

Towards Continuous Therapeutic Drug Monitoring of Venetoclax in Acute Myeloid Leukaemia: Emerging Roles of Wearable Biosensors, Artificial Intelligence, and Precision Dosing

Swarnendu Sahoo^{1*}, Eswaran Maheswari^{1*}, Nishil Gowda², Harish Kausik Kotakonda³

¹ Department of Pharmacy Practice, Faculty of Pharmacy, M S Ramaiah University of Applied Sciences, New BEL Road, MSR Nagar, Bangalore, Karnataka, India - 560054

² Department of Medical Oncology, Ramaiah Medical College, M S Ramaiah University of Applied Sciences, New BEL Road, MSR Nagar, Bangalore, Karnataka, India - 560054

³ DMPK & Clinical Pharmacology, Bugworks Research India Pvt. Ltd., Bengaluru, Karnataka, India - 560065

* Corresponding Author:

1. Dr. Swarnendu Sahoo

Email: ssahoo.1999.ss@gmail.com

2. Dr. Eswaran Maheswari

Email: maheswari.pp.ph@msruas.ac.in

Abstract

Venetoclax, after combining with hypomethylating agents (HMA) or low-dose cytarabine, has become a key therapy for acute myeloid leukaemia (AML) patients who are unsuitable for intensive chemotherapy. However, its clinical application is complicated by large inter-individual pharmacokinetic variability, a narrow therapeutic window, and clinically important drug-drug interactions. These factors may lead to variable exposure, dose limiting toxicities. Currently, conventional therapeutic drug monitoring (TDM) utilizes sampling, which usually provides limited information regarding exposure and restricts the individualization of dosing. This narrative review showcases the techniques for continuous monitoring of venetoclax in AML, focusing on the use of wearable biosensors and artificial intelligence (AI)-driven precision dosing. It also explores the potential of minimally invasive and wearable biosensors, such as electrochemical aptamer (EA)-based microneedle platforms. The review also evaluates the capabilities of model-informed precision dosing (MIPD) and novel digital twin technologies to translate frequent concentration measurements into meaningful dose adjustments and toxicity prediction. These technologies remain experimental, and a venetoclax-specific continuous-sensing platform is not yet available. Nevertheless, they may provide a path toward precision oncology. However, prospective clinical validation is required before they can be used in routine AML care.

Keywords: Acute Myeloid Leukemia, Venetoclax, Therapeutic drug monitoring, Biosensors, Model-informed precision dosing, Pharmacokinetics

How to cite this article: Swarnendu Sahoo^{1*}, Eswaran Maheswari^{1*}, Nishil Gowda², Harish Kausik Kotakonda³. Towards Continuous Therapeutic Drug Monitoring of Venetoclax in Acute Myeloid Leukaemia: Emerging Roles of Wearable Biosensors, Artificial Intelligence, and Precision Dosing. *Int J Drug Deliv Technol.* 2026;16(86s):255-271. DOI: 10.25258/ijddt.16.86s.32.

1. Introduction

Over the last decade, the treatment of acute myeloid leukaemia (AML) has undergone significant transformation.¹ Until recently, there have been few options for patients who were elderly or medically unfit, and success rates have been low with the currently available low-intensity treatments. In this context, the advent of venetoclax-based therapy was an important milestone. The combination of azacitidine and venetoclax showed better remissions and survival results than azacitidine alone in the landmark VIALE-A trial, making it a significant frontline treatment for patients not eligible for intensive chemotherapy.² These results facilitated the transition of venetoclax from being a promising targeted agent to a key treatment option in AML therapy. Venetoclax is a selective B-cell lymphoma 2 (BCL-2) inhibitor and a BCL-2 homology 3 (BH3) mimetic.³ It exerts antileukemic activity by restoring the process of apoptosis in malignant cells, which rely on BCL-2 for their survival. Venetoclax binds to BCL-2, displaces pro-apoptotic proteins, leading

to mitochondrial cell death.⁴ Due to this, it is rapidly adopted clinically in AML, in combination with hypomethylating agents (HMA) or low-dose cytarabine.⁵

Although it is effective, venetoclax therapy is challenging to manage in routine AML care due to the fact that the exposure of the drug is not consistent between patients.⁶ Prolonged cytopenias, particularly neutropenia, are common clinical problems that can cause treatment interruptions or dose modifications.² This scenario becomes more complex with the addition of azole antifungals either for prophylaxis or treatment. Azoles can inhibit cytochrome P450 3A (CYP3A) and significantly increase the exposure of venetoclax. During dose-adjustment studies in AML, the clinically significant venetoclax-posaconazole interaction was identified, and structured dose adjustment is recommended.^{7,8} This underscores the narrow therapeutic window of venetoclax, where inadequate drug exposure may lead to a lack of anti-leukemic activity, while

excessive exposure could result in the development of myelosuppression and infections.

Currently, exposure assessment is still largely based on episodic therapeutic drug monitoring (TDM). Most studies describe venetoclax pharmacokinetics in AML patients using sparse plasma sampling, typically focused on steady-state trough concentrations, and performed the quantification by LC-MS/MS.^{9,10} While these studies are informative, they also demonstrate the constraints of snapshot sampling, as a single trough value will not fully capture fluctuations in absorption, accumulation, and/or drug-drug interactions (DDI) over time. Overall, the available data suggest a shift toward more robust and flexible monitoring approaches to improve individualization and safety in venetoclax therapy in patients with AML.^{9,10}

This narrative review synthesizes the available literature from databases such as PubMed and Scopus, along with relevant FDA (Food and Drug Administration) regulatory documents and product information, to explore current advances and future directions in continuous TDM of venetoclax in AML. While previous literature has covered the pharmacology of venetoclax, TDM, wearable biosensors, or AI-driven decision support individually, an integrated overview of these topics involving continuous biosensing, pharmacometric modelling, AI-based decision support, and precision dosing of venetoclax in AML is currently lacking. This review aims to fill this gap by combining these complementary fields into a single conceptual framework. We aim to: (i) discuss the rationale for TDM of venetoclax in AML from a pharmacological and clinical perspective; (ii) discuss emerging wearable biosensor technologies for continuous drug monitoring with a particular emphasis on electrochemical aptamer (EA)-based microneedle platforms; (iii) discuss the integration of continuous sensing with model informed precision dosing (MIPD), Bayesian forecasting, artificial intelligence (AI) and digital twin technologies for individualised dosing; (iv) propose a conceptual framework which integrates continuous biosensing, pharmacometric modelling and AI enabled decision support for venetoclax precision dosing; and (v) identify the various challenges that need to be overcome before continuous monitoring of venetoclax can be grounded into routine AML care.

2. Pharmacological rationale for TDM of venetoclax

2.1 Pharmacokinetic characteristics of venetoclax

Although venetoclax is orally administered, it has a complex pharmacokinetics that may make routine administration difficult in AML patients.⁶ The absolute bioavailability of venetoclax is low under fasting condition, but exposure increases significantly when venetoclax is co-administered with food.¹¹ Food has been observed to increase

exposure to venetoclax by several fold.^{6,11} The absorption of the drug is relatively slow with a median time to reach the maximum concentration (C_{max}) of approximately 5-8 hours. It also exhibits a large apparent volume of distribution (V_d), which indicate widespread tissue distribution and not being confined to the intravascular space.^{6,12} Another important factor is protein binding. Venetoclax is highly plasma protein bound and less than 0.01% of the drug is unbound at clinically relevant concentrations.^{6,13} The mean blood to plasma ratio was 0.57, indicating that plasma concentrations may not necessarily represent the active fraction of venetoclax.¹⁴ The terminal half-life ($t_{1/2}$) of Venetoclax is approximately 26 hours, which allows for once-daily administration, although the drug exposure may be affected by food intake, disease characteristics, and co-administered drugs.^{6,15} Its metabolism is primarily mediated by CYP3A4/5 and results in the formation of the major circulating metabolite, M27.¹⁵ Human disposition studies and pharmacology summaries show that M27 is not likely to make a meaningful contribution to the antileukemic effect. Its clinical activity is expected to rely largely on the exposure to the parent drug and not on the accumulation of metabolites. The elimination is primarily faecal, with minimal urinary excretion. Therefore, renal clearance has a minor role in the overall disposition. This pharmacokinetic profile underscores that hepatic function and CYP3A-mediated drug interactions have a greater impact on venetoclax exposure compared to renal elimination in patients with AML.^{6,15}

2.2 Exposure-response and exposure-toxicity relationships

The exposure-response relationship of venetoclax is clinically relevant as higher drug exposure did not seem to proportionately increase efficacy, but increased the risk of toxicity.¹⁶ Recent real-world AML data indicated that higher venetoclax trough levels were associated with a higher risk of delayed neutropenia, with many patients later requiring a dose-intensity reduction or treatment discontinuation. In the same study, the patients with complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) had higher trough concentrations than the nonresponders, indicating that sufficient drug exposure is essential for treatment response but that excessive drug exposure is also associated with toxicity risk.¹⁷ A pharmacogenetic study in AML showed a wide variation in venetoclax levels and changes in exposure due to clinical cofactors. It highlighted the need to transcend the fixed-dose assumption.¹⁸ The drug can give strong blast reduction and deep remissions, but beyond a certain level of exposure, which is necessary for response, marrow suppression rises as the major limiting factor.¹⁹ Thus, the aim of the therapy is not necessarily to maximise drug exposure, but to

provide sufficient drug exposure for clinical response without excessive toxicity. Findings from a study indicate a narrow therapeutic window in which adequate exposures can be used for therapeutic benefit, but exposures might quickly escalate to the toxicity risk zone.^{6,17}

2.3 Pharmacokinetic variability and drug-drug interactions

One of the largest obstacles to achieving stable venetoclax exposure in AML is DDI. The azole antifungals are particularly relevant, as these are often required during induction and consolidation. Co-administration of posaconazole was shown to increase the C_{max} and overall exposure (AUC) of venetoclax by 7.1-fold and 8.8-fold, respectively, after adjusting for dose differences and nonlinear pharmacokinetics.²⁰ Real-world studies demonstrated that coadministration of venetoclax and posaconazole significantly boosts venetoclax exposure, which could lead to extended myelosuppression even with dose reductions.^{7,21} The same effect has been seen for other potent CYP3A inhibitors, including ketoconazole, suggesting that venetoclax exposure is highly sensitive to CYP3A inhibition.^{6,20} This interaction has not only theoretical consequences but has also been observed clinically. Antifungal prophylaxis is frequently needed at times when it is most challenging to control venetoclax exposure for patients with AML, requiring a parallel balance between the risk of fungal infection, excessive drug exposure and myelosuppression. Despite label-based dose reduction, exposure levels may show inter-patient variability, and the same nominal dose of venetoclax may have very different effects in patients treated with the same antifungal agent.^{8,17}

3. Limitations of conventional TDM and the necessity of continuous TDM

All these pharmacological variabilities make TDM an emerging approach to the optimization and individualization of venetoclax therapy. However, most monitoring is currently limited to being sparse and retrospective.^{10,22} Normally, a venous sample is taken at a fixed point in time, analysed by Liquid Chromatography - Tandem Mass Spectrometry (LC-MS/MS), and the results are interpreted after the patient has already received the same dose for a number of days. This means that while traditional TDM can help in adjusting the next cycle, it is not able to prevent a transient exposure spike that has already occurred in this cycle.^{9,10} The gap between dynamic drug exposures and static sampling strategies has driven interest in continuous, adaptive and model-informed approaches to AML management.^{6,17}

3.1. Limitations of intermittent blood sampling

Conventional intermittent blood sampling has the major drawback that it only gives a snapshot of exposure, not the complete picture. A single plasma concentration may be useful to confirm the presence

of a drug, but cannot describe how exposure increases, peaks and decreases over the dosing interval. TDM is most valuable in oncology for the drugs that have a narrow therapeutic window, high inter- and intra-patient variability of pharmacokinetics and a measurable relationship between drug concentration and effect.^{23,24} Although venetoclax is an ideal fit for this purpose, existing monitoring approaches do not take into account the full exposure profile and focus mainly on single time points.¹⁰

This is particularly significant in AML where the exposure to venetoclax is dynamic, rather than fixed. Population pharmacokinetic (PopPK) studies demonstrated that the drug exhibits consistent behaviour in the range of doses evaluated, but in real life, drug concentrations are still variable across patients.²⁵ This becomes more clinically relevant in the presence of azole antifungals and other covariates.¹⁹ If the trough is later found to be within an acceptable range, it does not necessarily mean that the patient did not have a high peak earlier in the interval; this issue would not be revealed by the sparse sampling.

3.2. Toxicity and underexposure concerns

Venetoclax poses a true exposure issue both ways. Excessive exposure is associated with prolonged myelosuppression on the one hand.¹⁷ Additionally, a real-world study revealed that there is a correlation between increased venetoclax exposure and delayed neutropenia beyond cycle 1.¹⁶ Underexposure, on the other hand, is a practical clinical issue. As AML is a disease with rapid clonal dynamics, effective venetoclax treatment requires continuous BCL-2 inhibition. Exposure-response analyses in AML did not reveal a clear relationship between venetoclax exposure and treatment efficacy within the range of doses studied, suggesting that efficacy may have already plateaued.¹⁹ This does not rule out the possibility of underdosing in some patients. Although empirical dose reduction to avoid neutropenia may be suitable in some instances, it may not always be the best approach for all patients. Dose reduction may help to reduce the toxicity, but without proper monitoring of exposure, there may be a greater risk for subtherapeutic drug levels and inadequate long-term disease control.

3.3. Need for precision dosing in AML.

AML is not a static disease, so the dosing of venetoclax should not be treated as a one-time calculation.²⁶ The marrow environment alters during treatment: the amount of tumour decreases, supportive drugs change, and the patient's tolerance for further marrow suppression also changes over time.^{27,28} Fixed-dose thinking is becoming more and more obsolete in modern AML treatment due to these changing conditions. The importance of personalized dosing with oral targeted therapies in the era of precision medicine has already been highlighted across the oncology literature,

particularly where interpatient pharmacokinetic variability is high, and dosing can be adjusted based on concentration.^{23,29} Now, Venetoclax also fits well in this scenario as its exposure is variable, toxicity is exposure-related, and the current monitoring regimen remains too limited to inform real-time adaptation.^{10,17}

Therefore, dosing schedules in AML must be designed dynamically and not in a static manner. In this regard, an effective monitoring system should not only confirm venetoclax exposure but also

Table 1. Comparison of conventional TDM versus continuous AI-enabled TDM in oncology

Feature	Conventional TDM	Continuous AI-Enabled TDM
Sampling modality	Invasive venous blood draws with LC-MS/MS analysis of venous plasma are the current practical basis for venetoclax TDM. ^{9,10}	Wearable microneedle-based sensing of dermal interstitial fluid is a minimally invasive technology and has already been shown to be feasible for real-time molecular monitoring in humans. ^{30,31}
Frequency of data	Sparse intermittent sampling or conventional TDM approaches provide isolated concentration points rather than a continuous trajectory. ^{9,10}	Continuous, high-temporal-resolution monitoring is the major advantage of microneedle-based aptamer sensors and related wearable interstitial fluid sensing platforms. ^{30,31}
Exposure metric captured	Conventional sampling usually reflects a single time-point plasma concentration, often used as an estimate of the trough or steady-state concentration. ^{9,10}	Dense time-series data can support reconstruction of exposure dynamics, including fluctuations relevant to C _{max} , AUC, and short-term concentration changes. This is

estimate exposure repeatedly over the dosing interval to maintain the drug level within the target therapeutic window. Continuous or near-continuous TDM is precisely made to fill the gap. It would not be a substitute for clinical judgment, but could provide a more realistic assessment of drug exposure than a trough sample, driven by growing evidence.^{16,17,19} The major differences between conventional TDM and the proposed continuous AI-enabled TDM approach are summarised in **Table 1**.

		a model-based capability rather than a proven venetoclax-specific clinical standard. ^{30,32}
Analyte measured	LC-MS/MS typically quantifies total venetoclax concentration in plasma after sample preparation. ⁹	ISF sensing is intended to interrogate the extracellular compartment and may better approximate the pharmacologically active unbound fraction of venetoclax. This remains a proposed translational advantage rather than a validated clinical fact. ^{30,31}
Analytical technique	Offline chromatographic-mass spectrometric quantification remains the reference laboratory method for venetoclax measurement. ^{9,10}	Real-time electrochemical aptamer-based sensing has already been demonstrated in humans for small molecules in dermal ISF and is the relevant prototype for continuous drug monitoring. ^{30,31}

Clinical turnaround time	Delayed and laboratory-dependent rather than real-time, because the workflow depends on sampling, transport, and off-line analysis. ^{9,10}	Near-real-time signal generation is the intended advantage of wearable electrochemical aptamer-based (E-AB) sensing. The published human microneedle study reported a lag of approximately 20 minutes, showing that clinically relevant temporal resolution is feasible. ³⁰
Decision support tool	Retrospective PopPK and model-based dose interpretation remain the standard analytical framework for sparse TDM data. ^{10,33}	Real-time Bayesian forecasting and digital-twin modelling are the proposed computational layer for continuous TDM and MIPD. ^{32,34}
Ability to capture DDI kinetics	Limited, because sparse sampling may miss rapid changes in exposure caused by strong CYP3A inhibition, such as posaconazole coadministration. ^{8,20}	Strong in principle, because dense time-series sensing plus Bayesian modelling could track exposure shifts during dynamic DDI conditions. ^{20,32}

It is important to note that the interpretation of AI-enabled continuous monitoring in Table 1 is based on the review of the current evidence and is not an explicit statement mentioned in the original studies. Abbreviations: LC-MS/MS, liquid chromatography-tandem mass spectrometry; TDM, therapeutic drug monitoring; C_{max} , maximum plasma concentration; AUC, area under the curve; ISF, interstitial fluid; PopPK, population pharmacokinetics; MIPD, model-informed precision dosing; CYP3A, cytochrome P450 3A; DDI, drug-drug interaction.

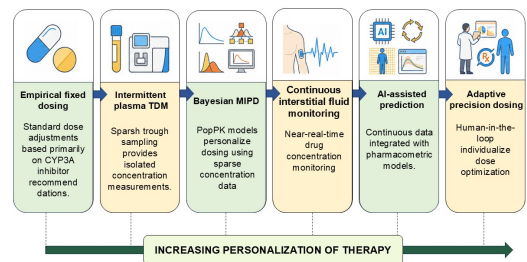


Fig. 1. Evolution of TDM and precision dosing strategies for venetoclax in AML

The progression of venetoclax TDM from traditional fixed-dose to future precision dosing approaches is illustrated in **Figure 1**. The figure highlights the increasing progression towards more individualized, data-driven approaches to optimize drug exposure and treatment outcomes.

4. Wearable and implantable biosensors for drug monitoring

4.1 Sensing principles and electrochemical platform

To bridge this gap between traditional blood sampling and true pharmacokinetic surveillance, a sensor platform needs to be developed that can repeatedly measure drug concentrations in a short time and without requiring a high workload for the laboratory. In this regard, reagentless E-AB sensing has become one of the most versatile sensing methods due to its rapid, modular and adaptable characteristics. It is applicable to difficult-to-track small molecule targets that are not amenable to conventional enzyme-based sensing methods.^{35,36} In general, this is the major engineering benefit of affinity-based biosensing, in which the signal is generated by molecular recognition and not by the intrinsic chemistry of the analyte.

4.2 Aptamer-based sensors

E-AB sensors are based on single-stranded nucleic acid aptamers, which are selected in vitro to bind a target with high affinity and selectivity.³⁷ The aptamer is attached to an electrode and contains a redox reporter, which means that when the target binds to the aptamer, there is a change in the electron transfer at the sensor surface that results in a measurable current change.^{38,39} This makes the platform attractive for TDM as it is continuous, direct and doesn't require enzymes, added reagents, or batch processing. In reality, this means that the sensor can report the change in concentration continuously whenever the drug concentration is changing, not after it has already occurred.^{36,39}

4.3 Microneedle platforms and interstitial fluid monitoring

In oncology, the sensing matrix is of significance as well. In frail, thrombocytopenic and neutropenic patients, repeated venous sampling is not ideal, and the device itself can become part of the clinical burden. Microneedle systems provide a more realistic alternative as they are minimally invasive

and are able to access dermal interstitial fluid (ISF) without the discomfort or infrastructure of repeated venipuncture.^{39,40} The first-in-human evaluation of real-time phenoxymethylpenicillin monitoring using a microneedle biosensor was reported by Rawson et al. (2019).⁴⁰ Friedel et al. (2023) reported the first real-time human molecular data collected with microneedle-enabled electrochemical aptamer sensors in dermal ISF.³⁰ Their device demonstrated clinically relevant lag times of approximately 20 minutes, much closer to dynamic monitoring than to traditional, intermittent laboratory-based testing. A major translational benefit of venetoclax may be not only access to ISF but also a better estimate of drug exposure, which can more accurately reflect the pharmacologically active fraction. Studies of vancomycin with aptamers have demonstrated that E-AB sensors may report the free drug, as opposed to total drug, which is clinically significant, as it is the free fraction of drug that is available for target binding and tissue effect.^{41,42} That makes ISF-based sensing attractive for a highly protein-bound agent like venetoclax. While there is existing evidence in the biosensor and pharmacology fields favouring the use of this technology for venetoclax TDM, it still needs to be prospectively validated for routine use.

Biosensor modality	Target matrix	Principle of detection	Advantages	Limitations	Clinical viability for AML venetoclax monitoring
Conventional LC-MS/MS	Venous plasma or serum	Chromatographic separation followed by mass-to-charge detection. ^{47,48}	High analytical sensitivity and specificity; established in TDM; validated methods for venetoclax quantification	Intermittent snapshot only; invasive venous sampling; delayed turnaround time in routine practice. ^{47,48}	High (current standard of care)

4.4 The implantable approaches and future feasibility.

Recent progress in biomedical engineering has resulted in the realization of fully integrated implantable electrochemical systems, which shows that drug-monitoring can be integrated into highly miniaturized sensor platforms.^{38,43} But the situation with AML is different when it comes to practical translation. Patients treated with venetoclax are often immunocompromised and may be at higher risk of developing bloodstream and catheter-related infections, especially those receiving chemotherapy.⁴⁴⁻⁴⁶ Therefore, a completely implantable intravascular sensor may be technically appealing, but is likely less feasible than a microneedle patch in this patient group. The microneedle ISF route seems to be the more feasible translation route in the current AML landscape.

Table 2 highlights the main features of the various biosensor platforms, including their sensing matrices, detection principles, strengths, weaknesses, and clinical feasibility for monitoring venetoclax in AML.

Table 2. Summary of biosensor modalities and their advantages and limitations

on in plasma is available. ^{9,47}					
Enzymatic biosensors	ISF or serum	Enzyme-catalyzed redox reaction with electrochemical readout, classically exemplified by glucose oxidase system. ^{49,50}	Mature, highly sensitive platform for electroanalytical and well-established in glucose monitoring. ^{49,50}	Best suited to chemically reactive analytes; not a practical platform for most chemotherapeutics, including venetoclax. ⁴⁹	Low (not suitable for venetoclax)
Microneedle E-	ISF	Binding-induced	Minimally invasive;	Biofouling, baseline drift,	Moderate to high

AB senso rs			confor mation al switch ing of a redox- tagged aptam er. ⁵¹	contin uous, real- time monit oring in huma n derma l ISF has been demo nstrat ed; comp atible with small- molec ule sensin g. ⁵¹	and nucleas e- related instabil ity remain importa nt translat ional barriers ; hydrog el protecti on can improv e in vivo stabilit y. ⁵²	(eme rgin g trans latio nal platf orm) .	senso rs	blo od	ting blood; implan table electro chemi cal sensor s are a recogn ized platfor m. ^{52,53}	reduc e depen dence on ISF- to- plasm a transl ation lag; impla ntable aptam er senso rs have been demo nstrat ed in vivo in roden ts. ⁵²	al sensors remain challen ged by foreign -body respons e, biofoul ing, and stabilit y concer ns. ^{52,53}
Impl anta ble intra vasc ular E- AB	Sys temi c ven ous ous y in circula	Affinit y- based sensin g directl y in circula	In princi ple, direct sampl ing could	Highly invasiv e; long- term implant able electro chemic	Very low (poo r fit for AM L).	Abbreviations: LC-MS/MS, liquid chromatography-tandem mass spectrometry; TDM, therapeutic drug monitoring; E-AB, electrochemical aptamer-based; ISF, interstitial fluid; AML, acute myeloid leukemia					

5. Continuous TDM with AI

Wearable sensors generate a stream of high-density pharmacokinetic data, which is only clinically useful if it can be translated to an interpretable dose recommendation. This is where AI and MIPD serve as the essential ‘computational layer’ that transforms raw concentration signals into exposure estimates, toxicology alerts, and dose recommendations. Recent reviews of TDM highlight the use of AI and machine learning for high-dimensional time-varying and clinically noisy data, which is precisely the case for continuous venetoclax monitoring.^{54–56} Essentially, MIPD combines prior knowledge with patient-specific measurements through PopPK models, then updates the estimate of an individual's pharmacokinetic parameters using Bayesian methods.⁵⁷ During a standard intermittent TDM workflow, a single concentration is used to optimize the previous model to estimate clearance (Cl), Vd, and exposure for the next dosing interval. Though that basic framework has already been proven to be effective in routine precision dosing, the new opportunity can continually update the model with the latest data, rather than waiting until the next isolated trough sample.^{55,58} This is where continuous venetoclax sensing can shift the current approach

from retrospective adjustment to near-real-time forecasting. Clinical variables such as weight, organ function, and co-medication can also be included, but the model becomes much more informative for interpreting the sensor output as a time series rather than a single measurement.^{54,56} This is especially relevant for venetoclax, as the drug may be measured in interstitial fluid instead of blood. The concentration of the drug in the sensing matrix might be slightly delayed compared with the systemic circulation.³⁷ The lag can be mapped, corrected for sampling delay and the likely systemic exposure over the next couple of hours or days can be estimated using an AI-based Bayesian updating. Continuous integration of sensor data in a validated PopPK model does not replace pharmacometric approaches, but rather complements and extends MIPD.^{32,56} The most sophisticated use of AI in the medical field is the evolution of medical digital twins. In the field of oncology, digital twins are becoming more frequently called virtual patients that are updated with clinical data to allow simulation of the disease course and treatment effects rather than mere observation.⁵⁹ Hernandez-Boussard et al. (2021) suggested that digital twins could be a

transformative approach to predictive oncology, and in 2025, Zhang et al. directly implemented this concept in the context of venetoclax-azacitidine therapy in AML.^{34,60} Their mechanistic ordinary differential equation (ODE) model predicted neutropenia based on longitudinal neutrophil counts and blast percentages, and they identified that continual updating increased the model accuracy. The study doesn't yet demonstrate that a full clinical digital twin is ready for routine AML care. However, it provides a proof of concept that the toxicity of venetoclax can be modelled dynamically in a patient-specific manner, and could be continuously updated with sensor-derived data.^{34,60}

When paired with real-time venetoclax exposure data, that digital twin can help to do more than just provide an explanation of the past. It may be used to assess future dosing situations, based on an estimate of the potential consequences of reducing, delaying or maintaining the prescribed dose. That is important because in AML, it is not only a matter of whether neutropenia will occur, but also whether a given dosing schedule can maintain blast suppression without prolonged marrow suppression. One way of quantifying that trade-off could be a digital twin.^{34,60}

Table 3 provides an overview of the major AI-supported computational strategies that may support continuous TDM and precision dosing, along with

One step further to digital twins is reinforcement learning (RL), which has been suggested in oncology precision dosing to optimize treatment decisions under uncertainty.⁶¹ Maier et al. (2021) demonstrated the possibility of a combination of RL and Bayesian data assimilation in MIPD in oncology.⁶¹ Subsequent machine-learning reviews of anticancer precision dosing highlighted RL-like methods as emerging techniques for dose individualization and exposure-related toxicity control.⁶² RL agent could potentially be trained to optimize the dosing for venetoclax therapy by keeping the drug exposure concentration within a desired therapeutic window while minimizing the frequency of severe neutropenia and treatment interruptions. That is a conceptual idea that will still need careful prospective validation, but it is a logical next step when continuous sensing and Bayesian forecasting are available. From this point of view, the future of continuous TDM could move beyond passive monitoring to adaptive dose management, where every dosage decision is continuously adjusted using new patient information to maximise efficacy and minimise toxicity.^{61,62}

their typical inputs, clinical applications and current level of maturity in oncology.

Table 3. Summary of AI approaches and their possible roles in precision dosing

AI and Model ling approach	Typical data inputs	Primary function	Clinical output & role in precision dosing	Maturity level in oncology
PopPK models	Patient demographic s, organ function, laboratory covariates, and dosing history	Establish baseline pharmacokinetic (PK) parameters, such as clearance and volume of distribution, using population- level prior	Provide a priori starting doses and covariate- based dose selection for subsequent individualization	High (current standard) - PopPK models remain the backbone of most MIPD systems and the default basis for many clinical dosing
Bayesian updating (MIPD)	PopPK priors plus sparse TDM concentrations and relevant patient covariates	Recalibrate PK parameters for the individual patient using Bayesian/MA P estimation	Support posterior or dose adjustment to reach a target exposure, such as AUC or trough concentration	Moderate to high - Bayesian methods are the dominant computational engine of MIPD software, but real-world implementation still depends on model validation and workflow

				integrat ion. ^{32,63}		and outco me feedba ck	n- making	adjustm ent	dosing, but safety, interpre tability, delayed drug effects, and prospec tive validati on remain major barriers. 61,64
Contin uous ML patter n recogn ition	Contin uous sensor data, treatm ent histor y, and conco mitant drug inform ation	Detect non- linear exposu re pattern s, drift, and anomal ies in near real time	Enable exposur e forecast ing and early warnin g signals for toxicity or undere xposure	Low (experi mental) - ML shows promise in antican cer dose individ ualizati on, but publish ed evidenc e remains limited and mostly non- continu ous. ^{56,62}					
Mecha nistic digital twins	Contin uous PK data, serial labora tory marke rs, and diseas e-state bioma rkers	Simulat e patient- specific disease and toxicity trajecto ries using mechan istic or semi- mechan istic models	Predict neutrop enic timelin es and support individ ualized treatme nt schedul ing	Emergi ng - recent AML digital twin work demon strates feasibili ty, but patient- specific accurac y still varies and larger validati on is needed. 32,34					
Reinfo rceme nt learn ing	Longit udinal clinica l data, contin uous PK stream s, bioma rkers,	Optimi ze dosing actions through reward- based sequent ial decisio	Potenti al closed- loop adaptiv e dose generat ion and autono mous	Very low (theore tical) - RL is promisi ng for oncolog y and precisio n					

The section ‘Maturity Levels in Oncology’ discussed in Table III is an editorial synthesis based on the current literature and has not been evaluated using a formal scoring system.

Abbreviations: TDM, therapeutic drug monitoring; AUC, area under the curve; ISF, interstitial fluid; PopPK, population pharmacokinetics; MIPD, model-informed precision dosing; ML, machine learning, MAP, maximum a posteriori, PK, pharmacokinetic.

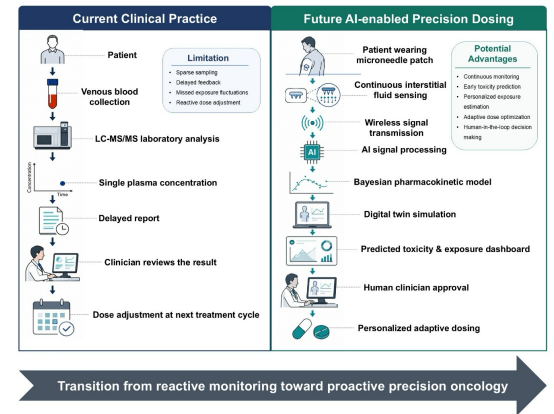


Fig. 2. Comparison between conventional TDM and future AI-enabled continuous precision dosing for venetoclax in AML

Figure 2 illustrates the difference between the existing intermittent TDM paradigm and a proposed continuous monitoring strategy, that aims to enable early treatment optimization and individualized dosing.

6. Proposed translational framework

A conceptual framework is proposed in Figure 1, which will demonstrate how the various technologies could be integrated in practice for continuous venetoclax monitoring in AML.

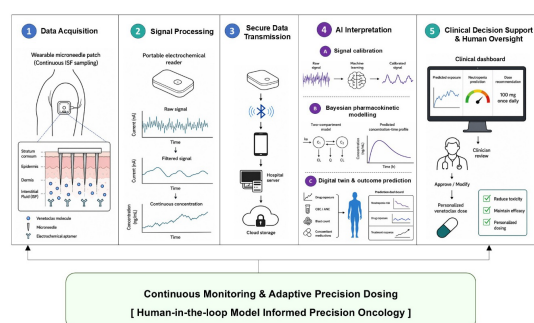


Fig. 3. Conceptual framework for continuous venetoclax monitoring and adaptive precision dosing in AML

(a) Data acquisition

This process starts with a minimally invasive microneedle patch, which is sterilised and placed in the dermis. The continuous sensing design features an aptamer layer that reaches into the dermal interstitial fluid and interacts with the drug in real time, with the electrode transducing the target binding into an electrochemical readout. The recent studies reveal that microneedle-enabled electrochemical aptamer system could realize real-time molecular monitoring in dermal interstitial fluid, showing its potential for translational biosensing.³⁰ The same reasoning could be applicable in the venetoclax setting to continuously capture a pharmacologically meaningful exposure signal, instead of one delayed plasma snapshot. This is an inference based on the literature available on biosensors, but it is consistent with the existing use of continuous molecular sensing in humans.³⁰

(b) Signal processing

A wearable potentiostat would then perform high-frequency electrochemical interrogation, and after filtering out the background noise, it would allow the target-related current to be separated from the nonspecific drift. This is not just for recording a waveform; it is about capturing the binding-related signal over a longer period to utilize in downstream modelling. Continuous aptamer-based sensing is especially appealing due to the ability to repeat measurements without requiring extra reagents, which would be ideal for long-term monitoring in an outpatient setting.³⁰

(c) Secure data transmission

The electrochemical signal produced by the wearable potentiostat needs to be securely sent to the downstream clinical decision-support infrastructure. In practice, the portable reader would communicate with a secure receiver, like a smartphone or a dedicated gateway via short-range wireless protocols like Bluetooth, and then the data would be transmitted to a hospital server or to a cloud-based analytics platform via secure channels. The literature on mHealth and wireless body area networks constantly highlights the need for access control, authentication, privacy authorization, and

Figure 3 depicts the proposed framework that integrates continuous TDM with computational decision support while maintaining human oversight to enable individual venetoclax dose adjustments. The framework is a conceptual model designed to direct future research and clinical translation, and is not clinically validated. It becomes clinically meaningful when the continuous signal is translated into a suitable pharmacometric interpretation that aids personalized dosing. MIPD approaches are specifically designed to read complex, longitudinal and clinically variable data to guide individualized dosing decisions.³²

secure key management in continuously monitored health systems, especially when sensitive patient information is shared via resource-constrained wearable devices.^{65,66} This transmission layer works as a liaison between the sensing device and the precision-dosing pharmacometric layer. It allows longitudinal data flow without compromising data integrity, confidentiality and patient privacy.

(d) AI interpretation and clinical action

Once the validated electrochemical measurements are securely transmitted to the clinical decision-support platform, they will enter the computational layer responsible for pharmacometric interpretation and individualized dose optimization. MIPD combines information from previous PopPK studies with Bayesian updating to translate a new patient measurement into an individualised estimate of parameters and prediction of dose. According to recent reviews, this approach is an exciting way forward in precision medicine, as dosing can be adjusted based on new information without having to wait for a new dosing cycle or a subsequent lab result.³² With a continuous venetoclax monitoring system, the model would provide continuous recalibration of exposure estimates, instead of relying on a single trough measurement. The same computational layer will then be used to translate the interstitial fluid signal to a predicted systemic exposure profile with a multi-compartment PK model. Continuous data can be utilized to develop personalized exposure profiles and forecast the risk of safe versus excessive drug exposure.

A digital twin can offer an additional layer of decision support to this oversight. Recent digital twin research within AML has shown that the model's predictive power increased as it was continually updated with new patient information.³⁴ In the proposed framework, continuous PK data would be incorporated into the digital twin, helping to understand drug exposure throughout treatment, as well as changes in bone marrow reserve and disease burden. If the model indicates that a new azole antifungal increases exposure to venetoclax, the dashboard might show the predicted toxicity curve before the onset of serious neutropenia. It

would provide a much richer view of what is going on inside the patient.³⁴

(c) Clinical decision support & human oversight

The final decision should be made by the clinician, even in a very automated system. In the foreseeable future, the most realistic system is not a completely autonomous closed-loop controller, but a human-in-the-loop system. In that design, the digital system would issue an alert, summarize the predicted risk, and provide a dose recommendation, but it would be up to the oncologist to decide whether to act on it. Clinicians can maintain control over treatment decisions by considering clinical symptoms, laboratory findings, bone marrow recovery, infection status, and other competing risks before making dose modifications.

7. Technical, ethical, and regulatory challenges

While the concept of continuous electrochemical sensing and AI-based dosing is appealing, multiple challenges must be addressed to make this approach part of routine AML care. The main difficulty is not in the availability of each component, but in achieving reliable integration of them in a complex clinical environment where accuracy, timeliness and patient safety are all essential.^{67,68} In practice, the biggest challenge for translation is to ensure the sensor platform, predictive model, and clinical decision-support system work seamlessly together as a whole and can make real-world clinical decisions, not just show feasibility in the lab.^{32,67}

7.1 Analytical validity and real-time accuracy

One of the biggest technical challenges is biofouling. When electrochemical sensors are inserted into biological fluids, proteins, lipids, salts, and cells can deposit on the sensor surface and, over time, cause the signal to become distorted.⁶⁹ Recent reviews of antifouling electrochemical sensing have highlighted that nonspecific adsorption is still a significant problem that can lead to reduced sensitivity, increased measurement drift, and reduced sensor lifetime, particularly in *in vivo* applications.^{68,70} The aptamer itself can also be susceptible to enzymatic degradation in the same environment, as natural DNA-based probes are still susceptible to cellular nuclease attack in physiological media. Due to this reason, *in vivo* signal degradation appears as a multifaceted problem that is exacerbated by surface fouling, target access limitations, and chemical instability.^{71,72}

Protection of the sensor surface and the nucleic acid recognition element is necessary to make a multi-day wearable device feasible. Anti-fouling strategies, especially zwitterionic polymer coatings, have consistently been demonstrated to suppress non-specific adsorption on biomedical surfaces, implants and biosensors, indicating their potential to sustain sensor functionality *in vivo*.^{73–75} Concurrently, xenonucleic acid (XNA) based technologies have the potential to further enhance

the longevity of EA sensors by minimizing signal drift caused by the nucleases in biological fluids.⁷²

While these strategies appear promising, they still need to be extensively validated in human biological matrices before they can be used clinically.

7.2 Calibration and reproducibility

A second barrier is calibration. In analytical chemistry, calibration is the process of comparing a measurement system to a reference standard to convert the signal into a reliable value. This is easy in the lab, but is more difficult when the sensor is intended to operate without manual adjustment for days on a patient.^{67,71} A venetoclax patch for guiding treatment must not only detect venetoclax binding events, but it must also have a sufficiently stable relationship between current and concentration, and that should not drift outside an acceptable range. Therefore, calibration and drift correction are considered as important design issues, rather than minor technical issues.^{32,71} Small temporal variations in sensor performance can be tolerated as long as computational methods distinguish true biological signals from artefacts caused by the ageing of the sensor and variability of the measurement. The strengths of MIPD and AI-based signal processing are that they can account for missing data, signal noise, and variability in physiology, but they need to be rigorously calibrated and externally validated.^{32,76}

7.3 Barriers to implementation in low-resource settings

The third challenge is about accessibility. The current conventional venetoclax TDM relies on LC-MS/MS, specialised laboratory procedures, and skilled laboratory staff. Published analytical methods mentioned that LC-MS/MS is highly informative, but also has cost and technical challenges that hamper wide use, particularly outside highly resourced centres.⁷⁷ Even if the patch itself were eventually made at a lower cost, there would still be a need for software, secure data handling, and a good analytics pipeline. That is, the device is just one component of the ecosystem; cloud services, server infrastructure, and support software are also part of the implementation burden.^{32,67,78}

Highly centralized systems can present adoption challenges in resource-limited hospitals, exacerbating the gap in healthcare. A more realistic translation model would be some localized or edge-based computing, where a core analysis could still take place even if the internet connection was unreliable or specialist support was not available. This interpretation is based on implementation literature and has not been directly tested in the context of venetoclax, but is based on known limitations of computational and laboratory resources.^{32,67}

7.4 Data privacy and regulatory approval

Lastly, there are significant privacy and regulatory concerns. Continuous monitoring generates sensitive health data that is transmitted wirelessly or stored in the cloud, and falls within the broader framework of health information protection.⁷⁹ For example, the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule sets standards for the protection of health information in the United States and requires safeguarding for the use, disclosure and security of health information.⁸⁰ Consequently, a secure system needs to be included during the design of venetoclax monitoring systems, not just applied at the end of development.^{80,81}

The regulatory pathway is also complex. This would actually operate as a combination product, which includes a physical sensing device coupled with software that interprets the signal and provides dosing information. The Food and Drug Administration (FDA) guidance acknowledges that software with an independent medical function could be considered SaMD and includes regulatory guidance for device software functions and AI/Machine Learning (ML)-enabled medical devices.^{67,78,81} Consequently, the level of evidence required would be far greater than for a basic assay. Before such a system would be utilized in clinical practice with AML, developers would have to demonstrate analytical validity, clinical utility, performance under operating conditions, cybersecurity protection, and safe human oversight.^{67,76}

8. Future research directions

A staged validation strategy will be necessary to advance the pathway from proof of concept to routine clinical care. The first priority for venetoclax monitoring is not necessarily clinical deployment, but the demonstration of stable, specific, and reproducible monitoring chemistry in a biologically relevant environment. Continuous EA sensing has successfully progressed beyond theory. A microneedle-enabled platform has demonstrated real-time molecular monitoring in human dermal interstitial fluid, and subsequent studies have extended this approach to antibiotic monitoring, such as vancomycin and gentamicin, in wearable microneedle formats. While these studies suggest the feasibility of continuous small-molecule sensing, there is still more work to be done with venetoclax-specific translation.^{30,31,82}

8.1 Preclinical development & validation studies

The next preclinical step is to develop a high-affinity, highly selective aptamer specific for venetoclax, followed by evaluation of its affinity in undiluted serum and interstitial fluid-like matrices, as well as in buffer. This is important since the in vivo sensing environment is chemically cluttered and subject to signal drift. The literature of published microneedle aptamer sensors has demonstrated that continuous sensing of dermal interstitial fluid is possible in human subjects, but also highlights the

challenges of matrix effects, signal stability, and surface fouling in translation.^{30,31} An important next step will be evaluation in large-animal models to determine insertion characteristics, tolerability, and foreign-body responses in tissue environments more similar to those in humans. This is in line with current microneedle development strategies, which assess microneedle penetration capacity, safety, and wearability prior to human trials.^{83,84}

8.2 Clinical trials and interdisciplinary collaboration

The initial human validation should be observational. The outputs from the wearable sensors should be validated against LC-MS/MS measurements under standard care conditions for agreement, lag time and analytical accuracy before having an impact on treatment decision. This approach is in line with current development of wearable sensors and with MIPD strategies that rely on validated data for clinical decision making.^{30,32}

After establishing analytic validity, a prospective randomized study is required to evaluate and compare standard empiric venetoclax therapy with AI-assisted, continuous TDM. Key clinical outcomes would be severe neutropenia, cycle delays, burden of infection, hospitalisation and retention of remission quality, including MRD negativity if applicable. A successful trial would have to demonstrate that the system is technically accurate and it enhances clinically meaningful outcomes without compromising disease control. Getting there will involve tight collaboration between the hematologists, biosensor engineers, pharmacometricians, and data scientists, since the platform is not only about chemistry and medicine, but also includes software and implementation science as well.^{32,34}

9. Conclusion

Although venetoclax has revolutionised the treatment of AML, the drug remains challenging to use due to its complex pharmacokinetics, DDIs, and toxicity. The reliance on occasional sampling provides only a small-scale idea regarding exposure and fails to provide the dynamic picture of changes in concentrations in a delicate haematological environment. Wearable microneedle-integrated electrochemical aptamer sensors could be a potential platform for continuous monitoring, and real-time ISF sensing has been demonstrated for selected small molecules in humans. Together with AI, Bayesian pharmacokinetic modelling, and digital-twin reasoning, this continuous signal opens the door to a vision of a true closed-loop precision dosing framework for AML. Even though there are still challenges to overcome like sensor stability, biofouling, calibration drift, regulatory approval and extensive prospective validation, the future of venetoclax monitoring appears to be moving towards a shift from sparse sampling toward continuous characterization of drug exposures. If

this bridge is successfully constructed, it can offer a better means of toxicity control while maintaining antileukemic effects and bringing AML therapy closer to real-time precision oncology goals

Acknowledgements

We acknowledge the contributions of librarians at M. S. Ramaiah University of Applied Sciences, Bengaluru, India, for providing access to the literature and support.

Author contributions

Swarnendu Sahoo: Conceptualization, Investigation, Formal Analysis, Visualization, Writing – Original Draft, Writing – Review & Editing, Project Administration. **Eswaran Maheswari:** Supervision, Investigation, Validation, Writing – Review & Editing. **Nishil Gowda:** Investigation, Validation, Writing – Review & Editing. **Harish Kausik Kotakonda:** Methodology, Formal Analysis, Validation, Writing – Review & Editing.

Conflict of interest

The authors declare no conflict of interest.

Data Availability Statement

Not applicable.

Declaration of AI-assisted Tools in the Writing Procedure

Grammarly was used to improve the English language, grammar, and overall readability of the manuscript. The authors carefully reviewed and approved the revised text and retain full responsibility for the final content. No AI-assisted tools were used to generate or prepare any figures or graphical abstracts presented in this manuscript.

Ethical Approval

Not applicable.

Funding

This paper was not funded.

References

1. Bhansali RS, Pratz KW, Lai C. Recent advances in targeted therapies in acute myeloid leukemia. *J Hematol Oncol* 2023;16(1). doi:10.1186/s13045-023-01424-6
2. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med* 2020;383(7):617-629. doi:10.1056/NEJMOA2012971
3. Roberts AW, Stilgenbauer S, Seymour JF, Huang DCS. Venetoclax in Patients with Previously Treated Chronic Lymphocytic Leukemia. *Clin Cancer Res* 2017;23(16):4527-4533. doi:10.1158/1078-0432.CCR-16-0955
4. Cao Q, Wu X, Zhang Q, Gong J, Chen Y, You Y, et al. Mechanisms of action of the BCL-2 inhibitor venetoclax in multiple myeloma: a literature review. *Front Pharmacol* 2023;14:1291920. doi:10.3389/fphar.2023.1291920
5. Garciaz S, Saillard C, Hicheri Y, Hospital MA, Vey N. Venetoclax in Acute Myeloid Leukemia: Molecular Basis, Evidences for Preclinical and Clinical Efficacy and Strategies to Target Resistance. *Cancers (Basel)* 2021;13(22):5608. doi:10.3390/cancers13225608
6. Salem AH, Menon RM. Clinical pharmacokinetics and pharmacodynamics of venetoclax, a selective B-cell lymphoma-2 inhibitor. *Clin Transl Sci* 2024;17(5):e13807. doi: 10.1111/cts.13807
7. Agarwal SK, DiNardo CD, Potluri J, Dunbar M, Kantarjian HM, Humerickhouse RA, et al. Management of Venetoclax-Posaconazole Interaction in Acute Myeloid Leukemia Patients: Evaluation of Dose Adjustments. *Clin Ther* 2017;39(2):359-367. doi:10.1016/j.clinthera.2017.01.003
8. De Gregori S, Gelli E, Capone M, Gambini G, Roncoroni E, Rossi M, et al. Pharmacokinetics of Venetoclax Co-Administered with Posaconazole in Patients with Acute Myeloid Leukemia. *Pharmaceutics* 2023;15(6):1680. doi:10.3390/pharmaceutics15061680
9. Yang X, Mei C, He X, He L, Lu X, Tong H, et al. Quantification of Venetoclax for Therapeutic Drug Monitoring in Chinese Acute Myeloid Leukemia Patients by a Validated UPLC-MS/MS Method. *Molecules* 2022;27(5):1607. doi:10.3390/molecules27051607
10. Kobayashi M, Yasu T, Suzaki K, Kosugi N. Utility of therapeutic drug monitoring of venetoclax in acute myeloid leukemia. *Med Oncol* 2022;39(12):259. doi:10.1007/s12032-022-01865-y
11. Salem AH, Agarwal SK, Dunbar M, Nuthalapati S, Chien D, Freise KJ, et al. Effect of Low- and High-Fat Meals on the Pharmacokinetics of Venetoclax, a Selective First-in-Class BCL-2 Inhibitor. *J Clin Pharmacol* 2016;56(11):1355-1361. doi:10.1002/jcph.741
12. Cheung TT, Salem AH, Menon RM, Munasinghe WP, Bueno OF, Agarwal SK. Pharmacokinetics of the BCL-2 Inhibitor Venetoclax in Healthy Chinese Subjects. *Clin Pharmacol Drug Dev* 2018;7(4):435-440. doi:10.1002/cpdd.395
13. Therapeutic Goods Administration (TGA). PRODUCT INFORMATION VENCLEXTA® (VENETOCLAX). 2017. Accessed August 15, 2026. Available from: <https://www.tga.gov.au/sites/default/files/auspar-venetoclax-171109-pi.pdf>

14. Levens AD, Rijstenbil J, Metscher E, von dem Borne P, Albersen A, Swen JJ, et al. Clinical Validation of Venetoclax Volumetric Microsampling in Patients with Leukemia with Assessment of Whole-Blood-to-Plasma Conversion Strategies and Self-Microsampling Feasibility. *Clin Pharmacokinet* 2026;65(6):863-882. doi:10.1007/s40262-026-01635-3
15. Liu H, Michmerhuizen MJ, Lao Y, Wan K, Salem AH, Sawicki J, et al. Metabolism and Disposition of a Novel B-Cell Lymphoma-2 Inhibitor Venetoclax in Humans and Characterization of Its Unusual Metabolites. *Drug Metab Dispos* 2017;45(3):294-305. doi:10.1124/dmd.116.071613
16. Puisset F, Raffoux E, Ades L, Huynh T, Itzykson R, Bouscary D, et al. Exposure toxicity of venetoclax in acute myeloid leukemia patients in the real-life setting: impact of high exposure on delayed neutropenia. *Haematologica* 2025;110(7):1649-1653. doi:10.3324/haematol.2024.286062
17. Kobayashi T, Sato H, Miura M, Fukushi Y, Kuroki W, Ito F, et al. Overexposure to venetoclax is associated with prolonged-duration of neutropenia during venetoclax and azacitidine therapy in Japanese patients with acute myeloid leukemia. *Cancer Chemother Pharmacol*. 2024;94(2):285-296. doi:10.1007/s00280-024-04673-5
18. Li Y, Wan Q, Wan J, Xiao X, Hu J, Yang X, et al. Plasma concentrations of venetoclax and Pharmacogenetics correlated with drug efficacy in treatment naïve leukemia patients: a retrospective study. *Pharmacogenomics J* 2024;24(6):37. doi:10.1038/s41397-024-00359-6
19. Brackman D, Eckert D, Menon R, Salem AH, Potluri J, Smith BD, et al. Venetoclax exposure-efficacy and exposure-safety relationships in patients with treatment-naïve acute myeloid leukemia who are ineligible for intensive chemotherapy. *Hematol Oncol* 2022;40(2):269-279. doi:10.1002/hon.2964
20. Agarwal SK, Salem AH, Danilov AV, Hu B, Puvvada S, Gutierrez M, et al. Effect of ketoconazole, a strong CYP3A inhibitor, on the pharmacokinetics of venetoclax, a BCL-2 inhibitor, in patients with non-Hodgkin lymphoma. *Br J Clin Pharmacol* 2017;83(4):846-854. doi:10.1111/bcp.13175
21. Sani B, Cignetti A, Loporati M, Sommariva S, Armenio M, Tenace V, et al. Real-World Experience with Venetoclax Therapeutic Drug Monitoring in Acute Myeloid Leukemia: Role of Posaconazole, Correlation with Safety and Efficacy. *Oncol Res* 2026. doi:10.32604/or.2026.078245
22. Yang Y, Zhao L, Wu Y. The venetoclax conundrum: Therapeutic drug monitoring of venetoclax: Correlation with response in Acute Myeloid Leukemia?. *Blood* 2025;146(Suppl 1):5234. doi:10.1182/blood-2025-5234
23. Stojanova J, Carland JE, Murnion B, Seah V, Siderov J, Lemaître F. Therapeutic drug monitoring in oncology - What's out there: A bibliometric evaluation on the topic. *Front Oncol* 2022;12:959741. doi:10.3389/fonc.2022.959741
24. Tamargo J, Le Heuzey JY, Mabo P. Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide. *Eur J Clin Pharmacol* 2015;71(5):549-567. doi:10.1007/s00228-015-1832-0
25. Philippe M, Guitton J, Favier B, Santana C, Nicolas-Virelizier E, Guillermin Y, et al. Venetoclax Pharmacokinetics in Real World AML Patients: A Real Candidate for Therapeutic Drug Monitoring. *Blood* 2022;140(Suppl 1):6179-6180. doi:10.1182/blood-2022-168327
26. Nancy M Nix AP. Acute Myeloid Leukemia: An Ever-Changing Disease. *J Adv Pract Oncol* 2019;10(Suppl 4):4-8. doi:10.6004/jadpro.2019.10.8.12
27. Skelding KA, Barry DL, Theron DZ, Lincz LF. Bone Marrow Microenvironment as a Source of New Drug Targets for the Treatment of Acute Myeloid Leukaemia. *Int J Mol Sci* 2022;24(1):563. doi:10.3390/ijms24010563
28. Pimenta DB, Varela VA, Datoguia TS, Caraciolo VB, Lopes GH, Pereira WO. The Bone Marrow Microenvironment Mechanisms in Acute Myeloid Leukemia. *Front Cell Dev Biol* 2021;9:764698. doi:10.3389/fcell.2021.764698
29. Lucas CJ, Martin JH. Pharmacokinetic-Guided Dosing of New Oral Cancer Agents. *J Clin Pharmacol* 2017;57(Suppl 10):S78-S98. doi:10.1002/jcph.937
30. Friedel M, Werbovetz B, Drexelius A, Watkins Z, Bali A, Plaxco KW, et al. Continuous Molecular Monitoring of Human Dermal Interstitial Fluid with Microneedle-Enabled Electrochemical Aptamer Sensors. *Lab Chip* 2023;23(14):3289-3299. doi:10.1039/d3lc00210a
31. Wu Y, Tehrani F, Teymourian H, Mack J, Shaver A, Reynoso M, et al. Microneedle Aptamer-Based Sensors for Continuous, Real-Time Therapeutic Drug Monitoring. *Anal Chem* 2022;94(23):8335-8345. doi:10.1021/acs.analchem.2c00829

32. Minichmayr IK, Dreesen E, Centanni M, Wang Z, Hoffert Y, Friberg LE, et al. Model-informed precision dosing: State of the art and future perspectives. *Adv Drug Deliv Rev* 2024;215:115421. doi:10.1016/j.addr.2024.115421
33. Wicha SG, Mårtson AG, Nielsen EI, Koch BCP, Friberg LE, Alffenaar JW, et al. From Therapeutic Drug Monitoring to Model-Informed Precision Dosing for Antibiotics. *Clin Pharmacol Ther* 2021;109(4):928-941. doi:10.1002/cpt.2202
34. Zhang Y, Martinez J, Tercan B, et al. Digital twin models for predicting venetoclax and azacitidine-induced neutropenia in patients with acute myeloid leukemia. *NPJ Digit Med* 2025;8(1):596. doi:10.1038/S41746-025-01978-4
35. Dauphin-Ducharme P, Yang K, Arroyo-Currás N, Kuusanmäki H, Emmert-Streib F, Chandraseelan JG, et al. Electrochemical Aptamer-Based Sensors for Improved Therapeutic Drug Monitoring and High-Precision, Feedback-Controlled Drug Delivery. *ACS Sens* 2019;4(10):2832-2837. doi:10.1021/acssensors.9b01616
36. Swensen JS, Xiao Y, Ferguson BS, Lubin AA, Lai RY, Heeger AJ, et al. Continuous, real-time monitoring of cocaine in undiluted blood serum via a microfluidic, electrochemical aptamer-based sensor. *J Am Chem Soc* 2009;131(12):4262-4266. doi:10.1021/JA806531Z
37. Sequeira-Antunes B, Ferreira HA. Nucleic Acid Aptamer-Based Biosensors: A Review. *Biomedicines* 2023;11(12):3201. doi:10.3390/biomedicines11123201
38. Downs AM, Bolotsky A, Weaver BM, Bennett H, Wolff N, Polsky R, et al. Microneedle electrochemical aptamer-based sensing: Real-time small molecule measurements using sensor-embedded, commercially-available stainless steel microneedles. *Biosens Bioelectron* 2023;236:115408. doi:10.1016/j.bios.2023.115408
39. Wu Y, Tehrani F, Teymourian H, Mack J, Shaver A, Reynoso M, et al. Microneedle Aptamer-Based Sensors for Continuous, Real-Time Therapeutic Drug Monitoring. *Anal Chem* 2022;94(23):8335-8345. doi:10.1021/acs.analchem.2c00829
40. Rawson TM, Gowers SAN, Freeman DME, Wilson RC, Sharma S, et al. Microneedle biosensors for real-time, minimally invasive drug monitoring of phenoxymethylpenicillin: a first-in-human evaluation in healthy volunteers. *Lancet Digit Health* 2019;1(7):e335-e343. doi:10.1016/s2589-7500(19)30131-1
41. Gonzalez D, Schmidt S, Derendorf H. Importance of Relating Efficacy Measures to Unbound Drug Concentrations for Anti-Infective Agents. *Clin Microbiol Rev* 2013;26(2):274-288. doi:10.1128/CMR.00092-12
42. Liu Y, Mack JO, Shojaee M, Shaver A, George A, Clarke W, et al. Analytical Validation of Aptamer-Based Serum Vancomycin Monitoring Relative to Automated Immunoassays. *ACS Sens* 2024;9(1):228-235. doi:10.1021/acssensors.3C01868
43. Chien JC, Baker SW, Soh HT, Arbabian A. Design and Analysis of a Sample-and-Hold CMOS Electrochemical Sensor for Aptamer-based Therapeutic Drug Monitoring. *IEEE J Solid-State Circuits* 2020;55(11):2914-2929. doi:10.1109/jssc.2020.3020789
44. Lafuente Cabrero E, Terradas Robledo R, Civit Cuñado A, García Sardelli D, Hidalgo López C, Giro Formatger D, et al. Risk factors of catheter-associated bloodstream infection: Systematic review and meta-analysis. *PLoS One* 2023;18(3):e0282290. doi:10.1371/journal.pone.0282290
45. Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S. Catheter-related bloodstream infections. *Int J Crit Illn Inj Sci* 2014;4(2):162-167. doi:10.4103/2229-5151.134184
46. Van Epps JS, Younger JG. Implantable Device-Related Infection. *Shock* 2016;46(6):597-608. doi:10.1097/SHK.0000000000000692
47. Adaway JE, Keevil BG. Therapeutic drug monitoring and LC-MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci* 2012;883-884:33-49. doi:10.1016/j.jchromb.2011.09.041
48. Avataneo V, D'Avolio A, Cusato J, Cantù M, De Nicolò A. LC-MS application for therapeutic drug monitoring in alternative matrices. *J Pharm Biomed Anal* 2019;166:40-51. doi:10.1016/j.jpba.2018.12.040
49. Juska VB, Pemble ME. A Critical Review of Electrochemical Glucose Sensing: Evolution of Biosensor Platforms Based on Advanced Nanosystems. *Sensors (Basel)* 2020;20(21):6013. doi:10.3390/S20216013
50. Guoqiang G, Liang Q, Yani Z, Pengyun W, Fanzhuo K, Yuyang Z, et al. Recent advances in glucose monitoring utilizing oxidase electrochemical biosensors integrating carbon-based nanomaterials and smart enzyme design. *Front Chem* 2025;13:1591302. doi:10.3389/fchem.2025.1591302

51. Friedel M, Werbovetz B, Drexelius A, Plaxco K, Heikenfeld J. Continuous Molecular Monitoring of Human Dermal Interstitial Fluid with Microneedle-Enabled Electrochemical Aptamer Sensors. *Lab Chip* 2023;23(14):3289-3299. doi:10.1039/d3lc00210a
52. Li S, Dai J, Zhu M, Arroyo-Currás N, Li H, Wang Y, et al. Implantable Hydrogel-Protective DNA Aptamer-Based Sensor Supports Accurate, Continuous Electrochemical Analysis of Drugs at Multiple Sites in Living Rats. *ACS Nano* 2023;17(18):18525-18538. doi:10.1021/acsnano.3C06520
53. Liu Y, Liu Z, Zhou Y, Tian Y. Implantable Electrochemical Sensors for Brain Research. *JACS Au* 2023;3(6):1572-1582. doi:10.1021/jacsau.3c00200
54. Kantasiripitak W, Van Daele R, Gijzen M, Ferrante M, Spriet I, Dreesen E. Software Tools for Model-Informed Precision Dosing: How Well Do They Satisfy the Needs? *Front Pharmacol* 2020;11:620. doi:10.3389/fphar.2020.00620
55. Minichmayr IK, Dreesen E, Centanni M, Wang Z, Hoffert Y, Friberg LE, et al. Model-informed precision dosing: State of the art and future perspectives. *Adv Drug Deliv Rev* 2024;215:115421. doi:10.1016/j.addr.2024.115421
56. Poweleit EA, Vinks AA, Mizuno T. Artificial Intelligence and Machine Learning Approaches to Facilitate Therapeutic Drug Management and Model-Informed Precision Dosing. *Ther Drug Monit* 2023;45(2):143-150. doi:10.1097/FTD.0000000000001078
57. Oda K, Saito H, Jono H. Bayesian prediction-based individualized dosing of anti-methicillin-resistant *Staphylococcus aureus* treatment: Recent advancements and prospects in therapeutic drug monitoring. *Pharmacol Ther.* 2023;246:108433. doi:10.1016/j.pharmthera.2023.108433
58. Maier C, de Wiljes J, Hartung N, Kloft C, Huisinga W. A continued learning approach for model-informed precision dosing: Updating models in clinical practice. *CPT Pharmacometrics Syst Pharmacol* 2022;11(2):185-198. doi:10.1002/psp4.12745
59. Wang H, Arulraj T, Ippolito A, Popel AS. From virtual patients to digital twins in immuno-oncology: lessons learned from mechanistic quantitative systems pharmacology modeling. *NPJ Digit Med* 2024;7(1):189. doi:10.1038/s41746-024-01188-4
60. Hernandez-Boussard T, Macklin P, Greenspan EJ, Gryshuk AL, Stahlberg E, Syeda-Mahmood T, et al. Digital twins for predictive oncology will be a paradigm shift for precision cancer care. *Nat Med* 2021;27(12):2065-2066. doi:10.1038/s41591-021-01558-5
61. Maier C, Hartung N, Kloft C, Huisinga W, de Wiljes J. Reinforcement learning and Bayesian data assimilation for model-informed precision dosing in oncology. *CPT Pharmacometrics Syst Pharmacol* 2021;10(3):241-254. doi:10.1002/psp4.12588
62. Teplytska O, Ernst M, Koltermann LM, Valderrama D, Trunz E, Vaisband M, et al. Machine Learning Methods for Precision Dosing in Anticancer Drug Therapy: A Scoping Review. *Clin Pharmacokinet* 2024;63(9):1221-1237. doi:10.1007/s40262-024-01409-9
63. Del Valle-Moreno P, Suarez-Casillas P, Mejías-Trueba M, Ciudad-Gutiérrez P, Guisado-Gil AB, Gil-Navarro MV, et al. Model-Informed Precision Dosing Software Tools for Dosage Regimen Individualization: A Scoping Review. *Pharmaceutics* 2023;15(7):1859. doi:10.3390/pharmaceutics15071859
64. Eckardt JN, Wendt K, Bornhäuser M, Middeke JM. Reinforcement Learning for Precision Oncology. *Cancers (Basel)* 2021;13(18):4624. doi:10.3390/cancers13184624
65. Horn Iwaya L, Ahmad A, Ali Babar M. Security and Privacy for mHealth and uHealth Systems: a Systematic Mapping Study. *IEEE Access* 2020;8:150081-150112. doi:10.1109/ACCESS.2020.3015962
66. Jahan M, Tuz Zohra F, Kamal Parvez M, Kabir U, Mohaimen Al Radi A, Kabir S. An End-to-End Authentication Mechanism for Wireless Body Area Networks. *Smart Health* 2023;29:100413. doi:10.1016/j.smhl.2023.100413
67. U.S. Food and Drug Administration. Content of Premarket Submissions for Device Software Functions. 2023. Accessed June 15, 2026. Available from: <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information->
68. Lin PH, Li BR. Antifouling strategies in advanced electrochemical sensors and biosensors. *Analyst* 2020;145(4):1110-1120. doi:10.1039/c9an02017a
69. Lenar N, Paczosa-Bator B. Why Sensors Fail in Biological Samples: Fouling, Blocking, Matrix Effects and Prevention

- Solutions. *Int J Mol Sci* 2026;27(12):5176. doi:10.3390/ijms27125176
70. Song Z, Han R, Yu K, Li R, Luo X. Antifouling strategies for electrochemical sensing in complex biological media. *Mikrochim Acta* 2024;191(3):138. doi:10.1007/s00604-024-06218-2
71. Sonntag O, Loh TP. Calibration – an under-appreciated component in the analytical process of the medical laboratories. *Adv Lab Med* 2023;5(2):148-152. doi:10.1515/almed-2023-0127
72. Leung KK, Gerson J, Emmons N, Heemstra JM, Kippin TE, Plaxco KW. The Use of Xenonucleic Acids Significantly Reduces the In Vivo Drift of Electrochemical Aptamer-Based Sensors. *Angew Chem Int Ed Engl* 2024;63(21):e202316678. doi:10.1002/anie.202316678
73. Li Q, Wen C, Yang J, Zhou X, Zhu Y, Zheng J, et al. Zwitterionic Biomaterials. *Chem Rev* 2022;122(23):17073-17154. doi:10.1021/acs.chemrev.2c00344
74. Moayedi S, Xia W, Lundergan L, Yuan H, Xu J. Zwitterionic Polymers for Biomedical Applications: Antimicrobial and Antifouling Strategies toward Implantable Medical Devices and Drug Delivery. *Langmuir* 2024;40(44):23125-23145. doi:10.1021/acs.langmuir.4c02664
75. Blackman LD, Gunatillake PA, Cass P, Locock KES. An introduction to zwitterionic polymer behavior and applications in solution and at surfaces. *Chem Soc Rev* 2019;48(3):757-770. doi:10.1039/c8cs00508g
76. U.S. Food and Drug Administration. Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations. 2025. Accessed June 15, 2026. Available from: <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information->
77. Barzani HAH, Sulaiman SH, Omer RA, Mer AH, Ali HS. Analytical techniques for methyl dopa and metabolites: a comprehensive review. *Drug Metab Rev* 2025;57(4):559-594. doi:10.1080/03602532.2025.2560487
78. U.S. Food and Drug Administration. Software as a Medical Device (SaMD). 2018. Accessed June 15, 2026. Available from: <https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd>
79. Jian W, Tabassum A, Li JP. Systematic survey on data security in wireless body area networks in IoT healthcare system. *Front Med (Lausanne)* 2024;11:1422911. doi:10.3389/fmed.2024.1422911
80. HHS. The HIPAA Privacy Rule. 2024. Accessed June 15, 2026. Available from: <https://www.hhs.gov/hipaa/for-professionals/privacy/laws-regulations/index.html>
81. U.S. Food and Drug Administration. Artificial Intelligence in Software as a Medical Device. 2025. Accessed June 15, 2026. Available from: <https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-software-medical-device>
82. Keyvani F, GhavamiNejad P, Saleh MA, Soltani M, Zhao Y, Sadeghzadeh S, et al. Integrated Electrochemical Aptamer Biosensing and Colorimetric pH Monitoring via Hydrogel Microneedle Assays for Assessing Antibiotic Treatment. *Adv Sci (Weinh)* 2024;11(41):e2309027. doi:10.1002/advs.202309027
83. Zheng M, Sheng T, Yu J, Gu Z, Xu C. Microneedle biomedical devices. *Nature Reviews Bioengineering* 2024;2(4):324-342. doi:10.1038/s44222-023-00141-6
84. Oliveira C, Teixeira JA, Oliveira N, Ferreira S, Botelho CM. Microneedles' Device: Design, Fabrication, and Applications. *Macromol* 2024;4(2):320-355. doi:10.3390/macromol4020019