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).

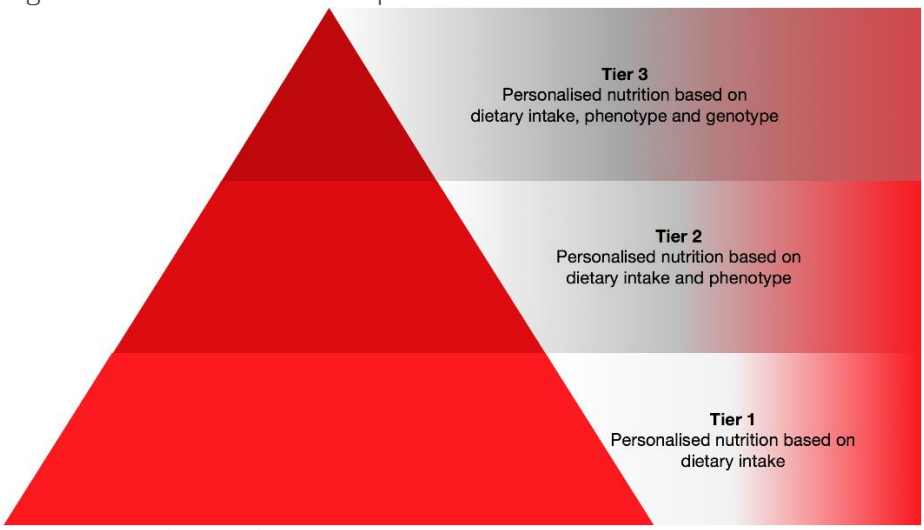
It is clear from human migration studies that the environment plays a critical role in the development of many diseases and it is not just genetics. Disease patterns, of for example obesity and diabetes changed, over time with migration. Our physical activity and dietary habits seem to have much greater 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).

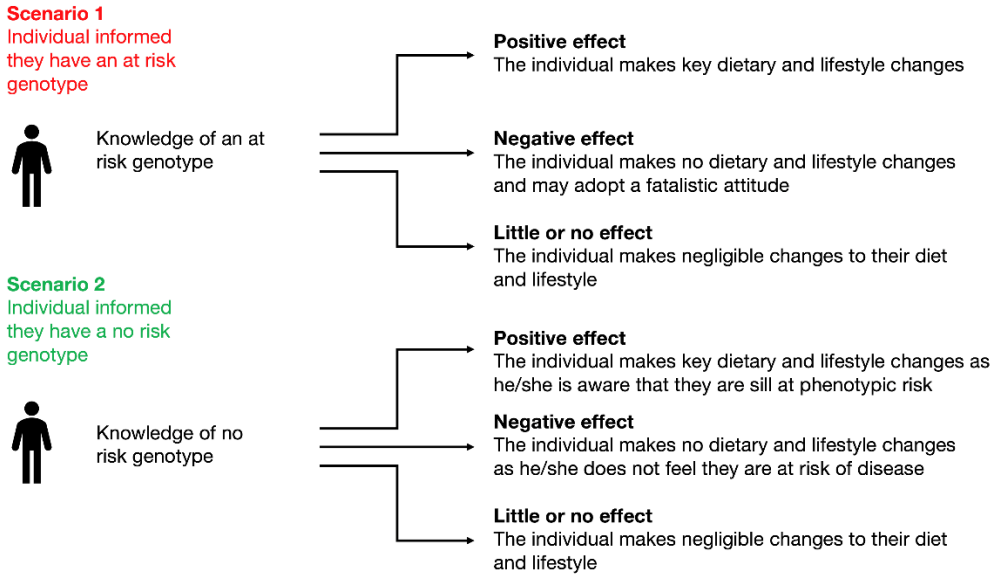
Some have argued that advice based on genotype is more powerful in modifying behaviour than other information. This concept has been referred to as "genetic exceptionalism" (Green & Botkin, 2003). Knowledge of the genotype can motivate individuals to make favourable changes to their lifestyle, thereby 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.

a. 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?
b. 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 ingested 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 exists 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).