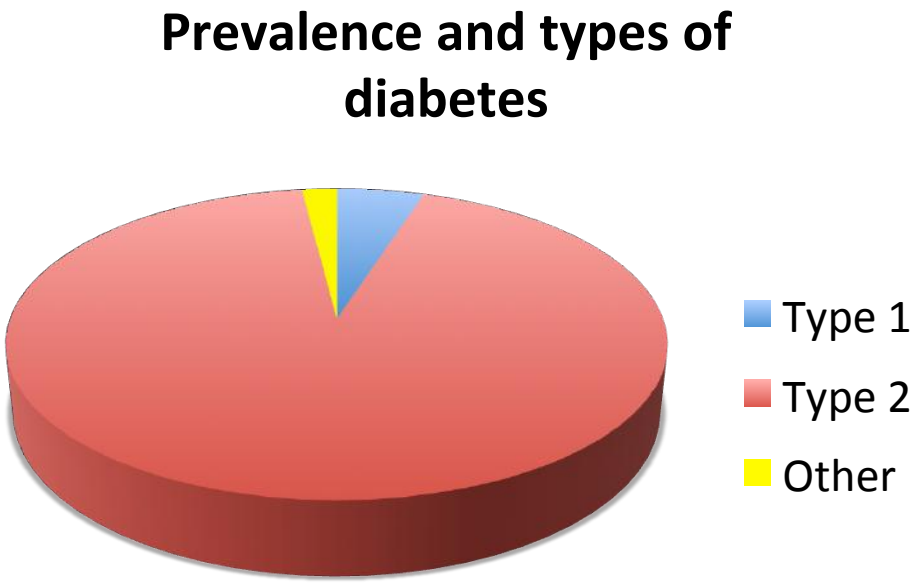
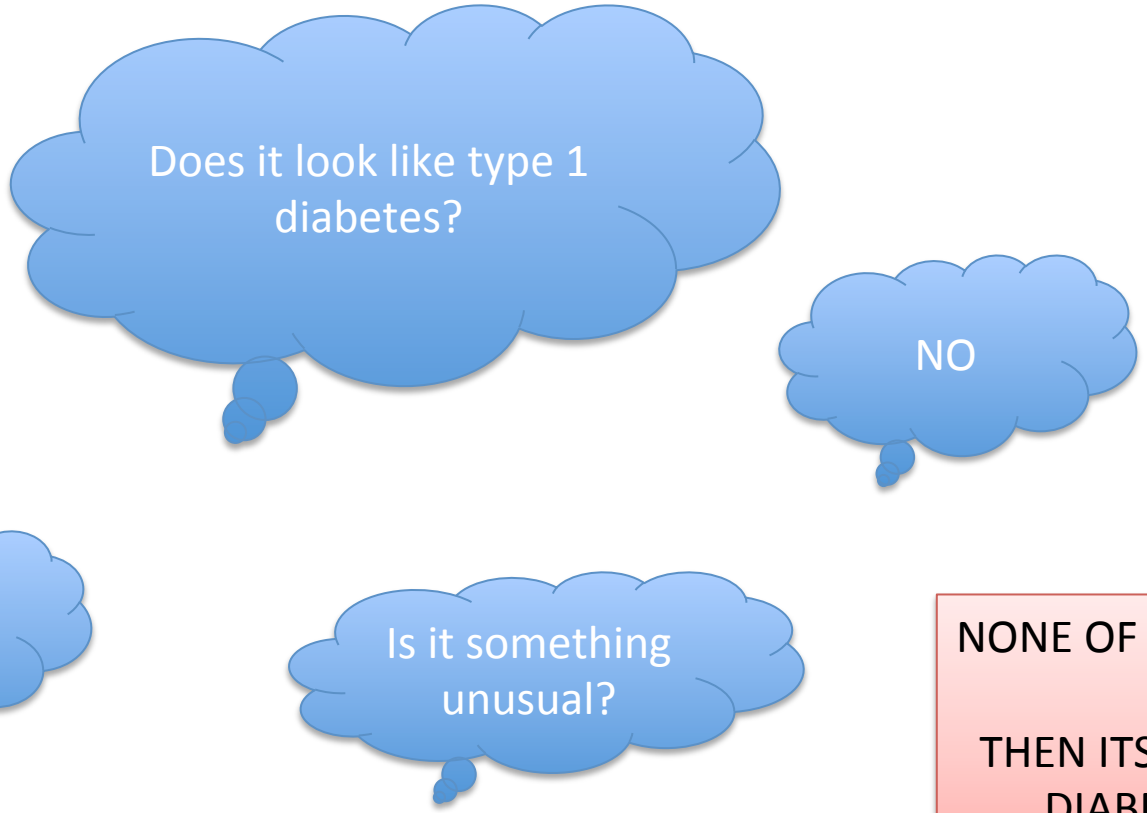
# Precision medicine:
## How to individualize treatment in Diabetes

Ewan Pearson
Professor of Diabetic Medicine
University of Dundee

# Is Diabetes really this simple?



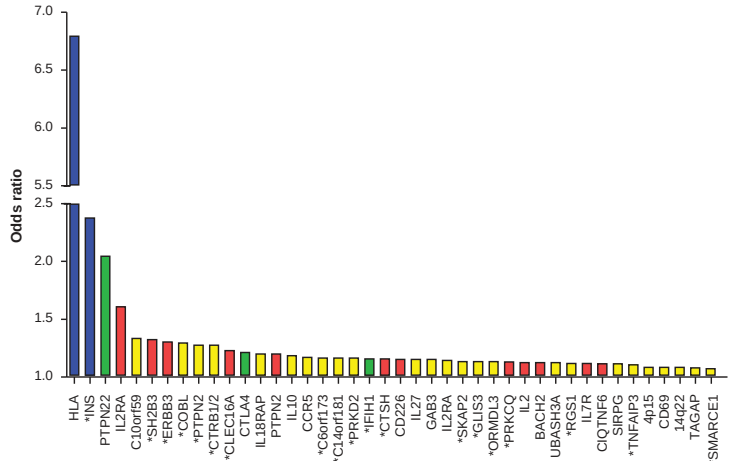
# The current ‘clinical medicine’ approach to stratification in diabetes



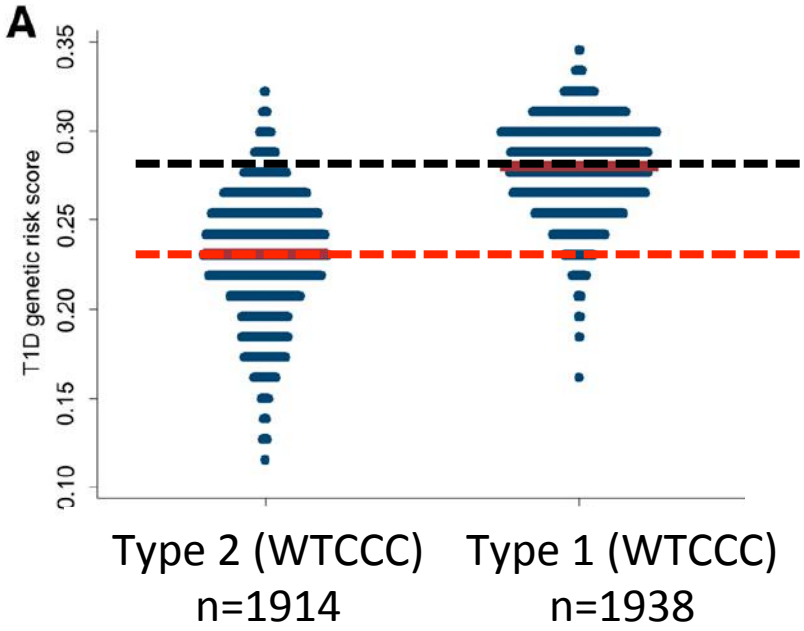
# Is it type 1 diabetes?

- C-peptide (0.36 – 1.12 nmol/L)
- GADA
  - IA2, GAD, ZnT8
- Genetic Risk score (HLA genotype)

# Type 1 – Genetic Risk Score




30 T1D associated SNPS
Sum of risk-increasing alleles weighted by risk
Measure T1D genetic predisposition
Similar discrimination from top 10 SNPs
Result: centile of T1D




High score – likely to be T1D

**50th centile**

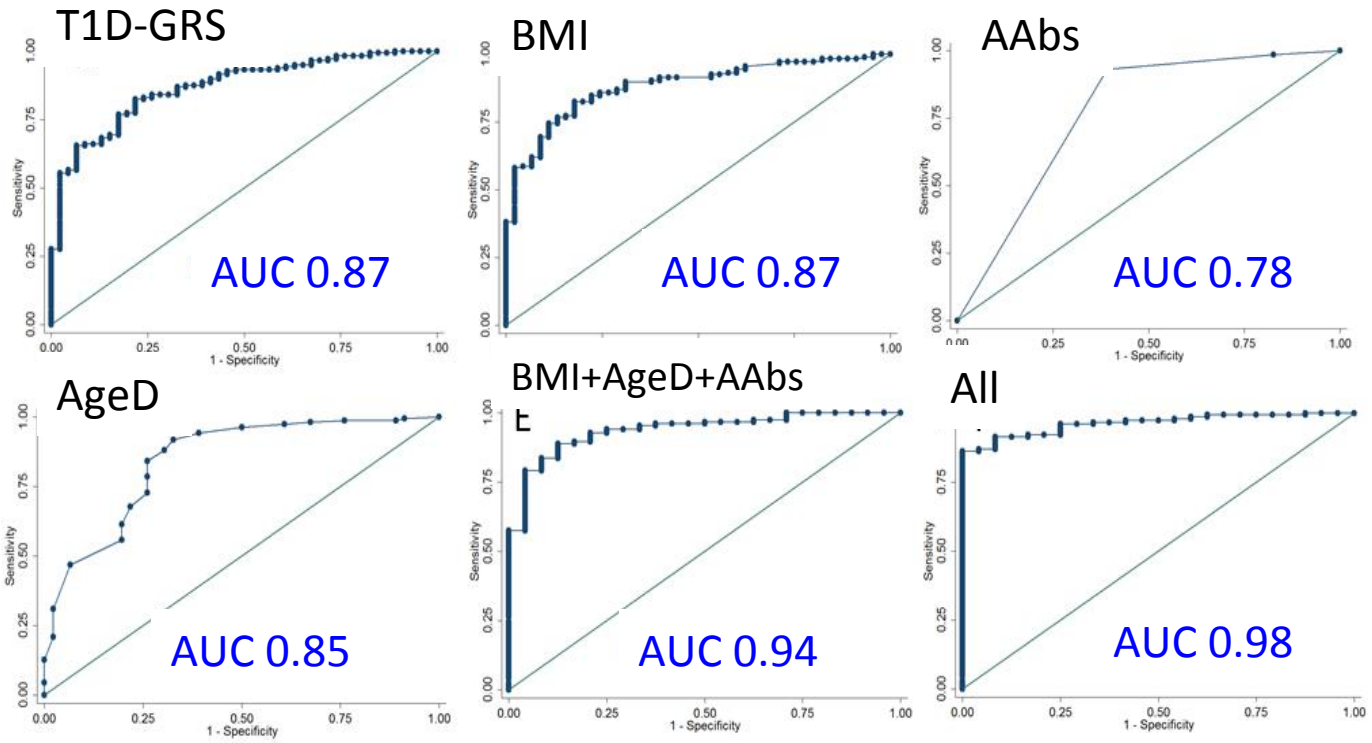
**5th Centile**

Low score - unlikely to be T1D

Interpretation depends on value and prior probability: Child Db 95% T1D
Adult Db >40 5% T1D

Oram et al Diabetes Care 2016

# Predicting insulin deficiency in patients diag. 20-40yrs
# T1D-GRS as good and additive to clinical & AAbs




223 patients diagnosed 20-40 yrs (classification difficult 21% T1D)
Predicting 3 yr insulin deficiency- clinically relevant outcome

T1D-GRS as good as and additive to: Antibodies, BMI, age diag
For best individual prediction integrate quantitative information

Oram et al Diabetes Care 2016

# So its not type 1 diabetes

**Non-type 1, Non-type 2 diabetes**

**MODY**
**Neonatal diabetes**
**Genetic IR - FPLD**
**Alcohol related**
**Haemochromatosis**

**Endocrinopathies**
**CFRD**

**Type 2 Diabetes**

**Typical features**

Obese
Family history (both sides of the family)

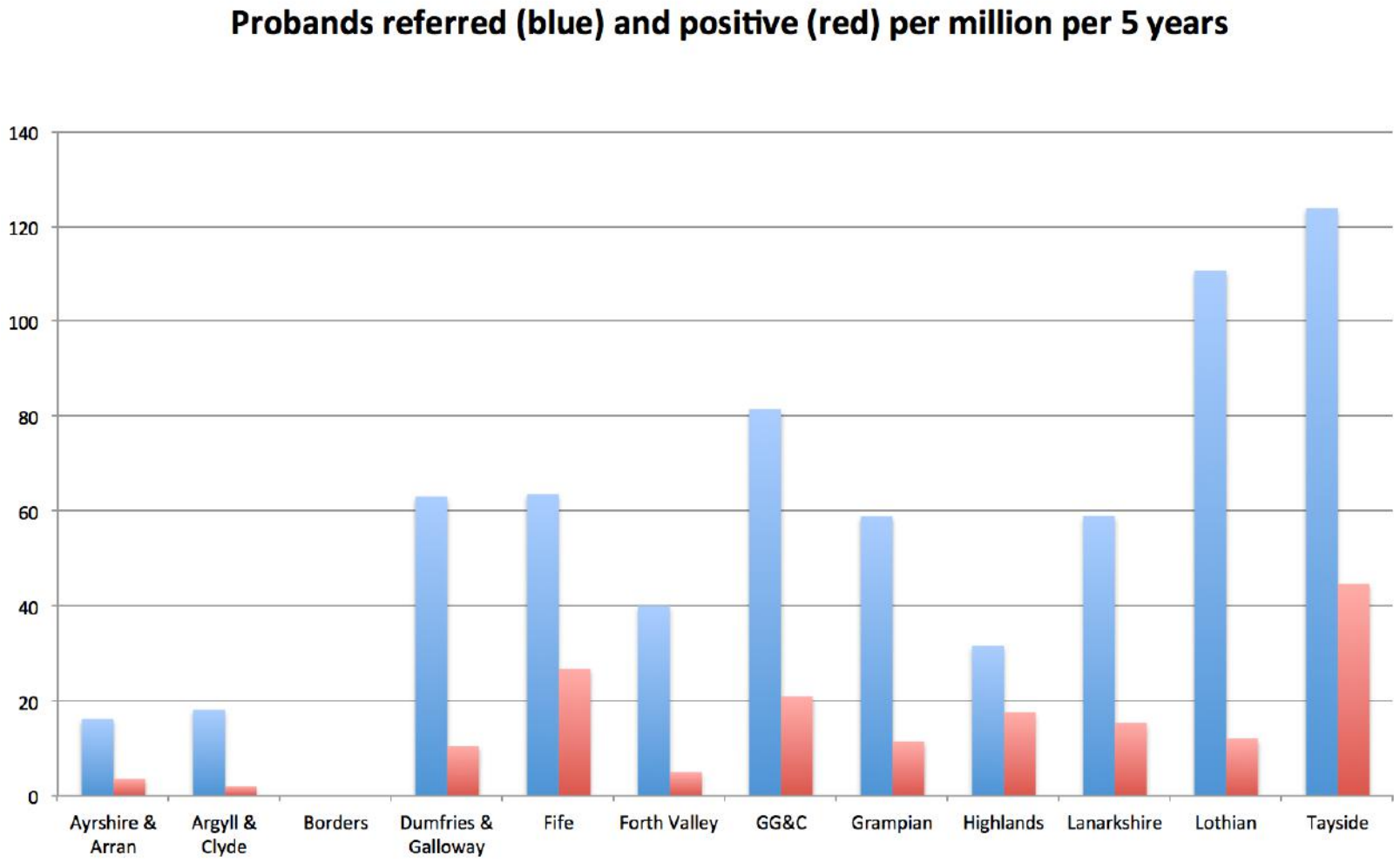
Low HDL

C-peptide
0.5 – 1.5nmol/L

# How can you identify MODY in your clinic?

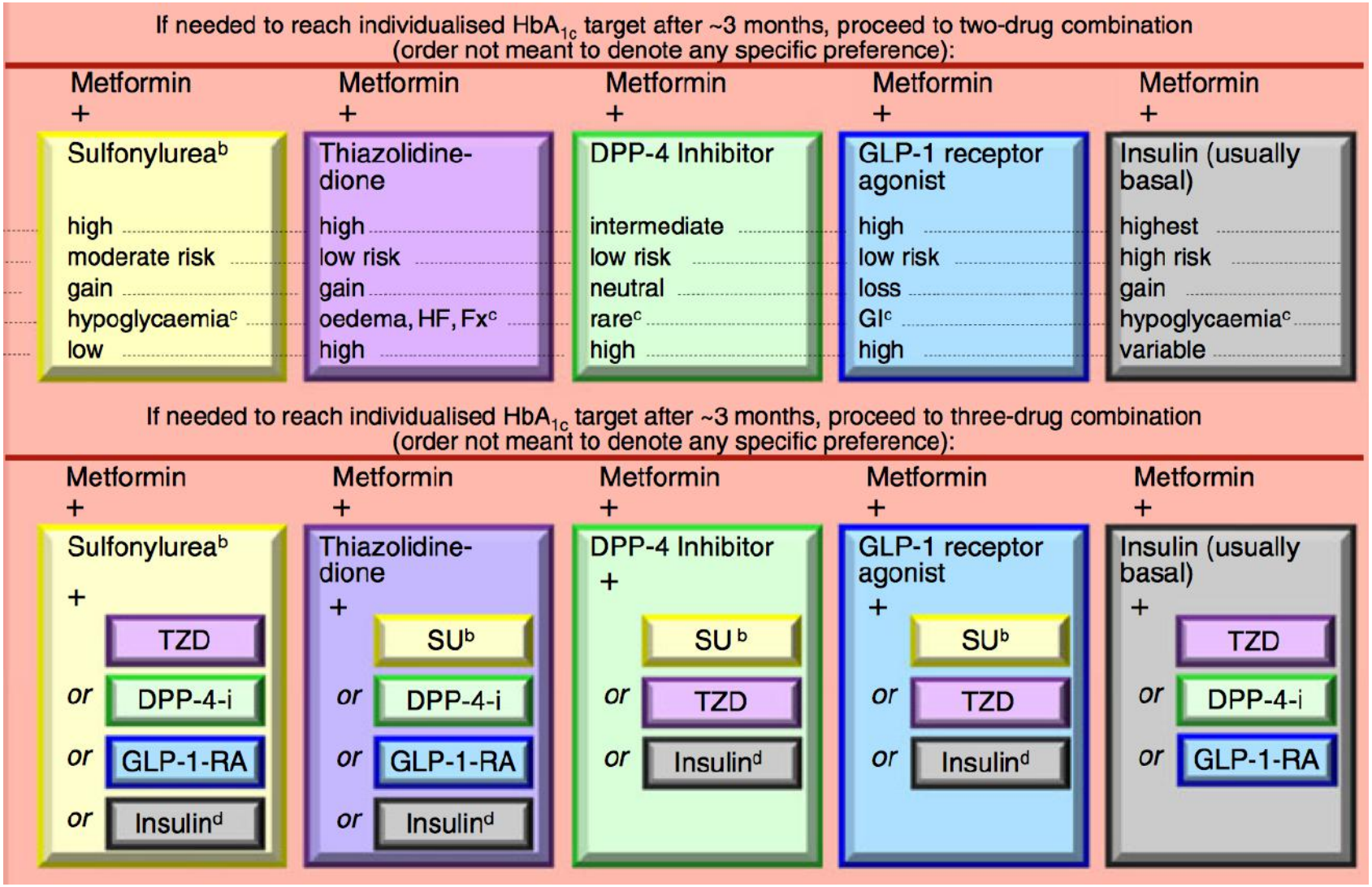
- Young onset (usually before age 25)
- Non insulin requiring (but may be treated with insulin)
- Usually a strong family history
  - Caution – can occur de novo;
  - Caution – GCK
- Do they have 'atypical' diabetes?
  - Slim
  - Absence of insulin resisitance
- hsCRP
  - Low in HNF1A
- Renal cystic kidney disease/Genital tract malformation
  - HNF1B
- Macrosomia and neonatal hyperinsulinemia
  - HNF4A

# Major differences in referrals by Health Board in Scotland



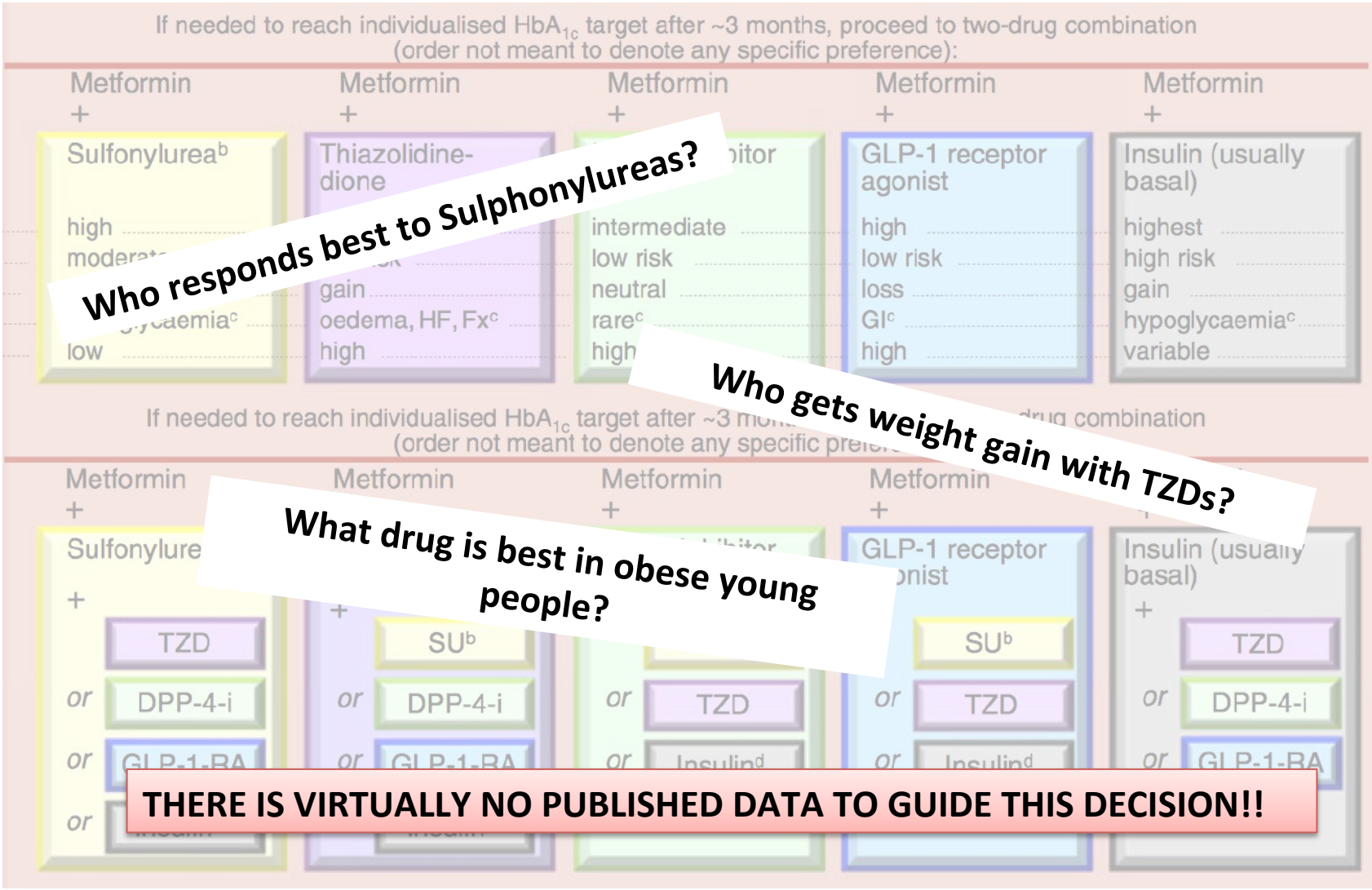
What about when it is (probably) type 2 diabetes – how can we choose what is the best treatment for the patient in front of us?

# Do the guidelines help us?



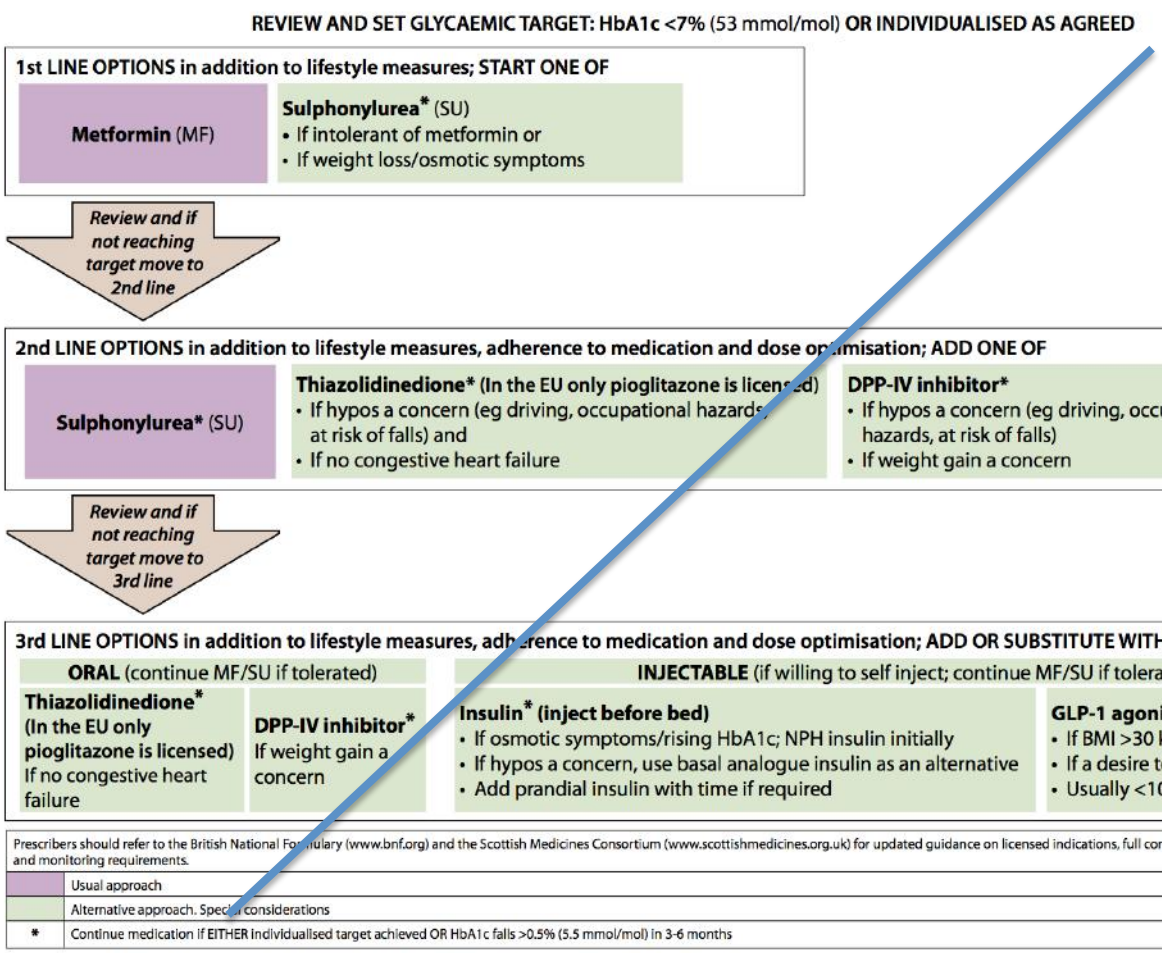

**ADA/EASD joint position statement**

# "Choice is based on patient and drug characteristics"




**ADA/EASD joint position statement**

# Why don't we just try a drug and see if it works?




* Continue medication if either individualised target achieved OR HbA1c falls >5.5mmol/mol in 3-6 months

# So do we stop ineffective drugs?

After starting first second line therapy, is the next treatment:

ADDED? i.e. third line treatment 81%

SWITCHED? i.e. alternative second line treatment tried 19%

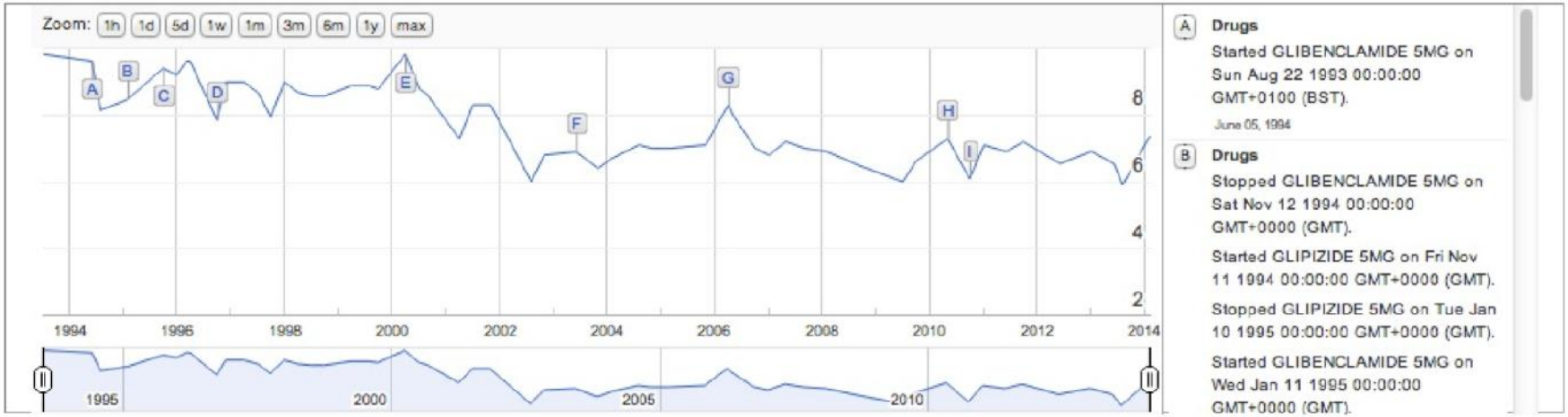
After starting first second line therapy **which is ineffective (the HbA1c does not fall more than 5.5mmol/mol)**, is the next treatment:

ADDED? i.e. third line treatment 78%

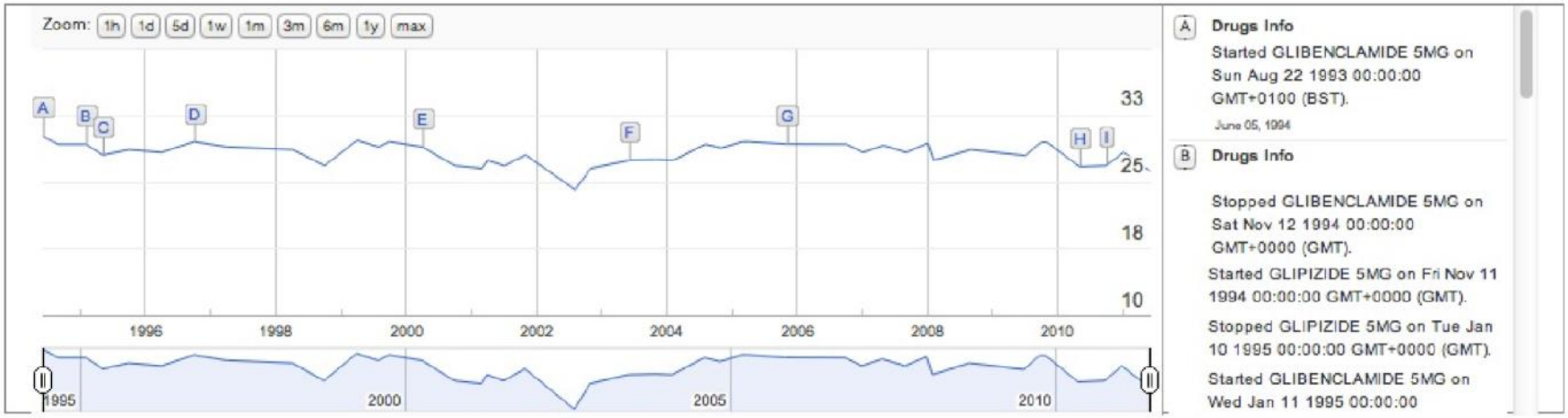
SWITCHED? i.e. alternative second line treatment tried 22%

# Solution? Better tools to review response to drugs

## HbA1c Results




## BMI Results



# An individualized approach: predicting who will respond to what drug best with least side effects


Person with Diabetes
Treated with Metformin
HbA1c 7.5% (58mmol/mol)

RESPONSE PREDICTION CALCULATOR

Age, Sex, BMI, Waist
Fasting insulin
Lipids
+/- Genotype (or WGS)
+/- Biomarker panel

Sitagliptin
Likelihood of response 88%
Likelihood of ADR 2%

Pioglitazone
Likelihood of response 50%
Likelihood of ADR 10%

SU
Likelihood of response 20%
Likelihood of ADR 1%

# MASTERMIND

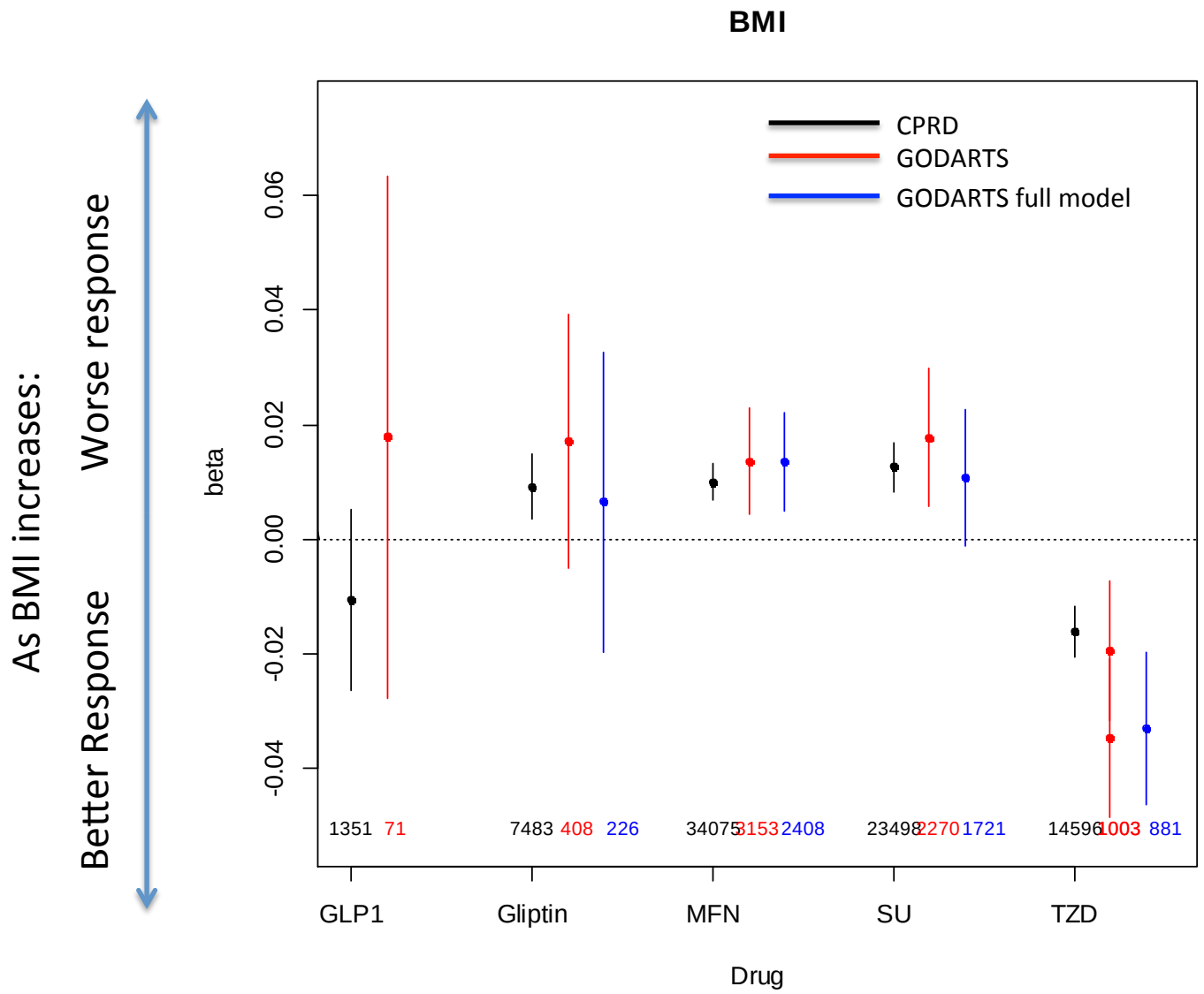
MRC APBI STratification Extreme Response Mechansim IN Diabetes

Andrew Hattersley & Ewan Pearson

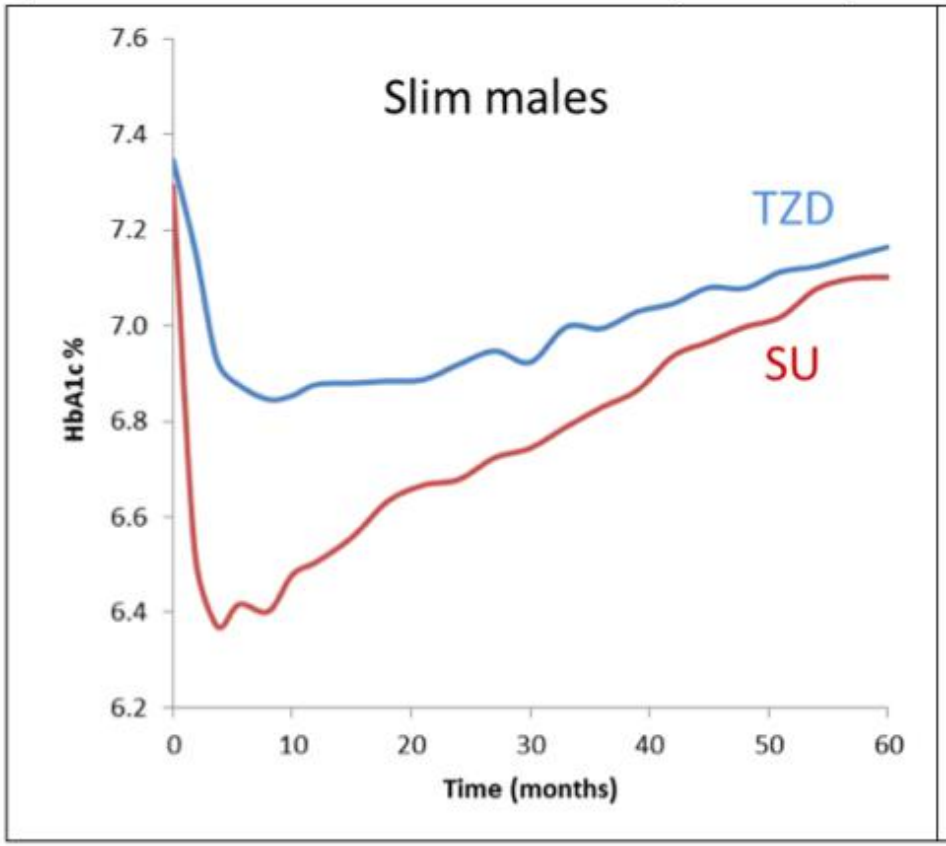
**What patient characteristics determine response to treatment in Type 2 diabetes?**

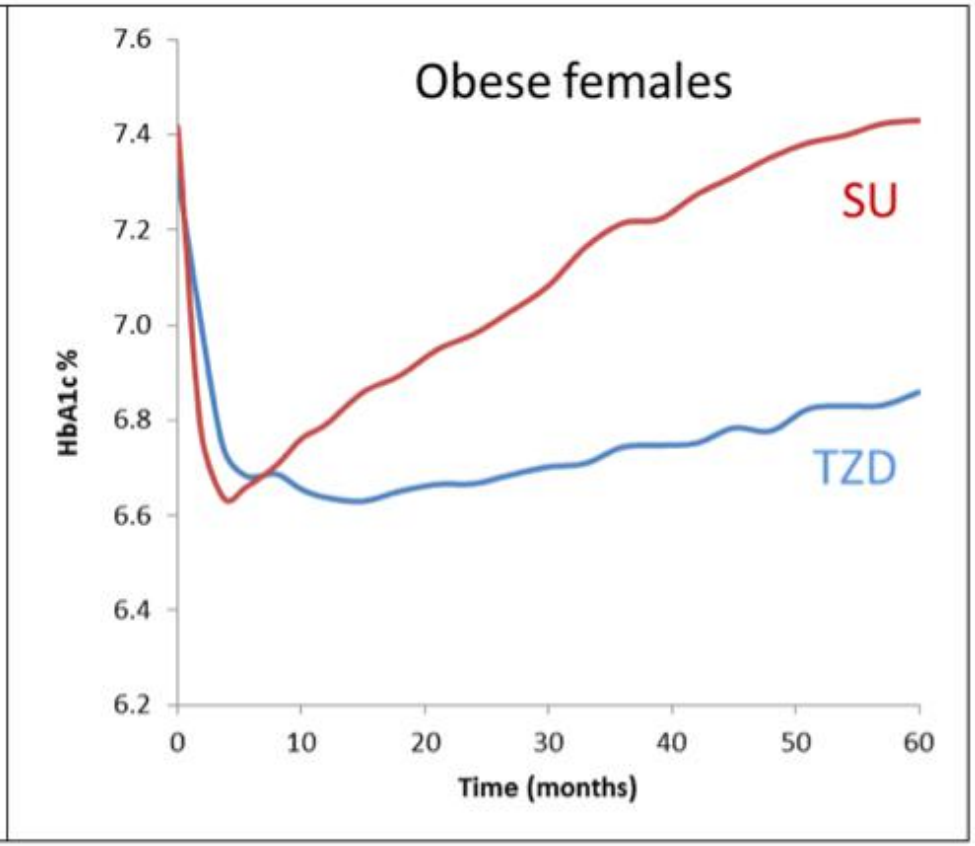
| CPRD | GoDARTS | UKPDS |
|---|---|---|
| Bev Shields | Louise Donnelly | Rury Holman |
| Mike Wheedon | Mike Lonergan | Orunsola Agbaje |
| Lauren Rogers | | |

# TZDs work better in more obese;
# Sulphonylureas and metformin work better in less obese



# Stratification in ADOPT




Unpublished. Perry et al. for the Mastermind Consortium

# An individualized approach: predicting who will respond to what drug best with least side effects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RESPONSE PREDICTION CALCULATOR

Age, Sex, BMI, Waist
Fasting insulin
Lipids
+/- Genotype (or WGS)
+/- Biomarker panel

**Slim Males -- SU; Obese Females - Pio**

# An individualized approach: predicting who will respond to what drug best with least side effects


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HbA1c 7.5% (58mmol/mol)

RESPONSE PREDICTION CALCULATOR

Age, Sex, BMI, Waist
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**What about genotype?**

# A subtype of sulphonylurea sensitivity in Type 2 diabetes

Person with Diabetes
Treated with Metformin
HbA1c 7.5% (58mmol/mol)

HNF1A MODY

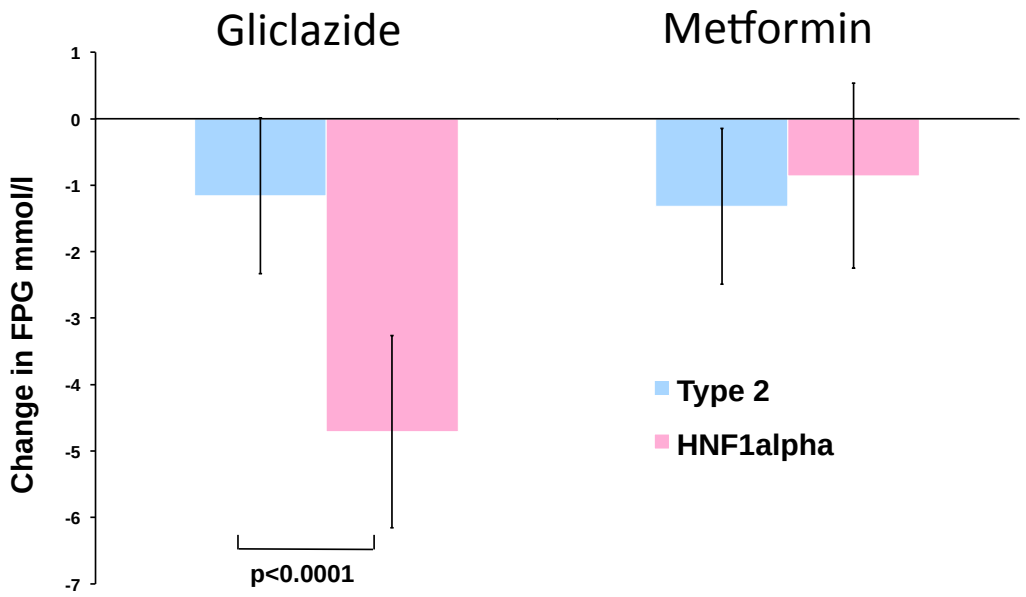
RESPONSE PREDICTION CALCULATOR

Age, Sex, BMI, Waist
Fasting insulin
Lipids
+/- Genotype (or WGS)
+/- Biomarker panel

| Sitagliptin | Pioglitazone | SU |
|---|---|---|
| Likelihood of response 50% | Likelihood of response 50% | Likelihood of response 99% |
| Likelihood of ADR 2% | Likelihood of ADR 1% | Likelihood of ADR 20% |

Figures are illustrative only!

# HNF1A MODY




Pearson et al. lancet 2003

# HNF1A MODY

Phenotypically Type 2DM

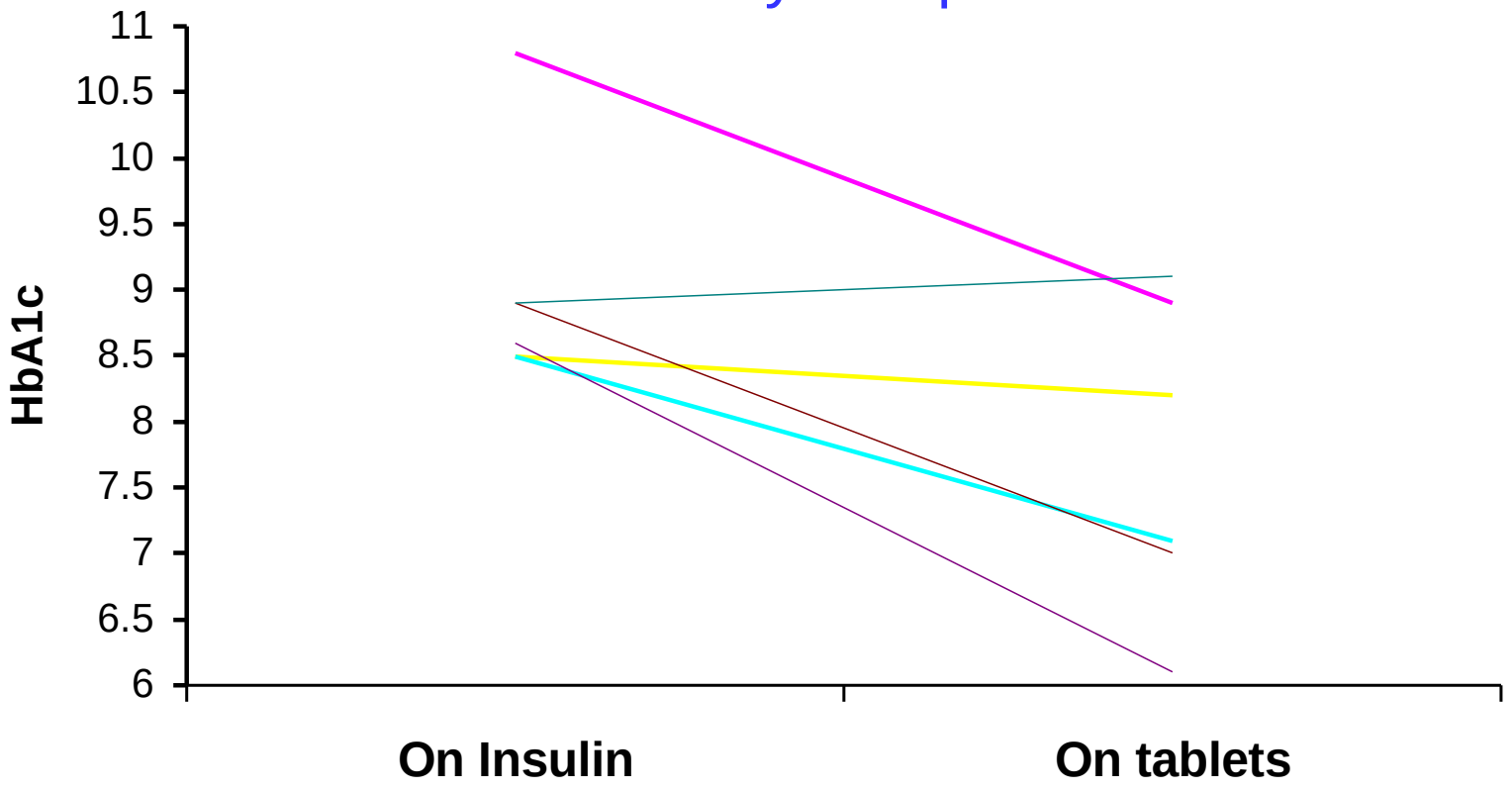
Yet SU sensitive

Changed from Metformin and Rosiglitazone to Gliclazide 80mg od

HbA1c from 8% to 7.2%

# Insulin Cessation in HNF1A MODY

Median time on insulin 20 years prior to transfer to SU




Shepherd Diabetes Care 2003

# Ah – but MODY is rare – what about genetic impact on drug response in 'type 2 diabetes'?


Person with Diabetes
Treated with Metformin
HbA1c 7.5% (58mmol/mol)

RESPONSE PREDICTION CALCULATOR

Age, Sex, BMI, Waist
Fasting insulin
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+/- Biomarker panel

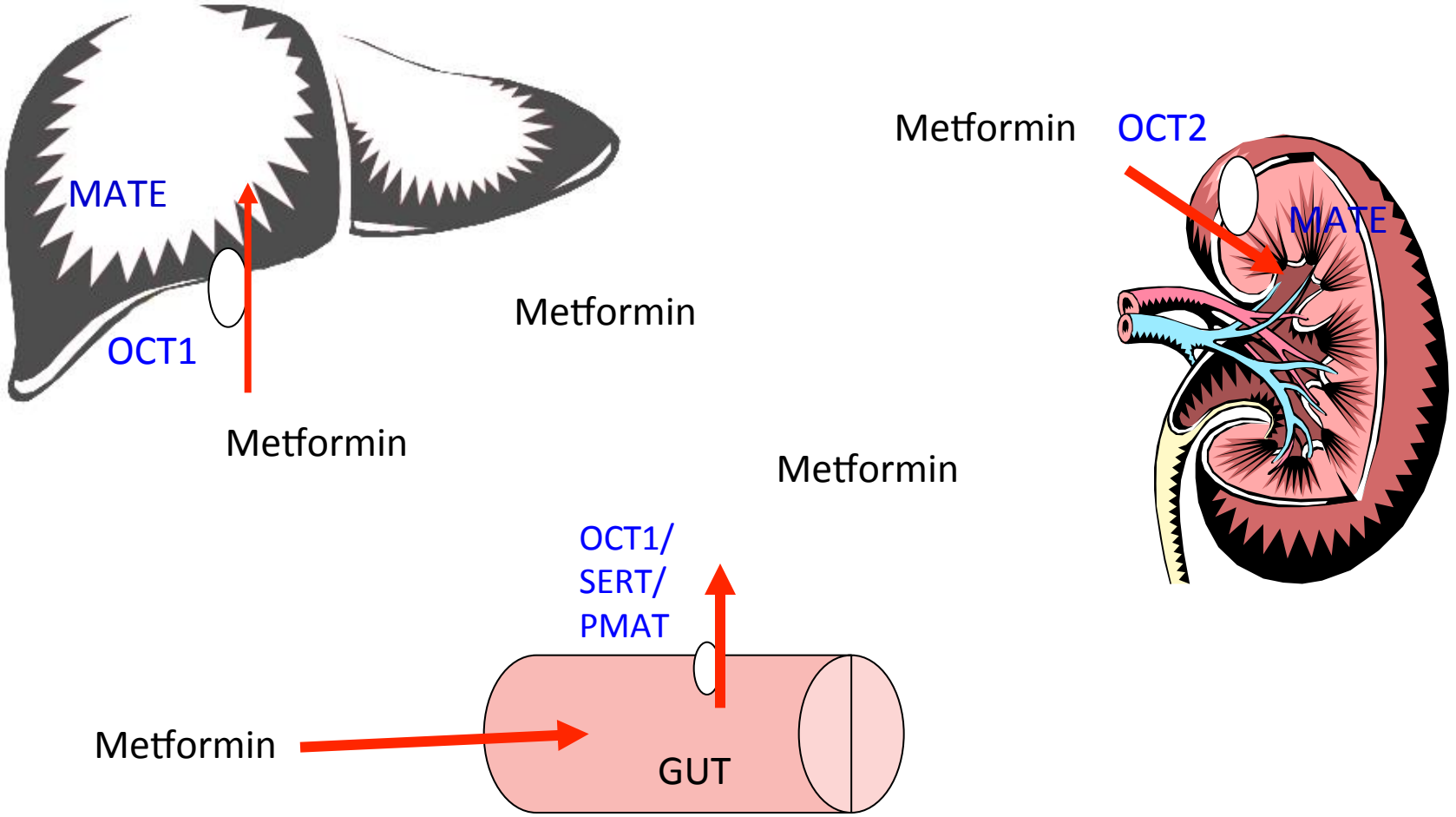
METFORMIN

THIAZOLIDINEDIONES

SULPHONYLUREAS

# METFORMIN

# Metformin Pharmacokinetics is well characterised: The role of organic cation transporters



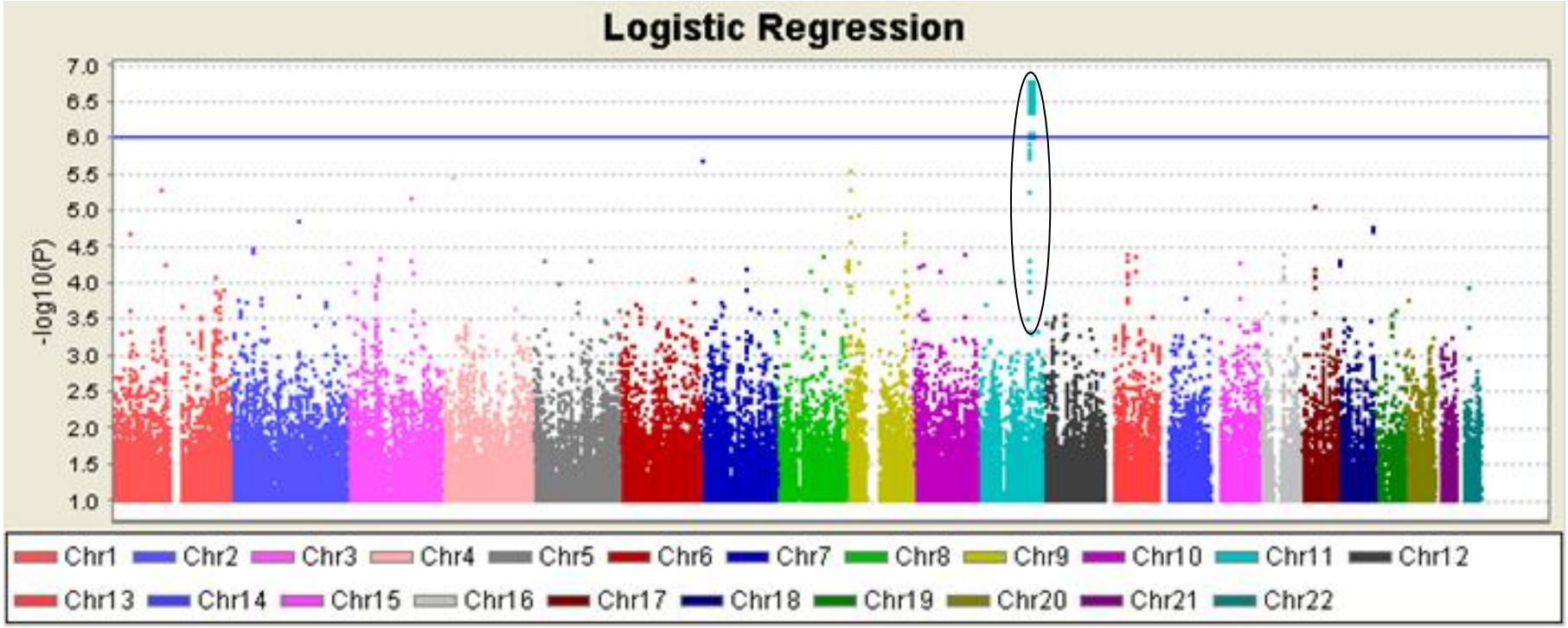
# MetGen Consortium


Metformin response in 20,000 individuals

No effect of OCT1, OCT2, OCTN1, MATE1, PMAT on metformin efficacy

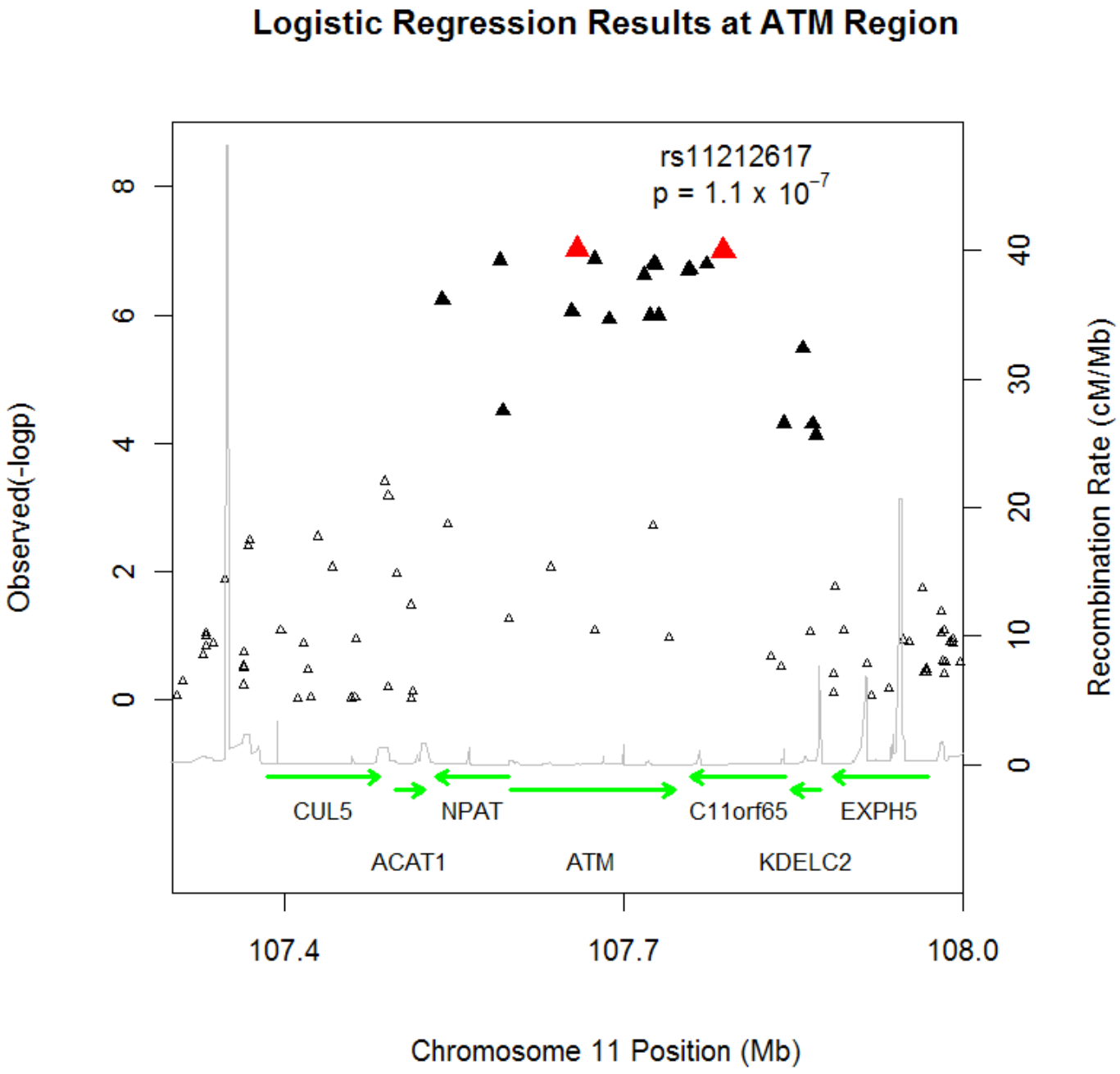
Does metformin work on the liver? Does it need to be absorbed at all? Could it all be a gut effect?

# Genome wide association study of glycaemic response to Metformin makes no assumption about mechanism




**Combined analysis (incl UKPDS) (n=4200)**
**OR 1.34 P=1.9*10-9**

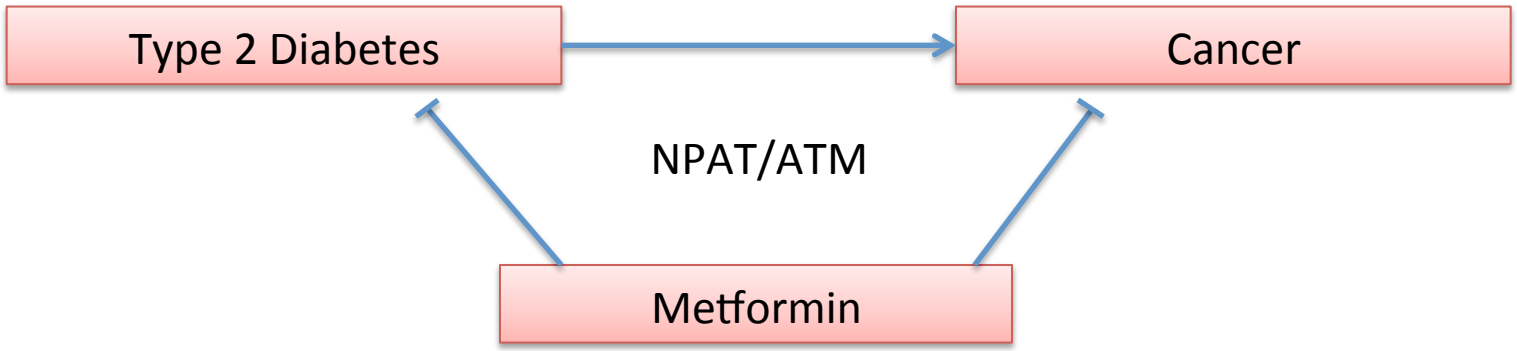
**Zhou, Bellenguez… …Palmer, Donnelly, Pearson Nat Genetics Feb 2011**




**Zhou, Bellenguez… …Palmer, Donnelly, Pearson Nat Genetics Feb 2011**

# NPAT/ATM

- ATM (a PI 3-kinase) main function is in controlling cell cycle progression after DNA damage
- Recessive mutations cause Ataxia Telangiectasia
  - Cerebellar ataxia
  - Malignancies - lymphoproliferative
  - Premature ageing
  - INSULIN RESISTANCE ++ and less commonly diabetes
- NPAT activates ATM, and is involved in cell cycle control



# Follow up work

MRC funding (£0.5M) to Calum Sutherland (with Rory McCrimmon, Mike Ashford, Colin Palmer)

Role of NPAT on weight and glucose response to Metformin

**Wellcome Investigator**

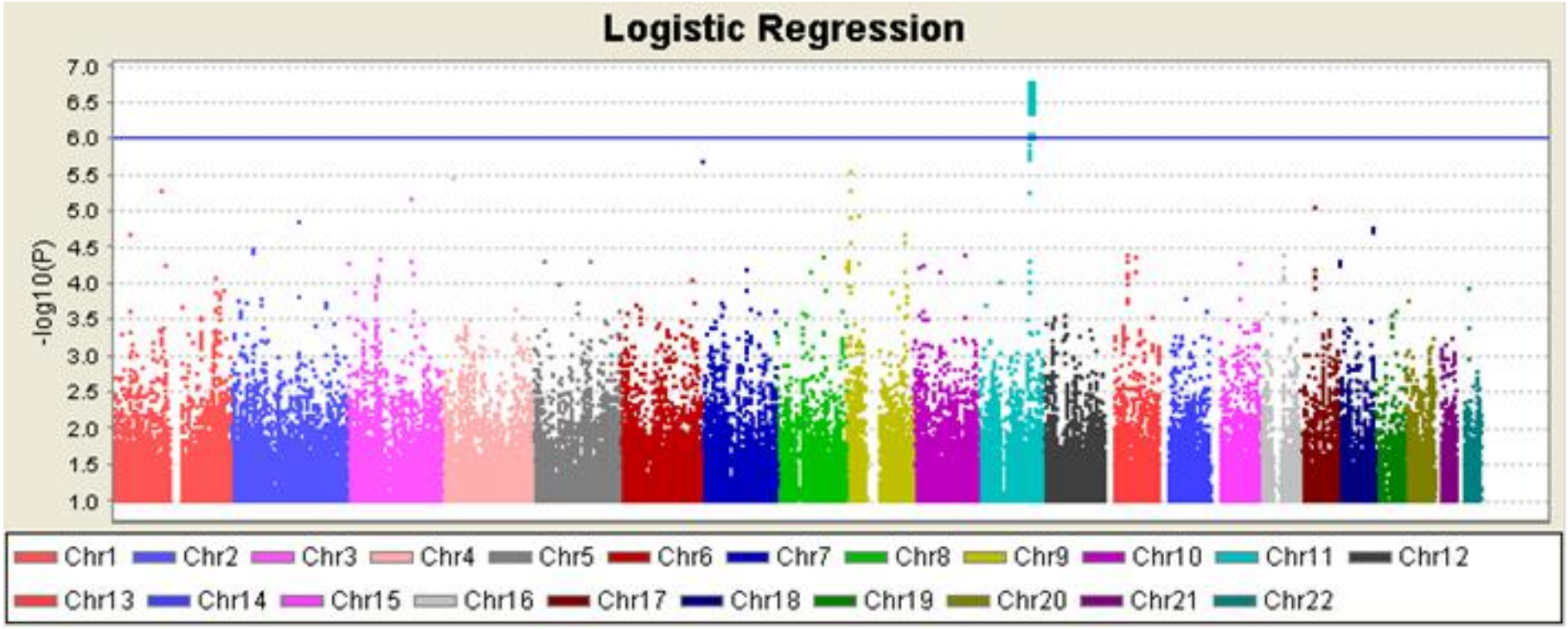
Patients with Ataxia Telangiectasia

Diabetes, Insulin Resistance, Fatty Liver, Cancer

Euglycaemic clamp studies, fat turnover, liver imaging, iPSCs

# Other genes involved?

Genome wide association study of glycaemic response to Metformin makes no assumption about mechanism

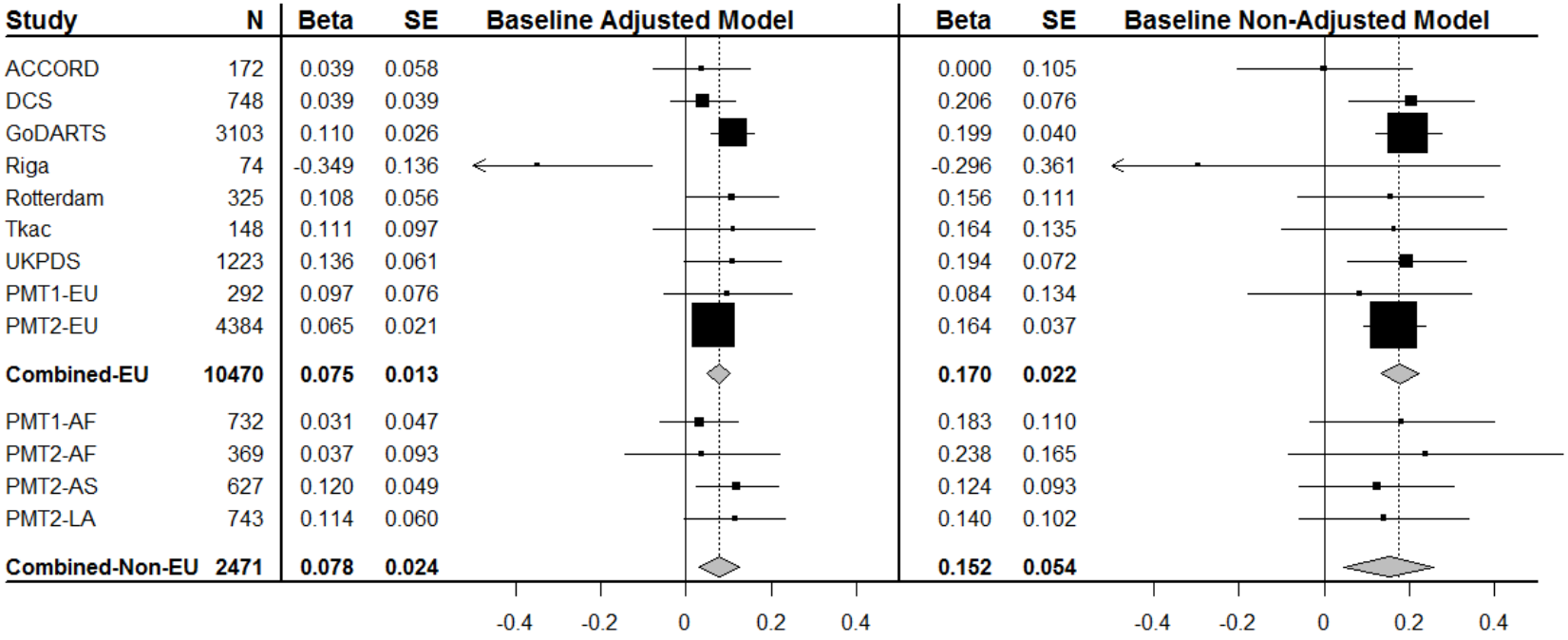


# *SLC2A2* (Glut2)

| | N | Baseline Adjusted | | | Baseline Non-Adjusted | | |
|---|---|---|---|---|---|---|---|
| | | Beta | SE | Pvalue | Beta | SE | Pvalue |
| GoDARTS GWAS Discovery* | 1478 | 0.127 | 0.038 | 0.001 | 0.226 | 0.054 | 3.50E-05 |
| GoDARTS Internal Replication* | 1625 | 0.1 | 0.038 | 0.0098 | 0.176 | 0.058 | 0.0024 |
| UKPDS Replication | 1223 | 0.136 | 0.061 | 0.014 | 0.194 | 0.072 | 0.0068 |
| **Meta-Analysis** | **4326** | **0.117** | **0.025** | **1.90E-06** | **0.201** | **0.035** | **7.00E-09** |

Beta is reduction in HbA1c from baseline per C allele at rs8192675

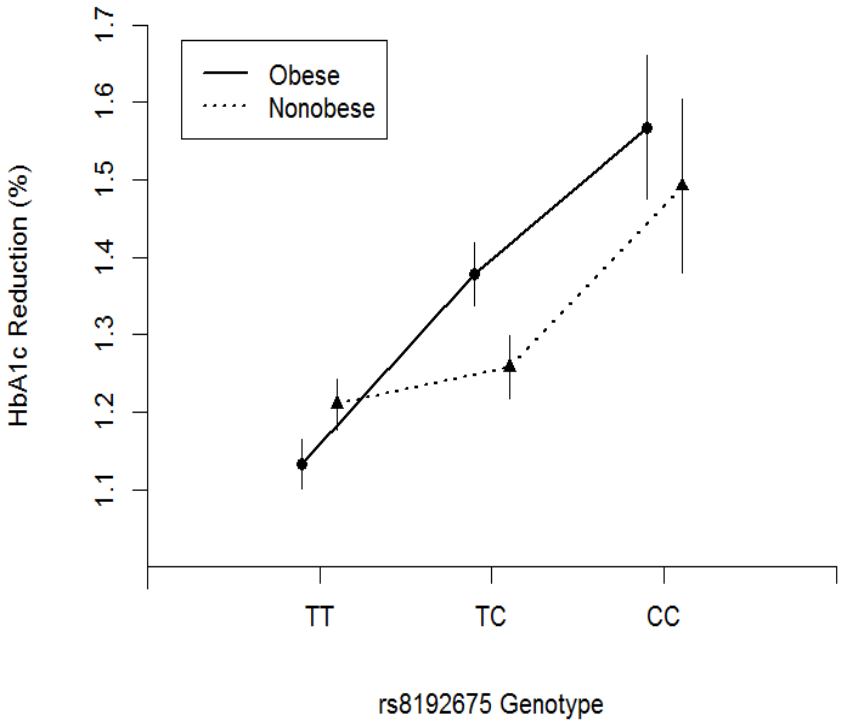
# Robust evidence that variation in Glut 2 alters response to metformin




0.15% greater reduction in HbA1c Per minor allele at rs8192675 in SLC2A2 (GLUT2)

# What's the effect size?

- Effect is greater in the obese
  - CC at rs8192675 4mmol/mol greater reduction in HbA1c than TT
  - Dose difference of 550mg metformin between these genotype groups
  - About half the effect seen for starting a new diabetes drug e.g. DPP-4 inhibitor



# Clinically important genetic effects on metformin treatment?

## GI intolerance with Metformin

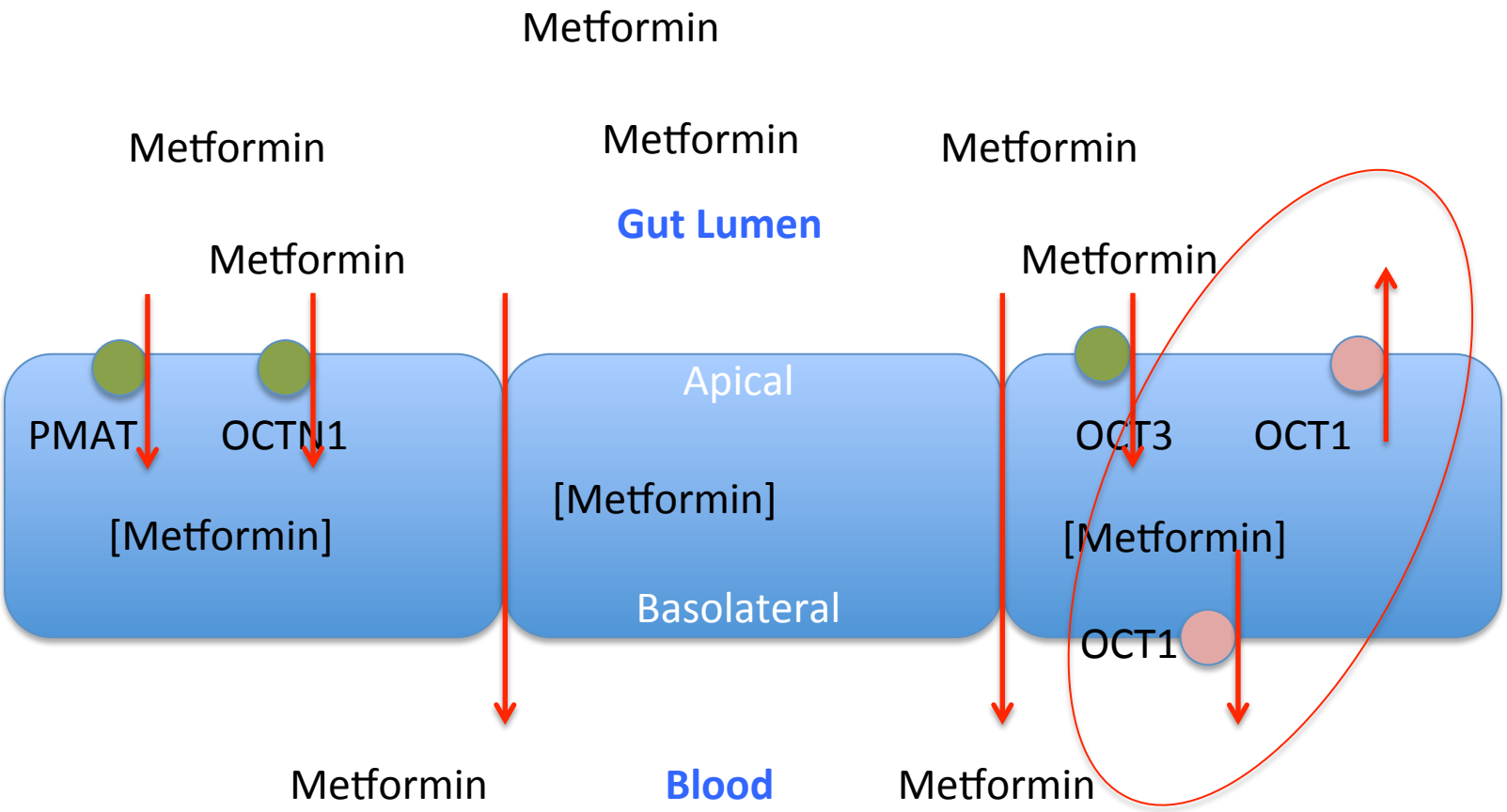
~20% of patients treated with Metformin have GI side effects with metformin treatment

~5-10% cannot tolerate metformin at all

Why?

Can we find a way to avoid intolerance in these individuals?

# Metformin and the gut enterocytes



# OCT1 transport

**Genetic variation**

**R61C**
**C88R**
**G401S**
**M420del**
**G465R**

**8% of us carry two loss of function variants**

**OCT1 Interacting Drugs**

TCA
PPI
VERAPAMIL
DILTIAZEM
DISOPYRAMIDE
QUINIDINE
PRAZOSIN
DOXAZOSIN
SPIRONOLACTONE
TRIMETHOPRIM
ROSIGLITAZONE
REPAGLINIDE

# Side effects

Tanja Dujic,[1] Kaixin Zhou,[2] Louise A. Donnelly,[2] Roger Tavendale,[2] Colin N.A. Palmer,[2] and Ewan R. Pearson[2]

## Association of Organic Cation Transporter 1 With Intolerance to Metformin in Type 2 Diabetes: A GoDARTS Study

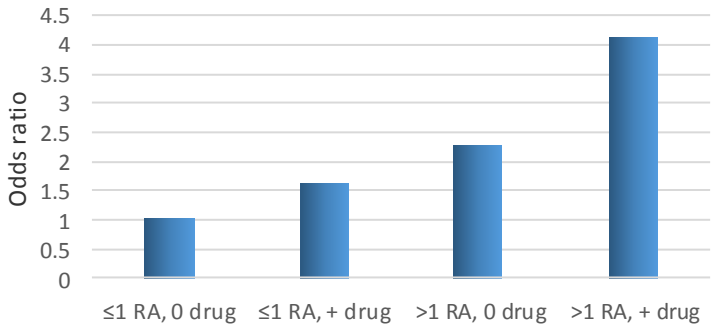
*Diabetes 2015;64:1786–1793 | DOI: 10.2337/db14-1388*

**Table 2—Logistic regression model of metformin intolerance**

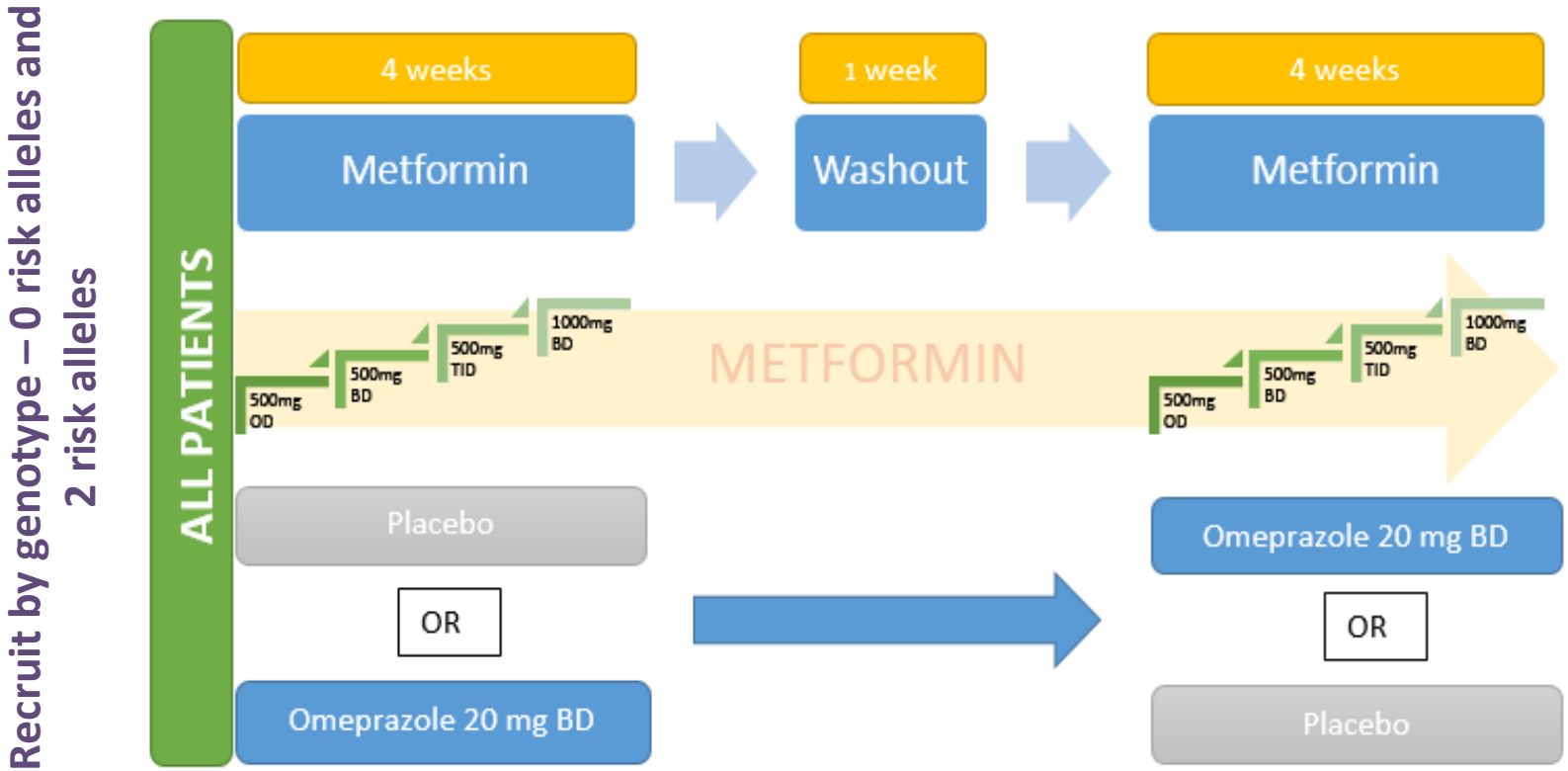
| | OR (95% CI) | *P* |
|---|---|---|
| Age | 1.10 (1.08–1.12) | <0.001 |
| Sex (females vs. males) | 1.85 (1.33–2.57) | <0.001 |
| Weight | 0.99 (0.98–1.00) | 0.064 |
| Use of OCT1-inhibiting drugs | 1.64 (1.20–2.25) | 0.002 |
| Two reduced-function OCT1 alleles | 2.41 (1.48–3.93) | <0.001 |

Logistic regression analysis included 205 intolerant and 1,650 tolerant patients.

Combined effect of OCT1 genotype and drug on metformin intolerance



# Validation in a Recruit by Genotype clinical trial




Randomised, placebo-controlled matched cross-over design.

# THIAZOLIDINEDIONES

Work best in obese females

Work best in insulin resistant (with fatty liver)

What about genotype?

Both Rosi and Pio are metabolised by CYP2C8

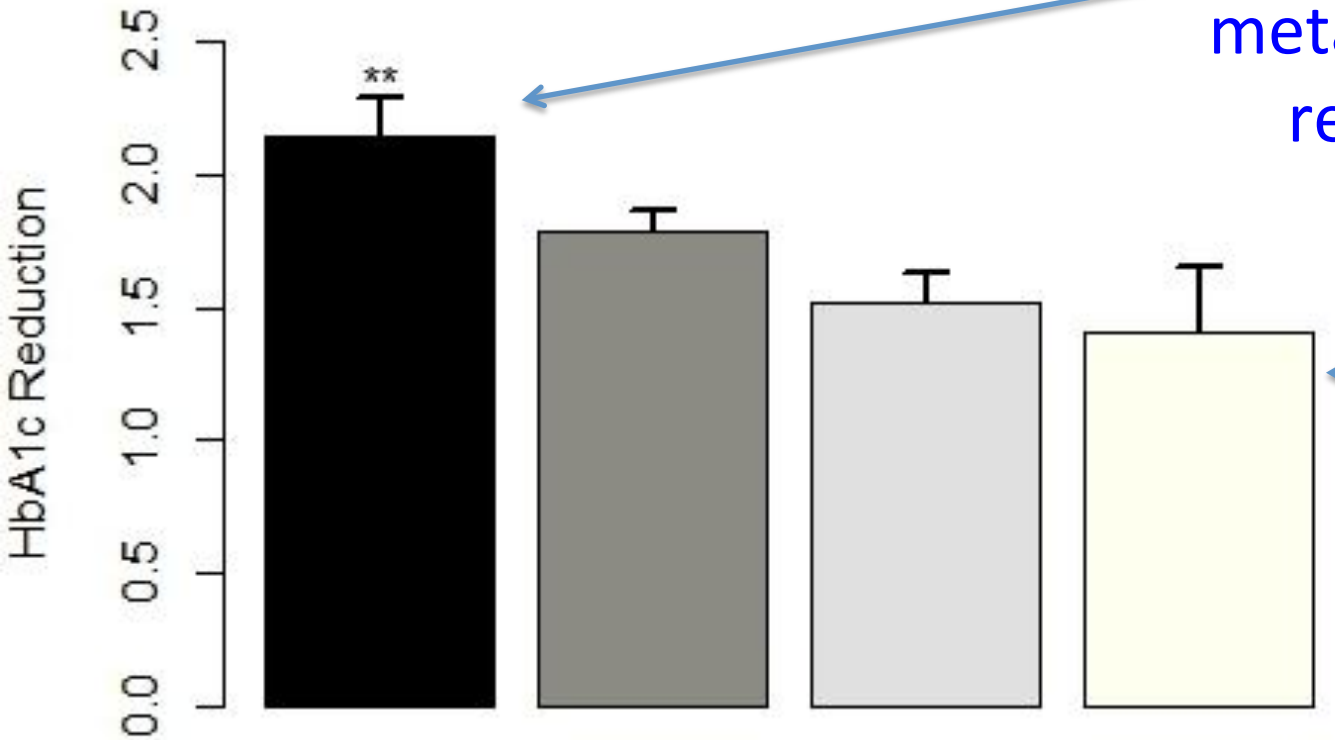
Variants in CYP2C8 *increase* metabolisim

Both are transported by SLCO1B1

Variants in SLC01B1 reduce transport

Dawed et al. Diabetes Care in press

# Glycaemic response to ROSIGLITAZONE



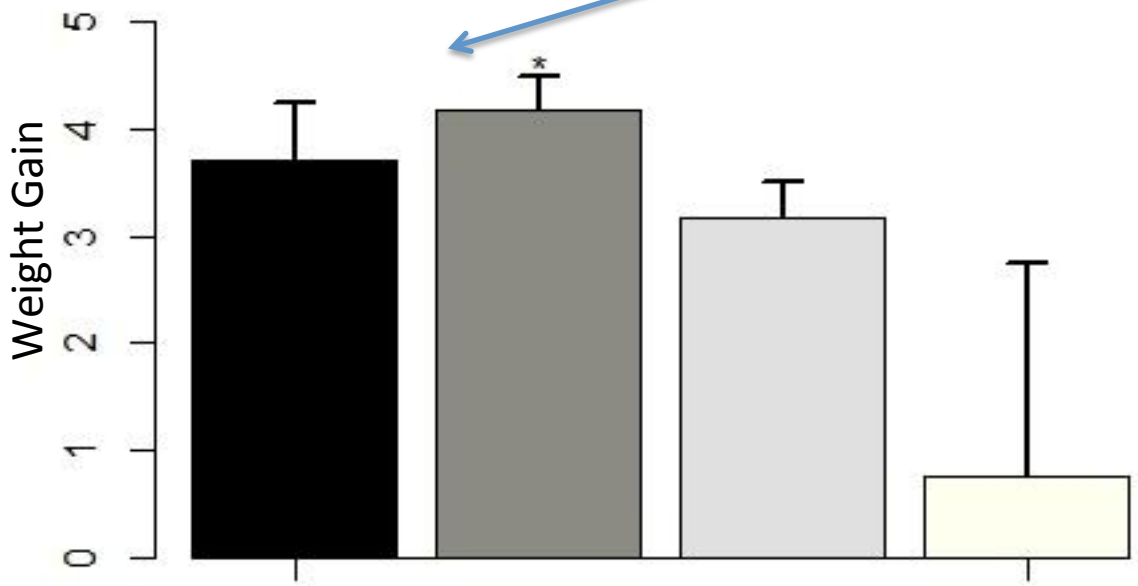

| | | | | |
|---|---|---|---|---|
| CYP2C8 | W/W | W/W | W/V | V/V |
| SLCO1B1 | W/V | W/W | W/W | W/W |

Patients with reduced transport and normal metabolism by CYP2C8 respond very well

Patients with normal transport and increased metabolism by CYP2C8 respond poorly

Dawed et al. Diabetes Care 2016

# Weight gain with ROSIGLITAZONE

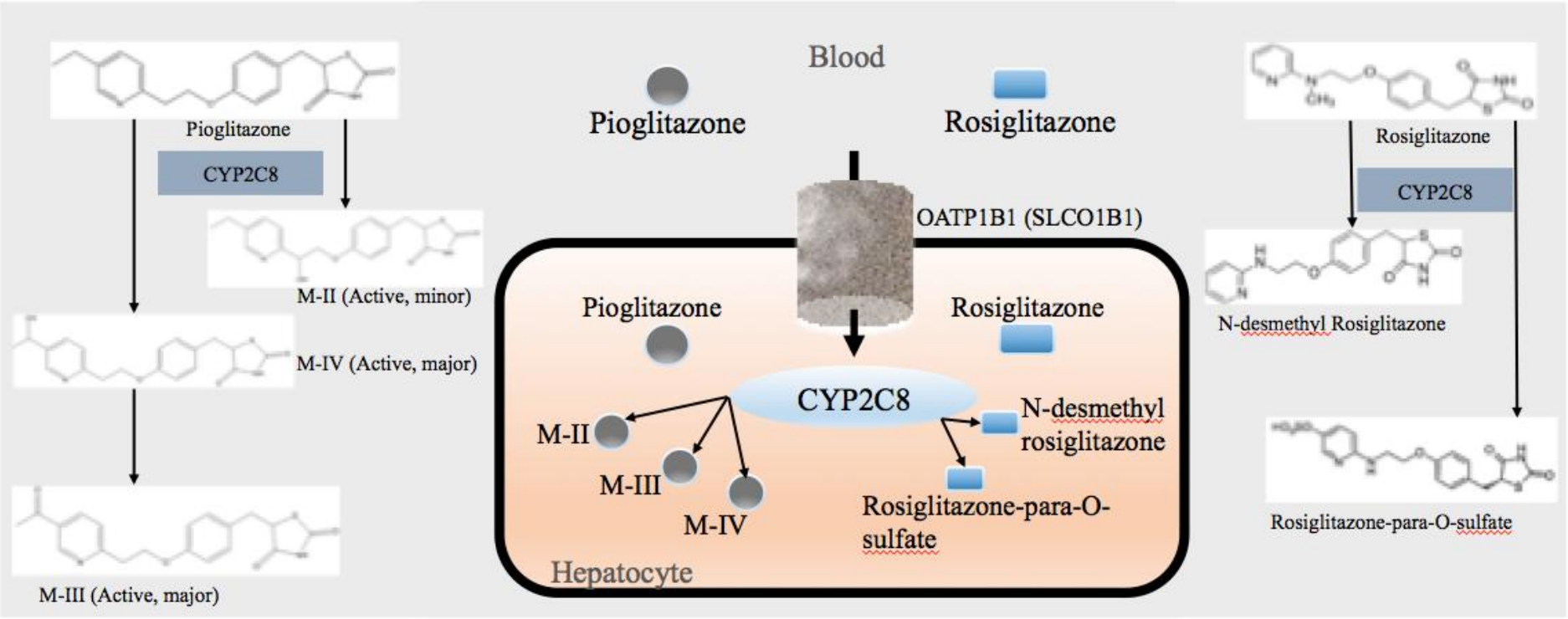



The genetically poor responders gain wait (4kg)

| | | | | |
|---|---|---|---|---|
| CYP2C8 | W/W | W/W | W/V | V/V |
| SLCO1B1 | W/V | W/W | W/W | W/W |

The genetically poor responders gain little weight

# Pharmacogenetic effect of CYP2C8 is seen for Rosiglitazone not Pioglitazone




Pioglitazone metabolites are active

Roisglitazone metabolites are inactive

Dawed et al. Diabetes Care 2016

# SULPHONYLUREAS

Slim Men

Genotype? CYP2C9 *2*2 or *2*3 or *3*3

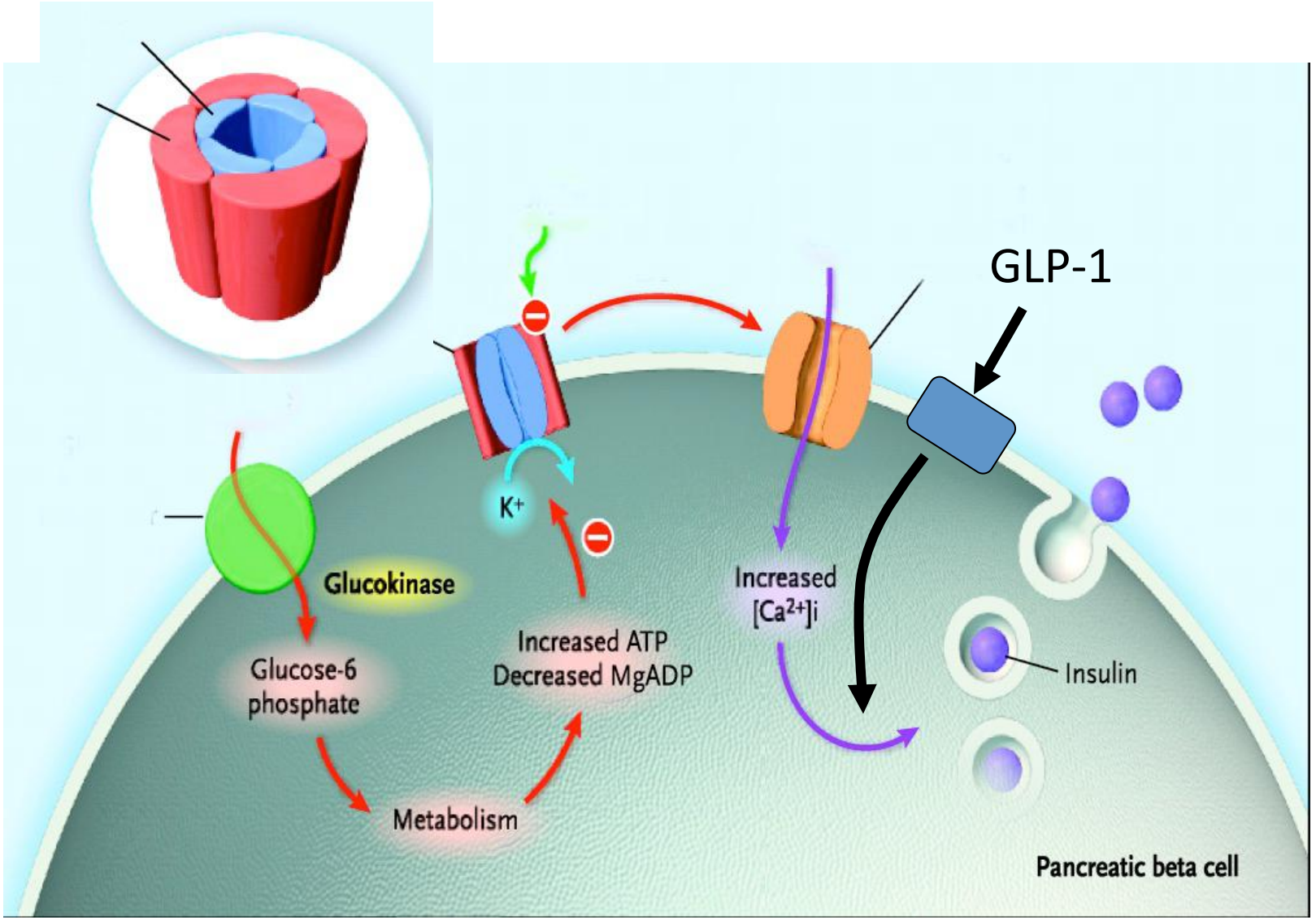
**6% of population**

**3.44 times more likley to achieve an A1c <7%**

Zhou et al. *CPT* 2009

Genotype? Genes altering Beta-cell function?

# The Beta cell & GSIS



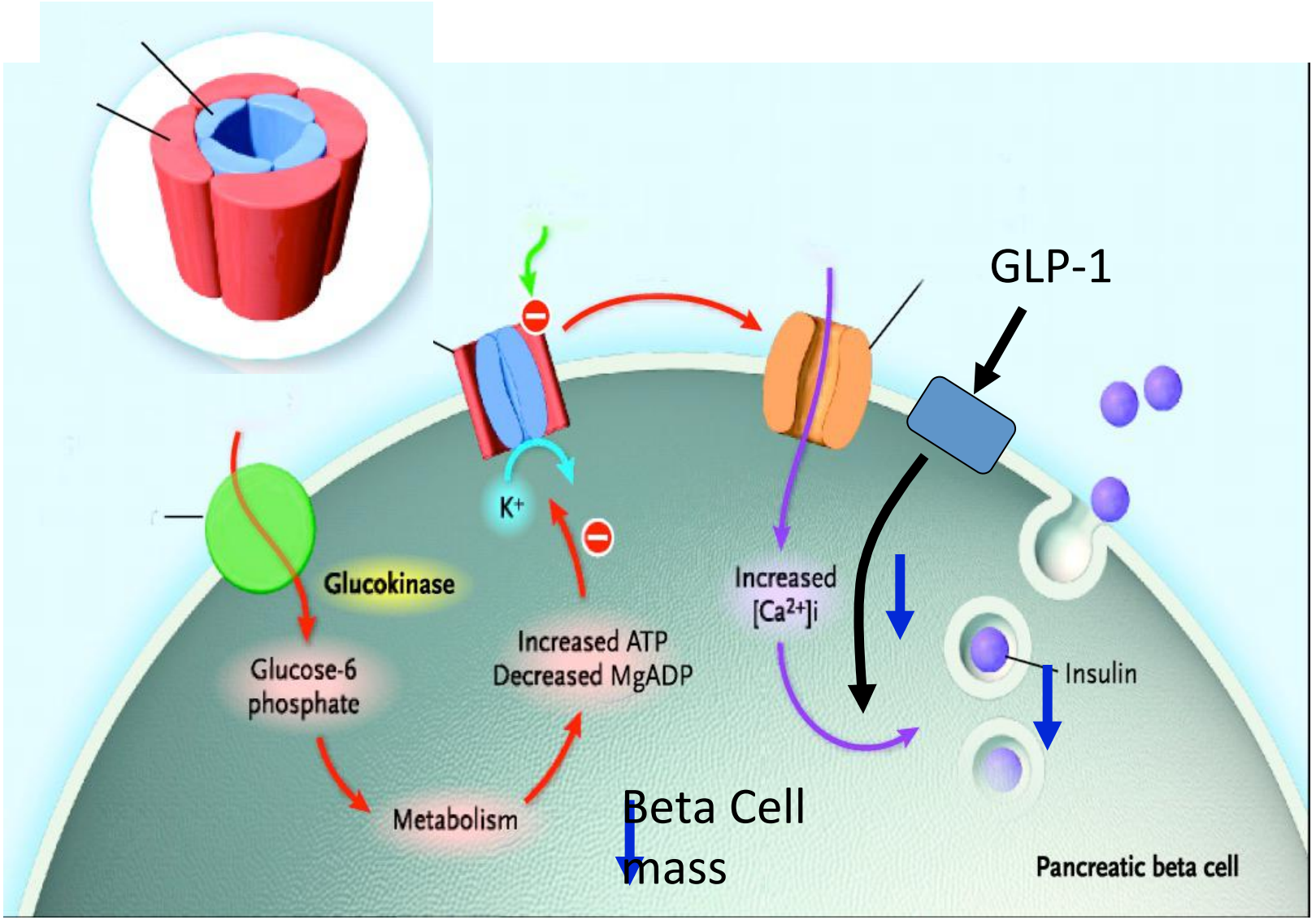
# TCF7L2

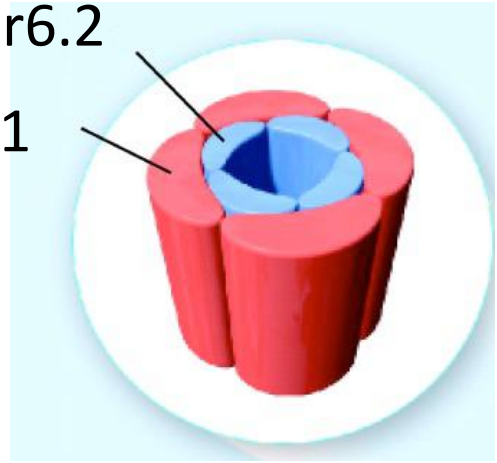
TT homozygotes at rs12255372 twice as likely not to achieve HbA1c < 7% within the first year of starting sulphonylureas than GG homozygotes

| **SULPHONYLUREA** (n=579) | | OR (95% CI) | p-value |
|---|---|---|---|
| TCF7L2 genotype | GT | **1.14 (0.78 to 1.68)** | **0.50** |
| | TT | **2.16 (1.21 to 3.86)** | **0.009** |
| Sex (Male=1; Female=0) | | 0.60 (0.41 to 0.87) | **0.007** |
| Age Diagnosed | | 0.99 (0.97 to 1.00) | 0.13 |
| HbA1c pre-treatment | | 1.30 (1.18 to 1.44) | **<0.001** |
| Dose (per 5% of maximum) | | 1.18 (1.10 to 1.27) | **<0.001** |
| Adherence (per 5%) | | 1.04 (0.99 to 1.10) | 0.13 |

Pearson et al. *Diabetes* 2007

# TCF7L2 and SU response






Ser1369Ala ABCC8. Ala is associated with greater response to gliclazide

1268 chinese participants. Prospective 8 week trial of response to Gliclazide

Exploratory group 661 with replication in independent cohort of 607

Compared to Ser/Ser:

Ala/Ser 2.7% greater response (FPG)

Ala/Ala 7.7% $p<0.001$

Feng Diabetes Care 2008

# Site of beta-cell defect determines response to sulphonylureas

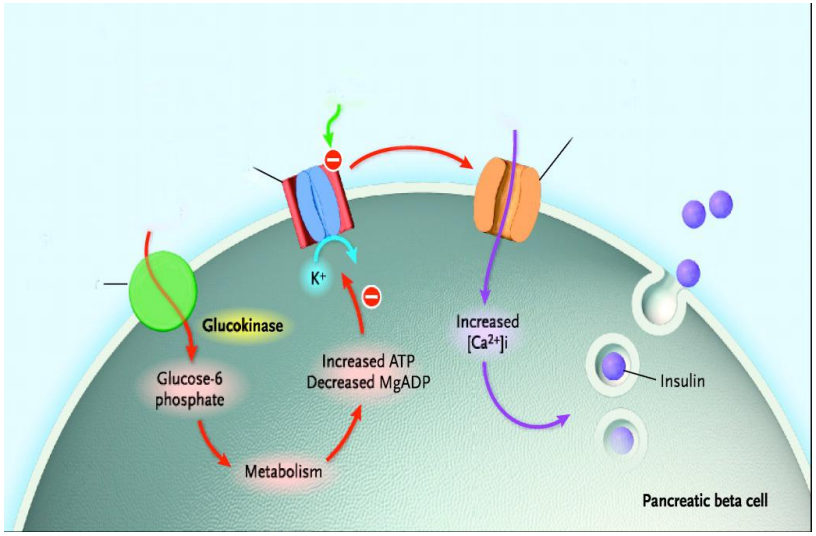
TCF7L2 diabetes risk variant decreases SU response

DOWNSTREAM of KATP (or beta-cell mass)

KCNJ11/ABCC8 diabetes risk variant increases SU response

UPSTREAM of KATP channel

HNF1A MODY risk variant (mutation) greatly increases SU response



# Which drug is best for your patient?

## Metformin

Best in slim people
Better with reduced GLUT2 transport

Side effects in those with reduced OCT1 transport

## TZDs

Best in obese women

Response and weight gain with Rosiglitazone altered by CYP2C8 and SLCO1B1 activity

## Sulphonylureas

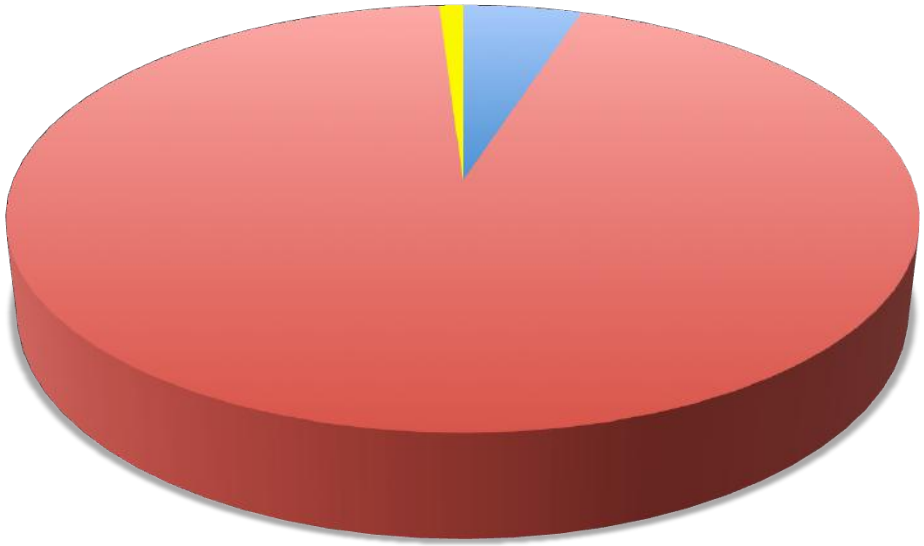
Best in slim men
3.44 times better in those who metabolise SU slowly (CYP2C9)
Better with KCNJ11/ABCC8 mutation
Worse in those with TCF7L2 risk variants
EXCELLENT in those with HNF1A/4A/ABCC8

## DPP-4i

Best in asians?

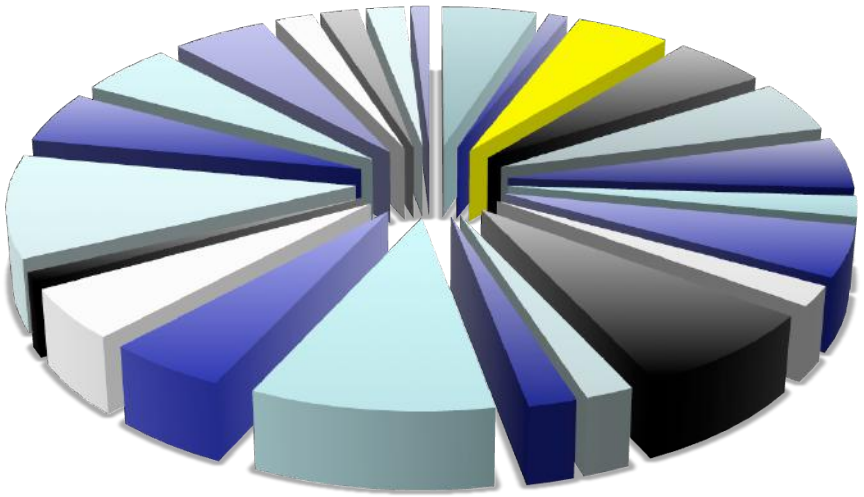
Response altered by CTRB1 variants

**The current 'simple view of diabetes'**



How?

**The future? Precision medicine in diabetes**



DIRECT

Innovative Medicines Initiative

# Diabetes REsearCh on patient sTratification

**25 Partners**

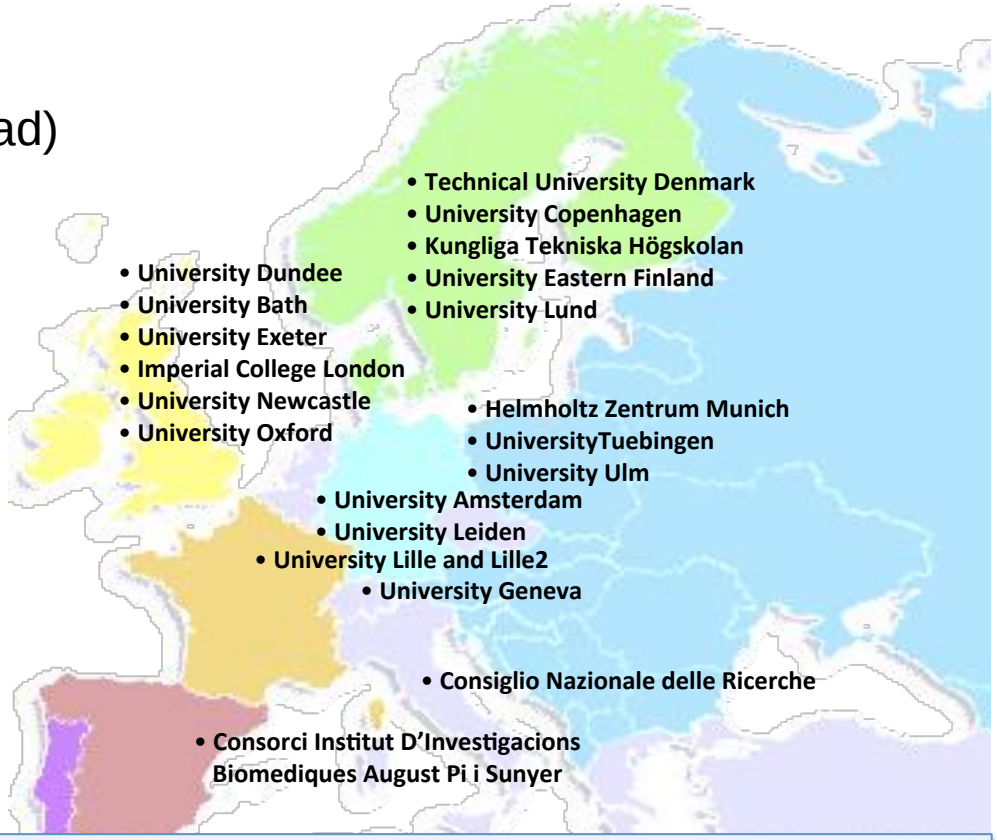
– 21 academic centers (Dundee lead)

– 4 pharmaceutical companies

Sanofi (coordinator), Lily, NovoNordisk, Servier

Funded by EU-FP7 (IMI) Public Private Partnership

€40M 7 year project




Genomic and non Genomic predictors of glycaemic deterioration and drug response; stratified clinical trials

# Anyone interested in a PhD?

- Physiology of Metformin action
  - Follow up on the role of Glut2 (SLC2A2) in diabetes onset, HbA1c variability, gut glucose absorption and metformin response
  - Email me – e.z.pearson@dundee.ac.uk

# Acknowledgements






http://diabetesgenetics.dundee.ac.uk