Dr Patrick Gladding

Cardiologist

North Shore Hospital, Auckland

Personalised and Genomic Medicine for GPs - Concurrent Workshop

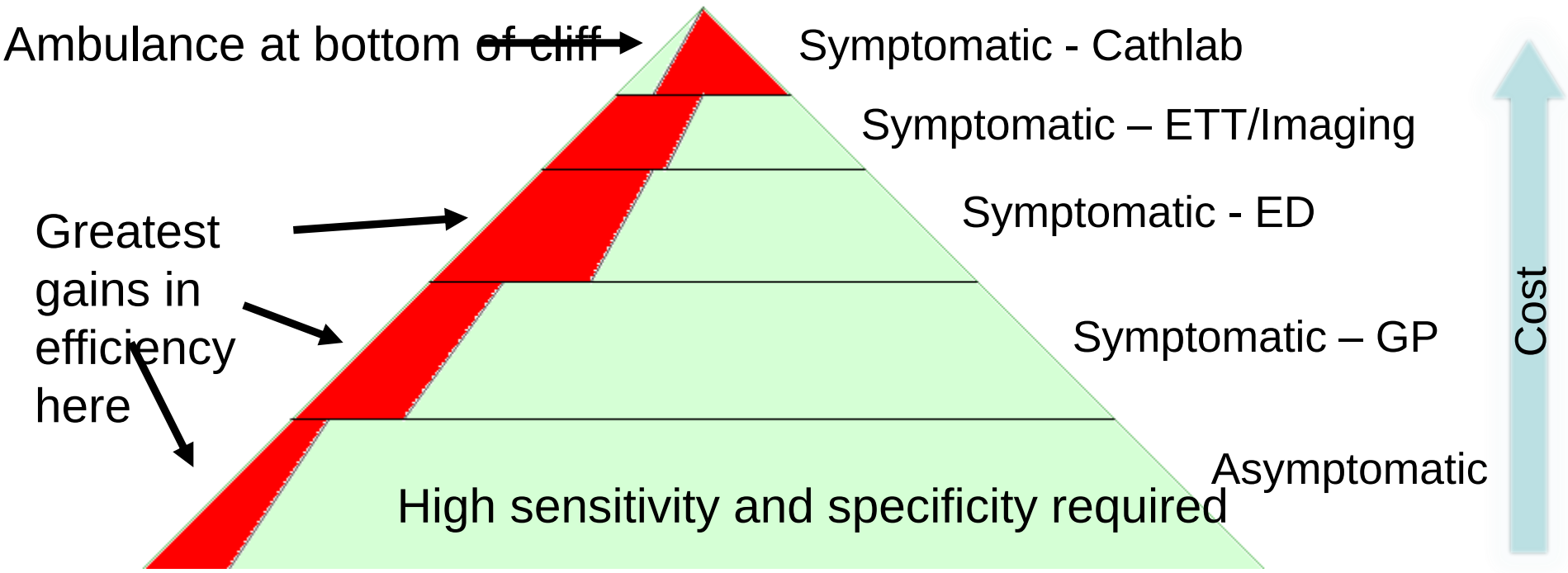
Saturday, 22 June 2013 Start 4:30pm Duration: 60mins Monet

Personalised medicine

Medicine for the Quantum age….

Dr. Patrick Gladding, MBChB, PhD
Cardiologist, WDHB

Medicine's needs

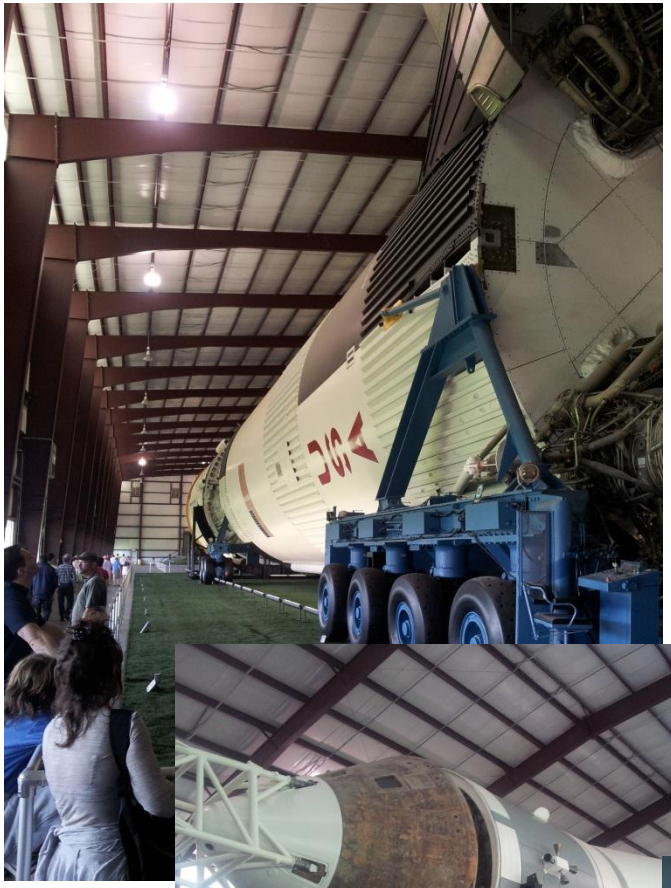


"There's plenty of room at the bottom"

- *Reference to nanotechnology and quantum mechanics*

Richard Feynman - American Physical Society, Caltech, December 29, 1959

Rocket science



Problems with contemporary medicine

- Clinical decisions are based on outdated clinical trial data
- Clinical trials have traditionally taken heterogeneous populations and demonstrated results only for the “average patient”

However

- Personalized risk predictions can be made using databases containing e.g. genomic data, imaging data (EMR) and models

Current medicine is reductionistic

"The whole is more than the sum of its parts."

– Aristotle, Metaphysica

Interconnected and Interdependent Systems

Translating Knowledge to Practice

Good Outcome

Intermediate Outcome

Bad Outcome

Outcomes From a Study

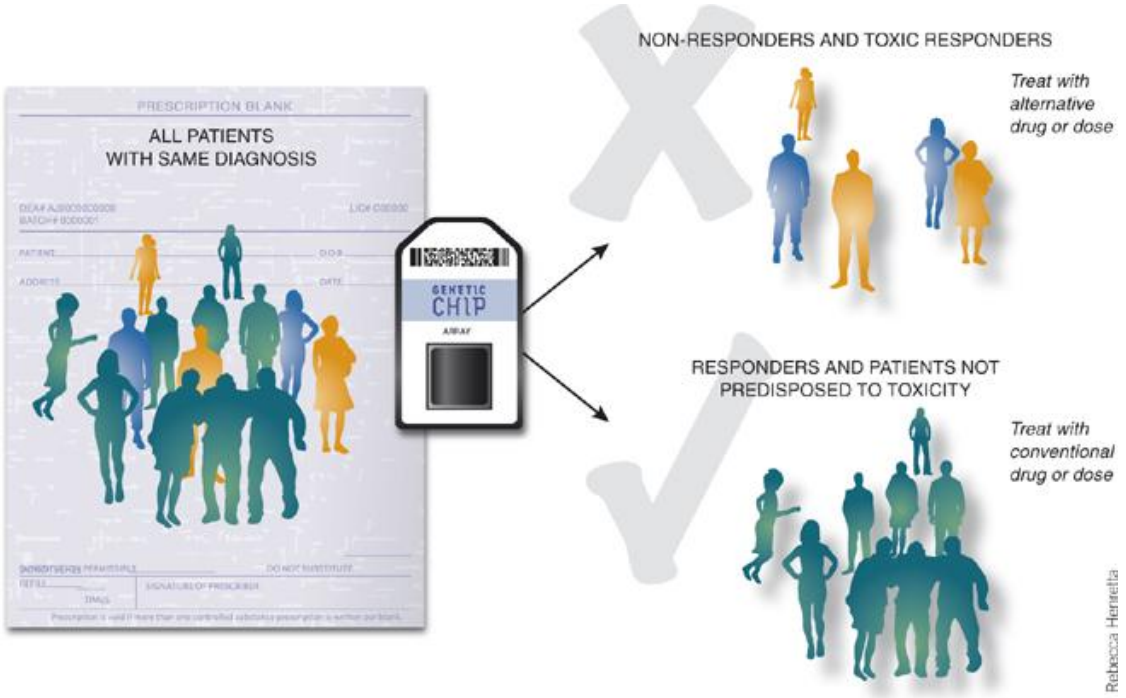
Mean Treatment Difference

Acute Coronary SYNDROMES

theheart.org Medscape EDUCATION

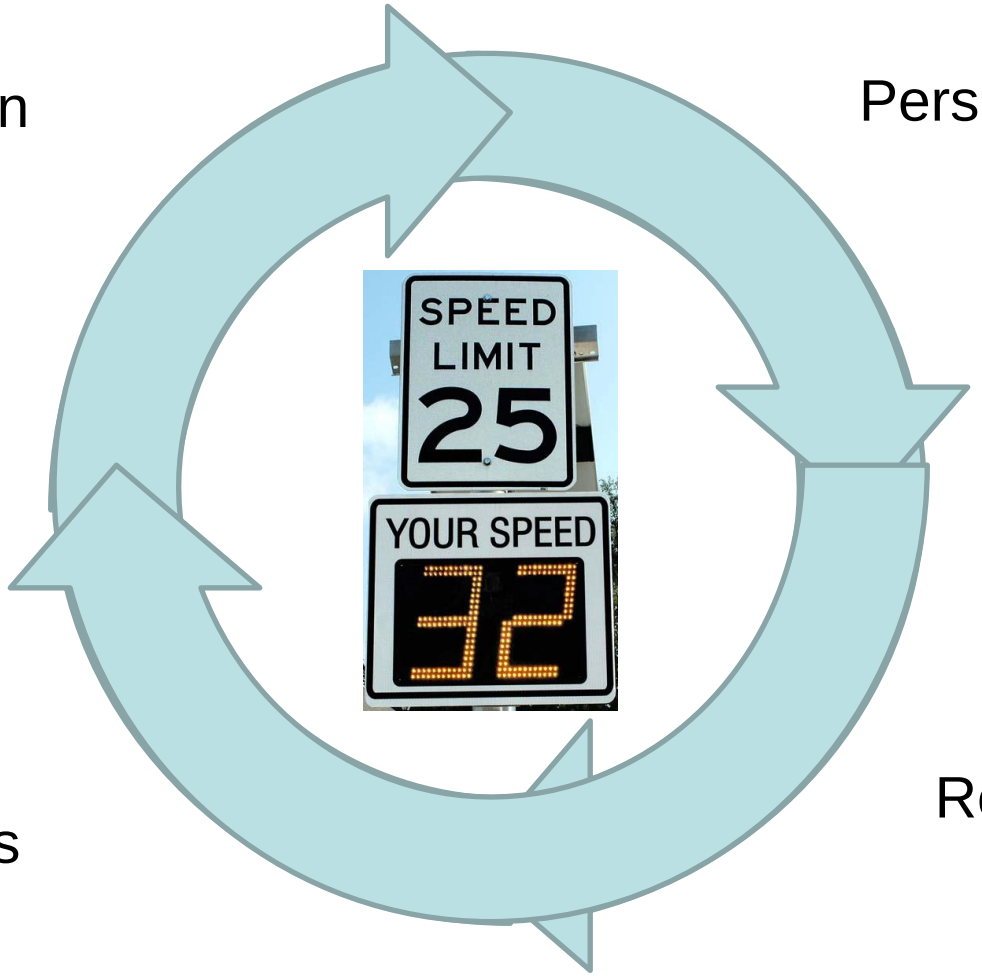

Translating Knowledge to Practice
Good Outcome
Intermediate Outcome
Bad Outcome
Outcomes From a Study
Risk Stratification
Acute Coronary SYNDROMES
theheart.org
Medscape EDUCATION

Personalised Medicine



- Its about:
  - populations as much as individuals
  - Increasing efficiency and resource utilisation
  - In a world of limited resources only option is to personalise

Feedback loops – giving patients their information

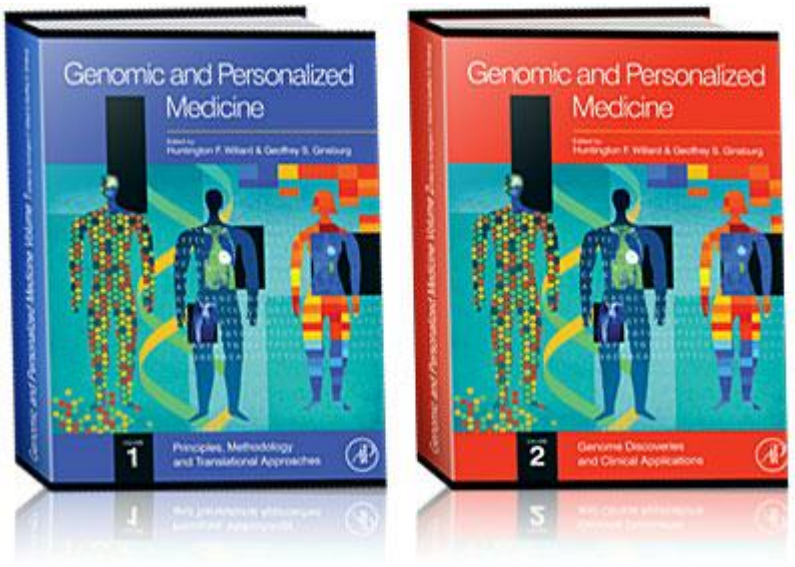


A Learning system

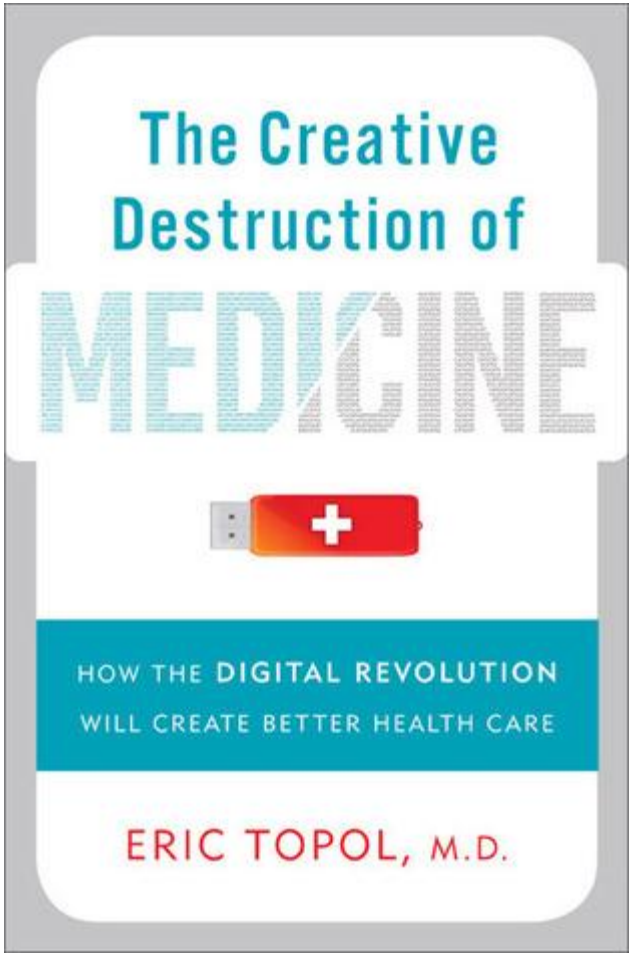
TED talks: Thomas Goetz

Genomic and Personalised Medicine

- Genomics, proteomics, metabolomics
- Information technology
- Artificial intelligence
- Supercomputing
- Imaging
- Nanomedicine
- Biosensors



Superconvergence



- Ubiquitous Cloud Supercomputing
- Low-cost genome sequencing
- Digital medicine
- mHealth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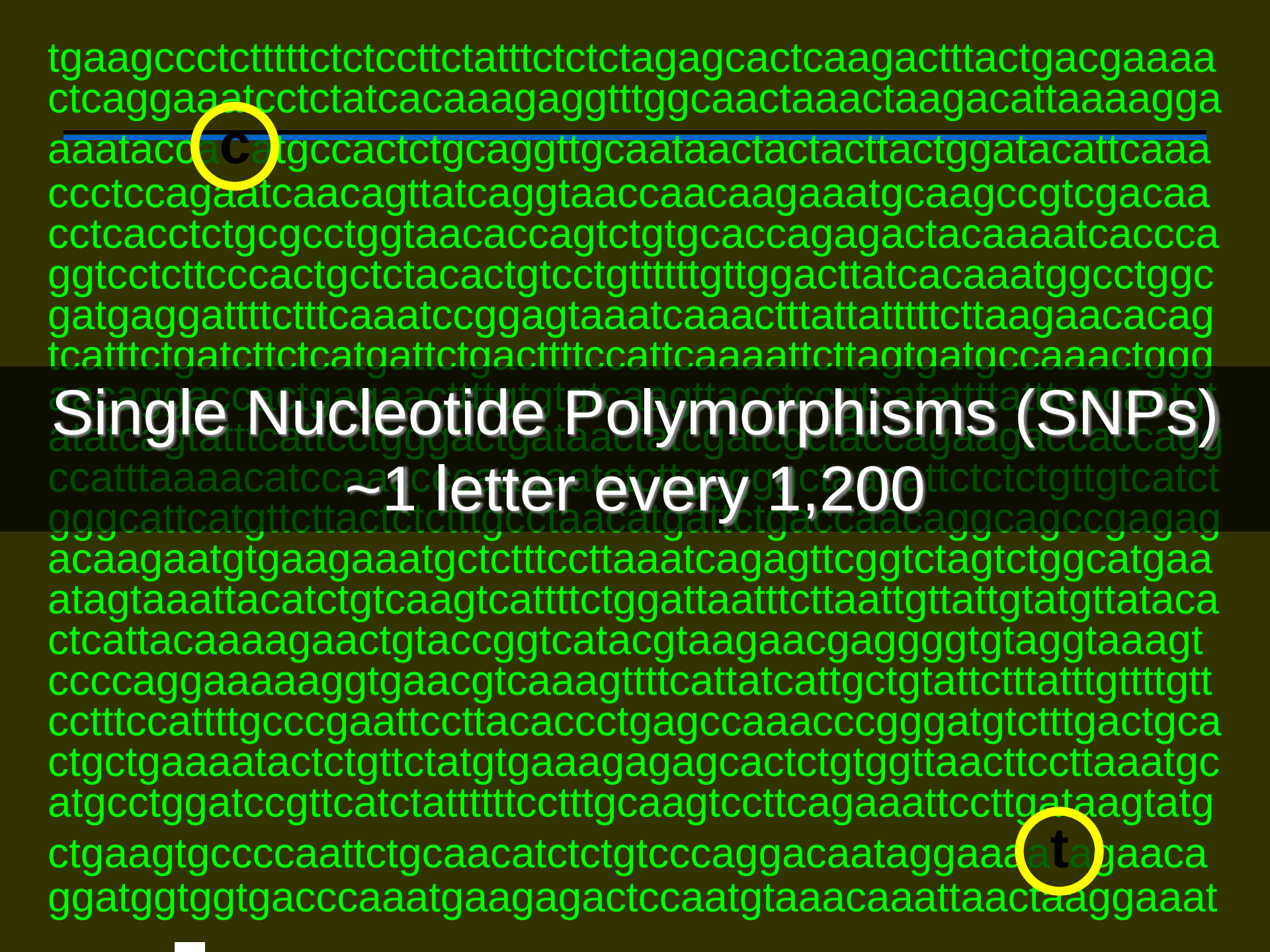
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tcatttctgatcttctcatgattctgactttccattcaaaattcttagtgatgccaaactggg
Single Nucleotide Polymorphisms (SNPs)
~1 letter every 1,200
gggcattcatgttcttactctcttgcctaacatgattctgaccaacaggcagccgagag
acaagaatgtgaagaaatgctctttccttaaatcagagttcggtctagtctggcatgaa
atagtaaattacatctgtcaagtcattttctggattaatttcttaattgttattgtatgttataca
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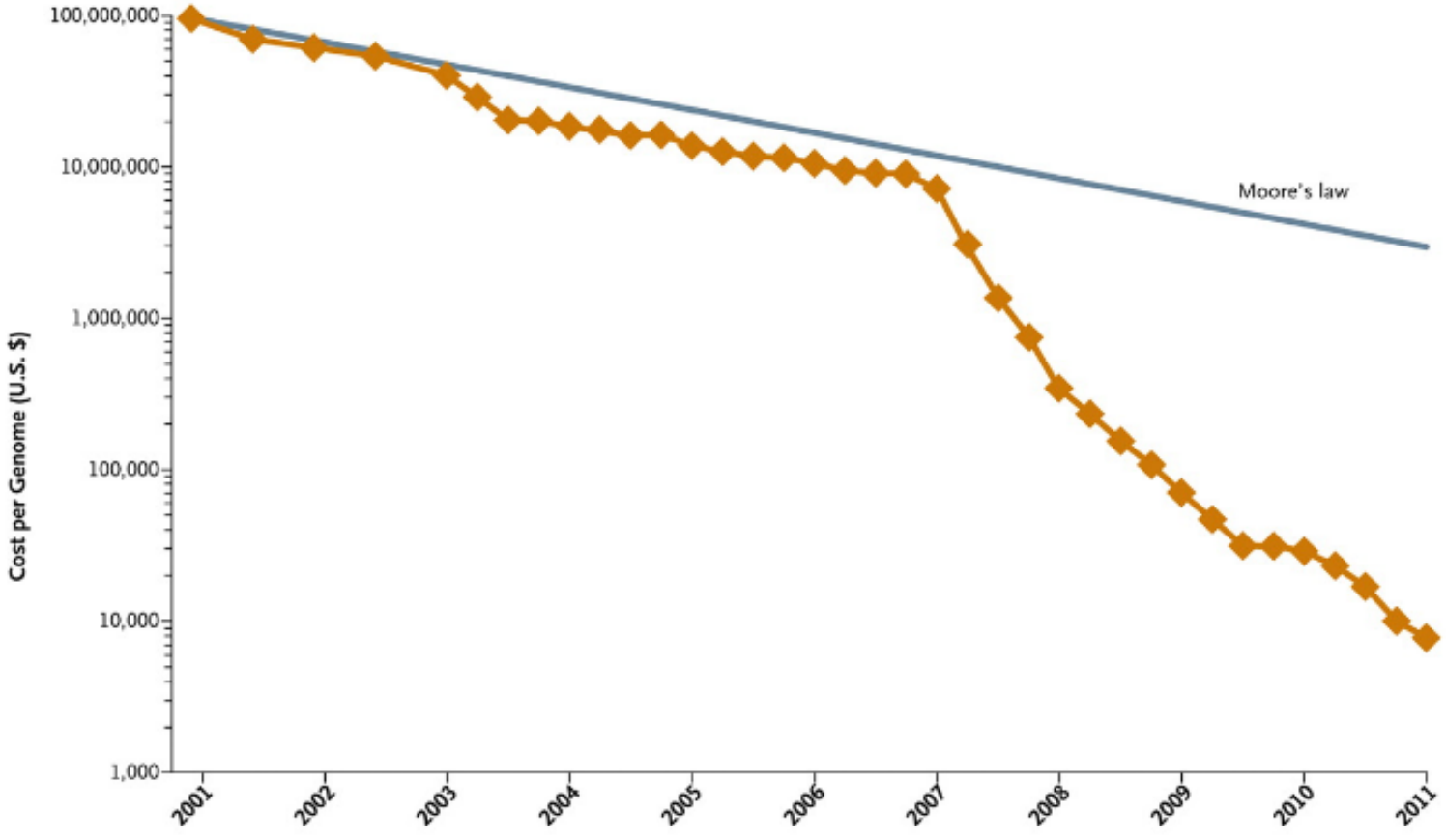
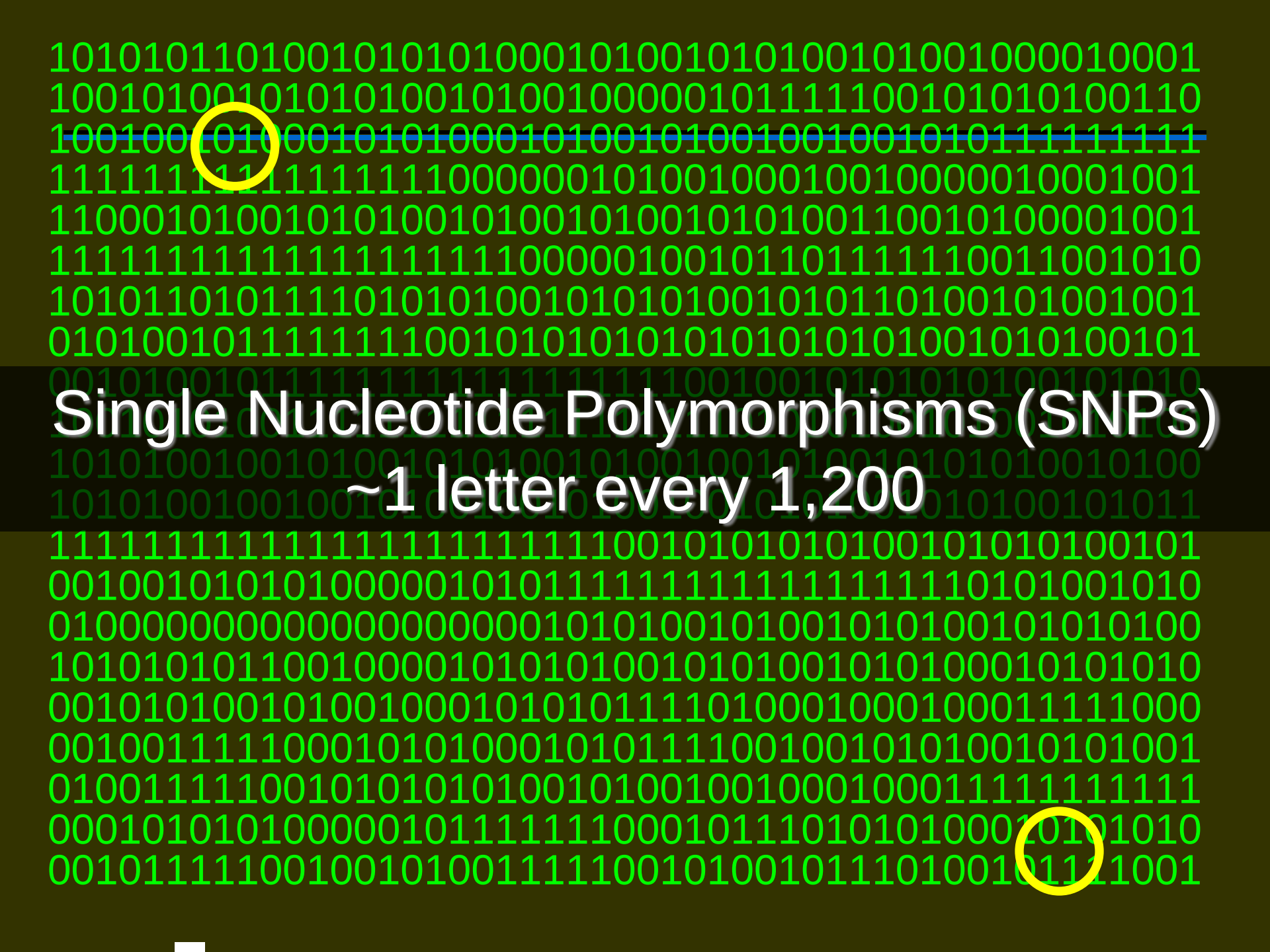
Genome sequencing > Exponential reduction in cost



NEJM 2012


Single Nucleotide Polymorphisms (SNPs)
~1 letter every 1,200

Pharmacogenomics

Tailoring treatment

Maximising efficiency

Epidemiology: Cholesterol hypothesis – too narrow

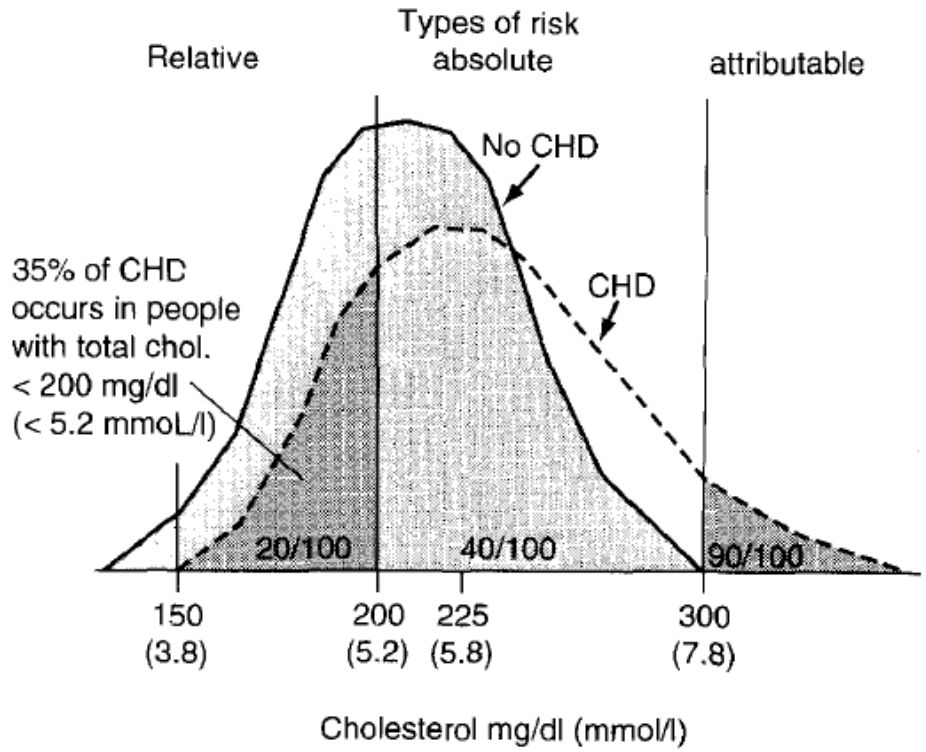


Fig. 1. The incidence of MI in relation to total cholesterol levels in the Framingham Study, 26 year follow-up. Taken from [29].

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Naveed Sattar, David Preiss, Heather M Murray, Paul Welsh, Brendan M Buckley, Anton J M de Craen, Sreenivasa Rao Kondapally Seshasai, John J McMurray, Dilys J Freeman, J Wouter Jukema, Peter W Macfarlane, Chris J Packard, David J Stott, Rudi G Westendorp, James Shepherd, Barry R Davis, Sara L Pressel, Roberto Marchioli, Rosa Maria Marfisi, Aldo P Maggioni, Luigi Tavazzi, Gianni Tognoni, John Kjekshus, Terje R Pedersen, Thomas J Cook, Antonio M Gotto, Michael B Clearfield, John R Downs, Haruo Nakamura, Yasuo Ohashi, Kyoichi Mizuno, Kausik K Ray, Ian Ford

Summary

Background Trials of statin therapy have had conflicting findings on the risk of development of diabetes mellitus in patients given statins. We aimed to establish by a meta-analysis of published and unpublished data whether any relation exists between statin use and development of diabetes.

Lancet 2010; 375: 735–42
Published Online
February 17, 2010
DOI:10.1016/S0140-

BMJ

BMJ 2013;346:f880 doi: 10.1136/bmj.f880 (Published 20 March 2013)

Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases

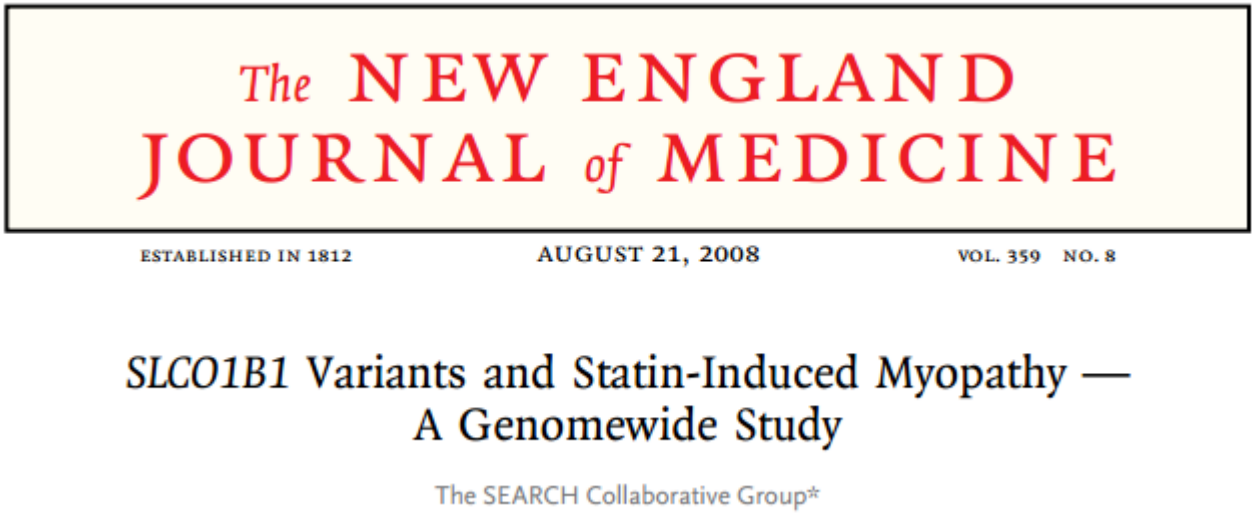
OPEN ACCESS

Colin R Dormuth *assistant professor*[1], Brenda R Hemmelgarn *associate professor*[2], J Michael

Conclusions Use of high potency statins is associated with an increased rate of diagnosis for acute kidney injury in hospital admissions compared with low potency statins. The effect seems to be strongest in the first 120 days after initiation of statin treatment.

- Being more selective for low and intermediate risk patients

Statin myopathy is predictable



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 21, 2008 VOL. 359 NO. 8

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group*

- Liver transporter gene variant accounts for 60% of myopathy cases
- Common in the population
- Patients with two gene copies have x16 risk of myopathy

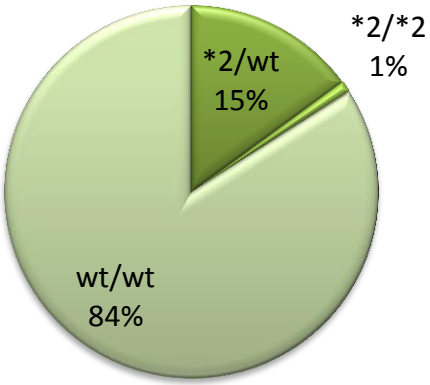
Personalised antiplatelet Rx

Increasing potency, bleeding risk and cost

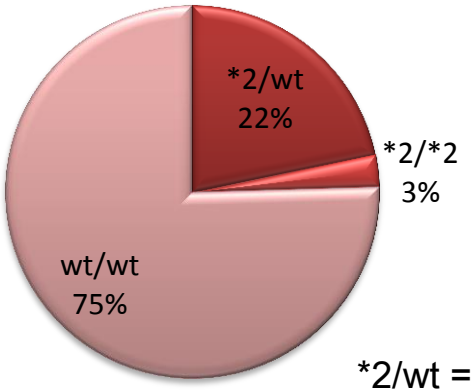
- Newer agents are only beneficial in nonresponders to old Rx

Ethnic rates of nonresponders

European

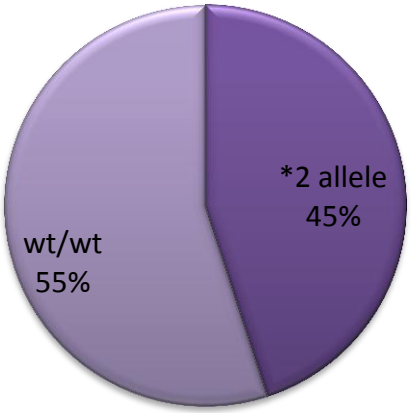


Maori

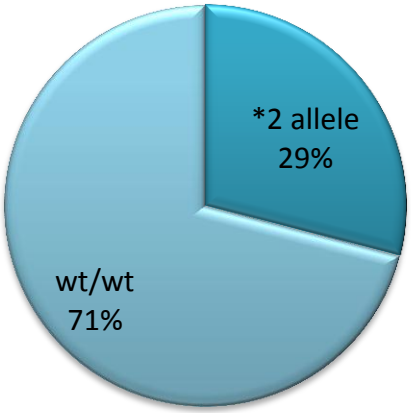


*2/wt = higher dose
*2/*2 = alternative drug

Pacific Peoples



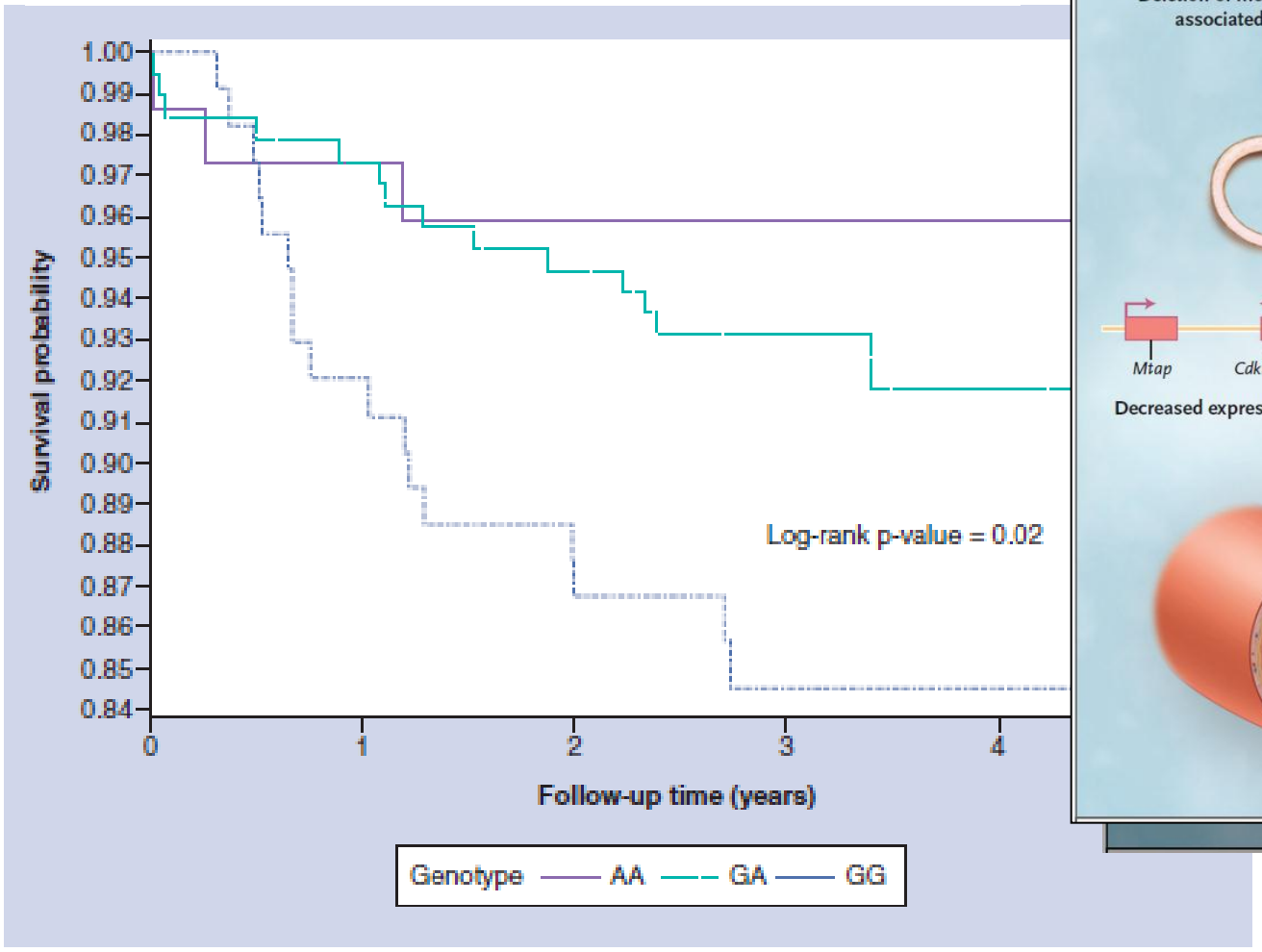
Asian



Genomic basis of disease

New insights

Longitudinal study of a 9p21.3 SNP using a national electronic healthcare database



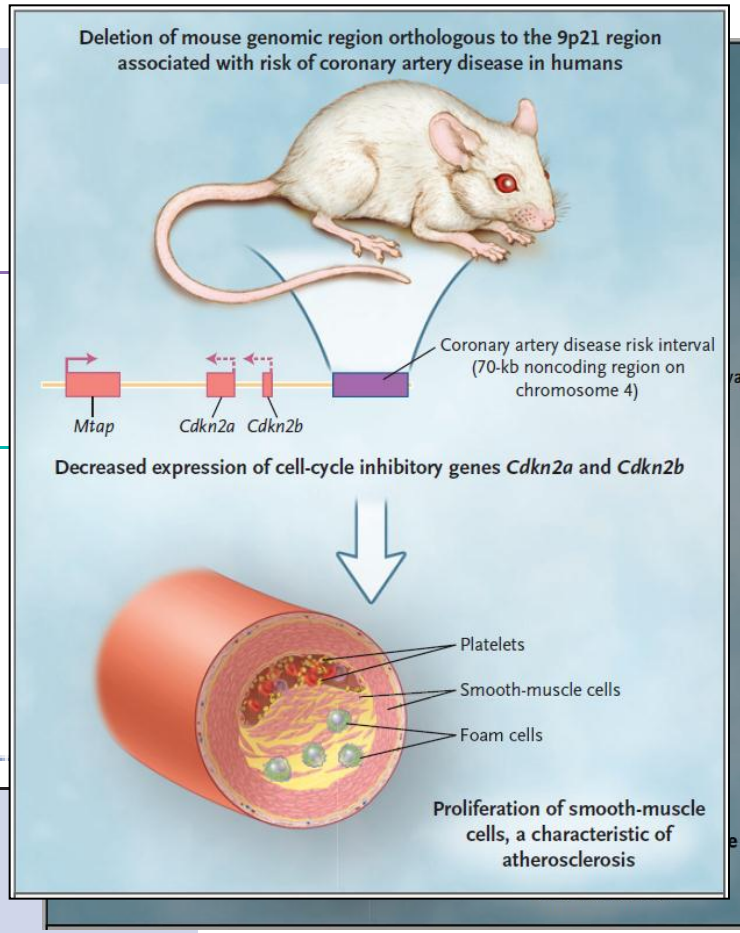


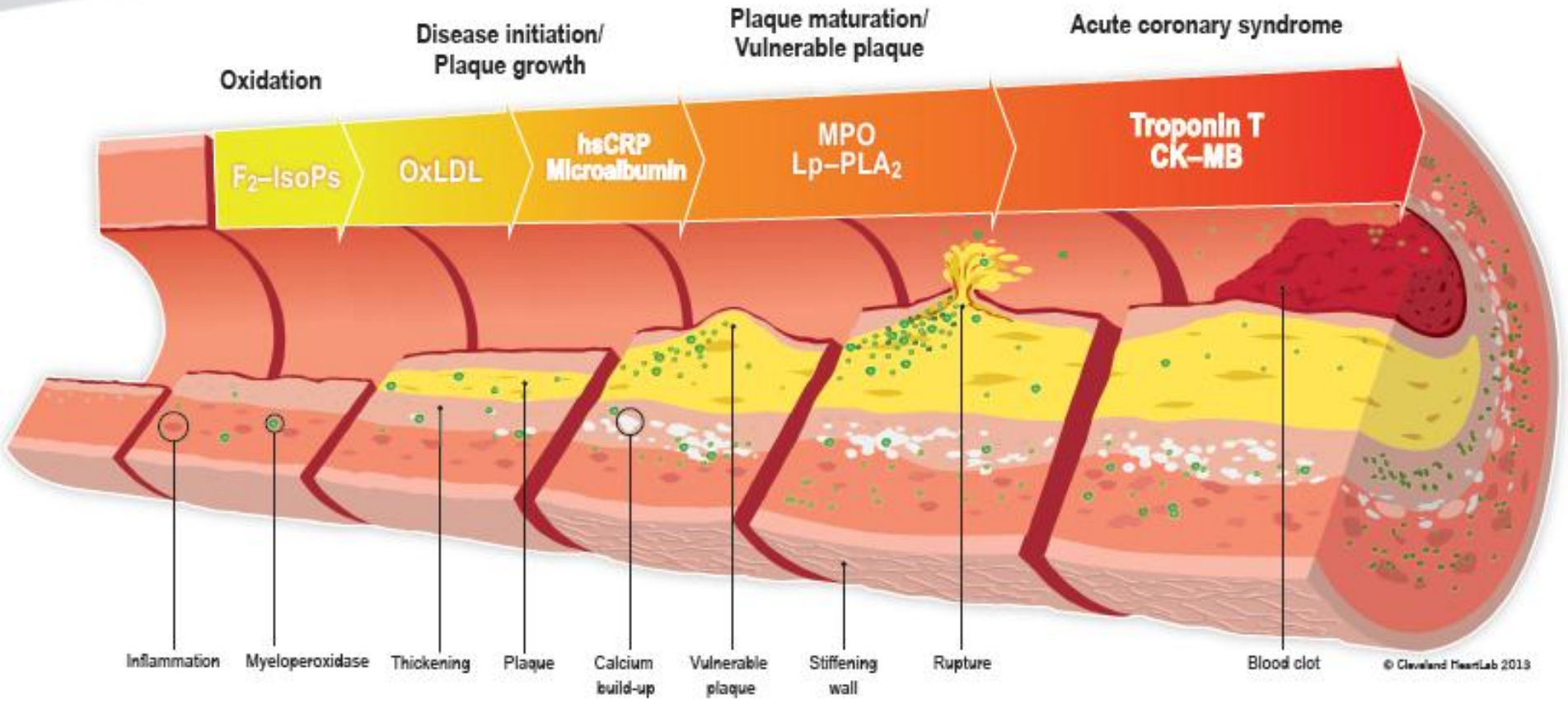
Figure 1. All-cause mortality and the rs10757278 genotype in patients with severe coronary artery disease.

Gladding et al. Personalized

Know your risk.

Inflammatory Biomarkers and the Progression of Atherosclerosis

The progression of atherosclerosis is marked by specific inflammatory biomarkers, and their levels can be measured to determine a patient's risk for heart disease and cardiac events.



Genomics altering treatment decisions

Genetics

Independent Susceptibility Markers for Atrial Fibrillation on Chromosome 4q25

Circulation. 2010;122:976-984.

Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. xx, No. x, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.01.070

Symptomatic Response to Antiarrhythmic Drug Therapy Is Modulated by a Common Single Nucleotide Polymorphism in Atrial Fibrillation

Babar Parvez, MD, Joseph Vaglio, MD, Shane
Gayle Kucera, RN, Tanya Stubblefield, RN, Sh
Dawood Darbar, MD

Nashville, Tennessee

Journal of the American College of Cardiology
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Vol. 55, No. 8, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.11.041

QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Chromosome 4q25 Variants and Atrial Fibrillation Recurrence After Catheter Ablation

Daniela Husser, MD,* Volker Adams, PHD,† Christopher Piorkowski, MD,* Gerhard Hindricks, MD,* Andreas Bollmann, MD, PHD*

Leipzig, Germany


Non-profit
Socially responsible
Virtual company
Jobs and NZ knowledge economy
LAB
TheranostiCs.
Your Genes. Your Health.

Disclosures - IP

ClevelandHeartLab

CardioMPO Australasia

Clopidogrel Pharmacogenomics
PCT phase US, China, Japan, Europe, Australia, New Zealand

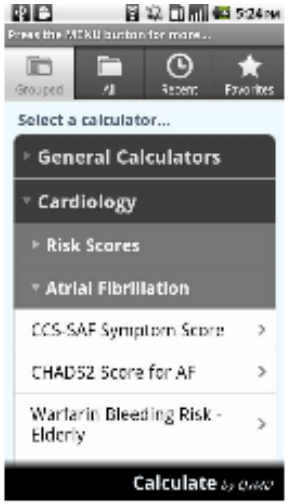
NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
NSBRI

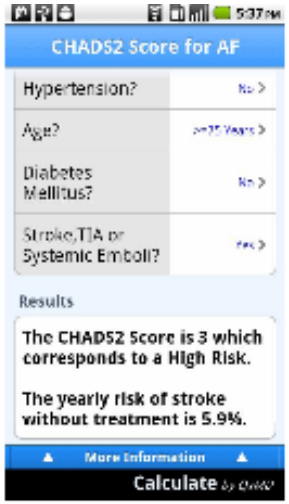
- Founder of non-profit Theranostics Laboratory
- USPTO issued patent; Licensing fees and royalties

Rapid low-cost genotyping - NSH

1

Waitemata District Health Board
Te Wai Awhina
Making a healthy difference to the community





- MALDI-TOF MS
  - Cheap <$30

2

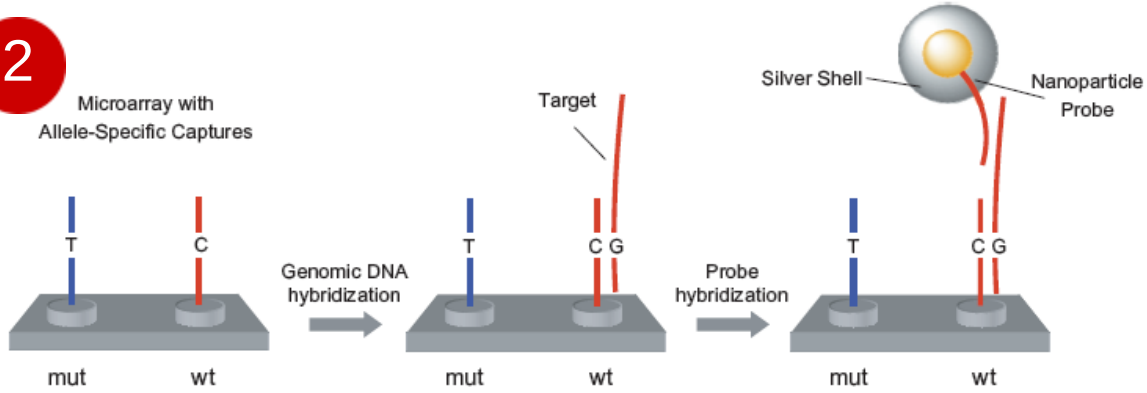


Figure 1. Fragmented unamplified genomic DNA and gold nanoparticle probes are sequentially hybridized to the SNP microarray containing capture probes representing the two possible alleles. After the two hybridization steps, the array is subjected to stringency washes and a silver development step. The scatter signal from the test sites is imaged subsequently to obtain genotyping results.

- Nanosphere
  - Rapid 2hrs
  - Blood->result
  - Clopidogrel/warfarin PGx
  - Norovirus
  - Hypervirulent C. diff

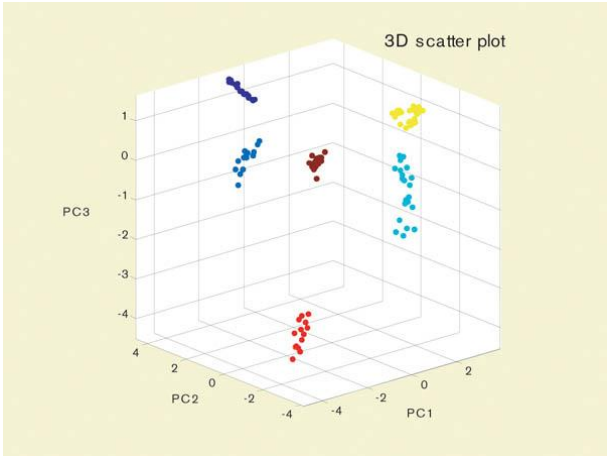
Mass Spectrometry MALDI-TOF

1

- Culture specimen
- Ionise
- Analyse

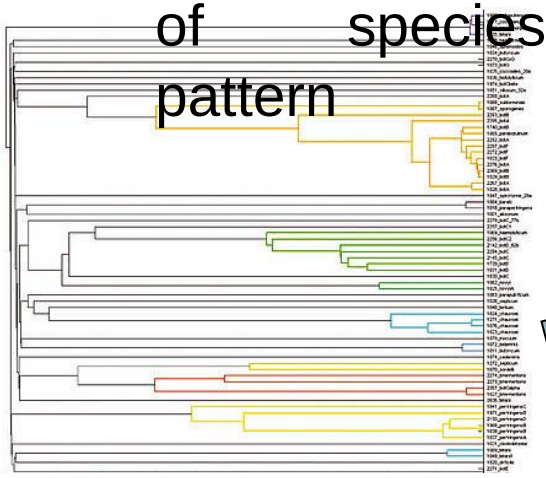
2

- Pattern recognition of spectral output
- 'Machine learning'



3

- Dendrogram: assignment of species pattern



4

Analyte Name	Analyte ID	Organism (best match)	Score Value	Organism (second best match)	Score Value
D2 (+++)	referenz	Escherichia coli DH5alpha BRL	2.382	Escherichia coli ATCC 25922 THL	2.226
D3 (+++)	MB 20	Burkholderia multivorans LMG 14293 HAM	2.457	Burkholderia dolosa DSM 16088 HAM	1.855
D4 (+++)	MB 20	Burkholderia multivorans LMG 14293 HAM	2.462	Burkholderia dolosa DSM 16088 HAM	1.996

- Species identification based on probabilisti

Cardiac mHealth projects

Cloud based Ultrasound

Remote advanced ECG

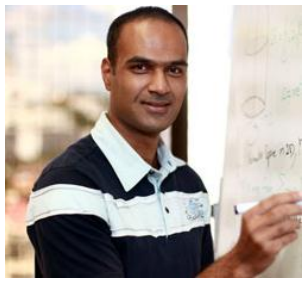
Waitemata District Health Board

Te Wai Awhina

Making a healthy difference to the community

Cardiac ultrasound project

- Modeling astronaut's heart
- NZ Employment



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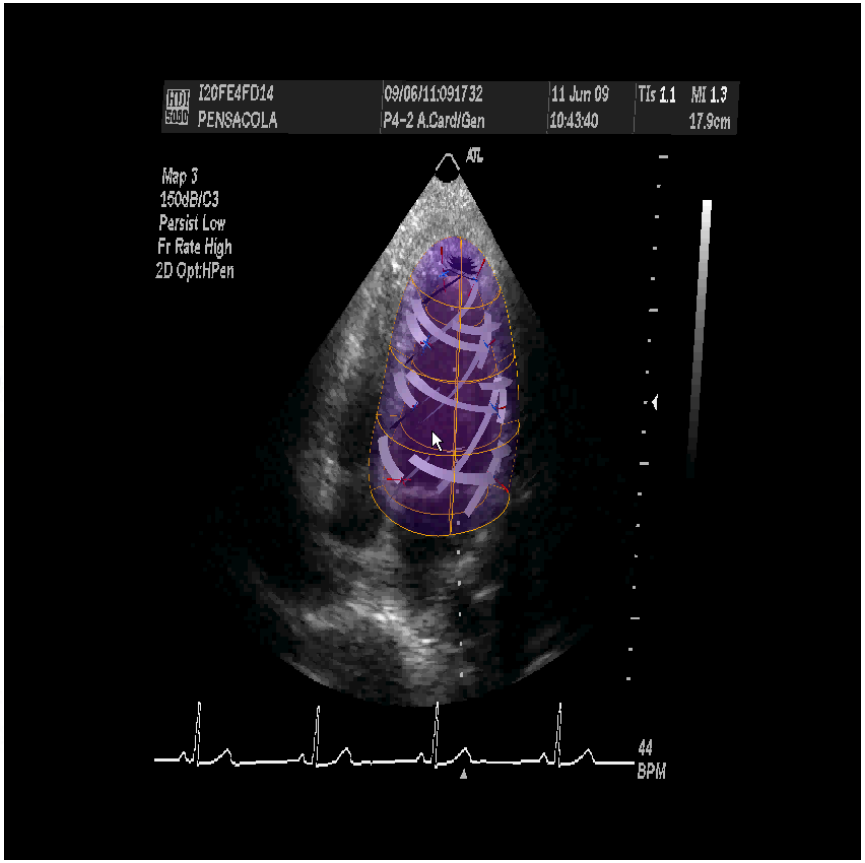
THE UNIVERSITY OF AUCKLAND
NEW ZEALAND
Te Whare Wānanga o Tāmaki Makaurau



Cleveland Clinic

NASA

Jagir Hussan ▼

ICMA v 1.0

AUCKLAND BIOENGINEERING INSTITUTE
THE UNIVERSITY OF AUCKLAND NEW ZEALAND

Auckland 03 Sept 12 10:47 NZST

MR. John E. Dtotu
5543AT75

Referring Physician: **Dr James Thomas**

1071, Kna street,
Kapiti Coast

04-971-3343

Male
10-12-1975

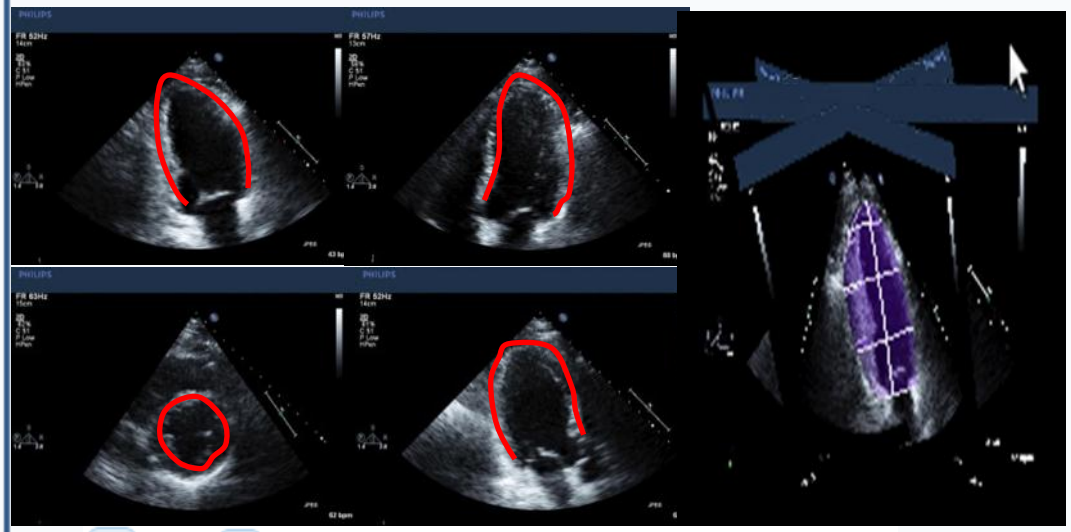
163 cm
90 kgs

Scans | Models

4Views | Stress14 | Pretrial | P4LVX

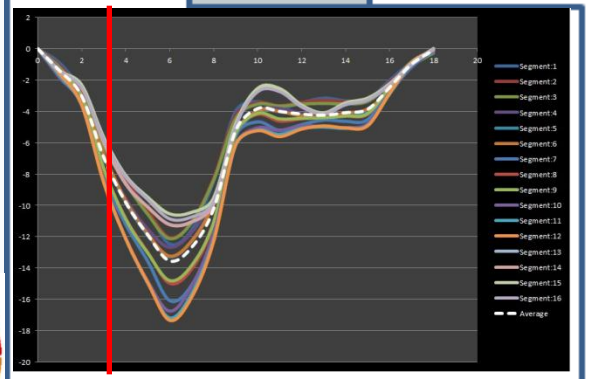
Created on: **31 Sept 2012** ***Created by:*** **Dr. Patrick Gladding** ***Status:*** **Validated (Dr James Thomas)**

Analysis | Worksheet



- [x] APLAX
- [x] 4CH
- [x] 2CH
- [ ] SAX
- [x] Surface
- [x] Lines

Normal | Fiber



Epi — Endo

CLEAR ALL SAVE

Software developed in New Zealand

Prof. Peter Hunter, Former astronauts Leroy Chao, Ellen Baker, David Hilmers, Robert Satcher; PI Dr. Jin Thomas

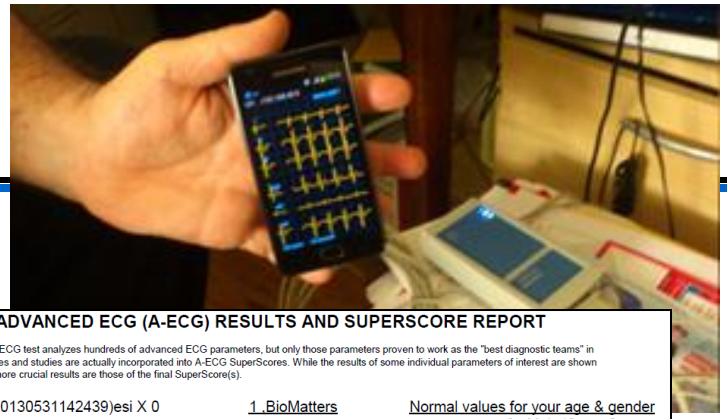
Advanced ECG analysis in the Community

Waitemata
District Health Board
Te Wai Awhina

Making a healthy difference to the community

Advanced ECG

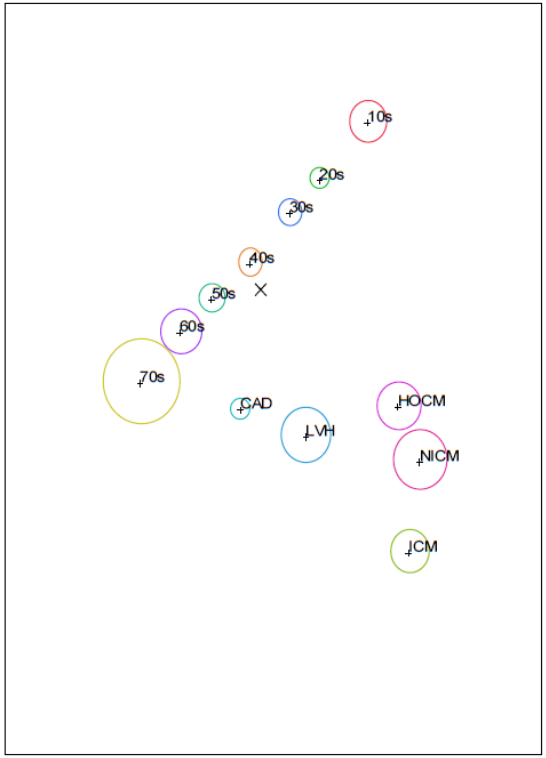
- WiFi based ECG
- Ultraportable, $3,000
- Deconvolutes ECG components
- Advanced pattern recognition, artificial intelligence



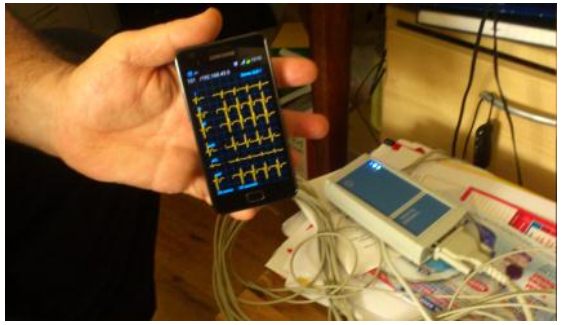
ADVANCED ECG (A-ECG) RESULTS AND SUPERSCORE REPORT

Note: the A-ECG test analyzes hundreds of advanced ECG parameters, but only those parameters proven to work as the "best diagnostic teams" in our databases and studies are actually incorporated into A-ECG SuperScores. While the results of some individual parameters of interest are shown below, the more crucial results are those of the final SuperScore(s).

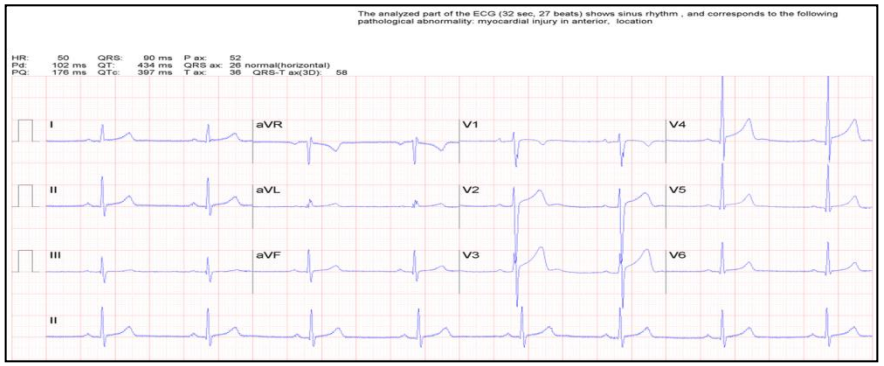
Date: (20130531142439)esi X 0	1 .BioMatters ↓	Normal values for your age & gender ↓[Male40s]	
3-Dimensional (3D) ECG (via Kors' transform):			
Spatial Mean QRS-T angle (deg.)	39	<	88
Spatial Peaks QRS-T angle (deg.)	17	<	52
Spatial Ventricular Activation Time (ms)	44	<	51
Z-lead QRS integral above 5 Hz (mV*ms)	1.80	<	12.79
3D QRS magnitude@20 ms (mV)	0.376	<	0.482
Spatial Ventricular Gradient (SVG, mV*ms)	0.113	>	0.056
Elevation angle of SVG (deg.)	31	>	25
X-lead area of T-wave (mV*ms)	52.9	>	18.2
Sagittal direction of QRS@30 ms (deg.)	137	>	40
Waveform Complexity (by singular value d			
Complexity ("PCA") Ratio of T wave (%)			
Intradipolar Ratio (IDR) of T-wave (%)			
QRS Wave Nondipolar Voltage Sum (mV)			
First Eigenvectors QRS-T angle (deg.)			



Advanced ECG for general practice

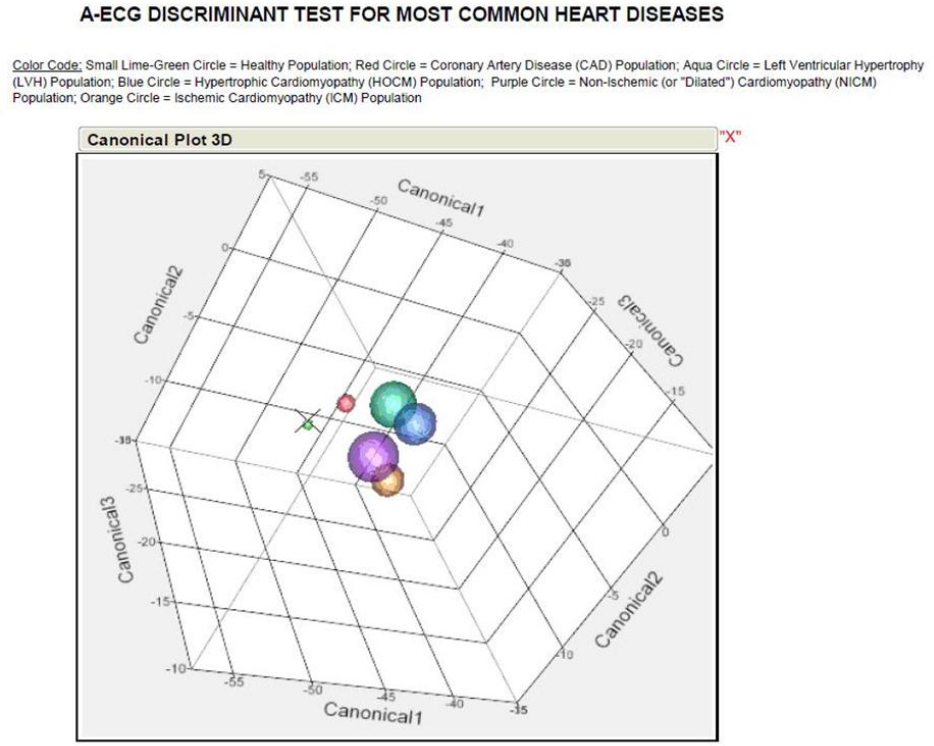


- Sensitive, high sampling frequency, accurate.



- Contact me for more details:

patrickg@theranosticslab.com



Waitemata District Health Board
Te Wai Awhina
Making a healthy difference to the community

Advanced ECG

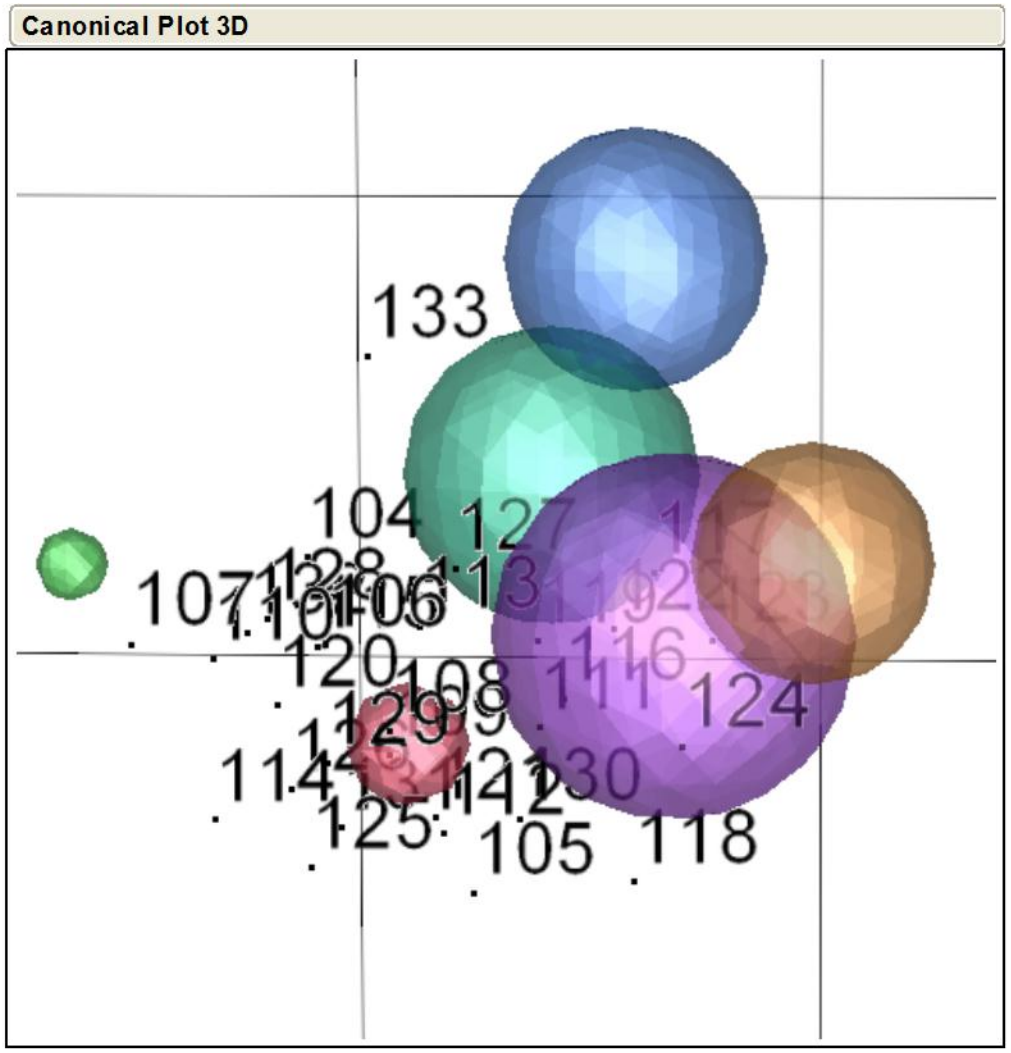
- Standard 12L snap-shot resting ECG from Mortara, Philips, Cardiax machine
- 12L ECG is ‘spectralised’ into multiple parameters
- Pattern recognition, artificial intelligence applied to resulting parameters
- Higher diagnostic yield than standard 12L ECG for CAD, HCM, NICM, ICM

Enhancement of ETT with AECG

- **Problem:** Limited access to exercise treadmill testing for patients with chest pain
- ETT Sensitivity 67%, specificity 78%

- n=58 patients (10 normal, 48 severe disease on coronary angio)
- All with positive treadmill “coronary disease”
- One excluded due to noise and six due to other cardiac abnormalities on echo

A-ECG results



- Lime - Healthy
- Red – CAD
- Blue - HCM
- Aqua - LVH
- Purple - NICM
- Orange - ICM

Advanced ECG - Results

- A-ECG sensitivity of 97.2% and specificity of 53% for the angiography results
- 8 healthy patients with abnormal ETT would have been identified correctly with A-ECG
- Theoretically reducing unnecessary invasive coronary angiograms by 53%
- Cost saving $528/A-ECG

Conclusion

- Personalised medicine is emerging as the fastest evolving field of medicine
- Significant relevance to general practice
  - Pharmacogenomics (statins, antiplatelets, dabigatran),
  - Genomics – inflammatory markers (MPO), atrial fibrillation
  - Informatics – advanced ECG
- Available through Theranostics Laboratory, North Shore hospital
- Needs your help!

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  - Acknowledgements: Innovation Hub, North Shore hospital laboratory staff


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