Personalized Medicine – A Definition

The “Molecular Age” makes PM possible!

- The term „personalized medicine“ emerged in the late 1990s with progress in the Human Genome Project as new (predictive) sciences with the appendix „-omics“ (genomics, proteomics, metabolomics) unfolded.

- Personalized medicine today applies molecular analysis for variations in genes, gene expression, proteins, and metabolites as well as (functional) imaging technologies.

- All these measurable “molecular entities” are called biomarkers. They are correlated with clinical factors, such as disease state, prediction of future disease states, drug response and/or treatment prognosis.

- They help physicians assign treatment for each patient with greater precision.

Personalized Medicine – A Definition

The Patient Therapeutic Continuum

Empirical medicine

- Nonsurgical procedures
- High response rate

Personalized medicine

- Predictive medicine
- Tailored treatment

Individuated medicine

- Predictive medicine
- Tailored treatment

Personalized medicine should not be understood as „segment-of-one“ but „sub-population“ medicine

Empirical Drug Therapy:

- Efficiency +
- Time

Personalized Medicine

Drug Therapy:

- Diagnostics
- Personalized medicine
- Treatment of disease
- Efficiency +
- Time

Empirical and PersMed Practice in Drug Therapy

What Personalized Medicine wants to achieve!
**Personalized Medicine**

**Cornerstones of Personalized Medicine**

- **Disease**: Currently indistinguishable clinical presentation for biologically distinct conditions.
- **Personalized Medicine**
  - **Treatment**: Multiple treatment options with heterogeneous responses for the disease.
  - **Biomarker**: A logistically & medically acceptable clinical biomarker

**Personalized Medicine – Not Always Required**

Why is Personalized Medicine Not Always Necessary?

- Patients with Major Adverse Events %
- Patients Responding %

**Availability of Human Tissue is Key for Personalized Medicine**

Promoters

- Politics, Payers, Patients: expectation of benefits for patients (efficacy, safety) and more efficient use healthcare resources
- Potential to reduce risks and/or requirements for market access (incl. potentially higher prices)
- Streamlining R&D processes through the application of biomarkers to limit operational cost:
  - Potential to reduce time, cost and failure rate of clinical trials
  - Potential to rescue drugs (e.g. failing in clinical trials)
- Multiple initiatives & consortia formed to promote personalized medicine (e.g. CPI, IMI, Personalized Medicine Coalition).
- FDA/EMEA mandate submission of pharmacogenetic data, multiple guidelines on biomarker & drug/diagnostic co-development.
- New legislations (USA):
  - Genetic Information Non-discriminatory Act 2007
  - Personal Health Care Initiative of HHS Secretary Michael Leavitt
Personalized Medicine

Promoters

IN THE Senate of the united states
A R I I

A BILL
To improve access to and appropriate utilization of valid, reliable and accurate molecular genetic tests for all nonsense: three helping to ensure the promise of personalized medicine for all americans.

1. Be it enacted by the Senate and House of Representatives,
2. Two of the United States of America in Congress assembled,
4. This Act may be cited as the “Genomics and Person-
5. alized Medicine Act of 2006.”
6. a. see summary
7. Congress (red acts the following) Schaefer.

PERSONALIZED

MEDICINE

Current Limitations

• Healthcare workforce (incl. physicians): currently no ade- quate training to make use of Personalized Medicine, not implemented in medical school curricula.
• Public may be inhibited by full participation in personalized medicine research or clinical care, unless full genetic privacy is put in place.
• Healthcare IT needed for linking patient information to genomic research (Electronic Medical Records).
• Regionally fragmented reimbursement policies hinder adaptation of diagnostic tests.

Growth Drivers

• Technology rapidly advancing: diagnostics expected to become one of the fastest growing sectors of medicine.
• Diagnostic companies on their own will look for business opportunities (e.g., developing test kits for blockbuster drugs).
• High risks and costs of “blockbuster model” makes personalized medicine also attractive for “Big Pharma”.
• Declines in productivity and innovation in drug development makes personalized medicine appealing.
• Drug developers need to develop appropriate diagnostics or—at least—develop the knowledge how biomarkers correlate with drug effects.

Growth Drivers – Payment by Results

Pricing Pills by the Results

• Velcade (bortezomib): treatment for first relapse in multiple myeloma.
• NICE* (UK) initially declined support due to poor value for money (£ 38.000 per QALY).
• Solution: After 4 cycles a 50% reduction in serum protein M needs to be achieved.
• Rebating the cost of ineffective drug cycles (£ 20.700 per QALY).
* National Institute for Health and Clinical Excellence.
Personalized Medicine

Challenges

- Ethical, regulatory & legal framework to be aligned
- IP needs to include biomarkers and/or drug/diagnostic combinations, licensing agreements likely to resolve upcoming issues in most cases.
- Resulting market segments of personalized medicine too small to re-finance development investments.

Key Messages:

Personalized Medicine is an inevitable trend:

“Personalized Medicine is the future, the only remaining question is how soon it will come about.”

Janet Woodcock, Deputy Commissioner for Operations, FDA

- Personalized Medicine will develop gradually rather than revolutionary with oncology currently in the lead.
- Diagnostics test increasingly required for access and reimbursement in health care markets in the future.
- All major pharmaceutical companies have implemented personalized medicine concepts.

Personalized Medicine – Marketed Drug/Diagnostic Combinations

<table>
<thead>
<tr>
<th>Example</th>
<th>Rationale</th>
<th>Company</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>Treats Her-2-positive breast cancer</td>
<td>Genentech</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td>ICH (Herceptin) and FISH (Path/visies) tests identify patients with Her-2-positive tumors (&gt; 15-25% of breast cancer patients)</td>
<td>Duke</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abbott</td>
<td>2002</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Kinase inhibitor for c-Kit positive c-kit</td>
<td>Novartis</td>
<td>2001</td>
</tr>
<tr>
<td>(Gleevec®)</td>
<td>c-kit positive tumors - detects protein present in tumors that Gleevec is designed to treat</td>
<td>Vertex</td>
<td>2004</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>First monoclonal antibody approved to treat patients with advanced colorectal cancer (opposed to other parts of the body)</td>
<td>ImClone/BMS</td>
<td>2004</td>
</tr>
<tr>
<td>(Erbirab®)</td>
<td></td>
<td>Merck</td>
<td>2004</td>
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Marketed Drug/Diagnostic Combinations

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<td>Gefitinib</td>
<td>Selective inhibitor of epidermal growth factor receptor’s (EGFR) tyrosine kinase domain indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)</td>
<td>AstraZeneca + Teva</td>
<td>2005</td>
</tr>
<tr>
<td>(Iressa®)</td>
<td></td>
<td>Genzyme</td>
<td>2005</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chimeric monoclonal antibody used in the treatment of B cell non-Hodgkin’s lymphoma, B cell leukemia, and some autoimmune disorders.</td>
<td>IDEC Pharmaceuticals (now Biogen Idec and Genentech (U.S.)) and Roche (EU)</td>
<td>1997</td>
</tr>
<tr>
<td>(Rituxan®)</td>
<td></td>
<td>PGa Health+</td>
<td>2007</td>
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</table>

Hans-Günter Schäfer, Boehringer Ingelheim Pharma GmbH & Co.KG, Germany
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<td>Warfarin</td>
<td>Blood-thinning drug.</td>
<td>Nanosphere Inc.</td>
<td>2007</td>
</tr>
<tr>
<td>(Coumadin®)</td>
<td>The Nanosphere Vericar Warfarin Metabolism Nucleic Acid Test is the first</td>
<td>(similar tests</td>
<td></td>
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<tr>
<td></td>
<td>FDA cleared genetic test detecting</td>
<td>also exist in</td>
<td></td>
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<td></td>
<td>important variants of CYP2C9 and VKORC1 responsible for metabolism</td>
<td>clinical setting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and efficacy, respectively.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Topoisomerase 1 inhibitor; main use in colon cancer, particularly in</td>
<td>Pfizer</td>
<td>1994</td>
</tr>
<tr>
<td>(Carnoza®)</td>
<td>combination with other chemotherapy agents</td>
<td>Third Wave</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>FDA cleared Invader UGT1A1 Molecular Assay detects variations in UGT1A1.</td>
<td>Technologies Inc.</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Oral HIV-1 entry inhibitor only effective in sub-population having the</td>
<td>Pfizer</td>
<td>2008</td>
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<tr>
<td>(Celsentri®)</td>
<td>CCR5 tropic virus.</td>
<td>Monogram</td>
<td>2008</td>
</tr>
<tr>
<td></td>
<td>Trofib - is a clinically validated recombiant HIV-1 co-receptor tropism</td>
<td>Bioscience</td>
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<td>Attacazarin</td>
<td>A nucleotide analog reverse transcriptase inhibitor (NRTI) used to treat</td>
<td>GSK</td>
<td>1999</td>
</tr>
<tr>
<td>(Dipen®)</td>
<td>HIV and AIDS, hypersensitivity is strongly associated with HLA-A2/68101 for</td>
<td></td>
<td></td>
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<td></td>
<td>which testing is now available in most western countries.</td>
<td></td>
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<tr>
<td>Bucindol</td>
<td>Bucindol was dropped from development by Stelwz Pharmaceuticals following</td>
<td>Amisuris</td>
<td>Not</td>
</tr>
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<td></td>
<td>Equivalent results in the 10,000 patient placebo-controlled Beta-Blocker</td>
<td>Discovery</td>
<td>approved</td>
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<td>Evaluation of Bucindol (BEST) trial in 1999.</td>
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<td>Retrospective analysis showed that patient's B22/68101 was related to</td>
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<td>efficacy. Amgen Discovery has licensed this molecule and is planning to</td>
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<tr>
<td></td>
<td>apply to the FDA for permission to market the drug along with the trial.</td>
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