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Workshop “Investing in eSafety”

Precision Medicine and Patient Safety

14 August 2014
In Ancient Greece, Rufus of Ephesus suggested that drugs have different effects on different people.
Origin

• In 1902, Archibald Garrod suggested individuals were different not only phenotypically, but also at the biochemical level.
The term ‘personalised medicine’ was coined in 1999 by Robert Langreth and Michael Waldholz (Wall Street Journal reporters) in an article to describe the development by pharmaceutical companies of:

“a cornucopia of personalized medicines that will produce huge profits into the next century”.

• Our ability to collect individual genetic and environmental data has been very limited until recently.

• One major milestone in overcoming those barriers was the Human Genome Project, which together with advances in DNA sequencing technologies, has facilitated a fast and affordable access to personal genetic variation data.

• This marked the beginning of the Genomic Medicine age in the early 2000’s
• Our increased knowledge about the **molecular causes of complex diseases** represents another key aspect of the advances that we are witnessing in this field.

• Microarray-based technologies opened the door to the study of functional aspects of DNA and protein expression, which has been referred to as **molecular medicine**.

Comprehensive molecular portraits of human breast tumours
The Cancer Genome Atlas
*Nature* **490**, 61–70
(04 October 2012)
• The term **P4 medicine**, coined by Leroy Hood, tries to amalgamate most of these previous objectives, making a greater emphasis on the importance of preventative and participatory medicine.
• US President’s Council of S&T noted that personalised medicine ‘refers to the tailoring of medical treatment to the individual characteristics of each patient’.

• It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.
Precision Medicine is an approach to discover and develop medicines, vaccines or routes of intervention (behavior, nutrition, etc.) that enable disease prevention and deliver superior therapeutic outcomes for patients, by integrating “Big Data”, clinical, molecular (multi-omics including epigenetics), environmental and behavioral information to understand the biological basis of disease.

This effort leads to better selection of disease targets and identification of patient populations that demonstrate improved clinical outcomes to novel preventive and therapeutic approaches.

C.M. Christensen et al.. The innovator’s prescription a disruptive solution for health care. McGraw-Hill, 2008
Work in this area is aimed at redefining disease classification, identifying common underlying causes and representing them into new taxonomies.

*Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* (2011)
<table>
<thead>
<tr>
<th>Disease area</th>
<th>Drug (Rx) and Companion diagnostic (CDx)</th>
<th>US approval</th>
<th>EU approval</th>
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<td>Rx</td>
<td>CDx</td>
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Herceptin targets the HER2 protein, present on cell surfaces. In some cancers, HER2 overproduction causes the uncontrollable cell growth driving the disease. HerceptTest identifies if an individual’s breast cancer involves HER2 overproduction: if so, they will respond to Herceptin. The HER2 marker was found during drug development. This was the first simultaneous approval of Rx and CDx. The product received subsequent approval for use in HER2-positive gastric cancer.

| HIV | Ziagen (abacavir) GSK/VIR Healthcare | HLA-B*57:01 screening assay | Dec 1998 | N/A: unbranded test | Jul 1999 | N/A: unbranded test |

Action of HIV’s reverse transcriptase enzyme is critical to the replication of the virus. Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir and abacavir-containing products. Extensive research established that patients who carry the HLA-B*5701 allele are at a high risk for experiencing a hypersensitivity reaction to abacavir.

| Breast cancer | Oncotype DX Genomic Health | N/A: Dx only | Not FDA-approved: use supported by literature | N/A: Dx only | 2007 |

Developed through retrospective studies on tissue archives, Oncotype Dx is a diagnostic tool that predicts the likelihood of breast cancer recurrence and the benefit of chemotherapy in about 60% of breast cancer cases. The test is now included in major treatment guidelines for breast cancer in the US, and receives a value-based reimbursement, which is based on clinical data demonstrating the test’s ability to restrict healthcare costs.

| Colorectal cancer | Vectibix panitumumab Amgen | EGFR pharmDX kit Dako thesarscreen®: KRAS RGQ PCR kit Qiagen | Sep 2006 | Sep 2006* | Jul 2012 | Yes |

Vectibix was designed to treat colorectal cancers overproducing a protein called EGFR. After going to market, it was found that EGFR overproduction does not indicate response to the Rx, and that individuals with this marker would not respond to therapy if they also carried a mutation in another protein, KRAS. Vectibix is now established as a stratifying marker, and a marker for the safety of using Vectibix in combination with a certain type of chemotherapy.

| Melanoma | Zelboraf (vemurafenib) Roche/Plexxikon | cobas® 4800 BRAF V600 Mutation Test Roche | Aug 2011 | Aug 2011 | Feb 2012 | Yes |

This drug was selected by Roche for development owing to knowledge of the biomarker: the drug showed effects in melanomas containing a particular mutation, V600E, in a protein called BRAF. The Rx and CDx were developed in parallel, and co-approved in one of the fastest FDA approvals in history (four months). Zelboraf was approved by NICE in November 2012.


A 2007 study linked a subset of NSCLC to the ALK fusion gene. This prompted a partnership between Rx and CDx manufacturers, and patient stratification using this CDx resulted in dramatic improvement in response rates. Approval was rapid both in the US and in the EU.

| Cystic fibrosis | Kalydeco (ivacafator) Vertex/ Cystic Fibrosis Foundation Therapeutics Inc. | G551D mutation test | Jan 2012 | N/A: unbranded test | Jul 2012 | N/A: unbranded test |

One of the first treatments to target the underlying cause of cystic fibrosis, Kalydeco was developed based on gene and protein data from sufferers of the disease. The ability to test for specific cystic fibrosis mutations was critical both during development and for post-approval use, yet a specific brand of test is not specified on the label.

| Melanoma | BRAF/MEK inhibitor (dabrafenib and trametinib) GSK | BRAFTM mutation kit (v600E & K) bioMerieux | In development |

This Rx:CDx combination is currently under development. The BRAF V600 mutations are present in approximately 50% of melanomas. Separately, the Rx showed positive results up to phase 3 trials. As a combination, they have shown promising results at phase 2, and are now at phase 3. GSK has been collaborating with bioMerieux to develop the CDx, which is being used to identify patients BRAF V600 status in the current phase 3 trials.
• Prior to initiating therapy with **abacavir**, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction

• **Clopidogrel**. platelet inhibitor indicated to reduce atherothrombotic events in patients with acute coronary syndrome, recent myocardial infarction, recent stroke or peripheral artery disease. Consider alternative treatment in patients identified as CYP2C19 poor metabolizers

• **Tamoxifen** – Breast Cancer – CYP2D6 genotype can help optimize the choice of breast cancer treatment.
Personalised vs Precision Medicine

Data sources:

Personalised Medicine
- Genomics (genomic variants)
- Phenotype (clinical records)

Precision Medicine
- Informal data sources
- Exposome (environmental data)
- Metabolomics
- Proteomics

PM combines the knowledge of the patient’s characteristics with traditional medical records and environmental information to optimize health.

PM does not only rely on genomic medicine but also integrates any other relevant information such as non-genomic biological data, clinical data, environmental parameters and the patient’s lifestyle.

**Personalised vs Precision Medicine**

**Personalised medicine**
- Improving therapy
  - Looking for the right drug for the right people
- Companion diagnostics to stratify patients
- Use of genomics data
- Static - “Snapshot”

**Precision medicine**
- Improving Diagnosis
  - Looking for the right drug for the right disease
  - New taxonomy of disease and disease reclassification
- New/refined diagnostics methods
- Use of molecular (-omics) and other (i.e. exposome) data sources
- Dynamic stratification - Modelling patient journeys
12 tumor types

- Leukemia (LAML)
- Lung adenocarcinoma (LUAD)
- Lung squamous (LUSC)
- Kidney (KIRC)
- Bladder (BLCA)
- Endometrial (UCEC)

Glioblastoma (GBM)
Head and neck (HNSC)
Breast (BRCA)
Ovarian (OV)
Colon (COAD)
Rectum (READ)

Omics characterizations

- Mutation
- Copy number
- Gene expression
- DNA methylation
- MicroRNA
- RPPA
- Clinical data

Thematic pathways
100 people commit their bodies to science in new study

on February 14, 2014 / in News 9:21 pm / Comments

CHICAGO (AFP) – One hundred people are about to donate their live bodies to science as part of an unprecedented new study that will examine how to improve personal health, researchers said Friday.

The Hundred Person Wellness Project, which begins next month, will require round-the-clock monitoring of its subjects, who are presumed healthy at the time of enrollment.

Scientists will start by sequencing the entire genome of each participant. Then, for the next 25 years, they will take regular measurements of sleep patterns, heart rate, gut bacteria, proteins that track organ health, blood samples, immune cell activity and more.

“What is unique about humans is their individuality,” said Leroy Hood at the American Association for the Advancement of Science annual meeting.

The idea is to “actually follow the transition of the heart, brain and liver from wellness to disease,” said Hood, president of the Institute for Systems Biology (ISB) in Seattle, Washington.
Building blocks

genomics, genomic epidemiology, bioinformatics and computational biology, molecular biology, biochemistry, stem cells, pharmacology, animal model testing, clinical trials, clinical epidemiology & biostatistics, clinical genetics, biomedical engineering, imaging, health economics, health services research.
Need for Patient-Specific Decision Support Assistance

Adapted from: Stead et al. 2011, Acad. Med.
Thank you for your attention