Bioethical Considerations for Human Nutrigenomics

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Abstract

This article gives an overview of the ethical issues in nutrigenomics research and personalized nutrition. The principles of research ethics, i.e., autonomy, beneficence, nonmalfeasance, and justice, are challenged by rapidly growing cross-border research activities utilizing existing and upcoming biobanks for studies of the interaction of genes with diet on risk of common diseases. We highlight the ethical issues, some unresolved, in international collaborative projects of which researchers should be aware. Personalized nutrition (tailoring diet on the basis of genotype) is one possible application of nutrigenomics research. However, until the scientific evidence concerning diet–gene interactions is much more robust, the provision of personalized dietary advice on the basis of specific genotype remains questionable. From the ethical and social perspective, nutrigenomics offers significant opportunities to improve public health by enhancing understanding of the mechanisms through which diet can be used to reduce the risk of common polygenic diseases.
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**NUTRIGENOMICS—INTRODUCTION TO THE CONCEPT**

Although it has been known for decades that certain nutrients can modify gene expression (78), high-throughput, postgenomic technologies—which twenty-first-century advances have made available for studying interactions between nutrition and the genome—have the potential to revolutionize the understanding of links between food and health. This is the niche occupied by the emergent science of nutritional genomics (nutrigenomics), which aims to reveal the intimate inter-relationships between nutrition and the genome and to provide the scientific basis for improved public health through dietary means.

As illustrated in Figure 1, individual genetic makeup influences nutritional needs and may modify dietary choices (111). In addition, the nature and amounts of foods influence gene expression at all levels of regulation, including via altered epigenomic markings (56). Genome-wide association studies are producing powerful evidence for links between (novel) genetic loci and risk of common human diseases (103, 121). However, since diet and other lifestyle factors are major determinants of these same diseases (125), it is highly likely that interactions between genotype and diet are important in determining the risk of most (if not all) common complex diseases. Proof of principle for this hypothesis has been provided by observational nutritional genetics studies where the outcome measures have been markers of disease risk, most notably cardiovascular disease (91). However, deoxyribonucleic acid (DNA) (and other biological material) in biobanks from cohort (and other) studies investigating relationships between dietary exposure and health outcomes provides a rich resource for novel studies of diet–gene interactions (72). Such studies are particularly powerful when the studies are large, dietary exposure (and other lifestyle factors) is characterized robustly, and there are hard end points such as diagnosis of disease or death from known causes. This has encouraged the development of consortia that cross national and continental borders to facilitate the pooling of resources, including biological samples and data as exemplified by the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (22).

To date, most studies have been relatively small scale, have focused on individual genes...
Conceptual model of interactions between nutrition and the genome underlying links between food and health. The science of nutrigenomics uses high throughput, postgenomics technologies to investigate these interactions.

(or haplotypes) and single nutrients, and have not addressed the complexity inherent in interactions between multiple genetic and multiple dietary factors (77). To determine causality, an extensive program of human intervention studies is needed, and its design should include prospective genotyping of volunteers (82) to maximize the likelihood of obtaining unequivocal results.

Until recently, much of the application of postgenomic technologies to understanding mechanistic interactions between nutrition and cell or tissue function and health has been devoted to studies in cells or model organisms. Given the costs of some of these technologies, the need to build expertise in their use, and the greater practical difficulties of human studies, this prioritization is understandable. However, over the past couple of years there has been a welcome emergence of nutrigenomics studies undertaken in human volunteers. Eady et al. (27) investigated the extent of, and factors responsible for, intra- and interindividual variation in transcription profiles for approximately 14,000 genes in peripheral blood mononuclear cells; this work provides important information for the design of future studies. In an examination of responses to eating breakfast (which included acetaminophen), van Erk et al. (114) observed 954 differentially expressed genes in blood, with approximately three times as many genes differentially expressed after a high-protein meal than after a high-carbohydrate meal. Obtaining samples of tissue other than blood cells is often an impediment in human studies, but Polley et al. (93) demonstrated that it is possible to investigate the proteome of the human colorectal mucosa using biopsy samples and to identify potential novel biomarkers of bowel cancer risk. In principle, metabolomic studies on easily accessible biofluids (e.g., plasma, urine, and saliva) could be incorporated readily into conventional nutrition study designs and so provide an opportunity to investigate the effect of the nutritional regime on a wide range of metabolites; such studies could greatly enhance understanding of the impact of the intervention. Walsh et al. (116) reported considerable inter- and intraindividual variation in metabolite profiles and concluded that the urinary metabolome provided a much better reflection of acute food intake than did plasma or saliva.

There is now significant international momentum behind the development and exploitation of nutrigenomics approaches for both...
NuGO: European Nutrigenomics Organisation

public and personal health (35, 57, 60, 84). This reinvigoration of nutrition research brings with it many challenges in terms of study design and ethics, and the latter is the subject of the remainder of this review.

HUMAN NUTRIGENOMICS RESEARCH—ETHICAL CONSIDERATIONS

Underlying Ethical Principles

In principle, human studies in nutrigenomics research do not have unique ethical issues. They are subject to the same basic ethical principles that apply to studies in biomedical or pharmacogenetics research. The four principles of protection of a research participant are autonomy (self-determination), beneficence (maximal benefit), nonmalfeasance (minimal harm), and justice (distribution of benefits and harms across groups in society) (85, 89, 127). These principles focused on experimental studies in which participants were subject to some form of intervention with less attention to issues arising in observational studies since the latter are perceived to have minimal harm because there is no intervention that can cause physical or psychological damage.

New Ethical Principles for a New Field in Nutritional Science?

The two aspects of nutrigenomics science that have challenged the traditional ethics of human research are the generation of genetic information and the conduct of large-scale population-based studies. The likely benefits in terms of improved health care or disease prevention that can be expected from (nutri)genomics research are, as yet, unclear (24). As such, participants in nutrigenomics research projects contribute to the generation of new information that, unlike clinical research, is unlikely to benefit the participating individuals (59). Therefore, societal values such as solidarity, public participation, and trust are emerging ethical principles in contemporary (nutrigenomics) research (12, 14, 66, 67). Reaching this balance is not possible with a static set of legal and ethical frameworks and needs continuing communication between researchers, research participants, politicians, ethicists, and lawyers with the aim of reaching the highest degree of consensus (67). For the field of nutrigenomics research, the European Nutrigenomics Organisation (NuGO) therefore has developed guidelines designed to assist researchers undertaking human nutrigenomics studies including biobank research (8, 34). The NuGO Bioethical Guidelines are based on officially published documents for which international agreement was achieved (19, 20) or that have been subject to thorough discussions among experts (39). The NuGO guidelines are available in an interactive Internet environment to allow researchers, ethics committees, and other stakeholders to use them and to provide feedback about their utility (34).

Informed Consent for Genomic Research

Ethical aspects of genotypic information. The independent expert group of the European Commission (EC) defined various perceptions influencing the debate about genetic testing (32). Two distinctly different perceptions can be identified. Genetic exceptionalism emphasizes the features of DNA-sequence information that distinguish it from other information because it identifies family relationships unequivocally, can be obtained from small amounts of biological material, may be used to predict future health events, may be of interest to third parties such as insurers, employers, or potential spouses, and can be recovered from stored specimens in the future (88, 98). The alternative position taken by the EC expert group is that “[g]enetic information is part of the entire spectrum of all health information and does not represent a separate category as such. All medical data, including genetic data, must be afforded equally high standards of quality and confidentiality at all times” (33). Public perceptions appear to favor genetic exceptionalism. The development of DNA fingerprinting for
forensic purposes, for paternity tests, and for detection of mutations responsible for monogenic disorders such as Huntington’s disease or Tay-Sachs disease has contributed to the belief that genes constitute a person’s identity or even destiny (88). This perception has to be addressed in the process of informing and obtaining consent of participants in nutrigenomics studies. An ethics committee evaluating a proposal for a nutrigenomics study may focus on genetic screening and disclosure of test results. International guidelines recognize the duty to disclose genotypic test results to research participant on the basis of the fundamental right to know (or not to know). However, particularly in the case of nutrigenomics research, where the consequences of particular genotypes may be unknown, such information may be provided on a group basis. Knoppers et al. (68) give a comprehensive overview of existing international guidelines on this issue. At the individual level, the World Health Organization (WHO) proposed disclosure of genetic information provided there is a clear clinical (health) benefit, as this will avert or minimize significant harm to the individual (provided there is no indication that the research participant would prefer not to know) (126).

The process of information and consenting. Several authors (9, 26, 73) have pointed out that the researcher responsible for communication with the research participant must be sensitive to the participant’s level of comprehension and use appropriate communication approaches. However, too much information can confuse and may increase the misconception of the participant. Eriksson & Helgesson (29) suggest a tool that identifies research participants who want only limited information. Currently, the system of informed consent focuses on the form to be signed by the participant; too little attention is paid to its role as a means for communication and education. The forms are perceived as a contract that protects the researchers and their institution (6) and tend to neglect the role of research participants as partners in the study (43). In this regard, the measures that take place when consent is withdrawn need to be communicated clearly. Although the participant has the right to request the obliteration of the sample and data, it is acceptable to anonymize by stripping all identifiers (unlinking). This is particularly important for prospective studies such as cohort studies, intervention trials, and biobank research because obliteration of samples and data may bias the results of the study and thus challenge their generalizability. In consequence, the interests of the sustaining participants and the public may be jeopardized. Issues of practicability also exist, especially in international studies, where samples and data may have been exchanged with other institutions. Retaining samples and data unlinked and anonymized would balance individual and societal interest (12, 30, 39).

In some cases, there may be a conflict between undertaking a methodologically unbiased study and giving the study participant full information. This is particularly difficult in studies with a dietary intervention because control persons may alter their intake of the food that is the subject of the hypothesis (73). In such cases, it may be ethically appropriate not to disclose the underlying hypotheses because research of a high standard is also of ethical value.

Benefits and Risks

Most nutrigenomics studies are likely to benefit society rather than the individual. Risks for the individual usually concern the confidentiality of medical, genetic, and other data and implications of potential dissemination of study results. In addition, benefit-risk assessments should consider the inconvenience associated with answering detailed questions on diet, health, and lifestyle and the potential discomfort involved in sample collection or caused by the intervention procedures (73). It has been assumed that altruism is the main motive of those participating in nutrigenomics studies, but Merz et al. (83) have pointed out that this fails to recognize the complex, sometimes competing, interests of individuals, researchers, public and private scientific institutions, financiers, and industry. Although better public health is the long-term...
common goal for all or most of the stakeholders in nutrigenomics studies, the internationally inconsistent legal status of the biological samples (parts of the body that cannot be sold or property that is conveyed by property rights), which are normally donated by study participants, makes it difficult to give ethical guidance on benefit sharing (12). The ethical aspects of commercialization of nutrigenomics research are currently under discussion (12, 15, 58, 83).

Biobanks in Nutrigenomics

Definition. A biobank is a repository of collected bodily substances or DNA often linkable to data on health or lifestyle of the donor (12, 28, 39). Related terms include gene bank, genetic biobank, DNA bank, or genetic database (14, 63). Large population-based gene banks such as DeCode (from Iceland), the BioBank UK, the Estonian Genome Project, or the Genome Database of the Latvian Population may be distinguished from other types of biobanks because they have made explicit from the outset that their purpose included population-based genetic research into the etiology of diseases. In the absence of a particular regulation for biobanks, biological material (samples) is considered as part of the human body, resulting in legal implications such as property status, whereas the linkable database associated with these samples is usually covered by data protection legislation. Therefore, in countries with large population-based biobanks, particular legal frameworks have been established that regulate both ethical and legal aspects of their operation (2, 3, 10, 50, 53, 54). Where such a regulatory framework is available, other types of biobanks are likely to fall under these acts. Other types of biobanks include smaller collections of samples and data from single studies or derived within a clinical context that are stored in a systematic manner and may be linked to health relevant data.

Ethical guidance for biobank-related research. The absence of an agreed international ethical and legal framework for biobank-related research poses a significant ethical challenge (12, 28). The national and international claims for more openness of biobanks for genomics research challenge the traditional legal and ethical framework for biomedical research and have implications for nutrigenomics research. However, most of the legally binding acts governing biobanks operate at national levels and are inappropriate for regulating international cooperation. Therefore, over the past 34 years, various international organizations have developed guidelines, most of which have no legal implication and are intended to define best practice (12). However, in practice, the validity and feasibility of the guidelines have been challenged because they neither explain why it is ethical to act in a certain way nor offer concrete practical guidance (31). As a consequence, international organizations such as the United Nations Educational, Scientific and Cultural Organization (113), WHO (123), Human Genome Organisation (52), and World Medical Association (128) have released guidelines that should guarantee biobank research activities are undertaken according to generally accepted ethical standards. Further guidelines for human genetic research databases are expected shortly from the Organisation for Economic Co-operation and Development. However, disputes about a variety of core issues of biobank research remain. These include:

- the legal status of stored biological material including DNA;
- the possibility of withdrawal of the consent at any time;
- the consequences of withdrawal of consent;
- the obligation to inform subjects of identifiable samples for whom an increased disease risk was detected;
- the access to the samples or genetic data by relatives after the death of the research participant;
- the participation of vulnerable subjects (such as children or incapacitated adults);
- the sharing of profits that might arise from commercial products that are developed using the samples;
- the ethical implications of anonymization of samples and data by irreversibly stripping all identifiers;
- the circumstances under which subjects should be recontacted to renew consent for the use of the sample in another research project and the situation in which consent could be waived;
- the definition of risks and benefits from genetic-based biobank research.

Recently, the German National Ethics Council (NER) released an “innovative and progressive opinion” (65) that includes a joint declaration by NER and the French National Consultative Committee on Ethical Issues (39). Their position is particularly progressive regarding the consent issue because waiver of consent (for existing sample collections) and broad consent (for upcoming biobanks) are ethically justifiable when accompanied by substantive protection by ethical review boards and oversight by data protection officers (39). In this way, anonymization of samples and ethical implications can be avoided. In contrast, in the United States and Canada, the most frequently recommended model is a multilayered consent, where the research participant can make choices to limit consent for the use of samples to the primary project only or to certain kinds of research in the future (9, 26, 28, 109). This may impair research not only at a practical level but also at a methodological level by risking the introduction of bias, because some ethnic or religious groups are more likely not to consent to future use of samples and data for particular types of research (1, 16, 45, 105). This may create an ethical issue at the societal level (14).

**Ethics in international cooperation.** Nutrigenomics research usually requires information on diet or nutritional status in addition to genetic and health-related data. Where the focus is on diet–gene interactions in population-based studies, larger numbers of subjects add power so there is considerable utility in combining samples and data from several (international) cohorts. To promote such collaboration, the umbrella organization Public Population Project in Genomics’ (P3G) was established (96). P3G is a not-for-profit organization whose objective is to promote collaboration between researchers in the field of population genomics to undertake large-scale genomic and epidemiologic research (96). Ethical guidance is part of the P3G initiative (95). The European counterpart is the coordination action on Promoting Harmonisation of Epidemiological Biobanks in Europe, where ethical and societal issues are also addressed (94). In practical terms, for international collaborations, the most sensitive issues include the width of the original consent to secondary use of samples and data, the definition of various levels of identifiability (anonymization) (28, 69), which has implications for the ethical frameworks that are applied to the biobank (28, 44), and the ethical oversight for international projects involving several countries (12). Figure 2 shows the principal difference in meanings of “anonymized” in the United States and in Europe. In the United States, anonymized data and samples are those where a link to identifying information exists but the researcher has no access to the linking key. Research with anonymized data has no restrictions and may even not need specific ethical approval (18, 44, 59, 90). In Europe, these are considered as coded samples and data with implications for their possible use (12, 19, 39). This difference in approach may have implications for collaborations between Europe and the United States. In the worst case, researchers who are not aware of the different regulations across countries might share data and samples unlawfully in international collaborations (63).

**Potential harm from biobank research.** A central issue in research ethics is avoidance of harm to the participant (85, 89, 127). Although no direct physical harm is expected from biobank research, several other kinds of harm should be considered (30, 48). Indirect physical harm could occur when a sample that was collected in a clinical setting was exploited subsequently for research purposes and no material remains for future medical care. Nonphysical harm refers to social, psychological, or...
Economical damage if sensitive information such as diagnoses or genetic test results ends up in inappropriate hands, i.e., if confidentiality is broken (7). Nutrigenomics research could lead to group harm due to stigmatization or prejudice if, for example, studies showed that certain sociodemographic or ethnic groups were at higher risk of certain disorders or diseases because of a higher prevalence of a certain gene-diet interaction (17, 30, 118). There may be moral harm through storing or exchanging biological material that was not subject to informed consent since it jeopardizes the subject’s autonomy, privacy, and personal integrity. Moral harm can also arise from lack of quality assurance (42), nonefficient use of samples and data, application of the wrong study design, or from exclusion of certain groups from benefits that arise from the research (30).

**Ethical implications of anonymization.** All guidelines and legal frameworks allow unrestricted research with unlinked (irreversibly) anonymized samples and data. This anonymization is ethically critical because it excludes the research participant from executing his or her right of autonomy and self-determination (112). When the link to identification data is destroyed, the research participant cannot oppose certain kinds of research being undertaken with his or her sample. Conversely, if participants could benefit personally from knowledge emerging from the research, it would not be possible to advise the participant when samples and data are unlinked (irreversibly) anonymized. Anonymization may not protect specific populations or social, ethnic, or religious groups from being stigmatized, which is why ethical review is of importance (6, 11, 17, 30, 39, 44, 48, 118). One possible solution to this problem is the establishment of a “sample trustee” as a firewall between the researcher and sample donor (7) or special routines for coding and storage of samples with restricted access to personal information (48). It should be the norm for any emerging biobank to double code, to store separately the clinical data, genetic information, and samples, and to restrict access to key codes (7, 34, 39).

**What Do Research Participants Think?**

In parallel to discussions among ethicists, lawyers, and politicians about ethical implications of new technologies in the past decade, empirical research has begun to reflect the opinion of research participants. However, this kind of research is still immature, and further systematic studies are needed. To date there have been two kinds of studies: one asks participants hypothetically whether they would donate a sample for genetic research and whether they would agree to sample storage for future use.
studies (64, 86, 105, 119), whereas the second type analyzes given or declined consents by participants of real studies (1, 16, 45, 47, 75, 79, 80, 108, 117). Although the majority of individuals (71%–95%) consented to such research, agreement to participate was lower among African Americans (16, 45, 80). Among Jews, willingness to participate was highest for conditions that are preventable or treatable (105), which would be a focus for nutrigenomics studies. Higher education, good self-reported health, having children, and positive history of genetic disease among family or friends were associated with greater willingness for sample donation in a Swedish population (64). However, when attitudes and beliefs were included in the multivariate analysis, positive attitude toward genetic research and trust in authorities’ ability to assess the benefits and risks of genetic research showed the strongest associations with willingness to donate a sample (64).

Some studies on hypothetical participation in studies focused on whether consent would be required in future studies on stored samples and whether individuals want to be informed of research results (86, 105, 119). Respondents felt that the need for consent was greater for clinically derived (versus research derived) samples, but few would request such consent when the name of the donor would not be disclosed to the researcher. About 90% of respondents would want to be informed about results even if they were of uncertain clinical relevance (119). Higher education was associated positively with a view that consent should be necessary for future research projects (105). In one American study of multilayer consent forms with several options, about two-thirds of participants in clinical trials did not complete the consent form for future use of the samples, possibly because they had problems with the multilayer design. Of those who filled in the consent form, 87% gave authorization for unlimited future research (16). Malone et al. (75) reported high assent rates for a multilayer consent to storage (93.7%), future use for other health problems (86.9%), and the repeated contact by the physician for further participation (84.3%). However, assent was also high to a one-paragraph statement appended to the clinical trial consent (89.4%). Those who participate in studies are often a highly self-selected group of people and ranged from 20% in a Jewish population (105) to 47%–49% in two Swedish and one U.S. study (64, 86, 119). The proportion of individuals who are not willing to consent to sample collection, storage, and genetic research may be rather high among the nonrespondents in those surveys. Nutrigenomics scientists should be aware that their studies may be biased to a certain extent by the sample of self-selected participants (1), but this is a feature of all research projects involving human subjects and is not unique to nutrigenomics.

PERSONALIZED NUTRITION—ETHICAL AND SOCIAL IMPLICATIONS

The Idea of Personalized Nutrition

In the early days of nutritional genomics, hopes were expressed that knowledge achieved in this field could be used to modify plants and meat to enhance their nutritional quality, through traditional methods as well as genetic modification (25). However, this has not become a strong trend, probably due to the negative reactions of the general public, especially in Europe, toward genetically modified food. Instead, nutrigenomics research has focused on other applications. Use of “omics” technologies aims at increased knowledge on effects of food on human metabolism, which may be the basis for more informed general food advice for the public. A major effort has been directed at understanding genetically determined differences between individuals, leading to the prospect for individual genotype-based, tailor-made nutritional advice—personalized nutrition (61, 62, 92).

Despite the great hopes expressed for personalization of nutrition based on genetic information, personalized nutrition is still considered premature. Whether this approach will be successful ultimately will depend on the predictive precision of the genetic information,
on the robustness of the gene-diet-disease relationship, and on the acceptance of the concept by the public (57).

**Observance**

Targeted individual health advice can be a strong motivator for behavior change. For example, those with phenylketonuria (PKU), a genetic disorder resulting in an inability to metabolize phenylalanine, have to follow a lifelong strict diet that is low in phenylalanine (71). With few exceptions, PKU sufferers observe these restrictions well, demonstrating that well-founded and precise personal information may be very effective. In another example, in the Whitehall study by Rose et al. (100), those whose examination had given evidence of exceptional risk received individualized advice on why they in particular would benefit from stopping smoking. More than 50% of them stopped smoking, compared with approximately 10% of those given routine antismoking advice (99, 100).

**Public Expectations from Personalized Nutrition**

Attitudes toward use of genetic information seem to depend on the application area. Medical and forensic applications are more easily accepted than are genetic modifications of food (74, 107). A recent Eurobarometer survey indicates that the majority of respondents support genetic testing for disease, but a sizeable minority is concerned about these medical uses of genetic information (38). Recent surveys indicate a strong consumer interest in the prospect of genetic tests aimed at dietary advice with identifiable health benefits, although concerns have been expressed in relation to privacy and the possibility of emotional reactions (76, 104). The strongest audience seems to be among a group actively seeking health information. It has been suggested that one-third of consumers will use genetic tests for personalized nutrition (55). However, this interest needs to be seen in a larger perspective.

**Food, Health, and Well-Being**

Food means much more than nutrition. Food is enjoyment as well as cultural and personal identity. A meal is a social event, an important manifestation of the relationship with others. This means that food is an important aspect of human happiness and well-being, and not only an instrument for health (49).

According to the WHO’s classical definition, “[h]ealth is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (122). This is a far-reaching and ambitious understanding of health, and it is unlikely that this can be achieved except in rare circumstances. More cautious definitions have been suggested by health philosophers. For instance, Nordenfelt (87) argued for a holistic theory of health described as a person’s ability, in normal circumstances, to realize his vital goals. Two aspects of this analysis of health stand out as important. First, health is subjective rather than objective. Second, health is not the only or final desire in a person’s life.

According to a recent Eurobarometer survey, “being in good health” was ranked among the top three items by three-quarters of the population in the European Union member states, and by two thirds in the acceding and candidate countries. Other important values were “sufficient income to meet my needs” and “having family members who are there when I need them.” The conclusion drawn in the report is that “quality of life is obviously understood as a multi-dimensional concept depending on several components rather than just one particular ingredient of well-being” (4). Philosophical analysis also invokes a broader understanding of well-being than health only. Well-being is described as informed and autonomous endorsement of the conditions of one’s life (110).

**“The Unhealthy Quest for Health”**

People in modern Western societies have exceptional possibilities for healthy living. Present society, as well as modern medicine,
offers better opportunities than ever to avoid health risks and to cure, retard, or mitigate diseases. As a total effect of all societal, medical, and individual efforts, the average life span in Western societies has more than doubled since the middle of the eighteenth century, and it is still increasing. However, this improved situation also brings greater hopes and expectations.

Robert Crawford (23) understood our time as characterized by exaggerated attention to personal health—“elevating health to a super value, a metaphor for all that is good in life.” By introducing the term “healthism,” he wanted to point out this societal phenomenon: an ideology where maintaining health and avoiding illness have become the supreme human values. Greenhalgh & Wessely (46) describe this healthism as a modern cultural, mainly middle class, phenomenon. Some of its expressions are strong health awareness, focus on lifestyle choices, use of food supplements, and concern about “unnatural” substances. A similar argument is offered in a recent report from the U.K.’s Food Ethics Council, which suggests that the government is reducing people’s autonomy because it assumes that consumers should see food primarily as a means to health. “This treats food like medicine and society like a hospital,” according to the Food Ethics Council (37). Geoffrey Rose (99) stated, “To be preoccupied with health is unhealthy.”

Although such comments may be one-sided or exaggerated, they point out that an overemphasis on health may reduce perceptions of health as well as limit the realization of well-being.

The Role of Genetic Testing
Genetic tests may be used for confirmatory diagnosis of specific genetic disorders as well as for predictive testing for asymptomatic individuals belonging to risk groups. In some cases, such as PKU, the corresponding disease can be effectively retarded by dietary intervention. However, in the monogenic disorders, knowledge of the phenotype is usually sufficient to initiate dietary intervention because it measures the expression of the disease. In complex polygenic diseases such as diabetes and hypertension, the predictive value of a single genotype is small compared with that of the family history of a person or other known risk factors (57, 115). However, especially with the expansion of genome-wide scanning studies, understanding of the genetic basis for polygenic disorders will increase, and genetic analysis may offer better predictions of disease risk. This is particularly important for diseases where the development of the pathology and its complications have long latency periods and are essentially irreversible, such as in type 2 diabetes and osteoporosis (57).

“Opportunistic screening” refers to ad hoc tests offered to those without symptoms or to a test made upon request from an individual patient without symptoms or known risk factors. Opportunistic screening is controversial but is often accepted in society when it can give predictive information on diseases that may involve a heavy burden for the person involved.

Should healthy people with no identified risks who ask to have a genetic test be offered that possibility? Most health professionals are reluctant to agree to such requests because respect for freedom of choice is not understood to mean that all technically possible services must be provided on request (120). Also, most who attend screening examinations are seeking not the discovery of hidden troubles, but rather reassurance that they have no unusual problems (99). At present, the evidence base for genotype-specific dietary advice is very limited. This situation may change, but it seems too early to estimate how autonomy and beneficence should be balanced against each other in such a possible future.

Genetic Counseling in Connection to Personalized Nutrition
Personalization of diet is not new, but genotyping as the basis for such advice opens a number of new possibilities and problems. Counseling
in a medical context is generally regarded to be sensitive and personal, deserving careful treatment, and considered a task for persons with appropriate professional training. Genetic counseling is often considered to be especially demanding (20, 33, 120). The European Commission comments on the current situation, “Genetic testing will soon become part of everyday healthcare systems, and patients and professionals will have to learn to make decisions on the need for a test as well as understanding its consequences” (33). The essence of their argument is that genetic exceptionalism is not needed in order to argue that genetic information should be handled with the same care as any medical information and should be subject to appropriate genetic counseling. As genetic information has become more easily available, this view has been challenged.

Following a test, the decision of what to eat may be influenced by disease-prevention reasons. However, dietary advice based on inconclusive or incomplete knowledge may result in unnecessary restrictions in lifestyle and doubtful health effects. Such considerations indicate that dietary advice based upon genetic tests should be handled with at least as much care as genetic counseling in general.

When genetic information is collected and used in formulating nutritional advice, a number of other well-known problems will reappear: the confidentiality and right to privacy of genetic information, the question of parental authority in relation to testing of children, and the risk of discrimination with respect to insurance and employment (97).

Tests Directly Sold to the Public

A market has grown for promoting different kinds of genetic analyses directly to public. The U.K.’s Human Genetics Commission lists 26 companies (as of November 17, 2007) offering genetic testing services via the Internet direct to the consumer or via a nonmedical intermediary, such as a pharmacist or alternative health practitioner. These companies offer a wide range of genetic tests of predispositions for diseases and disorders. The majority of them market tests combined with nutritional advice and, in some cases, with nutritional supplements, and at least one company offers biomarker assessment tests. Most of them sell their tests directly to consumers, and in some cases, the sale is combined with optional or mandatory counseling (51).

Recently, the marketing of genetic tests to consumers for personalized nutrition and lifestyle guidance received the attention of the U.S. Government Accountability Office (GAO), which investigated the legitimacy of test claims in order to evaluate the current regulation. According to the GAO’s report (70), all of the tests mislead consumers by making predictions that are medically unproven and meaningless. Some mislead consumers by recommending costly dietary supplements that may be unnecessary. The tests do not provide recommendations based on a unique genetic profile, but instead common-sense recommendations based on lifestyle information. The GAO’s report concludes that the predictions “may needlessly alarm consumers into thinking that they have an illness or that they need to buy a costly supplement in order to prevent an illness. Perhaps even more troubling, the test results may falsely assure consumers that they are healthy when this may not be the case” (70).

How should this situation be handled? The Council of Europe Working Party on Human Genetics discusses the question of genetic tests sold to the public (21). Different alternatives are proposed, from the restrictive view, “Genetic tests shall not be directly sold to the public” to the liberal view, “Where the law permits direct sale of genetic tests to the public, there shall be adequate regulation, in particular to ensure proper information and understanding of the implications of the test the person concerned.” The choice between these alternatives is left open.

Castle et al. (13) agree that the efficacy of the recommended dietary changes is not well documented but describe the information currently generated as nonstigmatizing and nonsensitive,
with mild informational impact and with minor potential harm. Others make the opposite estimation. Joost et al. (57) describe the current attempts to derive dietary recommendations based on the genotypes of the few single-nucleotide polymorphisms presently known to be associated with complex diseases as largely experimental, and emphasize the risk of disappointment and adverse effects if tests are introduced too early. Russo (101) describes such tests as “genetic horoscopes.”

Today, many health consumers are better informed than in the past about medical issues because of better education and greater accessibility to information through the Internet. But the integrity and well-being of the consumers who take genetic tests may still be at stake. Even with counseling, and perhaps much more without it, those involved may start worrying about their health. This may be a result of the mere focus on this kind of information, but the focus only intensifies if the test results identify health problems. However, according to Meijboom et al. (81), “‘Sowing worries’ might be an effective marketing strategy.”

At present, the principles of beneficence and nonmalfeasance are arguments that information on results of genetic tests and that counseling based upon such results should be offered on a personal basis by specially trained individuals because of the sensitivity of the information as well as the possibility of misunderstanding.

**Individual or Population Approach?**

Stronger efforts in promoting a healthy lifestyle are often called for because of the increasing prevalence of noncommunicable diseases (5). However, the efficacy of an individual approach to this problem is limited by the prevention paradox (99). In most cases, the burden of ill health comes more from the many who individually have a relatively low (inconspicuous) risk than from the few who face an obvious problem. According to Rose (99), social and economic factors are much more important than genetics in explaining diseases and limit the effectiveness of an individual (high-risk) approach to prevention. A similar assessment is made by the Food Ethics Council (37), which claims that many health problems can be better handled by political actions such as regulation of marketing, measures to tackle poverty, and health-oriented reforms of agricultural subsidies. This argument favors a population approach to prevention advice.

In the current situation, the value of genetically based nutritional advice for polygenic disorders is limited, and population-level advice may be more effective in improving public health. Whether nutritional genomics will lead to changes in population-wide health advice remains an open question (40). In some cases, specific advice could be directed at population groups in which the frequency of specific alleles in the population is high. For instance, in ethnic groups in which lactose intolerance is very high, such as African American (79%) or Asian (95%) (102), there is no need for genetic tests prior to dietary advice to avoid lactose-containing foods.

**Products Fabricated for Personalized Nutrition**

The nutritional genomics approach has created hopes that gene-based nutrition planning can one day play a significant role in preventing chronic disease, and industry has an interest in using this knowledge for commercial purposes. Some relevant questions in this respect include (a) whether the scientific evidence base is sufficiently strong to justify creating a special nutritional product; (b) how personalized-nutrition products can reach the correct target group; (c) whether the advent of personalized-nutrition products will encourage people to believe that only some individuals need to adopt a healthy diet or will create unwarranted or exaggerated hopes and expectations; and (d) how such a development can be counteracted.

For the foreseeable future, the number of people who have received personalized nutritional advice based upon genetic tests is likely to be fairly small and so the market for a new
generation of “functional foods,” targeted to these individuals, will be limited. In this situation, the food industry may be interested in creating a larger market for each product by developing the product and marketing it in such a way that it is considered healthy not only for people with a specific genetic constitution but also for others. This is an undesirable development because it may encourage the existing tendency to healthism.

Another potential problem with this development is that it will lead to medicalization of the diet and normal healthy foods may be overlooked. There is no industrial market for helping people make healthy choices among existing natural products. The Food Ethics Council comments, “Little money can be made by selling the fresh fruit and vegetables that form the mainstay of healthy eating advice” (37).

An alternative trajectory may be offered by the nutrigenomics approach in furthering understanding of normal metabolism and of how normal foods interact with our genome to influence health. This might contribute to increased public knowledge about healthy foods as well as raise consciousness that healthy foods matter.

Justice Questions

It is probable that the emerging market for personalized nutrition will mainly be offered to, afforded by, and used by a relatively small group of proactive health information seekers (55), which may increase existing health disparities within industrialized countries as well as between these and the developing countries. This has been described as still another example of the “health genomics divide” (106), a selective implementation of biotechnologies. Some consider this divide to be mainly a moral problem (41) and have called instead for use of nutrigenomics to reduce global health inequities (15).

As an alternative to individualized nutrition, population-based research on the role of race and genetics in health disparities has been initiated (36). The epidemic of noncommunicable diseases is growing (5) due to adverse changes in dietary patterns and reductions in physical activity, but it is also recognized that genetic variability is likely to play a role in determining susceptibility. The WHO speculated on targeted dietary advice for subgroups as a prevention strategy in developing countries (124, 125). However, this is not considered feasible at present because the multiple causes of complex diseases are not yet well understood, and changes in diet and lifestyle seem to be larger causal factors than is genetic susceptibility.

CONCLUSIONS

Nutrigenomics is a rapidly expanding field of research with ethical issues in respect to both protection of research participants and society’s interest in the prevention and treatment of common diseases by nutritional measures. The same four principles designed to protect research participants, i.e., autonomy, beneficence, nonmalfeasance, and justice, apply in nutrigenomics as well as in other types of biomedical research. However, the novel issues with respect of nutrigenomics research include (a) how to handle genotypic information that has no, or poorly understood, implications for the health or well-being of the research participant, and (b) the use of biobanks, especially when this includes sharing of data and/or samples internationally. Contrary to the usual position that research participants should be provided with personal data arising from the investigation, there is a case for not giving consenting participants “their” genotypic information. For biobanks, there are issues around whether, and how, volunteers can withdraw consent and the future use of stored samples.

Research on diet–gene interactions and, in particular, on the relationships between genotype, dietary exposure, and disease risk is a hot topic internationally. However, the scientific evidence base for the role of interactions between specific genotypes and components of the diet in the development of polygenic diseases is fragmentary and, in our view, is not
yet sufficiently robust to justify genetic testing as the basis for nutritional counseling (personalized nutrition). It is probable that a major benefit of nutrigenomics research will be an enhanced understanding of the mechanisms through which dietary factors interact with the genome to influence gene expression and cell function and, ultimately, health. The outcomes of such research may have societal benefits in increased public knowledge about healthy foods and raised awareness that healthy foods matter.

SUMMARY POINTS

1. Ethical considerations in human nutrigenomics include both research ethics and the societal implications of applications of this emerging science.
2. From a research perspective, the ethical issues are in the areas of informed consent, genotype information, biobanks, and the use and exchange of samples.
3. The two most ethically challenging aspects of nutrigenomics science are the use and communication of genetic information and the conduct of large-scale, population-based studies in an international context.
4. International legislation and regulations impinging on nutrigenomics research vary between countries with complex (and some unresolved) issues for transnational collaborations.
5. The benefits of nutrigenomics research for society in terms of improved health care or disease prevention remain unclear.
6. One much-hyped potential application of nutrigenomics research is personalized nutrition, but at present, the evidence base for genotype-specific dietary advice is very limited.
7. Promotion of the concept of personalized nutrition may have unintended and undesirable consequences, including medicalization of food choice and eating behavior.
8. The major societal benefit from nutrigenomics research is likely to be enhanced understanding of how food components and food interact with the human genome to influence health.

FUTURE ISSUES

1. What are the optimum approaches to international harmonization and standardization of legislation and regulations affecting nutrigenomics research?
2. How can the implementation of research ethics regulations in nutrigenomics research be an instrument to respect the integrity of research subjects and not only a bureaucratic act?
3. How can new technologies and media such as the Internet be used to enhance communication with research participants to address better the issue of informed consent?
4. Can nutrigenetic information at the individual level be used in the context of prevention of diseases and health care?
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DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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