GRID TECHNOLOGY IN TELEPATOLOGY AND PERSONALISED TREATMENT.

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Please, include names of authors, as well as their affiliation and work place!!!!!

SUMMARY

Histopathology requires automation, quality control and global collaborative tools. Usually the PIMS (Pathology information management system) automates samples, images and reports and progressively incorporates the PI (Pathology informatics), the D-PATH (digital pathology), e-PATH (electronic pathology), the PPH (Patho-pharmacology), virtual autopsy (VA) and all type of translational research in the PMIS. Not being subject to a specific standard, quality control follows ISO-13485:2003 on services and medical devices, ISO 17025:2005 on technical aspects; and ISO-15198:2003 for automate and quantifiable procedures that will be affected by the new European Directive on medical devices.

For the non-standardized pathology procedures, consumers' requirements is what define test and calibration procedures. The paper analysed the ***non-standardized procedures****: VS (Virtual Slides), GRID networking and Literature Based Discovery as tools for knowledge discovery of relevant relationships on image-diagnosis and personalized treatments. Standardized procedures available for search and annotation are the ISO/IEC 11179 Information Technology Metadata Registries specification, the ISO/IEC 13250:2003 for topics maps or MPEG-7 & 21 for images and the ISO/IEC 24800-3 for JPEG query search.*

The forthcoming innovations prepare to quality certify the so called "solo-pathology" robotic labs, supported by telepathology to reduce diagnostic errors and carrying out a relevant task on personalized treatment through GRID technology. In this environment the JPEG query search play a relevant role on images which metadata can be annotated on natural language.

KEY WORDS: Patho-informatics, solo-pathology, quality control, automatic-pathology, LBD techniques, MPEG, JPEG, ISO standards, GRID, PIMS.

1 INTRODUCTION

Quality control of the health-care laboratories include: (1) Management requirements according to ISO 9001:20001 norm or its equivalent ISO-13485:2003 (ISO 13250, 2003) for medical devices and services. (2) Technical requirements inside of the ISO 17025:2005 (ISO17025, 2005) norm for testing and calibration, the (3) ISO 15189:2007 or quality and competence of microbiological and clinical laboratories and (4) finally the norm ISO/TS 22367:2008, which are the technical specifications of risk reduction and risk management in laboratories.

The ISO 15189 norm was intended for microbiology and clinical laboratories, peculiar because their reports only have objective results without diagnostic interpretation.

The ISO 15189 includes management issues following ISO 9001 norm and technical issues following ISO 17025 norm. The technical direction responsible of quality-DTC is in charge to define **politics** and **objectives** (Service goal, level of services, Quality objectives) (Gimenez, 2007; SEAP, 2003) including **internal** and **external controls** (instrument calibration, reactive and systems). Everything should be documented in a **quality manual.**

1 Now in course the updating ISO 9001:2009

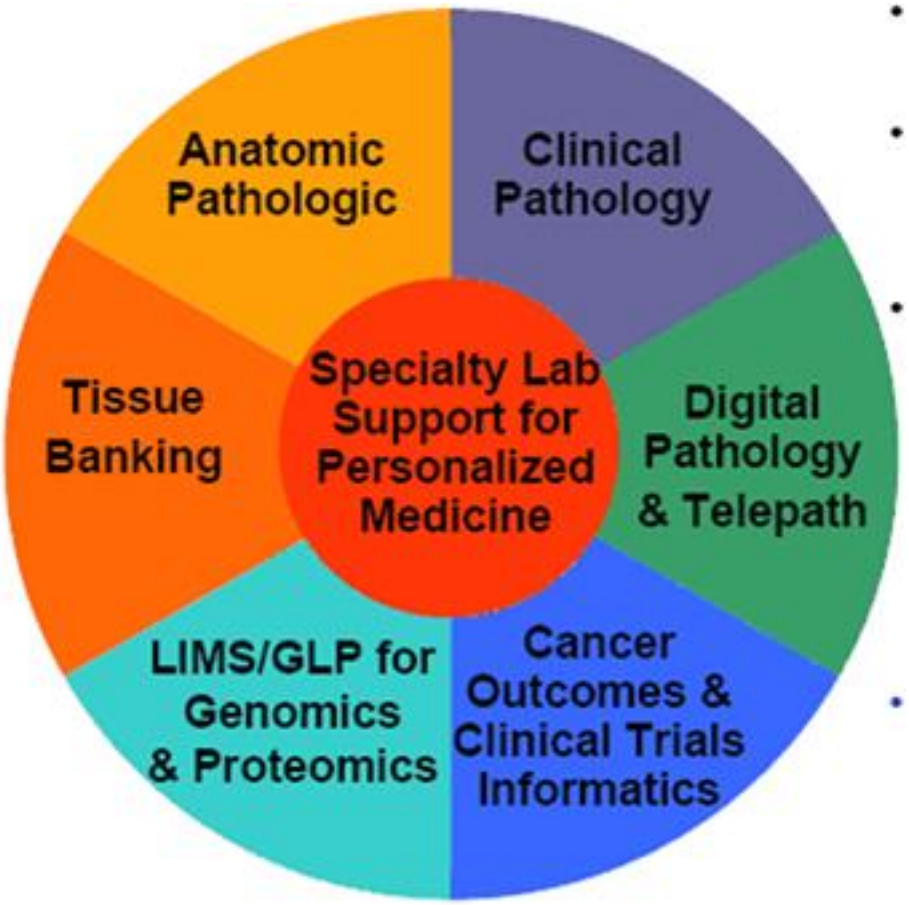

Table I. ISO 15189:2007 Critical points in laboratories.

Nowadays differences between clinical laboratories and pathology departments have shorted due to automation (VLA, 2006; Garcia-Rojo, 1998), quantitative pathology (FISH-HISH-cytogenetic and tumour markers, IHQ etc.) and pharmaco-pathology for therapeutic targets involving or not GRID diagnostic support of distributed computation (Schmitt, 2007).

A pathology department should consider the quality standards and risk management of the new EU directive of medical devices (ISO11073, 2008; IEC60601, 2006; ISO14971, 2007; DIR2007, 2007) together with technical advances of informatics (PI, 2008; Becich, 2008) digital pathology (D-AP) electronic pathology (e-AP), la tele-pathology (TP), virtual autopsy, pharmaco-pathology and translational research on aetiology and physiopathology of the illnesses. On this regard its patho-informatics service will be in charge of the LIS2 (Pearson, 2006)- PIS3 data and specimen flow, of reproducibility and traceability of digital images, of HIS4 and PACS5 integration and of data/image availability for cooperative work (autopsy room, operating theatre of the future etc.), automatic classification and annotation; together with anonymization, biobanking, mining etc. Aspects not yet considered in the pathology competency in some countries (SNCFP, 2005).

2 LIS= Laboratory Information System
3 PIS= Pathology Information System (AP-LIS in UK)
4 HIS= Hospital Information System
5 PACS= Picture archiving and communication systems

To be specific, the patho-informatics started with Tom Lincoln and Don Connelly in the 80s defining theoretical bases. In 1987 Ralph Korpman stressed the role of pathologist in medical informatics systems and in 1990 Bruce Friedman established the term "*pathology informatics*" (PI). At that time 1993 Greg Buffone and Bob Beck propose its sub-speciality in the field of pathology. Finally in 2002, Friedman carried out the first meeting in which the discipline of "*pathology bioinformatics*" was defined inside of the Bioinformatics. Since then, informatics in pathology is taking care of

1- Basis of the illnesses (aetiology-physiopathology) merging pathology, biochemistry and pharmacology (translational research).
2- Patient data security and confidentiality as well as access and responsibility in the clinical environment.
3- Tissue Banks, Management and mission (diagnostic and specimen provision).
4- Data exchange and its standards. Since the main mission of the patho-informatics is translational and interdisciplinary.
5- Web distance access and Management of big longitudinal and relational data bases from standardized clinical and research data.

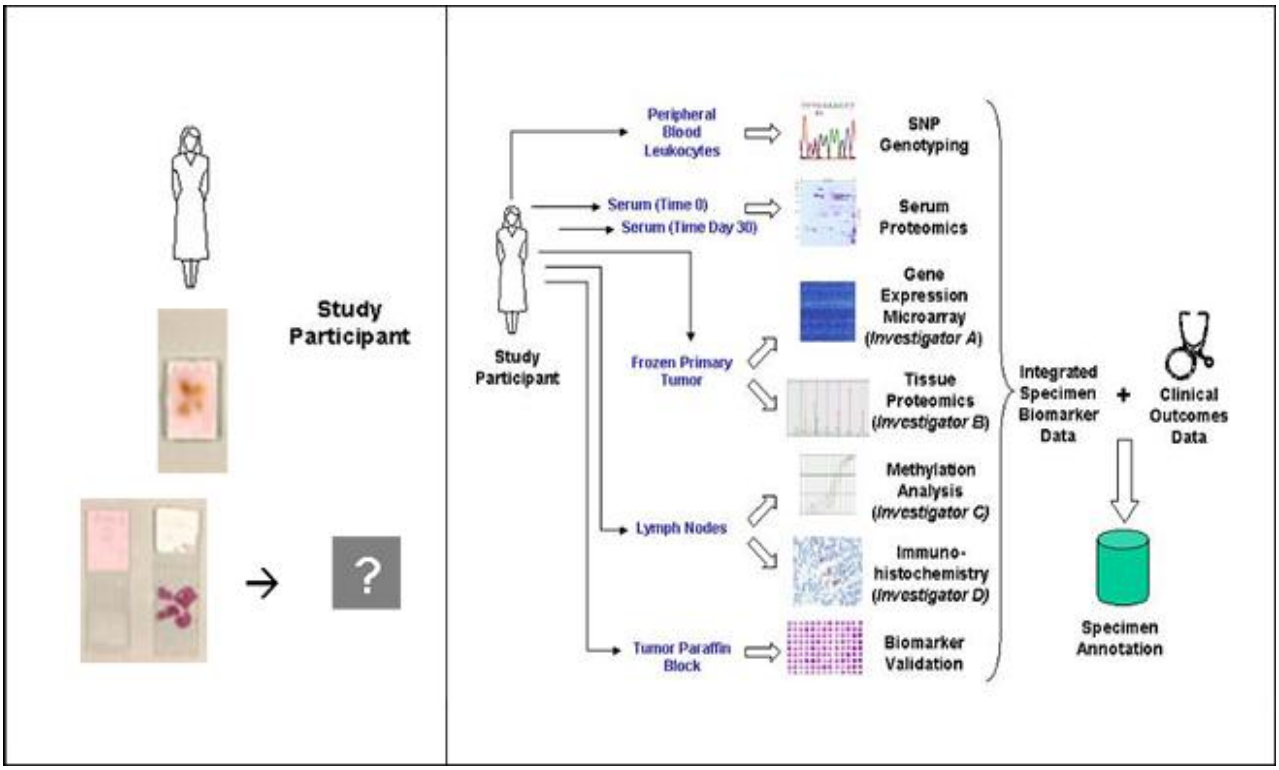

Figure 1. Role of the patho-informatics. GLP= *good laboratory practice*: PIMS= *pathology informatics management system*. from https://cabig.nci.nih.gov/workspaces/TBPT/tbpt-newcomer/workspaces/TBPT/TBPT_Newcomer_Introduction.ppt

But even considering the great number of standards already established most processes required specialists that also have to deal with *Plug & Play* IEEE 11073 standards from nomenclature to wireless transmission, with integrations such the ones of the IHE (*Integrated Health Care enterprise*) and bioengineering topics including telecommunications or medical device requirements.

2 UNE:EN 60601-1:2008, the PESS and telecommunications.

Medical devices (MD) containing one or more electronic programmable subsystems (PESS) are controlled by the UNE EN 60601-1:2008 norm. A PESS in any system based in one or more processing central units including the software and interface.

Software programs are systems almost impossible to completely verify, although requirements are specify in the technical report of medical software risk management AAMI-TIR32, it will be an International version in the IEC 80002. In this case software processes have to be considering special

and require validation before everyday use is allowed, in order to test possible danger for the patient or the operators (IEC 62304:2006). In fact not only have to follow the medical device norms but also have to assure basic security guarantee and functional guarantee.

This means that not only cannot produce danger, but that they have to demonstrate their efficacy.

In the new European directive of medical devices telecommunications are consider part of the MDDS (*Medical Device Data System)*. In the case of integration together with non-medical products, the integrator have to assure that fulfil the IEC 60601-1 norm.

In brief a MDDS is a device that translates data from one medical device to another.

3 THE NEW EU DIRECTIVE D-2007/47/CE

The directives applicable to medical devices (MD) are: D 90/385/EEC – RD 634/93, for active implantable MD (i.e.: pacemakers); D 93/42/EEC – RD 414/96, for general MD including active non-implantable MD (i.e.: x-ray equipments); Directive 98/79/EEC – RD 1662/2000, for MD for "in vitro" diagnosis (i.e: kit for blood glucose testing).

The new directive 2007/47/CE include the new definition of **Medical Device** particularly important in the pathology lab, because it defines any instrument, device or computer program, material or any other article used alone or in combination with others as well as any accessory including software produce by a company *to be used in humans for: (1) diagnosis, prevention, control, treatment o release of a disease; (2) diagnosis, control, treatment or release or compensation of a lesion or deficiency (3) research, substitution or changes of the anatomy or of a physiological process (4) control or regulation of the contraception, which expected action inside or outsider of the human body is not produced by pharmacological, immunologic or metabolic means, but which function can depend of such products.*

For all Medical Devices the CE label is mandatory and therefore not only should be visible in the laboratory devices but also in the software associated to those devices.

Software producers will be responsible during the whole active life of the product. Being a class I or low risk do not require compulsory audits unless there is a formal complain, but being a medical software will be regulated by the IEC 62304:2006 norm.

As soon as the new directive enter into force, around 2010, all software systems should carry a visible CE label and assure warranty of information (no secrecy of how they work and obtain parameters will be possible); of security (have to be previously tested); of functionality (will require a previous validation prior its function in the real world); of quality (the design system should fulfil the ISO-13485 quality design). If this is not fulfil, only could be consider **a demonstrator**.

4 MICRO-MACRO & VIRTUAL SLIDE IMAGES.

In an environment efficiently managed by the PIMS (*pathology information management system*) all macro-micro and virtual slide images should be stored and annotated at least with the SNOMED code extracted automatically from the pathology report created with an automatic dictation system including voice recognition. (García-Rojo, 1998; Liu, 2005; WIPO, 2008)

According our own definition of what is a Virtual Slide (costumer opinion since it is not yet standardized) *<<the goal of a Virtual slide is to get a complete digital image from and histological slide capable to be used for diagnosis and therefore (1) containing metadata for an accurate colour representation; (2) capable to be used for densitometry and quantification; (3)containing three-dimensional information (Z-plane focus) whenever necessary; (4) supporting digital zoom with diagnostic quality and (5) having quick distance management capable to visualize the ROIs (regions*

of interest); (6)containing standardized metadata6 for image knowledge mining and (7) occupying the minimum possible space in order to be managed efficiently by the hospital PIS, the HIS and the PACS;(8) being capable to be anonymized depending of whether it is an assistant sample or a bio-sample>>. Following this definition the majority of the market systems would not overpass a quality control check. To get managed by the HIS and PACS virtual slides should have less then 2 GB (maximum allowed in DICOM), for that reason the SSVS (small size virtual slide) technique developed by us has been shown ideal (Ferrer-Roca, 2008).

Obviously images coming from **virtual autopsies** should also be integrated (Thali , 2006; Dirnhofer, 2006) and the autopsy theatre transformed in a place with working flows similar to the ones existing in the ORF (*operating room of the future*), with ceiling suspended monitors voice commanded and touch sensitive screens, together with transportable Magnetic Resonance devices with or without magnetic positioning.

5 PIMS- ONTOLOGY and DATA MINING.

The PIMS (pathology information management system) (Tobias, 2006; CERNER, 2008; Apollo, 2008) include register, tracking, diagnostic support, speech recognition (CAMT, 2008), automatic extraction of the medical nomenclature (Ruch , 2006; Beckwith, 2006 ; Moore 1994) and classification through ontologies (OBO, 2008).

To provide scientific usability to the huge amount of data managed by each institutional PIMS, data must be anonymised and let them get accessed by the scientific community in private, publicly limited or in worldwide networks. To accomplish this at least three problems have to be faced: How to annotate the data; How to share it and How to find out the information, to finally search and access them efficiently either through CORBA or SOAP.

5.1 Annotate

Now a days great number of publicly data sources and services are available on the Internet being necessary to annotate an enormous amount of publicly data in a standardize manner to be inter-operable (OBO, 2008). The use of the **ISO/IEC 11179 family** (ISO11179, 2004) of Metadata Registry standards (e.g., ISO/IEC 11179, ISO/IEC 20943, ISO/IEC 20944, ISO/IEC 19763 or MMF) creates **Extended Metadata registries** (XMDR) of the type : *Semantic networks*, that is a graph based representation, nodes are concepts, and directed edges represent binary relationships (is-a, part-of, ...) ie., RDF and the UMLS Semantic Network at NLM (UMLS, 2008); RDF or Resource Description Framework, being a graph-based data model used for encoding metadata on the web. A kind of semantic network; Description logic*(DL)* as a restricted subset of first order logic widely used in knowledge representation applications and in large scale terminology systems, ie., Galen, SNOMED, ect,; OWL-Lite, OWL-DL, OWL-Full Ontology Web Language standardized by W3C Semantic Web working group. Built on top RDF. Semantic Web Rule Language *OWL + RuleML*, allows constraint specifications via RuleML, etc.

Metadata terminology data sets relevant for Medicine and already incorporated in the XMDR are:
Biomedical Domain, including: NCI (National Cancer Institute) terminology, UMLS (Unified Medical Language System), SNOMED (Systemized Nomenclature of Medicine, GO (Gene Ontology) and other biological ontologies such as the Open Biological Ontologies

- Chemical Domain such as chemical nomenclature, chemical code sets (CAS registry numbers), chemical reactions, chemical properties. Include: DOE's Collaboratory for Multi-scale Chemical Systems, EPA's Substance Registry System , Material Safety Data Sheets, Enzyme Commission Taxonomy, etc.

5.2 Share

The second part is to share the annotated data: DTD´s (Document Type Definition) or XML Schema (also called an XSD or XML Schema Definition) is used to define the grammar and validate the data being shared.

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6 Particularly **ISO/IEC 13250:2003** topic maps and **MPEG-7** and **MPEG-21**. and JBIG/JPEG (ISO/IEC JTC 1/SC 29/WG 1 - ITU-T SG16) extensions for JPEG query formats

The **ISO/IEC 8825** is the Extensible Markup Language (XML) ideal as a vehicle for interchange of both data and metadata, being the standard for metadata interchange the XMI (XML Metadata Interchange). The family of standards include the ISO/IEC 19501 Unified Modelling Language (UML); ISO/IEC 19502 Meta-Object Facility (MOF) ; **ISO/IEC 19503** XMI ; ISO/IEC 19757 Document Schema Definition Languages (DSDL); ISO/IEC CD 19763-3: MMF-Metamodel for ontology registration; ISO/IEC-9075-14 or SQL/XML related specifications; ISO 10303-28 XML-Schemas, etc.... In fact the SOAP (simple object access protocol) is an XML-based protocol that enables rich and automated web services.

Those ontology-driven information systems for search, integration and analysis take advantage of the **ISO/IEC 13250:2003** or topics maps XML syntax standard (ISO 23485, 2003) that use location address and hyperlinking modules following ISO/IEC 10744, as well as the **ISO-15836:2003** or Dubin Core metadata Element set or the **ISO/IEC 18023** for Synthetic Environment Data Representation using UML.

5.3 Query

To access this enormous amount of data it is necessary an efficient ontology query technique that allow to speed-up finding results, diagnosis or annotations among a huge number of samples and related data bases resulting in hypothesis that might inferred new discoveries on aetio-pathology or treatment. These techniques can be accessed at distance in a GRID environment in projects such as the *Shared Pathology Informatics Network* (SPIN) http://spin.nci.nih.gov/ or in the *Cancer Biomedical informatics grid* (**Figure 2**) containing many *open source* interoperable tools, modular and already validated.

Since bio-medical ontology is very large, **query processing strategies** are essential. Techniques similar to the ones proposed in (Ruckhaus 2008) can be used to efficiently perform the ontology query and reasoning tasks, and thus, facilitate the deduction of new properties of the concepts.

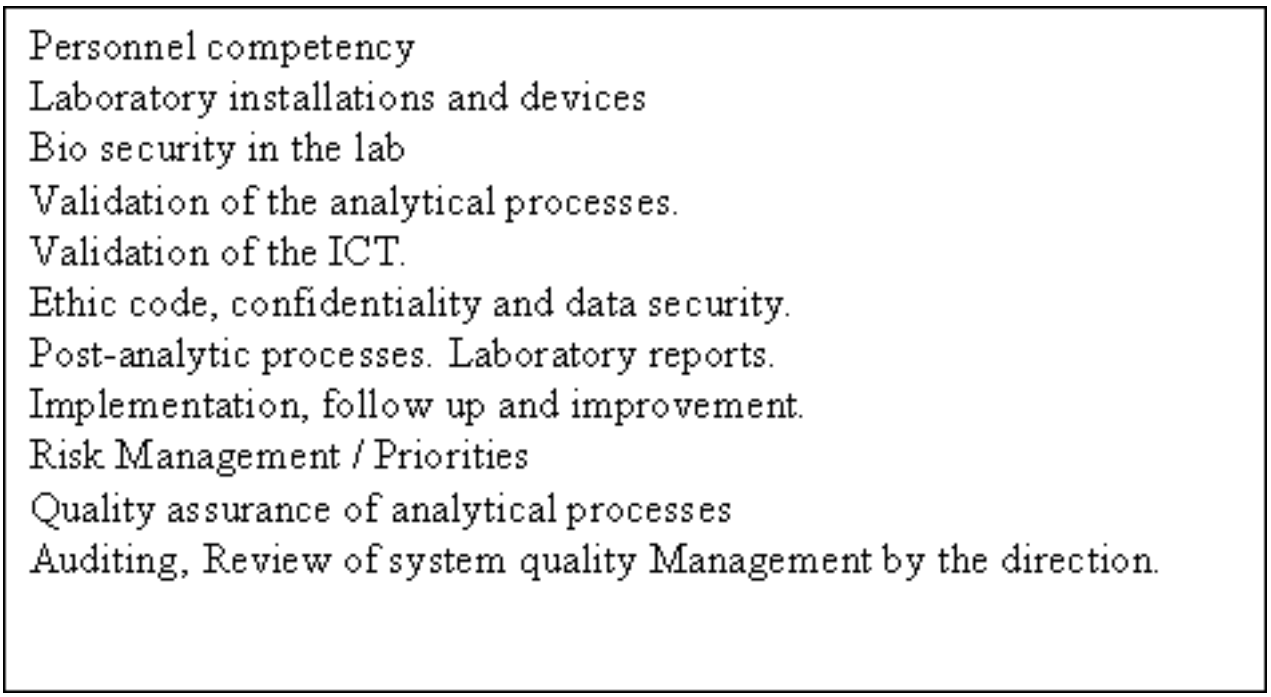

Figure 2 . The old fashion and the modern pathology department. Taken from Cancer Biomedicals informatic Grid. Tissue bank and pathology tools.
https://cabig.nci.nih.gov/workspaces/TBPT/tbpt-newcomer/workspaces/TBPT/TBPT_Newcomer_Introduction.ppt

In addition, *Text Mining* techniques have been developed to discover semantic associations between different concepts by traversing publications available in PubMed. Techniques on this area, known as **Literature Based Discovery** or **LBD** (Hristovski, 2006; Srinivasan, 2004), could be used in conjunction with any annotations and data in existing biomedical data sources to discover associations following the Electronic Discovery Reference Model (EDRM, 2008). Similarly *Image Mining* techniques can be developed taking advantage of the standardized image annotation systems and ontologies **ISO 19115/19139** standard on image metadata ontologies, MPEG-7 (MPEG Query Format-MPQF **ISO/IEC 15938-12** an XML based query language), MPEG-21 or **ISO 21000-14**, the **ISO/IEC CD 24800-3** for JPEG query search (ISO,2008) **ISO/IEC 15444-2** for JPX metadata set and DICOM.

This will become an essential element in pharmacopathology and translational research that involve a great number of specialities and research groups (Schmitt, 2007) but require incorporating new technologies together with their associated metadata. The TMA (Tissue Micro Array) techniques as well as the in situ hybridization (Lee, 2006) or the pharmacopathology (Begent, 2008) have already proposed their models. Whereas groups as the Laboratory Imaging digital Project (LDIP)(Berman, 2006) and the cancer GRID (caBIG, 2008) have used extensively metadata annotation agents following the ISO 11179 standard and avoid using DICOM standard due to its complexity.

6 STANDARDS IN GRID INFORMATION ACCESS.

Although several GRID architectures have been proposed to interoperate among dissimilar sources and services (Pollock, 2004; HealthGrid, 2004; Saltz, 2006) the harmonized-standardized flows, data formats, access and annotations techniques will spread the use, improving query results, particularly in pathology. Infrastructures such as *caBIG* (caBIG , 2005) are an example of a federated environment that connects data, resources and users using ISO/IEC 11179 standard for metadata registries.

In Internet, many metadata frameworks are present ranging from the simplicity of the Dublin Core Metadata Initiative (ISO 15836) to the complexity of Machine Readable Cataloguing (ISO 12083 XML-DTD; 12200; 12620; ISO 16642-Terminology Markup Language (TML)) and infrastructures of the W3C's Resource Description Framework (RDF) with their SPARQL query language. In semantic web, the open source Ontology Web languages OWL represent the data including the imaginery domain model, and WSDL (web services description languages) and OWL-S describe the pre-conditions, effects and inputs and outputs of the Service Oriented architecture on which the Web Services Agent transforms the sub-queries to XML Protocol (SOAP).

Medicine demands more complex representation then simply ISO 15836 with MeSH as Enterprise Vocabulary System (EVS). Should take advantage of whatever solutions provided by ISO/IEC 13250 or Topic maps XML syntax with its own **ISO 18048** TMQL or Topics maps query language and its **ISO 19756** or TMCL topic maps constrain language. TM allows modelling and representation of knowledge in an interchangeable form that can be extended by inference rules stored within the topic map.

Furthermore, medical images require even higher complexity taking advantage of their own specific standards such as MPEG Query Format- ISO/IEC 15938-12, MPEG-21 or ISO 21000, ISO/IEC CD 24800-3 for JP-query search (ISO, 2008) or JPEG search and retrieval and DICOM standard (Q/R SCP query-retrieve service class) with a Structured Interpretation Object Message template referencing the SNOMED-DICOM micro glossary and the XML MIRC7-document schema (Gentili, 2008; ORACLE, 2008).

Taking into consideration quality requirements for health care, pathology laboratories should take advantage of collaborative diagnosis and personalized treatment techniques in GRID (Oster, 2007)

Our proposed service can use existing Health-gridded environments, making public the knowledge discover and inferences obtain in image processing and incorporating LBD and JP-query search to help pathologist in “solo-pathology” practice.

7 MIRC= Medical Imaging Resource Center

In this environment images and virtual slides could be used as a Learning Objects (Ferrer-Roca, 2005) (**ISO/IEC 11404**) having a hierarchically structured metadata (IEEE-LOM) accessed using web services and ontologies (Moura, 2005).

7 CONCLUSIONS

Robots and distant diagnosis in a patho-informatics driven laboratory face a revolutionary way to practice pathology. This environment and the translational research require GRID-cooperation allowing data-base access, literature based discovery and knowledge discovery.

Considering that one of the main products in surgical pathology are images, a way to annotate them in natural language will facilitate their diagnostic search by query tools providing a world-wide atlas to support "solo pathology". On this achievement standardization of semantic annotations and specific searching engines are required. This will allow a widespread use of "solo-pathology" supported at distance.

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