EFLM
EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

The practical issues in Type 2 diabetes management - Pharmacogenomic considerations

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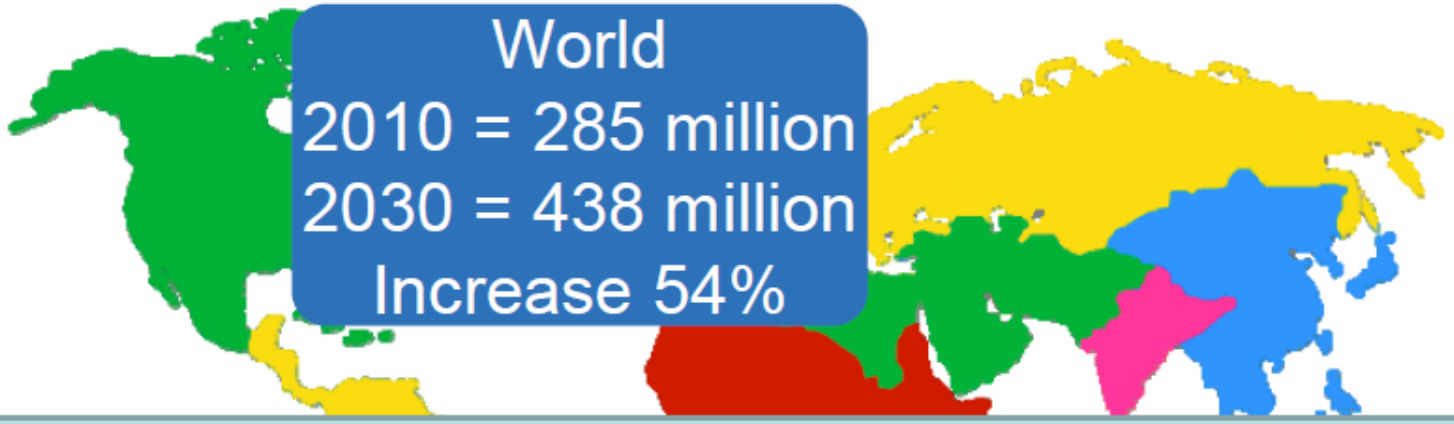
October 26, 2014.

Global Projections for the Diabetes Epidemic: 2010-2030 (millions)

1980-1990 by 18%.



2011- a staggering 366 million
2030 – 552 million

Dr Paul Zimmet, Baker IDI Heart and Diabetes Institute, Melburne Diabesity Conference, Brussels, EU Commission, Feb. 2012.

Shaw J. Diab Res & Clin Practice, 2009 *IDF Atlas 2009 www.idf.org*

European Commission

Baker IDI

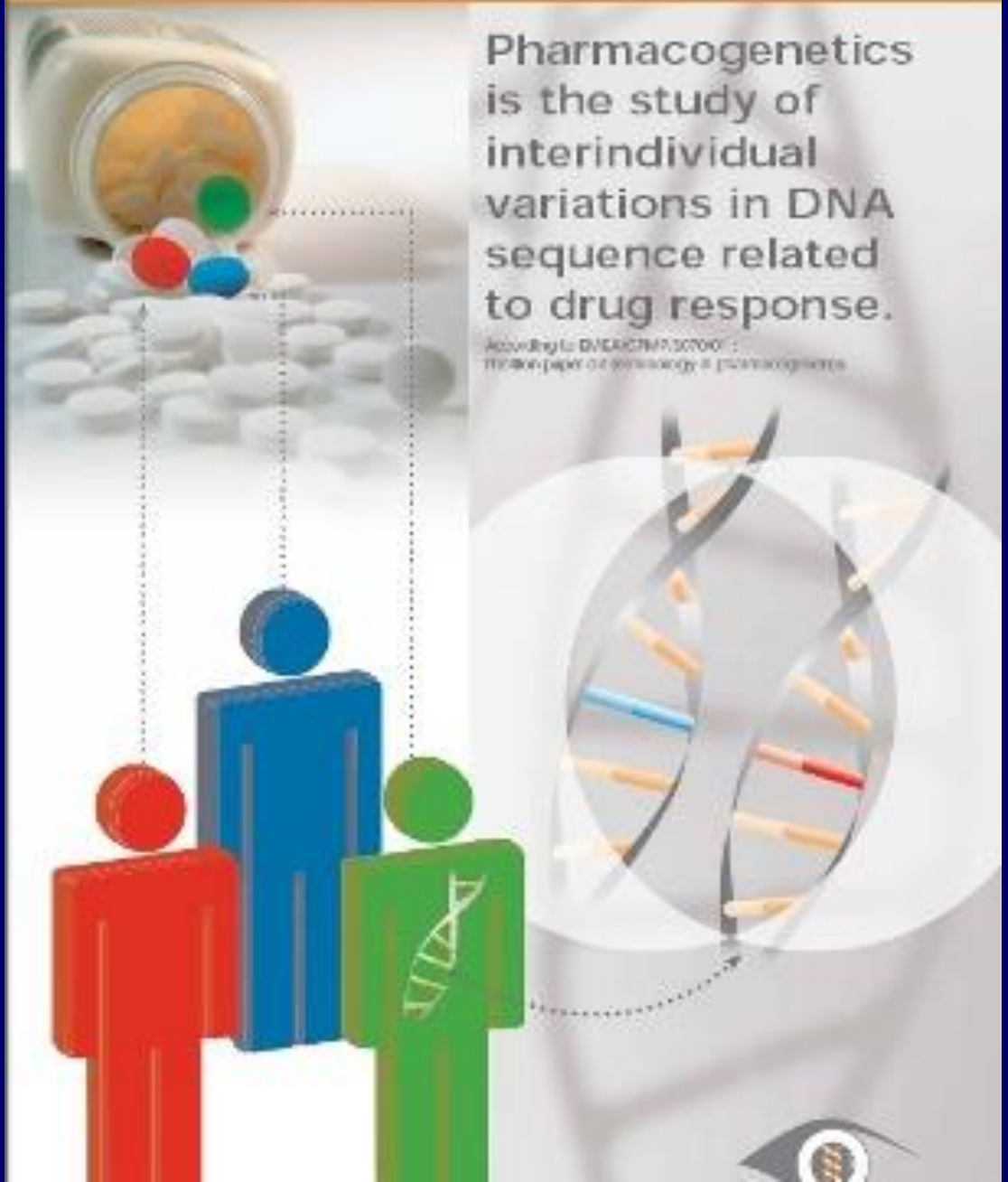
Diabesity

- **Obesity is driving the escalating diabesity epidemic: The biggest epidemic in human history.**
- **Continues to rise exponentially globally.**
- **Ageing, lifestyle change, and urbanisation have been targeted as the main drivers.**
- **By 2020, is set to bankrupt the economies of many nations unless action is taken.**

Dr Paul Zimmet, Baker IDI Heart and Diabetes Institute, Melburne
Diabesity Conference, Brussels, EU Commission, Feb. 2012.

European Commission

PHARMACOGENETICS



Pharmacogenetic Tests

- If genetic testing could be employed to predict treatment outcome, appropriate measures could be taken to treat T2D more efficiently and avoid extra costs for treating side-effects.
- Promote safe and cost-effective individualized diabetes treatment.

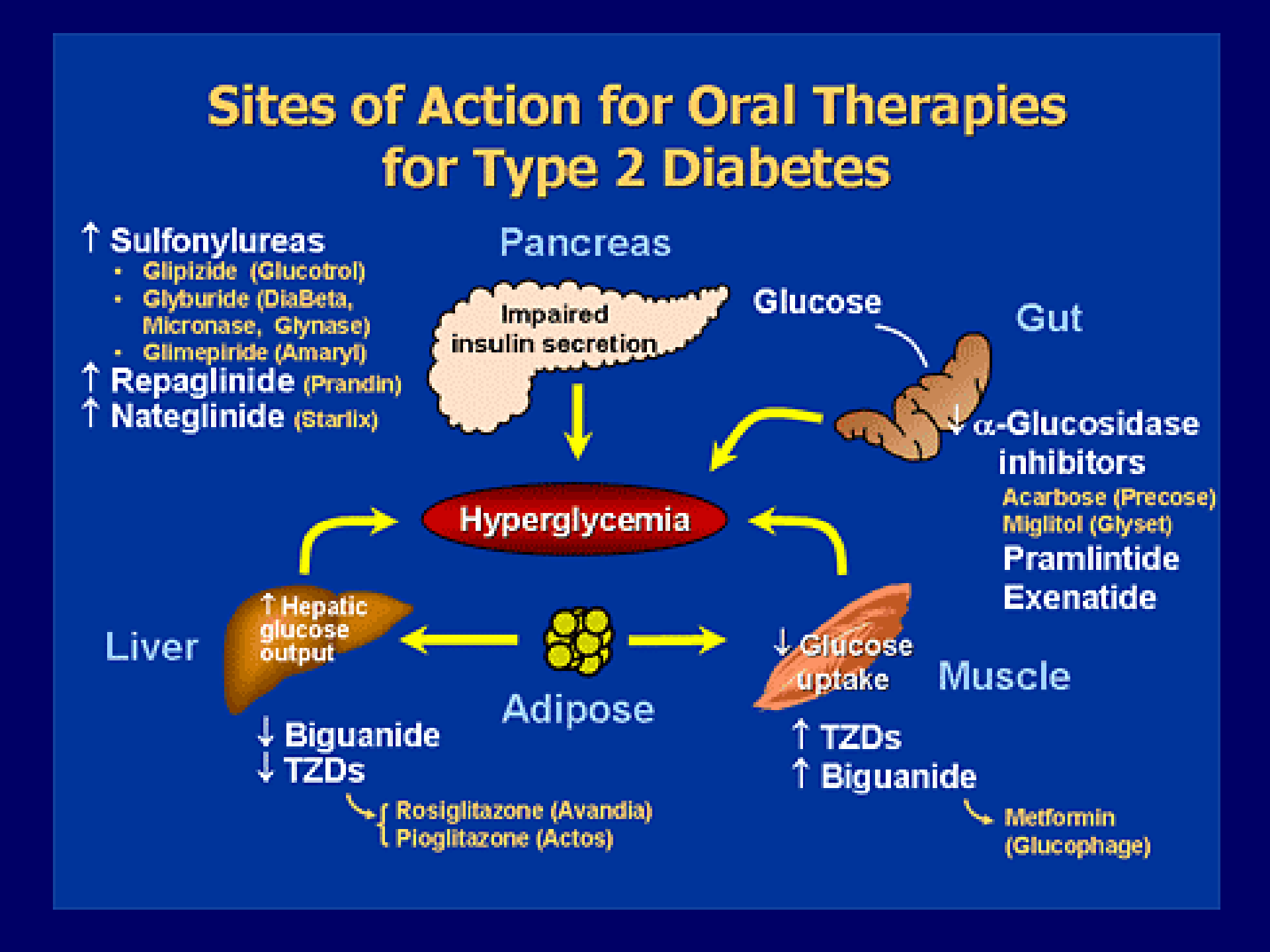
Pharmacogenomics in Diabetes

- T2D patients are often treated with more than one drug, including:
  - oral antidiabetic drugs (OAD), e.g.,metformin and sulfonylureas (SU).
  - drugs used to treat diabetic complications, such as dyslipidemia and hypertension (e.g., statins).

Oral Antidiabetic Drugs

Drug Class	Examples	Principal Mode of Action
Biguanides	Metformin	Decrease hepatic glucose production
Thiazolidinediones	Rosiglitazone Pioglitazone	Improve peripheral insulin sensitivity
Alpha-glucosidase inhibitors	Acarbose Miglitol	Delay carbohydrate absorption
Sulfonylureas	Glimepiride, Glipizide Glyburide, Gliclazide	Stimulate insulin secretion from pancreatic beta cells
Short-acting insulinotropic agents	Repaglinide Nateglinide	Stimulate insulin secretion from pancreatic beta cells

Sites of Action for Oral Therapies for Type 2 Diabetes



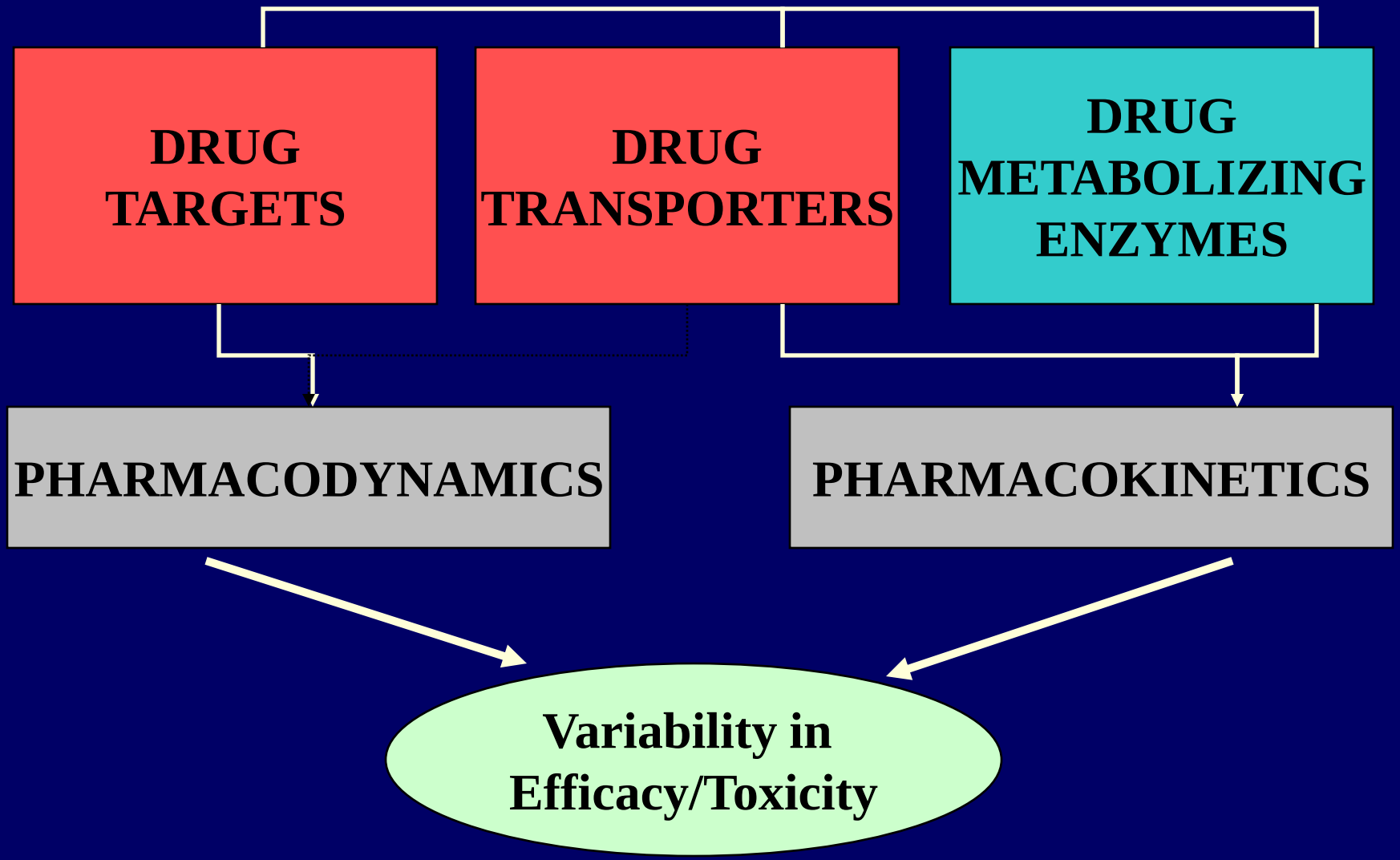
Pharmacogenomics in Diabetes

- Early stage of investigation.
- Although benefits from a personalized diabetes care are well established in patients with certain monogenic forms of diabetes, individualized treatment in more common polygenic forms of diabetes are also anticipated.
- GWA studies – identity of gene variants that impact on treatment response or side effects:
  - Severe hypoglycemia with sulfonylureas
  - Severe gastro-intestinal intolerance to metformin
  - Heart failure with thiazolidinediones

Pharmacogenomics in Diabetes

- The main objective is to improve drug therapy of diabetic patients.
- Analyze an association of genetic variations in:
  - drug-metabolizing enzymes (DME)
  - drug-transporters (DT)
  - specific drug targets with T2D treatment outcomes

Pharmacogenomics



Johnson JA. Trends in Genetics 2003: 660-666

Pharmacogenetics in Diabetes

- **Pharmacokinetic**
  - **Variation of tolbutamine hydroxylation – *CYP2C9* variation (Relling et al, J.Pharmacol.Exp.Ther. 1990, 252: 442-447).**
  - **Sulfonylurea treatment, 20 patients with severe hypoglycemia vs 337 without (Holstein et al, Br.J.Clin.Pharmacol. 2005, 60: 103-106).**
- **Pharmacodynamic**
  - ***TCF1* (encoding HNF1α) mutations - sulfonylureas as the first-line antidiabetic therapy for these patients.**
  - ***PPAR*γ – variation associated marginally with changes in insulin sensitivity and response.**
  - **Adiponectin, perilipin, lipoprotein lipase,…**

(Pearson E.R., Curr. Diabetes Rep. 2009, 9:172-181).

Pharmacogenetics and personalized treatment of type 2 diabetes

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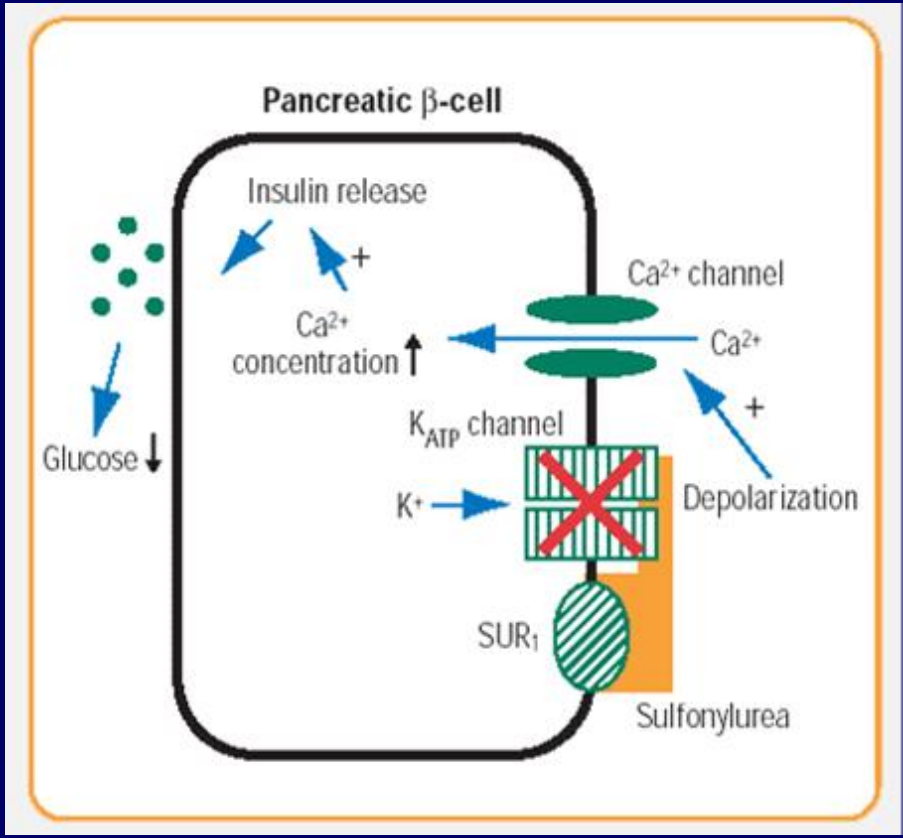
Summary of genetic variations involved in PGx of:

- **Sulfonylureas**
- **Thiazoldiendiones**
- **Meglitinides**
- **Biguanides**

Biochemia Medica 2013;23(2):154–71

SULPHONYLUREAS

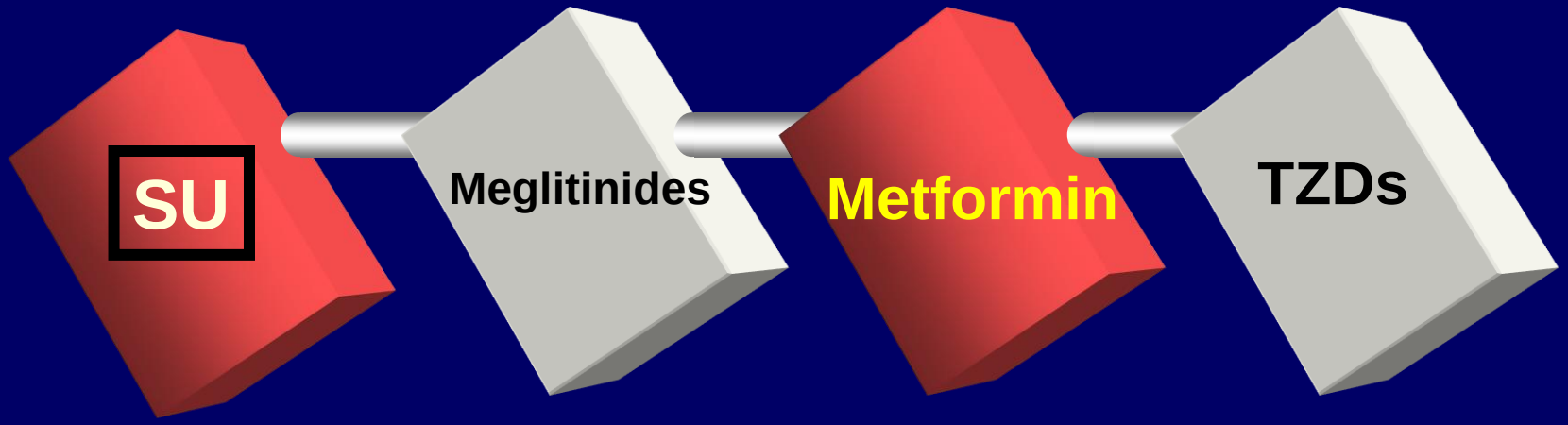
- **KATP channel is essential for glucose - stimulated insulin secretion from pancreatic β-cells, modulates glucose uptake into skeletal muscle, glucose production and release from the liver.**
- **KATP channels are assembled from:**
  - **Kir6.2 potassium ion channel - encoded by *KCNJ11***
  - **Sulphonylurea receptor 1 (SUR1) regulatory subunit - encoded by *ABCC8* gene**



PG of SULPHONYLUREAS

- SNPs of the genes encoding KATP channel are related to the efficacy of secretagogue drugs.
- A common Glu23Lys polymorphism (E23K) in ***KCNJ11*** is associated with an increased risk of SU therapeutic failure.
- ***KCNJ11*** variations have been associated with altered response to gliclazide and glibenclamide.
- Interestingly, the most promising gene variants affecting the SU response are those involved in drug pharmacodynamics, such as ***TCF7L2*** that encodes a transcription factor Tcf-4, involved in the regulation of cellular proliferation and differentiation.

Common genetic variations associated with OAD therapy outcomes



KCNJ11
TCF7L2
KCNQ1
ABCC8
CYP2C9

Analysis of *CYP2C9*2*, *CYP2C19*2*, and *CYP2D6*4* polymorphisms in patients with type 2 diabetes mellitus

Sabina Semiz[1*], Tanja Dujic[1], Barbara Ostanek[2], Besim Prnjavorac[1,3], Tamer Bego[1], Maja Malenica[1], Janja Marc[2] and Adlija Causevic[1]

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***Bosnian Journal of Basic Medical Sciences*. 2010;10:287-91.**

ORIGINAL ARTICLE

Analysis of *CYP3A4*1B* and *CYP3A5*3* polymorphisms in population of Bosnia and Herzegovina

Sabina Semiz[1], Tanja Dujić[1], Barbara Ostanek[2], Besim Prnjavorac[1,3], Tamer Bego[1], Maja Malenica[1], Barbara Mlinar[2], Janja Marc[2], Adlija Čaušević[1]

[1]Department for Biochemistry and Clinical Analysis, Faculty of Pharmacy, University of Sarajevo, Sarajevo, Bosnia and Herzegovina, [2]Department for Clinical Biochemistry, Faculty of Pharmacy, University of Ljubljana, Slovenia, [3]General Hospital Tesanj, Tesanj, Bosnia and Herzegovina.

Med Glas Ljek komore Zenicko-doboj kantona. 2011;8:84-9

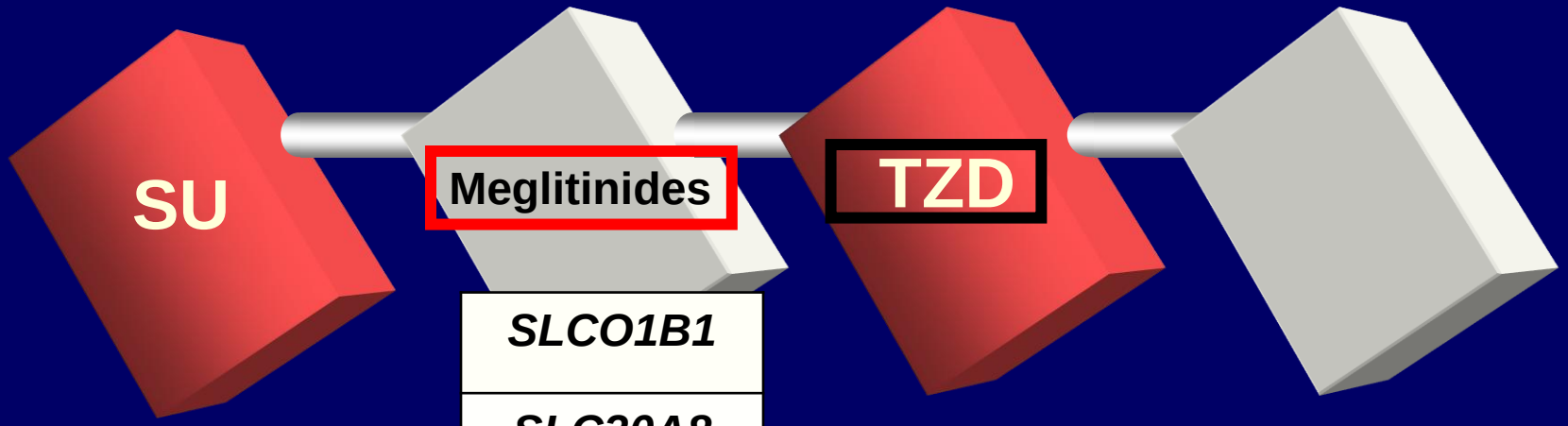
Meglitinides (glinides)

- A class of short - acting insulin secretagogues that act by binding to β - cells and closing KATP channel to stimulate insulin release.
- This is similar MOA of the sulfonylureas and both, meglitinides and SU, bind to the SUR1 subunit to inhibit channel activity.
- Due to their short action, repaglinide and nateglinide have a lower risk to induce hypoglycemia than SU.
- Furthermore, meglitinides offer an alternative OAD agent of similar potency to metformin, and may be indicated where side effects of metformin are intolerable or where metformin is contraindicated.

PG of Meglitinides

- ***SLCO1B1*** **gene encodes the organic anion-transporting polypeptide 1B1 (OATP1B1) that transports repaglinide into hepatocytes.**
  - **Major factor that significantly affects the repaglinide pharmacokinetics, consistent with an enhanced hepatic uptake by OATP1B1.**

Common genetic variations associated with OAD therapy outcomes



SU
KCNJ11
ABCC8
KCNQ1
TCF7L2
CYP2C9

Meglitinides
SLCO1B1
SLC30A8
MDR1
KCNQ1
KCNJ11
TCF7L2
NAMPT
CYP2C9

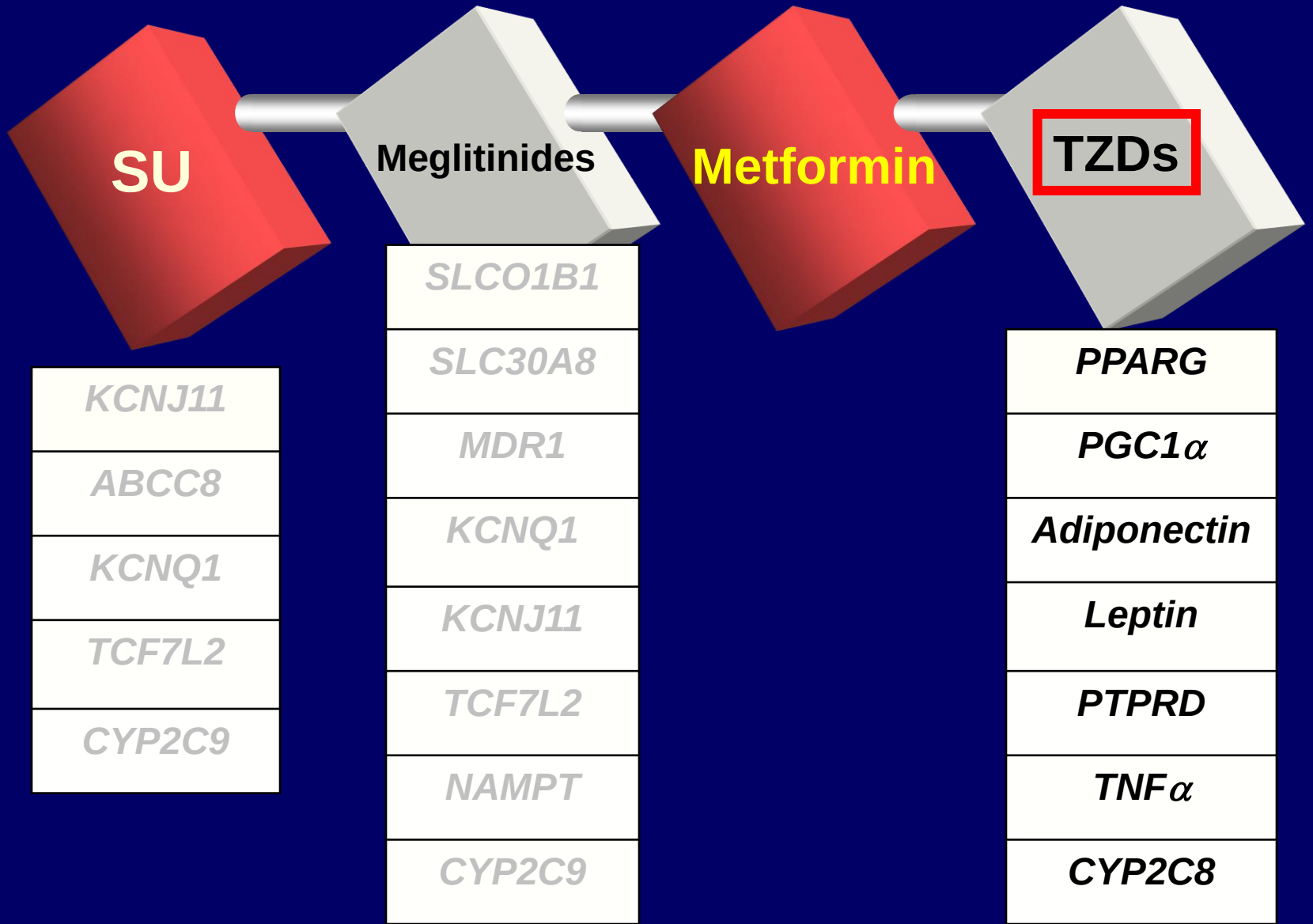
Thiazolidinediones (TZDs)

- Activate their molecular target PPARs (peroxisome proliferator - activated receptors).
- Bind with greatest specificity for PPARγ to promote adipogenesis and fatty acid uptake.
- By reducing circulating fatty acid levels and lipid availability in liver and muscle, these drugs improve the patients' sensitivity to insulin and reduce hyperglycemia.

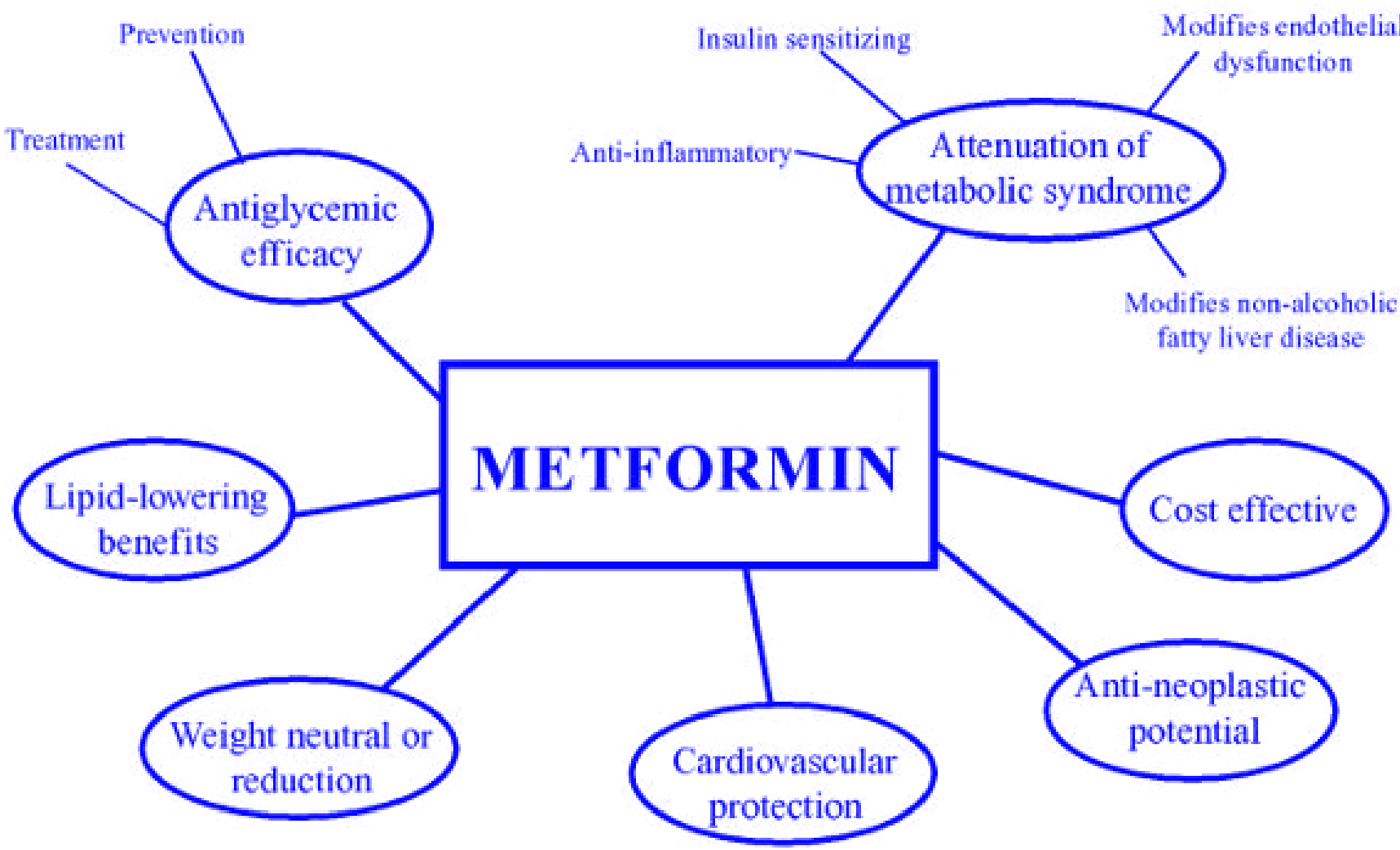
PG of TZDs

- Variation in PPARγ would likely affect response to TZD and this was suggested in a recent study that analyzed pioglitazone response.
- Recently, several additional gene variants have been also associated with the TZD therapy outcomes, including adiponectin, leptin, resistin, and TNF-α that are of a particular interest due to their important role in insulin resistance.

Common genetic variations associated with OAD therapy outcomes



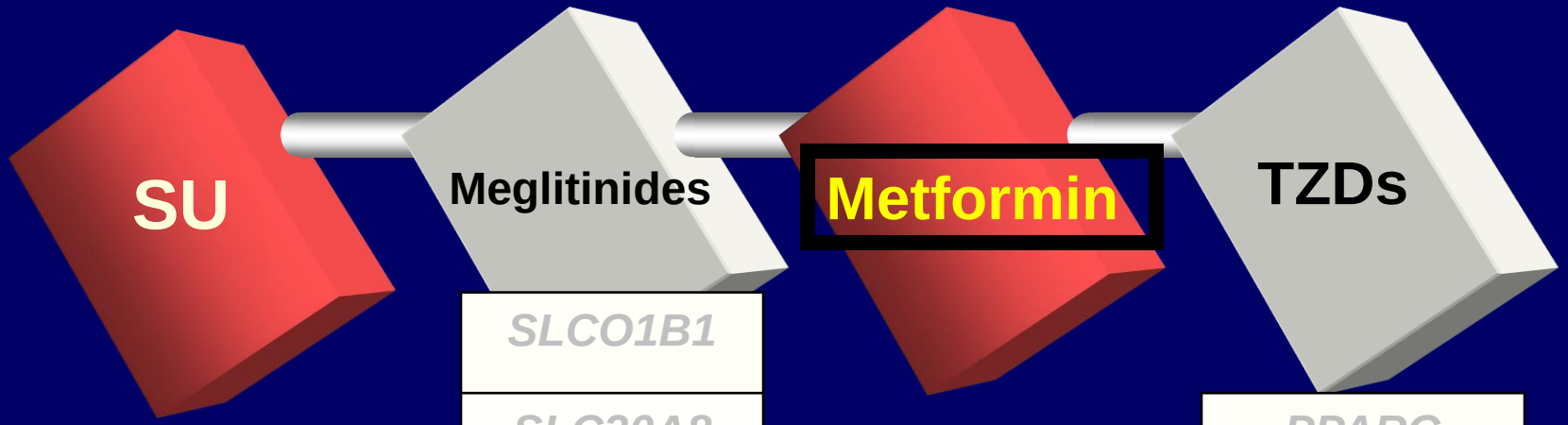
First-line drug used to treat newly diagnosed T2D



Pharmacogenomics of Metformin

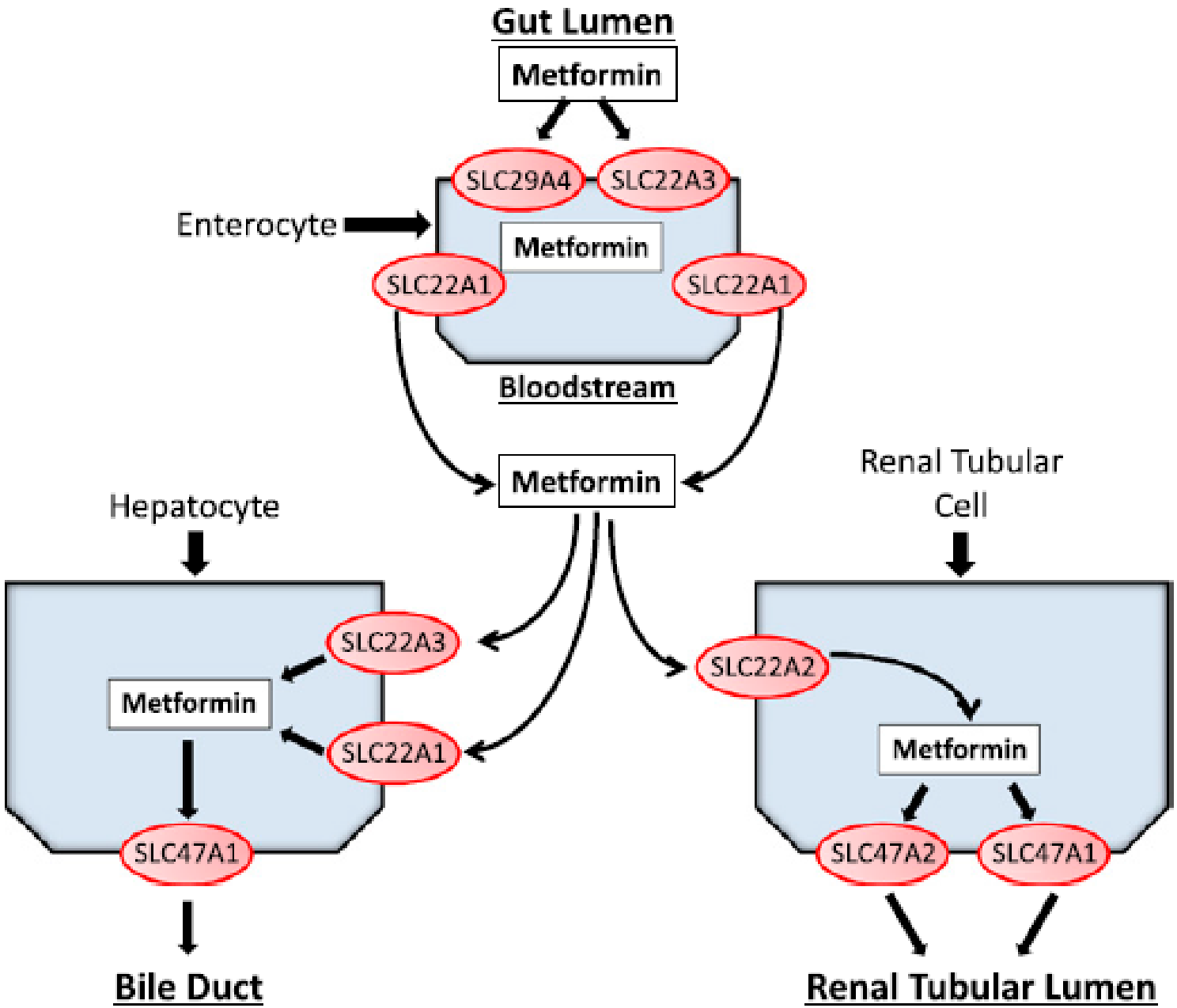
- **The glycemic response to metformin is highly variable.**
- **About 35-40% of patients receiving the drug do not achieve acceptable control of glucose levels.**
- **Associations with glucose-lowering effect of metformin in the at-risk population were found in:**
  - **Drug transporters - *SLC22A1* (OCT1), *SLC47A*1 (*MATE1*)**
  - **Drug target gene - *STK11***

Common genetic variations associated with OAD therapy outcomes



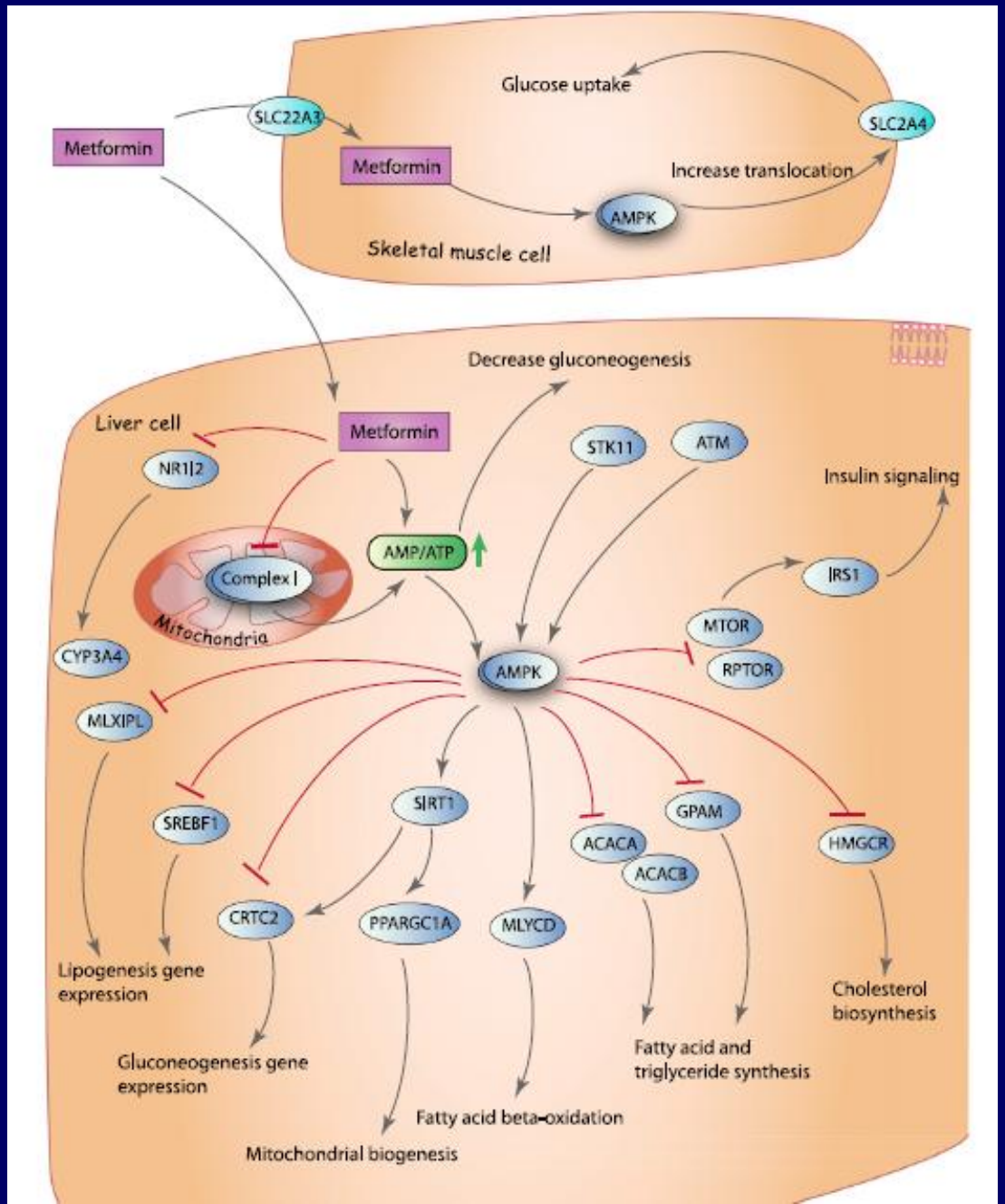
SU	Meglitinides	Metformin	TZDs
KCNJ11	*SLCO1B1*	*SLC22A1*	*PPARG*
ABCC8	*SLC30A8*	*SLC22A2*	*PGC1α*
KCNQ1	*MDR1*	*SLC47A1*	Resistin
TCF7L2	*KCNQ1*	*SLC47A2*	Adiponectin
CYP2C9	*KCNJ11*	*ATM*	Leptin
	TCF7L2		*TNFα*
	NAMPT		*CYP2C8*
	CYP2C9		

Metformin Pharmacokinetic Pharmacogenomics



Diabetes Volume 63, August 2014

Pharmacodynamic effects of metformin



Pharmacogenomics of Metformin

Table 1—List of the known metformin pharmacokinetic genes and select pharmacodynamic genes for which there are associations with a clinical response of metformin

Gene	Note	Summary of effects	References
SLC22A1	OCT1	Decreased function alleles linked to reduction in metformin effect on initial A1C and lipid responses; incidence of diabetes	18, 40, 41, 52–56
SLC22A2	OCT2	No associations with clinical outcomes, only changes in metformin PK reported	
SLC22A3	OCT3	No associations with clinical outcomes, only changes in metformin PK reported	
SLC47A1	MATE1	Increased metformin response to A1C; incidence of diabetes	18, 42, 52
SLC47A2	MATE2	Poorer response to metformin; changes in A1C	42, 43
SRR	Serine racemase	Associated with changes in FPG, PPG, and CHO	57
ATM	Serine/threonine kinase; SNP in large LD block with 6 other genes	Metformin treatment success by A1C	29–31
LKB/STK11	AMPK upstream kinase	Decrease in ovulation in women with polycystic ovarian syndrome on metformin; incidence of diabetes	18, 58
PRKAA1, PRKAA2, PRKAB2	AMPK subunits	Incidence of diabetes	18
ABCC8-KCNJ11	Subunit of β-cell potassium channel	Incidence of diabetes	18

CHO, cholesterol; FPG, fasting plasma glucose; LD, linkage disequilibrium; PK, pharmacokinetics; PPG, postprandial plasma glucose.

Aaron C. Pawlyk,[1] Kathleen M. Giacomini,[2] Catherine McKeon,[1] Alan R. Shuldiner,[3] and Jose C. Florez[4]

Diabetes Volume 63, August 2014

Study:
Pharmacogenomics of Metformin Treatment

- Patients are recruited prior to development of an overt diabetes (prediabetes) and prior to treatment.
- Thus, newly diagnosed diabetic patients are closely monitored for the drug effectiveness and development of adverse outcomes.

Research projects:

Pharmacogenetic factors associated with optimal therapy of Type 2 Diabetes.

Semiz, S. National grant from the Federal Ministry for Education and Science BH, 2012-2013.

Personalized Therapy of Type 2 Diabetes Through European Research Network

Semiz, S. Grant for EU-FP7 project preparation by the Council of Ministers BH, 2013-2014.

Study:
Pharmacogenomics of Metformin Treatment

- Characterize genetic variations of:
  - DT (e.g.,OCT, MATEs)
  - drug targets (e.g., AMPK, ATM)

- associated with T2D treatment outcomes:
  - HbA1c
  - FPG levels
  - Side-effects (GI)

- Explore genotype-phenotype associations.

Current Study Status

- Recruted about **100 T2D patients on metformin treatment** and collected blood samples.
- Large-scale phenotype are being collected, such as:
  - Hb1Ac, FPG, insulin, BP, total and HDL cholest.
  - anthropomorphic measures - BMI, waist circum.
- in following time intervals:
  - prior to therapy with metformin
  - 3, 6 months
  - **12 months**
- Explore genotype-phenotype associations
- Compliance with therapy,...
- Expect to finalize preliminary study by the end of 2014.

CONCLUSIONS

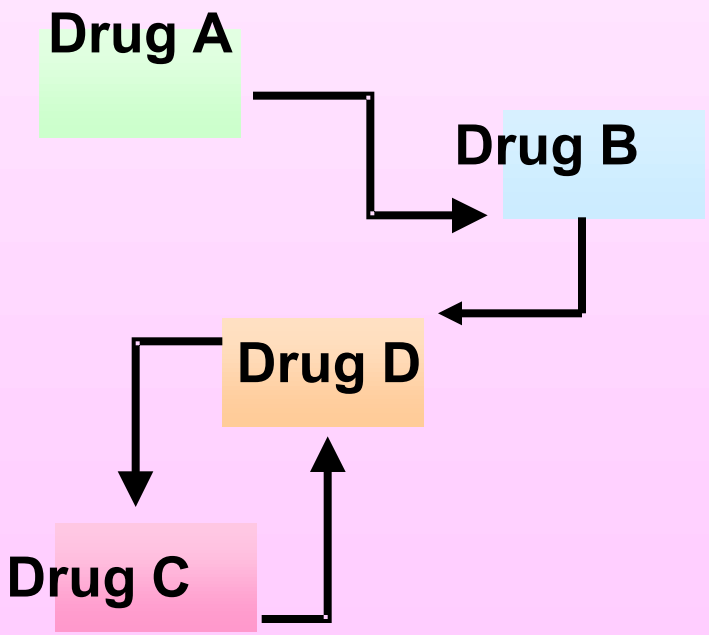
- PGx has the potential to promote safe and cost-effective individualized diabetes treatment.
- PGx studies on diabetes treatment performed to date are small and inadequately replicated, and must be further tested in adequately designed and rigorously conducted clinical trials.
- With recent scientific and technological advances, PGx has a great potential to yield therapeutic advances leading the way towards personalized diabetes care.

Targeted prescription of medicine: applied pharmacogenomics

Today

empirical prescription

"One drug fit all"

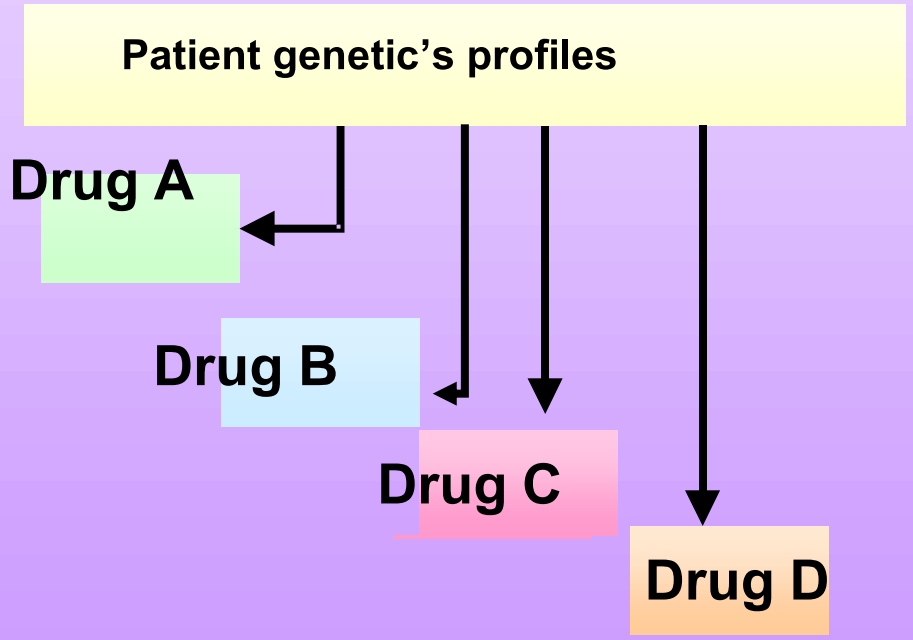


Individual physician experience
Cost: time, money & well-being

Future

Rational prescription

"individualized"



Informed physician diagnosis
Saving : time, money & patient's life

"Here's my sequence..."

The New Yorker

Acknowledgements

University of Sarajevo

Faculty of Pharmacy

- Adlija Čaušević
- Tanja Dujić
- Tamer Bego
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- Grant for EU-FP7 project preparation from the Council of Ministers BH (MCA), 2009; 2010, 2014.
- Erasmus Mundus – Mobility Programmes, 2010, 2014-2015.

University of Sarajevo

June 28, 2014

A CENTURY OF PEACE

after

THE CENTURY OF WARS