Biostatistics at a research center at the interface between biomedical and statistical science

Edler, Lutz; Kopp-Schneider, Annette; Benner, Axel
German Cancer Research Center, Department of Biostatistics,
Im Neuenheimer Feld 280,
D-69120 Heidelberg, Germany

Edler, Lutz
edler@dkfz.de
Kopp Schneider, Annette
kopp@dkfz.de
Benner, Axel
benner@dkfz.de

Summary
Biostatistics has been demanded increasingly in biomedical research since the 1960s for support in experimental design, mathematical and statistical modelling as well as computational statistics. This resulted in the establishment of biostatistical units in universities, research institutes and larger pharmaceutical companies; a development not without disturbances and regularly re-thinking the role of biostatistics and its justification at that places. This paper describes the mission, tasks and duties of a biostatistical unit located at a large research center on cancer, with responsibilities for biostatistical consulting as well as independent biostatistical research. Such a unit's research mission is the promotion of biostatistical methods in experimental cancer research, the enhancement of quantitative methods and the initiation and conduct of statistical research relevant for the center's mission for cancer research. The unit's consultation mission is to support the center's scientists in the design, analysis of their research projects, and to assist in appropriate communication and publication of their results. This paper presents an approach where consulting and expertise is combined with cooperation, on the basis of sound statistical science and original biostatistical research.

Key words: Biostatistics, Biometry, Cancer Research, Organizational Structure, Consultation, Collaboration, Computational Statistics, Design, Modelling, Data Analysis, Communication,.

1. Introduction

The field of biostatistics has been growing since around the 1960s, when biostatisticians were demanded for the application of mathematical and statistical methods and techniques in biological and biomedical sciences. In Germany, this development was initiated in 1960 by recommendations of a Science Committee stating the indispensability of medical statistics and data documentation for medical research. This initiative was enforced later (1973) by implementing a curriculum on Biomathematics for medical students. Another push forward came for biostatistics in 1976 when a new drug law asked for more quality, efficacy and safety for clinical studies, rendering *de facto* the application of statistical principles indispensable. As a result biostatistical science emerged in many countries as a discipline, referring to the 'application of statistics, probability, computing and mathematics to the life sciences, with the goal of advancing our knowledge' (Zelen, 1983).
Rethinking the role of a biostatistical unit at a research center is important when its existence is questioned from time to time by review committees, by administrative bodies, by financial sponsors, or by peer colleagues in or outside the institute. Questioning the necessity or independence of biostatistics becomes an issue when financial resources become short or when new biomedical branches start to compete in statistical topics, or when it becomes fashionable to restructure an institute. Then it becomes critical to explain the concept of biostatistics to scientists and stakeholders. One also has to argue for the justification of the discipline in a research center when it comes to the competition on resources. To be clear about the notation: We will use the two terms biostatistics and biometry exchangeable irrespective of some discussions on differentiating between biometry and biostatistics (Greenberg, 1983). Actually, our

department got its name almost 30 years ago when it was changed from Experimental Design to Biostatistics.
In the next section we will describe the role of a biostatistical unit in a biomedical research center by identifying general areas of statistics relevant for biomedicine. In chapter 2 we will show what is specific for a cancer research center. In chapter 3 and 4 we present our approach for a sustainable functioning of a biostatistical unit within a biomedical research center. As an example, work on biostatistical designs for animal experiments is emphasized. Misconceptions on biostatistics in such an environment are discussed in chapter 5. We will reflect on the optimal size of a biostatistical unit and the number and qualification of staff in chapter 6. In chapter 7 and 8 we address the essential role of cooperation and publication. Finally, future perspectives in a rapidly changing biomedical environment are discussed in chapter 9 together with a short summary.

2. On the Role of Biostatistics in a Biomedical Research Center

Biostatistics applies theories and methods of mathematics, probability theory, statistics, and computer science to scientific problems in biomedicine. Its scientific partners are interested to produce, analyze, and interpret quantitative data. They come from biology, chemistry, pharmacology, epidemiology, genetics, genomics and medicine in general. Therefore, biostatistics interfaces statistical science with biomedical science through statistical modelling and data analysis for understanding experimental results. Biostatistics has been demanded at less degree and rarely by biomedical disciplines of a more descriptive character, e.g. anatomy, surgery or supportive care of patients.
Most relevant for understanding the role of biostatistics has been the recognition of biological variability. That was already expressed when Karl Pearson defined biometry as 'science which applies the modern theory of statistics to the study of variation and correlation in living forms' (see Armitage, 1985). Explanation of variability through the use of statistical modelling has always been a major task and it is one of best descriptors of a biostatistician's work and his/her interaction with biosciences with the perspective that 'the statistician acting as a scientist must possess subject-matter knowledge' (Zelen, 1983).
The role of biostatistics has been commented in the same vain by Federer, 1984, Armitage, 1985, Carter et al. 1986, Ellenberg, 1990, and Gehan (2001). However, the role of a biostatistical core unit in a clinical research center has been addressed rarely; see e. g. Arndt & Woolson, 1991, although self-conception and understanding one's position in science is highly relevant for a successful work in that environment.
Most frequent and typical duties of a biostatistician in a biomedical environment are

- design of experiments and clinical trials, calculation of sample size and statistical power
- hypothesis testing and consulting therein in many variants
- frequentistic (parametric or nonparametric) or Bayesian statistical inference
- low- and high-dimensional regression analysis.

This work is impossible without applying computational statistics (Benner 1992 a,b). Equally important, however, is biostatistical thinking and use of general statistical principles on how to evaluate the data's uncertainty. In cancer research, where there is large variation in how cancer develops and is treated and where treatment outcome depends on prognostic factors, understanding of statistical error and its various sources is a key element of good biostatistical practice. Implementation of techniques against bias (e.g. randomization, stratification), refinement of statistical effect estimation, and application of methods for outcome validation (cross-validation, bootstrapping) are advanced tools frequently used.
In summary, the overall objectives of an in-house biostatistics unit at a cancer center encompasses a broad program of research, consulting, and teaching, with major emphasis on collaboration with clinical and laboratory investigators for study designs and data analyses. Biostatisticians interact with other investigators at the center to accomplish those goals, including prospective and retrospective studies, see also Geller (1989.

3. Biostatistics at the German Cancer Research Center

The importance of biostatistical science for cancer research and the establishment of biostatistics units in a cancer center have been recognized repeatedly. Only to mention three examples:
(i) The Biometric Research Branch (BRB) at the US National Cancer Institute (NCI, http://brb.nci.nih.gov/).
(ii) The program in Biomathematics and Biostatistics at the MD Anderson Cancer Center (http://www.mdanderson.org/departments/biostats/).
(iii) The University of Michigan and its "Biostatistics Training Program in Cancer Research" (http://www.sph.umich.edu/biostat/cancer_bio.htm).

At the German Cancer Research Center, after a period of employment of mathematicians for data analysis between mid 1960s to mid 1970s rather isolated in the center, a department dedicated to biometric services was established in 1975 as Department of Experimental Design within the former Institute of Documentation, Information and Statistics. The department was headed by Prof. Dr. Ernst Weber with duties in statistical design and evaluation methods, including the development of statistical software. In 1979 it was renamed Department of Biostatistics. A reorganisation during 1983 and 1986 changed the institute's name to Epidemiology and Biometry. Thereafter, a period of intensive discussions began within the institute as well as with authorities of the center on the future role of biostatistics induced by the retirement of the founding department head. Finally, also triggered by the center's reorganization when changing the institutes to so-called Research Programs, it was decided in 1989 to associate a Biostatistics Unit to a new established Research Program 'Bioinformatics' which later developed into a program on "Genome Research and Bioinformatics". During further organisational rearrangements the Biostatistics Unit was associated to the Research Program "Cancer Risk Factors" where, after some time, it re-attained its full independence as department. The department's profile is now defined by work for clinical trials, survival analysis and statistical genetics, a typical profile (Gehan, 2001). In addition, we developed interest in statistical topics associated with basic experimental research, e.g. toxicology, design of animal experiments and carcinogenic risk assessment. Typical are also dose-response analysis, complex survival data, sources of variation, association and correlation, methods for agreement and various multiplicity issues (interim analysis, closed testing procedures). Some of the statistical problems evolved through consulting and supporting biomedical PhD students and post docs. At the same time, the department educates and promotes itself PhD students in mathematics and statistics and human sciences and it provides working opportunities for post docs.

4. Tasks and Duties of a Biostatistical Department in Cancer Research

Biomedical researchers and, in particular, experimental or clinical cancer researchers who need biostatistical support demand from the collaborating biostatistician

- readiness for an intensive dialogue with biomedical researchers,
- basic knowledge of the biomedical research field,
- profound knowledge of statistical methods,
- know how to develop and adopt statistical methods for problem solving in a fast way, and
- access to and expert knowledge in statistical tools, including use of statistical software.

A portion of each biostatistician's time must be allocated to support the center's genuine activities by routine consultations, teaching and organizational matters. Open mind and communication skills are required for the dialog with all the center's cancer researchers. The most efficient methods to solve the statistical problems can only be found when biological basic knowledge on the specific investigation and its potential outcomes is collected, systematically ordered for biostatistical modelling, and put into the context of the statistical problem. That research will contribute to the following areas:

- Laboratory Assays
- Bioassays and Animal Experiments
- Molecular Genetic Assays and Genetics
- Cancer Epidemiology
- Clinical Trials and Therapeutic Research.

As a scientific unit, the department is responsible for both, biostatistical expertise and independent biostatistical research. That includes provision of biostatistical and computational support to all scientists of the center and carrying out statistical research useful for experimental oncology. The activities range from one time consultation and routine data analysis to extensive collaborations which result in joint publications in subject matter journals. New statistical methodology is developed and existing techniques are applied. Overall, this work is guided by the mission to promote biostatistical methods in experimental cancer research, to enhance quantitative methods in oncology and to initiate and conduct statistical research in areas relevant to solve the cancer problem. Following this, the department is active in the interpretation of quantitative information and the expression of the data's content in intelligible terms comprising statistical and mathematical modelling, as well as in giving advice on the acquisition and collection of data comprising experimental designs, data collection rules and quality control measures.

Below we exemplify such activities by three major research themes in Department of Biostatistics at the German Cancer Research Center (see also Table 1):

- *Statistical Genetics and Genomics and Methods in Translational Research.* High dimensional multivariable data obtained on modern molecular platforms are the starting point for the search for efficient statistical analysis methods aiming at the selection and identification of prognostic and predictive genes or other genetic or molecular entities relevant for cancer development or cancer treatment.
- *Preclinical Biostatistics*. Stochastic modeling guides to distinguish between biological hypotheses, helps to design, analyze and interpret data sets combining toxicological data with cancer incidence, proteomic and biomarker research.Unbiased statistical estimation techniques are needed to judge structural relationships between biological endpoints and factors of influence and to characterize stochastic variability. Identifiably, uncertainty and predictive power of the models must be investigated.
- *Statistical Methods in Oncological Clinical Research*. By close collaboration with clinicians, far beyond merely statistical support or assistance in data analyses, our contribution becomes a decisive part of designing and initiating new studies and we give critical thoughts to sources of bias and potentially competing interpretations of study results. Research in flexible adaptive designs and establishment of certified infrastructure for the biometrical support and analysis are developed and innovative methods suiting oncological trials and new treatment strategies are proposed.

The department's **service** for the center can be described as *Biostatistical Support and Statistical Methods for Experiments.* Biostatistics is engaged to improve the design, and analysis of various experiments. Thereby it is crucial to understand the factors that influence experimental results.

For illustration we like to mention statistical design of animal experiments where our biometric designs have become an integral part of the approval of the center's experiments involving vertebrates which are protected by German Animal Protection Law. Rules of the German Animal Protection Law require an explicit biometrical justification of the number of animals. In this process, scientists have to get approval through a governmental committee. One section of the application form is devoted to biometrical considerations. This defines the interaction with a biostatistics department. Meanwhile, biostatistical support in design is taken deliberately by almost all scientists of the center and the process of application could be improved and even accelerated. Basic steps of biometrical planning are the formulation of the biological research problem, definition of the experimental unit(s) and the quantitative endpoint(s), set up of the design structure and experimental groups, sample size calculations and recommendations for statistical analysis and where indicated, further statistical remarks for proper conduct, e.g. using randomisation.

It is obvious that mere calculation of sample sizes – the main motivation of contacting a statistician in most cases – is only one part of our work. Our clients appreciate the set up the formal plan where the treatment groups and the primary endpoints of the experiment are defined. Sometimes we even have to explain how to create a factorial design table. Preparation of those designs is time-consuming and involves often repeated discussions of the project with the experimentalist until a final design and a sample size estimate is found. Development of biostatistical methods for planning has become essential to generate sample size tables for getting an overview of possible constellations of design parameters.

A challenge has always been the use of statistical computing techniques. Statistical computing has been the most essential tool for biometry and at the same time a driving force for new statistical methods in science (Edler, 2005). On the other hand, there is an increasing lack of knowledge among experimentalists about the existence and correct use of statistical software. Service for scientists and laboratory staff, for consultancy and advice in correct handling of statistical software and for software validation is even more crucial now than in the past. One concept is to delegate routine analysis to the experimentalists by providing the adequate software and not take over non-standard evaluation.

Research areas as the three mentioned above represent the one dimension of the activity matrix. The second dimension is defined by the three a**ctivity types**

A. Consulting and expertise in biostatistics,
B. Cooperation in cancer research projects,
C. Original biostatistical research.

Note cooperation with experimentalists usually evolves over a rather long time (i.e. years). This applies in particular to clinical research such as Phase I-III trials. The strategic concept of a biostatistical unit in biomedical research should be to get into increased contact with biologists and clinicians via statistical consulting, then to proceed with them in joint projects, where statistics is needed and worth to be followed, and, finally, to approach and to solve statistical research problems connected with that work. Having obtained the appropriate biostatistical research results, this journey can go backwards by using them in

cooperative projects and in statistical consulting. For illustration we like to mention four examples: Engagement in methods for long-term animal experiments has lead to the study of statistical tumour-incidence-models e.g. using the proportional hazards model. Analysis of DNA repair data lead to the development of statistical methods for short-term tests. The studies of physiologically-based pharmacokinetic models lead to methods for estimating effective doses and to the investigation of uncertainty in risk assessment. And, research on carcinogenesis modelling lead to new results for tumour onset time distributions and to methods for the discrimination between different proposed mechanisms in carcinogenesis. All this work was only possible with the feed back from the experimentalists.
Note the unit has also to provide

- education in understanding statistical methodology,
- advice to the clients in the correct use,
- explanation of limitations of the statistical procedures and
- support in the interpretation of the results based on statistical calculations.

The approach chosen in our department is based upon the idea that biostatistics at a biomedical research center should understand itself neither as a mathematical statistics department with casual applications in cancer research nor as a general department of medical statistics with interest in biomedical research in general. In contrast, we postulate to serve as practical interface between biomedical and statistical science which can address almost immediately evolving important and specialized biomedical problems with need statistics. Such an activity profile requires competence to react to a broad spectrum of experimental research problems requiring methodology from mathematics, statistics, and computer science. The original biological problem always serves as guide to modelling and development of tailored statistical methodology. This work is very similar to a biostatistical consultancy unit in industry (Marquardt, 1981).

5. Four Typical Misconceptions of Biostatistics in Biomedicine

Next we discuss three often recovered misconceptions on the function of a biostatistics unit in and outside a biomedical research center.

(i) *Biostatisticians should work in the basic science department and not as an independent unit.*

Biostatisticians can work optimal only in an independent unit. The professional interaction with other biostatisticians and the support which single biostatisticians receive within a departmental structure from the colleague biostatisticians is a crucial component of the work itself and keeps her/him from becoming isolated or single-tracked. The independence of scientific work based on the principles described in the previous section is a prerequisite to provide sound and competent statistical support for research (see also Boyett, 1989).

(ii) *Biostatistics is primarily required for data analysis and it is needed on a case by case basis.*

The roles most frequently confused with that of a statistician appear to be those of being a programmer or database administrator. While a biostatistician, of course, needs expertise and experience in those areas in order to be able to develop successfully statistical methods, these functions can hardly be primary to a statistician. Data generated by studies must be managed and computer systems must be developed to facilitate data collection through added manpower for programming, database creation and management and sufficient secretarial support (Boyett, 1989). This work is however different from statistical thinking and the elaboration of statistical analyses which are based on scientific principles.

(iii) *Biostatistics can work automatically or at demand through software programs.*

This myth is sometimes located with investigators not realizing that some methods (e.g. Cox regression, mixed effect models) have taken a long time to be developed to the present state and cannot - and even should not- be applied by "running a program overnight" without a careful biostatistical analysis of the assumptions and peculiarities in the data and the results. Biostatisticians need some training to counter such arguments and to explain the true nature of statistics to biomedical researches who express this wrong opinion.

(iv) *Biostatistics is part of Bioinformatics.*

With the appearance of molecular sequence data and microarray data and with the intrinsic problems of screening and archiving these new and massive data sets grew in biomedicine the impression that bioinformatics tools would be the most appropriate methods to analyze these data. Data mining and clustering methods were overestimated in their potency and computer programs were just applied without a thorough statistical analysis of the research problems and the properties of ad hoc generated optimization algorithms. In the view of some leading biomedical researchers biostatistics was considered as part of bioinformatics, if statistics was realized at all as necessary for the analysis of the molecular data in general and the genomic data in particular. Although there were early warnings (Vingron, 2001) this attitude was not supportive for pursuing biostatistical research and service for design and analysis of high-dimensional genomic data, and has actually slowed down the generation of valid biomedical results and in some cases biomedical research has even been misguided by this misconception.

6. The Size and the Funding of a Biostatistics Unit

Almost all long-term research units seem to operate now at a minimum institutional subsistence level. Time schedules have to be followed, additional administrative work has to be accomplished, and personnel contracts with tough time limits cause uncertainties both for projects and staff. Nevertheless, sufficient staff is mandatory for the functioning of biostatistics in a research center and a balanced proportion of senior statisticians, post-docs, doctoral students and technicians is important for sustainability. A minimum of highly trained and flexible personnel for technical support, e.g. for data management and applied programming using R language or SAS is necessary, because of the rapid change of computing technologies. Important is also a full time working secretariat with 1-2 persons for handling the incoming requests for consulting and managing consulting as well, besides the standard duties.

One has to note that doctoral research students can provide help only temporarily and there is a delicate cost/benefit relationship between their contributions to general research in the unit and what they demand in support for their thesis project work, given the time constraints in funding, which is mostly no more than three years. One has also to note, that positions financed by extramural funds are not available for the "daily" needs of the center. Sometimes, staff can be supplemented for a few weeks by internship of students of mathematics and statistics. As helpful temporary support can be as important is that there are means to keep this work ongoing in the hands of the permanent staff. Although a substantial part of the work should be covered by extramural funding, in order to maintain a stable biostatistics unit, the center must provide support for unfunded time and efforts (see also Geller, 1989). Overall, the size of a biostatistical unit is determined by needs of the center, elicitation of own research funds, and elicitation of cooperative projects.

The number of heads in the unit depends on the overall size of the center and in particular of the number of scientist dealing with quantitative results originating from hypothesis-based biomedical research. In a center engaged in basic cancer research one may roughly estimate that 50% is strongly oriented towards quantitative science and that 50% of those do quantitative research needing statistics at some time. Some of those scientists may analyze their data in a descriptive manner using Excel, graphics programs with simple statistics implemented (t-tests, Kaplan-Meier curves), or JAVA applets from the internet. It is hard to estimate to what extent this suboptimal problem solving for statistical analysis is prevalent in a research institute and whether it suffices the researchers' needs. We note an increased usage, recently, and are concerned about possible harm. Assuming another default portion of about 50% among those scientists who definitively need biostatistical support one can estimate that about 10% of all scientist of a center are potential clients for a biostatistics unit. In a center like ours with about 2500 employees and about 1000 scientists including doctoral and master students the number of customers would be estimated as o 100 in a cross-sectional window of 1-2 years, a number actually supported by our files.

7. Scientific Cooperation

Collaboration with scientists of the center is fruitful only when long lasting. It is characterized by highly active phases followed by resting phases, wrapping up and then being active again. It is important to explain collaborating biomedical researchers both the benefits as well as the limitations of statistical methods when applied to their problem. A prerequisite therefore is that the biostatisticians is willing to think deeply into the subject-matter and puts a considerable amount of time and patience into the problem. It is quite natural that each contact results in a meeting with the client where the biomedical background is elaborated and the quantitative outcomes are identified. Next, it becomes very important to define together the research question(s) and the biological endpoints for a solid statistical evaluation. Development of written statistical analysis plans should become the rule. Sometimes one has to respond fast upon requests and must be willing and able to make short-term arrangements. Logistic skills and time management is needed for handling many cooperation at the same time with many scientists.

Collaboration with partners of other biometrical and statistical units is crucial for the progress of own biostatistical work. Purposive efforts lead to cooperation with computational statisticians and other biostaticians. Nationwide clinical cooperations support the recognition and appreciation of expertise accumulated in the unit and may then become basis of common projects with external funding. Good collaboration with biomedical partners requires regular contact and participation in biomedical section meetings, good collaboration with other biostatisticians requires attendance and exchange at statistical meetings like those of ISCB, ASA and ISI.

When biostatisticians are involved in the ongoing planning and monitoring of the clinical and laboratory studies, they should be present when studies are the first time discussed, and they should contribute to design aspects or to the discussion on the appropriateness of treatment endpoints. They also participate in reviewing the status of studies, and give presentations of data analyses. An excellent means of getting the biostatistical message to the partner is to participate in seminar series in biomedical departments and to volunteer for lectures on areas of statistics which you perceive as needing emphasis at the center (Boyett, 1989). However, a considerable part of education often must be face-to-face. The goal of collaboration has been formulated by Marvin Zelen as “The biostatistical scientists are often regarded by specialists in the subject-matter discipline as also being subject-matter scientists. They routinely present the results of their investigation at the scientific meetings of the speciality field.” (Zelen, 1983).

8. Publication and Evaluation

The success of a biostatistics department will primarily be judged by the scientific output in the form peer reviewed publications in journals which then define somehow the profile of the unit. A reasonable number of yearly publications is important and may range between 10-50 papers in a medium sized biostatistics unit. The journals range from applied statistics and biometry to subject research journals. The biometrical journals are for research results and the biomedical journals for cooperation results. An index of success is first or last authorship. Amongst other points is usage of impact factors questionable because of the obvious the imbalance of its level between biomedical and biostatistical journals.

Several procedures have been established for evaluating research units. Most prominent is the external review by an international group of experts resulting in a written report to the board of directors of the center. Therefore a written research report is prepared beforehand by the unit and an oral report is given during the review. The review commission gets detailed information during a site visit. Additional to these external reviews are in house information visit by the board of directors where the scientific staff of a department presents current research results.

Yearly reports are a disliked but necessary tool to summarize the unit's work and to reflect on achievements made. The unit has to contribute frequently to regular national and international conferences like the meetings of the International Statistical Institute, the Biometric Society, COMPSTAT, the International Society on Clinical Biostatistics (ISCB) and the national statistical societies.

9. Perspectives and Summary

The aim of this review was to demonstrate that an interactive concept of consulting, collaboration and research work can be pursued with success by a biostatistics department in a cancer center. Biostatistical consulting and expertise is important for composing biometrical designs. Research in modelling implies the definition and validation of new designs for novel types of experiments and studies. We realized the need of continuity to cover both the standard fields of biostatistics (e.g. experimental design, failure time analysis, non-parametric statistics) and evolving fields (e.g. clustering, machine learning, multiple comparisons, competing risks, methods for validation). We also want to stress that building and maintaining a biostatistics unit requires the vision to improve science through statistics and it takes quite a time to establish a functioning biostatistics unit, in sharp contrast to the short time it may take to destroy it by misconceptions and mismanagement.

In summary, one may say that a biostatistics unit/department

- is active at the interface between the biomedical disciplines and the mathematical and statistical sciences and should add value to the quality of the center;
- has to implement and foster continuously biostatistical methods in the biomedical disciplines through service and research;
- supports the center in total without giving preferences to some departments or groups;
- provides state of the art statistics, develops appropriate methods fit for purpose, disseminates and supports wide usage and it acts at national and international level.

REFERENCES

Armitage, P. (1985): Biometry and medical statistics. Biometrics *41*, 823-833.

Arndt, S., Woolson, R.F. (1991): Establishing a biostatistical core unit in a clinical research center. The Amer. Statistician *45*, 22-27.

Benner, A. (1992a): Linked views. In: Computational Statistics, Vol. 2. Eds.: Y. Dodge, J. Whittaker, Heidelberg: Physika 1992. S. 39-41.
Benner, A. (1992b): S-plus. A review. Computational Statistics *7*, 371-375.
Carter, R.L., Schaeffer, R.L., Marks, R.G. (1986): The role of consulting units in statistics departments. The American Statistician *40*, 260-264.
Chiang, C.L. (1985): What is biostatistics? (with response by M. Zelen) Biometrics *41*, 771-775.
Edler (2005): Computational Statistics und Biometrie: Wer treibt wen? Computational Statistics and Biometry. Which discipline drives which? GMS Med. Inform. Biom. and Epidemiol. 1, 27-43.
Ellenberg, J.H. (1990): Biostatistical collaboration in medical research. Biometrics *46*, 1-32.
Federer, W.T. (1984): Cutting edges in biometry. Biometrics *40*, 827-839.
Gehan, E.A. (2000): Biostatistics in the new millennium: the consulting statistician's perspective. Stat.Meth. Med. Res 9, 3-16.
Gehan, E.A. (2001): The role of the biostatistician in cancer research. Biom. Pharmacother. 55, 502-509.
Marquardt, D.W. (1981): Criteria for evaluating the performance of statistical consultants in industry. The Amer. Statistician *35*, 216-219.
Schmoor C, Eisele C, Graf E, Sauerbrei W, Klingele B, Hellmer A, Rossner R, Schumacher M. (1997): Arbeitsweisen des Methodischen Zentrums am Institut für Medizinische Biometrie und Medizinische Informatik der Universität Freiburg bei der biometrischen Betreuung klinischer Studien Informatik, Biometrie und Epidemiologie in Medizin und Biologie 28: 253-274.
Vingron M. (2001): Bioinformatics needs to adopt statistical thinking. Bioinformatics 17, 389-90.
Zelen, M. (1983): Biostatistical sience as a discipline: a look into the future. Biometrics *39*, 827-837.

Table 1: Schematic summary of major activities of the Department of Biostatistics at the German Cancer Research Center

RESEARCH

1. Statistical Genetics and Genomics and Methods in Translational Research

- Microarray Quality Control
- Good Microarray Analysis Practice
- Integrative (High-Dimensional) Data Analysis
- Molecular Marker Based Prognostic and Predictive Factors
- Design and Analysis of Pivotal Phase III Studies

2**. Preclinical Biostatistics**

- Carcinogenesis Models
    - Development of New Models
    - Applications on Experimental Data
    - Human Health Effects Models
- Molecular Genetic Bioassays
- Pharmacokinetic and Pharmacodynamic Models
- Risk Assessment Methodology and Statistics in Toxicology

3**. Clinical Oncology**

- Biometry for Design and Evaluation of Clinical Trials
    - Biometric Center for Phase I-III Studies
    - Clinical Cancer Trials for Treatment Optimization
- Statistical Methods for Observational Studies
- Automatic randomization
- Screening Studies

SERVICE

- Training and Education in Statistical Data Analysis
- Training and Education in Experimental Design
- Biometric Designs for Animal Experiments
- Data Management and Quality Assurance