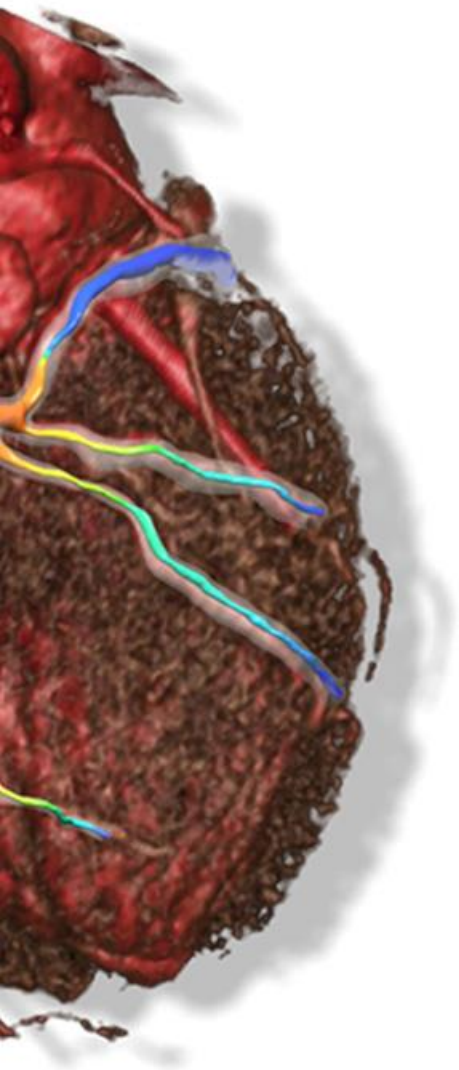
A SMARTool project workshop

CAD RISK PREDICTION AND STRATIFICATION: THE ICT APPROACH



SMARTool Genomics (and transcriptomics) for ATS risk prediction

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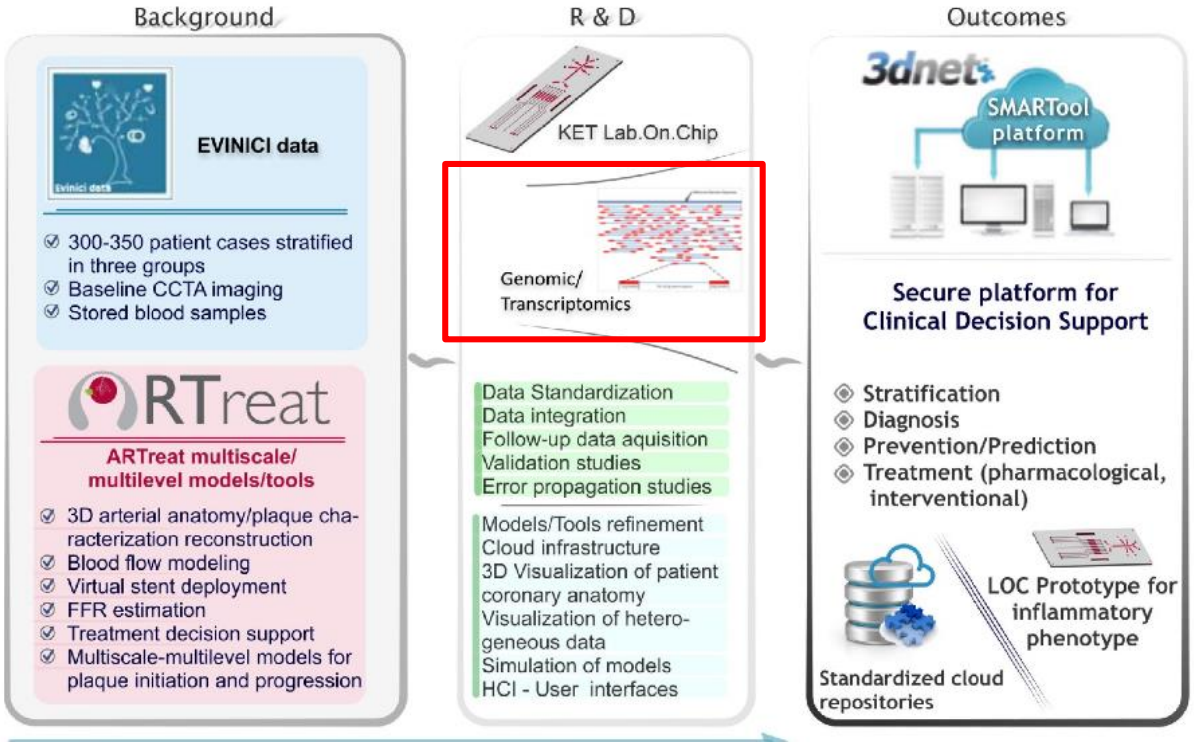
Tuesday 6th November 2018

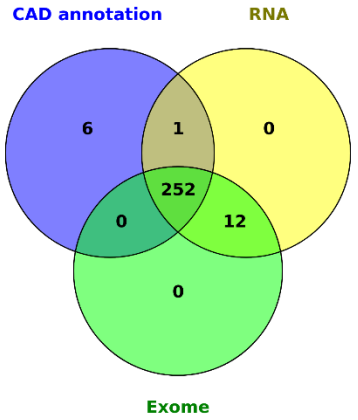
CNR Research Area Campus
Building A, Room 27
via Moruzzi, 1 Pisa - Italy

Horizon 2020
689068

SMARTool Genomics and transcriptomics data set



Exome: 264
RNA: 265
CAD annotation: 259



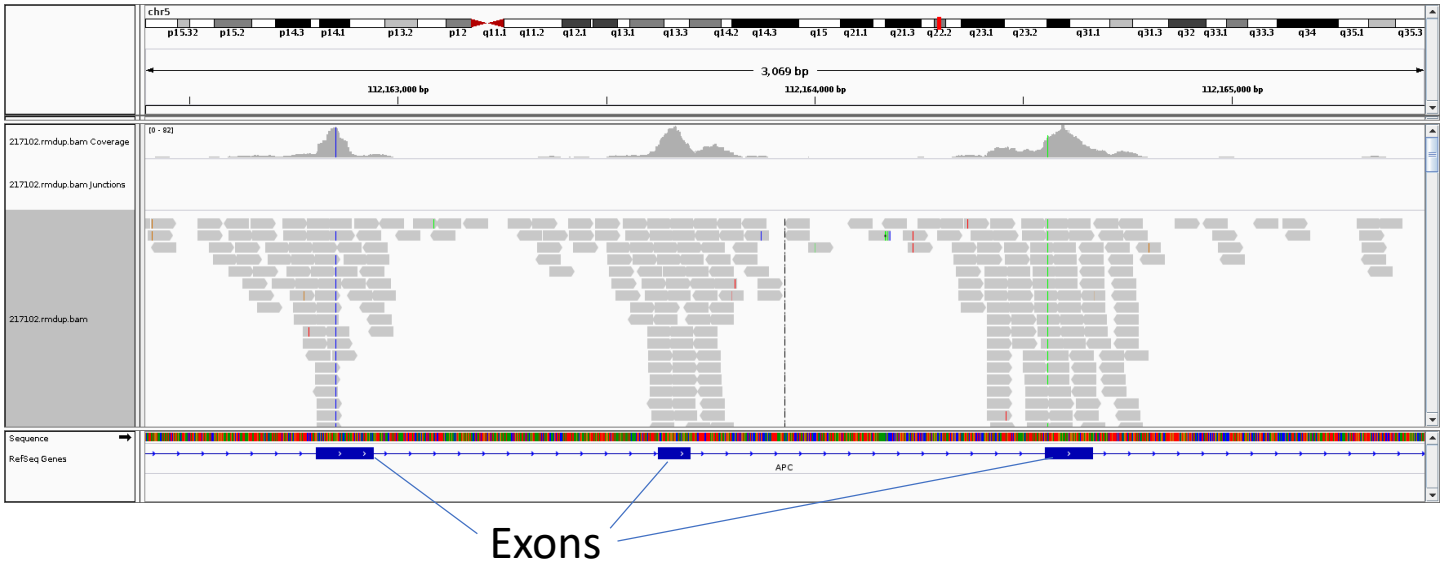
Goal 1: provide curated data as input for stratification algorithm

Goal 2: investigate CAD biology

SMARTool Genomics: Whole-exome sequencing

Coverage of 201,121 targets on 20625 genes, covering a total of 62 Mio bases

Example of coverage on Exons (https://software.broadinstitute.org/software/igv/)



+ Detection of variants (SNPs + indels) in the target regions
+ Copy-number polymorphisms by coverage comparison across the cohort
- Variants outside target regions (e.g. intronic, promoter, regulatory regions)

SMARTool Genomics: Whole-exome sequencing

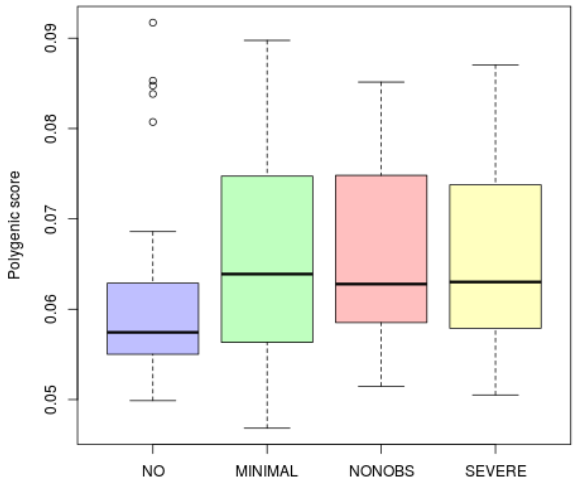
- median number of variants per sample: 29,228
- possible GWAS-type analysis for novel associations (limited by small sample number)

How to use the data for the stratification algorithm?

Polygenic risk score for CAD

Khera 2018, Nat Gen:

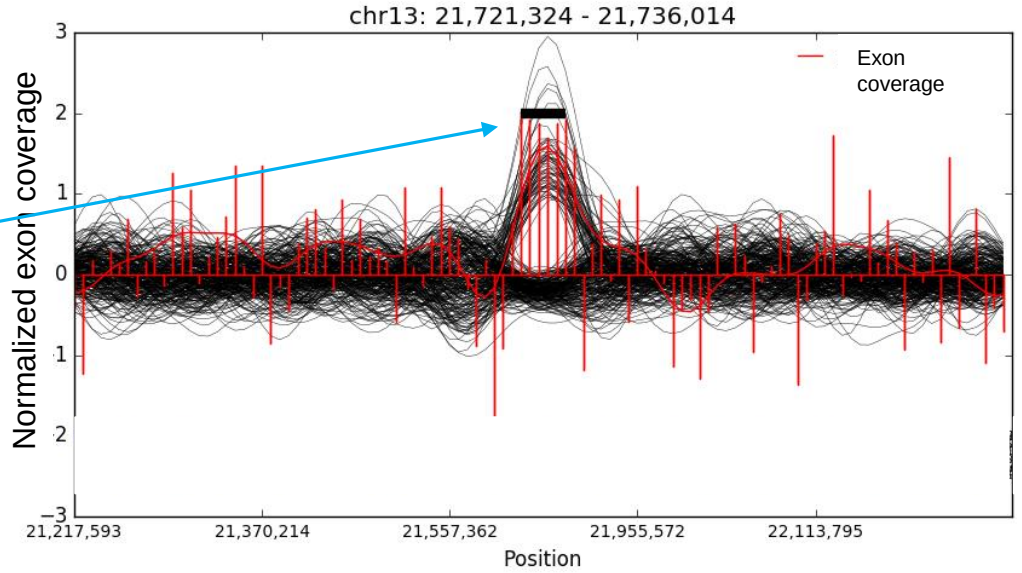
- Providing CAD risk weights for variants
- Cumulative risk as polygenic score



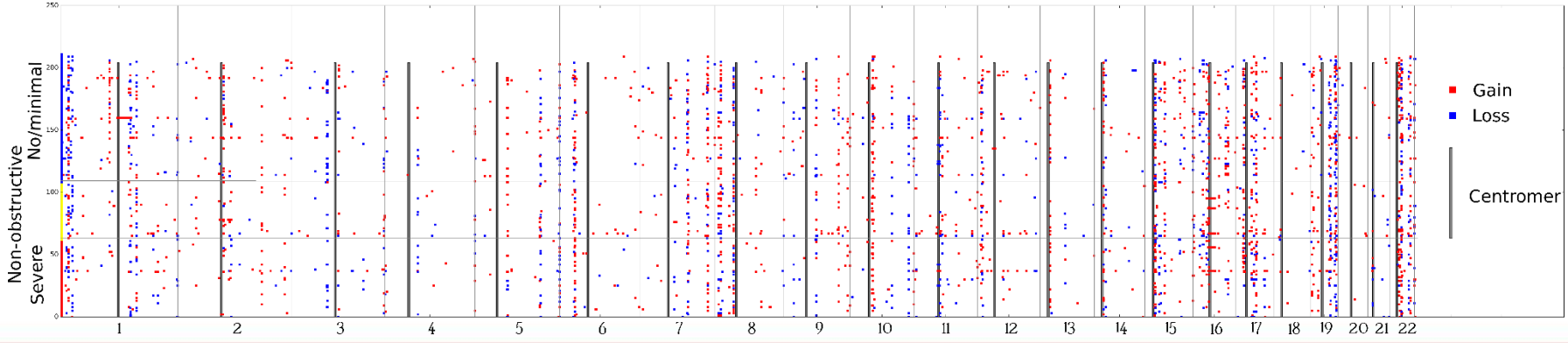
SMARTool Genomics: Copy-number changes

Example:
Conifer analysis

Potential gain



Recurrent chromosomal gains/losses across the SMARTool cohort



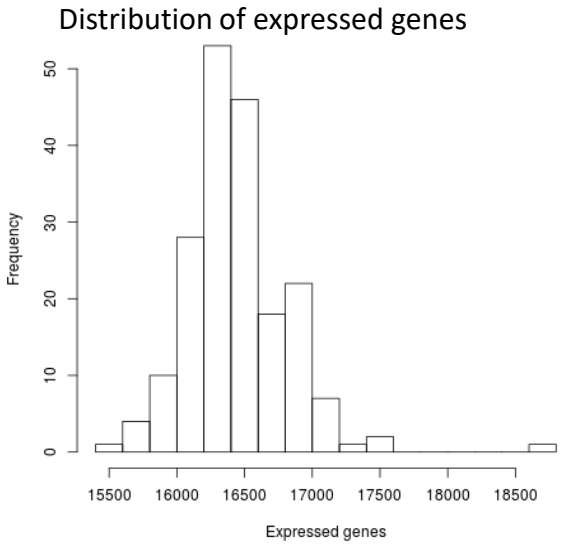
SMARTool transcriptomics data set: RNAseq

RNAseq:

- Higher dynamic range in RNAseq than microarrays
- no probes required, selection by polyA-tails
- gene expression of virtually all coding/long non-coding genes

Types of Analysis:

- gene expression
- differential gene expression
- pathway enrichment/gene signatures



SMARTool transcriptomics data set

Differential gene expression, example of extremes:

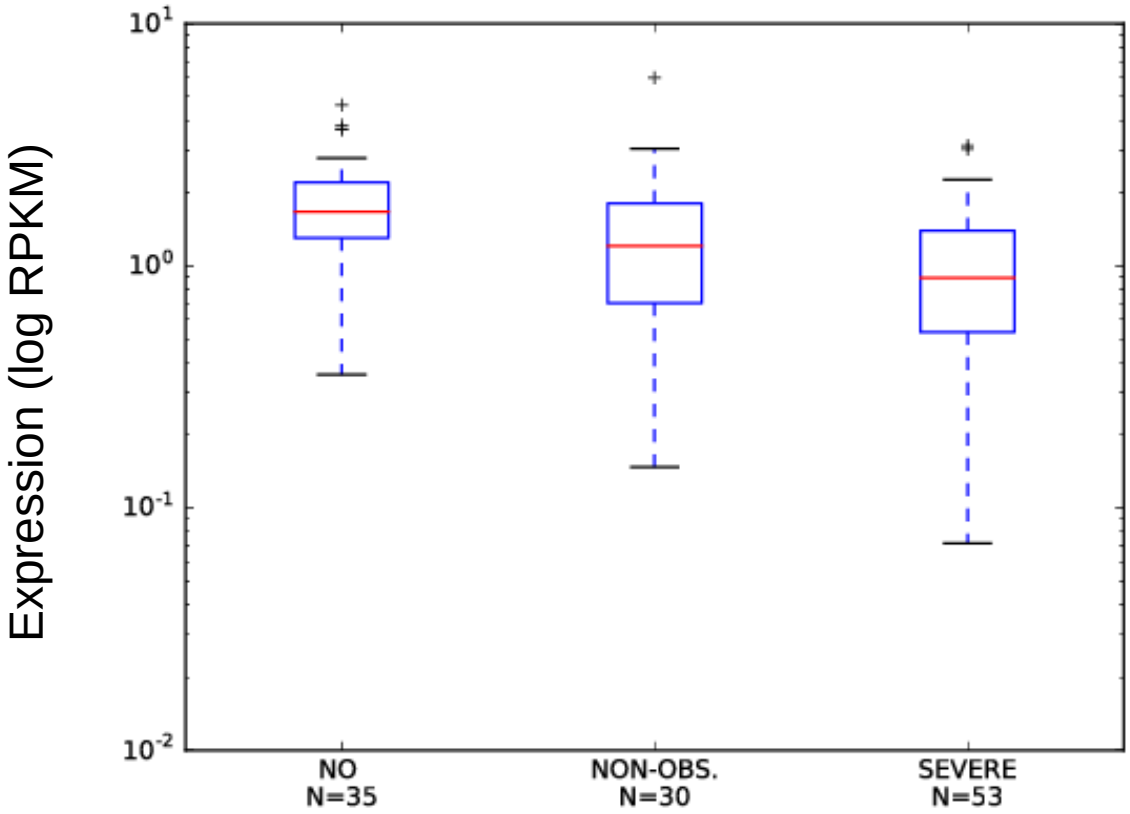
- no CAD (N=35) vs severe CAD (N=53)
- GO enrichment of differentially expressed genes (msigDB)

Enriched in NO CAD (142 Genes)
GO_HUMORAL_IMMUNE_RESPONSE_MEDIATED_BY_CIRCULATING_IMMUNOGLOBULIN
GO_COMPLEMENT_ACTIVATION
GO_ADAPTIVE_IMMUNE_RESPONSE
GO_HUMORAL_IMMUNE_RESPONSE
GO_IMMUNE_RESPONSE
GO_B_CELL_MEDIATED_IMMUNITY
GO_PROTEIN_ACTIVATION_CASCADE
GO_B_CELL_RECEPTOR_SIGNALING_PATHWAY
GO_REGULATION_OF_IMMUNE_SYSTEM_PROCESS
GO_LYMPHOCYTE_MEDIATED_IMMUNITY

Enriched in severe CAD (119 genes)
GO_IMMUNE_SYSTEM_PROCESS
GO_IMMUNE_RESPONSE
GO_DEFENSE_RESPONSE
GO_RESPONSE_TO_BACTERIUM
GO_DEFENSE_RESPONSE_TO_BACTERIUM
GO_RESPONSE_TO_BIOTIC_STIMULUS
GO_DEFENSE_RESPONSE_TO_OTHER_ORGANISM
GO_DEFENSE_RESPONSE_TO_FUNGUS
GO_DISRUPTION_OF_CELLS_OF_OTHER_ORGANISM
GO_ANTIMICROBIAL_HUMORAL_RESPONSE

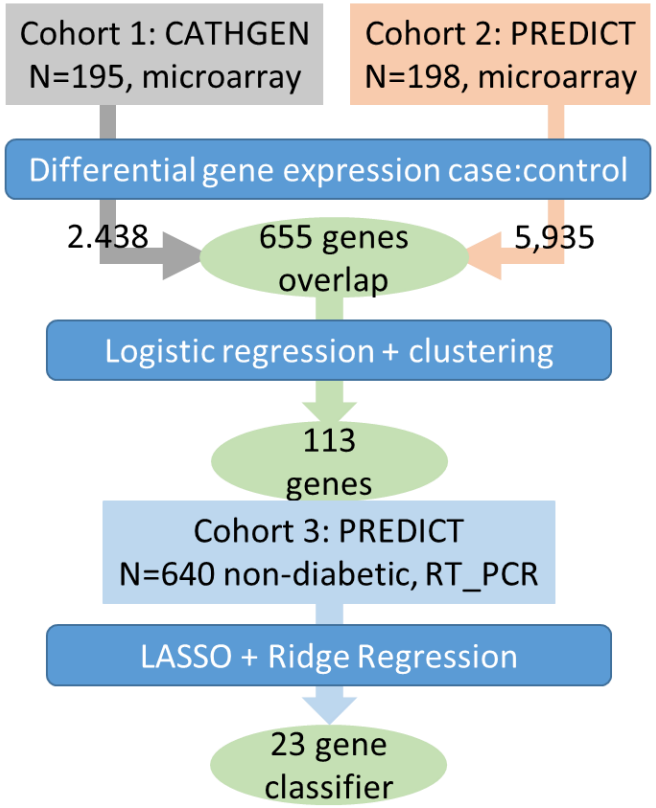
SMARTool transcriptomics data set

Single marker: Example of a gene correlating with disease stage

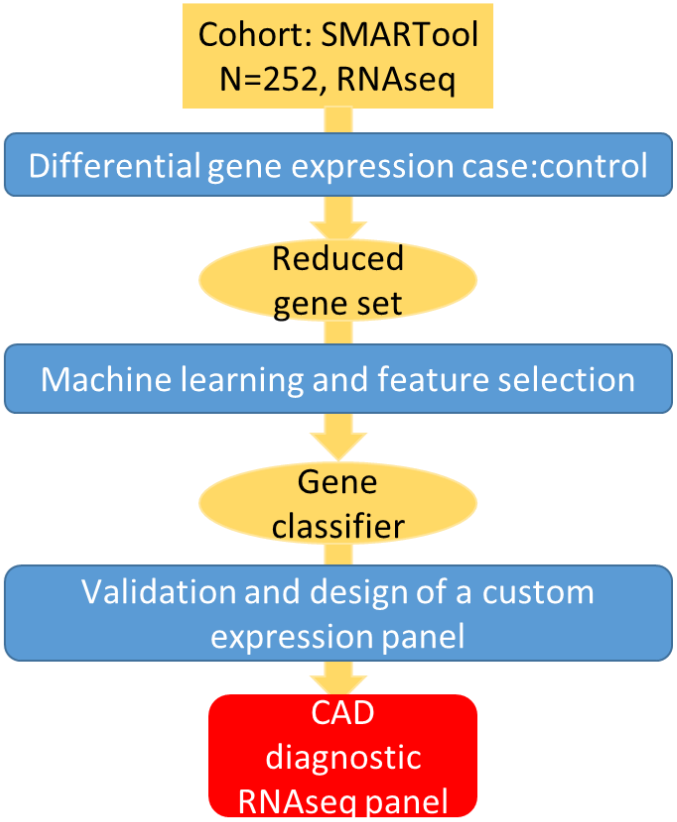


SMARTool transcriptomics data set

CorusCAD (stenosis) – workflow



SMARTool (plaque imaging) – plan



SMARTool: smaller cohort but more genes due to RNAseq

Summary & Outlook

Summary

- Genomic, transcriptomic and clinical data for 252 patients
- Genomic variants and copy-number changes to determine Genetic risk (polygenic score)
- Gene expression analysis for marker genes and altered Pathways/processes

Outlook

- Data will be used in the stratification algorithm
- Development of diagnostic RNAseq panel

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Simulation Modeling of coronary ARTery disease: a tool for clinical decision support

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