Academic Panel Session

DDT-KD Consortium

"Academic Insights for Biomarker Priorities and Candidate Pilot Project(s)"

Moderators:

Dr. Chirag Parikh (Yale)

Dr. Kumar Sharma (UCSD)

Panelists:

Dr. Ronald Perrone
(Tufts Medical Center)

Dr. Paul Palevsky
(Univ. of Pittsburgh School of Medicine)

Dr. Hiddo J. Lambers Heerspink
(University Medical Center Groningen)

Dr. Joseph Bonventre
(Brigham and Women's Hospital, Harvard)

Drug Development Tools for Kidney Disease

The PKD Outcome Consortium: A Success Story

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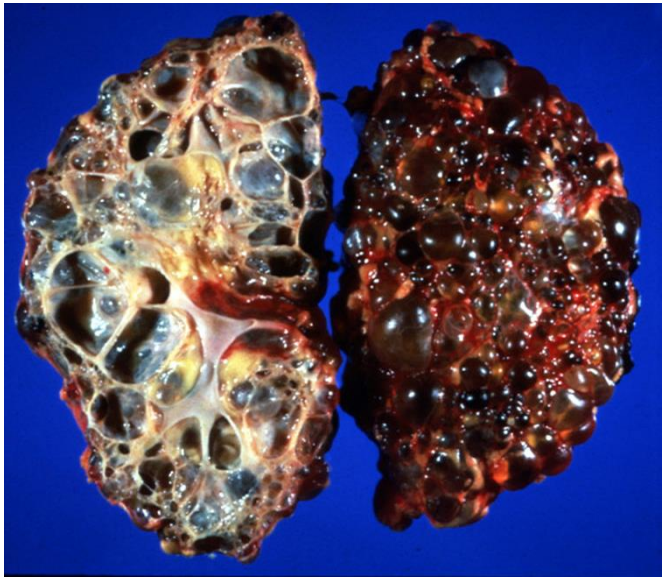
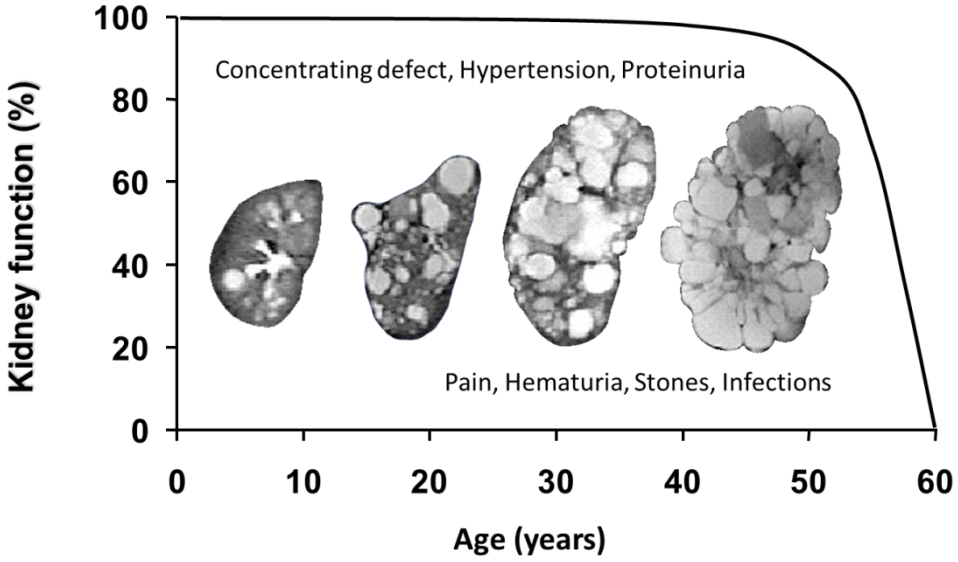
Dr. Ronald Perrone
Tufts Medical Center

The PKD Outcome Consortium: A Success Story

DDT-KD Consortium

- Progression of ADPKD to ESRD takes on average 56 years
- The manner of progression is such that kidney function (GFR or glomerular filtration rate) remains stable for many years, while enormous structural derangement of kidneys occurs
- Earlier biomarkers of kidney progression are needed





The Approach

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- Our goal was to create disease progression models to generate scientific consensus on the utility and reliability of total kidney volume (TKV) as a biomarker and clinical endpoint for the progression of ADPKD
- Multiple meetings with FDA, beginning 5/17/07
- Recommendation from FDA to construct disease model to ascertain linkage between TKV and rate of size increase and common secondary features of ADPKD
- Recognition that data residing in existing registries and being collected in ongoing clinical trials is not in a standardized format
- ***Collaboration with CDISC and C-Path to standardize data***

Created ADPKD-specific data standard

- 5 sets of case report forms (Emory, U of C, Mayo, CRISP, HALT)
- More than 1200 individual data elements
- 3 face-to-face meetings, multiple conference calls
- Full-time coordinator
- Required approximately one year prior to submission for public (global) comment
- Another 8+ months to complete mapping and data transfer to central database
- Context: small group of collaborative investigators working in a focused field

CDISC SDTM Therapeutic Area Data Standard

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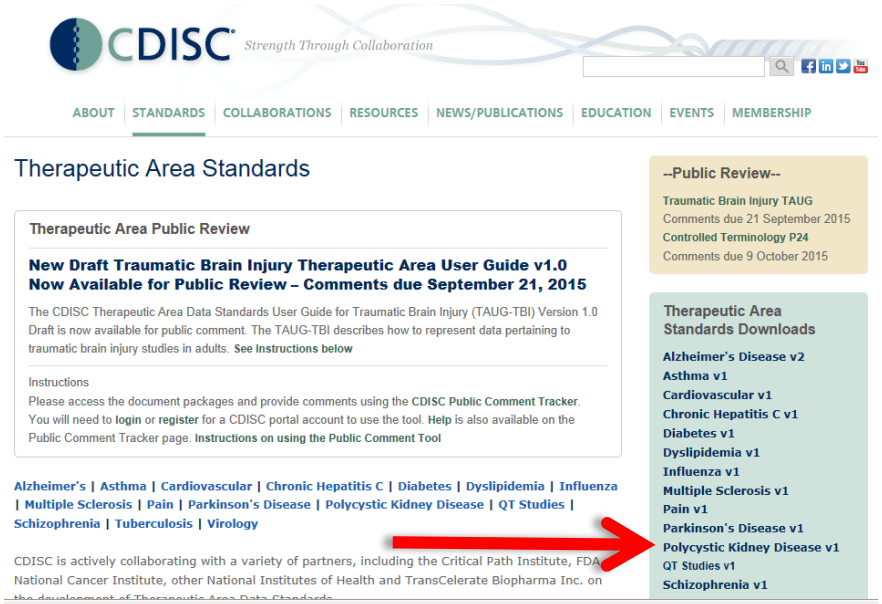
AJKD

Special Report

Therapeutic Area Data Standards for Autosomal Dominant Polycystic Kidney Disease: A Report From the Polycystic Kidney Disease Outcomes Consortium (PKDOC)

Ronald D. Perrone, MD,[1] Jon Neville, PSM,[2] Arlene B. Chapman, MD,[3] Berenice Y. Gitomer, PhD,[4] Dana C. Miskulin, MD,[1] Vicente E. Torres, MD, PhD,[5] Frank S. Czerwiec, MD, PhD,[6] Eslie Dennis, MBChB, FCP,[2] Bron Kisler, BS,[7] Steve Kopko, MS,[7] Holly B. Krasa, MS,[6] Elizabeth LeRoy, MPH,[2] Juliana Castedo, MD,[8] Robert W. Schrier, MD,[4] and Steve Broadbent, MBA[2]



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Data Used to Qualify TKV as Prognostic Enrichment Biomarker – August, 2015

DDT-KD Consortium

Qualification of Biomarker—Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (email: CDER-BiomarkerQualificationProgram@fda.hhs.gov).

FDA

Drug Development Tool (DDT) Type: Biomarker
Referenced Biomarker(s): Total kidney volume (TKV)

TKV is defined as the sum of the volume of the left and right kidneys.

On July 22, the **EMA** released a draft Qualification Opinion in support of Total Kidney Volume for use as a prognostic biomarker in clinical trials for patients with Polycystic Kidney Disease

II. CONTEXT OF USE

A. Use Statement

This draft guidance provides qualification recommendations for the use of TKV, measured at baseline, as a prognostic enrichment biomarker to select patients with ADPKD at high risk for a *progressive decline* in renal function (defined as a confirmed 30% decline in the patient's estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient's age and baseline eGFR as an enrichment factor in these trials.

B. Conditions for Qualified Use

1. *Quantitative Imaging Biomarker*

TKV should be calculated from the left and right kidneys measured with a validated and standardized image acquisition and analysis protocol within the trial. (Please see supporting documentation for details at Biomarker

Lessons Learned

DDT-KD Consortium

- Data Standards key
- Retrospective mapping of data standards is time consuming
- Ideally, data standards should be developed prospectively
- Standards should map to SDTM for regulatory analysis and/or submission
- Work with organizations like C-Path for optimal efficiency
- Data Standards facilitate collaborations and aggregation of data

Benefits to Patients

- More efficient recruitment to clinical trials
- Shorter and potentially less expensive trials
- Generate interest in drug development for ADPKD
- Create background for ultimate acceptance of TKV as a registration endpoint
- More therapeutics for ADPKD with benefit to patients and families

VA Clinical Trials & Combining Drug and Biomarker Development

DDT-KD Consortium Planning Meeting

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Dr. Paul M. Palevsky
University of Pittsburgh

ATN Study

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- Acute Renal Failure Trial Network (ATN) Study – completed
  - RCT comparing less-intensive to more-intensive strategy of renal replacement therapy in critically ill patients with established AKI
  - Enrolled 1,124 patients
- ATN Study Biorepositories
  - Serum and plasma samples collected on day 1 and day 8
    - 819 participants with day 1 samples
    - 573 participants with day 8 samples
    - 565 participants with both day 1 and day 8 samples
  - DNA Bank
    - 138 samples
      - 94 survived to day 60
      - 44 died before day 60

VA NEPHRON-D Study

DDT-KD Consortium

- Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study – completed
  - RCT comparing monotherapy with losartan to combination therapy with lisinopril and losartan in patients with type 2 diabetes mellitus, stage 2/3 CKD and overt proteinuria
  - 1,448 patients randomized and followed for a mean duration of 2.2 years
  - Primary endpoint of death, ESRD or decline in eGFR
- VA NEPHRON-D Biorepository
  - Plasma, serum and urine samples collected at baseline and year 1
    - 1,181 participants with at least one sample
    - 770 participants with samples from both time-points
  - DNA samples banked in approximately half of participants

PRESERVE Trial

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- Prevention of Serious Adverse Events Following Angiography (PRESERVE) Trial - ongoing
  - RCT comparing effectiveness of (2 x 2 factorial design):
    - IV sodium bicarbonate vs. IV saline
    - Oral NAC vs. placebo

    in high risk patients undergoing coronary and non-coronary angiography
    - Diabetic with eGFR of 15-60 mL/min/1.73 m^2
    - Non-diabetic with eGFR of 15-45 mL/min/1.73 m^2
  - Target enrollment: 7,680 patients; as of 21 Sept: 2,728 patients
- PRESERVE Biorepository
  - Plasma, serum and urine samples pre- and 2-4 hours post-angiography
    - Samples from 416 participants collected as of 16 Sept

MVP and PAL

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- Million Veteran Program(MVP) – ongoing
  - Conceived and implemented to promote genomic discoveries and advance personalized medicine
  - To link VA clinical data with genomic analysis
  - Target enrollment of 1 million veterans
    - Current enrollment >345,000 Veterans
    - Genotyping completed on first 200,000 Veterans
- Pharmacogenomic Analysis Laboratory (PAL)
  - Established in 2007 at Little Rock VA
  - Created to support pharmacogenomic studies and clinical trials within the VA Cooperative Studies program

Combining Drug and Biomarker Development

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- Inclusion of biomarker sample collection in drug development trials
  - Incremental cost of sample collection is small
  - Will permit development of sample libraries from well phenotyped population
- Validation of biomarkers during early-phase clinical trials
  - May permit insight into therapeutic pathways
  - May provide novel marker for proof of efficacy
  - May provide marker for responsive/non-responsive subgroups
- Conjoint use of biomarkers in phase 3 / 4 clinical trials
  - Well characterized phenotype of large number of enrolled patients needed for definitive biomarker validation
  - May provide value in defining response patterns or pathways

Roles for Novel Biomarkers in AKI Studies

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- Early diagnosis
  - AKI is not a single disease
  - Have biomarkers “underperformed” because we have not adequately differentiated between forms of AKI?
- Differentiation between subtypes of AKI
  - Pre-renal vs. intrinsic
- Risk assessment
  - Risk of development of AKI
  - Risk for progression of AKI
  - Risk of non-recovery
- Inclusion criteria for clinical trials
- Endpoints for clinical trials
  - Phase 2
  - Phase 3 / 4

Drug Development Tools for Kidney Disease

A European Perspective

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Dr. Hiddo J. Lambers Heerspink
University Medical Center Groningen

Current consortia focused on biomarkers / kidney disease in Europe

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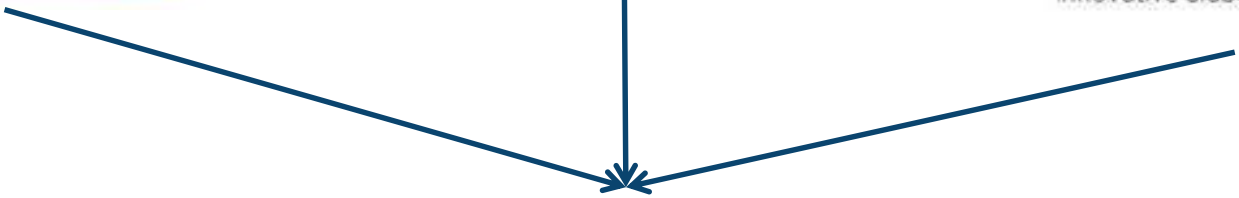
SEVENTH FRAMEWORK PROGRAMME

imi innovative medicines initiative

SysKid Collaborative Project Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment

KIDNEYCONNECT

SUMMIT surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools



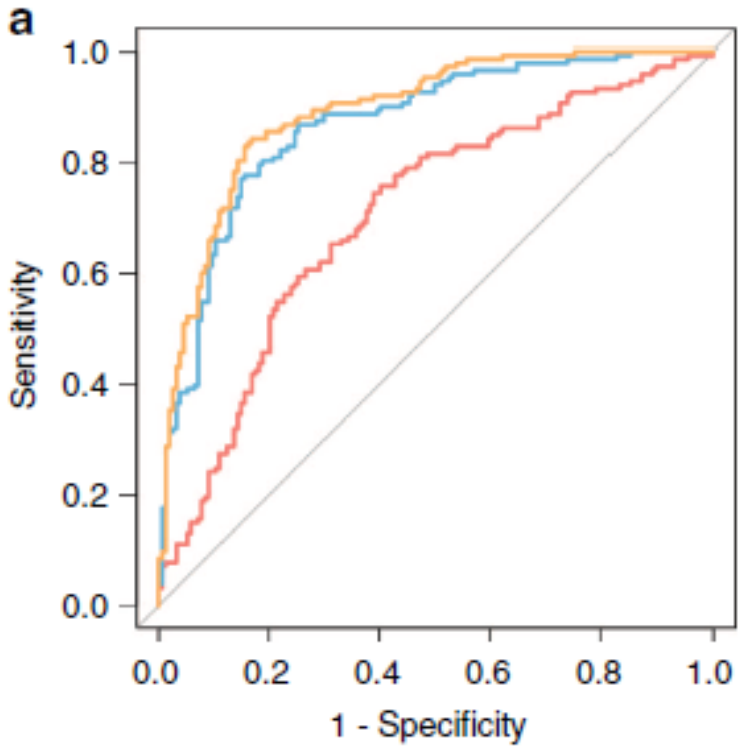
Develop and validate biomarkers for predicting diabetic kidney disease progression

Results from SUMMIT and SysKid

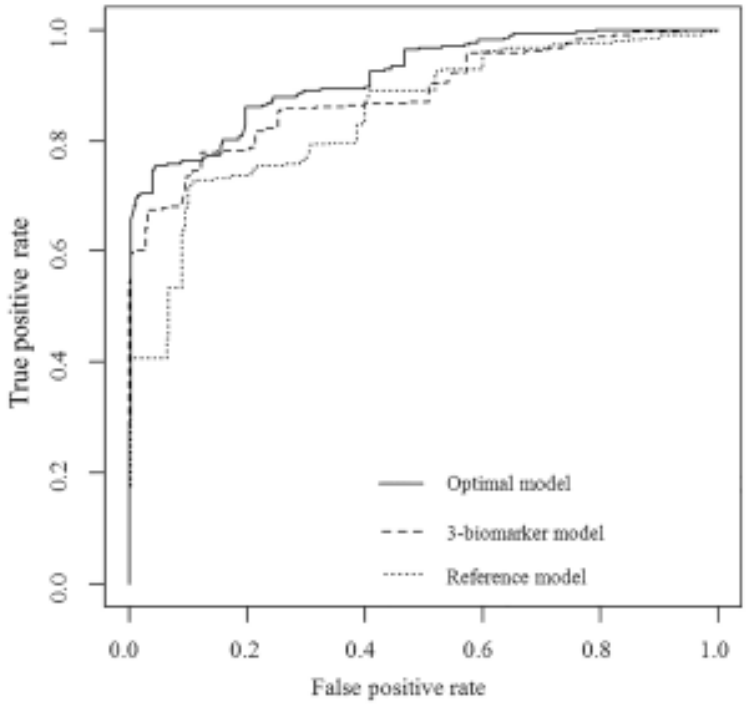
DDT-KD Consortium

SUMMIT
surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools

SysKid
Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment



Looker Kidney Int. 2015



Pena et.al. Plos One 2015

Collaboration

DDT-KD Consortium

- Collaboration between different consortia is critical:
  - The number of large trial and practice databases with high quality samples are few
  - Repositories are managed by different research groups which use their own platforms and analytic techniques leading to:
    - Heterogeneity in and fragmentation of results
    - Duplication of efforts

- Development of a large EU/US biomarker repository of all clinical trials / samples is necessary

NEW EU biomarker initiative in DKD

DDT-KD Consortium

Europe

United States

SysKid
Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment

KIDNEYCONNECT

SUMMIT
surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools

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YALE

UC San Diego HEALTH SCIENCES

Drug Development Tools for Kidney Disease

Analytic Issues for Biomarker Assays

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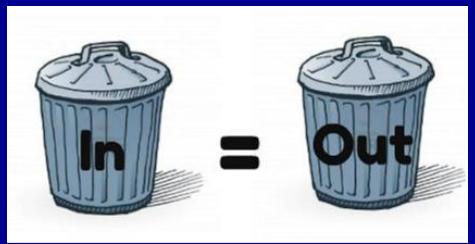
Dr. Joseph V. Bonventre
Harvard University

Two Paths to Garbage Results

Suspect Samples → Validated Assay → Garbage Results

Perfect Samples → Faulty Assay → Garbage Results



Pre-analytical Variables

- Sample collection process
- Sample thawing process
- Do the samples need manipulation including addition of protease inhibitors/ acidification or pH adjustment or protein precipitation
- Storage conditions and stability

Errors due to handling and processing of samples

- Improper storage of samples
  - Storage conditions
    - e.g. Variability in the temp of the freezer
  - Storage Containers
    - e.g Storage tubes
- Improper processing of samples
  - Thawing of samples
  - Mixing of samples
  - Vertexing of samples

Development and Validation of assay

- List of criteria that have to be tested in biological samples of interest from subjects with characteristics similar to those on whom the tests will be used:
  - Upper limit and lower limit of detection
  - Precision and accuracy
  - Linearity of dilution
  - Spike recovery
  - Interfering substances
  - Robustness

Normal urine matrix ≠ CKD urine matrix

Quality Control

- Incorporate proper quality control criteria including:
  - QC samples and precision samples to monitor the assay
  - Levey-Jennings plots to monitor assay drift
  - Westgard criteria to accept or reject an analytical run

Different sources of Errors

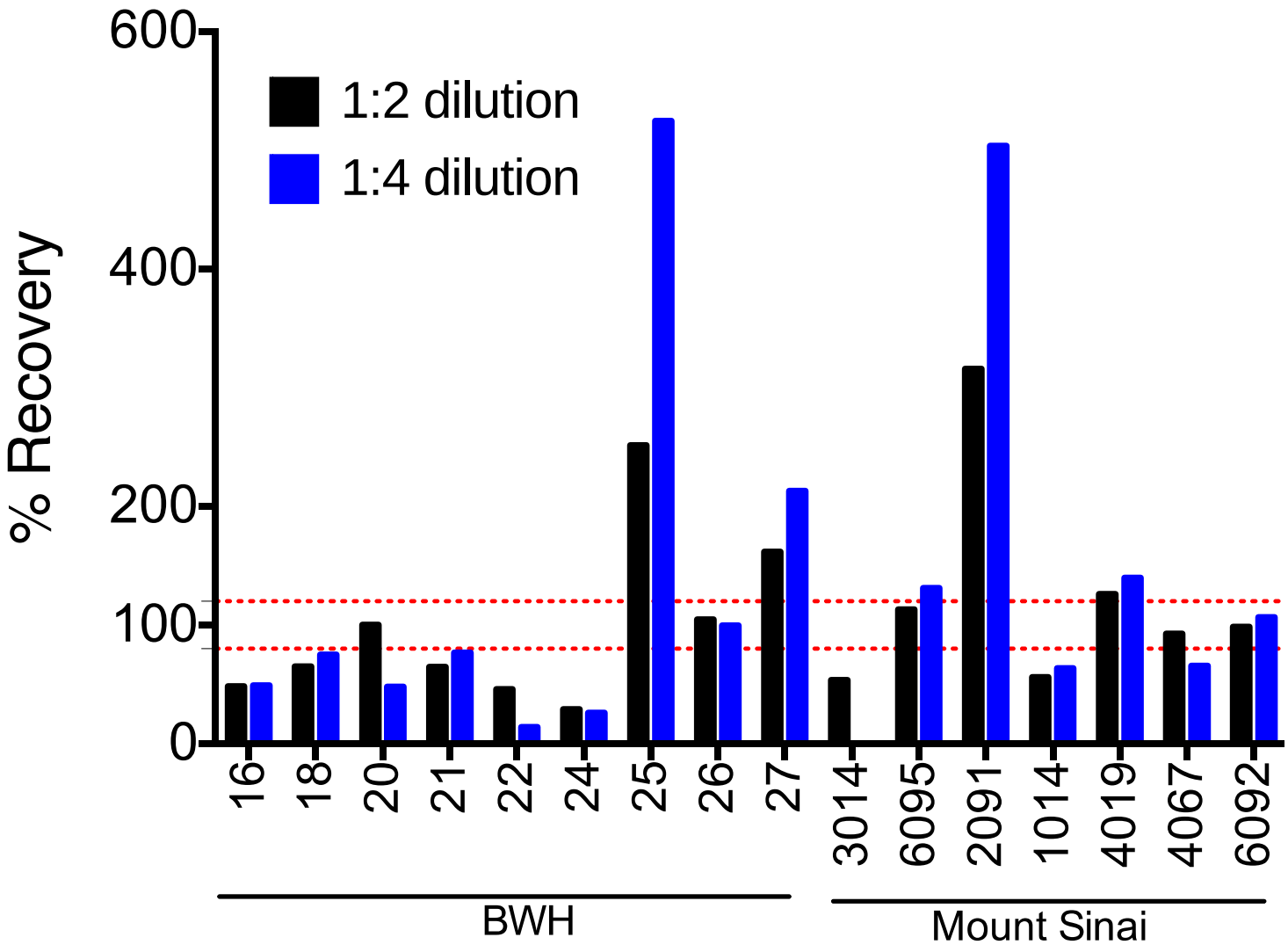
- Errors can occur due to:
  - Handling and processing samples
  - Use of unrefined assay
  - Wrong reagents (e.g.non-specific antibodies)
  - Instrument used in the measurement
  - Recording the measurement

Errors due to assay

- Validation of the assays
  - Lack of complete validation of the assays in the matrix of interest
    - e.g, Linearity of dilution & Spike recovery
    - e.g. Interference
- Cross use of the assays across different sample matrices where they have not been validated
  - E.g: use of assays that were developed to measure biomarkers in “normal” urine to measure biomarkers in CKD urine or normal or CKD plasma

- Commercial tests have often not been validated in plasma or urine of subjects with kidney disease.

Urinary C3a



Sample ID	ng/ml
16	256
18	0.305
20	0.092
21	0.099
22	0.057
23	0.015
24	0.062
25	15.662
26	0.712
27	0.109
1034	0.035
1059	<
3014	0.056
5044	0.018
6095	4.327
2091	22.007
1014	0.107
4019	0.558
4067	0.067
6092	0.778

Errors in the instrument & data recording

Errors in the Instrument

- Daily maintenance and routine calibration
- Is the instrument sensitive

Errors in data recording

- Assigning the wrong sample order in the template
- Assigning the wrong sample ID
- Assigning wrong statistical procedures.

Data Storage and Analysis

- Data backup, secure storage
- Data interpretation and statistical procedures