



## Irish section postgraduate winners

# Can metabotyping help deliver the promise of personalised nutrition?

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Over a decade since the completion of the human genome sequence, the promise of personalised nutrition available to all has yet to become a reality. While the definition was originally very gene-focused, in recent years, a model of personalised nutrition has emerged with the incorporation of dietary, phenotypic and genotypic information at various levels. Developing on from the idea of personalised nutrition, the concept of targeted nutrition has evolved which refers to the delivery of tailored dietary advice at a group level rather than at an individual level. Central to this concept is metabotyping or metabolic phenotyping, which is the ability to group similar individuals together based on their metabolic or phenotypic profiles. Applications of the metabotyping concept extend from the nutrition to the medical literature. While there are many examples of the metabotype approach, there is a dearth in the literature with regard to the development of tailored interventions for groups of individuals. This review will first explore the effectiveness of personalised nutrition in motivating behaviour change and secondly, examine potential novel ways for the delivery of personalised advice at a population level through a metabotyping approach. Based on recent findings from our work, we will demonstrate a novel strategy for the delivery of tailored dietary advice at a group level using this concept. In general, there is a strong emerging evidence to support the effectiveness of personalised nutrition; future work should ascertain if targeted nutrition can motivate behaviour change in a similar manner.

**Personalised nutrition: Cluster analysis: Metabotyping: Targeted nutrition**

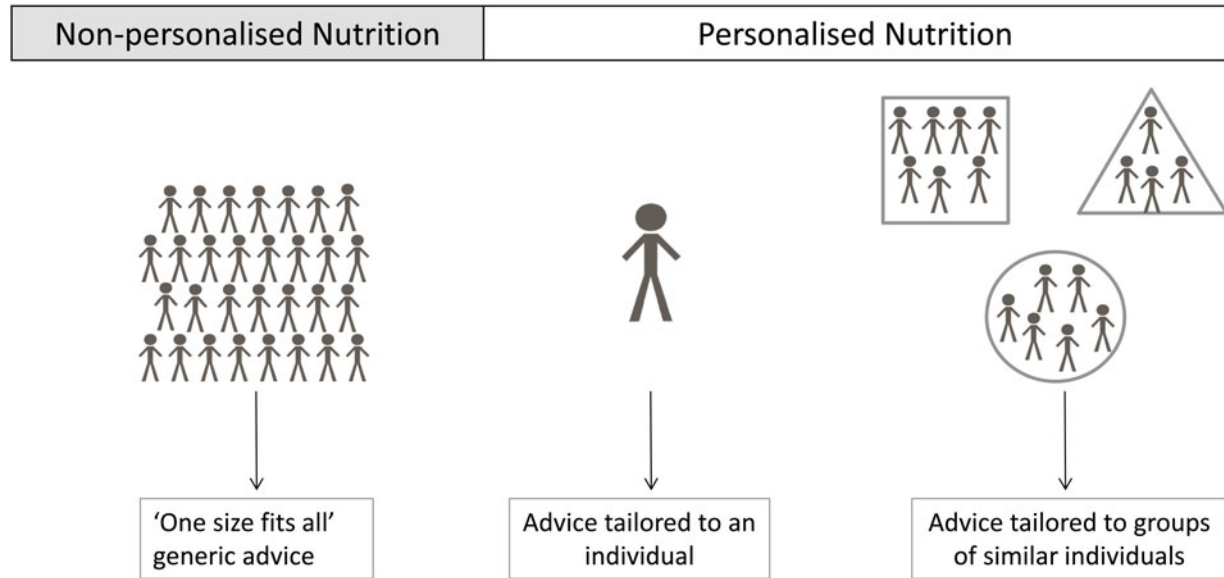
### The evolution of personalised nutrition

The concept of personalised nutrition (Fig. 1), whereby dietary advice is tailored to an individual, is not new. Potentially, its origins date back to 1950 when a review paper discussed the concept of genotrophic diseases and their relationship to nutrient intake<sup>(1)</sup>. This decade also saw the introduction of a controlled diet for successful treatment of phenylketonuria and hence, the beginnings of personalisation based on the identification of inborn errors of metabolism<sup>(2)</sup>. Following on from this, the common *APOE* polymorphism was first reported in the 1977<sup>(3)</sup> and since then researchers have been aware of its varying effect on lipid metabolism

disorders<sup>(4)</sup>. Furthermore, recommended daily allowances are personalised based on age, gender and life cycle<sup>(5)</sup>. However it was not until the completion of the human genome sequence in 2001 that the concept of personalised health including personalised nutrition was catapulted to the forefront and many believed that this would provide the solution to all chronic diseases<sup>(6,7)</sup>. Despite these advances, over a decade later, personalised nutrition is still not readily available for delivery at a population level.

The idea of personalised nutrition originally focused on functional genetic variations, known to affect gene-nutrient metabolism. In recent times, a more encompassing definition has emerged; personalised nutrition can be

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**Fig. 1.** The concept of personalised nutrition at an individual and group level. Non-personalised advice is generic healthy eating advice that is aimed at the population. This figure depicts the concept that personalised advice can be delivered at an individual level or at a group level to metabolically similar individuals.

delivered at varying levels where one level builds on the foundations of another<sup>(8)</sup>. Within this example, a three-tiered approach to personalised nutrition is taken, where level 1 personalised advice is based on assessment of the individual's diet, level 2 is based on diet and phenotypic markers such as BMI and blood markers e.g. cholesterol, glucose and level 3 personalised advice is based on diet, phenotype and genotypic information<sup>(9)</sup>. It is hypothesised that dietary advice that is personalised to the individual may be more successful in motivating changes in diet and lifestyle behaviour<sup>(10)</sup>. However, it is unknown what level of personalisation i.e. diet, phenotype and/or genotype is optimal for initiating such positive changes in diet and lifestyle. Therefore, the first objective of this review is to examine the effectiveness of personalised dietary advice in motivating behaviour change within the levels of personalised nutrition. The second objective is to explore new concepts to potentially deliver personalised nutrition on a wider scale. More specifically, the concept of metabotyping or the grouping of individuals with similar metabolic patterns (Fig. 1) will be discussed and its potential as a feasible public health tool for the delivery of personalised dietary advice will be examined.

#### Personalised nutrition – how effective is it?

The effectiveness of personalised nutrition can be examined within this concept of levels of personalised advice. While there are many studies in this area, in recent years, there has been a move towards internet-based interventions which can have many benefits over more traditional methods of intervention delivery such as convenience and scalability<sup>(11)</sup>. As a result the present review will focus, where possible, on internet and web-based interventions.

Table 1 illustrates some of the studies which focus specifically on changes in dietary intake such as increases in fruit and vegetables<sup>(13)</sup> and reduced fat intake<sup>(12)</sup>. Alexander *et al.*<sup>(13)</sup> examined changes in fruit and vegetable consumption by comparing an online untailored programme with a tailored behavioural intervention or a tailored behavioural intervention with an additional motivational programme in participants aged between 21 and 65 years ( $n$  2540). Average servings of fruit and vegetables increased by more than two servings across all study groups ( $P < 0.001$ ) with the greatest increase (+2.8 servings) observed among those participants in the tailored behavioural intervention with motivational counselling ( $P = 0.05$ )<sup>(13)</sup>. In the Self-Monitoring and Recording using Technology Trial, obese individuals were randomised to one of three groups including those who monitored their dietary intake by recording what they ate using a paper diary, those who self-monitored using a personal digital assessment device and those who used the personal digital assessment device and also received daily tailored feedback<sup>(16)</sup>. For analysis purposes, the investigators combined those in the first two groups who received no daily feedback and compared them with those in the third group to examine the effect of daily tailored feedback on changes in energy and fat intakes<sup>(16)</sup>. The group who received the daily feedback achieved a larger reduction in energy ( $-22.8\%$  v.  $-14.0\%$ ,  $P = 0.02$ ) and saturated fat ( $-11.3\%$  v.  $-0.5\%$ ,  $P = 0.03$ ) compared with those who did not receive the daily feedback<sup>(16)</sup>. Similar trends were found in other studies as shown in Table 1. A recent systematic review in the area concluded that online personalised interventions were more effective in increasing fruit and vegetable intake (weighted mean differences: 0.35 servings/d, 95% CI 0.28, 0.42;  $P < 0.0001$ ) than generic advice<sup>(11)</sup>. Overall, there is convincing evidence for

**Table 1.** Summary of studies evaluating effectiveness of personalised nutrition with a focus on changes in dietary measures

Author	Study design	Subjects	Methods	Main findings
Kroeze <i>et al.</i> <sup>(12)</sup>	6 month RCT	Healthy adults (n 588)	Randomised to one of four feedback groups: personal (P); personal-normative (PN); personal-normative-action (PNA), Generic	PNA is required to induce changes in fat intake and improve awareness of fat intake
Alexander <i>et al.</i> <sup>(13)</sup>	12 month RCT	Healthy adults aged 21–65 years (n 2540)	Randomised to one of three groups: control website; tailored website; tailored website and motivational interviewing counselling emails	Greatest increase in servings of fruit and vegetables in 3rd group compared with control ( $P = 0.05$ )
Wright <i>et al.</i> <sup>(14)</sup>	3 month RCT	Adults aged 40–65 years requiring CVD prevention (n 178)	Randomised to one of three groups: tailored printed dietary feedback; small group nutrition education sessions; wait-listed control	Greater increase in fruit intake in tailored group (0.3 serves/d, $P = 0.031$ ). All three groups showed a reduction in saturated fat
Hutchesson <i>et al.</i> <sup>(15)</sup>	3 month RCT	Overweight/obese adults (n 268)	Randomised to one of three groups: waiting-list control; basic version of commercial web-based weight loss programme; enhanced version of commercial web-based weight loss programme	Both basic and enhanced groups increased their percentage energy contribution from fruit and reduced energy-dense, nutrient foods compared with control ( $P < 0.001$ )
Ambeba <i>et al.</i> <sup>(16)</sup>	24 month RCT	Obese adults (n 210)	Randomised to one of three groups: paper diary (PD); personal digital assessment (PDA); PDA and daily feedback (DFB)	PDA and DFB had a larger reduction in energy ( $P = 0.02$ ), saturated fat ( $P = 0.03$ )
Springvloet <i>et al.</i> <sup>(17)</sup>	4 month RCT	Healthy adults aged 20–65 years (n 1349)	Randomised to one of three groups: basic; plus; control	Basic group had larger decreases in saturated fat than the control between baseline and both month 1 ( $P = 0.001$ ) and month 4 ( $P = 0.01$ )

RCT, randomised controlled trial.

the efficacy of a personalised approach for facilitating changes in dietary intakes.

There is a wealth of studies examining the effect of personalised programmes on weight loss<sup>(18–23)</sup> as depicted in Table 2. Bennett *et al.* conducted a 12-week randomised controlled trial among obese primary care patients with hypertension (n 101)<sup>(20)</sup>. Participants randomised to the control group received a generic weight loss programme. The intervention group had access to a website which provided participants with a series of tailored obesogenic behaviour change goals as well as receiving behavioural skills training and regular health coach support<sup>(20)</sup>. Intention-to-treat analysis demonstrated greater weight loss at 3 months (−2.56 kg; 95 % CI −3.60, −1.53) in the intervention participants (−2.28 (SD 3.21) kg) compared with the usual care group (0.28 (SD 1.87) kg). Collins *et al.*<sup>(23)</sup> performed a 12-week randomised controlled trial which randomised subjects to one of three groups: control: basic which had free access to a commercial web based weight loss programme; enhanced group who were provided with access to an enhanced version of the website (n 309). The web-based weight loss programme was designed to target important features of behaviour change such as self-efficacy, goal setting, self-monitoring, exercise and diet and social support. Those in the enhanced group also had access to personalised, system-generated enrolment reports detailing appropriate weight-loss goals and key behaviour changes required, weekly personalised e-feedback and a reminder schedule to continue to record their dietary intake and weight as well as the basic website features as described above. Individuals with access to a

commercial web-based weight loss programme had a reduction in their BMI by the end of the trial; there was no additional benefit of having access to the enhanced version of the website. In the Self-Help, Exercise and Diet using Internet Technology trial, subjects were randomised to either the resources programme (n 54), online programme (n 53) or control group (n 52)<sup>(25)</sup>. Those in the resources group received a weight loss DVD, handbook and support book targeted to men, a pedometer, measuring tape, kilojoule counting book and advised to record their weight, diet and physical activity. Those randomised to the online programme received the same resources as well as instructions on how to use an online food and exercise diary instead of a paper-based diary and received feedback on their food and exercise diary entries via email. At 6 months, significantly more weight was lost in the online (−4.7 kg; 95 % CI −6.1, −3.2) and resources (−3.7 kg; 95 % CI −4.9, −2.5) groups compared with the control (−0.5 kg; 95 % CI −1.4, 0.4). Both intervention groups also had significant improvements in BMI, per cent body fat, waist circumference, blood pressure, physical activity, quality of life, alcohol risk and portion size compared with the controls. A recent meta-analysis also demonstrated that personalised interventions resulted in greater weight loss in comparison with non-personalised advice (weighted mean differences: −1.83 kg 95 % CI −2.2, −1.4;  $P < 0.0001$ )<sup>(11)</sup>. Therefore there is good evidence to suggest that personalised weight loss interventions can result in greater weight loss compared with generic dietary advice.

Other studies have also investigated the effect of personalised advice with respect to changes in multiple dietary

**Table 2.** Summary of studies evaluating effectiveness of personalised nutrition with a focus on changes in phenotypic measures including body weight

Author	Study design	Subjects	Methods	Main findings
Tate <i>et al.</i> <sup>(18)</sup>	6 month RCT	Overweight/obese adults ( <i>n</i> 192)	Randomised to one of three groups: no counselling (control); computer-automated email feedback; human email counselling	At 6 months, weight loss greater in human email counselling group compared with computer automated or no counselling group
Hunter <i>et al.</i> <sup>(19)</sup>	6 month RCT	Overweight adults ( <i>n</i> 446)	Randomised to either behavioural internet treatment (BIT) or usual care (control)	After 6 months, BIT group lost more weight than those in usual care group ( $P < 0.001$ )
Bennett <i>et al.</i> <sup>(20)</sup>	3 month RCT	Primary care patients with obesity and hypertension ( <i>n</i> 101)	Randomised to receive either usual outpatient care (control) or web-based tailored intervention	Greater weight loss (−2.56 kg; 95 % CI −3.60, −1.53) among intervention (−2.28 (sd 3.21) kg) relative to control (0.28 (sd 1.87) kg)
Chambliss <i>et al.</i> <sup>(24)</sup>	3 month RCT	Overweight adults ( <i>n</i> 120)	Randomised to one of three groups: computerised self-monitoring with basic feedback; enhanced behavioural feedback; wait-list control	Both basic and enhanced groups lost more weight than control ( $P < 0.05$ )
Kraschnewski <i>et al.</i> <sup>(21)</sup>	3 month RCT	Overweight/obese adults ( <i>n</i> 100)	Randomised to web-based intervention or wait-list control group	Those in the intervention group lost −1.4 kg (95 % CI −2.2, −0.5), compared with those in control who gained 0.6 kg (95 % CI −0.3, 1.4) ( $P < 0.01$ )
Collins <i>et al.</i> <sup>(23)</sup>	3 month RCT	Overweight/obese adults ( <i>n</i> 309)	Randomised to one of three groups: control with no access to website; basic access to web-based programme; enhanced access to web-based programme	Both intervention groups lost more weight than control ( $P < 0.001$ ) but no differences observed between the intervention groups
Burke <i>et al.</i> <sup>(22)</sup>	24 month RCT	Obese adults ( <i>n</i> 210)	Randomised to one of three groups: paper diary (PD); personal digital assessment (PDA); PDA and daily feedback (DFB)	Only PDA and DFB group had significant weight loss ( $P = 0.03$ ). However, there were no significant differences between groups for percentage weight change over time
Morgan <i>et al.</i> <sup>(25)</sup>	6 month RCT	Overweight/obese men ( <i>n</i> 150)	Randomised to one of three groups: resources (gender-tailored weight loss material); online (resources plus website and e-feedback); wait-list control	Greater weight loss found in online group (−4.7 kg; 95 % CI −6.1, −3.2) and resources (−3.7 kg; 95 % CI −4.9, −2.5) compared with control (−0.5 kg; 95 % CI −1.4, 0.4)

RCT, randomised controlled trial.

and lifestyle factors such as diet, phenotypic measures, physical activity<sup>(26–29)</sup> and composite lifestyle score changes<sup>(30)</sup>. In an intervention which targeted both changes in physical activity and dietary intakes, the investigators reported that a tailored programme resulted in more significant lifestyle changes including increases in physical activity levels, decreases in fat and increases in fruit and vegetables intake<sup>(26)</sup>. Mouttapa *et al.*<sup>(29)</sup> reported similar results in women with respect to increases in dairy intake and decreases in weight. However, individually tailored feedback was not found to be more motivating regarding changes in multiple lifestyle behaviours in individuals with familial hypercholesterolemia<sup>(28)</sup>. One intervention investigated the effect of a tailored behaviour change programme on a composite lifestyle change score<sup>(30)</sup>. The investigators found the composite lifestyle score to be significantly higher in the high intervention group compared with the no/low intervention group ( $P = 0.009$ ). Therefore the evidence is mixed with regard to the effectiveness of personalised advice in changes in multiple lifestyle behaviours.

With regard to personalised advice at genotypic level, some of the key studies in the area are shown in Table 3. Arkadianos *et al.*<sup>(31)</sup> demonstrated a benefit in providing a nutrigenetic based diet for weight loss compared with a traditional weight management programme in those with a history of weight loss failures. The group observed no difference between the traditional weight management diet group (controls) and nutrigenetic diet group (cases) at 3 months, where both groups had lost weight. However a year later, those in the nutrigenetic group fared much better as they were more likely to keep the weight off ( $P < 0.023$ ) compared with the controls who on average, gained weight. The Risk Evaluation and Education for Alzheimer's Disease Study was a series of multicentre randomised trials which investigated the effect of *APOE* risk disclosure with respect to Alzheimer's disease on cognitively normal adults<sup>(32)</sup>. In the first Risk Evaluation and Education for Alzheimer's Disease Study, the investigators reported that those who were informed they had the risk *APOE* genotype were more likely to report making an Alzheimer's disease-specific



**Table 3.** Summary of studies evaluating the effectiveness of gene based personalised nutrition advice

Author	Study design	Subjects	Methods	Main findings
Arkadianos <i>et al.</i> <sup>(31)</sup>	Case control	Patients with history of weight loss failure ( <i>n</i> 93)	Cases followed a nutrigenetic diet and compared with patients following a traditional weight management diet	No differences between the groups at month 6 compared with baseline. At 12 months, nutrigenetic group were more likely to keep the weight off ( $P < 0.023$ )
Chao <i>et al.</i> <sup>(32)</sup>	12 month RCT	Individuals over 60 years with familial history of Alzheimer's disease (AD) ( <i>n</i> 162)	Randomised to receive AD risk assessment based on <i>APOE</i> genotype or AD risk assessment not based on genotype (control)	Those who learned they had the risk AD genotype ( <i>APO4</i> positive) were more likely to report making AD-specific health behaviour changes 1 year after genotype disclosure compared with those in the non-risk group ( $P = 0.02$ )
Bloss <i>et al.</i> <sup>(33,34)</sup>	12 month Observational	Employees who purchased direct-to-consumer (DTC) testing ( <i>n</i> 2037)	Reported any changes in anxiety, dietary fat and exercise from baseline to 3 months and again at 12 months following testing	No differences in anxiety, fat and exercise between baseline and month 3. No differences were found at 12 months in participants who completed follow-up ( <i>n</i> 1325)
Grant <i>et al.</i> <sup>(35)</sup>	3 month RCT	Overweight patients at phenotypic risk of type 2 diabetes ( <i>n</i> 108)	Randomised to receive either genetic testing or no genetic testing. Both groups attended a 12-week diabetes prevention programme	No differences between the groups in relation to self-reported motivation, programme attendance or weight loss
Nielsen & El-Sohemy <sup>(36)</sup>	12 month RCT	Healthy men and women aged between 20 and 35 years ( <i>n</i> 138)	Randomised to receive personalised DNA-based advice or general dietary advice (control)	At 3 months, no differences observed between the groups. At 12 months, difference in sodium reduction observed between <i>ACE</i> SNP risk group and control group ( $P < 0.008$ )
Frankwich <i>et al.</i> <sup>(37)</sup>	6 month RCT	Obese adults ( <i>n</i> 51)	Randomised to receive genetics-guided therapy (GT) or standard therapy (ST)	No significant differences were found between the groups in the percentage of those achieving 5 % weight loss at 8 or 24 weeks

RCT, randomised controlled trial.

health behaviour change compared with those with the non-risk genotype following a year after disclosure<sup>(32)</sup>. The second Risk Evaluation and Education for Alzheimer's Disease Study also showed that those with the risk *APOE* genotype had 4.75 times the odds of reporting a change in dietary supplement use compared with those with the non-risk variant ( $P < 0.0001$ )<sup>(38)</sup>. However, in contrast to these positive studies, Bloss *et al.* investigated changes in anxiety, dietary fat and exercise behaviour in individuals who received direct-to-consumer testing and reported no changes 3 months after testing<sup>(33)</sup> and the group reported similar results when they assessed the participants again a year later<sup>(34)</sup>. Grant *et al.*<sup>(35)</sup> investigated the effect of genetic testing in individuals at phenotypic risk of diabetes. Individuals were randomised to either undergo genetic testing or not undergo testing (*n* 108). Both groups then participated in a 12-week diabetes prevention programme. The investigators reported no differences between the groups in relation to self-reported motivation, programme attendance or weight loss<sup>(35)</sup>.

One of the most recent trials in the area demonstrated a benefit of genetic based dietary advice compared with general dietary recommendations. In this double-blind placebo controlled trial, participants were randomised to receive either genetic based dietary advice on five nutrition related SNP (*CYP1A2*, *GSTT1*, *GSTM1*,

*TASIR2* and *ACE*) for 12 months or general dietary recommendations with no genetic advice<sup>(36)</sup>. The authors reported no differences between the groups in relation to caffeine, vitamin C, sugar and sodium intakes between baseline and month 3. However, there was a significant difference observed between the risk group and control group at 12 months for the *ACE* gene with respect to reductions in sodium where mean change in sodium intake was  $-287.3$  (SEM 114.1) mg/d in the risk group compared with  $129.8$  (SEM 118.2) mg/d in the control group ( $P = 0.008$ ). In the MOVE! programme, individuals with BMI  $\geq 30.0$  kg/m<sup>2</sup> were randomly assigned to either the genetics-guided therapy group or standard therapy group<sup>(37)</sup>. Guided therapy participants were then matched to one of four possible diet types (balanced, low-carbohydrate, low-fat or Mediterranean) based on their risk of seven obesity related SNP (*APOA2*, *ADIPOQ*, *FTO*, *KCTD10*, *LIPC*, *MMAB* and *PPARG*). The investigators reported no significant differences between the guided therapy and standard therapy groups in the percentage of those achieving a 5 % weight loss at 8 weeks or at 24 weeks<sup>(37)</sup>. However, it is possible that the sample size (*n* 51) of this feasibility study may have been too small to detect any significant changes between the groups.

Overall, the evidence with respect to the effectiveness of personalised nutrition based on genetic information



is mixed with some studies demonstrating positive effects and others reporting no benefits. Furthermore, a Cochrane review in the area, concluded that there was not enough evidence to support the claim that genetic testing motivates individuals to change their behaviour and larger and better-quality randomised controlled trials were needed to further test this hypothesis<sup>(39)</sup>. To date, no study has examined the effect of varying levels of personalised advice in comparison with generic advice. Food4Me is an EU funded project which aimed to examine all aspects of personalised nutrition<sup>(40)</sup>. As part of Food4Me, a proof-of-principle study was conducted to test the effects of varying levels of personalised nutrition in motivating behaviour change compared with general healthy eating guidelines<sup>(40)</sup>. This was an internet-based intervention trial conducted across seven centres in Europe ( $n$  1607). Individuals were randomised to receive either healthy eating guidelines, level 1 personalised advice based on diet alone, level 2 personalised advice based on diet and phenotype or level 3 personalised advice based on diet, phenotype and genotype. Details of the study have been described elsewhere<sup>(40)</sup>. Findings from this intervention trial will decipher whether personalised advice delivered via the internet is effective in motivating behaviour change compared with generic healthy eating advice and which level of personalisation is most effective.

#### **Moving from individuals to groups: a novel use of phenotyping/metabotyping**

In recent years the concept of targeted nutrition has emerged which involves delivering tailored dietary advice at a group level rather than at an individual level. The process of grouping similar individuals based on their metabolic or phenotypic profiles is referred to as metabotyping<sup>(41–44)</sup>. A number of statistical tools can be employed to identify these metabotypes; some of the more common types include  $k$ -means analysis and hierarchical cluster analysis. In the field of personalised medicine, metabotyping may play a role by stratifying patients for the development of tailored healthcare solutions<sup>(45)</sup>.

Examples of this concept are also available from the medical literature where cluster analysis has been used to identify different phenotypes for a range of diseases including chronic obstructive pulmonary disease<sup>(46)</sup> and Parkinsons disease<sup>(47)</sup>. This concept has been particularly useful for multisymptomatic and multifactorial diseases where presentation and severity of the disease can differ from one individual to the next. An example of such a disease is asthma; metabotyping has been successful in the identification of varying asthma phenotypes that will in turn allow development of more tailored disease management approaches<sup>(48)</sup>. Similar methods have been applied in other respiratory diseases heterogeneous in nature including chronic obstructive pulmonary disease<sup>(46,49)</sup> and emphysema<sup>(50)</sup>. Other examples of the use of cluster analysis to identify sub-groups of patients include Parkinson's disease<sup>(47,51)</sup>, gout sufferers<sup>(52)</sup>, patients with back pain<sup>(53)</sup> and patients with hip fractures<sup>(54,55)</sup>.

Another interesting application of metabotyping is the identification of differential response to intervention studies including responses to drug treatments<sup>(56)</sup> and dietary interventions<sup>(57)</sup>. In the Genetics of Lipid Lowering Drug and Diet Network, family members from three generations were recruited and given fenofibrate therapy, in order to assess the variable response of TAG lowering in a genetically similar sample with heterogenous degree of dyslipidaemia<sup>(56)</sup>. In this sample of 775 participants, cluster analysis was applied to the baseline lipoprotein profiles and three distinct lipid-metabolic phenotypes/metabotypes were identified. Each of the clusters displayed varying responses to fenofibrate therapy. While both cluster 2 and cluster 3 responded positively to the therapy, little benefit was observed for cluster 1 due to the decrease in LDL particle rather than an increase which is usually associated with treatment<sup>(56)</sup>. This is a clear example of how this approach could be used to match the patient with the appropriate treatment. This concept has previously been applied to a nutritional intervention study where individuals were supplemented with vitamin D for 6 months to improve markers of the metabolic syndrome<sup>(57)</sup>. In this double-blind placebo controlled study, there was a significant increase in vitamin D status in the intervention group compared with the placebo group ( $P < 0.001$ ) but no improvements observed in any of the metabolic syndrome markers. However, following application of a clustering approach, a vitamin D responsive cluster was identified which had significant decreases in fasting insulin ( $P = 0.011$ ), homeostatic model assessment score ( $P = 0.006$ ) and C-reactive protein ( $P = 0.011$ )<sup>(57)</sup>. These clear examples from the literature demonstrate the potential benefit of grouping individuals based on similar characteristics, either for diagnosis and/or treatment. There is a great potential in this technique for the development of more personalised healthcare practices. However, while there are many examples of the use of cluster analysis to identify these metabolic sub-groups, there is a dearth in the literature with regard to the development of personalised health solutions for these groups.

#### **A proposed framework for the delivery of targeted nutrition**

Work from our centre has proposed a framework for the delivery of targeted nutrition based on a metabotype approach. The framework used a cluster analysis approach to define metabotypes and targeted nutrition advice is delivered by decision trees specific for each cluster. Using this approach, metabotyping was performed with total cholesterol, TAG, direct HDL cholesterol and glucose in a population of healthy Irish subjects<sup>(58)</sup>. The use of these commonly measured markers of metabolic health ensures future applicability across different studies. Three distinctly different clusters or metabotypes were identified across the population. Cluster 1 ( $n$  274) was characterised by high total cholesterol. Subjects in cluster 2 ( $n$  423) had low total cholesterol, TAG and glucose values and were the youngest group. Cluster 3

subjects ( $n$  178) were found to have the most metabolically unfavourable profile including high total cholesterol, TAG and glucose values, highest BMI and subsequently, greatest prevalence of the metabolic syndrome.

Targeted dietary advice was developed based on the characteristics of each cluster where cluster 1 subjects were given cholesterol lowering advice, cluster 2 were relatively healthy and encouraged to continue with their current healthy lifestyle and cluster 3 were given advice on how to lower their cholesterol, TAG and glucose levels. Using a decision tree method, branches of anthropometric (BMI and waist circumference) and blood pressure information were added which resulted in twelve targeted dietary advice messages per cluster. To test the ability of the targeted approach to deliver personalised nutrition, individualised dietary advice was compiled for a random selection of the participants ( $n$  99) and compared with the targeted advice. Overall good agreement was found between the methods with a mean match of 89.1 % (range 20–100 %) in terms of the dietary advice which would be given to a participant at an individual level compared with their targeted dietary advice based on their cluster membership.

To the best of our knowledge this is the first example of this type of approach or framework. The key advantages of such an approach are (1) use of routine biochemical measurements, (2) limited number of decision trees required and (3) easy automation which could enable the rapid delivery of targeted dietary advice in a variety of clinical settings. An example of where this approach could have major implications is the use in general practice clinics. In this scenario, patients are undergoing routine checks and the framework could be implemented with minimal effort. Recent data demonstrates that patients would like to receive dietary information from their general practitioner<sup>(59)</sup> but general practitioners feel they are unequipped to do this due to reported barriers such as heavy workload and lack of skills or training<sup>(60)</sup>. However, by adopting this framework, delivery of personalised nutrition could become a reality in general practice clinics. Future work will be directed towards demonstrating the applicability in a more diverse population.

### Conclusion

Overall, personalised nutrition appears to be more effective in motivating behaviour change compared with generic healthy eating advice with strong evidence available for level 1 and level 2 personalised approaches. In particular, there is good evidence to suggest that personalised advice can motivate specific dietary changes such as increasing fruit and vegetables or decreasing fat intake. Similarly, there is positive evidence that personalised advice can be more beneficial than generic dietary advice for individuals who need to lose weight. However, there is more research needed in the way of large scale intervention studies before any conclusions can be drawn in relation to genetic based personalised advice and its effectiveness in motivating behaviour

change. Metabotyping may be a useful approach for the identification of groups of similar individuals who consequently may have similar nutritional needs. Work described here from our centre demonstrates a novel application of this technique for the delivery of tailored dietary advice at the group level which may have huge potential for the delivery of personalised nutrition at a population level. Future work includes the further development of this proposed targeted nutrition framework; in particular, the testing of its efficacy to elicit dietary change in individuals. Furthermore, the metabotyping technique can be refined through the adoption of different clustering variables and validation of the process in other population groups. This framework could pave the way forward in terms of novel approaches to the delivery of tailored nutrition and help deliver the promise of personalised nutrition to all.

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### Conflict of interest

None.

### Authorship

C. B. O. D. drafted the outline of the manuscript, conducted the literature search and drafted the manuscript. M. C. W., M. J. G., E. R. G. and L. B. were responsible for critically reviewing the manuscript. All authors read and approved the final manuscript before submission.

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