Greater Copenhagen Health Science Partners

Patient-fokuseret forskning - kræver mange(s) kompetencer

GREATER COPENHAGEN
HEALTH · SCIENCE · PARTNERS

Personlig medicin (n=1)

Præcisions-medicin (n="få")

Præcisions-medicin har til formål at forbedre

a) stratifikation og b) timing

af sundhedsydelser ud fra det, **ALLEREDE BRUGER - PLUS**

a) molekylære sygdomsmekanismer og b) "omics"

1. Præcisions-*behandling* (Industrien)

- fordrer

2. Præcisions-*diagnostik* (Sundhedsvæsenet)

"tandem udvikling"

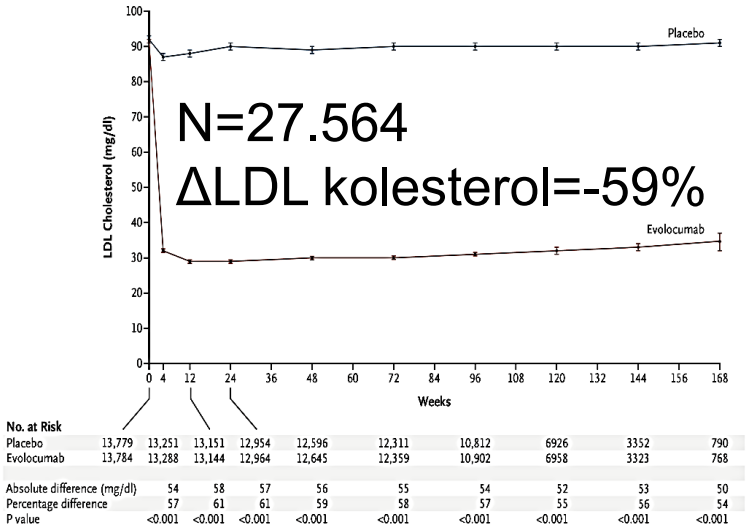
Schleidgen S et al. BMC Med Ethics 2013

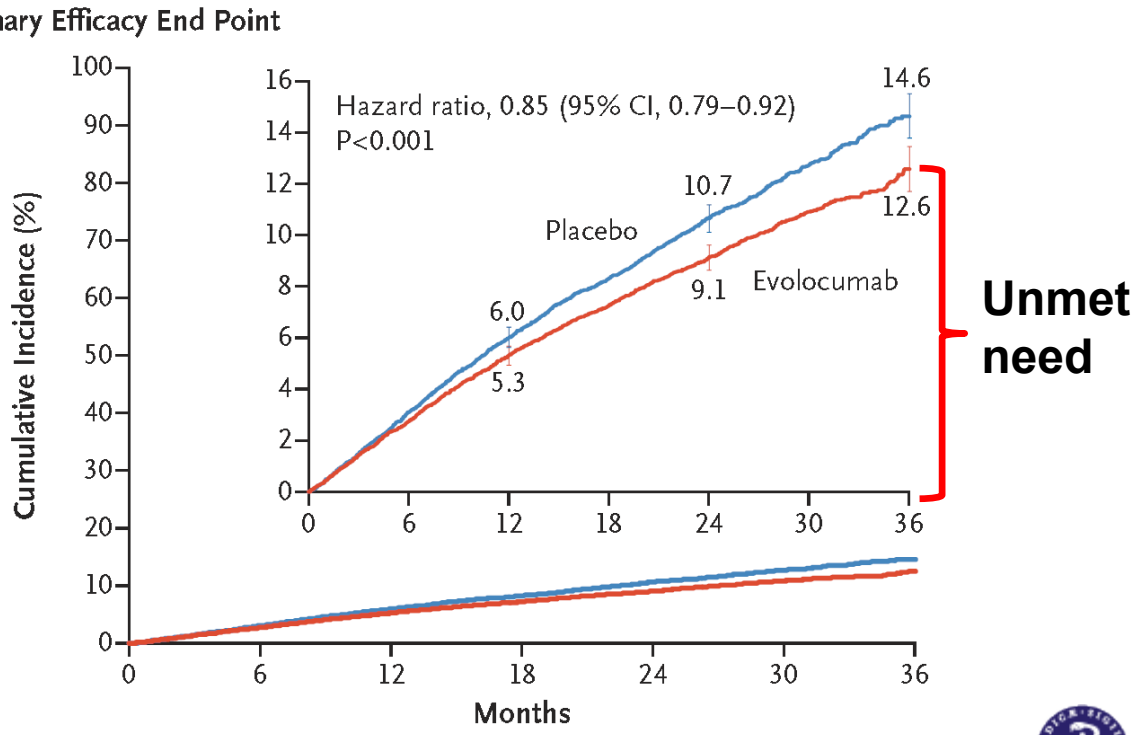
This article was published on March 17, 2017, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

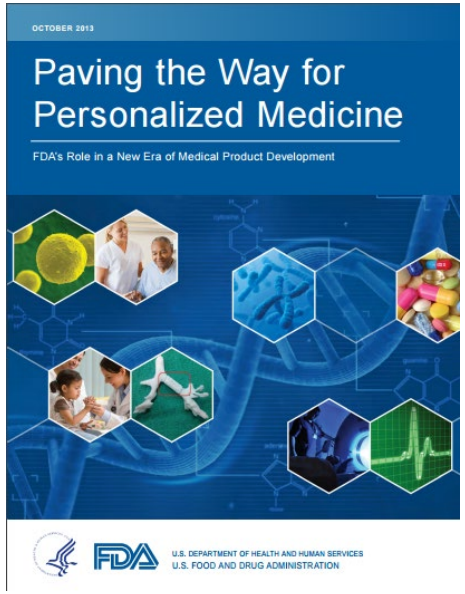
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

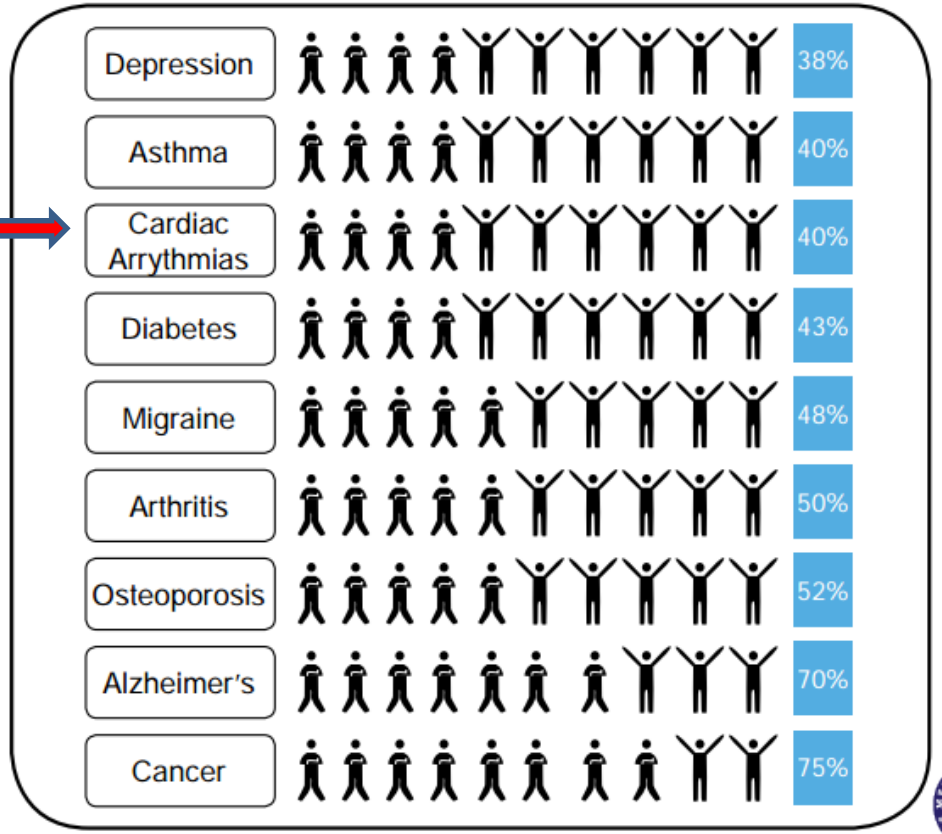




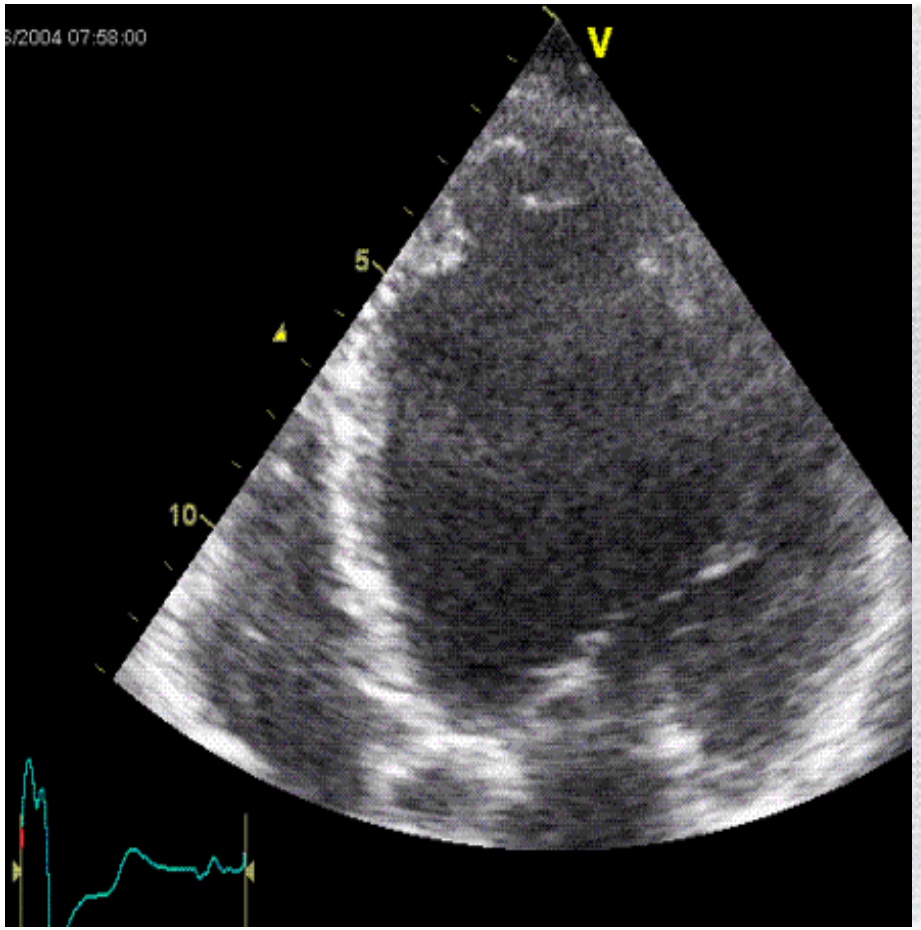
No. at Risk							
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

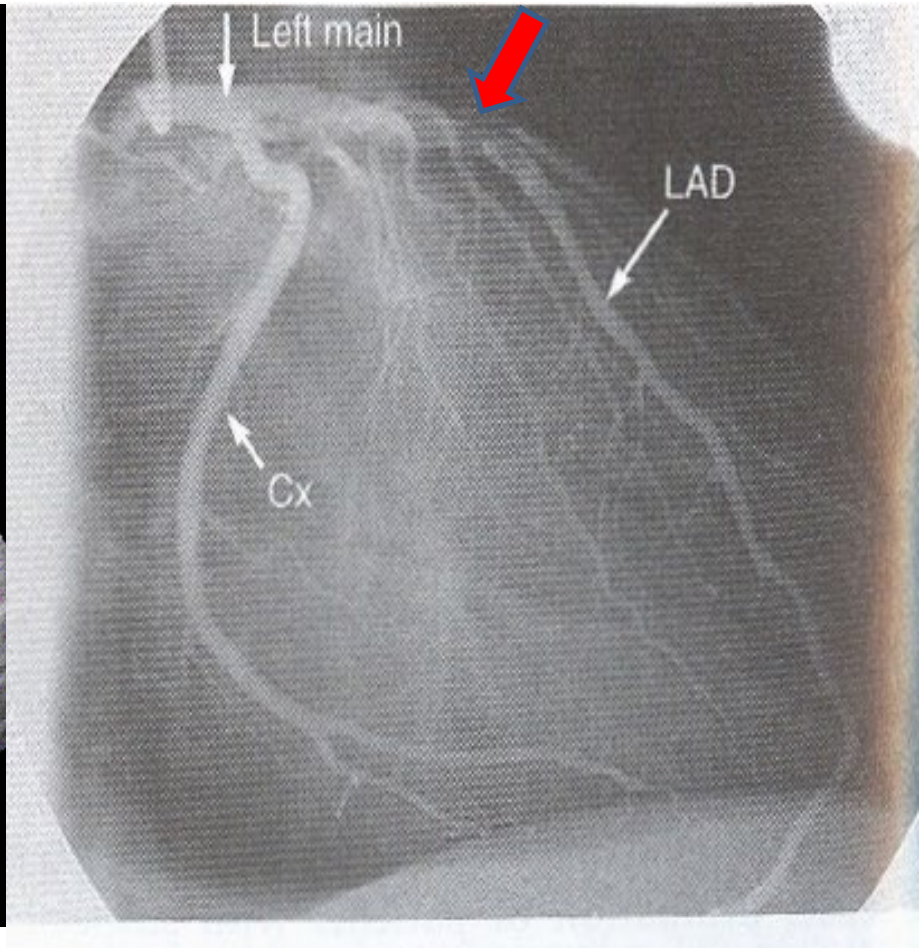
Personlig medicin
Fraktionen af patienter *uden* gavn af behandlingen



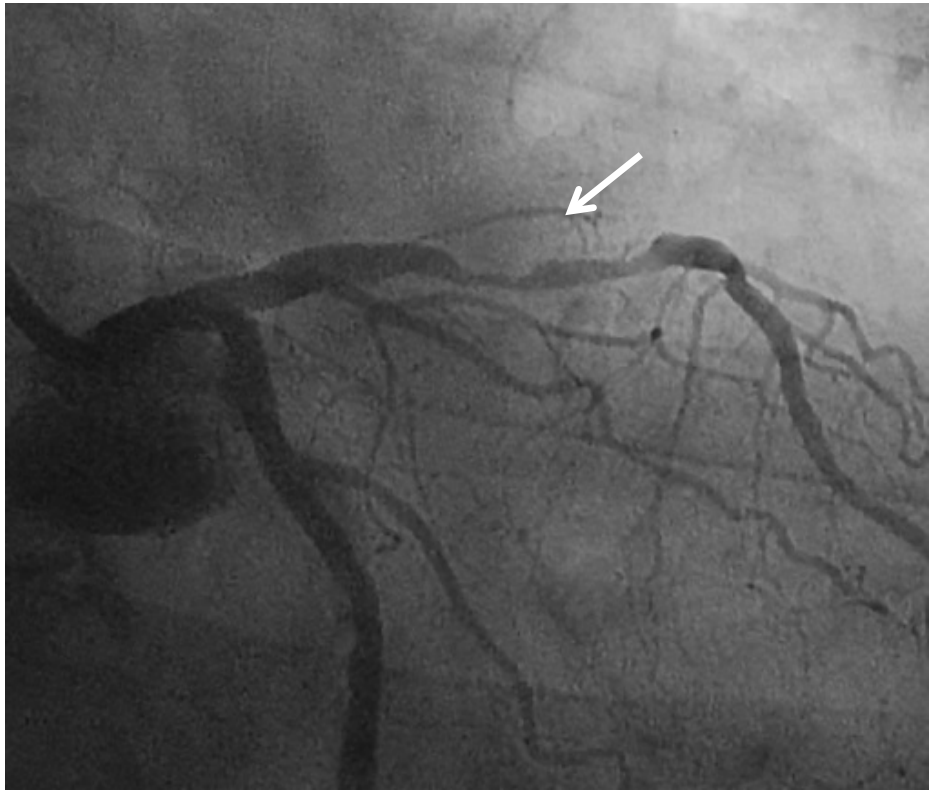


38 årig mand indlagt pga svære bryst-smerter og hjertestop - 50 min til ROSC



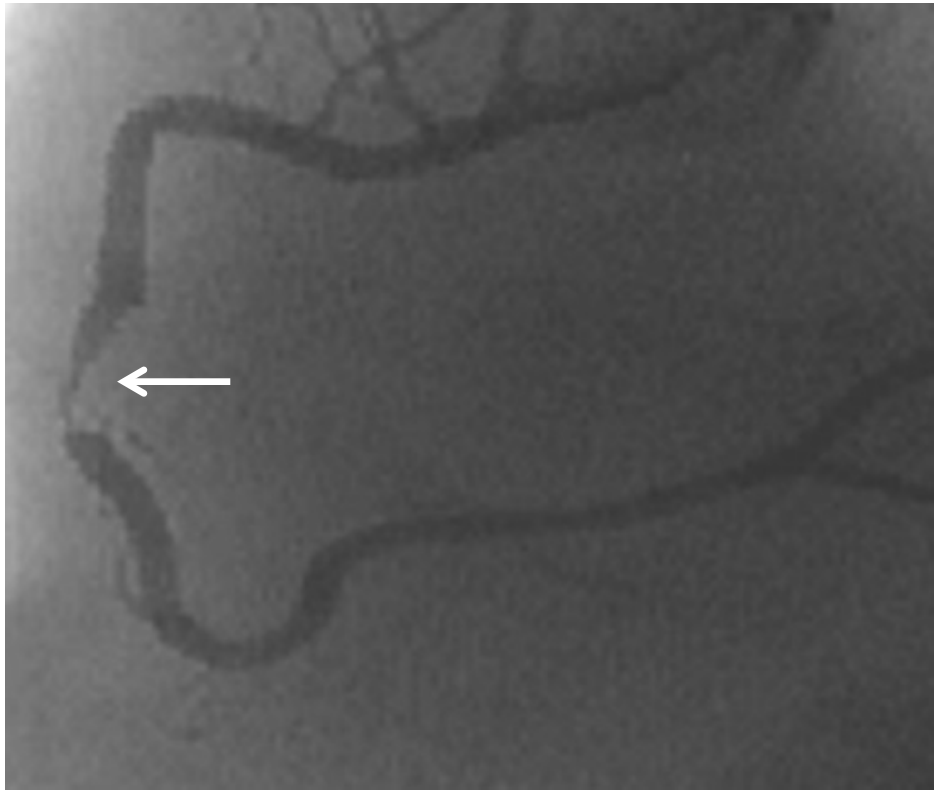


Core diagnostic in IHD; coronary angiography



Left coronary artery

Long, irregular, eccentric lesion in proximal LAD (arrow) in other-wise ”healthy” 38 y old man with severe angina.



Right coronary artery

Severe, eccentric mid-RCA lesion (arrow) in 51 y old marathon runner, STEMI referral .

Management of ischemic heart disease

Revascularisation

- Coronary artery bypass grafting (CAB
- Percutaneous coronary interventi
  - Drug eluting stents
  - Non-drug eluting sten

Pharmaco-theraphy

- Acetylic salicylic acid
- Beta-blockers
- Statins
- Nitrates as

Treatme idities

- Hy
- as
- ..

Reha tation

Follow-up

- 1-2 times per year

....for life .....

Rutine kardiologi – diagnostik og behandling "at a glance"

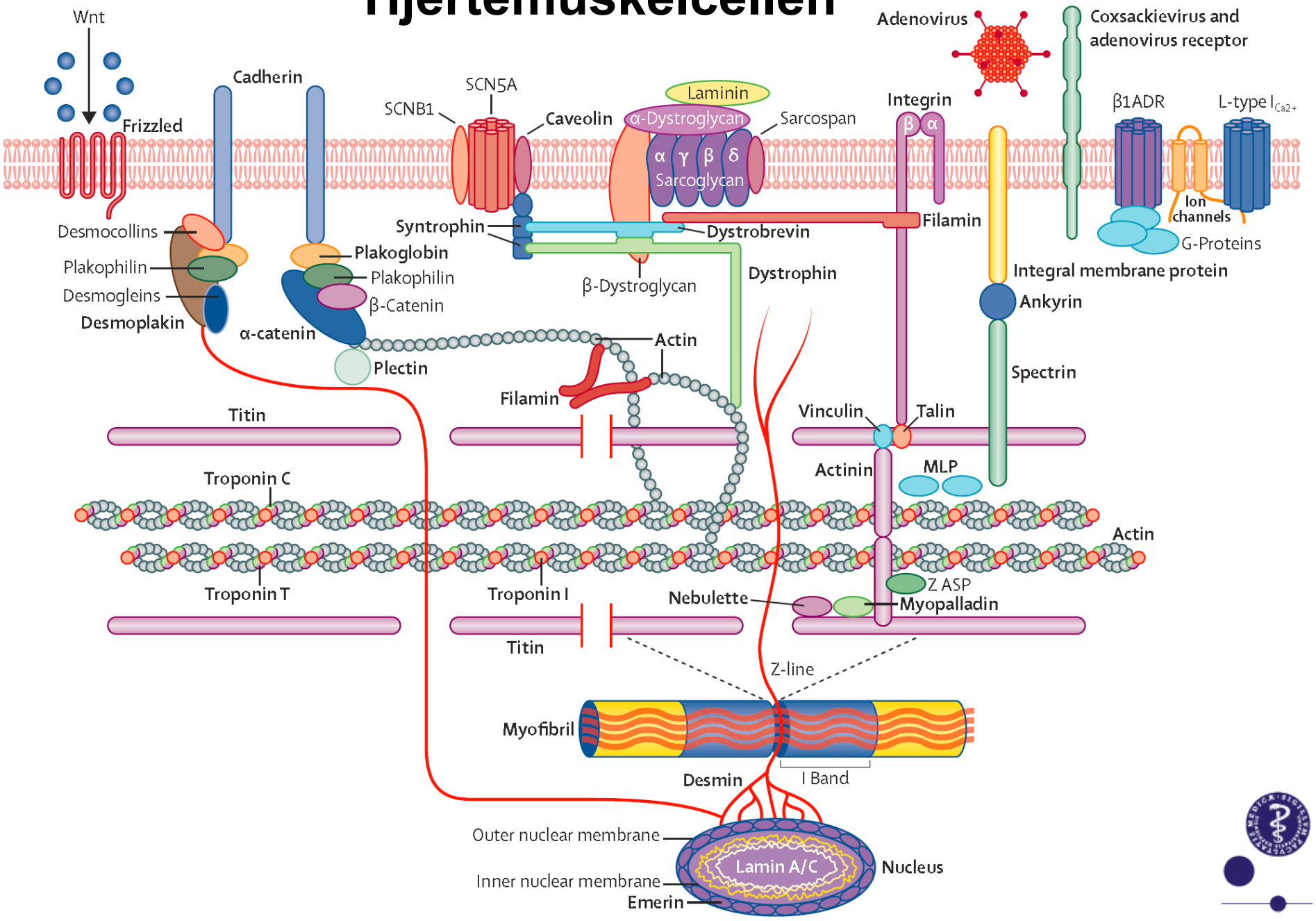
DIAGNOSTIK

- Syge-historie
- Klinisk undersøgelse
- EKG
- Ultralydskanning
- Kranspulsåre-undersøgelse
- Enzym-målinger
- Kolesterol-tal

BEHANDLING

- Revaskularisering
- Kolesterol-sænkning
- Arytmi-behandling
- Skift af hjerte-klap
- Hjertesvigt-behandling

Hjertemuskelcellen



Lancet 2017

”Unmet medical needs” indenfor kardiologien

Høj sygelighed – høj dødelighed

- for *ikke*-behandlede *og* for behandlede patienter

- ½ mio danskere lever med hjertesygdom
- 1 af 4 af os dør af en hjertesygdom

Alvorligheden af dette har ført til

1. Omfattende (over-) behandling
2. Stærkt focus på høj-risiko patienter
3. - men overset lav-risiko patienter

The burden of cardiovascular diseases in EU

- Each year cardiovascular disease (CVD) causes over 1.8 million deaths.
- CVD accounts for **37% of all deaths**.
- In 2015 almost **49 million people were living with CVD** in the EU.
- **33 mio people** are in **primary (20 mio)** or in **secondary (13.2 mio)** prevention for Ischemic Heart Disease.
- Over the past 25 years, the absolute number of CVD cases has increased in the EU.
- However, the age-standardised prevalence rate of CVD has fallen in most European countries.
- The disability-adjusted life years (DALYs) due to CVD is responsible for the **loss of 26 million DALYs** in the EU (19%).
- Overall CVD is estimated to cost the EU economy **€210 billion a year**.

The burden of ischemic heart disease

In Denmark (5.7 mio people)

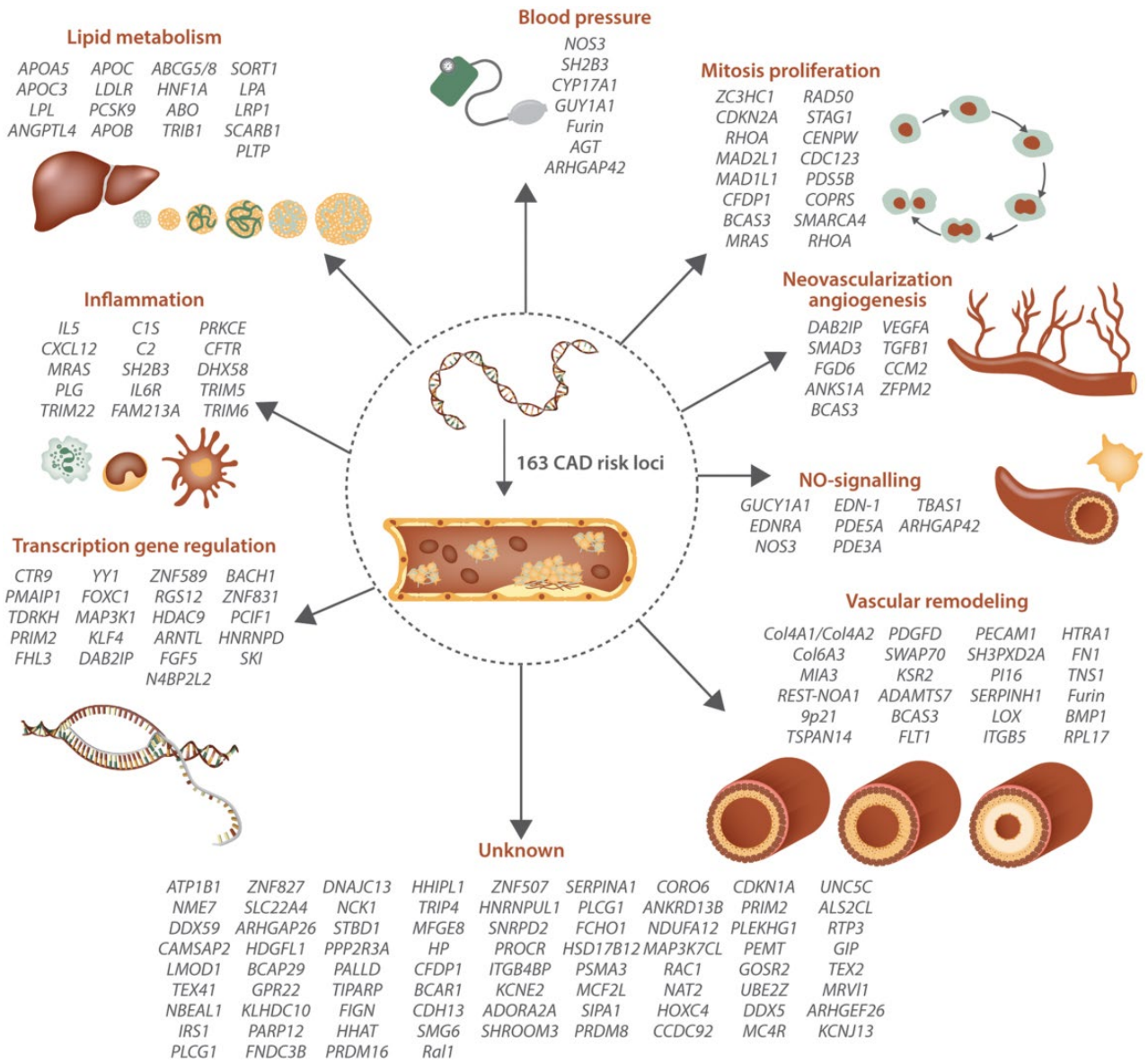
	Prevalence		Incidence	
AMI	53.406	**159.163 (34%)**	8.573	**18.563 (33%)**
Other IHD	105.757		9.990	
Atrial fibrillation	120.921		20.520	
Heart failure	60580		12.168	
Heart valve disease	32.668		5.721	
Apoplexia	86.231		13.629	
Total	**468.826**		**55.673**	

In EU (510 mio) 2015

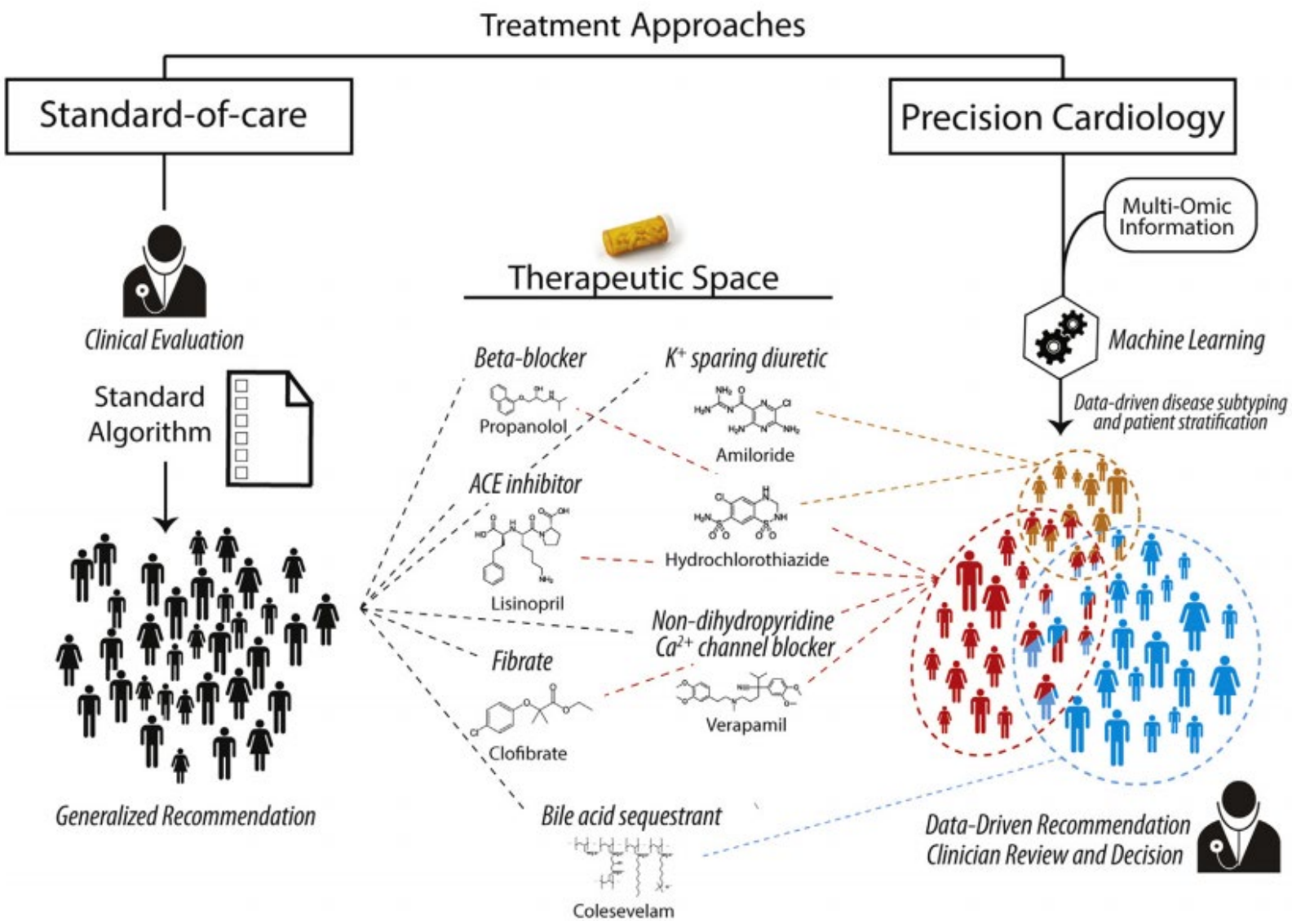
IHD (M; 7,3+F; 5,5) 13.200.000 (M;1,6+F;1,4) 3.000.000

European Cardiovascular Disease statistics 2015, HjerteTal.DK Hjerteforeningen

Genetikkens bidrag til bedre patient-behandling



Brug af genetiske analyser i klinisk diagnostik og behandling



JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 2, NO. 3, 2017
JUNE 2017:311–27

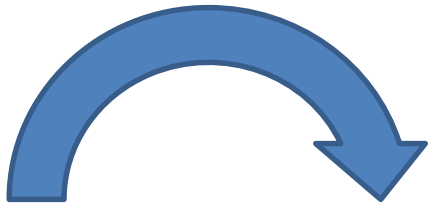
Johnson *et al.*
Machine Learning for Precision Cardiology

Integrated diagnostics

Advanced systems biology and medical informatics platform

Automated (SP) IHD pre-specified search in national registries

- Previous diagnoses
- Medications
- Family history
- Laboratory diagnostics
- Birth weight
- Complications during foetal life
- Previous vitals
- …
- ….



New patient with IHD

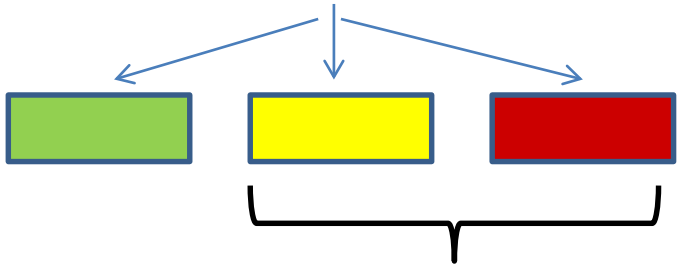
Clinical diagnostics

- Routine testing
- Advanced imaging (selected)
- Genetics
- Proteomics

Precise disease mechanisms

Precise diagnosis

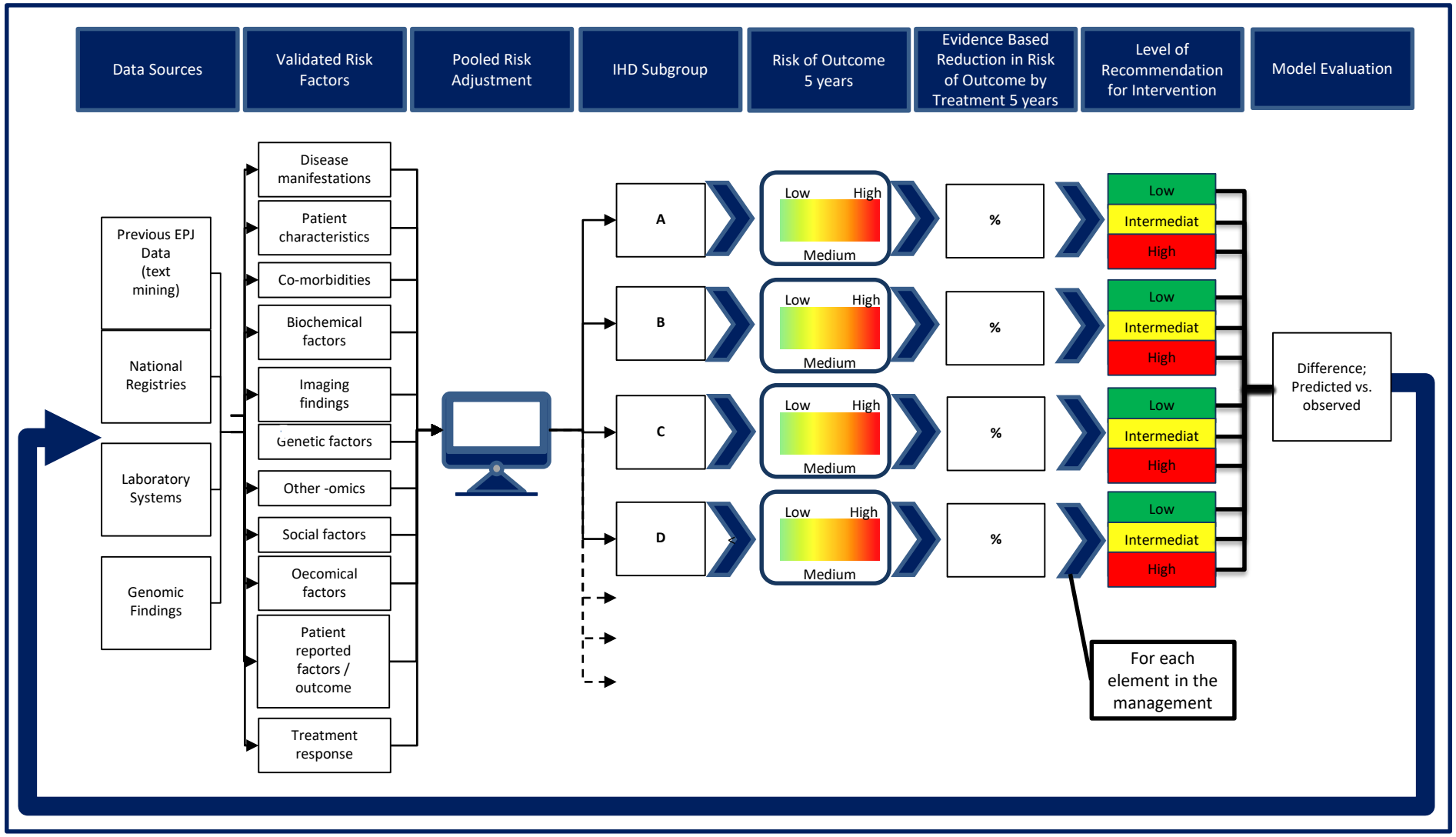
Risk stratification acc. to diagnosis

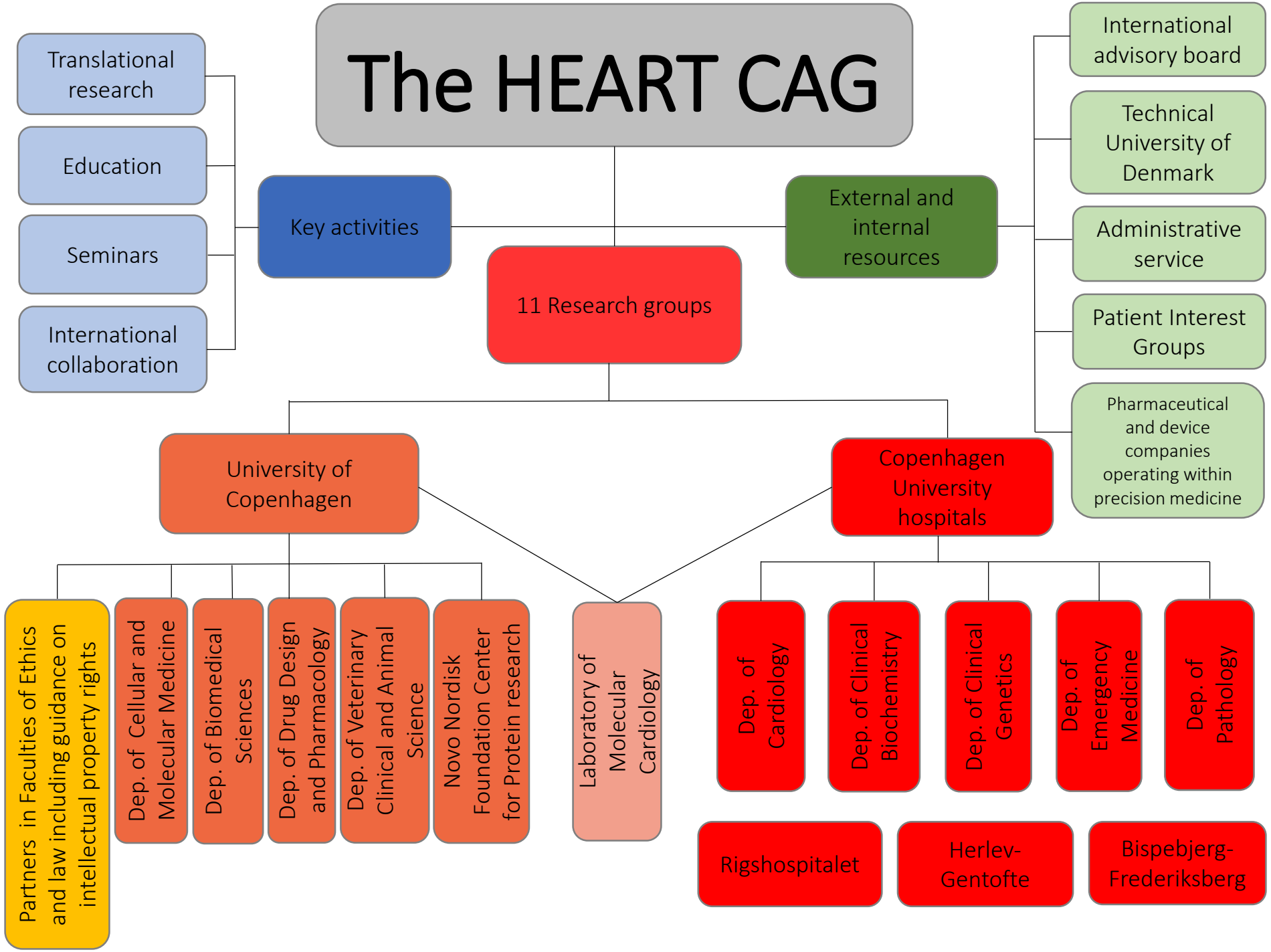


Randomised clinical trials for choice of

- Treatment
- Follow-up

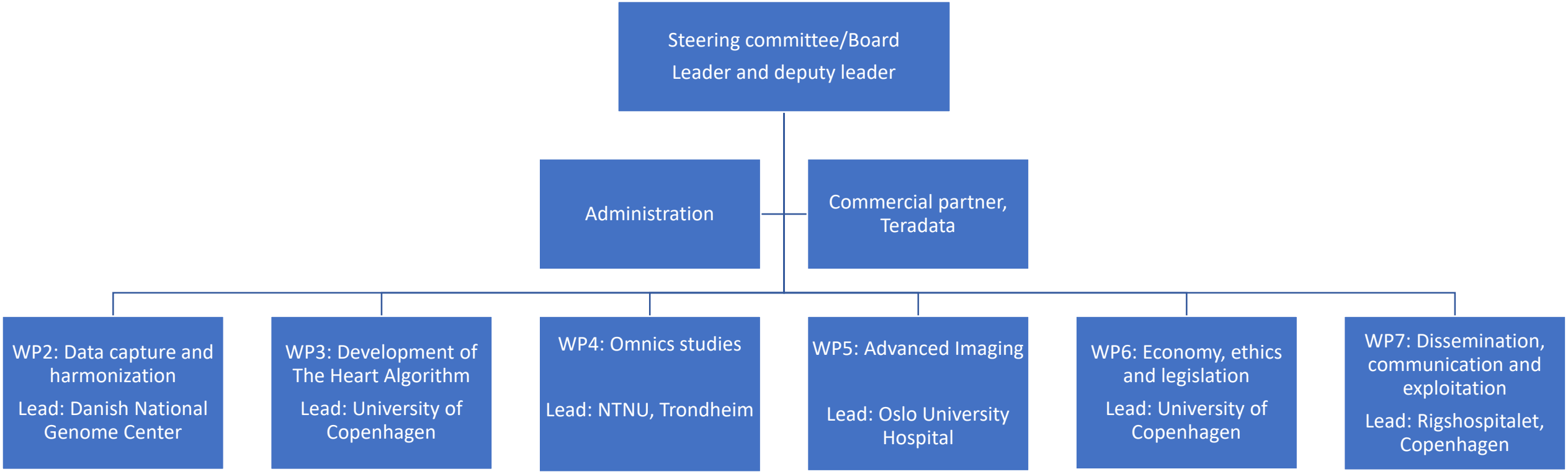
The Heart Algorithm; Ischemic Heart Disease (IHD)




The HEART CAG
Translational research
Education
Seminars
International collaboration
Key activities
11 Research groups
External and internal resources
International advisory board
Technical University of Denmark
Administrative service
Patient Interest Groups
Pharmaceutical and device companies operating within precision medicine
University of Copenhagen
Copenhagen University hospitals
Partners in Faculties of Ethics and law including guidance on intellectual property rights
Dep. of Cellular and Molecular Medicine
Dep. of Biomedical Sciences
Dep. of Drug Design and Pharmacology
Dep. of Veterinary Clinical and Animal Science
Novo Nordisk Foundation Center for Protein research
Laboratory of Molecular Cardiology
Dep. of Cardiology
Dep. of Clinical Biochemistry
Dep. of Clinical Genetics
Dep. of Emergency Medicine
Dep. of Pathology
Rigshospitalet
Herlev-Gentofte
Bispebjerg-Frederiksberg

UNIVERSITY OF COPENHAGEN | NTNU HUNT Research Centre | Oslo University Hospital | deCODE genetics | SUNDHEDS- OG ÆLDREMINISTERIET | REGION The Capital Region of Denmark

Nordic Personalised Medicine – PM HEART



Horizon 2020 TOPIC: … implementation of personalised medicine in healthcare

Scope: The projects should …. benefit for individuals as well as the implementability and economic viability of **personalised medicine** approaches in real life healthcare settings.

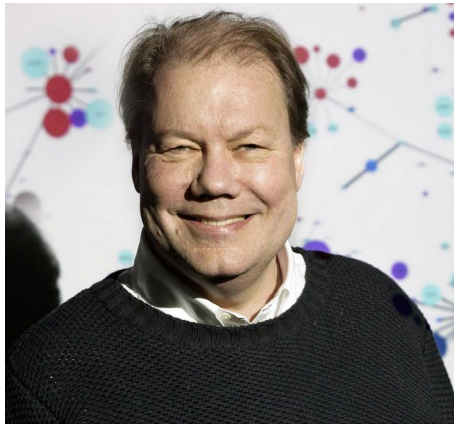
…. making use of a wide variety of data and proposing prediction, prevention or treatment solutions,
…… focussing on **diseases with high burden to society and including multi-morbidity conditions.**
The **use of big data** …. high performance computing is encouraged. ….economic, ethical, legal and societal aspects of the proposed action.
NOT … cancer and rare diseases
…. between EUR 18 and **EUR 20 million** would allow this specific challenge to be addressed appropriately.

NordForsk kr 22 mio

Work packages leaders

Professor Henning Bundgaard
The heart center, Copenhagen
University Hospital, Rigshospitalet

Peter Løngreen, Director
Computerome



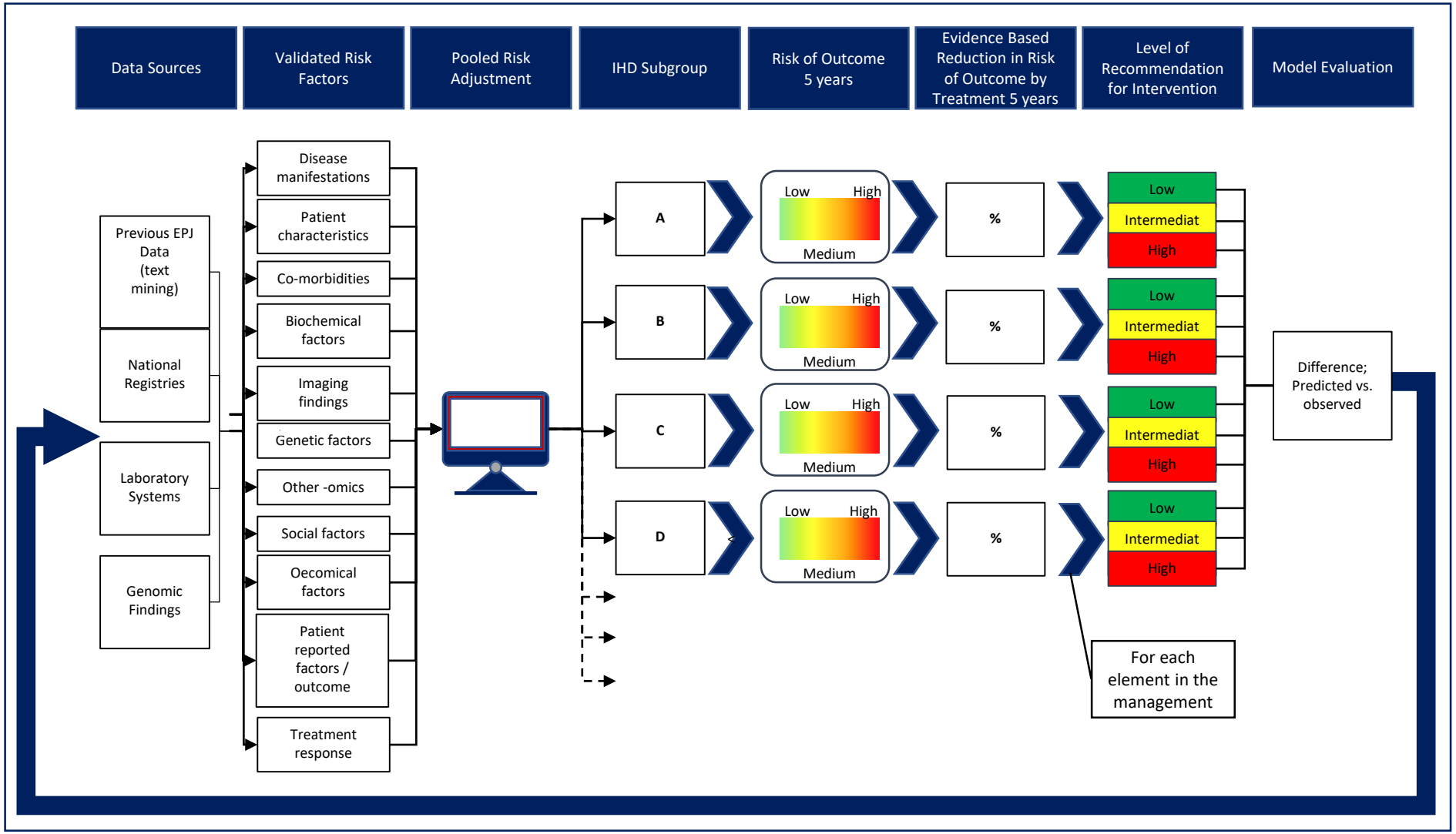
Professor Søren Brunak , Research Director
The Novo Nordisk Foundation Center
for Protein Research,
Copenhagen University Hospital

Professor Kristian Hveem
Department of Public Health and Nursing
Norwegian University of Science and Technology

Associate Professor Kristina Haugaa
Oslo University Hospital

Professor Mette Hartlev
Faculty of Law
University of Copenhagen

The Heart Algorithm; Ischemic Heart Disease (IHD)



Målet – visionen; udvikling af:

The Heart^{IHD} Algorithm

Præcisions-diagnostik og præcisions-behandling
af patienter med kranspulsåre-sygdom

- som et videnskabeligt basered *klinisk*
<u>beslutnings-støtte-værktøj</u>
til almindelig daglig klinisk brug i de
nordiske lande

Batter det så noget?

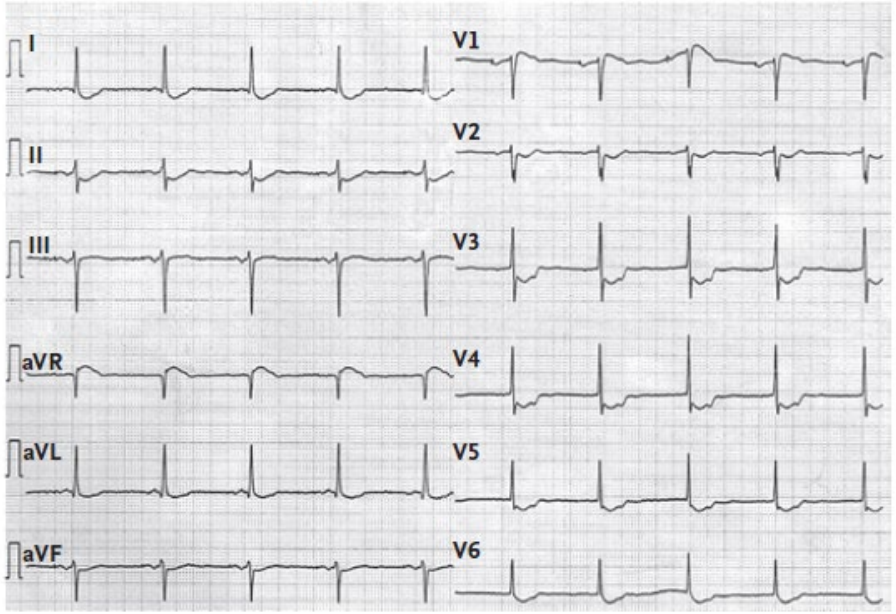
-kommer der noget ud af det?

The NEW ENGLAND JOURNAL of MEDICINE

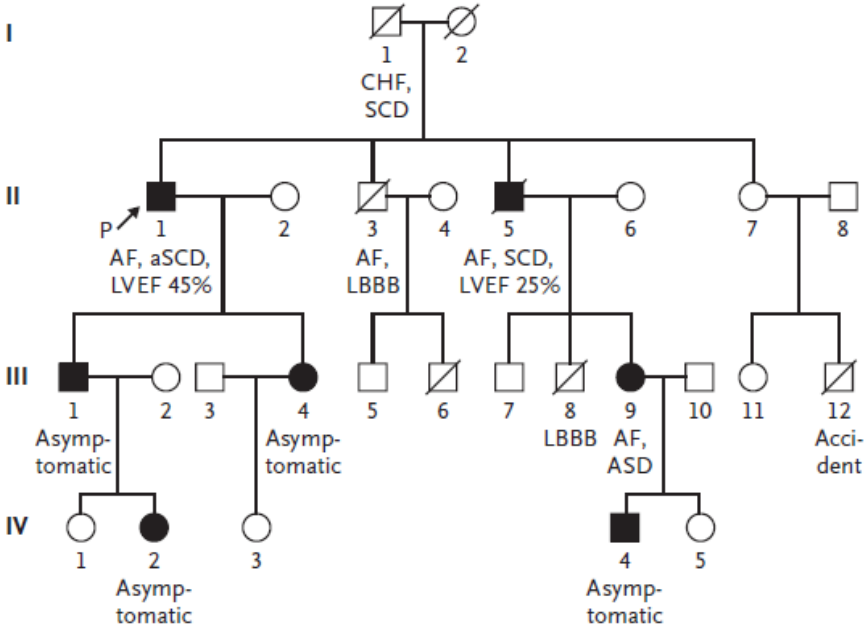
CORRESPONDENCE

A Novel Familial Cardiac Arrhythmia Syndrome with Widespread ST-Segment Depression

A 12-Lead ECG of the Family A Proband



B Pedigree of Family A



ESC European Society of Cardiology
European Heart Journal (2020) 41, 2618–2628
doi:10.1093/eurheartj/ehaa531

BASIC SCIENCE
Lipids

Genetic variability in the absorption of dietary sterols affects the risk of coronary artery disease

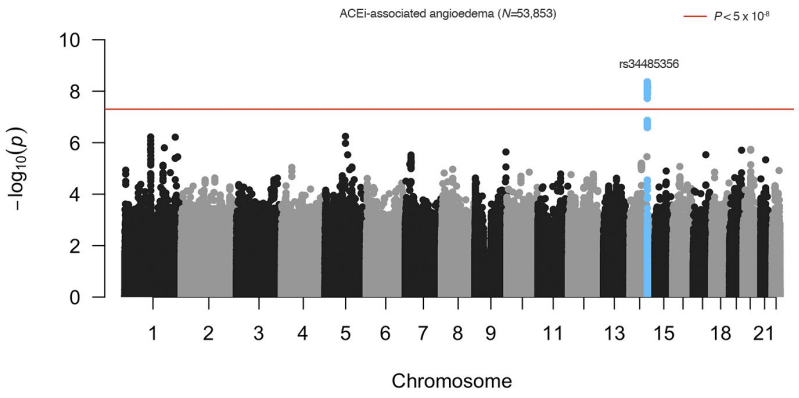
Anna Helgadottir,[1*] Gudmar Thorleifsson,[1] Kristjan F. Alexandersson,[1] Vinicius Tragante,[1,2] Margret Thorsteinsdottir,[3,4] Finnur F. Eiriksson,[3] Solveig Gretarsdottir,[1] Eythór Björnsson,[1,5,6] Olafur Magnusson,[1] Gardar Sveinbjornsson,[1] Ingileif Jonsdottir,[1,6] Valgerdur Steinthorsdottir,[1] Egil Ferkingstad,[1] Brynjar Ö. Jensson,[1] Hreinn Stefansson,[1] Isleifur Olafsson,[7] Alex H. Christensen,[8] Christian Torp-Pedersen,[9,10] Lars Køber,[11] Ole B. Pedersen,[12,13] Christian Erikstrup,[14] Erik Sørensen,[15] Søren Brunak,[16] Karina Banasik,[16] Thomas F. Hansen,[16,17,18] Mette Nyegaard,[19] Gudmundur I. Eyjolfssson,[20] Olof Sigurdardottir,[21] Bjorn L. Thorarinsson,[22] Stefan E. Matthiasson[23] Thora Steingrimsdottir,[6,24] Einar S. Bjornsson,[5,6] Ragnar Danielsen,[25] Folkert W. Asselbergs,[2,26,27] David O. Arnar,[1,6,25] Henrik Ullum,[15] Henning Bundgaard,[11] Patrick Sulem,[1] Unnur Thorsteinsdottir,[1,6] Gudmundur Thorgeirsson,[1,6,25] Hilma Holm,[1] Daniel F. Gudbjartsson,[1,28] and Kari Stefansson[1,6*]

CHB-finding; Common variants near *BDKRB2 (bradykinin receptor B2)* are associated angioedema in patients treated with angiotensin converting enzyme inhibitors

- Class 1 recommendation to use of RAS-inhibitors

(n=200.000 Danes) in

  - Hypertension
  - Heart failure
  - After myocardial infarction
  - In diabetic nephropathy



- Up to 1% develops angioedema
  - If in tongue, pharynx or larynx immediate <u>*life-threatening*</u>

Klinisk perspektiv

Udvikling af farmakologisk DNA chip (kr. 350 pr stk.) til at finde patienter med

- Risiko for alvorlige bivirkninger
- Ringe – eller INGEN - effekt af stoffet

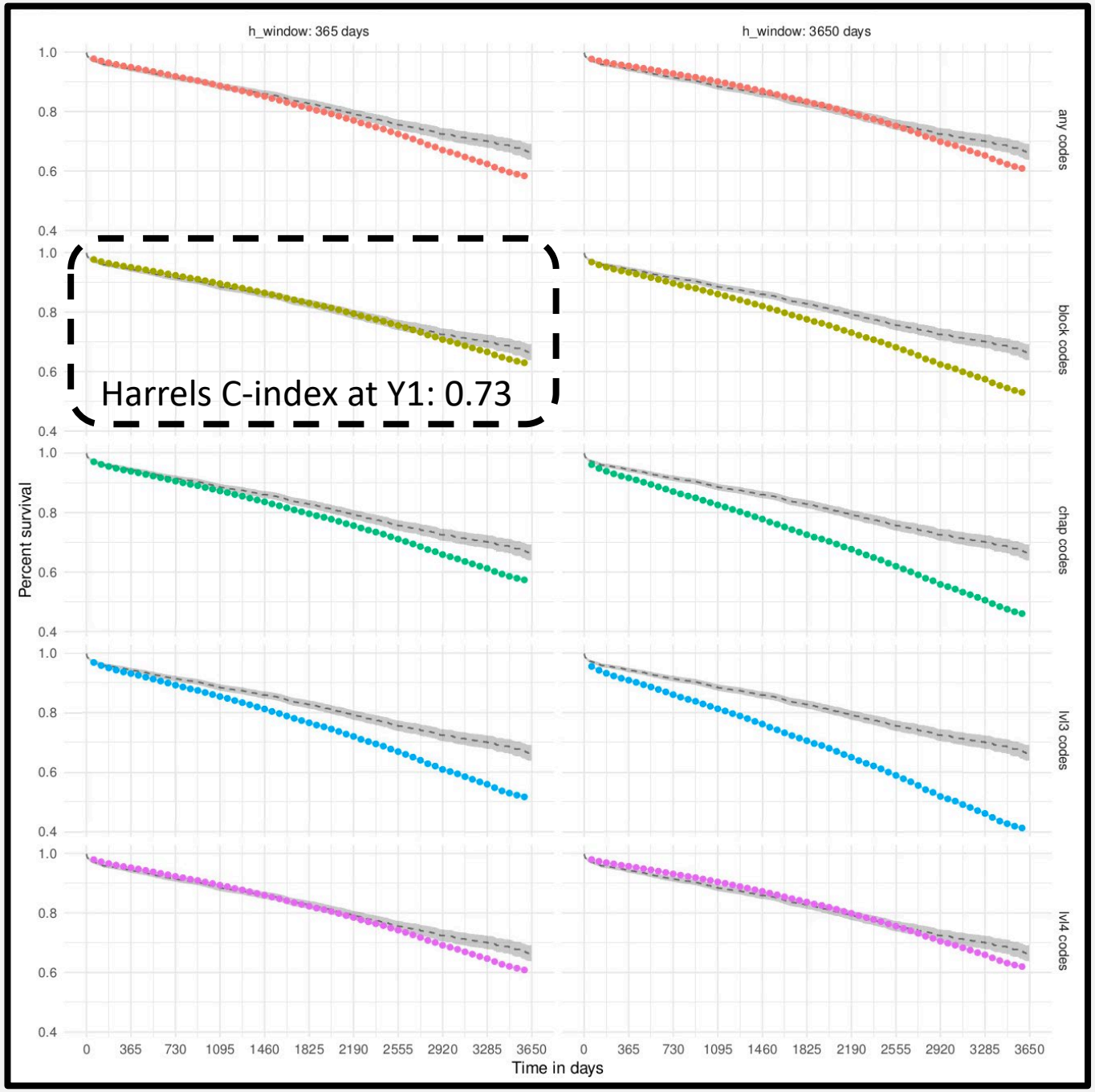
Det drejer sig om store grupper af lægemidler

- ACE-hæmmere (200.000 danskere)
- Kolesterolsænkning (650.000 danskere)
- Beta-blokkere (200.000 danskere)
- Blodfortynding (>300.000 danskere)
- ….

-dvs. kan få betydning for op mod 1 mio i DK – dvs. ca. ½ mio i RegH

Average predicted survival from neural networks

- Observed KM-estimates as reference
- Several models overly pessimistic
- In general, more aligned in the first 5 years
- 1 year h_window seems to perform better
- Without thorough tuning!
- Average survival is not that meaningful



Work in progress

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REVIEW ARTICLE

FRONTIERS IN MEDICINE

Treating Disease at the RNA Level with Oligonucleotides

Arthur A. Levin, Ph.D.

DISEASES AS DIFFERENT AS SPINAL MUSCULAR ATROPHY AND HYPERLIPidemias can now be treated with drugs that act on RNA. A new class of drugs — oligonucleotides — takes advantage of Watson and Crick's base-pairing rules to target disease-related RNAs. With information from the sequencing of the human genome, it is possible to design therapeutic oligonucleotides — solely on the basis of genomic information — that will change the expression of any protein, even those not amenable to traditional approaches involving small-molecule drugs (see video).

From Research and Development, Avidity Biosciences, La Jolla, CA. Address reprint requests to Dr. Levin at art.levin@aviditybio.com.

N Engl J Med 2019;380:57-70.
DOI: 10.1056/NEJMra1705346
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Spinal muscular atrophy
Hypercholesterolemia
Duchenne's muscular dystrophy

Sammenfatning

GREATER COPENHAGEN
HEALTH • SCIENCE • PARTNERS

Udvikling af personlig medicin kræver mange(s) kompetencer

Region Hovedstaden

Identificere forsknings-temaer ud fra patient-behov
Lægefaglig indsigt
Inddrage patienter
Patient-data
Kliniske undersøgelser
Justere eller ophøre med uvirksomme behandlinger
Indføre nye behandlingsmetoder

København Universitet / Danmarks Tekniske Universitet

Avancerede laboratorie-forskning – dyr og humane
-dyremodeller
-genetisk modificerede modeller
-omics
BIG-DATA management
Udvikling af nye teknikker – software og hardware
Etik, Jura, Økonomi
Folkesundhedsvidenskab

- udviklingen af sundhedsvæsenet afhænger af meget MERE tvær-sektoriel samarbejde

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Patient-fokuseret forskning - kræver mange(s) kompetencer

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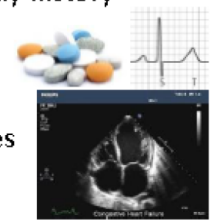
IMPROVED CARDIOVASCULAR HEALTH

DEEP PHENOTYPING

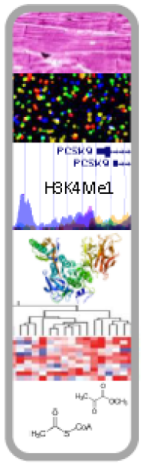
Expanded clinical diagnostic routine
Patient and family history
Symptoms
Medications
Disease course
Clinical outcomes
Imaging



SAMPLING

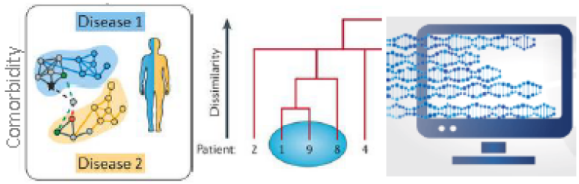
Blood
Urine
Myocardial & skin biopsies

MOLECULAR AND TISSUE ANALYSES



Tissue characterization
Genomics
Epigenomics
Proteomics
Transcriptomics
Metabolomics

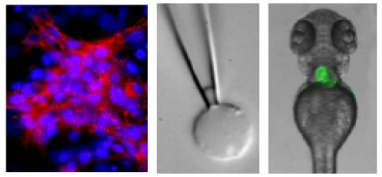
BIOINFORMATICS



Interpretation of complex data patterns

FUNCTIONAL VALIDATION

Cell and animal models



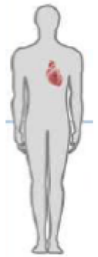
NOVEL DISCOVERIES

Phenotypes
Drug targets
Treatment responses

CLINICAL VALIDATION & IMPLEMENTATION

Precision diagnostics
Precision therapeutics
Computer-aided decisions

THE CARDIOVASCULAR PATIENT



Cardiomyopathies
Ischemic heart disease
Arrhytmia
Congenital heart defect