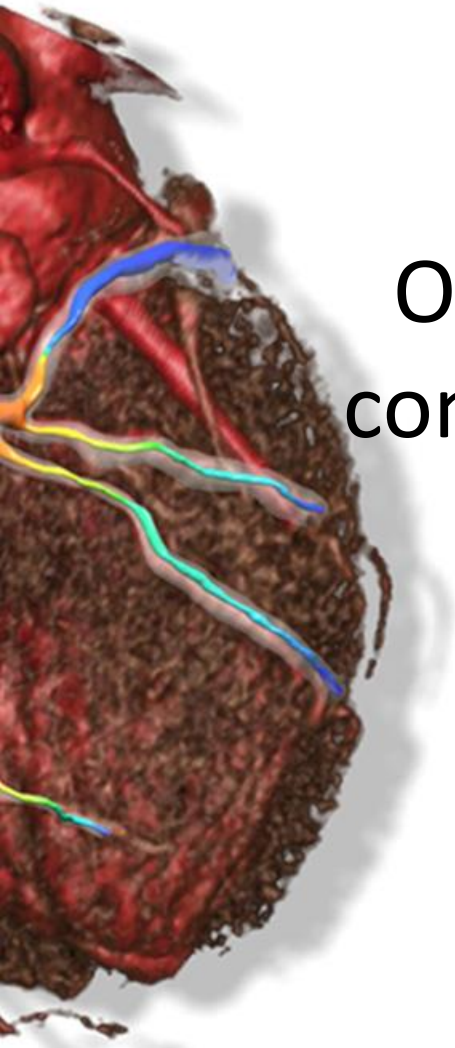
A SMARTool project workshop

CAD RISK PREDICTION AND STRATIFICATION: THE ICT APPROACH



Opportunities and challenges if computerized DSS in personalised medicine

Pál Maurovich-Horvat MD PhD MPH

Semmelweis University, Budapest

Tuesday 6th November 2018

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

Horizon 2020
689068

Key points

- Clinical decision support ensures consistent and appropriate resource utilization
- Big data requires novel statistical approaches to enable correlation of health information across multiple domains
- Healthcare AI needs clean data
- The ultimate goal is to achive better diagnostics and prognostication

Decision support systems

- Overutilization of imaging services can drive up healthcare costs and increase population health risk by causing needless subsequent evaluation of false positive and incidental findings

The goal DSS is to ensure consistent and appropriate resource utilization, thereby optimizing health benefits while reducing costs

- Underutilization can also drive up healthcare costs and cause patient harm by leading to missed diagnoses and delayed treatments

Brink et al. Eur Radiol (2017) 27:3647–3651

Decision support systems

Guiding physicians and even patients to appropriate imaging examination

Reducing variations in descriptions of findings and recommendations (diagnostic testing and therapies).

Combine data of multiple domains to implement precision medicine in daily practice

Brink et al. Eur Radiol (2017) 27:3647–3651

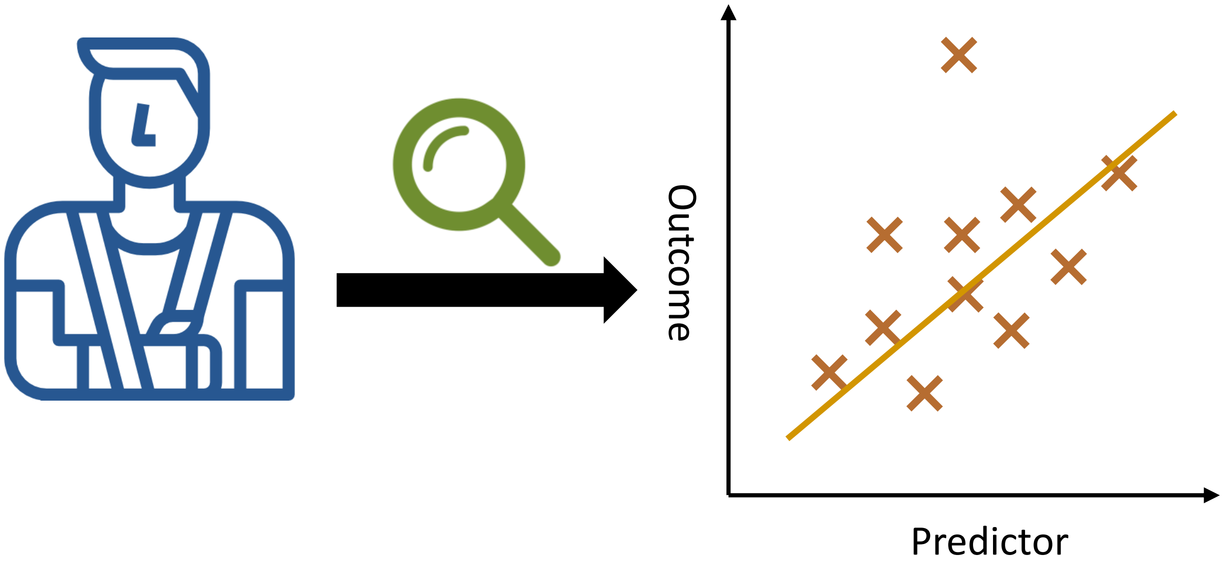
Traditional vs ML methods

- Traditional methods of healthcare decision-support systems required experts to provide the system with rules and guidelines in order to draw conclusions and insights
- With machine learning, we can train the system to deliver cognitive health insights by supplying the data and outcomes (cognitive assistants)

Key points

- Clinical decision support ensures consistent and appropriate resource utilization
- Big data requires novel statistical approaches to enable correlation of health information across multiple domains
- Healthcare AI needs clean data
- All these will allow better diagnostics and prognostication

Prediction currently



<u>Regression</u>

- Small sample sizes
- Few predictors
- Linear associations
- Few outliers

Big data

"Big data goes beyond size and volume to encompass such characteristics as variety, velocity, and with respect specifically to health care, veracity"

- Volume refers to the scale of the data
- Variety refers to the degree to which the data is structured or unstructured
- Velocity refers to the speed at which data is produced and collected
- Veracity refers to the data quality certainty.
- The "big" part of big data refers to volume, variety and velocity.

Big data in health care encompasses a wide range of domains including genomics, proteomics, phenotype information, and the electronic health record and medical imaging, inclusive of radiology, pathology, cytology, and laboratory medicine

Problems with current concepts

- New CVD risk scores with over 400 000 patients[1]
- Digital data is projected to reach 35 zettabytes (35 trillion gigabytes) by 2020, a 44- fold increase from 2009
- Google used 46 864 534 945 data points to predict hospitalization outcomes[2]
- Nonlinear association of BMI with all-cause and cardiovascular mortality[3]
- Transition from population-based to precision medicine[4]

<u>Regression</u>

- ~~Small sample sizes~~
- ~~Few predictors~~
- ~~Linear associations~~
- ~~Few outliers~~

1: Pylypchuk et al. *Lancet, 2018*
2: Rajkomar et al. *Nature Dig Med., 2018*
3: Zaccardi et al. *Diabetologia, 2017*
4: Dainis et al. *JACC Basic Transl Sci., 2018*

The use of AI promises better decision support for medical imaging, precision in diagnosis, and real-time correlation with other medical data

Machine learning and AI technologies can identify complex relations and patterns in data, revealing insights that would otherwise remain hidden.

What is Artificial Intelligence (AI)?

Artificial Intelligence

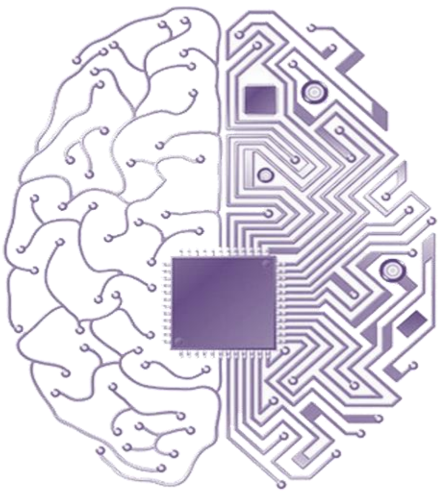
Natural Intelligence

Thinking Humanly	Thinking Rationally
"The exciting new effort to make computers think ... *machines with minds*, in the full and literal sense." (Haugeland, 1985) "[The automation of] activities that we associate with human thinking, activities such as decision-making, problem solving, learning ..." (Bellman, 1978)	"The study of mental faculties through the use of computational models." (Charniak and McDermott, 1985) "The study of the computations that make it possible to perceive, reason, and act." (Winston, 1992)
Acting Humanly	**Acting Rationally**
"The art of creating machines that perform functions that require intelligence when performed by people." (Kurzweil, 1990) "The study of how to make computers do things at which, at the moment, people are better." (Rich and Knight, 1991)	"Computational Intelligence is the study of the design of intelligent agents." (Poole et al., 1998) "AI . . . is concerned with intelligent behavior in artifacts." (Nilsson, 1998)

Stuart Russell, Peter Norvig: *Artificial Intelligence: A Modern Approach, Pearson Pub., 2009*

AI in medical domain

Artificial Intelligence



Input

Thinking

Acting

Natural Language Processing

Computer vision

Knowledge representation

Medical data

Machine learning

Machine learning

Automated reasoning

Robotics

Medical reasoning

Stuart Russell, Peter Norvig: *Artificial Intelligence: A Modern Approach, Pearson Pub., 2009*

Examples of ML in cardiovascular imaging

Input data

Conclusions

Clinical data

Clinical data + ML

Machine-learning Algorithms			
ML: Logistic Regression	**ML: Random Forest**	**ML: Gradient Boosting Machines**	**ML: Neural Networks**
Ethnicity	Age	Age	Atrial Fibrillation
Age	Gender	Gender	Ethnicity
SES: Townsend Deprivation Index	Ethnicity	Ethnicity	Oral Corticosteroid Prescribed
Gender	Smoking	Smoking	Age
Smoking	*HDL cholesterol*	*HDL cholesterol*	Severe Mental Illness
Atrial Fibrillation	HbA1c	Triglycerides	SES: Townsend Deprivation Index
Chronic Kidney Disease	Triglycerides	Total Cholesterol	Chronic Kidney Disease
Rheumatoid Arthritis	SES: Townsend Deprivation Index	HbA1c	*BMI missing*
Family history of premature CHD	BMI	Systolic Blood Pressure	Smoking
COPD	Total Cholesterol	SES: Townsend Deprivation Index	Gender

- Importance of specific parameters are different for ML models
- ML provides a subtle improvement in prediction of cardiovascular events

Algorithms	**AUC c-statistic**
BL: ACC/AHA	0.728
ML: Random Forest	0.745
ML: Logistic Regression	0.760
ML: Gradient Boosting Machines	0.761
ML: Neural Networks	0.764

ML significantly improves accuracy of cardiovascular risk prediction

6: Weng et al. PlosOne, 2017

Examples of ML in cardiovascular imaging

Input data

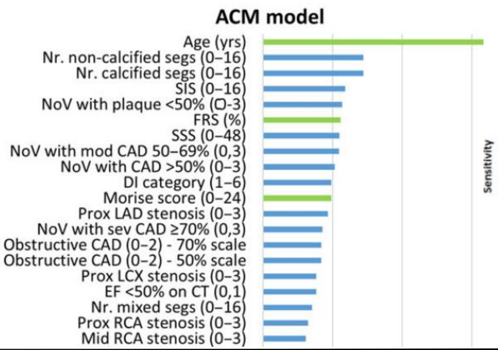
Clinical data

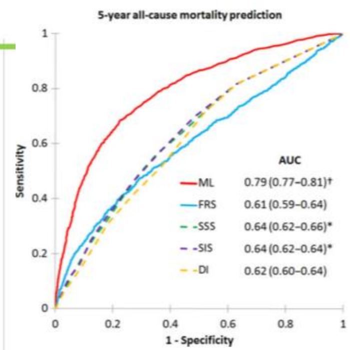
Clinical imaging reports

Conclusions

ML significantly improves accuracy of cardiovascular risk prediction[6]

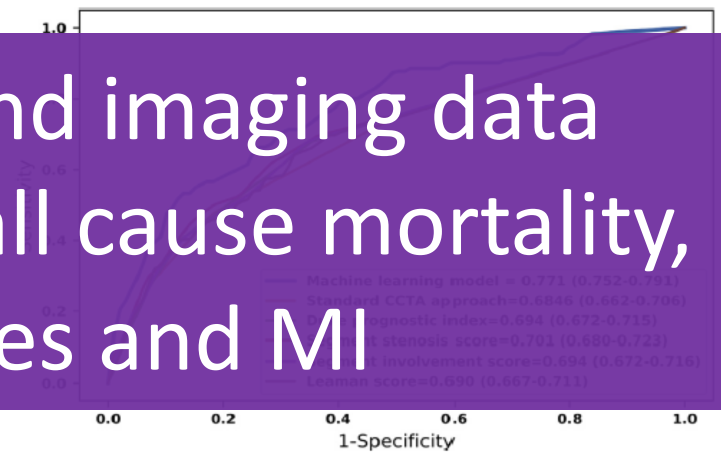
Clinical imaging reports + ML





- ML using clinical CCTA data outperforms existing models for ACM
- ML using clinical and imaging reports outperforms existing models to predict CVD events
- ML based algorithm can improve the integration of CCTA derived plaque information to improve risk stratification.

Rank	Death	RVI	Stroke	RVI	Atrial fibrillation	RVI
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
3	Cardiac troponin-T	0.31	NT-proBNP	0.25	Coronary Artery Calcium score	0.07



ML using clinical and imaging data outperforms 5-year all cause mortality, CVD outcomes and MI

6: Weng et al. *PlosOne, 2017*
7: Motwani et al. *EHJ., 2016*
8: Ambale-Venkatesh et al. *Circ-Res., 2017*
9: van Rosendael et al. *JCCT, 2018*

Examples of ML in cardiovascular imaging

Input data

Clinical data

Clinical imaging reports

Coronary vessels

Conclusions

ML significantly improves accuracy of cardiovascular risk prediction[6]

ML using clinical and imaging data outperforms 5-year all cause mortality[7],CVD outcomes[8] and MI[9]

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7: Motwani et al. *EHJ., 2016*
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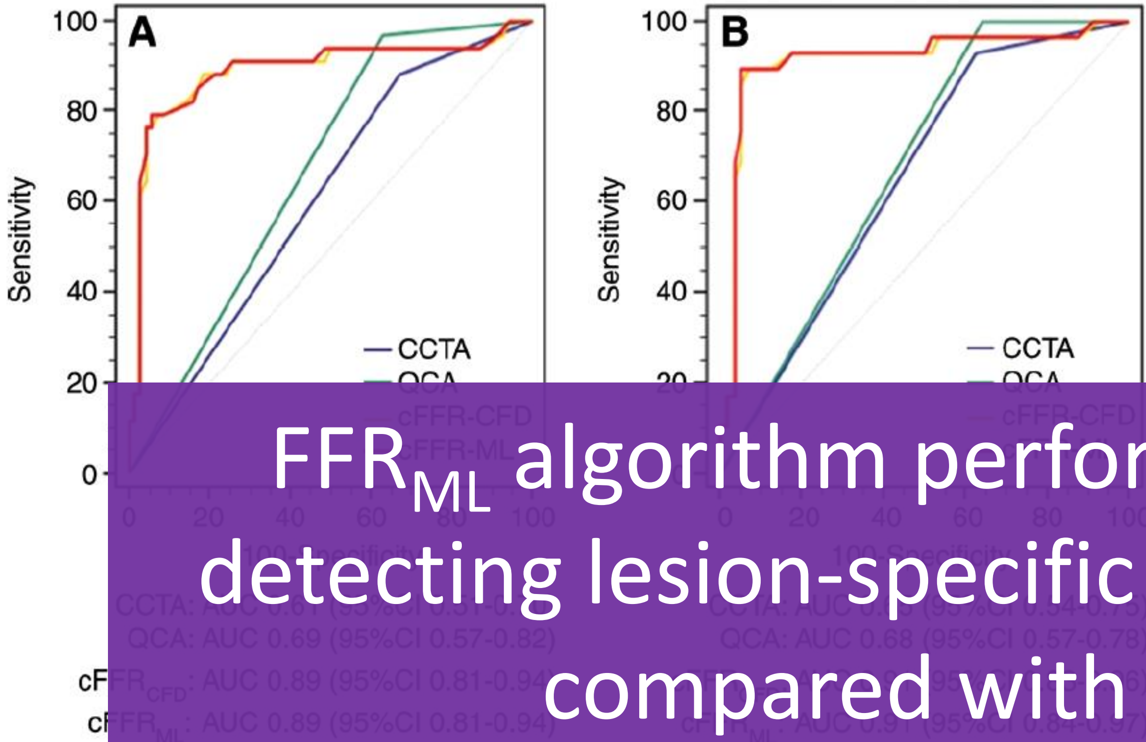
Coronary vessels + ML



- Per-lesion and per-patient level, FFR_{ML} showed a sensitivity of 79% and 90% and a specificity of 94% and 95%, respectively
- Per-lesion and per-patient level, FFR_{CFD} resulted in a sensitivity of 79% and 89% and a specificity of 93% and 93%, respectively

FFR_{ML} algorithm performs equally in detecting lesion-specific ischemia when compared with FFR_{CFD}

6: Weng et al. *PlosOne, 2017*
7: Motwani et al. *EHJ., 2016*
8: Ambale-Venkatesh et al. *Circ-Res., 2017*
9: van Rosendael et al. *JCCT, 2018*
10: Tesche et al. *Radiology, 2018*

Examples of ML in cardiovascular imaging

Input data

Clinical data

Clinical imaging reports

Coronary vessels

Radiomic parameters

Conclusions

ML significantly improves accuracy of cardiovascular risk prediction[6]

ML using clinical and imaging data outperforms 5-year all cause mortality[7],CVD outcomes[8] and MI[9]

FFR_{ML} algorithm performs equally in detecting lesion-specific ischemia when compared with FFR_{CFD}[10]

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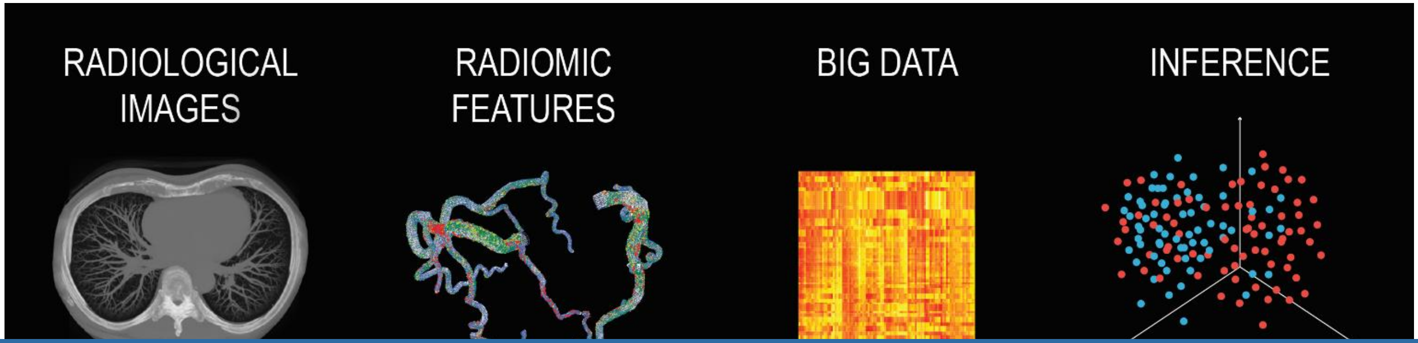
Radiomics

„Radiomics is the process of extracting numerous quantitative features from a given region of interest to create large data sets in which each abnormality is described by hundreds of parameters.”



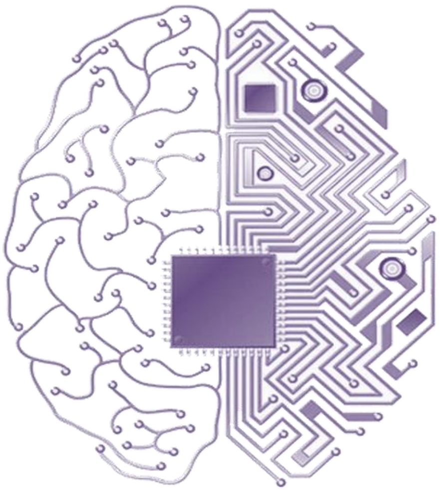
Data mining combined with radiomics, in which images are converted into mineable data and then correlated with genomic, clinical and other data sets for decision support , offers the option to discover new imaging features not detectable through human observation.

Gillies et al. *Radiology 2016*

Kolossváry et al. *Jour Thor Img*. 2018
Kolossváry et al. *Circ Card-Img*. 2017

AI in medical domain

Artificial Intelligence



Input → Thinking → Acting

Medical data

- Natural Language Processing
- Knowledge representation

Machine learning

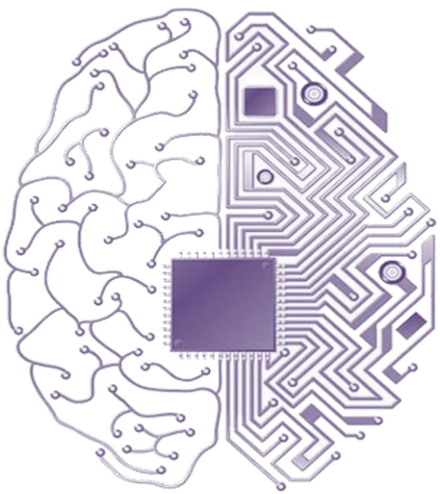
Medical reasoning

- Automated reasoning
- Robotics

Stuart Russell, Peter Norvig: *Artificial Intelligence: A Modern Approach, Pearson Pub., 2009*

AI in medical domain

Artificial Intelligence

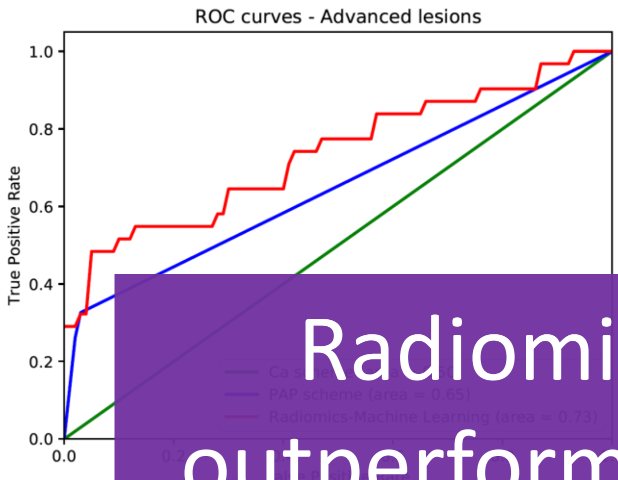


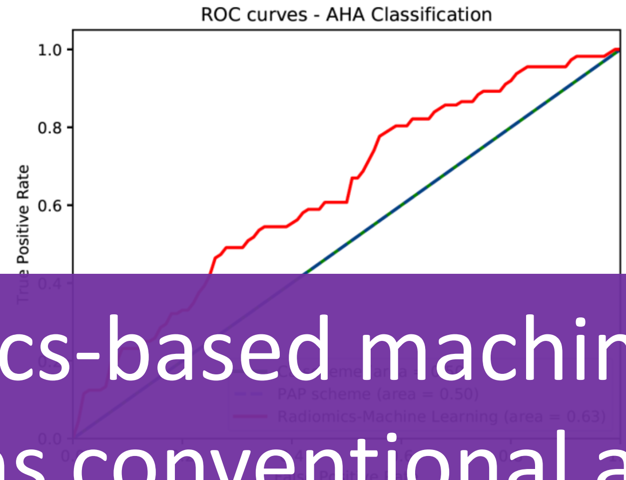
Input → Thinking → Acting

- Natural Language Processing / Computer vision — **Medical image**
- Knowledge representation — **Radiomics**
- Machine learning — **Machine learning**
- Automated reasoning / Robotics — **Medical reasoning**

Stuart Russell, Peter Norvig: *Artificial Intelligence: A Modern Approach, Pearson Pub., 2009*

Radiomics + ML





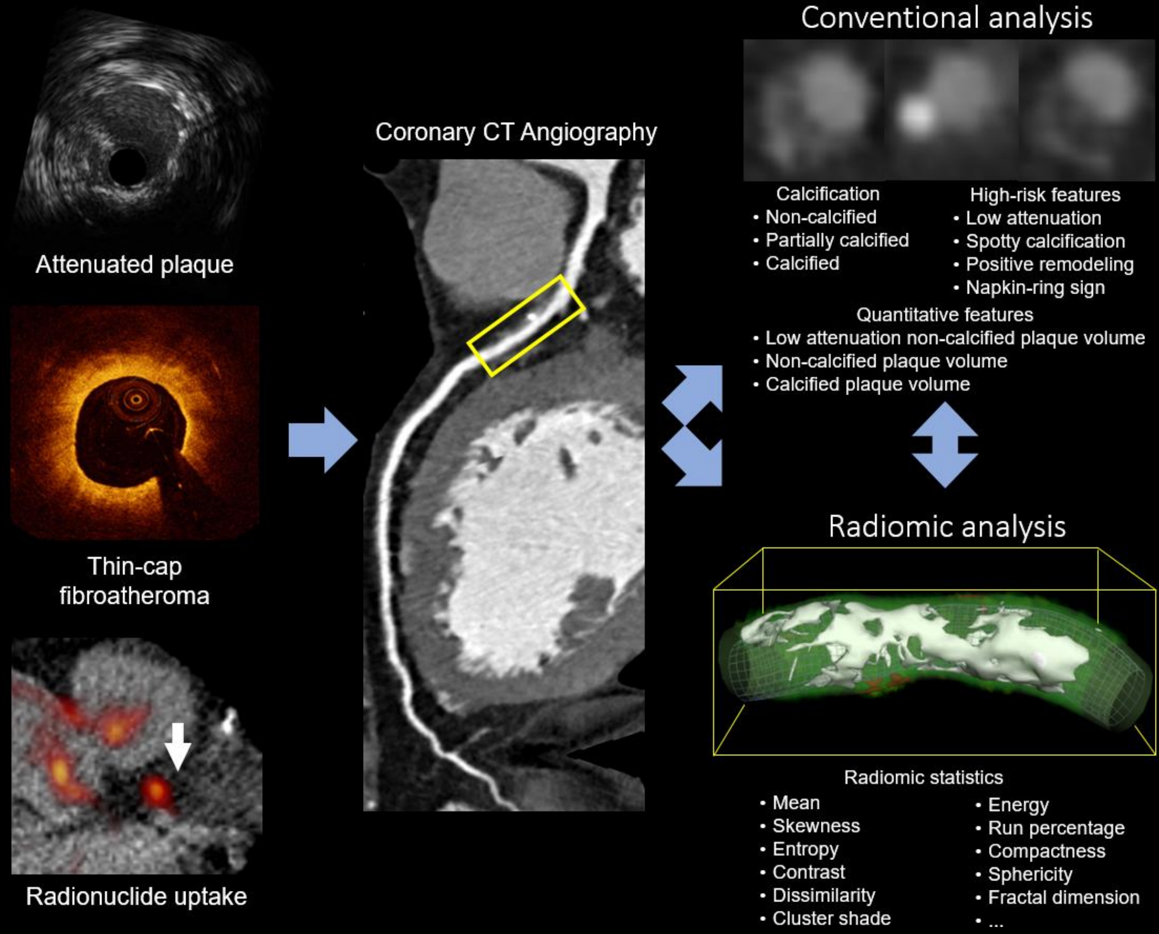
- Radiomics-based machine learning model outperformed traditional and PAP – schemes to identify advanced lesions based-on histology
- Radiomics-based machine learning model can classify coronary CTA cross-sections to the corresponding histological category with moderate accuracy

Radiomics-based machine learning outperforms conventional assessment to identify advanced lesions

Kolossváry, Maurovich-Horvat et al. *Submitted., 2018*

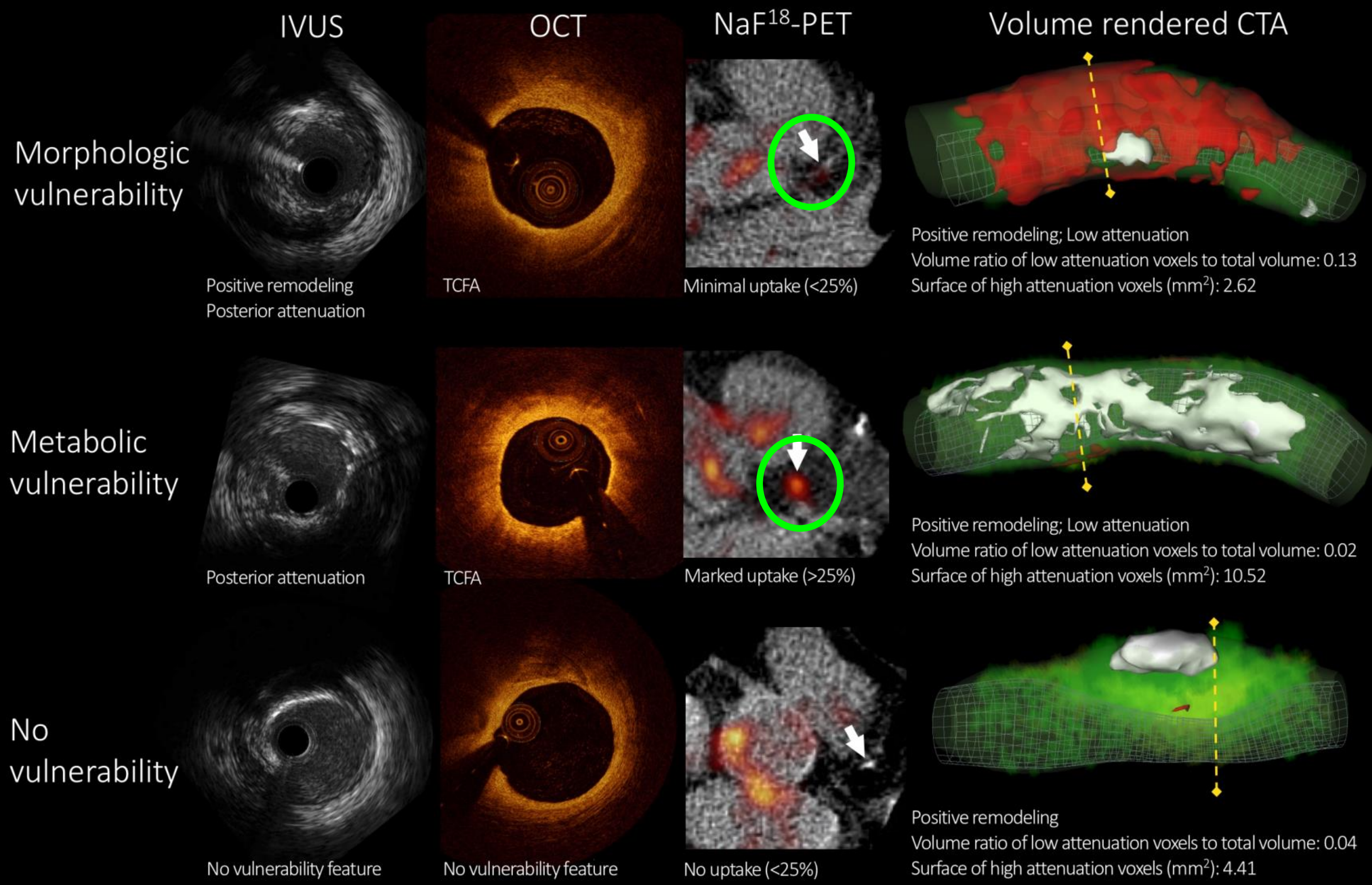
Can CT identify metabolic plaque activity?

Patients (n=25)	
Age (year)	62 [IQR: 59-69]
Male (n, %)	23 (92)
Body mass index (kg/m^2)	25 [IQR: 22-27]
Cardiovascular risk factors	
Hypertension (n, %)	12 (48%)
Diabetes mellitus (n, %)	8 (32%)
Hypercholesterolemia (n, %)	18 (72%)
Current smoker (n, %)	6 (24%)
Lesion Characteristics (n=44)	
Lesion locations	
Left main to LAD (n, %)	34 (77.3)
LCx (n, %)	3 (6.8)
RCA (n, %)	7 (15.9)
Quantitative CT angiography	
Reference vessel diameter (mm)	3.3 [IQR: 2.9-3.6]
Minimal lumen diameter (mm)	1.7 [IQR: 1.4-2.3]
Diameter stenosis (%)	45 [IQR: 33-52]
Lesion length (mm)	11.2 [IQR: 7.9-14.5]



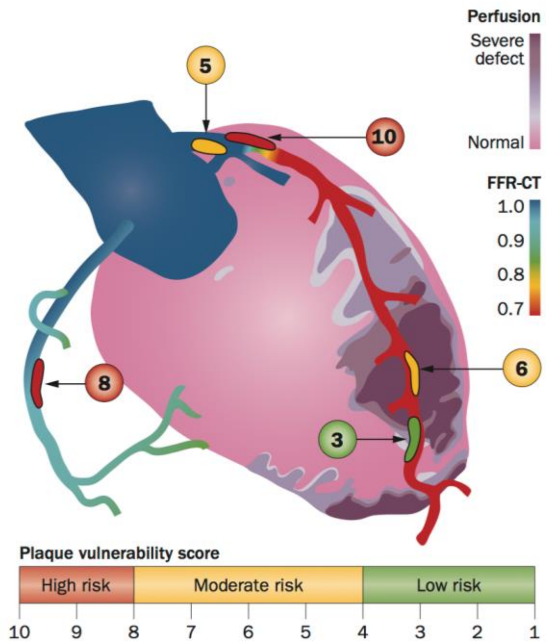
Kolossvary / Park / Lee / Koo / Maurovich-Horvat *submitted*

Metabolic vulnerability ≠ morphologic vulnerability



Kolossvary / Park/ Lee / Koo / Maurovich-Horvat *submitted*

Pan Coronary Vulnerability



1. Luminal narrowing
2. Plaque burden
3. Plaque morphology
4. Ischemic myocardium
5. Lesion specific ischemia
6. Adverse hemodynamic characteristics
7. Metabolic activity

Using AI to achieve precision phenotyping

Maurovich-Horvat P et al, Nature Rev Cardiol. 2014

Key points

- Clinical decision support ensures consistent and appropriate resource utilization
- Big data requires novel statistical approaches to enable correlation of health information across multiple domains
- Healthcare AI needs clean data
- All these will allow better diagnostics and prognostication

Healthcare AI needs clean data

- Healthcare data comes in so many different formats.. medical records are a mess!
- Healthcare AI depends upon clean, organized, and well-categorized data sets, “garbage in, garbage out”
- The data must be verified and dated with the identification of the responsible „owner” and it must be carefully defined and precisely formatted.

Structured and standardized reporting

The electronic health record is replete with inaccurate information, free text, conjecture, and assumptions. The health care vocabulary is imprecise; many terms often considered synonymous, in fact, have definitions that merely overlap

Coronary CTA structured and standardized reporting to generate clean data registry and clinical report

CCTA reporting

NAME
14 CTA

EXAMINATION DATE
11.06.2018 13:52

DATE OF BIRTH	GENDER	WEIGHT	BMI	HEIGHT	KNOWN RISK FACTORS
19.05.1985	male	96 kg	34.0 kg/m²	168 cm	DM DLP

INDICATION
Atypical chest pain.

PATIENT HISTORY
Inconclusive ergomertry (06.04.2018).

EXAM CHARCTERISTICS
Propspectively ECG-triggered, non contrast and contrast enhanced images were acquired of the heart with narrow FOV.

HEARTH RATE	RHYTHM
61/min	Sinus

CA-SCORE
56 equivalent to low cardiovascular risk category (75th percentile).

Scanner type	Siemens Somatom Force
Est. radiation dose	345 mGy x cm
Effective dose	4,83 mSv
Contrast agent	Iomeron 400
Type	95 ml
Quality	Excellent

MEDICATION

Metoprolol per os	Metoprolol iv.	Nitroglycerin sl.
100 mg	5 mg	0.8 mg

COMPLICATIONS
No adverse events were observed.

ANATOMY
Right dominant, normal coronary artery origin and course.

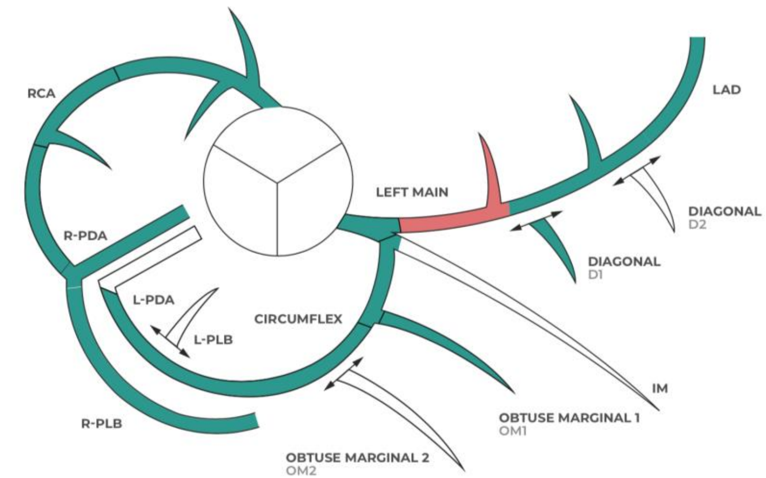
CAD-RADS 4A/V
Severe stenosis. CAD-RADS (TM) Further Cardiac Investigation: Consider ICA or functional assessment. Consider symptom-guided anti-ischemic and preventive pharmacotherapy as well as risk factor modification per guideline-directed care (Fihn et al. JACC 2012). Other treatments (including options of revascularization) should be considered per guideline-directed care (Fihn et al. JACC 2012).

SUMMARY
midLAD severe stenosis.

RECOMMENDATION
Intensified statin therapy and invasive coronary angiography is recommended.

Yours sincerely,

Dr. Pál Maurovich-Horvat



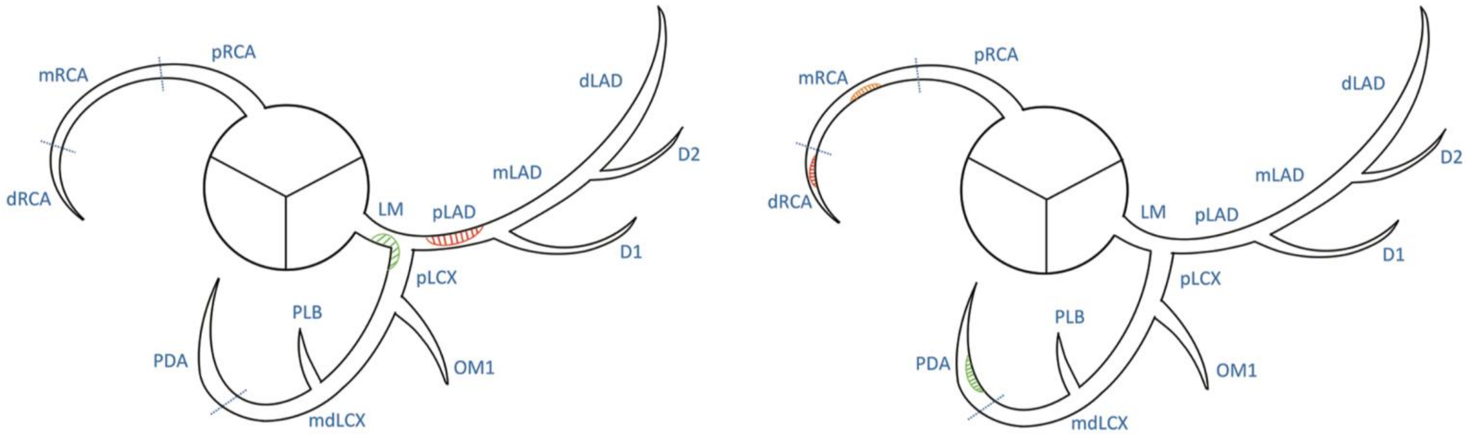
LM	NORMAL	0% No stenosis
pLAD	PLAQUE	70-99% Severe. *Partially calcified, positive remodeling, low attenuation*
mLAD	NORMAL	0% No stenosis
dLAD	NORMAL	0% No stenosis
Diag1	NORMAL	0% No stenosis
pLCX	NORMAL	0% No stenosis
mdLCX	NORMAL	0% No stenosis
OM1	NORMAL	0% No stenosis
pRCA	NORMAL	0% No stenosis
mRCA	NORMAL	0% No stenosis
dRCA	NORMAL	0% No stenosis
pdaRCA	NORMAL	0% No stenosis
plbRCA	NORMAL	0% No stenosis

CARDIAC MORPHOLOGY
The morphology of the valves are normal. The sizes of all cardiac chambers are normal. No abnormalities are visible in the myocardium and in the pericardium.

EXTRACARDIAC FINDINGS
No pathological lymph nodes are visible in the mediastinal and hilar regions. Normal lung parenchyma is visible in the scan volume.

DSS in coronary CTA reporting

Patient 1 | **Patient 2**



Patient 1

Plaque 1:	LM	Severe (70-99%)	Non-calcified
	pLCX	Mild (25-49%)	Partially calcified
Plaque 2:	pLAD	Severe (70-99%)	Partially calcified

Patient 2

Plaque 1:	PDA	Moderate (50-69%)	Calcified
Plaque 2:	mRCA	Moderate (50-69%)	Partially calcified
Plaque 3:	dRCA	Severe (70-99%)	Calcified

Patient 1

SSS = 7
SIS = 3
SSSi = 0.5
SISi = 0.21
3-vessel score = 2
Duke index = 100
CONRIFM score = 1.5% annual mortality (high)
Leaman score = 16.56
SYNTAX score = 20

Patient 2

SSS = 7
SIS = 3
SSSi = 0.5
SISi = 0.21
3-vessel score = 2
Duke index = 37
CONRIFM score = 0.7% annual mortality (low)
Leaman score = 1
SYNTAX score = 2

Kolossvary et al. Cardiovascular Diagnosis and Therapy 2017

CAD-RADS for acute chest pain
Coronary Artery Disease Reporting and Data System

	Degree of maximal coronary stenosis	Interpretation
CAD-RADS 0	0%	ACS highly unlikely
CAD-RADS 1	1-24%	ACS highly unlikely
CAD-RADS 2	25-49%	ACS unlikely
CAD-RADS 3	50-69%	ACS possible
CAD RADS 4	**A** – 70-99% or **B** – Left main >50% or 3-vessel obstructive disease	ACS likely
CAD-RADS 5	100% (Total occlusion)	ACS very likely

Modifiers

First	**modifier N (non-diagnostic)**
Second	**modifier S (stent)**
Third	**modifier G (graft)**
Fourth	**modifier V (vulnerability)**

Modifier vulnerability

Positive remodeling

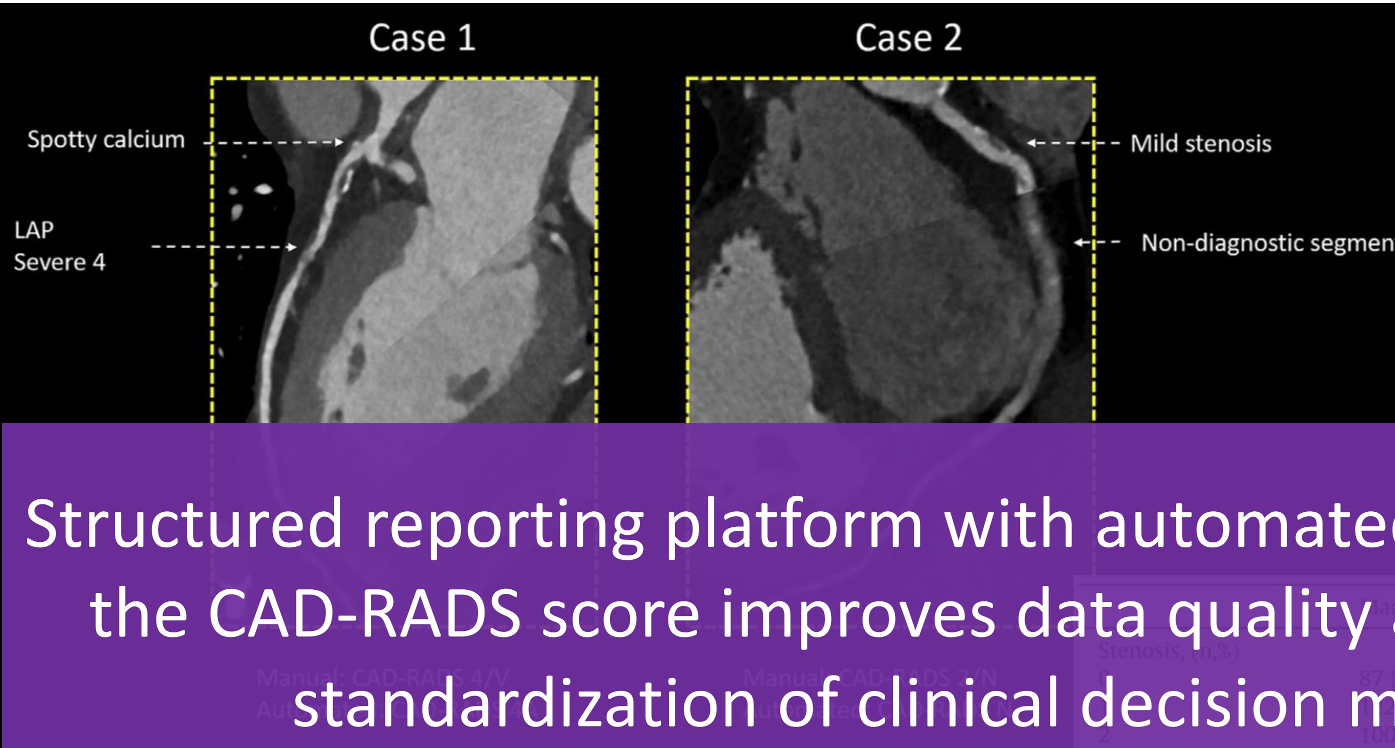
Low attenuation (<30 HU)

Spotty calcium

Napkin-ring sign

Cury et al. JCCT 2016

Structured reporting platform improves CAD-RADS assessment



Structured reporting platform with automated calculation of the CAD-RADS score improves data quality and supports standardization of clinical decision making.

	Manual	Automated	p value
Stenosis, (n,%)			0.008
0	87 (17.4)	90 (18.0)	
[illegible]	[illegible]	114 (22.8)	
2	100 (20.0)	93 (18.6)	
3	58 (11.6)	61 (12.2)	
4A	32 (6.4)	49 (9.8)	
4B	3 (0.6)	5 (1.0)	
5	19 (3.8)	25 (5.0)	
Non-existing	23 (4.6)	0 (0.0)	
N, (n,%)	75 (15.0)	86 (17.2)	0.027
S, (n,%)	30 (6.0)	46 (9.2)	<0.001
V, (n,%)	59 (11.8)	77 (15.4)	0.001
G, (n,%)	9 (1.8)	12 (2.4)	0.250

Szilveszter et al. JCCT 2017

Key points

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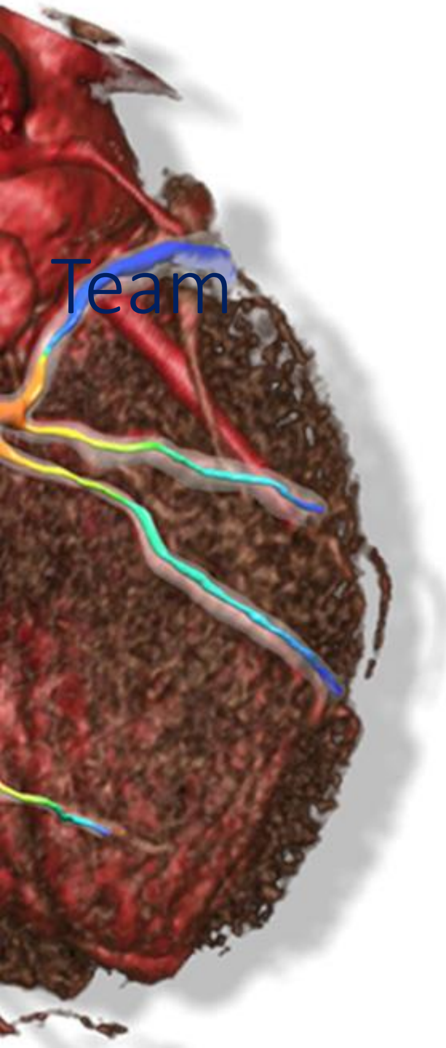
A SMARTool project workshop

CAD RISK PREDICTION AND STRATIFICATION: THE ICT APPROACH

Thank you!



Team

Tuesday 6th November 2018

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

Horizon 2020
689068

CIRG
Cardiovascular Imaging Research Group

GLOBAL Study

- Primary and secondary prevention of cardiovascular disease remains a significant medical and societal challenge.
- Personalized preventive strategies are needed (e.g.: biomarkers, imaging).
- Lack of biomarkers for atherosclerosis.
  - There are markers for intermediate phenotypes and prognostic markers, but no diagnostic biomarkers for atherosclerotic plaques.

Voros, Maurovich-Horvat et al. J Cardiovasc Comput Tomogr 2014:8(6); 442–451.

G3: The Platform

Clinical Study to Big Data to Biomarkers and Targets

G3's "GLOBAL" CLINICAL STUDY
7,500 Subjects

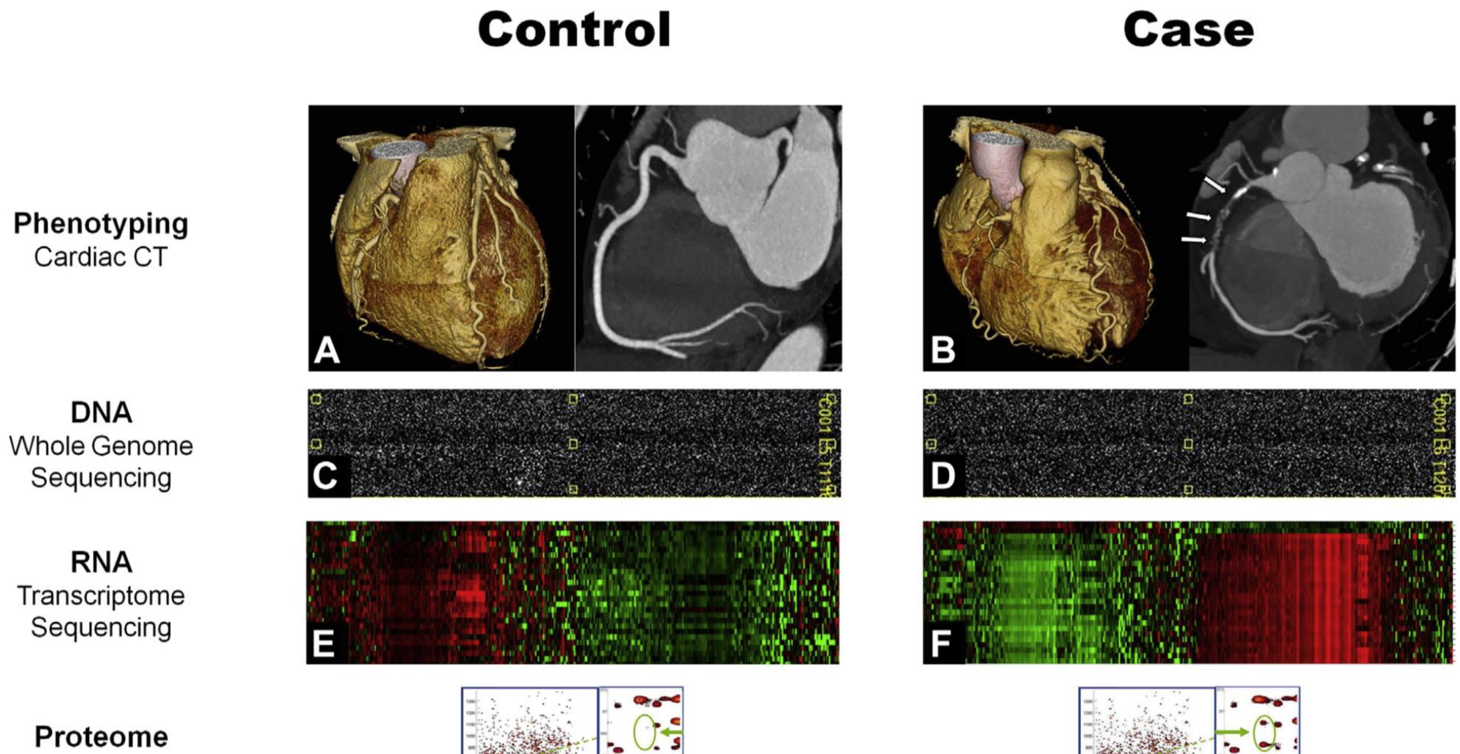
SPECTRUM OF CORONARY DISEASE

Controls: ~3500 Subjects	Cases: ~4000 Pts

BIG DATA: 22 TRILLION DATA-POINTS

Voros, Maurovich-Horvat et al. J Cardiovasc Comput Tomogr 2014:8(6); 442–451.

Patient level vulnerability



DSS utilizing AI will incorporate multiomic data to achieve personalized risk prediction

Voros S, Maurovich-Horvat P et al, JCCT 2014