



International Conference on Computational Science, ICCS 2011

# Towards a Virtual Research Environment for International Adrenal Cancer Research

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## Abstract

For many research areas, the need to collaborate across organizational and in certain cases national boundaries is essential. This is especially the case when dealing with rare diseases where a lack of data, information and/or sharing of expertise can cause delays in progressing the understanding and potential diagnosis/treatment of such diseases. Research into adrenal tumours is one such area where co-ordination of international cancer efforts is essential. The *European Network for the Study of Adrenal Tumours - Structuring clinical research on adrenal cancers in adults (ENS@T-CANCER)* project has recently been funded by the European Union to establish a state of the art Virtual Research Environment (VRE) supporting all aspects of international research and collaboration into the aetiology, diagnosis and establishing optimal treatment strategies for patients with adrenal cancer. It is envisaged that this VRE will comprise a portfolio of clinical databases for the different types of adrenal tumours that exist; support and integrate a seamless federation of adrenal tumour bio-banks with support for bio-sample tracking; support a wide range of *-omics* research into adrenal tumours and allow results to be shared amongst collaborators; offer advanced visualization services, and support several large-scale clinical trials comprising cohorts of patients with different kinds/treatments of adrenal tumours. This paper outlines the goals of the ENS@T-CANCER project and outlines the on-going implementation work. We show how security-oriented information can be collected and tracked through the VRE including supporting collection of clinical data sets and their linkage with associated bio-samples in an ethically-driven framework.

Keywords: Adrenal Tumours; biobanks; virtual research environments; ethics;

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## 1. Introduction

The combination of post-genomic research now possible through high throughput genomic data generation technologies coupled with the continued growth and application of the Internet and the associated scaling of hardware/software solutions to cope with the data deluge have lead to a maelstrom of research possibilities in the health/e-Health arena. The possibilities for *in-silico* biological research and move towards personalized e-Health medicine and treatment are now well documented [1,2]. However the possibility to collect and manage increasingly voluminous and heterogeneous individual-level clinical and biomedical data also raises numerous challenges and

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requirements that must be addressed on technologies and IT solutions put forward: ethics; information governance; confidentiality and the need for scientifically and ethically justified clinical research are paramount [3]. These issues are made increasingly complex when dealing with international biomedical research where different countries have different processes and structures for defining and enforcing ethically-driven research. As such, it is essential that research and information technology platforms visibly and overtly address the needs of the national bodies tasked with the responsibility with deciding whether a given research project is in the interest of the individuals involved and meets the national governance/legal demands on clinical/biomedical data access and usage, as well as meets the international demands of researchers wishing to conduct ethically-driven research.

There are numerous precedents that have already shown how successful international e-Health collaboration can be supported [4-6]. However the scope and scale of these projects has by and large, only focused on a subset of the demands facing the clinical/biomedical research community, and the actual translational impact of these systems into clinical care has more often than not, not been fully achieved. The ENS@T-CANCER project is a 5-year project that covers the breadth and depth of post-genomic biomedical research platform requirements covering establishment of clinical databases of individuals with different forms of adrenal cancer; biobanks for storing and labeling/tracking of biosamples from patients to be used by biomedical (omics) researchers; visualization support for improved understanding and analysis of the forms of tumours and their potential metastases, and importantly, support for large scale clinical trials where patient cohorts are recruited and used to test out the impact of targeted treatments based upon their genetic profiling.

This paper describes the background to the project as a whole and outlines the current work in progress. In section 2, we present background to adrenal tumours; the need for an international adrenal tumour network and outline the scope and involvement of the wider clinical/biomedical research community. In section 3, we focus on the implementation of the current adrenal cancer databases and how they are being used for a range of studies into adrenal cancer. In section 4, we outline the way in which the ENS@T-CANCER biobanking capability will be supported and describe how patient biosamples are linked and tracked with individual level patient data sets. Finally we describe the clinical trials that are planned and the way in which these will be supported in a user-driven, secure environment.

## 2. Background to Adrenal Tumours

The adrenal glands (the adrenal) are located in close vicinity to the upper kidney poles. The weight of the adrenals in adults is approximately 4g and is not affected by an individual's age, body weight or sex. The adrenal consists of two functionally distinct glands covered by a common capsule. The adrenal cortex is the outer layer of the adrenal gland and makes up approximately 90% of the adrenal weight. In the cortex, adrenal steroids such as the stress hormone *cortisol*, the blood pressure hormone *aldosterone* and adrenal androgens are produced. The adrenal medulla is located in the inner part of the adrenal gland. Within the medulla, the catecholamines *epinephrine* and *norepinephrine* are produced.

Both the adrenal cortex and medulla play an essential role in the body's adaptation to major stress. For example, in response to severe infection, trauma and shock, an individual's adrenal gland will, under normal circumstances, secrete enhanced amounts of cortisol and catecholamine. This response is necessary to maintain homeostasis during stress. In case of adrenal impairment, the stress response will be severely diminished and can ultimately lead to irreversible shock and in some cases death.

Tumours of the adrenal glands can arise in both the cortex and/or the medulla part of the adrenal gland. Typically, tumours from the adrenal cortex produce excess of steroid hormones including cortisol and aldosterone whilst tumours from the adrenal medulla produce excessive amounts of catecholamines. Adrenal tumours can be either benign or malignant. Often this separation is difficult to make through imaging analysis and requires a variety genetic analysis to determine. While malignant tumours of the adrenal gland are rare, up to 5% of the population can have so called adrenal *incidentalomas* - tumours of the adrenals found incidentally during investigation for an unrelated condition. The majority of these do not secrete hormones [7].

There are four primary adrenal tumour subtypes: aldosterone producing adenomas (APA); Pheochromocytomas and Paragangliomas (Pheo/PGL); Non-aldosterone cortical adrenal adenomas (NAPACA), and Adrenocortical carcinomas (ACC). Each of these subtypes has different manifestations; involves different molecular mechanisms and ultimately requires different treatment regimes for optimal patient care.

### 2.1. Aldosterone Producing Adenomas (APA)

Primary aldosteronism caused by aldosterone producing adenomas is the most frequent form of secondary hypertension accounting for more than 11% of referred hypertensive patients [8] and gives rise to conditions such as Conn's syndrome [9]. Despite the relatively high prevalence of primary aldosteronism, the molecular mechanisms underlying excess aldosterone production remain unknown. Whilst computed tomography and/or magnetic resonance imaging are often used to detect the adenoma and/or aldosterone-producing carcinoma, these can give misleading results regarding the precise cause of excess aldosterone.

### 2.2. Pheochromocytomas (PHEO) and Paragangliomas (PGL)

Catecholamine-producing tumours may arise in the adrenal medulla (pheochromocytomas) or in extra-adrenal chromaffin cells (paragangliomas). Their prevalence is about 0.2% in patients with hypertension [10] and 4% in patients with an incidentally discovered adrenal mass [11]. The tumours themselves may be sporadic or may present as part of any of several genetic syndromes, e.g. von Hippel-Lindau disease [12]. About 10% of tumours are malignant either at first operation or during follow-up, malignancy being diagnosed by the presence of metastases at sites where chromaffin cells should be normally absent, e.g. bones, liver, lungs, lymphnodes.

### 2.3. Non-aldosterone cortical adrenal adenomas (NAPACA)

Non-aldosterone secreting cortical tumours represent the most common benign adrenal tumour. These may be truly non-functioning, i.e. not associated with any hormonal excess, and are usually detected incidentally in patients undergoing radiological investigations (ultrasound, CT, MRI scanning) for other reasons. Malignancy rate in these lesions is very low - the majority of lesions are less than 3cm in diameter and can be treated conservatively [13].

Rarely the tumours may secrete cortisol. In the most florid example, Cushing's syndrome results and includes muscle wasting, thinning of the skin with bruising, osteoporosis, hypertension and diabetes mellitus. Removal of the adenoma is required to cure the condition. More rarely patients may have a genetic problem that results in autonomous production of cortisol from adenomas within the adrenals, e.g. McCune Albright syndrome [14]. The adrenals may also become tumorous when the adrenal glands develop an unusual pattern of receptor expression over and above the normal receptor that controls cortisol production.

### 2.4. Adrenocortical Carcinomas (ACC)

Adrenocortical carcinoma is a rare malignancy with incompletely understood pathogenesis and poor prognosis. Patients typically present with hormone excess through a given condition, e.g. Cushing's syndrome, or more often than not, a local mass that is incidentally discovered (median tumour size > 10cm). In patients not amenable to surgery, the drug *mitotane* remains the treatment of choice [15]. Monitoring of drug levels is mandatory for optimum results in patient treatment, especially when combined with other forms of treatment, e.g. radiotherapy. It is currently the case that postoperative disease free survival (at  $t \geq 5$  years) for patients with ACC is below 50% [16].

Given the rarity of the above kinds of adrenal tumours, the availability of a large collection samples, with associated clinical, biomedical/-omic data and accompanying treatment information is essential to better understand the differentiators of these tumour types; their aetiology and their associated molecular mechanisms. This would allow development of optimal treatment strategies tailored to individuals. A common platform that facilitates the collection and analysis of such samples and related clinical/biomedical information is thus highly desirable and is the focus of the ENS@T-CANCER project.

## 3. ENS@T Project

The European Network for the Study of Adrenal Tumours (ENS@T – [www.ensat.org](http://www.ensat.org)) was founded in 2002 from

a grant by the European Science Foundation by putting together three already existing national adrenal networks: COMETE in France, GANIMED in Germany, and NISGAT in Italy, along with teams from the United Kingdom all dedicated to the study of adrenal tumours. A core part of the scientific efforts of the ENS@T network has been based on the establishment of a common registry and associated standardized description of information related to the different types of adrenal tumours. The data models themselves have been developed throughout the course of the ENS@T network. These data models follow a similar form including a single patient/clinical information sheet and numerous related information sheets on biomaterials; follow-up; pathology; treatments; diagnostic procedures and tumour staging information as shown in Fig. 1.

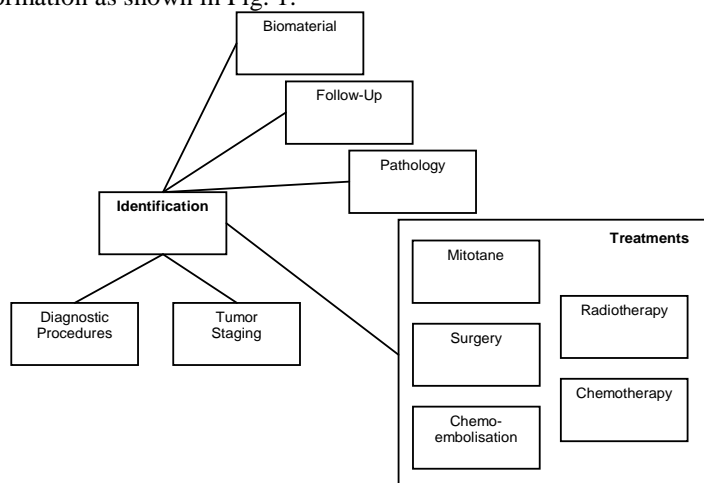


Fig. 1. Overview of the ENS@T Data Model Structure

Historically much of this information was collected in a country specific manner and did not encompass all adrenal tumour types or all related information required. Thus in France, much work was done in the collection of data sets related to ACC patients. A non-web based database was developed and physically distributed to collaborating partners (on a CD). It was recognized by the ENS@T network that an improved model of data collection and distribution was required. To this end, in 2009 the National e-Science Centre (NeSC) at the University of Glasgow ([www.nesc.ac.uk](http://www.nesc.ac.uk)) was appointed to realize a registry comprising four web-based clinical databases representing each of the adrenal tumour types identified previously and incorporating the extended data model shown in Fig. 1. The implementation of these databases was undertaken in a rapid prototyping manner and exploited the body of expertise in security-oriented web based software development expertise of NeSC. This work began in November 2009 and was completed within three months and is described in [17]. As discussed in [17], in undertaking this work it was important to recognize that all of the data models had been designed so that they were, to as great a degree possible, independent of patient specific/identifying information. Thus the *Identification* form only required information such as the year of birth and the sex of the individual, along with an identifier for the clinical centre that was responsible for dealing with the case itself (this may be where the patient is being treated directly or where they have been referred to). Upon completion of this form, i.e. when entering a given case, a unique ENS@T-specific identifier is created. It is this identifier that is used to link with all of the associated information sheets. The generated identifier is the only link to the patient's actual identity and requires a mapping file residing at the patient's hospital to establish that relationship. This anonymisation through data linkage based model satisfies the information governance requirements of the key protagonists involved and is in line with patient-protecting legislation such as the UK Data Protection Act (1998) [18].

Furthermore, since it was recognized that there would be multiple individuals in multiple countries, a protocol was defined for the naming convention to be used in the generation of ENS@T-specific patient identifiers. These identifiers follow a standard format: <Study Number>:<Subject Group>:<Country>:<Center>:<Subject Number>. As an example of this, the automatically generated identifier *IVFRPA3001* would indicate an identifier for an individual for study "1", who was a "Volunteer", from "France", at clinical centre "3" in "Paris" with identifier "001", i.e. this is the first patient registered from that centre. Other country-specific and centre specific

codes were defined and fully implemented for the patient specific identification information. This classification system has been design to be flexible and extensible.

Through follow up information, sites are able to update and track the information and data sets associated with any individual patient. The user interface for creating an ACC patient record is indicated in Fig. 2.

Fig. 2. ENS@T ACC Record Creation

It should be noted that the web-based registry supports an n-tier service architecture where user interface logic, e.g. the interface given in Fig. 2 is augmented with services (logical layer) that enforce rules on access and usage of the associated data (data layer). Each of these layers has associated security levels that restrict access to and usage of the associated data sets to individual authorized individuals. The technologies that have been applied to define and enforce this access control are described in more detail in [19-21]. In brief these exploit, role based access control solutions augmented with user defined security information. As an example of this, an ENS@T clinician is able to define the level of access to their centre's patient data records. Thus for example, through ethical considerations it might only be appropriate for a clinician to allow access to the patient details for biomedical researchers from that clinic; or for researchers in that country; for researchers across the recognized ENS@T community, or indeed for wider international researchers investigating adrenal tumours. This pull down menu option is illustrated in Fig. 2. It should also be recognized that obligations on defining the appropriate level of access control to data sets is left with the clinicians themselves, i.e. they are completely autonomous in deciding whether to share a data set with local, national or international collaborators. It is also the case that once a record is added to the registry, it can only be modified by that data owner, i.e. the contributing clinician.

The registry supports several basic capabilities: adding clinical/biomedical records and associated information; searching for records based on a set of given criteria, and support for export of data to different formats – typically CSV files so that they could be included in “local” statistical analysis software or spreadsheets. To leverage the historic data sets collected through the previous networks (COMETE, GANIMED and NISGET), existing data sets were directly incorporated into the ENS@T registry. These were extended and harmonized across the different adrenal tumour types to provide a consistent data model (aligned with Fig. 1). This extension has been an iterative process, where prototypes of the registry and the web-based data models were used as the basis for community wide consultation and agreement, i.e. the existing data models were not absolutely agreed and defined for all adrenal tumour types.

Data validation was directly supported in the registry through use of compulsory and optional fields; ensuring logical information was given, e.g. the year of birth was not in the future etc, and wherever possible use of predefined pull down menus lists and options - as opposed to support for text boxes for arbitrary information. This helped to standardize the information that is given as well as well as simplify the data searching models.

In essence the registry provides a security-oriented matchmaking service. Biomedical (-omic) researchers who wish to better understand the molecular mechanisms of different forms of adrenal tumours require access to

biomedical samples. Clinicians dealing with patients in hospitals are the primary source of such biosamples. Knowledge that a given ACC patient has been undergoing a course of treatment and their response to this treatment is an extremely valuable set of information that should ultimately guide clinical practice. However, in the post-genomic era it is now the case that the biomedical ('omic) analysis of samples from patients can lead to novel insights, treatments and molecular understanding through leveraging post-genomic models and technologies. This in turn demands international co-ordination and cooperation. The ENS@T work demonstrated such international coordination and cooperation and ultimately culminated in a major 5-year European Union proposal to establish a broader framework for adrenal tumour research: ENS@T-CANCER.

#### 4. ENS@T-CANCER Project

The ENS@T-CANCER project involves fifteen clinical/biomedical partners from across Europe and a single software provider: the University of Melbourne tasked with developing, supporting and maintaining the VRE. It is worth noting that the University of Melbourne is involved due to the relocation of the Director of NeSC to Melbourne along with core NeSC staff involved in the ENS@T project. The work on ENS@T-CANCER builds directly upon the ENS@T work to incorporate a richer and more extensive variety of clinical and biomedical data sets, bioinformatics support, imaging and visualization capabilities, and the conduct of several major clinical trials.

The VRE is the central point of all adrenal tumour research. Through the VRE biomedical researchers will be able to discover cases of interest and *in principle* have access to biosamples for analysis. This point has direct impact upon ethics. Whilst the ENS@T-CANCER project builds upon the ethical framework for recruiting patients into the ENS@T registry, given that tissue/biosamples will potentially be distributed to international collaborators a more demanding ethical framework is required. At the outset of data collection, the patient's themselves need to be fully informed of the clinical and potential research use of their data sets, i.e. the system design is based upon informed consent being established. The patient will be informed that he/she is free to interrupt and/or withdraw from any resultant ENS@T-CANCER study at any time without stating the reasons. Importantly, the patient will be reassured that their clinical management will not be affected by their decision to take part or not to take part in any related study. Exchange of biosamples places unique demands on the coordination and linkage of information within the VRE and the way in which ethics is realized.

##### 4.1. ENS@T CANCER Biobank Support and Secure Data Linkage

The linkage between patient identifiers in the ENS@T-CANCER registry, e.g. *IVFRPA3001*, and identifiers used for biomaterials needs to be both distinct and completely separated, i.e. it should never be possible to directly identify (through a given software query or direct observation of a particular software system) that a particular sample comes from a particular patient through use of the registry or other related IT system. However, it is equally important that the identifiers for individuals and for biosamples from those individuals are unambiguously related, i.e. there should be a direct mapping that exists between all samples and an individuals record. A range of biosamples have been identified that will be collected throughout the ENS@T-CANCER project that need to be stored, exchanged and ultimately tracked through the VRE as listed in Table 1 along with the shorthand codes used.



In the first instance (1.) a patient (*Mr X*) arrives at a clinical hospital – in this case in Paris, France with symptoms that might indicate a particular adrenal tumour mass. After further investigation and subsequent operation, the tumour is removed and sent for analysis at the local research laboratory associated with this hospital in Paris. The centre will typically (2.) generate their own local identifiers (*XYZI23*) used for sample management and tracking within the laboratory. This label is typically added to the test tubes/sample dishes in which the sample is stored (3.). Following analysis, it is established that the sample is a form of ACC and the clinician/hospital is subsequently advised of this (4.). After discussions with the patient, in addition to the treatment that they will receive, they are advised of the on-going research within the ENS@T-CANCER project. Subject to their acceptance (consent) to be involved in project, the clinician enters (5.) related information on the case into the ENS@T-CANCER registry (the ACC database). This includes the range of information outlined in Fig. 1. After completion of data entry, a unique identifier (*IPFRPAI-3*) is generated through the registry that the clinician keeps a local record of, i.e. this is the 3<sup>rd</sup> patient that this clinician has registered from his centre in Paris. The clinician advises the local research laboratory of this and they use the ENS@T-CANCER VRE to generate a unique identifier (*IPFRPAI-3TUM001*) for this patient's sample (6.) and attach this to the locally kept test tube/dish holding the sample (potentially alongside other local identification systems used). For simplicity we only consider the tumour tissue sample here (TUM) and do not consider the numerous other sample/types codes that would typically be collected as outlined in Table 1. This research laboratory is responsible for keeping track of the link (7.) between the ENS@T-CANCER generated identifiers (*IPFRPAI-3TUM001*) and the local in-house identifiers that are used (*XYZI23*) – which as stated, may include patient identifying information.

At some later point in time, a biomedical research involved in the ENS@T-CANCER project at the University of Birmingham, searches (8.) the ENS@T-CANCER registry for ACC patients that have particular characteristics, e.g. for individuals on certain courses of treatments; with different stages of metastases etc. Assuming a match is found and possibly after further direct follow up with the clinician involved (9.), a request is made for access to a particular biosample from this patient for further analysis. Assuming that ethic approval for such a data transfer has been agreed, a biosample (typically a portion of the tumour that was previously removed) is sent from the laboratory in Paris to Birmingham (10.). The request and sending/receipt of the biosample are registered and tracked in the VRE (11.) including information on the sender, requestor and sending/arrival times, along with the nature of the sample itself – in this case a tumour sample. The biomedical researcher at the University of Birmingham undertakes various analyses on the sample, e.g. proteomics analysis, and once completed, feeds this information back into the VRE (12.) for corroboration with the wider research community. Where consensus has been established regarding the findings of the analysis, this new information derived from the patient sample can potentially be used to directly impact upon the clinical care and treatment that the patient is currently receiving (13.).

In this scenario, at no time is any patient identifying information sent or received outside of the local hospital systems in Paris. The researchers in Birmingham do not need to know any further details regarding the patient other than that provided by the biosample itself and the information present in the registry. Furthermore the knowledge of sending and receiving of tissue samples is tracked and fully disclosed and available to future auditors. This is an essential component of the work to ensure that all aspects of ethically motivated and ethically driven research are being conducted. This includes paying due diligence to data privacy and information governance – both digital and physical.

The existing registry is based on an n-tier architecture, implemented in JSP using a Tomcat 7 container, connected to a MySQL database. Standard infrastructure security is applied (firewall port lockdown, container run using “default-deny” security policies, stealthed Internet visibility, etc). Programmatic security is also applied within the application code itself – consisting of SQL injection and byte-code input protection, input parameter inspection and session expiry after 15 minutes of inactivity. Auditing and tracking tools are implemented within the code for specific queries, and using standard tools such as Statcounter [26] and Google Analytics [27].

To implement the actual linkage described in Fig. 3, the VANGUARD solution will be used (Virtual ANonymisation Grid for the Unified Access of Remote Data-sets). This is an infrastructure based on the wrapped interconnection of messages between a viewer and a set of data guardians, mediated by agents, which – using a series of asymmetric encryption steps – are capable of joining returned results without ever viewing the data itself (subject to policies agreed between the parties involved). Figure 4 shows the conceptual implementation of the encrypted messages involved – for more details see [20].



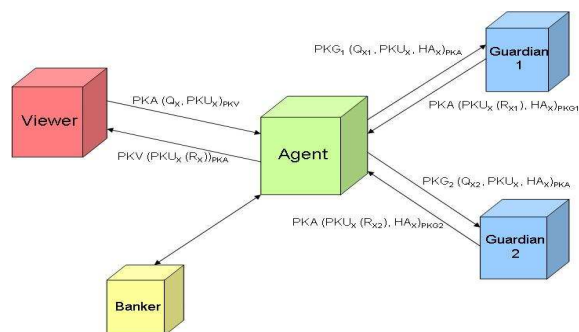


Fig. 4: The process of encrypted data returned to a viewer from a set of guardians, mediated by an agent and monitored by a banker component. Q = query, PK = public key of component, PK (subscript) = private key of component, H = identification hash to maintain consistency of returned results.

## 5. Conclusions

The ENS@T-CANCER project is now formally starting and will directly shape major research efforts in the area of adrenal tumour research. A key aspect of the work that will be undertaken will be the conduct of two major clinical trials: FIRSTMAPP and ADIUVO, both of which have been sponsored by major pharmaceutical companies to evaluate the drugs *sunitinib* [22] and *mitotane* and their effectiveness for Pheo/PGL and ACC patients respectively. Indeed, since the project has been funded other clinical trials have been identified by partners that have been agreed. The critical mass of patients and patient information is key to supporting this process and is difficult to achieve without international collaborative efforts. For example, a study regarding Prospective Monoamine-Producing Tumors that has been agreed will require a Phase 1 patient cohort of 2500 for diagnostic screening. After Phase 2 biochemical confirmation this will result in a potential 400 patients of which it is statistically expected that 200 patients will be diagnosed with the particular disease. The population of the ENS@T-CANCER registry databases is essential to undertaking such large scale clinical studies. The electronic case report forms (eCRFs) for this study and the related FIRSTMAPP and ADIUVO trials together with their various phases, will be directly incorporated into the VRE.

The work that has been undertaken thus far in ENS@T and now starting in ENS@T-CANCER is largely based on establishment and support of external web-based systems, i.e. outside of particular hospital environments. Another possibility would be to support automatic extraction of patient information directly from hospital/biomedical research laboratory systems or indeed supported federated access to patient data existing within hospital/clinical data management systems. Whilst technically feasible, the challenges in undertaking this model of data collection are considerably greater than the approach put forward here. These challenges are largely based around working with disparate IT personnel and policy makers. Such experiences have been captured in numerous projects and related efforts, e.g. [23-25]. Major efforts are currently on-going in many countries to address the challenges in access to distributed, heterogeneous clinical data sets, e.g. the National Program for IT within the UK major UK Connection for Health effort.

Whilst the work on ENS@T-CANCER is very much on-going, it is the case that the project has applied for and received ethical approval for the work. This process involved the drafting of an ethical approval document outlining the work as a whole; the need to exchange biosamples; the risks to the patient; the information to be made available to the patient; the kinds of data that would be collected; and the way in which the system would protect patient information. This document has subsequently been translated into various languages and presented by the clinical/biomedical partners to their associated national ethical committees. At present numerous partners have had acceptance/ethical approval for the project and are subsequently able to share clinical and biomedical data.

At the current time, the ENS@T-CANCER registry includes records on 133 patients with ACC of which 125 patients are alive, and 60 cases have existing biosamples that can be exchanged. The registry also contains information on 50 patients with Pheo/PGL of which all are currently alive and two have biosamples that have been collected and can be exchanged.

## Acknowledgements

The *European Network for the Study of Adrenal Tumours - Structuring clinical research on adrenal cancers in adults* (ENS@T-CANCER) project has been funded under the European Union Framework 7 Health initiative (grant agreement no: 259735) and by the European Science Foundation (ESF). We gratefully acknowledge their support.

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**Title:**

Towards a Virtual Research Environment for International Adrenal Cancer Research

**Date:**

2011-01-01

**Citation:**

Sinnott, R. O. & Stell, A. J. (2011). Towards a Virtual Research Environment for International Adrenal Cancer Research. Sato, M (Ed.) Matsuoka, S (Ed.) Sloot, PMA (Ed.) VanAlbada, GD (Ed.) Dongarra, J (Ed.) PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON COMPUTATIONAL SCIENCE (ICCS), 4, pp.1109-1118. ELSEVIER SCIENCE BV. <https://doi.org/10.1016/j.procs.2011.04.118>.

**Publication Status:**

Published

**Persistent Link:**

<http://hdl.handle.net/11343/32652>

**File Description:**

Towards a virtual research environment for international adrenal cancer research