Variants on Precision Medicine
- Conventional Therapeutics Paired with Advanced Diagnostics
- Somatic & Germline Gene Therapy, Regenerative Medicine

Implications for Evaluation of Safety, Efficacy and Effectiveness
- Smaller treatment groups: large-N RCTs problematic, costs rising
- Conventional: Less heterogeneity of treatment effects
- Genetic Medicine: More complexity and uncertainty (initially)

Regulatory Issues: EMA, FDA, PMDA, Health Canada
- Thresholds: Defining Evidentiary Standards and Treatment Groups
- Data Access and Quality: Ownership, Curation and Consent
- Analytics: Observation, Intervention and Causal Inference
- Keeping Commitments to Observe, Validate and Adapt
PRECISION MEDICINE

“Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle . . .”  US Precision Medicine Initiative
VERSION 1.0

TARGET CONVENTIONAL DRUGS ON NARROWER TREATMENT GROUPS

• Broad indications splintering into narrower indications
• Treatment groups splintering into smaller target populations
• Companion diagnostic tools and biomarkers key to target

How?

• Enabled by revolutions in genomic science and info technology
• Informed by evolving understanding of mechanisms and pathways
• Use genotypic and phenotypic data, registries, and health records to develop population specific takes on safety, efficacy and effectiveness and to reduce heterogeneity in treatment effects

To What?

Initial best applications in oncology, expanding to other diseases . . .
VERSION 2.0

CURRENT SOMATIC CELL GENE THERAPY (SCGT)

Single gene alterations to cure thalassemia, cystic fibrosis, hemophilia.

300+ SCGT now under development

2015 Bluebird LentiGlobin BB305 for β-thalassaemia at EMA FDA
2015 Obesity switch . . . Example of next generation SCGT?

- MIT Kellis lab decoded regulatory circuitry for FTO obesity locus.
- ID path for adipocyte thermogenesis ARID5B, rs1421085, IRX3, IRX5.
- Manipulated genetic switch, with pro-obesity & anti-obesity effects.
REPLACE
Engineer differentiated tissue/organ
Insert/transplant in subject
• Tracheal implants - Macchiarrini 2008, 2011
• Retinal Tissue Implant – Kurimoto 2011

REGENERATE
Trigger internal healing in subject
Insert extracellular matrix, modified stem cells
* Own cord blood stem cells
* Donor stem cells, marrow
Procymal for graft-versus-host disease
SCGT works in individual, GGT changes in germline will be heritable
2015 Huang@Sun Yat-sen U edited β-thalassaemia gene in 28 embryos.
Initial experiment failed, with many off target mutations.
Note: Efficiency of CRISPR Cas9 enables multiple gene interventions.
IRGC/OECD/UCL Conference on Planned Adaptive Regulation  
Panel 2.2 Adaptive Regulation of Precision Medicine  
8 January 2016  
Technical Developments and Regulatory Challenge  
Professor Kenneth A. Oye  
MIT Center for Biomedical Innovation

Outline

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RISK GOVERNANCE AND ECONOMIC ISSUES

LONGSTANDING ISSUES
• Patient demand for earlier access to breakthrough therapeutics
• Confounder cleansed RCT bad predictor of safety/effectiveness
• Patients unnecessarily exposed to risks during early use

EMERGING ISSUES
• Indications splintering into smaller genetically defined subgroups
• Increasing difficulty finding enough subjects for RCTs
• Limited competition among sponsors in smaller niches
• Payers demanding more evidence on effectiveness
• Novelty / complexity / uncertainty of gene therapies
• Ethics of human germline modification
OVERAL TREND IN R&D EFFICIENCY (INFLATION ADJUSTED)

Prices Climb | The cost of drugs is rising, especially for rare disorders.

A selection of some of the most expensive drugs, annual cost in the U.S.

<table>
<thead>
<tr>
<th>Drug (company)</th>
<th>Treats</th>
<th>Typical/Annual Cost</th>
<th>Target patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliris (Alexion)</td>
<td>Type of blood disease and also a kidney disorder</td>
<td>$440,000</td>
<td>10,000-12,000 world-wide</td>
</tr>
<tr>
<td>Naglazyme (BioMarin)</td>
<td>Rare enzyme disorder</td>
<td>$400,000</td>
<td>1,100 in developed countries</td>
</tr>
<tr>
<td>Elaprase (Shire/Sanofi)</td>
<td>Rare enzyme disorder</td>
<td>$375,000</td>
<td>2,000 world-wide</td>
</tr>
<tr>
<td>Cinryze (Shire)</td>
<td>Hereditary Angioedema</td>
<td>$350,000</td>
<td>6,000 in U.S.</td>
</tr>
<tr>
<td>Gattex (NPS)</td>
<td>Short Bowel Syndrome</td>
<td>$295,000</td>
<td>3,000-5,000 in U.S.</td>
</tr>
<tr>
<td>Harvoni (Gilead)</td>
<td>Hepatitis C</td>
<td>$94,500</td>
<td>3.2 million in U.S.</td>
</tr>
</tbody>
</table>

Source: Sector & Sovereign Research (price changes); Needham & Co. (drugs, patient population); Centers for Disease Control and Prevention (patient population)
Early Problems
Trials use inappropriate subjects. Deaths set back research.

Current Challenges
Genetically defined treatment groups with target patient pool ranging from n=medium to n=1
Complex lag structure on safety, efficacy and effectiveness

- Hard to do large n randomized trial
- Hard to predict lagged effects
Don't edit the human germ line

Heritable human genetic modifications pose serious risks, and the therapeutic benefits are tenuous, warn Edward Lanphier, Fyodor Urnov and colleagues.

A prudent path forward for genomic engineering and germline gene modification

By David Baltimore,¹ Paul Berg,² Michael Botchan,³,⁴ Dana Carroll,⁵ R. Alta Charo,⁶ George Church,⁷ Jacob E. Corn,⁴ George Q. Daley,⁸,⁹ Jennifer A. Doudna,⁴,¹⁰ Marsha Fenner,⁴ Henry T. Greely,¹¹ Martin Jinek,¹² G. Steven Martin,¹³ Edward Penhoet,¹⁴ Jennifer Puck,¹⁵ Samuel H. Sternberg,¹⁶ Jonathan S. Weissman,⁴,¹⁷ Keith R. Yamamoto⁴,¹⁸

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STEPS TOWARD ADAPTIVE PATHWAYS

Health Canada
Progressive Licensing Exercise (not approved) 2008
Parliament enacts safety reform /adaptive licensing 2014

European Medicines Agency
Pharmacovigilance legislation 2010
EFPIA planning IMI project on AL/MAPPs 2013
EMA/EUnetHTA 3 year post market data plan 2013
EMA AL Pilots 2014

US IOM  PCAST AND FDA
PCAST report recommends exploring SMU and AL 2013
Breakthrough product designation established 2012
• 64 requests for designation in year 1, 24 granted 2013
• 2 FDA-CMS parallel review pilot projects 2013

JAPAN PMDA
Conditional limited approval regenerative medicine 2014
Forerunner Review Assignment 2014
Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler\textsuperscript{1,2}, K Oye\textsuperscript{2,3,4}, LG Baird\textsuperscript{2}, E Abadie\textsuperscript{5}, J Brown\textsuperscript{6}, CL Drum\textsuperscript{2}, J Ferguson\textsuperscript{7}, S Garner\textsuperscript{8,9}, P Honig\textsuperscript{10}, M Hukkelhoven\textsuperscript{11}, JCW Lim\textsuperscript{12}, R Lim\textsuperscript{13}, MM Lumpkin\textsuperscript{14}, G Neil\textsuperscript{15}, B O’Rourke\textsuperscript{16}, E Pezalla\textsuperscript{17}, D Shoda\textsuperscript{18}, V Seyfert-Margolis\textsuperscript{14}, EV Sigal\textsuperscript{19}, J Sobotka\textsuperscript{20}, D Tan\textsuperscript{12}, TF Unger\textsuperscript{18} and G Hirsch\textsuperscript{2}

Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted, safe, efficacious therapy. By contrast, adaptive licensing (AL) approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. The concept of AL embraces a range of perspectives. Some see AL as an evolutionary step, extending elements that are now in place. Others envision a transformative framework that may require legislative action before implementation. This article summarizes recent AL proposals; discusses how proposals might be translated into practice, with illustrations in different therapeutic areas; and identifies unresolved issues to inform decisions on the design and implementation of AL.
ADAPTIVE LICENSING
Patient experience contributes to evidence development

FRONT END – PRE MARKET
Earlier approval
Conditional
Limit to patients on benefit/risk

BACK END – ON MARKET
Strengthen observation
• Registries
• EHRs
Analyze safety and effectiveness
Adapt label and license

KEY
Patients in interventional studies
Patients treated but unobserved
Patients treated and observed
REGULATION OF REGENERATIVE MEDICINE AND CELL THERAPY

• Patients demand access to therapies of last resort
• Less regulated – usually under provisions for surgery
• Placebo controlled trials unethical for surgery
• Need more post hoc observation on efficacy, safety, effectiveness
• Therapies need basket license, effects may vary by individual.
• Is Japan PMDA “conditional time limited approval” a fix?

Our Aim is to Restore Function in Diseased or Aged Tissues by Revitalizing Existing Cells or Transplanting New Ones.
FROM PREDICTION TO OBSERVATION AND MONITORING
Credit: Eichler OECD presentation 2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug &gt; Adverse Effect</th>
<th>Detection Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950-60s</td>
<td>Thalidomide &gt; phocomelia</td>
<td>10000 cases</td>
</tr>
<tr>
<td>2005</td>
<td>Natalizumab &gt; PML</td>
<td>3 cases</td>
</tr>
<tr>
<td>2009</td>
<td>Pandemrix &gt; narcolepsy</td>
<td>6 cases</td>
</tr>
</tbody>
</table>

Note: phocomelia low background / high visibility event
Note: MI in diabetics high background / low visibility events
WEAK ACCESS TO CLINICAL TRIALS AND OBSERVATIONAL DATA

- Property rights and clinical trials data – US and EU differences
- Property rights and observational data
- Consent requirements and public health exemption
- Data standards and protocols and commensurability
- Privacy assurances and data aggregation
- Privacy assurances and cybersecurity issues
WEAK EXISTING POSTMARKETING FOLLOWUP AND CONTROLS

2005 Ed Markey staff study
• 91 required postmarketing studies
• 45% not completed, many not started

2013 Moore-Furberg study of 20 drugs approved in 2008
• 8 expedited approval based on average of 5.1 years of clinical testing
• 12 standard approval based on 7.5 years of clinical testing
• 60% of required follow-up safety studies not completed by 2013

2013 Carpenter “hodgepodge of exceptions to rigorous premarket review”
• Approval based on testing in limited patient populations
• Use not restricted to limited patient populations
SOME OPPORTUNITIES AND GAPS

DESIGNING AND REFINING ADAPTIVE LICENSING
• EMA Adaptive Licensing Pilot Projects
• Simulations using data from previously approved drugs
• Assessing payer based methods of controlling access

POOLING INTERVENTION AND OBSERVATIONAL DATA
• Multinational trials to capture sufficient N
• IPR and licensing of data from registries, payers and EHR
• Privacy regulations and data sharing arrangements
• Cybersecurity and data protection
• Technical protocols and standards for interoperability
• Advanced methods for causal inference with large data
• Confirmation of associations on beneficial or adverse effects
• Going backwards from observation to intervention

POLITICAL ECONOMY
• Converting data owners (payers, providers, HMO) into developers?
• Drug licensing as pricing policy: creating competitive markets?