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Genomics & personalised medicine in practice: Monogenic Diabetes

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What is monogenic diabetes?

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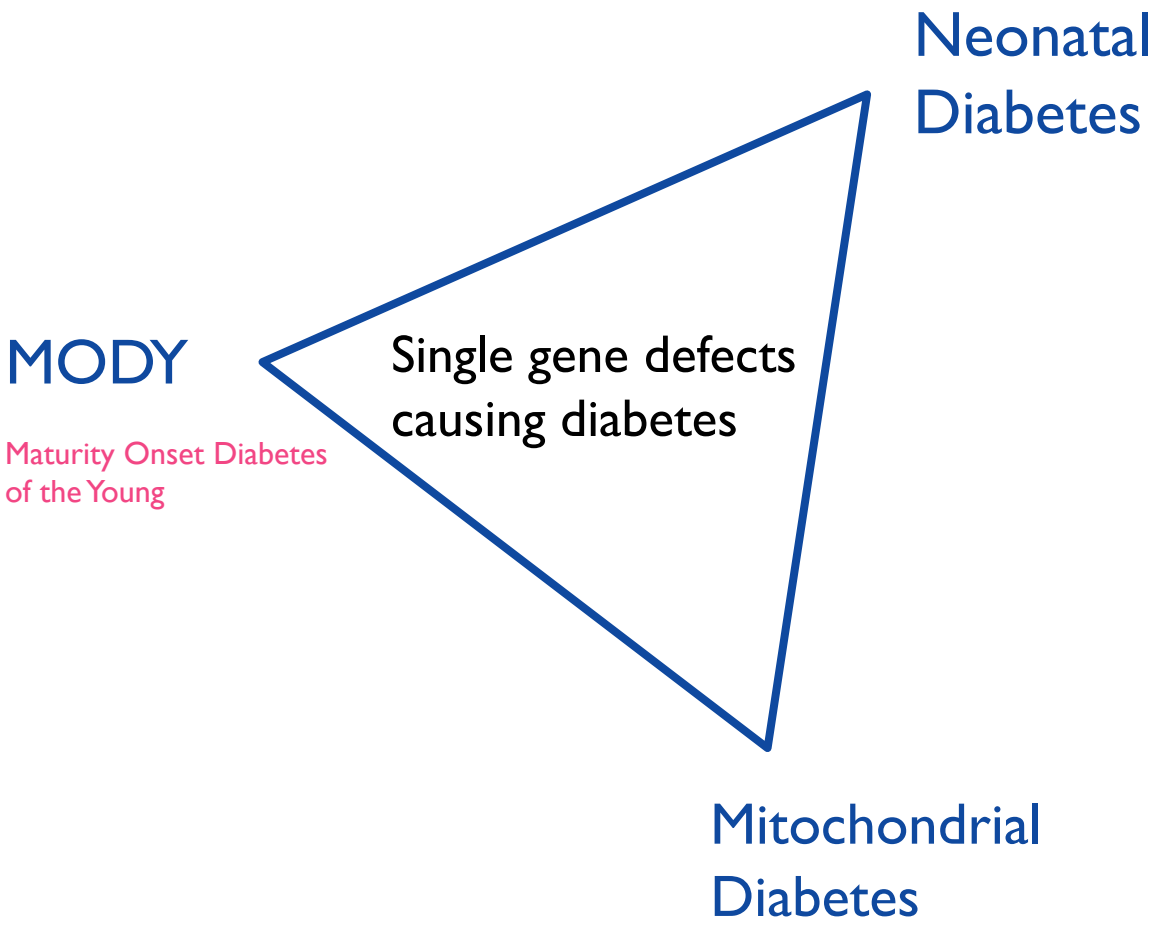
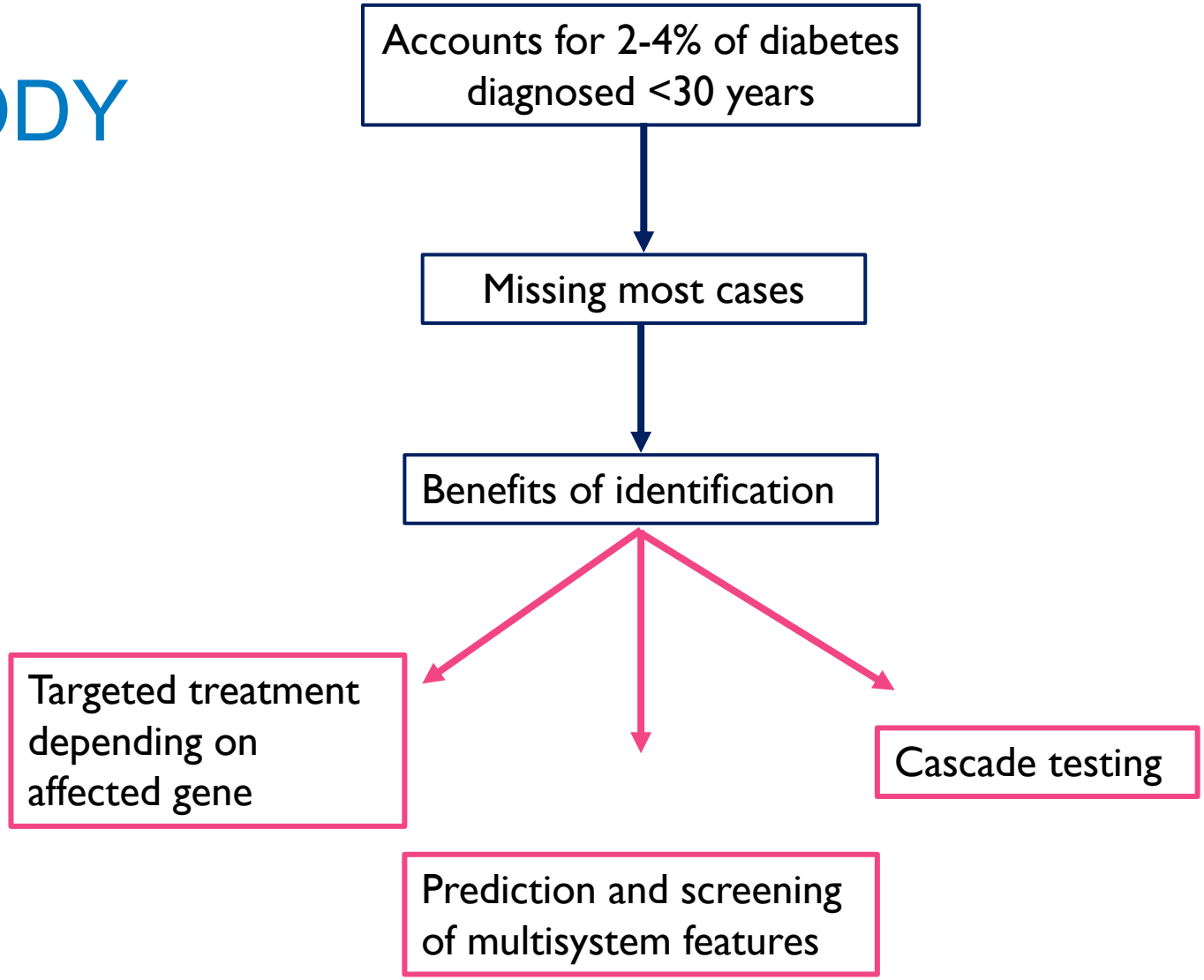


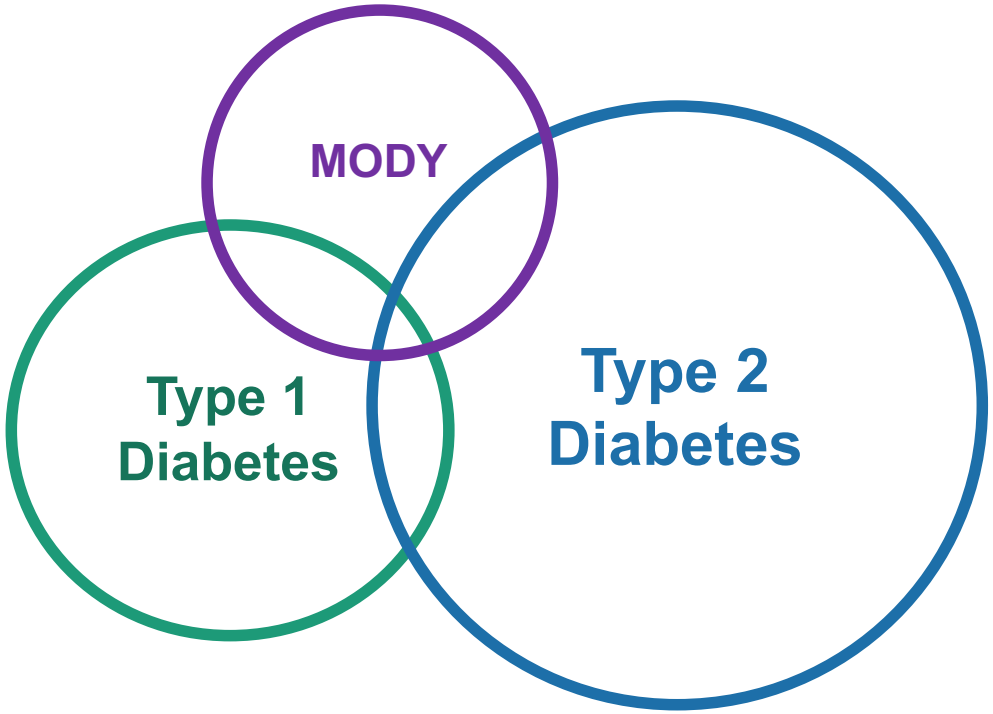
MODY


Accounts for 2-4% of diabetes diagnosed <30 years
Missing most cases
Benefits of identification
Targeted treatment depending on affected gene
Cascade testing
Prediction and screening of multisystem features

Traditional features of MODY

- Young age at onset
- Can manage without insulin
- Parent with diabetes

Stratify for genetic testing



Diabetes subtype matters

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28 year old man
Glucose 18 mmol/L
Thirsty ++

Another type?
- Insulin
- Tablets
- Nothing

Type 1 diabetes
- Insulin injections / pump/ islet cell transplantation
- Self-monitoring blood glucose
- Type 1 diabetes education
- Ketoacidosis prevention
- Carbohydrate counting
- Driving guidance &Employment

Type 2 diabetes
- Metformin /Sulphonylurea GLP1 agonists
- SGLT-2 inhibitors
- DPP4 inhibitors Different insulin regimes
- No routine glucose testing
- Type 2 specific education

Which genes?

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Gene	Protein function
HNF-1alpha	Beta-cell transcription factor
Glucokinase	Enzyme in glycolysis
HNF-4alpha	Beta-cell transcription factor
HNF-1beta	Beta-cell transcription factor
KCNJ11/ABCC8	ATP sensitive beta-cell K^+ channel

HNF1/4A: low-dose, once-daily sulphonylurea

KNCJ11/ABCC8: high-dose TDS sulphonylurea

Glucokinase: no treatment

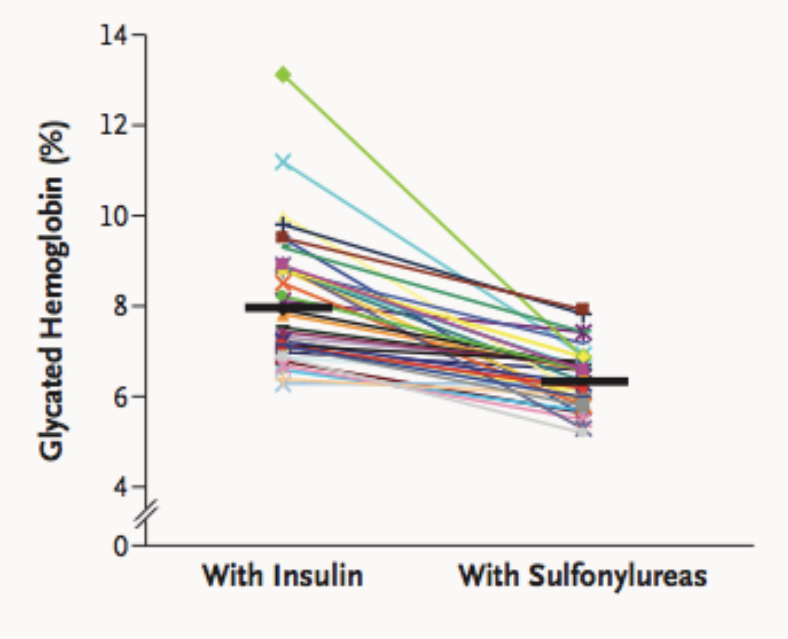
HNF1B: insulin and pancreatic enzyme replacement

Precise treatment better to standard care

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Switching from Insulin to Oral Sulfonylureas in Patients with Diabetes Due to Kir6.2 Mutations



Pearson et al, NEJM 2006; 355:467-477

Barriers to making a diagnosis

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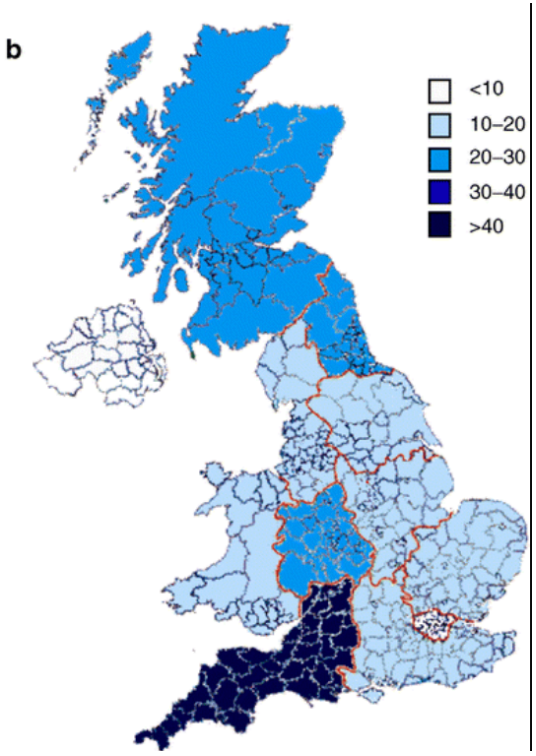
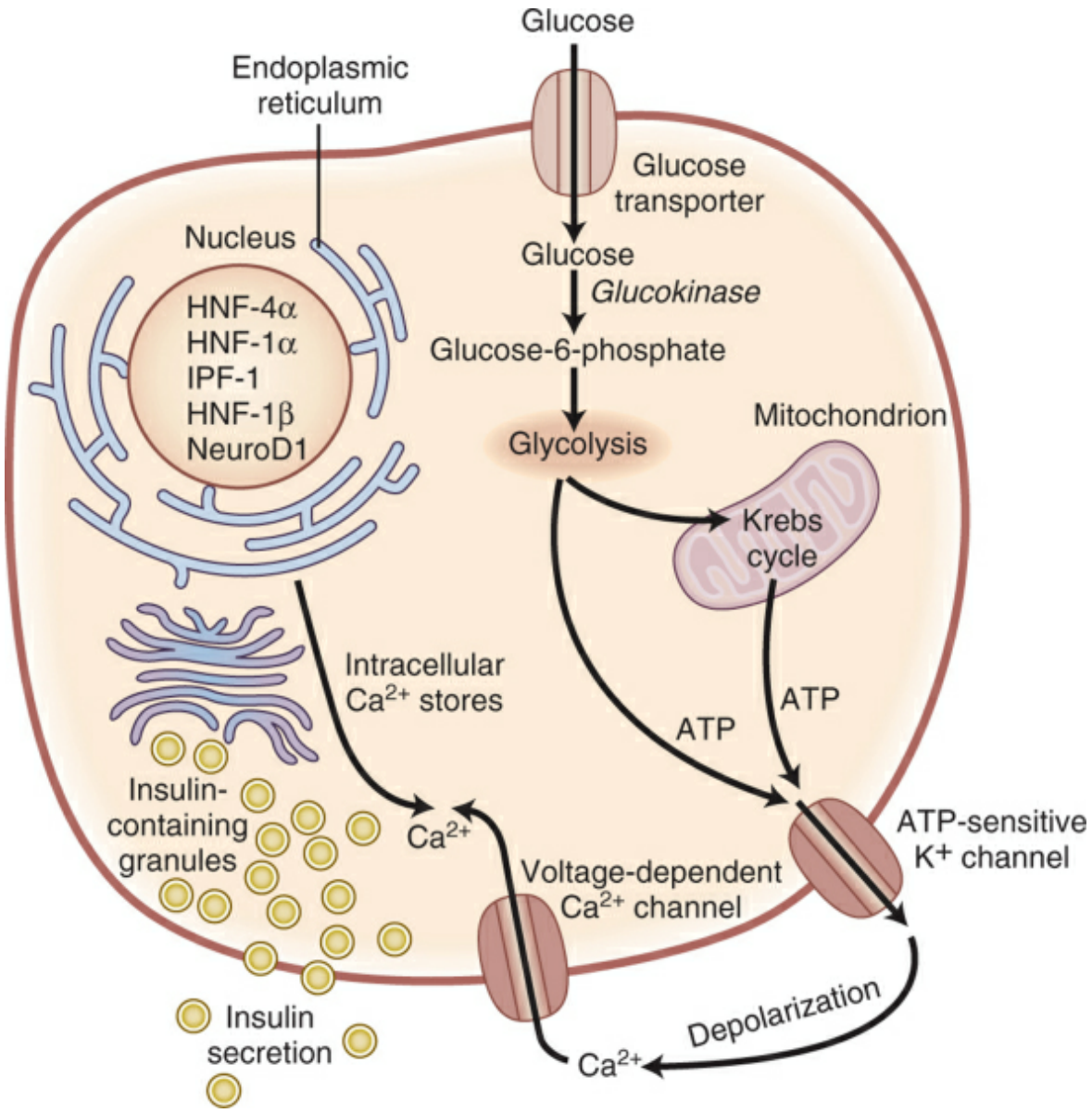
- Thinking about the diagnosis
- Clinical criteria non-specific
- Overlapping features with type 1/ 2 diabetes
- Cost of genetic testing
- Biomarkers not wholly discriminatory
- Risk of uncertain or novel variants



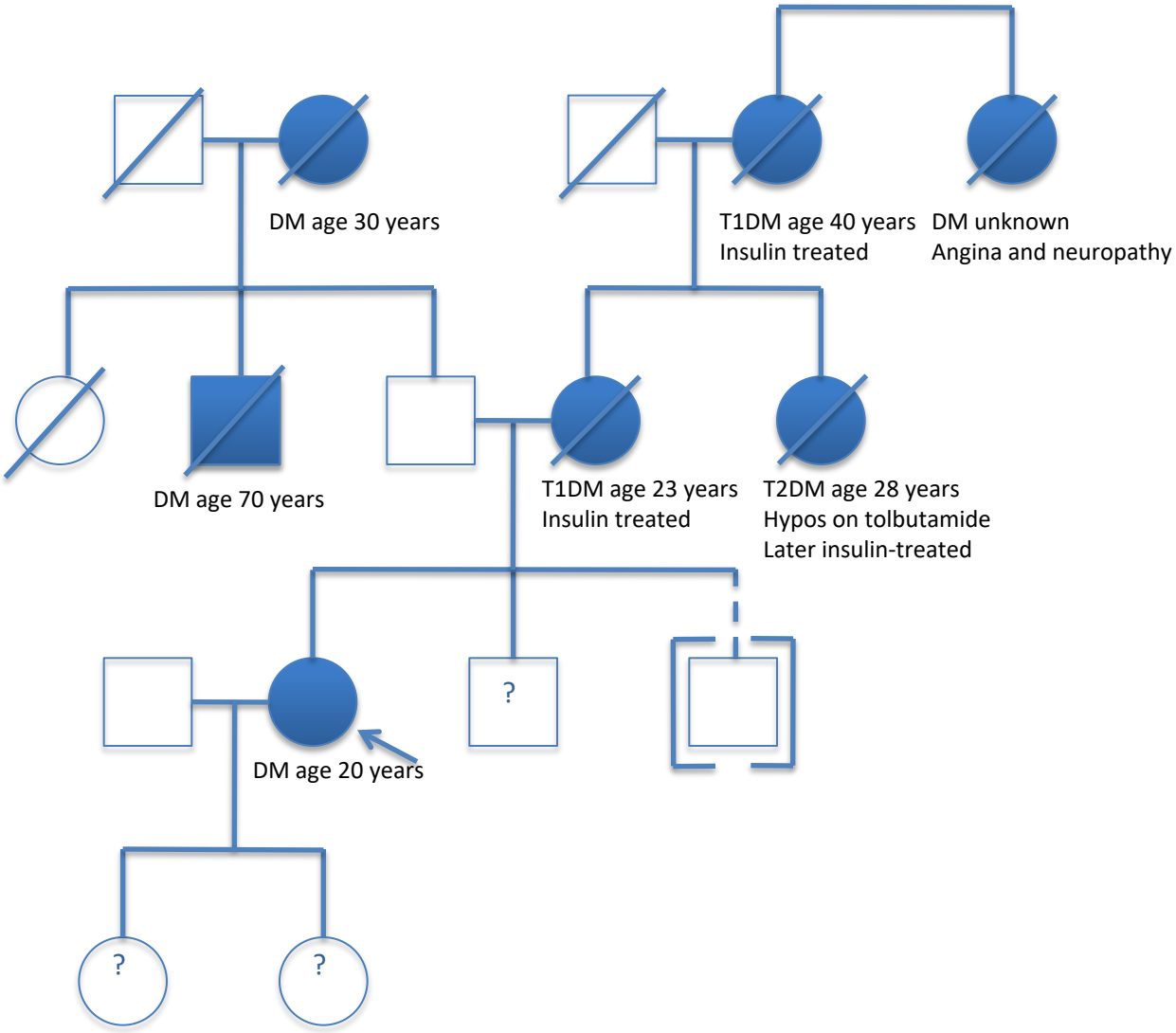
Shields et al 2012


Glucose
Endoplasmic reticulum
Glucose transporter
Nucleus
Glucose
Glucokinase
HNF-4α
HNF-1α
IPF-1
HNF-1β
NeuroD1
Glucose-6-phosphate
Mitochondrion
Glycolysis
Krebs cycle
Intracellular Ca2+ stores
ATP
ATP
Insulin-containing granules
Ca2+
ATP-sensitive K+ channel
Voltage-dependent Ca2+ channel
Depolarization
Insulin secretion
Ca2+

Case 1

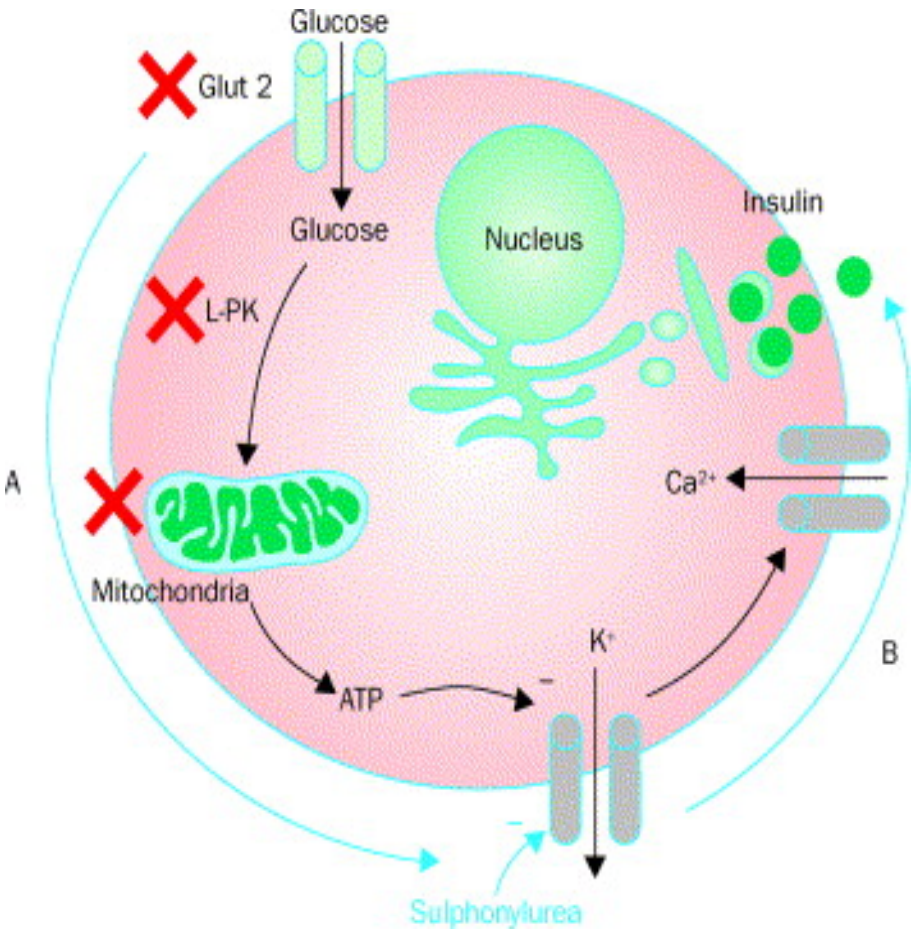
- 56 year old lady, diagnosed aged 20 years
- BMI 22 kg/m^2
- Managed on glimepiride 1mg
  - Profound hypoglycaemia
  - Dose reduced to 0.5 mg OD
  - HbA1c <53 mmol/mol (<7 %)
- 2011 – changed GP and queried type of diabetes

Family History



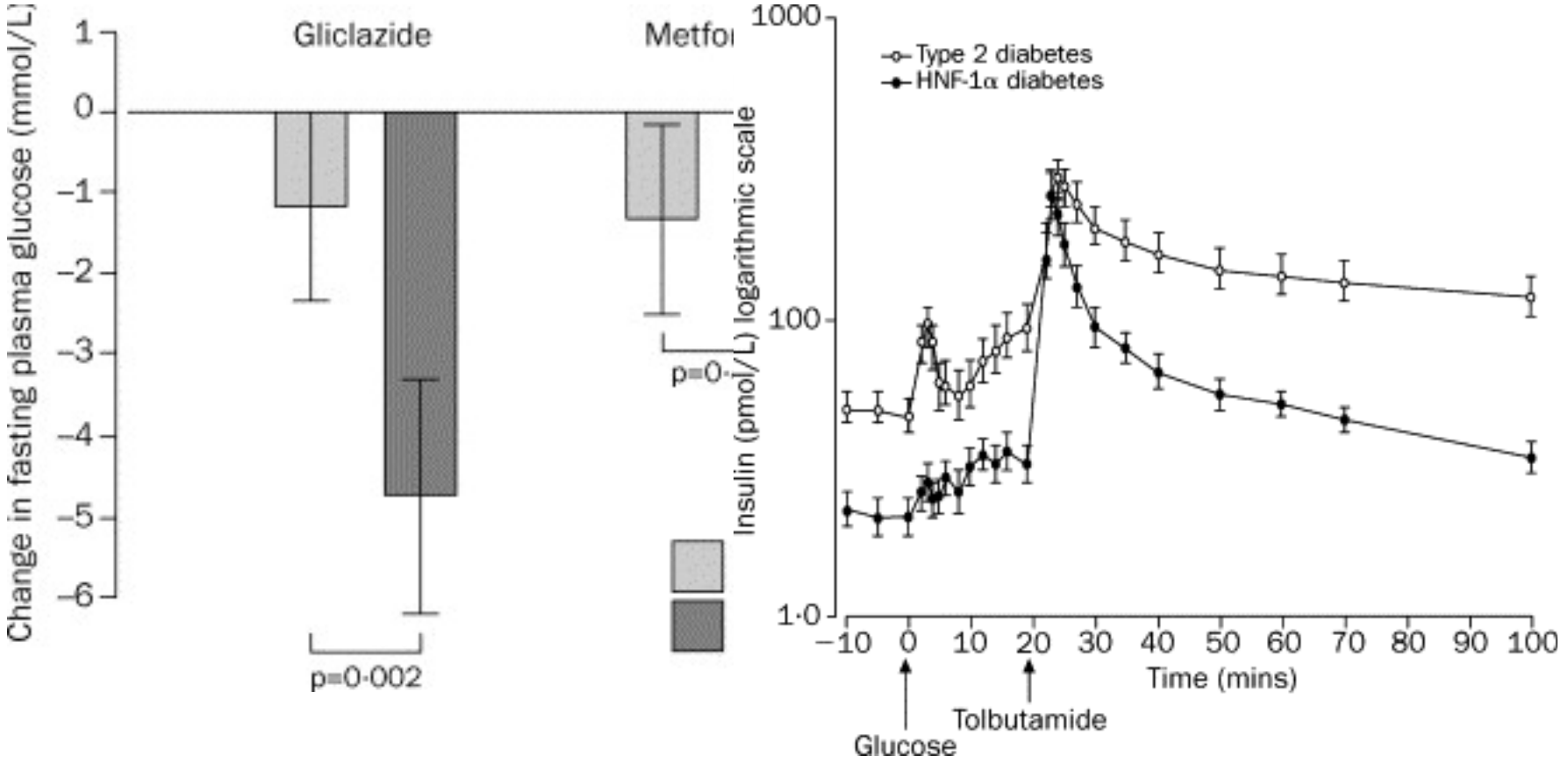
HNF1A Mutations

- Hepatic nuclear factor 1 α
  - Transcription factor normally stimulating insulin production
  - insulin production reduced, but only manifests when beta- cell function starts to naturally decline



Pearson et al, Lancet, 2003.

Sensitivity to Sulphonylureas



Pearson et al, Lancet, 2003.

Control improves with transition to sulphonylurea therapy

DIABETICMedicine
DOI: 10.1111/j.1464-5491.2009.02690.x

Short Report

A genetic diagnosis of *HNF1A* diabetes alters treatment and improves glycaemic control in the majority of insulin-treated patients

M. Shepherd, B. Shields*, S. Ellard*†, O. Rubio-Cabezas*‡ and A. T. Hattersley*

…but less likely to transfer off insulin the longer the duration

HNF-1 alpha

- Hypoglycaemia on low-dose sulphonylurea
  - effective first line treatment
  - Autosomal dominant
- At risk of future microvascular and macrovascular complications (higher than type 1 diabetes)
- May requiring insulin therapy in the long term

HNF-4alpha

- Similar to HNF1A
- 30% cases testing negative to HNF1A

- Differences
  - normal renal threshold
  - associated with fetal macrosomia
  - and neonatal hyperinsulinaemic hypoglycaemia

HNF4A biphasic phenotype

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Hyperinsulinism in utero and early life can lead to hypoglycaemia and macrosomia

Those with *HNF4A* progress to β-cell failure and diabetes in early adulthood

Pearson E et al. PLoS medicine 2007

HNF4A fetal hyperinsulinaemia

- Driving fetal growth
- In some cases (transient) neonatal hypoglycaemia: diazoxide
- Seen regardless of which parent affected

- Later in life diabetes

Case 2

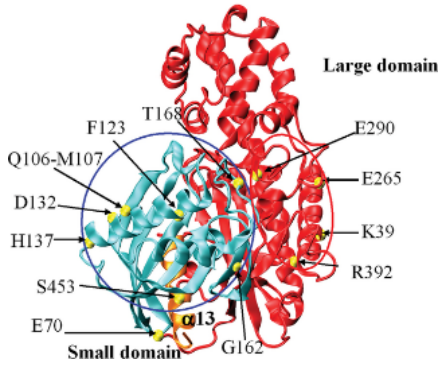
- 22 year old man
  - routine bloods at GP as feeling tired
  - random blood glucose 9.2 mmol/L
  - OGTT: 0min 6.3 mmol/L, 120 min 7.4mmol/L
- HbA1c 42 mmol/mol
- What further information would be useful?

What's the likely diagnosis?

- Impaired fasting glycaemia
- Impaired glucose tolerance
- Glucokinase MODY
- HNF1 alpha mody

Glucokinase

- Enzyme converting glucose to glucose-6-phosphate
- Beta-cell glucose sensing
- Mutations result in a higher set-point at which insulin secretion is triggered;
  - Classically fasting sugars 5.5-8 mmol/L
  - Post-prandial sugars are classically not raised



Patients with glucokinase mutations have stable, mild hyperglycaemia

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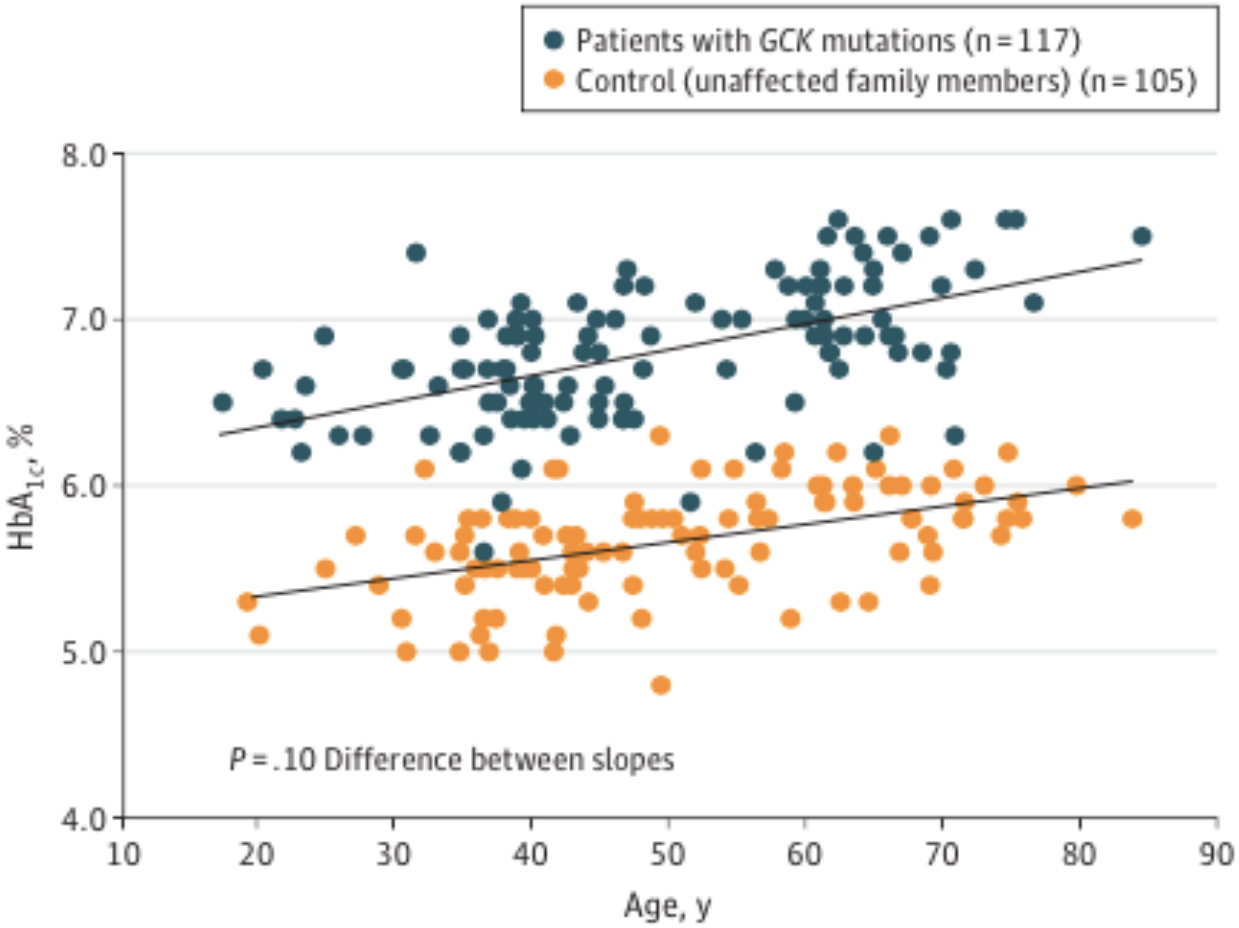
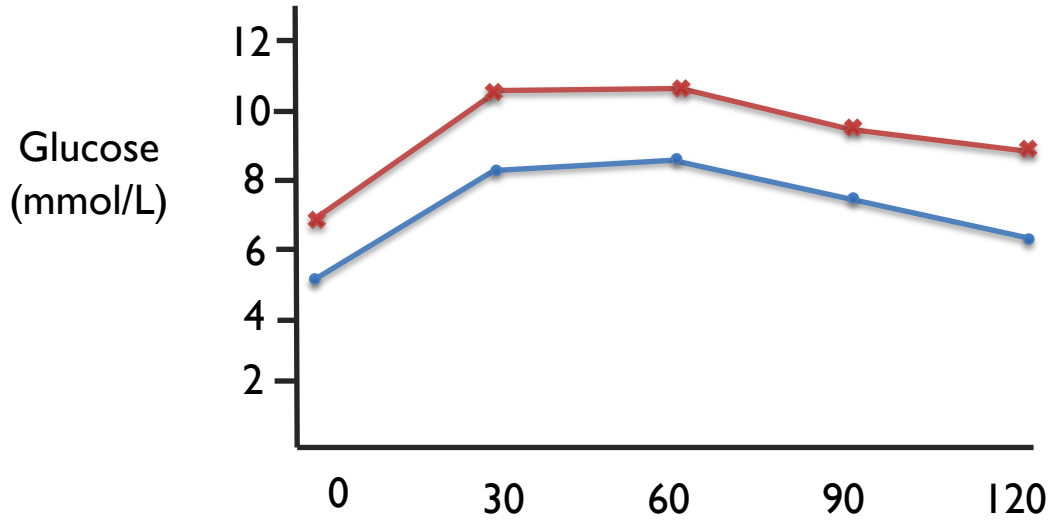


Mean HbA1c 6.7%

Steele et al, JAMA, 2014

GCK patients regulate glucose around a higher fasting set point

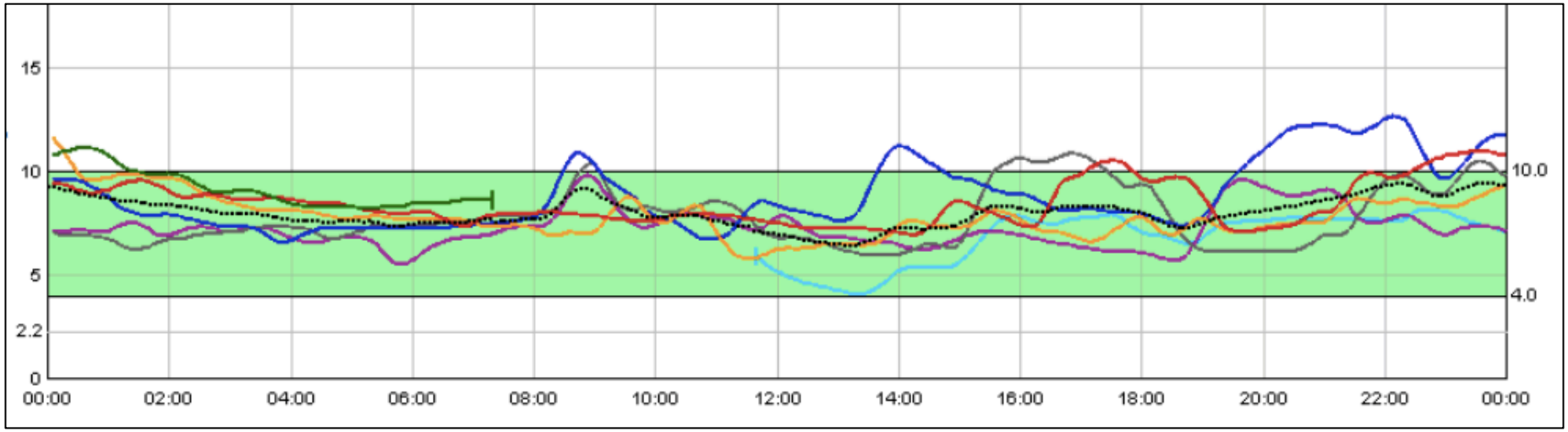


- Glucokinase patients have high fasting and low post-prandial plasma glucose

- Fasting >5.5mmol/L
- 2 hour increment <3mmol/L

Stride et al, Diabetologia, 2002.
With thanks to Anna Steele

Continuous glucose monitoring



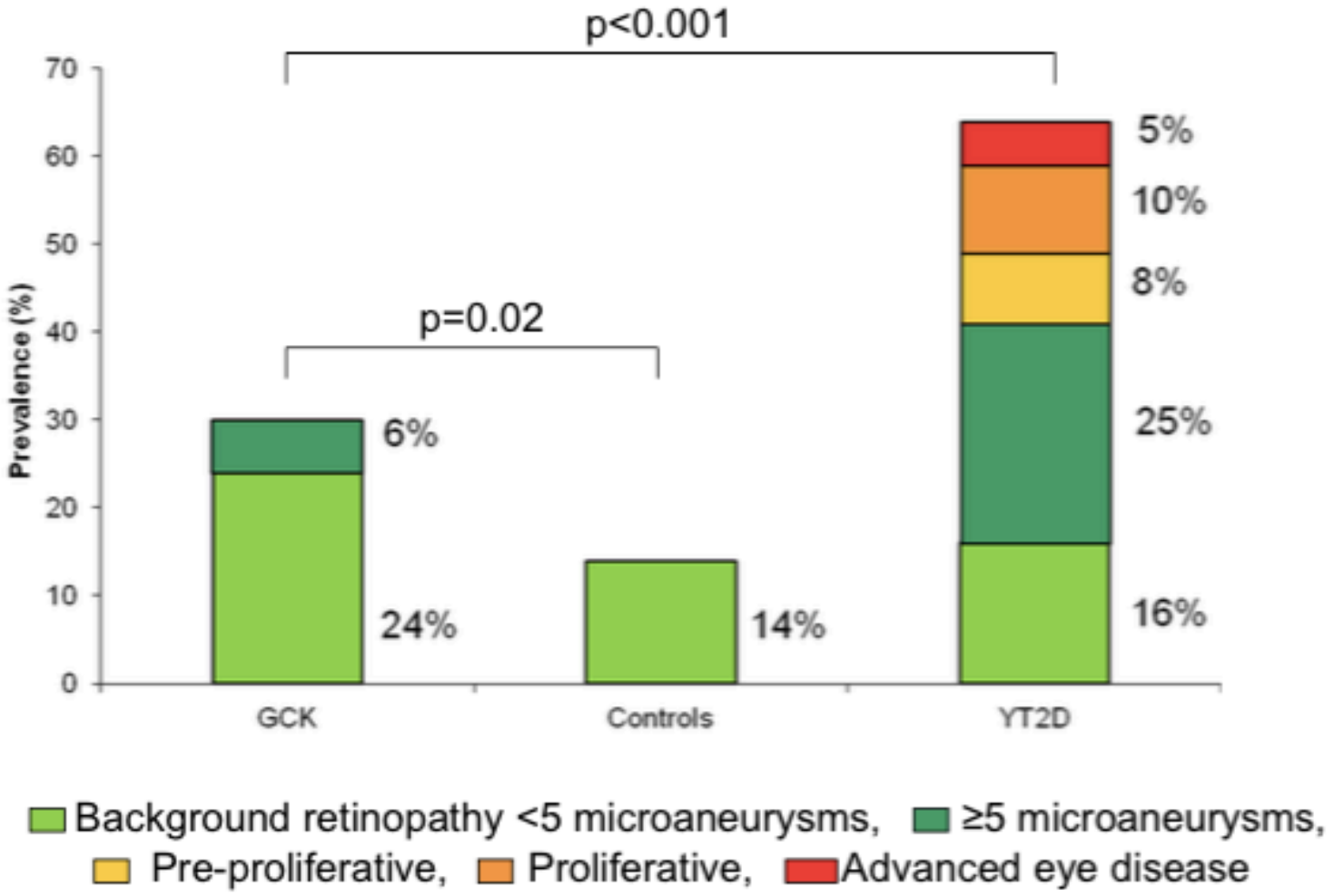
Trace for a GCK patient

On no treatment

JAMA. 2014;311(3):279-286. doi:10.1001/jama.2013.283980

Prevalence of Vascular Complications Among Patients With Glucokinase Mutations and Prolonged, Mild Hyperglycemia

Anna M. Steele, PhD; Beverley M. Shields, PhD; Kirsty J. Wensley, AdDip(Nursing); Kevin Colclough, BSc; Sian Ellard, PhD; Andrew T. Hattersley, DM



With thanks to Anna Steele

Why don’t complications develop?

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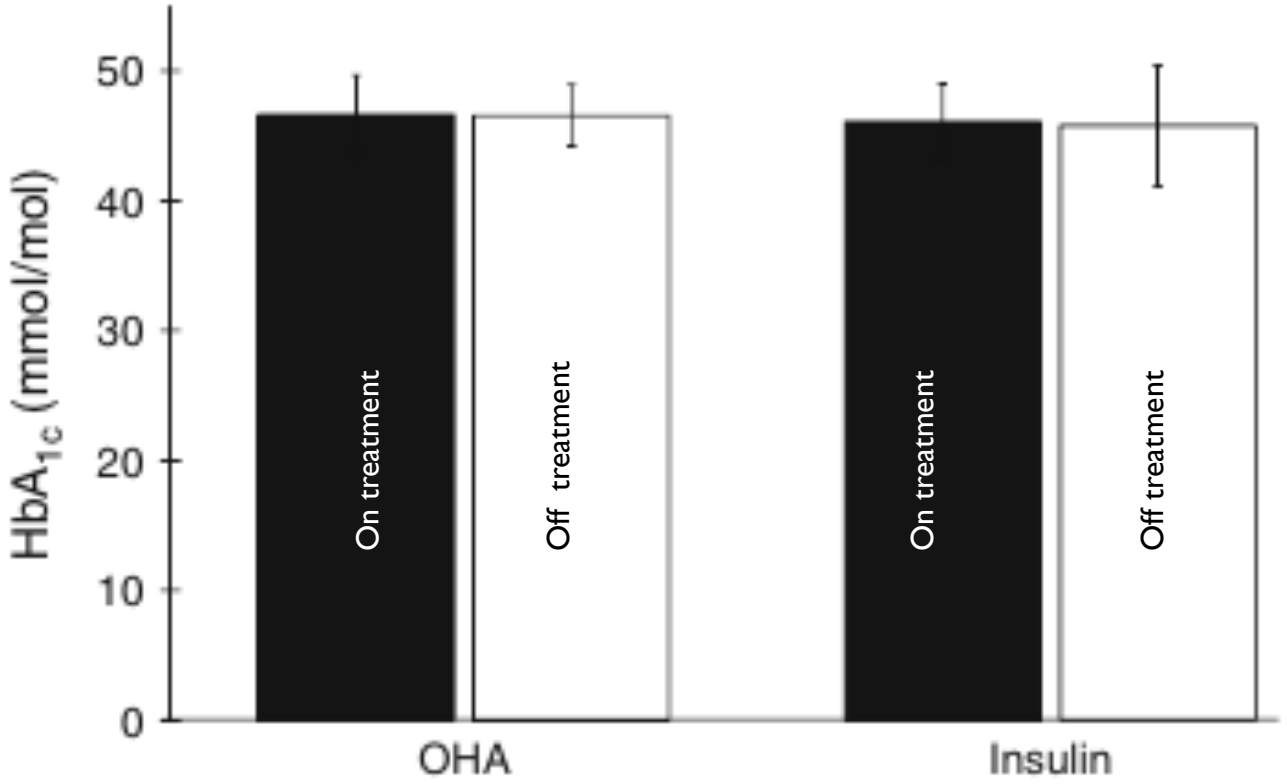
- Isolated risk factor
- Hyperglycaemia is mild and under homeostatic regulation
- Similar insulin resistance and obesity as general population
- ‘Normal’ lipid profile

Treatment does not alter glycaemic control in GCK MODY



Stride et al, Diabetologia 2014

Key clinical features

- Fasting hyperglycaemia, mild
- Small increment on OGTT
- Pregnancy

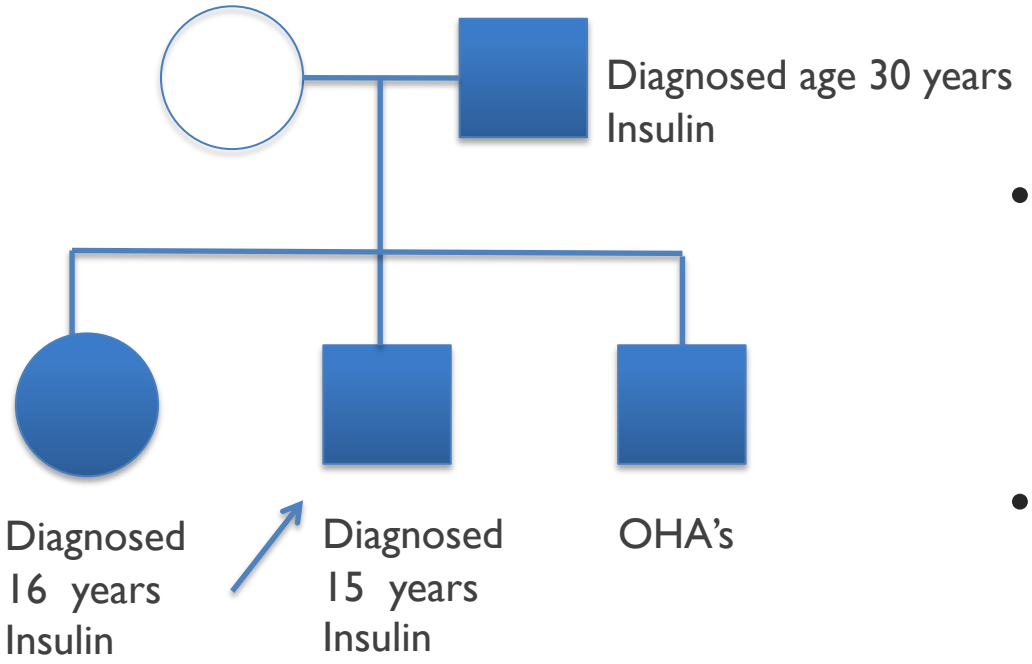
- Family history may be patchy

- Atypical for type 1 or type 2

HNF1 beta

- Also known as renal cysts and diabetes (RCAD)
- Predominantly a renal phenotype
  - diabetes usually develops after renal disease
  - genital tract malformations
  - tubulopathy – hypomagnasaemia
  - mildly deranged liver function
  - pancreatic atrophy
- 50 % whole gene deletions, often spontaneous

Case 3



- Bangladeshi family
- C-peptide ~400 pmol/L, antibody negative
- Genetic testing for HNF1-alpha requested in 2001
- Revealed novel variant of unknown significance
- Trial on gliclazide failed

Case 3

- Family studies planned to determine co-segregation

- But…
  - Index case noted to be hypomagnasaemic
  - Deranged LFTs

HNF1-Beta whole gene deletion

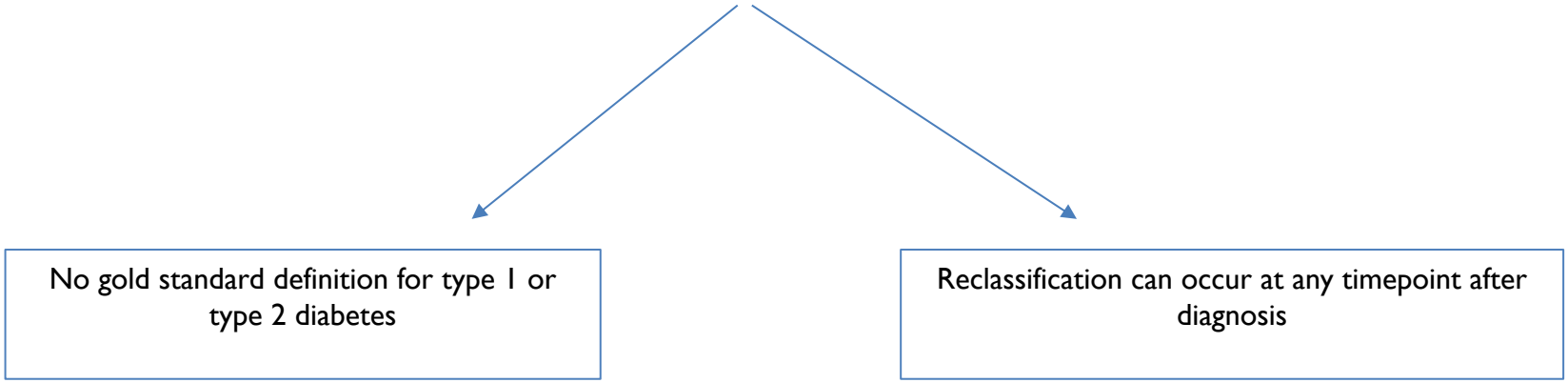
Key clinical features

- Renal phenotype
  - cysts, dysplasia
- Low magnesium, deranged LFT's
- Exocrine pancreatic failure
- More likely to require insulin

- Atypical for type 1 or type 2

Diabetes misclassification

How big of a problem is this?
challenging to ascertain



We are all seeing more grey cases

So, how do we decide?

1. There is no test that 100% accurately diagnoses diabetes subtype
   a) Genetic testing for monogenic diabetes

2. Age and body mass index (BMI) are the two factors most likely to influence type of diabetes

3. Age and BMI are increasingly poor at discriminating diabetes subtype

NICE guidelines [NG17]

Diagnose type 1 diabetes on clinical grounds:

ketosis

rapid weight loss

Aged <50 years

BMI <25 kg/m^2

history of autoimmune disease

Do not discount a diagnosis of type 1 diabetes if:

- BMI >25 kg/m^2 or
- Aged > 50 years

Children – assume Type 1 unless strong indications of another subtype

Solutions?

Clinical features

Overlap considerably

Pancreatic auto-antibodies

Low negative predictive value
Positive without diabetes

C-peptide

How do we interpret it at diagnosis?
No cut-offs are wholly accurate

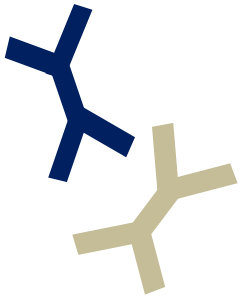
Time

Pancreatic Autoantibodies

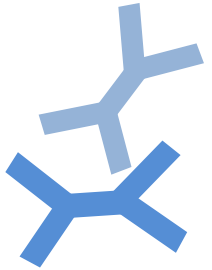
Glutamate decarboxylase (GAD-65)

Islet antigen 2 (IA-2)

Zinc transporter 8 (ZnT8)



- Primarily studied in a research setting to predict onset of type 1 diabetes
- Role in classification of diabetes is unclear
- Islet cell antibodies by immunoflouresence obsolete



6 Challenges in interpreting pancreatic antibodies

1. Antibody negativity does not exclude type 1 diabetes
2. Titres diminish with duration
3. People from some ethnic groups may have low rates of positivity
4. Less than complete testing
5. Some people without diabetes are antibody positive
6. Significance of single antibody positivity

Best practice

- What's the clinical question?
- Antibodies should only be measured to support a diagnosis of type 1 diabetes
- Type 1 diabetes is **not excluded** if antibodies are negative

Clinical suspicion high but antibodies negative → Do not defer insulin

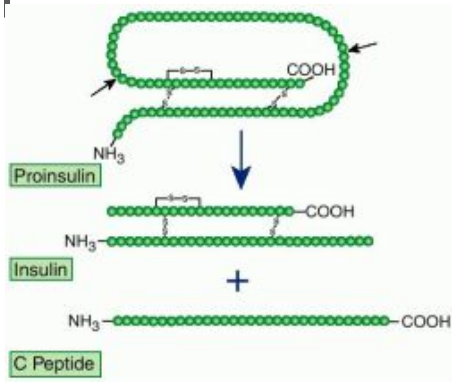
Clinical suspicion low and antibodies negative → Why measuring? Clear clinical question in mind

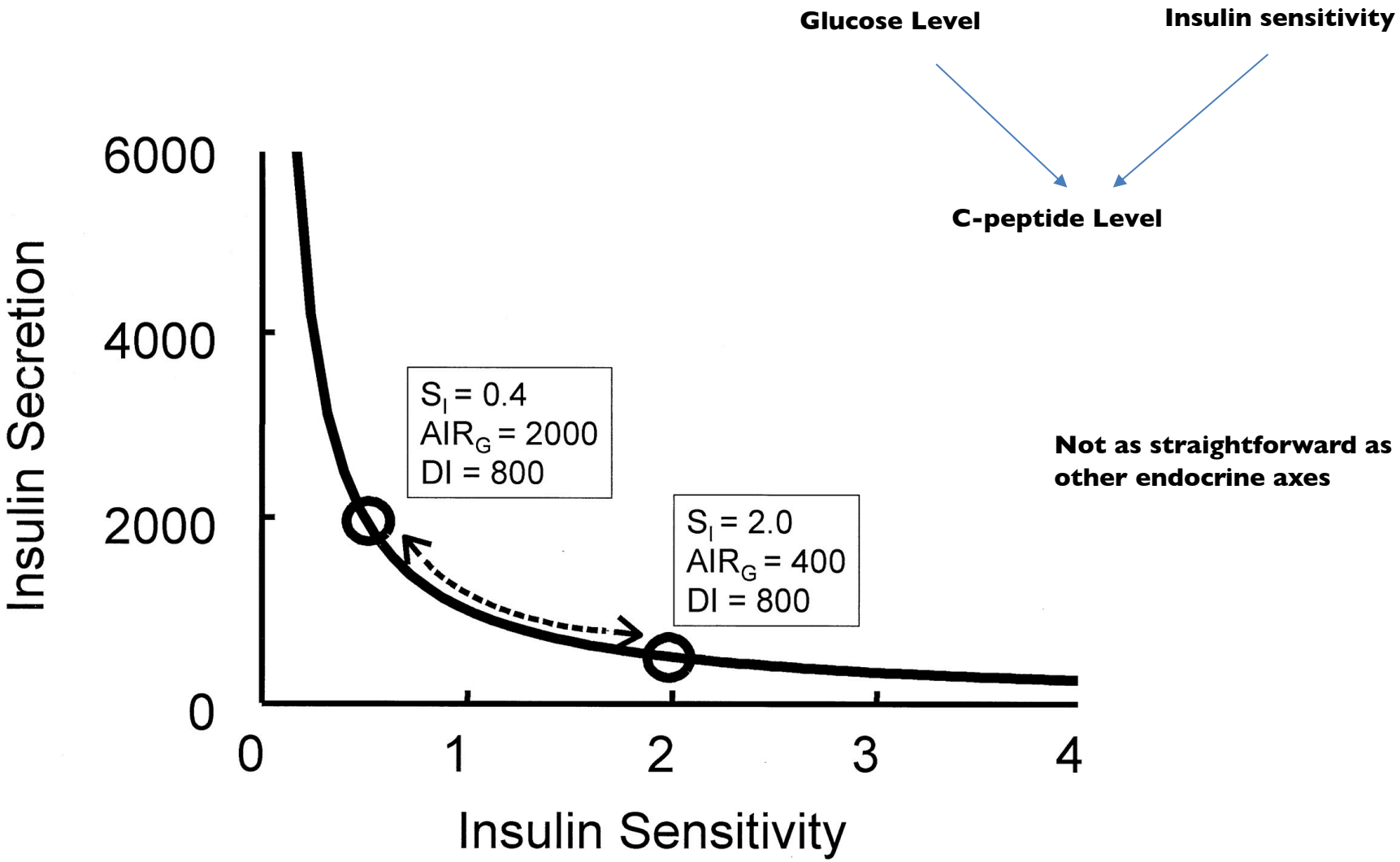
Clinical suspicion intermediate and antibodies positive → Supportive of type 1 diabetes

C-Peptide

- Cleavage product of pro-insulin
- Compared with insulin
  - Longer half-life
  - More stable than insulin
  - No first pass metabolism

- Established marker of beta-cell function
  - Also influenced by insulin sensitivity




Glucose Level
Insulin sensitivity
C-peptide Level
6000
4000
2000
0
Insulin Secretion
S_I = 0.4
AIR_G = 2000
DI = 800
S_I = 2.0
AIR_G = 400
DI = 800
0
1
2
3
4
Insulin Sensitivity
Not as straightforward as other endocrine axes

C-peptide

- No ‘normal ranges’ defined
- No robustly evaluated cut-off that delineates one type from another
- Not interpretable at diagnosis

What does a C-peptide level really mean?

- Need to know the contemporaneous glucose level
- And the clinical context
  - we're asking, does this patient need insulin?
  - could it be something other than type 1 diabetes

- **Low (<200 pmol/L) or undetectable**

  Assuming glucose >8mM

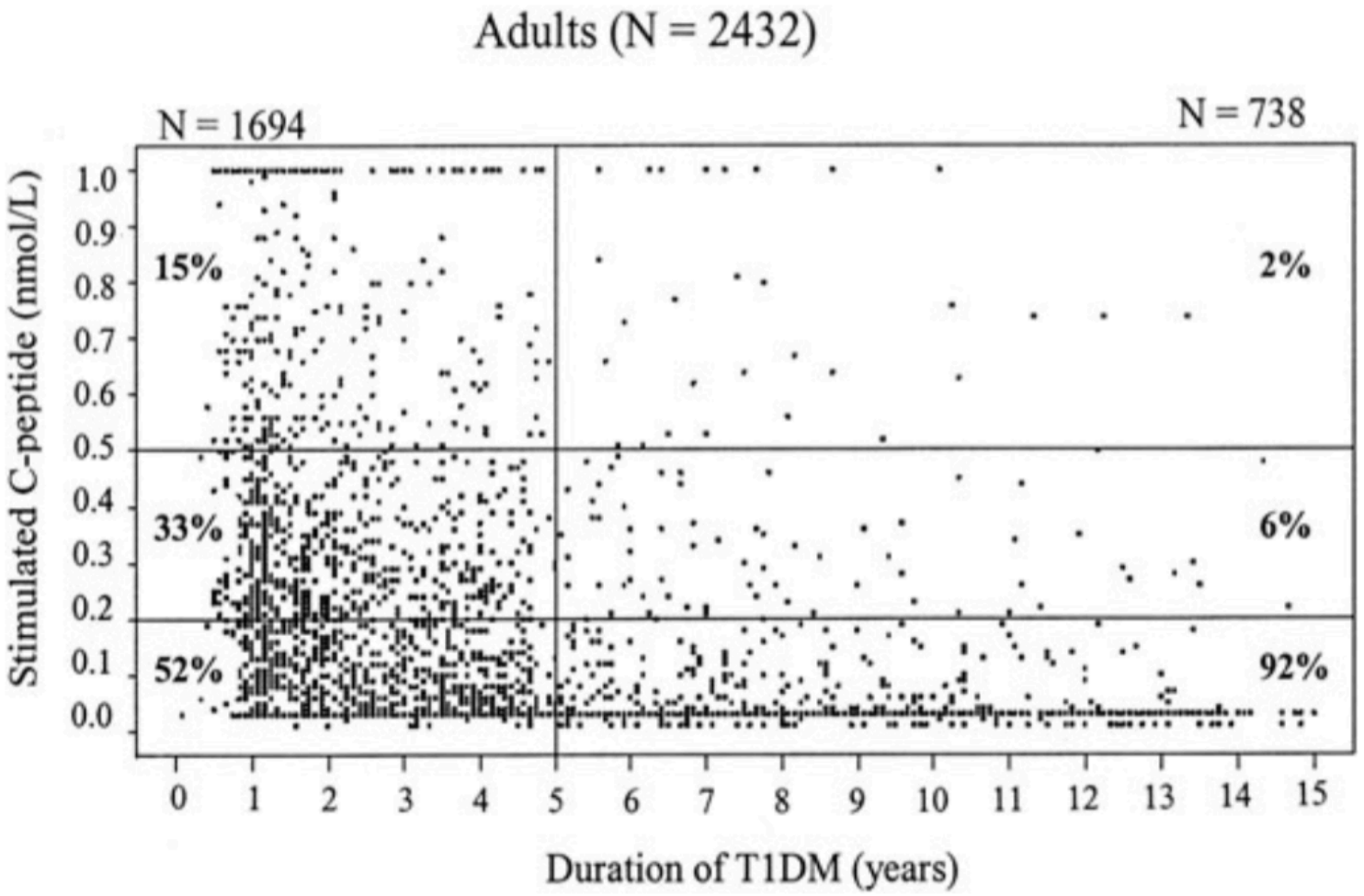
- Above 200 pmol/L
  - Difficult to say

Does this patient need insulin?

- C-peptide 1200 pmol/L + glucose 29 mmol/L
- C-peptide 1200 pmol/L + glucose 9 mmol/L

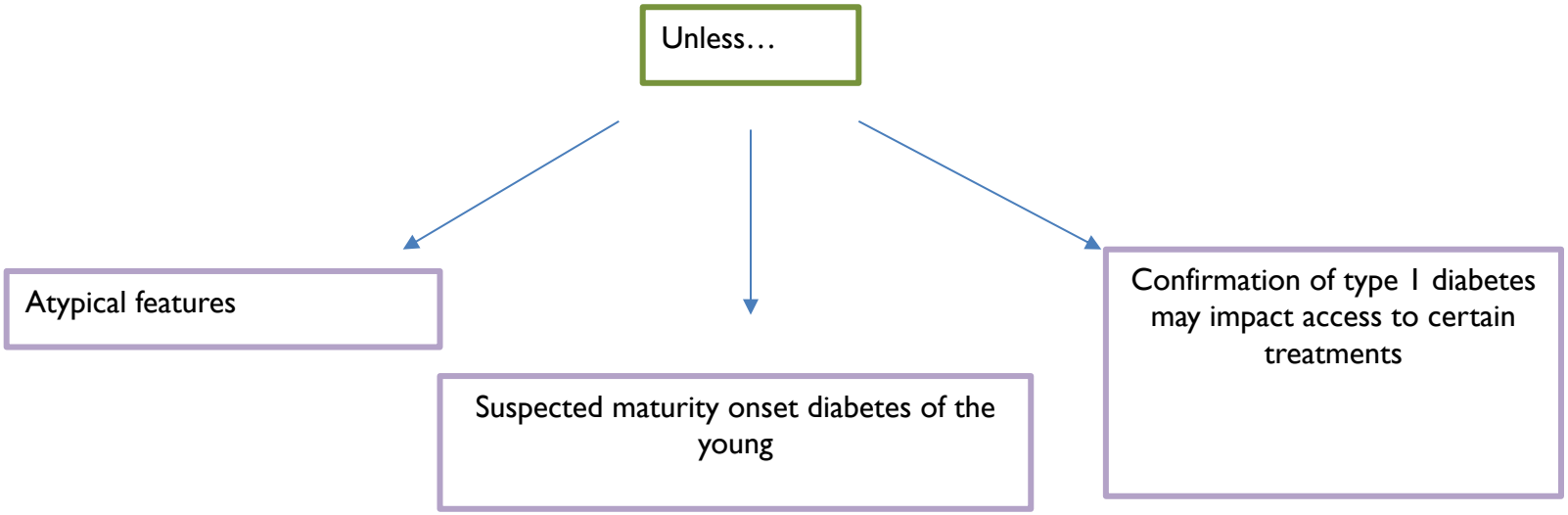
Spread of C-peptide in DCCT

A:



C-peptide & Antibodies

1.1.3 Do not measure C-peptide and/or diabetes-specific autoantibody titres routinely to confirm type 1 diabetes in adults. **[new 2015]**



If you suspect type 1 diabetes, DO NOT delay starting insulin
Specialist tests should be undertaken in specialist clinics

Power in combination

- Combine antibodies, C-peptide & Clinical features
  - Start to get powerful stratification
  - Need to evaluate in all ages and ethnic groups
  - Use these approaches to stratify for MODY testing

- C-peptide and pancreatic autoantibodies are biomarkers that can….
  - support clinical suspicion of type 1
  - support diagnosis of atypical cases
  - support requests for genetic testing

- C-peptide and pancreatic autoantibodies are biomarkers that can’t….
  - exclude type 1 diabetes
  - currently be applied with equal confidence to all ethnicities
  - be easily interpreted

Strategies to improve classification

1. Features in the history
2. Features on examination
3. Basic biochemistry
   - **Specialist biochemistry**
4. **Genetic testing**
5. Time
6. Improve our understanding - research!

Conclusion (1)

- Monogenic diabetes
  - Maturity onset diabetes of the young
    - HNF1A, HNF4A, HNF1B, GCK
    - Affected gene determines treatment
- Permanent neonatal diabetes
- Mitochondrial diabetes

Practical tips

- Think about MODY
  - Young adults & BAME groups
- Specialist tests (C-peptide / pancreatic auto-antibodies)
  - have a clear clinical question in mind before requesting
  - remember they are not diagnostic
  - best undertaken in diabetes clinic or with support from specialist team
- Genetic testing for MODY
  - Liaise with your local service

ICHT Service

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- Non-classical diabetes clinic
- Monthly 2nd Weds pm
- Referral assessment service (RAS) on e-referrals

- Feel free to email me: s.misra@nhs.net

A final case