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
Uptake of personalised medicine by the healthcare provider

P4a Medicine, University of Southampton

*(predictive*preventive*personalised*participatory*)=4

Prof Jens Lundgren

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WHO Collaborating Centre on HIV and Viral Hepatitis
Mission of PERSIMUNE Centre of Excellence

• In patients with immunodeficiency:
  – Identify *novel* host deference mechanisms, and 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

1. **Discovery circuit**
   - Immunologic characterization
   - Microbial Genetics
   - Clinical Immunological Imaging
   - Host Genetics
   - Pattern recognition

2. **Immune Deficiency Index**
   - Routinely collected hospital data

3. **Risk Guided Treatment**
   - Individualized daily routine treatment circuit

4. **Outcome evaluation**
   - Non-predictive elements
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


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

*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

Nitric Oxide

- **sGC**
- **GTP**
- **cGMP**

*Inactive platelet*

Abacavir

- **sGC**
- **GTP**
- **cGMP**

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

<table>
<thead>
<tr>
<th>Year of transplantation</th>
<th>CMV-related admission</th>
<th>Severe (≥ 30,000 cps/mL)</th>
<th>Moderate (10,000-29,999 cps/mL)</th>
<th>Mild (&lt; 10,000 cps/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007-2008</td>
<td></td>
<td>45%</td>
<td>15%</td>
<td>34%</td>
</tr>
<tr>
<td>2009-2010</td>
<td></td>
<td>53%</td>
<td>12%</td>
<td>29%</td>
</tr>
<tr>
<td>2011-2012</td>
<td></td>
<td></td>
<td>14%</td>
<td>4%</td>
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</table>

MATCH program implemented

MATCH Study Group: Cunha-Bang
Bacterial infections in the intensive-care unit and biomarkers of infection

Non-infectious condition

Primary Bacterial infection

Mono-organ failure

Multi-organ failure

Secondary Bacterial infection

Death

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)
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 hypersensitivity 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
The ‘gen -omics’ revolution - incorporating stratified medicine into medical education

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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.

3) www.hee.nhs.uk
Genomic investigations, used in the NHS since 1950’s
-a matter of scale - so why the issue?
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
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

[Diagram]

Health Education England – national perspective for NHS training

• 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.

**Undergraduate**
- 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

**Postgraduate**
- 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/
The public and NHS staff and students are learning how to use genomics at the same time.