To: Elizabeth Holmes[eholmes@theranos.com]
From: Ian Gibbons[/O=THERANOS ORGANIZATION/OU=FIRST ADMINISTRATIVE GROUP/CN=RECIPIENTS/CN=IGIBBONS]
Sent: Wed 7/2/2008 4:56:39 PM (UTC)
Subject: Latest clinical story

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Theranos Clinical Studies

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Stanford AML Study

Study outline

- Goals:
  - Follow course of chemotherapy
    - 18 Acute myeloid leukemia (AML) subjects in hospital for chemotherapy
    - Many progress to sepsis due to inactivation of the immune system due to the therapy
  - Document changes in ten biomarkers selected to be responsive to pathological processes and response to therapy
    - Create a database of medical and clinical information
    - Initiate development of prognostic algorithms
  - Evaluate performance of Theranos system
    - Two-plex assay (CRP/Protein C)

Infection

- Chemotherapy causes loss of active immunity
- Patients have a "central line" and often become infected
  - Almost all patients become febrile
- Infection can lead to sepsis (bacteremia)
  - Frequently fatal
- Sepsis causes loss of control of coagulation
  - Patient can bleed to death
  - Or have disseminated intravascular coagulation (DIC)

Markers and indications

- Acute phase (cell death etc.)
  - CRP
- Inflammation
  - TNFα, IL-1b, IL-6β, IL-8
- Coagulation control (sepsis)
  - Protein-C
- Sepsis
  - Procalcitonin

Study design

- Each patient has 2-4 blood draws/day
- Samples managed by John Chadwick (UK Medical student)
- Theranos receives 2 mL blood per draw
- Blood and plasma assayed by Theranos system
  - Two instruments
  - Protein-C, CRP duplex assay
- Plasma assayed for all markers
  - Reference laboratories
- Clinical information collected
  - Patient status and therapy
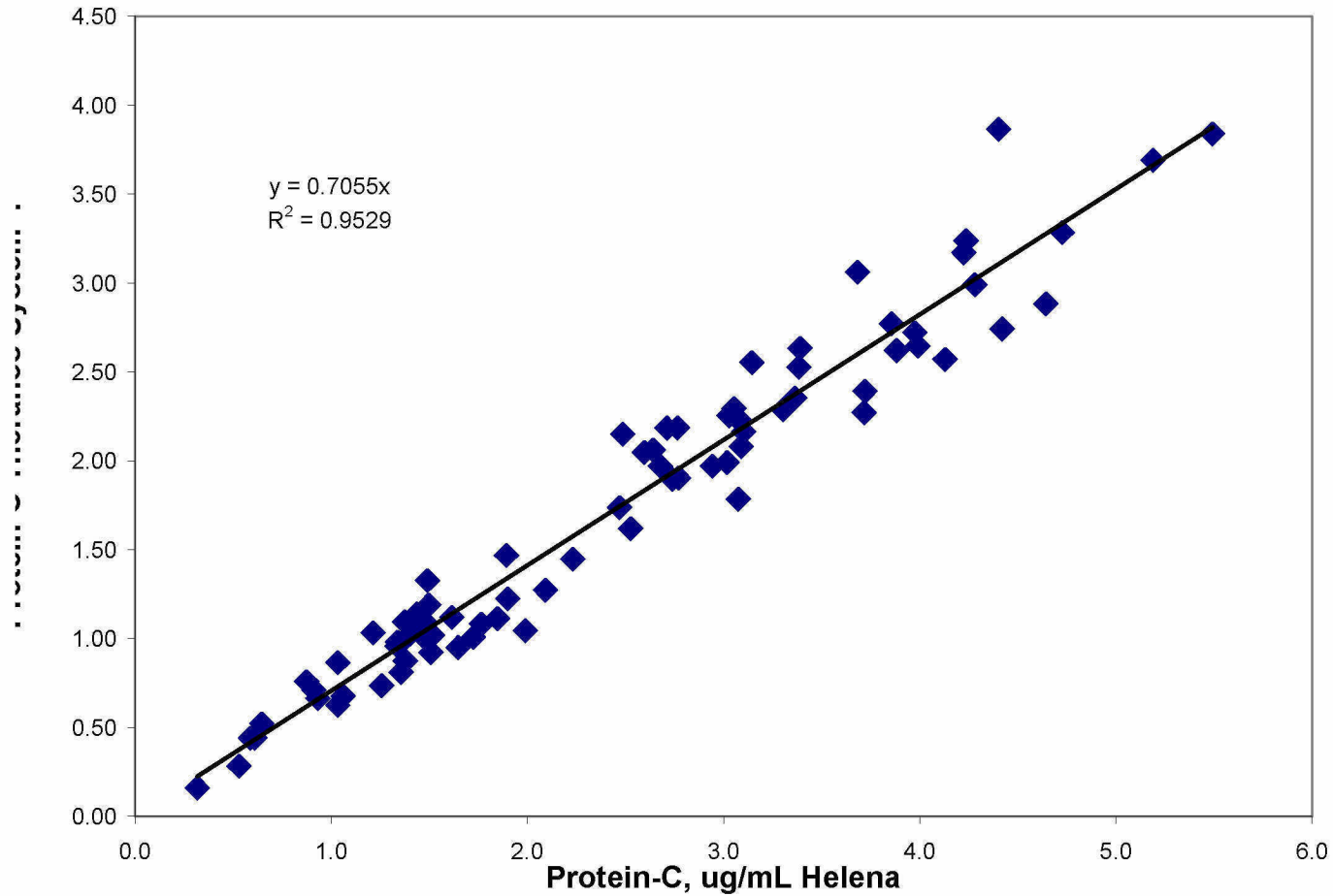 - All lab data + vital signs

Study status

- 18 patients enrolled
- 874 blood draws
- Blood analyzed at Theranos
- Study about 2/3 complete

Marker levels

- Protein-C
  - Normal 4 – 6 ug/mL
  - < 2 ug/mL is life threatening
  - < 1 ug/mL generally leads to death
- CRP
  - Normal < 3 ug/mL
  - Can increase to > 300 ug/mL in severe sepsis and other acute processes

Assay accuracy

Protein-C Assay correlation, Plasma

$y = 0.7055x$
$R^2 = 0.9529$

Protein-C, ug/mL Helena

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AML/Sepsis Trial: Blood samples

Assay accuracy versus reference

Protein-C Method Comparison

$y = 0.9404x + 0.0645$
$R = 0.95$

Protein-C, ug/mL in plasma Ref

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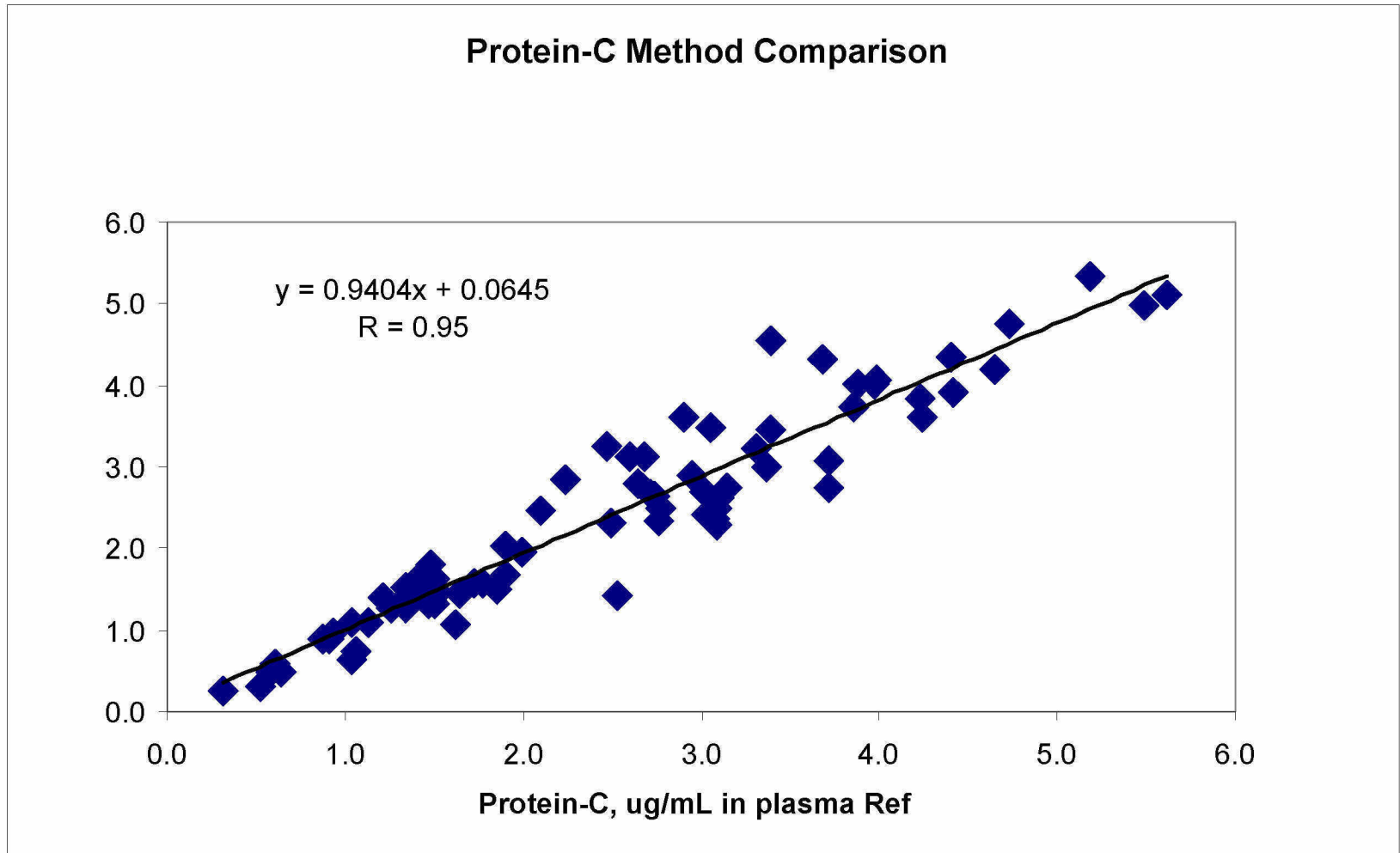
Patient 4

- 59 year man with newly diagnosed Precursor B cell ALL .

- Admitted with hypertension accompanying his disease.

- Given induction chemotherapy.

- Developed a severe infection and became septic after a biopsy of a throat lesion.

- Currently stable, in the ICU with some early signs of improvement.

Patient 4 ("Poster Patient")

Stanford Patient #004

Sepsis, Gram negative infection;

Patient in ICU

Protein C
CRP

Fever

Dangerously low
Protein-C

Patient regaining
coagulation control

Timepoint
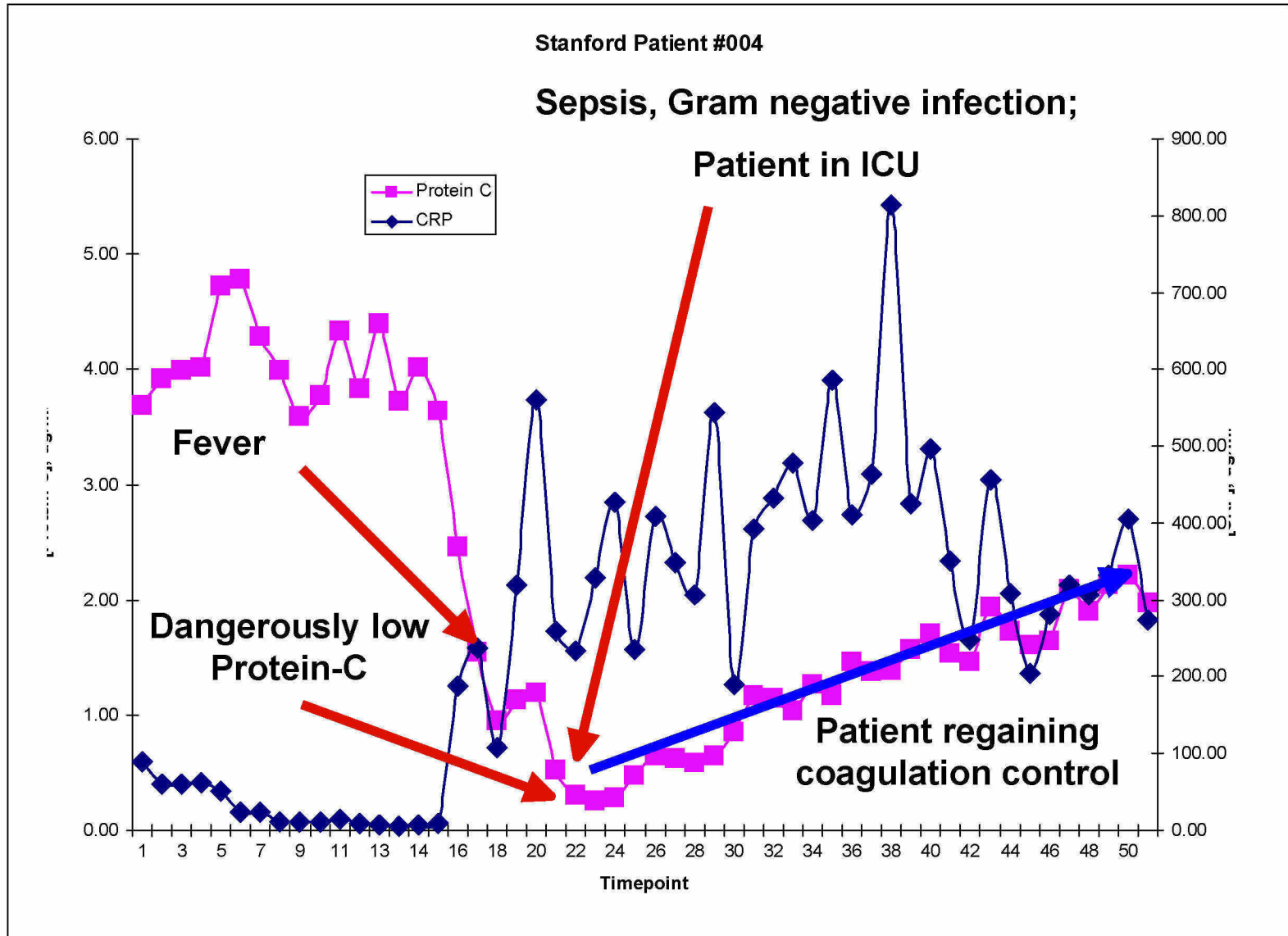
Patient 4: Relapse
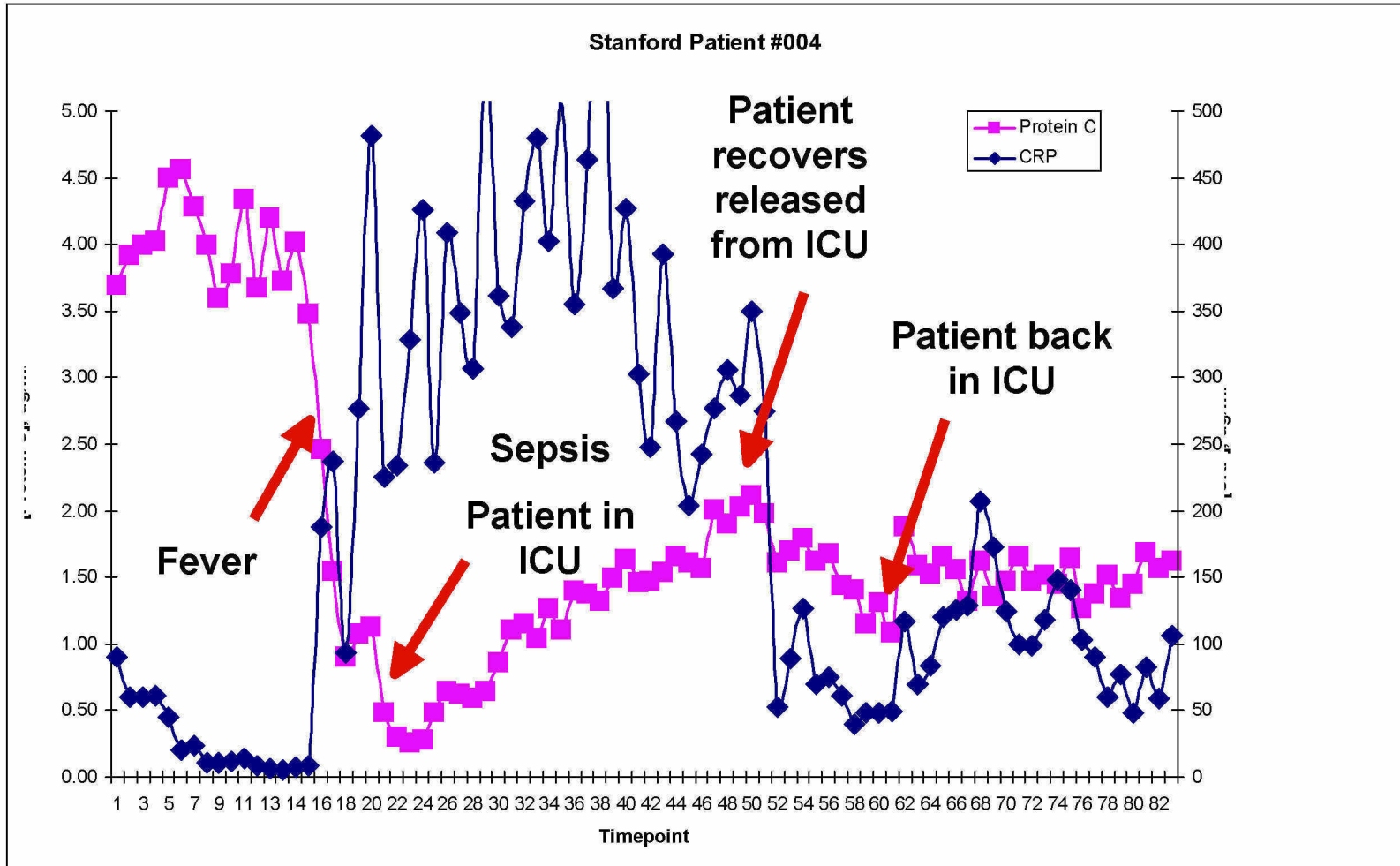
Multiple assays following disease and therapy Trajectory to sepsis

Data connected by time

Patient 4

Infection

Chemotherapy

Patient responding to antimicrobial therapy (in ICU)

Sepsis

Ln crp
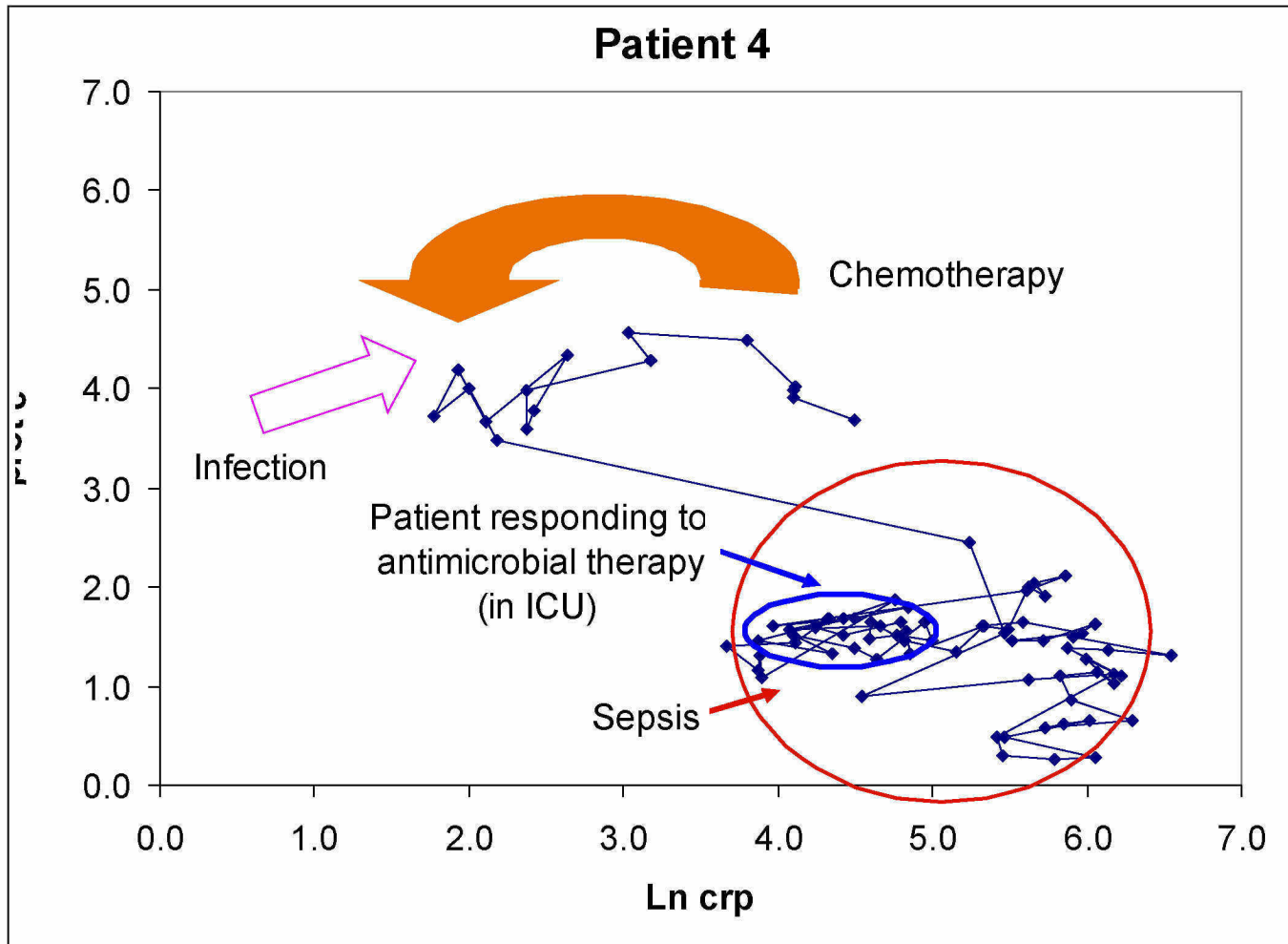
Patient 6
Febrile but no sepsis

Stanford Patient #006
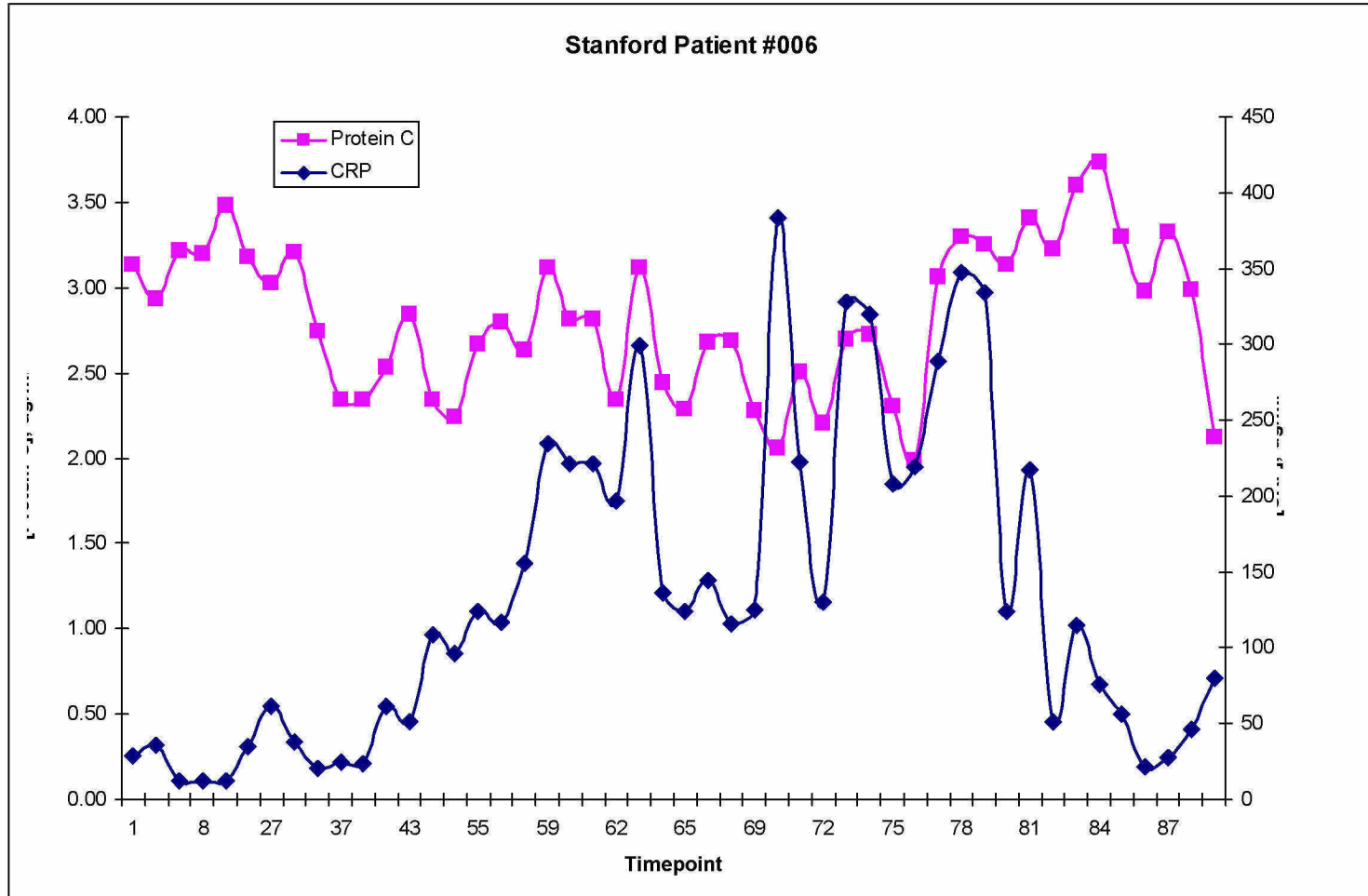
Generating statistical significance:
Stanford AML Study

- Number of analytes and possible outcomes mandate > 10 "evaluable" patients.

- Today we have less but we will be allowed to recruit subjects until we have 15.

- Analysis has begun with four evaluable subjects and two analytes.

Results from blood and plasma track
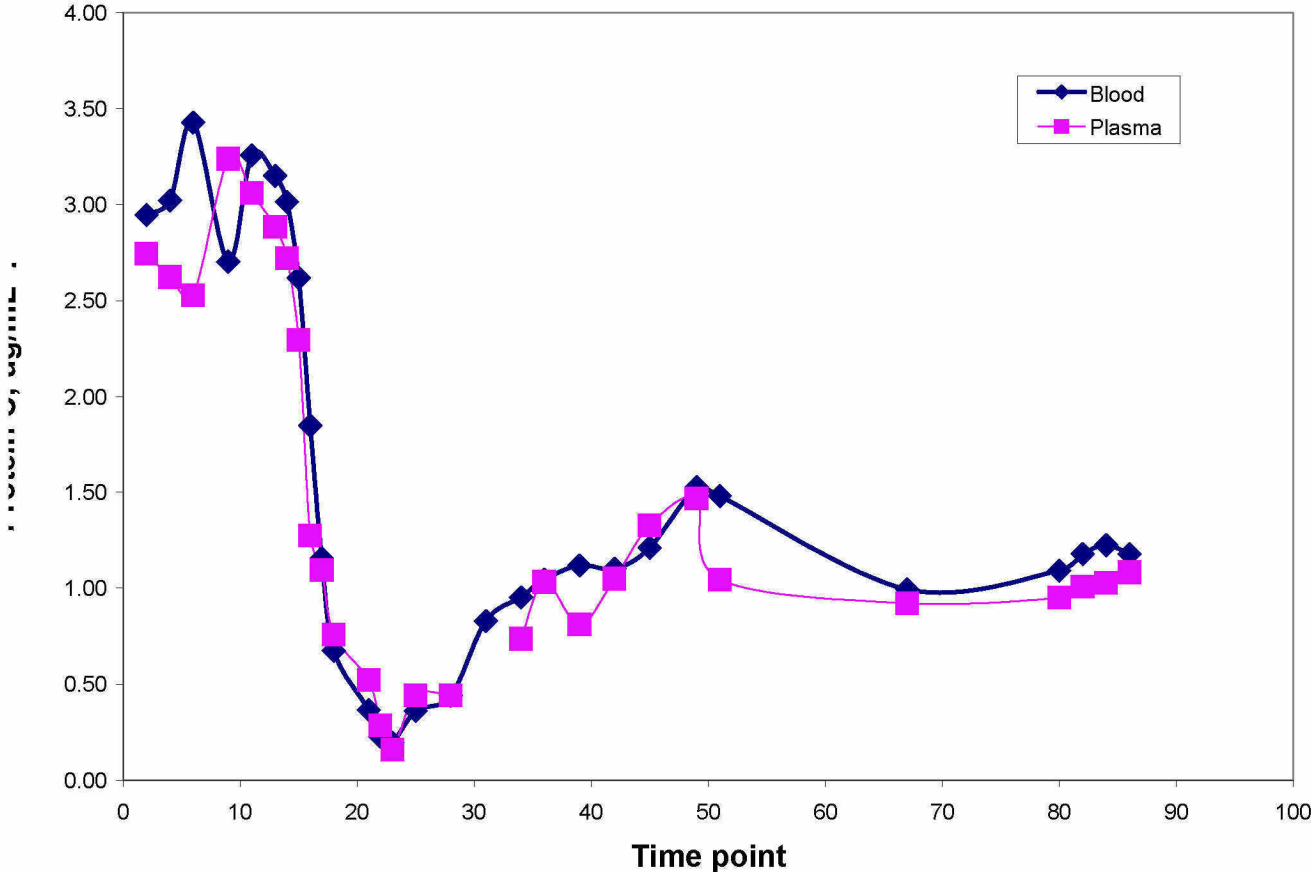

Log value time course: CRP Patient 4
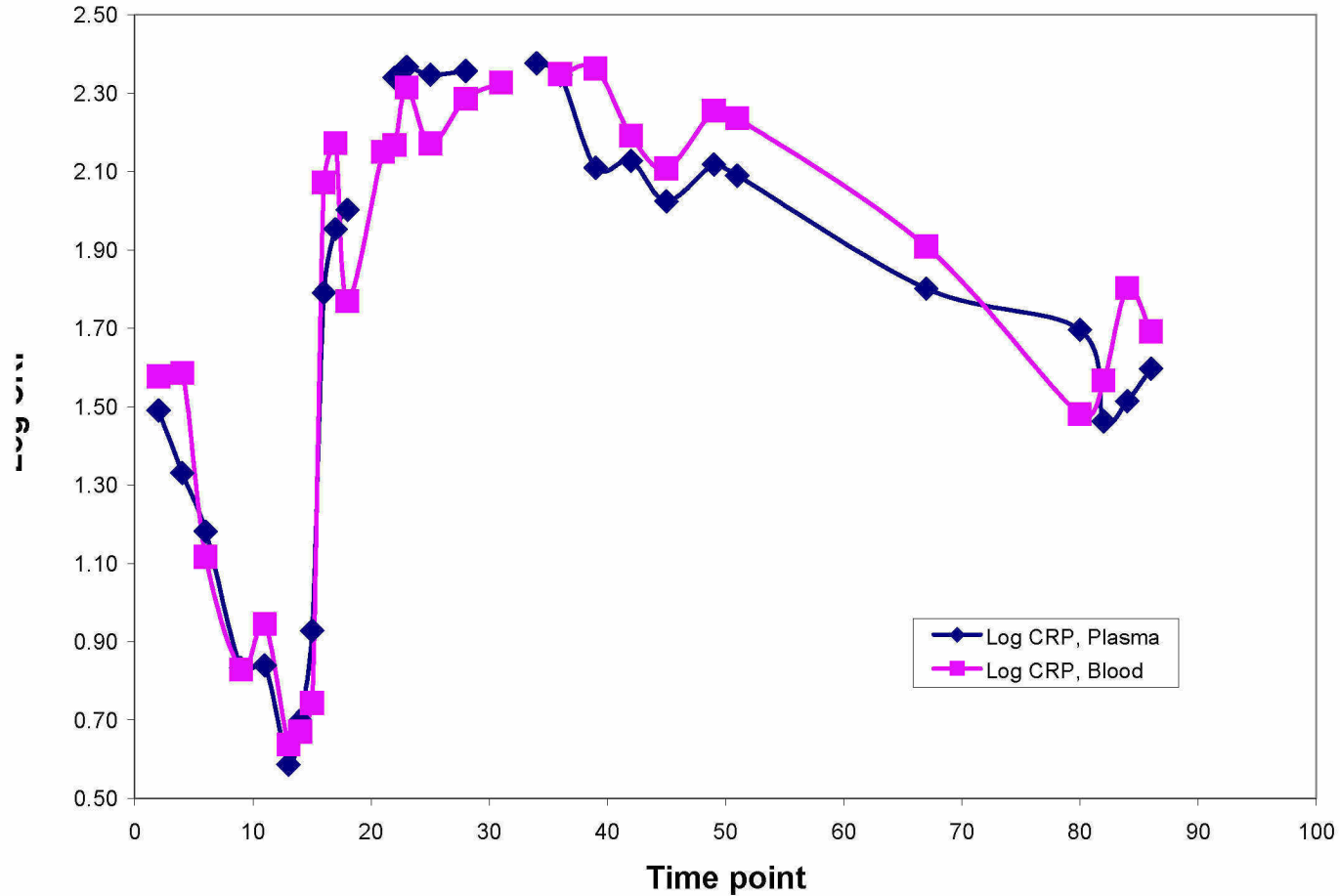
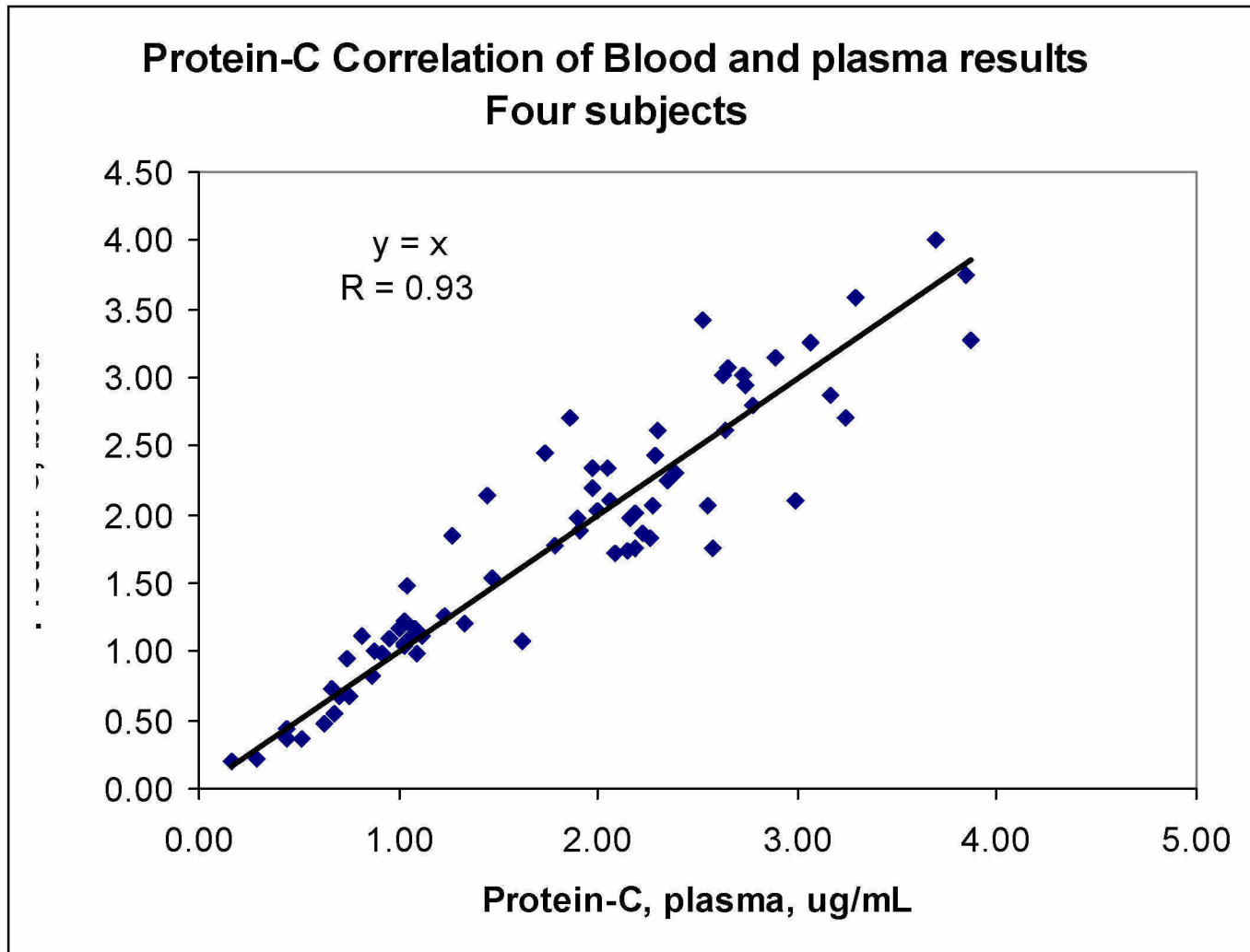# Patient 1: Plasma and blood

Patient 1
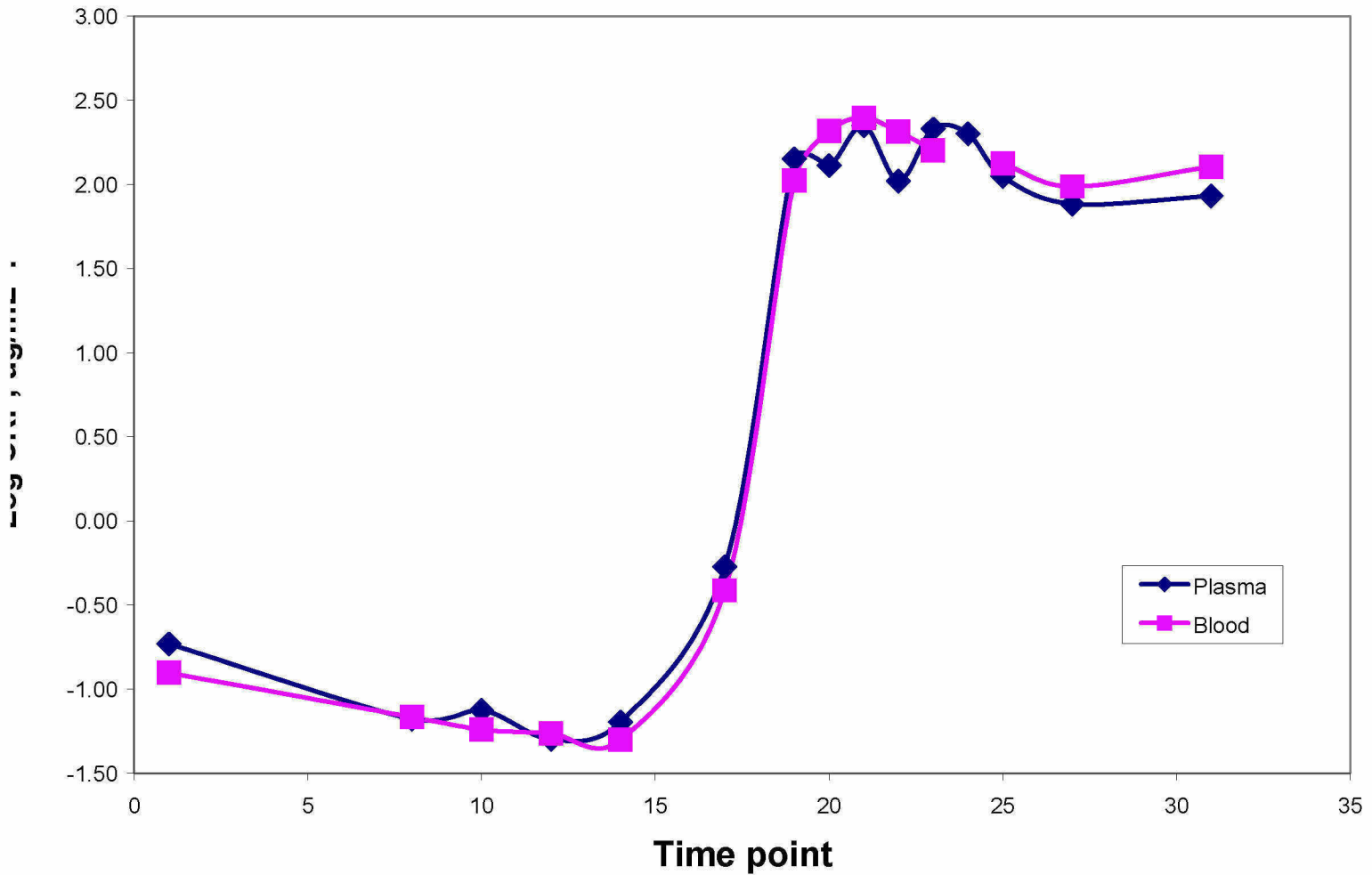
Blood versus plasma: Protein-C assay

Protein-C results: Patient 4 time course

Correlation of Protein-C results for blood and plasma

Protein-C Correlation of Blood and plasma results
Four subjects

y = x
R = 0.93

Protein-C, plasma, ug/mL

Precision of replicate signal data Stanford Clinical study

Each assay uses two tips for the sample and two for a control
Replicate results improve reliability and show how precise the system is
Data gathered over one month with 360 cartridges show calibration is stable

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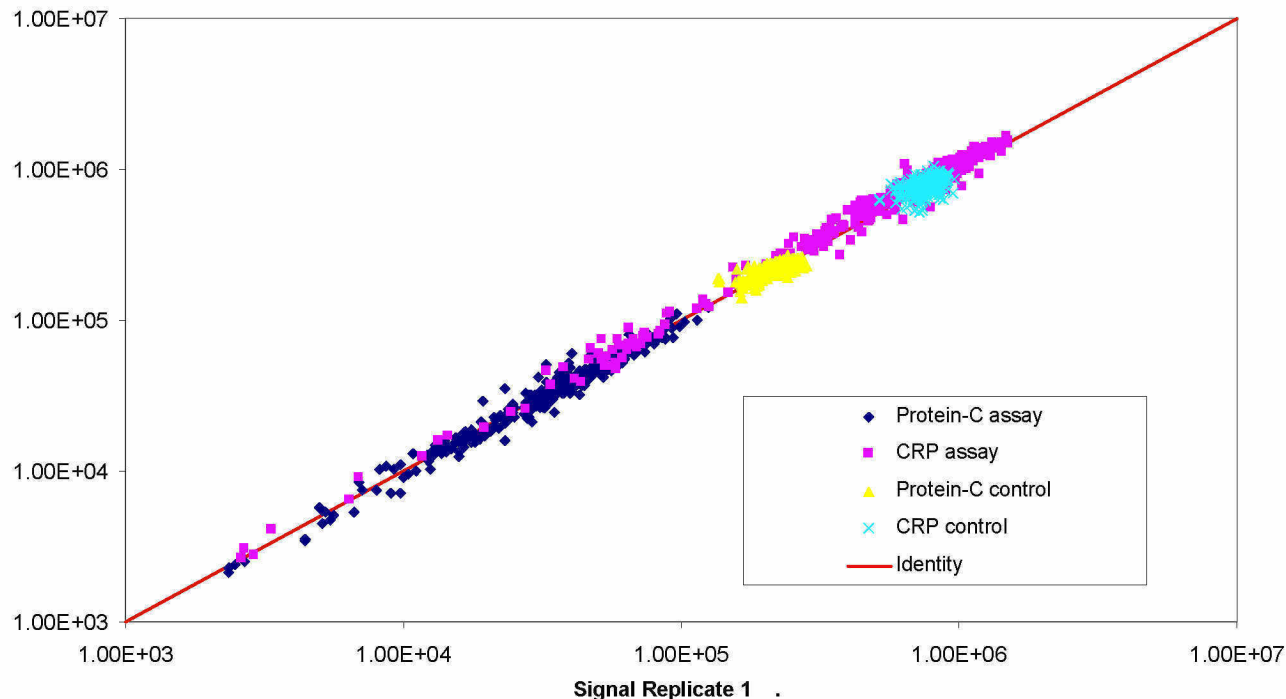
AML/Sepsis Study Conclusions

- Very clear patterns of disease progression, remission and effects of therapies are apparent.

- Good correlations with outcomes are apparent

- The samples will provide an excellent database for prognostic algorithm development and clinical assay validation.

- Assay results have been precise

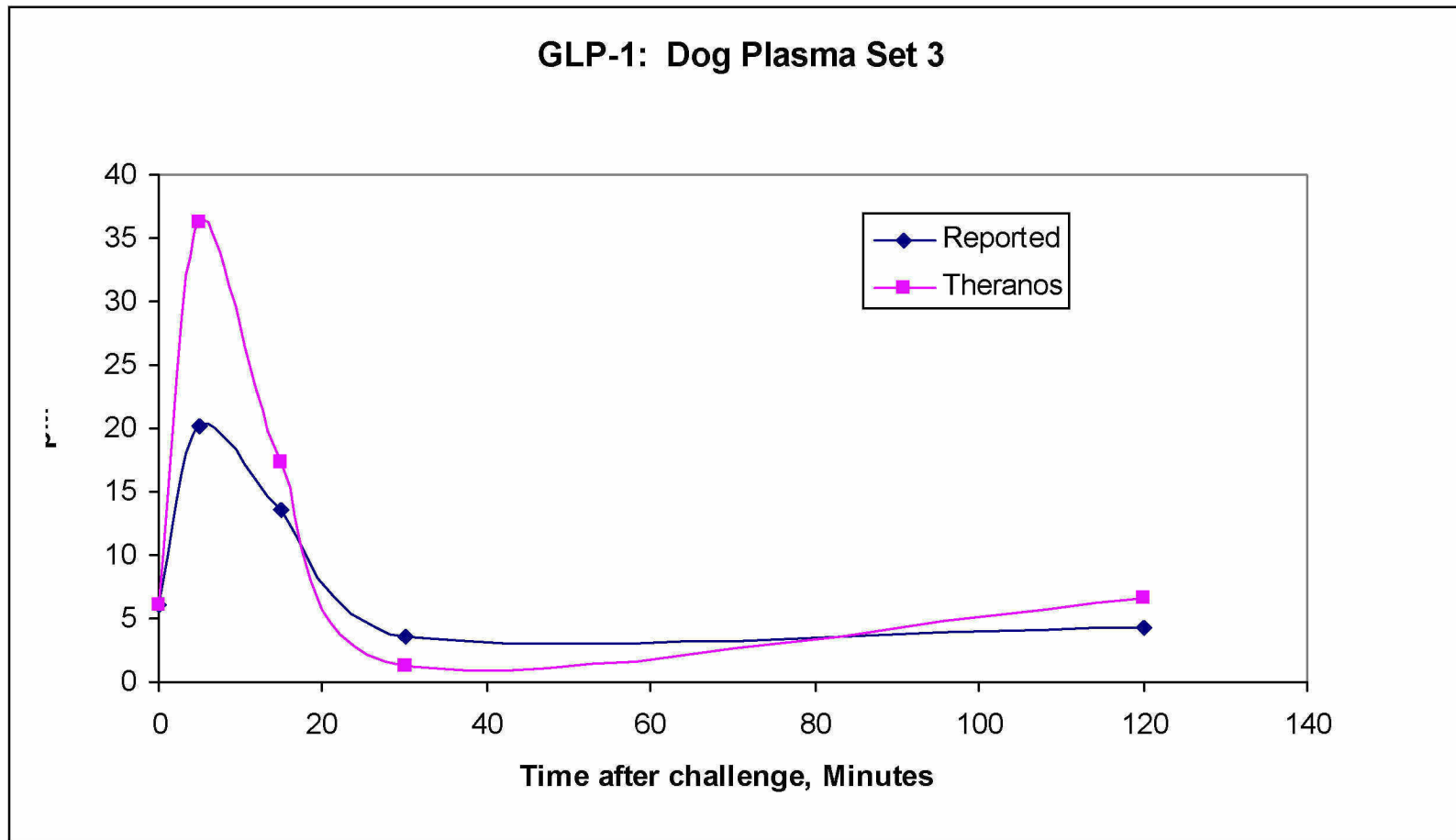- Study is about two thirds complete

Biomarkers of metabolism

Diabetes therapy

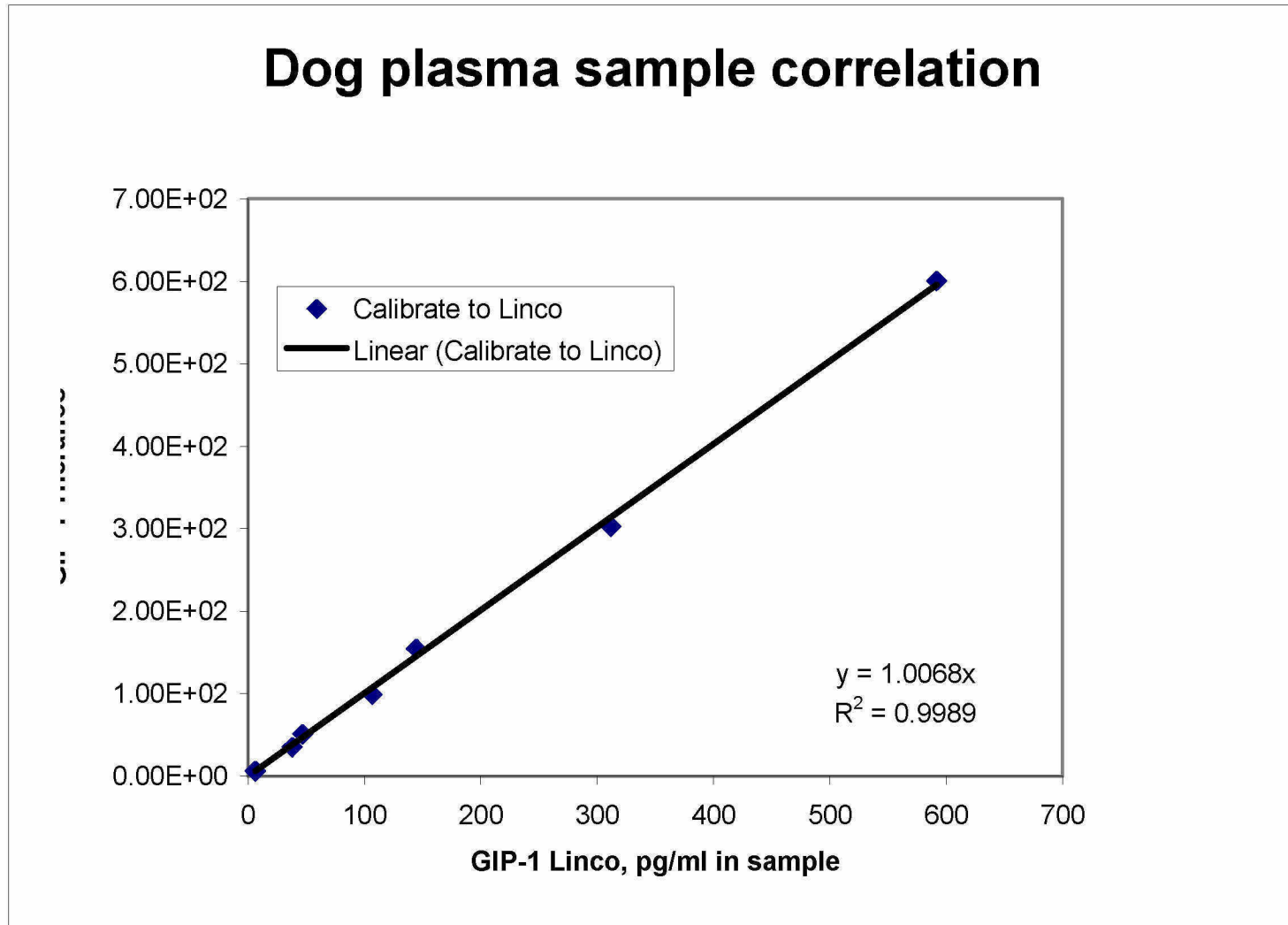## Use of human and animal models in phase 1 studies of drug therapy

Animal Studies

- Model is Dogs
- Challenge with glucose
- +/- Drug
- Measure hormone level kinetics
  - GLP-1, C-peptide
  - Short time course
  - Very unstable analyte (GLP-1
  - Samples are plasma
- Reference assays in ELISA kits
  - LOD 6 pM
  - Assays cannot be done in blood
- Theranos assays in instrumented system
  - LOD 1 pM
  - Assays can be done in blood

Study 2: Kinetics of Hormone Release

GLP-1: Dog Plasma Set 3

Correlation of results with predicate method

Dog plasma sample correlation

$y = 1.0068x$
$R^2 = 0.9989$

GIP-1 Linco, pg/ml in sample

Legend: ◆ Calibrate to Linco — Linear (Calibrate to Linco)
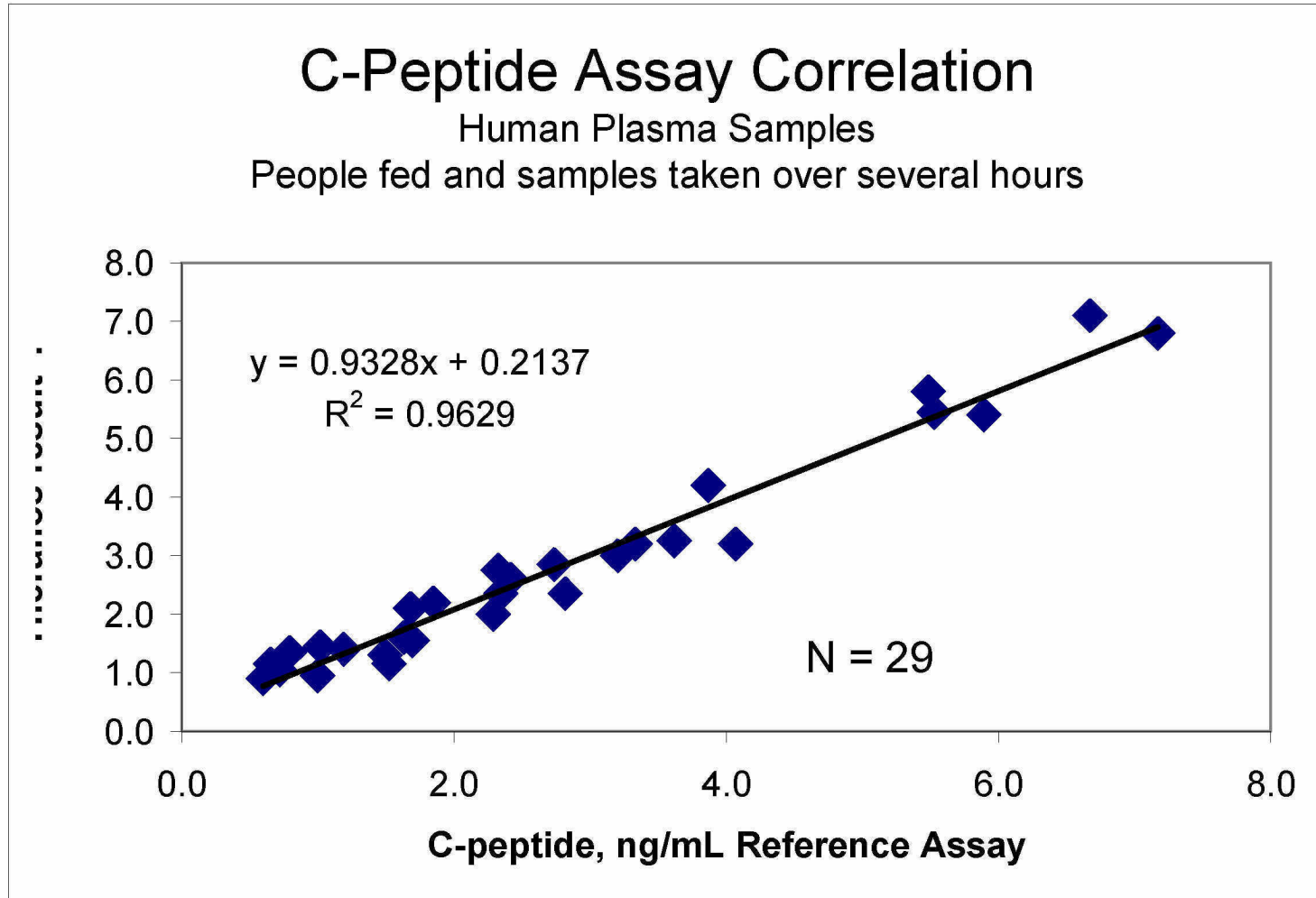
Conclusions

- We followed the time course of hormone (GLP-1) release and elimination in archived (frozen) plasma samples

- Results generally agreed with reference method.
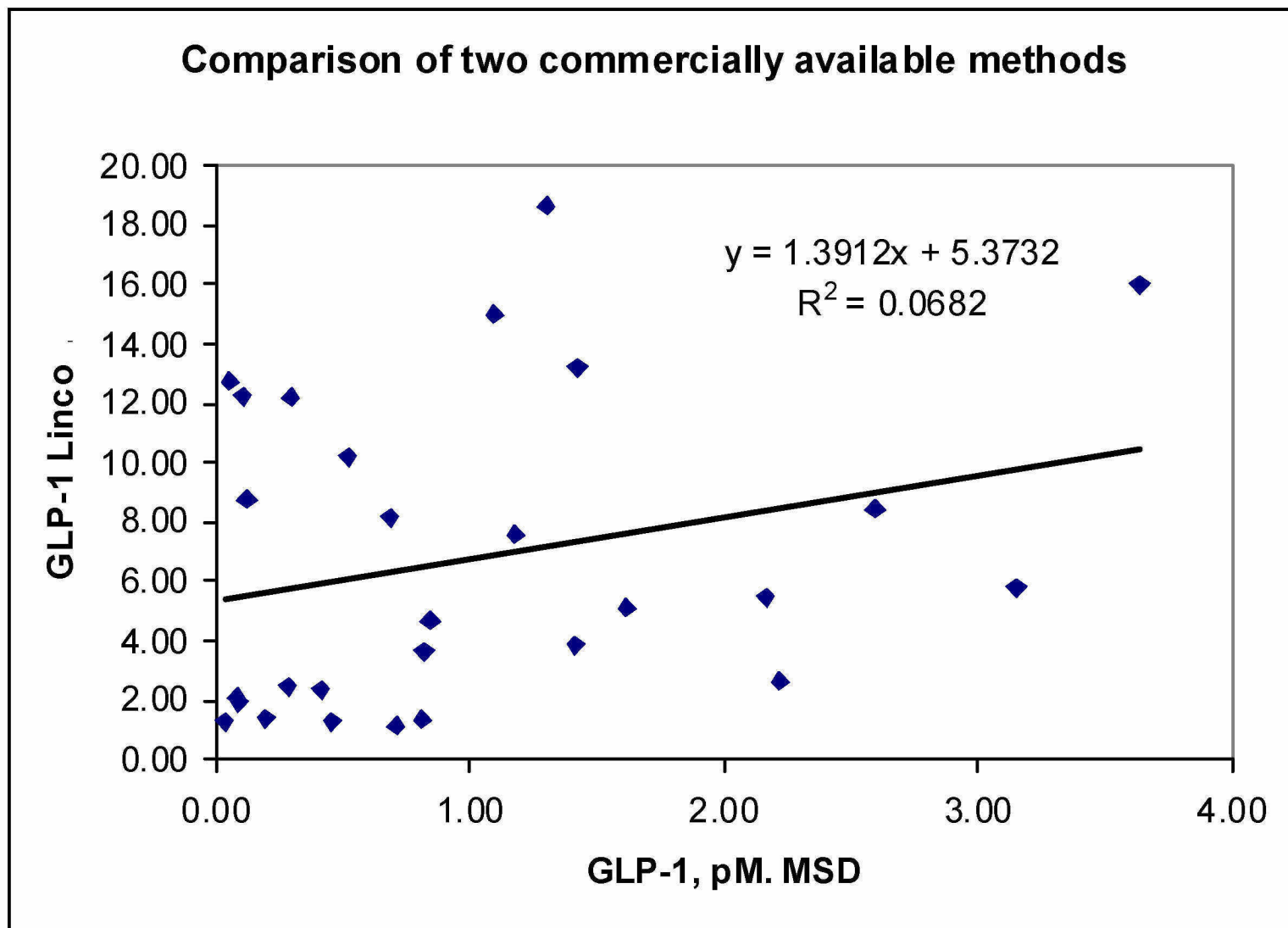
- Method will work for:
  - Humans
  - Rodents
  - Dogs

Human studies

- Assays conducted at remote site
- Archived plasma samples
- Pre and post-food challenge
- Hormones GLP-1 and C-peptide measured
- Levels close to or below the limit of the reference method
- Multiple Theranos instruments

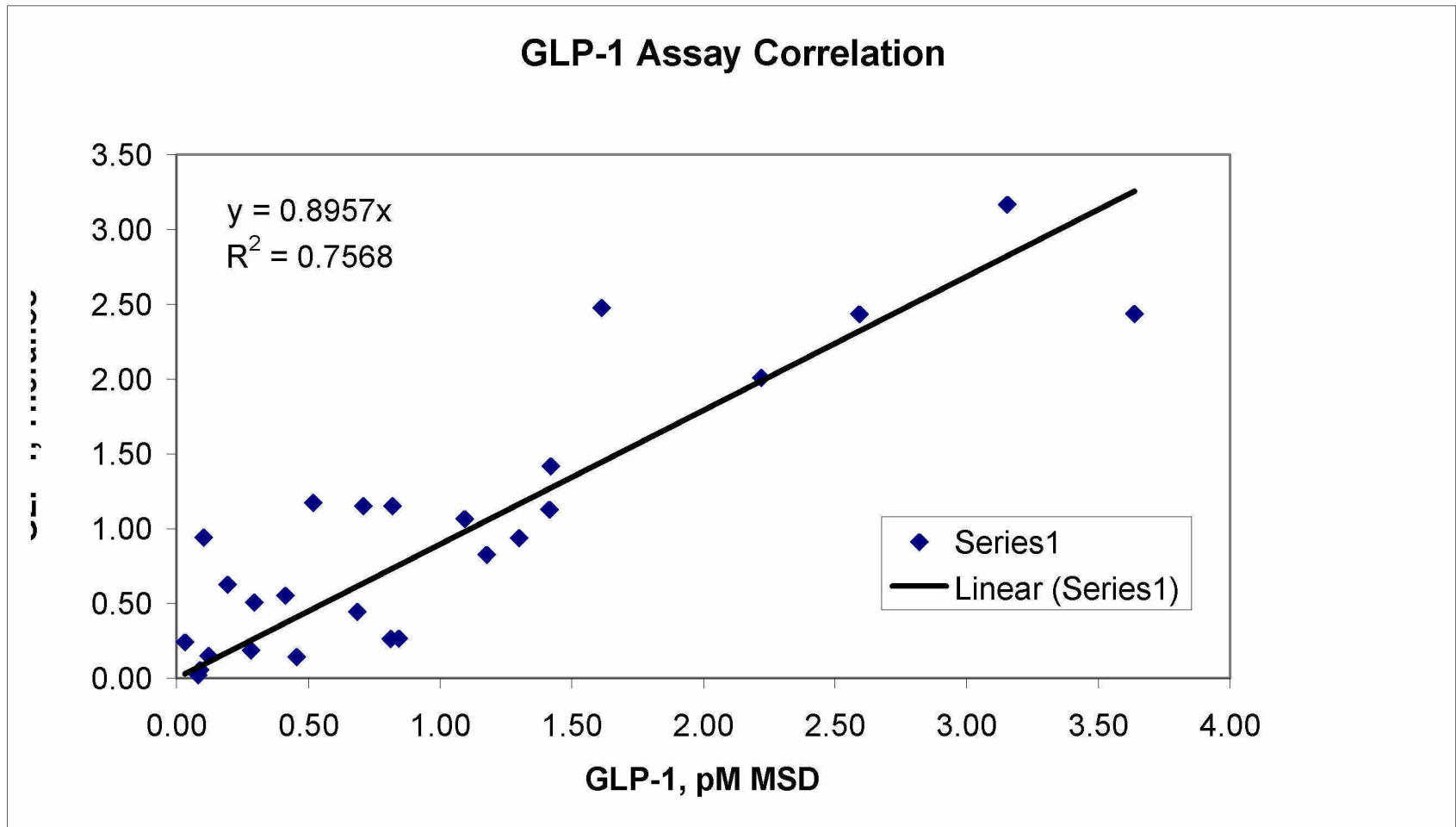# Data from external clinical studies (Drug companies)

C-Peptide Assay

C-Peptide Assay Correlation
Human Plasma Samples
People fed and samples taken over several hours

$y = 0.9328x + 0.2137$
$R^2 = 0.9629$

N = 29

C-peptide, ng/mL Reference Assay

How well do other companies do with difficult assays like GLP-1?

Comparison of two commercially available methods

$y = 1.3912x + 5.3732$
$R^2 = 0.0682$

GLP-1 Linco (y-axis)
GLP-1, pM. MSD (x-axis)

GLP-1 Assay: Method Comparison

Human subjects metabolic challenge

GLP-1 Assay Correlation

$y = 0.8957x$
$R^2 = 0.7568$

Series1
Linear (Series1)

GLP-1, pM MSD

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Human Pre-clinical Trial

Time course of hormone release

Legend:
- ◆ MSD
- ■ Theranos

X-axis: Time point (0 to 7)
Y-axis: 0.0 to 3.0
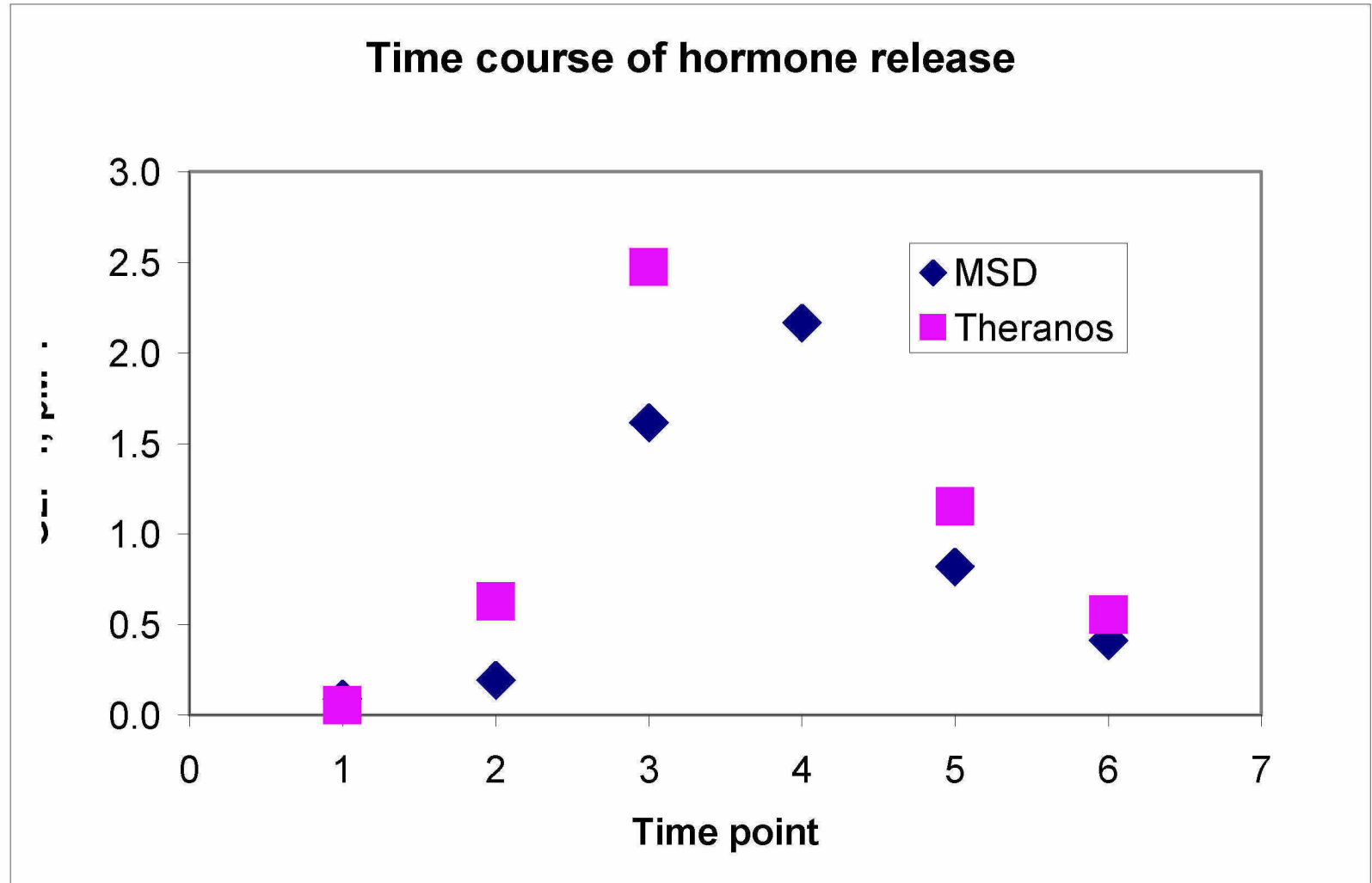
Subject 264: GLP-1

Subject 264
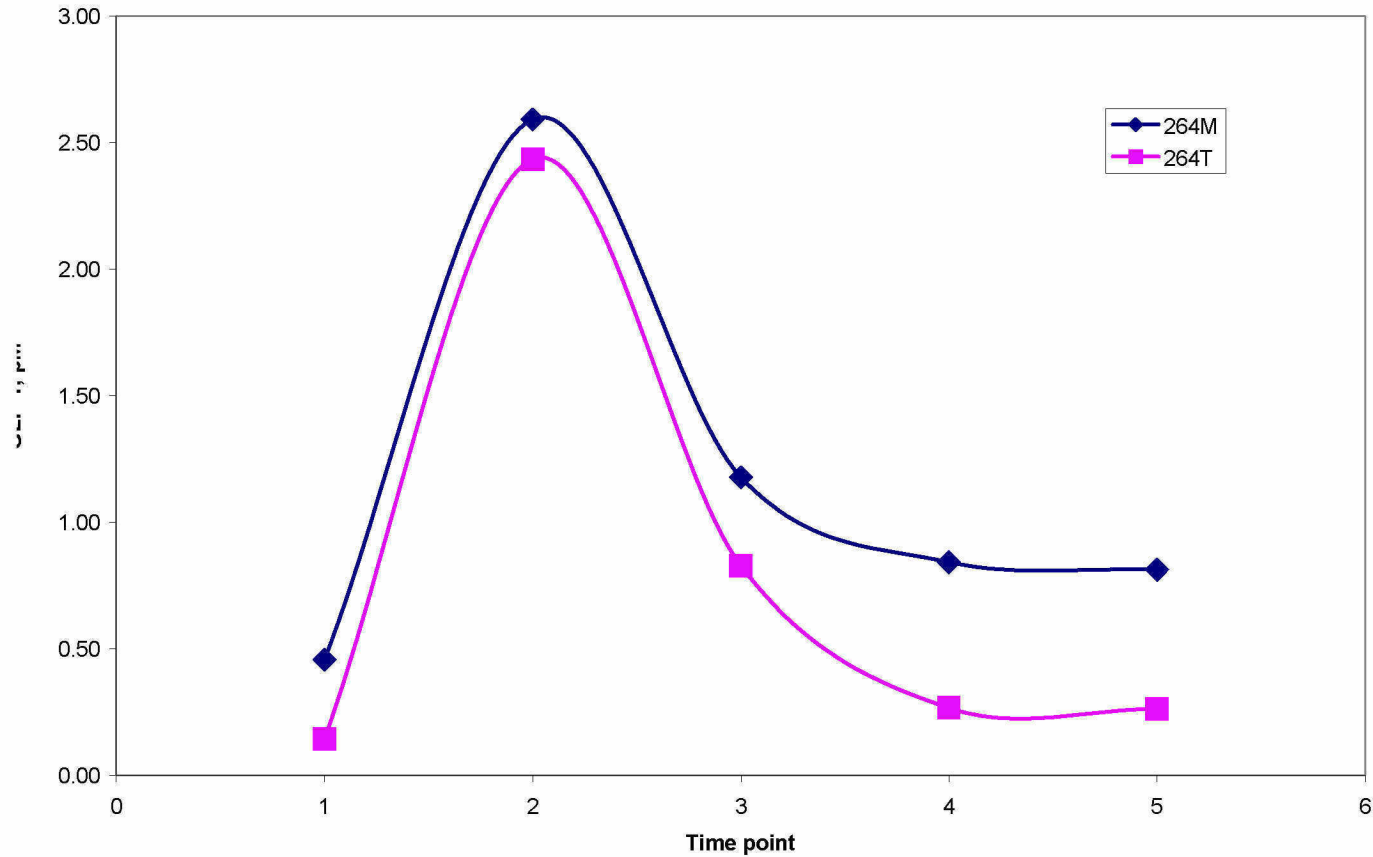
Subject 269: GLP-1

Subject 269

Subject 249: C-Peptide

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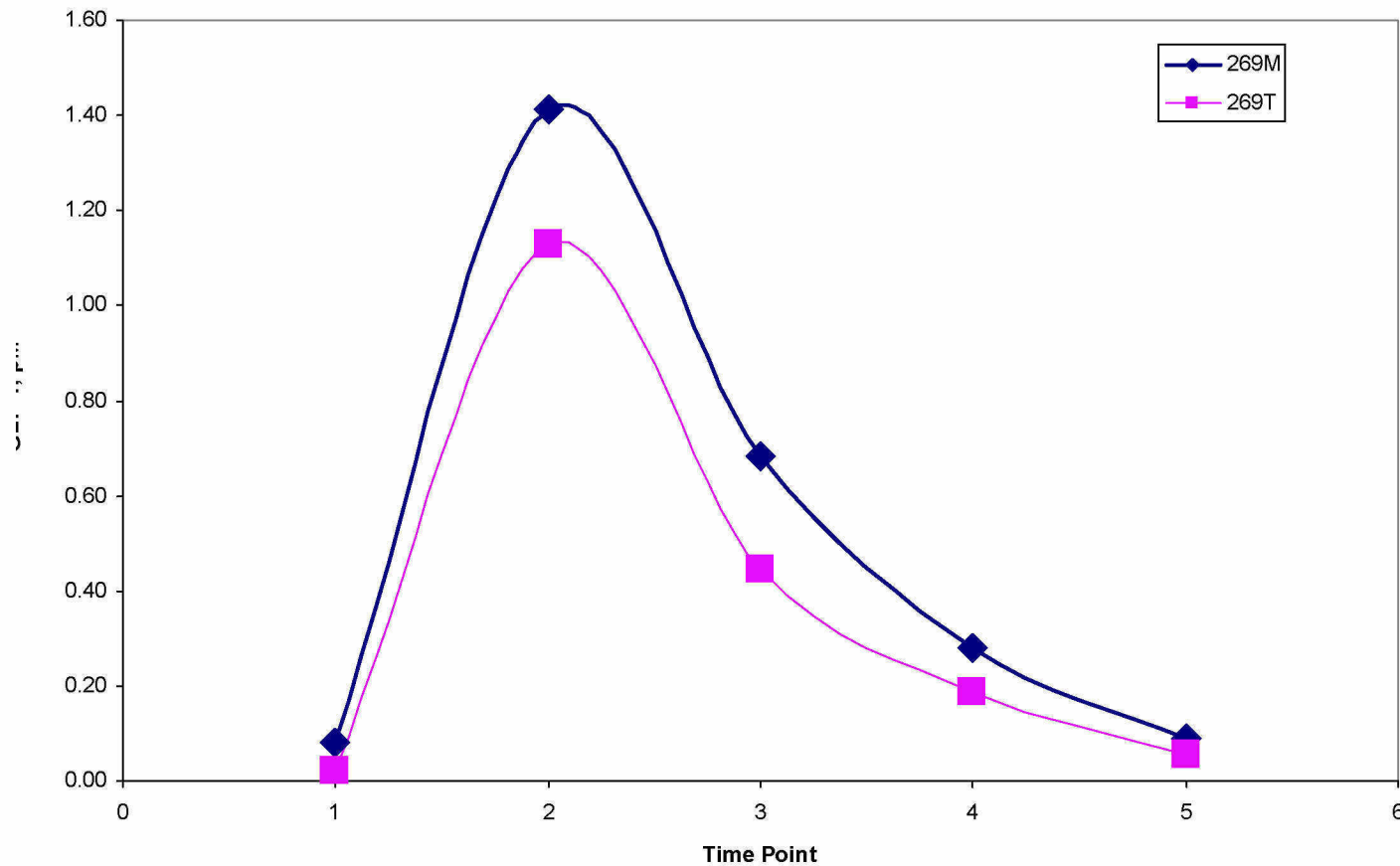
Subject 249: C-Peptide

249
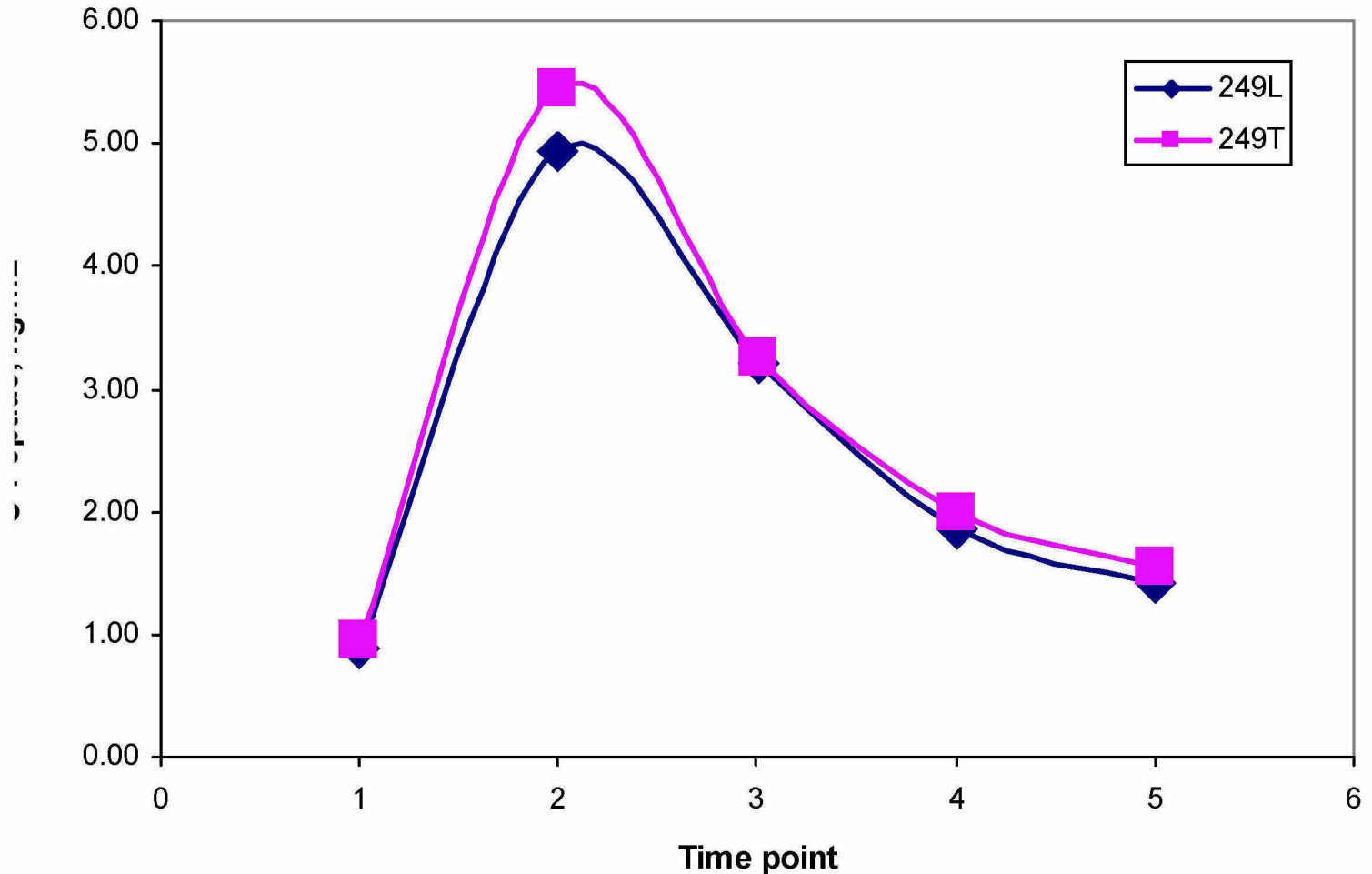
People respond differently
Multiplexed measurement of GLP-1 and C-peptide
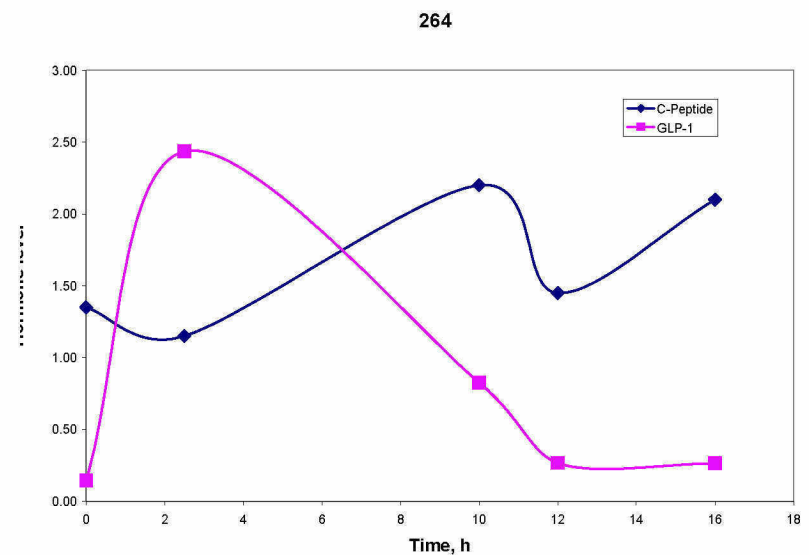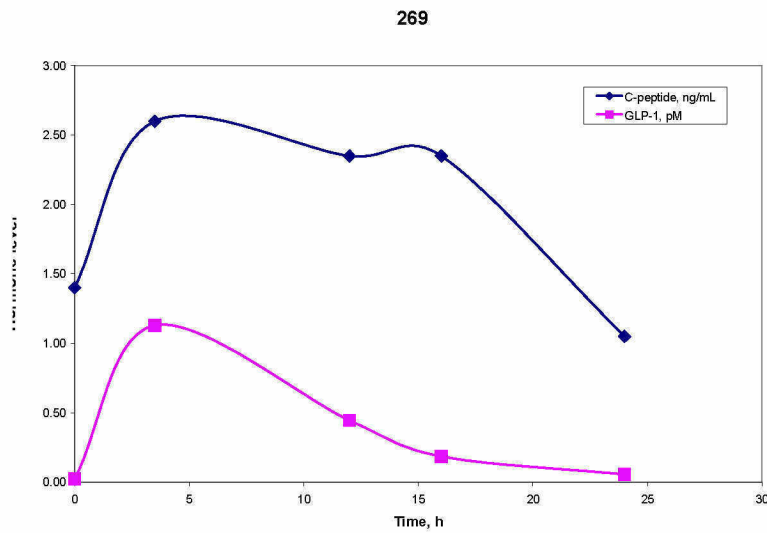
Using the server: Customer view

Theranos Server Output

Time Series Chart

Patient ID: 004
Click the image to view the large image in another window.

Protein C
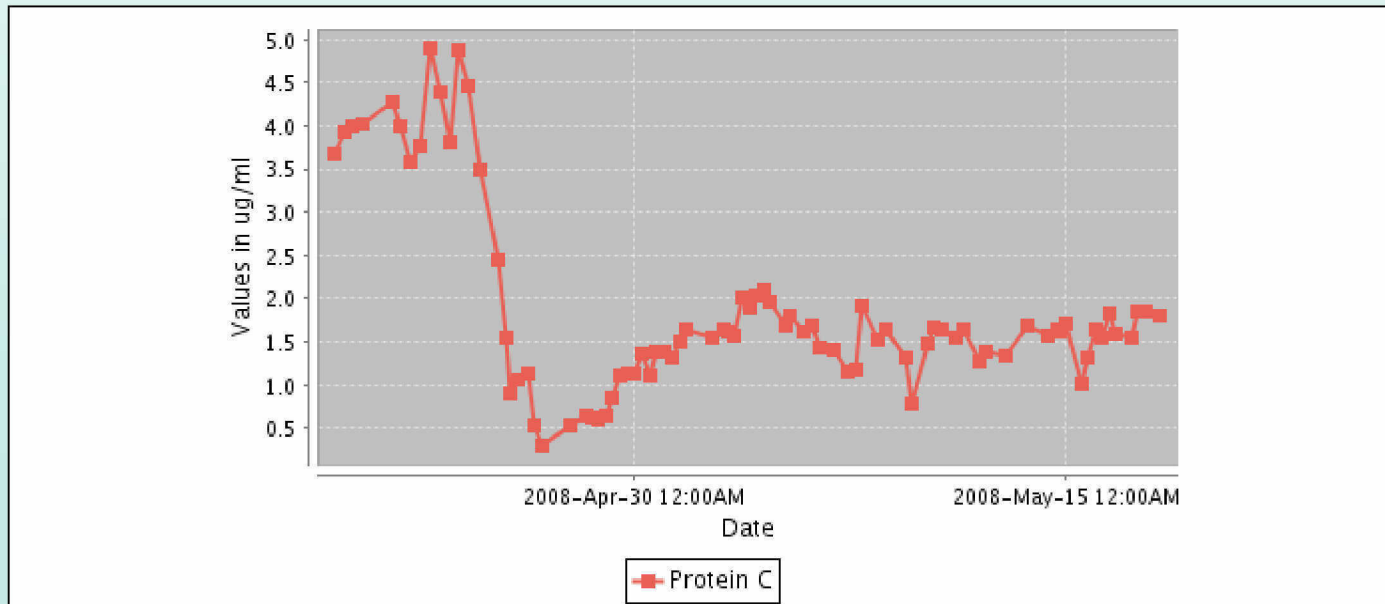
Export As CSV | Tabular Format | Chart Format
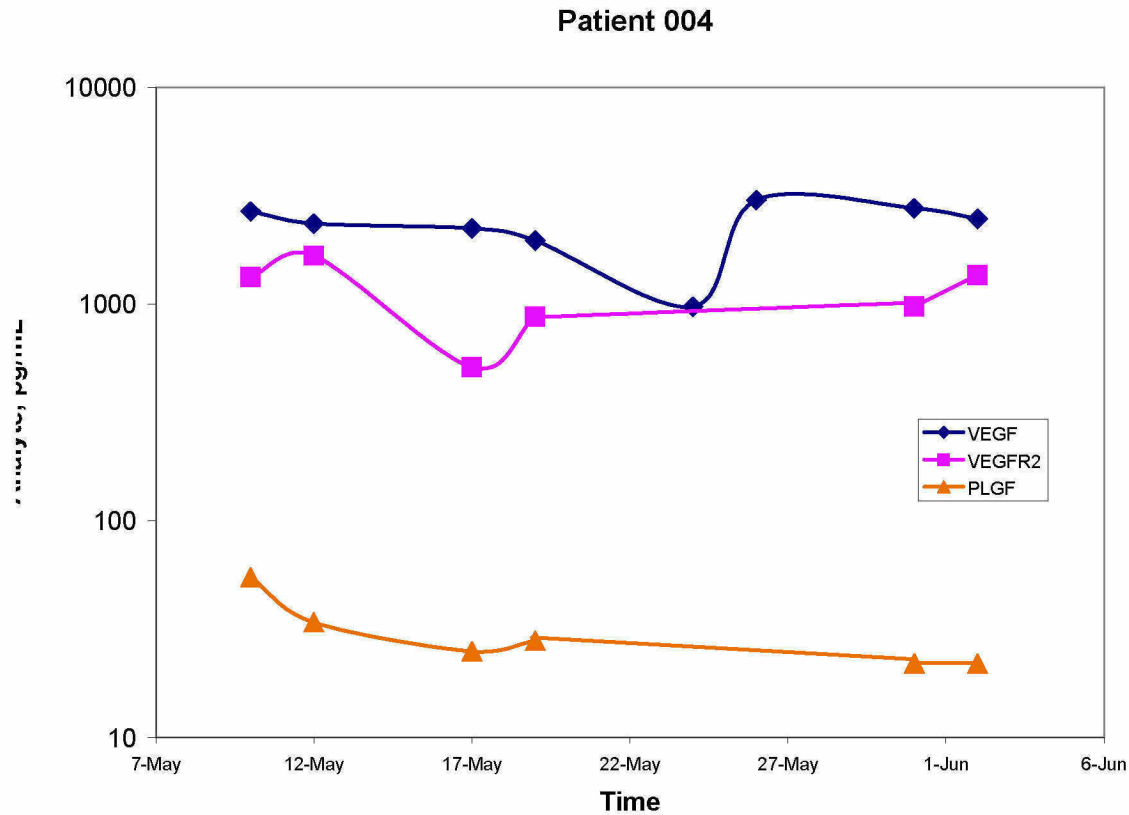
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Angiogenesis

- Many anti-tumor drugs target angiogenesis
- To grow, tumors must vascularize
- Markers are:
  - Vascular Endothelial Growth Factor (VEGF)
  - sVEGF Receptor (VEGFR2)
  - Placental growth factor (PLGF)
- All assays require high sensitivity and a wide dynamic range

Tennessee Oncology Study

- Theranos Instruments in patient's homes
- Fingerstick samples
- Analyte Ranges
  - VEGF (15 – 8,000 pg/mL)
  - sVEGFR2 (170 – 10,000 pg/mL)
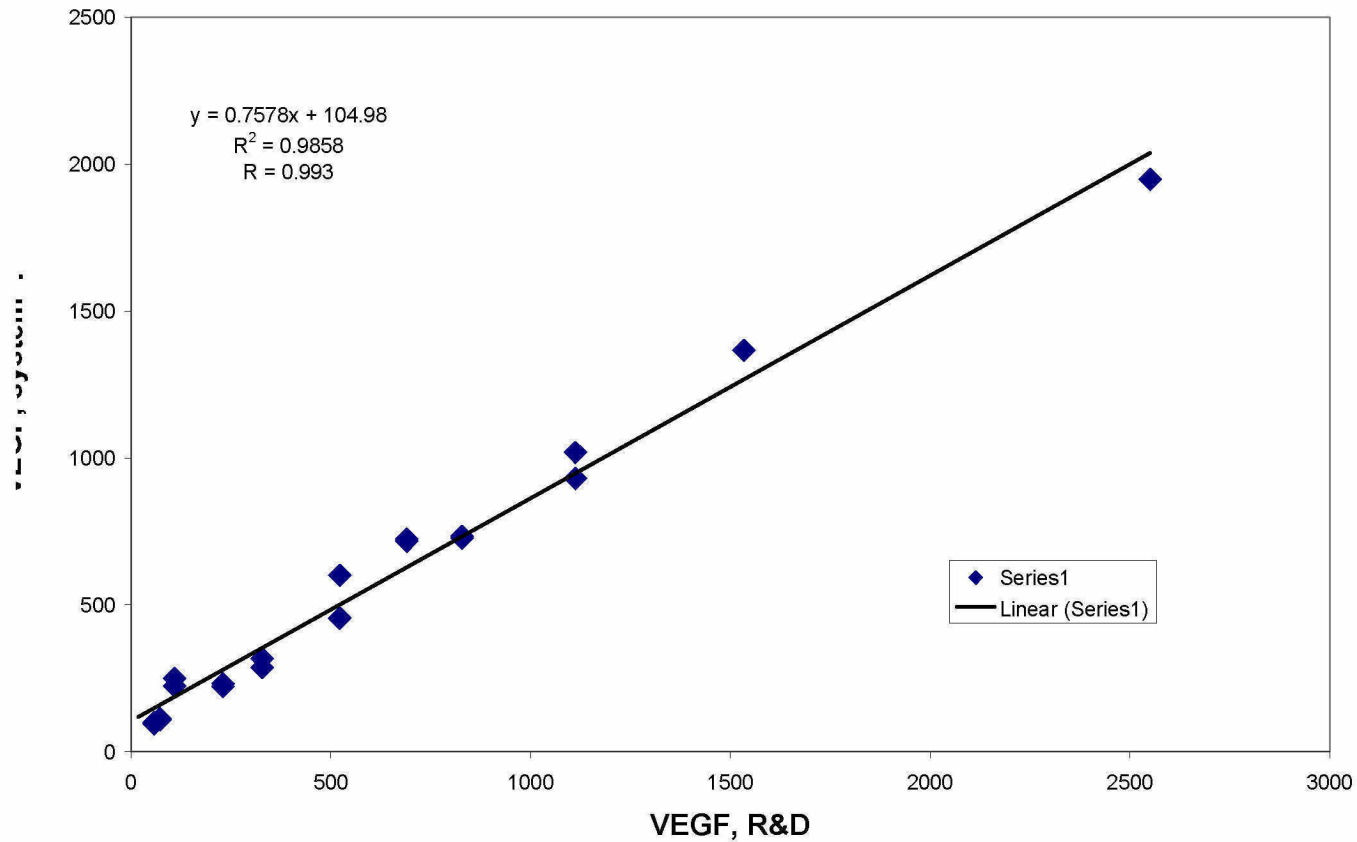 - PLGF (17 -750 pg/mL)

Monitoring Three Biomarkers of Angiogenesis
Cancer Outpatients

Patient 004

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Analytical Validation

(plasma samples)

VEGF clinical results

$y = 0.7578x + 104.98$
$R^2 = 0.9858$
$R = 0.993$

Legend: Series1 (◆), Linear (Series1) (—)

X-axis: **VEGF, R&D**

Possible response to Avastin Therapy (anti-VEGF)
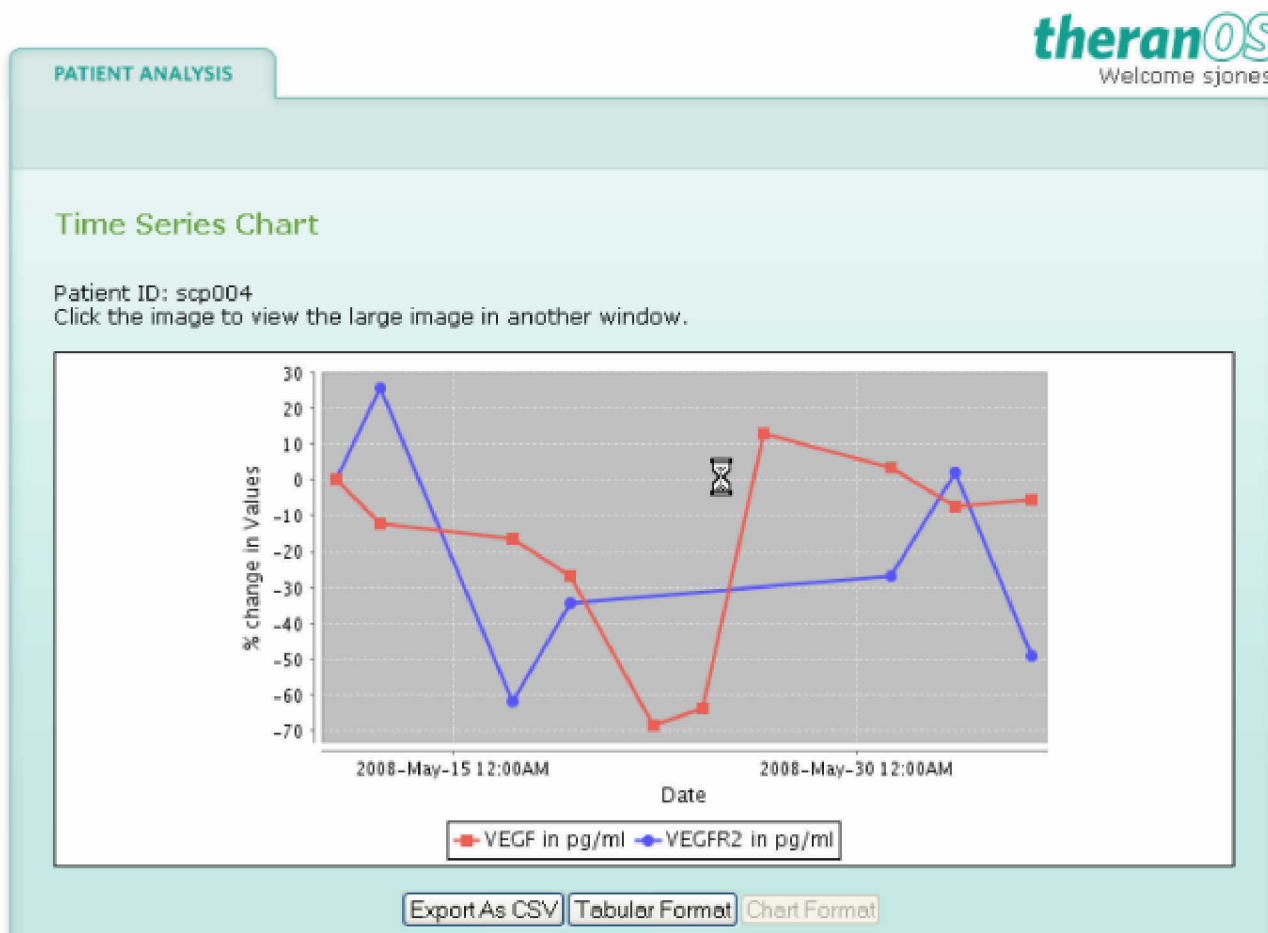
Osteoporosis Therapy

Scenario

- ## Novartis drug Reclast (zoledronic acid)
  - IV dose yearly
  - Used for cancer
  - Also being used for Osteoporosis
  - Zoledronic acid causes changes:
    - TNFα
    - IL-6
    - Other inflammatory cytokines

Theranos Evaluation

- Archived samples from Novartis
- Represent time courses following infusion
  - Several patients
- Markers measured in the Theranos system
  - IL-6
  - TNFα
  - CRP

Typical results for one subject

Patient "DMC"

Infusion

- IL-6 pg/mL
- CRP ug/mL
- TNFa pg/mL

Time Point (hours)
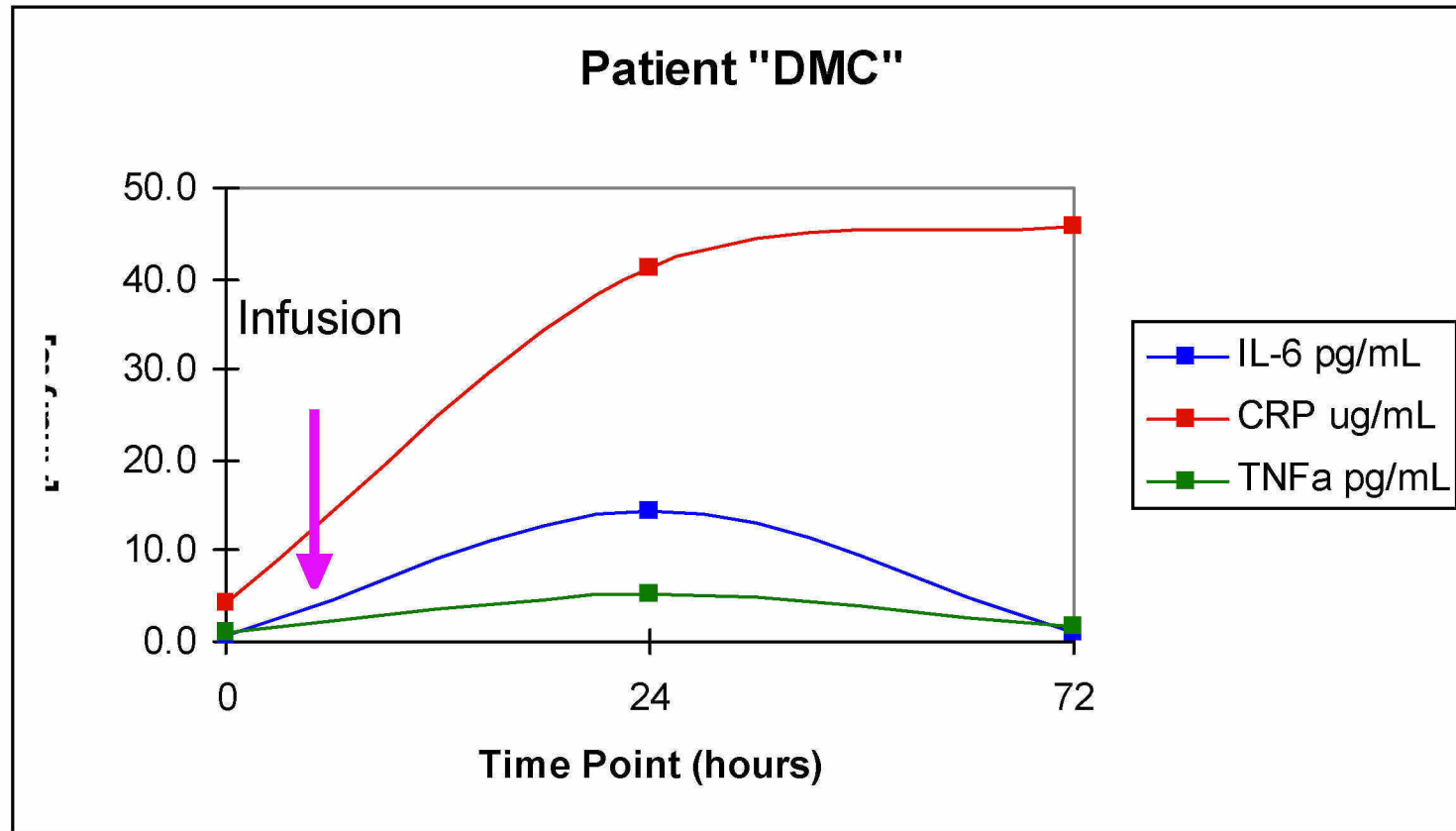
Huge variation between subjects
Both absolute levels and changes over time vary greatly