Editorial

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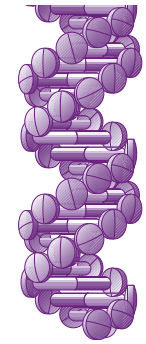
Pharmacogenomics



Multimorbidity, polypharmacy and pharmacogenomics in old age

"Genomic and epigenomic biomarkers might help in future in the appropriate care of elderly patients and in individualized deprescribing."

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Finding the right drugs at the right doses for each elderly patient is often challenging. And particularly in this context, appropriate consideration of molecular biomarkers of genomic and epigenomic variation is still at an early stage. The impact of the same pharmacogenomic signature may be quite different in children, younger adults and elderly. Drug research in humans at very old age in particular is a complex endeavor. In the development of new drugs, one wants to minimize the risks for study participants for ethical reasons and to minimize variation negatively affecting the statistical power. As a consequence, there are less data on drug efficacy and drug safety in specific vulnerable populations like children, women and the elderly. But we do need clinical evidence of the benefits and risks of drugs in the target population – the elderly being a major target group – and often the elderly have many risk factors and concomitant diseases. Consequently, studying pharmacogenomics in the old and in the very old population is challenging but should be addressed with appropriate clinical research. Here, we want to highlight some facts and concepts about pharmacogenomics in old age, multimorbidity and polypharmacy.

Pharmacogenomics in polypharmacy

Polypharmacy is often defined as a prescription of five or more drugs taken each day. This is quite common since many elderly patients suffer from more than three medically significant diseases. In this situation, polypharmacy is not *per se* maleficent for the patient [1]. Indeed, polypharmacy may be required and beneficial when considering all relevant diseases. But in reality, there are also cases of maleficent polypharmacy characterized by unnecessary medications, inappropriate medications with high risks for the elderly and neglect for the relevant comorbidities, interactions and genotypes. Undoubtedly, any polypharmacy, whether justified or not, confers significant risks from drug–drug, drug–disease and drug–gene interactions. In this situation, considering relevant biomarkers including the individual's genotypes may be an important factor to increase the patient's safety and well being. Unfortunately, both – the best medication in the elderly with multimorbidity and the best medication in carriers of many relatively rare genotypes – cannot be proven by conventional randomized controlled trials. This is not possible since there are too many different combinations of diseases and other individual constellations that are too rare to be studied all in clinical trials. And similarly, there are too many genetic variants increasing the risk of adverse drug effects to allow the study of these variants in typical randomized clinical trials [2]. However, physicians have solutions for such situations in which they cannot follow the route that was apparently the best according to clinical trials. The respective decision making considering the lack of evidence from randomized clini-

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cal trials may probably best be termed as rational drug therapy. This means considering all relevant knowledge about the patients, their diseases, the drugs, their interactions and about the relevant genomic variants, combined with the best available evidence on how to adjust drug treatment in each specific condition. As we know, this approach is also called 'individualized medicine' or 'precision medicine' but such terms may generate too exaggerated expectations.

> "...research on genomic and epigenomic variations in elderly patients suffering from multimorbidity and receiving polypharmacy presents important new challenges but also changes in clinical research, data analysis and clinical decision making."

Good knowledge on rational drug therapy has generated several lists of potentially inappropriate drugs in the elderly [3] . This knowledge and reasoning has also generated several rules for so-called 'deprescribing', meaning to reduce the number of drugs a patient has to take in the interest of the well being of the patient. Currently, there is no consideration of pharmacogenomics in the lists of potentially inappropriate drugs and in the suggested algorithms for deprescribing [4]. However, in several instances, there may be good reasons to prescribe a potentially inappropriate drug, and many drugs may become more appropriate if the patient's individual genotype is considered. Genomic and epigenomic biomarkers might help in future in the appropriate care of elderly patients and in individualized deprescribing.

Knowledge & prejudice about the role of pharmacogenomics in old & very old age

As a rule of thumb, many body functions decline in old age and interindividual variation increases. This functional decline may almost always have both environmental and heritable causes. One may find good reasons for both views, either that genomic variation plays only a small role in old people or that genomic variation plays even a bigger role compared with younger people. Arguments for a small role of genomic variation in the elderly are that acquired variation due to diseases and other life events apparently increases in the elderly while the typical inherited pharmacogenomic variation remains constant throughout life [5]. But there are not enough empirical data on that, and interestingly enough, there may be a significant age- and disease-related increase in genomic variation in somatic cells in apparently benign tissues [6]. However, at present, our understanding of the role of the latter type of acquired somatic mutations for drug efficacy or drug adverse reactions is at an early stage.

Indeed, there may be many arguments for an even bigger role of genomic variation in old age compared with youth. In the elderly, several pathways of drug elimination may be reduced or blocked by drug–drug interactions or age-related decline, for instance, in kidney function, and in such bottleneck-situations a genetic variation in drug membrane transport, drug metabolism or in a signalling pathway may become particularly critical. Here, we want to highlight four sometimes neglected research topics, namely age-related falls and fractures, cognitive decline, chronic pain and inflammation, and infectious diseases, where the elderly might particularly benefit from progress in pharmacogenomics and individualized medicine.

Falls and fractures are frequent causes of morbidity and mortality in later stages of life. There are multiple causes for falls and fractures of the elderly, and falls and fractures may be both disease conditions and adverse drug reactions. Several drug classes were reproducibly associated with fall risk. These drug classes include sedatives, antidepressants, antipsychotics and anti-Parkinson's drugs. Remarkably, nearly 50% of all these fall risk-increasing drugs are substrates of functionally highly polymorphic drug membrane transporters and drug metabolizing enzymes such as CYP2C19 or CYP2D6. While the disease itself is probably the most important risk factor, selection and dosage of these drugs according to the relevant genotypes might be beneficial for the elderly population [7]. There may by several particularly hazardous disease–drug–genotype combinations, but currently, there is not much empirical research data on that question.

Drug-induced cognitive impairment is particularly endangering for the elderly population. Also this condition is often disease related but it can be an adverse drug reaction or be caused by a particular combination of drugs and disease. Drug-induced cognitive impairment may be classified into a dose-related form observed in almost every recipient but with different intensity (e.g., after sedatives) and a more idiosyncratic form observed in a clinically relevant severity only in a currently poorly predictable subgroup of the population (e.g., fluoroquinolones, tacrolimus, or mefloquine). Genomic variation in drug metabolism, at the blood–brain barrier or in other structures of the CNS may be relevant in both types but identifying genomic and epigenomic biomarkers for the second idiosyncratic form may be particularly promising. Postoperative cognitive impairment may become obvious as confusion, disorientation or even psychotic symptoms after major surgery and may last for several days or even longer. Elderly patients appear to be at particular risk but the role of heritability and genomic biomarkers has

not been studied comprehensively in the context of postoperative cognitive impairment.

Chronic pain and inflammation most significantly reduce the quality of life in the elderly. Biomarkers of low-grade chronic systemic inflammation are among the best biomarkers available to characterize vulnerability and frailty in the elderly. Expression of these biomarkers may have a significant heritable basis [8]. Thus, further research on inherited and acquired genomic variations in the immune system may help to elucidate the background of this inflammation, which apparently goes beyond reactions to degenerative processes. Because of inflammation, many elderly patients regularly take nonsteroidal drugs and the risk for gastrointestinal bleeding from nonsteroidal drugs is nearly tenfold higher in elderly than in young patients. That risk increases even further when patients are treated with anticoagulants. Since this risk is dose and concentration related, it may be even higher if the elderly carry the *CYP2C9*3/*3* or **2/*3* genotypes [9], but there are only scarce empirical data.

Infectious disease is another frequent cause of suffering and finally of death in later stages of life. Apparently, there is significant dysregulation in the innate immune system but there is also significant age-related change in the adaptive immune system. With current analytical technologies, we are not only getting a much better understanding of immunosenescence [10], but we also have the tools to identify patients who are at a particularly high risk for infections. Based on this, antibiotic therapies, general health measures or event targeted interventions in the immune system could be individualized but further research is required in this area.

In conclusion, research on genomic and epigenomic variations in elderly patients suffering from multimorbidity and receiving polypharmacy presents important new challenges but also changes in clinical research, data analysis and clinical decision making [11,12]. Particularly if actionable biomarkers can be identified, such research may confer significant improvements in health of the elderly.

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