UNIVERSITY OF EXETER | Exeter Centre of Excellence for Diabetes Research

wellcome

MODY update
New test, bad genes and an old gene with a new twist

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Monogenic diabetes – clinically and genetically heterogenous

Neonatal diabetes

1:70-100,000

Under 6 months of age

Transient - 45%

Permanent - 45%

N=41

MODY

~3% under 30y

<35y

Autosomal dominant

Non-insulin-dependent diabetes

N=10

Syndromic diabetes

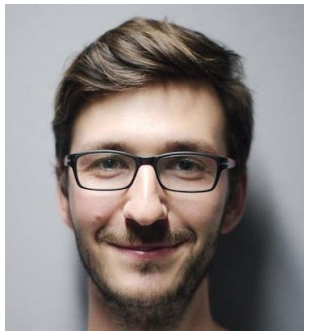
~1-3% under 30y

<25y

Diabetes is part of multi system syndrome

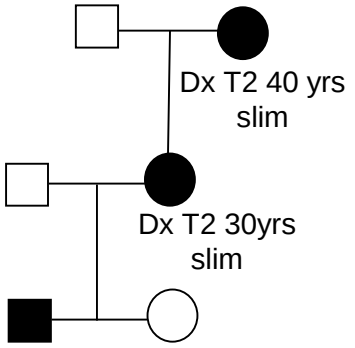
N=28

Young onset nonobese diabetes – suspected MODY



Bill – 24y

- Diabetes at 24y
- BMI – 21 kg/m2
- Insulin – basal bolus therapy
- HbA1c – 7.5% (58)
- Often misses insulin
- Mother and grandmother with diabetes



? Genetic testing

MODY Probability calculator – produce a probability of MODY based on clinical features

www.diabetesgenes.org

Age at diagnosis

Sex ○ Male ○ Female

Insulin Treatment ○ Yes ○ No

Time to Insulin
○ Not currently treated with insulin
○ Within 6 months of diagnosis
○ Over 6 months after diagnosis

BMI

HbA1c

Age

Parent with diabetes ○ Yes ○ No

Use of calculator -- 33% MODY
Not use of calculator -- 25% MODY

> 300,000 hits worldwide

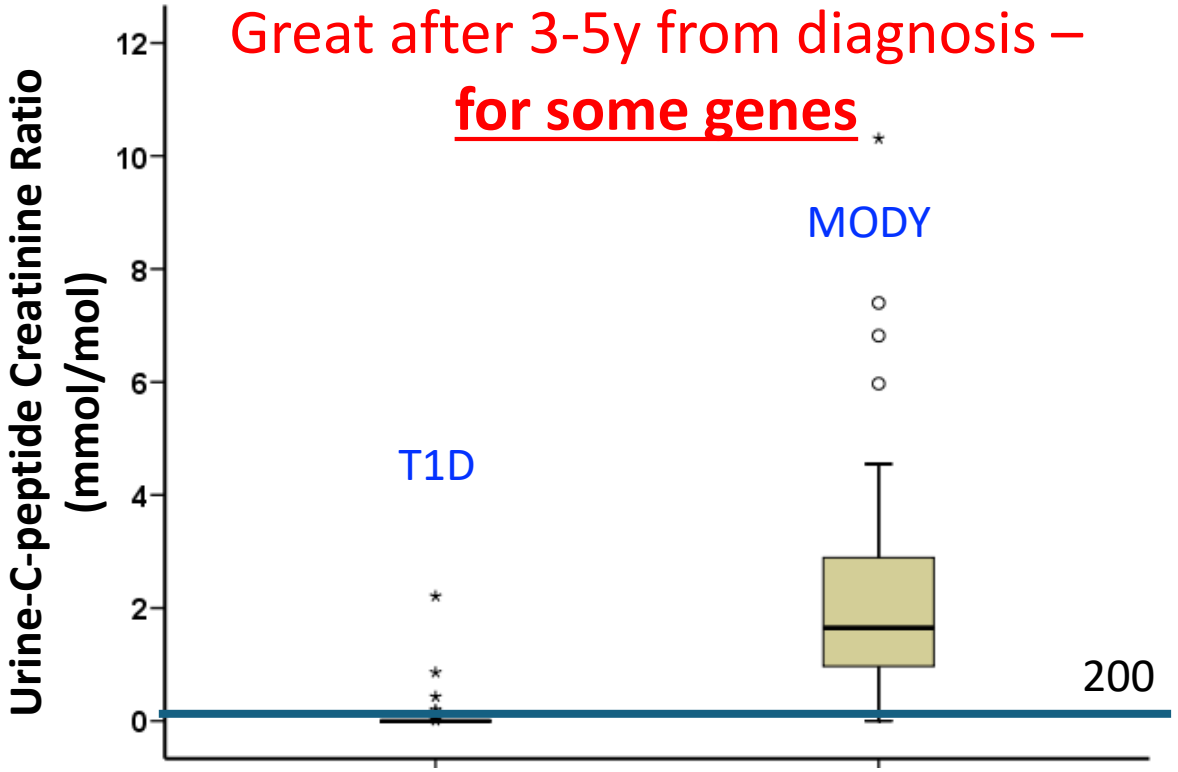
Works in other ancestries but modification is needed

Bev

Pang Diabetes care 2022
Shields Diabetologia 2012

C-peptide and islet autoantibodies are very good rule out test but with limitations

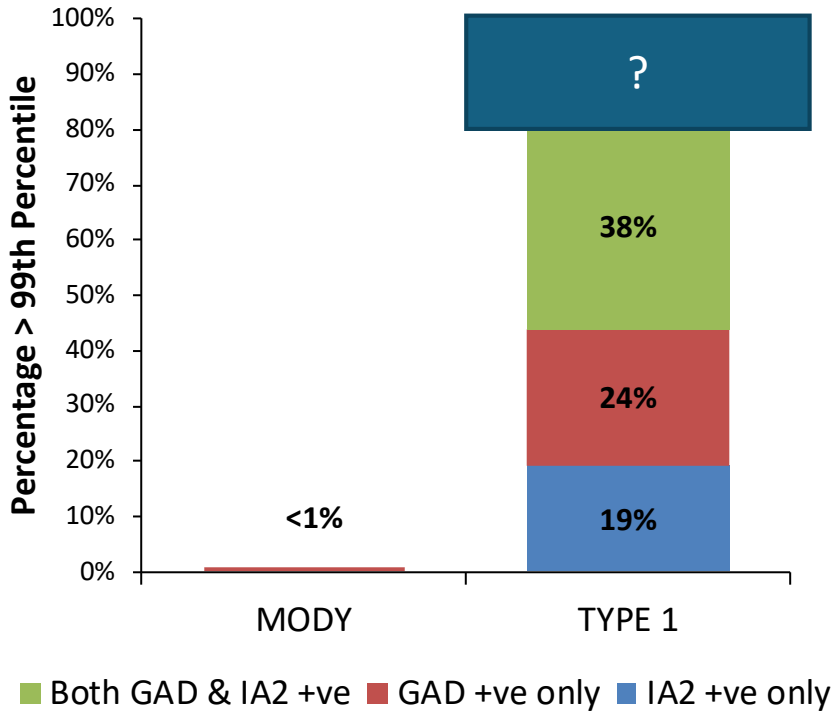
Great after 3-5y from diagnosis – **for some genes**



C-peptide >200 pmol/l at 5 y conferred 97% sensitivity and 96% specificity

Besser Diabetes care 2011

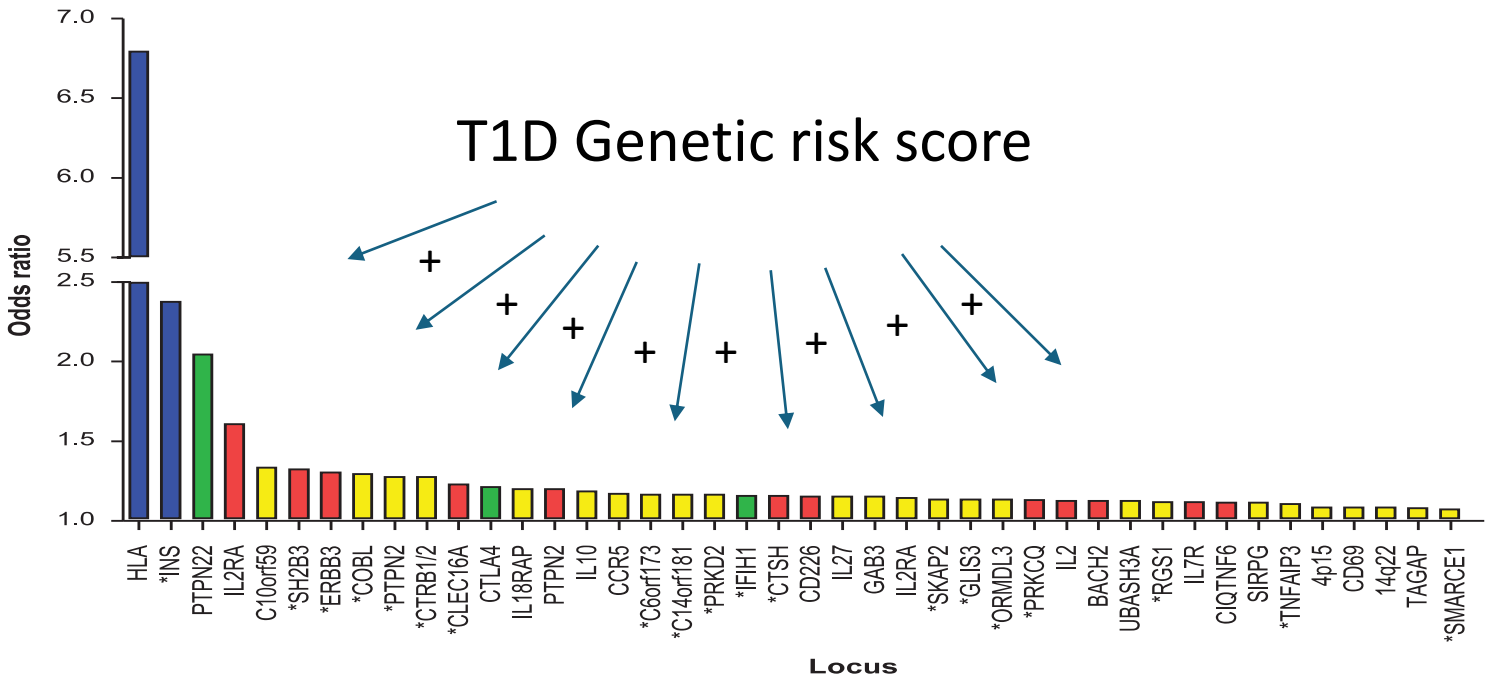
Useful at diagnosis, ~10% T1D Neg



Mcdonald Diabetic medicine 2011

Is there any biomarker that is useful in antibody negative cases irrespective of duration of diabetes?

T1D – high genetic predisposition
~90 genetic variants are associated with T1D



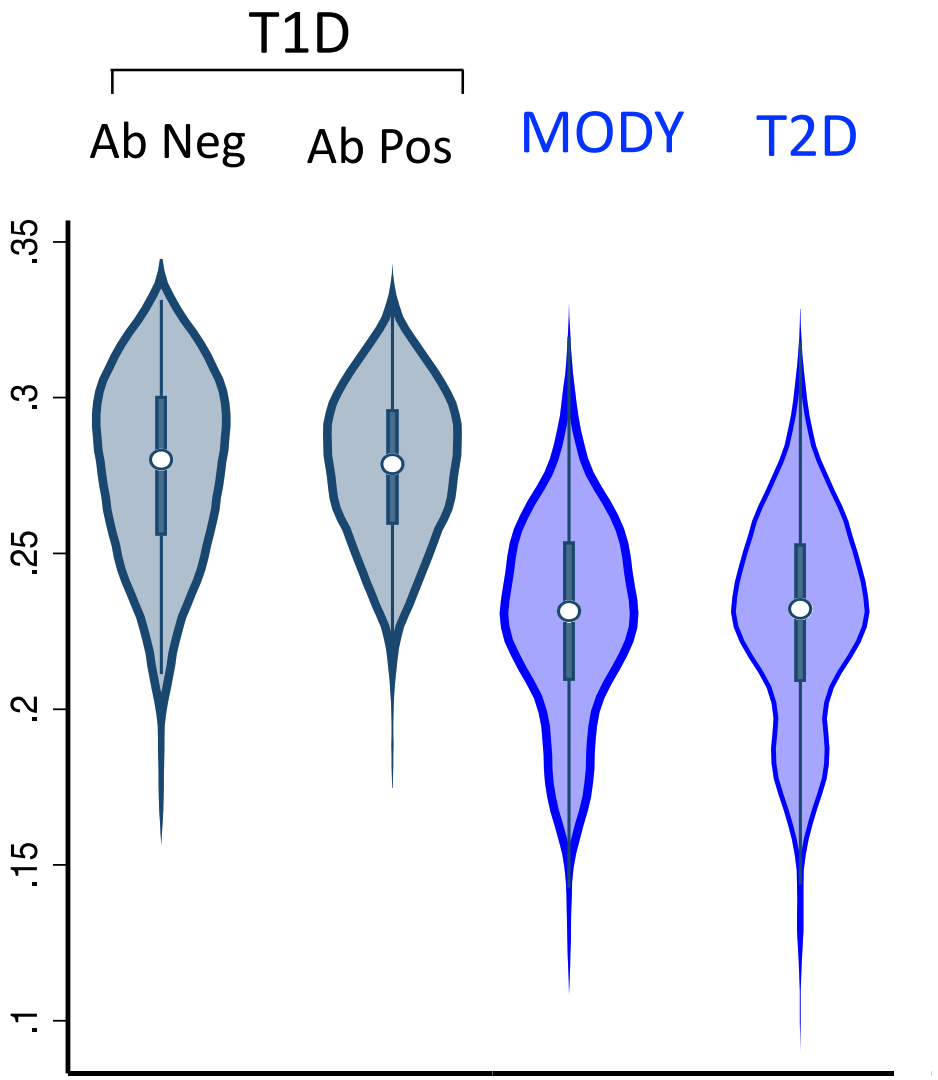
All combined - explained >80% susceptibility

HLA genes – strongest

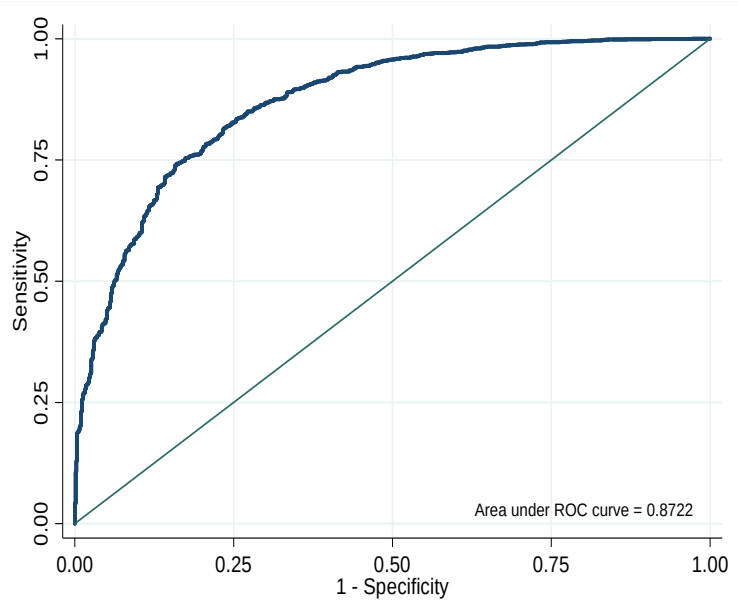
Noble Curr Diab report 2011

Chiou Nature 2021

T1D genetic risk score
DNA based test - discriminates T1D from monogenic or T2D



T1D-GRS
ROC AUC – 0.87



Mike

Rich

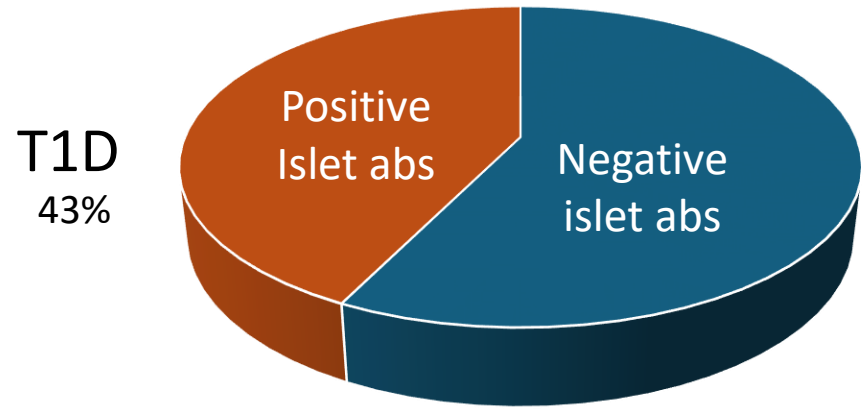
Thomas Diabetologia 2022

Patel Diabetes 2016

Oram Diabetes care 2016

T1DGRS – exclude patients from genetic testing in antibody negative cases OR provide diagnosis in gene negative patient

Clinically suspected having monogenic diabetes, N=157



T1D-GRS

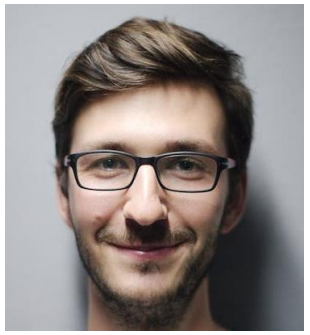
High → Monogenic diabetes N=0

Low → Monogenic diabetes N=12

Now part of the NHS MODY testing

Patel Diabetes care 2019

Young onset nonobese diabetes with persistent insulin secretion



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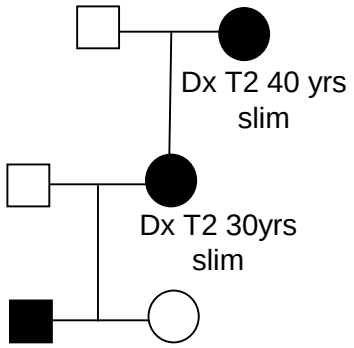
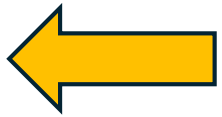


GADA/IA2A/ZnT8A – negative, Random C-peptide – 400 pmol
T1DGRS 8th centile

Commercial gene panel testing in US - KLF11 MODY

HNF4A-MODY (MODY 1)	125850	hepatocyte nuclear factor 4α	Due to a loss-of-function mutation in the HNF4α gene. 5%–10% cases.
GCK-MODY (MODY 2)	125851	glucokinase	Due to any of several mutations in the *GCK* gene. 30%–70% cases. Mild fasting hyperglycemia throughout life. Small rise on glucose loading. Patients do not tend to get diabetes complications and do not require treatment[11] outside of pregnancy.[12]
HNF1A-MODY (MODY 3)	600496	hepatocyte nuclear factor 1α	Mutations of the HNF1α gene (a homeobox gene). 30%–70% of cases. Most common type of MODY in populations with European ancestry.[13] Tend to be responsive to sulfonylureas. Low renal threshold for glucose.
PDX1-MODY (MODY 4)	606392	insulin promoter factor-1	Mutations of the IPF1 homeobox (Pdx1) gene. < 1% cases. Associated with pancreatic agenesis in homozygotes and occasionally in heterozygotes.
HNF1B-MODY (MODY 5)	137920	hepatocyte nuclear factor 1β	One of the less common forms of MODY, with some distinctive clinical features, including atrophy of the pancreas and several forms of renal disease. Defect in HNF-1 beta gene. 5%–10% cases.
NEUROD1-MODY (MODY 6)	606394	neurogenic differentiation 1	Mutations of the gene for the transcription factor referred to as neurogenic differentiation 1. Very rare: 5 families reported to date.
KLF11-MODY (MODY 7)	610508	Kruppel-like factor 11	KLF11 has been associated with a form of diabetes[14] that has been characterized as "MODY7" by OMIM.[15]



Some early MODY genes escaped detailed scrutiny

Wikipedia/
literature
N=14 genes

→

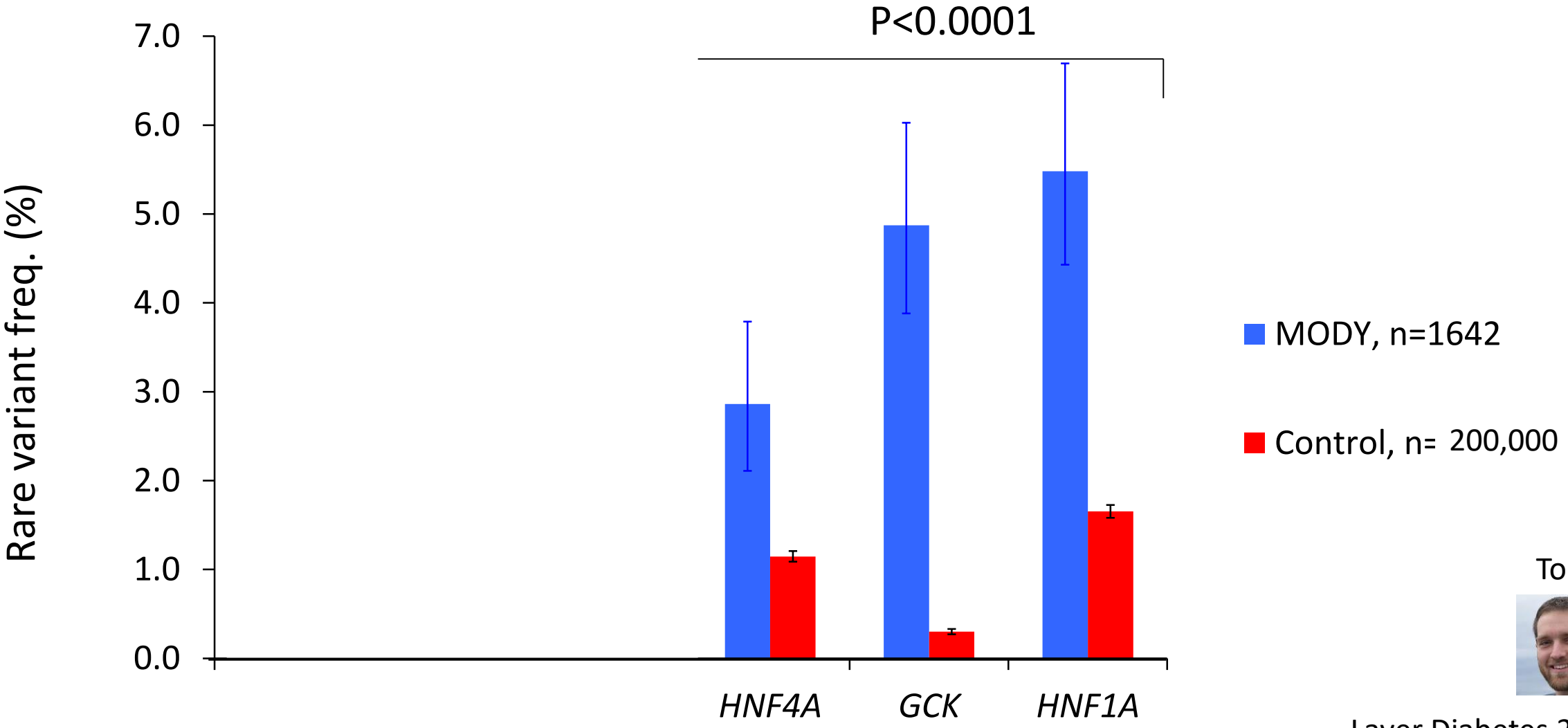
GCK
HNF1A
HNF4A
HNF1B

NEUROD1
PDX1
CEL
INS
KCNJ11
ABCC8
RFX6

BLK
KLF11
PAX4

Reported before access to the large population scale genome data

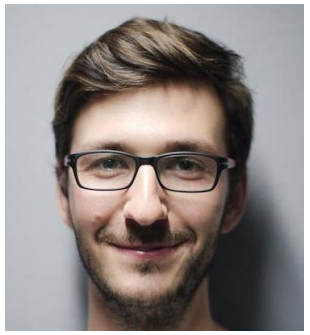
Rare variants in *BLK* , *KLF11* and *PAX4* are not enriched in MODY cohorts – Not MODY genes



Tom

Laver Diabetes 2022

Young onset nonobese diabetes with persistent insulin secretion



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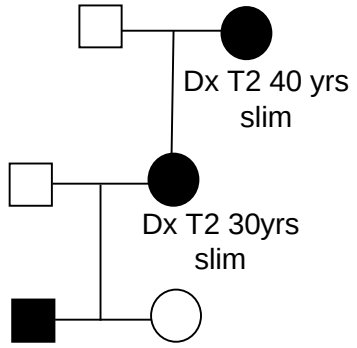


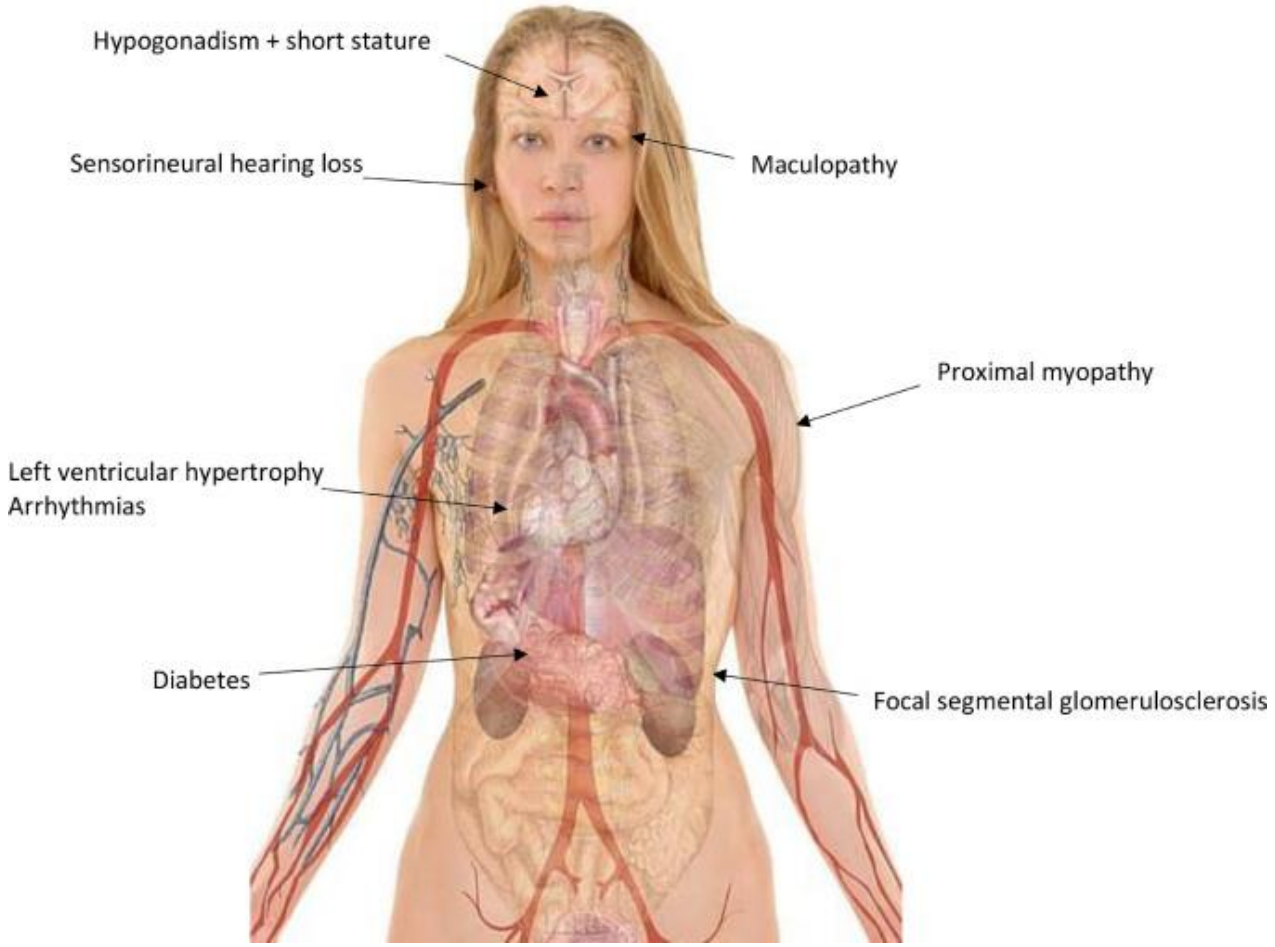
Gene panel Exeter

↓

m.3243A>G

Commercial gene panel testing in US - ~~KLF11 MODY~~

Maternally inherited diabetes and deafness (MIDD) or Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)



Variable clinical features

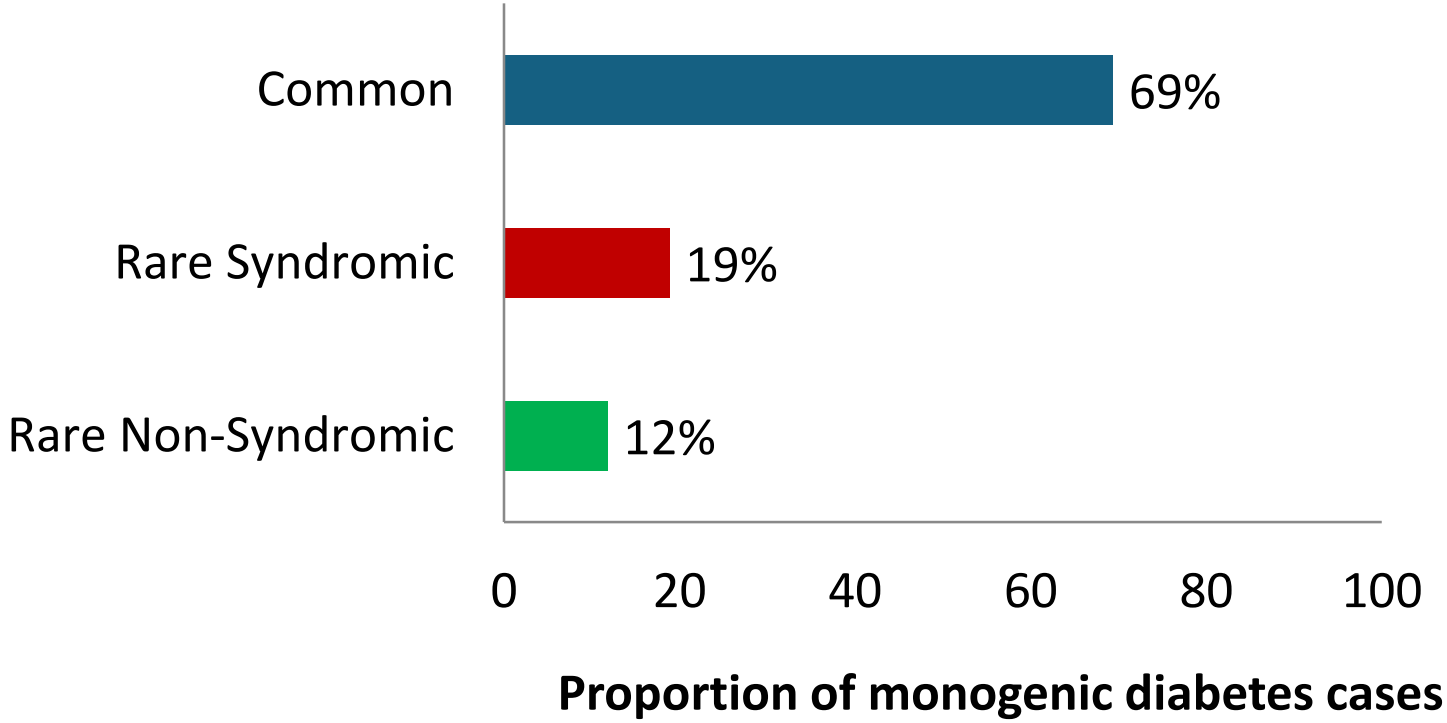
Patient information on web – scary !

Clinically selected Vs clinically unselected

Should we test syndromic diabetes genes in patients suspected of MODY?

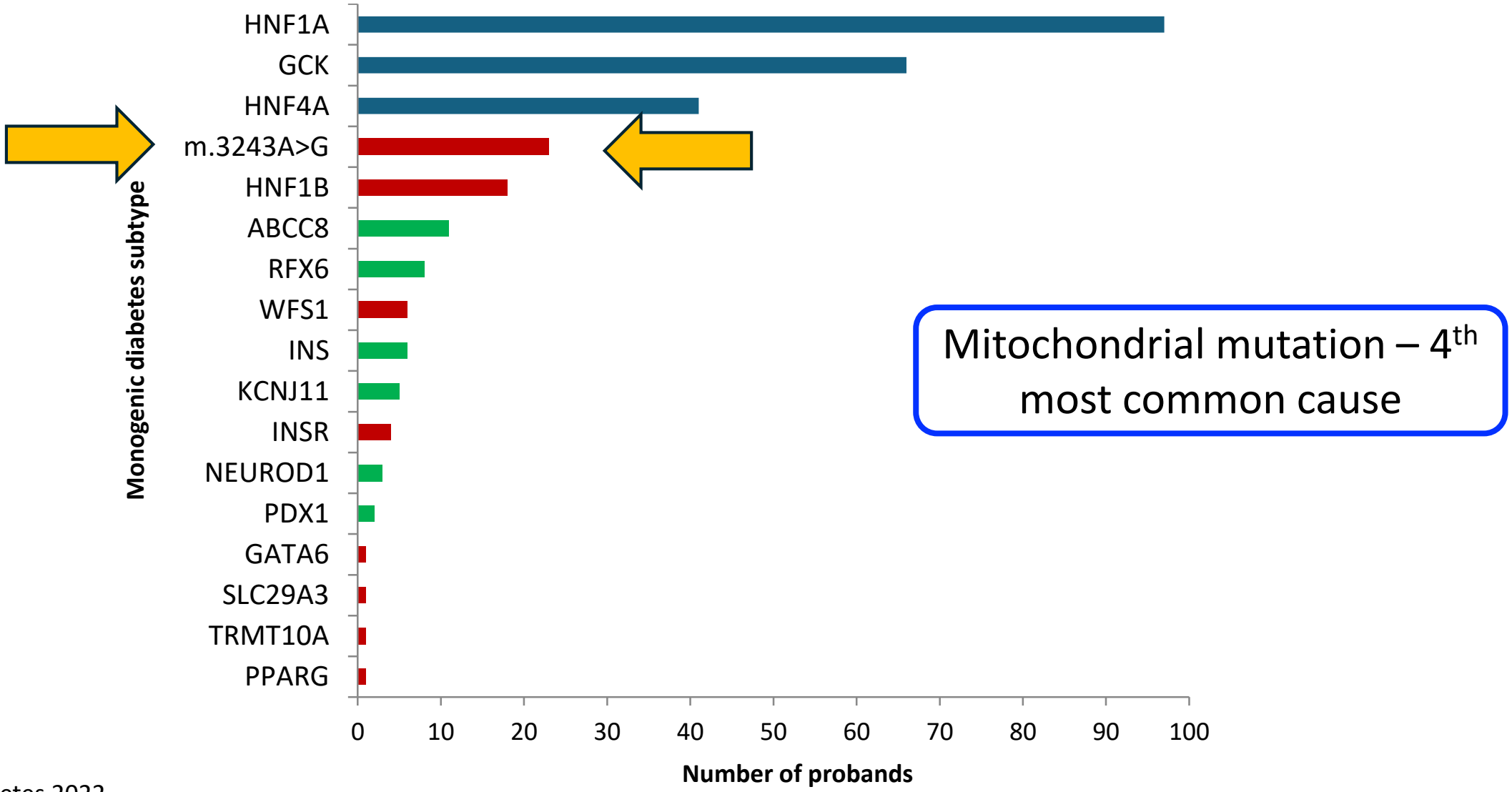
Mutation causing diabetes syndrome are common in clinically suspected MODY - 1 in 5 monogenic cases

N=1280 clinically suspected MODY → MODY and syndromic diabetes genes Test → N=297 Monogenic (23%)



Kev

Gene panel changed the most common gene list for MODY

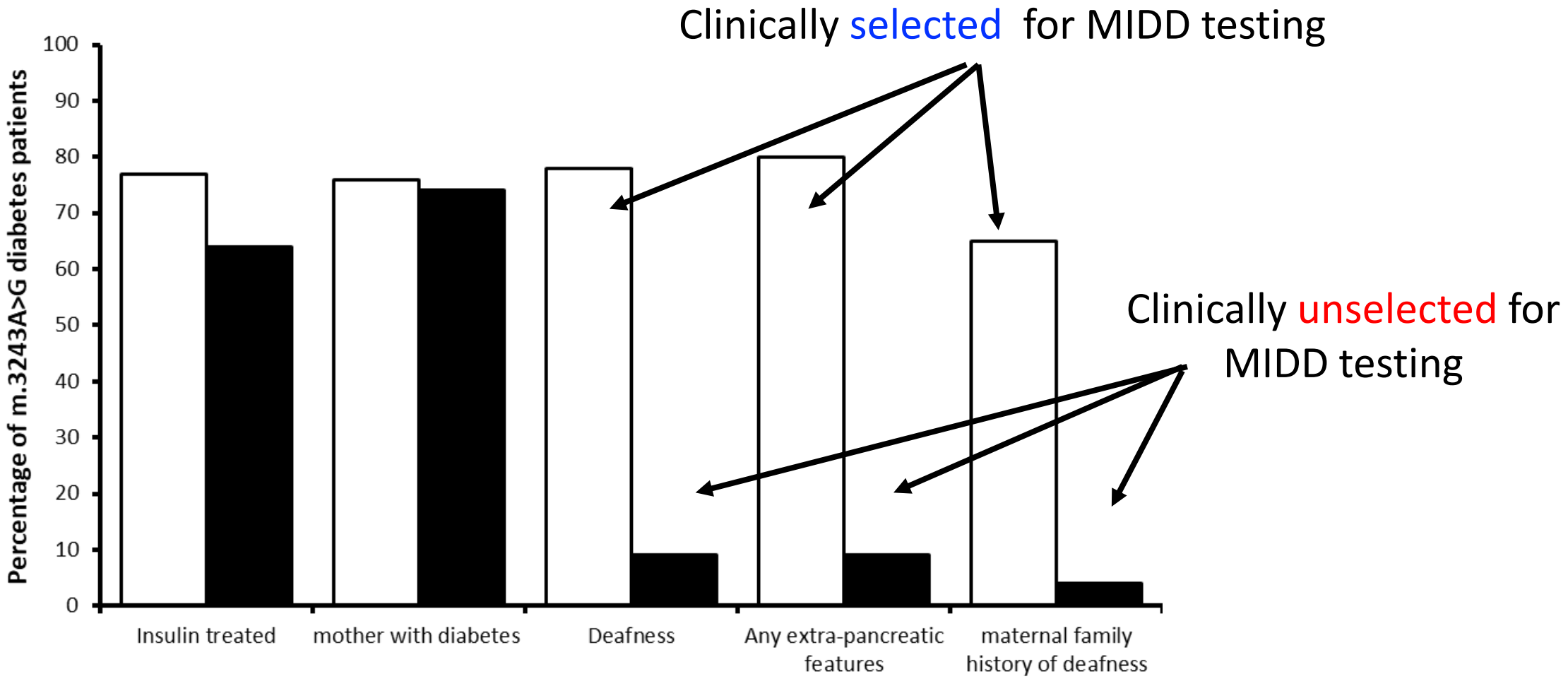


Mitochondrial mutation – 4th most common cause

Colclough Diabetes 2022

N=297

Less severe features of MIDD when clinically unselected



Kev

Colclough Diabetes 2022

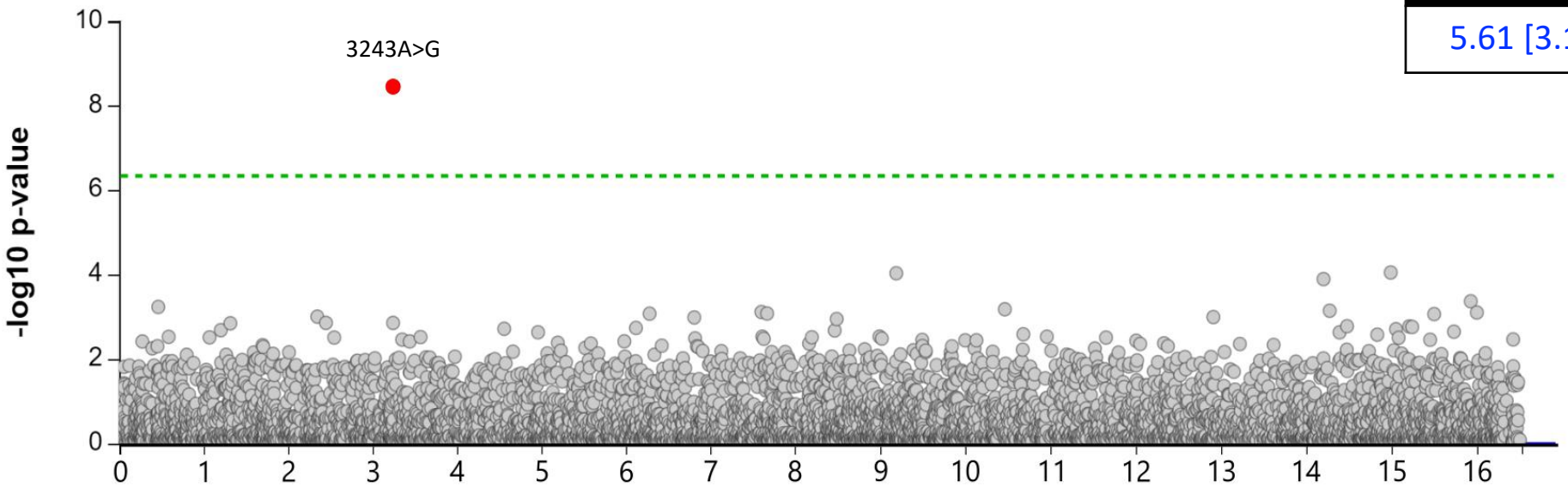
How common is m.3243A>G in population?

What are the clinical features of m.3243 A>G in clinically unsuspected cases?

~1 in 2000 people had an m.3243A>G variant in population and m.3243A>G is the only variant associated with diabetes

OR [95% CI]	P
5.61 [3.16 – 9.93]	$4x10^{-9}$

Diabetes

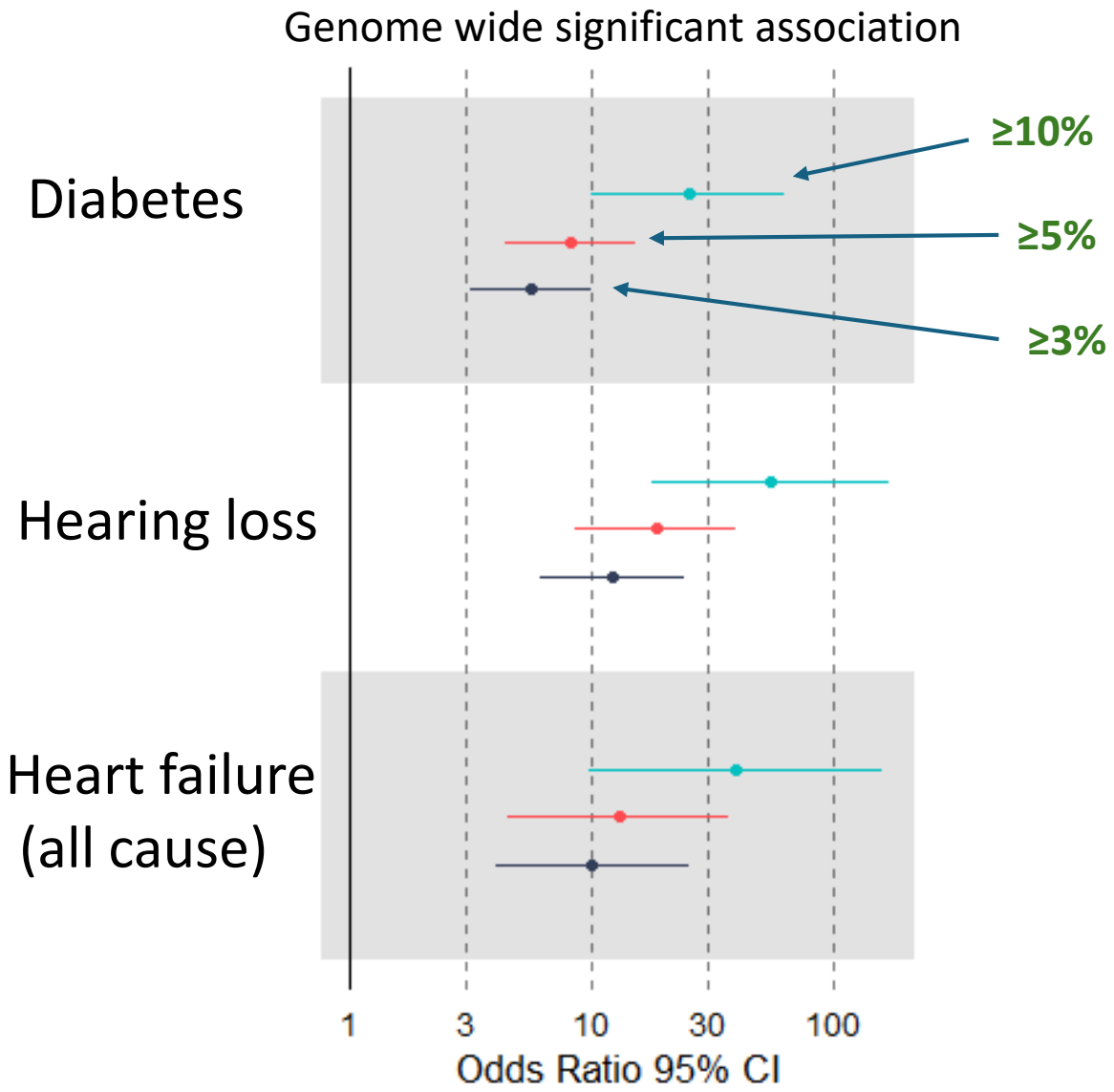


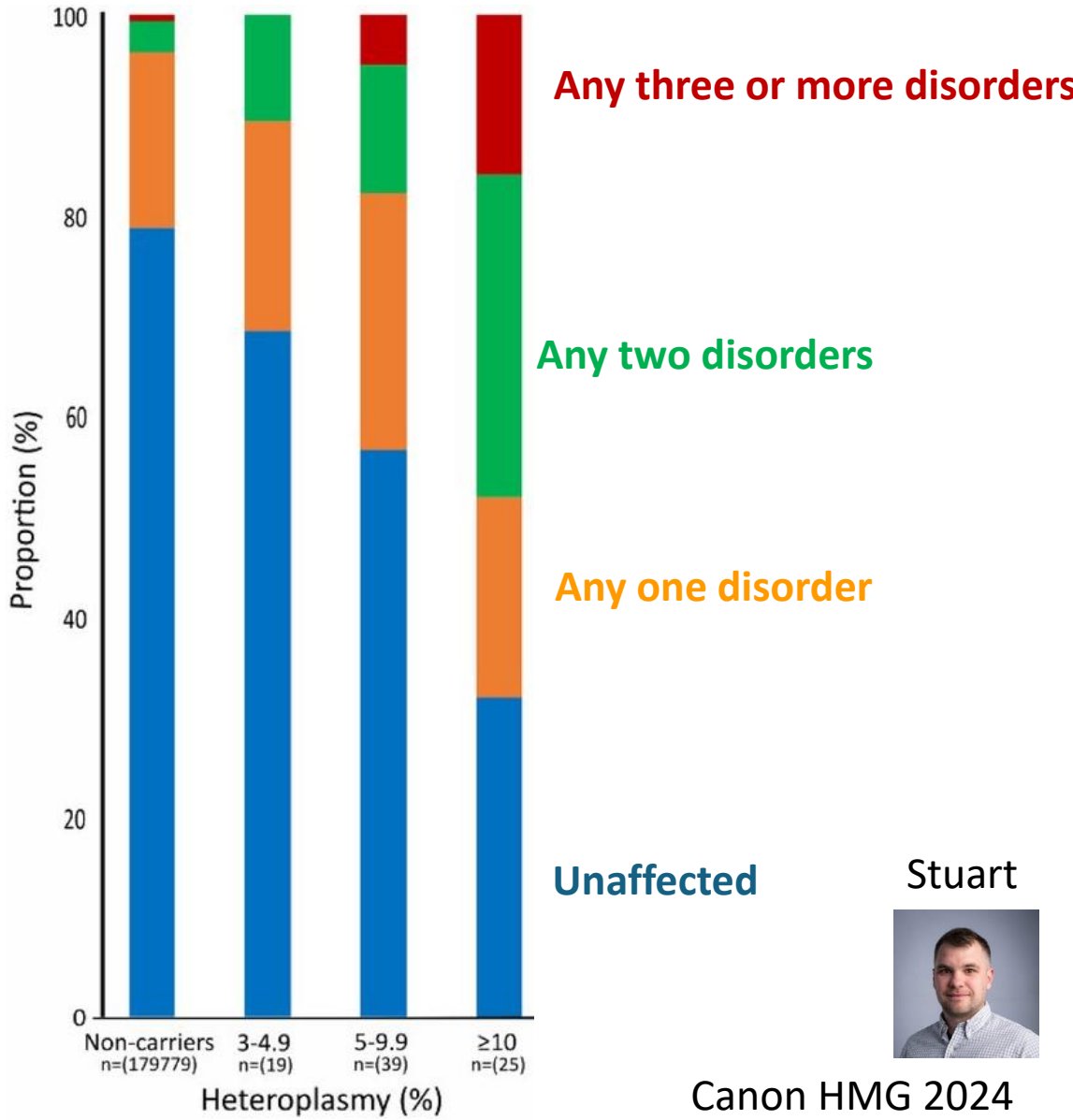
~1 in 2000 people had an m.3243A>G variant (n=83 >=3% mutation load)

Stuart

UK Biobank – whole genome – n=165,439

m.3243A>G impacts on heath depends on blood mutation load and milder disease when found in clinically unselected





Stuart

Canon HMG 2024

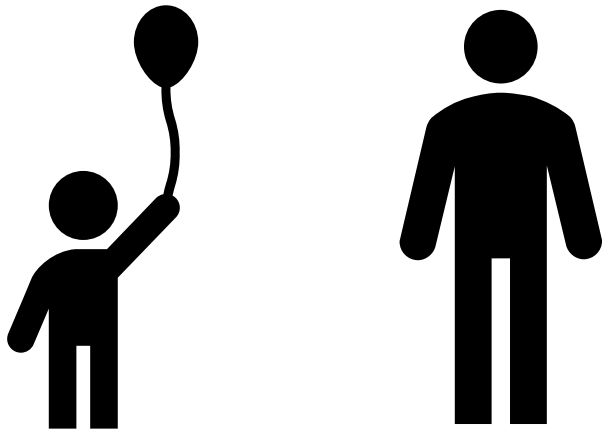
MODY – Take home message - 1

- T1D Genetic risk score – in antibody negative cases – available in NHS/commercially
- MODY patients should be tested for genes which typically causes syndromic diabetes
- Aware of the non-pathogenic genes
- m.3243A>G – clinical features based on mutation load and clinically unselected cases less severe

Genetic testing in young onset helpful but individuals diagnosed with diabetes > 40y are not routinely tested

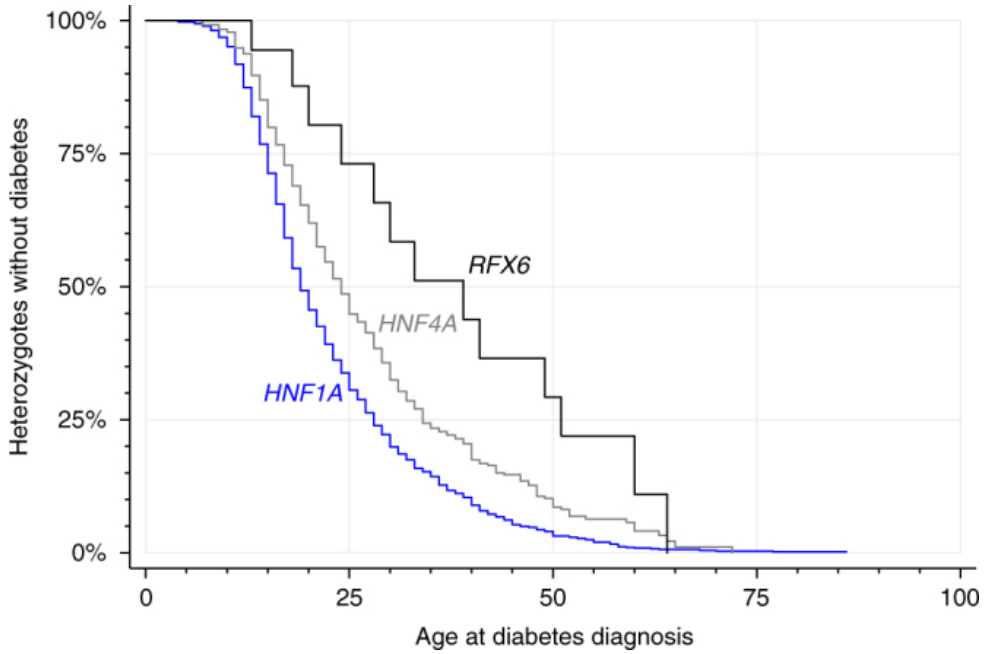
~2-4% diabetes < 30y have MODY

Genetic testing aimed at < 35y



Diabetes status:	Diabetes	Diabetes
Age:	17	50
Genetic testing:	Yes	No

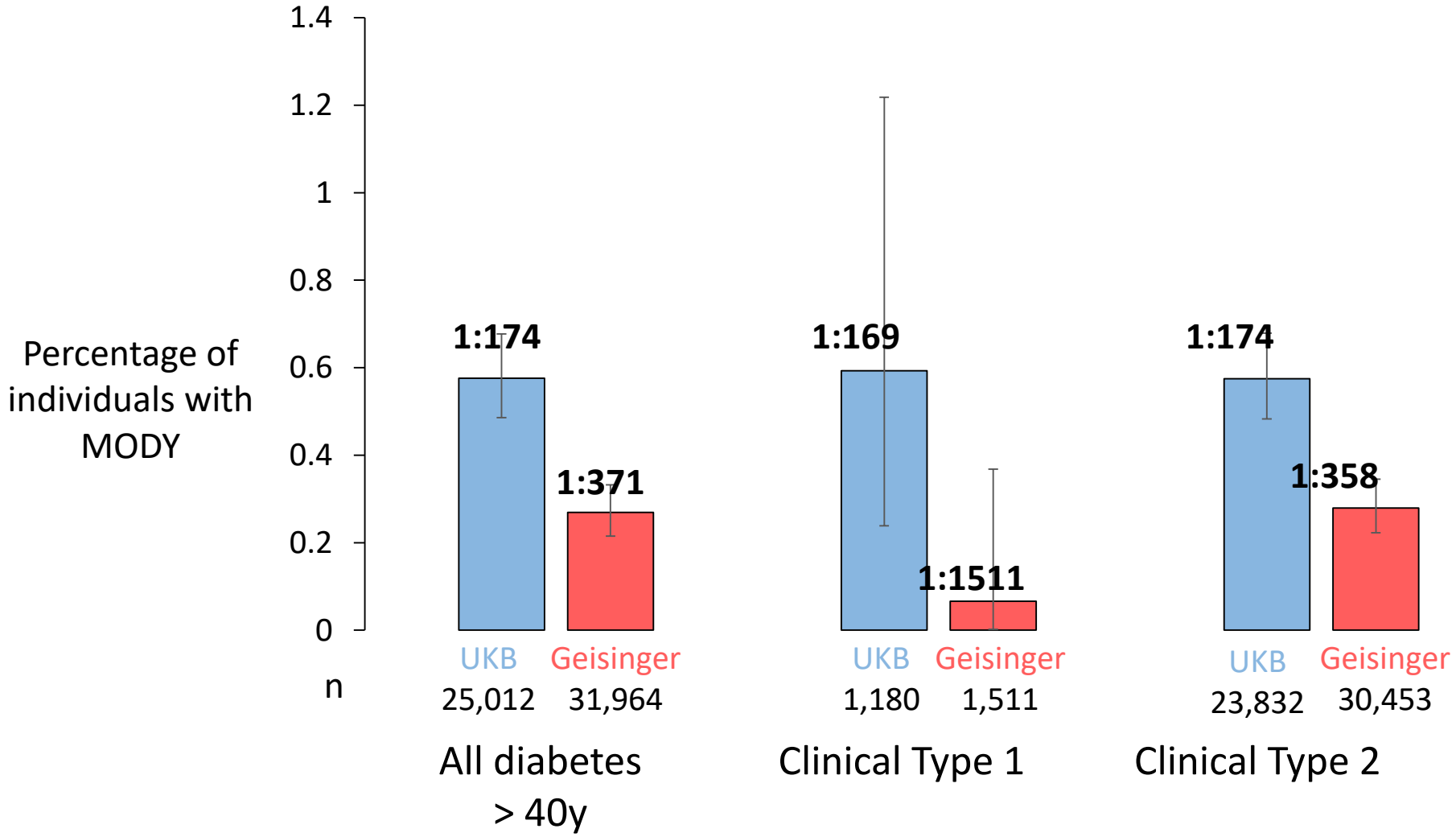
MODY can present later



How common ? Features ?

Shields, *Diabetes Care* (2017)
Patel, *Nature Comms* (2017)

1 in every 174 to 371 people diagnosed with diabetes >40y have MODY (~0.4-0.6%)

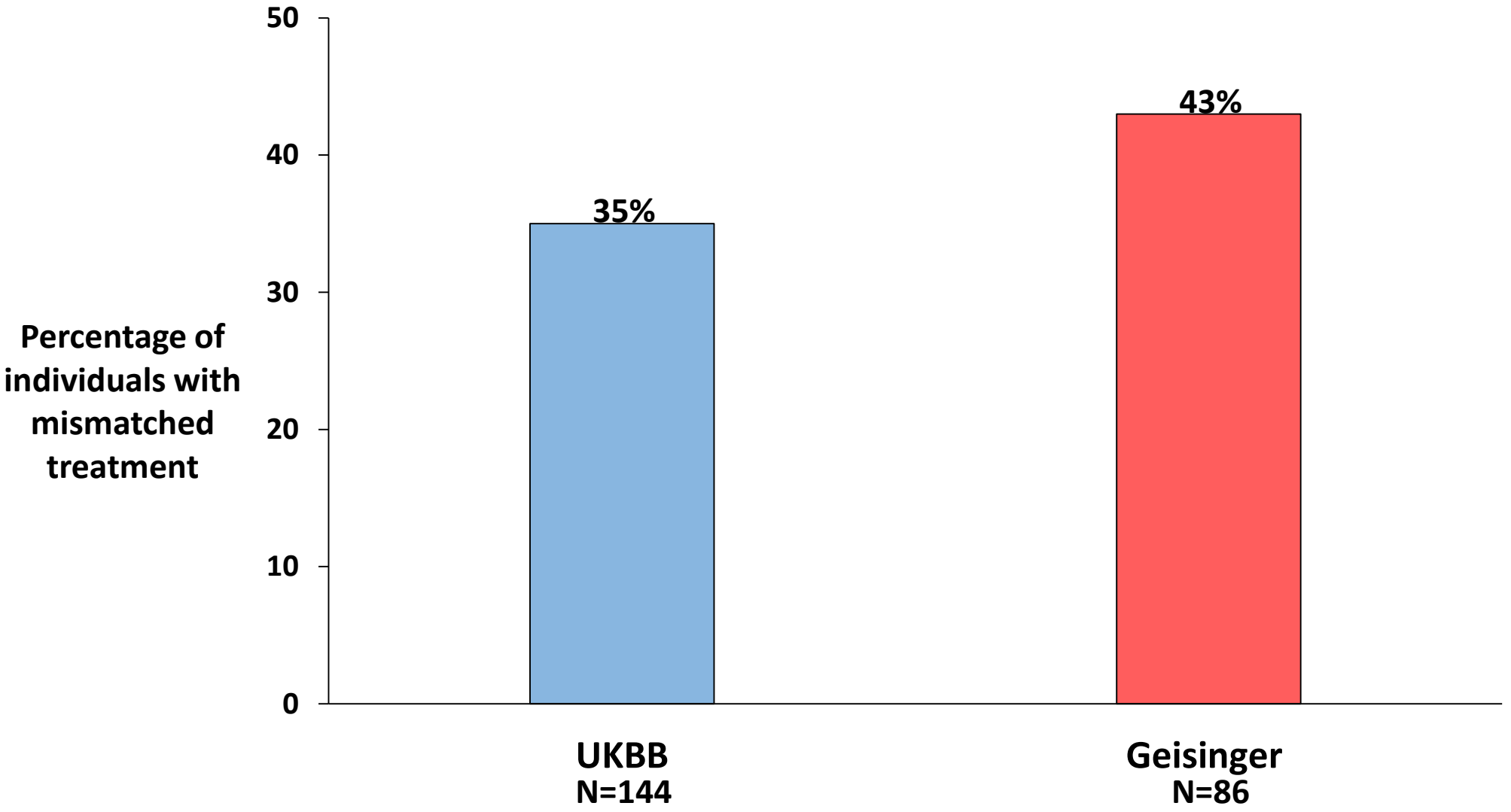


MODY N=144/86/7/1/137/85

Luke

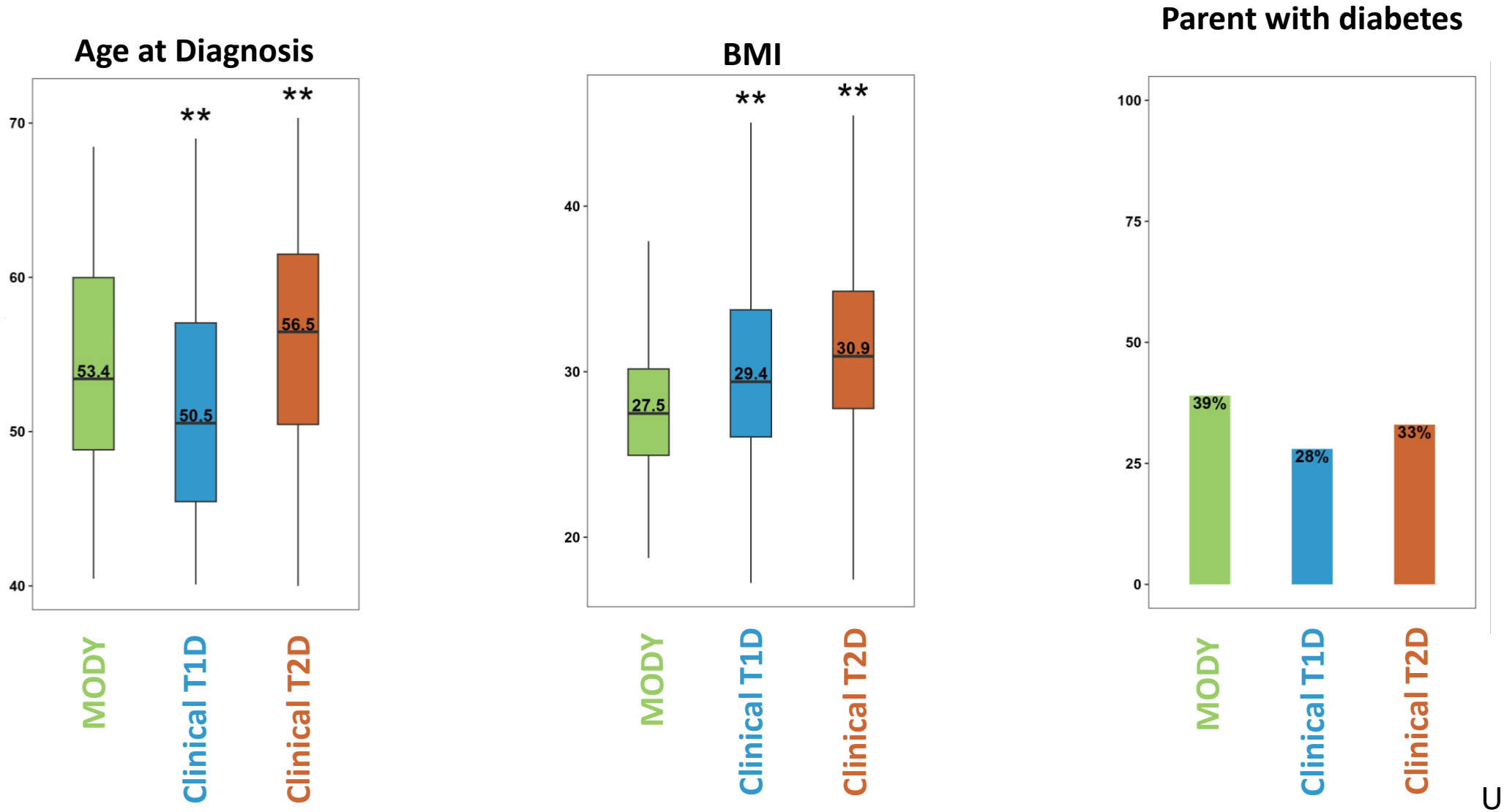
Unpublished

Up to 43% of people with MODY > 40y received a treatment mismatched for their genotypes



Unpublished

Clinical features of MODY >40y and Type 1 and 2 diabetes overlapping



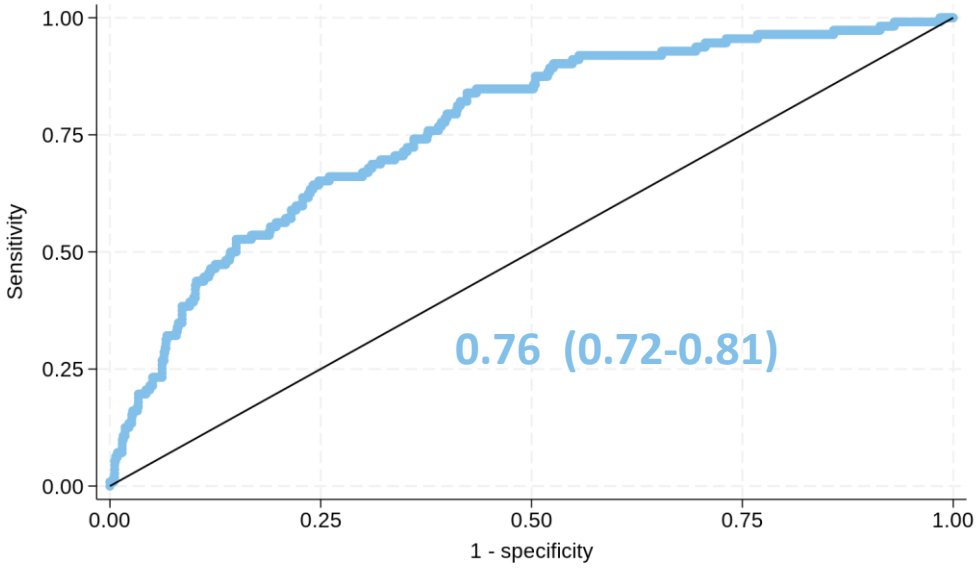
* p<0.01
** p<0.001

Luke

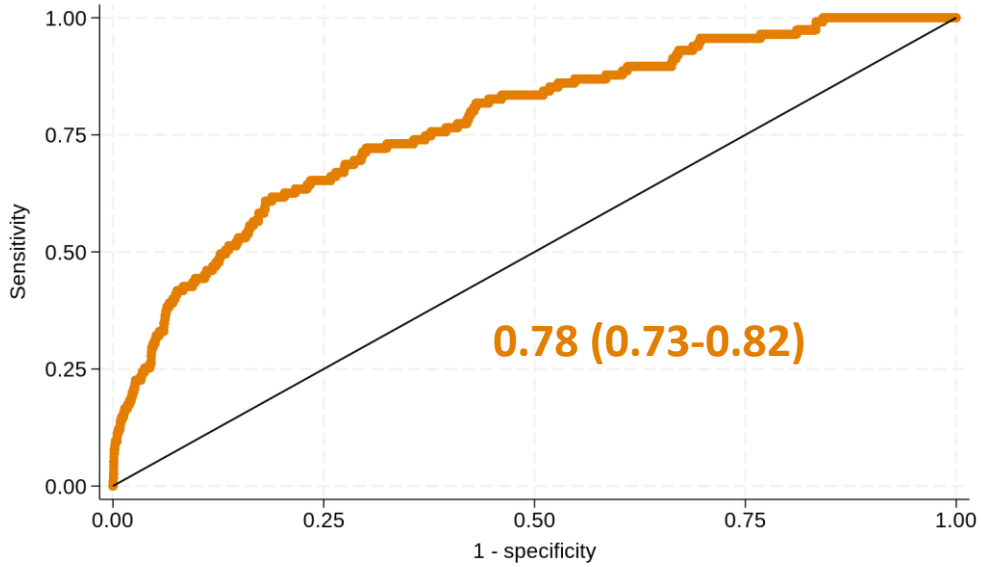
Unpublished

Clinical features cannot be used to discriminate MODY and non-MODY diabetes

MODY vs Clinical type 1 diabetes



MODY vs Clinical type 2 diabetes



Multivariable logistic regression: Age at diagnosis, Sex, Parent with diabetes, BMI, HbA1c, HDL, Total triglycerides, Genetic Risk score

Luke

Clinical suspected T1D = 888 (n MODY = 112)
Clinically suspected T2D = 19,660 (n MODY = 115)

MODY cases with extreme features cannot be effectively identified in individuals diagnosed with diabetes >40y

Group	N total	N MODY	MODY %	% of MODY missed
All	25,012	144	0.6%	0%
BMI < 30 parent with diabetes non-insulin treated	3,165	34	1.1%	76%
BMI < 25 parent with diabetes non-insulin treated	676	16	2.4%	89%

Luke

Unpublished

MODY in diabetes >40y – Take home message -2

- Uncommon - 0.4-0.6% prevalence
- Mistreated but difficult to identify using clinical features alone
- Unlikely to be routine clinical practice to test diabetes >40y and case by case discussion is needed

Acknowledgements

Fellows/Students

Luke Sharp
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Rebecca Myers
Tim Hall

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People with diabetes

Exeter NHS Genomic Lab

Rachel Van Heugten
Kevin Colclough
Martina Owens
Jayne Houghton

Exeter Colleagues

Andrew Hattersley
Maggie Shepherd
Mike Weedon
Elisa Defranco
Matt Johnson
Sarah Flanagan
Matthew Walkeling
Tom Laver

wellcome
UKRI Medical Research Council
uk biobank Enabling scientific discoveries that improve human health
DIABETES UK KNOW DIABETES. FIGHT DIABETES.
JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

56,976 with diabetes > 40y with genetic data from two different settings

UK Biobank:
Clinically unselected individuals from the UK
N=454,699

25,012 with diabetes > 40y

Age = 62y, BMI = 30.8
Clinically suspected T1D = 1,180 (4.7%)
Clinically suspected T2D = 23,832 (95.3%)

Geisinger (Replication):
American health care system-based cohort
N=170,333

31,964 with diabetes > 40y

Age = 65y, BMI = 34.7
Clinically suspected T1D = 1,511 (4.7%)
Clinically suspected T2D = 30,453 (95.3%)

Whole exome data

T1D = insulin treated from diagnosis
T2D = non-insulin treated or insulin not from diagnosis

One simple question – clue to the diagnosis

Mary

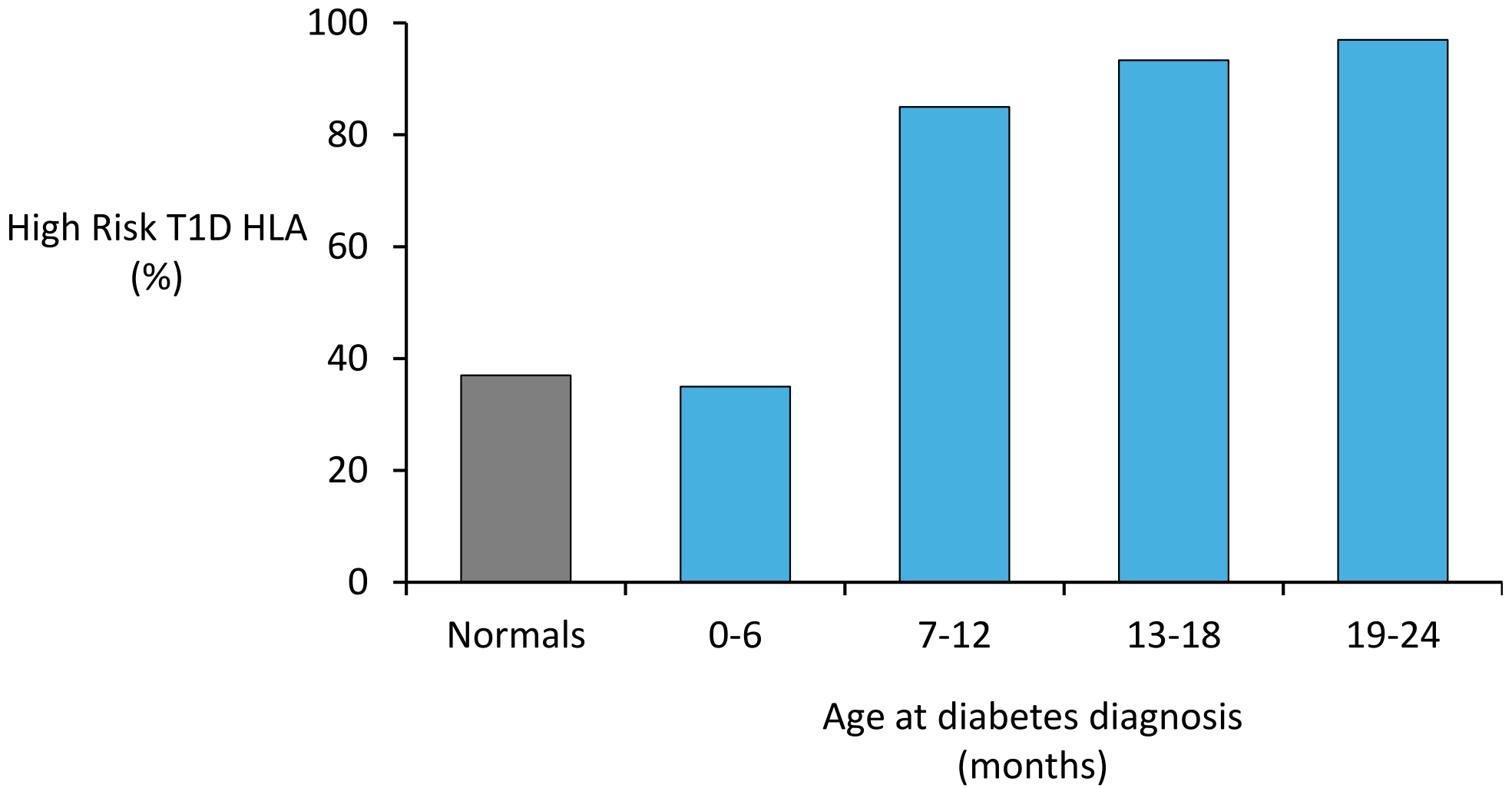
Age 39
Diabetes at age 28 ?T1D
BMI - 22.2, HbA1c - 54
No family history of diabetes
Insulin treated
Islet autoantibody –Neg
C-peptide 600 pmol/l

Gene panel for MODY negative

Transient diabetes at birth – lasted for 12 weeks,
Birth weight – 2.5 kg

Bowman CJD 2020
Temple gene reviews 2018

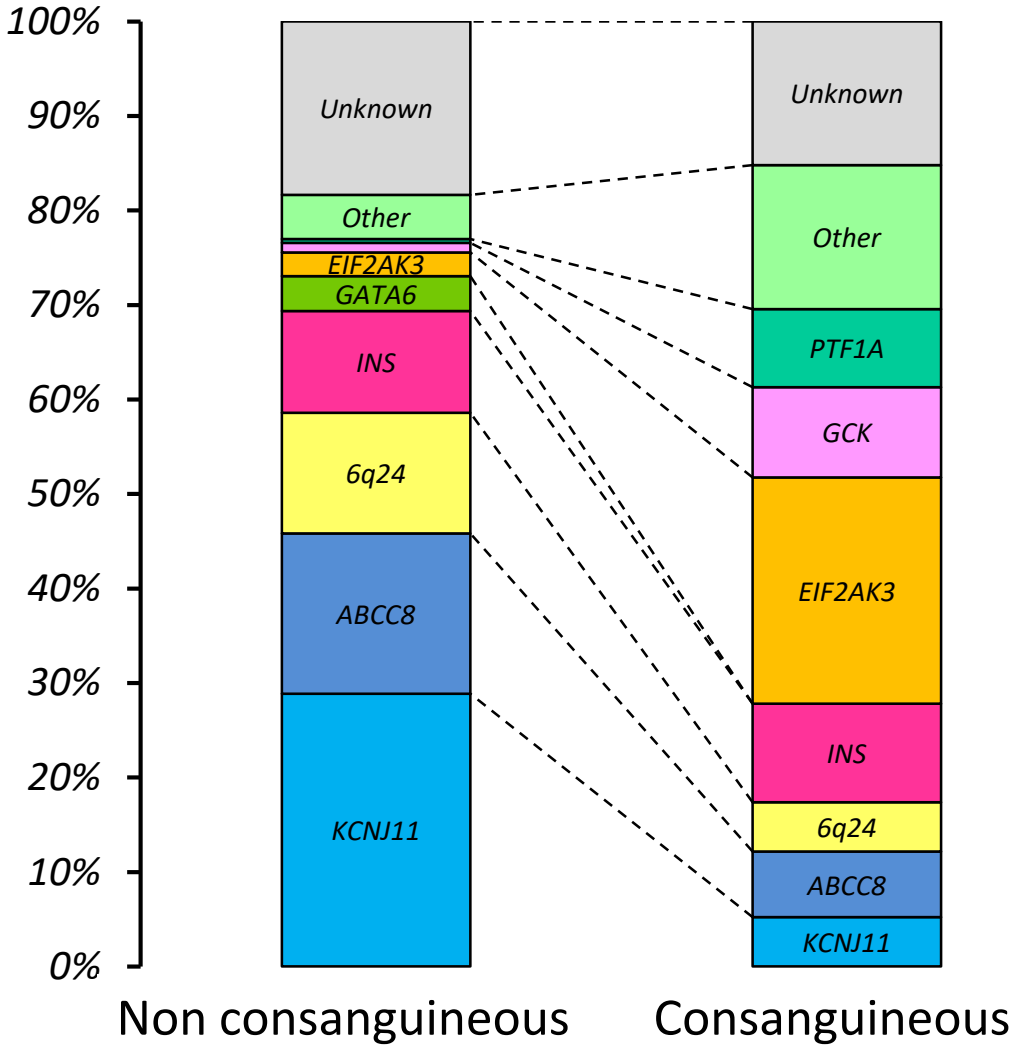
Diabetes diagnosed under 6 months is likely monogenic

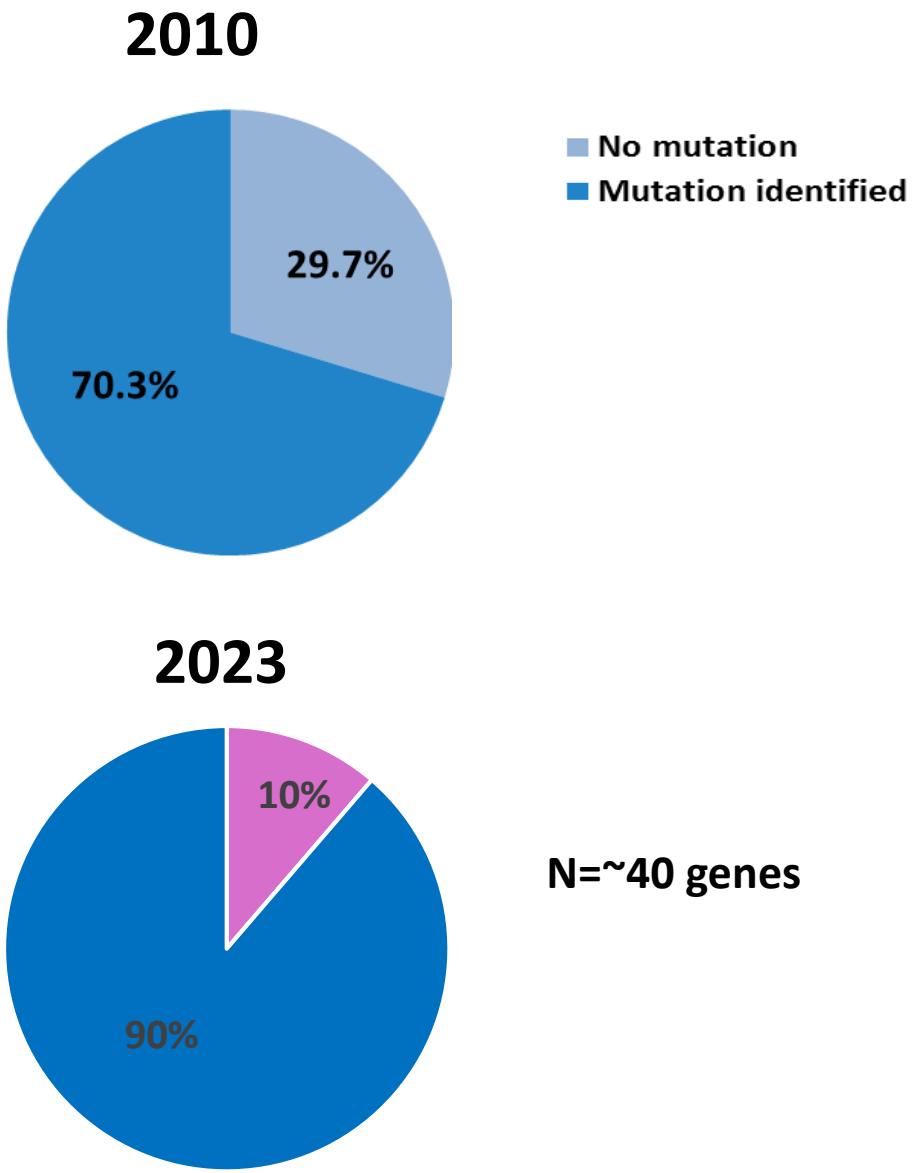


DR3 and/or DR4

Edghill, Diabetes 2006
Iafusco, Diabetologia 2002

Neonatal diabetes: ~90% Monogenic cause





Elisa De-Franco

Defranco Lancet 2015

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No family history of diabetes
Insulin treated
Islet autoantibody –Neg
C-peptide 600 pmol/l

Gene panel for MODY negative

Transient diabetes at birth – lasted for 12 weeks , BW – 2.5 kg

Diagnosis – TNDM with relapse

↓

>90% monogenic
- 6q24 defect – low dose SU
- KATP genes – low dose SU

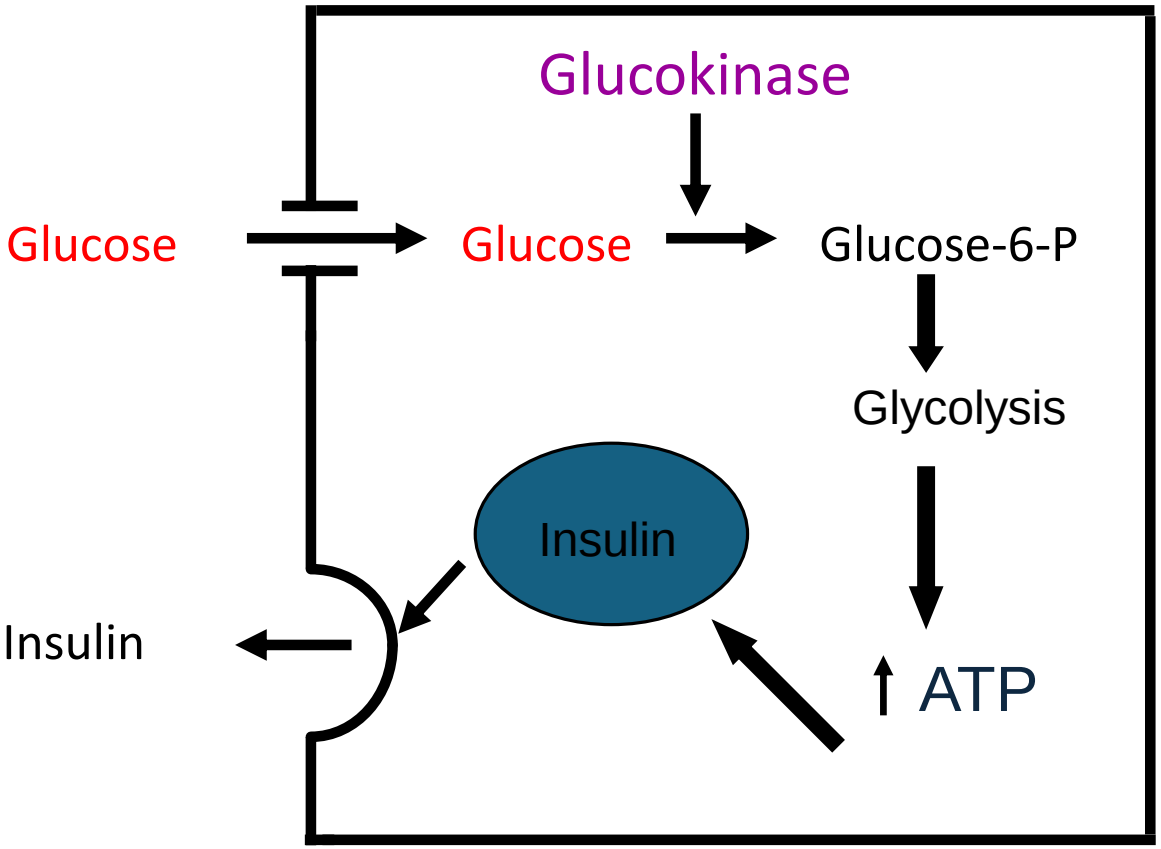
6q24 defect
20 mg gliclazide – HbA1c = 48

Bowman CJD 2020
Temple gene reviews 2018

Neonatal diabetes - Take home message

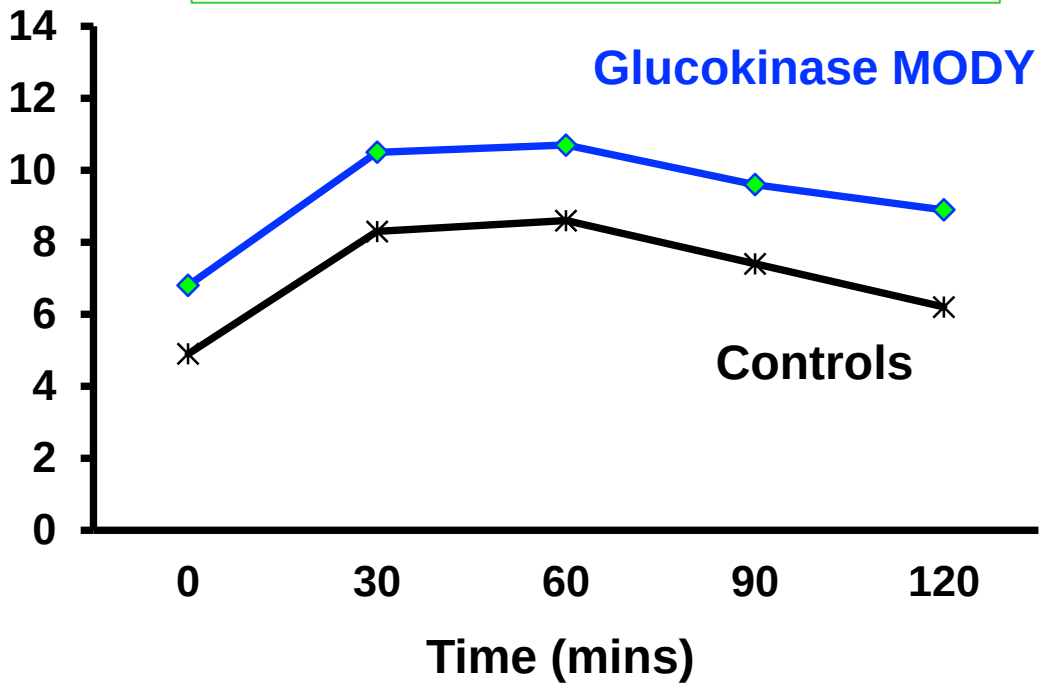
- Ask about age of diabetes onset in all your patients – diagnosed <6 months – transient or permanent – needs genetic testing
- Neonatal diabetes gene panel +/- methylation of 6q24
- Low dose sulphonylurea - transient KATP NDM and 6q24

Glucokinase –Pancreatic Glucose Sensor and inactivating mutation cause raised fasting glucose which is regulated



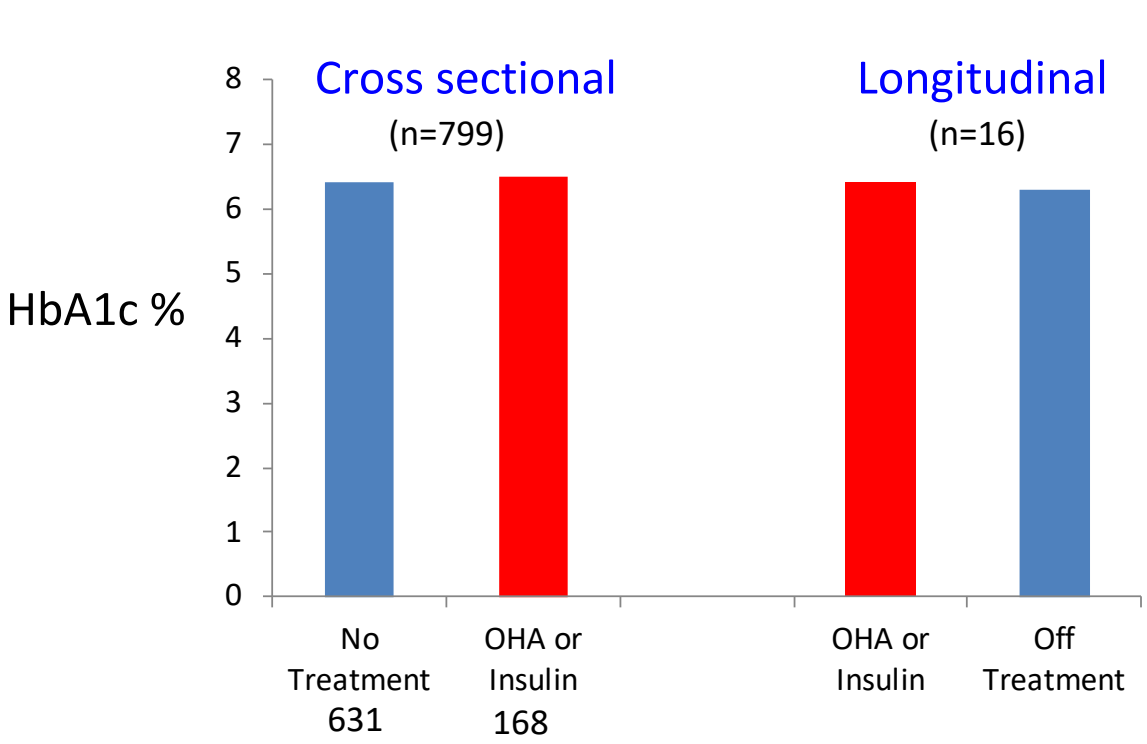
Fasting Glucose:

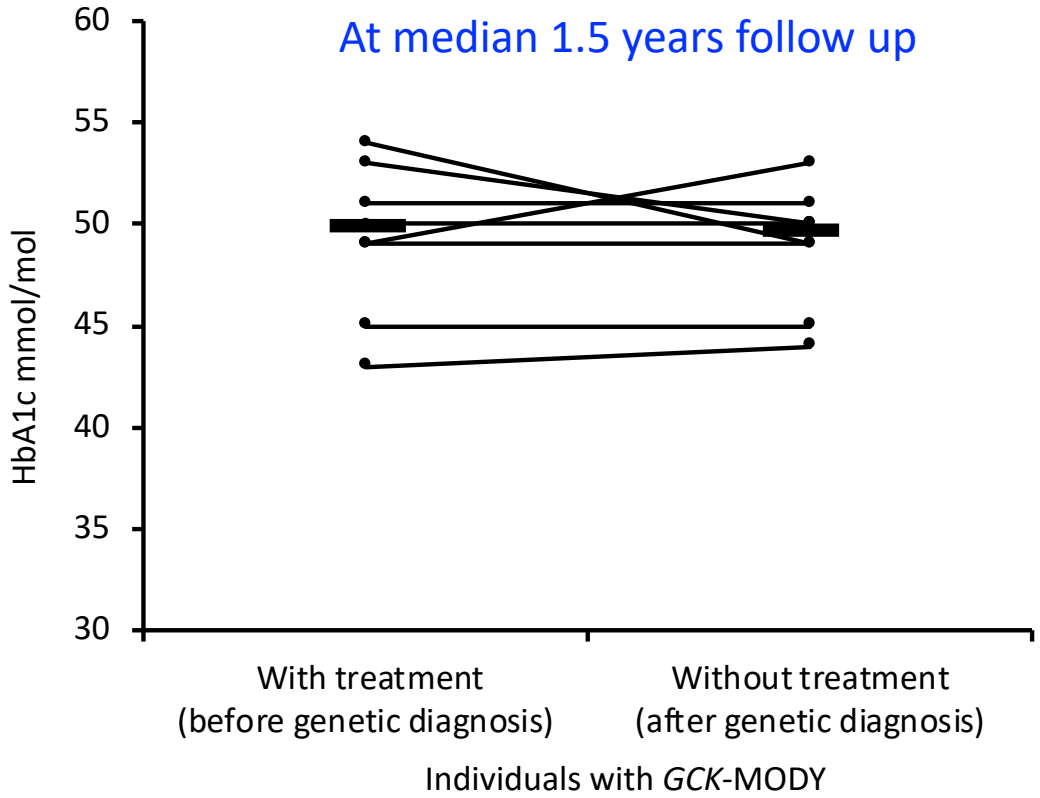
5.5 – 8.5 mmol/L (97-150 mg/dl)



- Fasting value raised
- 2-hr Increment: <4 mmol/l indicative
  <3 mmol/l expected

Glucokinase MODY - No need of treatment





No complications

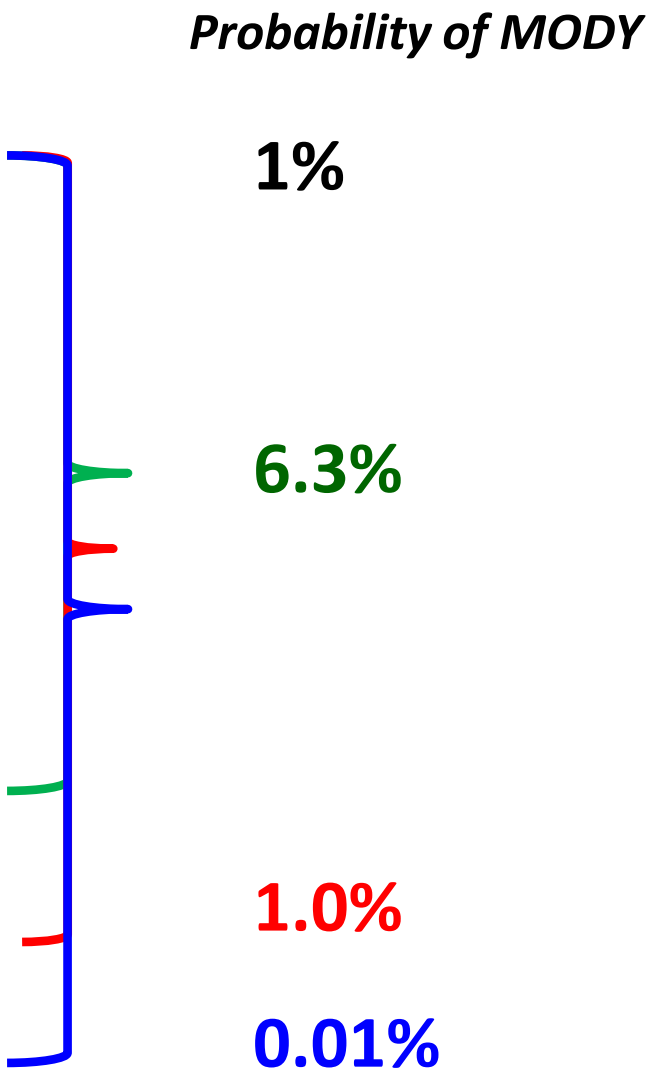
Stride Diabetologia 2014

Shepherd Diabetologia 2018

Can biomarkers and clinical characteristics be integrated to improve diagnostic accuracy?

Example in practice

- Insulin treated from diagnosis
  - Female
  - Diagnosed age 19, now 30
  - Parent with diabetes
  - HbA1c 7.9%
  - BMI 28 kg/m^2
- C-peptide negative
- GAD positive



Example in practice

Probability of MODY

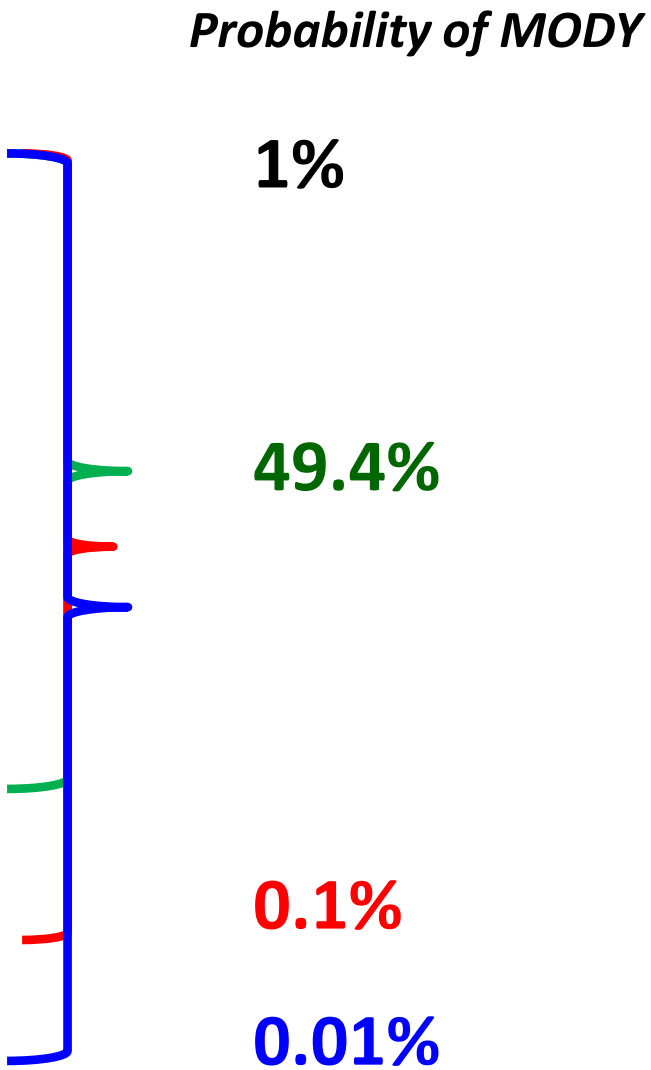
- Insulin treated from diagnosis — **1%**
- Female
- Diagnosed age 19, now 30
- Parent with diabetes
- HbA1c 7.9%
- BMI 28 kg/m^2

— **6.3%**

- C-peptide ~~negative~~ positive — ~~**1.0%**~~ **15.6%**
- ~~GAD positive~~ GAD/IA2 negative — ~~**0.01%**~~ **51.5%**

Example in practice

- Insulin treated from diagnosis
- Female
- Diagnosed age 19, now 24
- Parent with diabetes
- HbA1c 7%
- BMI 23 kg/m^2
- C-peptide negative
- GAD positive



Take home message - selecting patients of MODY genetic testing