Perspective

Quantifying your body:
A how-to guide from a systems biology perspective

Larry Smarr

University of California, San Diego, CA, USA

During the coming decade we will see an accelerated digital transformation of healthcare. Leading this change within the institutional medical community are both the move to digital medical records and the use of digital biomedical measurement devices. In addition to this institutional evolution, there is a non-institutional, bottom-up, unorganized, highly idiosyncratic movement by early adopters to "quantify" their own bodies. In this article, I share my decade-long personal experience of tracking many blood and stool biomarkers, which provide insight into the health or disease of major subsystems of my body. These results are interpreted in the context of the genetics of my human DNA and that of the microbes in my gut. Even though I am a computer scientist and not a medical professional, by using commercially available tests and a systems biology integrative approach, I have become an early example of Leroy Hood's vision of the emergence of predictive, preventive, personalized, and participatory (P4) medicine. It is an individual's story illustrating how each of us can contribute to realizing this paradigm shift.

Supporting information available online

1 The digital transformation of healthcare to a wellness paradigm

Quantifying oneself would have been only the stuff of dreams before the digital revolution. Much of the quantification can take place outside of traditional medical environments because of the rapid drop in the commercial cost of making time series measurements of key biological functions and of determining one's genetic code.

Today's ability to track and integrate health information would not have been possible without the rise of the mass market for cell phones. As unit shipments grew from millions to a billion per year, the cost of all the subcomponents dropped precipitously. This has enabled the rapid growth of private sector, foundation, and academic "wireless health" projects. Examples that I cover include consumer devices that allow digital self-tracking of daily steps, caloric burn, heart rate, sleep state, and stress levels. The data are uploaded to the devices' companies, who provide each consumer with their results in easy-to-understand graphical form.

In addition to external monitoring, the rapid technological progress means that it has become more and more economically feasible to make time series measurements of key biochemical variables. Lee Hood and his colleagues believe that within the next decade it will be possible to derive hundreds of data points from a small blood sample [1], thus paving the way to medicine that is predictive, preventive, personalized, and participatory (i.e. P4 medicine).

The cost of human genomic sequencing has seen an even more dramatic drop, from billions of dollars per genome in the late 1990s to thousands of dollars today. Sequencing of the highly variable regions of the genome has already become a commercial commodity, and very soon the whole genome will also be within many individuals' economic capabilities. Combining the time series biomarkers with genomic testing can revolutionize healthcare, by detecting diseases before symptoms occur, providing noninvasive monitoring of dis-

Correspondence: Prof. Larry Smarr, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093–0436, USA
E-mail: lsmarr@ucsd.edu

Abbreviations: CD, Crohn's disease; **CRP**, C-reactive protein; **HDL**, high-density lipoprotein; **IBD**, inflammatory bowel disease; **LDL**, low-density lipoprotein; **P4**, predictive, preventive, personalized, participatory; **SNP**, single nucleotide polymorphism

Box 1: The car analogy to personalized medicine.
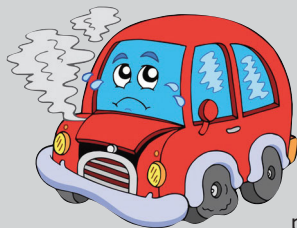
The paradigm shift required to make the change from today's medical practices to the predictive personalized medical care is revolutionary, but by no means unprecedented. A metaphor for this is how radically automobile "healthcare" has been digitally transformed over the past five decades by Moore's Law. In the late 1950s and 1960s, you took your car to the mechanic when you heard loud thumps or saw smoke come out of the engine. When you went in with such a "symptom," you invariably were told: "This is going to cost you," since you had burned up some key part of the mechanical or electrical systems. Cars in those days had limited lifetimes and typically "died of a chronic failure" before you reached 100 000 miles.

As microprocessors, flash memory, and sensors exponentially decreased in cost, car manufacturers could afford to put more electronic devices into cars to measure moment-by-moment functioning of every key subsystem. Rather than wait until you have a costly "symptom," you now take your car into a service facility every 10 000 miles for "preventive maintenance," during which the car's measurements are digitally read out and compared with a database of all other cars of the same model. Should the data be out of range of the "norm", then you get "personalized car service," which involves a repair on a specific set of items determined by the sensor readings. The end result is that your car at 200 000 miles runs just as well as the day you bought it.

Image credits: © KlaraViskova – Fotolia.com, © Mechanik – Fotolia.com

eases, and predicting which patients are most likely responsive to a given drug [2].

These trends will inevitably lead to a disruptive transformation of healthcare [3][i], changing from today's "treat the chronically ill" sickness paradigm to tomorrow's "prevent chronic illness from developing" wellness paradigm. Obviously, this will never be a complete transformation, but as the dominant paradigm shifts, it has the potential to make universal healthcare affordable [4].

This paper addresses three levels of digital monitoring of the body. At the highest level are the macro-variables such as nutritional input, exercise, sleep, and stress. The next layer is the traditional systems biology approach of cross-correlating measurements of the human genome, proteins, and metabolic products, deduced from saliva, blood, and stool tests. The third layer, which has only emerged in the past 5 years, is the measurement of the human microbiome metagenome and its proteins and metabolic products, primarily through stool tests.

2 Emergence of the quantified self movement

The radical change in how we keep our automobiles "healthy" provides an analogy to explain P4 medicine (see Box 1). Just as we take our car in for

maintenance check-ups (of the time series from the many sensors that are built into the car), tracking the body's state through time, by wearing either body surface or implantable sensors and by periodically giving blood, stool, or saliva samples for tests on a wide variety of molecules or microbial genetic sequences, leads to personalized preventive medicine. Comparison between each person's historic norms and the subpopulation with similar genetic makeup and environmental exposure allows the early detection of "signature" perturbations associated with diseased states. These perturbations, if left untreated, might lead to disease onset and eventual "symptoms" that often manifest only after irreversible damage has occurred. With the aid of advances in pharmacogenetics and bioengineering devices, very early detection can lead to therapies that correct these problems, and to providing feedback about behavioral changes that can promote a return to wellness.

As mentioned above, these technology developments are empowering a rapidly growing movement of personal quantification[ii]. Many have joined the quantifiedself.com movement to learn from each other and organize regional meet-ups. I was personally inspired to begin to track myself when I read the National Geographic articles[iii] on the "Experimental Man" by David Ewing Duncan [5]. In an

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i "The Measured Man," Atlantic Magazine July/August 2012 www.theatlantic.com/magazine/archive/2012/07/the-measured-man/9018/

ii "The Measured Life," MIT Technology Review July/August 2011 (www.technologyreview.com/featured-story/424390/the-measured-life/)

iii http://science.nationalgeographic.com/science/health-and-human-body/human-body/chemicals-within-us/

Table 1. A list of consumer products of various degrees of intensity, for self-monitoring of the four pillars of health: nutrition, exercise, sleep and stress management

	Nutrition	Exercise	Sleep	Stress management
Entry Level	**Fitbit** (www.fitbit.com) **Calorie Counter** (www.myfitnesspal.com) Both use database look-up to log food and analyze caloric intake	**Omron** (www.omron.com) Pedometer to measure steps	**Fitbit, BodyMedia** Both measure the time in wake vs. sleep state and the caloric burn per minute during sleep	**Meditation Oasis Apps** (Simply Being, Rest & Relax) (www.meditationoasis.com) Smartphone apps to help novices to mediate
Intermediate Level	**USDA Nutrition database** (http://ndb.nal.usda.gov/) **Humanafit.com** (iPhone and Android apps) Good food database lookup, with fat, carbohydrates, protein. Also measures workouts	**Fitbit** 3D accelerometer measures daily steps and caloric burn **Polar WearLink** (www.polarusa.com) measures heart rate and links to exercise equipment	**Lark** (www.lark.com) Only works with Apple devices. Doesn't measure REM amounts. Has push notifications for behavior modification.	**StressEraser** (www.stresseraser.com) Portable biofeedback device for breathing and HRV[a]
Advanced Level	**Self Nutrition Data** (http://nutritiondata.self.com/) **CRON-O-METER** (http://cronometer.com/) In addition to calories, fat, carbohydrates, protein both have detailed analysis of vitamins, nutrients, amino acids, minerals	**BodyMedia** (www.bodymedia.com) Able to sense skin temperature, galvanic skin response, and heat flux – also able to detect exercises such as yoga or free weights that do not involve stepping	**Zeo** (www.myzeo.com) Headband sensor records sleep state every 30 sec. Displays on bedside device and uploads to the cloud	**Heartmath's EM Wave Desktop PC** (www.heartmathstore.com) Wide range of biofeedback modes for PC driven by HRV pulse monitor

a) HRV: Heart rate variability.

era of social networks, it is not surprising that a number of web sites (Patients Like Me, Trusera, 23andme) are available for sharing of information amongst individuals who may have similar health problems or similar genetic profiles.

While there is considerable controversy about non-medically trained people taking personal responsibility for determining the detailed state of their own bodies and then making behavioral changes to achieve personal goals, it is unlikely that this trend will reverse. There are a number of powerful cultural forces driving this phenomenon: individual reaction against the U.S. obesity epidemic [6][iv], a healthcare system in which the average American gets less than 1 hour per year with their doctor, the widespread fascination with personal gadgets, a growing number of "apps" for our smart phones that enable personal tracking, and social network-enabled peer pressures to personally improve our own health.

3 External body tracking: The four pillars of health

What many consider [7, 8] to be the four "pillars of health" – nutrition, exercise, stress management, and sleep – can all be measured and tracked with a growing variety of consumer products (see some examples in Table 1). Most people can improve their overall health by using the biofeedback that these sensor systems produce to alter their lifestyle.

3.1 Nutrition

One of the major drivers of quantified health over the past decade has been weight loss through nutritional change.[v] While most people engage in weight loss through calorie counting, it should be noted that the nutritional profile of the food you

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iv www.cdc.gov/obesity/data/trends.html

v For the books I have found most useful for keeping me healthy and for my own nutrition program see http://lsmarr.calit2.net/repository/LS_reading_recommendations_FiRe_2011.pdf and www.xconomy.com/san-diego/2010/05/12/how-internet-pioneer-larry-smarr-lost-20-pounds-by-becoming-a-quantified-self

consume is equally important. Besides calories, one should measure the amount of protein, carbohydrates, and fats. It is also important to track the amount of fiber, sugar, and sodium. Ideally, one would like to track the amino acid spectrum (particularly important for vegetarians), the ratio of omega-3 to omega-6 essential fatty acids, and the vitamin, mineral, and micronutrients (see Table 1).

In my case, I took 12 days in which I ate at home and measured every gram or fluid milliliter of every ingredient, then used the nutrition tables provided by the US Department of Agriculture to convert to calories and to, grams of protein, carbohydrates, fats, sugar, sodium, and fiber. Putting all this in a spreadsheet and averaging over the 12 days of many different food types gave me a fairly accurate snapshot[vi] of what I was putting into my body.

The bathroom scale is one of the simplest and most effective ways of self-monitoring. You should weigh yourself at the same time once per day or per week and record the data over a year or more[vii]. It is thought to be best to lose weight slowly so that the body can have time to adapt all its internal biochemical cycles to the new equilibrium. I lost 25 pounds over 5 years[viii], or ~1 pound every 10 weeks, through regulating my diet and exercise levels.

In addition to the body mass index (BMI)[ix], there are various ways to measure the relative change in percentage of body fat over time: calipers for a pinch of skin at the neck, chest, and thighs[x], weight scales with electrical currents that go through the body, immersion techniques, etc. Tracking this relative measure shows that you lose body fat at different rates from different parts of your body. However, accurately determining your total body fat is more difficult. The best way is to have a full body scan[xi], which gives the 2D distribution of your body

fat and then integrates to come up with an absolute number.

3.2 Exercise

Measuring the daily caloric burn from exercise is the complement to measuring caloric intake. Not only does exercise reduce your future chance of cardiovascular disease [9] and reduce stress, it also releases a number of biochemicals, such as endorphins, serotonin, and neuron growth factor.

Walking is one of the simplest forms of exercise with health benefits of reduction in cardiovascular disease [10], so a number of commercial devices are available for measuring your daily steps. But it is important for your sustained health to measure the amount of time you spend in aerobic exercise, since the latter has many health benefits [11, 12]. Using a variety of consumer electronic products, one can measure the daily number of steps, stairs climbed, and caloric burn (see Table 1). Using a heart rate monitor, which wirelessly couples to exercise machines, you can adjust your exercise pattern so as to make a desired portion of your caloric burn aerobic.

Complementary to walking or aerobic exercise, resistance training builds lean body mass and is also critical for avoiding cardiovascular disease [13]. The extra muscle cells contain more [14] of the cellular "power stations," called mitochondria, which raise your overall metabolism. In addition to measuring your heart rate while exercising, it is also important to track your blood pressure, pulse, and resting heart rate, since high blood pressure is correlated [15] with increased risk of cardiovascular disease. There are a number of accurate consumer blood pressure monitors. Ideally, losing weight, gaining strength, regularly exercising, and lowering stress should lower your blood pressure and resting heart rate[xii].

3.3 Sleep

While many people may track their body's performance when they are awake, many do not think about monitoring the sleeping period, in which we spend more than a quarter of our lives. Spending a night in a sleep lab is still the only accurate way to measure all the aspects of the sleep state; however, these days, there are also consumer products emerging that approximate the sleep lab experi-

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[vi] For the results see Table 1 in my article "A 10-year detective story of digitally enabled genomic medicine" http://lsmarr.calit2.net/repository/092811_Special_Letter,_Smarr.final.pdf (hereafter referred to as "LS-SNS")

[vii] Many weight scales now have Bluetooth wireless connections from the scale to your personal computer so it is easy to create a time series of your weight.

[viii] See slide 14 of my presentation at http://lsmarr.calit2.net/presentations?slideshow=10522344

[ix] For a BMI calculator see e.g. www.mayoclinic.com/health/bmi-calculator/NU00597. For instance, in my case in the 6 years in which I dropped 25 pounds (2000–2006), I dropped from a BMI of 27 (overweight) to one of 23.6 (high normal) in 2006.

[x] See slide 8 of my presentation at http://lsmarr.calit2.net/presentations?slideshow=5394995. These relative measurements would indicate that by 2006 I had lost 1/3 of my body fat in 2000.

[xi] I use the GE Lunar DXA flatbed densitometry scanner, which we have in the Calit2 Exercise and Physical Activity Resources Center

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[xii] My resting heart rate fell from the mid-60s to the low-40s. I measured my blood pressure daily for a month with an average of 134/73 and an average pulse of 55.

ence with just a simple headband sensor or device you wear on your arm (see Table 1). Since the body carries out much of its physical and mental maintenance during sleep, having good sleep quality and quantity is very important to your health [16]. However, for the great majority of people who do not track the details of their sleep, this part of their life is unknown[xiii]. As in nutrition, exercise, and stress measurements, the biofeedback enables you to change behavior and "tune" your body to a healthier state – in my case, I've made a conscious effort to increase my sleep to 8 hours per day.

3.4 Stress reduction

Stress reduction is perhaps the least understood aspect of increasing your quality of life and reducing future disease states. Stress is directly translated into the body's biochemical systems [17]. There exists a very strong brain-gut neural connection (the colon is the most enervated organ in the body outside the brain) with major impacts on your health [18]. Stress can even alter your gut microbial ecology through the brain-gut-enteric microbiota axis [19].

There are a variety of methods (see Table 1) for modification of your stress level through biofeedback. Besides meditation, there is a quantitative method for measuring and reducing stress using your heart rate variation, measured by the series of absolute time intervals between heart beats. Using a pulse sensor coupled to a PC user interface, software allows one to measure and modify the dynamics of the sympathetic and parasympathetic nervous systems. This quantifies [20] (This field is termed "Heart Math") many states of human emotion, extending the quantified self from the physical regime into the psychological and emotional.

4 Internal body biomarker tracking

As we move from tracking the body from the outside to tracking biomarkers inside the body, we move into the realm of systems biology applied to medicine, as articulated by Hood and colleagues [21, 22]. The vision is that with the complete knowledge of the individual's genomic code and its variations across the population, combined with massive amounts of data on proteins (via proteomics) and metabolic products (via metabolomics), we can determine the state of major biochemical subsystems in the body and monitor their time evolution. Here I discuss my experiences in applying this systems approach to my own health.

4.1 Blood biomarker tracking

The blood system has long been known as a powerful "window" into the state of many of the major subsystems of the body. Currently, I track over one hundred variables (both molecules and blood cell types) in my blood with a time frequency of several months to several years. In the following sections, I organize these tests into the major subsystems of the body that are probed by the blood tests. My goal is to give an overview (for details see Supporting information) of what is possible in this body surveillance mode and to illustrate each with my own personal results.

My major conclusion is that most of the blood variables turn out to fluctuate within their normal ranges, but by tracking a large number of variables and using one's own historical data as an internal control, one can easily detect those few variables that are out of range and use that information to gradually home in on the underlying dysfunction in the body.

4.1.1 Measuring what to supplement

We can adjust the concentration of a variety of elements and molecules in our blood through food or supplements. By measuring their levels, we can determine if we need to alter our intakes. For instance, standard blood tests provide electrolyte levels; besides the common electrolytes (e.g. sodium, potassium, calcium, magnesium, etc.), I also test for the micronutrients that are essential for health (such as arsenic, chromium, cobalt, copper, etc.). In my case, blood tests revealed that my levels of chromium, copper, magnesium, molybdenum, and selenium were lower than optimal; therefore, I am taking supplements to bring them back up. I also test for a variety of nonessential elements in the blood and stool that can indicate adverse environmental exposures.

Equally essential to electrolytes and micronutrients are the levels of key vitamins and antioxidants. While consuming a diet rich in both is necessary, this does not always translate into adequate amounts in the blood. For instance, most Americans are deficient in vitamin D, which can be easily tested for [23]. Another problem, also not widely recognized, is that taking prescription drugs or even common foods such as grapefruit and garlic can alter the absorption of many biochemicals – for ex-

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[xiii] I have worn a Zeo sleep sensor headband for over 400 nights. I discovered that according to Zeo ~50% of my sleep is in REM, over twice that of the average 60-year-old American male in the Zeo database, even though my total time in deep sleep is about the same.

ample, the statin I take interferes with the body's synthesis of coenzyme Q10, an important component of the body's energy cycle. I therefore take supplements to counteract this effect. This is an area where asking the prescribing physician about possible needs for supplements can be beneficial.

4.1.2 Blood cell system

The blood cell system contains many clues about your body's health. A complete blood count (CBC) quantifies your white and red blood systems. It will give the white blood cell (WBC) count, which can rise if you have an infection, as well as the percentage of each of the five different types of white blood cells. The CBC also quantifies the red blood cells (RBCs), as well as several other parameters. Finally, a CBC also measures the platelet count and the mean platelet volume. Given the key role of the RBC in delivering oxygen throughout the body, the iron complex is closely associated with the health of the RBCs. The hemoglobin molecular complex has a heme molecule which has a central iron atom and contains the oxygen atoms. To get a profile of the iron sector, one needs to measure levels of iron, ferritin, vitamin B12 and folate (needed to make RBCs) once or more times per year, as well as the iron-binding capacity.

4.1.3 Blood sugar system

The glucose-insulin system controls blood sugar levels. High blood glucose promotes production of insulin by the pancreas. Insulin stimulates fats, muscles, and the liver to take up more glucose, thus bringing the blood-glucose concentration back down. Low blood-glucose promotes the production of glucagon, which stimulates release of glucose into the blood by storage tissues, and also induces hunger. The pursuit of a healthy nutritional diet leads directly to a focus on the body's glucose-insulin cycle [24]. Since I was initially diagnosed as pre-diabetic, I have repeatedly measured my glucose and insulin with fasting blood tests (see Supporting information) and have also taken a glucose tolerance test to look for insulin resistance.

4.1.4 Hormone system

Hormones provide the body with a messaging system, in which chemicals produced in the endocrine glands travel through the blood stream to other parts of the body, which adapt when they receive the hormone signals. Therefore, the health of these systems is critical since, if the hormones are not produced at the correct level, there can be a cascade of chemical changes throughout the body. For instance, the thyroid gland hormones, which are responsible for controlling metabolism in the cells in your body and which influence a number of other hormonal systems, can be measured. A number of hormones are tied to changes in our stress levels. Cortisol is one of the primary hormones produced by the adrenal endocrine glands and is intimately related to how your body handles stress. I found, using a saliva test, that I may have a depleted reserve of cortisol probably caused by living for too many decades under high stress. Since other hormones, such as testosterone, are lowered under stress, I also tested my testosterone level. Given these results, I am beginning to use some of the stress reduction techniques described above.

4.1.5 Liver and kidneys

The liver is one of the most complex biochemical processing organs in the body. It is responsible for detoxification of the blood and metabolizing food, alcohol, and medications. There are blood tests to monitor key liver enzymes, such as aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALK). My values have typically been within the normal range, except when I was on the prescription drug prednisone, in which case AST and ALT jumped above the upper limit and ALK dropped below its lower limit. All three reverted to normal ranges when I stopped taking the medication.

Similarly, the kidneys filter your blood to remove wastes, producing about 2 L per day out of ~200 L of blood processed. Given the high throughput of the kidneys, it is important to monitor kidney function and protein metabolism over time, using standard tests including blood urea nitrogen (BUN), creatinine, and uric acid.

4.1.6 Cardiovascular system

Coronary heart disease (CHD), the leading cause of death in the United States, often develops from the buildup of plaque in the coronary arteries. There are several imaging modalities available to measure this buildup, including multi-slice CT heart scans and whole body CT scans. In addition to visualizing the coronary arteries, the device computes a "coronary artery calcium score", which can help predict your risk of future heart attack [25][xiv]. Since my father died of congestive heart failure, brought on by major blockage of his coronary arteries, I have had both imaging modalities to see whether I am in danger of developing this debilitating disease.

[xiv] CAC over 100 indicates significant amounts of hard plaque in the coronary arteries. In July 2007 my CAC was 7.

Table 2. My cholesterol levels before and after regular use of statins

Cholesterol variable	Recommended	Mine before statin	Mine after statin
LDL	<130 mg/dL	100	45
LDL subclass pattern	A	A/B	A
HDL	>40 mg/dL	50	70
TG[a)]	<150 mg/dL	62	35
TG/HDL	<2	1.2	0.5
Apolipoprotein B	<110 mg/dL	80	46
Lipoprotein(a)	<10 mg/dL	11	4

a) TG, triglyceride

Several blood variables can also be measured to determine your likelihood of developing more plaque in the future. A variety of lipids and lipoproteins are often used to evaluate future risk for cardiovascular disease. The most accurate blood test is the vertical auto profile (VAP), which yields a number of predictive biomarkers for future heart disease. The most readily available tests are for LDL ("bad"), HDL ("good") cholesterol, and total cholesterol. However, several other quantities have a higher correlation with future heart disease than these three commonly followed markers. The ratio of triglycerides to HDL has been found to be one of the most powerful single lipid predictors of future heart disease [26]. Similarly, apolipoprotein B, another VAP test result, has more predictive power for future heart disease [27] than LDL. Finally, lipoprotein(a) is part of a VAP test, but it is more weakly associated [28] with future heart disease.

Therefore, changing these variables to healthier values has become a goal of medicine. One class of the most widely used pharmaceuticals to achieve this goal are thestatins [29], although this remains a controversial topic. I have found tracking all of the variables mentioned above that the use of statins certainly improves my values of these variables (see Table 2).

4.1.7 Inflammation
Inflammation has become widespread in Americans, enhancing the likelihood of a wide range of chronic diseases [30]. A major driver of this "inflammation epidemic" is the overconsumption of foods rich in omega-6 essential fatty acids rather than in omega-3s [31]. The ratio of intake of omega-6 to omega-3 drives the eicosanoid hormonal signaling system, which exerts control over the vascular system [32], inflammation, and the immune system.

A number of diets stress the need to avoid the typical American ratio [33] of nearly 20:1 omega-6 to omega-3 and bring it closer to ~2:1, which is what hunter-gatherers have and therefore the food in-

take regime under which most of our genetics evolved. High values of omega-3s in the blood are correlated with lowering [34] the risk of future heart disease, as is a low omega-6 to omega-3 blood serum ratio [35]. By altering my diet to reduce intake of omega-6, adding foods rich in omega-3s, and supplementing daily with omega-3 fish oil pills, I found that I had moved to very good values (see Supporting information), indicating that I had minimized inflammation-driving components from my food.

The sources of inflammation, however, are much more varied than the food we consume. It can also be driven by infections or autoimmune diseases. Therefore, it is important to measure your serum inflammation level directly. The most widely used biomarker is complex reactive protein (CRP). A high CRP indicates an increased risk of cardiovascular disease [36]. In fact, research has shown that high CRP is a stronger indicator of future cardiovascular events than LDL cholesterol [37]. That is, even if you have a low LDL, if you have a chronic elevated CRP, you have increased risk of future heart disease [38].

To my surprise I found that over the past 6 years, my CRP level was chronically elevated (see Table 3), so much so that I am in the high risk category for future heart disease and diabetes [39][xv]. This high level of inflammation was confirmed by two other blood serum inflammation biomarkers – the sedimentation rate and the levels of lipoprotein-associated phospholipase A2 (Lp-PLA2).

One possible source of inflammation is allergies to specific foods or airborne irritants. To determine whether the high value of my chronic inflammation was caused by this, I took several blood tests to check for elevated blood levels of immunoglobulin E (IgE). The tests looked for blood antibodies

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xv A CRP greater than 3 mg/L puts one in the high risk category for future heart attacks, and increases the odds of developing diabetes by 4–6× [39]. My CRP peaked at 27 mg/L in January 2012.

Table 3. My values of key inflammation and immunology variables

	Normal upper limit	My high value	Multiple of upper limit
Blood:			
CRP	1.0 mg/L	27 mg/L	27×
Stool:			
lactoferrin	7 µg/mL	900 µg/mL	128×
calprotectin	50 µg/g	2500 µg/g	50×
lyzosyme	600 ng/mL	1200 ng/mL	2×
sIgA	200 mg/dL	1300 mg/dL	6.5×

against over 100 foods and 36 airborne pollens. The results were 100% negative for all substances tested. These tests showed I do not have an acute reaction to the foods tested, it is likely that my chronic inflammation is not a result of allergies.

In summary, by blood tracking, I discovered that I had a persistent source of inflammation in my body, which could lead over time to cardiovascular disease. Given that this inflammation was not driven by my omega-6/omega-3 food intake or by allergies, what was the source of the chronic inflammation? To answer that question, I began to quantify another system, complementary to the blood.

4.2 Stool biomarker tracking

The gastrointestinal tract, while tightly coupled to the circulatory system, provides an important second window on your health. The colon contains ten times as many microbial cells as the number of human body cells, and is also the site of the majority of immune cells in the body. Commercial stool tests can probe the state of the microbial ecology, aspects of the innate and adaptive immune systems, and whether you are in an inflamed state, by measuring a variety of proteins. Specifically, lactoferrin is a glycoprotein shed from the surface of white blood cells (the most common type, neutrophils) as they respond to intestinal inflammation. Calprotectin is another protein associated with neutrophils. Lysozyme is an anti-bacterial enzyme secreted as part of the innate immune system. Finally, secretory immunoglobulin A (sIgA) is the principal antibody protein in the first line of mucosal adaptive immune defense.

In 2008 I began having several stool samples per year tested using Your Future Health (YFH) Blood Testing Company's Comprehensive Stool Test. What I discovered is summarized in Table 3. Although episodic, all four of the colon protein biomarkers were reaching quite elevated values compared to the normal expected range, confirming that the source of the inflammation measured by the CRP and sedimentation rate in my blood was

likely in the colon. High values of both lactoferrin and calprotectin have been shown to be differentiators between inflammatory bowel disease (IBD), a chronic incurable autoimmune disease, and irritable bowel syndrome (IBS) and other forms of colitis [40]. Furthermore, my peak lactoferrin and calprotectin values were comparable with values associated with people suffering from active IBD (see Fig. 1 in [41] and Fig. 2 in [42]).

Based on the high values of these biomarkers and images and biopsies from a colonoscopy, the diagnosis emerged that I have late-onset Crohn's disease (CD), which along with ulcerative colitis (UC) are the two forms of IBD. Less than 5% of patients with CD are detected after age 60 [43], so this was a fairly rare phenomenon. However, by looking at a variety of blood and stool markers, it was easily detected by their extreme values (Table 3) several years before I began to have acute symptoms of CD. Also looking at the time series that I made of these markers revealed the episodic flares that are characteristic of IBD [44][xvi]. The final confirmation was provided by MRI and CT imaging studies, which in 2011 definitively concluded[xvii] that the inflammation was confined to ~16 cm of my sigmoid colon.

5 Genomics

The pathogenesis of IBD (and often other autoimmune diseases) involves a genomic predisposition and an interaction with environmental factors [45], particularly those generated by our gut microbiome. For this reason, I expanded my quantification from time series of blood and stool biomarkers to genomic sequencing.

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xvi www.techlab.com/docs/posters/s1423_print.pdf.
xvii My physician is Dr. William J. Sandborn, Chief, Division of Gastroenterology & Professor of Medicine, UC San Diego

5.1 Human genome

In the middle of the past decade, several consumer companies (e.g. 23andme and Navigenics) began providing inexpensive saliva genetic sequencing services for one's single nucleotide polymorphisms (SNPs), the million or so bases along your DNA in which at least 1% of the human population has genetic variations. SNPs cover ~90% of all genetic variation among humans. Recently, exome sequencing of the 50 million bases that are part of the human gene coding regions began to be offered by 23andme for $1000 on a limited basis. However, the cost of obtaining a complete human genome (diploid DNA has 6 billion bases) is $10 000 or less per person sequenced in 2011. Estimates are that in less than 5 years there will be over 1 million full human genomes sequenced every year for prices comparable to today's exome sequencing. It seems likely that as the price of sequencing the full human genome falls below $1000 over the next decade, it will become a standard procedure.

Knowing that CD was an autoimmune disease, I searched 23andme for "Crohn's" and discovered that I had SNP[xviii] rs1004819, which from genome-wide association studies (GWAS) puts me at 80% higher risk for CD than the general population. This SNP was in the interleukin-23 receptor gene, which is associated with pro-inflammation. So I clearly had the "genetic predisposition" to CD, which was likely the long-sought source of inflammation that was chronically elevating my CRP, in spite of my anti-inflammatory nutrition. However, IBD seems to be co-created [46] by the host genetic polymorphism and disturbances in the colonic microbiome, so I now turned my attention to the genetic structure of my gut microbiome.

5.2 Gut metagenome

What I have discussed so far has been focused on the human cells in the body. But research has revealed that our human cells represently only 10% of the total cells in our "superorganism." Bacteria occur over all of the body's outer surfaces, which include not only the skin, but the entire GI tract, the ears and sinus cavities, and the urogenital tracts (see the special issue on the gut micrbiota in *Science* [47] and articles in *Nature* [48-50]). The great majority of these bacterial cells reside in the large intestine, possessing over 100 times the number of genes as human DNA. This makes the complex interactions between the human and microbe sys-

tems in the gut one of the most significant interfaces in the body [47].

Bacteria account for over 50% (by dry weight) of human stool [51]. Several groups of gut microbes can be cultured from stool tests, including *Bifidobacterium*, *Lactobacillus*, *Escherichia coli*, *Enterococcus*, *Bacteroides fraglis* group, and *Clostridium* species. Using the YFH stool tests that detected my high values of lactoferrin, I tracked the value of these bacteria groups over the past 4 years[xix]. I found that after I was prescribed a 10-day course of antibiotics in September 2008, it took 2–3 years for the populations of "good" bacteria to fully recover [52], and the values have fluctuated since. In the meantime, a wide range of "bad" bacteria showed up in the cultures at high levels. It may well be that my use of antibiotics in 2008 was related to my developing full CD symptoms in 2011, since similar delayed reactions have been reported [53].

Although tracking the composition of the gut bacterial community that can be cultured yields some insights, studying the complete interactive human/microbial system was quite difficult until 6 years ago, because some three quarters of the bacterial species are anaerobic and, therefore, not easily cultured. Since 2005, the rapid decrease in the cost of genetic sequencing methods has made a much more complete mode of analyzing the ecology of colonic bacteria possible. Several sequencing techniques can be used to delve into this complex system.

Autoimmune diseases such as IBD significantly disrupt the gut microbiome [54]. To see whether I have the major biodiversity collapse and missing genes that have been reported in CD patients, in 2012 I am having both phylogenomic and metagenomic sequencing carried out on my gut microbiome by the J. Craig Venter Institute in Maryland, with the computational analysis done at UCSD.

It may well be that CD can be stratified into several different diseases by looking at the human and microbial genetics and metabolic biomarkers to determine the physical basis for the disease. Heretofore attempts to define subpopulations of CD have been based on location of the inflammation or severity of symptoms [55]. However, it has been shown that there is disease stratification determined by the gut microbial ecology. Whereas commercial stool sample tests track only a few bacterial metabolites, researchers use mass spectrometry to carry out a complete metabolomic analysis of the gut microbiome. One result shows that CD that is localized in the ileum (ICD) can be clearly distin-

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[xviii] See Figure 15 in LS-SNS

[xix] As shown in Fig. 16 LS-SNS

guished from CD localized to the colon (CCD) via the different microbial metabolic signatures [56][xx].

Presumably, this difference in microbial metabolic products implies a different species diversity in these two cases. This has been verified [57] in a recent study of CD in twins who shows clear differences in the gut microbial species diversity in ICD and CCD. The logical conclusion is that ICD and CCD are different subtypes of the CD disease. Similarly, from the human DNA, the SNP GWAS have found a number of different human DNA polymorphisms in genes associated with different portions of the immune system. Some of these SNPs are correlated with ICD (see Fig. 1 in [58]).

Clinical trials are needed in which the phenotyping of the disease is correlated with these genetic and metabolic biomarkers to see if such disease stratifications are robust. In the near future, it should be possible to determine if these systems biology approaches to disease state definition and evolution can lead to more effective therapies, specific to the disease subtype, for minimizing the symptoms or even reversing the autoimmune diseases.

6 Systems biology of the superorganism

6.1 The personal omics profile

The systems biology vision requires high resolution determination of four major data components: genomics, transcriptomics, proteomics, and metabolomics (including lipidomics) of the individual. These can then be combined (see Fig. 1 in [59]) with imaging modalities and clinical records to support personalized medicine. The human genomics can be resolved at different levels: the roughly million bases at which 90% of human variation occurs (SNPs), the ~100 million bases which code for genes (exons), or at 6 billion bases (full diploid genome). The DNA expresses itself in specific locations and times through RNA, which can be sequenced, yielding "transcriptomics". Mass spectrometry enables "proteomics" in which the proteins derived from the DNA genes can be discovered, although these are also post-genomically altered. Finally, using mass spectrometry, the small molecules that are formed by the body's metabolism can be determined, "metabolomics". This metabolome includes a subset of fats (lipids) whose measurement yields "lipodomics" [60].

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xx I have submitted a stool sample to Jansson's team for metabolomic analysis to see if my colon-localized CD agrees with this research.

In conclusion, my personal research has revealed that even at the SNP resolution of the human genome, combined with time series of a few proteins and metabolic biomarkers for which there are commercially available tests, one can detect disease before it fully manifests itself with symptoms. Further, the biomarker time series provides a much more accurate picture of the evolution of the disease state than is possible by monitoring symptoms.

With the development of high-throughput laboratory techniques, the research frontier – using this same methodology, but with 1000× the number of data points in each sector than I used –can gain an early glimpse of the power of P4 medicine. A recent paper [61] illustrated this. Stanford geneticist Michael Snyder and his colleagues were able to resolve his complete genome at ultra-high resolution (140× coverage), and, over the course of 2 years, took blood samples about every month from which they derived his complete transcriptomics, proteomics, and metabolomics. As a result, he was able to track the alteration of these systems over time as he battled two viral attacks. He found that he had a genetic predisposition to type II diabetes and during one of the virus attacks he actually saw the disease begin to switch on. However, at present, this tour-de-force illustration of the future vision of systems biology can only be carried out in a major academic research laboratory. With decreasing costs something similar may become clinically possible within 10 years.

6.2 Beyond the personal omics profile

The next step is to expand Snyder's experiment to include the full human microbiome, so that one is studying the systems biology of the superorganism [62] and not just the human cells. This means that the genomics needs to include both the full human genome and the time varying microbial genome across the body's surface. The transcriptomics will be a combination of the transcripts of both human and the microbialRNA. This would be similar for the combined proteomics and metabolomics datasets. Researchers are already engaged in carrying out parts of this program. For instance, the study of the combined metabolic products of our human and microbial cells is termed "metabonomics" [63].

One breakthrough that this approach could lead to is the elucidation of the pathogenesis of autoimmune diseases. Given a specified genetic predisposition to such a disease, one should be able, by tracking the time evolution of the ecological diversity and metabolic products of the microbiome

along with human biomarkers, to unravel the series of events in which the host genetic SNP predisposition to autoimmunity translates into an alteration [64] of the gut microbial ecology and the onset of the autoimmune disease with its eventual symptoms.

7 Summary

Body quantification can be divided into two major sectors – macro non-invasive measurements and micro internal measurements. By comparison of one's own time series with population norms, it can become clear when a variable is far out of range. The greatest insight seems to come from multi-variant analysis involving several variables from different sources that have abnormal values. The example here of diagnosing my colonic CD came from observing that blood CRP, stool lactoferrin and calprotectin, colon microbe abundance, and a specific SNP all had abnormal values. This was confirmed by multiple body imaging modalities.

It would seem that this quantified-self approach will lead naturally to systems biology approaches. In particular, there seems to be a clear opportunity to build a systems model of the joint gene expression of the host and microbial DNA in the colon to see how major excursions from equilibrium can occur. As we gain a better understanding of the physical basis of disease states via systems biology, a new taxonomy of diseases will emerge, based on the genetic predisposition and underlying physical system changes over time, which will complement or even eventually replace the time-honored approach of disease classification from symptoms. Such a science-based disease classification should lead to much more personalized and effective therapies.

Conflict of interest: The author is a member of the Scientific Advisory Board of Complete Genomics, Inc.

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Larry Smarr is the founding Director of the California Institute for Telecommunications and Information Technology (Calit2), a UCSD/UCI partnership and the Harry E. Gruber professor in UCSD's Department of Computer Science and Engineering (CSE). Before that he served as founding Director of the National Center for Supercomputing Applications (NCSA). He is a member of the National Academy of Engineering and a Fellow of the American Physical Society and the American Academy of Arts and Sciences. He serves on the NASA Advisory Council to the NASA Administrator, the DOE ESnet Policy Board, and chairs the NSF Advisory Committee on Cyberinfrastructure. For eight years he was a member of the NIH Advisory Committee to the NIH Director, serving 3 directors. His life-streaming portal is http://lsmarr.calit2.net.

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