Does your patient have T1, T2 or MODY?

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T1 vs T2 diabetes

T1D

- Young (peak age onset 12)
- 0.25% prev
- Weight loss and osmotic symptoms
- Autoimmune destruction beta cells
- Beta cell antibodies 80-90%
- DKA
- Uncommonly overweight +/- insulin resistant

T2D

- Older (peak age 60)
- 5-10%
- Hyperglycaemic symptoms often with complications
- Insulin resistance +beta-cell destruction/dysfunction
- Antibody neg
- Commonly overweight
- High risk ethnic groups
- Often FH T2D
- DKA uncommon

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Case MB

- 42 yr old Afro-caribbean nurse presented to AMU unwell right loin pain, fever 38.5
- BMI 25 but recent weight loss, father T2D, 2 uncles T2D
- BG 28, ketones 6.8, pH 6.9, eGFR 55 Cr 130, HbA1c 128
- MSU Ecoli sepsis - pyelonephritis
- Started on DKA protocol and IV antibiotics
- Discharged on glargine and novorapid
- ICA and GAD antibody negative

- Reviewed in clinic, likely T2D, urine c peptide/Cr ratio high
- Insulin weaned, on metformin 2g - HbA1c 57mmol/mol

WHO Classification of Diabetes

Type 1

Type 2

and….“Other specific types - where underlying defect can be identified….”

- Genetic defects of beta-cell function (MODY)
- Genetic defects in insulin action
- Diseases of the exocrine pancreas
- Other endocrine diseases
- Infections
- Drugs
- Chemicals
- Syndromes associated with DM

Maturity-onset diabetes of the young (MODY)

Monogenic diabetes affecting β-cells

Clinically described in 1974:

- **Early onset DM (diagnosis <25 yr)**
- **Non-insulin dependent**
- **Autosomal dominant inheritance**

Estimated 1-2% diabetes

Often misdiagnosed as T1DM or T2DM

Ledermann Diabetologia 1995

Case: LG

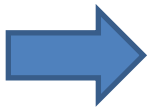
- Type 1 DM diagnosed aged 20y (2001)
- John Warin ward - genital herpes
- Glucose 27.7 mmol/L
- Urine glucose 3+, ketones 3+
- Lethargy, polyuria and polydipsia, recurrent thrush (no weight loss)
- Basal bolus insulin regime

Case LG

- OCDEM clinic
- Frequent DNA
- HbA1c 7.6 - 9.2%
- Weight gain 60.8 kg (BMI 23.5) to 78.9 kg (BMI 30.4)
- 1 unit insulin/ kg /day
- Referrals to dietician and DSN

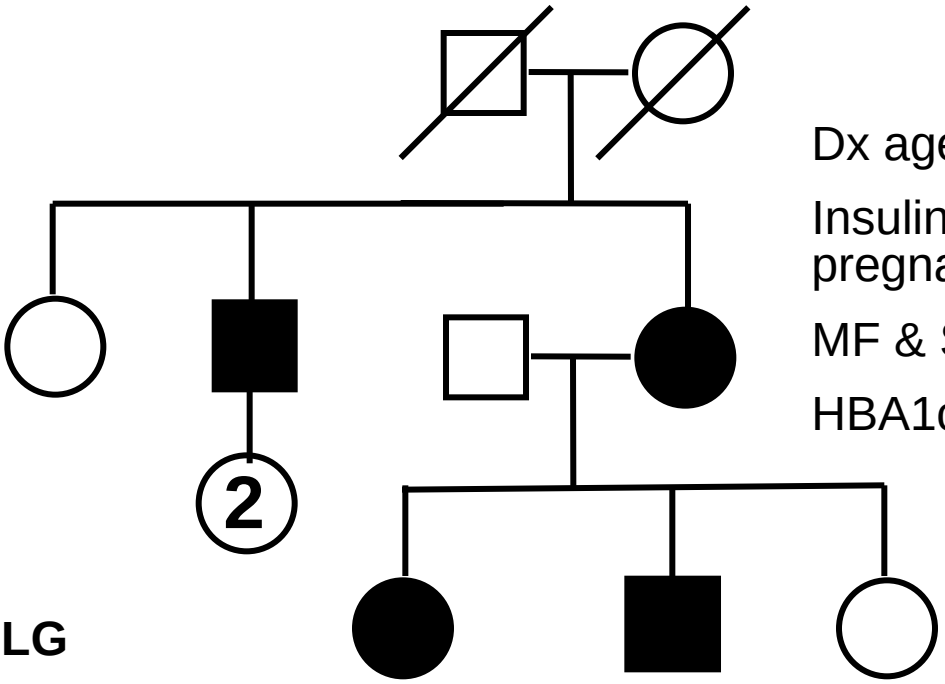
Case LG

2007 - 25 y brother diagnosed with T2 diabetes



Referred to young-adult onset diabetes clinic in 2008

Family tree - 2008



Dx age 24

Insulin during pregnancies

MF & SU

HBA1c 6.1%

LG

80 units insulin/day

BMI >30

HbA1c 8.6%

age 25

Diet + MF

HbA1c 8.5%

SU added -> hypos

Case LG

- C-peptide 0.49nmol/L – signifies endogenous insulin secretion

- Mutation:

  Hepatocyte Nuclear Factor 1 gene (*HNF1A*)
- Maturity onset diabetes of the young (MODY)

Case LG

- Insulin stopped
- Gliclazide 40mg od
- 24 hr DSN support

Case LG

- Insulin stopped
- Gliclazide 40mg od
- 24 hr DSN support

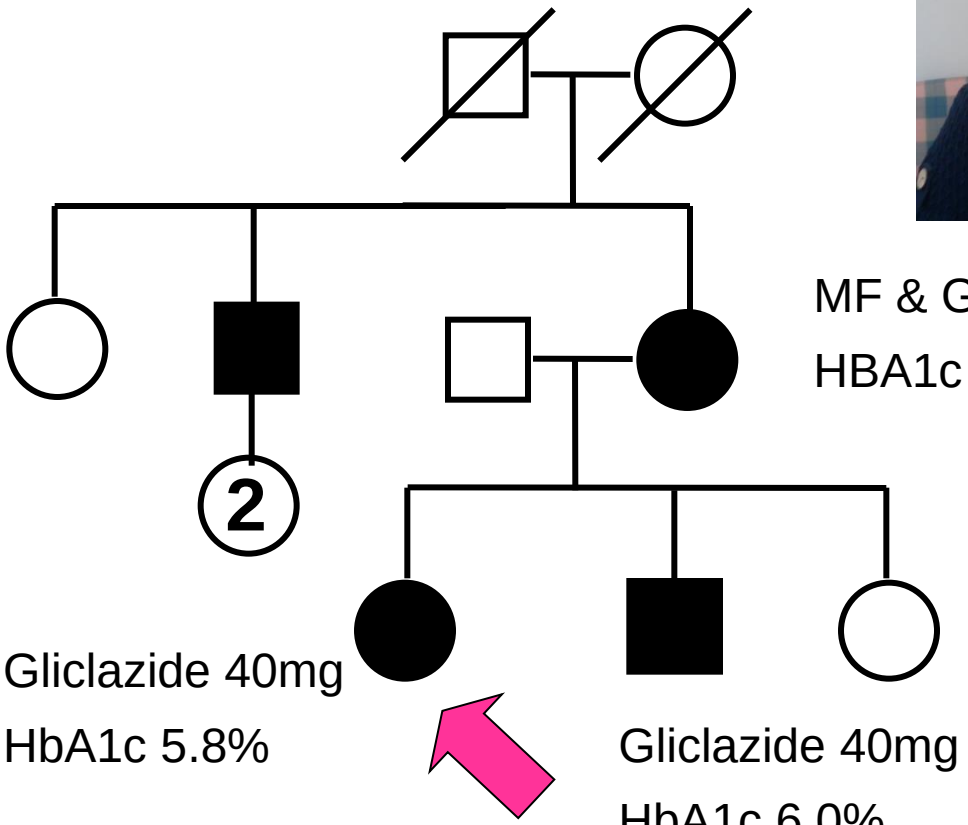
Weight:

78.9 kg → 60.4 Kg

HbA1c:

8.6% → 5.8 %

Family tree - 2010



MF & Gliclazide 80mg

HBA1c 6.4%

Gliclazide 40mg

HbA1c 5.8%

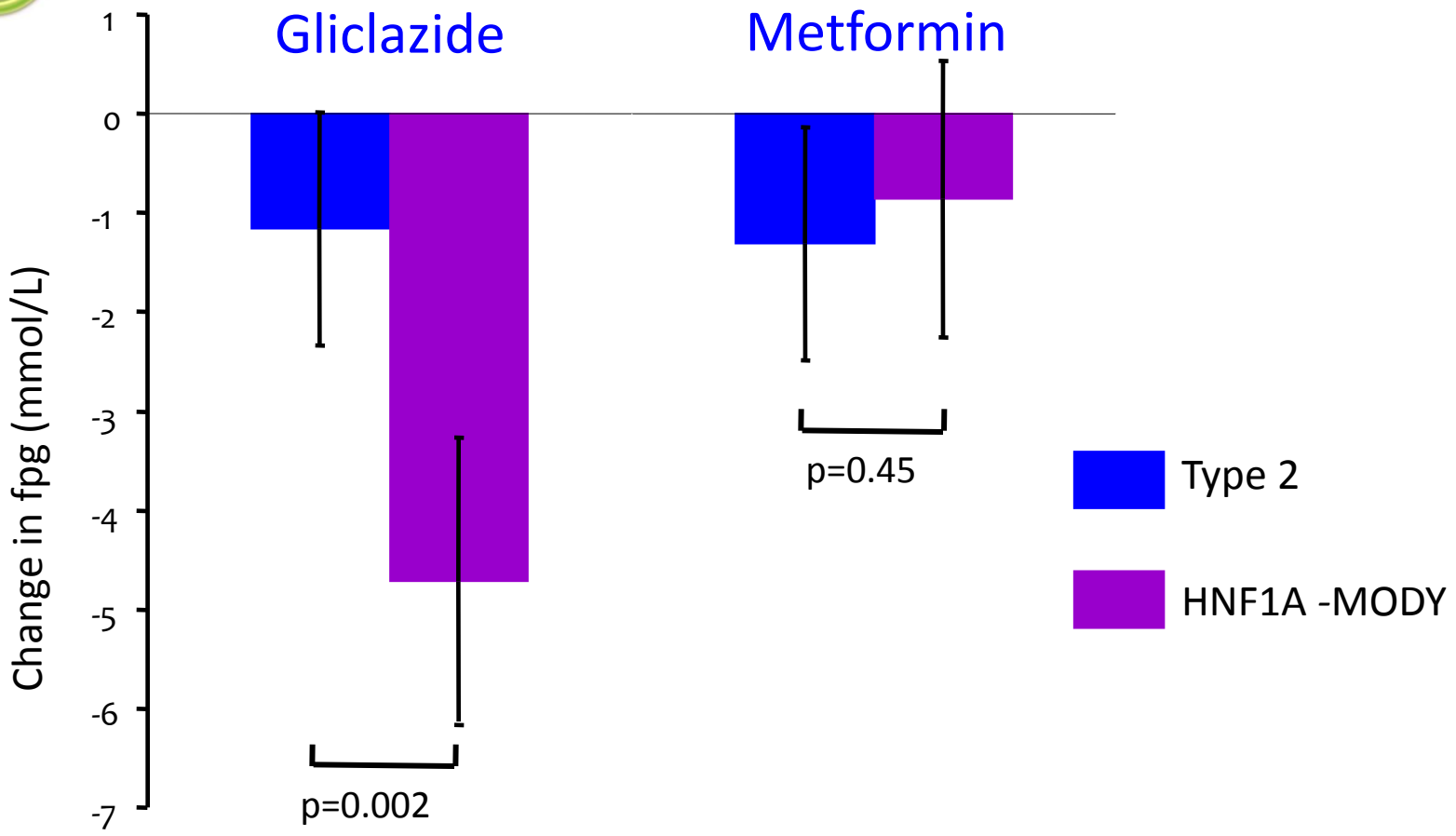
Gliclazide 40mg

HbA1c 6.0%

HNF1A/HNF4A-MODY

- Normoglycaemic in childhood
- Progressive β-cell dysfunction
- Diabetes presents in 2nd-4th decade
- Maintain some endogenous insulin production (diabetic ketoacidosis rare)
- Complication profile similar to type 1 diabetes
- Sensitivity to sulphonylureas (SU)

SU sensitivity in HNF1A-MODY



Pearson *et al* (2003) Lancet

Karen age 32

- Age 23 raised random glucose, normal fasting level:
  dietary advice
- 2008 – Oral glucose tolerance test confirmed diabetes: baseline 8.6 2hr 21.1
- BMI 22
- β–cell antibodies negative
- No family history of diabetes
- Commenced 80mg gliclazide
- Shaking episodes - resolved with chocolate

Found to have mutation in *HNF4A* gene

Glucokinase (*GCK*) MODY

- Mild lifelong fasting hyperglycaemia
- FPG 5.5-8.5 mmol/l, HbA1c <8%
- Rise in blood sugar after glucose load similar to non-diabetic (<3.5 mmol/l)
- Asymptomatic – diagnosed during routine screening
- Low level of diabetic complications (no sight threatening retinopathy in 50 yrs of GCK-MODY)

Treatment of GCK -MODY

- No trial data
- Observational data suggests treatment does not change HbA1c
- Recommend annual HbA1c in primary care
- Can get Type 2 diabetes if insulin resistant

Clare age 36

- Diagnosed age 33 during pregnancy
- FPG 7.1mmol/l, HbA1c 6.7%
- B-cell antibody negative at diagnosis
- Sister with ‘mild diabetes’, mother gestational diabetes, maternal uncle insulin-treated type 2 diabetes
- OGTT 2008 0hr 6.6mmol/l 2hr 7.5mmol/l
- *Glucokinase* mutation
- Discharged back to primary care
- Relatives invited for genetic testing

MODY is under-diagnosed

>80% UK MODY subjects remain unidentified
10-15 yr delay from diabetes diagnosis to MODY diagnosis

- Challenging due to overlap in clinical features
- Testing is opportunistic
- Reluctance to question original diagnostic label

MODY does present outside traditional phenotype

- Over 1/2 HNF1A-MODY subjects in UK present without classical MODY features [2]
- *De novo* mutations will not have family history of diabetes

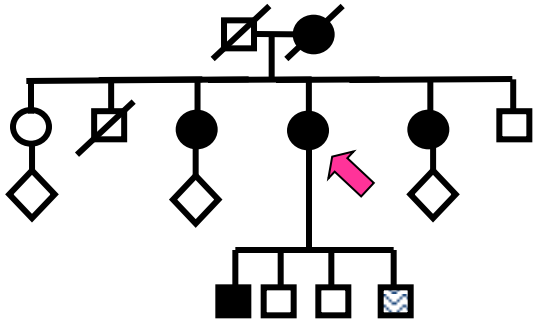
Shields *et al* (2010) Diabetologia

Diagnosis of MODY is important

- Confirmed molecular diagnosis facilitates tailored treatment and monitoring

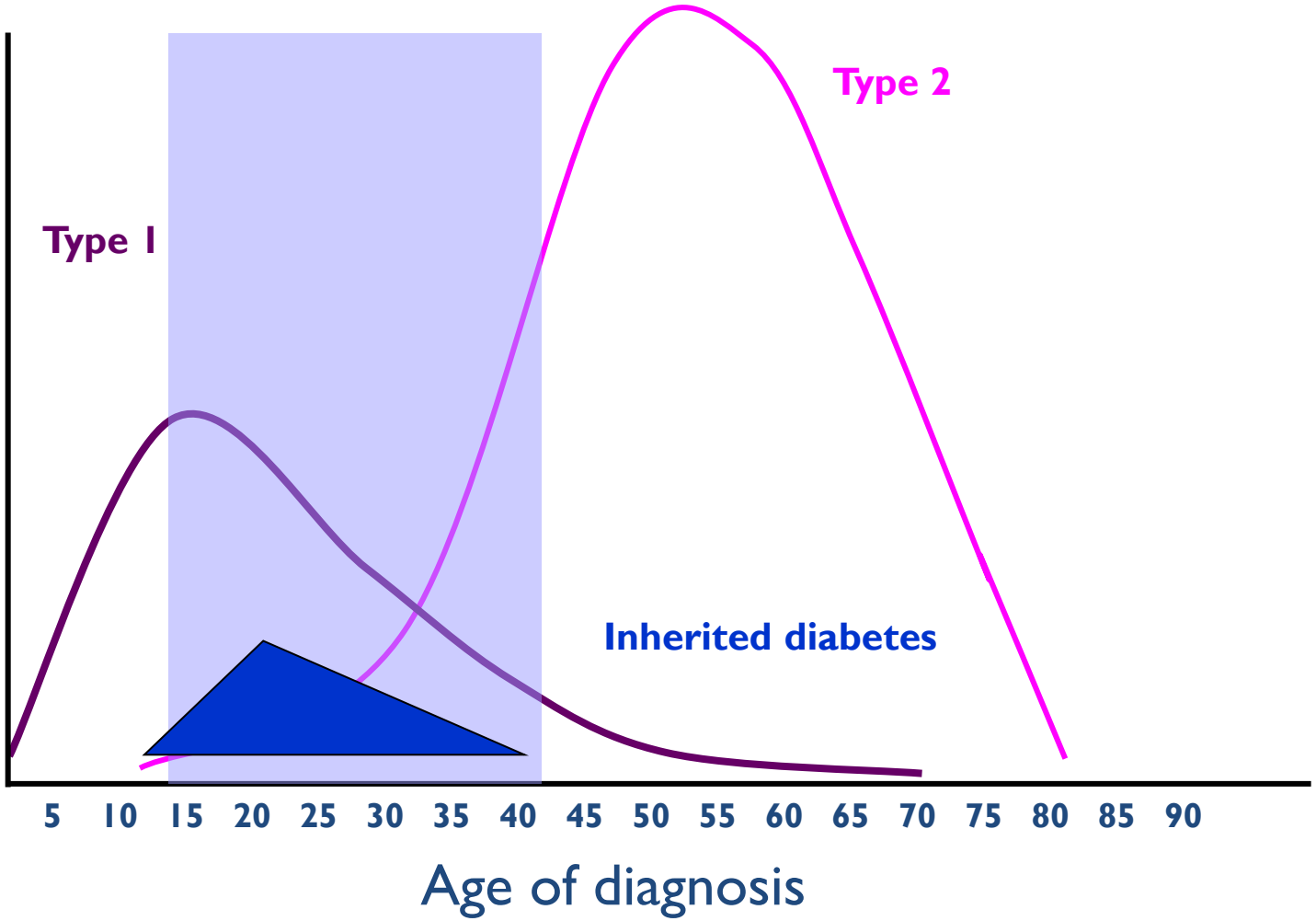
- Informs prognosis and clinical course

- Testing for relatives (diagnostic and predictive)



G Thanabalasingham slide

Young-adult onset diabetes



K Owen slide

Clinical clues to MODY

Type 1 diabetes

- Low insulin doses
- Insulin 'holidays'
- Negative antibodies
- Detectable c-peptide
- Strong family history

Type 2 diabetes

- Young onset age
- Absence of metabolic syndrome
- SU sensitivity
- Strong family history

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Investigating diabetes age<30 in primary care

Investigation of New Diabetes diagnosed before 30 years – Primary care version

NB: Diagnosed ≤19 years or presenting acutely – refer **all** to secondary care

Check Beta-cell antibodies – GAD/IA2

Any positive antibody → **Probable Type 1 diabetes** → Refer to secondary care

All tested Antibodies negative

Clinical Features include:
BMI>30 kg/m^2 with additional feature of insulin resistance (↑BP, ↑TG, ↑LFT, PCOS)

No → **Referral for assessment of aetiology**

Yes → **Probable Type 2 diabetes** → **Local education pathways but consider secondary care for younger patients with multiple risk factors**

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Investigating diabetes age<30 in secondary care

Investigation of New Diabetes diagnosed before 30 years – Secondary care version

NB: For those presenting acutely treat as per usual practice with insulin. Check aetiology later

Check Beta-cell antibodies – GAD/IA2
Check C-peptide if insulin treated

Any positive antibody
*C-peptide –ve

Probable Type 1 diabetes

+ve plasma *C-peptide:
>0.2 nmol/l or >0.6ng/ml
+ve urine *C-peptide:
> 0.2 nmol/mmol

Antibodies negative
*C-peptide +ve

Clinical Features include:
BMI>30 kg/m² with additional feature(s) of insulin resistance (↑BP, ↑TG, NAFLD, PCOS)

Yes

Probable Type 2 diabetes

No, so could it be monogenic?

Is this classic MODY?
Lean, C-peptide +ve, Ab-ve
DKA unlikely
Often FH of diabetes dx ≤ 45 years

GCK-MODY?
Asymptomatic
FBG 5.5-8.0 mmol/l
HbA1c <58/7.5%
FH IGT, GDM

HNF1A/4A- MODY?
CRP<0.5 (HNF1A)
↑BW, neonatal hypos (HNF4A)

Is this Mitochondrial diabetes?
Like MODY but with deafness, other neurology, maternal inheritance

Is this Severe Insulin Resistance?
Young-onset metabolic syndrome, PCOS, acanthosis, BMI seems too low
Lipodystrophy (look at legs)

Is this HNF1B- MODY?
Diabetes plus Cystic renal disease, GU anomalies

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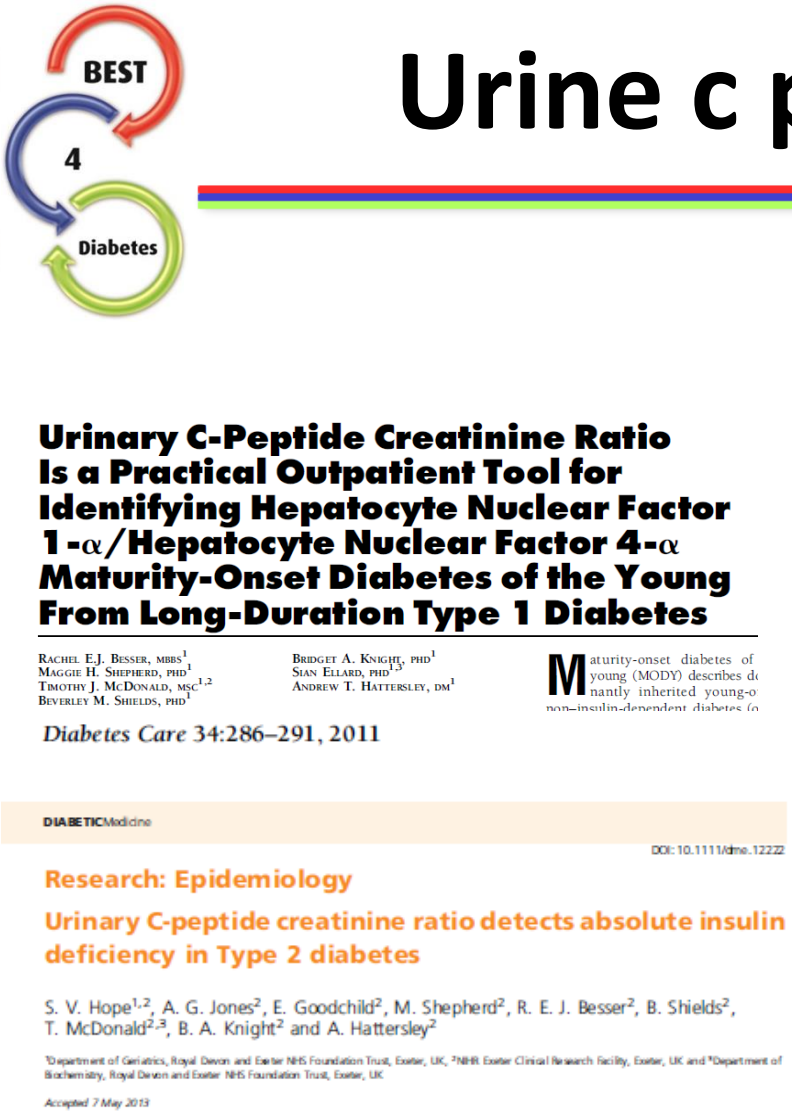
Urine c peptide/Cr ratio



Urinary C-Peptide Creatinine Ratio Is a Practical Outpatient Tool for Identifying Hepatocyte Nuclear Factor 1-α/Hepatocyte Nuclear Factor 4-α Maturity-Onset Diabetes of the Young From Long-Duration Type 1 Diabetes

RACHEL E.J. BESSER, MBBS[1]
MAGGIE H. SHEPHERD, PHD[1]
TIMOTHY J. MCDONALD, MSC[1,2]
BEVERLEY M. SHIELDS, PHD[1]
BRIDGET A. KNIGHT, PHD[1]
SIAN ELLARD, PHD[1,3]
ANDREW T. HATTERSLEY, DM[1]

Maturity-onset diabetes of young (MODY) describes d nantly inherited young-o non–insulin-dependent diabetes (o

Diabetes Care 34:286–291, 2011

DIABETICMedicine

DOI: 10.1111/dme.12222

Research: Epidemiology

Urinary C-peptide creatinine ratio detects absolute insulin deficiency in Type 2 diabetes

S. V. Hope[1,2], A. G. Jones[2], E. Goodchild[2], M. Shepherd[2], R. E. J. Besser[2], B. Shields[2], T. McDonald[2,3], B. A. Knight[2] and A. Hattersley[2]

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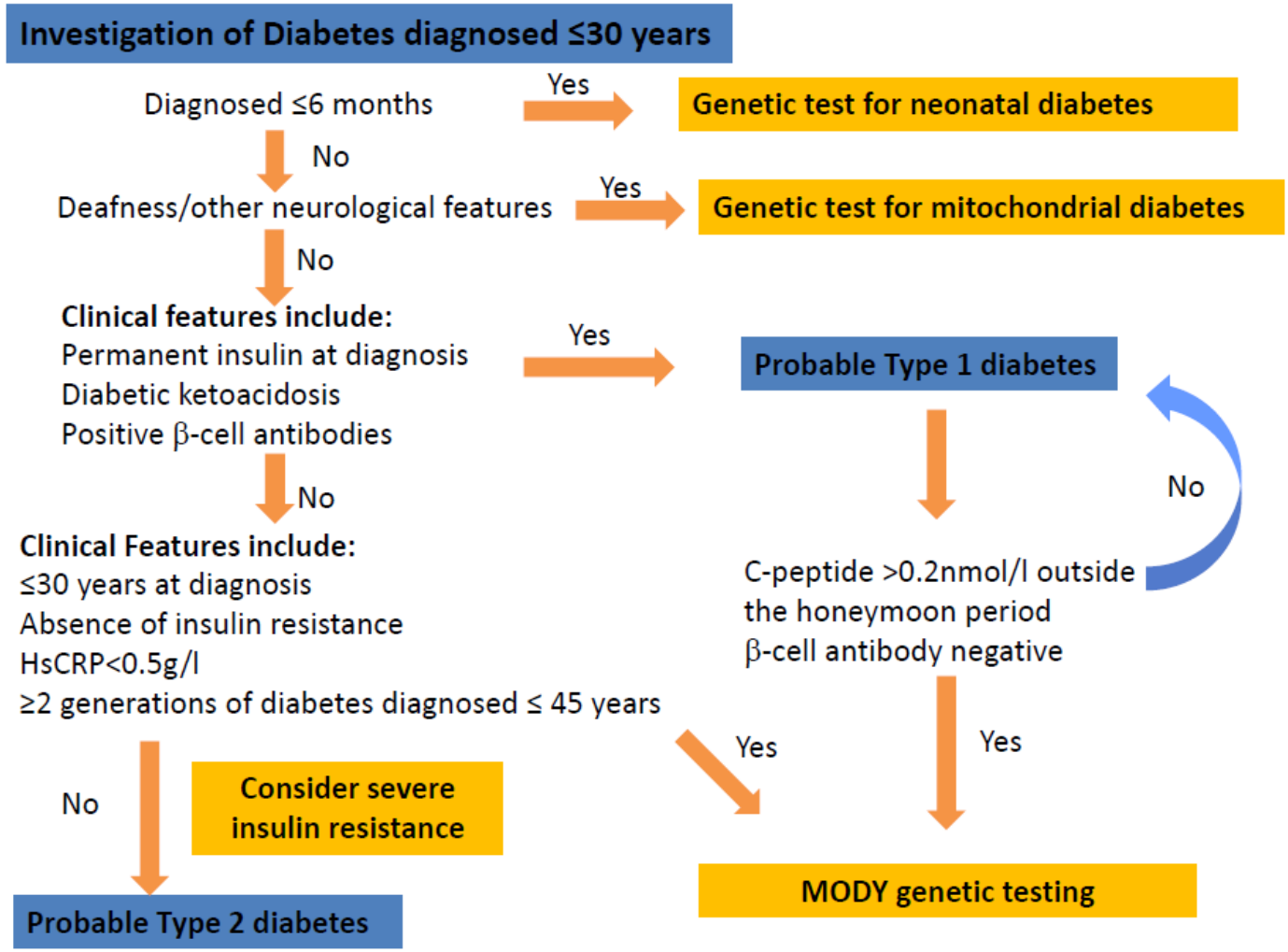
- Patient collects urine sample 2 hrs after breakfast – mon/tues/wed
- Drops to RBH path
- Sent to Exeter for analysis
- Results interpreted via http://www.diabetesgenes.org-content-urine-c-peptide-creatinine-ratio.url

Pathway to genetic testing



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Pragmatic route when you suspect ‘atypical diabetes’

- BMI <30, age<30, FH ‘young onset’ diabetes, low risk ethnicity, no FH T2D
- Check ICA/GAD antibody
- If negative discuss with Ian Gallen in virtual clinic or RBH via advice and guidance email to help arrange urine c peptide studies/serum c peptide
- Trial sulphonylurea +/- weaning of insulin
- Refer to Reading arm of YDX research study for genetic testing – research will cover the cost, result will take ~1 year as batch tested
- Await outcome of health economics studies