

**MOU- CHARITE-
UNIVERSITÄTSMEDIZIN
BERLIN**

COLLABORATION AGREEMENT / MEMORANDUM OF UNDERSTANDING

BETWEEN

Between the Terna Dental College and Hospital, Plot No. 12, Sector- 22, Nerul (W), Navi Mumbai, Maharashtra, India, Pin – 400706, hereafter referred to as Terna, represented by Dr. Shishir Singh

and

Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany, Tax Code DE 22 88 47 810, hereafter referred to as Charité, represented by Faculty Business Director (hereinafter Charité) with the executing unit: the Centrum 3 für Zahn-, Mund- und Kieferheilkunde Abteilung für Zahnerhaltung und Präventivzahnmedizin- / Departement of Oral Diagnostics & Digital Health & Health Services Research, located at, Abmannshäuser Str. 4-614197 Berlin,

WHEREAS

- the parties wish to establish a joint collaboration aimed at conducting research in the sector of machine learning in dental diagnostics;
- the parties wish to formalize this collaborative relationship through a dedicated agreement.

IT IS HEREBY AGREED

AND STIPULATED AS FOLLOWS

ARTICLE 1

The recitals form an integral part of this document.

ARTICLE 2

Through this agreement and for the entire scheduled duration, the parties undertake a scientific collaboration on the following research themes (*provided a detailed description of the research*):

STUDY SUMMARY:

Introduction

Caries is the most prevalent non-communicable disease worldwide, disproportionately impacting individuals from Low- and Middle-Income countries (LMIC). Conventional dental care, as practised in many high-income countries, is not in reach for the overall 4 billion people affected here and will remain unaffordable for years or even decades to come. Minimal Intervention Dentistry and Atraumatic Restorative Treatment have greatly reduced the technical requirements to practice high-quality dentistry even in LMIC contexts by allowing auxiliary non-dentist personnel, such as trained dental assistants, to expand their clinical duties. These approaches promise to make dentistry affordable, accessible and effective for the underserved majority worldwide. However, there is a bottleneck in the mass-implementation of Minimal Intervention Dentistry and Atraumatic Restorative Treatment. The crucial pre-requisite in the process of delivering them is diagnosis and treatment planning, a step which can only limitedly be delegated to auxiliary personnel.

Machine learning (ML), a field of artificial intelligence, has proven to be a powerful technique in

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diagnostics and decision support tasks. A popular field of machine learning is deep learning, where multi-layer (deep) neural networks are used to learn nonlinear patterns in data. For complex data structures such as images, so-called convolutional neural networks (CNNs) are most commonly used. In dentistry, CNNs are used to detect periapical and carious changes in periapical images, as well as periodontal bone loss in periapical and panoramic images, among others, all with acceptable or high accuracy.

The aim of this research project is to apply machine-learning, to provide a dental diagnosis and support treatment planning in the hands of non-dentists in LMIC. We will then establish feasibility, acceptability, and cost-effectiveness of this procedure to assist dental diagnosis and treatment planning in these settings.

Materials and methods

We plan to employ a deep-learning convolutional neural network (CNN) model for the photo-recognition in a feasibility and validation study-approach to study its diagnosis and treatment effects in-field in the settings we aim to serve.

To achieve this goal, we will make use of the widely available smartphones with cameras currently available in India, by creating an ML-based photo classifier (algorithm) that can be operated by non-dentists under a simple set of premises. This classifier will be trained on our native dental images, internally validated on a separate set of our native dental images, and then externally validated on the images provided from Terna. If the performance metrics in the external validation are low, the model will be retrained on a subset of the Indian images. The classifier aims to detect certain caries-related pathologies and suggest treatment pathways that have been pre-defined as cost-effective. The four dental diagnosis classes will be as following: sound surface/early carious lesion/advanced carious lesion/pulpal involvement, ulceration, fistula, abscess, root remnant.

Hypotheses

We hypothesize that the performance metrics e.g., accuracy, F1 score, in detecting and discriminating the four different diagnostic classes using the combination of photos + CNN will not be significantly different between AI and dentists, regardless of the setting in which the images were taken. We will further explore acceptability/applicability and cost-effectiveness of the classifier-based approach for preventive strategies in India.

ARTICLE 3

3.1 The parties agree that the collaboration pursuant to article 2 is subject to reciprocity.

3.2 The Parties shall ensure that (i) the Research Activities are performed in a professional and workman-like manner and in accordance with the state of the art in science and technology; (ii) they use qualified personnel with suitable training, education, competence and skill to provide the Research Activities; (iii) they comply with applicable laws and regulations in connection with any Research Activities, including any laws and regulations concerning the protection of personal data (including but not limited to the European General Data Protection Regulation); and (iv) that none of their personnel providing any Research Activities are restricted from doing so by any other

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contract, understanding or agreement.

ARTICLE 4

4.1 Terna shall provide Charité with photographs of the oral dentition as further described in Annex 1 hereto and in the format (collectively, "Data"). The specifications in Annex 1 may be jointly updated; any changes thereto shall only be valid if jointly signed by the Parties.

4.2 Charité shall analyze the Data and conduct further research based on such Data as further described in the research plan in Annex 2 hereto (collectively, "Research Activities"). The research plan in Annex 2 may be jointly updated; any changes thereto shall only be valid if jointly signed by the Parties.

4.3 The Parties shall provide each other in good time with any information required for the performance of the Research Activities.

4.4. Charité hereby declares its availability to promote, including on the proposal of the Department of Oral and Maxillofacial Sciences:

- conferences on the conducted activities.
- educational and/or professional training.

ARTICLE 5

5.1 The scientific supervisors for this collaboration agreement are:

- -for the Terna Dental College and Hospital: Dr. Shishir Singh
- for Centrum 3 für Zahn-, Mund- und Kieferheilkunde Abteilung für Zahnerhaltung und Präventivzahnmedizin- / Departement of Oral Diagnostics & Digital Health & Health Services Research: Prof. Dr. Falk Schwendicke

5.2 The supervisors are responsible for the proper execution of the project according to the work plan for their party. They have to organize and supervise the project and to promote its progress. The supervisors will also care for an appropriate stream of information to the other party and for the reporting as agreed before. The Parties shall meet regularly to discuss the project's progress and to clarify unsolved issues. The supervisors will determine the time, place, agenda and the participants of discussions/meetings.

5.3 Should a supervisor resign during the term of the project or for any other reason relinquish the project management, a staff member will be appointed by the respective party after informing the other party in writing about the proposed change. The replacement should be equally qualified to carry out the research work. If no agreement is reached within 4 weeks after receiving the written notification, the Agreement may be terminated prematurely for good cause.

ARTICLE 6

6.1 Work Results within the meaning of this Agreement are

- "Inventions" fit for protective rights according to § 1 German/ the respective Italian patent law
- "Qualified Know-How" according to the EU Directive No. 240/96 issued by the Commission on 31 January 1996,
- "Software" according to §§ 69a ff. German Urhebergesetz / the respective Italian patent law

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- "Basic Know-how" not fit for protective rights.

6.2 Any Work Results generated by staff members of Department shall belong to Department. Any Work Results generated by staff members of Charité shall belong to Charité. Jointly generated Work Results shall jointly belong to Department and Charité. Their share in the Work Results shall be determined in accordance with the significance of the contribution to the jointly generated Work Result. Neither Partner may assign any of its rights in the jointly generated Work Result without the prior consent of the other Partner, regardless of the name under which a protective right is registered.

6.3 In accordance with the provisions of the German Employee Inventions Act, the Parties shall claim for themselves all inventions and shares in inventions made under this Agreement which are eligible for protection as property rights. The Parties shall consult with each other regarding the most appropriate procedure for registering property rights, particularly in the case of joint inventions.

§7 RIGHTS OF USE

7.1 For duration of the Agreement the Parties shall grant each other a no-charge, nontransferable and non-exclusive right of use in the Work Results if and to the extent to which this is necessary for the successful performance of the Agreement.

7.2 In addition, the Parties shall grant each other at request and in so far as is legally permissible, solely for the duration and purpose of the research project, a nonexclusive, Non-sublicensable, non-transferrable, no-charge right of use in background protective rights.

7.3 The Parties shall enter into a separate agreement in respect of any desired utilization of the Work Results and/or background protective rights beyond the scope as specified above.

7.4 Both Parties shall be entitled to use the Work Results developed under this Agreement at no charge and in an unrestricted manner for scientific purposes (research and teaching).

7.5 Should either Party wish to abandon a property right, it shall first offer such right to the other Party in return for an appropriate consideration; should the other Party accept the property right offered, it shall acquire unrestricted title thereto. In this case, the party assuming the right shall also be responsible for payment of the accruing inventor's compensation.


ARTICLE 8

8.1 The Parties undertake to safeguard and promote the image of the joint initiative and of each Party. Specifically, the Parties' logos may be used in the context of the joint activities forming the subject of this agreement. This agreement does not confer any authority to use the university's name, brand or visual ID for commercial or advertising purposes. Any such use, which shall be exceptional and/or external to institutional activities, shall be regulated by specific agreements approved by the competent organs and compatible with the safeguarding of the university's image.


8.2 The use of logos extraneous to the institutional activities corresponding to the subject matter set forth in article 2 of this document requires the consent of the interested party.

ARTICLE 9

In addition to the above, other types of cooperation may be identified and put into practice, within the terms considered most suitable to achieve the aims of the agreement.

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ARTICLE 10

This collaboration agreement shall have a duration of 3 (three) years from the date it is signed and may be renewed for an equal period on the written agreement of the parties. On its expiry, the parties shall draw up a report evaluating the collaboration and the results achieved, and any future objectives.

ARTICLE 11

Each party may withdraw from this agreement with notice of at least 6 (six) months. Such notice must be sent to the counterparty by recorded delivery.

ARTICLE 12

Each party shall take out insurance cover as required by law for its staff who, through this agreement, are required to attend the premises in which the activities are to be carried out.

ARTICLE 13

13.1 The staff of both contracting parties are required to abide by the disciplinary and safety regulations in force in the location of the activities pursuant to this agreement.

13.2 Staff of both parties, including any external contractors appointed by the same, are obliged before accessing the locations of the activities pursuant to this agreement to acquire information concerning occupational health and safety measures, and to sign a dedicated statement to this effect.

ARTICLE 14

14.1 In the event of any dispute over the interpretation or performance of this contract, an amicable solution shall be sought.

14.2 The Parties shall carry out the work carefully and in accordance with recognized scientific standards. The Parties are aware of the success risk associated with research work. Due to the research character of the work, the Parties do not guarantee that any specific work result will be achieved or that the work result can be used or commercially exploited for a specific purpose or that it is free of third-party property rights. Where conflicting property rights become known to a party, that party shall immediately inform the other party.

Liability is limited to intent and gross negligence. This applies in particular but not limited to liability for consequential damages. This limitation of liability shall not apply to damages in connection with injury to life, body, health, regulations concerning the processing of (personal) data and concerning intellectual property rights as well as the violation of essential contractual obligations. Essential contractual obligations are those whose fulfilment is necessary to achieve the purpose of the contract. If necessary, the parties shall support each other in defending claims by third parties by providing the necessary declarations and/or documents. This applies in particular to patent law disputes.

Both parties will perform all compulsory efforts to store project essential events, results, and data and publications in a safe and accessible way.

ARTICLE 15

For the Department shall apply: This document shall be registered where it is to be enforced, pursuant to article 4 of the second part of the list of charges attached to Presidential Decree 131/1986.

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Registration fees are payable by the requesting party. Stamp duties are at the expense of the company.

ARTICLE 16

16.1 The Parties mutually acknowledge that they are aware that personal data provided, including verbally, for pre-contractual activities or in any case collected consequent to and during the performance of this agreement, shall be handled solely for the purposes of the agreement through consultation, processing, comparison with other data and/or any further manual or automated processing as well as, for statistical purposes and in an anonymous form only, through communication with public subjects where so requested for the pursuit of their institutional aims, and private subjects, in the case that the scope of the request is compatible with the institutional aims of the contracting parties, in the awareness that the failure to confer such data could lead to the non-or partial performance of the agreement.

16.2 Both parties will comply with all aspects of the General Data protection Regulation (GDPR) and applicable local laws.

16.3 By nature of the project data protection obligations will only occur to the extent that the personnel who will be involved in the implementation and performance of the project are reported to the other party and/or are subject to regulatory control. In this case all personnel will be asked to agree to this transfer of their personal data in writing for the specified purposes.

16.4 Due to the structure of the project the Parties need to exchange personal data about personal and in relation to patient data, human probes etcetera. They agree to work together on the basis of being common data controllers according to Art 26 GDPR.

ARTICLE 17

Changes to this Agreement must be made in writing. No subsidiary agreements have been made; should these be made, they must also be in writing.

ARTICLE 18

The Agreement is subject exclusively to German law. The place of jurisdiction shall be Berlin, Germany.

ARTICLE 19

Should individual provisions of this Agreement be invalid, the validity of the remaining provisions shall not be affected. In place of the invalid provision, a provision shall apply that comes closest to what the parties intended or would have intended if they had been aware of the invalidity of the provision. The same shall apply to any contractual loopholes.

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ON BEHALF OF TERNA:

Read and acknowledged
Place/Date

[Handwritten signature]

Dr. Shishir Singh

ON BEHALF OF CHARITÉ:

Read and acknowledged
Place/Date

Apr 2, 2012
[Handwritten signature]

Berlin

Dr. Jonas Gonsen-Rosai

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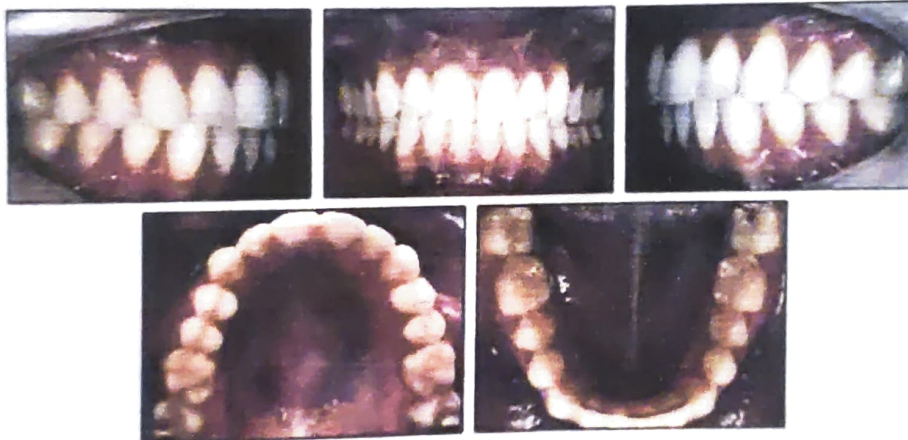
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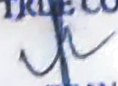
Annex 1


Data

Inclusion criteria and example of images to be collected

- Patient age: ≥ 18 years old
- Photos of all types of permanent dentition with at least 4 teeth present
- Metadata is required for each patient: Name, date of birth, gender, occupation, PIN code of address (if not available then provide name of area of residence), medical history (presence of diabetes, hypertension, any other, conditions for which medications are currently being taken)
- Number of photos required:
250 patients, where 5 photos will be required per 1 patient to be accepted in the study.
- Each patient should be assigned a unique number and that number should be used to label/name all the images from that patient.
- Type of photos from each patient: 1 frontal, 1 occlusal per jaw, and 2 lateral (right and left side, each).



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Annex 2

Research Plan

The ML classifier model will be externally validated on the images provided from Terna. If the performance metrics in the external validation are low, the model will be retrained on a subset of the images from Terna. The classifier aims to detect certain caries-related pathologies and suggest treatment pathways that have been pre-defined as cost-effective. The four dental diagnosis classes will be as following: sound surface/early carious lesion/advanced carious lesion/pulpal involvement, ulceration, fistula, abscess, root remnant.

The classifier's performance in detecting and discriminating the four different diagnostic classes will be assessed via metrics, such as, accuracy, F1 score, etc.

We will report results using two confusion matrices that will compare both the sensitivity and specificity in the 4 groups:

	India	Germany
Dentists		
AI		

We expect to analyse the statistical differences between the two groups using Pearson's chi-squared test to see if the differences accumulated in the diagnosis are of relevance.

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