When Collecting Patient Data Gets *Electronic*: The Upsurge of eHealth and The Importance of Big Data to Shape Modern Health Care

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The launch of the first smartphone, followed only a few years later by tablet computers, has profoundly changed the way we communicate and interact with each other. This upheaval is even more remarkable as it was accompanied by increasingly uninterrupted internet connectivity. The new information and communication technologies (ICTs) are now ubiquitous in our daily lives. It is easy now to share and process near-immediate information, should it be objective or subjective, private or professional, with those around us.

The field of health care is obviously no exception. Some even perceive medicine as one of the areas where new ICTs are the most promising [1]. No need to recall that information plays a key role in medical decision making. Much of the medical decision is based on information collected from the patient. In addition to objective biomedical parameters, physicians also consider patients' behaviors, risk factors, exposures, preferences, experiences, and feelings about diseases and treatments to make a decision.

Patient-reported outcomes (PRO) research and tools were developed for these reasons. PROs are usually collected in a standardized fashion during medical visits, clinical trials, or observational studies. This will probably not disappear, notably because it is a way to guarantee the quality and reliability of results. But now, admittedly, this information can be supplemented and enriched by new ICTs. ICTs increasingly allow the quasi-continuous monitoring of the patient's experience. The patient can complete a questionnaire and report on her own experience at home, at work, or at any other place of occupation by simply strumming on her mobile and connected device.

Implementing electronic PRO (ePRO) in a study could be seen as a burden as, compared to a paper questionnaire – the « e » typically adds studies (e.g., usability testing), logistics, and the costs (e.g., equipment; software development, testing and validation; patient and personnel training; data security). These additional steps and costs, however, need to be balanced against extra confidence in patient >

compliance, data accuracy, reduced variability of measurement, regulatory conformance, and study efficiency [2]. Regulatory guidelines on electronic source data and ISPOR Task Force recommendations help recognizing the enhanced integrity and accuracy of ePRO data collected by electronic devices [3-4]. In addition, randomized clinical trials being more and more complicated including samples which may not be representative of the real life population, initiatives of patient-centered websites such as www.patientslikeme.com, in collecting in a short time, data directly from a cohort of patients may support effective decision making [5].

Beyond efficacy data to support regulatory approval or reimbursement dossier, ePRO may also serve as safety endpoints [6]. The current pharmacovigilance reporting practice is so far from optimal that EU member states now accept direct consumer reports without medical confirmation. Direct information given by patients through electronic systems may benefit the assessment of the benefit/risk ratio of a new drug. This is not completely new, however, and ePRO serve already in a number of conditions to detect safety issues and to evaluate the tolerability of a new therapy, e.g. the Justice Symptom checklist in HIV [7] or the eColumbia Suicide Severity Rating scale (eC-SSRS) [8]. ePRO not only help to detect serious adverse events for notification to competent authority, but they may also improve the management of patients enrolled in clinical trials or followed in clinical practice, especially in case of warning symptoms of a severe or fatal adverse event. The standards for developing a self-reporting of potential adverse events by patients (PRO-AE), however, need to be set up. For example, should we use standardized questionnaires that may lack the ability to capture an unknown side effect, or open questions with all the technological challenges of data processing? Also, the involvement of proxies or caregivers is needed in some conditions, as there are some symptoms that patients may not be aware of and thus not able to report adequately (e.g. cognitive dysfunction, loss of memory).

On top of the efficacy and safety endpoints, ePRO is a powerful tool to engage the patient, at a population and individual levels, in the drug development process and in the management of his/her disease. Hence, before the beginning of the trial, surveys can be conducted to better understand the disease burden and endpoints of importance for the patients. Once the drug is on the market, clinically relevant actions can be based on ePRO scores, e.g., to increase drug adherence, improve communication quality between a patient and his/her doctor or ensure personalized care [9].

The step towards the "electronization" of PRO is even more remarkable as an increasing number of physiological and biomedical parameters can also be collected by intelligent applications. Blood glucose in diabetic patients, blood pressure in hypertensive patients, and peak flow in asthmatic patients are just a few of the concrete examples of medical parameters that new ICTs can empower the patient to follow non-invasively and quasi-continuously. Hence, the physician can have more than a few measures taken several weeks or months apart; instead, the evolution of a patient and her/his response to a given treatment can be appreciated quasi-continuously and can be sent to *subjects* themselves (e.g., direct feedback), to health care *professionals* (e.g., individual patient assessment or aggregated statistics of a targeted group of patients), or to the *organizations* (e.g., large-scale well-being assessments of employees). This unprecedented access to a large volume of real-time data coupled with the technology to analyze them on the fly can dramatically improve the evaluation of clinical and health outcome.

To measure and improve people's physical and psychological wellbeing, novel technologies have been developed, including a large-scale mobile application (SocialMood Labs, www.socialmoodlabs.com). The latter allows real-time contextual measurements to control for the numerous variables impacting measurement accuracy (i.e., *when, where,* and *how* the measurement is performed). The application presents users with a wide range of tests and questionnaires through the phone notification system. The application guarantees the randomization of the sampling throughout the day. The notifications can be presented even when the smartphone is not connected to the Internet. This is critical as behaviors, emotions, cognitions, and memories are likely to be biased if they are measured exclusively when users are online [10]. Tests involve various smartphone sensors, including the microphone, the touch screen, and the camera. These sensors yield rich and comprehensive assessment of patients' health. Direct and personalized feedbacks can be sent to the users via their phone. This technology can improve health and outcome evaluation since patients themselves perform measurements, in their environment, and continuously throughout the day. Tests can be implicit or explicit to avoid biases.

Beyond helping individuals measure and improve their well-being, such a technology also represents a tremendous opportunity for health care. In a large ongoing project, more than 70,000 subjects are currently reporting their everyday physical and psychological states. Using 1,000,000+ data points, the importance of emotions to predict people's behavior was recently demonstrated. Indeed, the happiness level of individuals at time t reliably predicts the type of activities they choose to engage in at time $t+1$ [11]. Five activities were significantly predicted by mood: working, resting, eating, doing sports, and leisure. This study indicates that mood significantly influences people's decisions about what to do next, stressing the importance of emotions in shaping decision making. This project highlights that rich data enable the detection of important effects that are typically hidden in many covariates. Contextual variables can be measured and regressed out.

The technology used by SocialMood Labs captures many real-time symptoms involving for instance movements, cognitive abilities or stress), *health behaviors* (e.g., sleeping, eating habits, time spent exercising), and *medication impact* such as treatment efficacy, adverse events and adherence. The control of many real-time factors leads to a decrease in the unexplained part of the variance and to an increase in the statistical power of currently health-related tests and measures that do not use such real-life momentary assessment. Interestingly, due to the large sample of data collected, a level of statistical power of similar magnitude as the current standard assessment tools could be achieved with much fewer subjects, substantially reducing the cost of clinical studies. Taken together, using ecological momentary assessment can have a great impact on the future of health and well-being research, allowing for the collection of big and rich datasets that will improve the diagnosis, the prognosis, and ultimately, the patient outcome.

There are, however, several regulatory, ethical, and methodological limitations/challenges in the use of these ICTs in the field of health care. The major challenge of all online surveys and cohorts is making sure that a patient self-reporting symptoms indeed has the condition under study. Current organizations running patient-centered websites acknowledge that they are currently unable to tell whether this is the case. Paul Wicks, a leader from PatientsLikeMe, stated in a recent blog that "to check would be hugely time consuming and might change the social contract of the site, essentially saying, we don't believe you, prove it." [5] Some kind of verification will inevitably be necessary if self-reported data are to be used in a dossier for drug approval or HTA assessment. While self-reported data in these patient-centered websites are issued from real life, there may be a selection bias, as patients that join those sites or used mobile health applications may already be highly involved in their care and comfortable with sharing health information. These "active seekers" may not be representative of the patients as a whole. There is also a responsibility of empowering patients with information kept before by doctors. Such is the example cited by PatientsLikeMe [5]. This website asked patients with amyotrophic lateral sclerosis (ALS) to complete a questionnaire (ALS functional rating scale) commonly filled-in by physicians. In the past, the resulting score was not shared with the patient. This tool has 12 questions that pertain to speech, swallowing, walking, etc., indicating the severity of the disease and how it would likely progress. PatientsLikeMe gave free access to this information for the patients themselves and provided them with the corresponding predictive curve of disease evolution. With only a few data points, it was possible to estimate if the patient has 10 years to live, 18 months, or less. On the one hand, that is useful information for the planning of the rest of patients' lives [5]. On the other hand, delivering such sensitive information may be harmful and stressful for patients not willing to know. Such information delivery should be associated with the possibility for the patient to contact or visit a psychologist or a caregiver. There is also a responsibility of the owners of all these increasing web-based cohorts, mobile health applications, registries, and databases developed by many stakeholders, with all the data being shared through

social networking, to ensure the privacy and confidentiality of ePRO and personal data. Finally, ePRO databases, especially through patient-centered websites use algorithms, especially for establishing a diagnosis with a certain probability (www.symcat.com), based on patients' self-reported information. Checking the adequacy and validity of these algorithms is of paramount importance.

The growing use of mobile technologies and the Internet opens new opportunities to capture the patient's voice and shape modern health care. In particular, the use of ICTs in health care facilitates the collection of larger volume of real-time and contextual measurements that enables the gathering of richer data to assess efficacy and/or safety of a product. In addition, ICTs facilitate the management of patients (enrolled in clinical trials and during clinical practice) and increase patients' responsibility in their own health. More work, however, is needed to guarantee the integrity and confidentiality of data collected through these new technologies.

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