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

Tuesday 12 May 2015
Heartbeat Education Centre, Southampton General Hospital

Session 3

Interdisciplinary approaches to stratified medicine
Biomarker discovery through creating an “information commons”: the EU Innovative Medicines Initiative U-BIOPRED project

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EFPIA Partners
Novartis
Almirall
Amgen
AstraZeneca
Boehringer Ingelheim
Chiesi
GlaxoSmithKline
Johnson & Johnson / Janssen
Merck
UCB
Roche / Genentech

SME’s
Aerocrine
BioSci Consulting
Synairgen
Philips Research

Patient organisations
Asthma UK
European Lung Foundation
EFA
Int Primary Care Respiratory Group
Lega Italiano Anti Fumo
Netherlands Asthma Foundation

website hosted by the ELF: www.ubiopred.eu
Definition of Asthma 2012

- A chronic inflammatory disorder of the airways
- Many cells and cellular elements play a role
- Chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing
- Widespread, variable, and often reversible airflow limitation
Biological agents launch timeline

- Target/MoA:
  - IgE
  - IL-5
  - IL-13
  - IL-4
  - IL-17

- Biological agents:
  - Mepolizumab (GSK)
  - Reslizumab (Teva)
  - Benralizumab (AZ)
  - Tralokinumab (AZ)
  - Lebrikizumab (Roche)
  - Dupilumab (Sanofi)
  - QGE-031 (Novartis)
  - QAX-576 (Novartis)
  - Broadalumab (Amgen/AZ)
  - Quilizumab (Roche)
  - MEDI-4212 (AZ)

- Timeline:
  - 2014
  - 2015
  - 2016
  - 2017
  - 2018
  - 2019
  - >2020

- Biosimilars
U-BIOPRED platforms

- Blood
- Bronchoscopy
  - Epithelial brushing
  - Bronchial biopsy
- Induced sputum
- Urine
- Exhaled breath

- Genomics
- Transcriptomics
- Proteomics
- Lipidomics
- Metabolomics
- Breathomics

www.ubiopred.eu
775 asthmatics

**Sample processing**

- **Sputum**: Lipid extraction, digestion, HMW contaminant removal, clean up
- **Serum**: Top 12 depletion, digestion, clean up

**LC-IMS-MS^E Analysis** (duplicate injections)

**Data pre-processing**: e.g. quantitation, normalisation, batch effect correction

**In-house developed scripts**

**Standard statistics**: R, DanteR, Matlab, OPLS

**Data mining and unsupervised grouping**

- Kohonen maps (ANN)
- Hierarchical clustering
- Topological Data Analysis (TDA)

**Feature selection**

**Machine learning classification** (e.g. SVM)
Topological data analysis (TDA): A Pioneering Approach

Topology is the study of shape

Topology is a branch of mathematics from the 1700s that studies continuity and connectivity of objects and spaces, utilizing the shape of data to derive meaning in data.

Our Differentiation is TDA

The combination of Topological Data Analysis (TDA) with machine-learning automatically creates topological networks revealing statistically significant patterns in complex data.

AYASDI

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Topological data analysis (TDA) in breast cancer

Zero event death
Low event death
High event death

Mixed event death

High event death
Low event death
Zero event death

These patients are eccentric (away from the center of the data)

Color scheme

patientsTVC_study2.csv
1558 dimensions, 272 points
This slide contains data that are subject of a manuscript in preparation and are, therefore, restricted.

The slides show several clusters of asthmatic patients created by TDA. These cluster are then assessed for their predictive value in the next slide.
Area Under the Curve (AUC)

<table>
<thead>
<tr>
<th>AUC</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.90</td>
<td>Excellent</td>
</tr>
<tr>
<td>&gt;0.80</td>
<td>Good</td>
</tr>
<tr>
<td>&gt;0.70</td>
<td>Fair</td>
</tr>
<tr>
<td>&gt;0.60</td>
<td>Poor</td>
</tr>
<tr>
<td>&gt;0.50</td>
<td>Fail</td>
</tr>
</tbody>
</table>

**Graphs:**

- **A:** ROC curves for different asthma groups.
- **B:** ROC curves for various groups and subgroups.
- **C:** ROC curves showing the performance of different groups with their respective AUC values.
So where is this taking us?
Handprints and Biomarkers of Handprints

- tryptase
- EDN
- MPO
- Periostin
- Eos + periostin + FeNO
- Protein X + lipid X
- PGD2 metabolites

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Definition of Asthma 2020

- A chronic inflammatory disorder of the airways composed of X phenotypes
- Mast cells, eosinophils, neutrophils, Th2 T-cells and their mediators play different roles in the different phenotypes
- Phenotype X is characterised by steroid unresponsiveness and phenotype Y is characterised by irreversible airflow limitation
- Phenotype X1 responds to drug B1, Phenotype X2 responds to biologic B2
Future developments

Stratified Medicine in Severe Asthma
UK Refractory Asthma Stratification Programme (RASP-UK)

Biomarkers predictive of responses to Omalizumab (anti-IgE):
Collaborative project with Novartis

NIHR Translational Research Partnership (TRP)
Diagnostics and Molecular Pathology

Tito Bacarese-Hamilton
Chief Technology Officer

11th May 2015
“It is more important to know what sort of person has a disease than to know what sort of disease a person has.”

Hippocrates, 460-370 B.C.
How the Diagnostics Industry Works

- **Doctors** (clinical utility)
- **Laboratories** (also develop own tests - LDTs)
- **Platforms** (instruments)
- **Content** (kits)
- **Diagnostic Companies**
The Diagnostic Business Model

System placement

- Dx company places systems
- Dx company finances systems
- High sales effort
- High up-front investment

Harvesting reagent stream: Sample prep and assay reagents

- Harvest reagent streams over long time - 5 year contracts
- Reagent stream refines instrument investment
- Low sales effort and high service effort
- Guaranteed business for years: stable cash-flow
Commercial Opportunities in Diagnostics

• Prices depend on application
• Development can be expensive
• Business driven by volume
  – £100M annual market good
  – >£1bn annual market excellent

<table>
<thead>
<tr>
<th></th>
<th>Products</th>
<th>Services</th>
<th>Average selling price</th>
<th>Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro Diagnostics</strong></td>
<td>$35bn</td>
<td>$55bn</td>
<td>$25</td>
<td>5-10%</td>
</tr>
<tr>
<td><strong>Molecular Diagnostics</strong></td>
<td>$4bn</td>
<td>$8bn</td>
<td>$125</td>
<td>10-20%</td>
</tr>
<tr>
<td><strong>Companion Diagnostics</strong></td>
<td>$200M</td>
<td>$700M</td>
<td>$450</td>
<td>20-30%</td>
</tr>
</tbody>
</table>
Diagnostic Value Proposition

• Biomarkers with clinical utility
• Ease of Use and convenience
• Quality
• Consistency
• Regulatory
• IP
What’s new about Molecular Pathology?

• Qualitatively
  – No change
  – No individual biomarkers we couldn’t measure 20 years ago

• Quantitatively
  – Major changes
  – Now possible to measure lots of biomarkers all at the same time
How are new technologies being applied within diagnostics?

• Discovery
  – Use ‘omic methods to scan many potential biomarkers to find the small number of most useful ones
  – Deliver this information to the doctor using “traditional” methods

• Delivery
  – Offer a test based on many potential biomarkers
    • Eg whole exome sequencing
    • Eg whole genome sequencing
Then and Now…..

• Traditional approach to diagnosis
  – Identify disease biomarkers
  – Prove biomarkers are associated with disease
  – Use presence of biomarker to diagnose disease

• Paradigm shift
  – Analyse many biomarkers associated with disease
  – Infer diagnosis from knowledge of what biomarkers mean, use of algorithms
Five applications for molecular pathology

• Predisposition
• Early Detection (Screening)
• Diagnosis
• Therapy Selection
• Monitoring
FDA bans 23andme personal genetic tests

The service offers to read genetic code, but critics have questioned the results.

The US Food and Drug Administration has imposed a ban on a company offering personal genetic screening to the general public.
Screening and Early Detection

• Best application from commercial perspective
  – Big numbers
• Some good examples, mainly in cancer
  – HPV screening
  – PSA screening
• Early detection of late onset diseases (eg Alzheimer’s, Parkinson’s), ideally if there is an intervention
• Novel advances in prenatal screening have created a large diagnostic opportunity
Diagnosis

• Diagnosis of the underlying causes of genetic diseases is clinically vital

• Not a great commercial opportunity
  - Low numbers
  - Not routine
Therapy Selection

• Unusual opportunity for diagnostic companies because of influence of price of drug

• Excellent opportunity but driven more by availability of therapies rather than diagnostics
Disease monitoring

• Good application

• Feasibility driven by access to sample

• Soluble nucleic acids in the blood are a novel and exciting source of a “liquid biopsy”
Barriers to Adoption

• Costs of test development/validation

• Clinical evidence
  – Robust clinical outcomes data
  – Submission/approval process
  – Approval data set vs Real world data

• Adoption pathway
  – Guidelines eg NICE do not guarantee re-imbursement
  – Crowded diagnostics innovation space (TSB, DEC, NIHR)
  – Changing regulatory environment (LDTs, IVDs, IVDD)
Success Will Require a New Model

Pharmaceutical Development and Marketing

Focus on the **drug**

**New Model**

Diagnostics Development and Marketing

Focus on the **diagnostic**

Focus on Total **Solution** for the Patient
Summary

• The diagnostics industry is based on clinical utility but needs volume to be commercially viable

• Best commercial opportunities for molecular pathology
  – Prenatal screening
  – Early detection of cancer
  – Early detection of late onset diseases (if there is a decent intervention)
  – Monitoring of cancer changes to alter treatment

• Challenges need to be overcome to address the opportunity (cost, clinical evidence, re-imbursement)