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REVIEW

Establishment of a cardiac biobank in a Department of Pathology and Laboratory Medicine

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Biobanks are considered to be important resources of Departments of Pathology and Laboratory Medicine allowing the clarification of relevant disease mechanisms and the improvement of the diagnosis, prognosis, and treatment of both pediatric and adult cardiovascular diseases. To successfully establish a cardiovascular biobank, it is important to consider the public opinion and views on it and the factors involved in the willingness of the public to participate in the donation of genetic material. The literature was systematically reviewed to identify the attitude and willingness of patients affected by congenital and acquired heart disease to participate in biobanking research. Six relevant studies were identified in which it was indicated that psychosocial and demographic characteristics, as well as the patient's medical condition, could influence patient and family members' attitudes and willingness to participate in research. In both congenital and acquired heart diseases, participation in biobank research activities was higher if patients and their families were approached when hospitalized, but not during the acute moment of their illness. Other quantitative and qualitative studies are required to improve patient and family participation in these research initiatives.

The great advancement made in the field of molecular biology and the sequencing of the human genome has led to a deeper understanding of the molecular basis of human diseases, thus entering in the era of personalized medicine. Despite the enormous and invaluable contribution of animal models in the understanding of both physiology and disease pathogenesis, human tissue sampling has become imperative for fulfilling the potential promise of personalized medicine. Therefore, it has become necessary to create infrastructures in which the processing, handling and storage of biological samples, as well as the management of the associated clinical information take place. During the past few decades, there has been an increased interest in the field of public health from researchers and scientists, which has led pathologists and biochemists to create human biological biobanks with the objective of increasing the knowledge about genetic, behavioural and environmental determinants of many diseases,

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supporting the development of new drugs and therapies and improving quality of life.

In 2008, the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) was established as a pan European research infrastructure and biobank network with the aim to support high quality biomolecular and medical research. The structure of the BBMRI network is represented as a "disturbed hub and spoke scheme" where the various biobanks, biomolecular resources and specialized technology centres are connected via their specific hub (Fig. 1). BBMRI has defined a generally accepted classification of biobanks, which distinguishes between only two major biobank formats with several subtypes characterized by distinct and complementary scientific value: population-based and disease-oriented biobanks (1). Population-based biobanks (longitudinal population-based biobanks, population isolates, and twin registries) collect samples and epidemiological/clinical data from volunteers without specific inclusion or exclusion criteria and aim to mirror the status of the general population (2). Disease-oriented biobanks (biobanks of tissue samples and clinical data also referred to as disease oriented or clinical biobanks) collect samples from patients suffering from a specific clinical condition with the aim of contributing to diagnostics, basic science research, drug and therapy development of specific diseases (3).

Numerous collections of biological material established all over the world are constituted especially from the donations of the patients and their families who, generously, have collaborated and continue to collaborate for the development of research. Thus, it is necessary to establish some regulations to address the practice of researchers also to promote interdisciplinary collaboration and a rigorous methodology, adhering with Ethical Committee requirements. The development of genetic and genomic technologies, the proliferation of databases containing large amount of genotypic and phenotypic data and wide-spread data sharing among institutions have led to the need to develop best practices for addressing ethical, legal and social issues (ELSI) of biobanking, thus protecting the participants in biobanking research (4, 5).

Biobanks and the Departments of Pathology and Laboratory Medicine

One of the most common way for biobanks to acquire specimens is to obtain residual or "leftover" specimens originally collected for clinical care from hospitals, clinical laboratories and pathology departments. For over two hundred years, pathological institutes have collected human tissue samples for histopathological analysis and further research. Thus, collections of paraffin embedded tissue samples may be considered the predecessor of today's biobanks. Moreover, in pathology and laboratory medicine as well as in biobanks, the pre-analytical phase, consisting in the preparation of the biological material for the subsequent analyses, impacts enormously on the results obtained from experiments. In biobanks, the pre-analytical phase consists of working according to standard operating procedures (SOPs) which are essential in modern laboratory medicine to obtain high quality samples, especially in the era of precision medicine. For all these reasons in most of the medical centres, biobanks are usually associated to Departments of Pathology and Laboratory Medicine and they have become an important component of the routine practice of pathology (6).

Biobank for cardiovascular research

Cardiovascular diseases (CVD) are the major cause of human morbidity and mortality worldwide, accounting for 45% of all deaths in European countries in 2016 (7) and almost a third of deaths worldwide (8). According to recent epidemiological information, despite continual improvements in preventive therapies, in Italy cardiovascular mortality represents 37% of all deaths (9) which has a huge impact on public health and on economic resources. The potential of cardiac tissue banking in cardiovascular research has long been recognized. The genetic susceptibility to CVD will be understood clearly when combined with genomics, proteomics and genotyping; hence, the potential of existing DNA biobanks and registries will help in finding answers to the genetic conundrum in CVD (10, 11). Furthermore, as highlighted in the BioHEART-CT cohort study, complex network and machine

learning approaches will be applied to biological and clinical datasets to identify new biomarkers for early diagnosis and to suggest new targeted therapeutics (12). Accordingly, there are major efforts worldwide to professionalize biobanks, including consenting and governance, biospecimens, risk factor and related data, informatics and linkage to electronic health records, in order to provide high quality preservation and storage of biological samples with a potential scientific impact in the era of personalized medicine and drug treatment (11, 13-16).

Within this study area, clinical care for patients with congenital heart disease (CHD) should require more consideration. Indeed, these patients have an increased risk of diverse adverse outcomes including arrhythmia, hypertension, heart failure etc. In order to facilitate the biomarker research in adults with CHD and associated diagnoses, a protocol to collect, process, and store biospecimens from adults has been developed (17).

A major advantage of a cardiovascular biobank is that it allows to conduct research on large sample sizes collected with standardized procedures combined with extensive phenotypic and genotypic data. In fact, several institutions all over the world have established human heart tissue biobanks. In 2017, an association for cardiovascular research was established in Italy as a result of the funding support received from the Italian Ministry of Health. The Cardiology Network includes 19 institutes, which represent excellence in the cardiovascular field, with the obvious advantage of collecting a large number of samples from diseased and healthy participants and thus strongly supporting the scientific progress towards personalized medicine in the area of heart disease. For the long term success of a biobank project it is important to know what the public opinion about these infrastructures is and the public willingness to participate. The theory of reasoned action (TRA), originally introduced in the field of Social Psychology, has been widely used to explain individuals' behaviour in health contexts (18, 19). The theory postulates that individuals' behavioural intention is influenced by their attitude and subjective norm, and that this in turn influences behaviour (Fig. 2). The research assessing attitude toward the consent process and widespread data is limited, however, a number of issues to be assessed have been identified: public knowledge and public views on biobanks, willingness to donate and to agree to sample storage, donors' motivation, perceived benefits and risks, influence of credibility and trust in research institutions, trust toward biobanks (20-24). The aim of this review is to explore the literature and to assess the general attitude of public to donate their biological samples linked with health information and to participate in cardiac research. Understanding patients' perceptions and characteristics can help in developing the best practices for biobanking in the fields of cardiovascular diseases.

METHODS

The authors analysed the theoretical background in the current literature about biobanks in cardiac patients in order to identify the characteristics and attitudes of patients affected by cardiovascular diseases (CVD) and to design an efficient protocol to assess the social attitudes towards the creation of a cardiac biobank in accordance with systematic review guidelines (25).

A systematic review of the literature was conducted in the database of PubMed using a combination of key words: "biobank", "biobanking", "social attitudes", "participation in the research", "cardiology", "cardiac surgery", "congenital heart disease", "adolescents", "heart failure", "cardiovascular", "myocardial infarction", "coronary artery disease". For the selection of the keywords, we have taken into consideration the keywords utilized in previous systematic reviews (20, 26). The initial search, carried out in September 2019 for all studies available from 2009, identified 497 studies, which were then selected on the inclusion criteria of keywords, English language and time of research. Papers, which were not in English, were excluded, as well as those with titles or abstracts not pertinent to the focus of this study. Finally, only 6 relevant studies regarding the attitude and willingness of patients affected by CVD to participate in biobanking were found (Fig. 3; Table I).

RESULTS

The results of the literature review show that there

is a lack of data regarding the social attitude and participation toward biobanking of patients affected by cardiovascular diseases. Among the 6 selected studies, 1 study investigated the opinion of biobank participants to be informed about unexpected genetic findings (27), 2 studies regarded participation of pediatric and adolescent patients with childhood–onset heart diseases (CHD) in biobanking (28, 29), 1 study assessed the attitudes and willingness of parents of CHD children to donate their children's biospecimens for future research (30), 1 study investigated the reasons why cardiovascular patients decline to participate and to enrol in a biobank (31), and 1 study proposed a methodology to explore the attitude of patients from a tertiary cardiology centre about participating in biomarker-based clinical trials (32).

The study of Haukkala et al. (27) on patients who experienced the process of receiving the long QT syndrome unexpected genetic information shows that participants mainly had positive experiences in the process and thought that genetics results should be returned to participants, in particular if they could be life-saving information.

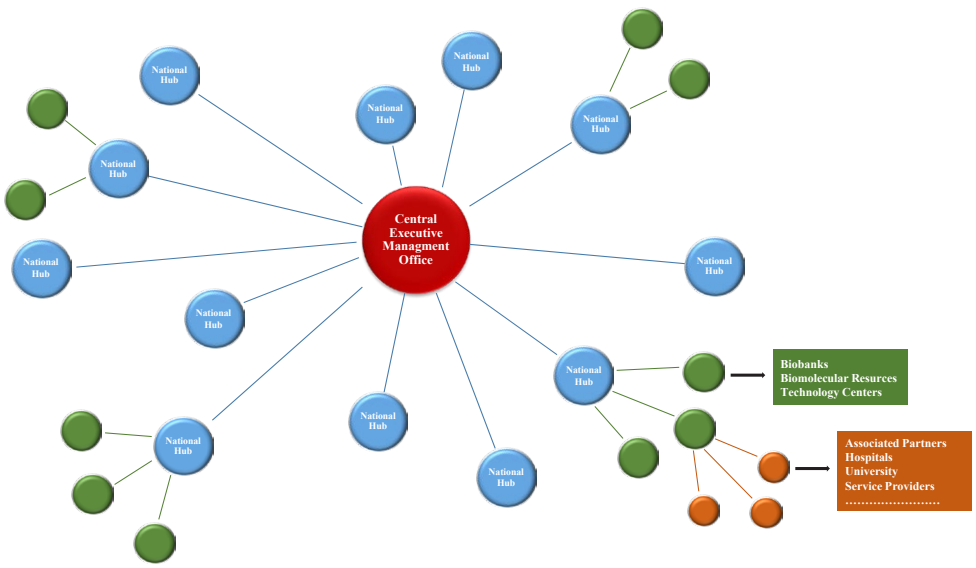

Fig. 1. *The distributed "hub and spoke" structure of BBMRI*

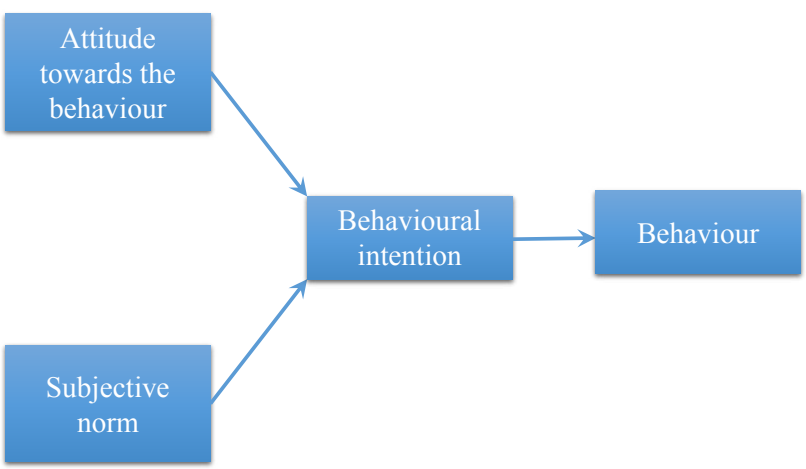

Fig. 2. *Diagram of the relationships in the Theory of the Reasoned Action*

Regarding the opinion and participation in biorepositories of pediatric and adolescent patients affected by cardiac diseases and their parents, two interesting studies were conducted in Canada (28, 29). When it comes to pediatric patients (2-16 years) participation in biobanking, pediatric consent rate was similar to that observed in the adult cohort and it was 100% for parents of CHD children (29). A high willingness to donate biological material has been observed in adolescents (14-18 years) who were in hospital and in their parents (28). However, a less altruistic approach toward pediatric biobanking was seen in adolescents surveyed in school settings and their parents. It is interesting to note that several features influenced pediatric or adolescent participation, including age, race, and the invasiveness of the procedure performed to obtain the biological sample. In addition, it seems that disease severity has a great impact on biobanking attitude. In adult vulnerable patients with cardiovascular disease presenting acute symptoms, critical diagnoses, emergency admissions and diminished capacity to comprehend, the 2 primary themes which emerged from explanations when declining to contribute to

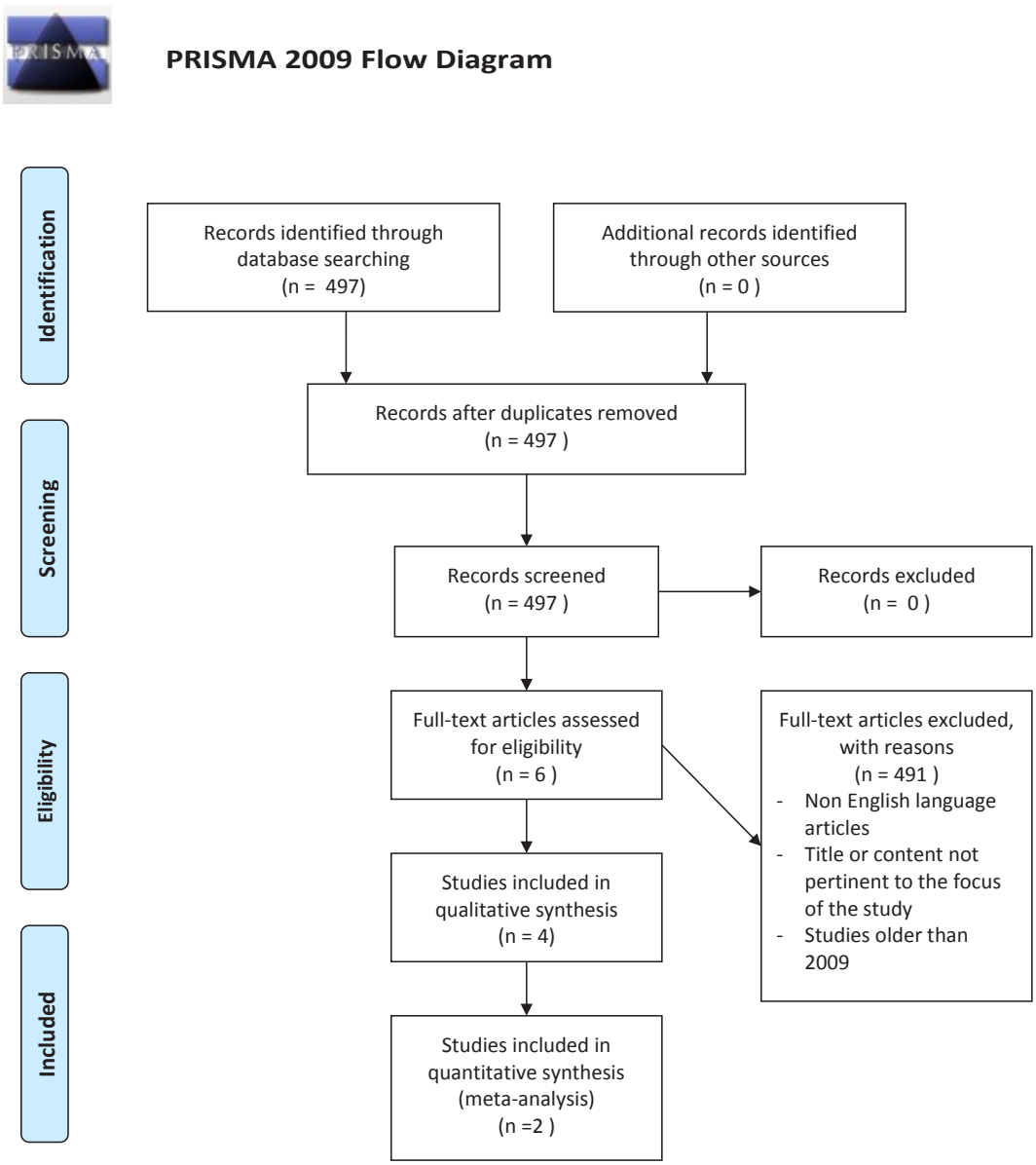

Fig. 3. *PRISMA flow-diagram of the systematic review (34). For more information, visit www.prisma-statement.org*

Table I. *Results of literature search on the social attitude and participation toward biobanking of patients affected by cardiovascular diseases*

Authors	Year	Country	Type of Study	Sample	Study description
Haukkala A et al. (27)	2013	Finland	Cross sectional study; questionnaires and interviews	27	How biobank study participants, who were found to have long QT syndrome (LQTS), a potentially life-threatening but treatable cardiac arrhythmia condition, experienced the process of disclosure of unexpected results and referral to health care.
Kong CC et al. (28)	2015	Canada	Exploratory survey	423	This survey assesses the opinion of adolescents (aged 14 - 18 years), both healthy and in the hospital clinic setting, and their parents regarding biobank participation and related subjects. In particular, willingness to donate biospecimens, appropriate age of assent and the perceived importance of reconsent when they reach the age of majority.
Papaz, T et al. (29)	2012	Canada	Longitudinal Research	3637	The study identifies specific barriers to pediatric participation in biorepositories relative to adults, and proposes strategies to improve ethical and responsible participation of pediatric-aged patients in large-scale genomics and biorepository-driven research without significantly increasing research burden for affected families.
Qiu S et al. (30)	2018	China	Exploratory survey	319	In this study, the aim is to examine factors that may influence Chinese parents' willingness to donate their children's biospecimens in pediatric wards. This may improve the participants' understanding and enhance participants' engagement in biospecimen donation. Furthermore, the authors try to determine whether willingness differed by parents' demographic and children's disease-based characteristics and to get an idea of parents' attitudes toward their children's participation in the consent for biospecimen research.
Williams, PH et al. (31)	2013	USA	Qualitative study	568	A qualitative study was conducted to explore 568 cardiac care patients' explanations of why they declined to contribute their samples to a future genomic research biobank.
Micheu, MM et al. (32)	2018	Romania	Descriptive, prospective and longitudinal single centre study	333	The research's aim is to explore the attitude of patients admitted in a Romanian tertiary cardiology center to take part in biomarker-based clinical trials. Variable assessed are demographics, medical history, attitudes toward biomarker-based clinical trials and trust in medical researchers.

research biobanking initiatives were intrusion and autonomy (31). Patients thought that the process was too intrusive considering their present illness status or hospitalization. Similar findings were found in parents of children with CHD who presented a lower consent rate when approached during situations of high stress, such as cardiac surgery or catheterization (29). Adult patients often give broad consent for the use of their tissues and blood specimens in research projects; however, little is known about the parent willingness to donate their children's biospecimens to be stored for future research. A study conducted

in China to assess attitudes and willingness of parents of children with CHD regarding donating biospecimens for future research, revealed that nearly 70% of parents were willing to donate, the most important motivation being that doing so might help other children. The willingness to donate was positively influenced by parents having a higher education level and the children's hospitalization history and negatively influenced by the potential physical discomfort for the children. The majority of the parents wanted to receive the research results related to their children's biospecimens (30).

CONCLUSIONS

The literature considered indicates that it is crucial to consider patient and family member psychosocial and demographic characteristics which can influence their attitudes and willingness to participate in research and provide consent to donate biological samples. Specific patient characteristics linked to their medical condition and the moment in patient healthcare trajectory (for example diagnosis, hospital admittance for intervention and follow-up) need to be considered.

In studies regarding cardiac disease (both congenital and acquired), patients who were hospitalized and their family members donated their biological samples more willingly than other patients who were not hospitalized in that moment. However, those who were hospitalized during the acute/critical phase of their illness did not feel that it was an appropriate moment to be approached for biological sample donation. There are also studies showing the opinions, feelings and attitudes of parents and their willingness to donate their children's biospecimens for use in pediatric research and for a hypothetical pediatric biobank. These studies confirm the need for specific policies dedicated to this kind of biobank, highlighting several variables which may influence the parents' opinions and decisions towards the donation, such as the nature of disease, younger age, race and the location of consent.

The consideration of all these elements will allow to structure efficient and tailor-made interventions aimed at educating specific patient populations, and to increase patient and family member participation in research and the probability to donate their biological samples. Finally, a multidisciplinary collaboration, which involves professional figures who can take into consideration these peculiarities, linked also to the psychosocial and ethical aspects, is highly recommended (33).

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