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**RARE DISEASE WORKSHOP SERIES**  
Improving the *Clinical Development Process*

# Intermediate Physiologic Measures of Clinical Function

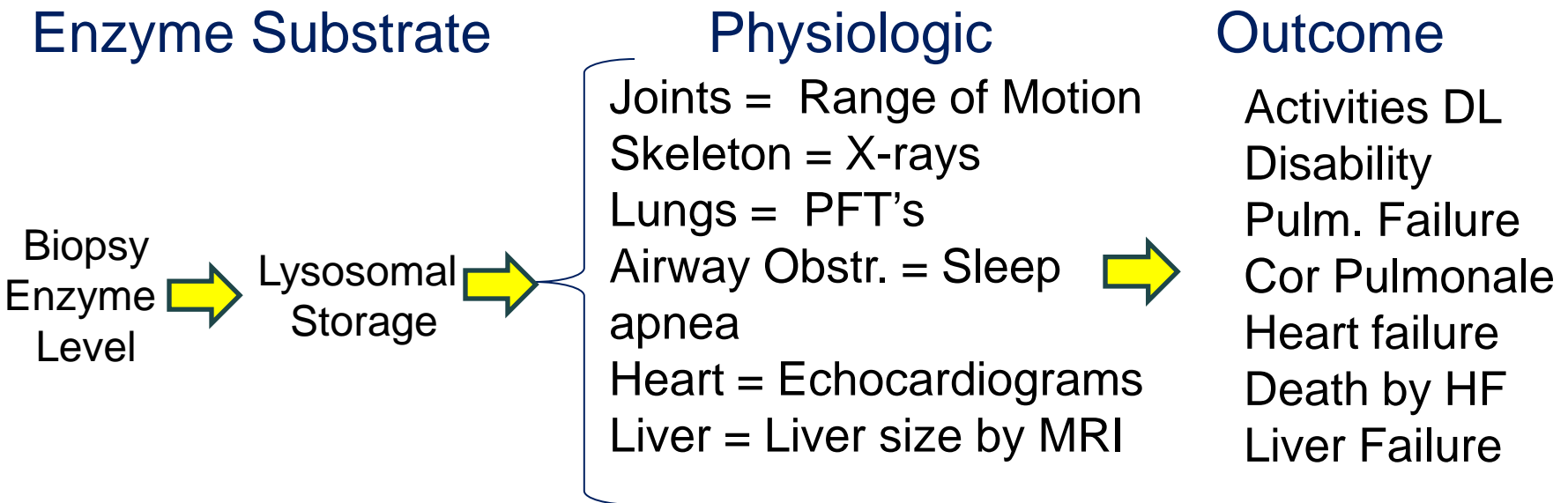
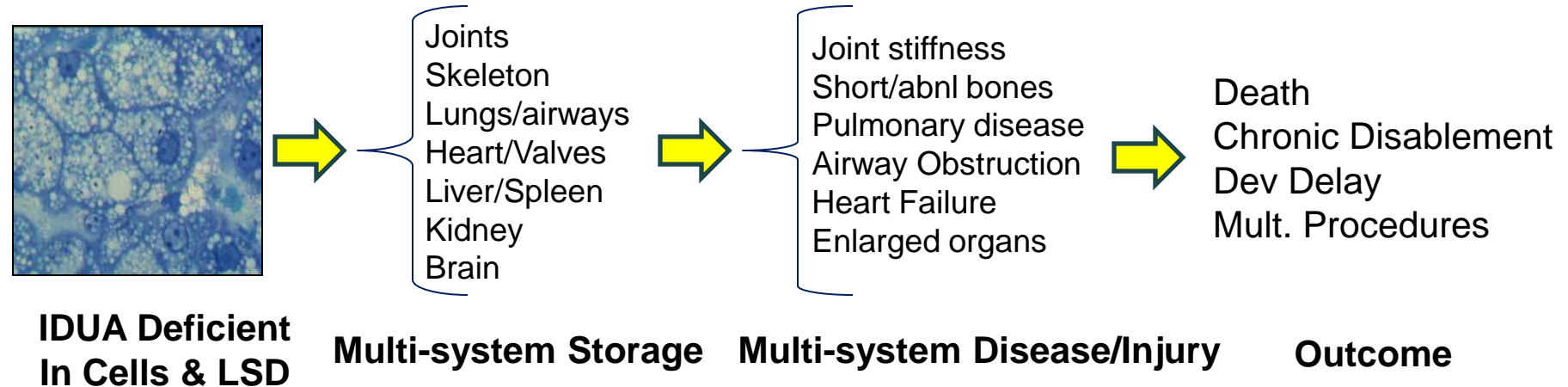
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# Spectrum of Endpoints of MPS I





# Physiologic or Intermediate Endpoints Clinically used in diagnosis and management but still considered surrogates

## Endpoint

- Forced Vital Capacity
- Joint Range of Motion
- Ventricular mass by echo
- Apnea-Hypopnea Index
- 6 minute walk test
- Nerve Conduction Tests
- Creatinine Clearance (GFR)
- Muscle strength

## Comments

if change is small  
not considered “functions”  
Size but not functions  
Sleep not a function  
Complex to interpret  
Nerve function  
If not threshold based  
If not small



## Advantages of intermediate endpoints

- Easier to measure precisely
- Quantitative, continuous variable power
- May eliminate effort or mood as issue
- Clinically used for diagnosis and management so often have “numbers”

## Disadvantages of intermediate endpoints

- Not Clinically clearly meaningful
- Not part of feels, functions, survives



# The value of intermediate physiologic endpoints should be recognized

- Closer to the clinical endpoint
- Quantitative and not effort dependent
- Interpretation of clinical benefit plausible
  - Common disease outcomes known
  - Criteria for diagnosis and management
  - Magnitude of real effects calibrated
- Some challenges remain



# Proving context of use and magnitude of change as relevant

- Is 10 degrees increase in MPS the same as for Factor VIII deficiency?
- Is an apnea-hypopnea index threshold for abnormality of 10 events/ hour sufficient to predict a decline that might lead to cor pulmonale?
- Does 4.5% increase in FVC really matter for outcome?



# Physiologic measures still intrinsically better than pure biomarker surrogates

- Closer to a clinical function
- Less assumed to be relevant to pathology
- Even if magnitude is uncertain, movement in right direction for a chronic disease can be a meaningful change in direction
- Need better ways to accept and use these measures