Heart Rhythm Congress, Birmingham, 11th October 2016

Personalized arrhythmia management

From a physician's perspective

Andrew Grace

University of Cambridge - Papworth Hospital

Consultant: Acutus Medical Inc., Bardy Diagnostics

Boston Scientific Inc. (member PSAB) and Founder, Electus Medical Inc.

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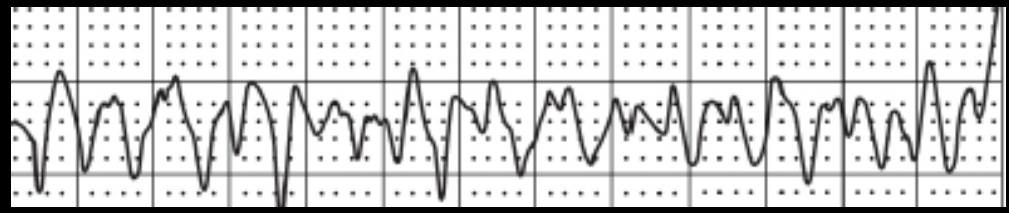

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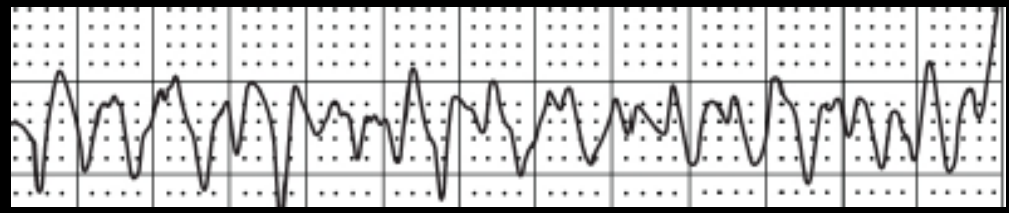

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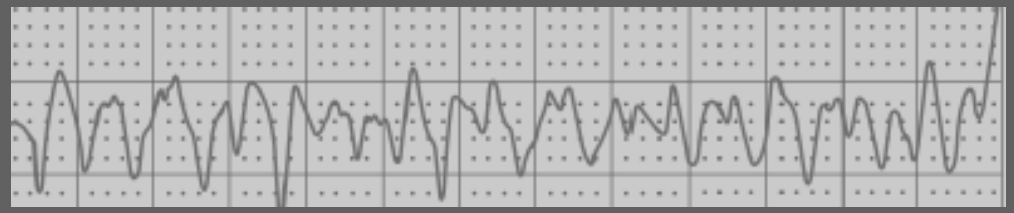

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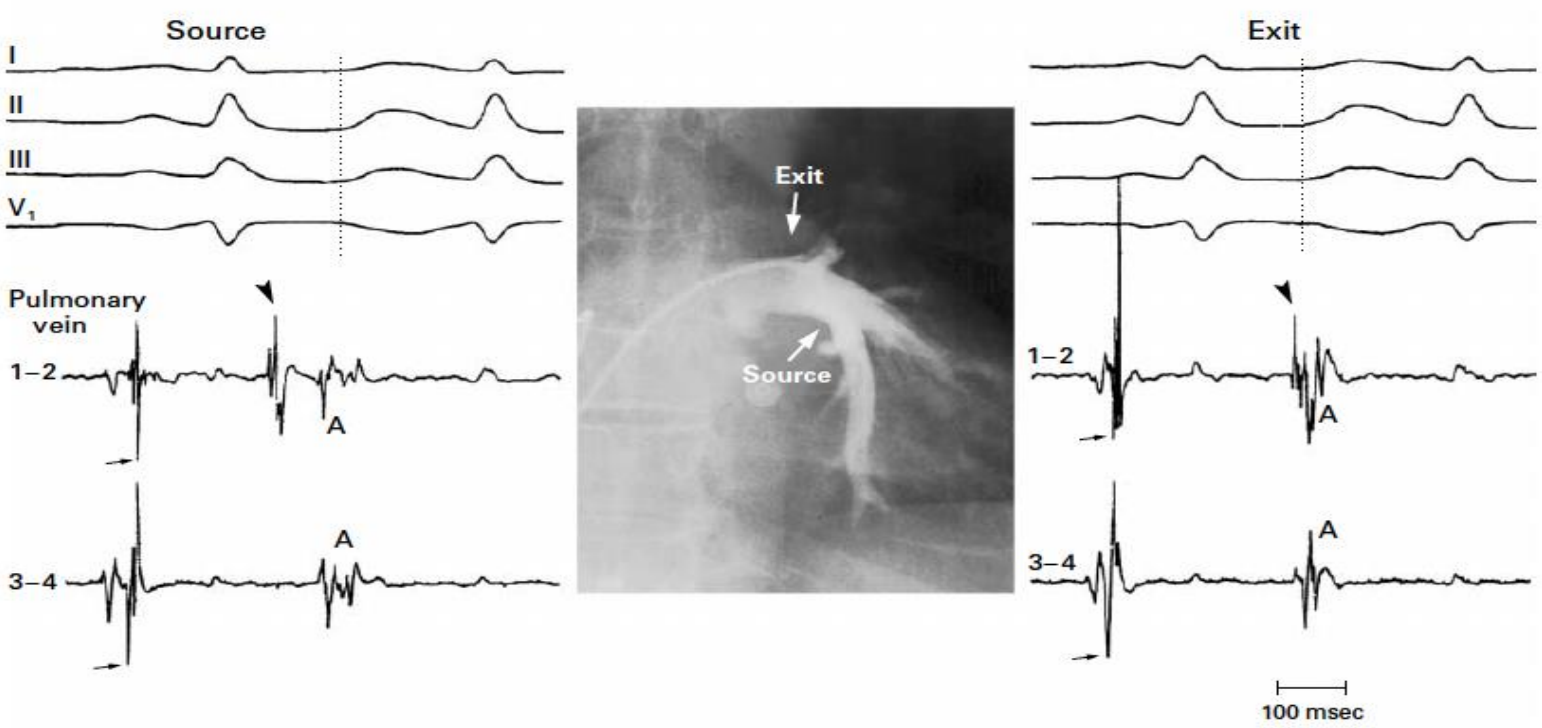
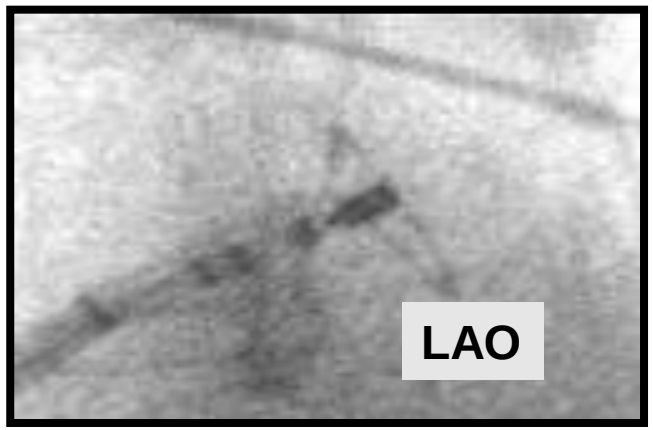
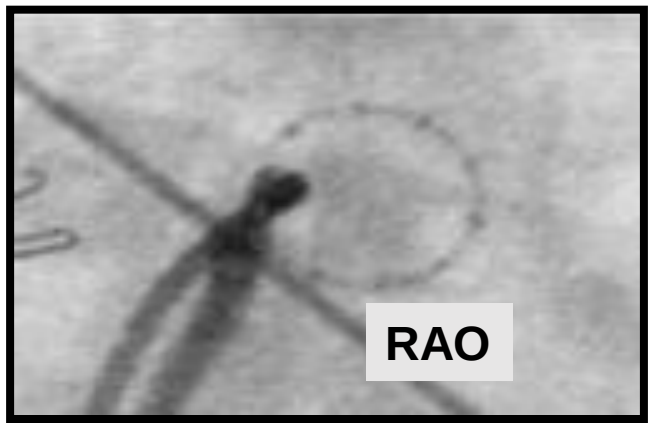
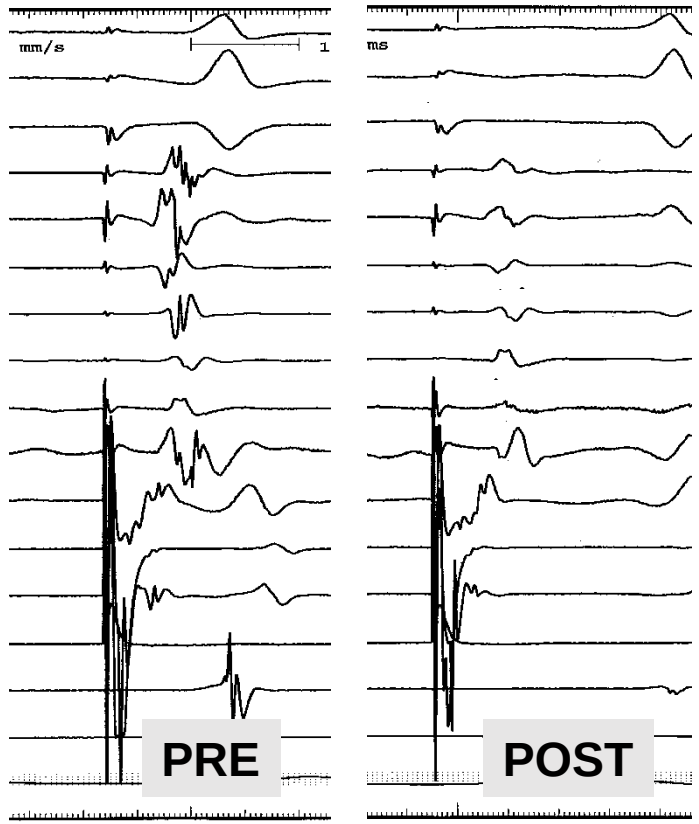
CURRENT EMPIRIC THERAPY AF

SPONTANEOUS INITIATION OF ATRIAL FIBRILLATION BY ECTOPIC BEATS ORIGINATING IN THE PULMONARY VEINS

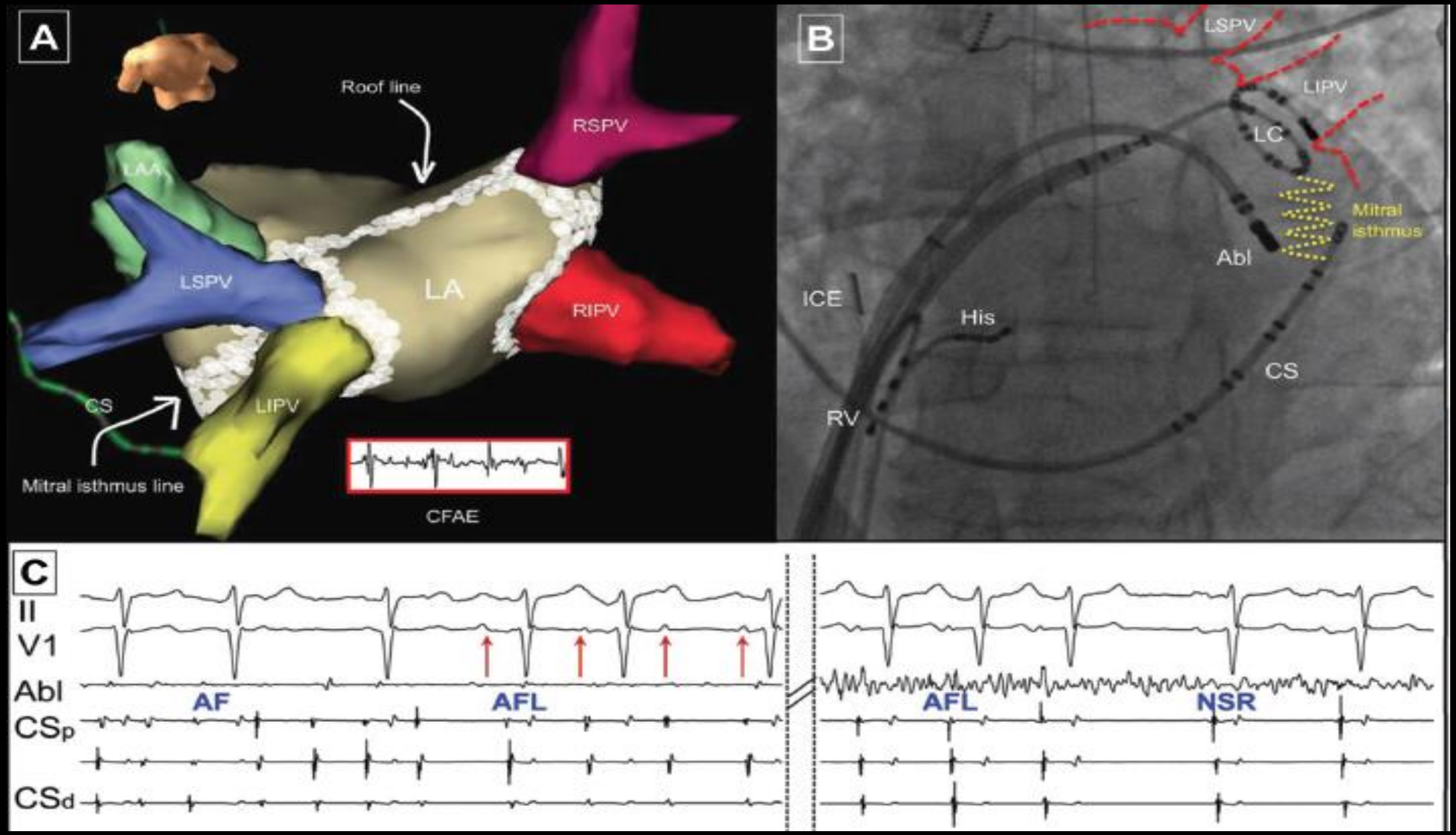








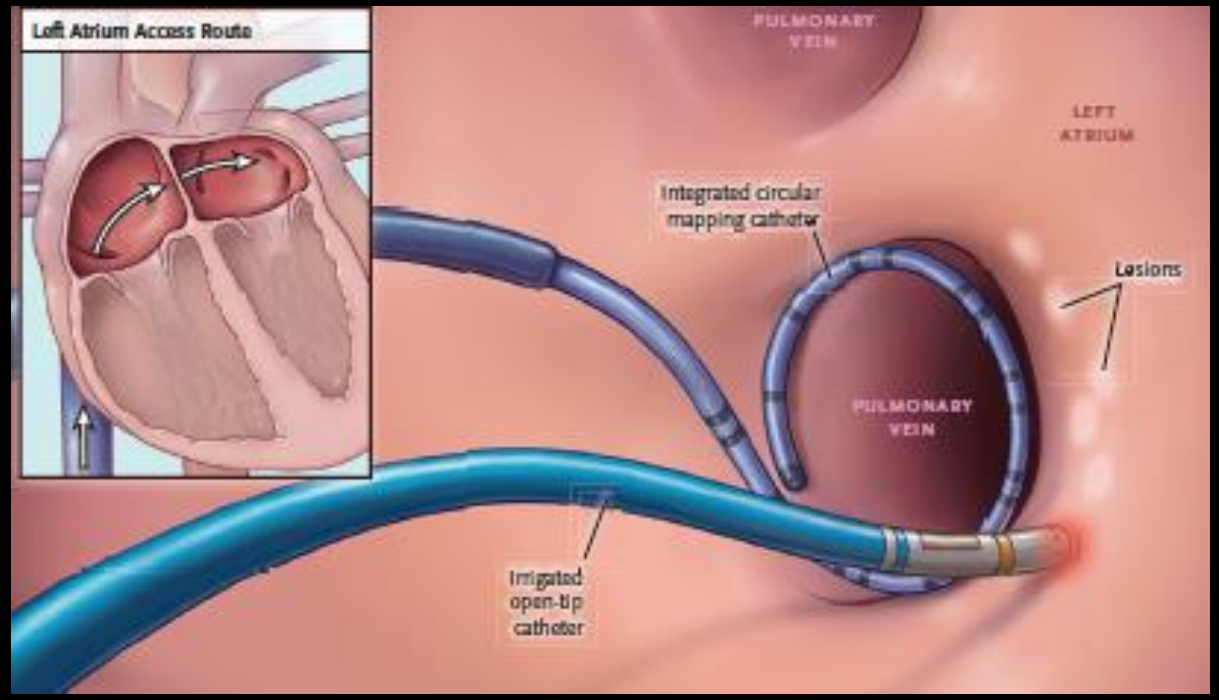
Haissaguerre et al. N Engl J Med 1998; 339:659



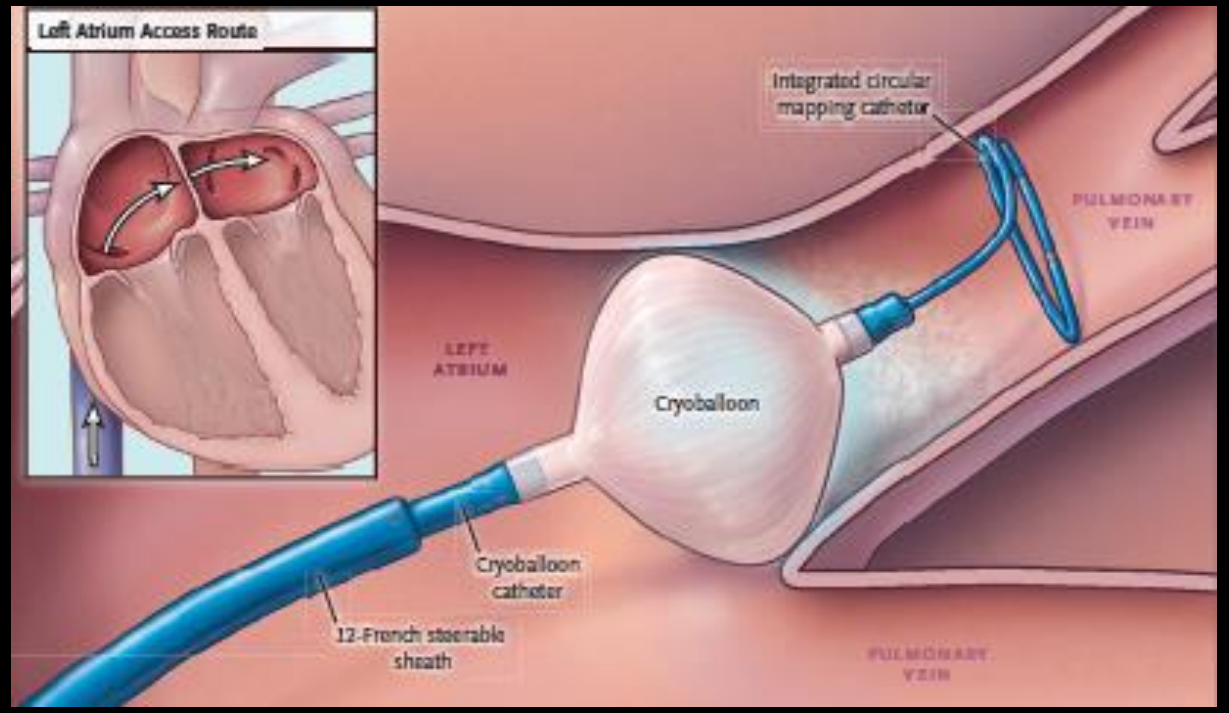
Tung et al. Circulation 2012; 126:223-9

Pulmonary Vein Isolation for Atrial Fibrillation

Conventional ‘point-by-point’

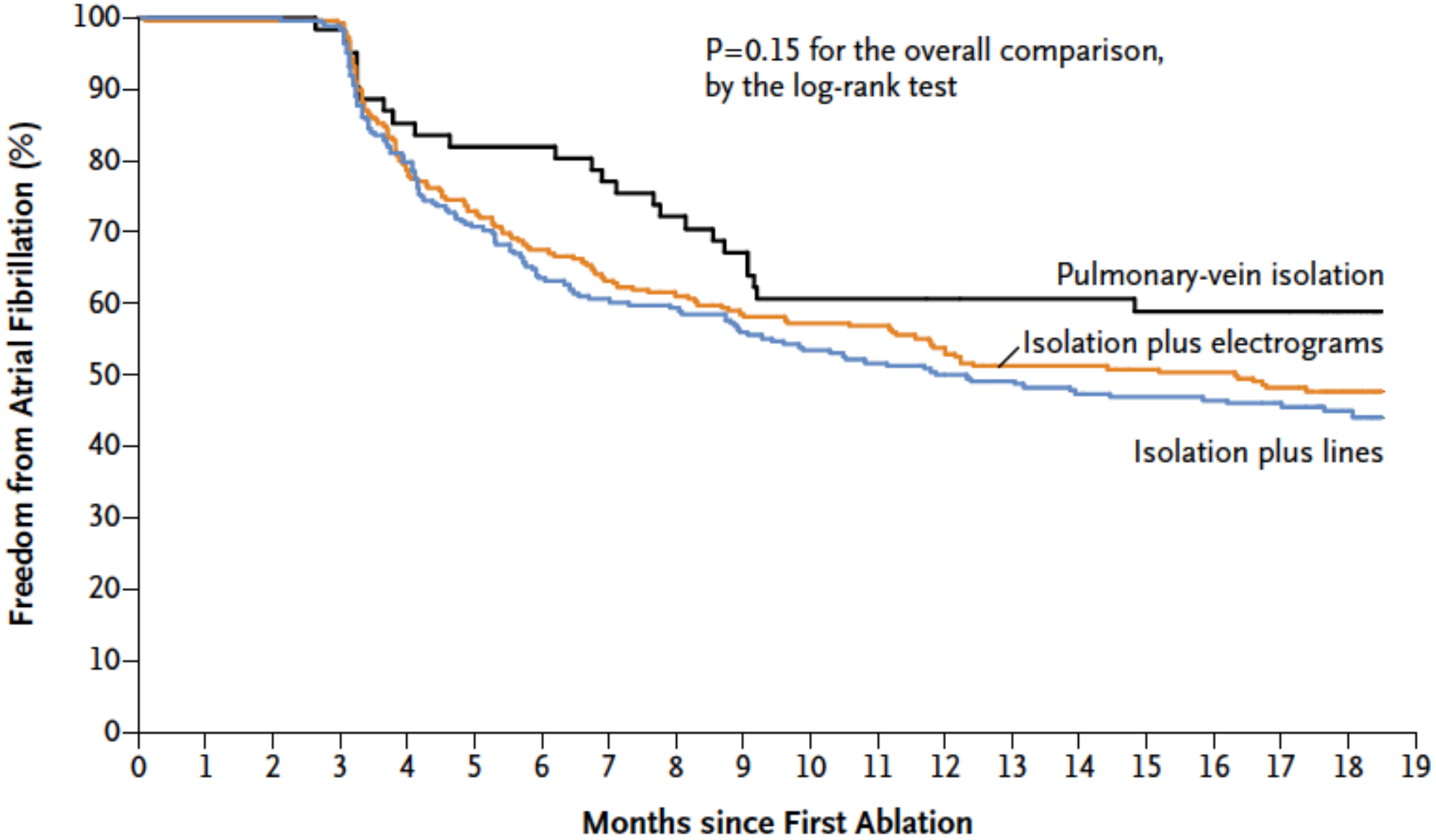


Single Shot ‘Cryoballoon’



FIRE AND ICE trial - Kuck KH *et al.* N Engl J Med 2016

Pulmonary Vein Isolation for Persistent Atrial Fibrillation



Verma *et al.* N Engl J Med 2015; 372:1812-22

‘PROGRESS IN SCIENCE DEPENDS ON NEW TECHNIQUES, NEW DISCOVERIES AND NEW IDEAS, PROBABLY IN THAT ORDER ’

Miranda Richardson, Nature 1908; 285: 358-9; Sydney Brenner, Genome Biology 2002;3:1013.1-1013.2

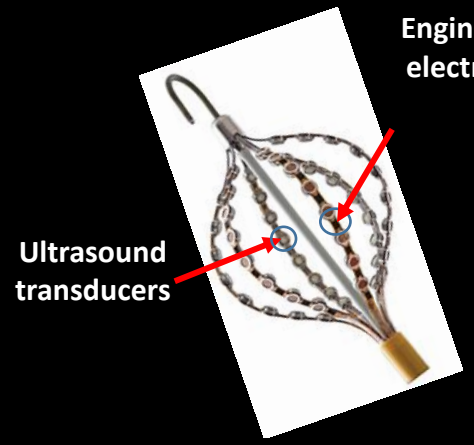
NEXT GENERATION DEEP PHENOTYPING

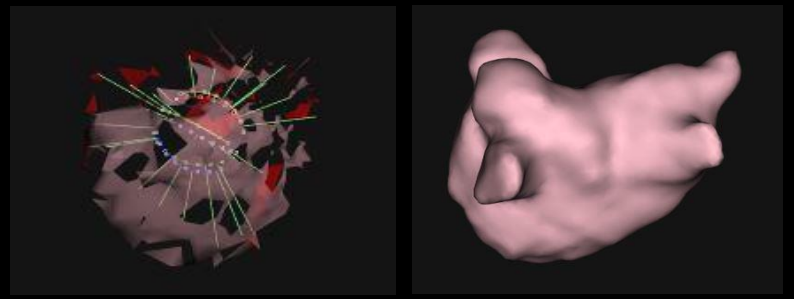
Panoramic High Resolution Dipole Density Mapping of Endocardial Activation

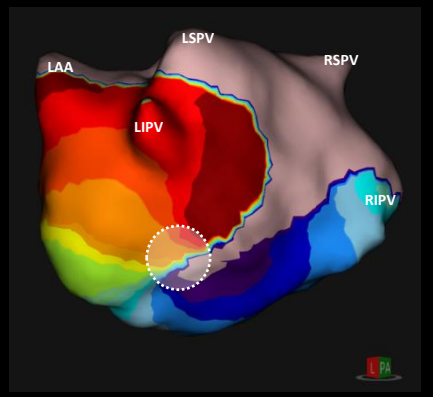
- Non Contact

- Ultrasound anatomy reconstruction
  - 3D surface is algorithmically reconstructed from ultrasound point set
  - Up to 115,000 points collected/min.

- Dipole density mapping
  - Quasi-static approximation of classical electrodynamics (cardiac activation slow compared to electrical field propagation)
  - Forward and inverse algorithms applied to derive dipole density
  - Intra-cardiac unipolar voltage sampled at 150,000/sec.







Identify and locate arrhythmic mechanisms

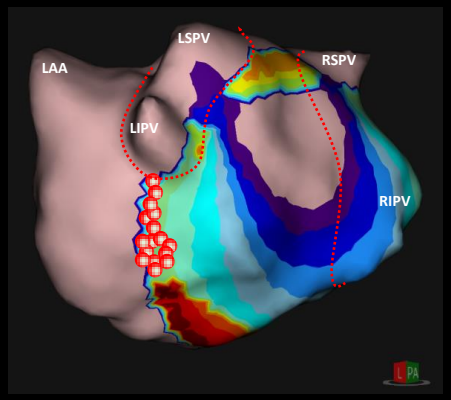
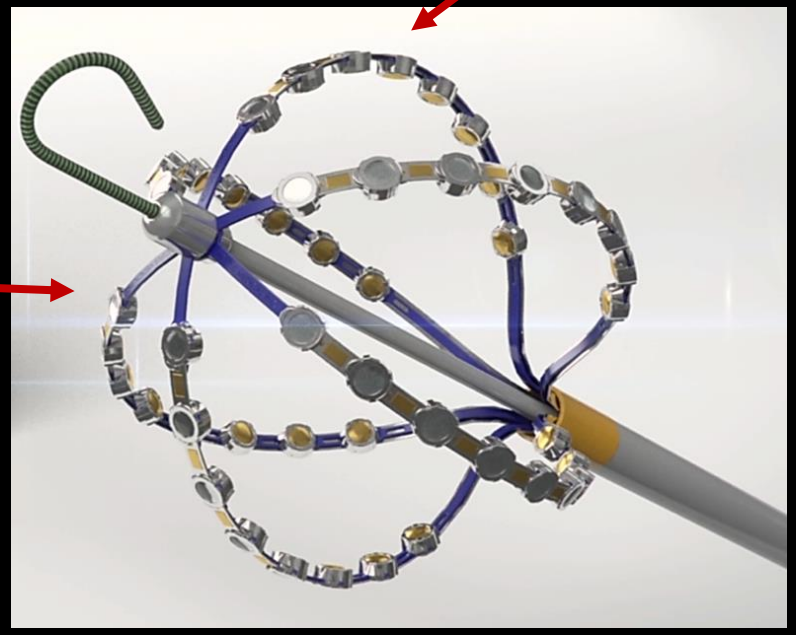


Image guided ablation strategy

Panoramic High Resolution Dipole Density Mapping of Endocardial Activation

48 Engineered Electrodes



48
Ultrasound
Transducers

115,000 ultrasound points/min.

150,000 unipolar voltage samples/sec.

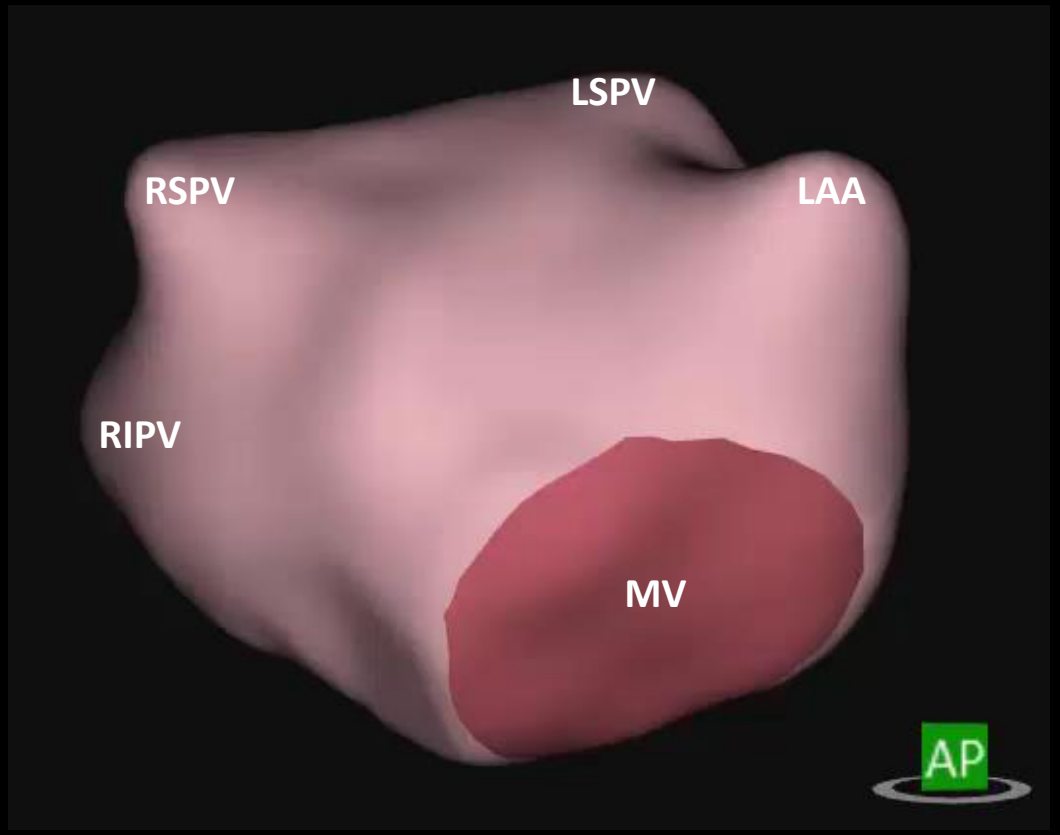
4x

Patient

- Male, b. 1960
- Recurrent persistent AF (since 2000)
- Many cardioversions/2 prior PVI

- 12m Amiodarone until 01.2016

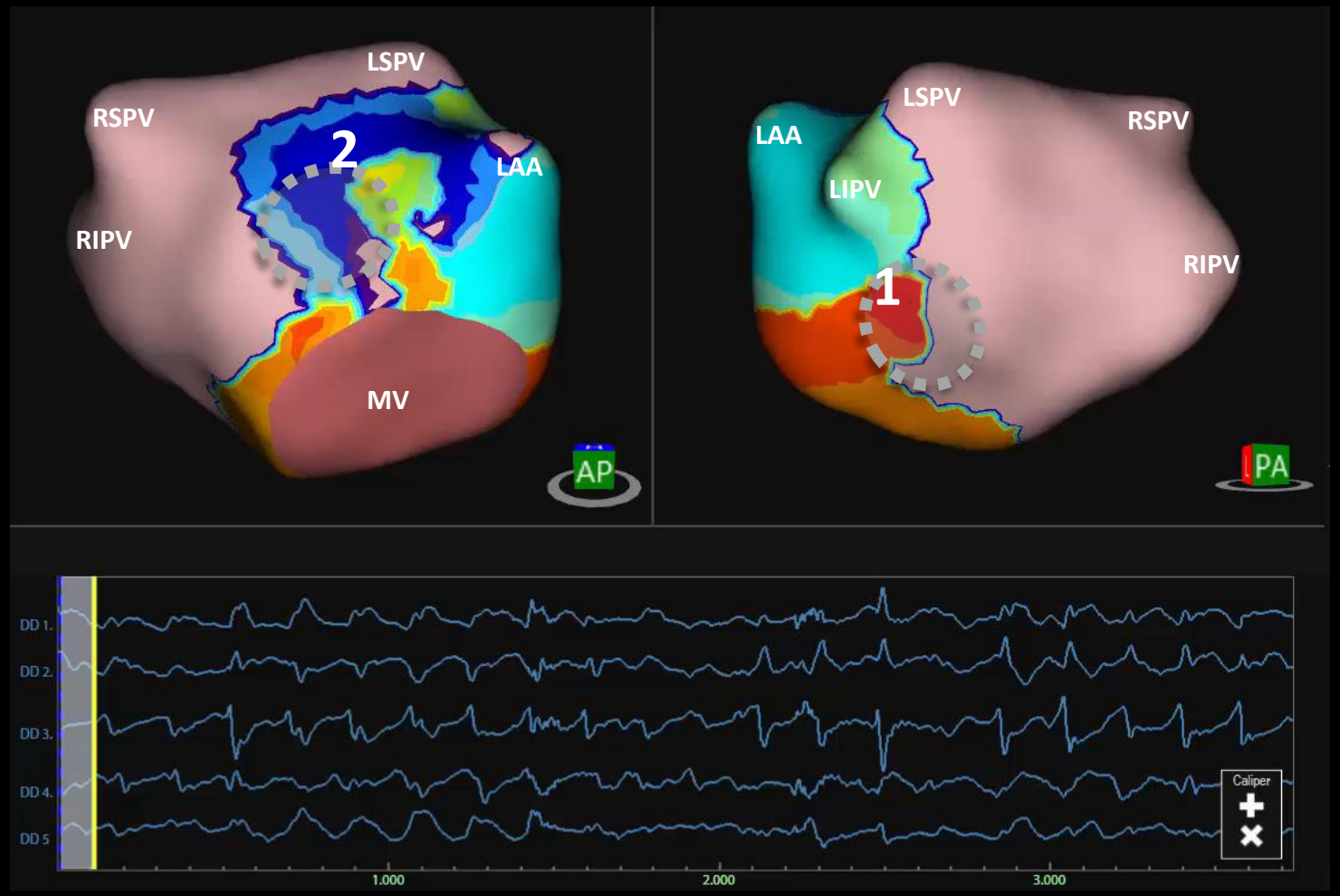
- Procedure 21st April 2016



*** CT October 2008:** LA 5.3; RSPV 1.7; RIPV 1.5; LSPV 1.7 (branch upper 1.3; lower 0.6)

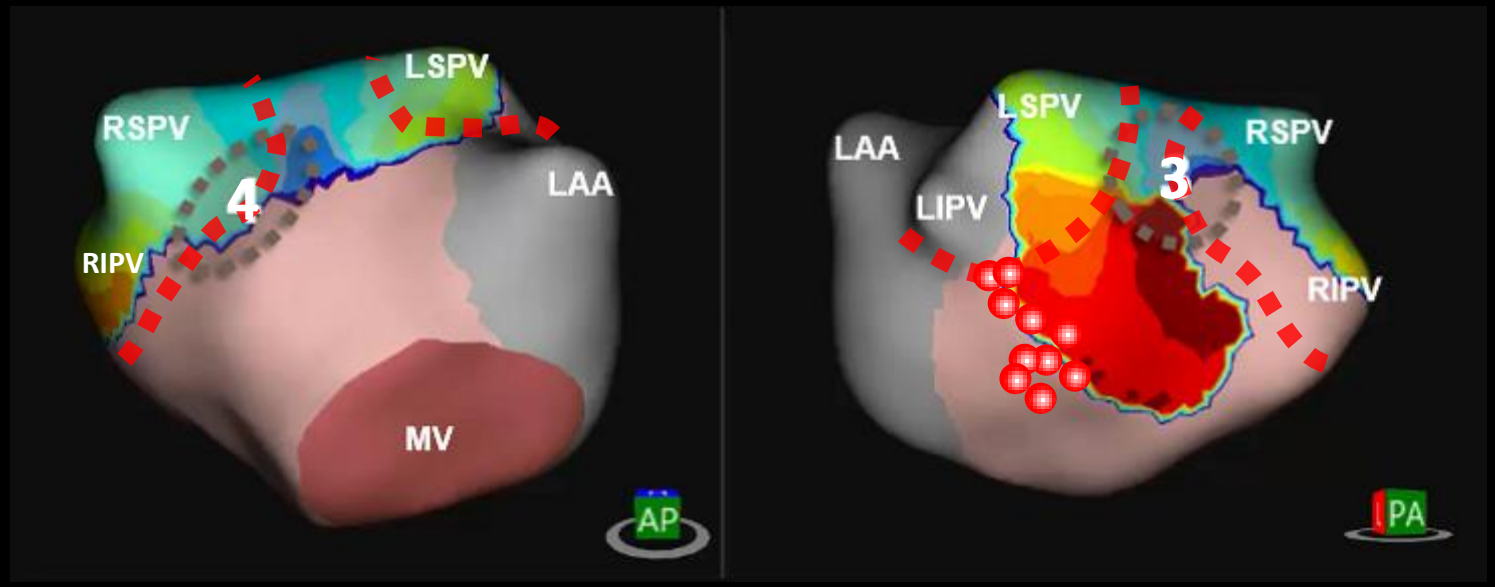
Initial Map AF – veins isolated from prior procedures

- Initial map showed two confined zones of *localized irregular activation* inferior to the LIPV antrum (zone 1) and on the anterior aspect of the roof (zone 2).



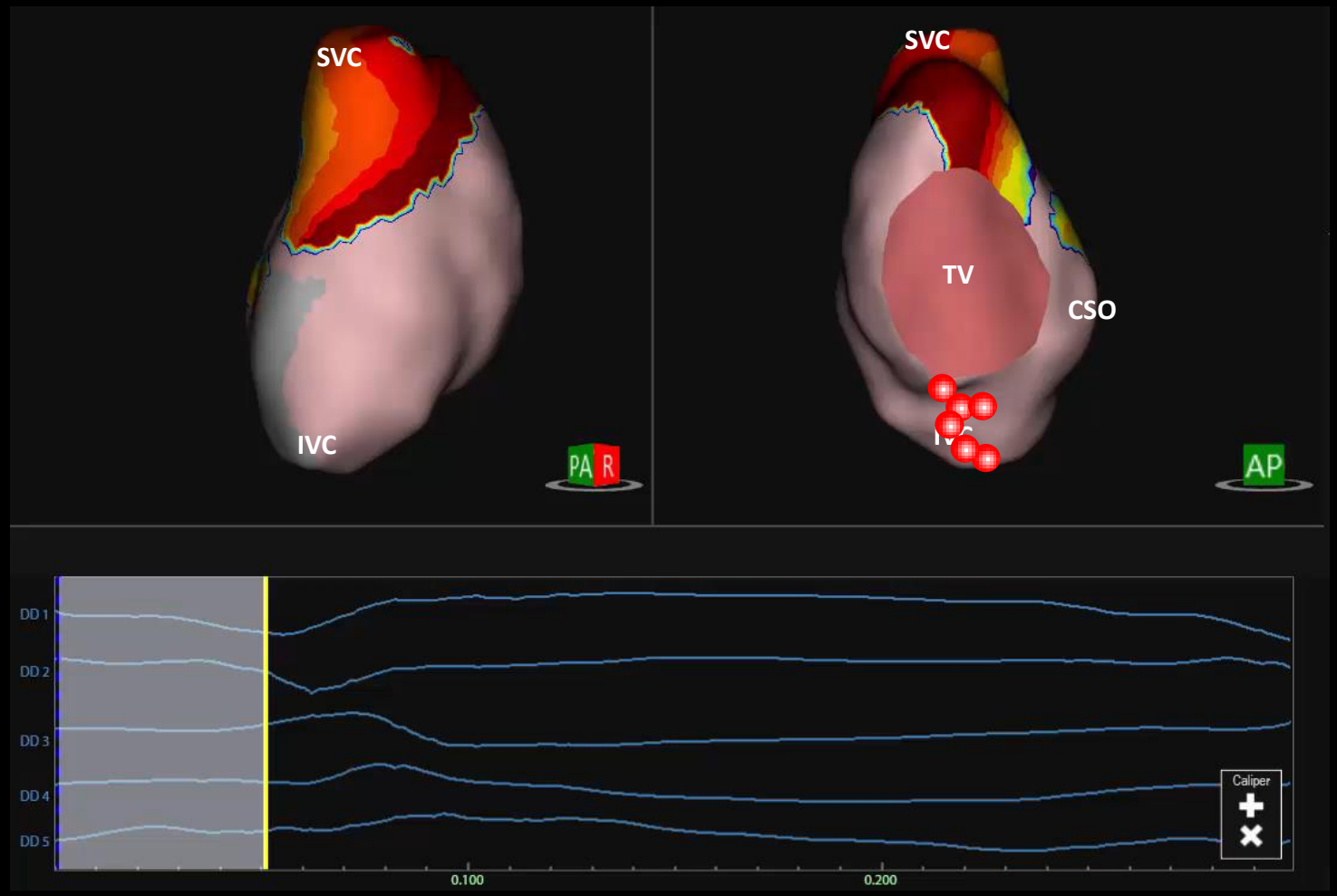
Left Atrial Ablation Strategy

- Initial ablation *area* inferior to the LIPV antrum (zone 1)
- Next wider RSPV/RIPV isolation



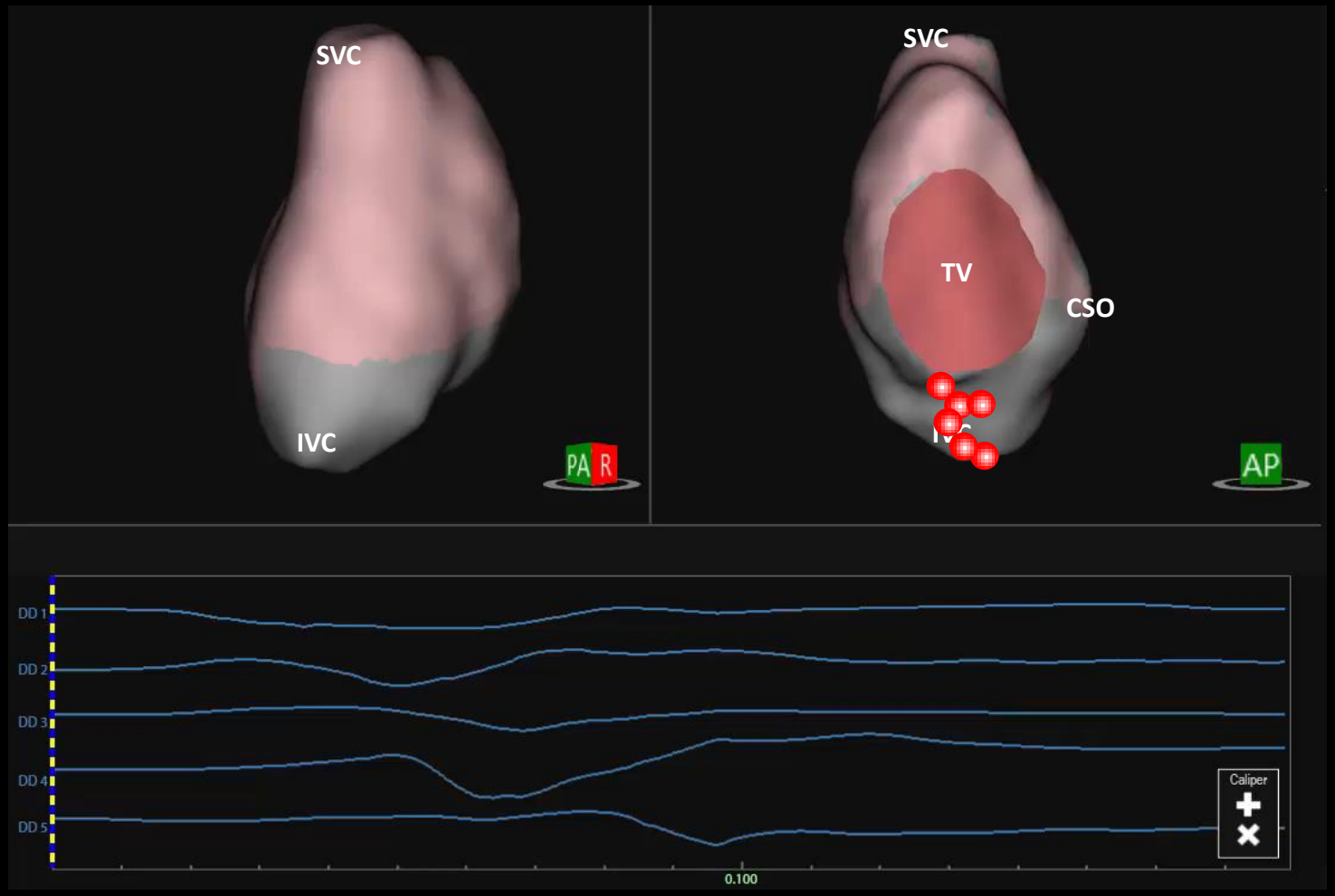
Limited Ablation Left Atrium converts to typical Flutter

- Counter-clockwise with rotation around the Crista and delayed conduction in the isthmus
- Standard CTI-line chosen for ablation



Sinus Rhythm Map

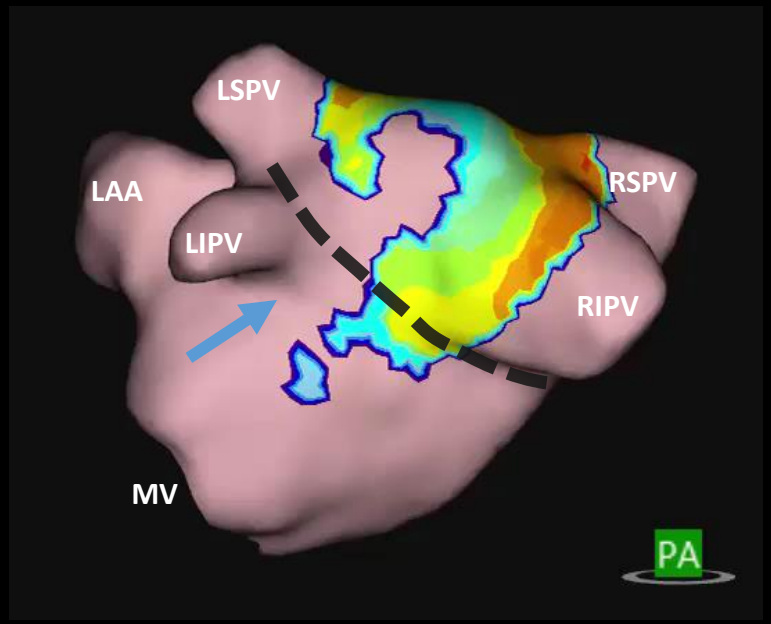
- Typical Flutter terminated during ablation across isthmus
- Ablation to sinus rhythm – maintained without drugs



Observed patterns

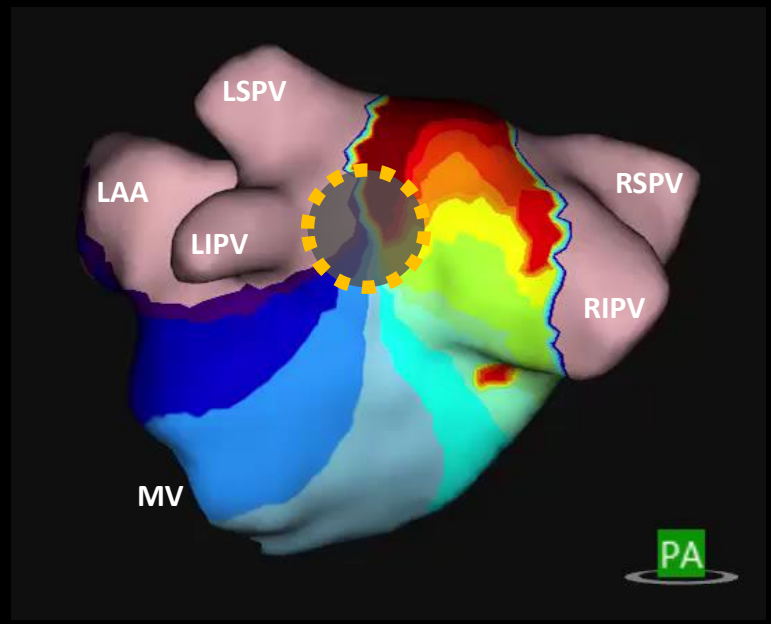
N = 119 observed patterns

Focal



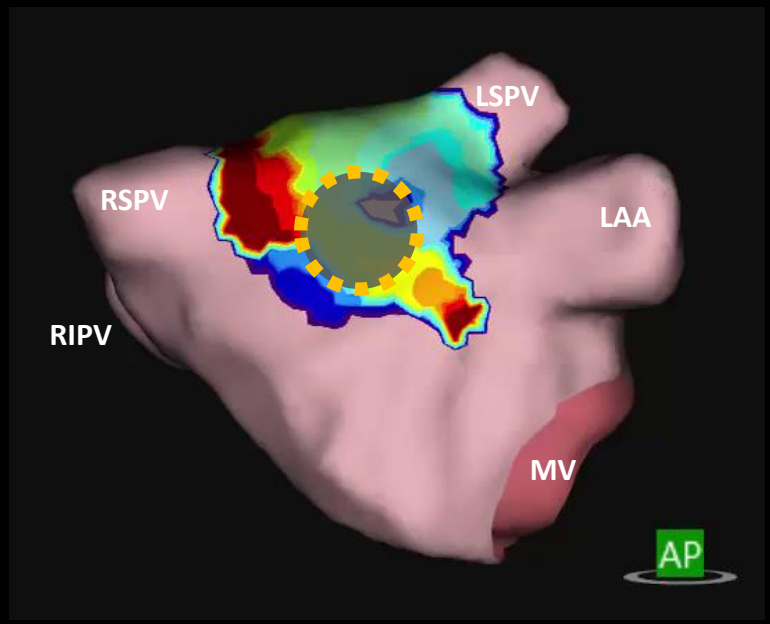
31.9%

Localized Rotational Activation



29.4%

Localized Irregular Activation



38.7%

Arrhythmia Phenotyping highly quantitative – possibility ‘precision medicine’

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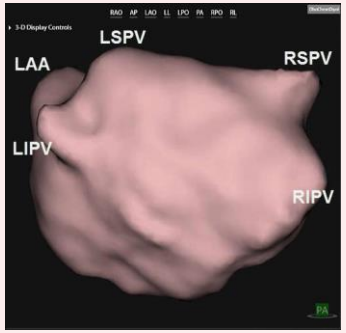

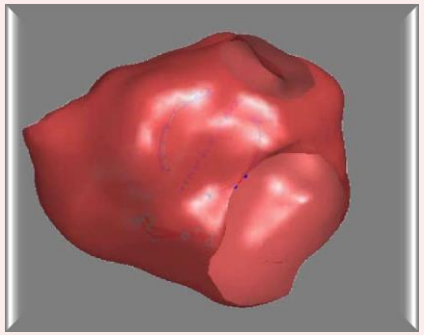

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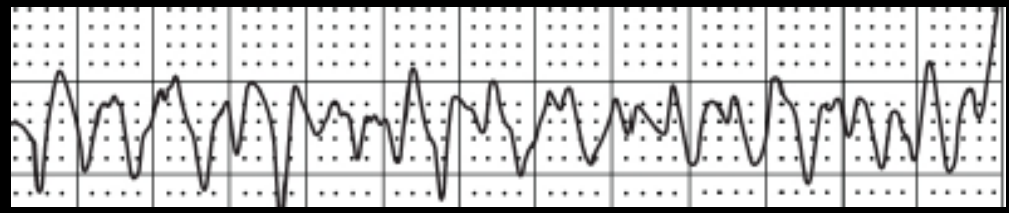

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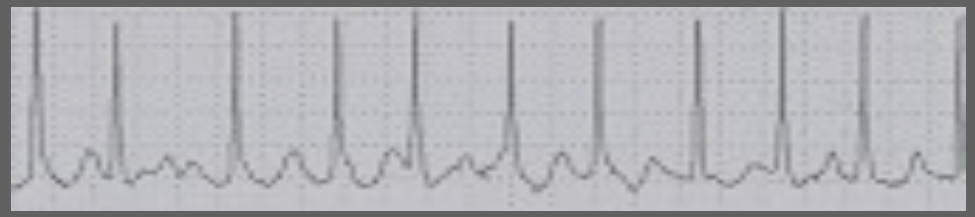

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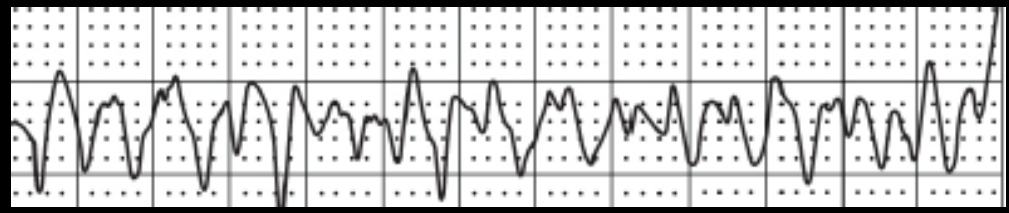

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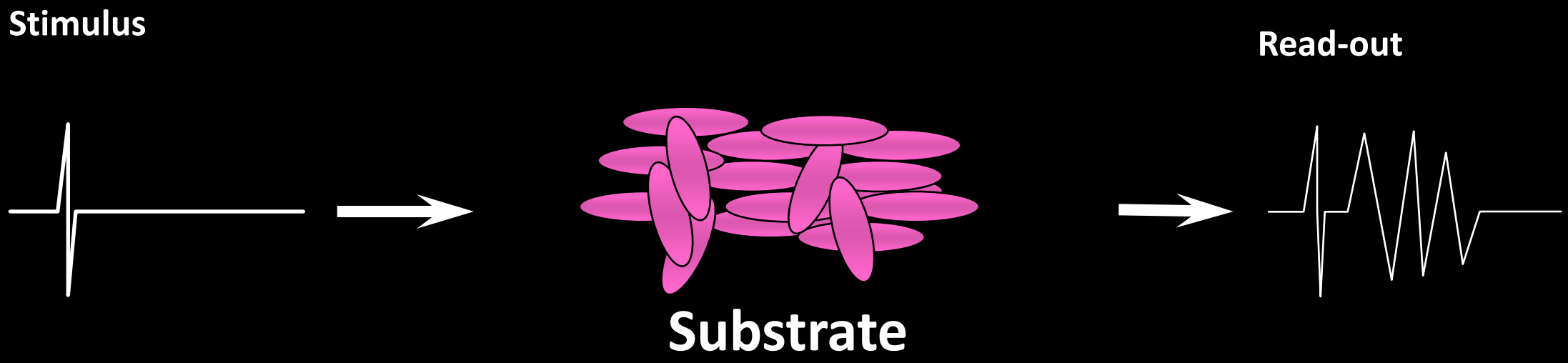

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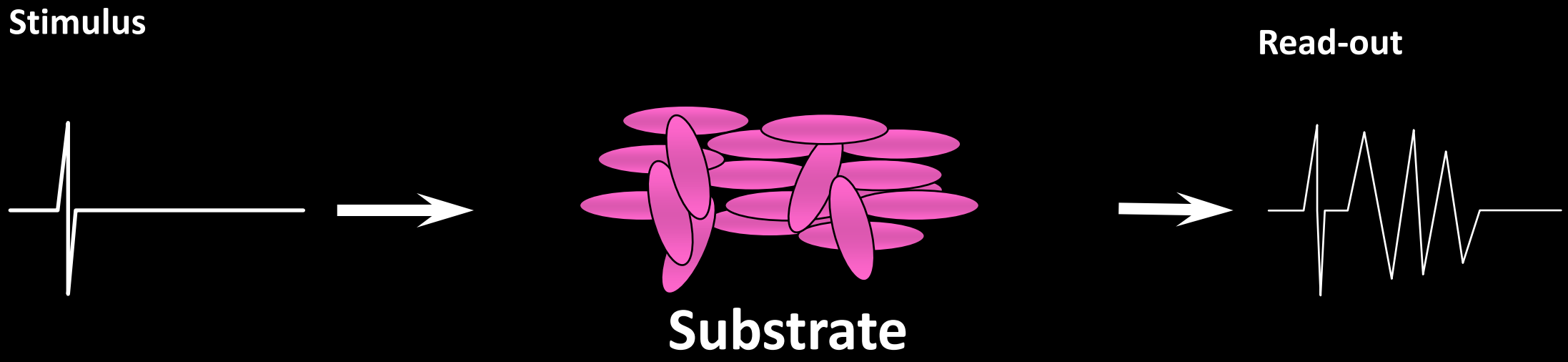
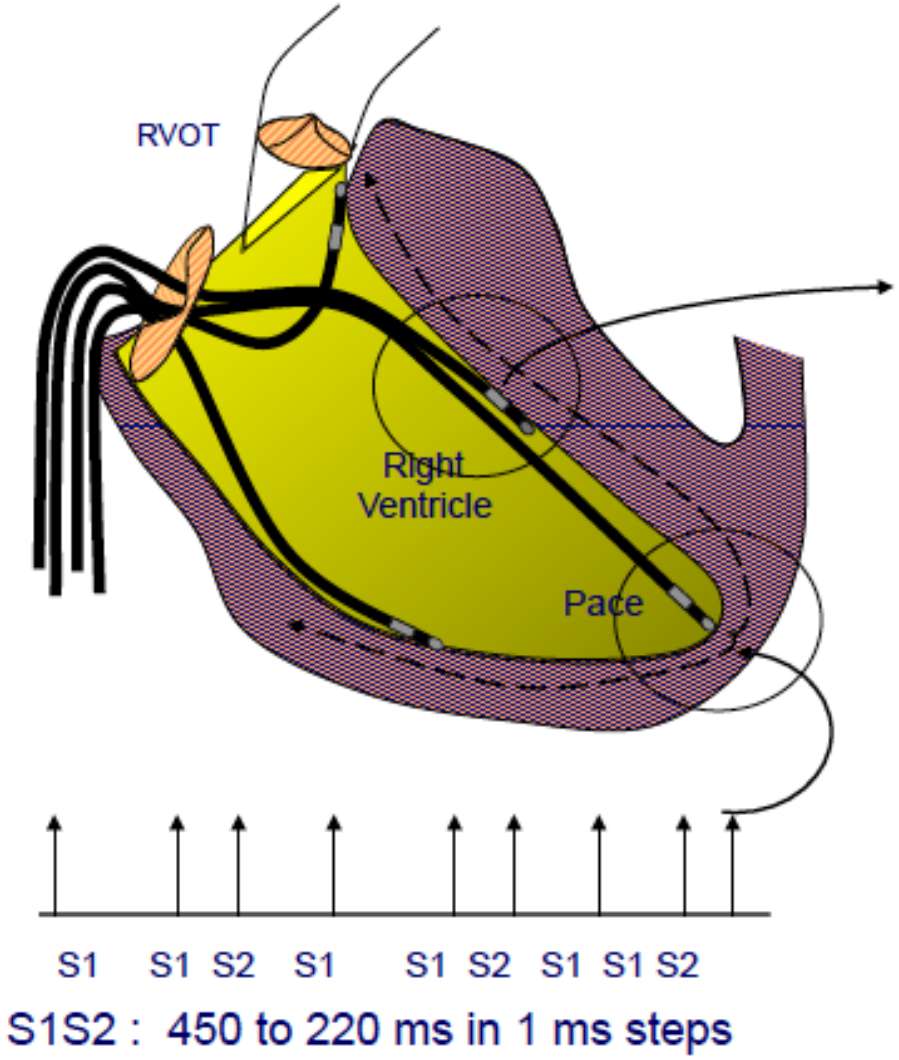
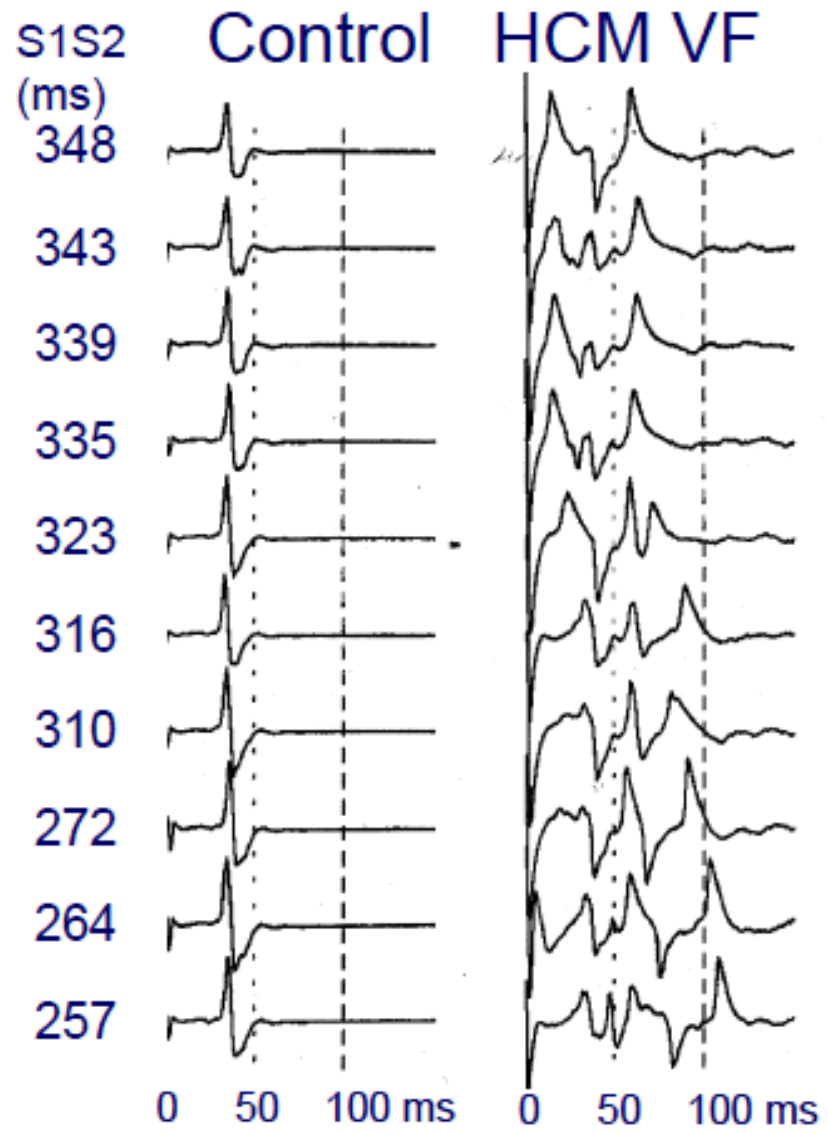


Objective to provide detailed phenotypes: biology, risk and rescue

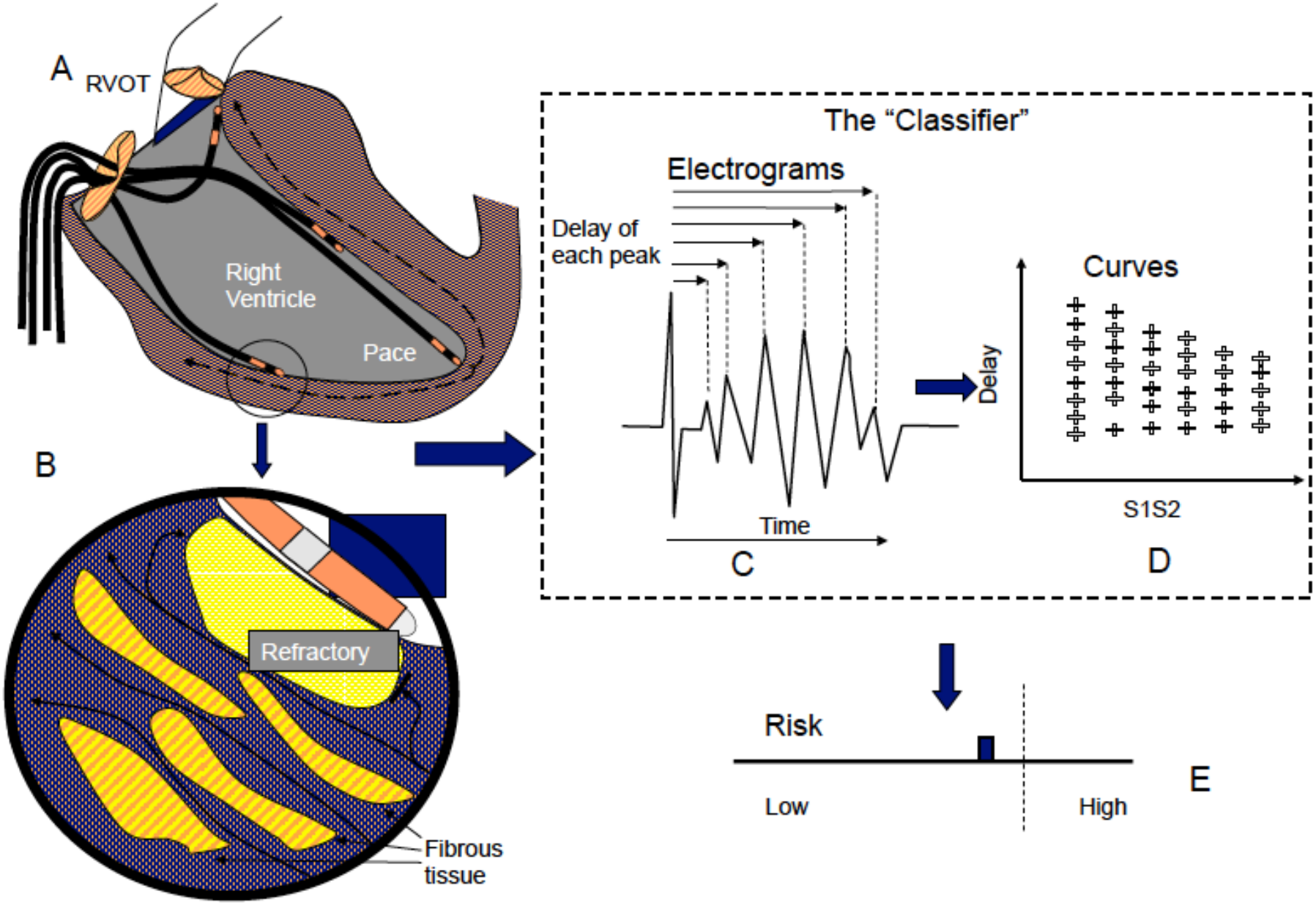
SCD IN HYPERTROPHIC CARDIOMYOPATHY: SLOWED CONDUCTION



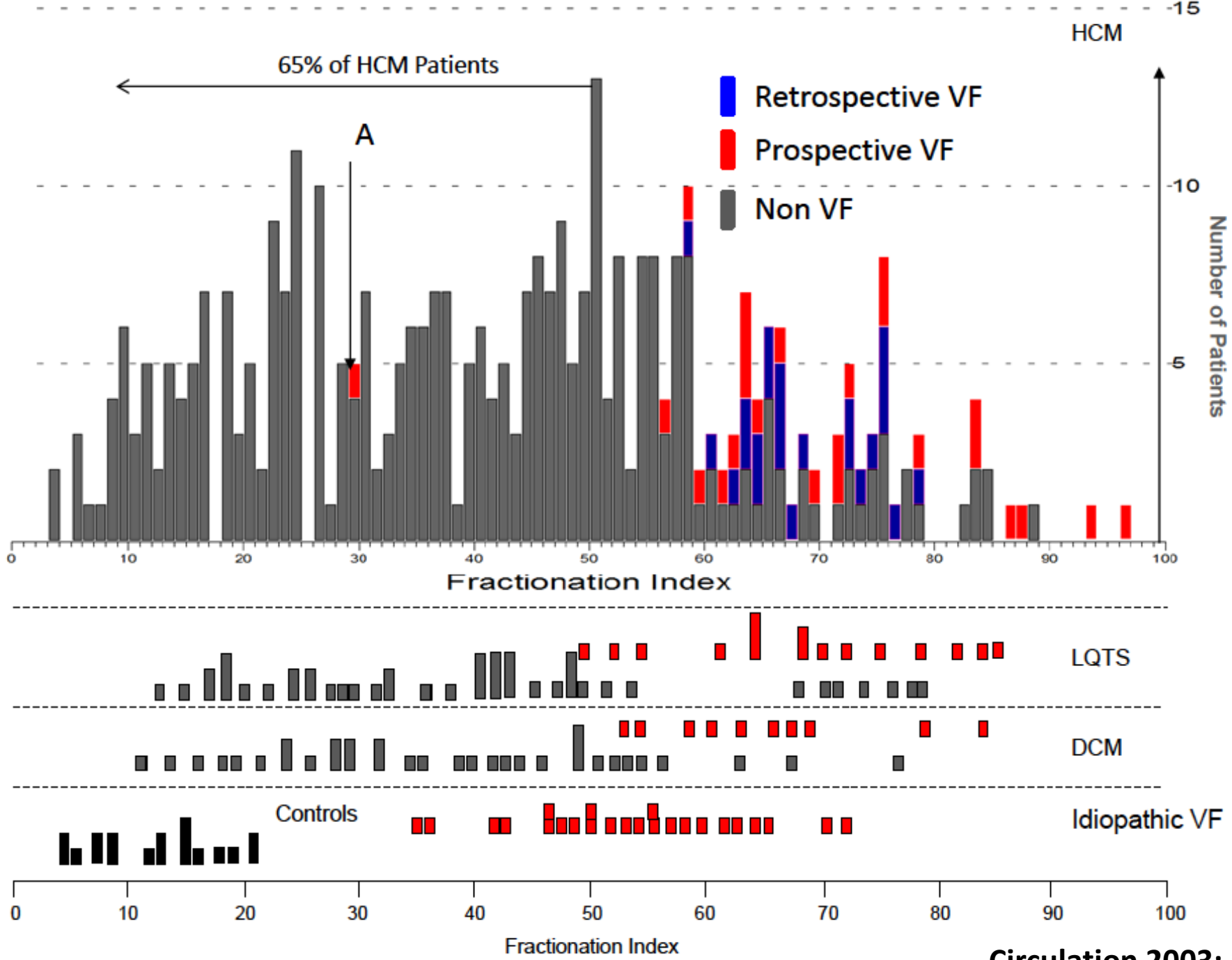


Circulation 1992; 86:467-474

SCD IN HYPERTROPHIC CARDIOMYOPATHY: GENERAL PRINCIPLES OF ANALYSIS



Circulation 2003; 107:2595-2600



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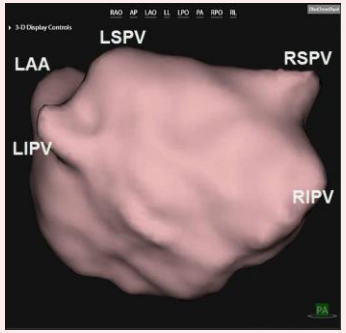

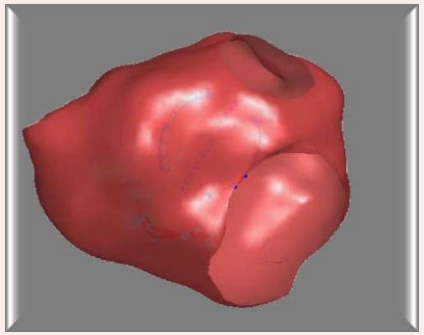

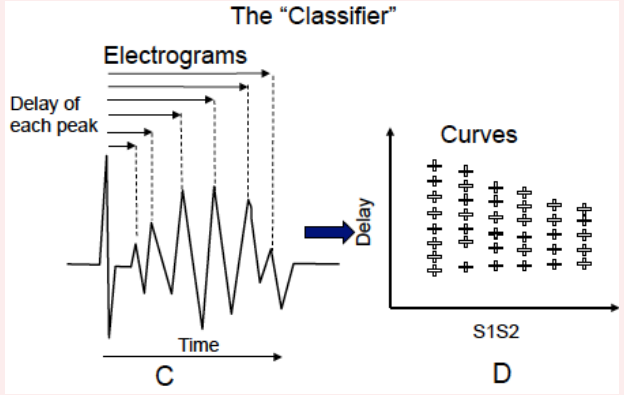

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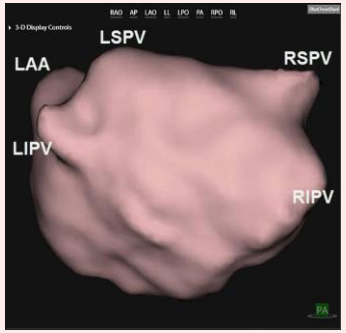
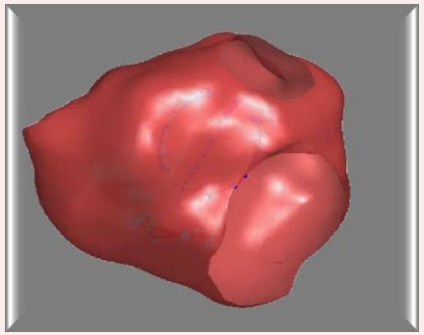
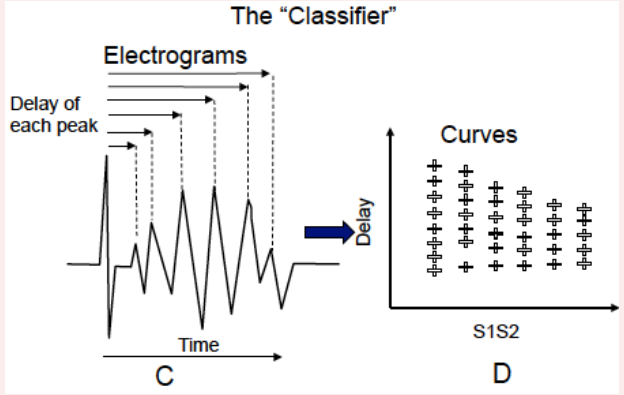
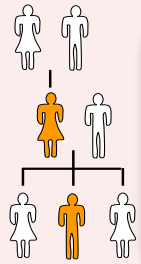
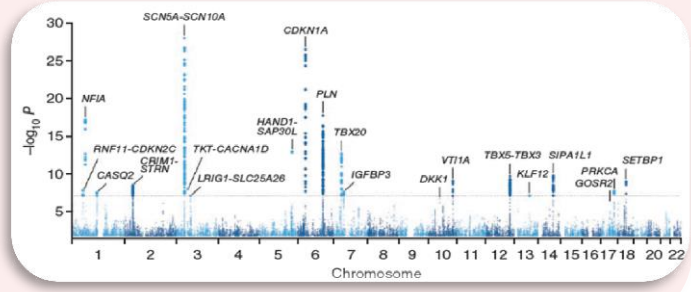






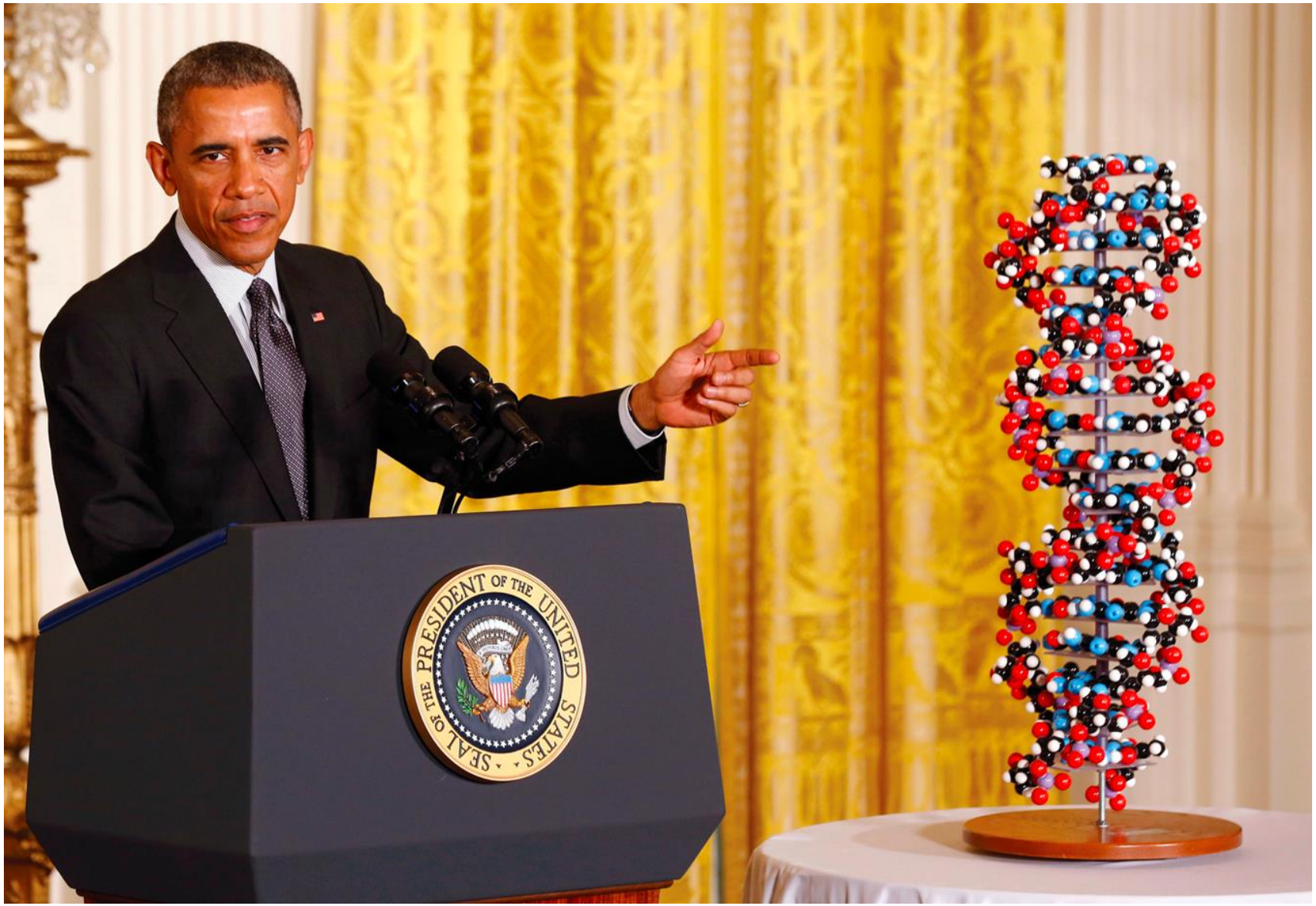
GENOMICS / POPULATIONS





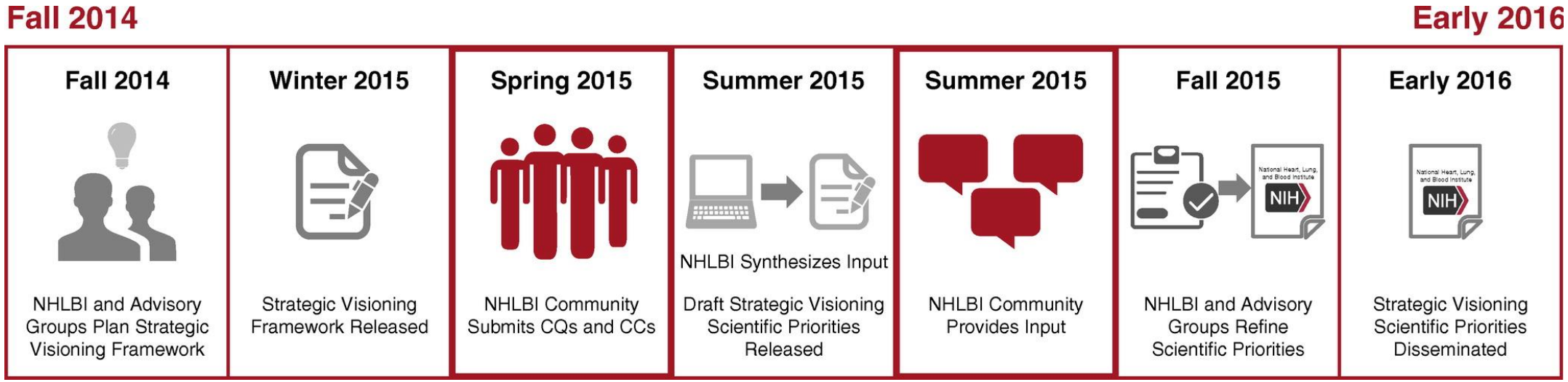
POPULATION LEVEL PHENOTYPING

Key Stakeholders are Committed to Precision Medicine



JL Fox Nature Biotechnology 2015 33:325

Precision Medicine and the NHLBI Strategic Vision 2015-2025

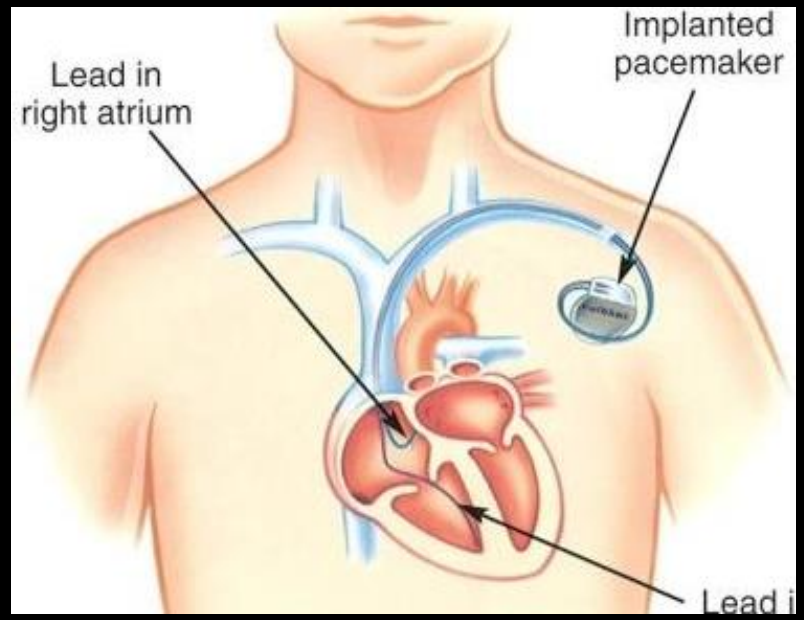


… ***what if*** *we could expand the frontiers of scientific knowledge and revolutionize how we diagnose, prevent, and treat disease by leveraging the power of big scientific data systems?*

Kiley et al. Am J Resp Crit Care 2015 191:489

Cardiac Pacemakers

Accurate phenotyping at scale



Monitored: clinical/electronic/EMR

Categorical phenotypes:
sinus node/AV node disease

Scale (f/u): 7000 at Papworth/350K in UK

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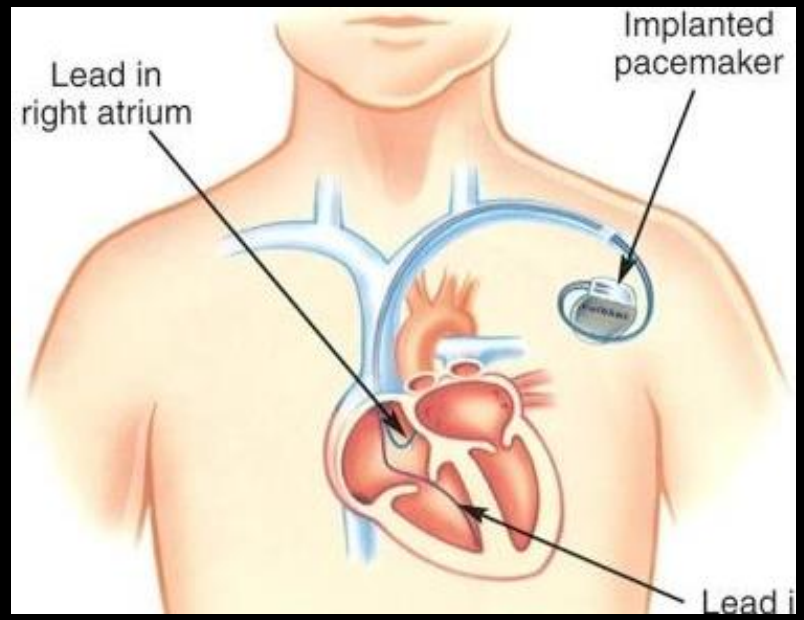
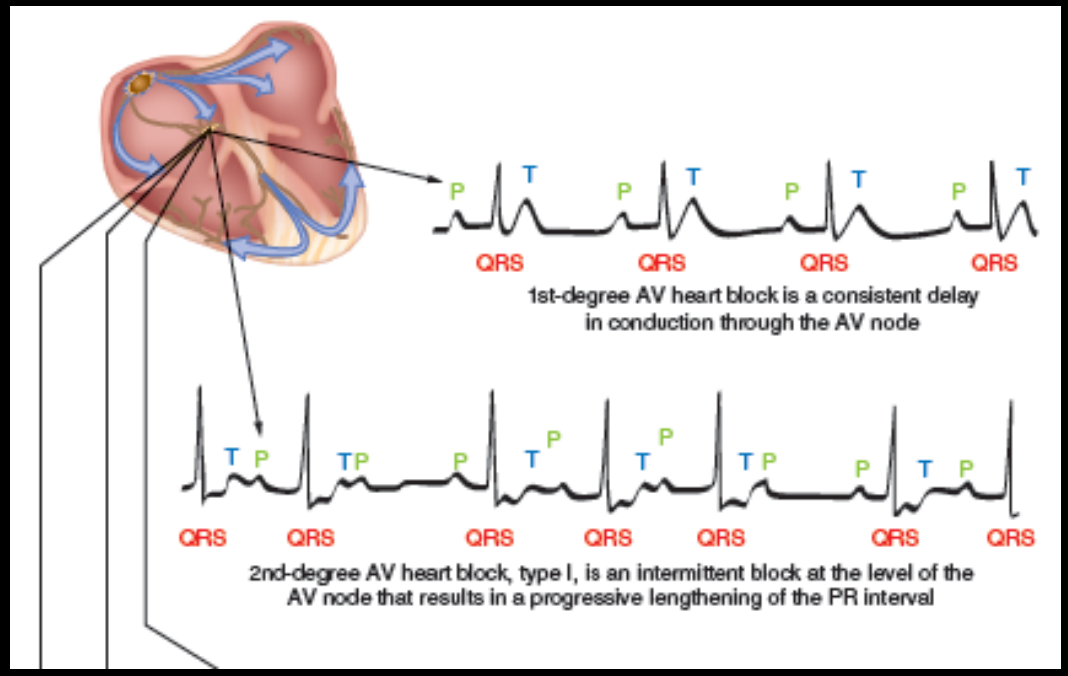
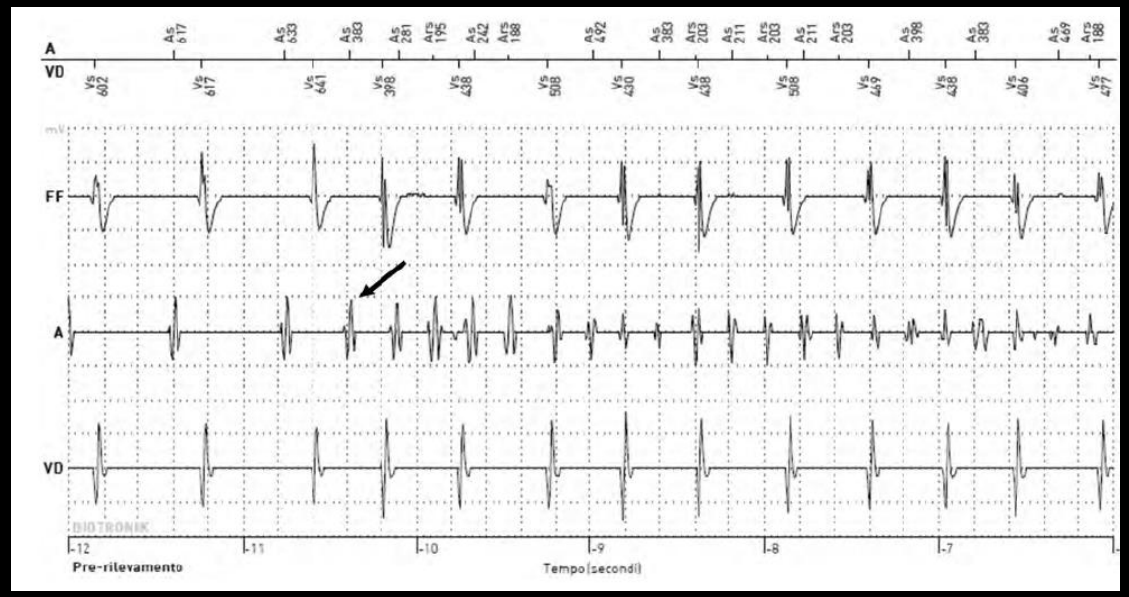






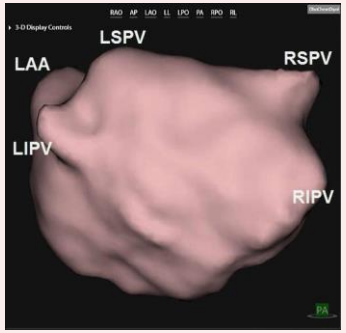
Monitored: clinical/electronic/EMR

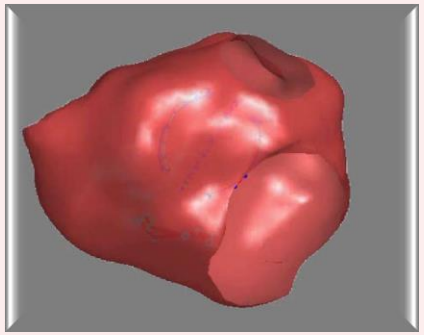
Categorical phenotypes:
sinus node/AV node disease

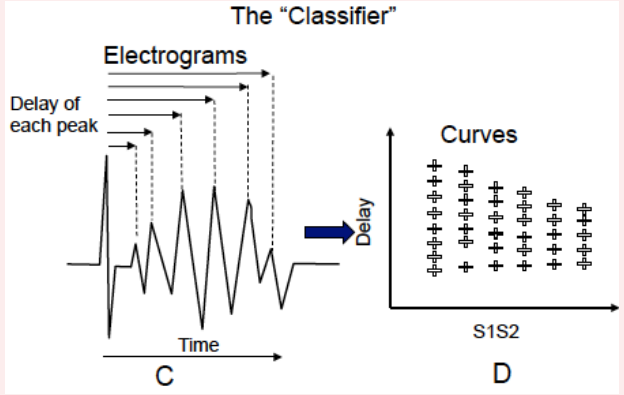
Scale (f/u): 7000 at Papworth/350K in UK

Arrhythmia Phenotyping highly quantitative – possibility ‘precision medicine’

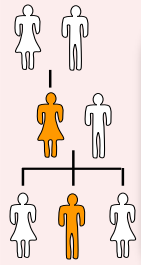
DEEP PHENOTYPING INDIVIDUALS

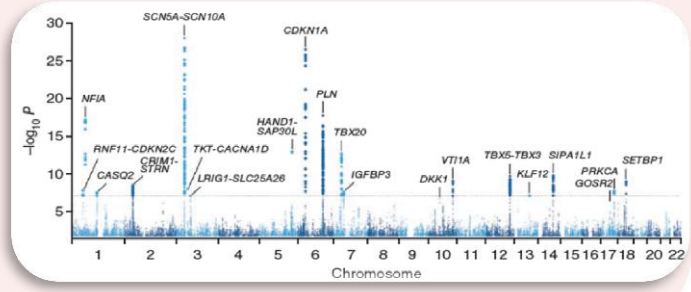




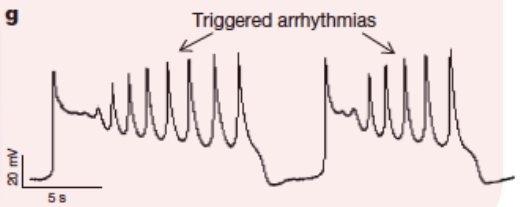


GENOMICS / POPULATIONS





MOLECULAR, CELLULAR STUDIES + DRUG RESCUE



Calum MacRae receives $75 million to pursue ‘One Brave Idea’ to beat coronary heart disease

By AMERICAN HEART ASSOCIATION NEWS

After 25 years of conducting scientific research and treating patients, Dr. Calum MacRae was frustrated with the industry’s typical way of studying diseases. So he started formulating a radically different approach.

He envisioned adding to the mix a wide variety of new factors, such as the shape of a person’s face and the quality of air they breathe. He’d then sift through all the data to find the hallmarks that indicate someone is likely to develop a disease long before traditional problems manifest – an early-warning system, of sorts, and a way to identify the first stages of a disease.

AMERICAN HEART ASSOCIATION NEWS **5th October 2016**

Personalized arrhythmia management

- Individual Deep Phenotyping- accessible, quantifiable, tractable, actionable
- Clearly defined populations (e.g. hypothetical risk, those with devices) allows clinical experiments at scale
- Broad implications – genomics, discovery, precision medicine