HELLENIC REPUBLIC
UNIVERSITY OF PATRAS
SCHOOL OF HEALTH SCIENCES
DEPARTMENT OF PHARMACY
LABORATORY OF PHARMACOGENOMICS
AND INDIVIDUALIZED THERAPY

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑ ΦΑΡΜΑΚΕΥΤΙΚΗΣ
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ΚΑΙ ΕΞΑΤΟΜΙΚΕΥΜΕΝΗΣ ΘΕΡΑΠΕΙΑΣ

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COMMENTS ON THE DOCTORAL THESIS OF Mr. ALIREZA TAFAZOLI

Pharmacogenomics studies play an essential role in characterization of gene-drug interactions within cells. It is considered as the main approach for utilization and implementation of personalized drug therapy in the age of precision medicine. However, despite of significant advances in the field, still several barriers prohibited it's integration into the routine clinical practice. These are included but not limited to lack of the background knowledge for the physician and clinicians in interpreting the test result and bringing such translational knowledge in to their practice, the deficiency of solid guideline and recommendations for many rare functional genetic variants in drug-related genes, no reimbursement for such tests in many healthcare systems around the globe, and so on. But perhaps the first reason would be the most important point to care, as it may hinder the fast development of pharmacogenomics guided treatment modifications for patients with rare and common diseases. To deal with the challenge, adding pharmacogenomics and clinical pharmacology courses through medical and pharmacy students' curriculum has been suggested previously. Also, allocation of more pharmacogenetics and pharmacogenomics investigations through local and/or global populations may add some significant insights in providing of evidence-based recommendations for several commercialized drugs.

Abovementioned introduction highlights the necessity of new research in the field of pharmacogenomics as one of the hot topics in future medicine and personalized therapy. Current dissertation aimed an extremely crucial subject with a prospective view to the upcoming area in pharmacogenomics as well. It discusses the utilization of such a knowledge in extracting data out of high throughput DNA sequencing approaches. Since, the number of genomic variants in new genotyping technologies (especially next generation sequencing [NGS] platforms) are expected to be very high, the employment of already existed pharmacogenomics-dedicated bioinformatic tools for computational analysis, data classification and prioritization, and finding out the true capacity of individuals for particular drug metabolism may directly help the interpretation of clinical pharmacogenomics test result in daily clinical setting.

Alireza Tafazoli did a great job as a deep study on clinical validity and utility of already existed and freely available pharmacogenomics-related bioinformatics software, which absolutely adds an important vision and deep perception for applying population scale pharmacogenomics research in different population. He also provided an algorithmic workflow for adapting such technologies in daily basis of clinical centers. Functional characterization and different outcomes for each tool investigated in details and discussed

properly. Furthermore, Alireza included two review articles that explained the approaches to deal with various types of variants in NGS result (as well as extremely rare variants and novel variants in less studied drug-related genes) toward the personalized medicine implementation. The limitations and opportunities for utilization of high throughput DNA profiling in clinical pharmacogenomics explored systematically in his other paper. Actually, when beginning his thesis with those comprehensive review papers made his dissertation's content strongly coherent and understandable, which may indicate his maturity in the field.
With the support and supervision of pioneers in the field (dr. Jesse Swen from LUMC, Netherlands) and experienced scientists in drug bioanalysis (prof. dr. hab. Wojciech Miltyk from MUB, Poland), Alireza was successful in finalizing his doctoral project in a completely well managed way and publishing an original article in a well-known dedicated journal from Nature Publishing Group, named as "The pharmacogenomics Journal" as well. Also, he published his review papers, directly related to his main Ph.D. project in Q1 journals from Frontiers and MDPI publication houses. Based on Alireza's maturity and independent qualifications in the area of pharmacogenetics and pharmacogenomics, I confirm his eligibility to receive doctoral degree in the field of medical sciences. Moreover, because of high quality of the scientific work for current dissertation I would like to ask for allocation of "distinction" to it.

Some minor comments:

1 - Complete Genomics should be changed to BGI, it has been taken over by the Chinese company for years now.

2 - Alireza needs to polish the text, e.g., add articles where missing, there are capital letters in the text, there are missing letters in words (e.g., references) etc.).

Questions for Alireza:

1- Please explain the potential impact of ignoring WGS in clinical pharmacogenomics studies (including yours). On the other side, you may discuss the advantage of your already applied platform as well.

2- Please provide your points on the lack of including drugs related to the frequently observed SNPs in the polish population. Did you consider that for your project?

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