HEALTH 2050: BIOINFORMATICS FOR RAPID SELF-REPAIR; A DESIGN ANALYSIS FOR FUTURE QUANTIFIED SELF

LUUK PA SIMONS[1]

[1] Delft University of Technology, Faculty of Computer Science, Delft, Netherlands, e-mail: l.p.a.simons@tudelft.nl

Abstract About 75% of our healthcare costs go to four domains (cardio-, onco-, neuro- and metabolic) of diseases which are largely preventable or even reversible. Instead, they are 'managed' and made chronic, not cured. This is very costly and unsustainable for the future. Research is showing new opportunities for enhancing our body's self-repair in a matter of hours or days. We want to empower personal cure with rapid feedback for self-management. What could be an intervention- and bio-feedback portfolio to promote health self-repair within hours or days? Using a cross-case design analysis, we found large differences across the four health domains regarding: intervention aims, (self-)measurement options, focus on symptoms vs causes, plus degree of attention for health self-management. Given recent developments in rapid cure, we advise advanced daily bioinformatics feedback, instead of current quarterly cycles, to improve our self-repair effectiveness.

Keywords: health, self-management, quantified self, bioinformatics, service design, personal medicine.

University of Maribor Press

DOI https://doi.org/10.18690/978-961-286-362-3.17
ISBN 978-961-286-362-3

1 Introduction

Many of the health beliefs circulating our society are outdated. Widely held views on aging, for example paraphrased as 'Many people assume that our manner of death is preprogrammed into our genes. High blood pressure by fifty-five, heart attacks at sixty, maybe cancer at seventy, and so on …' (Greger & Stone 2016, p. 5) have been refuted by a large body of recent health research (Lozano, 2012, Li, 2018, Willett, 2019). It turns out that key to our health is our self-repair: in virtually all our cells and tissues, damage is being repaired on a continuous basis (Li, 2019). This fact is largely unused by healthcare professionals, nor are we using how dynamically this can be improved (with biometric improvement feedback on an hourly or daily basis) by using healthy lifestyle choices on foods, exercise, sleep etc (Greger & Stone, 2016).

Unfortunately, health discoveries take decades to enter clinical practice (Balas & Boren, 2000) and old beliefs continue to pervade not just our society, but even our medical journals, especially regarding lifestyle and nutrition (Casazza, 2013). Analysis of the why, how and what of this problem, including the influence of fabricated pseudo-science by vested industries is a science in itself, see for example (Campbell & Campbell, 2016, Greger, 2019), and is outside the scope of this paper.

We must speed up adoption of health improvements which are based in solid science (Lozano, 2012, Li, 2018, Willett, 2019). We don't have the luxury to wait, since current healthcare practices are costly and unsustainable. Just as the Safeway CEO and the corporate Coalition to Advance Healthcare Reform have already calculated in 2009: with 74% of health costs arising from four conditions (cardiovascular disease, type 2 diabetes, obesity and cancer) which are largely preventable or reversible (Burd, 2009). Their disease processes take decades to progress and are sensitive to lifestyle (Ornish & Ornish, 2019). Thanks to recent insights, neurological (dementia) diseases can be tentatively added to this list: they are very costly as well, plus mostly preventable from cardiovascular and even Alzheimer's disease causes (Barnes & Yaffe, 2011, Barnard, 2014). And hopes are sparked by promising recent results in using broad spectrum health interventions to actually reverse brain damage and cognitive decline (Bredesen, 2018).

From a biological and health engineering perspective, some of the most promising recent health discoveries use our innate mechanisms for rapid bodily self-repair. In short, we want to help people experience and measure better health, possibly within a day, with rapid feedback of progress across a broad spectrum of health indicators.

We already knew the motto: 'Health happens between doctor visits.' Next, we would like to add: 'Health improvements can be shown overnight'. That is, if you use appropriate health interventions and feedback measurements. For design purposes, we take a '2050' view from the future, using 'optimism by method': on the one hand assuming maximum use of the dynamic nature of our biology for self-repair and on the other hand temporarily ignoring current healthcare barriers for adoption. Thus aiming for: what might be achievable in 'next level Quantified Self' for patient(citizen) empowerment and health improvement?

Our aim is to promote cure via rapid health self-repair feedback cycles. This needs an approach with personal iteration cycles, see Figure 1, using (Cross, 1994) goals analysis (problem space), intervention planning (solution space) and measurement portfolio (evaluation space).

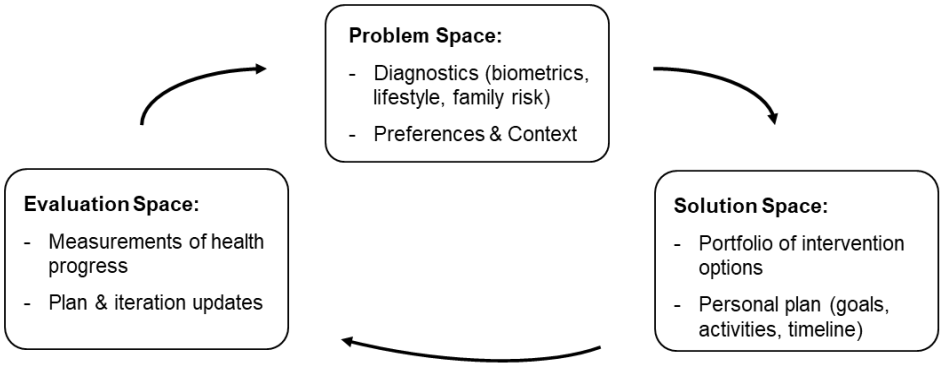

Figure 1: Personal iteration cycles for rapid health self-repair[1]

[1] This paper focuses mostly on the biology content and opportunities of self-repair. See Simons (2010, 2012 etc) for more details on the intervention processes and formats. Still, overall health iteration success depends on the full picture.

Thus, the main research question is: What could be an intervention- and bio-feedback portfolio to promote cure progression/health self-repair within days or weeks?

2 Method

Our research question is a design question. And the aim of this paper is to conduct a design analysis. The analysis is an example of design research rather than design science (Vaishnavi & Kuechler, 2004). Design science aims at generating knowledge on design, design research aims at generating (domain specific) knowledge for solving a given problem.
Our analysis will follow design cycle phases 1 and 2 of (Verschuren & Hartog, 2005): '1. first hunch' and '2. assumptions and requirements'. The design problem at hand aims to create personal support for people who want to make healthful lifestyle changes when faced with major life (-threatening) events like a heart attack or a chronic disease. Our 'first hunch' starting the design cycle is that personal health self-repair feedback on a (near-)daily basis may promote healthful behaviours and support health self-management choices.

To answer our main question it has to be broken down in sub-questions. Thus our main question regarding (near-)daily biofeedback for health self-repair will be covered via the design iteration sub-questions of problem-, solution- and evaluation space (Cross, 1994):

A) Which goals and ambition levels are feasible for health self-repair? (= Problem Space)
B) Which intervention and personal planning portfolio holds promise? (= Solution Space)
C) Which measurement and evaluation portfolio may aid progress? (= Evaluation Space)

Since our healthcare systems are hyperspecialized, it is no wonder that the four domains we focus on (cardio, onco, neuro and metabolic) vary widely in their current and emerging approaches on health, self-repair, patient empowerment, interventions or types of measurements. Given this diversity, we will conduct a cross-case analysis

across these four domains to find a first, exploratory set of answers to our research sub-questions. Our approach is similar to action research in the sense that we have a high level of 'access' to the current practices in these four domains[2] and at the same time we try to assess innovation options for health self-repair, given recent health discoveries as well as bioinformatics advancements.

3 Analysis

In sections 3.1 to 3.3 we answer the three research sub-questions. In each section we first discuss the differences and similarities across the cardio, onco, neuro and metabolic domains and then summarize the answers in a table. This cross-domain analysis provides the basis for the discussion and conclusion in section 4.

3.1 Which goals and ambition levels are feasible for health self-repair?

This section addresses feasibility of health self-repair. Given the space limitations here, we will refer to other sources for more extensive discussions of disease reversal options for each of the domains. For example, 'the book' on *cardiovascular disease* reversal was practically written by professor Ornish, not only with case-controlled proof of reversal early on (1990), but also with extensive follow up studies and publications (Ornish, 1998, Ornish & Ornish 2019). Still, this field is much broader (for an overview on this 'disease of affluence', see Greger & Stone 2016). And if we are looking for really fast health improvements, Jenkins et al (2003) have shown large LDL cholesterol reductions (-35%) within 14 days. More recently, the importance of vascular endothelial function has become clear for heart health. *Vascular function improves within hours of a healthy meal* (Murphy 2012, Lidder & Webb, 2013). As a motivating clip for young and old: the 'Game Changers' (2020) movie shows a humorous experiment halfway, where young athletes have over 300% percent improved erectile activity in the night directly after a healthy vegetable meal. Also for long term cardio benefits, lifestyle appears to trump medicine, as more extensively discussed elsewhere (Greger & Stone 2016). One example from that discussion. Statins are the most commercially successful drugs and most effective medication for cardiac disease. Still, a 100 people have to take the drugs (with all its side effects) for 6 years, in order to prevent a total of 3 heart attacks or deaths across

[2] By providing 6 months of lifestyle coaching (Simons, 2010, 2017) for literally thousands of patients and caregivers in all these domains, over the course of the past 10 years.

that group of 100 people. Lifestyle can do much better, with a 60% risk reduction of cardiac events in four years for 200 lifestyle participants of dr Esselstyn (2014), which is in line with the long term results of Ornish (1998). This again illustrates a further degree of disease reversal with lifestyle than with drugs. In conclusion, assuming people adopt the right health habits, the *cardio* domain holds much promise for adopting self-repair to enable faster, cheaper and better results.

For the *neuro(logy)* domain, a recent mantra has become: 'What aids heart health also aids brain health.' (Barnard 2014) We focus on dementia here, even though depression incidence shows remarkably similar lifestyle dependencies (McMartin 2013, Greger & Stone, 2016). The most common forms of dementia are cardiovascular dementia and Alzheimer's disease. Their worldwide incidence patterns show large variance similar to heart disease, depending on similar lifestyle patterns, which also help explain differences within Western populations (Barnes & Yaffe, 2011). Whereas prevention is quite feasible, treatment has proven itself difficult. No medication has been found that offers any form of cure, despite many multibillion dollar drug trials. According to dr Bredesen and others (Ornish & Ornish, 2019, Barnard, 2014) this is logical, since they were focusing on symptoms of brain defense (amyloid plaques), instead of addressing its multi-factor causes: usually inflammation, toxicity and the nutrient- and hormone-health of the blood supply (Bredesen, 2017, 2019). This asked for a multi-factor intervention program (across multiple health centers), which has shown large improvements for over 100 patients in for example memory, cognitive function and even hippocampus volume. Measurable improvements occur within weeks and in many individuals they last for years (Bredesen, 2017, 2019). In conclusion, and given the dire consequences of dementia in destroying your memory and personality, these are quite promising self-repair results indeed, driven by eating better and exercising better for example (Baker, 2010).

Regarding *metabolic* diseases, we focus on obesity and type 2 diabetes, since these are highly lifestyle dependent and they cause the majority of health and financial burdens of metabolic disease. Looking at the big picture: their worldwide incidence has very similar patterns to cardiovascular disease and dementia, with an important distinction that causation is more dependent on food patterns (overconsumption of high-energy-density junk- and animal foods and underconsumption of fibrous, whole plant foods) resulting in overweight, insulin resistance, glucose intolerance

and rapid aging at ever younger ages (Fuhrman & Sorensen, 2012). Fortunately, in terms of rapid repair, healthier eating and exercise can reduce medication needs within days and weeks, by improving insulin sensitivity, glucose tolerance and other health indicators (Simons 2016).

In terms of health self-repair, *oncology* is one of the toughest domains. On the one hand, we now know that the majority of cancer cases and deaths in the West are lifestyle dependent (lung, colorectal, prostate, breast cancer) with worldwide incidence patterns matching the previous diseases of affluence domains discussed. Several prevention strategies that work for the other domains, also help for cancer prevention (Campbell & Campbell, 2016). Unfortunately, 'Cancers are much easier prevented than cured. They are often diagnosed in their later stages, when they are harder to treat.' (Li, 2019) What does this mean for 'secondary' prevention, since most patients want to improve their health (risk) behaviors after the moment of diagnosis (Stull, 2007)? The good news is that we seem to be able to enhance our innate repair and defense mechanisms with healthy living. Not only in the initiation stage, but also in the growth and spread (metastasis) stages (Campbell 2017). And the less aggressive the cancer, the more healthy years this may buy us. For example, at three months as well as 5-year follow up, healthy lifestyle was successful for early prostate cancer (Ornish, 2005, 2013, Thomas, 2014). And for breast cancer, an average of five weeks between diagnosis and surgery was enough to significantly reduce tumor cell proliferation, enhance cell apoptosis and reduce metastasis risk in a randomized, placebo-controlled trial (Thompson, 2005). In summary: while healthy living prevention has most to offer for oncology, we are just beginning to scratch the surface of using our body's innate repair and defense mechanisms from the moment of diagnosis. And since tumors are more complex than atherosclerotic plaques for example, being able to try different lifestyle strategies and rapidly assess their impact (like we started doing for other cancer treatments) could be a very promising addition to personal treatment plans.

Table 1: Answers to: Which goals and ambition levels are feasible for health self-repair?

	Answer summary
Cardio & Metabolic	Promising health self-repair has been shown within days and weeks, with lifestyle repair trumping medicine.
Neuro & Onco	Neuro & Onco: both better preventable than curable. Neuro: first promising repair results with lifestyle. Hesitant progress in onco; some promising results.
Preferences & Context	Many patients make lifestyle changes around the moment of diagnosis. This is too often 'jumping to solutions' with insufficient considerations for evidence or quality of life preferences and context. Besides, public health prevention suffers from 'diluted' guidelines.

As stated in section 1, this paper focuses more on the biology- than on the process aspects of health self-repair planning, which have been discussed elsewhere (Simons, 2013, 2014, 2015, 2020). However, two process elements are important to highlight here. First, personal health choices are already highly prevalent around the moment of diagnosis, but often these are ill-informed choices. This is partly due to the fact that public health guidelines suffer from many forms of 'dilution', including (invalid) assumptions that people do not want to make big changes even if that would bring big gains. For a more extensive discussion see Greger & Stone (2016). Second, user preferences and (social-/family-) context matter a lot for the success of healthy living choices. But just like in other design settings, preferences can be highly dynamic, for example when health benefits are achieved. Thus they need to be part of explicit choices in the overall process.

3.2 Which intervention portfolio holds promise?

In terms of intervention options offered to patients, our first '2050' design goal is to achieve *significant measurable health improvements in the short term* (preferably hours, maybe days or weeks). Our second design aim is to make *optimal use of our body's innate repair and defense mechanisms*, given how precise and dynamic our body's own repairs generally are, if we don't actively distort them, see previous section (and for example Li 2019, Greger & Stone 2016). Third, we prefer interventions that also foster other long term health outcomes, thus creating *positive, instead of negative, side effects*. Our

fourth design goal may create trade off choices[3] with the previous goals: *attractiveness*, which includes broadness of choice and practical feasibility for the person/patient involved. This to increase healthy living motivation and long term sustainability.

So what do these four design goals mean for creating a suitable intervention portfolio (besides acknowledging that this portfolio must be sufficiently robust as well as flexible in the face of continuous evidence-based updates)? This is summarized in Table 2. An important question is how far we can come with 'relatively straightforward' generic health behaviors, or if we need very specific and personalized interventions? Fortunately, the research 'jury' has been out and is quite clear on this matter (Ornish & Ornish, 2019, Willett, 2019, Greger, 2019). For all our four health domains a few rules of thumb are valid. First, the health behaviors that best prevent a disease generally also best repair the damage. Second, we don't need separate 'health prescriptions' per domain: they are largely similar. The health benefits are to a very large extent (roughly 90%) achieved with the same core set of lifestyle behaviors regarding smoking, alcohol moderation, foods, physical activity, obesity, sleep and social support (Lozano, 2012, Ornish & Ornish, 2019), with genetics in these diseases counting for no more than 10%-20% at most (Willett, 2002). Some additional tweaks are sensible per conditions, see examples in footnote 3. Finally, as a third rule of thumb, the best lifestyle improvements are the ones that people actually continue doing, plus there is a dose-response: more behavior improvement means more health results. People best adopt plans and behaviors that they have chosen themselves (Gessnitzer & Kauffeld, 2015) and long term adherence is a combination of perceived behavior attractiveness, plus health benefits (Simons, 2020b). Thus, on a process level, personal goal setting and planning are important.

[3] For example, if people can create 80% of the expected results with only 2 lifestyle improvements, they will often prefer this to implementing 10 additional improvements for a next 10% gain.

Table 2: Answers to: Which intervention portfolio?

	Answer summary
Generic vs Personal Interventions?	From a biology perspective, generic health choices may provide a surprisingly large part (estim. 80%-90%) of expected results. Still, the *degree* of health improvement (which predicts results) largely depends on personal plans.
Cardio, Neuro & Metabolic	These three domains share similar mechanisms and lifestyle factors. With some detail adjustments for rapid repair boosting.[4]
Onco	Though repair mechanisms seem to benefit from healthy lifestyle, different cancers respond differently to lifestyle factors. Testing and adaptation needs to improve here.

One specific mention has to be made regarding the *oncology* domain and self-repair interventions. This field is still really in its infancy. Cancers do share many of the generic lifestyle factors with the other domains: smoking, alcohol moderation, foods, physical activity, obesity (Norat, 2010). But a large challenge is that different cancers appear sensitive to different lifestyle and dietary factors (see Gregor & Stone (2016) for an overview across many cancers), plus tumors are highly diverse. Even within the same person, colon cancer cells in one tumor may acquire more than 100 different DNA mutations over time, making tumor diverse in responding to changes in their environment (Langley & Fidler, 2007). At the same time, being able to test and assess rapid repair results from lifestyle interventions is important, in order to stop tumor progression early. This test cycle will depend on improved measurement and feedback, which is discussed in the next section.

3.3 Which measurement and evaluation portfolio may aid progress?

The area of health indicator measurements has enormously expanded over the past decades. And with the rise of *bioinformatics*, measuring genomics, proteomics, metabolomics etc, many new opportunities will emerge in the coming decades. Especially '*translational bioinformatics*,' bridging 'omics' and lifestyle diseases, including traditional public health biometrics (like oxidized LDL cholesterol, angiography for

[4] For example, salt reduction and endurance sports for endothelial function & blood pressure, low glycemic foods and resistance training for type 2 diabetes, and low-tox, high fiber foods for dementia.

plaques, or endothelial function via ultrasound or laser Doppler techniques for cardiovascular disease) is promising (Tenenbaum, 2016, Ravi, 2016). Still, the more options arise, the more important it becomes to be clear about measurement objectives and avoid 'jumping to solutions'.

If a measurement portfolio is to really empower individuals in their day-to-day health self-repair, this creates several design goals. We will start illustrating these design goals for the cardio domain, which has several lessons to offer, since it has the most extensive tradition of lifestyle self-management, measurement and feedback of the four domains. We discuss domain-specific issues in comparison to this *cardiovascular* reference.

A first goal is *reliability and validity* (including sensitivity and specificity): does it measure the relevant biological causal factors, and does it do so selectively enough? Second, the nice thing about the cardio domain is that we have learned to monitor behaviors (e.g. step counters), risk factors (e.g. blood pressure) and tissue health (endothelial function). In other words, our second goal is to measure a *broad array* of the most relevant inputs (like behaviors) and outputs (desired health results). A third goal is providing *rapid feedback*, since we are trying to capture hourly and daily improvements. Besides, our feedback aims also favor *Do-It-Yourself* (DIY) solutions, similar to current consumer blood pressure measurements, since regular home measurements provide a much more valid picture of the situation than a quarterly checkup at your doctor's. Fourth, given the aim for repeated DIY measurements, consumer market *cost/benefits* are important: they ideally are cheap, simple to deploy by an individual him-/herself and to interpret in terms of health behavior consequences. This latter step may often require some training by health professionals, like we do for LDL cholesterol or step counter readings.

If we compare the four domains we see large differences. The *metabolic* domain is close to the cardio domain in terms of DIY options with cheap, rapid blood sugar feedback for diabetics for example. (Although it's curious to see the focus on the symptom level readings of blood sugar or HbA1c, whereas insulin levels are much closer linked to biological disease causality. In terms of causal focus, the cardio domain is further ahead.) By contrast, the *neurology* and *oncology* domain have very few DIY measurement options, health feedback loops or even any health self-management support (apart from several cognition and memory tests that can be

done online). And a down-side in the neuro domain is a widely felt fatalism similar to 'we cannot help you anyway, so why bother with detailed diagnosis.' Bredesen complains that due to this fatalistic attitude even most neurologists omit many of the basic tests to confirm which type of Alzheimer's it is, and whether inflammation, malnutrition, toxicity or hormone imbalances are involved (Bredesen, 2019). Hopefully this will change in the future, since we now know these are modifiable health factors. Paradoxically, the onco domain is currently still the most dis-empowered in terms of health self-management (often treated by oncologists as being largely inconsequential compared to the tumor), however its emerging 'omics'/bioinformatics measurement portfolio may show us part of the route for the future, for two reasons. First, it stimulates development of 'omics' measurements, by for example routinely genotyping tumors and increasingly using biomarker assays for predicting recurrence or metastasis risk (Hatakeyama, 2017). Second, it has become increasingly normal to check within a few weeks whether a (chemo or immune) treatment is 'catching on.' This rapid feedback shows us the way for '2050' Quantified Self.

Table 3: Answers to: Which measurement and evaluation portfolio?

	Answer summary
Overall measurement goals	Reliability and validity, rapid feedback, broad (from behaviors to health results), Do-It-Yourself (DIY) options, consumer market cost/benefits (cheap, simple).
Cardio & Metabolic	Already some self-management measurement options available. Future consumer 'omics' can hopefully improve health feedback.
Neuro & Onco	Rapid growth of 'omics' feedback in the onco domain. This may soon aid better causal diagnosis in (multi-factor) neuro problems, next improve 'omics' health feedback for cardio and metabolism.

4 Discussion: Towards next level Quantified Self Bioinformatics

A previous '2050' vision for Quantified Self (QS) was crafted by Swan (2012). We would like to add 'next level' health ambitions to that vision. Quantified Self goals should mature further, beyond the focus (Swan, 2012) on data collection or research or prevention. The focus should be on cure and health. And the aim for QS bioinformatics to become a key contributor to health and cure results in 2050.

This aim is built on four premises. First, there is the rapidly growing array of options for rapid health repair feedback, see also section 3.3. Second, as discussed in section 3.2 and 3.3., health improvement and feedback options are generally welcomed by many patients around the moment of diagnosis. Third, research has increasingly shown that from a biology perspective, health self-repair is more effective than current 'best available' medical treatments (largely because self-repair is biologically more plausible and more advanced, thanks to millions of years of evolution) as discussed in section 3.1. Fourth, see also section 1, self-management for health repair is cheaper and supports a more sustainable healthcare system.

5 Conclusion

Health self-management has a lot to offer for a more sustainable and effective '2050' healthcare, if linked to bodily self-repair feedback cycles. This should be optimized for achieving and measuring health improvements in a matter of hours or days, based on insights from (near-real time and user friendly) bioinformatics. Especially when these data create a shared health progress view and dialogue with health professionals, this may promote truly collaborative health improvements in healthcare, with large and effective contributions from patients themselves.

References

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S. et al (2010). Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Archives of neurology*, *67*(1), 71-79.

Balas, E. A., & Boren, S. A. (2000). Yearbook of medical informatics: managing clinical knowledge for health care improvement. *Stuttgart, Germany*.

Barnard, N. D., Bush, A. I., Ceccarelli, A., Cooper, J. et al (2014). Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. *Neurobiology of aging*, *35*, S74-S78.

Barnes, D.E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet Neurology*, *10*(9), 819-828.

Bredesen, D. (2017). *The end of Alzheimer's: The first program to prevent and reverse cognitive decline*. Penguin.

Bredesen, D. E., Sharlin, K., Jenkins, D., Okuno, M. et al (2018). Reversal of cognitive decline: 100 patients. *J Alzheimers Dis Parkinsonism*, *8*(450), 2161-0460.

Burd, Steven A. (2009), "How Safeway Is Cutting Health-Care Costs," *Wall Street Journal*, Eastern Edition, June 12, A15.

Campbell, T. C. (2017). Cancer prevention and treatment by wholistic nutrition. *Journal of nature and science*, *3*(10).

Campbell, T. C., & Campbell II, T. M. (2016). The China Study: Revised and Expanded Edition: The Most Comprehensive Study of Nutrition Ever Conducted and the Startling Implications for Diet, Weight Loss, and Long-Term Health. BenBella Books, Inc.

Casazza, K., Fontaine, K. R., Astrup, A., Birch, L. L., et al (2013). Myths, presumptions, and facts about obesity. *New England Journal of Medicine*, *368*(5), 446-454.

Cross, N. (1994). *Engineering Design Methods; Strategies for Product Design* (2nd ed. ed.). Chichester: John Wiley & Sons.

Esselstyn CB, Gendy G, Doyle J, et al. (2014). A way to reverse CAD? J Fam Pract; 63:356-364b.

Fuhrman, J., & Sorensen, C. (2012). *The End of Diabetes*. HarperCollins.

Game Changers (2020) Netflix Movie, accessed 2 Feb 2020: https://gamechangersmovie.com/

Gessnitzer, S., & Kauffeld, S. (2015). The working alliance in coaching: Why behavior is the key to success. *The Journal of Applied Behavioral Science*, *51* (2), pp. 177-197.

Greger, M., & Stone, G. (2016). *How not to die: discover the foods scientifically proven to prevent and reverse disease*. Pan Macmillan.

Greger, M. (2019) How Not to Diet: The Groundbreaking Science of Healthy, Permanent Weight Loss. Flatiron Books.

Hatakeyama, S., Yoneyama, T., Tobisawa, Y., & Ohyama, C. (2017). Recent progress and perspectives on prostate cancer biomarkers. *International journal of clinical oncology*, *22*(2), 214-221.

Jenkins, D. J., Kendall, C. W., Marchie, A., Faulkner, D. A. et al (2003). Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *Jama*, *290*(4), 502-510. &BBC 'Truth about Food' http://news.bbc.co.uk/2/hi/uk_news/england/devon/5176300.stm

Langley, R. R., & Fidler, I. J. (2007). Tumor cell-organ microenvironment interactions in the pathogenesis of cancer metastasis. *Endocrine reviews*, *28*(3), 297-321.

Li, W. (2019). *Eat to Beat Disease: The Body's Five Defence Systems and the Foods that Could Save Your Life*. Random House.

Li, Y., Pan, A., Wang, D. D., Liu, X., Dhana, et al (2018). Impact of healthy lifestyle factors on life expectancies in the US population. *Circulation*, *138*(4), 345-355.

Lidder, S., & Webb, A. J. (2013). Vascular effects of dietary nitrate (as found in green leafy vegetables and beetroot) via the nitrate-nitrite-nitric oxide pathway. *British journal of clinical pharmacology*, *75*(3), 677-696.

Lozano, R., Naghavi, M., Foreman, K., Lim, et al (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet*, *380*(9859), 2095-2128.

McMartin, S. E., Jacka, F. N., & Colman, I. (2013). The association between fruit and vegetable consumption and mental health disorders: evidence from five waves of a national survey of Canadians. *Preventive medicine*, *56*(3-4), 225-230.

Murphy, M., Eliot, K., Heuertz, R. M., & Weiss, E. (2012). Whole beetroot consumption acutely improves running performance. *Journal of the Academy of Nutrition and Dietetics*, *112*(4), 548-552.

Norat, T., Chan, D., Lau, R., Aune, D., & Vieira, R. (2010). WCRF/AICR systematic literature review continuous Update Project Report. *Imperial College London*.

Ornish, D., Brown, S. E., Billings, J. H., Scherwitz, et al (1990). Can lifestyle changes reverse coronary heart disease?: The Lifestyle Heart Trial. *The Lancet*, *336*(8708), 129-133.

Ornish, D., Scherwitz, L.W., Billings, J. H., Gould, K.L. et al (1998). Intensive lifestyle changes for reversal of coronary heart disease. *Jama*, *280*(23), 2001-2007.

Ornish, D., Weidner, G., Fair, W. R., Marlin, R., et al (2005). Intensive lifestyle changes may affect the progression of prostate cancer. *The Journal of urology*, *174*(3), 1065-1070.

Ornish, D., Lin, J., Chan, J. M., Epel, E., et al (2013). Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *The lancet oncology*, *14*(11), 1112-1120.

Ornish, D., & Ornish, A. (2019). *Undo it!: How simple lifestyle changes can reverse most chronic diseases*. Ballantine Books.

Ravì, D., Wong, C., Deligianni, F., Berthelot, M., et al. (2016). Deep learning for health informatics. *IEEE journal of biomedical and health informatics*, *21*(1), 4-21.

Simons, L. P. A., & Hampe, J. F. (2010). Service Experience Design for Healthy Living Support; Comparing an In-House with an eHealth Solution. The 23rd Bled eConference, pp. 423-440. Accessed 2010 from www.bledconference.org

Simons LPA, Hampe JF, Guldemond NA. (2013). Designing Healthy Living Support: Mobile applications added to hybrid (e)Coach Solution. *Health and Technology*. 3 (1) pp.85-95. DOI 10.1007/s12553-013-0052-9

Simons LPA, Hampe JF, Guldemond NA. (2014). ICT supported healthy lifestyle interventions: Design Lessons. *Electronic Markets*. 24 pp. 179-192. DOI 10.1007/s12525-014-0157-7.

Simons LPA, Foerster F., Bruck PA, Motiwalla L & Jonker CM. (2015). Microlearning mApp Raises Health Competence: Hybrid Service Design. *Health and Technology*, 5 pp 35-43. DOI 10.1007/s12553-015-0095-1

Simons, L. P., Pijl, H., Verhoef, J., Lamb, H. J. et al (2016). Intensive Lifestyle (e) Support to Reverse Diabetes-2. In *Bled eConference* (p. 24), accessed Dec 20, 2016 www.bledconference.org.

Simons LPA, Hafkamp MPJ, Bodegom D, Dumaij A, Jonker CM. (2017). Improving Employee Health; Lessons from an RCT. *Int. J. Networking and Virtual Organisations*, Vol. 17, No. 4, pp.341–353. DOI https://doi.org/10.1504/IJNVO.2017.088485

Simons, LPA, Heuvel, AC van den, Jonker CM. (2020b). eHealth WhatsApp for social support: design lessons. *Int. J. Networking and Virtual Organisations*, Accepted (DOI will follow

Simons, LPA, Pijl M, Verhoef J, Lamb HJ, van Ommen B, Gerritsen B, Bizino MB, Snel M, Feenstra R, Jonker CM. (2020). e-Health Diabetes; 50 Weeks Evaluation. *Int. J. Biomedical Engineering and Technology*, Accepted (DOI will follow)

Stull, V., Snyder, D., & Demark-Wahnefried, W. (2007). Lifestyle Interventions in Cancer Survivors: Designing Programs That Meet the Needs of This Vulnerable and Growing Population. *J Nutr, 137*, pp. 243S-248S.

Tenenbaum, J. D. (2016). Translational bioinformatics: past, present, and future. *Genomics, proteomics & bioinformatics*, *14*(1), 31-41.

Thomas, R., Williams, M., Sharma, H., Chaudry, A., et al. (2014). A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer—the UK NCRN Pomi-T study. *Prostate cancer and prostatic diseases*, *17*(2), 180-186.

Thompson, L. U., Chen, J. M., Li, T., Strasser-Weippl, K., & Goss, P. E. (2005). Dietary flaxseed alters tumor biological markers in postmenopausal breast cancer. *Clinical cancer research*, *11*(10), 3828-3835.

Vaishnavi, V., & Kuechler, W. (2004). Design Research in Information Systems. Accessed Aug 16, 2009 from http://desrist.org/design-research-in-information-systems

Verschuren, P., & Hartog, R. (2005). Evaluation in Design-Oriented Research. *Quality and Quantity,* 39, pp. 733-762.

Willett, W. C. (2002). Balancing life-style and genomics research for disease prevention. *Science*, *296*(5568), 695-698.

Willett, W., Rockström, J., Loken, B., Springmann, et al (2019). Food in the Anthropocene: the EAT–Lancet Commission on healthy diets from sustainable food systems. *The Lancet*, *393*(10170), 447-492.