COMMENTARY

Challenges and Solutions for Future Pharmacy Practice in the Era of Precision Medicine

Olivia M. Dong, MPH,a,b Rachel M. Howard, BS,a,b Rachel Church, PhD,a Mackenzie Cottrell, PharmD, MS,a Alan Forrest, PharmD,a Federico Innocenti, MD, PhD,a,b Merrie Mosedale, PhD,a Angela Kashuba, PharmD,a Daniel Gonzalez, PharmD, PhD,a Tim Wiltshire, PhD,a,b,c

a Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

b Center for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

c Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Submitted July 13, 2017; accepted November 21, 2017; published August 2018.

As precision medicine research and its clinical applications continue to advance, it is critical for pharmacists to be involved in these developments to deliver optimal, tailored drug therapies for patients. To ensure pharmacists remain leaders in the field, the annual Pharmaceutical Sciences Conference convened by the University of North Carolina at Chapel Hill Eshelman School of Pharmacy focused on the role of pharmacy within precision medicine. This is a summary of the conference, highlighting the major challenges and solutions that will help advance individualized pharmacological methods within practice and research.

Keywords: precision medicine, pharmaceutical sciences, conference

INTRODUCTION

Clinical applications of precision therapy, such as therapeutic drug monitoring (TDM), or using drug concentrations in blood to adjust patient dosing, have been practiced for decades. Among new approaches that are being developed within the field, pharmacogenomics is one area that can be implemented now. Practicing pharmacists have noted that adequate training in pharmacogenomics is lacking.1 To address this issue, doctor of pharmacy programs, residency programs, and educational webinars through professional organizations have initiated programs that integrate pharmacogenomic training for students, trainees, and practicing pharmacists.2-6 For instance, the PharmGenEd, a pharmacogenomics education program, offers students, trainees, physicians, and pharmacists free access to web-based continuing education (CE) materials.7 Certification in pharmacogenomics has been previously offered at conferences and is also available from academic institutions, such as the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences.8,9 Other precision therapy approaches beyond pharmacogenomics are not a typical topic for CE programs even though they are anticipated to provide additional individualized pharmacological methods within pharmacy practice in the near future. Thus, it will be critical for pharmacists to stay current with these developments to ensure patients receive optimized drug therapies that are reflective of research advancements.

The University of North Carolina at Chapel Hill Eshelman School of Pharmacy hosts the Pharmaceutical Sciences Conference annually. In 2017, the conference was organized and hosted by the Division of Pharmacotherapy and Experimental Therapeutics whose mission is to generate and disseminate new knowledge in pharmacotherapy and accelerate its application to improve patient care. The conference goal was to highlight and provide knowledge about new directions for precision therapy that may impact the role of pharmacists. The conference, held on May 18-19, 2017 in Chapel Hill, North Carolina (https://pharmacy.unc.edu/chapel-hill-pharmaceutical-sciences-conference/) highlighted how precision medicine can change patient care and the role of pharmacy within the precision medicine field. This commentary provides an overview of the session topics and the challenges and solutions proposed by the speakers to move the field forward from both the perspectives of pharmacy education and scientific research.
Conference Description

The conference objectives were to gather clinical and research experts across different pharmaceutical areas to discuss key aspects of precision therapy and engage researchers, educators, and health care professionals in these discussions. The conference provided an invaluable opportunity for licensed pharmacists to learn about cutting-edge research and technologies within the field and allowed the option to earn 11 continuing education (CE) units.

A diverse group of 21 speakers contributed to this conference and provided their perspective, including 11 affiliated with UNC, six from outside academic institutions, three from the pharmaceutical industry, and one from the FDA. The speakers were organized into four distinct topic-sessions and covered 10 major themes (Figure 1). More than 200 individuals attended the conference with approximately half affiliated with UNC and the remaining affiliated with industry, clinical practice, or other academic institution. The majority (95%) of attendees were residents of North Carolina and 101 (49%) registered with a pharmacy license number. A poster session consisting of 18 posters and four featured presentations of top abstract submissions allowed researchers to highlight current findings in the field of precision medicine.

One major learning tool offered to attendees prior to the conference was pharmacogenomic (PGx) testing with DNA2Rx, a new assay recently developed by the UNC Center for Pharmacogenomics and Individualized Therapy. The test provides extensive information for 18 genes of pharmacogenetic relevance, and the results from this

Figure 1. The 10 major topics that were discussed at the Pharmaceutical Sciences conference.
testing were discussed during the conference in an effort to engage attendees in active learning of PGx information with their own personal genetic information.

The first session was focused on pharmacogenomics in precision medicine. PGx is an increasingly important component of the precision medicine field and will be critical for pharmacists because many medications can be optimized for individual genetic differences to achieve improved drug efficacy and reduce unwanted side effects. As PGx research continues to advance, the regulatory aspect, especially in light of new genomic technologies such as next-generation sequencing, will be responsible for developing guidance documents for proper PGx incorporation into the clinical workflow. Guidance documents are currently available for PGx data submissions with additional ones being developed for handling next generation sequencing diagnostic tests. The U.S. Food and Drug Administration (FDA) has approved 187 drug labels across various therapeutic areas that incorporate PGx information. Interpreting PGx information and understanding the impact it has on patient outcomes will become a vital competency for pharmacists and physicians as more PGx efforts are piloted and major bioinformatics implementation challenges are addressed to progress the implementation of genomic information clinically.11,12

Given this uptake in incorporating genomic information in drug prescribing and the growing consumer demand for better drug therapies, a major focus of this session was exposing conference attendees to basic concepts in this area. PGx information for the drugs with FDA approval was presented in report form for a virtual patient (Figure 2). A subset of the participants (77 or 37.5% of attendees) who elected to receive personal PGx results with DNA2Rx received their own personal PGx information to interpret. An additional 20 individuals signed up for PGx testing after this session. Incorporating PGx information in drug dosing will become a required skill for pharmacists as its use has increased. One way to ensure proper training among practicing pharmacists is to provide PGx testing during training programs to engage students in experiential, active learning. Ideally, key concepts introducing students to PGx should be offered at the undergraduate level and then more comprehensive PGx training should be available to trainees and other health care professionals, as is provided to UNC PharmD students. This way, pharmacists will begin practice with adequate PGx training, and CE programs can focus on more advanced PGx topic areas. Until then, it will be important for CE programs and other educational efforts to be available for pharmacists to gain the basic training in this area.

The second session discussed novel pharmacologic and phenotypic approaches to precision medicine. As technology and research advance in pharmaceutical sciences and medicine, many other pharmacological methodologies within precision medicine are being developed with great promise for clinical application and therapeutic outcomes. One of the challenges is the ability to determine which biomarkers and technologies are most informative or applicable to patient care. This session focused on three emerging novel approaches to precision medicine that will likely be incorporated into the standard of care in the future. These include using the following phenotypic approaches: adoptive T cell therapy, the microbiome, and metabolomics. Technologies that specifically deliver drug to their intended targets have been a popular area of ongoing research, especially for diseases such as cancer that can be particularly difficult to treat in the clinic as a result of

Figure 2. Pharmacogenomic Report Card. The result of the pharmacogenomic assay, DNA2Rx, for a virtual patient is encoded in the quick response (QR) code, which can be scanned (ie, smart phone applications, scanners, etc.) to view pharmacogenomic results and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines. The report is the size of a business card to allow patients to carry and access their results conveniently.

American Journal of Pharmaceutical Education 2018; 82 (6) Article 6652.
profiles are shaped by genetics, diet, environmental factors, and drug response. Technologies that allow users the ability to self-monitor numerous aspects of their lifestyle (eg, diet, exercise, medication) will be imperative in capturing a holistic understanding of the factors that influence interactions of the gut microbiome and drug response.

The last phenotypic approach discussed in this session was metabolomics, and a systems approach in understanding human disease and drug effects as these profiles are shaped by genetics, diet, environmental factors, and the gut microbiome. Metabolomics offers an in-depth understanding of the metabolic pathways that are perturbed in disease and may provide key insight into the underlying nuances in drug response that exist among individuals with the same disease diagnosis. Distinct forms of a disease can be characterized using the metabolome along with profiling responders and non-responders to drugs.14 Although the topics presented here were unique from one another, they demonstrate that many different approaches may be used to individualize drug therapies in the future. While many of these advances are still exploratory, it is incumbent on pharmacists to keep abreast of the rapidly changing approaches to precision therapy, with the expectation of comprehending and integrating data from these disparate fields into pharmacy practice. Although some of these methods are not yet actively incorporated into clinical practice, ensuring education programs at all levels (eg, undergraduate, professional graduate, and graduate), incorporating some degree of exposure (ie, seminars, electives, etc.) to help familiarize students with these promising areas of precision therapy will be critical. Making these topics available through CE programs will encourage current pharmacists to stay current with the changing landscape of research.

The third session focused on the role of quantitative clinical pharmacology in delivering precision medicine. Another area where precision medicine is progressing to improve the efficacy of drugs and maximize time spent within a drug’s therapeutic range is by individualizing drug dosing using pharmacometric techniques.15,16 The standard approach to developing drug dosing guidelines has always been based on clinical trial data, which comes from selected and restricted patient groups. This does not provide adequate guidance for individualizing dosing for those members of the population that do not fit within the clinical trial restrictions, and is especially important for drug dosing in special populations (ie, pediatric populations, the elderly, pregnant women).

This session emphasized moving away from the current paradigm of using drug dosing for the “average” patient population to one that incorporates data on real-time drug concentrations and prospectively using pharmacometric tools (ie, population modeling, pharmacokinetic/pharmacodynamic (PK/PD) modeling) to individualize drug dosing. These powerful modeling tools have the potential to achieve appropriate drug target ranges using multiple data inputs, and were demonstrated in a prospective, randomized study conducted with tacrolimus using the BestDose software.17 Incorporating these pharmacometric tools into the electronic medical records and leveraging existing patient information to inform these models are needed to optimize drug dosing. Several techniques during this session were discussed, including systems engineering feedback control, Bayesian adaptive control, and therapeutic drug monitoring (TDM). More prospective studies, cost-effectiveness analyses, and validated models in this area will facilitate better incorporation into the drug development process and clinical care workflow.18 Refinement and advancements are expected in this area, and future drug dosing may follow a completely different model than what is used today. The solutions in this session provided guidance for scientific and research challenges related to precision dosing for all patients. Pharmaceutical sciences programs at the graduate level should encourage the curriculum to incorporate new modeling techniques in coursework to help trainees incorporate these elements in their research and help advance efforts in this area.

The last session focused on the implementation of precision therapy. As discussed above, traditional “one-size-fits all” drug development was designed to discover treatments for the “average patient.” Research techniques and study designs will need to be altered from these traditional approaches to gather pertinent data that is unique to help advance the precision medicine field.

The goal of this session was to delve deeper into key aspects of precision medicine research that will help achieve eventual implementation in the clinical setting. Several study designs were discussed, including the N-of-1 studies, drug matching trials, and rapid learning systems. These study design strategies provide a more detailed
| Question                                                                 | Strongly Agree (%) | Agree (%) | Neutral (%) | Disagree (%) | Strongly Disagree (%) |
|------------------------------------------------------------------------|--------------------|-----------|-------------|--------------|-----------------------|
| The learning objectives listed on the brochure were met.                |                    |           |             |              |                       |
| Session 1                                                               | 74.0               | 26.0      | 0           | 0            | 0                     |
| Sessions 2 and 3                                                        | 64.7               | 34.3      | 1.0         | 0            | 0                     |
| Session 4                                                               | 69.8               | 28.1      | 1.0         | 1.0          | 0                     |
| The content of the programming met your educational needs and goals.    |                    |           |             |              |                       |
| Session 1                                                               | 64.4               | 32.7      | 2.9         | 0            | 0                     |
| Sessions 2 and 3                                                        | 58.8               | 35.3      | 2.9         | 2.9          | 0                     |
| Session 4                                                               | 65.6               | 31.3      | 2.1         | 1.0          | 0                     |
| The program enhanced my knowledge or skills.                            |                    |           |             |              |                       |
| Session 1                                                               | 72.1               | 25.0      | 1.9         | 1.0          | 0                     |
| Sessions 2 and 3                                                        | 63.7               | 33.3      | 2.0         | 1.0          | 0                     |
| Session 4                                                               | 71.9               | 24.0      | 2.1         | 2.1          | 0                     |
| The speaker was knowledgeable.                                          |                    |           |             |              |                       |
| Session 1                                                               | 76.9               | 23.1      | 0           | 0            | 0                     |
| Sessions 2 and 3                                                        | 72.5               | 26.5      | 1.0         | 0            | 0                     |
| Session 4                                                               | 76.0               | 22.9      | 1.0         | 0            | 0                     |
| The presentations and speakers were well organized.                     |                    |           |             |              |                       |
| Session 1                                                               | 67.3               | 30.8      | 1.9         | 0            | 0                     |
| Sessions 2 and 3                                                        | 62.7               | 34.3      | 2.9         | 0            | 0                     |
| Session 4                                                               | 65.6               | 32.3      | 2.1         | 0            | 0                     |
| The AV tools used effectively.                                          |                    |           |             |              |                       |
| Session 1                                                               | 53.8               | 37.5      | 6.7         | 1.9          | 0                     |
| Sessions 2 and 3                                                        | 48.0               | 45.1      | 5.9         | 1.0          | 0                     |
| Session 4                                                               | 51.0               | 40.6      | 8.3         | 0            | 0                     |
| The speakers use effective teaching and learning methods, including active learning. | | | | | |
| Session 1                                                               | 45.2               | 45.2      | 7.7         | 1.9          | 0                     |
| Sessions 2 and 3                                                        | 48.0               | 39.2      | 9.8         | 2.0          | 1.0                   |
| Session 4                                                               | 50.0               | 40.6      | 7.3         | 2.1          | 0                     |
| Were the learning assessment activities appropriate for the educational program? | Yes (%) | No (%) | | | |
| Session 1                                                               | 98.1               | 1.9       |             |              |                       |
| Sessions 2 and 3                                                        | 99.0               | 1.0       |             |              |                       |
| Session 4                                                               | 99.0               | 1.0       |             |              |                       |
| Was the presentation educational and free of commercial bias?           | Yes (%) | No (%) | | | |
| Session 1                                                               | 98.1               | 1.9       |             |              |                       |
| Sessions 2 and 3                                                        | 99.0               | 1.0       |             |              |                       |
| Session 4                                                               | 97.9               | 2.1       |             |              |                       |

Session 1: Pharmacogenomics in Precision Medicine (n=104)
Sessions 2 and 3: Novel Pharmacologic Approaches/Quantitative Clinical Pharmacology (n=102)
Session 4: Implementation of Precision Therapy (n=96)
and adaptive methodology in the research process to better individualize drug treatments for patients. For instance, the N-of-1 study design features a patient as the unit of observation instead of large cohorts, gathering more in-depth information to determine the optimal medical treatment at the individual level. For the genomic field, one challenge in conducting precision medicine research to find the genomic underpinnings of a particular phenotype is gaining access to adequate cohort sizes. Collaborations, especially among academia, health care, and industry, will be vital in being able to identify these cohorts. For example, 23andMe (https://www.23andme.com/) has genetic and phenotype information for more than two million participants, which can be leveraged to study a particular phenotype of interest. Access to such a large cohort has resulted in numerous collaborations with pharmaceutical companies and academic institutions to identify genetic markers pertinent in the development of therapeutics and in the understanding of diseases. Another key stakeholder group who influences the implementation of precision medicine in the clinical setting are health care payers. Coverage and reimbursement for PGx testing and procedures are vital for successful uptake and clinical use of precision medicine. Payers have their own set of requirements when providing favorable coverage, including demonstrating the cost-effectiveness of PGx tests. Pharmaceutical science programs at the undergraduate and graduate level can incorporate information from this section into the curriculum to expose students to more individualized research study designs and these concepts can be further reinforced through coursework or journal clubs. Seminars and professional events are also a valuable opportunity for trainees to gain exposure and engage with private companies and health care payers.

Evaluations from the Attendees

Attendees receiving CE units from the conference were required to fill out a survey that evaluated the program, and the responses received represent approximately half of the attendees. These attendees had an overwhelmingly positive response to the conference. For these three statements from the survey: the content of the programming met your educational needs and goals, the program enhanced my knowledge or skills, and the speaker was knowledgeable; greater than 90% responded with strongly agreed or agreed. When asked “how will you use this information in your practice,” most free-response answers related to improving care provided to patients in practice, proposing or advocating for genomic testing at a clinical site, including precision medicine in research efforts, and updating current educational materials being taught at institutions to include precision medicine. Other features of the conferences that were cited as valuable include the pharmacogenomic reports that improved engagement, the discussion of precision medicine beyond genomics, and the various perspectives that were presented (ie, regulatory, private companies, insurance companies, academia, etc.). Table 1 provides more detailed results from the survey data. Suggestions for future programming included academic drug development, a focused therapeutic area within precision medicine, and more workshops on precision medicine.

CONCLUSION

Pharmacists, along with the whole field of pharmaceutical developments and research, will play an important role in advancing precision or personalized therapies. Individualizing drug therapies can be incorporated in many ways, including using established pharmacogenomic information in drug prescribing, tailoring drug therapies based on key phenotypic data, and using pharmacometric modeling to individualize drug doses. Major collaborative efforts among academic and health care institutions and industries will be key in overcoming the challenges that are faced in the precision medicine field (ie, small sample sizes in research studies, insurance reimbursement, incorporation in the health care setting, etc.). While educating pharmacy learners and those already in pharmaceutical careers about developments in precision medicine is of prime importance, it is also important to consider clinical care over the next 10 years and in the longer term. The conference blended current approaches with research perspectives of future scientific advancements. Adequate training efforts in precision medicine, and learning opportunities as provided by conferences like this will be vital for pharmacists and other clinicians in providing optimal care to patients as this field continues to advance. Staying current with the research will ensure pharmacists and trainees are aware of the limitations with current practice, where advancements are needed to improve patient care, and understand the importance of advocating for initiatives that will improve patient care. It is a priority within the education field to ensure adequate training opportunities are available and are current with research advancements.

ACKNOWLEDGMENTS

Funding was received from the following groups: Abbvie, Bristol-Myers Squibb, Certara, The UNC Clinical Pharmacology and Analytical Chemistry Laboratory, DPET (Division of Pharmacotherapy and Experimental Therapeutics), Metabolon, The National Institute of
Environmental Health Sciences, North Carolina Biotechnology Center, Regeneron, and Dr. Dhiren Thakker.

REFERENCES
1. Schwartz EJ, Issa AM. The role of hospital pharmacists in the adoption and use of pharmacogenomics and precision medicine. Pers Med. 2017;14(1):27-35.
2. American Society of Health-System Pharmacists. Pharmacogenomics: webinars and presentations. 2017.
3. Adams SM, Anderson KB, Coons JC, et al. Advancing pharmacogenomics education in the core PharmD curriculum through student personal genomic testing. Am J Pharm Educ. 2016;80(1):Article 3.
4. Owusu-Obeng A, Weitzel KW, Hatton RC, et al. Emerging roles for pharmacists in clinical implementation of pharmacogenomics. Pharmacotherapy. 2014;34(10):1102-1112.
5. Remsberg CM, Bray BS, Wright SK, et al. Design, implementation, and assessment approaches within a pharmacogenomics course. Am J Pharm Educ. 2017;81(1):Article 11.
6. Springer JA, Iannotti NV, Kane MD, Haynes K, Sprague JE. Pharmacogenomics training using an instructional software system. Am J Pharm Educ. 2011;75(2):Article 32.
7. Lee KC, Ma JD, Hudmon KS, Kuo GM. A train-the-trainer approach to a shared pharmacogenomics curriculum for US colleges and schools of pharmacy. Am J Pharm Educ. 2012;76(10):Article 193.
8. UF to host inaugural precision medicine conference 2015. http://pharmacy.ufl.edu/2015/12/15/uf-to-host-inaugural-precision-medicine-conference/.
9. University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences: Pharmacogenomics Certificate Program 2017. http://www.ucdenver.edu/academics/colleges/pharmacy/AcademicPrograms/ContinuingEducation/CertificatePrograms/PGXcertification/Pages/PGXcert.aspx.
10. US Food and Drug Administration table of pharmacogenomic biomarkers in drug labeling. 2017.
11. Dunnenberger HM, Crews KR, Hoffman JM, et al. Preemptive clinical pharmacogenetics implementation: current programs in five US medical centers. Annu Rev Pharmacol Toxicol. 2015;55:89-106.
12. Dewey FE, Murray MF, Overton JD, et al. Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study. Science. 2016;354(6319).
13. Perica K, Varela JC, Oelke M, Schneck J. Adoptive T cell immunotherapy for cancer. Rambam Maimonides Med J. 2015;6(1):e0004.
14. Beger RD, Dunn W, Schmidt MA, Gross SS, Kirwan JA, Cascante M, et al. Metabolomics enables precision medicine: a white paper, community perspective. Metabolomics. 2016;12(10):149.
15. Gonzalez D, Rao GG, Bailey SC, et al. Precision dosing: public health need, proposed framework, and anticipated impact. Clin Transl Sci. 2017;10:443-454.
16. Darwich AS, Ogungbenro K, Vinks AA, et al. Why has model-informed precision dosing not yet become common clinical reality? lessons from the past and a roadmap for the future. Clin Pharmacol Ther. 2017;101(5):646-656.
17. Storset E, Ashberg A, Skauby M, et al. Improved tacrolimus target concentration achievement using computerized dosing in renal transplant recipients – a prospective, randomized study. Transplantation. 2015;99(10):2158-2166.
18. Neely M. Scalpels not hammers: the way forward for precision drug prescription. Clin Pharmacol Ther. 2017;101(3):368-372.
19. Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? Per Med. 2011;8(2):161-173.
20. Deverka PA. Pharmacogenomics, evidence, and the role of payers. Public Health Genomics. 2009;12(3):149-157.