

Statistics in Telemedicine

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1. Introduction

All those concerned with the decision-making, they take better decisions when they use all the available information with practical and interpretable way. Statistics provide methods for data collection and analysis to support the decision-making.

Statistics is the Science of collection, analysis and interpretation of observed data reported in attributes of natural or social phenomena. Utilization of statistical methods included in the content of Statistical Science, allows the collection, classification, presentation and analysis of data. The statistical methods are objective and have mathematical background and formulation.

The term *population* in the Statistics (Dodge, 2008; Everitt & Howel, 2005; Salkind, 2007) implies enumerations or measurements reported in a collection of beings or objects. A *sample* is a limited number of units and is extracted from the population under study according to the rules placed by the theory of sampling. The term data collection involves the process of measurement or enumeration of attributes of units of the population.

In Statistics two sectors are included (Dodge, 2008; Everitt & Howel, 2005; Salkind, 2007), the Descriptive Statistics and the Inferential Statistics. *Descriptive Statistics* provides the systematic, quantitative description of natural, social and other phenomena. Descriptive statistics involves the study as well as the presentation, with more convenient way, of the data that exhibit features and behavior of these phenomena. *Inferential Statistics* has as subject the generalisation of conclusions that follow from the descriptive statistical data analyses performed in a representative sample, despite the existence of sampling errors, the margin of which is determined by the statistical induction at the generalisation.

This study attempts to provide answers regarding various questions. It presents the framework of statistical studies in Telemedicine and describes the statistical methods used in Telemedicine research and evaluation (diagnostic tests, quality control, reliability analysis, sensitivity analysis, multivariate analysis, statistical pattern recognition and meta-analysis). It also exploits the potential of statistical use in testing capacity/overall performance, reliability/endurance and scalability/benchmarking of a web based telemedicine platform with different numbers of simulated users for a user-defined time and presents vulnerability statistics available for testing the security of a web based Telemedicine platform. It also describes questionnaire based statistics for the evaluation of patient's satisfaction and the contribution of statistics in new bio-markers detection. Further, qualitative and quantitative statistical techniques, regarding the electronic medical records

and bio-banks are also presented together with application based data analysis techniques (primary care, teleradiology, telecardiology, telepathology, teleoncology, teledermatology and home-telecare). Finally, the use of statistics in the design, evaluation and re-engineering of public telemedicine strategies is discussed.

2. Organisation of statistical studies in Telemedicine

Various types of statistical studies in health exist which can improve the implementation of Telemedicine. The basic characteristics of studies and their ideas are summarized as follows:

- Need of understanding of *disease causation*
- Need of description of *disease occurrence*
- Utilization for creation and hypothesis testing and evaluation of *Telemedicine and e-Health interventions*.

Fundamental characteristics of designing studies for statistical data processing in Telemedicine are the creation of aims and objectives and the adoption of appropriate methodology. The Epidemiologist (Fig. 1) studies the models of diseases development and the factors that influence these models.

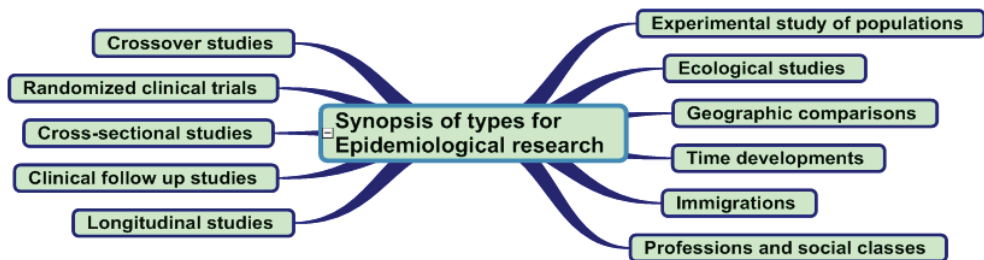


Fig. 1. Synopsis of types for Epidemiological research

The foundations of Epidemiology (Porta, 2008; Gordis, 2008; Rothman et al., 2008) are based on disease models, methods and approaches. Various epidemiological methods were developed at the pursuit of reasons of infectious diseases and epidemics. Epidemiology has also been proved effective in the localization of cross-correlations of cause-effect in non-infectious diseases as the use of narcotics, the suicide, the car accidents, the chemical poisonings, the cancer and the cardiopathies. Other advanced research sectors are Epidemiology of chronic diseases and behavioral Epidemiology.

As exploratory process, the Epidemiology constitutes the basis of public health and preventive medicine. It is used for the needs analysis for programs for diseases control, for the growth of prevention programs, for the planning of activities of health services and the identification of characteristics for *endemic diseases*, *epidemics* and *pandemics*.

Designs for epidemiologic research (Porta, 2008; Gordis, 2008; Rothman et al., 2008) are *Descriptive* and *Analytic*.

The aim of a descriptive design is the description of patterns and trends. These designs support the hypothesis formulation and the programme design. They determine the prevalence of a disease or the appearance of some other health outcome. They measure also risk factors and consequences in health outcomes. The risk factors and the consequences can be measured in connection (as a function) with the time.

The types of descriptive designs are (Abramson & Abramson, 2008; Abramson & Abramson, 2001; Porta, 2008; Gordis, 2008; Rothman et al., 2008):

- *Case Report*: the profile (model) of a patient is presented in detail from one or more clinical doctors.
- *Case Series*: a collection of cases is created by a case report that has been extended to include a number of patients with a given disease.
- *Surveillance Report*: The following stages are followed (i) data are collected with a standardized way for a disease as well as demographic elements, (ii) data collections are available (individual level) for a whole population, (iii) the appearance of a disease is examined per person, area and time. Systematic (*a-priori*) comparison of groups is not performed. The annual percentages or annual rates are many times attractive for the presentation of a tendency in connection with the time. Often the accumulative use of case reports is indicative of a new epidemic or a new disease.
- *Ecological Studies*: In these studies, all the population constitutes the object of analysis. The goal is to examine the ecological fallacy.
- *Correlation Studies*: They are comparable with ecological. The aim is to discover the power of the ecological cross-correlation.
- *Cross-sectional Studies*: Often, the interest of research is focused on the description of frequency and model or disease, or on a health-related outcome. The existing characteristics concern morbidity or some health related outcome and are measured simultaneously. Usually the collection of elements is realized via door-door visits, postal mail or with telephone interviews. There is no preselection of the cases or comparison groups (if they exist); post-hoc selection is realized.

The goal of an analytic design is to test the hypothesis of a relation existence between a risk factor and a disease or a health outcome. A measure of the association is selected, and the magnitude, the precision, and the statistical significance of the relationship are determined.

The types of analytical designs are (Abramson & Abramson, 2008; Abramson & Abramson, 2001; Porta, 2008; Gordis, 2008; Rothman et al., 2008):

- *Cross-sectional studies*: Apart from their descriptive use, sometimes are analytic. Preliminary selection of cases or comparison groups is not realized. Existing characteristics concern exposure or health outcome and are measured simultaneously. Consequently, the assessment of provisional result (temporality) in a relationship, which is revealed, is not possible.
- *Observational studies*: In this category, *longitudinal studies* are included. In a longitudinal study, the subjects are monitored in time with continuous or repeated follow-up of risk factors, health outcomes or both. The two types of longitudinal studies are (i) *Case-Control*: At this study, a population of cases and controls is selected that are comparable. The exposure or the risk factor between cases and controls is retrospectively measured. The exposure and the health outcomes are compared, between cases and controls, to test an *a-priori* hypothesis. (ii) *Cohort or Follow up*: The risk factor is measured to determine the exposed and non-exposed. This cohort is monitored in time, to find out the health outcome (morbidity). The *a-priori* hypothesis is tested at the end of the study period. (iii) *Intervention Studies*: In epidemiological research, the following designs can be applied: Clinical Trials, Field Trials and Intervention Trials.

There is software for epidemiological research design such as EPIINFO and WINPEPI (Abramson & Abramson, 2008; Abramson & Abramson, 2001) that are proposed to be used for the organization of statistical studies in Telemedicine.

3. Statistical methods used in Telemedicine research and evaluation

3.1 Power and sample size

An important issue in a statistical study is the determination of the appropriate sample size (Whitley & Ball, 2002d) needed to test a null hypothesis.

The effect size represents the magnitude of the effect and is usually known from previous research or specified from the researcher. Conventional values for effects have been suggested by Cohen (Borenstein et al., 2001). Alpha is the criterion required to establish statistical significance (usually set at 0.05).

The power (Whitley & Ball, 2002d) is the probability to detect and call significant the specified effect at the designated level of significance. As a general standard, power should be set to 80%. The higher the specified power (usually set between 80% and 95%), the larger the sample size.

Software is available to determine the sample size given the power, alpha and effect size and selecting the statistical analysis we want to apply. Note that when working with drugs and the study goal is to obtain FDA approval for use, then alpha should be set to 0.01, while keeping power at 95% (Borenstein et al. 2001).

Power and Precision, NQUERY Advisor, GPOWER, WINPEPI, SAS, NCSS-PASS can be used for the determination of power and sample size.

3.2 Diagnostic tests

Diagnostic tests or *Screening tests* are called the medical tests performed to detect and prevent diseases. These tests are the series of annual medical check-ups, blood tests, test Pap and various x-rays. Their goal is to detect diseases that cannot be detected with other way or for the discovery of a disease in premature stage (before the appearance of symptoms) to handle it in time and effectively. A characteristic of diagnostic tests is that if an individual has a positive outcome then it is probable to have the disease under investigation and consequently is submitted in more precise examinations or straight therapy (if the diagnostic test is extremely precise). In these cases, Bayes theorem is particularly beneficial. The *positive predictive value* of a diagnostic test is the probability of someone to be patient when the diagnostic test is found positive. The *negative predictive value* of a diagnostic test is the probability of someone not to be patient when the diagnostic test is found negative. *False negative case* is an individual who has the disease, but the diagnostic test is negative. When the individual does not have the disease, but the diagnostic test is positive we have a *false positive case*. In a study, we usually observe sensitivity and specificity. *Sensitivity* of a diagnostic test (or symptom) is the probability the test to be positive (or the symptom to appear) given that someone has the disease under investigation. *Specificity* of a diagnostic test (or symptom) is the probability the test to be negative (or the symptom not to appear) given that an individual does not have the disease under investigation. Both values should be high and close to one to have a suitable diagnostic test.

Usually, the measurements of diagnostic tests are performed using quantitative scale variables. In this case, we are interested in the *cutoff point* over which we consider that the test is positive (the point above which there is increased probability for the appearance of a disease). To select the cutoff point, we use ROC (Receiver Operating Characteristic) curve. A ROC curve (Bewick et al. 2004f) presents in a curve the combinations of false positive cases ($1 - \text{specificity}$) and sensitivity (in X and Y axes) for all the values observed in a

sample. Appropriate values as cutoff points are the values that are close to diagram's upper left corner (these have low count of false positive cases and high sensitivity).

Consequently ROC curves (Bewick et al. 2004f) are the graphical representation of the characteristics of a quantitative diagnostic test and help us to examine test performance for different points of a prognostic test. An important value in ROC curves is AUC (Area Under Curve). AUC measures the probability the value of a test for a patient to be higher from the value of a test for an individual without the under investigation disease. Of interest is the test of hypothesis $H_0: AUC = 0.5$ with alternative $H_1: AUC > 0.5$. The value $AUC = 0.5$ corresponds to a test that guesses randomly and has no prognostic ability.

WINPEPI, Stata, SPSS, NCSS, MedCalc, etc. can be used for the calculation of sensitivity and specificity and for ROC analysis.

3.3 Statistical quality control

Statistical quality control (Montgomery, 2004) is the collection of all methodologies that in collaboration with the management and marketing allows improving the productive process. A definition of quality with statistical meaning is: "a product or a service is of quality if it is adapted to the user requirements and is improved when its variability is minimized". Quality is also connected with a large number of characteristics that are related to whether the product will do the work for which it is intended, the reliability, etc. (Juran & Blanton Godfrey, 1999; Russel, 2000). Statistical quality control is constituted by three sectors: acceptance sampling, statistical process control and design of experiments.

Each productive process, independently of how well it is designed has a percentage of variability. This variability is the summation of variability of many small causes that are difficult to avoid. This variability is referred as a common form of variability, and a system that works with only the presence of this variability is considered to be under control. In a process also, other forms of variability may be present. These forms are mainly due to one of the following reasons: (i) erroneously regulated medical equipment, (ii) errors of medical equipment operator. These forms of variability are those that cause a process not to be under statistical control.

Telemedicine units should adopt the principles and administration of total quality management (Juran & Blanton Godfrey, 1999; Russel, 2000) and include the 5Qs: quality planning, quality laboratory process, quality control, quality assessment and quality improvement.

QI Analyst 3.5. by SPSS, SAS Quality Improvement, STATIT Quality Control First Aid Kit, STATISTICA, MINITAB 16, NCSS can be used for Statistical Quality Control.

3.4 Reliability statistics

The consistency of a collection of measurements is called reliability (Koran, 1975a; Koran, 1975b). Regarding its assurance in Telemedicine studies, four classes of reliability estimates exist (Dodge, 2008; Everitt & Howel, 2005; Salkind, 2007), all examining the variation of measurements.

Measurements can be taken, with the same method or instruments, by different observers (inter-rater reliability), or by a single observer under the same conditions (test-retest reliability including intra-rater reliability). Inter-method reliability deals with measurements derived using different methods or instruments on the same individual. Internal consistency reliability deals with the consistency of measurements across items within a test.

WINPEPI can be used for the calculation of reliability statistics (Fig. 2).

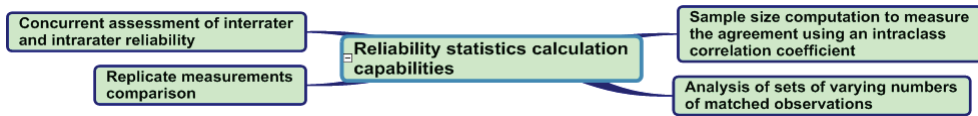


Fig. 2. Reliability statistics

3.5 Sensitivity analysis

Sensitivity analysis exploits the degree in which the conclusions can change if the values of the key variables or hypotheses statements change.

As examples, the following can be applied in Telemedicine:

The user may want to examine how power is affected changing the values of effect size, sample size and alpha. This analysis is provided using as software the GPower or Power and Precision.

Financial projections may show the effect of different hypotheses related to the expenses for telecommunications and other resources. A special problem in the evaluation of Telemedicine is the stability of the technology or the environment. With the technologies of data collection, communication and presentation aiming to improve healthcare quality simultaneously reducing cost, the evaluators may focus on (i) how sensitive the results may be in technological change, (ii) how to design the analysis to assess the impact of changes.

A cost-benefit analysis can include a sensitivity analysis that incorporates different hypotheses about the time and the cost of improvements or replacements in hardware or software (Briggs et al., 1994; Hamby, 1995).

3.6 Hypothesis testing

The Inferential Statistics are the sector of applied statistics that deals with the generalization of the descriptive statistics conclusions in the population.

Hypothesis testing is the effort of estimating unknown population parameters using samples, realizing the testing of concrete hypotheses about the under investigation population parameters. More analytically, the problem faced is how from the data of a sample, we can decide if a hypothesis must be rejected in the population. After the selection and the determination with clarity of the problem under investigation, what follows is the formulation of the hypothesis that is to be checked.

The hypotheses under consideration are not proved with testimonies, only they cannot be denied. In the hypotheses involved in a research study, some hierarchy can exist. Often, for the initial hypothesis the expression inquiring is used, while, for the one that results in the end, the term functional is used. The hypothesis should be solid and relatively easy in the testing. General hypotheses are not recommended. The hypotheses should not be incompatible with things that are already known and should be based on the existing knowledge.

The ways of a hypothesis formulation are an important point in the statistical analysis. We do not check the functional hypothesis, but the logic of the opposite one called the *null hypothesis*. In the case that the null hypothesis is rejected, then we accept the alternative hypothesis. The null hypothesis we usually denote it with H_0 and its alternative with H_1 . The results of a decision that will be taken in significance level alpha in connection with what happens in the population are presented in the following Table 1.

Acceptance decision	Reality	
	True H0 (Null Hypothesis)	False H0 (Null Hypothesis)
H0 Null	Correct Decision	Error type II
H1 Alternative	Error type I	Correct Decision

Table 1. Correct decision and error types in statistical hypothesis testing process

As *error type I*, we define the probability to reject H0 while this is in effect. This error is also called significance level alpha of the test. As *error type II*, we define the probability to accept H0 while this is not in effect. In each test, what is of interest is to reduce error type I.

A decision tree for the statistical analysis of two variables is presented (Fig. 3).

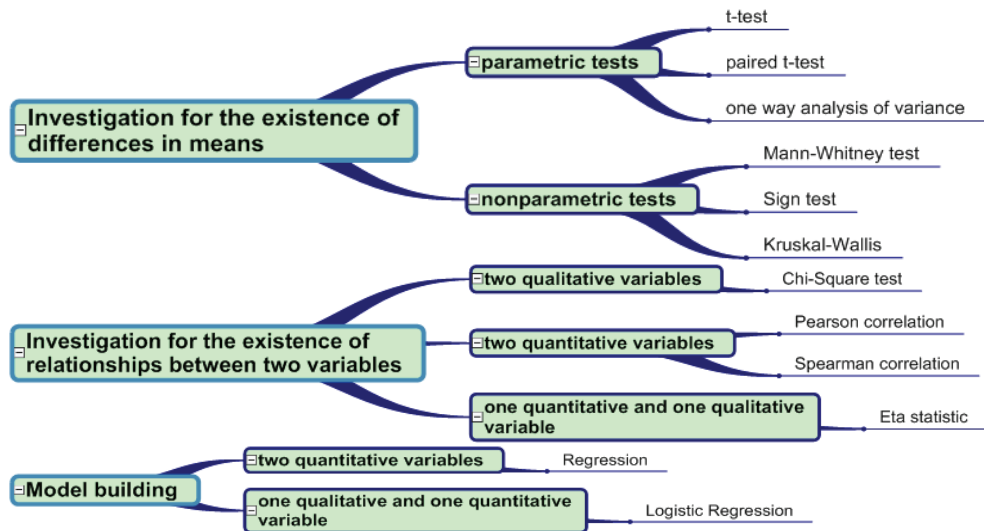


Fig. 3. Decision tree for the statistical analysis of two variables

Statistical data analysis principles (Matthews & Farewell, 2007; Bowers, 2008; Harris & Taylor 2003) are available in the form of reviews (Whitley & Ball, 2002a; Whitley & Ball, 2002b; Whitley & Ball, 2002c; Whitley & Ball, 2002e; Whitley & Ball, 2002f; Bewick et al., 2003; Bewick et al., 2004a, Bewick et al., 2004b; Bewick et al., 2004c; Bewick et al., 2005).

Various statistical packages are available to test a hypothesis involving two variables or for multivariate analysis: STATISTICA, SPSS, SAS, NCSS, MINITAB, StatView, Medcalc, Stata, BMDP and StatXact with Cytel Studio (non parametrics).

3.7 Multivariate analysis

In most cases, many variables are involved in the statistical analysis (Stevens, 2002; Rabe-Hesketh & Everitt, 2007; Landau & Everitt, 2004). Depending on the measurement scales of the data various data analysis options are available (Fig. 4).

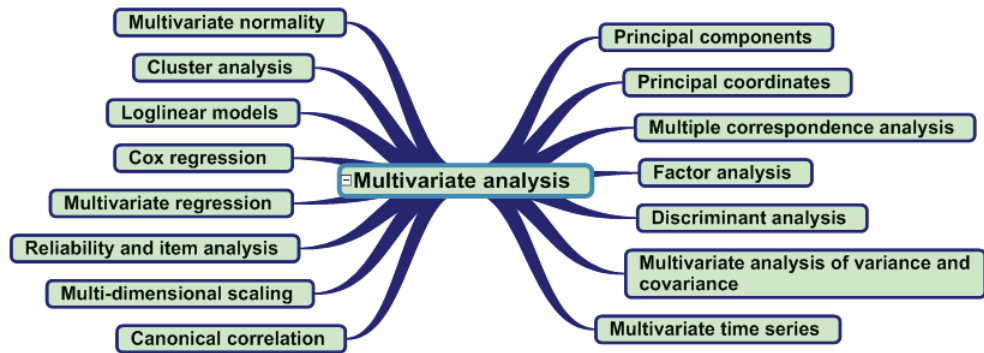


Fig. 4. Statistical techniques for multivariate data analysis

3.8 Statistical pattern recognition

Statistical pattern recognition is concerned with discrimination and classification both supervised and unsupervised (Webb, 2002). Two related approaches to supervised classification are the estimation of probability density functions and the construction of discriminant functions. There are also nonlinear models (projection-based methods) and the decision-tree approach to discrimination. Unsupervised classification or clustering is the process of grouping to discover the presence of structure. Statistical methods are also used in feature generation and feature selection (Theodoridis & Koutroumbas, 2009; Webb, 2002). Statistical pattern recognition has application in biosignal processing and medical image analysis.

Various statistical packages are available for discriminant analysis such as NCSS, SPSS, STATISTICA, and BMDP. For clustering, statistical packages are BMDP, Stata, NCSS, Statistica, SPSS, etc. A significant Statistical Pattern Recognition Toolbox (STPRTOOL) has been developed for MATLAB (Frank & Hlava, 2004).

3.9 Meta-analysis

Meta-analysis allows for general inspection of evidence for clinical problems and necessary with the exponential increase of information in medicine (Borenstein et al., 2009). Meta-analysis uses data from many different studies that deal with the same subject. This allows (i) the calculation of a total/ concise result from all the studies called *pooled effect*, (ii) extensive detection of systematic errors and calculation of differences (*heterogeneity*). Meta-analysis uses objective quantitative mathematical methods to summarize study data. Meta-analysis can be used in studies that are (i) empirical rather than theoretical, (ii) contain quantitative results, (iii) investigate the same relationships, (iv) results are presented with the same comparative statistical manner and (v) are comparable for the main question. Explicit criteria of studies choice and rejection are needed. Wide inquiring fields require detailed criteria. Strict criteria create a problem of generalization of results and relaxed criteria create a problem of results reliability. The study of *fixed effects* (results of different studies differ only from chance) is conducted using the Mantel-Haenszel method, and the study of *random effects* (results are not homogeneous) is conducted using DerSimonian & Laird method. Heterogeneity is tested using Cochran Q or the indicator of inconsistency (Higgins et al., 2003).

Statistical packages available are: RevMan (Cochrane), STATA (metan), SPSS (using macros), R (rmeta), Comprehensive meta-analysis and Meta-analyst.

4. Commonly used statistical methods in Telemedicine diagnosis

4.1 Analyzing validity

An ideal research technique is characterized from *validity* which means that it measures correctly what has to be measured (Dodge, 2008; Everitt & Howel, 2005; Salkind, 2007). Sometimes, an established framework is defined to determine the validity of a method. In the practice, therefore, the validity should be examined indirectly. Usually two ways are used. A technique, which has been simplified and standardised in order to be suitable for use in research, can be compared with the best conventional clinical examination. Alternatively a measurement can be evaluated from its ability to predict a future disease. Examining validity through prediction ability may require the existence of many subjects in the study. When the purpose of a research or a test is based on the separation of subjects (e.g. as cases or controls, exposed or not exposed), validity is analyzed classifying the subjects with positive or negative outcomes, on the basis primarily of the research method and secondarily with the typical control test. A contingency table can be derived with the true positive, true negative, false positive and false negative outcomes. From this table sensitivity, specificity, *systematic error* and *predictive value* can be calculated.

4.2 Analyzing repeatability

Repeatability analysis (Salkind, 2007) can be organized as a separate study, for example, a sample of individuals with a second examination, or x-ray samples checked twice. Even a small sample can be reliable if (i) it is representative and (ii) duplicate tests are independent. If repeatability analysis is performed as a part of a pilot study, then care is needed to ensure that the subjects, the observers and the working conditions are representative of the main study. Repeatability is easy to be checked when the material can be transferred and stored (e.g. histologic samples and medical images). Repeatability analysis is useful when there is no acceptable standard to assess the validity of a measurement. Poor repeatability usually is related with poor validity or indicates that the measured characteristic is differentiated in time. In both cases, the results should be interpreted carefully. It is stressed that repeatable discoveries do not guarantee that the method that was used is valid. Repeatability can be checked from the same observer (realizes the measurement in two separate cases) and between observers (with comparison of measurements that became from different observers in the same subject). The repeatability of measurements for scale variables can be summarized with the standard deviation of the repeated measurements or with the coefficient of variation. The pairs of measurements from the same observer or different observers, the extent and the divergence can be presented in a scatterplot. For qualitative characteristics, such as clinical symptoms and indications, the results are initially presented in a contingency table (with the true positive, true negative, false positive and false negative outcomes) and then Kappa statistic is calculated. The minimal value of the Kappa statistic is less than zero (poor repeatability) and the highest is one (perfect repeatability).

4.3 Using statistics to serve clinical objectives

A Telemedicine program may have different outcomes that are proportional to the population under study and the health status of the specific group during the application

time. The type and health status of the application group have direct repercussions both in quality and the access possibility of a patient. Proportional are also benefits from the reduction of patient cost of care.

The plan is to collect data regarding: (i) standard and variable program costs, (ii) use of services from the participating patients, (iii) demographic characteristics of patients and clinical history, (iv) presentation of symptoms and complaints, (v) health status, (vi) symptoms risk, (vii) operational capability, (viii) analysis of symptoms, and (viii) characteristics of the teleconsultations.

In clinical level the following items should be recorded and evaluated:

- Demographic characteristics of patients and their clinical history.
- Symptoms of present disease.
- Evidence of reliable transmission and evaluation of data acquired from the physical examination of patients and the parameters acquired from telemedicine medical devices.
- Use of telemedicine services from the patients and recording of medical problems during program use.
- Changes in the ways of patient access (number of teleconsultations, teleconsultation type, and cost of diagnostic examinations).
- Changes in patient treatment with evaluation of the changes in the pharmaceutical treatment (change of drug, dose and the way of issuing of pharmaceutical substances, cost of these changes) and the therapeutic methods used (number, type and cost of surgical interventions).
- Changes in the medical or nursing visits, number of hospitalizations (morbidity) and mortality of patients.
- Improvement of quality of life and mental health of patients with the use of special questionnaires.

5. Statistics in testing the performance of a Web-based Telemedicine platform

There is the potential of statistics use (Fig. 5) in testing, capacity/overall performance, reliability/endurance and scalability/benchmarking of a web based telemedicine platform with different numbers of simulated users for a user-defined time.

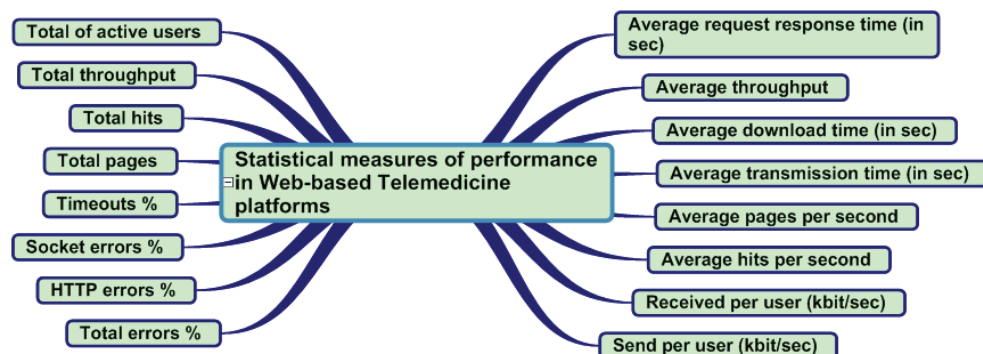


Fig. 5. Statistical measures of performance in Web-based Telemedicine platforms

Software that is proposed to be used is WAPT 6.0 and NEOLOAD.

Furthermore, in the Telemedicine network, each computer and medical device reliability and history should be continuously monitored regarding application failures, operating system failures, various other failures and warnings.

6. Statistics in testing the security of a Web-based Telemedicine platform

The percent of various security vulnerabilities (Web Application Security Consortium, 2008) in time (on a daily basis diagram) should be monitored for a web based telemedicine platform (Fig. 6).

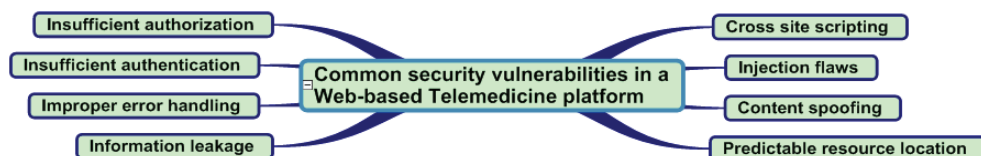


Fig. 6. Common security vulnerabilities in Web-based Telemedicine platforms

Software that can be used to produce security audits for Web based Telemedicine platforms is Acunetix.

7. Questionnaire based statistics for the evaluation of patient satisfaction

Herein, the strategy and the steps to get valid comparative data and analyze it, are presented.

Three types of questionnaires can be used: to the patient, to the provider and to the organization.

The questionnaires should be valid and reliable. In a questionnaire creation process, it is necessary to determine the reliability (internal consistency) of the new instrument. It is difficult to assess the quality of data collected during a research process. It is easier to evaluate the accuracy of the research tool used for data collection. This assessment is comprised by the analysis of validity and reliability. Each stakeholder class (patient, provider, organization) has expectations and satisfaction sentiments for the quality of information, services and operations which are offered. The goal is to identify the most significant factors that cause the highest level of dissatisfaction and have the bigger effect with respect to e-healthcare quality and the costs.

A method to test questionnaire validity: When the factors that produced the highest level of dissatisfaction are derived, using a questionnaire, a representative sample of each category stakeholder can be interviewed and asked to complete a new short questionnaire. This research will determine how appropriate, complete and comprehensive are the questions in a group of evaluators that have certain knowledge of the content. This process allows confirming questionnaire validity.

A method to test questionnaire reliability: To evaluate the reliability level of the questionnaires different methods can be used (test-retest method, split halves method). The reliability of internal consistency can be measured calculating Cronbach’s coefficient alpha. An additional scale can be included to measure the questionnaire internal consistency. This scale can be defined with the characterization “satisfied/dissatisfied” and can be included in

the evaluation of each factor measuring quantitatively also the strength of the characterization (from poor to high). This "direct" evaluation should be related with each factor score measured from the strength of characterization. The same scale can be included at the end of the questionnaire, to provide an evaluation of the stakeholder overall satisfaction with aspects for the Telemedicine system, services and information. These scales allow the selection and the representativeness of the factors and their characterizations to evaluate stakeholder satisfaction for a telemedicine system. These added scales can be used, during experimental research, to validate the internal consistency of the questionnaire. Various multivariate statistical analyses can be performed on the questionnaires with focus on reliability analysis (for Cronbach's alpha coefficient calculation) and exploratory and confirmatory factor analysis.

Experimental processes to compare a Telemedicine treated group with an alternative, traditional care, group: During the pilot study to evaluate a Telemedicine program, patients with a known disease should be included that are exposed to health risk justifying the need of telemedicine and the highest benefit from it. The patients should be divided in two groups: the telemedicine group and the control group. The control group should be comprised from patients similar in age and sex and with the same disease and will receive regular traditional health monitoring (no telemedicine treatment).

Data Analysis: All the data (electronic recordings of medical signals, images and text) should be collected in the electronic medical record and the specialized questionnaires be collected and stored in a database.

The two groups of patients that participate in the study can be compared to find out if there are statistical significant differences in the following aspects:

- The diagnostic access, from the recording of the number, the type and the cost of diagnostic examinations needed during the study period.
- The therapeutic treatment from recording the changes in the pharmaceutical therapy using the drug type, the drug dose, the way of issuing the pharmaceutical substance, the cost of drug dose during the study period.
- The chirurgical therapeutic methods needed, recording the number, the type of surgery and the cost of surgery during the study period.
- The number and the cost of medical or/and other visits recorded during the study period.
- The number of hospital admissions (morbidity) during the study period and the cost of hospitalization.
- The number of patient deaths (mortality) during the study period.
- Quality of life and mental health, using analysis on appropriate questionnaires.

8. Exploit the use of statistics in new biomarkers detection

A biomarker is a measurable factor that is associated with a medical condition (a gene variant, a metabolite, a pattern of gene activity, etc.). Drug development process is most benefited from biomarkers that allow the early detection, diagnosis, and prognosis of diseases. It is an enormous challenge to analyze using statistics 'omics' data (genomics, transcriptomics, proteomics, metabolomics, interactomics, regulomics) (Lee, 2010).

A synthesis of available statistical techniques for new biomarkers detection is presented in Fig. 7.

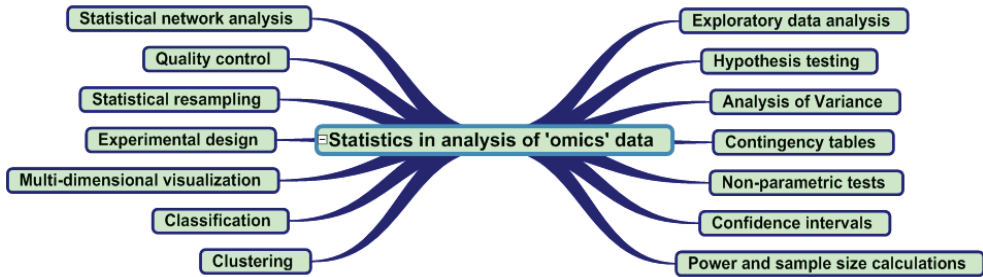


Fig. 7. Statistics in analysis of ‘omics’ data

Statistical packages in bioinformatics available are R and Bioconductor.

9. Qualitative and quantitative techniques regarding electronic medical records and biobanks

9.1 Statistics regarding the electronic medical records

Electronic medical records, apart from numerical measurements, also contain images, biosignals and text. Statistical analysis on numerical measurements (Fig. 3, Fig. 4), images (Fig. 8, Fig. 9), biosignals (Fig. 10), and text (Fig. 11), has already been applied.

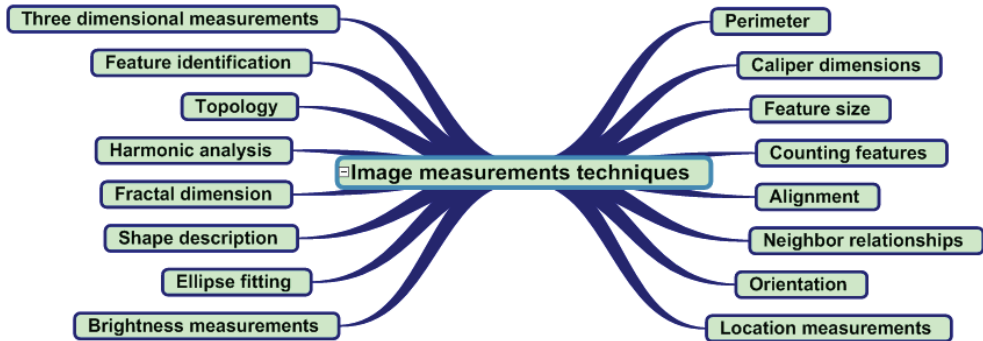


Fig. 8. Image measurements techniques (Russ, 1995)



Fig. 9. Statistical image analysis techniques applied on image measurements

For spatial statistical image analysis SpatStat library is available in R as well as the Image Processing Toolbox in MATLAB.

Statistical packages that perform time series analysis on quantitative biosignal data are SPSS, NCCS, Statistica, SAS, Stata, BMDP, etc.

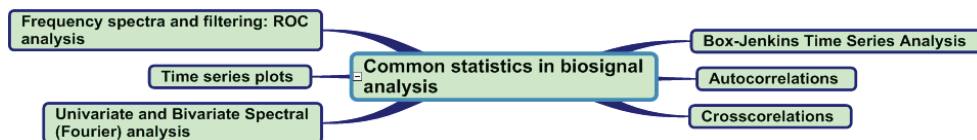


Fig. 10. Statistical analysis techniques applied on biosignals measurements

It also exists specialized software for biosignal analysis including statistics such as g.Bsanalyze and SIGVIEW.

For qualitative analysis of the texts included in the electronic patient records, NVIVO software can be used which allows after coding the extraction of relationships and the exploration of models produced. For mixed-model qualitative data analysis using coding, annotating, retrieving and analyzing small and large collections of documents and images in the electronic patient record, QDA Miner with WordStat & Simstat software can be used.

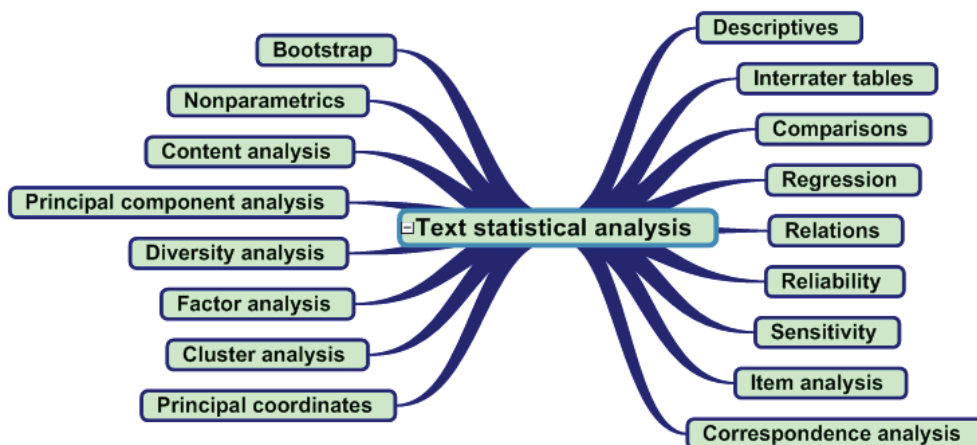


Fig. 11. Statistical analysis techniques applied on text data

9.2 Epidemiology using biobanks

Biobanks are repositories of human biological material linked to clinical data (medical and lifestyle data) for evaluation of interactions between the environment and genes. The ultimate goal is to understand the disease development process. Biobanks are categorized in (i) *prospective*: biological material is collected at study start and health status is monitored over subsequent years, and (ii) *retrospective*: biological material from people who have already developed a disease is collected, over subsequent years, to track down the association between environment, genes and the diseases.

The number of cases is essential for a reliable analysis. Other points of interest are the quantification of metadata acquired and biobanks security auditing. The ultimate goal is the creation of an *epidemiological meta-database* using regulations, standardized methodologies and coordination across biobanks. Ethical considerations involved are (i) the privacy of the donor and (ii) who owns the samples. Informed consent of the donor is a pre-requisite in storing data (in a biobank), as well as the established policies from biobanks.

There are various facilitations for epidemiology using biobanks (Fig. 12).

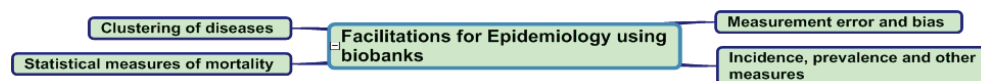


Fig. 12. Epidemiology using biobanks

Clustering of disease

Clustering of disease (Mantel, 1967; Manly, 1986) can be realized spatial, temporal and spatial temporal using data from electronic medical records. *Spatial* clustering of disease may be attributed to the population distribution, the relationship of disease with diet, the habits, the environment or the profession. Chi-square test can be used for statistical decision-making. *Temporal* clustering of disease may be attributed to seasonal variation, systematic trends or in rapid increases due to additional factors. Again, Chi-square test can be used for statistical decision-making. *Spatial temporal* clustering of disease concerns cases, where they are neighboring in the space (spatial) and simultaneously they are neighboring in the time (temporal) because of the existence of pestiferous factors, environmental episodes in regional scale or local immigrations. The main spatial temporal association in the appearance of a disease can involve the existence of certain infectious or environmental reasons. Mantel's test is used for the control of space-time interaction (Manly, 1986).

Quantification of disease frequency in populations

Disease frequency measurement in populations requires the careful formulation of diagnostic criteria. It has also been observed that the morbidity in populations is presented as development of severity. The two measures of disease frequency are *incidence* and (point or period) *prevalence*. Herein, we assume that the percentages in the exposed population are comparable with those of the unexposed individuals. Exposure can assess risk factors for which suspicions exist that they cause the disease (Bewick et al., 2004d). There are measures used to summarize the comparisons of morbidity percentages between populations: relative risk, attributable risk, population attributable risk, and attributable proportion. Most epidemiological studies are based on observation and compare persons that differ with a lot of ways, known and unknown. If the morbidity risk is determined by such differences varying from the exposure under consideration, then we can say that there is confounding of the classification factors (e.g. age and sex) in relation to morbidity. Confounding is handled using (i) (direct or indirect) standardization or (ii) mathematical modeling (e.g. logistic regression).

Statistical measures of mortality

Mortality is used to describe death as a disease outcome. Statistics are derived from data written in death certificates. In the published mortality tables, the actual numbers and the rates of death per sex, age and causality are presented. In clinical trials for diseases that lead to death the health outcome can be defined as case mortality or survival rate. Survival curves (Bewick et al., 2004e) can be drawn from the survival rates in different times.

Incidence, prevalence and other measures

The terms of incidence and prevalence have been defined concerning the presence of disease and can be extended to include other situations. Certain healthcare results do not necessarily describe incidence or prevalence. Alternatively, the following measures (related with a year) can be used: birth rate, fertility rate, infant mortality rate, stillbirth rate, and perinatal mortality rate.

Measurement errors and bias

The epidemiological studies measure characteristics of the populations. The parameter of interest may be the morbidity percentage of a disease, the prevalence of an exposure and more often a measure of association between the exposure and disease. Given that the studies are realised in human subjects and are conditioned by practical and ethical restrictions, the danger of bias exist. The possible cases of bias are (i) *Selection bias*: Selection bias is required to be examined when a sample is determined and in the cases the answers are not complete. (ii) *Information bias*: Bias also results from errors in the measurement of exposure or the severity of a disease. Bias can not be abolished entirely from epidemiological studies. The aim therefore is to ensure that it exists in a minimal degree, examining their possible impact and taking it into consideration when interpreting the results. The measurement errors in the exposure or the disease may be a valuable source of bias in epidemiological studies. Consequently at the implementation of research it is necessary to assess the quality of measurements.

Useful statistical packages for epidemiological research that can be used are EPIINFO and WINPEPI.

10. Telemedicine application based data analysis techniques

Exploiting the fundamental telemedicine applications (primary care, teleradiology, telecardiology, telepathology, teleoncology, teledermatology and home-telecare) it is obvious that text, biosignals and images are transferred. For these data types, various statistical data analysis techniques can be applied in the electronic medical records (Fig. 8, Fig. 9, Fig. 10, Fig. 11) collected using Telemedicine.

Furthermore, performance (Fig. 5) and security auditing statistics (Fig. 6) are required to be collected during monitoring of the telemedicine application and network.

Statistics can be extracted also using data from teleconsultations and telediagnosis (presented previously as statistics used to serve clinical objectives) as well as from evaluating the patient's and provider's satisfaction (presented as questionnaire based statistics) using questionnaires. Another important feature for Telemedicine diagnosis processes is careful statistical reliability analysis (Abramson & Abramson, 2008; Abramson & Abramson, 2001; Koran, 1975a; Koran, 1975b).

11. Statistics use in the design and re-engineering of public Telemedicine strategies

In the current era of Telemedicine and e-Health, all nations are interested in developing national strategies for the improvement of quality and reliability of Telemedicine. Material provided by WHO (World Health Organization, 2006a; World Health Organization, 2006b) can be used as effective assistance to this effort. Legal frameworks regarding the implementation of Telemedicine within a country as well as in trans-border care should be taken into account in this process accompanied with ethical issues, issues related to patient safety, patient empowerment and evaluation.

Statistical quality control can be used in the design and re-engineering of Public Telemedicine strategies. Statistical analysis of teleconsultations information and electronic

medical records (including genomic information) collected practising Telemedicine and e-Health provides enormous possibilities in decision-making (Fig. 13) and in facilitating epidemiological studies.

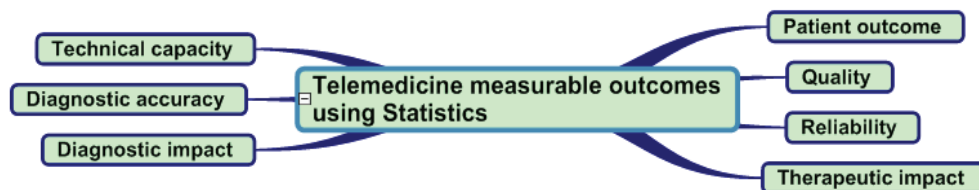


Fig. 13. The contribution of Statistics in Telemedicine

12. Conclusion

There was a lack in the scientific literature regarding a systematic presentation of statistical methods in Telemedicine. This work uncovered opportunities and challenges related to the contribution of statistical data processing in Telemedicine. It is our hope that the guidelines presented herein, in the form of concept maps, will serve as telemedicine assessment instruments for the improvement of Telemedicine systems and services. Future work will be focused on producing detailed statistics review frameworks for all Telemedicine applications accompanied with case studies.

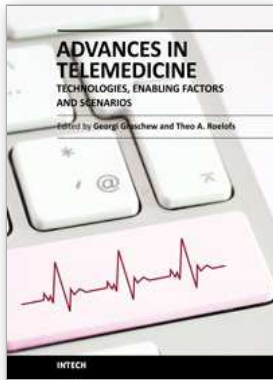
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Innovative developments in information and communication technologies (ICT) irrevocably change our lives and enable new possibilities for society. Telemedicine, which can be defined as novel ICT-enabled medical services that help to overcome classical barriers in space and time, definitely profits from this trend. Through Telemedicine patients can access medical expertise that may not be available at the patient's site. Telemedicine services can range from simply sending a fax message to a colleague to the use of broadband networks with multimodal video- and data streaming for second opinioning as well as medical telepresence. Telemedicine is more and more evolving into a multidisciplinary approach. This book project "Advances in Telemedicine" has been conceived to reflect this broad view and therefore has been split into two volumes, each covering specific themes: Volume 1: Technologies, Enabling Factors and Scenarios; Volume 2: Applications in Various Medical Disciplines and Geographical Regions. The current Volume 1 is structured into the following thematic sections: Fundamental Technologies; Applied Technologies; Enabling Factors; Scenarios.

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