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

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 heath 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

VERSION 2.5
EMERGING SOMATIC CELL GENE THERAPY (SCGT)

2015 Obesity switch . . . Example of next generation SCGT?

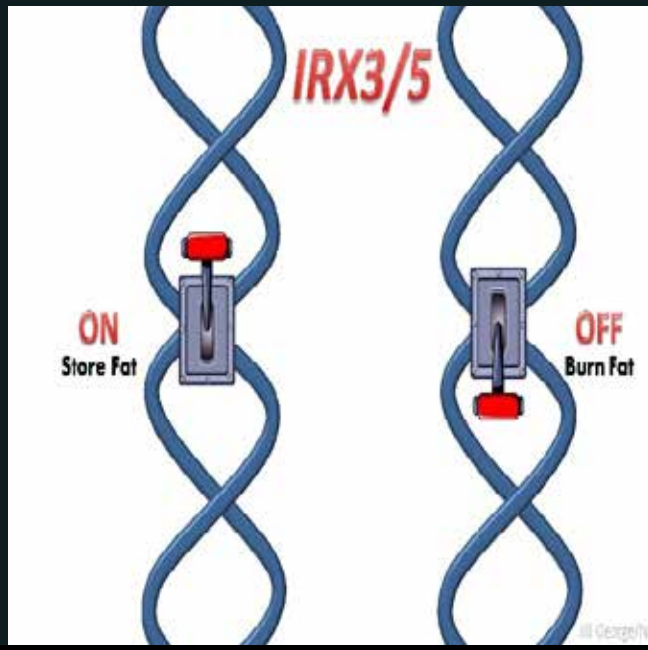
- MIT Kellis lab decoded regulatory circuitry for FTO obesity locus.
- ID path for adipocyte thermogenesis ARID5B, rs1421085, IRX3, IRX5.
- Manipulated genetic switch, with pro-obesity & anti-obesity effects.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 3, 2015 VOL. 373 NO. 10

FTO Obesity Variant Circuitry and Adipocyte Browning in Humans

Melina Claussnitzer, Ph.D., Simon N. Dankel, Ph.D., Kyoung-Han Kim, Ph.D., Gerald Quon, Ph.D., Wouter Meuleman, Ph.D., Christine Haugen, M.Sc., Viktoria Glunk, M.Sc., Isabel S. Sousa, M.Sc., Jacqueline L. Beaudry, Ph.D., Vijitha Puviindran, B.Sc., Nezar A. Abdennur, M.Sc., Jannel Liu, B.Sc., Per-Arne Svensson, Ph.D., Yi-Hsiang Hsu, Ph.D., Daniel J. Drucker, M.D., Gunnar Mellgren, M.D., Ph.D., Chi-Chung Hui, Ph.D., Hans Hauner, M.D., and Manolis Kellis, Ph.D.



VERSION 3.0
REGENERATIVE MEDICINE

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

VERSION 4.0
GERMLINE GENE THERAPY (GGT)

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.

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RISK GOVERNANCE AND ECONOMIC ISSUES

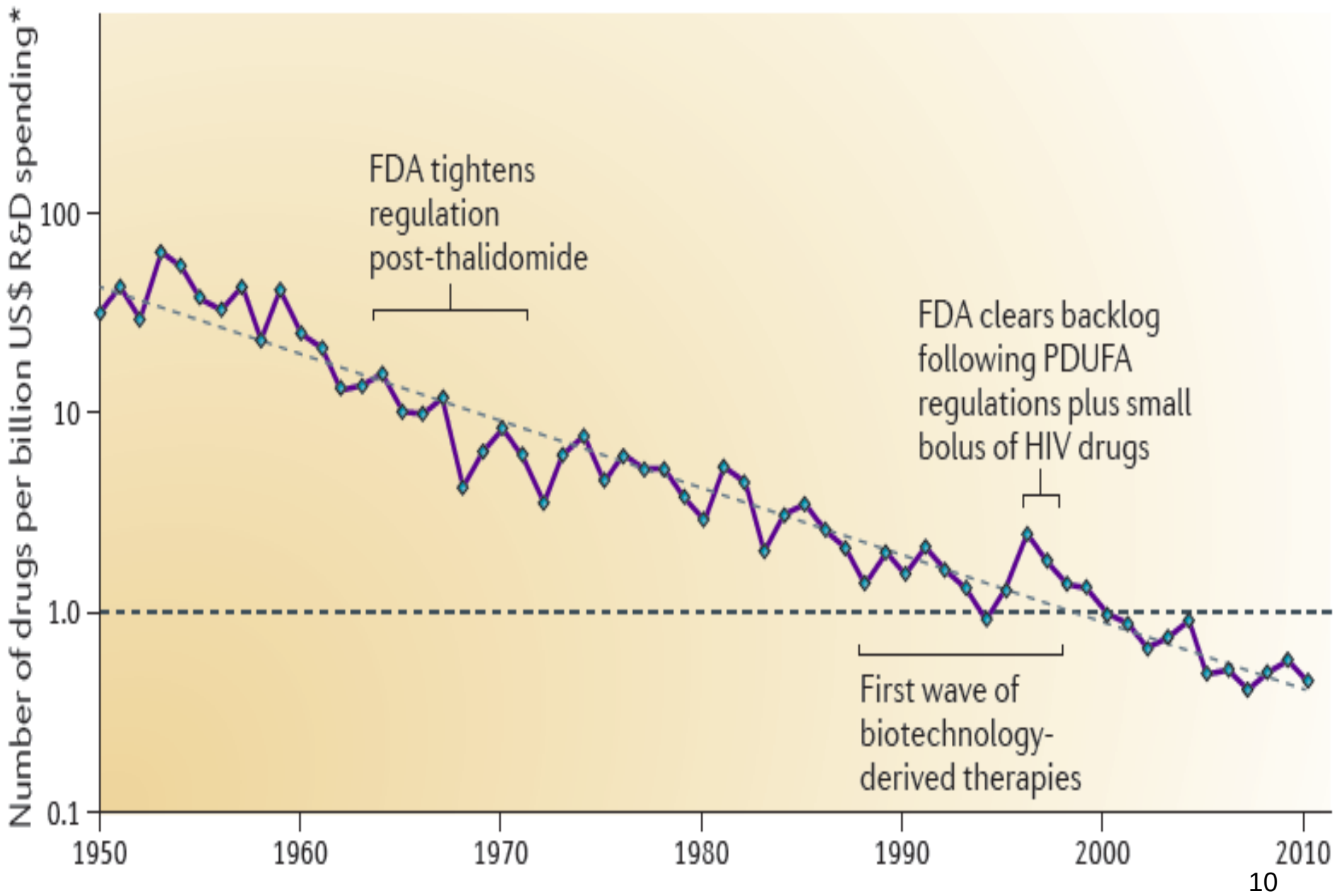
LONGSTANDING ISSUES

- Patient demand for earlier access to break through 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 sub-groups
- 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

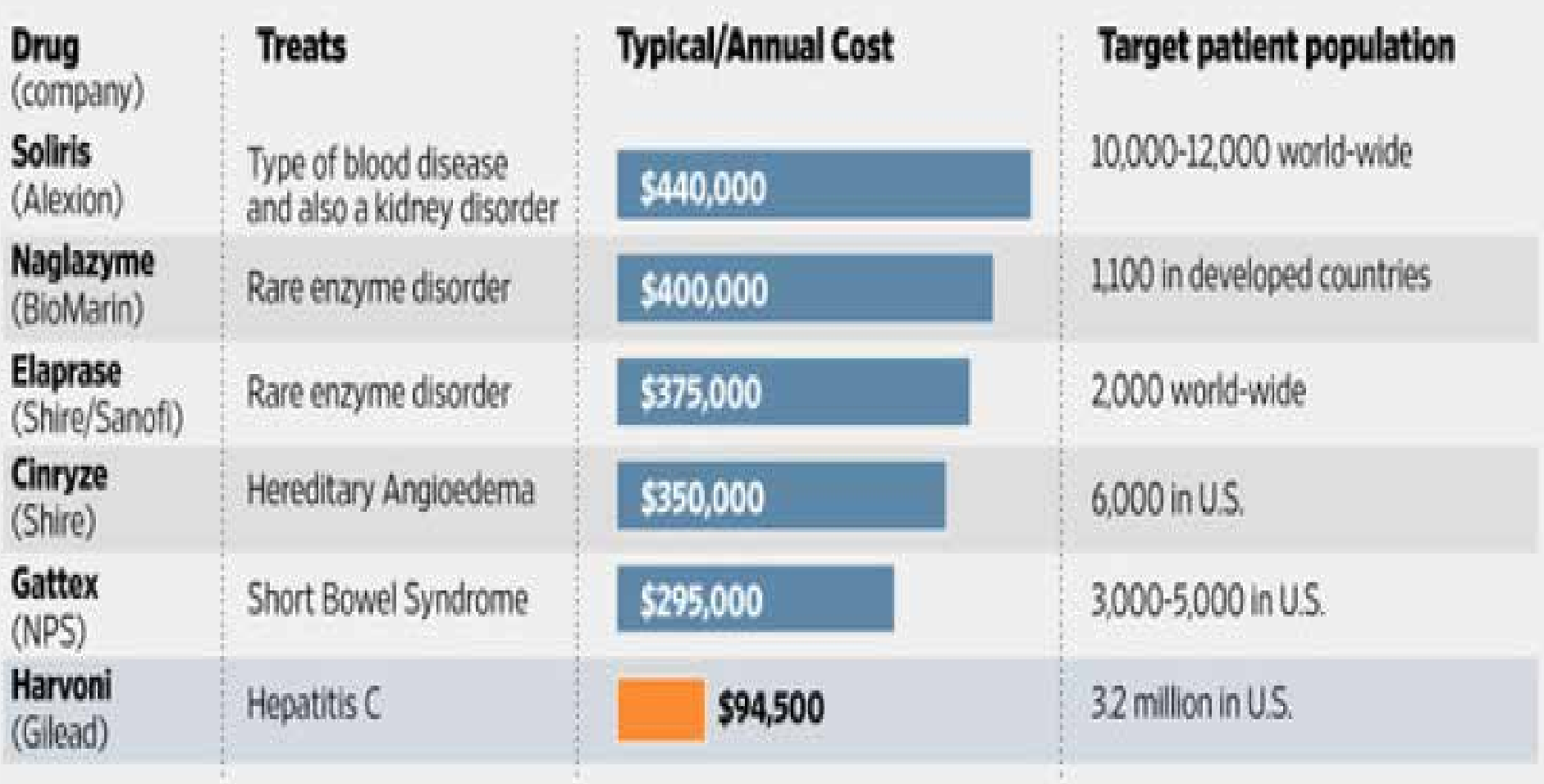
OVERAL TREND IN R&D EFFICIENCY (INFLATION ADJUSTED)



Scannell et al, *Nature Review Drug Discovery*, March 2012.

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.



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

Source: Sector & Sovereign Research (price changes); Needham & Co. (drugs, patient population); Centers for Disease Control and Prevention (patient population)

*Adjusted for inflation

The Wall Street Journal

GENE THERAPY: EARLY PROBLEMS, CURRENT CHALLENGES


Penn gene therapy destroyed teen's lungs

How a storied medical team misjudged what went wrong


Public Interest Group Calls for Public Disclosures in Gene Therapy Death

Contact: Osagie Obasogie
510-625-0819, ext 310

Troubling new revelations have emerged this week in the death of an Illinois woman in a gene therapy trial for arthritis, prompting the Center for Genetics and Society to call on the federal government to consider firmer regulatory action.

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

nature

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.

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ScienceExpress Perspective

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. Yamamoto[4,18]**

[1]California Institute of Technology, Mail Code 147-75, Pasadena, CA 91125, USA. [2]Stanford University School of Medicine,

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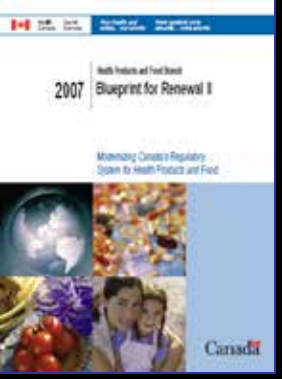
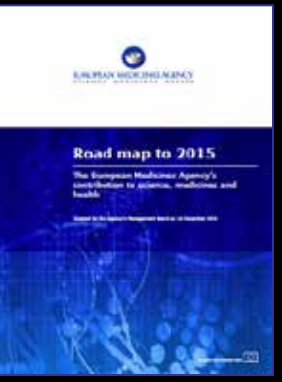




STEPS TOWARD ADAPTIVE PATHWAYS

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

nature publishing group

Open

See COMMENTARY page 378

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

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

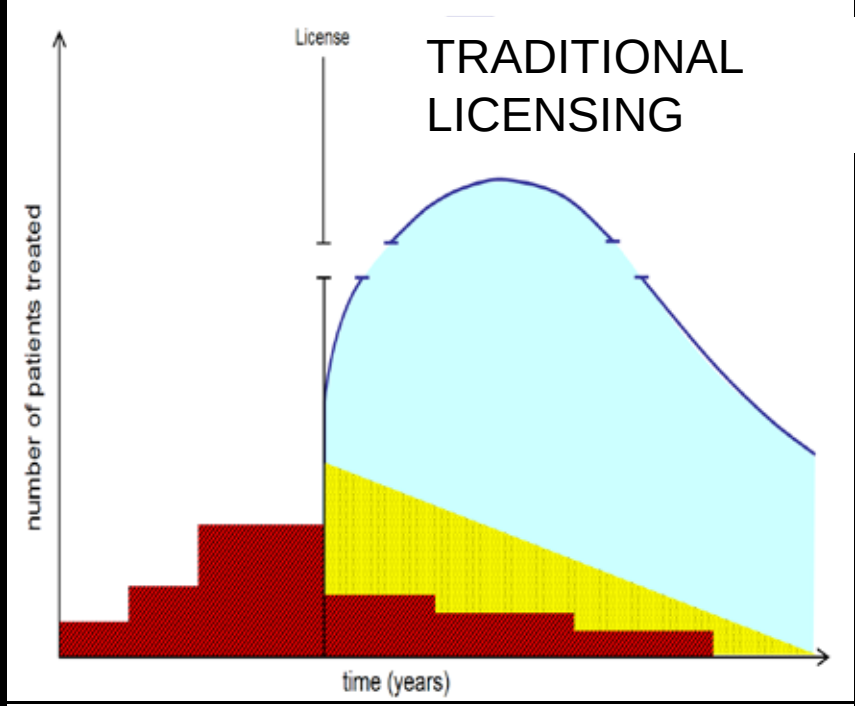
ADAPTIVE LICENSING
Patient experience contributes to evidence development

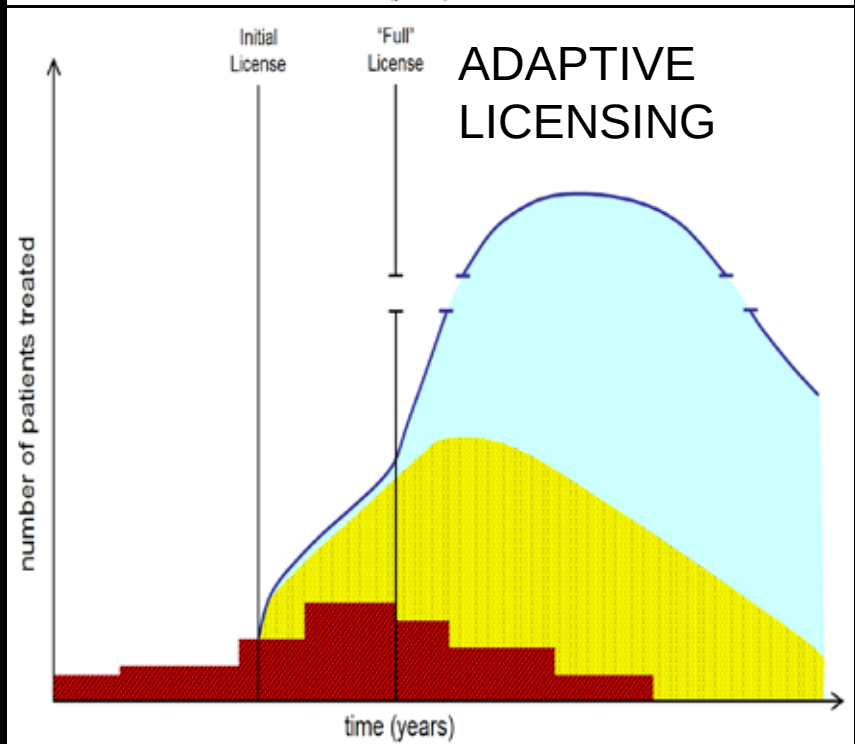
<u>FRONT END – PRE MARKET</u>
Earlier approval
Conditional
Limit to patients on benefit/risk

<u>BACK END – ON MARKET</u>
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



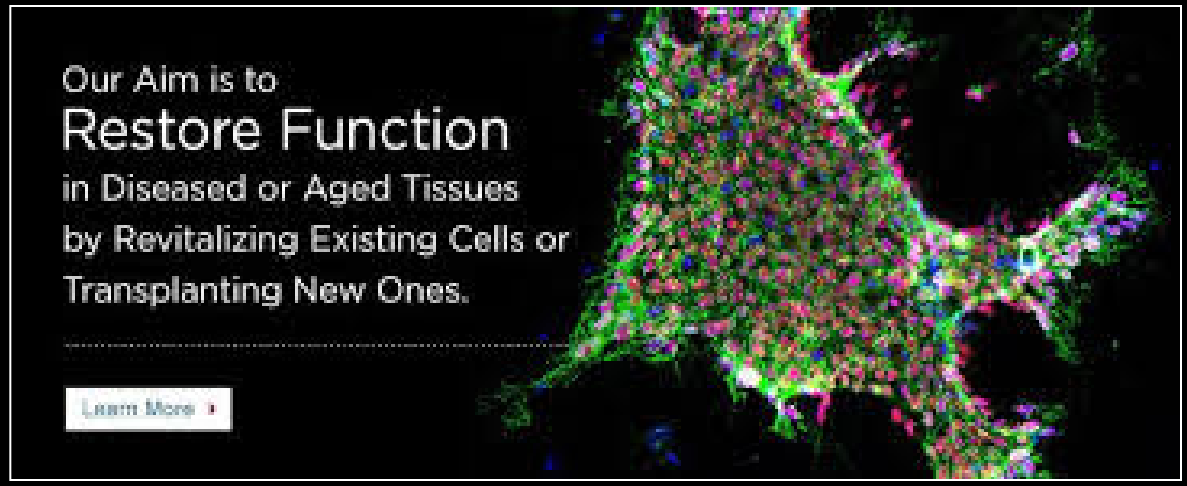


REGULATION OF REGENERATIVE MEDICINE AND CELL THERAPY

- 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?

REGENERATIVE MEDICINE FOUNDATION

CELL THERAPY FOUNDATION



FROM PREDICTION TO OBSERVATION AND MONITORING
Credit: Eichler OECD presentation 2014

Year	Drug > Adverse Effect	Detection Threshold
1950-60s	Thalidomide > phocomelia	10000 cases
2005	Natalizumab > PML	3 cases
2009	Pandemrix > narcolepsy	6 cases

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?