CONGRESSO REGIONALE SID-AMD | Calabria 2024

"L'approfondimento genetico"

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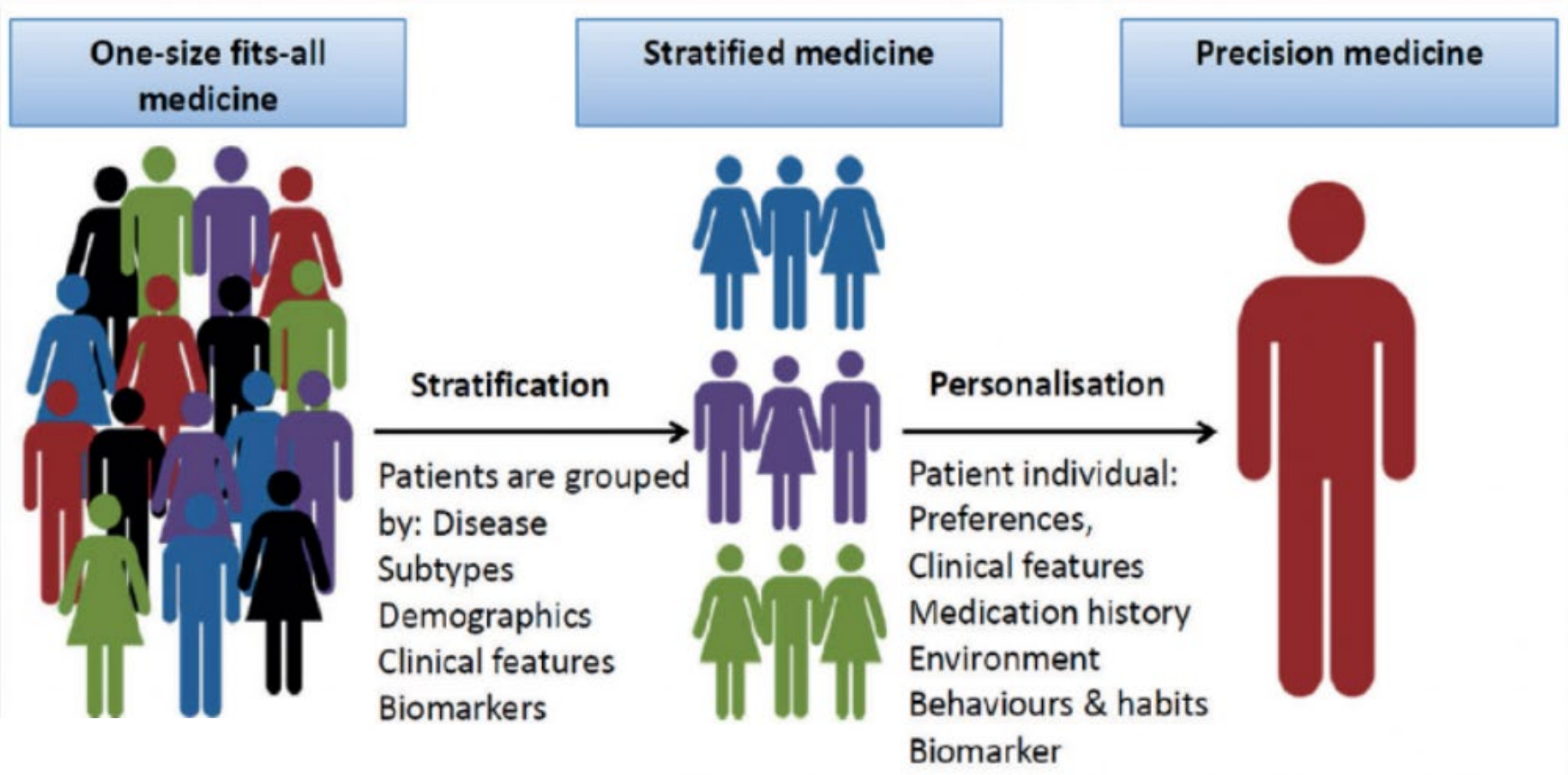
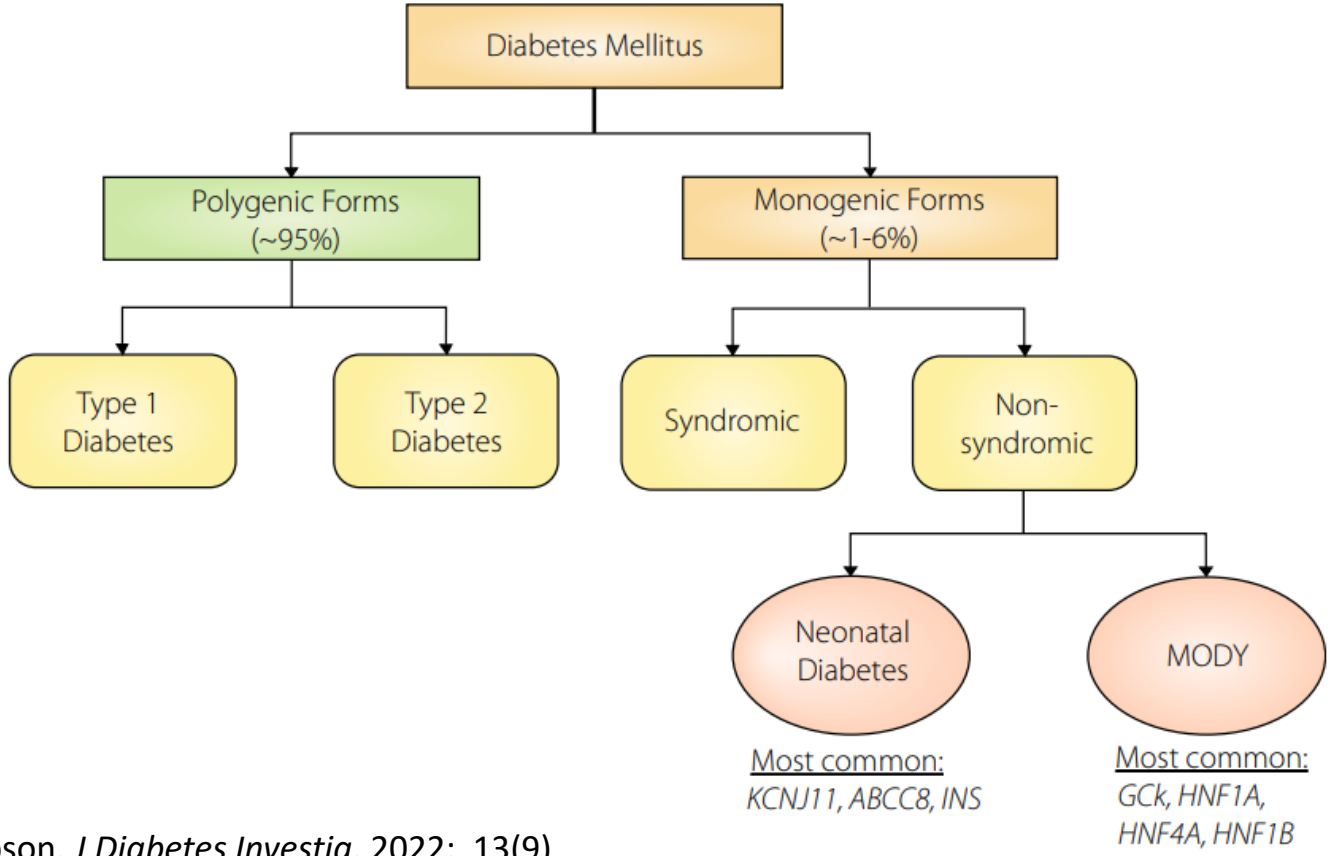
Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient or subpopulation.



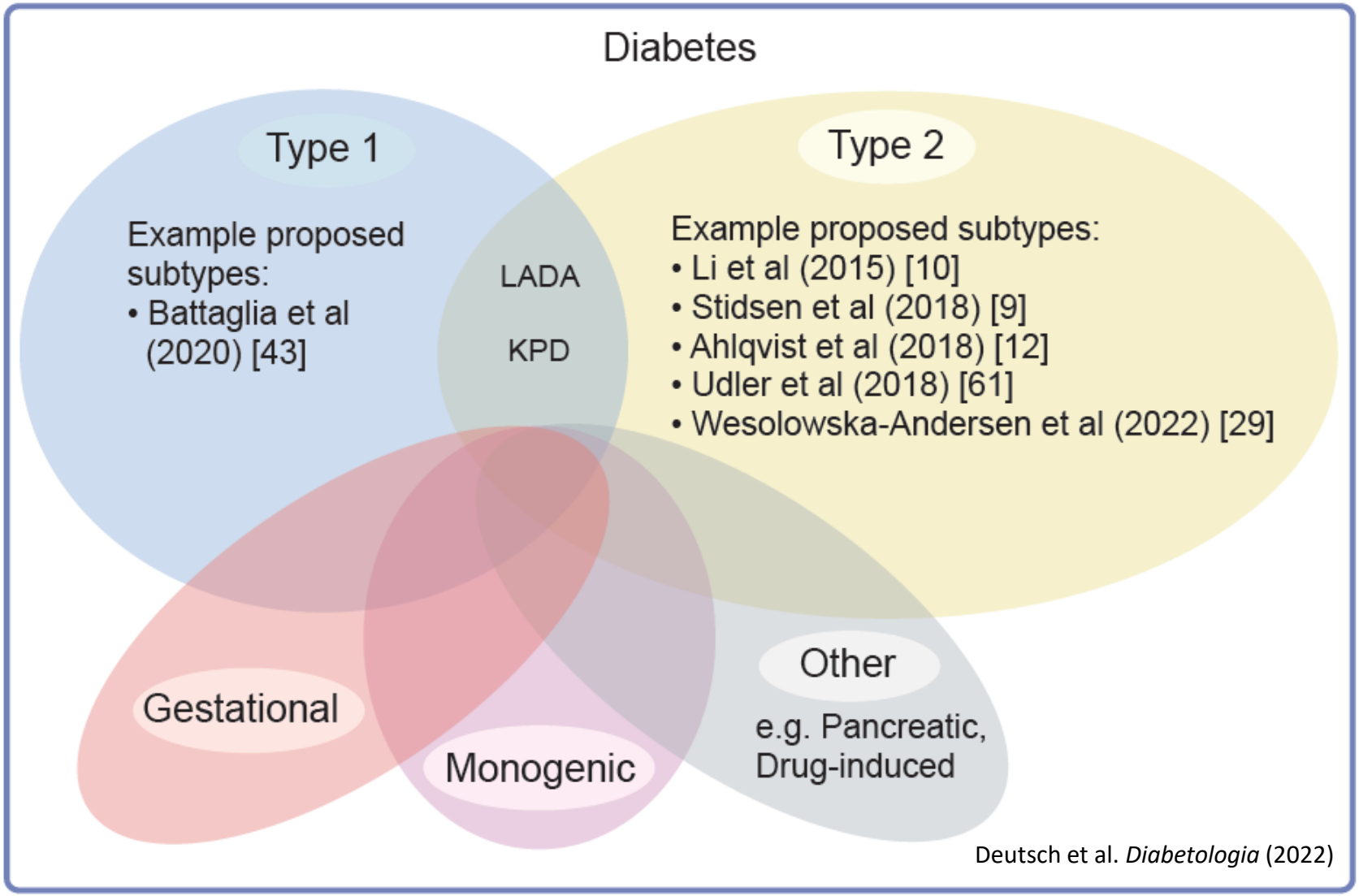
Precision diabetes is when a precision medicine approach is used to improve treatment of patients with diabetes.

Monogenic diabetes of the young in relation to different forms of diabetes mellitus

Monogenic diabetes is a heterogeneous group of disorders that includes various clinical conditions associated with hyperglycaemia, which are mostly due to impaired function or altered development of the islets of Langerhans (including pancreatic β-cells, which secrete insulin), with only rare impairment of pancreatic exocrine function, and are linked to a single, pathogenic, genetic alteration.



Tosur and Philipson. *J Diabetes Investig*. 2022; 13(9)



It has been estimated that about 50–80% of patients with MODY are either undiagnosed or misdiagnosed as type 1 or type 2 diabetes and might be inadequately treated.

Caratteristiche per diagnosi differenziale tra il MODY e le forme più comuni di diabete

	MODY	**Diabete tipo 1**	**Diabete tipo 2**
Età all'insorgenza nelle prime 3 decadi di vita	Molto frequente	Molto frequente	Infrequente
Storia familiare	Molto frequente	Infrequente	Frequente
Cheto-acidosi	Molto infrequente	Frequente	Molto infrequente
Prevalenza sovrappeso/obesità	Simile a quella della popolazione generale	Simile a quella della popolazione generale	Molto frequente
autoAb pancreatici	Assenti	Presenti	Assenti
C-peptide sierico	> 0.6 ng/ml	< 0.6 ng/ml	>> 0.6 ng/ml
Dislipidemia aterogena (TG e HDL-C)	Infrequente	Infrequente	Frequente
Caratteristiche cliniche extra-pancreatiche	Possibili	Assenti	Assenti

Disease-Genes involved in monogenic diabetes

MODY

Gene	Inheritance mode	Genomic location
GCK	Autosomal dominant or recessive	7p13
HNF1A	Autosomal dominant	12q24.31
HNF4A	Autosomal dominant	20q13.12
PDX1	Autosomal dominant	13q12.2
HNF1B	Autosomal dominant	17q12
NEUROD1	Autosomal dominant	2q31.3
CEL	Autosomal dominant	9q34.13
INS	Autosomal dominant	11p15.5
ABCC8	Autosomal dominant	11p15.1
KCNJ11	Autosomal dominant	11p15.1
GATA6	Autosomal dominant	18q11.2
WFS1	Autosomal dominant or recessive	4p16.1
TRMT10A	Autosomal recessive	4q23
PCBD1	Autosomal recessive	10q22.1
GATA4	Autosomal dominant	8p23.1
APPL1	Autosomal dominant	3p14.3
RFX6	Autosomal dominant	6q22.1
MAFA	Autosomal dominant	8q24.3
SLC19A2	Autosomal dominant or recessive	1q24.2
ONECUT1	Autosomal dominant	15q21.3
m.3243A>G	Maternal	Mitochondria
KCNK16	Autosomal dominant	6p21.2

Neonatal diabetes (without other atypical features)

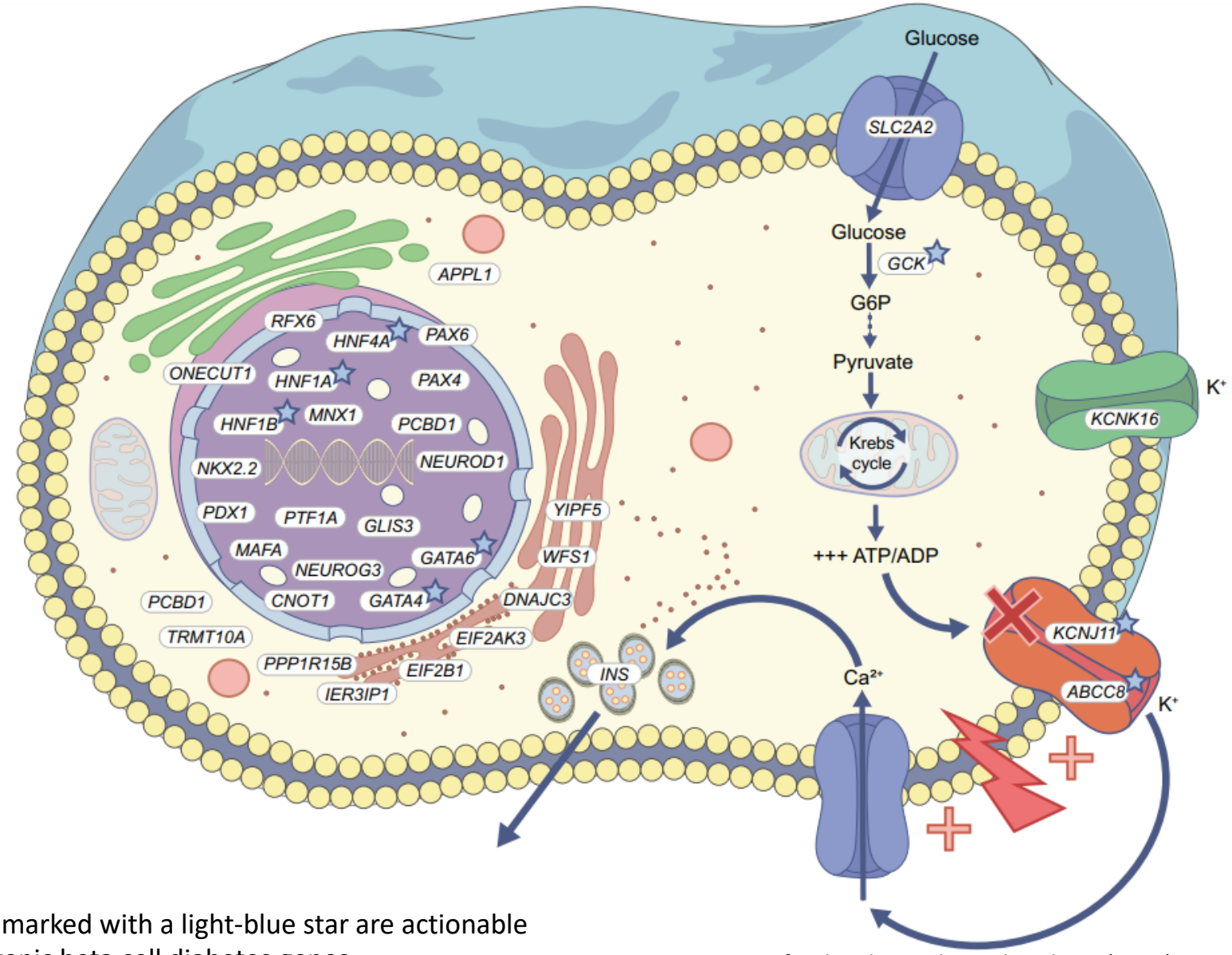
Gene	Inheritance mode	Genomic location
HNF1B	Autosomal dominant	17q12
GCK	Autosomal recessive	7p13
KCNJ11	Autosomal dominant or recessive	11p15.1
ABCC8	Autosomal dominant or recessive	11p15.1
INS	Autosomal dominant or recessive	11p15.5
GATA6	Autosomal dominant	18q11.2
GATA4	Autosomal dominant	8p23.1

Syndromic, including neonatal and early-onset diabetes

Gene	Inheritance mode	Genomic location
m.3243A>G	Maternal	Mitochondria
HNF1B	Autosomal dominant	17q12
AIRE[a]	Autosomal dominant or recessive	21q22.3
PDX1	Autosomal recessive	13q12.2
SLC2A2	Autosomal recessive	3q26.2
WFS1	Autosomal dominant or recessive	4p16.1
SLC19A2	Autosomal recessive	1q24.2
EIF2AK3	Autosomal recessive	2p11.2
FOXP3[a]	X-linked recessive	Xp11.23
PTF1A	Autosomal recessive	10p12.2
GLIS3	Autosomal recessive	9p24.2
CEL	Autosomal dominant	9q34.13
PAX6	Autosomal recessive	11p13
STAT5B[a]	Autosomal recessive	17q21.2
CISD2	Autosomal recessive	4q24
RFX6	Autosomal recessive	6q22.1
NEUROD1	Autosomal recessive	2q31.3
NEUROG3	Autosomal recessive	10q22.1
IER3IP1	Autosomal recessive	18q21.1
ZFP57	Autosomal recessive	6p22.1
MNX1	Autosomal recessive	7q36.3
GATA6	Autosomal dominant	18q11.2
DNAJC3	Autosomal recessive	13q32.1
STAT3[a]	Autosomal dominant	17q21.2
TRMT10A	Autosomal recessive	4q23
GATA4	Autosomal dominant	8p23.1
NKX2-2	Autosomal recessive	20p11.22
CDKN1C	Autosomal dominant	11p15.4
PPP1R15B	Autosomal recessive	1q32.1
LRBA[a]	Autosomal recessive	4q31.3
IL2RA[a]	Autosomal recessive	10p15.1
FOXA2	Autosomal dominant	20p11.21
CNOT1	Autosomal dominant	16q21
YIPF5	Autosomal recessive	5q31.3
EIF2B1	Autosomal dominant	12q24.31
MIA3	Autosomal recessive	1q41
STAT1[a]	Autosomal dominant	2q32.2
MANF	Autosomal recessive	3p21.2
ONECUT1	Autosomal recessive	15q21.3

Bonnefond et al. *Nature Reviews Disease Primers* (2023) 9:12

Genes involved in monogenic diabetes encode proteins that play a key role in pancreatic β-cells



Genes marked with a light-blue star are actionable monogenic beta cell diabetes genes.

Bonnefond and Semple. Diabetologia (2022) 65:1782–1795

communications medicine

ARTICLE

https://doi.org/10.1038/s43856-023-00369-8 OPEN

The use of precision diagnostics for monogenic diabetes: a systematic review and expert opinion

Rinki Murphy[1,2,208]✉, Kevin Colclough[3,208], Toni I. Pollin[4,208], Jennifer M. Ikle[5,6], Pernille Svalastoga[7,8], Kristin A. Maloney[4], Cécile Saint-Martin[9], Janne Molnes[8,10], ADA/EASD PMDI*, Shivani Misra[11,12], Ingvild Aukrust[8,10], Elisa de Franco[13], Sarah E. Flanagan[13], Pål R. Njølstad[7,8], Liana K. Billings[14,15,209], Katharine R. Owen[16,17,209] & Anna L. Gloyn[5,6,18,209]✉

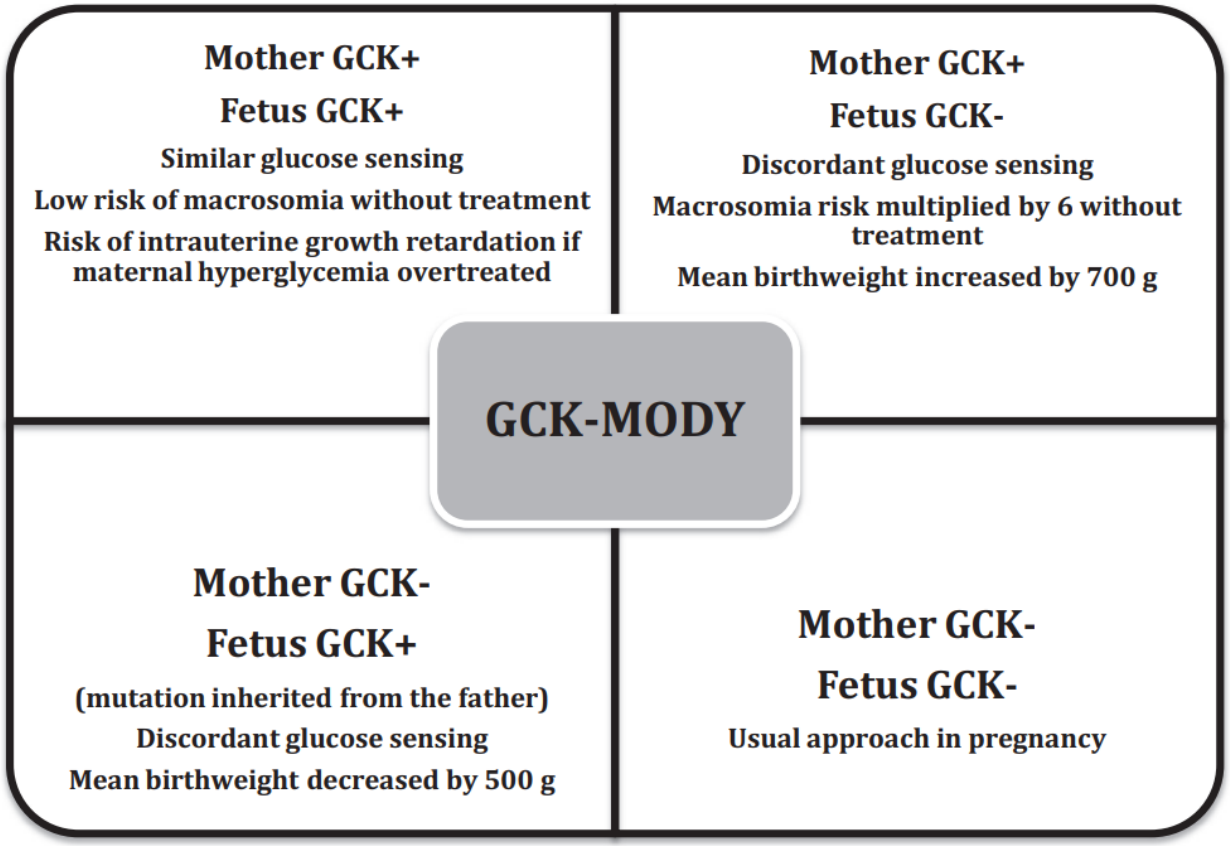
Table 3 Recommendations based on the synthesis of evidence for who to test for monogenic diabetes.

Recommendation	Who to test for monogenic diabetes	Grade
1	All patients diagnosed with diabetes before the age of 6 months should be tested for monogenic forms of neonatal diabetes using the large-gene panel.	A
	All patients diagnosed between 6 and 12 months should be tested for monogenic forms of neonatal diabetes using the large-gene panel. No demonstrable yield of monogenic etiology to support reflexive genetic testing patients diagnosed with diabetes between 12-24 months.	B
2	Women with gestational diabetes and fasting glucose above 5.5 mmol/L without obesity* should be tested for GCK etiology.	B
3	Those with persisting, mild hyperglycemia (HbA1c 38–62 mmol/mol, or fasting glucose 5.5–7.8 mmol/L) at any age, in the absence of obesity* should be tested for GCK etiology.	A
4	People without obesity under the age of 30 years who are either autoantibody negative and/or have retained C-peptide levels should be tested for monogenic diabetes using a large-gene panel	A

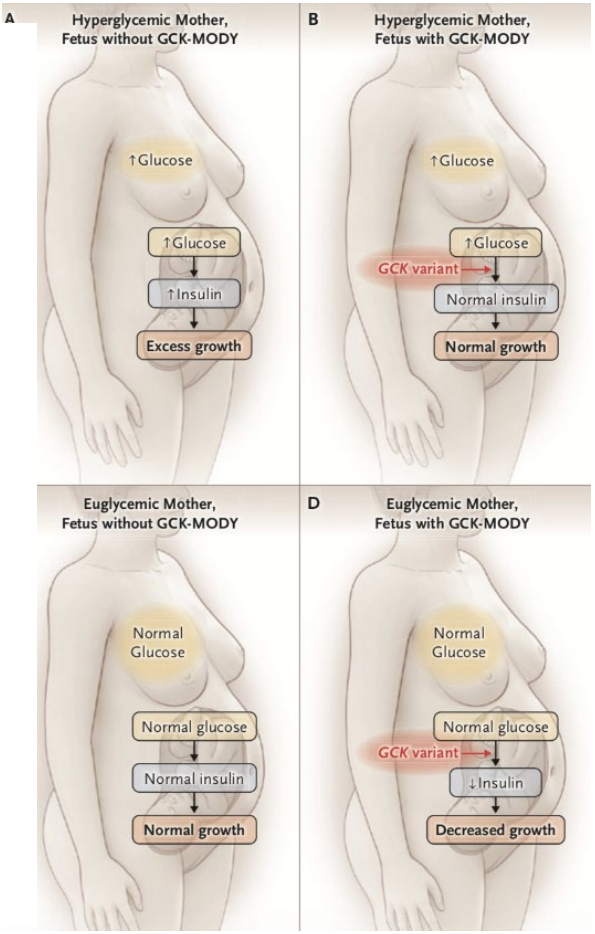
*by selecting those who are of normal weight or underweight (rather than those who are non-obese) to offer genetic testing to, increases the specificity but reduces the sensitivity for detecting GCK and may be considered a less costly approach.

Monogenic disorders account for 1–2% of all cases of diabetes diagnosed during pregnancy, with GCK-MODY being found in one in three patients with a fasting glucose ≥100 mg/dL (5.5 mmol/L) and normal weight (BMI,25 kg/m2).

It is important to correctly identify patients with GCK-MODY because its clinical course and management differ substantially from those of other types of diabetes in pregnancy.

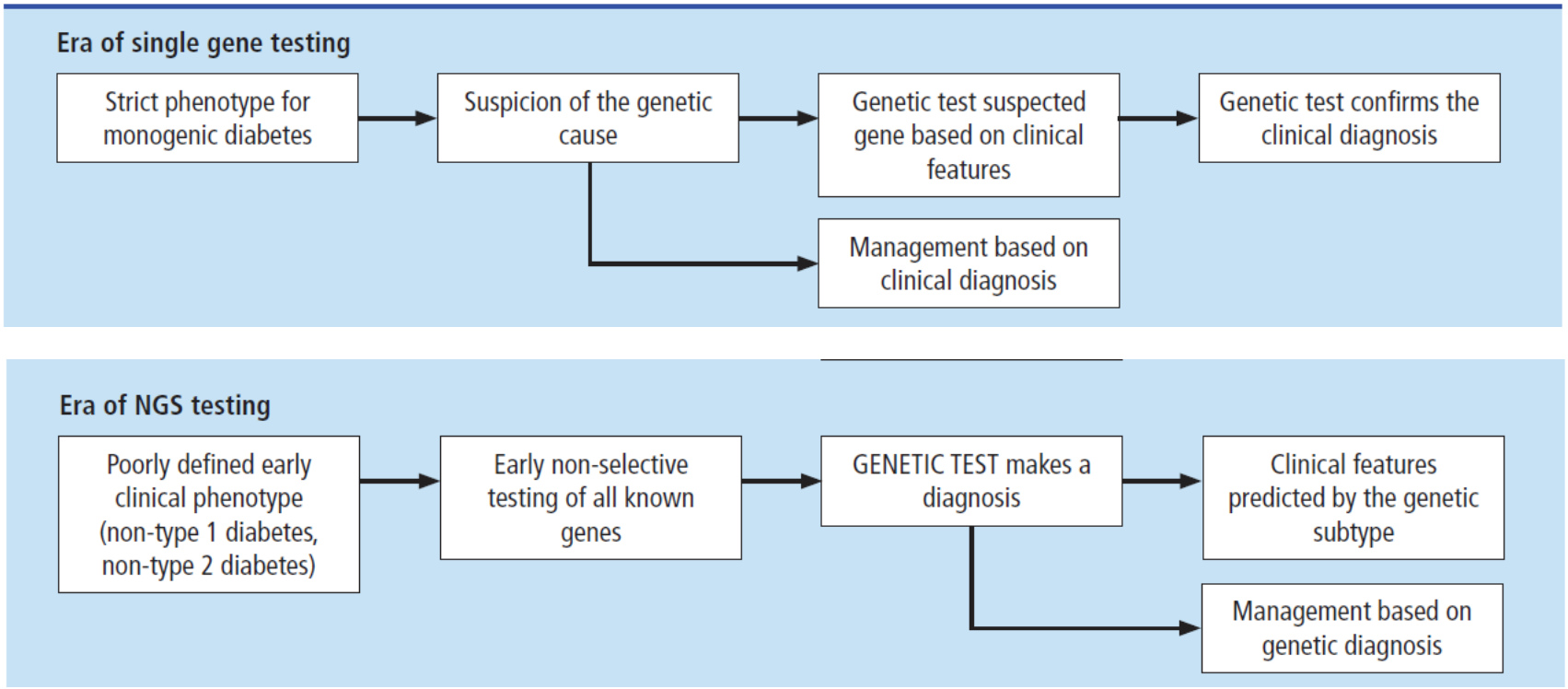


Lachance et al. Canadian Journal of Diabetes 2016



Udler et al. N Engl J Med. 2020

Paradigm shift in monogenic diabetes diagnosis



Patel K et al. PRACTICAL DIABETES. 2022; Vol. 39 No. 4

With the advent of next generation sequencing (NGS) technology, all genes can be tested in a single assay. This non-selective approach requires only enough phenotypic information to exclude common polygenic diabetes.

The genetic test makes the diagnosis which then predicts the expected clinical outcome and determines the appropriate management

Table 1—Clinical implications of some common and important causes of monogenic diabetes

Gene	Inheritance/phenotypes	Disease mechanism/special features	Importance of genetic diagnosis
GCK	AD: *GCK*-MODY (common) AR: *GCK*-NDM (very rare)	Reduced function of glucokinase enzyme raises set point for insulin secretion that is otherwise normal; high population prevalence of causal variants (~1 in 1,000)	***No treatment needed*** for most patients (except possibly during pregnancy)
HNF1A	AD: *HNF1A*-MODY (common)	LOF of β-cell transcription factor; glucosuria is common; risk for benign hepatic adenomas (rarely can become large and/or complicated)	Excellent glycemic control usually possible with low-dose oral sulfonylureas
HNF4A	AD: *HNF4A*-MODY (uncommon)	LOF of β-cell transcription factor; carriers may have history of large birth weights and/or hyperinsulinemic hypoglycemia	Often responsive to low-dose oral sulfonylureas
HNF1B	AD: *HNF1B*-MODY (uncommon)	LOF of pancreatic/renal transcription factor; renal cysts/genitourinary malformations (may be more penetrant than diabetes); hypomagnesemia; exocrine pancreatic insufficiency, altered liver function tests, hyperuricemia, developmental delay (as part of chromosome 17q deletion syndrome)	Optimal treatment for diabetes not well established; genetic diagnosis will inform monitoring and management of other features
ABCC8	AD/AR: *ABCC8*-NDM (common) *ABCC8*-MODY (rare)	Activating missense mutations in β-cell K_{ATP} channel SUR1 subunit impair glucose-stimulated insulin secretion; NDM may have a spectrum of neurodevelopmental dysfunction	Usually responds to high-dose oral sulfonylureas; genetic diagnosis facilitates monitoring/intervention for neurodevelopmental problems
KCNJ11	AD: *KCNJ11*-NDM (common) *KCNJ11*-MODY (rare)	Activating missense mutations in β-cell K_{ATP} channel Kir6.2 subunit impair glucose-stimulated insulin secretion; NDM often have a spectrum of neurodevelopmental dysfunction	Usually responds to high-dose oral sulfonylureas; genetic diagnosis facilitates monitoring/intervention for neurodevelopmental problems
6q24 (imprinted locus)	Most common cause of transient NDM	Overexpression of maternally imprinted 6q24 genes causes impairment of β-cell development and function; after remission of NDM within first year of life, diabetes will often recur in adolescence or adulthood	Diabetes recurring later in life is often responsive to noninsulin therapies
INS	AD/AR: *INS*-NDM (common) AD: *INS*-MODY (rare)	Missense mutations cause insulin protein misfolding and progressive β-cell death (other mechanisms occur more rarely)	Early intensive insulin treatment; future treatments may feasibly target molecular mechanism(s)

AD, autosomal dominant; AR, autosomal recessive; Kir6.2, inward rectifier potassium channel 6.2; SUR, sulfonylurea receptor.

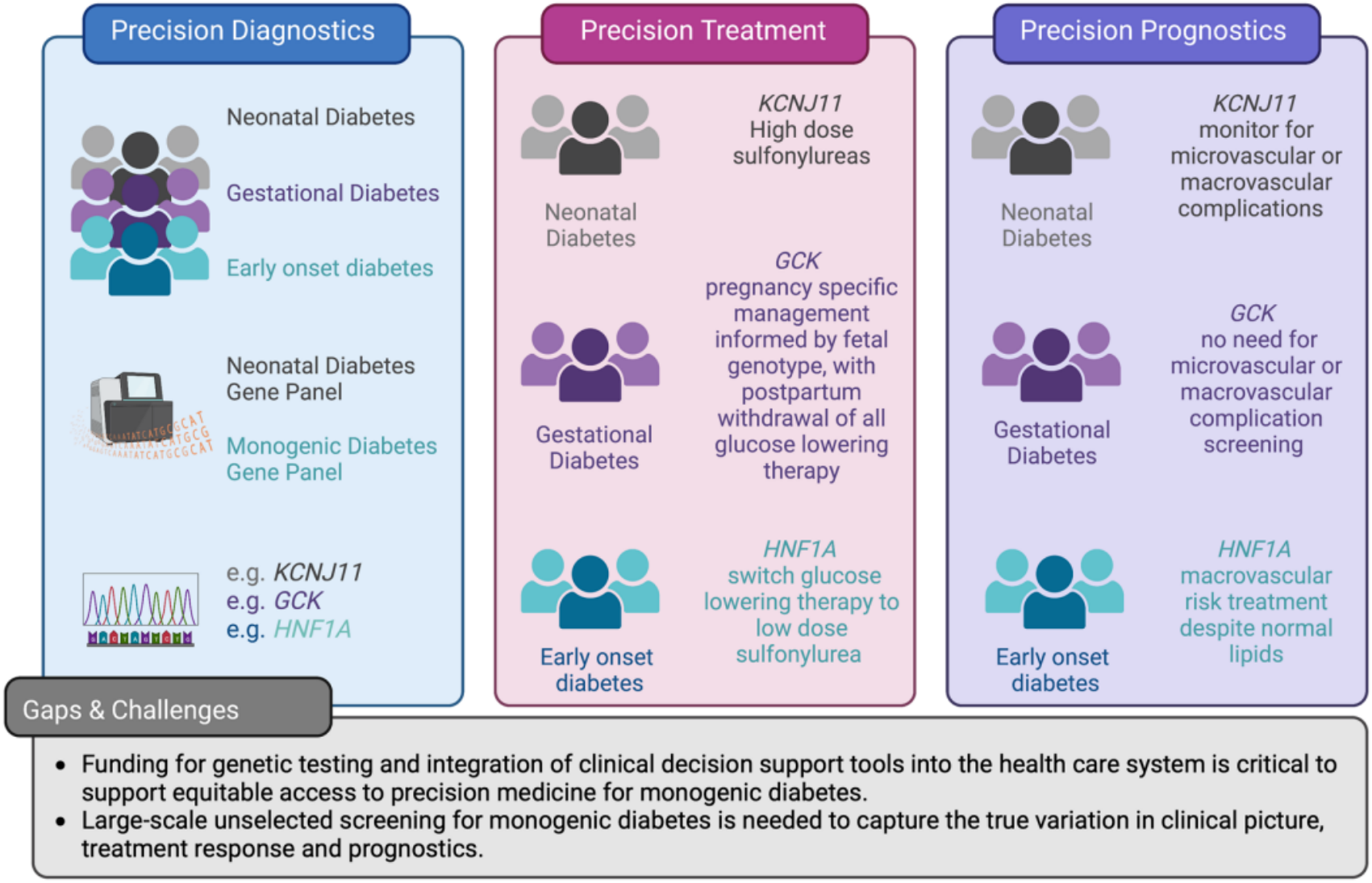
NO treatment

Low SU treatment

High SU treatment

NO insulin treatment

insulin treatment



Murphy R. et al. Commun Med (Lond). 2023; 3(1):136.

CONCLUSIONI

❖ Il diabete monogenico è una realtà clinica che a tutt'oggi NON viene adeguatamente attenzionata e diagnosticata pur rappresentando uno dei pochi ambiti in cui la medicina di precisione può essere applicata con successo.

❖ Il Next generation Sequencing (WES, WGS) fornisce uno strumento potente sia per la conferma diagnostica (genetic testing) che per la ricerca (identificazione di nuovi geni-malattia) per il diabete monogenico.

❖ L'offerta del test genetico da parte del laboratorio deve essere fatta tenendo sempre in considerazione lo stato dell'arte relativo ai geni-malattia da includere e la reale validità diagnostica del risultato che viene comunicato al paziente.

❖ Il test genetico dovrebbe essere effettuato esclusivamente in laboratori con comprovata esperienza in ambito diabetologico ed il risultato dovrebbe essere sempre discusso nell'ambito della consulenza genetica.

❖ Il Dialogo virtuoso fra diagnostica e Ricerca va incentivato e perseguito al fine di Incrementare la conoscenza nell'ambito del diabete su base genetica e consentire un ampliamento dell'offerta diagnostica che risulti di reale utilità al paziente.

Thank you for your attention