Your Diet Tailored To Your Genes:

Preventing Diseases or Misleading Marketing?

A report by GeneWatch UK

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Preventing Diseases or Misleading Marketing?

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1. Executive Summary

This report considers the new science of 'nutrigenomics' (nutritional genomics) a spin-off from the Human Genome Project and the idea of 'personalised nutrition'. Nutrigenomics is being promoted as the solution to chronic diet-related diseases such as heart disease, cancer and diabetes. The report asks whether tailoring our diets to our individual genetic make-up, or to other individual biological differences, will be good for health.

The focus of commercial interest in nutrigenomics is in achieving two overlapping aims:

- developing new food products which can be marketed as providing health benefits to consumers ('functional foods');
- *individualising* diet tailoring our diets to our genes and perhaps to other biological measurements.

The implied *health* strategy behind nutrigenomics depends on several assumptions that:

- '*personalised nutrition*', based on individual biological differences, should be the ultimate aim of nutrition research;
- people's risk of obesity and of developing chronic diseases is different depending on their individual genes and other biological factors and that these differences can be identified and the risks quantified;
- people should therefore be tested to find out their genetic make-up, and perhaps monitored for other biological changes, and advised to eat different foods (or take different supplements) depending on the results;
- doing so will reduce their individual risk of common diseases and also reduce the incidence of obesity and chronic conditions in the population as a whole;
- people will want to take genetic tests, and perhaps other types of tests as well, and will change their diets as a result;
- this approach to health will be affordable, cost-effective and socially acceptable.

This report considers whether these assumptions are valid and gives an overview of diet and health and the industries promoting nutrigenomics as a mechanism of opening new markets.

Diet, health and the food industries

In 2000, the WorldWatch Institute estimated (based on United Nations and World Health Organisation figures) that the number of overweight people in the world for the first time matched the number of undernourished people at least 1.1 billion each. Diseases related to over-eating are now widely recognised as a major, growing threat to global health. The consequences are serious in affluent societies but these diseases already affect more people in low- and middle-income countries than in wealthy ones, and their impact is also expected to increase more rapidly in these poorer countries.

Since the 1960s, advice on how to avoid chronic, diet-related diseases such as heart disease has included: do not get overweight; restrict saturated and total fats; favour fresh vegetables and fruits; avoid heavy use of salt and refined sugar; and get plenty of exercise. These recommendations have changed little over the years and subsequent research has reinforced the message that these are the most important dietary changes that can help to prevent chronic disease. However, there is an enormous gap between existing dietary guidelines and what people actually eat.

The role of the food industry in the global epidemic of obesity and chronic disease has been widely recognised, alongside other societal changes, such as ageing populations and a major reduction in the amount of exercise that many people get. However, the food, supplements, diet and pharmaceutical industries are also all involved in society's response to these diseases.

The food industry

The food industry can have a major impact on dietary health because its need to be profitable and achieve growth can sometimes conflict with the steps needed to prevent chronic diseases. This is reflected in the contradiction between the industry's need to make customers eat more of their products (for example, by advertising, increasing portion sizes and introducing new products) and the need for many people to eat less to avoid overweight and obesity. Other factors are the competition to make food tasty but cheap (leading to products high in sugar, fat and salt) and fast, mass-produced and convenient (leading to more processed foods and fast food chains).

Concern about the impacts of unhealthy diets, particularly on children, has grown in recent years and is being seen as a major weak spot for the industry. In addition to the impacts on their businesses of bad publicity, food companies are becoming increasingly concerned about their legal liability for obesity, following a lawsuit filed by a group of overweight Americans against several US fast food companies in 2002. Some major companies have begun to respond to consumer concern, public criticism and legal threats by altering their product lines. However, these voluntary changes are not all healthy and the industry continues to oppose regulation that could limit levels of fat, sugar or salt in processed foods or restrict advertising to children. Although factors such as price still dominate, 'wellness' is now seen as a key marketing trend in the food industry. Food manufacturers' search for growth is also driving attempts to design new 'healthier' foods and market them at a premium.

The supplements industry

Many people no longer get all their nutrients from food: they also take dietary supplements. Supplements include vitamins, herbs, minerals and other products, including sports nutrition products. The nutritional supplements industry is increasingly dominated by a few large companies, although many smaller companies – some with a strong commitment to natural health and avoiding additives – also exist. However, evidence for the value of supplements in preventing disease is contradictory and in excess, some supplements can be damaging to health. BASF and DSM are two leading manufacturers of supplements with an active research interest in nutrigenomics.

The diet industry

The global weight-loss market is $240 billion and the diet industry is expected to grow significantly as a result of rising levels of obesity. The diet industry is not clearly defined but includes: lower calorie and low-fat foods and drinks; weight-loss supplements and meal replacements; weight-loss centres; weight-loss medicine (ranging from supervised diets to surgery); and pharmaceuticals (anti-obesity drugs). The effects of low-fat foods on health are complex and depend on marketing practices as well as the impacts of the food on health. For example, the shift from full-fat to low-fat milk may have helped to reduce the incidence of heart disease, but sales of fizzy drinks (replacing fat with sugar) have increased more rapidly than sales of low-fat milk. Similarly, artificial sweeteners and diet drinks have done nothing to reduce sugar consumption.

Functional foods

The production of 'techno' or 'functional' foods is one of the food industry's responses to some consumers' desire to simplify healthy eating. Functional foods are modified to include added nutrients or other substances to give claimed health benefits. Modifying the nutritional content of food is different from selling supplements, because people may be less aware of what they are consuming. Functional foods go one step further than fortification of foods such as breakfast cereals: they blur the line between foods and medicines. The current market in functional foods is for 'lifestyle' products that may in some cases benefit individual consumers (such as probiotic yoghurts): they are unlikely to bring major benefits (or harms) to population health (such as a change in the incidence of heart disease or cancer). In the future, more functional foods are expected to target the 'big killer' diseases: these new foods may include genetically modified (GM) foods and foods intended to alter appetite, moods or behaviour. DuPont, Cargill, Syngenta, BASF and Dow Agro Sciences are all interested in the potential of GM functional foods. The emerging science of nanotechnology may also play a role.

The pharmaceutical industry

The pharmaceutical industry is also becoming more important in relation to diseases that are strongly influenced by diet. Some pharmaceutical companies are also interested in using genetic tests to 'predict and prevent' disease and sell preventive medication. Two pharmaceutical companies, Abbott Laboratories (which owns Ross Nutritionals) and Bristol-Myers Squibb (owner of Mead Johnson Nutritionals), are also major manufacturers of medical foods (usually used in hospitals, for example in tube feeding) and have begun to market some functional food products via retailers.

Historically, the practice of medicine has involved the diagnosis and treatment of disease, while public health measures have attempted to reduce the incidence of disease in a population. However, increasingly, medication is now prescribed to reduce risk of future illness. Selling medication to treat risk factors rather than diseases is immensely profitable for the pharmaceutical industry: statins (to lower cholesterol levels) are now the biggest selling prescription drugs in the world with sales of $30.2 billion in 2004. While these drugs can save lives, expanding their use to ever larger numbers of people has been criticised by some doctors because lifestyle changes are usually cheaper and more effective and avoid the risk of side-effects. Although functional foods are sometimes promoted as an alternative to medicines such as statins, it is more likely that people who are encouraged to believe that they are 'genetically susceptible' to future illness will be sold both medication *and* functional foods *and* supplements.

In addition to preventive medication for chronic disease, another area where the use of medication is likely to expand is in treating obesity. The market for obesity drugs is predicted to reach $3.2 billion by 2013, with high hopes for new blockbuster drugs with fewer side-effects. Although studying the genetics of obesity has not yet led to any new treatments, researchers hope that it will help them develop better drugs. In common with most existing anti-obesity drugs, these new drugs target the brain (stimulating or inhibiting appetite) rather than the digestive system. However, it is unclear whether drugs that suppress appetite will really help change eating patterns. There are also ethical concerns about the implications of using drugs to change behaviour and the possibility of unintended side-effects. Although some people clearly need better medication, safety is a particular concern for anti-obesity drugs because of the likelihood that they will end up in widespread use for cosmetic reasons. Again these concerns are not removed, and may be increased, by the idea of developing functional foods which affect appetite.

Personalised diet as a health strategy

In its simplest form, nutrigenomics is based on the idea that diet should be tailored to an individual's genetic make-up or genotype (this is sometimes called nutrigenetics). A person's genome is the inclusive set of all their 25,000 or so genes. The genes are the parts of the DNA sequence that contain the cell's instructions for making proteins. The study of the genome is called genomics. Nutrigenomics research may also include other biological measurements (not just a person's genetic make-up). In the future, some of these other measurements may also be used to 'personalise' nutrition or to help design new functional foods.

To study the connection between genes and diet, scientists need to understand how an individual's genetic make-up (genotype) relates to their physical characteristics or risk of disease (called their 'phenotype'). For example, they need to find out whether people with particular genes are more likely than others to put on weight, develop diabetes or get high blood pressure when they eat certain foods (such as foods high in fat, sugar or salt). They also need to be able to measure accurately what people are eating, and other factors that affect response to diet, such as exercise.

There is major scientific disagreement about the role of human genetic variation in most cases of common, complex diseases. One theory is that common genetic variants lead to susceptibility to common diseases in rather a simple way. However, increasing evidence suggests that each genetic variant has only a small effect on risk and that many genes may interact together, perhaps in complex ways. If this is the case it may prove impossible to identify the different genes and to work out who is at highest risk of different diseases.

To the food industry, nutrigenomics provides an opportunity to design new products, attempt new 'personalised' marketing strategies (based on genetic test results, or, in the longer term, on other biological measurements) and to claim that it is responding to public concern about the growing epidemic of diet-related disease. The aim is to prevent disease and improve quality of life through functional foods and tailored diets. However, the business model relies on patent-protected, value-added products commanding a premium price. Future marketing is expected to operate via customised communication directed towards individuals (for example, using direct or internet marketing or home delivery).

A wide range of companies is expected to play a role in personalised nutrition, as a means of adding value to the food supply chain. These include:

- biotech companies who plan to undertake gene-based testing of consumers;
- processed food and supplement companies, who will formulate new products and test and manufacture them;
- food and feed ingredients companies, who will produce new 'value-added' food ingredients;
- food processing companies who will process foodstuffs to concentrate or extract desirable food components;
- agricultural biotechnology companies who will apply genomics and genetics to crops and meat-producing animals to increase components with human health value.

Some biotech companies are already marketing genetic tests combined with dietary advice or supplements: their claims have been widely criticised by geneticists who consider them misleading and at best premature. The major food ingredients companies BASF and DSM have invested in one controversial testing company (the former UK company Sciona, now relocated to the USA) as a means to 'personalise their product offerings'. Major food manufacturers, such as Nestlé, Kraft and Unilever, are also investing heavily in nutrigenomics research.

Numerous research projects are being funded by governments in partnership with industry, many with the aim of increasing food industry competitiveness. These include networks such as the EU-funded European Nutrigenomics Organisation (NuGO), which held a major conference 'From Nutrigenomics to Personalised Nutrition' in November 2005.

Scientific evidence for the role of genes in diet-related disease

The scientific evidence for the role of genes in susceptibility to obesity, type 2 diabetes, heart disease, cancer, allergies, osteoporosis and neurological disorders is weak and contradictory, except in a few special cases. Genes do play an important role in the body's cells and how they respond to diet, and gene-diet interactions do appear to exist at the level of individual genes and nutrients. But in most cases, genetic differences appear to make only small and subtle differences to a person's risk of diet-related disease and hence very little difference to the foods that they should eat. Diets contain multiple foods, foods contain multiple nutrients and the body digests these nutrients through multiple biological pathways, involving many different genes and other factors. Because of this complexity, the evidence suggests that the 'individually tailored diet' is more of a marketing concept than a scientific one.

For example:

- More than 600 different genes and regions of DNA have been associated or linked with human obesity. Some very rare mutations have been found which lead to overeating and extreme obesity in some children. However, no common genetic variation has been confirmed to play a significant role in determining who is overweight or obese in the general population.

- The biggest area of study has been whether the effectiveness of a low-fat or low-cholesterol diet depends on what genes a person has. However, genetic tests have been found to be of little use in identifying people who respond best to low-fat diets.

- One common genetic variation is known to play a role in how people respond to folate or folic acid supplements. However, this genetic variation makes so little difference compared to other factors that it is not useful to decide who should take these supplements or change their diet.

There may be exceptions for particular diseases, or special cases of 'familial' (largely inherited) forms of some diseases, where mutations in a single gene dominate an individual's risk. But tailoring dietary advice to these genetic tests is useful only in a few specific cases: where a genetic test is a good predictor of a disease and where gene-diet interactions are large (so that people at 'high genetic risk' have most to gain by changing their diets). Lactose intolerance is one example, although it does not necessarily need a genetic test for diagnosis.

Some nutrigenomics research may help increase understanding of diet-related diseases, by helping to identify the different biological factors and dietary factors that may be involved. However, this does not mean that 'personalised' or genetically tailored diets will be a good approach to tackling the growing incidence of chronic diet-related disease. This is because small and uncertain differences in risk may be enough to help researchers find clues to our biology: but large, well quantified differences in risk are needed before it makes sense to tailor diets to our genes.

The detailed review of the scientific evidence in this report concludes that, in general, the idea that 'personalised diets', tailored to individual genetic make-up, are a good way to reduce the incidence of diet-related disease is built on a large number of questionable assumptions. The myths include:

- *Myth 1: it is possible to extrapolate from simple and rare examples.* Evidence from the major food intolerances (such as lactose intolerance) or rare genetic diseases (such as phenylketonouria) is often extrapolated to other diseases (such as heart disease, or adult-onset diabetes) to argue that people's diets should be matched to their genes. However, these genetic conditions are unusually simple and/or vary rare they do not involve so many different genetic, social, lifestyle, economic and environmental factors as most common diseases. Strong gene-diet interactions, which mean that conditions such as adult lactose intolerance occur only in people with certain genetic mutations, are probably the exception rather than the rule.

- *Myth 2: our <u>future</u> health can be predicted from our diet and our genes.* Evidence that not everyone who eats a poor diet gets ill is often cited to imply that genetic factors must determine which individuals will get a particular disease. Evidence that biological factors (such as cholesterol levels) vary between individuals is also often assumed to mean that the variation must be caused by genetic differences. This deterministic view is wrong because chance usually plays a role, as do other (non-genetic) factors. It also implies that predicting diseases will be unrealistically simple scientists will never be able to see perfectly into the future. Even if all the genetic and environmental factors involved in a disease were known this does not mean complex disease is predictable. In most cases, our future health is likely to be much harder to predict than the weather is and basing diets on misleading health predictions could do more harm than good.

- *Myth 3: genetic differences explain the higher risk of some diseases in different ethnic groups.* Because some diseases are more common in different ethnic groups (for example, diabetes in the Pima Indians in Arizona, or hypertension in African-Americans) it is often assumed that this must be because of genetic differences. However, different social, cultural and environmental factors could also be to blame. The populations at highest risk of obesity and type 2 diabetes are marginalised, dependent on food aid and subject to practices such as the fat dumping of unhealthy food products.

- *Myth 4: twin studies prove that genetic differences are important.* Twin studies that calculate 'heritability' make numerous questionable assumptions and always overestimate the importance of genetic differences in common diseases by an unknown amount. High heritability does not mean that environmental factors are unimportant – the most effective way of reducing a disease with high heritability may still be to change environmental factors (including diets or social and economic factors). Heritability also says nothing about whether there is an interaction between genes and diet and hence provides no information about whether genetic tests are likely to be useful to target dietary advice.

- *Myth 5: dietary advice should be targeted at those at highest genetic risk.* If there is no gene-diet interaction, targeting dietary advice at those at 'high genetic risk' will not help to reduce the incidence of the disease and could even increase it. This is because those at highest risk could have less to gain (or no more to gain) by changing diets than the rest of the population. Often, there will be better ways to target resources than using a genetic test. In addition, targeting advice at a minority of the population is likely to be less effective than public health approaches which seek to change the diet of the population as a whole.

- *Myth 6: family studies show that genetic factors are important.* Diseases which run in families may do so by chance or because of shared genes, shared diets, other social, economic and environmental factors, or a complicated combination of all of these. Evidence that diseases run in families does not necessarily mean that inherited genetic factors are important.

- *Myth 7: genetic factors and geneenvironment interactions have already been identified for many diet-related diseases.* Most genetic association studies (the statistical studies linking genes with diseases) later turn out to be wrong. The small number of genetic factors that are known to play a role in common diseases usually make only a small difference to a person's risk, or are found only in a small minority of cases. Most gene-diet interactions have yet to be confirmed by further studies and existing studies are too small or badly designed to distinguish a real effect from chance. In any case, an interaction between a single gene and a single dietary factor does not necessarily mean that diet should be tailored to a person's genes – this will depend on how lots of different factors work together.

- *Myth 8: 'personalisation' of dietary advice is more effective than public health interventions.* There is little evidence that genetic test results help people to change their behaviour and some evidence that they may encourage people to look for medical solutions. There is no such thing as 'individual' risk and genetic risk categories are not 'personalised' because genes do not make a person who they are or determine their future, even when dietary factors are included. Genetic categories also ignore many other (medical and social) factors that may be much more important to the person who is being tested. Research also suggests that population-based interventions (such as changing prices) are more likely to be effective than individualised ones. The poor suffer more from poor nutrition because foods high in fat and sugar are a cheaper way to satisfy the appetite, not because they need advice that's tailored to their genes.

The health and wider social implications of personalised nutrition

Claims for a future of 'personalised nutrition' ignore the increasing scientific recognition of biological complexity, which makes individual risks inevitably uncertain and hard to predict. In practice, in many circumstances 'personalised nutrition' could harm health by:

- targeting the wrong dietary advice at the wrong people (either by wrongly identifying those at 'high genetic risk', or wrongly implying that they have most to gain by changing diet);
- confusing healthy-eating messages (for example, by implying that existing dietary advice is 'guesswork', and by different companies selling many different products and conflicting advice);

- undermining public health approaches (implying that only a minority of people with 'bad genes' need to eat a healthy diet);
- 'medicalising' genetic risk (increasing costs and side-effects by encouraging people to buy medicines, supplements and functional foods instead of fruit and vegetables);
- diverting resources (including research resources) from more effective approaches; and
- promoting a 'false solution' to the current epidemic of diet-related disease.

As well as the lack of benefit for health, there are also wider social and ethical issues raised by 'personalised nutrition' including:

Diverting science. Personalising diets is a deeply questionable research priority. The focus on genetics and genomics as a means to tackle diet-related disease is technology and market driven it has not been informed by an assessment of the likely benefits to health. Rather than shifting the focus of research from medicines to public health, this strategy seeks to turn foods into medicines and prevention into personalised marketing.

Undermining public health. Tailoring diets to genetic make-up raises major concerns because privatising and individualising dietary advice could easily confuse and undermine healthy-eating messages.

Misleading consumers. Genetic testing involves significant potential for consumers to be misled about their health through a lack of regulation of genetic tests and the confusing and contradictory information they will be sold.

Privacy, stigma and discrimination. Concerns include: how personal genetic data will be stored and used, including for research or 'direct marketing' of products; whether the police or governments will be given access to commercial genetic databases; and whether people will be required to reveal genetic test results to insurers or employers.

Ethnicity and race. Studies of the genetics of diet-related disease and appetite can detract from the social and economic factors that lead to poor health in marginalised populations. Unless genetic testing is genuinely useful to guide treatment, promoting genetic explanations for diet-related disease can be counter-productive – wrongly implying that nothing can be done to change the situation.

Health inequalities. Health inequalities continue to play a significant role in life expectancy in the UK and elsewhere and an over-emphasis on genetic risk factors can divert resources from addressing the major social and economic determinants of ill health. It is obvious that a strategy designed to produce and market 'value-added' foods based on individual genetic profiles is not the strategy most likely to tackle health inequalities. Unless the current biases in agriculture and food supply are tackled, the poorest quality food, highest in fat and sugar, will continue to be marketed to the poorest people.

'Personalised choice' a contradiction? The vision of personalised diets implies that people should trust genetic testing companies and food manufacturers to tell them what their ideal diet is. Despite the rhetoric of choice, the implication is that people should simply follow the 'expert' recommendations and consume the products sold to them on the basis of their test results. Real choice requires empowering people and tackling vested interests, not genetic tests.

Patenting and profiteering. The business driver for personalised nutrition is that new 'functional foods' can be patented and command a premium price. This means that companies will claim monopolies over these new foods or their ingredients (typically for 20 years or more), just as pharmaceutical companies do with medicines. Genetic tests are also patented. This means that 'genetic information' is treated as an invention and subject to intellectual property rights, even though patenting gene sequences is extremely controversial and may distort research.

Good for business? Although the reasons why food manufacturers have identified 'personalised nutrition' as an area of growth are clear, it is less clear that this business strategy will be successful. The major limitations of the science and the potential for nasty surprises, as well as privacy concerns, risk a loss of public trust.

Costs and resources. With the whole population potentially 'at risk' and eligible for preventive medication, the cost implications of 'genetic susceptibility' testing have been described as '*staggering*'. However, it is difficult to analyse cost-effectiveness when the validity and usefulness of genetic tests has not been assessed and people's responses to the results are largely unknown. Because the costs of diet-related disease are so high, even a small reduction in the effectiveness of public health measures (by confusing healthy-eating messages, or diverting resources) could be substantial.

Conclusions and recommendations

The food and biotechnology industries, and many of the scientists they fund, have widely promoted the idea that the ultimate goal of nutritional research should be 'personalised nutrition', involving individual diets based on a person's genes and, perhaps in the longer term, on other biological measurements and continual monitoring. However, the scientific evidence does not support the conclusion that such an approach will benefit health. In most cases, personalised diets are neither desirable nor achievable. For most diet-related diseases in most people, the key to prevention lies not in individual biological differences but in tackling the 'politics of food' and issues such as food industry marketing practices, socio-economic deprivation, health inequalities, transport and the lack of sports facilities in schools.

'Personalised nutrition' is therefore a false solution to the problem of diet-related disease. The main components of a healthy diet are well known, but risk becoming lost in the food industry's efforts to open new market opportunities. Therefore, GeneWatch UK believes that 'personalised nutrition' should not be a research priority. However, this approach is gaining considerable political and financial support from the public and private sectors at the expense of other areas of research which are likely to have greater benefits for health.

GeneWatch UK believes there is an urgent need for governments to:

- prioritise public health (the social and economic determinants of health), not 'personalised nutrition', and tackle the 'politics of food';
- tackle inequalities, empower people to change their diets and health, and involve them in deciding what action and research would help to make a difference;
- end gene patenting, which distorts the 'knowledge-based' economy, and stop commercial interests from dominating the research agenda;
- require medical oversight and statutory regulation of genetic tests – including an independent pre-market assessment of whether they are valid and useful for health;
- adopt new legislation to prevent genetic discrimination and protect privacy.

2. Introduction

> *'There is a small but growing field called "nutrigenomics" that is seeking to combine the increasing insights from genomics to our understanding of how dietary choices affect our health. Nutrigenomics envisions a future in which personalized genetic profiling takes the guesswork out of deciding what you should eat. By adjusting nutrient composition in a person's diet according to genetic profiles, gene-based nutrition planning could one day play a significant role in preventing chronic disease.'*
>
> Dr Mark B. McClellan, then US Federal Drug Agency Commissioner, 1 July 2003 [1]

This report considers the new science of 'nutrigenomics' (nutritional genomics) a spin-off from the Human Genome Project and the idea of 'personalised nutrition'. It asks whether tailoring our diets to our individual genetic make-up, or to other individual biological differences, will be good for health.

Nutrigenomics has been defined by an international group of biologists, ethicists and sociologists as 'a multi-disciplinary approach for the comprehensive investigation of the influence of diet and individual genetic variation as risk factors for chronic disease'.[2] It covers a broad area of research, which includes how food interacts with our biology in general, not just our genes. However, many scientists, funded by the food industry, biotech companies and governments, have stated that the ultimate aim of nutrigenomics is to tailor nutritional requirements to the *individual*. As well as research, nutrigenomics includes an implied *health* strategy that depends on several assumptions:

- that personalised nutrition, based on individual biological differences, should be the ultimate aim of nutrition research;
- that people's risk of obesity and of developing chronic diseases is different depending on their individual genes and other biological factors and that these differences can be identified and the risks quantified;
- that people should therefore be tested to find out their genetic make-up, and perhaps monitored for other biological changes, and advised to eat different foods (or take different supplements) depending on the results;
- that doing so will reduce their individual risk of common diseases and also reduce the incidence of obesity and chronic conditions in the population as a whole;
- that people will want to take genetic tests, and perhaps other types of tests as well, and will change their diets as a result;
- that this approach to health will be affordable, cost-effective and socially acceptable.

The term 'nutrigenetics'[3] is more specific than nutrigenomics; it is focused on the study of how individuals respond to different foods depending on their genetic make-up alone.
Because nutrigenomics extends beyond genetics to include other biological factors, some aspects might still be useful even if the above assumptions do not hold. For example, research might provide some clues about how our diets influence our health by looking at how different nutrients behave inside the body, including interactions at the level of the genes and proteins inside our cells. It is possible that this type of research could lead to new dietary recommendations for the population as a whole as a result of this better understanding. However, the focus of commercial interest in nutrigenomics is in achieving two overlapping aims:

- developing new food products which can be marketed as providing health benefits to consumers ('functional foods');
- *individualising* diet tailoring our diets to our genes and perhaps to other biological measurements.

Although new food products need not necessarily be tailored to an individual's genes, the food industry sees these aims as part of a single approach to tackling diet-related disease. For example, the food industry's research body, the International Life Sciences Institute (ILSI), states: '*Achieving optimal nutrition by using functional foods aims at optimising the physiological functions of each of us to ensure maximum well-being, health and quality lifespan. A diet might also have to match our unique biochemical needs. Accordingly, an optimal selection of nutrients in such a diet will rely on a better understanding of the interactions among genes, nutritional factors and disease, because these can determine the responsiveness of a specific individual to both the beneficial and adverse effects of his or her diet*'.[4]

The advocates of personalised nutrition claim that as well as delaying the onset of disease it could optimise and maintain human health[5]. It is part of 'personalised medicine' which aims to achieve a major shift from treatment of disease to 'prediction and prevention' based on an individual's genes. [6]This includes the idea of recommending medication as well as lifestyle advice, supplements and new 'functional foods' to healthy people who are identified as genetically susceptible to future illness.

This report considers the pros and cons of personalised nutrition, including its scientific basis; its potential for reducing the incidence of diet-related disease; its regulation; and the role of the food and other industries in promoting this strategy for health.

Section 3 begins with an overview of what is known about the importance of diet for health, including how what we eat affects the incidence of obesity and chronic diseases, such as heart disease and cancer. As part of the context for the new science of nutrigenomics, it also considers the role of the food, diet and supplements industries in promoting new products that claim to tackle diet-related diseases, including 'functional foods', which might be marketed in future as tailored to a customer's genetic make-up. This part of the report addresses the issue of *equality* and the role of social, economic and commercial factors in diet, health and disease. It questions whether personalised nutrition is an approach that is likely to prevent chronic diseases in the populations most in need.

Sections 4 to 8 of the report consider the science of nutrigenomics and nutrigenetics. Section 4 explains the ideas and the science behind personalised nutrition. Section 5 outlines who is involved in nutrigenomics research and identifies companies who are already marketing human genetic tests with associated dietary advice or supplements. Sections 6, 7 and 8 then summarise what is known about the relationship between individual genetic make-up and diet-related conditions, including obesity, heart disease and diabetes. These sections question the likely *effectiveness* of personalised nutrition in preventing chronic diseases, even in those populations most likely to have access to genetic tests and individualised dietary advice or food products.

Section 9 of the report describes how sales of genetic tests and associated products are regulated and considers the potential health and social consequences of personalised nutrition. As well as issues of equality and of effectiveness, this section considers other issues related to the *ethics* of widespread genetic testing, such as the potential for nasty surprises, genetic discrimination by insurers or employers, and impacts on individuals' privacy. It argues that personalised nutrition is the wrong research priority for health, and that misleading marketing of genetic tests and associated products also risks a major loss of public trust.

3. Nutrigenomics in context

This section considers the role of diet in disease and the role of the food and other industries in influencing our health. It also outlines the role of supplements, diet products and 'functional foods' as part of the commercial response to public concerns about diet and health. Social, economic and commercial factors play an important role in influencing what we eat and who is sick or healthy. They also influence what research is done and who has access to new products.

1.1 Our diets and our health

Diet plays an important role in health[7]. Under-nutrition (lack of sufficient food, or of important vitamins and minerals) can lead to illness and death through malnutrition, nutrient deficiencies and increased susceptibility to infectious diseases (Box 3.1). On the other hand, over-eating, or eating too much of the wrong foods, can lead to obesity and increase the risk of chronic diseases, such as diabetes, heart disease and some cancers (Box 3.2). In 2000, the WorldWatch Institute estimated (based on United Nations and World Health Organisation figures) that the number of overweight people in the world for the first time matched the number of undernourished people – at least 1.1 billion each.[8] Diseases related to over-eating are now widely recognised as a major, growing threat to global health.

Box 3.1. Malnutrition and under-nutrition

Nearly 30% of people in the world suffer from malnutrition, which causes some 60% of the 10.9 million deaths in children under five in the developing world. Iodine deficiency affects more than 700 million people, causing brain damage and mental retardation, while vitamin A deficiency is a major cause of childhood blindness and also increases susceptibility to infection.[9] In rich countries, illnesses due to under-nutrition are now rare. However, poverty continues to be associated with nutrient deficiencies even in American children. The consequences include growth retardation and anaemia due to iron deficiencies.[7] Dietary surveys of British adults have reported lower intakes of many vitamins and minerals in those who are unemployed, receiving benefits or in the two lowest social classes. Similar results have been reported for children from less-advantaged homes.[10]

Box 3.2. Diet and chronic diseases[11,9]

Throughout the world, 'western' diets, high in fat and energy and with more animal-based foods, are replacing more traditional plant-based diets and people are getting less physical exercise. The trend is towards a higher energy density diet (i.e. one with more calories in the same amount of food), with more fat and added sugar in foods; greater saturated fat intake, mostly from animal sources (meat and dairy products); and reduced intakes of complex carbohydrates, fibre, fruit and vegetables. This 'nutrition transition', along with other factors such as ageing populations, leads to a sharp increase in obesity and related chronic diseases.

The World Health Organisation (WHO) now refers to a global 'epidemic' of obesity and has warned that many low and middle-income countries are suffering a 'double burden' of both under-nutrition and obesity.[12] Obesity levels in South Africa, for example, are now similar to those in the USA.[13] The rates of increase in obesity are also much higher in Asia, North Africa and Latin America than they are in the USA. These increases are driven partly by demographic shifts, towards more elderly people in the populations of many countries. However, there have also been rapid increases in the consumption of fats, sugars and meat and dairy products. At the same time, physical activity levels have also changed significantly. There is a shift away from high-activity work such as farming, mining and forestry towards more sedentary jobs. Ownership of cars and televisions has also increased rapidly, leading to greater inactivity during leisure time.

Chronic diseases that are related to diet and nutrition include diabetes, heart disease, some cancers, bone disease (osteoporosis) and dental diseases. In 2001, chronic diseases caused about 60% of deaths and 46% of the global burden of disease, and this proportion is expected to increase. By 2020, chronic diseases are expected to account for three-quarters of all deaths worldwide. Although thought of as 'diseases of affluence', most of these deaths already occur in developing countries. Of the 35 million people who will die in 2005 from heart disease, stroke, cancer and other chronic diseases, only 20% will be in high-income countries.[14]

In the early 20th century, infectious diseases were the leading causes of death even in wealthy countries. Government nutritionists in the USA, for example, advised people to eat more of a greater variety of foods, to overcome nutritional deficiencies and related disorders. Food policies focused on providing a sufficient and reliable food supply. However, by the 1960s, advice began to appear on how to avoid chronic diseases such as heart disease: do not get fat; restrict saturated fats (in meat and dairy products) and total fat; favour fresh vegetables and fruits; avoid heavy use of salt and refined sugar; and get plenty of exercise. The importance of diets rich in fruit and vegetables, limited in foods and fats of animal origin, and balanced in calories was highlighted in major government reports in the USA and Europe in the late 1980s[7].

These recommendations have changed little over the years and subsequent research has only reinforced the most important dietary changes that can help to prevent chronic disease. The latest recommendations adopted by the World Health Assembly in 2004 are summarised in Box 3.3.

Box 3.3. Global strategy on diet, physical activity and health[15]

World Health Assembly recommendations for diet are:

1 achieve energy balance and a healthy weight;
2 limit energy intake from total fats and shift consumption away from saturated fats to unsaturated fats and towards the elimination of *trans*-fatty acids;†
3 increase consumption of fruits and vegetables, and legumes, whole grains and nuts;
4 limit the intake of free sugars;
5 limit salt (sodium) consumption from all sources and ensure that salt is iodised.‡

In addition, the World Health Assembly recommends that individuals engage in adequate levels of physical activity throughout their lives.

† These fats (found in margarine and hydrogenated vegetable oils) also raise cholesterol levels.
‡ The reference to iodising salt (adding iodine) has been added to tackle iodine deficiency (Box 3.1), rather than chronic disease.

Although the main constituents of a healthy diet are well known, there is an enormous gap between existing dietary guidelines and what people actually eat (Box 3.4).

Box 3.4. What people eat in Europe and the USA

According to dietary surveys in 14 European Union states, by 1999 less than 50% of the population in most countries was meeting recommended dietary targets for particular types of foods. Guidelines for fat and saturated fat intake were met by more than half the population in only one country (Portugal), and fruit and vegetable guidelines were met by more than half the population in only a few other Mediterranean countries. In all 14 countries, less than half the population met dietary fibre guidelines. Even when people achieve one target (such as for fat) they tend to miss another (such as for sugar), so that very few people are actually eating a healthy diet.[16]

A 1994 survey in the UK found that only one in 2,000 people were meeting four or more of the criteria for a healthy diet.[16] Based on a national shopping survey in 2003/4, the average person in the UK ate only 3.7 portions of fruit and vegetables a day, compared with the recommended minimum of 5 portions.[17]

A US study in 2005 found that only 3% of Americans followed all four good health rules: don't smoke; maintain a normal weight (BMI of less than 25 – see Box 6.2); eat fruit and vegetables (five servings a day); and get some exercise (half an hour a day).[18] Another study of teenagers in California found that two-thirds drink sodas (fizzy drinks) every day and half eat fast food every day, but only a quarter eat five or more servings of fruit and vegetables.[19]

Changing people's diets so that they are healthier could therefore make a major impact on the incidence of chronic diseases (Box 3.5).

Box 3.5. Preventing chronic diseases

Chronic diseases are largely preventable diseases – an estimated 80% of heart disease, stroke and type 2 diabetes, and 40% of cancer could be avoided through healthy diets, regular physical activity and avoidance of tobacco use.[20] The World Health Organisation (WHO) has calculated that the disease burden in northern and central Europe could be decreased by 34% by doubling the intake of fruit and vegetables; by 78% by eliminating obesity; by 12% by eliminating smoking; and by 9% by eliminating alcohol consumption.[21] A global goal of reducing chronic disease death rates by an additional 2% could avert some 36 million deaths by 2015, mostly in low- and middle-income countries.[14] The scientific knowledge to achieve this goal already exists – the challenge is to implement it.[20]

Although chronic diseases are on the increase, this does not mean that prevention doesn't work. For example, many wealthier countries have been successful at reducing the incidence of heart disease (although the challenges may be different in poorer countries).

Significant public health successes have been achieved through dietary changes in some countries. For example, in the North Karelia region of Finland an 82% reduction deaths from heart disease was achieved between 1972 and 1997, due to a major health drive involving changing diets to include less fat and more fruits and vegetables and helping people to quit smoking. Major dietary changes were achieved through community action and the pressure of changing demand on the food market.[22]

More recently, in Poland, deaths from coronary heart disease fell by 38% in men and 42% in women aged 45-64 years, between 1990 and 2002. Major changes in diet, particularly an increase in consumption of polyunsaturated fats (rapeseed oil and soya bean oil) probably account for most of the reduction in deaths.[23] This was achieved by changes in agricultural policies (including an end to food subsidies for animal fats), rather than health policies (which tend to focus on education and behavioural change).[24]

Deaths from heart disease also fell in many other countries during the 1980s – with increases largely confined to central and eastern Europe and Asia.[25] In the countries achieving the biggest rates of change, about two-thirds of the reduction in deaths was due to fewer heart attacks (which might be due to healthier diets or other changes in risk factors) and about one-third was due to better survival rates (probably due to better treatment).[26] In England and Wales, deaths from heart disease fell by 54% between 1981 and 2000. One recent study has attributed these changes to: fewer people smoking (leading to an estimated 29,715 fewer deaths); lower cholesterol levels, due to dietary changes (an estimated 5,770 fewer deaths) and the use of the cholesterol-lowering drugs called statins (an estimated 2,135 fewer deaths); and lower blood pressure (leading to an estimated 5,870 fewer deaths without using medication, and 1890 fewer deaths from using blood pressure-lowering medication).[27] The study concluded that policies should prioritise population-wide tobacco control and healthier diets.

Health inequalities play a significant role in life expectancy and chronic disease, including diet-related diseases. Lack of food, famine and malnutrition are still the biggest problems for poor people in the poorest countries. However, in most middle-income countries the poorest people are now those at the *highest* risk of obesity and chronic diseases, such as heart disease and diabetes.[11]

In Argentina, for example, the diet of the poor has shifted since the 1960s, from a varied balanced one, to one which depends on only 22 basic products, which are selected to satisfy the appetite but are high in fats and sugars.[28] There has also been a major movement from rural areas into the cities, reducing both time and opportunities for exercise. Poor women often allow children and other family members to eat the more nutritious foods and fill up on bread and sweetened teas. Many mothers are obese but also anaemic and lacking in essential micronutrients and iron. It is also common to find overweight or obese mothers with malnourished children.[29]

Even in the UK, poorer families tend to eat less healthily, consuming less fruit and vegetables and wholemeal bread and more white bread and processed meat products. Women in low-income groups are particularly likely to skip meals and go short of essential nutrients. Children in low-income families also tend to eat more saturated fat and sugar and fewer vitamins, minerals and dietary fibre.[30]

These differences in diet are not primarily due to lack of information about what is healthy or unhealthy, but are more likely to be due to the much lower cost per calorie of foods high in fat and sugar.[31] Other factors include food industry marketing practices (Section 3.2): 'value' and 'economy' products tend to be the highest in fat and sugar;[28,30] poor labelling (especially for salt content);[32] and lack of access to affordable transport or healthy foods in local shops ('food deserts').

However, the relationship between poverty and chronic disease is not straightforward – there is also some evidence that low socio-economic status in itself is bad for health, in addition to its effects on diet (Box 3.6). Other factors, such as smoking, also play a major role.

Box 3.6. Health inequalities[33,34,35,36,37,38]

There is some evidence that economic and social circumstances affect health in two ways: both through the direct effects on material circumstances (such as the effect of poverty on diets) and through the effect of inequality on factors such as low control in the workplace, anxiety, low social support, depression, insecurity, stress and education.

The Whitehall study of British civil servants found a gradient in health even among those who are not poor, indicating that people with a higher socio-economic position have better health and live longer lives. Relative position in the social hierarchy, and whether a person lives in a more egalitarian or more unequal society, may affect health more than income does in relatively wealthy countries. In eastern Europe, inequalities in health within individual countries appear to be more strongly related to education than to measures of economic well-being.

However, there are some disagreements between researchers about whether income or income inequality has a more important effect on health, and whether inequality is harmful largely because of psychological effects, or because it affects people's material circumstances (such as their local transport and health infrastructure), over and above the direct effect of their individual income.

Poverty and inequality may also lead to intergenerational effects, with deprivation in childhood influencing the risk of some diseases in adulthood, independently of continued social disadvantage.

3.2 Our diets and the food industry

The food industry includes agricultural businesses (producing crops and animals); food processors and manufacturers; packaging and transport companies; shops and supermarkets; vending machines and restaurants (including 'fast-food' restaurants and school canteens).

The global food retail market is worth US$3,500 billion.[39] The USA is the biggest market but sales in China are growing the fastest. The UK grocery market in 2003 was worth £115 billion.[30]

Some parts of the food industry are more powerful than others and receive a larger slice of the profits. In 2000, US consumers spent $661 billion on food, of which 19% went to farmers and 81% to marketing. Between 1990 and 2000, marketing costs (including labour, packaging and energy use) rose by 57%, while the farm value of food rose by only 16%.[41] Retailers – at the top of the food supply chain – have the most control over the market. In Europe, about 100 buying desks, based in supermarket chains, have the power to stipulate the specifications that farmers and suppliers have to meet: affecting more than 3 million farmers and producers and 160 million consumers.[42] This means that corporations, not just governments, now have a major influence over food and agricultural policy, and ultimately public health.

There is something of a battle for power in the food industry between the major retailers and food manufacturers (those with the top brands). The former see creating and retaining customer loyalty as the most important issues and want manufacturers' top concern to be food safety guarantees. The latter see product innovation as their main concern and have high expectations for technological innovations such as functional foods (see Section 3.5).[43] Both retailers and manufacturers are expected to consolidate further, so that the industry is increasingly dominated by a few major companies.

In 2002/3, the top 100 food manufacturers accounted for a total of US$710 billion in sales (Table 1 shows the top ten).[44] The top ten retailers which account for an even greater proportion of food sales are shown in Table 2.

Table 1. Top ten food manufacturers, 2002/3[45]

Company	Headquarters	Food sales (US$ billions)	Main products
Nestlé S.A.	Switzerland	54	Diversified
Kraft Foods Inc.	USA	30	Diversified
Unilever PLC	UK/Netherlands	26	Diversified
PepsiCo Inc.	USA	25	Drinks and snack foods
Archer Daniels Midland Co. (ADM)	USA	23	Ingredients and Grain-based products
Tyson Foods Inc.	USA	23	Meat and poultry
Cargill Inc.	USA	22	Grain-based foods
ConAgra Inc.	USA	20	Diversified
The Coca-Cola Co.	USA	20	Drinks
Mars Inc.	USA	17	Confectionery

Table 2.Top ten food retailers, 2003/4[46]

Company	Headquarters	Number of stores	Sales (US$ billions)
Wal-Mart Stores	USA	5,164	245
Carrefour	France	10,704	65
Ahold	Netherlands	9,407	59
Kroger	USA	3,667	52
Metro	Germany	2,411	49
Tesco	UK	2,294	38
Costco	USA	400	38
Albertsons	USA	1,688	36
Rewe Zentrale	Germany	12,077	35
Aldi	Germany	6,609	34

The food industry can have a major impact on dietary health because its need to be profitable and achieve growth can sometimes conflict with the steps needed to prevent chronic diseases.[7] This is reflected in the contradiction between the industry's need to make customers eat more of their products (for example, by advertising, increasing portion sizes and introducing new products) and the need for many people to eat less to avoid overweight and obesity. Other factors are the competition to make food tasty but cheap (leading to products high in sugar, fat and salt) and fast, mass-produced and convenient (leading to more processed foods and fast food chains).

Advertising and marketing practices may also affect what people eat, and children are likely to be particularly vulnerable. A 1996 survey of children's television in 13 industrialised countries found that confectionery, pre-sweetened breakfast cereals and fast-food restaurants accounted for more than half of all food advertisements.[47] Adverts for healthier foods such as fruit and vegetables were very rare.

For every $1 spent by the World Health Organisation (WHO) on trying to improve the nutrition of the world's population, some $500 is spent by the food industry on promoting processed foods.[48] In 2000, the food industry spent an estimated $40 billion on advertising worldwide (Table 3 shows the biggest spenders), mostly in North America, Europe and Japan. In the USA, for example, the food industry spent $26 billion (4% of food expenditures) on advertising: 50% was spent by manufacturers, 25% by food service companies and 15% by retailers.

Table 3. The world's biggest food advertisers, 1999/2000[48]

Company	Advertising spend (US$ billions)
Nestlé	1.9
Coca-Cola	1.5
McDonald's	1.2
Mars	1.1
Pepsi	0.7
Danone	0.7
Kellogg's	0.6

Concern about the impacts of unhealthy diets, particularly in children, has grown in recent years and is being seen as a major weak spot for the industry. Influential events and publications include the McLibel trial[49] (in which McDonald's sued two London activists for criticising their food, labour practices and adverse impact on the environment); the book 'Fast Food Nation'[50] (about the fast food industry in the USA); and the film 'Supersize Me'.[51]

In addition to the impacts on their businesses of bad publicity, food companies are becoming increasingly concerned about their legal liability for obesity, following a lawsuit filed by a group of overweight Americans against several US fast food companies in 2002.[52] The plaintiffs alleged that McDonald's, Burger King and Kentucky Fried Chicken had misled customers and knowingly served foods that cause obesity and disease. Although there has not yet been a successful legal case, the investment bank J. P. Morgan Chase & Co. ranks the five most at-risk food companies for further obesity-liability lawsuits as Hershey Foods Corp., Cadbury Schweppes Ltd, Coca-Cola Co., PepsiCo Inc. and Kraft Foods Inc.[44]

Some major companies have begun to respond to consumer concern, public criticism and legal threats by altering their product lines (see Box 3.7). Although factors such as price still dominate, 'wellness' is now seen as a key marketing trend in the food industry. However, these voluntary changes are not all healthy and the industry continues to oppose regulation that could limit levels of fat, sugar or salt in processed foods or restrict advertising to children.

Box 3.7. Changing product lines[53]

PepsiCo says it has embarked on a major overhaul of all its products to reduce levels of fats, salts and sugars. Its new 'SmartSpot' scheme will identify products that meet certain nutritional criteria.

General Mills says it has significantly reduced the sugar content of some of its cereals and has announced that it intends to reformulate all its breakfast cereals to use wholegrains.

McDonalds has significantly changed its menu and its marketing, introducing salads and fruit. However, its salads appear to have more fat than its burgers[54,55] and its new 'Apple Dippers' come packaged in slices with a carton of caramel dip.[56]

Kraft says it is putting a cap on portion sizes and developing new guidelines for nutrition and advertising to children[57] and that it has reduced the levels of salt in some of its cheese products and snacks.[58]

Nestlé has introduced a 'whole grain guarantee' on its breakfast cereals and says it has also cut the salt and sugar content. However, it has been criticised because not all products with the guarantee are made entirely of whole grains and some still contain high levels of salt and sugar.[59]

In addition, the food industry is funding and coordinating research into obesity and diet-related diseases. Individual companies fund their own research, but the industry also has an international research institute, called ILSI (Box 3.8).

Box 3.8. The International Life Sciences Institute (ILSI)

ILSI was founded by Coca-Cola and other food manufacturers in 1978 to defend food industry interests.[60] It now describes itself as 'a nonprofit, worldwide foundation that seeks to improve the well-being of the general public through the advancement of science'.[61] Its members include all the major food companies worldwide.[62]

ILSI says it aims to 'utilize its strategic alliances and global network to bring scientific solutions to important public health issues'. It has identified four key issues for research: overweight/obesity, food biotechnology, functional foods and risk assessment.

Because the food industry includes food production (farming and fishing), processing, storage and transport, it has major impacts not only on health, but also on the environment. Issues include, for example, the use of pesticides, genetically modified crops, over-fishing, air transport and soil depletion. Environmental impacts, such as soil depletion, climate change and over-fishing, also affect the current and future availability of nutrients, and hence people's diets and health. Industrially produced ('factory-farmed') meat, for example, contains different types of fats from traditional game meat, and hence has very different implications for health. In addition, industrial meat production requires much greater energy inputs than the food energy it outputs, creating an unsustainable system of production that contributes to malnutrition in low-income countries.[63] Environmental issues are not discussed in this report, but it is worth remembering that they are also part of the politics of food and play an important role in decisions about the future of our food supply. Similarly, food policies affect social justice and the working conditions of packers and farm labourers.

Processing and packaging also affect nutrients, such as the levels of vitamins and minerals in packaged salads and white flour. Additives such as colourings and flavourings are often used in foods of poor nutritional value and some food preservation methods can make unhealthy processed foods (such as canned fatty meats) cheaper than fresh, healthy ones.[16]

3.3 The supplements industry

Many people no longer get all their nutrients from food, they also take dietary supplements. Supplements include vitamins, herbs, minerals and other products, including sports nutrition products. A recent US study found that 48% of men and 56% of women reported regular use of multivitamins and up to 75% of white women took at least one supplement a week.[65] Global supplements sales in 2000 were US$50 billion; in 2003, the US supplements industry reached US$20 billion in sales.[66]

The nutritional supplements industry is increasingly dominated by a few large companies, although many smaller companies – some with a strong commitment to natural health and avoiding additives – also exist.[67] The top producers are NBTY Inc. (a US-based supplement specialist with sales of $1.65 billion, which owns the FSC and GNC brands and Holland & Barrett in the UK) and three major pharmaceutical companies: Wyeth (owners of the Solgar and Centrum brands), Otsuka Pharmaceutical (which sells C-MAX vitamins in Japan and the Nature Made brand in the USA) and Bayer (whose brands include Berroca and Sanatogen both purchased from Roche in 2004 and One a Day). NBTY has recently bid to take over Solgar vitamins from Wyeth.[68] In the USA, most supplements are now sold in supermarkets, followed by mass merchandisers and health food stores. Wal-Mart has made the biggest recent increase in market share.[69] In the UK, Boots and the Belgian company Omega Pharma (owner of the Healthcrafts brand) also produce supplements, and many supermarkets market their own brands.

Vitamin supplements are only a part of the supplements market, with global sales of about US$2 billion. Market value has been falling because of the entry of Chinese companies selling at a cheaper price. The Dutch food ingredients company DSM is the leading producer (with 27% of the market in 2003) followed by the German chemical company BASF. Vitamins E, C and A accounted for more than 65% of sales in 2002.[70] For a long time these vitamins have been regarded as protective, potentially reducing the risk of heart disease, cancer and other diseases.[71] However, more recently, vitamins A and E have been associated with *increases* in risk in several major clinical trials (Boxes 3.9 and 3.10). A recent review of the effects of these vitamins on the risk of gastrointestinal cancers (cancers of the digestive system, including bowel cancer) also found no evidence of a protective effect with, instead, a possible increase in overall mortality.[72]

Box 3.9. Vitamin A, beta-carotene and cancer risk

Vitamin A plays an important role in cell growth and division and since the 1980s some studies have suggested that this vitamin, or related chemicals called carotenoids, may reduce the risk of cancer. Carotenoids are dark coloured pigments found in plants, some of which can be converted to vitamin A by the body: beta-carotene is the most important of these.[73]

However, in the 1990s, two major clinical trials examining the effect of beta-carotene supplements gave unexpected results, showing an *increased* risk of lung cancer in smokers who took these supplements.[74,75]

Box 3.10. Vitamin E and heart failure

In March 2005, a major clinical trial involving over 7,000 patients with vascular disease or diabetes for seven years found no effect of vitamin E in preventing cancer, heart attack, stroke, angina or death from heart disease. The study also found an increased risk of hospital admission for heart failure in people taking vitamin E.[76]

The conclusions of the trial prompted an angry response from the supplements industry, via its trade body in the USA, the Council for Responsible Nutrition.[77]

Whether it is supplements or medication that are being studied, assessing what works in prevention is much harder than finding out what works to treat disease. Small beneficial or harmful effects may be hard to distinguish, yet can add up to large numbers of people who could be either helped or harmed once the product is in widespread use. Because people with healthier lifestyles are more likely to use supplements, it may also be hard to separate their effects from other factors in preventing diet-related disease.[65]

The deregulation of dietary supplements in the USA in 1994, which led to rapid growth in the supplements industry, has been criticised by some nutritionists for failing to require the industry to meet science-based standards of efficacy and safety.[7] New regulations are now being introduced in the European Union, aimed at assessing the safety of dietary supplements.[78]

The studies described in Boxes 3.9 and 3.10 are not conclusive and many people argue that it is up to people to decide whether to take supplements or not. But the situation may be different if these vitamins or other nutrients are added to the food supply: these issues are discussed in Section 3.5.

3.4 The diet industry, diet drinks and low-fat products

The global weight-loss market is $240 billion[79] and the diet industry is expected to grow significantly as a result of rising levels of obesity.[80,81]

In Europe, there is a €93 billion (£62.3 billion) market in diet foods, diet drinks and weight-control supplements. The market is driven more by concerns about appearance than about health. In the USA, an estimated 71 million Americans were dieting in 2004 and about $46 billion was spent on weight-loss product and services.[82] Germany is Europe's biggest market for diet foods (€19.6 billion in 2002) and the UK the second biggest (€15.6 billion).

Increasing levels of obesity are seen as the main driver for growth, but people are also disillusioned about the diet industry: largely because only about 1-2% of dieters achieve permanent weight loss.[83,84] The evidence for the long-term effectiveness of many diets is mixed, although there is some evidence that low-fat diets can work[85] and that adding exercise, behaviour therapy or anti-obesity drugs (see Section 3.6) can improve the effectiveness of dietary advice[86]. A recent study also raised some concern that, except in the very overweight and those with weight-related diseases such as type 2 diabetes and heart disease, the long-term physiological damage caused by dieting may outweigh the short-term benefits of losing weight.[87,88] In contrast, exercise, as in many other studies, was found to be beneficial. Although the evidence that dieting is harmful is limited and not definitive, losing weight is difficult for individuals. From a health perspective, it is clearly preferable to avoid weight gain in the first place.

The diet industry is not clearly defined but may be considered to include: lower calorie and low-fat foods and drinks; weight-loss supplements and meal replacements; weight-loss centres; weight-loss medicine (ranging from supervised diets to surgery); and pharmaceuticals (anti-obesity drugs). Table 4 shows one breakdown of the diet industry market in the USA.

Table 4. The US diet industry, 2002[89]

Market segment	**Sales (US$ billions)**
Diet soft drinks	14.86
Artificial sweeteners	1.79
Health club revenues	13.52
Commercial weight loss centres	1.44
Medically supervised diet programmes	2.12
Anti-obesity drugs	0.748
Low calorie/diet entrees	2.07
Meal replacements and appetite suppressants	2.38
Diet books, cassettes and exercise videos	1.38
Total industry	**39.85**

Weight-control foods accounted for 2.4% of global food and drink sales in 2000. Fat reduction in dairy products (not included as part of the diet industry in Table 4) accounted for 39% of the total value, while low-calorie or sugar-free soft drinks represented 34%. One of the fastest growing sectors of the market is low-fat and calorie reduced snacks, including biscuits, sweets and cakes.[90] The popularity of the Atkins diet has also led to a recent boom in the sale of low-carbohydrate products by the food industry, including low-carb ice creams and beers. However, the diet appears to be falling out of favour and people seem to be more sceptical about the diet products than the diet itself.[91]

The effects of low-fat foods on health are complex and depend on marketing practices as well as the impacts of the food on health. For example, the shift from full-fat to low-fat milk may have helped to reduce the incidence of heart disease, but sales of fizzy drinks (replacing fat with sugar) have increased more rapidly than sales of low-fat milk.[7] The fat removed from low-fat milk also remains in the food chain and is simply used in other products, such as cream, ice cream and bakery products.[92] Low-fat foods have also had little impact on rising levels of obesity. Food companies have removed the fat from many products but replaced it with energy-dense substitutes (especially refined carbohydrates), which do nothing to reduce overeating.[93]

Similarly, artificial sweeteners and diet drinks have done nothing to reduce sugar consumption. In the USA, 28% of all drinks consumed (by volume) are sodas (sweetened fizzy drinks).[94] Diet sodas, using artificial sweeteners, now account for an increasing proportion of soft drink sales. However, from 1970 (soon after artificial sweeteners were introduced) to 1997, the amount of sugar per person per year in the US food supply *increased* from 122 pounds to 154 pounds. This is because, although the proportion of diet sodas sold went up, the total quantity of soda sold per person also doubled and marketing increasingly targeted children (including via schools). In practice, most individuals who use artificial sweeteners do not reduce the amount of sugar they consume.[7]

Weight-control supplements include products that claim to reduce appetite, burn fat or prevent fat digestion. Until late 2003, when it was banned by the US Federal Drugs Administration (FDA) due to serious side-effects (including heart attack, stroke and death) the biggest selling weight-loss supplement was the herbal supplement Ephedra.[95,96,97] Many of the same companies who made profits from Ephedra, now make alternative weight-loss supplements, with total US sales of about US$1.2 billion a year.[98]

Advertising for weight-loss products and services has been widely criticised: a survey of US ads by the Federal Trade Commission (FTC) found that many made exaggerated claims, lacked scientific evidence and used misleading and deceptive techniques.[99]

Anti-obesity drugs are considered in Section 3.6. Surgical procedures, such as stomach stapling, are also sometimes used to treat extreme obesity. There is a risk of side-effects and complications and surgery can fail to work if people do not develop a healthy lifestyle afterwards: up to 25% of patients need surgery again after five years.[100] The number of US residents undergoing weight reduction surgery increased four-fold between 1998 and 2002.[101]

3.5 Techno-foods and health claims for foods

> *'Our supermarket shopping lists are turning into prescription pads: garlic to prevent heart disease, broccoli and green tea to prevent cancer, milk for strong bones, and Cheerios to keep our cholesterol down. It does not seem unreasonable to request impartial and evidence-based guidance for shoppers as they choose which medicines – er, foods – to put in their carts.'*
>
> Douglas Kamerow, Editor, British Medical Journal USA[102]

'Techno-foods' are foods and drinks that have been manufactured to confer health benefits beyond the nutritional value of the foods themselves.[7] They are generally marketed to appeal to people's desire for uncomplicated ways to follow dietary advice and achieve 'optimal nutrition'. These foods include:

- foods enriched or fortified with vitamins, minerals, protein, fibre or other substances;
- 'lesser evil' foods formulated to be low in calories, fat, sugar, salt, caffeine, allergens or other unhealthy ingredients.

Some of the same ingredients used in supplements (Section 3.3), especially vitamins and minerals, can be added directly into foods. Food fortification has played a significant role in ending nutrient deficiencies and conditions such as rickets, goiter and pellagra in most people in developed countries, beginning with the addition of iodine to salt in the early 1900s and the addition of vitamin D to milk in 1931. In some cases, fortification was first introduced to compensate for a loss of nutrients during food processing (for example, in white flour).

Manufacturers began to fortify cereals in the 1950s, but marketing breakfast cereals with health claims began in earnest with Kellogg's All-Bran in 1984. Kellogg's undermined the regulatory restrictions that then existed on health claims for foods in the USA, by getting the National Cancer Institute (NCI) to endorse a claim on its cereal boxes that high fibre foods may reduce the risk of cancer.[7] Thousands of food products are now fortified, including unhealthy products such as sweets, sweetened drinks and breakfast cereals and snacks high in sugar or salt. Many of these products are highly profitable but of questionable nutritional value.

Existing 'lower evil' low-fat foods and diet foods are considered above in Section 3.4. However, new food products called 'functional foods' are also being developed, which include ingredients intended to be good for health.

'Functional foods' have been defined as foods that have been demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects. The effect must be relevant to an improved state of health and well-being and/or reduction of risk of disease. Functional foods go one step further than other techno-foods: for example, they are intended to lower cholesterol, rather than simply be low in fat, and to 'optimise' nutrient intake in healthy people, rather than simply prevent nutrient deficiencies. Although functional foods blur the line between foods and medicines they must remain foods and must demonstrate their effects in amounts that are consumed as part of the normal diet (they are not pills).[4] Functional foods are a major area of growth for the food industry (Box 3.12).

Box 3.12. Functional foods as a growing market

In 2000, the global market for functional foods was US$52 billion.[103] The term 'nutraceuticals' is sometimes used to cover all types of 'techno-foods' as well as vitamins, minerals and supplements. Between 1998 and 2002 the nutraceuticals market grew by 37.7%, but by 2002 while the market for functional foods was still growing, the market for vitamins, minerals and supplements had begun to fall.[104] Future growth is expected to lie mainly in the functional foods market: one estimate of future market size is US$300 billion within ten years.[105] By 2003, sales of functional foods had reached US$22 billion in the USA,[106] while the Japanese nutraceuticals industry reached sales of about $30 billion in 2004.[107] The UK nutraceuticals market was valued at US$1 billion in 2001 and predicted to grow steadily at 8% to 2005.[108] However, despite strong growth, functional foods are still a relatively small part of the global food business.

The food industry expects nutrigenomics to play a role in developing new functional foods, demonstrating the biological effects of these foods (including providing evidence to meet regulatory requirements), and tailoring functional foods to an individual's genetic make-up.[4] The role of nutrigenomics in the future development and marketing of future functional foods is discussed in Section 4. Some more information about existing products and research is given below.

Modern functional food research began in Japan, with a large-scale government-funded research project beginning in 1984. More than 200 functional food products (including soft drinks, yoghurts, biscuits, cookies, sugar, candy, pudding, soy bean curd, vinegar, chocolate and powdered soup) had been approved under the Japanese Food for Specified Health Use (FOSHU) regulations by May 2001.[109]

Some of the main ingredients in functional foods, including probiotics, prebiotics and plant sterols, are described in Box 3.13. Most of the recent product development and growth has been in cholesterol-lowering products, especially margarines, and probiotic yoghurts (see Box 3.14). Worldwide, the pro- and prebiotics market was worth about US$6 billion in 2004. The UK has become a key market for 'techno-foods' and is currently ranked third in the world behind the USA and Japan. Table 5 shows a breakdown of the UK techno-foods market in 2001, including both fortified and functional foods.

Box 3.13. Some functional food ingredients[110, 4]

Vitamins and minerals Many vitamins and minerals are essential dietary components, however their long-term effects on diseases such as heart disease and cancer are less well understood (see Boxes 3.9 and 3.10). Vitamins, minerals and fibre are commonly added to breakfast cereals. There is some evidence that the mineral selenium may reduce the risk of some cancers, although most studies have been of poor quality.[72] This has led to the development of some new products such as selenium-enriched bread.

Fish and flax oils (PUFA) Fatty acids called 'long-chain omega-3 polyunsaturated fatty acids' (or omega-3 PUFA) are found in fish oils (including two fatty acids called DHA and EPA) and linseed oils (a fatty acid called ALA). There is some evidence that fish oils may reduce the risk of heart disease and that they might also play a role in brain health.[111] The ratio of omega-6 fatty acids (from increased use of sunflower and other oils; and intensive farming of cattle fed on grains) to omega-3 fatty acids has increased substantially compared to traditional diets.[112] However, the relative merits of these different types of polyunsaturated fats and oils (all of which are healthier than saturated fats) are still a matter of scientific debate.[113] Omega-3 fortified eggs and milk can be produced by feeding chickens or cattle on feed containing fishmeal or flax, and these are now sold as functional foods.

Probiotics are live bacteria that are considered beneficial in the gut. Mainly added to yoghurts or fermented dairy products, they are intended to relieve lactose intolerance, stimulate the immune system to reduce gut infections and reduce recurrence of some types of inflammatory bowel disease (IBD). Some studies have indicated beneficial effects,[114] however the role of 'good' and 'bad' gut bacteria is still poorly understood.[115]

Prebiotics are non-digestible ingredients that stimulate existing bacteria in the gut. These may influence the immune system or the body's ability to absorb minerals such as calcium.

Synbiotics are combinations of probiotics and prebiotics.

Phytochemicals are biologically active chemicals in plants, many of which may have beneficial health effects.[116] Some plants have been genetically modified (see Box 3.18) to try to increase the levels of some phytochemicals in the diet. However, conventional breeding may also be used in some cases.[117] Alternatively, some of these plant chemicals may be added to other foods, or used to feed hens or cattle (as is the case with omega-3 milk and eggs, described above). Phytochemicals include thousands of different chemicals. Some relevant groups of chemicals are: polyphenols, phytoestrogens, phytosterols, phytates and lectins, some of which are discussed below.

Polyphenols include **flavenoids**, chemicals which have their highest concentration in the outer layers of fruit and vegetables, such as apple peel. **Catechins** are one type of flavenoid, found in large quantities in green tea. Polyphenols are considered to be powerful **antioxidants**. Until recently, these were thought to protect against cancer by mopping up 'reactive oxygen species' (or 'free radicals') which can damage molecules inside the body and may contribute to disease and ageing.[118] However, the role of antioxidants is not fully understood and recent research has found that the levels obtained from food may be too low to have any substantial direct effect.[116]

Phytoestrogens mimic the human hormone oestrogen. They include **isoflavonoids** and **lignans**, mainly found in soybeans and flaxseed.[116] The main interest is in their possible protective effect against cancer, based on high soybean consumption in Asian countries (where rates of prostate and breast cancer are low) and on some experiments in rats. Phytoestrogens may also be harmful to health if consumption is too high.

Phytosterols (plant sterols and stanols) play a similar role in plants to cholesterol in humans. They can interact with cholesterol in the intestine to reduce its absorption. They occur naturally in the diet, especially vegetarian diets, but are now being added to functional foods such as margarines. There is some evidence that these products can lower cholesterol levels and hence reduce risk of heart disease, however they may also reduce the absorption of some vitamins.[119,120]

Carotenoids are dark-coloured plant chemicals (see also Box 3.9), some of which may be converted to vitamins in the body. **Lycopene** (found in tomatoes and some fruit) is one example of a carotenoid that has been promoted for its possible protective effect against cancer. However, a 1999 advert for Heinz tomato ketchup in New York Times magazine that claimed that lycopene 'may help reduce the risk of prostate and cervical cancer' was withdrawn after complaints from a nutritionist.[7] This claim had not been authorised by the Food and Drugs Administration (FDA): of 12 studies, five support a reduction in risk of prostate cancer in people consuming lots of tomatoes or lycopene, but seven do not.[121] Another issue is that ketchup also contains sugar and salt and cannot be considered a health food because it is commonly eaten with hamburgers and chips.

Box 3.14. Some functional food products

Yakult is the leading brand of probiotic yoghurt in Japan. Danone's Actimel™, popular in Europe, has been renamed DanActive Immunity Cultured Dairy Drink in the USA, where consumers are more wary of probiotic drinks. The Meiji brand, which includes probiotic candies, is also popular in Japan.[122]

In the UK, Dairy Crest has launched St Ivel Advance, a milk enriched with omega-3 oils.[123] The company ran advertisements featuring fertility expert Professor Robert Winston and including the claim: 'Experts in children's development believe more Omega-3 may enhance a child's concentration and learning'.[124] Winston was criticised because St Ivel had failed to clear the claim with the Joint Health Claims Initiative (Box 3.16), which currently believes the evidence for cognitive benefits of omega-3 to be uncertain.[125]

Many companies now sell omega-3 eggs (also called 'designer eggs'): including Freshlay's Vita Eggs (UK), Eggland's Best Eggs (USA and UK) and Pilgrim's Pride EggsPlus (USA).[126,127]

The UK supermarket Waitrose is now selling selenium-enriched bread.[128]

Proctor & Gamble's fat substitute Olestra (a soybean oil) was first patented in 1971 and went on sale in the USA as 'Olean' products in 1998, including in chips marketed by Frito Lay. However, the FDA insisted on a warning notice amid concerns that olestra could cause diarrhoea in some people and reduce the absorption of some vitamins. Sales were disappointing, despite a massive marketing campaign.[7]

The Raisio Group first introduced its Benecol™ margarine containing phytosterols in Finland in 1995. Unilever followed with its own brands of phytosterol-containing margarine, including Take Control™ and Flora ProActive™.[129]

Coca-Cola plans to launch a range of fruit juices with added plant sterols[130]. The company is concerned that it has been under-performing since 1997 because it missed consumer trends. One of its competitors, CadburySchweppes, recently announced a 5% rise in profits, due largely to the introduction of diet and vitamin-enriched versions of drinks.

Table 5. The UK techno-foods market in 2001[108]

Product category	Market size (US$ millions)
Breakfast cereals	263
Spreads	197
Energy drinks	186
Juices, juice drinks and dilutables	123
Probiotic dairy drinks	78
Probiotic yoghurts	68
Eggs	18
Mineral water	15
Soft cheese	9
Cereal bars	9
Soya milk	6
Beverages	6
Pasta, bread, milk and pasta sauces	24
Total	**1,000**

Currently, functional food products are a niche market. As well as the extra costs involved in their production, their value to food manufacturers is in preserving their identity as high-value products. For example, phytosterol spreads have 7% of the market in the UK, with buyers paying a near 300% premium at retailers. Eggs high in omega-3 have 34% of the US market and consumers pay almost a 200% premium for them. These products will not reach poorer consumers, unless governments subsidise them as an alternative to cholesterol-lowering drugs like statins (see Section 3.6).[131] However, this idea has little merit as higher levels of omega-3 are also found in free range eggs,[112] oily fish and flax seed, and phytosterols can also be obtained from eating vegetables (Box 3.13).

The first techno-food was arguably powdered formula milk for babies (see Box 3.15). This is just one example that illustrates the importance of regulating health claims for foods and the difficulties in assessing claims and controlling marketing. In Europe, powdered baby milk and some other foods, mostly intended for people with medical conditions, are now classified as 'dietetic foods' and have to meet certain regulatory requirements. However, these requirements do not cover most functional foods. The food industry argues that functional foods are distinct from dietetic foods because they are intended for basically healthy consumers,[4] however this distinction is not clear cut.

Modifying the nutritional content of food is different from selling supplements, because people may be less aware of what they are consuming. The potential implications of altering the food supply are illustrated by the example of vitamin A (beta-carotene). Scientists from Nestlé and elsewhere have stated that 'a major shift in the carotenoid content of the food supply was underway' when the two large intervention trials of beta-carotene supplements described in Box 3.9 were completed.[132] The unexpected results (the supplements increased, rather than decreasing, the risk of lung cancer in smokers) showed the food and agriculture industries that they needed to be much more cautious before altering the vitamin content of the food supply in a major way. The results of the beta-carotene trials are often given as a reason for investing in nutrigenomics as a way to better understand the effects of different nutrients on health, but they also highlight the importance and the difficulties in regulating functional foods, and the potential dangers of altering the food supply. Some nutritionists also argue that the functional foods approach leads to a misleading focus on single nutrients, instead of plant-based diets in general.[133]

Regulation is important not only to ensure food safety. Because diet-related diseases are so common, misleading information about which foods are healthy can undermine public health and lead to an increase, rather than a reduction, in the incidence of these diseases. The former FDA Commissioner Mark McClellan stated in 2003:

'…there are opportunities ahead for health gains through innovation to improve how people can use foods to make their diets healthier. But in order to provide proper incentives for the development of these "next-generation" foods, as well as for making short-term improvements in foods already on the market and healthy dietary choices based on them, it's not enough simply for us to determine that the foods are safe. There has to be a clear regulatory path that enables food producers to make truthful, science-based claims about the health benefits offered by their products'.[1]

Existing regulations and proposals for regulation are discussed in Box 3.16.

The difficulties in assessing safety are also complicated by the fact that both foods and supplements can interact with medicines, causing side-effects.[134]

Box 3.15. Powdered baby milk

Powdered baby milk was first concocted in 1867 in an attempt to replicate the nutrients in mother's milk. By the 1890s, Nestlé's 'Best for Babies' powdered milk was being manufactured and distributed by a New York City firm[135]. However, by 1898, evidence had emerged that babies who were fed proprietary foods and condensed milk had higher mortality rates than babies who were breast-fed. Nestlé's approach to marketing powdered milk formula, particularly in developing countries, has remained controversial ever since.[136,137]

Box 3.16. Regulating health claims for foods[138]

Functional foods are currently unregulated in the European Union, but the European Commission is working with the food industry to develop a regulatory framework. The Commission's PASSCLAIM project (Process for the Assessment of Scientific Support for Claims on Foods) is working with the food industry to develop criteria for the evaluation of claims.[139] In the meantime, in the UK, functional foods are subject to a voluntary code of practice under the Joint Health Claims Initiative (JHCI), which is endorsed by the Food Standards Agency and major stakeholders.[140] The JHCI approves claims that can then be used to market food products, on the basis that 'the totality of the evidence substantiates the food claim'. The most recent claim approved, following an application by a coalition of supplement and food ingredients companies and the Scottish fishing industry, was: 'Eating 3g weekly, or 0.45g daily, long chain omega-3 polyunsaturated fatty acids, as part of a healthy lifestyle, helps maintain heart health.' This claim can now be used to market products containing omega-3 fish oils, provided certain conditions are met.[141] However, some marketing claims for omega-3 oils have already breached this voluntary code (Box 3.14).

In the USA, food claims are authorised by the Food and Drug Administration (FDA).[7,142]

Unlike mass fortification of basic foods such as salt, flour and milk, the current market in functional foods is for 'lifestyle' products that may in some cases benefit individual consumers, but are unlikely to bring major benefits (or harms) to population health (such as a change in the incidence of heart disease or cancer).[143] However, food manufacturers see the 'second generation' of functional foods as a key part of their response to the rise in diet-related diseases. The results of an industry survey on disease conditions expected to drive functional foods development over the next five years are shown in Table 6. The 'big killers' – heart disease and cancer – top the list. Areas of research of interest to the food industry are outlined in more detail in Box 3.17.

Table 6. Conditions considered influential in future functional foods development (2002 survey of European manufacturers) [144]

Condition	% considering influential in next 5 years
Heart disease	49
Cancer	37
Osteoporosis	27
Gut health	21
Obesity	37
Immune system	17
Bowel function	11
Arthritis	3
Mood/cognitive performance	7
Neural tube defects (spina bifida)	8

Box 3.17 Research areas in functional foods[4]

Foods to promote optimal development and growth for pregnant mothers and young children
Includes foods intended to modify the composition of breast milk, early child growth, sensory and cognitive abilities (including food preferences), developing immune response and increasing bone mass. Some infant formula products and nutritional drinks are already being marketed.[145]

Foods to optimise metabolism
Includes creating effects on blood sugar levels and carbohydrate release to tackle diabetes and obesity.

Foods to promote optimal defence against oxidative stress
Intended to counter the effects of oxidants on ageing and associated illnesses such as cancer.

Foods to promote optimal heart health
Includes modifying dietary fats and fatty acids, for example incorporating fats from fish oils into other foods or adding plant sterols.

Foods to promote gut health
Includes attempts to create a healthier balance of gut microflora using probiotics, prebiotics and synbiotics.

Functional foods to improve optimal mental performance
Includes ideas such as a 'magic lunch' (that avoids a post-lunch dip in concentration) and foods for exam performance or countering depression or failing memory.

Functional foods to promote optimal physical performance and recovery
Includes the development of improved oral rehydration products and liquid foods for athletes.

Outside Japan, major research institutes involved in functional foods R&D include the Center for Enhancing Foods to Protect Health (USA),[146] the Center for Designing Food to Improve Nutrition (USA),[147] the Nutraceuticals Institute (USA),[148] the Center for Environmental and Rural Health (USA),[149] the College of Agricultural and Environmental Sciences, UC Davis (USA), the Vegetable and Fruit Improvement Center (USA),[150] Washington State University Center for Integrated Biotechnology,[151] VTT Tailored Technologies for Future Foods Programme (Finland),[152] the Centre for Advanced Food Studies (Technical University of Denmark),[153] the National Centre of Excellence in Functional Foods (Australia),[154] the Dutch Centre for Human Nutrigenomics,[155] the Agrotechnology and Food Innovations research programme (the Netherlands)[156] and the Guelph Food Technology Center (Canada).[157]

In the future, functional foods may include genetically modified (GM) foods (see Box 3.18) and foods intended to alter appetite, moods or behaviour (see Box 3.19). The emerging science of nanotechnology may also play a role (Box 3.20).

Box 3.18. Genetically modified 'functional foods'

The 'next generation' of genetically modified (GM) crops are likely to be modified to seek to increase the content of vitamins and minerals; contain healthier fats, oils or sugars; cause fewer allergies or have enhanced flavour. Some products under development, such as GM 'golden rice', have been promoted as the solution to world hunger and nutrient deficiencies.[158] More recently, the biotech industry has started to promote research on GM foods, such as soybeans and salads modified to produce omega-3 fatty acids (fish oils), as the answer to obesity and related diseases.[159,160] Some scientists also advocate genetically modifying probiotic bacteria in order to bring enhanced benefits to gut health.[115]

In addition to the issues raised by functional foods in general, the production of GM foods with altered nutritional profiles may raise new food safety issues, as well as concerns about cross-contamination of non-GM crops and wildlife[161]. There are also question marks over whether genetic modification can reliably produce the desired levels of nutrients in foods.

Researchers are also genetically modifying some animals in attempts to alter the nutritional content of meat and milk. Experiments include adding a spinach gene to pigs to produce pork with less fat; and genetically modifying cows to produce milk with more protein or less lactose (to reduce allergies and expand the market). This type of research raises major animal welfare concerns.[162]

Box 3.19. 'Psycho foods': functional foods to alter appetite and mood.

Research on functional foods coordinated by the food industry's research body, the International Life Sciences Institute (ILSI), now includes the psychological and behavioural functions of food. For example, ILSI's Functional Food Science in Europe (FUFOSE) project included research to investigate the effects of foods on appetite control, cognitive performance and mood.[163] The aim of research on appetite control at the University of Leeds (UK) is to develop functional foods that make people feel full: to prevent weight gain or help weight loss. Research on cognitive performance includes effects on reaction time, attention, vigilance and memory. The idea is that these functional foods will affect brain function, like the anti-obesity drugs described in Section 3.6. One issue is possible side-effects – the researchers note that: 'Since food manipulations may affect multiple functions, the challenge is to design foods with good satiety control that do not impair mental performance; or alternatively to engineer foods that optimise cognitive performance without compromising satiety.'

Some scientists are concerned about the ethical implications of developing drugs which alter appetite control, because it implies controlling people's desires and altering their personalities.[164] Similar concerns have been raised for drugs that alter memory or mood.[165] Functional foods designed to alter appetite, mood or behaviour may pose greater problems than these drugs. For example: regulation and medical oversight is likely to be weaker for foods than for medicines; more people may consume foods than medicines; and it may be hard to distinguish altered from unaltered foods. In addition, the interests of the food industry may not coincide with the public interest (see Section 9).

Box 3.20. Nanotechnology and functional foods[166,167]

A nanometre is a one thousand millionth of a millometre, so nanoscience is the science of the very small. Nanotechnology includes a wide range of technologies, but some involve food and agriculture, including nano-scale food additives with applications in functional foods. For example, the chemical company BASF produces a nano-scale version of its carotenoids,[168] such as lycopene (see Box 3.13), and companies including Unilever and Kraft are developing 'nanocapsules' to deliver added ingredients in food. The ETC Group has raised a wide range of concerns about nanotechnology, including the lack of discussion about its social implications and the potential impacts on farmers in developing countries. Many scientists have now accepted that nanoparticles may have unexpected impacts on health and the environment, which need to be investigated.

3.6 The pharmaceutical industry

'The worried weighty constitute the largest – and wealthiest – drug market in history. And every drug maker in the developed world wants a share.'[169]

Although nutrigenomics focuses on the role of nutrients in preventing disease, the role of the pharmaceutical industry is important because it also markets medication intended to reduce the risk of the same diseases. Some pharmaceutical companies are also interested in using genetic tests to 'predict and prevent' disease and sell preventive medication.[6] Two pharmaceutical companies, Abbott Laboratories (which owns Ross Nutritionals)[170] and Bristol-Myers Squibb (owner of Mead Johnson Nutritionals),[171] are also major manufacturers of medical foods (usually used in hospitals, for example in tube feeding) and have begun to market some functional food products via retailers.[172]

Historically, the practice of medicine has involved the diagnosis and treatment of disease, while public health measures have attempted to reduce the incidence of disease in a population. However, increasingly, medication is now prescribed to reduce risk of future illness. Selling medication to treat risk factors rather than diseases is immensely profitable for the pharmaceutical industry: for example, statins (to lower cholesterol levels) are now the biggest selling prescription drugs in the world.[173] Sales of statins grew 11.2% between 2003 and 2004, bringing the pharmaceutical industry $30.2 billion in sales.[174]

While these drugs can save lives, expanding their use to ever larger numbers of people has been criticised by some doctors because lifestyle changes are usually cheaper and more effective (see also Box 3.5) and avoid the risk of side-effects.[175] The role of the pharmaceutical industry in influencing guidelines for lowering cholesterol (which influence the market size) is therefore controversial[176] as is the recent approval of over-the-counter sales for statins.[177]

One argument used in favour of functional foods is that they provide a better or cheaper alternative to medication such as statins. However, an alternative view is that functional foods contribute to 'medicalisation' and to the idea that healthy people are all patients at risk of becoming sick. If this is the case, it is more likely that people encouraged to feel at high risk (because of genetic tests or other types of tests) will be sold both medication *and* functional foods *and* supplements.

In addition to preventive medication for chronic disease, another area where the use of medication is likely to expand is in treating obesity. The market for obesity drugs is predicted to reach $3.2 billion by 2013, with high hopes for new blockbuster drugs with fewer side-effects.[178] An estimated 127 million American adults are now overweight or obese, but currently only one in 25 obese people in the USA have prescriptions for drug treatment, with many insurers refusing to pay or patients abandoning medication due to ineffectiveness and side-effects. Nevertheless, the world's biggest selling anti-obesity drug, Xenical, generated revenues of US$472.6 million in 2004.[174]

Although studying the genetics of obesity has not yet led to any new treatments, researchers hope that it will help them develop better drugs.[179,180] In common with most existing anti-obesity drugs, these new drugs target the brain (stimulating or inhibiting appetite) rather than the digestive system.[183,351,169,181,182] However, it is currently unclear whether drugs that suppress appetite will really help change eating patterns.[183] There are also ethical concerns about the implications of using drugs to change behaviour[164] and the possibility of unintended side-effects. Although some people clearly need better medication, safety is a particular concern for anti-obesity drugs because of the likelihood that they will end up in widespread use for cosmetic reasons.[180] In 1996-8, of the almost 5 million US adults who used prescription weight loss pills, a quarter were not overweight.[184] Again these concerns are not removed, and may be increased, by the idea of developing functional foods which affect appetite (Box 3.19).

3.7 Governments and public health

'Obesity is a disease of society, not of the individual … It is a major issue of public health, which requires urgent attention not from health-care professionals, but from politicians.'

Diabetes expert at Nottingham City Hospital, 1998[185]

'...the relevant features of obesity-promoting diets may not be the percentage of energy from sugar or fat but rather high palatability and low energy cost. These issues are inextricably linked to agricultural commodity prices, imports, tariffs, and trade. Americans are gaining more and more weight while consuming more added sugar and fats and are spending a lower proportion of their income on food. No longer a purely medical issue, obesity has become a societal and public health problem.'

Nutritionists at the universities of Washington and Seattle, 2004[31]

'A logical response to the increasing sedentariness of modern society would be to lower the energy density of foods and reduce portion sizes; the precise opposite of fast food marketing practices.'

UK nutrition scientists, 2003[186]

The advocates of functional foods, such as hot-dogs modified to reduce appetite or contain healthier fats, often claim that the public health approach to tackling obesity and diet-related diseases has failed because people don't listen to healthy-eating messages.[187] However, others argue that public health approaches have been continually undermined by the economics of the food industry and other factors.[188] Dietary recommendations since the 1950s have tended to focus on telling the individual what to eat and have neglected social, cultural, economic and environmental factors. Promotions, pricing, packaging, advertising and availability all encourage consumers to eat more food, not less, and the food industry spends billions of dollars on food promotion, thousands of times more than the budgets of public health education programmes.

Researchers have found that the poor in Argentina do not eat what they want, or what they know they should eat but what they can afford.[28] They know what foods they should eat, but they choose foods that are rich in carbohydrates, fats and sugars because they are cheap, filling and tasty and satisfy their appetites at low cost. The food industry fosters this behaviour by targeting the poor with mass, low-quality products that are cheaper but higher in fat and sugar. These food marketing practices are global: they also affect low-income families in the UK who suffer from 'food poverty'.[30] Recently, governments have become aware of the enormous and growing costs of obesity on healthcare systems and the economy in general. The estimated annual cost of medical expenses and lost income as a result of complications of adult obesity in the USA is about US$70 billion.[351] In Europe, these costs may account for 5-10% of all health costs in EU countries[189]. The cost of diet's impact on health is now a key factor driving policy changes in many countries[190]. However, there is major disagreement about the extent to which 'voluntary' measures (favoured by the food industry) can deliver changes, in comparison to regulation.

It is important that policies are coordinated if major changes in diets, such as an increase in fruit and vegetable consumption, are to lead to better health.[191] Changing agricultural and food policies, rather than health policies, have helped to achieve major reductions in heart disease in Poland (Box 3.5). However, despite some reforms, agricultural subsidies, such as the Common Agricultural Policy (CAP) in Europe, still strongly favour the overproduction of bulk animal fats, dairy products, sugar and refined starches.[192] In 2003-4, the largest recipient of CAP payments in the UK was the sugar company Tate & Lyle. Multinational companies, such as Nestlé, Cadbury's and Kraft, and dairy product manufacturers, such as Meadow Foods, also received substantial payments.[193]

A public health approach to preventing obesity and chronic diseases is one which focuses on changing the social and economic factors that lead people to eat poor diets.[188,16] Such an approach would recognise that a priority is the availability and cost of healthy, nutritious food for all, especially the most vulnerable: access to good, affordable food makes more difference to what people eat than health education.[194] This also means tackling conflicts of interest: such as resistance from some companies, for example, to reducing the levels of salt in processed and fast food.[195]

In addition, public health research has been neglected despite its enormous importance in reducing the incidence of disease. Obesity research, for example, has been targeted mainly at individuals, where most interventions result in only small amounts of weight loss and have little impact on the obesity epidemic: social and environmental interventions have largely been ignored.[196] In the UK the Health Development Agency found that not more than 0.4% of medical research output (measured by academic publications) is relevant to public health intervention research.[197]

3.8 Summary

Nutrigenomics research takes place in a context where diet-related diseases are some of the world's biggest killers and an 'epidemic of obesity' is occurring. The impacts of this epidemic are serious in affluent societies, but already affect more people in low- and middle-income countries. These less affluent countries are undergoing a 'nutrition transition' and are suffering a double burden of both infectious and chronic disease.

The role of the food industry in the global epidemic of obesity and chronic disease has been widely recognised, alongside other societal changes in employment, transport and use of leisure time, which have led to major reductions in the amount of exercise that many people get. However, the industry's potential role in tackling the epidemic is more controversial. Food manufacturers' search for growth is driving investment in functional foods – attempts to design new 'healthier' foods and market them at a premium.

The success of the pharmaceutical industry in marketing cholesterol-reducing drugs (statins) has sparked enormous interest in selling products to healthy individuals to reduce their 'personal risk' of future chronic disease. The food industry is now seeking to apply these principles to foods and food ingredients.[198] Rather than increasing the availability of existing healthy products (such as vegetables), or making regulated reductions in the levels of salt, sugar and saturated fats in processed foods, this means designing new 'value-added' products and marketing them as tailored to an individual's personal risk of future illness.

There are questions not only about the health implications of these foods themselves, but also about what this approach will mean for poorer people, who are at the highest risk of most diet-related disease. Functional foods are targeted at richer consumers, who can afford the extra cost. This does nothing to help lower socio-economic groups who are more likely to be the victims of fat dumping, 'food deserts' and segregated marketing: the mass marketing to lower socio-economic groups of cheaper, processed products high in fat and sugar.

The context reviewed above suggests that personalised nutrition is at best irrelevant to the majority of people likely to suffer from chronic diseases in the future – people in poorer countries or in lower socio-economic groups in wealthy countries. Worse, it may divert resources from tackling the wider social and economic determinants of health and the politics of food.

The remainder of this report considers the role that the science of nutrigenomics is expected to play in delivering the food industry's aim of personalised nutrition in those populations who are most likely to have access to it. This includes the likely effectiveness of this approach to health (Sections 4 to 8) and its broader social implications (Section 9).

4. ‘Personalised nutrition’ as a health strategy

This section describes the ideas behind 'personalised nutrition' as a strategy for reducing diet-related disease. It first describes the broad research field known as nutrigenomics, then considers the specific idea of tailoring diets to a person's genes (sometimes called 'nutrigenetics').

4.1 The science of nutrigenomics

Although not all nutrigenomics research is about personalised nutrition, developing new functional foods and individualising diets are the main commercial aims.

In its simplest form, nutrigenomics is based on the idea that diet should be tailored to an individual's genetic make-up or genotype (this is sometimes called nutrigenetics). A person's genome is the inclusive set of all their 25,000 or so genes. The genes are the parts of the DNA sequence that contain the cell's instructions for making proteins. The study of the genome is called genomics.

To study the connection between genes and diet, scientists need to understand how an individual's genetic make-up (genotype) relates to their physical characteristics or risk of disease (phenotype). For example, they need to find out whether people with particular genes are more likely than others to put on weight, develop diabetes or get high blood pressure when they eat certain foods (such as foods high in fat, sugar or salt). They also need to be able to measure accurately what people are eating, and other factors that affect response to diet, such as exercise (this is discussed in Section 6.1).

The Human Genome Project produced an account of the sequence of the genome of an 'average' person (a mixture of several different people's genomes). Research continues which investigates human genetic variation – how this sequence can differ between different people to make each individual's genotype (or their own unique genetic make-up). Rare genetic differences are called mutations, and common genetic variations (occurring in more than 1% of a population) are called polymorphisms. One major initiative is cataloguing the simplest form of these variations (called single-nucleotide polymorphisms, or SNPs). A SNP (pronounced 'snip') occurs when only a single nucleotide (chemical letter) in the DNA sequence varies. There are thought to be some 100,000 to 300,000 SNPs in human genes, which may either influence phenotype directly or be used as markers by researchers when they look for important genetic variants.[199] Other types of genetic variation include copy-number polymorphisms (CNPs).[200]

Because the genome is the same in every cell, a person's genome can be studied using a blood sample or sometimes a mouth swab. Although it is now technically possible to sequence an individual's whole genome, this is still prohibitively expensive. Usually genetic tests look at individual genetic polymorphisms (common genetic variations) occurring in particular genes. A typical test might look for genetic variations in several genes that have all been claimed to play a role in susceptibility to the same disease.

However, the relationship between genes and disease (genotype and phenotype) is often complex, making it hard to predict a person's likelihood of common illnesses from their genes. Because biology involves much more than genes, many scientists now argue that common diseases cannot be understood by studying genes and diet alone[198].

Much nutrigenomic research now includes how different dietary components affect gene expression, as well as how different genotypes affect a person's response to their diet. Genes contain instructions for making proteins but they do this via a different chemical called 'messenger RNA'. Not all the instructions are 'switched on' in every cell: cells in the liver, brain or lungs are said to *express* different proteins. Gene expression also changes with time, in response to the environment (including different diets) and can also change when somebody is ill (for example, the genes expressed in cancer cells are different from normal cells). The expressed genome (also called the transcriptome) is all the genes that are switched on inside a cell at any one time. The expression of many different genes at once can now be measured using instruments called 'gene chips', which identify the messenger RNA inside a cell. However, this technique is limited by the difficulties in accessing some parts of the body in live human beings (for example, the liver is important in a person's response to diet, but is hidden inside the body). There are also major difficulties in interpreting gene expression data.

Although several studies have now taken place on the effects of nutrients on gene expression in human cells, understanding is still very limited.[201] Gene expression may be used in future as a way to try to quantify an individual's dietary requirements, or perhaps just to try to understand how different nutrients, such as fish oils, affect biological processes.[202,203]

Other types of measurements of proteins and metabolism (Boxes 4.1 and 4.2) are also beginning to be considered. This shift to different types of information (and combining this information using a new science called 'systems biology') may be necessary because there is a growing recognition that genes alone do not dominate biology.[204] However, because the ways in which all these different processes work together to cause disease is not well understood, there are many disagreements about the types of measurements that should be prioritised and about what the data means. There are thousands of different genetic variations and different chemicals in food, all of which may interact.[205]

Box 4.1. Proteins and the proteome

The collection of all the proteins in a cell (about a million) is called the proteome. The proteome is more complex than the genome and so far there is no routine way to separate and quantify all the proteins in a sample. In addition, the three-dimensional structure of proteins and their interactions are important, and there are therefore millions of different ways they can be modified to produce complex different functions.[206] Scientists are just beginning to try to catalogue the human proteome, looking at the proteins in different tissues types and how these are affected by diseases such as cancer.[207] There are still major difficulties in interpreting proteomic data.[208]

Box 4.2. Metabolism and the metabolome

Metabolomics is the study of the entire set of metabolites within a sample or cell.[206] This means that the metabolome is the complete set of all chemicals produced by human beings thought to be about 2,000 compounds.[209] At present the technology does not exist to quantify the metabolome fully.

Human metabolic profiles change from hour to hour and are influenced by many factors including exercise, smoking and medication use, as well as diet.[210]

Despite this complexity, one idea behind nutrigenomics research is to use the complete set of gene expressions (the transcriptome), or alternatively the metabolome (Box 4.2), as a 'biomarker'.[211,212] Because measuring cholesterol has proved such a successful way to market 'risk reducing' medication (see Section 3.6), both the pharmaceutical and food industries are extremely interested in finding other tests, or 'biomarkers', that can also be 'treated', long before a person becomes ill. Biomarkers are important in functional food development, because to demonstrate a benefit to health a biomarker (such as cholesterol levels) must be changed by eating the functional food (such as a cholesterol-lowering margarine) and the biomarker must be shown to be linked to the risk of a given diet-related disease (such as heart disease).[213]

Like blood pressure and cholesterol levels, but unlike genetic make-up, measurements of gene expression or a person's proteome and metabolome change with time. Companies interested in personalised nutrition see these measurements as an additional set of measurements to genetic testing during an individual's life. However, it is not obvious whether changes in gene expression or metabolism can be reliably interpreted to show that a person is at high risk of developing a diet-related disease. Some scientists argue that there are good reasons why diets are not usually tailored to metabolic markers, including the lack of confidence in these factors as markers of outcome (future health or disease), their enormous variability, dangers with misinterpretation, and the likelihood that the same metabolic profile may be good for some diseases and bad for others.[210] The level of surveillance that would be required might also be unacceptable, the predictions limited in value and the potential for 'medicalisation' could be enormous.

4.2 Nutrigenetics – diet and genes

This section focuses on nutrigenetics – the idea of tailoring your diet to your genetic make-up (genotype) – because research in this area is most advanced. It asks what role genetic differences might play in a person's likelihood of developing a diet-related disease and how this information might be used to create 'personalised' dietary advice.

For many rare genetic disorders, the symptoms of disease (the phenotype) can be directly related to a mutation in a particular gene (the genotype). In some cases, symptoms can be avoided, or at least reduced, by a change in diet, bringing major benefits to health (see Box 4.3 for an example).[214]

Box 4.3. The genetic disorder PKU[215]

People with the rare genetic disorder Phenylketonuria (PKU) lack the ability to break down an amino acid (a building block for proteins) called phenylalanine. These people require a diet that has lower amounts of phenylalanine than normal. High-protein foods are avoided and measured amounts of cereals, starches, fruits and vegetables, along with a milk substitute are usually recommended. Severe problems with brain development can occur if children with PKU are not treated. In the UK and the USA and many other countries all children are given a blood test at birth to see if they have this disorder.

However, although diet can be very important for some people with genetic disorders, the focus of nutrigenomics and functional foods research is not these rare disorders, but healthy people who may be at risk of much more common conditions such as heart disease, cancer and osteoporosis (bone thinning). These conditions are known as 'multifactorial' or complex diseases because they involve many different factors, including many different genes and other biological factors, exposure to multiple environmental factors such as diet, smoking and pollution, and complex interactions between these factors.[216] Some of the important exposures may occur before a person is even born, others may occur much later on in life. Chance may also play an important role[217] and so do social and economic factors (Box 3.6). This means that there is not a simple relationship between genetic make-up (genotype) and phenotype (the symptoms or disease that someone might develop later on in life).

Many common conditions such as heart disease and some cancers have rare 'familial' forms which are largely inherited. Rare mutations in a limited number of genes often explain these cases, but do not inevitably lead to illness, and do not explain the vast majority of cases. Again, the focus of nutrigenomics is not on these 'familial' cases, but on the possibility that much larger numbers of people are genetically susceptible to common forms of heart disease and cancer.

There is major scientific disagreement about the role of human genetic variation in most cases of common, complex diseases. One theory is that common genetic variants lead to susceptibility to common diseases in rather a simple way. However, increasing evidence suggests that each genetic variant has only a small effect on risk and that many genes may interact together, perhaps in complex ways.[218] If this is the case it may prove impossible to identify the different genes and to work out who is at highest risk of different diseases.

Section 6 considers the evidence for the role of genetic differences in different diet-related diseases. However, before considering this evidence it is important to think about how it might relate to the idea of personalised nutrition. Suppose scientists could work out who was at 'high genetic risk' of common diet-related diseases (such as type 2 diabetes). How might testing a person's genes be used to 'predict and prevent' these diseases?

There are two approaches to using genetic tests to personalise diets:

- Find the people with both 'high risk' genes and a 'high risk' diet (by testing people's genes) and advise these people to make an extra effort to change their diet – remembering, of course, that they cannot change their genes, but they can change what they eat.
- Market products such as functional foods, supplements or medicines to everyone who has the 'high risk' genes.

These two approaches are not mutually exclusive, but are considered in turn below.

4.2.1 Tailoring dietary advice to genes

One purpose of persuading people at 'high genetic risk' of a diet-related disease to change their diet is to reduce the incidence of that disease in the population, and therefore improve health – the aim is to have fewer people getting diabetes, for example. However, because common diseases are complex (they involve many different factors) this approach is not as simple as it is for the genetic disorder described in Box 4.3.

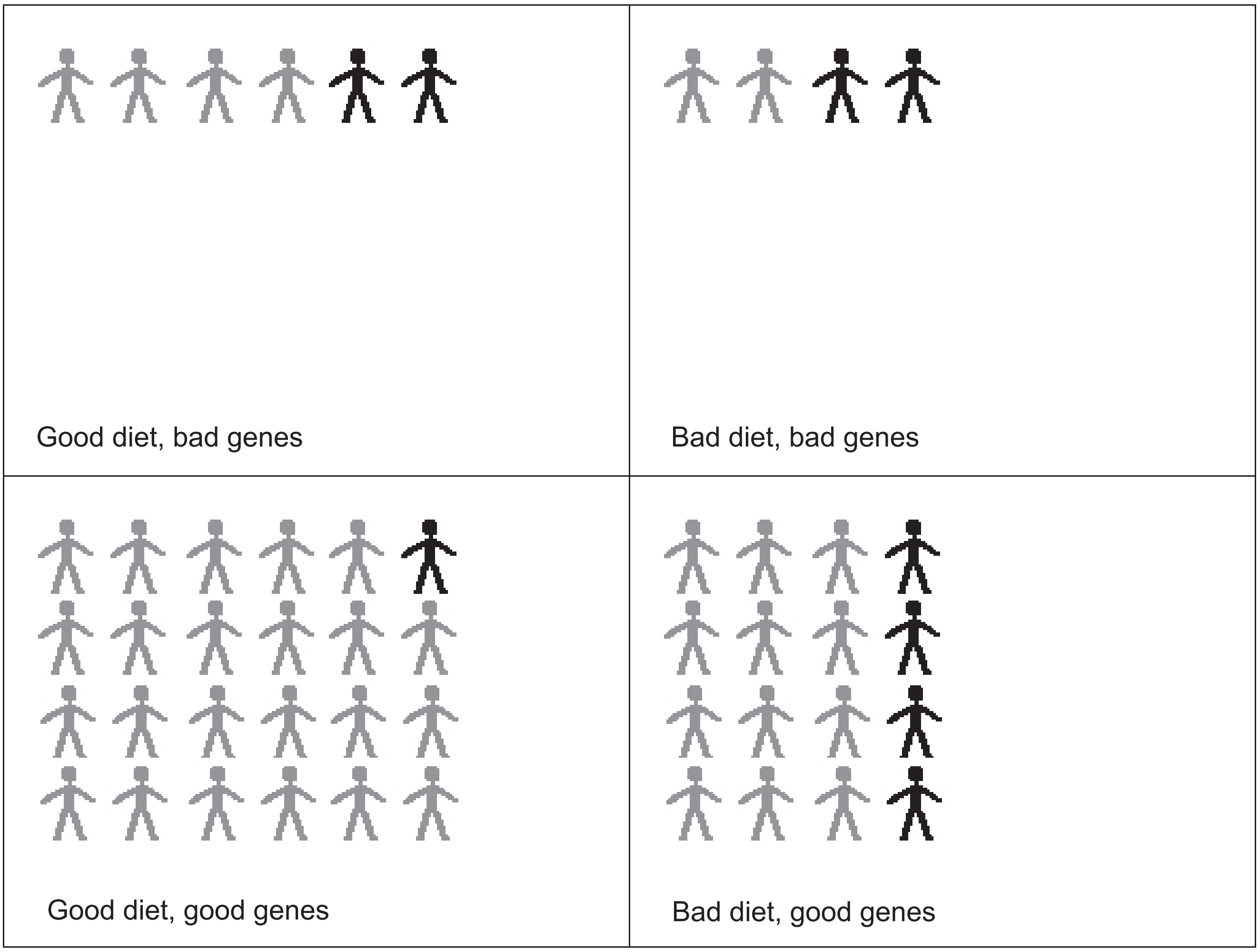
Figure 1 shows an imaginary population divided into four categories, according to the genes they have and whether they eat a high or low risk diet. The risk of getting the imaginary diet-related disease is different for each category, and so are the numbers of people in each group. However, although people with the high risk genes are more likely to get ill, many people with these genes will not get the predicted disease and many people without them will.

Even if people can be told their genetic risk correctly, and they take the advice that they are given, targeting the people with high risk genes may not be good for population health. There are three main reasons for this:

i) *targeting the high risk group is often much less effective than changing the diet of the whole population*. Unless the bad health effects of a high-risk diet occur only in the people with high risk genes, there will be people in the 'low risk genes, high risk diet' group (see Figure 1) who also get the diet-related disease. In many cases, *more* people in this group will get the disease, because there will usually be more people in it. In situations like this, most cases of disease will be missed by targeting dietary advice at the people at high genetic risk. This effect is well known and occurs for many risk factors, not just genes. It is one reason why policies targeting people at high risk, rather than trying to change conditions for the population as a whole, have limited potential to reduce the incidence of disease[219];

ii) *the people who have **most to gain** by changing diets may not be the same as those who are at the highest genetic risk*. It is often assumed that it is more important for the people at high genetic risk to change their diets. However, this is not necessarily true. The impact on population health depends on *which group has more to gain* by changing their diet, not on which group is at highest risk. This depends on whether the *reduction in risk* that can be achieved by changing diets is larger for the people at high genetic risk than the people at low genetic risk. If it is, there is said to be a 'gene-diet interaction'. In the imaginary example in Figure 1, the genetic test is not a useful way to decide who should change their diet, even though it correctly identifies who is at high genetic risk. This is because the people at high genetic risk in Figure 1 have *less to gain* by changing diets (they reduce their risk by less) than the people at low genetic risk (this can be thought of as a negative gene-diet interaction);

Figure 1: A population divided into groups according to genetic makeup, diet and risk of an imaginary common disease. The figures coloured black represent the proportion of each group expected to go on to develop the disease.



iii) *deciding who to target may be difficult if the dietary factor being studied causes more than one disease*. Figure 1 shows an imaginary population at risk of a *single* disease. But unhealthy diets can cause many different diseases (for example, eating lots of sugary foods can increase the risk of dental caries, type 2 diabetes and obesity, and the latter increases the risk of other diseases, such as some cancers). It is possible (even likely) that people who are more susceptible to some of these diseases will be less susceptible to others. With multiple diseases caused by a single dietary factor, using genetic tests to decide who to advise to eat less sugar then becomes very difficult. This is much more likely to confuse people than the simple message that too much sugar is unhealthy. The problem of multiple diseases is complicated further by the fact that foods contain many different nutrients and diets contain many different foods. For example, a diet based on junk foods high in fat, sugar and salt will increase the risk of most of the 'big killer' diseases. This means that more genetic research is unlikely to change the basic message everyone should try to avoid too much of these foods, whatever genes they have.

Although targeting the high risk group for dietary advice may be ineffective or even harmful (because the wrong advice may be given to the wrong people, and public health messages undermined), it often suits commercial interests (see Box 4.4). This makes it even more important to consider carefully whether this is the right approach.

Box 4.4. 'Genetic predisposition' to lung cancer: the role of the tobacco industry.

The tobacco industry has been heavily involved in funding academic research into 'genetic predisposition' to lung cancer[220,221] despite the fact that twin studies show there is no significant inherited component.[222,223] The (false) idea behind this research was that only a minority of smokers with 'bad genes' would need to quit to protect their health. In practice, testing smokers for supposed 'genetic susceptibility' to smoking-related diseases could mislead them about the risk of smoking and falsely reassure some people into thinking that they do not need to quit.[224,225]

4.2.2 Food products tailored to your genes

The second approach is to market products such as functional foods, supplements or medicines to everyone who has the high risk genes, whether or not they make other changes to their diet. This approach is the one that offers the most potential profits to the food, supplements and pharmaceutical industries. However, it may also lead to 'medicalisation': increasing the costs of disease prevention compared to a public health approach and risking side-effects. The potential for medicalisation is enormous, because practically everyone can be classified as genetically susceptible to something, using genetic tests. This is because there are so many common genetic variations (polymorphisms) in the human genome, so tests which identify them have potentially staggering implications for the number of people who might be advised they are 'susceptible' to future illness.

Increasing the number of tests increases the likelihood that someone is classed as genetically susceptible to a disease. For example, suppose a panel of 22 genetic tests each identified 5% of the population as 'at risk'. If the whole population took this panel of 22 tests, two-thirds of the population would have at least one 'at risk' test result[226]. However, tests for genetic susceptibility to common diseases typically have limited predictive value: many people with the high risk genetic variation do not get the disease and many people without it do. This results in large 'numbers needed to treat' to prevent one case of disease.[227,228] Unless these genetic tests are highly predictive, most people may take functional foods, supplements or medicines to try to prevent conditions that they would never have developed. These problems are likely to be exacerbated by the difficulties in assessing the safety and effectiveness of foods designed to reduce risk rather than to treat disease (Section 3.5). Although in the longer term, one aim of nutrigenomics is to develop 'biomarkers' to help to assess the benefits and safety of functional foods, it is far from clear that this is achievable and major uncertainties are likely to remain (Section 4.1).

5. Nutrigenomics: who's involved

The science of nutrigenomics aims to individualise (and privatise) dietary advice, by marketing genetic tests combined with personal advice on diet and with other products, such as supplements. It also aims to take the current market for functional foods one step further, by designing foods with enhanced health benefits tailored to 'at risk' individuals or groups.[229] Although these are the main commercial aims, some nutrigenomic research could also lead to new understandings in biology. This section examines who is involved in nutrigenomics research and identifies the companies who are already selling genetic tests linked with dietary advice or advice to take supplements. What tests are or might become available and what products might be marketed?

5.1 Major research projects

Table 7 shows the major international nutrigenomics research projects. Some of these are specifically designed to study nutrigenomics, others are major studies of diet and disease, to which a genetic component has been added. The table also includes some population biobanks – large-scale genetic databases which link DNA samples to lifestyle data. These biobanks will include some studies looking for interactions between genes and diet, but they will also include some other types of research. Studies that look at genetic factors only, and do not include dietary information (including genetic studies of diet-related diseases such as obesity, diabetes, heart disease and cancer) are not included in the table.

Table 7. Major research projects including diet and genes

Name	Project	Participants	Funding	Countries
AARP Diet and Health Study	http://dietandhealth.cancer.gov/index.html Dietary study of 500,000+ retired people: now starting to collect saliva samples to include genetics.	US National Institutes of Health (NIH).	NIH.	USA
BioProfile Nutrigenomics	www.nutrigenomik.de	Part of a regional network in the Berlin-Brandenburg region.	Up to €18 million from the German federal ministry for science and technology.	Germany
Center of Excellence for Nutritional Genomics	http://nutrigenomics.ucdavis.edu	University of California Davis, USDA Western Human Nutrition Center, Children's Hospital of Oakland, Ethnic Health Institute.	US$6.5 million over 5 years from the National Center for Minority Health and Health Disparities (NCMHD) of the US National Institutes of Health (NIH).	USA
Centre for Human Nutrigenomics	www.nutrigenomics.nl	Wannigen University & Research Centre, TNO Nutition and Food Research, University of Maastricht, National Institute of Public Health and Environment, Nizo Food Research.		The Netherlands

Diet, Obesity and Genes (DiOGenes)	www.diogenes-eu.org Plans a DNA bank of over 13,000 people. About 700 obese/ overweight adults and their children will be put on 5 different diets to try to identify gene-nutrient interactions associated with changes in body weight.[230]	30 organisations, including the food companies Unilever, Nestlé and Danone and the biotech companies Integragen, Biovision and Nizo. The project aims to match diets to consumer needs and to develop functional foods that limit appetite.	€14.5 million from EU.	15 European countries
European Longitudinal Study of Parents and Children companies. (ELSPAC)	www.alspac.bris. ac.uk/elspac/index. shtml Mothers and children from pregnancy to age 15. Although the stated aim is to look at genetic and environmental factors, few studies have included genetics to date. However the data includes diet and a DNA bank (in UK).	Coordinated by University of Bristol, UK Includes medical research institutes in Brno, Athens, Douglas, Moscow and Kiev.	Depends on individual countries – includes government, charities and some companies. Food companies contributing funds to ALSPAC (the UK part) include Coca-Cola UK Ltd, Cow & Gate and Nestlé.	UK, Isle of Man, Czech Republic, Slovakia, Russia, Ukraine, Greece
European Prospective Investigation into Cancer And nutrition (EPIC)	www.iarc.fr/epic Primarily a study of diet and cancer, now includes 400,000 blood samples and some nutrigenomic research.	17 research centres in 7 European countries, coordinated by International Agency for Research on Cancer. Nutrigenomics collaboration with the Nutritional Epidemiology Branch of the US National Cancer Institute.	European Commission plus local support for each centre (from governments and cancer charities).	10 European countries
European Nutrigenomics Organisation (NuGO)	www.nugo.org/ everyone	22 partner organisations.	€17.7 million over 6 years from the European Commission (EC). Expects to be self-funding from 2010.	10 European Union countries
LipGene	www.lipgene.tcd.ie Diet, genomics and the metabolic syndrome: an integrated nutrition, agro-food and economic analysis.	25 laboratories, including some commercial companies (BASF, Unilever).	€12.5 million from the EU.	European countries
Mediterranean Diet, Cardiovascular Risks and Gene Polymorphisms (Medi-RIVAGE)	www.a-nutritional-supplements.com/con f04a19.htm An intervention study in 300 patients, involving 3 diets (Mediterranean, low-fat and standard Western). Includes interactions between genes and dietary fats[231].	Based at INSERM (National Institute of Health and Medical Research), in Marseille, France.	French government plus agro-food companies.	France

Nutrigenomics Consortium	www.genomics.nl /homepage/research/ Innovative_clusters/ nutrigenomics	Centre for Medical Systems Biology (CMSB), Wageningen Centre for Food Sciences, AVEBE, Royal Cosun, CSM N.V., DLO, DSM, Netherlands Dairy Association, NIZO Food Research, TNO Nutrition and Food Research, Unilever N.V., University Maastricht, Waageningen University and Research Centre.	Part of the Netherlands Genomics Initiative (funded by the Dutch Government).	The Netherlands
Nutrigenomics New Zealand	www.nutri genomics.org.nz	AgResearch Ltd, University of Auckland, HortResearch Ltd and Crop & Food Research Ltd.	NZ$92 million from the New Zealand Government.	New Zealand
OsteoDiet	osteodiet.ucc.ie	7 European research institutes.	European Commission 1998-2002.	European countries
Program for Genetic Interaction (PROGENI)	www.biostat.wustl. edu/progeni 5 studies, 4 involving diet: GET READI and GOLDN (both looking at genetic response to dietary fats), GenSALT (genes, salt and blood pressure) and HAPI Heart (looking at both salt and fats).	Each project based at a different US research institute.	US National Heart, Lung and Blood Institute.	USA
UK Biobank	www.ukbiobank. ac.uk Aims to recruit half a million adults to study interactions between genes and the environment, including diet.	The biobank will be set up as a charity, but researchers from universities and companies will pay to use it.	The Wellcome Trust plus the UK Medical Research Council, Department of Health and Scottish Executive.	UK

Table 7 is not exhaustive and does not include projects or centres in individual universities. Many of the projects listed are networks designed to link different institutes and partners in the food and biotech industries. An example of a network is given in Box 5.1. Most other studies listed are 'biobanks', which link DNA samples with other medical information, including data on diets. An example of a biobank is described in Box 5.2.

Box 5.1. NuGO – a 'Network of Excellence'

The European Nutrigenomics Organisation (NuGO) is a 'Network of Excellence' funded by the European Union. It claims that nutritional disorders in the UK and other European countries are 'unique to affluent societies' and that in Europe 'optimal nutrition rather than adequate nutrition is the greater problem'. It aims to 'define individual response to nutrients and refine the requirements for population subgroups' including people with diseases such as diabetes

but also healthy 'at risk' individuals based on genetic variations ('nutrigenetics'). The aim of its activities as a whole is
'to strengthen the competitive arm of the European food industry, facilitating its growth as a knowledge-based business, targeted at evidence-based healthier food production as well as promoting understanding in the ethical, social legal, economical and scientific issues of concern, for consumers and scientists alike, in defining, creating and choosing diets for optimal health'.[232]

NuGO held a major conference 'From Nutrigenomics to Personalised Nutrition' in November 2005.

Box 5.2. UK Biobank

UK Biobank aims to collect DNA samples from 500,000 volunteers between the ages of 45 and 69. The genetic data will be linked with lifestyle information taken from an initial questionnaire and information about subsequent sickness, medication and causes of death taken from the volunteers' medical records. Recruitment is expected to take around five years, beginning in 2006, and total allocated funding is now £61.5 million. However, the project has been extremely controversial among scientists[233] and has been criticised for being a 'politically driven project' by the House of Commons Science and Technology Committee.[234]

One of the main concerns is that the biobank will not be able to quantify the gene-environment interactions it is supposed to detect and will give spurious and misleading results.[235] Other concerns include whether this approach is good for health; how privacy will be protected; and the role of commercial interests (including gene patenting).[236,237,238]

5.2 The role of the food, pharma and biotech industries in nutrigenomics

'We are moving from an agrifood business to an R&D-driven nutrition, health and wellness company.'

Luis Cantarell, head of nutrition division, Nestlé, 2003[239]

'We are now beginning to understand how food is not just the cultural spine of our society, or merely a source of nutrients, but can also be a positive influence on our health, or even a prophylactic treatment for disease. With this understanding comes the challenge for FFWB [Future Foods for Wellbeing], *to achieve increased public awareness that a healthy diet for the 21st century can include specific foods appropriate for an individual's lifestage, health status and genotype.'*

Future Foods for Wellbeing: An expert panel's view of the next 25 years. IGD, 2003[240]

'As it becomes possible to assess an individual's genetic susceptibility to disease, it will become possible to create special foods and medical treatments uniquely tailored to help manage that susceptibility.'

The European Food Information Council (EUFIC), 2003[241]

To the food industry, nutrigenomics provides an opportunity to design new products, attempt new 'personalised' marketing strategies (based on genetic test results) and to claim that it is responding to public concern about the growing epidemic of diet-related disease. The aim is to 'prevent disease and improve quality of life through functional foods and tailored diets'.[242] However, the business model relies on 'patent protected, value-added products' commanding a premium price.[243] Future marketing is expected to operate via customised communication directed towards individuals (for example, using direct or internet marketing or home delivery).

A wide range of companies is expected to play a role in personalised nutrition, as a means of adding value to the food supply chain (Table 8).

Table 8. Personalised medicine and the food industry supply chain[244]

Company type	Example companies	Role in personalised nutrition
Biotech/genetic testing companies	Sciona/Cellf IL Genetics/Alticor	Gene-based testing of consumers.
Processed food and supplement companies	Kraft General Mills Nestlé Danone Wyeth Shaklee	Product formulation, testing and manufacturing.
Value-added food and feed ingredients companies	DeGussa/Galapagos DSM/Roche Danisco/Wellgen Kemin BASF	Production of biotech-derived oils, nutrients, phytochemicals and other functional food ingredients.
Primary processors	ADM Cargill Fonterra Campina Tyson Foods Bunge	Processing to concentrate or extract desirable food components.
Agricultural biotechnology companies	DuPont Cargill/Metamorphix Syngenta BASF Dow Agro Sciences	Genomics and genetics applied to crops and meat-producing animals to increase components with human health value.

Most genetic testing companies are small and have yet to make a profit. Some receive income from alliances with other companies, or venture capital funding from the food industry. Companies currently involved in nutrigenomics are shown in Table 9. Some are already marketing genetic tests, often combined with supplements, but others are still at the research and development stage. Many other genetic testing companies exist and may also decide to do this type of testing in the future.

Table 9. Genetic testing companies directly involved in nutrigenomics

Company	Products	Marketing & future plans
Alpha-genics (USA)[245]	'JeneJuice' is a 'sports and performance beverage blended to match your genetic make-up' (to be launched in 2006). Vending machines will mix the drink on the spot based on the person's genetic profile and activity.	The company plans to track and evaluate up to 1 million people in real time, combining gene expression data with data about diet and health.
Genecare (South Africa)[246]	For heart disease, tests 12 gene variants in 10 genes in a single 'nutrigenomics assay'. Includes: lipid metabolism; folate and homocysteine metabolism; iron homeostasis; thrombosis; hypertension and inflammation. For cancer, the NutriGene test includes:	Has trained more than 400 dieticians in South Africa to implement diet and lifestyle information based in part on genetic test results.

	detoxification; dietary folate uptake; oxidative stress; oestrogen exposure.	
GeneLex (USA)[247]	The company's nutritional genetic test includes 19 genes for heart health, bone health, B vitamin, detoxification, antioxidants, inflammation and insulin sensitivity. Costs US$395, or $525 with in-depth nutritionist's view of results, or $645 with a DNA diet consultation.	Via the internet. Many other types of genetic tests also sold.
GeneLink (USA)[248]	Sells a 'Nutrigenetic Profile' for oxidative stress, circulatory and heart health, bone health, immune function and the ability to combat environmental toxins.	Markets via partner companies direct to consumers.
Genova Diagnostics (USA)[249]	Sells 'Osteo', 'Cardio', 'Detoxi', 'Immuno' and 'Neuro' genomic profiles.	Markets mainly via alternative health practitioners and supplements' distributors. See also Box 5.3.
IL Genetics (USA)[250]	Currently marketing a test for genetic susceptibility to gum disease via dentists (IL-1 gene). This is not a nutritional genetic test, but has been criticised by scientists.[251]	Research focus on inflammation, including in: heart disease, osteoporosis, rheumatoid arthritis and Alzheimer disease. Also weight management. IL Genetics has a strategic alliance with the direct-marketing company Alticor (USA) to develop and market novel nutritional and skincare products.
Integragen (France)[252]	Currently offers tests for a rare inherited form of type 2 diabetes (MODY), but plans to market susceptibility tests in future.	The MODY test is a valid test currently used by genetic health services. Future marketing strategies unclear, but is involved in the DiOGenes research project (Table 7).
Nutrigenetics[253]	Plans to market a nutrigenetics SNP test.	
Nutragenomics[254]	Not yet marketing tests but involved in R&D.	Its management team is active in promoting the idea of personalised nutrition.[255,256,257,258,259,260,261,262]
Progenika (Spain)[263]	Developed 'Lipochip' for the pharmaceutical company Lacer, to diagnose the inherited condition familial hypercholesterolaemia (see Section 6.2.4.1).	Is seeking partners in the pharmaceutical industry to market its 'IBD chip', which tests 42 genes linked with inflammatory bowel diease.[264]
Sciona (USA)[265]	'Cellf' test kits include: heart health (12 genes); bone health (4 genes); insulin resistance (5 genes); antioxidant and detoxification (5 genes); inflammation health (6 genes). Each kit costs US$126.	Marketed in four retailers (pharmacies) in the USA. Claims to have sold over 10,000 tests prior to launching Cellf in August 2005. See also Box 5.3.
TLC International (South Africa)[266]	The 'TLC-DNA Program' includes susceptibility tests for heart disease and cancer, together with dietary and lifestyle advice.	Via its 'International Lifestyle Clinics' and its website. Claims to be operating in over 100 countries.

Most of the companies in Table 9 have their headquarters in the USA. However, at least two companies have marketed genetic tests in the UK (Box 5.3).

Box 5.3. Marketing nutrigenetic tests in the UK: Sciona and Genova Diagnostics

The UK company Sciona was forced to withdraw genetic tests combined with dietary advice from the Body Shop in 2001, following criticism from leading scientists.[267,268,269,270,271,272] It has now relocated to the USA and has obtained new investment from the major food ingredients companies DSM and BASF (Box 5.6) and relaunched its product as the Cellf genetic test kits. The US company Genova Diagnostics (formerly Great Smokies Diagnostics Laboratories) was also criticised for its 'Genovations' tests,[273,274] which claim to identify genetic susceptibility to heart disease, osteoporosis, immune disorders and some cancers. It continues to market in the UK via individual complementary health practitioners, together with recommendations for supplements and medicines.[275,276,277]

Although currently small and unprofitable, biotech companies like these are seen by governments as a key part of the 'knowledge-based' economy and therefore have considerable political support (Section 5.3). However, other, much larger companies have much more power to decide how nutrigenomics develops. Boxes 5.4, 5.5 and 5.6 contain examples of investment and research in nutrigenomics by the food industry's research institute ILSI, by the major food manufacturers, and by chemical companies making food ingredients and supplements.

Box 5.4. Nutrigenomics investment and research by ILSI

The food industry's research group, the International Life Sciences Institute (ILSI, see Box 3.8) is heavily involved in nutrigenomics research. For example, ILSI Japan coordinates a nutrigenomics research group at the University of Tokyo – 27 companies are involved (including Meiji Seika, Nisshin Floor Milling, Morinaga Diary, Kao, Taiyo Chemical and Coca Cola).[278] ILSI South East Asia's '1st International Conference on Nutrigenomics – Opportunities in Asia' will be held in Singapore in December 2005.[279]

Box 5.5. Examples of investment and research by food manufacturers

Nestlé

Nestlé held an International Nutrition Symposium in 2004 on personalised nutrition.[280] Its research on individual genetic differences is linked with plans to develop molecules and ingredients 'to target body fat, muscle growth, cholesterol metabolism, gut comfort, energy expenditure and calcium metabolism'.[281] The Nestlé Research Center has published numerous scientific review papers on nutrigenomics in collaboration with the University of California Davis and the US biotech company Lipomics Technologies, Inc. These scientists see nutrigenomics as enabling 'the choice of foods to maintain optimal metabolism' and the 'characterisation of individual responsiveness to dietary manipulation'.[282] They argue that individual genetic differences will be able to predict dietary response in only some cases and that measuring the whole metabolic response will be important.[198,283] In particular they advocate a 'complementary approach' which envisions that healthy 'patients' are genotyped early in life to define their metabolic baseline and then reassessed throughout their lifetime to assess their current health status.[284] They argue that 'personalised assessment will be necessary' to identify optimal diets and that recent health problems are 'the result of dietary imbalances and the inability to control metabolism accurately within a range of lifestyles'.[285] Ultimately they wish to design a diet that improves ('optimises') health in healthy individuals by recommending additional nutrient intakes on an individual basis.[286]

Unilever

Unilever is also investing in nutrigenomics research. However, researchers at Unilever argue that genetic tests for conditions such as type 2 diabetes are many years away from the doctor's surgery and that it remains to be seen to what extent genotyping for individual needs will guide healthy food selections.

Kraft
In response to concerns about obesity, Kraft has set up a 'Worldwide Health and Wellness Advisory Council', which includes a number of nutrigenomics researchers. A document from 1993 highlights Kraft's interest in three areas: antioxidants and their influence on cancer and cardiovascular disease; nutritional influences on improved immune function; and nutritional influences on maintenance of cognition with ageing.[289]

Cargill
In December 2002, Cargill announced it would expand its venture capital investments to include emerging technology companies developing new food applications. One area it plans to target is nutrigenomics and 'foods addressing obesity, diabetes, heart health and diagnostic tools for home use'.[290,291] It already invests in a genomics research company and a number of companies developing 'nutraceuticals'.[292] Cargill's Food Technology Development Center has invested US$10 million in a new biotechnology centre at the University of Minnesota and more than $1 million for a professor to work on the interface between genomics, nutrition and health.[293]

Box 5.6. Examples of investment and research by chemical companies

BASF
The world's largest chemical company BASF (Germany) is a major supplier of vitamins, enzymes and amino acids to the food industry. It undertakes research in biotechnology, nanotechnology and GM crops and foods. BASF Venture Capital has invested US$1.1 million in the controversial company Sciona, which sells genetic tests linked with nutritional advice (see Box 5.3).[294] BASF Venture Capital also invests in companies such as Advanced BioNutrition, which is developing functional foods 'to prevent disease'.[295] BASF is already adopting an approach to personalised nutrition, which would include a role in genetic testing, ingredient production, formulation and sales and new business models.[296,297] It is currently developing a vending machine, jointly with the dairy product company Fonterra, to sell milk-based drinks that have been 'personalised' by the addition of specific health ingredients targeted at particular groups of people. As part of its approach to personalised nutrition, BASF Plant Science is developing genetically modified plants with enhanced omega-3 fatty acids.

DSM
DSM (the Netherlands) is a chemical company with a major interest in food industry ingredients and supplements (it bought Roche Vitamins in 2003).[298] DSM's 'recent Life Science Products innovations' include a strain of probiotic bacteria, a green tea extract, a fatty acid it claims is of great importance to the well-being of infants and unborn children, and a sports drink.[299] DSM Venturing is also an investor in the genetic testing company Sciona (Box 5.3).[300] DSM states that Sciona's genetic tests 'open up the opportunity for product manufacturers to personalize their product offerings', including using the concept of personalised nutrition to sell its products.

Other companies have invested in the technologies used to identify genes or gene expression, or in the computer systems needed to analyse the data. These include companies selling gene testing technologies (such as gene chips) and computer companies such as IBM. Companies investing in metabolomics (Box 4.2) – potentially for drug discovery as well as nutrigenomics – include Beyond Genomics Inc., Lipomics Technologies Inc., Paradigm Genetics Inc., Penome Discoveries Inc., SurroMed Inc. and Syngenta International AG.[284]

Most pharmaceutical companies have not shown an interest in developing functional foods, because the profit margins on drugs are much larger. However, two pharmaceutical companies (Abbott

Laboratories and Bristol-Myers Squibb) are involved in functional foods, others are interested in using the same marketing strategy ('personalised' or 'predictive' medicine) to sell more medication to healthy people (Section 3.6), and some also manufacture supplements (Section 3.3).

Although genetically modified foods are not a necessary part of personalised nutrition, the development of genetically engineered foods that 'consumers truly believe will benefit themselves' is seen by food industry consultants as another important step in 'eroding resistance to genetically modified organisms' (GMOs).[244] Agricultural biotech companies such as Syngenta and Monsanto may therefore also play an important role in the development of personalised nutrition.

5.3 The role of governments

> *'Over the next decade … it should be possible to identify more genetic factors that increase the likelihood of people developing a given disease. There will then be the option to test people for a predisposition to that disease, or a higher-than-normal risk. Preventive and monitoring services could then be tailored to an individual's needs.*
>
> *Following on from this, the way external factors and genes interact to cause disease or protect us from disease will be better understood. This information will allow people with certain genetic profiles to avoid foods, chemicals or environmental factors, such as smoking, which are particularly risky for them.'*
>
> The UK Department of Health, 2003[301]

> '…*while the first generation of genetically modified food products were designed to increase crop yields, the next generation of genetic modification might be aimed at making these foods healthier in a person's diet. Foods might even be designed with the specific genetic profiles of different categories of people in mind. People particularly susceptible to cholesterol might choose to buy avocados grown to be low in saturated fats.*'
>
> Mark McClellan, FDA Commissioner, 2003[1]

Governments see genetics and genomics as a key part of the knowledge-based economy. This makes them reluctant to regulate genetic tests (Section 9.3.1) and keen to support small biotech companies and genetic research.

In the UK, Prime Minister Tony Blair has cited genetic 'prediction and prevention' as a key part of future scientific developments.[302] The Government's 2003 White Paper on genetics (cited above) endorsed the idea of testing people for individual predisposition to disease and the planned role of the UK Biobank (Box 5.2) in quantifying gene-environment interactions. No assessment of the science, health or social implications was made in developing this policy. Nor has there been any public consultation or debate on why this vision of personalised medicine (including personalised nutrition) has been adopted.

In addition to the Medical Research Council's (MRC) support for UK Biobank, the Department of the Environment, Food and Rural Affairs' (DEFRA) Sustainable Farming and Food Research Priorities Group has identified the need to prioritise the knowledge base for nutrigenomics.[303] The Biotechnology and Biological Science Research Council's (BBSRC) agri-food research programme also has a priority theme on 'genotypic variation and response to diet' and a focus on genomics in its diet and health programme.[304] These priorities are likely to have been influenced by the Government's emphasis on science being 'wealth generating' and by commercial interest in nutrigenomics, rather than an assessment or debate about whether this is the best strategy for health.

5.4 Summary

The food industry is investing heavily in nutrigenomic research, with a view to selling new value-added products, as part of a new marketing strategy called personalised nutrition. Many small genetic testing companies are already marketing genetic tests together with supplements or dietary advice. The major food ingredients companies BASF and DSM are investing in the genetic testing company Sciona, which has been widely criticised for misleading customers, and which was forced to withdraw its genetic tests from the Body Shop in 2001.

There are many major national and international research projects involving the food industry and university scientists. This research is backed by governments as part of their desire to see growth in the knowledge-based economy. However, there has been little public discussion and no independent assessment of the implications of nutrigenomics or personalised nutrition for health. The effectiveness of this approach depends both on the science, considered in Section 6 below, but also on what tests and products are likely to be marketed, and their regulation (discussed in Section 9).

6. Role of genes in diet-related disease

This section examines the evidence for the role genes play in diet-related disease. It begins with an outline of the types of evidence used to try to identify and quantify the role of genes in diseases. It then examines the evidence for the role of genetic differences in common diet-related diseases. It looks in particular at whether it is possible to decide who is at 'high genetic risk' of common diseases and, if so, whether this is a useful way to decide who should eat different diets, foods or food ingredients. This section assumes that people will have access to genetic tests and genetically tailored products and advice. The main question asked is whether the approach of tailoring diets to an individual's genes is likely to make a major impact on the incidence of obesity and chronic diseases.

6.1 Types of evidence

Many different types of evidence are relevant to deciding whether or not nutrigenomics is likely to play a major role in reducing the incidence of common diet-related diseases.

Genetic association studies are the statistical studies which try to quantify the risk of developing a disease in people with a particular gene. These studies are notoriously unreliable.[305] A 2002 review found that over 600 positive associations between common gene variants and disease had been published, but only six had been consistently replicated (one in 100 of the original studies).[306]

Because genetic association studies typically give many conflicting results, it is necessary to combine the results of many studies in a **meta-analysis**. A 2001 paper found that the first study often suggests a stronger genetic effect than subsequent studies, suggesting that early 'discoveries' need to be treated with particular caution.[307] A 2003 study, which examined the results of 55 meta-analyses of genes linked to common, complex diseases, found that only 16% of genetic associations included (nine links between genes and common diseases) were subsequently replicated with formal statistical significance, without heterogeneity (variability) or bias.[308]

Another type of study, called a **genetic linkage** study[309] has also played a role in the genetics of nutrition (such as lactose intolerance and coeliac disease).[310] However, when the genetic effect is small, genetic association studies are more common.

Measuring diet, exercise and other environmental factors is also notoriously difficult.[311] Misreporting is a major problem, with people typically claiming to eat more healthily than they actually do. This does not necessarily mean that people are lying: people are often unaware of how much they eat, particularly between meals, or they may change what they eat as a result of being studied. However, this problem can cause serious errors, particularly because overweight people tend to under-report most, which can lead to false conclusions being drawn (see also Section 6.2.1).[312]

Even laboratory experiments introduce errors and uncertainties in measuring diet.[313] Laboratory experiments can also be misleading because other more important factors (such as the amount of exercise that people get) are artificially controlled during the experiment.

Gene-diet interactions are highly complex and difficult to quantify.[314] At the population level, the statistical definition of gene-environment interaction is 'a different effect of environmental exposure on disease risk in persons with different genotypes'. The main problem is the number of choices that researchers have about which genetic and environmental factors to include and how to combine them. This gives rise to a statistical problem called 'multiple testing'. 'Fishing expeditions' for either genetic or environmental factors in disease usually give spurious results because scientists can adjust their hypothesis to fit the data they have found. This can be likened to drawing a target round a bullet hole, rather than shooting at a target – it does not demonstrate that the hypothesis is valid. In effect, the multiple testing problem means that scientists can always add in new genetic or environmental factors to explain their results, but these explanations may be entirely false. Some researchers have argued that there are so many different ways of combining all these factors that, although it is possible to identify genetic factors in common diseases, it is impossible to quantify their effects on risk.[315] Dealing with statistical confounders (other factors that might explain a statistical association) in studies of gene-environment interaction is also much more difficult. This is because statisticians cannot simply subtract out the known effects of factors such as smoking if more than one gene and one environmental factor is involved.[316]

Twin studies are often used to claim that genetic factors are important in determining a given disease or behaviour. They are based on the fact that identical (monozygotic) twins share all their genes, but non-identical (dizygotic) twins share only half their genes. The likelihood of both identical twins in a pair getting the same disease (called 'concordance') is often higher than the likelihood of both non-identical twins in a pair getting the disease. In the 'classical twin study' this information is used to calculate a number called heritability, which is supposed to be a measure of whether differences in a trait (such as height) between individuals in a given population, are largely due to differences in their genes or in their environment. However, twin studies are also one of the most widely criticised types of study. Although errors in the data can certainly be important, the main criticisms of twin studies are about how the data are analysed and interpreted (Box 6.1).[317]

The fact that heritability calculated from twin studies can often exaggerate the importance of genetic differences is important because twin studies are often cited as a reason why it is important to tailor dietary advice to people's genes.[318] Heritability is also often wrongly interpreted – high values do not mean that environmental factors are unimportant.[319] This is true even when heritability accurately reflects the importance of genetic differences (compared to environmental differences) in explaining differences between individuals in a population. For example, the heritability of lung cancer would probably be high in a population where everybody smoked, because *differences* in how much people smoked would not be important in determining who got the disease. But if everyone stopped smoking, the incidence of lung cancer would fall dramatically. Finally, estimates of heritability on their own tell us nothing about the importance, or unimportance, of gene-environment (or gene-diet) interactions because these are assumed to be zero when it is calculated (Box 6.1).

Box 6.1. 'Heritability' depends on questionable assumptions[320]

In order to calculate heritability from twin data, scientists make various assumptions about how genes and the environment affect a person's risk or likelihood of having a particular trait (for example, being obese). These assumptions include:[321]

- there are no gene-environment interactions;
- there are no gene-gene interactions;
- identical and non-identical twins share the relevant environmental factors to the same extent (for example, identical twins are assumed to be no more likely than non-identical twins to eat the same diet as their twin).

Some or all of these assumptions are likely to be false for most diet-related diseases.[322,323] One of many possible concerns is that the intrauterine environment (the environment in the womb) may be more similar for identical twins, as they are more likely than non-identical twins to share the same supply of blood and nutrients from the placenta. This would break the third assumption listed and may be important if early nutrition plays a role in 'programming' adult chronic disease (see the 'thrifty phenotype hypothesis', Section 6.2.1).

If any one of these three assumptions is incorrect, the calculated heritability will at best be an *overestimate* of the importance of genetic differences. In some situations it will be entirely meaningless (for example, a high heritability can occur even in the complete absence of genetic factors).[324] The same is true for all measures of how diseases run in families ('familial aggregation') – they can be significant even in the complete absence of any genetic component of the disease, because families also share their environments and dietary habits.[325]

Some diet-related diseases are more common in some **ethnic groups** than others. If known differences in diet and their effect on health have been accounted for, the remaining differences could be due to different genes in different populations. However, there are many other possible explanations, including other unknown dietary factors, or other socio-economic or environmental effects that are not understood or have not been measured. Whether genetic differences explain different rates of disease in different populations is therefore largely unknown.[326,327]

A relatively new technique called **admixture mapping** is being developed to try to identify genes that may increase the risk of different diseases in different populations.[328,329] The idea is to try to calculate the proportion of an individual's ancestry that has come from different populations (for example, in Native American populations, some individuals will have more Native American ancestry than others) and to see if this measure of admixture (calculated using genetic differences) is correlated with people's risk of disease. However, if admixture is also correlated with unmeasured environmental, social, cultural or behavioural factors, a genetic interpretation of this correlation will still be unreliable.[330]

People's **psychological responses** to genetic test results are also important, because even if a test genuinely identifies people who have most to gain by changing diets, it might not motivate them to do so.[331] It is possible that people identified as at higher risk could become fatalistic and less likely to change their diets as a result of a genetic test and/or that people identified as at lower risk become complacent and are falsely reassured that they do not need to eat a healthy diet. In either of these situations, genetic testing could actually *increase* the number of cases of disease in the population tested, or it could make testing ineffective or not cost-effective compared to other approaches.[332]

Despite the importance of people's psychological responses to genetic testing, there have been relatively few studies. People's responses are likely be complex and vary between individuals[333] and simplistic assumptions may be wrong.[334]

6.2 Genes and diet-related diseases

> *'The time is approaching when it will be possible to use genetic testing to screen for the risk of various diseases and to determine an individual's ideal health promoting diet'.*
>
> The European Food Information Council (EUFIC), 2003[241]

This section reviews the evidence for claims like these, made by the food and drinks industry body EUFIC. It focuses on genetic association studies (the statistical studies linking genes to different diseases) and studies of gene-diet interactions. Can an individual's risk of common diet-related diseases such as heart disease and diabetes be predicted from their genes, and is this likely to be possible in future? Is this type of testing useful to decide an individual's diet?

6.2.1 Obesity

Many geneticists have suggested that obesity prevention might one day be targeted at genetically susceptible individuals.[335,336,337,338] However, it is questionable whether a minority of people are susceptible to obesity, due to their genetic make-up, and whether targeting dietary advice, or special foods and medicines, at this group of people will help reduce the current epidemic of obesity. This section explores whether some people are genetically susceptible to obesity and, conversely, whether some people can eat whatever they like, without getting fat or becoming unhealthy. It asks whether obesity can be predicted from a person's genes and explores the scientific basis for genetically targeted prevention.

People are considered overweight or obese when their body weight is higher than is considered healthy for their height – the most common scientific measure of this is called body mass index or BMI (see Box 6.2).

In general, obesity is caused by an imbalance in energy intake and expenditure. In other words, eating too much (too many calories) and exercising too little (not burning enough calories) leads to an increase in body weight, because the extra energy is stored as body fat.[339] This 'energy gap' (the difference between calories consumed and calories burnt up) is increasing in many populations throughout the world, and only a small imbalance can lead to weight gain.[340,341,342]

Although weight gain is usually caused by eating too much food and exercising too little, this effect is complicated by the different effects of changing the amounts of different types of foods (such as fats, sugars, carbohydrates, fibre and proteins) in a person's diet, and by the protective effect of different types of exercise. Most of these effects are not fully understood.[189] However, the ready availability of energy-dense foods (such as chips, chocolate and doughnuts, fast foods and fizzy drinks[343] which provide more calories in the same quantity of food) appears to make overeating more likely.[93,186,344] In contrast, foods which contain more water and fewer calories, such as vegetables and fruit, help people to feel full while eating fewer calories.

Box 6.2. Measuring obesity[345,346,11]

The simplest way to measure obesity is by calculating body mass index (BMI). This is calculated by dividing a person's weight in kilograms by the square of their height in metres. It measures body mass (how heavy a person is for their size). Adults with a BMI over 30kg/m^2 are considered clinically **obese**. Nearly one-third of the adult population in the USA is now obese, and obesity in women in some countries such as Egypt and South Africa is nearly as common as in the USA.

Adults with a BMI over 25kg/m^2, but less than 30kg/m^2, are considered **overweight**. A further one-third of the US adult population is overweight, as is a similar percentage of the population of most industrialised and many middle-income countries.

Although BMI is a quick and easy way to measure obesity, it has some limitations.[347,348,349] For example, some athletes have high BMI because of very dense muscle tissue and being fit may also protect some overweight people from bad health. Waist-to-hip ratio may be a much better measure of heart attack risk than BMI[350] because fat around the waist (called **central obesity**) appears to be more harmful to health than fat around the hips. In addition, being underweight (BMI<18.5) also carries serious health risks and the dangers of eating disorders such as anorexia should not be ignored.

Being overweight is not a disease in itself, and some people who are classified as overweight may be much fitter than others (Box 6.2). However, overeating and being overweight is considered a major health problem because it increases the risk of a wide range of chronic diseases such as stroke, heart disease, type 2 diabetes and some cancers. The direct effects of excess weight on muscles and bones can also increase the likelihood of a range of health problems such as back pain, hernias, arthritis and breathing problems. The incidence of obesity and associated chronic disease is rising rapidly (see Box 3.2) and childhood obesity is becoming a major problem, particularly in the USA, the UK and southern Europe.[11] In England in 2003, more than one in four children were overweight or obese.[355] Between 50% and 85% of obese children stay obese in adulthood and the risk of adult disease may remain high even in those who manage to lose weight. Obesity may also sometimes lead to psychiatric problems for women[352] and children[351,352,353] (including poor self-image and depression).

The major worldwide increase in obesity and being overweight cannot be due to an increase in 'genes for obesity' because changes in the frequency of different genes in a population happen only very slowly. Its causes are the major changes in diets and levels of physical activity described in Box 3.2. However, there are different theories about why some people put on more weight than others (Box 6.3).

Box 6.3. Why do some people put on more weight than others?

In reality, all these factors will be involved to some extent and interact in complex ways.[354] However, researchers have different views about their relative importance.

- **Biological differences** The amount of body fat a person has is controlled by biological functions that regulate appetite (energy intake) and metabolism (energy use). This system helps to keep us alive by making us feel hungry when we don't eat. But it seems less effective at preventing us becoming overweight. Small imbalances in this 'homeostatic system' can lead to increases or decreases in weight, so genetic differences in either appetite or metabolism, or both, could lead to some people putting on more weight than others.[340]

- **Social and economic factors** These can include lack of access to healthy foods in some disadvantaged areas ('food deserts'); cultural differences in diets; the costs and availability of different types of foods;[31] the types of employment and leisure activities available to different socio-economic groups; the content of school meals and how foods are produced and marketed (the politics of food).[64] Socio-economic factors may also affect health directly, as well as influencing diets and physical activity (Box 3.6).

- **Individual choices** Some people may choose to eat more food, or different types of foods, than others, or to exercise less, for reasons that may have nothing to do with biological differences. If people's choices are not completely determined by a combination of their biology and their environment (including social and economic factors) this will limit our ability to predict who is likely to become obese or overweight.

There is evidence that social and economic factors do play a role in obesity. In most middle-income economies the poorest people (groups with lower socio-economic status) are at the *highest* risk of obesity. This includes countries such as Mexico, Brazil, Turkey and South Africa.[11] In high-income countries, such as the UK and the USA, obesity is also associated with low socio-economic status. In England in 2003, children living in households with the lowest incomes had higher rates of obesity than those from households with the highest incomes (15.8% versus 13.3%). Levels of obesity were 5% higher among children from the most deprived areas (16.4%) compared with children from the least deprived (11.2%) and children living in inner city areas were particularly prone to obesity. However, there is some evidence that the relationship between poverty and obesity is complex and changing, at least in the USA, with more rapid increases in weight now occurring at higher levels of income.[356] The same study also found that there are differences in how poverty affects obesity rates in different ethnic groups and between men and women.

If tailoring diets to genetic make-up is a useful way to reduce the incidence of obesity, genetic differences must be important in influencing who becomes overweight, and interactions between genes and diet must also be important – so that some people have more to gain than others by adopting a particular diet (Section 4.2.1). What is the evidence that genetic differences are important in determining which individuals become overweight or obese in countries where there is plenty of food?[340,357]

Evidence from twin studies and ethnic differences

The results of studies in families and twins are often used to argue that genetic differences must play a major role.[358,359,360,361,362,363,364,365] However, high heritability measured by twin studies tells us very little about the importance of genetic factors, and nothing about gene-diet interactions (Section 6.1). Family studies are also difficult to interpret because diseases can run in families because of shared diets and socio-economic factors, not just shared genes.[366,367,368] For example, people who are overweight tend to have overweight pets as well as overweight children, even though they don't share any genes with their pets.[369]

Another reason often given for believing that genetic differences are important is the simple observation that not everybody living in countries with plenty of food (such as the USA) becomes obese – surely this must mean that some people put on more weight than others because they have different genes? However, this observation could be explained partly by chance; by other factors, including socio-economic factors and the lifestyle choices people make (Box 6.3); or by other biological mechanisms, such as nutrition in the womb or in early childhood. The same is also true of the evidence that some populations, such as Pacific Islanders, African-Americans or the Pima Indian population in the USA are at particularly high risk of becoming obese (Boxes 6.4 and 6.5).

Box 6.4. Obesity in different ethnic groups

The prevalence of obesity differs in different ethnic groups and in theory this could be due to differences in their genetic make-up. For example, in the USA obesity is more common in African-American and Mexican-American women than in Caucasian women. However, disentangling genetic factors from other social, cultural and economic factors is notoriously difficult and is complicated by the fact that different ethnic groups do not consist of genetically distinct races (see Section 9.5).

A particularly high incidence of obesity occurs in some Pacific Island populations and in the Pima Indians of Arizona (see Box 6.6). However, these populations are also characterised by a high dependency on imported foods or food aid, low socio-economic status and a loss of traditional food practices. Native Americans, like indigenous peoples everywhere, are marginalised and suffer substantially poorer health than the general population.[371]

Poor diets in the Marshall Islands have been linked to the high consumption of imported foods, US food aid and fat dumping (the marketing of unwanted high fat animal by-products, such as canned meat, to lower socio-economic status populations); traditional beliefs about body shape, which view fatter people as healthy and attractive; and meals which commonly consist of only two items, omitting vegetables.[372]

A controversial genetic study on another Pacific Island, Kosrae, led by Jeff Friedman of Rockefeller University (the discoverer of leptin, see Box 7.1), aims to find out whether many of the islanders are genetically predisposed to large appetites and obesity-related diseases (in 1994, 88% were obese or overweight). However, local health officials maintain that it is Kosrae's reliance on canned and packaged foods – including spam and turkey tails – provided by a US grant, together with new methods of preparing food (such as frying bananas with sugar) that are the problem. There is also a lack of exercise, linked with increased car use and more sedentary jobs.[373]

Even if genetic differences are part of the explanation for the high incidence of obesity in these populations, it is unclear how this information would help people to change their diets in the context of their disempowerment and dependency on food aid.

If genetic differences are important in determining who becomes obese or overweight, this implies that there are important differences between individuals in the biological system that regulates weight (Box 6.3). These differences could affect appetite (energy intake) or metabolism (energy use).

Evidence from food intake studies

For many years, scientists believed that obese people tended to put on more fat than lean people even when they ate and exercised the same amount. In other words, biological differences in metabolism – perhaps determined by a person's genes – tended to make some people fatter than others. This view led to the 'thrifty gene' hypothesis (Box 6.5). Early research in the Pima Indian population in Arizona supported the idea that genetic differences may be important (Box 6.6). However, the evidence for this idea has been largely undermined by better measurements of people's metabolism (see Box 6.7). This evidence led scientists to realise that fatter people tend to under-report the amounts that they eat when they take part in dietary surveys (in practice obese people tend to omit about one-third of the calories they eat). In other words, it isn't true that some people can eat what they like while others put on lots of weight without eating very much. It is now known that an individual's level of physical activity is the most important factor in how much energy they use up.[346]

The difficulties with dietary surveys are so great (Section 6.1) that there is still no direct evidence of a correlation between obesity and food consumption in developed nations,[346] with the exception of one recent experimental study in a group of Pima Indians in Arizona.[374] Even the link between low physical activity and obesity is very difficult to measure and has only recently been directly established.[375,376,377] Instead, the evidence comes from the observed effects of changing diets and lifestyles in developing countries (Box 3.2) and from migration studies. Many such studies have shown that people migrating from countries in Africa, Asia or South America to the USA, Australia and Europe tend to rapidly increase in body mass index as a result of their changed environments. For example, a major US study of 201 million adults found that the longer an immigrant lives in the USA the more likely they are to be obese. The study found that the prevalence of obesity was 8% among immigrants living in the USA for less than one year but 19% among those living there for more than 15 years, compared to 22% among US-born individuals.[378]

Box 6.5. The thrifty genotype hypothesis

The thrifty genotype hypothesis was first proposed by Neel in 1962.[379] The theory is that people who stored more fat would have had a survival advantage in the past, because it helped them to live through times of famine. But in today's environment – where food is plentiful in many countries – the same genes (the 'thrifty genotype') would be a disadvantage, because people with these genes would tend to become overweight or obese and to develop type 2 diabetes.[380] This has led to many attempts to try to identify 'obesity genes' in Native American and Pacific Island peoples. However, other social and/or biological factors could explain why obesity is more common in these populations, and the genetic differences that would confirm the thrifty gene hypothesis have not been found (see Boxes 6.6 and 6.8).

Box 6.6. Obesity in the Pima Indians

The Pima Indians of Arizona are a Native American population who have been studied for more than 40 years by the US National Institutes of Health (NIH). A study by NIH researchers in 1988 claimed to show that low resting metabolism predicted weight gain in this population, and that low metabolism clustered in families.[381,382] This study was widely taken to support the 'thrifty gene' hypothesis (Box 6.5). However, this experiment has now been contradicted by other studies in a different group of Pima Indians who live in Mexico.[383,384,385] The Pima Indians in Mexico are not obese because they expend significantly more energy in physical activity and have healthier diets.[386]

Although the children of obese parents in the Pima Indian population of Arizona are more likely to be obese themselves, it remains unknown whether this effect is due to shared genes or shared environmental effects (including diet and exercise). [374,387,388]

A different type of study has found that those Pima Indians with lower BMI and without diabetes have more European ancestry (measured by the frequency of different genes), suggesting that obesity and diabetes in the Pima Indians is due to genetic factors.[389] This technique has also been used to draw similar conclusions about obesity in a (much smaller) study of African-American women.[390] However alternative explanations for these findings are also possible, including cultural or other factors.

Box 6.7. Obesity and metabolic differences[391]

For most of the 20th century, many scientists believed that obese people had bodies which needed less energy than non-obese people. Several dietary studies found that people with higher body mass index (BMI) ate *less* than leaner people. This suggested there were differences in how much energy different people's bodies burnt up (called 'thermogenesis') even when they were resting. A type of body tissue – called 'brown adipose tissue' (BAT) or brown fat – was also found which converts energy (especially fat from the diet) into heat, without storing it as body fat. Mutations in a gene called ADRB3, which affects brown fat, were also linked with obesity. All this evidence supported the idea that biological differences exist that make some people more likely to store body fat and others more likely to burn it up, even when they don't exercise.

However, beginning in the 1980s, better techniques were developed to measure how much energy people used when they were resting. This new evidence did not support the idea that obese people burnt up less energy when resting than lean people. It also helped to demonstrate that obese people do eat more energy (calories) than lean people, but they tend to under-report what they eat when they take part in dietary surveys (see Section 6.1). Most studies now agree that differences in metabolism when resting do not explain why some people get fatter than others:[392,393] how much people eat and exercise is probably much more important.

Because the early evidence has not been supported, many researchers no longer consider that the thrifty gene hypothesis is adequate to explain why some people are more likely to become overweight or obese than others. One alternative theory is the 'thrifty phenotype' hypothesis. The idea is that differences in the mother's diet while the baby is in the womb are more important than the baby's genetic make-up in influencing its future risk of obesity and chronic diseases.[394,395,396] However, although there is good evidence that the mother's diet does play a role, scientists do not yet agree on its relative importance.[397,398] The protective effect of infant breast feeding against childhood and adolescent obesity also highlights the importance of early nutrition.[399,400] It may, therefore, be important to consider nutritional factors throughout a person's life, including before and after birth.

Evidence from genetic studies

Another way to study the importance of genetic differences in obesity is to try to find the genes involved and study how important they are in influencing whether people become obese or overweight. About 40 single-gene disorders or chromosomal abnormalities have obesity as one of the symptoms, usually alongside other symptoms such as learning difficulties.[380,402] However, these disorders are very rare.

Perhaps because scientists long overestimated the importance of inherited differences in metabolism, efforts to find genes linked with common obesity have focused on metabolism and particularly on the role of brown adipose tissue (see Box 6.7) in burning up fat, although other studies have also investigated the genes involved in appetite.[401] Overall, more than 600 different genes and regions of DNA have been associated or linked with human obesity.[402,403,404] A total of 358 genetic association studies, involving 113 different genes, had reported significant associations by the end of October 2004. Eighteen genes have been supported by at least five independent association studies. However, because other studies have produced contradictory results, none of these genes has been confirmed to play a significant role in determining body mass index (BMI) in the general population.[413,336] Early excitement about the ADRB3 gene (linked with brown fat, see Box 6.7) has largely turned to disappointment.[405,406,407, 409] Other well studied genes include ADRB2,[408, 409, 410] TNF−α[409] and PPAR-γ.[411,412] At most these genes account for only a very small fraction of the individual variation in BMI. Some other genes, including the leptin receptor gene (LEPR), are discussed in Section 7.1, because they are linked with brain function (appetite) rather than metabolism.

One recent review considered only genes that had been linked to central obesity (a high body mass index, combined with a large waist, see Box 6.2).[413] This study found that none of the 31 genes linked to central obesity were statistically significant when all the evidence was combined (i.e. the link between these genes and central obesity did not meet the usual standards for scientific evidence).

One possible reason that the search for common obesity genes has been unsuccessful is that many different genes are involved, but each has only a small effect.[414] Interactions between different genetic factors may also be important.[415] If so, this causes some fundamental problems for geneticists (see Section 6.1). In addition, differences in individual metabolism are probably much less important than previously thought. Differences in environment – including diets, exercise and socio-economic factors – seem to play a bigger role.[416]

If diets to prevent obesity were to be personalised based on genetic make-up, genetic differences in metabolism must be important *and* there must be significant gene-diet interactions at the population level (Section 4.2.1). This means that the combined effects of genes and diets on obesity must also be known *and* it must be demonstrated that a minority of genetically susceptible people have much *more to gain* by changing diets than most of the population. A strong gene-diet interaction implies that some people are more genetically susceptible to obesity than others, but only if they eat too much – these people can maintain a normal weight provided they are careful about what they eat. It also implies that other people can eat too much without putting on much weight, so it is not so important for these individuals to eat fewer calories. Before using these genetic tests it is obviously important to be sure about the evidence for this, otherwise some people might be falsely reassured that they do not need to eat a healthy diet. In addition, the fact that unhealthy diets can cause many different diseases will limit the benefits of targeting dietary advice at those who are genetically susceptible to obesity (see Section 4.2.1). This is because overeating may increase the risk of illnesses such as type 2 diabetes and heart disease, even in people who do not become overweight.

Some evidence that gene-diet interactions may be important in obesity is provided by experimental studies which involve overfeeding twins, but these studies are very small (involving only 12 pairs of twins).[417,418] By keeping environmental factors fixed (feeding everyone the same diet and giving them the same exercise regime) this type of experiment is bound to emphasise genetic differences. Even so, one genetic variation in the ADRB2 gene accounted for only about 7% of the variance (differences) in weight gain in this study[419] and the effect of other genetic variations was smaller.[420,421,422,423]

Although some other studies have looked at gene-diet interactions in obesity most results are based on small single studies and may not be confirmed.[424] Already, conflicting results have been reported for interactions between weight loss and the ADRB3 and PPARγ2 genes discussed above.[418] The conclusions that can be drawn from this type of study are in any case limited by study size; the many different possible explanations for an observed effect; and by the difficulties in measuring diets accurately (Section 6.1). It is also unclear how these results would be translated into dietary advice, because of the effects of unhealthy diets on different diseases, such as type 2 diabetes and heart disease. Even if some people are not genetically susceptible to putting on weight from eating a poor diet, or find it easier than others to lose weight, this does not mean that they will not suffer other adverse health effects from eating too much fat or sugar (see Section 4.2.1). In addition, only two US studies have examined the potential behavioural consequences of genetic testing for obesity risk and ease of weight loss.[425] One study suggested that some people may be falsely reassured that they do not need to change their diets by a negative genetic test result.[426]

Much research into the genetics of obesity has now shifted emphasis to look at genes that might influence behaviour, i.e. how much people eat, which foods they eat, and how much they exercise. Instead of genetic differences influencing metabolism, it is possible they might affect how much a person eats (their appetite) and perhaps how much they exercise. Rather than implying that some people are more genetically susceptible to obesity than others when they eat the same foods, this research is part of 'behavioural genetics': it assumes that some people are more likely to eat unhealthy foods than others, because their genes affect the food and lifestyle choices that they make. Because its implications for health are very different, this type of research and its implications are discussed separately in Section 7.1.

6.2.2 The metabolic syndrome (Syndrome X)

Another response to the lack of success in identifying genetic factors in common obesity is to study not obesity itself, but a condition called the 'metabolic syndrome' (also known as 'Syndrome X' or 'insulin resistance syndrome' (IRS)). Definitions of the metabolic syndrome vary, but they include the glucose intolerance and insulin resistance associated with increased risk of type 2 diabetes (see Section 6.2.3) and the cholesterol levels and high blood pressure associated with increased risk of heart disease (see Section 6.2.4), combined with central obesity (a high body mass index, with a large waist).[427] A new definition has recently been agreed.[428]

The likelihood of a person having metabolic syndrome increases with age and it may be a more important predictor of ill health than a person's body mass index. However, one study has found that combining risk factors into the metabolic syndrome is less useful than existing established methods of assessing a person's risk of type 2 diabetes and heart disease separately.[429]

Because studies of the metabolic syndrome as a group of risk factors began relatively recently, there are relatively few twin and family data and no scientific agreement on the importance of genetic compared to environmental factors.[430,431,432] Twin studies in any case remain limited by the assumptions made (they use the classical twin model).[433] Multiple genes (including, but not limited to, genes that have previously been linked to obesity, diabetes and hypertension) are under investigation.[434]

Although changes in diet and exercise may be the most effective treatment, the metabolic syndrome also provides a potentially massive market for 'pre-symptomatic' (preventive) drugs (see Section 3.6).[435,436,437] Market size is estimated at US$30 billion.[438] A major international project, called GEMS (Genetic Epidemiology of the Metabolic Syndrome), is now being funded by the pharmaceutical company GlaxoSmithKline to explore the 'genetic basis of the metabolic syndrome'.[439] This type of study does not measure dietary factors and shifts the emphasis from tackling socio-economic factors to developing new drugs. Researchers are also investigating the effects of plant extracts on the metabolic syndrome[440] and a possible new application could be the development of new functional foods.

In the meantime, there has been more research into the genetics of individual chronic diseases associated with obesity, such as type 2 diabetes and heart disease. These are discussed below.

6.2.3 Diabetes

Diabetes is a group of disorders that result in high blood sugar levels (hyperglycaemia). The body either lacks the ability to make the hormone insulin or does not use it properly. Insulin is needed to make sugars and starches in the blood available to give the body energy.[441] If blood sugar levels become too low or too high they can lead a person to pass out and can be life-threatening. Diabetes also increases the risk of other diseases such as heart disease, blindness, nerve damage and kidney damage.

Type 1 diabetes (sometimes called 'juvenile diabetes' or 'insulin dependent diabetes') is usually diagnosed in children and young adults – in this type of diabetes the body does not produce the insulin it needs. Genetic variations in HLA genes (see Box 6.16) and some other genes influence the risk of developing type 1 diabetes.[442,443] However, most patients do not have these genetic variations, so other factors may also be important. The focus of nutrigenomic research is the much commoner, diet-related, type 2 diabetes, so type 1 diabetes is not considered further here.

Type 2 diabetes (sometimes called 'adult onset diabetes' or 'non-insulin dependent diabetes', NIDDM) accounts for about 90% of diabetes cases globally. In the past two decades there has been an explosive increase in the number of people diagnosed with diabetes worldwide, primarily because of ageing populations, more sedentary lifestyles and increased obesity. The number of adults with diabetes in the world is projected to increase to 300 million by the year 2025: over 75% of these people will be living in developing countries, mainly in urban areas.[445] In addition, although formerly known as 'adult onset diabetes' (usually starting over the age of 45) the condition is beginning to be observed in children.

Type 2 diabetes develops over time as the body gradually stops producing enough insulin (abnormal 'insulin secretion') or the cells in the body stop using it properly (called 'insulin resistance'). Type 2 diabetes is initially treated with lifestyle changes and/or medication. Some people may subsequently start to need insulin injections. The complications associated with untreated or poorly controlled type 2 diabetes (such as blindness, heart attacks, strokes and poor blood supply to the limbs – sometimes leading to the need for amputations) are a major cause of serious ill health worldwide.

Diabetes is diagnosed by testing blood sugar (glucose) levels. People with high levels (measured after fasting – at least eight hours without eating – and also two hours after a glucose drink) have diabetes. People with levels between normal and high are said to have 'impaired glucose tolerance' and be at high risk of developing diabetes in the next five to ten years.[444]

Being overweight is a major risk factor for type 2 diabetes, accounting for perhaps 80-95% of cases.[189] However, the distribution of fat seems more important than body mass index (BMI) – people with central obesity (more fat around the waist) are at higher risk of insulin resistance[446] and waist size is a good predictor of insulin sensitivity.[447] Small-scale attempts to prevent diabetes using lifestyle changes have varied in success, but a large-scale study in China considerably reduced the incidence of type 2 diabetes using a combination of improved diets and physical activity.[448] A US study has also found that lifestyle intervention could reduce the incidence of diabetes by 58% and that this was more effective than preventive medication (using the drug metaformin).[449]

The relationship of type 2 diabetes with socio-economic status is complex, with one study finding that in Denmark (one of Europe's richest countries) children with the most educated and highest earning parents had least insulin resistance, while the opposite was true for children from Estonia and Portugal.[450] A study of over 4,000 British women found that insulin resistance was strongly associated with adverse social circumstances in childhood or adulthood.[451]

Twin studies for type 2 diabetes have given highly variable results, finding between 40% and 100% of identical (monozygotic) twins having type 2 diabetes if their twin does. However, there is good reason to think that the higher values result from bias in the way twins were selected in earlier studies. Heritability for type 2 diabetes appears to be lower than for type 1, but results depend on the assumptions made (Section 6.1).[452] Heritability of blood glucose levels varies between 10% and 72% in different studies, and heritability of insulin levels varies between 8% and 37%,[453] so the role of genetic differences is unclear.

The incidence of diabetes varies significantly between different ethnic groups,[454] with particularly high levels in Pacific Islanders[455] and Native Americans (Boxes 6.4, 6.6 and 6.8). Although some scientists still favour the thrifty genotype hypothesis to explain these differences (Box 6.5), others have concluded that environmental factors play an overwhelming role in influencing the prevalence of diabetes and hypertension in different populations.[456]

An intensive search for genes linked with diabetes in the Pima Indian population of Arizona, has so far failed to reveal any conclusive results (Box 6.8).

Box 6.8. Diabetes in American Indians[457,458,459]

A high prevalence of type 2 diabetes was first noticed by the US National Institutes of Health in the Pima Indian population of Arizona in 1963 (see also Boxes 6.4 and 6.6). Over 60% of adults in this population develop the disease and other American Indian populations are also at high risk. However, although some possible 'candidate genes' (genes that may play a role in the disease) have been identified, none has yet been confirmed to play a major role in this population.

One early study identified a variation in the HLA gene which was thought to nearly triple the risk of type 2 diabetes in Native Americans from the Pima and Papago tribes. However, this has since been shown to be an error.[460,461] Although the search for genes continues,[462] poor foetal nutrition could provide an alternative explanation for the high incidence of diabetes in the Pima Indian population;[463] as could social and economic factors.

A rare inherited form of type 2 diabetes, called Maturity-Onset Diabetes of the Young (MODY) can result from mutations in any one of at least six different genes.[464,465] In addition, mutations in genes in the mitochondria (inherited via the mother's egg) can cause another rare form of diabetes (accounting for about 1% of cases).[466] However, environmental factors (including diet) are important in most cases of diabetes, and most links between common genetic variations and increased risk have proved difficult to confirm. As for obesity, the complexity of gene-gene and gene-environment interactions appears likely to account for this limited success.[467] To date, over 250 genes have been studied for their role in type 2 diabetes and the majority of studies have failed to find any association.[468] A common genetic variation in the KCNJ11 gene appears to slightly increase risk.[409,469] The CAPN10 gene[470] and the IRS-1 gene[471] may also have a small effect but results are very inconsistent. A common genetic variation in the PPAR-γ gene, which slightly *reduces* risk, may affect more cases.[472]

There have been very few studies of gene-diet interactions in diabetes. One study has found a gene-diet interaction between a common variation in the PPAR-γ gene (see also Section 6.2.1) and the ratio of different types of fat in the diet.[473] However, it is unclear whether this small single study really has the statistical power to detect this gene-diet interaction, or whether this finding might have occurred by chance (see Section 6.1). The authors believe that this research is of prime importance in understanding the mechanisms of disease rather than in altering any current public health advice[3], and warn against overly simplistic interpretations of the data, since many different biological factors are likely to be involved.

6.2.4 Heart disease

'Genetic-epidemiological studies of CHD (Coronary Heart Disease) have been dogged by an over-optimism regarding the likely size of the genetic effects present which has, thus far, rendered most results very unreliable.'

Geneticist at Newcastle, UK (2002)[474]

This section asks whether some geneticists are right to argue that genetic testing will improve predictions of heart disease in individual patients,[475] and whether targeting dietary advice, or functional foods at those individuals at greatest genetic risk will really help to reduce the incidence of this disease.

Heart disease is the leading cause of death in developed countries, including the UK. It is expected to become the leading *global* cause of death by 2020. This expected increase is due partly to ageing populations, but also because most smokers now live in developing countries and the adoption of western lifestyles – partly influenced by the marketing strategies of the tobacco industry and fast food companies – is also expected to increase blood pressure, unhealthy high-cholesterol diets and physical inactivity.[476,477,478] Environmental factors such as air pollution also contribute to many deaths from heart disease.[479]

Low socio-economic status, in childhood or in adulthood, significantly increases the risk of heart disease, although it is unclear to what extent this is due to different lifestyle factors (such as smoking and diet) or other social and psychological factors (see Box 3.6).[480,481,482,483]

Atherosclerosis (the accumulation of fatty substances in the walls of the arteries) is the main cause of heart disease and stroke, particularly in westernised societies, where it is the cause of about 50% of all deaths. Coronary artery disease (also called 'ischaemic heart disease') develops when one of the arteries supplying blood to the heart becomes blocked, limiting or stopping the supply of oxygen to the heart. Narrowed arteries can cause chest pains known as angina, and a completely blocked artery can cause a heart attack (called 'myocardial infarction' by doctors). Most heart attacks, however, are caused by a blood clot (thrombus) forming suddenly where the artery has narrowed, blocking blood flow to the heart. Established risk factors for atherosclerosis include smoking, high-fat diets and lack of exercise.[484] High blood pressure and cholesterol levels are significant predictors of death due to coronary heart disease.[485]

There is evidence that heart disease runs in families, however the importance of shared genes, compared to shared environments, is unknown.[486,487] Twin studies have calculated heritabilities for death from heart disease,[488] cholesterol levels[489] and blood pressure.[490]

Research on genes and gene-diet interactions has focused mainly on biological explanations for people's cholesterol levels and blood pressure. This means that fats and salt are the main dietary factors that have been considered. These are discussed in turn below, together with another less well established risk factor, levels of a chemical called homocysteine, which is linked with folate (a micro-nutrient) in people's diets.

Many other genes have been investigated for their possible role in coronary artery disease; however most of the associations are controversial.[491] Only genes that may interact with dietary factors (and hence could be relevant to personalised nutrition) are considered below.

6.2.4.1 Cholesterol and dietary fats

The levels of different fats (lipids) in the blood can affect a person's risk of heart disease.[175] Cholesterol is a fat which plays several important roles in the body, including in the brain and in some hormones, including sex hormones. Some cholesterol comes from the diet but most is made in the liver. There are two types, HDL cholesterol ('good' cholesterol) and LDL cholesterol ('bad' cholesterol), which differ in the way they are transported in the blood. Raised levels of bad (LDL) cholesterol were first linked with increased risk of heart disease in 1957, and the current era of treatment to lower cholesterol levels began in 1987 with the introduction of the first statin drug (Section 3.6). Cholesterol is not a health risk in itself, but bad cholesterol is thought to start the process of inflammation in the arteries which can lead to atherosclerosis and ultimately block an artery and cause a heart attack. In contrast, high levels of good (HDL) cholesterol appear to have a protective effect. High levels of bad cholesterol and other fats called triglycerides, and low levels of good cholesterol are called 'dislipidaemia'.

There is a rare inherited form of high cholesterol levels called familial hypercholesterolaemia (FH), which is caused by mutations in the LDL receptor gene (there are over 350 possible mutations).[492,493] FH occurs in about one in 500 people, so although rare compared to heart disease in general it is one of the commonest genetic disorders. People with FH are advised not to smoke and to eat a healthy diet, and are given cholesterol-lowering medication (statins) to lower their risk.[494] Some other (rarer) forms of this condition are caused by mutations in different genes. Some recent research has suggested that genetic tests for FH may lead people to believe more strongly in cholesterol-lowering medication and less strongly in the efficacy of changing diet.[495]

The idea that genetic differences influence cholesterol levels in a much larger number of people is partly based on family and twin studies (see Section 6.2.4). Some researchers have also argued that differences in cholesterol levels between different populations may reflect an interaction between genes and diet.[496] However, other explanations, including nutrition in the womb, or other differences in diet, are also possible.

In addition, experimental studies have shown that some people's cholesterol levels increase more than others when they eat a high-fat diet.[497,498,499] This variability in response to a high-cholesterol diet has led many researchers to conclude that genetic differences explain why some people (called 'hypo-responders') can eat high-cholesterol foods with very little adverse effect, but others (called 'hyper-responders') find that their cholesterol levels increase significantly, potentially threatening their health. However, there are some major problems with drawing this conclusion from these studies, because variability can be caused by other environmental and biological factors (such as age).[500,501,502,503] One important factor in response to a low-cholesterol diet is an individual's baseline diet and cholesterol level at the start of the experiment – individuals with poor diets and high cholesterol levels have more potential to achieve change than those who are already at low risk. Some studies have also shown that the response to diet is poorly reproducible when the experiment is repeated in the same individuals.[504] Variability that is not reproducible cannot be due to genetic factors, and may be partly random (due to chance). Other experiments disagree on how reproducible the variation is.[505,506] At best, these studies are too small and inconclusive to demonstrate that genetic differences are important for most people, and they tend to suggest that other factors may play a bigger role in the variability of cholesterol levels.

Because of the high incidence of heart disease in wealthy countries, and the evidence for the role of cholesterol, interactions between genes and dietary fats (lipids) has been one of the main areas of nutrigenomic research. Large numbers of different genes involved in lipid metabolism and the transport of fats in the blood have been investigated. The most extensively researched genes include Apolipoprotein E (APOE) and other lipoprotein genes; Lipoprotein Lipase (LPL) and other lipase genes; and Cholesterol Ester Transfer Protein (CETP) and some other transfer and binding protein genes.[502,507] Lipoproteins carry fats around the body; lipases are enzymes, made by the pancreas or liver, which break down dietary fats; transfer proteins like CETP are involved in transferring cholesterol between lipoproteins. Genetic differences in any or all of these biological processes could affect an individual's risk of developing heart disease when they eat a high-fat diet.

The link between genetic variations in the APOE gene and heart disease has been found to be statistically significant in a meta-analysis of nine genetic association studies (including nearly 9,000 people). However, the results showed significant variability between different studies.[308] Three meta-analyses of different variations in the LPL gene and risk of heart disease failed to reach statistical significance.[308]

The APOE gene has three common forms, known as APOE2, APOE3 and APOE4, leading to six different genotypes (because every individual has two copies). People with the E4 variant have the highest cholesterol levels and people with the E2 variant the lowest, but the E3 variant is the most common. These different genotypes appear to account for up to about 7% of the variation in total and bad (LDL) cholesterol levels in the general population, although their effects may be less important in children and the elderly.[508]

The APOE gene has been the most widely studied for gene-diet interactions, however these studies have found very mixed results.[362] Some studies have found that an individual's response to a low-fat (or low-cholesterol) diet depends on which form of the APOE gene they have, however this accounts for only a small proportion of the variation in response (4% in one study).[509] Perhaps because the effect of APOE genotype is at most a minor factor in response, other studies have found different, contradictory results.[510] A meta-analysis of 26 different controlled trials (which included a much larger number of participants than previously studied) found possible small effects of APOE genes on response to diet, but the responses to total saturated fat and to the cholesterol-raising effects of coffee were in opposite directions (the former producing a bigger effect in E4 carriers, and the latter a smaller one).[511] The authors concluded that knowledge of the APOE genotype may be of little use in the identification of people who respond best to dietary change. Other genes may also play a role, but the evidence is also contradictory,[512] showing that the lipid response to diet is highly complex.[513,514] One study has attempted to identify gene-diet interactions between the consumption of plant stanols (used in cholesterol-lowering margarines, see Boxes 3.13 and 3.14) and several genes involved in lipid metabolism, including APOE. It found no statistically significant relationships.[515]

The conflicting results from different studies probably reflect the complexity of gene-gene and gene-environment interactions (possibly including factors such as smoking and drinking alcohol,[516,517] as well as diet and weight), so that the effect of the APOE gene – and other, less well studied genetic variations – is probably smaller and more complicated than originally thought. Both the frequency of each genetic variation (such as APOE4) and its implications for health are likely to vary between different populations and at different times, as environmental exposures (including diet) change and people migrate between different countries.[518] If so, this limits both the usefulness of this type of test for personalising medical or dietary advice and the likelihood of obtaining reliable results from statistical studies (Sections 4.2.1 and 6.1).

To some extent, commercial research has now shifted emphasis from reducing levels of bad (LDL) cholesterol to increasing good (HDL) cholesterol. However, studies on the genetics of HDL cholesterol have also produced many conflicting results.[519] Many of the genes identified may be 'false positives' (occurring by chance) and even the most consistently replicated links between genetic variations and HDL cholesterol levels (the APOE, CETP and LIPC – Hepatic Lipase – genes) do not explain much of the difference in HDL levels between individuals. Numerous genetic and environmental factors are now thought to interact and gene-environment interactions have been reported between many different genes and the response to dietary fats, HDL levels and other factors (including smoking, alcohol, weight and physical activity). However, it is questionable whether these studies have the statistical power to tell the difference between real and chance effects (Section 6.1).

Scientists have now identified different types of bad (LDL) cholesterol, which vary in the size and density of the particles. Small, dense particles are thought to be more likely to lead to atherosclerosis and some scientists argue that LDL particle size (and hence risk of heart disease) may be influenced by genetic factors and involve gene-diet interactions.[520] One area of research is the effects of fish oil (omega-3 fatty acids, see Boxes 3.13 and 3.14) on cholesterol levels and particle sizes in people with different genes.[521,491] One clinical trial has found a different response to fish oil supplements in people with different forms of the APOE gene – suggesting that people with the APOE4 form might benefit less than others from these supplements.[522] However, the effect of fish oil supplements on cholesterol levels varies in different studies and the trial was not large enough for the effect of the APOE4 gene to be statistically significant.

6.2.4.2 Blood pressure and salt

Blood pressure is a measure of how hard a person's blood is pushing against the walls of their arteries. Blood pressure is highest when the heart beats (called systolic blood pressure) and lowest when the heart is at rest (called diastolic blood pressure). Both these numbers are measured when a person has their blood pressure taken. High blood pressure (hypertension) increases the risk of heart disease, heart failure, stroke and kidney problems. In about 5% of cases high blood pressure can be explained by an identifiable cause, such as a blocked artery. This is called 'secondary hypertension'. But in most cases (about 95%) there is no obvious cause: this is known as 'essential hypertension'.

Globally, about 972 million people had hypertension in 2000 (about 333 million in developed countries and 639 million in developing countries).[523] The most important known modifiable risk factors for hypertension are high salt intake, alcohol intake, obesity and low physical activity.[524]

Nutrition in the womb may also play an role in future blood pressure (Section 6.2.1) and there is also some evidence that breast feeding as infants may reduce the risk of high blood pressure in children.[525]

The role of salt in hypertension has been extremely controversial, partly because the food industry has consistently opposed public health measures to reduce the level of salt in processed foods. Most scientists now recognise that salt intake plays a role in blood pressure (although it is not the only factor)[526,527,528] and many scientists have advocated restrictions on the level of salt in processed foods.[529] However, others have opposed such measures, arguing that more evidence is needed.[530] There is no doubt that, while salt is necessary in the human diet, the quantities consumed today are significantly higher than in traditional diets. Of the average daily salt intake in the USA, only 10% is naturally contained in food, 15% is actively added by consumers and 75% is added by manufacturers. Salt improves flavour and palatability, increases shelf life and adds inexpensive weight, thus increasing profits.[531]

Many traditional communities – in the Americas, Asia, the Pacific Region and in Africa – have been identified in which hypertension is rare. Evidence that this effect is environmental, rather than genetic, is provided by migration studies, which all show that blood pressure rises in these populations when they move to an urban environment[532] although factors other than increased salt may play a role.[555]

An important issue in the debate has been the apparent variability in 'salt-sensitivity' between individuals or different populations, which (like variability in cholesterol levels) is often assumed to be due to genetic differences.[524]

Similar to the thrifty gene hypothesis (Box 6.5), one possible explanation for variability in salt-sensitivity between individuals or different ethnic groups is that some people have 'thirsty genes', which make them more salt-sensitive. However, it is not clear why this might have been an evolutionary advantage in the past: adding salt to food does not appear to have been a biological necessity for hunter-gatherers or for early agriculturalists, but it probably became a cultural necessity for preserving food and making cheese.[531] A genetic explanation for differences in blood pressure in different ethnic groups is now being questioned, partly because few thirsty genes have been identified.[534] Other factors, such as stress and racism, might explain the higher rates of hypertension in African-Americans, for example. Two studies involving international comparisons of European-origin and African-origin populations have now concluded that the role of environmental factors in hypertension in these populations (consistent with a transition to an industrialised lifestyle) has been underestimated.[456,535] The authors of the second paper argue that too much emphasis on genetic factors is a distraction from the more relevant issue of identifying and reducing the preventable causes of hypertension.

There are some rare genetic disorders which lead to severe hypertension at an early age, however many complex mechanisms affect blood pressure in most people.[536] The most studied gene for common hypertension is the angiotensinogen gene (AGT), which plays a role in the biological system which stimulates thirst and appetite for salt. Common variations in this gene appear to increase the risk of hypertension: studies have shown mixed but generally positive results and a meta-analysis has found a modest but significant increase in blood pressure in people with this genetic variation.[537] However, a more detailed meta-analysis in 2003 found that the link between genetic variations in the AGT gene and essential hypertension was no longer statistically significant when the first studies are excluded.[538] This may mean that the early studies are biased in some way. Some studies have suggested that the AGT gene plays a role in a person's response to dietary salt (their salt sensitivity) and a genetic test for this has been marketed by Myriad Genetics – however, this test now appears to have been withdrawn from sale (Box 6.9).

Box 6.9. Marketing genetic tests for hypertension and salt-sensitivity

Myriad Genetics, based in Salt Lake City, has been awarded four patents on the AGT gene, which form the basis of its CardiaRisk™ genetic test.[539] When the test was launched in 1998, Myriad claimed that it would 'assist physicians both in identifying which hypertensive patients are at a significantly increased risk of developing cardiovascular disease, and identifying which patients are likely to respond to low salt diet therapy and antihypertensive drug therapy'.[540] Until at least 2002, Myriad claimed that the TT variant of the AGT gene had been associated with 'greater responsiveness of borderline hypertension to sodium restriction and weight loss', citing the 1997 abstract of a conference paper to support this claim.[541,542] However, when this study was published in a peer-reviewed scientific journal in 1998 it was clear that this effect was, at best, extremely variable and of borderline statistical significance.[543] By 1999, other researchers had concluded that it was 'unlikely' that this genotype could serve as an early genetic marker of salt sensitivity.[544]

In 2000, Myriad formed an alliance with Laboratory Corporation of America, to market its genetic tests, including CardiaRisk.[545] However, according to the US Centers for Disease Control and Prevention, by 2003 Myriad had decided not to further pursue the test's introduction into the marketplace, because cardiologists had found it to be of limited value.[546] Many US health insurers will not pay for the test, regarding it as 'experimental, investigational or unproven'[547,548] and the test is no longer listed as a product on the company's website.

Many other genes have been investigated for a possible role in hypertension, but none has been firmly established.[536] As for other chronic diseases and risk factors, a simple view of the genetics of hypertension is likely to be over-optimistic because so many different biological mechanisms are involved.[549]

6.2.4.3 Homocysteine and folate

Homocysteine is an amino acid (a building block for proteins) that plays an important role in metabolism. Levels of homocysteine in a person's blood are affected by their levels of folate and other B vitamins, with low folate levels leading to high homocysteine. A person's age and sex and whether they drink alcohol or caffeine or smoke can also affect the levels of homocysteine in their blood.[550] Like cholesterol levels, high levels of homocysteine are a possible 'biomarker' for an increased risk of heart disease, however this is disputed by some scientists and the most recent, largest study did not find a link.[551,552]

People can increase their intake of folate by taking folic acid (the form of folate found in supplements), eating folate-rich foods (including liver and vegetables such as broccoli, sprouts and spinach)[553] or eating fortified foods (usually breakfast cereals).

A common genetic variation in the MTHFR gene appears to affect the levels of homocysteine in a person's blood. Several (but not all) studies have found that this effect occurs only in people who also have low folate levels.[554,555,556,557,558,559] This suggests a gene-diet interaction, which would imply that people with this genetic variation can make more difference to their homocysteine levels by taking folic acid than other people can. This effect has been found in several (small) clinical trials in the UK,[560] Germany[561] and Japan,[562] suggesting that this genetic test could in theory be useful to decide who needs to take folic acid or to eat foods higher in folate. However, even if homocysteine was important in heart disease risk (which is disputed), less than 2% of the variability in levels is thought to be due to the common variation in the MTHFR gene.[563] Genotyping to decide who would benefit most from taking folic acid supplements is therefore pointless.[564]

Dietary folate is important in preventing 'neural tube defects' (which include conditions such as spina bifida) in babies. Women of child bearing age are now recommended to eat a healthy diet and take folic acid supplements, especially when planning a pregnancy.[565,566] The link between the TT variant of the MTHFR gene in the mother or baby and an increased risk of neural tube defects has been confirmed in some meta-analyses.[308] However, variable results have been obtained in different studies and it is clear that multiple genetic factors are likely to be involved and the interactions between genes and different nutrients are likely to be complex.[567,568] Although the MTHFR gene may play a role, there is no good argument for restricting folic acid supplements only to women with the TT variant – this would be likely to do much more harm than good because other women also need to make sure they get enough folate to reduce the risk to their babies.

The possible role of folate, homocysteine and the MTHFR gene in stroke and colon cancer is considered in Sections 6.2.5 and 6.2.6.

6.2.4.4 Marketing genetic tests for heart disease susceptibility

Many of the genetic testing companies listed in Table 9 already market tests that claim to identify susceptibilities to heart disease and give genetically tailored dietary advice. The MTHFR gene and other folate metabolism genes are often included, as are lipid metabolism genes such as the CETP and LPL genes. Marketing of these tests has been criticised by geneticists, partly because other tests (such as tests of cholesterol levels) are currently better at predicting risk and aiding treatment decisions.[569] This is because existing tests measure the cumulative consequences of both genes and diet (as well as other biological and environmental factors). Other concerns include the potential for 'nasty surprises'. In particular, the company Genova Diagnostics (formerly Great Smokies Diagnostics Laboratory) has included the APOE gene in its 'CardioRisk' tests, despite the fact that common genetic variations in this gene have been linked with an increased risk of Alzheimer disease, and testing this gene is therefore not recommended (Box 6.17).

6.2.5 Stroke

A stroke is caused by a sudden interruption of the blood supply to the brain. There are two main kinds: an ischaemic stroke occurs when a blood vessel becomes blocked; an hemorrhagic stroke occurs when a blood vessel ruptures and bleeds. Ischemic strokes are more common (about 80-90% of cases). In both types of stroke, brain cells die as the supply of oxygen and nutrients to part of the brain is interrupted. This can affect many different functions including movement, thinking and memory. In severe cases strokes can cause paralysis or death.

Stroke is the third commonest cause of death worldwide (after heart disease and all the different types of cancer combined). Two-thirds of stroke deaths occur in less developed countries.[570]

Atherosclerosis (the accumulation of fatty substances in the walls of the arteries, see Section 6.2.4) is the main cause of ischaemic stroke (as it is for heart disease), however there are many subtypes that may be due to other factors.

The risk of stroke increases with age and the most important avoidable risk factor is high blood pressure. Heart disease, smoking, high cholesterol levels, obesity and binge drinking also increase risk. There is therefore an important role for diet in reducing the risk of stroke.

Black Americans have a higher incidence of stroke than white Americans. However, a recent study found that this could be explained solely by known risk factors and lower income.[571] This study suggests that there can only be a very limited role for genetic differences between these two ethnic groups. The results of twin studies have been variable[572,573,574] but tend to suggest that the importance of genetic differences in stroke may not be substantial. Stroke also runs in families, but this could be due to shared genes, or shared environments, or both.[575,576]

A rare form of stroke called CADASIL is caused by mutations in a single gene and there appears to be an interaction between this gene and smoking (which is associated with an earlier age of onset).[577]

The genetics of stroke risk factors such as blood pressure, heart disease, cholesterol levels and obesity are discussed above in Sections 6.2.4 and 6.2.1.

Some studies have also looked directly at the risk of stroke or at the accumulation of fatty substances (atherosclerosis) in the carotid arteries (the main arteries in the neck that supply blood to the brain).[577]

A link between genetic variations in the APOE gene (see also Section 6.2.4.1) and ischaemic stroke was confirmed in a meta-analysis in 2003.[308] However, a number of more recent studies have failed to find an effect. As with the risk of heart disease (Section 6.2.4.1) it seems likely that this gene does play a role, but the effect is small and may be modified by other factors, such as smoking and drinking. Studies have given conflicting results about the role of the AGT gene (which has been linked with hypertension, see Section 6.2.4.2), and the role of several other genes.[577] Although one recent study has concluded that there is a causal link between homocysteine levels and stroke,[578] others have questioned whether this is a real effect (as they have for heart disease, see Section 6.2.4.3).[551] Although this study concludes that genetic variations in the MTHFR gene play a role in stroke, the effect is small and variable and the authors do not suggest that diets should be tailored to these genetic differences.

Studies of gene-diet interactions have focused on risk factors such as cholesterol levels and blood pressure (see Sections 6.2.4.1 and 6.2.4.2), rather than directly on the risk of stroke. One study has looked at interactions between multiple possible genetic risk factors and other factors (hypertension, diabetes, smoking and drinking), two of which (hypertension and diabetes) are influenced by diet.[579] However, it is questionable whether this study was large enough to reliably identify these interactions. In any case the results do not lead to any obvious conclusions about tailoring diets to a person's genes to reduce the risk of stroke.

6.2.6 Cancer

There were 10 million new cases, 6 million deaths, and 22 million people living with cancer in the world in 2000. Slightly more new cases and deaths were occurring in less developed than developed countries. However, by 2020 projections suggest that 9 million new cases will occur in less developed countries compared with 6 million in more developed regions, rising to over 17 million (less developed countries) and 7 million (more developed countries) by 2050.[580] The highest priority in cancer prevention is tobacco control, but the World Health Organisation recommends encouraging consumption of locally produced vegetables, fruit and agricultural products; avoidance of the adoption of western style dietary habits; and policies to tackle alcohol consumption, increase physical exercise and reduce obesity. The WHO estimates that medical knowledge is now sufficiently advanced to prevent at least one-third of all cancers.[581]

Diet plays an important role in increasing or decreasing the risk of developing some cancers. However, there are significant uncertainties about the role of diet in cancer and the effects depend on the type of cancer. The commonest cancers in terms of new cases in 2000 were lung cancer (the commonest cancer in men, largely due to smoking), breast cancer (the commonest cancer in women), colorectal cancers (bowel cancers), stomach cancer and liver cancer.[580] However, there are significant differences between countries. More developed countries tend to have higher rates of bowel, breast and prostate cancer, and developing countries sometimes have higher rates of cancers of the oesophagus (gullet), stomach and liver. The different rates of different types of cancer in different countries, and the results of migration studies,[582,583,311] tend to suggest that diet is likely to play an important role in at least some types of cancer. However, many other factors, including viruses and pollution (including toxic chemicals or radiation), can increase the risk of cancer and in many cases the relative importance of different environmental factors is unknown.

Many studies have attempted to clarify the role of diet in different types of cancer, but they often give conflicting results, mainly to do with the difficulties in measuring diet, separating the effect of one dietary factor from another, and the difficulties in being sure that other factors (confounders) do not explain an observed link. Nevertheless, there is convincing evidence for a role of diet in some types of cancer (Box 6.10).

Cancer is a complex disease and how it develops and spreads is not fully understood. However, it is thought to be caused by damage to the DNA inside a person's cells, including mutations and other types of damage, which then cause some cells (cancer cells) to grow out of control. Most mutations are thought to arise during a person's lifetime (called 'somatic' mutations) but some people can be born with mutations ('germline' mutations) that increase their risk of cancer, often at an unusually early age. Mutations in genes which increase the risk of breast and ovarian cancer and of colorectal cancer are some of the best studied (Box 6.11). These mutations occur in familial (largely inherited) forms of cancer, however they account for only a small proportion of cancers.

Box 6.10. Diet, nutrition and cancer[311]

There is convincing evidence from a variety of studies that being **overweight or obese** increases the risk of several types of cancer – these are cancers of the bowel (colorectum), gullet (oesophagus), womb lining (endometrium), kidney, and breast cancer in post-menopausal women. Physical activity also reduces the risk of colon cancer and possibly of breast cancer. This means that after tobacco, overweight/obesity is arguably the most important known avoidable cause of cancer in populations with western patterns of cancer incidence.

High **alcohol consumption** is also clearly related to an increased risk of cancers of the mouth and throat, gullet, liver and breast. Eating large quantities of Chinese-style salted fish (in some Asian populations) also increases the risk of throat cancer. Food contaminated with aflatoxin (due to a fungus growing on peanuts and other foods) increases the risk of liver cancer, but possibly only in regions where infection with hepatitis (the main cause) is common.

There is evidence that **fruit and vegetables** probably decrease the risk of cancers of the mouth, gullet, stomach and bowel. However, this protective effect has been difficult to prove and may be relatively modest. There is also evidence that **preserved meat and red meat** increase the risk of bowel cancer and that fish may be protective;[584] salt preserved foods and salt increase the risk of stomach cancer; and that very hot drinks increase the risk of cancers of the mouth, throat and gullet.

There is evidence from some large studies that **dietary fibre** protects against bowel cancer.[585,586] However, other large studies have found no protective effect. This could be because people did not consume enough dietary fibre in these studies; or because some types of fibre are more important than others; or because fibre itself is not protective, but something else to do with eating plant based foods is beneficial.[587] Whatever the reasons, eating a diet rich in plant foods, in the form of fruit, vegetables and whole grain cereals, appears to reduce the risk of colon cancer.

There is currently insufficient evidence to establish a protective effect of various other dietary components (including soya and fish oils, and various vitamins and minerals and other plant constituents). There is also insufficient evidence to establish an increased cancer risk from animal fats or various chemicals produced by overcooking meat.

Box 6.11. Familial cancers of the breast, ovaries and colon[588,589,590]

Mutations in either of two genes called BRCA1 and BRCA2 have been associated with a lifetime risk of breast cancer of between 45% and 87%. Mutations in these genes are thought to account for about 5% of breast cancer cases, and also increase the risk of ovarian cancer. Only women with a very strong family history of these cancers are recommended to take these genetic tests and the results are often inconclusive. Some women with mutations choose to have surgery to remove their breasts to reduce their risk. Recently, a study of about 1,000 women with mutations in these genes has found that losing excess weight in the period between age 18 and age 30 may reduce the risk of breast cancer in these women, although later weight change did not influence risk.[591]

Familial adenomatous polyposis (FAP) is a largely inherited form of colorectal cancer. About 0.5% to 1% of colorectal cancer is thought to be due to mutations in these genes.

Lynch Syndrome is a form of hereditary colorectal cancer (called 'hereditary nonpolyposis colorectal cancer' or HNPCC) associated with mutations in the family of MMR genes (including four genes: hMSH2, hMLH1, PMS1, PMS2). About 3-5% of colorectal cancer is thought to be due to Lynch Syndrome.

The evidence that susceptibility to more common forms of cancer is influenced by genetic make-up is less well established. Evidence from twin and family studies is considered in Box 6.12.

Box 6.12. Twin and family studies of cancer

The largest and most recent twin study, using more than 44,000 twins from Sweden, Denmark and Finland, found statistically significant heritabilities for prostate cancer (42%), colorectal cancer (35%) and breast cancer (27%).[222] However, the study concluded that environment plays the major role in most types of cancer. The study used the classical twins method, which can overestimate the importance of genetic factors (Section 6.1). The twins were all born before 1958.

There is also good evidence that cancers run in families (relatives of someone with cancer tend to be at higher risk).[592] However, this could be explained by shared environments as well as by shared genes.

Most research on gene-diet interactions has focused on bowel (colorectal) cancer, because there is reason to expect that diet may play an important role in this type of cancer (Box 6.10); there are some known largely inherited forms (Box 6.11) and the evidence from twin studies (Box 6.12) has been taken to imply that other inherited genetic differences could be important. Three-quarters of colorectal cancer is estimated to be sporadic (i.e. with no significant inherited component), but 18% may be due to family history.[590] However, although this is often assumed to mean that other genes must be involved, shared diets or environments could also be important.

One of the main areas of study has been the MTHFR gene discussed in Section 6.2.4.3, because folate metabolism may also play a role in colorectal cancer. The Human Genome Epidemiology Network (HuGE) reviewed the evidence for a role of the MTHFR gene in colorectal cancer in 2004.[559] It found that in most studies the TT variant of the MTHFR gene (which may *increase* the risk of some other diseases, Sections 6.2.4.3 and 6.2.5) was associated with a moderately *reduced* risk of colorectal cancer. This is the opposite of what might have been expected, however most studies did not reach statistical significance. Evidence on other genetic differences was very limited. The review concluded that the evidence was not strong enough to advocate population testing.

The other area of research in gene-diet interactions relates to individual susceptibility to cancer-causing chemicals (carcinogens), such as those formed when meat is cooked at high temperature. A number of 'metabolic genes' have been identified which are involved in the metabolism of toxic or cancer causing chemicals. Some common variations in these genes appear to slightly increase (or decrease) the risk of different types of cancer; however, the risks are small and not firmly established. One gene, called NAT-2, has two common forms, one of which appears to slightly increase the risk of colon cancer but reduce the risk of bladder cancer; however, different studies show conflicting results.

A recent review calculated that the risks attributable to this type of genetic susceptibility were overall lower than those related to smoking or other environmental risk factors[593] and concluded that screening for this type of genetic variation is currently not advisable.

This conclusion is not altered by a more recent study of the GSTM1 and GSTT1 genes, both of which have common variations which result in no enzyme being produced.[594] People with these genes probably have higher levels of chemicals called isothiocyanates in their bodies, which come from eating some green vegetables such as broccoli, cabbage and sprouts (known as 'cruciferous vegetables'). The lack of the enzyme means that the body does not break down these chemicals as easily, and this might help reduce the risk of cancer because it is thought (but not proven) that isothiocyanates could have a protective effect. The recent study found a protective effect in non-smokers whatever genes they had. However, the protective effect in smokers was stronger in those with the genetic variations in the GSTM1 and GSTT1 genes that helped to increase the levels of isothiocyanates. Although this paper strengthens the evidence for a protective effect of cruciferous vegetables, it does not suggest that people need advice that's tailored to their genes. The result makes no difference to public health advice: smokers should quit smoking if they wish to reduce their risk of lung cancer (about 90% of cases occur in smokers) and non-smokers should eat plenty of vegetables if they wish to further reduce their risk.

Many of the companies listed in Table 9 already market tests they claim are associated with 'detoxification', including the GSTM1, GSTT1 and other genes. Sales of these tests have been criticised by cancer geneticists, who argue that 'the exaggerated claims of the marketplace are corrosive to the public's trust in genetic research'.[271]

6.2.7 Food intolerances

Because many genetic disorders involve enzyme deficiencies, there are many rare forms of intolerance to certain components in a normal diet. For example, some people cannot digest sugars in fruit (fructose intolerance). Other genetic disorders alter the ability of the body to use certain sugars or other components of the diet.

Most of these genetic disorders are rare and do not imply that genetic differences are important in determining the foods that most people should eat. However, there is good evidence that severe reactions to at least two foods (fava beans and milk) and to alcohol can have a genetic cause in much larger numbers of people (see Boxes 6.13, 6.14, 6.15). For example, globally most adults cannot digest large quantities of milk and even in the USA this is the commonest food intolerance (affecting about one in ten people).

In all these cases, some people are born with a genetic make-up that means they lack the enzymes needed to properly digest these foods. This means that there is evidence of strong gene-diet interactions (i.e. only people with the genes associated with intolerance tend to suffer a severe reaction to the food or drink).

The genetic differences discussed in Boxes 6.13 and 6.14 follow a pattern that may be explained by different dietary and other histories across the globe. Lactose intolerance, for example, is common in Asia but much rarer in northern Europe, where there is a long history of farming cattle and consuming dairy products. Because the symptoms are often rather obvious a genetic test is not always necessary to identify any of these reactions (although it may help explain them). Other types of tests may also be available – for example there are tests for lactose intolerance that can directly measure the individual's ability to digest milk, which changes over time.[595]

Box 6.13. Fava beans[596,597]

The ancient Greeks and Persians knew that some people become sick when eating fava beans or breathing in the pollen from these plants, but others do not. This sickness, called 'favism', involves nausea, dizziness and tiredness as a result of anaemia and jaundice. It is caused by mutations in the G6PD gene which cause a deficiency in this enzyme. Dozens of different mutations exist and they vary in their impacts – ranging from a mild deficiency to complete lack of the enzyme. Mutations are relatively common in Africa (where they affect up to 20% of some populations), the Mediterranean (4-30%) and southeast Asia because, although they have some harmful effects on health, they also increase resistance to malaria.

Box 6.14. Milk[598,599]

Babies can digest their mother's milk, but many lose this ability as they grow older. This 'adult lactose intolerance' is very common, particularly in Asia. Globally, most adults are lactose intolerant and cannot digest large quantities of milk. Symptoms vary but can include vomiting and diarrhoea. Lactose tolerance (the ability to digest milk) in adults is rarer, but is more common than intolerance in Europe and North America. It is caused by a genetic variation (polymorphism) that is particularly common in adults in northern Europe. The genetic variation occurs in a gene that appears to influence the expression of another gene called LCT. When it is expressed (switched on) the LCT gene produces a protein (lactase) that is needed to digest milk. Scientists have found a correlation between long-term dairy consumption in a population (over some 5,000 years) and the frequency of lactose tolerance. This implies that populations who kept cattle evolved to be able to continue to digest milk as adults, i.e. the gene that switches on lactase in adults became more common in these populations because dairy products became an important source of food.

Box 6.15. Alcohol [600,601,602,603]

The ALDH2 gene has a well studied common genetic variation that results in the enzyme it produces being inactivated. This limits the body's ability to breakdown alcohol in the liver and results in a build-up of a chemical called acetaldehyde, which leads to acute alcohol intoxication. Symptoms include facial flushing, nausea and dizziness. This genetic variation is more common in east Asia, where about 50% of some populations may lack the enzyme, than it is in other parts of the world.

Common genetic variations in two other genes, ADH2 and ALDH1A1, also affect alcohol metabolism. Again, the variants that increase sensitivity to alcohol are more common in East Asian populations than elsewhere in the world. The reasons for the high frequency of alcohol sensitivity in East Asia are not fully understood.

Some scientists have argued that the examples of genetic intolerance to milk, fava beans and alcohol mean that food choices should be tailored to genetic differences, taking into account our own evolutionary past.[604] However, others argue that these examples are unusually simple – most people will now be a very complex mixture of different genes and food habits, making it impossible to match different foods to different people in a simple and straightforward way.[605] In other words, the relatively predictable reactions to certain foods described above are probably the exception rather than the rule.

Although Boxes 6.13, 6.14 and 6.15 provide some clear examples of genetic factors in food intolerance, it is also worth remembering that this does not mean that people who are tolerant (i.e. can easily digest) these foods will not suffer adverse health effects. In fact, over-consumption of full-fat milk and alcohol in European countries – where both are well tolerated – has major adverse impacts on public health.

6.2.8 Allergies and inflammatory diseases

Food allergies are generally less well understood than food intolerances. They involve an immune reaction which builds up over time, rather than an inability to digest the food.[606] Allergies usually occur to foods that are common in the diet. For example, rice allergy is frequent in Japan and codfish allergy in Scandanavia. Allergies to shellfish, nuts (especially peanuts), fish, eggs, milk and soy are relatively common. Gluten sensitivity (coeliac disease) involves an immune reaction to gluten, which is found in wheat, rye and barley. Peanut allergies can be particularly severe and can cause a sudden drop in blood pressure which may be fatal.

Allergic reactions are thought to involve a 'sensitisation' phase during early childhood or adolescence, when people first encounter the food or other substance that they become allergic to (the allergen). This is followed by a 'challenge' phase, when further exposure to the allergen causes a complex immune reaction, which may involve various symptoms such as itching, sneezing or breathing difficulties. The main treatment is usually to try to avoid the food that causes the allergy.

The genetics of diseases which involve inflammation of the skin, lungs or bowel, such as eczema, asthma and inflammatory bowel disease, may share some common features.[607] However, these are all complex diseases, which involve many different biological and environmental factors. Their incidence increased significantly during the 20th century, indicating the importance of changing lifestyles or environment.[608]

A general predisposition to develop allergic reactions is called atopy. Atopic individuals have high levels of molecules called IgE in their blood, which are involved in allergic reactions. One study of 107 pairs of twins in the USA found that identical (monozygotic) twins were more likely to share atopy with their twin than non-identical twins were.[609] However, the difference was not statistically significant. Many geneticists have tried to identify genetic factors that cause or contribute to atopy or allergic diseases and immune reactions, including food allergies such as gluten sensitivity (coeliac disease)[610] and inflammatory bowel diseases (the two main forms of which are Crohn's disease and ulcerative colitis). Most of these studies have shown the mixed results typical of genetic studies of complex diseases. However, there is some relatively strong evidence for an important role of genetic differences in Crohn's disease and in coeliac disease.

The best established link is between three genetic variations in the CARD15 (previously called NOD2) gene and susceptibility to Crohn's disease (a bowel disease which affects about 0.15% of people in western Europe and North America). At least one of these genetic variations is thought to lead to an impaired defence against bacteria. These genetic variations in CARD15 seem to carry a much higher risk than is usual for genes involved in complex diseases. One genetic variation can increase risk two- to four-fold, or 17-fold if two or more genetic variations are combined,[611] and these genetic variations appear to account for 15-22% of cases of Crohn's disease, probably by causing an abnormal immune response to microbial infections.[612] However, the evidence for the role of other genes is weaker, and most seem to have only a small effect on risk.[607,613,614] The genetics of ulcerative colitis (which is about twice as common as Crohn's disease) is less well understood.

It has been suggested that probiotics may help ease inflammatory bowel disease by altering the bacteria living in the gut, although the role of these bacteria is not fully understood (see Box 3.13).[615] However, there is no evidence that these functional foods can play a role in preventing inflammatory bowel disease or allergies in people who are identified as genetically susceptible to future illness.

Coeliac disease is an intolerance to gluten (mainly found in wheat). Its prevalence is uncertain but it may occur in as many as one in 100 adults. However, there is no clear medical consensus on who has coeliac disease because this depends on how sensitivity to gluten is defined.[616] It can be diagnosed by testing for the antibodies produced by the intolerance, although there are some limitations to this type of test.[617] Following a gluten-free diet is the main treatment. Because only people who are intolerant need to avoid gluten (unlike foods high in fat, sugar and salt, which are likely to be bad for everyone), coeliac disease is an example of a condition where genetic testing could in theory be useful, particularly for people who do not have obvious symptoms. Genetic variations in the HLA genes (Box 6.16) are known to play an important role, with one variation increasing risk by a factor of 250,[618] and most people with coeliac disease appear to have one of two common genetic variants in their HLA genes. However, not everyone with these genes develops the condition, making it hard to predict who will benefit from a gluten-free diet. HLA gene testing appears to be more useful to rule out coeliac disease in people who do not have these genetic variations than it is to predict who will develop the disease.[616] Other genes are thought to be involved, but have not been confirmed.[619,620] Environmental factors – perhaps including infant feeding patterns – may also influence who develops coeliac disease, but are poorly understood.[621,622]

Box 6.16. Immune response and HLA genes[618]

Human leucocyte antigen (HLA) genes are involved in the body's immune response. This includes both normal responses to infection[623] and the abnormal responses that can cause so-called 'autoimmune' diseases such as rheumatoid arthritis.[624] It is these genes that are tested for a 'match' when someone receives an organ or bone marrow from a donor, to try to minimise the body's rejection of the donated cells or tissue. The HLA genes in a region of the human genome known as the 'major histocompatibility complex' (MHC) include more than 1,000 different common genetic variations in eight different locations, making the consequences for each individual extremely complex to predict. Different genetic variations in the HLA genes have been linked to an increased risk of a wide range of different conditions, including arthritis, multiple sclerosis, type 1 diabetes and some cancers. However, most of these complex diseases remain poorly understood.

It is possible that the risk of other allergies, such as eczema and asthma, could be reduced by changing diets. For example, some studies have shown relations between diet and asthma, related to higher salt intake, low selenium, or reduced vitamin C, vitamin E, or certain polyunsaturated fats.[625] It is also possible, although not confirmed, that breast feeding may have a protective effect. However, studies have not yet shown that changing diets can make a significant difference to the likelihood of developing asthma. Other factors, such as dust mites, pollution and smoking are probably much more important. Many scientists also think that early exposure to infections may help protect children from developing asthma later in life.

6.2.9 Osteoporosis, falls and fractures

Falls and fractures in the elderly are a major public health problem. In the UK about 30% of people over 65 and 50% of people over 80 will fall in a given year.[626] Many of these falls lead to fractures because bones become thinner and break more easily as people become older. Osteoporosis is defined as having significantly weaker or thinner bones than an average young person, increasing the risk of fractures. Post-menopausal women, especially those over age 75, are at highest risk because reduced levels of the sex hormone oestrogen can increase bone loss. The main measure of osteoporosis is bone mineral density (BMD), however, as with many risk factors, the definition of what is normal is somewhat contentious because testing BMD in younger post-menopausal women could be used to expand the drug market for preventive medication, perhaps with little relative benefit compared to potential harms and costs.[627]

Because bone mass increases during childhood and adolescence, diet and exercise during this time is thought to affect bone strength. Vitamin D (which occurs in some foods and is also made in the body in response to sunlight) and calcium (mainly from milk) are both thought to be important. Although there is no doubt that calcium is needed for healthy bones, and very low calcium intakes may be harmful, it is less clear whether drinking more milk in childhood or adolescence makes a significant difference to bone strength.[628] The amount of exercise taken seems to be the most important factor in developing strong bones in adolescence. Vitamin D can also influence how much calcium is absorbed from food, and vitamin D deficiency can lead to rickets. Many elderly people are vitamin D deficient, however there is conflicting evidence about whether vitamin D supplements can reduce fractures.[629]

Twin and family studies of the heritability of bone mass have given variable results, which seem to vary with age and the bones studied.[630,631] The usual caveats to interpreting these results apply (Section 6.1).

The most thoroughly studied gene is the vitamin D receptor gene (VDR).[632] A common genetic variation in the VDR gene was first linked with lower bone mineral density (BMD) in 1992, however corrections to the original paper subsequently showed a weaker effect. Since then, the results of different studies have been contradictory, showing at most a small effect on BMD. The most recent meta-analysis found that individual genetic variations in the VDR gene were not associated with osteoporosis on their own, but suggested that a combination of different genetic variations (called a 'haplotype') may increase risk.[633] Studies of the effect of the VDR gene on fracture risk have also produced contradictory results.

Links between risk of osteoporosis and more than 100 other genes have been studied, but none of them are firmly established.[632,634] A meta-analysis of common genetic variations in the ESR1 (estrogen receptor alpha gene) involving more than 5,000 women found a slightly (1-2%) higher bone mineral density (BMD) in women with the XX genotype, and a significantly lower fracture risk.[635] This effect is insufficient to explain much of the variability in bone mineral density in the female population, and also suggests that other measures of bone strength may be more important in influencing the risk of fractures. Another large study (of over 2,000 people) subsequently found that a combination of genetic variations (a haplotype) in ESR1 increased fracture risk.[636] However, the exact role of the ESR1 gene and its effect on risk remains uncertain.

To date, studies of gene-environment interaction in osteoporosis have been rather limited and the importance of such interactions is unknown.[631]

Many of the companies listed in Table 9 already market nutrigenetic tests they claim are linked with bone health; they typically include the VDR and other genes. The validity of these tests is questionable and there is no evidence that people should eat different diets or take different supplements if they have different common variants of these genes.

6.2.10 Brain disease and neurodegenerative disorders

There is some evidence that diet may be important in the decline in brain function which occurs as people age, including in the major neurodegenerative disorders, Alzheimer disease (the commonest form of dementia) and Parkinson disease.

Alzheimer disease involves the progressive degeneration and death of neurons in the brain, affecting memory and behaviour. Parkinson disease also involves the degeneration of neurons, but in a different region of the brain, affecting the ability to control body movements and causing shaking. Both disorders are incurable and poorly understood, although medication may help slow disease progression or control the symptoms. Both conditions are on the increase because of ageing populations.

Alzheimer disease occurs in about 6-10% of people over the age of 65 in the UK and the USA.[637] One study has found a significant difference between incidence of Alzheimer disease (adjusted for age) in the USA compared to Nigeria, which might be due to environmental or genetic differences.[638] This is the first time a study using the same methods in two different populations has shown a significant difference in incidence rates (rates between countries may also vary because of different methods use to identify dementia).

The role of diet in Alzheimer disease is unknown, although several studies suggest that a lower calorie intake may reduce risk.[639] One recent Californian study has also suggested that obesity in middle age increases the risk of future dementia.[640] However, relatively few studies have been done and these findings are not conclusive. Low folate levels, and high levels of homocysteine (discussed in Section 6.2.4.3) may also increase risk, although again studies have been limited. Suggestions that vitamin E might prevent or delay the onset of illness have not been supported by a recent clinical trial.[641] Many factors other than diet, perhaps including pollution,[642] might increase the risk of dementia, and factors such as being physically and mentally active also appear to reduce the risk.[643] However, the main risk factor is age (with less than 1% of people under 70 affected, but up to 30% by age 90)[644] and only age and family history are consistently associated with Alzheimer disease in all studies.

Alzheimer disease runs in families, with first degree relatives (brother, sister or child) of someone with Alzheimer's about 3.5 times more likely to develop the condition.[644] However, this could be due to environmental or lifestyle factors rather than genetics. A recent study of 14,435 individuals aged 65 and older from the national Swedish twin registry found that identical (monozygotic) twins were somewhat more likely than non-identical (dizygotic) twins to share their twin's risk of dementia.[645] However, this may or may nor mean that genetic differences are important (Section 6.1).

Mutations in three genes (the amyloid precursor protein, presenilin-1 and presenilin-2 genes) result in very rare inherited forms of Alzheimer disease.[644,646] If someone has one of these mutations their risk of developing Alzheimer disease is very high, but these mutations account for less than 1% of cases. Rare inherited forms of Parkinson disease also exist and so far four genes have been identified (the SNCA, UCH-L1, PRKN and DJ-1 genes).

Genetic research in neurological disorders suffers from the usual difficulties in replicating results (Section 6.1). For example, out of 127 associations reported between different genes and Alzheimer disease in a single year, only three were replicated in three or more independent studies.[646] However, one susceptibility gene (APOE) is considered to be fully established: the APOE4 form of this gene has been consistently linked with an increased risk of Alzheimer disease (Box 6.17). The APOE4 gene may also slightly increase the risk of Parkinson disease, but this link is much less well established than the link with Alzheimer disease. Recently, a meta-analysis has found a weaker but still significant link between genetic variations in the ACE gene and Alzheimer disease. However, the authors suggest that this effect is probably due to a different nearby gene, rather than the ACE gene itself.[647] No link with common genetic variations in the LRP1 (lipoprotein receptor related protein) gene was found in another meta-analysis.[648] It is possible that other genes may play a role, but none is yet confirmed.[649]

Box 6.17. Alzheimer disease and the APOE gene

The APOE gene discussed in Section 6.2.4.1, that influences cholesterol levels, has also been linked with an increased risk of Alzheimer disease. Although the results of different studies vary, the APOE4 variant significantly increases risk when all the studies are combined.[650,644] The frequency of APOE4 varies considerably in different populations.

Although APOE testing is often used in research, its history has been controversial and most clinicians oppose its use in clinical practice.[651] The main reason that testing the APOE gene is currently not recommended for either diagnosis or prediction of Alzheimer disease is because it is not accurate enough (it has a very poor predictive value).[652,653] Many people without the APOE4 genetic variant get the disease and many people with it do not. In addition, there is no obvious benefit to using a predictive test when there is no known treatment to reduce the risk.

Many scientists argue that the link between APOE genotype and risk of Alzheimer disease indicates an important role of diet – particularly cholesterol levels – in this disease. However, several recent studies have not supported the idea of a link between cholesterol levels and risk of Alzheimer disease.[654,655,656] There is currently no suggestion that specific dietary advice should be targeted at people with the APOE4 gene.

One recent study has found a gene-environment interaction between the APOE4 gene and drinking alcohol in middle-age (but not old age): risk of dementia increased with increasing alcohol consumption, but only in those individuals with at least one copy of the APOE4 genetic variation.[657] However, other studies have given conflicting results.[658]

In general, genetic studies of these disorders may provide clues to disease mechanisms, but appear unlikely to be able to quantify risk sufficiently accurately to be of use to individuals, or to overcome concerns about creating unnecessary fear of future illness. This is likely to limit the potential to provide reliable genetically tailored dietary advice.

6.2.11 Vitamin and mineral deficiencies and overload

Some rare genetic disorders affect the body's ability to break down and use vitamins and minerals.[214] In one recent example of research, scientists have discovered mutations in a gene that are responsible for a rare inability to process vitamin B, which may cause breathing, feeding, visual and developmental difficulties in babies.[659] Although more common genetic variations in the MTHFR gene also affect the body's ability to metabolise B vitamins (folate), unlike some rare mutations they do not cause a severe deficiency. The implications of these common genetic variations for health are poorly understood and the effect is very small compared to other factors (see Sections 6.2.4.3 and 6.2.6), so that tailoring dietary recommendations to these genetic variations makes little sense.

The body's ability to use minerals, such as iron, can also be influenced by genetic factors. Haemochromatosis is an inherited disorder of iron metabolism, which involves an increased absorption of iron from the diet.[660] In about one in 200 northern Europeans this is caused by mutations in both copies of the HFE gene, although other genes may also be important, especially in different populations. Although people with mutations in just one copy of the HFE gene are much more common (perhaps 20% of some European populations),[661] this does not appear to increase their absorption of iron from food.[662]

Haemochromatosis is difficult to diagnose because iron overload occurs slowly over many years and initially causes non-specific symptoms such as tiredness or abdominal pain. Over time excess iron accumulates in the body (known as 'iron overload') and can damage organs such as the liver, pancreas and heart. However, it can be treated by regular blood letting (phlebotomy), which reduces the risk of organ damage by removing iron from the blood, making early detection and treatment beneficial. Dietary recommendations include limiting red meat consumption; however, iron cannot be removed except by blood letting, so dietary changes alone are insufficient to treat this condition.[663] For people without haemochromatosis, too little iron in the diet can lead to anaemia, so it is also important that only people with iron overload limit iron intake.

Various measures of iron levels in the blood can be used to diagnose haemochromatosis; however, there is no clear definition of the disease because not everyone with raised iron levels goes on to develop serious symptoms. Alternatively, or in addition, genetic testing can be used. However, neither biochemical nor genetic tests are currently recommended for population screening. This is because many people with mutations never develop symptoms – one study has suggested that only 1% of people with two mutated copies of the HFE gene go on to develop significant clinical disease.[664,665,666,667] Another more recent study concluded that genetic screening could be useful because it allows the individuals who have been identified to be followed up with other tests and, if necessary, treatment by bloodletting.[668,669]

In general, it seems likely that common genetic variations (polymorphisms) make only small differences to an individual's ability to metabolise vitamins and minerals, limiting the usefulness of tailoring dietary recommendations to a person's genes. However, rarer mutations may make more difference and in some cases genetic testing may be useful to help diagnose diseases where changing diet may be part of treatment.

7. Genes, food preferences and mood

Section 6 considered the evidence that some people are more genetically susceptible to disease than others, even when they eat the same foods. However, some research is also looking at the relationship between genes, diet and behaviour: including how genes affect food choices and how genes and diets may act together to influence behaviour, including which foods people choose to eat, their appetite and mood. One reason for the interest in this area of research is that genetic differences in metabolism do not seem to be very important in influencing who becomes overweight or obese (Section 6.2.1), but, at least in some rare cases, mutations in some genes can affect a person's appetite or eating behaviour. In addition, the food industry is interested in developing functional foods that affect appetite or mood (Box 3.19) and the pharmaceutical industry has a major interest in developing new drugs that suppress appetite (Section 3.6).

Studying the influence of genetic differences on eating behaviours is at an early stage. It is part of the science of 'behavioural genetics' which has a long history of controversy and misleading claims.[670] Despite many controversial claims, *none* of the statistical links made between genes and the behaviour of healthy people has yet been firmly established. They are not statistically significant (i.e. they do not meet normal standards for scientific evidence) when all the data are combined.[671]

However, different foods are known to have psychological effects: for example, foods may influence mood and appetite and some may be addictive or have medicinal uses (for example, in Chinese or herbal medicine). Drinks containing caffeine (including tea, coffee and Red Bull) or alcohol already sell partly because of their effects on the human brain. Some genetic differences are known to play a role in taste, which may influence food preferences. Addiction also has a biological basis and some scientists think that genetic differences play an important role. This section outlines research on the role of genes in food preferences, appetite and taste.

7.1 Food preferences, appetite and obesity

> *'You've got millions of people telling you “doctor I just look at a cream bun and I gain a kilogram”, and we were so stupid as to believe them. The universal impression by doctors and everyone else is that metabolism must underlie weight differences. We've spent hundreds of millions of research dollars looking at various energy-sparing schemes in the body, searching for metabolic effects. And we've roundly failed to find any. To put it bluntly, the thrifty gene might be better called the greedy gene.'*
>
> Professor Andrew Prentice, London School of Hygiene and Tropical Medicine, 2002[169]

Partly because differences in metabolism have been shown to be less important than previously thought in determining who becomes overweight (Section 6.2.1), there is increasing interest in studying the role of genetic factors in influencing appetite (in simplistic terms, looking for the 'greedy gene') and food choices (particularly why people prefer foods high in fat and sugar).[672] This research is leading to new collaborations between behavioural and genetic scientists in an attempt to provide a 'psychobiological' explanation of food intake.[313]

In rare cases, genetic mutations in a single gene can cause obesity (Box 7.1). All these known genetic mechanisms involve overeating (i.e. behavioural changes in food consumption), rather than different biological responses to the same amount of food, showing that genetic differences can play a major role in appetite.[93] They are all part of the same biological pathway (known as the leptin pathway) that regulates food intake.

Box 7.1. Leptin and obesity[380,169,673,401]

Leptin deficiency In 1994, American scientists discovered two genetic mutations in the 'ob' gene, responsible for making mice obese. This gene contains the instructions for making a hormone called leptin which plays a role in controlling appetite. Scientists at Cambridge University then found leptin deficiency in two children in 1997 and subsequently successfully treated them with leptin injections. Later, partial leptin deficiency was discovered in 13 members of three unrelated families of Pakistani origin who were unusually fat.[674] Although the discovery of leptin may contribute to a better understanding of the mechanisms of appetite (particularly the human response to starvation),[675] only a handful of families with extreme forms of obesity in early infancy are thought to have mutations in this gene. The 1994 discovery generated enormous media excitement and a dispute between scientists. One member of the team involved (Jeff Friedman of Rockefeller University, see also Box 6.4) filed a patent and was accused by others of cutting them out of the credit – and potential financial reward – for the discovery. The US company Amgen paid $20 million up front for the rights, reportedly the highest amount ever for a university-held patent. However, initial excitement about leptin as a treatment for obesity has now died away because, although lack of leptin can cause obesity, increasing leptin levels in most people does not help to reduce appetite.[179]

Leptin receptor gene (LEPR) Leptin binds to the leptin receptor (coded for by the 'db' gene), which was discovered and patented by Millennium Pharmaceuticals in 1996. One family has been identified with leptin receptor mutations, causing extreme obesity similar to that found in individuals with leptin deficiency, as well as growth retardation.

Pro-opiomelanocortin (POMC) One effect of leptin binding to its receptor is to increase expression of the POMC gene. Two children with mutations in POMC have been found who were obese and also had red hair and adrenal deficiency.

Proconvertase (PC1 or PCKS1) The enzyme PC1 breaks down POMC and so is part of the leptin pathway. In 1997, Cambridge University scientists identified a woman with a mutation in PC1 who had developed extreme obesity in childhood.

MC4R deficiency MCR4 deficiency is the commonest form of obesity caused by mutations in a single gene. The MC4R receptor is part of the leptin pathway. More than 50 different mutations in the melanocortin 4 receptor (MCR4) gene have been found in different families. Mutations are thought to be present in about 0.5% to 4% of obese children in different populations.[676] Some mutations seem to have less effect than others, leading to normal obesity (with perhaps an earlier age of onset), rather than extreme forms. The lack of MCR4 causes an intense feeling of hunger in children, but the effect lessens in adolescence.

Finding genes which play a role in appetite might help improve understanding of the biological mechanisms involved and could lead to new drug treatments for obesity (see also Section 3.6).[677,678] Some scientists also believe that one day lifestyle advice could be tailored to these individual genetic differences i.e. the methods used to try to help people change their diets would be different depending on what genes they have.[679] However, all the genetic mutations described in Box 7.1 are extremely rare. This approach would therefore depend on identifying genetic differences that are important in influencing appetite or food choices in a much larger number of people.

Some evidence of the role of genetic differences in appetite and food choices is available from twin studies.[680,681,682,683,684,685,686,687] The usual problems with interpreting twin studies apply (see Section 6.1) – in particular the classical twins method can exaggerate the importance of genetic differences and minimise the role of culture, environment and individual choices. Even so, most twin studies have found that genetic differences seem to have only a relatively modest effect on food choices, although one more recent study has given higher heritability estimates (particularly for eating considered to be 'emotionally induced').[688]

Common genetic variations exist in the leptin receptor gene (LEPR); however, a meta-analysis combining studies involving 3,263 people found no evidence of a statistically significant link with body mass index (BMI) or waist size.[689,690] Only a few studies of gene-diet interactions have been done for genes that might play a role in appetite, so no firm conclusions can be drawn about effects on weight loss.[418]

Although studying very rare conditions may help to understand the biological mechanisms of appetite control, it is still not clear whether there are major genetic differences in appetite or food preferences in most healthy people. A preference for fatty, sugary foods is common, especially in children, and may be linked to the advantage in survival this provides in times of dietary scarcity. But this does not necessarily mean that major genetic differences in food preferences exist between most individuals. Social, economic and cultural factors could be much more important in influencing what people eat, and tackling them may be more important in achieving dietary change.[31,28,372] Sustained consumption of fat and sugar may also influence appetite, in such a way as to increase consumption.[691]

One application of studying the genetics of appetite is to try to develop functional foods which help to suppress appetite (Box 3.19). These might use genetics as one tool to help research and development, in the same way as anti-obesity drugs. Or such foods might be 'personalised' – meaning different functional foods for different people, depending on their genes.

In one example of this type of research, the BioPsychology research group at Leeds University which is investigating the potential for functional foods with effects on appetite and behaviour (Box 3.19) is also trying to work out the role that genes may play in influencing people's appetite and food preferences. Currently this research is at an early stage: it involves the classification of different eating patterns in different people, beginning with high-fat and low-fat eating patterns. In the future, these researchers wish to examine the interaction between genes and culture in influencing food choices, and to work with molecular biologists to identify the gene variants involved.[692,693]

The European research project DiOGenes (Table 7), which includes the food companies Danone, Nestlé and Unilever in its consortium, also involves food technology studies to 'develop food characterized by consumer liking and preferences but at the same time by enhanced satiety signals that limit intake'.[230] The researchers involved claim that the insights involved will 'pave the way for new concepts in the design of functional food products that enhance weight control capability in susceptible people'. Smaller companies involved include the French genetic testing company IntegraGen[694] and the Dutch food research company Nizo.[695]

7.2 Taste

Human tongues can taste five basic flavours: salt, sweet, sour, bitter and umami (the flavour of monosodium glutamate). Our sense of taste is also strongly affected by our sense of smell. There is good evidence that some genetic differences play an important role in how bitter some foods taste to different people (Box 7.2).

Box 7.2. Bitter vegetables and PTC[696,697,698,699,700]

In 1931, a chemical called phenylthiocarbamide (PTC) was accidentally found to have a strong bitter taste to some individuals, but very little taste to others. A related chemical called PROP (6-n-propylthiouracil) also shows the same effect, and similar chemicals are found in some bitter vegetables such as cabbage, broccoli, Brussels sprouts and cauliflower.

Most of the variation in PTC taste sensitivity between individuals is due to genetic variations in the TAS2R38 gene. However, other genes are also likely to be involved. Although people used to be divided into 'tasters' and 'non-tasters', there is considerable overlap between these categories. Some people (called 'super-tasters') find the bitterness of PROP extremely strong.

These genetic differences can to some extent explain why some people have a strong dislike for bitter-tasting vegetables. However, the sensitivity to bitterness decreases with age and the response to particular foods may also depend on other factors (such as whether broccoli is cooked). Children who taste bitterness strongly are more likely to prefer sweet foods, but other factors (probably cultural) have an influence, and the effect of the TAS2R38 gene on preference for sweet foods appears not to persist to adulthood. These genetic differences also seem to have some effect on people's response to other tastes and mixtures.

Although taste undoubtedly influences food choices, cost and convenience play a major role.[701] Thus, low-income families are the most likely to consume diets high in sugar and fat because they provide dietary energy at very low cost.

The Californian biotechnology company Senomyx is trying to use knowledge of the genetics of taste and measures of gene expression (Section 4.1) to develop new compounds for flavouring foods. It has research agreements with companies including Nestlé and Coca-Cola. It argues that if it is successful it could dramatically reduce the amounts of sugar, salt and other flavourings used by food manufacturers.[702]

8. Limited scientific evidence for genetically tailored diets

'To date, if at all, candidate genes have been weakly and imprecisely related to chronic disease phenotype when they occur. This is despite many millions of dollars spent in research funding and years of searching, which might also suggest publication bias.'

Scientists in the UK, Cameroon, Jamaica and France, 2001[456]

'Despite decades of research few genes have been found that play anything but a minor role in complex traits like heart disease, autism, schizophrenia or intelligence. The reason may be that such genes simply don't exist. Rather than being "caused" by single genes these traits may represent a network perturbation generated by small, almost imperceptible, changes in lots of genes.'

UK geneticist Johnjoe McFadden, 2005.[703]

'The short answers, to the questions of lack of predictive power of gene analysis and of why we have thrown out the facts rather than the theory, are not too difficult. The explanation formulated here is that polygenic [multiple gene] *disease and growth regulation are not linear processes and cannot therefore be fully analyzed by a linear logic. Rather, they are representatives of complex adaptive systems that are innately unpredictable.'*

US biologist Richard Strohman, 2000[704]

Given the hype around nutrigenomics and nutrigenetics, there is remarkably little evidence that genetic differences can allow us to predict who will suffer from most common diet-related diseases. With the exception of the major food intolerances (to milk, fava beans and alcohol) the body's ability to respond to different diets is complex and likely to be extremely hard to predict from a person's genetic make-up. Even in an ideal world (where genetic tests reach those most in need, and people change their diets as a consequence) the efficacy of genetically tailored diets is likely to be limited by the complexity of human diets and of our biology.

In general, the idea that personalised diets, tailored to individual genetic make-up, are a good way to reduce the incidence of diet-related disease is built on a large number of questionable assumptions (Box 8.1).

Box 8.1. Nutrigenetics: some myths

1. Extrapolation from simple examples

Evidence from the major food intolerances (such as lactose intolerance) or rare genetic diseases (such as PKU) is often extrapolated to other diseases (such as heart disease, or adult-onset diabetes) to argue that people's diets should be matched to their genes. However, these genetic conditions are unusually simple and/or vary rare – they do not involve so many different genetic, social, lifestyle, economic and environmental factors as most common diseases. Strong gene-diet interactions, which mean that conditions such as adult lactose intolerance occur only in people with certain genetic mutations, are probably the exception rather than the rule.

2. Our future health can be predicted from our diet and our genes

Evidence that not everyone who eats a bad diet gets ill is often cited to imply that genetic factors must determine which individuals will get a particular disease. Evidence that biological factors (such as cholesterol levels) vary between individuals is also often assumed to mean that the variation must be caused by genetic differences. This deterministic view is false, because chance usually plays a role, as do other (non-genetic) factors. It also implies that predicting diseases will be unrealistically simple – scientists will never be able to see perfectly into the future. Even if all the genetic and environmental factors involved in a disease were known this does not mean complex disease is predictable. In most cases, our future health is likely to be much harder to predict than the weather is and basing diets on misleading health predictions could do more harm than good.

3. Genetic differences explain the higher risk of some diseases in different ethnic groups

Because some diseases are more common in different ethnic groups (for example, diabetes in the Pima Indians in Arizona, or hypertension in African-Americans) it is often assumed that this must be because of genetic differences. However, different social, cultural and environmental factors could also be to blame. The populations at highest risk of obesity and type 2 diabetes are marginalised, dependent on food aid and subject to practices such as the fat dumping of unhealthy food products.

4. Twin studies prove that genetic differences are important

Twin studies which calculate heritability make numerous questionable assumptions and always overestimate the importance of genetic differences in common diseases by an unknown amount. High heritability does not in any case mean that environmental factors are unimportant – the most effective way of reducing a disease with high heritability may still be to change environmental factors (including diets or social and economic factors). Heritability also says nothing about whether there is an interaction between genes and diet and hence provides no information about whether genetic tests are likely to be useful to target dietary advice.

5. Dietary advice should be targeted at those at highest genetic risk

If there is no gene-diet interaction, targeting dietary advice at those at high genetic risk will not help to reduce the incidence of the disease and could even increase it. This is because those at highest risk could have less to gain (or no more to gain) by changing diets than the rest of the population. Often, there will be better ways to target resources than using a genetic test. In addition, targeting advice at a minority of the population is likely to be less effective than public health approaches which seek to change the diet of the population as a whole.

6. Family studies show that genetic factors are important

Diseases which run in families may do so by chance or because of shared genes, shared diets, other social, economic and environmental factors, or a complicated combination of all of these. Evidence that diseases run in families does not necessarily mean that inherited genetic factors are important.

7. Genetic factors and gene-environment interactions have already been identified for many diet-related diseases

Most genetic association studies later turn out to be wrong. The small number of genetic factors that are known to play a role in common diseases usually make only a small difference to a person's risk, or are found only in a small minority of cases. Most gene-diet interactions have yet to be confirmed by further studies and existing studies are too small or badly designed to distinguish a real effect from chance. In any case, an interaction between a single gene and a single dietary factor does not necessarily mean that diet should be tailored to a person's genes – this will depend on how lots of different factors work together (it will depend on the combined statistical effect at the population level).

8. Personalisation of dietary advice is more effective

There is little evidence that genetic test results help people to change their behaviour and some evidence that they may encourage people to look for medical solutions. There is no such thing as individual risk and genetic risk categories are not personalised because genes do not make a person who they are or determine their future, even when dietary factors are included. Genetic categories also ignore many other (medical and social) factors that may be much more important to the person who is being tested. Research also suggests that population-based interventions (such as changing prices) are more likely to be effective than individualised ones. The poor suffer more from poor nutrition because foods high in fat and sugar are a cheaper way to satisfy the appetite, not because they need advice that's tailored to their genes.

Genes do of course play an important role in the body's cells and how they respond to diet, and gene-diet interactions do appear to exist at the level of individual genes and nutrients. But in most cases genetic differences appear to make only small and subtle differences to a person's risk of diet-related disease and hence very little difference to the foods that they should eat. Diets contain multiple foods, foods contain multiple nutrients and the body digests these nutrients through multiple biological pathways, involving many different genes and other factors. Because of this complexity, the evidence suggests that the 'individually tailored diet' is more of a marketing concept than a scientific one.

There may of course be exceptions for particular diseases, or special cases of familial (largely inherited) forms of some diseases, where mutations in a single gene dominate an individual's risk. But tailoring dietary advice to these genetic tests is useful only in a few specific cases: where a genetic test is a good predictor of a disease and where gene-diet interactions are large (so that people at high genetic risk have most to gain by changing their diets). Lactose intolerance is one example, although it does not necessarily need a genetic test for diagnosis.

Some nutrigenomics research may also help increase understanding of diet-related diseases, by helping to identify the different biological factors and dietary factors that may be involved. However, this does not mean that personalised or genetically tailored diets will be a good approach to tackling the growing incidence of chronic diet-related disease. This is because small and uncertain differences in risk may be enough to help researchers find clues to our biology: but large, well quantified differences in risk are needed before it makes sense to tailor diets to our genes.

Currently it also seems unlikely that common genetic variations will have a large enough effect on response to diet for it to be necessary to change existing dietary guidelines for the population as a whole.[705] Although genetic differences can play an important role in taste, social and cultural factors appear to be much more important in food choices. Appetite-reducing foods are unlikely to overcome the economics of fat dumping or other practices which target products high in fat and sugar at low-income consumers. It is also unclear why food industry research on taste, mood and food choices would not continue to be used to market the most profitable products, rather than the healthiest ones.

9. The potential negative health and social impacts of nutrigenomics

'Screening for chronic disease with as yet undiscovered genuine genetic markers will not only detect very few individuals but, of great concern to both the individuals "detected" and for those paying for any such programme, will do so imprecisely and unreliably.'

Scientists in the UK, Cameroon, Jamaica and France, 2001[456]

Although genetic testing combined with dietary advice has been widely promoted as a means to tackle common diet-related diseases, the reality is very different. Claims for a future of personalised nutrition ignore the increasing scientific recognition of biological complexity, which makes individual risks inevitably uncertain and hard to predict. In practice, in many circumstances personalised nutrition could harm health by:

- targeting the wrong dietary advice at the wrong people (either by wrongly identifying those at high genetic risk, or wrongly implying that they have most to gain by changing diet);
- confusing healthy-eating messages (for example, by implying that existing dietary advice is guesswork, and by different companies selling many different products and conflicting advice);
- undermining public health approaches (implying that only a minority of people with bad genes need to eat a healthy diet);
- medicalising genetic risk (increasing costs and side-effects by encouraging people to buy medicines, supplements and functional foods instead of fruit and vegetables);
- diverting resources (including research resources) from more effective approaches; and
- promoting a false solution to the current epidemic of diet-related disease.

Widespread genetic testing also has social implications, including potential impacts on privacy or on access to insurance. The implications of this future vision for health and for society are discussed further below.

9.1 Personalised diets: diverting science

'[Public health] *problems are exacerbated by the concentration of funding on biomedical research and the failure to confront and work with vested interests, which promote and sustain unhealthy behaviour patterns.'*

Robert Beaglehole (World Health Organisation) and co-authors, 2004[706]

'The dearth of [public health] *evidence is not unrelated to the lack of funding of public health intervention research with funding from research organisations and the private sector heavily directed towards clinical, pharmaceutical, biological and genetic research – and the lack of a clear and coherent set of Government priorities for the public health research which does exist.'*

Derek Wanless, 2004[707]

Many scientists, funded by the food industry, biotech companies and governments, have stated that the fundamental goal, and the next great challenge, of the nutritional sciences is to *tailor nutritional requirements to the individual* and thereby optimise diets for health.[708,282,568] However, personalising diets is a deeply questionable research priority. The focus on genetics and genomics as a means to tackle diet-related disease is technology- and market-driven – it has not been informed by an assessment of the likely benefits to health. Rather than shifting the focus of research from medicines to public health, this strategy seeks to turn foods into medicines and prevention into personalised marketing.

An alternative aim for nutrition science is 'to contribute to a world in which present and future generations fulfil their human potential, live in the best of health, and develop, sustain and enjoy an increasingly diverse human, living and physical environment'.[709] This approach recognises the importance of social and environmental issues, such as where food comes from, and the importance of improving the health of populations, not just of individuals. In contrast, the aim of personalised nutrition excludes this important context and ignores the politics of food.

Nutrigenomics research prioritises the development and marketing of new 'healthier' food products, because financial growth is a priority for food manufacturers, and because they want to market 'wellness' to improve their profits and their public image. Individualising dietary advice, based on genetic test results, also allows this 'knowledge' to be privatised and sold as a commodity. Wealth generation through science and technology (particularly the knowledge-based economy) drives the policies of many governments. This has led to policies which allow gene sequences to be patented and the links between genes and diseases to be claimed as 'inventions' in patents for genetic tests. This genetic knowledge (information) can be marketed, even though most of it is wrong (misinformation), because genetic tests are not properly regulated.

The food industry aims to market wellness while increasing profits – but what is best for food manufacturers may not be what is best for health. Plenty of healthy foods (mainly plant-based foods: such as fruits, vegetables and whole grains) already exist and are likely to remain cheaper than premium-priced functional foods and individually tailored products. Access to fruit, vegetables and whole grains can be a problem for lower socio-economic groups, who may live in 'food deserts' or not be able to afford these foods, but this problem will not be solved by introducing new, more expensive products. The priority for health is not to make new foods, but to find out what will work in terms of helping people change their diets and live healthier lives, especially people in lower socio-economic groups and poorer countries. These people need healthy foods to be cheaper and more accessible, not more expensive – which means tackling the politics of food, including the role of agriculture, food companies, governments and supermarkets.

Using functional foods to tackle diet-related disease also poses major challenges to regulators, not just in assessing safety, but also in establishing whether there are any real benefits to health. Marketing practices as well as the properties of the foods themselves influence their impact on the health of populations. The examples of diet fizzy drinks and low-fat cakes and biscuits highlight the serious limitations of this approach to health. Individual products cannot substitute for a healthy, balanced diet. They are often healthy in only limited respects (for example, lower in fat but no lower in calories and still lacking in nutrients) and are marketed in the context of a general increase in consumption of the less healthy versions of the same products (meaning more fizzy drink and cake consumption overall).

Some nutrigenomics research may contribute to better understanding of the mechanisms of diet-related disease. This is because small genetic differences (and other biological measurements) may be enough to give scientists new clues about how these diseases work. However, nutrigenomics research is inextricably linked with its commercial aims, including personalising diets and identifying new 'magic bullet' ingredients for functional foods. This health strategy can work only if genetic tests are useful in deciding who should get which dietary advice – something which is unlikely for most diseases in most people – and if the multiple effects of different foods and diets can be reduced to single chemicals. There are dangers in promising too much, raising unrealistic expectations, and in confusing public health messages.[3]

For governments, there is little doubt that public health intervention research – not personalised nutrition – should be the priority in tackling diet-related disease. This requires a major shift in the allocation of resources. However, food companies should also question the merits of pursuing individualised nutrition in the face of the growing evidence of its scientific limitations, and the potential for misinforming and misleading customers.

9.2 Undermining public health?

> *'Current lifestyles predisposing to diabetes are a societal problem and need to be tackled at this level rather than at the level of the individual and it could be counter-productive if some individuals gained the impression that genetic differences might make them less susceptible to diabetes and thus not at risk from whatever lifestyles they choose.'*
>
> UK geneticist Dr Nick Wareham, 2004[3]

Tailoring diets to genetic make-up raises major concerns because privatising and individualising dietary advice could easily confuse and undermine healthy-eating messages. Personalising dietary advice, based on genetic make-up, is a marketing strategy not a scientific one. Because unhealthy diets increase the risk of many different chronic diseases, it makes little sense to try to find out which individuals will benefit most from eating less junk food and more fruit and vegetables. The scientific difficulties in predicting who has most to gain from which dietary changes are likely to prove insurmountable for most common diseases in most people. There is also little evidence to suggest that genetic test results will motivate more people to eat healthily (and some evidence that testing will encourage them to turn to medical solutions). The marketing of existing nutrigenetic tests reveals the significant potential for misleading interpretations and advice, and for multiple confusing and conflicting messages and products sold by different companies.

Despite the marketing claims of existing genetic testing companies, current public health advice is not guesswork and genetic tests do not improve the accuracy of dietary advice. Public health approaches have also not been failures, as significant reductions in heart disease in developed countries show. However, these approaches are continually undermined by the politics of food, including food industry marketing practices. Because personalised nutrition is a false solution to dietary disease it can also undermine public health approaches by misleading politicians and the public about what action and research is really needed.

There is also significant potential for conflicts of interest in personalised nutrition. The food and biotech industries intend to sell their own dietary advice and profit from the products they design to correct the 'biological imbalances' that they identify. It is naive to expect the processed food or fast food industries to advocate that most customers eat fewer salty, fatty products because this would undermine their own commercial interests. It is also not obvious why future applications of 'psycho foods' (foods designed to alter appetite or mood) would be restricted to marketing healthier products, rather than whatever is most profitable. Additives such as flavourings are currently typically used in foods of *poor* nutritional value, to make them more acceptable to consumers: there is no obvious reason to expect that studying the genetics of taste will change this marketing strategy.

9.3 Misleading consumers

> *'If we are going to truly reap the benefits of our ability to analyze our own genes, we must be honest about what we can understand and what we can't. Without this understanding, the information we glean from our genes will end up lining the pockets of the most mendacious at the expense of the most credulous.'*
>
> Evan Lerner, Council for Responsible Genetics, USA[710]

Genetic testing involves significant potential for consumers to be misled about their health through a lack of regulation of genetic tests and the confusing and contradictory information that will arise.

9.3.1 Genetic testing unregulated

In the UK, genetic tests can be marketed directly to people without a regulatory assessment[711,712] despite many published criticisms of direct-to-consumer sales of genetic tests in scientific journals.[713,714,715,716] The inadequate regulation of genetic tests means that companies can make their own interpretations of what a person's genes mean for their health and what action they should take. In fact, most of these tests have not been established as clinically valid (Box 9.1) and even those genetic variations that are genuinely linked with an increased risk of a particular disease, are not useful to decide who should eat which foods or take particular supplements (they have no clinical utility, Box 9.1).

> **Box 9.1. Assessment of genetic tests**[717]
>
> **Analytical validity** is how well the test measures the correct sequence of DNA, which depends on laboratory methods and quality assurance.
>
> **Clinical validity** refers to the accuracy of the test in diagnosing or predicting risk of a given a health condition.
>
> **Clinical utility** depends on how useful the test is for deciding who should be offered a particular health intervention. Even if a test is valid it is unlikely to be useful if there are better ways to decide who should be given a particular medicine or product (e.g. a different type of test or means of diagnosis), or if health advice (such as advice to stop smoking or eat healthily) should be the same for people with both positive and negative results.

Current practice in the USA is that tests that are packaged and sold as kits to multiple laboratories require pre-market approval or clearance by the Federal Drugs Administration (FDA). This means that the FDA will in some cases make an assessment of the clinical validity of the test (but not usually its clinical utility). However, a major loophole exists because tests that are not supplied as kits but provided as 'clinical laboratory services' (most genetic tests) receive no assessment of either clinical validity or clinical utility. The FDA has the authority to regulate these 'home brew' tests but currently chooses not to do so,[718] despite the concerns of several expert bodies about this situation.[719,720]

In Europe, there is no regulatory assessment of any clinical data relating to genetic tests. The relevant European legislation is the Medical Diagnostic Devices Directive (93/42/EEC, as amended) and the In Vitro Diagnostic Devices (IVD) Directive (98/79/EC). This Directive focuses mainly on analytical validity, but where a laboratory makes clinical claims for a test (such as that it can predict susceptibility to a particular disease) it may need to have some data to support the claim. However, there is no pre-market assessment of this data and no existing system by which this could be done.

The IVD Directive is implemented in the UK via the Medical Devices Regulations 2002.
In the UK, the Government's advisory body, the Human Genetics Commission (HGC), has considered the issue of the sale of genetic tests direct to the public. It published its report *Genes Direct* in April 2003.[721] The HGC concluded that 'most genetic tests that provide predictive health information should not be offered as direct genetic tests' and that companies wishing to sell genetic tests should have to 'convince a regulator that the test is suitable'. However, it provided no credible mechanism for this process to take place. The HGC recommended that the Medicines and Healthcare Regulatory Agency (MHRA) should oversee the wider issues such as clinical validity, clinical utility and the advice given to customers. However, the Government has not responded to the HGC's advice and no assessment currently takes place. In the meantime, a voluntary code of practice for assessing and monitoring genetic testing services, adopted by a previous committee, has been withdrawn.[722]

9.3.2 Confusing advice

The privatisation and individualisation of dietary advice is likely to lead to many different and potentially confusing recommendations, depending on the genes included and how the uncertain risks of dozens or hundreds of different genetic variations are combined. Each genetic testing company will have different licensing deals to direct-market supplements, medication and functional foods based on the results of genetic tests. Recommendations which do not involve prescription medicines, including recommendations to eat functional foods, are likely to be marketed directly to individuals, perhaps via e-mail, mobile phone, direct mailings, door-to-door distributors, or offers linked to supermarket smart cards. No individual will be classified as 'normal' following a panel of multiple genetic tests: such genetic testing would therefore allow a massive expansion in the market for personalised health and wellness products, including functional foods.

There is also considerable potential for nasty surprises, such as the APOE4 genetic test sold to identify susceptibility to heart disease, but which has a significant association with risk of Alzheimer disease. Personalised products, such as functional foods, may also have unintended consequences for a person's health. Products intended to be marketed using this approach include genetically modified (GM) foods, 'psycho foods' (foods intended to alter appetite or mood) and foods with added nanotech ingredients.

Finally, there are implications for individual privacy and human rights including:

- how personal genetic data will be stored and used, including for research or direct marketing of products;
- whether the police or governments will be given access to commercial genetic databases;
- whether people will be required to reveal genetic test results to insurers or employers (see Section 9.4).

9.4 Privacy, stigma and discrimination

Implementing personalised nutrition requires large-scale databases of genetic data and lifestyle advice, linked either temporarily or permanently with biological samples (blood spots or cheek cells from a mouth swab). Biobanks raise many important issues, including how consent is obtained for different uses of the information and how privacy can be guaranteed. These databases may be owned and controlled by governments and health services, or by commercial companies, or a combination of the two. The laws to protect genetic privacy and prevent genetic discrimination (for example, by insurers and employers) vary considerably from country to country.[723]

Some genetic tests included in nutrigenetic panels (especially the metabolism genes, linked with the body's response to chemical pollutants and possible susceptibility to cancer) are the same ones of interest to employers who may wish to identify potential employees who are supposedly genetically susceptible to hazardous chemicals in the workplace.[724] Many trade unions are opposed to this idea, because genetic tests are poor predictors of who is likely to become ill and may be used to undermine attempts to make the workplace safe for all.[725] There is also concern that tests which supposedly identify people susceptible to heart disease might be used to try to cut the costs of early retirement, by restricting people's pension rights based on their test results.

In the UK, there are no laws to prevent employers using genetic test results to refuse someone a job, and only a voluntary agreement between the Government and insurers, which currently prevents insurers using most genetic test results for most policies.[726] This agreement expires in 2011 and it is currently unclear what policy will be adopted after that date. Genetic discrimination by insurance companies would *not* require commercial testing companies to reveal results to them – the insurance industry would simply make policies invalid if customers did not reveal test results when asked to do so.

In the UK, the police may also seek access to genetic databases for forensic purposes, provided they can convince a judge that this is in the public interest.

9.5 Ethnicity and race

> *'I told her I had come to* [the Pima Indian reservation town] *Sacaton, the front lines of the weight battle, in order to find out what really works in fighting obesity. She looked at me and shrugged. "We're the last people who could tell you that," she said.'*
>
> The Pima Paradox, 1998[727]

Historically, genetic explanations for disease have been used against ethnic minority groups, causing stigma and discrimination, and being used to justify colonialism and eugenics.[728]

Some scientists argue that tailoring diets to ethnicity or race may be one consequence of nutrigenomics.[729] However, because of the history of slavery, colonialism and racism, many ethnic minorities in countries such as the UK and the USA suffer from social and economic conditions likely to have an adverse impact on their health. It is very difficult to disentangle these effects from the effects of different genes. Human beings are all one species and biologically distinct races do not exist.[730] To some extent broad geographical ancestry (for example, Africa, Europe or Asia) can be predicted from the frequency of different genes;[731] however, the results depend on the regions considered, the number of genes tested and the extent to which populations have mixed in the past.[732] The relationship between skin colour and ancestry is also complex[733,734] and appears to have been influenced by social factors (the racist treatment of people identified as black).[735]

Unless genetic testing is genuinely useful to guide treatment, promoting genetic explanations for diet-related disease can be counter-productive. For example, using changes in diet and physical activity to prevent diabetes in the Pima Indian population in Arizona has been dismissed by some researchers as impossible to achieve, on the assumption that their high rate of diabetes is due to genetic factors. Despite decades of research on this population, culturally appropriate programmes to prevent the illness, such as the Native American Diabetes Project, are only just beginning to be implemented.[736]

Diabetes prevention can depend critically on cultural perceptions of health and illness: which are influenced by many factors including the history and marginalisation of Native American peoples. Among other factors, a number of studies have found a sense of fatalism (or surrender to factors seen as beyond people's control) to be a barrier to preventing diabetes in American Indian[737] populations – including a belief that American Indian descent leads to an increased susceptibility to diabetes, and that diabetes is inherited and is inevitable in individuals with a strong family history of the disease.[738,739,463]

In the Pacific Islands, studies of the genetics of appetite also detract from the social and economic factors that make imported sugar and canned, fatty meats such a major part of many people's diets.

Another issue is 'biopiracy': the patenting of gene sequences by researchers in an attempt to claim monopolies for new genetic tests and treatments. Many indigenous peoples oppose gene patenting, feeling that it conflicts with their own values.[740] The Australian company Autogen was forced to drop claims to have negotiated rights to access the gene pool of the entire population of Tonga, following protests from church and community leaders.[741]

9.6 Health inequalities

> *'In a modern world, atherosclerosis is an almost evolutionary certainty'*
>
> Cover of International Journal of Clinical Practice, Supplement 134, sponsored by AstraZeneca

Health inequalities continue to play a significant role in life expectancy in the UK and elsewhere and an over-emphasis on genetic risk factors can divert resources from addressing the major social and economic determinants of ill health.[742]

It is obvious that a strategy designed to produce and market techno-foods based on individual genetic profiles is not the strategy most likely to tackle health inequalities. Genetic tests and functional foods will be targeted at relatively wealthy consumers in developed countries – those whose social and economic circumstances usually mean that they are at the lowest risk of most chronic diseases. This emphasis on new food products also ignores the limited range of food choices available to the most disadvantaged groups, who tend to eat less expensive but less healthy diets.[31] Unless the current biases in agriculture and food supply are tackled, the poorest quality food, highest in fat and sugar, will continue to be marketed to the poorest people.

Although it is possible that multiple genetic tests (or even whole genome scans) will be provided for everyone (perhaps at birth) via health services such as the UK's National Health Service (NHS) at some point in the future,[743] increasing access to expensive but ineffective technologies is hardly the approach most likely to benefit the poor and marginalised. This approach is unlikely to be cost-effective (Section 9.10) and is driven by a desire to achieve the maximum growth for companies (food manufacturers and pharmaceutical and biotech companies), not the maximum benefit to public health. In developing countries – where increases in chronic diseases are the most rapid – the idea of genotyping most individuals and offering 'tailored diets' has rightly been described as an 'impossible dream'.[744]

The advocates of a genetic approach to obesity argue that 'the drive to eat is to a large extent hardwired, and differences in weight are genetically determined' and that obesity is not a personal failing but a 'battle against biology'.[357] This neglects the lack of evidence that populations can be divided into 'genetically susceptible' and 'relatively resistant' individuals (Sections 6.2.1 and 7.1) and the harm that could be caused by misleading predictions of who is most at risk. But, perhaps more importantly, it ignores the important role of socio-economic factors. Although rightly recognising that it is important not to blame individuals, this view lets politicians and the food industry off the hook by implying that an obesity-promoting environment and unhealthy food production systems are inevitable.

The emphasis on genetic factors can also give poor families, and marginalised ethnic groups, the often misleading impression that heart disease or type 2 diabetes runs in their family as a result of shared genes – rather than shared diets, socio-economic factors and environment. A possible consequence is an over-emphasis on preventive medication, leaving unhealthy diets and lack of exercise as problems that are never tackled. The individualised approach of personalised nutrition could also make government action and investment in tackling health inequalities (such as 'food deserts') less likely. The impact of health inequalities on risk is usually much greater than the impact of genetic differences, and affects much larger numbers of people. It therefore makes more sense from a public health perspective to study what will help people living in poorer countries, or in low-income areas, to change their diets. This includes tackling fat dumping and food industry practices such as the mass marketing of cheaper products high in fat and sugar at lower socio-economic groups.

Because healthy foods, such as fruit and vegetables, contain multiple nutrients, it is extremely unlikely that a 'magic bullet' ingredient can be extracted, added to processed foods and generate a significant improvement in public health. Although this approach has worked well for nutrient deficiencies (helping to eliminate several serious deficiency diseases in developed countries), it is much less likely to be an effective way to tackle the multiple effects of over-consumption on the human body. Even if they make some marginal improvements to health, and avoid nasty surprises, functional foods, sold at a premium to the 'worried well', will not save the world from the current epidemic of obesity and diabetes. In many cases (such as omega-3 designer eggs) consumers are simply charged more for manufacturers to restore nutrients that already exist in less intensively farmed or unprocessed products. Furthermore, an approach that treats diseases caused by major shifts towards unhealthy diets and lack of exercise as an evolutionary certainty, and an inevitable consequence of modernity and progress, can only undermine attempts to implement more radical approaches and to divert attention from the politics of food (Section 3.7).

9.7 Personalised choice a contradiction?

> *'Nobody is eating exactly what you are. Your diet is uniquely tailored. It is determined by the specific demands of your genetic signature, and it perfectly balances your micronutrient and macronutrient needs.'*
>
> A vision of the future of nutrigenomics from New York Times Magazine, 2003[745]

> *'The ultimate goal of health care is to establish sufficient knowledge of genetic variation and environmental inputs to be able not only to understand these terms, but to use them to predict future outcomes and thus to redesign an individual's environment to improve their health'.*
>
> Scientists from Nestlé and Lipomics Technologies, 2002[212]

Food is about pleasure, culture and sociability, as well as having implications for our health. People also express their identity and beliefs through food: for example whether they are vegetarian or eat only halal meat.

Yet the vision of personalised diets implies that everyone should eat a different diet, based on their genes (and perhaps on other tests of their metabolism, that change with time). Further, it implies that people should trust genetic testing companies and food manufacturers to tell them what their ideal diet is. The testing companies often claim that nutrigenetics will take the guesswork out of deciding what to eat – the marketing vision could also be taken to imply that people should take the deciding out of deciding what to eat. The implication is that people should simply follow the expert recommendations and consume the products sold to them on the basis of their test results. One issue is whether individuals want to be the type of person who, as a way of life, takes genetic tests before deciding what to eat.[746] Another is the implications for shared meals and the social interactions associated with them – what happens in these situations if everyone is following different dietary requirements determined by their genes?[747]

The Food Ethics Council argues that the British Government's 'Choice' agenda is distorted by the uncritical adoption of the concept of personalisation being promoted by the food industry. The marketing strategy for personalised nutrition is not the same as making the food industry more responsible and accountable. This requires empowering people and tackling vested interests, not nutrigenetic tests. Targeting deprivation, using public procurement to improve meals in schools and hospitals, broadening research policy and regulating business are all important aspects of delivering better nutrition.[748]

Much of the language used to promote genetic testing claims people have a right to know their genetic risk status as a pre-condition of informed choice. Understanding geneenvironment interactions is seen to enhance risk assessment and provide an informed basis for exposure control and lifestyle adjustments for those deemed to be at risk. But this genetic worldview promotes genetic categories as more important than other social categories and masks the role of different powerful interests.[749] The food industry (like the pharmaceutical industry) clearly has an interest in promoting the concepts of individual genetic susceptibility, personalised nutrition (or medicine), and the potential role of individual nutrients in optimising health. But most personal genetic information relating to common, complex disease is more appropriately described as 'genetic misinformation'. It has little to do with informing choice.

9.8 Patenting and profiteering

The business driver for personalised nutrition is that new functional foods can be patented and command a premium price. This means that companies will claim monopolies over these new foods or their ingredients (typically for 20 years or more), just as pharmaceutical companies do with medicines.

Genetic tests are also patented. This means that genetic information is treated as an invention and subject to intellectual property rights, although the nature of the invention may be disputed and unclear.[750] Many patents for genetic tests include claims for the DNA sequence itself: this is one of the commonest ways of claiming a patent on a gene sequence.[751] Many people are opposed to gene patents because they allow discoveries about life itself to be claimed as inventions by commercial companies. This type of patent allows companies to charge monopoly prices, claim licensing payments for future uses of the gene sequence, and may restrict research.[752]

In addition, the availability of gene patents, and the basis on which they are granted, drives research in particular directions, because patent laws help to define what is genetic knowledge and what can be claimed to be a commercially useful invention.[753,754] Thus, universities and companies may prioritise research that identifies genetic factors in disease because they can be patented, even though other factors or different types of research may be more important.

9.9 Good for business?

Although the reasons why food manufacturers have identified personalised nutrition as an area of growth are clear, it is less clear that this business strategy will be successful. The major limitations of the science and the potential for nasty surprises, as well as privacy concerns, risk a loss of public trust.

Investors also appear unaware of the poor prospects for predicting risk from genetic tests, the notorious unreliability of genetic association studies, and the difficulties in quantifying gene-diet interactions. Although investors usually have a process of scientific diligence they may be almost as vulnerable as consumers are to companies who 'cherry pick' and misinterpret academic papers to support misleading marketing strategies.

It is also unclear what retailers, including pharmacists and supermarkets, have to gain from personalised nutrition. If genetic testing and personalised products appear in their stores (rather than solely via direct marketing) they may be at the front line of a consumer backlash if nasty surprises do occur. However, they will have little control over or access to the scientific data collected by commercial testing or food ingredients companies.

Genuinely healthy alternatives may also benefit businesses, but the companies which profit may be different. For example, selling more local fruit and vegetables through farmers' markets benefits farmers rather than food manufacturers.

9.10 Costs and resources

With the whole population potentially 'at risk' and eligible for preventive medication, the cost implications of genetic susceptibility testing have been described as 'staggering'.[755] However, it is difficult to analyse cost-effectiveness when the validity and utility of genetic tests have not been assessed and people's responses to the results are largely unknown. This leads to a wide range of views of whether a particular test is good for health at all, and if so whether it is cost-effective. Very few assessments have been done, but one commercially available test for genetic susceptibility to gum disease (which, like all susceptibility tests, is controversial)[251] gave a range of results from a saving of US$830,140 per 1,000 patients (with some cases prevented), to a cost of US$300,430 (with the number of cases increased).[332]

It is questionable whether functional foods will cut costs by replacing medication (such as statins) as some have claimed: an increase in sales of both types of product is more likely. However, consumers rather than health services are expected to pay for foods.

Because the costs of diet-related disease are so high, even a small reduction in the effectiveness of public health measures (by confusing healthy-eating messages, or diverting resources) could be substantial.

10. Conclusions and recommendations

The food and biotech industries, and many of the scientists they fund, have widely promoted the idea that the ultimate goal of nutritional research should be personalised nutrition, involving individual diets based on a person's genes and, perhaps in the longer term, on other biological measurements and continual monitoring.

GeneWatch UK disagrees that personalised nutrition should be a research priority and questions the lack of public involvement in adopting this dubious commercial aim. In most cases, personalised diets are neither desirable nor achievable because:

- For most diet-related diseases in most people, the key to prevention lies not in individual biological differences but in tackling the politics of food and issues such as food industry marketing practices, socio-economic deprivation, health inequalities, transport and the lack of sports facilities in schools. Personalised nutrition is therefore a false solution to the problem of diet-related disease.

- Personalised nutrition is about selling the idea of 'wellness', not about improving health: it is a marketing strategy, not a scientific concept. It seeks to 'medicalise' the problem of diet-related disease, by testing and monitoring the 'worried well' and marketing new products at a premium to the wealthy, supposedly to 'optimise' their health.

- This marketing strategy involves personalising and privatising dietary advice, based on genetic tests (and perhaps other types of tests) sold by commercial companies. Some companies are already falsely claiming that public health advice is 'guesswork' and that genetic tests improve the accuracy of dietary advice. They are marketing misleading and inaccurate interpretations of people's genes and what they mean for their health. As this industry expands and provides multiple and conflicting dietary advice and products, there is significant potential to confuse and undermine healthy-eating messages. Some people may be falsely reassured that they are not at risk of particular diseases, with serious consequences for their health.

- New 'value-added' products such as functional foods are expensive and unnecessary and may have unintended consequences for human health. The consequences of altering the food supply will be hard to predict and difficult to identify or correct should something go wrong. Controversial products are expected to be part of this marketing approach, including: genetically modified (GM) foods, 'psycho foods' (designed to alter appetite or mood) and nanotech ingredients.

- The idea of tailoring diets to genetic make-up is based on a false and outdated view of the role of genes. For most common diseases in most people, an individual's risk is not predictable, because multiple environmental and biological factors interact. What is predictable is the outcome of major shifts in diets on the health of populations.

Governments and investors are in danger of falling for their own misleading hype about the 'genetic revolution', particularly the prospects for genetic 'prediction and prevention' of common, late-onset diseases. This leads to bad policies and bad investments. Personalised nutrition means the food industry will sell its own dietary advice and profit from the products designed to correct the 'biological imbalances' that it identifies. This undermines attempts to move towards more corporate responsibility and improve the nutritional quality of the food supply for all. Misleading marketing of genetic tests and associated products also risks a major loss of public trust.

If all nations become 'fast food nations', premature deaths and disability from diet-related disease will inevitably increase, adversely affecting the lives of literally millions of people. The predicted global epidemic of obesity, heart disease, diabetes and some types of cancer is not an inevitable consequence of 'progress', but a situation that requires urgent political action. GeneWatch UK recommends that governments:

- Prioritise public health (the social and economic determinants of health), not personalised nutrition, and tackle the politics of food;
- Tackle inequalities, empower people to change their diets and health, and involve them in deciding what action and research would help to make a difference;
- End gene patenting, which distorts the 'knowledge-based' economy, and stop commercial interests from dominating the research agenda;
- Require medical oversight and statutory regulation of genetic tests – including an independent pre-market assessment of whether they are valid and useful for health;
- Adopt new legislation to prevent genetic discrimination and protect privacy.

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