Recent advances in monogenic diabetes

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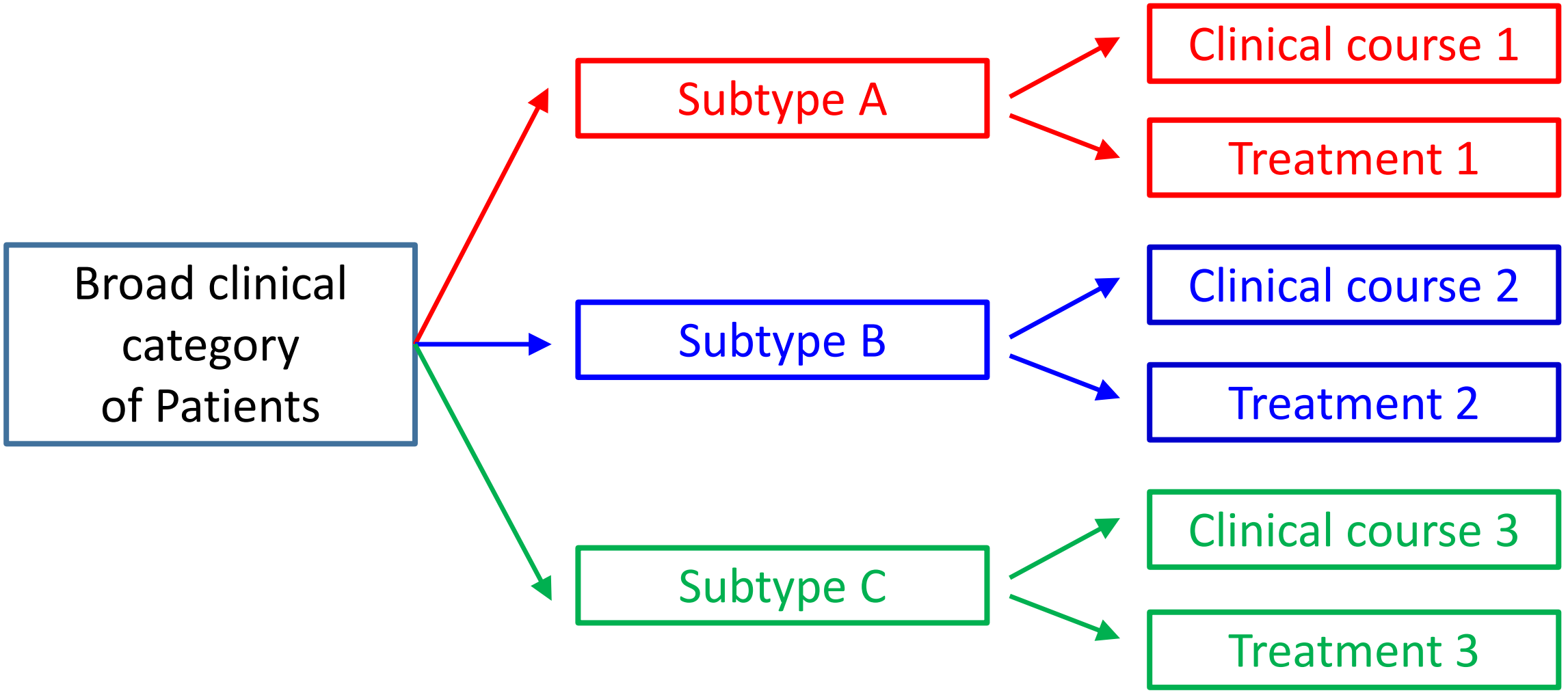
UNIVERSITY OF EXETER | MEDICAL SCHOOL

One approach to precision medicine is correctly defining and diagnosing subtypes of diabetes to improve clinical care



Monogenic diabetes are some of the best examples of Precision Medicine

MODY

Defining subtypes
Improves Clinical Care

Neonatal diabetes

Defining subtypes
Improves Clinical Care

Severe Insulin resistance

Defining subtypes
Improves Clinical Care

Maturity-onset diabetes of the young (MODY): was diagnosed by clinical criteria

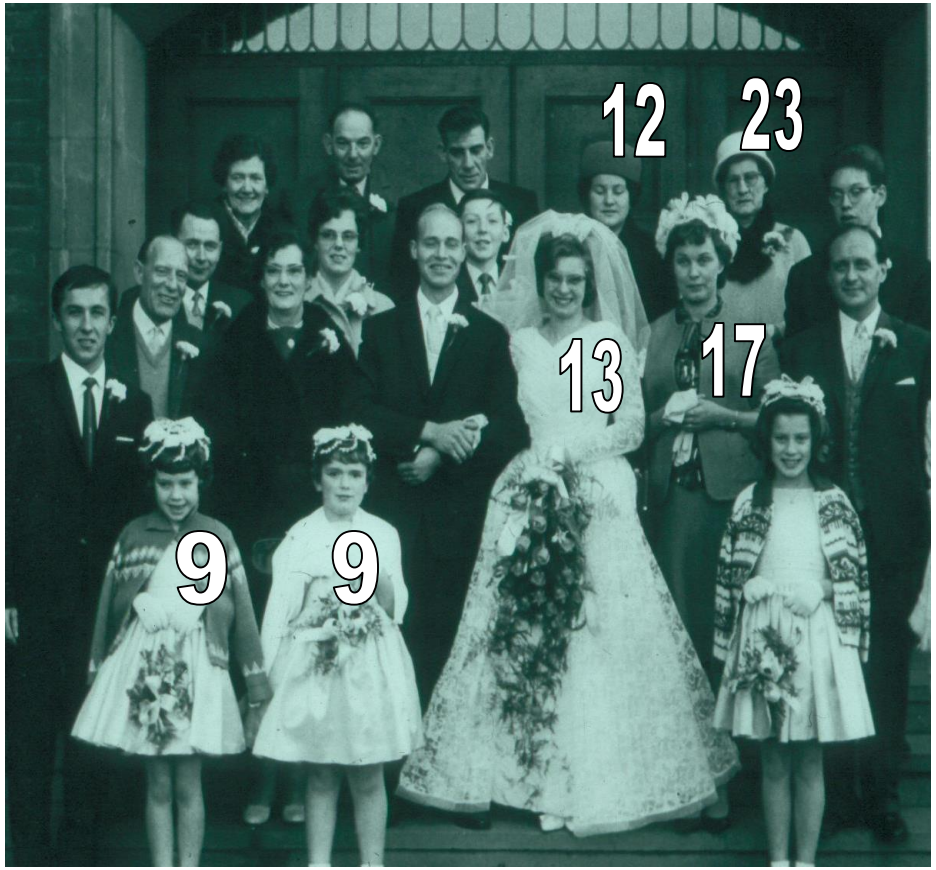
Early diagnosis of diabetes (<25)

Non insulin-dependent diabetes

Autosomal dominant inheritance

Caused by a single gene defect

Defect in beta-cell function

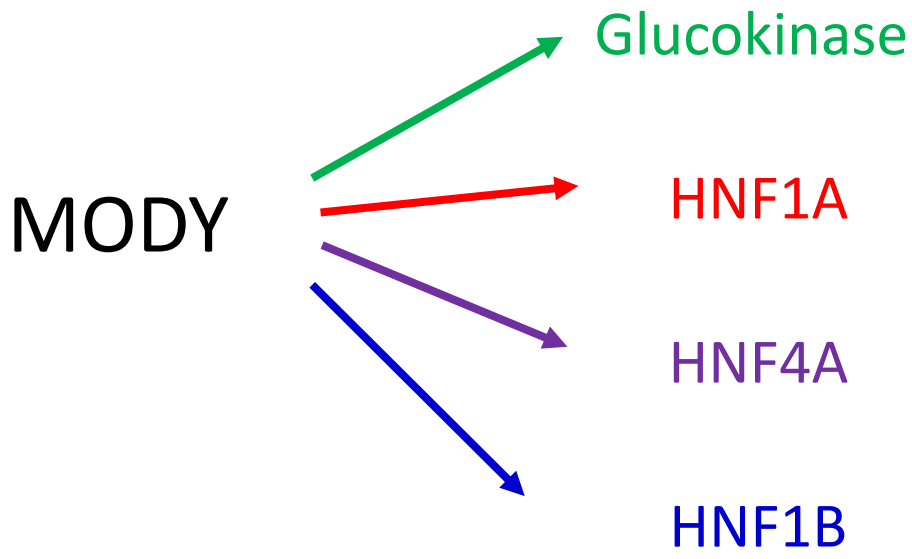


Tattersall (QJM 1974)

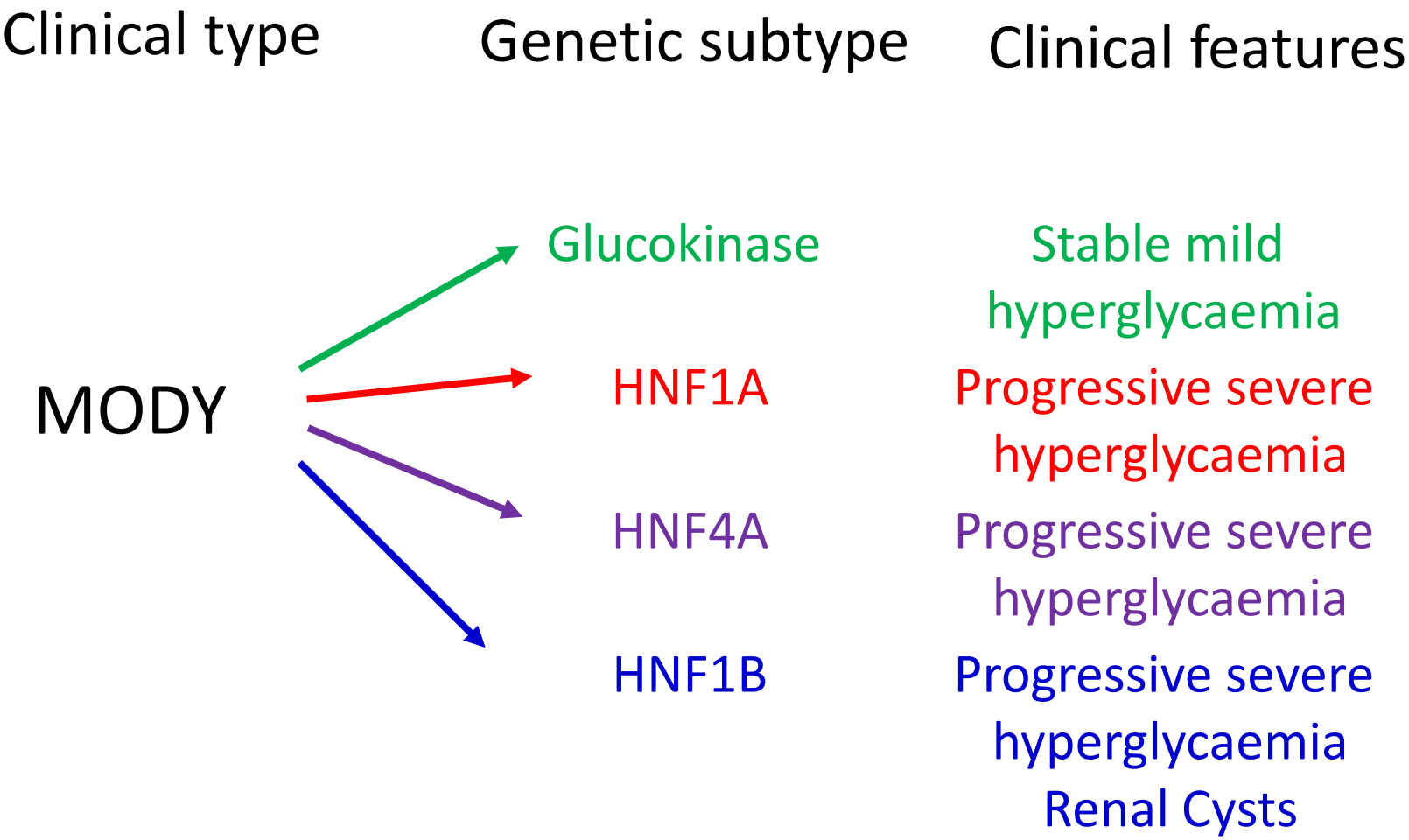
Defining the genetic causes of MODY defined new subtypes

Clinical type

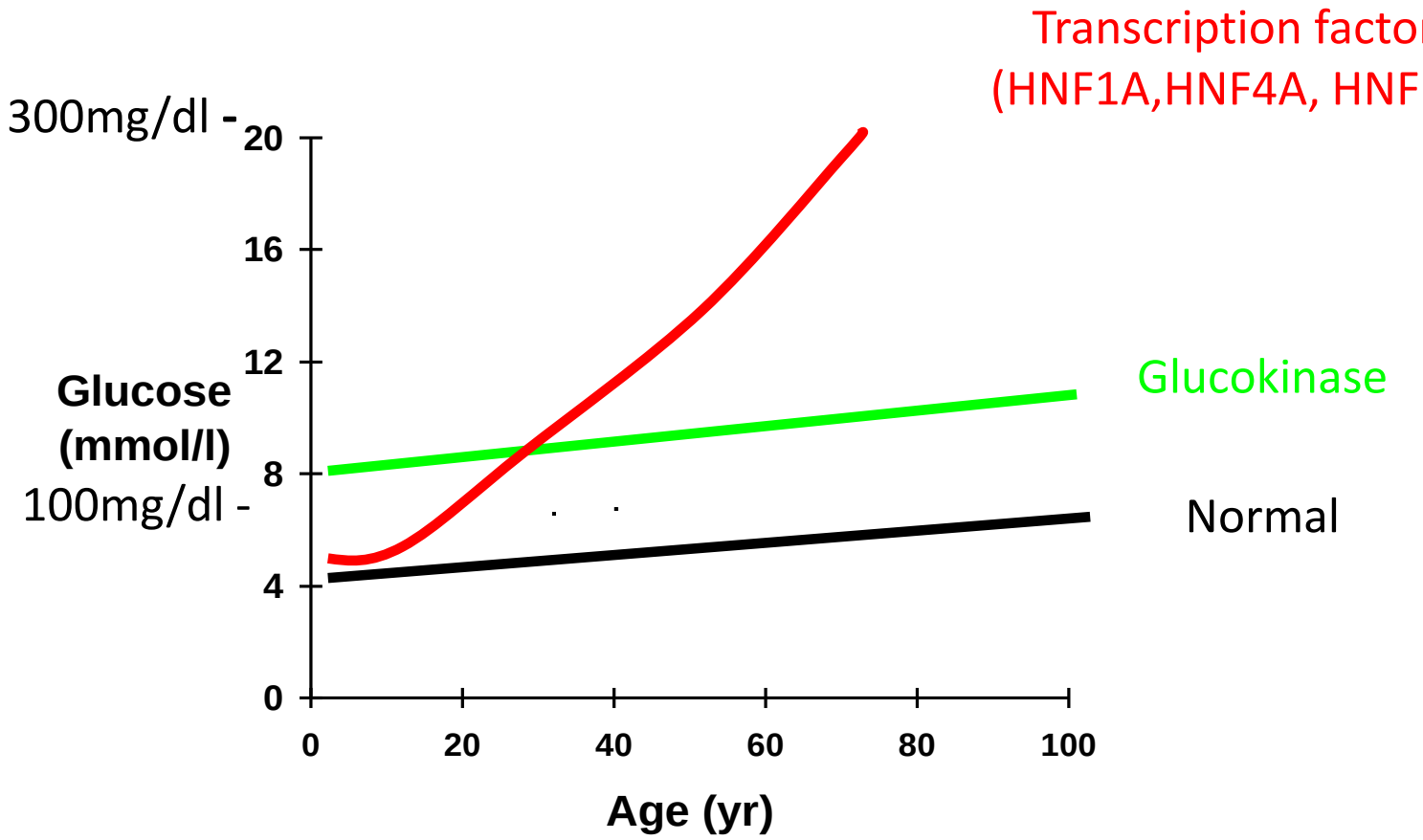
Genetic subtype



Defining the genetic causes of MODY defined new subtypes that differed in clinical course

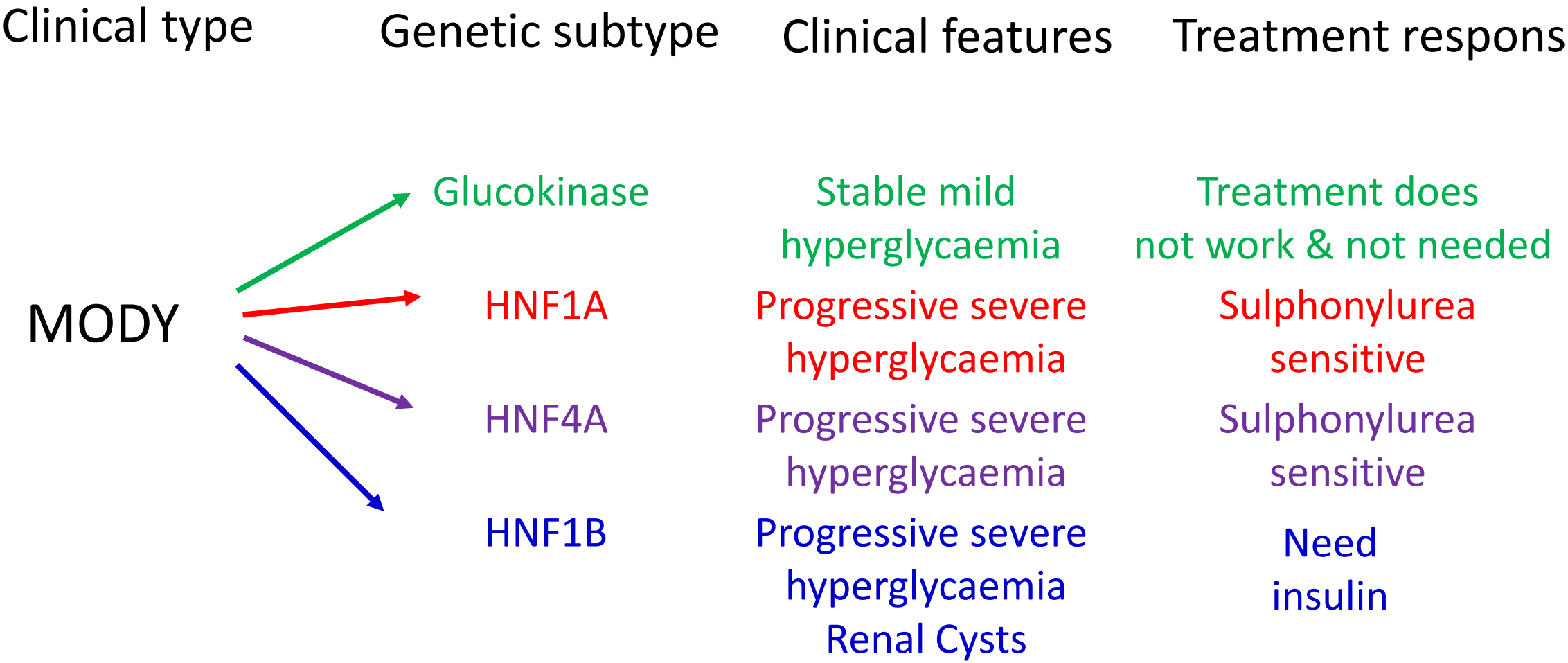


Heterogeneity of glycaemia progression in different genetic subtypes



Stride & Hattersley Annals of Medicine 2002

Defining the genetic causes of MODY defined new subtypes that differed in clinical course and treatment response



MODY is 1-3% of paediatric and adult diabetes

In Paediatric (<20 years) National or multiple clinics prevalence 1-3%

Large scale studies based on sequencing at least Islet AA –ve (+/- CP positive)

Prevalence	Total	Population
0.7%	3382	Norway Johansson Diabetologia 2017
1.2%	3850	USA multi-ethnic SEARCH - Pihoker JCEM 2013
1.3%	3966	Sweden BDD Carlson Diabetes Care 2020
1.6%	3618	Italy 15 Paediatric clinics- diabetes only, Delvecchio JCEM 2017
2.6%	608	SW England – UNITED- Shepherd Diabetes Care 2016
3.2%	3125	Poland - Fendler Diabetologia 2012
6.3%	3781	Italy 15 Paediatric clinics- diabetes+IGT, Delvecchio JCEM 2017

Variation relates to extent GCK included – (ie was incidental hyperglycaemia included in cohort?)

Adult MODY– only one population based studies 3.5% all diagnosed < 30 years

3.5% patients with diabetes diagnosed under 30 years Shields Diabetes Care 2017
≅0.4% all diabetes

Implications of low Prevalence of MODY

Saying no MODY 97-99% accurate!
But every clinic 1-3% have MODY

Population screening inefficient

Selection for testing is very difficult
- sensitive or specific ?

Precision Monogenic Diabetes

Right person?

choosing who to test

Right time?

close to diabetes diagnosis

Right test?

right method

right genes

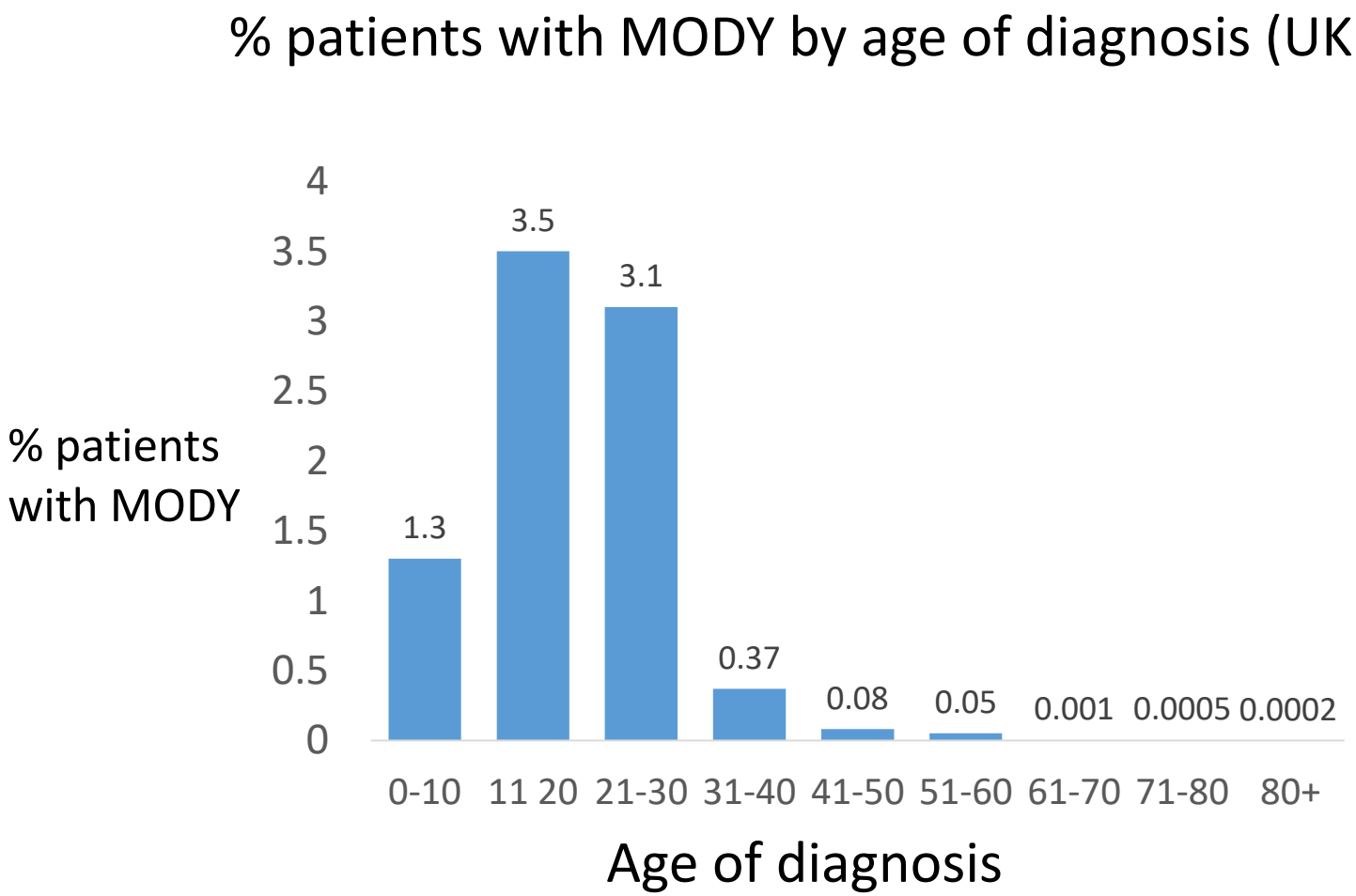
right interpretation

Right clinical management?

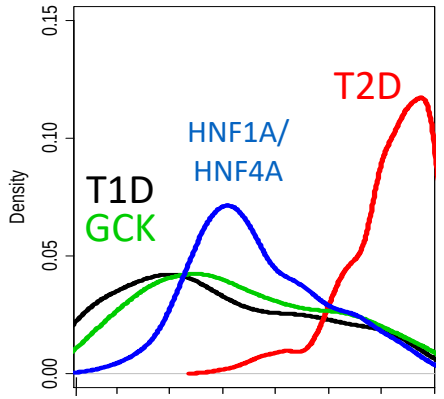
right treatment outside pregnancy

right treatment in pregnancy

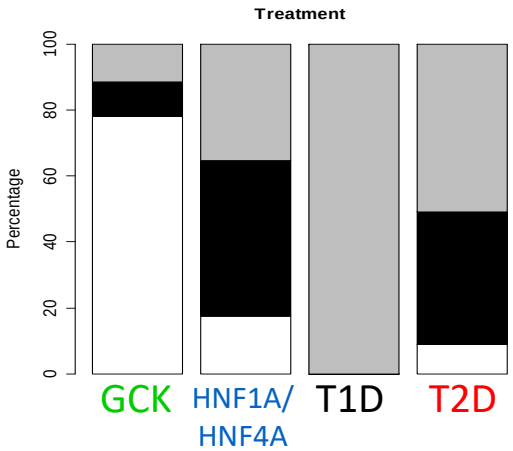
Right patient – caution if diagnosed > 35 years
prior odds extremely low



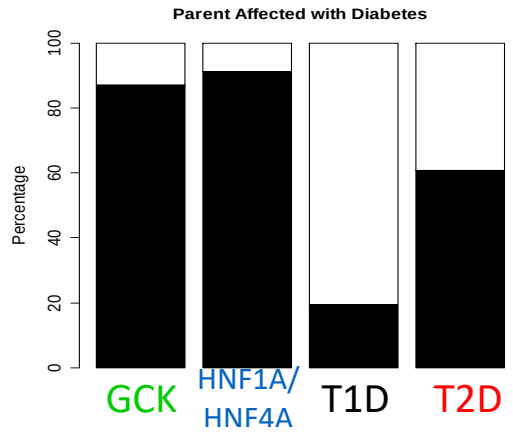
Right patient – no clear cut offs



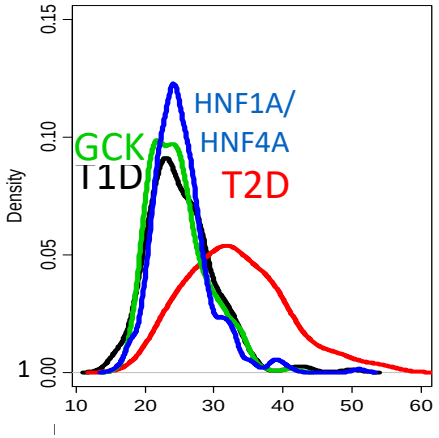
Age Diagnosis yrs



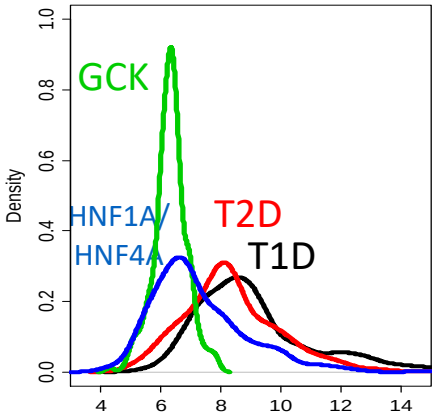
Treatment



Parental diabetes



BMI kg/m²



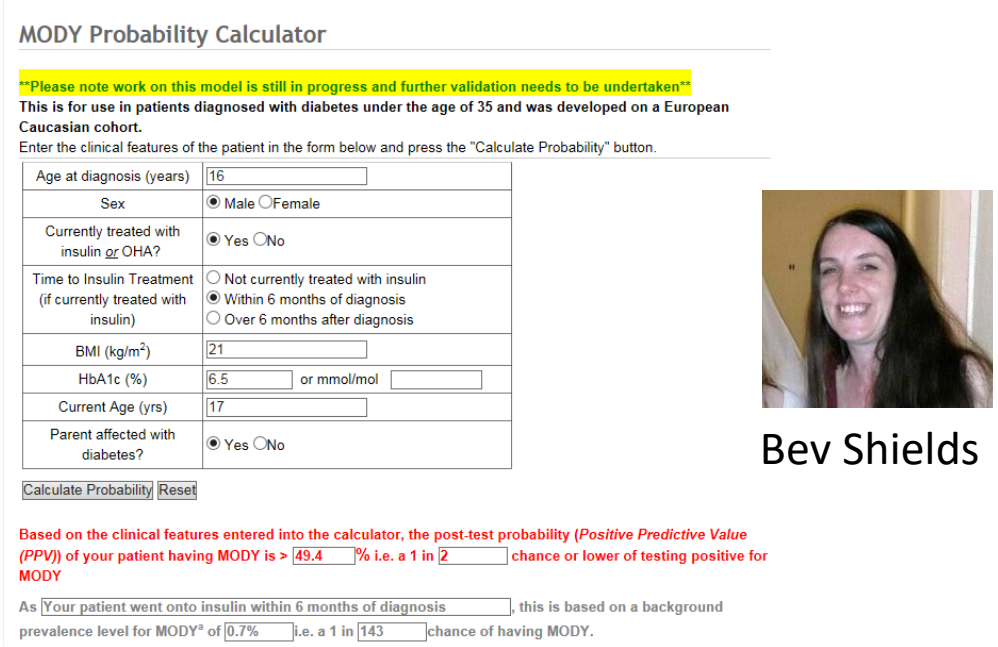
HbA1c %

Shields et al
Diabetologia 2012

Solution: combine all clinical information in single probabilistic model

Right patient- use a MODY Probability calculator

Web- based



MODY Probability Calculator

Please note work on this model is still in progress and further validation needs to be undertaken
This is for use in patients diagnosed with diabetes under the age of 35 and was developed on a European Caucasian cohort.
Enter the clinical features of the patient in the form below and press the "Calculate Probability" button.

Age at diagnosis (years)	16
Sex	◉ Male ○ Female
Currently treated with insulin *or* OHA?	◉ 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/m^2)	21
HbA1c (%)	6.5 or mmol/mol
Current Age (yrs)	17
Parent affected with diabetes?	◉ Yes ○ No

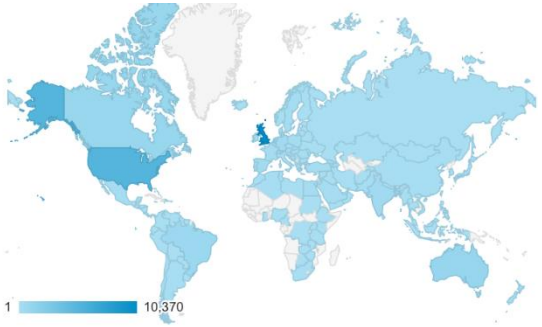
Calculate Probability Reset

Based on the clinical features entered into the calculator, the post-test probability (*Positive Predictive Value (PPV)*) of your patient having MODY is > 49.4 % i.e. a 1 in 2 chance or lower of testing positive for MODY

As Your patient went onto insulin within 6 months of diagnosis, this is based on a background prevalence level for MODY[a] of 0.7% i.e. a 1 in 143 chance of having MODY.

Bev Shields

> 200,000 hits worldwide



App for mobile phones

Diabetes Diagnostics

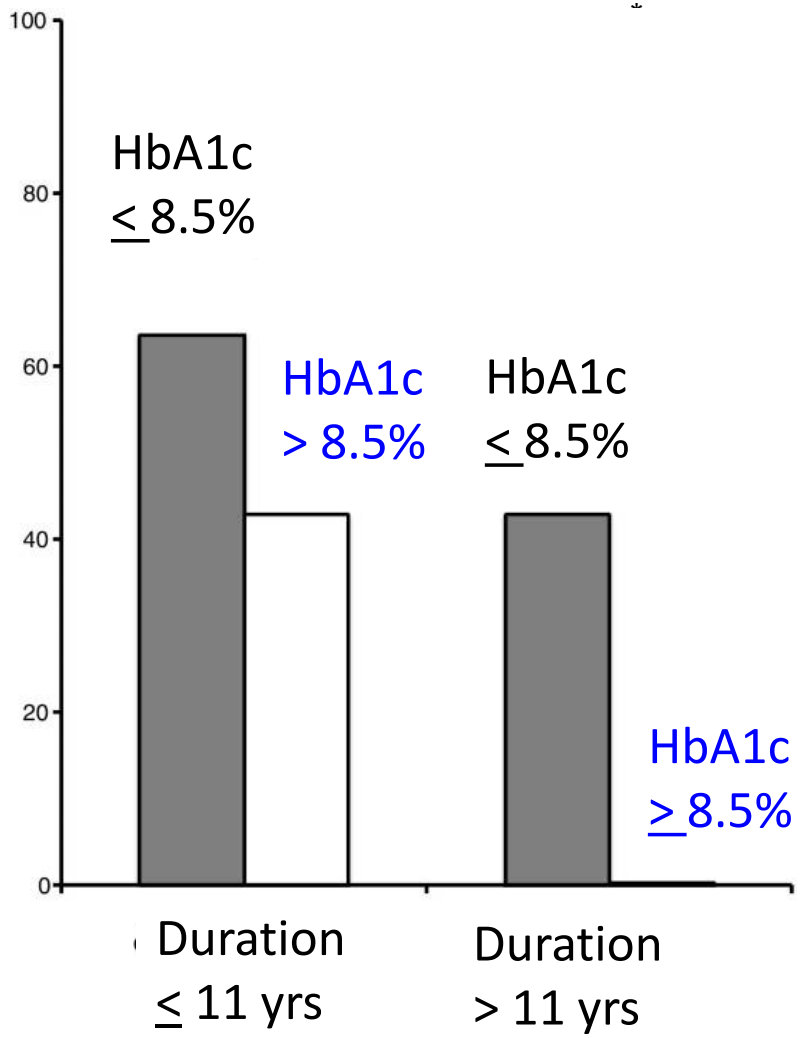
Free App for Apple phones and Android
> 15,000 downloads

Shields et al Diabetologia 2012

Right time: don't leave it late!

HNF1A/HNF4A less likely to transfer off insulin when diagnosis delayed

% patients achieving
HbA1c < 7.5%
On SU alone



MODY diagnosis often delayed

UK mean 6 years after diagnosis
Often when changes doctor

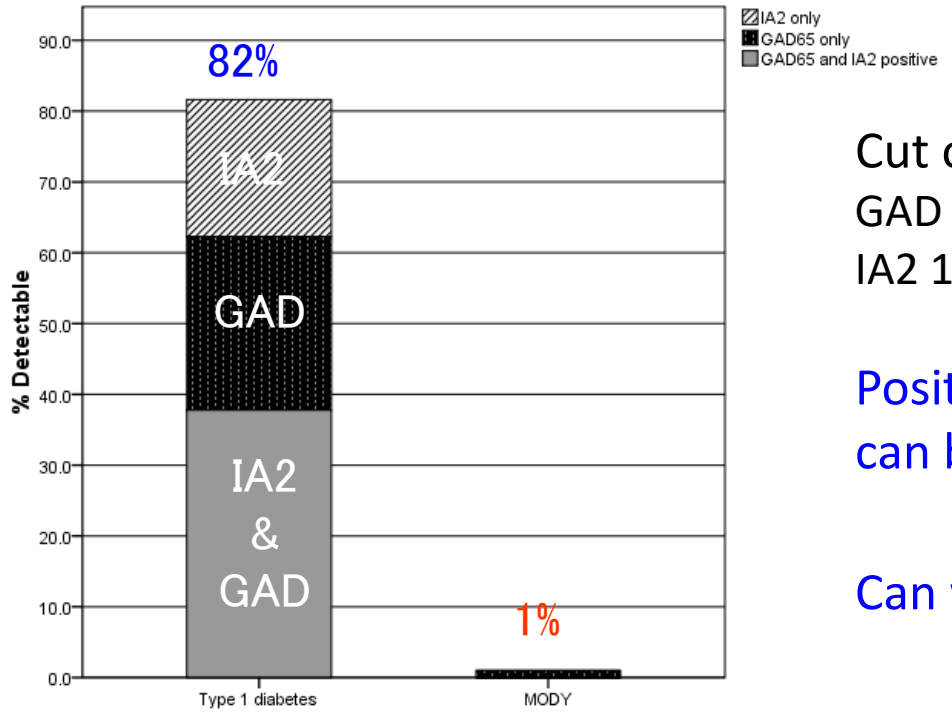
Hardest to diagnose subtype
at diagnosis of diabetes

Shepherd
Diabetologia. 2018

Improving MODY testing by making diagnosis more rapidly

Most diagnosis of MODY > 5yrs post diabetes diagnosis
Can antibody testing improve on this?

GAD65 and IA2 antibodies



T1D
n=98

MODY
n=508

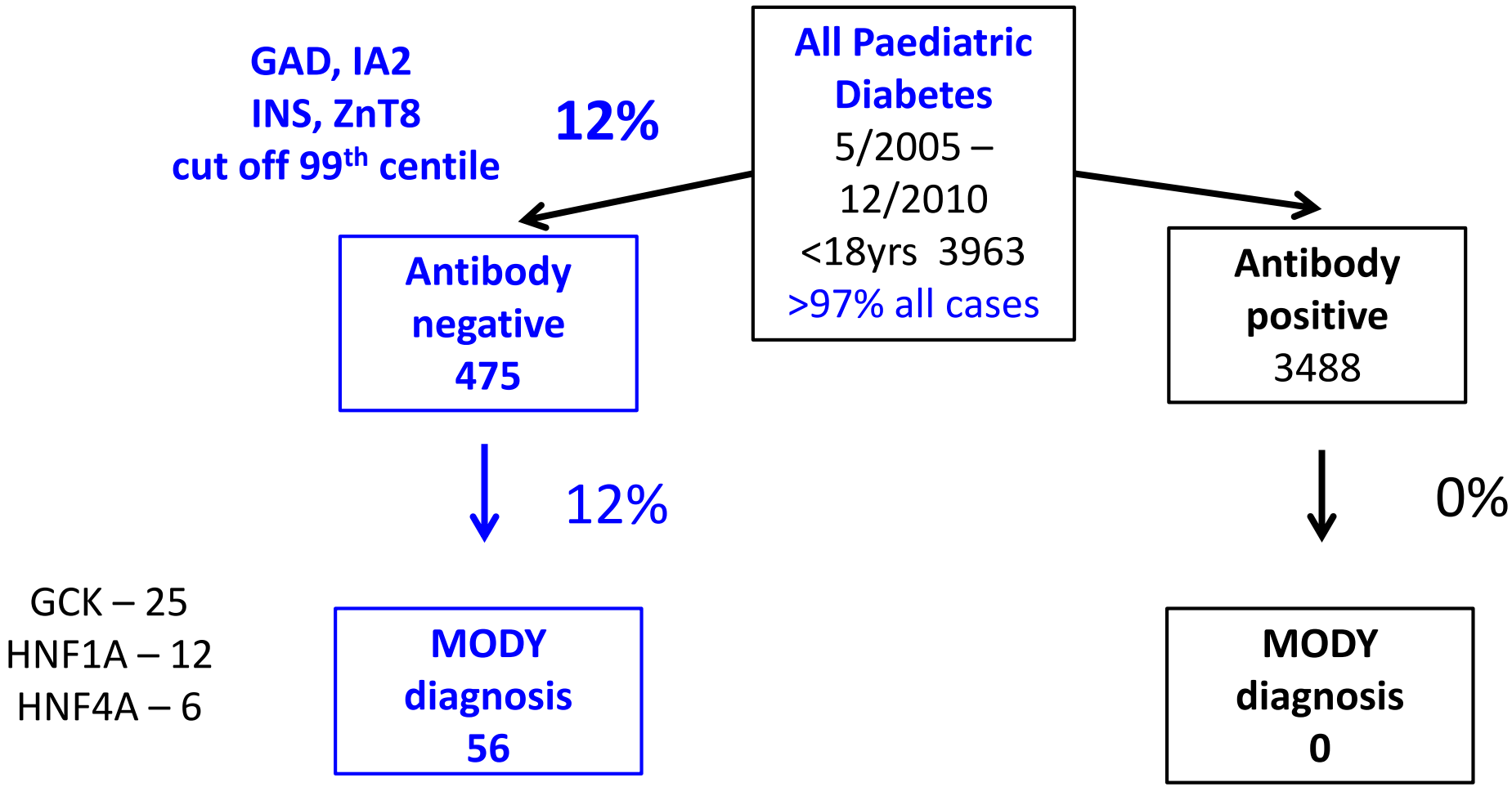
Cut off 99th centile
GAD 52 WHO units/ml
IA2 15 WHO units/ml

Positive antibodies
can be used to exclude

Can we do at diagnosis?

McDonald et al Diab Med 2011

Universal antibody screening at diagnosis finds most cases early



Prevalence MODY ≥1.3%
All in the antibody negative

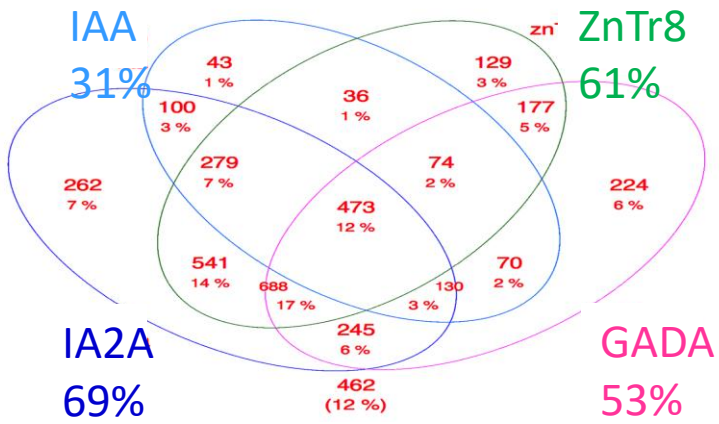
Carlsson, Shepherd et al
Diabetes Care 2020

Best screening policy for MODY at diagnosis in paediatric diabetes?

Test all antibody negative-detects 100% MODY

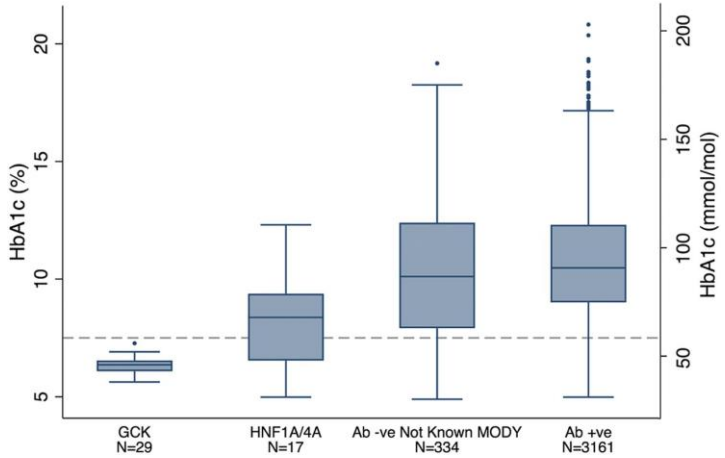
Test as many autoantibodies as possible!

4 antibodies (IAA, IA2, GAD, ZnTr8) negative
Test 12% patients- 1 in 8 positive
3 antibodies (IA2, GAD, ZnTr8) negative
Test 13% patients – 1 in 9 positive
2 antibodies (IA2, GAD) negative,
Test 18% patients – 1 in 12 positive



Discriminatory clinical features

1. Lack hyperglycaemia symptoms 13% V 80%
2. Initial HbA1c low 7.0% v 10.2%
3. Parental diabetes 63% v 12%
4. Absent ketoacidosis 0% v 12%



Test antibody negative and (initial HbA1c < 7.5% or affected parent)

96% MODY detected Test 3% all patients
More efficient (1 in 3 positive) but more missed cases

Carlsson, Shepherd et al
Diabetes Care 2020

Best screening policy for MODY at diagnosis in Adult diabetes?

If clinically Type 1 – ie insulin treated from diagnosis

As paediatrics - Test as many autoantibodies as possible!

Unlike Paediatrics usually GAD positive but IA2 and ZnTr8 do add

Consider MODY testing if 3 antibody negative – especially if family history or HbA1c low at diagnosis

C peptide helpful > 3 years after diagnosis - as random non fasting C peptide > 400 pmol/l

If clinically Type 2 – ie not insulin treated

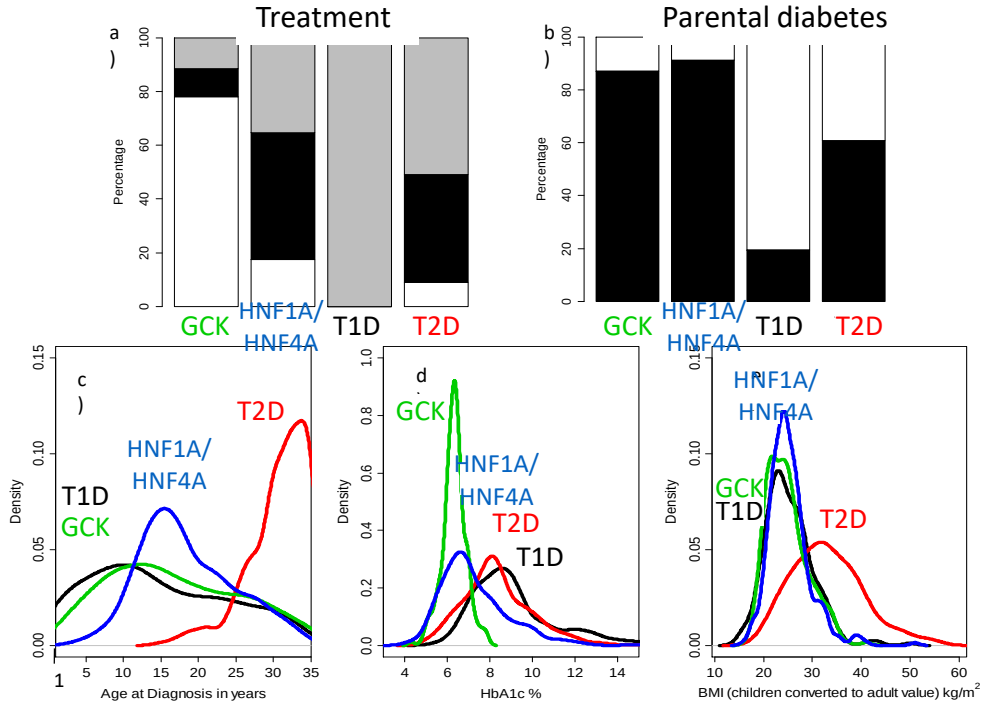
Antibodies unhelpful

Clinical features helpful

– BMI, age of diagnosis

use MODY calculator (google)

See Diabetesgenes.org



Shields et al Diabetologia 2012

Right test – right method

Next Generation Sequencing
Revolution in clinical care

Test all known NDM and MODY genes (n=51) in a single targeted NGS panel .
100% sensitive and specific.
Detects deletions and duplications
Diagnosis within 21 days.

Now testing all genes independent of phenotype

Sanger testing

Only when only testing one specific gene
GCK: esp paediatric and GDM patients 66%+ve in UK

Sian Ellard

Ellard et al Diabetologia 2013

Right test – right genes for MODY

MODY

Test all “MODY” genes? n=15
Test all real MODY genes? n= 12
Test all real, easily interpretable,
high penetrance MODY genes n =4

New genes
RFX6 (Patel et al Nature Communications 2017)

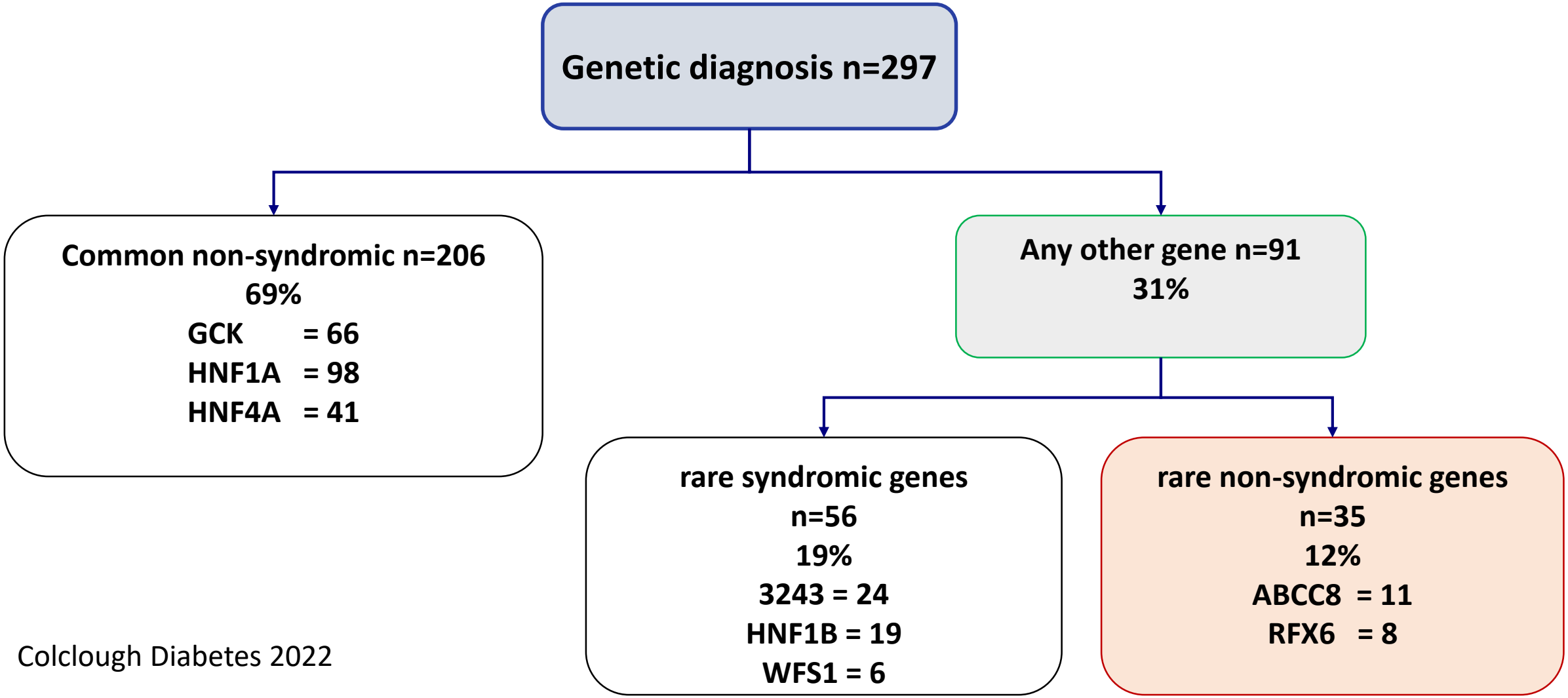
Robust * Highly penetrant Haploinsufficency pathogenic	GCK HNF1A HNF4A HNF1B
Robust BUT specific mutations only Haploinsufficency not pathogenic	ABCC8 KCNJ11 INS PDX1 CEL
Robust BUT low penetrance Haploinsufficency pathogenic	NEUROD1 RFX6
Not Robust mutations in first descriptions not pathogenic (too frequent) No published support	KLF11 PAX4 BLK

Right test – right genes “MODY +”

Differential diagnosis (add to the MODY panel)

T1D – TID-GRS SNPS	Very helpful to* pick up ab neg T1D (Patel Diabetes 2016)
MIDD-3243	Commonest after GCK HNF1A & HNF4A (Colclough Diabetes 2022)
Severe Insulin Resistance INSR FPLD –Lamin AC,PPARG	Often not recognised (Colclough Diabetes 2022)
Monogenic autoimmunity	AIRE, IL2RA, FOXP3, LRBA, STAT1, STAT3, STAT5B,
Recessive/Syndromic –	WFS1, SLC19A2 commonest if consanguineous(Patel in press)

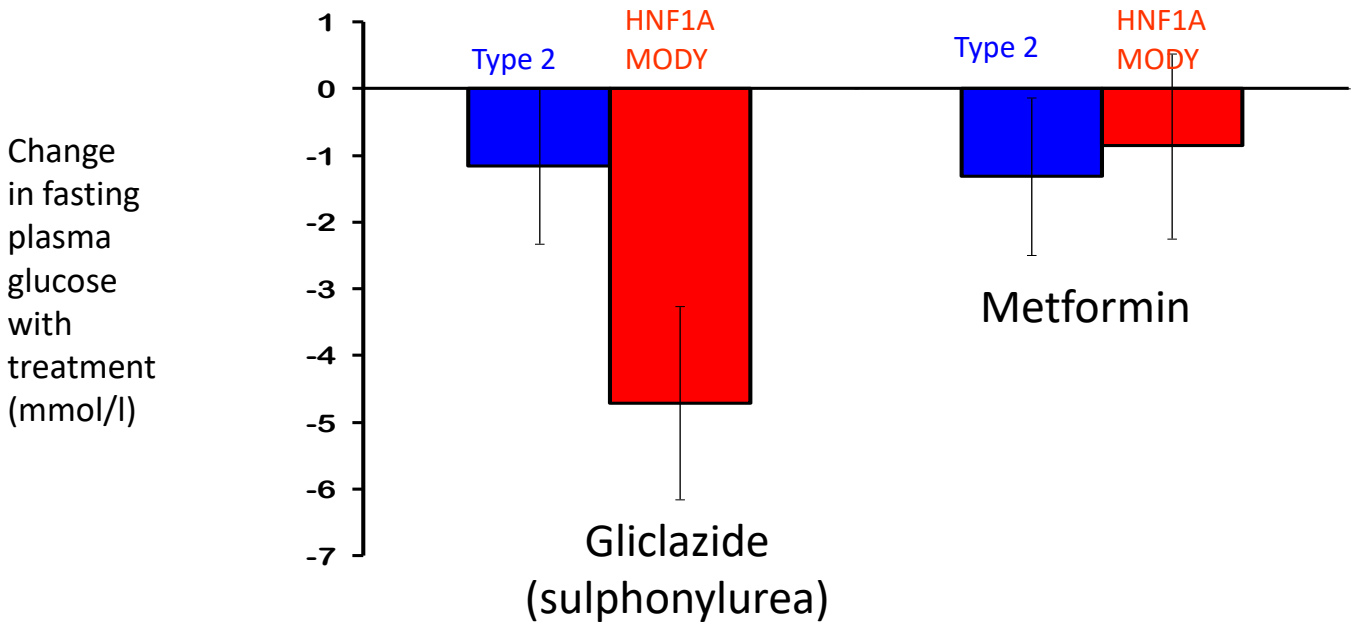
tNGS identifies additional 30% patients with rare subtypes of monogenic diabetes



Colclough Diabetes 2022

Right management outside Pregnancy: Pharmacogenetics has a large impact in HNF1A MODY

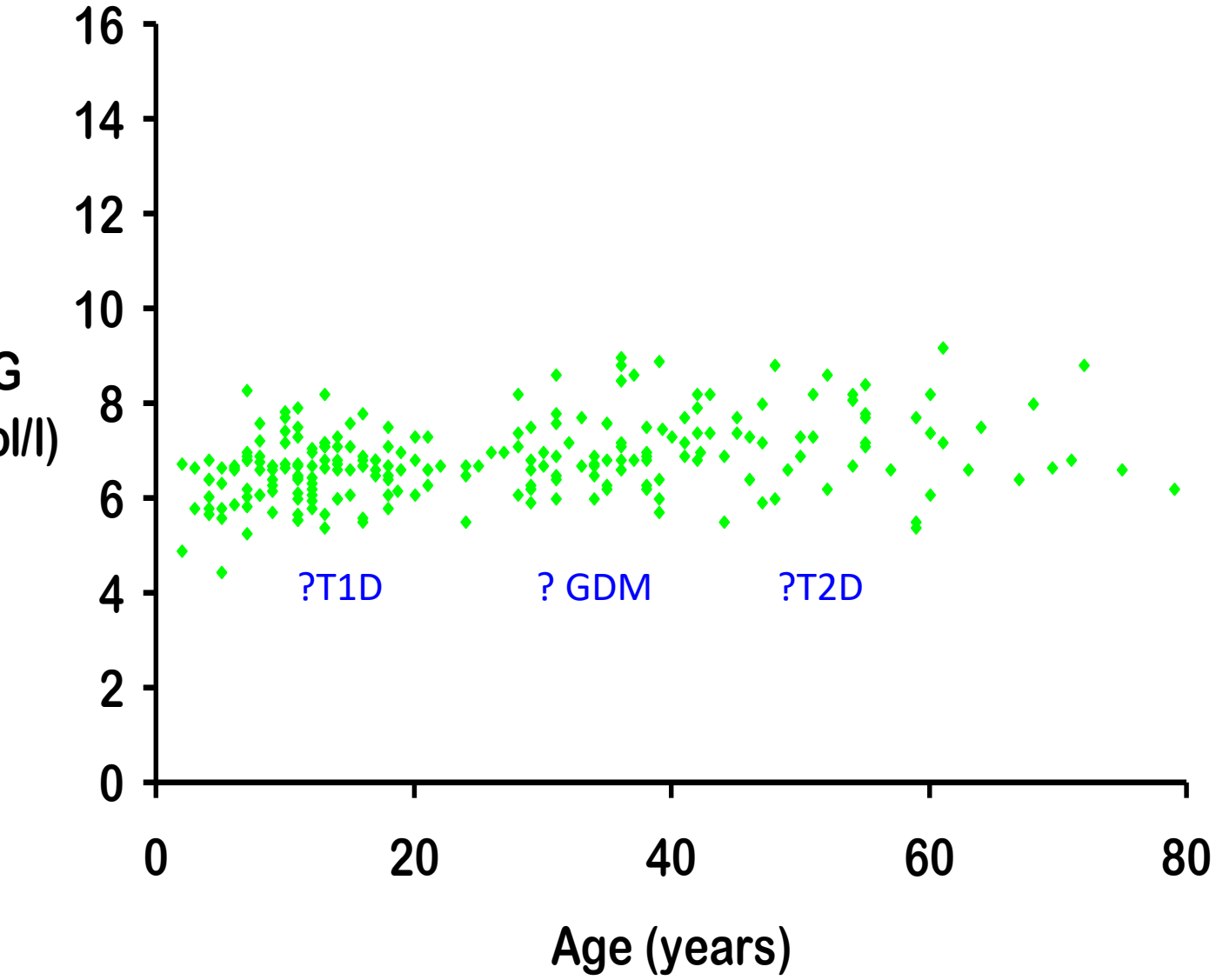
Crossover Trial:HNF1A MODY patients respond
4 x better to Sulfonylureas than T2D patients

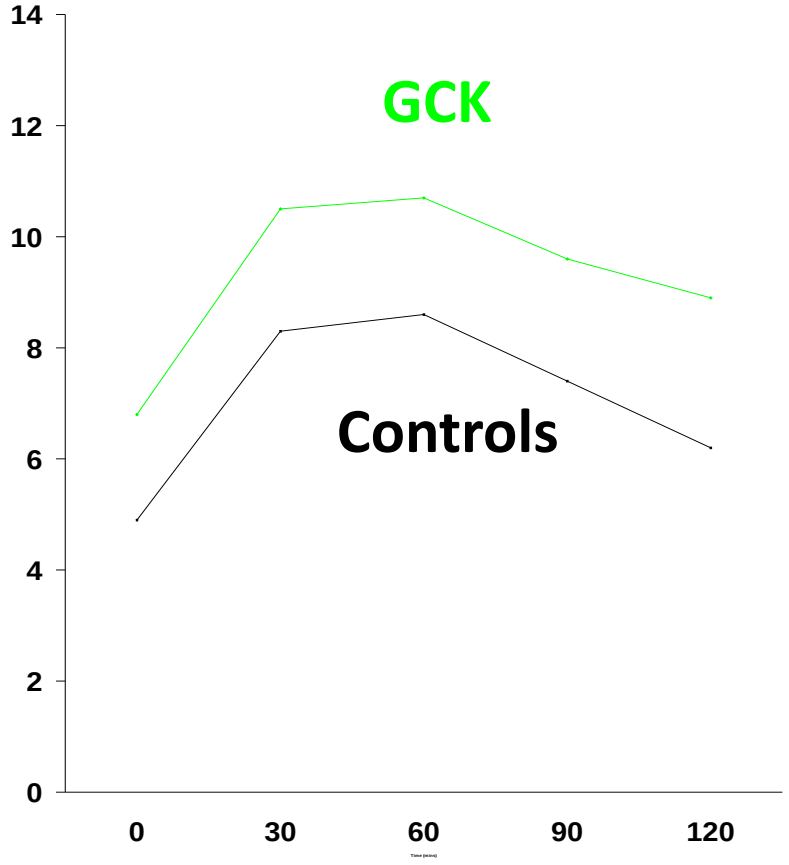


Pearson et al Lancet 2003

Recent trials support GLP-1 and DPP4i after SUs

Right management outside pregnancy: Glucokinase stable raised fasting glucose & regulate glucose in OGTT

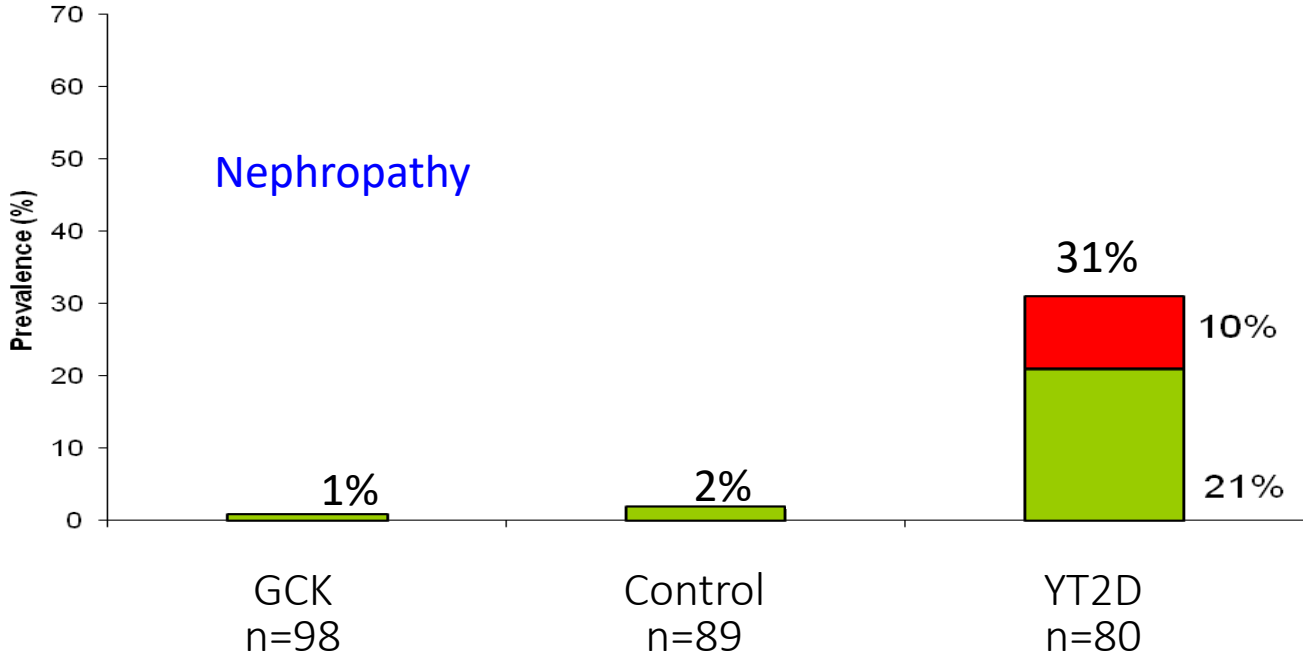




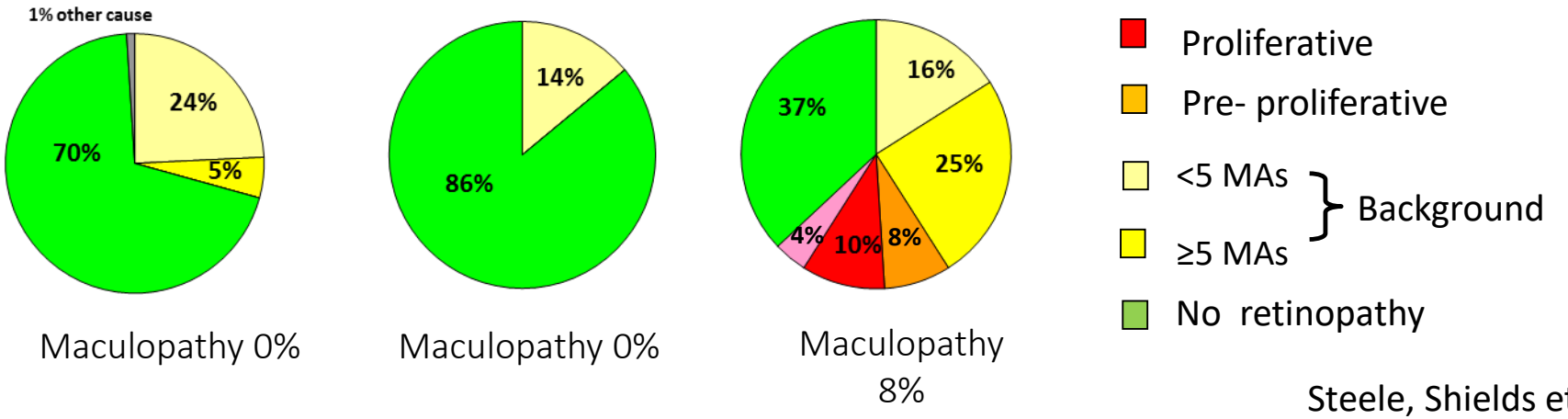
European MODY Consortium (n =245) Stride et al Diabetologia 2002

GCK Patients do not need treatment

GCK patients untreated for 50 yrs have no significant microvascular complications



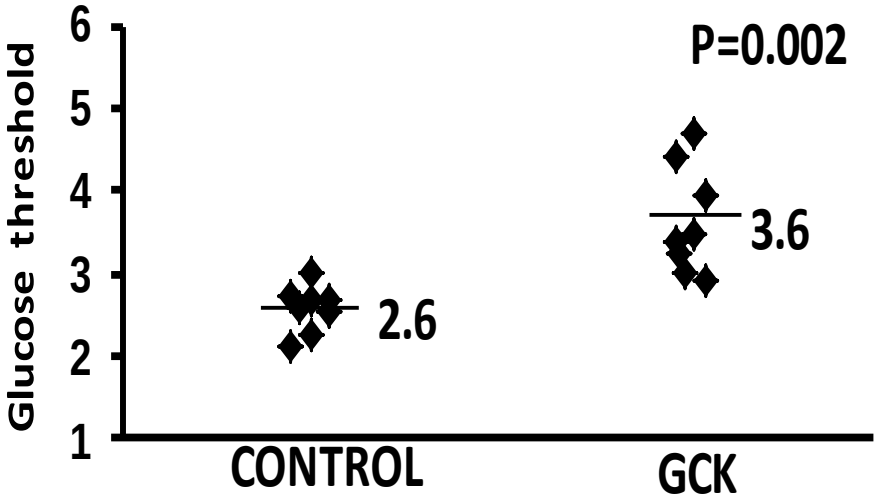
Retinopathy



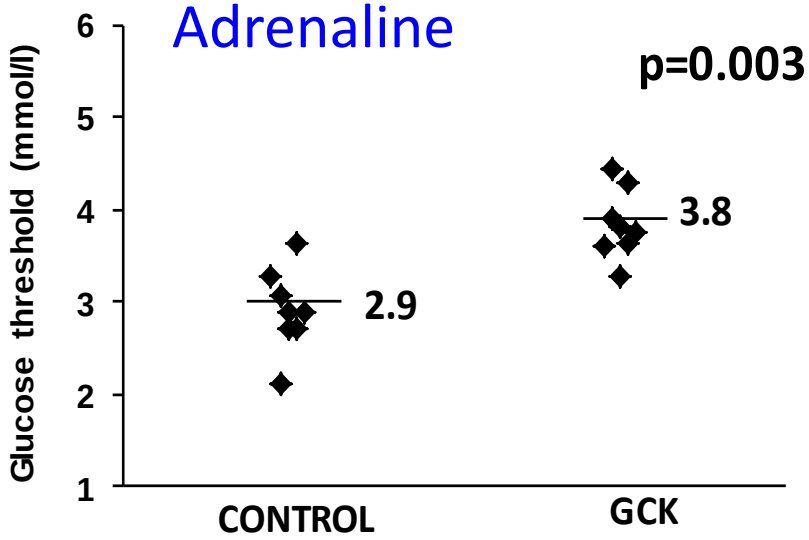
Steele, Shields et al JAMA 2014

Glucokinase MODY patients counter regulate if glucose lowered by insulin to "normal" glucose values

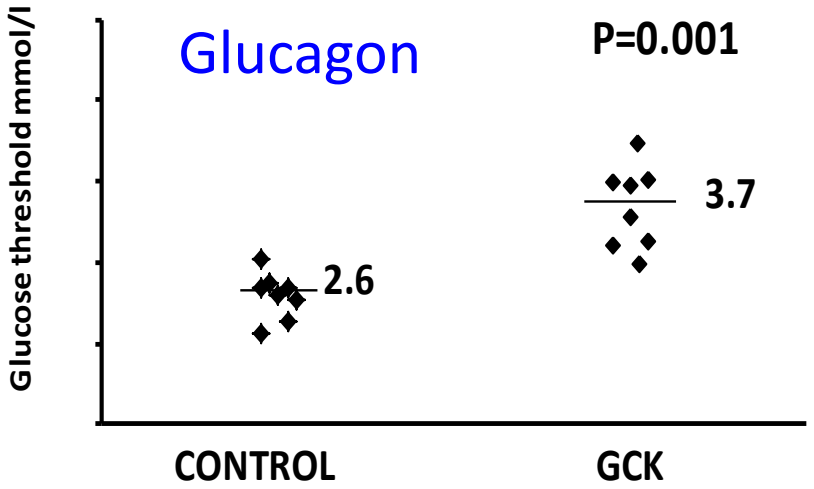
Symptoms



Adrenaline

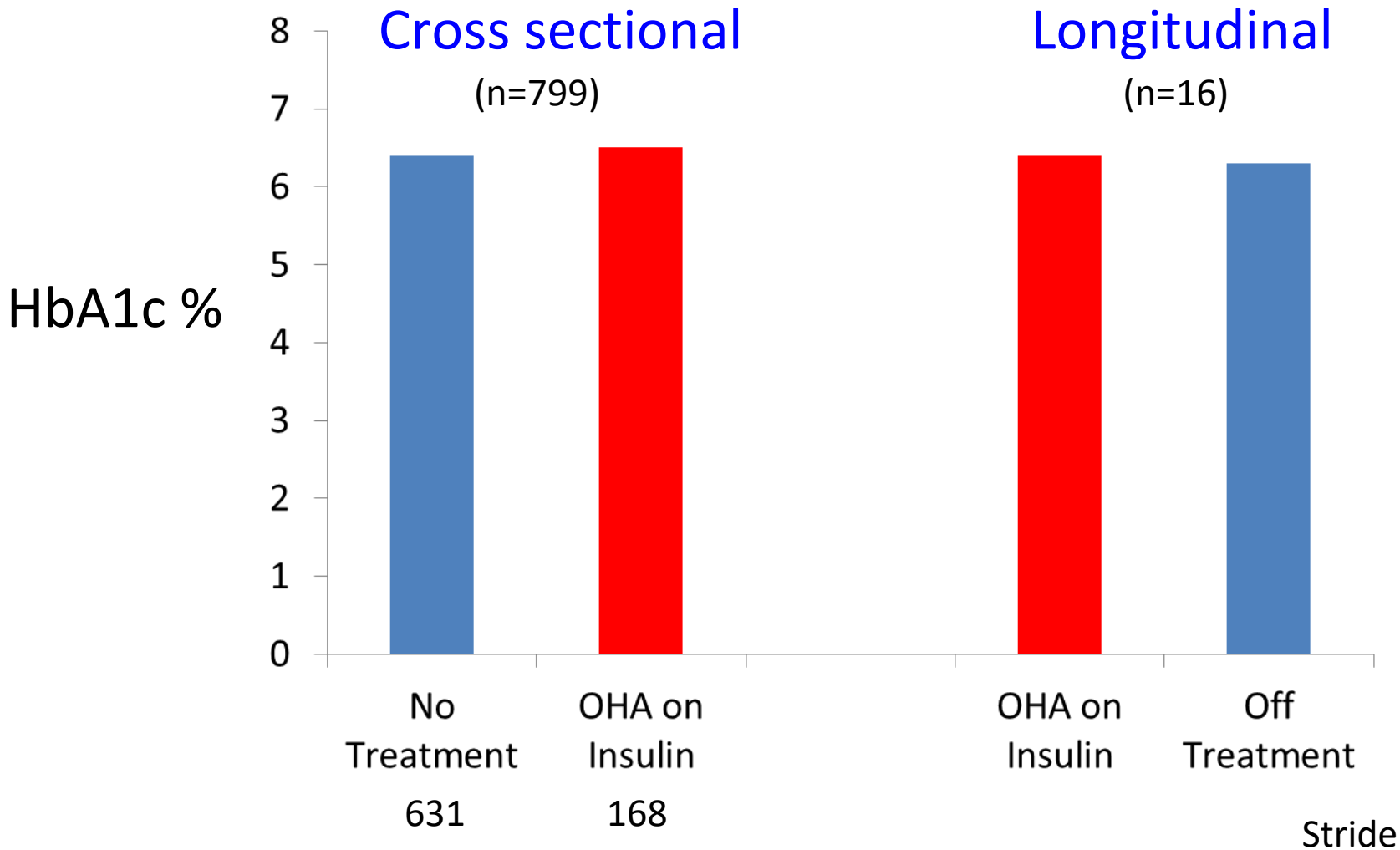


Glucagon



Chakera et al Mol Metab. 2018

Glucokinase MODY Patients do not benefit from treatment
HbA1c unaltered by treatment



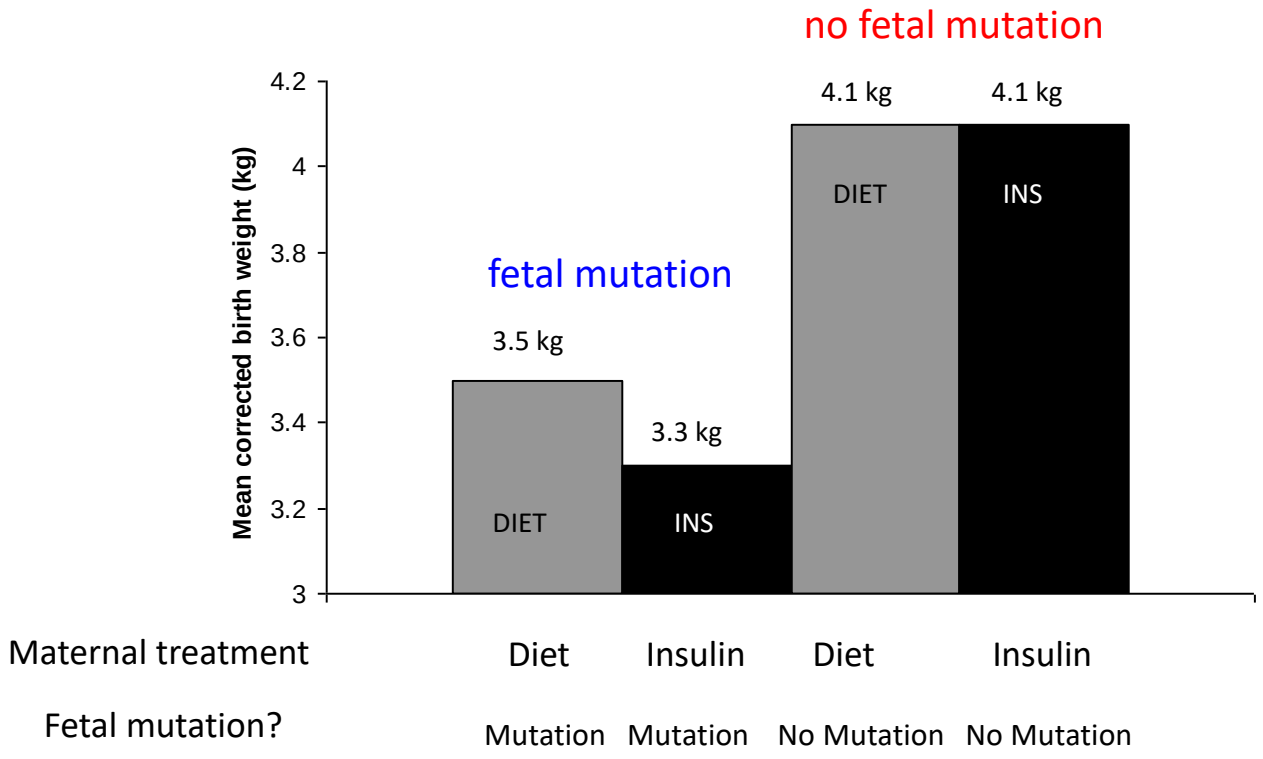
Stride et al (Diabetologia 2014)

*

Right management – in pregnancy

Management of GCK-MODY in pregnancy (3rd trimester)

Fetal mutation not insulin treatment determines fetal outcome in GCK pregnancy



Spyer et at Diabetic Medicine, 2009

Pregnant woman with glucokinase-MODY

Fetus does not inherit mutation

Assess indirectly by US A/C > 75th centile

Measure directly if CVS or Amnio sample

Cell free DNA

Fetus inherits mutation

?Insulin to prevent macrosomia in last trimester Deliver 38 weeks

No treatment needed

?Deliver 40 weeks

Chakera *et al*. Diabetes Care 2015

Monogenic Diabetes Non-invasive Pre Natal diagnosis
Possible & highly accurate

GCK MODY diagnosis and mother consented to NIPD

Lab posts cffDNA collection tube and mouth swab for father (cf DNA quantification) Samples returned to lab.

Develop ddPCR assay for specific mutation

Fetal genotype reported with guidance for pregnancy care

89 pregnancies

GCK
>38 different mutations
Maternal GCK MODY

HNF4A
>15 different mutations
Maternal HNF4A MODY
Paternal HNF4A MODY

KCNJ11/ABCC8 NDM
2 different mutations
Maternal KCNJ11 NDM
Paternal KCNJ11 & ABCC8 NDM

Results

95% (85/89) able to give result
(can design probe, fetal cell free DNA >3%, sufficient counts)

100% accurate when give result (compared to fetal testing)
14/14 paternal
71/71 maternal

Caswell et al Clinical Chemistry 2020 and unpublished

Precision monogenic diabetes

Right person?

choosing who to test

Right time?

close to diabetes diagnosis

Right test?

right method

right genes

right interpretation

Right clinical management?

right treatment outside pregnancy

right treatment in pregnancy

Why has stratification to genetic subtypes by MODY been successful?

MODY testing used clinically worldwide

>5,000 in UK genetically diagnosed MODY

3.5% diabetes < 30 yr (Shields et al Diabetes Care 2017)

Genetically defined subtypes

1. Robustly defined/ diagnosed
2. No over lap between subtypes
3. Different aetiology for subtypes

Has clinical utility as allows identification of

- Different clinical course
- Different treatment response

Can a stratified approach defining subtypes also work for Type 2 diabetes?

Monogenic defined subtypes

Based on rare genetic variant in single gene

1. Robustly defined/ diagnosed
2. No over lap between subtypes
3. Different aetiology for subtypes

Has clinical utility because the subtypes allows identification of:

- Different clinical course
- Different treatment response

Clinical or polygenic defined subtypes within T2 Diabetes

Based on continuous data so:

1. Not robustly defined/ diagnosed
2. Clear over lap between subtypes
3. Not different aetiology for subtypes

Clinical utility?

Not better than using individual outcome prediction to identify

Dennis, Lancet D & E 2019

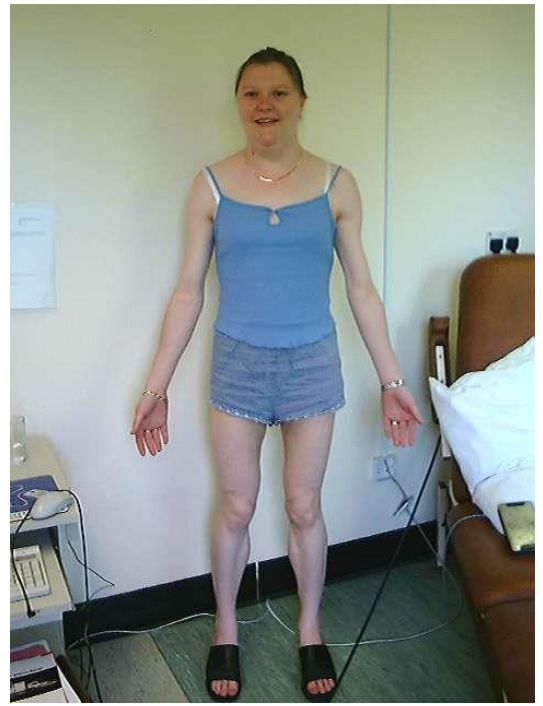
Diagnose monogenic diabetes and improve clinical care

MODY

Defining subtypes
Improves Clinical Care

Neonatal diabetes

Defining subtypes
Improves Clinical Care



Severe Insulin resistance

Defining subtypes
Improves Clinical Care

The Exeter Diabetes Research Team 1995-2021

Gene discovery: Sian Ellard, Sarah Flanagan, Mike Weedon, Elisa De Franco, Anna Gloyn, Hana Lango-Allen, Kevin Colclough, Richard Caswell, Jayne Houghton, Anne-Marie Patch, Tim Frayling, Mike Bulman Annet Damhuis, Andrew Parrish, Matthew Wakeling, Matt Johnson,

Genetic Clinical Research : Maggie Shepherd, Tim McDonald, Ewan Pearson, Oscar Rubio-Cabezas, Coralie Bingham, Rachel Besser, Katherine Owen, Anna Steele, Gill Spyer, Ali Chakera, Kash Patel, Pam Bowman, Michelle Hudson, Richard Caswell, Ines Barroso

Type 1 and Type 2 Clinical research:, Tim McDonald, Richard Oram, Angus Jones, Bev Shields, John Dennis, Nick Thomas, Rob Andrews,Anita Grubb, Mike Weedon, Susie Hammersley, Beatrice Knight, Kash Patel, Lauren Rodgers, William Henley, Willie Hamilton, Chris Hyde, Noel Morgan Sarah Richardson, Pia Leete, Mark Russell, Abby Willcox, Michelle Hudson, Anita Hill, Suzie Hammersley, Catherine Angwin, Gill Baker,

Royal Devon and Exeter Clinical team:, Doctors, Nurses, Dieticans and clinical staff working at the RD & E diabetes and endocrine clinic

National & International Collaborators

The UK team

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Clinical Features of Severe Insulin Resistance – possible monogenic aetiology

In a non-obese and often normal weight person

- Acanthosis nigricans (look for it)
- Polycystic Ovary Syndrome (hyperandrogenism, hirsutism, menstrual irregularity, cystic ovaries on U/S)
- If diabetes may need very high insulin dose

NOT Hypertension, NOT high TG/ low HDL,
NOT fatty liver
- markers of ectopic fat a *cause* of severe IR not a result of severe IR

Best example:
Type A Insulin Resistance due to IR mutation
Treatment metformin and insulin. Not increased CVS risk

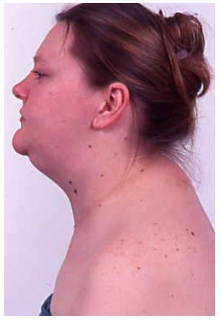
Severe insulin resistance due to partial lipodystrophy

Features of severe insulin resistance despite being normal weight

Acanthosis Nigricans
Polycystic ovaries, virilisation, menstruation irregularity,
Very high fasting insulin & C-peptide

Features of Ectopic Fat

Hypertension
Hyperglycaemia
High TG, Low HDL
Fatty liver



Features of Cause of Ectopic fat

Central obesity/ may be buffalo hump
Thin limbs with prominent veins
Loss of gluteal folds
Pseudo hypertrophy of limb muscles
Mutation in multiple genes including LAMIN A, PPARG, POLD1 etc

Stratification in severe insulin resistance is different – most genetic subtypes and polygenic partial lipodystrophy similar course & need similar treatment

Very poor pick up - insulin resistance hard to detect <5% cases in UK identified

Genetically defined subtypes

1. Robustly defined/ diagnosed
2. No over lap between subtypes
3. Different aetiology but PLD similar pathophysiology requiring similar treatment approach.

Has clinical utility as allows identification of patients with specific pathophysiology who need specific treatment even if not monogenic

Severe Insulin Resistance have different aetiologies but many have a similar clinical course and similar treatment requirements