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Ethical concerns caused by integrative patient empowerment solutions for personalized medicine*

W. Kuchinke

Abstract— **Personalized medicine that promises targeted treatments with high therapeutic effectiveness requires an unmatched degree of participation of the patient. To enable this high degree of patient empowerment, the project p-medicine developed a Patient Empowerment Tool that is part of a clinical research infrastructure consisting of data management, data warehouse, biobank access, imaging, simulation and decision support tools. Patient autonomy is enhanced by giving patients access to their data and by providing means for informed choices and consent. Because the highly integrative nature of the Patient Empowerment Tool raised ethical concerns, an ethical requirements analysis was carried out, resulting in the assignment of five ethical clusters. The one concerned with the Patient Empowerment Tool was used to identify several concerns, like the access to unfavorable information or negative diagnosis, incomprehensible risk/benefit display, and other factors that may overstress certain patients. From the ethical point of view, the user interface should contain different profiles and control mechanisms to protect the patient and to provide an adaptable and intelligent display of information, sufficient guidance and help for users from vulnerable populations as well as for patients with life threatening diseases.**

I. Introduction

Advances in genomic and proteomic research have led to the development of targeted diagnostics and therapeutics that apply knowledge of an individual's genetic and physiological conditions for a more personalized approach to healthcare. A patient and a physician might use pharmacogenomics information to make more informed choices about alternative treatment regimens. But personalized medicine is a disruptive innovation that requires the development of new processes, new way of collaboration, software tools and business models for stakeholders involved. Personalized medicine will shift the nature of the patient's relationship with the physician and will increase the patient's ability to understand and to control the choice between treatments. Increasingly, patients will be supported by Patient Empowerment Tools to ensure their autonomy. Two key challenges have emerged for patient participation and personalizing medicine: first, the loss of privacy associated with tailoring medication and treatment to a particular individual and second, the increasing needs for information gathering, data sharing, data interpretation, and associated with it the improvement of ways to inform and train physicians and patients.

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W. Kuchinke is with the Coordination Centre for Clinical Trials (KKS), Heinrich-Heine University, Düsseldorf, Germany (0049-21181-16142; e-mail: kuchinke@med.uni-duesseldorf.de).

II. Personalized Patient Empowerment

It has become the current understanding that for successful healthcare an integrated approach is necessary, involving predictive, preventive, personalized and participatory medicine. This approach results in major changes, like the shift from medical decisions to informed therapeutics based on diagnostics and a "patient-centered" approach [1]. Therefore, beyond the integration of genomic medicine and predictive biomarkers into practice, patient empowerment and a more participatory medicine are gaining importance [2]. This requires, besides sharing of information between patients and healthcare providers, new insights in patient involvement, such as informed consent, patient reported outcomes (PRO), decision support aids and new ethical issues. Patient empowerment and participatory medicine are especially crucial in paving the way towards optimized healthcare for life-threatening diseases as well as complex and chronic diseases.

The FP7 project p-medicine (From data sharing and integration via VPH models to personalized medicine) [3] is developing an IT infrastructure to accelerate personalized medicine and personal clinical research [4]. p-medicine tools, like ObTiMA data management system, Patient Empowerment Tool, data mining, biobank access, and Oncosimulator will all interact with each other and be accessible through a single web portal. Such a highly integrated infrastructure enables the new level of information integration required for personalized medicine, but also has raised new levels of ethical concerns.

III. Integrative Patient Empowerment Tool

p-medicine develops a Patient Empowerment Tool with the aim to help patients to understand their medical documentation and to empower them to make informed choices [5]. It is part of a clinical research infrastructure consisting of data management, data warehouse, biobank access, imaging, simulation and decision support tools. In line with the aim to support personalized clinical trials, the empowerment tool enables patients to understand their whole data set that the hospital has collected and the different kind of data that were collected to inform a personalized treatment. This process implies that patients are able to understand medical statements, as well as legal and ethical considerations. The empowerment tool will monitor and implement donors' decisions on research to be performed on data and biosamples like tissues and cells. In general, this includes the patient's written informed consent which is mandatory for participating in clinical trials and for the use of human biomaterial in research. A multi-layered consent

concept is offered, which enables patients to make individual choices. The Patient Empowerment Tool will also support the collection of patient reported outcome data (PRO), for example Quality-of-Life data. Data input covers patient data, psycho-cognitive data, biobank data, clinical trials data, and informed consent data. Output data is decision support data, data about available clinical trials, biobank information, and informed consent management. In summary, the Patient Empowerment Tool will put patients in control over the use of their data.

Software tools like clinical data management systems that are used for GCP (Good Clinical Practice) clinical trials must undergo a special assessment, called computer system validation (CSV). Computer system validation provides documented evidence that the system (consisting of hardware, software, network, users) will reliably do what it is designed to do, and that it will comply with the applicable rules and regulations. The system must operate predictably according to its specifications [6]. When an empowerment tool is employed in a clinical trial (e.g. PRO, informed consent) it must be system validated to comply with all GCP requirements [7]. For the conduct of clinical trials, ethical requirements are covered by GCP [7]. But, are all ethical issues related to the use of a Patient Empowerment Tool considered in GCP and related regulations? There are a number of ethical challenges to the development and clinical application of software tools for personalized medicine, like the ones about privacy, safety, autonomy, phenotypic expression, justice and genetic group identities [8], that because of the integrative nature of these empowerment tools are only insufficiently covered by GCP and related regulations. Here we present an ethical evaluation of the Patient Empowerment Tool of p-medicine supporting patients in participating in cancer clinical trials and based upon the evaluation suggestions for the development of user interfaces that may be exemplary for similar tools.

IV. Approach and Methods

Legal and ethical experts in the p-medicine group conducted an ethical analysis and identified ethical concepts in correlation to the Patient Empowerment Tool. Based on the 4 pillars of medical ethics [9] (beneficence / non-maleficence, privacy / confidentiality, autonomy, justice) ethical concepts were put into relation to the use of the tool in personalized clinical trials [10, 11]. The identified relevant ethical aspects were organized in ethical requirement clusters, corresponding ethical concerns were formulated and suggestions for a user interface model addressing these concerns were developed.

V. Results

After identifying ethical issues, five ethical requirements clusters were assigned: informed consent, access to own data, display of information, data collection (patient reported outcome) and vulnerable populations. The Patient Empowerment Tool increases patient autonomy giving patients access to his/her data and allowing differential decisions about the use of their data and samples. The ethical issues associated with employing an empowerment tool reach from general ones (privacy, decision, risk for patient, risk / benefit assessment, autonomy), to ones specific for clinical trial participation (adverse events, equipoise, trial withdrawal, quality of life, Ethics Committee, informed consent) to ones concerned with vulnerable populations (life threatening diseases, pediatric trial, geriatric studies, cancer treatment) (Figure 1).

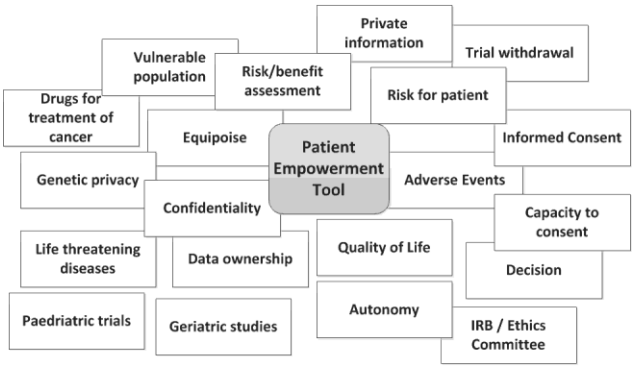

Figure 1. Ethical requirements cluster for the Patient Empowerment Tool.

A. Analysis of ethical requirements cluster

In a next step, it was analyzed, what can go wrong with using an empowerment tool for the patient (Table 1), and how the protection of patients' autonomy can be improved by employing a suitable software user interface (Table 2). To assess the ethical impact of personalized medicine, we must also anticipate how patient empowerment might go wrong in the practice [12]. The Patient Empowerment Tool may give the patient access to unfavorable information and a negative diagnosis, or wrong information and it may as a consequence overstress certain patients. In addition, it may display data in a way difficult to understand (e.g. prognosis or simulation data), and represent data in a confusing way. To prevent these difficulties, the user interface might be adapted in a suitable way (Table 2).

The ethical requirements analysis showed that most issues arise due to the lack of an intermediary level between

TABLE I. ETHICAL ISSUES OF PATIENT EMPOWERMENT TOOL

Nr.	Scope of Ethical Requirements Cluster	
	Cluster	***Issues***
1	Informed consent	Capacity to consent, trial withdrawal, decisions about secondary use of data and samples, autonomy
2	Access to own data	Access to images, unfavorable results, understanding lab data, false positive results, false negative results, privacy, right not to know, wrong information
3	Display of information	Understanding medical terminologies, legal and regulatory issues, risk/benefit evaluation, probabilities
4	Data collection	Quality of Life / adverse event, understanding of medical terminology, privacy, usability, user interface
5	Vulnerable population	Life threatening diseases, pediatric / geriatric studies, emotional stress, decision, risk/benefit, equipoise

TABLE II. ADAPTION OF USER INTERFACE TO ETHICAL ISSUES

Nr.	Elements of patient empowerment	
	Element	*User interface*
1	Decision-making power	Suitable and adaptable display of information, correctness check
2	Access to information and resources	User profiles, help and guidance functions, decision what to show and what to hide
3	Range of options for choise	User profiles, help and guidance functions
4	Assertiveness	User profiles dependent information display
5	Critical thinking	Help and guidance functions, communication functions
6	Learning about and expressing anger	User profiles, help and guidance functions, communication functions
7	Feeling part of a group	User profiles, communication functions
8	Understanding that patients and trial participants have rights	User profiles, help and guidance functions, personalized adjustment
9	Feeling that the individual can make a difference	Help and guidance functions, clinical trial information, communication functions
10	Change in one's life	User profiles, help and guidance functions

the patient and the data sources and information display. Usually, during the use of Patient Empowerment Tools, patients have access to their data without a context, filter or a physician providing context, help and guidance. Therefore, the software solution and here especially the user interface (GUI) must provide the necessary supportive functions (Table 2). The display of information must be adapted to the abilities of the patient and to his/her anxiety level. In this way, patient's autonomy and decision ability can be supported in a better way than through searches in social media, where exposure to medical information is often rather unstructured, biased and lacks quality control.

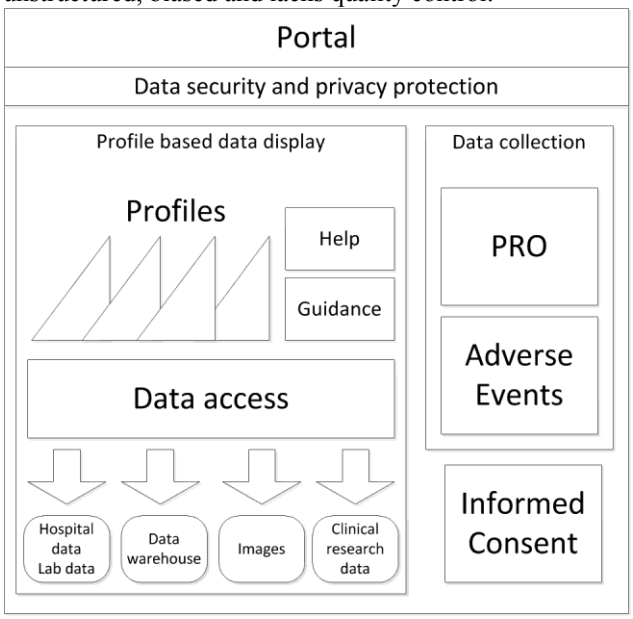

Figure 2. Suggestion for the structure of the user interface of the Patient Empowerment Tool providing profiles, help and guidance services (PRO=patient reported outcome, user profiles are shown as triangles).

B. Model for an ethical compliant user interface structure

We suggest a model for a user interface structure where the central access is through a portal and data security as well as privacy is built into the framework (Figure 2). Data access goes through a series of adaptable profiles with support by help and guidance functions. The user interface should include user profiles for different levels of medical literacy, computer literacy and anxiety (Figure 2). In a first line of support, profiles for cancer patients, patients with life-threatening diseases, pediatric trials, and chronic diseases are provided. In a second line of support, the patient can modify his/her profile and change a subset of specifications, for example define which information he wants to see or which information should be hidden (the right to know vs. the right not-to-know). Sufficient on-line guidance, special help for users from vulnerable populations, special help/guidance for patients with life threatening diseases have to be linked to the corresponding profiles. In this way the patient using the Patient Empowerment Tool to access his data or to give an informed consent is protected against the impact of unfavorable information that may put him into a situation where he has to decide under emotional stress. On the other hand, help and guidance is provided to support patients to understand medical terminology. For example, the p-medicine infrastructure will generate simulation and prognosis data (e.g. simulation of tumor growth based on identified mutations and drug resistances). Because the adequate display of these simulation and prognosis data may be a problem for different groups of patients, depending on the profile chosen different kinds of data and different ways to display data (e.g. as percent vs. absolute numbers) support the capability of the patient to understand results.

Connected to the profile we suggest the provision of adaptable help and guidance tools. The connection to the different profiles allows the adaption of the help functions to the specific needs of the user. It should be possible for the patient to change specifications for these help and guidance functions according to his specific needs, which may change according to his therapeutic situation that is different after knowing of a life-threatening disease, during a treatment plan, and after participating in a clinical trial. Practical examples would be the provision and display of information about risks, alternatives and benefits, adaption of the user interface to the level of comprehension (e.g. option to acknowledge certain information), include the possibility for the patient to obtain more information, to accept or decline information, inclusion of decision aids (which identify biases or misconceptions), display of risks according to the patient's risk perception (e.g. Number needed to treat, absolute risk reduction, risk expressed in natural numbers).

C. Autonomy for the informed consent process

The Patient Empowerment Tool will ease the way patients will understand and write their informed consent, allowing for a fine-grained expression of choices. This approach may

enhance the capacity to understand the informed consent by providing information to appreciate any consequences of trial participation and thereby support patient's autonomy and risk/benefit evaluation important for an independent choice. To support this approach, sufficient information about a clinical trial can be provided (e.g. covering research procedure, and purposes, potential risks, benefits, and the ability to withdraw from the trial), enabling the potential trial participant to understand the consequences of participating in a trial.

Another requirement demands that all capture of patient data with p-medicine tools has to be accurate, reliable and correct [13]. When p-medicine tools are not used correctly, they will provide the Patient Empowerment Tool with inaccurate data and in the end will pose a risk for the patient. Thus, the system should provide validating functions to avoid errors. Another key aspect that has to be considered is the privacy of the participants. Patient data has to be kept confidential at all steps and only processed by authorized parties [14].

VI. Discussion

Advocates of personalized medicine maintain that it is revolutionary not just in what it can reveal, but in how it will enable patients to take control of their health. But we should not assume that patient empowerment always yields positive outcomes [12]. The promise of patient empowerment has another side that is the relocation of responsibility for health care away from social and medical persons onto the patient. Here the Patient Empowerment Tool can provide sufficient online information for the patient, aided by a user-friendly and intelligent GUI, to help him to understand the medical condition, the treatment, and the study and to appreciate the consequences of participating in a trial.

The commonly used definitions of empowerment are mainly based on the view that autonomy is part of people's self-determination, and that empowerment is a procedural process [16]. Patient empowerment needs to be seen as a dynamic and creative process that is formed by the individual's own psychological conditions, values and activities [17]. Thus, a Patient Empowerment Tool must consider ethical as well as associated psychological aspects.

The Patient Empowerment Tool is especially considering the psychological aspects to protect vulnerable users. Vulnerable patients usually show a higher likelihood and severity of harm to the dangers of clinical trials. Thus in ethical respects, the stronger party has to protect the weaker one and protection is also a consequence of securing the principles of autonomy, non-maleficence and justice [18]. Factors to consider in determining vulnerability of a clinical trial participant include the impairment of the competence to protect own interests (e.g. when choosing informed consent), the voluntariness of the subject's consent and the presence of physical / psychological conditions which leaves the subject especially liable. In this respect, a Patient Empowerment Tool can be especially useful for the vulnerable patient. Considering the ethical issues that might arise due to vulnerability and life-threatening diseases of these patients, the Patient Empowerment Tool can, by employing user profiles and help and guidance functions, adapt to their special needs.

In summary, an ethical assessment is a useful addition to the usual requirements engineering process, validation and usability testing of patient empowerment software.

VII. Conclusion

The development and employment of a Patient Empowerment Tool can profit from a comprehensive analysis of ethical issues. By considering ethical requirements, in addition to social and psychological components of the functionality, suggestions for an improved and helpful user interface structure could be made. Using filters, profiles and guidance components the user interface of the tool is able to provide tailored responses to the information needs of the patient.

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