasn't actually planning to talk about folic acid with my comment but I think it is precisely the example that illustrates the benefits of personalized nutrition for the reasons you stated. I think it is clear that we don't have the tools yet to be able to fully deal with personalizing nutrition and I don't think anybody wants too personal nutrition. The case of folic acid is I think the precise reason why impersonalized nutri-
tion is problematic because you are making recommendations for an entire population. In a sense you treat many thousands of people to find one you need to treat. As one of the people who was in the committee that voted to fortify grain products in the United States for folic acid I can spend a lot of time talking about that. I think if we had, for example, the ability to determine who was going to be personalized that would actually be an advantage in this case. Now we have all of our nutrition recommendations that treat the great fraction of the population that doesn’t need to be treated.

Dr. Hernell: I completely agree with you; if we had that information we would not have had this discussion.