Leveraging Biomarkers in Early Clinical Drug Development for Metabolic Disease Therapies

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Overview of Presentation

- What is driving the need for innovation in early clinical research?
- Are biomarkers new?
- Why include biomarkers in early drug development?
- What are some examples?
  - Type 2 Diabetes
  - Lysosomal Storage Diseases
- What are the challenges?
  - Novel Biomarkers
  - Analytical Issues
  - Complex Study Logistics
- Summary

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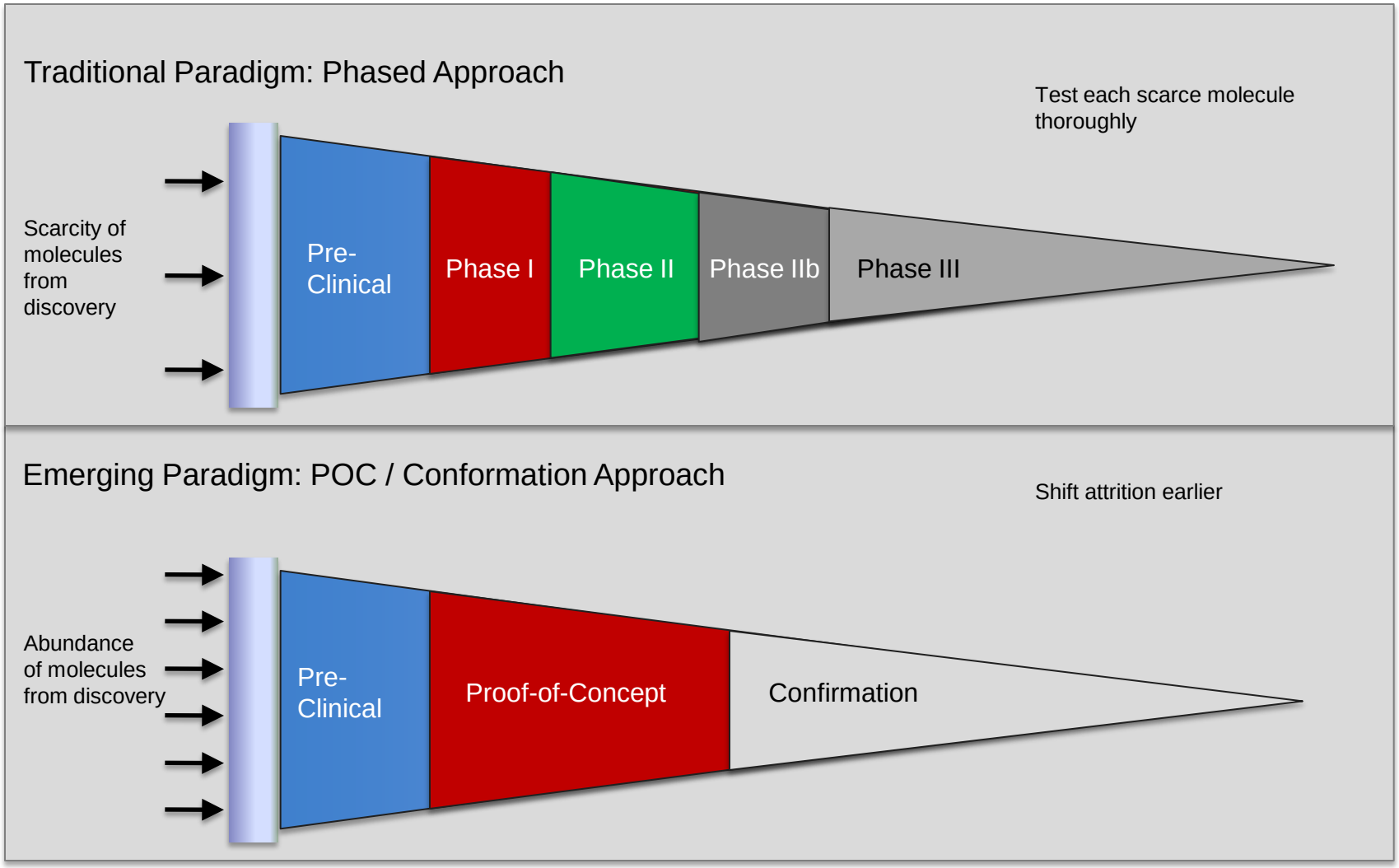
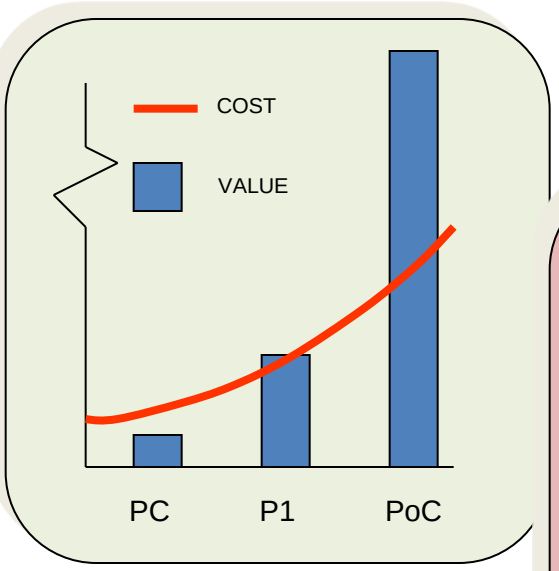
Clinical Development is Evolving



Source: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010

Importance of Proof-of-Concept Studies

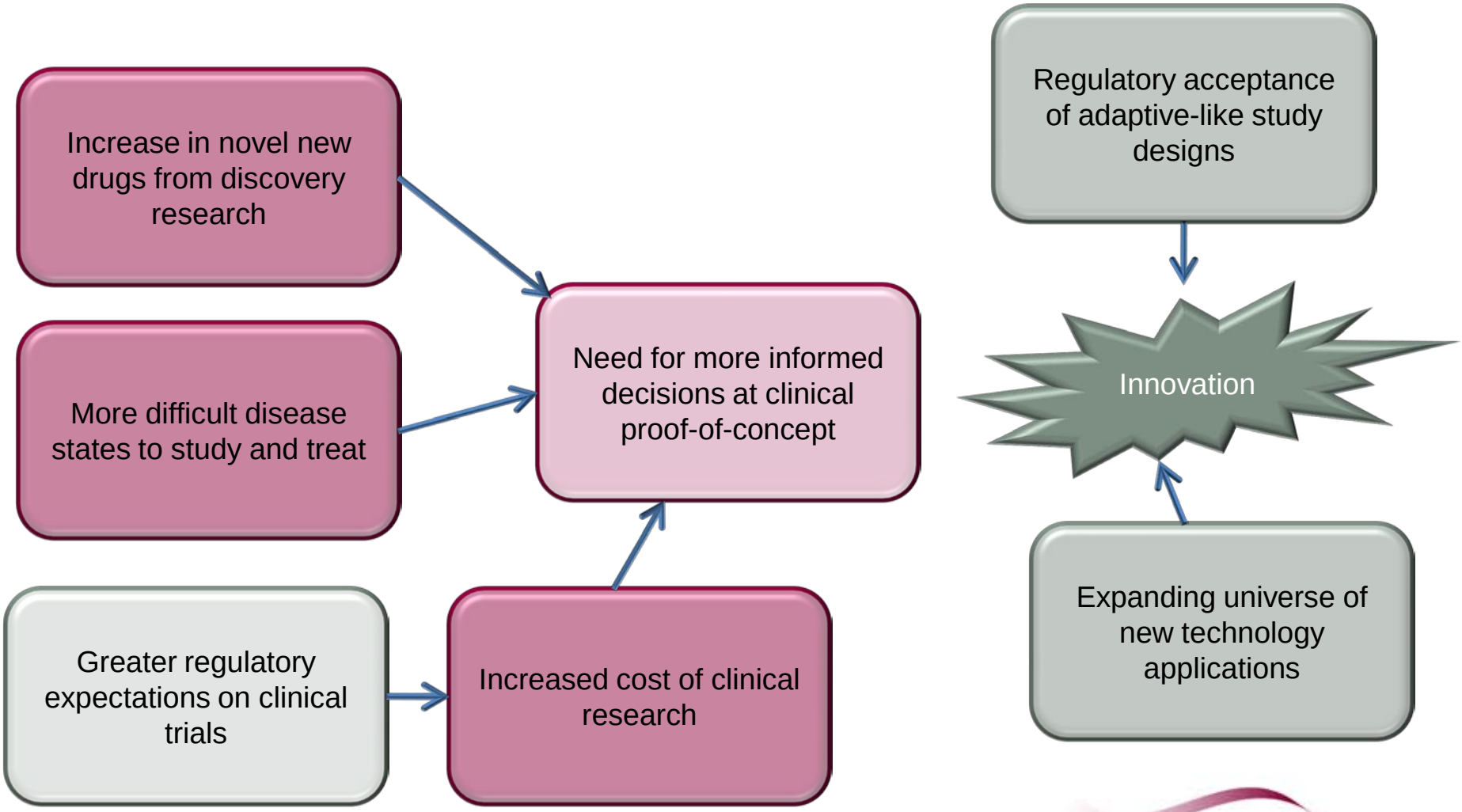
Defines Product Value For the First Time



% Chance of Reaching Market	
Preclinical	0.1-1
FIH study	5-10
POC study	10-30

Typical Costs ($million)	
IND tox study	0.5 – 1.0
FIH study	0.7 – 1.4
POC study	2 - 20

The Pressure is On for Proof-of-Concept!



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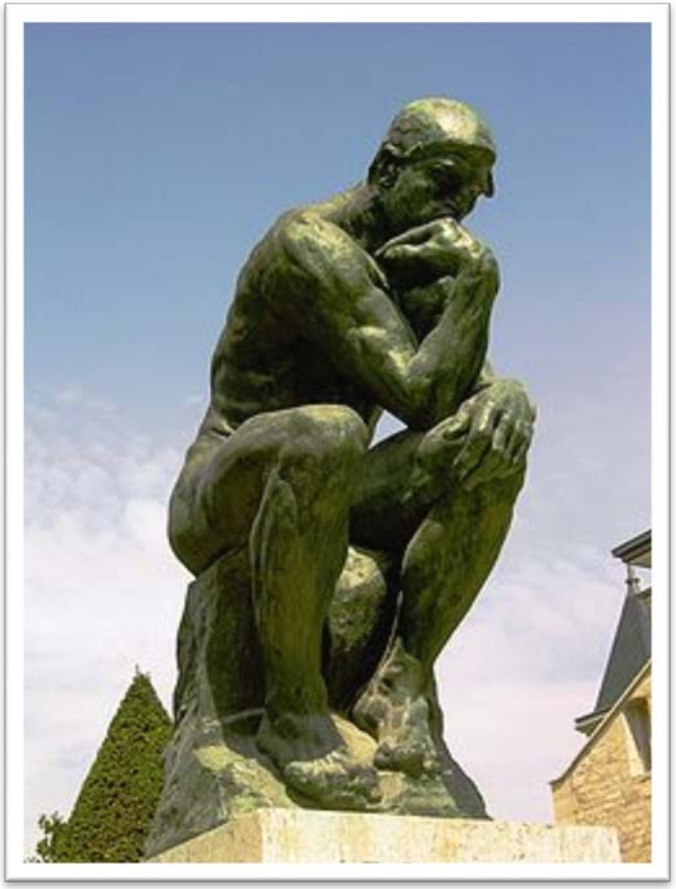
What is a Better Decision?



- One made earlier
- With greater confidence
- More efficiently

Better data, faster, cheaper

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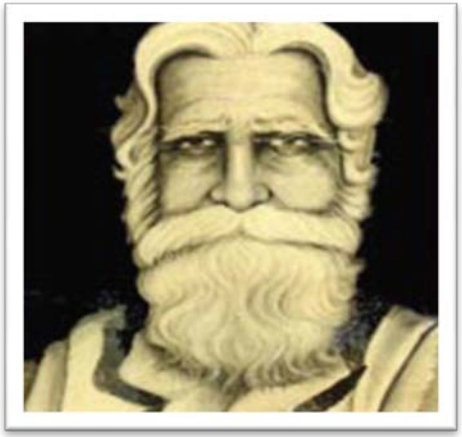
Q: Are Biomarkers New?

A. Biomarkers Are Not New.



Sushruta (clinician in India, 600 B.C.)

Recorded that urine of diabetic patients attracted ants

= Diagnostic biomarker for diabetes

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Other Early Milestones in Biomarker Development

- **1555** **Józef Struś** first measured blood pressure
  (by placing increasing weights on the skin over an artery until the pulse no longer lifted the weight)
- **1895** **Wilhelm Röntgen** discovered x-rays
  → imaging biomarkers
- **1896** **Henri Becquerel** discovered radioactivity
  → radiodiagnostics
- **1901** **Willem Einthoven** invented the first ECG apparatus

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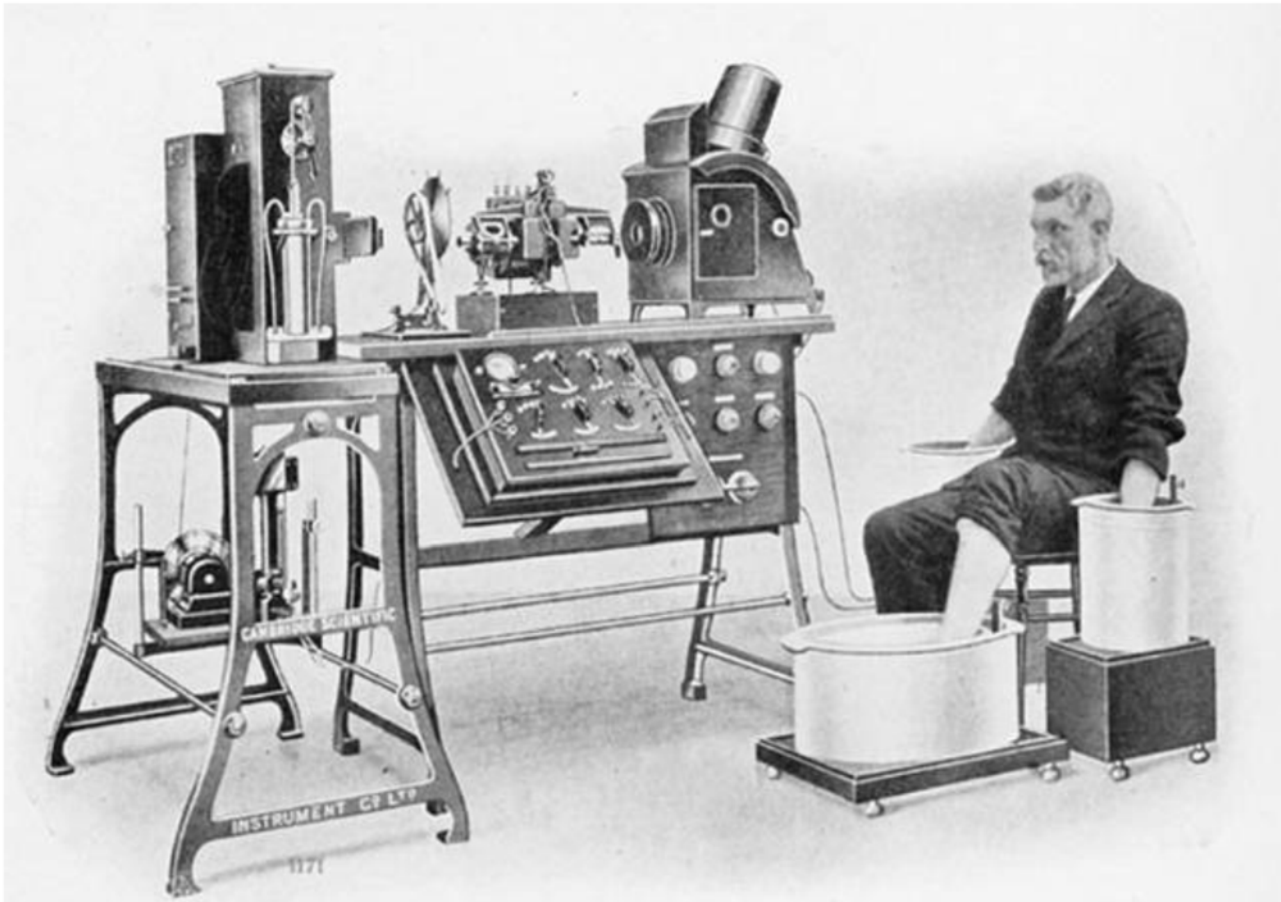
An Early ECG Device



PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSED IN JARS OF SALT SOLUTION

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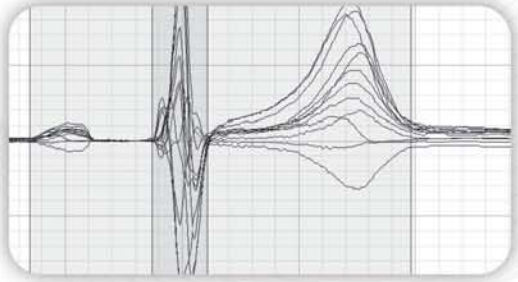
The Hybrid Phase I/ ECG Core Laboratory

- Phase I focus only
- Single vendor with unified functionality
- Single database
- Single PM, DM, stats

BLUETOOTH HOLTER

- Instant ECG review
- Computer generated date/time stamp
- Preconfigured demographics
- Single device to acquire safety ECGs during Holter recording
- 1000 sample/second acquisition
- Up to 48 hours ECG collection

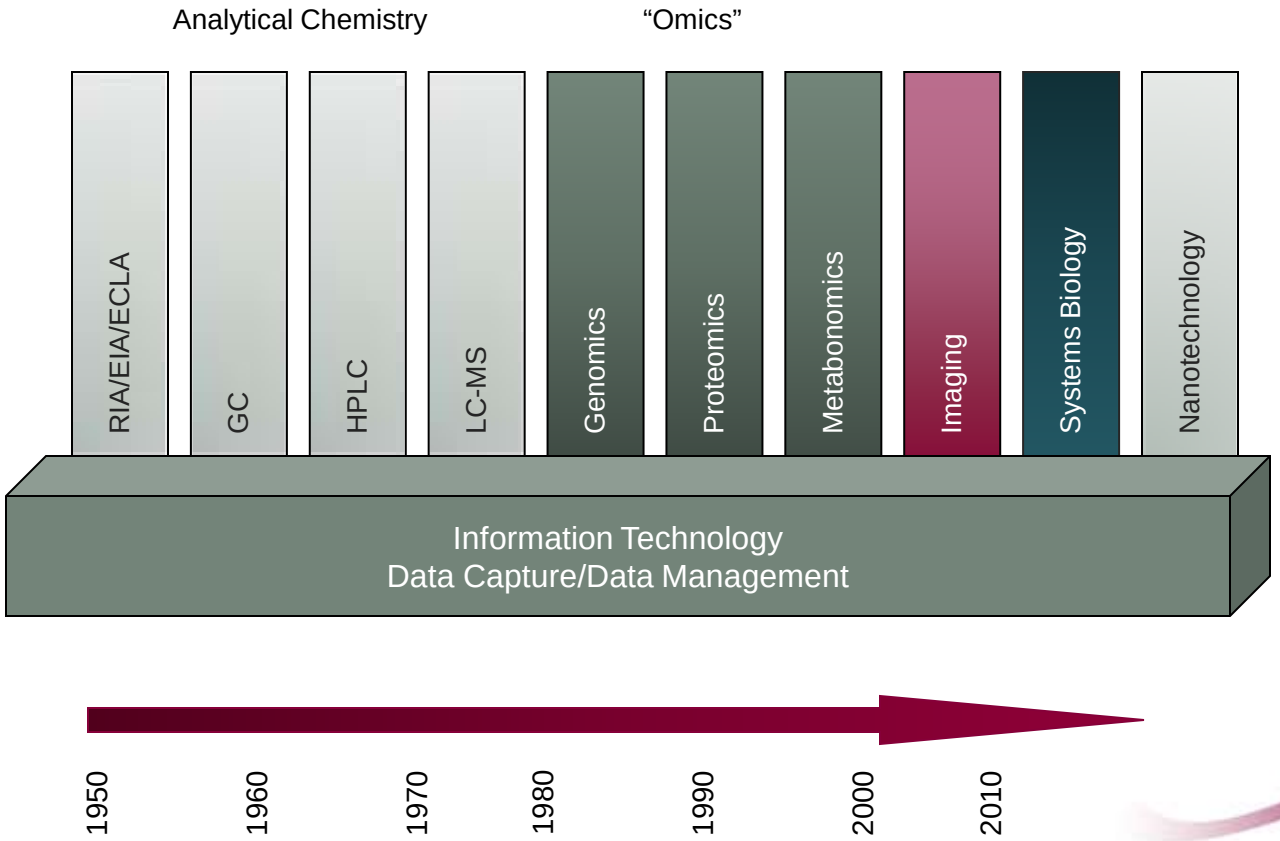
HIGHLY AUTOMATED ECG PROCESSING



- Automated, optimized ECG extractions from Holter
- Normal ECGs measured automatically providing lower variabiliy=better data
- Cardioloigst only review approximately 10-20%
- Faster data turnaround

Modern Era of Biomarkers – New Technology Drives Innovation

1950s to present day



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Biomarkers and Decision-Making

- Key question: How will the biomarker(s) advance the drug's development?

- Primary purpose of biomarkers is to enable better decisions

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Diabetes

- Diabetes affects nearly 25.8 million people (8.3% of the population) in the U.S.
  - 18.8 million diagnosed
  - 7.0 undiagnosed
- > 35% of U.S. adults > 20 years have pre-diabetes
- > 50 of U.S. adults > 65 years have pre-diabetes
- Leading cause of kidney failure, nontraumatic limb amputations and new cases of blindness
- Major cause of heart disease and stroke
- 7th leading cause of death

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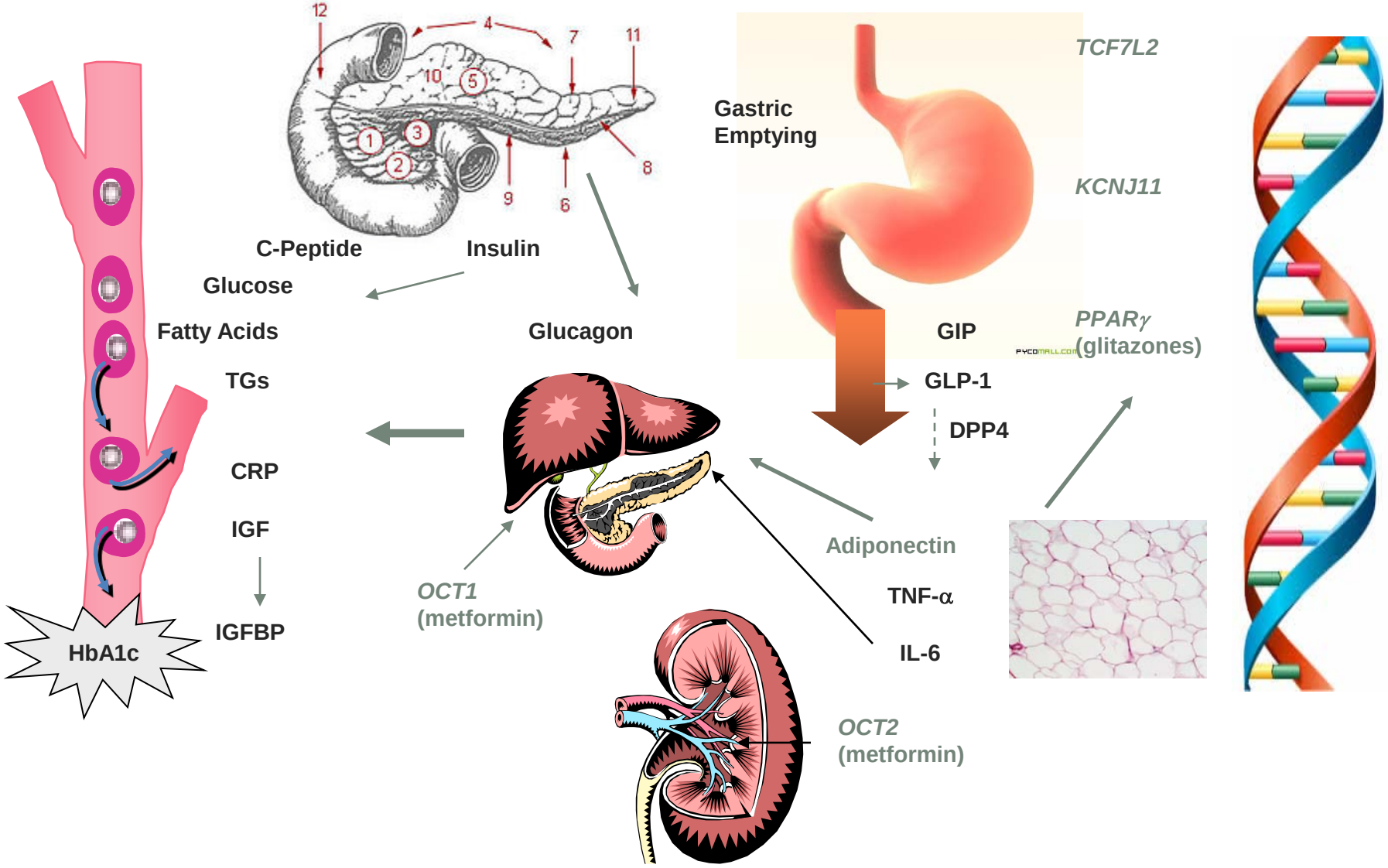
Plethora of Biomarkers for Diabetes



Considerations in Evaluating a Candidate Biomarker

- Clinical relevance
  - Ideally, should be related to MoA of the drug and the clinical endpoint
- Sensitivity and specificity to treatment effects
  - Ability to detect the biomarker or change in biomarker in the target population
- Reliability
  - Ability to measure the biomarker analytically with accuracy, precision, robustness and reproducibility
- Practicality
  - Is the biomarker non-invasive? Is it suitable to implement in multi-site trials?
- Simplicity
  - Simpler is better for translating a biomarker from lab bench to bedside

SAD Study of a Novel DPP-4 Inhibitor in Mild Diabetic Patients

Sequence	Patients	Treatment Periods		
		P1	P2	P3
1	N = 5	PLA	75 mg	200 mg
2	N = 5	25 mg	PLA	200 mg
3	N = 5	25 mg	75 mg	PLA

Sequence	Patients	Treatment Periods		
		P'1	P'2	P'3
4	N = 5	PLA	100 mg	300 mg
5	N = 5	50 mg	PLA	300 mg
6	N = 5	50 mg	100 mg	PLA

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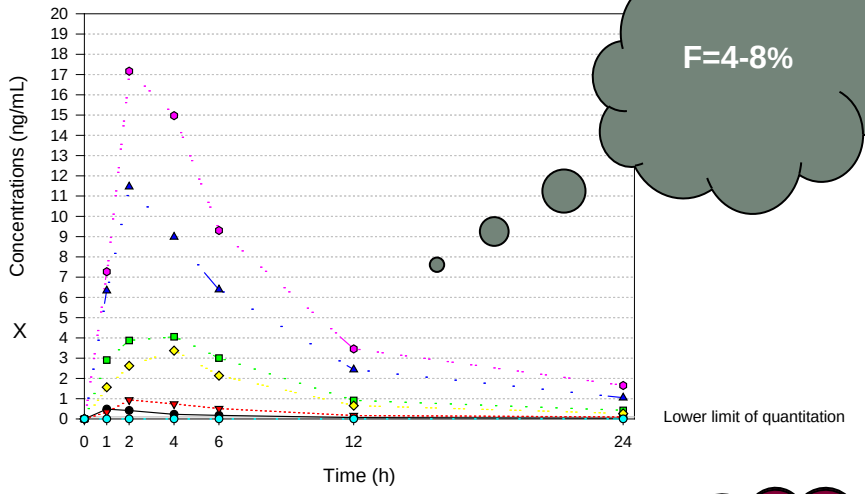
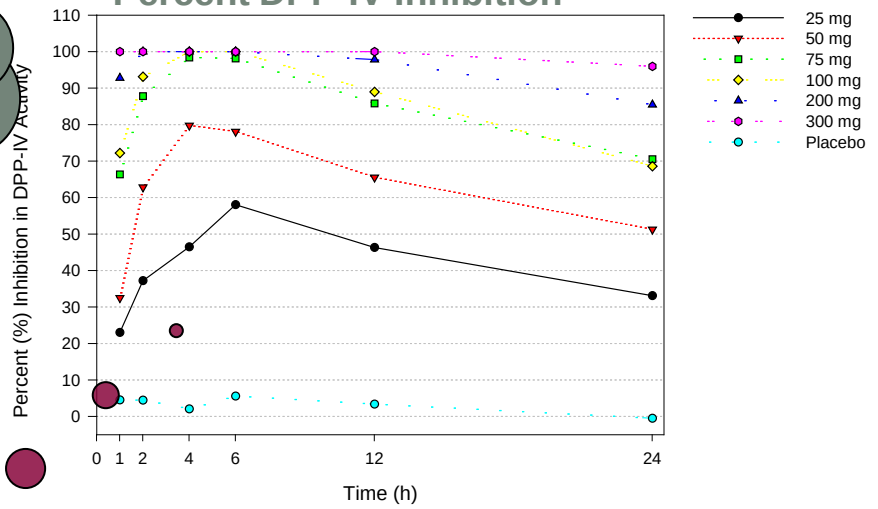
Results of SAD Study in Mild Diabetic Patients: *Early Evidence of Efficacy*

Drug Plasma Concentration

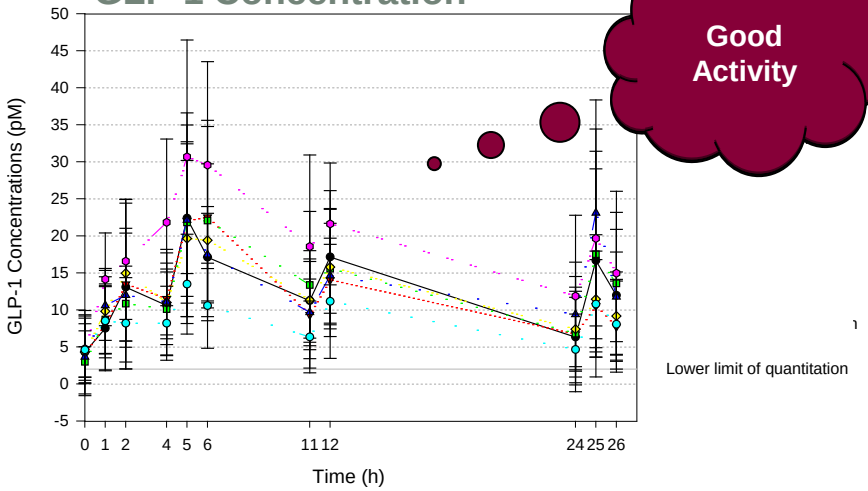


F=4-8%

Percent DPP-IV Inhibition

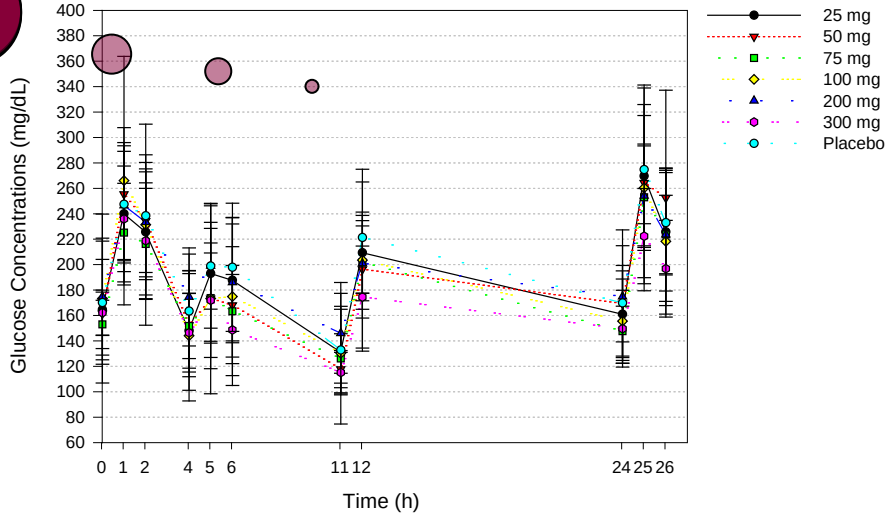


GLP-1 Concentration



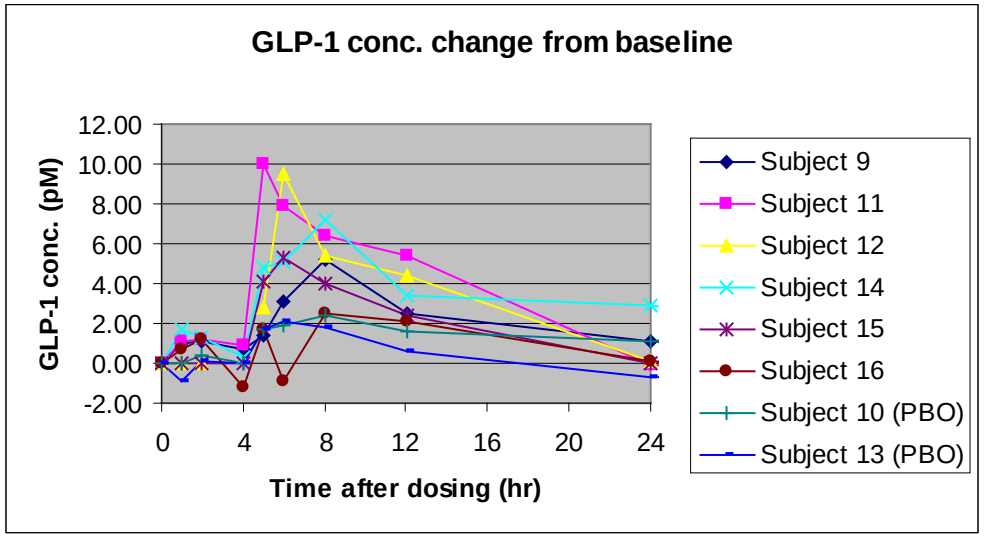
Good Activity

Glucose Concentration



SAD Study of Novel DPP-4 Inhibitor in Healthy Volunteers

High Inter-subject Variability in Postprandial GLP-1



Meal

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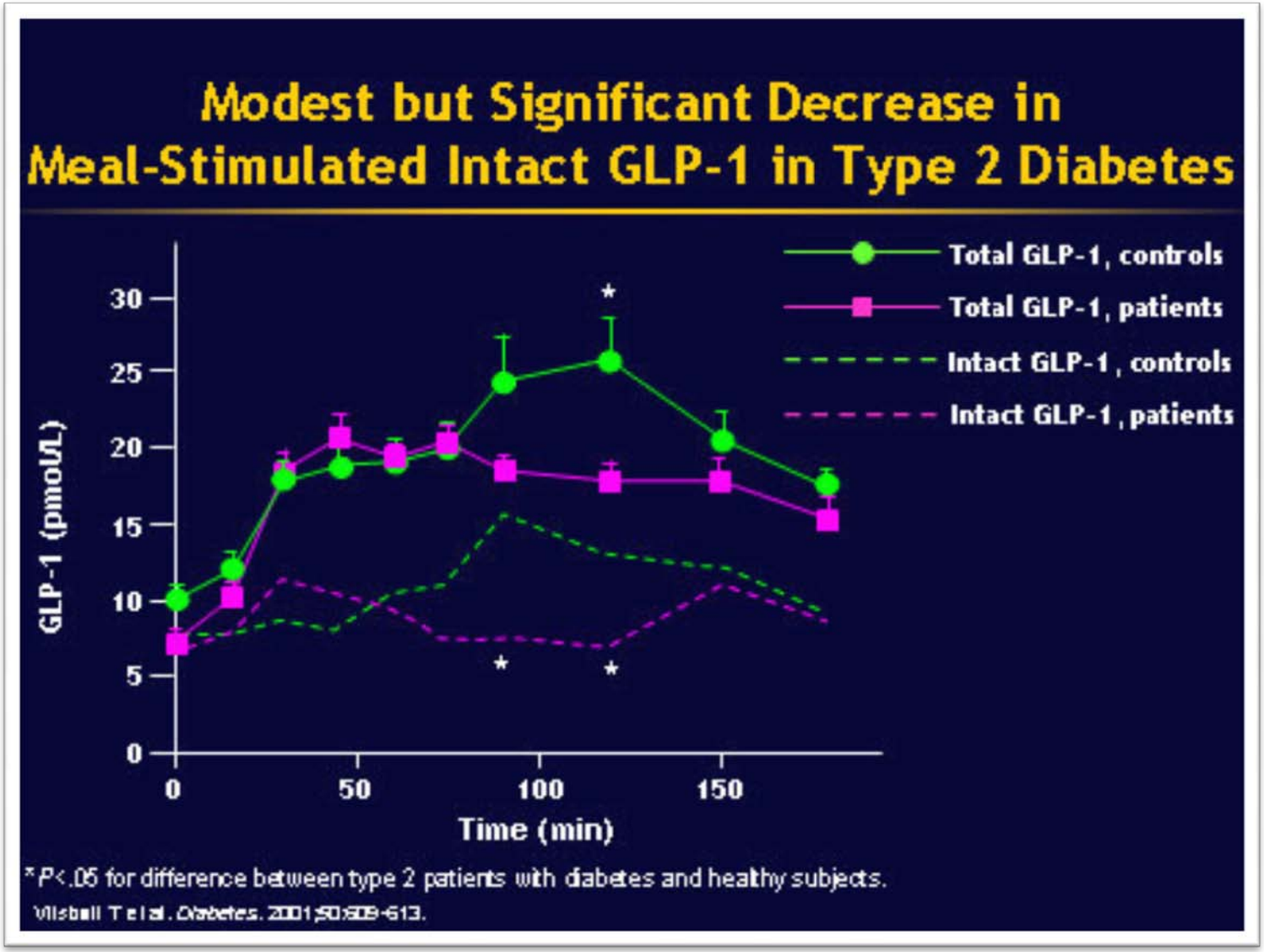
GLP-1 Response to Meal is Different Between Healthy Volunteers and Type 2 Diabetics



Lysosomal Storage Diseases

- Rare inherited metabolic disorders that result from defects in lysosomal function
- Usually caused by the deficiency of a single enzyme involved in the metabolism of a lipid, glycoprotein or mucopolysaccharide, resulting in the excess accumulation of its substrate in the lysosomes
- Examples – Fabry disease, Gaucher disease, Pompe disease

Fabry Disease

- X-Linked inborn error of metabolism
- Subnormal or absent activity of lysosomal hydrolase, α-galactosidase A (αGal A)
- Progressive globotriaosylceramide (GL-3) accumulation in tissues leading to end-organ impairment
- Most morbidity and mortality attributable to renal, neurologic and cardiac disease
- Therapies for Fabry Disease
  - Enzyme Replacement Therapy
  - *Chaperone Therapy?*

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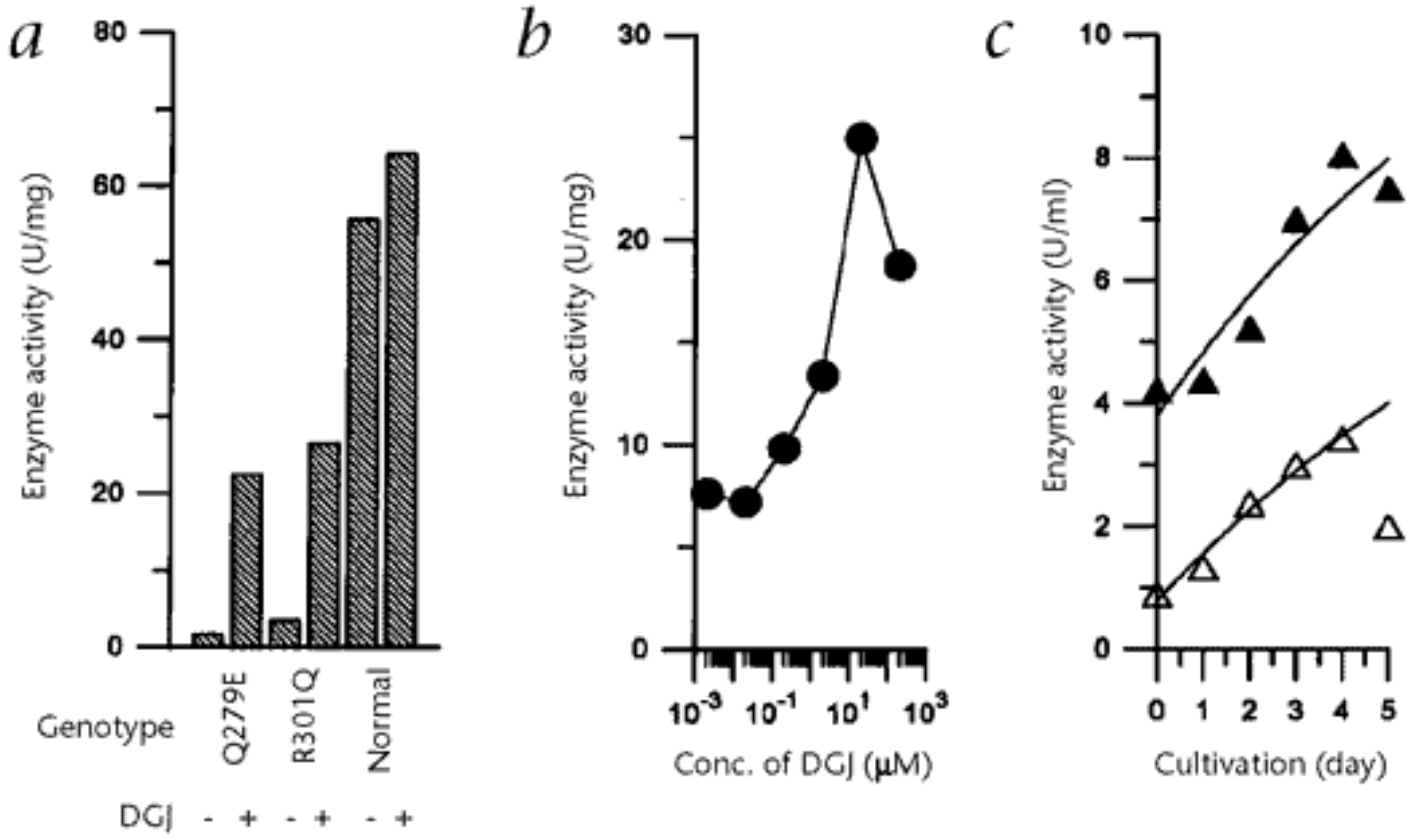
In Vitro Studies During Discovery Demonstrated αGal A as a Mechanism of Action Biomarker



Enhancement of αGal A in lymphoblasts from patients with Fabry disease

Ref: Fan *et al.*, Nature Medicine 3: 112-115, 1999

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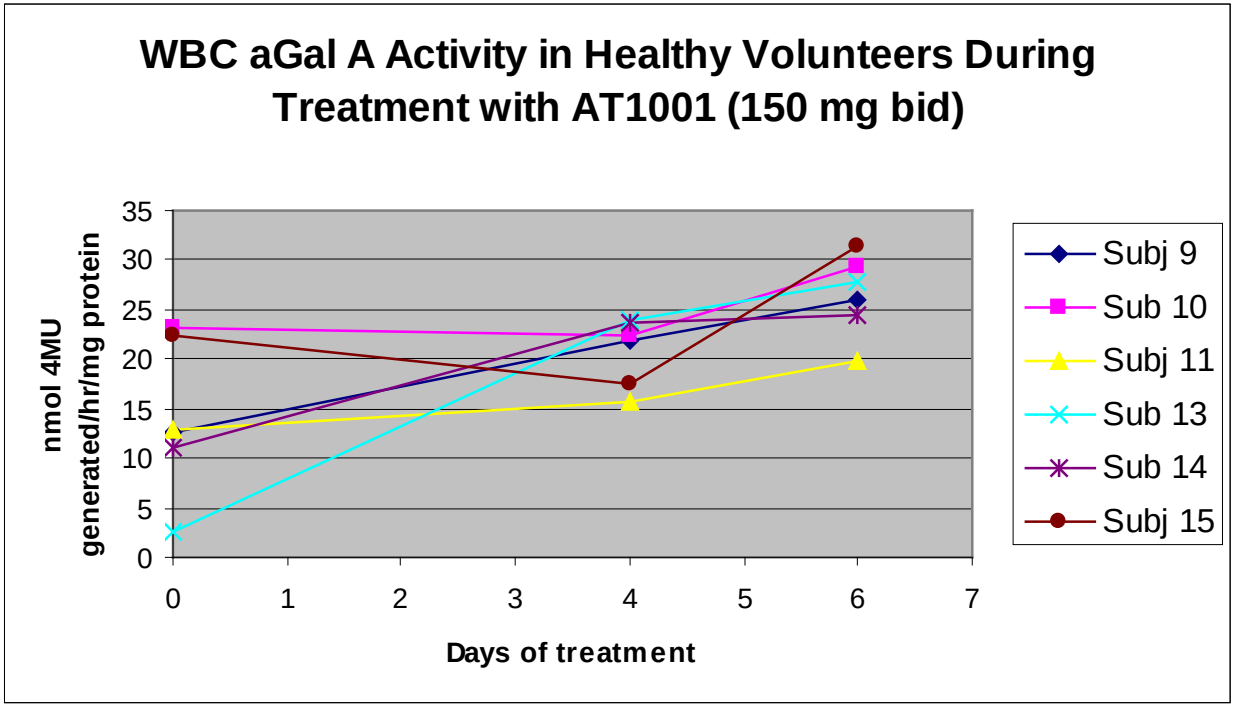
PD Biomarker Incorporated into Phase I Clinical Development Program



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Gaucher Disease

- Most common lysosomal storage disease
- Autosomal recessive inheritance
- Subnormal or absent activity of lysosomal acid β-glucocerebrosidase (GCase)
- Progressive accumulation of substrate glucocerebroside in tissues leading to end-organ impairment
- Most morbidity and mortality attributable to hepatosplenomegaly, bone and neurologic disease
- Therapies for Gaucher Disease
  - Enzyme Replacement Therapy
  - Miglustat (enzyme inhibitor that decreases production of substrate)
  - *Chaperone Therapy?*

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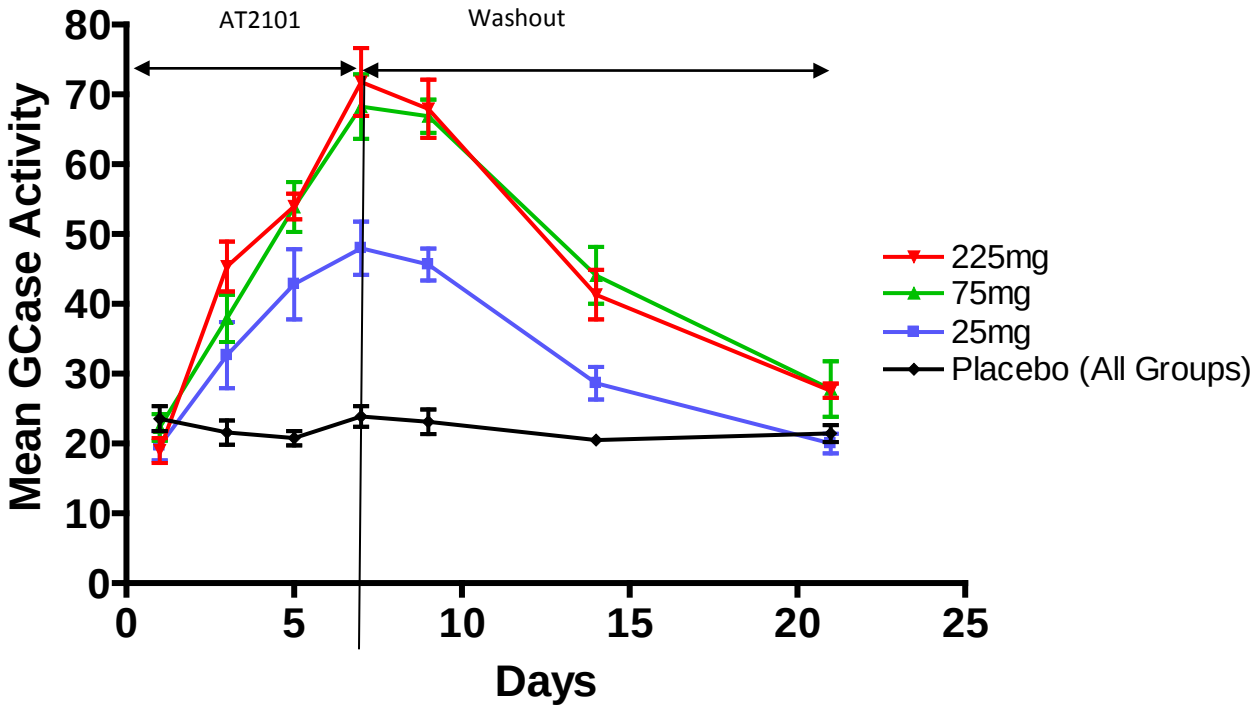
GCase as PD Biomarker in Phase I MAD Study

GCase activity in white blood cells during repeated daily oral doses of AT2101 for 7 days followed by a 14-day wash-out period



DJ Palling et al., Am. College Med Genetics, Nashville, Tennessee, March 2007 (poster presentation)

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Clinical Relevance of Biomarkers:

- If a biomarker is to be used to differentiate between healthy individuals and those with a disease, need to determine a priori the descriptive statistical parameters for the two populations
  - Mean, range, variance
  - Is there population overlap?
  - How does the population difference compare to the measurement error?
- May need to first conduct a survey study to collect data
- Determine appropriate sample size (based on statistical power to detect meaningful difference)

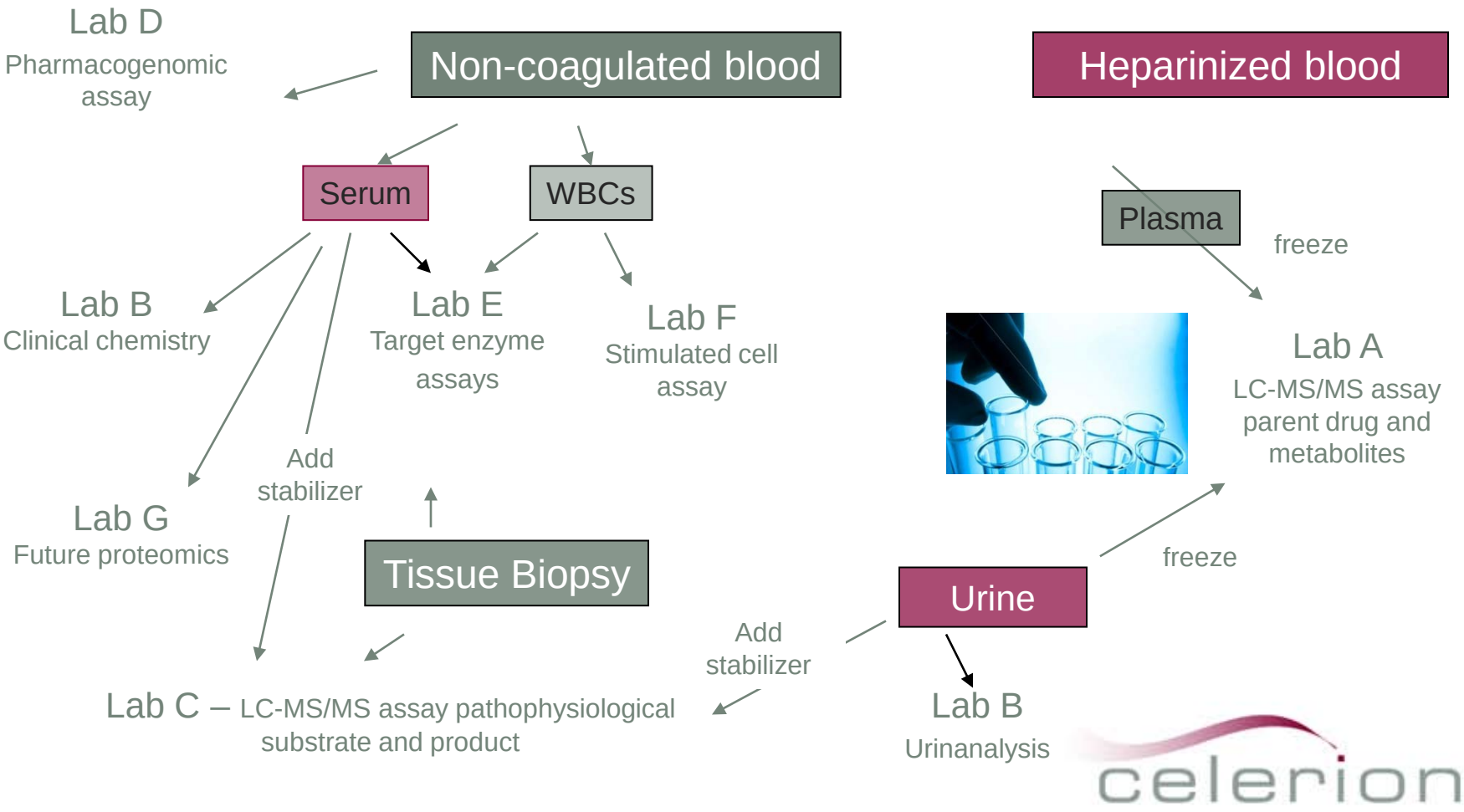
Normal Range and Variation of the Biomarker

- *Example: Novel drug for treatment of a rare metabolic disease caused by an enzyme deficiency*
  - Phase II study: Patients were “pretreated” for 2 weeks with the drug to determine if they were “responders”. Only responders were to be enrolled in a 12-week open-label trial
    - Original definition of responder was “If baseline enzyme activity is less than 1% of normal, then Day -15 enzyme activity must be at least 2% of normal”

- *Key Issue: Need to define “normal”*
  - Measured enzyme activity in healthy subjects (N=21)
  - AVG = 22.8 nmol/mg protein
  - SD = 5.7, Range = 11.0 - 33.5
    - Cannot discern an increase from 1% to 2% of normal
    - Changed inclusion criteria based on X-fold increase from baseline for individual patient

Complex Sample Collection and Processing

Example – Phase IIa study – 14 tests, 7 labs



Challenges and Learnings

- Time to develop assay (translate from lab bench to clinic)
  - Assay through-put, sensitivity & specificity, reliability
- Defining normal baselines for novel assays
  - Can be readily done in early phase
- Complex sample collection and processing
  - Role of project management
  - Staff training (mock runs)
  - Barcode system to reduce errors, maintain chain of custody

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Challenges and Learnings (…continued)

- High demands on data management and data analysis; quantity and speed
  - Integrated IT solutions
- Ethical issues (e.g. tissue banking, privacy, data integrity)
  - Issues must be recognized early and solutions developed early
- Evolving regulatory environment
  - Engage early with regulatory agencies

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Summary

- Purpose of biomarkers is to enable better decisions
- Question to be answered should drive the technology used
- Understand biomarker variability and clinical relevance in study populations
- Recognize challenges and plan early

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