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Machine Learning to Diagnose Complications of Diabetes

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Abstract

Machine learning (ML) uses computer systems to develop statistical algorithms and statistical models that can draw inferences from demographic data, structured behavioral data, continuous glucose monitor (CGM) tracings, laboratory data, cardiovascular and neurological physiology measurements, and images from a variety of sources. ML is becoming increasingly used to diagnose complications of diabetes based on these types of datasets. In this article, we review the current status, barriers to progress, and future prospects for using ML to diagnose seven complications of diabetes, including five traditional complications, one set of other systemic complications, and one prediction that can result in favorable or unfavorable outcomes. The complications include (1) diabetic retinopathy, (2) diabetic nephropathy, (3) peripheral neuropathy, (4) autonomic neuropathy, (5) diabetic foot ulcers, and (6) other systemic complications. The prediction is for outcomes in hospitalized patients with diabetes. ML for these purposes is in its infancy, as evidenced by only a limited number of products having received regulatory clearance at this time. However, as multicenter reference datasets become available, it will become possible to train algorithms on increasingly larger and more complex datasets and patterns so that diagnoses and predictions will become increasingly accurate. The use of novel choices of images and imaging technologies will contribute to progress in this field. ML is poised to become a widely used tool for the diagnosis of complications and predictions of outcomes and glycemia in people with diabetes.

Keywords

artificial intelligence, complications, diabetes, diagnosis, machine learning, prognosis

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Introduction

Diabetes is consistently ranked among the leading causes of disability-adjusted life years (DALYs)—a metric that accounts for both premature death and years lived with the disease—in both the United States and globally.[1,2] Despite advances in therapeutic strategies, diabetes has remained a major contributor to premature mortality and morbidity over the past two decades,[3] primarily due to its associated microvascular and macrovascular complications.[4]

Early diagnosis and proactive management of complications are critical to improving outcomes. Artificial intelligence (AI) technologies are increasingly enabling earlier and more accurate detection of diabetes and its complications, supporting clinicians through predictive analytics, and empowering patients with personalized treatment recommendations and real-time monitoring.[5,6] However, the performance of current machine learning (ML) algorithms remains limited, not only due to the lack of sufficient diabetes-specific databases, but also because of the scarcity of multicenter, clinically diverse data, as well as the suboptimal quality of and limited integration with electronic health records (EHRs).[7]

Most current ML algorithms for diabetes remain confined to research settings, with limited external validation and uneven implementation in clinical practice.[8] Overcoming these barriers may be possible through attention to features of databases, which support the development of sound ML models, as presented in Table 1.[9] These features lead to more robust and higher-quality ML algorithms, essential for realizing the transformative potential of AI in diabetes prevention, diagnosis, and long-term management.

In this paper, we review the current landscape of ML-based tools developed to diagnose or predict complications of diabetes. We highlight both their scientific potential and the clinical barriers to implementation, aiming to inform and guide future efforts to integrate ML into real-world diabetes care.

Table 1. Features of a Sound Reference Database for Developing a High-Quality ML Algorithm.

	Features	Benefits
1	Relevant (Quality)	Improves Effectiveness
2	Multisource (Quantity)	Reduces Bias
3	Clean Images and Data	Improves Accuracy
4	Common Data/Reporting Standards	Improves Reliability
5	Detailed Phenotype/Demographics	Improves Completeness
6	Cleanly Annotated Data	Improves Consistency
7	Validation of Data	Increases Confidence
8	Addressing Fairness	Promotes Equity and Builds Trust
9	Publicly Accessible Database	Promotes Confidence by Patients
10	Understandable Output	Promotes Uptake by Clinicians
11	Integration into the EHR	Promotes Uptake by Researchers

Abbreviations: EHR = electronic health record; ML = machine learning.

Tools Needed for Data Analysis Using ML

Currently, ML commonly uses six types of tools for diagnosis of diabetic complications. These include data preprocessing to clean and impute data,[10] frameworks to enable model training,[11] evaluation to validate models,[12] image processing to analyze visual data,[13] data integration to merge data from multiple sources,[14] and pipelines to sustain solutions once data integration is in place.[15] To help improve the accuracy of ML to diagnose or predict diabetes complications, there exist needs for larger and more diverse datasets of diabetes patients to improve generalizability, interoperability standards to combine datasets, greater transparency to support trust by clinicians and regulators, and better integration with workflows to demonstrate value.[16-18] For clinicians, three ML-powered devices are cleared by the US Food and Drug Administration (FDA) to diagnose any diabetic complication. These devices for diagnosis or treatment of five diabetic complications are presented in Table 2. All three employ deep learning algorithms to analyze retinal images for diabetic retinopathy and deliver point-of-care diagnostic decisions autonomously, without the need for specialist oversight.

Explainable AI (also known as XAI) is an important approach to understand the factors that have gone into complex ML conclusions. XAI has become increasingly important in the past decade as ML models have become increasingly complex and opaque.[19] Examples of XAI methods include Shapley values, LIME (Local Interpretable Model-agnostic Explanations), Saliency maps, and Attention maps.[20] These are methods that provide insight into why an ML model made a particular prediction by showing which data elements were most influential for a given prediction. The use of XAI supports trust, transparency, and confidence in actionable insights in ML-driven decision making.[21] XAI is helpful to a clinician who is weighing advantages and disadvantages of a diagnostic algorithm that favors sensitivity (with attendant false positives who might require inconvenient and costly retesting) or an algorithm that favors specificity (with attendant missed cases who might progress in severity because of a delayed diagnosis).[22] When ML-powered screening is used for making diagnoses, it is necessary to establish guardrails to plan criteria for follow-up screening because of the risks of false positives and false negatives.

ML to Diagnose Retinopathy

- Multiple ML models using fundus photography have demonstrated high diagnostic performance for detecting diabetic retinopathy, with three systems now FDA-cleared and integrated into national screening programs.

Table 2. Machine Learning Applications for the Diagnosis and Prediction of Five Diabetes-Related Complications, Including Retinopathy, Nephropathy, Peripheral Neuropathy, Autonomic Neuropathy, and Foot Ulcers.

Complication	Current clinical status	FDA-cleared products in use	Products in development
Diabetic Retinopathy	The most patients with any diabetes complication are being diagnosed with this complication	Yes—three products: 1. IDx-DR (now known as Luminetics Core by Digital Diagnostics) 2. Eye Art (Eyenuk) 3. AEYE-DS (AEYE Health)	Yes
Diabetic Nephropathy	ML models show strong diagnostic and prognostic potential using biopsy and clinical data	No	Yes
Peripheral Neuropathy	ML applied in early detection using corneal confocal microscopy, clinical data, and wearable sensors	No	Yes
Autonomic Neuropathy	ML used to predict cardiovascular autonomic neuropathy using EHR and wearable sensor data	No	Yes
Diabetic Foot Ulcers	ML used for classification of wounds and risk prediction; not yet widely adopted	Yes	Yes

This table outlines the current clinical status and specific ML-based tools or models described in the text, including those cleared by the FDA in use and those under development.
Abbreviations: AEYE-DS = AEYE Diagnostic Screening; EHR = electronic health record; IDx-DR = Intelligent Diagnostics for Diabetic Retinopathy; ML = machine learning.

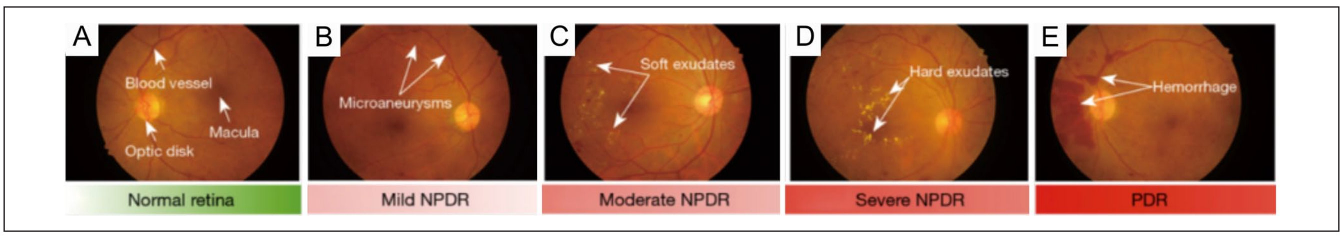

Figure 1. Representative fundus images depicting the progression of diabetic retinopathy (DR). (A) Normal retina. (B) Mild non-proliferative diabetic retinopathy (NPDR) with microaneurysms. (C) Moderate NPDR with soft exudates. (D) Severe NPDR with hard exudates. (E) Proliferative diabetic retinopathy (PDR) with hemorrhages. These abnormalities are key features used by clinicians and machine learning (ML) models for DR detection and grading. Images were modified from the open-source Indian Diabetic Retinopathy Image Dataset (IDRiD).[23] Adapted from the original composite layout created by Mateen et al[24] under the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

- Despite strong performance, many models are limited by their narrow datasets, inconsistent labeling standards, and a lack of demographic subgroup reporting.
- Future ML systems in diabetic retinopathy are shifting toward personalized risk prediction, multimodal integration, and equitable deployment through smartphone-based tools and models like DeepDR+.

Current Status of ML to Diagnose Retinopathy

Diabetic retinopathy (DR), a leading cause of preventable blindness worldwide, is a microvascular complication of diabetes characterized by progressive retinal damage. Because DR progression varies widely across patients, implementing consistent screening practices across different clinical settings remains a challenge. As seen in Figure 1, traditional DR diagnosis relies on fundus photography interpreted by trained graders or ophthalmologists using the Early Treatment Diabetic Retinopathy Study (ETDRS) or International Clinical Diabetic Retinopathy (ICDR) scales, which are systems used to classify the severity of DR.[25] However, manual grading is time-consuming and can vary significantly between reviewers.[26]

ML, a subset of AI, has emerged as a promising tool for automated DR detection. Deep learning models—particularly convolutional neural networks (CNNs), which are designed to learn and process grid-like data such as images—can recognize patterns in fundus images to classify disease.[27] Fundus images are generated by capturing reflected light from the interior surface of the eye, providing a two-dimensional (2D) representation of the three-dimensional (3D) retinal structures, including the retina, optic disk, macula, and blood vessels.[28] In 2018, Intelligent Diagnostics for Diabetic Retinopathy (IDx-DR) became the first FDA-cleared autonomous ML diagnostic system. In a prospective trial of 900 patients in primary care clinics, IDx-DR demonstrated 87.2% sensitivity and 90.7%

specificity for detecting more-than-mild diabetic retinopathy (mtmDR), enabling autonomous diagnosis in settings without a specialist.[29]

Recent systematic reviews support the broader accuracy of ML screeners. A 2021 systematic review and meta-analysis of 60 studies reported pooled sensitivity of 95% for mtmDR, with area under the curve (AUC) values exceeding 0.97.[30] National screening programs in Europe have begun incorporating ML tools as first-pass graders. In Scotland and Portugal, systems such as iGradingM and Retmarker have automated triage, reserving ophthalmologists for borderline cases.[31] These advances demonstrate that ML systems can improve access to DR screening without compromising accuracy.

Tools Needed for Better ML to Diagnose Retinopathy

Despite recent advances, most ML systems for DR face limitations in their development and deployment. One of the most pressing challenges is limited dataset diversity. Many models are trained on datasets from single regions or health systems, which reduces their generalizability to other populations. Model performance can vary significantly based on the diversity of training data, with underperformance observed when applied to populations or imaging conditions not represented in the original dataset.[24] Further limitations are posed by the lack of demographic subgroup reporting in published ML evaluations. A 2025 review found that only 21% of ophthalmic ML tools reported performance by ethnicity, limiting our ability to evaluate potential biases in models.[31] Future development should prioritize multiethnic, multicenter training datasets that clearly report dataset demographics and imaging protocols.

Another major bottleneck is labeling inconsistency. Manual DR grading relies on subjective interpretation of fundus imaging using ICDR or ETDRS severity scales, but inter-grader disagreement remains high.[26] According to Ong et al,[31] many datasets use majority-vote labeling without adjudication, introducing label noise that can compromise model performance. Moreover, evaluation reports often omit details about grader experience, duration, or calibration protocols, making it difficult to assess label reliability.[31]

High-quality image acquisition is critical, regardless of whether ML algorithms or human graders interpret the results. A study conducted in Sri Lanka found that 43.4% of non-dilated fundus images were ungradable, a rate that dropped to 12.8% after pupil dilation.[32] Variability in image quality can compromise both diagnostic accuracy and the reliability of training datasets. Automated image quality checks or protocols for re-imaging may be necessary to preserve model performance. Given that dilation can often be invasive and impractical, there is a need for imaging technologies that can ensure high-quality images without it.

The Future of ML to Diagnose Retinopathy

As ML systems continue to evolve, their role in DR diagnosis is expanding beyond disease classification toward more personalized risk prediction. One major area of advancement is risk-based screening interval modeling. DeepDR+ was trained on 717,308 fundus images across longitudinal cohorts and has the ability to predict progression risk rather than current disease status. DeepDR+ was validated across eight multiethnic cohorts, and achieved concordance indices ranging from 0.786 to 0.802.[33]

Another growing application area is smartphone-based ML screening, which has the potential to decentralize DR detection. A 2023 systematic review by Prayogo et al[34] reported that smartphone adapters with ML integration achieved sensitivities from 52% to 92% and specificities from 73% to 99% for detecting any DR. With enough standardization and training, these smartphone-based systems could enable in-home DR screening and remote diagnoses.

Multimodal ML systems are another promising frontier, combining fundus photographs with clinical variables such as hemoglobin A1c, blood pressure, or even renal function. Combining multimodal imaging techniques, including optical coherence tomography (OCT)—which noninvasively captures high-resolution cross-sectional images of tissue using visible and infrared light—with fundus photography can enhance diagnostic accuracy.[24,35] Such models could also help coordinate DR screening with more comprehensive diabetes care.

To realize the full potential of these future ML tools, regional validation studies and the public sharing of dataset demographics will be critical to ensure robust and non-biased models. The next generation of DR-focused ML systems will move beyond detection alone, and if successfully implemented, such systems could help reduce vision loss globally.

ML to Diagnose Diabetic Nephropathy

- Numerous studies have focused on developing ML models that use non-invasive clinical, laboratory, and imaging data to predict or diagnose diabetic nephropathy, with meta-analyses confirming robust performance (AUC/c-index typically fall between 0.81 and 0.97).
- In contrast, only a limited number of studies have applied ML to interpret renal biopsy data directly, but these biopsy-based ML models can achieve exceptionally high diagnostic accuracy.
- The use of multiple label-free imaging modalities of kidney biopsies interpreted with ML can identify subcellular structures to make diagnoses without compromising limited tissue samples.

Current Status of ML to Diagnose Diabetic Nephropathy

ML has rapidly advanced as a potential auxiliary diagnostic tool for diabetic nephropathy (DN). Traditionally, the diagnosis of DN relies on a combination of clinical features, laboratory data, and histopathological assessment, with renal biopsy serving as the gold standard. Non-diabetic renal diseases (NDRD) are highly prevalent among patients with diabetes and can be misdiagnosed as DN.[36] In 2020, Kitamura et al[37] demonstrated that deep learning models analyzing immunofluorescent renal biopsy images could achieve AUCs up to 1.00 in distinguishing DN from NDRD. These algorithms can autonomously identify subtle histopathological patterns, such as peripheral vessel loop changes or peripheral capillary abnormalities, that may be overlooked by pathologists. In 2023, Fan et al[38] developed a model that was able to differentiate DN from other glomerular diseases, such as IgA nephropathy, with overall accuracy rates exceeding 70%. Shickel et al[39] introduced a spatially aware transformer-based framework that leverages both handcrafted histological features and the spatial relationships among glomeruli in whole slide biopsy images to predict progression to end-stage renal disease (ESRD) in patients with DN. Their model outperformed recurrent neural networks (RNNs), XGBoost, and logistic regression, achieving an AUC of 0.97 for two-year ESRD prediction. Notably, the use of self-attention and pairwise distance embeddings enabled the model to capture complex spatial patterns in kidney pathology, which are often difficult for pathologists to quantify manually, suggesting that their model may offer significant advantages for patient-level prognostication in DN.

Complementing these approaches, recent innovations have focused on leveraging advanced imaging techniques to enhance biopsy-based diagnosis. Conventional staining of biopsy specimens can limit the optical wavelengths that can interrogate a specimen. The use of multiple label-free imaging modalities of kidney biopsies within a single setup can identify morphological, lipidomic, and metabolic biomarkers at subcellular resolution in tissue samples from controls and people with diabetes, using ML, as presented in Figure 2.[40] Multiple sets of stereoscopic images can be taken of a kidney biopsy from a range of viewing angles, collated, digitally constructed and interpreted with ML as a 3D dataset with unique features of diabetic kidney disease. This method provides high-throughput evaluation of 3D tissue architecture while also preserving samples for additional testing.

Given the invasive nature of renal biopsies, ML has also emerged as a promising non-invasive tool for predicting and diagnosing DN. Recent advances demonstrate that ML models—including random forest (RF), gradient boosting machine (GBM), logistic regression (LR), support vector machine (SVM), and extreme gradient boosting (XGB)—can integrate multimodal data (clinical, laboratory, imaging, and genetic features) to distinguish DN from NDRD with high accuracy (AUC: 0.81-0.97).[41-43] A meta-analysis of 23 studies by Chen et al[42] revealed that both LR and non-LR models achieved pooled AUCs >0.80 for DN prediction, with LR offering comparable performance to more complex algorithms while maintaining superior interpretability and computational efficiency. When performance is comparable, simpler models like LR are preferable to more complex ML algorithms (such as RF, GBM, SVM, and XGB) for transparency, efficiency, and robustness, which are important factors to consider in healthcare settings, where trust as well as resource constraints are central concerns. More recently, Dai et al[43] systematically reviewed 34 studies and, similarly to Chen et al, reported that ML models achieved pooled c-indices (a similar metric to AUC) of >0.80 for both DN prediction and diagnosis, further supporting ML's utility for early screening and risk assessment in clinical practice. These models consistently identified estimated age, systolic blood pressure, glomerular filtration rate, urine albumin-creatinine ratio, hemoglobin A1c (HbA1c), creatinine, body mass index, and low density lipoprotein cholesterol (LDL-C) as key predictors.[42,43] These findings highlight ML's potential to replace invasive diagnostic workflows while enabling early, personalized risk stratification to aid clinical diagnosis of DN.

Tools Needed for Better ML to Diagnose Diabetic Nephropathy

Despite advances in improving ML accuracy in DN prediction and diagnosis mentioned above, several areas of improvements are necessary to enhance the clinical utility of ML for DN prediction and diagnosis. First, multicenter, well-annotated datasets (ie, making sure that a population on which an ML model is based must be specified to determine whether an ML-based model pertains to a given patient) are essential to address overfitting and improve ML model generalizability across datasets, as most current studies rely on small, single-center cohorts with limited external validation. Second, standardized reporting and validation protocols—such as Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) and Prediction model Risk Of Bias Assessment Tool (PROBAST)—should be universally adopted to improve transparency, reproducibility, and risk of bias assessment across studies.[44,45] Feature selection and data preprocessing methods must also be clearly documented, as inconsistent approaches contribute to heterogeneity and limit comparability across studies. Third, prospective studies and regulatory frameworks are needed for translating ML models from research to clinical practice, and for ensuring that model predictions are actionable and safe for patient care. Retrospective designs dominate current research, contributing to high bias risks in many studies reported in the literature.[42,43] Regulatory oversight is particularly vital for "black-box" algorithms (eg, deep neural networks) to ensure trustworthy predictions.

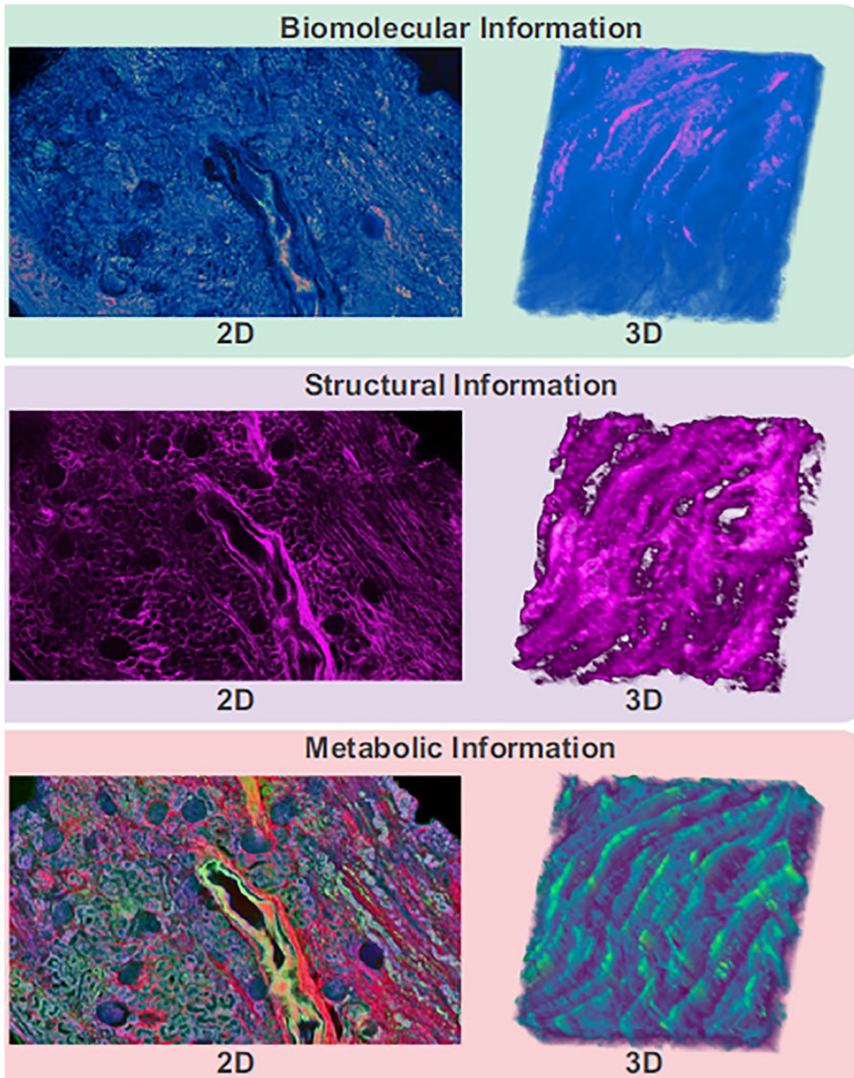

Figure 2. Label-free optical platform of a kidney biopsy from a person with a diabetic nephropathy. 2D and 3D images of information (biomolecular, structural, and metabolic) from a kidney biopsy of a patient with diabetic nephropathy, generated by machine learning (ML) and obtained with a multiple modalities platform. Image reproduced from Fung et al[40] under the CC-BY 4.0 license (https://creativecommons.org/licences/by/4.0/).

Finally, the development of user-friendly clinical decision support tools and online calculators may facilitate the adoption of ML models in routine nephrology practice.

The Future of ML to Diagnose Diabetic Nephropathy

Looking ahead, the future of ML in DN prediction and diagnosis is expected to shift toward less invasive approaches. Hybrid diagnostic workflows may soon combine ML analysis of renal biopsy images with non-invasive data sources—such as retinal imaging and metabolomics—to provide earlier detection and personalized risk stratification to aid diagnosis of DN, as illustrated in Figure 3. Unlike traditional ML models that process different data types (such as images and clinical variables) separately, transformer-based systems can learn relationships across diverse data modalities in a unified framework, making them particularly well-suited for combining retinal imaging with clinical metadata for DN diagnosis. For example, transformer-based systems called Trans-MUF have demonstrated AUCs up to 0.989 in distinguishing DN from NDRD, comparable to traditional clinical methods.[46] A recent study by Zhang et al[14] employed an integrative bioinformatics and ML approach to identify key glomerular injury genes associated with DN. Using multiple ML algorithms, including Least Absolute Shrinkage and

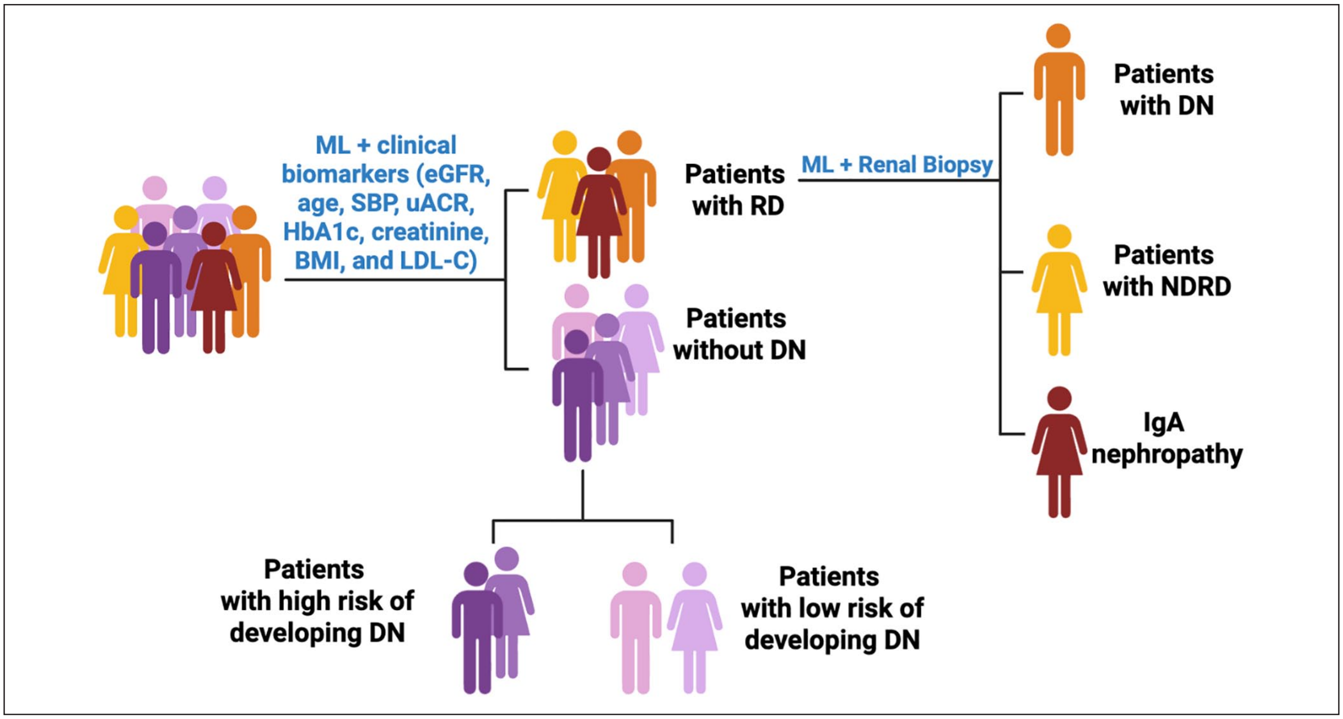

Figure 3. Schematic overview of ML approaches for the diagnosis of diabetic nephropathy versus other kidney diseases using clinical biomarkers and renal biopsy data. Figure created with BioRender.com. Abbreviations: BMI, body mass index; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein cholesterol; NDRD, non-diabetic renal disease; RD; renal disease; SBP, systolic blood pressure; uACR, urine albumin-creatinine ratio.

Selection Operator (LASSO), support vector machine—recursive feature elimination (SVM-RFE), and RF, they identified robust diagnostic biomarkers with AUCs exceeding 0.94, which have been validated across independent cohorts. Their work exemplifies how multiomics data combined with ML can uncover novel molecular signatures for DN, paving the way for precision diagnostics and targeted therapies. The use of multiple label-free imaging modalities will improve the accuracy of biopsy diagnoses. The field is progressing toward a future where DN diagnosis may primarily rely on sophisticated, multimodal ML systems to reduce the need for invasive procedures, such as renal biopsies, and yet also lead to improved patient outcomes.[47] Ongoing improvements in data quality, external validation, and regulatory oversight will be necessary to realize the full potential of ML in DN prediction, diagnosis, and management.

ML to Diagnose Peripheral Neuropathy

- Diagnosis of peripheral neuropathy is hampered by low sensitivity—low specificity clinical measures and subjective evaluations often play a role.
- ML represents a promising axis between the complexity of the nervous system and data evaluation, set to improve diagnostic accuracy, but large complete datasets are needed.
- ML holds potential and promise for the securement of early detection, diagnosis, and treatment for peripheral neuropathy, which are all greatly needed.

Current Status of ML to Diagnose Peripheral Neuropathy

Detection and monitoring of diabetic peripheral neuropathy (DPN) in clinical practice is recommended in most clinical guidelines including consensus statements from the Toronto Diabetic Neuropathy Expert Group[48] and the American Diabetes Association.[49] Despite the frequent occurrence, screening for DPN is at times neglected, leading to considerable diagnostic delay and insufficient preventative measures. The reasons for this are many, but most important are the lack of quick and reliable screening methods for painful and painless neuropathy.[50] Current clinical practice is therefore often limited to screening for severe large fiber damage and loss of protective sensation with either a 10 g monofilament or by testing vibration sensation with either a tuning fork or using biothesiometry, as recommended by the National Institute for Health and Care Excellence (NICE).[51,52] Only in more select cases are research-based methodologies employed. The clinical diagnosis of peripheral neuropathy remains an area dominated by insufficient low-sensitivity; low-specificity bedside clinical endpoints and subjective evaluations often plays a diagnostic role. The development

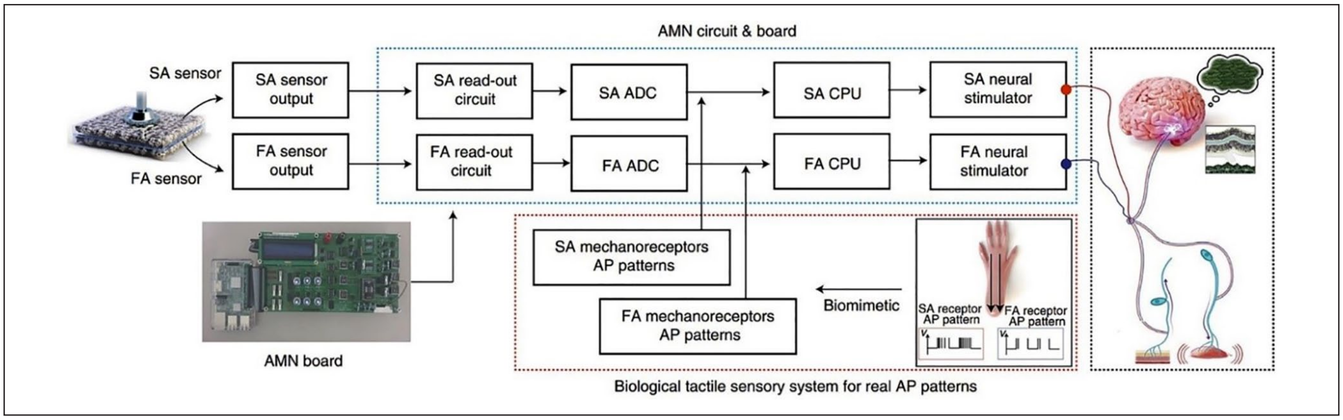

Figure 4. The signal-processing procedure in an artificial tactile sensing system. It shows how signals from two types of sensors, slowly adapting (SA) and fast adapting (FA), are processed through an artificial mechanoreceptor neural board. This processing method mimics the responses of real nerve cells to pressure and vibration stimuli, which replicates the sensory functions of biological skin. Figure reproduced from Chun et al[54] under the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

of novel diagnostic clinical tools is ongoing,[53] but will not be available for bedside use for some years to follow. As of now, ML and AI have not been used for diagnostic purposes in DPN, but a small number of proof-concept studies within neuropathy in general have been carried out pointing toward the feasibility and utility of these methods in future clinical use. See Figure 4 for an example of an artificial tactile sensing system.[54]

Tools Needed for Better ML to Diagnose Peripheral Neuropathy

The prerequisites for the adoption of ML in describing peripheral neuropathy naturally rely on the available dataset and contents. Diagnosis correlates directly with a specific disease classification. Computational ML is a powerful tool to classify peripheral neuropathy based on a minimal amount of clinical data, symptoms, and patient history. Early detection is an integral diagnostic focus, enabling timely treatment and interventions and, to this aspect, much more sensitive clinical diagnostic tools are needed for this purpose, but are not yet available, nor are the reference data. Risk prediction at a satisfactory level will require an array of parameters—individual, clinical, demographic, socioeconomic, and patient-reported outcomes. For all these three main areas (classification, early detection, and risk prediction), the use of ML relies on the availability of comprehensive datasets of the mentioned parameters. Each dataset must be of substantial magnitude for ML training and validation purposes. They must be of complete and high clinical quality and accuracy as a foundation for ML to diagnose peripheral neuropathy. Most available datasets are institutional and limited in various ways and datasets between institutions are rarely compatible. The main tools needed to utilize ML to diagnose peripheral neuropathy are very large data-complete databases on all aspects of neuropathy and ML training on these datasets, to overcome the inborn challenges of this very complex bio-psycho-social condition.[55]

The Future of ML to Diagnose Peripheral Neuropathy

ML may very well be the key to unlocking "the conundrum of an enigma of painful and painless peripheral neuropathy."[56] ML has already shown great promise within other aspects of neuropathy, such as neuroimaging analysis, heart rate variabilities, and cornea confocal microscopy, but these achievements build on comprehensive datasets. The learnings, however, can be utilized in the adoption of ML as a tool for diagnosing peripheral neuropathy.

There is little data available for applying ML to peripheral neuropathy. The conundrum and enigma signify obstacles to our understanding of the pathophysiology of diabetic neuropathy. Accurate validated types of measurements of clinical deficits are needed to reach a secure diagnosis and a mechanism-based treatment. These are huge unmet clinical needs that will not be met unless ML is implemented in research and clinical practice.[55,56] This exemplifies the need to further develop and better understand how ML can be applied to diagnose peripheral neuropathy.

ML to Diagnose Autonomic Neuropathy

- Autonomic neuropathy (AN) is prevalent (affecting up to 50% of people with diabetes). ML methods are increasingly explored to streamline detection and improve early diagnosis.

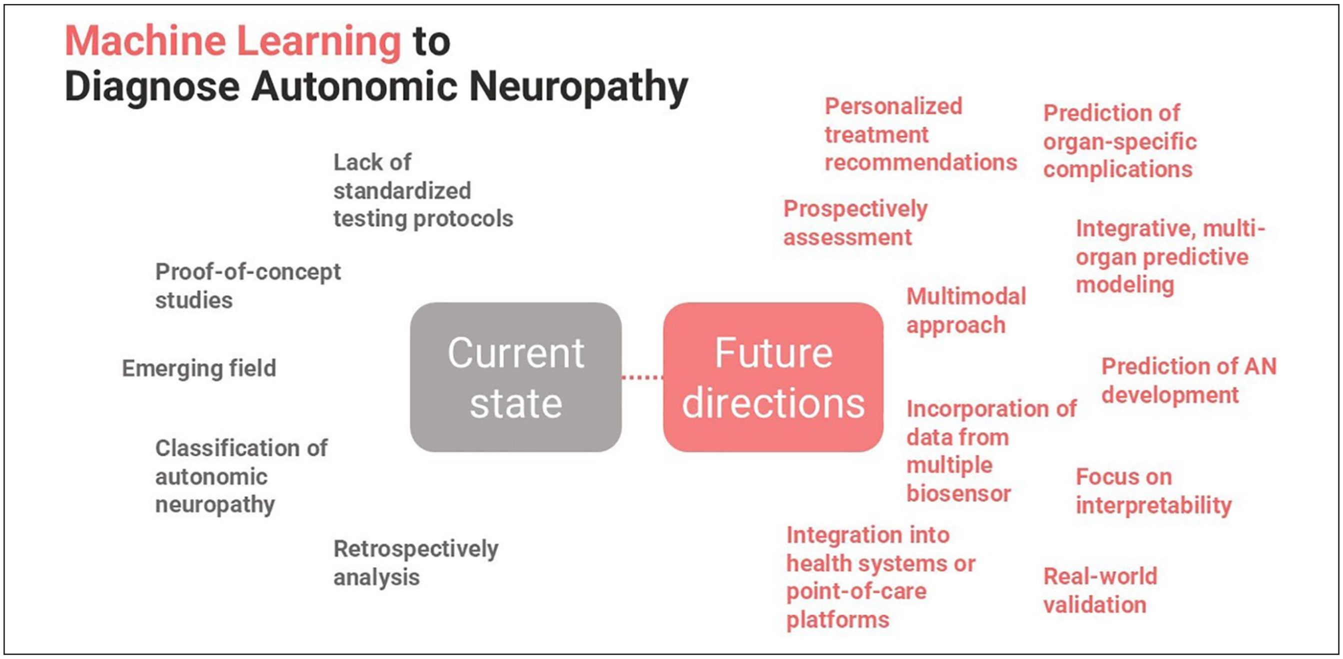

Figure 5. Overview of current state and future directions of machine learning to diagnose autonomic neuropathy in patients with diabetes.
Abbreviation: AN = autonomic neuropathy.

- Current ML applications show promising accuracy in explorative studies, but at this time, clinical adoption remains limited.
- ML is proving to be most useful for the diagnosis and risk prediction of AN. The identification of cardiac AN is based on analysis of data from 12-lead electrocardiograms (ECGs), cardio-flex tests (CARTs), and heart rate variability (HRV).

Current Status of ML to Diagnose Autonomic Neuropathy

AN is a highly under-diagnosed and often subclinical complication of diabetes. Prolonged high blood glucose levels can damage nerves throughout the body, leading to AN.[57] Patients with AN encounter substantial challenges in disease management, including dysregulated glycemic control and a significantly elevated risk of cardiometabolic complications and major cardiac events. Emerging treatment strategies emphasize that early identification and continuous monitoring are critical for effective disease management. ML presents a promising approach for enhancing diagnostic accuracy and supporting the development of individualized treatment strategies.

ML may enhance diagnostic accuracy by identifying subtle, multivariate patterns in current golden standard CARTs, ECGs, and HRV. The implication is that ML confirmed the diagnostic importance of these reflex tests, possibly adding sensitivity by also including age and inflammation markers. As Figure 5 indicates, direct head-to-head comparisons between ML approaches and traditional diagnostic criteria in terms of sensitivity and specificity have largely been conducted retrospectively.[58] Recent research highlights the potential of ML in various clinical contexts. For instance, ML has been employed to classify gastroparesis, a condition in which the stomach empties its contents into the small intestine more slowly than normal,[59] based on glycemic variability data derived from continuous glucose monitoring.[60] Abdalrada et al[58] developed an ML model that showed strong potential for early-stage cardiac autonomic neuropathy (CAN) detection using Ewing's tests—which assess autonomic nervous system function by measuring responses to specific stimuli—achieving an receiver operating characteristic–area under the curve (ROC AUC) of 0.962.[61] These examples illustrate that ML can potentially boost detection accuracy, and pinpoint which factors are most indicative of AN.

However, despite the promising performance of many ML models in identifying AN, most have been developed using limited sample sizes from specific datasets.[62] The lack of external validation has constrained their generalizability and applicability to broader patient populations.

Tools Needed for Better ML to Diagnose Autonomic Neuropathy

Several developments are needed to elevate ML-driven AN diagnostic. First, comprehensive data resources and external validation of models are crucial. New large-cohort studies using dedicated on-site equipment for the AN-diagnoses provide more solid, age-specific normal values.[63] However, longitudinal follow-up data is also needed to enable ML models to better stratify risk and distinguish patients likely to develop complications.[64] Finally, ML tools must be interpretable and user-friendly. Clinicians should be able to understand which features drive an algorithm's output, fostering trust in ML-based diagnoses. Developing interfaces that seamlessly incorporate ML analysis into clinical workflows will further facilitate adoption.

The Future of ML to Diagnose Autonomic Neuropathy

ML for AN-diagnosis is an emerging field. In the future, ML models could be embedded into diagnostic systems, functioning alongside traditional methods to improve sensitivity and stratify clinical risk. In particular, multimodal models that integrate various AN tests (eg, CARTs and sudomotor function), patient characteristics, medical history, data from wearable devices, and radiological imaging hold significant promises for advancing diagnostics. With continued validation and emphasis on interpretability, these models have the potential to enable earlier, more precise, and efficient diagnosis of AN. While the development of diagnostic algorithms is essential, it is equally important at the current stage to establish evidence-based management pathways for patients following a confirmed AN diagnosis.

ML to Diagnose Diabetic Foot Ulcers

- Thermal imaging combined with deep learning, particularly CNNs, has demonstrated high accuracy in identifying early signs of diabetic foot ulcers (DFUs), offering a non-invasive and proactive diagnostic tool.
- The use of thermograms for diagnosing DFUs is based on the principle that the risk of developing a DFU if a region of a foot is warmer than the other foot, and especially if the temperature difference exceeds 2.2°C or 4.0°F, but ML can make risk predictions with much smaller temperature differences.

Current Status of ML to Diagnose Diabetic Foot Ulcers

Diabetic foot ulcer, when left untreated, can lead to serious complications, including gangrene and amputation.[65] The physical and economic burden associated with DFU-related hospitalizations underscores the need for improved preventive care and diagnostic tools.[66] One such tool is thermal imaging, which detects early signs of DFUs by analyzing intra-foot and inter-foot temperature differences that result because of complications from diabetic neuropathy and peripheral artery disease.[67] ML algorithms have demonstrated effectiveness in sorting the pixelated images produced from thermal imaging, allowing for accurate DFU detection and risk assessment. Combined with ML, thermal imaging can preemptively identify regions where ulcers are likely to develop.

Deep learning (DL), a subfield of ML that uses multilayered neural networks to model complex patterns, has shown success in various medical domains such as radiology and ophthalmology. Muralidhara et al developed a CNN-based system to diagnose DFUs that was trained on thermograms from people with and without diabetes. Their model demonstrated high performance, with a mean accuracy of 0.9827, sensitivity of 0.9684, and specificity of 0.9892, suggesting DL is a promising tool for DFU diagnosis.[68]

Tools Needed for Better ML to Diagnose Diabetic Foot Ulcers

There is a lack of standard methodology for detecting and grading thermal images across ML systems, such as the range of temperature values.[68] Establishing standardized protocols would enhance the reliability and comparability of ML models.

While the Diabetic Foot Ulcer 2020 (DFU2020) database is effective for classifying and predicting the risk of DFUs, the availability of more publicly accessible thermal imaging datasets is crucial for improving ML diagnosis of DFUs. Currently, progress is hindered by limitations such as the high cost of acquiring medical images, the low frequency of certain pathologies, and the scarcity of labeled images.[67] These limitations can result in data imbalance, where ML models become biased toward overrepresented groups, reducing sensitivity and accuracy for underrepresented ones.[68]

The Future of ML to Diagnose Diabetic Foot Ulcers

To address data limitations, the Instituto de Astrofísica de Canarias–Tecnología (IACTEC) in the Canary Islands applied data augmentation techniques to expand its dataset and minimize overfitting, a scenario where a model performs well on trained data but poorly on new unseen data. Although IACTEC primarily focuses on astrophysical applications, it has expanded its technology to also cover medicine, including developing datasets specifically for DFU research. As seen in Figure 6, the augmentation methods include rotation, scaling, flipping, and cropping, along with histogram matching to improve contrast. These techniques helped IACTEC achieve a classification accuracy of 95%,[67] suggesting how augmentation could be effectively applied to ML models targeting DFUs, and helping increase the size and variability of the training data used for prediction.

To assess models for bias, the PROBAST checklist can be used.[69] Future models should be trained on larger, more diverse datasets that include both individuals with and without diabetes to enhance generalizability and reduce bias. Utilizing multicenter studies or larger patient cohorts could

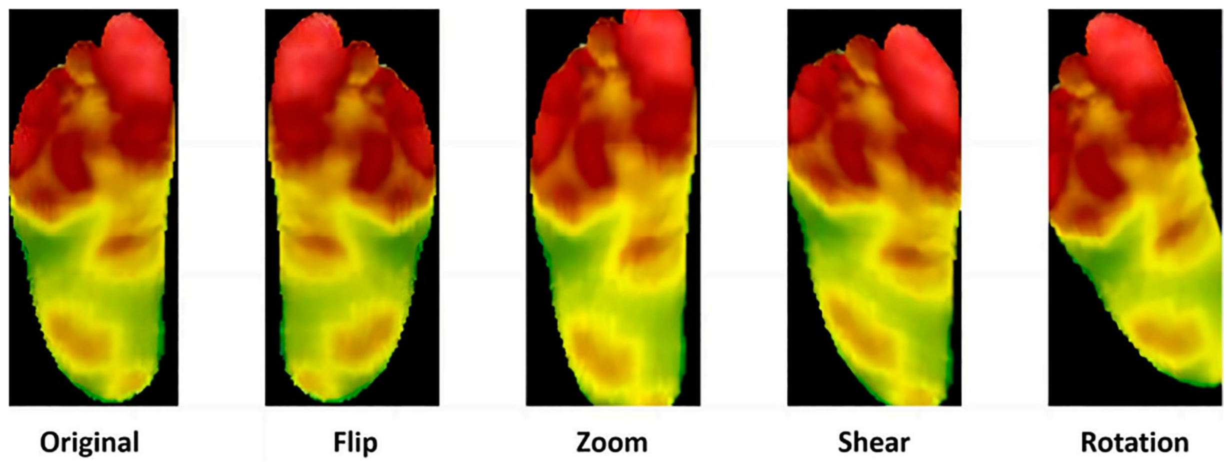

Figure 6. Examples of preprocessing techniques used on thermal images of diabetic foot ulcers to augment datasets while limiting overfitting. Figure reproduced from Muralidhara et al[68] under the CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

maximize available data while minimizing bias. This need for broader, more inclusive training data further highlights the need for more publicly accessible datasets.

For diagnosing and predicting healing for DFUs, factors such as wound area, depth, and granulation tissue percentage are critical indicators of wound status. To further expand upon these clinical markers, models are being developed and improved using tissue color proportions to classify wound tissue into necrosis, slough, and granulation.[70] In doing so, these models will be incorporated into clinical practice to predict wound management and lead to better outcomes for those with DFUs.

ML to Detect Other Systemic Complications From Images of the External Eye

- ML models have achieved promising results for detecting signals of diabetes and some associated ophthalmological, neurological, and systemic complications via analysis of external eye images captured by diverse imaging modalities; performance remains inconsistent or poor for detecting hepatic, renal, thyroid, and cardiovascular comorbidities.
- Detection of biomarkers for diabetes and associated complications may be enhanced by training multimodal hybrid algorithms on significantly larger samples of external eye images that have been labeled according to comprehensive, accurate, and time-matched electronic medical record (EMR) data from more diverse populations.
- Future deployment of ML systems that screen external eye photographs from patients' smartphones could dramatically increase early diagnosis and intervention for serious complications of diabetes and facilitate patient self-management, especially in remote and under-resourced settings; however prospective studies are required to collect large image datasets for model development and validation and to guide real-world implementation.

Current Status of ML to Detect Other Systemic Complications From Images of the External Eye

Research spanning almost two decades has demonstrated that ML algorithms can detect signals of diabetes[71-73] and its complications[74-78] in retinal photographs, sometimes detecting biomarkers that humans cannot perceive. Though groundbreaking, ML-assisted retinal screening has limited scalability because imaging requires expensive cameras, occasional pharmacologic pupil dilation, and proficiency in capturing gradable photographs. The external structures of the eye can also manifest signs of diabetes[79] and are more easily and inexpensively imaged than the retina. Therefore, ML-assisted screening of external eye images could provide scalable alternatives for detecting biomarkers of diabetes and its complications.

Emerging research into ML detection of diabetes-related biomarkers in external eye images has shown promising results across several imaging modalities (Table 3). Diverse models reliably classified DPN in corneal confocal microscopy (CCM) images,[80-85] achieving areas under the curve up to 99%.[83] Corneal nerve morphology in CCM accurately predicts DPN risk and progression,[94,95] but CCM is not routinely used for this purpose; however, if ML-enabled CCM screening for DPN were to become standard practice in eye and diabetes care, the increase in early detection could prevent many cases of disabling neurological damage. Regardless, these studies confirm that the external eye expresses

Table 3. Publications That Report the Performance of Machine Learning Algorithms for Detecting Biomarkers of Diabetes and Related Diseases and Complications From Images of the External Eye.

Image type	Publication	Model type	Biomarker/disease	Select performance metrics
Corneal confocal microscopy images	Meng et al[80]	Modified ResNet-50	DPN	AUC = 0.95 (95% CI: 0.83-0.99)
	Preston et al[81]	Modified ResNet-50	DPN	F_1 score = 0.91 (95% CI: 0.74-1.0)
	Qiao et al[82]	U2Net	DPN	AUC = 0.75
	Ben Rabah et al[83]	Vision Transformer	DPN	AUC = 0.99
	Scarpa et al[84]	CNN	DPN	Classification accuracy = 96%
	Chen et al[85]	Swin Transformer Network	DPN	AUC = 0.94 (95% CI: 0.82-1.00)
Slit-lamp photographs	Ghugare et al[86]	CNN	Diabetes mellitus	Classification accuracy = 96%
	Xiao et al[87]	ResNet-101	Hepatobiliary diseases	AUC = 0.74 (95% CI: 0.71-0.76)
			Liver cirrhosis	AUC = 0.90 (95% CI: 0.88-091)
			NAFLD	AUC = 0.63 (95% CI: 0.60-0.66)
			Cholelithiasis	AUC = 0.58 (95% CI: 0.55-0.61)
Fundus camera external eye photographs	Babenko et al[88]	TensorFlow + CNN	HbA1c ≥ 9%	AUC = 73.4 (95% CI: 71.8-75.0)
			Cholesterol ≥240mg dl^{-1}	AUC = 62.3 (95% CI: 60.0-64.7)
			Triglycerides ≥200 mg dl^{-1}	AUC = 67.1 (95% CI: 64.9-69.2)
			Mild-or-worse DR	AUC = 80.2 (95% CI: 78.9-81.6)
			Moderate-or-worse DR	AUC = 84.0 (95% CI: 82.7-85.3)
			Severe DR	AUC = 88.7 (95% CI: 87.3-90.1)
			VTDR	AUC = 86.7 (95%CI: 85.3-88.2)
			DME	AUC = 84.7 (95% CI: 82.9-86.5)
	Babenko et al[89]	CNN	Albumin <3·5 g/dL	AUC = 77.0 (95% CI: 74.6-79.4)
			ALT > 29.0 U/L	AUC = 66.7 (95% CI: 65.0-68.4)
			AST >36.0 U/L	AUC = 61.7 (95% CI: 59.3-64.1)
			Calcium <8.6 mg/dL	AUC = 71.6 (95% CI: 68.2-75.0)
			eGFR <60.0 mL/min/1.73 m^2	AUC = 80.3 (95% CI: 78.2-82.4)
			Hb <11.0 g/dL	AUC = 82.5 (95% CI: 80.3-84.6)
			Platelets <150.0 × 10^3/μL	AUC = 71.0 (95% CI: 68.0-74.0)
			TSH >4.0 mU/L	AUC = 62.5 (95% CI: 57.5-67.6)
			Urine ACR ≥300.0 mg/g	AUC = 74.6 (95% CI: 71.0-78.2)
Digital camera photographs	Li et al[90]	HMT-Net	Diabetes	AUC = 0.82
Smartphone camera photographs	Kato et al[91]	Residual U-Net	Anemia (Hb <11.0 g/dL)	AUC = 0.74
	Appiahene et al[92]	CNN	Anemia	Accuracy = 92.5%
	Çuvadar and Yilmaz[93]	CNN & MLP	Hb concentration (g/dL)	R^2 = 0.86

*Babenko et al[88] and Babenko et al[89] reported multiple AUCs for each biomarker, including for different validation sets, different sample subgroups, and images with specific regions masked or colors removed. For each biomarker presented here, the results are from the validation set with the highest AUC, for the whole available sample rather than for any specific subgroups, and for whole images without any masked regions or colors removed.
95% CI = 95% confidence interval; ACR = albumin-to-creatinine ratio; ALT = alanine transaminase; AST = aspartate aminotransferase; AUC = area under the curve; CNN = convolutional neural network; DME = diabetic macular edema; DPN = diabetic peripheral neuropathy; DR = diabetic retinopathy; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; HbA1c = hemoglobin A1c; MLP = multilayer perceptron; NAFLD = non-alcoholic fatty liver disease; TSH = thyroid-stimulating hormone; VTDR = vision-threatening diabetic retinopathy.

ML-detectable DPN biomarkers, which might be similarly measurable in more commonplace imaging modalities like photography.

When applied to slit-lamp photographs, which are images of the eye's anterior segment captured using a slit lamp microscope,[96] CNNs reliably classify diabetes (accuracy = 96%),[86] and can outperform retina-based models for detecting some hepatobiliary diseases (AUC = 0.74-0.90)[87] that are highly comorbid with diabetes.[97] One algorithm, trained on external eye photographs that were captured by fundus cameras during DR screening and labeled according to multiparametric patient-matched EMR data, detected vision-threatening diabetic retinopathy/diabetic macular edema (VTDR/DME) (AUC = 75.0-86.7), renal insufficiency (AUC = 71.6-87.7), and anemia (AUC = 73.8-82.5) with moderate-to-good precision, but was somewhat less accurate for hyperglycemia, hypocalcemia, and hypoalbuminemia (AUC = 67.6-77.0).[88,89]

Tools Needed for Better ML to Detect Other Systemic Complications From Images of the External Eye

It is not always clear why MLs underperform for some biomarkers but not others. Apart from the possibility that some systemic conditions simply have negligible ocular manifestations, other contributing factors likely include poor image quality and small, homogenous samples with limited generalizability.[81,91,90] Disagreement between ML and ground-truth EMR data may be partly attributable to label inaccuracy, particularly for discordant blood chemistry classifications (eg, lipids, thyroid hormones, and liver enzymes; AUC = 58.1-67.1),[88,89] since levels may have fluctuated in the intervals between blood and photograph acquisition. Future studies should optimize label fidelity through concurrent acquisition of photographs and clinical data, and through comprehensive expert review of EMRs, potentially aided by large language models (LLMs), which are AI systems that understand, generate, and manipulate human language.[98] Performance might be further improved by multimodal algorithms with hybrid architectures to handle diverse and complex data;[85] better classifier threshold tuning;[85] optimal lighting, angle/distance, and camera features;[88] and more complete knowledge about which image segments/features most influence performance.

The Future of ML to Detect Other Systemic Complications From Images of the External Eye

Inexpensive smartphones equipped with ever-improving cameras and AI capabilities are ubiquitous and portend the arrival of ML systems that will automatically screen for multiple disease biomarkers by directly analyzing external eye photographs via patients' smartphones. Consumer-grade phones presently achieve similar resolution to fundus cameras, and their photographs may already be amenable to algorithmic detection of relevant biomarker signals; for example, existing models accurately classify conjunctival smartphone photographs for anemia,[92,93] which, according to two recent review articles, is present in 35% of individuals with diabetes.[99,100]

Future algorithms should be trained on accurately labeled external eye photographs of thousands of people with diabetes across diverse populations from several different smartphone models. No such image repositories exist, necessitating multisite prospective studies to capture photographs during routine clinic visits, including retinal, foot, and kidney screenings.

Algorithms could become widely available through user-friendly phone apps, which would allow automated home-based self-screening and monitoring by people with diabetes. However, smartphone-based external eye screening should not be considered a replacement for established gold-standard diagnostic procedures; rather, it could support early detection and serve as a supplementary triage tool to risk-stratify and prioritize patients, issue recommendations for lifestyle changes and follow-up, and alert providers when abnormalities are detected. The resulting improvements in detection and management of serious systemic diseases and their risk factors could greatly reduce morbidity and mortality, particularly among populations in remote and resource-limited settings.

ML to Predict Outcomes in Hospitalized Patients With Diabetes

- ML applications for hospitalized diabetes patients have expanded significantly, with 55% of studies focusing on glycemic outcomes, 22% on in-hospital mortality, and 8% addressing non-glycemic adverse events.
- Few ML models exist for insulin dosing, possibly because of a lack of structured data on carbohydrate intake and meal timing, as well as the rarity of successful daily transitions from uncontrolled to controlled glucose.
- Future developments are expected to integrate ML models directly into EHR systems, shifting from research to clinical application, with prospective utility testing focusing on clinical outcomes and user acceptability.

Current Status of ML to Predict Outcomes in Hospitalized Patients With Diabetes

The predominant application of ML models in hospitalized patients—accounting for 55% of studies[101-127]—has been the prediction of glycemic outcomes, primarily focusing on hypoglycemia (Figure 7a). Figure 7b presents the inclusion criteria, showing that most ML models focus broadly on diabetes or hyperglycemia, with fewer studies targeting specifically type 1 (T1D) or type 2 diabetes (T2D), or specific conditions such as hypoglycemia, treatment with antihyperglycemic medications, or subcutaneous insulin. Figure 7c highlights studies on subpopulations such as critically ill or septic patients,[110,113,115,119,128-131] hyperglycemic crises,[132-134] perioperative care,[118] coronary heart disease or acute myocardial infarction,[135-137] hypertension,[138] heart failure,[139] stroke,[140] and COVID-19.[132,141] Glycemic outcome ML models have evolved to deliver dynamic predictions of hospitalizations.[105,108,110,113,114,119-121,124-126] Figure 7d shows that the majority (63%) predict hypoglycemia,[101-107,109,112,114,116,118,119] while 19% forecast glucose value.[108,110,113,115] In addition, 4% predict dysglycemia,[111] 7% predict nocturnal hypoglycemia,[117,126] and 7% predict the 3-level classification of glucose

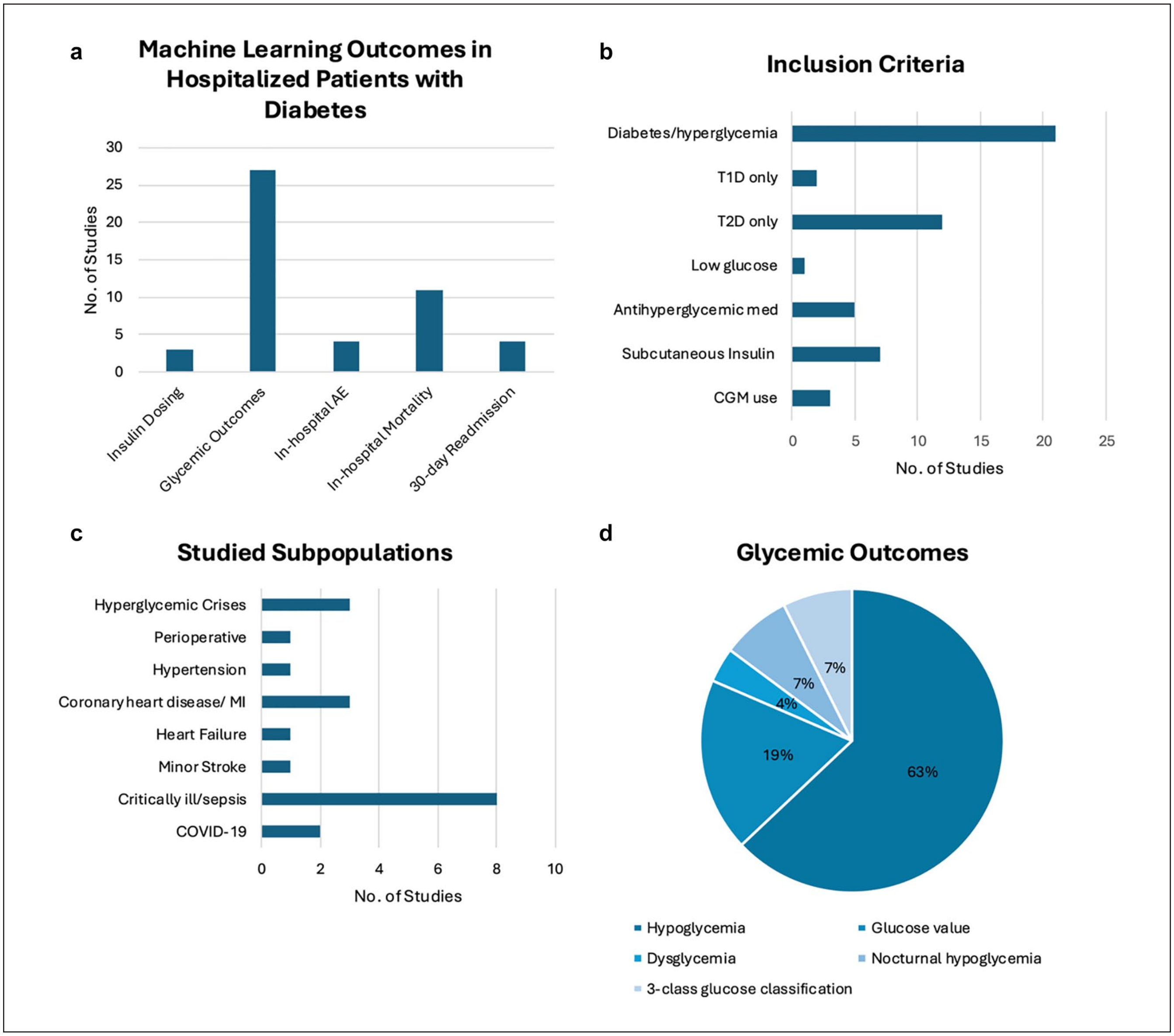

Figure 7. Application of machine learning (ML) models in hospitalized patients (a). Outcome distributions of 49 ML studies on hospitalized patients with diabetes. (b). Inclusion criteria of ML studies. (c). Studied subpopulations in ML studies. (d). Distribution of glycemic outcomes in ML studies. AE = adverse event; MI = myocardial infarction; T1D = type 1 diabetes; T2D = type 2 diabetes; Med = medication; CGM = continuous glucose monitor; three-class glucose classification = hypoglycemia, normoglycemia, hyperglycemia; dysglycemia = hypoglycemia or hyperglycemia.

(hypoglycemic, controlled, hyperglycemic).[120,121] Recent reviews summarize ML models for inpatient hypoglycemia[142,143] and diabetes management[144] models, detailing predictors, ML techniques, prediction horizons, and performance metrics. Notably, most models for glycemic outcomes of hospitalized patients developed retrospectively lack external validation on a variety of different populations.

Beyond glycemic outcomes, ML has extended to other clinical status outcomes, such as adverse events, mortality, and healthcare utilization in hospitalized patients. As shown in Figure 7a, eleven studies (22%) predicted in-hospital mortality,[128-130,132,133,135,136,138,141,145,146] four (8%) focused on non-glycemic adverse events[131,137,139,140] and 30-day readmissions,[134,147-149] and three (6%) examined insulin dosing optimization.[150-152] Adverse events in diabetes patients included atrial fibrillation,[137] pressure injuries,[131] acute kidney injury in heart failure patients,[139] and neurological deterioration poststroke.[140]

Tools Needed to Better ML Applications for Hospitalized Patients With Diabetes

Despite the challenges of insulin management—a medication with a narrow therapeutic index—few ML models exist for insulin dosing in the hospital.[150-152] One barrier to model development is the frequent absence of structured data on carbohydrate intake timing and quantity. Reinforcement learning needs ample examples of successful glucose transitions (ie, moving uncontrolled to controlled glucose) with insulin dose changes, which may be infrequent in real-world hospital data.[153-155]

Future research should prioritize multicenter studies with larger samples to validate ML models exhibiting high predictive accuracy in internal validations, with more emphasis on predicting optimal insulin dosing. Real-world implementation studies that integrate algorithms into EHRs and clinical decision support (CDS) tools linked to medication or glucose management workflows are necessary. Evaluating the clinical utility of ML-based CDS tools is essential to understanding their impact on clinical outcomes and user acceptability in inpatient settings. Notably, a recent randomized controlled trial demonstrated that an ML-based insulin CDS system was noninferior to traditional management for achieving glycemic control in T2D patients, with good acceptance among clinicians.[152] This study is noteworthy as it is one of the few to utilize ML models to assist clinicians in selecting insulin doses and to evaluate the model against the standard of care. Further research is needed to develop additional ML models for predicting insulin doses, both at the time of admission and dynamically throughout hospitalization. Unlike proprietary commercial products, published models have the potential to enhance our understanding of the factors influencing insulin dosing in complex hospitalized patients.

The Future of ML for Hospitalized Patients With Diabetes

In the coming years, we expect broader development and deployment of ML models within native EHR platforms, leveraging advantages in workflow integration, data security, compliance, and maintenance. Beginning in fiscal year 2026, hospitals will be required to report rates of severe hyperglycemia and hypoglycemia as part of electronic clinical quality measures, potentially incentivizing health systems to invest in ML-based CDS to improve glycemic outcomes.[156] In addition, LLMs could aid in interpreting glycemic patterns with contextual insights (eg, "Blood glucose values rose after prednisone was started"). While LLMs are not optimized for precise numeric forecasting, hybrid models combining time-series ML with LLMs could enhance clinicians' contextual awareness and facilitate therapeutic decision-making (eg, "Consider reducing glargine from 28 to 22 units because of a hypoglycemic episode last night").

Conclusion

ML is rapidly reshaping diabetes care, offering promising solutions for early and accurate diagnosis and prediction of a broad range of diabetes-related complications. From retinopathy and nephropathy to neuropathy, foot ulcers, and inpatient glycemic management, ML has demonstrated optimal diagnostic performance, particularly in image-based and data-rich scenarios. These advances can support earlier detection and prognosis, which can potentially reduce the incidence and severity of diabetes complications. However, widespread clinical integration remains challenging. Key issues, including limited dataset diversity, inconsistent labeling, lack of external validation, and restricted interpretability, need to be addressed in order to improve the quality of many ML models. Future efforts should prioritize the development of multiethnic, well-annotated, prospective datasets for training and validation, and explainable, user-friendly tools. As ML models evolve toward multimodal frameworks and real-time deployment via smartphones and electronic health records, they hold great potential to personalize care, close diagnostic gaps, and reduce healthcare disparities.

ML is closing the loop in diabetes management by integrating diagnostics, risk prediction, and therapeutics into continuous, personalized, and largely automated cycles of care. Practical applications range from early diagnosis and targeted screening for complications like those described in this article, to real-time decision support and therapy adjustment that can help prevent serious complications or life-threatening events. As data integration and algorithm transparency improve with enhancements by LMMs and AI agents, ML will become a standard, trusted element for clinicians to deliver closed-loop, context-aware, and personalized care for treating diabetes and its complications. The potential for ML to become established for diagnosis and treatment of diabetes and its complications will be realized when technical advancement and interdisciplinary collaboration go hand in hand to ensure safe, equitable, and impactful implementation.

Abbreviations

2D, two-dimensional; 3D, three-dimensional; 95% CI, 95% confidence interval; ACR, albumin-to-creatinine ratio; AE, adverse event; AEYE-DS, AEYE Diagnostic Screening; AI, artificial intelligence; ALT, alanine transaminase; AN, autonomic neuropathy; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; CAN, cardiac autonomic neuropathy; CART, cardio-reflex test; CCM, corneal confocal microscopy; CDS, clinical decision support; CGM, continuous glucose monitor; CNN, convolutional neural networks; DCCT, Diabetes Control and Complications Trial; DFU, diabetic foot ulcer; DL, deep learning; DME, diabetic macular edema; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; DRL, deep reinforcement learning; ECG, electrocardiogram; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate; EHR, electronic health record; EMR, electronic medical record; ESRD, end-stage renal disease;

ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fast adapting; GBM, gradient boosting machine; Hb, hemoglobin; HbA1c, hemoglobin A1c; HRV, heart rate variability; IACTEC, Instituto de Astrofísica de Canarias—Tecnología; ICDR, International Clinical Diabetic Retinopathy; IDRiD, Indian Diabetic Retinopathy Image Dataset; Dx-DR, Intelligent Diagnostics for Diabetic Retinopathy; Labs, clinical lab tests; LASSO, Least Absolute Shrinkage and Selection Operator; LDL-C, low density lipoprotein cholesterol; LIME, Local Interpretable Model-agnostic Explanations; LLM, large language model; LR, logistic regression; Med, medication; MI, myocardial infarction; ML, machine learning; MLP, multilayer perceptron; mtmDR, more-than-mild diabetic retinopathy; NAFLD, non-alcoholic fatty liver disease; NDRD, non-diabetic renal disease; NICE, National Institute for Health and Care Excellence; NPDR, non-proliferative diabetic retinopathy; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; PRO, patient-reported outcomes; PROBAST, Prediction model Risk Of Bias Assessment Tool; RD, renal disease; RF, Random Forest; RNN, recurrent neural network; ROC AUC, receiver operator characteristic–area under the curve; SA, slowly adapting; SBP, systolic blood pressure; SVM, support vector machine; SVM-RFE, support vector machine–recursive feature elimination; T1D, type 1 diabetes; T2D, type 2 diabetes; TRIPOD, Transparent Reporting of a multivariable Prediction model for Individual Prognosis or Diagnosis; TSH, thyroid-stimulating hormone; uACR, urine albumin-creatinine ratio; UKDPS, United Kingdom Prospective Diabetes Study; VTDR, vision-threatening diabetic retinopathy; XGB, eXtreme Gradient Boosting.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JC and JFo are employees of EyePACS Inc. CNH is a consultant for Liom. JFl is co-owner of Medicus Engineering. SLC is a consultant for Medicus Engineering, Roche Diagnostics, and has received research grants from i-SENS. DK is a consultant for Afon, Atropos Health, Embecta, GlucoTrack, Lifecare, Novo, SynchNeuro, and Thirdwayv. AS, MS, HZ, PS, NE, DA, NM, TW, and YCT have nothing to disclose.

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