Opinion Paper

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Personalized medicine in diabetology: why C-peptide standardization is essential for translating research into clinical practice

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Abstract: Personalized medicine has advanced in diabetology over the past decade. Diabetes is diagnosed based on measures of glycaemia, i.e. glycated hemoglobin (HbA_{1c}) and glucose, and the classification distinguishes type 1, type 2, gestational diabetes, and specific forms. Especially type 2 diabetes has clinically long been recognized as a heterogeneous metabolic disorder driven by diverse pathophysiological mechanisms. Data-driven approaches have identified distinct sub-phenotypes, offering a more nuanced understanding of diabetes and prediabetes heterogeneity. Identified subgroups differ in clinical characteristics, the risk of disease progression and developing long term complications. Implementing pathophysiology-based classification and emerging therapeutic decision tools requires additional laboratory biomarkers to estimate beta-cell function and insulin resistance. Fasting C-peptide has emerged as the most informative and broadly applicable biomarker and analytical comparability between laboratories has become a prerequisite for translating research findings into guidelines and clinical practice. Efforts to standardize C-peptide measurement have shown that results from different laboratories and assay manufacturers vary widely, even when using the same WHO reference material. Studies consistently demonstrate that recalibrating assays with serum-based, matrix-appropriate reference samples – rather than pure reference reagents – greatly improves agreement across methods. Although a full reference measurement system is now available, significant variability persists and broad implementation remains incomplete despite compelling evidence supporting its effectiveness. The remaining challenge is therefore no longer the development of appropriate reference materials or analytical procedures, but their consistent implementation across manufacturers. Addressing this final step is essential for enabling personalized diabetes care and will ultimately benefit both patients and manufacturers by improving clinical decision-making.

Keywords: personalized medicine; C-peptide standardization; beta-cell function; diabetes sub-phenotypes; precision diabetology

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Laboratory biomarkers in diabetology

In addition to the clinical presentation of the patient, the diagnosis of diabetes mellitus is based on laboratory parameters of glycaemia such as HbA_{1c} and plasma glucose, biomarkers that are world-wide standardized [1, 2].

Implementation of standardized HbA_{1c} measurement enabled the generation of internationally comparable results and units, providing a critical foundation for its evolution from a marker of glycemic control and treatment efficiency to a globally accepted diagnostic criterion with uniform cut-off values in 2010. In many countries, HbA_{1c} now serves as the primary diagnostic test for diabetes. The broad

clinical implementation of diabetes diagnostic screening was only possible because internationally accepted analytical standards – such as IFCC/NGSP frameworks for HbA_{1c} and ISO 17511 metrological traceabilityfor plasma glucose – ensured comparable results across healthcare systems [3, 4]. To prevent misclassification, both international [1] and German national guidelines mandate strict legal analytical error limits alongside to preanalytical glycolysis inhibition for glucose determination to guarantee absolute clinical validity [5, 6].

Islet autoantibodies, particularly tyrosine phosphatase-related islet antigen 2 (IA 2) and glutamic acid decarboxylase (GAD) antibodies, which are indispensable for the diagnosis of type 1 diabetes have achieved a high degree of harmonization, as standardization is not feasible due to the intrinsic nature of these analytes [7].

As diabetes classification and treatment are increasingly guided by underlying pathophysiology rather than glycaemia alone [8], assessment of endogenous insulin secretion has emerged as a clinically relevant feature of metabolic phenotyping that requires additional biomarkers. Individuals with similar degrees of hyperglycemia may differ substantially in beta-cell function [8, 9], with important implications for diabetes classification, disease progression, risk for complications, and therapeutic decision-making. Among currently available biomarkers, C-peptide represents the most established measure of endogenous insulin secretory capacity and provides information on (pre)diabetic metabolism that cannot be inferred from glucose concentrations or HbA_{1c} alone. Beyond direct measurement of insulin secretion, taking into account possible age- and sex-dependent reference ranges [10, 11], C-peptide can also be incorporated into mathematical models of beta-cell function and insulin resistance [12]. In particular, C-peptide-based HOMA (Homeostasis Model Assessment) [13, 14] approaches are increasingly used in epidemiological studies and precision medicine frameworks [15]. In addition to glucose, both insulin and C-peptide measurements from a single fasting blood sample are valid inputs for HOMA calculations.

C-peptide is produced by proteolytic cleavage of proinsulin in β-cell secretory granules and is co-secreted equimolarly with insulin. Compared with insulin, it has greater circulating and preanalytical stability [16], higher serum concentrations, and is not affected by hepatic first-pass extraction. Moreover, because C-peptide is absent from exogenous insulin preparations, it can also be applied in patients receiving insulin treatment. Furthermore, insulin still has a much higher inter-method variation than C-peptide, limiting the comparability of results from different studies and different laboratories. As C-peptide increasingly forms the basis of biomarker-derived classification and treatment algorithms, ensuring analytical comparability across assays through implementation of standardization will become essential for their broad clinical implementation.

Current clinical applications of C-peptide

The most established clinical application of C-peptide is the assessment of insulin deficiency in individuals with uncertain diabetes classification [1, 2]. This has gained particular importance with the increasing recognition of adult-onset type 1 diabetes. Epidemiological studies indicate that a substantial proportion of type 1 diabetes occurs only after the age of 30 years, often with a clinical presentation that overlaps with type 2 diabetes [17, 18]. In such individuals, diabetes-associated autoantibodies provide information on disease etiology, whereas C-peptide directly informs on the clinically relevant question of residual insulin secretory capacity. Current recommendations in diabetology therefore recognize C-peptide as a useful additional information to islet-cell autoantibody testing, when diabetes classification remains uncertain.

Importantly, the clinical utility of C-peptide is not restricted to distinguishing type 1 from type 2 diabetes. In pancreatogenic diabetes, advanced type 2 diabetes, and other insulinopenic phenotypes, C-peptide provides a functional assessment of beta-cell reserve that complements traditional etiological classification and can guide therapeutic insulin replacement [1, 2]. This distinction is clinically relevant because insulin deficiency exists on a continuum rather than as a binary trait. Residual insulin secretion may persist for decades in some individuals with type 1 diabetes, whereas profound beta-cell failure can develop in long-standing type 2 diabetes [9]. Although not yet widely applied, the possibility to measure C-peptide in urine, particularly following stimulation, could also enable noninvasive assessments of beta-cell function in the future [19]. Consequently, C-peptide offers a functional framework for characterizing diabetes that extends beyond conventional diagnostic categories.

In addition, the therapeutic implications of endogenous insulin secretion are increasingly recognized. While hyperglycemia reflects the (insufficient) balance between insulin secretion and insulin action, C-peptide provides direct information on the capacity of the endocrine pancreas to meet this demand. Low C-peptide concentrations identify clinically relevant insulin deficiency and can prompt initiation or intensification of insulin therapy. Conversely,

preserved C-peptide levels suggest residual beta-cell function and may favor non-insulin-based treatment strategies, including incretin-based therapies or SGLT2 inhibitors.

For this purpose, the fasting C-peptide-to-glucose ratio (CGR), calculated as fasting C-peptide (pmol/L) divided by fasting plasma glucose (mg/dL), has been proposed as a pragmatic tool for pathophysiology-based treatment selection [20]. In a well-characterized diabetes cohort, CGR values <2 were associated with severe insulin deficiency and a need for insulin therapy, values of 2 to <5 suggested consideration of basal insulin in combination with non-insulin glucose-lowering agents, whereas values of ≥5 indicated preserved endogenous insulin secretion and predominantly non-insulin-based treatment strategies [20](Figure 1).

The simplicity and clarity of this algorithm illustrate the potential of C-peptide-based biomarkers to support individualized therapeutic decision-making [21]. However, its broader clinical implementation requires careful consideration of analytical limitations. The proposed cut-offs were generated using C-peptide measurements generated with one single manufacturer's assay and can only be validly applied in a general population if the C-peptide results are comparable between different manufacturers and clinical laboratories. It underscores the need for standardization of metabolic biomarker, particularly C-peptide measurements, as analytical comparability between laboratories must be ensured before results from individual clinical studies can be translated into routine clinical practice and clinical guidelines.

Although these thresholds have gained attention, particularly in German diabetes care, and are discussed in current German Diabetes Association (DDG) recommendations [2], they have not yet been directly incorporated into major international guidelines. The American Diabetes Association (ADA) Standards of Care acknowledge the value of interpreting C-peptide concentrations in conjunction with concurrent plasma glucose levels for diabetes classification [1] but do not specifically endorse the CGR as a clinical decision tool. Broader implementation of CGR-based treatment algorithms will therefore require independent prospective validation and standardization of C-peptide measurements. This represents a prerequisite for translating such approaches into routine clinical care.

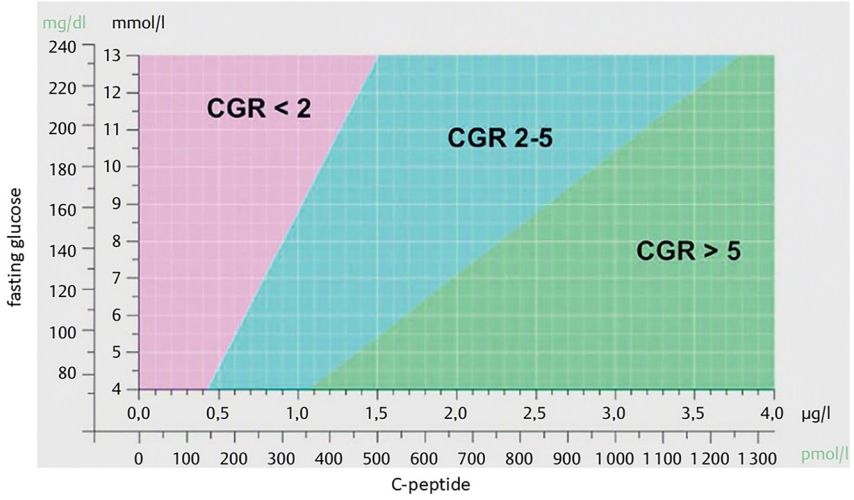

Figure 1: Nomogram for proposed clinical decision thresholds for the fasting C-peptide-to-glucose ratio (CGR). The fasting C-peptide-to-glucose ratio (CGR) is calculated as fasting C-peptide (pmol/L) divided by fasting plasma glucose (mg/dL). The figure illustrates proposed CGR thresholds for the assessment of endogenous insulin secretion. A CGR <2 has been proposed to indicate severe endogenous insulin deficiency and a likely need for insulin therapy. A CGR of 2 to <5 suggests impaired endogenous insulin secretion, in which basal insulin in combination with non-insulin glucose-lowering agents may be considered. A CGR ≥5 indicates preserved endogenous insulin secretion and may support predominantly non-insulin-based treatment strategies. These thresholds are based on proposed pathophysiology-based treatment concepts, are discussed e.g. in current German DDG recommendations, but have not yet been prospectively validated or incorporated into other international treatment guidelines. Different units of measurement are reported by different laboratories (C-peptide in pmol/L or µg/L), glucose in mmol/L or mg/dL). The nomogram can be used for easy and simple determination of the CGR for different units. Modified with permission from Fritsche A. Diabetologie. 2023;19:112–116. https://doi.org/10.1007/s11428-022-00992-4.

Future perspectives in personalized diabetology

A major conceptual shift in diabetology has been the transition from glucose-centered disease classification towards multidimensional phenotyping [8]. Diabetes is increasingly recognized as a heterogeneous disease in which the balance between insulin secretion and insulin resistance is one major determinant of disease progression, complication risk, and therapeutic response.

Data-driven subclassifications of both diabetes and prediabetes consistently identify beta-cell function and insulin resistance as major determinants of disease heterogeneity [22, 23]. A landmark example of this concept was provided by Ahlqvist et al. who applied a cluster analysis to a large cohort of newly diagnosed individuals with diabetes [22]. Using only six, routinely available parameters, the authors identified five clusters of patients with distinct phenotypic features. Those parameters are GAD antibodies, age at onset of diabetes, body mass index (BMI), hemoglobin A1c (HbA_{1c}), C-peptide based homeostasis model assessment (HOMA) [13, 14] estimates of β-cell function (HOMA2-B), and insulin resistance (HOMA2-IR), all of which can be determined in a clinical routine setting. The five diabetes clusters, that are named by their main characteristics, do not only differ in phenotype but more importantly in the risk for disease progression and development of diabetes-related complications [24–27]. Those are: Severe Autoimmune Diabetes (SAID), Severe Insulin-Deficient Diabetes (SIDD), Severe Insulin-Resistant Diabetes (SIRD), Mild Obesity-Related Diabetes (MOD), and Mild Age-Related Diabetes (MARD) (Figure 2). These five clusters showed remarkable reproducibility across a diverse range of participants, encompassing various patient origins and ethnic backgrounds [15]. In these analyses, individuals with impaired insulin secretion exhibit distinct trajectories of glycemic deterioration and complication risk compared with predominantly insulin-resistant phenotypes [28](Figure 2). Together, these findings demonstrate that pathophysiological characteristics provide clinically meaningful information beyond conventional glucose-based disease classification and could become the future basis for sub-phenotype-based personalized therapeutic approaches [28]. Some studies have further extended this concept by incorporating deep phenotyping data including oral glucose tolerance tests, body fat distribution, using advanced whole-body magnetic resonance imaging and magnetic resonance spectroscopy data of liver fat content to identify clusters [23]. However, the complexity of these approaches limits their implementation in routine clinical care. To facilitate the application in larger cohorts or everyday healthcare, easy and widely available biomarkers are needed. Laboratory tests, ideally determined from a single fasting blood samples are particularly attractive for this purpose. Among currently available biomarkers, fasting C-peptide (together with glucose) is especially attractive because it provides quantitative information on endogenous insulin secretion while also enabling estimation of insulin resistance through mathematical models. It therefore captures two central pathophysiological dimensions underlying diabetes heterogeneity. Thus, C-peptide is increasingly evolving from a marker of beta-cell function to a tool for multidimensional pathophysiological phenotyping and subclassification.

Whether incorporation of C-peptide-derived measures [12] into routine clinical algorithms will improve therapeutic outcomes still remains to be tested. Current evidence is largely observational, and prospective intervention studies demonstrating clinical benefit are still under way. Nevertheless, the integration of insulin secretion and insulin resistance into disease classification provides a biologically plausible framework for precision diabetology and may ultimately support more personalized therapeutic strategies in diabetes care. Achieving this goal requires analytically comparable C-peptide measurements.

Developments towards C-peptide standardization

Translation of biomarker-derived decision thresholds into routine clinical practice requires analytically comparable measurements across laboratories, assays, and manufacturers. This comparability is best achieved through biomarker standardization. For C-peptide, this is of particular importance because quantitative measurements increasingly underpin pathophysiology-based classification and treatment algorithms.

A prerequisite for standardization is that the analyte fulfills fundamental requirements. A biomarker should be (a) molecularly well defined, (b) available in a pure form, (c) stable, and (d) commutable [7]. In addition, a complete reference measurement system requires both suitable reference materials and a reference measurement procedure to establish traceability [7, 29, 30]. These principles are consistent with the requirements of ISO 17511:2020, which defines the metrological traceability hierarchy for values assigned to calibrators and control materials. Furthermore, ISO 17511:2020 emphasizes the importance of commutability

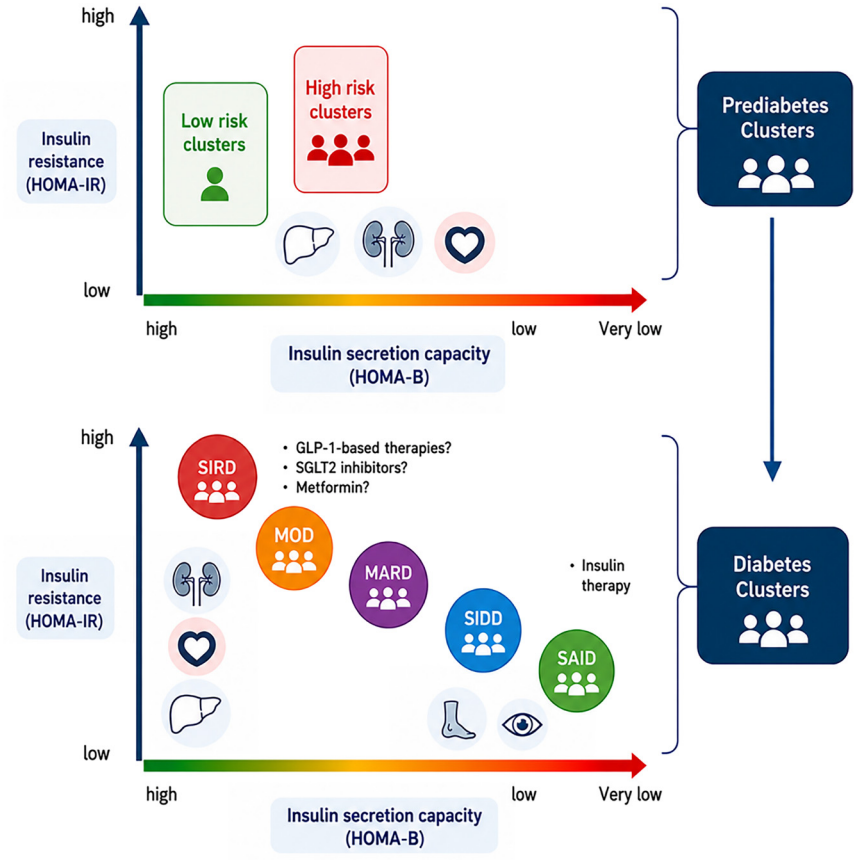

Figure 2: Pathophysiology-based phenotyping across the spectrum from prediabetes to diabetes. Schematic representation of the relationship between insulin secretion and insulin resistance across prediabetes and diabetes subgroups (clusters). The illustrated subgroups were originally identified by multivariable data-driven clustering approaches in prediabetes [23] and diabetes [22], in which measures of insulin secretion and insulin resistance were among the key variables enabling subgroup identification. Although not exclusively defining the original clustering algorithms, the two principal pathophysiological dimensions are represented here by HOMA-B and HOMA-IR to illustrate differences in endogenous insulin secretory capacity and insulin resistance between subgroups. The proposed therapeutic strategies, marked with "?", reflect current pathophysiological concepts as discussed in the literature but have not yet been validated in prospective intervention trials. HOMA-B: homeostasis model assessment of β-cell function; HOMA-IR: Homeostasis model assessment of insulin resistance; SAID: Severe autoimmune diabetes; SIDD: Severe Insulin-Deficient Diabetes; SIRD: Severe Insulin-Resistant Diabetes; MOD: Mild Obesity-Related Diabetes; MARD: Mild Age-Related Diabetes; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose cotransporter 2.

of reference materials used within the calibration hierarchy to ensure that calibration relationships are transferable to patient samples [31].

C-peptide fulfills these biological and analytical prerequisites particularly well. It is a chemically well-defined peptide consisting of 32 amino acids with a known molecular weight and sufficient stability for storage and shipment. Consequently, an international World Health Organization (WHO) reference reagent (NIBSC code 84/510) was introduced for calibration of C-peptide immunoassays already approximately ten years after the discovery of human C-peptide in 1967 [32]. However, despite availability of this reference material, clinically relevant differences between laboratories and methods persisted. Furthermore, off-line calibration with the pure WHO reference reagent (NIBSC code 84/510) alone did not improve inter-method comparability. These findings prompted the establishment of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) C-peptide Standardization Committee in 2002.

Subsequent international comparison studies consistently identified the principal limitation of the first generation of standardization efforts. In the international comparison organized by the NIDDK committee, C-peptide measurements obtained with 10 analytical methods across 15 laboratories in 7 countries showed substantial inter-method differences that persisted despite calibration against the WHO reference material [33]. Importantly, recalibration using matrix-appropriate patient serum samples markedly reduced assay variability, demonstrating that appropriate calibration materials rather than the reference analyte itself represented the critical determinant of assay agreement.

This concept was further strengthened by the work of Little et al. [34], who introduced a liquid chromatography-mass spectrometry (LC-MS)-based reference measurement procedure for assay recalibration. In this international comparison involving 15 laboratories and nine C-peptide assays, all immunoassays systematically overestimated C-peptide concentrations compared with the reference method. Following recalibration using LC-MS-assigned serum samples,

these systematic differences were no longer statistically significant, and agreement between methods improved substantially. These studies established LC-MS as the analytical reference method and demonstrated that serum-based recalibration represents an effective strategy for improving comparability between assays. Subsequently, LC-MS-based reference measurement procedures were accepted into the Joint Committee for Traceability in Laboratory Medicine (JCTLM) database [35, 36]. In these documents the recalibration of C-peptide assays by the manufacturers using pooled serum samples as secondary reference materials is described. These findings closely align with the principles established in ISO 17511:2020 [31]. Firstly, it is demonstrated that metrological traceability alone is insufficient to ensure comparability of patient results if the calibration hierarchy does not adequately reflect the clinical sample matrix. Secondly, the study demonstrates that the quality of the entire reference measurement system – including the selection of reference materials and calibration strategy – exerts a more significant influence than the mere availability of a higher-order reference material. Thirdly, the results support the ISO 17511:2020 concept that each step in the traceability chain must preserve equivalence between calibration materials and native patient samples to achieve consistent measurement results across methods.

Because of the disappointing results of earlier studies, the WHO recognized an urgent need for a standard for human C-peptide harmonization. Based on the new findings, the WHO developed a new international C-peptide standard (NIBSC code 13/146), which replaced the exhausted WHO 84/510 material [37]. The NIBSC material was produced for the calibration of C-peptide immunoassays and not as primary reference material in the isotope dilution-MS reference measurement system. In addition to NIBSC 13/146, another reference material is available which is listed in the JCTLM database and is suitable for the ID-MS reference management system [29, 38].

However, the introduction of a new reference material alone did not resolve the remaining discrepancies between assays. The Joint Committee for traceability in Laboratory Medicine (JCTLM) established a complete reference measurement system using the NMIJ certified reference material (6901-b) together with mass spectrometry as the primary reference procedure, thereby providing the framework required for full assay standardization [29].

A number of recent studies have consistently confirmed both the magnitude of the remaining problem and the feasibility of its solution [30, 39]. In a large nationwide comparison involving 94 laboratories in China, inter-measurement system variability reached 24.5 %, despite acceptable within-system precision [39]. The study included five pooled patient serum samples and two additional serum samples for recalibration. Recalibration using patient serum-based samples reduced inter-system variability to 5.7 %.

Comparable findings were reported by Hörber [30], comparing five widely used C-peptide assay platforms using 50 patient serum samples. Despite traceability of all assays to the same WHO reference material (84/510), differences of up to 36 % were observed between two assay systems while the other three assay platforms showed similar C-peptide results.

The authors therefore emphasized the need for continued participation in external quality assessment programs to control their comparability with other clinical laboratories and that there is urgent need to implement the standardization process. This urgent need has recently been reinforced by Kabytaev et al. and Schleicher et al. [40, 41].

The most recent international comparison [42] extended previous work by directly involving assay manufacturers. Although most manufacturers already calibrated their assays against the same WHO reference material (NIBSC code 84/510), only two manufacturers used the more recent WHO reference material (NIBSC code 84/510). Recalibration using matrix-appropriate serum samples again substantially reduced both systematic bias and inter-assay variability. Importantly, this study demonstrated that the remaining discrepancies can largely be addressed within existing analytical platforms by appropriate recalibration rather than by developing fundamentally new analytical technologies.

Although standardized serum calibrators ensure analytical traceability across assay platforms, some inter-laboratory differences of C-peptide may persist due to pre-analytical handling. Although less vulnerable to *ex vivo* degradation caused by variables like delayed centrifugation and ambient storage temperatures than insulin, additional implementation of strict Standard PREanalytical Code (SPREC) protocols will be necessary to eliminate field-level bias [16, 43].

Taken together, the available evidence provides a consistent framework. C-peptide fulfills the biological requirements for standardization, a complete reference measurement system is available, and multiple independent studies have demonstrated that serum-based recalibration markedly improves agreement between assays. The remaining challenge is therefore no longer the development of appropriate reference materials or analytical procedures, but their consistent implementation by assay manufacturers. Addressing this final step is essential to achieve analytically comparable C-peptide measurements and thereby enable reliable transfer of biomarker-derived decision thresholds into diabetes guidelines and routine clinical practice.

Conclusions

Manufacturers still hesitate to adopt the current standardization program because they anticipate substantial costs from assay recalibration, including analytical revalidation, documentation updates, and new regulatory submissions [40]. They also expect added expenses for updating labels and adapting customer quality-control systems. Nevertheless, the evidence summarized here indicates that the remaining challenge is no longer the development of suitable reference materials or reference measurement procedures, but their consistent implementation across manufacturers and laboratories. Standardization of C-peptide measurement is therefore not only an analytical objective but a prerequisite for translating pathophysiology-based diabetes classification and biomarker-derived treatment algorithms into routine clinical practice. As precision diabetology increasingly relies on quantitative assessment of insulin secretion and insulin resistance, analytically comparable C-peptide measurements will become essential for establishing robust clinical decision thresholds, enabling their incorporation into guidelines, and ensuring consistent patient care across healthcare systems. Successful implementation will ultimately benefit patients through more individualized diagnosis and treatment and support broader adoption of C-peptide-based biomarkers into clinical practice.

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Use of Large Language Models, AI and Machine Learning Tools: ChatGPT was used to graphically enhance Figure 2. DeepL was used for language editing.
Conflict of interest: M.H. reports lecture fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, Daichii Sankyo, Lilly, Novartis, Novo Nordisk, and Sanofi. He also served on advisory boards for Boehringer Ingelheim, Chiesi, and Lilly. He is currently a board member for the German Diabetes Association (DDG). E.S., M.K. and A.P have nothing to report.
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