La diagnosi del diabete tipo 2: luci e ombre

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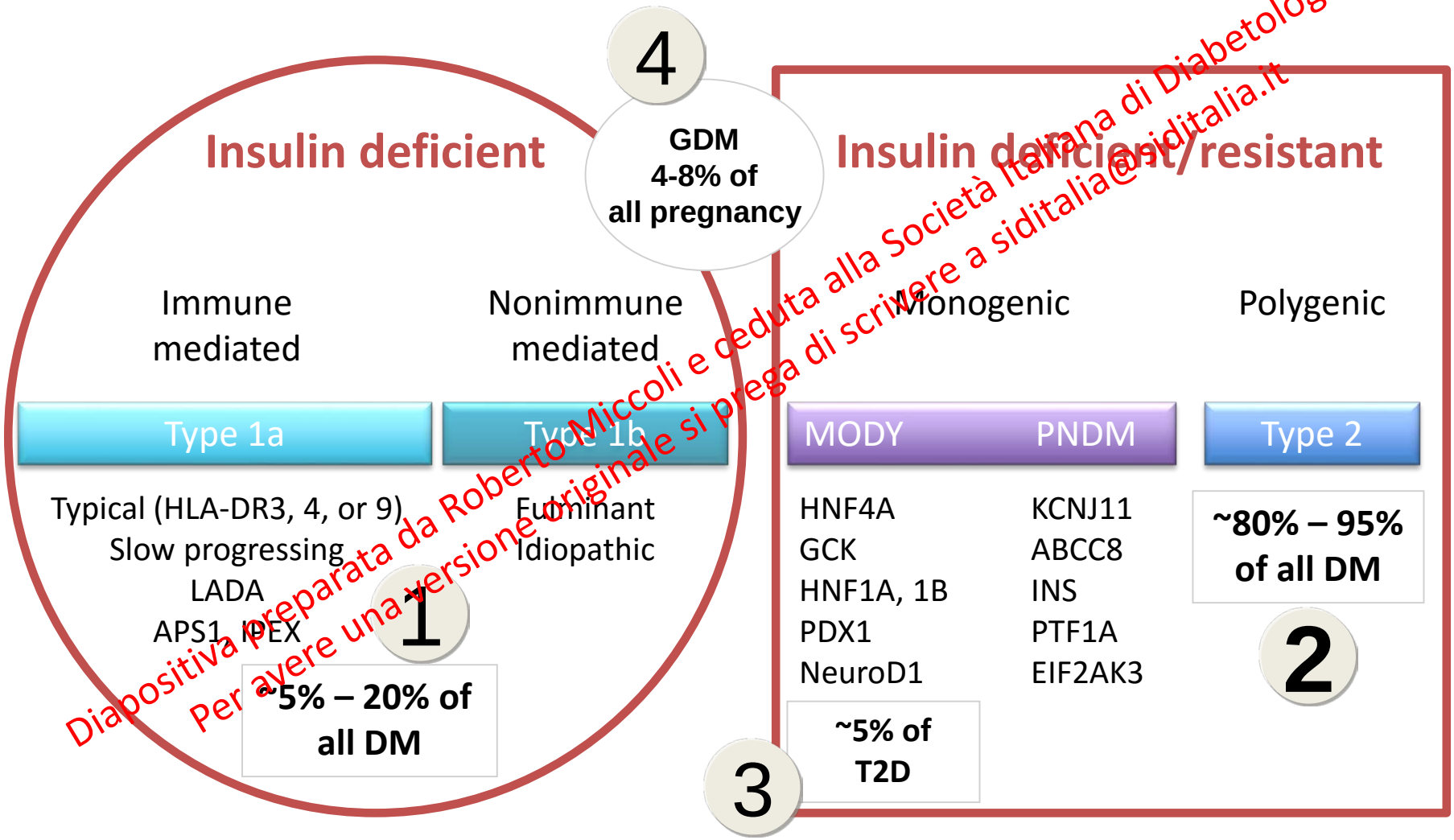
Definition of Diabetes

- Diabetes mellitus (DM) is a family of metabolic diseases characterized, defined and diagnosed by chronic hyperglycaemia resulting from defects in insulin secretion and insulin action (ADA, Diabetes Care 2006).

- Since the late 19th century, diabetes mellitus has been subdivided into *two broad categories*. In the first, the patients are typically young and lean with normal blood pressure and usually a rapid onset of symptoms. This is in contrast with the second group, where the patients are older, obese and hypertensive, and usually have an insidious onset (Gale EA Diabetes 2001). .

- This distinction, based on phenotype, is consistent with the current distinction between Type 1 diabetes (DM1) and Type 2 diabetes (DM2).

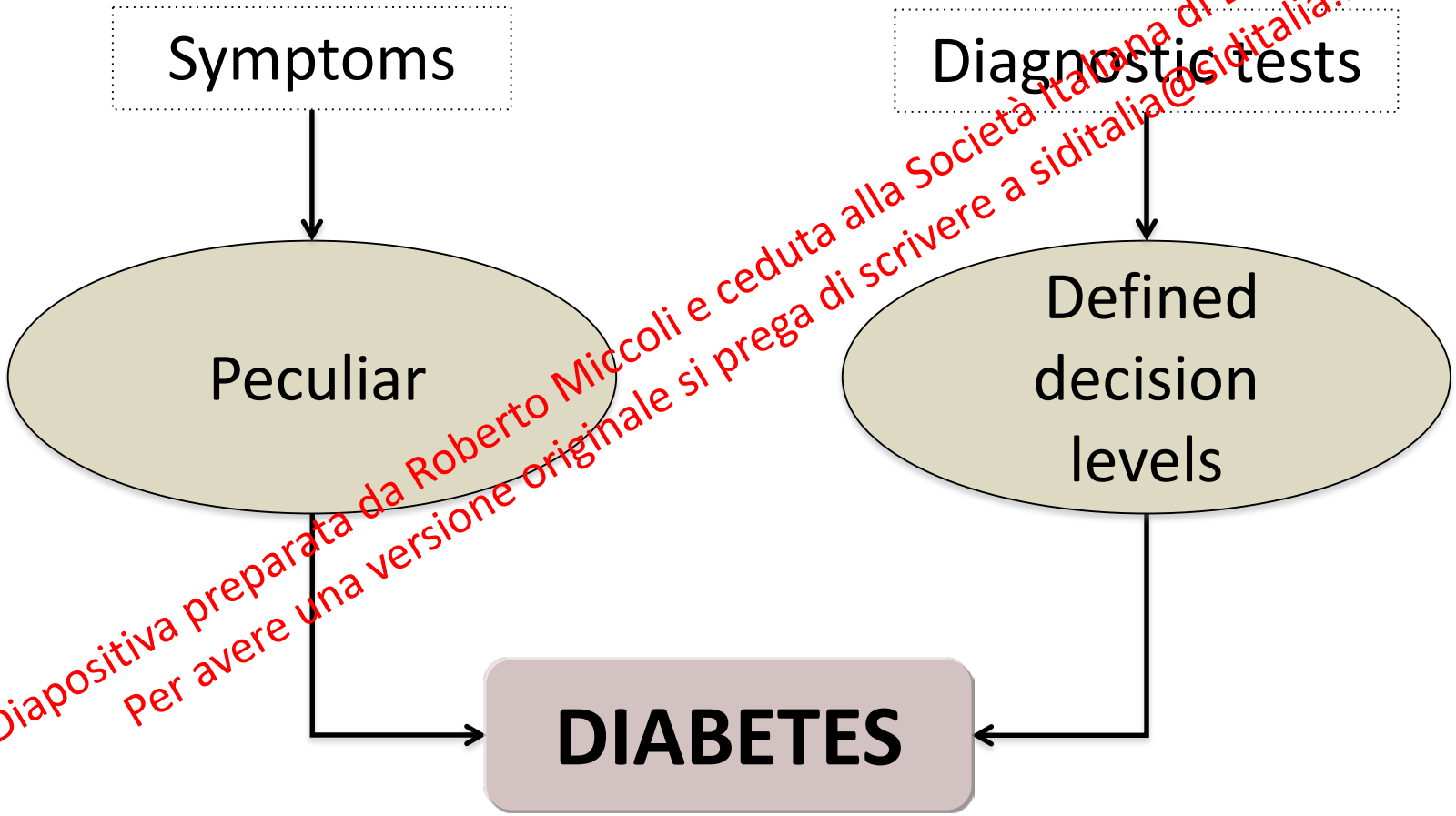
Etiologic Classification of Diabetes



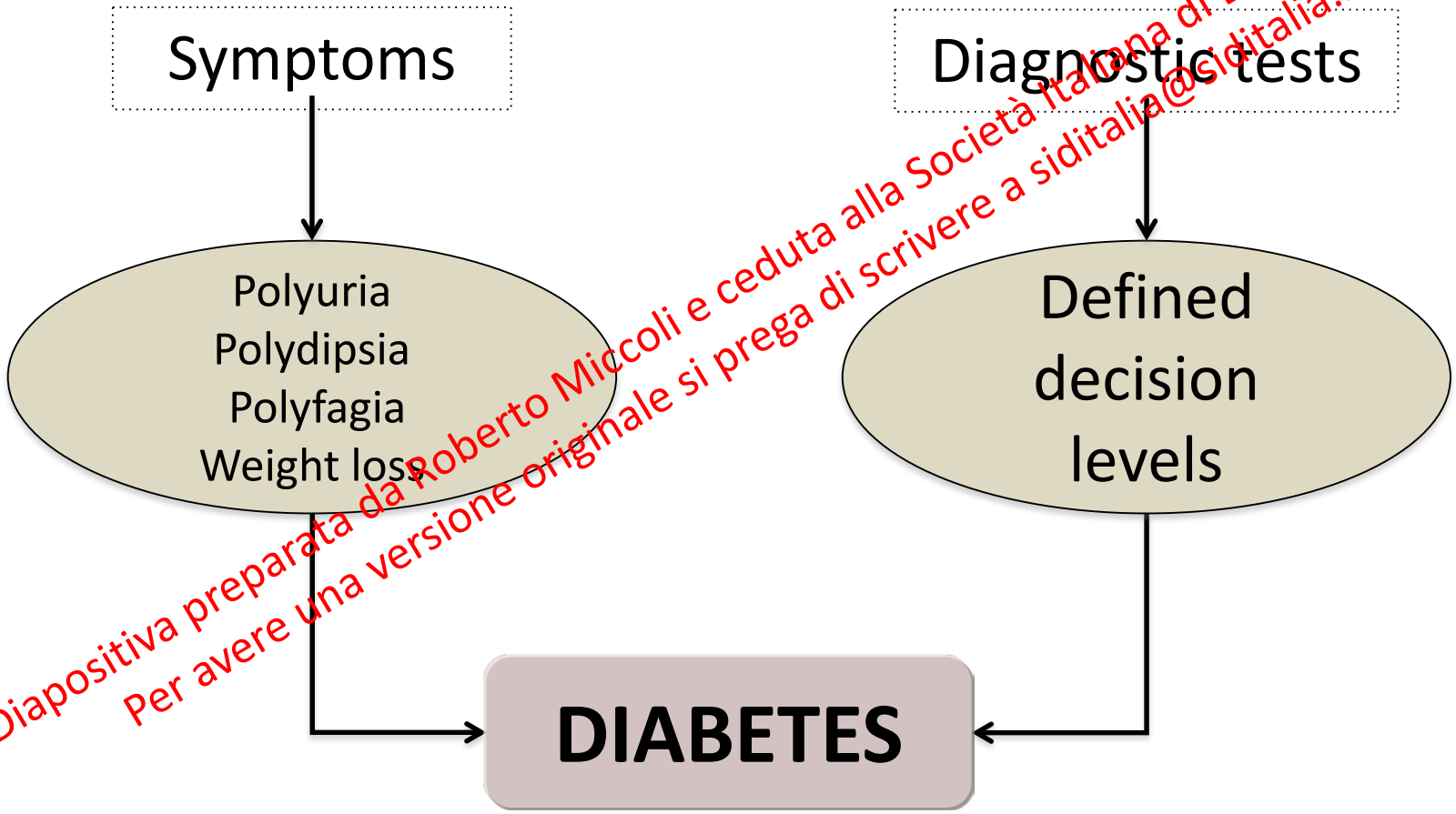
APS1, autoimmune polyendocrine syndromes 1; HLA, human leukocyte antigen; IPEX, immunodeficiency, polyendocrinopathy, enteropathy, X-linked syndrome; LADA, latent autoimmune diabetes of adults; MODY, maturity-onset diabetes of the young; PNDM, permanent neonatal diabetes mellitus.

Adapted from Rewers M. *Diabetes Metab J.* 2012;36:90-97.

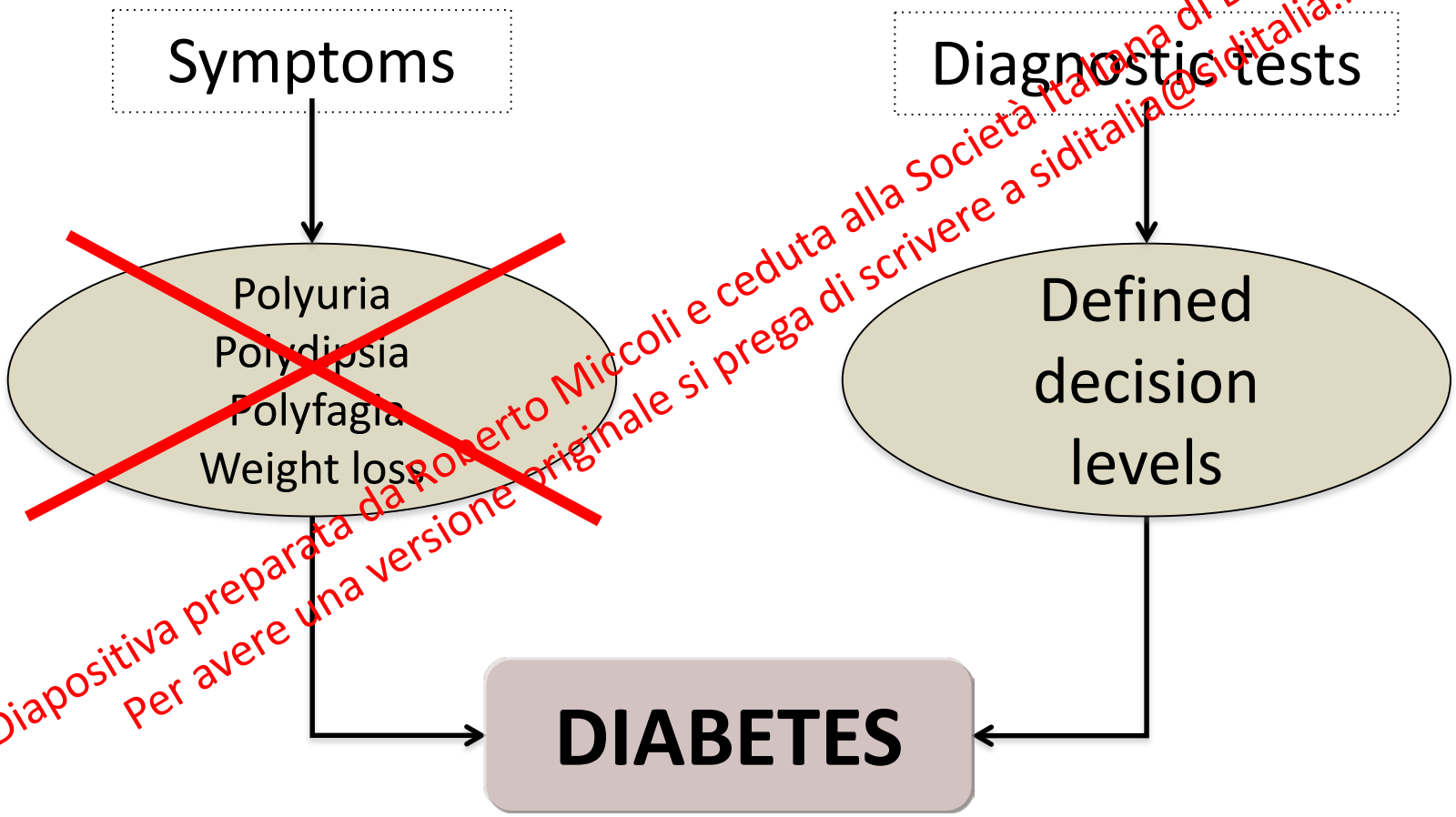
Diagnosis of type 2 diabetes



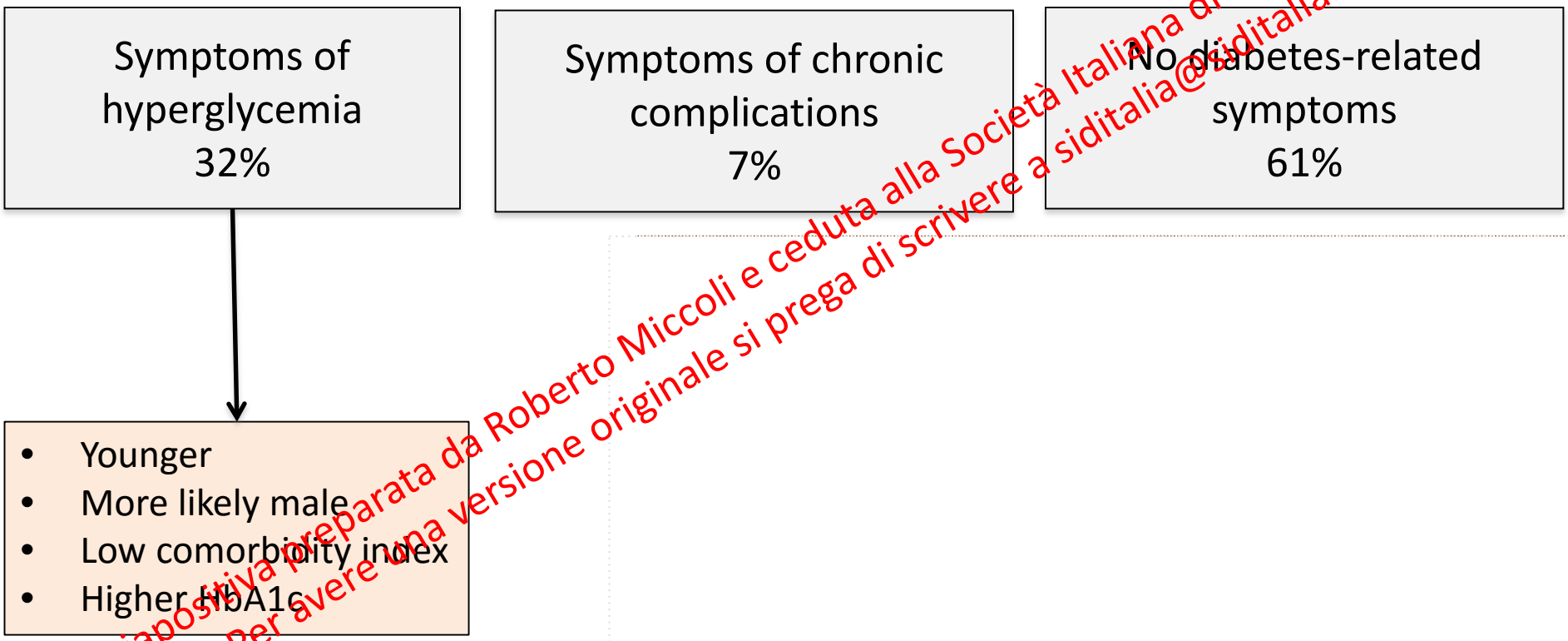
Diagnosis of type 2 diabetes



Diagnosis of type 2 diabetes



Type of symptoms and visit at the time of diagnosis in patients with type 2 diabetes



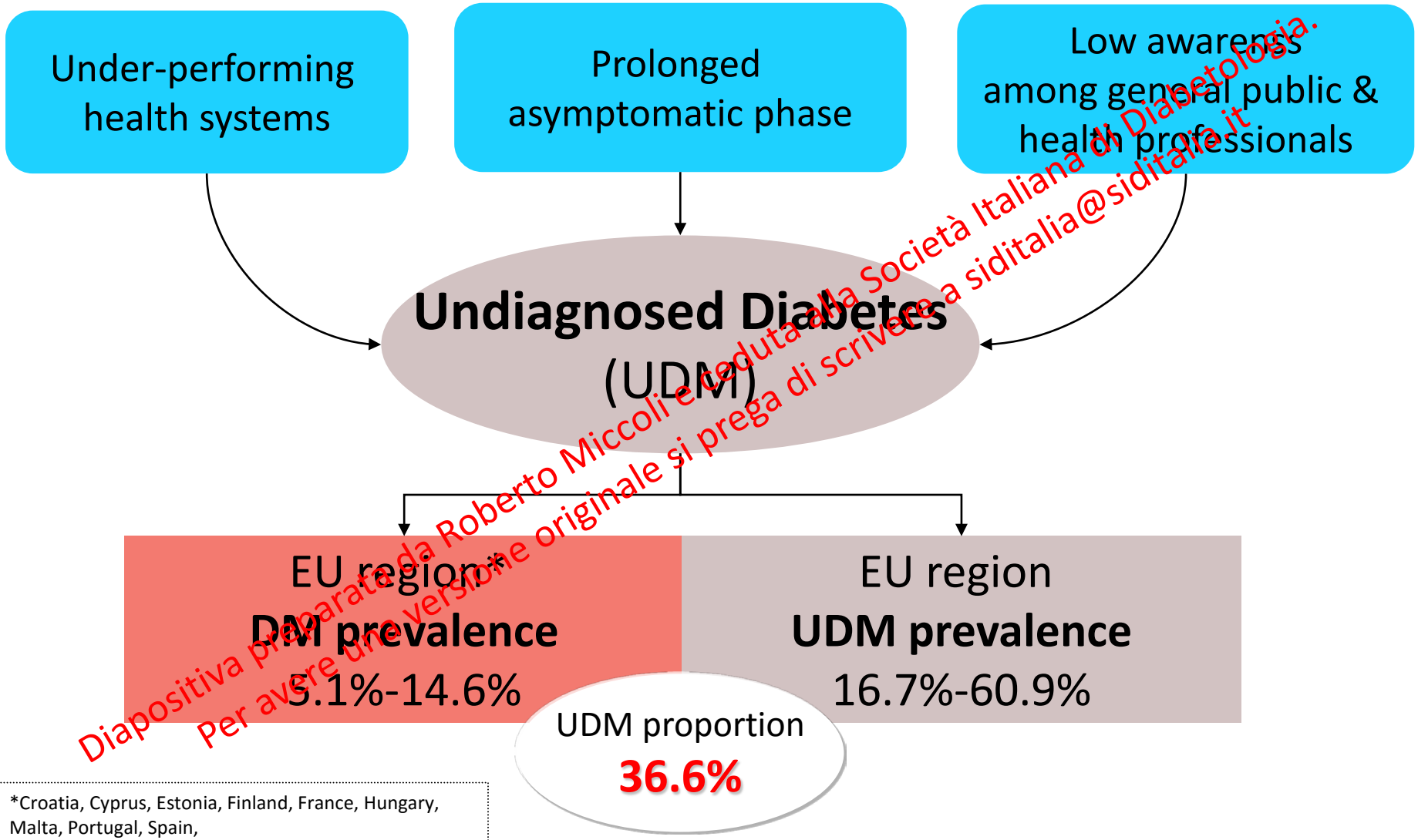
O'Connor PJAnn Fam Med 2006;4:15-22

Diagnostic Criteria for Prediabetes and Diabetes in Nonpregnant Adults

Normal	High Risk for Diabetes	Diabetes
FPG <100 mg/dL	IFG FPG ≥100-125 mg/dL	FPG ≥126 mg/dL
2-h PG <140 mg/dL	IGT 2-h PG ≥140-199 mg/dL	2-h PG ≥200 mg/dL Random PG ≥200 mg/dL symptoms
A1C <5.5%	37 to 46 mmol/mol (5.5 to 6.4%)	>48 mmol/mol (≥6.5%)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PG, plasma glucose.

Diagnosed vs undiagnosed diabetes

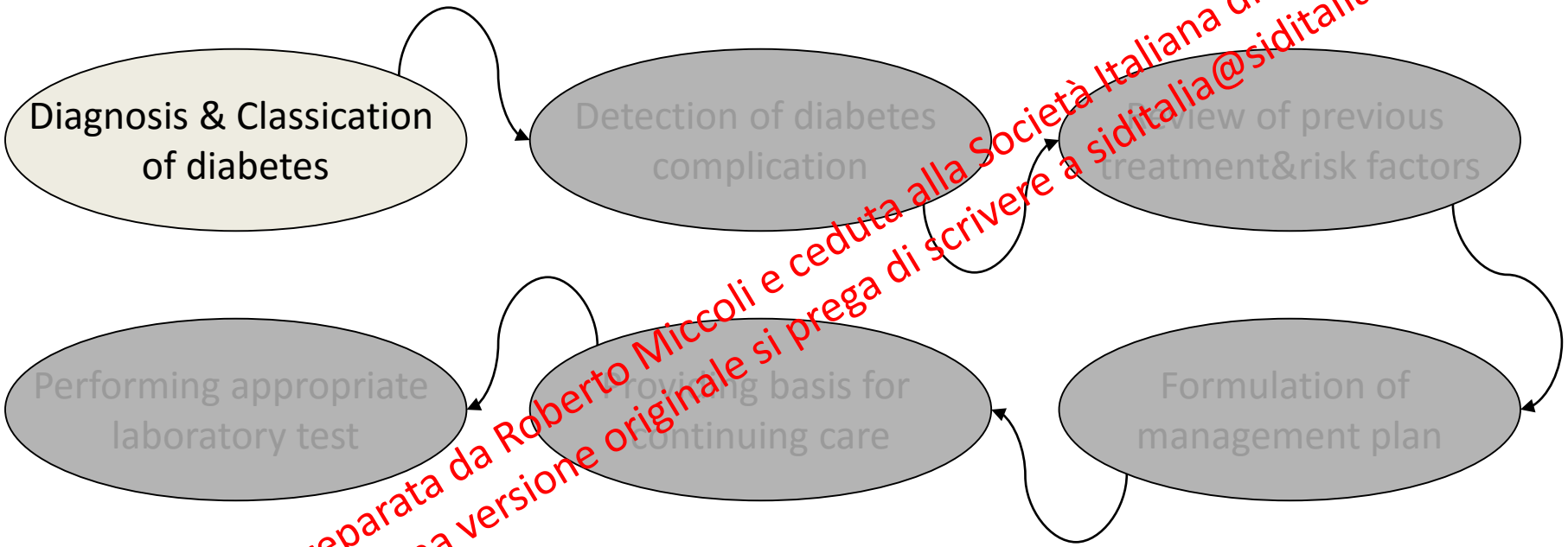


*Croatia, Cyprus, Estonia, Finland, France, Hungary, Malta, Portugal, Spain, United Kingdom

BeagleY J. IDF Atlas Diabetes Res Clin Pract. 2014: 103: 150-60.

Initial evaluation of the patient with diabetes mellitus

Complete medical evaluation



Adapted from Standards of Medical Care in Diabetes 2014

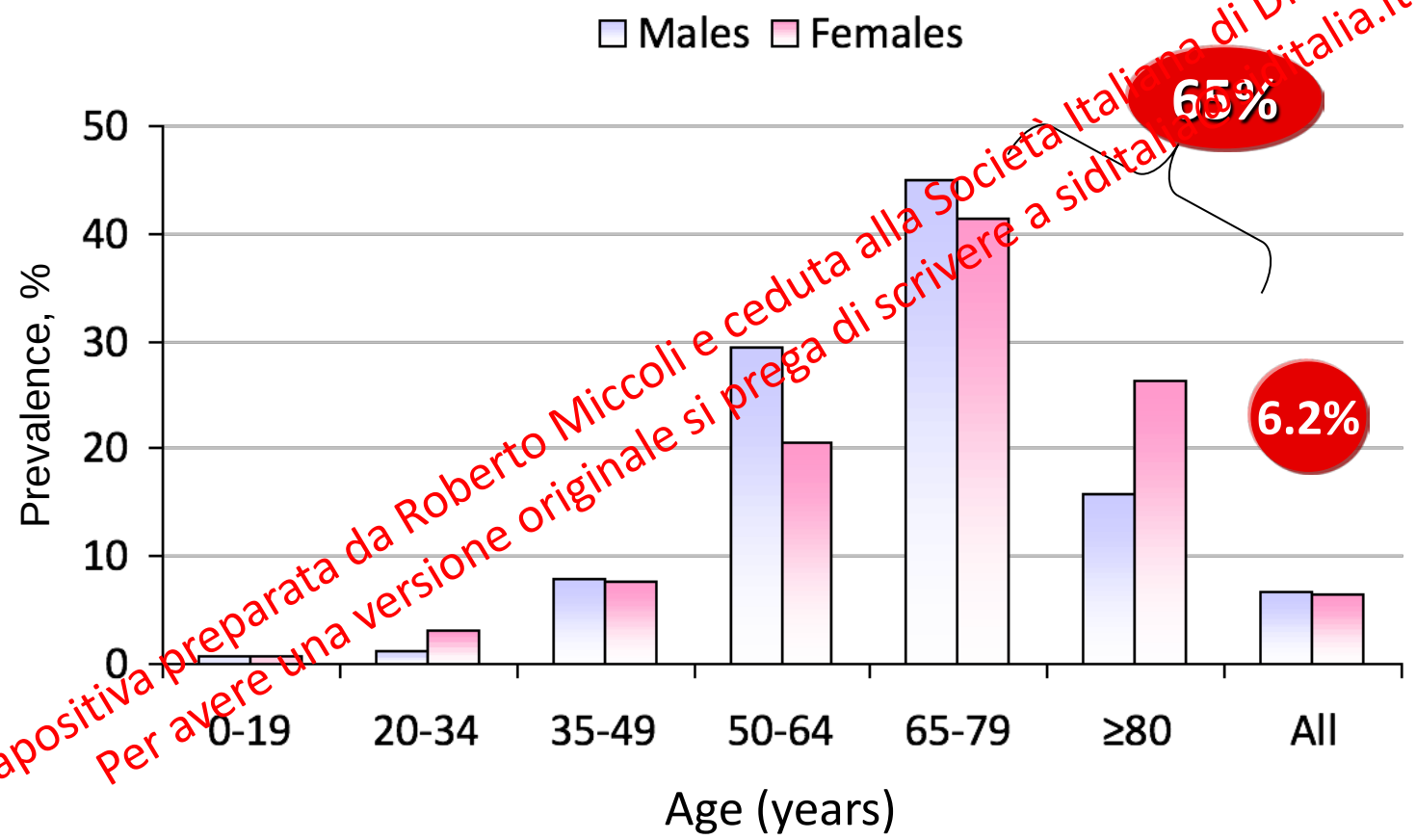
Components of the comprehensive diabetes evaluation

Medical history

- Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding)
- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
- Diabetes education history
- Review of previous treatment regimens and response to therapy (A1C records)
- Current treatment of diabetes, including medications, medication adherence and barriers thereto, meal plan, physical activity patterns, and readiness for behavior change
- Results of glucose monitoring and patient's use of data
- DKA frequency, severity, and cause
- Hypoglycemic episodes
  - Hypoglycemia awareness
  - Any severe hypoglycemia: frequency and cause
- History of diabetes-related complications
  - Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)
  - Macrovascular: CHD, cerebrovascular disease, and PAD
  - Other: psychosocial problems,* dental disease*

Medical history

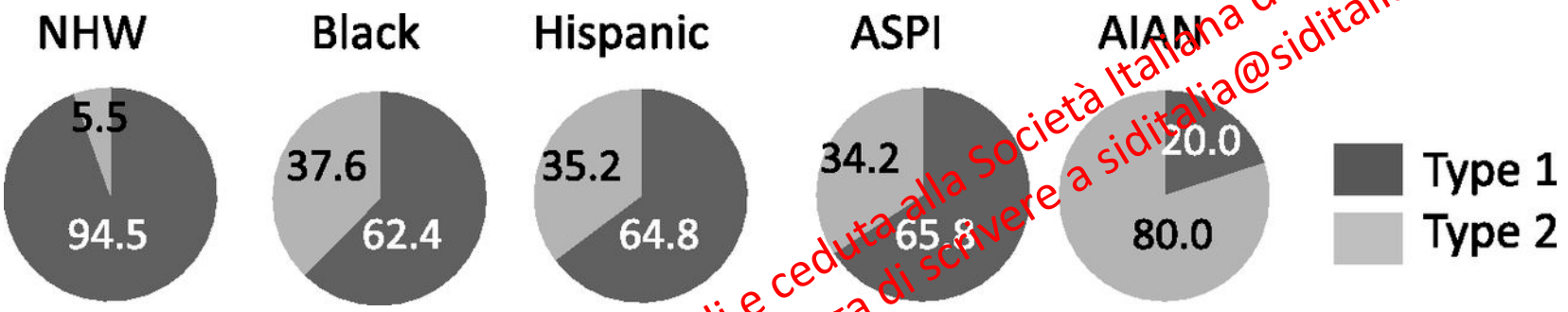
Prevalence of diabetes in Italy by age and gender



Adapte from ARNO-Diabetes Observatory 2015

Type 2 diabetes is increasingly diagnosed in youth

Proportion of type 1 and type 2 diabetes among 15–19 year olds in SEARCH by race/ethnicity



- The occurrence of type 2 diabetes in youth has been documented in several studies over the past decade (Endocrinol Metab Clin North Am 1999J Pediatr 2005, JAMA 2007) and is thought to be secondary to coincident increases in obesity in the general population.
- In addition, there are multiple less common types of diabetes in youth such as monogenic forms (Diabetes 2007; Pediatr Diabetes 2013).

Hispanic White (NHW), non-Hispanic black (black), Hispanic, Asian/Pacific Islander (ASPI), or American Indian/ Alaskan Native (AIAN).

David J. Pettitt et al. Dia Care 2014;37:402-408

Components of the comprehensive diabetes evaluation

Medical history
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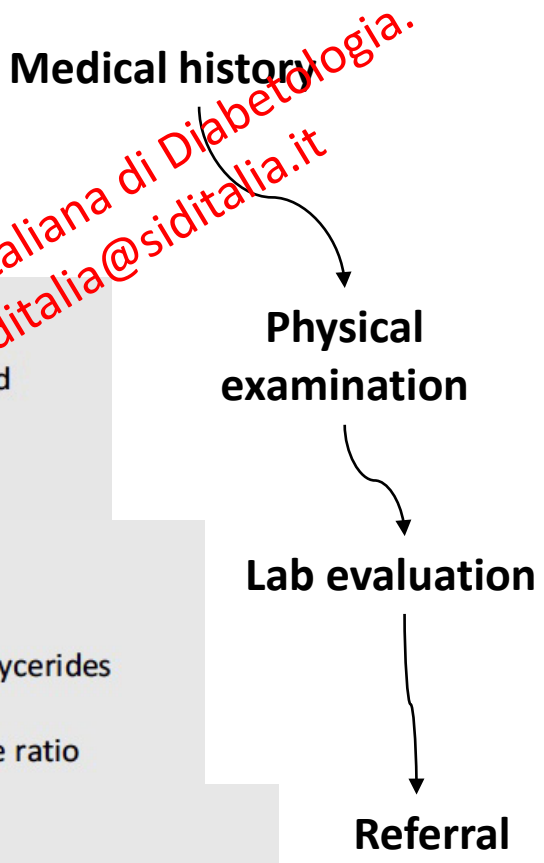
- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
- Diabetes education history
- Review of previous treatment regimens and response to therapy (A1C records)
- Current treatment of diabetes, including medications, medication adherence and barriers

Physical examination
- Height, weight, BMI
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination*
- Thyroid palpation
- Skin examination (for acanthosis nigricans and insulin injection sites)

Laboratory evaluation
- A1C, if results not available within past 2–3 months
- If not performed/available within past year
  - Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides
  - Liver function tests
  - Test for urine albumin excretion with spot urine albumin-to-creatinine ratio

Referrals
- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for MNT
- DSME
- Dentist for comprehensive periodontal examination
- Mental health professional, if needed



Adapted from Standards of Medical Care in Diabetes 2014

Clinical chracteristics of newly diagnosed patients with Type 2 diabetes

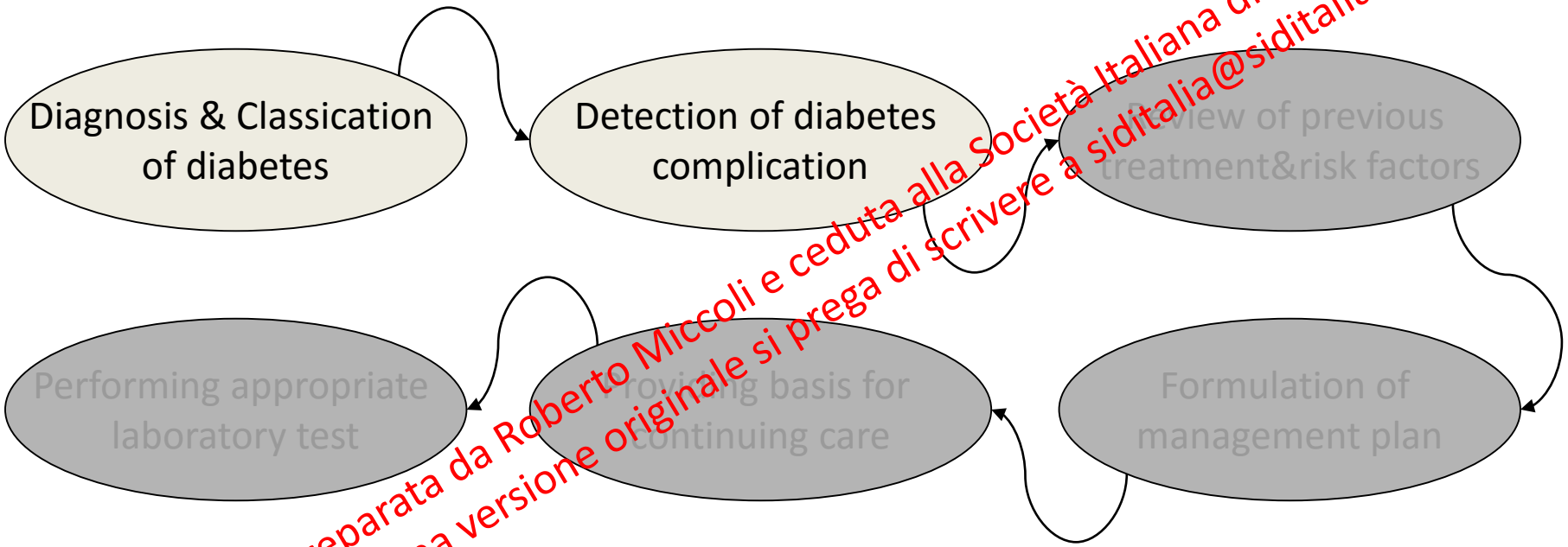
Characteristic	Not diabetes	Diabetes
Number of participants	205	205
Age (years), mean (SD)	57 (9.8)	58 (9.7)
Random glucose (mmol/L), mean (SD)	5.2 (1.2)	10.6 (3.7)
Fasting glucose (mmol/L), mean (SD)	5.0 (1.0)	6.9 (1.9)
Cholesterol (mmol/L), mean (SD)	7.28 (1.53)	6.68 (1.23)
Systolic blood pressure (mmHg), mean (SD)	152.2 (25.8)	161.7 (24.7)
Diastolic blood pressure (mmHg), mean (SD)	89.8 (11.3)	91.4 (12.5)
Body mass index (kg/m^2), mean (SD)	26.1 (3.5)	29.7 (4.9)
Waist–hip ratio, mean (SD)		
Women	0.83 (0.06)	0.88 (0.08)
Men	0.93 (0.04)	0.94 (0.05)
Hypertension[a], *n* (%)	102 (50)	140 (68)
Smoking, *n* (%)		
No smoking	140 (68)	148 (68)
Current smoking	35 (17)	42 (21)
Unknown	30 (15)	22 (11)
Education, *n* (%)		
<10 years	144 (70)	155 (76)
10–12 years	25 (12)	20 (10)
≥13 years	9 (4)	5 (2)
Unknown	27 (13)	25 (12)
Exercise frequency, *n* (%)		
<1 per week	59 (29)	93 (45)
1–3 per week	82 (40)	61 (30)
≥4 per week	31 (15)	26 (13)
Unknown	33 (16)	25 (12)

Patients with newly diagnosed diabetes are older adults, were more often hypertensive, had higher BMI, and were less likely to exercise compared with the group without diabetes.

Dale AC. European Heart Journal (2009) 30, 1372–1377

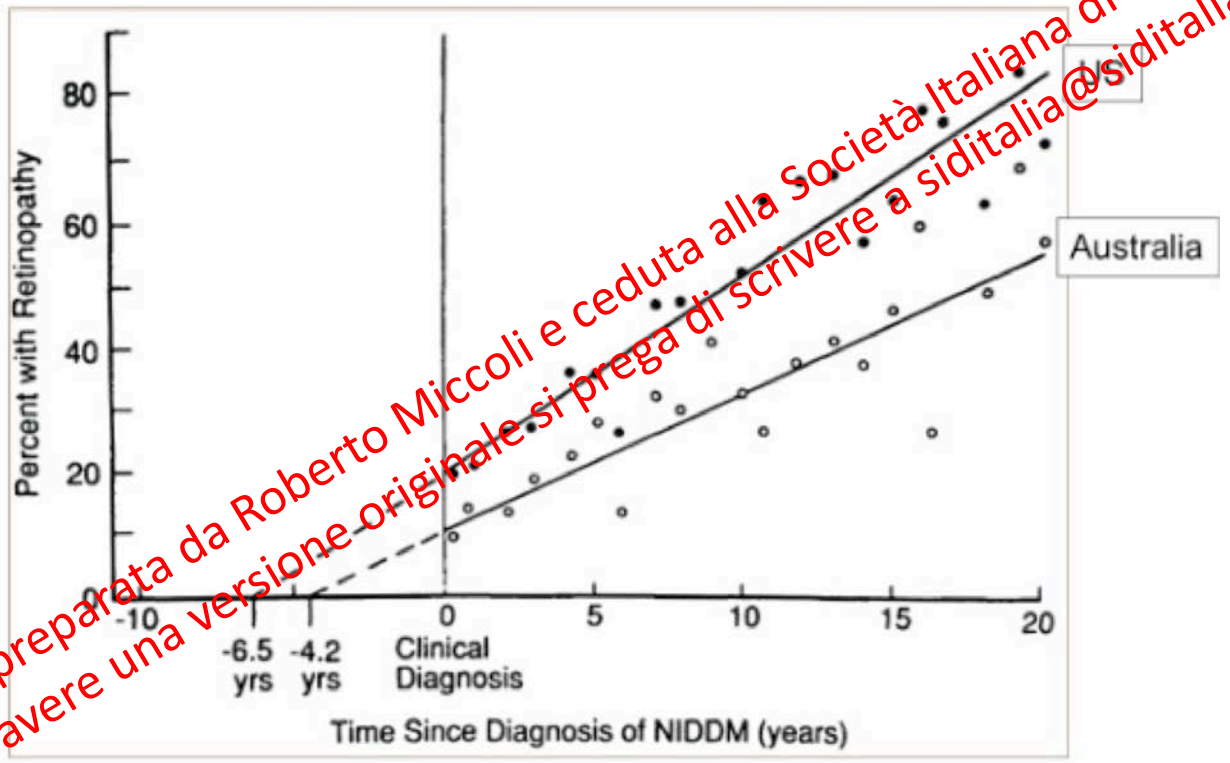
Initial evaluation of the patient with diabetes mellitus

Complete medical evaluation



Adapted from Standards of Medical Care in Diabetes 2014

Correlation between known duration of diabetes and clinically significant morbidity



Harris MI, Diabetes Care. 1992; 15: 815-9

Estimating the Delay Between Onset and Diagnosis of Type 2 Diabetes From the Time Course of Retinopathy Prevalence.

Summary

- Any DR start to develop 3.89 years before the clinical diagnosis of diabetes in the Older Onset-NIT groups.
- ModDR start to develop in the OO-NIT group an estimated 2.66 years before

Since about 15% of adult population may suffer from impaired glucose regulation without having full-blown T2DM, and since altered fasting glucose is associated with increased risk for DR, at least part of these "hidden" years may be spent in a pre-diabetic state, accounting for delay and incomplete diagnosis of diabetes.

- Restricting the model to data from patients with onset of T2DM after puberty brought the estimate down to 4.39 years (2.66 + 1.73).

Porta M et al. Dia Care 2014;37:1668-1674

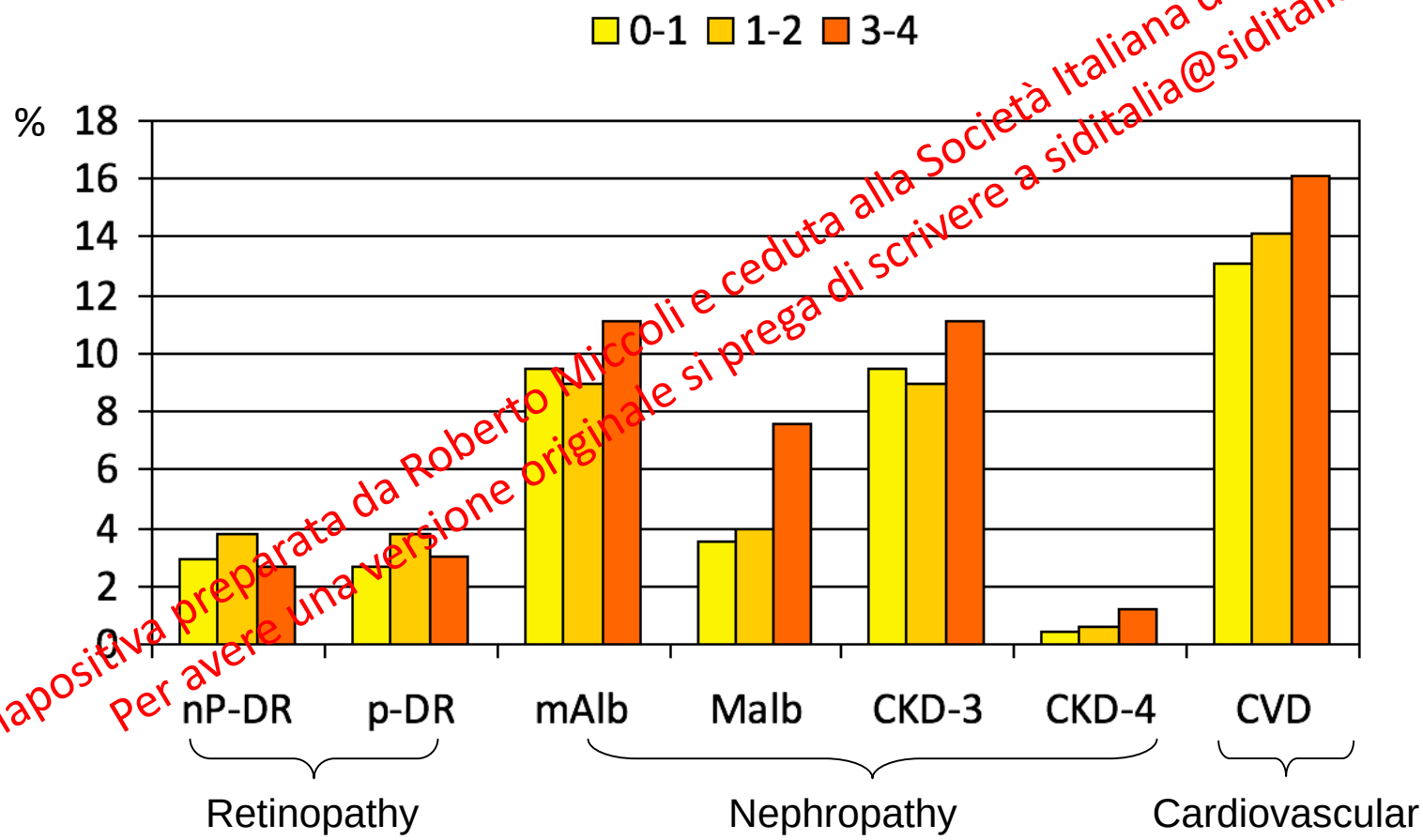
Established CVD at baseline in newly diagnosed diabetes patients

	No Diabetes	Diabetes
Total CVD, n (%)	27 (13)	44 (22)
Angina pectoris	16 (8)	30 (15)
Myocardial infarction	11 (5)	14 (7)
Stroke	5 (2)	12 (6)

Adapted from Dale AC. European Heart Journal (2009) 30, 1372–1377

Prevalence of micro- and macrovascular complications <5 years after diagnosis of diabetes

The RIACE Study



G. Penno, unpublished data

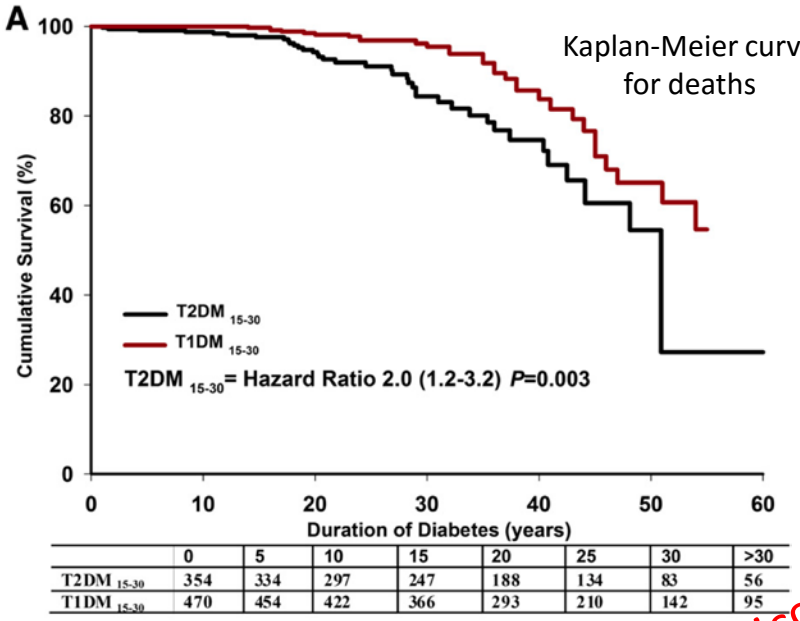
A Kaplan-Meier survival curve for T2DM15–30 (**n** = 357) and T1DM15–30 (**n** = 470) patients. **B**: Kaplan-Meier survival curve for T2DM15–30 and all T1DM (age of onset ,30 years) (**n** = 870) patients.

Long-Term Complications and Mortality in Young-Onset Diabetes

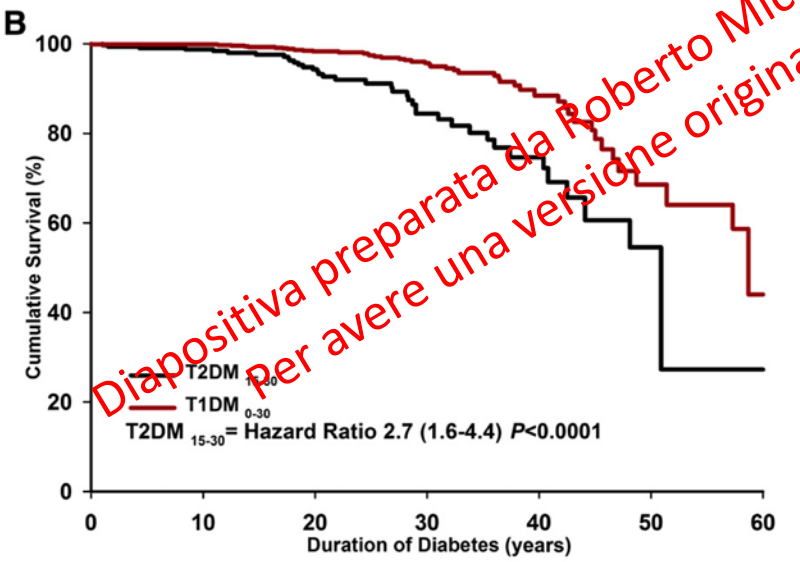
Costantino MI, Diabetes Care 36:3863–3869, 2013

CONCLUSIONS Young-onset T2DM is the more lethal phenotype of diabetes and is associated with a greater mortality, more diabetes complications, and unfavorable cardiovascular disease risk factors when compared with T1DM.

Kaplan-Meier curve for deaths

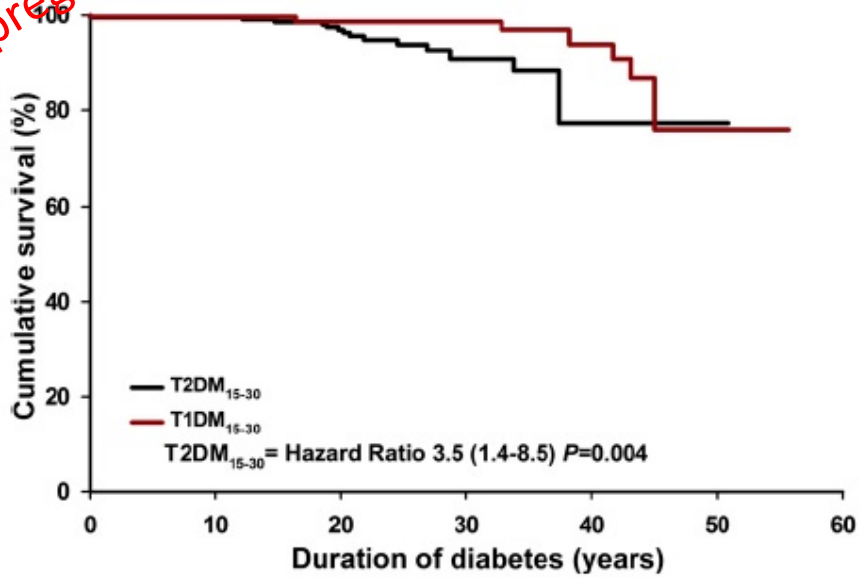


	0	5	10	15	20	25	30	>30
T2DM 15-30	354	334	297	247	188	134	83	56
T1DM 15-30	470	454	422	366	293	210	142	95



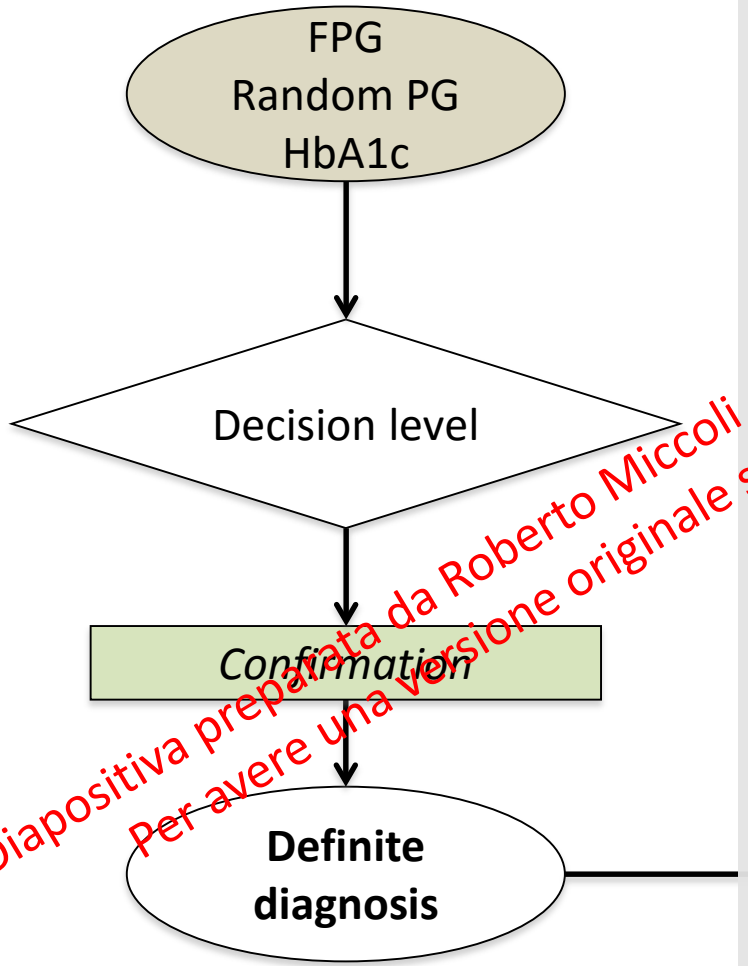
	0	5	10	15	20	25	30	>30
T2DM 15-30	354	334	297	247	188	134	83	56
T1DM <30	870	854	808	704	574	431	290	170

Kaplan-Meier curve for cardiovascular deaths

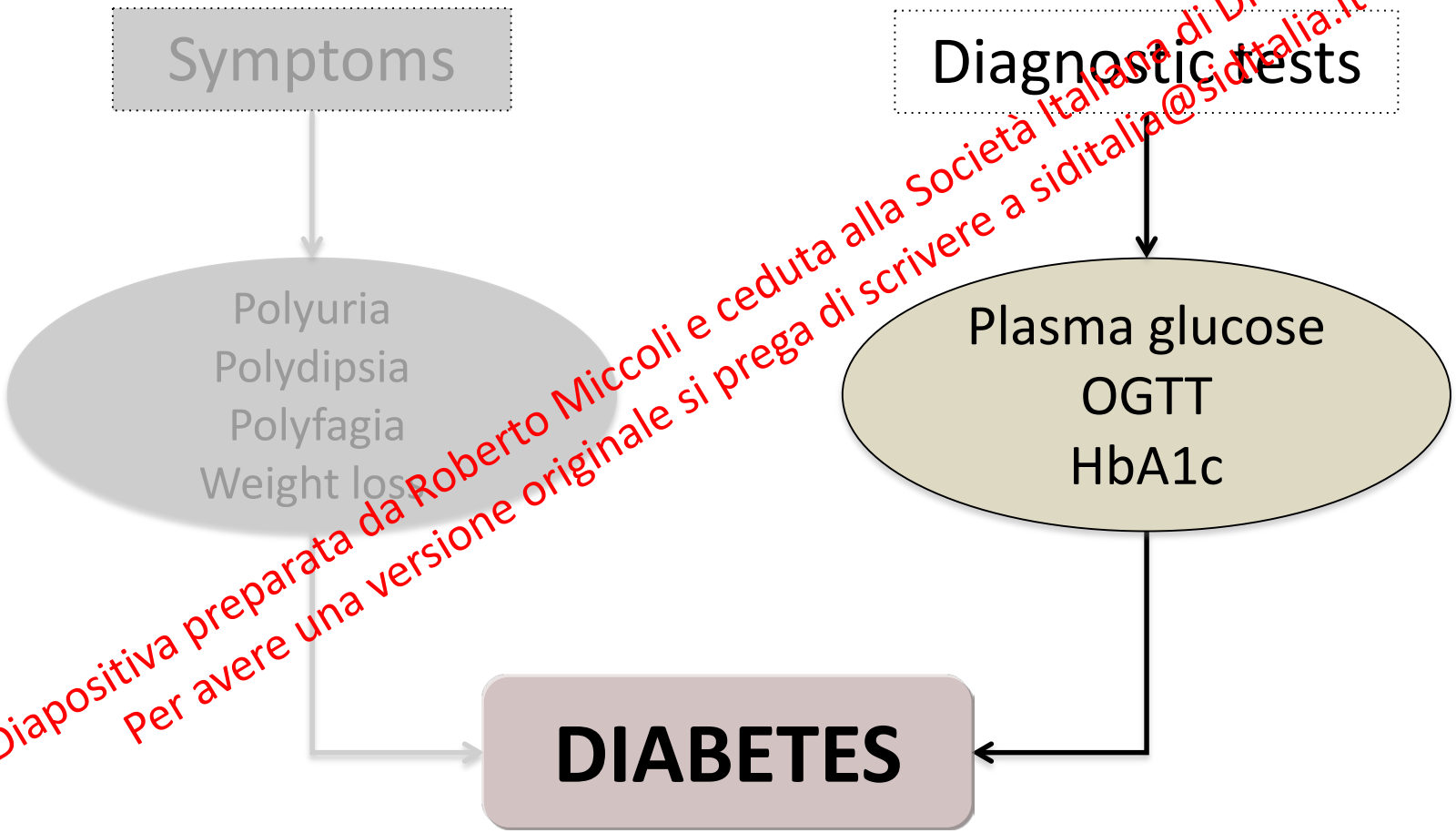


	0	5	10	15	20	25	30	>30
T2DM15-30	329	311	275	226	171	118	72	47
T1DM15-30	445	429	397	342	272	193	126	81

“Other” forms of diabetes exist



Diagnosis of type 2 diabetes



Laboratory aspects of testing in diabetes diagnosis

• The diagnosis of diabetes is established by identifying the presence of hyperglycemia.

Fasting PlasmaGlucose ≥ 126 mg/dl

Random Plasma Glucose ≥200 mg/dl

2h post-load (OGTT) Plasma Glucose ≥ 126 mg/dl

Recommendations

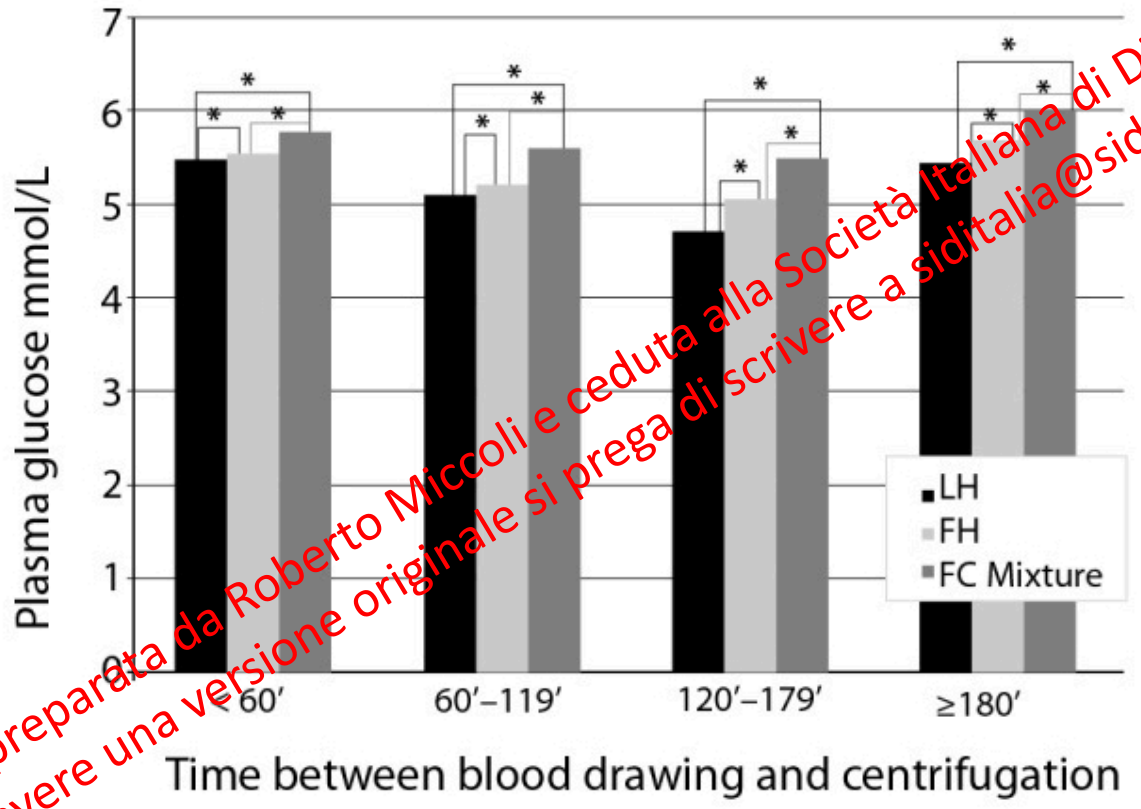
• When glucose is used to establish the diagnosis of diabetes it should be measured in venous plasma. **A (high)**

• Plasma glucose should be measured in an accredited laboratory when used for diagnosis of or screening for diabetes good practice point. **(Good Practice Point)**

• There are insufficient published data outcome to support a role for portable meters and skin-prick (finger-stick) blood samples in the diagnosis of diabetes or for population screening. **C (moderate)**

Sacks DB. Diabetes Care 2011 34:e61–e99

Glycolysis affects glucose determination in routine clinical setting



LH - lithium-heparin tube. FH - Sodium-fluoride and sodiumheparin containing tube.
FC-Mixture - Sodium-fluoride, citrate buffer and sodium EDTA containing tube

The use of an immediate inhibitor of the glycolysis has to be regarded as necessary. The FC mixture (NaF/citrate buffer/Na2EDTA) seem to be suitable for this purpose, while NaF alone is not.

Bonetti G. -SIBioC. Biochemia Medica 2016;26(1):68–76

What to do if unequivocal hyperglycemia is absent

- If unequivocal hyperglycemia is absent, then HbA1c, FPG, and OGTT results should be confirmed by repeat testing. The ADA recommends repeating the same test for confirmation, since there will be a greater likelihood of concurrence. However, the diagnosis of diabetes is also confirmed if the results of 2 different tests are above the diagnostic thresholds. *(Diabetes Care 2012)*

- If a patient has had 2 different tests and the results are discordant, the test that has a result above the diagnostic threshold should be repeated. A second abnormal result on this test will confirm the diagnosis. *(WHO 2006)*

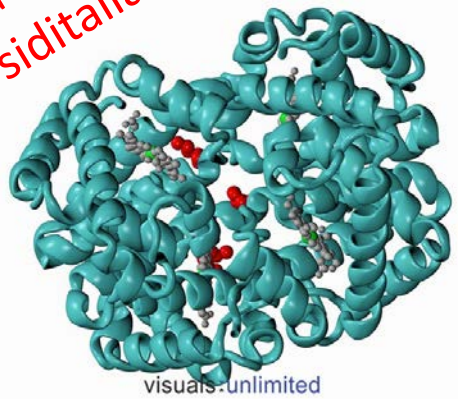
- In asymptomatic patients whose random serum glucose level suggests diabetes (>140 mg/dL), an FPG or HbA1c level should be measured. An FPG level of 100-125 mg/dL is considered an impaired fasting glucose (IFG), and an FPG level of less than 100 mg/dL is considered a normal fasting glucose. However, an FPG of 91-99 mg/dL is a strong independent predictor of future type 2 diabetes. *(Brambilla P. Diabetes Care 2011)*

A1c for diagnosing diabetes

*Since 2009 an international expert committee appointed by the ADA, the European Association for the Study of Diabetes, and the International Diabetes Association recommended the HbA1c assay for diagnosing type 1 and type 2 diabetes mellitus (*Diabetes Care 2009*).*

Advantages of HbA1c testing over glucose measurement:

- Captures long-term glucose exposure
- Has less biologic variability
- Does not require fasting or timed samples
- Is currently used to guide management decisions

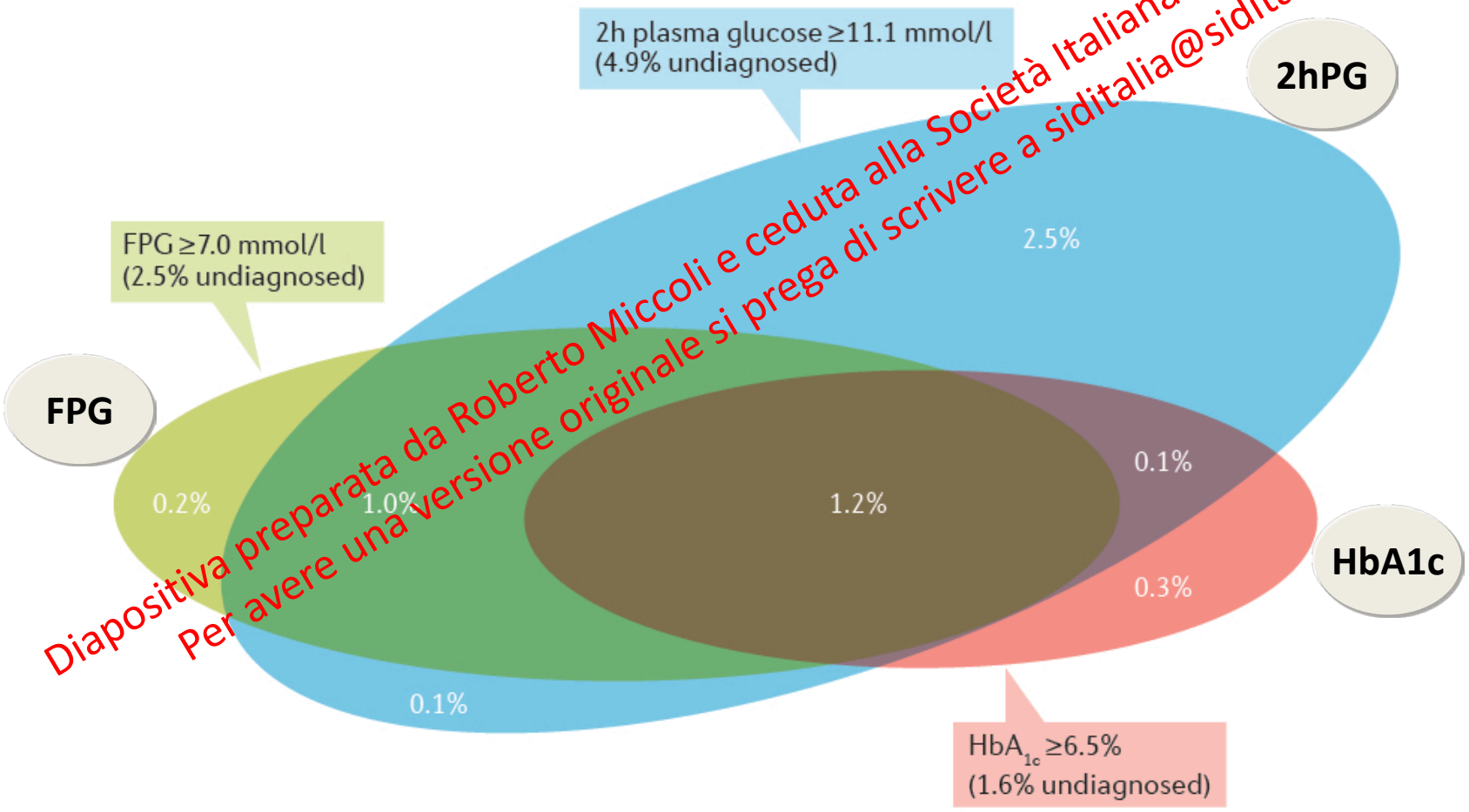


• Laboratories should use only HbA1c assay methods that are certified by the national glycohemoglobin standardization program (NSGP) as traceable to the DCCT reference . The manufacturers of HbA1c assays should also show traceability to the IFCC reference method. **(Good Practice Point)**

Sacks DB. Diabetes Care 2011 34:e61–e99

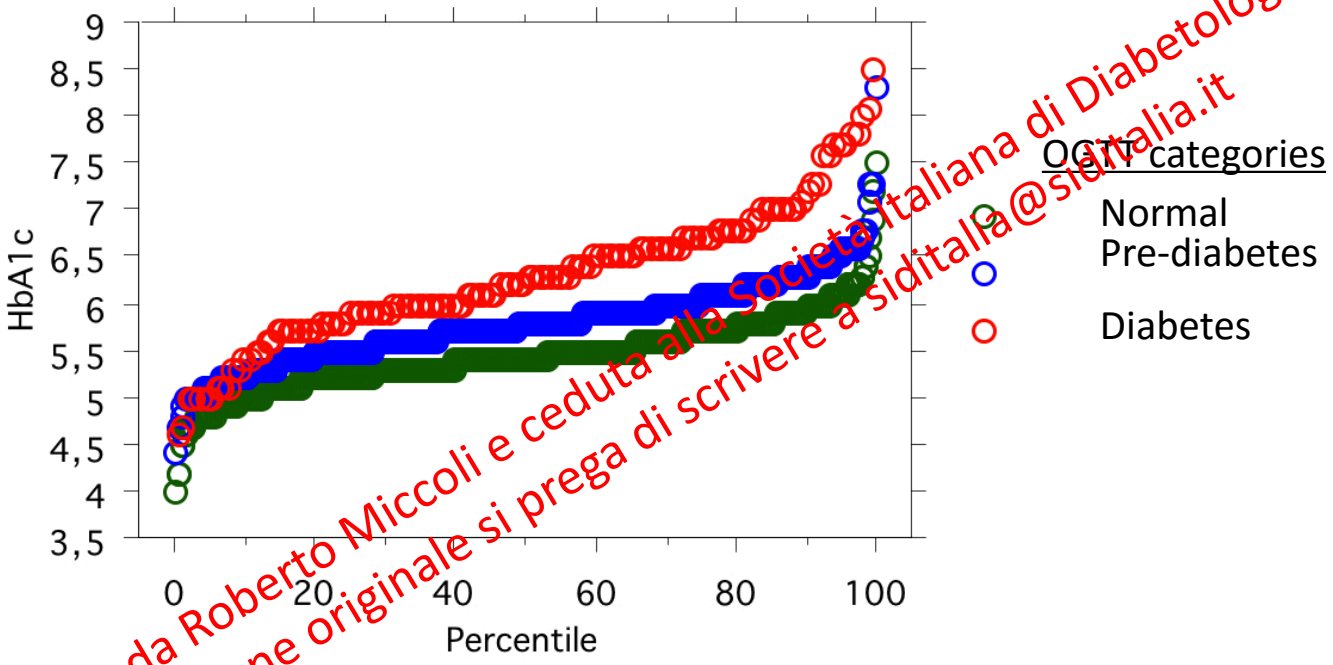
FPG, 2h-PG and HbA1c do not identify all the same individuals as having diabetes mellitus

US population aged 20–74 years (NHANES 2005–2006, n = 2,017) with undiagnosed diabetes mellitus by three diagnostic criteria



Adapted from Cowie CC. Diabetes Care 2010; 33: 562-568

Percentile distribution and correct classification by A1C - GENFIEV study (n. 845)



A1C / OGTT	<6	6-6.4	≥6.5	
Normal	86	12	2	100
Pre-diabetes	58	32	10	100
Diabetes	25	32	43	100

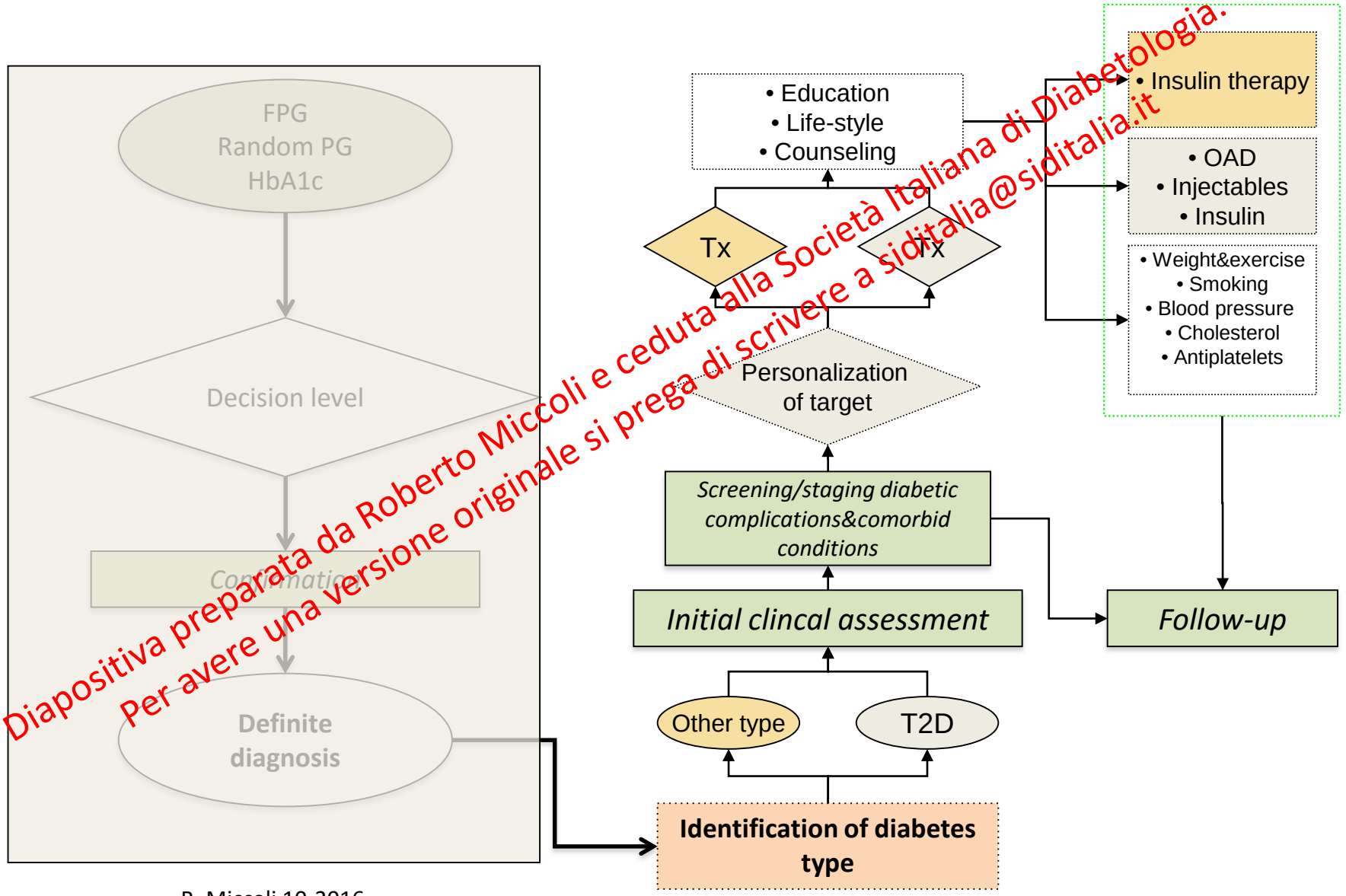
R. Miccoli 2010 unpublished

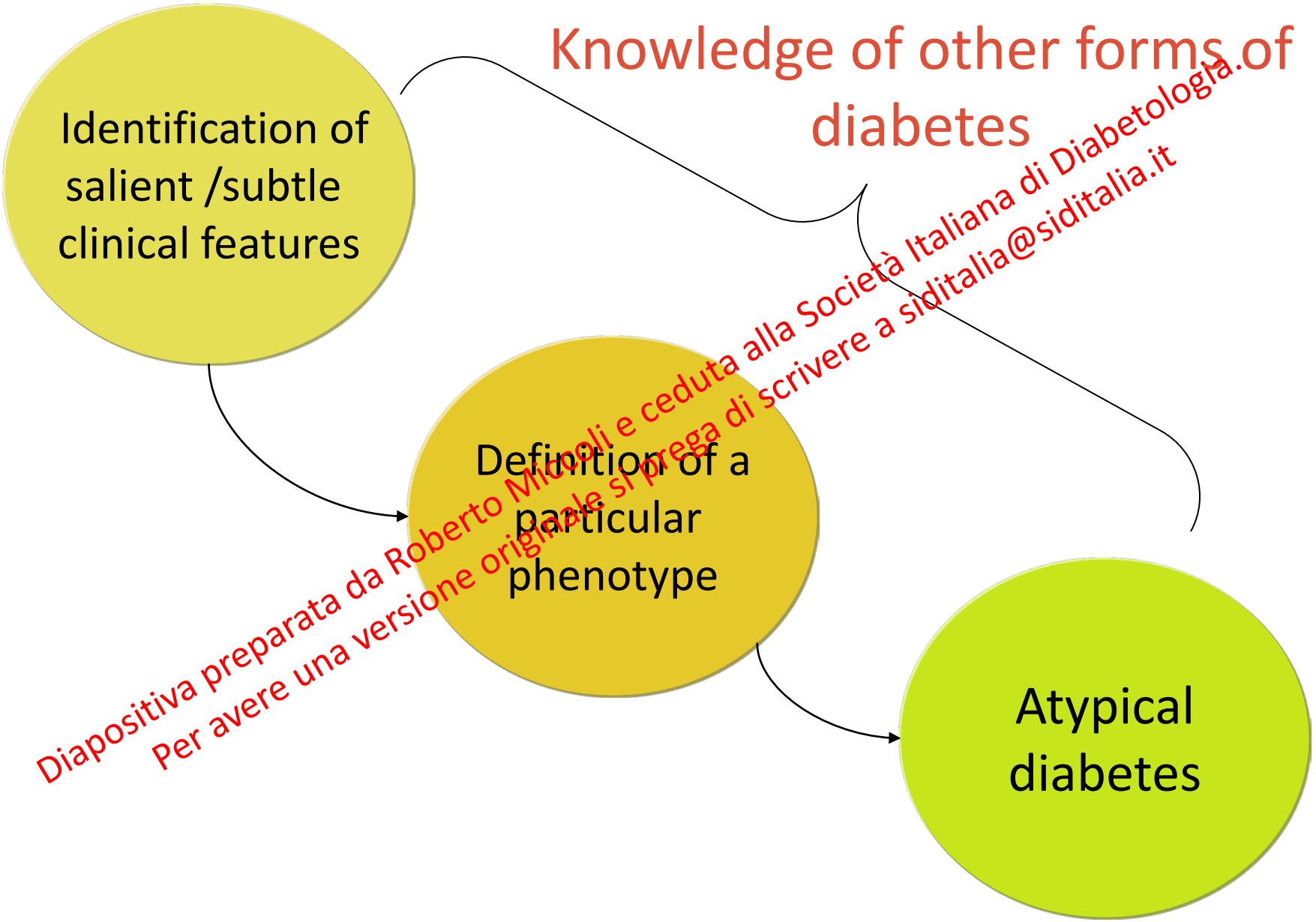
Is hemoglobin A_{1c} (HbA_{1c}) testing appropriate for diagnosis (and screening)of type 2 diabetes mellitus?

Agreement between HbA_{1c} and fasting plasma glucose (FPG) or oral glucose tolerance testing (OGTT) is poor:

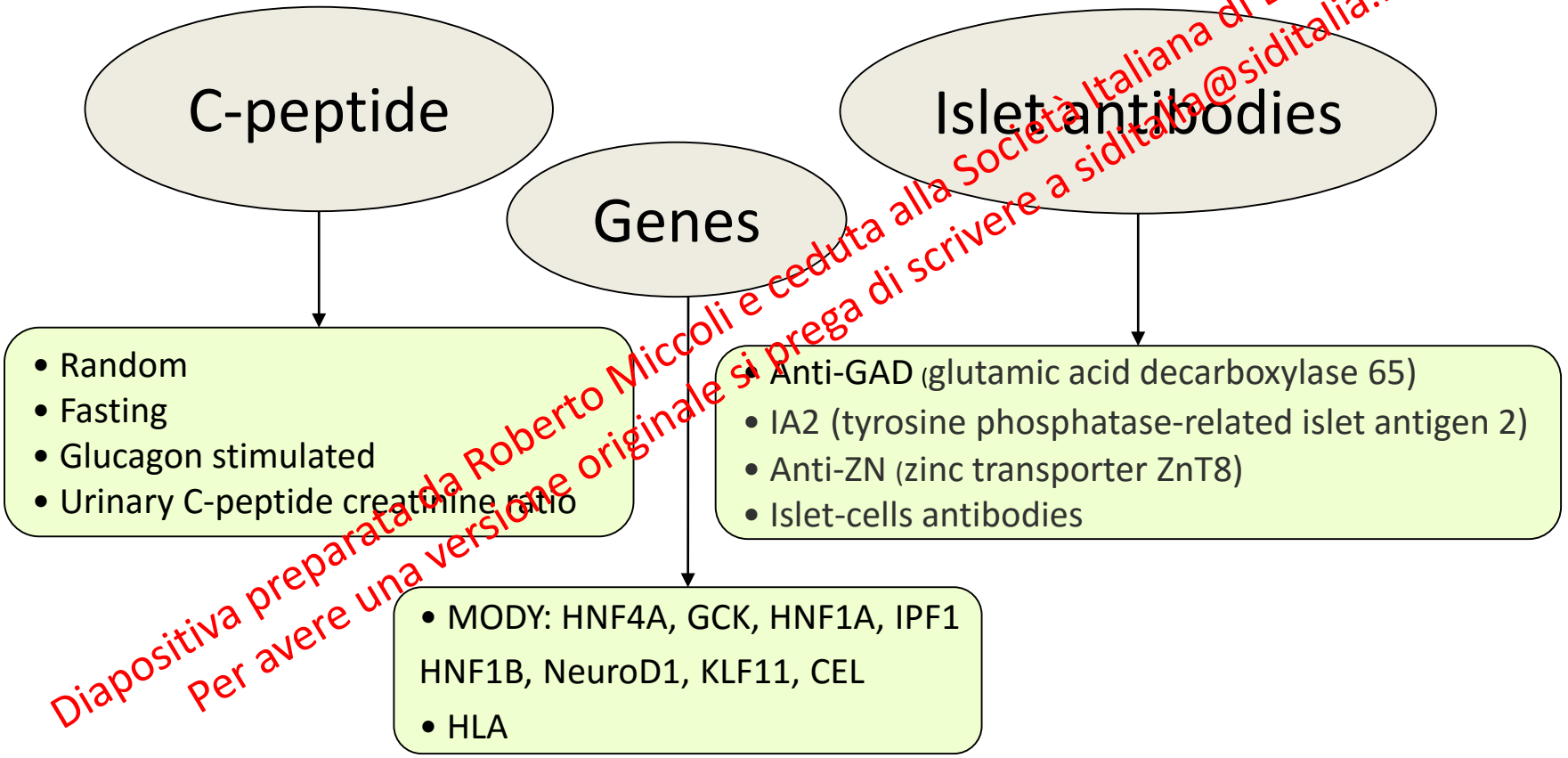
- 25% to 27% agreement for HbA_{1c} and FPG *(Farhan S 2012, Bernal-Lopez MR 2011)*
- 22% to 33% agreement for HbA_{1c} and OGTT (*Farhan S 2012 , Cosson E 2011, Mostafa SA 2010*)
- Some studies find HbA_{1c} (≥6.5%) would diagnose less diabetes than OGTT (*Farhan S 2012, Malkani S 2011, Cowie CC 2010)* (eg, HbA_{1c} missed 60% of the cases OGTT diagnosed)
- Some find HbA_{1c} (≥6.5%) would diagnose more diabetes than OGTT (eg, OGTT missed 35% of the cases HbA_{1c} diagnosed). (*Bernal-Lopez MR 2011, Cosson E 2011, Mostafa SA 2010, Malkani S 2011)*

Assessment of diabetes at diagnosis

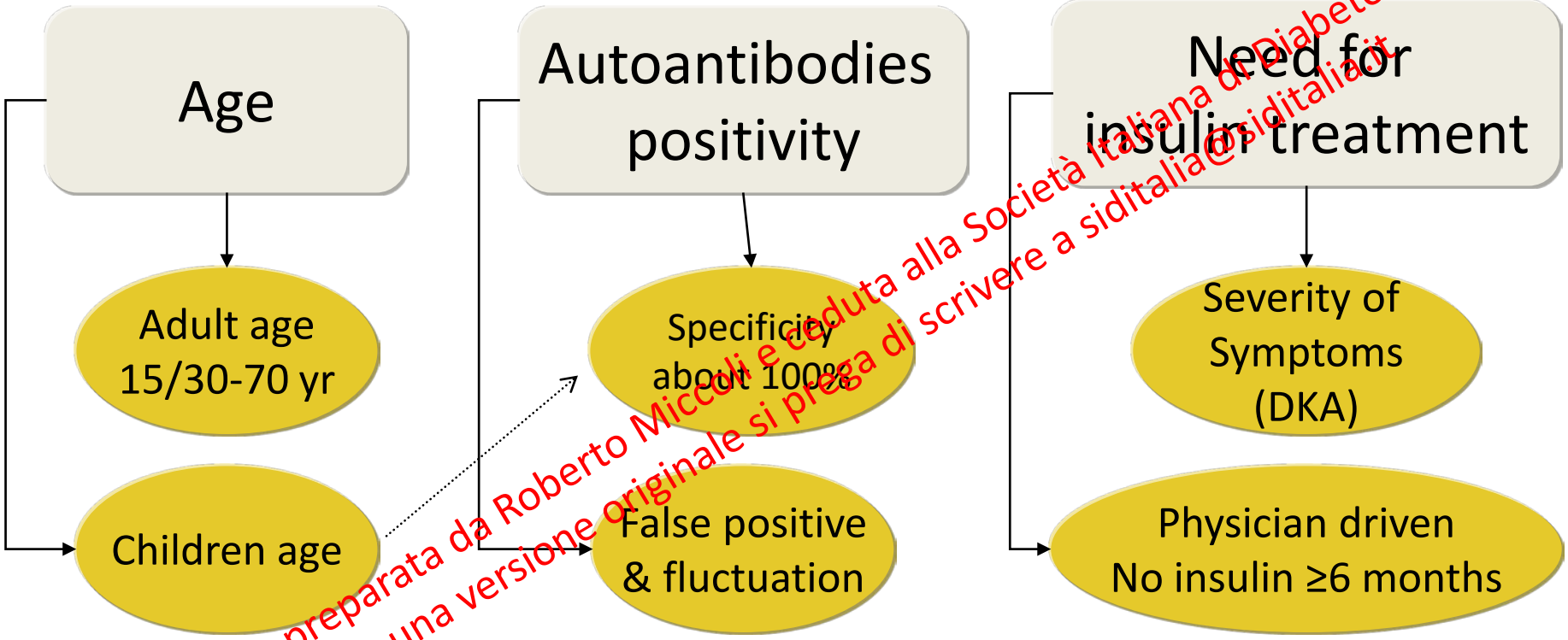



Knowledge of other forms of diabetes
Identification of salient /subtle clinical features
Definition of a particular phenotype
Atypical diabetes
Diapositiva preparata da Roberto Miccoli e ceduta alla Società Italiana di Diabetologia.
Per avere una versione originale si prega di scrivere a siditalia@siditalia.it

Tests for diabetes subtype



Type 2 diabetes vs Autoimmune diabetes



Latent autoimmune diabetes of the adult (LADA) is an autoimmune diabetes defined by adult-onset, presence of diabetes associated autoantibodies (DAA), and no insulin treatment requirement for a period after diagnosis.

Adapted from Laugesen E. Diabet. Med. 2015; 32: 843–852

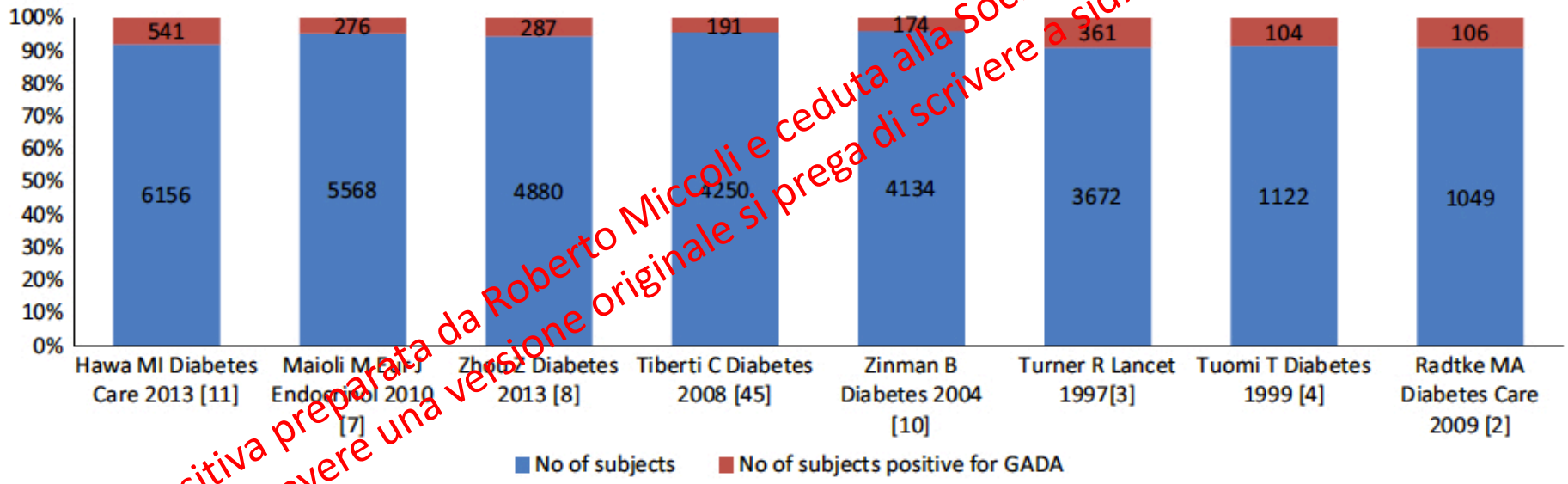
Prevalence of patients with glutamic acid decarboxylase antibodies (GADA) among patients diagnosed with Type 2 diabetes

	Patients with Type 2 diabetes (*n*)	Number of patients positive for GADA (%)	Number of patients designated LADA (%)	Antibody used in definition LADA definition	Mean age (years)	Specified age range recruited (years)
Hawa *et al.*, *Diabetes Care* 2013 [11]	6156	541 (8.8)	598 (9.7)	1 or more antibodies (GADA, IA-2A, ZnT8A)	54.4	30–70
Maioli *et al.*, *Eur J Endocrinol* 2010 [7]	5568	276 (5)	276 (5)	GADA	NA	35–70
Zhou *et al.*, *Diabetes* 2013 [8]	4880	287 (5.9)	287 (5.9)	GADA	51.3	30 or above
Tiberti *et al. Diabetes* 2008 [45]	4250	191 (4.5)	191 (4.5)	GADA	NA	NA
Zinman *et al. Diabetes* 2004 [10]	4134	174 (4.2)	174 (4.2)	GADA	Weighted 56.5	30–75
Turner *et al. Lancet* 1997 [3]	3672	361 (9.8)*	430 (11.7)	GADA or ICA (not clearly defined)	52.6	25–65
Tuomi T Diabetes 1999 [4]	1122	104 (9.3)	104 (9.3)	GADA	Weighted 69.7	NA
Radtke *et al. Diabetes Care* 2008 [2]	1045	106 (10.1)	106 (10.1)	GADA	Weighted 67.8	20 or above

*Overall prevalence among age groups. Age: 34–44 years (14%), 45–54 years (9%), 55–65 years (7%). LADA, latent autoimmune diabetes in adults; IA-2A, insulin antibodies 2A; ZnT8, zinc transporter 8 antibodies). NA, Not Available.

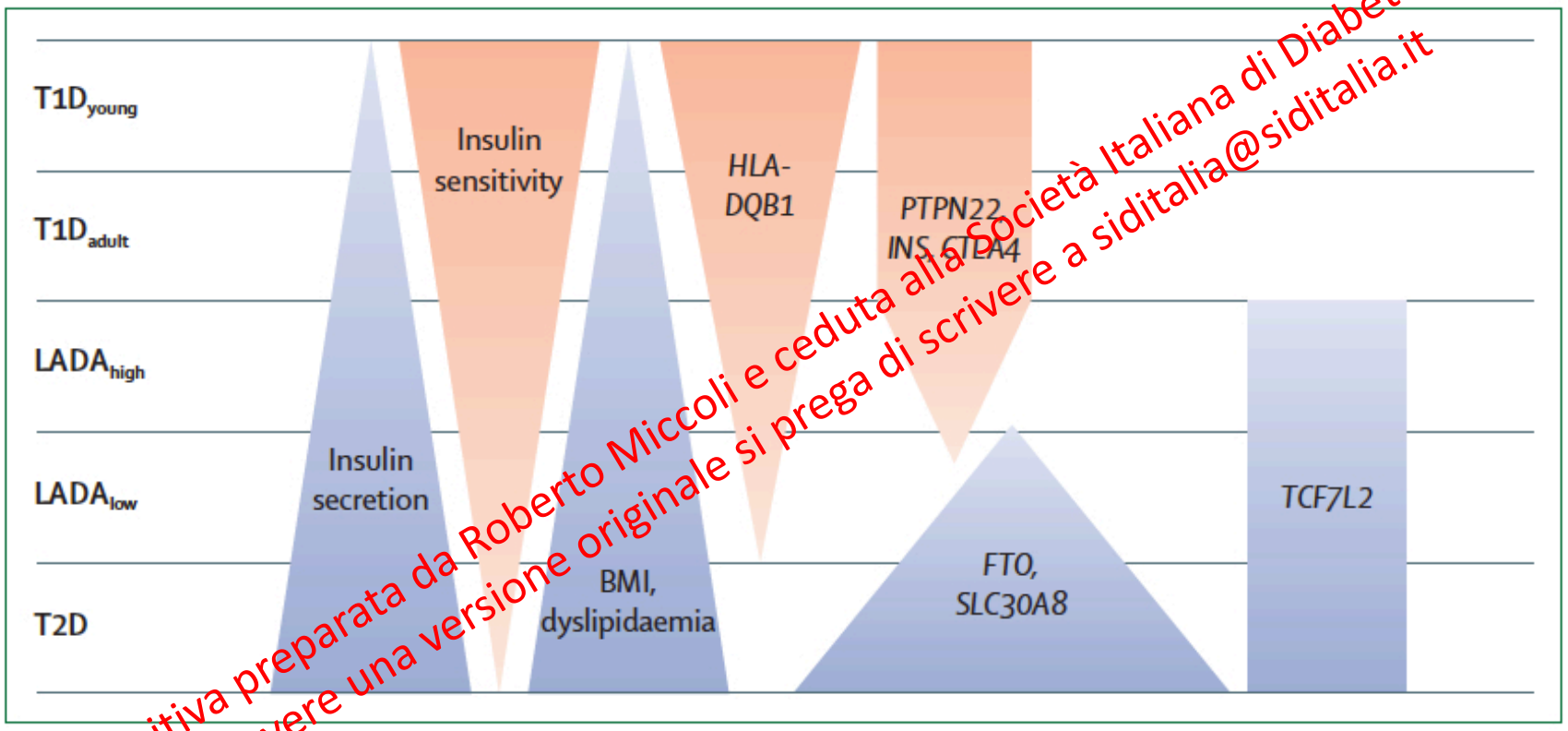
Laugesen E. Diabet. Med. 2015; 32: 843–852

Prevalence of patients with glutamic acid decarboxylase antibodies (GADA) among total number of patients diagnosed with type 2 diabetes



Laugesen E. Diabet. Med. 2015; 32: 843–852

A schematic view of factors aff ecting the phenotype of diabetic subgroups



Genetics has provided clear support for the view that LADA is between adult-onset type 1 diabetes and GAD-antibody-negative type 2 diabetes, sharing genetic and clinical features with both forms, thereby justifying the term hybrid diabetes.

Tuomi T. Lancet 2014; 383: 1084–94

LADA vs type 2 diabetes

There are no clear clinical features that distinguish autoimmune diabetes from Type 2 diabetes.

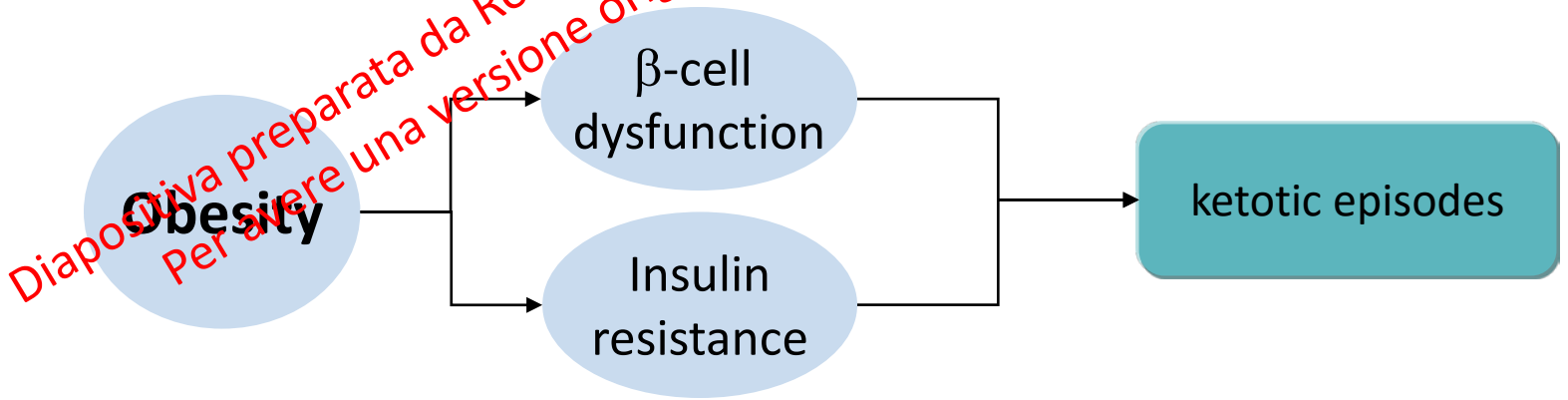
- There is a tendency for adult patients with GADA, even when noninsulin requiring, to be younger at diagnosis and leaner with a greater tendency to progress to insulin treatment.
- LADA shares genetic features with both type 1 and type 2 diabetes.
- Within a cohort of GADA-positive adult patients, the GADA titre and the number of DAA impact the clinical and biochemical differences from Type 2 diabetes.
- Is not possible to identify patients with LADA without screening.
- Clinical phenotype should drive management strategy.

Adapted from Laugesen E. Diabet. Med. 2015; 32: 843–852

Other hybrid forms of diabetes

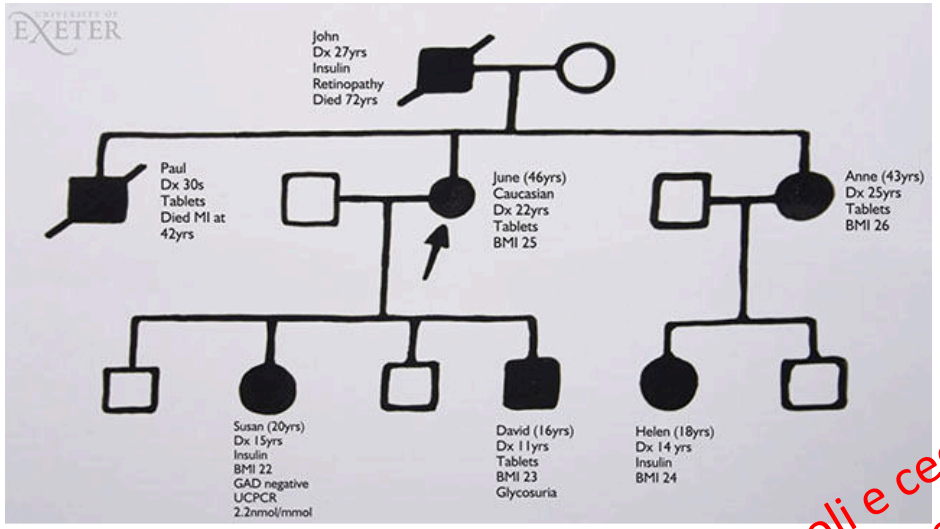
Ketosis-prone diabetes in adults

- Features of both type 1 and type 2 diabetes without the autoimmune characteristics of LADA
- African-American youths in the Flatbush suburb of Brooklyn, NY, USA; sub-Saharan-African descent
- Ketosis and severe insulin deficiency; 76% later achieve remission from insulin dependency
- Ketotic relapses preceded by progressive hyperglycaemia



Adapted from Winter WE. N Engl J Med 1987; 316: 285–91. Mauvais-Jarvis F. Diabetes 2004; 53: 645–53; Umpierrez GE Diabetes Care 2006; 29: 2755–57.

Family trees and other forms of type 2 diabetes



- Taking a good family history is a key skill which can also aid the recognition of individuals likely to have other forms diabetes.
- Be aware that the information may be very sensitive and include personal issues such as family break ups, miscarriages, stillbirths and bereavements.
- An accurate family history may help indicate whether genetic testing is appropriate and may reveal family members previously thought to have Type 1 or Type 2 diabetes who may also benefit from genetic testing, confirming one unifying diagnosis.
- If a family history is not taken, a patient's relatives are less likely to be considered.
- Taking a family history can also identify other family members who may be at risk of developing the condition.

1. Autosomal dominant inheritance

2. A young age of onset of diabetes

3. Non-insulin requiring diabetes

\+

Antibody negative status

MODY ← **Genetic testing**

Adapted by Miccoli R. 2016 from https://www.futurelearn.com/courses/diabetes-genomic-medicine/0/steps/10049

Monogenic Diabetes

Monogenic diabetes accounts for approximately **1–2% of diabetes cases** and results from mutations that primarily reduce b-cell function.

There are *two major classifications* of monogenic diabetes: maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus (NDM).

The clinical diagnosis of **MODY** has been typically based on the following criteria:

- family history of diabetes
- autosomal dominant mode of inheritance
- insulin independence (nonketotic diabetes mellitus) and age at onset below 25 years *(Fajans SS. N Engl J Med 2001; 345:971 – 980).*

The MODY classification of monogenic diabetes contains at least **six** well known **subtypes**. Of the MODY subtypes, hepatocyte nuclear factor (HNF)1A- MODY (MODY3) constitutes 20 – 50% of all MODY cases, glucokinase (GCK)-MODY (MODY2) approxi- mately 20 – 50% of cases, and HNF4A-MODY (MODY1) and HNF1B-MODY (MODY5) each approximately 5% of cases *(Stride A. Ann Med 2002; 34:207–216. Ellard S Diabetologia 2008; 51:546–553)*

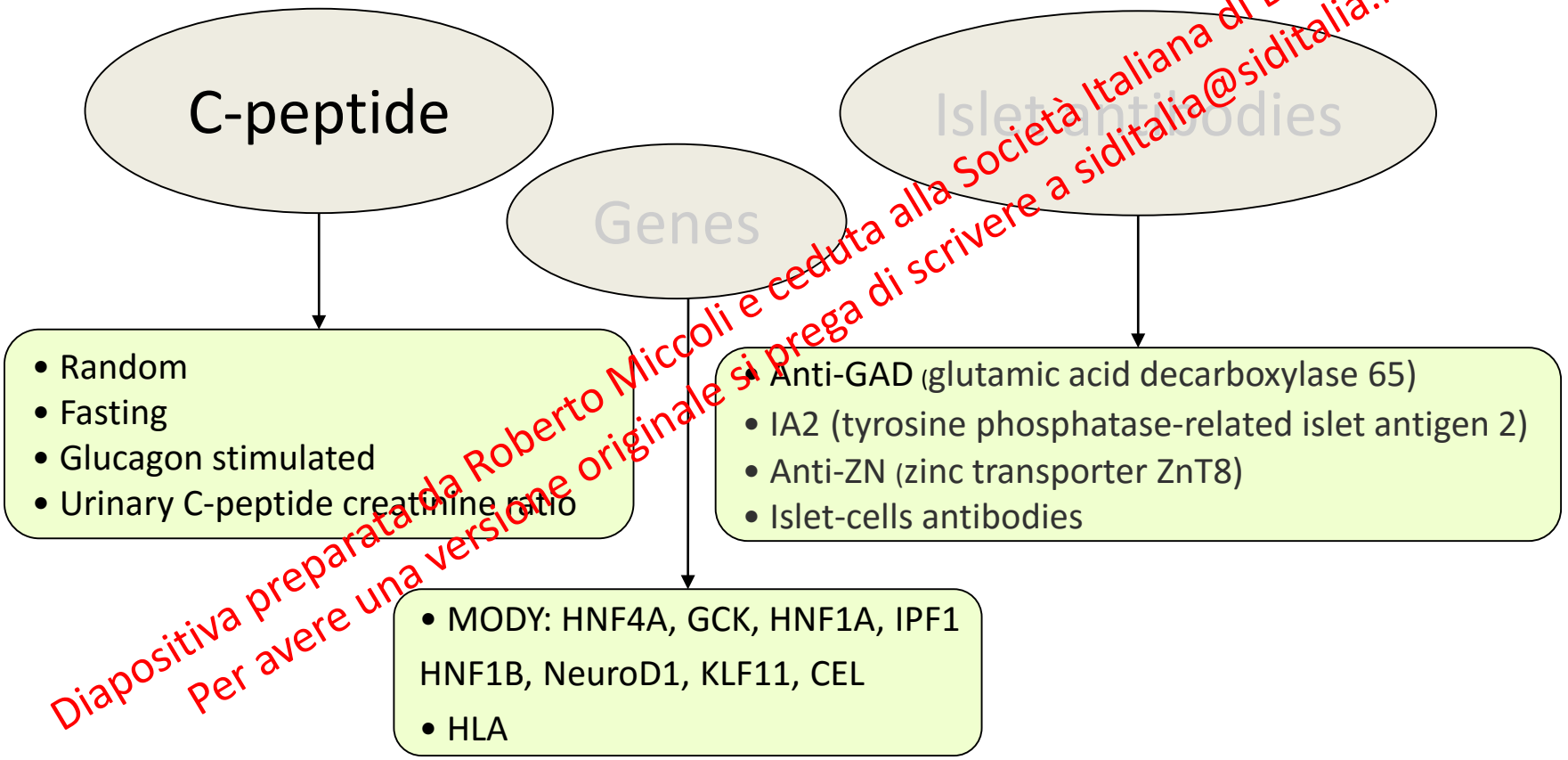
Clinical comparison between type 2 diabetes mellitus, HNF1A diabetes, ketosis-prone diabetes and latent autoimmune diabetes of adulthood

Characteristic	Type 2 diabetes	Type 1 diabetes	HNF1A diabetes (monogenic)	Ketosis-prone diabetes	Latent autoimmune diabetes of adulthood
Mode of inheritance	Polygenic, with environmental interaction	Polygenic, class II HLA	Monogenic, autosomal dominant	Polygenic; increased frequency of HLA alleles associated with type 1 diabetes	Polygenic, with environmental interaction
Age at presentation	Variable (usually adulthood)	Young	Young (often < 25 yr	Variable (usually adulthood)	> 30 yr (adult, by definition)
Penetrance, %	Variable (10–40)[7]	Incomplete (< 25)	High (80–96)[7]	Variable (< 50)	Similar to type 1 diabetes
Body habitus	Obese	Non-obese	Non-obese	Typically obese	Non-obese
Ethnicity	High prevalence worldwide	White	White, European ancestry	Afro-Caribbean or Hispanic, with strong family history of phenotypic type 2 diabetes[5]	Similar to type 1 diabetes
β-Cell antibodies, %	< 10[8]	> 85[3]	< 1[3]	< 30[5]	100 (by definition)[6]
First-line therapy	Metformin in most patients	Insulin	Low-dose sulfonylurea	Insulin during acute presentation; up to 60% of patients require insulin by 10 yr after diagnosis[5]	Insulin independence for at least 6 mo, progressing to insulin dependence over time[6]

Note: HNF1A = hepatocyte nuclear factor 1α, HLA = human leukocyte antigen.

McDonald TJ. Diabet Med 2011;28:1028-33 - Balasubramanyam A. Endocr Rev 2008;29:292-302 - Naik RG. J Clin Endocrinol Metab 2009;94:4635-44 - Fajans SS. N Engl J Med 2001;345:971-80 - Wroblewski M. Diabetes Care 1998;21:250-5.

Tests for diabetes subtype



Suggested C-peptide thresholds to support clinical decisions in patients with diabetes

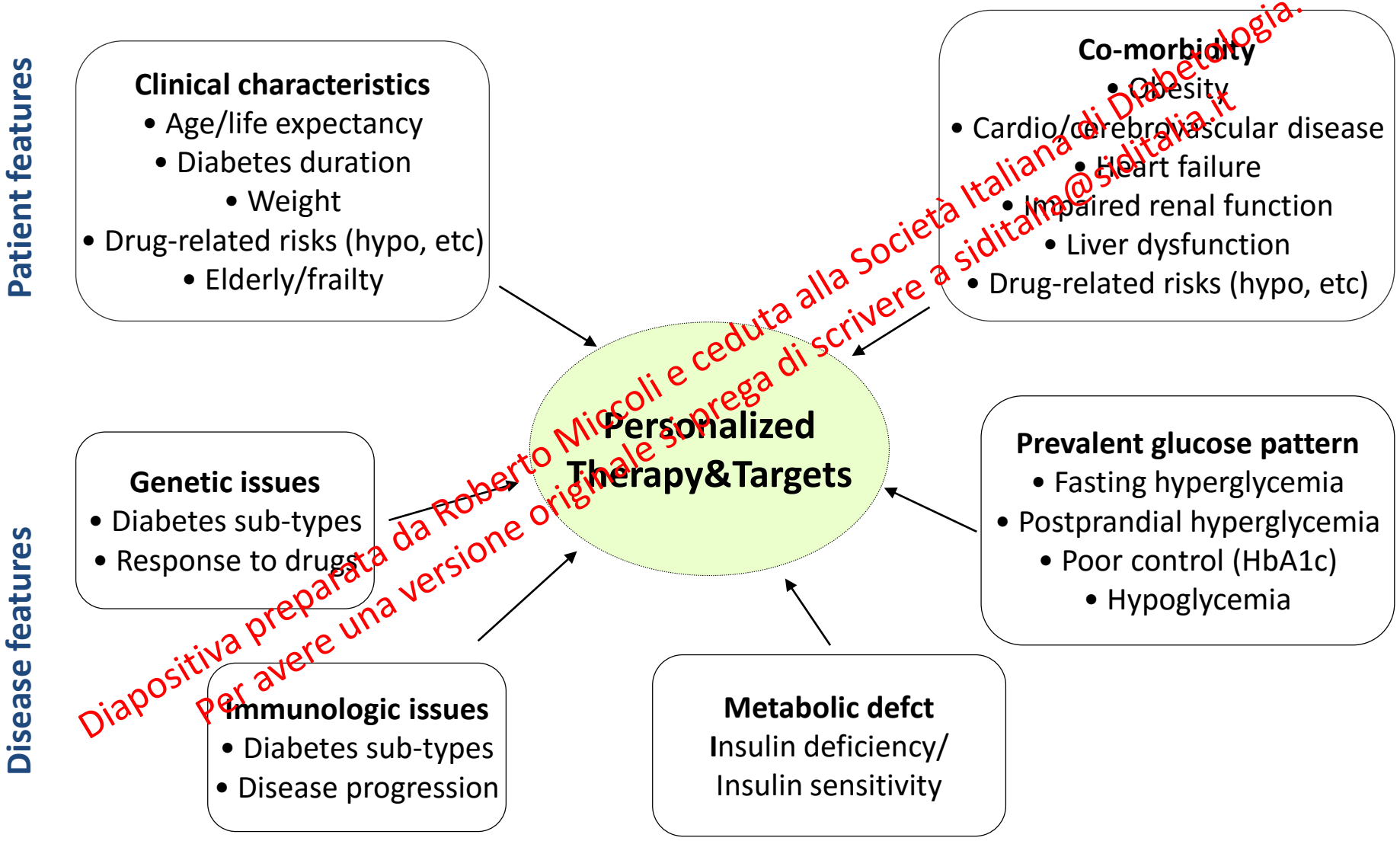
- *Where there is uncertainty as to diabetes subtype, C-peptide measurement may aid diagnosis and appropriate management.*
- This is particularly in long-standing (> 5 years) insulin-treated diabetes, where retained substantial C-peptide secretion may be strongly indicative that Type 1 diabetes is unlikely, and therefore Type 2 diabetes or MODY should be considered.
- The large overlap between C-peptide levels in patients with Type 2 diabetes who do and do not require insulin for glycaemic control goes against the use of C-peptide in this context.
- Evidence for a clinical role of C-peptide in predicting response to specific hypoglycaemic agents is weak.

	Stimulated C-peptide (non-fasting random/post-glucagon/mixed-meal test) (nmol/l)*	Fasting C-peptide (nmol/l)	Post-home meal urine C-pepide:creatinine ratio (nmol/mmol)
Absolute insulin deficiency/absolute insulin requirement	<0.2	<0.08	0.2
Likely T1D/inability to achieve glycemic control with non-insulin therapies	<0.6	<0.25	<0.6
Suggest T2D or MODY (<30 years) diabetes in a patient with presumed T1D >3-5 years post-diagnosis	>0.2	>0.08	>0.2
Consider MODY/T2D in young onset diabetes at diagnosis	>1	>0.4	>1.1

*1 nmol/l=3.0 ng/ml

Adapted from Jones AG. Diabet Med. 2013; 30: 803–817

Phenotype-based initial evaluation of T2D

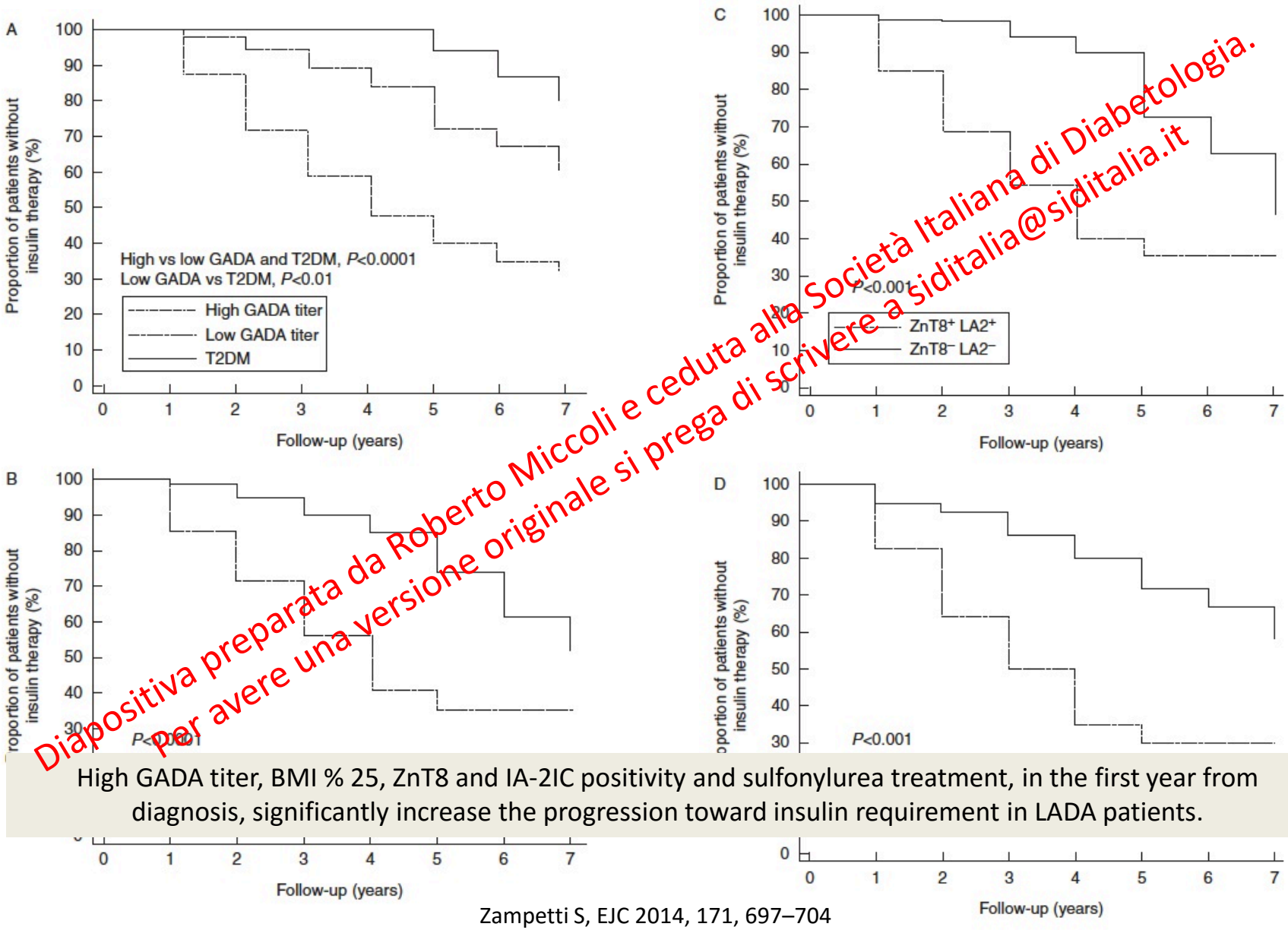


Conclusioni

- La diagnosi del DT2 dovrebbe rappresentare un momento fondamentale per comprendere le caratteristiche del paziente e i rischi (potenziali) della malattia.
- La diagnosi precoce e lo screening possono contribuire a ridurre l'impatto del DT2.
- Conoscere l'eziologia del DT2 può aiutare il clinico a definire le terapie più appropriate per un determinato paziente.
- Il DT2 ad insorgenza giovanile è gravato da una prognosi peggiore.
- La valutazione iniziale deve essere approntata con metodologie adeguate (standard&informatizzate). Può contribuire ad implementare il registro di patologia.
- Il programma della terapia e dei controlli deve essere definito, fin dall'inizio, in base alle caratteristiche individuali, e condiviso con il paziente.

Unite for Diabetes - World Diabetes Day 2016

Proportion of subjects, requiring insulin during 7-year follow-up, LADA with high or low GADA titer, andtype 2 diabetes - *NIRAD Study*



High GADA titer, BMI % 25, ZnT8 and IA-2IC positivity and sulfonylurea treatment, in the first year from diagnosis, significantly increase the progression toward insulin requirement in LADA patients.

Zampetti S, EJC 2014, 171, 697–704

The clinical utility of C-peptide measurement in the care of patients with diabetes

Where there is uncertainty as to diabetes subtype, C-peptide measurement may aid diagnosis and appropriate management.

• This is particularly in long-standing (> 5 years) insulin-treated diabetes, where retained substantial C-peptide secretion may be strongly indicative that Type 1 diabetes is unlikely, and therefore Type 2 diabetes or MODY should be considered.

• The large overlap between C-peptide levels in patients with Type 2 diabetes who do and do not require insulin for glycaemic control goes against the use of C-peptide in this context.

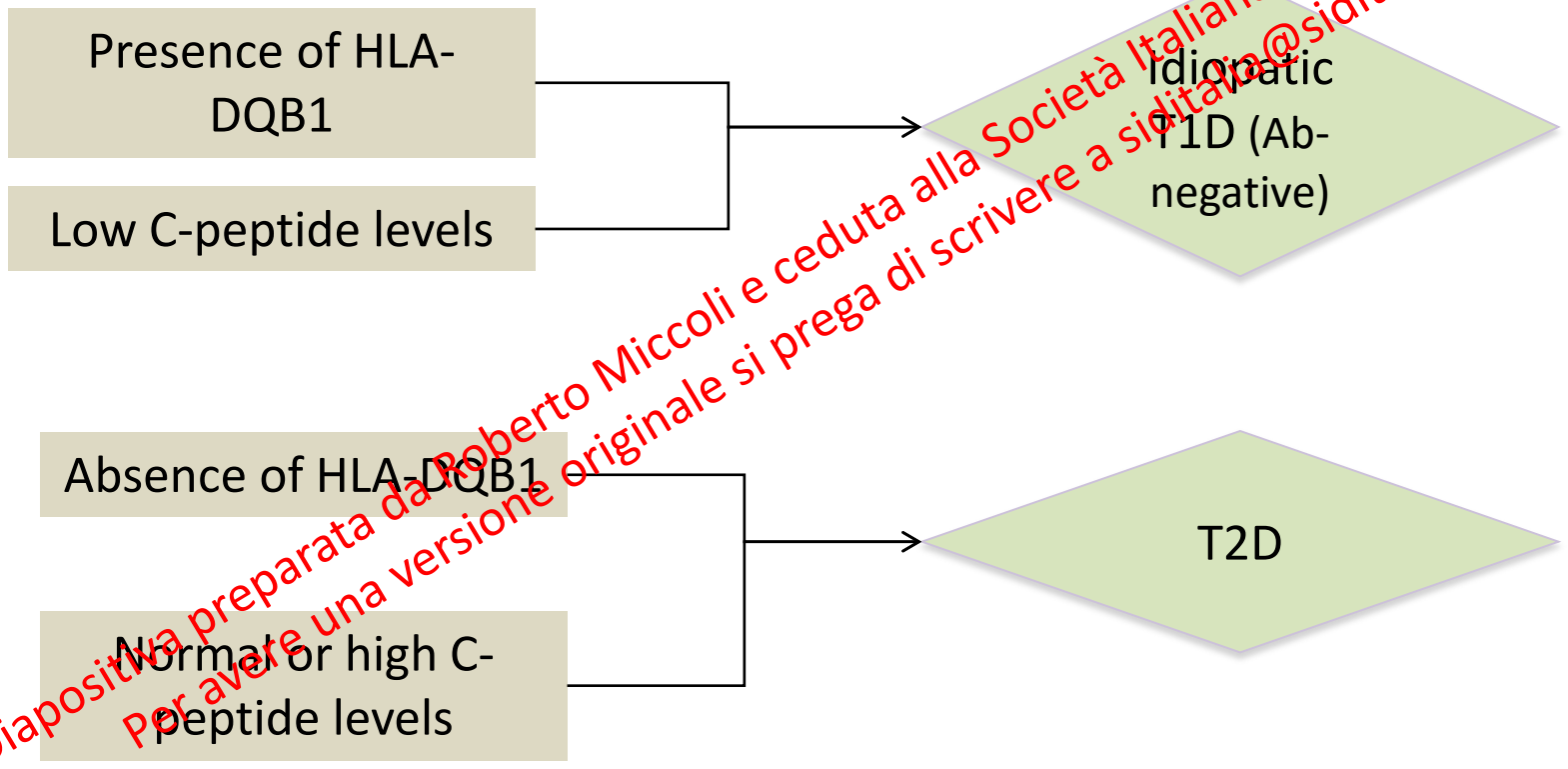
• Evidence for a clinical role of C-peptide in predicting response to specific hypoglycaemic agents is weak.

Suggested C-peptide thresholds to support clinical decisions in patients with insulin-treated diabetes

Clinical role	Stimulated (non-fasting 'random'/post-glucagon/ mixed-meal test) (nmol/l)	Fasting (nmol/l)	Post-meal home meal urine C-peptide:creatinine ratio (nmol/mmol)
Absolute insulin deficiency/absolute insulin requirement	< 0.2	< 0.08	< 0.2
Likely Type 1 diabetes/inability to achieve glycaemic control with non-insulin therapies	< 0.6	< 0.25	< 0.6
Suggests Type 2 or monogenic (MODY) diabetes in a patient with presumed Type 1 diabetes > 3–5 years post-diagnosis	> 0.2	> 0.08	> 0.2
Consider MODY/Type 2 diabetes in young onset diabetes at diagnosis	> 1	> 0.4	> 1.1

Diabetes Care 2003; 26: 832–836 - Scand J Clin Lab Invest 2000; 60: 687– 693 - Endocr Pract 1999; 5: 305–313 - J Clin Endocrinol Metab 2003; 88: 5090–5098 - Diabetes Care 2011; 34: 286– 291 - Diabetes Care 2012; 35: 1206–1212 - Pediatr Diabetes 2012; 13: 45–50

Clinical diagnosis and the usefulness of C-peptide in the classification of diabetes mellitus



Bakhtadze E. Diabetologia 2006; 49(8):1785-94.

The three key features that may suggest possible maturity-onset diabetes of the young (MODY) in insulin-treated individuals

Key features (all three need to be present)	Additional details	Notes
Autosomal dominant inheritance of diabetes.	One parent will also have diabetes and the diabetes may be traced back through the three or more generations with the diabetes being inherited from parent to child.	Monogenic diabetes does not "skip" a generation.
Young age of onset.	Diabetes diagnosed <25 years of age in at least one family member.	Age at diagnosis of diabetes may be variable in other family members through the generations.
Non-insulin-dependent diabetes.	People may have been treated with insulin from diagnosis but will have measurable C-peptide >5 years post-diagnosis.	Other patients may be on diet or tablet treatment, clearly indicating non-insulin dependence.
Other features may be present in addition to the three key features, e.g. sensitivity to sulphonylureas, macrosomia and neonatal hypoglycaemia or renal cysts.		

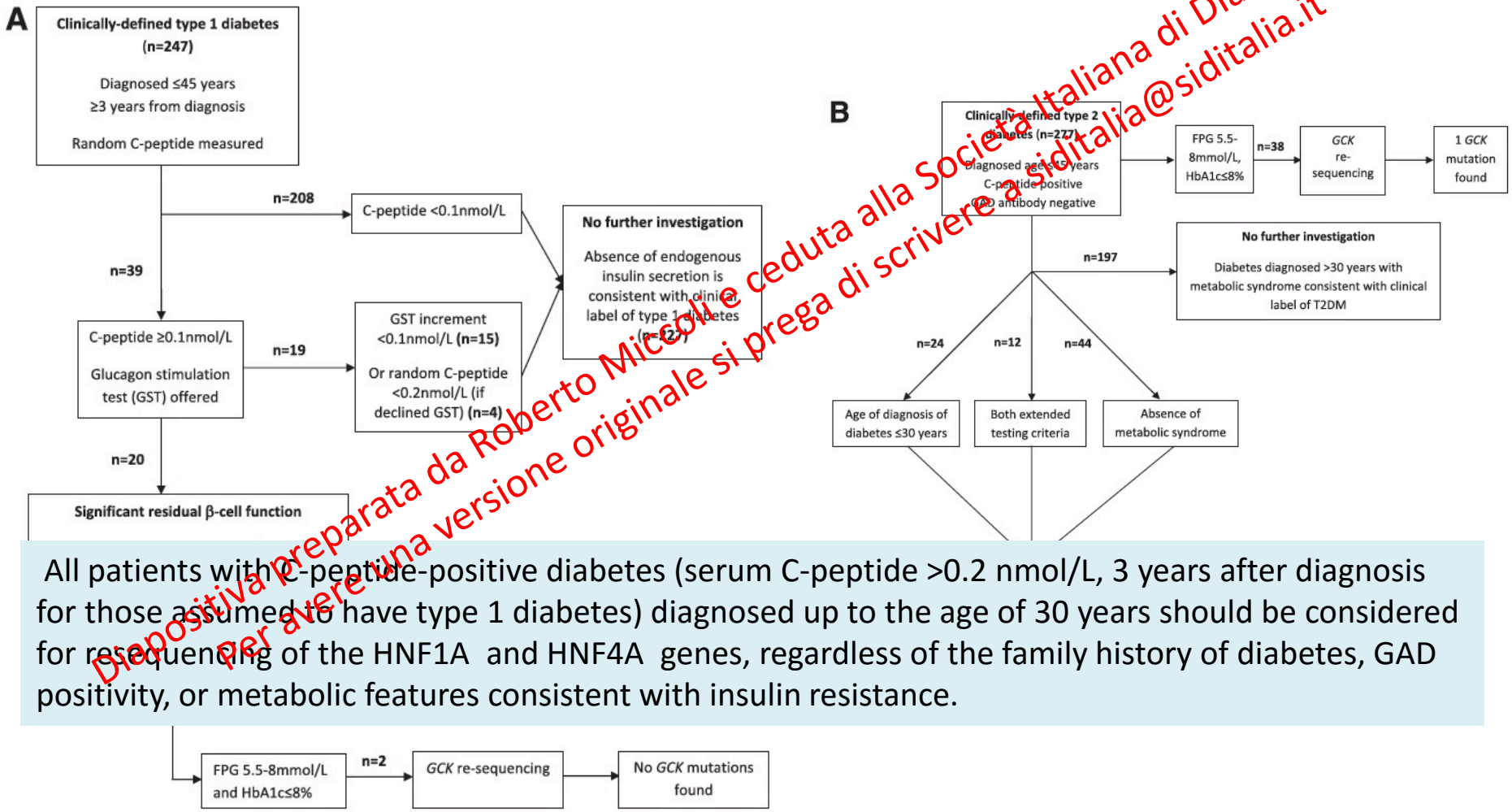
Shepherd M, Hattersley A, 2010

Maturity onset diabetes of the young (MODY): more commonly identified gene mutations

Type	Genetic defect	Frequency	Beta cell defect	Clinical features	Risk of microvascular disease	Optimal treatment
1	Hepatocyte nuclear factor-4-alpha	<10 percent	Reduced insulin secretory response to glucose	Normal renal threshold for glucose	Yes	Sulfonylureas
2	Glucokinase gene	15 to 31 percent	Defective glucokinase molecule (glucose sensor), increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion	Mild, stable, fasting hyperglycemia, often diagnosed during routine screening. Not progressive.	Generally no	Diet
3	Hepatocyte nuclear factor-1-alpha	52 to 65 percent	Abnormal insulin secretion, low renal threshold for glucose	Low renal threshold for glucose, +glycosuria	Yes	Sulfonylureas
4	Insulin promoter factor 1	Rare	Reduced binding to the insulin gene promoter, reduced activation of insulin gene in response to hyperglycemia	Rare, pancreatic agenesis in homozygotes, less severe mutations result in mild diabetes	Yes	Insulin
5	Hepatocyte nuclear factor-1-beta	Rare		Pancreatic atrophy, renal dysplasia, renal cysts, renal insufficiency, hypomagnesemia	Yes	Insulin
6	Neurogenic differentiation factor-1	Rare	Pancreatic development		Yes	Insulin

Naylor R, Clin Endocrinol (Oxf) 2011; 75:422. Ramesh SC, Indian J Pediatr 2011; Dec 10 [ePub]. Thanabalasingham G, BMJ 2011: 343:d6044.

Strategy for Identifying Maturity-Onset Diabetes of the Young (MODY)

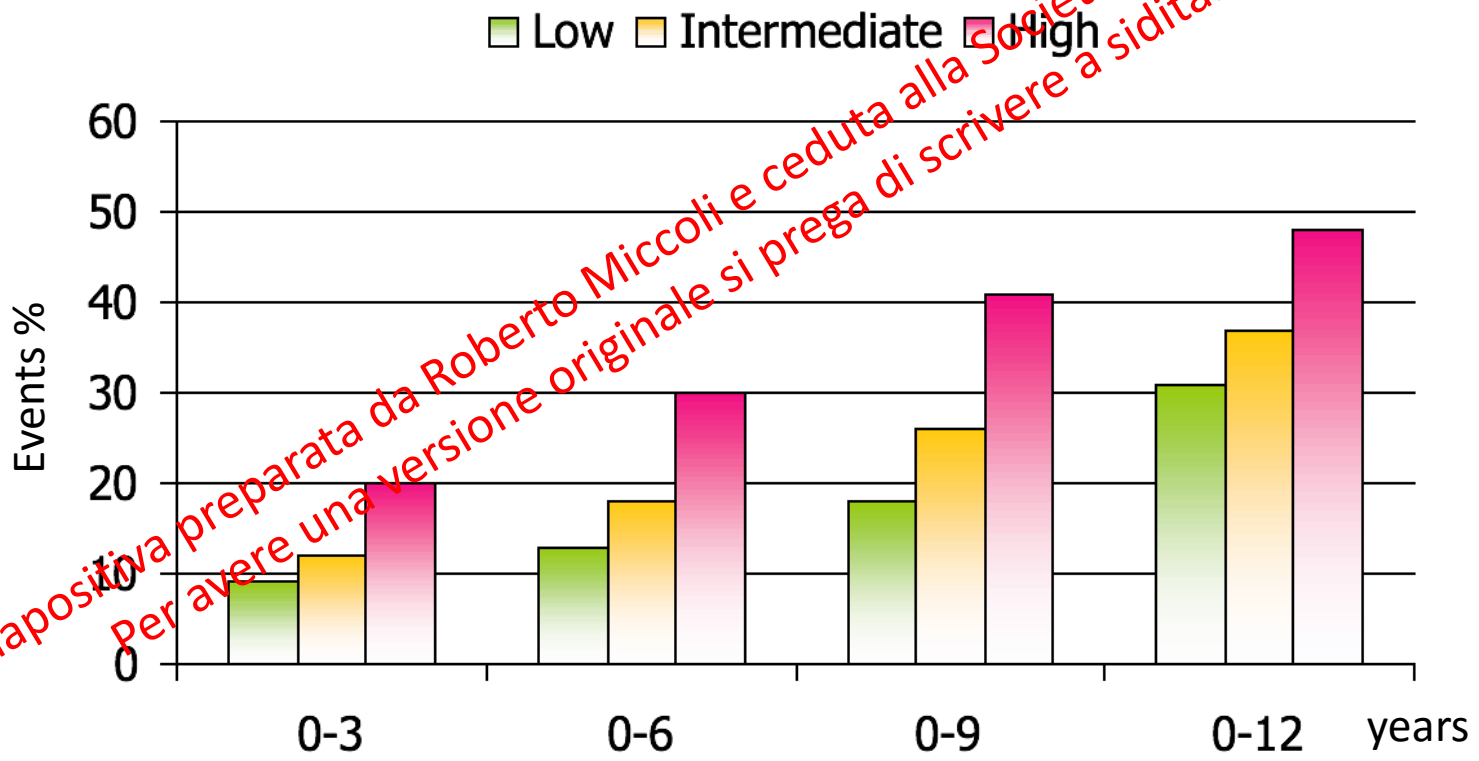


All patients with C-peptide-positive diabetes (serum C-peptide >0.2 nmol/L, 3 years after diagnosis for those assumed to have type 1 diabetes) diagnosed up to the age of 30 years should be considered for resequencing of the HNF1A and HNF4A genes, regardless of the family history of diabetes, GAD positivity, or metabolic features consistent with insulin resistance.

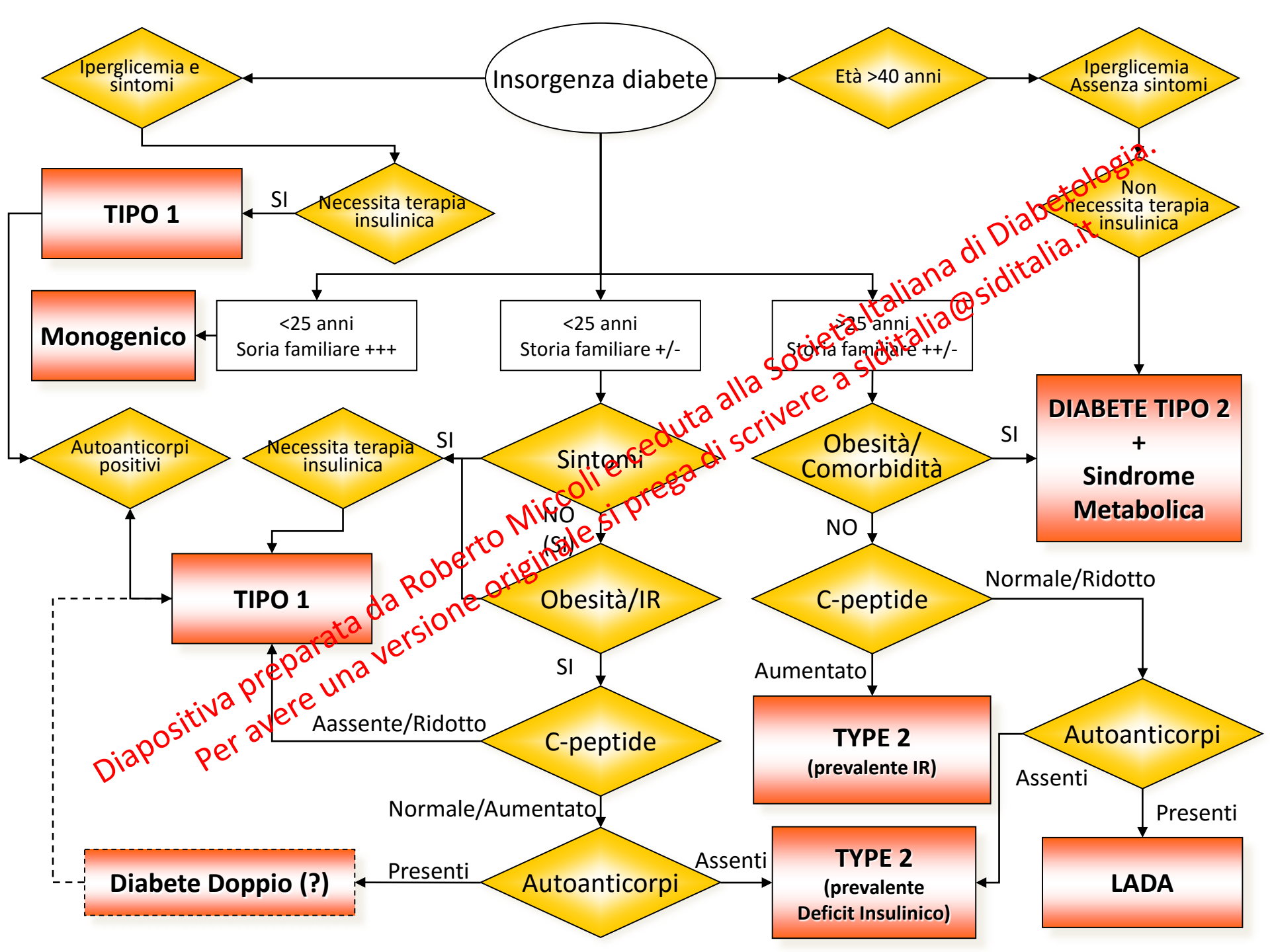
Thanabalasingham G, Diabetes Care 35:1206–1212, 2012

Lower fasting plasma glucose levels at diagnosis of T2D are associated with improved outcomes

U.K. Prospective Diabetes Study 61



Colagiuri S. Diabetes Care 2002; 25: 1410-1417



“Occorre fermare il male quando inizia: non serve preparare la medicina quando la malattia si è fatta forte a causa di lunghi ritardi”

Ovidio, *Remedia Amoris*

Diabetes can be classified into the following general categories

1. Type 1 diabetes
due to βcell destruction, usually leading to absolute Insulin deficiency

5-10%

3. Gestational diabetes (GDM)
diagnosed in the 2nd or 3rd trimester of pregnancy that is not clearly overt diabetes

4-8%
of pregnancy

Latent Autoimmune Diabetes of the Adult **(LADA)**

6-12%

2. Type 2 diabetes
due to a progressive loss of insulin secretion on the background of insulin resistance

90-95%

4. Specific types of diabetes due to other causes
(Maturity onset diabetes of the young [**MODY**]), diseases of the exocrine pancreas, etc)

<5%%

Ketosis-prone diabetes is uncommon and notably found in Hispanics and patients of African origin. By way of contrast, LADA is comparatively common. As 2–12% of patients with apparent Type 2 diabetes actually have autoimmune diabetes, and as Type 2 diabetes is so much more prevalent than childhood-onset Type 1 diabetes, it follows that LADA is more prevalent than childhood-onset Type 1 diabetes.

Leslie

We Can Change the Natural History of Type 2 Diabetes

- Unfortunately, we waste the first years of the natural history when the disorder is easiest to treat.
- Moreover, when we do make the diagnosis, we do not treat in a way that lowers glucose levels to normal.
- As a consequence, the disease tends to progress, and patients need more and more medications.

But this natural history is not inevitable.

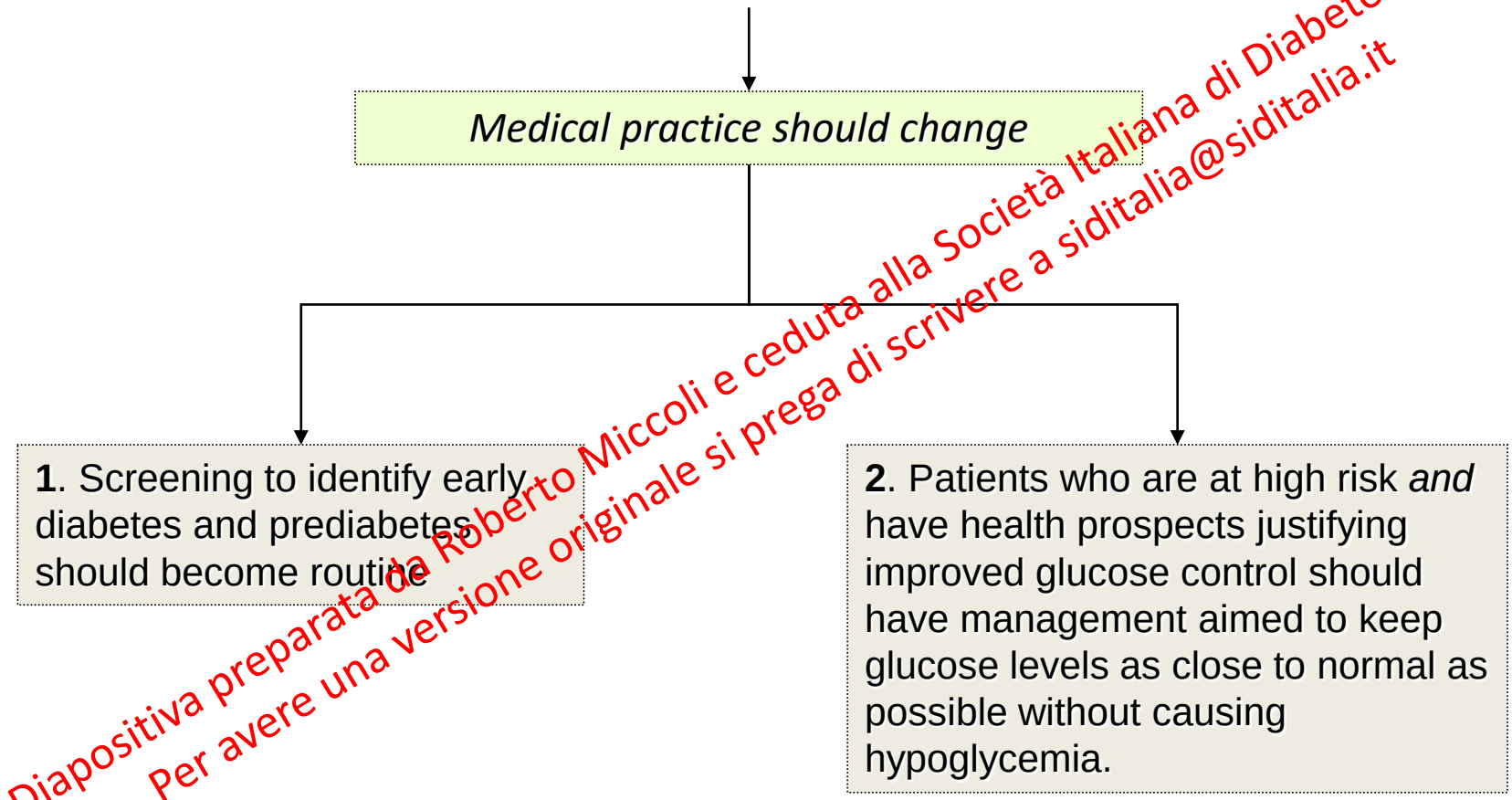
• In patients who are early in their natural histories and already have prediabetes,

1)identifying the problem at such an early stage, and

2)keeping glucose levels normal or near-normal, will change the natural history of the disease preventing or delaying progression from prediabetes to diabetes, and reducing the associated development of diabetes complications.

Phillips LS, Diabetes Care 2014; 37:2668-2676.

Changing the natural history of diabetes



Phillips LS, Diabetes Care 2014; 37:2668-2676.

Rethinking type 2 diabetes as a heterogeneous disease

When to suspect monogenic diabetes

If initially thought to have type 2 diabetes:

- Not markedly obese or diabetic family members who are normal weight
- Acanthosis nigricans not detected
- Ethnic background from a low prevalence type 2 race, e.g. European Caucasian
- No evidence of insulin resistance, fasting Cpeptide within normal range (300-1000pmol/l)
- Features of a specific genetic subtype of monogenic diabetes

Usefulness of autoantibodies measurement

Test	T1D	T2D	LADA
Anti-GAD	60% (adults) 73% (children)	7-34% (adults)	If present: PPV 93% insulin treat. before 3 yrs (age: 15-34) If absent: NPP 49% NO insulin treat. before 3 yrs (age: 15-34)
Anti IA2	40% (adults)	2.2% (adults)	If (age: 15-34 yrs) present: PPV 75% insulin treat. before 3 yrs
Anti-β-cell	84% (children)	4-21%	If present: 86% insulin treat. before 3 yrs (age 15-34 yrs)
One Ab present*	85-90%	17%	

**Presence of one Ab in control subjects: 1-2%*