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Updating cancer research with patient-focused networks

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Multidisciplinary patient-centered networks offer access to difficult-to-get samples and initiate projects from human material. Improving such networks to include ‘living’ samples could be transformative, not only for research but for clinical trial design, especially when focused on unmet clinical needs, such as brain metastasis.

A novel strategy to challenge unmet cancer needs

Aiming to make an impact on cancer patients, researchers often initiate projects on experimental models and it is only when a major discovery is found that the search for patient samples begins. Confirmation of the finding in patient-derived samples is mandatory to claim that this finding is not exclusive to mice (if this was the model used), but that it could be translated into humans. However, the current strategy is inefficient due to many aspects, such as difficulty in allocating samples, the time required to acquire samples, and the number of samples needed to get a conclusive result. This effort usually involves variables such as discussions with several institutions, control of preanalytical errors, and completion of legal and ethical requirements.

We have implemented a network of 18 hospitals, with a backbone of a biobank and a basic/translational laboratory, in order to benefit the translation of discoveries from

the laboratory to patients, as well as to initiate research projects with patient-derived observations. The uniqueness of this coordinated effort is that, beyond common samples [i.e., formalin-fixed, paraffin-embedded (FFPE); fresh-frozen; plasma], we have built a ‘living’ biobank offering the possibility to perform functional experiments in patients (Figure 1). Given that hospitals are involved within the discovery process, they are not just sample suppliers but active network members who lead subsequent clinical efforts to move those findings into the patient.

This network has proven to be extremely valuable to study an unmet clinical need, such as brain metastases [1,2]. Access to surgically extracted metastases is frequently challenging because noninvasive approaches such as immunotherapy are improving the control of disseminated disease. Thus, this approach allows us to gain easier access to many samples, including brain metastases. Since its inception in 2021, the Spanish National Network of Brain Metastasis, under the acronym RENACER (‘rebirth’ in Spanish), has required human brain metastases to be incorporated into every research project, along with providing the possibility to test specific drugs in patient-derived material (Figure 2).

Herein, we discuss the value of establishing patient-centered networks for advancing cancer research, with a focus on our experience in starting RENACER.

Creating a network

As the Spanish National Cancer Research Centre (CNIO) is a research center, our project started by collaborating with a single health-care institution. Over 3 years this became a very successful collaborative experience [3], only because the clinicians involved (Dr Angel Pérez, neurosurgeon, Dr Juan Manuel Sepúlveda, medical oncologist, Dr Aurelio Lain, pathologist; Hospital 12 de Octubre, Madrid) were interested in

research as a vehicle to make clinical impact. However, it was evident that we needed to partner with additional hospitals to fulfill our goals.

The logistics involved in gaining access to ‘living’ samples from neurosurgeries is not trivial and multiplying it by several additional hospitals requires a different set of skills to create a high-quality collection. Biobanks are instrumental in guaranteeing that the effort to generate high-quality cohorts will provide an open frame to access and share samples, data, as well as to bridge scientific collaborations both nationally and internationally. Moreover, biobanks are skilled in dealing with regulatory issues regarding the use of human specimens; therefore, their involvement helps to fulfill the national and European ethical and legal requirements, such as informed consent, material/data transfer agreements, as well as the commitments established by the RENACER collaborative network. In particular, the CNIO Biobank oversees the minimization of preanalytical variables, such as transport, sample handling, and storage to ensure high-quality biospecimens, and serves as a coordinator of planned surgeries between external entities (hospitals), shipment and handling, processing and storage of biospecimens, and curation of clinical data.

A major challenge in utilizing these networks is its maintenance over time. Many aspects require continuous attention, such as acquisition and curation of associated clinical data, gathered in a RedCap database, during the progression of the disease. Frequently, this effort is part of the commitment clinicians make when joining RENACER, but it is challenging to balance their health-care demands at the hospital with the acquisition of a large amount of data for scientific purposes. In our experience, the use of clinical data managers is vital in supporting clinicians with this task, a role that we have recently included in RENACER.

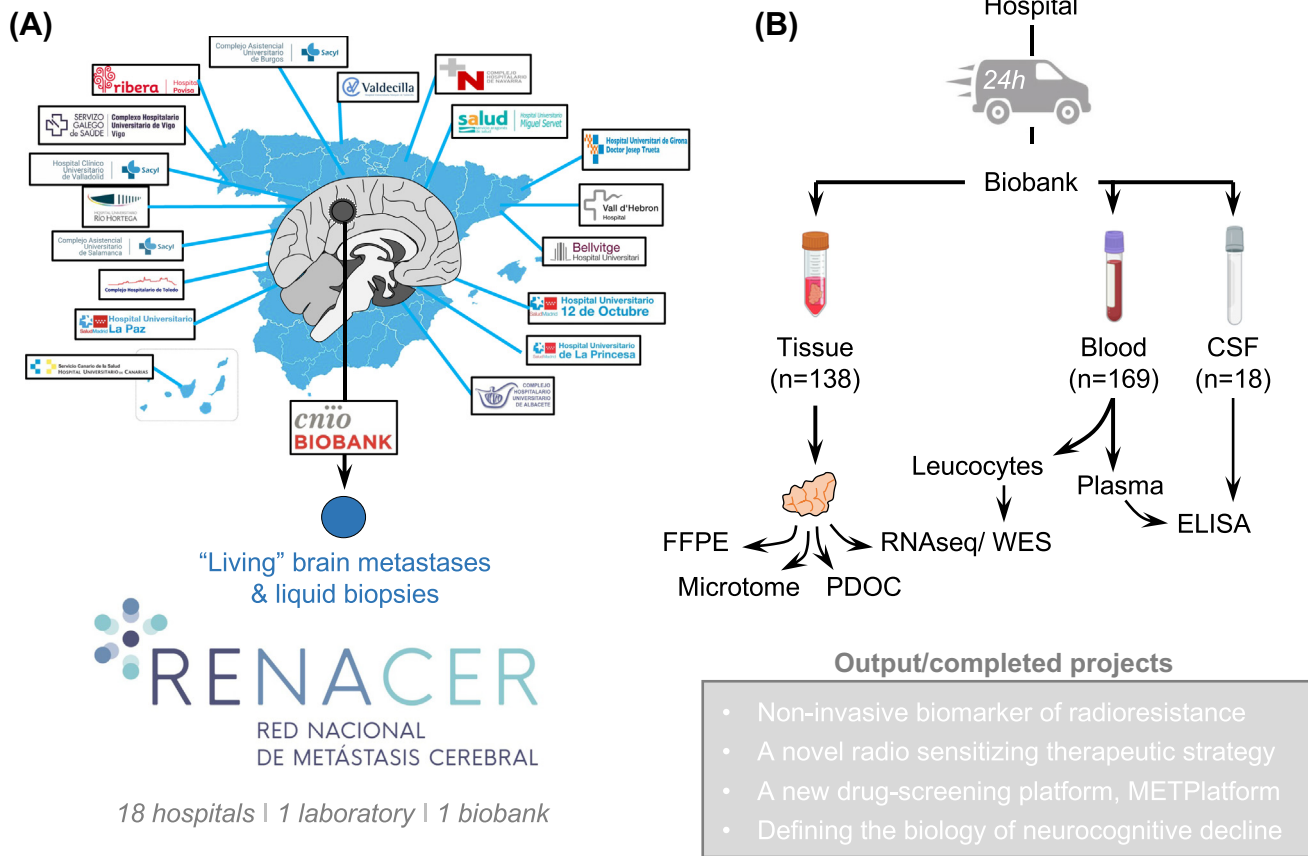


Figure 1. RENACER as a nation-wide effort to generate 'living' human brain metastases samples. (A) Eighteen hospitals are part of the National Network of Brain Metastases, which is dedicated to collecting high-quality samples, including 'living' brain metastases and liquid biopsies, coordinated by the Spanish National Cancer Research Centre (CNIO) biobank. (B) A schema of the established pipeline for human sample processing and its use. Completed projects are also depicted. Abbreviations: CSF, cerebrospinal fluid; FFPE, formalin-fixed, paraffin-embedded; PDOC, patient-derived organotypic culture; WES, whole exome sequencing.

In addition, RENACER is committed to engaging with the needs of its members and the community; therefore, annual network member gatherings and frequent Board of Directors meetings are

scheduled so that members can share achievements and discuss new ideas. As patients are crucial in RENACER, because they serve as donors during a difficult brain metastasis neurosurgery, we

strongly believe that it is pivotal to empower patients. Therefore, RENACER has included GEPAC (The Spanish Group of Cancer Patient), which is one of the largest organizations of patient advocates in the country, in its Board of Directors and, thus, they are invited to monthly meetings where they ensure that the network represents the interest of cancer patients.

Increased research impact and faster delivery to patients

In only 2 years, RENACER has provided invaluable resources to the scientific community [4–6]. Samples included in these

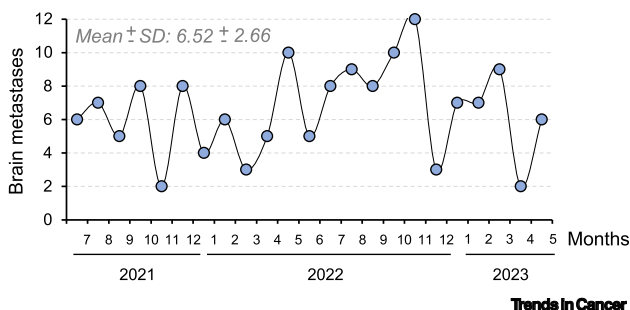


Figure 2. Brain metastases collected in RENACER. A graph indicating the frequency per month of brain metastases samples (i.e., tissue and/ or liquid biopsy). The mean number of brain metastases/month during the 23 months of establishing the network is indicated. Abbreviation: SD, standard deviation.

studies involve regular FFPEs, omics data, and 'living' specimens. Beyond tissue samples, RENACER has profiled, with RNAseq and whole exosome sequencing, more than 150 brain metastases. All this data will be translated into a RENACER Precision Medicine Portal safe system for (meta)data storage, accession, and consultation of patients' genomics and associated clinical data.

Since RENACER is associated with a network of hospitals, these research findings can be quickly translated into further clinical studies. Indeed, a biomarker compatible with liquid biopsy that was initially discovered in experimental models [5] is now part of a prospective multi-institutional study to evaluate it as a non-invasive strategy to predict the response to radiotherapy [7].

As public-private collaborations and transfer of knowledge is crucial, RENACER has also partnered with pharmaceutical companies to launch a clinical trial to test a novel radiosensitizer in patients with brain tumors (NCT05635734) [5]. In addition, research contracts have been signed to exploit patient-derived organotypic cultures (PDOCs) as avatars, thus providing the possibility to generate biomarkers of sensitivity or resistance to specific drugs. Identification of biomarkers could improve the design of clinical trials by using molecular markers to stratify patients, which would ultimately benefit enrolled patients.

Evolving networks beyond RENACER

As RENACER is still in its infancy, we continue to identify areas to grow. For instance, brain imaging is currently being incorporated in a pilot study. We envision that imaging, through the lens of radiomics, could provide enormous benefits in the future by linking noninvasive imaging findings with relevant aspects of the disease and/or response to specific treatments.

As a long-term effort, we plan to standardize the acquisition of neurocognitive evaluation of all patients that are included in RENACER through collaboration with experts in the field (neuropsychologists, neurologists, neuroscientists) that created the adequate tools to implement this important part of the clinical history [8]. Often patients with brain metastasis present with neurocognitive changes due to clinical progression of disease or side effects from standard treatments [6]. With a neurocognitive assessment in place, we can evaluate quality of life within RENACER. Such an effort not only requires the aforementioned tools, but also new specialties within the network, such as clinical neuropsychologists as well as specific research equipment and expertise to develop cancer-neuroscience approaches [6]. We consider this effort necessary to provide a better clinical management for patients with brain metastasis, which should incorporate strategies to prevent or minimize the neurocognitive impact derived from brain metastasis and/or their treatments.

While RENACER is currently focused on the brain, patients with brain metastases have disseminated disease affecting other organs. Therefore, it would be ideal to collaborate with other networks specialized in extracranial metastases. These efforts would provide regulated and open access to valuable biospecimens. More importantly, they will provide the unique opportunity to systematically perform drug-screening using PDOCs established from multiorgan metastases, as we have developed for those affecting the brain [4]. As cancer patients continue to die mainly due to disseminated disease, we consider that the development of such an approach is crucial to bring personalized medicine to metastatic disease and not only the primary tumor.

Concluding remarks

Given the enormous amount of knowledge and resources contained in RENACER, a

natural evolution of such a network is to contribute to the National Health System, which could facilitate long-term sustainability and fully exploit the benefits of this emerging strategy to society.

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Declaration of interests

None are declared by the authors.

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