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The history and challenges of biochemical genetics markers and the development of qualification criteria for surrogate endpoints intended for use in Accelerated Approval

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Kakkis EveryLife Foundation
Development of Treatments for Ultra-Rare Disorders is Challenging: Rarity or Difficult Biology

- Paucity of clinical data regarding disease or biomarkers
  - Not enough patients or prior data to verify biomarkers
- Chronic progressive diseases with variability
  - Irreversible and variable disease in different body systems
- Longer term of disease progression
  - Low precision/accuracy methods to assess function
- Separation of disease progression and clinical outcome
  - Disease progresses early but clinical presentation delayed
- No validated surrogate measures of disease reversal
  - Biochemistry or imaging or pathology
Ultra-rare: Mucopolysaccharidosis VII

Ultra-rare lysosomal storage disease caused by a deficiency of β-glucuronidase

- Liver enlargement, skeletal deformations, developmental delay
- MPS VII is ultra rare: 1:~1,000,000+
  - World estimate ~200 patients
- Enzyme therapy successful 16 years ago¹
- Three approved MPS Enzyme Therapies


Osteoblast vacuolization before and after enzyme replacement therapy
Difficult Biology:  
Recessive Dystrophic Epidermolysis Bullosa  
• Fragile skin/blisters due to deficiency of type VII collagen  
• Key challenge: intradermal injection  
• Recombinant C7 in Col7a-/- mice decreased blistering and significantly prolonged survival  
• Data first available ~ 2002, results published in 2008

Delay between pathology and CNS outcome

*NCL2 Ceroid lipofuscinosis type 2*

- Also found prominently in PKU, *Adrenoleukodystrophy* & *MPS I*
Accelerated Approval Pathway
Made for serious and life threatening diseases in which clinical endpoints are difficult

- Long delay between treatment effect and clinical outcome
  - Common in rare CNS diseases
- Quantifying disease effect is challenging
  - Epidermolysis bullosa
- Extreme rarity of the disease
  - Surrogate allows greater certainty of a treatment effect
Historical Use of Surrogates in Rare Diseases

- **Biochemical/Blood test endpoints**
  - Cystadane for homocystinuria
  - Urea cycle drugs Ucephan, Buphenyl
  - Cystagon for cystinosis
  - Ceredase/Cerezyme for Gaucher
  - Kuvan for PKU
  - Plasma homocystine
  - Plasma ammonia
  - Cystine, Creatinine CL
  - Hct, Plt
  - Plasma Phe level

- **Imaging**
  - Ceredase for Gaucher
  - Exjade iron removal
  - Factor VIII joint damage Ind.
  - Liver/spleen size by MRI
  - Liver iron content
  - MRI of joint cartilage

- **Pathologic endpoint**
  - Fabrazyme for Fabry
  - Score of renal path.
Approvals via Accelerated Approval Regs
Usage of the Subpart H or E approvals in 1st 16 years: 64 NDA’s and 9 BLA’s since 1992*

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Number of Accelerated Approvals</th>
<th>Surrogate endpoint</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>25</td>
<td>Tumor size/PFS</td>
<td>Most pivotal studies without a control group</td>
</tr>
<tr>
<td>HIV</td>
<td>29</td>
<td>CD4 or viral load</td>
<td>Combination therapies also approved</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>Variety</td>
<td>PAH, hormones, iron, Crohns, MS, antibiotics</td>
</tr>
<tr>
<td>Genetic</td>
<td>1*</td>
<td>Renal pathology</td>
<td>Fabrazyme</td>
</tr>
</tbody>
</table>

* Kuvan was approved using a Phe endpoint, but received a full approval

Taken from the FDA.gov website table on accelerated approvals
Accelerated Approval Can Work
Surrogate Endpoints Changed HIV Treatment

New Accelerated Approval Regulations put into Effect

25 NCE drugs in a 16 year period
All accelerated approvals
Metabolic Surrogate Endpoints in RD Studies

New endpoints with new drug in never studied disease

- Nearly impossible to use surrogate/Accel Appr.
  - Little independent prior clinical data to support use
  - One regulatory precedent in Fabry, only
  - Phenylalanine in PKU had extensive clinical data

- Concerns about the use of surrogates
  - Correlates are not predictive of clinical outcome
  - Clinical results is what matters
  - Failures to predict clinical outcomes or adverse effects

- Surrogates in rare genetic diseases are likely to be more predictive of clinical outcome than most validated surrogates in use today
PAH Enz. Defective In Liver

Blood Phe

Blood Pressure is the measurement of force applied to artery walls

Brain injury High Phe level

Calibration Question: How much does how much?

Measure Blood Phe Level

Degree of long-term Brain Injury

Treatment effect mechanism is directly on underlying disease?

BH4 Increases PAH in Liver

[ Blood Phe]

BBB

Brain injury reduced due to lower Phe level
What should it take for an ultra-rare disease to use the Accelerated Approval Pathway?

• Level 3 surrogate: “reasonably likely to predict benefit” per Subpart H *
  – The meaning is not defined and this is the problem

• Fleming’s requirements for a surrogate
  – Must accurately represents a direct effect on a clinical outcome, not a parallel pathway to disease mechanism
  – Clinical evidence that intervention is not adverse
  – Must fully capture net effect on clinical endpoint
  – Must be strong and durable effect
  – Specific to a drug MOA and specific indication

* Fleming 2005 “Surrogate Endpoints and FDA’s Accelerated Approval Process”, p72
Surrogate Endpoints And FDA’s Accelerated Approval Process

The challenges are greater than they seem.

by Thomas R. Fleming

‘A Correlate Does Not A Surrogate Make’

EXHIBIT 1
A Reason For The Unreliability Of A Proposed Surrogate Endpoint: The Proposed Surrogate Is Not In The Causal Pathway Of The Disease Process


NOTES: Correlates are useful for disease diagnosis or for assessing prognosis. Valid surrogates are useful for replacement endpoints. See discussion in text. CEA is carcinoembryonic antigen, PSA is prostate-specific antigen.
Bad surrogates from mostly common disorders should guide, not prevent, their use in Rare Diseases

<table>
<thead>
<tr>
<th>Disease and Intervention</th>
<th>Surrogate</th>
<th>Clinical</th>
<th>Settings in Figure 1†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiologic disorder</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Ventricular arrhythmias</td>
<td>Survival</td>
<td>+++</td>
</tr>
<tr>
<td>Encaenide; flecaenide</td>
<td>Atrial fibrillation</td>
<td>Survival</td>
<td>+</td>
</tr>
<tr>
<td>Quinidine; lidocaine</td>
<td>Cardiac output; ejection fraction</td>
<td>Survival</td>
<td>+</td>
</tr>
<tr>
<td>Congestive heart failure</td>
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<td></td>
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<tr>
<td>Milrinone; flosequinar</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Elevated lipid levels</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fibrates; hormones; diet; lovastatin</td>
<td></td>
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<td></td>
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<tr>
<td>Elevated blood pressure</td>
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<td></td>
<td></td>
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<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention</td>
<td>Prostate biopsy</td>
<td>Symptoms; survival</td>
<td>+++†</td>
</tr>
<tr>
<td>Finasteride</td>
<td>Tumor shrinkage</td>
<td>Survival</td>
<td>+</td>
</tr>
<tr>
<td>Advanced disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorouracil plus leucovorin</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV infection or AIDS</td>
<td>CD4 levels; viral load</td>
<td>AIDS events; survival</td>
<td>+</td>
</tr>
<tr>
<td>Antiretroviral agents</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Bone mineral density</td>
<td>Bone fractures</td>
<td>+</td>
</tr>
<tr>
<td>Sodium fluoride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>Bacterial killing; superoxide production</td>
<td>Serious infection</td>
<td>++</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td></td>
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</tbody>
</table>

* AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; + = likely or plausible; ++ = very likely.
† A = surrogate end point not in causal pathway of the disease process; B = of several causal pathways of the disease, the intervention only affects the pathway mediated through the surrogate; C = the surrogate is not in the pathway of the intervention’s effect or is insensitive to its effect; D = the intervention has mechanisms of action that are independent of the disease process.
‡ In settings in which only latent disease is prevented.
Historical failures of surrogates in RD

• Chronic Granulomatous Disease
  – In vitro acidification of macrophages
  – Assay/Biomarker problem: Did not reflect full immune activation effect of the drug and bad surrogate for immune activation

• Adrenoleukodystrophy
  – Very long chain fatty acids in plasma
  – Plasma levels do not reflect brain compartment

• Late Onset Pompe Disease
  – Hand held dynamometry (muscle strength) improved but missed
  – Walk test worked better and was statistically significant
  – Integration/synthesis of effects can be lost using surrogates
Expectations for Predictive Precision for Metabolic Surrogates are Too High

• A one dimensional biomarker cannot possibly predict complex N-dimensional clinical biology and outcome
  – Multi-system disorders with variable patterns in each organ
  – Age/irreversible effects overlaying on response variation

• Single clinical endpoints are not necessarily more accurate measures of overall clinical outcome
  – Clinical endpoints not predictive of other clinical endpoints
  – May not reflect overall clinical disease impact

• A qualified surrogate that measures general disease reduction effect can be most useful
  – Clinical outcome will vary based on many disease variables
  – Better tool for guiding individual therapy
  – Integrates overall result, not just one clinical evaluation
Linear predictions like this should not be required nor necessary

**EXHIBIT 3**
Hazard Ratios For Disease-Free Survival (DFS) Versus Overall Survival (OS), Studies Of Adjuvant Colon Cancer, November 2003

<table>
<thead>
<tr>
<th>OS hazard ratio</th>
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<tbody>
<tr>
<td>1.2</td>
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<tr>
<td>1.1</td>
</tr>
<tr>
<td>1.0</td>
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<td>0.9</td>
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<td>0.7</td>
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<tr>
<td>0.6</td>
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<tr>
<td>0.5</td>
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</table>

<table>
<thead>
<tr>
<th>DFS hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>0.6</td>
</tr>
<tr>
<td>0.7</td>
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<tr>
<td>0.8</td>
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<td>0.9</td>
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<tr>
<td>1.0</td>
</tr>
<tr>
<td>1.1</td>
</tr>
<tr>
<td>1.2</td>
</tr>
</tbody>
</table>

**SOURCE:** U.S. Food and Drug Administration, data from randomized trials, 20 November 2003.

**NOTE:** Three-year DFS versus five-year OS as an endpoint for adjuvant colon cancer studies.
A starting place: Criteria for qualifying RD surrogates

1) Disease Criteria
   • Cause of disease clearly understood
   • Pathophysiology mechanisms reasonably understood

2) Drug Criteria
   • Drug mechanism of action is direct and known
   • Drug pharmacokinetics, pharmacodynamics and metabolism are relevant to the disease process being treated

3) Biomarker Criteria
   • Biomarker has direct relationship to important disease process
   • Biomarker assay is sensitive and specific with a sufficient dynamic range and able to calibrate change with change in pathology
   • Sampling compartment predicts disease compartment/tissue

4) Preclinical Model Data Criteria
   • Preclinical treatment studies show dynamic dose-response relationship on pathophysiology: “calibration for disease effect”
   • Preclinical studies show a clinical effect but cannot be required to show a clinical effect since models not clinically the same
   • Survey of human disease show a relationship to biomarker
Examples today for review and evaluation

- Blood levels of neurotoxic compounds
  - Decrease the toxic compound should predict effect
- Urinary excretion of critical substrates
  - Urinary substrate reflects total or local disease burden
- Anatomy or physiology of disease
  - Structure predicts function and tissue disease burden
- Inflammatory or disease pathology markers
  - Disease measured in tissues reflects overall disease
- Spinal fluid substrates for brain disease
  - Substrate/disease level in brain can be reflected in CSF
- Histologic and serum markers for muscle disease
  - Lessons from Duchenne on interpretation and using markers of expression and injury