REVERT

taRgeted thErapy for adVanced cororEctal canceR paTients

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 848098.

The European REVERT Project: An ai-based dss for treatment selection

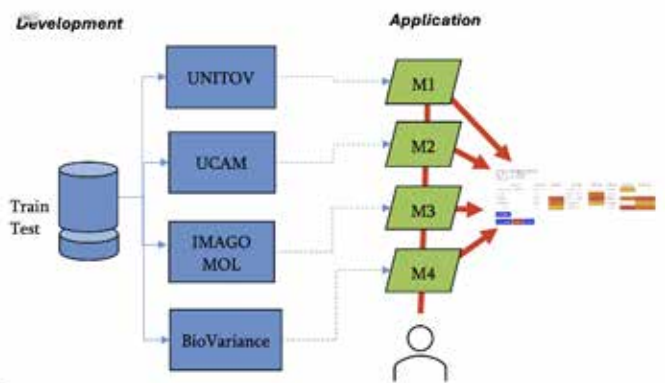

Figure 1: *A multi-party Decision Support System Model based on artificial intelligence*

FIND OUT HERE ABOUT THE EUROPEAN REVERT PROJECT, AN AI-BASED DSS FOR TREATMENT SELECTION

The REVERT project is built around predictive medicine and artificial intelligence (AI). The Consortium includes 22 top-performing research, biobanks and clinical centres, as well as four small-medium enterprises (SMEs) from five European countries, whose expertise spans from computer science to biomarker discovery, omics sciences, and clinical oncology settings, with a shared focus on advancing personalised medicine through AI-health research and development.

AN AI-BASED DSS FOR TREATMENT SELECTION

To this end, REVERT aims to create an AI-based decision support system (DSS) that can aid the oncologist in determining the best combinatorial treatment for patients diagnosed with unresectable metastatic colorectal cancer (mCRC) in a personalised medicine context.

To accomplish its objective, the REVERT project has collected mCRC data from various sources (clinical databases, biobanks' datasets and real-world data) to build a dedicated database for training and testing different AI classifiers to construct the REVERT DSS.

As Professor Fiorella Guadagni, the Coordinator of the EU-funded REVERT project, explains, the REVERT Consortium has achieved a strong operational synergy among its partners, leading – among other outcomes – to the creation of a DSS that can provide insight into the patient's response to the currently available drugs.

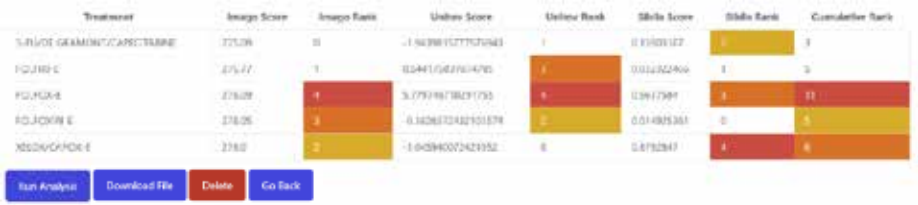

Figure 2: *DSS Interface for Clinical Centres*

MULTI-PARTY, RESPONSIBILITY-SHARING AI ALGORITHMS FOR A PERSONALISED THERAPEUTIC INTERVENTION

REVERT paves the way for building AI prediction systems in the field of medicine, in general, and cancer treatment, in particular. Indeed, one of the significant obstacles to the wide adoption of these systems is their opacity, which undermines clinicians' trust in AI. Explainable AI is the current approach to gaining the trust of clinicians, and it is extremely promising.

Yet, it has an inherent limitation: it relies on a single model built using a set of data and a single algorithmic approach.

In REVERT, we defined a novel approach to gain the trust of clinicians: the multi-party, responsibility-sharing AI algorithms, as explained by Prof Fabio M. Zanzotto, Computer Scientist and Professor at the University of Rome Tor Vergata in Italy. The idea is straightforward.

Trust is built by consensus of different AI algorithms based in the four different AI centres of the project: University of Rome Tor Vergata (UNITOV), Fundacion Universitaria San Antonio (UCAM) in Murcia, Spain, BioVariance Gmbh in Tirschenreuth, Germany, and Universitatea Tehnică, Gheorghe Asachi" din Iaşi, Associate Member of the IMAGO-MOL Cluster in Romania. Indeed, whenever decisions are crucial, different AI voices are better than a single assertive AI voice.

MORE ON AN AI-BASED DSS FOR TREATMENT SELECTION

The AI approach to building the overall DSS of REVERT is then defined in addition to this very simple idea.

The AI DSS of REVERT consists of four different AI classifiers developed independently by the four centres and applied independently. The classifiers' final aim is to suggest a ranked list of possible treatments for an enrolled patient. Therefore, in REVERT, we defined two novel measures to evaluate such classifiers acting as rankers of treatments: the Average Ranking Score and the Smoothed Average Ranking Score.

In the development phase, the four centres have been provided with the same set for training and testing. The four centres were free to explore any combination of features and any machine learning algorithm. We set up a leaderboard to foster competition among centres and track the models' evolution based on different algorithms. At the end of the development phase, each centre was forced to select the best model, and that model was entered into the pool of the four models for the final DSS of REVERT realised with a secure web application.

In the application phase, clinical centres use the web application to obtain a ranked list of treatments for the enrolled patient. The ranked list is then given to the clinician, who makes the final decision on the specific treatment to give to the enrolled patient.

CLINICIANS' TRUST IN ADVANCED AI SYSTEMS FOR TREATMENT SELECTION

Through distributing responsibilities, REVERT fosters a novel method of increasing clinicians' trust in these advanced AI systems for treatment selection.

To assess its effectiveness in helping clinicians select the best therapeutic option on a case-by-case basis, the REVERT DSS is currently being applied to patients enrolled in a clinical prospective, not-for-profit, interventional, premarket medical device "early phase" Study launched in March 2023 under the coordination of the "Tor Vergata" University Clinical Centre in Rome (ClinicalTrials.gov PRS ID: NCT05396807) and the participation of six medical oncology units from three different European countries, which results will be made available by the end of the year.

DOI: https://doi.org/10.56367/OAG-042-11226
First Published: 26th March 2024 - Last Modified: 15th April 2024 - Published in: Open Access Government

Helping doctors treat advanced colorectal cancer

What makes some people with unresectable metastatic colorectal cancer (mCRC) respond well to treatment and others not? The REVERT project seeks to improve targeted therapy for mCRC patients by combining predictive medicine and AI.

The EU-funded REVERT project has developed an AI-based decision support system (DSS) to help clinicians find the best treatment combination for individual patients with mCRC. The DSS is currently being tested in a clinical study carried out at six medical oncology units in three European countries.

According to the European Cancer Information System, colorectal cancer is the third most diagnosed cancer in men (after prostate and trachea, bronchus and lung (TBL) cancers) and the second most diagnosed cancer in women (after breast cancer), accounting for 13 % of all new cancer diagnoses in the EU in 2022. It is also the second biggest cause of cancer death in men (after TBL cancer) and the third in women (after breast and TBL cancers), responsible for 12.3 % of EU cancer deaths in that year.

When colorectal cancer metastasises, cancer cells from the colon or rectum spread to other parts of the body, such as the liver, lungs or lymph nodes. In some cases, mCRC patients can undergo curative resection – surgery to remove all malignant tissue. However, mCRC usually has a dismal prognosis and treatment is for the most part palliative in nature, since the vast majority of patients have unresectable mCRC and less than 20% survive beyond 5 years in Europe.

A SYSTEM TO SUPPORT CLINICAL DECISIONS

To create a DSS capable of assisting clinicians in identifying the most suitable treatment combinations for unresectable mCRC patients, REVERT collected colorectal cancer data from a wide range of sources: clinical databases, UK Biobank data sets and real-world data. Adopting a personalised medicine approach, they developed an improved innovative model of combinatorial therapy that identifies the most efficient and cost-effective therapeutic intervention for patients with unresectable mCRC.

"The consolidation of the REVERT database (RDB) – hosted on an Amazon Web Services bucket – was a prerequisite for the development of a DSS to determine the optimal treatment option for individual patients, which is now being tested in a clinical trial involving patients with unresectable mCRC," reports an article posted on 'Open Access Government'. The clinical trial is being held in six medical oncology units in Spain, Italy and Romania. According to clinical trial coordinator Prof. Mario Roselli of REVERT project partner University Hospital Tor Vergata, Italy, the clinical study aims to further individualised treatment for unresectable mCRC patients by determining the most effective therapeutic option on a case-by-case basis.

"In addition to the DSS devised for the clinical trial, the ML-based 7-Gene Algorithm, which consists of mutation profiles of seven genes (KRAS, BRAF, ERBB2, MAP2K1, TSC2, TP53, and APC) showed a statistically significant accuracy as a classifier to distinguish between patients who responded to first-line chemotherapy and those who did not," reports the article. "Further studies are currently involving next-generation DNA and RNA Sequencing, which are being used to perform drug sensitivity analyses and identify novel potential drugs for improved predictive models for tailored treatment of mCRC."

REVERT (taRgeted thErapy for adVanced colorEctal canceR paTients) ends in December 2024.

Published in: CORDIS EU Research results
Link: https://cordis.europa.eu/article/id/449266-helping-doctors-treat-advanced-colorectal-cancer?WT.mc_id=exp

The European Revert Project: Assisting clinicians in patient treatment

STARTING IN JANUARY 2020, THE EUROPEAN REVERT PROJECT IS NOW IN ITS FINAL PHASE. THE PROJECT BLENDS PREDICTIVE MEDICINE AND AI TO ENABLE CLINICIANS TO QUICKLY AND ADEQUATELY TREAT PATIENTS

The main objective is to develop a decision support system (DSS) using artificial intelligence (AI) that can assist clinicians in identifying the most suitable combinatorial treatment for individual patients diagnosed with unresectable metastatic colorectal cancer (mCRC).

To achieve its goal, the REVERT project has gathered colorectal cancer data from diverse sources – clinical databases, biobanks' datasets and real-world data – to assess their potential in identifying the key factors contributing to effective responses against mCRC, as Professor Fiorella Guadagni, the Director of the Biobank BioBIM and Biomarker Discovery and Advanced Technologies (BioDAT) Laboratory at the IRCCS San Raffaele in Rome and the Co-ordinator of the EU-funded REVERT project, explains.

Predictive medicine and AI are central to the REVERT project, featuring a European network of 22 top-performing research and clinical centres located in five European countries as well as long-established biobanks and several small and medium enterprises (SMEs), all contributing through their experience and real-world data. AI models, data management, biomarker discovery, omic sciences, and clinical oncology settings are among the skill sets of all partners, whose focus is on research and development in AI-Health to advance personalised medicine.

Operational synergy in planning activities has been successful for the REVERT Consortium throughout the duration of the project, leading to the development of various AI algorithms that can provide information on disease prognosis and response to currently available drugs.

AI ALGORITHMS FOR A PERSONALISED THERAPEUTIC INTERVENTION

The close collaboration between computer scientists and physicians has been instrumental in all phases of project activities to harness technology's potential to improve medical treatment. To date, several AI models capable of predicting treatment response against mCRC have been trained. This has been made possible thanks to the availability of large databases on mCRC from a significant number of certified biological banks as well as clinical and research centres that have served for the implementation of an ICT framework for integrating, extracting and harmonising data always in compliance with up-to-date data protection standards.

The consolidation of the REVERT database (RDB) – hosted on an Amazon Web Services bucket – was a prerequisite for the development of a DSS to determine the optimal treatment option for individual patients, which is now being tested in a clinical trial involving patients with unresectable mCRC.

The definition of rational predictive models based on machine learning (https://doi.org/10.3390/ijms22094394) and their implementation (arXiv:2205.06234v2) represented the basis for real-world testing and optimisation of AI predictors, always taking into account that the rationale for a DSS's suggestion must be understood before using it. This is known as explainable AI.

Analyses were, thus, performed by IT Partners on the RDB using a variety of interpretable machine learning models, where the target variable was the progression-free survival with respect to the date of the first-line treatment.

The best combination of learning results and explainability was finally chosen to deploy the DSS – and a mobile app – to assist clinicians in their decisions.

Notably, although the system is designed to help the oncologist, medical professionals are ultimately responsible for choosing the most suitable treatment for individual pa-

tients. Clinicians, indeed, are informed by the system but retain the ability to consider alternative measures while considering the patient's profile.

IN VITRO VALIDATION OF AI MODELS FOR TAILORED TREATMENT OF MCRC

In addition to the DSS devised for the clinical trial, the ML-based 7-Gene Algorithm, which consists of mutation profiles of seven genes (KRAS, BRAF, ERBB2, MAP2K1, TSC2, TP53, and APC) showed a statistically significant accuracy as a classifier to distinguish between patients who responded to first-line chemotherapy and those who did not (https://doi.org/10.3390/ cancers14082045). Further studies are currently involving next-generation DNA and RNA Sequencing, which are being used to perform drug sensitivity analyses and identify novel potential drugs for improved predictive models for tailored treatment of mCRC.

The establishment of organoids from patients' tumour biopsies and the use of molecularly imprinted polymer (MIP) probes against sialic acid, as used in the REVERT project, provide an interesting setting to test conventional and innovative marker-based drug combinations and compare their effects with the response to treatments administered to the patient from whom the organoid was derived. In addition, organoids are currently being used in experimental studies to validate the algorithm's ability to accurately predict the response of cells to the most- commonly administered first-line treatment options.

In the end, these studies will provide more chances to investigate the effectiveness of currently available or new combinatorial therapies.

THE REVERT PROJECT CLINICAL STUDY

Testing and validation of the AI predictive model in the oncology setting in order to improve clinical practice and management of healthcare services for cancer patients is the focus of the REVERT clinical study, a clinical prospective, no-profit, interventional, premarket medical device "early phase" study launched in March 2023 under the co-ordination of the University Hospital 'Tor Vergata' of Rome (ClinicalTrials.gov PRS ID: NCT05396807) and the participation of 6 medical oncology units from three different European countries.

The main objective is to aid in the progression of individualised treatment for patients with unresectable mCRC by determining the most effective approach on a case-by-case basis, as explained by the clinical trial coordinator Prof. Mario Roselli, Director of the Medical Oncology Unit at the University Hospital Tor Vergata and Full Professor at the same University.

The DSS – previously trained through retrospective evaluation of the clinical profiles of patients from the RDB, who were defined as 'responders' or 'non-responders' based on their response to treatment – is currently being applied to new patients who have been enrolled in the clinical study to evaluate its performance in helping investigators choose the best therapeutic option.

DOI: https://doi.org/10.56367/OAG-041-11204
First Published: 16th January 2024
Last Modified: 24th January 2024
Published in: Open Access Government

Decision support for personalised treatment

Artificial intelligence (AI) tools could help the transition towards more personalised treatment of disease. Researchers in the REVERT project are developing a decision support system designed to assist clinicians in identifying the most suitable treatment for individual patients diagnosed with metastatic colorectal cancer (mCRC), as Professor Fiorella Guadagni explains.

Metastasis, the spread of colorectal cancer beyond the site of the primary tumour, poses a significant threat and can be fatal in severe cases. The location and number of metastatic lesions play a crucial role in determining the most effective treatment approach for the individual patient. Professor Fiorella Guadagni, the Director of the Biobank BioBIMTM and Biomarker Discovery and Advanced Tecnologies (BioDAT) Laboratory at the IRCCS San Raffaele in Rome and the Coordinator of the EU-funded REVERT project, emphasises the value of this information in predicting optimal treatment outcomes. The REVERT project aims to consolidate colorectal cancer data from different sources to improve disease management. "We want to use existing biobanks that store comprehensive colorectal cancer datasets and assess their potential in identifying the key factors contributing to effective responses against mCRC," she explains.

REVERT PROJECT

The REVERT project has access to data on metastatic patients from biobank samples across Europe, including information on treatment. Significant efforts are being made within REVERT to harmonise the data and ensure compliance with modern data protection standards. The next crucial step is to consolidate this data into the REVERT database for detailed analysis.

Professor Guadagni explains, "We already have retrospective information from various studies that allow us to determine the response of patients to certain front-line therapies. The project's IT specialists have analysed this data to predict treatment response."

This valuable information will drive the development of a decision support system to determine the optimal treatment option for individual patients, which will then be tested in a clinical trial involving patients with mCRC [see box-out text]. Professor Guadagni continues, "The project will develop different algorithms to identify the most appropriate treatment course for patients with specific characteristics."

In parallel to the clinical trial, an in vitro study is being conducted with organoids, miniature organ-like structures. The aim of this study is to evaluate the algorithm's ability to accurately predict the response of these cells to initial treatment. Professor Guadagni emphasises that the in vitro study provides additional opportunities, stating, "We can compare the effectiveness of the two most commonly administered first-line treatment options and explore the efficacy of other drugs or new combinatorial therapies." Identifying potential new combinatorial therapies is a major focus of the project.

Professor Guadagni adds, "We wanted to ensure that there was enough time for clinical validation of the algorithm. It is trained with data whose treatment outcomes are already

known, and then validated with a separate dataset to ensure accurate discrimination."

While the system is designed to support clinicians, the ultimate responsibility for determining the most appropriate treatment for individual patients rests with the medical professionals. Recognising the expertise of clinicians, Professor Guadagni highlights the importance of a clear basis for the system's recommendations. She explains, "No one will use a decision support system without understanding the rationale behind its suggestions. This is called explainable AI." Even if the system suggests a particular combinatorial treatment based on patient characteristics, clinicians have the option to consider alternative actions. Professor Guadagni explains, "The system informs clinicians about patients who will respond effectively to first-line treatment and provides the best combination of treatments under certain circumstances. The system empowers clinicians to modify or adjust the treatment while considering the profile of the individual patient."

There are several biobanks storing data on colorectal cancer cases. We want to use them, evaluate them, and see if they can help us find out which factors lead to an effective response against metastatic colorectal cancer.

WIDER RELEVANCE

The project's research focuses primarily on colorectal cancer due to the availability of a large dataset and its significant impact on mortality rates. However, Professor Guadagni highlights that the results of the project are also relevant for other medical conditions, particularly other forms of cancer. She explains, "These algorithms have the ability to predict an individual's response to treatment based on the available dataset. The algorithms can be applied to datasets associated with different diseases, they are not limited to colorectal cancer."

Close collaboration between IT specialists and physicians is essential in achieving this and harnessing technology's potential to improve medical treatment. Professor Guadagni emphasises the multi-disciplinary nature of the project, stating, "We have been working with computer scientists for more than 20 years, fostering mutual understanding and jointly identifying the necessary steps to achieve our common goals."

Ongoing research also looks into understanding why certain patients respond favourably to therapies while others do not.

Any new insights gained can be incorporated into the decision support system. Extensive sample analyses are being carried out, using metabolomics technologies and next generation sequencing (NGS) to gather comprehensive information. Professor Guadagni stresses the effectiveness of NGS in identifying differences between patients, which contributes to the ongoing development of tools and systems that assist clinicians in treating colorectal cancer more effectively.

However, while artificial intelligence can play a major role in improving medical treatment, Professor Guadagni emphasises the importance of clear boundaries. She stresses that it must be ethical, non-discriminatory, fully controlled by clinical doctors, and explainable.

Considerable care has been taken to ensure that the research is conducted in compliance with current regulations while enabling efficient data-sharing among partners and a wider network of interested parties. This is key to the continuous development of AIbased healthcare tools, a complex endeavour with numerous factors to consider. Professor Guadagni acknowledges the importance of a dedicated support group consisting of specialised individuals, including lawyers and IT experts. She underlines their commitment to adhering to the existing rules, despite the complexities involved.

VALIDATION CLINICAL TRIAL

A clinical study has been launched which focuses on testing and validating the predictive model developed in the REVERT project in an oncology setting. The aim is to improve clinical practice and management of healthcare services for cancer patients.

This study is focused on colorectal cancer, which is the third-most common form of cancer in men and second amongst women, and is a correspondingly high priority in research. It is estimated that colorectal cancer accounted for 12.7% of all new cancer diagnoses across the EU in 2020.

The aim is to help move towards a more personalized mode of treating patients with unresectable metastatic colorectal cancer by identifying the most effective intervention for each individual, with researchers working to validate the clinical decision support system developed in REVERT.

"The clinical study will test the predictive efficacy of Artificial Intelligence on a case-by-case basis from a 'personalized' perspective," explains Prof. Mario Roselli, Director of the Medical Oncology Unit at the University Hospital Tor Vergata, where he also serves as a Full Professor.

"The predictive algorithm has been previously 'trained' through retrospective evaluation of the clinical profiles of patients already treated at the Oncology Units participating in the project and who, based on their response to treatment, have been defined as 'responder' or 'non-responder'.

"This algorithm, applied to new patients enrolled in the clinical study, will allow investigators to be supported in choosing the best therapeutic option."

Published: Autumn 2023 edition
Published in: EU Research
Link: https://euresearcher.com/autumn-2023/ (pag. 70-71)

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Cover: graphical representation of the REVERT Project Design.