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Bio-banking in dentistry- golden age Era - A systematic review

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Abstract
Biobanks are not-for-profit services for the collection, processing, storage and distribution of biological samples and data for research and diagnostic purposes. The biobank is known and established, a capital asset for the process of precision medicine, for supporting and improving research clinically and biomedically. Vast evolution in the tract of biomedical research manifolds the situation for requirement and lasting difficulty of acquirement, preservation, and analysis of human samples. In dentistry, biological materials and data obtained from questionnaires investigating oral conditions can be stored and used for large-scale studies on oral and systemic diseases. To give some examples: gene expression microarrays obtained on bio-banked specimens were used in the identification of genetic alterations in oral cancer; efforts to identify genetic mechanisms behind dental caries have been based on an integrative analysis of transcriptome-wide associations and messenger RNA expression. Cryo-preservation of dental pulp stem cells is a common practice in tooth biobanks.

Keywords: Biobanking, microassay, biomedicine, cryopreservation

Introduction

The biobank is nowadays considered a primary resource for the development of precision medicine. A biobank is defined as "a non-profit service unit, aimed at collecting, processing, storing and distributing human biological samples and data related to them, for research and diagnosis. It is officially recognized by the competent health authorities, applies a quality system and guarantees the rights of those involved". [1] Biobanks form a foundation to modern biomedical research, better understanding of disease mechanisms and development of novel therapies and diagnostic tools for common diseases. This is particularly important for the grand societal challenges regarding the health of the ageing population, but also to better understanding the role of environment and nutrition to human health. It must be emphasized that in global context, the long tradition of collecting and storing human biospecimens and associated data (i.e. biobanking) is an unquestionable European strength. [2] If biobanks receive adequate support and are able to solve the technical issues and maintain societal acceptance, a pan-European biobanking and biomolecular resouces Research Infrastructure (BBMRI established under ERIC regulation) will become a major asset in the global competition in addressing the heath-related grand challenges. [3] Several guidelines on the design and development of biobanks have been published by professional societies of individuals and organizations. The ISO 20387:2018 "Biotechnology - Biobanking - General requirements for biobanking" is addressed to all biobank. The requirements cover major aspects, such as the definition of an advisory board, and the mission of a biobank in terms of the types of sample and/or disease considered, the related data and procedures, and the approval of a relevant institutional review board and/or medical ethics committee. [4] Therefore, it is interest to describe biobanking with another important requirement for biobanks concerns the management of all contributors' informed consent to the project in accordance with General Data Protection Regulations (GDPR 679 2016) before any medical procedures, and all biological samples collected need to be pseudonymized to preserve donors' privacy.

Storage method of bio-banking

The types of sample stored vary according to the biobank's mission. Blood and DNA are the most common, but many other different specimens can be collected too, including: (1) fluids, such as saliva, urine, tears, etc.; (2) blood corpuscles; and (3) tissues. While pathological repositories are the most common, biobanks can also store biospecimens and data from healthy volunteers. Pseudonymized samples should be processed as soon as possible after collection, and stored immediately as necessary, depending on the characteristics of the specimens (e.g. at −80 ◦C, in liquid nitrogen or in formalin). Storing several aliquots allows for a greater exploitation of biological samples for clinical and research. The strategic work of BBMRI-PP had several dimensions and can be looked upon from very different perspectives. On one hand, BBMRI will operate as a bridge between sample donors (either patients or healthy individuals) and scientists performing biomedical research in academic or pharmaceutical settings. It will also operate as a firewall preventing certain types of sensitive information from flowing inappropriately between donors and researchers. BBMRI has and will be responsibilities toward patients and toward researchers. In addition, it will be responsible towards researchers to provide the highest possible quality of biospecimens and data to support research excellence. Concerning the strengths during the BBMRI-PP, the scheme has clearly been beneficial to bringing unforeseen cohesion to the European biobanking scene: an increasing number of biobanks from an increasing number of EU Member States and associated states have applied for associate member status in BBMRI-PP (and most have received it, too). The WP structure of BBMRI has also helped to establish national biobanking networks and to structure their activities. Also, governments and Ministries have recognized the importance of this process and several European countries have made huge financial commitments towards national biobanking activities. (Table 1)

Table 1: Biobanks in general usage criteria and most frequently collected specimens.

Biological sample category	Name and website, where available (last accessed 20 April 2021)	Location	Material stored	Mission
Pathological	Coriell Institute for Medical Research https://www.coriell.org/	USA	Wide range of biological samples Research on human genetic disease	Research on human genetic disease
Pathological	International Agency for Research On Cancer (IARC) Biobank (IBB) https://ibb.iarc.fr	French	Wide range of biological samples, including oral cancer samples	To find biomarkers
Pathological, data B	BioResource Center, RIKEN https://web.brc.riken.jp/en/	Japan	Various oral diseases biosamples including oral cancer, disorders of the hard tissue of teeth, diseases of supporting structure of teeth.	To receive strategically and systemically deposit/donation, manage, upgrade and distribute bioresources and the associated information in order to promote science, technology, and innovation
Healthy	BioEden Tooth Cell Bank https://www.bioeden.com/uk/	United Kingdom	Stem cells from pulp	For patients' personal therapeutic use
Pathological, healthy, data	UK biobank https://www.ukbiobank.ac.uk	United Kingdom	Wide range of biological samples, including saliva and teeth	Research purposes
Pathological, healthy, data	Malaysian Periodontal Biobank	Malaysia	Plaque	To find biomarkers for diagnosis, prognosis, therapy, to improve patient management

Table 2: Bio- Banks in dentistry: A summary of the most frequently collected biospecimens and their uses.

Material	Collection method	Media	Temperature	Timing	Uses	Conservation method	Main references
Saliva	Rinse mouth with warm water, then spit into a sterile Collection tube (approx. 1.0–2.5 ml) without touching the inside of the tube. None 4 ◦C using cold packs or ice Within 24 h (max48 h) Genetic research and correlations with other pathologies −80 ◦C Woo and Lu (2019) [63] **Note**: prior to saliva collection, avoid using mouthwash, fluoride rinse, food, drinks, chewing gum, or smoking.	None	4 ◦C using cold packs or ice	Within 24 h (max48 h)	Genetic research and correlations with other pathologies	−80 ◦C	S. Mate (2014) ([10]
Deciduous teeth	Rinse teeth in clean water, without using detergents, and leave to dry overnight before placing them in a tube. Or Curylofo-Zotti *et al*. (2018) [64] Biobank personnel inspect the teeth. If a tooth has visible traces of blood, is still damp and/or smells, it is rinsed in distilled water and dried overnight before its examination and recording of variables	None	Room temperature	Variable, depending on the bank's mission	Study the effects of environmental and dietary factors on health.	4 ◦C (refrigerator) −10 ◦C (freezer)	D.Smith *et al*. (2012) [15]
Adult teeth	Extracted teeth are placed in sealed containers containing 75% alcohol.	75% alcohol	Freezer or refrigerator	Variable	Procure and store teeth, then process them to obtain bone graft substitutes	Room temperature	P. Mazur (1984) [15]
Adult teeth	After extraction, superficial dirt is removed with tap water and neutral soup	Deionized water	Room temperature	Immediately after extraction	Research purposes	4 ◦C or −10 ◦C	D.Gauo *et al* (2000) [12]
Stem cells from dental pulp (DPSC)	Extracted teeth are placed in tubes containing Dulbecco's modified Eagle's medium (DMEM) with 20% fetal bovine serum (FBS).	Dulbecco's modified Eagle's medium (DMEM) with 20% fetal bovine serum (FBS)	4 ◦C	Tooth processed within 24 h.	Studies on undifferentiated mesenchymal cells and DPSC culture −80 ◦C	−80 ◦C	C.A. Amorim (2011) [17]

Bio banking ans its key features

Although the term "biobank" first appeared in scientific publications in 1996 [4, 5], there is still no agreement on a precise definition. The term "biobank" has been gradu ally adopted to describe any collections of biospecimens or human genetic data suitable for research purposes [6]. One of the first definitions, i.e. "a collection of biological material and the associated data and information stored in an organized system, for a population or a large subset of a population", was introduced by the Organization for Economic Cooperation and Development (OECD) [5, 7]. This description was later updated to depict biobanks as "structured resources that can be used for the purpose of genetic research and which include (a) human biological materials and/or information generated from the analysis of the same and (b) extensive associated information". Sample types stored go on to the biobank's operation. The common biobanks are of Blood and DNA, and many more various specimens could be gathered too, such as biological fluids, and tissues. The pathological depository is the one commonly seen in biobanks, but even bio-specimens from healthy volunteers and their data can also be stored. The acceleration in requirement and need for research in the field of dentistry, particularly in the tract of oral oncology,

OPMD, and the developing grounds regarding the linkage with oral and systemic disorders, has made the need for biobanking in the field of oral health. Watson and Barnes proposed a schema for classifying human research biobanks that was adopted by the Canadian Tumour Repository Network (CTRNet) [18, 20]. This system enables the categorization of biobanks following four functional elements: the type of donor/participant, the col lection methods and design (e.g. retrospective or prospective accrual, size and scope), the features of the biospecimens (e.g. the predominant type of biospecimen preservation, such as fixed or frozen) and the nature of the brand and intended users (e.g. single group, institution or multiple users) (Table 2) To accommodate advances in biotechnology and life sci ence, the concept of biological resource centres (BRCs), infrastructures consisting of service providers and reposito ries of living cells, genomes of organisms and information relating to heredity and the functions of biological systems, was introduced by OECD [11]. Based on these definitions, boundaries between biobanks and other research collections cannot be considered clear-cut [6]. However, the European Commission highlights that biobanks are devoted to col lecting biological samples and associated data for medical scientific research and diagnostic purposes and to organizing these in a systematic way [12]. In addition, the key factor that distinguishes a biobank from any other type of research collection is that established governance mechanisms are in place to allow outsiders access to resources in a systematic way.

What to know when building a biobank?

Given the complexity of biospecimen handling and man agement, setting up a biobank may be challenging. Harati and colleagues tried to provide indications for the creation of a biobank, including accreditation, standards of practice and funding issues [16]. A guidance document pro duced by the government of South Australia suggests that a defined purpose or business plan is key, and governance, funding and other financial considerations, data and speci men management and consent must be considered [9]. In addition, the process of accreditation and the observation of the standards of practice allow biobanks to operate professionally and to provide biological specimens of adequate quality [17]. It is necessary to prioritize ethics, privacy, informed con sent, data security and standardization. According to the IARC, developing biobanks involves ethical, legal and social issues (ELSI) and requires the design of governance systems [3]. IARC's recommendations are based on guidelines that incorporate the knowledge gained from pro jects such as Standardization and Improvement of Generic Preanalytical Tools and Procedures for *In Vitro* Diagnostics (SPIDIA), BBMRI – Large Prospective Cohorts (BBMRI LPC) and the International Genomics Consortium (IGC) as well as the European Committee for Standardization (French, Comité Européen de Normalisation, CEN), Tech nical Specifications for molecular *in vitro* diagnostic exami nations and International Organization for Standardization (ISO) norm.

A focus on cancer-oriented biobanks:

Cancer-oriented biobanks aim to collect and store human biological samples for cancer research. To date, cancer-oriented biobanks are based on the collection of biological samples from patients with a specific disease (cancer) and controls, i.e. healthy tissues from cancer patients, and rep resent a long-term source of human biological samples with associated information, collected at the time of diagnosis and during consecutive therapeutic phases (e.g. before and during therapy, at follow-up and in case of relapse). Since tissue samples are key elements in most of the cases in these biobanks, an important role is played by pathology laboratories which (i) handle specimens, (ii) assess and ensure the adequacy of fresh sampling and (iii) represent the tissue curators and are responsible for FFPE specimen archives. In addition, linic al pathology laboratories are involved in the collection of whole blood and derivatives for routine purposes: this is important since liquid biopsies are collected in different scenarios, including clinical trials and translational studies [12, 13]. Pathology laboratories may represent the connection between samples and biobanks, or they could be part of a given biobank; nevertheless, strict collaboration with pathology laboratories is necessary in light of the control of preanalytical issues, such as cold ischaemia time and time to fixation (the latter for FFPE tissue specimens), which are essential to guarantee the quality of tissue sam ples and their derivatives for molecular (high-throughput) analyses. In this respect, for FFPE tissue samples, the time of fixation is also important since formalin fixation impacts DNA/RNA fragmentation and therefore affects the success of downstream molecular analyses. Recently, the temperature of formalin fixation has been shown to matter [14, 15] and cold fixation can be considered when aim ing to obtain a lesser degree of nucleic acid degradation. (Table 3)

Table 3: International standard ISO for biobanking: scopes and structure

ISO document	Scope	Main features discussed within the document	Key points ("take home messages")
ISO 20387:2018	To define the general, require ments for the competence, impartiality and consist ent operation of biobanks, including quality control requirements	General requirements	The requirements defined by ISO 20387:2018 concern resources, processes, manipulation, QC of biological material and associated data and the quality management system
ISO/TR 22758:2020	To provide support in the implementation of the requirements by ISO 20,387:2018 • To achieve staff expertise and the proper quality of biological material and data	Structural requirements Resource requirements Resource requir Quality management system requirements ements	A biobank should have procedures for safe handling, packaging, transport and reception relevant to the bio logical material concerned and should ensure the trace ability of biological material and associated data from collection and acquisition or reception to distribution and disposal or destruction. ISO 20387:2018 emphasizes that when the material for the biobank

	collections		coincides with samples requiring clini cal assessment and/or diagnosis, the process should be performed by qualified personnel and that specimen collection should never affect patient care ISO 20387:2018 emphasizes that when the material for the biobank coincides with samples requiring clini cal assessment and/or diagnosis, the process should be performed by qualified personnel and that specimen collection should never affect patient care

Bio banking in relation to periodontics

The aim of the prospective cohort study that was developed by the UK biobank (UKB) was to investigate the role of genetic, environmental and lifestyle factors in the causes of the most common diseases of middle age. The project began in 2007 and, by 2011, it had enrolled more than half a million volunteers from 40 to 69 years old from among the population registered for primary healthcare provision under the National Health Service. Participants' anthropometric and other physiological characteristics, including height, weight, bone mineral density, and blood pressure, as well as information on lifestyle, health and socioeconomic factors, were collected according to standardized protocols.

Table 4: Represents the oral samples roles title of the UK biobank approved research

Terms	Title of the UK Biobank approved research
Dental, teeth, periodontal, caries, oral	Associations of oral and gut microbiome-related exposures with cancer risk and mortality
Dental, oral	Relationship between oral health, dietary intake and nutritional status among middle- and older-aged adults in the UK
Saliva	Salivary biomarkers of a healthy diet and development of type 2 diabetes
Saliva, periodontal, caries, oral	Genetic and environmental risk factors associated with oral health
Tooth, teeth, oral	Investigating aetiology, associations and causality in diseases of the head and neck
Teeth	Relationship between oral health, dietary intake and nutritional status among middle- and older-aged adults in the UK
Periodontal, oral	Investigating the association between periodontal disease and systemic diseases
Oral	Potential causal interplay of lifestyle factors, sex hormones, oral health and chronic diseases
	Epidemiology of head and neck cancer
Dentistry	No results
Pulp	No results
Gingiva	No results

Bio samples collected for periodontal examination:

Biospecimens stored in a biobank may come from healthy donors as well as from patients. In the former case, the samples derive from biological material that would normally be discarded, such as umbilical cord blood or the placenta. The focus of this type of biobank is often prevention, involving efforts to associate exposure to various factors with diseases that might develop later on. This is the approach of a biobank collecting exfoliated deciduous teeth established as part of the Norwegian Mother and Child Cohort Study (MoBa) in 2008 [4]. The collection of teeth has become a powerful resource for obtaining important information on environmental exposure and nutrition in fetal life and early infancy. It has been demonstrated that traces of toxic and essential elements can become incorporated in the dental tissue during tooth formation, and they could serve as biomarkers of disease and nutritional status. By 2011, the MoBa tooth biobank had collected 9798 deciduous teeth from 7400 children at a mean age of 6.75 years, from among the 108,000 participants in the MoBa study during the years from 2008 to 2016 (with a response rate around 24%). Parents collected deciduous teeth in polypropylene tubes, after rinsing them in water without any use of detergents and drying them overnight. They then sent them, together with a signed informed consent form to the MoBa biobank, where they were registered and stored in dry conditions at room temperature. One or more types of deciduous teeth from the same donor without selection for a specific tooth type were collected at the MoBa. Teeth with caries or abrasions, and signs of root resorption were also included. (Table 4)

Bio-banks with data on oral diseases

Data obtained from self-report questionnaires and clinical examinations conducted by oral health professionals can be useful to clinicians and researchers, even without any associated sample collection. The Japanese Ministry of Education, Culture, Sports, Science and Technology launched the BioBank Japan (BBJ) Project in 2003 with the aim of providing evidence for the implementation of personalized medicine by constructing a large, patient-based biobank (BBJ). BioBank Japan Project collects DNA and serum samples from 12 medical institutions in Japan and recruited approximately 200,000 patients diagnosed with one or more of 47 target diseases, including periodontal disease [17]. An interesting genome-wide analysis that combined clinical and self-reported oral health data from the UKB and other clinical studies led scientists to identify 47 novel risk loci for dental caries. The results showed that, along with heritability, smoking, education, personality traits and metabolic measures also play a part in the likelihood of developing dental caries [18]. The genetic mechanisms behind dental caries were investigated by means of an integrative analysis of transcriptome-wide associations and messenger RNA expressions at the UKB [19]. A study to ascertain the prevalence of facial pain and examine the hypothesis that symptoms are associated with socio-demographics, dental health, adverse psychological factors, and pain elsewhere in the body was conducted using

UKB data [6]. Cross-sectional population data were obtained from the biobank, which recruited over 500,000 people in 2006−2010. The prevalence of facial pain was found to be lower than previously reported, and more common in women. Its multifactorial etiology was confirmed, also by significant associations found with psychological distress and a strong correlation with pain elsewhere in the body. (Table 5)

Table 5: Oral bio samples for analysis

Bio-banks	Liquid	Solid-Biopsy tissue
Biobanks, which store pathological oral samples	Saliva, Blood, Oral rinses, Gingival crevicular fluid, Oral swabs stored in liquid, Cell lysates of various patholo gies	Formalin-fixed archives, Frozen tissue, Tooth specimens, both deciduous and adult (peri odontally compromised and decayed), Dental stem cells (from dental pulp, periodontal liga ment, apical papillae, follicles) Dental plaque
Biobanks, which store healthy oral samples	Saliva, Blood, Oral rinses, Gingival crevicular fluid, Oral swabs stored in liquid Celllysates of normal oral mucosa.	Formalin-fixed archives and frozennormal tissue, Tooth specimens, both deciduous and adult, Dental stem cells (from dental pulp, periodontal liga ment, apical papillae, follicles

Czesnikiewicz-Guzik *et al*. (2019) examined data from the UKB (~750,000 participants) to seek an association between hypertension and periodontitis using two experimental approaches. First, they demonstrated a significant association between 4 single nucleotide polymorphisms (SNPs) linked to periodontitis (SIGLEC5, DEFA1A3, MTND1P5, and LOC107984137) and blood pressure (BP) phenotypes using a Mendelian randomization analysis. Support for their results then came from a randomized controlled trial comparing the effect of intensive non-surgical periodontal treatment with that of conventional care (control), and assessing average systolic 24-h ambulatory BP at 2 months. A reduction in systolic BP correlated with an improvement in periodontal status in patients given intensive periodontal treatment [9]. Considering a subsample of 1517 out of 17,937 eligible individuals registered in the Copenhagen Aging and Midlife Biobank, rosing *et al*. (2019) found tooth loss and prosthetic restorations associated with a worse self-reported oral health compared with having a full dentition, but not with worse self-reported general health and satisfaction with life

Future perspectives

Now it is most necessary of an hour for considering bio banks as a major functioning unit and not to reckon them as an inactive compendium of samples and data. They are now a dynamic asset, endlessly germinating, rising, and pioneer ing, leading towards newer proficiency and delivery of new knowledge domains necessitate. More informative goals for the future in respect of developing biobanks must consider, due to the ever-growing international communication system and mutuality of data and samples. The widespread information and importance of biological tissues and their utilization in the field of research should be propagated to all private practitioners, hospitals, and institu tions. It is also worth commenting on whether the collecting or usage of oral samples through biobanks in routine clinical den tistry is quiet and not executable, as some protocols and prob lems have still not been amply addressed. It may be regarding the period, method, and many detailed procedures for storing oral samples, and even the ethical rules and regulations that are yet required on the usage of biospecimens. Even though bio banking is qualified for preserving samples for the long term, their properties might alter with time, and the analyses may vary accordingly. This problem is faced especially in the case of stem cells which are cryopreserved for longer periods and their efficacy, which, is still not addressed completely.

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