Opinion Paper

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Is laboratory medicine ready for the era of personalized medicine? A survey addressed to laboratory directors of hospitals/academic schools of medicine in Europe

DOI 10.1515/cclm-2015-0171
Received February 18, 2015; accepted March 23, 2015; previously published online April 17, 2015

Abstract: Developments in "-omics" are creating a paradigm shift in laboratory medicine leading to personalized medicine. This allows the increase in diagnostics and therapeutics focused on individuals rather than populations. In order to investigate whether laboratory medicine is ready to play a key role in the integration of personalized medicine in routine health care and set the state-of-the-art knowledge about personalized medicine and laboratory medicine in Europe, a questionnaire was constructed under the auspices of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) and the European Society of Pharmacogenomics and Personalised Therapy (ESPT). The answers of the participating laboratory medicine professionals indicate that they are aware that personalized medicine can represent a new and promising health model, and that laboratory medicine should play a key role in supporting the implementation of personalized medicine in the clinical setting. Participants think that the current organization of laboratory medicine needs additional/relevant implementations such as (i) new technological facilities in -omics; (ii) additional training for the current personnel focused on the new methodologies; (iii) incorporation in the laboratory of new competencies in data interpretation and counseling; and (iv) cooperation and collaboration among professionals of different disciplines to integrate information according to a personalized medicine approach.

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Keywords: laboratory medicine; "-omics" technologies; personalized medicine.

Introduction

Results reports issued by clinical laboratories regularly provide a "healthy" population – based on reference intervals [1, 2]. While the reported results stem from a particular individual, the population perspective commonly dominates when interpreting the results. This is very important for many phenotypes under strong and genetic influences, for example, VEGF (vascular endothelial growth factor), ApoE (apolipoprotein E), and haptoglobin (60%, 30%, and 20% of genetic variability, respectively) [3–5]. References to populations have served health care excellently; however, the time has now come for a paradigm shift for laboratory data interpretation toward an increased focus on the genomics [6, 7], proteomics [8], metabolomics [9], and other individual properties of patients (i.e., sex, ethnicity, and age) [10] to provide optimal diagnosis and treatments [11]. According to the EU Commission, "Personalised medicine refers to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention" [12]. This rapidly developing science-driven approach to health care promises substantial benefits for patients, clinicians, and health-care systems [13, 14].

Personalized medicine is focused on tailoring medical treatments to the characteristics of patient's profile stratified by biomarkers [15–17]. To reach this goal, the communication among professionals, doctors, and patients should be implemented [18], with a benefit for society, industry, and patients, who can become aware of their own health care, and this may contribute to improve the adherence to treatment recommendations [19], as a recent questionnaire in Japanese population have demonstrated [20].

The implementation of personalized medicine will imply a steep increase in the number of performed screening or diagnostic tests and a larger volume of data to be gathered, analyzed, and translated into information to serve as guidance for clinical decisions [21–23]. Substantial upfront investments are furthermore needed for instrumentation, structural changes, education, and training efforts [9, 24–27].

The need to join forces to achieve this aim is clearly represented by the joining of different competencies and technologies through the organization of a constructive collaboration between different professional personnel and working units. A key role in the establishment of networks, which are essential for the development and support of this new discipline, is obviously in charge of laboratories that stand between the research activities and the clinical applications. Moreover, they should be conceived as the reference point for the meeting of different expertise and the development of integrated solutions.

While personalized medicine presents many opportunities for treating patients, several challenges have also been identified for the implementation [12, 28, 29]. It has often been difficult to translate basic research into clinic and health care, in other words "from the bench to bedside" [12]. Companion diagnostics are the most important tools of personalized medicine; however, there is a lack of regulation in this field. To date, many initiatives are also in process to harmonize the current regulatory on requirements for molecular diagnostics in Europe and the United States.

Laboratory medicine is asked to play a key role in the personalized medicine approach; however, it is not clear if this development is shared by the laboratory medicine directors and if/how some activities have been already planned at the local or national level to reach this goal. To investigate whether laboratory medicine is able to implement new diagnostic tools, expertise and commands, and the proper state-of-the-art knowledge about personalized medicine and laboratory medicine in Europe, the joint working group "Personalized Laboratory Medicine" of the EFLM (European Federation of Clinical Chemistry and Laboratory Medicine) and ESPT (European Society of Pharmacogenomics and Personalised Therapy) societies compiled and conducted the questionnaire "Is Laboratory Medicine ready for the era of Personalized Medicine?."

Materials and methods

Questionnaire

The questionnaire (Supplemental Data, Appendix A, that accompanies the article at http://www.degruyter.com/view/j/cclm.2015.53.issue-7/cclm-2015-0171/cclm-2015-0171.xml?format=INT) was based on six parts:

1. The introductive part was focused on the description of the participating laboratories.
2. Part 1 investigated the idea of personalized medicine.
3. Part 2 evaluated the role of laboratory medicine in personalized medicine.

4. Part 3 explored the available facilities to support implementation on personalized medicine in the laboratory of the participant.
5. Part 4 examined the role of laboratory medicine in supporting teaching activities for personalized medicine.
6. Part 5 considered the role of European societies (such as the EFLM and ESPT) in personalized medicine.

An official letter was sent to the national representatives of the EFLM and ESPT societies (Supplemental Data, Appendix B), inviting them to identify a selected group of laboratory directors of the main hospitals/academic schools of medicine of their countries where technological tools in "-omics," and facilities of bioinformatics, pathology, and pharmacology should be available. The questionnaire included questions and open areas for comments where the participants could express their thoughts on the different topics.

Answers from the participants were collected via the link https://it.surveymonkey.com/s/WG-PLM-questionnaire. The deadline for the questionnaire was May 20, 2014.

Results

Questionnaire: introductive part

Forty-eight laboratories from 18 European countries participated in this survey, as reported in Supplemental Data, Appendix C, Figure 1.

A personalized medicine approach represents the joining of different competencies and technologies obtainable through the organization of a constructive collaboration between institutional authorities involving professional personnel and of different competencies and working units, from research units to laboratory medicine and clinicians. Therefore, the coordinator of all these partners plays a critical role. To this purpose, in the questionnaire, we asked to participating laboratories who is the "decision maker" for the implementation of health-care policy in the hospital (question 2) (Supplemental Data, Appendix C, Figure 2).

The "decision maker" in charge for the implementation of a new health-care policy in the hospital differs throughout Europe. Different governmental institutions, (i.e., health technology assessment) and European, national, and supra-national professional societies (via guidelines) are involved, underlining the interdisciplinary nature and the need for collaboration among differ partners for the implementation of new health-care policies (as suggested in the comments).

The area of competence of the participating laboratories varied among the following fields: oncology, pharmacology, hematology, genetics, and microbiology/virology (Supplemental Data, Appendix C, Figure 3). Some of the participants were not directly involved in personalized medicine (21%).

The main analytical tests were based on molecular biology procedures (Supplemental Data, Appendix C, Figure 4). The number and kind of tests performed by participating laboratories related to personalized medicine was broad: from 100 (for hemochromatosis, JAK-2 mutation, and thiopurine *S*-methyltransferase) to 150,000 assays/year (for genetic tests) (Supplemental Data, Appendix C, Figure 5). Within each category, several kinds of assays are performed (Supplemental Data, Appendix C, Table 1).

Most (70.6%) of the participants performing laboratory activities (corresponding to 50% of total participants) showed a prior experience in the acquisition of large-scale molecular data both by analytical methods for molecular analysis (question 3) and by -omics platforms (Supplemental Data, Appendix C, Figure 6).

The EU Commission issued a document to define the "use of '-omics' technologies in the development of personalized medicine" [12], which was sent with the questionnaire in order to promote the interest, and the diffusion of this document and to collect the opinion of the laboratories on topics discussed (question 4) (Supplemental data, Appendix C, Figure 7). Only 39.5% read the document, and most of them appreciated its content, underlining the useful meaning of this reference text for the development of the personalized medicine approach.

Questionnaire: part 1 – on personalized medicine

This part of the questionnaire was focused on the opinion of the surveyed laboratories on personalized medicine. The results show that the majority of laboratories agreed about the importance of this new discipline to improve the European patients' conditions achievable through diagnostic tools and treatments tailored to individuals rather than to a population of patients (question 6) (Supplemental Data, Appendix C, Figure 8). Specific comments were that "this approach can be useful for differential diagnostics" and that "for this to become reality, however, there

needs to be a landslide breakthrough in the approach of translational research. Every body fluid or tissue of one single patient, taken during the timeline from intake to therapy monitoring and end-stage disease (cure or death) must be sequenced for RNA, DNA, proteins, and metabolites. Only then we will be able to piece the puzzle together and benefit from the obtained knowledge, saving and preventing the high cost of health care; nevertheless, a laboratory sustained that 'one size fits all' concept will be useful for the majority of the patients."

The majority opinion (87%) was that cooperation and collaboration between health-care professionals is becoming a pressing need to consolidate a personalized medicine approach (question 7). In light of this issue, the participants suggested that many actions should be performed to improve the integration of knowledge (question 8) by (i) improving new data protection laws that safeguard patient's privacy but permitting wider circulation of data for research and health care (a suggestion was represented by the electronic integration and another comment suggested to realize clear rules for the use of patient's personal data) (16.5%); (ii) implementation of new collaboration mechanisms to move research into health systems (15%); (iii) providing information and communication technologies for efficient generation, analyzing, managing, and sharing of big data sets (15%); (iv) investing in the motivation and in additional training for health-care professionals (15%); (v) creation of national and/or European networks for sharing professional competencies in specific fields (15%); (vi) defining a coordination among the several fields involved in the patients' management (pharmaceuticals, diagnostics, and imaging) (11.2%); and (vii) engaging patients as active partners in the health-care system (11.2%) (Figure 1).

Questionnaire: part 2 – on the role of laboratory medicine in personalized medicine

This part of the questionnaire was aimed to investigate the role of laboratory medicine in personalized medicine. Most of the participants underlined the key role of laboratory medicine to support the implementation of personalized medicine in the clinical setting (question 9), even if some additional requirement and relevant changes could be needed (question 10). In particular, comments for "relevant changes" suggested an improvement in the collaboration between research and clinic for the enhancement of technologies and expertise. The "additional requirements" concerned new competencies, technological facilities, and training for the current personnel, with the same distribution (question 11).

The main suggestions for the competencies regarded the upgrade of information management by the collaboration with bioinformatics and biophysics in relation to -omics technology platforms, and the collection, elaboration, and interpretation of these data for clinical and epidemiological purposes. The technological facilities should be focused on informatics and statistical data analysis to harmonize data analysis and quick exchange of information between doctors and laboratories and vice versa. The required competencies and the technologies should be improved by training courses on molecular genetics, proteomics, biomarker discovery, pathophysiology, epidemiology, diagnosis, and treatment in order to match the output results with the clinical matters. Suggestions for the "fields of additional training course for current personnel" were focused on discovery of biomarkers, molecular genetics and proteomics, pathophysiology, epidemiology diagnosis, and treatment (Supplemental Data, Appendix C, Figure 9).

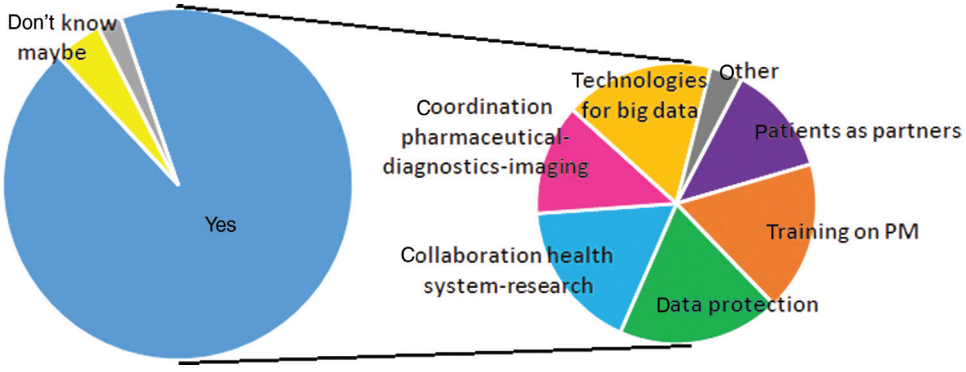

Figure 1: Answers to questions 7 and 8, "Do you agree that there is the need to improve cooperation and collaboration between different disciplines to integrate information suitable for a Personalized Medicine approach?" and "If YES in the above question, which of the following sentences should be particularly relevant?" (multiple options).

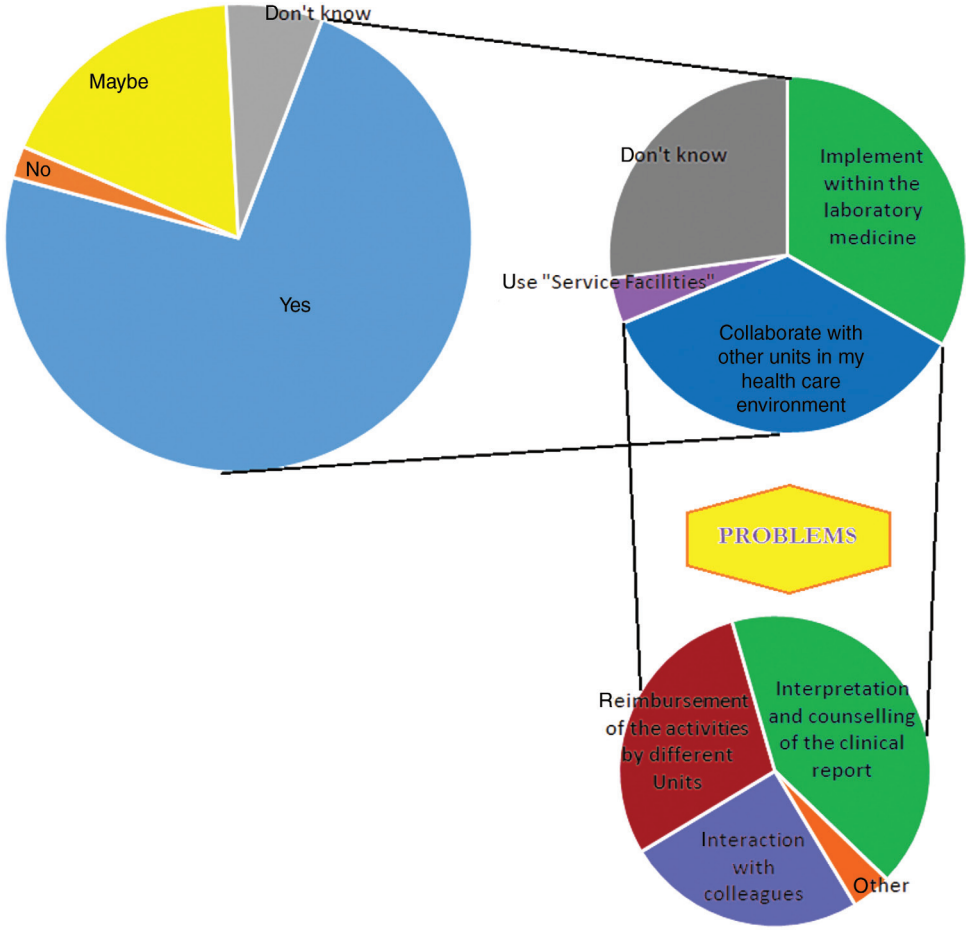

Figure 2: Answers to questions 12, 13, and 14, "Current technological tools and expertise available in the department of laboratory medicine are mainly addressed to the analysis of proteins, enzymes, electrolytes, etc., whereas it is expected that personalized medicine will require the integration of these results with '-omics' data"; if YES, "what do you think is the approach you would be interested to follow?"; and "if you said I will evaluate the possibility to collaborate with other units available in my heath-care environment in order to cover the missing facilities, which kind of problems do you think you have to face with?"
*Other: obtaining and sharing resources.

Questionnaire: part 3 – on the available facilities to support implementation of personalized medicine in your environment

The requirements for the integration of -omics with the "traditional analysis of proteins, enzymes, electrolytes, etc.," in laboratory medicine, such as the role of collaboration among different units, were investigated (questions 12 and 13).

Most of the participants suggested an integration between the -omics and traditional approach through the implementation of the missing technologies in laboratory medicine or the collaboration with other units in the same health-care environments in order to cover for the missing facilities (Figure 2). A comment suggested the integration between phenotypic and genotypic data.

Questionnaire: part 4 – on the role of laboratory medicine in supporting teaching activities on personalized medicine

This part of the questionnaire was aimed to define the role of laboratory medicine in supporting the teaching activities (questions 15 and 16). The answers revealed that most of the participating laboratories agreed about the need for appropriate training activities during the curriculum of clinicians, biologists, and laboratory technicians and for professionals who currently are already active in the field, mainly for young people. One laboratory suggested that these training courses should be restricted to specialists in clinical biochemistry (Supplemental Data, Appendix C, Figure 10). Up to now, only 41% of participating laboratories are involved in planning courses/

activities focused on personalized medicine. The 29% are not involved in a dedicated training activated for personalized medicine; however, this topic is the issue of several courses.

We further investigated the role of universities in personalized medicine training activities: who will be involved in the teaching, and at which level of education this approach should be implemented? (question 17) (Supplemental Data, Appendix C, Figure 11). Fifty-eight percent of the laboratories were interested in taking part; however, it was not clear who should take care of the organization and at which level of education these courses should be implemented. Different suggestions were proposed: someone proposed to start the education during the graduation courses, others at the end of the graduation, and others in postgraduate courses or by creating dedicated masters; only one laboratory declared to be already involved in courses including personalized medicine training activities. Some of them suggested introducing these educational issues in courses for physicians; others suggested extending to biologists, technicians, and technologists.

Questionnaire: part 5 – on the role of the European societies EFLM and ESPT in personalized medicine

European scientific societies, such as the EFLM and ESPT, should play a role in the facilitation processes for the implementation of the personalized medicine approach in the health-care system (questions 18 and 19). Most of the laboratories agree with this sentence, underlining the crucial role of these societies for the implementation process; in particular, participating laboratories suggested the development of guidelines/documents and creation of interdisciplinary working group for health-care professionals as fundamental activities of these international societies (Supplemental Data, Appendix C, Figure 12).

Discussion

The answers of the participating laboratory medicine professionals clearly indicate that they are aware that personalized medicine can represent a new and promising health model. However, they believe that this model, in order to be successfully implemented, requires an improvement in the cooperation and collaboration among professionals of different disciplines (e.g., clinical pharmacology and clinical genetics) to integrate information suitable for a personalized medicine approach. Whereas they are aware that laboratory medicine should play a key role to support the integration of personalized medicine in the clinical setting, the participants of this survey think that the current organization of laboratory medicine needs additional/relevant implementations such as (i) new technological facilities in -omics, (ii) additional training for the current personnel focused on the new methodologies, and (iii) incorporation of new competencies in data interpretation and counseling in the laboratory.

This survey suggests a strategic plan that should be considered both by health-care providers and by scientific societies of laboratory medicine. First, the implementation of personalized medicine should be tested in a limited number of centers (academic/hospitals) possessing a wide range of competencies and facilities in -omics and bioinformatics. These centers should then be supported to gain the missing technological facilities and appropriately trained for this aim.

Medical laboratories, including, e.g., clinical chemistry, bacteriology, virology, immunology, pharmacology, anatomical pathology, cytology, and transfusion medicine, have evolved out of different medical and research traditions and are used to progress on their own. The advent of advanced information technologies, automation, and measurement technologies provides unique opportunities for the synergies and the consolidation among different specialized laboratories [21]. However, these synergies are seldom utilized to their full extents except by large laboratory corporations. Unfortunately, medical laboratories in academic environments are lagging behind in this aspect. This creates difficulties in freeing up economic resources that can be used to introduce or expand -omics based on measurement systems, information technologies, and on the proper knowledge base. Hopefully, developments in these areas could speed up as the academic environments are likely to command the best skill and knowledge resources for developing -omics-based diagnostic methods.

Conclusions

The development of personalized medicine by -omics technologies offers new opportunities for the treatment of patients in the European Union. This approach has the potential of making health-care providers able to offer better-targeted treatment, avoiding medical errors and reducing adverse reactions to drugs. In addition, this

approach fits with the new stratification strategy necessary for controlling treatment in pharmacogenomics and also for the better definition of reference values influenced by biological variation (i.e., age and sex) [30] and other lifestyle factors (i.e., tobacco, nutrition, and so on) [1, 10]. Moreover, the comparability, or the unification, of laboratory reference values [16] is required by the "mobility" of patients and the need of sharing information among different health-care units, as well as by the globalization of laboratory-related markets.

That is why the joint working group "Personalized Laboratory Medicine" of the EFLM and ESPT societies has planned the questionnaire "Is Laboratory Medicine ready for the era of Personalized Medicine?" The answers to the questionnaire underlined that laboratory can play a key role in the development of personalized medicine. Nevertheless, some improvements should be implemented in the management of laboratory due the increase of the application in -omics technologies and their outputs. In particular, new platforms for data analysis should be implemented, and collaboration among different professional experts and units should be harmonized under the coordination of European scientific societies such as the EFLM and ESPT in order to give "the better answer to each patient."

Laboratory medicine professionals are asked to play a key role in this area; however, relevant changes in the structure of laboratory medicine seem necessary in order to meet the new requirements. The EU document "Use of '-omics' technologies in the development of personalised medicine" [12] states that "personalized medicine is not a revolution but an evolution" and laboratory medicine professionals are willing and able to participate actively in this evolution.

Acknowledgments: Matthias Schwab was supported in part by the Robert Bosch Foundation (Stuttgart, Germany), the Federal Ministry for Education and Research (BMBF, Berlin, Germany, grant 0315755), and the DFG KFO 274 (grant SCHW858/1-1).

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Financial support: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Supplemental Material: The online version of this article (DOI: 10.1515/cclm-2015-0171) offers supplementary material, available to authorized users.