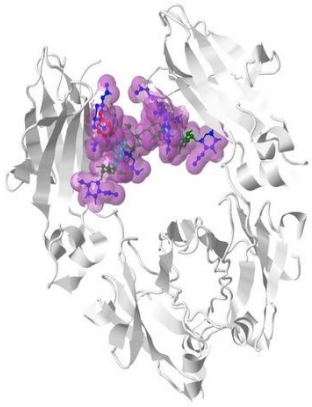
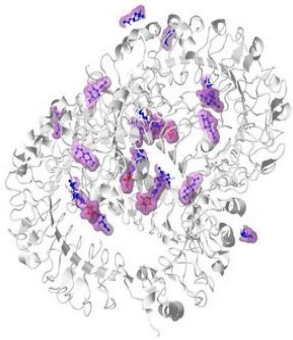
Glikozilacija proteina i personalizirana medicina

Gordan Lauc
University of Zagreb &
Genos Glycoscience Research Laboratory

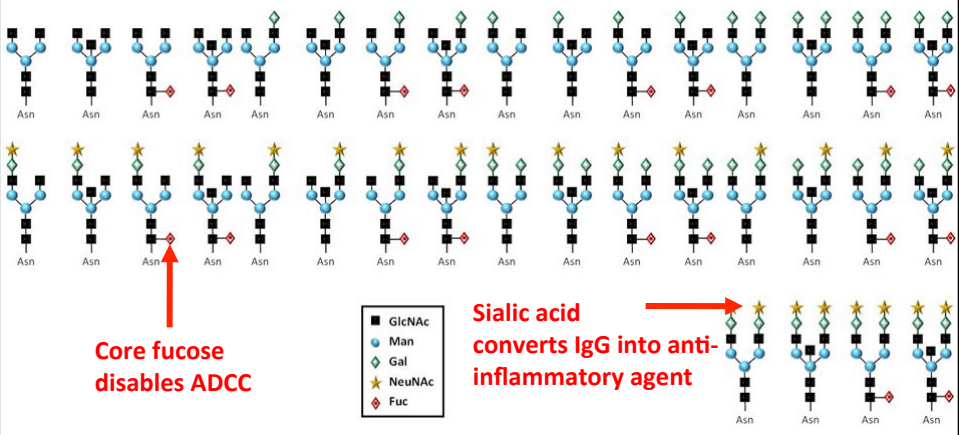
WO2014203010; US2016103137, WO2012042020; WO2011015944; WO2009044213

Glycans are important structural component of nearly all proteins



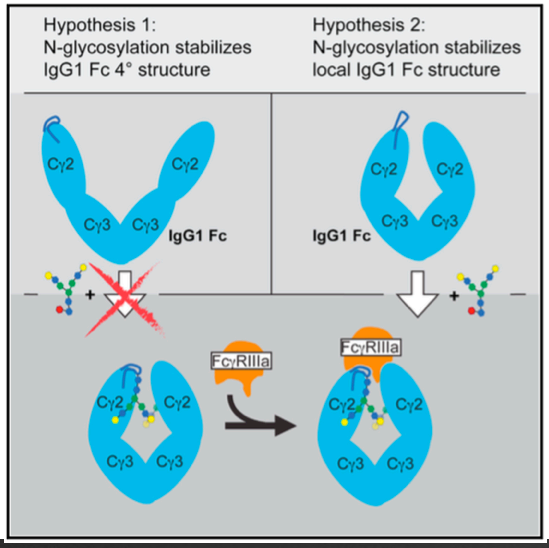


A number of different glycans can be attached to IgG

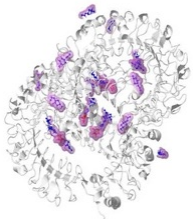


GENOS www.genos-glyco.com

Small local effects of glycans on protein structure can have dramatic physiological efects



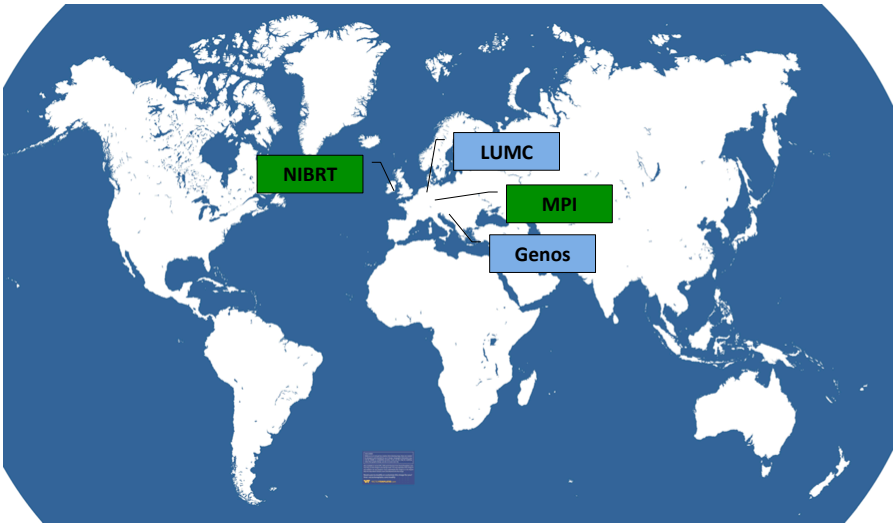
Alternative glycosylation is analogous to coding mutations



Subedi and Barb, *Structure*, 2015

GENOS www.genos-glyco.com

High-throughput glycomics is globally deficient



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Osam od 10 najprodavanijih lijekova u Europi su glikoproteini

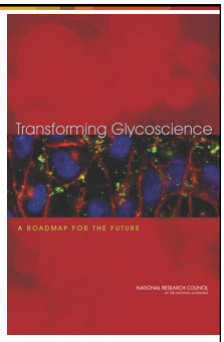
	2008	2009	2010	2012	2013
1	Lipitor (atorvastatin)	Lipitor (atorvastatin)	Seretide (fluticasone/ salmeterol)	Humira (adalimumab)	Humira (adalimumab)
2	Seretide (fluticasone/ salmeterol)	Seretide (fluticasone/ salmeterol)	Lipitor (atorvastatin)	Seretide (fluticasone/ salmeterol)	Seretide (fluticasone/ salmeterol)
3	Plavix (clopidogrel)	Plavix (clopidogrel)	Humira (adalimumab)	Herceptin (trastuzumab)	Enbrel (etanercept)
4	Herceptin (trastuzumab)	Enbrel (etanercept)	Enbrel (etanercept)	Enbrel (etanercept)	Herceptin (trastuzumab)
5	Enbrel (etanercept)	Herceptin (trastuzumab)	Herceptin (trastuzumab)	Lipitor (atorvastatin)	Mabthera (rituximab)
6	Zyprexa (olanzapine)	Humira (adalimumab)	Lovenox (enoxaparin)	Mabthera (rituximab)	Remicade (infliximab)
7	Lovenox (enoxaparin)	Lovenox (enoxaparin)	Mabthera (rituximab)	Lovenox (enoxaparin)	Lovenox (enoxaparin)
8	Glivec (imatinib)	Glivec (imatinib)	Avastin (bevacizumab)	Remicade (infliximab)	Avastin (bevacizumab)
9	Pantozol (pantoprazole)	Zyprexa (olanzapine)	Remicade (infliximab)	Avastin (bevacizumab)	Lucentis (ranibizumab)
10	Symbicort (budesonide/ formoterol)	Mabthera (rituximab)	Glivec (imatinib)	Spiriva (tiotropium)	Lyrica (pregabalin)
Biological					

http://gabionline.net/Reports/Biologicals-dominate-Europe-s-best-sellers

GENOS www.genos-glyco.com

2012: US National Academies

- "glycans are directly involved in the pathophysiology of every major disease"
- "additional knowledge from glycoscience needed to realize the goals of personalize medicine and to take advantage of the substantial investments in human genom proteome research and its impact on hum health"



Walt et al, National Academies Press, 2012

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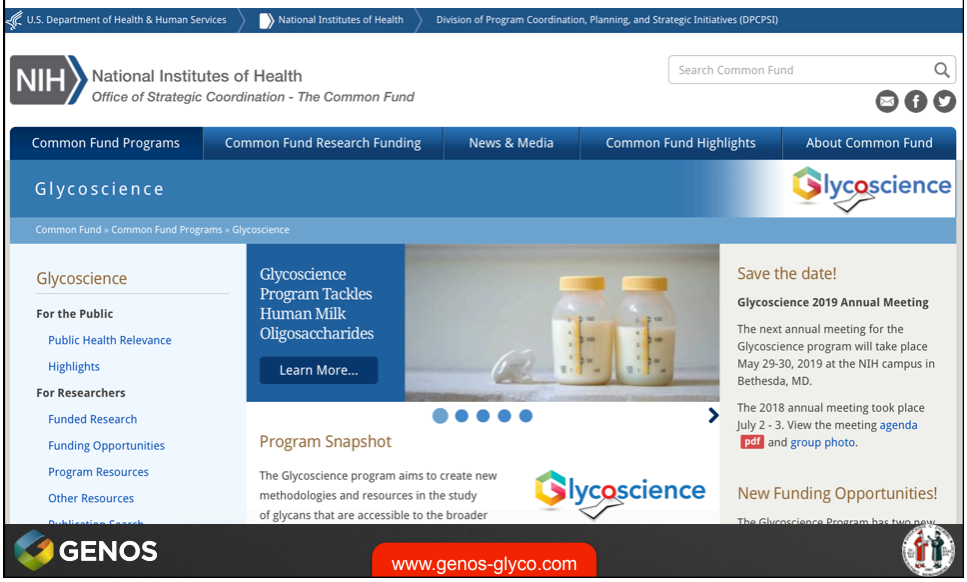
NIH office for Strategic Coordination launched The Common Fund programme for glycoscience



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Genos is global leader in high-throughput glycomics

nature methods

TECHNOLOGY FEATURE

Metabolism: sweeter paths in glycoscience

Vivien Marx

Carbohydrates are tough molecules to study, but glycoscientists are developing and democratizing the needed tools.

Stanford: Carolyn Bertozzi; Harvard: Richard Cummings; Genos: Gordan Lauc

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Genos and our partners already invested over Euro 30 million in glycan analysis and analysed over 70,000 samples

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	800	2000
PTSD	600	600
Total	27,900	42,500

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Main Genos research papers in 2017/2018

Rad	IF	RANK
Suchre et al, Nature Communications 8:14357	12.4	3/64
Shen et al, Nature Communications 8:447	12.4	3/64
Benedetti et al, Nature Communications 8:1483	12.4	3/64
Bermingham et al, Diabetes Care, 41:79-87	13.4	5/143
Šimurina et al, Gastroenterology, 154:1320	20.8	1/80
Krištić et al, Nature Chemical Biology, 14:516.	15.1	5/290
Clerc et al, Gastroenterology, 155:829-843	20.8	1/80
Menni et al, Circulation Research, 117.312174	14.0	1/70
Lauc et al, Nature Communications 9:2916	12.4	3/64

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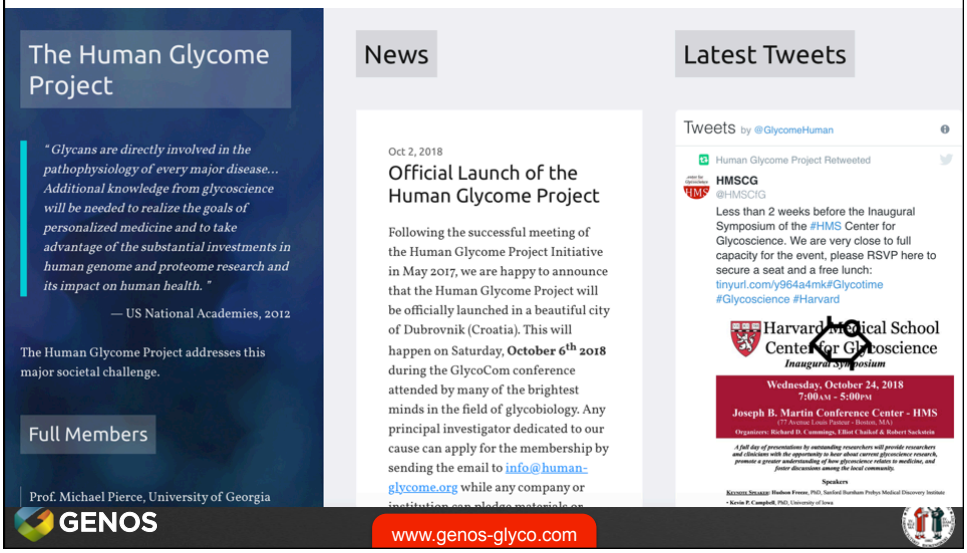
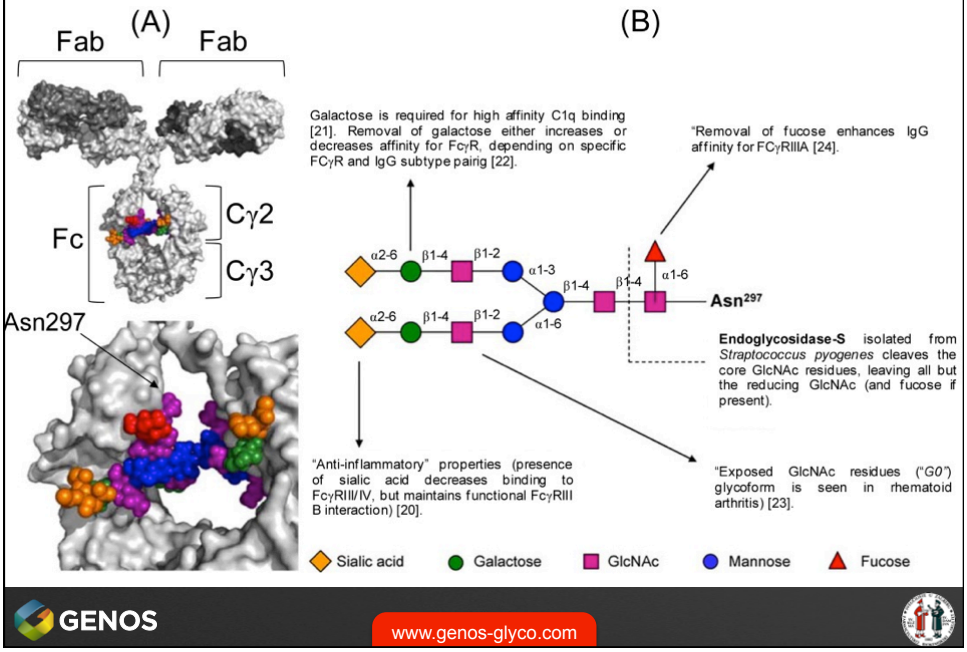
The Human Glycome Project was launched on Oct 6th, 2018 in Dubrovnik

human-glycome.org **glycomehuman**



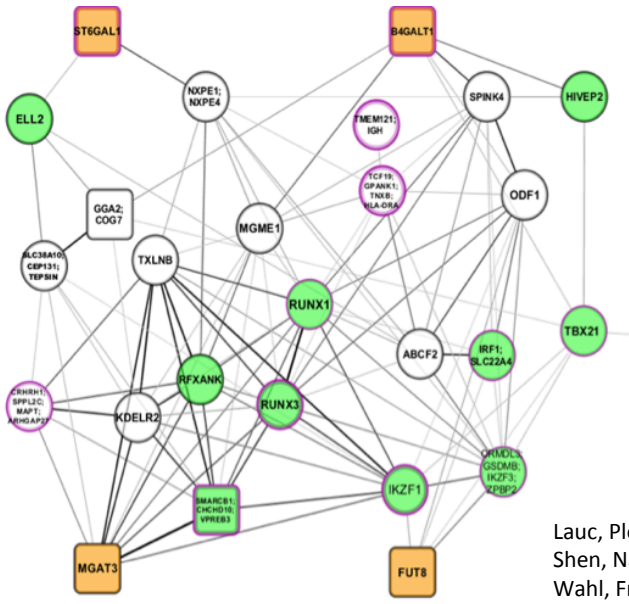
GENOS www.genos-glyco.com

IgG glycosylation is functionally important



GENOS www.genos-glyco.com

Complex genetic regulation of IgG glycosylation



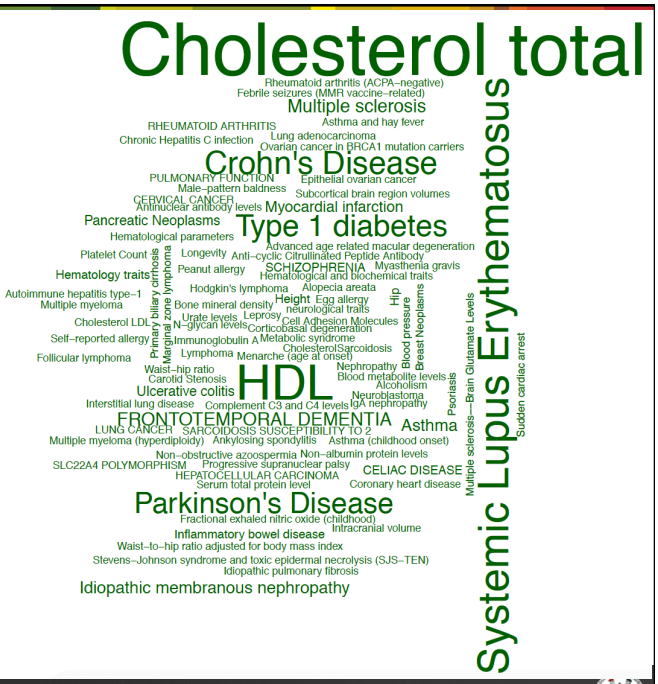
Prof. Yurii Aulchenko

Lucija Klarić

Lauc, Plos Genet, 2013
Shen, Nat Comm, 2017
Wahl, Front Immunol, 2018

GENOS www.genos-glyco.com

Genes that govern IgG glycosylation show pleiotropy with multiple diseases and traits



94 different phenotypes have at least one SNP in common

Size of letters depends on number of SNPs in common

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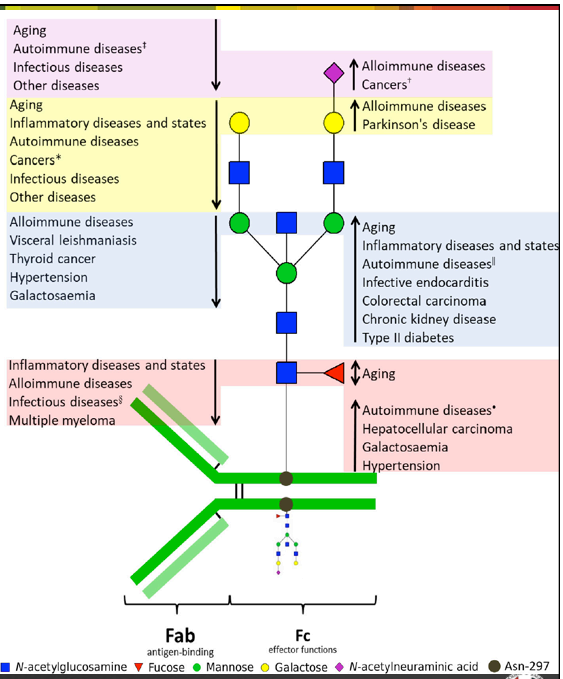
Changes in IgG glycosylation associate with numerous diseases



Ivan Gudelj

Marija Pezer

Gudelj et al, *Cellular Immunology*, 2018

GENOS www.genos-glyco.com

Glycan biomarkers developed in Genos

1. **GlycanAge** – biomarker of biological age
   - Awarded patents in EU, USA and China
   - Sales starting in EU and China
2. **DiabRisk** – predicts risk of type 2 diabetes
   - PCT patent application favourably evaluated
   - Entering national phases
3. **CardioRisk** – Predicts CVD risk
   - Patent application in preparation

GlycanAge – the best biomarker of biological age

IgG glycome composition is an excellent biomarker of chronological and biological age

Ivan Gudeli

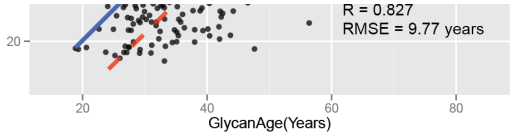
Jasminka

Journals of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
doi:10.1093/gerona/glt202

Guest Editorial

Are Glycans the Holy Grail for Biomarkers of Aging? (Comment on: Glycans Are a Novel Biomarker of Chronological and Biological Age by Kristic et al.)

David G. Le Couteur,[1,2,3] Stephen J. Simpson,[3,4] and Rafael de Cabo[5]



Gudelj et al, Int J leg Med, 2015

Kristić et al, J Gerontol, 2014

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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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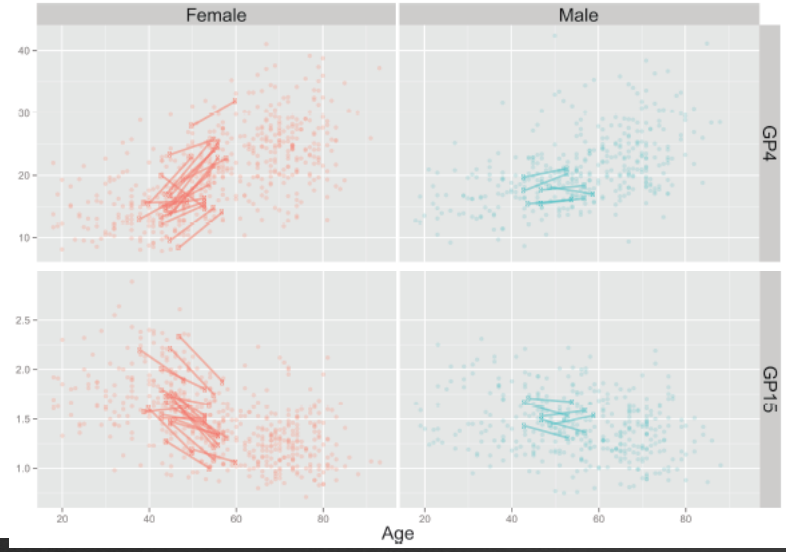
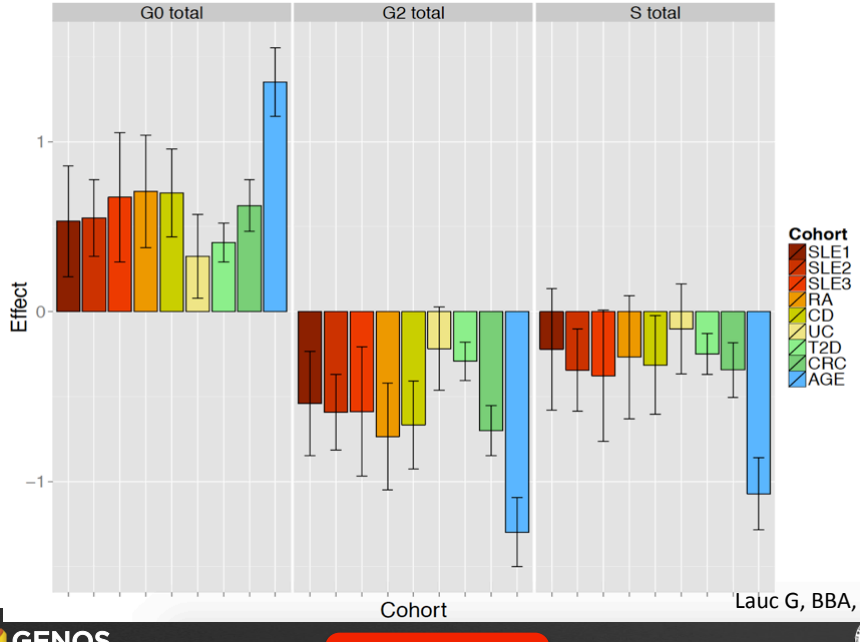
Changes within an individual generally follow trends observed in a population



GENOS www.genos-glyco.com

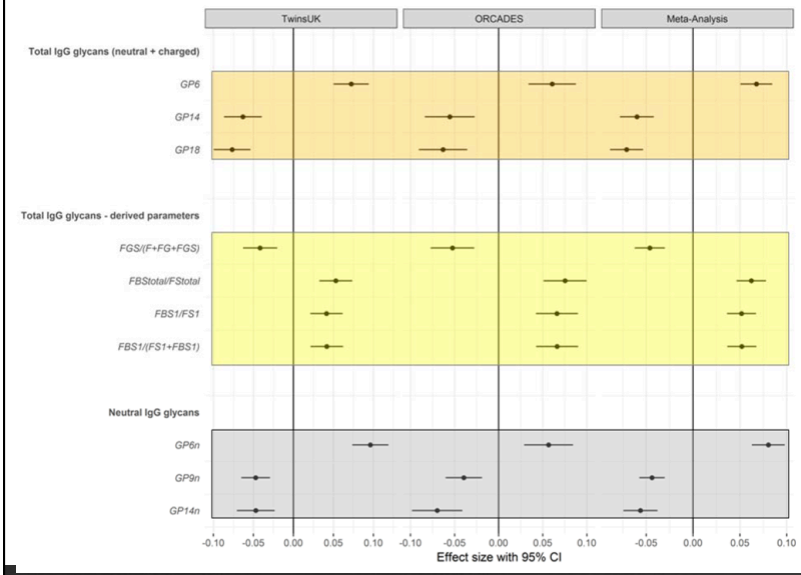
Changes of IgG glycome in many diseases resemble ageing



Lauc G, BBA, 2016

GENOS www.genos-glyco.com

IgG glycome strongly associates with cardiovascular disease risk score



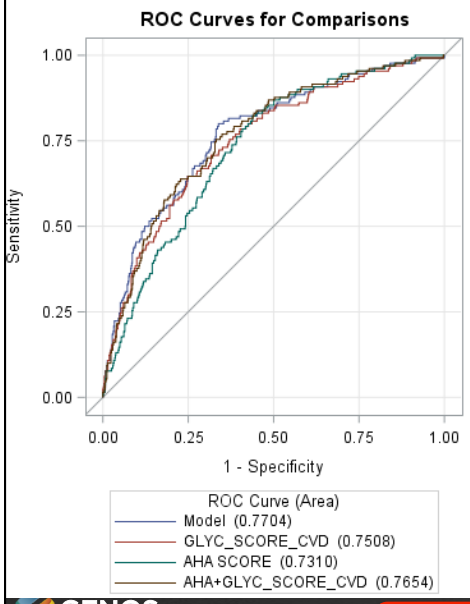
Prof. Tim Spector

Prof. Jim Wilson

Menni et al *Circulation Res*, 2018

GENOS www.genos-glyco.com

CardioRisk can predicts future CVD events



Parameter	C-Index
GlycScore + AHA	0.7 (0.65, 0.75)
GlycScore (+age & sex)	0.7 (0.64, 0.75)
AHA Score	0.68 (0.62, 0.73)

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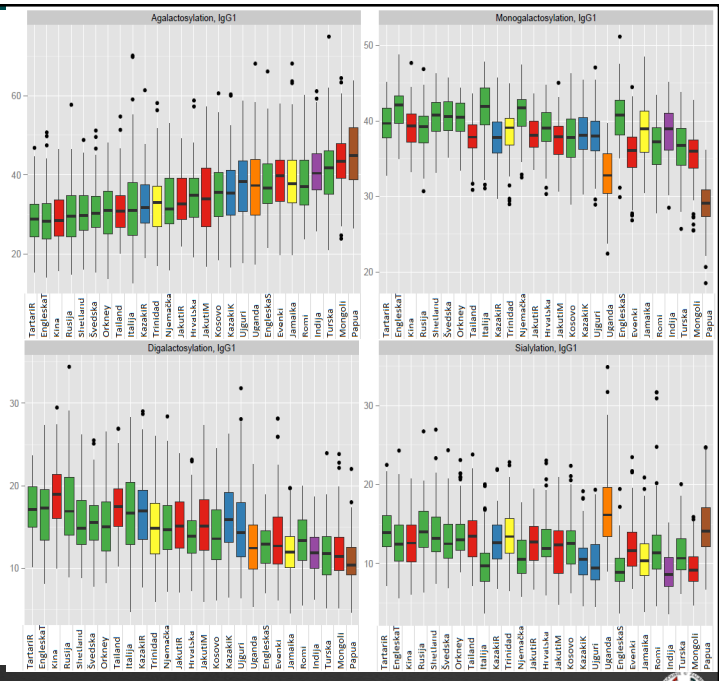
Inter-individual differences dominate over genetic variation in IgG galactosylation

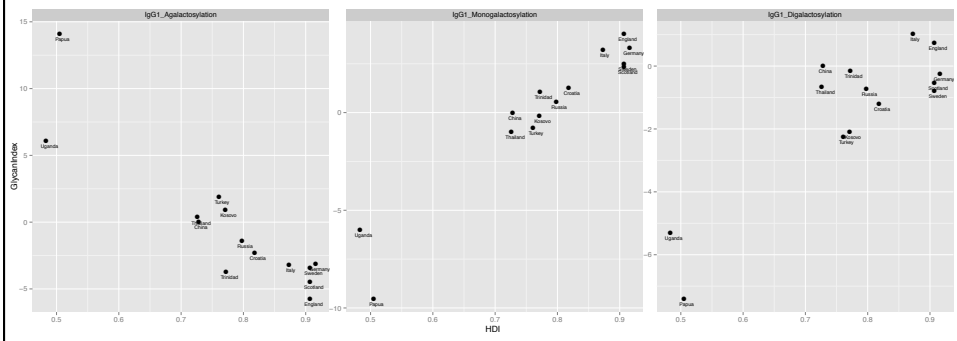


27 populations, 100 individuals from each

- As wide as possible age span
- Fully randomised accross 32 96-well plates
- IgG Fc glycosylation analyses on glycopeptide level by LC-MS
  - Separate data for IgG1, IgG2+3 and IgG4

GENOS www.genos-glyco.com

Galactosylation of IgG strongly associates with expected lifespan and the "Human Development Index"



27 populations, 100 individuals from each

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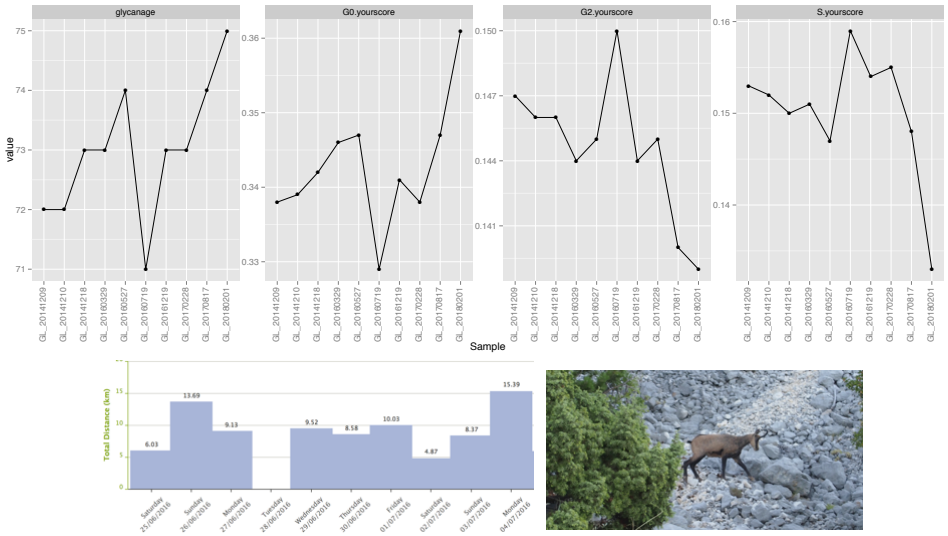
GENOS www.genos-glyco.com

Can we change our GlycanAge?



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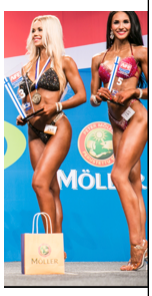
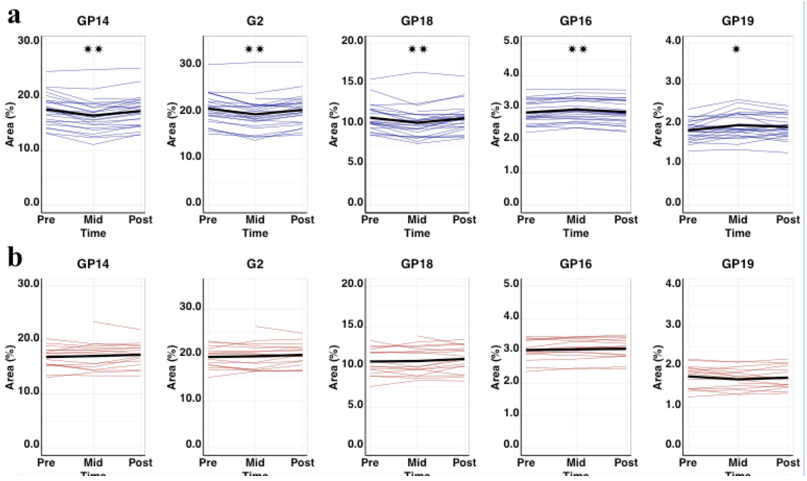
Intensive excersize makes IgG glycome more pro-inflammatory, but only transiently

Prof. Markus Perola





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Lifestyle interventions can change IgG glycome composition even in older adults

Prof. Eline Slagboom

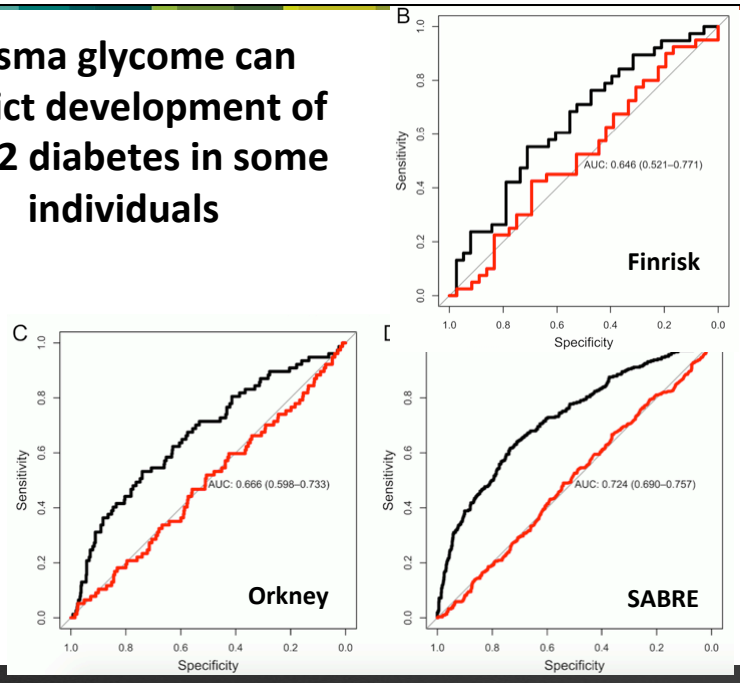
www.impactaging.com AGING, January 2016, Vol. 8 No 1

Research Paper

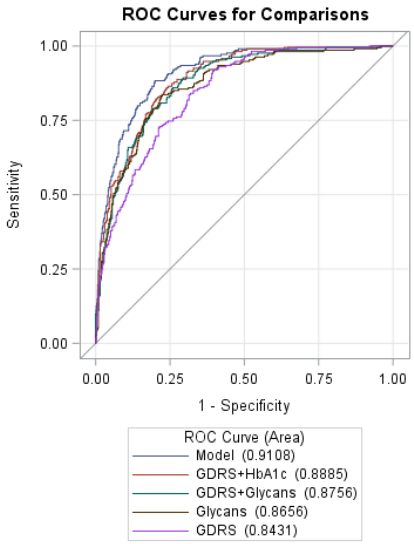
Metabolic effects of a 13-weeks lifestyle intervention in older adults: The Growing Old Together Study

Ondine van de Rest[1,#], Bianca A.M. Schutte[2,#], Joris Deelen[2,#], Stephanie A.M. Stassen[3], Erik B. van den Akker[2,4], Diana van Heemst[3], Petra Dibbets-Schneider[5], Regina. A. van Dipten-van der Veen[1], Milou Kelderman[1], Thomas Hankemeier[6], Simon P. Mooijaart[3], Jeroen van der Grond[5], Jeanine J. Houwing-Duistermaat[7], Marian Beekman[2], Edith J.M. Feskens[1], and P. Eline Slagboom[2]

Plasma glycome can predict development of type 2 diabetes in some individuals



T2D – predictive performance



Parameter	C-Index
GDRS+HbA1c+Glycans	0.84 (0.8, 0.87)
GDRS+Glycans	0.81 (0.77, 0.85)
GDRS+HbA1c	0.83 (0.8, 0.87)
GlycScore (+age)	0.8 (0.76, 0.84)
GDRS	0.79 (0.75, 0.83)

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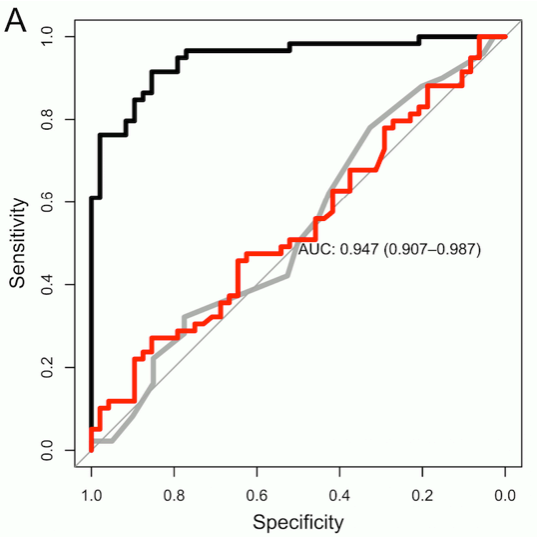
Glycan biomarkes in prediction of diabetes

- Changes in the glycome (the DiabRisk® test) are visible several years before any other symptoms
  - elevated blood glucose of HbA1c
- Only a subgroup of future diabetes patients (10 – 20%) have this risk factor
  - Altered glycans are not only a biomarker, but active effector in disease development
  - We need a new clasification of diseases
- Ongoing clinical trials to see whether this risk is preventable by lifestyle or pharmacological interventions

Keser et al
Diabetologia, 2017

GENOS www.genos-glyco.com

DiabRisk test is starting large clinical trials in China



亿阳集团
Bright Oceans Corporation

DiabRisk

Keser et al, *Diabetologia, 2017*

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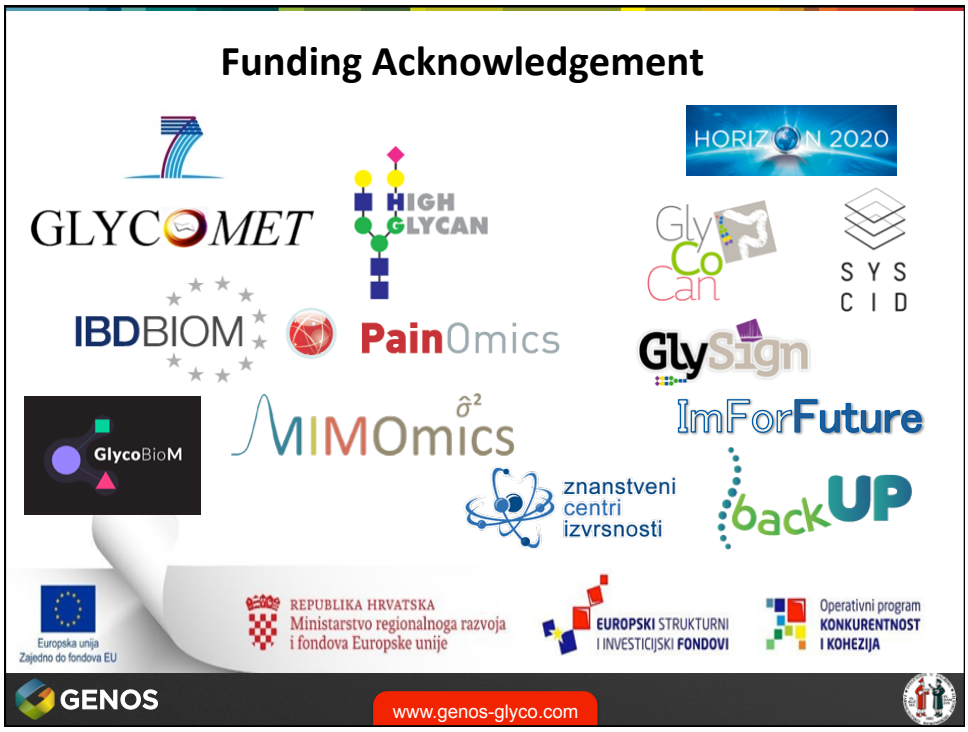
Glyco-group in Zagreb

GENOS www.genos-glyco.com


Funding Acknowledgement
GLYCOMET
HIGH GLYCAN
HORIZON 2020
GlyCoCan
SYSCID
IBDBIOM
PainOmics
GlySign
GlycoBioM
MIMOmics
ImForFuture
znanstveni centri izvrsnosti
backUP
Europska unija
Zajedno do fondova EU
REPUBLIKA HRVATSKA
Ministarstvo regionalnoga razvoja i fondova Europske unije
EUROPSKI STRUKTURNI I INVESTICIJSKI FONDOVI
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