ANNEX II. LIQUID BIOPSY

The following specifications of the not covered need are orientative and are formed at the time of signature of the agreement with the information and knowledge the SAS had at that time. Therefore, these specifications may vary as the state of the art evolves and is updated in each of the areas.

1. Precision medicine in Cancer

Precision medicine (MP) is a concept that refers to adaptation of the medical treatment to the individual characteristics of each patient. It implies that decisions about the treatment or prevention of disorders would be taken based on the integration of the genomic and molecular characteristics of the tumour, the information about the clinical situation and habits of the patient.

The concept of MP is especially important in disorders such as cancer, where evolutionary dynamic changes are produced on a time level as well as spatial level that require exhaustive and continuous following in patients affected by cancer. MP goes beyond the term of genomic medicine, as there are non-genomic factors that are included in the concept of precision medicine.

MP arises, as an answer to the need of better understanding of molecular, genetic, cellular and functional aspects of cancer that enable better handling of the patient.

Cancer is a very heterogeneous disorder. The existence of this diversity has generated that current classifications of cancer based on information from source tissue, histological aspects or type of organs affected by metastasis, are too simplistic, as they offer biological information limited to the tumour. Cancer is a disorder that varies from patient to patient genetically and phenotypically, even when having the same tissue origin. The tumoral process of each person is unique and it develops and evolves in a unique way. This genetic and phenotypical diversity helps explain the reason for the different pharmacological therapies that exist today.

Therefore, one of the greatest challenges we are up against today when it comes to treating patients is the complex nature of the disorder due to the molecular diversity and dysfunction of the signalling networks that derive from it. The greatest challenge to obtain optimal results in treatment response are based on the complex nature of the disorder. MP with its holistic focus in understanding the basics of biology along with new genomic and proteomic technologies as well as bio-computer tools will enable not only knowing specific mechanisms of the development of the disorder in each patient

and choosing the best treatment in an individualized way but also will enable identification of new bio-markers that will provide new therapeutic goals.

Personalized medicine is transforming clinical and biomedical research and health care both from a conceptual point of view as well as methodological and there are extraordinary opportunities to improve public health and probably reduce costs of the health system. Application of MP to the field of oncology is currently for most governments and countries the main bet of this initiative to achieve short term impact. A National Strategy with consensus will be key for implanting Precision Medicine in the National Health System.

2. State of the art in Diagnostic Devices and Tumour Detection

Molecular diagnosis of tumours and their supervision by means of non-invasive methods represents an important change in the paradigm for MP. Tumours are very diverse insofar as genetic variability in its widest conceptual margin and sampling of its totality is a challenge to carry out correct molecular diagnosis. Tissue biopsy is by definition an invasive procedure and reflects the tumoral state at a specific time point of development of the disorder. However, the tumoral process is a dynamic one, whereby tumour cells have the capacity to adapt to different micro-environmental pressures they are subjected to, either the pathological process itself, which implies dumping of cells to the blood system and later colonization of new different organs from those of the tumour at source, as well as the pressure of the biological chemotherapy treatments and radiotherapy. Therefore, management of the cancer patient and follow up of the tumoral disorder, require additional techniques that reflect the true status of the disorder at each moment of evolution of the cancer. In this context is where techniques of liquid biopsy (BL) appear, as complementary tools and alternatives to conventional techniques. With the development of sensitive techniques, it is possible to detect today genetic mutations and alterations in fundamental genes both of the development of the tumour as well as in goal genes for treatment with specific medication. Liquid biopsy is defined as the detection of bio-markers in body fluids using non-invasive techniques that enable follow up and monitoring the patient, this last a key concept in precision medicine. There are several types of markers that are identified as liquid biopsy, mainly the analysis of circulating tumoral cells (CTC) and circulating nucleic acids free from cells (particularly, circulating DNA tumoral (ctDNA)). Recently analysis of micro-vesicles has been incorporated as well as exosomes that are freed in peripheric blood around the primary tumour and/or metastasis or the analysis of protein and plaque profiles. A BL provides the genetic landscape and the epigenetic characteristics of all the tumours and offers the opportunity to trace genetic changes in a systematic and sustained way in time. The response to treatment and development of acquired resistance can also be monitored by means of this type of analysis, offering a unique opportunity in follow up of patient, as the procedures of tissue re-biopsy are not very feasible in most cases. Details of the genetic profile

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of the tumour enable a diagnosis in basal moment as well as prediction of progression of the disorder and response to therapies. The BL can be used in cancer screening, stratification of the patient and monitoring. However, although from a technical and methodological point of view and clinical application it is being proven in many studies, that there is a gap that is real and important between the possibility of its being used and its daily application in patients in hospitals in a routine and universal way. The future project of LB in PM must include the cost-effectiveness, reproducibility and repeatability of the results, and the comparison of productivity of the BL and existing tissue biopsy in patients with cancer. On the base of this perspective, we can adopt the optimal strategy and efficient medication based on the characteristics of the tumour.

3. Not covered need

The diagnosis for classification of cancer patients and prescription of medication is based on analysis of tumoral tissue that has serious limitations: access, is painful, costly, not always possible and can only give information about the status of the disorder in specific concrete areas of the evolution of the tumour process, that by definition is dynamic. The direct consequence of this absence of biological information of the tumoral process is the incapacity to choose the treatment and follow up that is most suitable for the patient and which can be accompanied by over treatment.

The prognostic and predictive value of the analysis of solid tumours, based on tumoral biopsies, in general, has limitations to evaluate in an agile, non-invasive and economically assumable way the evolutive process of the cancer and the metastasis, which makes incorporation necessary of new methodologies that can cover current limitations. The reason for this project line consists in development of multiplex analysis prototype for detection of circulating bio-markers (CTC, miRNA, cfDNA and exosomes) in blood in cancer patients for monitoring the efficiency of the therapies as well as for improving prognosis and cancer diagnosis, based on analysis technology of liquid biopsies.

4. General goals

With this line of action an attempt is made of developing a prototype that can permit identification and characterization of biomarkers in blood (CTCs, exosomes, miRNA and free DNA) in an

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automatic and simultaneous way for early diagnosis as well as personalization and monitoring of treatment of the patients.

Parallel to this is the need for design and implantation of a clinical protocol that is integral for determination of blood biomarkers (CTCs, exosomes, miRNA and free DNA) that will span gathering of the sample all the way to the clinical decision.

Generation of the prototype will be centrered around cancer patients affected with solid breast tumours and colon tumours in early stages and metastasis (eventually lung, prostrate and pancreas).

5. Specific goals

i. Diagnose the patient in a simple and less invasive way.

ii. Monitoring response to treatment and establish personalized treatments.

iii. Prognose apparitions of relapses.

iv. Reduce production costs and suitable costs for large volumes required.

v. Generate meta-analysis that back decision taking.

vi. Develop a transversal protocol, within health systems that enables integral management of the process.

6. Expected results

i. Reduction of time in obtaining diagnosis/prognosis per case.

ii. Improvement of follow up of the patient.

iii. Improve choice and effectiveness of the treatment.

iv. Improve effectiveness of resistance to treatment.

v. Improve cost effectiveness versus current techniques.

7. Impact indicators to be considered

i. No. Tests/new patient/year.

ii. Percentage of patients susceptible for treatment review based on test results.

iii. Increase of survival and/or reduction of mortality. Percentage of prognosis improvement of survival as opposed to conventional technologies.

iv. Reduction of number of inefficient treatments in proportion to estimated savings versus current oncological medical treatment.

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Nº 2[illegible]

TIMBRE DEL ESTADO

0,03 EUROS

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v. Unit cost in euros of the test versus conventional standard.

vi. Expected savings because of reduced ineffective health care/new patient/year.

vii. Total savings expected due to reduced non-effective health care/new cancer patients/year.

viii. Estimated savings in ineffective oncological medication with the solution per new case.

ix. Total estimated savings in oncological medication in patients.

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.

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Málaga, November 5, 2018.

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