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Table of Contents

Introduction

The overall aim of the U-PGx project is to implement guided personalised medicine and pharmacogenomics testing in routine health care in several EU countries. One of the main challenges of the project is to take account of the diversity of health systems and European citizens, in order to obtain a new model of personalized medicine, through pre-emptive PGx testing (across a multitude of gene-drug combinations and without focusing on specific drugs or biomarkers), whose can be applied to all EU countries. The mission of U-PGx is to demonstrate that pre-emptive genotyping can be used in clinical practice and in routine patient care, in cost-effective, and with better outcomes for patients.
However, while pharmacogenomics offers many possibilities, it also raises many social, ethical and legal issues that need to be addressed before its implementation in routine health care systems. Our WP is dedicated to this problematic and must ensure that the project complies with European standards and requirements on clinical research relative to implementation of PGx. This includes ELSI education to all participants in this project.

At the European level, the legal and ethical frameworks keep pace with scientific developments. The trend is towards the harmonization of national legislations of Member States (MS) and Regulations are increasingly replacing the Directives, in order to impose common rules to all MS and to limit national interpretations. There is a continuous updating of ELSI framework on which the U-PGx project must be based.

The implementation of preventive PGx tests in a real clinical context implies which an important volume of data on multiple phamacogens is discovered and collected. It raises many questions such as patient information, patient informed consent, storage and management of results in the best interest of patients and in case of genome exploration at large, secondary findings, anonymization of the data or protection of patients' rights and of their privacy.

The aim of this deliverable is to take stock of the elements which will serve as an ethical and legal basis for the future guidelines of the U-PGx project, following collect and consideration of the different needs, expectations and wishes of the U-PGx participants. This was achieved through a quantitative analysis based on responses to a questionnaire sent to the UPGx partners in order to identify their education needs.

Methodology

In order to identify ethical, legal and societal implications (ELSI) education needs of the U-PGx participants, we circulated via emails during October 2016 a detailed questionnaire which we asked them to return.

The questionnaire is attached at the end of this document.

1/ Structure of the questionnaire

Identification of the questions posed to the U-PGx Consortium members

The proposals of education we submitted in our questionnaire were based on:

- Experience with other genetic testing technologies and previous European projects in which our team members participated and the ethical challenges they already encountered.
- The current legal reforms occurring at the European Union level in the domain of genomics
- Elements already identified in an internal work in our team and listed in the Minutes of the 6 month's report WP8 2016-06-09.
- Brainstorming on the discussions and needs expressed by the members of the consortium during the U-PGx meeting organized on the 27-28 September 2016 in Athens.

The first part of the questionnaire was posing general questions. The aim was to identify means and methods of education we could develop to produce useful work for project participants in the future. This questioned, for example, the need for information or the interest in procedural elements about ethical and legal domains. Preferences were also interrogated about communication to the general public, but also to members of the Consortium among themselves on their ELSI training needs, for example with the proposal to organize internal debates on ethical issues.
The second part of the questionnaire was focusing on specific issues which seemed relevant to the U-PGx project. Today, the genome sequencing technologies (in particular the whole genome sequencing) and the data processing methods are constantly evolving. Proposing a solid legal framework in which clinical practice can effectively develop genomic medicine is one of the major challenges facing by the European Union. It is in this direction that legal changes at national and Community level have been undertaken in recent years and promise to upset the functioning of routine healthcare systems. This part of the questionnaire was also divided in two parts. Firstly, the shifting nature of the current legal framework for personalized medicine requires constant vigilance and to be informed of

developments, given that current and future scientific research projects in the European Union will be subject to new requirements (e.g.: including texts like the General Data Protection Regulation or the In Vitro Diagnostic Medical Devices Regulation). Secondly, personalized medicine includes ethical issues which are inseparable from clinical reality; that is why researchers and clinicians (and more generally all those working in the U-PGx project) must be prepared and informed on concrete issues such as consent, protection of patients' privacy, return of incidental findings, etc.

At the end of the questionnaire, a specific part was devoted to open questions where respondents could freely express their needs not presented previously.

In the first part of the questionnaire, we asked to answer the questions just by "yes" or "no", with the possibility of making additional comments. In the second part we added, for each topic, proposals of education forms (possible multiple answers):

- a stand-alone training session
- education included in another event of U-PGx (e.g. conference)
- on line training
- access to on line documentation

2/ Questionnaire time-line

In our time-line, the initial closing date to receive the questionnaires filled in was October 31, 2016 and the months of November and December were our period of analysis of results. We have analysed the answers which we present here mainly on quantitative aspects in order to produce the report D8.2 on ethical issues, guidelines, governances model and principles fort patients included in U-PGx (month 18) with a thorough qualitative analysis.

As the report could be updated to month 18, the questionnaire continued to circulate until May 15, 2017, in order to gather as much information as possible on the education needs of U-PGx participants.

Results

Of the total questionnaires sent (37), we received 16 responses. All returned questionnaires were complete and all respondents used the pre-responses we had incorporated. In addition to the identified ethical issues, we received four additional proposals on other issues we have listed at the end of this report.
To the question "would you like more information on this subject?" for each identified issue,

the responses were predominantly positive but there was always at least one negative response.

1: Identified ethical issues: general questions

Templates for information to patients, consent forms, material transfer agreements

Although senior researchers in U-PGx are used to such practices, it may be important to assure that young researchers throughout the project have the necessary basis to conform their research in compliance with the ethical and legal framework operating at date. That is why previous international projects including biomarkers like MeDALL[1] or EuroTARGET[2], in which our team has already participated, can serve as a basis and example of these procedural questions.

On this point, apart from two negative responses, all the participants in the questionnaire responded they needed templates for all our proposals to information to patients, consent forms, material transfer agreements and general information about previous projects (maybe discussions considering mistakes and lessons learned in order to be prepared in case they appear). A guide for the health researcher, with information on the legislation in force in different areas was also requested.

Communication with the general public about genetic matters

In our questionnaire, we reminded to the U-PGx consortium members how communication with the general public also had its ethical dimensions and how it was important to consider this issue in future publications and in public events of the U-PGx project.

We received 2 negative responses and 14 positive responses (including eight without additional comments). The analysis of the responses indicates the need for documentation on how to communicate with the general public regarding pharmacogenomics: thinking on a strategy to sensitize the general public (not only the scientific public) and how to give an understandable but scientifically and ethically correct information, information about press releases in EU countries, templates for oral presentations when the study results will be

[1] MeDALL (Mechanisms of the Development of ALLergy): http://www.medalldatabase.com/
[2] EuroTARGET (Targeted therapy in Renall cell cancer: Genetic and Tumour related biomarkers for response and toxicity): http://www.eurotargetproject.eu/main.asp?VID=1&kat1=10&kat2=157&kat3=

disclosed, existing examples of communication[3] were thus mentioned as needs. Education included in another event of U-PGx was also once requested.

General ethical framework in Europe

Considering that ethical compliance is a main requirement of EU research projects and that pharmacogenomics raises many questions (underlying exploration of the genome) such as patient information consent, management of results in the best interest of patients, secondary findings, data anonymization, etc.; we asked participants if they were interested by training and education on this topic, as an online publication of international texts.

Apart from 1 negative response, all participants responded favorably.

Organizing debates around ethical issues

In consideration of the continuous updating of the European ethical and legal framework and our willingness to ensure that the WP8 work is a living part of the project, **we proposed to incorporate debates on a selected topical ethical issue, at future U-PGX events**, to sensitize all participants and to review their training needs.

We received 11 positive responses including 1 request for incidental findings and reporting information to patients and volunteers. We also received 4 negative responses and 1 mixed response. The respondent raised the interest of such debates on issues that the project should address during the clinical trial, but considered that the current concern was the installation and implementation of the testing procedures.

2: Identified ethical issues: specific questions

Recently applicable EU Clinical trial regulation

The way clinical trials are conducted in the EU will undergo a major change when the Clinical Trial Regulation comes into operation in 2016 (adopted on April 16 2014 and entered into

[3] The experience of the Pharmacogenomics Laboratory Open Day in Ljubljana (Slovenia) for the last four years where clinical collaborators researchers present their annual results to students, scientists, the general public and patients is an example of successful communication about genetic matters. This event could serve as a way for nourish our reflection.

force on 16 June 2014 and applicable by October 2018[4]). Actually, the entry into force will six months after publication in the OJEU notice of the European Commission stating that the EU Portal and Database are operational. The EU Portal is a single entry point for submission of information relating to clinical trials and the EU Database will contain all data submitted via the EU Portal.

Apart from a negative response, 12 respondent requested education included in another event of U-PGx on this topic. In addition, 5requested on line training and 7 requested access to on line documentation. We also received 3 requests for a stand-alone training session on this topic.

Recently adopted new General Data Protection Regulation (GDPR)

The EU has adopted a new regulation on data protection, called General Data Protection Regulation (GDPR) which aimed to harmonize data management in the MS. It replaces Directive 95/46/EC on data protection. It came into force on May 2016 and UE Member States have to apply it by May 2018. It impacts directly on the U-PGx project that will cover all the data storage and management whose use is likely to allow direct or indirect identification of patients. It requires to be respected in the data management plan.

Apart from a negative response, 11 respondents asked for both education included in another U-PGx event (and that for three of them) and on line training/documentation. 5 respondents only requested on line training/documentation. We also received 1 request for a stand-alone training session.

In vitro diagnostic medical devices regulation in preparation (revision of the IVD Directive)

The EU legislation's aim is to be adapted to the technological and scientific progress in the sector. Until 2012, it was governed by the 1998 Directive that became necessary to revise. In September 2012, the European Commission adopted a proposal for a Regulation of the European Parliament and of the Council on medical devices and in vitro diagnostic medical devices. Revisions included the extension of the scope of the legislation, for example the integration of genetic testing as IVD in a new category. To trade such products in the EU, manufacturers will have to be in compliance with the new regulation within 3 years (for

[4] The time line for the effective application of the Clinical trial regulation will be describe in the next Deliverable D8.2

Medical Devices) and 5 years (for IVD Medical Devices)**.** As all the U-PGx test are considered as in vitro medical device[5], it is of crucial importance for U-PGx participants to be aware of this regulation.

On this topic, 12 responses required on line documentation/training (and for 3 of them only on line documentation/training) while 8 responses also required education included in a future U-PGx event and one for a stand-alone training session. 2 respondents didn't want further information on this new regulation.

Exchanging samples and data between countries

The collection, storage, processing and transfer of biological samples and data lead to critical issues concerning data protection. The legal texts differ from one country to another concerning the samples and establish strict rules of use and import/export of such data and samples. These activities must ensure security and anonymity while allowing their use by researchers. Although samples will be used in the country of the patients, if exchanges are planned a solid education in the domain is needed because sample exchange is not regulated of EU level but at national level.

An education included in another event of U-PGx was requested seven times, and on line documentation and training eleven times. While two respondents didn't ask for additional information, two requested a stand-alone training session.

Return of results

The large scale or whole genome sequencing suggests the discovery of secondary results and raises the question of the communication of these unsolicited results to patient in compliance with his-her rights (eg right to/not to know). Ethically, it's the primary issue raised by the communication of results to patient and there is no consensus in Europe, so far. This question of disclosure of incidental findings must be incorporated into the informed consent form.

An education on the ethical aspects of return of results in genomics was largely solicited by the respondents. 8 of them asked for education to be included in another U-PGx event; 10 requested training and information online, especially as a reference. A stand-alone

[5] This legal regime will be analysed in the D8.2 to be delivered at month 18.

training session was also requested three times. At last, two of them did not wish further information on this topic.

Patients' rights in Europe

Genomics presents challenges in assuring the protection of basic rights. Equitable access to health care, protection of the privacy of patients and of their medical information, information and consent before collecting genetic data, are rights that pharmacogenomics must absolutely respect and implement beyond theory. Despite a desire for harmonization, at European level, that protection is implemented differently from one country to another.

On this point, the majority (9/16) of respondents would like to receive education at a conference on a future event U-PGx and also requested access to on line documentation/training. 2 respondents requested a stand-alone training session. Finally, one respondent wished to receive training but did not have a preference for form; two others did not wish to receive additional information on this topic.

3: Open questions

In addition to our questionnaire we have received requests for training and education about:

- Direct-to-consumer pharmacogenomics tests
- Over-the-counter pharmacogenomics tests
- Definition about differences between pharmacogenomics and predictive genomics tests
- A specific question on the legal framework for adverse drugs reaction and the duration of standard treatments in genomics.

4: Schematic table of ELSI needs expressed in the questionnaire

We established in a summary table all the subjects covered in the questionnaire. Numbers in parentheses indicate the number of responses received for each proposal.

Table I: *Summary of needs expressed in the questionnaire*

First part	
Templates	- Information to patients - Consent forms - Material transfer agreements
Communication with the general public	- Interest (14 respondents) - No interest (2 respondents)
Organizing debates around ethical issues	- Interest (11) - No interest (4) - Interest but for later (1)
General ethical framework in Europe	- Online publication of international texts (15) - No interest (1)
Second part	
EU clinical regulation	- Education to be included in another U-PGx event (10) - On line training (5) - Access to on line documentation (7) - Stand-alone training session (3) - No more information (1)
GDPR	- Education to be included in another U-PGx event (10) - On line training (7) - Access to on line documentation (7) - No more information (1)

Revision of the IVD Directive	- Education to be included in another U-PGx event (8) - On line training (6) - Access to on line documentation (9) - No more information (2)
Exchanging samples and data between countries	- Education to be included in another U-PGx event (7) - Access to on line documentation (8) - On line training (5) - Stand-alone training session (2) - No more information (2)
Return of results	- Education to be included in another U-PGx event (8) - Access to on line documentation (8) - On line training (3) - Stand-alone training session (3) - No more information (2)
Patients' rights in Europe	- Education to be included in another U-PGx event (9) - Access to on line documentation (7) - On line training (2) - No more information (2)
Third part	
Open questions	- Direct-to-consumer pharmacogenomics tests - Over-the-counter pharmacogenomics tests - Definition about differences between pharmacogenomics and predictive genomics tests - A specific question on the legal framework for adverse drugs reaction and the duration of standard treatments in genomics.

Conclusion

After the analysis of the responses to this questionnaire on the needs for education in ELSI of pharmacogenomics we can prioritize the following actions:

1/ Design a dedicated ELSI session in the next annual meeting of U-PGx after the consultation of the Consortium members based of the issues identified in this report.

2/ To propose and to design according to the means dedicated in the Grant

Agreement a webinar on an ELSI topic chosen amongst the identified issues.

3/ To take into account some of the issues identified in this survey to start drafting the program of the Summer School (D8.3).

In addition the possibility to offer regular updates on the advancement of the regulations' implementation and of the ethical positions relevant for U-PGx project should be considered to be drafted for example either on the website of the project or through a newsletter if it is envisaged by the coordination.

Abbreviations

ELSI Ethics, Legal and Societal Implications

GDPR General Data Protection Regulation

IVD In Vitro Diagnostic

MS Member States

U-PGx Ubiquitous Pharmacogenomics

Annex I: Questionnaire sent to participants

Proposals of education

WP8 - ELSI

In view of deliverable 8.1 Report on ELSI education needs (M12), we need to gather the needs, wishes and expectations of U-PGx participants recording education/training in the domain of ethics and related regulation.

At European level, the legal and ethical framework keeps pace with scientific developments. The trend is the harmonization of national legislation of member countries and regulations are increasingly replacing the directives, in order to impose common rules to all member countries and to limit national interpretations. There is a continuous updating of ELSI framework on which the U-PGx project must be based.

Beyond topics to be discussed, we would like to know the form in which you prefer to receive education/training. We can propose, for each topic, summer schools, special session on the ELSI aspects or inclusion of a conference on a future event U-PGx.

The following questionnaire focuses on points of interest WP8 has identified. But feel free to express needs on other topics. You will find at the end of the questionnaire an open question for this purpose.

1. **General questions**

1.1: General ethical framework in Europe.

The ethical compliance is a main requirement of EU research projects. Pharmacogenomics raises many questions (underlying exploration of the genome) such as patient information consent, management of results in the best interest of patients and in case of genome exploration at large, secondary findings, anonymization of the data. More broadly, besides what concerns directly U-PGx, ethical issues may also regard the involvement of children, patients and vulnerable populations, the use of human embryonic stem cells, privacy and data protection issues, research on animals and non-human primates. We only propose in the following topics related to U-PGx.

Do you wish education/training on the general ethical framework in Europe, as an online publication of international texts in this domain? YES or NO

1.2: Organizing debates around ethical issues.

In consideration of the continuous updating of the European ethical and legal framework, it would be interesting for the U-PGx project to set up debates on a selected topical ethical issue, at future U-PGX events, to sensitize all participants and to review their training needs. The aim is to ensure that the WP8's work is a living part of the project.

Are you interested in such debates and would you like to participate at the next meeting of the consortium? YES or NO

1.3: Templates for information to patients, consent forms, material transfer agreements.

Previous international projects can serve as a basis and example of these procedural questions. Although senior researchers in U-PGx are used to such practices, it may be important to assure that young researchers throughout the project have the necessary basis.

Do you want information about it? YES or NO

If so, please tell us which templates or information you need.

1.4: Communication with the general public about genetic matters.

Communication with the general public also has ethical dimensions and it is important to consider in future publications and public events of the U-PGX project.

Do you want information about it? YES or NO

If so, please tell us which templates or information you need.

2. Specific questions

2.1: Recently applicable EU Clinical trial regulation

The way clinical trials are conducted in the EU will undergo a major change when the Clinical Trial Regulation comes into operation in 2016 (adopted on April 16 2014 and entered into force on 16 June 2014). Actually, the entry into force will six months after publication in the OJEU notice of the European Commission stating that the EU Portal and Database are operational. The EU Portal is a single entry point for submission of information relating to clinical trials and the EU Database will contain all data submitted via the EU Portal.

Do you wish education/training on this recently applicable EU Clinical trial Regulation? YES or NO

Would you prefer?

- A stand-alone training session?
- Education included in another event of U-PGx?
- On line training?
- Access to on line documentation?

2.2: Recently adopted new General Data Protection Regulation (GDPR)

The EU has adopted a new regulation on data protection, called General Data Protection Regulation (GDPR) and aimed to harmonize data management in the MS. It replaces Directive 95/46/EC on data protection. It came into force on May 2016 and UE Member States have to apply it by May 2018. It impacts directly on the U-PGx project that will cover any data storage and management whose use is likely to allow direct or indirect identification of patients. It requires to be respected in the data management plan.

Do you wish education/training on this new General Data Protection Regulation? YES or NO

Would you prefer?

- A stand-alone training session?
- Education included in another event of U-PGx?
- On line training?
- Access to on line documentation?

2.3: In vitro diagnostic medical devices regulation in preparation (revision of the IVD Directive)

Here, the EU legislation's aim is to be adapted to the technological and scientific progress in the sector. Until 2012, it was governed by the 1998 Directive that became necessary to revise. In September 2012, the European Commission adopted a proposal for a Regulation of the European Parliament and of the Council on medical devices and in vitro diagnostic medical devices. Revisions included the extending of the scope for legislation, for example the integration of genetic testing as IVD. They will apply the new regulation within 3 years (for Medical Devices) and 5 years (for IVD Medical Devices)**.** As the entire PGx test is considered as in vitro medical device, it is of crucial importance for U-PGx participants to be aware of this regulation.

Do you wish education/training on this in vitro diagnostic medical devices regulation? YES or NO

Would you prefer?

- A stand-alone training session?

- Education included in another event of U-PGx?
- On line training?
- Access to on line documentation?

2.4: Information about rules for exchanging samples and data between countries.

The collection, storage, processing and transfer of biological samples and data lead to critical issues concerning data protection. The legal texts differ from one country to another concerning the samples and establish strict rules of use and import/export of such data and samples. These activities must ensure security and anonymity while allowing their use by researchers. Although samples will be used in the country of the patients, if exchanges are planned a solid education in the domain is needed because sample exchange is not regulated of EU level but at national level.

Do you wish education/training on these rules for exchanging samples and data between countries? YES or NO

Would you prefer?

- A stand-alone training session?
- Education included in another event of U-PGx?
- On line training?
- Access to on line documentation?

2.5: Ethical aspects of return of results in genomics.

The large scale or whole genome sequencing suggests the discovery of secondary results and raises the question of the communication of these unsolicited results to patient in compliance with his-her rights (eg right to/not to know). Ethically, it's the primary issue raised by the communication of results to the patient and there is no consensus in Europe, so far.

Do you wish education/training on these ethical aspects of return of results in genomics? YES or NO

Would you prefer?

- A stand-alone training session?
- Education included in another event of U-PGx?
- On line training?

- Access to on line documentation?

2.6: Patients' rights in Europe.

Genomics presents challenges in assuring the protection of basic rights. Equitable access to health care, protection of the privacy of patients and of their medical information, information and consent before collecting genetic data, are rights that pharmacogenomics must absolutely respect and implement beyond theory. Despite a desire for harmonization, at European level, that protection is implemented differently from one country to another.

Do you wish education/training on rights of patients in Europe? YES or NO

Would you prefer?

- A stand-alone training session?
- Education included in another event of U-PGx?
- On line training?
- Access to on line documentation?

2.7: Open questions.

If you have particular questions on ethical aspects about U-PGx, that you would wish to explore through education/training action.