

Opinion Paper

Michael Vogeser*

From therapeutic drug monitoring to total drug monitoring and drug-omics

<https://doi.org/10.1515/cclm-2020-0339>

Received March 18, 2020; accepted April 11, 2020

Abstract: In view of the role of pharmacotherapy in medicine, on the one hand, and the powerful technical possibilities that are now available on the other hand, therapeutic drug monitoring is a surprisingly neglected area of laboratory medicine. In this viewpoint article, an “omics approach” to pharmacovigilance and drug monitoring is proposed and discussed. A realistic goal for laboratory medicine in the 21st century should indeed be to enable clinicians to check whether the right drug is present in the right patient with an appropriate blood concentration for each compound.

Keywords: drug-omics; immunoassay; individualization; mass spectrometry; pharmacokinetics; therapeutic drug monitoring.

Drug therapy is undoubtedly a cornerstone of medicine. A considerable part of the efforts in medicine is aimed at the follow-up and optimization of drug therapy. This includes a wide range of measures, from blood pressure measurement for the individualization of antihypertensive drugs, to pharmacokinetic drug monitoring. The objectives of this latter PK-monitoring include the verification of patient adherence, correct use, integrity of pharmaceutical preparations, and the investigation of a possible influence of genetic variables, organ dysfunction or comedication on ADME – absorption, distribution, metabolism and excretion of a drug or its active metabolites. Based on the observed blood drug concentrations, an individualization of drug dosage is considered – thus closing the loop to therapeutic drug monitoring (TDM). This therapeutic loop differentiates therapeutic drug monitoring from forensic drug testing or drug testing in pharmacological research.

The concept of therapeutic drug monitoring has been applied for decades, but only addresses a very limited range of drugs today – including in particular, lithium, methotrexate, vancomycin or immunosuppressants in transplant medicine. Tricyclic antidepressants are also routinely tested because of their narrow therapeutic window – the blood concentration range between inefficiency and toxicity. Theophylline and digoxin – classic targets of conventional TDM – no longer play a major role in therapy today. Until now, TDM has generally been used to control toxicity by dose limitation; optimizing the efficiency of treatment by escalating the dosage has been less in focus.

With the availability of powerful, highly reliable and almost universally applicable mass spectrometric techniques – especially isotope dilution liquid chromatography-tandem mass spectrometry (LC-MS/MS) and orbitrap technology – clinical pathology has the tools to test virtually all small molecule drug substances for more than two decades now [1]. Highly automated immunoassay systems, on the other hand, have the potential to monitor antibody-based (large molecule) drugs – and also patients’ antibodies to these compounds that impair their efficacy. In particular, these “biologicals” now account for a very significant proportion of total drug spending in industrialized countries.

This discrepancy between today’s technological possibilities and the very limited application of therapeutic drug monitoring in medical practice is surprising and hard to understand.

In 2020, clinical pathology will provide sequencing of the entire genome, generating huge amounts of data. Imaging technologies today include whole-body CT scans in the emergency room, PET-CT, angio-CT and NMR techniques, which provide physicians with incredible sets of clinically relevant and actionable data.

It would be in keeping with these 21st century diagnostic standards that clinical pathology is generally able to verify that the *right* substance is present in the *right* patient at the *right* concentration range. This should be a reasonable and appropriate expectation of clinicians. It is surprising that laboratory medicine is so modest in

*Corresponding author: Prof. Dr. med. Michael Vogeser, Institute of Laboratory Medicine, Hospital of the University of Munich (LMU), Marchioninistr. 15, 81377 Munich, Germany, Phone: +49 89 4400 73221, E-mail: michael.vogeser@med.uni-muenchen.de

its goals, so conservative and unambitious in this diagnostic area, and also that here clinicians seem to be undemanding.

In fact, analytical chemistry in food and environmental analysis using GC-MS, LC-MS/MS and, increasingly, orbitrap technology is able to detect and quantify, for example, several hundred pesticides in complex biological matrices with low detection limits [2] – whereas typical mass spectrometry (MS) methods in clinical chemistry have so far only been applied to detect and quantify slightly more than ten analytes. MS methods are highly specific as they evaluate molecular decay patterns for detection, and they are matrix-independent due to the application of the principle of stable isotope dilution. Thus, from a technological point of view, there is no reasonable doubt that clinical pathology could, in principle, achieve comprehensive, essentially complete monitoring of all therapeutic drugs; and more generally, essentially all xenobiotics, including, for example, persistent organic pollutants that potentially act as endocrine disrupters.

Once the ability to measure blood concentrations is a given, routine monitoring and individualization of dosage would certainly not become the routine standard for *all* compounds. However, constellations can be expected for essentially every drug, where at least the verification of compliance or correct application is of importance. On the other hand, there are indeed a growing number of compounds for which it is very likely that routine drug monitoring will be useful as a standard to increase efficacy and safety – but has not yet been widely implemented in clinical practice. These include antibiotics used for severe infections in the context of antibiotic stewardship [3], where significant deviations of ADME characteristics from normal are very common. Cystic fibrosis transmembrane conductance regulator modulators are highly efficient in many patients with cystic fibrosis but are subject to drug interference due to metabolism by hepatic cytochrome enzymes [4]. This is also true for many compounds in the rapidly growing field of oral tumor therapy (OTT) [5, 6] – including, for example, CDK 4/6 inhibitors for the treatment of advanced breast cancer – where adherence is often only partial. While non-adherence is an individual decision of the patient, in clinical trials it is essential that the effects are evaluated in relation to the achieved drug concentrations in the blood.

Terms such as personalized medicine are nowadays used very predominantly in connection with genetic testing, although therapeutic drug monitoring – the assessment of the effective phenotype in the interaction of genetic background, organ function, behavior and environment – clearly contributes to the personalization of medicine.

A comprehensive “*drug-omic*” approach to laboratory testing will undoubtedly be subject to criticism. Concerns include the challenge of regulatory hurdles for both commercially distributed and laboratory developed tests. Widespread evaluation of blood drug concentrations will suggest dosage changes outside the range covered by the product information of the particular drug in many cases. Although this is not formally prohibited, as a physician is in principle free in his therapeutic decisions, such constellations obviously have a liability dimension. For some drugs and in certain dosage situations there is no dose-response relationship. Not for all compounds clear target concentration ranges are established so far. And, there will be fears that the availability of comprehensive data on blood drug concentrations could further contribute to the data overload that physicians are currently facing.

It is likely that the pharmaceutical industry in general will express such concerns about the implementation of a comprehensive drug monitoring initiative. For these companies, the prospect that drug monitoring of an active ingredient could potentially become mandatory poses a threat, as it would create barriers for doctors to prescribe such drugs. The term “*companion diagnostics*” has so far only been used to describe the selection of anti-tumor compounds that target specific mutations. More generally, however, this concept can be understood as the idea of having a blood test available for every substance used in treatment – in the sense of total drug monitoring. In fact, with the increasing availability of blood tests for therapeutic drugs, it may in turn become an important and attractive perspective for pharmaceutical companies to have the possibility to verify appropriate drug concentrations in individual patients. This could, for example, help to identify non-adherence as a cause of individual therapeutic failure rather than questioning the efficacy of the drug itself. Thus, the option of comprehensive drug monitoring could finally also be of interest to the pharmaceutical industry, because a safer and more transparent drug therapy could be brought to market more easily. Consequently, it could become standard practice to provide a blood test together with every new drug.

From a logistical point of view, only some of the drug tests require very short-term diagnostic availability; this is especially true for antibiotic tests in critically ill patients. Such a test should ideally be available within a few hours in the respective hospital laboratory. For most tests – companion tests in a more general form – shipment to centralized laboratories with a total turnaround time of 24–48 h will be acceptable. Continuous improvement of

the transport logistics for diagnostic samples and also the networking of laboratories with large central laboratories in the regions can provide suitable diagnostic services for comprehensive drug monitoring.

More pharmacokinetic data obtained in routine settings will require the involvement of clinical pharmacists and clinical pharmacologists in order to make appropriate use of these growing volumes of information. Close and lasting collaboration between laboratory specialists (providing the data) and clinical pharmacologists and clinicians (interpreting and processing these data) will be required.

In a future arena of full drug monitoring, laboratory developed tests (LDTs) are likely to compete with the solutions provided by the IVD industry. So far, the IVD industry's interest in TDM seems to be remarkably low. Profit expectations are uncertain, reflecting the conservative attitude of most clinicians towards TDM based on the conventionally limited availability of testing (as a chicken and egg problem). However, technological reasons also play a role: immunoassay technology – which has been the main technological basis of the IVD industry's revenues to date – is not an ideal technology for a drug-omic approach: the smaller the molecular size of the targets, the more challenging the development of specific antibodies. As immunoassay technology in its standard configurations is not a parallelized technology, a comprehensive immunoassay-based analyzer for overall drug monitoring would require hundreds of reagents on board, each with sensitive handling requirements and varying shelf lives. Although most individual drugs could be addressed with a quantitative immunoassay of acceptable quality, a panel of hundreds of small drugs on one immune-analyzer system seems almost impossible to perform. On the other hand, quantitative assays targeting antibody-based drugs (biologicals) pose a major challenge for the routine application of MS. For such drugs – which now contribute significantly to overall healthcare costs – immunoassay seems to be and remain the technology of choice. Immunoassay-MS hybrid assays are also likely to find their way into the TDM arena.

For a widespread multi- and mega-parametric application of MS in clinical routine laboratories it is obvious that the practicability of the respective analysis platforms has to be drastically improved. Indeed, the complete automation of quantitative MS analysis – as it has been a standard for immunoassays for decades – is a very big challenge, however, a *conditio sine qua non* for routine total drug monitoring with MS. This challenge can best be addressed through private-public partnerships between academia and industry. That such full automation is

actually possible in principle has recently been demonstrated by the marketing of a completely closed MS/MS-based analysis system [7].

Providing scientific data on the clinical benefit and cost-effectiveness of a total drug monitoring approach will be the difficult and probably impossible: The golden standard of double-blind studies, as it applies to drugs, is in principle not applicable to diagnostic tests. Even comparisons between institutions that may or may not have implemented some form of total drug monitoring in the future will hardly be useful, as almost every single hospital has its own profile in terms of patient populations, equipment and therapeutic portfolio. In this context, it is important to recognize that indeed not all questions in medicine can be answered with a strictly statistical approach. In many areas of medicine, plausibility and sound judgment remain the key to making important decisions. Indeed, the benefit of most standard diagnostic tests is obvious and undisputed but has never been demonstrated in prospective studies. Wherever possible, controlled studies should also be carried out in diagnostics, but inherent barriers to the realization of such approaches in some areas should not be an obstacle to any innovation. It is very reasonable – for example – to assume that blood concentrations of an administered antibiotic found below the minimum inhibitory concentration of a bacterial pathogen in a bloodstream infection are most likely therapeutically less effective than a concentration above the minimum inhibitory concentration. However, a prospective therapeutic study designed to prove this is ethically highly questionable and ultimately flawed.

Considering the enormous importance of drug therapies in medicine as a whole worldwide and based on obvious pathophysiological mechanisms, the vision of an “omic” concept of drug monitoring clearly seems to have the potential to significantly improve clinical outcomes in the future. Consequently, highly multiplexed and comprehensive pharmacokinetic drug monitoring – combining the properties of immunoassays and MS according to their respective optimal applications – can be expected to be a key area for growth and development in clinical pathology for the benefit of our patients.

Author contributions: The author has accepted responsibility for the entire content of this manuscript and approved its submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: Author states no conflict of interest.

References

1. Vogeser M, Zhang V. Understanding the strategic landscape surrounding the implementation of mass spectrometry in the clinical laboratory: a SWOT analysis. *Clin Mass Spectrom* 2018;9:1–6.
2. Wong JW, Wang J, Zhan K, Hayward G, Wittenberg JG. Pesticides: an update on mass spectrometry approaches. In: *Encyclopedia Food Chemistry*. Amsterdam, The Netherlands: Elsevier, 2019:433–8.
3. Zander J, Paal M, Vogeser M. The role of mass spectrometry in antibiotic stewardship. *Clin Mass Spectrom* 2019;14:31–3.
4. Lopes-Pacheco M. CFTR modulators: the changing face of cystic fibrosis in the era of precision medicine. *Front Pharmacol* 2019;10:1662.
5. Spring LM, Wander SA, Zangardi M, Bardia A. CDK 4/6 inhibitors in breast cancer: current controversies and future directions. *Curr Oncol Rep* 2019;21:25.
6. Verheijen RB, Huixin Y, Schellens JH, Beijnen JH, Steeghs N, Huitema AD. Recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. *Clin Pharmacol Ther* 2017;102:765–76.
7. Benton SC, Tetteh GK, Needham SJ, Mücke J, Sheppard L, Alderson S, et al. Evaluation of the 25-hydroxy vitamin D assay on a fully automated liquid chromatography mass spectrometry system, the Thermo Scientific Cascadion SM Clinical Analyzer with the Cascadion 25-hydroxy vitamin D assay in a routine clinical laboratory. *Clin Chem Lab Med* 2020;58:1010–7.