Outcome and Evidence

The future role of technology in Healthcare systems

Frankfurt Institute for Advanced Studies | Colloquium, March 20, 2014
H. Requardt, CEO Siemens Healthcard
## The medical outcome measures hierarchy

<table>
<thead>
<tr>
<th>Tier</th>
<th>Health status achieved or retained</th>
<th>Outcome - the healthcare system's view</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td>Survival</td>
<td><strong>Principals of value-based health care delivery</strong></td>
</tr>
<tr>
<td></td>
<td>Degree of health/recovery</td>
<td>- Achieved clinical status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Achieved functional status</td>
</tr>
<tr>
<td>Tier 2</td>
<td>Time to recovery and return to normal activities</td>
<td>- Care-related pain/discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Reintervention/readmission</td>
</tr>
<tr>
<td>Tier 3</td>
<td>Sustainability of health</td>
<td>- Long-term clinical status</td>
</tr>
<tr>
<td></td>
<td>Sustainability of health and nature of recurrences</td>
<td>- Long-term functional status</td>
</tr>
</tbody>
</table>
|       | Long-term consequences of therapy (e.g. care-induced illnesses) | **Value** = 
|       |                                   | Health outcomes that matter to patients |
|       |                                   | Costs of delivering the outcomes       |

**Source:** NEJM, Dec 2010

- Achieved clinical status
- Achieved functional status
- Care-related pain/discomfort
- Complications
- Reintervention/readmission
- Long-term clinical status
- Long-term functional status

Value is measured for the **care of a patient's medical condition** over the full cycle of care:
- Outcomes are the **full set of health results for a patient's condition** over the care cycle
- Costs are the **total costs of care for patient's condition** over the care cycle

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**What is outcome?**

**Patient and healthcare system view**

- Survival
- Degree of health/recovery
- Time to recovery and return to normal activities
- Disutility of the care or treatment process (e.g. diagnostic errors and ineffective care, treatment-related discomfort, complications, or adverse effects, treatment errors and their consequences in terms of additional treatment)
- Sustainability of health/recovery and nature of recurrences
- Long-term consequences of therapy (e.g. care-induced illnesses)
Measuring healthcare outcomes on a society level
DALYS are the ultimate currency of health

DALY
Disability Adjusted Life Years is a measure of overall disease burden, expressed as the cumulative number of years lost due to ill-health, disability of early death

YLD
Years Lived with Disability

YLL
Years of Live Lost

GLOBAL top 20 burden of diseases and disease risk factors in 2010 (expressed as a percentage of DALY)

Cancer
Cardiovascular and circulatory diseases
Chronic respiratory diseases
Cirrhosis
Digestive diseases
Neurological disorders
Mental and behavioural disorders
Diabetes, urogenital, blood and endocrine diseases
Musculoskeletal disorders
Other non-communicable diseases
HIV/AIDS and tuberculosis
Diarrhea, lower respiratory infections and other common infectious diseases
Neglected tropical diseases and malaria
Maternal disorders
Neonatal disorders
Nutritional deficiencies
Other communicable diseases
Transport injuries
Unintentional injuries
Intentional injuries
War and disaster

Healthy life
Disease or disability
Early death
Expected life years

DALYs are the ultimate currency of health.
What is Evidence and Evidence-based Medicine?  
The level of evidence drives clinical decisions

The hierarchy of clinical evidence and recommendations

<table>
<thead>
<tr>
<th>Level A</th>
<th>Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend that procedure or treatment is useful/effective</td>
<td></td>
</tr>
<tr>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level B</th>
<th>Limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td></td>
</tr>
<tr>
<td>Evidence from single randomized trial or nonrandomized studies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level C</th>
<th>Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td></td>
</tr>
<tr>
<td>Only expert opinion, case studies, or standard of care</td>
<td></td>
</tr>
</tbody>
</table>

The increasing proportion of recommendations for which there is no conclusive evidence highlights the need to **expand the evidence base** from which clinical practice guidelines are derived.


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The evidence-dependency of outcomes

The outcome-dependency of evidence

The relationship between clinical evidence generation and clinical practice - acting in partly different worlds

- **Patient initial conditions**
- **Processes**
- **Indicators**
- **Health (outcomes)**
- **Patient experience/engagement**
- **Structure**
- **Reimbursement**

**Clinical practice for heterogeneous patient populations**

- **Scientific evidence generation within controlled clinical trial frameworks**

**Indicators**
- E.g. PSA, gleason score, surgical margin

**Protocols/guidelines**
- E.g. staff certification, facilities standards
Adverse outcomes based on insufficient evidence generation

Example: The Contergan Disaster

- Medication: Thalidomide (Contergan)
- Market approval 1957
- Indication: Sedative, hypnotic drug esp. for pregnant women
- Manufacturer: Grünenthal
- Adverse side effects: severe congenital malformations and high mortality in ~10,000 newborns

Other major drug scandals

Medication: **Fen-Phen**
- (fenfluramine/phentermine)
- Indication: Anti-obesity drug
- Market approval: 1970s
- Manufacturer: Wyeth
- Adverse side effects: Fatal pulmonary hypertension and valvular heart disease in min. 50.000 patients

Medication: **Lipobay**
- (in combination w/ Gemfibrozil)
- Indication: Lipid-lowering drug
- Market approval: 1997
- Manufacturer: Bayer Pharma
- Adverse side effects: hundreds of reported cases of rhabdomyolysis, ~100 deaths

Medication: **Vioxx** (Rofecoxib)
- Indication: anti-inflammatory drug
- Market approval: 1999
- Manufacturer: Merck & Co
- Adverse side effects: causing between 88,000 and 139,000 heart attacks and strokes, 30 to 40 percent of which were probably fatal

1) Amelia, Phocomelia, Bone defects, Ear and eye abnormalities, Facial palsy, Congenital heart defects, Urinary and genital tract malformations
2) Mortality in ~40% of infants at or shortly after birth

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Healthcare Innovation - Technical feasibility does not necessarily translate into clinical applicability

The value added process

Preclinical Research → Industrial Development → User trials, Clinical studies → Regulatory Approval → Reimbursement

High initial investment with long "waiting time" to return on invest.

Typical risks
Financing, Intellectual property and patenting, Realization/Implementation, Market acceptance, Liability and loss risks, ...

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H. Requardt, CEO Siemens Healthcare
70 years History of Radiation Therapy with Protons and Ions — still awaiting solid clinical evidence

Today: Particle therapy in clinical centers, e.g.
- **US:** Francis H. Burr PTC, Boston; MD Anderson, Houston; University of Florida...
- **Europe:** HIT, Heidelberg; CNAO, Milano; RPTC, Munich; ICPO, Orsay...
- **Asia:** HIBM, Hyogo; NCC, Kashiwa; Shizuoka; PMRC, Tsukuba...

1996/97 First tumor conform radiation with **scanned beam - protons** at PSI (Villigen, Switzerland), **12C-Ions** at GSI (Darmstadt, Germany)

1993 First center for **12C-ions therapy** in Chiba (Japan)

1990 First center for proton therapy in Loma Linda (USA)

1975 LBL irradiated for the first time with ions (helium, carbon, neon)

1974 First proton therapy at the Harvard Cyclotron

1957 Uppsala started with proton treatment

1954 LBL (Lawrence Berkeley Laboratory, USA) started radiotherapy for deep located tumors with protons

1946 R. R. Wilson proposed charged particles (p, ions) for applications in radiotherapy
Adverse outcomes due to evidence generation reaching its limits

Clinical rationale
Proof-of-principle

Research installation

First-in-men application

Clinical installations

Outcome evidence generation

Cancer incidence

Preclinical Research
Industrial Development
User trials, Clinical studies
Regulatory Approval
Reimbursement
Value propositions depend on business models

Benchside business
» The medical scientists «

Give me what you can ...

Academic value
Pushing the technological boundaries of imaging and diagnostics

Business model
Research grants, third-party funds, clinical reimbursement

Bedside business
» The clinical heroes «

Give me what I need!

Clinical value
Optimizing the value chain to clinical reimbursement

Business model
Clinical reimbursement
### PET radiopharmaceuticals for precision medicine

**Promises and reality**

#### Selection of PET-markers in preclinical and clinical research

- **18F-DOPA**: neuroendocrine tumors
- **18F-FLT**: cell proliferation
- **18F-MISO**: hypoxia
- Copper 64 (ll)-diacetyl-bis (N4-methylthiosemicarbazone): hypoxia
- **18F-2-(2-nitro-hydrogen-1-imidazol-1-yl)-N-(2,2,3,3-pentafluoropropyl)-acetamide**: idem
- **18F-FES**: binds to estrogen receptor
- **11C-Thymidine**: cell proliferation
- **18F-Fluorocholine**: choline kinase activity
- **l-[methyl-11C]methionine**: AA metabolism
- **O-(2-18F-fluoroethyl)-l-tyrosine**: idem
- **18F-6-fluorodihydroxyphenylalanine**: idem
- **18F-galacto-arginine-glycine-aspartate**: angiogenesis
- **4-18F-Fluorobenzoyl-annexin V**: apoptosis
- **11C-1-Methionine**: AA metabolism
- **11C-Taurine**: idem
- **18F-6-fluorodihydroxyphenylalanine**: idem
- **4-18F-Fluorobenzoyl-annexin V**: apoptosis
- **11C-1-Methionine**: AA metabolism
- **11C-Taurine**: idem

---

#### PET radiopharmaceuticals approved by the FDA

- **18F Sodium Fluoride**: injection as a bone imaging agent to define areas of altered osteogenic activity
- **11C-Choline**: for PET imaging of patients with suspected prostate cancer recurrence

#### NON-PROPRIETARY:

- **18F-FDG**: for evaluation of glucose metabolism in oncology
- for evaluation of myocardial hibernation
- for identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures
- **13N-Ammonia**: for evaluation of myocardial blood flow
- **82Rb-Chloride**: for assessing regional myocardial perfusion in the diagnosis and localization of myocardial infarction

#### PROPRIETARY:

- **18F-Florbetapir**: ²-amyloid neuritic plaque density in adult patients with cognitive impairment
- **Oxygen 15-water**: blood flow
- **Gallium 68 (68Ga)-DOTA-Phe1-Tyr3-octreotide**: Somatostatin receptors
- **Gluc-Lys (18F-fluoropropionyl-TOCA)**: idem
- **68Ga-DOTA-Tyr3-Thr8-octreotide**: idem
- **68Ga-DOTA-1-Nal3-octreotide**: idem

---

**2 new radiopharmaceuticals approved in the last 15 years**

Non-proprietary: 18F-FDG

Proprietary: 18F-Florbetapir

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Radiopharmaceuticals for precision medicine

Justifying high risk investments is precarious business

R&D cost and time-to-market

1) Representative of a typical top ten selling drug
Success rate of therapeutic drug development (Phase I-III): ~10%

Rule of thumb for positive business case (proprietary radiopharmaceutical):

Peak revenue e R&D costs

<table>
<thead>
<tr>
<th>Product</th>
<th>Modality</th>
<th>Company</th>
<th>Global annual Sales ($ millions)</th>
<th>First approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnipaque®</td>
<td>X-ray</td>
<td>GE</td>
<td>401</td>
<td>1985</td>
</tr>
<tr>
<td>Iopamiron®</td>
<td>X-ray</td>
<td>Schering</td>
<td>295</td>
<td>1981</td>
</tr>
<tr>
<td>Ultravist®</td>
<td>X-ray</td>
<td>Schering</td>
<td>290</td>
<td>1985</td>
</tr>
<tr>
<td>Visipaque®</td>
<td>X-ray</td>
<td>GE</td>
<td>224</td>
<td>1996</td>
</tr>
<tr>
<td>Magnevist®</td>
<td>MR imaging</td>
<td>Schering</td>
<td>370</td>
<td>1988</td>
</tr>
<tr>
<td>Omniscan®</td>
<td>MR imaging</td>
<td>GE</td>
<td>195</td>
<td>1992</td>
</tr>
<tr>
<td>Cardiolite®</td>
<td>Nuclear</td>
<td>BMS</td>
<td>405</td>
<td>1980</td>
</tr>
<tr>
<td>Myoview®</td>
<td>Nuclear</td>
<td>GE</td>
<td>274</td>
<td>1996</td>
</tr>
<tr>
<td>FDG</td>
<td>Nuclear</td>
<td>Multiple</td>
<td>190</td>
<td></td>
</tr>
</tbody>
</table>

Adrian D Nunn et al., J Nucl Med, 2006
Uncertainties in marketing new imaging biomarkers
Regulatory hurdles deter innovation

**Regulatory**
Current Good Manufacturing Practices (cGMP), part 212

**Approval**
Requirement of either IND, NDA, or ANDA status for all PET radiopharmaceuticals
Prognostic markers: Proof of patient outcome required

**Reimbursement**
CMS coverage? Full or partial? Additional studies required → delays in clinical adoption

Between 2003 and 2007:
**Time-to-approval:** 65% increase
**Administrative costs:** 75% increase

Mayor, S. et al., BMJ 2011

**Glossary of terms:**
IND - Investigational New Drug; NDA - Approved New Drug Application; ANDA - Abbreviated New Drug Approval; NME - New molecular entity

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Personalized diagnostics: A challenge for evidence based medicine
Orphanization of diseases by molecular characterization

Example
A disease entity formerly known as lung cancer

Lung Cancer

SCLC 20-25%

NSCLC 70-80%

NSCLC (all types)

- Oat cell-cancer
- SCLC int. types
- Combined forms

Squamous cell carcinomas

Adenocarcinomas

Improved disease characterization

Multiplication & diversification of disease subgroups

Smaller patient populations

Smaller revenue expectation per population

Traditional disease classification systems?

Traditional disease oriented
- Study design?
- Regulatory framework?
- Approval criteria?
- Orphan biomarker approval?

Conventional evidence generation?

Same R&D invest?
Pharma and diagnostics industry under pressure
When investments do not meet their return

Estimated full cost of bringing a new chemic entity to market
(Million USD, year 2011)

The climate of innovation is a key driver for all in vitro and in vivo diagnostic players
Alternatives to drive the individualization of medicine? 
Personalized medical information for $99

### The offering

**Personalized Genome Service**
- "Health reports on 254 diseases and conditions"
- "A first step in prevention" enabling users to "take steps toward mitigating serious diseases" such as diabetes, coronary heart disease, breast cancer.

**Technology and database:**
- Illumina OmniExpress Plus, analyzing hundreds of thousands of SNPs out of the more than 10 million SNPs estimated to be in the human genome.

### The results

#### Disease risks

<table>
<thead>
<tr>
<th>Disease</th>
<th>Your Risk</th>
<th>Average Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>36.1%</td>
<td>21.9%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>22.4%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Primary Biliary Cirrhosis</td>
<td>0.58%</td>
<td>0.34%</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>0.20%</td>
<td>0.14%</td>
</tr>
</tbody>
</table>

#### Carrier status

- Alpha-1 Antitrypsin Deficiency: Variant Absent
- Agenesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN): Variant Absent
- Autosomal Recessive Poly cystic Kidney Disease: Variant Absent
- ARSACS: Variant Absent
- Beta Thalassemia: Variant Absent
- Bloom’s Syndrome: Variant Absent
- BRCA Cancer Mutations (Selected): Variant Absent
- Canavan Disease: Variant Absent

### Traits

- Alcohol Flush Reaction: Flushed
- Bitter Taste Perception: Can Taste
- Earwax Type: Dry
- Eye Color: Light Brown
- Hair Curl: Slightly Curlier Hair on Average

### Drug response

- Alcohol Consumption, Smoking and Risk of Esophageal Cancer: Increased
- Clopidogrel (Plavix®) Efficacy: Reduced
- Warfarin (Coumadin®) Sensitivity: Increased
- Abacavir Hypersensitivity: Typical
- Oral Contraceptives, Hormone Replacement Therapy and Risk of Venous Thromboembolism: Typical

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SNP = Single Nucleotide Polymorphism

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Once you obtain your Genetic Information, **the knowledge is irrevocable. You should not assume that any information** we may be able to provide to you, whether now or as genetic research advances, **will be welcome or positive.** You should also understand that as research advances, in order for you to assess the meaning of your DNA in the context of such advances, you may need to obtain further services from 23andMe or from your physician or other health care provider.

You may learn information about yourself that you do not anticipate. This information may evoke strong emotions and has the **potential to alter your life and worldview.** You may discover things about yourself that trouble you and that you **may not have the ability to control or change** (e.g., your father is not genetically your father, surprising facts related to your ancestry, or that someone with your genotype may have a higher than average chance of developing a specific condition or disease). These outcomes could have social, legal, or economic implications.

The laboratory may not be able to process your sample, and **the laboratory process may result in errors.** Even for processing that meets our high standards, a small, unknown fraction of the data generated during the laboratory process may be un-interpretable or incorrect (referred to as "Errors").

**You should not change your health behaviors solely on the basis of information from 23andMe.** Make sure to discuss your Genetic Information with a physician or other health care provider before you act upon the Genetic Information resulting from 23andMe Services. For most common diseases, **the genes we know about are only responsible for a small fraction of the risk.** There may be unknown genes, environmental factors, or lifestyle choices that are far more important predictors. If your data indicate that you are not at elevated genetic risk for a particular disease or condition, **you should not feel that you are protected.** The opposite is also true; if your data indicate you are at an elevated genetic risk for a particular disease or condition, **it does not mean you will definitively develop the disease or condition.** In either case, if you have concerns or questions about what you learn through 23andMe, you should contact your physician or other health care provider.

**Genetic research is not comprehensive.** While we measure many hundreds of thousands of data points from your DNA, only a small percentage of them are known to be related to human traits or health conditions. In addition, many ethnic groups are not included in genetic studies. Because interpretations provided in our service rely on these published studies, some
Innovations lacking outcome evidence are denied regulatory approval

**Relationship between the heritability, genetic complexity and predictive ability of personal genome testing**

- **High Heritability**
  - Monogenic disorders
    - Perfect predictive ability

- **Low Heritability**
  - Complex diseases
    - Poor predictive ability

**FDA Warning Letter**

November 22, 2013

Most of the intended uses for PGS listed on the 23andMe website are **medical device uses** under section 201(h) of the FD&C Act. Most of these uses have not been classified and thus require premarket approval or de novo classification...

To date, 23andMe has failed to provide adequate information to support a determination that the Personal Genotyping Service (PGS) is substantially equivalent to a legally marketed predicate for any of the uses for which 23andMe is marketing it...

**We still do not have any assurance that 23andMe has analytically or clinically validated the PGS for its intended uses**...

There is still no scientific evidence to support the marketing claims of 23andMe, and the tests are unlikely to accurately predict disease risk...

**Therefore, 23andMe must immediately discontinue marketing the PGS** until such time as it receives FDA marketing authorization for the device.
Orphan diseases: Scientific progress generates huge burdens for future personalized disease management

Orphan/rare diseases at a glance

Rare diseases are **life-threatening or chronically debilitating conditions** affecting no more than 5 in 10,000 people in the EU. Most of these people suffer from diseases affecting less than 1 in 100,000 people.

About **7,000 distinct rare diseases exist**, affecting between 6% and 8% of the population in total.

About **30 million people in the European Union (EU)** suffer from a rare disease.

On average, **five new diseases** are described **every week** in the medical literature.

**80% of rare diseases have identified genetic origins**, and affect between 3% and 4% of births. Other rare diseases are due to degenerative and proliferative causes.

The number of scientific publications about rare diseases continues to increase, particularly those identifying new syndromes. However, **fewer than 1,000 diseases benefit from even minimal amounts of scientific knowledge**. These tend to be the rare diseases that occur most frequently.

For less frequent rare diseases, medical and scientific knowledge is largely lacking.
The discovery of rare diseases already led to drug approvals covering a wide range of indications.

Cumulative number of ultra-rare metabolic disorders over time (for three prevalence categories)

Drug approvals for rare diseases have increased from fewer than 10 to more than 202

Indication spectrum of designated orphan drugs

Note: All medicines approved for rare diseases include first-line approvals and subsequent approvals for new disease areas.


Source: FDA
Entering the era of next-generation sequencing speeds up the pace of discovery of rare-disease-causing genes

Work over the past 25 years has resulted in the identification of genes responsible for ~50% of the estimated 7,000 rare monogenic diseases...

High pace of discovery of novel rare-disease-causing genes using whole-exome sequencing

- More than 180 novel genes discovered to date
- Remaining 3,500 genes expected to be identified by 2020

Low rate of approval of medicinal products for the treatment of rare diseases

- Only 75 new approvals of orphan drug products expected in Europe in the next 20 years

For a large number of diseases, given their congenital nature and the fact that they often involve structural defects in early development or are overwhelmingly severe, the prospect of a definitive therapy is unlikely.

For the remainder of disorders for which there may be an existing therapeutic opportunity, the diversity and number of rare diseases combined with the small numbers of patients for each disorder effectively precludes, for all but a fraction of conditions, traditional costly drug discovery approaches.

Source: Kym M. Boycott et al., NATURE REVIEWS | GENETICS | OCTOBER 2013

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Therapeutic successes in rare diseases come at a price - Example Gaucher's disease

Pathophysiology

Hereditary deficiency of the enzyme glucocerebrosidase

\[ \rightarrow \] Abnormal amounts of glucosylceramide store in macrophages, spleen, liver, kidneys, lungs, brain and bone marrow

Prevalence (of type 1 Gaucher's disease \(^1,2\)):

- 1 in 50,000 to 1 in 100,000 in the general population
- 1 in 855 in the Ashkenazi Jewish population

Manifestations

Gaucher's disease - a phenotypic continuum

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Skeletal disease</td>
<td>2° neurologic involvement</td>
</tr>
<tr>
<td></td>
<td>Visceral disease</td>
<td>Hydrocephalus, cardiac valve calcification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myoclonic epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital ichthyosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurologic manifestations</td>
</tr>
<tr>
<td>95% Type 1</td>
<td>5% Type 2 + 3</td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic approach

Enzyme replacement treatment with intravenous recombinant glucocerebrosidase (imiglucerase)

Cost of treatment

- 600,000 EUR/year (year 1 and 2)
- 300,000 EUR/year (continued for life)

Cumulative treatment cost per patient

Mio. EUR

Prevalence (of type 1 Gaucher's disease \(^1,2\)):


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Gaucher's disease
Shortage of medication – treatment allocation?

The New York Times

September 15, 2011
Enzyme Drug Is in Short Supply Again

Genzyme's flagship drug, Cerezyme, is in short supply again.
In a letter to health care providers sent Tuesday, Genzyme said adult patients would probably receive only one dose a month instead of the usual two, from October through January. The drug, which costs $200,000 a year or more, treats Gaucher disease, a rare inherited enzyme deficiency.

Genzyme attributed the new shortfall to a temporary decrease in Cerezyme yields, combined with changes to our product release processes and procedures that lengthen the overall time it takes to release Cerezyme. A spokeswoman said the yield has since been restored to normal.
The company was forced to temporarily close its main factory, in Boston’s Allston neighborhood, in June, 2009 because of viral contamination. It did not restore full supplies of Cerezyme until January of this year, much later than it initially expected.

April 15, 2010
Genzyme Drug Shortage Leaves Users Feeling Betrayed

Because of a drug factory shutdown, Jeannine Lipez of Lock Haven, Pa., says she can no longer even walk across the street without getting spasms in her left leg and will probably need an operation to replace an artery.

Carol Fink of Yountville, Calif., says lack of the medicine she needed left her constantly in pain, sapped her energy and made her thinking fuzzy.

For Dr. William Schubert, an obstetrician and gynecologist in Pocatello, Idaho, the factory shutdown may have contributed to an even worse outcome. Even as his wife and doctor raced to find doses of the drug he needed, Dr. Schubert's heart deteriorated rapidly. He died on March 6, at the age of 63.

Which patients should receive preferred treatment when medication is not sufficient for all patients?
Early detection strategies for preventive medicine
Creating new patients that don't need treatment?

Low-dose CT lung cancer screening reduces mortality in high-risk populations by 20%, but ...

... ~96% of patients with positive screening test result do not have lung cancer ...

→ USD 240,000 to avoid one lung cancer death

Dual Selective Photon Shield
Collimation: 2x 192 x 0.6 mm
Spatial resolution: 0.24 mm
Rotation time: 0.25 s

Tube setting: 100 kV Sn
0.1 mSv

Ground glass nodules (GGNs)
Partial-solid nodules

National Lung Screening Trial,

Courtesy of UMM, Mannheim, Germany
Paving the way to preventive medicine - National Lung Cancer Screening Trial Performance analysis

Patients at risk for Lung Cancer
(age >55y, >30 pack years)
Lung Cancer Prevalence in risk population 1:100

Poor enrichment of Lung Cancer patients by CT screening

Findings other than Lung Cancer
68%, thereof 99.8% true negative 0.2% false negative

7.5%
24.5%, thereof 3.6% true positive 96.4% false positive

Health resource use and complications of "patients"

- 14.4% Follow-up chest X-ray
- 49.8% Follow-up chest CT scan
- 8.3% Follow-up PET/CT scan
- 1.8% Percutaneous biopsy
- 1.8% Bronchoscopy w/ biopsy
- 2.2% Bronchoscopy w/o biopsy
- 0.7% Mediastinoscopy
- 1.3% Thoracoscopy
- 2.9% Thoracotomy
- 0.06% Major complications
- 1.3% Intermediate complications

Patients at risk for Lung Cancer
Envisioning the integration of in-vitro and in-vivo assays for advanced lung cancer screening

Patients at risk for Lung Cancer (age >55y, >30 pack years)

Lung Cancer Prevalence in risk population 1:100

1. Rule-in IVD
   - Sputum based
   - Protein based
   - DNA-based
   - Breath based

   89%, thereof
   - 99.9% true negative
   - 0.1% false negative

   11%, thereof
   - 8.8% true positive
   - 91.2% false positive

2. Biopsy

   11%, thereof
   - 26.1% true positive
   - 73.9% false positive

   89%, thereof
   - 99.2% true negative
   - 0.8% false negative


1) Assumed sensitivity/specificity: 95/90%
Outcomes of precision medicine
Overcoming the traditional way of evidence generation

Professor Zapinsky proved that the squid is more intelligent than the housecat when posed with puzzles under similar conditions

Evidence-based Medicine
A milestone of the past at a crossroads
How can the pace of evidence keep track with the pace of innovation?
**Precision Medicine: Change of evidence criteria as an enabler for future medical innovation?**

<table>
<thead>
<tr>
<th>This generation medical innovation</th>
<th>Next generation medical innovation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test, approve, reimburse, apply clinically per disease</td>
<td>Test, approve, reimburse, apply clinically per underlying mechanism (this may be more than one in a given disease and multiple diseases that share same mechanisms)</td>
</tr>
<tr>
<td><strong>Traditional way forward:</strong> Definition of indication spectrum by randomized controlled trials</td>
<td><strong>Possible future way forward:</strong> Definition of indication spectrum by disease-relevant pathomechanisms</td>
</tr>
<tr>
<td><strong>Evidence criterion:</strong> Disease/Patient</td>
<td><strong>Evidence criterion:</strong> Pathophysiological process</td>
</tr>
<tr>
<td>One drug targets one or few (known) disease(s) with the same mechanism</td>
<td>One mechanism underlies many (unknown) disease(s)</td>
</tr>
<tr>
<td>Treat the disease</td>
<td>Identify target</td>
</tr>
<tr>
<td>Improve survival</td>
<td>Develop therapeutic agent</td>
</tr>
<tr>
<td>Improve symptoms</td>
<td>Identify alternative therapeutic targets</td>
</tr>
<tr>
<td>Inherited complexity limitations</td>
<td>Monitor therapy</td>
</tr>
<tr>
<td>Identify additional diseases/disease states with same pathophysiology</td>
<td>Direct treatment/change patient management</td>
</tr>
<tr>
<td>Eligible for model-based innovation?</td>
<td></td>
</tr>
</tbody>
</table>
New constructs of medical evidence generation in clinical routine

The Randomized Registry Trial - The Next Disruptive Technology in Clinical Research?

Incorporating randomization into clinical registries to combine the most important features of prospective randomized trials (RCT) with those of large scale clinical registries, enabling an inexpensive, unselective enrollment of large numbers of patients in a prospective Registry based Randomized Clinical Trial (RRCT) with complete follow-up on mortality through registries.

RRCT
Evaluation of therapeutic options available/used in routine clinical care

RCT
Approval of new pharmaceutical agents and medical devices

Applying global standards of care amenable to measurement in clinical routine

Example: The International Consortium for Health Outcomes Measurement (ICHOM)


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The abundance of rare diseases requires viable outcome criteria and investment scenarios.

### U.S. and European regulatory bodies stimulating orphan medicinal product development

- **Orphan Drug Act**
- **Committee for Orphan Medicinal Products (COMP)**
- **Examples**
  - Germany: G-BA/IQWIG
    - Acceptance of lower levels of significance (p-values > 0.05)
    - No randomized controlled trials required
  - UK: NICE
    - Adjusted decision rules for cost effectiveness of orphan drugs
  - Netherlands: MVWS/CVZ
    - Waiver of pharmacoeconomic aspects such as cost-, effectiveness-, and cost-effectiveness analyses
  - US: FDA
    - Acceptance of smaller study populations
    - Acceptance of observational studies

### Specific national regulations for health economic analyses of orphan drugs

<table>
<thead>
<tr>
<th>U.S.</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual <strong>grant funding</strong> (US), grants from EU and Member State programs to defray the cost of clinical testing</td>
<td></td>
</tr>
<tr>
<td><strong>Fee reductions and tax credits</strong> for the costs of clinical research, including applications for marketing authorization, inspections and protocol assistance</td>
<td></td>
</tr>
<tr>
<td>Assistance in clinical research <strong>study designs</strong> and guidance to meet regulatory requirements</td>
<td></td>
</tr>
<tr>
<td><strong>Accelerated regulatory approval process</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Market exclusivity</strong> for a 7- to 10-year period of exclusive marketing after an orphan drug is approved</td>
<td></td>
</tr>
<tr>
<td>Waiver of Prescription Drug User Fee Act (PDUFA) filing fees (over $1,000,000 per application for FY 2009)</td>
<td></td>
</tr>
</tbody>
</table>

**Examples**

- **Germany: G-BA/IQWIG**
  - Acceptance of lower levels of significance (p-values > 0.05)
  - No randomized controlled trials required
- **UK: NICE**
  - Adjusted decision rules for cost effectiveness of orphan drugs
- **Netherlands: MVWS/CVZ**
  - Waiver of pharmacoeconomic aspects such as cost-, effectiveness-, and cost-effectiveness analyses
- **US: FDA**
  - Acceptance of smaller study populations
  - Acceptance of observational studies
Medical plausibility and significant benefit as precursor for medical outcome

Medical plausibility as requirement to applications for designation as orphan medicinal products

**Medical plausibility**

<table>
<thead>
<tr>
<th>General requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) The characteristics defining a distinct condition should <strong>determine a group of patients in whom development of a medicinal product is plausible</strong>, based on the pathogenesis of the condition and pharmacodynamic evidence and assumptions.</td>
</tr>
<tr>
<td>b) Recognized distinct medical entities are generally considered as valid <strong>conditions</strong> and <strong>are defined in terms of their</strong> specific characteristics, e.g. <strong>pathophysiological, histopathological, clinical characteristics</strong>.</td>
</tr>
</tbody>
</table>

**Justification of medical plausibility**

The application should contain **details of the rationale for the use of the medicinal product in the proposed orphan indication**, including:

- A description of the medicinal product and a **discussion of its mechanism of action**, as far as it is known at the time of application
- A **discussion of the relevance of in vitro and in vivo preclinical models** in the context of the condition
- **Preliminary preclinical** (in vitro or in vivo) or clinical data
- **Comparative data**, if available

Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation

EMA/COMP/15893/2009

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Medical plausibility and **significant benefit as precursor for medical outcome**

Elements required to support the assumption of significant benefit for an orphan designation

**Significant benefit**

- A new treatment is of "significant benefit" if it provides a **clinically relevant advantage (improved efficacy, improved safety)** or a major contribution to patient care.
- At the time of designation, significant benefit should be **based on well justified assumptions**. Assumptions of potential benefit(s) should be plausible and where possible **based on sound pharmacological principles**.
- In general a demonstration of **potentially greater efficacy**, an **improved safety profile**, and/or **more favourable pharmacokinetic properties** than existing methods may be considered to support the notion of significant benefit.
- Other **compliance-promoting features or evidence to show fewer interactions** with food or other medicinal products, where these are relevant may also be considered.

**Justification of significant benefit**

- Orphan applications may be made at any stage of the development, **‘significant benefit’ will be based on the available evidence at the stage of designation** and should make reference to appropriate scientific literature or the results of comparative studies, whether of a definitive or preliminary nature.
- **Preclinical data and preliminary clinical information** may be added as supportive evidence.
- When comparative data are not available, a **critical review comparing authorized treatments and the proposed Orphan Medicinal Product** may provide justification.
- The **COMP must look at the rationale for development of the medicinal product in the proposed orphan indication**.

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Article 3 of Commission Regulation EC 847/2000

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Machine-readable data and knowledge will shift paradigms

**Data domain**

**Unstructured data**
- **Patient-specific**
  - Diagnostic data
  - Imaging
  - In-Vitro diagnostics
  - Physical examinations
  - Genome, Proteome
  - ...
  - Patient record
  - Family data
  - Diseases

**Experience domain**

**Disease models**
- **Non-patient-specific**
  - Disease causalities
    - Infectious diseases
    - Addiction
    - Cancer
    - Diabetes
    - ...
  - Physician
    - Education
    - Experience

**Action domain**

**Therapy**
- Therapy selection
- Treatment
- Post-treatment result evaluation
- Aftercare
Model-based evidence to stimulate clinical innovation?

### Data domain

- **Structured data**
  - **Patient-specific**
    - Diagnostic data
      - Imaging
      - In-Vitro diagnostics
      - Physical examinations
      - Genome, Proteome
      - ...
    - Patient record
      - Family data
      - Diseases

- **Non-patient-specific**
  - Comprehensive models
    - Anatomical m.
    - Physiological m.
    - Biochemical m.
    - Metabolomic m.
    - ...

- **Patient model(s)**

### Knowledge domain

### Action domain

- **Individualized therapy**
  - Therapy selection
  - Treatment

- **Diagnosis & therapy proposals**

- **Falsification**
  - Post-treatment result evaluation
  - Aftercare

---

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March 20, 2014

H. Requardt, CEO Siemens Healthcare
Personalized disease models: Enabling advanced views into the future...

Example: Cardiac Imaging today

How can imaging information be integrated to provide additional value?

- Cardiac MRI
- Cardiac CT
- 4D Echocardiography
The Unified Heart Model: Anatomy and dynamics from multi-modal imaging data
Heart Imaging and Sensing: Creating a Personalized Model

<table>
<thead>
<tr>
<th>Patient Level</th>
<th>Observations</th>
<th>Computational Models</th>
<th>Multiscale Modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ Level</td>
<td>Imaging Modalities</td>
<td>Anatomy, Function, Flow</td>
<td>Fluid-Structure Interaction</td>
</tr>
<tr>
<td>Tissue Level</td>
<td>Myocardial Motion</td>
<td>Myocardial Fibers</td>
<td>Contraction Model</td>
</tr>
<tr>
<td>Cell Level</td>
<td>Electrical Mapping</td>
<td>Electrophysiology</td>
<td>Molecular Models</td>
</tr>
</tbody>
</table>

**BioMarkers**
- BNP, D-Dimer, Troponin
- Myoglobin, CKMB, CRP
- Hemostasis Markers

**Molecular Models**
- Cell-Cell interaction
- Molecular signaling
- Metabolism

**Imaging Modalities**
- DT MRI

**Tissue Biomechanics**
- Contraction Model
Computational Intracardiac Fluid Dynamics facilitate simulation and planning of therapeutic interventions
Precision Medicine is complexity management
Moving towards model-based evidence generation

Ensuring outcome-oriented innovations in the era of precision medicine
Medical diagnostics meets IT

Degree of Orphanization

Molecular level
Cellular level
Tissue level
Organ level
Disease

Content:
Clinical understanding

Building upon clinical understanding

Building upon the data and process infrastructure

Data capture and sharing

MU 1

Disease (state) related ("indication")
Pathophysiological process related
Model-based, big data driven

Clinical Evidence
MU – Meaningful Use

Outcome orientation

Improved outcomes

Disease

Organ level

Tissue level

Cellular level

Molecular level

Degree of Orphanization

Content:
Clinical understanding

Ensuring outcome-oriented innovations in the era of precision medicine
Medical diagnostics meets IT
Thank you for your attention.

Frankfurt Institute for Advanced Studies Colloquium, March 20, 2014

H. Requardt, CEO Siemens Healthcare

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