Detecting Metabolic Associated Multi-Morbidities at Scale

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Global MASH 2024

Outline

SomaSignal® Tests

- MASH SomaSignal® Tests – Consistent Performance
- Residual Cardiovascular Risk Test
- Kidney Prognosis Test
- Glucose Tolerance Test

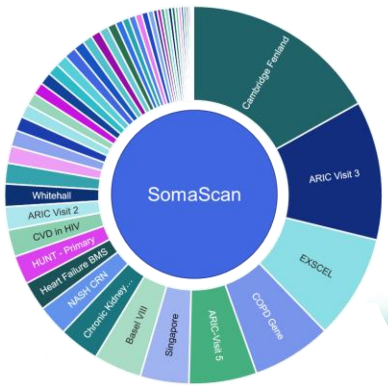
Measuring Multi-Morbidities at Scale

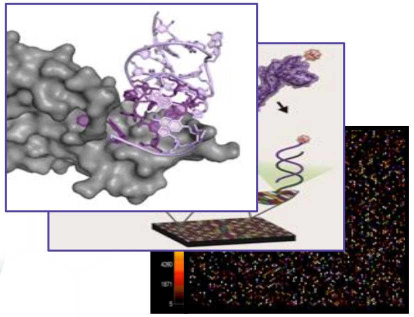
Conclusions

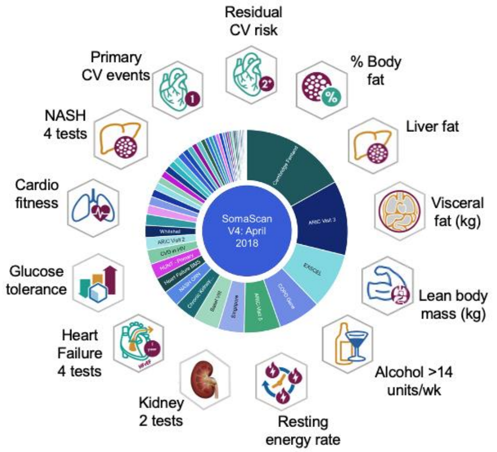
SomaSignal® Tests (SSTs)

SomaSignal® Tests translate protein measurement data into clinical tests

Machine learning relates proteomic measurements to clinical endpoints







Samples + Clinical Data

Clinical truth standards for:

- Future outcomes
- Current State
- Impact of behaviors

Representation of intended use populations

Protein Measurement

SomaScan Assay technology

Currently up to 11,000 measurements

Interpretation & Analysis

Application of machine learning to identify patterns of proteins relating to truth standards

Unique tools and datasets to account for impact of model stability, robustness, interference

SomaSignal Tests (SSTs)

SSTs are predictive models that incorporate data from the SomaScan assay to assess current health and disease risk

SST models are typically in the tens of proteins in size

Adding a new SST can be done in-silico

Research Article
NAFLD and Alcohol-Related Liver Diseases
JOURNAL OF HEPATOLOGY

Defining the serum proteomic signature of hepatic steatosis, inflammation, ballooning and fibrosis in non-alcoholic fatty liver disease

Arun J. Sanyal[1,*], Stephen A. Williams[2], Joel E. Lavine[3], Brent A. Neuschwander-Tetri[4], Leigh Alexander[5], Rachel Ostroff[2], Hannah Biegel[5], Kris V. Kowdley[6], Naga Chalasani[7], Srinivasan Dasarathy[8], Anna Mae Diehl[9], Rohit Loomba[10], Bilal Hameed[11], Cynthia Behling[10], David E. Kleiner[12], Saul J. Karpen[13], Jessica Williams[14], Yi Jia[2], Katherine P. Yates[15], James Tonascia[15]

Journal of Hepatology **2023**. vol. ■ | 1–11

nature medicine
Nat Med. 2019 25: 1851-1857

Plasma protein patterns as comprehensive indicators of health

Stephen A. Williams, Mika Kivimaki, Claudia Langenberg, Aroon D. Hingorani, J. P. Casas, Claude Bouchard, Christian Jonasson, Mark A. Sarzynski, Martin J. Shipley, Leigh Alexander, Jessica Ash, Tim Bauer, Jessica Chadwick, Gargi Datta, Robert Kirk DeLisle, Yolanda Hagar, Michael Hinterberg, Rachel Ostroff, Sophie Weiss, Peter Ganz & Nicholas J. Wareham

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CARDIOVASCULAR DISEASE

A proteomic surrogate for cardiovascular outcomes that is sensitive to multiple mechanisms of change in risk

Williams *et al.*, *Sci. Transl. Med.* **14**, eabj9625 (2022) 6 April 2022

SomaSignal® Tests: Current Validated Portfolio

PROGNOSTIC FOR MAJOR ADVERSE HEALTH OUTCOMES

Primary Cardiovascular Risk – 4 year
What is this patient's risk of having a heart attack, stroke, or heart failure within the next 4 years?

Midlife Dementia Risk
What is this patient's chance of developing dementia in the next 20 years?

Cardiovascular Residual Risk – 4 year
What is this patient's risk of having *a second* heart attack, stroke, or heart failure in the next 4 years?

5-year Dementia Risk For age 65 or older
What is this patient's chance of developing dementia in the next 5 years?

Heart Failure Prognosis HFrEF –12 months
What is this HFrEF patient's heart failure prognosis in the next 12 months?

Heart Failure Prognosis HFpEF –12 months
What is this HFpEF patient's heart failure prognosis in the next 12 months?

Kidney Prognosis
What is the prognosis of this patient's kidney function?

Lung Cancer
What is this patient's risk of developing lung cancer?

55 µl Blood

Unique tests

Tests which predict existing measures; compete on cost, risk, convenience

CURRENT METABOLIC STATE

Glucose Intolerance
In response to simple sugars, does blood glucose spike to unhealthy levels?

Visceral Fat
How much fat is around this patient's organs?

Liver Fat
Does this patient have excess fat in the liver?

Cardiorespiratory Fitness – VO_2 Max
What is this patient's aerobic fitness level?

Body Fat Percentage
What is this patient's body fat percentage?

Lean Body Mass
What is this patient's lean body mass?

Resting Energy Rate
How many calories does this patient burn at rest or when not doing physical activity?

NON-ALCOHOLIC FATTY LIVER DISEASE

NASH Steatosis
Predicting the histological components of liver steatosis

NASH Inflammation
Predicting the histological components of lobular inflammation

NASH Ballooning
Predicting the histological components of hepatocellular ballooning

NASH Fibrosis
Predicting the histological components of liver fibrosis

At-risk NASH
Predicting the presence of NASH and significant fibrosis that is likely to progress

SOCIAL-BEHAVIORAL

Alcohol Impact
Are the effects of weekly alcohol consumption evident?

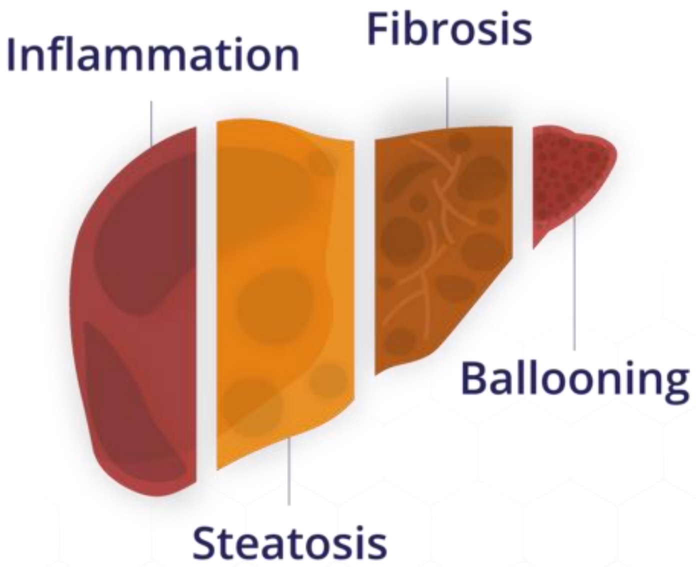
Tobacco Exposure
Has this patient been exposed to tobacco smoke?

STANDARD BIOTOOLS somalogic

MAFLD & MASH Proteomic Model Development

Develop protein-based current state models in serum with biopsy as the truth standard

1. Utilize machine learning to develop binary classification models for each NAS component and fibrosis across the NAFLD/NASH spectrum
2. Assess utility for monitoring longitudinal change during therapy
3. Validate models on external data
4. Relationship with cardiometabolic tests



Binary Decision Thresholds by NAS Score		
Component	**Negative**	**Positive**
Steatosis	0	1, 2, 3
Lobular Inflammation	0, 1	2, 3
Hepatocyte Ballooning	0	1, 2
Fibrosis Stage	0, 1a, 1b, 1c	2, 3, **4**

MASH Component Models

- Protein analytes for each model (in rank order of degree of contribution to the models)
- 35 unique proteins, 2 proteins shared by 2 models
  - adamts-like protein 2
  - prostaglandin reductase 1
- Enrichment for metabolic proteins associated with fatty acid degradation, glucose metabolism, oxidative stress, inflammation and extracellular matrix degradation

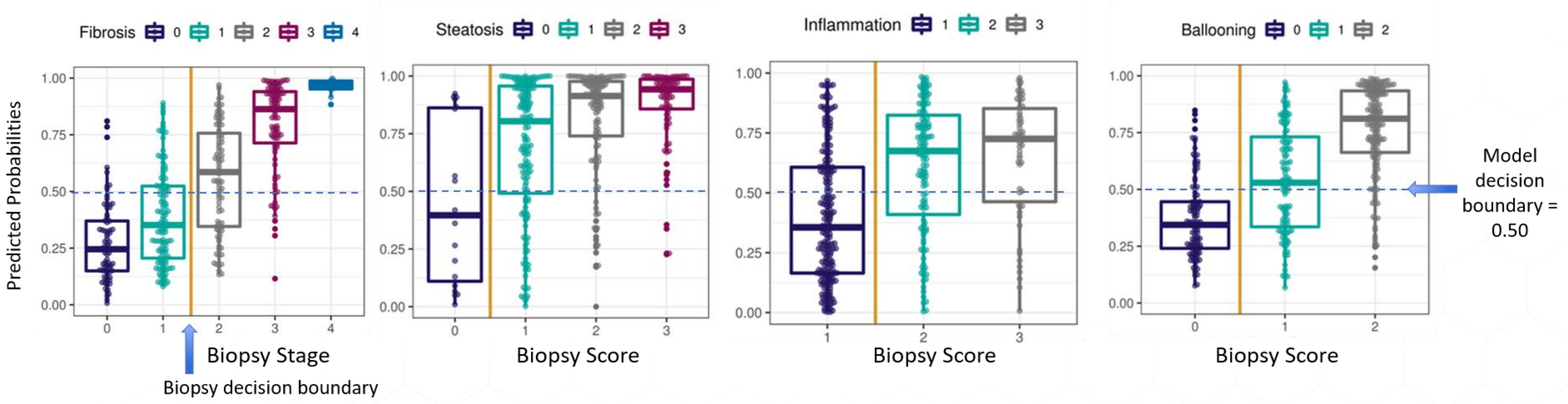
Protein Analytes in Each Model

Fibrosis	Ballooning	Inflammation	Steatosis
adamts-like protein 2	aldo-keto reductase family 1 member b10	aminoacylase-1	insulin-like peptide insl5
complement component c7	prostaglandin reductase 1	dolichyl-diphospho-oligosaccharide protein glycosyltransferase subunit 1	fatty acid-binding protein 12
neurofascin	adamts-like protein 2	uncharacterized protein c1orf198	atp-dependent dna helicase q1
collectin-11	cytotoxic t-lymphocyte protein 4	transcriptional repressor ctcf	beta-glucuronidase
vascular endothelial growth factor receptor	calponin-2	serum amyloid a-2 protein	inhibin beta c chain
protein wnt-5		low affinity immunoglobulin gamma fc region receptor iii-b	beta-hexosaminidase subunit beta
procollagen-lysine; 2-oxoglutarate 5-dioxygenase 3		adiponectin	beta-ala-his dipeptidase
fc receptor-like protein 3		thioredoxin reductase 1	growth hormone variant
		maleylacetoacetate isomerase	prostaglandin reductase 1
		tumor-associated calcium signal transducer 2	bpi fold-containing family b member 1
		peptide yy	glutamate receptor ionotropic; delta-2
		c-c motif chemokine 23	serine/threonine-protein kinase/ endoribonuclease ire1
		procollagen c-endopeptidase enhancer 2	
		low molecular weight phosphotyrosine protein phosphatase	

J Hepatol (2023) Apr;78(4):693-703.

MASH component model predictions vs. Observed biopsy results

Paired Validation Results from NASH CRN Studies



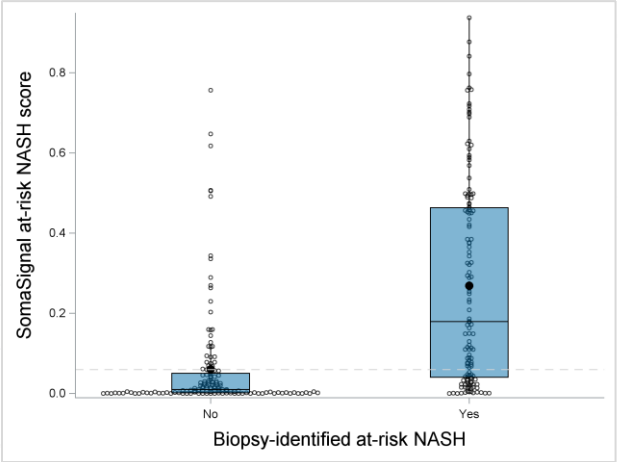
Fibrosis
AUC: 0.85

Steatosis
AUC: 0.79

Lobular Inflammation
AUC: 0.72

Hepatocyte Ballooning
AUC: 0.83

At-risk MASH in LITMUS Metacohort



AUC = 0.85

J Hepatol (2023) Apr;78(4):693-703.

MASH SST consistency, across multiple cohorts and assay version

	n	Assay Version	Steatosis	Inflammation	Ballooning	Fibrosis	Significant Fibrosis	MASH	at-risk NASH	Advanced Fibrosis
CRN/Pivens/Flint validation	392	v4.0 (5k)	0.79	0.72	0.83	0.85	N/A	N/A	0.85	N/A
Litmus Metacohort	264	v4.0 (5k)	N/A	0.70	0.75	0.87	N/A	0.76	**0.81**	0.90

Litmus Metacohort: Diagnostic Accuracy Study: For people with MASH and clinically significant fibrosis, no single or multimarker score significantly reached the predefined AUC 0.80 acceptability threshold.

MASH SomaSignal Test

AUC = 0.81 (0.75-0.86)

	Number of participants with biomarker data	NASH and clinically significant fibrosis*			Advanced fibrosis†		
		Number of participants with target condition	AUC for marker	AUC for FIB-4	Number of participants with target condition	AUC for marker	AUC for FIB-4
CK-18 M30	795	280 (35%)	0·69 (0·65–0·73)	0·70 (0·66–0·73)	224 (28%)	0·70 (0·66–0·74)	0·79 (0·75–0·82)
CK-18 M65	817	281 (34%)	0·70 (0·66–0·74)	0·69 (0·65–0·73)	228 (28%)	0·70 (0·66–0·74)	0·79 (0·75–0·82)
PRO-C3	444	160 (36%)	0·68 (0·63–0·74)	0·73 (0·68–0·78)	126 (28%)	0·75 (0·70–0·80)	0·76 (0·71–0·81)
PRO-C6	229	95 (41%)	0·68 (0·61–0·75)	0·70 (0·63–0·77)	82 (36%)	0·71 (0·63–0·78)	0·73 (0·66–0·80)
PRO-C4	391	155 (40%)	0·63 (0·57–0·68)	0·72 (0·67–0·77)	123 (31%)	0·66 (0·60–0·71)	0·75 (0·70–0·81)
NFS	933	327 (35%)	0·66 (0·62–0·69)	0·69 (0·66–0·73)	265 (28%)	0·75 (0·72–0·79)	0·77 (0·74–0·81)
APRI	966	335 (35%)	0·68 (0·64–0·71)	0·69 (0·66–0·73)	273 (28%)	0·72 (0·68–0·75)	0·77 (0·74–0·81)
ELF	919	306 (33%)	0·67 (0·63–0·71)	0·68 (0·65–0·72)	249 (27%)	0·80 (0·76–0·83)	0·77 (0·74–0·81)
SomaSignal	264	122 (46%)	0·81 (0·75–0·86)	0·66 (0·60–0·73)	95 (36%)	0·90 (0·86–0·94)	0·72 (0·66–0·79)
MACK-3	538	185 (34%)	0·76 (0·71–0·80)	0·69 (0·64–0·73)	131 (24%)	0·74 (0·69–0·79)	0·76 (0·71–0·80)
Cao 2013	635	236 (37%)	0·67 (0·63–0·72)	0·69 (0·65–0·73)	189 (30%)	0·68 (0·64–0·73)	0·79 (0·75–0·83)
ADAPT	444	160 (36%)	0·77 (0·73–0·81)	0·73 (0·68–0·78)	126 (28%)	0·85 (0·81–0·89)	0·76 (0·71–0·81)
FIBC3	440	159 (36%)	0·74 (0·69–0·79)	0·73 (0·68–0·78)	124 (28%)	0·82 (0·78–0·87)	0·76 (0·71–0·81)
ABC3D	440	159 (36%)	0·74 (0·69–0·79)	0·73 (0·68–0·78)	124 (28%)	0·81 (0·76–0·85)	0·76 (0·71–0·81)
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CAP-VCTE	263	125 (48%)	0·61 (0·54–0·67)	0·66 (0·60–0·73)	91 (35%)	0·61 (0·54–0·69)	0·71 (0·65–0·78)

Data are n, n (%), or AUC (95% CI). AUC=area under the receiver operating characteristic curve. FIB-4=Fibrosis-4 index for liver fibrosis. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. *NAFLD Activity Score ≥4 and fibrosis stage ≥2. †Fibrosis stage ≥3.

Table 2: Diagnostic accuracy of single biomarkers and multimarker scores compared with FIB-4 in the same subgroup

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Lancet Gastroenterol Hepatol (2023) Aug;8(8):714-725.

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Litmus Study Cohort	1044	**v4.1 (7k)**	N/A	N/A	N/A	N/A	0.86	0.79	**0.83**	0.92

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LITMUS Study Cohort: N=1044

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Litmus Metacohort: 35% at-risk MASH

MASH SomaSignal Test
NNT = 4

Litmus Study Cohort: 38% at-risk MASH

MASH SomaSignal Test
NNT = 4

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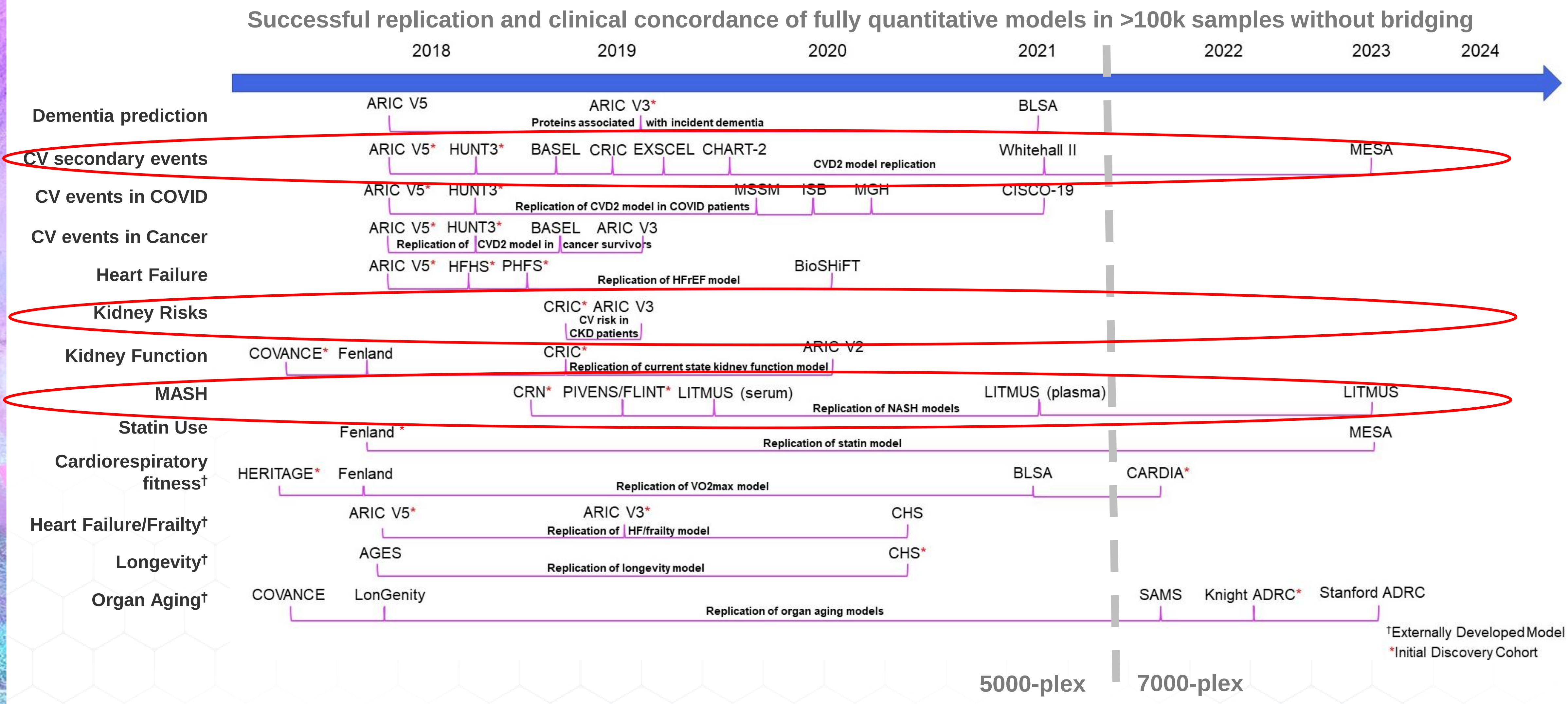
	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Number of marker-positive participants with biopsy per 100 (95% CI)	Number of true positives* per 100 (95% CI)	Number needed to test (95% CI)
SomaSignal	0·06	0·67 (0·59–0·75)	0·82 (0·59–0·75)	35 (30–40)	24 (20–26)	4 (4–5)
ADAPT	6·91	0·47 (0·39–0·55)	0·88 (0·83–0·91)	24 (21–28)	16 (14–19)	6 (5–7)
MACK-3	0·53	0·41 (0·34–0·48)	0·89 (0·85–0·92)	21 (19–25)	14 (12–17)	7 (6–8)
PRO-C3	24·05 ng/mL	0·33 (0·25–0·40)	0·92 (0·88–0·94)	17 (14–20)	11 (9–14)	9 (7–11)
FIBC-3	0·84	0·28 (0·21–0·35)	0·93 (0·89–0·96)	14 (11–18)	10 (7–12)	10 (8–14)
LSM-VCTE	16·4 kPa	0·26 (0·21–0·32)	0·93 (0·90–0·95)	14 (11–16)	9 (7–11)	11 (9–14)
CK-18 M30	573·80 IU/L	0·25 (0·20–0·30)	0·93 (0·91–0·95)	13 (11–15)	9 (7–11)	11 (9–14)
Cao 2013	1·74	0·22 (0·17–0·28)	0·94 (0·92–0·96)	12 (9–14)	8 (6–10)	13 (10–16)
PRO-C6	14·25 ng/mL	0·18 (0·11–0·26)	0·96 (0·91–0·98)	9 (6–13)	6 (4–9)	16 (11–26)
PRO-C4	433·35 ng/mL	0·12 (0·08–0·18)	0·97 (0·94–0·99)	6 (4–9)	4 (3–6)	23 (16–37)
CK-18 M65	1283·55 IU/L	0·12 (0·09–0·16)	0·97 (0·95–0·98)	6 (5–8)	4 (3–6)	24 (17–33)
No marker	..	..	..	100	35	..

95% CIs are based on bootstrapping. Thresholds correspond to a liver-biopsy screen failure rate of 33%, assuming a prevalence of 35% for NASH and clinically significant fibrosis. Markers are ranked according to the number of participants with biopsy-confirmed NASH and clinically significant fibrosis per 100 participants tested with the marker, if liver biopsy is restricted to marker-positive participants only. No acceptable threshold was found for ABC3D, APRI, ELF, NFS, FIB-4, or CAP-VCTE. NASH=non-alcoholic steatohepatitis. *Confirmed by liver biopsy.

Table 3: Thresholds for diagnostic screening used to identify NASH and clinically significant fibrosis

SST consistency, across multiple cohorts and assay versions



STANDARD BIOTOOLS

somalogic

Proteomic surrogate endpoints for early, effective decisions

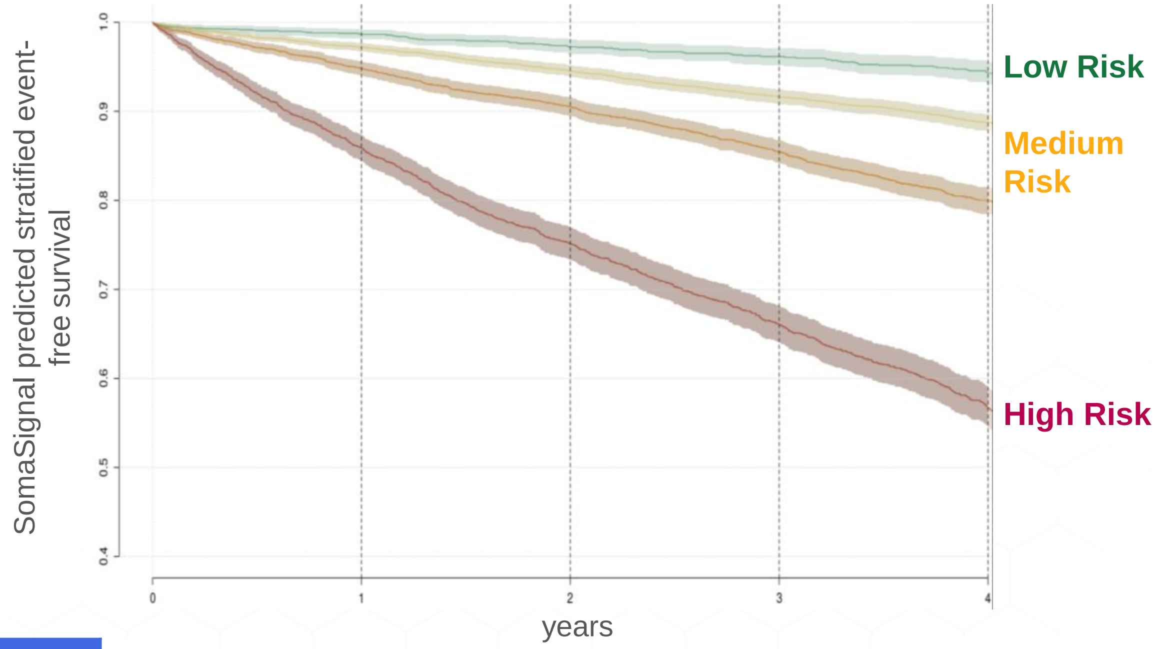
27 proteins

Secondary (Residual) Cardiovascular (CV) Risk Test

27-protein model predicts likelihood of CV event (MI, stroke, HF hospitalization, all-cause death) **within 4 years**

Intended use populations:

- stable CVD
- > age 65 with no prior CVD history
- > age 40 presenting with non-acute symptoms for suspected o-CAD diabetes
- CKD +/- prior CVD history



Training and testing:

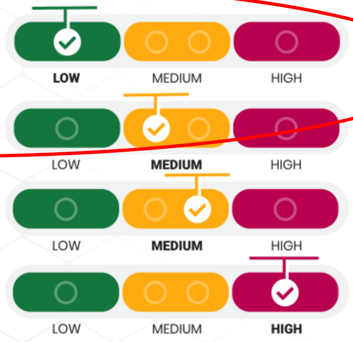
Norwegian cohort **N=744**

C-Index: 0.70 vs 0.56 for modified ASCVD; positive Net Reclassification Index

Test performance with independent replication cohorts

Independent Replication Cohorts			
Cohort	**Cohort size**	**C-Index**	**AUC**
US cohort	992	0.70	0.74
US over age 65	4207	0.70	0.73
Black US population over age 65	800	0.71	0.75
Suspected o-CAD primary	1688	0.79	0.81
Suspected o-CAD secondary	2418	0.71	0.75
Diabetes	2523	0.69	0.71
Chronic kidney disease	3305	0.72	0.78

	Risk % Range	Report View
Low Risk	0.00 to ≤7.50	
Medium Risk	7.51 to ≤25.00	
	25.01 to ≤50.00	
High Risk	50.01 to 100.00	



Williams et. al., *Sci Transl Med* (2022) Apr 6;14(639)

Kidney Prognosis

Predicts the **relative risk** of developing at least one of the following conditions of Progressive Chronic Renal Insufficiency (PCRI) within 4 years.

10 proteins

PCRI here is defined as:

- 50% decline in estimated Glomerular Filtration Rate (eGFR),
- Initiation of kidney dialysis
- Development of eGFR < 15 ml/min/1.73m^2
- Becoming a candidate for kidney transplantation

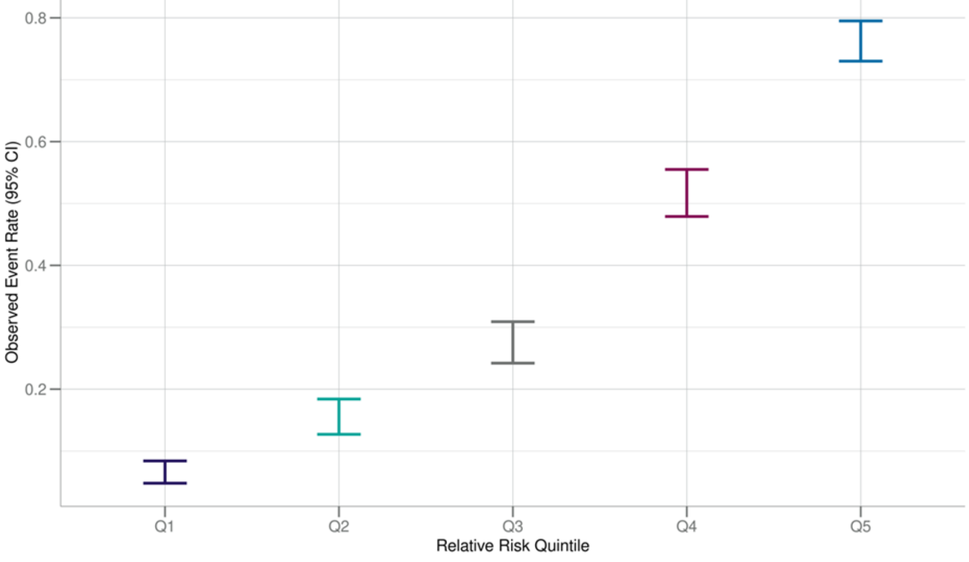
US cohort:
N = 3305 participants with CKD (chronic kidney disease) stages I-V; Reference study population: average age 59.7, PCRI of 27% in 4 years, and eGFR of 43 ml/min/1.73m^2

Test performance with independent replication

Area Under the Curve (AUC) of **0.79**

Compared with Kidney Failure Risk Equation[1] AUC of 0.77

Note: The average group in the study had chronic kidney disease, were aged 59.7 and had an EGFR of 41.4 (Stage 3b). In this group, 27% had a 50% reduction in EGFR or had developed end stage renal disease.



Report View

	PCRI Rate	RR range	Relative % change
1	6.5%	0 -0.36	99.9% - 64.0% reduced risk
2	15.6%	0.37 - 0.70	64.0% - 30.0% reduced risk
3 (average)	27.4%	0.71 - 1.21	30.1% reduced, 21.0% increased risk
4	51.6%	1.22 - 1.95	21.1% - 95.0% increased risk
5	76.2%	1.96 - 3.24	95.1% - 224.0% increased risk

Sample report text:
Your risk of developing end stage kidney disease is 2.5 times the risk than the average person with chronic kidney disease from our study population.

[1] Tangri N, Stevens LA, Griffith J, et al. JAMA 2011;305:1553-1559;

Glucose Tolerance

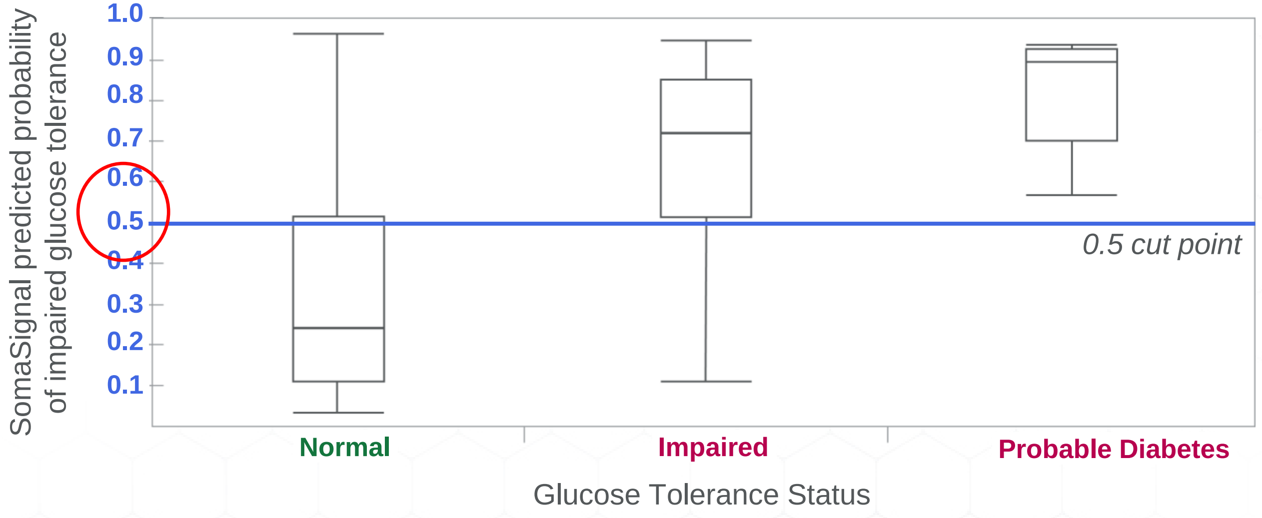
41 proteins

Predicts likelihood of having impaired glucose tolerance evaluated with 2-hour oral glucose tolerance test

UK cohort:
N = 11,747 participants with Oral Glucose Tolerance Test results at 2-hour post glucose challenge

Test performance with independent replication

Area Under the Curve (AUC) of **0.76**
Sensitivity of 0.79
Specificity of 0.73
Accuracy of 0.74



Report View

NORMAL TOLERANCE ✓ | IMPAIRED TOLERANCE

NORMAL TOLERANCE | IMPAIRED TOLERANCE ✓

Glucose Tolerance Status

Normal 2-hr glucose
< 7.8 mmol/L

Impaired 2-hr glucose
≥ 7.8 - 11.1 mmol/L

Probable diabetes 2-hr glucose
≥ 11.1 mmol/L

Williams et. al., *Nat Med* (2019) Dec;25(12):1851-1857; Internal R&D

STANDARD BIOTOOLS somalogic

FDA Biomarker Qualification Program: RCVR DDT submission

- Letter of Intent (LOI) submitted June 6, 2022
- “Reviewable” memo received March 17, 2023
- “Accepted” memo received October 20, 2023
- Qualification Plan submitting Summer 2024
- **Proposed COU**: Prognostic biomarker to predict the four-year risk of cardiovascular outcomes (myocardial infarction (MI), stroke, hospitalization for heart failure (HF), or death). Used for enrichment and stratification in clinical trials, and to monitor the presence of adverse or beneficial change (or lack of change) due to treatment.
- **Intended Use Population**: Participants in clinical trials aged over 40 who have evidence of cardiovascular disease (prior cardiac events or heart failure, peripheral vascular disease, abnormal coronary imaging) or drivers of cardiovascular risk (diabetes, kidney disease).”

FDA Biomarker Qualification Program: MASH DDT submissions

LOI submitted: August 23, 2023

Reviewable: April 5, 2024

- Pharmacodynamic/response biomarker to aid in the monitoring of biological responses related to pharmacological intervention for the treatment of Non-Alcoholic Steatohepatitis. Used to non-invasively inform on changes in each of the histological components of liver biopsy including steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis, and to infer the time course and/or exposure-response of drug benefits in-between pairs of biopsies.

LOI submitted: September 26, 2023

Reviewable: April 5, 2024

- Diagnostic enrichment composite biomarker intended for use to identify patients with at-risk NASH and likely to have liver biopsy histopathologic findings of nonalcoholic steatohepatitis (NASH) and with a nonalcoholic fatty liver disease activity score (NAS) ≥4 and liver fibrosis stages ≥2 (by Brunt/Kleiner scale); and thus appropriate for inclusion in liver biopsy-based NASH drug development clinical trials focused on advanced fibrotic stages of NASH.

Measuring Multi-Morbidities at Scale

MASH, CVD, CKD and T2D: Multi-morbidities

› Curr Hepatol Rep. 2020 Sep;19(3):315-326. doi: 10.1007/s11901-020-00530-0. Epub 2020 Jun 29.

Cardiovascular Disease in Nonalcoholic Steatohepatitis: Screening and Management

Hersh Shroff [1], Lisa B VanWagner [1 2]

Affiliations + expand

PMID: 33585157 PMCID: PMC7879797 DOI: 10.1007/s11901-020-00530-0

Review › Curr Vasc Pharmacol. 2018;16(3):254-268. doi: 10.2174/1570161115666170621081638.

The Co-Existence of NASH and Chronic Kidney Disease Boosts Cardiovascular Risk: Are there any Common Therapeutic Options?

Marianna Papademetriou [1], Vasilios G Athyros [2], Eleni Geladari [3], Michael Doumas [2 4], Costas Tsioufis [5], Vasilios Papademetriou [3]

Review › J Hepatol. 2020 Apr;72(4):785-801. doi: 10.1016/j.jhep.2020.01.013. Epub 2020 Feb 12.

NAFLD as a driver of chronic kidney disease

Christopher D Byrne [1], Giovanni Targher [2]

Affiliations + expand

PMID: 32059982 DOI: 10.1016/j.jhep.2020.01.013

Review › Arterioscler Thromb Vasc Biol. 2022 Jun;42(6):e168-e185. doi: 10.1161/ATV.0000000000000153. Epub 2022 Apr 14.

Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association

P Barton Duell, Francine K Welty, Michael Miller, Alan Chait, Gmerice Hammond, Zahid Ahmad, David E Cohen, Jay D Horton, Gregg S Pressman, Peter P Toth; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease

PMID: 35418240 DOI: 10.1161/ATV.0000000000000153

Review › Ann Hepatol. 2020 Mar-Apr;19(2):134-144. doi: 10.1016/j.aohep.2019.07.013. Epub 2019 Sep 23.

Chronic kidney disease in patients with non-alcoholic fatty liver disease: What the Hepatologist should know?

Stefania Kiapidou [1], Christina Liava [1], Maria Kalogirou [1], Evangelos Akriviadis [1], Emmanouil Sinakos [2]

Review › Nat Rev Nephrol. 2022 Nov;18(11):696-707. doi: 10.1038/s41581-022-00616-6. Epub 2022 Sep 14.

Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease

Kunihiro Matsushita [1 2 3], Shoshana H Ballew [4 5], Angela Yee-Moon Wang [6], Robert Kalyesubula [7 8], Elke Schaeffner [9], Rajiv Agarwal [10]

Affiliations + expand

PMID: 36104509 DOI: 10.1038/s41581-022-00616-6

Review › Curr Diab Rep. 2021 Mar 19;21(5):15. doi: 10.1007/s11892-021-01383-7.

The Relationship Between Type 2 Diabetes, NAFLD, and Cardiovascular Risk

Cyrielle Caussy [1], Adrien Aubin [2], Rohit Loomba [3 4 5]

Affiliations + expand

PMID: 33742318 PMCID: PMC8805985 DOI: 10.1007/s11892-021-01383-7

Review › J Hepatol. 2018 Feb;68(2):335-352. doi: 10.1016/j.jhep.2017.09.021. Epub 2017 Nov 6.

Hypertension, diabetes, atherosclerosis and NASH: Cause or consequence?

Amedeo Lonardo [1], Fabio Nascimbeni [1], Alessandro Mantovani [2], Giovanni Targher [3]

Affiliations + expand

PMID: 29122390 DOI: 10.1016/j.jhep.2017.09.021

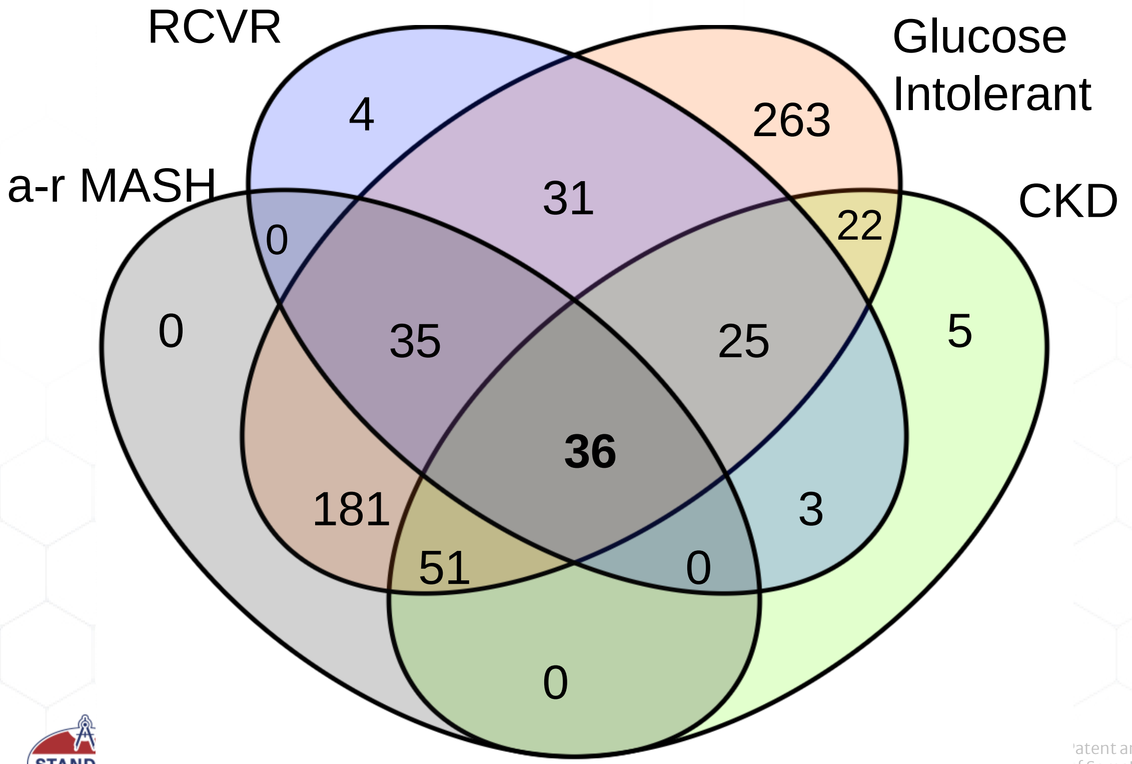
Assessing multi-morbidity in metabolic associated diseases

- SSTs can be used to assess at-risk MASH, cardiovascular disease risk, progressive chronic renal insufficiency risk and glucose tolerance (T2D) in observational cohorts and therapeutic trial populations
  - Results from a blood sample can provide a comprehensive understanding of metabolic associated disease risk, in addition to current metabolic parameters
  - Results from proteomic risk and current state evaluations are responsive to change and can be used to provide a more holistic evaluation of therapeutic response
- Overlap is assessed for these 4 categories
  - At-risk MASH
  - Cardiovascular risk
  - Kidney prognosis
  - Glucose Tolerance (T2D)
- Broad cardiometabolic health assessments enabled by suite of SSTs

Multi-morbidity in a MAFLD/MASH Population

Litmus Study

Number of individuals with SST Results (n=760)			
at-risk MASH	**RCVR**	**Glucose Tolerance**	**CKD Prognosis**
Not at-risk = 457 At-risk = 303	Low RCVR = 626 High RCVR = 134	GT = 116 GIT = 644	Low CKD = 618 High CKD = 142

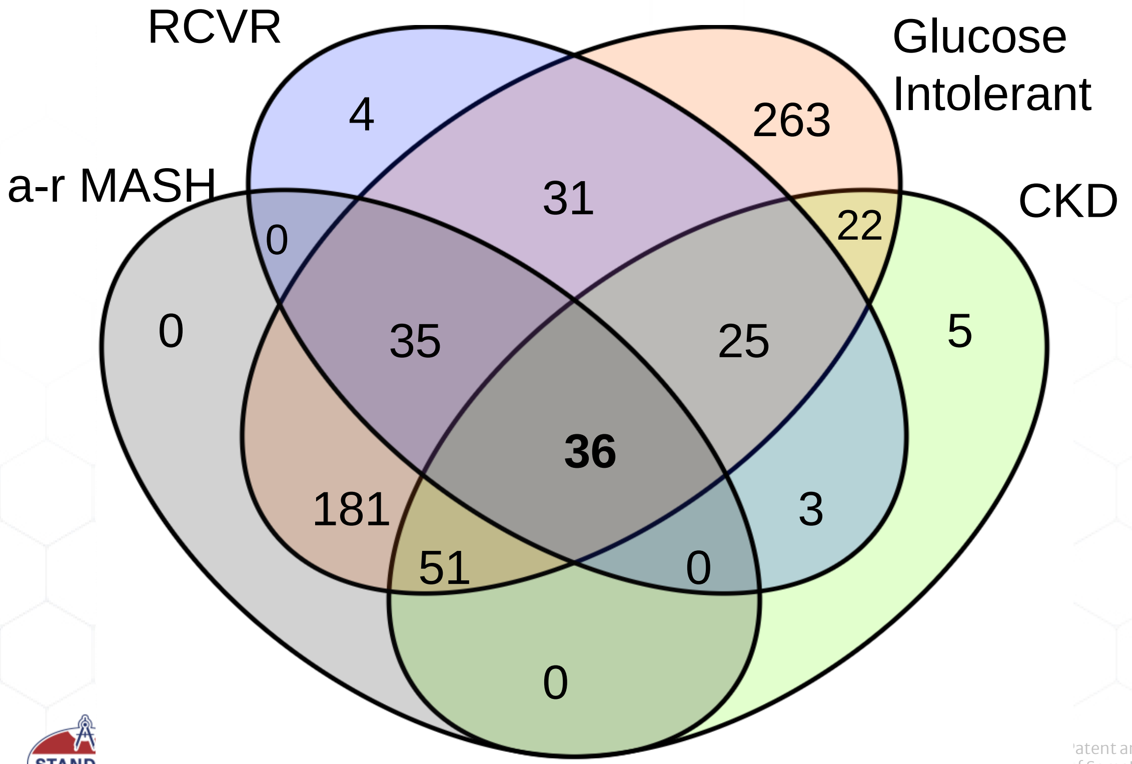


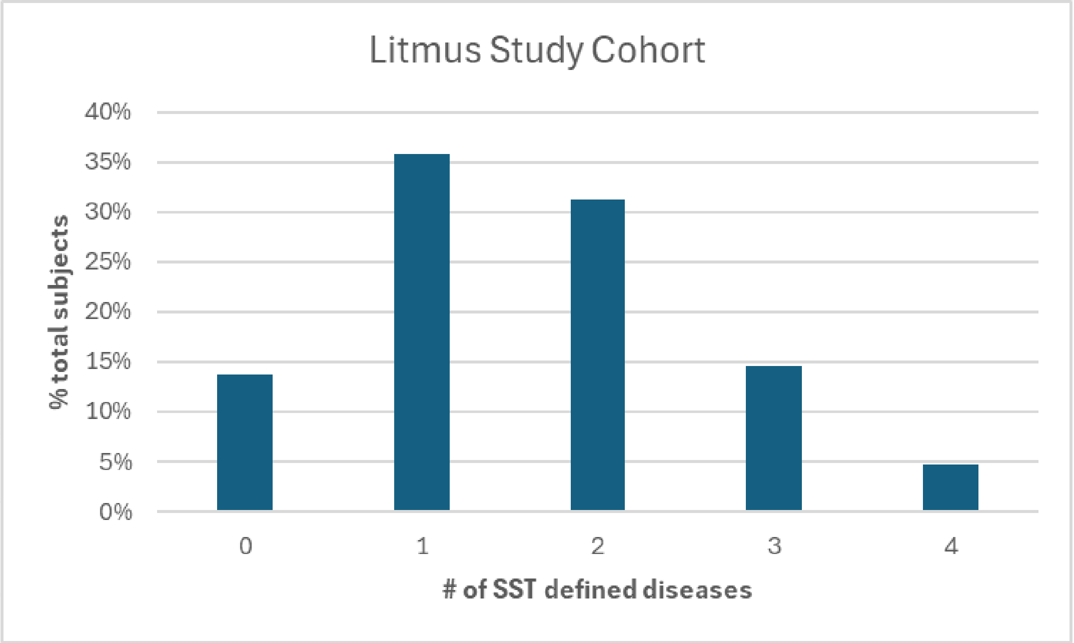
- Litmus Study cohort: Diagnostic accuracy study in patients with suspected MASLD
  - Inclusion:
    - > 18 years with a liver biopsy and paired serum sample and/or imaging markers
    - Suspected MASLD
  - Exclusion:
    - Excessive alcohol consumption
    - Chronic liver disease, viral Hep B or C

Multi-morbidity in a MAFLD/MASH Population
Litmus Study

Number of individuals with SST Results (n=760)

at-risk MASH	RCVR	Glucose Tolerance	CKD Prognosis
Not at-risk = 457 At-risk = 303	Low RCVR = 626 High RCVR = 134	GT = 116 GIT = 644	Low CKD = 618 High CKD = 142

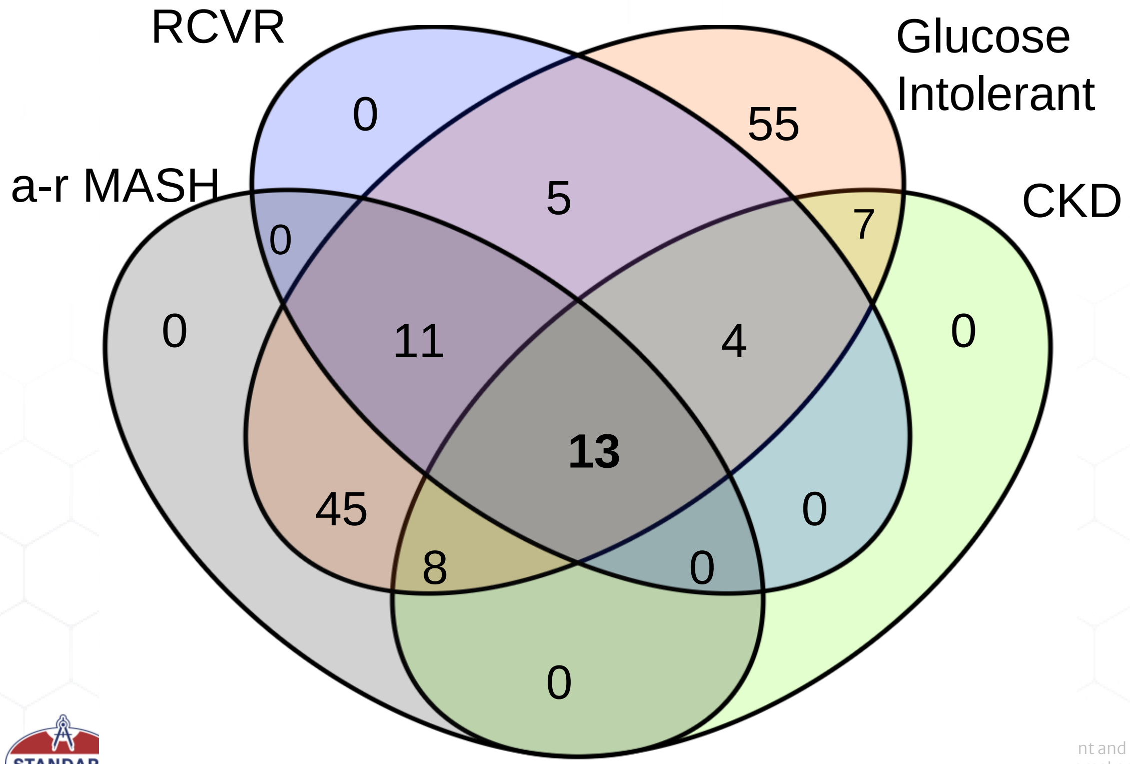


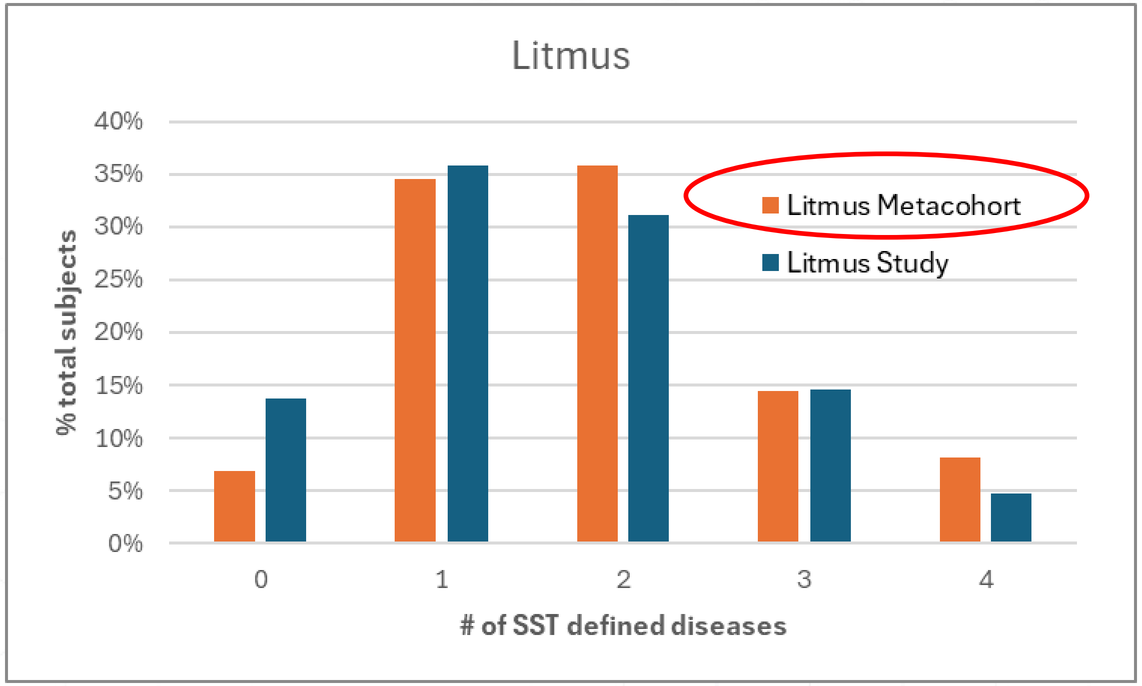


Multi-morbidity in a MAFLD/MASH Population
Litmus Metacohort

Number of individuals with SST Results (n=159)

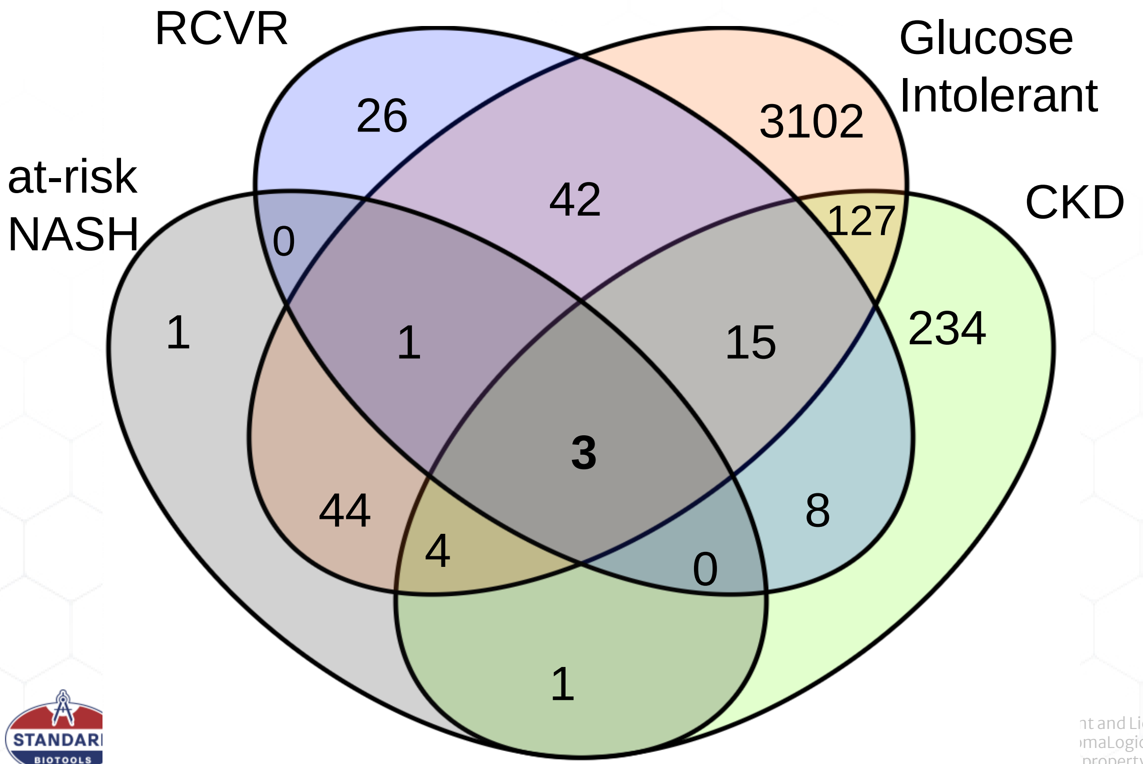
at-risk MASH	RCVR	Glucose Tolerance	CKD Prognosis
Not at-risk = 82	Low RCVR = 126	GT = 11	Low CKD = 127
At-risk = 77	High RCVR = 33	GIT = 148	High CKD = 32





Multi-morbidity in an Observational Cohort
Fenland Study

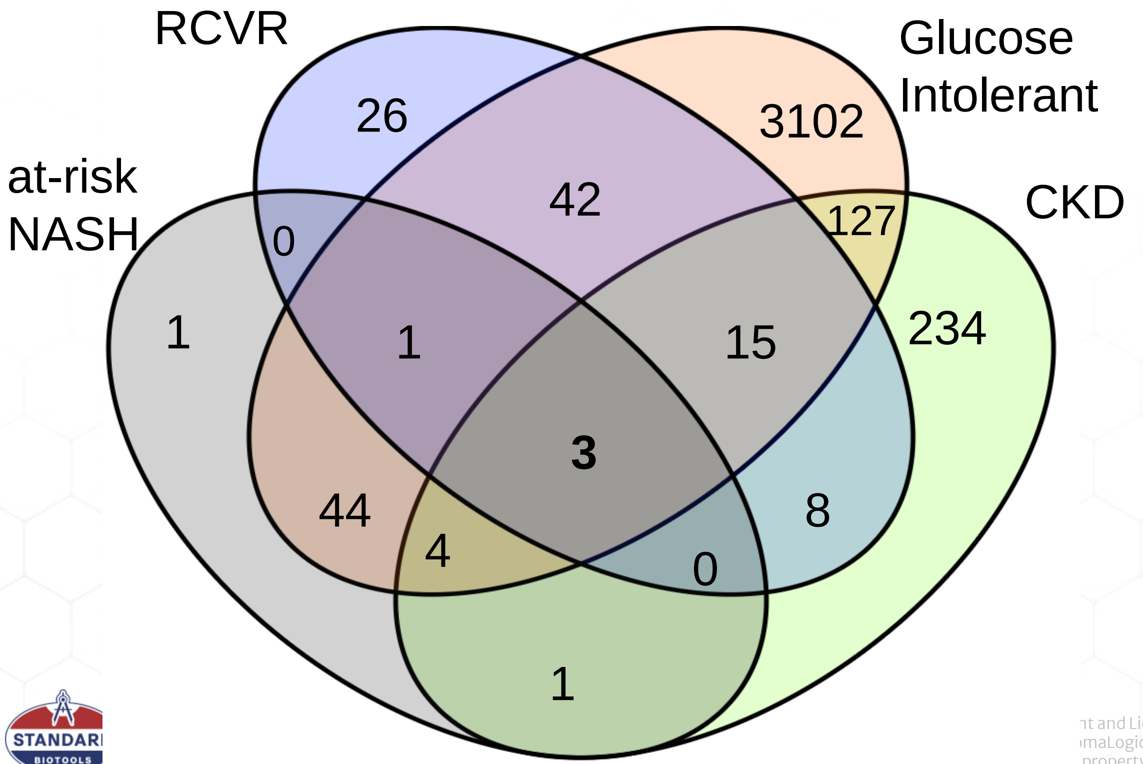
Number of individuals with SST Results (n=11,994 Phase 1)			
at-risk MASH Not at-risk = 11,940 At-risk = 54	**RCVR** Low RCVR = 11,899 High RCVR = 95	**Glucose Tolerance** GT = 8,656 GIT = 3,338	**CKD Prognosis** Low CKD = 11,602 High CKD = 392

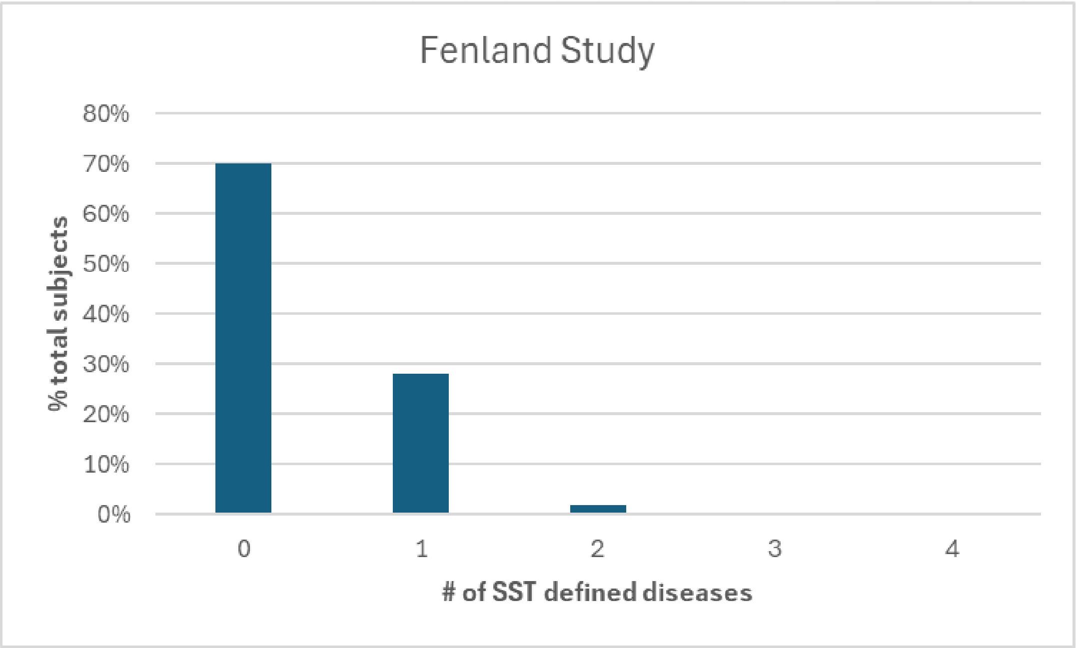


- Fenland Study: Investigate the interaction between environmental and genetic factors in determining obesity, type 2 diabetes and related metabolic disorders.
  - Enrollment Phase 1: 2005-2015, Phase 2:2014-2020
  - Inclusion:
    - M/F born between 1950-1975 (29-64 y, ave = 48 Phase 1), (39-67 y, ave = 55 Phase 2)
    - Registered at participating GP practices in Cambridge, Elly, Wisbech UK
  - Exclusion:
    - Diabetes
    - Psychotic illness, terminal illness, pregnancy, inability to walk unaided

Multi-morbidity in an Observational Cohort
Fenland Study

Number of individuals with SST Results (n=11,994 Phase 1)			
at-risk MASH Not at-risk = 11,940 At-risk = 54	**RCVR** Low RCVR = 11,899 High RCVR = 95	**Glucose Tolerance** GT = 8,656 GIT = 3,338	**CKD Prognosis** Low CKD = 11,602 High CKD = 392



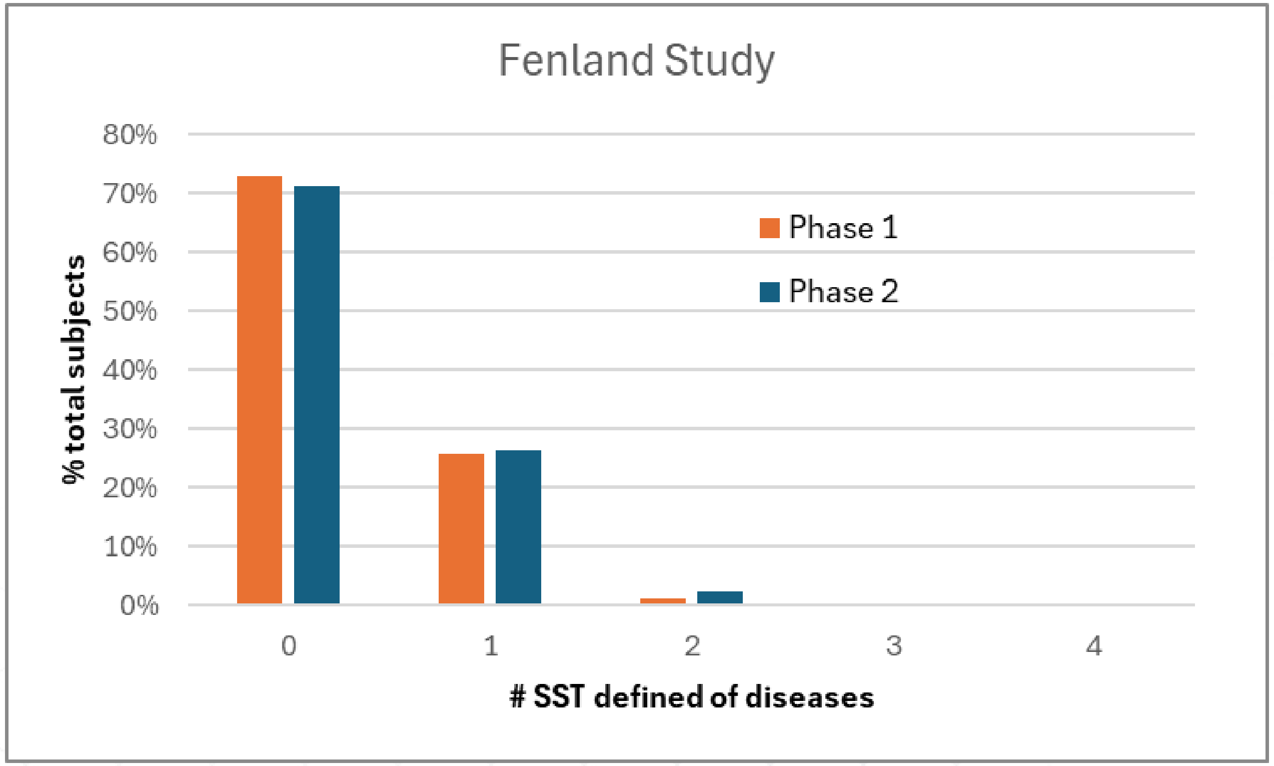


Multi-morbidity in an Observational Cohort
Fenland Study

- Fenland Study: subjects with both Phase 1 and Phase 2 samples

- Phase 1: 29-64 years, ave = 48
- Phase 2 39-67 years, ave = 55

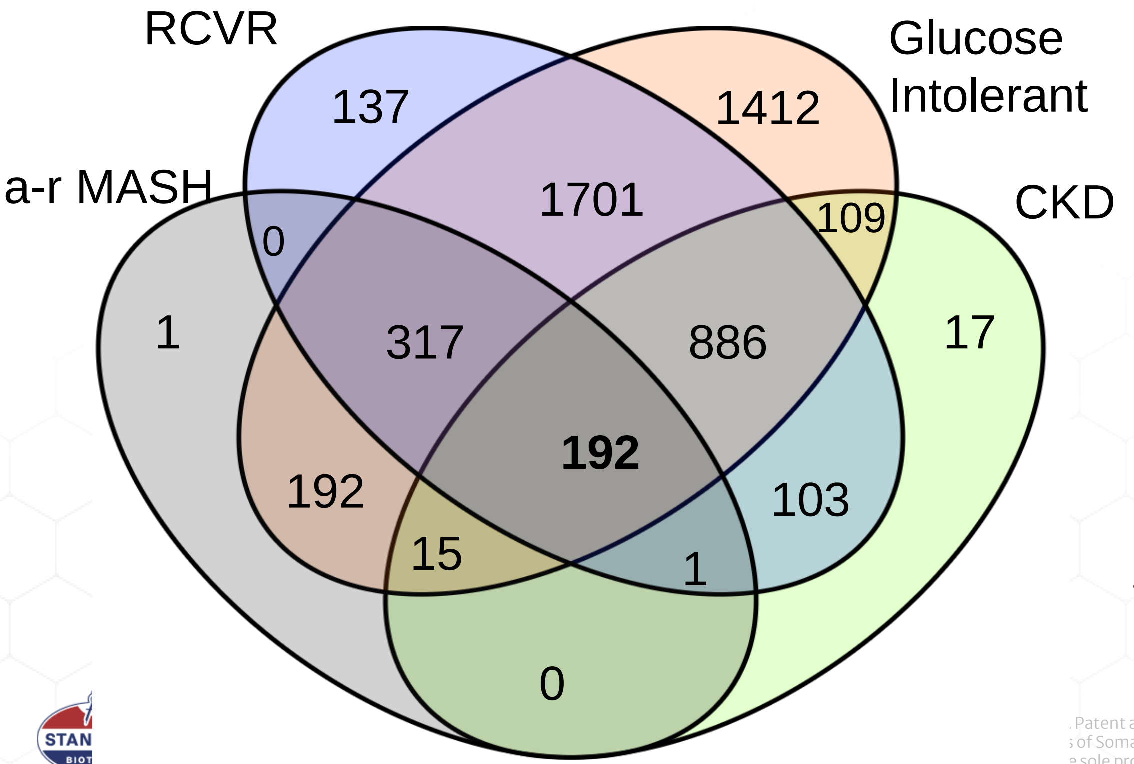
- Increase in multi-morbidity with age



Multi-morbidity in a Type 2 Diabetes Treatment Study
EXSCEL Study

Number of individuals with SST Results (n=5,241 Baseline)

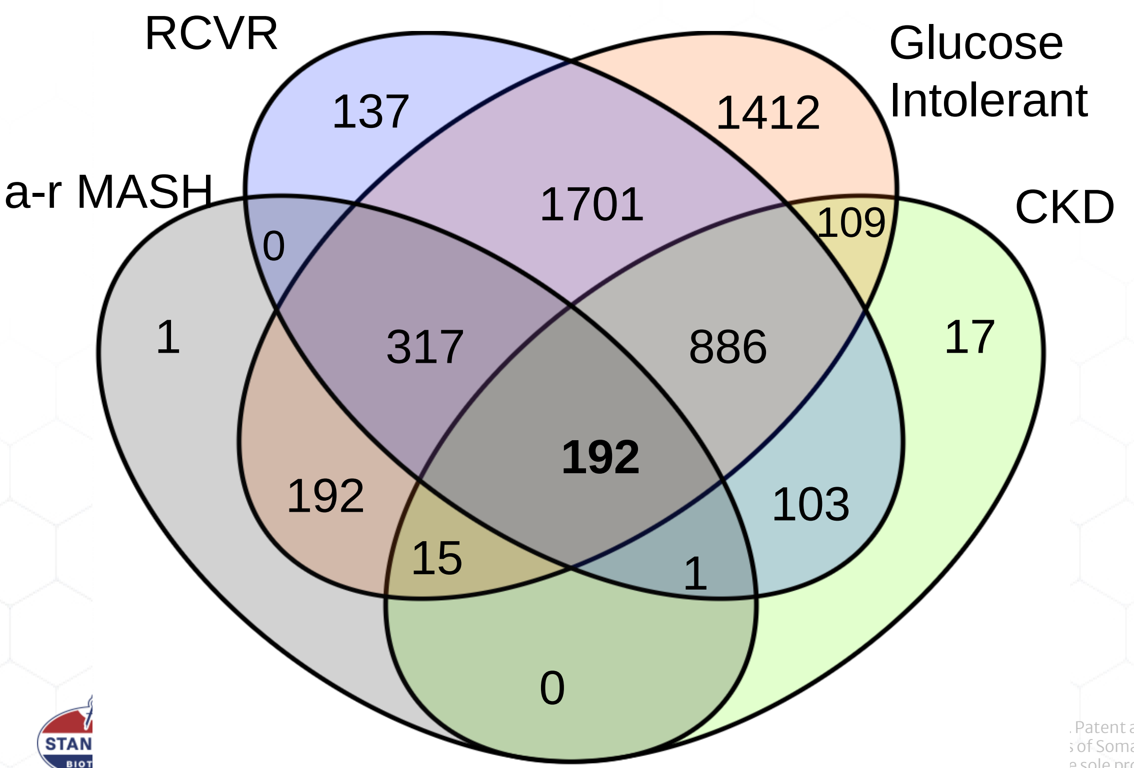
at-risk MASH	RCVR	Glucose Tolerance	CKD Prognosis
Not at-risk = 4,523	Low RCVR = 1,904	GT = 417	Low CKD = 3,918
At-risk = 718	High RCVR = 3,337	GIT = 4,824	High CKD = 1,323

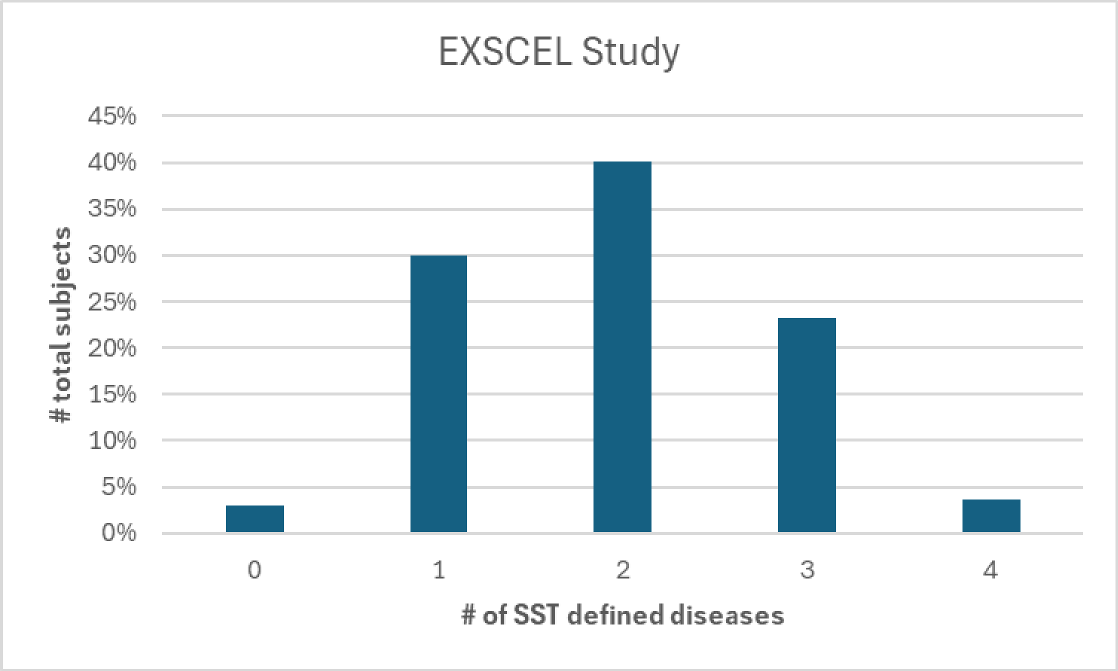


- EXSCEL: Exenatide Study of Cardiovascular Event Lowering Trial:A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus
  - Inclusion:
    - Patient has type 2 diabetes mellitus
  - Exclusion Criteria:
    - Type 1 diabetes mellitus, or a history of ketoacidosis.
  - Treatment: 12 months
    - Placebo: subcutaneous injection, matching volume, once weekly
    - Exenatide: subcutaneous injection, 2 mg, once weekly
- Outcome
  - Major adverse cardiovascular events did not differ significantly between patients who received exenatide and those who received placebo.

Multi-morbidity in a Type 2 Diabetes Treatment Study
EXSCEL Study

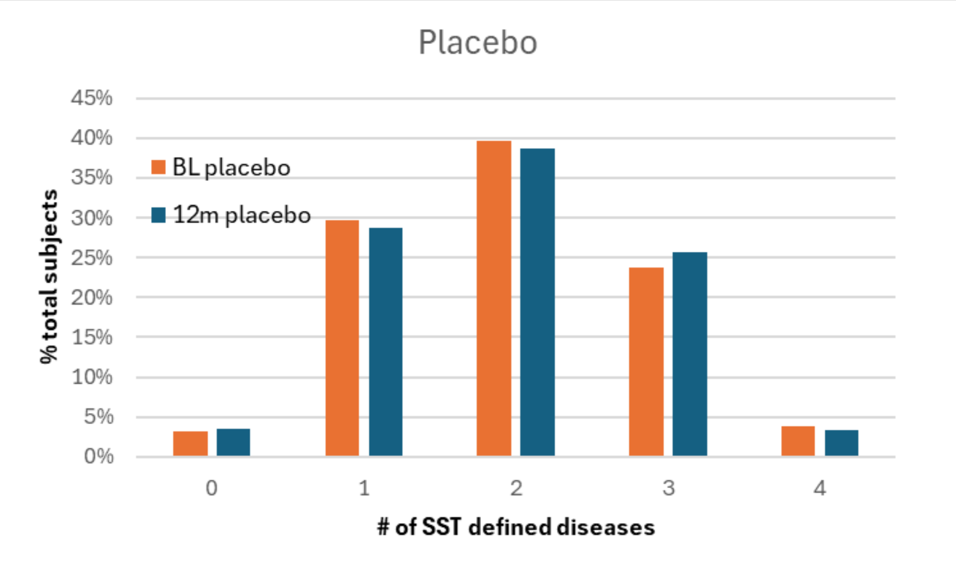
Number of individuals with SST Results (n=5,241 Baseline)			
at-risk MASH Not at-risk = 4,523 At-risk = 718	**RCVR** Low RCVR = 1,904 High RCVR = 3,337	**Glucose Tolerance** GT = 417 GIT = 4,824	**CKD Prognosis** Low CKD = 3,918 High CKD = 1,323

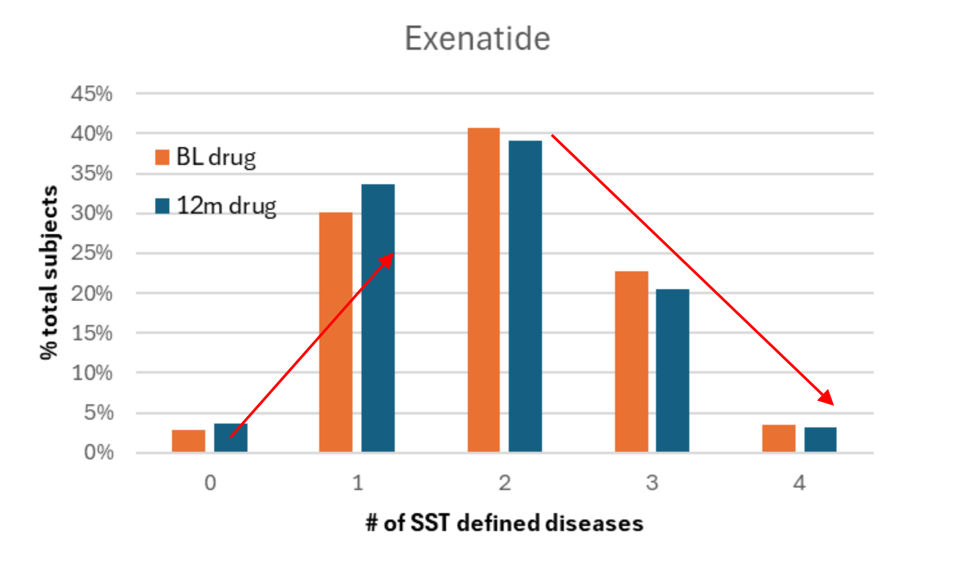




Multi-morbidity in a Type 2 Diabetes Treatment Study
EXSCEL Study

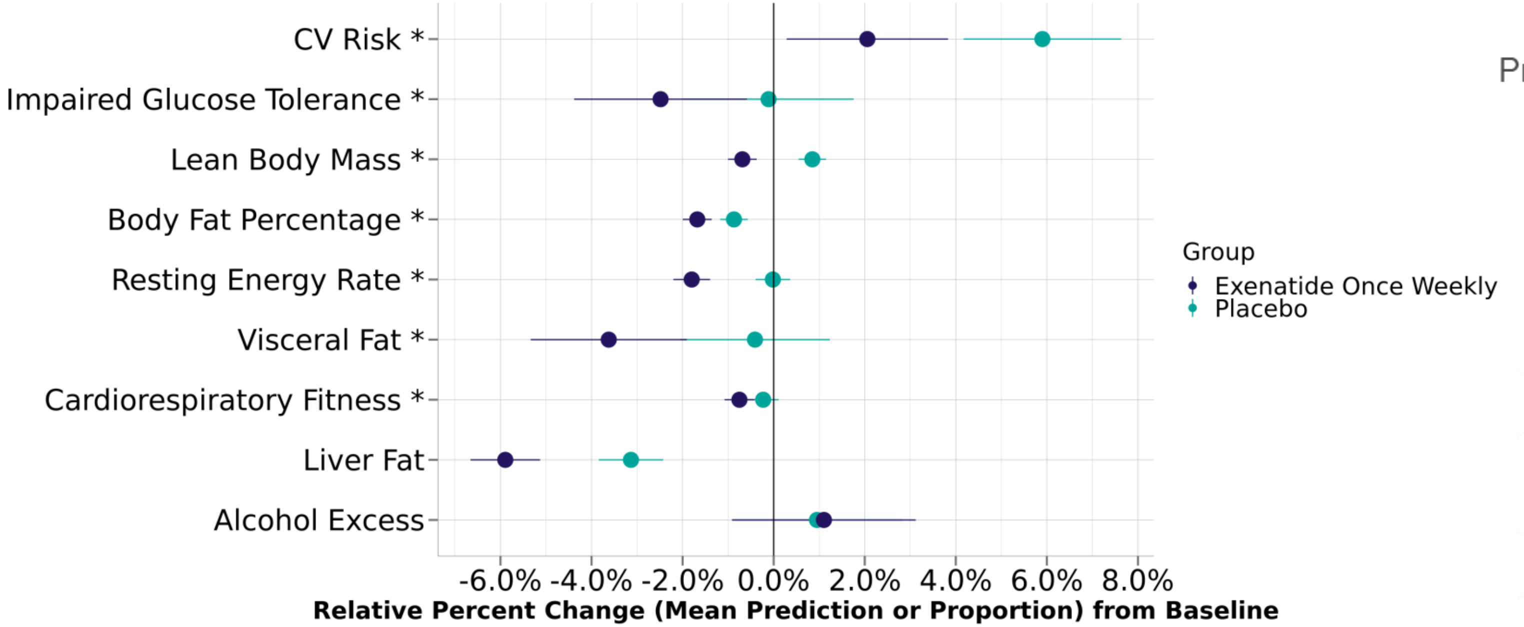
- EXSCEL Study: BL and 12m paired samples
- Placebo: No trend in multi-morbidity
- Exenatide: Decreases in multi-morbidity
  - Greater percentages in 0, 1 disease categories
  - Lower percentages in 2, 3 and 4 disease categories
- Broad cardiometabolic health improvement with GLP1-ra Intervention
- With significant cardiovascular risk improvement, potential to reduce trial size, duration





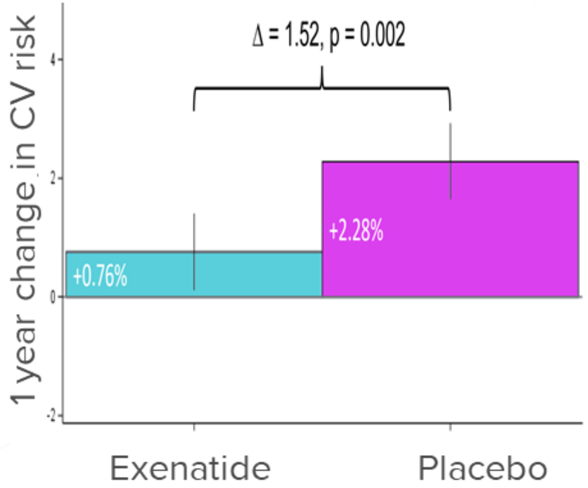
Cardiometabolic Health Improvement with GLP-1RA Intervention

Potential for smaller, shorter trials?



* Indicates significant change

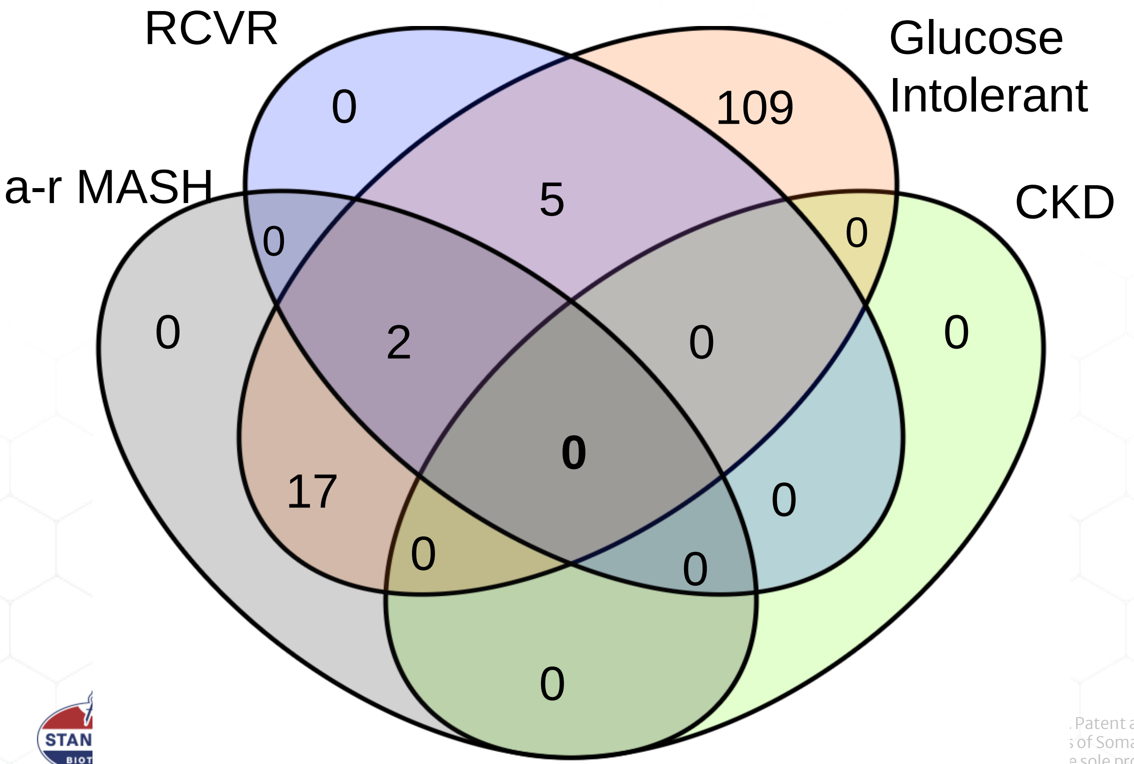
Proteomic detection of benefits of exenatide in 8% participant years vs. outcomes study



Detected a 1.5% difference

Multi-morbidity in a Type 2 Diabetes Treatment Study
DIADEM-I Study

Number of individuals with SST Results (n=143 Baseline)			
at-risk MASH Not at-risk = 124 At-risk = 19	**RCVR** Low RCVR = 136 High RCVR = 7	**Glucose Tolerance** GT = 10 GIT = 133	**CKD Prognosis** Low CKD = 143 High CKD = 0

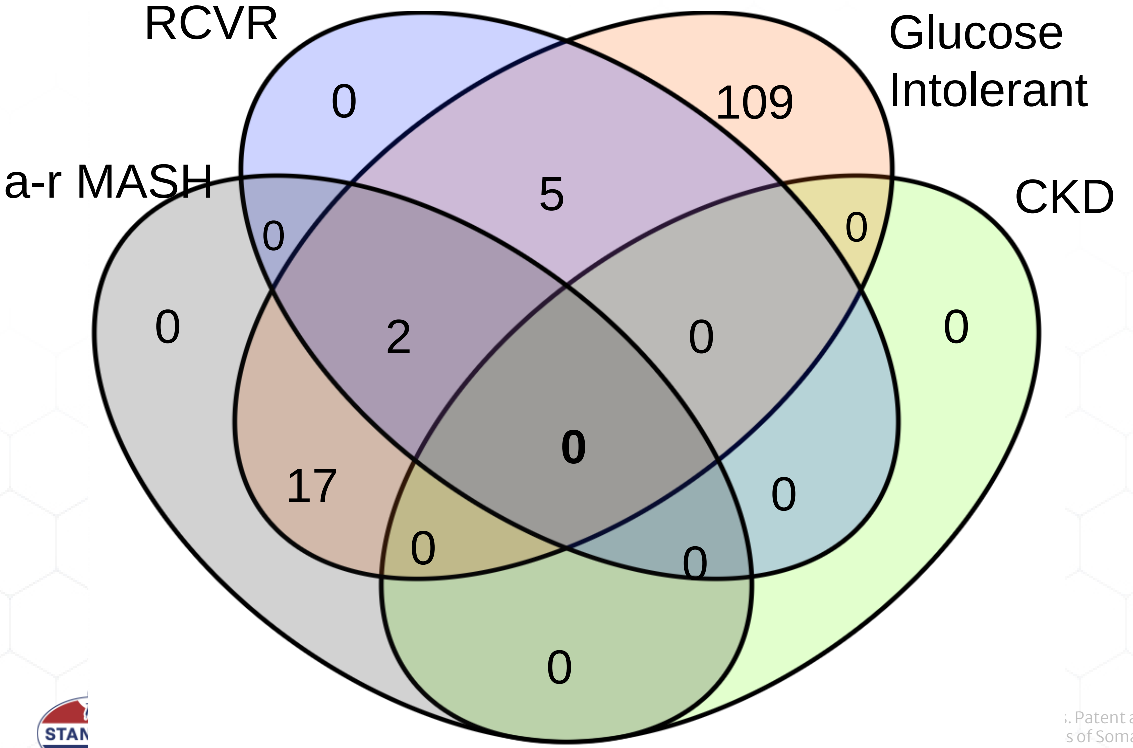


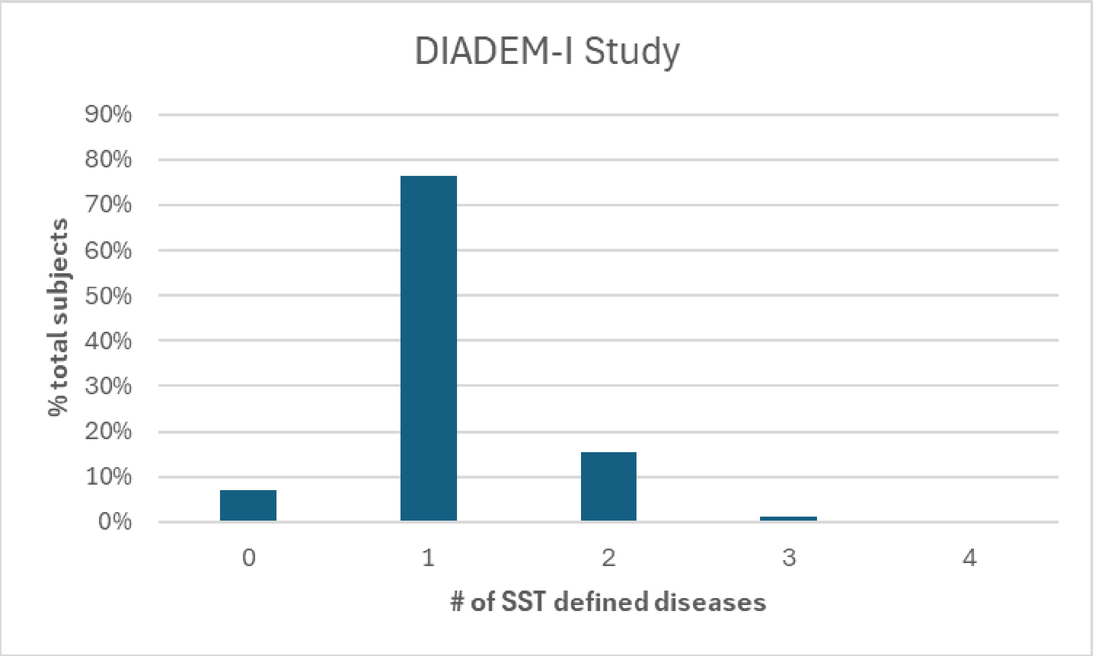
- DIADEM-I: Compared the effects of an intensive lifestyle intervention (ILI) with usual medical care (UMC)
  - Inclusion:
    - Aged 18-50
    - Type 2 diagnosis within the previous 3 years
  - Exclusion Criteria:
    - Type 1 diabetes, CV event past 6m, Stage 3 CKD
  - Treatment: 48 weeks
    - Intensive Lifestyle Intervention: Low-energy diet meal replacement, physical activity support
    - Usual Medical Care:Usual diabetes care based on clinical guidelines
- Outcome
  - ILI led to significant weight loss at 12 months and diabetes remission in 60% of participants

Multi-morbidity in a Type 2 Diabetes Treatment Study
DIADEM-I Study

Number of individuals with SST Results (n=143 Baseline)

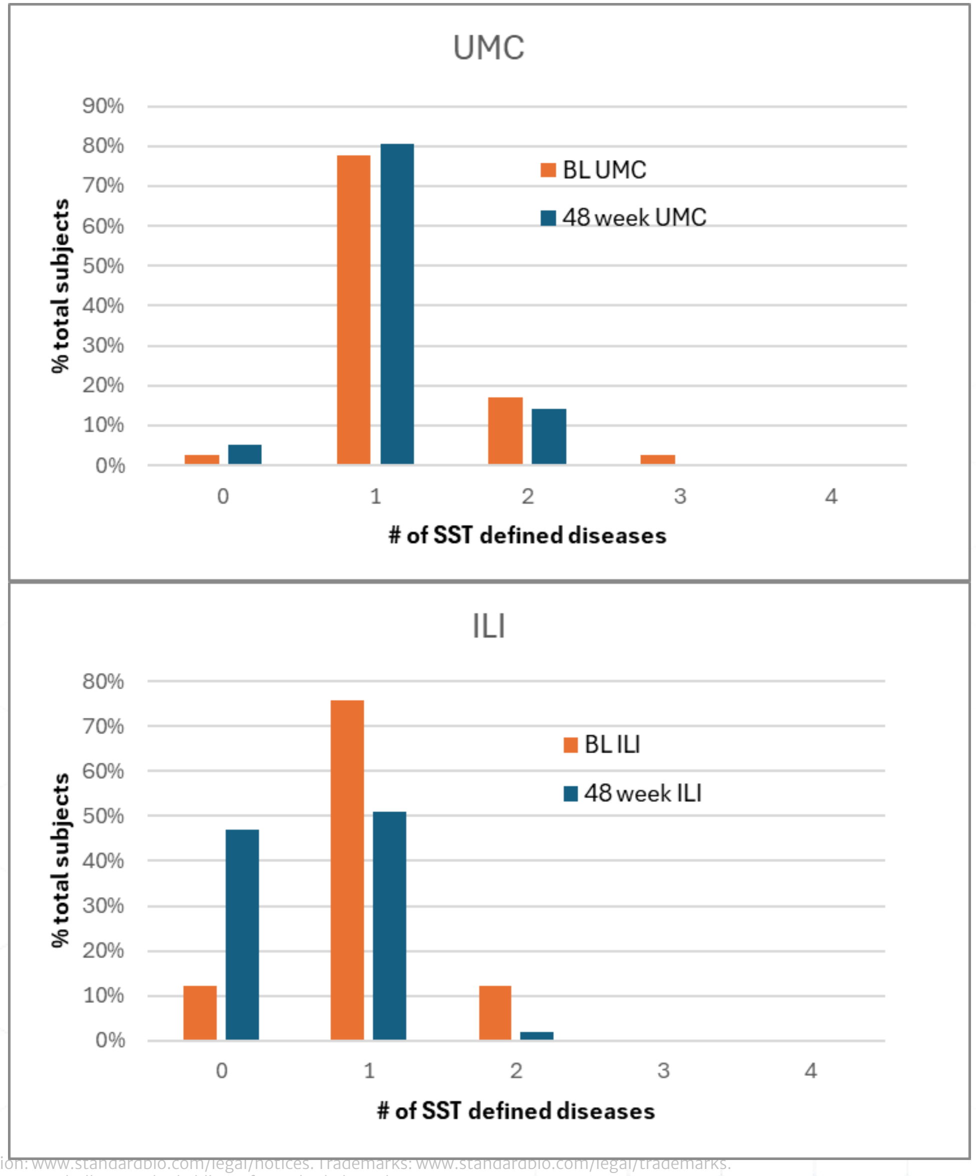
at-risk MASH	RCVR	Glucose Tolerance	CKD Prognosis
Not at-risk = 124	Low RCVR = 136	GT = 10	Low CKD = 143
At-risk = 19	High RCVR = 7	GIT = 133	High CKD = 0



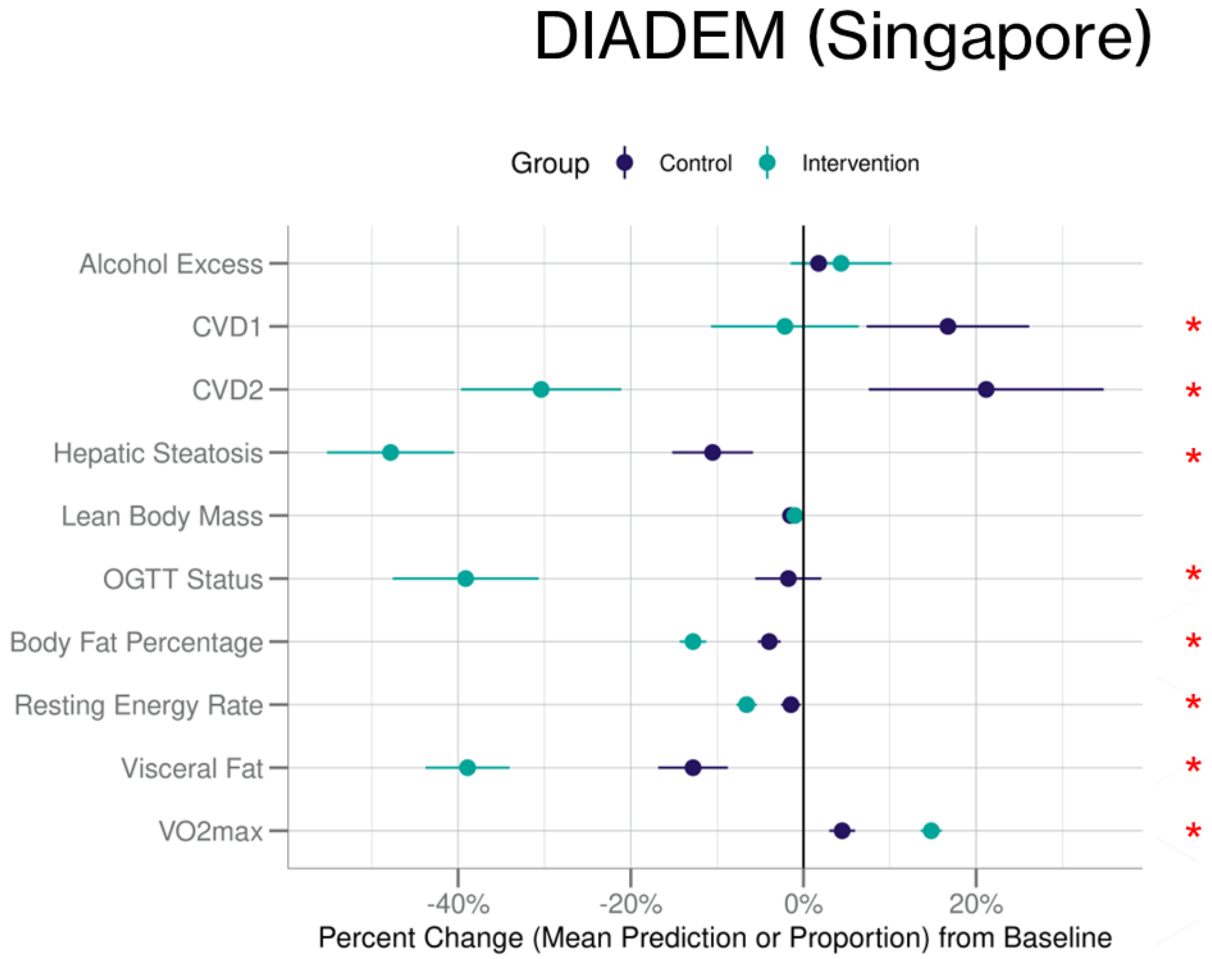


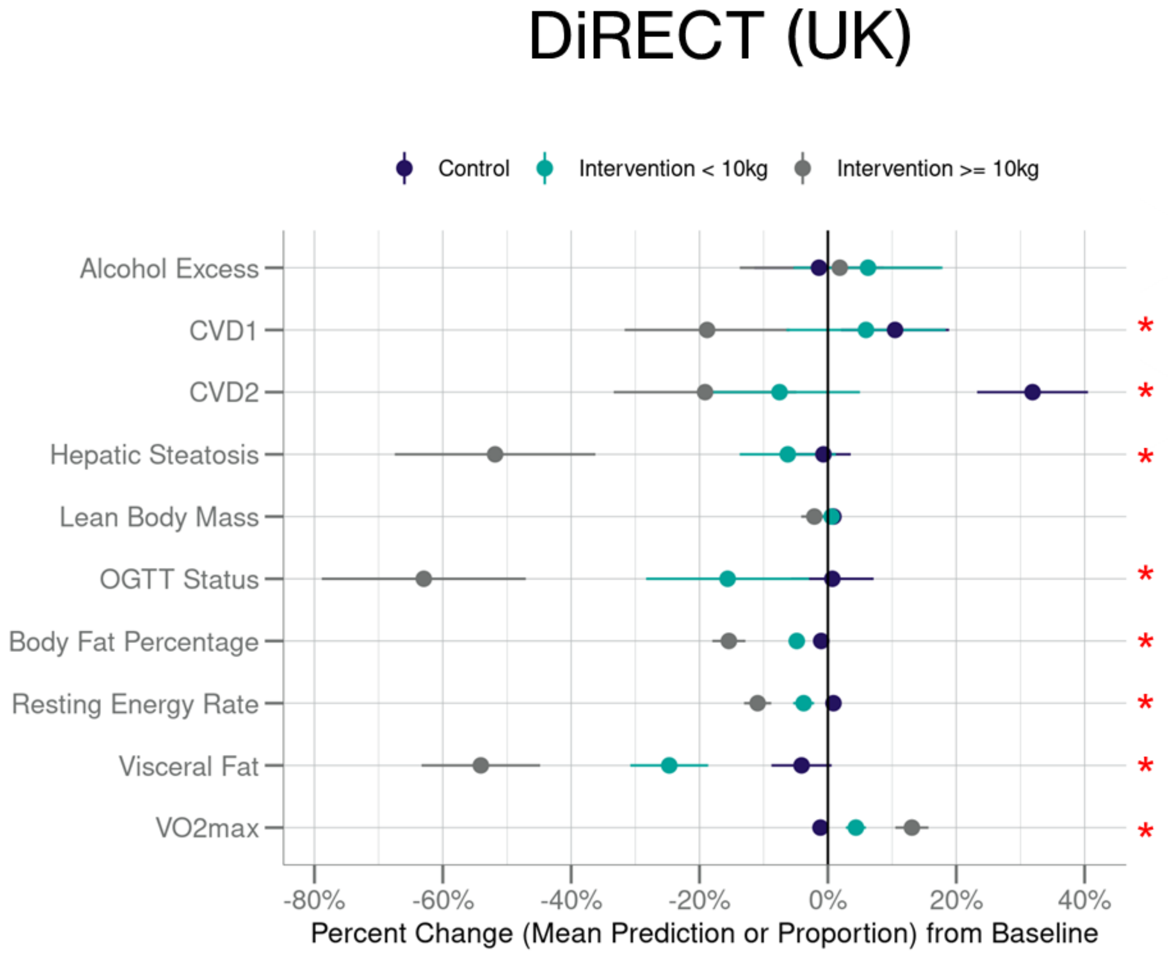
Multi-morbidity in a Type 2 Diabetes Treatment Study
DIADEM-I Study

- DIADEM-I: BL and 48w paired samples
- UMC: Slight reduction in multi-morbidity
  - Lower percentages in 2 and 3 disease categories
  - Greater percentages in 0 and 1 disease categories
- ILI: Significant reduction in multi-morbidity
  - Lower percentages in 1, 2, and 3 disease categories
  - Significantly greater percentage in 0 disease category
- Broad cardiometabolic health improvement with ILI



Cardiometabolic Health Improvement with ILI

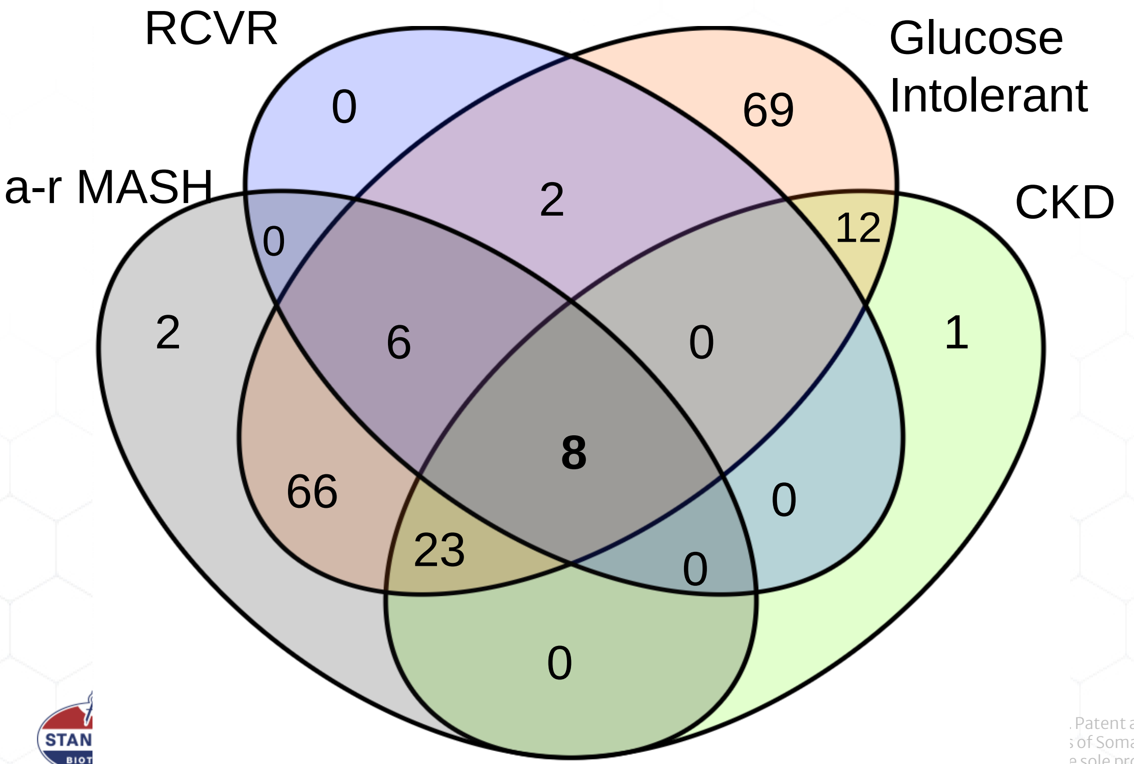




Diabetes Care 2023;46(11):1949-1957

Multi-morbidity in a MASH Treatment Study
PIVENS Study

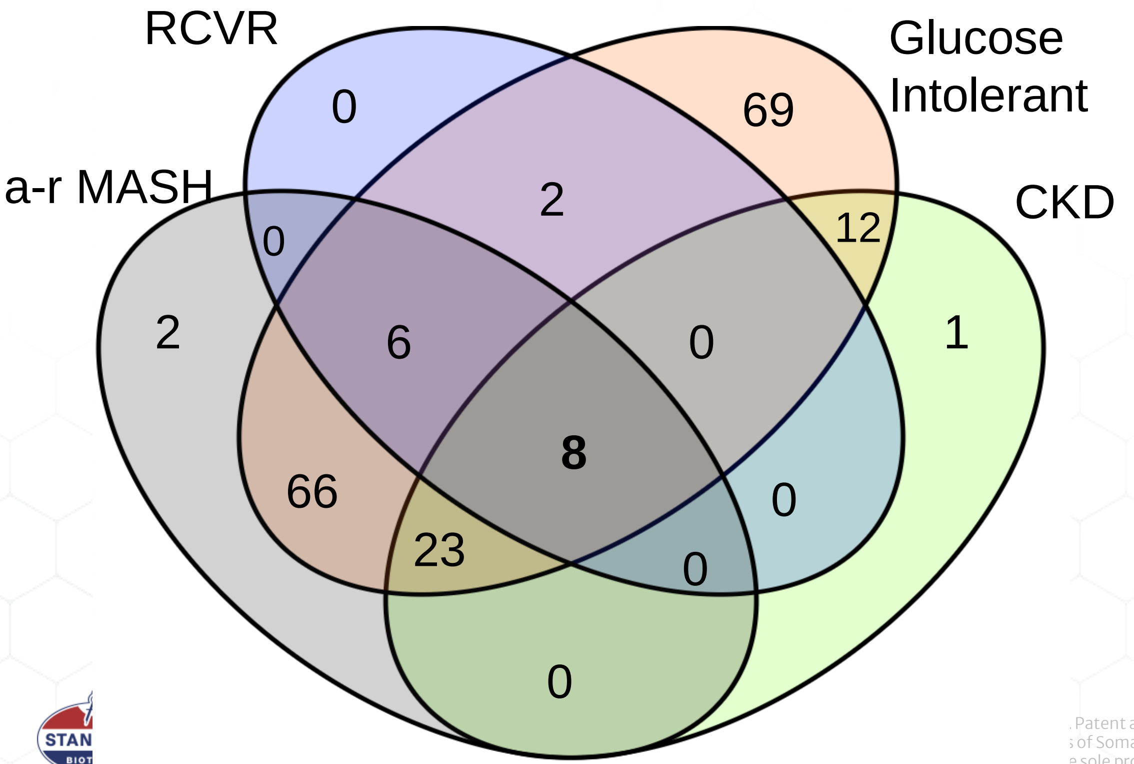
Number of individuals with SST Results (n=206 Baseline)			
at-risk NASH Not at-risk = 101 At-risk = 105	**RCVR** Low RCVR = 190 High RCVR = 16	**Glucose Tolerance** GT = 20 GIT = 186	**CKD Prognosis** Low CKD = 162 High CKD = 44

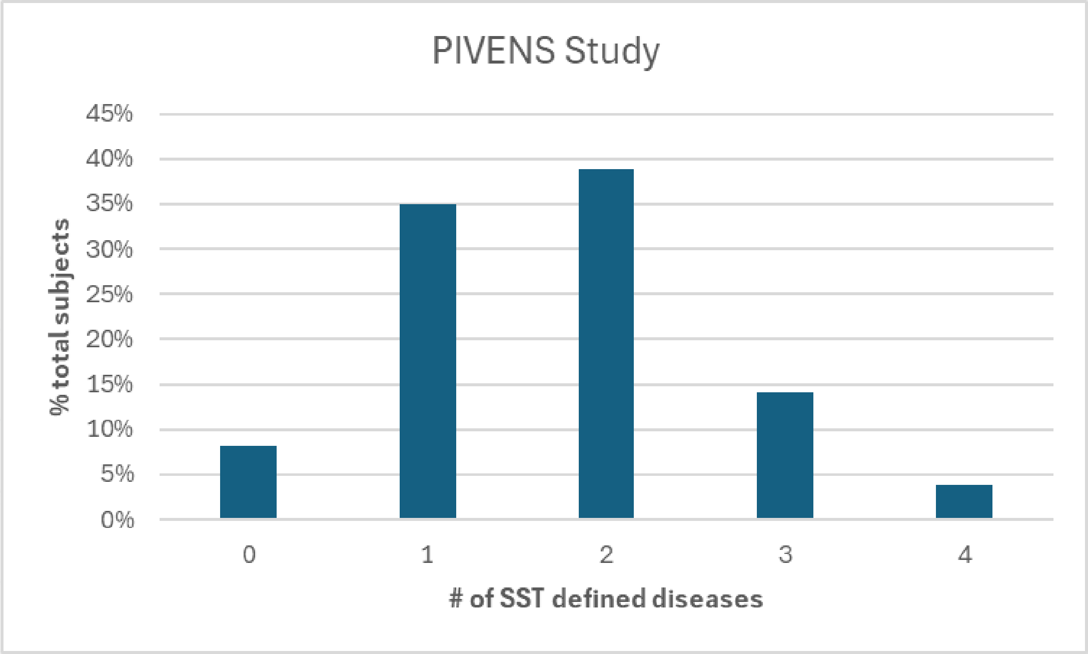


- PIVENS: RCT, Pioglitazone and Vitamin E in NASH subjects
  - Inclusion:
    - Aged 18+
    - NASH by biopsy
  - Exclusion Criteria:
    - Diabetes
  - Treatment: 96 weeks
    - Pioglitazone: 30 mg daily
    - Vitamin E: 800 IU daily
    - Placebo
- Outcome
  - Vitamin E significant, Pioglitazone not significant NASH improvement.

Multi-morbidity in a MASH Treatment Study
PIVENS Study

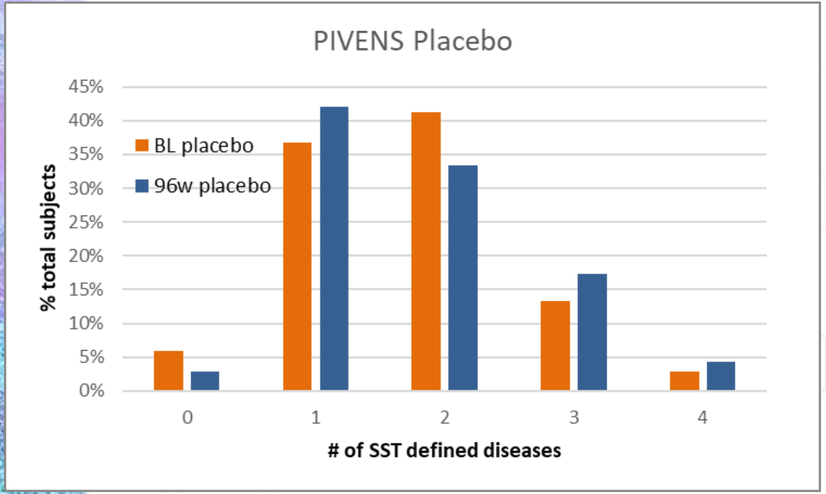
Number of individuals with SST Results (n=206 Baseline)			
at-risk NASH Not at-risk = 101 At-risk = 105	**RCVR** Low RCVR = 190 High RCVR = 16	**Glucose Tolerance** GT = 20 GIT = 186	**CKD Prognosis** Low CKD = 162 High CKD = 44

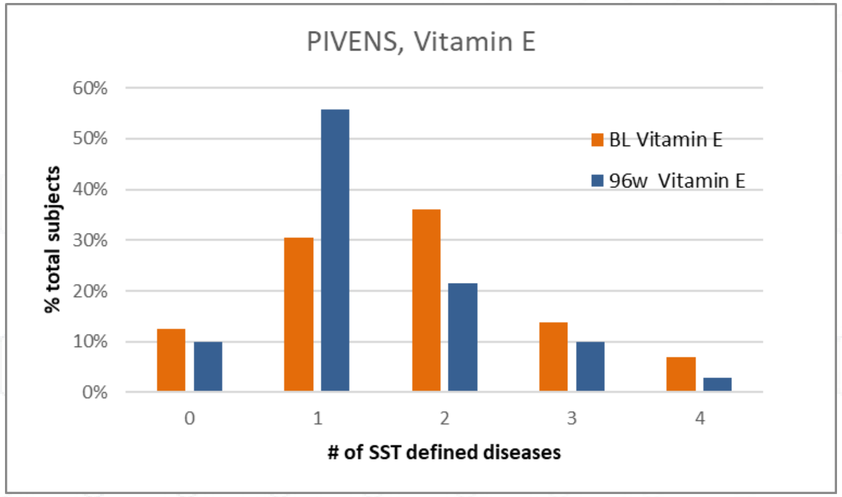


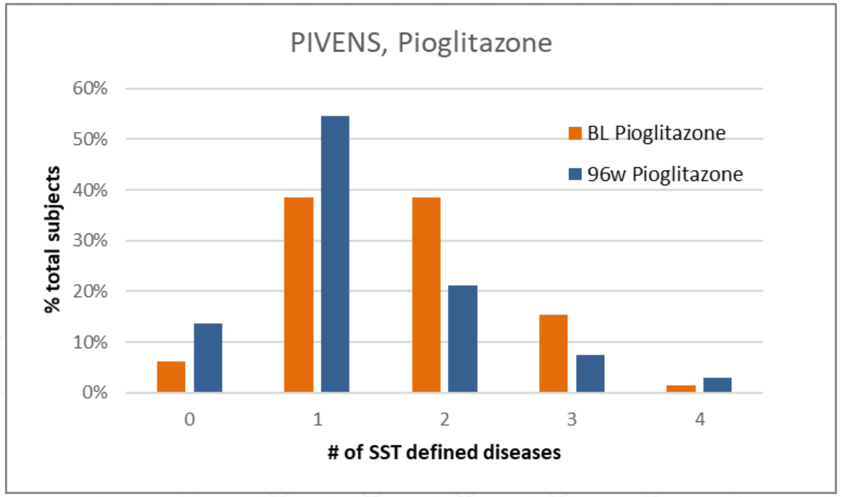


Multi-morbidity in a MASH Treatment Study
PIVENS

- PIVENS Study: BL and 96w paired samples
- Placebo: Trending toward Increased multi-morbidity
- Vitamin E: Decreases in multi-morbidity
  - Lower percentages of individuals with 2, 3 and 4 disease
- Pioglitazone: Decreases in multi-morbidity
  - Greater percentages of individuals with 0 and 1 disease
  - Lower percentages of individuals with 2 and 3 diseases

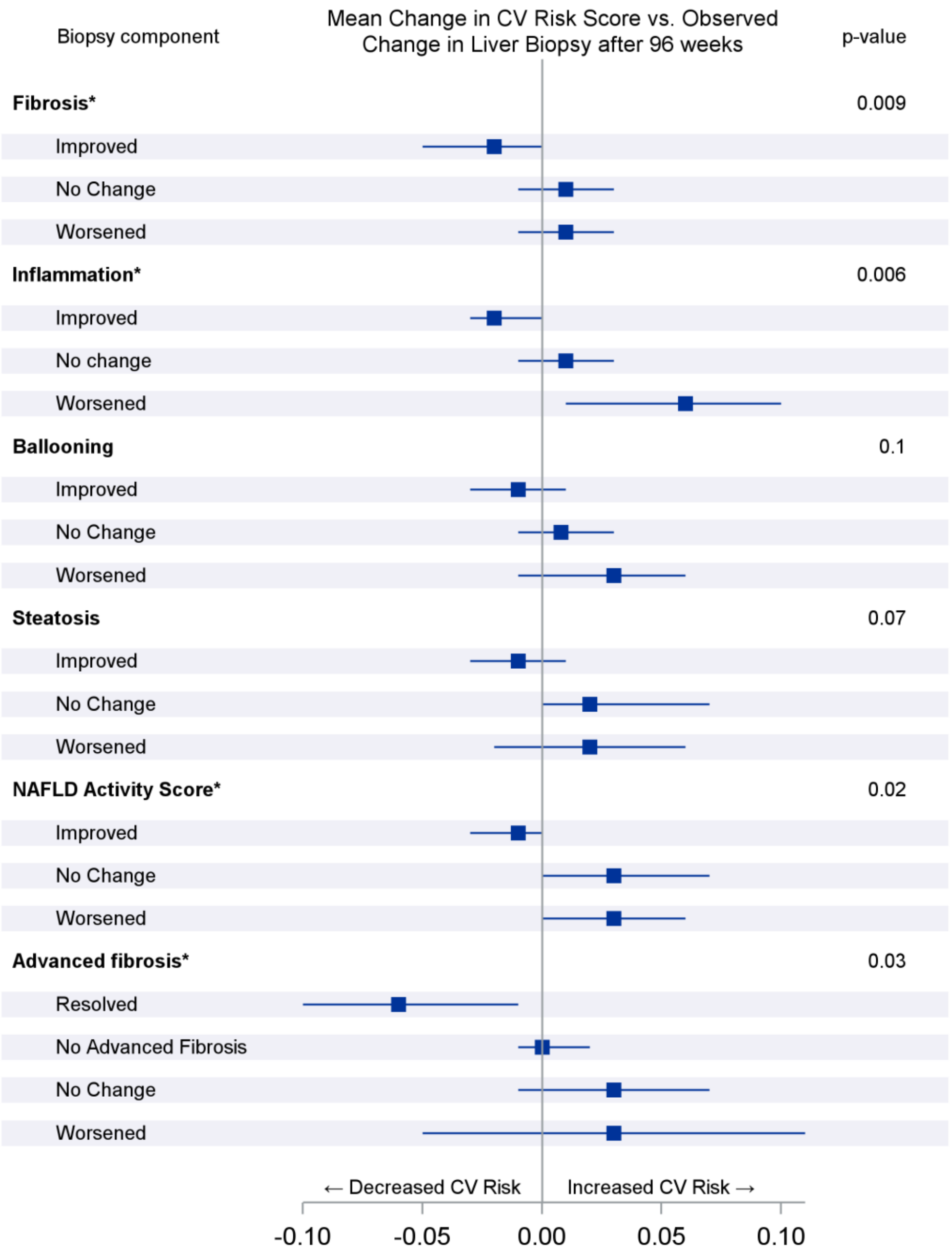






Improved Cardiovascular Risk in the PIVENS trial

- Improvement in fibrosis, hepatic inflammation, NAFLD activity score and Advanced fibrosis were associated with improved proteomic CV risk scores regardless of treatment arm.
- Because this was a post-hoc analysis, additional prospective validation of these findings is warranted.
- This study provides evidence that proteomic profiling can be used to track changes in surrogate endpoints such as CV risk profiles in response to therapy in NASH/MASH trials.



Hinterberg et. al., AHA poster, 2023

Conclusions

Conclusions

- The SomaScan® assay can currently provide ~11,000 measurements
  - High levels of coverage across every major biological pathway
- SomaSignal® Tests developed for RUO and LDT use
  - Prognostic for Major Health Outcomes
  - Current Metabolic State
  - MASH
  - Impact of Social Behaviors
  - DDT submissions for RCRV and MASH SSTs
- MASH SSTs
  - Outperform >17 common screening/diagnostic single/multi-biomarkers (Metacohort and Litmus Study Cohort)
  - Associate with longitudinal changes upon therapeutic interventions
- Assessing metabolically associated multi-morbidities at scale possible with the SomaScan Assay
  - A simple blood draw can provide a deeper understanding of clinical trial populations (“know your patient”)
  - Significant overlap across at-risk MASH, CVD, CKD and T2D
  - Disease specific treatments, provide broad improvement to metabolic associated diseases

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