Stratified, personalised or P4 medicine: a new direction...

Tuesday 12 May 2015
Heartbeat Education Centre, Southampton General Hospital

Session 4

The future of stratified healthcare

#StratMed2015

Rigshospitalet

Faculty of Health and Medical Sciences

PERSIMUNE

CENTRE OF EXCELLENCE FOR PERSONALISED MEDICINE OF INFECTIOUS COMPLICATIONS IN IMMUNE DEFICIENCY

chip Centre for Health + Infectious Disease Research

Uptake of personalised medicine by the healthcare provider

P4[a] Medicine, University of Southampton

[a](predictive*preventive*personalised*participatory)=4

Prof Jens Lundgren

@ProfJLundgren

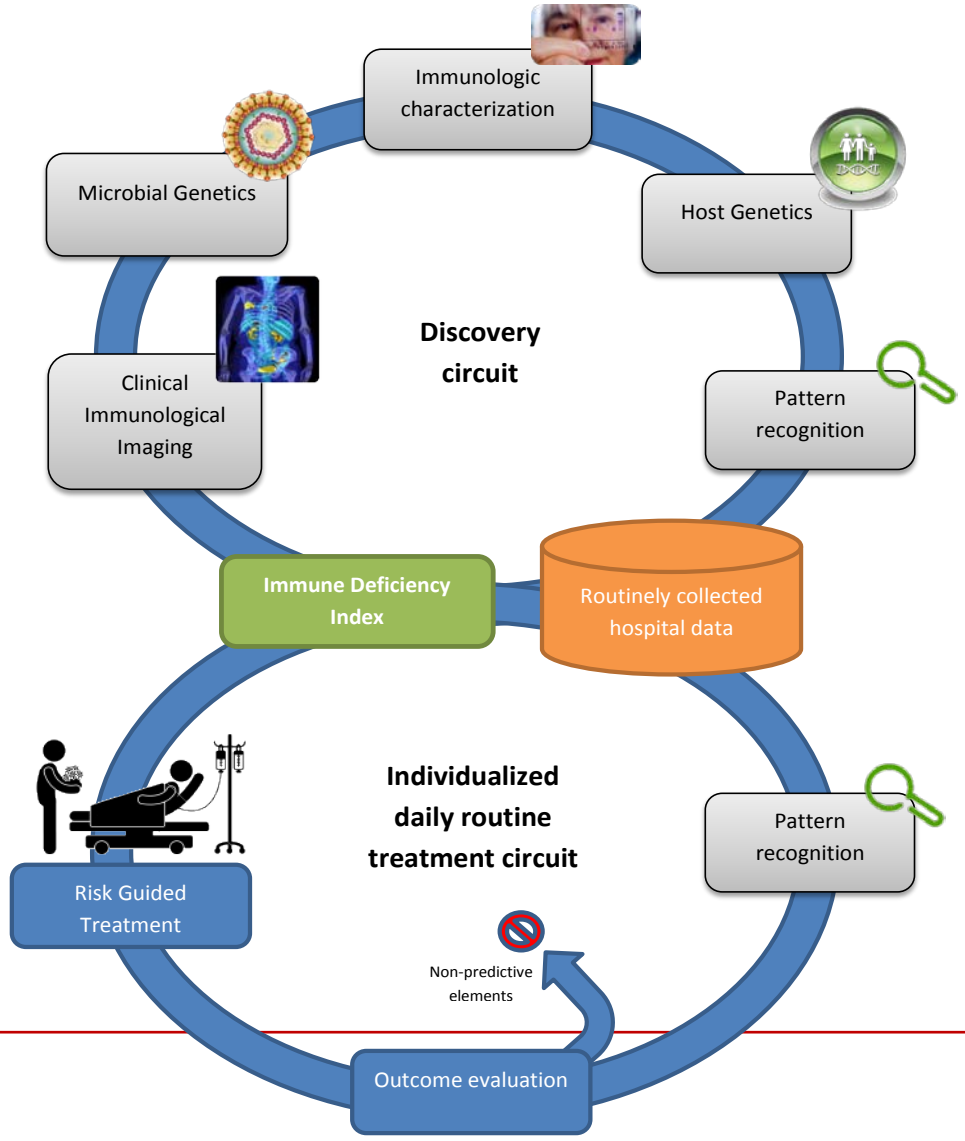
WHO Collaborating Centre on HIV and Viral Hepatitis

Danmarks Grundforskningsfond
Danish National Research Foundation

Mission of PERSIMUNE Centre of Excellence

- **In patients with immunodeficiency:**
  - **Identify *novel* host deference mechanisms, <u>and</u> the *pattern* of novel and already known mechanisms that best *explains* the *variation* in contracting infection(s)**
  - **From this formulate "*immunodeficiency indices*"**
    - **Capture knowledge of this variation**
    - **Validated prospectively**
    - **Used for further individualise care**

The circuits of PERSIMUNE



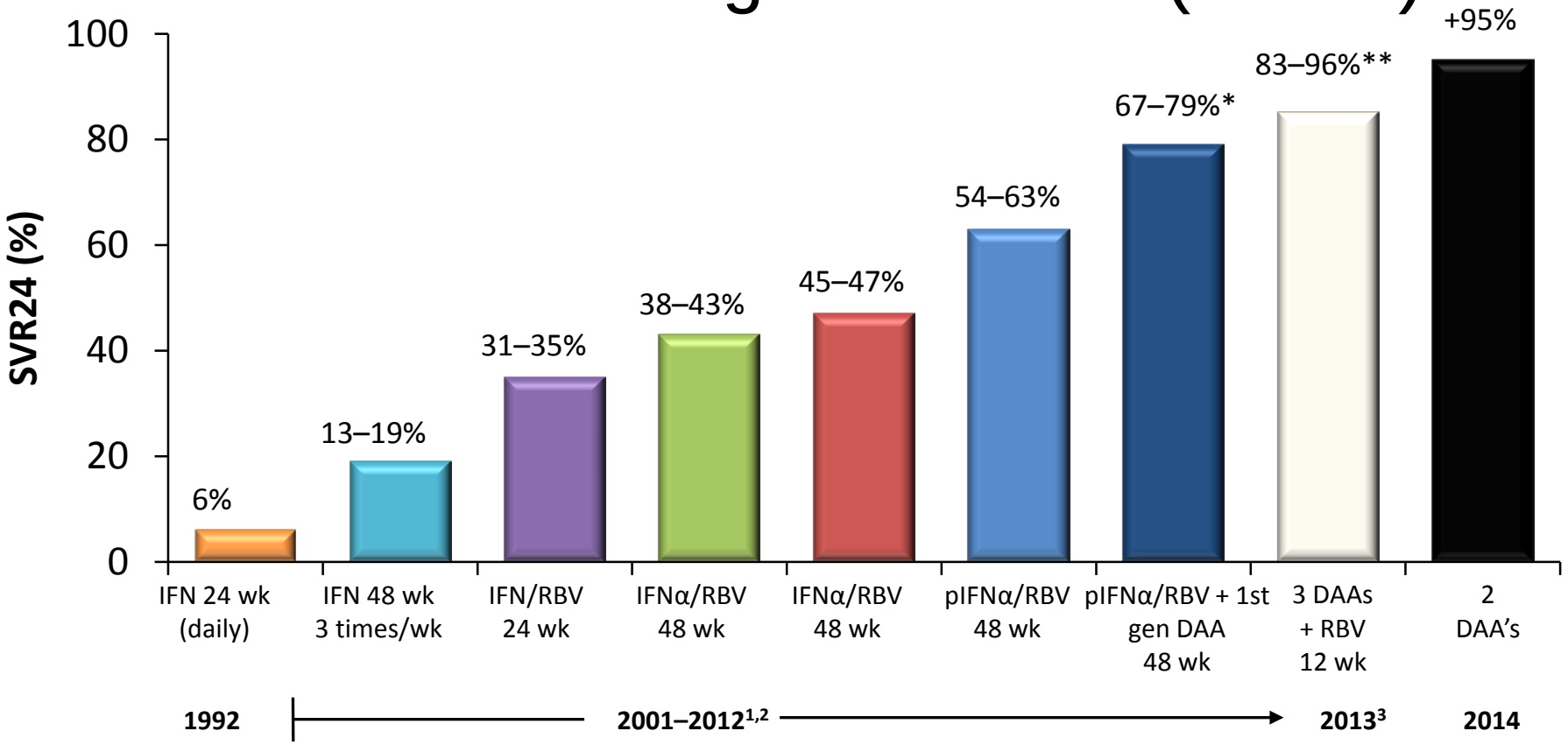
Healthcare providers contemporary challenges

- Comfort level adhering to overarching principle of providing care
  - Provide most effective interventions
  - while not causing excessive harm (*primo non nocere*)

- Treatment decisions increasingly individual patient data driven
  - The trained eye, deduction from experience – necessary but subjective
  - Complex – maintain overview – rely on data-analysis i.e. computers (!)
  - Differentiating between absolute and relative benefit

- Decisions should be evidence based
- Results from RCT's major driver of revisions of guidelines
  - Mostly head-to-head comparisons
    - Population effectiveness – insuff power to test for interaction for subgroups
  - Rarely designed to compare strategies – e.g. population vs individualised

Cure success in Hepatitis C virus: the era of direct-acting antivirals (DAAs)



*In patients with HCV genotype 1; ** In treatment-naïve patients; IFN, interferon; RBV, ribavirin; SVR, sustained virologic response

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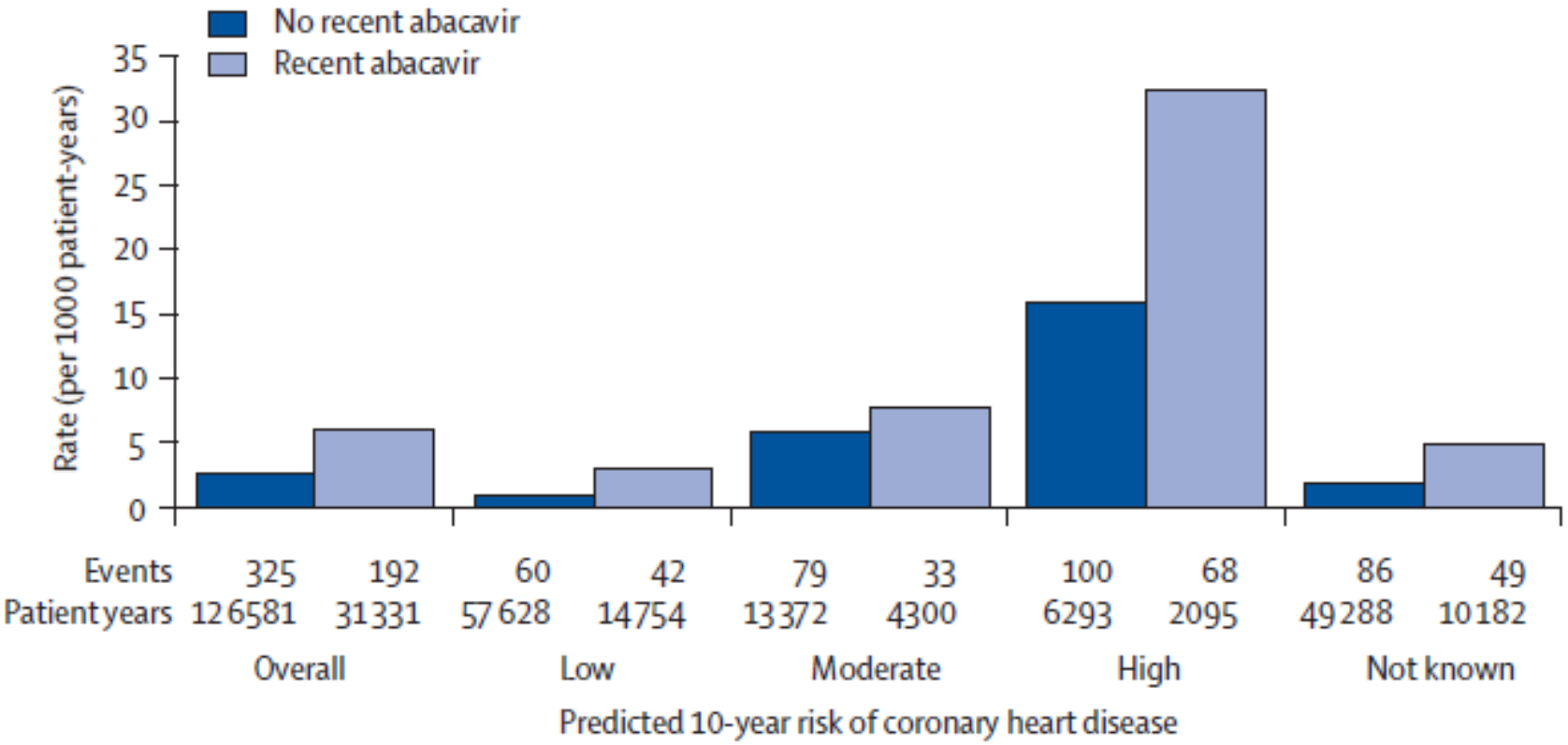
1. Adapted from Manns MP, et al. Gut 2006;55:1350–59. 2. Tran TT. Am J Manag Care 2012;18(14 Suppl):S340–9. 3. Kowdley KV, et al. EASL 2013. Abstr 3. Available at: www.clinicaloptions.com/Hepatitis/Conference%20Coverage/Amsterdam%202013/Viral%20Hepatitis/Capsules/3.aspx. Accessed 25Jul13

Relative vs absolute benefit of DAA's for HCV

- HCV may cause health-threatening liver fibrosis & specific types of extrahepatic manifestations
  - most infected are asymptomatic for decades
  - How needs treatment when ?

- Pivotal RCT's compares different types of drug combinations
  - Inclusion criteria broad – most included wo/ liver impairment
  - Very effective (+95% chance of cured after 3 mts of treatment)
  - = most guidelines released in 2015 recommend treatment to all
  - Uncertain clinical benefit if no/limited liver fibrosis
    - Only fraction will progress over lifetime
    - Treatment requires significant resources
    - Rare adverse effects not yet determined
    - Still at risk of reinfection after DAA-induced cure – risk behaviour ?

Unanticipated association* between abacavir use and raised risk of myocardial infarction



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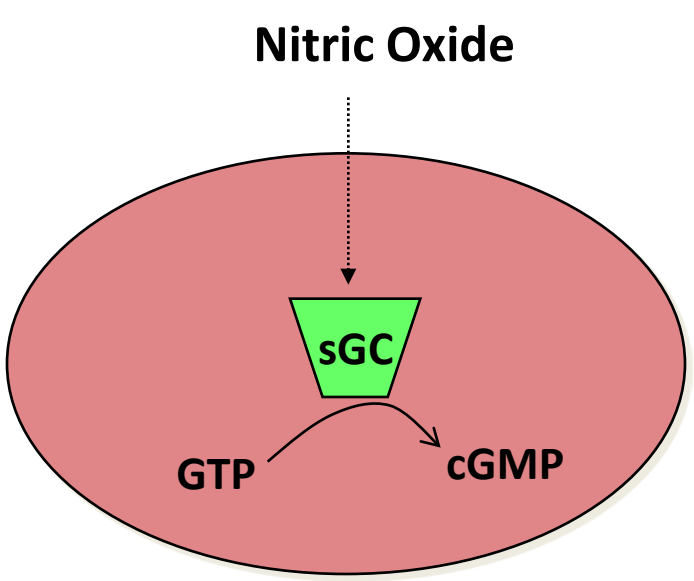
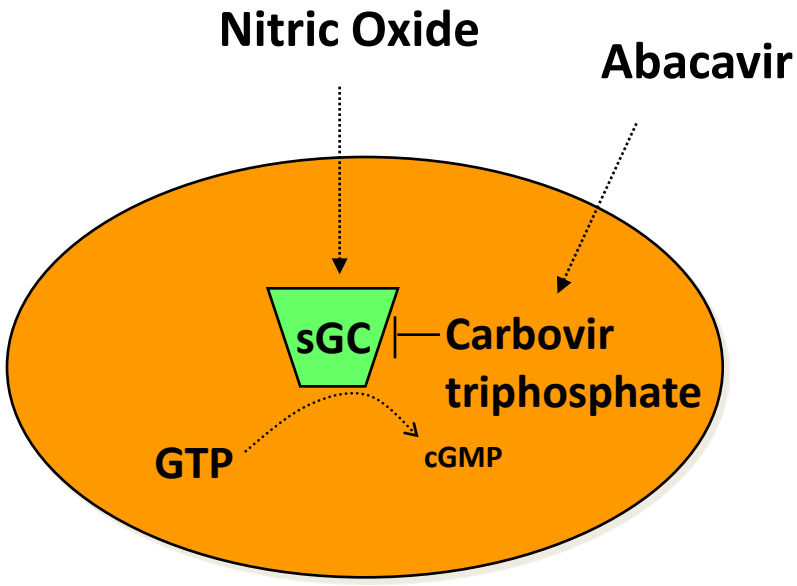
*45,000+ observational study of HIV+ - most on antiretroviral therapy

D:A:D study group: Lancet 2008

Abacavir, a Competitive Inhibitor of Guanylyl Cyclase (sGC), Increases Platelet Reactivity



Inactive platelet

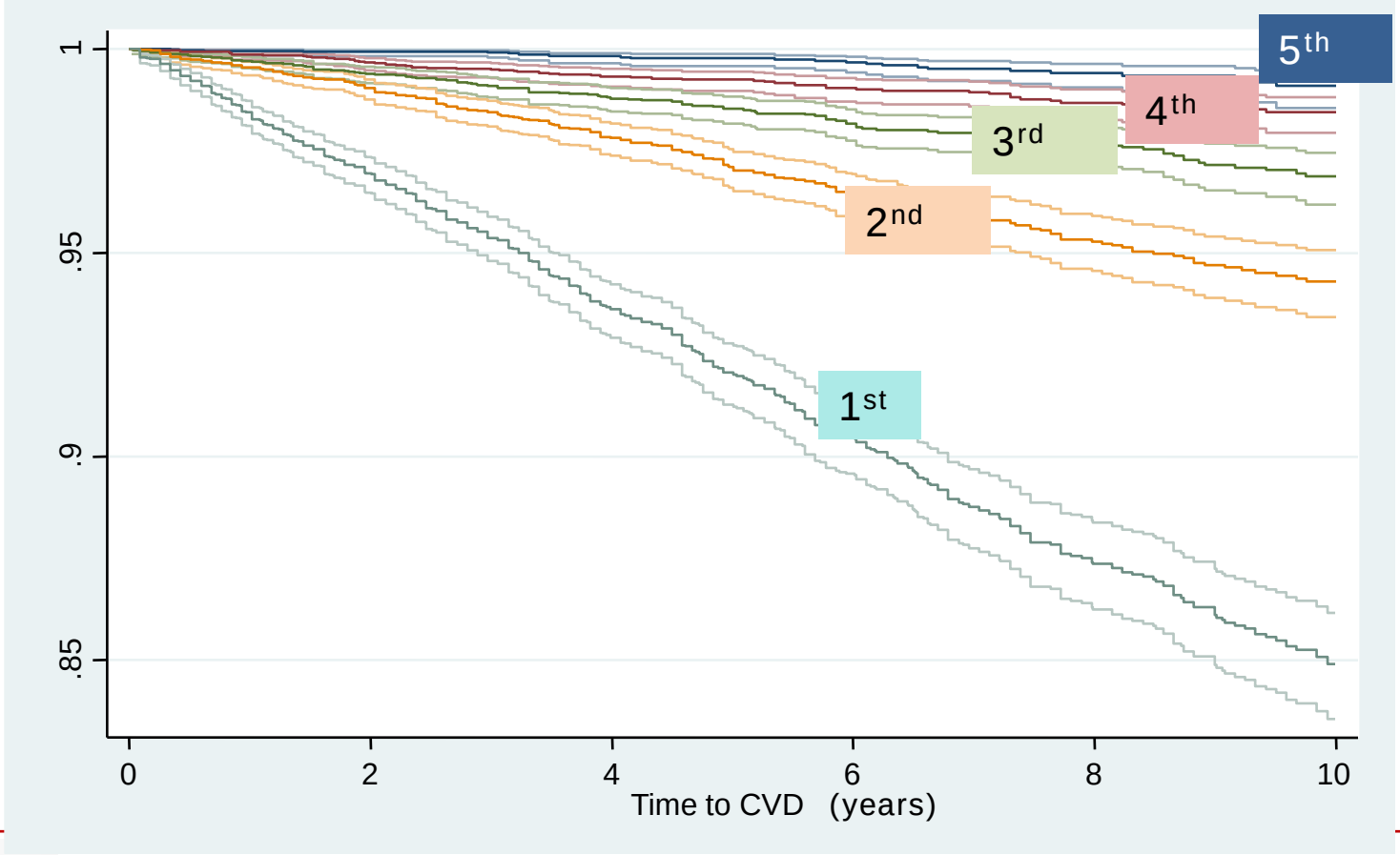


Increased platelet activity
Increased MI risk

Baum et al, JID 2011

Time to CVD by risk quintile: D:A:D risk equation

Probability of remaining free of CVD

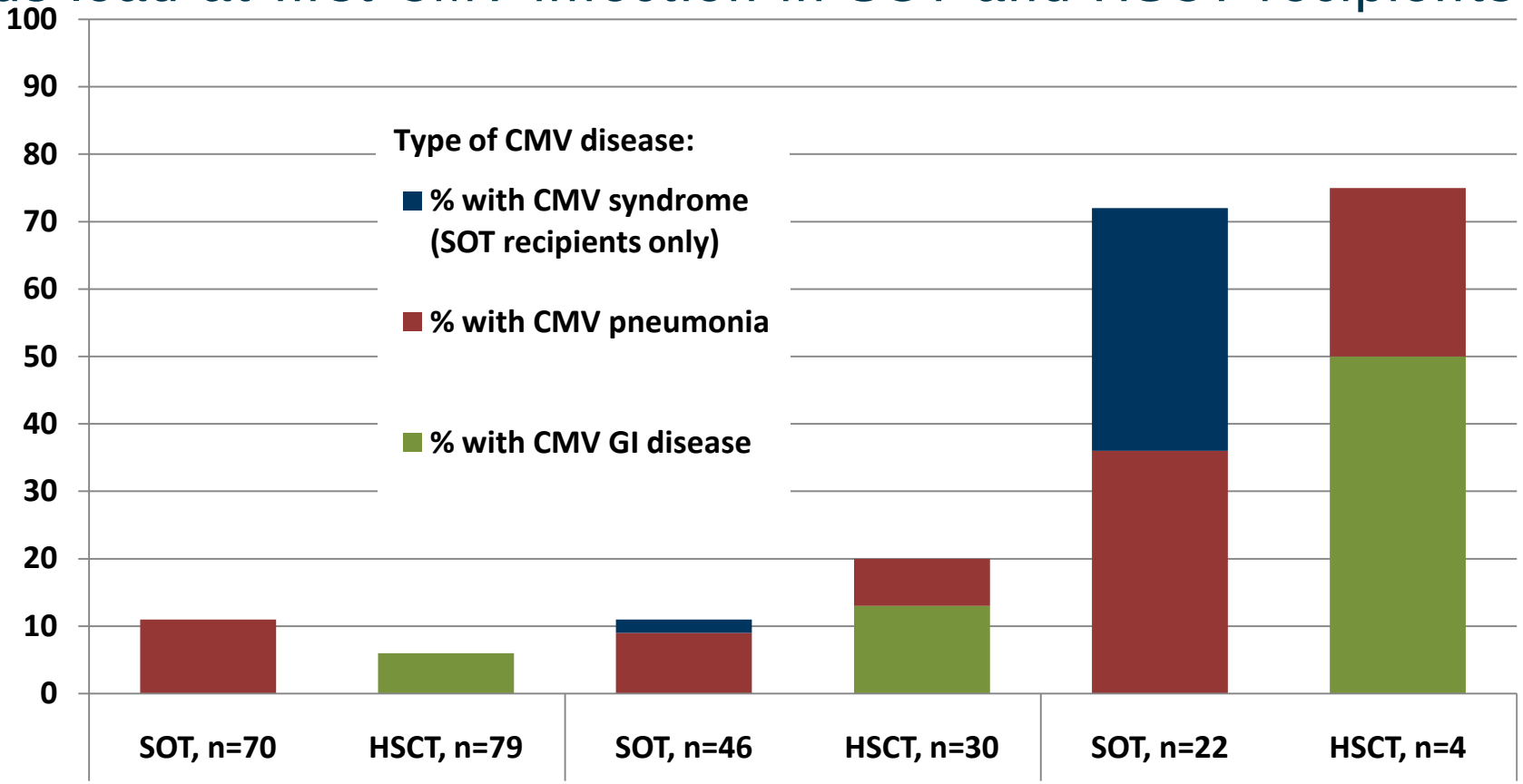


D:A:D study group: Friis-Møller *et al*, EJPC 2015

Cytomegalovirus disease in transplant recipients

- Occurs in 30%
- Pre-emptive (diagnose and treat emerging infection) approach works
- At my hospital
  - 50% developed disease
  - Cause: insufficient screening w/ CMV PCR in at risk patients
  - Solution – MATCH program:
    - screening and preventive medicine formulated in 29 algorithms according to a priori risk allocation
    - IT platform developed – real-time access to medical and diagnostic serves
    - Generates alerts if not adhering to algorithm
      - no news is good news – have to trust IT is real-time all-time

Prevalence of CMV disease (by type) according to diagnostic virus load at first CMV infection in SOT and HSCT recipients



Virus load (VL) of the diagnostic CMV PCR in plasma

MATCH study group: Lodding et al, ESCMID, 2015

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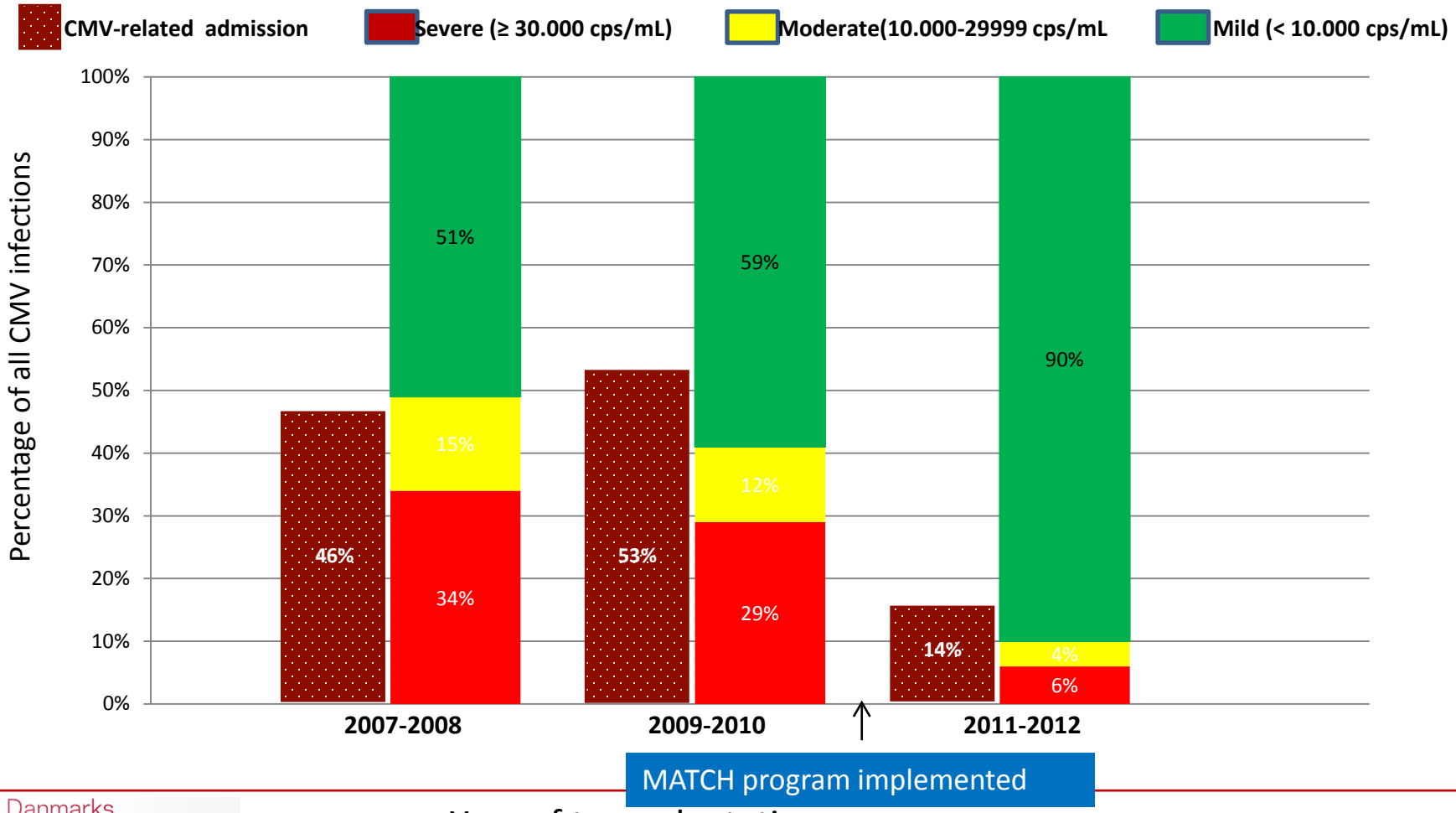
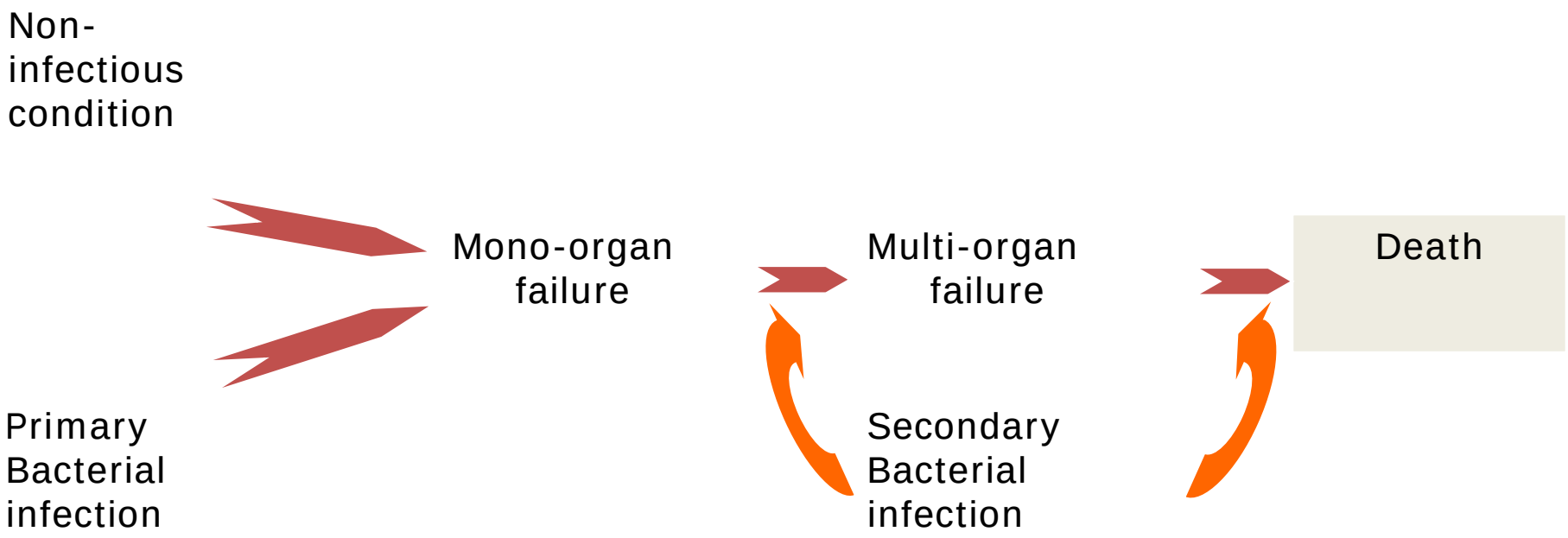
Severity of CMV infection at the time of diagnosis and CMV related hospital admission rates



Bacterial infections in the intensive-care unit and biomarkers of infection

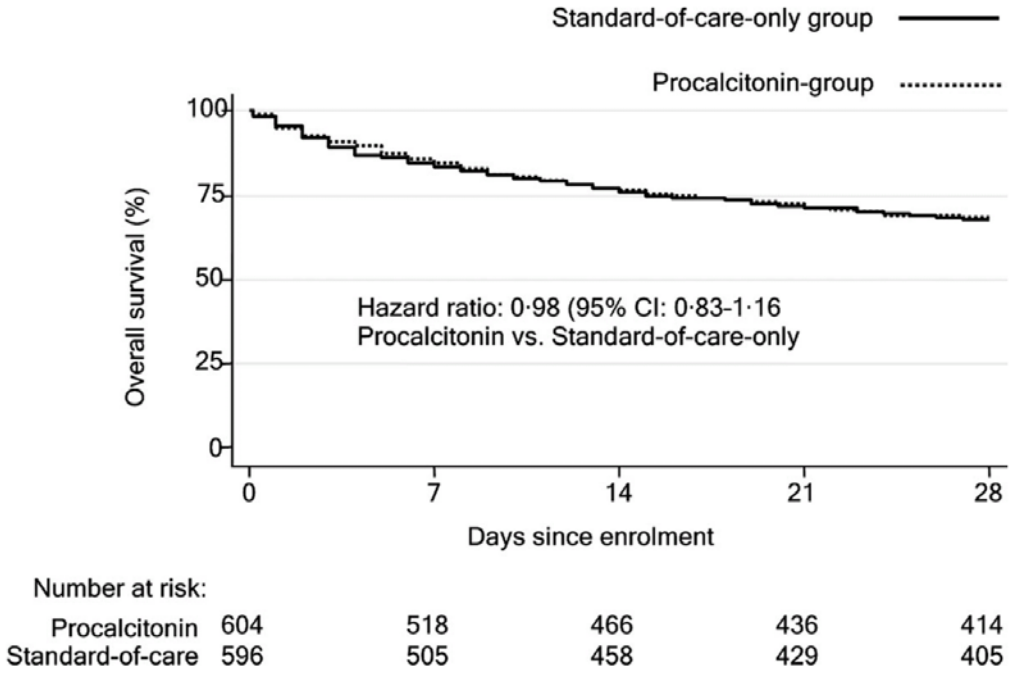


Research question: will real-time access to a biomarker assumed to predict uncontrolled bacterial infection (w/ protocol-defined excallation of antibiotic therapy) benefit patient's outcome ?

Procalcitonin (PCT) vs standard-of-care: difference in antibiotic consumption & chance of 28 day survival

PCT relative to control arm

- Tazocin
  - RH (1.83 (1.33-2.52); p<0.0001)
- Ciproxicin
  - RH (1.47 (1.14-1.90) p=0.003)
- Fluconazol and/or vancomycin
  - RH (1.78 (1.32-2.40); p<0.0001)



Jensen , CCM, 2011

Other P4 Medicine in infectious diseases examples

- Identification and drug resistance evaluation of the specific bacterial causes of pneumonia and sepsis
- HLAB57 haplotype determines risk of abacavir induced hypersentitivity reaction
  - If HLA B57*01 pos (10% of population): +90% develops reaction
  - HLA typing now standard of care
- Genetic detection of viral resistance to antiretroviral agents
  - If present: treatment failure rate increases 2-10 fold
  - Screening of new admitted for transmitted drug resistance
  - Viral failures screened for selected drug resistance

Reflections on introducing P4 medicine

- Requires robust scientific rationale and evidence on impact
  - Clinical unmet need
  - Biological understanding of processes explaining variation in outcome (preferable)
  - Mechanism of technology used to differentiate intervention understandable
  - Quantify population attributable risk from technology
  - Demonstration of benefit to patient outcome from introduction of a P4 medicine intervention
    - RCT's preferred
      - Simplest research question: does access to technology affect outcome
    - Study outcomes relevant to physicians
- Handle conflicts-of-interest
- Involve specialised physicians as early as possible

UNIVERSITY OF Southampton
School of Medicine

University Hospital Southampton NHS
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The ‘gen -omics’ revolution - incorporating stratified medicine into medical education

Karen Temple
Prof of Medical Genetics
Faculty of Medicine
University of Southampton
Honorary Consultant in Clinical Genetics, University Hospital Southampton

P4 medicine
personalised, preventative, predictive and participatory

Modern genomics – sequencing at unprecedented speeds and low cost

Improving diagnosis

Targeting treatment

Transforming medical care in the 21st century

UK healthcare training programmes: genomics content and extent found to be deficient

- A 2013 National Genomics and Genetics Education Centre review of 187 UK healthcare trainees' curricula, showed that there was significant **disparity in the content and amount** of genomics teaching across professions

- A recent 2015 study of medical schools in USA and Canada showed that most respondents felt the amount of **time spent** on genetics was insufficient preparation for clinical practice

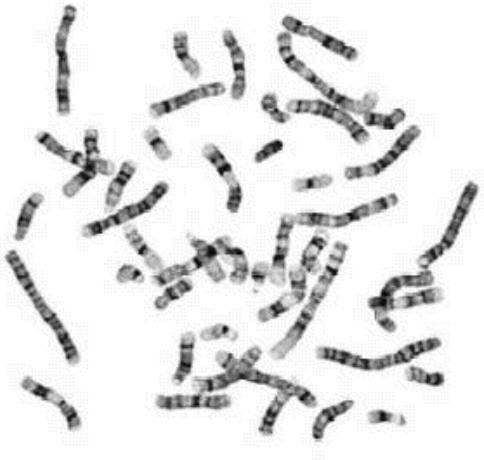
1) Plunkett-Rondeau J, Hyland K, Dasgupta S. Training future physicians in the era of genomic medicine: trends in undergraduate medical genetics education Genet Med. 2015 Feb 12. doi: 10.1038/gim.2014.208. [Epub ahead of print]

1) Baars MJ, Scherpbier AJ, Schuwirth LW, et al. Deficient knowledge of genetics relevant for daily practice among medical students nearing graduation. *Genet Med* 2005;7:295–301

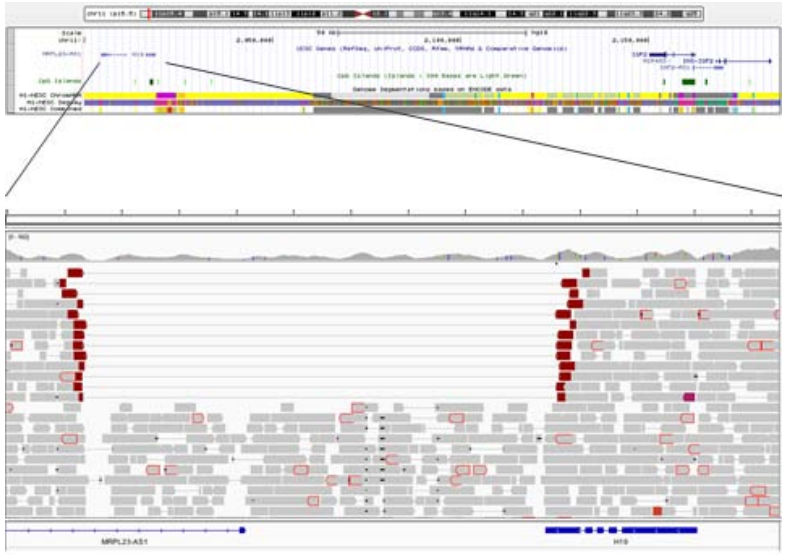
2) Challen K, Harris HJ, Julian-Reynier C, et al.; GenEd Research Group. Genetic education and non-genetic health professionals: educational providers and curricula in Europe. *Genet Med*

3) www.hee.nhs,uk

Genomic investigations, used in the NHS since 1950's
-a matter of scale - so why the issue?



Karyotype

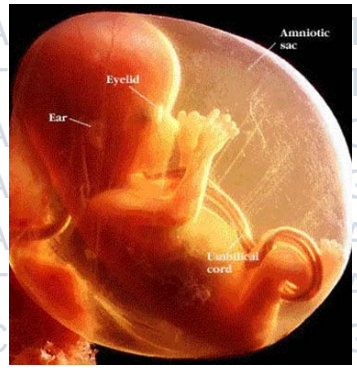


Genome

Personalised medicine/P4 medicine/ stratified medicine – a need to change education culture is recognised but challenging to deliver?

- Stratified medicine demands a culture change – treat the patient's disease and not the disease in general; a requirement to influence many current teachers
- 'Personalised medicine' – means something different to most health professionals – ie person centred/ personal responsibility v person specific pathology of disease
- Curricula; institutional resistance to change eg validated courses in advance

Genomics – the specific challenges – the complexity

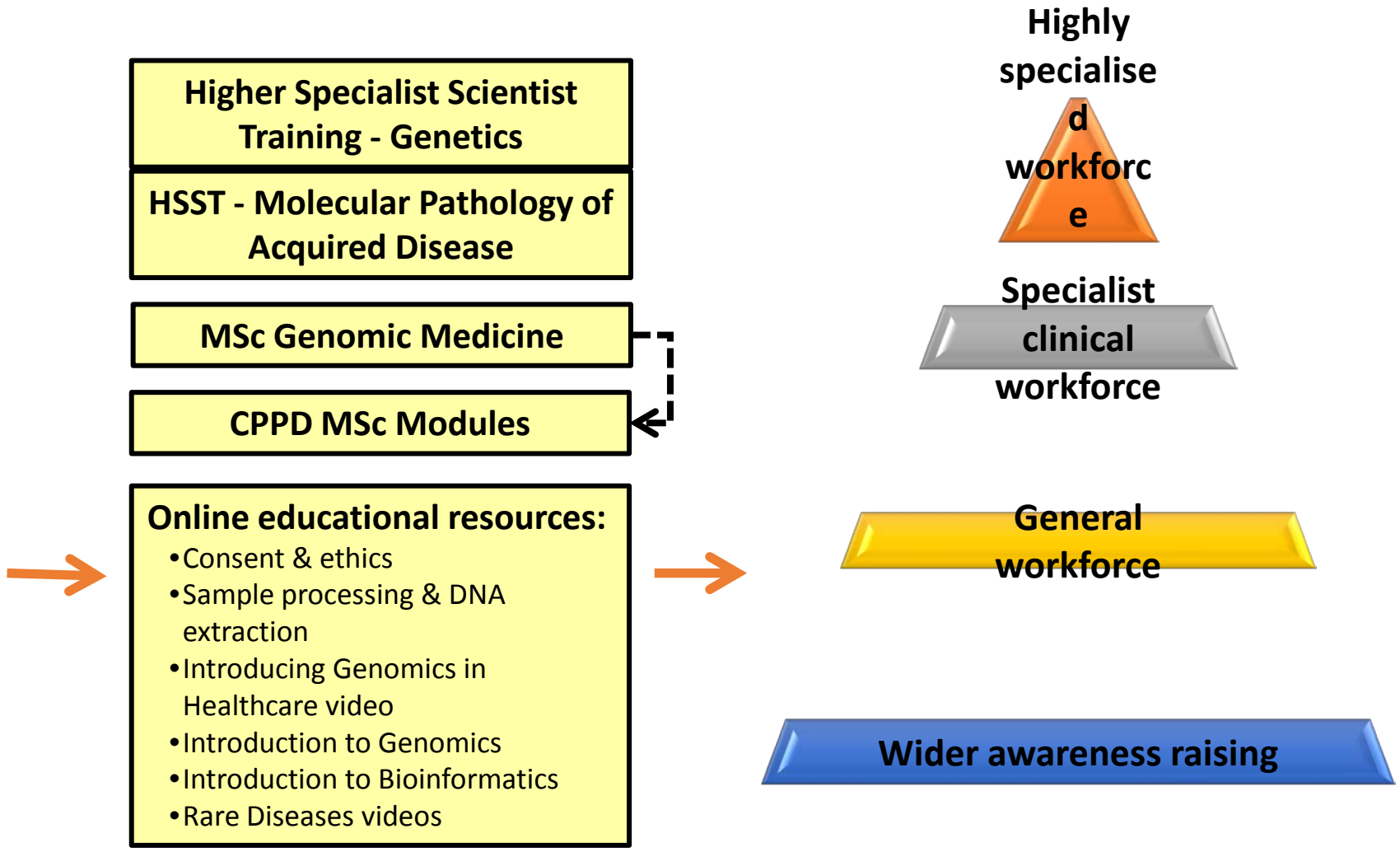


- genome and epigenome architecture
- New subject, requiring maths, statistics, ‘omics science, computing, ethics – students arrive with poor key skills;
- Core subject crossing all specialties - existing teaching staff have significant skills gap
- access to big data computing infrastructure for large classes/off site learning
- predicting the future/prevention in the NHS/ risk to relatives - family medicine
- Consent/data protection around the use, sharing and storage of genomic information
- lack of critical mass of expert ‘omic fluent faculty

Health Education England – national perspective for NHS training

Genomics Education

- an active web site and ‘go to’ place for access to Genomics Education materials
- a curriculum for a Genomic Medicine Masters programme and procured 9 HEI’s to deliver the MSc, CPPD modules, PG Cert and Diploma
- increased capacity and capability by funding additional training

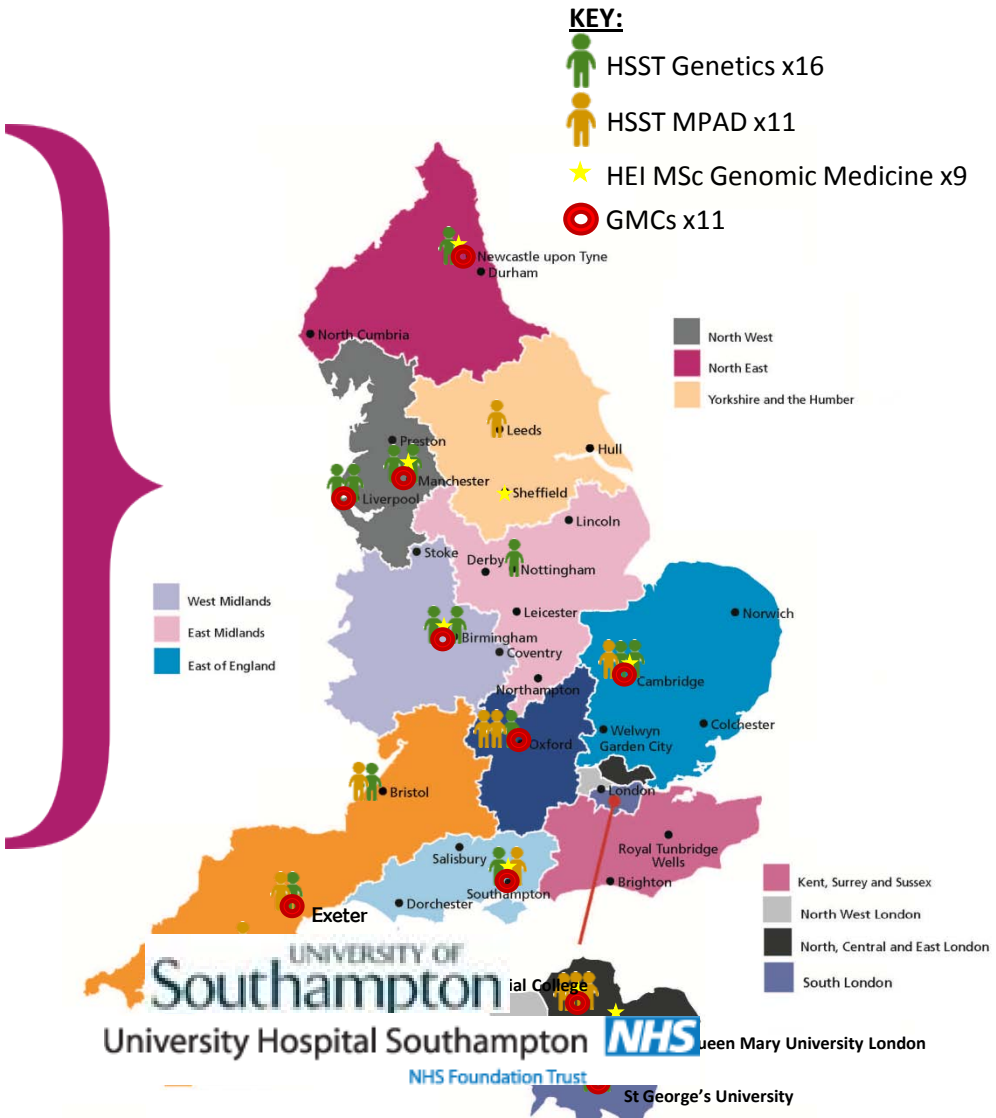


www.hee.nhs.uk/ : http://www.genomicseducation.hee.nhs.uk/

Geographical location of Genome medicine centres, Higher Education institutions and Higher Specialist training commissions

- 11 Genomic Medicine Centres
- 9 HEI providers for MSc Genomic Medicine, 550 funded places and 900 CPPD modules
- 27 additional HSST commissions:

(16 genetics, 11 Molecular Pathology of Acquired Disease)



The University of Southampton is proactive in developing a genomics medicine education agenda

Linking the emphasis on ‘patient-listening’ based teaching, to the scientific basis of patient-specific disease - a comprehensive Personalised Medicine approach.

<u>Undergraduate</u>

Dedicated genomics education team
Work closely with the vertical curriculum implementation group
New genomics lectures and tutorials in years 1, 2 and 3 of BM
Genomics ethics and law – on line/ lectures/ tutorials
On-line genomics material for students
Student selected unit for medical genomics in year 3
In-depth student placements in genomics and informatics
Inspire program – senior academic student leadership in research

<u>Postgraduate</u>

Southampton Genomic Medicine MSc
diploma/CPPD
A foundation of useful teaching materials.

Southampton MSc in Genomic Medicine

- A full time option delivered over 1 year
- Part time – 2 years blended learning format
- Flexibility delivered by core modules and optional modules
- Access to individual modules CPD
- Combinations of credit modules that can lead to PG Cert or PG Diploma
- A significant research component in the MSc linked to 100,000 Genomes Project

http://www.genomicseducation.hee.nhs.uk/GenomicsMSc/

P4 medicine

University of Southampton School of Medicine

University Hospital Southampton NHS
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The public and NHS staff and students are learning how to use genomics <u>at the same time</u>