The Virtuous Circle of the Quantified Self: A Human Computational Approach to Improved Health Outcomes

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"What I've found to be most amazing about these forums thus far is the ability of patients to identify common side effects, formulate solutions, test them, and confirm their general efficacy all in a matter of days, when it would take researchers weeks or even months to generate the same knowledge."— Patient with ALS discussing potential treatments on the forum of the ALS Therapy Development Institute (ALSTDI, www.als.net)

Introduction

Until recently, medical data was hand-written, inconsistently recorded, difficult to exchange between medical systems, and inaccessible to the patients it was written about. With the advent of electronic health records, disease registries, and patient portals, this state of affairs is changing rapidly. The *nature* of medical data collected is changing too, from a trained professional's observations of signs and symptoms to more objective measurement such as blood tests, genomic scans, imaging data, or even sensor data from medical devices. Patient self-report is also taking an increasingly prominent role as regulators and payers grant increasing authority to the experience of the patient (Basch et al. 2012).

The fact that data is held *about* a person is hardly new; governments, banks, insurers, and retailers have been collecting civic, financial, and behavioural data about us for a long time. But medical data has some unique attributes: of extreme local importance, it's considered highly private (often stigmatizing), can have high financial value, and when inaccurate has severe consequences.

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In the past decade, what was once a collection of dry, static observations silo'd away in a filing cabinet are now dynamic, interactive and fluid data that are perceptible, correctable, and influential on the behavior of the data's subject: the patient. That's because the real revolution of digital health data is that patients increasingly have the potential to see, generate, share, interpret, and alter their own data—"*Nothing about me without me*". Through technology and crowd sourcing, patients will increasingly gain the power to analyse data about themselves too, with the aim of creating value not only for themselves but also other patients like them. The tantalizing promise is not just that the cure to their disease may lie in their data but that they themselves might be the ones that discover it. In a world of crowd sourced medical computation, who cures cancer? We all do.

Patients Go Online

People with serious illnesses have been using the Internet to connect for a long time. Howard Rheingold documents an experience from 1986 when his young daughter was bitten by a tick that they weren't sure how to remove. It was late at night, and while his wife left a message at the pediatrician's he was able to log in to virtual community the "The WELL" and get the medical advice he needed before the pediatrician's office had even returned his wife's phone call (Rheingold 1993). One of the first online communities, the WELL was created by "Whole Earth Catalog" (WEC) founder Stewart Brand a year earlier and brought a technological platform to the 1960s counter-cultural tendencies originally nurtured by that group, such as distrust of authority, emphasis on do-it-yourself "tools", and the sharing of information.

As access to the Internet widened in the 1990s, increasing numbers of patients diagnosed with serious conditions (and their caregivers) took to the Internet to learn about their disease, connect with other patients, and share their experiences (Lester et al. 2004). Discussion groups with similar ground rules to The WELL flourished on pre-Web systems such as USENET, Compuserve and even email list-servs that allowed patients to organize under the banners of their diagnoses. Such patient groups typically preceded the adoption of the Internet by the "official" disease nonprofits or health professionals by many years. In 1993, one group of researchers at Massachusetts General Hospital (MGH) surveyed the fragmented nature of the online field and attempted to address this divide by building a safe, moderated environment for people with neurological disorders to meet and communicate. The website's name was "BrainTalk" and it became an online home to tens of thousands of patients, a model for smaller disease-specific communities, and one of the first communities about which papers were written in the peer-reviewed scientific literature (Lester et al. 2004).

The technology of the day permitted systems like BrainTalk to operate as "bulletin boards" or "forums", less technically sophisticated than the social networks of today, but with rich narrative content and a strong sense of community. A member could register with an email address, pick a username to anonymise themselves, and enter key demographics such as age, sex, location, and diagnoses. Forum tools

allowed patients to post new conversation "threads" and reply to these asynchronously at any time, but the fora were generally open to non-registered readers too, known as "lurkers".

In parallel to these neurologically focused message boards, caregiver activist Gilles Frydman founded the Association of Online Cancer Resources (ACOR) in 1995 for patients diagnosed with cancer. By creating over 200 support groups for patients with each of the specific subtypes of cancer and using the ubiquitous medium of email, ACOR has gone on to serve over 600,000 patients and caregivers.

Throughout the 1990s ACOR and other online health boards rapidly gained an international following, with topics on BrainTalk ranging from getting a diagnosis, how to communicate with healthcare professionals, tips to cope better with disease, and even alternative medicines (Lester et al. 2004). Anonymity was prevalent, which served to protect patients from identification but also made it difficult to verify who you were actually talking to. Healthcare professionals often lurked silently on communities like ACOR or BrainTalk, but for reasons of professional liability rarely chose to participate in discussions. Patients however, held no such reservations and shared crucial treatment tips with one another. For instance members of the epilepsy community on BrainTalk shared tips on clever ways to "hack" their daily doses of medication to be used to interrupt an ongoing seizure by grinding them up and administering the solution as a liquid to halt the ongoing damage of a severe seizure. Belatedly, professional bodies such as the American Medical Association (AMA) have recently produced "social media policies" that lay out the ground rules for how medical professionals could (if they desire) become a real part of such communities, (Policy 2011) but unfortunately the 20 year latency has not helped to foster online links between clinicians and patients. Left to their own devices, patients have taken up greater responsibility for their own care and that of their fellows.

> When I talk to my doctor, I hear myself asking questions that my online 'family' needs to know. It's as if all these other people—the members of my group—are asking questions through me. And whatever answers I hear from my doctor, I know I'll share with them on line.—Anonymous BrainTalk patient (Lester et al. 2004)

Early research literature focusing on the Internet was particularly concerned with the potential for poor and misleading information gathered online. However, thorough quantitative assessments from the BrainTalk group showed the actual level of misinformation was low: less than 6 % of forum posts on an open forum (Hoch et al. 1999). Others proposed theoretical harms that could result too, such as misunderstanding caused by the limited nonverbal cues available to participants, excessive dependence on a support group, emotional distress caused by reading "triggering" materials, breach of confidentiality, premature intimacy, excessive emotional intensity, and potentially unsafe relationships (Waldron et al. 2000). By contrast, Eysenbach suggested that researchers' focus on negative aspects of online communities and discussion of *potential* rather than *recorded* harms risked obscuring the potential benefits of such tools (Eysenbach 2003), and it is worth noting that all the potential harms noted above are just as feasible in an offline support group. From the perspective of BrainTalk patients for instance, few patients felt that inaccurate information affected them and the forums met an unmet need caused by the inability of health-care providers to answer questions or provide relevant information

(Hoch and Ferguson 2005). Relative to the commonplace harms visited upon patients in a hospital setting, for instance, the number of recorded cases of serious harm arising from patients using the Internet have been low (Crocco et al. 2002), though some subgroups such as those with mood disorders (Bessière et al. 2010) or eating disorders might be particularly vulnerable (Rouleau and von Ranson 2011).

While much of the progress in online communities appeared to have passed unnoticed by much of the medical profession during this period, a small cadre of clinicians, researchers, and activists calling themselves the "e-patient scholars" sought to redress the balance. In what became a manifesto, BrainTalk's director (and former medical editor of the Whole Earth Catalog) Dr. Tom Ferguson described an "e-patient" as one who is not just "electronic" but also equipped, enabled, empowered, and engaged in their own health care (Ferguson 2007). In a white paper completed posthumously after Dr. Ferguson lost his battle with multiple myeloma, the e-patient scholars laid out their anthropology of "citizens with health concerns who use the Internet as a health resource, studying up on their own disease… finding better treatment centers and insisting on better care, providing other patients with invaluable medical assistance and support, and increasingly serving as important collaborators and advisors for their clinicians."(Ferguson 2007)

In their white paper, Ferguson and his team lay out a number of startling anecdotes where patients interacting over the web were able to diagnose rare disease, avoid iatrogenic harms from the medical establishment, and support one another to plug gaps in the medical system (Ferguson 2007). While on an individual basis these stories were important, a constant refrain echoed from the traditional medical establishment: "The plural of anecdote is not data".

Patient Communities for Conducting Research: Early Opportunities and Limitations

From a human computation perspective this represented the greatest limitation of such systems at the time; forum posts were just stories—incomputable, subject to bias, dramatic license, or even outright confabulation. For the newly diagnosed patient (or "newbie"), entering such communities could be an overwhelming experience, with each forum having its own myriad social ties and histories, and each individual member having a rich offline history, only some of which was reflected online and could be hard to wade through. For instance an experienced forum member on BrainTalk might have tens of thousands of forum posts, and coming to understand where they were coming from on a given issue might require hours of reading. Therefore as they grew in scale, understanding narrative text risked becoming an inherently un-scalable proposition.

From the early online researcher's perspective, in the absence of modern techniques such as natural language processing, much of the existing textual information archived was unusable by researchers due to its sheer volume. Furthermore the unique nature of online interactions with its slang, emoticons, and hyperlinks didn't lend itself to existing forms of discourse analysis, never mind the ethical issues of

conducting research as a "lurker". However two types of researchers that embraced online methods were able to quickly collect data in a scientifically rigorous framework; qualitative health services researchers and survey researchers.

For instance, in 2006 qualitative content analysis of over 5,200 email messages in ten ACOR lists was used to identified key themes and outcomes related to participation in the system (Michael Bowling et al. 2006). Like Ferguson's analysis of Braintalk and other sites, users of ACOR offered one another information about treatments, provided emotional support, advised one another on interacting with medical professionals, and offered many strategies for active coping (Meier et al. 2007). In 2005, oncology researchers created an online structured survey of fatigue and quality of life for patients with cancer of the bone marrow and were able to rapidly recruit a sample of over a thousand individuals through the ACOR mailing lists to validate their instrument (Mesa et al. 2007). This became a highly cited paper in the field including references in clinical trial designs and the development of new patient reported outcomes. Challenges from that era remain relevant today, however, such as the difficulty of calculating an accurate response rate and thereby accounting for response bias (Michael Bowling et al. 2006).

Although early days, credible scientific researchers were now successfully applying formal methods to extract useful data from content that had been previously construed as "purely anecdotal" or the purview of "internet users with too much time on their hands". To really take off as a research tool, however, the early online patient communities would have to find a way to maintain the benefit of textual narrative, strong relationships, emoticons, and hyperlinks, but also to support these with the objective data with which researcher were more familiar. Websites that patients found useful lacked credibility to researchers because they relied on "anecdote" or unsystematic clinical observations, which sit at the bottom of the pyramid of medical evidence for treatment decision making (Guyatt et al. 2000). In the layers above this are physiologic studies, observational studies (and systematic reviews thereof), randomized controlled trial (and systematic reviews thereof), and at the top of the pyramid the "N of 1 randomized trial" (Gabler et al. 2011). In order to climb the pyramid, online communities would take advantage of two converging technological trends: increased patient access to electronic medical records (EMRs), and the burgeoning availability of collaborative "Web 2.0" technologies that upgraded the level of measurement accessible to patients.

From Sharing Anecdotes to Controlling Their Data

> Gimme my damn data; it's all about me so it's mine—E-Patient Dave

The traditional doctor's office visit involves the creation of structured data (the medical notes) from unstructured anecdote (the medical history). Historically, medical notes have served as an *aide memoire* for clinicians and a means of record keeping and communication with colleagues, but were never intended to be read by patients. The advent of electronic medical records (EMRs) means that barriers for patients to access them are lowering rapidly. Systems such as "My Health*e*Vet"

within the Veteran's Administration (VA) have shown that most patients (84 %) find accessing their records useful, and about half felt it improved their communication with their healthcare provider (Nazi et al. 2013). While patients have been enthusiastic, physicians have shown less support and focused more on the potential for problems such as increasing their workload or changing how they would document things in the record (Ross et al. 2005). Within the United States, resistance is likely to be overcome to some extent by the Health Information Technology for Economic and Clinical Health (HITECH) act of 2009, which offers financial incentives to physicians that offer "meaningful" use of EMRs to their patients (Jha 2010). Such incentives may be needed to conquer institutional inertia; within the VA pilot, only 6 % of doctors had told their patients about the system (Nazi et al. 2013), and so widespread adoption will require continuous encouragement.

Some early patient adopters found individual benefits from their EMRs (with data managed by health providers) or personal health records (PHRs, with data controlled by patients, sometimes using imported health provider data). For example the now famous case of "E-patient Dave" started when cancer patient Dave deBronkart downloaded all of his medical records into the now defunct "Google Health". What he found was disturbing: incorrect dates, missing diagnoses, misdiagnoses, and most disturbingly of all, no mention of his allergy to steroids (deBronkart 2009). When it comes to research, scientists might do well to heed E-patient Dave's words of warning, but also his call to arms at TEDx Maastrict: *"Let patients help"*.

Patient, Know Thyself

In medical measurement, the ability of *objective* tools and measures to circumvent biases of human perception makes them preferred data sources wherever possible. However they require trained professionals with sophisticated equipment, and despite medical advances many conditions lack objective measures. In such cases, *subjective* measures may be applicable, though they are inevitably less reliable, repeatable, or sensitive.

A typical subjective clinician-lead tool is the clinical symptom assessment, which manifests as an interview between doctor and patient. For a wide range of illnesses, standardized measurement scales have been devised, often with accompanying training to ensure a level of consistency across clinical staff. Such measurements are the mainstay of many clinical approaches to studying and managing serious, chronic or progressive illnesses. The biggest limitations of clinical symptom reporting are that they are resource intensive (relying on expensive staff) and cannot be done frequently enough: typically, that means once or only a few times each year.

Another source of subjective data derives from the patient's perspective, unguided by a clinician such as a symptom diary or a patient-reported outcome questionnaire. Symptom diaries might be prescribed by clinicians managing a chronic asthma patient, for example, as a tool to tease out particularly complex interactions between environment, behaviour and disorder, which occur primarily outside of the care environment. Individually, symptom diaries may allow individuals to pinpoint

behaviours or circumstances that precipitate worsening symptoms and at a group level became increasingly recognized as potentially valuable in clinical trials (Santanello et al. 1997). One significant limitation of these tools (particularly when completed on paper) is the "parking lot effect" which finds less diligent patients scrambling to complete their assigned homework in the minutes just before their next clinic visit (Stone et al. 2003).

Keeping with the topic of patient-reported measures, self-report questionnaires have historically been common in psychiatry, where a patient's own thoughts are the most reliable predictor of outcomes. Measures such as the Beck Depression Inventory (Beck et al. 1961), developed in the 1960s differed from earlier psychiatry models in that they took the patient's direct experience (and even the terminology they used for symptoms) and quantified them through simple scoring systems that mapped to theoretical models of disease (such as anhedonia, negative self cognitions, and somatic symptoms in the case of depression). Outside of psychiatry, self-report gained increasing prominence in the late 1980s as measures of "health-related quality of life" was increasingly recognized as an important adjunct to objective measures (Tarlov and Trust 1989) in conditions like human immunodeficiency virus (HIV) or cancer.

More recently a broader range of generic and disease-specific questionnaires have been developed, called "patient reported outcomes" (PROs), which have raised to a standard of reliability where appropriately developed (Food US. Drug Administration 2009) self-report questionnaires are increasingly used as endpoints in trials (Basch 2012), and indeed these tools have come to form a core feature of the next generation of online tools for medical human computation. Crucially, they provide patients themselves with access to the same standard of measurement as has traditionally been available only to medical professionals. This wider distribution of self-made and shareable tools would have been welcomed by the founders of the Whole Earth Catalog and has recently formed the basis for a more disruptive approach to computing outcomes in medicine: finally, we can let patients help.

Medicine 2.0

The Internet loves a buzzword, and in 2004 the term "Web 2.0" was coined to describe the plethora of Internet sites that allowed users (rather than central authorities) to collaborate and contribute dynamic (rather than static) user-generated content in entertainment (e.g. YouTube), photography (e.g. Flickr), knowledge (e.g. Wikipedia), and even friendship (E.g. Facebook) (Van De Belt et al. 2010). "Medicine 2.0" (or "Health 2.0") refers to the use of these Web 2.0 technologies (and philosophies) to increase patient participation and empowerment through the use of new information and communications technologies (with or without professional involvement), using social networking to develop a new type of health care collaboratively through more effective use of medical data (Van De Belt et al. 2010).

One community that exemplifies this movement is the website PatientsLikeMe. The company was founded in 2004 by brothers Ben and Jamie Heywood to help

Fig. 1 Patient profile of the inspiration for PatientsLikeMe, Stephen Heywood

find creative solutions for their brother Stephen Heywood, who was diagnosed with amyotrophic lateral sclerosis (ALS) aged just 29. A family of MIT graduates, they partnered with their friend Jeff Cole to create a site that took the scientific rigor of a clinical trial and matched it with the personal connectivity of an online dating site. Based near their *alma mater* in Cambridge Massachusetts and opened in 2006, the online ALS community had features of the older online communities like Braintalk such as a forum, but focused on structured, rather than unstructured data. ALS patients could enter their own PRO, the ALS Functional Rating Scale (Revised) (Cedarbaum et al. 1999), which was widely used in clinical trial research but not normally available to patients. Not only did they make it available but they helped patients to graph their displays visually over time, with the declining slope of their ALSFRS-R score profiled against the relative rates of decline of every other patient "like them" in the system (see Fig. 1). In addition, every member who completed this PRO was given a virtual avatar to represent them, known as the "stickman", which boiled down the technical questions of the ALSFRS-R into an easily

understood set of iconography colour coded from green (an unaffected body region) to red (severe disability). Therefore a patient with severe problems speaking and swallowing (red head on their stickman) but who was still able to walk, breathe, and self-care (green legs, chest, and arms) would be able to quickly scan through the list of other patients and so quickly find a "patient like me".

Virtuous Circle

By using these newly acquired PRO tools to upgrade their level of data collection from anecdotal to observational, patients set a new benchmark in elevating their discourse to become closer to that of traditional health researchers. Learning more about themselves through PROs and visualization tools yielded benefits too, illustrated as a "virtuous circle" in Fig. 2. This diagram outlines the ways in which patients on PatientsLikeMe can not only track their progress with medical data, but use this data to connect with other patients who are most like them; they don't just have to listen to whoever is chattiest in the forum or logged on most recently, they could search for another ALS patients who was young at their age of onset, who lives in Massachusetts, or who had tried baclofen for stiffness. Tools which were unavailable even in the most advanced ALS clinic in the world were now in the hands of patients to collect their own data, form their own hypotheses, and eventually, develop their own research.

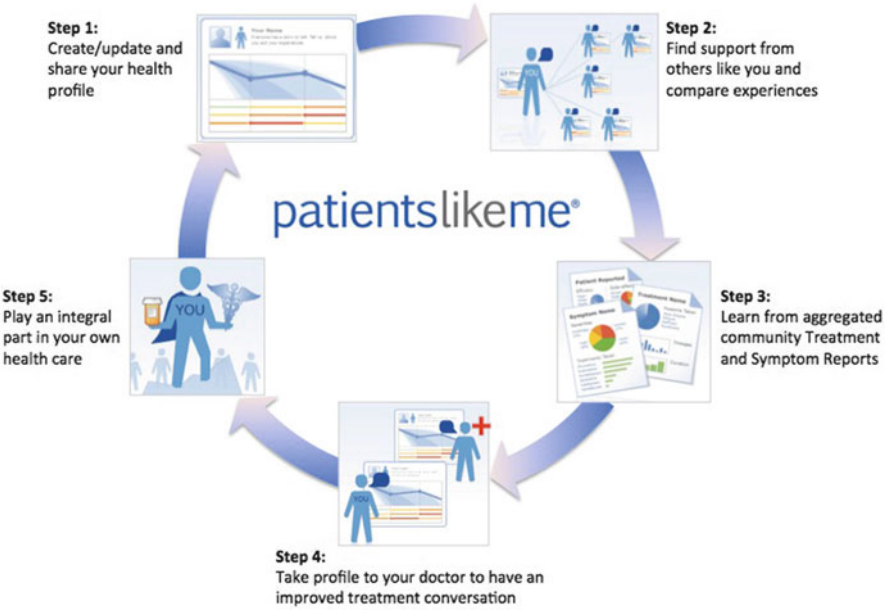

Fig. 2 The "virtuous cycle" of shared human computation underlying PatientsLikeMe

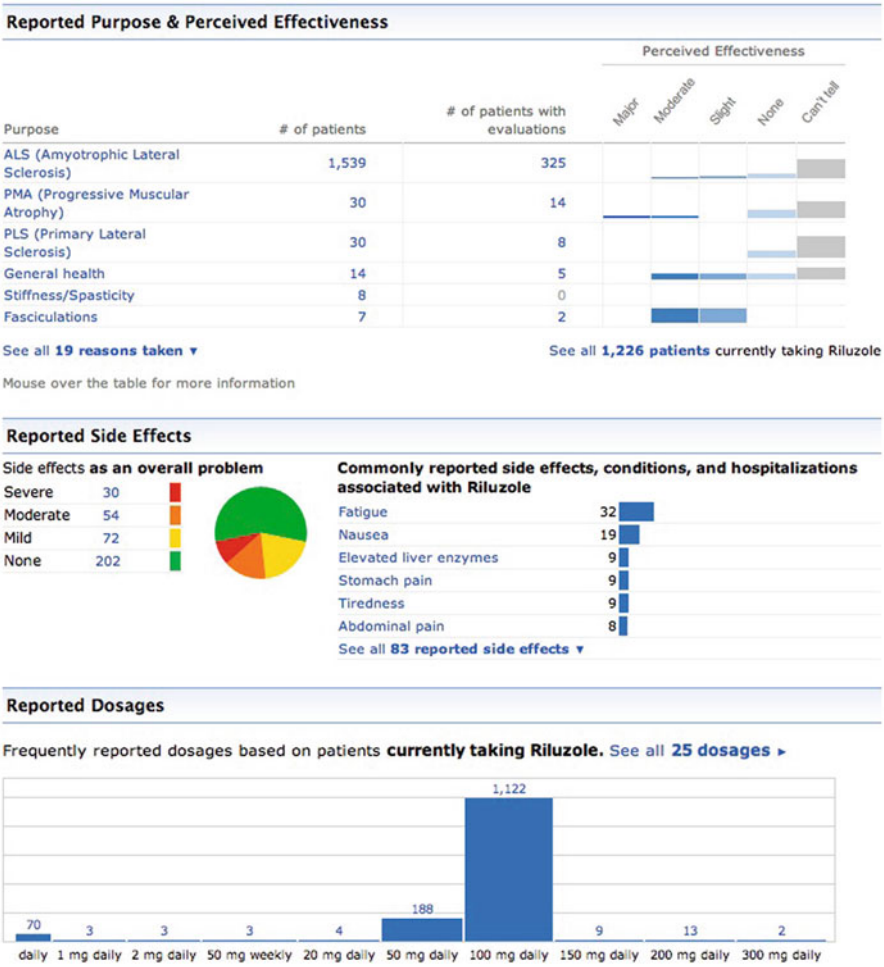

Fig. 3 Treatment report for the drug Riluzole® consisting of aggregated self-report data from individual ALS patients. Note that recommended dosage of Riluzole is 50 mg twice daily; this "real world" data shows outliers (300 mg) but also a low rate of erroneous entries (e.g. 1 mg daily)

Even without the desire to personally conduct their own human computation work, the site encouraged the interplay between the provision of social support in creating machine-readable data, and encouraged members to donate this data towards aggregated reports which allow members to see themselves in the context of, say, everyone else taking the same drug as them along with the side effects and dosage range (Fig. 3) or experiencing the same symptom including the severity and treatment options (Fig. 4).

Preliminary evidence for the virtuous cycle comes from two self-reported surveys in the peer-reviewed literature. The first was conducted in six communities

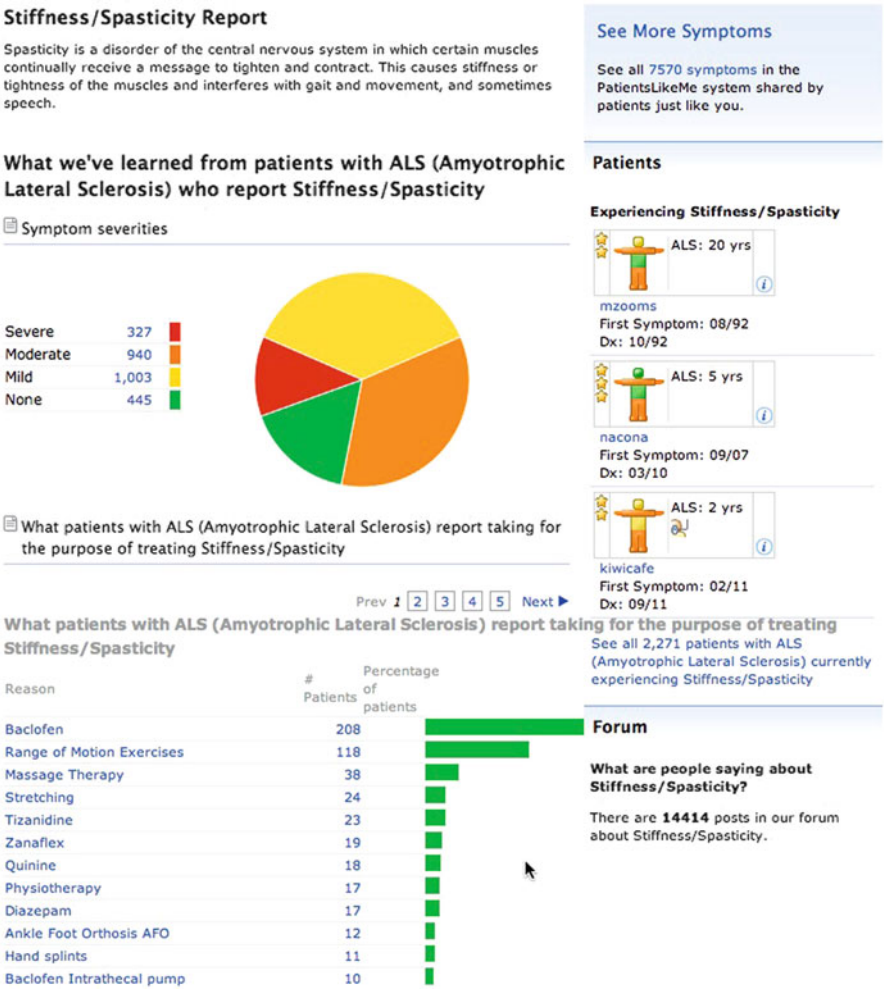

Fig. 4 Symptom report for stiffness and spasticity among ALS patients including perceived severity, recommended treatments, individual reports, and relevant forum-based discussions

(ALS, MS, Parkinson's disease, HIV, fibromyalgia, and mood disorders), and identified a number of perceived benefits to those engaged in the circle (Wicks et al. 2010). More than half of patients responding (57 %) found PatientsLikeMe to be helpful for understanding the side effects of treatments—in part because rather than the flat list of alphabetically listed side effects identified in trials that are reported in the prescribing information, the data available to patients comes from other patients like them, filtered through their unique experience but aggregated through visualization (Fig. 3). Most patients (72 %) reported value in using the system to learn about symptoms they experienced (Fig. 4)—by allowing patients not only to

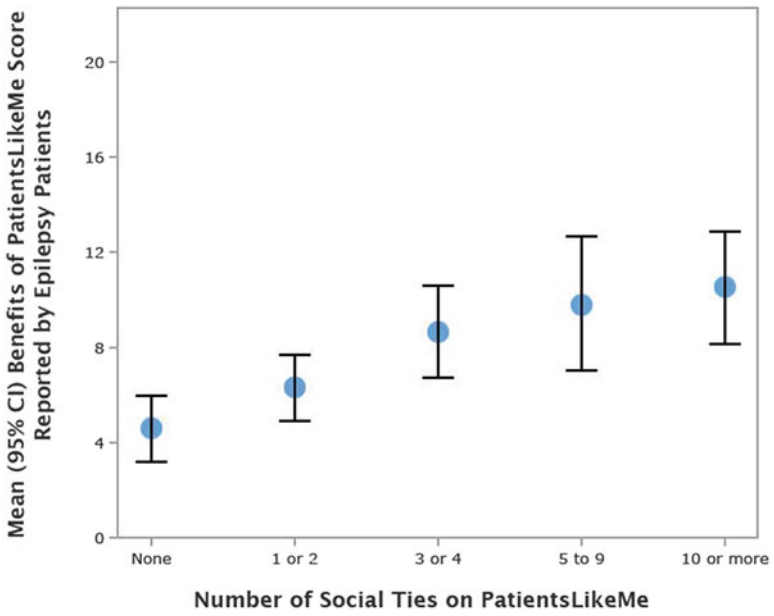

Fig. 5 "Dose effect curve for friendship"—Benefits experienced from using PatientsLikeMe (y-axis) against number of "connections" with other members in the community (x-axis) (Reproduced with permission from Wicks et al. 2012)

longitudinally track their own symptoms but also to use powerful search tools to help find and connect to other patients with similar experiences in order to learn from them. Perhaps most encouraging of all, a substantial minority (42 %) reported being more involved in their treatment decisions as a result of their use of the system and most patients (66 %) reported their healthcare professional team were supportive of their use of PatientsLikeMe.

One question arising from this study was the degree to which these benefits were only really accruing to those who engaged more deeply in the system, and therefore the cycle. A second study was created to replicate the original study in a newer community, epilepsy, and to build in an additional hypothesis to test whether the degree of social involvement was relevant. Within the epilepsy community a number of similar benefits were reported in terms of observations about treatments, symptoms, and management of their condition, as well as some intriguing condition-specific benefits which have triggered further study; 30 % of users felt they got better care as a result of using PatientsLikeMe, 27 % improved their medication compliance, 27 % reported reduced treatment side effects, 18 % felt they needed fewer ER visits, and 17 % reported that specifically from interacting with the site they had sought out an epilepsy specialist (Wicks et al. 2012). The epilepsy study also shed further light on the role of peer interaction in use of the site. In constructing a score of potential benefits experienced by epilepsy users, ranging from 0 to 20, the most predictive variable (even accounting for number of logins) was the number of social ties that a given patient had with other patients on the website (Fig. 5). Importantly

then, it is not just the presence of data-tracking tools or even aggregated reports that was key in providing energy to the virtuous circle—it was interaction and engagement with other human actors who could interpret, contextualize, and help to synthesize diverse sets of data to address specific challenges. The authors referred to this finding as "a dose-effect curve for friendship". This finding is current being explored further in a more formal setting in collaboration with the Epilepsy Centers of Excellence (ECOE) of the VA.

Accelerating Research Through Human Medical Data Sharing

Since the site's early days, the PatientsLikeMe team included a number of scientists who worked alone and in harmony with external collaborators to begin climbing the pyramid of scientific credibility that could be achieved on the platform. An early study drew upon the experience of forum members experiencing a highly unusual symptom; uncontrolled outbursts of yawning—dozens, even hundreds of times per day, which in patients with a weakened jaw muscle due to the atrophy of ALS could become painfully dislocated. In response, the PatientsLikeMe team added a symptom "excessive yawning" to their standard battery of items and within a matter of weeks gathered data from 539 ALS patients and published the results, their first scientific output in a peer-reviewed article (Wicks 2007). By contrast, in prior studies using paper-and-pencil based methods it had taken a year's solid recruitment efforts just to recruit 104 patients from the largest ALS center in Europe (Wicks et al. 2007).

While "building a better mousetrap" for observational research was somewhat gratifying, the unique nature of online communities to enable human computation would help the team not only climb the credibility pyramid, but bring new entrants to participate. Cathy Wolf is a quadriplegic psychologist, writer, and poet who has lived with ALS for 17 years, and is only able to communicate via advanced technologies such as muscle sensors, eye gaze trackers, and even brain-computer interfaces. One day, as she used PatientsLikeMe to measure her decline in function on the ALSFRS-R scale, she scored a zero and realized that as far as researchers were concerned, she'd "bottomed out" of the scale. In response she wrote *"I have NOT bottomed out! If (researchers) can't think of objective measurements for PALS on the ventilator, let me educate him/her."* For instance, on the "communication" part of the scale, once a patient lost their ability to speak or write, they scored a zero. But as Cathy herself said *"there is a range of communication… Some talk, some use a physical keyboard, some use an onscreen pointing keyboard, some use multiple switch scanning, some single switch scanning. These are related to motor ability."* It became clear quickly that digital technology was allowing patients to have new experiences of disease that had never been measured before. And so, with Cathy as a co-author, PatientsLikeMe conducted the first study to survey patients who'd "bottomed out" of the traditional research scale to find out what they could still do. In all, they gathered data from 326 patients, many of whom were too sick to make the journey to hospital for traditional research visits, and together the team

published a study that developed three new "extension" items called the ALSFRS-EX (Extension) which covered the remaining ability of patients to communicate emotion in their facial expressions; to manipulate switches with their fingers, and to move around inside their own homes even when they couldn't walk outside (Wicks et al. 2009). In this way, the participation of citizen scientists enabled by an online platform allowed patients to be "participants" in research in the truest sense of the word.

In 2013, PatientsLikeMe was awarded a grant by the Robert Wood Johnson Foundation which will permit the development of an "Open Research Exchange" to allow developers of new PROs to prototype their questionnaires on PatientsLikeMe to more rapidly validate them with patient input. It is hoped that by accelerating the developing of PROs, patients with more conditions will be able to realize the same benefits as the ALS community has found in having a PRO they can control that is taken seriously by the wider medical community.

From Phenotype to Genotype

Around the time PatientsLikeMe was making strides in the phenotypic world of human computation, on the other coast of the United States in Mountain View California, 23andMe was doing the same for the genomic world. Founded in 2006 the company sold genetic tests normally only available to clinicians and researchers direct to the consumer ("DTC Genetics") in order to provide entertaining insights ("how closely related are you to Cleopatra?"), support genealogy research ("what's your maternal haplotype?"), and increasingly, support clinical research ("what sort of mutations do we find in individuals with Parkinson's disease?"). The company caused ethical controversy at the time of its launch because in later versions of the product, consumers could reveal their risks of highly predictive single nucleotide polymorphisms for disease-causing genes such as BRCA-1 (breast cancer) and APOE-4 (Alzheimer's disease).

Leaving such controversies aside for our purposes, the primary interest to medical human computation lies in the company's commitment to combine genotypic and phenotypic data to find new discoveries. 23andMe first started establishing their scientific credibility by replicating benign known findings such as genetic variation underlying skin freckling or hair curl using online distributed methods (Eriksson et al. 2010). This replication would set the stage for later discoveries such as new reported associations between genes and human health traits like myopia (Kiefer et al. 2013). In support of further opportunities for human computation, participants in 23andMe are able to download their data and upload it to other "citizen science" communities. In this way many people can be "data donors" and leave the more complex analysis to those with the skills and expertise to do so (Swan et al. 2010). Although the advantage clearly lies with the organization itself to most rapidly make new discoveries, it is certainly possible that the next generation of health discoveries could originate from among their 200,000 members.

Supporting the expanded need for self-educating among their members, both 23andMe and PatientsLikeMe embrace "open access publishing" which allows a wider swathe of readers to access their scientific output than might otherwise be possible—in this way their members can more readily contribute data, ideas, and their own analyses to the human computational field. By contrast, the traditional medical establishment does research *to* patients—it extracts data *from* them, *blinds patients* in clinical trials as to their own treatment arm to maintain the integrity of the experiment, and then withholds the findings from the very people who participated by publishing their findings in closed-access journals. No wonder then, that as patients become more educated and engaged, they also become more dissatisfied with the status quo and less willing to be an obedient subject of centralized computation.

Whose Trial Is It Anyway?

Observational studies and correlational analyses are all well and good, but they never cured a patient of anything. The only way that Medicine 2.0 could effect major change in medicine was to climb the next layer of the pyramid to human research trials. The double-blind randomized placebo controlled trial (RCT) has been a gold standard of medicine since the 1950s. Randomizing one group of patients to receive active treatment and another to receive a sugar pill, (with neither patients nor healthcare professionals knowing who was in what group) was the only reliable way to factor out many biases which could cloud the quality of medical decision-making. For all the plaudits it has earned in medicine, however, patients themselves have not always been so enthusiastic.

In the early 1980s, people with HIV had no effective treatment and a bleak prognosis. In 1988 more than a thousand patients vocally expressed their anger and frustration to the US Food and Drug Administration (FDA) at their headquarters in Maryland about the maddeningly slow pace of RCTs to find effective treatments for their conditions. In the context of a rapidly lethal and infectious disease, waiting for early stage testing to be completed in healthy volunteers, rather than patients, felt like an unnecessary delay. After all, the patients reasoned, what safety issue that a drug has could be worse than HIV? Furthermore the idea that a doctor might intentionally provide a placebo that he knew would do nothing seemed particularly objectionable. Within a week the FDA updated their regulations to speed approvals for HIV research, but the seeds of patient revolution had already been sown.

Some HIV patients taking part in trials would swap pills or redistribute them amongst their fellow patients, even giving their medication to sympathetic pharmacists to try and decipher which were placebos (Murphy 2004). The groundswell of dissatisfaction among HIV patients was an early signal that patients could "hijack" a trial and even force regulators to speed their bureaucratic processes under enough pressure, but what happened next was truly revolutionary.

Gastrointestinal stromal tumor (GIST) is one of the most severe of the 200 or so cancers with which one could be diagnosed. Affecting the soft tissue of the gastrointestinal tract, GIST frequently metastasizes rapidly to the peritoneum and liver, is resistant to chemotherapy, and, left untreated, confers a median survival time of less than 2 years after metastasis. As a relatively rare disease with an incidence rate of only 6–15 cases per million people per year, recruiting sufficient patients to power a clinical trial has always been challenging, and so the role of non-profits in GIST has included not just the provision of information or support, but also assistance with clinical trial recruitment. In 2000 a large clinical study was initiated by the drug company Novartis® for their new drug Gleevec® with an aim to recruit some 800 patients with the disease to test for the drug's effect on survival and metastasis.

In addition to the trial data collected by Novartis, an Internet based patient non-profit, "The LifeRaft Group", set about collecting patient-reported questionnaires over the Internet from those taking Gleevec, their dosage, side effects, response to treatment, and via their caregivers, even their death. No participant was excluded from the study; it included all comers whether they were already in an authorized clinical trial or were receiving the drug from their doctor as part of routine care. Using retrospective self report data of all comers, the LifeRaft Group correctly anticipated the result; patients most recently reporting the lowest dose of Gleevec died after a median of 5 years, while the median patient most recently taking the higher dose were still alive at the time of survey (Call et al. 2010). Subsequently verified by traditional RCTs, the authors themselves were keen to point out that their data provided a "real-world complementary perspective to that seen in investigator-initiated randomized trials". It wasn't perfect, but it was a pivotal point showing that patient self-reported data had utility.

Nevertheless, in the case of GIST the data was submitted by a distributed group of patients but analysis remained in the hands of a centralized organization. Later in the 2000s, as tools for collaboration and analysis became more widely available, human medical computation seized upon a small finding to demonstrate its full potential.

A Patient-Lead Clinical Study Online

"Now, we monitor, watch and wait."—Leo Greene—ALS patient and journalist (http://www.dailybulletin.com/leosstory/ci_8089973)

In early 2008, an Italian group of clinicians published a study entitled "*Lithium delays progression of ALS*" in the prestigious *Proceedings of the National Academy of Sciences* (PNAS) (Fornai et al. 2008). In their study they compared 28 ALS patients on Riluzole®, the only approved drug for ALS (which provides 2–4 months additional lifespan (Miller et al. 2012)) to just 16 ALS patients on Riluzole and lithium carbonate. During the 15-month observation window a third of the Riluzole-only patients died, compared with none of the group supplementing their Riluzole with lithium. Even before the PNAS paper was officially published word spread through

Fig. 6 PatientsLikeMe's ALS lithium study tool profile of advocate Humberto Macedo (Reproduced with permission from Wicks et al. 2011)

the community as enterprising ALS patients used "Google Translate" to interpret Italian-language conference abstracts describing the findings. As a widely available drug for the treatment of bipolar disorder, many patients with ALS begun sourcing the drug off-label from sympathetic doctors, in the hope that they might see the type of near-miraculous slowing of disease that Fornai et al. reported (Frost et al. 2008).

This time it was patients who lead the charge. ALS patient Humberto Macedo (living in Brazil) and ALS caregiver Karen Felzer (whose father suffered from ALS) collaborated to build a website where ALS patients could find out more about lithium, and links to a "Google Spreadsheet" that would allow patients who had obtained lithium off-label to track their progress using self-reported side effects, dosages, and even ALSFRS-R scores. Around this time the research team at PatientsLikeMe believed they could offer a more robust method of data capture and so modified their platform to collect more orderly structured data, such as ensuring that the ALSFRS-R was presented in a consistent fashion, and that side effects could be entered in a structured manner to allow later analysis (see Fig. 6).

In the space of a few months, there were over 160 ALS patients reporting their use of lithium with the tool; ten times the sample of the original PNAS paper. Furthermore, the open nature of the tools available such as Google Spreadsheets and PatientsLikeMe meant that patients themselves were extracting the data, visualizing it, and running their own statistical tests on the data to try and discern treatment effects. Although they lacked the statistical or methodological sophistication of a formal clinical trial, it was hoped that if Fornai et al.'s results were true, then even such crude measurement would discern a treatment effect quickly. For the first time in a decade the mood of the ALS community was ebullient and energized—an effective treatment was finally here.

Unfortunately however, the halting of progression failed to materialize. Patients worsened, some of the early advocates (sadly, including both Humberto

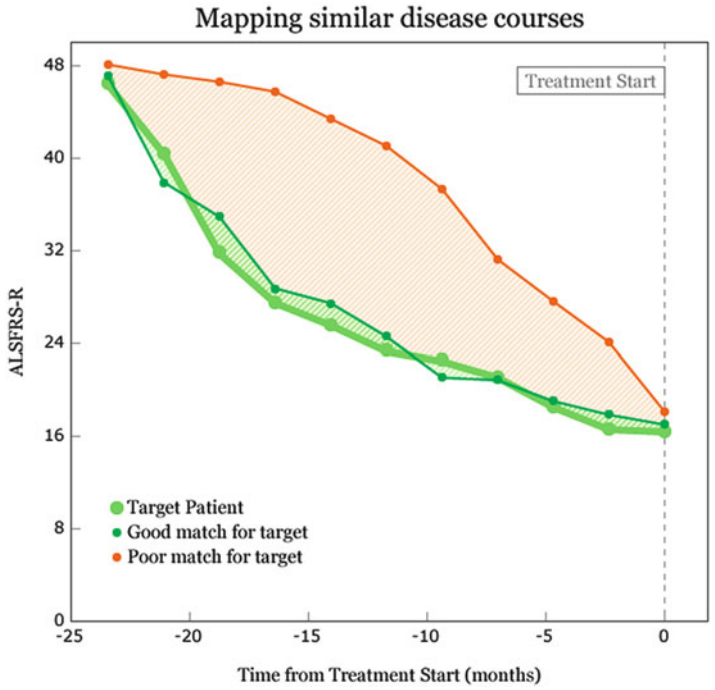

Fig. 7 Dots represent ALSFRS-R scores of two hypothetical patients progressing along different paths, who by traditional matching criteria would be considered comparable. The ellipse describes distance in progression curves; the PatientsLikeMe matching algorithm minimizes this area for each patient (Reproduced with permission from Wicks et al. 2011)

and Karen's father) passed away from complications of their ALS. The research team at PatientsLikeMe worked through a number of analytical approaches that would resolve the question as best as it could be worked through with the data to hand, finally culminating in a publication in *Nature Biotechnology* that described a novel matching algorithm, the disappointing results, and a de-identified copy of the entire ALS dataset so that others could try it for themselves (Wicks et al. 2011).

In order to account for the lack of a placebo arm in their open, self-reported clinical trial, PatientsLikeMe harnessed the collective power of the broader ALS community who were *not* self-experimenting with lithium by matching between three and five members of the ALS community with each lithium-taking patient. Unlike a traditional RCT that can only collect data at the study's baseline, the online community had already been passively submitting their ALSFRS-R outcome data for years before lithium was even identified. Therefore the researchers were able to match each lithium-taking patient with those non-lithium taking patients who were most similar to them along their entire disease course up until the point of deciding to take the drug (Fig. 7). This was the first truly patient-initiated study where an entire community donated their collective experiences to identify a potential cure

for their disease. Unlike Gleevec in GIST, however, sadly lithium didn't work. The five traditional RCTs commissioned by government funders and non-profits around the world were all halted for futility—nobody ever replicated Fornai et al.'s findings again (Armon 2010).

How Continuous Automated Measurement Supports Human Computation

In each of the examples provided thus far, online medical discoveries have relied upon patient-reported data; whether it's survival in GIST through responding to a survey, the identification of traits through questions on 23andMe, or the completion of validated patient reported outcome measure on PatientsLikeMe. Because this data is easily provided by patients and, pending validation, can potentially rise to the same level of clinical relevance as a clinical measurement, they were an obvious place to start. But relative to these subjective measures, a truly automated, sensor-based objective measurement has the potential to add an additional level of sophistication: the measurement might be taken without any human intervention or initiation, for example, by a passive sensor like an accelerometer or GPS at the same point in time every day. This would allow surreptitious objective medical recording of a patient's health state such as their mobility, mood, or other physiological characteristics absent the "Hawthorne Effect" which means people tend to alter their behavior when they're being measured. Thanks in large part to tremendous advances in technology over the last century, such automated, objective, continuous symptom measurement is emerging outside of the intensive care unit or astronaut training center.

With the advent of "always on", objective, wearable monitoring devices such as the FitBit One, Nike+, and Jawbone UP, coupled with smartphone apps, it is now easier than ever to continuously record health-related measures such as pulse rate, activity, sleep duration and calorific intake. Enabled by this technology, a loose-knit global movement called "The Quantified Self" has emerged. These individuals use technology to record continuous objective data about their health, often sharing it freely with like-minded individuals to amass large-scale records of changing health data over time. Such data can be mined using statistical tools to detect changes in health status or even perform "n of 1" experiments (Swan 2012) which in a medical context are at the peak of the evidence pyramid. Correlating these sensor-derived data feeds with environment, social or genetic data may lead to insights that, if acted upon appropriately, could significantly alter the course of an individual's health or disease. It is not an unreasonable prediction that, as the monitoring technology becomes more ubiquitous and tangible, and individual and public health benefits become clear, we will likely see that continuous objective symptom recording will eventually become the norm for a significant fraction of the population.

Much as Moore's law predicts that the number of transistors on an integrated circuit doubles every 18 months or so, an extension of this law predicts that the price-to-performance ratios for many kinds of digital consumer products, such as

smartphones, drops at a corresponding rate. This means that objective symptom monitoring technology will inevitably become so inexpensive and non-intrusive, that data from an entire population of millions could be recorded at almost negligible cost. A company like Apple or Google's access to smartphone data, for instance, would be unparalleled in human history and tantamount to a large-scale real-time sensor network. Wearable computing technologies such as Google Glass add a new dimension of head-mounted image or video capture—imagine tracking an outbreak of flu through facial recognition software in a population of citizens wearing such devices.

Glimpses of this new era of population-scale symptom recording are emerging through studies of the mass-scale details of telephone conversations held by mobile telephone companies, or Internet search firms. These studies have unearthed characteristic patterns of social interactions that appear to correlate with mental health and psychosocial disorders, such as the mapping of Google searches for mental health problems mapping to seasonal trends (Ayers et al. 2013). Based on billions of internet keyword searches from across the globe, the Google Flu Trends project has even been able to predict localized influenza outbreaks in real-time, with better accuracy and more rapidly than traditional influenza monitoring methods used by the US Centers for Disease Control (Dugas et al. 2013).

Because such observational data on symptoms has previously been unavailable, epidemiology has, historically, been unable to model the time variation of symptoms across a population. The arrival of ubiquitous personal digital sensing technology will likely change this situation, so that very large scale, classical epidemiological models will, for the first time, have the empirical data to make real-time predictions on the outcome of critical public health decisions.

The Ultra-low Cost, Global Reach of the Parkinson's Voice Initiative (PVI)

There is no simple blood test or other biomarkers for another neurological disease that requires careful monitoring: Parkinson's disease. Parkinson's is generally assessed in the clinic behaviorally, by asking patients to tap their fingers together in front of them or by observing the rate at which their limbs shake or how they walk. Research by one of the authors (Max Little) and collaborators, has demonstrated that it is possible to quantify the symptoms of Parkinson's disease on an objective, clinical scale, by a sophisticated combination of algorithms that analyze voice recordings and statistical machine learning (Little et al. 2009). Using lab-quality recordings, it was shown that this approach can achieve up to 99 % accuracy in replicating an expert clinical diagnosis of Parkinson's (Tsanas et al. 2012), and an error of less than the disagreement of two qualified experts, about the severity of symptoms (Tsanas 2010). The simplicity of recording the voice using a wide array of digital microphones available to most of the global population, raises the

question of whether the standard, global telephone network could be used. In this way the potential for patients themselves to take charge of their own sensors and integrate them into their own daily management is far greater than when collection is tethered to sophisticated lab equipment.

To address this, one needs to ask: will this technology work outside the lab? For a technology to be ubiquitous, it should be possible to reproduce the results without using specialized hardware or controlled settings. The PVI is an attempt to test the accuracy of the voice-based Parkinson's algorithms on telephone-quality recordings collected in a largely uncontrolled way. Participants contributed to the project by calling a number in one of nine countries, and going through a short set of vocal exercises lasting about 3–5 min in total. At the end of the 6-month data collection phase of the project, a remarkable 17,000 participants had donated voice recordings in English, Spanish, French and Portuguese, achieved at a total collection cost of just $2,000. At the time of writing, the analysis phase is ongoing.

Other efforts by the same group have provided people with Parkinson's disease and healthy with Android smartphones. In order to crowd-source better algorithms to help distinguish patients from controls, the authors collaborated with the Michael J Fox Foundation (MJFF) to release the passive behavioral data collected alongside clinical and other demographic data to a "Kaggle" analysis competition for a grand prize of $10,000. The competition received over 20 novel submissions, of which 2–3 were deemed by the co-applicant to be 'high quality'. These submissions included diverse feature extraction and machine learning approaches for making predictions, with, in some cases, around 90 % accuracy in separating Parkinson's patients from healthy controls.

Once diagnosed, Parkinson's disease is particularly interesting because the drugs used to treat its symptoms are very effective; a moderately disabled patient who cannot move, speak, or think clearly when they are "off" as a result of their disease can be restored to an active and fluid "on" state through the use of dopamine-stimulating drugs such as levodopa or dopamine agonists. These drugs, however, have side effects such as uncontrollable movements and can wear off in effectiveness over time—therefore it's important to carefully manage the drug regimen and fine-tuning of the time of day and dosage of anti-Parkinsonian medication can optimize the proportion of "on" time during the day for several hours.

Sara Riggare is a woman who has lived with Parkinson's disease for several decades, and as part of her PhD studies at the Karolinska Institute is building smartphone applications that allow her to monitor her degree of disability objectively through a finger-tapping test which is prompted by a medication reminder. In this way Sara serves as a "patient-researcher" who intends to "co-produce" research and crowd source data and potentially management algorithms through the use of distributed data tools. Although an early pioneer, we propose that as subsequent generations are diagnosed with life-changing illnesses they will view it as their responsibility not just to participate in studies, but to design them, to run them, to publish them, to critique them, and to harness their learnings to manage their own condition day by day with the support of their healthcare providers.

Implications for the Future

In this chapter we have seen how the potential for medical human computation evolved from the unstructured qualitative discussions of the pre-web Internet to modern forms of scientific co-production and human computation that empower patients to truly participate in research. As the potential of these systems matures we believe that there are major gains to be made in simple-to-use analytics platforms that can de-mystify some of the more technically complex aspects of medical research such as statistics or hypothesis testing, and make clinical discovery for patients that live with the disease as common an activity as online shopping. These co-producers will no more need to analyse the statistical complexities underlying hypothesis testing than an online shopper needs to understand logistics chains.

There remain a number of major challenges to be addressed to attain this goal however. First is the issue of bias—to date it seems likely that the most active users of online systems are those patients who are younger and more educated (Bove et al. 2013). Although these can be addressed to some degree by over-sampling those who are under-represented, today's tools simply can't reach those who don't use the Internet or digital technology. This should get easier over time but there will probably be an inevitable "digital divide" that will remain unbridged for many people living with disease today.

Second is the issue of verification—until patient's electronic medical records can be securely authenticated at low cost it is impossible to confirm that someone self-reporting themselves as having ALS or Parkinson's disease truly does so. Although today there are few incentives for fraudulently pretending to have a serious disease like this, as the healthcare establishment begins to take more notice of such data, this is likely to change. It will be important not to lose some of the benefits that anonymity provides, however, and many patients remain afraid they will lose insurance cover or be discriminated against if they can be explicitly identified alongside their medical information. Until these policy failings are resolved there will be an inherent tension between identification and anonymity.

Third is the issue of privacy—the examples given in this chapter have concerned some of the most severe and disabling diseases a patient can experience—and so perhaps these individuals are less likely to mind the risks to their privacy against the severity of their diseases. But the worry for many developed health economies is not the rare lethal disease; it is the widespread chronic disease like diabetes, obesity, mood disorders, or back pain. It remains less clear whether patients with these disorders are as engaged with their health to submit regular data for research purposes nor whether they are willing to risk their privacy for the sake of conditions which may only be of mild or moderate intensity. Within this are very real concerns about discrimination, stigma, and loss of opportunity such as insurance coverage or hiring due to disclosures around health, which can only be addressed by legislation. Ferrari and Viviani explore these issues in more detail in the chapter "Privacy in Social Collaboration".

Finally there is the delicate issue "*cui bono"* (who benefits?). Patients donating their data to for-profit companies free of charge, analysts donating their cognitive surplus to improve the lives of people they'll never meet, and new organizations having access to big datasets that reveal more than we can possibly predict about ourselves—we approach this issue with hope and optimism based on the mission-lead nature of the organizations involved so far. But there is nothing to say that the tools described here couldn't also be used *against* patients—in raising insurance premiums on those who don't take their GPS-confirmed exercise, in refusing medical treatment to those who don't submit themselves to passive monitoring, in manipulating the prices of interventions to those who are shown to benefit the most through a quirk of genetics, perhaps even governments restricting the rights of people thought to be exposed to communicable diseases.

We agree with the patients who have themselves pioneered in this field; for now, the benefits outweigh the risks, but we must remain diligent and vigilant. The potential for empowering patients to join researchers in the quest to fight disease is incredible—we don't accelerate progress just by "standing on the shoulders of giants"—we accelerate progress by creating more giants.

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