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Definition, Classification and Diagnosis of Diabetes Mellitus *

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Definition of Diabetes Mellitus

Diabetes mellitus is the collective term for heterogeneous metabolic disorders whose main finding is chronic hyperglycaemia. The cause is either a disturbed insulin secretion or a disturbed insulin effect or usually both.

Gestational Diabetes

Glucose tolerance disorder that occurs or is diagnosed for the first time during pregnancy [1].

Type 1 diabetes

- β-cell destruction that leads to an absolute insulin, deficiency mostly transmitted immunologically,
- Checkpoint inhibitor-induced diabetes,
- LADA (latent autoimmune diabetes in adults): classified as type 1 diabetes (▶ **Table 1**).

Type 2 diabetes

- Can range from a predominant insulin resistance with a relative insulin deficiency to a largely secretory defect with insulin resistance.
- Is often associated with other diseases (e. g. the metabolic syndrome).

Other specific types of diabetes

- Exocrine pancreatic diseases (e. g. pancreatitis, cystic fibrosis, hemochromatosis),
- Endocrinopathies (e. g. Cushing's syndrome, acromegaly, pheochromocytoma),
- Medically-chemically induced (e. g. glucocorticoids, neuroleptics, interferon- alpha, pentamidine).

Genetic defects of the β-cell function (e. g. MODY forms)

- Genetic defects of insulin action,

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- Other genetic syndromes which can be associated with diabetes,
- Infections,
- Rare forms of autoimmune diabetes.

Diagnostic Criteria of Diabetes Mellitus

Measured variable venous plasma glucose:

- Occasional plasma glucose value of ≥ 200 mg/dl (≥ 11.1 mmol/l),
- Fasting plasma glucose of ≥ 126 mg/dl (7.0 mmol/l) (fasting time 8–12 h),
- OGTT 2-h value in venous plasma ≥ 200 mg/dl (≥ 11.1 mmol/l) (for specifications for the procedure see ▶ **Table 2**),

Measured variable HbA1c:

- HbA1c ≥ 6.5 % (≥ 48 mmol/mol Hb),

Abnormally elevated fasting glucose levels

IFG (impaired fasting glucose) for the fasting glucose range of 100–125 mg/dl (5.6 mmol- 6.9 mmol/l) in venous plasma.

Disturbed glucose tolerance

IGT (impaired glucose tolerance) corresponds to a 2-h plasma glucose value in oGTT in the range of 140-199 mg/dl (7.8-11.0 mmol/l) with fasting glucose values of < 126 mg/dl (< 7.0 mmol/l).

Many people with a glucose tolerance disorder have IFG and IGT.

Diagnostic Procedure

The recommended diagnostic procedure is shown in ▶ **Fig. 1**. The differential diagnostic criteria for type 1 diabetes and type 2 diabetes are listed in ▶ **Table 1**. The criteria for the diabetes types LADA and MODY are shown in ▶ **Fig. 2,3**. Diabetes diagnosis resulting from a disease of the exocrine pancreas is based on the criteria in ▶ **Table 3**.

Only quality-assured laboratory methods may be used to measure venous plasma glucose and HbA1c for diagnosing diabetes.

This is defined in the guidelines of German Medical Association for Quality Assurance in Laboratory Medical Examinations (Rili-BÄK) uniformly for central laboratories as well as for point-of-care testing (POCT) [5]. Participation in interlaboratory comparisons has so far not been mandatory for POCT methods used in practices. However, if POCT systems are approved by the manufacturer for diagnostic use, we also recommend successful participation in external interlaboratory comparison for use in diagnostics.

The current gold standard for diabetes diagnostics is the measurement of glucose in venous plasma.

Procedure for measurement results close to decision limits

A measurement on which the diagnosis is based should be confirmed promptly (e. g. within 14 days) using a new blood sample. Confirmation can be done by determining the other of the two measured variables (▶ **Fig. 1**).

Measurement of the same variable can be repeated or in the case of a diabetes diagnosis with findings in the grey area, a diffe-

▶ **Table 1** Differential diagnostic criteria for common diabetes types at diagnosis. Data according to National Care Guideline Type 2 Diabetes; www.versorgungsleitlinien.de.

	Type 1 diabetes[1]	Type 2 Diabetes	MODYs
Aetiology	Autoimmune, genetic predisposition	Genetic predisposition, multifactorial	Monogenic
Heredity	Variable	Variable	Autosomal dominant; diabetes in ≥ 3 generations
Frequency among all diabetes types	5–10 %	90–95 %	Approx. 2 %
Pathogenesis	Autoantibodies, absolute insulin deficiency	Insulin resistance and secretion disorder up to insulin deficiency	mutation of genes of transcription factors or glucokinase of β-cells
Typical age of manifestation	Childhood to adulthood	Adulthood	Youth to early adulthoo
Clinical manifestation	Acute polyuria, polydipsia, severe hyperglycaemia, ketoacidosis	slow onset, often secondary diseases, moderate hyperglycaemia	Slow onset, variable hyperglycaemia
Comorbidities	Autoimmune thyroiditis, celiac disease	Visceral obesity, hypertension, Diabetes (also called Metabolic Syndrome)	Renal cysts depending on MODY type
Tendency to ketosis	Yes	No	No
Weight	Normal weight	Overweight	Normal weight
Plasma insulin/C-peptide HOMA-B2	Reduced to lacking	Often high at beginning, then reduced	mostly diminished
autoantibodies	Yes	No	No
Insulin resistance HOMA-R3	o	Yes	No
Therapy	Insulin	Lifestyle modification measures, oral antidiabetics, insulin	possibly none, OADs, insulin (depending on MODY type)

[1] LADA (latent insulin-dependent diabetes in adulthood) is associated with a slow loss of beta cell function. The LADA has a rapid failure of oral antidiabetics. In case of suspicion of LADA: recommend analysis of GAD antibodies. [2, 3] HOMA-B or Homa-R Homeostasis Model Assessment to quantify the β- cell reserve2 and insulin resistance[3].

rent variable (i. e. either glucose or HbA1c) should always be determined in order to reduce disturbance or influence variables.

If there are discrepancies regarding the diagnostic cut-off for two different measured variables, the higher value should be confirmed by a new measurement. If the values are in the grey area, a check in 3–6 months is recommended.

▶ **Table 2** Oral glucose tolerance test (oGTT).

Performing the 75-g oGTT-oral glucose tolerance test-according to WHO guidelines
Performing the test in the morning ▪ After 8–12 h of fasting from food, nicotine and alcohol ▪ After a ≥ 3-day carbohydrate-rich diet (≥ 150 g carbohydrates per day) ▪ Sitting or lying (no muscular effort); no smoking before or during the test
At point in time 0, drink 75 g glucose (or equivalent amount of hydrolysed starch) in 250-300 ml water within 5 min. ▪ Children 1.75 g/kg (maximum 75 g) ▪ Venous blood sampling at the points in times 0 and 120 min ▪ Proper sample processing and storage
Test contraindicated for intercurrent diseases, for gastrointestinal resection or gastrointestinal diseases with altered resorption or if diabetes mellitus has already been diagnosed. The completion of the glucose solution by the physician himself instead of by the manufacturer is rejected by the DDG for liability and medical reasons; see statement by KLD and AGDT on the DDG website.

Pre-analytics of glucose measurement

Adequate preanalytical handling of blood is very important. Precautions must be taken to ensure that glycolysis is completely inhibited in the blood samples by using suitable blood collection tubes

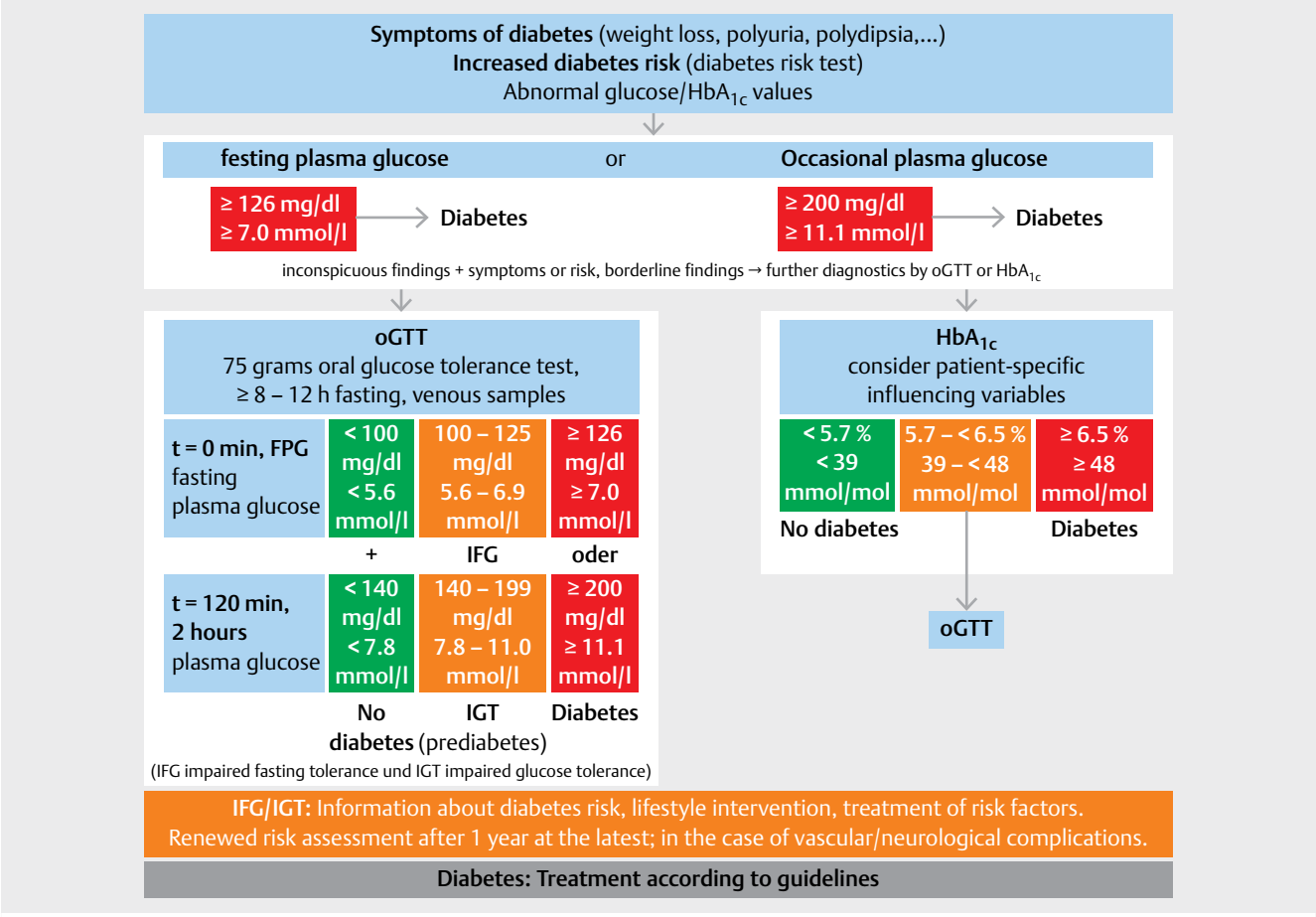
For this the addition of citrate plus fluoride is necessary; fluoride alone is not sufficient. The blood collection tubes with glycolysis inhibitors currently on the market exhibit various handling problems (▶ **Table 4**).

Alternatively, it is recommended to centrifuge tubes immediately after blood collection without immediate and complete glycolysis inhibition. If a time window of 30 min until centrifugation is exceeded, the samples should be discarded due to the glycolysis process. After centrifugation, the plasma supernatant must be separated from the blood cells. This is done during centrifugation with a gel (gel tube). It is also possible to decant the plasma supernatant immediately after centrifugation.

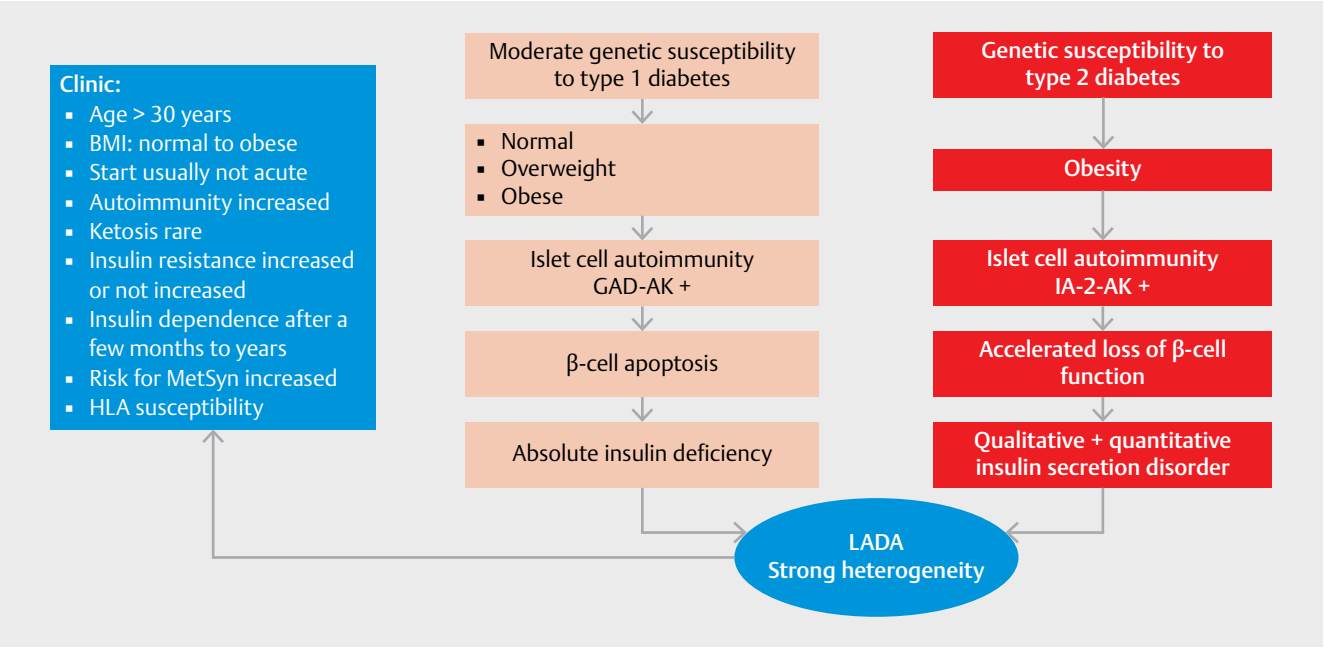
Consistent and optimal preanalytical handling of the blood collection tubes can lead to a higher diabetes diagnosis rate in practice. This is not over-diagnosing. The diagnostic cut-offs used in the following are to be scientifically tested.

HbA1c for diagnosis

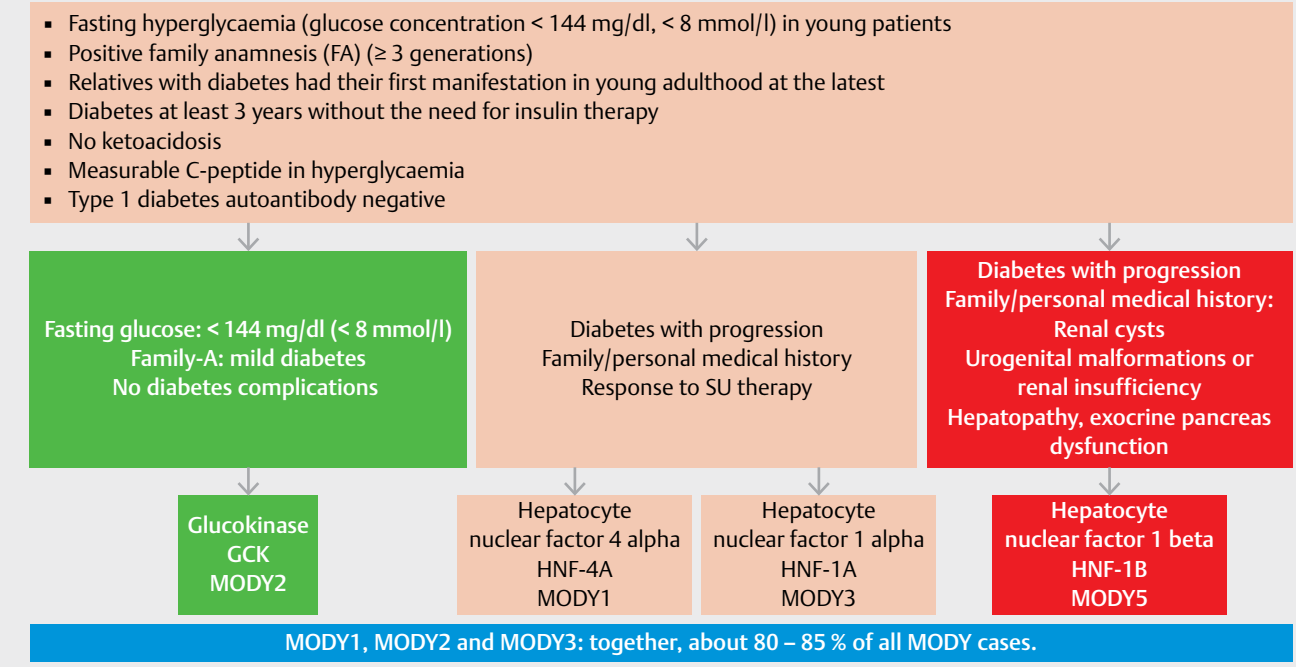
At present, the use of the HbA1c value for diagnosis is not generally recommended, especially since the permissible deviation for internal and external quality control has so far been ± 10 %



▶ **Fig. 1** Algorithm for the diagnosis of diabetes. [rerif]



▶ **Fig. 2** LADA diagnostic criteria. According to [2]. [rerif]



▶ **Fig. 3** Diagnostic algorithm of the most important MODY forms. According to: [3] and MODY Probability Calculator (www.diabetesgenes.org/mody-probability-calculator). [rerif]

and ± 18 % respectively. Both requirements will be significantly lowered in the version of the Rili-BÄK currently being revised: initially to ± 5 % for internal quality assurance and to ± 3 % after a two-year transition phase. In the case of external quality assurance, the value is reduced to ± 8 %. These measures significantly improve the usability of HbA1c as a diagnostic medium.

If diabetes is diagnosed with an HbA1c measurement, then a confirmation measurement with HbA1c is not meaningful because the HbA1c value can be influenced by various factors (▶ **Table 5**). In addition to the differences resulting from the methods, also the increase of the HbA1c which can be an absolute 0.4–0.7 % (4–8 mmol/mol Hb), which is independent of diabetes and comes

▶ **Table 3** Diagnosis of exocrine pancreatic disease [4].

Criteria	expression
Main criteria (all must be present)	▪ Exocrine pancreatic insufficiency (documented by stool tests for elastase-1 or a direct functional test) ▪ Pathological imaging of the pancreas (endosonography, MRI, CT) ▪ Lack of markers for type 1 diabetes
Additional criteria	▪ Impaired beta cell function (e. g. HOMA-B, C-peptide glucose quotient) ▪ No highly increased insulin resistance (e. g. HOMA-IR) ▪ Reduced incretin secretion (e. g. GLP-1, pancreatic polypeptide) ▪ Low serum values of fat-soluble vitamins (A, D, E and K)

▶ **Table 4** Commercially available blood collection vessels that achieve complete glycolysis inhibition by the addition of fluoride and citrate (current status 17.07.2017, see manufacturers' homepages).

Manufacturer	Product name	Correct filling absolutely necessary	Sufficient mixing required	Correction factor
Greiner bio-one	Vacuette® FC-Mix	No	10 times	No (granules)
Kabe	Primavette®, KABEVETTE®	Yes	Few times	1.16 (liquid additive)
Sarstedt	S-Monovette GlucoEXACT®	Yes	Few times	1.16 (liquid additive)
Greiner bio-one tubes (Vacuette® FC-Mix) contain a granulate in the blood collection tubes. The tubes must be swivelled 10 times after filling the blood to achieve a sufficient solution and mixing with the glycolysis inhibitor. Experience with the blood collection tubes from Sarstedt (S-Monovette GlucoEXACT®) and Kabe (Primavette®, KABEVETTE®) shows that dilution errors occur when the tubes are not completely filled. The laboratory must reliably identify such tubes in order to identify and exclude from analysis tubes that are not correctly filled according to the manufacturer's specifications and to take into account the dilution factor of 1.16.				

▶ **Table 5** Influencing variables that lead to an influence[a] or falsification[b] of the HbA1c value.

1.	Haemoglobin variants (HbS, HbE, HbF, HbC, HbD and others) ▪ The extent of the interference depends on the measuring method used. [a, b]
2.	Conditions with increased or decreased lifespan of erythrocytes, haemolysis induced by drugs such as cephalosporins, iron deficiency anaemia, new blood formation as part of anaemia treatment, after phlebotomy, after splenectomy or diseases of the spleen, liver or kidney[a]
3.	Chemical modifications of haemoglobin[b], including uraemia (carbamylated Hb), high-dose long-term therapy with acetylsalicylic acid (acetylated Hb)
4.	Haemolysis-causing drugs, e. g. cephalosporins[b]
5.	Inhibition of glycation (e. g. long-term therapy with ascorbic acid or vitamin E). The clinical significance of this phenomenon is not well understood. [b]
6.	Pregnancy[a]
7.	Ethnicity and age (HbA1c increases with age, so that the age of diagnosis criterion should be adjusted. In addition, the possible role of alternative parameters such as fructosamine or glycated albumin is discussed)[a]
8.	Blood transfusion

with age, restricts the use of HbA1c for the diagnosis of diabetes especially in the range below 53 mmol/mol Hb (7.0 %) [6].

Quality assurance

The internal quality control must be carried out every working day with suitable control material. Successful participation in external quality assurance is required once per quarter.

This applies to all laboratory systems and to POCT "unit use" systems (individual test strips or cuvettes, according to the definition of the Rili-BÄK), which are also intended by the manufacturer for diagnosis.

Minimal difference

How should a single measured value be evaluated taking into account the measurement uncertainty of measurement results?

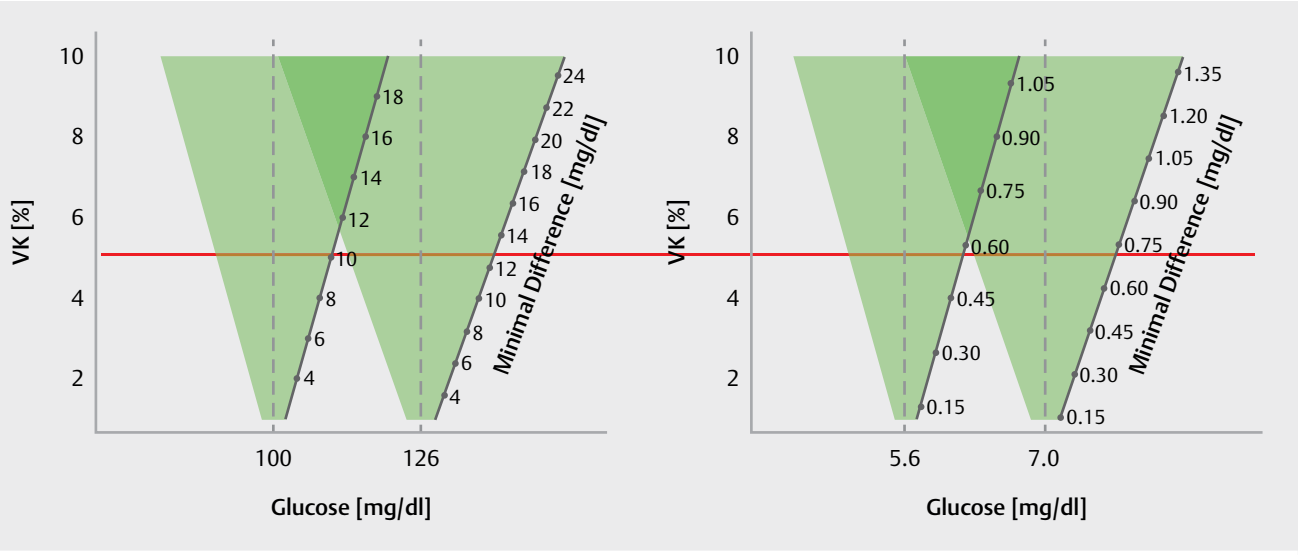
In the case of measurement results, there is generally the question of whether the deviation from the diagnostic cut-off is so far removed from this decision limit (i. e. greater than the minimum difference (MD), see below) that this measurement value can clearly be assessed as lower or higher.

VK % = CV [%], Glukose [mg/dl] = Glucose [mg/dl], Glukose [mmol/l] = Glucose [mmol/l]

In such cases the MD should be used for assessment.

In order to meet clinical requirements, analytical variability should be expressed in absolute values at the decision limits. The so-called MD is a simple tool to illustrate the meaning of the random error to the user and is calculated from the standard deviation (SD) (MD = 2 × SD) (▶ **Fig. 4**).

This MD, which can be obtained from the respective laboratory, gives concrete concentrations in absolute values above which a measured value differs from a diagnostic cut-off. At a fasting glucose cut-off of 126 mg/dl (7.0 mmol/L), the MD should not be greater than 12.6 mg/dl (0.7 mmol/L). The same applies to an HbA1c cut-off of 48 mmol/mol Hb (6.5 %). The MD should not be greater than 2 mmol/mol Hb (0.3 %).



▶ **Fig. 4** Minimal difference, expressed in the unit of glucose determination (mg/dl or mmol/l) for the diagnostic cut-offs considered a function of the coefficient of variation. If the measured values are below the overlapping area of the drawn funnels, the diagnostic cut-offs can be analytically differentiated from each other and thus used for the diagnosis. [rerif]

▶ **Table 6** Diagnosis of gestational diabetes (75-g oGTT). Diabetes is confirmed when 1 criterion is met. For the pre-analytics of glucose determination, refer to the guideline for gestational diabetes; adequate inhibition of glycolysis is necessary.

	Venous plasma	
	mg/dl	mmol/l
Fasting	≥ 92	≥ 5.1
60 min	≥ 180	≥ 10.0
120 min	≥ 153	≥ 8.5

Screening

For primary screening for diabetes, a diabetes risk test and/or measurement of occasional glucose in venous plasma is recommended.

The following questionnaires are recommended:

- German Diabetes Risk Test (https://drs.dife.de/),
- FINDRISK Questionnaire (https://www.diabetesstiftung.de/findrisk).

In the case of high questionnaire scores, manifested cardiovascular disease or the presence of excess weight with other risk factors, e. g. hypertension, dyslipidaemia (elevated triglyceride or LDL cholesterol or decreased HDL cholesterol), or a positive family history of type 2 diabetes in first-degree relatives, gestational diabetes or PCO (polycystic ovarian syndrome), or non-alcoholic fatty liver as described in ▶ **Fig. 1**.

Although a lot of data on the prevalence of diabetes mellitus has been collected in various fields in Germany, there is no comprehensive screening for the proportion of diabetics in hospitals. According to a study carried out by the University Hospital of Tübingen, 24 % of newly admitted patients had prediabetes and 22 % manifested diabetes where for every 6th diabetic, the disease was not known [8]. The authors therefore recommend screening every admitted patient over 50 years of age for diabetes.

Gestational Diabetes

The cut-offs in the oGTT given in ▶ **Table 6** are based on the results of the HAPO study [1]. They differ only slightly from the previously valid values. Nowadays, one too-high value is enough for diagnosis, whereas previously two values had to be high.

INFORMATION/ LINKS

Addresses on the Internet
http://www.deutsche-diabetes-gesellschaft.de

- Current version of the evidence-based guidelines: https://www.deutsche-diabetes-gesellschaft.de/leitlinien.html

Outlook

For some time now, attempts have been made to more precisely classify type 2 diabetes, which presents itself as a very heterogeneous group. Based on large Scandinavian studies, L. Groop and his research group have proposed to divide type 2 diabetes into 4 subgroups (clusters) using age at diabetes diagnosis, BMI and the laboratory parameters HbA1c, GAD autoantibodies, C-peptide and HOMA-B or HOMA-R. The aim of this project is to develop a new type of diabetes management system for the treatment of diabetes. This new classification also defines subgroups which, for example, have a high probability of suffering from diabetic retinopathy (cluster 2) or diabetic nephropathy (cluster 3) [9]. The authors point out that the new classification can also lead to therapy optimisation. Since this new subclassification was also verified in co-

horts of other countries, it could also be put into practice in the future.

Recently, in a large prospective study of the German Diabetes Study Group, a heterogeneous group of people with diabetes was subjected to extensive phenotyping at the time of diagnosis and followed up for 5 years [10]. It was possible to discover clusters with specific risk patterns, especially with regard to the development of polyneuropathy and NAFLD. This is another milestone in the subclassification of people with type 2 diabetes.

After much preliminary work by A. Ziegler's research group in Munich in cooperation with international centres, it was shown that with the presence of several autoantibodies against β- cell peptides in early childhood, the probability of manifestation of type 1 diabetes within 15 years is very high (high predictive value) [7]. If the pilot therapy studies already underway are positive, general screening for risk markers in early childhood could be introduced across the board [11].

Conflict of Interest

A. Petersmann received consulting and contract fees from Tosoh Bioscience, Radiometer, Roche Diagnostics, Nova Biomedical, Siemens Healthineers, Becton Dickinson. D. Müller-Wieland declares potential conflicts of interest: Member of Advisory Boards and has received lecture fees: Amgen, Boehringer Ingelheim, MSD, AstraZeneca, Novo Nordisk, Sanofi U.A. Müller has not received any personal fees or travel expenses from pharmaceutical companies since 2010. His working group received research support from Fresenius Medical Care, VDBD, Diabeteszentrum Thüringen e. V., Haemopharm, NOVO Nordisk, Abbott, Pfizer Pharma, European Association for the Study of Diabetes on a third-party account of the University Hospital Jena. R. Landgraf declares the following potential conflicts of interest: Advisory Boards: Lilly Deutschland, Novo Nordisk Pharma; presentation fees: AstraZeneca, Berlin Chemie, Lilly Deutschland, Novo Nordisk Pharma. Other activities: Authorized representative of the Executive Board of the German Diabetes Foundation, Steering Committee for the Development and Updating of the National Care Guidelines for Diabetes M. Nauck received consulting and contract fees from Tosoh Bioscience, Radiometer, Roche Diagnostics, Nova Biomedical, Siemens Healthi- neers, Becton Dickinson. G. Freckmann is medical director and managing director of the IfDT (Institut für Diabetes-Technologie Forschungs- und Entwicklungsgesellschaft mbH at the University of Ulm, Ulm), which carries out clinical studies on medical products for diabetes therapy on its own initiative or on behalf of various companies. GF/IDT has received lecture/consultancy fees from Abbott, Ascensia, Dexcom, LifeScan, Menarini Diagnostics, Metronom Health, Novo Nordisk, Roche, Sanofi, Sensile and Ypsomed. L. Heinemann is a shareholder of Profil Institut für Stoffwechselforschung GmbH, Neuss, and of ProSciento, San Diego, USA. He is a consultant to a number of companies developing new diagnostic and therapeutic options for diabetes therapy. E. Schleicher received lecture fees from Nova Biomedical.

German Diabetes Association: Clinical Practice Guidelines

This is a translation of the DDG clinical practice guideline published in Diabetologie 2019; 14: S111-S118, DOI https:// doi.org/10.1055/a-0898-7266.

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