TIMBRE DEL ESTADO
0,03 EUROS
TRES CÉNTIMOS DE EURO
ON4665722
CLASE 8.ª
FEDER
Fondo Europeo de Desarrollo Regional
Una manera de hacer Europa
UNIÓN EUROPEA
JUNTA DE ANDALUCIA
Servicio Andaluz de Salud
CONSEJERÍA DE SALUD

ANNEX I. PADIGA: INITIATIVE OF DIGITAL TRANSFORMATION OF PATHOLOGICAL ANATOMY IN ANDALUSIA

The following specifications of the not covered need are a guide line and could evolve at the same time as the state of the art becomes more updated in each one of the areas.

1. Pathological Anatomy

Pathological Anatomy (PTA) is a central service in the value chain of health care in a great number of health problems with great prevalence and impact in the lives of citizens and patients: cancer and precursor injuries, transplants, degenerative diseases, skin diseases, inflammatory gut disease, glomerulonephritis, etc. In all of these cases, PTA occupies a fundamental place in the scientific knowledge of the disease and is a basic resource for quality in clinical practice. As well as this, it is a clinical specialty located strategically as a direct translational link with basic research, and is critical for new developments in molecular based medicine (genome, proteomic, etc.) and personalized and precision medicine in which some of its tools, such as liquid biopsy, require the knowledge provided by PTA.

PTA is involved in a high percentage of hospital context diagnosis (100% in cancer cases) and determines in many cases, the prognosis of the disorder and choice of treatment.

It´s transcendence in multiple clinical processes is generating growing interest by citizens in this specialty, which is fundamental for better understanding decision taking in the disorder and as a central axis in development of new therapeutic targets, mainly but not exclusively, in cancer.

In spite of its transcendence in multiple clinical processes, its participation is still considered in many cases, as an external and auxiliary component, its relevance being diluted and losing part of the potential impact of its development.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

Organization of the PTA service is based on a work flow with two parts that are very different: one technical part (done by PTA specialist technicians) and another part of interpretation (done by cytotechnicians and pathologists) of images and molecular data. The first phase (histotechnology, cytotechnology and molecular techniques) implies laboratory techniques, some that are very specific to PTA (macroscopic inclusion, tissue fixation, microtomy) and other techniques shared with other specialties (use of tissue dyes and cells, molecular techniques). The interpretation phase is based, above all on microscopic images, but also raw molecular data obtained in the technical phase.

Both phases of pathological anatomy are still manual and/or almost handcrafted to a great degree, as opposed to other lines of service in the areas of general diagnosis (clinical analysis laboratory) and image in particular (Radiology and Nuclear Medicine). This lack of automatization implies a high time consumption and of resources in the generation process, a higher error risk and a loss of chances in activities of greater value, such as interpretation and analysis of the image.

It should be noted that in the current model and situation the lack and difficulty in renovation of human resources with expert knowledge in areas of super specialization such as neuropathology, nephropathology, electronic microscopy and others, as well as the risk of future loss of accumulated expert knowledge in the Andalusian Public Health System.

As existing digitalization techniques, these are limited and consist in proprietary solutions that are not based on standards, which makes inter operativity difficult between the systems and increases dependency from the provider and therefore costs of implantation and technological renovation.

Current technologies and organization of work in PTA makes difficult accessibility to information, generation and capitalization of knowledge and collaborative inter and intra disciplinary work.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

TIMBRE DEL ESTADO
0,03 EUROS
TRES CÉNTIMOS DE EURO
ON4665720
CLASE 8.ª
FEDER
Fondo Europeo de Desarrollo Regional
Una manera de hacer Europa
UNIÓN EUROPEA
Servicio Andaluz de Salud
CONSEJERÍA DE SALUD

2. State of the Art

Technology, available today, means a great opportunity to automatize and optimize processes both in the technical phase, to generate images and molecular data in as uniform a manner as efficiently possible (automatized tinctures, which also reduce exposure to noxious chemical products), as well as the interpretation phase of the images (for example, automatizing the biomarker quantification) and molecular data (the system offers detected relevant mutations).

Experience in digital radiology with the start-up of systems for filing and communication of images (PACS) integrated with their information system (RIS) have managed to:

a) reduce by over 70% the response times,

b) lost studies have been practically eliminated (before digital radiology these losses were of 10%),

c) avoid costs of fungibles and

d) other intangible benefits and costs, such as satisfaction of the professional requesting the radiological study, that of the patient and that of radiologists and specialist technicians.

All of these indicators can be transferred to the experience of pathological anatomy.

The microscopic image, as essential material support of the PTA, is susceptible to digitalization (digital preparations) and consequently, computerization and therefore of application and development of artificial intelligence tools.

Applications for artificial intelligence in cytology are in use since over 10 years ago in automatic screening of cervical cancer, but its use is limited. Development of new solutions based on deep learning or neural convolutional networks will enable greater development of automatized systems not only in cytology screening of cervical cancer, but also in histopathology of applied precision in automatized screening of colon cancer or breast cancer or in the automatic evaluation of kidney transplant biopsies. There already are solutions

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

that enable automatic detection of tumour areas in primary tumours and in metastasis in digital preparations.

These techniques of artificial intelligence will also enable defining digital strategy of implementation of bio-markers, which will have a significant impact in the organization, as by being possible to automatically quantify those bio-markers, they will enable optimizing management of the samples (frequently sparse, such as in endoscopic biopsies) and reactants, by being able to automatize multiplexation techniques (simultaneously carry out multiple bio-markers in the same tissue) and tissue matrixes or AMT (simultaneously carry out the same bio-marker in the tissues of multiple patients).

Artificial intelligence enables integration of morphological information of the microscopic image with genetic data of the tissue and liquid biopsy, giving way to the concept of "digital bio-marker" applied to precision histopathology.

Digitalization is also an opportunity for the future of professionals and for undertaking some of the problems clinical practice of APT faces from the point of view of human resources and professional development (renovation of human resources and super-specialization…), as well as capitalization of expert knowledge of the Andalusian Public Health System.

3. Not covered need

Greater automatization is necessary in all the processes of Pathological Anatomy, both in the technical phase (production of intermediate products, such as blocks of paraffin or histological preparations), as well as, above all, the diagnostic phase.

The increase in the work load, which we can estimate at 5% per annum of average increase in the number of anatopathological studies per year and the lack of PTA specialists can be alleviated, partly, by means of organizational changes based on digital pathology that offers a secure platform, of quality and efficiency, to dynamically adapt to clinical demand. Improvements in quality and efficiency of the diagnostic flow are essential for maintaining and even improving quality, precision and reproducibility parameters, necessary in APT.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

Histological preparations or cytological ones today are fragile, their dyeing is not permanent and occasionally they can become lost or broken by handling or when sent to consultation to other centres. Digital preparations offer a secure format for management, transfer or storage and are a diagnostic base capable of being transmitted immediately, without the limitations of conventional preparations.

Current organization of most of the PTA departments is based on a work by demand system, where processing and information is done of the samples that arrive to each centre. A system based on digital preparations would enable greater flexibility in work organization in each centre and between different centres of the department network of the APT which are constituted as a single Service, which enables balancing workloads in the different centres and enables super specialization of a greater number of pathologists and cyto-technicians in the network.

Especially relevant is an improvement in the safety of the patient, optimizing aspects related to traceability of the samples and associated images, thereby avoiding errors in all the process phases and improvement of anatomopathological diagnosis quality, as an essential base of clinical decision taking, by enabling development of an integrated system of bi-directional communication between physicians and nurses requesting the information and pathologists.

Currently available solutions in digital pathology are fundamentally based on proprietary systems, generally closed, where even the format of the image in digital preparations can be proprietary.

It is necessary to innovate in the design of a work station in digital pathology, up to the standards of inter-operativity, ergonomics and clinical efficiency available in other specialties such as radiology.

4. Strategic Goals

A) Development and implantation of a regional Network Service based on open solutions of Digital Pathology.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

Digitalization is an opportunity for transformation of the organization and establishment of a new relational model and service offering of Pathological Anatomy based on collaborative work in Network with the different agents involved (integrated cooperation network), with high impact.

The proposal, in this sense, is geared around creating and developing a collaborative network in three phases:

- Connected. All the information systems involved are interrelated.
- Integrated. The network is totally integrated in the health organization, enabling optimal distribution and re-distribution of work, in such a way that the PTA of the entire Andalusian Public Health System works as a single integrated virtual UGC.
- Scalable. The model can be exported and its final scope must be European. Pathologists of other autonomic communities and other countries collaborate in the network, and are external actors that participate in a secure way in consultations for second opinions, in realization of very specialized techniques and new services not yet available until now.

B) Development of a Platform of advanced solutions based on Artificial Intelligence.

- Evaluate artificial intelligence technologies, including big data and deep learning (computerized pathology or intelligent digital pathology) in its application in screening and diagnosis in digital pathology.
- Clinical use of automatic tools for digital image analysis or diagnostic aid (CAD) for improving detection of areas of interest and quantification of signs and intensities (such as the expression of inmunohistochemical or FISH in biomarkers) by means of integration of digital images to management systems in the units of Pathological Anatomy.
- Quality measurement tools in cancer diagnosis after implantation of digital pathology (sensitivity, specificity, false positives/negatives, predictive value positive/negative). Bias analysis and variability in subjective interpretation in diagnosis and quantification of bio-markers.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

- Apply internal and external quality guarantee systems to value the quality of the technique and suitability of the diagnosis.

5. Specific goals (if advisable)

- Create an Advanced Services Network of Pathological Anatomy in the Andalusian Public Health System, where all the SAS hospitals are integrated.
- Fit the Andalusian Public Health System with scanning systems for histological and cytological preparations and integrate the already existing systems in some of the centres of the Advanced Service Network.
- Replace conventional microscopes with digital pathology work stations.
- Design an open management regional system and storage of digital preparations based on international standards of inter-operativity, fundamentally DICOM, HL7 and SNOMED-CT, according to recommendations of IHE.
- Integrate in the Network the following information systems, based on standards and integration contracts defined by the SSPA:
    - PTA (SIAP-primary care information system) information systems,
    - Biobank information system (nSIBAI),
    - Clinical station (DIRAYA) in primary and hospital,
    - Request and return module for analytical test results (MPA),
    - PACS/VNA.
- Integrate artificial intelligence system in the following functionalities:
    - In digital preparations:
        - Detection of areas of interest (example, delimit glomerulus in kidney pathology or detect areas of carcinoma in biopsies) in digital preparations.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

TIMBRE DEL ESTADO
0,03 EUROS
TRES CÉNTIMOS DE EURO
ON4665715
CLASE 8.ª
FEDER
Fondo Europeo de Desarrollo Regional
Una manera de hacer Europa
UNIÓN EUROPEA
JUNTA DE ANDALUCIA
Servicio Andaluz de Salud
CONSEJERÍA DE SALUD

- Search for content in images. Locate similar cases.
- Quantification of inmunohistochemical biomarkers by means of analysis in automatic imaging.

- In case management:
  - Assign priority to cases in which by AI detection of an area of malignant tumour is detected.
  - Aid to diagnosis system in intra-operational biopsies.
  - Aid to diagnosis of screening in gynaecological cytology.
- Data of the anatomopathological report:
  - Improve sensitivity and specificity of anatomopathological diagnosis.
  - Check of report quality according to clinical guidelines.
- Molecular data:
  - Correlation of molecular and morphological data.
- Clinical decisions:
  - System of aid in clinical decision taking integrating clinical data and anatomopathological data.
- Ongoing training:
  - Organized library of cases of interest.

6. Expected impacts

Digitalization and its effects in processed potential, optimization of processes and in network cooperative work (de-localization) will have a great impact in:

- Improvement in care quality:
  - Equity. All citizens, regardless of where they live, have access to the best pathology study of their possible disorders and their prevention.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

- Quickness of the service.
- Precision.
- Care effectiveness.
- Integration with the Digital Clinical History of the patient.
- Reduction in test repetitions.
-

- **Professional Development:** sub-specialization, learning, training.

- Improvement in health organization: reference centres, Network services (super-specialists that can be located in any centre). The organization can accumulate knowledge of the more specialized pathologists in certain areas.
- **Generation and spreading of knowledge:**
  - Generation, retention and capitalization of knowledge.
  - Socialization of knowledge: access to the image by other professionals and patients.
  - Encouragement of R+D+r.

- Greater visibility and competitive positioning:
  - Attraction focus for professionals who want to participate in this new model of digital transformation.
  - Internationalization (establishment of national and international networks, rendering of services to third parties).

❖ **Impact in the Sustainability of the Health System:**

- Care: the Network enables guaranteeing a high quality specialized service to patients of the entire System and with greater response times as well as development of new services (care and research).
- Economic: improvement in efficiency of the resources that permit increasing productivity and re-distribution of resources (for example, less consumption of human resources in automatic tasks; lower cost of equipment replacement as these are based on standard systems, etc.).

María Presentación Á...
Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

- Sustainability of the solution: The quality improvement of diagnosis and effectiveness, enable undertaking necessary technological renovation.

7. Expected results

- Productivity improvement.
- Lower study costs.
- Improvement in diagnostic response time.
- Improvement in response for second opinion.
- Improvement in cancer patient stratification.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

8. Impact indicators to be considered

Indicator 1: Productivity improvements. **Cost per study reduction**.

Current cost: 150 euros/study. Foreseen saving: 11,30 euros/study (7,5%).

Goals:

- Cost study associated to productivity, after optimization in the work circuits.
- Costs related to special and molecular techniques.
- In Andalusia (estimate based in surgical data activity in the SSPA: 380.049 surgical interventions per year) would generate around 478.000 cases of PTA studies which would mean around 3.710.000 preparations (glass slides) per year. With these activity figures, thanks to digital pathology, annual savings would be of 5,4 million euros per year and after 5 years, the savings would be of 27 million euros.

Indicator 2: **Diagnostic response time:**

Current response time: 5 days. Improved response time: 4,3 days (13% improvement).

Goals:

- Study of response time for issuing the anatomopathological report.
- Measuring the impact in the interval between the first symptom and treatment of the disorder;

Economic estimate of that savings:

- Waiting list reduction.
- Hospital stay reduction.
- Unnecessary consultation numbers reduction.

We estimate an average of 70 euros per day in response time in pathological anatomy per study. Supposing an average savings of 50

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

euros per study (by reducing 0,7 days in response time), for 200.000 studies/year, this means a saving of 10.000.000 euros.

Indicator 3: **Second opinion time:**

Average time for current response: 7 days. Improved response time: 1 day of diagnostic second opinion.

Goal: study of response time in consultations of cases to other centres.

Besides, with time the number of second opinions is reduced, as the work is distributed in a better way for competencies of each professional and there is better access to similar cases, avoiding the need to consult an expert. The economic impact of this indicator is in a great degree included in indicator 1 (productivity improvement).

Indicator 4: **Better stratification of cancer patients**:

Avoid costs of over treatment and errors in cancer: 5 million euros/250.000 studies in 5 years.

Error rate or over treatment is estimated at 0,4% (for example, melanoma diagnosis) and 15% (interpretation of HER2 in breast cancer). Supposing a rate of 2% of error/overtreatment, means 5.000 cases with errors, in other words, an average of 1.000 euros per error.

Goals:

- Adherence to clinical guides that enable therapeutic decision adapted to current clinical guidelines.
- Evaluate sensitivity and specificity of anatomopathological diagnosis.
- Results study geared to the citizen.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25

TIMBRE DEL ESTADO

0,03 EUROS

TRES CÉNTIMOS DE EURO

ON4665710

CLASE 8.ª

FEDER
Fondo Europeo de Desarrollo Regional
Una manera de hacer Europa
UNIÓN EUROPEA

JUNTA DE ANDALUCIA
Servicio Andaluz de Salud
CONSEJERÍA DE SALUD

Mrs. María de la Presentación Aguilera Crespillo, Official Sworn Translator-Interpreter appointed by the Spanish Ministry of Foreign Affairs and Cooperation, does hereby certify that the prior translation is a faithful and complete translation from Spanish into English of the original document.

María de la Presentación Aguilera Crespillo

Málaga, November 6, 2018.

María Presentación Aguilera Crespillo
Intérprete Jurado de Inglés
Sworn certified official translator
Nº 25