Développement et utilisation d'une plateforme d'intégration d'information appliquée aux anévrismes intracrâniens

Bijlenga, Philippe Alexandre Pierre

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG
Hôpitaux Universitaires de Genève

Clinical Medicine Section
Department of Clinical Neurosciences
Service of Neurosurgery

Biomedical Information Integration for Neurovascular Clinical Management and Research

Thesis submitted to the Medical School of
the University of Geneva

for the degree of Privat-Docent
by

Philippe Alexandre Pierre BIJLENGA

GENEVA

2012

Table of contents

Foreword

Since the beginning of the XXIst century, the systematic exploration of the world and the scientific construction of knowledge have accelerated exponentially. Computing and computer networks allow global information communication and integration to dramatically modify lives. The World Wide Web gives people immediate access to a global pool of knowledge using dedicated tools such as web browsers (Internet Explorer, Netscape, Firefox, Safari, Mozilla, Google Chrome, etc.) and search engines (Google, Yahoo, Baidu, Ask, AOL, etc). More specialized library and database browsers allow access to more specific information such as: 1) the current edition of a few thousand newspapers of the world (www.onlinenewspapers.com, www.world-newspapers.com), 2) video-sharing (www.youtube.com) 3) life science and biomedical abstracts and references (http://www.ncbi.nlm.nih.gov/PubMed, apps.webofknowledge.com), 4) bioinformatics resource portals allowing access to resources useful for life sciences (expasy.org/) or rare diseases (www.orpha.net) research. The World Wide Web also supports personal broadcasting (blogging) and social networking (Facebook, Twitter) that reshape society and human relationships.

With regards to health, scientific advances in microbiology and infectious diseases, increased understanding of human patho-physiology, cardiovascular diseases and oncology -just to cite the top ranked causes of death- significantly improved longevity.

The next challenge is to deliver continuously up-dated and relevant knowledge and technology to professionals around the globe to improve health and safety of care.

We believe that the development of information technologies will support the educational effort, the interaction platforms and the construction of a representation of health and disease globally that will allow each person to preserve himself, care providers to improve their standards, researchers to discover and industry to develop more efficient therapies.

We report here a new paradigm of care that is intimately linked to teaching and that provides data to Research & Development allowing for better compliance with the latest standards of care. We expose how it should build evidence to support current and future clinical practice. We show how information

integration is enhanced by modern network computing and can be applied in many different ways in medicine.

The format of this report mirrors the traditional structure of a scientific communication. It starts with an introduction explaining issues at stake and prior developments resulting in the current situation and paving the way for a new paradigm and aims of research. The next section reports on the material, methods, developments and strategies that were used and designed to explore the feasibility and potential impact of the introduction of the paradigm into practice.

To perform the proof of concept the @neurIST project limited the scope to intracranial aneurysm..

Focusing on intracranial aneurysms is motivated by a constellation of rationales.

1) Intracranial aneurysm is a prevalent disease affecting 3.2% (95% CI 1.9-5.2) of the population (1).
2) There is a life threatening risk associated with the rupture of the aneurysm. It is estimate that 10% of patients die from the rupture before reaching medical assistance. The mortality despite best care was 16.7% (95% CI 11.9-22.7%) for patients admitted with a ruptured intracranial aneurysm in Swiss hospitals during the year 2009. A significant proportion (35%; 95%CI 28-44%) of survivors suffer long term disability. Only 42% (95%CI 35-52%) of patients surviving have no or very light symptoms having no impact on performance.(2).
3) The median age of patient that suffer of the disease is young (55 years) (2).
4) Patients affected with an intracranial aneurysm have an average low annual rate of rupture of 0.95% (95% CI 0.79 to 1.15) but rupture risk varies tremendously with aneurysm size, rupture and presence of other risk factors (3). The projection of the natural history of the disease needs to be customized to each patient.
5) Risk associated with the treatment are significant with 1.7% mortality and 6.7% overall morbidity (4).Risk vary with both aneurysm types and treatment methods used.
6) Emerging new technologies like endovascular coiling, stent assisted coiling and flow diverter stents implantation challenge the former gold standard treatment by microsurgical clipping of intracranial aneurysms (5). Each technique has specific indication and quandary and develops rapidly.

7) Most of the patho-physiology remains unknown (6) but exploration and knowledge grows fast (search using the term “intracranial aneurysm” yields 22472 items in Pubmed and 915 items for year 2011).

A selection of original works performed using tools and data generated by the @neurIST project illustrate how information technologies applied to the field of intracranial aneurysms allow observing the disease, improving knowledge, collaboration and monitoring the impact of new therapies with much more accuracy than ever before.

Executive summary

The aim of this work is to describe a vision for a new paradigm of care involving an advanced information system.

The aims of this information system are defined as follows:

A) Improve compliance to best practice, guidelines of care and evidence based medicine

B) Promote efficiency and reveal bottlenecks in medical care systems

C) Generate missing evidence

D) Facilitate interaction and collaboration between care providers, scientists and industry, promoting Research & Development

E) Enhance education of care providers

We describe the development steps of a first prototype of information system, its implementation and use. The design of the information system has started with an ontological identification and classification of entities needed to describe the chosen disease – intracranial aneurysms. Terms and inter-relations were defined resulting in a Clinical Reference Information Model (CRIM). All stakeholders related to the disease were interviewed to define needs and requirements and later aggregated in four generic groups: care providers, researchers, service providers, manufacturers. A generic architecture of the information system was designed using the CRIM and the specifications defined by the stakeholders. Concomitantly,

1) a study protocol was written to generate data and results proving the validity of the new paradigm of care,

2) tools were developed and

3) users trained.

We report on a selection of scientific works and illustrate the impact such a system could have if implemented on a large scale.

In just a few years the project was able to collect information and contribute significantly

1) to the discovery of genetic loci associated with the disease.

2) to the identification of a gene expression signature in the circulating blood cells allowing the identification of patients affected by intracranial aneurysm.

3) to improve the personalized evaluation of the risk associated with the natural history of unruptured intracranial aneurysm.

4) to improve the safety and quality of the treatment and management of intracranial aneurysms.

Using the developed tools it was easier to follow the global evolution in the field and grasp a more detailed understanding of the disease.

We finally present prospects for the future and propose specifications regarding the development of infrastructures, software and hardware.

This work represents the latest developments, understanding and prospects resulting from the @neurIST project that was funded from April 2006 to April 2010 by the European Commission for Information, Society and Technology. The author was involved as a member of the Project Board and was responsible for the clinical and biomedical data collection and for the clinical impact assessment. He led a multidisciplinary team of 15 scientists involved in information technologies, genetics, transcriptomics, epidemiology, neuro-interventional radiology, neurosurgery, ethics, flow simulation and systematic literature reviews. Besides the EU funding for the @neurIST project, the author's other scientific work was supported by the Swiss National Fund Grant 3100A0-116770, the Theodore Ott Foundation, the Schmeidheiny Fund, the Société Académique de Genève and the SYNTHES Research Prize.

1. Information and Health Care System Overview

Medical care is a service to the population that involves many professionals whose aim is to optimize health and costs. It interacts highly with Research & Development. It is extremely impacted by the education of all professionals involved. The health care system mixes both private and public sectors.

Historically, and as still observed in some instances, medical care was bought directly from care providers when needed by individuals in a "fee-for-service" business model. Care providers were chosen by reputation and proximity. In 1694, the concept of health insurance was introduced by Hugh the Elder Chamberlen (1630-1720, London UK). Health insurance covers the risks of incurring medical expenses over a defined period of time. It is a contract between the insurance and the individual and, sometimes includes a third party (e.g. employer) exposing the individual to a risk. The contract defines diseases and treatments covered, as well as the choice of care providers. To protect their population and promote health, each government lay out its own legal framework.

Currently the main actors in health care systems are:

1) **Governments** that lay out the legal background to promote homogenous care access and safety

2) **Health insurers** that optimize access to care at the lowest price

3) **Providers of care and medical products** that optimize their products and services to increase their market share

4) **All individuals** who wish to keep or recover their best health

In poor countries, a direct correlation binds health (measured as the life expectancy at birth) and financial resources allocated to care. In contrast, above 3000 US$ purchasing power parity (PPP) spent per capita for health, this spend no longer correlates to health. Most probably other factors such as average education and training in self-responsible behavior of the population, organized as opposed to market-driven care delivery, optimized resource allocation, coherent policies and structured leadership, explain the big differences between investments and general health observed in the western world.

Clusters of countries sharing similar institutions or health care systems have been identified. They can be

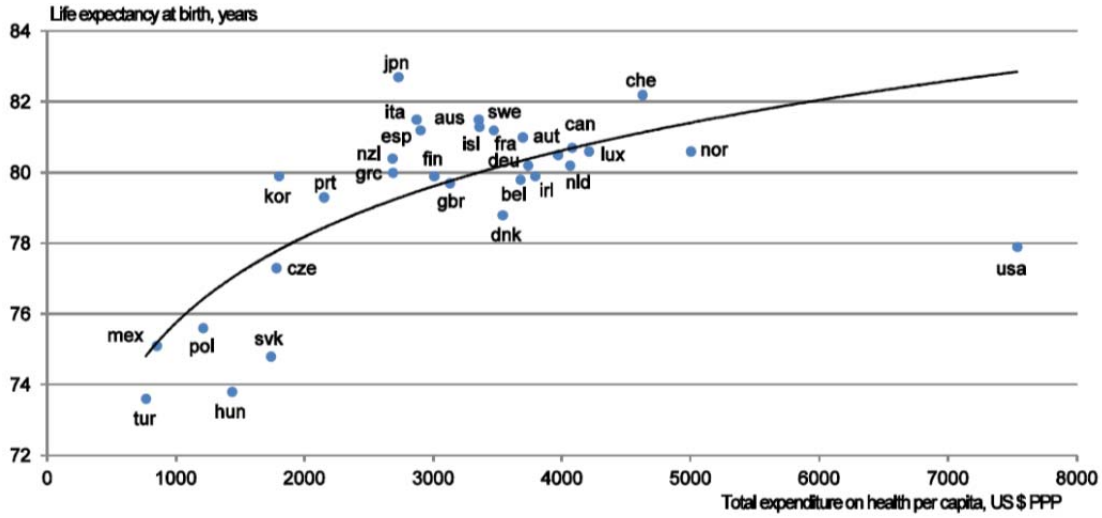


Figure 1: Average life expectancy at birth versus health spending per capita

classified according to a balance between systems solely relying on market mechanisms versus more centralized command-and-control systems. The analysis shows that all systems have strengths and weaknesses. Nevertheless, countries balancing market mechanisms with strong legal frameworks seem to perform better. Experts project that efficiency may be improved such that without impacting on the progression of care quality, savings on health spending could approach 2% of GDPs on average in the OECD.

2. Overview of avenues to improve care and health systems

In a world where an aging population aspires to ever improved access and outcome of care, current health systems are no longer economically sustainable. Continuous successful development of new technologies pushes everyone's aspirations towards rescuing patients from challenging diseases and promotes an ideal of health at an unaffordable cost. In order to pursue this odyssey, a thorough improvement in efficiency is needed.

Improvement implies a clear aim and a recursive process of monitoring, analyzing, projecting, deciding and acting, as well as the ability to adapt to discovery.

As is our representation of the world, our understanding of health and care, as well as our aims in health and care are refining. The aim of fighting death and disease at any cost when limits were set by knowledge, knowhow and technologies is now challenged. There is an ongoing ethical, social and political debate to define the acceptable aims of care and health systems. The WHO Constitution states that the institution's objective is "the attainment by all people of the highest possible level of health". Health was defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [WHO definition of Health, 1946]. In other words, the goal is the attainment for all people on earth of the highest possible well-being. If we look at the tools used to monitor health around the globe we observe that measurements are still not adapted. From 1960 to nowadays the main index used to estimate the quality of a health system was the life expectancy. Since 2001, WHO publishes statistics using Health-Adjusted Life Expectancy (HALE) estimates and more recently multidimensional sets of indicators were developed to monitor the efficiency, quality of the systems, performance of institutions and their policies. Now that tools to assess people's well-being are designed and implemented, there are several issues in resources management, such as:

a) Managing the end-of-life

b) Optimizing and sharing resources to avoid wastage

Both issues require the improvement of current practice and systems.

Knowledge grows through scientific work funded by governments, private corporations or charitable organizations. Validation of knowledge is obtained by a review process performed by experts in the field

(peers) and resulting in the publication of scientific observations and conclusions. The quality of the scientific evidence obtained in medicine is ranked according to the methodology used to obtain the information and results in management recommendations or guidelines that are classified in levels. The validation process is subject to various biases and in most fields of medicine evidence is rare and the confidence in recommendations is classified as reasonable or potentially useful. Most of the knowledge is based on aggregated experts' opinions.

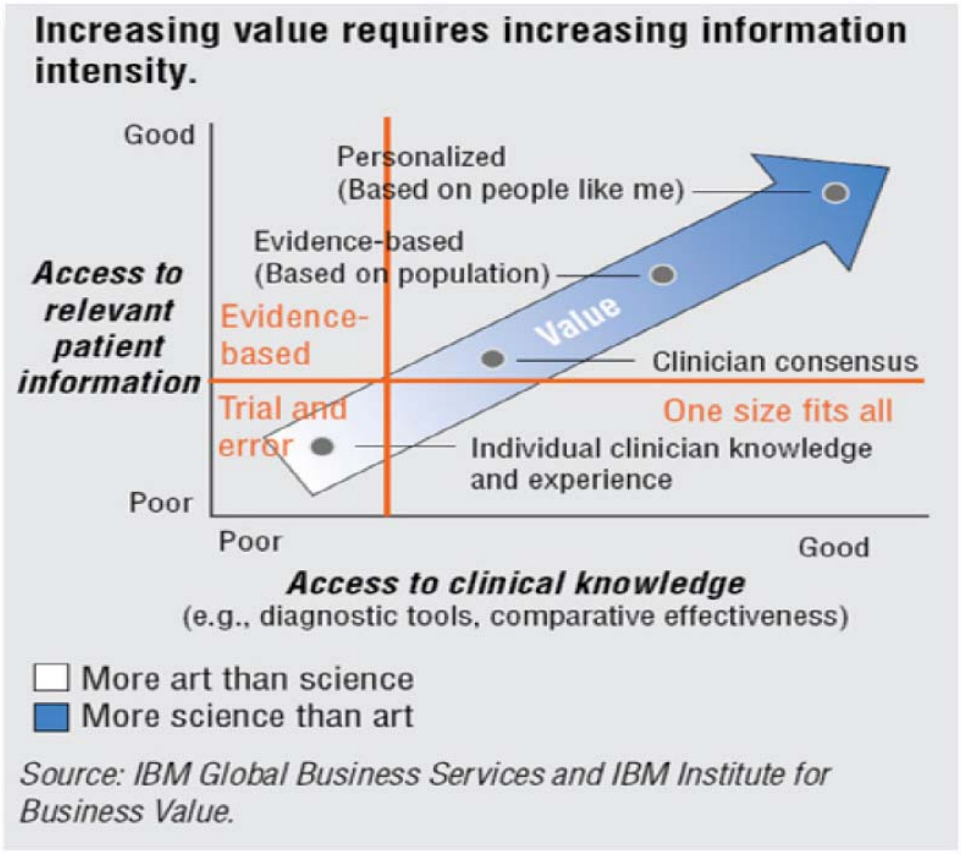


Figure 2: Evolution of medicine from art to science requires increasing the information intensity. Tools to gather more robust and detailed knowledge and appropriately matching it to each patient at a affordable cost is needed.

Medicine is an art to provide the best care and outcome to patients using knowledge, experience and intelligence. Care providers are certified initially in mastering the art of medicine according to governments' requirements and need to show efforts in keeping up-to-date. Certification is key in controlling the quality of care provided.

To improve efficiency, some governments enforce gate keepers to control geographic medical density or reduce unnecessary medical consumption. Health insurers negotiate contracts with care provider associations to control costs by organizing care networks. Another option is to provide better and more

transparent information to the population about quality and price of health care services and rely on competition.

It seems that globally the pressure to improve efficiency will be driven economically and health insurers are currently changing their marketing strategies under the pressure of the market and governments. Health insurers are optimizing administrative costs, increasing market share to improve their negotiation position with care providers. Now health insurers seek to promote an optimization of care.

The aims are to modify the medical management to place less emphasis on managing care and more emphasis on managing health itself. It will require improving the transparency of risk factors for disease, diseases, care, outcome and costs as well as clear justifications for:

1) higher prices for specific products, and

2) investments in Research & Development.

Improving information transparency should modify branding in the medical world. Objective measurements assessing results of care on health will replace reputation, qualifications, affiliations and word-of-mouth in rating and retribution of care providers in a way that should benefit patients and society.

The aims are shared between all main actors but barriers to success have been identified:

1) Consumers' mistrust of health insurers

2) The misalignment between health insurers and care providers

3) The fragmentation and complexity of medical and care information

4) The need to introduce a new actor: Providers of information technologies (IT)

It is speculated that change should start with the education of care providers and the development of information technology tools that focus on a better co-ordination of care delivery, adherence to best practice and evidence-based medicine. It is believed that pay-per-performance models could enforce those practices.

In order to improve well-being, it is crucial that patients, care providers, biopharmas, biotechs, regulators and health insurers confront information and define pertinent biomarkers to measure efficacy and safety of care and products. In a market-driven environment, transparency must be guaranteed to maintain an

unbiased representation of health. It has been universally recognized that care providers will have to take more responsibility in monitoring, documenting and reporting health and care delivery, and to ensure that it conforms to explicit standards.

This significantly shifts the workload away from the primary task and will require resources to:

1) establish a quality and safety-monitoring structure

2) promote the rebuilding of processes explicitly to deliver better outcomes

3) improve the technology and information systems to support these new processes.

There are enormous barriers against proactive thoughtful collaboration between health care suppliers, providers, industry, governments and insurers as each are formidable stakeholders in their own right. None is inclined to act against its own interests even if it is only in the short term. Nevertheless, there are lots of win-win opportunities to be generated as long as common goals are agreed and, most importantly, valid information made transparent.

The @neurIST project

The @neurIST project addressed all the above mentioned issues by focusing on a single medical condition -intracranial aneurysms- whilst ensuring the developments remained easy to export to other fields.

The @neurIST project worked on developing an information platform to collect pertinent information from the best source as soon as observed. It integrated heterogeneous information about patients, their diseases, treatments and outcomes with tailored metrics and tools to assess individual risks. It generated databases allowing the assessment of risk factors covering genetics, gene expression, morphology and clinical information as well as computational simulations. It created tools to explore, analyze and present information in a comprehensive format adapted to clinicians, scientists, industrial partners and health system managers.

3. Clinical and biomedical data collection process

According to the Organization for Economic Cooperation and Development (OECD), health costs are constantly increasing and represent more than 10% of the Gross National Product of Western World countries. Projections predict an increase by more than 30% in the next 20 years. There is therefore a political pressure to increase the efficiency of the health system optimizing resources and potentiating synergies between health partners. Two different strategies are being progressively implemented worldwide.

One strategy initiated at Yale University School of Medicine (USA) is to record the averaged cost to treat a disease (diagnostic related group: DRG) and identify deviations to average between different care providers. In this strategy, hospitals are only covered for justifiable costs. The response of hospitals to this economical threat is to generate justifications. This strategy is thus not outcome weighted and there is a risk of decreasing the investments in complex cases thus lowering costs but increasing mortality.
The second strategy was initiated in the New England Medical Center in Boston (USA) in 1985. It is an adaption of the industrial processes of quality management and standard operating procedures adapted to clinical practice introducing the concept of clinical pathways. A clinical pathway is more than standards of care or guidelines. For each specific medical condition a set of steps is identified. For each step a series of criteria is set, as targets, roles and deadlines are precisely defined. Data is recorded using adapted data collection tools. It is claimed that the use of clinical pathways should monitor and optimize hospital resources, identify bottle necks and improve work flow, thus decreasing unnecessary investigation and in-hospital stay. It is expected that 80% of the patients could be managed following a clinical pathway. Priority to establishing clinical pathways should be given to diseases that are at high risk, high cost and high volume, with a predictable course, involving multiple disciplines and benefiting of some expert consensus on care.
Stroke has been one of the first conditions targeted. Currently there are still few scientific demonstrations that the use of a clinical pathway does impact the outcome for patients. In stroke, it could be shown that patients managed using a clinical pathway suffered less rehospitalisation. In acute coronary diseases,

diagnostic recommendations and guidelines were better followed and hospital stays significantly reduced. In another field, it has been demonstrated that clinical pathways support the care of patients suffering from dementia.

According to OECD statistics, spending on Research & Development account for 2.3% of GDPs in the Western World countries and resources allocated to health research and development represent 0.12% of GDPs. Large variations are observed between countries ranging from less than 0.02% to more than 0.2% in the United States of America. It can reasonably be expected that funding for research and development will remain at the current levels or decline as a result of economical pressures on most OECD member countries. Simultaneously the cost of clinical trials increased dramatically. Between 1980 and 1990 the costs of clinical trials for drug development increased 5-fold quicker than preclinical work. Most of the costs are related to data collection in the clinical environment. Much can be optimized in merging the data collection within the standard clinical trial process. There are therefore strong needs to optimize research platforms.

The aim of the @neurIST project was to develop and evaluate a system to collect and integrate biomedical information to improve the management of cerebral aneurysms, gather evidence by monitoring health, promoting new knowledge discovery and development of new treatments. The primary working hypothesis was that in western countries there is a tendency to overtreat and that cost could be reduced by optimizing the use of resources by focalizing efforts on people at risk.
Clinical information represents a major source of relevant information including patient history, environmental risk factor exposure, symptoms, clinical signs, treatments, clinical evolution as well as imaging interpretation repeatedly reassessed over time. In most European hospitals information is initially collected and documented by physicians in paper files. Laboratory and imaging data are stored digitally in databanks. Some clinical pertinent information is stored in the header of imaging data files stored in DICOM format. Data acquisition for billing is performed by trained personnel reading the notes and codified by diagnosis and interventions using the International Classification of Diseases (ICD-10) and International Classification of Health Interventions (ICHI).

Overall, the information available digitally in the current electronic Health Records (eHR) was insufficient to fulfill the needs of the project regarding the stratification of patients for: a genetic study, epidemiology investigations and disease specific subtypes, severity and treatment group outcome association studies. Therefore the need to design a prototype of advanced information platform was identified. The various steps in design and developments are reported below.

4. The @neurIST Paradigm of Care

@neurIST developed, used and evaluated an information technology and infrastructure for the management and processing of heterogeneous data associated with the diagnosis and treatment of cerebral aneurysms.

The central ambition of the project was to demonstrate the extent to which clinical practice could be advanced by the introduction of integrated access to rich and novel sources of clinically-relevant data. A major challenge was to develop a computer interface that would allow homogeneous access to inhomogeneous information stored across geographically separated systems with a multiplicity of incompatible interfaces and disparate semantic vocabularies. This information was meant to support training, research, clinical decision making, treatment planning and the development of new therapies. This technology was intended to be transferrable to other medical conditions.

One of the key features of the @neurIST paradigm of care is that Data Collection and Medical Record keeping is merged to create a virtual replica of the clinical reality (patient database).

An inference engine extracts information to support clinical activities, teaching, research and development.

@neurIST data is stored in a Biomedical Data Information System composed of Clinical Databases and a Federated Research Database. It is structured to support two simultaneous activities.

- Information acquisition and structuring (area in red in figure 3)
- Information access and enrichment (area in green in figure 3)

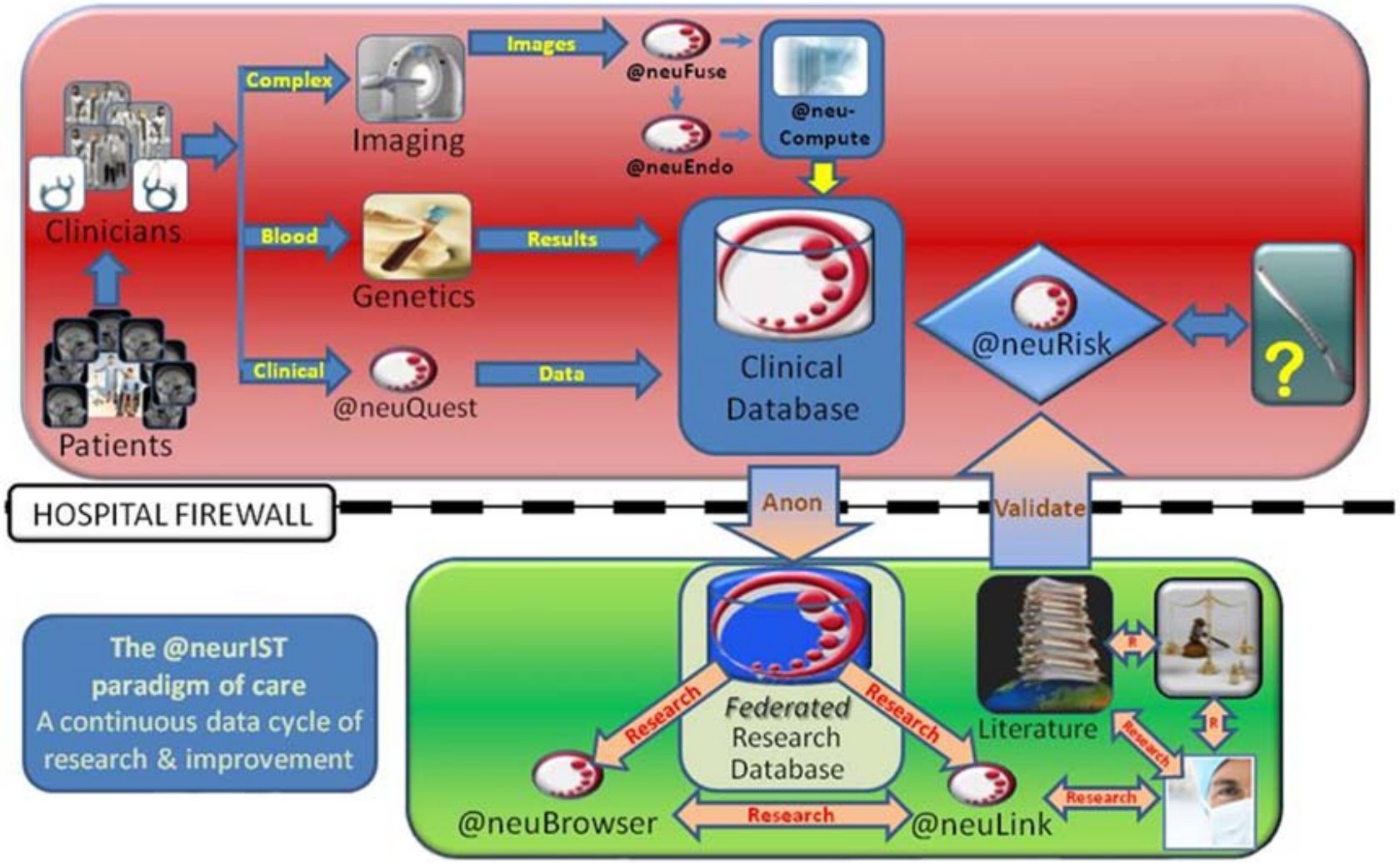


Figure 3:The @neurIST Paradigm of Care

The acquisition of data closely mirrors the current clinical practice. It helps structuring clinical practice and, by integrating information, allows clinicians to understand a wider clinical picture than before. Standardization allows mapping of information across institutions and promotes multicentre, as well as international information exchange on diseases.

The access and enrichment loop examines the use of data and tools in the clinical environment to further improve the system. It also provides information for basic and applied research, and analyses the ability to generate knowledge using the system.

The system is divided in functional suites described below (figure 3):

@neurIST Ontology: Standardisation of Vocabulary

The @neurIST Ontology is a data model that collects, organizes and links entity types relevant to the project. It structures the vocabulary and provides relations for defined associations between entities. The @neurIST Ontology enables reliable communication.

@neuQuest: Standardised Care and Data

@neuQuest provides a standardised interface to the @neurIST patient data repository. By formalising the data recorded at each step in the patient-care pathway it enforces consistency of approach, procedures, terminology and data storage.

@neuFuse: Data Analysis and Fusion

@neuFuse merges diagnostic, modeling and simulation data into a coherent representation of the patient's condition, accessible through a common interface. It allows predictive simulations based on patient and domain-specific data, and standardizes communications.

@neuRisk: Personalised Risk Assessment

@neurRisk integrates information from multiple sources to enable optimal decision-making. It combines data captured using @neuQuest with knowledge generated by literature review, data mining and physics-based simulation into a single measure of relative risk for each of the various treatment alternatives.

@neuEndo: Endovascular Planning and Device Design

@neuEndo simulates the treatment procedure, allowing optimization and the identification of putative pitfalls. It combines patient-related information with knowledge provided by @neuLink and @neuRisk, and uses @neuFuse to display appropriate geometry for visualisation by the clinician and the patient.

@neuBrowser: Exploration of the Database

The @neuBrowser is a research tool that allows scientists to explore the content of the database. It allows testing hypothesis by performing statistical analysis of associations comparing selected scenarios.

@neuLink: Information Integration for Knowledge Discovery

@neuLink integrates information from disparate sources to enable better understanding of the disease. It combines data captured by clinical partners using @neuQuest with knowledge generated by literature review, data mining and the results of @neurIST's own genetic, gene-expression and computationally analytical studies to support an optimal research strategy.

5. Design of the information platform

5.1 Selection of concepts, terms and definitions relevant to the disease

An initial list of relevant items traditionally recorded was generated from an audit of activity of the neurovascular teams in Geneva, Lausanne and Cambridge. The list was extended following a review of the published experience of G. Yasargil, B. Weir, R. Spetzler, and C. Drake; and was grouped into topics. Extensive literature searches were done in PubMed, topic by topic, to check for relevant items that had not been included. A data flowchart was designed. Redundancies were identified and eliminated. This first step resulted in the initial version of the Clinical Reference Information Model (CRIM)

The second step was to confront the CRIM to the needs of all stakeholders to verify that the minimal data set required for each and the formats of information collection were adequate.

Representatives of the following putative users were involved:

• Researchers

Geneticists, biologists, epidemiologists, clinical trialists, scientists involved in complex image processing.

• Hospitals & Clinicians

Physicians, radiologists, surgeons, intensive care specialists, nurses, administration, quality control, resource optimization and last but not least information technician.

• Device Manufactures

Research and development department, customized device design, quality control and treatment outcome auditing.

• Service Providers

Disease progression simulation, risk analysis, treatment simulation

• Regulatory Authorities

Patient safety, ethics and practice monitoring, data protection, intellectual property and ownership protection, national and global disease and research monitoring entities

• Patients

The third step involved checking definitions and interoperability with at least the two previous major works in the field: the ISUIA and ISAT studies.

The CRIM (release 5) contains 541 unique attributes pertaining to the clinical history of a patient, including: 190 multiple choice items indexed with integer value (35.12%), 123 Boolean items (22.74%), 70 date attributes (12.95%), 115 numerical attributes (21.81%), and 43 text fields (7.95%). These attributes are organized around 8 categories: administrative information, personal history, sign and symptoms, vital signs and laboratory results, imaging data and the associated findings, treatment and follow-up.

The CRIM served as a starting point to develop the @neurIST ontology. Ontology comes from the Greek and means the science of that which is, in other words "the philosophical study of the nature of being, existence or reality as such, as well as the basic categories of being and their relations". The purpose of developing the ontology is to allow semantic mediation to resolve conflicts between different data sources. Semantic allows giving a meaning to terms in their context. In information technologies, semantic mediation is an advanced data integration concept that allows integrating information from different sources by bridging the semantic differences among them. The semantic glue to link together different data sources is provided by the ontology. Data sources are annotated using the common ontology and can subsequently be accessed using ontology concepts. The semantic wrapper can be used interactively by human experts or automatically by software applications. Semantics play a key role for reusable data integration and other value-added services like smart discovery, query optimization, etc. In @neurIST, semantic mediation bound data from different databases for different types of users. It can be illustrated by the following exemple. The ontology gives the ability to **automatically search** the most relevant information **tailored to a specific patient** (as described in the @neurIST database) using biomedical open access databases (i.e. PubMed abstracts and available full text articles), **to analyze it** and **to report on it**. It allows to "glue" a patient's descriptive data from the hospital information system to the universal knowledge reported in plain text and accessible through the world wide web.

The @neurist final ontology (relevant to the intracranial aneurysm disease) contains more than 14.000 lexicon entries, 1600 Unified Medical Language System (UMLS) mappings, more than 3000 classes, more than 100 relationships, and more than 2100 definitions. It can be accessed on the web at http://ontology.aneurist.org.

5.2 Architecture of the information system

The @neurIST System has been designed as several subsystems which were developed by different partners and deployed on various platforms across a wide geographic area. To allow integrating this heterogeneous mixture of systems @neurIST took a service oriented approach, whereby the different capabilities offered by suites and components are exposed as services on the internet.

The "@neurIST System and Prototype Vision Statement" was:

> "….The specific clinical focus will be cerebral aneurysms. However, the reference architecture will be generic. Future prototype implementations will also illustrate how @neurIST could be used in other clinical domains…"

The functional reference architecture (figure 4) captures this spirit and built an architecture where the underlying component interactions are preserved to the maximum extent possible even when extended to clinical cases beyond aneurysms. Generic applications, as well as the application suites specific to treatment of aneurysms (addressed by the @neurIST project) are reported.

The different capabilities needed in @neurIST were modeled as services, following the Service Oriented Architecture (SOA) principles. These principles are used for designing and developing software in the form of inter-operable services that are well-defined functionalities built as software components that can be re-used for different purposes.

The components in @neurIST offer specific functions, and a service can be defined as one where a group of components come together to offer a functionality. In the simplest case, a service can be made up of a single component. Hence the terms components and services are interchangeable in this document. For example, accessing data spread across different sites involves querying the data on multiple databases (data mediation service), as well as transporting huge amounts of data (data transfer service).

These individual functions are performed by specific services in the system and the functionality as a whole is offered as a data access service (DAS or @neuInfo) with the underlying complexity hidden

from the end user. In @neurIST, services are realized as web/grid services and have a well defined interface through which they interact with other services and client applications.

Figure 4 shows the different participating entities that use the @neurIST system and their respective local infrastructures. The application suites are distributed to the different centers based on their assumed roles, though this might not reflect the actual implementation. For instance, it is possible that a researcher from a research institute makes use of application suites such as @neuFuse and @neuRisk (normally restricted to clinicians in hospitals) to evaluate risks based on new research inputs unearthed by the @neuLink system.

For the sake of clarity, it is easier to divide the components shown in the reference architecture into the following categories:

- System Components
- Application Suites
- Infrastructure Components
- Biomedical Info Structure (BioIS).

The system components provide functions that are basic to the functioning of the overall system. Components coming under this category include the ones that provide services such as discovery, ontology, central certificate authority, global policy enforcement components, etc.

The application suites provide the tools for the users of the system to employ within an overall aneurysm treatment plan while they in turn use the system and infrastructure components to communicate with the clinical infrastructures and services offered by the @neurIST service providers (e.g. simulation service providers).

The infrastructure components of @neurIST provide functions dealing with data access and computational services. The components here are grouped under @neuInfo (for data access related services) and @neuCompute (for computational simulation services). The communication middleware used by the @neurIST components is shown as a blue ring in Figure 4.

The BioIS is a set of components located in a clinical centre such as the data repositories used to store all clinical @neurIST data, pseudonymisation, normalization, logging and the filtering components and includes the data access service provided by the infrastructure components.

A fully functional system requires a robust security infrastructure that controls the access to services provided by the system and protects the data handled within the system. Since security is present throughout the system in the form of access control and enforcement
points, it is represented as a green circle surrounding all the components inside @neurIST.
The security infrastructure also includes the components offering the functions of privacy, filtering, logging and the @neurIST certificate infrastructure.

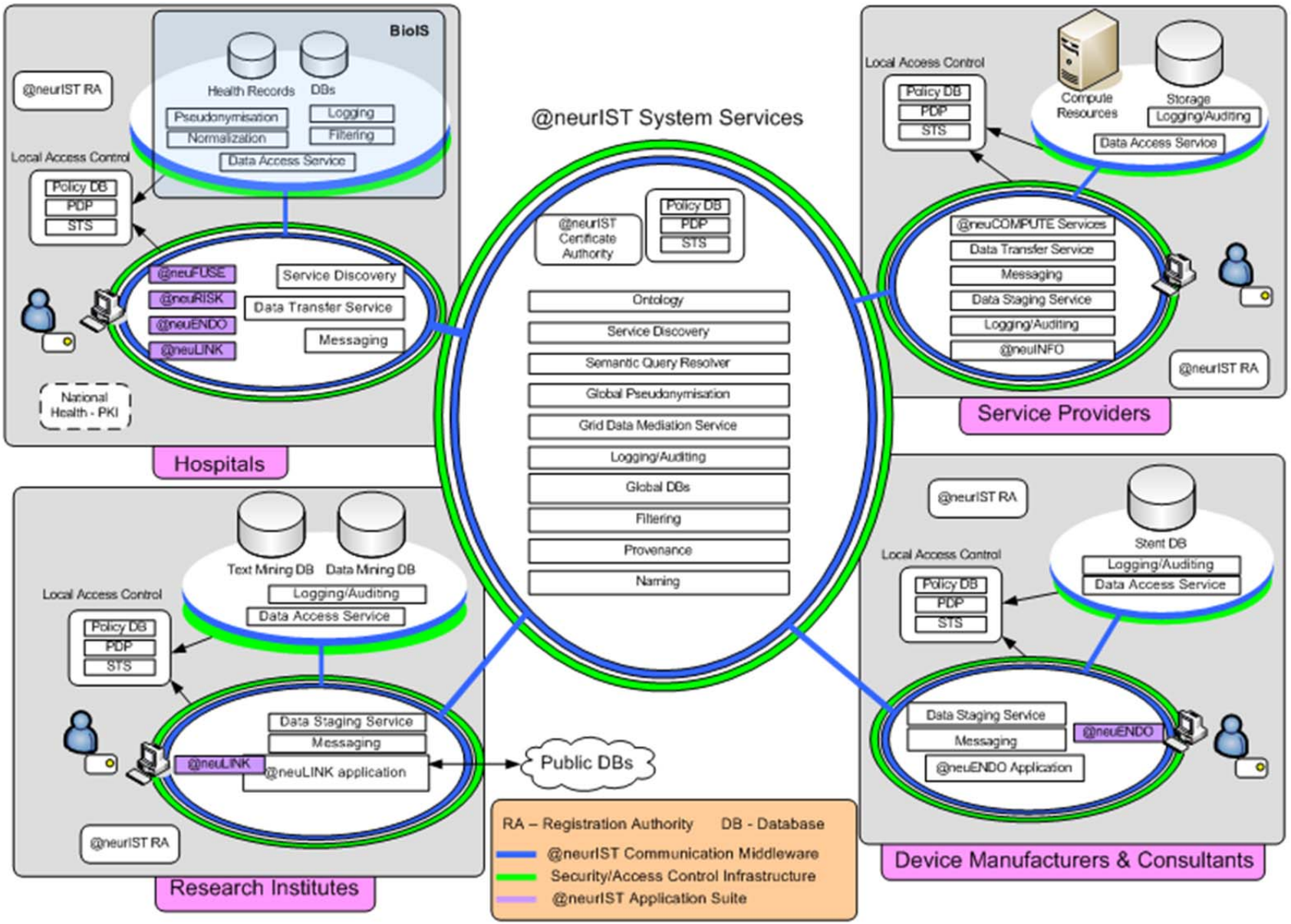


Figure 4: Information system generic architecture

5.3 Design of data collection processes and tools

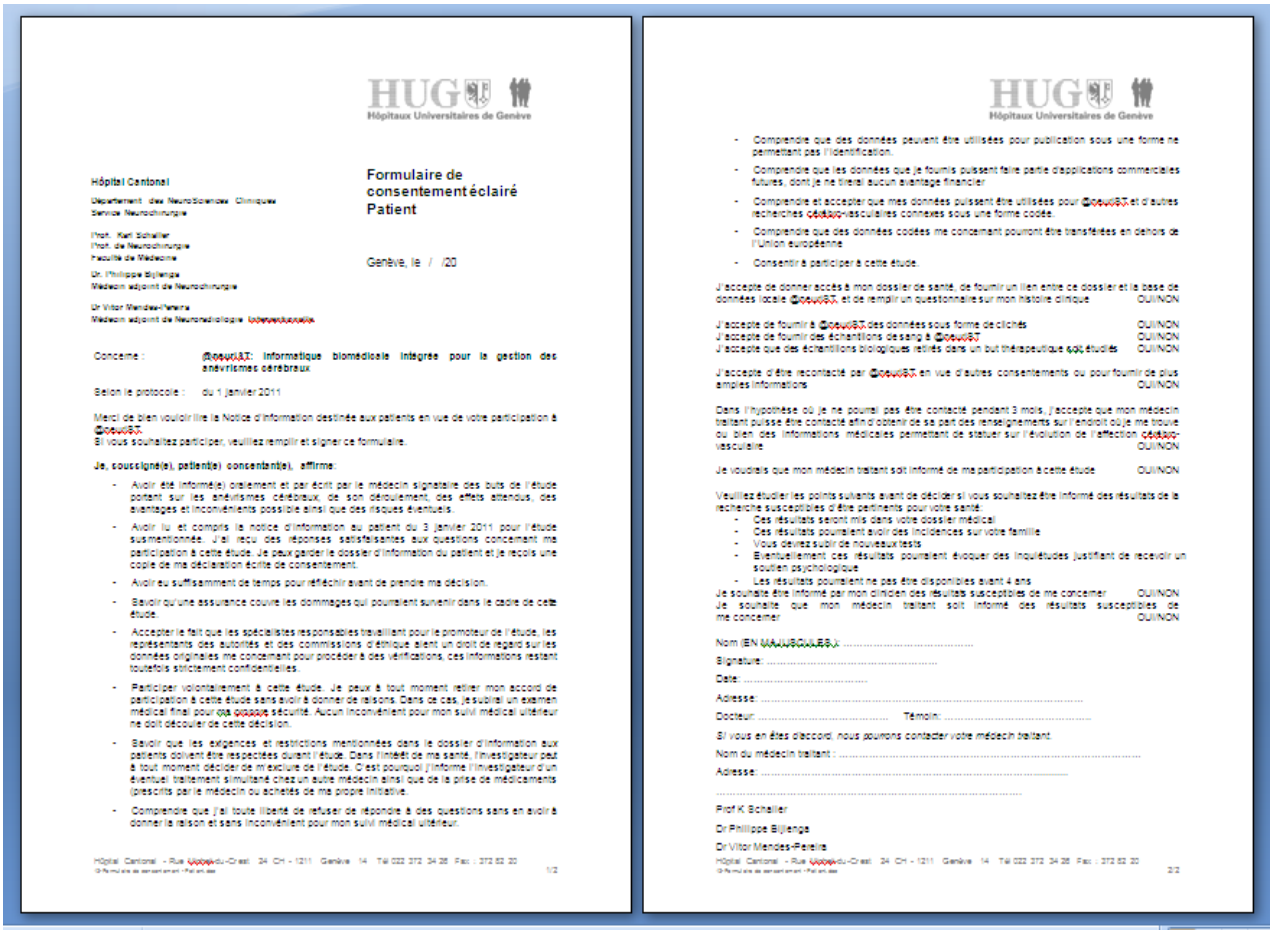
The collection and storage of descriptive (CRIM) and representative (images and volumes) clinical and biological information, as well as pointers to stored biological samples was supported by the Biomedical Information System (BioIS).

For ethical and economical reasons, it was decided to use data collected in the course of standard medical practice and stored using hospital resources. A unique exception was agreed regarding the retrieval of venous blood samples for transcript (mRNA) and DNA storage and study.

To reduce as much as possible variability in data collection across participating centers, a data collection protocol and a participant manual was written and medical practice was homogenized to some extent. All clinicians involved in data collection were trained for clinical research best practice and @neurIST definitions and protocols during two single day training sessions. During the sessions, clinicians learned how to inform patients and relatives, collect consent, collect medical information and describe observations as well as filling the data forms generating the @neurIST database. The protocol defining time and requirement for angiographic imaging, blood and aneurysm domes collection were presented. The post processing of biological samples and labeling with pseudonymised bar codes was presented to laboratory technicians participating to the project.

All patients were informed orally and in writing of the project's aims, the pros and cons of their participation, as well as the risks of participating. Consent to participate was voluntary and without any obligation and could be withdrawn at anytime. Patient had the option to accept or decline to be informed about risks identified during the discovery phase which could potential impact there health or that of family members in the future. By accepting to be informed, patients delegate the decision regarding the pertinence and validity of information to local ethical committees. They were given the opportunity to name a contact person of their choice and a general practitioner. They were informed that data would be shared in an anonymous format across the world and might be used for commercial purposes. It was clearly specified that patients or relatives would never benefit financially from any commercial use of their data. Consent or refusal of all patients were recorded and stored in appropriate

location in paper and digitally in the database (figure 5). When patients were unable to consent a provisional acceptance was obtained from the next of kin and confirmed whenever possible thereafter.



HUG
Hôpitaux Universitaires de Genève

Hôpital Cantonal

Formulaire de consentement éclairé Patient

Genève, le / /20

Concerne : @BrainIT: Informatique biomédicale intégrée pour la gestion des anévrismes cérébraux

Selon le protocole : du 1 janvier 2011

Merci de bien vouloir lire la Notice d'information destinée aux patients en vue de votre participation à @BrainIT.
Si vous souhaitez participer, veuillez remplir et signer ce formulaire.

Je, soussigné(e), patient(e) consentant(e), affirme:

- Avoir été informé(e) oralement et par écrit par le médecin signataire des buts de l'étude portant sur les anévrismes cérébraux, de son déroulement, des effets attendus, des avantages et inconvénients possible ainsi que des risques éventuels.
- Avoir lu et compris la notice d'information au patient du 3 janvier 2011 pour l'étude susmentionnée. J'ai reçu des réponses satisfaisantes aux questions concernant ma participation à cette étude. Je peux garder le dossier d'information du patient et je reçois une copie de ma déclaration écrite de consentement.
- Avoir eu suffisamment de temps pour réfléchir avant de prendre ma décision.
- Savoir qu'une assurance couvre les dommages qui pourraient survenir dans le cadre de cette étude.
- Accepter le fait que les spécialistes responsables travaillant pour le promoteur de l'étude, les représentants des autorités et des commissions d'éthique aient un droit de regard sur les données originales me concernant pour procéder à des vérifications, ces informations restant toutefois strictement confidentielles.
- Participer volontairement à cette étude. Je peux à tout moment retirer mon accord de participation à cette étude sans avoir à donner de raisons. Dans ce cas, je subirai un examen médical final pour ma propre sécurité. Aucun inconvénient pour mon suivi médical ultérieur ne doit découler de cette décision.
- Savoir que les exigences et restrictions mentionnées dans le dossier d'information aux patients doivent être respectées durant l'étude. Dans l'intérêt de ma santé, l'investigateur peut à tout moment décider de m'exclure de l'étude. C'est pourquoi j'informe l'investigateur d'un éventuel traitement simultané chez un autre médecin ainsi que de la prise de médicaments (prescrits par le médecin ou achetés de ma propre initiative.
- Comprendre que j'ai toute liberté de refuser de répondre à des questions sans en avoir à donner la raison et sans inconvénient pour mon suivi médical ultérieur.

Hôpital Cantonal - Rue Micheli-du-Crest 24 CH - 1211 Genève 14 Tél 022 372 34 26 Fax : 372 83 20
Formulaire de consentement Patient

1/2

HUG
Hôpitaux Universitaires de Genève

- Comprendre que des données peuvent être utilisées pour publication sous une forme ne permettant pas l'identification.
- Comprendre que les données que je fournis puissent faire partie d'applications commerciales futures, dont je ne tirerai aucun avantage financier
- Comprendre et accepter que mes données puissent être utilisées pour @BrainIT et d'autres recherches cérébro-vasculaires connexes sous une forme codée.
- Comprendre que des données codées me concernant pourront être transférées en dehors de l'Union européenne
- Consentir à participer à cette étude.

J'accepte de donner accès à mon dossier de santé, de fournir un lien entre ce dossier et la base de données locale @BrainIT, et de remplir un questionnaire sur mon histoire clinique OUI/NON

J'accepte de fournir à @BrainIT des données sous forme de clichés OUI/NON
J'accepte de fournir des échantillons de sang à @BrainIT OUI/NON
J'accepte que des échantillons biologiques retirés dans un but thérapeutique soit étudiés OUI/NON

J'accepte d'être recontacté par @BrainIT en vue d'autres consentements ou pour fournir de plus amples informations OUI/NON

Dans l'hypothèse où je ne pourrai pas être contacté pendant 3 mois, j'accepte que mon médecin traitant puisse être contacté afin d'obtenir de sa part des renseignements sur l'endroit où je me trouve ou bien des informations médicales permettant de statuer sur l'évolution de l'affection cérébro-vasculaire OUI/NON

Je voudrais que mon médecin traitant soit informé de ma participation à cette étude OUI/NON

Veuillez étudier les points suivants avant de décider si vous souhaitez être informé des résultats de la recherche susceptibles d'être pertinents pour votre santé:

- Ces résultats seront mis dans votre dossier médical
- Ces résultats pourraient avoir des incidences sur votre famille
- Vous devrez subir de nouveaux tests
- Eventuellement ces résultats pourraient évoquer des inquiétudes justifiant de recevoir un soutien psychologique
- Les résultats pourraient ne pas être disponibles avant 4 ans

Je souhaite être informé par mon clinicien des résultats susceptibles de me concerner OUI/NON
Je souhaite que mon médecin traitant soit informé des résultats susceptibles de me concerner OUI/NON

Nom (EN MAJUSCULES) : .....
Signature : .....
Date : .....
Adresse : .....
Docteur : ..... Témoin : .....
Si vous en êtes d'accord, nous pourrons contacter votre médecin traitant.
Nom du médecin traitant : .....
Adresse : .....
.....

Prof K Schaller
Dr Philippe Bijlenga
Dr Vitor Mendes-Pereira

Hôpital Cantonal - Rue Micheli-du-Crest 24 CH - 1211 Genève 14 Tél 022 372 34 26 Fax : 372 83 20
Formulaire de consentement Patient

2/2

Figure 5: Consent forms defining data to be collected, frame for use of data and obligations regarding feedback to patient.

Data collection was designed to follow a disease specific clinical pathway resulting from a careful literature review, practice auditing in European clinical centers and experts opinions. The 30 stage process recommended for developing a clinical pathway according to K. Vanhaecht & W. Sermeus was followed. Multiple interdisciplinary meetings involving medical, paramedical and administrative professionals covering all aspects of management, care, imaging and administration of the cases suffering the disease were held to improve the pathway through and iterative process. A Gant chart with milestones set just prior to treatment (time of rupture in cases suffering a bleed), just after treatment, at hospital discharge and at each follow-up according to a defined program was produced (figure 6). For each milestone a minimal and an extended data set was defined allowing a broad range of data to be collected. A multidimensional evaluation chart (compass) was designed to check again that all relevant data to all stakeholders was captured (figure 7).

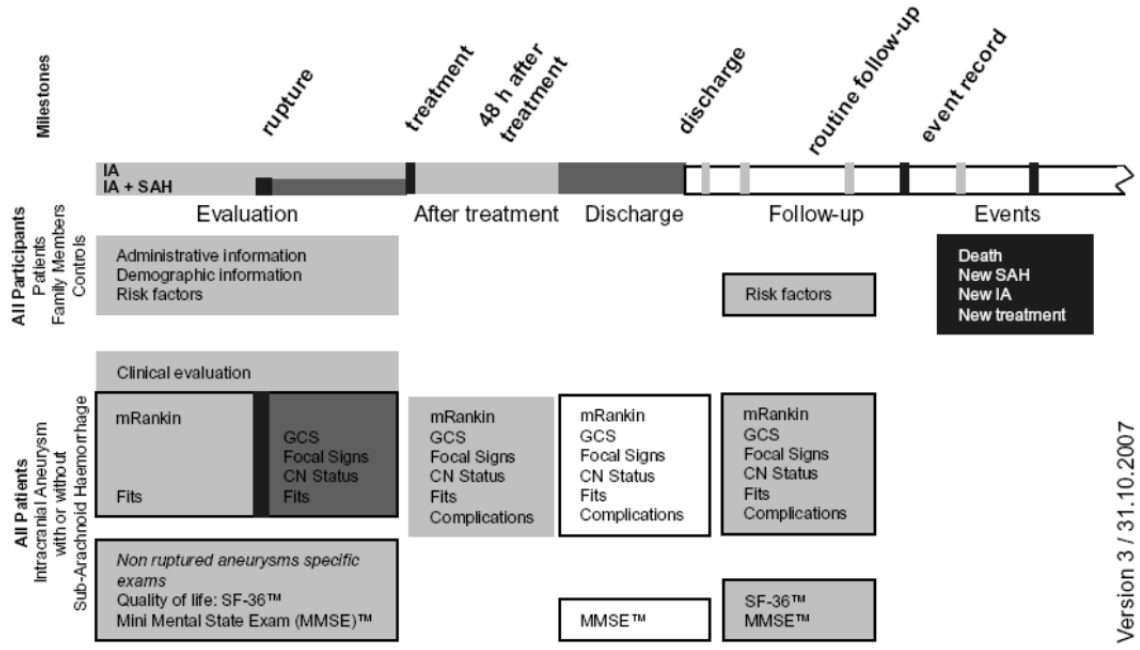


Figure 6: Clinical pathway Gant chart

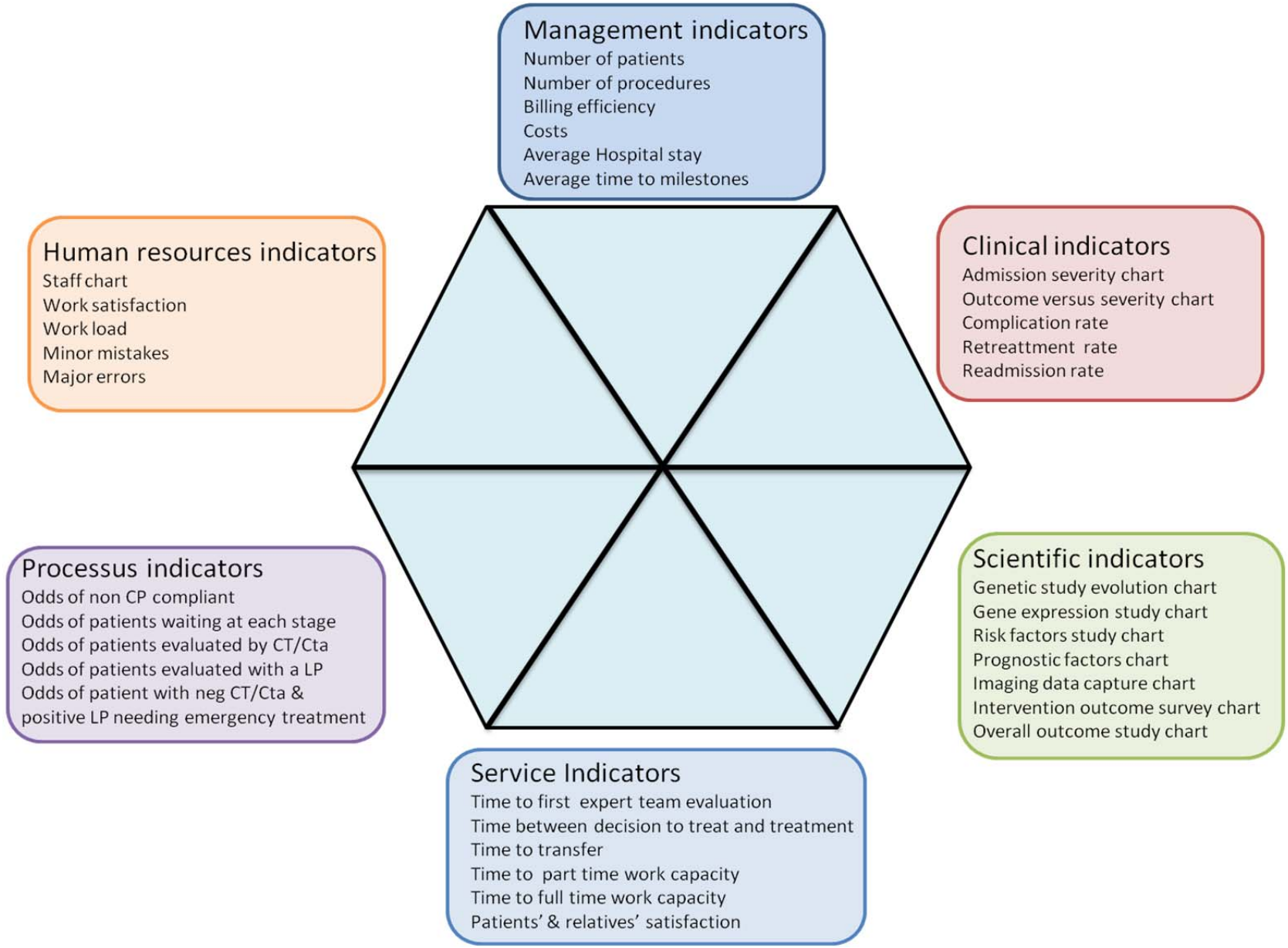


Figure 7: Multidimensional evaluation chart

Adequate data collection forms were designed tailored to the different users and stages of care and tested first in their paper version (figure 8).

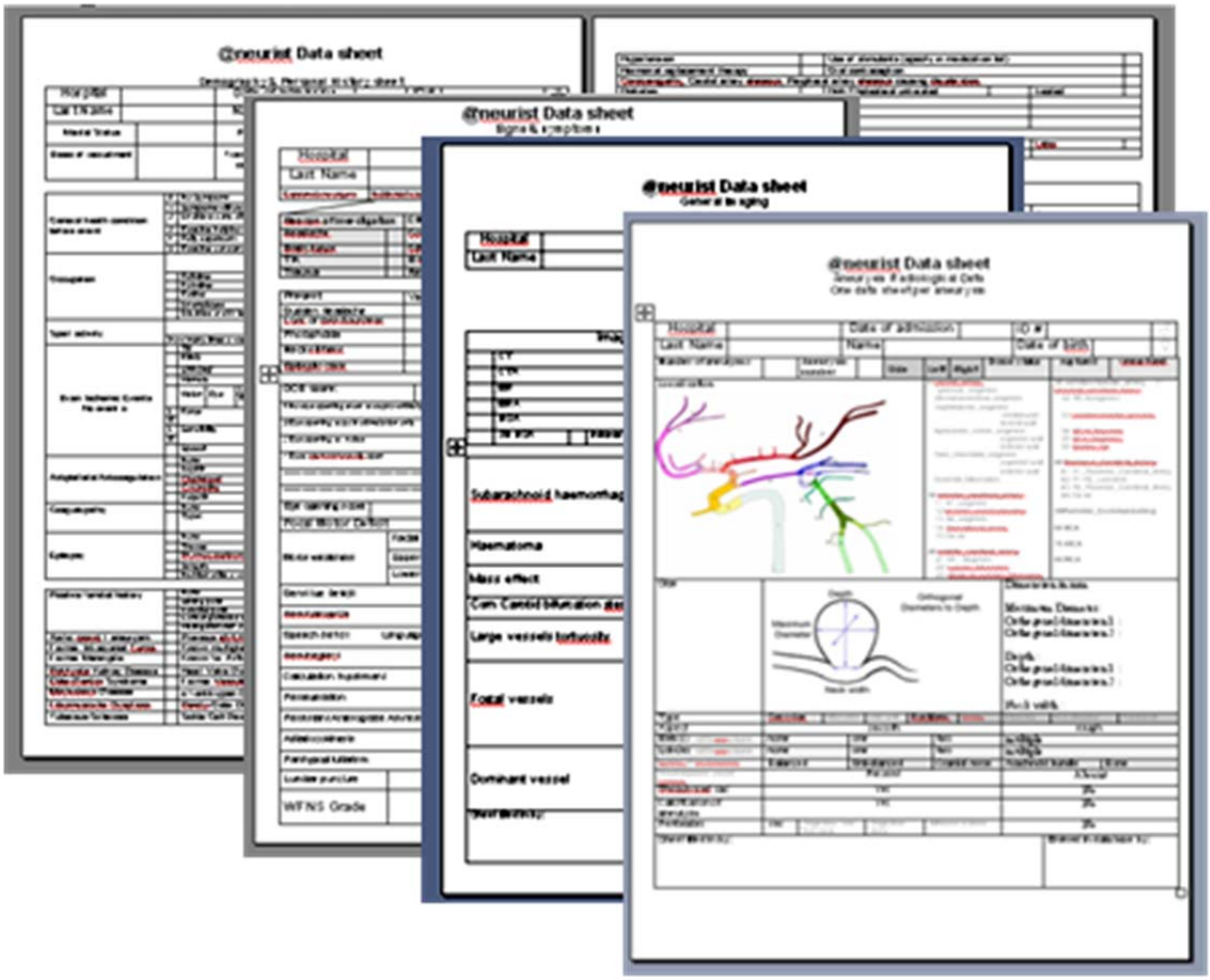


Figure 8: Data collection forms – paper version

According to the above described process the CRIM was improved and frozen. Two different data collection tools were developed.

The @neuQuest software integrates all data items listed in the CRIM. It is a stand-alone software running on Windows operating system. The @neuQuest suite requires Microsoft Windows XP or later with version 2 of the Microsoft Dot.Net framework installed.

The @neuQuest application window provides the user with options to open existing data files and create new data files (one file for each participant). After opening a data file the user can browse to different sections of the data (figure 9) to review previously entered values and add/edit/remove data where required. Entered data is displayed in a format suitable for the specified data type, i.e. text in

editable text boxes, options in drop down lists, dates in calendar controls, etc. The ontology definition of each data item is displayed on request when pointing the cursor allowing users to see what each data item represents.

Arrays of data sets, such as information on each collected biological sample, can be entered into @neuQuest using special array entry controls. The array controls show what data sets have already been inserted and provide buttons to add, edit, or remove data sets. @neuQuest also includes the functionality to scan patient DICOM imaging studies and retrieve from Picture and Archiving Communication Systems (PACS) and auto complete data sets.

@neuQuest uses icons to show the completeness of the collected data. Green ticks indicate data is completed and red crosses show data is missing. Warning triangles are used to show partially completed data, with red triangles to show missing mandatory data and yellow triangles to show missing data but that it is not mandatory.

Changes to data are saved as the user browses through the data entry areas and makes modifications. All changes to data include an audit trace of the user modifying the data and the date it was performed. It creates one XML document per patient containing all the clinical data from the recruitment to follow-up. It is not solely a data collection tool but also the best way to understand and review the CRIM.

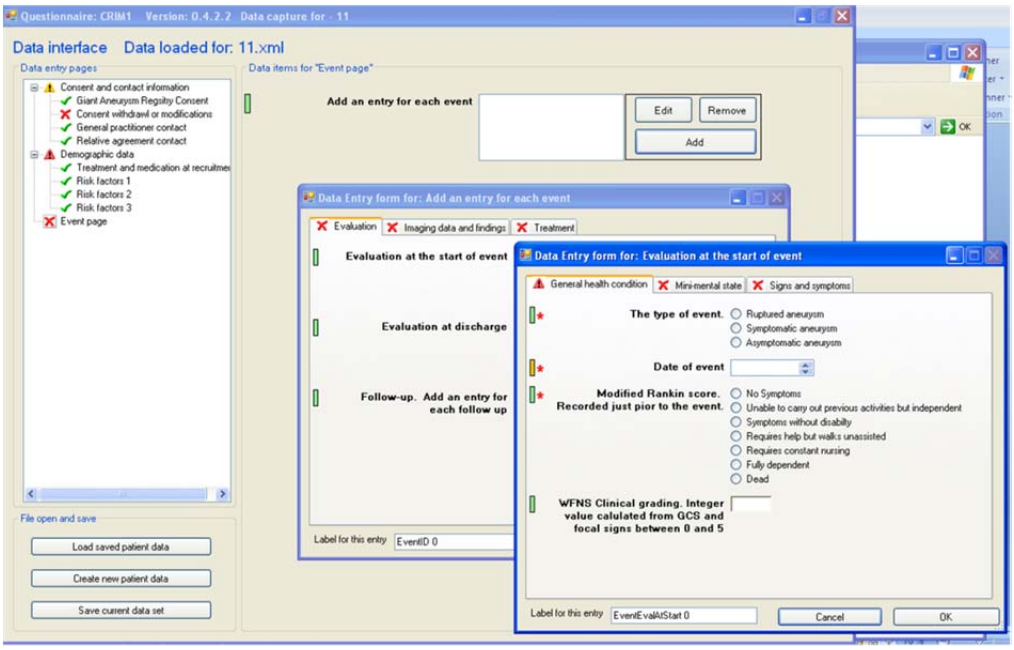


Figure 9: Data collection forms – generic digital format

A bespoke version of the data acquisition software (called @neuQuest-DPI; DPI: Dossier Patient Integré) demonstrating the ability of data acquisition to be integrated into, as opposed to "added on top of" the hospital information system has been implemented in Geneva. @neuQuest-DPI involved the creation of eleven forms to collect @neurIST CRIM compliant data (figure 10).

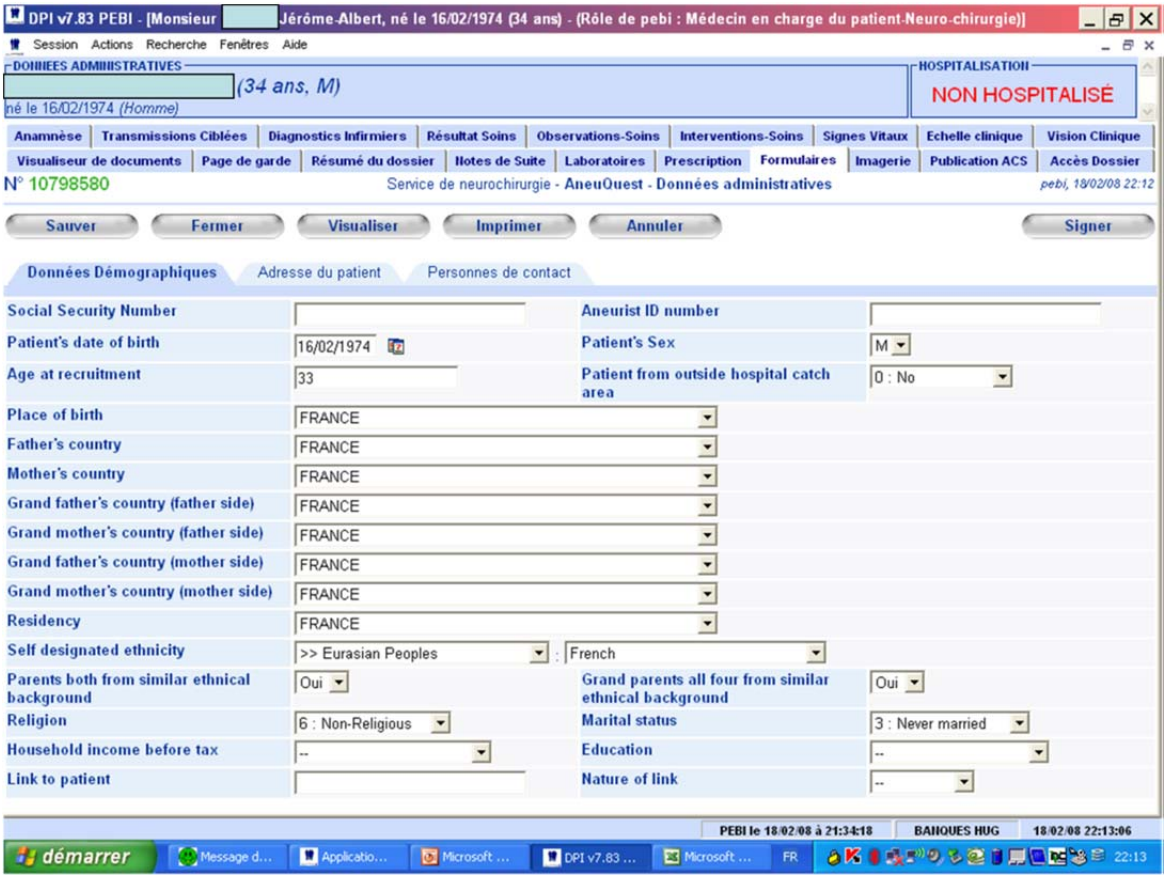


Figure 10: Data collection forms – digital format integrated in the hospital information system

5.4 Data retrieval for use

To access and analyze collected data, two export formats are provided. It has been identified early in the project that data to be exported and federated outside of each hospital's firewall should not allow uncontrolled re-identification. It was stated that local principal investigators and ethics committees in each hospital were responsible for the adequate handling of data within the hospital firewall. Data exported outside the firewall had to be modified to make direct identification of patients impossible but also had to allow re-identification in case of ethically questioned situations. Therefore the identity of patients is pseudonymized using a dedicated software application.

Pseudonymized data is a specific form of anonymized data where identifying information is removed from structured and unstructured data and each case is identified by a pseudonym. The removal of identifying information is based on a list of items that have to be stripped of the data, as well as measures taken to avoid recognition of the individual from the remaining information (i.e. face recognition from 3D imaging files).

Thereafter data can be exported:

1) locally as a mysql database that can be used for local auditing and local clinical research purposes under the full responsibility of the local principal investigator

2) shared between institutions as "non identifiable information" and "pseudonimized" mysql database containing clinical data and imaging data exposed to the web under strict access role control.

During the course of the project priority was given to the federated use of data and therefore little effort was invested in developing local database exploitation tools.

As described above in the architecture section, the biomedical data collection is a service (BioIS) composed of multiple components to allow the functionality of providing biomedical information to the Data Access Service (DAS).

Two architecture models have been adopted for the BioIS:

- the anonymized database model (ANO model)
- the On-The-Fly model (OTF model).

In the ANO model a dedicated database, local to the operating hospital is used to store the anonymized data in a network demilitarized zone (DMZ) which is part of the hospital network positioned between the hospital's inner and outer firewalls. A copy of identifiable clinical data is retained within the inner network of the hospital (Clinical Information System CIS) and is the means for entering updated information over the course of care. De-personalisation and pseudonymization are performed prior to data transfer from the CIS to the less restrictive DMZ.

In the On-The-Fly model (OTF model) no additional database is operated to manage the pseudonymized data sets. Instead, the CIS is used directly and the pseudonymization is performed as part of the data retrieval process in response to queries received by the BioIS. The CIS serves as the local database and allows secure connections from Data Access Service via an intermediating software (connector software) residing in the DMZ of clinical centres. The CIS is only accessible by the particular BioIS components residing in the local DMZ and is not accessible by any system outside the clinical centre firewall. Depersonalisation and pseudonymization are performed "on-the-fly" on the out-going data.

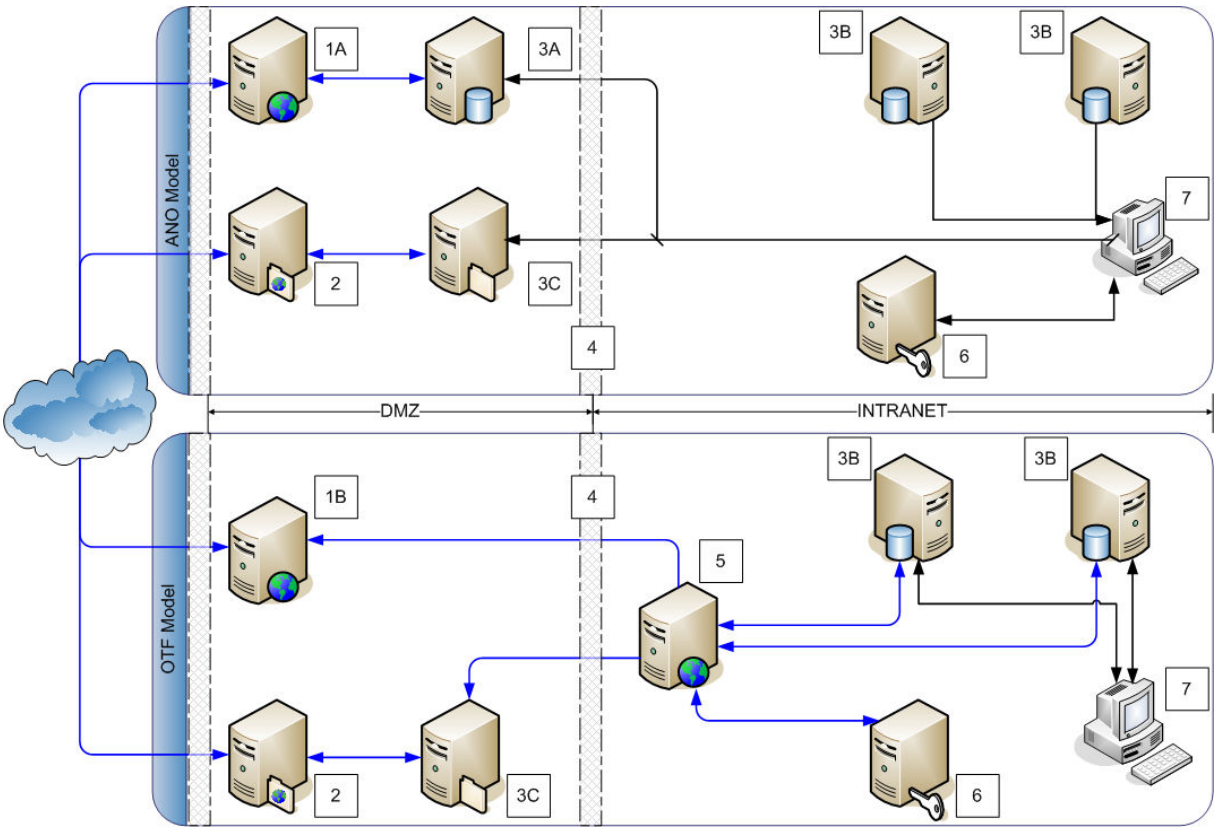


Figure 11: Two BioIS implementations

Figure 11 above shows the two BioIS implementations. The components labeled in the figure are described below:

• 1A and 1B: data access service (DAS)

• 2: pseudonymized image service (AIS)

• 3A: pseudonymized database

• 3B: hospital databases

• 3C: pseudonymized image repository

• 4: firewall

• 5: data mediation service (DMS)

• 6: pseudonym generator

• 7: data acquisition platform.

Blue arrows show the data flow while accessing @neurIST data and black arrows show the data flow during @neurIST clinical data collection.

The BioIS components can be categorized into three categories according to their functionalities: data storage, data access and data security components.

Data Storage:

The main difference between the two BioIS implementations resides in the location of the clinical data which implies 2 ways of retrieving the data. For the ANO model, a relational database is used to store the @neurIST clinical data and the images are stored as flat files. These data are stored in the hospital DMZ and they are pseudonymized (3A and 3C in figure 11). For the OTF model, the clinical information system (CIS) is used to store the participants' data (3B in figure 11). A data mediation service is required in the intranet to map the local data structure into the @neurIST one (5 in figure 11). It is important to point out that the images are not yet managed in an "on-the-fly" manner for the OTF model and are stored and accessed in the same way as in the ANO model. The reason is that the pseudonymization process of images produced by MRI cannot yet be fully automated and requires some minor but necessary human actions.

Data access components

Clinical data is accessed via a data access service or DAS (1A and 1B in figure 11). This component is an implementation of the @neuInfo data service. When using the ANO model, the @neurIST clinical database is accessed directly by the DAS. When using the OTF model a request task is written down in a specific directory by the DAS and a service from the hospital intranet will retrieve the request and send it to the data mediation service for execution.

Imaging data is shared via an access image service (AIS). This component is an implementation of the Fura virtual file server. Fura is a self-contained software that allows the distribution of applications on heterogeneous interconnected computational platforms. Fura features web-based Graphic User Interface, wizard-guided installation and Web Service compliance. The images can be accessed using the Fura agents or via the Fura portal.

Security components

The first security component deals with patient privacy and confidentiality (6 in Figure 12). The pseudonymisation service removes or transforms all identifying information before data leaves the hospital intranet. The patient ID, study UID and series UID are transformed in a reversible way. The second security component is the authentication and authorization service providing security to the BioIS.

The concept of the @neurIST data node was introduced early in the project when it became apparent that the individual software components from each partner were quite complex to install and configure. Whilst each partner put efforts into minimising this administrative load, the total effort to install them all and, more importantly, understand how they interacted with each other in a single system became quite overwhelming for a system administrator in the clinical institutions. This complexity could easily have led to the worst case scenario which is a set of services that appear to work individually but have significant defects interacting due to miss-configuration. For this reason it was decided that a single Virtual image (based on VMWare) would be produced simplifying the job of deploying a set of @neurIST services. Because all of the different components of the system have been installed or verified by the software designers it is much easier to verify the configuration details and have confidence in the overall security of the system.

The core components of the @neurIST data node services are:

- Fura File sharing system
- Voluntary Genomics Data Submission (VGDS) data query services
- Apache web server
- Java Tomcat service container
- Security relationship manager
- MySQL database
- Security Shell (SSH) server
- Network File System (NFS) file sharing services

In addition to the @neurIST specific components, significant efforts have been put into hardening the server operating system in general so it is capable to safely run on the internet. This process involved configuring the following features:

- Security Enhanced Linux operating system (SELinux) for all exposed services
- Firewall
- Intrusion detection
- Software updates
- Nagios® active monitoring system

In addition to this hardening it is also necessary when dealing with virtual machines of any kind to construct the distributed (base) operating system in such a way as to avoid creating components that will become invalid when the server is installed in a new institution. An example of such an item would be the encryption certificates used for web services, if these are not regenerated for every server instance after they are deployed, the services will not function correctly. For this reason effort was put into identifying all such "site specific" components of the system and scripts were generated so the local system administrator could simply execute them with a minimal amount of effort and complete the deployment in a very short period of time. Examples of the site specific items that need to be considered are:

- Image storage
- Database backups
- Hostname
- Email alerts
- HTTPS certificates

As a final effort to ensure the system is as easy to manage as possible, and therefore safe, a lot of management scripts were produced to aid everyday functions that system administrators are required to carry out. Tasks such as the backup of the core database and emailing untoward activity to the administrators are all catered for.

The result of this work is that the time to deploy the @neurIST BioIS data node, a very complex data hosting environment, has been dramatically reduced so that an expert systems administrator can set it up in approximately an hour, and a less experienced systems administrator can easily accomplish this in a day.

Documentation is available for system administrators to carry out the deployment, but it has not been made public for security reasons.

5.5 Implementation plan

The strategy adopted was the development and use of tools to improve the screening for the disease, as well as the management of each case and to optimize each treatment.

Challenges identified within each of these activities were:

- Improving the screening for the disease required a better understanding of the pathological process. The disease is multi-factorial, and improving understanding necessitates the collaboration of a broad spectrum of scientists with very different backgrounds.
- Improving care management required first a set of standards and guidelines, then monitoring of practice variations and impact of those variations on outcome. The clinical management of each case is complex and involves a high integration of information in a short period of time and by a wide range of specialists. A further tier of difficulty arises from the lack of data establishing the relative significance of the information, and more fundamentally by the disparate physical location of documents within hospitals.
- The optimization of treatment requires training, assistance, building of experience that is then shared with an international community of experts. This requires improving communication by developing and using new computational resources at a higher level (more clinical centers involved and more time to evaluate outcomes of recruited cases) than could be explored using the @neurIST system during the limited time of the project.

Successful implementation requires adhesion by all stakeholders. This can be achieved by progressively improving work efficiency of key partners.

Modifications to practice are likely to be introduced progressively by:

1. Standardization of clinical reporting using Ontology and Clinical Data Collection Protocols.
2. Reducing redundant clinical administrative workload, optimizing information collection and reporting to downstream stakeholders (medical reporting of treatments and observation, follow-up scheduling, billing).

3. Improving decision support, selecting the most relevant information for each specific case and optimizing information display.
4. Displaying patient specific information in association with data of similar cases stored:
    i. in the local database (@neurBrowser)
    ii. in the database populated by all contributing clinical centers (@neuBrowser via @neuInfo)
    iii. published in the literature as case series or guidelines (@neuLink, @neuRisk)
5. Increasing new knowledge and evidence generated from co-ordinated multidisciplinary analysis of data collected using validated procedures and quality controls.
6. Optimal visualization of computer simulations of the disease's natural evolution, treatments and expected treatment results for the purpose of:
    i. informing patients (personalized models) or
    ii. assisting surgical preparation and execution (augmented reality)
7. Optimizing computer simulations using patient adapted models extrapolated from existing stored data on patient populations to generate Virtual Patient Metaphor.

We outline below the plan that was defined.

Clinical workflows can usually be modeled as successions of enquires, decisions and actions, each supported by guidelines, standards, and simulations that are becoming increasingly automated.

Typically, a clinical workflow can be summarized in the following steps:

- Identification of the optimal investigative process to understand and inform about the specific clinical case.
- Definition of the most appropriate treatment scheme (in the case of intracranial aneurysms, is the lesion to be observed or should it be treated).
- Selection of the most appropriate technology (in the case of intracranial aneurysms, the method to secure the lesion).
- Post-treatment reassessment (define method and periodicity of reevaluation).

In the pre-@neurIST era the complete intracranial aneurysm workflow was unassisted. Most actions, enquiries and decisions were recorded on separate paper documents, often stored in separate files within different departments or even different hospitals. The decisions on how to evaluate, treat and follow-up were mainly governed by the personal experiences of the responsible physicians. Objective measurements that enable reliable prediction of risk and guidelines in care remained under strong debate.

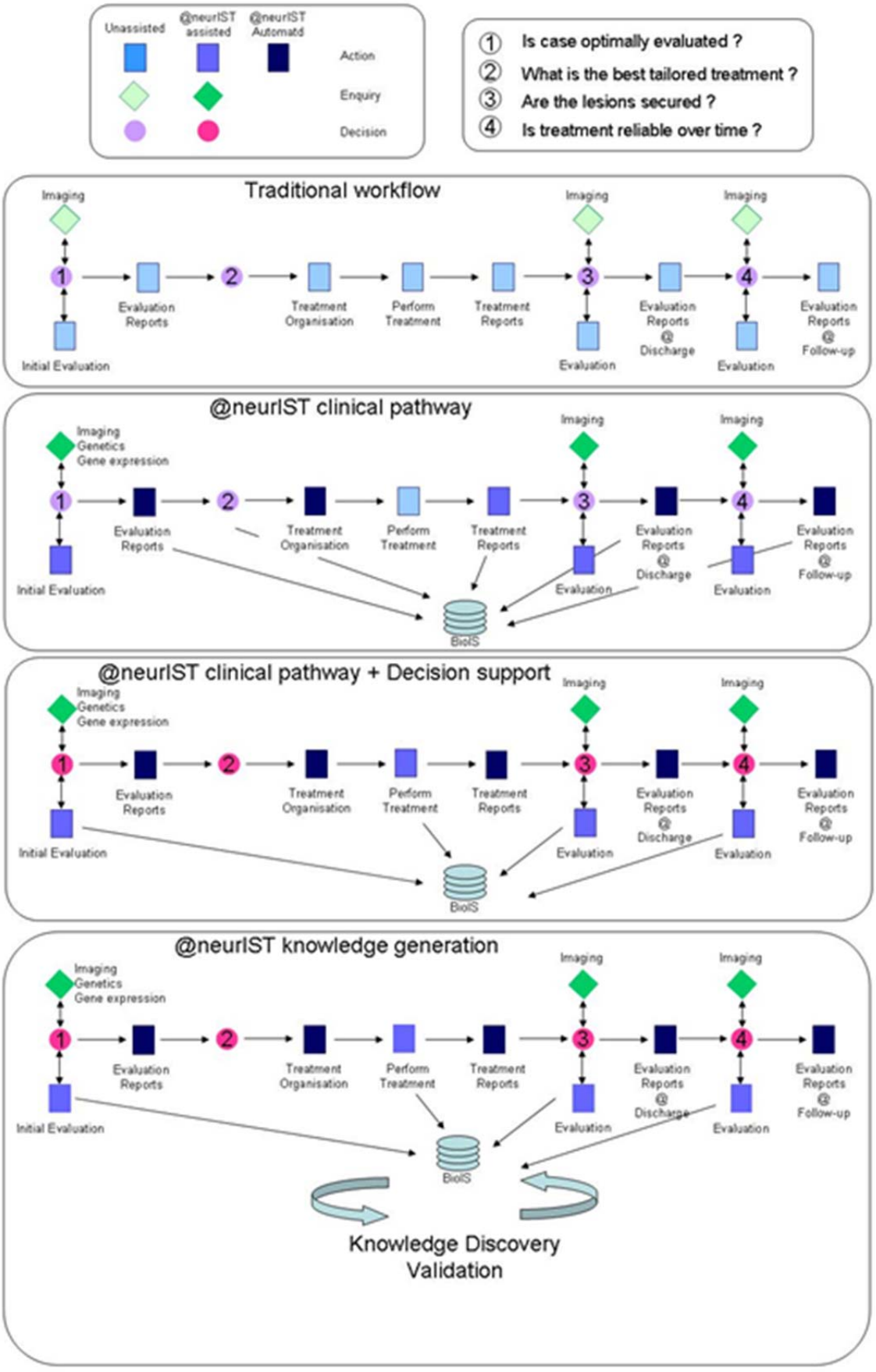


Figure 12: Clinical data collection: a progressive integration in the clinical environment

The vision of the @neurIST project is to build tools to revolutionize the decision-making process into 3 steps:

- **Step1**: introduction of tools to promote the transition from hand-written notes to centralized digital patient health records.
- **Step 2**: bringing decision support tools to the clinic
- **Step 3**: improving the decision support tools by the analysis of the information collected in step 1 and step 2 in a continuous iterative process that could ultimately be automated.

5.6 Design of the evaluation of the system

Methods were defined by which the introduction of the sophisticated information infrastructure of the @neurIST project into the clinical environment would be evaluated. In keeping with the project's alignment around a portfolio of key user cases, the evaluation was structured to examine performance in the context of the five identified generic workflows highlighting Risk Analysis, Knowledge Discovery, Aneurysm Characterisation, Stenting Optimisation and Multi-Case Analysis.

In scope assessments performed were:

- Impact of the @neurIST system and tools on clinical practice, evaluating both benefits and costs
- Evaluation of the quality of data and usability in different domains and for different needs
- Evaluation of the system's usefulness at hospital level
- Impact and visibility of the @neurIST results in the clinical area

Out of scope assessments performed by more technical partners of the project were:

- Assessment of platforms for suites
- Assessment of implementation and architecture
- Development of exploitation plans for future applications

The evaluation process was designed with three phases in mind:

1. Assess clinical needs and capacity for the tools, including:
    - Clinician's interest in the tools for each workflow
    - Workload generated by induced changes in practice
2. Feedback on the tools and their use:
    - Evaluation of the quality of information collected for the purposes and users identified in @neurIST
    - Testing of prototype tools for interaction, time requirements, etc.
3. Assess integration of the tools in clinical practice and contribution to research
    - Testing of impacts of the tools in controlled situations
    - Assessment of new knowledge discovered in @neurIST and implementation of any new knowledge in the decision support system
    - Exploration of possibilities to implement new knowledge, automatically and in real-time in the system

Evaluation of the impact of the @neurIST system needed the implementation and technical validation of the IT infrastructure before any realistic assessment could be performed. Implementation and technical validation of the system, allowing secured and robust use while protecting patient privacy, was achieved late in the project. It was therefore expected that only a prototype version of the @neurIST system could be evaluated limiting the general conclusion to a proof of principle rather than a quantitative measurement of impact.

6. Data collection

6.1 Overall recruitment

Recruitment started in the first centre in June 2007. All other centers had received ethics approval and started recruiting by March 2008. All centers collected clinical information, blood samples and cerebro-vascular 3D imaging using MRI, CT or digital subtracted angiography (figure 13).

Each centre reported the number of cases consented as well as the number of clinical files, imaging and blood samples obtained. Collection of blood samples for genetics and transcriptomics was closed in August 2009. Recruitment for clinical and imaging data continued at the discretion of individual sites.

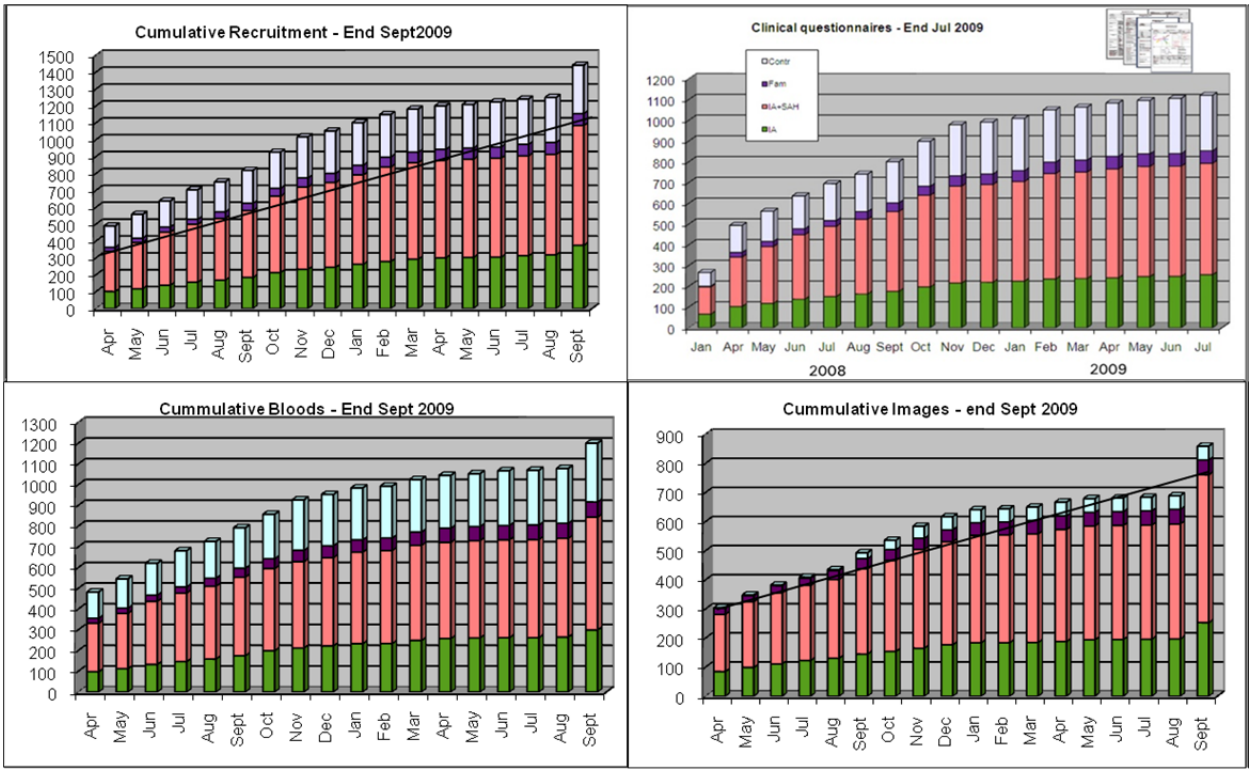


Figure 13: Rate of data collection between April 2008 and September 2009

6.2 Database content

Using the @neuQuest data collection tool it is possible to record every piece of information that could be pertinent to the disease, but most cases contain information on a small fragment of the complete information model. It is therefore necessary to explore the content of the databases to check if it contains the required information to fit the purpose of a study or a suite. A component of the @neuLink suite, @neuBrowser allows such exploration.

An example of such use is to address the question of knowing how many cases are described in the databases for which the collected data covers all research studies supported by @neurIST: genetics, transcriptomics, imaging, and complex tool chain processing.

The snapshot in figure 3 shows that 228 cases described in the databases are genotyped, had blood retrieved in PAXgene for transcriptomics, and are documented with clinical information, cerebrovascular information and imaging. 137 cases suffered a subarachnoid haemorrhage from the rupture of an aneurysm, 88 are patients with unruptured aneurysms, and 3 are members of families genetically prone to have aneurysms (figure 14).

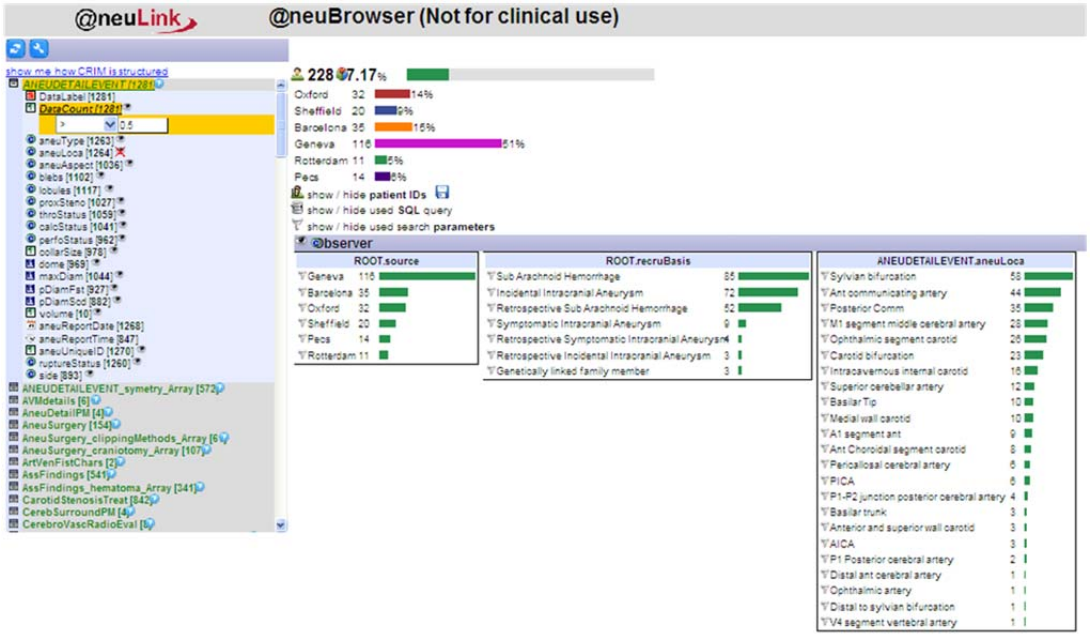


Figure 14: Data management tool - @neuBrowser screenshot

The database content at the end of the project in February 2010 is described and discussed below.

Table 1: Number of participants recruited and information collected in @neurIST – February 2nd 2010

Recruitment status February 2nd 2010

	Consents	Clinical Info	Cases with imaging	Cases with blood samples
Declared collected	1255	1120	697	1068
Visible in the BioIS	1255	1009	495	949

Consents

The number of cases declared as being consented by clinicians and the number of cases consented visible in the database using the @neuBrowser matched after considerable efforts.

In contrast with other clinical centers where dedicated personnel retrospectively collected information from the clinical files and populated the database, UNIGE progressively involved the clinical team in data collection using tools to assist clinical workup. Consenting for @neurIST was performed by trained clinicians and performed as part of the routine work. During the first months of recruitment everything was performed on paper only and as a result, a batch of consent forms was lost. Patients were progressively re-consented when visiting for follow-up purposes. Loss of paper forms in the clinical environment is a long-lasting and well identified issue. At the institutions' level, a similar observation has been made for mandatory written consents collected prior to any intervention that are often missing from the paper files (20%). As a consequence, the consent process has been modified. Instead of recording the consent on paper and retrospectively up-dating the electronic health record, the electronic health record is filled out, the consent is printed and the printed version is signed and stored by both the patient and the local study manager. The consent is formally confirmed in the letter to the General Practitioner if the patient agreed and the letter is stored in the electronic health record.

Descriptive information (Clinical Information)

The number of cases documented with clinical information that can be seen through the @neuBrowser matches well the numbers declared. It reflects that clinical information is strongly linked with obtaining consent from the patient to be included in the project. The match declines when requesting more information. All consented cases are documented with respect to age and gender. Hundred eleven cases (10%) had missing information regarding familial history, smoking status, hypertension status, multiple aneurysm status.

The details for many of the phenotype fields used in the downstream analysis were not filled by the clinical centers. Thus, in accordance with local clinical policies of not testing for specific conditions unless there is clinical suspicion of its presence, the proper interpretation of an unfilled phenotype field is "not tested – assumed negative". This may cause some weakness in the clinical data, but is more reflective of real-world clinical information. In the case of intracranial aneurysms, most of the relevant phenotypes are likely to be in evidence in the patient's medical history prior to the diagnosis of the aneurysm, so the numbers of misclassified cases is likely to be insignificant. The costs of testing all risk factor conditions would add prohibitively to the cost of clinical and research practice.

Descriptive information (Imaging Information)

There are two hurdles in descriptive information storage. Some participants have no or inadequately formatted imaging. For example, healthy volunteers were recruited without imaging on the one hand, and, on the other hand, some patients were investigated in other clinical centers providing films only. The dataset resulting from the scanning of films was considered unusable. Cases were considered appropriately documented with imaging only when at least one initial 3D imaging was obtained by CT-angiography, MR-angiography or DICOM stored reconstructed 3D rotational angiograms.

The discrepancy between the number of cases declared as recruited with imaging and the number of cases with a description of the imaging in the database is explained below. Describing the content of image series is a demanding task that can only be performed by a trained clinician. In most pilot centers it was performed by personnel directly involved in the complex tool chain processing as image users or trained data collectors. The project being an IT project the resources allocated to data

collection were kept to a minimum trying to develop tools to assist clinicians in their daily reporting tasks. Those tools were developed but were not mature enough to be used in the clinical environment lacking user-friendliness and robustness. Therefore imaging information collection was not yet merged with standard clinical practice at the end of the project. It took more than a year after the project completed to improve the database content and document missing information by reviewing imaged cases.

Representative information (Image series):

Only image series that can be retrieved using the @neuBrowser were taken into account.

Some imaging datasets had to be discarded because of difficulties encountered when processed using the automated segmentation tools. One such difficulty arose as a consequence of the automated de-facing tool being applied to MR images that had better static tissue suppression than those of the test data used when programming the tool, with the result that vessels of interest were corrupted during defacing. This issue having been identified, the de-facing tool was revised to better adapt to individual scanner properties and to allow the operator to make adjustments to ensure a successful defacing operation.

Unfortunately, it is only after data is examined by an expert in post-processing that their suitability and quality for research use can be assessed; this creates extra work for both the clinical site staff uploading the images and the image analysts in downloading and reviewing images that are not usable for morphodynamics and hemodynamics. With the @neuFuse tool adding the functionality of data quality assessment, it is hoped that the screening of images can in part be shifted to the data quality process, and that feedback about image quality to the clinical centers can allow better upstream control of image quality.

The primary causes of images not being usable were:

- MRI and 3dXA image series obtained in some clinical centers that satisfied the clinical needs were too distorted for morphodynamic studies and were rejected.

- Images from CT-Scan are sometimes difficult to process because of vessels in contact with bone making the segmentation very difficult.
- Angiograms are sometimes subject to incomplete contrast filling mostly in large lesions resulting in artifacts leading to dataset rejection.

Given the extensive workload to perform the complete imaging task on each imaging file, more than 240 cases were processed and the resulting derived data stored in the database.

Biological samples

Blood was collected and stored for genotyping and exploration of expression of genes in the circulating blood cells. The collection and genotyping of blood sample represents a good illustration of the inherent limits in data collection in the clinical environment. All consented cases should have been giving blood but in practice, samples were declared as obtained from only 1068 participants (85%). Blood samples were labeled and recorded in the database for only 949 participants (89% of cases declared to be collected). Finally blood samples from 825 participants were genotyped. All genotypes could be associated with a phenotypic description. Gender and age were available for all genotyped samples but detailed information as specified in the minimal data set was available for only 650 participants (52% of consented subjects).

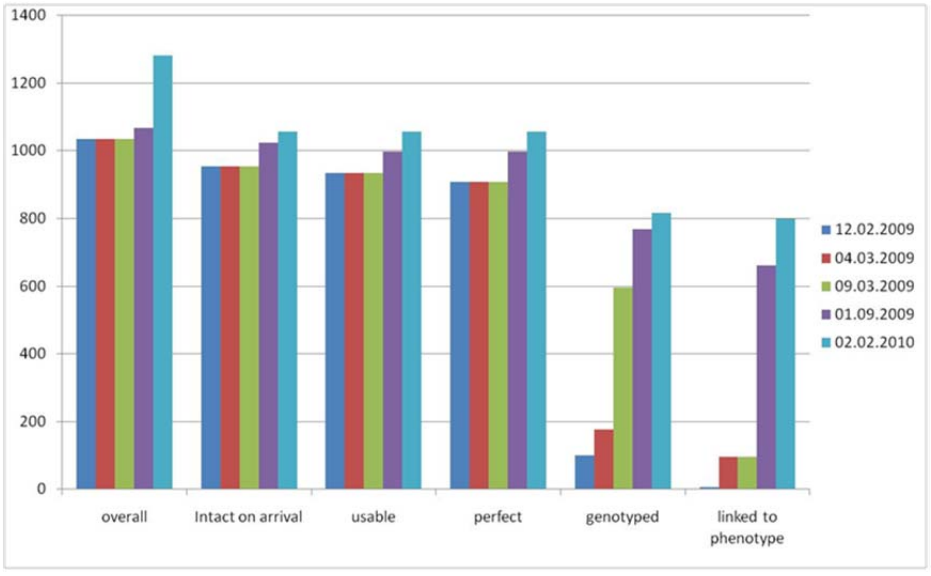


Figure 15: Biological samples processing for genotyping – time frame and information loss

As illustrated in figure 15, there are multiple steps separating the collection of blood samples at the bed-side from storage of digitalized whole genome scans in the database. From left to right: the first decline in the number of blood samples corresponds to samples collected late in the project that could not be shipped before the closure of the experiment. A second drop is due to samples lost in transportation or degraded. A third drop is secondary to a political decision. It has to be noted that after discussion with a research group from Yale it was decided to join efforts. To maximize the genotyping of affected subjects using the allocated funding it was confirmed at the consortium level that only patients and no healthy volunteers would be genotyped and that genetic information on healthy volunteers would be gathered from other available sources. Nevertheless blood from 226 healthy volunteers was obtained and stored for later use. All genotyped subjects could be mapped back to their clinical files but detailed clinical information was available in the BioIS for only 650 patients. Later work allowed increasing this yield.

The gene expression study made use of blood retrieved in PAXgene tubes from 466 participants. Clinical information allowing stratification and case selection was obtained in 328 cases and 138 healthy volunteers. Information on type and location of aneurysms was obtained in 196 patients. 282 subjects (99 controls, 11 familial case, 79 patients with intracranial aneurysm without rupture and 93 cases with Subarachnoid Haemorrhage) from @neurIST Clinical centers and 6 subjects from Yale University were screened using the Illumina human HT12 beadarray for quantitative gene expression in circulating blood cells. Unused samples were stored for validation steps and future research projects.

6.3 Data collection process

A key epidemiological principle to bear in mind when considering the final utility of the @neurIST data is that the context of any observation has to be defined.

Each recruitment center therefore identified and evaluated the stability over time of the recruitment population. The geographic definition of the recruitment area for each hospital and the associated demographic data was taken into consideration. Each recruited participant was confirmed as residing within the hospital recruitment area or not.

Consecutive recruitment is mandatory to avoid case selection bias. It is easily understandable that the uneven collection of data is not randomly distributed. Extreme situations either suffer a lack of interest or require too much work to be systematically documented. Continuous monitoring of the data collection process and verification it is consecutive is extremely important.

To warrant accurate information, data needs to be collected according to a protocol, using a unique definition and personnel collecting the information need to be trained and certified. The inter-rater reliability for each item collected should be measured. The above mentioned requirements cannot be met optimally when data is collected retrospectively.

Data was therefore labeled regarding the residency of participant, consecutiveness of recruitment and degree of accuracy. This allows the identification of subsets of data in the BioIS that are of the required quality to serve as validation resources.

Collecting prospective consecutive exhaustive information is resource expensive and requires solid infrastructures. Logistically and financially, it has not been possible during the course of the @neurIST project; however, the Geneva University Hospital invested large efforts to converge toward this target. In addition, considerable weight has been placed on retrospective recruitment in order to obtain the required numbers of blood samples in time for the genetics and transcriptomics studies. Therefore, most of the data is not optimally suited for epidemiologically validated research. The data can however be used for hypothesis generation; and results may be validated using optimal datasets.

In the prospect of real-time automated evidence extraction to support clinical decision making, all processes will need to be tested, validated, certified, audited and database content protected against any kind of corruption.

To evaluate the quality of data provided by the different clinical centers involved in @neurIST, we defined 3 criteria, so far:

- Completeness: nothing needs to be added
- Robustness: ability to cope with challenge
- Resource friendliness: easy and inexpensive to learn, understand, use, deal with and maintain.

The degree of IT development of the clinical centers participating in the @neurIST project was very broad. Some centers provided data using the whole range of @neurIST tools and complied with stringent requirements. Other centers did not have the resources to deploy all developments and one center joined the project only to provide data to the genetic study using none of the @neurIST infrastructure but MS Office Excel and e-mails. It was interesting to evaluate the impact of the implementation of @neurIST tools on completeness, robustness, and resource friendliness of the collected information.

University Klinik Bonn (UKB) was invited to join the @neurIST consortium to increase the volume of cases included in the genetic study. The data was collected according to a local research protocol. The amount of information collected was limited to the age of the patient, gender, ethnicity and DNA. It is an academic center of excellence equipped with standard information tools.

- Completeness of data is perfect according to the local research protocol but covers only a part of the minimal data set defined in the @neurIST protocol.
- Robustness of data collection is uncertain.

  The recruitment is retrospective and not consecutive. Processes laid out in the @neurIST protocol were not followed for recruitment or for collection of blood samples or clinical data.
- Resource friendliness of the data collection process is meager.

Extraordinary resources to reprocess information are needed. Information is stored either in paper files or Excel sheets and images are stored on films. The amount of work required to extract more information to be added on the original Excel sheet is insuperable.

The observation illustrates the limitation associated with the separation between clinical and research activities as well as unstructured documentation of information in paper files. A lot of information is lost or stored but almost inaccessible. The balance between the limited data amount collected with high robustness and the enormous workload to improve the data set to fit other purposes then originally planned prevents data recycling.

In non-pilot clinical centers data collection tools were provided by developers, research team members were trained. The data was collected from clinical files and paper forms designed for the purpose of the @neurIST project. No local image archiving system (PACS) was available. Some imaging data sets were uploaded to the @neurIST system directly from CD-Roms. This infrastructure resulted in the following evaluation:

- Completeness of data is moderate to poor.

  All descriptive data items were collected but considering the lack of local PACSystems, imaging information was missing for most cases.
- Robustness of data collection is moderate to poor.

  Consecutive recruitment is not guaranteed, but the @neurIST protocol guided recruitment and data collection.
- Resource friendliness of the data collection process is moderate to poor.

  Patient histories and the preparation and uploading of data to DMZs require manual intervention for each case. Image capture and storage are automated to some extend with routine clinical work but the lack of digital archives results in massive data loss as the rescue of imaging data that has not been collected initially is to work-intensive. Hosting of data by other centers has proven problematic to organize because it needs regular interaction of qualified personnel from both centers.

Pilot clinical centers in @neurIST (USFD, UOXF.HJ, MI-EMC, HCPB) recruited cases and collected data according to the defined minimal dataset. All centres have part of the data collection process merged with the routine clinical practice and store images in a PACS.

- Completeness of data is moderate to good.

  As noted, many clinical history items of interest as phenotypes are not explicitly tested in routine clinical practice, and so non-response is taken as a negative response.

- Robustness of data collection is moderate.

  Consecutive recruitment is not guaranteed, but the @neurIST protocol was followed for recruitment and data collection, and adaptations of clinical practice may be progressively modified to allow consecutive recruitment.

- Resource friendliness of the data collection process is moderate to good.

  Collection of imaging and storage is merged with routine clinical practice, but recording of clinical history happens in parallel to clinical practice. The use of the @neuQuest allows data transfer to DMZs to be performed in batches with minimal intervention.

Only the University Hospital of Geneva started merging the collection of clinical information into the routine clinical environment and recruited cases both prospectively and consecutively as of April 2007.

- Completeness of data is good to excellent.

  As for other sites, not all phenotypes are explicitly tested but any later discovery is automatically updated to the electronic clinical file.

- Robustness of data collection is moderate to good.

  Consecutive recruitment is ruled in but no quality check or verification procedure has been implemented yet.

- Resource accessibility of the data collection process is excellent.

  Collection of clinical information and imaging as well as the storage of information is merged in routine clinical practice. Nevertheless the use of the information platform is not mandatory

for all aspects of the clinical pathway and the compliance of users is still low. The use of the "on-the-fly" approach to data access by the @neurIST system minimizes the need for human interaction in data preparation.

To fully integrate data collection and data quality check mechanisms in routine clinical practice, further developments and training are required. It is expected, if the University Hospital of Geneva maintains its efforts, to reach the level where the minimal data set is collected completely with numerous internal controls and sign-offs allowing the highest robustness of data with an automated prospective consecutive recruitment using a system entirely merged in the clinical practice and integrated in the medical file management between 2013 and 2015.

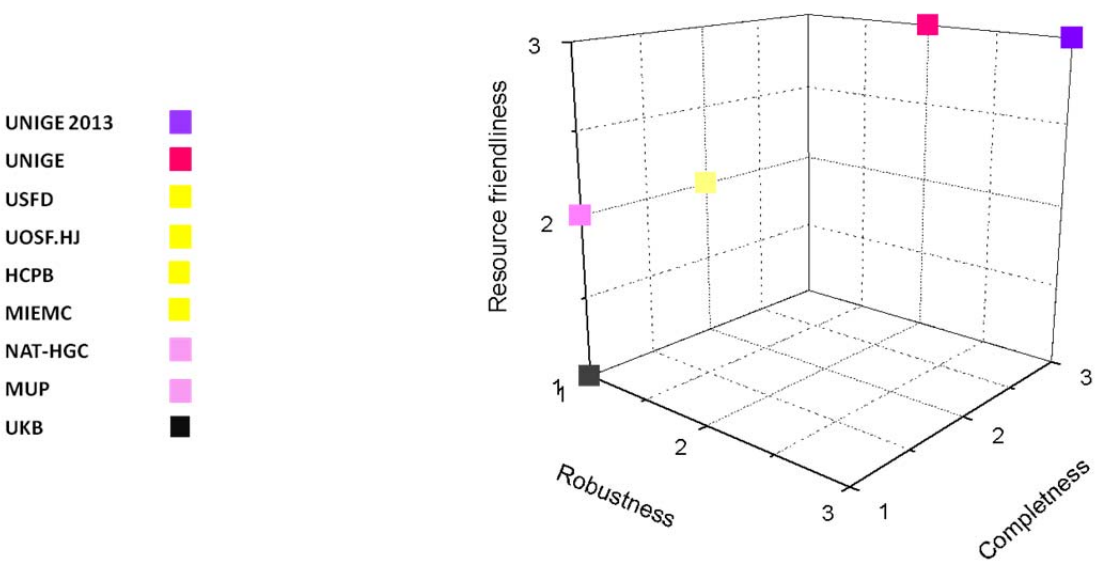


Figure 16: Impact of information technologies on clinical data collection

7. Selection of results

7.1 Current criteria for identification and optimal treatment of patients suffering from intracranial aneurysms

This section is an overview of the work performed by Mike Clarke using the Cochrane literature review methodology. The purpose was to list known risk factors associated with subarachnoidal bleeding or presence of intra-cranial aneurysms to define pertinent information to be collected from participants. The relative risk associated with the presence or absence of factors was calculated whenever possible to generate a predictive model.

It also reports the results of an international audit of neurosurgeons and neuro-interventional radiologists performed by the author to identify factors used to decide or involved in the decision making on how to treat an intracranial aneurysm.

Risk factors for aneurysmal subarachnoid haemorrhage were assessed with a systematic review of reviews (Cochrane Collaboration). Reviews were selected by performing a bibliographic database search for loci, genes and protein, as well as risk factors associated with subarachnoid haemorrhage or intracranial aneurysms. The search on PubMed retrieved 145 records and on EMBASE 2339. Records were checked twice. A total of 417 full text articles were obtained and checked.

7.2 Information integration to optimize screening – who to treat

Currently intracranial aneurysm screening can solely be performed by magnetic resonance imaging (MRI) or X-ray Computed Tomographic scanning (CT-Scan). Screening with non-invasive imaging is not recommended in general except in three populations defined below. For people corresponding to those populations, the risk of being affected is estimated to be 4 times higher than average population and it seems patients suffer SAH at a younger age. Screening should be started at the age of 30 for females and 35 for males and should be repeated on a regular basis.

Ten percent of patients affected by intra-cranial aneurysms are member of those populations at risk.

Currently identified populations at risk of aneurismal SAH.

1) all directly genetically linked family members when already two directly genetically linked members suffered a subarachnoid hemorrhage. This group represents 9.6% [8.1-11.2] of patients identified with intra-cranial aneuryms.

2) patients suffering of Autosomal Dominant Polycystic Kidney Disease. This group represents 1.8% [1.5-2.2] of patients identified with intra-cranial aneurysms.

3) patients suffering rare genopathies like Ehler-Danlos, Marfan, Osteogenesis Imperfecta, Neurofibromatosis, Infantile Cortical Hyperostosis, Tuberous Sclerosis. This group represents 0.16% [0.07-0.3] of patients identified with intra-cranial aneurysms.

Genetic:

There is currently no genetic preclinical test available to identify a population at risk of suffering an intracranial aneurysm rupture. Nevertheless large efforts were focused on identifying genetic loci associated with the disease. An automated review of the literature using the @neuLink suite and the complete PubMed database of article titles, abstracts and available free text allowed measuring the relative entropy of chromosome locations associated with the terms subarachnoid hemorrhage or intracranial aneurysm respectively as compared to any other terms. This allowed us to identify that by decreasing entropy chromosomes: 5, 19, 7, 4 (chromosomes where PKD2 gene is located), 14, 16 (chromosomes hosting the PKD1 gene), 22, 9, 6 and 2 were studied in association with subarachnoid

hemorrhage. The same analysis performed on the term “intracranial aneurysms” reveal that all chromosomes except chromosomes 11 and 13 were studied and reported. The seven highest entropies were associated with chromosomes 7, 19, 5, 17, 16, 4 and 14 in decreasing order of relative entropy. All seven except chromosome 17, are represented in both subarachnoid haemorrhage and intracranial aneurysm groups.

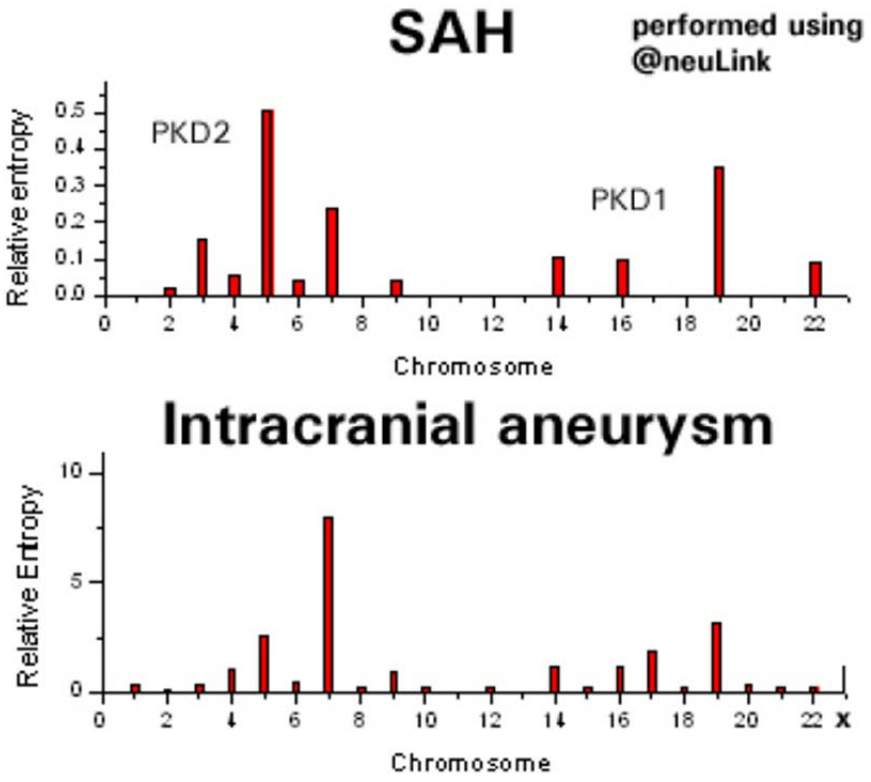


Figure 17: Automatic literature review measuring the association of chromosomes with the disease

Three systematic reviews were identified which assessed the evidence from genetic linkage studies. Biros and Golledge reported a review, and meta-analysis, of studies assessing the linkage of autosomal genome sites with familial intracranial aneurysm. The meta-analysis identified a region of chromosome 17 (17p12-q21.33) and of chromosome 3 (3q27.3-3qter) which were statistically significantly associated with intracranial aneurysm at $p<0.01$.

Ruigrok et al undertook a systematic review of studies of patients with intracranial, thoracic aortic or abdominal aortic aneurysms to compare the genetic loci that had been found to be linked to the aneurysm, in order to identify possible common genetic risk factors for the three different aneurysms. They conclude that there are five genetic loci that may include genes associated with intracranial aneurysms and aortic aneurysms: 3p24-25, 4q32-34, 5q, 11q24 and 19q.

In an earlier review, which was more wide ranging in its coverage of research into the genetics of intracranial aneurysms and subarachnoid haemorrhage reported genetic loci associated with intracranial aneurysms on 7q11, 14q22 and 5q22-31 (Japan); on 19q13.3 (Finland); on 2p13 (The Netherlands), and on 1p34.3-36.13 (USA).

Two other reviews and the first whole genome association study on intracranial aneurysms were identified but did not meet the eligibility criteria as systematic reviews. Information provided was used nevertheless in the below summary table 2 for completeness.

Genetic loci	Chromosome	Arm	Region	Original study	BG	R8	R5	KI	N	WGAS reported p values
1p36.1-34.3	1	p	3	Nahed et al 2005	Yes	Yes	Yes	Yes	Yes	1.00E-05
1p33	1	p	3	Onda et al 2001	No	No	No	No	Yes	1.00E-05
1p22.1	1	p	2	Onda et al 2001	No	No	No	No	Yes	1.00E-05
2q33.1	2	q	3	Bilguvar et al 2008						1.00E-07
2p13	2	p	1	Roos et al 2004	Yes	No	Yes	Yes	No	
2p15-14	2	p	1	Roos et al 2004	No	No	No	No	Yes	
2q13	2	q	1	Onda et al 2001	No	No	No	No	Yes	
3q29	3	q	2	Onda et al 2001	No	No	No	No	Yes	1.00E-05
4p16.1-15.3	4	p	1	Olson et al 2002	No	No	No	Yes	Yes	1.00E-05
4q34.1	4	q	3	Onda et al 2001	No	No	No	No	Yes	1.00E-05
5q22-31	5	q	2	Onda et al 2001	Yes	Yes	Yes	Yes	Yes	1.00E-06
5p14.3-15.2	5	p	1	Verlaan et al 2006	No	Yes	No	No	No	1.00E-06
5q	5	q		Roos et al 2004	Yes	No	No	No	No	1.00E-06
5q14.3	5	q	1	Onda et al 2001	No	No	No	No	Yes	1.00E-06
5q15	5	q	1	Onda et al 2001	No	No	No	No	Yes	1.00E-06
6q14.1	6	q	1	Olson et al 2002	No	No	No	Yes	Yes	
7q11	7	q	1	Onda et al 2001	Yes	Yes	Yes	Yes	Yes	
7p22.2	7	p	2	Olson et al 2002	No	No	No	Yes	Yes	
7q11	7	q	1	Farnham et al 2004	No	No	Yes	Yes	No	
7q34	7	q	3	Olson et al 2002	No	No	No	Yes	Yes	
7p14.1	7	p	1	Onda et al 2001	No	No	No	No	Yes	
7q11	7	q	1	Yamada et al 2003	No	No	No	Yes	No	
7q21.1	7	q	2	Onda et al 2001	No	No	No	No	Yes	
7q22.1	7	q	2	Onda et al 2001	No	No	No	No	Yes	
8q11.12-12.1	8	q	11	Bilguvar et al 2008						1.00E-07
9p21.3	9	p	21	Bilguvar et al 2008						1.00E-07
9p24.2	9	p	2	Onda et al 2001	No	No	No	No	Yes	1.00E-07
11q25	11	q	2	Ozturk et al 2006	Yes	Yes	No	No	Yes	
11q13.2	11	q	1	Onda et al 2001	No	No	No	No	Yes	
11q25	11	q	2	Onda et al 2001	No	No	No	No	Yes	
	12			Bilguvar et al 2008						1.00E-06
13q14.2	13	q	1	Onda et al 2001	No	No	No	No	Yes	
14q22	14	q	2	Onda et al 2001	Yes	Yes	Yes	Yes	Yes	
14q23-31	14	q	2	Ozturk et al 2006	Yes	Yes	No	No	No	
14q34.2	14	q	3	Olson et al 2002	No	No	No	Yes	Yes	
14q22	14	q	2	Ozturk et al 2006	No	No	No	No	Yes	
14z23-31	14	z	2	Onda et al 2001	No	Yes	No	No	No	
14q24.2	14	q	2	Onda et al 2001	No	No	No	No	Yes	
14q24.3	14	q	2	Onda et al 2001	No	No	No	No	Yes	
	16									1.00E-06
17p12-q11.2	17	p	1	Yamada et al 2004	Yes	No	No	Yes	Yes	
17p11.2	17	p	1	Onda et al 2001	No	No	No	No	Yes	
18p11.4	18	p	1	Onda et al 2001	No	No	No	No	Yes	
19q13.2-13.3	19	q	1	Yamada et al 2004	Yes	Yes	No	Yes	Yes	
19q13.2-13.4	19	q	1	van der Voet et al 2004	No	Yes	Yes	Yes	Yes	
19q13.1-13.3	19	q	1	Olson et al 2002	No	Yes	No	Yes	Yes	
19q13.3	19	q	1	Mineharu et al 2007	No	Yes	No	No	No	
	21			Bilguvar et al 2008						1.00E-06
Xp22.2-22.1	X	p	2	Yamada et al 2004	Yes	No	No	Yes	Yes	
Xp22.2	X	p	2	Olson et al 2002	No	No	No	Yes	Yes	

Table 2: Genetic loci associated with the disease

BG: Biros and Golledge ; R8: Ruigrok et al 2008; R5: Ruigrok et al 2005; KI: Krischek and Inoue; N: Nahed et al; WGAS: Whole Genome Association Study Yasuno et al 2010

Candidate genes

One systematic review (Ruigrok et al) was identified which assessed studies that had investigated the association of candidate genes with intracranial aneurysms or subarachnoid haemorrhage. However, the small number and little size of the studies searching for specific candidate genes make it difficult to identify reliably whether or not there is an association and Ruigrok et al conclude "few of the studies that showed association with SAH and intracranial aneurysms have so far been replicated ... the studies showing association may have been hampered by false-positive findings and small sample sizes in subsequent studies to confirm the association". Two other reviews were identified that did not meet the eligibility criteria as systematic reviews. Nevertheless information provided was used to establish the proposed list of candidate genes below.

The apolipoprotein E (APOE) gene produces a glycoprotein, apoE, which has three common isoforms. These are encoded by three alleles of the gene, ε2, ε3 and ε4. Genotypes that contain the ε4 allele (ε4+) are associated with higher cholesterol levels than the relatively common ε3/ε3 genotype, while ε2+ genotypes are associated with lower levels. The gene has been studied widely in vascular disease. Three systematic reviews were identified investigating the research into its association with subarachnoid hemorrhage.

Sudlow et al reported a systematic review of APOE and stroke in 2006, which included some results for subarachnoid hemorrhage. These have a total of 237 cases and 1655 controls. The meta-analyses found a small, statistically significant, increase in the odds of being a case rather than a control for people with the ε4 allele (odds ratio 1.4, 95% CI 1.0 to 2.0). The reviewers noted that they were not aware of any published theoretical basis for such an association. With regard to the ε2+ genotypes, their meta-analyses yielded an odds ratio of 1.1 (95% CI 0.8 to 1.8), which is not statistically significant.

Two reviews were also identified of the relationship between APOE and outcome following the subarachnoid haemorrhage.

Lanterna et al reported a systematic review in which they centrally collected patient data from seven of the 13 potentially eligible studies in 2007. The main meta-analysis of clinical outcomes excluded two outlier studies, including five studies with a total of 457 patients of whom 118 had had poor outcomes.

They calculated an odds ratio for good outcome of 2.56 (95% CI 1.61 to 4.07) for ε4- compared to ε4+, indicating that ε4- patients were significantly more likely to avoid an event such as death, dependency or severe cognitive impairment in the months after their subarachnoid haemorrhage. Their meta-analysis of delayed ischaemia used four studies (303 patients, 87 events) and produced an odds ratio for the avoidance of delayed ischaemia of 2.04 (95% CI 1.22 to 4.60) for ε4- compared to ε4+, again indicating that ε4- patients had better outcomes.

Martinez-González and Sudlow reported a systematic review to assess the effect of APOE on the outcome of stroke, focusing on acute ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage. A total of 547 patients were included in the meta-analyses of death or dependency (157 such outcomes), which produced a relative risk of 1.40 (95% CI 1.06 to 1.84) for ε4+ versus ε4-, indicating a worse outcome for patients with the ε4 genotype.

Therefore APOE ε4 allele seems more to be associated with a poor outcome after subarachnoid blood but may also be associated with a higher likelihood of bleeding from an aneurysm although the mechanism is unknown.

Candidate gene	Associated disease	# of original study	# studies reported in	R5	KI	N
Angiotensin-converting enzyme (17q23)	Blood pressure and volume disregulation	4		3	4	0
Apolipoprotein E (6q26-27)	Atherosclerosis and thrombosis	1		0	1	0
Collagen type 1 (7q22.1)	osteogenesis imperfecta, Ehlers–Danlos syndrome, Infantile cortical hyperostosis	1		1	1	0
Collagen type 3 (2q31)	Ehlers–Danlos syndrome, Dupuytren's contracture	4		1	3	2
Elastase and α1 antitrypsin (19p13.3, 14q32)	Elastin destruction, pulmonary emphysema	7		2	2	5
Elastin (7q11.23)	William's syndrom, pulmonary emphysema	5		0	5	3
Endoglin (9q33-9q34.1)	hereditary hemorrhagic telangiectasia type 1	5		3	5	3
Endothelial nitric oxide synthase (7q36)	vascular tonus regulation	4		0	4	3
Fibrillin (5q23-31)	Marfan syndrom	2		1	1	1
Heme oxygenase-1 (22q13)	pro-inflamatoiry state	1		0	1	0
Interleukin 1-beta (2q14)	pro-inflamatoiry state	1		0	1	0
Lysyl oxidase (5q23.2)	cross-linking of collagen and elastin dysfunction	2		2	2	0
Metalloproteinase-1, 3, 12 (11q22.2)	turnover of extracellular matrix dysfunction	2		2	0	0
Metalloproteinase-9 (20q11.2-13.1)	turnover of extracellular matrix dysfunction	4		4	3	0
NADPH oxidase (16q24)	atherosclerosis	1		1	0	0
Phospholipase C (20q12-13.1)	Blood pressure hypertension	1		1	1	0
Polycystin (16p13)	PKD-1	6		0	0	6
SERPINA3 (14q32.1)	pro-inflamatoiry state	1		0	1	0
TIMPS 1, 2, 3 (Xp11.3-11.23, 17q25 22q12.3)	turnover of extracellular matrix dysfunction	1		1	1	0
Transforming Growth Factor-beta receptors (9q, 3p, 1p)	Marfan syndrom	2		0	0	1

Table 3: Genes associated with the disease

R5: Ruigrok et al 2005; KI: Krischek and Inoue; N: Nahed et al

Known risk factors for subarachnoid heamorrhage in the general population

The systematic review of reviews performed by Mike Clark as part of the @neurIST project revealed 24 risk factors reported in 27 separate articles. Those factors are categorized and listed in table 4. Factors are either patient characteristics which cannot be changed by an intervention, characteristics of the aneurysm, clinical and medical history, family history and finally factors relating to the time, day and month or season of the subarachnoid haemorrhage.

Factor	Number of eligible reviews
Sex	5
Age	4
Ethnicity	4
Site of aneurysm	4
Size of aneurysm	3
Symptoms before the SAH	3
Previous SAH	1
Blood pressure	4
Cholesterol	3
Diabetes	1
Body mass index	3
Polycystic kidney disease	4
Smoking	5
Alcohol	4
Aspirin	1
Thrombolysis	1
Oral contraceptives	5
Hormone replacement therapy	2
Spinal manipulation	1
Physical activity	2
Family history of SAH	1
Apolipoprotein E gene	1
Other genetic factors	3
Time of day, weekday or season	2

Table 4: List of risk factors and number of available reviews

Gender was identified as an important influence on the risk of subarachnoid hemorrhage in many of the eligible articles. Some of the reviews presented results separately for men and women and this will be discussed below with some significant examples.

The most comprehensive review that dealt in detail with the association between sex and subarachnoid haemorrhage was by de Rooij et al, updating an earlier review from the same research team. The update and its earlier version cover studies published from 1960 to October 2005 on the incidence of subarachnoid haemorrhage in the general population. Searches were done on MEDLINE, and included the retrieval of records that were found using the "related articles" feature and reference lists were

checked until no new publications were found. The de Rooij et al review identified 37 studies that reported the results separately for men and women. Their Poisson regression analysis showed that for each additional percentage point of women in a study population, the incidence of subarachnoid haemorrhage rose by 1.07 times (95% confidence interval (CI) 1.04 to 1.10). In 18 studies, the incidence for men and women was reported separately. The overall annual incidence obtained by combining these studies was 10.5 per 100,000 (95% CI 9.9 to 11.2). It was 9.2 per 100,000 (95% CI 8.4 to 10.2) for men and 11.5 per 100,000 (95% CI 10.6 to 12.6) for women. The incidence was 1.24 (95% CI 1.09 to 1.42) times higher for women compared to men.

The De Rooij et al review included an assessment of the relationship between age and the incidence of subarachnoid haemorrhage. They were able to use data on the mean age of the study population from 37 studies and explored this in a univariate Poisson regression analysis. In populations with a mean age of 35 years, the annual incidence per 100,000 was 8.6 (95% CI 8.0 to 9.2). For every year of increase in the mean age, incidence increased by a factor of 1.06 (95% CI 1.05 to 1.07). Using the 20 studies that reported on the incidence within specific age groups, de Rooij et al obtained an overall annual incidence for all ages combined of 13.9 per 100,000 (95% CI 13.3 to 14.5).

Age	Risk per 100 000 per year (95% CI)
<25 years	2.0 (1.6 to 2.6)
25-35 years	7.7 (6.8 to 8.8)
35-45 years	10.5 (9.0 to 11.3)
45-55 years	19.5 (17.8 to 21.4)
55-65 years	24.8 (22.7 to 27.2)
65-75 years	25.4 (23.1 to 28.0)
75-85 years	26.2 (22.5 to 30.4)
>85 years	31.3 (24.6 to 39.8)

Table 5: Incidence of subarachnoid hemorrhage by age group

As discussed above some articles presented results separately for men and women and the most robust observation of an inter-gender difference shows a significant increased risk of subarachnoid bleeding in elderly women between 65 and 85 years of age as compared to men.

Sex and age	Incidence ratio (95% CI)
< 25 years, women compared to men	1.36 (0.82 to 2.27)
25-35 years, women compared to men	0.67 (0.51 to 0.88)
35-45 years, women compared to men	0.65 (0.51 to 0.82)
45-55 years, women compared to men	0.91 (0.76 to 1.09)
55-65 years, women compared to men	1.15 (0.95 to 1.38)
65-75 years, women compared to men	1.26 (1.04 to 1.54)
75-85 years, women compared to men	1.50 (1.07 to 2.10)
> 85 years, women compared to men	0.84 (0.49 to 1.44)

Table 6: Incidence ratio for subarachnoid hemorrhage, women compared to men

Regarding other risk factors for subarachnoid hemorrhage in the general population, an overview of the relative risks is reported in the figure below. For Body Mass Index (BMI), alcohol consumption (less than 150 gr/week) and smoking there seems to be a gender effect. Slim males seem to be protected as compared to females with similar BMI. Not surprisingly, the amount of alcohol associated with a significant increase of risk seems to be lower for women than for men. The interval of confidence increases dramatically in the group of women consuming >150gr/week of alcohol and may be linked to inaccurate reports.

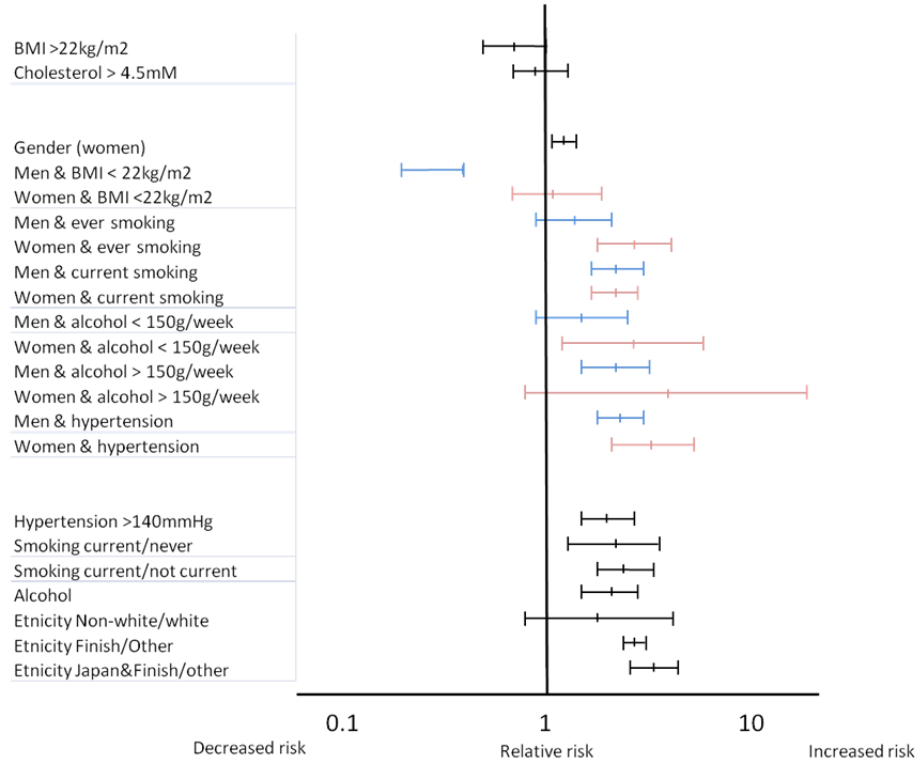


Figure 18: Relative risk of subarachnoid hemorrhage - combined risk factors

Hypertension, smoking and alcohol consumption are all risk factors with a relative risk above two. In a significant fraction of the population those risk factors are cumulated and there is no understanding of the influence of possible interactions on the risk of subarachnoid hemorrhage.

Studies exploring the risk of diabetes could not reveal a significant effect. Although there seems to be an effect of oral contraceptives (increasing the risk) and hormone replacement therapy (decreasing the risk) nothing significant could be demonstrated.

7.3 Information integration to optimize screening – when to treat:

Known risk factors for rupture of known aneurysms

The literature review revealed five studied factors. The review of metaanalysis allowed to estimate relative risks that are reported in figure 19.

The size of the aneurysm is associated with almost a linear increase of relative risk compared to aneurysms of less than 5mm size. The incidence of rupture of small aneurysms is difficult to estimate as few are incidentally observed and followed up and the rate of rupture is so small that observation of such events is very rare. Most often aneurysms are treated if the risk is considered low. In some institutions aneurysms are followed up by regular imaging and treated before rupture if demonstrating an increase in size or modification in shape based on the hypothesis that stable legions have a negligible risk of rupture being in a "healthy" state as opposed to growing lesions that are considered in a "diseased" state and may be at risk of blasting. As yet, there is no evidence in the literature that confirms this hypothesis.

Symptoms leading to the discovery of the aneurysm are important factors to estimate the risk of rupture. It must be taken into account that aneurysms that compress cranial nerves or brain tissue to the extent of inducing clinical symptoms are either rapidly growing or large. Similarly, aneurysms causing strokes in downstream vascular territories are frequently large lesions. Therefore, this factor is most probably a surrogate of size and there is no information on the difference between aneurysms of a similar size and location that are or not symptomatic.

From our point of view, location is the second independent most important factor to take into account. From the literature review, we are able to show that there are: very safe, safe and dangerous locations. In contrast to ISUIA the dangerous locations include sites on the anterior cerebral artery as well as the bifurcation of the posterior communicating artery, on the internal carotid artery and on all posterior circulation vessels (all vessels of the vertebro-basilar system and posterior cerebral arteries). The very safe location is the cavernous portion of the carotid artery. This observation is easily explained by the presence of dura between the bone and the subarachnoid space that offers a strong resistance and may substitute to the vessel wall.

Age is the third most important factor to take into account and we observe that patients above 60 years of age are significantly more at risk of suffering an aneurysm rupture.

Finally it was suggested that a prior history of subarachnoid bleeding could be associated with a higher risk of suffering of a second bleed. Our literature review showed a none-significant trend suggesting it should be examined in more detail.

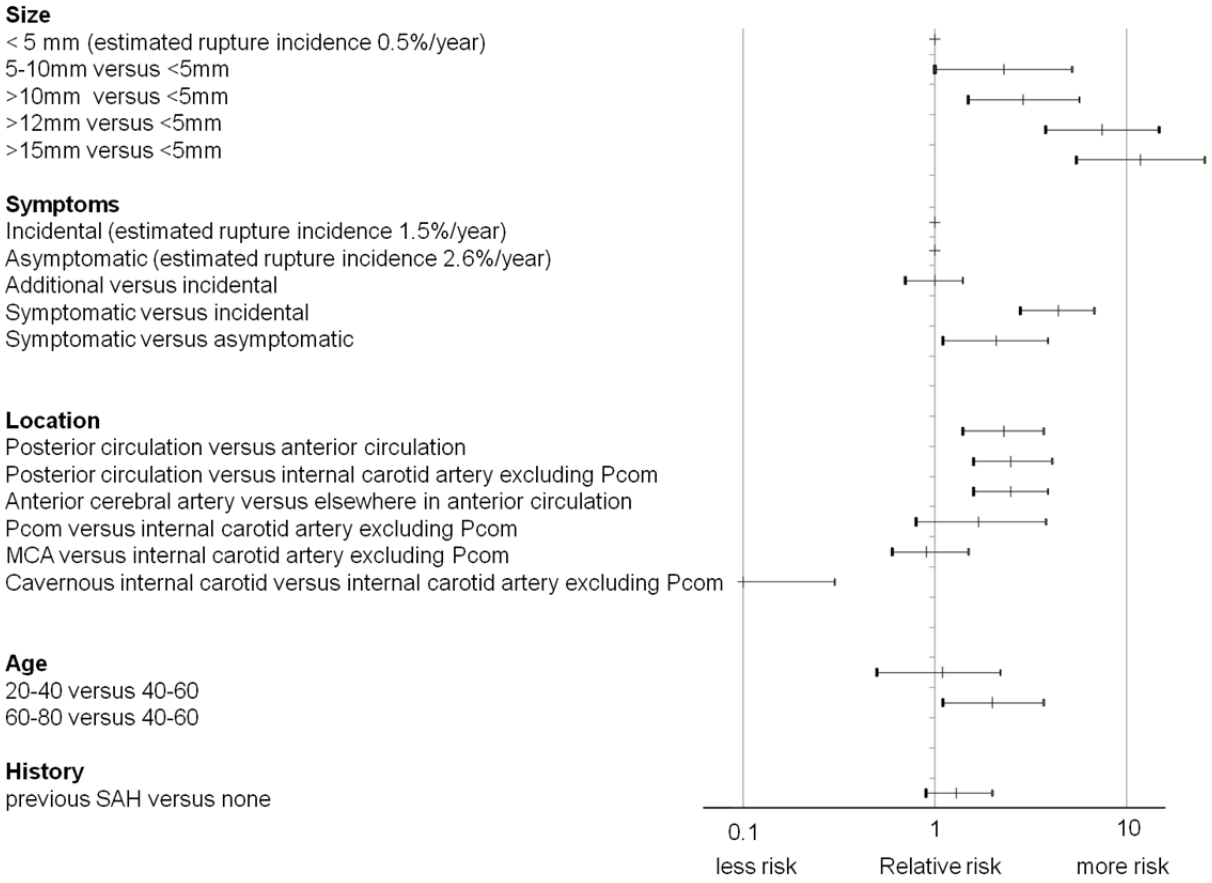


Figure 19: Risk factors of aneurysm rupture – relative risk

7.4 Criteria relevant for choosing the aneurysm securing method

Evaluation of criteria used by physicians to decide on treatment modality (clipping or coiling) was performed with a web-based audit contacting neurovascular experts worldwide. Sixty-one criteria were found from the literature and were scored on a scale ranging from 1 (not pertinent) to 10 (highly pertinent). Sixty experts worldwide (USA, Japan, Europe), 36 cerebrovascular neurosurgeons, 22 endovascular interventionists and 2 doing both were contacted using a web-based questionnaire. Twenty two (36%) answered the questionnaire.

The criteria were aggregated in categories relating to how the information would be collected. All information about the genetic background was considered of little interest for decision making in general. In contrast, elements of patient history, clinical condition and institution capabilities were considered relevant. Experts considered that the most important source of information for decision making resides in imaging.

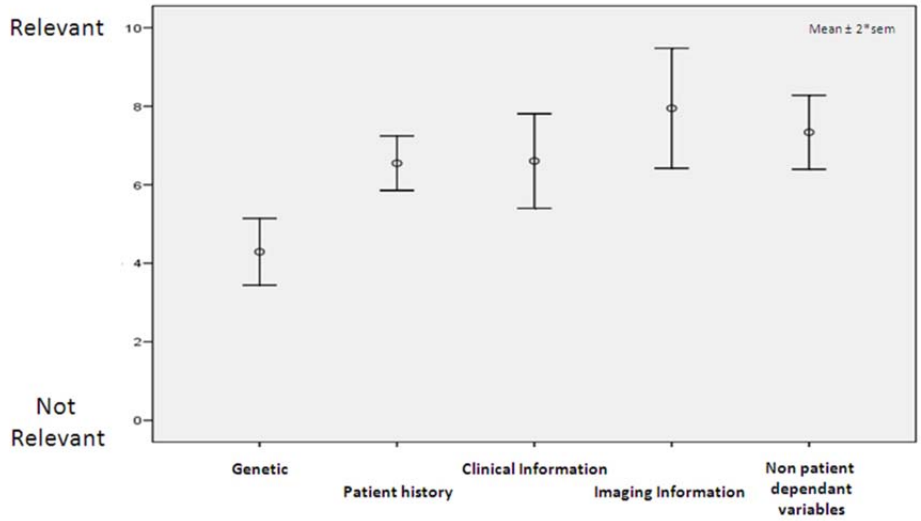


Figure 20: Clinical information and relevance regarding the decision to treat intracranial aneurysm

Reviewing section by section in more detail, it appears that most surgeons and interventionists are interested in knowing if there is a genetic background for coagulopathy. There is also some interest in knowing if there are connective tissue abnormalities. Other classic genetic conditions suspected to be associated with intracranial aneurysm formation such as alpha 1 antitrypsin deficiency, polycystic kidney disease or a familial positive history for intracranial aneurysms do not seem to have a relevance when choosing the treatment modality.

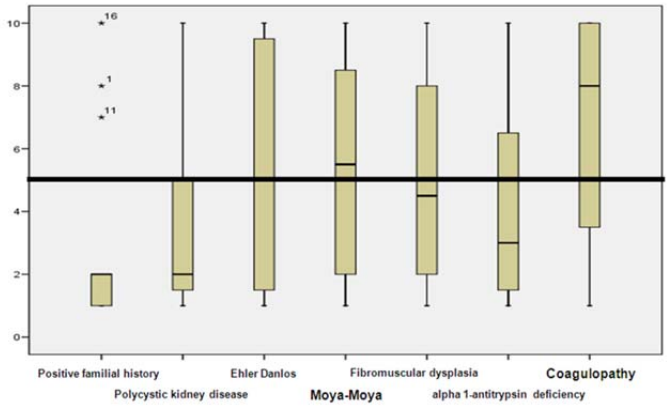


Figure 21: Information about patient clinical history and relevance regarding the choice of intracranial aneurysm's treatment modality.

Information obtained from the patient interview may greatly impact the decision of how to treat. The vast majority of specialists consider that the treatment modality is the choice of a well informed patient. Risk of pregnancy or treatment with combined antiplatelet therapy, are generally taken into consideration as well as refusal of blood transfusion. There is no impact of the professional activity on the decision.

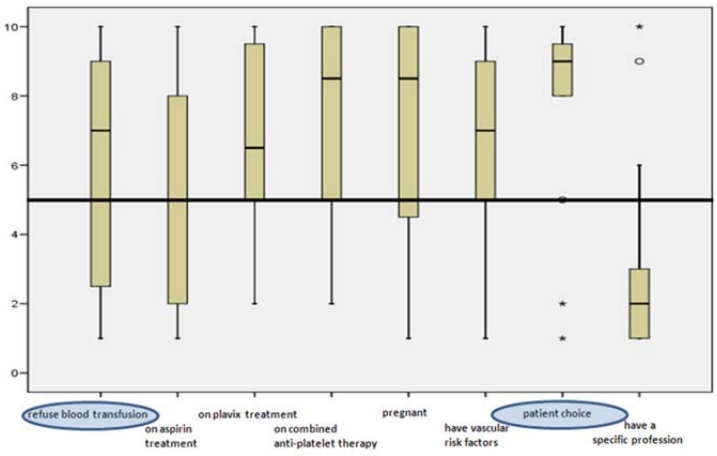


Figure 22: Anamnestic information and relevance regarding the choice of intracranial aneurysm's treatment modality.

Some items of clinical evaluation have a great impact on the choice of treatment modality. The life expectancy and the patients' co-morbidities are rated as very relevant information, as well as the clinical grade after emergency corrective actions have been performed but prior to securing the aneurysm. In contrast, focal or cranial nerve deficits are rated as less relevant. Occurrence of seizures or the patient's weight were not considered relevant information.

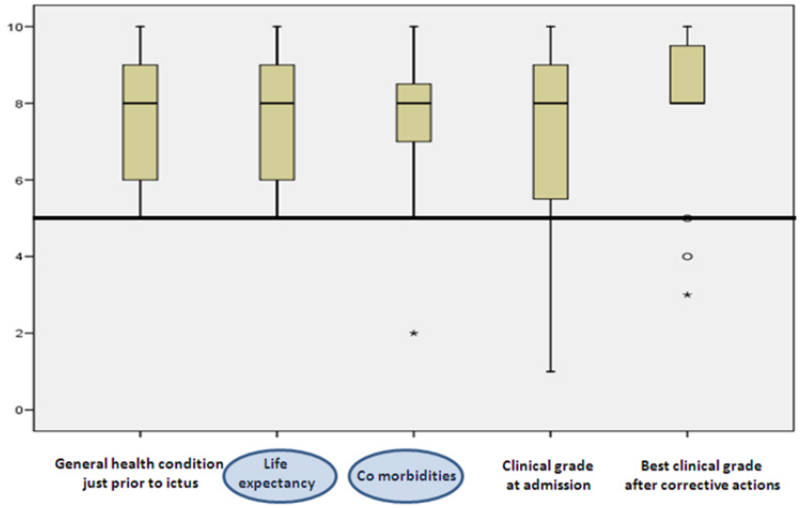


Figure 23: Most relevant information obtained from clinical evaluation to choose the treatment modality.

Imaging information is unanimously rated as of utmost importance. The size of the possible hematoma and the mid line shift is recognized by all as key in deciding whether to clip or coil an aneurysm. Information about vessel occlusion, the location of the aneurysm and aneurysm related information like the presence of calcifications or the dome to neck ratio scored slightly less on the relevance scale. To the contrary, the measurement of quantity of blood in the subarachnoid space, the presence of intraventricular blood or hydrocephalus are not relevant to the decision.

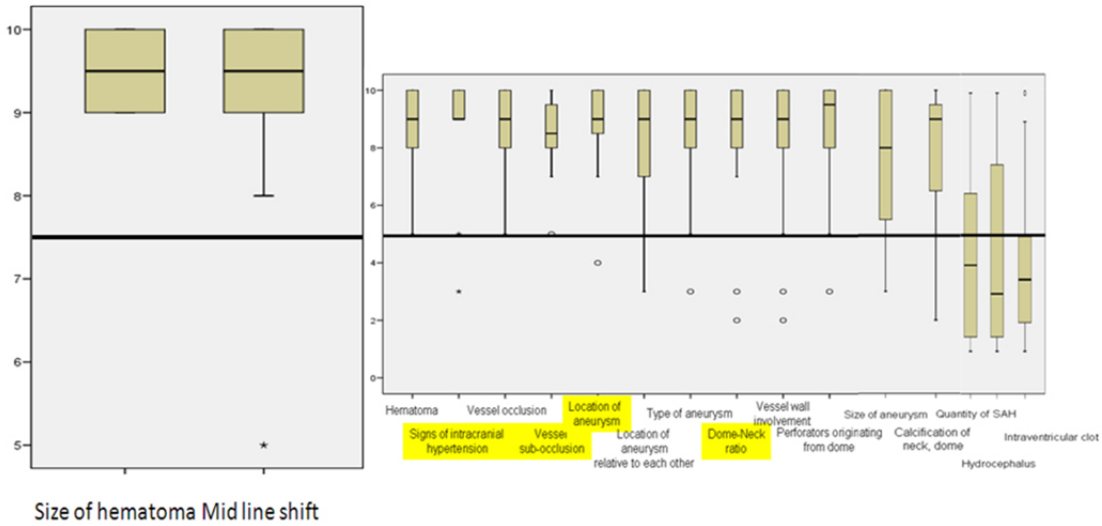


Figure 24: Relevance of information obtained from imaging (CT/CTA) to choose the treatment modality

It has been recognized that skills, access to the treatment platform and availability of the team have a high impact of the final treatment modality used.

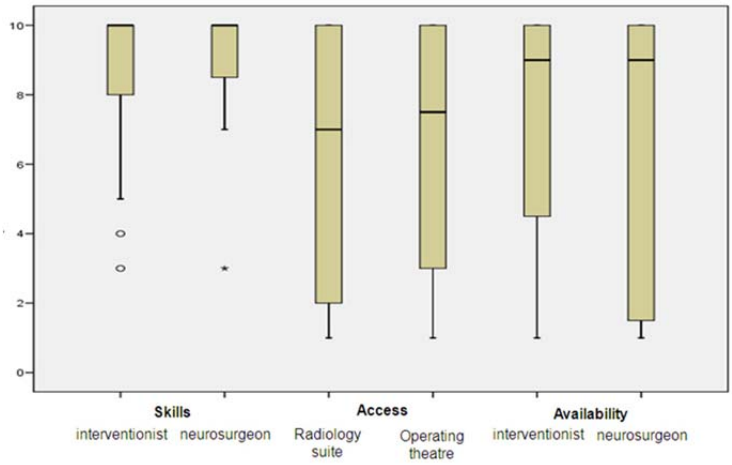


Figure 25: Impact of skills, access to infrastructures and availability of surgeons on treatment modality used.

Interestingly, some items were rated differently by neurosurgeons and interventional radiologists. Aspirin treatment and nature of focal deficits, refusal of blood transfusion and handedness are relevant criteria for interventional radiologists (endovascular) but not for neurosurgeons. The knowledge about a perforating artery originating from the dome of the aneurysm is relevant for all, but surgeons rate it higher than endovascular. Interestingly the perception of the fraction of patients treated using one or the other modality is significantly different. This difference remains if we analyse answers coming from the same institutions. Both most probably overestimate.

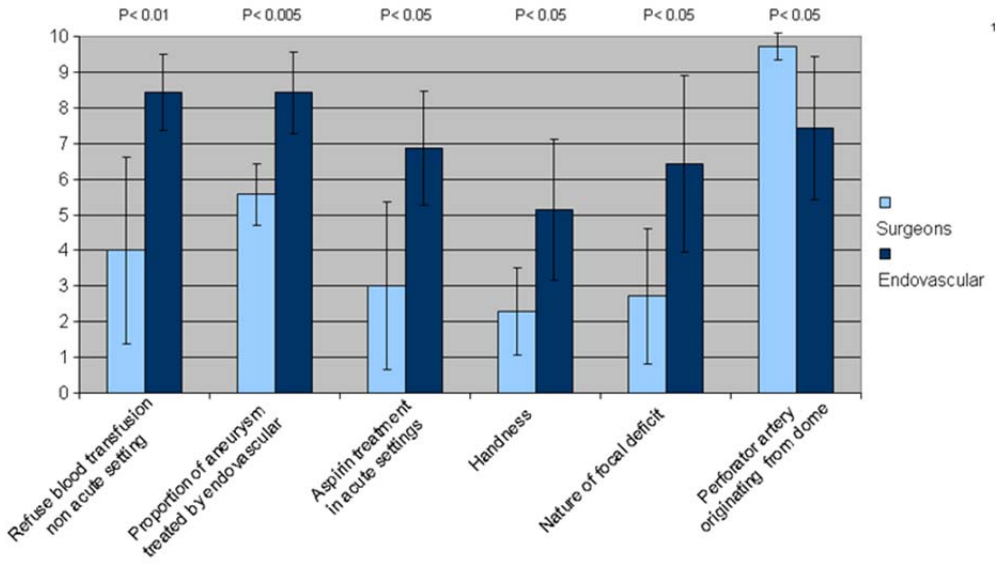


Figure 26: Differences in relevance rating between neurosurgeons and interventionists

The most relevant criteria resulting from the survey were selected to be included in the standard evaluation of patients recruited in the @neurIST project. The analysis of these specialists' opinions revealed how complex the decision making process is and confirmed our belief that one treatment modality will not fit all cases and that classical trials will never allow building evidence that covers the increasing complexity of the process. Emerging new developments like stents and medical treatments will add options that will need to be tailored. Tools to accelerate sharing of high quality experience in the context need to be developed.

7.5 Discovery of new screening tools – who to treat

Whole Genome Association Study

During the course of the @neurIST project, blood samples and clinical information were collected for the purpose of a whole genome association study. The plan was to search for single nucleotide polymorphisms that would be associated with the disease. Variations in the human genetic code are essential in determining each individual. Variations may locate in genes or intergenic regions. Some genetic regions are highly conserved between different subjects meaning that any variation induces a major effect reducing the survival and reproduction of the affected subject. Those variations are usually eliminated by natural selection. If one disease induces a negligible impact on initial survival, fertility and survival of the offspring than it can be expected to find genome variations associated with the disease in the population. Those variations do not need to be in genes but may be in regions that participate in the regulation of gene expression or in silent areas that are functionally linked to coding or modulating genome. Those variations if associated with a disease can be used as markers of the disease and sometimes lead to the discovery of a mechanism of disease.

Intracranial aneurysms are present in about 2% of the population and affect the patients late in life which reduces the natural selection pressure on the genetic traits. The likelihood to find SNPs associated to the disease was considered reasonable. The chance of discovering SNPs associated with the disease increases 1) with the density of the whole genome exploration, 2) the exclusion of SNPs that would be in non-random association at two or more loci and 3) a high occurrence frequency of each SNP in the population. It was decided to perform the experiment with as many SNPs as technically possible and at least 500000 SNPs covering uniformly the whole human genome. This minima allows to statistically explore the human genome with a marker every 6kbases which is in the order of magnitude of the human genes length (average length 3kb). SNPs: 1) with missing rates larger than 5%, 2) P value of the exact test of Hardy-Weinberg equilibrium smaller than 0.001 and 3) minimal allele frequency less than 1% were excluded.

Minimal required sample size estimation was based on genetic simulations. It was defined that to have 80% chances to identify at least one loci associated with an increase in the relative risk between 1.2

and 2 with a type I error rate of 10^{-6} as required for whole genome association studies, the study groups should include at least 400 subjects per experimental condition.

During the course of the project it was decided to increase the chances and robustness of the exploration by merging data globally.

Data from 2780 patients and 12515 healthy subjects on 831532 SNPs were analysed and then replicated using two Japanese cohorts of 3111 patients and 1666 controls and 12 selected SNPs.

The analysis resulted in the identification of 3 new and in the confirmation of 2 previously observed loci associated with the intracranial aneurysms in chromosomes 18, 13 and 10 as well as chromosome 8 and 9 respectively.

The most significant association was detected in the non-coding region 9p21.3 near CDKN2A and CDKN2B genes. The same allele is associated with non diabetic coronary artery disease.

The other previously reported loci in region 8q11.23-q12.1 showed a similarly robust association. This region is in proximity with the SOX17 gene (SRY related High Mobility Group (HMG) box where SRY stands for Sex determining region Y and SRY protein determines male sex initiation) which is involved in the early development of the endoderm and vessels.

On chromosome 10 the loci 10q24.32 was strongly associated with presence of intracranial aneurysms and within the first intron of the CNNM2 gene encoding for cyclin M2. This gene is also associated with coronary artery disease, blood pressure variations and dominant hypomagnesaemia.

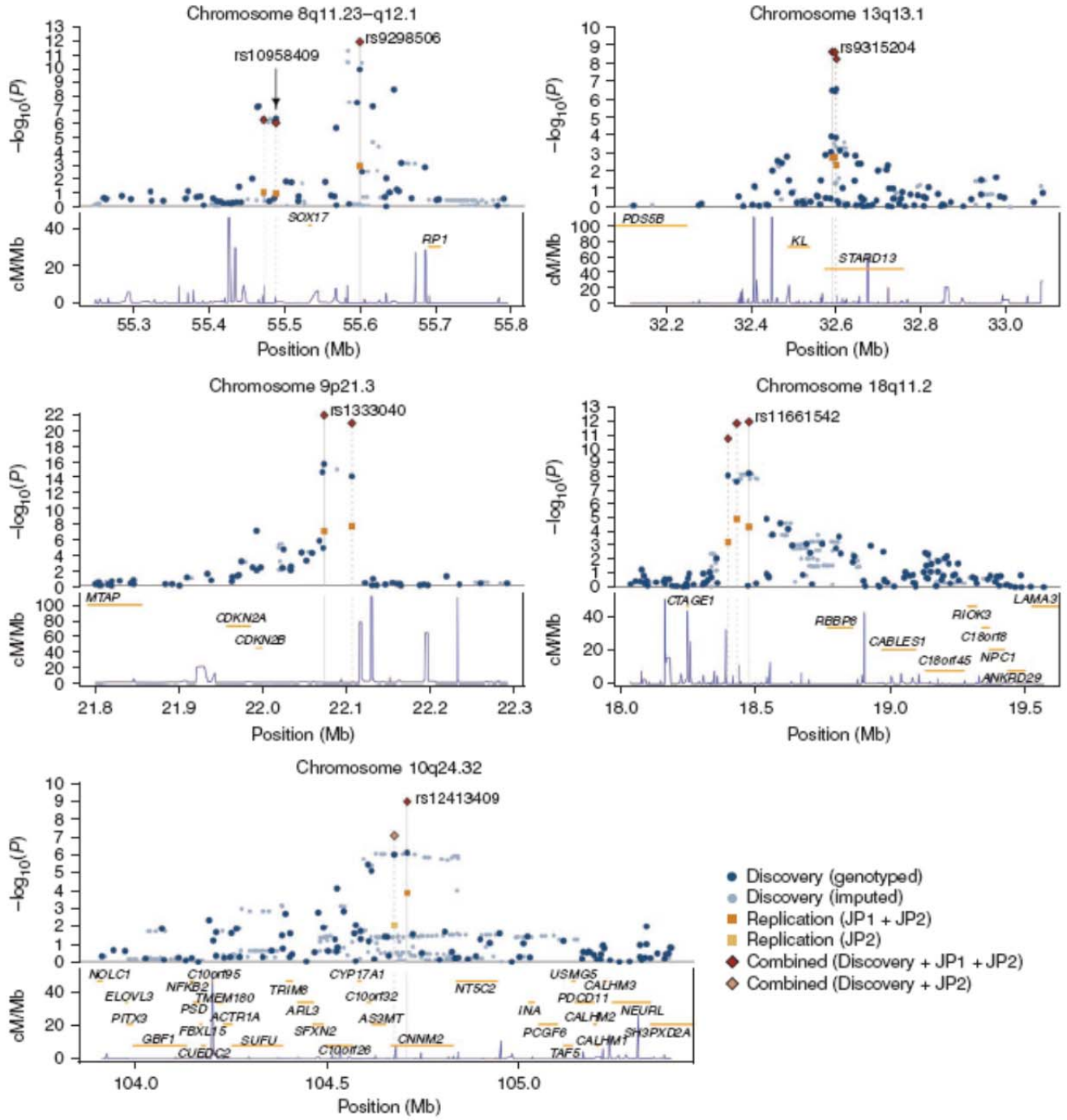


Figure 27: Genetic loci associated with sporadic cases of intracranial aneurysms discovered by the whole genome association study

The loci on chromosome 13 region q13.1 (13q13.1) falls in the 7th intron of STARD13 (encoding the StAR-related lipid transfer (START) domain containing 13). Two SNPs are strongly associated with the intracranial aneurysms and are missense (lysine to arginine) and synonymous coding variants of STARD13, respectively. STARD13 contains the Rho-GAP and C-terminal STAR-related lipid transfer (START) domains and its overexpression results in suppression of cell proliferation. Deleted in liver

cancer 2 (DLC2) suppresses cell transformation by means of inhibition of RhoA activity. Another gene that has been implicated in aging phenotypes, KL (encoding klotho), is located nearby. Finally, the loci 18q11.2 on chromosome 18 showed a very strongest association with intracranial aneurysms and a single, RBBP8 (encoding the retinoblastoma binding protein 8), is located within an extended linkage disequilibrium interval. It influences progression through the cell cycle by interacting with BRCA1.

Locus	SNP	Position	Genes	Risk allele	Cohort	*P* value	$\log_{10}$ (Bayes)	PPA	Per-allele OR (95% CI)	Control RAF	Case RAF
8q11.23	rs10958409	55,489,644	*SOX17*	A	Discovery	4.2×10^{-7}	4.64	0.8128	1.24 (1.14–1.35)	0.15, 0.19	0.18, 0.22
					Replication	0.12	–0.11		1.08 (0.98–1.20)	0.28	0.29
					Combined	9.0×10^{-7}	4.30	0.6685	1.17 (1.10–1.25)		
8q12.1	rs9298506	55,600,077	*SOX17*	A	Discovery	1.2×10^{-10}	7.94	0.9999	1.33 (1.22–1.45)	0.81, 0.76	0.85, 0.81
					Replication	0.0012	1.56		1.21 (1.08–1.36)	0.79	0.81
					Combined	1.3×10^{-12}	9.85	$1.0–1.4 \times 10^{-6}$	1.28 (1.20–1.38)		
9p21.3	rs1333040	22,073,404	*CDKN2A, CDKN2B*	T	Discovery	2.5×10^{-16}	13.41	$1.0–3.9 \times 10^{-10}$	1.32 (1.24–1.41)	0.56, 0.45	0.63, 0.53
					Replication	1.0×10^{-7}	5.18		1.31 (1.19–1.45)	0.66	0.72
					Combined	1.5×10^{-22}	19.48	$1.0–3.3 \times 10^{-16}$	1.32 (1.25–1.39)		
10q24.32	rs12413409	104,709,086	*CNNM2*	G	Discovery	7.9×10^{-7}	4.29	0.6621	1.38 (1.22–1.57)	0.91, 0.91	0.94, 0.93
					Replication	0.00014	2.34		1.23 (1.10–1.37)	0.74	0.77
					Combined	1.2×10^{-9}	7.00	0.9990	1.29 (1.19–1.40)		
13q13.1	rs9315204	32,591,837	*KL, STARD13*	T	Discovery	3.3×10^{-7}	4.73	0.8443	1.21 (1.13–1.31)	0.21, 0.33	0.24, 0.39
					Replication	0.0019	1.36		1.18 (1.06–1.31)	0.24	0.27
					Combined	2.5×10^{-9}	6.72	0.9981	1.20 (1.13–1.28)		
18q11.2	rs11661542	18,477,693	*RBBP8*	C	Discovery	5.6×10^{-9}	6.39	0.9959	1.21 (1.14–1.30)	0.49, 0.44	0.54, 0.47
					Replication	4.5×10^{-5}	2.79		1.22 (1.11–1.34)	0.61	0.65
					Combined	1.1×10^{-12}	9.92	$1.0–1.2 \times 10^{-6}$	1.22 (1.15–1.28)		

Genomic locations for SNPs are based on NCBI build 36, and risk alleles are aligned to the forward strand of the reference sequence. Control and case risk allele frequencies (RAFs) for the discovery cohort are shown in the form: RAF of European cohort, RAF of Finnish cohort. $\log_{10}$ (Bayes) indicates the logarithm of the Bayes factor in favor of association. PPA, posterior probability of association. Genes closest to the listed SNPs within the same LD regions are shown.

Table 7: SNPs associated with intracranial aneurysms and odd ratio of risk allele presence in patients versus controls

Given the study design it is expected that most of the variants with a genetic relative risk higher than 1.25 and a minor allele frequency of more than 10% have been identified.

There may be another loci associated with the disease with genetic relative risk between 1.16 and 1.25 but to confirm this, it requires the analysis of an even larger cohort using SNPs with lower minor allele frequency.

Given the observation that there is a fourfold increase in the risk of intracranial aneurysm among siblings of cases as compared to the general population it is accepted that the genetic background is more a predisposition than a determination to suffer the disease. We therefore strongly believe that genetic risk markers like SNPs should be combined with traditional risk factors such as gender, blood pressure, alcohol consumption and smoking, to perform preclinical identification of individuals who are at a high risk of intracranial aneurysm formation and rupture. This will also increase our understanding of the mechanisms involved in the disease to discover possible medical treatments.

7.6 Discovery of new screening tools – when to treat

Detecting intracranial aneurysms and evaluating the risk using a blood test

Intracranial aneurysm is a potential lethal disease that significantly reduces the quality of life if not disables affected people once ruptured or discovered. There is hence a great interest in identifying markers of the disease and allowing the quantification of the risk induced by the disease and the treatments. Currently, the universally recognized marker of the disease is the visualization of a typical morphological deformation of an intracranial vessel by imaging. Nevertheless, the estimation of the prediction of the risk associated with the discovery of an aneurysm and its treatment is hazardous. It has been estimated that screening of the whole population using non-invasive imaging was not economically nor ethically beneficial. In some families, multiple individuals are affected by intracranial aneurysms and it is recommended to screen selected members when two directly genetically linked individuals are identified with at least one intracranial aneurysm. The association of polycystic kidney disease with intracranial aneurysms and the risk of suffering of a subarachnoid bleeding has been identified as strong. A screening with non-invasive imaging of cerebral vessels is recommended as well.

Nevertheless, physicians are facing major difficulties in balancing the risks and predicting the impact on a patient's life of the discovery of an intracranial aneurysm, mainly because:

1) Evolution of the disease is multifactorial and ill understood.
2) High risk lesions are mostly also dangerous to treat
3) Treatments may not fully protect patients in the long term.

There is an interest in developing tools that would integrate information to improve the prediction of suffering a poor outcome from the disease and focus care on those cases.

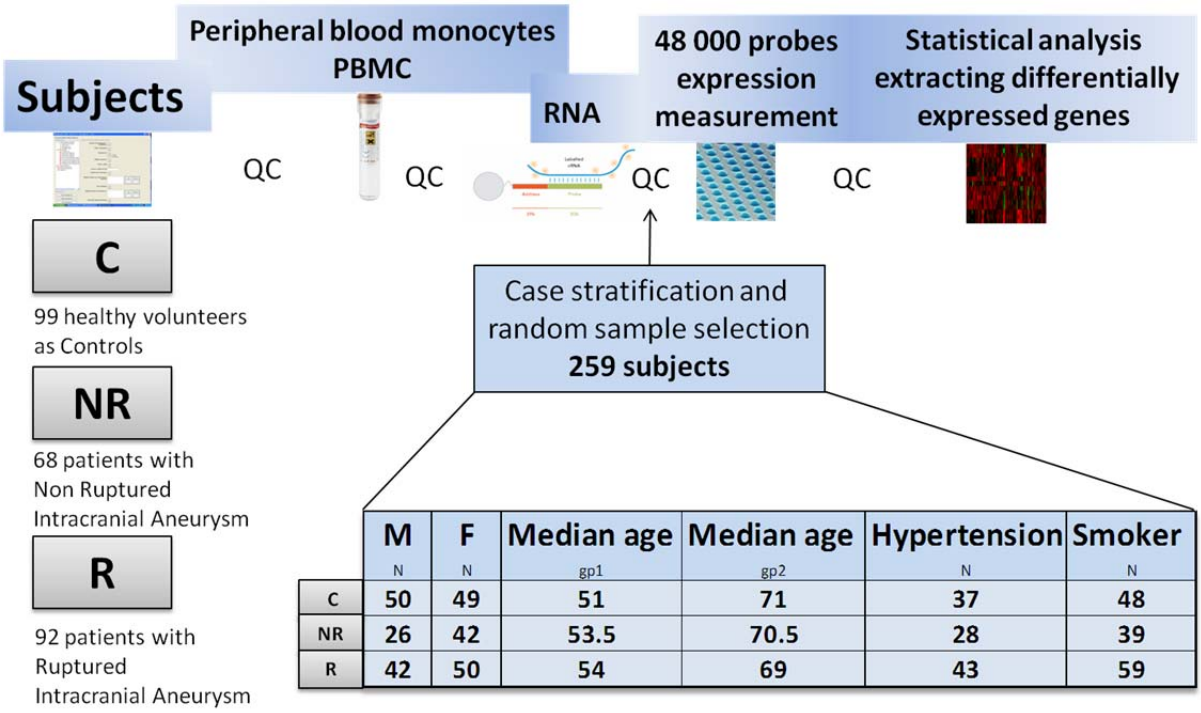
Blood is a tissue of easy access that biologically and mechanically interacts with the vessel wall. It interacts with all other tissues, as well as with the environment. It has an essential role in transporting nutrients and waste, maintaining body homeostasis, signaling between distant organs and protecting against mechanical, biological and chemical aggression.

Therefore, it is a first choice organ to explore in the prospect to identify markers of the disease. It may allow the identification of factors that are a) inducing aneurysm formation or b) participating in the reaction of the body to the disease. It may allow the discovery of markers of the severity of the disease. It may lead to the discovery of biological mechanisms that could be medical targets to fight the disease.

Circulating peripheral blood mononuclear cells (PBMC) play a critical role in the surveillance of the body for signs of infection, inflammation and disease. The use of PBMC as a detection tool has been successfully shown with diseases such as Parkinson, Alzheimer, Crohn's disease, rheumatoid arthritis, human prostate tumors, aging, as well as cardiovascular diseases such as atherosclerosis, coronary artery disease, and arterial hypertension. Interestingly the use of PBMC has also been recently, successfully used in the classification of thoracic aortic aneurysm.

Blood was collected from healthy volunteers, patients that had intracranial aneurysms or suffered subarachnoid haemorrhage from the rupture of an intracranial aneurysm. A subset of samples was selected from the three groups to form a study cohort with age and gender matched cases.

The messenger RNA was extracted, purified and quality checked from the blood samples. The gene expression profile was measured using the Illumina Human HT12 bead array platform and screened for 48000 probes allowing the analysis of more than 25000 annotated genes and Expressed Sequence Tags.



	M N	F N	Median age gp1	Median age gp2	Hypertension N	Smoker N
C	50	49	51	71	37	48
NR	26	42	53.5	70.5	28	39
R	42	50	54	69	43	59

Figure 28: Gene expression modifications in circulating blood cells associated with the disease - Experimental design and study groups

A list of the top 500 differentially expressed genes was obtained using a linear model. The analysis was then repeated 500 times using different combinations of 80 controls and 60 cases (Bootstrapping computer based analysis method). Genes were considered as significantly differentially expressed if the observation was reproduced in more than half of the analysis.

188 genes were discovered to be differentially expressed between healthy volunteers and patients suffering a subarachnoid bleeding. 64 genes were distinctly expressed between patients with at least one intracranial aneurysm and patients that suffered the rupture of the aneurysm. Most interestingly, 42 genes were observed differentially expressed between healthy volunteers and patients with unruptured intracranial aneurysms.

The most consistently differentially expressed gene between healthy volunteers and cases affected with non ruptured aneurysms is PDE5A. PDE5A is a cGMP specific phosphodiesterase that is important in the vascular muscle relaxation and is regulated by androgens. It is involved in erectile dysfunction and pulmonary hypertension. PDE5A is the pharmacological target of sildenafil well known under the trade name Viagra®.

Recently a study reported that inhibition of PDE4 reduced cerebral aneurysm progression in an animal model (Yagi K et al. Neurosurgery. 2010).

Using gene ontology, differentially expressed genes were aggregated to identify biological processes, metabolic functions or as cell constituents involved in the disease.

It was observed that in circulating blood cells of patients with unruptured aneurysms as compared to healthy volunteers, biological processes of cell-cell junction assembly and Wnt-receptor signaling pathway were highly significantly modified. In circulating blood cells, Wnt-receptor signaling pathway is involved in transendothelial migration of monocytes. The most significant metabolic function affected is the cyclic nucleotide-dependent protein kinase activity and the most altered expression of cell constituents are anchoring junctions. Overall, the different observations confirm the hypothesis that circulating blood cells act or react on or with the vessel wall and that it can be measured.

Symbol	expression in NR
PDE5A	Down
TRABD	UP
PRDX6	Down
PTGDS	Down
EWSR1	Down
WBP11	Down
CAST	Down
TPD52L2	UP
RUFY1	Down
FOXN3	Down
PLIN2	UP
ZNF839	UP
hCG_178628	Down
SLC27A2	UP
OR52D1	Down
IFFO1	UP
AJAP1	UP
DSC1	Down
HNMT	UP
GP2	UP
ZNF688	UP
DPP8	Down
FRMPD4	Down
UPK1A	UP
ASB2	UP
MR1	UP
PIP5K1B	UP
AQP1	UP

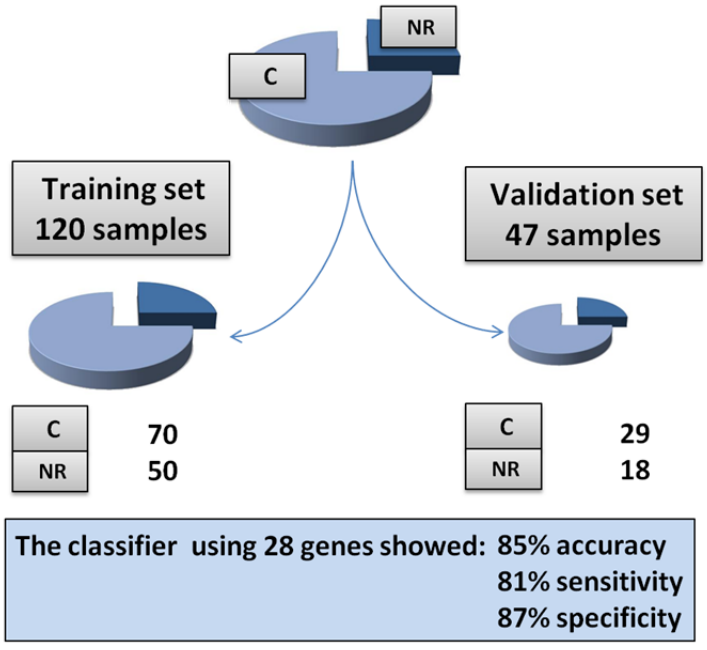


Figure 29: Identification of intracranial aneurysms based on the gene expression signature of circulating blood cells

Selecting a set of 28 genes and using a training set of cases, it was possible to identify a signature expression profile specific to cases with non ruptured aneurysms and design a sample classifier. Testing the performance of the classifier on a second set of samples we measured remarkably high accuracy (85%), sensitivity (81%) and specificity (87%).

Further work is needed and it would be of utmost interest to explore the expression profile of circulating blood cells from patients with growing aneurysms or from patients with unruptured aneurysms that bleed shortly after the aneurysm discovery and blood sample pouring.

We therefore believe that the strategy exploring the gene expression profile of circulating blood cells opens new horizons in understanding the disease and may provide a powerful tool helping to screen and select cases that will benefit the most of an intervention.

Evaluation of the risk of rupture of intracranial aneurysms from angiographic imaging

According to the International Study of Unruptured Intracranial Aneurysms (ISUIA), the risk of rupture of intracranial aneurysms can be stratified using the location of the aneurysm in the cerebro-vascular tree, the size of the aneurysm and the prior history of subarachnoid bleeding. For the purpose of the study, aneurysms were grouped according to three locations:

1) Cavernous intracranial coratid artery,

2) Anterior circulation (AC)

3) Posterior circulation (PC) including aneurysms located in the internal carotid artery next to the posterior communicating artery.

It was concluded that anterior circulation (AC) aneurysms of less than 7mm of diameter have a minimal risk of rupture.

However, it is of general experience that anterior communicating artery (AcoA) aneurysms are frequent and most of them rupture below the size of 7 mm. Therefore it was decided to conduct a study that would explore the risk associated with aneurysm rupture using more precise definitions of aneurysm location. The first aim was to answer the question “Do AcoA aneurysms behave differently from other anterior circulation aneurysms?”

Information on patients suffering intracranial aneurysms was collected during the multicenter @neurIST project between April 2007-2010. Comparisons were made between ISUIA reported figures and @aneurIST. The odds of new aneurysm diagnosed as unruptured or ruptured were compared between groups classified by location and size in order to estimate the rupture risk.

Findings

Of 499 unruptured aneurysms in the @neurIST study, 350 were found in the anterior circulation(AC). Aneurysms located in the AcoA or anterior cerebral artery were significantly more frequently observed in @neurIST(18.2%) than in the ISUIA study(10.3%; p<0.0001). Analysing the @neurIST recruited cases, the odds ratio for rupture of aneurysms was significantly higher than average for AcoA (OR 2.5; 1.867-3.322 95% CI) and posterior circulation (PC) than for internal carotid artery and middle cerebral artery (OR 0.693; 0.503-0.954 95% CI).

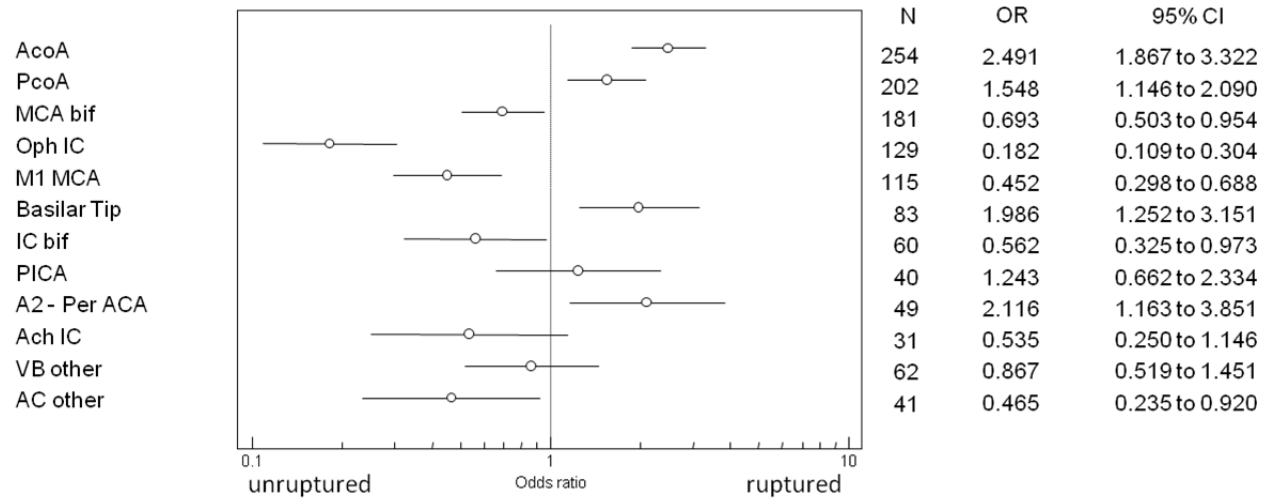


Figure 30: Frequency and risk of rupture of intracranial aneurysms according to location

When comparing aneurysms of similar size located in two different locations in the anterior circulation, it is obvious that AcoA have a higher risk of rupture at small size than middle cerebral artery bifurcation aneurysms,

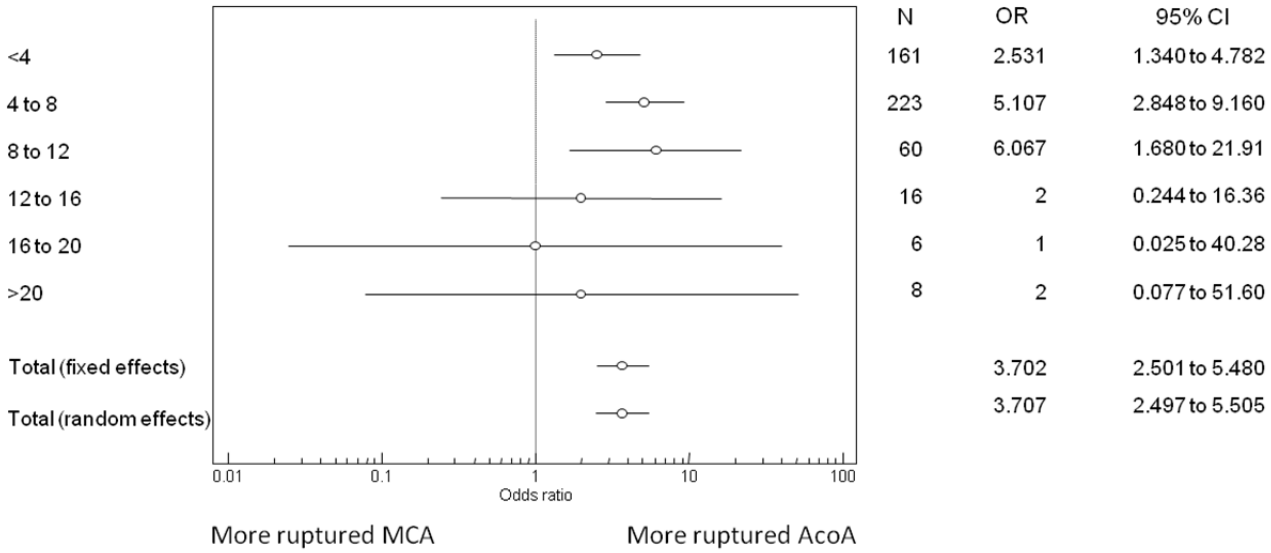


Figure 31: The risk of rupture at small aneurysm size is higher in some locations than other

In the ISUIA study it was suggested that a threshold justifying aggressive intervention to treat an aneurysm was reached with aneurysms located in the anterior circulation with a size larger than 7mm when patients never suffered any prior subarachnoid bleeding. The group of aneurysms located in the anterior circulation as defined by the ISUIA study with a size between 7 and 12 mm was used as a reference against which all other aneurysm groups were compared. Aneurysm groups showing smaller odd ratios of ruptured aneurysms are considered safe in contrast to groups with equal or higher odd ratios that are considered dangerous and should be considered for aggressive treatment. AcoA aneurysms of less than 7mm were significantly more frequently observed ruptured (OR 2.1; 1.36-2.27 95%CI) than the reference indicating aggressive treatment should be considered.

	<7mm			7-12mm		
	ruptured/total	OR	95%CI	ruptured/total	OR	95%CI
ACA+MCA+ICA	234/528	0.824	0.585 to 1.160	**86/175**	**1**	**0.658 to 1.521**
ICA+MCA	106/344	0.461	0.317 to 0.670	39/112	0.553	0.339 to 0.901
ACA	130/210	1.682	1.120 to 2.526	47/64	2.861	1.525 to 5.366
AcoA	112/167	2.107	1.360 to 3.266	39/50	3.669	1.765 to 7.628
PC	127/223	1.369	0.920 to 2.038	73/116	1.757	1.088 to 2.837

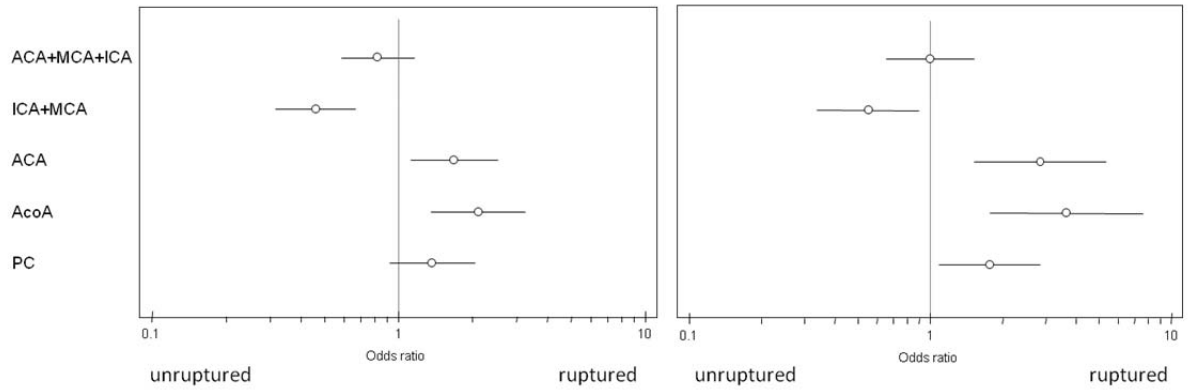


Figure 32: Risk of aneurysm rupture according to location and size

It can be concluded that the population of the cohort and design of ISUIA does not allow to extrapolate AC observations to estimate the risk of rupture of AcoA aneurysms. The risk of rupture of aneurysms located in the AcoA and distal anterior cerebral artery should be considered equivalent to similar size PC aneurysms.

7.7 Optimizing the surgical treatment

Historically, the treatment of intracranial aneurysms has been surgical. The introduction of operative microscope and microsurgical techniques, as well as the development of micro-vascular clips has transformed the outcome for patients suffering from the disease. Since 1992, the microsurgical clipping of aneurysms has been challenged as the unique satisfactory treatment. The development of endovascular micro-catheters and micro-coils allows the occlusion of aneurysms using the vascular lumen as a natural pathway, navigating from the femoral artery in the groin to the target even in very distal and small cerebral arteries. More recently, the modification of coronary stents to be softer and made of a thinner mesh allows the remodeling of the vessels by modifying the flow and promoting thrombosis. None allows a perfect treatment of all lesions. Patients benefit from the adequate design of treatment strategies using all techniques in conjunction and, if possible, simultaneously.

The surgical treatment suffers from the need for transcranial access through small corridors surrounded by delicate brain tissue. The degree of freedom to visualize or work around the lesion is restricted. There is only a limited perception of the volume using binocular vision. Perception of the effect of clipping on the flow needs special measure. Finally, developing the skills for safe and efficient surgery is a long process based on mentoring and experience.

Figure 33: Enhancement of perception and ergonomic display of information to improve traffic security as an example to improve surgical performance

The next step in improving surgery will most probably be the ability to better plan and tailor each intervention to the specificities of each patient and improve the perception and ergonomy of the surgical environment. As developed in the automotive industry, safety may be improved by increasing the perception of the driver using infrared cameras and head-up displays to visualize what cannot be perceived by the human eye. Compute and display navigation maps optimally to focus the attention on

the road and potential hazards. Use voice or sound signals to warn the driver of upcoming direction changes or obstacles.

An integrated hybrid endovascular and surgical treatment environment has been designed. Three dimensional anatomical representation is acquired using imaging performed before the intervention. The information is registered and fitted to the reality using neuronavigation. Navigation information is displayed in real-time in the microscope eye piece on surgeon's request. Cerebral activity is monitored using motor or sensitive evoked potentials and any changes are reported orally to the surgeon. Vascular flow may be visualized using fluorescence microscopy and the injection of fluorescent dye in the blood. Three dimensional verification of the anatomy is performed by intra-operative high resolution angiographic digital rotational angiography.

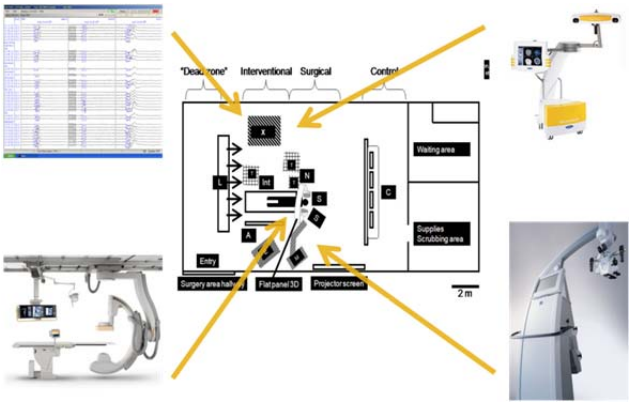


Figure 34: Hybrid operation theatre equipped with an angiography suite, neuro-monitoring, neuronavigation and neurosurgical microscope

Experience Feb 2008- Sept 2009

Surgeries	75 patients	
Clipping	51 patients	63 aneurysms
AVM resection	15 patients	
EC-IC Bypass	3 patients	
Dural fistulas	6 patients	

Per-op 3D-angiographies	N=63	%
Correction of incomplet clipping	N=12	19.0
Correction of stenosis	N=2	3.2
Failure to correct leaving micro remnant	N=1	1.6

Intraoperative MEP & SEP	N=21	%
Surgical induced reversible modifications	N=2	9.5
Irreversible modifications	N=0	0.0
Ischemic lesion on discharge CT	N=0	0.0

Table 8: Neurovascular experience using the hybrid operation theatre and results

The use of intra-operative high resolution angiographic imaging allows the identification of remnants or the accidental occlusion of small perforators that may not be visible in the surgical visual field. The impact of a vascular stenosis is easily visualized on the dynamic angiogram showing regional contrast migration delay or contrast stagnation in downstream dilated vessels.

Clipping quality is increased by the frequent use of proximal vascular temporary clipping to allow rapid aneurysm dissection and optimal exposition avoiding the bleeding from inadvertent dome rupture. The safety of the temporary clipping is guaranteed by continuous monitoring of motor evoked potentials and restoration of the flow at the first sign. Electrophysiology allowed early detection of perforators accidentally kinked or clipped that would most probably not have been detected by careful surgical exploration alone.

In some rare cases, a small remnant visible on the angiogram could not be visualized directly in the operative field, hidden behind the anatomical structures. Completion of a perfect exclusion of the aneurysm neck would have required a complex revision of the performed reconstruction. Detailed study and visualization of the remnant using semitransparent projections matching the operative field allowed clipping of the dog ear whilst preserving nearby perforators under virtual image control. Such experiences pave the way to minimize surgical trauma while keeping safety high. Integration of virtual images updated by ultrasound and endoscopic tools may provide a visual environment that would allow performing the operation through a few burr holes reducing tissue retraction damage even further.

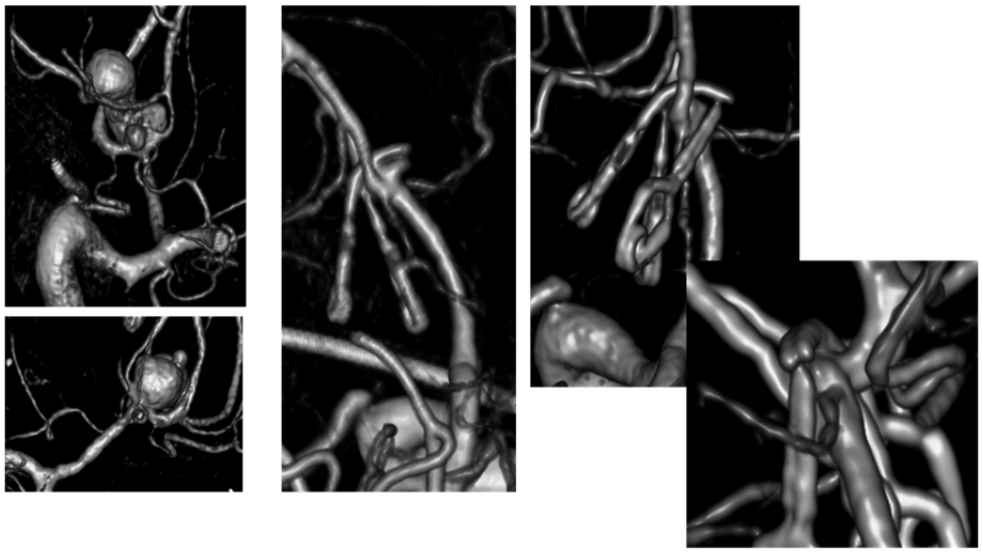


Figure 35: Illustrative case showing the clipping of an anterior communicating aneurysm. A hidden remnant was subsequently clipped while preserving a close by important perforator artery

7.8 Optimizing the early follow-up after subarachnoid heamorrhage

Patients surviving the initial trauma induced by aneurysm subarachnoid heamorrhage (SAH) face two classical intracranial complications: cerebro-vascular spasm and malresorbtive hydrocephalus. Cerebro-vascular spasm is a serious condition that encounters for 20 to 30% of delayed neurological deficits that are responsible for 10% of death secondary to SAH and 11% of disabilities. Cerebral vasospasm usually develops 4–9 days after SAH and resolves within 2 weeks. It is diagnosed with angiography, transcranial Doppler ultrasonography (TCD), or the occurrence of otherwise unexplainable Delayed Ischemic Neurological Deficits (DIND). Cerebral angiography, a gold standard in the diagnosis of vasospasm, allows assessment of irregularities and narrowing of intracranial cerebral arteries with a 0.1% procedure-associated complication rate. Perfusion CT with CT angiography is another potentially promising screening test. TCD is commonly used as a second choice, and has 99% specificity, 67% sensitivity, 97% positive predictive value, and 78% negative predictive value.

In poor clinical grade SAH patients, both coma and pharmacological sedation obscure clinical diagnosis of DINDs. As in most cerebro-vascular conditions, the efficacy of any vasospasm treatment (triple-H therapy, angioplasty, etc.) on clinical outcome highly relies on the clarity and accuracy of the diagnosis allowing for a correction and restoration of cerebral blood flow before irreversible damage occurs. Most poor clinical grade SAH patients need intra-ventricular drainage or intracranial pressure monitoring to manage hydrocephalus and brain edema. Recording and on-line analysis of the intracranial pressure variations induced by systemic blood pressure variations allow for the evaluation of the ability of the cerebro-vascular system to keep a stable and homogenous brain perfusion. During vasospasm the ability of cerebral vessels to dilate in response to low systemic blood pressure is altered and requires aggressive treatments with vasopressors, optimized reology and cardiac ventricular filling. The mean arterial blood pressure required to avoid hypoperfusion and chronic ischemia is currently estimated. The ability to identify cerebrovascular vasospasm and determine the optimal cerebral perfusion pressure to target using intracranial pressure measurements in correlation with systemic arterial blood pressure was explored.

The evaluation of the initial ability to maintain a constant cerebral blood flow using the PRx index (calculated from the correlation of intracranial pressure variations with systemic blood variations) allows an early stratification of patients with high or low chances of survival at 3 months. In most cases with poor regulatory mechanisms (high PRx) changes in cerebral perfusion pressure by increase of the mean arterial blood pressure does not show an improvement. Like patients suffering severe head trauma, cerebrovascular autoregulatory mechanisms may be affected by alteration in autonomic nervous system, regional biochemical mechanisms and mechanical compression of the vessels by brain edema.

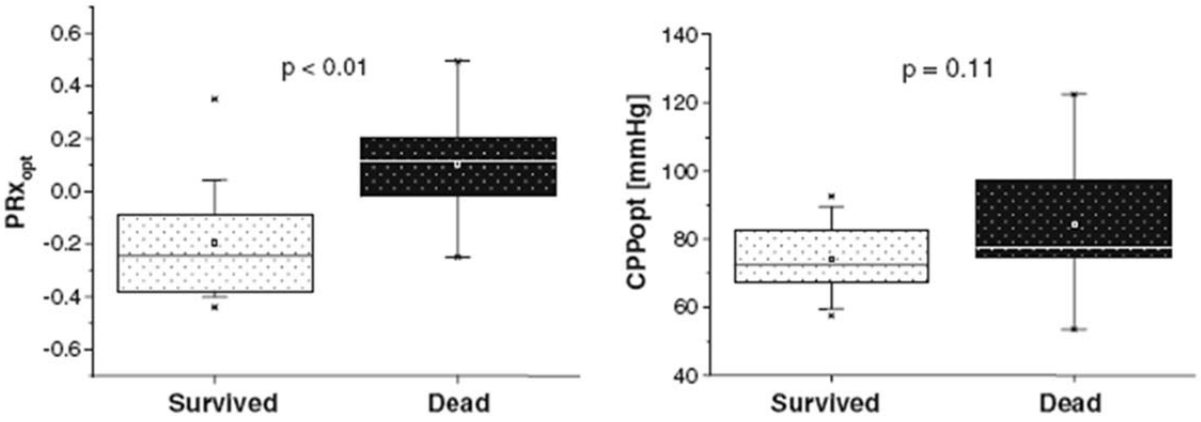


Figure 36: Cerebrovascular autoregulation assessed using PRx and optimal cerebral perfusion pressure in patients that survived or died after a SAH

In contrast, when monitoring the index of reactivity and the optimal perfusion pressure over time during the 2 weeks after the ictus, an increase of the perfusion pressure was observed in all cases but significantly higher in patients where vasospasm was confirmed by angiography or CT-Scan delayed non treatment induced ischemic lesions.

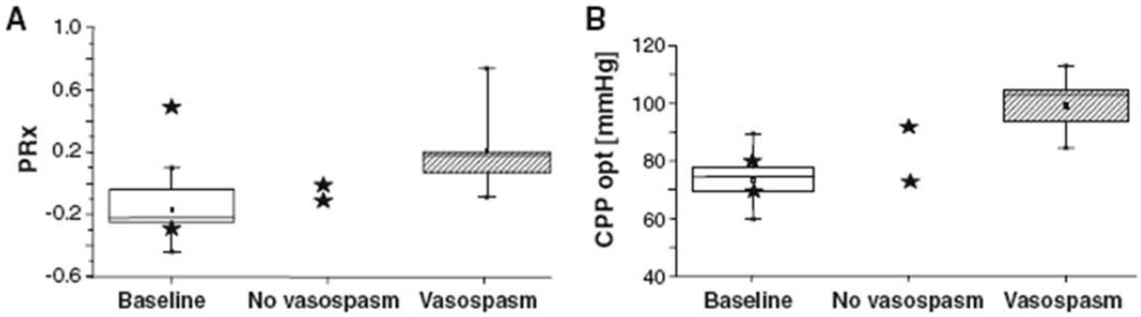


Figure 37: PRx and cerebral perfusion pressure increase in presence of cerebral vasospasm

It can be concluded that the measurement and on-line analysis of the cerebral vaso-reactivity and identification of an optimal cerebral perfusion pressure (CPPopt) allows the identification of spasm. The impact of CPPopt oriented therapy on the clinical outcome needs further work to be validated as a clinical standard.

7.9 Auditing the performance of clinical management

Prospective and consecutive data collected in Geneva between April 2007 and December 2009 was analyzed to assess:

1) the initial characteristics of the patient population affected by intracranial aneurysm in the Geneva recruitment area
2) the frequency of each aneurysm securing modality used
3) the patient average outcome score 1 year after treatment for each severity group

The aim was to measure the performance of care when starting the implementation of a standardized practice. This evaluation should then be used as a reference to assess the impact of new knowledge and technical developments.

All patients were treated following the current state of the art and the rationale supporting decisions was recorded. Management strategies were always discussed during a multidisciplinary team meeting made up of at least one neurosurgeon and one interventional neuroradiologist and as often as possible an intensive care specialist.

Ruptured aneurysms were all secured within 24 hours of admission and patients were monitored for occurrence of hydrocephalus and cerebrovascular vasospasm during 20 days. Symptomatic vasospasm was treated by an escalating strategy starting with hyper hydration, controlled hypertensive therapy, balloon angioplasty and decompressive craniectomy in case of brain edema with intractable intracranial hypertension. External ventricular drainage was inserted when radiological hydrocephalus was associated to a significant decrease of the level of consciousness.

Patients diagnosed with unruptured intracranial aneurysms localized in the anterior circulation as defined in the ISUIA study with a maximal diameter of 7mm were observed according to a follow-up protocol including a clinical evaluation and cerebrovascular imaging at 6 months, 1 year, 2 years and 5 years of discovery as long as no morphological changes of the dome were observed. Aneurysms were secured using microsurgery, endovascular coiling, stenting or hybrid strategies.

The majority of surgical procedures were performed under motor evoked neuromonitoring and angiographic control was performed latest within a few hours after clipping if not obtained intra-operatively. The vessel patency was routinely checked using indo cyanine green fluoroangiography.

All surviving patients were assessed at 1 year after treatment.

297 patients were recruited, most of whom were diagnosed with unruptured aneurysms.

Figure 38: Intracranial aneurysms – Geneva consecutive recruitment 2007-2009

The 3 most prevalent locations for aneurysm formation were respectively the sylvian bifurcation, the anterior communicating complex and the posterior communicating artery. The average aneurysm size was 6.47mm.

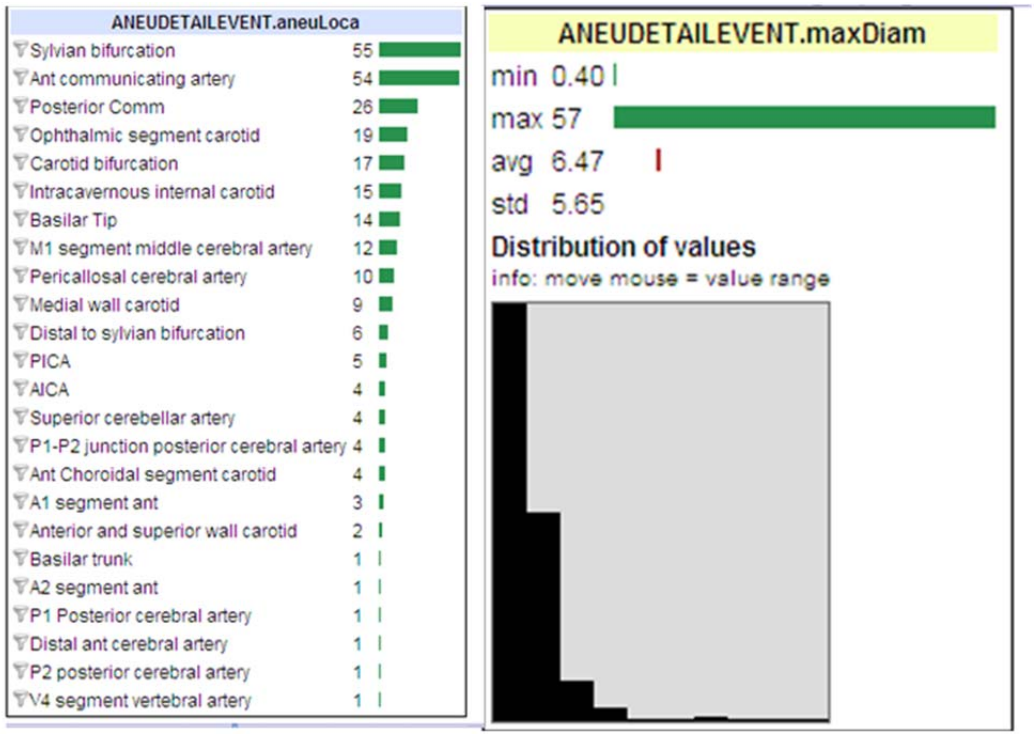


Figure 39: Distribution of aneurysms by location and size

Most unruptured aneurysms were observed. Patients were screened for rupture risk factors like smoking, hypertension and cholesterol level or statin treatment and closely monitored by general practitioners.

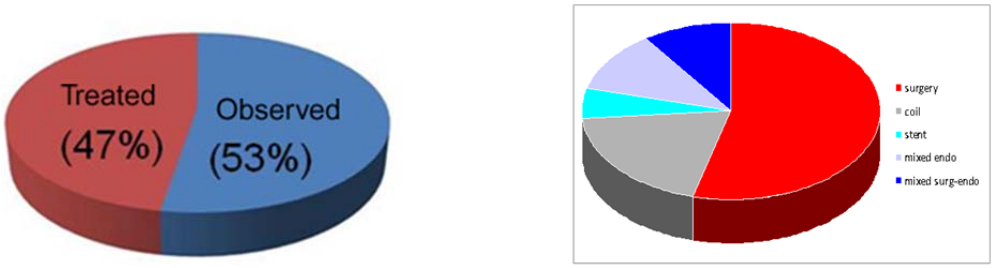


Figure 40: Patients diagnosed with at least one intracranial unruptured aneurysm
Left pie chart: proportion of patients observed or treated.
Right pie chart: distribution of treated patients according to treatment modality

For those aneurysms considered to need aggressive treatment, the choice treatment modality was decided by a multidisciplinary meeting. Location of the aneurysm, the dome to neck ratio, the size, the presence of perforating arteries originating from the dome or close to the aneurysm neck, common carotid bifurcation arteriosclerosis were used in making the decision Stenting with flow diverters was increasingly used for proximal carotid lesions (carotid-cavernous and ophthalmic segment of the internal carotid artery) towards the end of the survey.

The overall mortality was 1.3% and the morbidity rate 1.3%.

Regarding patients suffering ruptured intracranial aneurysms, most were admitted with severe thunder clap headaches and no neurological deficits (56% WFNS grade 1). Less than 19% of the patients were in coma before the aneurysm treatment (WFNS grade 5).

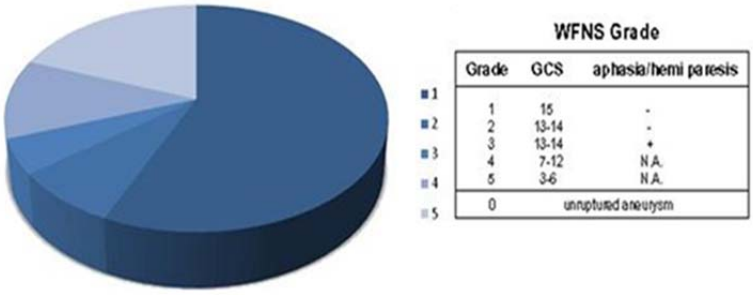


Figure 41: Distribution of patients with SAH according to WFNS clinical severity grade on admission. Admitted in Geneva University Hospital between 2007-2009

All patients were candidates for treatment but a few died before. The aneurysm was secured in 98% of the cases.

The ratio surgical/endovascular treatment was almost 1 to 1.

7% of the cases were treated using a combined approach mixing surgical and endovascular methods.

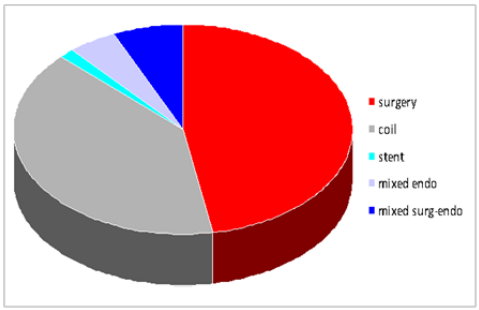


Figure 42: Distribution of patients suffering SAH according to treatment modality

The WFNS grade was a good predictor of outcome. Mortality increased almost linearly from 2% in WFNS 1 grade patients to 50% in WFNS 5 grade patients. It can be emphasized that more than 30% of patients suffering an initial WFNS grade of 5 recover without disabilities affecting their independence (mRankin <2). As expected from the initial presence of focal deficits, the highest rate of morbidity was observed in the group of patients that suffered a WFNS 3 grade.

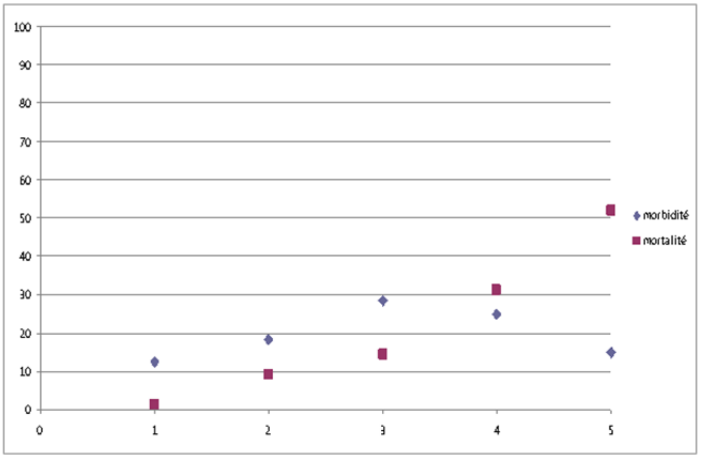


Figure 43: Mortality and morbidity according to admission WFNS clinical severity grade

Those observations will now be used as a reference to assess the evolution of the impact of the disease on society and the effect of improved screening, decision making and new treatment strategies that are progressively introduced.

8. Discussion

Information and health care system:

The main weakness in medical care is transmission of information. It has strong impact on trust, safety and costs. Until recently, each clinician was investigating patients himself, requesting specialized opinions on specific questions, building and finally "knowing" his/her own patients' records. Each physician needed only punctual exchange of limited amount of information with some specialized colleagues. If multiple physicians were taking care of a same patient, each would individually log the clinical history and records in private files. In some countries, care for each citizen is orchestrated by a one physician who is in charge. The physician is in charge of educating patients, treating them and keeping track of the health log. In most countries, it is the patient's choice to have a general physician or family doctor. In some, it has either never really existed or has been lost. It is often up to the patients to choose which specialist would be able to "fix" their problem. This often leads to poor disease prevention, sometimes inadequate consultation if not overload of community emergency facilities. Nevertheless, care has mainly been an individual relationship between one doctor and his patient. With growing complexity, care is moving towards interaction of patients with networks of care givers. This requires improving communication from a short, handwritten "request for opinion from" to more robust, pertinent and efficient models.

The primary aim of the @neurIST project was to demonstrate the feasibility and impact of the deployment of an information system to be used according to a new paradigm of care. Each health issue is approached systematically according to a care pathway. Care pathways contain steps and requirements to move from one step to the next one. Care pathways should allow the inclusion of a vast majority of cases. The reasons to exclude a case are recorded to either improve the pathway or to redirect the case to a more adequate pathway. The initial design of care pathways is performed according to rules by a team of experts representing all care givers. Care givers use the information system to collect and share information systematically. A first essential concept is to collect each piece of information from the most pertinent expert directly and to avoid all data transcription. A second essential concept is that all pertinent pieces of information are to be reviewed and signed off by the

expert clinician or team in the field prior to moving on to the next step. A third essential concept is that the outcome of all cases is to be recorded.

The @neurIST project demonstrated that the management of intracranial aneurysms was a complex topic. Standards of management are recommended on the basis of low degree of evidence. Due to the large number of variables decision making is difficult. A prototype of information platform was designed, implemented and used in clinical centers. In its current version it was used in parallel to traditional paper documents and mostly by trained project members rather than by clinical staff. Benefit for clinical data transmission, care and safety could not be demonstrated yet. In contrast, the project showed that "using a paradigm of care" allowed the collection of a great amount of high quality data allowing the extraction of information covering all aspects of a disease from the genetics to the treatments and outcomes. In a few years and with relatively little resources devoted to bio-medical scientific exploitation, it built a remarkable body of evidence and pioneered new tools to deal with the classically difficult clinical task of managing multiple interdependent variables.

Building up the standards for an architecture of a complete patient health record is a tremendous task. Different initiatives are underway. Google offered a service to patients (Google health) with the possibility to fill in a web-based health record, use tools to find the most appropriate local physician or automatically keep track of medication with the aim of promoting data transmission. The service did not perform as expected and has been closed in January 2012 due to the lack of users (43).

Other systems such as "Save-my-life" have recently been launched based on data collected by patients themselves (41). The service offers the storage of vital medical information on a protected server, it generates a single lifelong QR code (Quick Response: two dimension bar code) that can be printed on stickers or permanently accessed using mobile phones. The code can be scanned and information displayed instantly using any mobile phone and any QR code reader free application. It is the responsibility of the user to decide which information to make available or not. Most experts forewarn against the dangers of conflicts between data comprehensiveness and data protection. Because data may be exposed to third parties, important information may be omitted from the clinical record and by

such misinform care givers potentially exposing the patient to some hazards. Currently, the level of trust put in such systems by care givers is very low.

The most recent extreme example of personal health management is the movement called "Quantified Self" that aims to improve self-knowledge through numbers (42). The movement started in 2007 as a collaboration of users and tool makers who share an interest in self-knowledge through self-tracking. During the first international conference in May 2011 major aims were defined:

1. Define how to measure self
2. Further develop, use and validate new measurement tools
3. Define how to share and use measurements

Until recently, the movement was mainly oriented towards health and sports' performance but it is also now exploring dimensions such as well-being, mood and love status. In August 2012, Rajiv Mehta was invited to give a lecture at the Health Informatics Conference (HIC 2012) and introduced the concept of the future of healthcare by innovation at the edge (crowd) in contrast to innovation at the center (companies, universities). Innovation at the edge is driven by citizens who are given tools to better monitor their health (44).

It is expected that, as observed in the computing industry, providing tools to the crowd dramatically accelerates developments. Rajiv Mehta claims it will impact the future of healthcare by shifting from medical empowerment to personal empowerment. Inherent to empowerment of non-professionals, is the risk of amateurism. This will however be compensated by the natural selection of ideas generated by a high number of individuals based on real-world data. The movement has begun and is now considered as inevitable. It has been stated that healthcare providers should now learn, follow and lead to stream ideas.

The main issues reported in the development of web-based individual health records are data protection, access control, as well as careful update by patients or physicians. Due to possible legal exposure, time-consuming task and the absence of retribution, most physicians are reluctant to fill out such electronic records. Most of the time, patients are left alone without assistance facing a complex

task often resulting in a poor result. Integrating data collection with the normal process of care within the confinement of a hospital solves those issues.

Electronic hospital information systems have been developed world-wide to share medical information, track activity and code diagnosis and care for billing purposes. Information is either collected in plain text, laboratory values, DICOM image files or billing codes. The most relevant information to understand each case is contained in the plain text that is of easy access to humans educated in the field but not exploitable by non-specialized personnel or computers. It has been shown that information extracted from billing codes compared to data prospectively collected in scientific databases does not meet good quality standards with lots of missing and inaccurate information. Extreme caution has to be applied when extracting information from databases regarding consecutivity of cases collection and quality of case transcription in codes. Those two issues have been resolved in structuring and reducing the most pertinent observations to be collected through forms (containing clickable ticks and drop-down multiple choice labels) and by letting the collected data be checked by experts at key times during the clinical journey.

We are convinced that infrastructure, hardware and software developments could extremely positively impact on the issue of high quality data collection, as well as on care and on optimization of the use of resources.

Scientific use of data:

Intracranial aneurysm (IA) is a challenging disease exposing middle age patients to high morbidity and mortality. A significant proportion of the population is affected but only a minority of the patients suffers (1). The understanding of the underlying patho-physiological mechanism of the disease is rudimentary. The diseases seems to be a dynamic process with multiple stages (initiation, growth, remodeling, rupture) (7) spending very different and unpredictable time scales (8). It is obvious to all experts in the field that intracranial aneurysm is not one disease but one expression of many different diseases or the result of the accumulation of multiple risk factors (6),(9).

Clinical decision making is currently mostly based on the status of the aneurysm, the shape, location and size. Ruptured or symptomatic IA requires prompt aggressive treatment and expensive observation in a specialized environment for at least 2 weeks with the need of a lifelong follow-up in all cases and often neuro-rehabilitation. Incidentally discovered IA need a systematic evaluation that integrates information regarding familial and patient history, habits and environmental factors as well as cerebro-vascular and aneurysm anatomy. The risks of the natural history and of aggressive treatment have than to be extrapolated for each patient and balanced. The decision between observing and how to treat is impaired by a high grade of imprecision in the estimation of risks and benefits and often a balance close to equipoise (10).

Those observations motivated the organization and collection of information and biomedical data to better identify and link factors involved in the disease. Genetic, gene expression, morphological and morphodynamic data as well as clinical observation, treatment and outcome measurements were collected prospectively in the @neurIST cohort shared and analyzed.

- New genetic markers of risk associated with the disease have been discovered.
- A gene expression signature in circulating blood cells has been identified.
- The clinical decision algorithm for the management of saccular unruptured IA has been improved.
- Developments to improve surgical safety and care have been explored.
- A report of the impact of the disease in Geneva and Switzerland is presented.

Genetic:

Most of the knowledge accumulated so far regarding genetic variations associated with the disease focused on rare conditions representing less than 1% of the patients and less than 3‰ of the population. It was therefore interesting to evaluate the importance of the genetic background in the population of patients, excluding patients having a positive familial history or any genetic condition known to be associated with the presence of intracranial aneurysms. Blood samples were collected globally from patients diagnosed with intracranial aneurysms and healthy volunteers. A whole genome association study was performed searching for small nucleotide polymorphisms that would be more frequently observed in patients than in healthy controls. Eight new loci were discovered, linked to genes and to biological functions (11, 12). A total of 44 loci are now identified to be associated with the formation of intracranial aneurysms and are evenly distributed over the genome sparing only chromosome 15,21 and Y (13), (14), (15), (16), (17), (18), (19), (20), (21), (22), (23), (24), (25), (26), (27). Thirty four genes are proposed to alter a cellular function that lead ultimately to the disease (25), (28), (29). A interaction as been observed between the loci in 7p14.1 and smoking (27) supporting the hypothesis that multiple factors may cumulate and increase the risk.

Some candidate genes are involved in the construction of the cerebro-vascular tree by adjusting cell proliferation and apoptosis during development and aging, angiogenesis, cell adhesion, extracellular matrix, protease or antiprotease. Some other candidate genes are involved in the homeostasis of the cerebro-vascular tree by modulating the vascular tone or the vessel wall remodeling. Finally, a class of candidate genes produce inflammatory or cell migration factors. None of the genetic marker is strong enough to be used as a screening tool but combined with traditional risk factors such as smoking, blood pressure or excessive alcohol consumption may allow the preclinical identification of individuals at risk of intracranial aneurysm formation and rupture (12),(27). The identification of signaling pathways associated with intracranial aneurysm pathogenesis opens avenues for the development of pharmacological strategies that may have therapeutic value in the prevention of intracranial aneurysm rupture.

Gene expression:

To improve our ability to identify a population at risk, it was suggested that the study of the gene expression profile of circulating blood cells could allow:

- the detection of factors inducing intracranial aneurysm formation.
- the detection of reactions in response to vascular wall injury.

By comparing the gene expression profile of circulating blood cells obtained from patients and healthy volunteers, forty two genes were identified as differentially expressed. By selecting the 28 most differentially expressed genes it was possible to develop a classifier using a gene expression signature. The classifier correctly identified the samples with 85% accuracy. A similar strategy has been successfully used for the identification of patients suffering thoracic aortic aneurysms (30), Parkinson's (31), Alzheimer's (32) as well as many other affections. Nevertheless the classifier needs to be further validated and refined prior to be clinically exploitable.

Clinical decision algorithm:

Our work also aimed at improving the estimation of the risk of rupture of intracranial aneurysms. The two most important factors used to estimate the risk of rupture of an incidentally discovered aneurysm are the location of the aneurysm and the maximal dome size. The ISUIA study reported the estimation of the 5 year rupture risk for aneurysms clustered according the location and size. Three location groups were used: intracavernous, anterior circulation and posterior circulation. Interestingly it was shown that patients with incidentally discovered aneurysms less than 7mm located in the anterior circulation that were not treated were exposed to a negligible risk (10). The publication raised a strong debate because it was in contradiction with clinician's perception, in particular because aneurysms located in the anterior communicating artery (AcoA) are reputed to rupture at diameters lower than 7mm.

We used the data collected during the @neurIST project to test if the cluster of aneurysms located in the anterior circulation had a homogenous behavior and evaluated the relative risk between groups. We observed that aneurysms are mostly located in the anterior communicating artery. The odd ratio of ruptured aneurysms is ~5 when comparing small aneurysms in the AcoA to similar size aneurysms in

the middle cerebral artery bifurcation. Concomitantly and using a complementary approach, the Unruptured Cerebral Aneurysm Study of Japan reported a similar observation (3). We also observed that females are more prone for aneurysm formation but males are more exposed to suffer a subarachnoid haemorrhage when affected by the disease.

We therefore recommend aggressive treatment of all intracranial aneurysms larger than 4mm except when located in the internal carotid artery or middle cerebral artery where the threshold is raised at 7mm. To improve the predictive power more independent variables need to be taken into account. New tools need to be developed to help clinician's.

Development to improve safety of surgery and care:

During aneurysm surgery, patients are mostly exposed to strokes or incomplete clipping. A high resolution of the particularities of the patient cerebro-vascular and aneurysm anatomy allows a better preparation of the surgery. This result in minimally invasive exposure and reduces cerebral retraction injuries. Continuous electrophysiological monitoring during the intervention captures situations at risk and prompts rapid reactions, i.e. an accidental clipping of a hidden small perforating artery can be corrected. High resolution intra-operative imaging of the cerebro-vascular anatomy is essential to confirm the quality of the surgical treatment. Vessel occlusion, stenosis or kinking and aneurysm clipping can be visualized using indocyanine green videofluoangiography, angiography or computed tomography. The adjunction of a neuro-navigation system allows the co registration of the imaging information with the patient. Ultimately augmented reality visualizes projections of the segmented 3D models of the vessels in the microscope guiding the surgeons. In Geneva, since February 2008 all elective and some emergency neurovascular surgeries were performed in a so called hybrid operating theatre. Despite the use of indocyanine green videofluoangiography a significant fraction of aneurysms were clipped incompletely and required correction. On final angiographic control, complete exclusion of aneurysms was obtained in all cases. Since January 2012 Most of the neurovascular surgery is performed with augmented reality. The concept and preliminary results were presented at meetings but details and real impact on clinical outcome is currently analyzed and will be reported in the near future.

Improvement of the monitoring and treatment of vasospasm following SAH.

Despite best management and treatment of intracranial aneurysms some patients suffer and die from ischemic insults secondary to cerebro-vascular vasospasm. Cerebro-vascular vasospasm is a narrowing of the cerebral vessels usually starting 3 days after an intracranial aneurysm rupture and lasting up to 3 weeks. The exact pathophysiological mechanisms remain mostly unknown (33). The best prediction factor for the occurrence of clinically significant vasospasm is the amount and extension of subarachnoid blood seen on admission CT-Scan. Different predictive models have been progressively developed by adding demographic, clinical and treatment factors resulting in predictive value up to 0.960 ± 0.044 (34). Nevertheless there is a consensus that the management of cerebro-vascular vasospasm relies on the rapid detection of the initiation of the phenomenon and the pertinent reaction of the treatment team (35). Treatment first aims are to keep a physiological cardiac output and blood oxygen transport capability. The traditional management of cerebro-vascular vasospasm is the so-called "triple H therapy" for hyperhydration, hemodilution and hypertension. It has been shown in animal models that the most beneficial treatment is hypertension and that hemodilution could in fact event be dangerous (36). Vasospasm often predominates in the large cerebral vessels in the basal cisterns and severe vessel narrowing can be irreversibly forced by balloon angioplasty. Intra-arterial infusion of vasodilators is sometime performed but it is well known that the effect remains temporary. Surgical cisternal or intra-ventricular deposit of nicardipine prolonged release implants shows promising results (37). With the exception of the cisternal deposit of drug releasing pellets all interventions are triggered successively by the progression of the vasospasm severity. In most patients the best monitoring tool is frequent clinical examinations and measurement of the consciousness level and focal deficits using scores like the GCS or the NIH-SS. In comatose patients, the sensitivity of both scores is significantly reduced. Trans-Cranial Doppler recording of blood velocities in cerebral arteries is commonly used as a monitoring tool but is time consuming and highly dependent on the operator's expertise. Most comatose patients are monitored using intra-ventricular drains or intra-cerebral pressure captors. We explored the possibility to identify and optimize the management of cerebro-vascular vasospasm using intra-cranial pressure and intra-arterial pressure analysis. We found that strong disturbances of the cerebro-vascular autoregulation on the initial investigation was a

outcome predictor of death. In most subjects an optimal perfusion pressure (CPPopt) can be identified where autoregulation mechanisms are the strongest. The CPPopt increases between baseline recordings and periods of vasospasm and is highest in symptomatic patients. It has been suggested to use the CPPopt as a target pressure to tailor the hypertensive treatment (38). Further prospective studies are needed to validate CPPopt targeted therapy. The main limitation of the study remains that most of the patients suffering of SAH do not routinely receive intracranial monitoring. The concept has been improved using Trans-Cranial Doppler and near-infrared spectroscopy (NIRS) derived cerebo-vascular autoregulatory evaluations. It is now reported that disturbed autoregulation in the first 5 days after SAH increase the risk of delayed cerebral ischemia(39) .

Impact of subarachnoid hemorrhage in Switzerland

Using the tools developed during the @neurIST project and the data collected in Geneva we were able to analyze some characteristics of the population of affect subjects. We observed that in Geneva almost half of the patients were investigated prior to subarachnoid hemorrhage with unruptured incidentally discovered aneurysms. All patients with subarachnoid hemorrhage are treated within 48 hours and most within the first 24 hours after ictus. During the study period, microsurgical clipping and endovascular treatments were equally frequently performed and rare cases were treated using both techniques. Patients were then closely monitored for vasospasm and an escalating protocol starting with invasive arterial monitoring and hypertensive therapy followed by balloon angioplasty and intra arterial vasodilator injection was used. Despite best efforts significant morbidity and mortality were observed. The mortality increases almost linearly with worth admission clinical grade as previously described and ranges from 2% at best to 50% in the case of patients admitted in deep coma. Nevertheless we conclude from our survey that 30% of the patients admitted in the worth clinical grade still have a chance to recover without severe disabilities and may live an independent life. The work initiated a project: the Swiss-Subarachnoid hemorrhage Outcome Study (Swiss-SOS) that aimed at picturing the current status of care and outcomes after SAH in Switzerland. Results were recently published and show that in Switzerland and in 2009, at least 278 patients suffered an SAH. SAH killed 15% of the affected patients (40 patients a year) and severely disables 30% (85). Most of the patients

recovered a decent life although only 15% recovered towards a completely normal life (2). The Swiss SOS observation is significantly different to the traditional 30% patients dying, 30% of severely disabled patients and 30% of good recovery. Using the same definition 55% of the patients that suffered a SAH in 2009 benefited of a good recovery. This type of outcome survey is essential to measure the impact of the disease on the society and progress made in the management of the condition. The collection of information required a lot of good will and a significant effort from all clinical centers. A tool that could collect the information and simultaneously help in decision making, support standardized reporting and automated billing would tremendously improve the data collection quality and reduce the costs of retrospective database population from clinical files. With an adequate information platform, we could image to provide a yearly SAH outcome report monitoring the improvements in management and the impact of new technologies.

9. Conclusion and prospects

Each generation faces innovations that transform humanity. Medicine and health have considerably benefitted from advances in science, technology, development of industrial processes and globalization of communications and the economy. A major innovation of the late XXth century was the internet "(…) a global system of interconnected computer networks that use the standard Internet Protocol Suite (TCP/IP) to serve billions of users worldwide" (Wikipedia). The internet eases the sharing or exchange of information among users as never before. Internet has been adopted to support communication and in many different fields, from leisure to business, covering almost all aspects of education and knowledge. Nevertheless, for evident security reasons, parts of the computer network are hidden to the World Wide Web behind firewalls. Hospitals developed internal communication networks that are protected against abusive access to confidential information about patients or internal businesses. The @neurIST project explored the limitations and possibilities to use clinical information stored in hospital information systems for the benefit of health and knowledge and to improve standards of care. It developed tools allowing the preservation of security, protecting patients against inappropriate use of information. It designed a paradigm to optimize care and information exchange with scientists and industry to allow a better measure of the impact of a disease on society, identify resources available for treatment and research, validate discoveries and implement new standards of care. It defined the requirements for the automation of such systems.

It is estimated that by investing in the development of information tools prototyped and designed in the project, security of care could be optimized and costs of unnecessary or inadequate investigations and treatments could be saved.

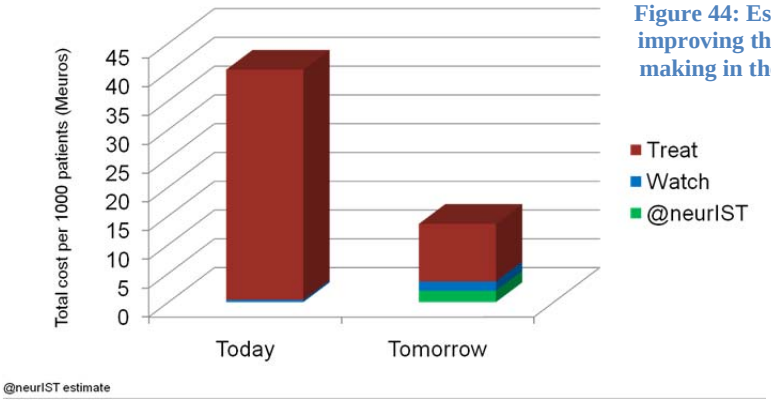


Figure 44: Estimation of savings to be expected by improving the use of information and supporting decision making in the treatment of intracranial aneurysms

The project has demonstrated the ability to share heterogeneous biomedical information between hospitals, academic and industrial institutions to significantly increase the knowledge of a disease. It showed how care and research could be potentiated by the integration of various types of information on a powerful internet-based platform. Between January 2006 and March 2010 the scientific output of the project has increased continuously and left a remarkable inheritance that will be measurable in the future.

On the basis of what has been learn in the @neurIST project we define the following needs to improve rapidly the quality of care and clinical research.

The needs by order of priority are:

1) Collection of high quality and pertinent data from patients and clinicians
2) Integration of information to reduce redundant work
3) Access and processing of data to display information to fit multiple tasks and stakeholders
4) Share data between institutions at European or global level.
5) Reduce administrative burdens associated: with fundraising, solving legal and ethical issues when performing international studies and negotiating terms and conditions when collaborating with industries.

To fulfill the above listed needs the community will need infrastructures, software and hardware developments. Specifications were defined by a group of experts and is currently circulated through the medical community with the intention to generate a consensus and launch coordinated projects.

Infrastructure specifications:

1) Medical terms and definitions should be standardized by European academic societies.
2) The minimal data sets for a generic medical record to be collected and stored by hospital should be defined by law at the European level. (malpractice prevention).
3) The minimal data set to support a diagnosis or justify an intervention should be checked and signed off to allow billing. (best practice promotion)
4) Data models used in research projects should be defined by medical societies in order to support knowledge. The certification of academic institutions should be granted according to the amount and quality of data collected and shared. (evolution of knowledge)
5) Care givers, institutions and care networks should be certified regarding data: collection, management, and use for care, as well as activities in development and academic research with special emphasis on safety and ethical considerations.
6) Institutions and care networks should be audited regarding data collection, management, and use for care, as well as activities in development and academic research with special emphasis on safety and ethical considerations.

Software specifications:

1) Data collection using a dedicated information tool that should primarily aim at reducing redundant actions performed by clinicians.
2) Raw data should be collected and signed off by certified personnel or educated patients.
3) Processed data should be linked to its set of raw data and both should be signed off by senior experts.
4) Medical data should be shared between institutions within a network or identified peers while preserving patient data confidentiality.
5) A data management tool should be able to review data collected for each case and compared to other similar cases within their local database or within the institution network.

6) Medical reports should be generated from the database at predefined stages of the patient investigation and treatment. This aims at replacing the present plain text reports.
7) Medical performance evaluation tool should deliver aggregated outcomes after treatment according to initial severity stratifications for each diagnosis as well as resources used and costs.
8) Data management tool and interfaces to support scientific use of data and interaction with medical industry.

Hardware specifications:

Since the priority of a medical staff is patient care, tools to document medical observations and activities should be adapted to the users. Interaction with a keyboard, away from the patient and in parallel of care, considerably reduces the user-friendliness.
Hardware should be adapted or created to allow data collection “while observing” or “while intervening” or “while deciding”. These should be integrated to clinical instruments and in the environment. Tablets most probably have an important role to play.

Proposed priority topics

1) Neuro-oncology

Intracranial tumors remain a challenging disease with a high impact on society. The incidence is stable over time with 20cases per 100.000 inhabitants per year. The potential impact of the disease on the life of patients is extreme. The median survival after diagnosis ranges from a few weeks to years rarely decades. The potential impact on life quality is high. Neuro-oncology is a highly multidisciplinary field involving general practitioner, neuro-radiologists, neurologists, neurosurgeons, histopathologists, neuro-oncologists, radio-oncologists, basic scientists, pharma and device industries. Significant advances in case stratification and treatments are currently transforming practice and prognosis.

European research in the field is well organized by the European Organisation for Research and Treatment of Cancer (EORTC). Two work groups are involved in neuro-oncology:

1) Brain tumour group
2) Radiation oncology group

There is a recognized need and impetus to generate on a pan-European level:

1) biobank of tissue,
2) standards of care,
3) standards for clinical trials,
4) interactions with industry.

The field will strongly benefit from the development and implementation of an information integration tool. The highly successful track record and experience of the community make them a first choice stakeholder.

The field could be a flagship for conditions benefiting of the interaction of a high number of experts from very different backgrounds, with rapidly evolving basic science knowledge and treatments using very sophisticated tools and technologies that all need to be integrated.

Registries to merge:

Biobanks

Clinical trials databases

Quality of life and outcome study

Technologies to integrate:

- Multimodal information display for diagnosis and decision support (nano to metric scale, morphological, metabolical functional and environmental information)

-Multimodal imaging & navigation for surgery, radiation therapy and follow-up

2) Neuro-vascular:

Cerebrovascular diseases represent the third most frequent cause of death after cardiac arrest and neoplasm. The current major long-term aims are to identify the population at risk and improve treatment safety. In the short term, the aim is to improve the management of cases that suffered either an ischemic or hemorrhagic stroke with related complications to improve the survival and quality of life. The neurovascular field also involves a broad spectrum of protagonists: general practitioners, emergency specialists, neuroradiologists, neurologists, neurosurgeons, interventional neuroradiologists, intensive care specialists, neurorehabilitation specialists.

Significant advances in the understanding of molecular and pathophysiological mechanisms involved in very multi-factorial diseases as well as recent developments of new treatment strategies let us expect a major change in prognosis of affected individuals with a strong impact on society. The community will benefit from rapid dissemination of innovation and transparent reporting of results.

Industry partners are biotechnology companies involved in diagnostic tests, pharmaceutical companies for medical treatments, device companies producing stents, coils or clips, as well as companies involved in imaging and simulation and navigation.

The field could be a flagship for conditions benefiting of highly multicentre interactions to

increase the recruitment rate for rare conditions and rapid dissemination of innovation with a big impact on society.

Registries to merge:

Giant Aneurysm Registry

Swiss SAH Outcome Study (SOS) Registry

Swiss by-pass registry with extension to central Europe

@neurIST genetic and epidemiology data base

Technologies to integrate:

-Multimodal information display for diagnosis and decision support (nano to decimetric scale, environment, morpho-dynamic, flow, biophysical simulations, treatment simulation information.

-Multimodal imaging & navigation for endovascular intervention and minimally invasive transcranial microsurgery and follow-up.

3) Spine

Back pain is a major society issue and an important market for pharmaceutical and medical devices companies. The field of spine involves a reduced number of protagonists. It principally involves general practitioners, neurosurgeons and orthopedic surgeons in both academic institutions and private practice. Significant progress in the understanding of mechanisms of pain and of biomechanics of the spine, as well as developments in prosthetic devices let us extrapolate an increased success rate with a reduction in treatment costs as well as workforce loss.

The field could be a flagship for conditions requiring small data sets but exposed to a large community of users with strong impact on the medical device industry.

Registries to merge:

Spine Tango Registry	www.eurospine.org/p31000381.html
Swedish spine registry	www.4s.nu/patientsida_eng/index.html
Keops system	www.keops-spine.fr

4) NEURO-trauma

Severe brain injury is a leading cause of death and disability affecting mostly young adults. Correct evaluation of initial conditions (severity stratification) and optimization of care improving care teams reactivity to unexpected events during the acute phase, strongly impacts outcomes. The field of brain trauma involves emergency specialists, neuro-radiologists, neurosurgeons, intensive care specialists and nurses and neuro-rehabilitation specialists. The challenge here is to comply with standards of care and collect bed-side monitoring data over a period of time ranging from a few days to weeks.

Advances in multimodal monitoring and analysis in conjunction with better understanding of autoregulation dysfunctions allows the design of personalized target-oriented treatments. Auditing the compliance to objectives and effects of optimized treatments on outcome will allow defining tomorrows' brain trauma management guidelines.

The field could be a flagship for conditions requiring the collection and analysis of data at high rate (100Hz – 1/3600 Hz) and over long periods of time in multiple centers. It will have an impact on the understanding of physiological and pathological dynamic multi-organ processes impacting on brain perfusion, metabolism and function and hopefully on patient recovery decreasing exposure to the secondary lesions.

<u>Registries to merge:</u>

ICM+ software community registry

BrainIT database

The medical community seeking assistance from the information technology community and policy makers. Five essential issues have been identified by the neurosurgical and medical community. Neurosurgical topics are proposed to pioneer model health, disease and treatments. Remarkable natural bridges with other medical specialties exist to spread it to the entire human body with the aim of improving health globally and at an affordable price.

10.References

Forword

1. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet neurology. 2011 Jul;10(7):626-36. PubMed PMID: 21641282. Epub 2011/06/07. eng.
2. Schatlo B, Fung C, Fathi AR, Sailer M, Winkler K, Daniel RT, et al. Introducing a nationwide registry: the Swiss study on aneurysmal subarachnoid haemorrhage (Swiss SOS). Acta neurochirurgica. 2012 Oct 6. PubMed PMID: 23053275. Epub 2012/10/12. Eng.
3. Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. The New England journal of medicine. 2012 Jun 28;366(26):2474-82. PubMed PMID: 22738097. Epub 2012/06/29. eng.
4. Kotowski M, Naggara O, Darsaut TE, Nolet S, Gevry G, Kouznetsov E, et al. Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. Journal of neurology, neurosurgery, and psychiatry. 2012 Sep 25. PubMed PMID: 23012447. Epub 2012/09/27. Eng.
5. Hwang JS, Hyun MK, Lee HJ, Choi JE, Kim JH, Lee NR, et al. Endovascular coiling versus neurosurgical clipping in patients with unruptured intracranial aneurysm: a systematic review. BMC neurology. 2012 Sep 22;12(1):99. PubMed PMID: 22998483. Epub 2012/09/25. Eng.
6. Krings T, Mandell DM, Kiehl TR, Geibprasert S, Tymianski M, Alvarez H, et al. Intracranial aneurysms: from vessel wall pathology to therapeutic approach. Nature reviews Neurology. 2011 Oct;7(10):547-59. PubMed PMID: 21931350. Epub 2011/09/21. eng.

Information and Heath Care System Overview

1. Dunn PM. The Chamberlen family (1560-1728) and obstetric forceps. Arch Dis Child Fetal Neonatal Ed. 1999;81(3):F232-4. Epub 1999/10/19.
2. OECD. Health care systems: Getting more value for money. OECD, editor2010.

Overview of avenues to improve care and heath systems

1. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946, signed on 22 July 1946 by the representatives of 61 States. 1946.
2. Mathers CD, et al. Methods for Measuring Healthy Life Expectancy. Health system performance assessement: debates, methods and empiricism. Geneva: World Heatlh Organization; 2003.
3. Matheson D, Wolff T. Next Generation medical Management: Strategic Responses for Suppliers and Providers. 2009.
4. Stiglitz J. Information and the change in the paradigm in economics. 2001 December 8, 2001. Report No.
5. WHO. The World Health Report 2004: Changing History. Geneva: World Health Organization; 2004.

Clinical and biomedical data collection process

1. Campbell H, Hotchkiss R, Bradshaw N, Porteous M. Integrated care pathways. BMJ. 1998;316(7125):133-7. Epub 1998/02/14.
2. Cannon CP, Hand MH, Bahr R, Boden WE, Christenson R, Gibler WB, et al. Critical pathways for management of patients with acute coronary syndromes: an assessment by the National Heart Attack Alert Program. Am Heart J. 2002;143(5):777-89. Epub 2002/06/01.
3. contributors W. ICD-10Auguts 24, 2012 October 6, 2012. Available from: http://en.wikipedia.org/w/index.php?title=ICD-10&oldid=508978957.

4. contributors W. Digital imaging and communications in medicineOctober 2, 2012 October 6, 2012. Available from: http://fr.wikipedia.org/w/index.php?title=Digital_imaging_and_communications_in_medicine&oldid=83628057.
5. De Luc K. Are different models of care pathways being developed? International Journal of Health Care Quality Assurance. 2000;13(2):80-6.
6. Fetter RB, Thompson JD, Mills RE. A System for Cost and Reimbursement Control in Hospitals. Yale Journal of Biology and Medicine. 1976;49:123-6.
7. Kwan J, Sandercock P. In-hospital care pathways for stroke: a Cochrane systematic review. Stroke. 2003;34(2):587-8. Epub 2003/02/08.
8. OECD. Health care systems: Getting more value for money. OECD, editor2010.
9. Taylor WJ, Wong A, Siegert RJ, McNaughton HK. Effectiveness of a clinical pathway for acute stroke care in a district general hospital: an audit. BMC Health Serv Res. 2006;6:16. Epub 2006/03/01.
10. Thompson JD, Fetter RB. Simulation of Hospital Systems. Operations Research. 1965;3(5):689-711.
11. Vanhaecht K, Sermeus W. Scénario pour l'élaboration d'un itinéraire clinique, sa mise en oeuvre et son évaluation. Plan en 30 étapes du "réseau itinéraires cliniques"2003. Available from: http://www.nkp.be/franais/le-plan-en-30-etapes/index.html.
12. Vickrey BG, Mittman BS, Connor KI, Pearson ML, Della Penna RD, Ganiats TG, et al. The effect of a disease management intervention on quality and outcomes of dementia care: a randomized, controlled trial. Ann Intern Med. 2006;145(10):713-26. Epub 2006/11/23.
13. Zander K, Bower K. Blueprint for Transformation. Nursing Case Management. 1987.
14. Zander K, Bower K. Implementing systems for managing care. Boston: 2000.

Design of the information platform

1. Boeker M, Stenzhorn H, Kumpf K, Bijlenga P, Schulz S, Hanser S. The @neurIST ontology of intracranial aneurysms: providing terminological services for an integrated IT infrastructure. AMIA Annu Symp Proc. 2007:56-60. Epub 2008/08/13.
2. Drake CG, Peerless SJ, Hernesniemi J. Surgery of vertebrobasilar aneurysms: London, Ontario, experience on 1,767 patients. Wien, New York: Springer Medicin; 1996.
3. Gonzalez LF, Alexander MJ, McDougall CG, Spetzler RF. Anteroinferior cerebellar artery aneurysms: surgical approaches and outcomes--a review of 34 cases. Neurosurgery. 2004;55(5):1025-35. Epub 2004/10/29.
4. Gonzalez LF, Amin-Hanjani S, Bambakidis NC, Spetzler RF. Skull base approaches to the basilar artery. Neurosurg Focus. 2005;19(2):E3. Epub 2005/08/27.
5. Hanel RA, Spetzler RF. Surgical treatment of complex intracranial aneurysms. Neurosurgery. 2008;62(6 Suppl 3):1289-97; discussion 97-9. Epub 2008/08/22.
6. Iavindrasana J, Depeursinge A, Ruch P, Spahni S, Geissbuhler A, Muller H. Design of a decentralized reusable research database architecture to support data acquisition in large research projects. Stud Health Technol Inform. 2007;129(Pt 1):325-9. Epub 2007/10/04.
7. Iavindrasana J, Lo Iacono L, Muller H, Periz I, Summers P, Wright J, et al. The @neurIST project. Stud Health Technol Inform. 2008;138:161-4. Epub 2008/06/19.
8. Inci S, Spetzler RF. Intracranial aneurysms and arterial hypertension: a review and hypothesis. Surg Neurol. 2000;53(6):530-40; discussion 40-2. Epub 2000/08/15.
9. Kobayashi S, Orz Y, George B, Lee KC, Alexander MJ, Spetzler RF, et al. Treatment of unruptured cerebral aneurysms. Surg Neurol. 1999;51(4):355-62. Epub 1999/04/13.
10. Lawton MT, Spetzler RF. Surgical management of giant intracranial aneurysms: experience with 171 patients. Clin Neurosurg. 1995;42:245-66. Epub 1995/01/01.
11. Little AS, Garrett M, Germain R, Farhataziz N, Albuquerque FC, McDougall CG, et al. Evaluation of patients with spontaneous subarachnoid hemorrhage and negative angiography. Neurosurgery. 2007;61(6):1139-50; discussion 50-1. Epub 2007/12/29.

12. Little AS, Kerrigan JF, McDougall CG, Zabramski JM, Albuquerque FC, Nakaji P, et al. Nonconvulsive status epilepticus in patients suffering spontaneous subarachnoid hemorrhage. J Neurosurg. 2007;106(5):805-11. Epub 2007/06/05.
13. Ponce FA, Albuquerque FC, McDougall CG, Han PP, Zabramski JM, Spetzler RF. Combined endovascular and microsurgical management of giant and complex unruptured aneurysms. Neurosurg Focus. 2004;17(5):E11. Epub 2005/01/07.
14. Riina HA, Lemole GM, Jr., Spetzler RF. Anterior communicating artery aneurysms. Neurosurgery. 2002;51(4):993-6; discussion 6. Epub 2002/09/18.
15. Riina HA, Spetzler RF. Unruptured aneurysms. J Neurosurg. 2002;96(1):61-2. Epub 2002/01/17.
16. Schievink WI, Link MJ, Piepgras DG, Spetzler RF. Intracranial aneurysm surgery in Ehlers-Danlos syndrome Type IV. Neurosurgery. 2002;51(3):607-11; discussion 11-3. Epub 2002/08/22.
17. Spetzler RF, Riina HA, Lemole GM, Jr. Giant aneurysms. Neurosurgery. 2001;49(4):902-8. Epub 2001/09/21.
18. Vishteh AG, Spetzler RF. Blister or berry aneurysm. J Neurosurg. 1999;91(6):1062-3. Epub 1999/12/10.
19. Weir B. Subarachnoid Hemorrhage: Causes and Cures. New York: Oxford University Press; 1998.
20. Wilson CB, Spetzler RF. Operative approaches to aneurysms. Clin Neurosurg. 1979;26:232-47. Epub 1979/01/01.
21. Yasargil MG, Smith RD, Young PH, Teddy PJ, Roth P. Microneurosurgery: Clinical Considerations, Surgery of the Intracranial Aneurysms and Results. Stuttgart, New York: Thieme New York: Thieme Stratton; 1984.

Architecture of the information system

1. Benkner S, Arbona A, Berti G, Chiarini A, Dunlop R, Engelbrecht G, et al. @neurIST: infrastructure for advanced disease management through integration of heterogeneous data, computing, and complex processing services. IEEE Trans Inf Technol Biomed. 2010;14(6):1365-77. Epub 2010/05/04.
2. Dunlop R, Arbona A, Rajasekaran H, Lo Iacono L, Fingberg J, Summers P, et al. @neurIST - chronic disease management through integration of heterogeneous data and computer-interpretable guideline services. Stud Health Technol Inform. 2008;138:173-7. Epub 2008/06/19.
3. Elger BS, Iavindrasana J, Lo Iacono L, Muller H, Roduit N, Summers P, et al. Strategies for health data exchange for secondary, cross-institutional clinical research. Comput Methods Programs Biomed. 2010;99(3):230-51. Epub 2010/01/22.
4. Rajasekaran H, Iacono LL, Hasselmeyer P, Fingberg J, Summers P, Benkner S, et al., editors. AneurIST Towards a system architecture for advanced disease management through integration of heterogeneous data, computing, and complex processing services. Proc 21st IEEE Int Symp Comput-based Med Syst; 2008; University of Jyväskylä, Finland.

Selection of results

1. Clarke M. Systematic review of reviews of risk factors for intracranial aneurysms. Neuroradiology. 2008;50(8):653-64. Epub 2008/06/19.
2. Gieteling EW, Rinkel GJ. Characteristics of intracranial aneurysms and subarachnoid haemorrhage in patients with polycystic kidney disease. J Neurol. 2003;250(4):418-23. Epub 2003/04/18.
3. Rinkel GJ, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke. 1998;29(1):251-6. Epub 1998/01/28.

Genetics

1. Bilguvar K, Yasuno K, Niemela M, Ruigrok YM, von Und Zu Fraunberg M, van Duijn CM, et al. Susceptibility loci for intracranial aneurysm in European and Japanese populations. Nat Genet. 2008;40(12):1472-7. Epub 2008/11/11.
2. Biros E, Golledge J. Meta-analysis of whole-genome linkage scans for intracranial aneurysm. Neurosci Lett. 2008;431(1):31-5. Epub 2007/12/11.
3. Farnham JM, Camp NJ, Neuhausen SL, Tsuruda J, Parker D, MacDonald J, et al. Confirmation of chromosome 7q11 locus for predisposition to intracranial aneurysm. Hum Genet. 2004;114(3):250-5. Epub 2003/11/08.
4. Mineharu Y, Inoue K, Inoue S, Yamada S, Nozaki K, Hashimoto N, et al. Model-based linkage analyses confirm chromosome 19q13.3 as a susceptibility locus for intracranial aneurysm. Stroke. 2007;38(4):1174-8. Epub 2007/02/27.
5. Nahed BV, Seker A, Guclu B, Ozturk AK, Finberg K, Hawkins AA, et al. Mapping a Mendelian form of intracranial aneurysm to 1p34.3-p36.13. Am J Hum Genet. 2005;76(1):172-9. Epub 2004/11/13.
6. Olson JM, Vongpunsawad S, Kuivaniemi H, Ronkainen A, Hernesniemi J, Ryynanen M, et al. Search for intracranial aneurysm susceptibility gene(s) using Finnish families. BMC Med Genet. 2002;3:7. Epub 2002/08/03.
7. Onda H, Kasuya H, Yoneyama T, Takakura K, Hori T, Takeda J, et al. Genomewide-linkage and haplotype-association studies map intracranial aneurysm to chromosome 7q11. Am J Hum Genet. 2001;69(4):804-19. Epub 2001/09/06.
8. Ozturk AK, Nahed BV, Bydon M, Bilguvar K, Goksu E, Bademci G, et al. Molecular genetic analysis of two large kindreds with intracranial aneurysms demonstrates linkage to 11q24-25 and 14q23-31. Stroke. 2006;37(4):1021-7. Epub 2006/02/25.
9. Roos YB, Pals G, Struycken PM, Rinkel GJ, Limburg M, Pronk JC, et al. Genome-wide linkage in a large Dutch consanguineous family maps a locus for intracranial aneurysms to chromosome 2p13. Stroke. 2004;35(10):2276-81. Epub 2004/08/28.
10. Ruigrok YM, Elias R, Wijmenga C, Rinkel GJ. A comparison of genetic chromosomal loci for intracranial, thoracic aortic, and abdominal aortic aneurysms in search of common genetic risk factors. Cardiovasc Pathol. 2008;17(1):40-7. Epub 2007/12/28.
11. Ruigrok YM, Rinkel GJ, Wijmenga C. Genetics of intracranial aneurysms. Lancet Neurol. 2005;4(3):179-89. Epub 2005/02/22.
12. van der Voet M, Olson JM, Kuivaniemi H, Dudek DM, Skunca M, Ronkainen A, et al. Intracranial aneurysms in Finnish families: confirmation of linkage and refinement of the interval to chromosome 19q13.3. Am J Hum Genet. 2004;74(3):564-71. Epub 2004/02/12.
13. Verlaan DJ, Dube MP, St-Onge J, Noreau A, Roussel J, Satge N, et al. A new locus for autosomal dominant intracranial aneurysm, ANIB4, maps to chromosome 5p15.2-14.3. J Med Genet. 2006;43(6):e31. Epub 2006/06/03.
14. Yamada S, Utsunomiya M, Inoue K, Nozaki K, Inoue S, Takenaka K, et al. Genome-wide scan for Japanese familial intracranial aneurysms: linkage to several chromosomal regions. Circulation. 2004;110(24):3727-33. Epub 2004/12/01.
15. Yamada S, Utsunomiya M, Inoue K, Nozaki K, Miyamoto S, Hashimoto N, et al. Absence of linkage of familial intracranial aneurysms to 7q11 in highly aggregated Japanese families. Stroke. 2003;34(4):892-900. Epub 2003/03/22.

Candidate genes

1. Krischek B, Inoue I. The genetics of intracranial aneurysms. J Hum Genet. 2006;51(7):587-94. Epub 2006/06/01.
2. Nahed BV, Bydon M, Ozturk AK, Bilguvar K, Bayrakli F, Gunel M. Genetics of intracranial aneurysms. Neurosurgery. 2007;60(2):213-25; discussion 25-6. Epub 2007/02/10.
3. Ruigrok YM, Rinkel GJ, Wijmenga C. Genetics of intracranial aneurysms. Lancet Neurol. 2005;4(3):179-89. Epub 2005/02/22.

Risk factors for SAH in general population

1. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365-72. Epub 2007/05/02.
2. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke. 2005;36(12):2773-80. Epub 2005/11/12.
3. Linn FH, Rinkel GJ, Algra A, van Gijn J. Incidence of subarachnoid hemorrhage: role of region, year, and rate of computed tomography: a meta-analysis. Stroke. 1996;27(4):625-9. Epub 1996/04/01.
4. Rinkel GJ, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke. 1998;29(1):251-6. Epub 1998/01/28.
5. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke. 2007;38(4):1404-10. Epub 2007/03/03.

Risk factors for rupture of known aneuryms

1. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke. 2007;38(4):1404-10. Epub 2007/03/03.
2. Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD, Jr., Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003;362(9378):103-10. Epub 2003/07/18.

Genetics discovery

1. Yasuno K, Bakircioglu M, Low SK, Bilguvar K, Gaal E, Ruigrok YM, et al. Common variant near the endothelin receptor type A (EDNRA) gene is associated with intracranial aneurysm risk. Proc Natl Acad Sci U S A. 2011;108(49):19707-12. Epub 2011/11/23.
2. Yasuno K, Bilguvar K, Bijlenga P, Low SK, Krischek B, Auburger G, et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. Nat Genet. 2010;42(5):420-5. Epub 2010/04/07.

Detecting intracranial aneurysm and evaluating the risk using a blood test

1. Yagi K, Tada Y, Kitazato KT, Tamura T, Satomi J, Nagahiro S. Ibudilast inhibits cerebral aneurysms by down-regulating inflammation-related molecules in the vascular wall of rats. Neurosurgery. 2010;66(3):551-9; discussion 9. Epub 2010/02/04.
2. Yilmaz S, Bijlenga P, Rashid M, Collot-Teixeira S, Brocheton J, Proust C, et al. Gene Expression Signature in Peripheral Blood Cells Detects Intracranial Aneurysm - Top 10 Abstract. Neurosurgery. 2010;67:540.

Evaluation of the risk of rupture of intracranial aneurysm from angiographic imaging

1. Bijlenga P, Ebeling C, Jaegersberg M, Rogers A, Waterworth A, Summers P, et al. Risk of rupture of small anterior communicating artery aneurysms is similar to posterior circulation aneurysms. Stroke. submitted.
2. Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. N Engl J Med. 2012;366(26):2474-82. Epub 2012/06/29.

Optimizing the surgical treatment

1. Bijlenga P, Mendes Pereira V, Schaller K. Clipping of MCA aneurysms: how I do it. Acta Neurochir (Wien). 2011;153(7):1361-6. Epub 2011/06/07.
2. Schaller K, Kotowski M, Pereira V, Rufenacht D, Bijlenga P. From intraoperative angiography to advanced intraoperative imaging: the geneva experience. Acta Neurochir Suppl. 2011;109:111-5. Epub 2010/10/21.

Optimizing the early follow-up after SAH

1. Bijlenga P, Czosnyka M, Budohoski KP, Soehle M, Pickard JD, Kirkpatrick PJ, et al. "Optimal cerebral perfusion pressure" in poor grade patients after subarachnoid hemorrhage. Neurocrit Care. 2010;13(1):17-23. Epub 2010/04/21.

Discussion

1. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet neurology. 2011 Jul;10(7):626-36. PubMed PMID: 21641282. Epub 2011/06/07. eng.
2. Schatlo B, Fung C, Fathi AR, Sailer M, Winkler K, Daniel RT, et al. Introducing a nationwide registry: the Swiss study on aneurysmal subarachnoid haemorrhage (Swiss SOS). Acta neurochirurgica. 2012 Oct 6. PubMed PMID: 23053275. Epub 2012/10/12. Eng.
3. Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. The New England journal of medicine. 2012 Jun 28;366(26):2474-82. PubMed PMID: 22738097. Epub 2012/06/29. eng.
4. Kotowski M, Naggara O, Darsaut TE, Nolet S, Gevry G, Kouznetsov E, et al. Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. Journal of neurology, neurosurgery, and psychiatry. 2012 Sep 25. PubMed PMID: 23012447. Epub 2012/09/27. Eng.
5. Hwang JS, Hyun MK, Lee HJ, Choi JE, Kim JH, Lee NR, et al. Endovascular coiling versus neurosurgical clipping in patients with unruptured intracranial aneurysm: a systematic review. BMC neurology. 2012 Sep 22;12(1):99. PubMed PMID: 22998483. Epub 2012/09/25. Eng.
6. Krings T, Mandell DM, Kiehl TR, Geibprasert S, Tymianski M, Alvarez H, et al. Intracranial aneurysms: from vessel wall pathology to therapeutic approach. Nature reviews Neurology. 2011 Oct;7(10):547-59. PubMed PMID: 21931350. Epub 2011/09/21. eng.
7. Humphrey JD. Cardiovascular Solid Mechanics: Cells, Tissues and Organs. New York: Springer-Verlag; 2002.
8. Chmayssani M, Rebeiz JG, Rebeiz TJ, Batjer HH, Bendok BR. Relationship of growth to aneurysm rupture in asymptomatic aneurysms </= 7 mm: a systematic analysis of the literature. Neurosurgery. 2011 May;68(5):1164-71; discussion 71. PubMed PMID: 21307791. Epub 2011/02/11. eng.
9. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke; a journal of cerebral circulation. 2005 Dec;36(12):2773-80. PubMed PMID: 16282541. Epub 2005/11/12. eng.
10. Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD, Jr., Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003 Jul 12;362(9378):103-10. PubMed PMID: 12867109. Epub 2003/07/18. eng.
11. Yasuno K, Bakircioglu M, Low SK, Bilguvar K, Gaal E, Ruigrok YM, et al. Common variant near the endothelin receptor type A (EDNRA) gene is associated with intracranial aneurysm risk. Proceedings of the National Academy of Sciences of the United States of America. 2011 Dec 6;108(49):19707-12. PubMed PMID: 22106312. Pubmed Central PMCID: 3241810. Epub 2011/11/23. eng.

12. Yasuno K, Bilguvar K, Bijlenga P, Low SK, Krischek B, Auburger G, et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. Nature genetics. 2010 May;42(5):420-5. PubMed PMID: 20364137. Pubmed Central PMCID: 2861730. Epub 2010/04/07. eng.
13. Nahed BV, Seker A, Guclu B, Ozturk AK, Finberg K, Hawkins AA, et al. Mapping a Mendelian form of intracranial aneurysm to 1p34.3-p36.13. American journal of human genetics. 2005 Jan;76(1):172-9. PubMed PMID: 15540160. Pubmed Central PMCID: 1196421. Epub 2004/11/13. eng.
14. Onda H, Kasuya H, Yoneyama T, Takakura K, Hori T, Takeda J, et al. Genomewide-linkage and haplotype-association studies map intracranial aneurysm to chromosome 7q11. American journal of human genetics. 2001 Oct;69(4):804-19. PubMed PMID: 11536080. Pubmed Central PMCID: 1226066. Epub 2001/09/06. eng.
15. Bilguvar K, Yasuno K, Niemela M, Ruigrok YM, von Und Zu Fraunberg M, van Duijn CM, et al. Susceptibility loci for intracranial aneurysm in European and Japanese populations. Nature genetics. 2008 Dec;40(12):1472-7. PubMed PMID: 18997786. Pubmed Central PMCID: 2682433. Epub 2008/11/11. eng.
16. Roos YB, Pals G, Struycken PM, Rinkel GJ, Limburg M, Pronk JC, et al. Genome-wide linkage in a large Dutch consanguineous family maps a locus for intracranial aneurysms to chromosome 2p13. Stroke; a journal of cerebral circulation. 2004 Oct;35(10):2276-81. PubMed PMID: 15331791. Epub 2004/08/28. eng.
17. Verlaan DJ, Dube MP, St-Onge J, Noreau A, Roussel J, Satge N, et al. A new locus for autosomal dominant intracranial aneurysm, ANIB4, maps to chromosome 5p15.2-14.3. Journal of medical genetics. 2006 Jun;43(6):e31. PubMed PMID: 16740915. Pubmed Central PMCID: 2564548. Epub 2006/06/03. eng.
18. Olson JM, Vongpunsawad S, Kuivaniemi H, Ronkainen A, Hernesniemi J, Ryynanen M, et al. Search for intracranial aneurysm susceptibility gene(s) using Finnish families. BMC medical genetics. 2002 Aug 1;3:7. PubMed PMID: 12153705. Pubmed Central PMCID: 119849. Epub 2002/08/03. eng.
19. Farnham JM, Camp NJ, Neuhausen SL, Tsuruda J, Parker D, MacDonald J, et al. Confirmation of chromosome 7q11 locus for predisposition to intracranial aneurysm. Human genetics. 2004 Feb;114(3):250-5. PubMed PMID: 14605871. Epub 2003/11/08. eng.
20. Yamada S, Utsunomiya M, Inoue K, Nozaki K, Miyamoto S, Hashimoto N, et al. Absence of linkage of familial intracranial aneurysms to 7q11 in highly aggregated Japanese families. Stroke; a journal of cerebral circulation. 2003 Apr;34(4):892-900. PubMed PMID: 12649519. Epub 2003/03/22. eng.
21. Ozturk AK, Nahed BV, Bydon M, Bilguvar K, Goksu E, Bademci G, et al. Molecular genetic analysis of two large kindreds with intracranial aneurysms demonstrates linkage to 11q24-25 and 14q23-31. Stroke; a journal of cerebral circulation. 2006 Apr;37(4):1021-7. PubMed PMID: 16497978. Epub 2006/02/25. eng.
22. van der Voet M, Olson JM, Kuivaniemi H, Dudek DM, Skunca M, Ronkainen A, et al. Intracranial aneurysms in Finnish families: confirmation of linkage and refinement of the interval to chromosome 19q13.3. American journal of human genetics. 2004 Mar;74(3):564-71. PubMed PMID: 14872410. Pubmed Central PMCID: 1182270. Epub 2004/02/12. eng.
23. Mineharu Y, Inoue K, Inoue S, Yamada S, Nozaki K, Hashimoto N, et al. Model-based linkage analyses confirm chromosome 19q13.3 as a susceptibility locus for intracranial aneurysm. Stroke; a journal of cerebral circulation. 2007 Apr;38(4):1174-8. PubMed PMID: 17322081. Epub 2007/02/27. eng.
24. Biros E, Golledge J. Meta-analysis of whole-genome linkage scans for intracranial aneurysm. Neuroscience letters. 2008 Jan 24;431(1):31-5. PubMed PMID: 18069126. Pubmed Central PMCID: 2267929. Epub 2007/12/11. eng.
25. Ruigrok YM, Rinkel GJ, Wijmenga C. Genetics of intracranial aneurysms. Lancet neurology. 2005 Mar;4(3):179-89. PubMed PMID: 15721828. Epub 2005/02/22. eng.
26. Ruigrok YM, Elias R, Wijmenga C, Rinkel GJ. A comparison of genetic chromosomal loci for intracranial, thoracic aortic, and abdominal aortic aneurysms in search of common genetic risk

factors. Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology. 2008 Jan-Feb;17(1):40-7. PubMed PMID: 18160059. Epub 2007/12/28. eng.
27. Foroud T, Sauerbeck L, Brown R, Anderson C, Woo D, Kleindorfer D, et al. Genome screen in familial intracranial aneurysm. BMC medical genetics. 2009;10:3. PubMed PMID: 19144135. Pubmed Central PMCID: 2636777.
28. Krischek B, Inoue I. The genetics of intracranial aneurysms. Journal of human genetics. 2006;51(7):587-94. PubMed PMID: 16736093. Epub 2006/06/01. eng.
29. Nahed BV, Bydon M, Ozturk AK, Bilguvar K, Bayrakli F, Gunel M. Genetics of intracranial aneurysms. Neurosurgery. 2007 Feb;60(2):213-25; discussion 25-6. PubMed PMID: 17290171. Epub 2007/02/10. eng.
30. Wang Y, Barbacioru CC, Shiffman D, Balasubramanian S, Iakoubova O, Tranquilli M, et al. Gene expression signature in peripheral blood detects thoracic aortic aneurysm. PloS one. 2007;2(10):e1050. PubMed PMID: 17940614. Pubmed Central PMCID: PMC2002514. Epub 2007/10/18. eng.
31. Mutez E, Larvor L, Lepretre F, Mouroux V, Hamalek D, Kerckaert JP, et al. Transcriptional profile of Parkinson blood mononuclear cells with LRRK2 mutation. Neurobiology of aging. 2011 Oct;32(10):1839-48. PubMed PMID: 20096956. Epub 2010/01/26. eng.
32. Schipper HM, Maes OC, Chertkow HM, Wang E. MicroRNA expression in Alzheimer blood mononuclear cells. Gene regulation and systems biology. 2007;1:263-74. PubMed PMID: 19936094. Pubmed Central PMCID: PMC2759133. Epub 2007/01/01. eng.
33. Pluta RM, Hansen-Schwartz J, Dreier J, Vajkoczy P, Macdonald RL, Nishizawa S, et al. Cerebral vasospasm following subarachnoid hemorrhage: time for a new world of thought. Neurological research. 2009 Mar;31(2):151-8. PubMed PMID: 19298755. Pubmed Central PMCID: PMC2706525. Epub 2009/03/21. eng.
34. Dumont TM, Rughani AI, Tranmer BI. Prediction of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage with an artificial neural network: feasibility and comparison with logistic regression models. World neurosurgery. 2011 Jan;75(1):57-63; discussion 25-8. PubMed PMID: 21492664. Epub 2011/04/16. eng.
35. Koenig MA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. Continuum (Minneapolis, Minn). 2012 Jun;18(3):579-97. PubMed PMID: 22810250. Epub 2012/07/20. eng.
36. Muench E, Horn P, Bauhuf C, Roth H, Philipps M, Hermann P, et al. Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. Critical care medicine. 2007 Aug;35(8):1844-51; quiz 52. PubMed PMID: 17581487. Epub 2007/06/22. eng.
37. Schneider UC, Dreher S, Hoffmann KT, Schmiedek P, Kasuya H, Vajkoczy P. The use of nicardipine prolonged release implants (NPRI) in microsurgical clipping after aneurysmal subarachnoid haemorrhage: comparison with endovascular treatment. Acta neurochirurgica. 2011 Nov;153(11):2119-25. PubMed PMID: 21858650. Epub 2011/08/23. eng.
38. Bijlenga P, Czosnyka M, Budohoski KP, Soehle M, Pickard JD, Kirkpatrick PJ, et al. "Optimal cerebral perfusion pressure" in poor grade patients after subarachnoid hemorrhage. Neurocritical care. 2010 Aug;13(1):17-23. PubMed PMID: 20405341. Epub 2010/04/21. eng.
39. Budohoski KP, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, Bulters D, et al. Impairment of Cerebral Autoregulation Predicts Delayed Cerebral Ischemia After Subarachnoid Hemorrhage: A Prospective Observational Study. Stroke; a journal of cerebral circulation. 2012 Nov 13. PubMed PMID: 23150652. Epub 2012/11/15. Eng.
40. I save my life. Available from: http://www.isavemylife.com.
41. contributors W. Quantified SelfOctober 4, 2012 October 6, 2012. Available from: http://en.wikipedia.org/w/index.php?title=Quantified_Self&oldid=515981266.
42. contributors W. Google HealthSeptember 1, 2012 October 6, 2012. Available from: http://en.wikipedia.org/w/index.php?title=Google_Health&oldid=510226052.
43. Rajiv M, editor. The Future of Healthcare: Innovation at the Edge. The Health Informatics Society of Australia 2012; 2012 30 July - 2 August 2012; Sydney.

11.Aknowledgments

I would like to thank:

Prof N de Tribolet who trained me in neurosurgery and taught me the art of decision making, stimulated my curiosity and supported my research.

Prof D Rüfenacht who initiated the @neurIST project with some other project board members and trusted me, inviting me to join the @neurIST adventure as a member of the project board and leader of the biomedical data collection and integration.

All project board members, Alex Frangi, Rod Hose, Guy Lonsdale, Martin Hofmann-Apitius, Tony Arbona, Peer Hasselmeyer, Robert Dunlop and again Daniel Rüfenacht. I discovered with them the complexity and enjoyed the unique experience of such a giant and ambitious project. Thank you for the extremely enriching experience having to explain on one side the clinical life, functioning and issues as well as the requirements needed to perform biomedical research and understand all aspects of management, computing, modeling and knowledge extraction from massive amount of complex data.

The management team Gina Alioto, Aurelio Ruiz, Toshiyasu Ichioka "Itchi" always behind everything, working hard to keep thing on track teaching management skills, supporting and requesting loud what should have been done yesterday. Thank you for your diplomacy and friendship.

All the members of the @neurIST biomedical data collection and integration work packages,

Paul Summers who assisted me setting up and managing the workpackage, worked extremely hard for the @neurIST study protocol and performed most of the quality control. It was a great pleasure to work and meet together.

Jimison Iavindrasana, Nicolas Roduit, Francis Klumb, Rodolphe Meyer, Alan Waterworth and Steven Wood, all members of the team writing the codes to allow the collection of clinical information and imaging and then transforming data sets to be accessed from the "@neuInfo system" and generate the distributed database of @neurIST.

Jessica Wright, JeremyWilkins, Bernice Elger and Derick Beyleveld the team supervising and checking best practice was followed in clinical research, discussing and solving all kinds of ethical and legal questions that arose during and after the project.

Saliha Yilmaz, John McGregor who opened my eyes over the world of gene expression and opened a fascinating futuristic avenue for diagnostic tools.

Sophie Collot-Teixeira, Carole Proust, François Cambien, Murat Gunel for the performance of genotyping almost 1000 samples in a few months and pooling thousands of genomes to identify loci associated with the presence of sporadic intracranial aneurysms.

Mike Clark from whom I learn the basic principles of a Cochrane review.

Miriam Sturkenboom from whom I learn the basic principles of epidemiology.

Christian Ebeling, Christophe M Friedrich and Martin Hofmann-Apitius behind the @neurIST data merging systems and @neuLink suite that I enjoyed using to search for genetic loci, genes and all

kinds of risk factors browsing all data on the web. Also thak you both for providing the @neuBrowser, the tool that visualize the content of the data base and allows to explore the disease as never before. Thank you for having provided a wonderful observation tool I call the “diseasescope”, the tool that allows you to observe a disease like a microscope and a telescope magnify what can’t be seen with the naked eye.

My dear colleagues: Alain Reverdin, Ivan Radovanovic and Karl Schaller who were managing and operating neurosurgical vascular patients in emergency when I was travelling. My neuro-interventionists colleagues Hasan Yilmaz, Zolt Kulcsár, Daniel Rüfenacht, Vitor Mendes Pereira, Ana Paula Narata and Ana Marcos Gonzales with whom we organised a common outpatient consultation for neurosurgical vascular diseases and with whom we always managed to have a multi-disciplinary meeting before treating any patient whatever the time of the day. I also would like to thank Shahan Momjian, Enrico Tessitore, Benoit Jenny, Asita Sarrafzadeh and Benedict Rilliet with whom I interacted daily in neurosurgical care. Finally last but not least Yvan Gasche, Paulo Merlani, Déborha Pugin, the team of neuro-intensivists I enjoy working with and debating.

My colleagues in the field outside Geneva: Juan Macho, James Byrne, Jordi Blasco Stuart Coley, Tamas Doczi, Elio Vivas, Teresa Sola, Umang Patel, Pankaj Singh who all participated in the design and collection of information for the @neurIST project besides treating patients.

All residents that spend some time in the Service de Neurochirurgie in Geneva and those how spend a lot of time obtaining consents from patients and dealing with the @neurIST digital forms to introduce the data in the database.

Thank you also to my MD-PhD thesis mentors Charles R. Bader and Laurent Bernheim. With them I experienced the contrast between searching and building knowledge exploring biological mechanisms and applying knowledge to treat patients. The gap is huge between two universes working at different scales and with different time lines. Two universes populated by very different communities. It reinforced my motivation to bridge the gaps between basic and clinical research.

Dear Carlo, thank you for the immense work you perform every day fructifying the heritage you received. You manage, organize, transform, revolutionize, correct, teach, treat and listen. You involve yourself and promote us globally as well as at the European and Swiss level. You build a team and we are proud to be part of it.

Thank you to my family, my parents, my wife Nathalie, my daughter Lara and my son Léonard who enlighten my life. Thank you for the resilience and the tolerance you all have and the support you offer to give me the opportunity to invest as much time and energy in my work.