

## Proposal Statistics Seminar

### Statistical Design and Analysis of Clinical Performance Evaluation of IVD (Diagnostic studies)

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## 1 Introduction

### 1.1 Presentation of ACOMED statistik

ACOMED statistik, Leipzig, is a company founded by Dr. Thomas Keller in 2003. It offers services in the field of statistical planning and evaluation of experiments in life sciences and clinical studies. Customers include companies in the pharmaceutical and diagnostics industry as well as research groups from universities and other public research institutes throughout Europe (focus on Germany and Switzerland) and US.

Statistical services within the design and evaluation of method validations as well as diagnostic clinical studies are a main focus.

Dr. Thomas Keller (ACOMED statistik, Leipzig) can refer to excellent references. Please refer to the list of references and publications.

The diverse experience gained in interdisciplinary cooperation with physicians and scientists from the life sciences is incorporated into the statistics seminars offered by Dr. Keller.

### 1.2 Statistics Seminars

The statistics seminars are aimed at physicians and scientists in the field of life sciences. As a rule, the seminars are offered as in-house seminars. Dr. Keller also participates in seminar series (BB-Life Berlin-Brandenburg, FORUM-Institut Heidelberg, ProCell-Academy Heidelberg, Biosaxony). Dr. Keller is a physicist by profession (focus on biophysics) and before founding ACOMED statistik he worked as scientific assistant at Leipzig University and as the head of research and development in a biotech company, where he was significantly involved in the development of a point-of-care device. Therefore, Dr. Keller can refer to practical experience in laboratory work such as measuring, pipetting etc. and the corresponding quality assurance.

## 2 What you can expect from the seminar

### 2.1 Specific characteristics

The following characteristics distinguish the seminars:

- "Statistics without formulas." Of course, formulas are also presented, but the seminars are designed in such a way that the basic understanding of statistical facts should be awakened.
- "Statistics - not a foreign language". The experience of multi-professional teams from laboratories and clinics means that statistical data is communicated in the language of the user. Statistical terms are of course presented, but only used to the extent necessary.
- "Data of the audience as examples". It has proven itself to ask questions, application examples and data sets of customers and listeners in advance and to use them as examples in the seminars. This increases the target-orientation of the seminar contents, the motivation of the listeners and the learning effect.
- Small MS-Excel<sup>TM</sup>-tools developed by ACOMED statistik are used within the seminar by the participants to perform simple calculations.
- The participants discuss examples of diagnostic studies in small working groups.

### 2.2 Participants

The seminar is aimed at product managers as well as managers and scientists of the R&D from IVD companies, clinical laboratories and university research groups. The audience includes those responsible for quality assurance and regulatory affairs, too. The seminar is also suitable for statisticians who want to familiarize themselves with the specifics of statistical design and analysis of diagnostic studies.

### 2.3 Aim of the seminar

The aim of the seminar is to enable the participants to evaluate and classify the results of diagnostic studies from a statistical point of view. They know the necessary statistical concepts and methods which are necessary for the design and analysis of clinical performance studies. After the seminar, they will be able to set up corresponding study protocols. Furthermore, they are able to perform basic analyses.

## 2.4 Practical aspects

It has proven itself to split full-day seminars over two half days (afternoon + following morning). As a rule, there are no additional costs.

Typically 3 – 16 participants are expected.

It is preferred if the scripts are printed by the customer.

Certificates are issued.

The seminars can be presented in German (preferred) or in English<sup>1</sup>.

## 2.5 Software

The seminars can be combined with software training courses (Excel, Analyse-It, R etc.). As a rule, the customer is responsible for providing the hardware and software.

## 2.6 Software training (Analyse-It™)

In terms of analysis of clinical performance studies and method validation experiments, Dr. Keller provides software trainings for software Analyse-It™ and Medcalc™.

These software trainings contain statistical and methodological background as listed in chapter 3 as well.

Dr. Keller is mentioned as an official partner of the website of Analyse-It™. It would be possible to use temporary licenses within the seminar.

## 2.7 Example data

Complete dataset of the diagnostic study [Keller 1998] (Lung cancer study, see chapter 5) are used within the seminar for several purposes.

In addition, open source articles are used.

However, data sets provided by the customer in advance are welcome.

# 3 Contents of the Seminar

## 3.1 Measures of diagnostic accuracies

Probabilities, conditional probabilities

How to calculate and interpret prevalence, Sensitivity/specificity, PPV/NPV, DLR+/DLR-  
ROC curve as research tool, area under curve (AUC)

Accuracy measures when the reference standard is replaced by a comparator method

Why composite measures (accuracy, Youden-index) are not appropriate

## 3.2 Phases of diagnostic studies

Within the seminar, the approach according GMDS<sup>2</sup> is used, but can be adapted according customers requests

### 3.2.1 Phase I: Technical and methodological investigations

Cut-off determination and its uncertainty, pitfalls in cut-off determination

Influence of analytical performance on diagnostic accuracy

### 3.2.2 Phases II and III: Estimation of diagnostic accuracy

Case-control vs. cohort design

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<sup>1</sup> (please note somewhat limited skills in English language)

<sup>2</sup> GMDS (1990). Memorandum for the Evaluation of Diagnostic Measures. J Clin Chem Clin Biochem 28, 873-9

Selection and spectrum bias

Role of consecutive enrollment

### 3.2.3 Phase IV study (optional)

Design of diagnostic efficacy studies (including therapeutic consequences and clinical outcome)

## 3.3 Design of diagnostic studies

### 3.3.1 Clinical aspects

Intended use of the test and its representation in the clinical study (Study population, diagnostic pathway, rule of the test [new test, add-on, triage])

Choice of reference standard

Definition of objectives and endpoints

Biases in diagnostic studies

### 3.3.2 Statistical aspects

Estimation vs proof

Definition of performance limits

Comparison with other tests

Statistical hypotheses and testing

## 3.4 Analysis of diagnostic studies

Reporting of the results with confidence intervals

Analysis of covariates

## 3.5 Reporting results of clinical trials

Standard of reporting results of diagnostic accuracy studies (STARD 2015)<sup>3</sup>

## 4 Additional contents

The following list comprises items which are not typically presented in the seminar but can be included:

- Software solutions Analyse-It™, Medcalc™, ACOMED Excel-tools (incl. software training)
- Clustered data
- Questionnaires
- Requirements of the FDA
- Prediction and Prognosis
- Multiparameter studies, marker combinations
- Clustered data
- Specific designs (VOPT, enrichment designs)
- Phase IV studies
- Application of general linear (mixed) models in analysis of diagnostic studies
- Practical aspects (study protocol, statistical analysis plan, ...)

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<sup>3</sup> [www.stard-statement.org](http://www.stard-statement.org)

## 5 Publications related to this topic

- Bach T, Bastian P, Blana A, Kaminsky A, Keller S, Knoll T, Lang C, Promnitz S, Ubrig B, **Keller T**, Qvick B, Burger M; OPTIC III Study Group (2016). Optimised photodynamic diagnosis for transurethral resection of the bladder (TURB) in German clinical practice: results of the noninterventional study OPTIC III. *World J Urol.*; DOI: 10.1007/s00345-016-1925-0
- Reimer M, Hüllemann P, Hukauf M, **Keller T**, Binder A, Gierthmühlen J, Baron R (2016). Prediction of response to tapentadol in chronic low back pain. *Eur J Pain.*; DOI: 10.1002/ejp.926
- Lorenz K, **Keller T**, Noack B, Freitag A, Netuschil L, Hoffmann T (2016). Evaluation of a novel point-of-care test for active matrix metalloproteinase-8: agreement between qualitative and quantitative measurements and relation to periodontal inflammation. *J Periodontal Res.* DOI: 10.1111/jre.1239
- Hagen A, Albig M, **Keller T**, Stumm M, Entezami M (2015). Suspicious Prenasal Skin Thickness-to-Nasal Bone Length Ratio: Prevalence and Correlation with Other Markers in Second and Third Trimester Fetuses with Down Syndrome. *Ultraschall in Med.* DOI <http://dx.doi.org/10.1055/s-0034-1399285>
- Bergeron, C, Ikenberg, H, Sideri, M, Denton, K, Bogers, J, Schmidt, D, Alameda, F, **Keller, T**, Rehm, S, Ridder, R and for the PALMS Study Group (2015), Prospective evaluation of p16/Ki-67 dual-stained cytology for managing women with abnormal Papanicolaou cytology: PALMS study results. *Cancer Cytopathology.* doi: 10.1002/cncy.21542
- Kuhlmann JD, Wimberger P, Bankfalvi A, **Keller T**, Schöler S, Aktas B, Buderath P, Hauch S, Otterbach F, Kimmig R, Kasimir-Bauer S (2014). ERCC1-Positive Circulating Tumor Cells in the Blood of Ovarian Cancer Patients as a Predictive Biomarker for Platinum Resistance. *Clin Chem.* 2014 Jul 11. pii: clinchem.2014.224808.
- Mick G, Baron R, Correa-Illanes G, Hans G, Mayoral V, Frías X, Sintes D, **Keller T** (2014). Is an easy and reliable diagnosis of localized neuropathic pain (LNP) possible in general practice? Development of a screening tool based on IASP criteria. *Curr Med Res Opin* 30, 1357-66
- Ikenberg H, Bergeron C, Schmidt D, Griesser H, Alameda F, Angeloni C, Bogers J, Dachez R, Denton K, Hariri J, **Keller T**, von Knebel Doeberitz M, Neumann MH, Puig-Tintore LM, Sideri M, Rehm S, Ridder R for the PALMS study group (2013). Screening for Cervical Cancer Precursors with p16/Ki-67 Dual-stained Cytology: Results of the PALMS Study. *J Natl Cancer Inst* 105, 1550-7
- Becker R, **Keller T**, Kiesewetter H, Fangerau H, Bittner U (2013). Individual risk assessment of adverse pregnancy outcome by multivariate regression analysis may serve as basis for drug intervention studies: retrospective analysis of 426 high-risk patients including ethical aspects. *Arch Gynecol Obstet* 281, 41-8
- Neumann A, **Keller T**, Jocham D, Doehn C: Human placental alkaline phosphatase (hPLAP) is the most frequently elevated serum marker in testicular cancer]. *Aktuelle Urol.* 2011 Sep;42(5):311-5
- Jung R, Jacobs U, Krumbholz M, Langer T, **Keller T**, De Lorenzo P, Valsecchi MG, van der Velden VH, Moericke M, Stanulla M, Harbott J, Panzer-Grumayer, van Dongen JJM, Pieters R, Schrappe M, Rascher W, Metzler M (2010): Bimodal distribution of genomic MLL breakpoints in infant acute lymphoblastic leukemia, *Leukemia* 24:903-907
- Denton KJ, Bergeron C, Klement P, Trunk MJ, **Keller T**, Ridder R (2010): The sensitivity and specificity of p16INK4a Cytology versus HPV Testing for Detecting High-Grade Cervical Disease in the Triage of ASC-US and LSIL Pap Cytology Results. *Am J Clin Pathol* 134:12-21
- Bergeron C, Ordi J, Schmidt D, Trunk MJ, **Keller T**, Ridder R (2010): Conjunctive p16INK4a Testing Significantly Increases Accuracy in Diagnosing High-Grade Cervical Intraepithelial Neoplasia. *Am J Clin Pathol* 133:395-406
- Sack U, Biereder B, Elouahidi T, Bauer K, **Keller T**, Trobs RB (2006): Diagnostic value of blood inflammatory markers for detection of acute appendicitis in children. *BMC Surg.* 28, 6-15.
- Jung K, Lein M, Butz H, Stephan C, Loening SA, **Keller T** (2006): New Insights into the Diagnostic Accuracy of Complexed and Total Prostate Specific Antigen Using Discordance Analysis Characteristics. *Urology* 175, 1275-1280
- Müller V, Witzel I, Pantel K, Krenkel S, Lück HJ, Neumann R, **Keller T**, Dittmer J, Jänicke F, Thomssen C (2006): Prognostic and Predictive Impact of Soluble Epidermal Growth Factor Receptor (sEGFR) Protein in the Serum of Patients Treated with Chemotherapy for Metastatic Breast Cancer. *Anticancer Res.* 26, 1479-1488
- Keller T**, Butz H, Lein M, Kwiatowski M, Semjonow A, Luboldt H-J, Hammerer P, Stephan C, Jung K (2005): Discordance Analysis Characteristics (DAC) as a New Method to Compare the Diagnostic Accuracy of Tests: the Example of Complexed Versus Total Prostate-Specific Antigen. *Clin Chem* 51, 532-539
- Heiss C, Hoesel LM, Wehr U, **Keller T**, Horas U, Meyer C, Rambeck W, Schnettler R (2004): Vitamin K in combination with other biochemical markers to diagnose osteoporosis. *Biomarkers* 9, 479-488
- Heiss C, **Keller T**, Wehr U, Mohr A, Lommel D, Meyer Ch, Rambeck WA, Schnettler R (2004): Biochemical Markers and their Significance in Postmenopausal Osteoporosis - A new Method in the Diagnosis of Osteoporosis? *Biomed Technik* 49: 262-268s
- Nuber A, **Keller T**, Bitterlich N, Gillissen A, Leonhardt P (2002): Diagnosis And Monitoring Of Therapy Of Lung Cancer With A Tumor Marker Profile: Comparing CYFRA 21-1, CEA And NSE With Fuzzy Logic-Based Tumor Marker Profiles. 98th International Conference of the American Thoracic Society, May 17-22, Atlanta, Band of Abstracts, p. A48
- Halm U, Rohde N, Klapdor R, Reith HB, Thiede A, Etzrodt G, Mossner J, **Keller T** (2000): Improved sensitivity of fuzzy logic based tumor marker profiles for diagnosis of pancreatic carcinoma versus benign pancreatic disease. *Anticancer Res.* ; 20:4957-60
- Keller T**, Bitterlich N, Hilfenhaus S, Bigl H, Löser T, Leonhardt P (1998): Tumour markers in the diagnosis of bronchial carcinoma: new options using fuzzy logic based tumour marker profiles. *J Cancer Res Clin Oncol* 124: 565-574

## 6 References (statistical design and analysis)

If not other stated, Germany is the location.

### 6.1 Universities and public research organizations

Charité Berlin, Pediatric Oncology, Urologa  
CLSI Subcommittees EP9 and EP25, Utah, USA  
Fraunhofer Institute for Celltherapy and Immunology, Leipzig  
IRMM (Institute for reference materials, Gent, Belgium)  
University of Leipzig, Immunology  
University of Düsseldorf, Pediatric Oncology  
University of Dresden, Clinical lab (gynaecology)  
University of Erlangen, Clinical lab (pediatrics),  
University of Essen, Clinical Lab (gynaecology)  
University of Gent (Belgium), Clinical lab

### 6.2 IVD-companies

Bayer Diagnostics GmbH, Fernwald (now Siemens AG)  
Beckmann Coulter GmbH (Krefeld, and Nyon/Schweiz)  
Brahms GmbH, Berlin-Henningsdorf  
Dentognostics GmbH  
GILUPI GmbH, Potsdam  
Greiner Bio-One GmbH (Frickenhausen, sowie Rainbach/Österreich)  
Lophius Biosciences GmbH, Regensburg  
LifeCodexx AG, Konstanz  
MTM laboratories AG (now Roche Diagnostics)  
R-Biopharm AG, Darmstadt  
Sysmex Europe GmbH, Norderstedt  
And others

## 7 References (statistical training)

Beckmann Coulter GmbH, Krefeld and Nyon/Schweiz  
BB Life, Berlin  
Biosaxony academy, Dresden/Leipzig  
Boehringer Ingelheim Pharma GmbH & Co. KG (Biomarker-Unit), Ingelheim  
FORUM-Institut, Heidelberg  
Fachhochschule Kärnten, Klagenfurt, Austria  
Fraunhofer Institute for Celltherapy and Immunology, Leipzig  
Lonza Cologne GmbH, Cologne  
IBBL (Integrated BioBank of Luxembourg)  
mibe Arzneimittel GmbH, Brehna  
ProGen Biotechnik GmbH, Heidelberg  
R-Biopharm AG, Darmstadt  
Sysmex Europe GmbH, Norderstedt  
TRM Leipzig  
TU München  
Vet Med Labor GmbH, Ludwigsburg  
and others