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Health 2050: faster cure via bioinformatics and quantified self; a design analysis

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Abstract: Four areas make up 75% of our healthcare costs: cardio-, onco-, neuro- and metabolic diseases. These are largely preventable, even reversible. Instead, they are currently often 'managed' and made chronic, not cured. This is too costly. Research is showing new opportunities for enhancing our body's self-repair in a matter of hours or days. Our research question: what could be an intervention- and bio-feedback portfolio to promote health self-repair within hours or days? There are large cross-domain differences regarding: intervention aims, (self-)measurement options, focus on symptoms vs. causes, plus degree of attention for health self-management. Given recent research into rapid cure, we advise advanced daily bioinformatics feedback, using molecular biomarkers. This creates a quantified self 'endoself', showing key biological opportunities for cure and self-repair. Thus, we shift from the current 'antibiotics/external fix' paradigm of healthcare to a 'wound healing' paradigm, improving use of resources in health.

Keywords: health; self-management; quantified self; non-communicable diseases; NCDs; bioinformatics; service design; personal medicine.

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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Many of the health beliefs circulating our society are outdated.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 and Stone, (2016), p.5] have been

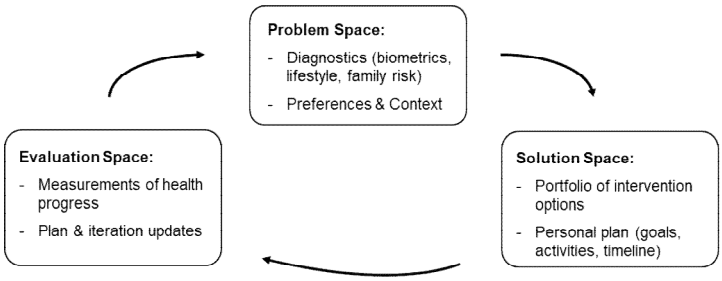
refuted by a large body of recent health research (Lozano et al., 2012; Li et al., 2018; Willett et al., 2019). It turns out that key to our health is our self-repair: in virtually all our cells and tissues, damage is being repaired on a continuous basis (Li, 2019). This fact is largely unused by healthcare 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 and Stone, 2016).

Unfortunately, health discoveries take decades to enter clinical practice (Balas and Boren, 2000) and old beliefs continue to pervade not just our society, but even our medical journals, especially regarding lifestyle and nutrition (Casazza et al., 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 and Campbell (2016) and 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 et al., 2012; Li et al., 2018; Willett et al., 2019). We do not 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). There disease processes take decades to progress and are sensitive to lifestyle (Ornish and Ornish, 2019). Thanks to recent insights and intervention studies, 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 and Yaffe, 2011; Barnard et al., 2014). And hopes are sparked by promising recent results in using broad spectrum health interventions to actually reverse brain damage and cognitive decline (Bredesen, 2017; Bredesen et al., 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.

Figure 1 Personal iteration cycles for rapid health self-repair



Notes: This paper focuses mostly on the biology content and opportunities of self-repair. See Simons and Hampe (2010) and Simons et al. (2013, 2014, 2015, 2017) for more details on the intervention processes and formats. Overall health iteration success depends on the full picture.

We already knew the motto: "Health happens between doctor visits." Next, we would like to add: "Large health self-repair 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 (QS)' 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).

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 and 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 and Hartog (2005):

1 first hunch

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 hyperspecialised, 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[1] 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 Section 3.1 to Section 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 summarise the answers in a table. This cross-domain analysis provides the basis for the discussion and conclusions 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 (Ornish et al., 1990), but also with extensive follow up studies and publications (Ornish et al., 1998; Ornish and Ornish, 2019). Still, this field is much broader [for an overview on this 'disease of affluence', see Greger and 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 et al., 2012; Lidder and 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% 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 and Stone, 2016). One example from that discussion, statins is 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 six years, in order to prevent a total of three heart attacks or deaths across that group of 100 people (Trewby et al., 2002). Lifestyle can do much better, with a 60% risk reduction of cardiac events in four years for 200 lifestyle participants of Esselstyn et al. (2014), which is also in line with the famous long-term results of Ornish et al. (1998). This again illustrates more disease reversal with lifestyle than with drugs. In conclusion, when people adopt the helpful 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 et al., 2014). We focus on dementia here, even though depression incidence shows remarkably similar lifestyle dependencies (McMartin et al., 2013; Greger and 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 and 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 Bredesen (2017), Bredesen et al. (2018), Ornish and Ornish (2019) and Barnard et al. (2014,) this is logical, since they were focusing on symptoms of brain defence (amyloid plaques), instead of addressing its multi-factor causes: usually inflammation, toxicity and the nutrient- and hormone-health of the blood supply. A multi-factor intervention program across multiple health centres was started, 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 several years (Bredesen, 2017; Bredesen et al., 2018). 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 known causal factors like eating better and exercising better for example (Baker et al., 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 and 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 (Greger and Stone, 2016; Simons et al., 2016, 2022a).

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 and 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 after the moment of diagnosis a majority patients want to improve their health behaviours (Stull et al., 2007)? The good news is that we seem to be able to enhance our innate repair and defence 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 five-year follow up, healthy lifestyle was successful for early prostate cancer (Ornish et al., 2005, 2013; Thomas et al., 2014). And for breast cancer, an average of five weeks between diagnosis and surgery was enough to significantly reduce tumour cell proliferation, enhance cell apoptosis and reduce metastasis risk in a randomised, placebo-controlled trial (Thompson et al., 2005). In summary: while healthy living *prevention* has most to offer for oncology, we are just beginning to scratch the surface of cure (Li, 2019): using our body's innate repair and defence mechanisms from the moment of diagnosis. And since tumours are more complex than atherosclerotic plaques for example, being able to try different lifestyle strategies and rapidly assess their impact (like oncologists 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 and metabolic	Promising health self-repair has been shown within days and weeks, with lifestyle repair trumping medicine.
Neuro and onco	Neuro and onco: both better preventable than curable. Neuro: first promising repair results with lifestyle. Hesitant progress in onco; some promising results.
Preferences and 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 and Hampe, 2010; Simons et al., 2013, 2014, 2015, 2017). 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 and 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, user preferences need to be part of explicit choices in the iteration plans, see Figure 1.

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 defence mechanisms*, given how precise and dynamic our body's own repairs generally are, see previous section (and for example, Li, 2019; Greger and Stone, 2016). Third, we prefer interventions that also foster other long-term health outcomes, thus creating *positive side effects, instead of negative side effects*. Our fourth design goal may create trade off choices[2] with the previous goals: *attractiveness*, which includes broadness of choice and practical feasibility for the person/patient involved. This is 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 summarised in Table 2 and explained hereafter. An important question is how far we can come with 'relatively straightforward' generic health behaviours, or if we need very specific and personalised interventions? Fortunately, the research 'jury' has been out and is quite clear on this matter (Ornish and Ornish, 2019; Willett et al., 2019; Greger, 2019). For all our four health domains a few rules of thumb are valid. First, the health behaviours that best prevent a disease generally also best repair the damage. Second, we do not 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 behaviours regarding smoking, alcohol moderation, foods, physical activity, obesity, sleep and social

support (Lozano et al., 2012; Ornish and 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 note in Table 2. 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 behaviour improvement means more health results. People best adopt plans and behaviours that they have chosen themselves (Gessnitzer and Kauffeld, 2015) and long-term adherence are a combination of perceived behaviour attractiveness and health benefits (Simons, 2021; Simons et al., 2020, 2022c). Thus, on a process level, personal goal setting and planning are important.

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 and metabolic	These three domains share similar mechanisms and lifestyle factors. With some detail adjustments for rapid repair boosting.*
Onco	Though repair mechanisms seem to benefit from healthy lifestyle, different cancers respond differently to lifestyle factors. Testing and adaptation needs to improve here.

Notes: *For example, salt reduction and endurance sports for endothelial function and blood pressure. Or low glycemic foods and resistance training for type 2 diabetes. Or low-tox, high fibre foods for dementia.

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 and obesity (Norat et al., 2010). But a large challenge is that different cancers appear sensitive to different lifestyle and dietary factors [see Gregor and Stone (2016) for an overview across many cancers], plus tumours are highly diverse. Even within the same person, colon cancer cells in one tumour may acquire more than 100 different DNA mutations over time, making tumour cells diverse in responding to changes in their environment (Langley and Fidler, 2007). At the same time, being able to test and assess rapid repair results from lifestyle interventions is important, in order to stop tumour 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 expanded enormously 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’ is promising (Tenenbaum, 2016; Ravì et al., 2016), bridging ‘omics’ and lifestyle diseases, including traditional public health biometrics (like for cardiovascular disease: oxidised LDL cholesterol, angiography for plaques, or endothelial function via ultrasound or laser Doppler vasodilation assessment). Still, the more options arise, the more important it becomes to be clear about measurement objectives and to avoid ‘jumping to solutions’.

If a measurement portfolio is meant 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 behaviours (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 behaviours) 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 goals warrant *do-it-yourself* (DIY) solutions, similar to current consumer blood pressure devices, 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 behaviour consequences. This latter step may often require some training by health professionals, like currently provided for LDL cholesterol or step counter readings.

Table 3 Answers to: which measurement and evaluation portfolio?

	Answer summary
Overall measurement goals	Reliability and validity, rapid feedback, broad (from behaviours to health results), do-it-yourself (DIY) options, consumer market cost/benefits (cheap, simple).
Cardio and metabolic	Already some self-management measurement options available. Future consumer 'omics' can hopefully improve health feedback.
Neuro and onco	Rapid growth of 'omics' feedback in the onco domain. Maturing 'omics' may soon aid diagnosis in (multi-factor) neuro problems.

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 is 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 et al. (2018) 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. 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 and incorrectly assumed by oncologists to be largely inconsequential), 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 tumours and increasingly using biomarker assays for predicting recurrence or metastasis risk (Hatakeyama et al., 2017). Second, it has become increasingly normal to check within a few weeks whether a (chemo or immune) treatment is 'catching on' and should be continued or discontinued. This rapid feedback and iteration update shows us the way towards a '2050' QS.

4 Discussion: towards next level QS-bioinformatics

A previous '2050' vision for QS was crafted by Swan (2012, 2013), laying an appealing foundation for the 'participatory biocitizen' using big data and advanced bioinformatics. But conceptually and practically, our proposition is that we should move this vision one important step further, in order to reap greater benefits, faster.

Thus, we first address implications for theory and for practice. Next, we discuss generalisability, limitations and next steps.

4.1 Implications for theory and concepts

Whereas the previous QS 2050 vision proposed by Swan (2012, 2013) assumes that we should focus on data collection and qualitative individual feedback loops to discover important relationships between behaviours and health, this would actually move us back a few steps in time [since much more is already known on the biology level then Swan (2013) assumes, as we will illustrate in Section 4.2, practical implications], wasting precious opportunities to improve the quality of life and health for patients.

A 2050 QS vision deserves to move beyond the goals of research, exploration or prevention. It deserves to be built on a new and recently emerging health paradigm. Not only: 'health happens between doctor's visits', but also 'large health self-repair can be shown overnight'. For QS, we should explicitly include the goals of cure and self-repair feedback. And QS bioinformatics should aim to become a key contributor to *cure results* towards 2050.

We propose that this updated QS vision should be built on a health paradigm shift, grounded in recent biological findings. The *'antibiotics/external fix' metaphor* for healthcare is mostly outdated, since it does not apply to the main health burdens of today, which are: diseases of affluence. For these diseases, cure generally does not come from a pill or surgical procedure 'repairing' the body, even though our healthcare policy – funding and – treatment practices are currently still based on this philosophy. However, for these 'non-communicable diseases' (NCDs), most of the best options for a real cure come from within, using the self-repair mechanisms already in place.

Maybe a *'wound healing' metaphor* better suits the new health paradigm: we can help the body by keeping the wound clean, preventing recurrent damages and providing nutrients, but the actual healing comes from within. Biologically, this metaphor fits nicely, since inflammatory and growth regulators are not only key to wound healing, but also to the cardio-, onco-, neuro- and metabolic conditions addressed in this paper (Li, 2019; Ornish and Ornish, 2019; Greger and Stone, 2016; Bredesen et al., 2018).

This paper has highlighted several of the research studies that are showing us that from a biology perspective, health self-repair is often more effective than current 'best available' medical treatments[3] as discussed in Section 3.1. This self-repair can either be helped or be hampered, depending on foods, physical activity, stress, sleep, medication, etc. In chronic conditions, close monitoring of effects is needed (Wickramasinghe and Goldberg, 2010). We have illustrated that the health benefits that can be obtained from self-repair are larger and occur much faster than most people think (health professionals, policy makers and patients alike). And we have illustrated that this principle applies to a broad array or our main health problems.

When we are limiting the role of health behaviours to 'prevention' in our health policy and funding, we are misinterpreting the biggest opportunity of this new 'wound healing' paradigm. Health behaviours cannot only bring the 'ounce' of prevention, but also the 'pound' of cure. This does require a well-designed set of rapid repair feedback measurements, which is where QS and bioinformatics can have a large contribution, as is discussed below.

Moreover, these self-repair feedback mechanisms must be embedded in professional Self-management support practices (Jonkman et al., 2016) and a patient empowerment network (Ricciardi et al., 2013). When we use synergies of biology- and coach professions, large improvements can be achieved, like for example, a blood pressure reduction from 145/92 to 126/86 mmHg on average, in 11 days (Simons et al., 2022b), using lifestyle and self-repair feedback.

4.2 Implications for practice

There are two important lessons for practice. First, on the level of the individual patient, there are key instances where cure (or partial repair) can be achieved faster and with higher quality via the 'wound healing' QS approach than with standard care. Second, on the levels of health policy – funding and – treatments, we propose a large shift. Not only from the 'antibiotics/external fix' to the 'wound healing' metaphor of healthcare, but also by changing the healthcare we provide. We will show that with clever bioinformatics, the QS 'exoself' proposed by Swan (2013) can move to next level 'endoself' contributions.

To illustrate impacts on the *individual patient level*, the growing biological insights into cardiovascular health over the past decades may provide us with an inspiring blueprint. Roughly, we can distinguish four phases:

1 First, until the 1950s, heart attacks (infarctions) were mostly viewed as the heart being 'worn down/old'.

2 Second, roughly from the 1950s to the 1990s, health researchers started reasoning about atherosclerotic plaques, cholesterol, smoking, thrombosis, etc. And multiple studies showed the early and decades-long buildup of fatty streaks and atherosclerosis in the majority of US teenagers and in 77% of the soldiers (22 years old on average) who died in the Korean War (Enos et al., 1953; Voller and Strong, 1981). It was learned that in most NCDs there is a decades-long buildup of damage ('wounding') before symptoms show up at the clinical horizon.

3 During Phase 3, roughly from the 1990s to the 2010s, attention shifted to the large role of inflammation in vascular (endothelial) cells, including discoveries that statins

may be helpful not just via lowering cholesterol, but also via lowering inflammation and inflammation markers like CRP (Jenkins et al., 2003).

4 We are now in Phase 4, from the 2010s until the 2030s (?), where the active health-promoting contributions of a healthy vascular system are increasingly recognised and used. There are significant antioxidant, anti-inflammatory, anti-aging, pro-recovery and pro-performance contributions of healthy endothelial cells, vascular smooth muscle cells and blood components (Li, 2019; Greger and Stone, 2016).[4] In Phase 4, in order to increase endothelial function as well as biological performance, athletes are using berries, cherries (Howatson et al., 2010) or greens for faster next-day recovery (Murphy et al., 2012). Or beet juice for increased energy output during matches (Lidder and Webb, 2013). Or patients are using increased fibre intake and daily physical activity to quench inflammation and improve vascular and neural performance (Bredesen, 2017; Ornish and Ornish, 2019).

The *societal implications* illustrated by this cardiovascular case history are:

1 Thanks to thousands of researchers during the past 12 (!) decades, we have gained a much deeper knowledge of vascular health and its contributions to our general health. Our main practical challenge regarding our health knowledge is not that our scientists are ignorant and need much help in exploratory research from QS. Instead, the challenge is in actually using this knowledge to coach/educate people (Lehto et al., 2013; Gupta et al., 2015) in order to start healing themselves. And the bigger challenge is to change health treatment and funding systems such, that physicians are incentivised to move patients from the 'antibiotics/external fix' to the 'wound healing' paradigm.

2 We should aim for a next level 'exoself' in QS. The 'exoself' is a powerful QS concept and Swan (2013) focuses it mostly on management of existing concerns (e.g., stress levels or exercise goals), extending the self with extra sensors (Lopez et al., 2011; Kari et al., 2017). However, the more we learn about the biology of health, the more we may need an 'endoself': learning about our internal biology systems that are 'new' to us, but that have large health impact. In this paper, we focus on endothelial (dys)function since this a large health factor for the majority of NCD patients, but more relevant 'endoself' spheres are emerging (e.g., microbiome-, inflammation- or aging processes).

3 Hence, QS efforts should move beyond 'letting a 1,000 flowers bloom'. Innovation quality and health impacts will improve when we collectively aim for the 'biggest bang for our health bucks', using the state-of-the-art health and biology expertise.

4 A benefit of this approach is that this will *enhance two forms of know-how*. First, how to improve measurement, connect data models [a huge and growing challenge (Sfakianakis et al., 2010)] and provide useful feedback. There are generally trade-offs between simple, low cost, safe solutions and questions of external validity and reliability. For endothelial function, Brocq et al. (2008) and Steyers and Miller (2014) discuss hopes for biomarkers to show a broader picture of endothelial health than only the vasodilation effects now measured in most standard tests. Vasodilation is currently easiest to measure, and physicians now call it 'endothelial health'

measurement, which is quite an oversimplification. The second form of know-how, very much in the spirit of QS discovery, aims for ever deepening knowledge. In our vascular example: how to increase vascular health such that it has optimal health and performance benefits? And how to measure, show Manogaran and Lopez (2017) and use those benefits in an 'endoself'?

5 As a final benefit: this approach is much cheaper (Greger and Stone, 2016; Ornish and Ornish, 2019), as is also explained in Section 3. By actively using the bodily self-repair mechanisms which are already in place, fewer of the expensive 'external fixes' are needed in healthcare. So we must change our funding and treatment choices in healthcare. We should make better use of the 'wound healing biology' that our evolution already put in place (and which is current ignored to our peril).

4.3 Limitations, generalisability and next steps

Perhaps the biggest limitation is that our QS for health 2050 vision do not consist of 'objective truths' in the way a temperature can be a relatively objective truth. We think this vision is the type of self-fulfilling social truth that we have to make true, if we want it to become true.

A second limitation is that we have been 'optimistic by design', proposing that many people do want health self-repair and assuming that current healthcare barriers can be overcome. In practice, a lot will depend on the question if we can shift from 'reimbursement-based' to really 'evidence-based' medicine (Ornish and Ornish, 2019) This shift will also depend on the paradigm shift from 'antibiotics/external fix' thinking to 'wound healing' thinking. Then, our evidence assessment questions will also shift from 'does this pill lower a risk marker?' to 'did the body move into repair mode?'

Regarding generalisability, a limitation is that we only addressed four health domains (cardio, onco, neuro and metabolic) and that even in these four domains there are large differences in culture, opportunities and barriers. Regarding next steps and generalisation, the route forward will differ per domain, see also the analyses in Section 3. Still, in each domain, we see trends towards the Phase 4 'wound healing' approach described in Section 4.2 for vascular health.

Useful next steps in bioinformatics would be to summarise complex biomarker analyses (which can be done quite cheaply in future consumer products with sensors on a chip to analyse 'omics' in urine for example) into understandable 'endoself' conclusions.

Societal next steps would be to have a wider adoption of the solutions illustrated in this QS vision. This will depend on a dose of luck, plus a coalition of the willing: health (policy) innovators plus a group of front-runner patients who really want to improve their health, not just 'keep it manageable' using ever increasing medication levels. We know the willing individuals exist, see for example, the large blood pressure improvements that were achieved, using daily biofeedback and lifestyle competence building (Simons et al., 2022b). We aim to bring patients, policy and innovators together on this road to move health innovation to the next phase.

5 Conclusions

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 optimised for achieving and measuring health improvements in a matter of hours or days. Currently, several health interventions already deliver powerful repair results. This will become even more powerful when feedback is based on insights from near-real time bioinformatics and integrated into a user friendly 'endoself'. Especially when these data create a shared health progress view and dialogue with health professionals, this can promote truly collaborative health improvements in healthcare, with significant contributions from patierents themselves.

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Notes

1 By providing six months of lifestyle coaching (Simons and Hampe, 2010; Simons et al., 2017) for literally thousands of patients and caregivers in all these domains, over the course of the past ten years.

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

3 Largely because self-repair uses biologically more advanced solutions then the crude mechanisms of medication or surgery. Self-repair solutions which have been honed in millions of years of evolution.

4 If we realise that about 85% of our new cell investments [which amount to about 20,000,000 kilometres of new DNA every hour! (Li, 2019)] are aimed at regenerating a healthy blood stream, we can appreciate the high priority this has for our body.