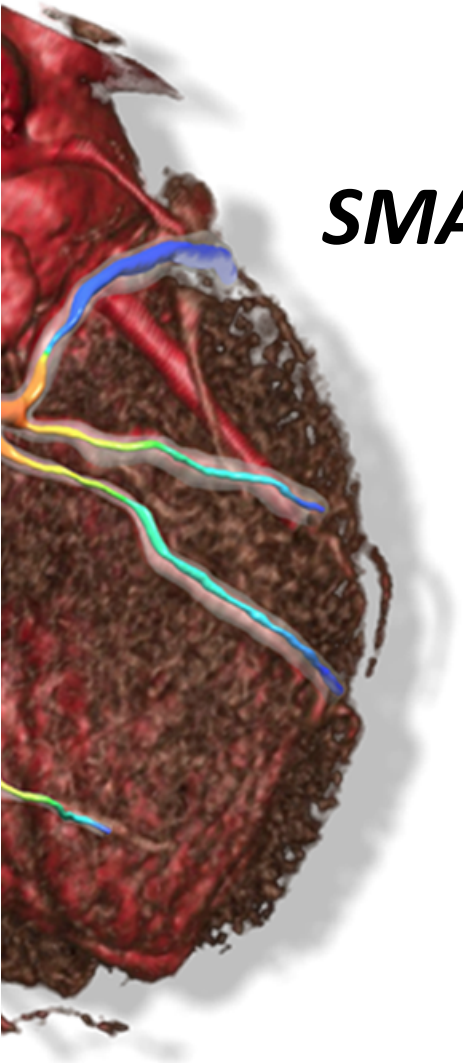
A SMARTool project workshop

CAD RISK PREDICTION AND STRATIFICATION: THE ICT APPROACH



SMARTool Lipidomics for ATS risk prediction and Point of Care devices

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Tuesday 6th November 2018

CNR Research Area Campus
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Horizon 2020
689068

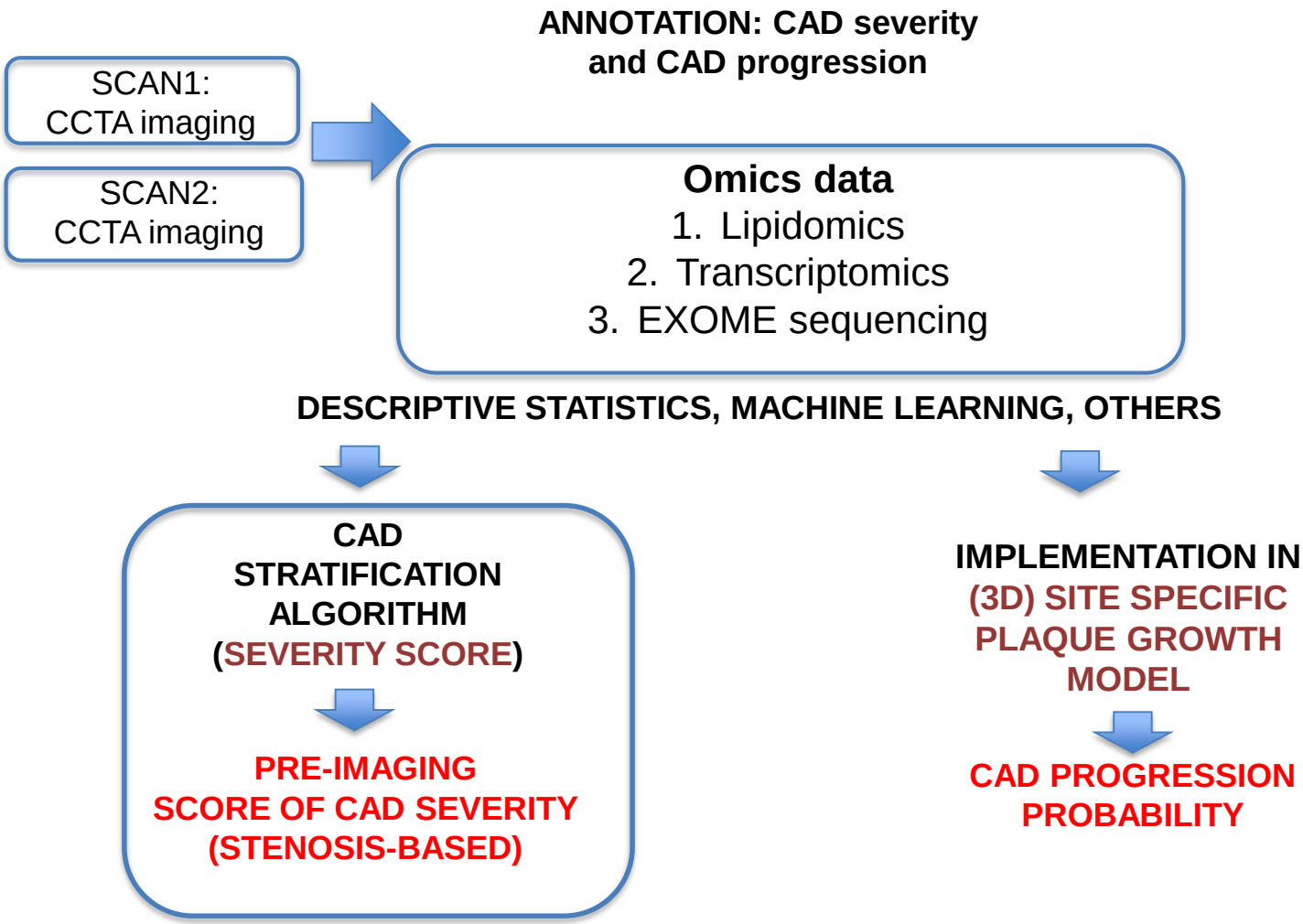
MAIN ENDPOINTS OF MOLECULAR CHARACTERIZATION IN SMARTool

1. To characterize the genotype and phenotype of CAD patients and select the **best molecular markers** of **CAD SEVERITY AND PROGRESSION**

2. To develop **point-of-care technologies** to measure selected markers directly in blood

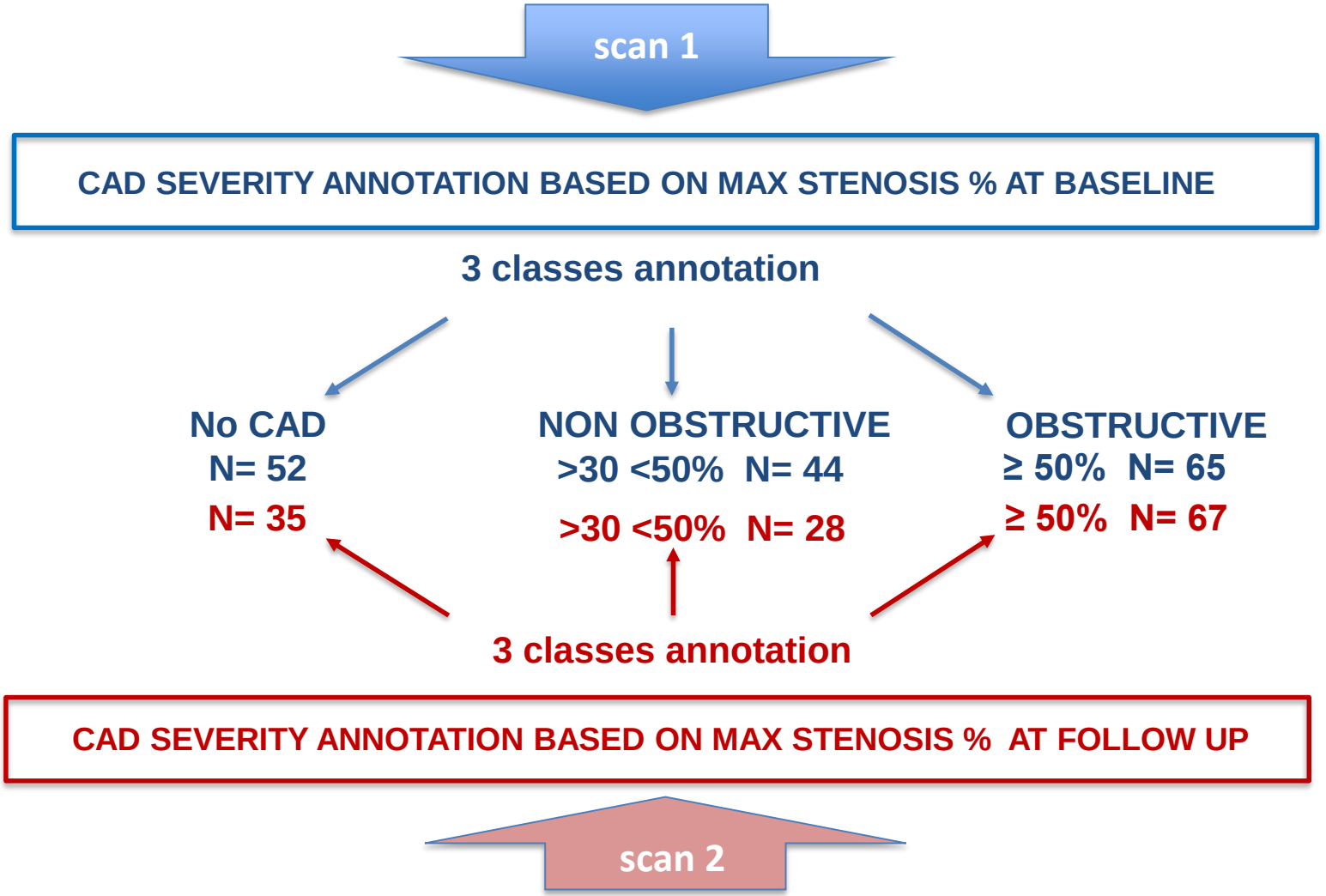
3. To create a pre-imaging algorithm based on gender, age and molecular variables with an additive value to stratify risk of CAD presence and severity

OMICS IN SMARTool

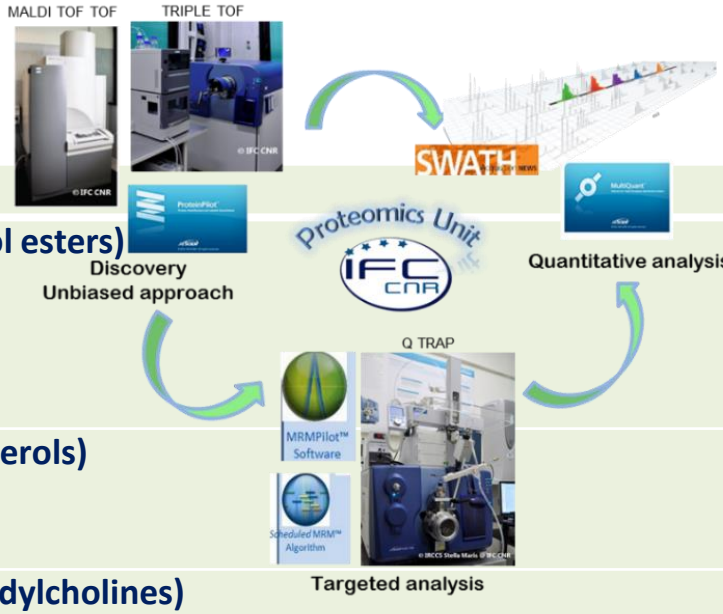


PTS ANNOTATION OF CAD SEVERITY

N= 259 with LUMC visual analysis completed



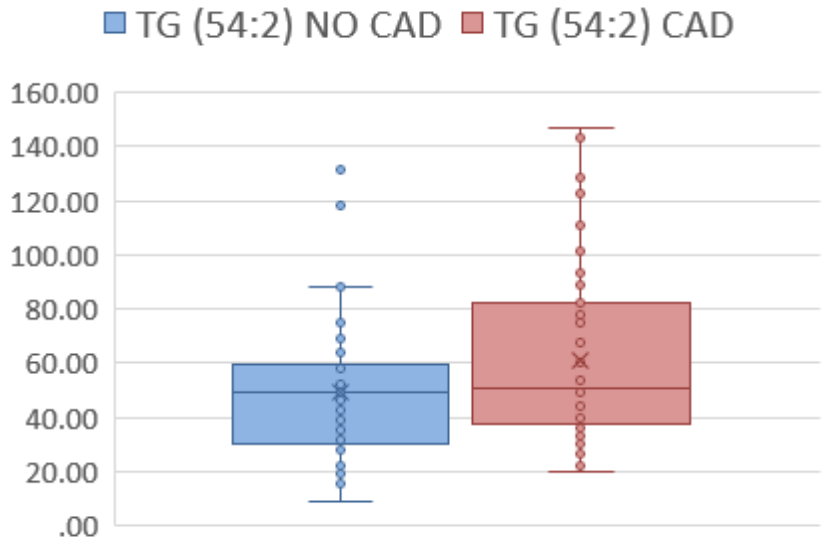
WHICH LIPIDS, HOW AND WHY?

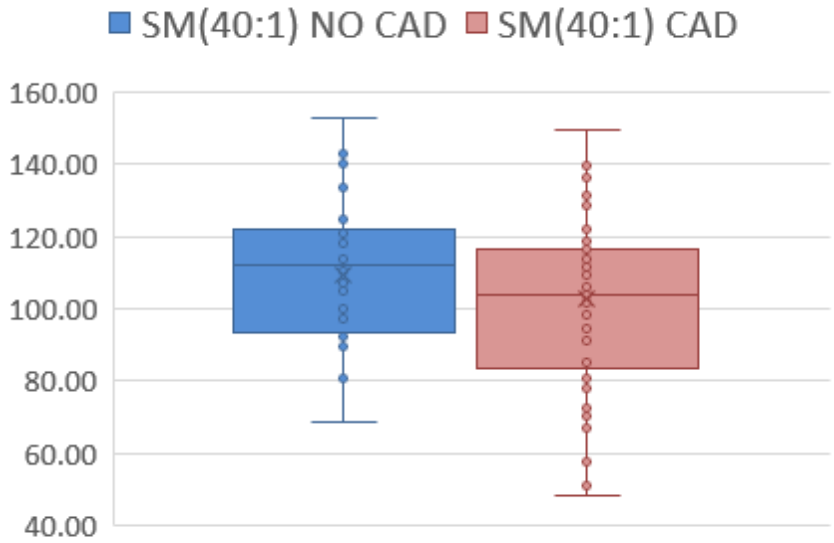


	CVD Role
CE (cholesterol esters)	**Cheng et Al Atherosclerosis 2015** found association with fraction of necrotic core and lipid burden by NIRS with many CE species in the ATHEROREMO-IVUS population (N=574). **Stegemann et al Circulation 2014** In Brunek trial (N=685) they found CE(16:1) as one informative marker of CVD event (stroke, MI, sudden death) prediction in 10 years
TG (triacylglycerols)	**Stegemann et al Circulation 2014** In Brunek trial (N=685) they found TG(54:2) as one informative marker of CVD event (stroke, MI, sudden death) prediction in 10 years
PC (phosphatidylcholines)	**Paapstel et al Nutrition metabolism and cardivascular disease 2018** found in N=50 CVD pts and N=50 healthy subjects an inverse relationship between PCs and arterial function/ inflammation molecules
PE (phosphatidylethanolamines)	**Meikle et al ATVB2011** Association between PEs and symptomatology (= 140 pts stable angina vs unstable angina) **Stegemann et al Circulation 2014** In Brunek trial (N=685) they found PE(36:5) as one informative marker of CVD event (stroke, MI, sudden death) prediction in 10 years **Ellims et al European Heart Card Imaging 2014** found in N=100 patient with CCTA a significant association between PEs and burden of non – calcified plaques
Cer (Ceramides)	**Cheng et Al Atherosclerosis 2015** found association with fraction of necrotic core and lipid burden by NIRS with many Cer 18:1 16:0 in the ATHEROREMO-IVUS population (N=574).
SM (Shingomyelins)	**Fernandez et al Plos One 2013** SM38 species predict cardiovascular events in N= 420 cases.

THE THREE CLASSES MULTIVARIATE ANALYSIS IN SMARTool: BASELINE DATA

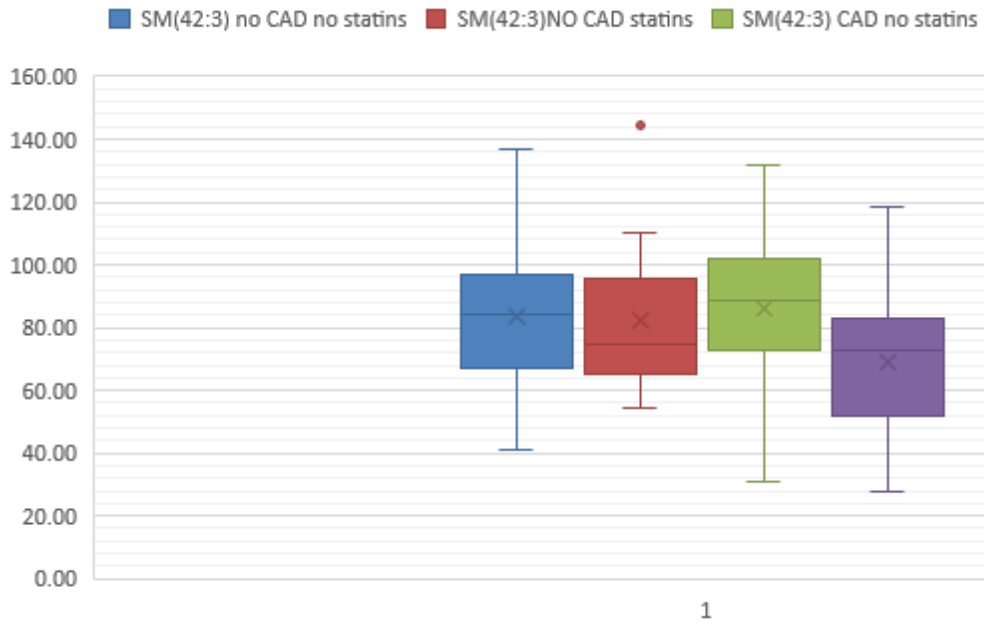
Feature	ANCOVA			
	Class	LDL	Statins	Class*Statins
Cer_d18_1_16_0_	0.025	0.031	0.127	0.920
PC_38_4_	0.046	0.790	0.340	0.507
PS_38_6_	0.019	0.406	0.683	0.255
PS_40_6_	0.029	0.510	0.707	0.079
SM_34_1_	0.011	0.019	0.092	0.196
SM_40_1_	0.038	0.000	0.099	0.232
TG_54_2_	0.01	0.617	0.080	0.075





SMARTool SPHINGOMYELINS AND STATIN USE: FOLLOW UP DATA

Feature	ANCOVA				
	Class	LDL	TG	Statins	Class*Statins
SM_36_2_	0.007	0.009	0.762	0.810	0.019
SM_38_2_	0.002	0.002	0.312	0.339	0.026
SM_42_4_	0.006	0.113	0.091	0.136	0.013
SM_42_3_	0.008	0.020	0.126	0.661	0.007



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ORIGINAL ARTICLE

Lipidomic approach to evaluate rosuvastatin and atorvastatin at various dosages: investigating differential effects among statins

Sandrin C. Bergheanu[a], Theo Reijmers[b], Aeilko H. Zwinderman[c], Ivana Bobeldijk[d], Raymond Ramaker[d], An-Ho Liem[e], Jan van der Greef[b,d], Thomas Hankemeier[b] and J. Wouter Jukema[a]

THE ADDITIVE VALUE OF LIPID CLASSES IN ATS RISK PREDICTION

Stegemann et al reported in the Brunek cohort a strong relationship between TG54:2 and cardiovascular events at 10 years

Cheng et al reported in ATHEROREMO trial an association between Cer18:1 16:0 and lipid burden determined by NIRS

Fernandez et al. showed that SM38 was the only lipid species associated with increased risk of future cardiovascular events.

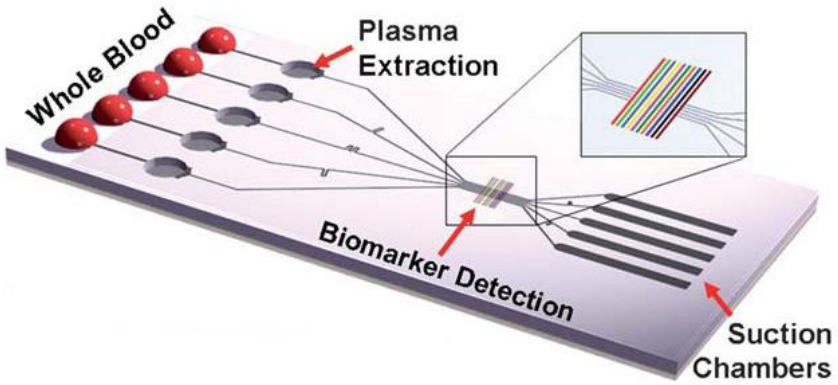
SMARTool is the first longitudinal trial with a double CCTA able to assess association of lipid species with:

- CAD severity
- CAD progression
- CCTA assessed plaque features

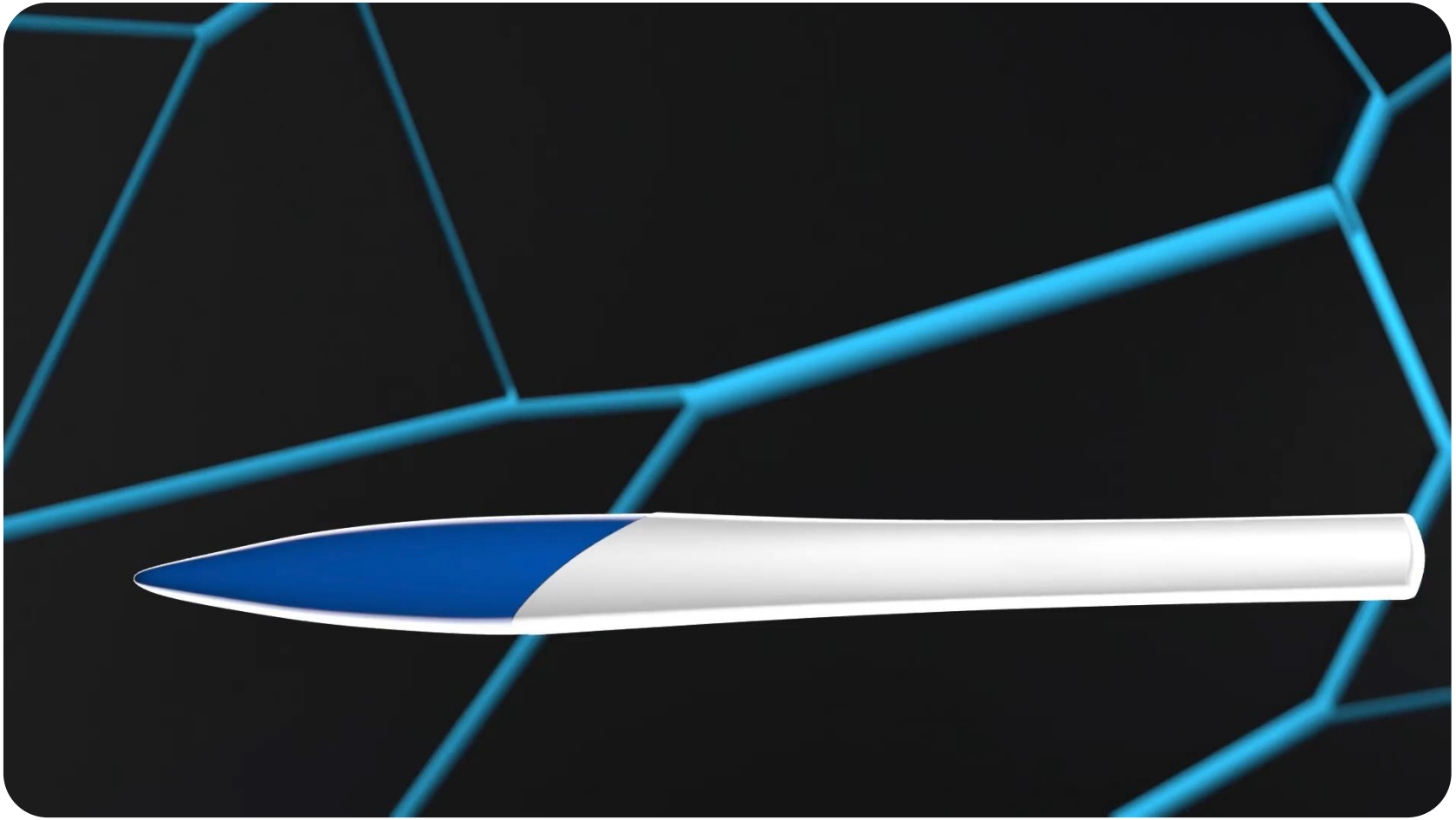
ATS RISK STRATIFICATION AND PREDICTION OF PROGRESSION

Point of Care device in SMARTool: PROOF OF CONCEPT

LAB ON A CHIP



Next generation of POC devices



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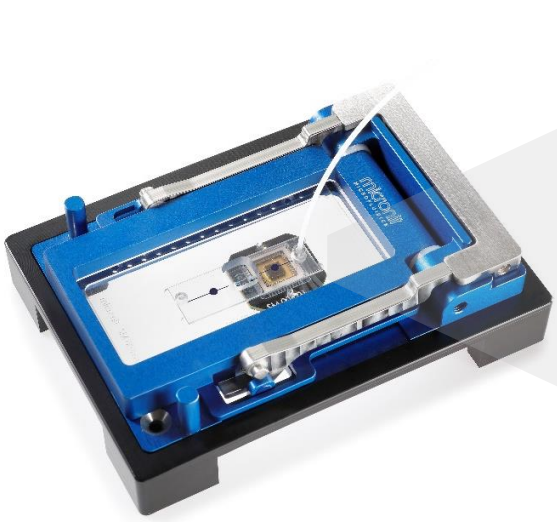
THE DESIGN OF ELISA ON CHIP: ANTIBODY IMMOBILIZATION AND CAPTURE

ELISA on chip for the detection of cardiovascular biomarkers



Antibody immobilization

Surface passivation

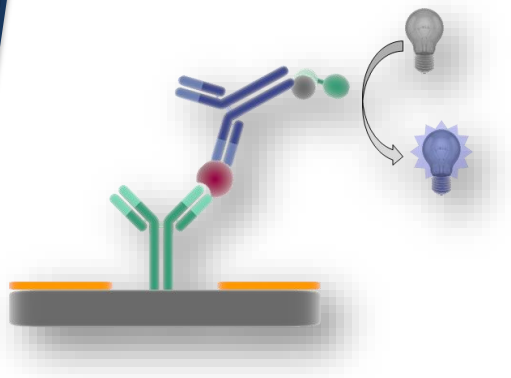
Antigen capture

Detection antibody

Labeling

Detection

Washing



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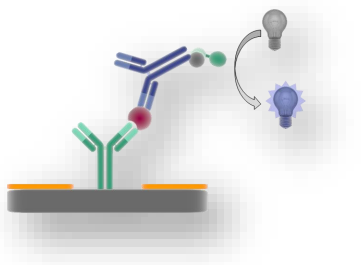
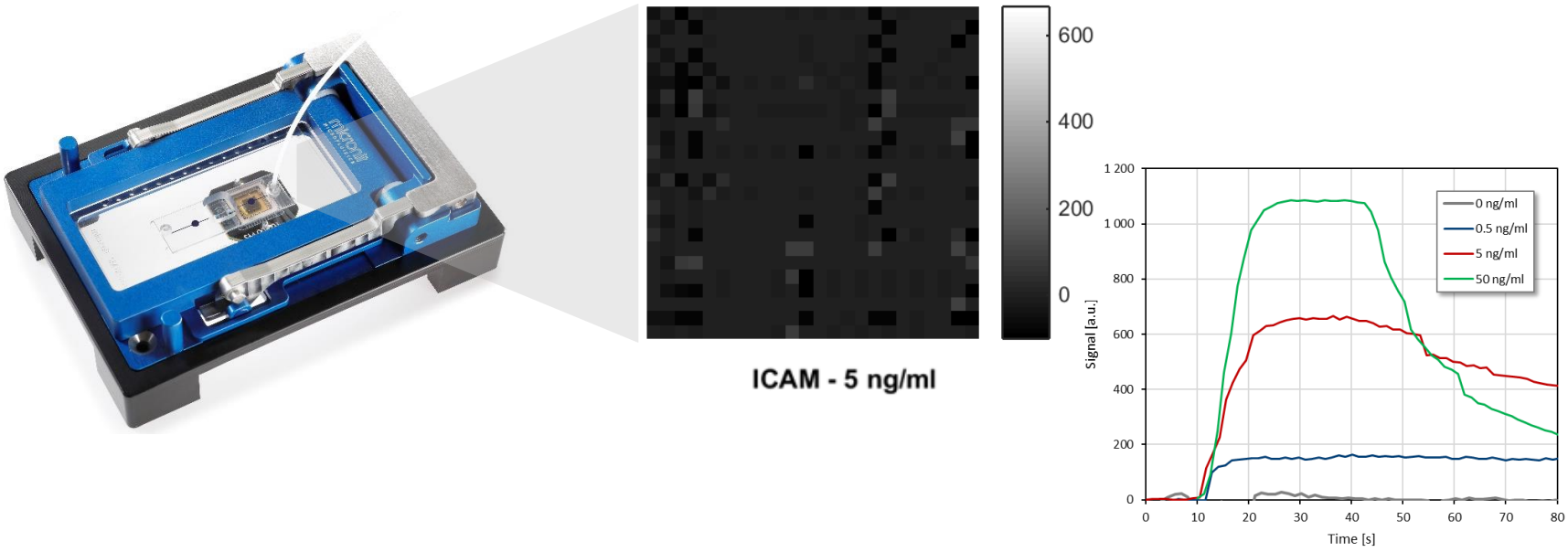
THE DESIGN OF ELISA ON CHIP: DETECTION

ELISA on chip for the detection of CAD-relevant markers with a detection based on chemiluminescence





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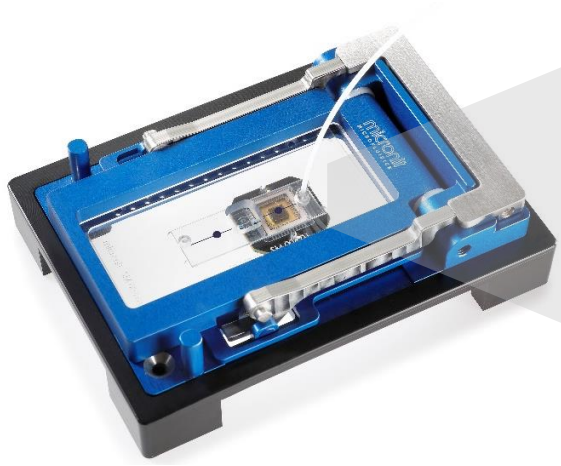
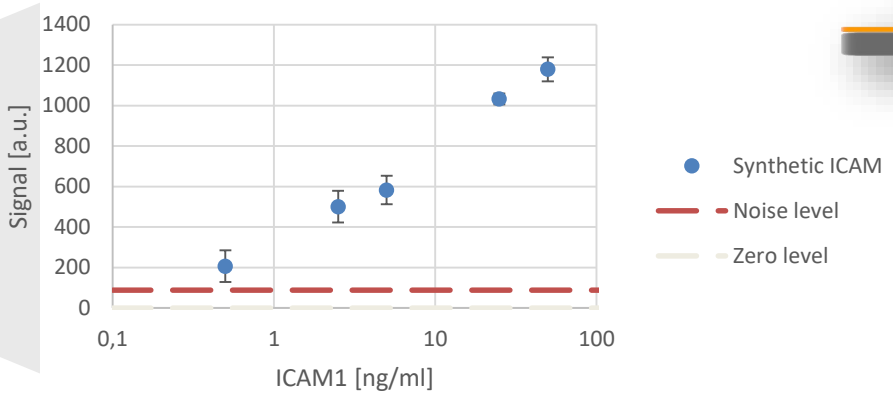
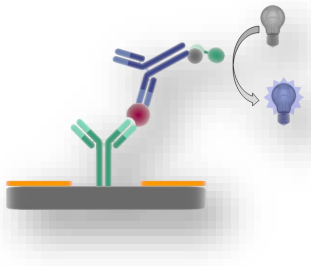
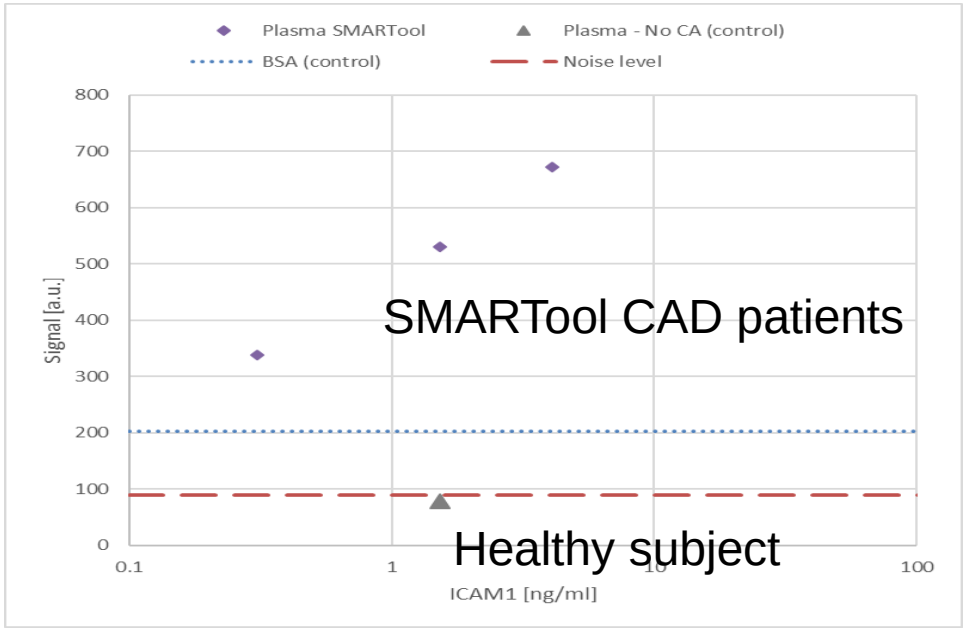
ELISA ON CHIP FOR ICAM-1









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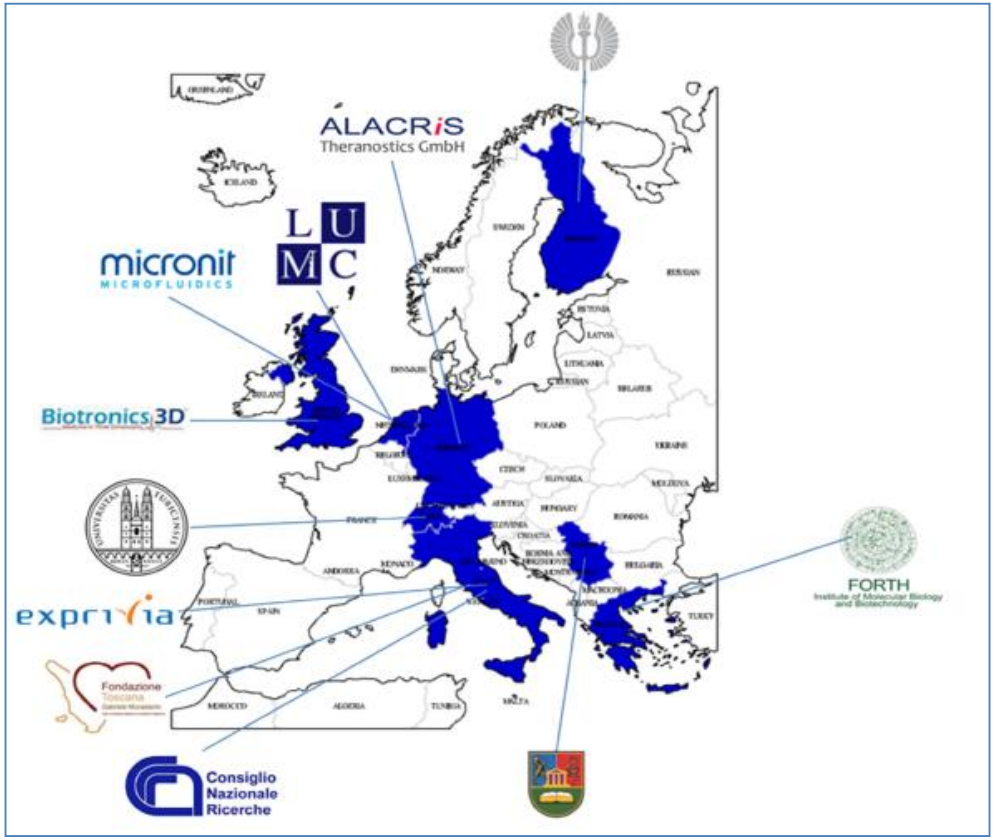
SMARTool

- ✓ SMARTool H2020-project started in 2016 and will end in 2019.
- ✓ The **clinical learning phase** of SMARTool consisted in a clinical trial of a suspected SCAD population, with a previous CTA performed 6-7 years before and biohumoral characterization. CTA was repeated together with an enlarged molecular characterization during SMARTool
- ✓ The **technical learning phase** of SMARTool consists of: (i) the development of a PIM (pre imaging probability) algorithm based on molecular information and assessed by CTA. (ii) The refinement of ARTreat 3D-based models: 3D reconstruction model and plaque growth model prediction refined and assessed by CTA scan pairs in SMARTool. (iii) The development of SMART FFR by CT, validated by ICA. (iv) The development of a virtual angioplasty tool.
- ✓ The **final outcome of SMARTool** is an integrated Decison Support System for CAD patient management in a cloud-enviroment

THANK YOU



This project has received funding from the EU-H2020 Research and Innovation Programme under Grant Agreement N 689068

ANALYSIS OF COVARIANCE – ANCOVA

- The equality of lipids means across the defined groups (class, statins therapy), adjusted for the effect of LDL and triglycerides, was tested using the 1- or 2-way ANCOVA method.

- **ANCOVA** is a general linear model including both ANOVA (categorical) and regression (continuous) predictors:

  - $y_{ij} = \mu + a_i + \beta(x_{ij} - \bar{x}) + \varepsilon_{ij},$
  - $\mathrm{H}_0\colon\ \alpha_1 = \alpha_2 = \cdots = \alpha_K$

y_{ij}: j^{th} observation of the dependent variable in the i^{th} group

x_{ij}: j^{th} observation of the covariate in the i^{th} group

μ: overall mean of the dependent variable

$\bar{x}$: mean of the covariate

a_i: the effect of the i^{th} level of the independent variable

β: slope of the line

ε_{ij}: random disturbances

Main assumptions

- Normality of residuals ε_{ij}
- Linearity of regression
- Homogeneity of regression slopes

Box Plots

- Baseline: Cases vs. Controls