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# On-demand drug quantification: an increasing need in pediatric patients



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The use of off-label and unlicensed medications is common and necessary in pediatrics. However, it poses potential risks due to lower levels of evidence on the pharmacokinetic (PK) profile, drug efficacy, and safety profile (i.e., pharmacodynamics [PD]), and potential genetic modifiers of PK and PD. In general, the PK variation is not only significant along the developmental trajectory but also within specific age and disease categories. Accordingly, when expected clinical effect is not realized or when adverse events are observed, the lack of evidence-based specific information on established drug doses and achieved drug concentrations results in challenges for the optimal clinical care for children.

Various international initiatives (e.g., Pediatric Trials Network) as well as policies from regulatory agencies (e.g., Food and Drug Administration, European Medicines Agency) aim to close the information gap for drugs that are already used as well as those that are currently in development, respectively. While these initiatives are an important first step to improve pharmaceutical care for children, a gap remains in achieving the goals of precision medicine for the individual child.

The measurement of drug concentrations in plasma, serum, or whole blood to guide pharmacotherapy (i.e., therapeutic drug monitoring [TDM]) has been employed since the 1960s. Drugs are eligible for TDM when (1) the clinically effective and toxic drug concentrations lie close to each other (i.e., narrow therapeutic window), and (2) significant inter- and intra-individual variation in the PK profile exists. More recently, the use of TDM has expanded to biologic agents that are associated with high costs and have a risk for anti-drug antibody formation. In these cases, TDM may allow for lower health care-related costs as well as facilitate clinical approaches that support prolongation of the therapeutic use of a specific agent.

In most situations where TDM is used, the target concentrations are predefined. However, there are many situations outside of traditional TDM when knowing drug concentration profiles in a unique patient can improve their clinical care. For example, in our practice, it has helped to determine the absorption profile of trametinib in a patient with altered gastrointestinal anatomy and function due to lymphatic malformation. In addition, we investigated serum drug concentrations in patients who were suspected to have altered drug metabolism, either because of genetic predispositions (i.e., pharmacogenetics) or because of drug–drug interactions. The data obtained did not only allow clinical decision making and treatment individualization but also provided a better understanding of the patient's condition and their drug-handling processes. These individual cases subsequently fueled research questions and allowed application of the new knowledge in other patients.

At this moment, the availability of drug concentration measurements by clinically accredited laboratories (i.e., Clinical Laboratory Improvement Amendments, International Organization for Standardization 15189) is limited to drugs with established TDM guidance, including antimicrobials, antipsychotics, antiepileptics, immunosuppressants, and cardiac drugs. Also, most clinical laboratories are limited to TDM tests that are commercially available on automated instruments. In contrast, very few assays are available for therapeutic agents that entered the market in the past decade. This includes a variety of small molecules as well as biologic agents that are relatively infrequently used in pediatric populations and may be prescribed off label, such as oral anti-neoplastic agents and anti-inflammatory agents. As their use is restricted to relatively small patient populations, often with complex conditions, the PK profiles within these populations are generally not well understood, which can predispose the patient to treatment inefficacy and adverse events. The lack of availability of drug concentration measurements of many novel agents therefore disproportionately affects the pediatric population. If on-demand drug assay systems were available, it will not only help individual children in a specific clinical context but would also serve as a research platform for advanced PK analyses to enrich pediatric PK data for many drugs.

To increase the access to such drug concentration measurements, new assays need to be developed within a nimble environment that can adjust to the ever-changing clinical need and allow for rapid integration into clinical care. These laboratory tests should not require batch analysis and have a short turnaround time (e.g., days versus weeks), so clinicians can adjust treatment plans quickly. Clinical diagnostic companies are unlikely to fulfill this gap due to high development costs, the lengthy regulatory approvals process, and return on investment considerations for drugs with low test demand. One way to achieve this goal may be to employ or develop multiplex assays that use liquid chromatography tandem mass spectrometry (LC-MS/MS) instrumentation that can determine drug concentrations for a group of compounds in the same analysis, rather than using a drug-specific assay. This way, the infrequent use of a specific assay will not result in its early discontinuation because of the tension between high maintenance costs and infrequent use. Ideally, commercially developed standards that contain varying drug concentrations of multiple compounds will increasingly become available to allow centers to implement multiplex assays rather than develop these independently.

At the institutional level, there should be sufficient funding for the development of new assays, as well as the costs to maintain the infrastructure of a LC-MS/MS core. First, existing assays may be consolidated in a multiplex assay to reduce the costs of the existing TDM catalog. Second, regional networks of collaborating laboratories could support and streamline these efforts to prevent

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unnecessary duplication of assay development and maintenance, which reduces the overall costs. Third, due to the limitations in availability, the development of a vast TDM program may generate revenue from both clinical as well as research partners, in both pediatric and adult settings, which could support the cost of maintenance.

From a system perspective, regulatory support will be required to facilitate an expeditious transition of laboratory assays that are developed "in-house" from a developmental stage into a stage ready for clinical care implementation. This process should not only be quick on one hand but also ensure high-quality laboratory procedures that are required when test results are used for clinical decision making on the other.

Many efforts focus on the individualization of pharmacotherapeutic management in medicine. While certain approaches are based on population data (e.g., pharmacogenetics), the availability of TDM is valuable for assessing the actual drug concentration attained in the patient and will provide an additional layer of safety and understanding of the individual biologic processes involved in drug handling. Until the access to TDM testing opportunities is improved, we believe that the use of, and access to, currently available assays could be optimized. For example, an online catalog of TDM tests that is available in a large geographic region (i.e., North America, Europe, Asia), including sample requirements, turnaround time, and pricing, would facilitate testing.

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Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data: R.H.J.V. and S.I. Drafting the article or revising it critically for important intellectual content: R.H.J.V., B.J., T.R.L., and S.I. Final approval of the version to be published: R.H.J.V., B.J., T.R.L., and S.I.

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## ADDITIONAL INFORMATION

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