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ABSTRACT:

This deliverable is the fourth and last issue of a series of 4 periodic newsletters to be published by the CHIC consortium after each project period. The fourth issue of this annual newsletter provides an overview about the completed CHIC project written by Prof. Georgios Stamatakos, Coordinator of the CHIC consortium. The main achievements of the project as well as thirty representative potential products of the project are described. The newsletter also includes a short article on the assessment of the CHIC project by the European Commission. Other sections feature recent publications by CHIC partners as well as the announcement of upcoming events.

KEYWORD LIST:

Periodic Newsletter, dissemination material

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[1] **R**=Report, **P**=Prototype, **D**=Demonstrator, **O**=Other

[2] **PU**=Public, **PP**=Restricted to other programme participants (including the Commission Services), **RE**=Restricted to a group specified by the consortium (including the Commission Services), **CO**=Confidential, only for members of the consortium (including the Commission Services)

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A brief overview of the completed CHIC project

by Georgios S. Stamatakos

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In silico medicine (ISM) [http://en.wikipedia.org/wiki/In_silico_medicine], an emergent scientific and technological domain based on clinically driven and clinically oriented multiscale biomodelling, appears to be the latest trend regarding the translation of mathematical and computational biological science to clinical practice through massive exploitation of information technology. *In silico* (i.e. on the computer) experimentation for each individual patient using their own multiscale biomedical data is expected to significantly improve the effectiveness of treatment in the future, since reliable computer predictions could suggest the optimal treatment scheme(s) and schedules(s) for each separate case. Additionally, validated cancer multiscale models can serve as the basis for the development of platforms for the conduction of *in silico* trials. Due to the predominant manifestation of cancer at all spatiotemporal scales of biocomplexity, *in silico* oncology (ISO) appears to be the paradigm *par excellence* of *in silico* medicine.

The CHIC project aimed at advancing ISM through the paradigm of ISO in the following aspects: **1. Fundamental (Basic) Science** (development of highly innovative clinically driven and oriented complex

hypermodels and Oncosimulators by different modelling groups) **2. Information Technology** (semantic description of cancer models and hypermodels, development of a secure technological infrastructure and tools and services supporting the semi-automatic accessibility, execution and reusability of models as well as the building of hypermodels) **3. Clinical Medicine** (clinical drive and relevance of hypermodel building, clinical adaptation and partial clinical validation of hypermodels and Oncosimulators). The actual components developed by CHIC include a hypermodelling infrastructure consisting primarily of a hypermodelling editor, a clinical research (or clinically relevant) application framework (CRAF), a hypermodelling execution environment, an infrastructure for semantic metadata management, a hypermodel repository, a hypermodel-driven clinical data repository, a distributed metadata repository and an *in silico* trial repository for the storage of executed simulation scenarios. Multiscale models and data are semantically annotated using the developed ontological and annotating tools. An image processing and visualization toolkit, and cloud and virtualization services were also developed. The CHIC tools, services, infrastructure and repositories can provide the community with a collaborative interface for exchanging knowledge and sharing work in an effective way. A number of developed features and tools enhance usability and accessibility.

In order to ensure clinical relevance and foster clinical acceptance of hypermodelling, the whole endeavour was driven by the clinical partners of the consortium. Highly innovative cancer hypermodels collaboratively developed by the consortium cancer modellers have provided, among other things, the framework and the testbed for the development of the CHIC technologies. The following four paradigmatic cancer types have been addressed: **nephroblastoma**, **non small cell lung cancer**, **glioblastoma** and **prostate cancer.** Treatment with a variety of therapeutic modalities including **chemotherapy**, **radiation therapy**, **immunotherapy** and **hormone therapy** has been considered and simulated.

Clinical adaptation and partial clinical validation of the developed hypermodels and hypermodel Oncosimulators have been successfully conducted. Further retrospective validation is now needed in order to more fully substantiate the candidacy of the CHIC hypermodels and Oncosimulators for undergoing prospective clinical trial based validation. This is a necessary step in order to definitely prove the clinical credence and the clinical value of the hypemodels and the Oncosimulators as clinical decision support systems (CDS) before an eventually large scale translation into the clinical routine.

Achievements of the CHIC project

by Georgios S. Stamatakos

The novelty created by the large scale transatlantic CHIC project (http://www.chic-vph.eu/) has been impressive and multifaceted. It refers to a host of aspects of fundamental (basic) science, biomedical technology and future clinical medicine related to the quantitative understanding of cancer and the patient individualized treatment optimization of the disease. An exemplary key novel characteristic of CHIC has been the large scale intercontinental cancer multimodeller hypermodelling strategy supported by cutting edge software engineering technologies. The latter enable the technologically facilitated semi-automatic creation of new patient-centred cancer hypermodels by reusing pre-existing simpler component models (or hypomodels) and combining them in several scientifically and clinically plausible ways. CHIC has exploited to the fullest the great potential of geographically distributed world leading research teams active in the fields of multiscale cancer modelling, biomedical informatics technologies and clinical medicine. Clinical medicine has served as both the driver of the entire endeavour and the ultimate envisaged end user of its outcomes.

Clinical adaptation and partial clinical validation of the innovative, integrative and multiscale CHIC cancer hypermodels concerning the paradigmatic cancer

types of nephroblastoma, non small cell lung cancer, glioblastoma and prostate cancer have been conducted in full agreement with the CHIC description of work (DoW). The strict legal and ethical framework developed by the legal partners of CHIC, being in line with the European legislation, has been fully implemented and observed throughout the implementation of the project. The preliminary partial clinical validation of the developed hypermodels, largely based on retrospective imaging, histological, molecular and clinical data has demonstrated the great potential of cancer hypermodels and Oncosimulators to be viewed as candidates for clinical decision support systems (CDS) and/or cores of future in silico trial platforms. It should be noted, however, that additional retrospective validation work for the developed hypermodel and Oncosimulators is needed in order to more fully substantiate and support their "candidacy" for undergoing validation through prospective clinical trials so as to definitely assess both their clinical validity and clinical value.

In order to support the development, the execution and the multifaceted utilization of hypermodels, a host of advanced technological components were created, tested and validated. These include inter alia the Clinically Relevant Application Framework (CRAF), the Hypermodelling Editor, the Data-, Model-, In Silico Trial- and Metadata-Repositories, the model execution framework, a strategy for semantically annotating hypermodels and special visualization kits. A successful and efficient utilization of the private cloud dedicated to CHIC also took place.

Further retrospective validation of the hypermodels, following the completion of the CHIC project, will be carried out on a bilateral or small former CHIC participating organization groups basis, in accordance with the intellectual property rights framework and other provisions developed and agreed upon during the implementation of the CHIC project.

Regarding the eventual prospective clinical validation of hypermodels, certain exploratory steps have already been taken, including focused discussions initiated by the project's assistant clinical coordinator Professor Norbert Graf within the framework of the International Society for Pediatric Oncology (SIOP). An eventually successful outcome of the further retrospective clinical validation of the hypermodels in conjunction with a number of scientifically persuasive demonstrations of the hypermodels to clinical trials funding bodies is expected to pave the way for the design of new prospective clinical trials aiming inter alia to test and validate the hypermodels and the corresponding Oncosimulators. Sustainability of the CHIC technological platform has been ensured for 1.5 years after the completion of the project.

Before their eventual prospective clinical validation, the hypermodels and the Oncosimulators developed within the framework of the CHIC project can - and in fact already - serve as research platforms for the better quantitative exploration and the understanding of the natural phenomenon and the disease of cancer as well as for educational purposes. These include inter alia the education and the training of biomedical scientists and engineers on the current accumulated quantitative multiscale biomedical knowledge related to cancer and its treatment, the training of young clinical doctors on the natural behaviour of cancer through the use of special visualization technologies, the education and the training of cancer patients and/or their parents or custodians (in the case of children) and the education of the general public about cancer (health literacy).

The interest of the broader clinical community for the CHIC outcomes has been strong. Representative examples of related actions include the invitation to present and demonstrate CHIC in the International Conference on Pediatric Oncology and Clinical Peditatrics (Toronto, Canada 11-13 August 2016) and the invitation made by the European Association for Clinical Pharmacology and Therapeutics (EACPT) to the CHIC coordinator Research Professor Georgios Stamatakos to present CHIC as a keynote lecture in the EACPT2017 Conference (Prague, June 24-27 (http://www.eacpt2017.org/). An invitation made by the same clinical association regarding the submission

of a scholarly paper reflecting the aforementioned keynote lecture content - to be eventually published in the Clinical Therapeutics Journal with which the latter collaborates - further demonstrates the clinical interest for the achievements of the CHIC project. On top of this, a major multinational industrial organization and CHIC partner (PHILIPS) have expressed their strong interest in participating in the further validation and eventual industrial exploitation steps regarding the CHIC outcomes.

In summary, the project has fully and successfully achieved all its objectives. Of particular note is the special emphasis put on the clinical relevance of the endeavour as a response to the independent reviewers' highly constructive and illuminating suggestions.

Thirty representative (potential) products of the CHIC project

by Georgios S. Stamatakos

In this section a list of representative (potential) products developed either totally or partly within the CHIC framework is provided. Each element of the list contains the name of the product along with its following characteristics indicated within parentheses: envisaged use, nature (e.g. software), sector of application, and the start of commercial or any other use. The previous characteristics are separated by a vertical bar (|) It is noted that the listing order does not imply any order of importance of the products. *Specific intellectual property rights apply to each (potential) product.*

P1. NEPHROBLASTOMA ONCOSIMULATOR

(Clinical Decision Support System (CDS) and in silico trial core following the eventually successful completion of its prospective validation. Educational tool for in silico oncology/medicine | Software | Medical, Pharmaceutical | 2017)

P2. NEPHROBLASTOMA MULTI-MODELLER HYPERMODEL

(Clinical Decision Support System (CDS) and in silico trial core following the eventually successful completion of its prospective validation. Educational tool for in silico oncology/medicine | Software | Medical, Pharmaceutical | 2017)

P3. LUNG CANCER ONCOSIMULATOR

(Clinical Decision Support System (CDS) and in silico trial core following the eventually successful completion of its prospective validation. Educational tool for in silico oncology/medicine | Software | Medical, Pharmaceutical)

P4. LUNG CANCER MULTI-MODELLER HYPERMODEL

(Clinical Decision Support System (CDS) and in silico trial core following the eventually successful completion of its prospective validation. Educational tool for in silico oncology/medicine | Software | Medical. Phramaceutical | 2017)

P5. LUNG CANCER STATISTICAL HYPERMODEL

(Clinical Decision Support System (CDS) following the eventually successful completion of its prospective validation. Educational tool for in silico oncology/medicine | Software | Medical, Pharmaceutical | 2017)

P6. GLIOBLASTOMA HYPERMODEL

(Clinical Decision Support System (CDS) following the eventually successful completion of its prospective validation. Educational tool for in silico oncology/medicine | Software | Medical, Pharmaceutical | 2017)

P7. PROSTATE CANCER PHARMACOKINETIC AND PHARMACODYNAMIC HYPOMODEL FOR HORMONAL TREATMENT

(Clinical Decision Support System (CDS) and in silico trial core following the eventually successful completion of its prospective validation. Educational tool for in silico oncology/medicine | Software | Medical, Pharmaceutical | 2017)

P8. PROSTATE CANCER MULTI-MODELLER HYPERMODEL

(Clinical Decision Support System (CDS) and in silico trial core following the eventually successful completion of its prospective validation. Educational tool for in silico oncology/medicine | Software | Medical, Pharmaceutical | 2017)

P9. MODEL REPOSITORY

(Use of existing hypomodels and hypermodels. Development of new hypermodels | Software | Medical, Pharmaceutical | 2017)

P10. CONTENT OF THE MODEL REPOSITORY

(Use of existing hypomodels and hypermodels. Development of new hypermodels | Software | Medical, Pharmaceutical | 2017)

P11. IN SILICO TRIALS REPOSITORY

(Exploitation of already completed hypermodel executions. Storage of new hypermodel executions | Software | Medical, Pharmaceutical |2017)

P12. CONTENT OF THE IN SILICO TRIALS REPOSITORY

(Exploitation of the predictions of already executed treatment scenarios | Software | Medical, Pharmaceutical | 2017)

P13. THE ENTIRE TECHNOLOGICALLY INTEGRATED CHIC PLATFORM

(In silico Medicine research including in silico trials and cancer treatment optimization| Software | Medical, Pharmaceutical | 2017)

P14. VPH-HF SOFTWARE FRAMEWORK FOR THE EXECUTION OF HYPERMODELS

(Software framework for the execution of hypermodels | Software | Medical | 2017)

P15. VPH-HE SOFTWARE FOR THE DEVELOPMENT OF HYPERMODELS

(Software framework for the development of hypermodels | Software | Medical | 2017)

P16. CLINICAL RESEARCH APPLICATION FRAMEWORK (CRAF)

(Use of basic science computational models and their results in a clinical setting | Software {Medical | 2017)

P17. HYPERMODELLING EDITOR

(Visual design of integrative computational models for cancer research | Software | Medical | 2017)

P18. DrEye

(A flexible and easy to use platform, for intuitive annotation and segmentation of tumour regions | Software | Medical | 2017)

P19. OPEN SOURCE MODELLING SOFTWARE: MICROVESSEL CHASTE

(Computational biology | Software | Medical, Pharmaceutical | 2017)

P20. ANGIOGENESIS HYPOMODELS FOR NEPHROBLASTOMA AND LUNG CANCER HYPERMODELS

(Computational biology | Software | Medical, Pharmaceutical)

P21. MATHEMATICAL (HYPO) MODEL FOR MONITORING PSA DYNAMICS AFTER RADICAL PROSTATECTOMY (RP) TO PREDICT THE TIMING OF RECURRENCE

(Tumour recurrence risk estimation | Software | Medical | 2017)

P22. MATHEMATICAL (HYPO) MODEL BASED ON PERISURGICAL PARAMETERS VALUES AT RADICAL PROSTATECTOMY (RP) TO PREDICT THE RISK OF PROSTATE TUMOUR RECURRENCE BY MEANS OF A NOMOGRAM

(Tumour recurrence risk estimation| Software | Medical | 2017)

P23. MATHEMATICAL (HYPO)MODEL BASED ON PERISURGICAL PARAMETERS VALUES AFTER RADIOTHERAPY TO PREDICT THE RISK OF PROSTATE TUMOUR RECURRENCE BY MEANS OF A NOMOGRAM

(Tumour recurrence risk estimation| Software | Medical | 2017)

P24. ON-LINE CLINICAL DECISION SUPPORT SYSTEM FOR PROSTATECTOMIZED PATIENTS RUNNING ON THE 'MY HEALTH AVATAR' PLATFORM

(Clinical Decision Support System (CDS) | Software | Medical | 2017)

P25. CLINICAL DATABASE SYSTEM

(Data sharing service | Software | Medical | 2017)

P26. BRAIN SEGMENTATION SYSTEM (BRATUMIA)

(Software tool to automatically segment brain tumours | Software | Medical |2017)

P27. PSEUDONYMISATION TOOLS

(Pseudonymization of multiscale clinical data | Software | Medical | 2016)

P28. SECURITY TOOLS AND SERVICES

(Security for multiscale clinical data and hypermodelling services | Software | Medical |2017)

P29. SOFTWARE LIBRARY AND SYSTEM COMPONENTS FOR SEMANTIC DATA MANAGEMENT

(Multiscale data and model processing, hosting and related activities | Software | Medical | 2017)

P30. CONCEPTUAL MODEL FOR THE ANNOTATION OF BIOLOGICAL AND CLINICAL DATA

(Multiscale data and model processing, hosting and related activities | Software | Medical |2017)

CHIC progress assessed by the European Commission services as "Excellent" twice

The latest CHIC review was conducted by five independent experts appointed by the European Commission, on 21 November 2016. Its outcome was particularly encouraging. The formal assessment reads: "Excellent progress (the project has fully achieved its objectives and technical goals for the period and has even exceeded expectations)." This is the second time that the CHIC progress has been rated as excellent. The previous excellent assessment of the CHIC progress was based on the review conducted on 29 January 2016.

Events / Announcements

Participation and keynote lecture in 13th European Congress of Clinical Pharmacology and Therapeutics

CHIC coordinator Research Professor Georgios Stamatakos will present CHIC as a keynote lecture in the EACPT2017 Conference (Prague, June 24-27 (http://www.eacpt2017.org/).

The main focus of the congress will be the role of clinical pharmacology in personalized pharmacotherapy, both a priori – pharmacogenetics – and a posteriori (therapeutic drug monitoring).

The aim of the conference is also to show, the future potential and fundamental role clinical pharmacology plays in modern health science.

CHIC publications

For a list of representative CHIC publications, please refer to: http://chic-vph.eu/publications/

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Please visit us at **www.chic-vph.eu**

Disclaimer

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