

1.1 Personalised medicine

1.1.1 What is personalised medicine?

We are living in a world where increasingly products are offered to meet specific personal needs. It is now possible to design your own shoes, choose the colour scheme of your new bicycle, you can send personalised post cards, get shirts with your name etc. We have also seen such changes in medicine. Precision medicine was a term introduced in the US to describe medical solutions that are personalised based on genetic tests. Precision nutrition or personalised medicine is a young but rapidly advancing field of healthcare that takes into account each person's unique clinical, genetic, genomic, and environmental information. In 2001 the Humane Genome Project was launched (Lander et al., 2001; Venter et al., 2001) with the aim to sequence all three billion base pairs of the human genome. The subsequent completion of this work in 2003 meant a major breakthrough in science and many believed that this would revolutionise medicine through the ability of identifying individuals at risk of disease. The concept of personalised medicine developed where, only individuals with a risk for a disease would be targeted with a specific intervention.

Proponents argue that the nature of diseases—including their onset, their course, and how patients might respond to drugs or other interventions—is as individual as the people who have them. Personalized medicine is about making the treatment as individualized as the disease. It involves identifying genetic, genomic, and clinical information that allows accurate predictions to be made about a person's susceptibility of developing disease, the course of disease, and its response to treatment. (Mirsaeidi, M 2012, <https://bit.ly/2QM1pwy>)

In order for personalized medicine to be used effectively by healthcare providers and their patients, these findings must be translated into precise diagnostic tests and targeted therapies. This has begun to happen in certain areas, such as testing patients genetically to determine their likelihood of having a serious adverse reaction to various cancer drugs. (Gundert-Ramy, Dimovski, Gajovic, 2012, <https://bit.ly/2Bb5Jvp>)

Specific advantages that personalised medicine may offer patients and clinicians include:

- “The ability to make more informed medical decisions
- Higher probability of desired outcomes thanks to better-targeted

therapies

- Reduced probability of negative side effects
- Focus on prevention and prediction of disease rather than reaction to it
- Earlier disease intervention than has been possible in the past
- Reduced healthcare costs” (Foroutan, 2015. <https://bit.ly/2QrvK45>)

Personalised medicine can be used to decide whether a patient will respond favourably or unfavourably to a particular drug. An example of this, is the often quoted example of the drug trastuzumab (Herceptin) and the so called HER2/neu test. The HER2/neu test is used to determine whether the drug trastuzumab is likely to be effective in treating a woman with breast cancer. Trastuzumab is only effective on tumors with an overexpression of the HER2/neu-receptor, something seen in approximately 15% to 20% of breast cancer cases. In all other cases the drug is not useful. A simple test can thus substantially reduce the cost of an otherwise generic treatment.

Genetic tests can also help to determine whether a patient will be more likely to have a serious adverse response to certain drugs. For example, patients with HLA-B*1502 are more likely than other patients to have dangerous skin reactions after taking the drug carbamazepine (which is used to treat epilepsy). A simple HLA-B*1502 test before the start of carbamazepine treatment makes it easier to manage the adverse reactions.

These are a couple of examples where a genetic tests has shown value. There is, however, much debate about its added value and the limitations of the approach. An ideal genetic test for clinical purposes would have 100% sensitivity and specificity and identify a genetic disorder with certainty (Coote & Joyner, 2015). “In addition to this the test would need to be clinically actionable and provide information that could not otherwise be obtained in normal clinical practice”.

Unfortunately, few genetic markers have these characteristics. Usually, the presence of a particular genetic polymorphism or haploid pattern is associated with only a slight increase in the risk of development of a certain disease or a differential response to a therapeutic drug. (Coote & Joyner, 2015. <https://bit.ly/2QMJlm5>)

Gene scores for several risk variants are also typically not clinically informative. For example, these scores are not useful for complex diseases such as cardiovascular disorders and diabetes. In these diseases there are well known and large gene-environment interactions and behavioural interventions have proven to be highly effective at lowering of patient risk of disease (Joyner & Paneth, 2015. <https://bit.ly/2UCLmAh>).

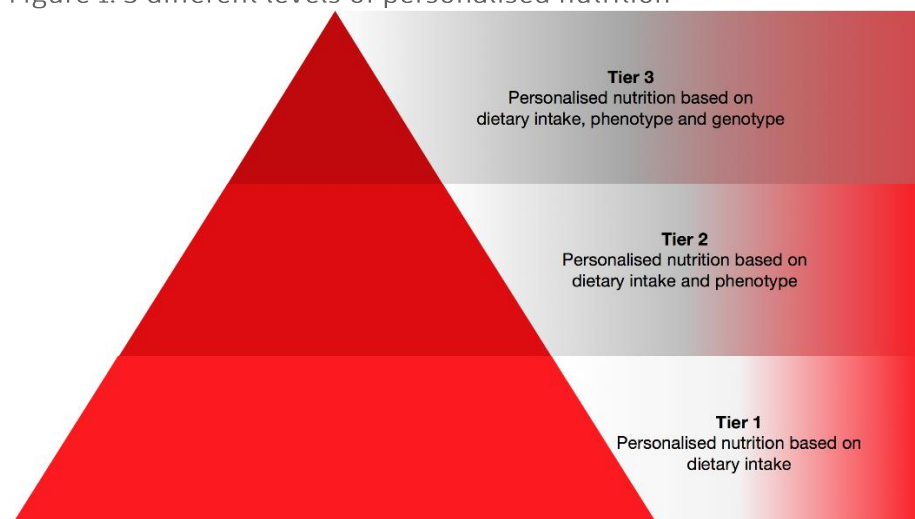
It is clear from human migration studies that the environment plays a critical role in the development of many diseases and it is not just genetics. Disease patterns, of for example obesity and diabetes changed, over time with migration. Our physical activity and dietary habits seem to have much greater effects on the disease risk than only genetic factors. "Novel ideas also suggest soft inheritance with mechanisms such as maternal-fetal programming that makes human phenotypes more complicated than simply being based on coding regions of DNA" (Archer, 2015. <https://bit.ly/2QMF7uv>).

1.1.2 Personalised nutrition for health

Soon after the introduction of personalised medicine, this concept developed to the concept of personalised nutrition, where tailored dietary advice would be delivered to individuals based on their diet and lifestyle factors (Gibney & Walsh, 2013). Till that point in time, the common approach of public health advice included a number of generic recommendations that were the same for everyone. Sometimes it is argued, especially by dietitians, that personalised nutrition is not new and has been practised for many years prior to this. As we will see below, this may be correct (at least to some degree) because there are different levels of personalisation in medicine as well as in nutrition.

Ronteltap et al (Ronteltap, van Trijp, Berezowska, & Goossens, 2013) identified three different levels of personalised nutrition. At the basis we find the typical tailored advice a dietitian would provide based on an individual's dietary intake. For example, the dietary analysis reveals a low intake of a nutrient and this nutrient is then increased in the modified diet or supplemented if the issue is difficult to solve with changes in diet. The second tier of personalised nutrition is based on an individual's diet as well as phenotypic markers such as anthropometric measurements of blood biochemical markers. An example of this is low vitamin D status. When this is measured vitamin D3 may be supplemented. The third level, the top of the pyramid, builds on the previous two levels but includes genotypical information. An analysis of the genetic information is used to provide more detailed information about the "ideal diet" and "ideal nutritional choices" of an individual.

Figure 1: 3 different levels of personalised nutrition



Source: (Ronteltap et al., 2013)

It is common for dietitians who work in clinical settings to provide the first two levels of personalised nutrition: nutrition advice based on dietary intake information, anthropometric measurements and blood chemistry measurements. However, the third level is often seen as the ultimate level of personalisation and a professional service including information about genotype is less readily available (O'Donovan, Walsh, Gibney, Gibney, & Brennan, 2016). Having said this, several companies now target consumers directly with genetic testing (the value of such tests will be discussed in a separate section on direct to consumer (DTC) testing).

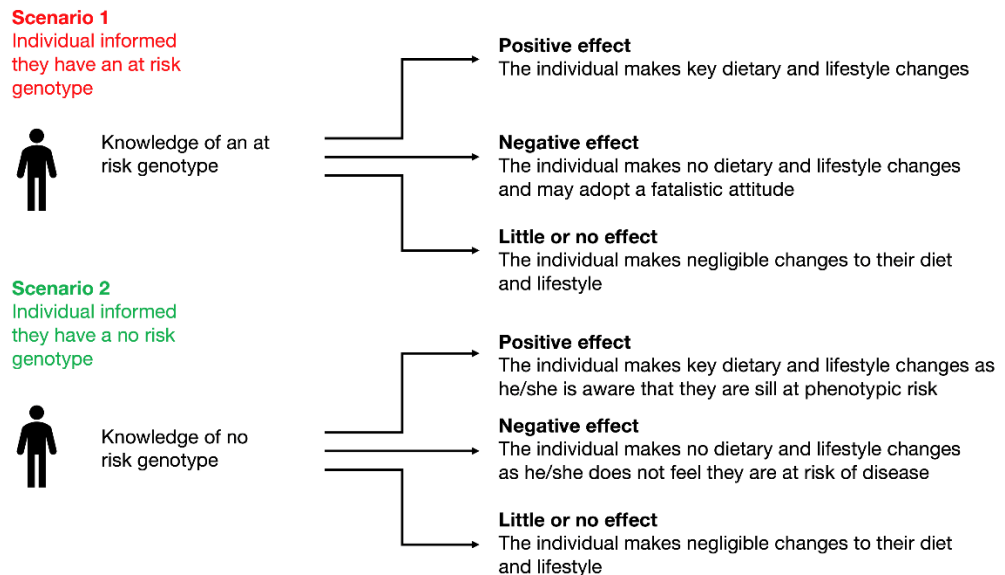
Some have argued that advice based on genotype is more powerful in modifying behaviour than other information. This concept has been referred to as “genetic exceptionalism” (Green & Botkin, 2003). Knowledge of the genotype can motivate individuals to make favourable changes to their lifestyle, thereby contributing to disease prevention (Hamburg & Collins, 2010). Others have argued that the opposite could also be true: a genetic test could result in a fatalistic attitude; The patient will receive the genotype information and concludes that “nothing can be done because it is genetic”. Indeed Bouwman and te Molder (Bouwman & te Molder, 2009) concluded that patients may adopt a fatalistic attitude and decreased self-efficacy. In this case, genetic testing had the opposite effect of what was hoped.

Hollands (Hollands et al., 2016) described three ways in which genetic information could affect behaviour (Figure 1 scenario 1): Firstly, the communication of the genotype and disease risk may motivate behaviour change, and may do this more than any other information.

Secondly, knowledge of the genetic risks may demotivate the individual because the genetic component may suggest that there is nothing that can be done about it. Thirdly, it is possible that knowing the genotype and disease risks has no impact on behaviour change at all, or the changes are minimal (Hollands et al., 2016). This model was later modified by O'Donovan

et al (O'Donovan, Walsh, Gibney, Brennan, & Gibney, 2017) who suggested that in fact the picture is a little more complicated because sometimes a no risk genotype may be communicating and this could also lead to 3 different outcomes. Figure 2 depicts the different scenarios.

Figure 2: Different ways in which information about genotype can influence behaviour.



Source: O'Donovan et al. 2017. p.3.

Although personalization could be achieved by taking into account dietary, phenotypic and genotypic characteristics, the important question that needs to be addressed is whether personalised nutrition will result in better, more sustained, or more cost effective behaviour changes, or result in greater gains in health, than conventional dietary advice. The fact that we can measure something does not necessarily mean it is also better or even useful.

- Is there sufficient evidence to base genotype-based dietary advice on? How confident can we be that if we measure a certain genotype they will also respond better to certain interventions?
- If people receive genotype based advice are they more likely to change their behaviour in favourable ways that result in improvements in health?

a. Is there sufficient evidence to base genotype-based dietary advice on?

This question requires understanding of the evidence on which such advice is based. We need to understand the strength of the evidence, before we can draw firm conclusions and give well-informed advice. There are several

levels of evidence that are required in order to form a complete picture and give good advice. Ultimately, we need to know that the risk of a disease is linked to genetic factors that modulate individual biological responses to certain nutrients.

1. We need evidence that a disease is linked with a reduction in the risk of developing a disease: for example, a high dietary fish oil intake is associated with a lower risk of cardiovascular disease.
2. Then we need to understand the mechanism so we can study causality in experimental studies. In the above example, it has been postulated that EPA and DHA intake can lower triglyceride levels in blood, which may reduce the risk of cardiovascular disease.
3. Next, we need to have evidence from studies that show that certain genotypes will result in different responses to the nutrition intervention. There is evidence that some people do respond favourably to EPA and DHA intake under controlled conditions. However, there is also substantial evidence that some people may have an increased TG as a result of increased EPA/DHA intake.
4. Then we would need intervention studies where individuals with different genotypes receive similar treatment and the effects are compared to a placebo.
5. Further studies should then investigate dose response relationships, exclude other genetic factors that could play a role and so on. Of course, there is also a risk that an intervention to reduce risk for one particular disease could inadvertently increase the risk of another and this should be studied as well. For example, excluding certain foods from the diet could help with some symptoms but could cause other unexpected issues longer term.

It is obvious that we need to build a solid case with multiple, often large scale studies, before we can confidently say that individuals with different phenotypes should eat differently to reduce the disease risk. Often these studies are not available and it will take many years and a lot of funding before these studies are performed and in many cases they may never be performed.

b. Are people more likely to change their behaviour in favourable ways that result in improvements in health?

Whether information about a person's genotype will result in more positive changes in behaviour than traditional approaches is still subject to a lot of debate. Studies have produced mixed results with some showing improvements, some showing no difference and some showing negative effects. It is difficult to draw firm conclusions from the existing studies, but one conclusion seems justified: there is no convincing evidence that a genetic testing will result in superior improvements in behaviour (Celis-Morales, Lara, & Mathers, 2015).

1.1.3 Personalised sports nutrition

There are a lot of parallels between personalised nutrition and personalised sports nutrition. The main difference is that the goal and thus the outcome measurement of personalised nutrition is usually “health”, whereas the goal of sports nutrition is usually primarily “performance” related. It is possible to see a trend in the sports nutrition recommendations which have evolved from generic to more specific and flexible recommendations. We can illustrate this with an example of carbohydrate recommendations.

In the 1980s it was common practice to recommend diets with 65-70% of energy derived from carbohydrate (Costill, 1988; Costill & Miller, 1980). Although it was clear to the authors that this applied to serious athletes performing glycogen depleting exercise regularly, these results were extrapolated to all athletes in the popular media.

An example of this is if we look at the IOC guidelines from 1991 (Devlin & Williams, 1991), the recommendation was “In athletic events of high intensity and long duration (such as multiple sprint sports and endurance sports) performance is generally limited by carbohydrate availability. High carbohydrate diets (even in excess of two-thirds of total energy) maximize carbohydrate (glycogen) stores and improve performance in such activity. A high carbohydrate diet is also necessary to sustain high-intensity training on a daily basis”. Carbohydrate requirements were usually expressed as a percentage of daily energy intake. The average population has an intake of approximately 45-50% carbohydrate, athletes were advised to be in the 60-70% range.

The expression of carbohydrate needs in percentages was abolished several years later and carbohydrate needs were expressed in g/kg body weight.

In 2003 the IOC consensus meeting on sports nutrition concluded:

“Athletes should aim to achieve carbohydrate intakes to meet the fuel requirements of their training programme and to optimize restoration of muscle glycogen stores between workouts. General recommendations can be provided, but should be fine-tuned with individual consideration of total energy needs, specific training needs and feedback from training performance:

Daily recovery: moderate duration/low-intensity training: 5–7 g × kg⁷¹ × day⁷¹

Daily recovery: moderate to heavy endurance training: 7–12 g × kg⁷¹ × day⁷¹

Daily recovery: extreme exercise programme (4–6 + h per day): 10–12 + g × kg⁷¹ × day⁷¹

In 2009 the guidelines were changed to:

Carbohydrate recommendations for athletes range from 6 to 10 g/kg body weight). Carbohydrates maintain blood glucose levels during exercise and replace muscle glycogen. The amount required depends on the athlete's total daily energy expenditure, type of sport, sex, and environmental conditions." (Rodriguez, DiMarco, Langley, 2010, <https://bit.ly/2QrqcGJ>).

In these guidelines it was acknowledged that different groups of athletes may have different needs and these needs may change with changing environments.

In 2016:

"General guidelines for the suggested intake of carbohydrate to provide high carbohydrate availability for designated training or competition sessions can be provided according to the athlete's body size (a proxy for the size of muscle stores) and the characteristics of the session.

Light: Low intensity or skill-based activities 3–5 g/kg/d

Moderate: Moderate exercise program (eg, ~1 h per day) 5–7 g/kg/d

Moderate to high: 1–3h Moderate to high-intensity exercise 6–10 g/kg/d

Very High: Extreme commitment 4–5 h/d mod-high intensity exercise 10–12 g/kg/d"

So generally a higher carbohydrate intake is recommended when exercise intensity and duration increases, but the recommendations also state:

"During other sessions of the training program, it may be less important to achieve high carbohydrate availability, or there may be some value in deliberately exercising with low carbohydrate availability to enhance the training stimulus or adaptive response.

Various tactics can be used to permit or promote low carbohydrate availability including reducing total carbohydrate intake or manipulating the timing of training in relation

to carbohydrate intake (eg, training in a fasted state, undertaking two bouts of exercise in close proximity without opportunity for refueling between sessions".

So essentially the recommendations slowly evolved from rather static and generic high carbohydrate intake recommendations (without specifying the athlete or the goal(s) of that athlete) to carbohydrate intake recommendations dependent on the activity level to a periodised nutrition approach (A. E. Jeukendrup, 2017. <https://bit.ly/2RPp3W5>).

Similarly, carbohydrate intake recommendations during exercise have evolved in similar way. Initially the advice was to ingest some carbohydrate during exercise, then the amounts were specified (30-60 grams), but this was done without mentioning what event, what athlete and what goal? Later, more detailed guidelines were developed (A. Jeukendrup, 2013) that took into account the duration of the activity, the goals of the athlete and to some extent the level of the athlete. Personalization in sports nutrition means tailoring it to the individual needs and goals of the athlete.

When personalised nutrition is used in the context of sport, it becomes even more complicated and there is even less evidence, with the existing evidence mostly from small scale studies.

The evidence we would need here is:

- A nutrition intervention can affect performance (for example caffeine -5 mg/kg 1 hour before exercise- can improve 1h cycling time trial performance)
- There are responders and non-responders (The majority of athletes will respond but some may have negative effects or may not notice much of the caffeine effect)
- This is related to genotype (genes have been identified that are associated with different metabolism of caffeine)
- Athletes with certain genotypes respond better to a treatment than others (these studies are currently still missing, and conclusions are extrapolated).

It is important to note that “performance” is complex and usually we only measure surrogate measures of performance and hope that this will translate into actual performance benefits. If performance was defined differently, for example team sport performance, skills performance or sprint performance, the conclusions could differ significantly.

From these examples it is clear that the nutritional needs of an athlete can vary enormously depending on the level of the athlete, the goals of that athlete, the environmental conditions and so on. Personalisation, therefore, should be based primarily on these factors. Nevertheless, there is a lot of discussion about further personalisation based on genotype and several

companies have offered DTC testing to athletes. We will discuss DTC tests as part of personalising nutrition for athletes in more detail. As we will see, there is little or no evidence that such further personalisation is meaningful or helpful. However, there are a number of examples where genotype could, at least in theory, result in differential nutrition advice to athletes. Here we will briefly discuss genes involved in fat metabolism and genes involved in caffeine metabolism.

Fat metabolism

In a number of studies we have observed remarkable differences in fat metabolism between individuals, especially during exercise (Randell et al., 2017; Venables, Achten, & Jeukendrup, 2005). Roke et al (Roke, 2017) identified that individuals with higher whole-body fat oxidation at rest, were major carriers of the *FADS2* gene (involved in the encoding of enzymes responsible for the endogenous production of Omega-3s) and had increased alpha-linolenic acid (a pre-cursor for the endogenous production of Omega-3s) conversion efficiency. Similarly, a number of single nucleotide polymorphisms have been reported to be responsible for over 30% of the variation in the change of circulating triglyceride concentration following a longitudinal endurance training program (Sarzynski et al., 2015), which in turn could be linked to fat oxidation rates. It is thus not unthinkable that certain genes are linked to differences in substrate use at rest and during exercise.

However, many other factors affect fat metabolism. Research into the genes that are related to fat metabolism is still in its infancy and thus from a practical point of view there is little we can learn from measuring such genes. Therefore, concluding for example that a low-carbohydrate or high-carbohydrate diet is better suited for an individual is premature; and high or low carbohydrate advice is more dependent on the short term and long term goals of the individual as well as training load and other variables.

Caffeine

The effect of genotype on the ergogenic effects of caffeine present without doubt the best example we have in sport science of how measuring a gene could result in personalised nutrition advice. We discussed two genes that affect how individuals respond to caffeine. There are a number of studies that support this idea and the role of these genes is fairly clear. However, even in this example, where we have a relatively large number of studies, we have conflicting results, possibly as a result of small studies and varying study designs. If it is difficult to distill meaningful guidelines and we could perhaps get a better answer by trial and error, or by asking someone if they respond well to caffeine?

1.1.4 Problem with interpreting variable responses

Variable responses in performance (and other outcome measures) are common in studies and in real life competition. These differences are sometimes interpreted at individual level: this athlete did not improve with this treatment and that athlete did. Sometimes these are referred to as responders and non-responders which have become popular buzz words in the field of sport science these days. If a study shows no difference on average, people start to look at individual responses. "Some individuals will have improved as a result of a treatment, training program or supplement. Some others show a decrement. On average there is no difference." (Jeukendrup, 2015, <https://bit.ly/2Gf91DM>)

For example, above we looked at individual responses to caffeine. The ones that show positive effects are quickly called responders and the ones with no or even negative effects are the non-responders. Let's consider the following example. We have a diet that we hypothesize will improve performance compared to a control diet. The results show no difference on average, but some respond better with the new diet and some performed better with the control diet. If you now label the individual who responds in a positive as a responder you make a very important assumption.

That is, that this individual will always respond in the same way to that diet. This, unfortunately, may not be true. Any athlete or coach can tell you that performance varies from day to day. Some days are better than others. There are on- and off days and these are usually notoriously hard to predict." (Jeukendrup, 2015, <https://bit.ly/2Gf91DM>)

So, when some individuals show a positive response, this could be, at least partly, because they have an "on-day", and individuals who had a negative response may have had an "off-day". If measurements and tests that have large day to day variability are used, these differences can be substantial. For example, if we use a cycling test to exhaustion at a moderate intensity, we know that there is very large day to day variation. The same person with the same diet may perform much better one day compared to another.

Thus, the positive or negative response may have been a result of day to day variation rather than differences in individual responses. It is also possible that equipment measures slightly different one day compared with the next. This is totally unrelated to the genotype.

A study can only really determine that someone is a responder or non-responder by showing that the observed effects are consistently negative or consistently positive for that person. Very few papers that discuss responders and non-responders do not have multiple trials to provide this evidence. Therefore, it is not justified to refer to these individuals as responders and non-responders.

Next time you read about responders and non responders ask these questions:

- Do we know the day to day variation of the measurement (variation that would exist if the treatment was the same)
- Did they base conclusions of responders and non responders on repeated measurements or just a single measurement per treatment.
- I am sure that there are responders and non-responders in many cases and it makes sense to use the terms. However, the terms are often being used without sufficient evidence. (Jeukendrup, 2015, <https://bit.ly/2Gf91DM>)

A great review of this topic was written by Atkinson and Batterham (Atkinson & Batterham, 2015).

1.2 Personalised sports nutrition

1.2.1 DTC testing or a different approach?

Direct To Consumer (DTC) tests have become common. Although genetic testing for diagnostic reasons is mostly done at select medical institutions with existing expertise and extensive research facilities (as technologies advance), self diagnostics are being developed by a number of companies. These companies now offer genetic tests (DTC). You can buy a saliva test kit for as little as £60 (US\$80, 70 Euros). A saliva sample is sent to the company and the sample will run through a gene chip “and sent back both ancestry information and more than 200 health reports indicating one’s risk of getting or carrying the gene mutation for a disease such as cystic fibrosis or breast cancer or their response to drug therapies”. (Hof, 2014. <https://bit.ly/2PxAuQp>) Some of these companies received a serious slap on the hand from the FDA who reiterated that a medical device that provides disease diagnostics is subject to explicit FDA approval. Other firms offer genetic tests through doctors, which gets around the issue of FDA approval.

The Human Genome Project and continuing improvements in DNA sequencing technologies have revolutionized the identification of genetic disorders. These technological “advances have radically changed genetic testing from an expensive and burdensome undertaking to a rapid and less costly option for many purposes. The utility of “next-generation” sequencing has been found to establish the diagnosis for hundreds of genetic disorders.” (Lindor, Thibodeau, Burke, 2017. <https://bit.ly/2QQ7iJg>).

“The ready availability of genomic information has led to the question of whether there would be clinical benefit of sequencing the genome of individuals who are not seeking a diagnosis” (Lindor, Thibodeau, Burke, 2017. <https://bit.ly/2QQ7iJg>).

Could genomic screening in generally healthy people provide anticipatory insights for their health care? Apart from the obvious ethical questions, these methods have also been criticized because there are few studies and little evidence to base conclusions and advice on.

These tests are now being offered to athletes where the interest is primarily in performance rather than overall health. In this field, there are virtually no studies and thus it is even more difficult to draw conclusions with confidence. Existing tests lack specificity, sensitivity and explanatory power. With companies going directly to consumers without the help of a medical

practitioner or other expert, it is up to the company and the consumer to interpret the results of the gene analysis. The consumer is usually not equipped to understand the limitations of the techniques and therefore it is easy to see how results get over or under-interpreted. Also, it is likely that companies have different levels of quality control. This is illustrated by examples that can easily be found on the internet. A reporter ordered test kits from a number of companies and sent in her saliva sample for analysis. The results were not entirely surprising: results were far from uniform and differed greatly between the companies. The conclusions and recommendations varied widely and were opposite in some instances. This is what happens with tests and it is therefore important to realize these limitations. If someone can interpret the outcome with this background, the information can be interesting and fun, but what if people do not have the background?

DTC testing is developing in the right direction. DTC 2.0 is more regulated, has increased medical (expert) integration, more quality control of the analytical process, requires user comprehension validation. However, the strictest regulation will most likely be reserved for the high risk categories. Sport does not fall in those categories.

In order to produce meaningful advice to an athlete based on genetic tests, we need to understand the relationship between relevant genes, the nutrient and performance. Such studies are scarce and in many cases non-existent, and therefore our knowledge about the gene-nutrient-exercise interactions (known as nutrigenomics) is very limited. The path to uncovering gene-nutrient interaction effects on performance is complex. It is clearly a demanding line of research because of the rigorous controls needed on all aspects of an intervention, the large sample size required as we are dealing with expectation of a small effect size, and high research costs. Progress in personalized sports nutrition can occur only if we are committed to carefully planned and well-executed human research in the future. (Parker, 2018. <https://bit.ly/2Bnrj07>).

1.2.2 Personalise based on what really matters

Let's take an example. Current recommendations for carbohydrate intake are between 0 and 90 grams per hour of exercise depending on the goals, the level of the athlete, and the duration of exercise. This is a very large range. From research studies we know that during prolonged exercise there is a dose response relationship (i.e. 60 g/h would result in better performance

than 30 g/h for example). It is possible that genetic differences between individuals affect the response to carbohydrate feeding. Some may benefit more than others. This is pure speculation though because we have no data to support this hypothesis. We could theorize which genes may be responsible for possible differences in response to the same carbohydrate feeding. However, in studies responses have been quite similar between individuals and even if genetic differences exist these differences would be small. The differences in performance between carbohydrate intake rates between 30g/h and 60g/h would be several magnitudes larger. Therefore, it is fair to conclude that, at least in this particular example, the other factors far outweigh the influence of a genetic component.

Although it may be too early to base advice on genomic information, personalised nutrition in sports may have a slightly different meaning. Prescribing appropriate nutrition to an athlete, depends much more on other factors such as exercise intensity and duration than on genetic differences between people. In our definition of personalised nutrition, all factors that influence the nutrition needs of an individual should be taken into account to come up with a personalised nutrition plan.

Factors that should be considered in a personalised nutrition plan.

THE GOALS

- Winning, personal bests, optimal performance
- Making it to the finish line
- Losing weight
- Health
- Gaining muscle

THE EVENT

- Duration of exercise
- Intensity of exercise
- Sport
- Playing position in team sports
- Discipline
- Activity
- Race
- Training

THE INDIVIDUAL

- Genetics
- Body mass
- Fitness
- Differences in sweat rates
- Differences in metabolism

- Different preferences
- Different tolerances

THE ENVIRONMENT

- Weather
- Altitude

Here we will discuss some of the factors in previously listed. Of course, the goal of the athlete is one of the main factors: maybe the most important one. If someone's goal is to lose weight or gain weight, the approach may be the opposite. If an endurance athlete wants to burn fat or train his fat oxidative capacity, the approach will be different from aiming for an optimal performance. A triathlete may want to beat his personal best in a race or he may just want to make it to the finish line in one piece. The nutrition strategy can be quite different.

Next, the event needs to be considered: is it training or racing, is it high intensity or low intensity, is it shorter or longer duration. This will determine energy expenditure but also substrate use. It will determine whether nutrition can have an effect on performance or not. In a team sport we may have different players with different needs. The most obvious one is a goal keeper in football who will have different needs than a central midfielder. An attacking player may have different needs than a defending player.

Then there is the individual him or herself. Body weight and body composition will affect the nutritional needs but also the level of the athlete. A recreational football player will likely need less energy than a professional football player. Individuals have different sweat rates even at the same exercise intensity and same weather conditions. So, we need to take individual sweat rates into account. Individuals may also differ in their metabolism. Although studies confirm these differences there is less evidence at present to suggest different nutritional needs but is certainly not unthinkable.

Another really important factor are personal preferences and tolerances. Allergies and intolerances have to be part of the personalisation of course once they are confirmed medically.

Gastro-intestinal problems are a common issue in sport, especially during very high intensity exercise or long duration exercise. In order to minimise the risk of developing gastro-intestinal problems, it is important to find out if foods influence these complaints and if so which foods should be avoided to minimise the risk. This will be highly individual.

Personal preferences are important. This includes taste of the food or product (flavour profile). Cultural differences need to be taken into account. But we also need to work on personalised solutions for players for common goals. For example, if we recommend an intake of 45 grams of carbohydrate

at half time, some players may want to take this as a drink, some as a gel and water, other in the form of solid foods. There are many ways to achieve this goal and every player may want to get to the goal in a slightly different way.

The practical difficulty with personalisation in a team sport is obvious. It is not possible to cook differently for every player of the team. Therefore we can work with buffets, and provide a range of options together with an education program helping players to make the right choices.

Summary

The concept of "personalized" medicine is being extended to the field of nutrition. It is now accepted that nutrients (i.e., macronutrients, micronutrients) alter molecular processes such as DNA structure, gene expression, and metabolism, and these in turn may alter disease initiation, development, or progression.

Undoubtedly there are also links to human performance and therefore personalised nutrition is gaining momentum within the field of sports sciences. Individual genetic variation can influence how nutrients are assimilated, metabolized, stored, and excreted by the body and this in turn could have effects on adaptation, performance or recovery.

Although the use of nutrigenomics in sports nutrition could potentially be the future, it is important to recognize that the nutrigenomics in sport is in its infancy and there are a number of limitations drawbacks that currently make this technique less useful. On the other hand, studies have demonstrated other ways to personalize nutrition in ways that take into account the goals of the individual, the exercise intensity and duration, the weather conditions and other factors that influence the individual's nutritional needs. This is a different way to take into account the individuals nutritional needs that is simpler and perhaps more relevant to the athlete. Although there is some progress in this field, there is a lot to be discovered and a lot of work that needs to be done before we can really make "personalized sports nutrition" accessible to all athletes.

1.2.3 The personalisation myths

One may wonder why we discuss myths at all. Why spend time on things that do not work or things that are scams. The answer is that these myths and scams are part of the reality and when athletes come to us with questions about fad diets, magic supplements or nutritional science fiction we need to be prepared with an answer. The myths discusses in this course are common ones in a team sport environment and the discussion should

help the reader to dispel myths at an early stage with sound evidence based arguments that will make sense to the athlete.

The myth of the blood type diet

The blood type diet seems to be the ultimate personalized diet. A link between ABO blood group and diet was proposed by P.J. D'Adamo in his book "Eat Right For Your Type" published in 1996. The 'Blood-Type' diets have gained widespread attention from the public with more than 7 million copies sold in over 60 languages, and making the New York Times bestseller list.

In this book, D'Adamo claims that the optimal diet for any one individual depends on the person's ABO blood type. Each blood type supposedly represents genetic traits of our ancestors, including which diet they evolved to thrive on. (Wang, García-Bailo, Nielsen, El-Sohemy, 2014. <https://bit.ly/2LqfeOD>).

Here is an example of what each blood type is supposed to eat:

Type A: Called the agrarian, or cultivator. People who are type A should eat a diet rich in plants, and completely free of "toxic" red meat. This closely resembles a vegetarian diet.

Type B: Called the nomad. These people can eat plants and most meats (except chicken and pork), and can also eat some dairy. However, they should avoid wheat, corn, lentils, tomatoes and a few other foods.

Type AB: Called the enigma. Described as a mix between types A and B. Foods to eat include seafood, tofu, dairy, beans and grains. They should avoid kidney beans, corn, beef and chicken.

Type O: Called the hunter. This is a high-protein diet based largely on meat, fish, poultry, certain fruits and vegetables, but limited in grains, legumes and dairy. It closely resembles the paleo diet.

D'Adamo also recommends various supplements to help with tummy troubles and other issues he says people with type O tend to have.

Thus the "'Blood-Type' diet advises individuals to eat according to their ABO blood group to improve their health and decrease risk of chronic diseases such as cardiovascular disease." (Wang, García-Bailo, Nielsen, El-Sohemy, 2014. <https://bit.ly/2LqfeOD>).

So far the theory. Now where is the evidence? Till recently, these claims were all theory and there was no evidence. This does not stop believers who argue that absence of evidence is not the same as evidence of absence!

Therefore researchers from the University of Toronto embarked on a large scale study with 1,455 study participants to see if there was any merit in the blood type diet. The authors came to a clear conclusion: "The way an individual responds to any one of these diets has absolutely nothing to do with their blood type and has everything to do with their ability to stick to a sensible vegetarian or low-carbohydrate diet,". (Wang, García-Bailo, Nielsen, El-Sohemy, 2014. <https://bit.ly/2LqfeOD>).

The researchers took an existing population of mostly young and healthy adults who provided detailed information about their usual diets and provided fasting blood that was used to isolate DNA to determine their ABO blood type and the level of cardiometabolic risk factors, such as insulin, cholesterol and triglycerides. Diet scores were calculated based on the food items listed in Eat Right for Your Type to determine relative adherence to each of the four 'blood-type' diets.

The associations observed between each of the four blood-type (A, B, AB, O) diets and the markers of health were independent of the person's blood type.

There are many more of these diets and other "personalized" nutrition plans that are not evidence based and are more marketing and finance driven than science driven. For example, the analysis of hair to give athletes a custom nutrition plan accompanied by "special" supplements" by the company is an example of this. Or some of the non-clinical tests out there for allergies or intolerances (usually IgG testing) is another example. This will be discussed in the following section.

There are many more of these diets that make profound claims, but provide no real evidence. The evidence used is often based on selective use of the literature, pseudoscience or even manufactured.

1.2.4 Back to basics

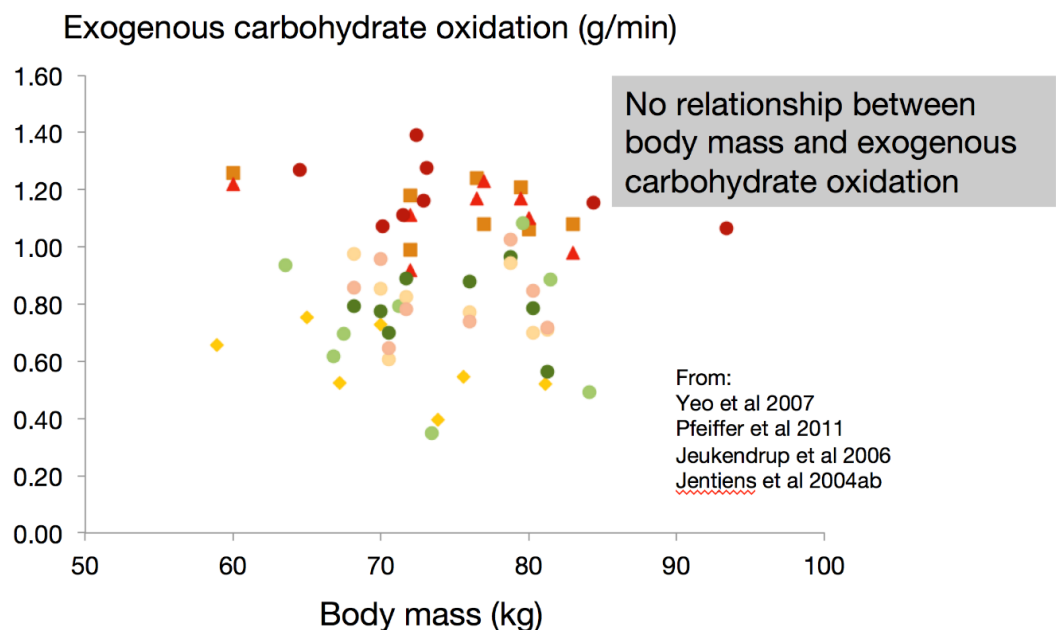
We talked a lot about personalisation and the importance of it. We discussed all the factors that need to be considered in a personalised nutrition plan and also some factors that may be less important. We even discussed some of the myths. However, it is important not to forget that, although no two people are the same, fundamentally we are not that different. Our physiology is largely the same: carbohydrates and fat get absorbed in the same way, regulation of gastric emptying is not different, glycolysis and its regulation are the same and so on.

This means that there are a number of fundamental issues that do not change and do not require personalisation. Carbohydrate is an important fuel for high intensity exercise for every individual! Protein is required for

protein synthesis in every individual. Dehydration can affect performance in every individual.

Sometimes we do not even have to take body weight or composition into account. For example, we studied exogenous carbohydrate oxidation for many years and in a large number of individuals. One of the initial findings was that maximal oxidation rates of ingested carbohydrate was 60 g/h. This was the case in smaller individuals but also in larger individuals. We also found that when certain combinations of carbohydrates were used, this number could be exceeded. But this happened both in smaller and in larger individuals. It was remarkable that in all these studies, oxidation rates between individuals seemed fairly consistent. Some of the individual in these studies were around 60kg and some were around 90kg. Despite weight being 50% different, oxidation rates were similar and there was no obvious correlation between weight and exogenous oxidation rates. In Figure 3 the results from several studies are plotted. Each point is a person in a study with their maximal exogenous carbohydrate oxidation rate.

Figure 3: No correlation between exogenous carbohydrate oxidation and bodyweight. Probably because maximal exogenous carbohydrate oxidation rate is limited by absorption and absorptive capacity of the gut is not dependent on body weight



Jeukendrup Curr Opin Clin Nutr Metab Care. 2010 Jul;13(4):452-7

Clearly there was no correlation between body mass and exogenous carbohydrate oxidation rates. The explanation we gave was that the main factor determining exogenous carbohydrate oxidation rates is absorption. Absorptive capacity is not necessarily different between smaller and larger individuals and we have suggested that it is more dependent on regular

carbohydrate intake than any other factor. In a later module we will discuss training the gut and we will see that the gut and the absorptive capacity of the gut will vary depending on the diet.

So the take home message is that we are all humans with largely the same physiology. We may need to personalise nutrition to optimise performance, but it cannot be true that different people will get opposite advice for the same purpose.

References

- Archer, E. (2015). The mother of all problems. *New Scientist*, 225, 32–33.
- Atkinson, G., & Batterham, A. M. (2015). True and false interindividual differences in the physiological response to an intervention. *Exp Physiol*, 100(6), 577–588. doi:10.1113/EP085070
- Bouwman, L. I., & te Molder, H. F. (2009). About evidence based and beyond: a discourse-analytic study of stakeholders' talk on involvement in the early development of personalized nutrition. *Health Educ Res*, 24(2), 253–269. doi:10.1093/her/cyn016
- Celis-Morales, C., Lara, J., & Mathers, J. C. (2015). Personalising nutritional guidance for more effective behaviour change. *Proc Nutr Soc*, 74(2), 130–138. doi:10.1017/S0029665114001633
- Coote, J. H., & Joyner, M. J. (2015). Is precision medicine the route to a healthy world? *Lancet*, 385(9978), 1617. doi:10.1016/S0140-6736(15)60786-3
- Costill, D. L. (1988). Carbohydrates for exercise: dietary demands for optimal performance. *Int J Sports Med*, 9, 1–18.
- Costill, D. L., & Miller, J. M. (1980). Nutrition for endurance sport: carbohydrate and fluid balance. *Int J Sports Med*, 1, 2–14.
- Devlin, J. T., & Williams, C. (1991). Final consensus statement: foods, nutrition and sports performance. *Journal of Sports Sciences*, 9(suppl).
- Foroutan, B. (2015) Personalized Medicine: A Review with Regard to Biomarkers. *Journal of Bioequivalence & Bioavailability* 07:244–256. doi:10.4172/jbb.1000248
- Gibney, M. J., & Walsh, M. C. (2013). The future direction of personalised nutrition: my diet, my phenotype, my genes. *Proc Nutr Soc*, 72(2), 219–225. doi:10.1017/S0029665112003436

Graham, T. E. (2001). Caffeine and exercise: metabolism, endurance and performance. *Sports Med*, 31(11), 785-807.

Green, M. J., & Botkin, J. R. (2003). "Genetic exceptionalism" in medicine: clarifying the differences between genetic and nongenetic tests. *Ann Intern Med*, 138(7), 571-575.

Guest, N., Corey, P., Vescovi, J., & El-Sohemy, A. (2018). Caffeine, CYP1A2 Genotype, and Endurance Performance in Athletes. *Med Sci Sports Exerc*, 50(8), 1570-1578. doi:10.1249/MSS.0000000000001596

Gundert-Ramy U, Dimovski A, Gajovic S, (2012) Personalized medicine – where do we stand? Pouring some water into wine: a realistic perspective. Croatian Medical Journal. Aug; 53(4): 314–320. doi: [10.3325/cmj.2012.53.314]

Hamburg, M. A., & Collins, F. S. (2010). The path to personalized medicine. *N Engl J Med*, 363(4), 301-304. doi:10.1056/NEJMp1006304

Hof, R (2014) Seven Months After FDA Slapdown, 23andMe Returns With New Health Report Submission. Forbes Magazine. <https://bit.ly/2PxAuQp>.

Hollands, G. J., French, D. P., Griffin, S. J., Prevost, A. T., Sutton, S., King, S., & Marteau, T. M. (2016). The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. *BMJ*, 352, i1102. doi:10.1136/bmj.i1102

Jeukendrup, A. (2013). The new carbohydrate intake recommendations. *Nestle Nutr Inst Workshop Ser*, 75, 63-71. doi:10.1159/000345820

Jeukendrup, A. E. (2017). Periodized Nutrition for Athletes. *Sports Med*, 47(Suppl 1), 51-63. doi:10.1007/s40279-017-0694-2

Jeukendrup, A. E., & Gleeson, M. (2018). *Sport Nutrition: an introduction to energy production and performance* (3rd edition ed.). Champaign IL: Human Kinetics.

Joyner, M. J., & Paneth, N. (2015). Seven Questions for Personalized Medicine. *JAMA*, 314(10), 999-1000. doi:10.1001/jama.2015.7725

Lander, E. S., Linton, L. M., Birren, B., Nusbaum, C., Zody, M. C., Baldwin, J., . . . International Human Genome Sequencing, C. (2001). Initial sequencing and analysis of the human genome. *Nature*, 409(6822), 860-921. doi:10.1038/35057062

Lindor N, Thibodeau S, Burke L (2017) Whole-Genome Sequencing in Healthy People. *Mayo Clinic proceedings*. 92(1):159-172. doi: 10.1016/j.mayocp.2016.10.019.

Loy, B. D., O'Connor, P., Lindheimer, J. B., & Covert, C. F. (2015). Caffeine is ergogenic for adenosine A2A receptor gene (ADORA2A) T allele homozygotes: a pilot study. *J Caffeine Res*, 5(2), 73-81.

Meeusen, R., Roelands, B., & Spriet, L. L. (2013). Caffeine, exercise and the brain. *Nestle Nutr Inst Workshop Ser*, 76, 1-12. doi:10.1159/000350223

Mirsaeidi, M (2012) Personalized medicine approach in mycobacterial disease. *National Institute of health*. 1(2): 59–64. doi: [10.1016/j.ijmyco.2012.03.001]

O'Donovan, C. B., Walsh, M. C., Gibney, M. J., Brennan, L., & Gibney, E. R. (2017). Knowing your genes: does this impact behaviour change? *Proc Nutr Soc*, 76(3), 182-191. doi:10.1017/S0029665116002949

O'Donovan, C. B., Walsh, M. C., Gibney, M. J., Gibney, E. R., & Brennan, L. (2016). Can metabotyping help deliver the promise of personalised nutrition? *Proc Nutr Soc*, 75(1), 106-114. doi:10.1017/S0029665115002347

Pickering, C. (2017a). Is caffeine responsiveness in your genes? Retrieved from <http://www.mysportscience.com/single-post/2017/09/22/Is-caffeine-responsiveness-in-your-genes>

Pickering, C. (2017b). Is caffeine responsiveness in your genes? Retrieved from <http://www.mysportscience.com/single-post/2017/09/22/Is-caffeine-responsiveness-in-your-genes>

Randell, R. K., Rollo, I., Roberts, T. J., Dalrymple, K. J., Jeukendrup, A. E., & Carter, J. M. (2017). Maximal Fat Oxidation Rates in an Athletic Population. *Med Sci Sports Exerc*, 49(1), 133-140. doi:10.1249/MSS.0000000000001084

Roke, K. (2017). Exploration of the perceived and actual benefits of omega-3 fatty acids and the impact of FADS1 and FADS2 genetic information on dietary intake and blood levels of EPA and DHA. *Appl Physiol Nutr Metab*, 42(3), 333. doi:10.1139/apnm-2016-0700

Ronteltap, A., van Trijp, H., Berezowska, A., & Goossens, J. (2013). Nutrigenomics-based personalised nutritional advice: in search of a business model? *Genes Nutr*, 8(2), 153-163. doi:10.1007/s12263-012-0308-4

Sarzynski, M. A., Davidsen, P. K., Sung, Y. J., Hesselink, M. K., Schrauwen, P., Rice, T. K., . . . Bouchard, C. (2015). Genomic and transcriptomic predictors of triglyceride response to regular exercise. *Br J Sports Med*, 49(23), 1524-1531. doi:10.1136/bjsports-2015-095179

Silva, D., & Moreira, A. (2015). The role of sports and exercise in allergic disease: drawbacks and benefits. *Expert Rev Clin Immunol*, 11(9), 993-1003. doi:10.1586/1744666X.2015.1058158

Venables, M. C., Achten, J., & Jeukendrup, A. E. (2005). Determinants of fat oxidation during exercise in healthy men and women: a cross-sectional study. *J Appl Physiol*, 98(1), 160-167.

Venter, J. C., Adams, M. D., Myers, E. W., Li, P. W., Mural, R. J., Sutton, G. G., . . . Zhu, X. (2001). The sequence of the human genome. *Science*, 291(5507), 1304-1351. doi:10.1126/science.1058040

Womack, C. J., Saunders, M. J., Bechtel, M. K., Bolton, D. J., Martin, M., Luden, N. D., . . . Hancock, M. (2012). The influence of a CYP1A2 polymorphism on the ergogenic effects of caffeine. *J Int Soc Sports Nutr*, 9(1), 7. doi:10.1186/1550-2783-9-7

Yang, A., Palmer, A. A., & de Wit, H. (2010). Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology (Berl)*, 211(3), 245-257. doi:10.1007/s00213-010-1900-1