北院區長庚研究計劃審核評估委員會

【研究計劃核定清單】

2019 年 7 月 18 日

主持人	郭昶甫	單位	風濕過敏科	案號	CLRPG3H0012	計劃期限	2019/07/01~2020/06/30

計劃名稱:醫療人工智能(AI)核心實驗室

□ 、衛生署計畫

■ 、長庚醫學研究計劃

□ 、國科會研究計畫

□ 、其他委託計畫

本計劃經評審委員評估結果意見如下：

項　目	核定經費	院外經費	院內經費	說　明
人事費	9,905,029	0	9,905,029	第>九年學士級專任助理一名、第一年碩士級專任助理三名、第二年碩士級專任助理五名、博士後研究員六名、第一年學士級專任助理一名
消耗性材料藥品費	0	0	0	
儀器設備費	20,997,000	0	20,997,000	筆記型電腦*2、伺服器及儲存設備*1、電腦工作站*10
儀器設備及技術服務平台使用費	0	0	0	
有關研究他項費用	3,625,000	0	3,625,000	
合　計	34,527,029	0	34,527,029	

審核意見與建議：

1.經審查，中間報告優良，建議繼續補助下一年度維持計劃執行。

同意本計劃進行，請依規定簽認(1)研究計劃執行同意書及(2)主持人須知（醫院院內首頁表單櫃下載107年版本後空白表單）簽章後寄至林口醫研部，始得啟用經費。(執行同意書請完整填寫當年度之計畫編號、名稱、經費、執行期間)

依「長庚醫學研究計畫管理辦法」規定：**研究計劃核准後**，計劃主持人應衡量欲採購項目之市場性及是否有現貨交運等，以評估採購作業所需期間，依核定之設備及材料項目內容，儘早提出請購並完成領料作業。**所有領購、請購、領料作業皆須於計劃執行期間內完成。**

依規定以下之經費不在補助範圍：郵電費、影印費、差旅費、論文發表費、圖書費、文具費、資訊軟體費、電腦及電腦周邊設備費。

註:1.計劃章請自行刻印，模式如右：

2.經費核銷作業方式，請詳閱「長庚醫學研究計畫管理辦法」（刊於院內首頁規章法令）

3. 經研審會一次審定之多年期計劃第二年起(上年度計劃執行期滿前**二個月**)需繳交中間報告，經研審會評估通過後始得核給下一年度經費

長庚研究計畫專用章	
編　號	CLRPG3H0012
主持人	郭昶甫
有　效 期　間	自 2019 年 07 月 01 日 至 2020 年 06 月 30 日
本案各項儀器設備需經採購核決始予生效	

長庚醫學研究計劃審核評估委員會 啟

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廠商贊助研究計畫

【□人體■非人體研究計畫核定清單-首次申請/續申請】

主持人	郭昶甫	單位	醫療人工智能核心實驗室	案號	SMRPG3I0011	計畫期限	2019/01/15-2020/01/31
		科別代號	3SF00				

計劃名稱： 醫療影像核心技術開發。

□ 衛福部計畫核准案號：部授食字第　　號

□ 長庚人體試驗倫理委員會同意證明：

項　目		核定經費	院外經費	院內經費	說　明
研究計劃經費	人事費	8,953,575	8,953,575	0	
	消耗性材料藥品費	1,495,960	1,495,960	0	
	儀器設備費	0	0	0	
	業務費	204,000	204,000	0	
	有關研究他項費用	4,095,960	4,095,960	0	
	管理費	0	0	0	百萬以下提撥 15%，超過部份提撥 5% 下限為 1 萬，上限為 20 萬
	小計	14,749,495	14,749,495	0	
研究藥品管理費		0	0	0	
總　計		14,749,495	14,749,495	0	

審查意見：

擬同意開立帳號，帳號期限 108/01/15 至 109/01/31，且不收取管理費。

長庚醫療財團法人 林口長庚紀念醫院 長庚研究計劃審核評估委員會 對內專用

廠商贊助研究計畫專用章	
編　號	SMRPG3I0011
主持人	郭昶甫
有效期間	自 108 年 01 月 15 日 至 109 年 01 月 31 日
外部機構贊助主持人核決	

註：計畫章請自行刻印，模式如右：

註一：所有協助主持人執行試驗之院外研究人員(包括研究護師)，應向所在院區申請臨時識別證，恪遵醫院規範；若造成醫院損害，需依損害情況加以賠償。

註二：**以匯款方式入帳者，請儘可能由國內分公司或代理單位匯入新台幣；若由國外匯入，務請於匯款文件加註試驗編號。**已匯入之款項請儘速填報繳款單，以利經費之使用。

註三：依試驗進度分期撥款，第一次繳款需於試驗起始 15 日前，惟試驗帳戶之金額不得超支為負。

註四：**自 94 年 6 月起，試驗帳號為每年核給。**

註五：上期計畫案號到期後如經費仍有餘款，將全數於到期後下月 10 日前轉移至下一年度。

Contract Number: PMS20182693HT01

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

This Agreement is made and entered into as of [**January 1st 2019**] ("Effective Date") by and between:

1. **PAII Inc.** a corporation organized and existing under the laws of the United States of America, or USA, having a principal place of business in **Palo Alto**, California, (hereinafter "Company" or "PAII"); and **Bethesda**, Maryland, USA.
2. Chang Gung Memorial Hospital, Linkou, organized and existing under the laws of Taiwan, having an address at No.5, Fuxing St., Guishan Dist., Taoyuan City 333, Taiwan (R.O.C.), (hereinafter "Collaborator" or "CGMH").

(each a "party" and together the "parties")

Article 1. Introduction

This CRADA between PAII and CGMH will be effective when signed by the Parties. The research and development activities that will be undertaken by the Parties in the course of this CRADA are detailed in the Research Plan, attached as Appendix A. The staffing, funding, and materials contributions of the Parties are set forth in Appendix B.

Article 2. Definitions

The terms listed in this Article will carry the meanings indicated throughout the CRADA. To the extent a definition of a term as provided in this Article is inconsistent with a corresponding definition in the applicable sections of either the United States Code (U.S.C.) or the Code of Federal Regulations (C.F.R.), the definition in the U.S.C. or C.F.R. will control.

2.1 "**Affiliate**" means any corporation or other business entity controlled by, controlling, or under common control with Collaborator at any time during the term of the CRADA. For this purpose.

2.2 "**Background Invention**" means an Invention conceived and first actually reduced to practice before the Effective Date.

2.3 "**Collaborator Materials**" means all tangible materials not first produced in the performance of this CRADA that are owned or controlled by Collaborator and used in the performance of the Research Plan.

2.4 "**Confidential Information**" means confidential scientific, business, or financial information provided that the information does not include:

(a) information that is publicly known or that is available from public sources;

(b) information that has been made available by its owner to others without a confidentiality obligation;
(c) information that is already known by the receiving Party, or information that is independently created or compiled by the receiving Party without reference to or use of the provided information; or
(d) information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the subject matter of the Research Plan.

2.5 "**Cooperative Research and Development Agreement**" or "**CRADA**" means this Agreement, edited from the version to the Federal Technology Transfer Act of 1986, as amended (15 U.S.C. §§ 3710a *et seq.*), and Executive Order 12591 of April 10, 1987.

2.6 "**CRADA Data**" means all recorded information first produced in the performance of the Research Plan.

2.7 "**CRADA Materials**" means all tangible materials first produced in the performance of the Research Plan other than CRADA Data.

2.8 "**CRADA Subject Invention**" means any Invention of either or both Parties, conceived or first actually reduced to practice in the performance of the Research Plan.

2.9 "**Effective Date**" means the date of the last signature of the Parties executing this Agreement.

2.10 "**Government**" means the Government of the United States of America.

2.11 "**PAII Materials**" means all tangible materials not first produced in the performance of this CRADA that are owned or controlled by PAII and used in the performance of the Research Plan.

2.12 "**Invention**" means any invention or discovery that is or may be patentable or otherwise protected under Title 35 of the United States Code, or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act, 7 U.S.C. §§ 2321 *et seq.*

2.13 "**Patent Application**" means an application for patent protection for a CRADA Subject Invention with the United States Patent and Trademark Office ("U.S.P.T.O.") or the corresponding patent-issuing authority of another nation, such as Patent Cooperation Treaty (PCT) application.

2.14 "**Patent**" means any issued United States patent, any international counterpart(s), and any corresponding grant(s) by a non-U.S. government in place of a patent.

2.15 "**Principal Investigator(s)**" or "**PI(s)**" means the person(s) designated by the Parties who will be responsible for the scientific and technical conduct of the Research Plan.

2.16 "**Research Plan**" means the statement in Appendix A of the respective research and development commitments of the Parties.

Article 3. Cooperative Research and Development

3.1 **Performance of Research and Development.** The research and development activities to be carried out under this CRADA will be performed solely by the Parties identified as above unless specifically stated elsewhere in this Agreement.

3.2 **Research Plan.** The Parties recognize that the Research Plan describes the collaborative research and development activities they will undertake and that interim research goals set forth in the Research Plan are good faith guidelines. Should events occur that require modification of these goals, then by mutual written agreement the Parties can modify them through an amendment, according to Paragraph 13.6.

3.3 **Use and Disposition of Collaborator Materials and PAII Materials.** The Parties agree to use Collaborator Materials and PAII Materials only in accordance with the Research Plan, not to transfer these materials to third parties except in accordance with the Research Plan or as approved by the owning or providing Party, and, upon expiration or termination of the CRADA, to dispose of these materials as directed by the owning or providing Party.

3.4 **Third-Party Rights in Collaborator's CRADA Subject Inventions.** If Collaborator has received (or will receive) support of any kind from a third party in exchange for rights in any of Collaborator's CRADA Subject Inventions, Collaborator agrees to ensure that its obligations to the third party are both consistent with Articles 6 through 8 and subordinate to Article 7 of this CRADA.

Article 4. Reports

4.1 **Interim Research and Development Reports.** The PIs should exchange information regularly, in writing and/or oral meeting. This exchange may be accomplished through meeting minutes, annual reports, detailed correspondence, and circulation of draft manuscripts.

4.2 **Final Research and Development Reports.** The Parties will exchange final reports of their results within four (4) months after the expiration or termination of this CRADA. These reports will set forth the technical progress made; any publications arising from the research; and the existence of invention disclosures of potential CRADA Subject Inventions and/or any corresponding Patent Applications.

4.3 **Fiscal Reports.** If PAII has agreed to provide funding to Collaborator under this CRADA and upon the request of PAII, then concurrent with the exchange of final research and development reports according to Paragraph 4.2, Collaborator will submit to PAII a statement of all costs incurred by Collaborator for the CRADA. If the CRADA

has been terminated, Collaborator will specify any costs incurred before the date of termination for which Collaborator has not received funds from PAII, as well as for all reasonable termination costs including the cost of returning PAII property or removal of abandoned PAII property.

Article 5. Financial

5.1 **Timing.** PAII shall pay the funding with the amount set forth in Appendix B to collaborators in CGMH every month, upon the full execution of this agreement. The funding is exclusive of VAT and any other taxes, if applicable.

5.2 **Method.** All funding shall be paid in US Dollars by PAII in accordance with the PAII-CGMH jointly agreed instructions set forth in Appendix B or later provided by CGMH . PAII's invoicing requirements are set forth in appendix B.

5.3 **Taxes.** In the event that the Funding is subject to any levy and tax, including, but not limited to withholding tax, income tax, service tax, sales tax or VAT, by local, regional or federal government authorities in USA and Taiwan, CGMH shall pay to the applicable tax authorities, whether on its own or PAII's behalf, such amount of levy and tax and, if applicable, penalties and interest, as will result in CGMH receiving the full amount of the Funding and PAII shall provide CGMH with a copy of the withholding tax certificate or other tax filing documentation evidencing payment was made promptly following payment of the levy or tax.

Article 6. Intellectual Property

6.1 **Ownership of CRADA Subject Inventions, CRADA Data, and CRADA Materials.** For PAII and CGMH through this CRADA collaboration, the producing Party will retain sole ownership of and title to all CRADA Subject Inventions, all copies of CRADA Data, and all CRADA Materials produced solely by its employee(s). The Parties will own jointly all CRADA Subject Inventions invented jointly and all copies of CRADA Data and all CRADA Materials developed jointly.

6.2 **Prior Intellectual Property Right.** All data, documents, information, trademarks, slides, image, chart, design, know how, algorithms, trade secret, proprietary methodologies and solutions, software and other items owned, developed or licensed by each Party and/or any of each Party's Affiliates before the effective date of CRADA and used for the performance of the Services under such CRADA and all Intellectual Property Right (IPR) associated therewith (collectively, the "Prior IPR") are and shall remain the sole and exclusive property of the said Party or the said Party's Affiliates, licensors or suppliers.

6.3 **Reporting.** The Parties will promptly report to each other in writing each CRADA Subject Invention reported by their respective personnel, and any Patent Applications filed thereon, resulting from the research and development activities conducted under this

CRADA. Each Party will report all CRADA Subject Inventions to the other Party in sufficient detail to determine inventorship, which will be determined in accordance with U.S. patent law. These reports will be treated as Confidential Information in accordance with Article 8. Formal reports will be made by and to the Patenting and Licensing Offices identified on the Contacts Information Page herein.

6.4 **Filing of Patent Applications.** Each Party will make timely decisions regarding the filing of Patent Applications on the CRADA Subject Inventions made solely by its employee(s), and will notify the other Party in advance of filing. Whether jointly filing a Patent Application on joint CRADA Subject Inventions should be determined by the Parties' agreement. Either party should notify the other Party of its decision within sixty (60) days of an Invention being reported. If one Party fails to notify the other Party of its decision within that time period or notifies the other Party of its decision not to jointly file a Patent Application, then the other Party has the sole right to file a Patent Application on the joint CRADA Subject Invention and solely owns the Patent. Neither Party will be obligated to file a Patent Application. Either Party will place the following statement in any Patent Application it files on a CRADA Subject Invention: "This invention was created in the performance of a Cooperative Research and Development Agreement between PAII and Collaborator." If either Party files a Patent Application on a joint CRADA Subject Invention, then the filing Party will include a statement within the Patent Application that clearly identifies the Parties and states that the joint CRADA Subject Invention was made under this CRADA.

6.5 **Patent Expenses.** All preparation and filing expenses, prosecution fees, issuance fees, post issuance fees, patent maintenance fees, annuities, interference expenses, and attorneys' fees for a Patent Application and any resulting Patent(s) on the CRADA Subject Inventions made solely by one Party's employee(s) or on the joint CRADA Subject Inventions that the other Party decides not to jointly file a patent application should be borne by the Party solely. All preparation and filing expenses, prosecution fees, issuance fees, post issuance fees, patent maintenance fees, annuities, interference expenses, and attorneys' fees for a Patent Application and any resulting Patent(s) on joint CRADA Subject Inventions should be borne by the Parties jointly. PAII has the first exclusive licensing right on a patent that is solely invented by the Collaborator, according to a licensing term to be negotiated case by case, and may waive its exclusive option rights at any time, and incur no subsequent financial obligation for those Patent Application(s) or Patent(s)

6.6 **Prosecution of Patent Applications.** The Party filing a Patent Application will provide the non-filing Party with a copy of any official communication relating to prosecution of the Patent Application within thirty (30) days of transmission of the communication. Each Party will also provide the other Party with the power to inspect and make copies of all documents retained in the applicable Patent Application or Patent file. The Parties agree to consult with each other regarding the prosecution of Patent Applications directed to joint CRADA Subject Inventions. PAII and Collaborator will cooperate with each other to obtain necessary signatures on Patent Applications, assignments, or other documents.

Article 7. Licensing

7.1 **Background Inventions.** Other than as specifically stated in this Article 6, nothing in this CRADA will be construed to grant any rights in one Party's Background Invention(s) to the other Party, except to the extent necessary for the Parties to conduct the research and development activities described in the Research Plan.

7.2 **PAII's License Option to CRADA Subject Inventions.** With respect to Collaborator's rights to any CRADA Subject Invention made solely by its employee(s) or made jointly by a Collaborator employee(s) and a PAII employee(s) for which a Patent Application was filed, Collaborator's hereby grants to PAII an exclusive option to elect an exclusive or nonexclusive commercialization license. The license will be substantially in the form of the appropriate model of license agreement and will fairly reflect the nature of the CRADA Subject Invention, the relative contributions of the Parties to the CRADA Subject Invention and the CRADA, a plan for the development and marketing of the CRADA Subject Invention, the risks incurred by PAII and Collaborator, and the costs of subsequent research and development needed to bring the CRADA Subject Invention to the marketplace. The field of use of the license will not exceed the scope of the Research Plan.

7.3 **Exercise of PAII's License Option.** To exercise the option of Paragraph 7.2 PAII must submit a written notice to the Collaborator's Patenting and Licensing Contact identified on the Contacts Information Page within three (3) months after either (i) PAII receives written notice from Collaborator that the Patent Application has been filed or (ii) the date on which Collaborator files the Patent Application. The written notice exercising this option will include a completed "Application for License to Inventions" and will initiate a negotiation period that expires nine (9) months after the exercise of the option. If Collaborator has not responded in writing to the last proposal by PAII within this nine (9) month period, the negotiation period will be extended to expire one (1) month after Collaborator so responds, during which month PAII may accept in writing the final license proposal of Collaborator. In the absence of PAII's exercise of the option, or upon election of a nonexclusive license, Collaborator will be free to license the CRADA Subject Invention to others. These time periods may be extended at the sole discretion of Collaborator upon good cause shown in writing by PAII.

7.4 **Collaborator License in PAII Sole CRADA Subject Inventions.** Pursuant to 15 U.S.C. § 3710a(b)(2), for CRADA Subject Inventions made solely by an employee of PAII, PAII grants to **Collaborator** a nonexclusive, nontransferable, irrevocable, paid-up license to practice the CRADA Subject Invention internally only.

Article 8. Rights of Access and Publication

8.1 **Right of Access to CRADA Data and CRADA Materials.** PAII and Collaborator agree to exchange all CRADA Data and to share all CRADA Materials. If the CRADA is terminated, both Parties agree to provide CRADA Materials in quantities needed to

complete the Research Plan. Such provision will occur before the termination date of the CRADA or sooner, if required by the Research Plan.

8.2 **Use of CRADA Data and CRADA Materials.** The Parties will be free to utilize CRADA Data and CRADA Materials internally for their own purposes, consistent with their obligations under this CRADA. The Parties may share CRADA Data or CRADA Materials with their Affiliates, agents or contractors provided the obligations of this Article 8.2 are simultaneously conveyed.

(a) **CRADA Data.**

Collaborator and PAII will use reasonable efforts to keep CRADA Data confidential until published or until corresponding Patent Applications are filed. To the extent permitted by law, each Party will have the right to use any and all CRADA Data in and for any regulatory filing by or on behalf of the Party.

(b) **CRADA Materials.**

Collaborator and PAII will use reasonable efforts to keep descriptions of CRADA Materials confidential until published or until corresponding Patent Applications are filed. Either Party may distribute CRADA Materials made solely by the other Party only upon written consent from the other Party or the other Party's designee.

8.3 **Confidential Information.** Each Party agrees to limit its disclosure of Confidential Information to the amount necessary to carry out the Research Plan, and will place a confidentiality notice on all such information. A Party orally disclosing Confidential Information to the other Party will summarize the disclosure in writing and provide it to the other Party within fifteen (15) days of the disclosure; otherwise, the information will not be recognized as Confidential Information after the time period. Each Party receiving Confidential Information agrees to use it only for the purposes described in the Research Plan.

8.4 **Protection of Confidential Information.** Confidential Information will not be disclosed, copied, reproduced or otherwise made available to any other person or entity without the consent of the owning or providing Party except as required by a court or administrative body of competent jurisdiction, or federal law or regulation. Each Party agrees to use reasonable efforts to maintain the confidentiality of Confidential Information, which will in no instance be less effort than the Party uses to protect its own Confidential Information. Each Party agrees that a Party receiving Confidential Information will not be liable for the disclosure of that portion of the Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given a reasonable opportunity to seek a court order to enjoin disclosure.

8.5 **Protection of Human Subjects' Information.** The research and development activities to be conducted under this CRADA are not intended to involve human subjects or human tissues within the meaning of 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

8.6 **Duration of Confidentiality Obligation.** The obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined in Paragraph 2.4 or three (3) years after the expiration or termination date of this CRADA. Collaborator may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

8.7 **Publication.** The Parties are encouraged to make publicly available the results of their research and development activities. Before either Party submits a paper or abstract for publication or otherwise intends to publicly disclose information about a CRADA Subject Invention, CRADA Data or CRADA Materials, the other Party will have thirty (30) days to review the proposed publication or disclosure to assure that Confidential Information is protected. Either Party may request in writing that the proposed publication or other disclosure be delayed for up to thirty (30) additional days as necessary to file a Patent Application.

Article 9. Representations and Warranties

9.1 **Representations and Warranties of PAII.** PAII hereby represents and warrants to Collaborator that:

(a) PAII has the requisite power and authority to enter into this CRADA and to perform according to its terms, and that PAII's official signing this CRADA has authority to do so.

(b) To the best of its knowledge and belief, neither PAII nor any of its personnel involved in this CRADA is presently subject to debarment or suspension by any agency of the Government which would directly affect its performance of the CRADA. Should PAII or any of its personnel involved in this CRADA be debarred or suspended during the term of this CRADA, PAII will notify Collaborator within thirty (30) days of receipt of final notice.

(c) Subject to Paragraph 12.3, and if and to the extent PAII has agreed to provide funding under Appendix B, PAII is financially able to satisfy these obligations in a timely manner.

9.2 **Representations and Warranties of Collaborator.** Collaborator hereby represents and warrants to PAII that:

(a) Collaborator has the requisite power and authority to enter into this CRADA and to perform according to its terms, and that Collaborator's official signing this CRADA has authority to do so.

(b) Neither Collaborator nor any of its personnel involved in this CRADA, including Affiliates, agents, and contractors are presently subject to debarment or suspension by any agency of the Government. Should Collaborator or any of its personnel involved in this CRADA be debarred or suspended during the term of this CRADA, Collaborator will notify PAII within thirty (30) days of receipt of final notice.

Article 10. Expiration and Termination

10.1 **Expiration.** This CRADA will expire on the last date of the term set forth on the Summary Page. In no case will the term of this CRADA extend beyond the term indicated on the Summary Page unless it is extended in writing in accordance with Paragraph 13.6.

10.2 **Termination by Mutual Consent.** PAII and Collaborator may terminate this CRADA at any time by mutual written consent.

10.3 **Unilateral Termination.** Either PAII or Collaborator may unilaterally terminate this CRADA at any time by providing written notice at least ninety (90) days before the desired termination date. Collaborator may, at its option, retain funds transferred to Collaborator before unilateral termination by PAII for use in completing the Research Plan for 90 days.

10.4 **Funding for Collaborator Personnel.** If PAII has agreed to provide funding for Collaborator personnel and this CRADA is mutually or unilaterally terminated by Collaborator before its expiration, then PAII agrees that funds for that purpose will be available to Collaborator for a period of three (3) months after the termination date or until the expiration date of the CRADA, whichever occurs sooner. If there are insufficient funds to cover this expense, PAII agrees to pay the difference.

10.5 **New Commitments.** Neither Party will incur new expenses related to this CRADA after expiration, mutual termination, or a notice of a unilateral termination and will, to the extent feasible, cancel all outstanding commitments and contracts by the termination date.

Article 11. Disputes

11.1 **Settlement.** All disputes between the Parties arising out of, or relating to, this Agreement, or the breach, termination or invalidity hereof, whether before or after termination hereof, shall be resolved in accordance with this Article 11. If a dispute arises between the Parties, the Parties shall attempt to reach resolution through good faith direct discussions between their respective senior executives having authority to resolve the dispute.

Arbitration. If a dispute has not been resolved within forty-five (45) days after the commencement of mediation or within sixty (60) days after initiation by either Party of an attempt to reach resolution through good faith direct discussions, then either Party may initiate a demand for arbitration under the UNCITRAL Arbitration Rules as then in effect and, except as set forth herein, the dispute will be arbitrated in accordance with such rules. The arbitration shall be final and binding. The arbitration shall be conducted before a panel of three (3) arbitrators. Each Party shall select an arbitrator and the selected arbitrators shall mutually agree upon a third. The arbitration shall be held in a mutually agreeable location or, if the parties cannot agree upon a location within ten (10) days after the arbitrator panel has been constituted, at a location deemed fair to the Parties by the arbitrators. The arbitration shall be conducted in English. Each Party shall bear the costs of its own counsel fees and expenses and half of the costs of the arbitration, unless the arbitrators determine that the non-prevailing Party should bear more of the costs and expenses, Judgment upon an award rendered by the arbitrators may be entered by any court having jurisdiction thereof.

Right to Seek Equitable Relief. Notwithstanding any other provision of this Article, either Party may bring suit in a court of competent jurisdiction for equitable relief from the other Party's alleged breach of its confidentiality obligations without first mediating or arbitrating the issue.

11.2 **Continuation of Work.** Pending the resolution of any dispute or claim pursuant to this Article 11, the Parties agree that performance of all obligations will be pursued diligently.

Article 12. Liability

12.1 **NO WARRANTIES.** EXCEPT AS SPECIFICALLY STATED IN ARTICLE 9, THE PARTIES MAKE NO EXPRESS OR IMPLIED WARRANTY AS TO ANY MATTER WHATSOEVER, INCLUDING THE CONDITIONS OF THE RESEARCH OR ANY INVENTION OR MATERIAL, WHETHER TANGIBLE OR INTANGIBLE, MADE OR DEVELOPED UNDER OR OUTSIDE THE SCOPE OF THIS CRADA, OR THE OWNERSHIP, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE OF THE RESEARCH OR ANY INVENTION OR MATERIAL, OR THAT A TECHNOLOGY UTILIZED BY A PARTY IN THE PERFORMANCE OF THE RESEARCH PLAN DOES NOT INFRINGE ANY THIRD-PARTY PATENT RIGHTS.

12.2 **Force Majeure**. Neither Party will be liable for any unforeseeable event beyond its reasonable control and not caused by its own fault or negligence, which causes the Party to be unable to perform its obligations under this CRADA, and which it has been unable to overcome by the exercise of due diligence. If a *force majeure* event occurs, the Party unable to perform will promptly notify the other Party. It will use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the *force majeure* event.

Article 13. Miscellaneous

13.1 **Governing Law**. The construction, validity, performance and effect of this CRADA will be governed by U.S. federal law, as applied by the federal courts in the District of Columbia. If any provision in this CRADA conflicts with or is inconsistent with any U.S. federal law or regulation, then the U.S. federal law or regulation will preempt that provision.

13.2 **Compliance with Law**. PAII and Collaborator agree that they will comply with, and advise their contractors and agents to comply with, all applicable statutes, Executive Orders, HHS regulations, and all FDA, CDC, and Group policies relating to research on human subjects (45 C.F.R. Part 46, 21 C.F.R. Parts 50 and 56) and relating to the appropriate care and use of laboratory animals (7 U.S.C. §§ 2131 *et seq.*; 9 C.F.R. Part 1, Subchapter A).

13.3 **Waivers**. None of the provisions of this CRADA will be considered waived by any Party unless a waiver is given in writing to the other Party. The failure of a Party to insist upon strict performance of any of the terms and conditions hereof, or failure or delay to exercise any rights provided herein or by law, will not be deemed a waiver of any rights of any Party.

13.4 **Headings**. Titles and headings of the articles and paragraphs of this CRADA are for convenient reference only, do not form a part of this CRADA, and will in no way affect its interpretation.

13.5 **Severability**. The illegality or invalidity of any provisions of this CRADA will not impair, affect, or invalidate the other provisions of this CRADA.

13.6 **Amendments**. Minor modifications to the Research Plan may be made by the mutual written consent of the Principal Investigators of both parties. Substantial changes to the CRADA or extensions of the term will become effective only upon a written amendment signed by the signatories to this CRADA or by their representatives duly authorized to execute an amendment. A change will be considered substantial if it directly expands the range of the potential CRADA Subject Inventions, alters the scope or field of any license option governed by Article 7, or requires a significant increase in the contribution of resources by either Party.

13.7 **Assignment**. Neither this CRADA nor any rights or obligations of any Party hereunder shall be assigned or otherwise transferred by either Party without the prior written consent of the other Party. The Collaborator acknowledges the applicability of 41 U.S.C. § 15, the Anti Assignment Act, to this Agreement. The Parties agree that the identity of the Collaborator is material to the performance of this CRADA and that the duties under this CRADA are nondelegable.

13.8 **Notices**. All notice given under this Agreement must be in writing and be addressed to the recipient Party at the address shown in the Information page or to such other address as a Party may substitute by notice. Notices must be sent by commercial courier via express, priority or similar service or by email. Notices sent by commercial courier shall

be deemed to have been given as of the date that the commercial courier completes delivery and notices sent by email shall be deemed to have been given on the date that the recipient Party affirmatively confirms receipt by email or in writing to sender.

13.9 **Independent Contractors.** The relationship of the Parties to this CRADA is that of independent contractors and not agents of each other or joint venturers or partners. Each Party will maintain sole and exclusive control over its personnel and operations.

13.10 **Use of Name; Press Releases.** Each Party agrees to provide proposed press releases that reference or rely upon the work under this CRADA to the other Party for review and comment at least seven (7) days prior to publication.

13.11 **Reasonable Consent.** Whenever a Party's consent or permission is required under this CRADA, its consent or permission will not be unreasonably withheld.

13.12 **Export Controls.** Each Party will comply with all applicable U.S. export control laws and regulations, including the Export Administration Act of 1979, as amended and its associated Export Administration Regulations ("EAR") and U.S. International Traffic in Arms Regulations ("ITAR") (All such U.S. export control laws and regulations collectively, "U.S. Export Controls"). Collaborator agrees to comply with U.S. export law and regulations. If Collaborator/PAII has a need to transfer any CRADA Materials made in whole or in part by the CRADA collaboration, to a person located in a country other than the United States, to an Affiliate organized under the laws of a country other than the United States, or to an employee of Collaborator/PAII in the United States who is not a citizen or permanent resident of the United States, Collaborator/PAII will acquire any and all necessary export licenses and other appropriate authorizations.

13.13 **Entire Agreement.** This CRADA constitutes the entire agreement between the Parties concerning the subject matter of this CRADA and supersedes any prior understanding or written or oral agreement.

13.14 **Survivability.** The provisions of Paragraphs 3.3, 3.4, 4.2, 4.3, 5.3, 5.4, 6.1-9.2, 10.3-10.5, 11.1, 12.1-12.3, 13.1-13.3, 13.10 and 13.14 will survive the expiration or early termination of this CRADA.

SIGNATURES BEGIN ON THE NEXT PAGE

SIGNATURE PAGE

ACCEPTED AND AGREED

BY EXECUTING THIS AGREEMENT, EACH PARTY REPRESENTS THAT ALL STATEMENTS MADE HEREIN ARE TRUE, COMPLETE, AND ACCURATE TO THE BEST OF ITS KNOWLEDGE. PAII AND COLLABORATOR ACKNOWLEDGES THAT IT MAY BE SUBJECT TO CRIMINAL, CIVIL, OR ADMINISTRATIVE PENALTIES FOR KNOWINGLY MAKING A FALSE, FICTITIOUS, OR FRAUDULENT STATEMENT OR CLAIM.

FOR PAII:

_____ 2/11/2019

Date

Director, President, CEO

FOR COLLABORATOR:

_____ 108. 1. 15

Signature Date

Typed Name

Title

APPENDIX B

STAFFING, FUNDING AND MATERIALS/EQUIPMENT CONTRIBUTIONS OF THE PARTIES

Staffing of CGMH: Five Clinical PIs from CGMH

- Dr. Chang-Fu Kuo (M.D., Ph.D., Chief Clinical Principal Investigator; zandis@adm.cgmh.org.tw ; Director/Attending Physician/ Professor in Rheumatology/Immunology and Allergy, Linkou Chang Gung Memorial Hospital)
- Dr. Dar-In Tai (M.D., Ph.D., Clinical Principal Investigator; tai48978@cgmh.org.tw ; Attending Physician and Full Professor, Division of Gastroenterology and Hepatology, Linkou Chang Gung Memorial Hospital)
- Dr. Tsung-Ying Ho (M.D., Clinical Principal Investigator; albertyho@gmail.com; Attending Physician and Assistant Professor, Department of Nuclear Medicine, Linkou Chang Gung Memorial Hospital)
- Dr. Chien-Hung Liao (M.D., Clinical Principal Investigator; gymetliao@gmail.com ; Attending Physician and Assistant Professor, Department of Traumatology and Emergency Surgery, Specialties in Emergency medicine, Trauma and critical care, hepatobiliary surgery, gastrointestinal surgery, Linkou Chang Gung Memorial Hospital)
- Dr. Chi-Tung Cheng (M.D., Clinical Principal Investigator; atong89130@gmail.com ; Attending Physician and Assistant Professor, Department of Traumatology and Emergency Surgery, Linkou Chang Gung Memorial Hospital)
- Two Research nurses to be recruited by CGMH to support clinical data preparation and curation

This CRADA is under the general consulting from Dr. Tzu-Chen Yen (M.D., Ph.D., yen1110@adm.cgmh.org.tw , Professor and Director, Center for Advanced Molecular Imaging and Translation, Director, Center for Academia and Industrial Collaboration Linkou Chang Gung Memorial Hospital)

Staffing of PAII: Dr. Le Lu (Ph.D., lvle746@pingan.com Director of PAII Inc. Bethesda Lab) and 7~10 Research Staff at PAII Inc. Bethesda Research Laboratory

FUNDING & Materials: PAII shall pay the funding with the amount of US Dollars of $40,000 to collaborators in CGMH every month, upon the full execution of this agreement. After the execution, the payment is also pending upon the satisfaction approval of periodic reviews from both parties of PAII and CGMH every following six months. The funding is exclusive of VAT and any other taxes.

Title:

Quantification of liver fibrosis and steatosis with ultrasound images by artificial intelligence and deep learning methods.

Keyword: Liver fibrosis, liver steatosis, ultrasound, non-invasive detection, computer-aided quantitative, deep learning

Investigator

Dar-In Tai MD, PhD

Professor in Medicine

Chang Gung Memorial Hospital, Linkou Medical Center

Abstract

Liver fibrosis is an important prognostic factor for chronic liver diseases. The evaluation and precise staging of fibrosis are very important in determination of long-term screening policy and initiation of appropriate therapeutic regimens in patients with chronic liver diseases. Liver biopsy is the gold standard for staging of liver fibrosis, but it is an invasive procedure with notable risk of complications, sampling variability and difficult to be repeated. Many non-invasive modalities, such as APRI, FIB4, 2D imaging and elastography, has been developed in recent 10 years. Most of them have good accuracy on fibrosis evaluation, but influence by inflammation greatly. MR, CT and 2D US imaging are less affected by inflammation. They are widely used clinically on multiple purposes. The main drawback of these studies is not being considered as an objective fibrosis diagnosis. In addition to fibrosis, the prevalence of liver steatosis is increasing in new generation and may interact with liver fibrosis. It should also be important to obtain an objective steatosis score form US imaging. The steatosis may also interfere the interpretation of liver fibrosis by US images. Recent advance on deep learning by artificial intelligent methods have open a window to develop an objective and quantitative assessment score on imaging-based fibrosis measurement. From patients received liver histology study or longitudinal imaging studies, artificial intelligence and deep learning process can characterize the relative severity order of images representing the fibrosis or steatosis condition over multiple time points. We can design triplet deep neural network to learn the ordering cost, or similarity cost, by preserving all possible relative or qualitative orders by conditional random sampling. We assume that if the ordering constraints among a large quantity of image triplets can be preserved, the learned or trained triplet network should be considered as valid. After training, it is straightforward that this triplet network can also be fed with single images to generate a valid fibrosis or steatosis assessment score per image. This process will be validated by histology or the outcome from long term followed patients.

Materials

Volunteers

For preparation different US machines information, 100 hundred volunteers will be study by different machine on the same times.

Specific liver parenchyma diseases

Images from patients with liver cysts, liver calcification, benign or malignant tumors will be collected for specific disease pattern recognition.

Patients

A. Patients in the training stage:

1. One thousand chronic hepatitis B carriers received liver histology study with good quality of 2D US images will be evaluated for fibrosis score.
2. None B None C patients received Fibroscan study will be evaluated for steatosis score on 2D US images.

B. Patients in the validation stage:

1. A validation study for both fibrosis and steatosis will be carried out in an independent series of 2000 patients received both liver histology and US studies.
2. Patients received long term US follow-up and showed a clear trend of improving or deteriorating status.

Goals of this study:

1. To establish an objective liver fibrosis score from 2D US images.
2. To establish an objective liver steatosis score from 2D US images.
3. Pattern recognition in specific liver diseases such as liver cysts, calcification, benign or malignant tumor.
4. Interpretation of liver fibrosis under the present of liver steatosis in 2D US images and vice versa.

Introduction

Liver fibrosis is an important prognostic factor for chronic liver diseases (1). The degree of hepatic fibrosis is positively correlated with liver cancer and mortality (1,2). Many therapeutic guidelines have indicated that those patients with significant liver fibrosis warrant aggressive specific therapy (3-5). In patients with chronic liver diseases, the evaluation and precise staging of fibrosis are very important in determination of long-term screening policy and initiation of appropriate therapeutic regimens. Liver biopsy is the gold standard for the diagnosis and staging of liver fibrosis. However, this is an invasive procedure with notable risk of complications, sampling variability, low patient acceptance and difficult to be repeated (6,7,8). In recent decade, many non-invasive modalities are becoming popular. These including AST to Platelet Ratio Index (APRI), fibrosis-4 (FIB4) and elastography (1,2,9-14). Most of the non-invasive modalities has good accuracy on fibrosis evaluation only when inflammation activities is minimal (8,14). MRI, CT and ultrasound (US) 2D imaging are less affected by inflammation (1,2,15,16). They are widely used clinically in multiple purposes. The main drawback of these studies is not being considered as an objective fibrosis diagnosis. In early cirrhosis or severe fibrosis, the experience of the operator become very important. Recent advance on deep learning by artificial intelligent methods have open a window to develop an objective and quantitative assessment score on imaging-based fibrosis measurement (17-22). Several such studies focus on US imaging had been reported (23-29). However, the case numbers were quite small and many of them without histology information.

In addition to fibrosis, the prevalence of liver steatosis is increasing in new generation (30-32) and may interfere with the diagnosis of liver fibrosis (33). It should also be important to obtain an objective steatosis score form US imaging. Several quantitative methodologies had been published (34-37). The control attenuation parameter (CAP) measured by Fibroscan is the main steatosis evaluation modality. However, the correlation between CAP and

histology steatosis score is linear if liver fat cell fraction is lower than or equal to 40%. The CAP become plateau if liver fat cell fraction above 40% or CAP value greater than 290 dB/m (36,37).

In more details, the novelty and unique challenge is that this type of quantitative score cannot be directly labeled by human observer. However, from longitudinal imaging studies, we can identify if the patient is getting worse or better so that the relative severity order of images representing the fibrosis or steatosis condition (over multiple time points) can be obtained. Thus, we can design triplet deep neural network to learn the ordering cost, or similarity cost, by preserving all possible relative or qualitative orders (by conditional random sampling (38). We assume that if the ordering constraints among a large quantity of image triplets can be preserved, the learned or trained triplet network should be considered as valid (arguably the best we can do given all constraints). After training, it is straightforward that this triplet network can also be fed with single images to generate a valid fibrosis or steatosis assessment score per image. In this study we will develop the objective liver fibrosis scores by deep leaning from longitudinal ultrasound images collected in long term follow up HBsAg carriers, non-B non-C patient who received both Fibroscan and US studies. After the deep learning procedure, the result will be validated in liver histology proven cases.

Materials

A. Three groups of patients will be selected for learning study:

1. **Patients received liver histology study**

   Patients received liver needle biopsy for diagnosis of chronic liver disease and patients received surgery for liver tumors will become our study materials

2. **Long term followed chronic hepatitis B carrier.**

The “HBsAg carrier clinics” of Chang Gung Memorial Hospital in Taipei and Linkou medical centers have been in operation since 1980 and have provided an easily accessible service for chronic HBsAg carriers. Most subjects who visited “HBsAg carrier clinics” were asymptomatic at entry. They visited this clinic because of incidental detection of HBsAg on blood donation, general checkup, workup for non-liver disease, or referral from our outpatient department as a stable HBsAg carrier with normal ALT. After entry, these HBsAg carriers were followed every 3 to 12months with ALT, alpha-fetoprotein (AFP), and ultrasonography (US) as the basic tools. All these data were key into hospital computer and can be assess easily under the approval of IRB. Up to March 2012, this data base had collect 274300 times follow-up data from 21200 patients. We will select patients who has been follow-up for more than 10 years after 2002. This is due to most of images were stored digitally since 2002. We expect to collect 1000 cases with known outcome and good images from this series. These patients will be classified into improved (Figure 1) or worsen (Table 1) group based on the ultrasound fibrosis score and clinical data. Each selected case will have a series of images span yearly for at least 10 years. Computer aid deep learning for establish an objective fibrosis score will be done from these series of images. We will update our data from 2012 to 2018 after the approval of this proposal.

Figure 1. A patient with decrease liver fibrosis after entecavir therapy for 10 years

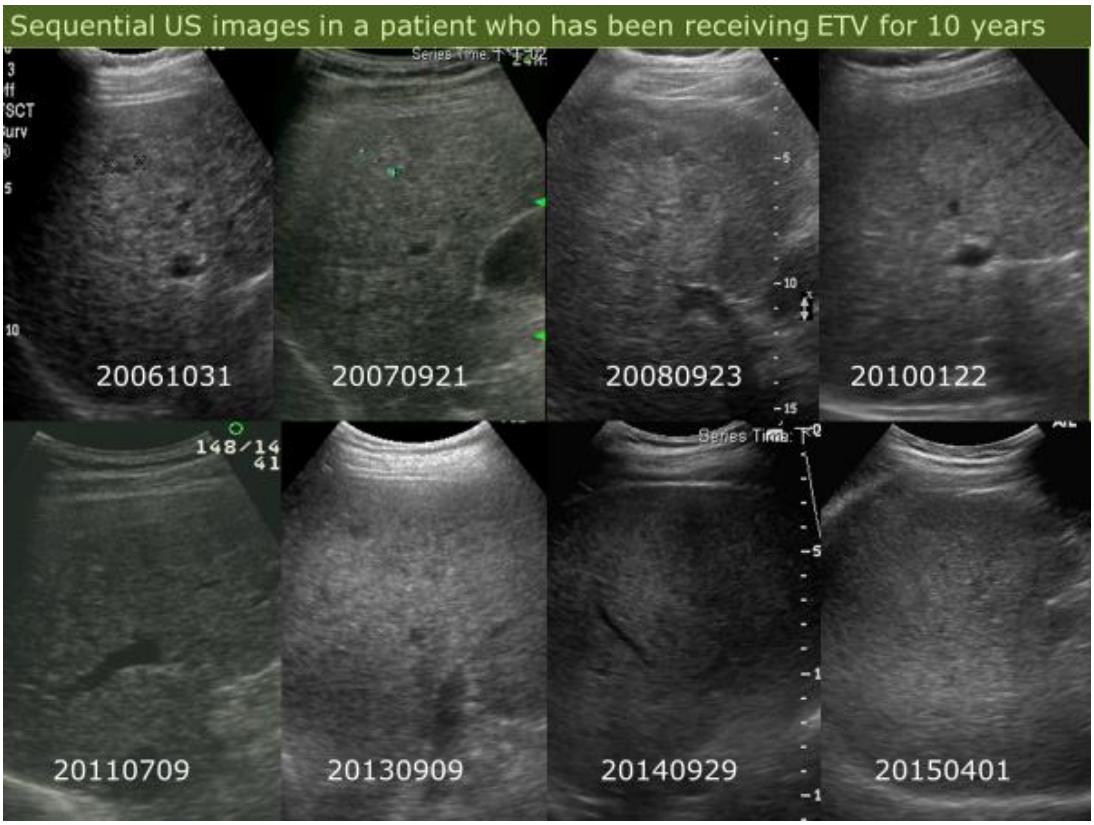


Table 1 An example of data from HBsAg carrier with fibrosis progression

Chart NO	EXMDAT	SGOT	SGPT	AFP	MARKS	ECHO
84853**	20020323	27	34	5		CH
84853**	20020929	24	34	4		CH
84853**	20030323	25	37	7	S+	FL
84853**	20031011	118	244	7		FL
84853**	20031022	129	307		E-	FL
84853**	20031029	164	321			
84853**	20031105	164	317			FL
84853**	20031112	147	316			
84853**	20031119	199	346			
84853**	20031126	226	417		D/-	
84853**	20031203	219	427			
84853**	20031220	147	312			
84853**	20040103	50	100			
84853**	20040306	29	32			
84853**	20040424	23	30	9		CH7
84853**	20041106	37	50	9		CH
84853**	20050521	41	58	15		Cir
84853**	20050924	55	90	6		CH,Cir
84853**	20051129	54	75	6		
84853**	20060217	40	58	7		Cir
84853**	20060711		48	10	S+	Cir
84853**	20061121		26	10		Cir
84853**	20070319		39	5		Cir
84853**	20070716		31	4		Cir
84853**	20071105		28	4		CH7-8
84853**	20080227		30	4	S+	CH7,T
84853**	20080522		35	5		Cir
84853**	20080811		30	5		Cir,T
84853**	20081120		31	4		Cir
84853**	20090312	30	34	5		Cir,T
84853**	20090407	24	34	6.6	S+	Cir
84853**	20090605	27	33	4		Cir
84853**	20090827	25	27	5.3		Cir
84853**	20091217	26	38	6.2		Cir
84853**	20100727	23	28	6		Cir,T

3. None B None C patients received Fibroscan study.

US has been used in measurement of steatosis for more than 30 years. It is common to classified US brightness into mild, moderate and severe steatosis. An example can be seen in (Figure 2). The diagnosis of steatosis is quite subjective by conventional US. Control attenuation parameter (CAP) of Fibroscan is a commercially available non-invasive steatosis evaluation modality (). Fibroscan measure steatosis well if liver fat fraction is lower than 40% (36,37) Figure 3). Above that the correlation between CAP and fat fraction become plateaus. Therefore, additional modality to improve the steatosis measurement are needed. We will collect images from patients received both Fibroscan and conventional ultrasound studies. Computer aid deep learning for establish of steatosis score will be done from US 2D images and correlated with Fibroscan.

Figure 2. US finding of liver steatosis according to histology fat cell percentage

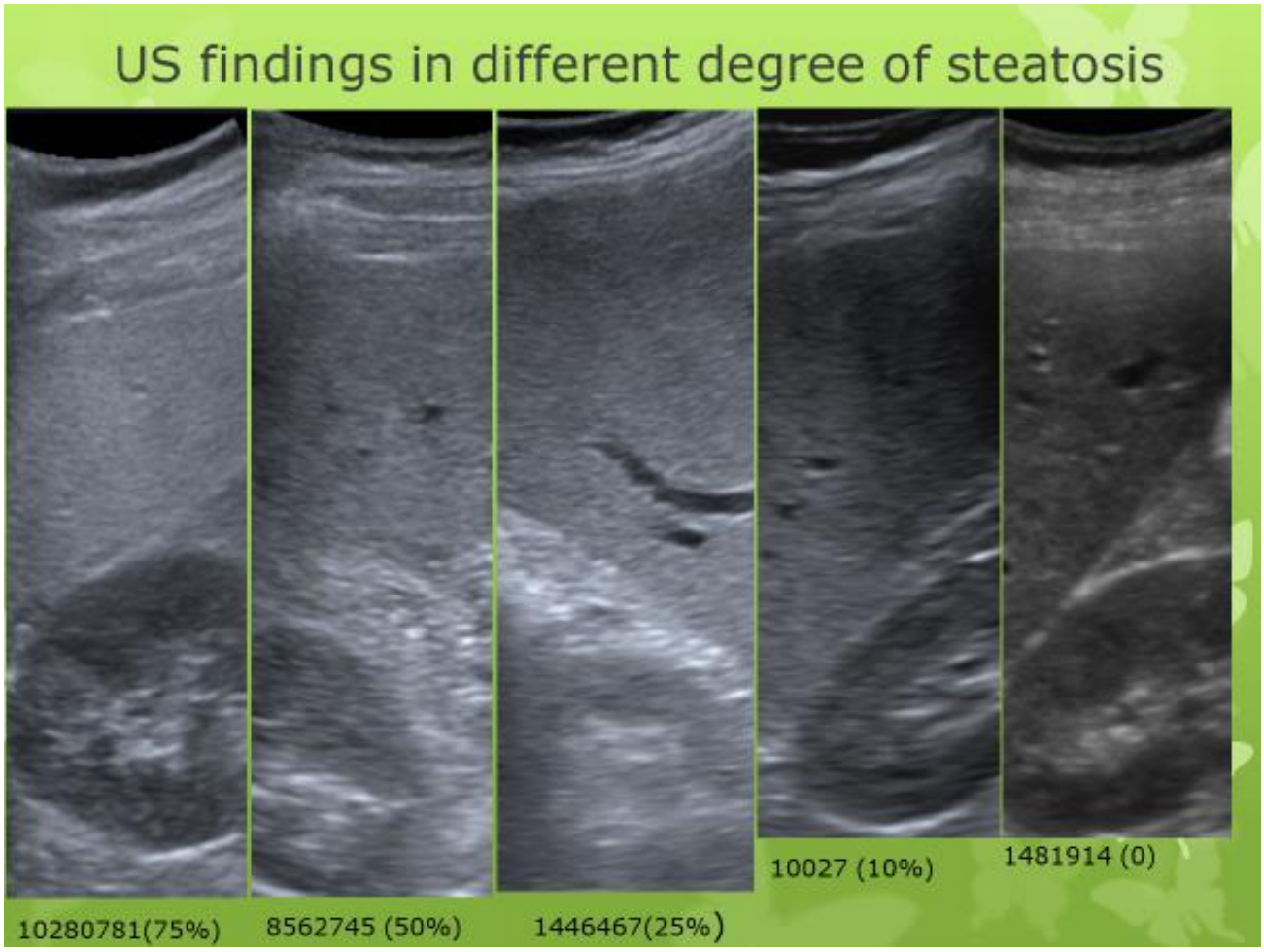
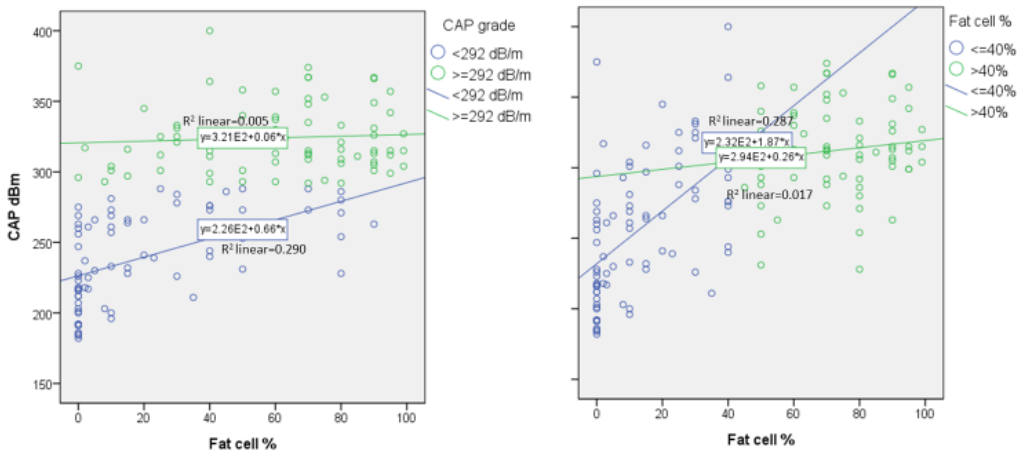


Figure 3 Correlation of control attenuation parameter with liver histology fat fraction. The correlation was linear if the liver fat cell fraction was lower than or equal to 40%. The CAP plateaued if liver fat cell fraction exceeded 40% or was greater than 292 dB/m.

Correlation of fibroscan CAP and Histology fat grade on Biopsy group



Right now, 400 patients had been collected. We plan to collect more than 1000 patients by providing free Fibroscan study in NBNC patients.

Pattern recognition of specific liver parenchymal lesion

During AI learning process, several common liver parenchymal lesion may appear in the US images. It will be important to let the AI machine understand and exclude this lesion for parenchymal fibrosis and steatosis interpretation.

Interaction of liver fibrosis and steatosis.

It is our experience as well as others, a brightened liver in hepatic steatosis will mask the coarseness of liver parenchymal. Thus the fibrosis score may be underestimated by human eye. We hope that AI learning process may overcome this issue

Preliminary case selection

We have been collecting data of patients received both liver histology and elastography studies since 2011. Up to Aril 2018 more than 700 patients had been collected. This group of patients will become our validation group to validate the result of computer-aid deep learning. This group may also be used to compare between AI quantified image data with current non-invasive modalities. In addition, more than 350 NBNC patients received Fibroscan study had been collected.

Methods

A. 2D US image selection

Conventional diagnostic ultrasound offers great diagnostic accuracy and robustness. However, it is difficult to make objective scale by human eye. When we intend to do computer-aid deep learning, additional problem appeared. The quality of ultrasound images can be easily influenced by machine settings, the characteristics of ultrasonic waves, different bland of machines, the interactions between ultrasound and body tissues, and other uncontrollable factors. To decrease the variation, we will fix the US image obtained from two locations. One is left hepatic lobe at midline abdominal (LLM), the other is R hepatic lobe at right intercostal space. The right lobe should include two types of images, one includes liver and gallbladder (RLG), the other includes liver and kidney (RLK). Only image with good quality and performed by 3-4 mega Hertz convex probe will be selected.

B. Image Augmentation for Deep Learning

For collecting thousands of training images in different situation, image augmentation will be developed to generate training data from the original 2D US images data set. Image Augmentation will manipulate the selected 2D US images to create many altered versions of the same image. This both provides more images to train on, but can also help expose our classifier to a wider variety of lighting and coloring situations so as to make our classifier more robust.

C. Histogram Equalization of images

We will try to find a standardized procedure to unify all US images. 1. Histogram Equalization increases contrast in images by detecting the distribution of pixel densities in an image and plotting these pixel densities on a histogram. The distribution of this histogram is then analyzed and if there are ranges of pixel brightnesses that aren't currently being utilized, the histogram is then "stretched" to cover those ranges, and then is back projected onto the image to increase the overall contrast of the image. 2. Contrast Stretching takes the approach of analyzing the distribution of pixel densities in an image and then rescales the image to include all intensities that fall within the 2^{nd} and 98^{th} percentiles.

D. Quantification of liver contour

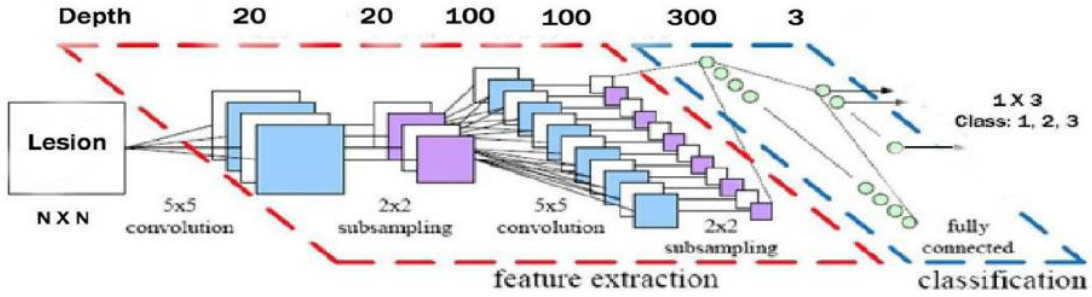
The liver capsule on an ultrasound image will be extracted. Based on the extracted liver capsule, we will perform a deep convolutional neural network (CNN) model to extract features from the image patches cropped around the liver capsules. A trained support vector machine (SVM) classifier will be applied to classify the sample into normal or abnormal

cases (39). We will try to make diagnosis of liver cirrhosis according to liver contour.

E. Quantification of liver parenchyma

After extraction of image data, the deep learning will be done by artificial neural network (ANN). ANN is a computational model that imitates the way the human brain deals with information (40). ANN is self-learning and self-organizing and has strong fault tolerance ability. ANN is a network of highly interconnected neurons operating in parallel. The neurons are organized into three layers: input, hidden, and output. The values of input layer are multiplied by weight and passed on to hidden layer. Several hidden layers can exist in one neural network. In hidden layers, neurons combine the weighted inputs according to activation function and threshold value, and then using it to determine the output. Detection and classification neural networks, such as back propagation neural network (BPNN), probabilistic neural network (PNN), convolutional neural network (CNN) and self-organizing map (SOM), are often used in the field of diffuse liver diseases (41).

Figure 3. An example of CNN architecture. The input is an N ×N image. Two convolutional ‘blocks’ follow the input with 5×5 filters and 2 × 2 max pooling. Two fully connected layers with 300 and 3 nodes respectively follow the convolutional layers. The dimension of the feature map reduces from N to N/2 – 2 after each convolutional layer. Fully connected layers take the output of the feature extraction layers



F. Pattern recognition of specific liver diseases

Some of the diseases associated with coarse liver parenchymal image, but not related to liver fibrosis. Patients with multiple tiny cysts are one of such examples. We will examine several such cases to see whether computer aid diagnosis can make a differentiation or not.

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