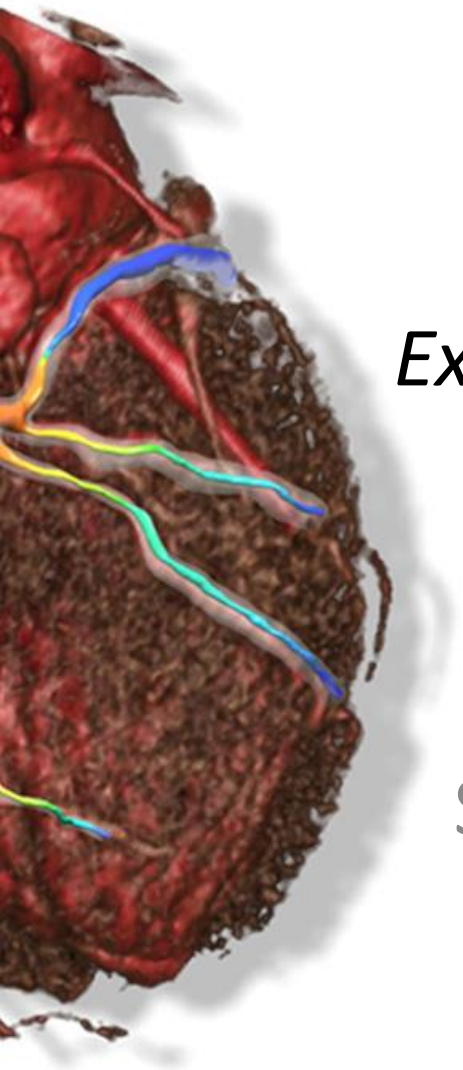
A SMARTool project workshop

CAD RISK PREDICTION AND STRATIFICATION: THE ICT APPROACH



Expected clinical and health-economics impact of DSSs in CAD

G. Pelosi, M.D.

SMARTool Scientific Manager

Tuesday 6th November 2018

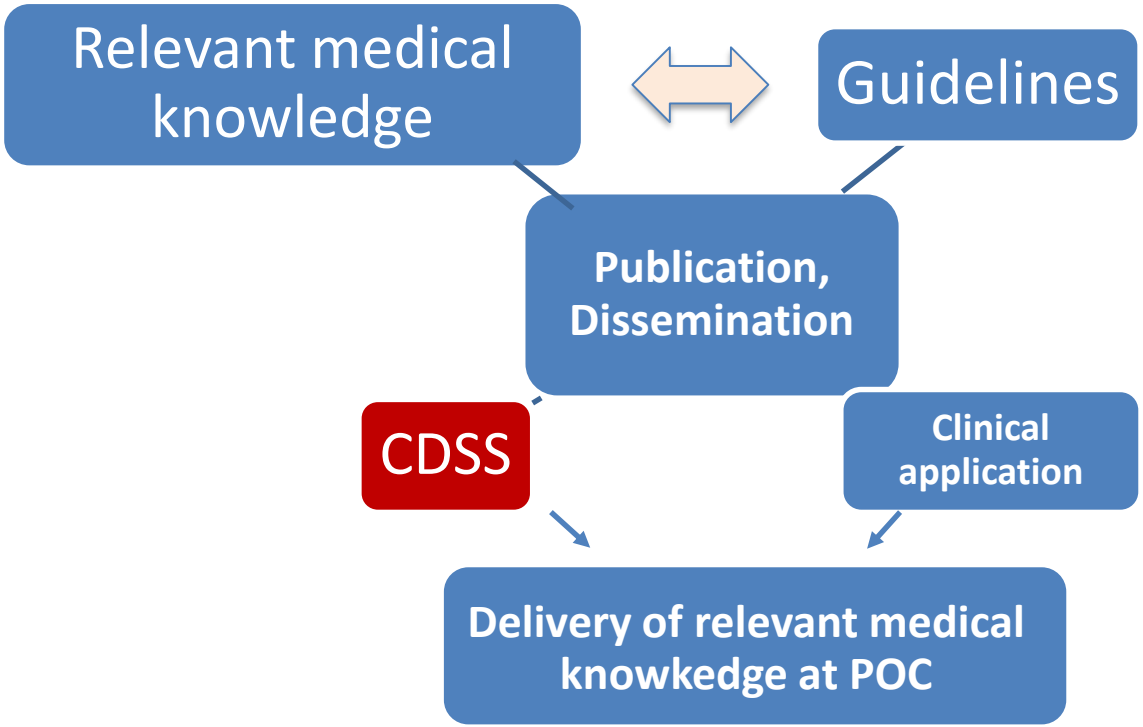
CNR Research Area Campus
Building A, Room 27
via Moruzzi, 1 Pisa - Italy

Horizon 2020
689068

Clinical Computerised Decision Support Systems

Clinical Computerised Decision Support Systems (CDSS) is a technology that provides patient-specific medical knowledge at the point of need.

> *"Clinical decision support systems (CDSS) link health observations with health knowledge to influence health choices by clinicians for improved health care"*
> *Robert Hayward (Centre for Health Evidence)*



CDSS and machine learning

Quantitative risk prediction in medicine has been based on classical statistical learning from structured data sources.

Currently, according to P4 (Predictive, Preventive, Personalized, Partecipatory) Medicine, Artificial Intelligence applications are overtaking conventional guidelines-based DSS.

"Will the incremental improvements in discriminative performance demonstrated in machine learning research will ultimately drive a major shift in clinical care ? "

Shah et al, JAMA. 2018 Jul 3;320(1):27-28

Factors driving the adoption of AI and deep learning in CDSS

- Adaptability of deep learning to analysis of heterogeneous data
- Rapid-diffusion of open-source deep learning programs
- Strengths of digital imaging over human interpretation
- Digitization of health-related records and data sharing
- Adequacy of today's basic deep learning technology to deliver improved performance as data sets get larger.

Naylor CD, JAMA. 2018 Sep 18;320(11):1099-1100

Challenges in CDSS adoption

Why do clinical decision support systems designed for direct interactive use by clinicians have challenges of credibility and adoption when the literature has demonstrated a diagnostic accuracy that rivals the performance of expert clinicians?

Shortliffe E and Sepulveda M JAMA Nov.2018

Main reasons for not adopting CDSS

- **Lack of trust-worthy evidence.**
- **Mismatch with routine medical decision-making processes**
- **Lack of transparency on how output decisions are made**

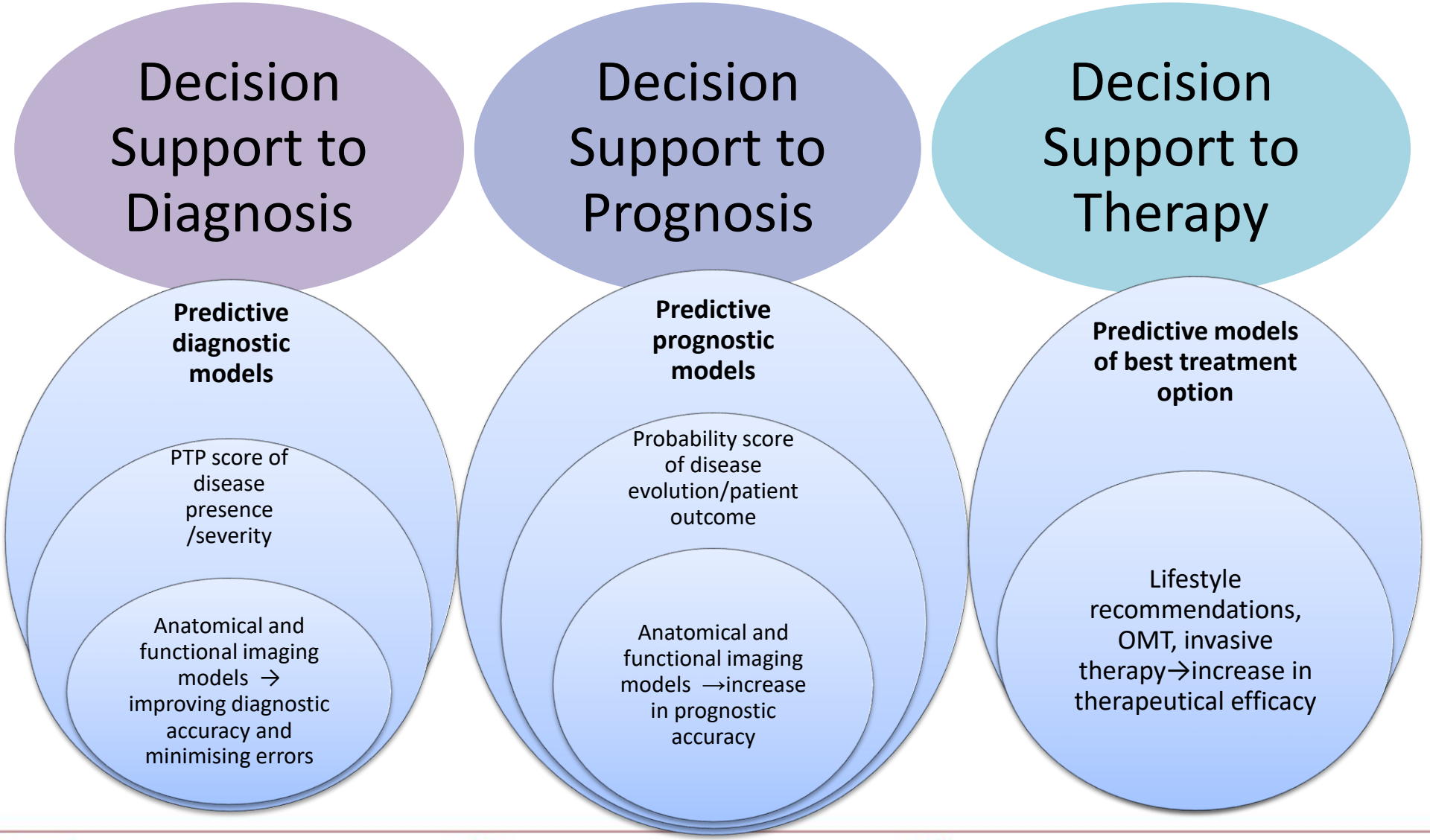
- **Limitation of medical user's autonomy**
- **Environmental, clinical, and social constraints of clinical practice not included**
- **Tacit clinical knowledge not included**

Success factors for clinical application of CDSS

- **Transparency** → A CDSS requires transparency so that users can understand the basis for any advice or recommendations that are offered.
- **Efficiency** → A CDSS should be efficient in terms of time requirements and must blend into the workflow of the busy clinical environment.
- **Easy to use** → A CDSS should be intuitive and simple to learn and use so that major training is not required and it is easy to obtain advice or analytic results.
- A CDSS should reflect an understanding of the **pertinent domain** and the kinds of questions with which clinicians are likely to want assistance.
- A CDSS should offer advice in a way that recognizes the expertise of the user, it is designed to **inform and assist but not to replace a clinician**.
- A CDSS should have rigorous, peer-reviewed scientific evidence establishing its **safety, validity, reproducibility, usability, and reliability, but for many decisions there is no single "right answer."**

Shortliffe E and Sepulveda M JAMA Nov.2018

Trust-worthy evidence and CDSS targets



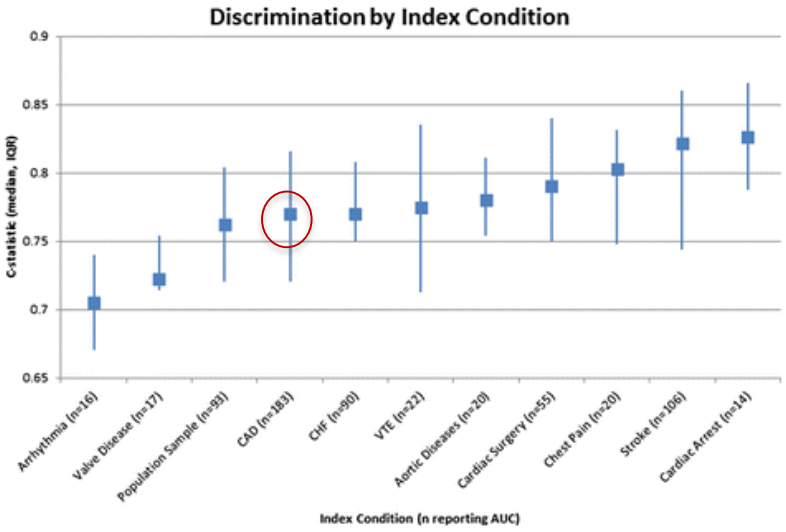
Predictive models and CDSS

Predictive Analytics and Comparative Effectiveness (**PACE**) database Registry http://pace.tuftsmedicalcenter.org/cpm/

265 Clinical predictive models for patients with CAD (1990-2015)

Predictive risk models outperform physicians in prognostic accuracy

The number of models continues to increase, though model performance is often inadequately reported and calibration is infrequently assessed



Wessler et al. Diagn Progn Res. 2017;1(20):1-8

Table 3 Time trends for reporting discrimination and calibration and providing a calculator

Time period	Total models (*n*)	Discrimination		Calibration		Calculator	
		Reporting AUC (%)	*p* for trend	Reporting calibration (%)	*p* for trend	Providing calculator (%)	*p* for trend
1990–1995	75	31	< 0.0001	58	0.39	0	< 0.01
1996–2000	102	49		48		0	
2001–2005	171	61		53		1	
2006–2010	285	72		65		3	
2011–2015	450	71		57		4	

Shortcomings of predictive models in CDSS

- **Discrimination vs Calibration**. C statistics, AUC and ROC are used to establish that patients with the outcome have *significantly higher risk predictions than those without*; but how many of x patients with a given risk prediction have really the outcome (*observed-to-expected ratio*)? Poor calibration can lead to harmful decisions.

- **Identification of Risk-Sensitive Decisions**. A prediction model can be relevant and influence clinical decisions only when the risk threshold for a certain decision is very close to the population average risk.

- **User Trust, Transparency, and Commercial Interests:** Hospital administrators and clinicians are not always familiar enough with the statistical methodology to critically evaluate the products they purchase

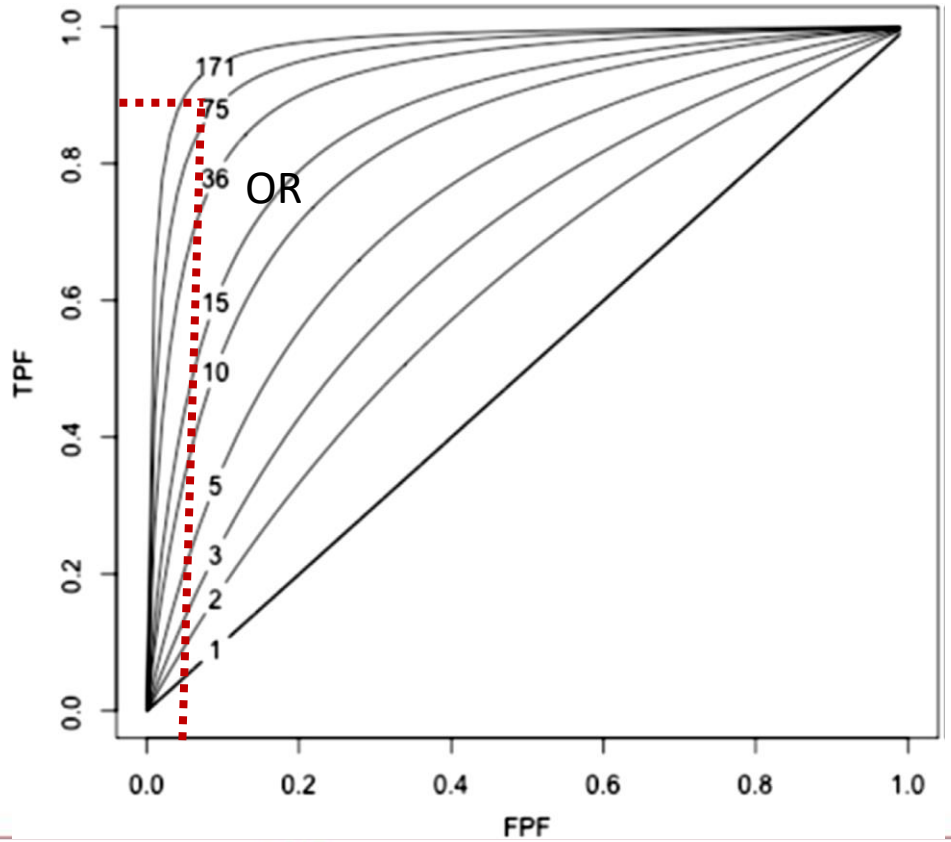
- **Data Quality and Heterogeneity:** The quality of prediction models depends on the quality of the data on which they are derived. Prediction model results depend on the derivation data sample.

Statistical significance vs Clinical significance
Discriminatory accuracy and odd ratio

In order to obtain a **good discriminatory accuracy (DA) of a biomarker**, such as a true positive fraction (TPF = number of cases with positive marker/total number of cases) = 90% (10% FN) and a false positive fraction (FPF=number of controls with positive marker/number of controls) = 5% (NPV=95/100), we need very high values of OR.

Promotion of screening by biomarkers as well as treatment of risk factors with a low discriminatory accuracy may lead to unnecessary costs or side effects respectively.

Merlo J et al. SSM - Population Health 3 (2017) 684–698



The utility of PTP predictive models
The example of PROMISE minimal risk model

JAMA Cardiology | Original Investigation

Identification of Patients With Stable Chest Pain Deriving Minimal Value From Noninvasive Testing

The PROMISE Minimal-Risk Tool, A Secondary Analysis of a Randomized Clinical Trial

Christopher B. Fordyce, MD, MHS, MSc; Pamela S. Douglas, MD; Rhonda S. Roberts, MSPH; Udo Hoffmann, MD, MPH; Hussein R. Al-Khalidi, PhD; Manesh R. Patel, MD; Christopher B. Granger, MD; John Kostis, MD; Daniel B. Mark, MD; Kerry L. Lee, PhD; James E. Udelson, MD; for the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Investigators

Question Is it possible to create a risk tool to identify intermediate-risk patients with stable chest pain unlikely to benefit from noninvasive testing?

Findings In this secondary analysis of a randomized clinical trial, 1243 of 4631 patients (26.8%) with stable chest pain had normal coronary arteries (without atherosclerosis) and no long-term clinical events. These minimal-risk patients can be identified with good discrimination using pretest clinical characteristics alone.

Meaning A clinical tool using readily available pretest variables discriminates such minimal-risk patients, for whom deferred testing may be considered.

10 clinical variables were correlated with normal CCTA results and no clinical events (**C statistic = 0.725 for the derivation and validation subsets**; 95%CI, 0.705-0.746): younger age; female sex; racial or ethnic minority; no history of hypertension, diabetes, or dyslipidemia; family history of premature coronary artery disease; never smoking; symptoms unrelated to physical or mental stress; and higher high-density lipoprotein cholesterol level. Across the entire PROMISE cohort, this model was associated with the lowest rates of severely abnormal test results (1.3% for CCTA).

Table 2. Factors Associated With Minimal Risk in the Final Derivation Model[a]

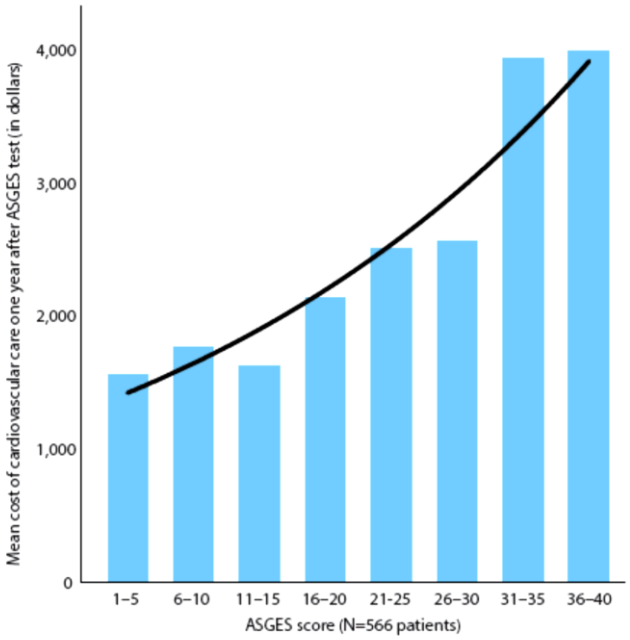
Factor	Odds Ratio (95% CI)[b]	*P* Value	χ^2
Age (per 5-y decrease)	1.50 (1.41-1.60)	<.001	160.0
Female sex	2.59 (2.13-3.16)	<.001	90.8
Racial or ethnic minority	1.29 (1.05-1.59)	.01	6.1
No hypertension	1.55 (1.29-1.85)	<.001	22.7
No dyslipidemia	1.43 (1.19-1.72)	<.001	14.9
Never smoker[c]	1.66 (1.40-1.98)	<.001	32.6
No family history of CAD	1.34 (1.06-1.68)	<.001	24.4
No diabetes	1.48 (1.23-1.78)	.0	7.3
Symptoms unrelated to physical or mental stress[d]	1.48 (1.23-1.78)	.007	6.0
HDL-C (per 5-point increase)	1.04 (1.01-1.07)	.01	6.3

Potential Economical Advantages of PTP model application (AGES model)

Clinical effectiveness and economic efficiency are strictly related

European Heart Journal – Quality of Care and Clinical Outcomes (2016) 2, 245–260

FIGURE
As ASGES goes up, so do cardiovascular costs



ASGES=age/sex/gene expression score.

Economic Outcomes of a Precision Medicine Blood Test To Assess Obstructive Coronary Artery Disease: Results from the PRESET Registry

Joseph A. Ladapo, MD, PhD,[1] Matthew J. Budoff, MD,[2] Pejman Azarmina, MD, MSc,[3] David Sharp, DO,[4] Alice Baker, MPH,[3] Bruce Maniet, DO,[5] Lee Herman, MD,[6] Mark Monane, MD, MS[3]

[1]David Geffen School of Medicine at UCLA, Los Angeles, Calif.; [2]UCLA, Torrance, Calif.; [3]CardioDx Inc., Redwood City, Calif.; [4]Doctors for Health, Omaha, Neb.; [5]Bells Medical Clinic, Bells, Texas; [6]Johns Creek Primary Care, Suwanee, Ga.

Results: The analysis included 566 patients, 51% of whom were women and the median age was 56. Forty-five percent had a low ASGES. The mean cost of cardiovascular care for patients in the year following ASGES was $1,647 for patients with a low ASGES versus $2,709 for those with an elevated score (39% reduction, *P*=.03 by Wilcoxon rank test). This relationship remained after multivariate analysis that adjusted for patient demographics and clinical covariates (*P*<.001).

Conclusion: The ASGES helped identify patients with low current likelihood of obstructive CAD. These patients had lower costs of cardiovascular care during one year of follow-up. Early reductions in cardiac referrals at 45 days among these patients persisted at one year.

Potential Advantages of PTP models

Identifying patients unlikely to benefit from potentially expensive testing and who may be managed conservatively has many potential economic and process-of-care advantages.

- **Reduction in unnecessary testing: saving time, anxiety, and cost for patients**
- Reduction in radiation exposure
- Reduction in false-positive test results that could lead to more invasive, unnecessary procedures.

Economical advantages of non invasive imaging computational models (the case of FFRCT)

	Per-patient level	Per-vessel or per-lesion level
Number of included studies	5	7
Number of subjects	833	1377
Sensitivity	0.89 (0.85–0.93)*	0.84 (0.80–0.87)
Specificity	0.76 (0.64–0.84)	0.76 (0.67–0.83)
Positive likelihood ratio	3.68 (2.41–5.61)	3.51 (2.44–5.03)
Negative likelihood ratio	0.14 (0.09–0.21)	0.21 (0.16–0.27)
Diagnostic odds ratio	26.21 (13.14–52.28)	16.87 (9.41–30.25)
Diagnostic score	3.27 (2.58–3.96)	2.83 (2.24–3.41)
AUSROC	0.90 (0.87–0.92)	0.86 (0.83–0.89)

Pooled diagnostic performances of FFRCT at the per-patient level and at the per-vessel or per-lesion level
Sci Rep. 2016 Jul 5;6:29409.

Prospective Longitudinal Trial of FFRCT

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER
VOL. 68, NO. 5, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.05.057

ORIGINAL INVESTIGATIONS

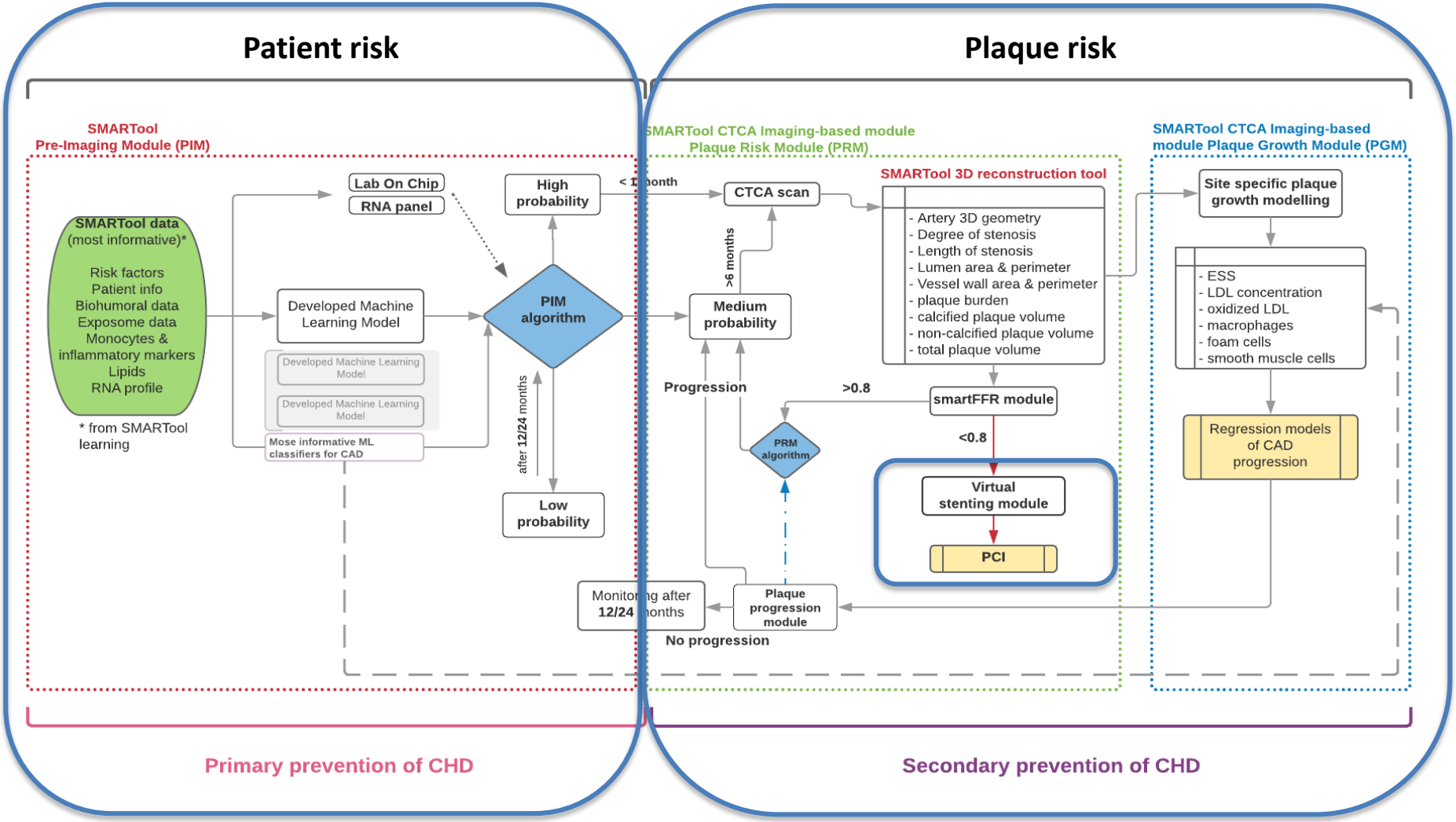
1-Year Outcomes of FFR_{CT}-Guided Care in Patients With Suspected Coronary Disease

The PLATFORM Study

Pamela S. Douglas, MD,[a] Bernard De Bruyne, MD,[b] Gianluca Pontone, MD,[c] Manesh R. Patel, MD,[a] Bjarne L. Norgaard, MD,[d] Robert A. Byrne, MB BCh,[e] Nick Curzen, BM,[f] Ian Purcell, MD,[g] Matthias Gutberlet, MD,[h] Gilles Rioufol, MD,[i] Ulrich Hink, MD,[j] Herwig Walter Schuchlenz, MD,[k] Gudrun Feuchtner, MD,[l] Martine Gilard, MD,[m] Daniele Andreini, MD,[c] Jesper M. Jensen, MD,[d] Martin Hadamitzky, MD,[e] Karen Chiswell, PhD,[a] Derek Cyr, PhD,[a] Alan Wilk, BS,[n] Furong Wang, MD,[n] Campbell Rogers, MD,[n] Mark A. Hlatky, MD,[o] on behalf of the PLATFORM Investigators

CONCLUSIONS In patients with 49% pre-test probability of coronary artery disease, stable chest pain and planned invasive coronary angiography, care guided by CTA and selective FFRCT was associated with equivalent clinical outcomes and QOL, and lower costs, compared with usual care over 1-year follow-up. (The PLATFORM Study: Prospective LongitudinAl Trial of FFRct: Outcome and Resource IMpacts [PLATFORM]; NCT01943903)

Conceptual Design of SMARTool CDSS



Strenghts of SMARTool CDSS

- **Multilevel CDSS (Integration of patient-specific and artery-specific clinical targets of decision support to diagnosis, prognosis and treatment) → Multiple decisions at different pathological/clinical stages of severity from asymptomatic untreated subjects to suspected SCAD, diagnosed CAD, revascularised CAD.**
- **Web-based on cloud environment → Web-based decision support systems facilitate individualized risk estimates and personalized treatment recommendations.**
- **Deployment of omics data into a clinically exploitable PTP score.**
- **Use of POC devices for screening of pre-imaging PTP of CAD : LOC and RNA panel kit**

Pre-imaging PTP model: Development

LEARNING

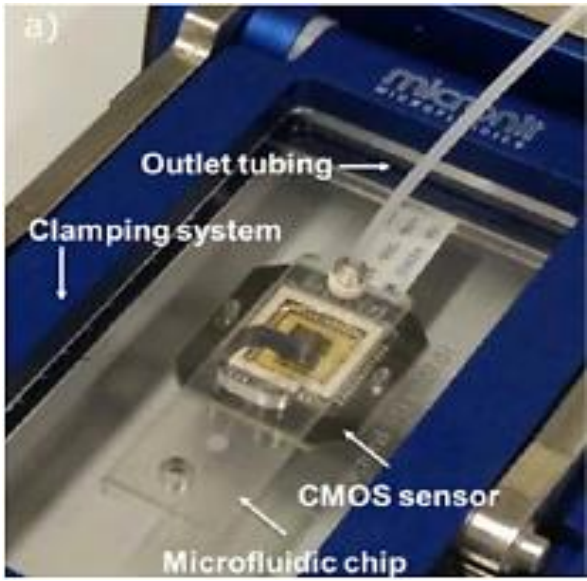
Molecular & Omics data collection

Lipids, RNA, DNA
Biohumoral data, Monocyte and Inflammatory markers

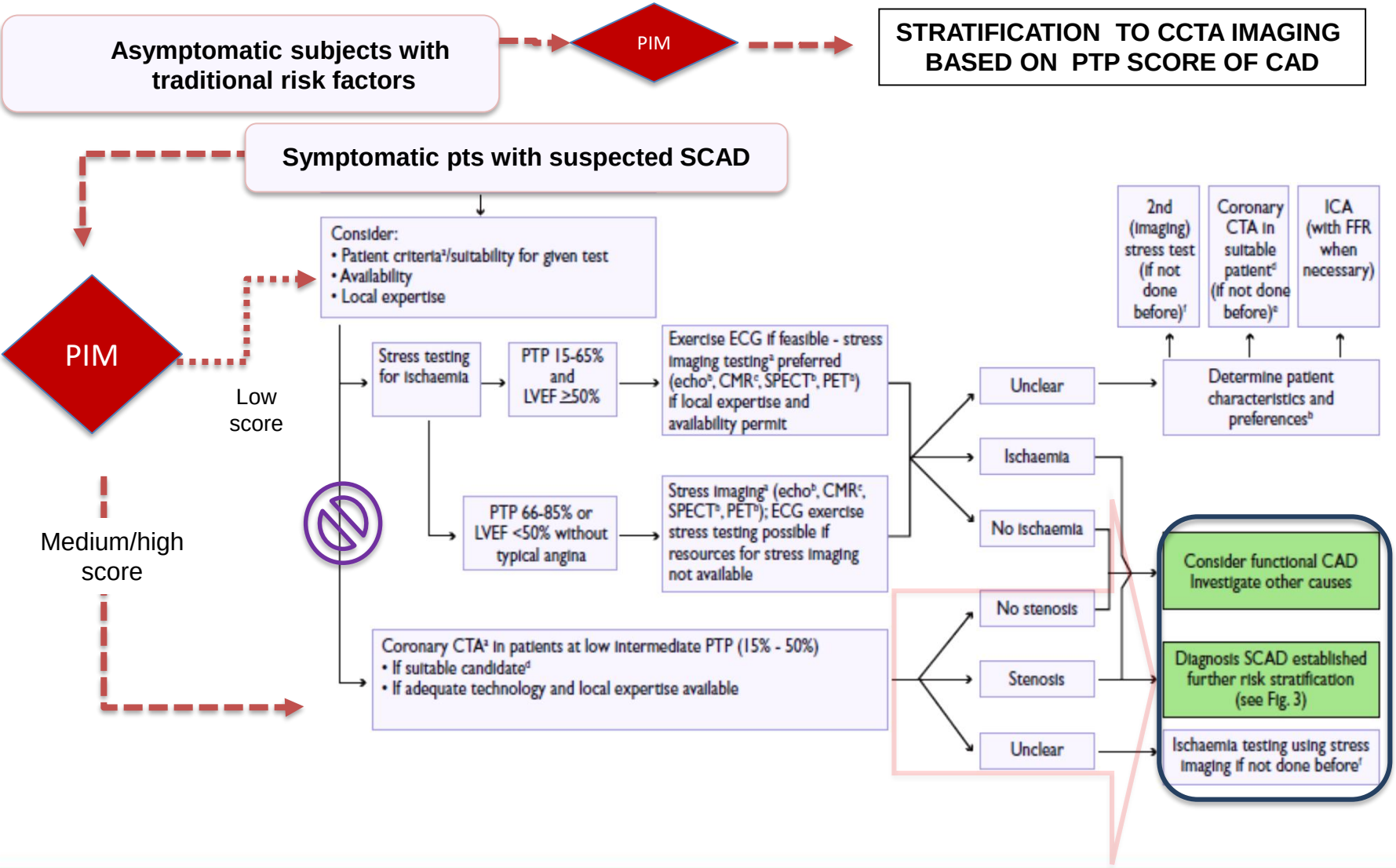
Selection of discriminative molecular markers of CAD presence/severity

POCT solution for CDSS

Lab-on-Chip & RNA Panel



Pre-imaging PTP model: ESC guidelines and SMARTool CDSS



Pre-imaging PTP model: expected advantages

EXPECTED CLINICAL AND ECONOMIC BENEFITS

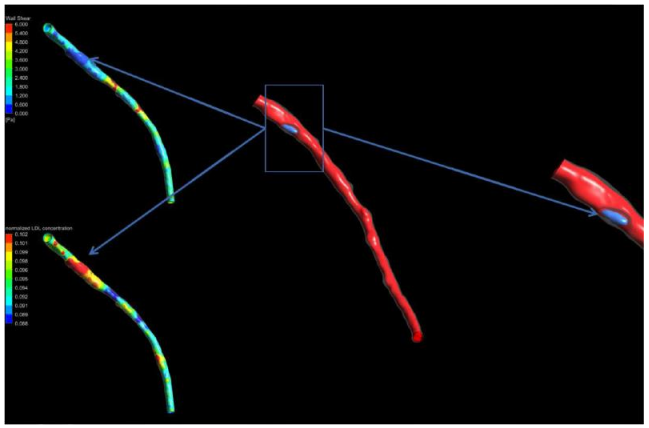
- In **primary prevention**: stratification of asymptomatic patients according to PTP score of CAD
- In **secondary prevention**: a reduced number of unecessary CTA in patients with chest pain and low PTP score of clinically significant CAD.
- Overall reduced costs for health care services and society

AVAILABLE PACKAGES ON THE MARKET

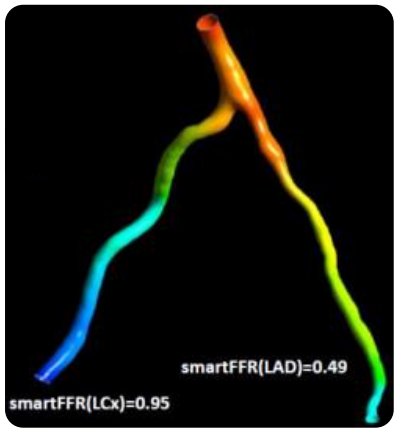
The only equivalent available package on the marker is the US-product named Corus® CAD which produces the AGES score : it is blood-based gene expression test that provides a current-state assessment for non-diabetic patients with symptoms that are suggestive of obstructive CAD demonstrating a high negative predictive value

CTA-based computational models

CT scan
DICOM repository

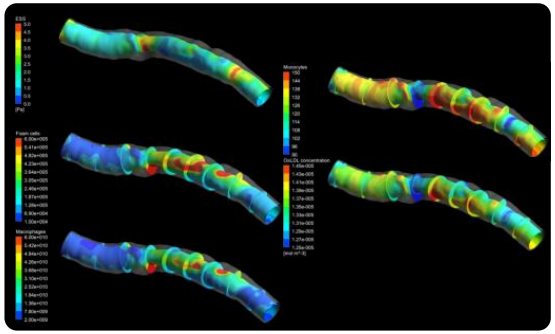


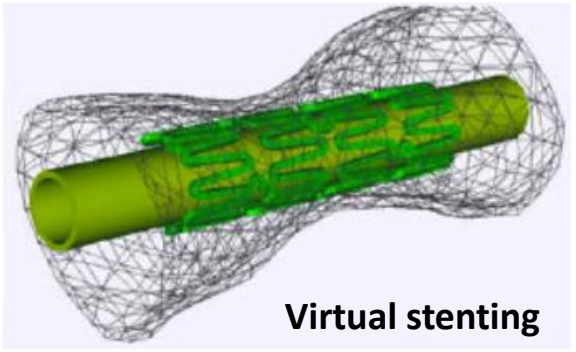
CT coronary image 3D reconstruction and segmentation



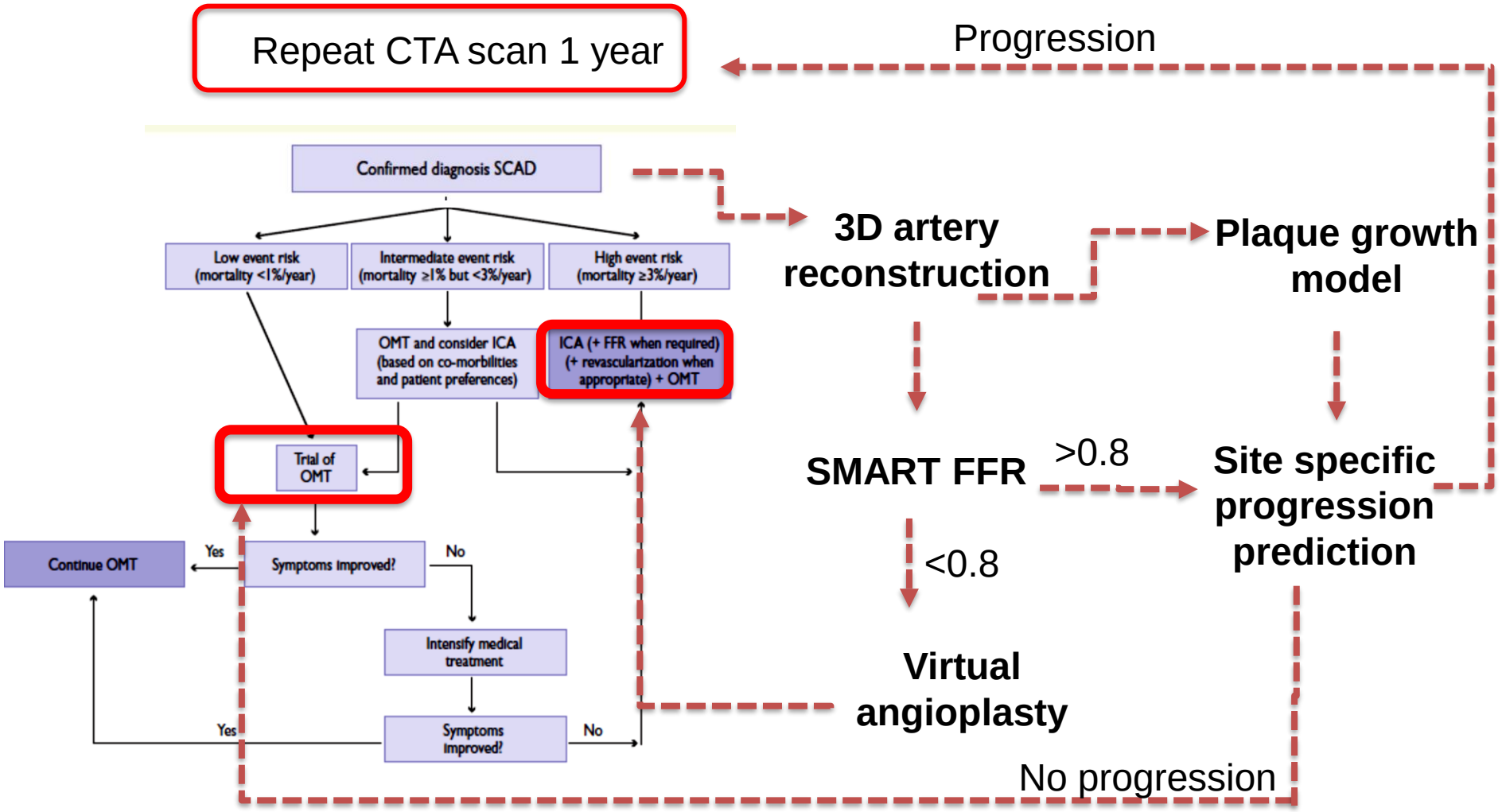
SMART FFR

Plaque growth model





CTA-based computational models: ESC guidelines and SMARTool CDSS



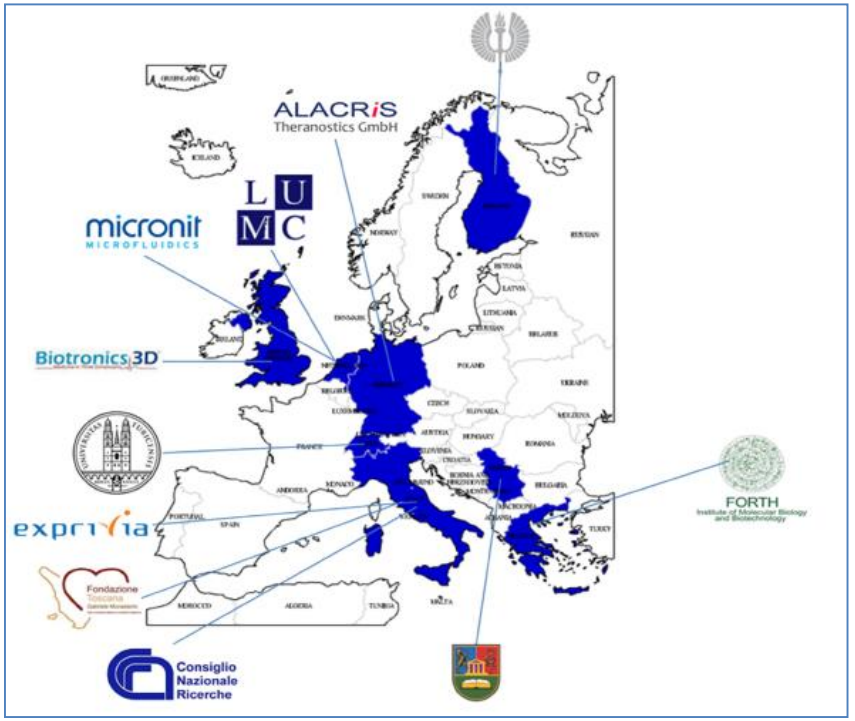
CTA-based computational models: expected clinical and economic benefits

	SMARTool service/device	SMARTool Benefits
Treatment decision after CCTA	Virtual Functional Flow Reserve (smartFFR), Shear Stress estimate and Plaque Progression model	Comprehensive anatomical, evolutive and functional assessment of single plaques and plaque-related stenosis. Better decision on revascularization
Perform revascularization	Virtual Stenting Module	Better planning and optimal deployment of stent
Revascularization after stenting decision	Virtual Functional Flow Reserve (smartFFR), Shear Stress and Plaque Progression	Better assessment of revascularization efficacy

Thank you

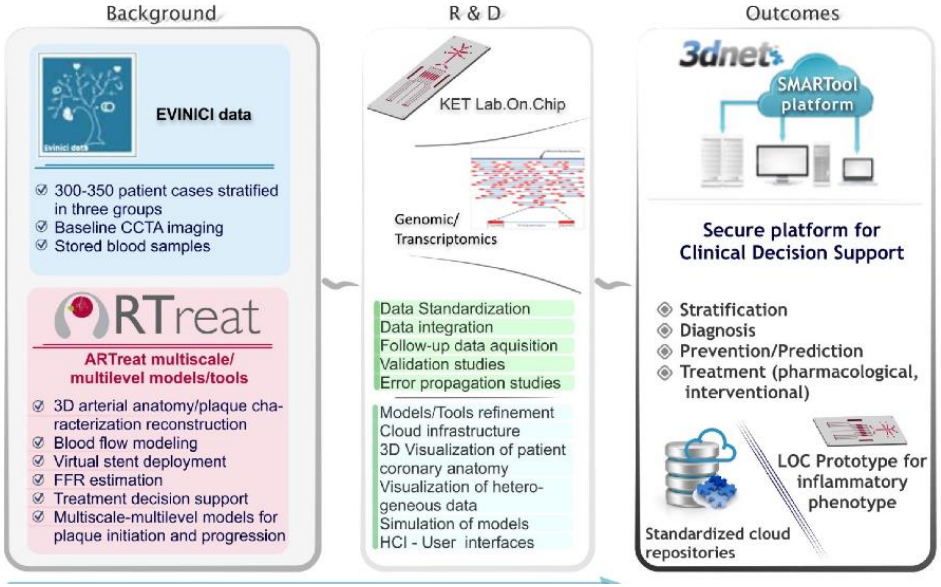
The estimation of risk is not an exact science : the challenge is to use the tools that we have appropriately rather than to expect major refinements in an inexact science.

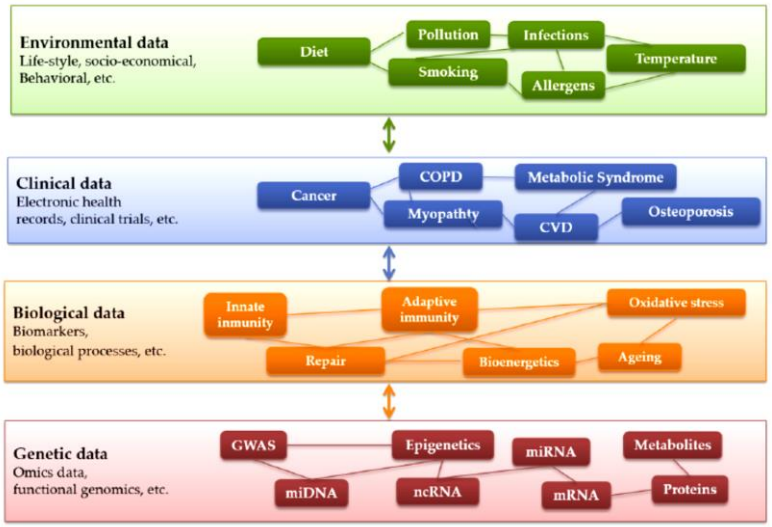
Risks in estimating risk. I M Graham and MT Cooney, European Heart Journal (2014) 35, 537–539.



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

Background of SMARTool CDSS design





Cano *et al. Journal of Translational Medicine* 2014, **12**(Suppl 2):S10
http://www.translational-medicine.com/content/12/S2/S10

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Biomedical research in a Digital Health Framework

Isaac Cano[1*], Magí Lluch-Ariet[2], David Gomez-Cabrero[3], Dieter Maier[4], Susana Kalko[1], Marta Cascante[1,5], Jesper Tegnér[3], Felip Miralles[2], Diego Herrera[5,6], Josep Roca[1,7], Synergy-COPD consortium

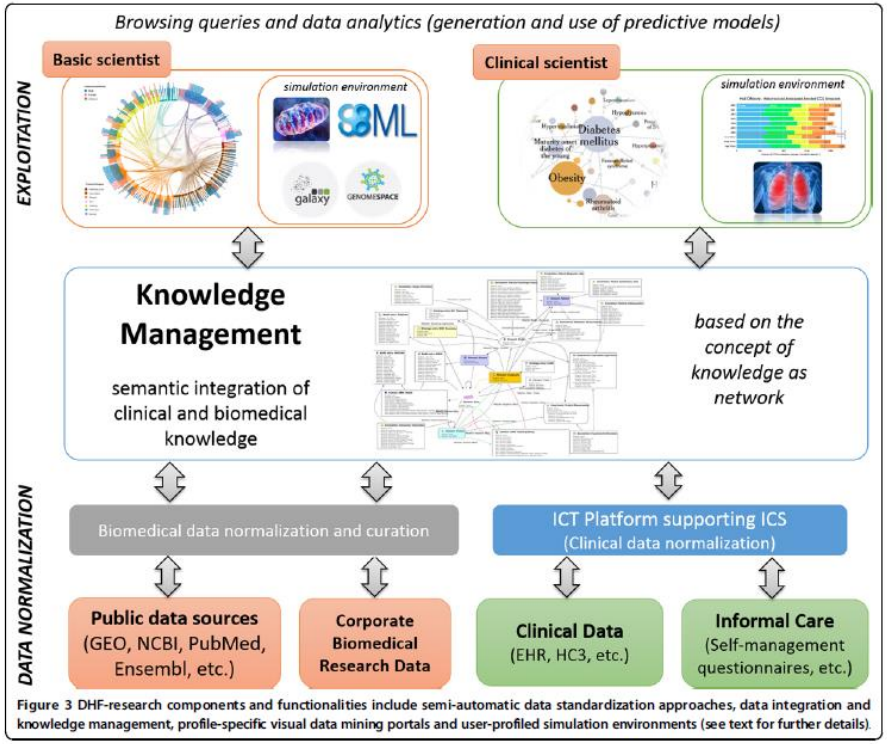
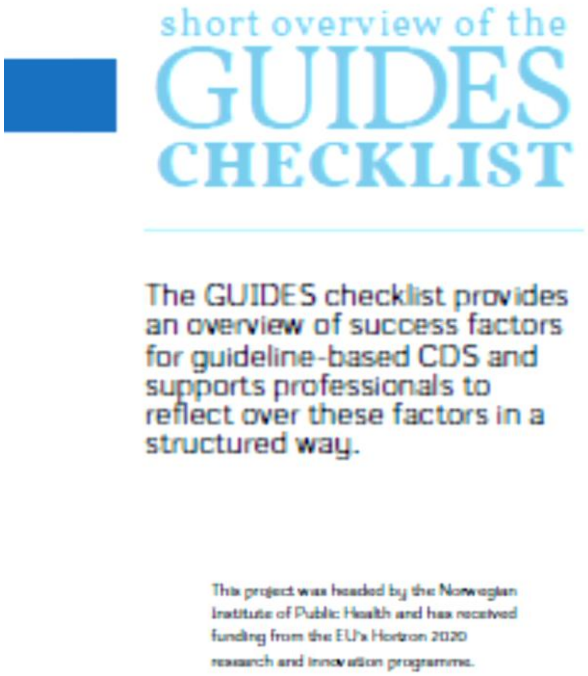


Figure 3 DHF-research components and functionalities include semi-automatic data standardization approaches, data integration and knowledge management, profile-specific visual data mining portals and user-profiled simulation environments (see text for further details).

Changing healthcare practice : CDS systems



https://www.guidesproject.org/

Domain 1: CDS context

1.1 CDS can achieve the defined quality objectives

1.2 The quality of the patient data is adequate

1.3 Stakeholders and users accept CDS

1.4 CDS can be added to the existing workload, workflows and systems

Domain 2: CDS content

2.1 The content provides trustworthy evidence-based information

2.2 The decision support is relevant and accurate

2.3 The decision support provides an appropriate call to action

2.4 The amount of decision support is manageable for the target user

Domain 3: CDS system

3.1 The system is easy to use

3.2 The decision support is well delivered

3.3 The system delivers the decision support to the right target person

3.4 The decision support is available at the right time

Domain 4: CDS implementation

4.1 Information to users about the CDS system and its functions is appropriate

4.2 Other barriers and facilitators to compliance with the decision support advice are assessed/addressed

4.3 Implementation is stepwise and the improvements in the CDS system are continuous

4.4 Governance of the CDS implementation is appropriate

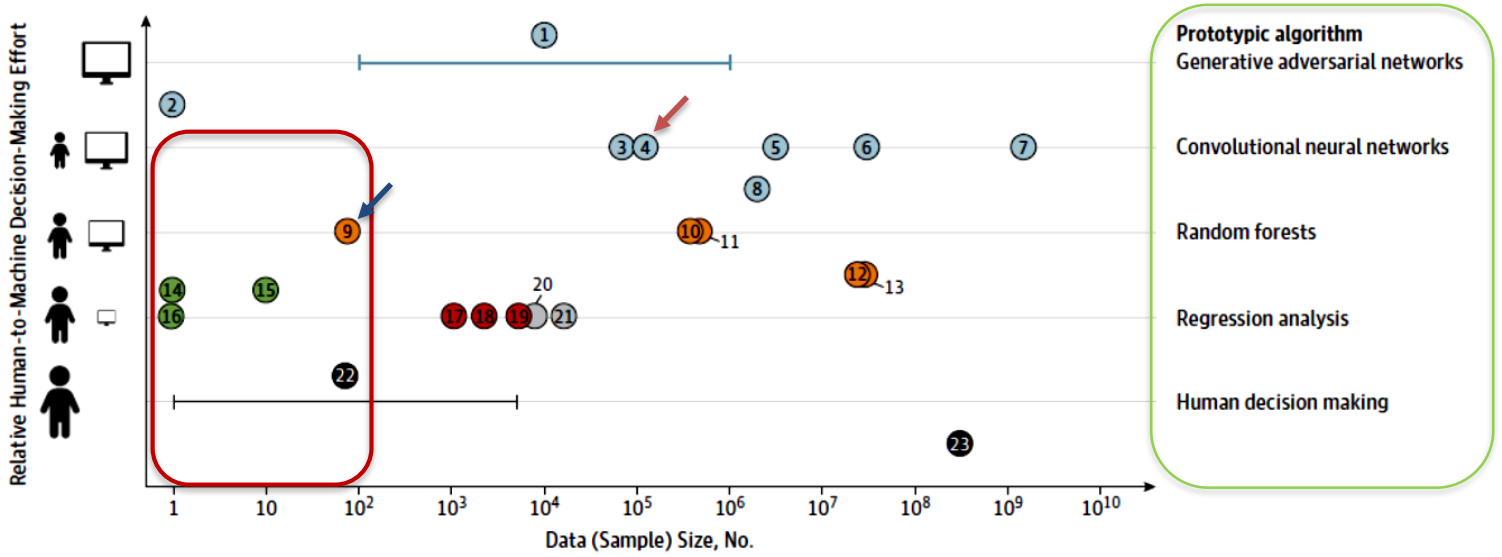
Success factors for clinical application of CDSS

	Total score
1.1 CDS can achieve the defined quality objectives	64
1.2 The quality of the patient data is adequate	47
1.3 Stakeholders and users accept CDS	43
1.4 CDS can be added to the existing workload, workflows and systems	71
2.1 The content provides trustworthy evidence-based information	106
2.2 The content is relevant and accurate	76
2.3 The decision support provides an appropriate call to action	28
2.4 The amount of decision support is manageable for the target user	9
3.1 The system is easy to use	44
3.2 The decision support is well delivered	13
3.3 The system delivers the decision support to the right target person	23
3.4 The decision support is available at the right time	24
4.1 Information to users about the CDS system and its functions is appropriate	2
4.2 Other barriers and facilitators to compliance with the decision support advice are assessed/addressed	7
4.3 Implementation is stepwise and the improvements in the CDS system are continuous	19
4.4 Governance of the CDS implementation is appropriate	12

Van de Velde et al. Implementation Science (2018) 13:86

Supervised, semisupervised and unsupervised machine learning

Figure. The Axes of Machine Learning and Big Data



Deep learning

1. Generative adversarial networks (2014)
2. Google AlphaGo Zero (2017)
3. ATM check readers (1998)
4. Google diabetic retinopathy (2016)
5. ImageNet computer vision models (2012-2017)
6. Google AlphaGo (2015)
7. Facebook Photo Tagger (2015)
8. Prediction of 1-y all-cause mortality (2017)

Classic machine learning

9. Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling (2002)
10. EHR-based CV risk prediction (2017)
11. Netflix Prize winner (2006)
12. Google Search (1998)
13. Amazon product recommendation (2003)

Expert AI systems

14. MYCIN (1975)
15. CASNET (1982)
16. DXplain (1986)

Risk calculators

17. CHA_2DS_2-VASc Score for atrial fibrillation stroke risk (2017)
18. MELD end-stage liver disease risk score (2001)
19. Framingham CV risk score (1998)

Randomized Clinical Trials

20. Celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis (2002)
21. Use of estrogen plus progestin in healthy postmenopausal women (2002)

Other

22. Clinical wisdom
23. Mortality rate estimates from US Census (2010)

Beam AL, Kohane IS. Big data and machine learning in health care. JAMA. doi:10.1001/jama.2017.18391

Main reasons for adopting DSS

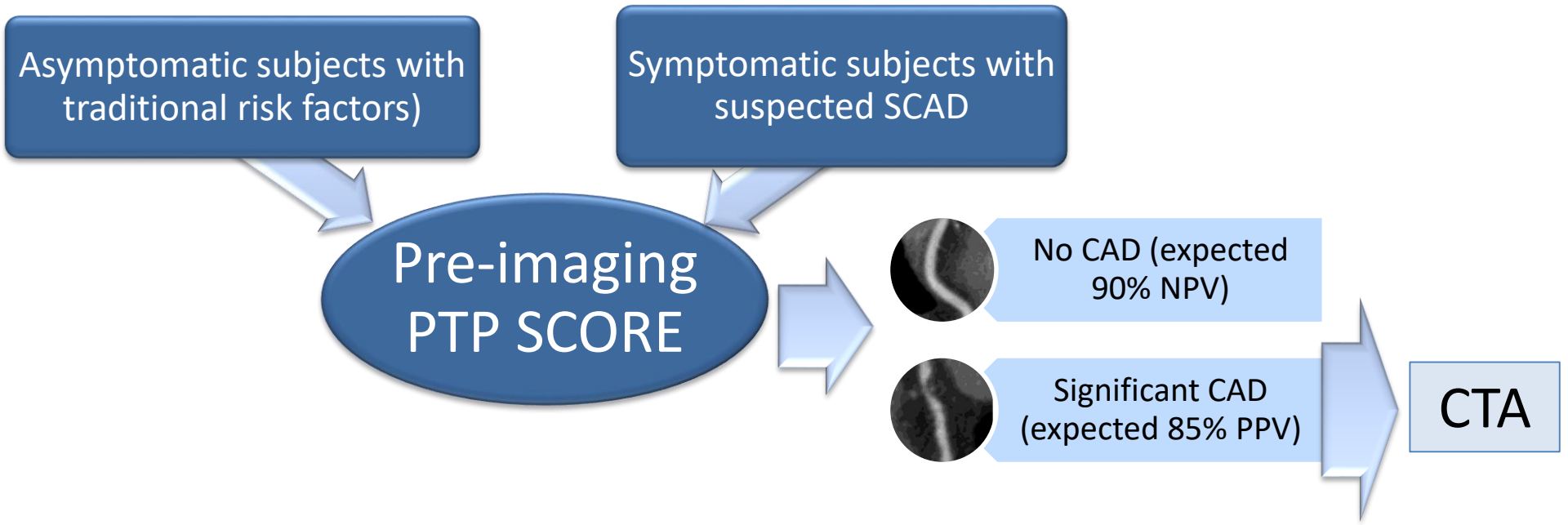
- DSS may be more effective when the advice is provided automatically and displayed on-screen and when the suggestions are more patient-specific.
- DSS interventions combined with other strategies also improves adherence.
- Providing DSS directly to patients may also positively affect adherence.

The certainty of the evidence is low to moderate for all factors.

Trial : PROSPERO, CRD42016033738 *Implement Sci. 2018 Aug 20;13(1):114.*

Pre-imaging PTP model: Conceptual Architecture

Point-of-Care assay for pre-imaging rule-out of CAD	
LOC assay of blood biomarkers of CAD	RNA panel kit assay of selected transcripts



SMARTool CDSS PLATFORM