



Review Article

Biobanking in dentistry: A 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. 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 biobanked 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. One of the largest studies on facial pain was conducted using Biobank data. Cryopreservation of dental pulp stem cells is a common practice in tooth biobanks. With the exception of teeth and pulp, also leftover oral soft and hard tissues may represent a source of healthy samples that has rarely been exploited as yet. While biobanks are increasingly attracting the attention of the scientific community and becoming economically sustainable, a systematic approach to this resource in dentistry seems to be lacking. This review illustrates the applications of biobanking in dentistry, describing biobanked pathological and healthy samples and data, and discussing future developments.

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1. 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]. The purpose of biobanks is mainly to support and improve clinical and biomedical research. They are useful not only for specific research projects, but also for sharing samples and data across countries, in large collaborative research efforts, which is particularly important in the case of rare diseases and genetic studies.

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

operators preserving biological materials. 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. 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 [2].

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 purposes.

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Table 1
Examples of biobanks in dentistry, by biological sample category (pathological or healthy oral source material). Other sources of information can be found at the following web sites: <https://specimencentral.com/biobank-directory/>, <https://www.biobanking.com/directory/>, <https://www.bbmri-eric.eu>.

Biological sample category	Name and website, where available (last accessed 20 April 2021)	Location	Year of establishment	Material stored	Mission
Pathological	Coriell Institute for Medical Research https://www.coriell.org/	USA	1960	Wide range of biological samples	Research on human genetic disease
Pathological	International Agency For Research On Cancer (IARC) Biobank (IBB) https://ibb.iarc.fr	French	1965	Wide range of biological samples, including oral cancer samples	To find biomarkers
Pathological	EuroBioBank network http://www.eurobiobank.org	Europe	2001	Wide range of biological samples, including saliva	Research on rare diseases
Pathological	BioResource Center, RIKEN https://web.brc.riken.jp/en/	Japan	2001	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.
Pathological, data	BioBank Japan https://biobankjp.org/en/index.html	Japan	2003	DNA, serum, medical records of 47 diseases including periodontitis.	Provide evidence for the implementation of personalized medicine by constructing a large, patient-based biobank.
Pathological	Malaysian Oral Cancer Database and Tissue Bank System	Malaysia	2006	Tissue bank since 2015 Cancer tissue, saliva, buccal cells related to oral cancer	To facilitate oral cancer research in Malaysia
Healthy	Store-a-Tooth Stem Cell Bank http://www.store-a-tooth.com/	USA	2006	Stem cells from pulp	For patients' personal therapeutic use
Healthy	BioEden Tooth Cell Bank https://www.bioeden.com/uk/	United Kingdom	2006	Stem cells from pulp	For patients' personal therapeutic use
Healthy	Population Lifelines https://www.lifelines.nl/researcher	Netherlands	2006	Saliva	Population-based cohort and biobank
Pathological, healthy, data	UK biobank https://www.ukbiobank.ac.uk	United Kingdom	2007	Wide range of biological samples, including saliva and teeth	Research purposes
Pathological	Istituto Tumori 'Giovanni Paolo II' https://www.sanita.puglia.it/web/ircs/bioanca	Italy	2008	Head and neck cancer tissues	Research on head and neck cancer
Healthy	Biobank of the Norwegian Mother and Child Cohort Study https://www.fhi.no/en/more/biobanks/	Norway	2008	Samples mainly from children, including deciduous teeth	To study the effects of environmental and dietary factors on health
Healthy	Korea Tooth Bank (KTB) http://www.brts.co.kr/	Korea	2009	Tooth-banking facility	To procure and store teeth, then process them to obtain bone graft substitutes.
Healthy	Hospital Tooth Bank (HTB) at Seoul National University Bundang Hospital (SNUBH) https://www.snubh.org/dh/en	Korea	2010	Tooth-banking facility	To procure and store teeth, then process them to obtain bone graft substitutes
Pathological	Malaysian Periodontal Biobank	Malaysia	2011	Plaque	To find biomarkers for diagnosis, prognosis, therapy, to improve patient management

Table 1 (Continued)

Biological sample category	Name and website, where available (last accessed 20 April 2021)	Location	Year of establishment	Material stored	Mission
Healthy	HUNT Biobank https://www.ntnu.edu/hunt/hunt-biobank	Norway	2011	Wide range of biological samples, including buccal swabs	Study purposes
Healthy, data	Tohoku Medical Megabank Organization https://www.megabank.tohoku.ac.jp/english/	Japan	2011	Blood, saliva, breast milk, plaque, urine. Oral health questions (through questionnaire), oral health test (physiological exam) MRI exams	To combine medical and genomic information during the rebuilding of the community medical system, and to support health and welfare in the Tohoku area
Healthy	Biobanca-SDN https://www.sdn-napoli.it/irccs-sdn/biobanca-sdn/	Italy	2012	Limited variety of biosamples, including saliva	Population study for prevention
Healthy	Qatar Biobank https://www.qatarbiobank.org.qa/home	Qatar	2012	Measurements, blood, urine, saliva	To investigate major determinants of ill-health and well-being in Qatar, public health
Pathological	Tokyo Medical and Dental University Disease BioResource Center (TMDU BRC) https://www.tmd.ac.jp/cmn/amr/minv/biobank.html	Japan	2013	Peripheral blood-derived DNA, saliva-derived DNA, serum, plasma, frozen surgical specimens, FFPE for tissue arrays	To collect high-quality samples with highly accurate clinical information to provide the basis for the utilization of ICT technologies such as medical big data and AI in the future. To support research in the medical field.
Data	Okadai Biobank http://biobank.ccsv.okayama-u.ac.jp/	Japan	2015	Biological samples (tissue, blood, urine, etc.)	To use biological samples and medical information as a base to promote medical research and to provide advanced medical care to patients.
Healthy	Shanghai Zhangjiang Biobank http://www.shbiobank.com	China	2016	Clinical informations Stem cells from pulp	For patients' personal therapeutic use, and storage service for associations
Healthy	Biobanca UPO https://www.uniupo.it/upobiobank	Italy	2016	Limited variety of biosamples, including saliva and swabs	Population study
Pathological, data	National Center Biobank Network (NCBN) https://ncbiobank.org/en/home.php	Japan	Unknown	Serum, plasma, DNA, RNA, solid tissue, spinal fluid, and others	Research and cure diseases that have a significant impact on national health.
Healthy	Kaiser Permanente Research Bank https://researchbank.kaiserpermanente.org/	USA	Unknown	Limited variety of biosamples, including saliva	Population study
Healthy	Servizio di biobanca del Policlinico di San Martino https://www.ospedalesanmartino.it/ricerca-scientifica/introduzione-crb/biobanche-e-servizi.html	Italy	Unknown	Limited varieties of biosamples, including saliva	Population study

Table 2
Biobanks in dentistry: a summary of the most frequently collected biospecimens and their uses.

Material	Collection method	Transport			Uses	Conservation method	Main references
		Media	Temperature	Timing			
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. 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	Woo and Lu (2019) [63]
Deciduous teeth	Teeth collected by parents Rinse teeth in clean water, without using detergents, and leave to dry overnight before placing them in a tube. 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.	–20 °C 4 °C (refrigerator) –10 °C (freezer) Or Solution of distilled water alone, distilled water with thymol, 70% ethanol, 10% formalin, and phosphate-buffered saline with thymol Or Dry, at room temperature	Verdonck-de Leeuw et al. (2019) [34] Tvinnereim et al. (2012) [44] Curylofo-Zotti et al. (2018) [64]
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	Pang et al. (2017) [40]
Adult teeth	After extraction, superficial dirt is removed with tap water and neutral soap	Deionized water	Room temperature	Immediately after extraction	Research purposes	4 °C or –10 °C	Curylofo-Zotti et al. (2018) [64]
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	Ferroni et al. (2015) [46]

Table 2 (Continued)

Material	Collection method	Transport			Uses	Conservation method	Main references
		Media	Temperature	Timing			
Buccal swab	Use the swab to rub the inside of both cheeks for 30–45 s for each cheek Swabs are placed in a sterile round-bottomed tube and allowed to air dry	If the tooth is to be processed immediately after extraction: phosphate-buffered saline. Polystyrene containers	4 °C	DPSC can be obtained up to 120 h hours after extraction Within 48 h	DNA sampling and genetic studies	–80°	Bressan et al. (2012) [45] Woo and Lu (2019) [63]
Plaque	Isolate sampling site with cotton rolls. Remove supragingival plaque with curettes and cotton pellets. Dry the site and remove subgingival plaque with sterile curettes.	Modified Stuart medium Scrapings are stored in sterile dnase-free and rnase-free polyethylene tubes containing 1 ml of phosphate-buffered solution.	In freezer or refrigerator	Immediately after	Association studies and population studies (to provide consistent numbers of patients with periodontitis and case controls)	–80 °C	Vaithilingam et al. (2015) [4]
Oral cancer biospecimens	Note: In patients with periodontitis, sampling is done at four or more sites with the deepest probing depths showing bleeding on probing. Note: In healthy subjects, sampling is done at interproximal sites showing no bleeding on probing. Subgingival scrapings are collected from the base of the pocket up to the gingival margin. Tissues surplus to diagnostic requirements, collected during biopsy, surgery or follow-up	Liquid nitrogen	–160 °C	Immediately after collection	Study the genetics underlying oral cancer development at both single-gene and genome/proteome-wide level	–80 °C Formalin	Zain et al. (2013) [15]

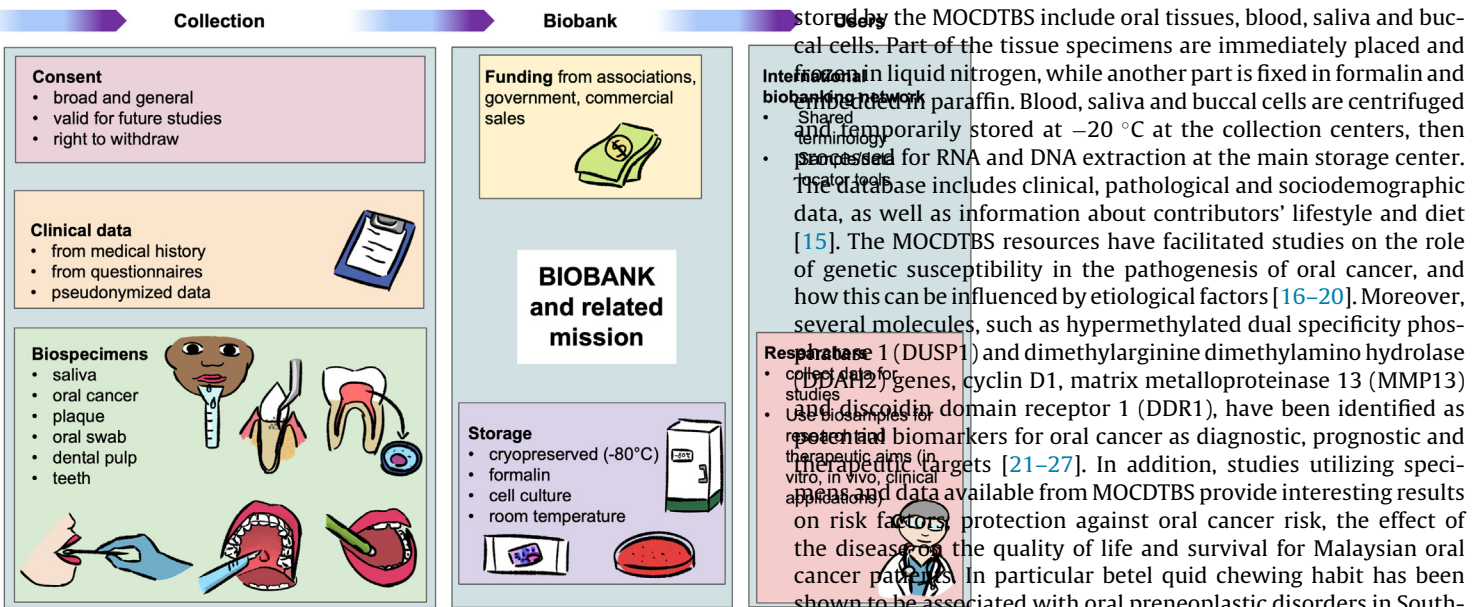


Fig. 1. Schematic flow chart concerning the biobank in dentistry.

The increasing demand for research in dentistry, and in particular in the field of oral oncology and the growing evidence of a link between oral and systemic disorders, have led to biobanking entering the field of oral health (Table 1). The most common biobanked specimens are saliva, adult and deciduous teeth, dental pulp cells, oral biopsies, buccal swabs and oral washes (Table 2). Some national programs (e.g. in Norway, Malaysia and the UK) are already generating interesting and promising results. For instance, it has been reported that stored blood, plaque or saliva samples have contributed to immunoproteomic and genetic studies aiming to identify biomarkers and genetic polymorphisms in periodontal disease [3–6]. Constituents of saliva have been found linked to oral diseases such as caries, periodontal diseases and cancer, and to systemic disorders like Sjogren's syndrome, cystic fibrosis, cardiovascular diseases, diabetes and HIV [7]. Stem cells of dental origin have been widely studied using *in vitro* and *in vivo* systems, and their intriguing capacity to reconstitute different dental and non-dental tissues has attracted the interest of several research groups in recent years [8].

Information coming from self-administered, structured questionnaires, possibly matched with other records (e.g. oral examinations) can also be stored and serve as a source of data for large-scale studies on oral and systemic diseases [9–13] (Fig. 1).

At this time, biobanking is a topic of growing interest to the scientific community, and also of economic interest, but a systematic description of the structure and potential of this resource in dentistry still seems to be lacking. The aim of the present review is to describe biobanking applications in dentistry. It covers articles that report on the pathological and healthy samples involved, and the related information on the donors, before going on to discuss possible future developments.

2. Biobanks of pathological oral samples

Several biobanks for specific purposes have been developed. The Malaysian Oral Cancer Database and Tissue Bank System (MOCDTBS) [14], and the Malaysian Periodontal Database and Biobank System (MPDBS) were established to collect samples and data from patients with oral disorders. Data and samples are collected from patients with malignant and pre-malignant oral lesions and from healthy subjects. The specimens collected, processed and

stored by the MOCDTBS include oral tissues, blood, saliva and buccal cells. Part of the tissue specimens are immediately placed and frozen in liquid nitrogen, while another part is fixed in formalin and embedded in paraffin. Blood, saliva and buccal cells are centrifuged and temporarily stored at -20°C at the collection centers, then processed for RNA and DNA extraction at the main storage center. The database includes clinical, pathological and sociodemographic data, as well as information about contributors' lifestyle and diet [15]. The MOCDTBS resources have facilitated studies on the role of genetic susceptibility in the pathogenesis of oral cancer, and how this can be influenced by etiological factors [16–20]. Moreover, several molecules, such as hypermethylated dual specificity phosphatase 1 (DUSP1) and dimethylarginine dimethylamino hydrolase 1 (DDI1) genes, cyclin D1, matrix metalloproteinase 13 (MMP13) and discoidin domain receptor 1 (DDR1), have been identified as potential biomarkers for oral cancer as diagnostic, prognostic and therapeutic targets [21–27]. In addition, studies utilizing specimens available from MOCDTBS provide interesting results on risk factors, protection against oral cancer risk, the effect of the disease on the quality of life and survival for Malaysian oral cancer patients. In particular betel quid chewing habit has been shown to be associated with oral preneoplastic disorders in Southern Asian populations and HPV16-specific IgG and IgM antibodies could represent a significant indicator of risk factors in oral squamous cell carcinoma in female patients [28–30]. Conversely, high serum levels of retinol and α -tocopherol affords protection against oral cancer risk, and patient survival and prognostic indicators are not influenced by ethnicity [15,31,32].

Saleh et al. conducted a study to identify genes differentially expressed between cancerous and normal oral tissues. To do so, they combined data from microarray experiments on formalin-fixed, paraffin-embedded tissues and data in the MOCDTBS. The gene expression microarrays obtained on biobanked oral cancer specimens revealed genes that were involved in regulating apoptosis, the cell cycle, metastasis and cell adhesion, including BCL2A1, BIRC5, MMP1, MMP9 and ITGB4 [33].

The NETHERlands Quality of life and Biomedical Cohort (NET-QUBIC) was described as a longitudinal observational cohort study in the field of head and neck cancer [34]. A biobank was established in parallel with the data collection. Frozen tissues, blood components and oral rinses were collected at the baseline, and at 6, 12 and 24 months. Multiple oral rinse and saliva samples were obtained. Saliva was collected with salivettes, which were centrifuged at 2000 g for 10 min, aliquoted and stored at -20°C . By the time of publication (in 2019), 739 patients with cancer and 262 informal caregivers had been recruited at 5 of the 8 centers in the Netherlands. Data and samples were stored according to FAIR (findable, accessible, interoperable, re-usable) principles. By granting researchers access to the NET-QUBIC data warehouse and biobank, the mission is to enable new research lines in clinical (e.g. optimizing treatment for elderly patients), biological (e.g. liquid biopsy analysis for detecting relapses), health-related quality of life (e.g. the impact of toxicity on quality of life), and interrelated research (e.g. health-related quality of life in relation to biomarkers and survival).

The University of Malaya started the Malaysian Periodontal Database and Biobank System (MPDBS) to facilitate studies on periodontitis. Using a validated classification system, data and biospecimens were obtained from 400 patients with chronic periodontitis (300 of them with a severe form), and 100 healthy controls. Blood and subgingival plaque samples were collected and processed from the start of the study, while saliva sampling was added later. Sample collection was accompanied by the acquisition of data on patients' demographics, medical history, clinical periodontal parameters, anthropometric measurements, socioeconomic status, habits, impact on oral health-related quality of life,

and prostheses [4]. The data and specimens collected are intended for use in studies focusing on research questions relating to genetic, microbiological and immunological aspects of chronic periodontitis. MPDBS resources have already contributed to demonstrating that immunoglobulin M (IgM) from sera of patients with severe chronic periodontitis could be used as biomarkers of the disease [3]. A cross-sectional study on obese subjects (who made up a significant number of the patients contributing to the MPDBS) found a very high prevalence of periodontitis (73.9%) among obese Malaysians [35].

The Tohoku Medical Megabank Organization baseline oral microbiome study involved 1349 participants, who underwent physiological measurements and an oral examination, completed a dental questionnaire, and provided biospecimens (saliva and dental plaque) [36]. Whole saliva (without centrifugation), supernatant saliva, salivary sediment, supragingival plaque from right molar teeth, supragingival plaque from left molar teeth, and tongue swabs were collected and stored in the Tohoku Medical Megabank at -80°C . Saliva and plaque microbiotas were analyzed using 16S rRNA gene sequencing. Differences in microbial composition and community structure were found in saliva and plaque. A greater diversity of the species in saliva and plaque coincided with more severe periodontal disease. Co-occurrence network analysis revealed strong positive and negative associations for microbial taxa in plaque and saliva with periodontitis-associated biofilm formation. The *Actinobacteria* and *Bacilli* classes showed a positive correlation in saliva.

Extracted teeth can be collected in biobanks for various purposes. Periodontally compromised or decayed teeth have the potential to serve as autogenous material for the reconstruction of alveolar ridge deficiencies in periodontal and implant surgery. Kim et al. (2010) introduced the AutoBT (autogenous tooth bone graft material). Extracted teeth are stored in 75% alcohol and kept in a refrigerator or freezer until they are sent to the clean rooms of the Korea Tooth Bank for processing. In the clean room, any remaining soft tissues are scraped off and the teeth are crushed into particles between 300 and 800 μm in diameter. The particulate is washed, defatted, decalcified, and lyophilized. After sterilizing with ethylene oxide, the final graft material is stored at room temperature ready for clinical use. In this case, the tissue bank serves the purpose of collecting and preparing samples for returning to the same donor patient in the form of a bone graft, or for use in animal studies, *in vitro* and *in vivo* [37]. The physical and chemical properties of AutoBT seem to make it effective for treating alveolar bone defects in the course of implant therapy [38–40]. To give an example, a prospective, randomized clinical trial was conducted to compare anorganic bovine bone with AutoBT for post-extraction alveolar bone augmentation, the vertical dimension of the alveolar bone, histomorphometry and implant stability (ISQ). No statistically significant differences were found between the measurements obtained in the two groups [40].

A first collection of clinical samples from the oral cavity was created in the UK biobank in 2009, where saliva samples are collected alongside other specimens, such as blood and urine [5,41]. 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 [5,41,42]. The questionnaire administered also included dental questions regarding any pres-

ence or absence of mouth ulcers, painful gums, bleeding gums, loose teeth, toothache, and/or dentures. From 2012 to 2020, the UKB approved 500 research projects (463 ongoing and 37 completed), 3 of which involved the use of saliva samples (UK Biobank. . .c2021) (Table 3) [43].

3. Biobanks of healthy oral samples

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 [44]. 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.

In recent years, several studies have demonstrated that biological material stored in biobanks can be a promising resource for therapeutic applications too. Stem cells have shown great potential for clinical applications in the field of regenerative medicine. Dental tissues – including pulp, apical papillae, follicles and periodontal ligaments – are a rich source of multipotent stem cells [8,45,46]. Stem cells from human exfoliated deciduous teeth have a strong capacity for proliferation and multilineage differentiation, and they can be accessed easily and noninvasively. They also remain undifferentiated and stable after long-term cryopreservation at the biobank, making them a potentially valuable source for tissue engineering and cell-based regenerative therapies [47]. *In vitro* and *in vivo* research has shown that dental stem cells can differentiate under certain conditions into odontoblast-like cells, and can be used for dental tissue engineering purposes, for pulp tissue restoration, lost periodontal ligament regeneration, and tooth structure generation [48]. Recently, stem cells of the apical papilla (SCAPs) have demonstrated regenerative properties when implanted *in vivo* using an organotypic model composed of human root segments. Indeed, *de novo* formation of dentin-like and pulp-like tissue were observed in the empty canal space of root segments after injection of SCAPs embedded in a platelet-rich plasma (PRP) scaffold and implanted in immunodeficient rats [49]. Dental stem cells can also regenerate into adipocytes, neuron-like cells, glial cells, osteoblasts, chondrocytes, melanocytes, myotubes, and endothelial cells. This would point to their potential clinical applications not only in dentistry, but also in many other situations [50]. Dental stem cells might be used, for instance, in the treatment of neurological and neurodegenerative pathologies, liver dysfunction, cardiovascular diseases, musculoskeletal disorders, and autoimmune diseases, minimizing the risk of rejection [51].

Table 3

UK Biobank approved research in the field of dentistry. Data retrieved from the UK Biobank website using specific queries regarding main dental terms (<https://www.ukbiobank.ac.uk/enable-your-research/approved-research>, retrieved on 30 March 2021).

Terms ^a	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

^a Some approved research can be found using multiple terms.

Thanks to their versatility, the ready accessibility of the tissue of origin (obtained during routine procedures, and from material that is usually discarded), dental stem cells have an appeal that has led to the development of numerous biobanks specializing in their collection. The first tooth bank, named “Three Brackets” was established at Hiroshima University in 2005. This was followed by the opening of other institutional centers or private companies for storing autologous dental stem cells. The largest and most experienced dental stem cell banks are currently located in the USA (BioEden, Stem Save, Store-a-Tooth), Europe (Bergen, Future Health), India (Stemade Biotech, Store your cells), Japan (Teeth Bank, Advanced Center of Tissue Engineering, Hiroshima University), Taipei (Taipei Medical University), and China (National Dental Stem Cells Bank) [52,53].

Dental stem cell banking has so far focused on cells contained in the pulp of human deciduous and permanent teeth, and wisdom teeth especially. SHED have demonstrated a minimal risk of oncogenesis and a higher proliferation and survival rate than adult dental pulp stem cells [54]. Not all teeth are suitable for stem cell recovery, however. They should have a red-colored pulp (a sign of cell viability), and no evidence of disease, such as apical abscesses, tumors or cysts [51]. Stem cells are preferably extracted from healthy teeth. They could be isolated from carious teeth too, albeit with a lower cell recovery and a higher expression of inflammatory molecules [55,56]. Deciduous incisors and canines are recommended for optimal results, while deciduous teeth distal to the canines and molars are generally not used for dental stem cell harvesting [51].

4. Biobanks 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 [57].

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 [58]. 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 [59].

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 [60]. 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.

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 [10].

Another study (Morse et al. 2014) involving 1517 participants drawn from the same Danish biobank reported that tobacco consumption was positively related, while alcohol consumption is inversely related with tooth loss. Oral examinations were performed by trained hygienists and questionnaires were self-administered. The study chose covariates based on data from the biobank, which enabled them to ascertain – prior to testing – which variables were most likely to be associated with the number of missing teeth, and with smoking and drinking habits [12].

Abbood et al. (2018) ran two case-control studies (self-reported cases and diagnosed cases) to investigate the link between ankylosing spondylitis (AS) and oral health using data and patients from the UKB. The cases were identified by means of an interview for the self-reported patients, and from the clinical records for the diagnosed cases. The study was then conducted using a self-report

questionnaire on respondents' oral health. The results showed an association between AS and oral ulcers [11]. Further studies will be needed to establish the link between AS and specific oral conditions.

Another study focused on the association between self-reported poor oral health and the risk of gastrointestinal cancer. Participants provided data on their oral health using self-report questionnaires, and they were followed up longitudinally until primary gastrointestinal tumor was diagnosed. The study involved 469,628 volunteers from the UKB and lasted 8 years. An association emerged between self-reported poor oral health and increased risk of hepatobiliary cancer, but not for the risk of any other gastrointestinal cancers [13].

5. Future perspectives

It is very important not to consider biobanks as static archives of samples and data. They are a dynamic resource, continuously evolving, improving and innovating, developing new techniques and serving new scientific requirements. The overall future goals of the development of biobanks should include an ever-increasing international networking and sharing of data and samples. As an example, the BBMRI-ERICs (BBMRI-European Research Infrastructure Consortium) Sample Locator (retrieved as a "request sample" link at <https://directory.bbMRI-eric.eu>, 16 March 2021) is a federated tool enabling researchers to query biobanks about individual-level data stored in the Connectors of different biobanks in order to find out which biobanks host the samples and/or sample-related data meeting the researchers' needs. A Minimum Information About Biobank Data Sharing (MIABIS) terminology has been developed to describe samples, sample donors, and events [61].

Specifically as regards biobanks in dentistry, some aspects need to be further explored. Not all the biological material recoverable in dentistry is currently stored in repositories. The chances of retrieving further data and valuable samples could be increased by developing new biobanks for collecting uncommon biospecimens, such as alveolar bone, periodontal ligament, loose and adherent gum. Cells derived from these tissues may provide hope for future applications not only in bone and periodontal regeneration, but even for treating various systemic diseases [62].

It is also worth mentioning that the collection or use of oral samples from biobanks in everyday clinical work is still not feasible because some issues have yet to be fully addressed. For example, how long oral samples should be stored remains to be seen, and ethical regulations are still needed on the use of biospecimens (especially dental stem cells). Although biobanking is certified for long-term preservation, samples may change with time, and the analyses conducted on them when they were collected may no longer exactly reflect their condition. In the case of stem cells, whether they could still be used effectively after very long-term cryopreservation remains to be established.

6. Conclusion

Biobanking in dentistry represents an efficient tool for effectively advancing research and clinical translation on oral and systemic disorders. It should also help to generate therapeutic benefits and be a fundamental step towards personalized medicine.

Data availability

Raw data and other supplementary material are available at the following repository: <https://osf.io/7zpcj>.

Author contributions

All authors contributed equally to the manuscript, gave final approval and agree to be accountable for all aspects of the work.

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