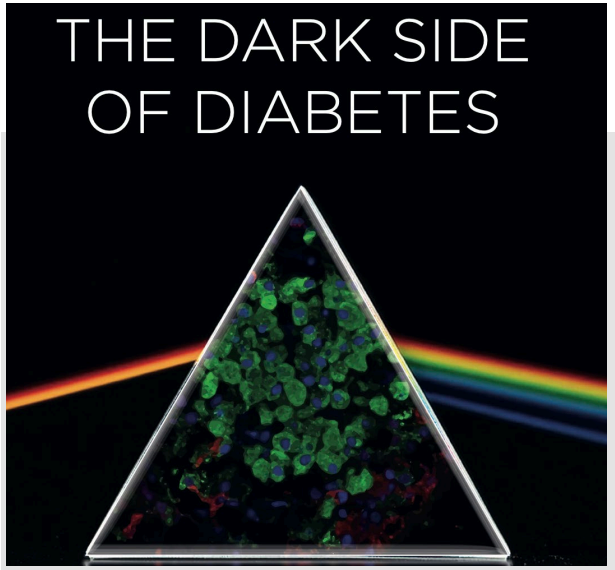


IL MODY:
inquadramento clinico e terapia

Irene Rutigliano
UOC Pediatria
Casa Sollievo
della Sofferenza

Società Italiana di Diabetologia | 1964-2024

Disclosures

Consultations fees and sponsorships:

Kyowa Kirin

Amyrt Pharma

Erbozeta

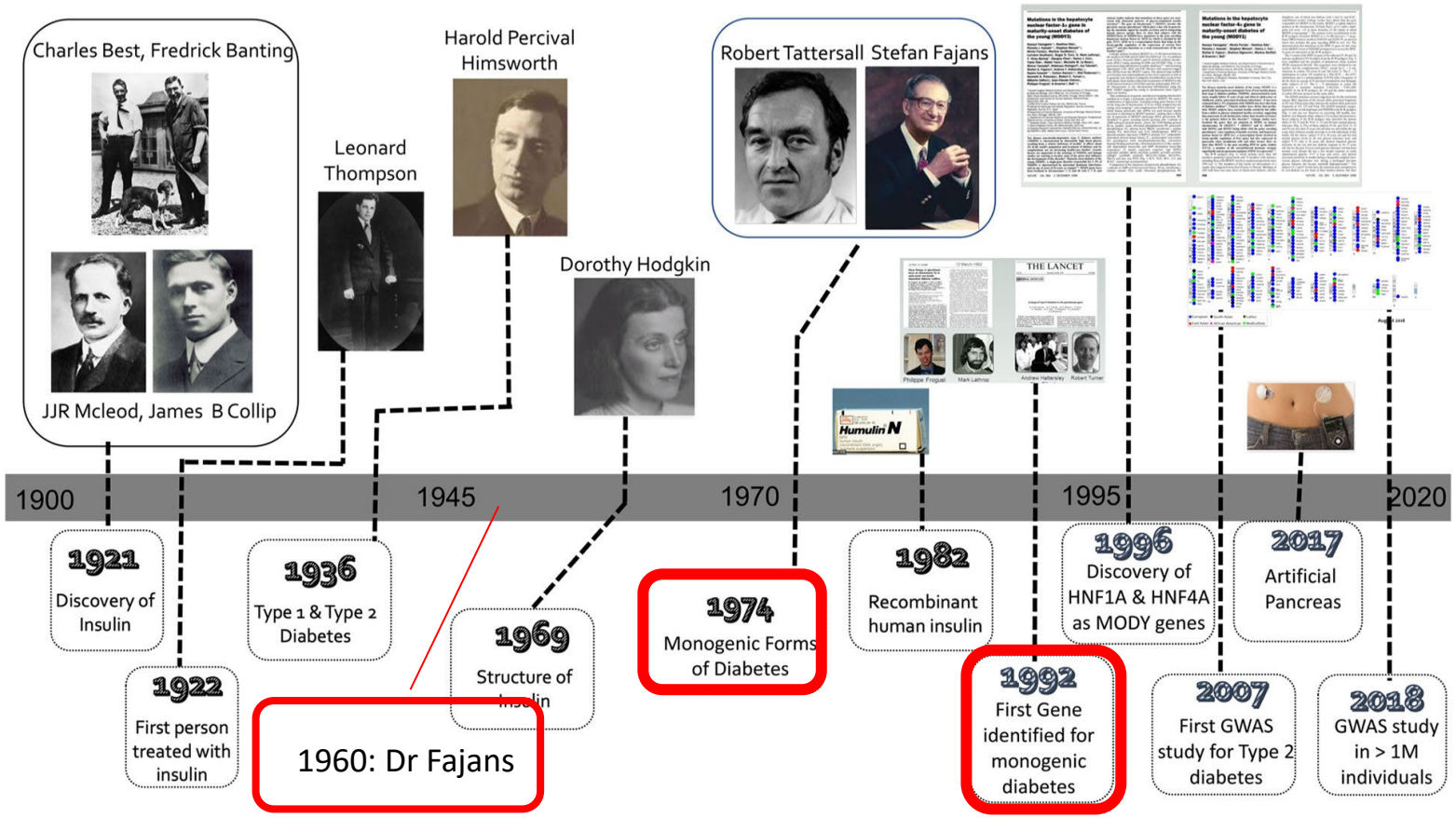
Agenda:

Definizione - Epidemiologia

Come e quando sospettarlo

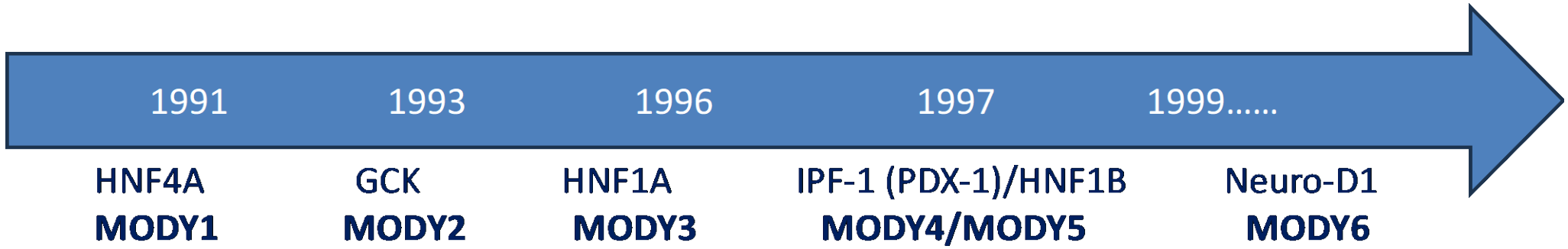
Come diagnosticarlo

Come trattarlo



Ikle JM, Gloyn AL. 100 YEARS OF INSULIN: A brief history of diabetes genetics: insights for pancreatic beta-cell development and function. J Endocrinol. 2021 Jul 22;250(3):R23-R35.

Heterozygous Gene Mutations Identified in MODY



HNF = Hepatocyte nuclear factor
IPF = Insulin promoter factor
PDX-1 = Pancreatic duodenal homeobox-1

IL DIABETE O I *DIABETI*?

- I. Type 1
  - β-cell destruction, usually leading to absolute insulin deficiency
  - Immune mediated (characterized by presence of one or more autoimmune markers)
  - Idiopathic
- II. Type 2
  - Insulin resistance with relative insulin deficiency and subsequent hyperglycemia
- III. Other specific types
  - A. Common forms of monogenic diabetes[a]
    - MODY
      - HNF4-A MODY
      - GCK MODY
      - HNF1A MODY
      - HNF1B MODY
    - Neonatal diabetes
      - KCNJ11
      - INS
      - ABCCB
      - 6q24 (PLAGL1, HYMA1)
      - GATA6
      - EIF2AK3
      - FOXP3
  - B. Genetic defects in insulin action
    - INSR
    - Congenital generalized lipodystrophy
    - Familial partial lipodystrophy
    - PIK3R1 (Short Syndrome)
  - C. Diseases of the exocrine pancreas
    - Pancreatitis
    - Trauma/pancreatectomy
    - Neoplasia
    - Cystic fibrosis-related diabetes
    - Hemochromatosis
    - Transfusion-related iron overload
  - D. Endocrinopathies
    - Acromegaly
    - Cushing's syndrome
    - Hyperthyroidism
    - Pheochromocytoma
    - Glucagonoma
    - Somatostatinoma
  - E. Drug- or chemical-induced
    - Insulin resistance and deficiency
      - Glucocorticoids
      - Nicotinic acid
      - Atypical antipsychotics
      - Protease inhibitors (first generation)
      - Statins
    - Insulin deficiency
      - β-blockers
      - Calcineurin inhibitors
      - Diazoxide
      - Phenytoin
      - L-asparaginase
      - Pentamidine
      - Thiazide diuretics
    - Insulin resistance
      - β-adrenergic agonists
      - Growth hormone
  - F. Infections
    - Congenital rubella
    - Enterovirus
    - Cytomegalovirus
  - G. Uncommon forms of immune-mediated diabetes
    - Anti-insulin receptor antibodies
    - Polyendocrine autoimmune deficiencies APS I and II
  - H. Other genetic syndromes sometimes associated with diabetes
    - Down syndrome
    - Klinefelter syndrome
    - Turner syndrome
    - Friedreich's ataxia
    - Myotonic dystrophia
    - Porphyria
    - Prader–Willi syndrome
- IV. Gestational diabetes mellitus (GDM)

Abbreviations: HNF, hepatic nuclear factor; GCK, glucokinase.

Pediatr Diabetes. 2022;23:1160–1174.

At the time of speaking…

Definizione

Diabete Monogenico

Gruppo eterogeneo di disordini dovuti a
mutazioni in singoli geni
coinvolti nell'omeostasi del glucosio

- Diabete neonatale
- Maturity Onset Diabetes of the Young (MODY)
- Diabete sindromico

At the time of speaking…

Maturity Onset Diabetes of the Young:
Historical definition

- Early onset: < 25 aa
- Soggetti magri - normopeso
- Ereditarietà autosomico dominante (familiarità)
- Funzione insulinica preservata senza segni di processi autoimmunità (no necessità di terapia insulinica) – NO KAD

Tattersall RB, Fajans SS. A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. Diabetes. 1975 Jan;24(1):44-53.

Definizione

PRIMA

Esordio < 25 aa

Soggetti magri - normopeso

Familiarità

Non necessità di terapia insulinica

Assenza di chetoacidosi

OGGI

Casi con diagnosi/esordio tardivo

Eccesso ponderale

Mutazioni de novo

Spesso la terapia adeguata è insulinica

Possibile KAD

At the time of speaking…

Epidemiologia

Popolazione generale: ~ 60.000.000

Diabete ignoto: ~ 1.000.000

Diabete noto: ~ 4.000.000

Tipo 1: *~ 200.000 (5%)*

LADA: *~ 200.000 (5%)*

Tipo 2: *~ 3.500.000 (87%)*

Secondario: *~ 50.000 (1.5%)*

Monogenico: *30-40.000* <------

0.5-5% dei pazienti con T2D
5-6% dei pazienti pediatrici
1-2% delle donne con GDM

Modificato da Stima dall'Osservatorio ARNO Diabete CINECA-SID

At the time of speaking...

Diabete monogenico: che fare?
Le tre domande del clinico

1. Come e quando sospettarlo
2. Come diagnosticarlo
3. Come monitorarlo e trattarlo

At the time of speaking…

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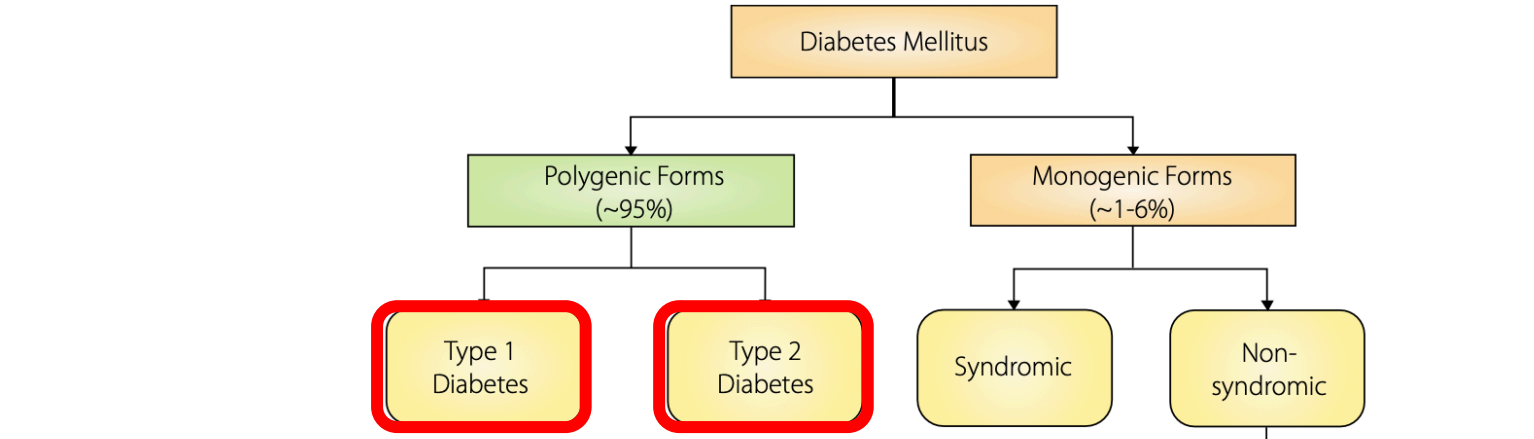
At the time of speaking…

Come e quando sospettarlo



CARATTERISTICHE EXTRA-PANCREATICHE

Esordio prima dei 6 mesi
Ab negativi
Familiarità
Fx beta cell preservata (pC>0.6ng/ml)
Remissione >3- 5 aa
Basso fabbisogno di insulina

Esordio <45 aa
Assenza di obesità
Assenza di segni di IR e/o markers di sindrome metabolica
Distribuzione del grasso
Storia familiare

Precision diabetes: Lessons learned from maturity-onset diabetes of the young (MODY)

Mustafa Tosur[1]*, Louis H Philipson[2]

J Diabetes Investig Vol. 13 No. 9 September 2022

At the time of speaking…

Diagnosi differenziale tra DM, DT1 e DT2

Caratteristiche storiche del MODY

Tattersall

Trasmissione autosomico-dominante

il soggetto che sviluppa la malattia ... tto sarà affetto

Esordio precoce (< 25 anni)

Magri - Normopeso

	DT1	DM	DT2
Insorgenza < 30 aa	Molto frequente	Molto frequente	Infrequente
Storia familiare	Infrequente	Molto frequente*	Frequente
Chetoacidosi	Frequente	Molto infrequente	Molto infrequente
Sovrappeso/obesità	Infrequente	Infrequente	Molto frequente
Dislipidemia aterogena	Infrequente	Infrequente	Frequente
Caratteristiche sindromiche	Assenti	Possibili**	Assenti
Ab pancreatici	Presenti	Assenti	Assenti
C-peptide sierico (ng/ml)	< 0,6	> 0,6	>> 0,6

* Particolarmente sospetta se coinvolge ≥ 3 generazioni

**cisti renali o altre malformazioni urogenitali, disturbi uditivi, disturbi visivi, lipodistrofia, anemia megaloblastica, acanthosis nigricans in soggetti magri, malformazioni cardiache o pancreatiche, diabete insipido.

SID 2022 -- Documento di orientamento clinico sul diabete monogenico. V. Trischitta et al.

At the time of speaking...

Real Life

Caratteristiche storiche del MODY

Tattersall 1974

-Trasmis omico-dominante

il s zigote sviluppa la malattia

l un affetto avrà la malattia

- Esordio ecoce (25 anni)

- Normopeso

Caratteristiche attuali del MODY

Clinical features	
Age at diagnosis of diabetes (Y)	13 (8 - 18)
Age at genetic diagnosis (Y)	17 (11 - 35)
Females	46 (68%)
BMI (Kg/m^2)	21 (19 - 24)
Extra-pancreatic features	2 (3%)
Parent(s) with diabetes	61 (90%)
HbA1c (%)	6.1 (5.8 - 6.5)
Only diet	40 (59%)
Non-insulin therapy	12 (18%)
Insulin (+/- non-insulin therapy)	16 (23%)

Data are median value (25th – 75th percentile) or percentage

Marucci A et al, Acta Diabetologica 2022

At the time of speaking…

MODY-DM: come e quando sospettarlo

- Storia familiare: ereditarietà aut. dom. (MODY)
- Età precoce di insorgenza, in assenza di KAD
- Assenza di obesità
- Negatività degli autoAb
- Lieve iperglicemia, non progressiva (GCK)
- Caratteristiche extra-pacreatiche: anomalie renali (HNF1B), glicosuria (HNF1A), macrosomia/ipoglicemia neonatale (HNF4A), disfunzione pancreatica esocrina o cisti pancreatiche (CEL), ipoacusia (mitocondriale, WFS1), lipodistrofia (LMNA, PPARG), anemia megaloblastica (SLC1A2), iperinsulinismo in soggetti magri (INS)
- Storia di macrosomia, ipoglicemia neonatale, diabete neonatale

https://www.diabetesgenes.org/exeter-diabetes-app/ModyResult

Diabetologia (2012) 55:1265–1272
DOI 10.1007/s00125-011-2418-8

ARTICLE

The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes

B. M. Shields · T. J. McDonald · S. Ellard · M. J. Campbell · C. Hyde · A. T. Hattersley

Age at diagnosis

Sex

Treatment info

BMI

HbA1c

Current age

Parent w diabetes

Ethnicity

Syndromic features

EXETER DIABETES

MODY Probability Calculator

Age at diagnosis (years)

Sex: Male Female

Currently treated with insulin **or** tablets: Yes No

Time to insulin treatment (if currently treated with insulin):
- Not currently treated with insulin
- Within 6 months of diagnosis
- Over 6 months after diagnosis

BMI (kg/m²)

HbA1c (%) or

HbA1c mmol/mol

Current Age (years)

Parent affected with diabetes: Yes No

Ethnicity: White Non-white

Other:
- Renal cysts
- Deafness
- Partial lipodystrophy
- Severe Insulin Resistance in absence of obesity
- Severe obesity with other syndromic features

Calculate Reset

At the time of speaking…

https://www.diabetesgenes.org/exeter-diabetes-app/ModyResult

EXETER DIABETES

MODY Results

Based on the clinical features entered into the calculator, the probability of your patient having MODY is

4.6% (a 1 in 21.7 chance of having MODY)

As your patient is treated with insulin, they may benefit from testing C-peptide and islet autoantibodies prior to diagnostic molecular genetic testing for MODY.

If C-peptide is <200pmol/L then the patient will have <1% chance of MODY.
If the patient tests positive for islet autoantibodies, they will have a <1% chance of MODY.
If the patient has a C-peptide >200pmol/L, then the probability of MODY will increase substantially.

C-peptide and antibody testing

A diagnosis of MODY must be confirmed by molecular genetic diagnostic testing.

At the time of speaking…

Table 1
Molecular bases of MODY.

MODY subtype	Affected gene	Gene function	Mutation type	Pathogenesis of hyperglycemia	Other features
MODY 1	hepatocyte nuclear factor (HNF) 4α (*HNF4α*)[5]	-hepatocyte differentiation[39] -gastrointestinal tract development[39] -lipid and glucose metabolism,[39] detoxification of xenobiotics[40] -control of F9 expression[41]	over 100 substitutions and frame-shift mutations[42,43]	fetal and infantile hyperinsulinism due to reduced ER Ca^{2+} levels and increased store-operated Ca^{2+} entry[44] exhaustion of β pancreatic cell reserve in adulthood[44]	dyslipidemia -elevated LDL, low HDL, and low TGs[17] hemophilia B Leiden - reduced factor IX synthesis in the liver[41]
MODY 2	glucokinase (*GCK*) gene[19]	GCK controls glucose phosphorylation rate in liver and pancreas based on serum glucose levels[45]	over 600 different GCK mutations, such as missense, nonsense, frameshift, and splice site mutations[46]	abnormal glucose sensing, resulting in a higher threshold for glucose-stimulated insulin secretion[19]	neonatal diabetes mellitus in homozygotes and compound heterozygotes with inactivating mutations[45]
MODY 3	hepatocyte nuclear factor (HNF) 1α (HNF1α)[47]	-β cell maturation, insulin secretion[20] -controls expression of GLUT2, clotting factors and sodium–glucose cotransporter 2 (SGLT2)[20] -activates CRP transcription[48]	missense, translocation, nonsense, splice mutation, in-frame amino acid deletion, insertion, duplication, or partial and whole gene deletion[47]	decreased expression of K + ATP channels in β pancreatic cells, coupled with increased Ca^{2+} signals, leading to insulin hypersecretion*[49] long-term hyperinsulinemia causes exhaustion of β pancreatic cells[49]	prothrombotic clot structure, therefore higher risk of diabetes complications[50] decreased transcription of CRP gene[48] decreased SGLT2 expression in the renal tubules: impaired urinary glucose reabsorption and glycosuria[48]
MODY 4	pancreatic duodenal homeobox-1 (*PDX1*)[51]	-maturation and differentiation of common pancreatic precursor cells[51] -transcriptional activator of insulin (*INS*), somatostatin (*SST*), *GCK*, islet amyloid polypeptide gene (*IAPP*), and *GLUT2* gene[51]	>150 missense coding mutations described, heterozygous mutations result in MODY 4 phenotype[52]	β pancreatic cell apoptosis and defective insulin secretion[53]	dorsal pancreatic agenesis and exocrine pancreas deficiency in two heterozygous patients[54] pancreas agenesis or hypoplasia, exocrine pancreatic insufficiency and permanent neonatal diabetes in homozygous patients[5,19,55]
MODY 5	hepatocyte nuclear factor-1B (*HNF1B*)[56]	-development of nephron and pancreas[56] -upregulation of urate reabsorption in renal tubule[57] -renal magnesium reabsorption[58]	most common (50%): entire gene deletion within a chromosomal microdeletion of 17q12[59]	decreased insulin secretion caused by pancreatic hypoplasia[56] impaired insulin-induced suppression of glucose production in the hepatocytes (i.e., hepatic insulin resistance)[56,60]	pancreatic hypoplasia[56] multi-cystic kidney dysplasia and anomalies in Mullerian and Wolffian derivatives[56,60] liver abnormalities with high TGs and low HDL[60,61] hyperuricemia with or without gout[57,60,62] hypomagnesemia[58,60,63]
MODY 6	neurogenic differentiation 1 (*NEUROD1*)	-α and β pancreatic cell differentiation, β cell proliferation, islets of Langerhans formation[64] -activates *INS* transcription[65] -terminal neuronal differentiation and migration of neurons in the cerebellum, hippocampus, inner ear and retina[66]	16 missense or truncated mutations of *NEUROD1* have been genetically characterized[67]	diminished β cell mass at birth, disorganized architecture of Langerhans islets and diminished insulin secretion[64]	learning difficulties, speech delay, hearing difficulties, and/or impaired vision[68] permanent neonatal diabetes and severe neurological abnormalities, such as cerebellar hypoplasia, profound sensorineural deafness, mental retardation and convulsions in homozygous patients[69]
MODY 7	Kruppel-like factor 11 gene (*KLF11*)[19]	-suppression of exocrine pancreas cell growth[65,70,71] -upregulates *INS* expression β pancreatic cells in the state of hyperglycemia[72] -upregulates *PDX1* expression[73] -upregulates the expression of free radical scavengers, such as catalase and superoxide dismutase (SOD)[19]	four missense mutations (R29Q, Q62R, T220M, and A347S) have been associated with MODY 7 thus far[67]	Impaired insulin production[72]	Pancreatic cancer due to cell overgrowth[19]
MODY 8	carboxyl-ester lipase gene (*CEL*)[18]	cholesterol and lipid-soluble vitamin digestion and absorption in the duodenum[18]	some single-bp deletion mutations in the proximal segments of VNTR region in the CEL have been associated with MODY 8[74]	misfolding and cytotoxic aggregation of the CEL protein impairs insulin secretion[74]	early pancreatic atrophy and pancreatic lipomatosis, pancreatic cysts later in life[74–76] increased risk of chronic hereditary pancreatitis[75]
MODY 9	paired box 4 (*PAX4*) gene[77]	β cell δ differentiation during embryogenesis[77] β cells regeneration later in life[77] insulin production control through *PDX1* and *NKX6.1* upregulation[78]	missense mutation - R164W[77] shear mutation–- IVS7–1)[77] deletion C374-412del39[77] missense mutations c.593C > T (A198V), c.377 A > G (p. D126G), c.55C > T (p.R19W), C.92G > T (p.r.31 l) and C·487C > T[77]	disrupted β and δ cells differentiation, resulting in α cells predominance and increased glucagon secretion[77] lack of basal insulin secretion[79]	
MODY 10	*INS*	encodes for pre-proinsulin[67]	at least 11 *INS* mutations are associated with MODY 10 (mostly missense)[80]	misfolded proinsulin molecules accumulate in the β pancreatic cells, leading to ER stress and triggering β cell apoptosis[67,80] progressive impairment of insulin secretion due to a defective insulin production and decreased β cell mass[80]	neonatal diabetes mellitus (more common than MODY 10)[67]
MODY 11	B-lymphocyte kinase gene (*BLK*)[81]	-development of β pancreatic cells[82] -insulin synthesis and secretion in response to postprandial glucose spike through *PDX1* and *NKX6.1* activation[19,82]	missense mutations[81]	decreased β cell mass[19] impaired glucose-stimulated insulin secretion due to reduced postprandial *BLK* expression[19,81]	environmental factors, such as hypercaloric diet and/or physical inactivity can provoke the diabetic phenotype in individuals harboring the mutation[67,83]
MODY 12	*ABCC8*[84]	encodes sulfonyl-urea receptor 1 (SUR1), a subunit of an ATP-sensitive potassium (K-ATP) channel in β pancreatic cell plasma membranes[84]	missense mutations[65]	gain-of-function mutations: K-ATP channel remains open in the presence of an increased ATP/ADP ratio, which reduces calcium influx and insulin secretion[65,85] inactivating mutations: permanent β cell depolarization, constitutive insulin secretion, irrespective of serum glucose levels[86]; hyperinsulinemia causes exhaustion of β cells[86]	altered function of neurons: hypsarrhythmia, epilepsy and developmental delay[87]
MODY 13	*KCNJ11*[88]	encodes for Kir6.2 subunit of K-ATP channels[88]	gain-of -function and loss-of-function missense mutations[65,86]	*KCNJ11* mutations can either be activating or inactivating, leading to hypo- or hyperinsulinemia, respectively[65,86]	neurological abnormalities[87]
MODY 14	adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1 (*APPL1*)[67,89]	-cell proliferation and apoptosis[89] -insulin signaling and interaction between adiponectin and insulin[89,90]	missense loss-of-function mutations[91,92]	decreased β cell survival, impaired postprandial insulin secretion, and impaired insulin sensitivity[19,67,90]	

RFX6 UK
NKX6.1 India

At the time of speaking...

Marurity-onset diabetes of the young

Gene	Locus	Clinical features		T
GCK	7p15-p13	Mild asymptomatic hyperglycemia	MODY 2	N
HNF1A	12q24.2	Renal glucosuria	MODY 3	S
HNF4A	20q12-q13.1	Macrosomia and neonatal hypoglycaemia, renal Fanconi syndrome (mutation specific), Hepatic disfunction	MODY 1	S
HNF1B	17q12	Renal developmental abnormalities, genital tract malformations	MODY 5	I
KCNJ11	11p15	Proband or relatives may have history of TNDM and/or neuropsychological difficulties	MODY 13	H
ABCC8	11p15	Proband or relatives may have history of TNDM and/or neuropsychological difficulties	MODY 12	H

Pediatr Diabetes. 2022;23:1188–1211.

ETA' ESORDIO PATTERN IPERGLICEMIA RISPOSTA AL TRATTAMENTO E FOLLOW UP

At the time of speaking…

Distribuzione delle forme più comuni in Italia

Gene	Subtype	Frequency (%)
HNF4A	MODY 1	5-8
GCK	MODY 2	57-42
HNF1A	MODY 3	14-18

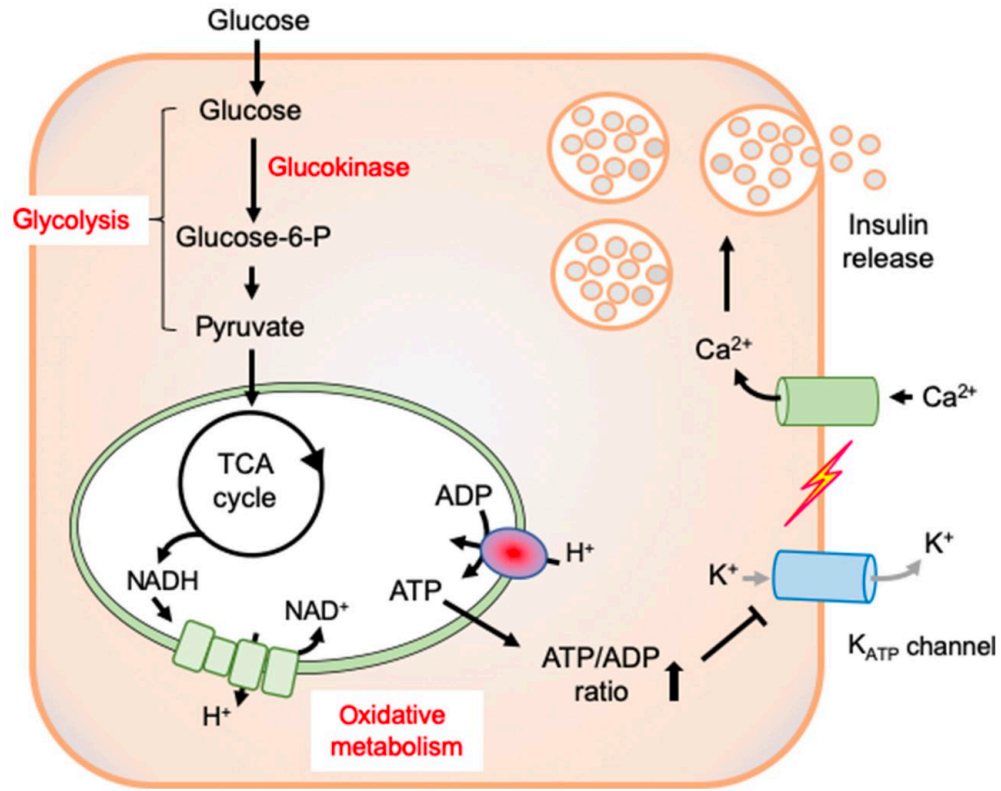
Delvecchio M et al, Diabetes Care 2014
Marucci A et al, Acta Diabetologica 2022

At the time of speaking…

GCK-MODY, MODY 2, DIABETE GCK

- Forma più comune
- Glicemia a digiuno: 100-145 mg/dl, HbA1c <7.5%
- Asintomatici
- OGTT: delta 60 mg/dl
- Bassa prevalenza di complicanze

- No terapia→ 2-6% GD



Trends in Endocrinology & Metabolism, February 2023, Vol. 34

At the time of speaking…

Casi clinici: per riflettere…

LUCA

PN 2.450 kg (7°pc)

Età: 8 aa H<-2DS, TG 25°-50°PC

Glicemia 109 mg/dl, HbA1c 5.9%

OGTT: glicemia 0’ 112 mg/dl, glicemia 120’ 173 mg/dl

Peptide C 0.8 ng/ml

AutoAb neg

ERNESTO

PN 2.970 kg (10°pc)

Età: 9 aa H<-2DS, TG 50°PC

Glicemia 109 mg/dl, HbA1c 5.9%

OGTT: glicemia 0’ 94 mg/dl, glicemia 120’ 104 mg/dl

Peptide C 1.07 ng/ml

AutoAb neg

MUTAZIONE IN ETEROZIGOSI DI GCK

At the time of speaking…

SCARSA CRESCITA E GCK: QUALE RELAZIONE?

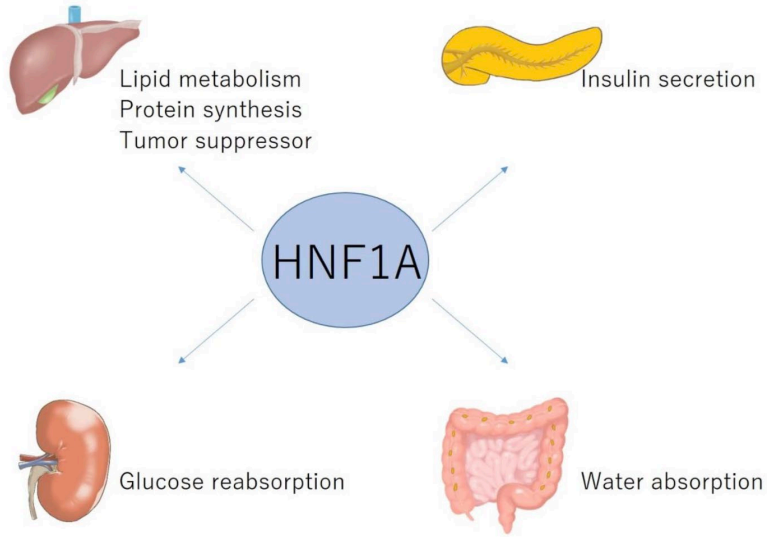
Caetano LA, Jorge AA, Malaquias AC, Trarbach EB, Queiroz MS, Nery M, Teles MG. Incidental mild hyperglycemia in children: two MODY 2 families identified in Brazilian subjects. Arq Bras Endocrinol Metabol. 2012 Nov;56(8):519-24.

Li X, Liu L, Liang C, Sheng H, Zhao X. Maturity-onset diabetes of the young 2 with a novel mutation of glucokinase gene in a Chinese boy and the clinical follow-up. Zhonghua Er Ke Za Zhi. 2014 Nov;52(11):867-71.

At the time of speaking…

MODY 3, HNF1A-MODY, DIABETE HNF1A

- Alla nascita: ipoglicemia transitoria e iperinsulinismo
- Variabile presentazione clinica
- Diagnosi: 63% <25 aa, 79% <35aa, 96% 55 aa
- OGTT: delta >90 mg/dl
- Glicosuria
- Complicanze micro e macro
- Adenomi epatici



SGLT2

Int. J. Mol. Sci. **2022**, *23*, 3222.

At the time of speaking...

Antonio

Esordio 16 aa, BMI 50°pc

Madre DM2 (metformina)

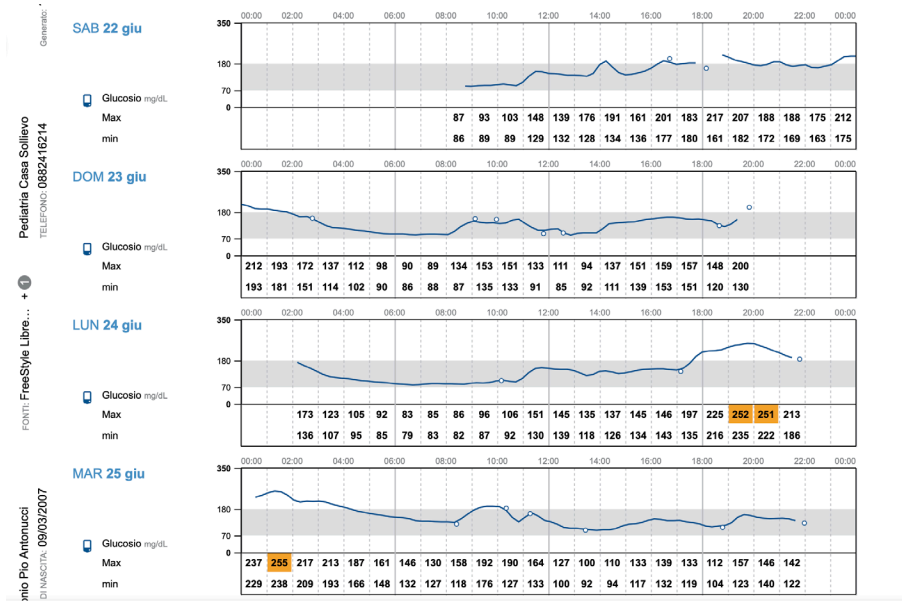
Glicemia 224 mg/dl,
HbA1c 9.2%, pH 7.37

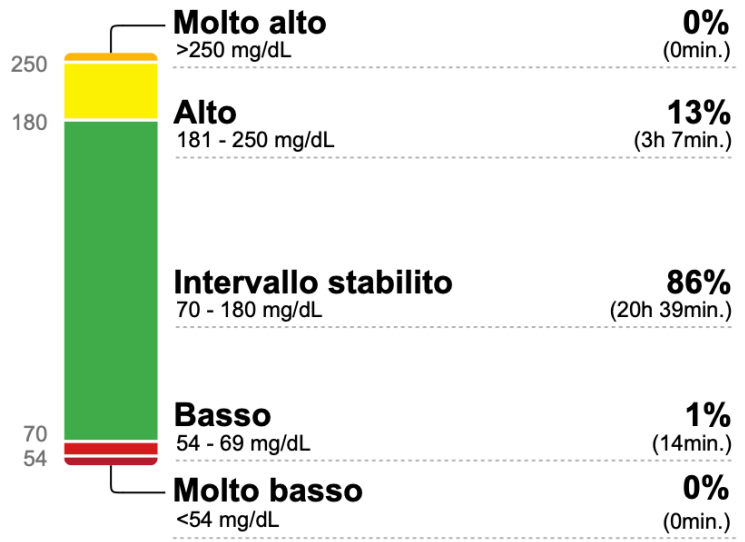
Ab neg

Peptide C 1.9 ng/ml

Mody c: 75.5%

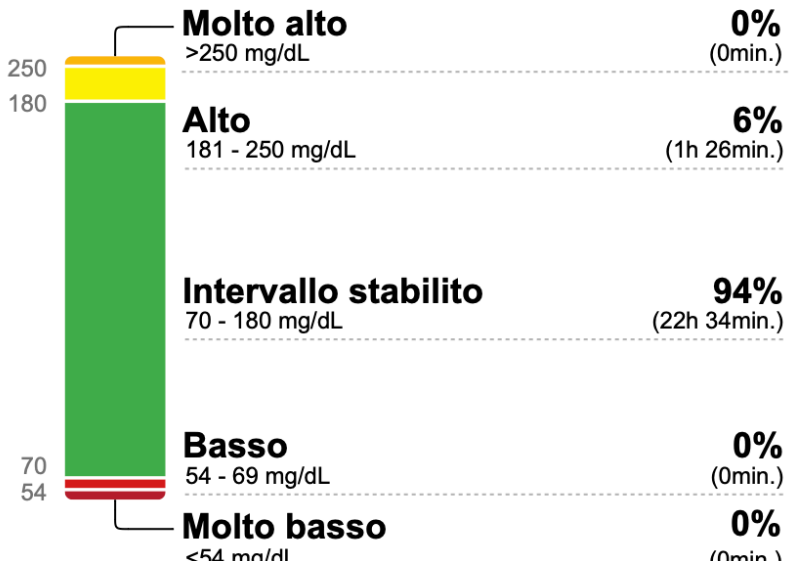
Mutazione in eterozigosi di HNF1A

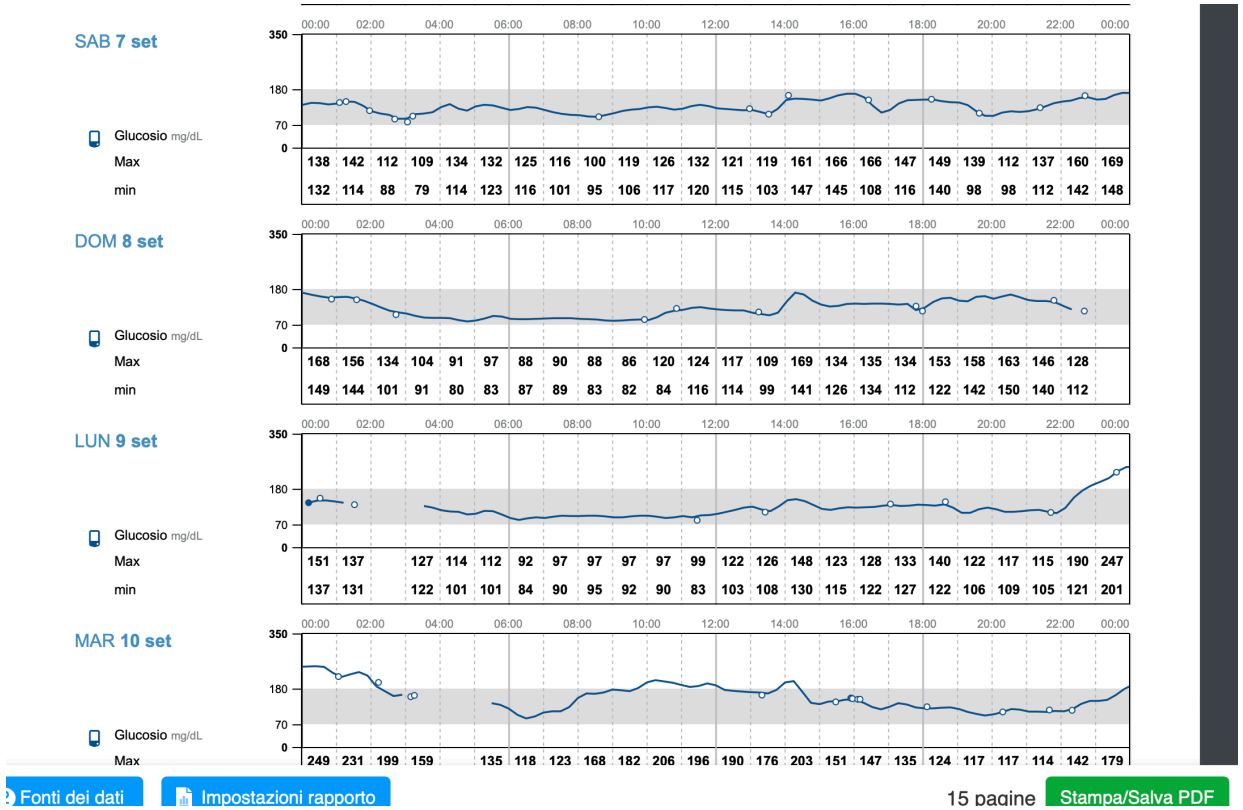




At the time of speaking...

TEMPO NEGLI INTERVALLI





At the time of speaking...

Diabete monogenico: che fare?
Le tre domande del clinico

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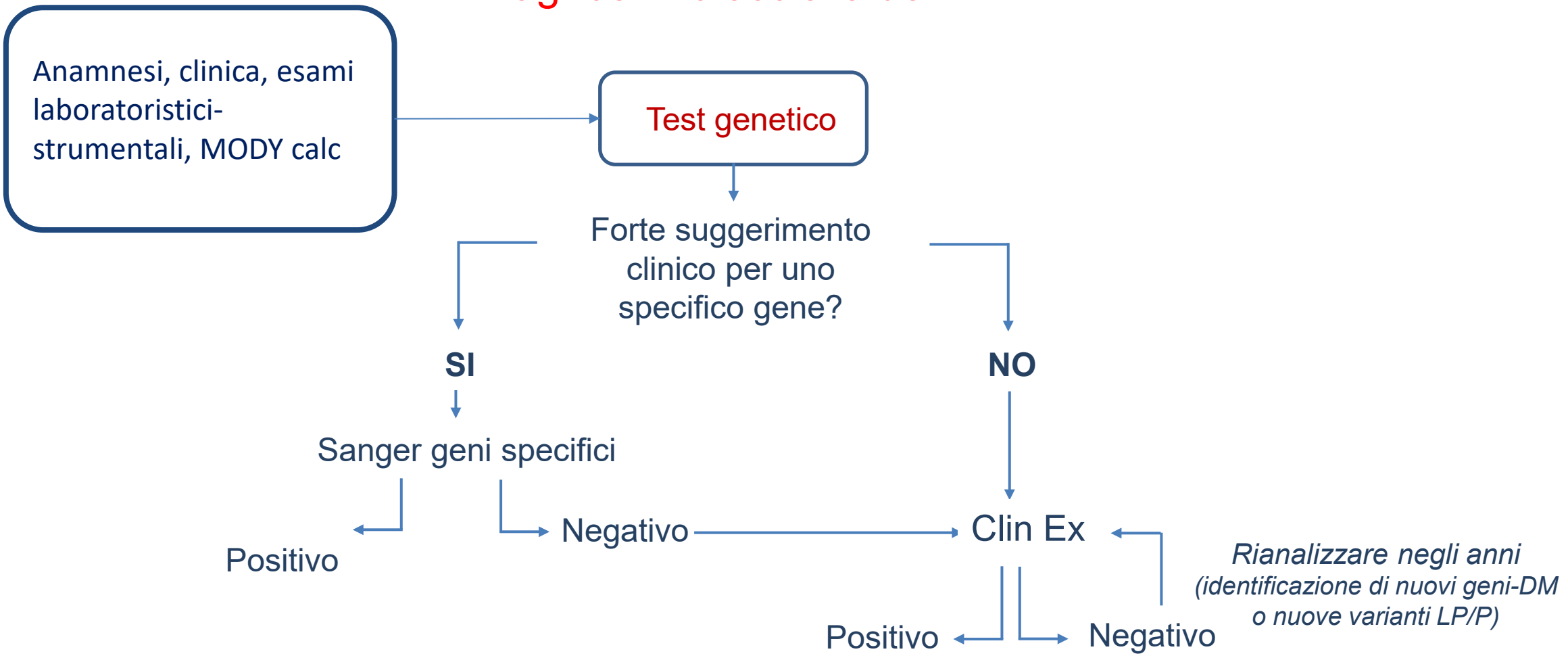
At the time of speaking…

Diagnosi molecolare del DM



At the time of speaking...

https://www.siditalia.it/clinica/linee-guida-societari/send/80-linee-guida-documenti-societari/5557-documento-sid-orientamento-clinico-sul-diabete-monogenico

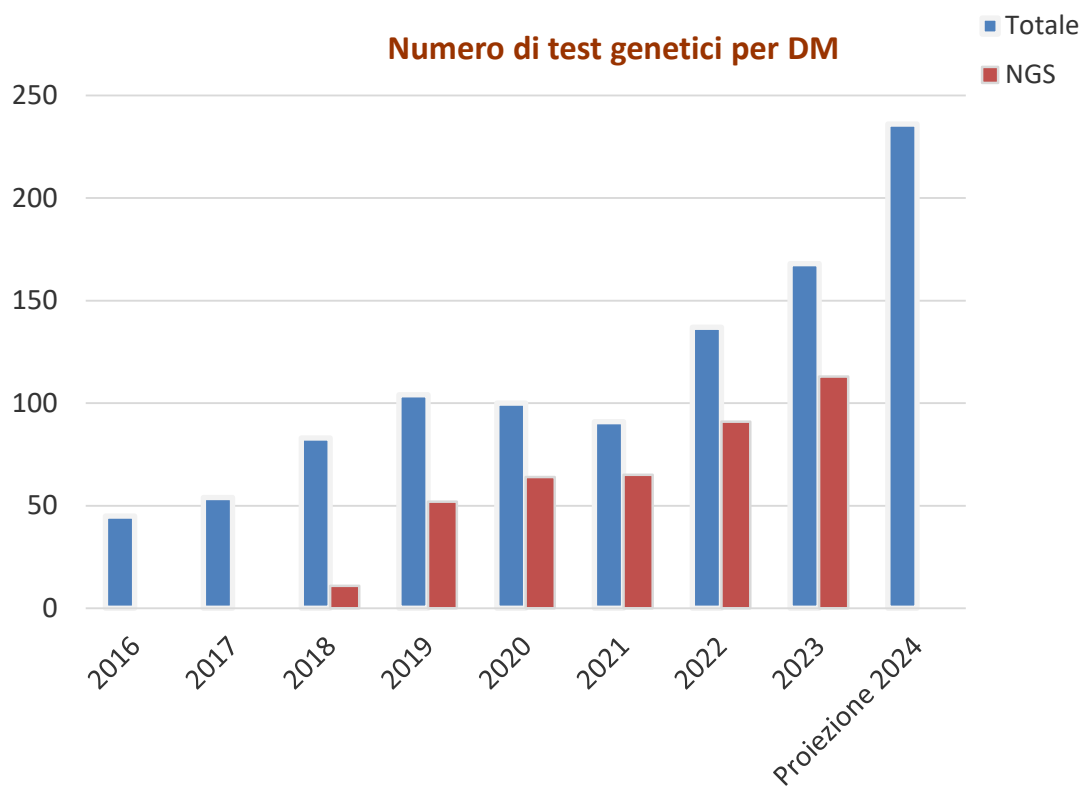
DOCUMENTO DI ORIENTAMENTO CLINICO SUL DM

Regione	Città	Istituzione	Laboratorio e sito Web	Riferimenti	E-mail e recapito telefonico
CALABRIA	Reggio Calabria	Grande Ospedale Metropolitano Bianchi Melacrino Morello	UOSD Genetica Medica https://www.gomrc.it/uosd-genetica-medica/	Dr. Corrado Mammì	geneticamedica@ospedalerc.it 0965 397274
CAMPANIA	Napoli	Università di Napoli	CEINGE https://www.ceinge.unina.it	Dr.ssa Nadia Tinto	nadia.tinto@unina.it 081 3737898
EMILIA ROMAGNA	Bologna	IRCCS Policlinico Sant'Orsola	Laboratorio di Genetica Medica https://www.aosp.bo.it/content/genetica-medica-seri	Dr.ssa Amalia Conti	amalia.conti@aosp.bo.it 051 2143694
LAZIO	Roma	Ospedale Pediatrico Bambino Gesù	Unità Operativa Complessa Laboratorio di Genetica Medica https://www.ospedalebambinogesu.it/laboratorio-di-genetica-medica-94894/	Dr. Antonio Novelli Dr. Rosario Ruta	antonio.novelli@opbg.net rosario.ruta@opbg.net 06 6859 2038
LIGURIA	Genova	IRCCS Istituto G. Gaslini - Ospedale Pediatrico	Laboratorio di Diabetologia U.O.C. Clinica Pediatrica https://www.gaslini.org/reparti/clinica-pediatrica-ed-endocrinologia/	Dr. Alessandro Salina Dr.ssa Concetta Aloi	labdiabetologia@gaslini.org 010 5636406
LOMBARDIA	Milano	IRCCS Ospedale San Raffaele	Servizio di Genetica Molecolare e Citogenetica https://medicinadilaboratorio.hsr.it/genomicadiagnostica.html	Dr.ssa Paola Carrera	laboratorio.genetica@hsr.it citogenetica.lab@hsr.it 02 2643.2316
PIEMONTE	Novara	Azienda Ospedaliero Universitaria Maggiore della Carità	SCDU Biochimica Clinica https://www.maggioreosp.novara.it/attivita-assistenziale/strutture-sanitarie/biochimica-clinica/	Prof. Umberto Dianzani Prof.ssa Mara Giordano	umberto.dianzani@maggioreosp.novara.it mara.giordano@med.uniupo.it 0321 3732087
	Torino	Azienda Ospedaliero Universitaria Città della Salute e della Scienza	SC Immunogenetica e Biologia dei Trapianti https://www.trapiantipiemonte.it/immunogenetica/	Prof.ssa Silvia Deaglio	silvia.deaglio@unito.it consulenzeNGS@trapiantipiemonte.it 011 6336521
PUGLIA	San Giovanni Rotondo (FG)	IRCCS Casa Sollievo della Sofferenza	Laboratorio di Ricerca di Diabetologia e Endocrinologia https://operapadrepio.it/it/ricerca-scientifica/gruppi-di-ricerca/endocrinologia	Prof. Vincenzo Trischitta Dr.ssa Rosa Di Paola Dr.ssa Antonella Marucci Dr.ssa Claudia Menzaghi	vincenzo.trischitta@operapadrepio.it r.dipaola@operapadrepio.it a.marucci@operapadrepio.it c.menzaghi@operapadrepio.it 0882 416277
SARDEGNA	Cagliari	Ospedale Pediatrico Microcitemico A. Cao	SSD Laboratorio di Genetica e Genomica https://www.aobrotzu.it/index.php?xsl=7&s=53877&v=2&c=4698	Dr.ssa Stefania Murro Dr.ssa Arianna Ventrella	stefania.murru@aob.it arianna.ventrella@aslcagliari.it 070 52967932
TOSCANA	Firenze	Azienda Ospedaliero Universitaria Meyer	SOC Genetica Medica https://www.meyer.it/cura-e-assistenza/attivita-sanitarie/212-genetica-medica	Dr.ssa Rosangela Artuso	r.artuso@meyer.it 055 5662942
	Pisa	Azienda Ospedaliero Universitaria Pisana - Ospedale S. Chiara	S.O.D. Genetica Molecolare https://www.ao-pisa.toscana.it/index.php?option=com_content&view=article&id=407:sd-genetica-molecolare&catid=112&Itemid=113	Dr.ssa Antonella Fogli	a.fogli@ao-pisa.toscana.it 050 992907
VENETO	Verona	Azienda Ospedaliera Universitaria Integrata	Laboratorio di diagnostica molecolare, Unità Operativa Complessa di Pediatria B https://www.aovr.veneto.it/dipartimenti-sanitari/-/departments/pediatria-ad-indirizzo-diabetologico-e-malattie-del-metabolismo/informazioni-generali	Dr.ssa Giovanna Contreas	giovanna.contreas@aovr.veneto.it 045 8127662

At the time of speaking…

Diagnosi molecolare del DM

IRCCS Casa Sollievo della Sofferenza



	Numero di test genetici	
anno	**TOT**	**NGS**
2016	45	0
2017	54	0
2018	83	11
2019	104	52
2020	100	64
2021	91	65
2022	117	81
2023	168	113

At the time of speaking...

Pick-up rate of MD testing…too low!

Authors	Sequencing	Pick-up rate (%)
Saint-Martin C et al, 2022	NGS (18 MD-genes)	18
Colclough K et al, 2022	NGS (27 MD-genes)	23
Marucci A et al, 2022	NGS (23 MD-genes)	45
Rapini N et al, 2022	NGS (35 MD-genes)	45

At the time of speaking…

Diabete monogenico: le tre domande del clinico

1. Come sospettarlo
2. Quale test genetico (e dove)
3. Come monitorarlo e trattarlo

At the time of speaking…

nature reviews disease primers https://doi.org/10.1038/s41572-023-00421-w

Primer Check for updates

Monogenic diabetes

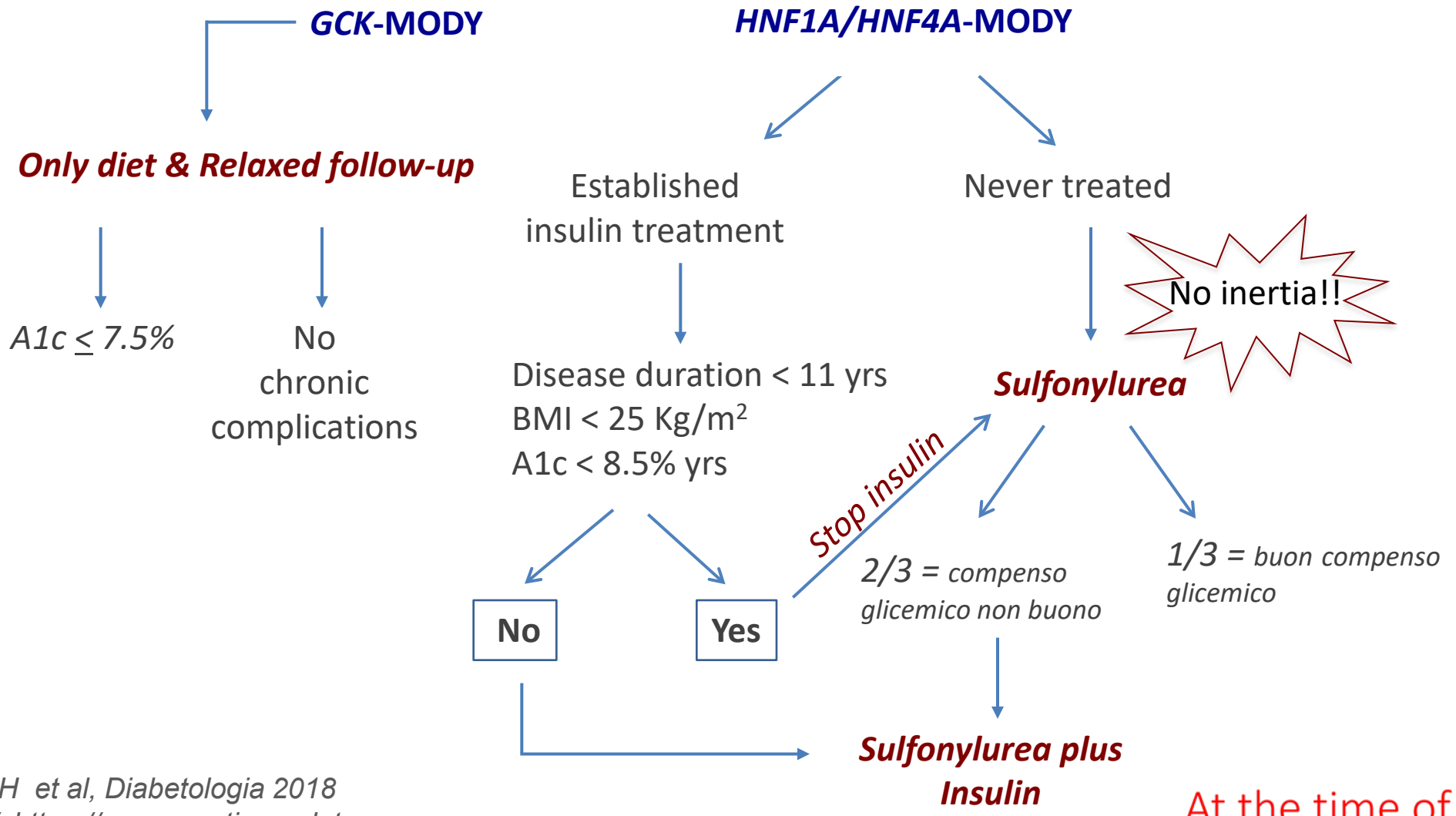
Amélie Bonnefond[1,2,3], Ranjit Unnikrishnan[4], Alessandro Doria[5,6], Martine Vaxillaire[1,2], Rohit N. Kulkarni[5,6], Viswanathan Mohan[4], Vincenzo Trischitta[7,8] & Philippe Froguel[1,2,3]

Table 3 | Precision medicine approaches for management of some forms of monogenic diabetes

Form of diabetes	Precision medicine[a]	
	Treatment	Monitoring[b]
Dominant *GCK*-diabetes	Unnecessary	Relaxed
Dominant *HNF1A*-diabetes	Oral sulfonylureas and GLP1 analogues	Liver
Dominant *HNF4A*-diabetes	Oral sulfonylureas	NA
Dominant *HNF1B*-diabetes	Magnesium supplements 92% cases	Renal, urinary, genital, gonadal and exocrine pancreatic function
Dominant *CEL*-diabetes	NA	Exocrine pancreatic function
Dominant *ABCC8*-diabetes	Oral sulfonylureas	Neurodevelopment
Dominant *KCNJ11*-diabetes	Oral sulfonylureas	Neurodevelopment
Dominant *GATA4*-diabetes	NA	Cardiac function
Dominant *GATA6*-diabetes	NA	Cardiac function
m.3243A>G-diabetes	NA	Hearing and cardiac function

At the time of speaking...

Management of the most common MODY subtypes: a good example of precision medicine



Sheperd MH et al, Diabetologia 2018
Trischitta V, https://www.practiceupdate.com

At the time of speaking...

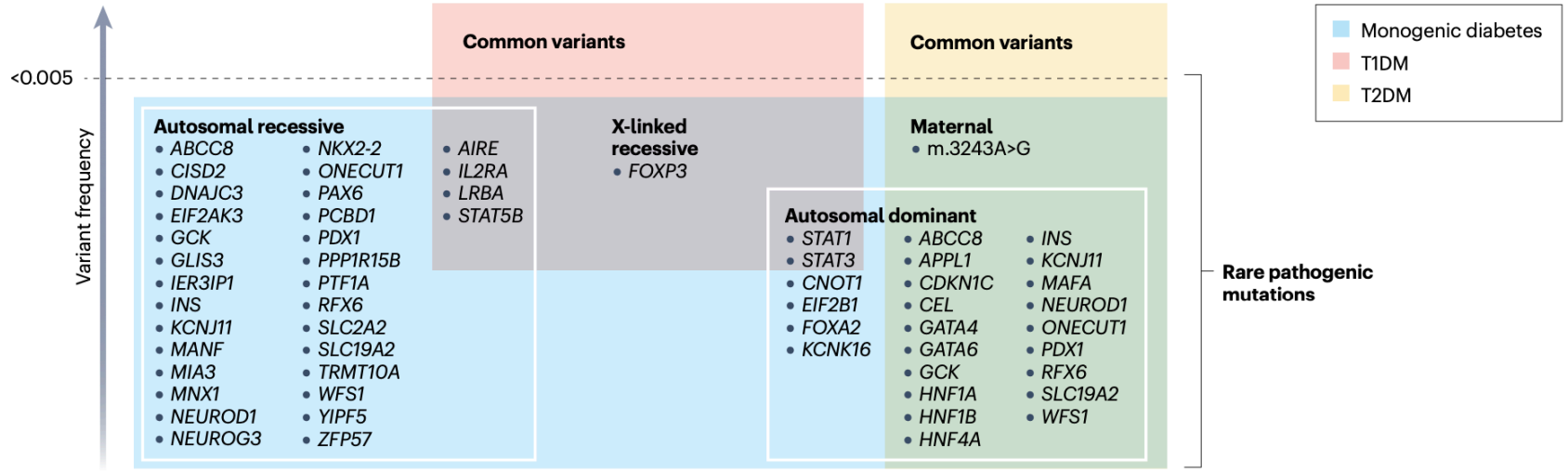
Fermo restando che….

Diritto alla diagnosi

Maturity-Onset Diabetes of the Young (MODY): Making the Right Diagnosis to Optimize Treatment.

Can J Diabetes. 2016 Oct;40(5):449-454

IL DIABETE O I *DIABETI*?



Nature Reviews Disease Primers | (2023) 9:12

At the time of speaking…

Take Home ~~messages~~ words

EARLY ONSET

OVERLAP

DIAGNOSI

TERAPIA

ETEROGENEITA’

FOLLOW UP

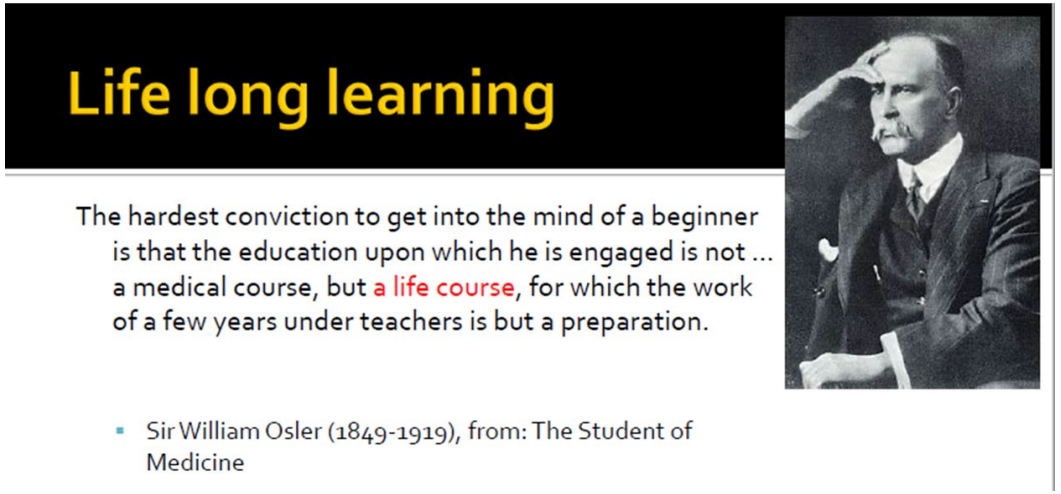
PREVENZIONE

PRECISIONE

CONOSCENZA

«There is no dark side of the moon, really. Matter of fact it's all dark. The only thing that makes it look alight is the sun»

Eclipse, 1973



THE DARK SIDE OF DIABETES

MILANO
FABBRICA DEL VAPORE
20 SETTEMBRE 2024

SID
Società Italiana di Diabetologia
1964-2024