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<b>Authors</b>	<ul style="list-style-type: none"> <li>• <b>Mirella Filocamo</b> (Biobank Director and TNGB Coordinator)</li> <li>• <b>Chiara Baldo, Stefano Goldwurm, Alessandra Renieri, Elena Pegoraro, Maurizio Moggio, Marina Mora, Giuseppe Merla, Luisa Politano, Barbara Garavaglia, Luca Sangiorgi</b> (Biobank Directors)</li> <li>• <b>Lorena Casareto</b> (TNGB Administrative Assistant)</li> </ul>

## 1 - INTRODUCTION

### 1.1 Presentation of the Telethon Network of Genetic Biobanks

Genetic Biobanks (biospecimens and associated data) are an important resource for diagnostic and research purposes.

The objective of the Telethon Network of Genetic Biobanks (TNGB) is to interconnect and to coordinate Biobanks currently supported, as core facilities, by the Italian Telethon Foundation. The Network has been designed to be the first national, standardized biospecimen resource related to genetic diseases. Its mission is to support research on genetic diseases, including rare ones, by facilitating access to quality human biological resources (i.e. cell lines, tissues, nucleic acids, sera/plasma, etc.) of interest to the scientific community, patients and families.

We wish to mention here Franca Dagna Bricarelli, who passed away on December 2014. Franca is well remembered for her fundamental role in founding The Telethon Network of Genetic Biobanks and defining the governance structure and key organizational elements described in The Charter. She served TNGB as Coordinator Emeritus until 2014. Franca will remain as an inspiration to all of us.

### 1.2 Founding Partners of Telethon Network of Genetic Biobanks

The Network includes the following Biobanks:

- **Cell Line and DNA Biobank from patients affected by Genetic Diseases (Acronym: IGG-GB)**  
 Director: Mirella Filocamo (Coordinator)  
 U.O.S.D. Centro di Diagnostica Genetica e Biochimica delle Malattie Metaboliche, Istituto G. Gaslini, Genova
- **Galliera Genetic Bank - DNA, Cell lines and Tissue Bank (Acronym: GGB)**  
 Director: Chiara Baldo (Partner 1)  
 S.C. Laboratorio di Genetica Umana, E.O. Ospedali Galliera, Genova
- **Parkinson Institute Biobank (Acronym: PIB)**  
 Director: Stefano Goldwurm (Partner 2)  
 Centro Parkinson, Istituti Clinici di Perfezionamento, Milano
- **Cell lines and DNA bank of Rett syndrome, X-linked mental retardation and other genetic diseases (Acronym: biobankUNISI)**  
 Director: Alessandra Renieri (Partner 3)  
 Medical Genetics, University of Siena; Genetica Medica, Azienda Ospedaliera Universitaria Senese, Siena

#### Neuromuscular Biobanks (Joint Neuromuscular Biobanks)

- **Neuromuscular Bank of Tissues and DNA samples (Acronym: NMTB)**  
 Director: Elena Pegoraro (Partner 4)  
 Dipartimento Neuroscienze SNPSRR, Università di Padova, IRCCS San Camillo, Venezia
- **Bank of muscle tissue, peripheral nerve, DNA and cell culture (Acronym: biobankNMD-Milan)**  
 Director: Maurizio Moggio (Partner 5)  
 U.O.D. Malattie Neuromuscolari e Rare, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Centro Dino Ferrari, Università Studi Milano, Milano

- **Cell, tissues and DNA from patients with Neuromuscular Diseases (Acronym: NeuMD)**

Director: Marina Mora (Partner 6)

Laboratorio di Biologia Cellulare, U.O. Malattie Neuromuscolari e Neuroimmunologia, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano

Each Biobank stores biospecimens from patients and families affected by genetic diseases, including rare and “orphan” disorders. The Network is endorsed by UNIAMO (Italian Federation of about 100 Associations of patients with rare diseases).

### 1.3 Joining Partners of Telethon Network of Genetic Biobanks (see point 9.3)

- **Genomic and Genetic Disorders Biobank (Acronym: GGDB)**

Director: Giuseppe Merla (Partner 7)

Medical Genetics Unit, IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo (FG)

- **Naples Human Mutation Gene Biobank (Acronym: NHMGB)**

Director: Luisa Politano (Partner 8, Joint Neuromuscular Biobank)

Cardiomiologia e Genetica Medica, Dipartimento di Medicina Sperimentale, Seconda Università di Napoli e Azienda Ospedaliera Universitaria SUN, Napoli

- **Cell line and DNA Bank of Genetic Movement Disorders and Mitochondrial Diseases (Acronym GMD-MDbank)**

Director: Barbara Garavaglia (Partner 9)

U.O. Neurogenetica Molecolare, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano

- **Biobank of Genetic Samples (Acronym BIOGEN)**

Director: Luca Sangiorgi (Partner 10)

S.S.D. Genetica Medica, Istituto Ortopedico Rizzoli, Bologna

### 1.4 Objectives

Genetic Biobanks are an important resource for diagnosis and research - both basic research and research applied to the treatment of genetic diseases. Several examples illustrate how access to relatively large numbers of biospecimens and associated data has played a pivotal role in the identification of genetic disease genes, susceptibility genes and the development of novel treatment.

The purpose of the Telethon Network of Genetic Biobanks is therefore to coordinate well-qualified Biobanks in order to improve access to human biological resources in the biomedical community. The Network creates harmonious environments that ensure the protection of the privacy and confidentiality of donors and their family members throughout the entire process of collection, storage, and use of biospecimens and data information.

The main Network’s objectives can be summarised as follows:

- interconnecting and coordinating the Genetic Biobanks already supported by the Italian Telethon Foundation;
- developing a centralized bioinformatics system designed to facilitate Network presentation and external access to the biospecimen collections;
- harmonizing ethical, legal and quality standards;
- increasing collections and distribution of high quality biospecimens for research in the field of rare diseases;
- enhancing collaborations within the biomedical community, stimulating research projects;
- offering a service to researchers for the development of their studies;
- collaborating with Patients’ Associations in promoting the Network services within Patients’ Associations;
- opening the Network to new members according to Telethon policy;

- collaborating on common projects with European and International Biobanks.

## 2 - ORGANIZATION AND GOVERNANCE OF THE NETWORK

The governance structure of the Network comprises the following bodies:

**2.1. Network Board (NB)**, the executive body of the Network composed of the Coordinator and the Biobank directors. The Network Board meets at least twice a year. It takes advantage of open-source or free collaboration products, such as video conferencing, document sharing and collaborative writing.

### Role of the Network Board:

- establishing an annual work plan;
- defining the strategic orientation of the Network;
- setting up working groups according to the work plan;
- making modifications and amendments to the Network organisation and the Charter;
- updating Telethon and SIGU (Italian Society of Human Genetics) Genetic Biobank Guidelines;
- defining terms of use of the TNGB name and logo;
- establishing collaborative policies with Patients' Associations.

The Network Board undertakes to produce an **Annual Report** for the Telethon Scientific Committee for Biobanks, summarizing all the activities of the Network and the results that have been achieved.

**2.2.** The **Coordinator** is elected by the Network Board for the whole duration of the grant. The tasks of the Coordinator are:

- guaranteeing management of the Network;
- organizing the Network and Advisory Boards' meetings;
- coordinating working groups according to the Network work plan;
- ensuring implementation of the decisions taken during the assembly;
- providing a written summary of the meetings to the Network Board members;
- reporting to the Network Board on all activities, including any opinion/advice received from the Advisory Board;
- reporting and relating to the Telethon Scientific Office and other Telethon structures.

**2.3.** A **Coordinator Emeritus**, as support of the Coordinator and the Biobank Directors, can be nominated for the whole duration of the grant by the Network Board. The tasks of the Coordinator Emeritus are:

- attending the meetings of Network and Advisory Boards;
- interacting with Uniamo (Italian Federation of Rare Genetic Diseases) and other Patients' Associations;
- participating in scientific meetings to promote the Network development at both national and international level.

A formal agreement will be stipulated between the Coordinator Emeritus and TNGB, and will include reimbursement and attendance fees.

**2.4.** An external **Advisory Board (AB)** is established to provide consultative support to the Network and will refer to the Coordinators. The Network Board nominates a chairperson chosen among AB members. This board, including legal, ethical and technical experts, supports the Network management in setting policies, but is not involved in day-to-day operational

aspects of decision-making or approval. In particular, the Advisory Board supports the Network by providing expert advice on the following topics:

- TNGB governance strategies;
- TNGB Charter and TNGB documents (i.e. informed consent and material transfer agreement);
- usage rules and access priority criteria;
- supporting the Network involvement in European projects on biobanking and rare genetic diseases;
- promoting the national and international development of Network;

Additionally the AB will arbitrate the following issues:

- conflicts between Biobank directors and users, concerning priority criteria in the use of materials from the Biobanks;
- conflicts among Biobank directors concerning sample and data management;
- non compliance or violation of the principles governing the Network as stated in the Charter.

The Advisory Board will meet at least once a year. The Network's remote collaboration tools, such as audio/videoconferencing, will be used, whenever this is necessary to ensure the participation of the Coordinator and/or Telethon.

A formal agreement will be stipulated between each member of the AB and TNGB, and will include reimbursement and attendance fees.

**2.5.** In case of retirement/resignation of a Biobank Director or of the Coordinator, the successor of the outgoing Director/Coordinator will be nominated by the Network Board through the following procedures in compliance with Telethon policy regarding the substitution of the Principal Investigator (PI) for a Telethon grant:

- the Coordinator will be replaced by a successor, elected by the Network Board among the Biobank Directors;
- if a Biobank Director resigns or retires, he/she must inform the Network Coordinator and Partners, as well as the Telethon Scientific Coordinator, about the vacancy;
- the outgoing Biobank Director will nominate a successor;
- the nominated successor has to be a person approved by the Host Institution;
- granting of Telethon funds to the successor Biobank Director must be approved by Telethon Scientific Committee for Biobanks after evaluation of the successor's CV (as per Telethon policy regarding substitution of a PI for a Telethon grant),
- the successor will take over daily operations related to Biobank administration before the departure of the outgoing Biobank Director;
- the new Director will be introduced at the first meeting of the NB, and will be obliged to adopt the principles and to adhere to the policies of the Network.

**2.6.** To leave the Network, a written official notice by the Director of the outgoing Biobank is required to announce the decision. The communication, with the specifications constituting cause for leaving, will be considered at the following NB meeting and all procedures should be formalized by the end of the financial year.

Membership revocation is subjected, and contextual, to the renunciation to the ongoing Telethon grant by the Biobank Director.

The existing agreements related to the outgoing Biobank (see 10.1, 10.2) should be considered settled and new ones stipulated with another partner, if agreed by all parties.

### **3 - PURPOSE OF THE CHARTER**

This Charter is the Constitution Document of the Telethon Network of Genetic Biobanks, which

sets out the principles agreed upon by the Members of the Network.

In particular, the Charter recalls the ethical guidelines endorsed by Members of TNGB, defines the organisation and governance of the Network and establishes the duties attached to membership.

The NB may modify the Charter and the Network organisation, after consultation with the AB. The AB must always be informed and consulted, but its approval is not necessary. Any modification has to be approved by the majority of the NB participants during an official meeting of the NB, where the Charter modification was previously put on the agenda. The Coordinator and the Biobank Directors (or their deputies) must vote. In the event of a tie, the Coordinator will decide on the issue. The modified Charter will then be submitted to the Telethon Scientific Committee for approval.

#### 4 - ETHICAL GUIDELINES OF TNGB

The Network adopts appropriate security measures at different levels:

- sample cryptification (identifiable samples);
- confidentiality and data protection;
- written informed consent for collection, storage and distribution;
- distribution to scientific community regulated through evaluation and approval of the project for which the samples are requested.

For all the ethical, legal and societal issues, the Network adopts the principles enunciated. Reference documents are:

- **Recommendations issued by the Oviedo Agreement, 1997** (Convention on Human Rights and Biomedicine, Oviedo, 4<sup>th</sup> April 1997)  
<http://www.portaledibioetica.it/documenti/001316/001316.htm>
- **Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes (CETS n. 203), 2008** (Strasbourg, 27<sup>th</sup> November 2008)  
<http://conventions.coe.int/Treaty/EN/Treaties/Html/203.htm>
- **Telethon - SIGU Guidelines for Genetic Biobanks, 2003**  
<http://biobanknetwork.telethon.it/Pages/View/Documents>
- **International Declaration on Human Genetic Data, 2003** (16<sup>th</sup> October 2003, 32<sup>nd</sup> session, the General Conference of UNESCO - The International Declaration on Human Genetic Data)  
[http://portal.unesco.org/en/ev.php-URL\\_ID=17720&URL\\_DO=DO\\_TOPIC&URL\\_SECTION=201.html](http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO=DO_TOPIC&URL_SECTION=201.html)

The Network operates abiding by the Italian Privacy and Data Protection Laws in force, including:

- **Italian Data Protection Authority (*Garante Privacy*), Personal Data Protection Code**, Legislative Decree no. 196, 30<sup>th</sup> June 2003, published in *Official Gazette No. 174 of the Italian Republic*, 29<sup>th</sup> July 2003, and possible subsequent amendments
- **Italian Data Protection Authority (*Garante Privacy*), General Authorisation for the processing of genetic data**, 12<sup>th</sup> December 2013, published in *Official Gazette No. 302 of the Italian Republic*, 27<sup>th</sup> December 2013, and possible subsequent amendments
- **Italian Data Protection Authority (*Garante Privacy*), General Authorisation to process personal data for scientific research purposes**, 1<sup>st</sup> March 2012, published in *Official Gazette No. 72 of the Italian Republic*, 26<sup>th</sup> March 2012, and possible subsequent amendments

#### 5 - INFORMATION TECHNOLOGY (IT) INFRASTRUCTURE

The partners have adopted a common IT infrastructure. The common software application suite handles the core Biobank data and the full superset of patient and sample data currently collected by each Biobank, with optional modules used to handle sample/pathology subsets for which some partners collect specific data. The system manages and monitors the complete work flow of sample submission and sample requests. Data aggregation and publishing are completely automated. Network governance and coordination is aided by the use of open-source or free collaboration products for project management, video conferencing, document sharing and collaborative writing.

The official TNGB website is <http://biobanknetwork.telethon.it/> where Users can find all information related to the Network.

## **6 - ACCESS TO SAMPLES**

Sample request and submission are fully handled online by IT system and are shared through the Request Control Panel (RCP) by all Network partners as well as by the Telethon Program Manager. Users are requested to fill in an on-line request form and, once the request is received on the RCP, the NB accepts or rejects it on the basis of the basic rules of access listed below (point 6.1). Assuming approval, Users are requested to send a signed hard-copy of the material transfer agreement form to the referring Biobank.

Samples will be made available to users for research purposes, provided that an adequate portion of the samples derived from individuals affected by undiagnosed and rare diseases are safeguarded to the patient's advantage to allow retrospective analysis. Consequently, the Biobank Director will never send out the last vial related to a particular specimen for research purposes, because it has to be kept for diagnostic analysis.

### **6.1. Basic Rules of Access**

Basic rules of access are as follows:

- adequate aliquot of sample to be saved for patient/family, aimed at retrospective analysis;
- sample distribution to qualified professionals working at research or medical institutions;
- appropriate justification for use (description of the research project, grant sponsor, expected results);
- use of signed material transfer agreement form;
- acceptance of Biobank rules that are:
  1. samples supplied cannot be used for commercial purposes;
  2. biospecimens cannot be distributed to other investigators without written permission of the Biobank director;
  3. samples provided must be used only for the research project declared by the Principal Investigator (PI);
  4. if results obtained with Biobank specimens are included in a scientific report, the investigators are expected to acknowledge the Biobank for having provided the biospecimens, and to send a paper reprint to the Biobank;
  5. feeding back the analytic results from each single sample to the Biobank Director, in order to support further research;
  6. paying for shipping and distribution services (see point 6.2).

### **6.2. Charges**

The TNGB provides its services on a basis of non economic gain. However, Biobank distribution service might be subject to cost recovery. The costs of some consumables associated with the distribution operations are charged to the users through administrative mechanisms that may differ between Biobanks, this is depending on the administrative procedures of the host Institution. The official TNGB cost recovery list for researchers operating in public/non-profit

organisations has been published on the Network website upon the NB approval. A different cost list, approved by NB, is applied to researchers operating in private companies and available upon request.

### 6.3. Particular Requests and Controversies

It is envisaged that particular requests or controversies will require a devoted approval procedure by a third-party committee, hereafter referred to as the **Approval/Appeal Panel (AP)**. The panel will be composed by one of the members of the Advisory Board, one of the members of the Telethon Biobank Committee, and by a third external member selected among the International Scientific Community. The composition of the AP will be concerted with Telethon according to the peer-review-based procedures.

Such requests/controversies include, but are not limited to:

- requests for samples available in more than one Biobank. The Biobank Directors will reach an agreement as to who is best entitled to satisfy the request. If an agreement between Biobank Directors is not reached, the AP is contacted;
- competing requests for scarce samples. The Biobank Director will suggest and justify a **priority list** that needs to be approved by the AP;
- requests from private for-profit organisations (such as pharmaceutical companies)
- questionable scientific justification for the use of the samples, or any request that appears not to be adequately funded. The AP will decide whether to satisfy the request;
- all requests that have not been approved by the Biobank Director or that raise unforeseen issues. The AP will decide whether to endorse the refusal of the request: if deemed necessary, the panel will present the case to the Network Board and to the Advisory Board for discussion.

The Biobank Director will send the requests to the AP, including an explanatory note illustrating the reasons for the controversy.

**Note:**

*In case of rejection, an appropriate justification in writing will be added to the Telethon Annual Report by the referring Biobank director.*

### 6.4. Biobank Director requests

The Biobank Directors do not have any advantage/special treatment in the access to samples for research purposes and their requests have to fulfil all the rules reported above. The Biobank Directors and their research group must request the samples using the same online form as other researchers. In this way their requests will be accessible to all partners and to the Telethon program officer through the IT management system.

To ensure transparency of possible conflicts of interests, self-request number of each Biobank should be compared with the total number of the external requests received and detailed in the Annual Report.

## 7 - Sample Back-up

### 7.1. General Rules

In order to minimize the risk of losing important samples the Network Biobanks plan the sample back-up as follows:

- a **master stock** is produced, whenever possible, and is used to generate the distribution stock;
- the **biological material** is preserved, if possible, by at least two methods (whole blood/DNA, whole blood/cell line, RNA/cell line);
- **each biospecimen** (e.g. whole blood, DNA, RNA) is subdivided into several very small aliquots to avoid repeated freezing and thawing; in the case of cryopreserved cell lines, a

minimum number of 4 cryotubes from the original biological material must be ensured, and out of these at least one cryotube is stored in another container and in another place;

- the divided and aliquoted samples are stored in different containers and locations, under the responsibility of the Biobank Director.

**Note:**

*When banking biological material, it is essential to always preserve a sample aliquot for the **patient/family**. In view of events such as power loss, fire, flooding, earthquakes, user errors etc. samples and aliquots should be divided and stored in separate buildings or, ideally, at separate sites.*

## 7.2. Difficulties with Sample Back-up

There are, however, circumstances in which the biological material cannot be easily aliquoted due to sample scarcity/characteristics.

Exemplifications:

- **foetal samples** collected after abortion;
- **tissue samples**, for which planning the storage of aliquots would imply the collection of an amount of material that would be detrimental to the individual undergoing biopsy.

Another important point to be considered is that there are sample types requiring swift storage, to which a back-up relocation could therefore potentially cause damage rather than yield a benefit.

Sample back up in neuromuscular collections may be hampered due to the following issues:

- neuromuscular diseases are rare;
- the samples are perishable;
- the size of the muscle sample taken is small for ethical reasons\*;
- muscle biopsies cannot be repeated for ethical reasons;
- it is not easy to divide the samples and place them in different tissue Biobanks\*;

\*The available sample may be even smaller for several practical reasons:

- *critical physical conditions of the patient;*
- *scarce availability of tissue due to disease severity;*
- *muscle involved in the disease not easily accessible for biopsy;*
- *patient age (i.e. babies and children).*

## 8 – QUALITY ASSURANCE (QA)

To minimize errors the Network Biobanks have developed a quality assurance (QA) system that guarantees that the biological samples and related data are of adequate quality.

The system will be a continuous process that aims at measuring, evaluating and continuously re-evaluating quality and, if necessary, changing and improving it. Therefore, the QA system involves all the Biobank operators and covers all management activities including planning, implementation, documentation, assessment, and improvement.

Each Biobank regularly updates the QA processes related to:

- data management (coding and registration);
- storage systems;
- safety plan;
- training schedules;
- adherence to Standard Operating Procedures (SOPs) (<http://biobanknetwork.telethon.it/Pages/View/Documents>);
- equipment maintenance and repair.

## 9 - MEMBERSHIP TO TNGB

Conditions of access to TNGB and/or withdrawal of membership are the responsibility of the Telethon Committee.

### 9.1. Benefits of Membership

TNGB Partners will benefit by:

- sharing a wide number of biospecimens related to rare genetic diseases;
- having a high visibility through TNGB website;
- being an acknowledged national infrastructure;
- belonging to the first national Network on rare genetic diseases;
- having the necessary requirements to access international projects/funding.

### 9.2. Undertaken Duties

TNGB Partners will undertake to:

- comply with the principles defined in the *TNGB Charter*;
- adopt TNGB SOPs and guidelines concerning informed consent, privacy, sample management, priority access criteria and quality control;
- regularly update the information on the biological samples in the central database according to the minimum dataset defined by TNGB;
- ensure the accuracy of any information on the samples;
- inform the Network of scientific publications resulting from the use of biological samples provided through the TNGB;
- actively contribute to the TNGB's development through regular participation to meetings and its promotion.

### 9.3. New Membership

- the criteria that have to be met to qualify as a TNGB member are under the responsibility of Telethon;
- new entries are requested to submit a letter of intent to Telethon;
- newly approved Biobanks will receive temporary annual financial support with the aim of facilitating their integration within Network activities;
- full integration will be achieved at the end of the year, upon approval by the Telethon Committee for Biobanks.

### 9.4. Penalties in the event of non-compliance with TNGB Charter

Pre-defined conditions whereby penalties can be imposed in the event of any non-compliance with the Charter and Network policies are the sole responsibility of Telethon Committee. All Biobank Directors agree to produce an **Annual Report** for the Telethon Scientific Committee with the detailed description of:

- Network activities;
- Network and Biobank services;
- adherence to Network principles and rules.

The implementation of any legal penalties will rest on the Annual Report, which will cover activities of the Network and of the single Biobanks.

## **9.5. Authorship/Collaboration**

It is understood that the main objective of the Network is to provide the scientific community with biological samples and related data as a service. This service will be acknowledged as such in any ensuing scientific publication and will not necessarily entail co-authorship of the publications by the Network's members.

If, however, the Biobank's staff actively participates in the scientific activities described in the publication, besides providing biological samples from the Biobank, co-authorship will be admissible.

If Biobank members use biological samples from their Biobank and produce a scientific publication as first or last author, they should comply with the same rules followed by external researchers.

## **10 - AGREEMENTS**

### **10.1. Agreements between TNGB and Patients' Associations**

TNGB can make agreements with national and international Patients' Associations. Each agreement should be regulated by a written document approved by the Network Board who selects the Biobank/Biobanks providing the required service.

TNGB and the Association should completely accept the respective Charters.

The agreement should describe all the requested and the provided services. It will be detailed the economic aspect and all the "sample in and out" procedures.

### **10.2. Agreements between TNGB Partners**

The Network can benefit from Biobank services in order to fill possible technical gaps. In this regard written agreement can be made between Biobank Directors to provide services to each other.

Services should occur following the "sample in and out" rules.

If the sample information is maintained in the database of each involved Biobank, it should be published only once in the TNGB catalogue, the decision depending on the parties involved.