

GENOS

Glikani kao supragenomski markeri u personaliziranoj medicini

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University of Zagreb &
Genos Glycoscience Research Laboratory

KING'S College LONDON

WO2014203010; US2016103137; WO2012042020; WO2011015944; WO2009044213

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Efficient patient stratification is the holy grail of precision medicine

Patient population **Treatment**

Standard approach
Treatment A (effective in 20% of target population; 80% is waste)

Tailored approach
Treatment A
Treatment B
Treatment C
Treatment D

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Despite technical success, the Human Genome Project did not fulfill expectations of both general and scientific public

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Genes do not define everything

Only 20% of longevity and 30% of most complex diseases is genetic

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Genetic polymorphisms are very far away from the phenotype

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Glycans are important structural component of nearly all proteins

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2012: US National Academies

- “glycans are directly involved in the pathophysiology of every major disease”
- “additional knowledge from glycoscience will be needed to realize the goals of personalized medicine and to take advantage of the substantial investments in human genome and proteome research and its impact on human health”

Walt et al, National Academies Press, 2012

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Glycan analysis is very complex

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High-throughput glycomics is globally deficient

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NIH office for Strategic Coordination launched The Common Fund programme for glycoscience

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With over 100,000 analysed samples Genos is the global leader in high-throughput glycomics

Cohort	Plasma glycome	IgG Glycome
10001 Dalmatian	2,000	5,000
Orcades	2,000*	3,000
TwinsUK	4,000	4,500
KORA	-	2,000
SABRE	2,000	-
EPIC	3,500	3,500
Global population study	-	2,700
FINNRISK	-	1,200
Estonian biobank	-	1,300
China	1,000	2,000
CRC	2,000	2,000
IBD	3,000	5,700
SLE	-	1,200
Type 1 Diabetes	3,000	1,000
Type 2 Diabetes	3,000	4,000
Down syndrome	-	800
Low back pain	6,000	2,000
PTSD	600	600
Total	33,100	42,500

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Mining the gold from big glycomics datasets

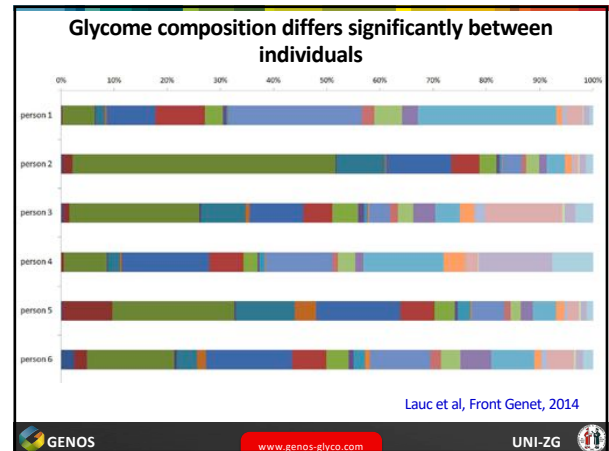
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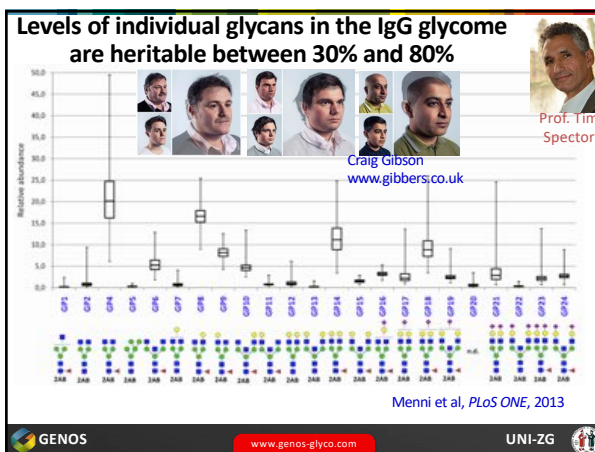
Glycomics is becoming a mainstream science

High-impact papers in 2017- 2019	IF	RANK	High-impact papers in 2017 - 2019	IF	RANK
Suchre et al, Nature Communications 8:14357	12.4	3/64	Krištić et al, Nature Chemical Biology, 14:516.	15.1	5/290
Shen et al, Nature Communications 8:447	12.4	3/64	Šimurina et al, Gastroenterology, 154:1320	20.8	1/80
Benedetti et al, Nature Communications 8:1483	12.4	3/64	Clerc, Gastroenterology, 155:829-843	20.8	1/80
Lauc et al, Nature Communications 9:2916	12.4	3/64	Monaghan, Gastroenterology, published online	20.8	1/80
Birmingham et al, Diabetes Care, 41:79-87	13.4	5/143	Josipović et al, Nucl Acid Res, published online	11.1	14/298
Juszczak et al, Diabetes Care, dc180422	13.4	5/143	Klarić et al, Science Advances, in press	12.8	4/69
Menni et al, Circulation Research, 117.312174	14.0	1/70	Peng et al, Circulation, published online	23.1	1/65

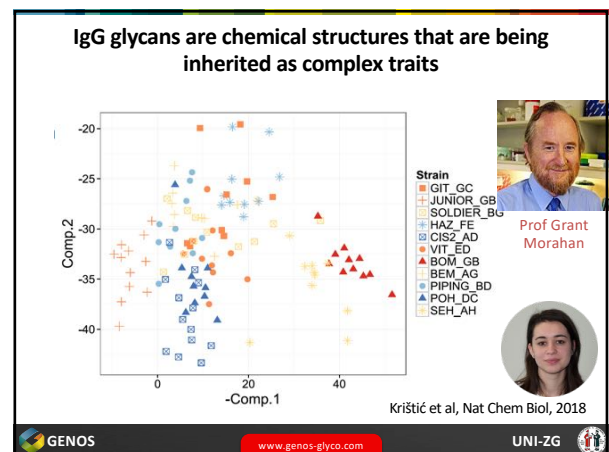
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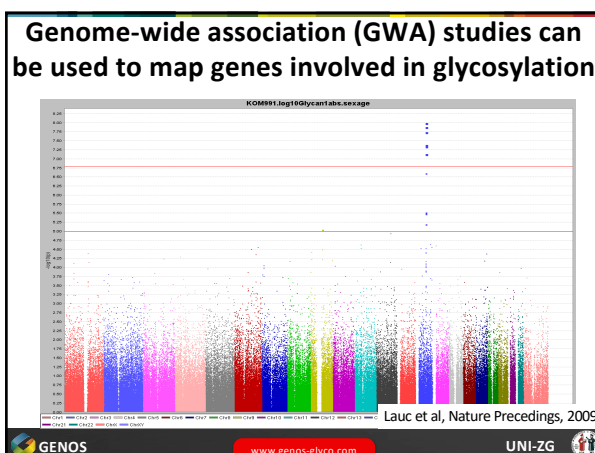
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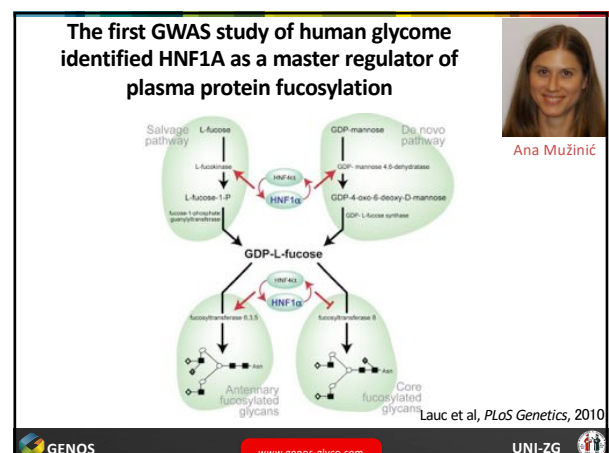
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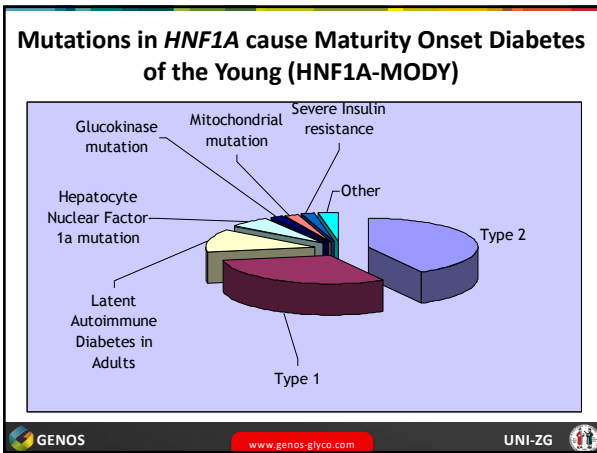
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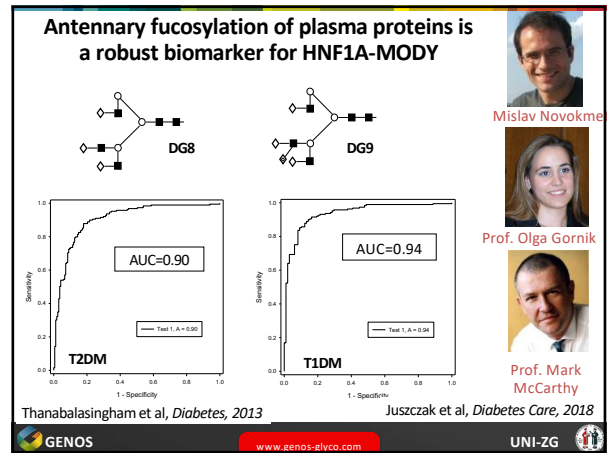
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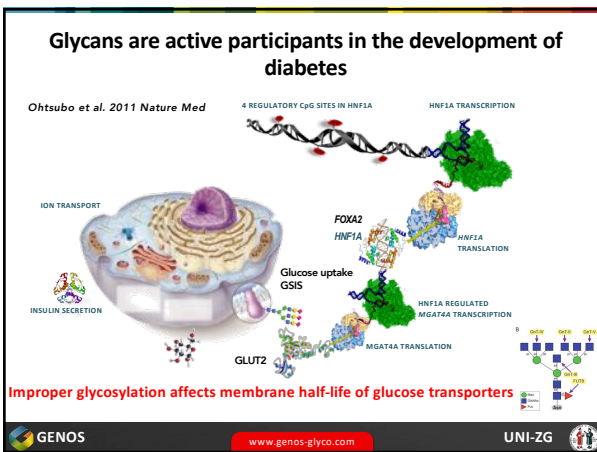
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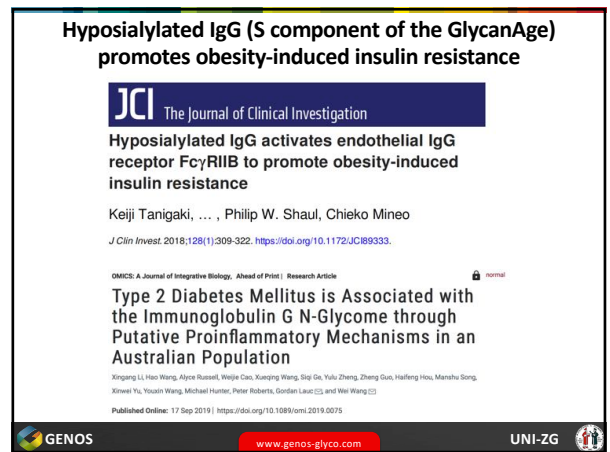
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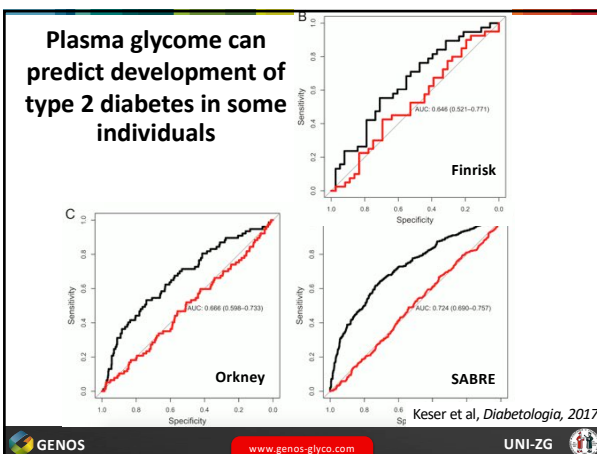
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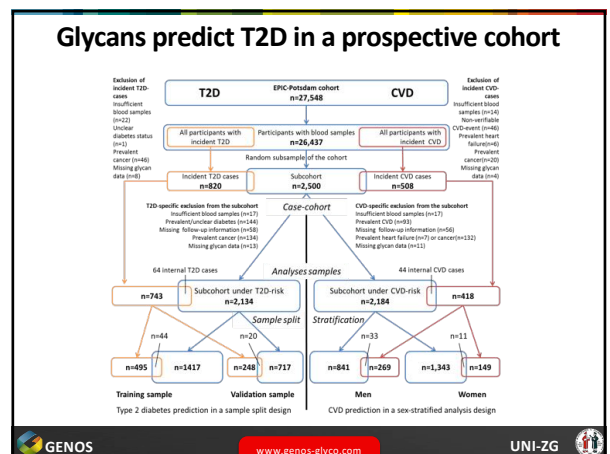
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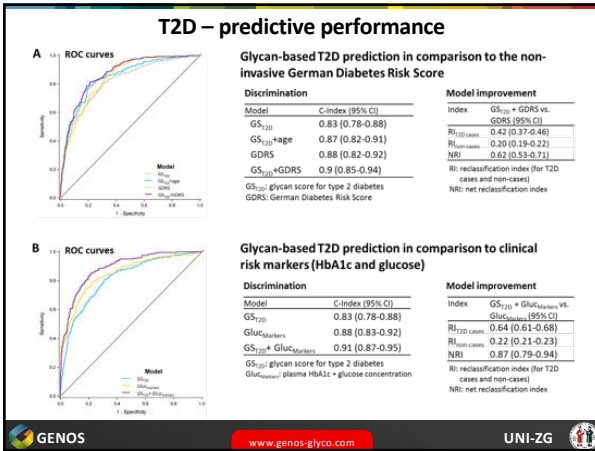
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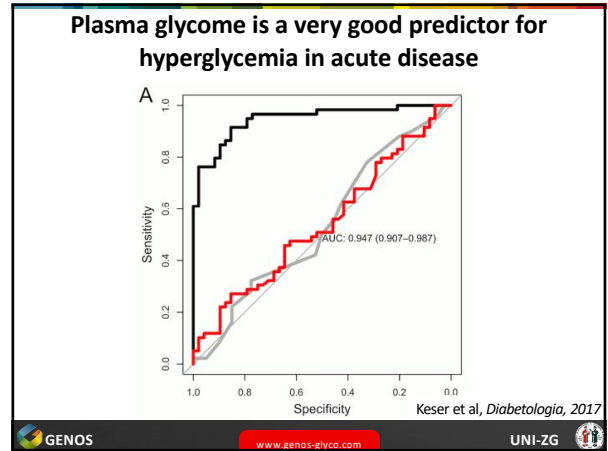
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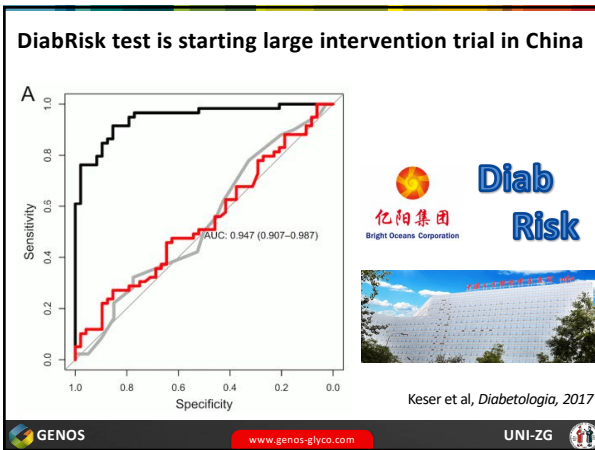
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Glycan biomarkers in prediction of diabetes

- Changes in the glycome (**the DiabRisk® test**) are visible several years before any other symptoms
 - elevated blood glucose of HbA1c
- Apparently only a subgroup of future diabetes patients (~20%) have this risk factor
 - Altered glycans are not only a biomarker, but active effector in disease development
 - We need a new classification of diabetes
- Ongoing clinical trials to see whether this risk is preventable by lifestyle or pharmacological interventions

Keser et al, *Diabetologia*, 2017

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IgG glycosylation is functionally important

Garber K, *Nature Biotechnology*, 2018

Galactose is required for high affinity C1q binding [21]. Removal of galactose either increases or decreases affinity for FcγR, depending on specific FcγR and IgG subtype pairing [22].

*Removal of fucose enhances IgG affinity for FcγRIIIa [24].

Endoglycosidase-S isolated from *Streptococcus pyogenes* cleaves the core GlcNAc residues, leaving all but the reducing GlcNAc (and fucose if present).

*Anti-inflammatory properties (presence of sialic acid decreases binding to FcγRIII/IV, but maintains functional FcγRIII B interaction) [20].

*Exposed GlcNAc residues ("G0") glycoform is seen in rheumatoid arthritis [23].

Legend: Sialic acid (yellow diamond), Galactose (green circle), GlcNAc (pink square), Mannose (blue circle), Fucose (red triangle)

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Regulation of IgG glycosylation is very complex

Dr. Christian Gieger

Annika Wahl

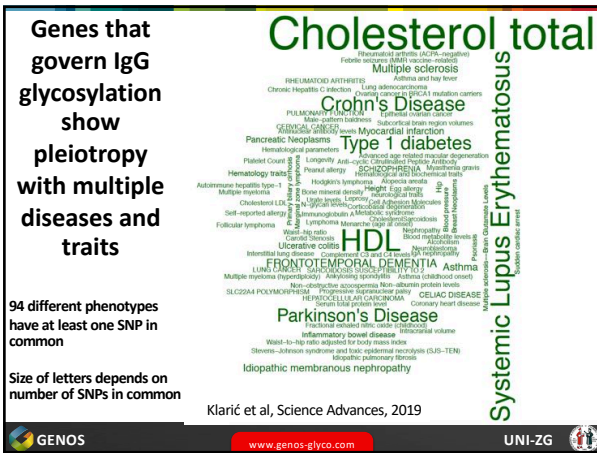
Prof. Yurii Aulchenko

Lucija Klarić

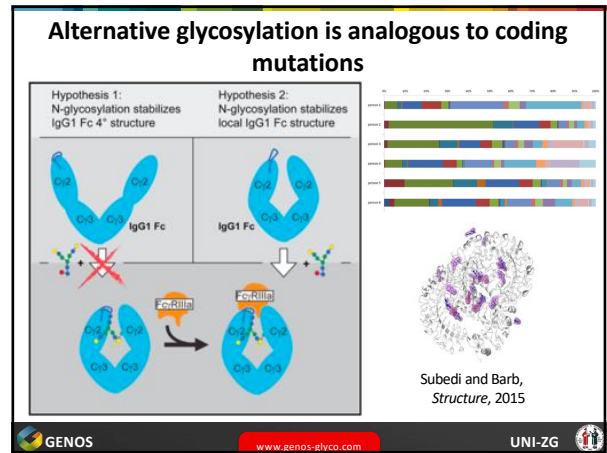
Lauc, *Plos Genet*, 2013
Shen, *Nat Comm*, 2017
Wahl, *Front Immunol*, 2018
Sharapov, *Hum Mol Genet*, 2019
Klarić, *Science Advances*, 2019

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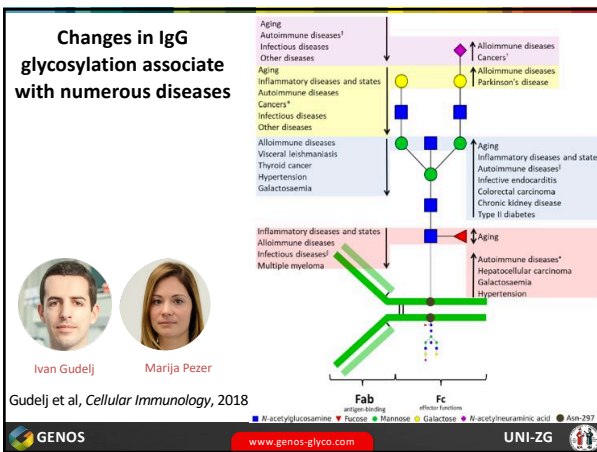
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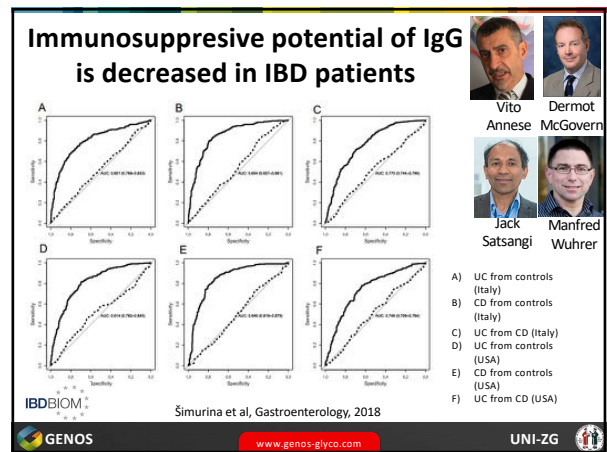
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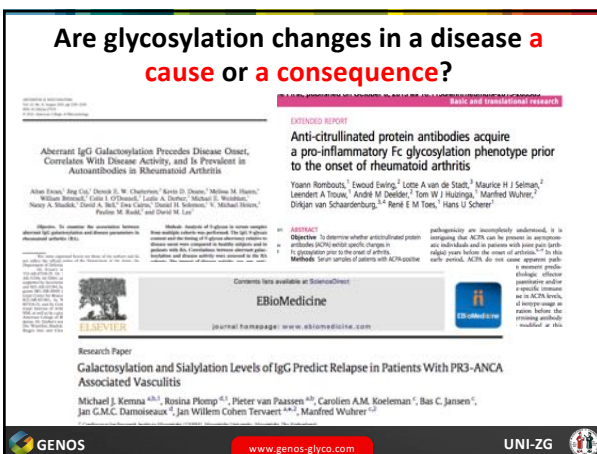
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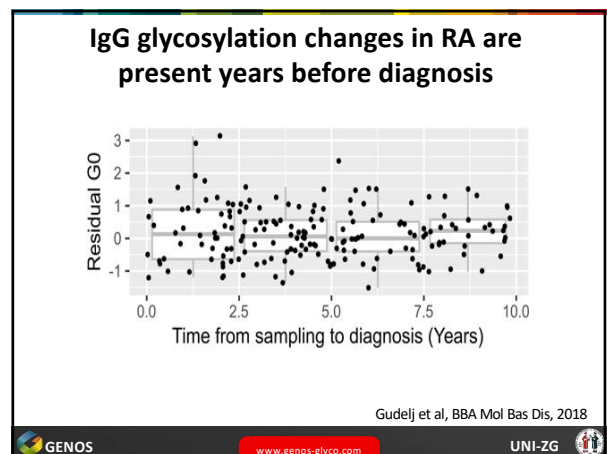
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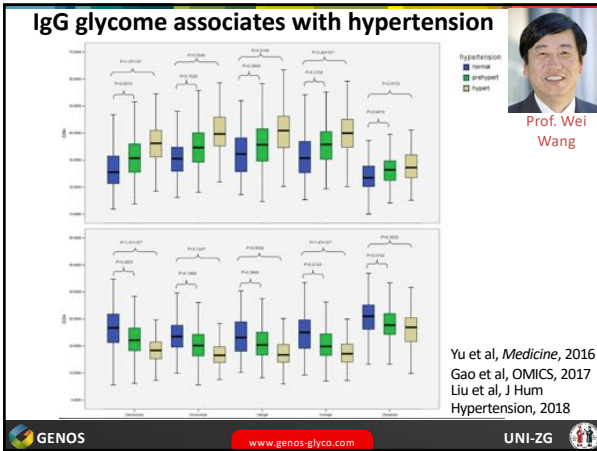
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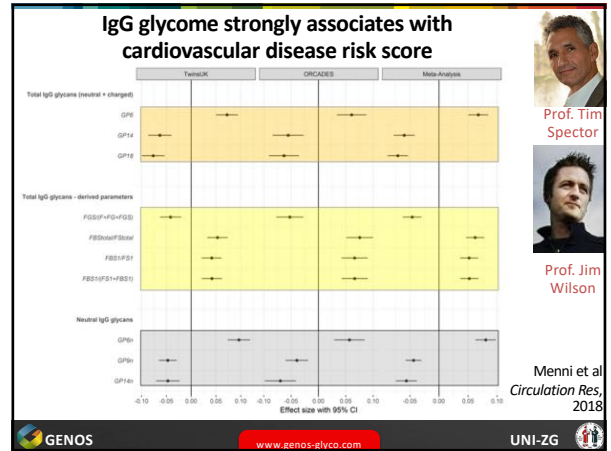
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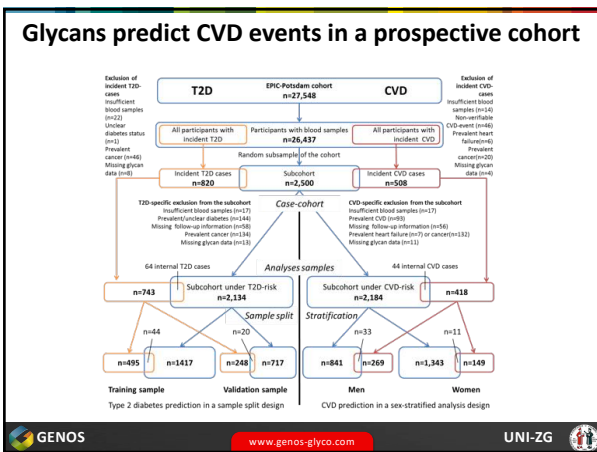
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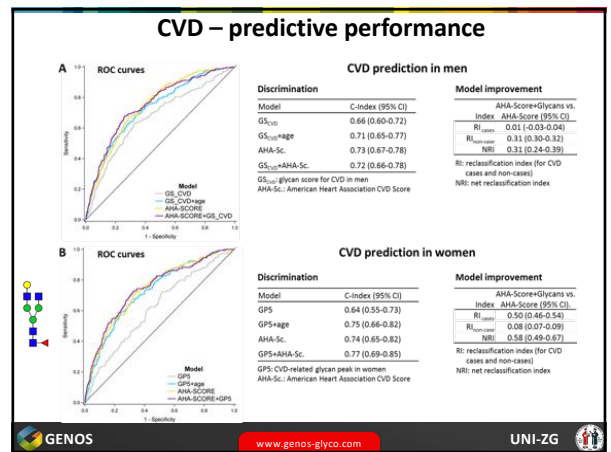
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IgG glycosylation may be a functional effector in the development of hypertension

Obesity and Hypertension

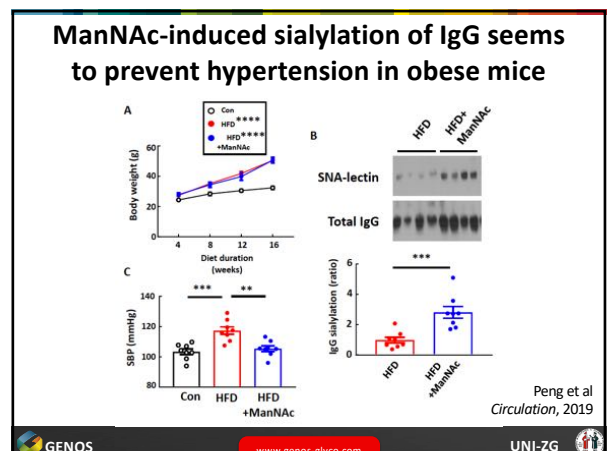
IgG Receptor FcγRIIB Plays a Key Role in Obesity-Induced Hypertension

Nathan C. Sundgren, Wanpen Vongpatanasin, Brigid-Meghan D. Boggan, Keiji Tanigaki, Ivan S. Yuhanna, Ken L. Chambliss, Chieko Mineo, Philip W. Shaul

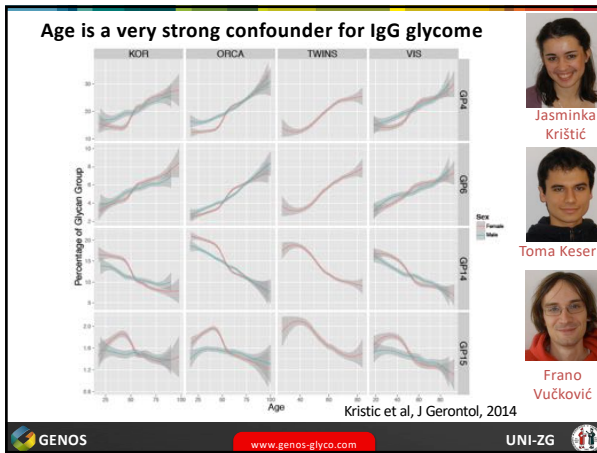
Sundgren et al *Hypertension*, 2015

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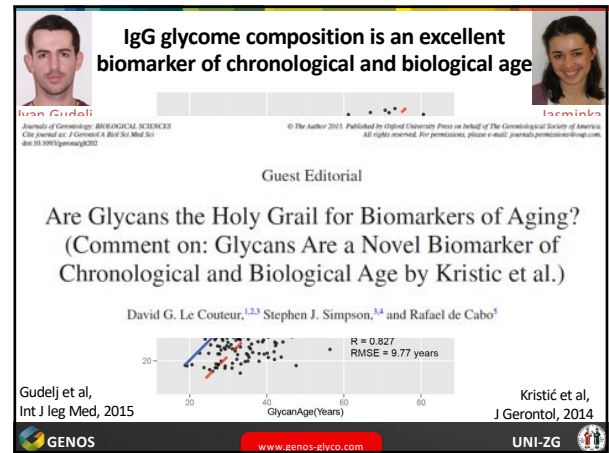
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After correcting for chronological age, glycan age index associates with "unhealthy" life

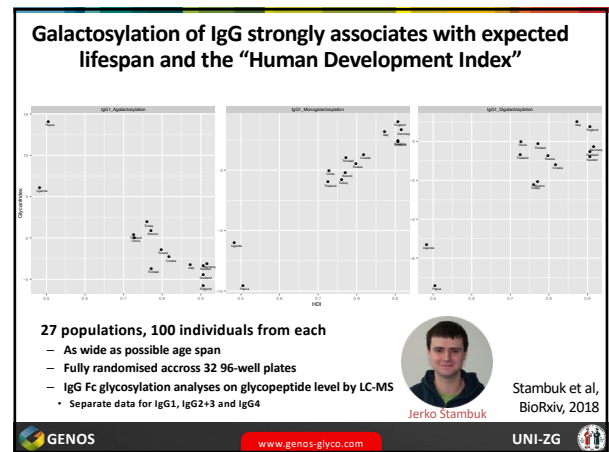
	Orkney		Vis and Korcula	
	Beta	p	Beta	p
Insulin	0.0755	9.22E-08	0.0402	3.50E-01
Fibrinogen	0.0157	1.98E-06	0.0167	8.83E-05
HbA1c	0.1106	2.63E-06	0.0084	3.16E-03
BMI	0.0585	1.67E-04	0.0344	1.04E-02
Triglycerides	0.0092	1.75E-04	0.0140	1.20E-04
Glucose	0.0113	2.09E-04	0.0091	4.77E-02
Waist circumference	0.1468	2.08E-04		
Calcium	0.0010	2.35E-04	0.0002	7.04E-01
D-dimer	2.9670	8.24E-04		
Cholesterol	0.0036	3.07E-01	0.0201	5.51E-08
LDL	0.0031	3.26E-01	0.0146	6.08E-06
Uric acid	1.0773	4.02E-02	0.7620	9.68E-04

Note: HbA1c = glycosylated hemoglobin; BMI = body mass index; LDL = low-density lipoprotein; p = p value; beta = regression coefficient.

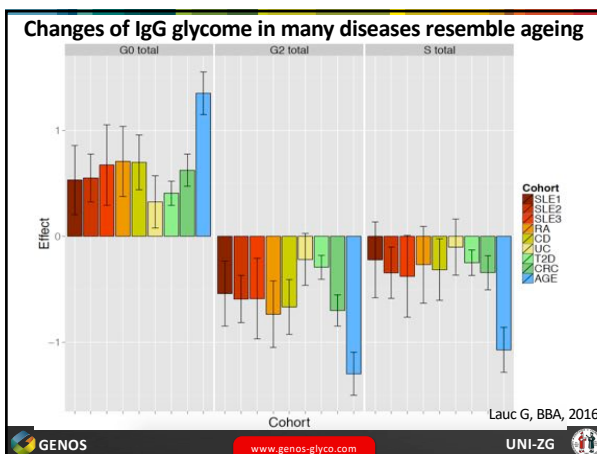
Kristic et al, J Gerontol, 2014

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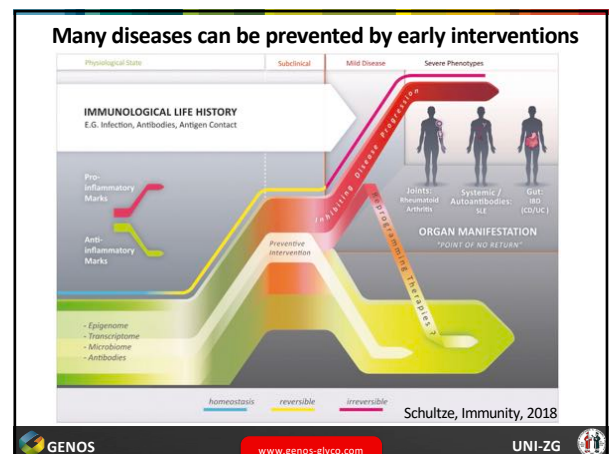
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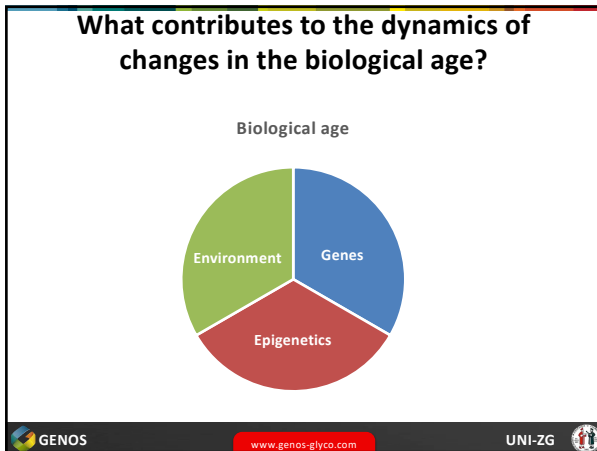
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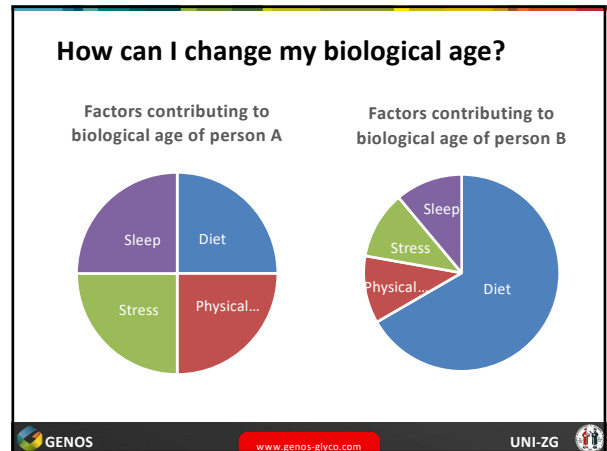
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GlycanAge test is available commercially

GLYCANAGE®

BLOOD COLLECTION CARD

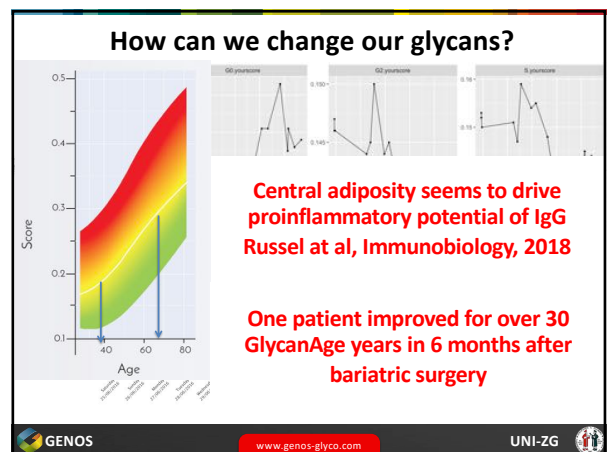
INSTRUCTIONS FOR TESTING

St. Catherine SPECIALTY HOSPITAL

www.glycanage.com

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Lifestyle interventions can change IgG glycome composition even in older adults

Prof. Eline Slagboom

www.impactaging.com AGING, January 2016, Vol. 8 No 1

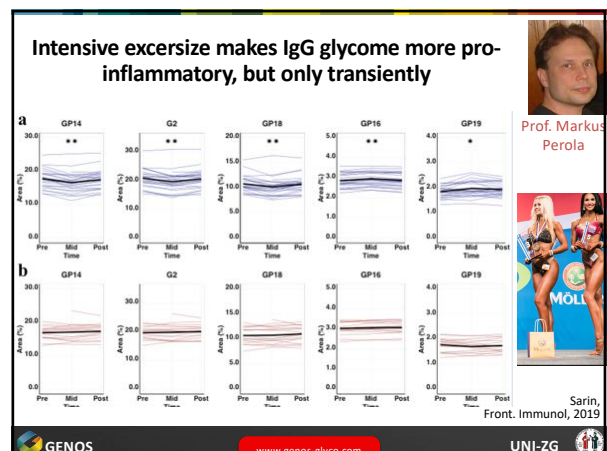
Research Paper

Metabolic effects of a 13-weeks lifestyle intervention in older adults: The Growing Old Together Study

Ondine van de Rest^{1,2}, Bianca A.M. Schutte^{2,4}, Joris Deelen^{2,4}, Stephanie A.M. Stassen³, Erik B. van den Akker^{2,4}, Diana van Heemst¹, Petra Dibbets-Schneider², Regina A. van Dipten-van der Veen¹, Milou Kelderman¹, Thomas Hankemeier⁶, Simon P. Mooijaart³, Jeroen van der Grond⁵, Jeanine J. Houwing-Duistermaat⁷, Marian Beekman², Edith J.M. Feskens¹, and P. Eline Slagboom²

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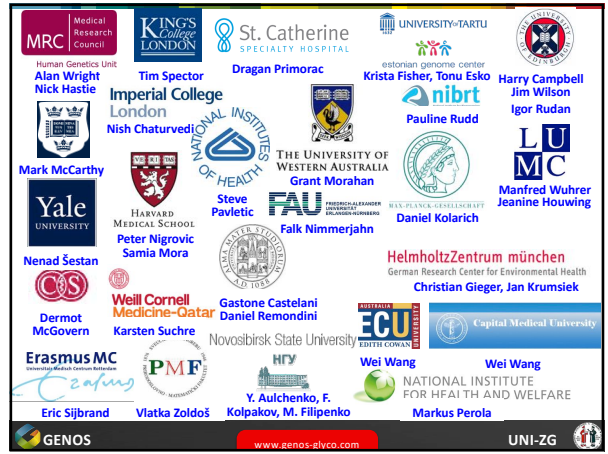
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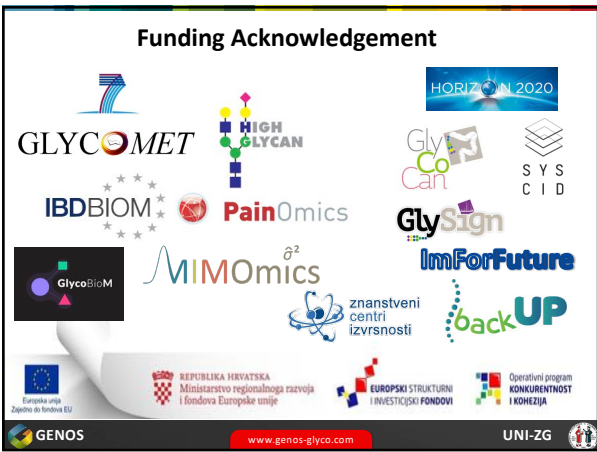
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