Case Studies in Personalized Nutrition

Personalized Nutrition and Lifestyle Medicine for Healthcare Practitioners
Edited by Lorraine Nicolle, this series of accessible, evidence-based, practical guides is essential reading for practitioners and students of clinical nutrition, and all other primary and complementary healthcare professionals interested in an approach that responds to the unique health needs of every individual. Each book in the series is a powerful new tool to help practitioners achieve significant clinical improvements for their clients/patients through the cutting-edge paradigm of personalized nutrition and lifestyle medicine.

Lorraine Nicolle MSc is a Registered Nutritionist (MBANT) and an educator and author in personalized nutrition. www.lorrainenicollenutrition.co.uk

in the same series

Using Nutrigenomics within Personalized Nutrition
A Practitioner's Guide
Anne Pemberton
ISBN 978 1 84819 413 7
eISBN 978 0 85701 368 2

Mitochondria in Health and Disease
Ray Griffiths
Foreword by Lorraine Nicolle
ISBN 978 1 84819 332 1
eISBN 978 0 85701 288 3

of related interest

Biochemical Imbalances in Disease
A Practitioner's Handbook
Lorraine Nicolle and Ann Woodriff Beirne
ISBN 978 1 84819 033 7
eISBN 978 0 85701 028 5

The Functional Nutrition Cookbook
Addressing Biochemical Imbalances through Diet
Lorraine Nicolle and Christine Bailey
ISBN 978 1 78592 991 5
eISBN 978 0 85701 052 0

Case Studies in Personalized Nutrition

Part of

Personalized Nutrition and Lifestyle Medicine for Healthcare Practitioners *series*

Angela Walker

Foreword by Lorraine Nicolle

SINGING DRAGON

LONDON AND PHILADELPHIA

Figure 2.1 is adapted from Sackett 1996 with kind permission from the Institute for Work Based Learning.
Figure 2.2 is reprinted from Murad *et al.* 2006 with kind permission from BMJ Publishing Group Ltd.
The Functional Medicine Matrix (in the colour plate and Figure 9.4) is reprinted from the Institute for Functional Medicine with their kind permission.

First published in 2020
by Singing Dragon
an imprint of Jessica Kingsley Publishers
73 Collier Street
London N1 9BE, UK
and
400 Market Street, Suite 400
Philadelphia, PA 19106, USA

www.singingdragon.com

Library of Congress Cataloging in Publication Data
A CIP catalog record for this book is available from the Library of Congress

British Library Cataloguing in Publication Data
A CIP catalogue record for this book is available from the British Library

ISBN 978 1 84819 394 9
eISBN 978 0 85701 351 4

Printed and bound in Great Britain

Contents

Foreword by Lorraine Nicolle *7*

Acknowledgements *11*

Terminology *13*

1 Introduction and Setting the Scene 15
Angela Walker

2 The Evidence Base in Personalized Nutrition 21
Miguel Toribio-Mateas and Angela Walker

3 Functional Laboratory Testing in Personalized Nutrition 38
Angela Walker

4 Recurrent Urinary Tract Infections (UTIs) with Antibiotic Dependency 72
Practitioner: Lorraine Nicolle

5 Chronic Fatigue Syndrome 101
Practitioner: Helen Lynam
Additional contribution to case write-up: Angela Walker

6 Morbid Obesity and Weight Loss Resistance 141
Nutrition Practitioner: Romilly Hodges
Case Physician: Kara Fitzgerald

7 Cognitive Health through Gut–Brain Communication 178
Practitioner: Miguel Toribio-Mateas

8 A Personalized Nutrition Approach to Suspected Metabolic Syndrome 215
Practitioner: Jo Gamble
Additional contribution to case write-up: Angela Walker

9 Gastrointestinal Health and the Gut–Brain Axis 253
Practitioner: Elspeth Stewart
Additional contribution to case write-up: Angela Walker

10 Autoimmunity with Intestinal Permeability and Fructose Intolerance 294
Practitioner: Claire Sehinson

11 Endometriosis and Hormonal Health 327
Practitioner: Lorna Driver-Davies
Additional contribution to case write-up: Angela Walker

12 Learnings and Conclusions 357
Angela Walker

Appendix A: Drug–Nutrient Interaction Checker *366*

Useful Resources *370*

About the Contributors *372*

Subject Index *376*

Author Index *383*

2
The Evidence Base in Personalized Nutrition

Miguel Toribio-Mateas and Angela Walker

Clinical decisions in personalized nutrition practice must have a rational basis that is substantiated by scientific evidence. This makes professionals practising personalized nutrition evidence-based practitioners. This chapter will discuss the wider definition of evidence, including but not limited to the randomized controlled trial (RCT), and explore how practitioners can develop a comprehensive rationale for the application of food- and lifestyle-based recommendations.

Background to evidence-based medicine (EBM)

The concept of evidence-based medicine (EBM) was first discussed in a landmark paper entitled 'Evidence based medicine: what it is and what it isn't' (Sackett *et al.*, 1996). Sackett emphasized the importance of making clinical decisions based only on the best available evidence and explored the idea that not all evidence is created equal. Importantly, he advocated the use of evidence and clinical expertise concurrently in order to successfully implement the concept of EBM into clinical practice.

> Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. (Sackett *et al*., 1996, p.71)

A later update to the original model for EMB introduced two new considerations (Sackett, 2000). First, it stressed the importance of taking client values and preferences into account when making clinical decisions. Second, to extend the concept of clinical research beyond the restricted context of laboratories and clinical trials, Sackett encouraged medical practitioners to view themselves as researchers in their own clinical practice. This call for clinicians to become practitioner-researchers is powerful and still very much applicable to practitioners of personalized nutrition today.

Traditional hierarchy of evidence-based practice

Most practitioners of personalized nutrition are not medically trained. Therefore, the term evidence-based practice (EBP) is more appropriate in this context. EBP will be used instead of EBM for the rest of this chapter.

One of the goals of EBP is to educate clinicians in the understanding and use of published literature to optimize clinical practice (Djulbegovic and Guyatt, 2017). Not all evidence is equal. The evidence-based practitioner will take the totality of evidence into account, which means consideration of negative as well as positive evidence. Cherry-picking of evidence must be avoided.

There is a recognized hierarchy to types of evidence that informs EBP, which is shown in Figure 2.1. In this traditional pyramid, systematic reviews and meta-analysis are at the top as having highest quality, followed by randomized controlled trials, cohort studies, case-control studies and case series/reports. Expert opinion is classed as having the poorest quality.

As illustrated in Figure 2.1, unfiltered or primary sources provide evidence concerning a topic under investigation. Primary resources – for example, articles that appear in scientific journals that are indexed in databases such as PubMed – have a higher place in the hierarchy of evidence than other sources of information that have not been peer-reviewed. In the age of Instagram, it is important to realize that blogs

and social media posts are classed as expert opinion and are therefore seen to have the lowest quality in an EBP hierarchy of evidence. Filtered or secondary sources are summaries and analyses of the evidence derived from and based on unfiltered primary sources. Filtered sources are useful in clinical practice as they provide an appraisal of the quality of studies and often make recommendations based on 'tried and tested' evidence.

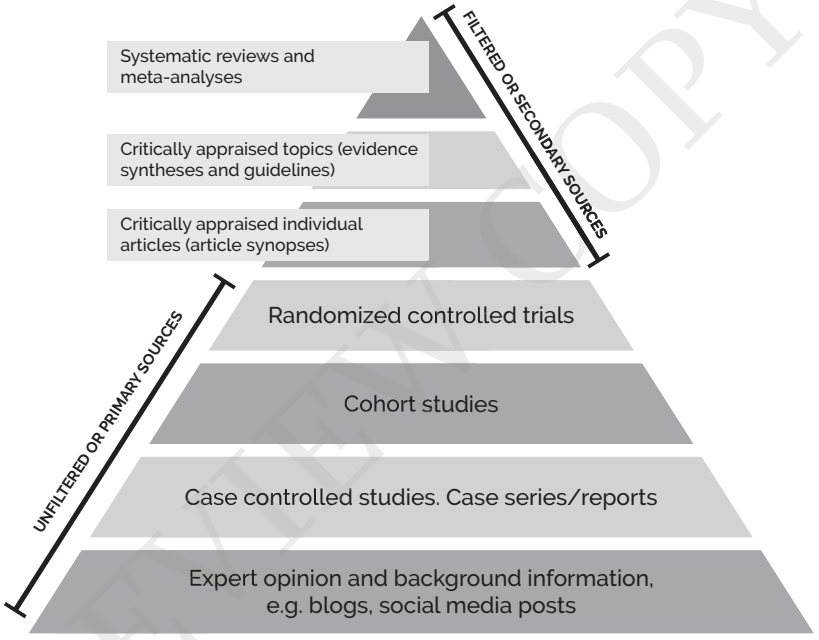

Figure 2.1 A representation of the hierarchy of evidence-based practice as a pyramid
Source: Based largely on Sackett (1996), reinterpreted by Toribio-Mateas

Modifications and critiques of the EBP model

Murad and colleagues (2016) proposed a modification to the traditional pyramid where systematic reviews are removed from the top of the pyramid and used as a lens through which other types of studies should be appraised and applied. This is depicted in Figure 2.2. Under this

approach, systematic reviews (the process of selecting the studies) and meta-analyses (the statistical aggregation that produces a single effect size) are 'tools to consume and apply the evidence by stakeholders' (Murad *et al*., 2016). This development of the EBP embraces the use of clinical insight by practitioners as initially conceived by Sackett (1996, 2000). In a clinical setting where individualization of care is paramount, and where clinicians and clients make collaborative decisions, this approach is welcomed and represents a more pragmatic and intelligent interpretation of EBP.

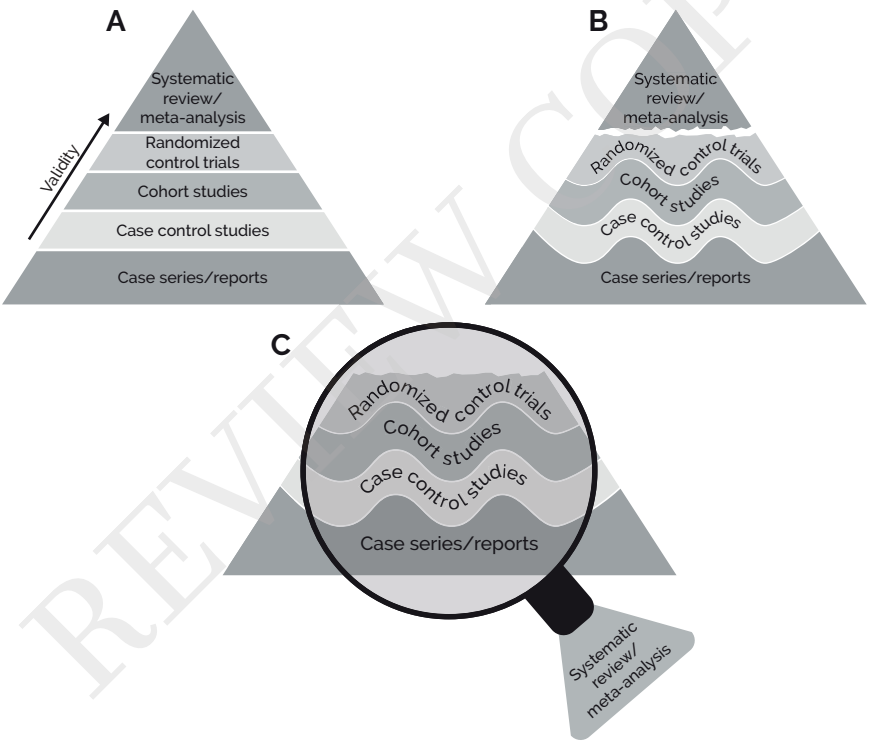

Figure 2.2 A modified evidence-based practice pyramid
Source: Reproduced with permission from Murad et al. *(2016)*

That EBM or EBP has provided a beneficial framework for the application of scientific evidence in healthcare settings is without question. However, the model is not perfect and has attracted criticism, even

from some of the leading voices of the EBP movement. A noteworthy example is provided by Trisha Greenhalgh, Professor of Primary Health Sciences and leader of the Evidence-Based Medicine Renaissance Group at Oxford University. Greenhalgh has openly critiqued the fact that 'the gold standard' in the EBP model – the systematic review – has been idealized as representing a tool to remove bias from scientific research that has put it at the top of what she calls a 'spurious hierarchy of systematic over narrative reviews' (Greenhalgh, Thorne and Malterud, 2018, p.1). For many EBP proponents, qualitative research is seen as 'a poor cousin', while Greenhalgh argues that qualitative and quantitative research are equally important, but just 'different and potentially complementary form[s] of scholarship' (p.4). A full critique of EBP is beyond the scope of this chapter, but readers may be interested in the work of Rycroft-Malone *et al*. (2012) who consider the traditional systematic review approaches to be too specific and inflexible.

Complex systems or linear, cause-and-effect relationships?

The randomized controlled trial, at the heart of the EBP pyramid, is typically attempting to map and investigate a linear, cause-and effect relationship (Katerndahl, 2009; Sibbald and Roland, 1998). The human body can perhaps be more accurately described as a complex adaptive system. A study on the perception of complexity in medicine within published papers on the topic found a growing recognition that systems in nature, including those involved in the workings of the human body, involve many different components which interact in non-linear ways (Sturmberg, Martin and Katerndahl, 2014). To evaluate nutritional science in a *purely* linear fashion without consideration of synergistic and non-linear relationships risks becoming a reductionist approach.

For example, zinc is necessary as a cofactor for more than 300 enzymes (McCall, Huang and Fierke, 2000). Zinc has a structural role in plasma membranes (O'Dell, 2000) and a regulatory role in gene expression, acting as a transcription factor (Truong-Tran *et al*., 2000). Zinc interacts with other nutrients – for example, when taken in a high dose, it can negatively

affect the bioavailability of copper (Abdallah and Samman, 1993). Furthermore, the zinc ion is thought to have a regulatory role on major cellular ions including sodium (NA^+), potassium (K^+) and calcium (Ca^+) (Maret, 2017). In addition, there is a documented synergistic relationship between zinc and vitamin A whereby the antioxidant function of vitamin A is more effective when zinc levels are adequate (Matos *et al*., 2012, 2018). An RCT measuring the impact of zinc supplementation on a single health outcome may not therefore measure the full impact on the complex and adaptive system of an individual.

Embracing complexity

Other areas of science can perhaps assist healthcare practitioners to embrace complexity. An agreement and certainty diagram is a conceptual model for complex problem solving developed in the field of organizational dynamics (Stacey, 1996). The model provides an interesting framework for considering the complexity within a practitioner/client healthcare consultation. Figure 2.3 shows a version of this model adapted from the original model and how it can be applied to the healthcare setting.

It can be said that mainstream health evidence, with a focus on testing linear relationships via randomized controlled trials, is located in the bottom left-hand corner of Figure 2.3, with high certainty and high agreement (Martin and Félix-Bortolotti, 2010).

Is that approach really appropriate when dealing with a complex system such as the human body? Could that approach be too reductive and simplistic to achieve best results when dealing with individuals who have genetic, epigenetic and lifestyle variability?

Translation of science into the context of successful personalized nutrition practice requires recognition of the non-linearity principles that characterize complex health systems. David Katerndahl is a Medicine Professor at the University of Texas Health Science Centre who studies the application of complexity science to the study of family and community medicine. According to Katerndahl, embracing complexity has the power to improve clinical practice:

Understanding the non-linear dynamics of phenomena both internal and external to our patients can (1) improve our definition of 'health'; (2) improve our understanding of patients, disease and the systems in which they converge; (3) be applied to future monitoring systems; and (4) be used to possibly engineer change.

Doctors who successfully practise the 'art' of medicine may recognize non-linear principles at work without having the jargon needed to label them. (Katerndahl, 2009, p.755)

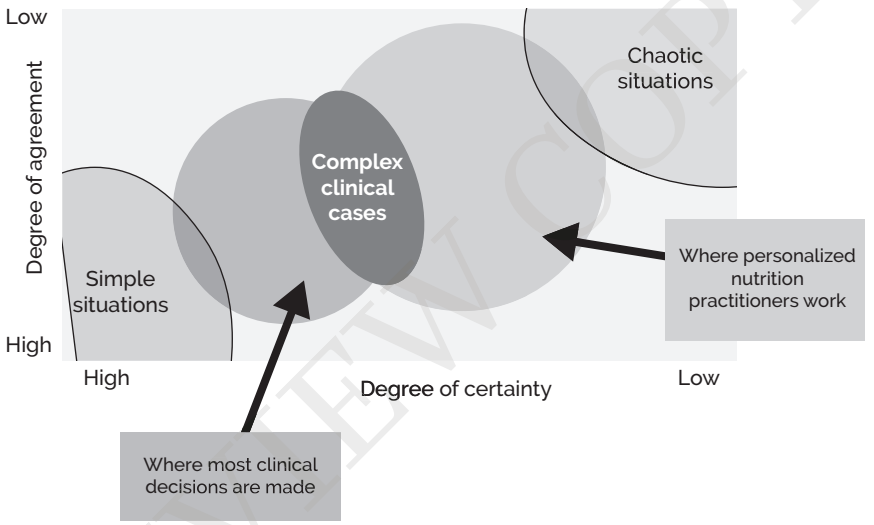

Figure 2.3 A 'certainty-agreement' diagram illustrating the context where personalized nutrition practitioners operate compared with other clinicians
The diagram aims to illustrate the context where most clinical decisions are made when following linear guidelines to tackle simple situations (e.g. supplement with vitamin B12 if B12 deficiency has been identified by means of testing) versus a situation that is chaotic in nature, typically featuring a complex set of overlapping symptoms. In this kind of unchartered territory, practitioners need to make sense of complexity by drawing from appropriate scientific evidence while using their clinical insight.
Source: Adapted from Stacey (1996) and Plsek and Greenhalgh (2001) by Toribio-Mateas

Importance of the client story

> We are never illness or disease but, rather, always their sum in the world of day-to-day experience. Illness and disease are not closed systems but mutually constitutive and continuously interacting worlds. In the patient's case, it is always experience as well; we are always in contact with our own worlds of physical and emotional pain and experience – and thus identity – that cannot be reduced to the external zone of intersection between society and the men and women who constitute it. (Rosenberg, 2002, p.258)

This quotation, taken from a paper by Charles Rosenberg, Professor of the History of Science and Medicine at Harvard University, eloquently captures the role the client story. The rich texture of the client story has psychosocial and emotional aspects that are as important as the physical manifestations of disease.

Innes and colleagues (2005) propose that the narrative between client and practitioner has its own agency as a 'complex responsive process', and, further, that clients are nervous about their doctor 'reducing their story to the level of a technical description' (Innes *et al*., 2005, p.49).

In fact, the interaction between the practitioner and client in the face of complexity and paradox can be key to tackling complex conditions such as chronic pain (Brown, 2009). The nascent nature of the personalized nutrition profession has provided the perfect environment for professionals in this field to work 'at the edge of chaos', continuously identifying patterns in their clients' narratives that enable them to make sense of reality so that they can generate recommendations that are appropriate, safe and meaningful.

A key skill needed to manage working with complexity is reflective practice. The concept of reflective practice was initially developed by Donald Schön, a visiting professor at Massachusetts Institute of Technology.

Schön claims that reflection-in-action is 'central to the "art" by which practitioners sometimes deal well with situations of uncertainty, instability, uniqueness, and value conflict' (Schön, 1983, p.50). Discussing reflection in biomedical professions, he argues that case

histories are a key part of 'the physician's process of inquiry – the way in which he perceives and describes the patient, his manner of listening to the patient's descriptions of his complaints, the process by which he identifies possible explanations, conceives of strategies of diagnosis or treatment, and tests them' (Schön, 1983, p.317).

As the cases in the following chapters show, the context, narrative and sense-making between the client and practitioner is an integral part of the personalized nutrition process. The practitioners use coaching skills (active listening, targeted restatements, questioning, clarifying) combined with education to help the client implement the recommendations and achieve their health goals. The client timeline and the interpretation of tests become practical tools which help to organize, structure and inform the client's story. These tools and skills become the foundations of the developing therapeutic relationship. It is therefore proposed that the personalized nutrition clinical approach embraces many of the key elements which assist the practitioner to embrace complexity.

What does evidence look like in complex adaptive systems?

There are impressive examples of studies which aim to embrace the complexity and paradox of nutritional biochemistry in a clinical trial setting. Teams led by Dr Terry Whals have studied the impact of a multimodule approach (modified Paleolithic diet, exercise, stress reduction) to multiple sclerosis and demonstrated the effectiveness of this approach (Bisht *et al*., 2014; Lee *et al*., 2017). Dr Dale Bredesen has published case studies on an integrated personalized nutrition approach for successfully reversing Alzheimer's disease (Bredesen *et al*., 2016). A prospective study demonstrated proof of concept for an integrated personalized, nutrition and psychology approach to chronic fatigue (Arroll and Howard, 2012), which is currently at ethics approval stage to take into a fully randomized controlled study.

These examples illustrate that traditional clinical research *can* be conducted on a personalized nutrition approach. It is hoped these studies will pave the way for more like them. In the meantime, is it

true that evidence is lacking for personalized nutrition? The absence of evidence is not the same as evidence of absence, a point that has been highlighted in discussions on evidence-based medicine (Altman and Bland, 1995; Djulbegovic, Elqayam and Dale, 2018; Sola, Dieppa and Rogido, 2007).

Furthermore, as has been discussed above, taking a more comprehensive view of evidence-based practice may lead to better solutions for complex clinical situations. In the context of personalized nutrition, there is evidence and it often needs to be collated from a wider range of sources.

Evidence from a wide range of sources

A personalized nutrition practitioner will use a wide range of sources of evidence. Let us take a specific example. The practitioner is considering whether there is evidence to support supplementing magnesium for a client.

- A starting point may be to ask, 'Are there filtered sources of evidence – a review or a meta-analysis for using magnesium in a client with similar characteristics?'
- There is a meta-analysis for magnesium use in hypertension and diabetes (Wu *et al*., 2017).
- My client doesn't have hypertension or diabetes, but she has hypothyroidism and she is very anxious, and has some characteristics of metabolic syndrome.
- There are no primary or secondary sources for using magnesium in exactly that scenario.
- Looking from a systems biology perspective:
  - Magnesium is key for mitochondria function (Pilchova *et al*., 2017).
  - Magnesium adenosine triphosphate (ATP) produced in the mitochondria through oxidative phosphorylation is central to any function that requires energy, plus magnesium is involved

in iodine uptake, which is documented in a peer-reviewed article (Moncayo and Moncayo, 2017).

- Meta-analysis on the use of magnesium in anxiety found a poor quality of evidence (Boyle, Lawton and Dye, 2017). There is, however, some supportive evidence from clinical studies for the use of magnesium in anxiety (Boyle, Lawton and Dye, 2016).
- Magnesium plays an essential role in the N-methyl-d-aspartate (NMDA) receptor, serving to block the calcium channel. Via this molecular function it has a role in normalizing neurological function and avoiding neurological excitotoxicity (Kirkland, Sarlo and Holton, 2018).
- Experiential evidence from the practitioner's own clinic and discussions with peers is that magnesium is helpful for clients who have anxiety, and that some have found it to be most effective in the glycinate form.
- Is there specific evidence to substantiate magnesium glycinate? No, but experientially that seems to be the case.
- Furthermore, reviewing the client's diet, the practitioner estimates her magnesium intake from diet to be quite low. The practitioner considered testing red blood cell magnesium, but, given that magnesium has low potential for harm when used at a sensible dose, elects to supplement 300 mg magnesium as glycinate, as part of an integrated programme.

Is that evidence-based? Yes, even though some EBM practitioners may argue that the decision to supplement magnesium is based on critical thinking and not on primary research from clinical or epidemiology study designs in the hierarchy pyramid and/or filtered or secondary analysis of these. Person-centred practitioners evaluate the evidence available and use a systems biology logic, applying it to the individual case in order to make a decision. This decision is then compounded by the assessment of dietary deficiency which should also be routinely corrected in practice.

Patient-reported outcome measures (PROMS)

Patient-reported outcome measures (PROMs) such as the Measure Yourself Medical Outcome Profile (MYMOP) (Paterson, 2004, 1996; Paterson and Britten, 2000; Price, Merer and MacPherson, 2006) are useful tools in this process of clinical inquiry *and* can help a clinician gather data generated within their own practice. This client-reported data on measures of wellbeing enables the practitioner to assess client progress prior to and post-interventions, and provides an opportunity for clinicians to become practitioner-researchers and build a primary evidence base that bridges the gap where other types of evidence may not be available. PROMS have been found to be useful for capturing data describing the issues of greatest concern to clients (Sales *et al*., 2018), thereby 'humanizing' the results of clinical trials where participants are just seen as a number.

The original model for EMP advocated that the client's own preferences should be factored into decision making (Sackett, 2000). This has been reinforced by the GRADE working group which aims to develop a common, sensible and transparent approach to grading quality (or certainty) of evidence and strength of healthcare recommendations (Andrews *et al*., 2013). This is key to decision making in personalized nutrition. Clients typically feel more empowered when they know why the decisions they are taking about what to eat are expected to have an impact on their health. PROMS provide a structured way to keep the client's priorities central to the clinical approach.

All the cases in the following chapters use some form of PROMS. Some are fully validated tools, such as the Measure Yourself Medical Outcome Profile (MYMOP) used in Chapter 7. Some are only validated by their use in clinical practice but haven't followed the validation process of the MYMOP. An example is the Medical Symptom Questionnaire (MSQ) featured in Chapter 6, which is commonly used by functional medicine practitioners. In the rest of the cases the practitioner either asks the client to rate their top symptoms on a scale of 1 through to 10 (1 being as good as it could be, 10 being as a bad as it could be) and these scores

are tracked in each appointment. Alternatively, the practitioner tracks progress through the qualitative assessment of lifestyle – for example, how much time they can spend on an activity or how frequently a symptom occurs. The advantage of using a validated tool is twofold. First, its interpretation is standardized and hence easy to understand by other practitioners who may be involved in a case. Second, its output can be used to contribute to broader research. While non-validated tools may accommodate a client's individuality, they are not suitable for research purposes as they introduce a high level of heterogeneity that can contribute to bias.

Benefit versus harm

Most rational decision making in EBM is to initiate an intervention where the expected benefits outweigh the expected harm (Djulbegovic *et al*., 2018). If the potential to harm is high, then the evidence to justify the use of an intervention must be much more robust. For nutrients and foods, the potential for harm is far lower than for pharmaceutical agents.

This isn't to say that practitioners shouldn't be mindful of any potential harm, particularly when recommending therapeutic foods. Could an individual make him/herself sick by drinking too much kefir, eating too much broccoli or using an excessive amount of olive oil? Potentially yes, but the risks are generally low. Examples do exist – for example, foods high in histamine (which can also be foods generally considered 'healthy') may cause a problem for someone who has difficulty with histamine. Drug–food interactions must also be considered, such as that between grapefruit juice and statins (Ando *et al*., 2005). Thus, when working with foods in a therapeutic manner, it is wise for practitioners to be observant of any potential risks, but to focus on benefits which, in most cases, are more likely to outweigh any serious potential harm. (Drug–nutrient interactions are described in Appendix A and are discussed in the relevant cases where medications are taken.)

Evidence presented in the case studies

In each of the eight case studies, the basis of the rationale for decisions taken is provided. This includes sharing the practitioner thinking on what the underlying factors are in a case, as well as the evidence to support the specific food- and lifestyle-based interventions.

Given the complexities involved, each of the clinical decisions taken could include hundreds of individual components. The approach to presenting the evidence is a pragmatic one. To cover the totality of evidence (positive and negative) in each and every decision would be extremely lengthy and not terribly interesting to the reader. In each case study the goal has been to provide a breadth of evidence for the approach taken. In some places a greater breadth of evidence has been discussed; in other areas evidence is presented in less depth. Importantly, it is intended to demonstrate that the clinician in each case is embracing the evidence from a wide range of sources (the full pyramid of Figures 2.1 and 2.2), that they are applying clinical expertise as well as published evidence, and that client values and preferences are taken fully into account. Finally, the way that the client narrative, reflective practice (from the Q&A) and the therapeutic relationships are used within each case demonstrates how the practitioners have learned to embrace the complexity and indeed use that to further the clinical journey.

Evolving the evidence base for personalized nutrition

Is there more that could be done to build a robust evidence base in personalized nutrition? The short answer is yes. Work is already in hand with professional bodies in the industry to develop more effective tools. Emerging technologies for data collection and analysis, such as artificial intelligence and natural language processing, as well as data sharing may facilitate the process of incorporating patient-reported outcomes into trials and routine clinical practice (Wheat *et al*., 2018), leading to the evolution of person-centered healthcare (Perez Botero, Thanarajasingam and Warsame, 2016). With an approach that uses

systematic reviews and meta-analysis as a lens through which to evaluate other types of evidence such as case studies and observational or non-randomized studies, it is hoped that this book will help to establish the role of case studies within the wider evidence base for personalized nutrition.

Acknowledgements

Angela Walker and Miguel Toribio-Mateas contributed equally to the writing of this chapter. Toribio-Mateas created Figures 2.1 and 2.3.

References

Abdallah, S.M., Samman, S., 1993. The effect of increasing dietary zinc on the activity of superoxide dismutase and zinc concentration in erythrocytes of healthy female subjects. *European Journal of Clinical Nutrition* 47, 327–332.

Altman, D.G., Bland, J.M., 1995. Statistics notes: Absence of evidence is not evidence of absence. *BMJ* 311, 485. https://doi.org/10.1136/bmj.311.7003.485

Ando, H., Tsuruoka, S., Yanagihara, H., Sugimoto, K. *et al*., 2005. Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. *British Journal of Clinical Pharmacology* 60, 494–497. https://doi.org/10.1111/j.1365-2125.2005.02462.x

Andrews, J.C., Schünemann, H.J., Oxman, A.D., Pottie, K. *et al*., 2013. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *Journal of Clinical Epidemiology* 66, 726–735. https://doi.org/10.1016/j.jclinepi.2013.02.003

Arroll, M.A., Howard, A., 2012. A preliminary prospective study of nutritional, psychological and combined therapies for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in a private care setting. *BMJ Open* 2. https://doi.org/10.1136/bmjopen-2012-001079

Bisht, B., Darling, W.G., Grossmann, R.E., Shivapour, E.T. *et al*., 2014. A multimodal intervention for patients with secondary progressive multiple sclerosis: Feasibility and effect on fatigue. *Journal of Alternative and Complementary Medicine* 20, 347–355. https://doi.org/10.1089/act.2014.20606

Boyle, N.B., Lawton, C., Dye, L., 2017. The effects of magnesium supplementation on subjective anxiety and stress – a systematic review. *Nutrients* 9. https://doi.org/10.3390/nu9050429

Boyle, N.B., Lawton, C.L., Dye, L., 2016. The effects of magnesium supplementation on subjective anxiety. *Magnesium Research* 29, 120–125. https://doi.org/10.1684/mrh.2016.0411

Bredesen, D.E., Amos, E.C., Canick, J., Ackerley, M. *et al*., 2016. Reversal of cognitive decline in Alzheimer's disease. *Aging* 8, 1250–1258. https://doi.org/10.18632/aging.100981

Brown, C.A., 2009. Mazes, conflict, and paradox: Tools for understanding chronic pain. *Pain Practice* 9, 235–243. https://doi.org/10.1111/j.1533-2500.2009.00279.x

Djulbegovic, B., Elqayam, S., Dale, W., 2018. Rational decision making in medicine: Implications for overuse and underuse. *Journal of Evaluation in Clinical Practice* 24, 655–665. https://doi.org/10.1111/jep.12851

Djulbegovic, B., Guyatt, G.H., 2017. Progress in evidence-based medicine: A quarter century on. *Lancet* 390, 415–423. https://doi.org/10.1016/S0140-6736(16)31592-6

Greenhalgh, T., Thorne, S., Malterud, K., 2018. Time to challenge the spurious hierarchy of systematic over narrative reviews? *European Journal of Clinical Investigation* 48, e12931. https://doi.org/10.1111/eci.12931

Innes, A.D., Campion, P.D., Griffiths, F.E., 2005. Complex consultations and the 'edge of chaos.' *British Journal of General Practice* 55, 47–52.

Katerndahl, D.A., 2009. Lessons from Jurassic Park: Patients as complex adaptive systems. *Journal of Evaluation in Clinical Practice* 15, 755–760. https://doi.org/10.1111/j.1365-2753.2009.01228.x

Kirkland, A.E., Sarlo, G.L., Holton, K.F., 2018. The role of magnesium in neurological disorders. *Nutrients* 10. https://doi.org/10.3390/nu10060730

Lee, J.E., Bisht, B., Hall, M.J., Rubenstein, L.M. *et al*., 2017. A Multimodal, Nonpharmacologic intervention improves mood and cognitive function in people with multiple sclerosis. *Journal of the American College of Nutrition* 36, 150–168. https://doi.org/10.1080/07315724.2016.1255160

Maret, W., 2017. Zinc in cellular regulation: The nature and significance of 'zinc signals'. *International Journal of Molecular Sciences* 18. https://doi.org/10.3390/ijms18112285

Martin, C.M., Félix-Bortolotti, M., 2010. W(h)ither complexity? The emperor's new toolkit? Or elucidating the evolution of health systems knowledge? *Journal of Evaluation in Clinical Practice* 16, 415–420. https://doi.org/10.1111/j.1365-2753.2010.01461.x

Matos, A., Souza, G., Moreira, V., Luna, M., Ramalho, A., 2018. Vitamin A supplementation according to zinc status on oxidative stress levels in cardiac surgery patients. N*utrición Hospitalaria* 35, 767–773. https://doi.org/10.20960/nh.1666

Matos, A.C., Souza, G.G., Moreira, V., Ramalho, A., 2012. Effect of vitamin A supplementation on clinical evolution in patients undergoing coronary artery bypass grafting, according to serum levels of zinc. *Nutrición Hospitalaria* 27, 1981–1986. https://doi.org/10.3305/nh.2012.27.6.5891

McCall, K.A., Huang, C., Fierke, C.A., 2000. Function and mechanism of zinc metalloenzymes. *Journal of Nutrition* 130, 1437S–46S. https://doi.org/10.1093/jn/130.5.1437S

Moncayo, R., Moncayo, H., 2017. Applying a systems approach to thyroid physiology: Looking at the whole with a mitochondrial perspective instead of judging single TSH values or why we should know more about mitochondria to understand metabolism. *BBA Clinical* 7, 127–140. https://doi.org/10.1016/j.bbacli.2017.03.004

Murad, M.H., Asi, N., Alsawas, M., Alahdab, F., 2016. New evidence pyramid. *BMJ Evidence-Based Medicine 21*, 125–127. https://doi.org/10.1136/ebmed-2016-110401

O'Dell, B.L., 2000. Role of zinc in plasma membrane function. *Journal of Nutrition* 130, 1432S–6S. https://doi.org/10.1093/jn/130.5.1432S

Paterson, C., 2004. Seeking the patient's perspective: A qualitative assessment of EuroQol, COOP-WONCA charts and MYMOP. *Quality of Life Research* 13, 871–881. https://doi.org/10.1023/B:QURE.0000025586.51955.78

Paterson, C., 1996. Measuring outcomes in primary care: A patient generated measure, MYMOP, compared with the SF-36 health survey. *BMJ* 312, 1016–1020.

Paterson, C., Britten, N., 2000. In pursuit of patient-centred outcomes: A qualitative evaluation of the 'Measure Yourself Medical Outcome Profile'. *Journal of Health Services Research and Policy* 5, 27–36. https://doi.org/10.1177/135581960000500108

Perez Botero, J., Thanarajasingam, G., Warsame, R., 2016. Capturing and incorporating patient-reported outcomes into clinical trials: Practical considerations for clinicians. *Current Oncology Reports* 18. https://doi.org/10.1007/s11912-016-0549-2

Pilchova, I., Klacanova, K., Tatarkova, Z., Kaplan, P., Racay, P., 2017. The involvement of Mg2+ in regulation of cellular and mitochondrial functions. *Oxidative Medicine and Cellular Longevity* 2017, 6797460. https://doi.org/10.1155/2017/6797460

Plsek, P.E., Greenhalgh, T., 2001. Complexity science: The challenge of complexity in health care. *BMJ* 323, 625–628.

Price, S., Mercer, S.W., MacPherson, H., 2006. Practitioner empathy, patient enablement and health outcomes: A prospective study of acupuncture patients. *Patient Education and Counselling* 63, 239–245. https://doi.org/10.1016/j.pec.2005.11.006

Rosenberg, C.E., 2002. The tyranny of diagnosis: Specific entities and individual experience. *Milbank Quarterly* 80, 237–260.

Rycroft-Malone, J., McCormack, B., Hutchinson, A.M., DeCorby, K. *et al*., 2012. Realist synthesis: Illustrating the method for implementation research. *Implementation Science* 7, 33. https://doi.org/10.1186/1748-5908-7-33

Sackett, D.L., 2000. The fall of 'clinical research' and the rise of 'clinical-practice research'. *Clinical Investigative Medicine* 23, 379–381.

Sackett, D.L., Rosenberg, W.M., Gray, J.A., Haynes, R.B., Richardson, W.S., 1996. Evidence based medicine: What it is and what it isn't. *BMJ* 312, 71–72.

Sales, C.M., Neves, I.T., Alves, P.G., Ashworth, M., 2018. Capturing and missing the patient's story through outcome measures: A thematic comparison of patient-generated items in PSYCHLOPS with CORE-OM and PHQ-9. *Health Expectations* 21, 615–619. https://doi.org/10.1111/hex.12652

Schön, D.A., 1983. *The Reflective Practitioner*. Basic Books.

Sibbald, B., Roland, M., 1998. Understanding controlled trials. Why are randomised controlled trials important? *BMJ* 316, 201.

Sola, A., Dieppa, F.D., Rogido, M.R., 2007. An evident view of evidence-based practice in perinatal medicine: Absence of evidence is not evidence of absence. *Jornal de Pediatria* 83, 395–414. https://doi.org/10.2223/JPED.1702

Stacey, R., 1996. *Strategic Management and Organisational Dynamics: The Challenge of Complexity to Ways of Thinking about Organisations*, 1st ed. Pearson Education.

Sturmberg, J.P., Martin, C.M., Katerndahl, D.A., 2014. Systems and complexity thinking in the general practice literature: An integrative, historical narrative review. *Annals of Family Medicine* 12, 66–74. https://doi.org/10.1370/afm.1593

Truong-Tran, A.Q., Ho, L.H., Chai, F., Zalewski, P.D., 2000. Cellular zinc fluxes and the regulation of apoptosis/gene-directed cell death. *Journal of Nutrition* 130, 1459S–66S. https://doi.org/10.1093/jn/130.5.1459S

Wheat, H., Horrell, J., Valderas, J.M., Close, J., Fosh, B., Lloyd, H., 2018. Can practitioners use patient reported measures to enhance person centred coordinated care in practice? A qualitative study. *Health and Quality of Life Outcomes* 16, 223. https://doi.org/10.1186/s12955-018-1045-1

Wu, J., Xun, P., Tang, Q., Cai, W., He, K., 2017. Circulating magnesium levels and incidence of coronary heart diseases, hypertension, and type 2 diabetes mellitus: A meta-analysis of prospective cohort studies. *Nutrition Journal* 16, 60. https://doi.org/10.1186/s12937-017-0280-3