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ORIGINAL PAPER

SEEIIST – a new research facility for tumor treatment and biomedical investigations with proton and ion beams

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Abstract

Purpose A project for the establishment of an international intergovernmental scientific organization in the region of South East Europe (South East European Institute for Sustainable Technologies - SEEIIST) is currently in progress. SEEIIST is an intergovernmental effort supported by nine countries from the region (Albania, Bosnia and Herzegovina, Bulgaria, Greece, Kosovo (This designation is without prejudice to positions on status, and is in line with UNSC 1244 and the ICJ Opinion on the Kosovo Declaration of Independence.), Montenegro, North Macedonia, Serbia and Slovenia, while Switzerland is an observer). The main goals of the project are to establish a unique research infrastructure and to form a research nucleus in the region of South-East Europe, to boost the technology transfer from European laboratories like CERN and others, to promote collaboration between science, technology, and industry, to mitigate tensions between countries in the region, and to provide platforms for the development of education.

Methods The research infrastructure will include a powerful next-generation accelerator that will provide proton and ion beams for tumor treatment and biomedical research. The center will comprise of three rooms for patient treatment and two large experimental halls.

Results A wide pre-clinical and clinical research program in the fields of radiobiology, medical physics, medical imaging, biophysical modeling and planning of patient treatment, design and investigation of new materials, production of isotopes for diagnosis, and treatment of patients are envisaged.

Conclusions This infrastructure is unique for Europe and will attract researchers from all European countries to perform their investigations.

Keywords Particle therapy · Proton and light ion beams · Tumor treatment · SEEIIST

1 Introduction

The South East European International Institute for Sustainable Technologies (SEEIIST) is a new international research infrastructure to be based in South East Europe. The idea of SEEIIST is both to develop new opportunities for cutting-edge research and technology for the benefit of the region and help build mutual trust, as has been successfully demonstrated in the cases of other international research laboratories, such as CERN (European Organization for Nuclear Research) in Europe and SESAME (Synchrotron-Light for Experimental Science and Applications in the Middle East).

SEEIIST is based on a Declaration of Intent signed in 2017 by Albania, Bosnia and Herzegovina, Bulgaria, Kosovo[1], Montenegro, North Macedonia, Serbia, and Slovenia. Croatia declared its interest but postponed a final decision *ad referendum*. Greece initially took on an observer status, which was changed to full membership in 2021. Switzerland joined the project as an observer. The Declaration of Intent was followed by a Memorandum of Cooperation signed in 2019 by six Prime Ministers of the SEE region (Albania, Bosnia and Herzegovina, Bulgaria, Kosovo, Montenegro and North Macedonia) at the Summit of the Berlin Process in Poznan, Poland.

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[1] This designation is without prejudice to positions on status, and is in line with UNSC 1244 and the ICJ Opinion on the Kosovo Declaration of Independence.

Two options were proposed by leading scientists: a synchrotron light facility for research in physics, biology, environment, and archaeology and, as an alternative, a heavy ion facility for treatment of tumors with proton and ion beams and for the performance of bio-medical research. In the core of both facilities is a synchrotron accelerator of electrons in the first case [1] and protons and heavier ions in the second [2]. Both were considered to be relevant for the region as they would promote research and technology, contribute to the creation of new jobs, fight brain drain, and improve relations between countries. When presented to the Steering Committee (SC) of the project for a decision, after careful analysis the heavy ion facility was chosen.

In recent years, cancer diseases have become a leading cause of death in Europe, showing a significant increase. Figure 1 presents data on registered new cases of cancer in three countries from the Southeastern European region (Bulgaria, Slovenia, and Croatia), normalized per 100,000 people. As seen, there is a clear trend of increase in the number of registered new cases. Figure 2 displays data for several European countries, including countries from the Southeastern European region [3]. It illustrates the ratio of the number of deaths to the number of new cases of cancer. The mortality rate is significantly higher for countries in the South East European region compared to the European average. There are two main reasons for this data: firstly, late diagnosis of cancer diseases due to a lack of modern screening equipment and, secondly, a lack of access to modern treatment options for such patients.

Radiation therapy is one of the primary methods complementing surgical and chemical tumour treatments. The number of patients undergoing radiation therapy is continuously increasing, and the methods used are developing rapidly, becoming more effective. Radiotherapy, especially therapy in which tumours are irradiated with beams of protons and light ions, has undergone significant development in recent years. Due to the specific properties of these particles when passing through matter, this method achieves a significantly better preservation of surrounding healthy tissues and a higher efficacy, especially in cases of radiation-resistant tumour formations. In recent years, there has been an exponential growth in newly constructed centres for particle therapy (especially devoted to proton therapy), leading to an increase in the number of patients undergoing such treatment. Currently, 117 centres for particle therapy operate worldwide, with 12 of them using Carbon ion beams. Moreover, 38 centres are in the process of construction (6 with Carbon ion beams). By 2022, over 311,000 patients had undergone particle therapy treatment, with 46,700 treated with carbon ions [16]. Figure 3 shows the centres for treating patients with protons and ions in Europe. It is obvious that such centres are completely missing in the Southeastern European region. This results in patients from this region having very limited access to the most effective modern cancer treatment.

The total population of the countries participating in the project is approximately 43 million. If we add the population of the European part of Turkey, this figure increases to 75 million. We assessed the expected number of patients eligible for proton and light ion therapy in the countries participating in the project. This assessment took into account data on registered new cases of cancer, the type and stage at which the tumour is first observed, national treatment protocols, and existing protocols for treating patients with protons and light ions. It should be noted that the national protocols vary significantly, especially in regard to the relative percentage of patients eligible for radiation therapy. The expected number of patients per year is estimated at 1400 for the project member states and 2450 for the entire region. This estimate is extremely conservative, and these figures should be considered as the minimal number of patients. In order to meet the needs of the region at least 2–3 centres for particle therapy should be established within it.

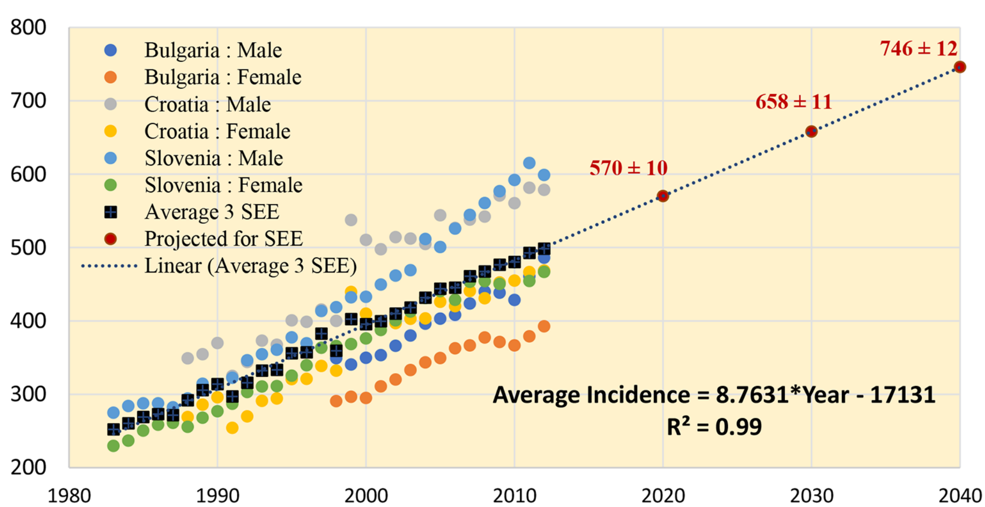

Fig. 1 Combined 3 SEE country incidence crude rates: all cancers (except nonmelanoma skin cancers), all ages, females and males (NS) [3]

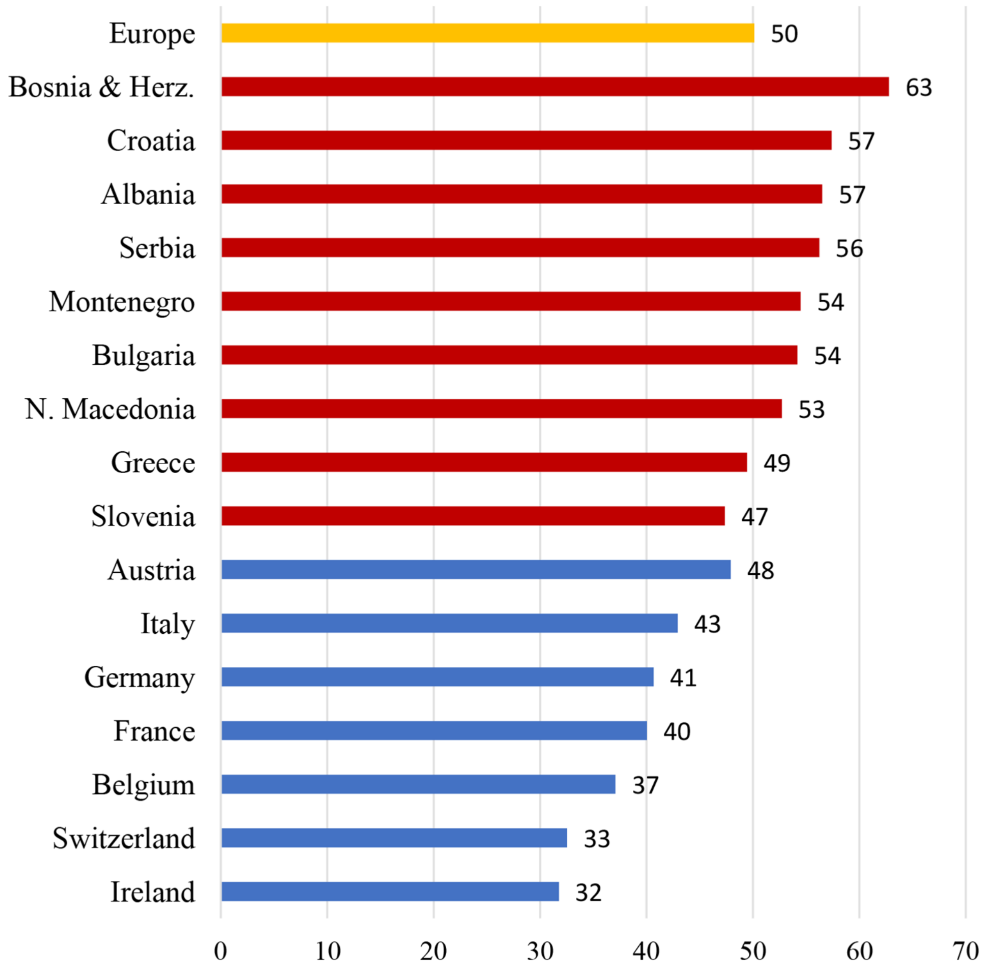

Fig. 2 Mortality-to-incidence 2018 [%] [3]

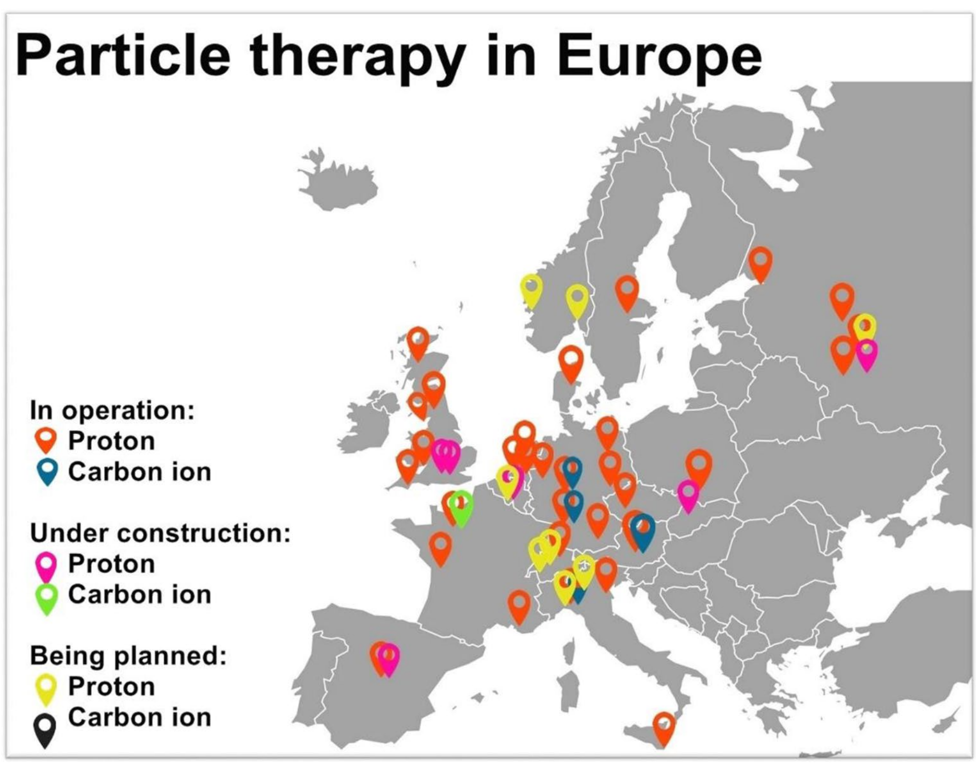

Fig. 3 Particle therapy centers in Europe

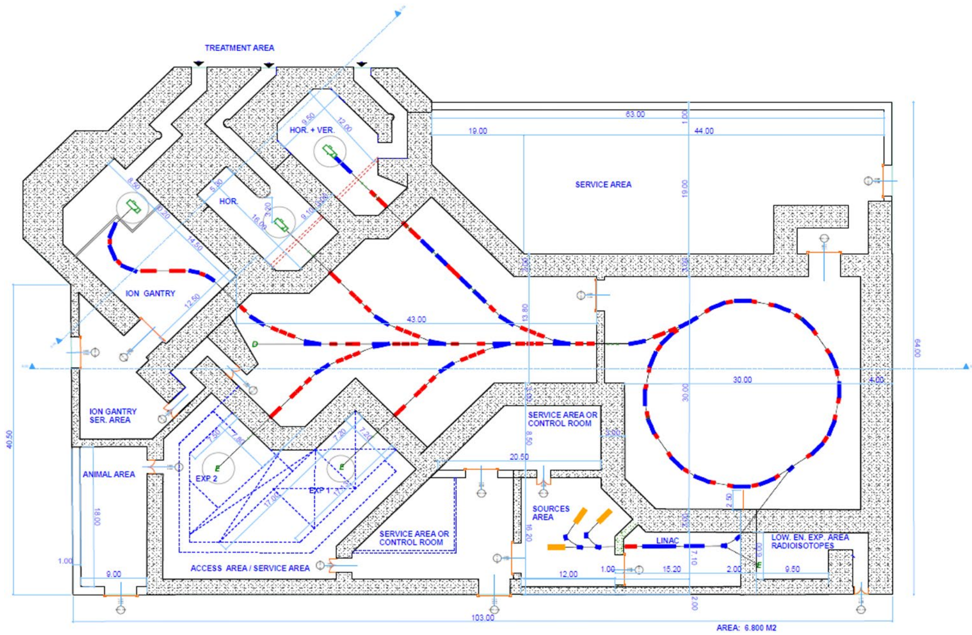

Fig. 4 The SEEIIST accelerator complex

Table 1 Accelerator medical parameters

Beams	p, He_2^+, Li_3^+, Be_4^+, B_5^+, C_6^+ (O_8^+)
Beam range	from 3 g/cm^2 to 27 g/cm^2
Bragg peak modulation steps	0.1 g/cm^2
Adjustment accuracy	$\leq \pm 0.025$ g/cm^2
Average dose rate	2 Gy/min (for a volume of 1000 cm^3)
Dose delivery precision	$\leq \pm 2.5\%$
Beam size	4 to 10 mm FWHM
Beam size step	1 mm
Beam size accuracy	$\leq \pm 0.2$ mm
Beam position step	0.1 mm
Beam position accuracy	$\leq \pm 0.05$ mm
Field size	2×2 cm^2 to 20×20 cm^2 (for H and V fixed beams)

2 The SEEIIST research complex

The core facility of SEEIIST encompasses an accelerator complex providing proton and ion beams for biomedical research and patient treatment. The accelerator complex (see Fig. 4) includes ion sources generating beams of p, He^{2+}, Li^{3+}, Be^{4+}, B^{5+}, C^{6+}, O^{8+}, a high current linear accelerator, and a synchrotron accelerating protons up to energies between 60 and 250 MeV and light ions up to energies in the range of 120–450 MeV/n [4]. The energy can be adjusted in steps of 0.02 MeV (p/pmax = $1.7.10^{-5}$). Accelerated particle beams are transported to three patient treatment rooms and two large experimental halls. Two of the patient treatment rooms are equipped with both horizontal and vertical beams, while the third initially features a horizontal beam, with a later installation of a superconducting gantry capable of directing precisely proton and ion beams toward patients. The beam size can vary between 4 and 10 mm in each direction, with a step change of 1 mm. The beams will be directed with an accuracy of 0.05 mm, with their position adjustable in 0.1 mm steps. The maximum number of particles in a beam spill is expected to reach up to 10^{10} protons or up to 4×10^8 carbon ions. The accelerator will feature a slow beam extraction system, allowing the application of a standard patient irradiation scheme with approximately 60 spills within 2–3 min. A notable feature of this accelerator is the fast beam extraction system, enabling the so-called Flash Therapy, thanks to its high beam intensity and the ability to rapidly extract the particle beam within microseconds. The synchrotron will be equipped with warm magnets, and its design is a significantly improved version of the accelerators installed at CNAO (Pavia, Italy) [5, 6] and MedAustron (Austria) [7, 8], both based on PIMMS (Proton-Ion Medical Machine Study) design developed at CERN [9, 10]. Particle beams intended for biomedical research will be delivered to the experimental halls using two independent parallel transport lines, each distributable to various targets within the experimental hall. This accelerator complex design will facilitate parallel and independent conduction of experimental research and patient treatment. The high intensity of accelerated beams will also allow the linear accelerator to be used for the production and study of various isotopes for diagnostic or cancer treatment. The design of individual elements of the accelerator complex is developed by a large international team as part of the HITRIplus project [11]. This project also includes the design of a superconducting gantry to be installed in the third patient treatment room at a later stage. The main medical parameters of the accelerator complex are provided in Table 1. The necessary infrastructure for patient reception and preparation, scientific research, and training, as well as administrative services, will be built around the accelerator complex. In addition, a state-of-the-art diagnostic imaging complex is planned, which will be used both for cancer diagnosis and for precise monitoring of the treatment process. The Center is designed to allow the later replacement of the synchrotron with a new one based on superconducting technology.

One of the main requirements for such research centers is to ensure the full, efficient, and sustainable utilization of the built infrastructure for a long period of time. To achieve this, a detailed business plan for the project has been prepared. It considers the necessary expenses for infrastructure construction, funding methods, timelines for construction, commissioning and certification, revenues from patient treatment and other services for external clients, maintenance and operation costs of the complex, expenses for scientific research, and further development of the infrastructure.

SEEIIST is an international intergovernmental organization that will fulfil three main functions: biomedical research, development of new methods and protocols for tumour treatment using accelerated protons and ions, and training of specialists and scientists in the field of hadron therapy. Since the primary function of this organization is to conduct research, it is assumed that at least 50% of the accelerator's time during working days will be used for this purpose. The accelerator is expected to provide beams 24 h a day, 7 days a week. The program also includes necessary stops for technical maintenance, support, and system development. When estimating the expected number of treated patients, the following basic parameters were taken into account. Patient treatment will be performed during the day for 5 working hours, utilizing the three rooms designated for this purpose. It is assumed that each patient irradiation will occupy the room for 30 min. The efficiency of room usage is assumed to be 95%. The accelerator is expected to be used for patient irradiation 250 days a year. Under these assumptions, it is anticipated that approximately 6700 patient irradiations (fractions) will be conducted annually, corresponding to a full course of treatment for about 400 patients. This is a highly conservative estimate, as it does not account for the possibilities of parallel patient treatment and scientific research.

3 Additional infrastructure

The main goal of SEEIIST is not only to build a unique scientific infrastructure that will enable scientists from the participating countries to conduct research at the highest level, but also to take leading positions in the field of cancer radiotherapy. In order to provide a more comprehensive approach and increase the interest of local communities in the project's member states, it has been decided, in addition to the central infrastructure, to establish hubs located in countries other than the host country of the central infrastructure (accelerator complex). These hubs will work in close collaboration and synergy with the central complex. The number and profiles of these hubs are not decided yet. At the moment, the creation of the following hubs is under discussion: *Digital Hub*, which will be devoted to the collection of information about patients, characteristics of their diseases, treatment methods and results, with the information intended to be used to establish various new diagnostic and treatment methods, including the development of methods using artificial intelligence; *Accelerator Development Hub*, which will be focused on the development of accelerators and technologies related to their application in medicine; *Animal Research Hub*, which will be dedicated to conducting scientific research using small and large animals; *Medical Imaging Hub*, which will contribute in the development of new technologies for diagnostic imaging; and *Education Hub*, which will provide training of students and specialists in the field of cancer radiotherapy.

The possibility of setting up a solar power plant that would cover the accelerator complex's electricity needs is being discussed. The construction of these hubs will proceed in parallel with that of the central infrastructure, with a significant portion of them starting operations before the accelerator complex is fully operational.

4 Research program

The Center for Hadron Therapy is a unique research center that offers excellent conditions for a wide range of scientific investigations. Research in SEEIIST can be divided into two main categories: clinical and non-clinical studies.

The clinical studies will be focused on the development of new techniques and methods for diagnosis and treatment of tumours with proton and ion beams, as well as on the improvement and further development of existing therapeutic schemes and methods based on the therapeutic results achieved. One of the main directions will be the development of new treatment protocols using Flash Therapy [12–15] and methods for treatment of moving organs.

The non-clinical studies will include: research in the fields of medical radiation physics and radiation biology in the adaptive or transitional phase (translational research); development and testing of detectors of ionizing radiation for monitoring and real-time control of the therapeutic process, measurement and control of patient dose, and medical imaging based on the measurement of the induced radioactivity in the patient; development of medical devices for the needs of newly developed or improved methods and techniques of proton and ion therapy; animal therapy and related research (including for large animals); low-energy nuclear physics; development of new materials and investigation of their properties; and production of standard and new isotopes for medical applications.

Research at the Centre will be carried out on a project basis by scientific teams (collaborations) that bring together researchers from different scientific organizations and medical institutions from the region, the rest of Europe, and other countries.

Collaborations are formed for the realization of research projects. The Centre provides collaborations with accelerator time to implement their investigations. Collaborations build their budgets with funds from team-members organisations, as well as funding from national and international sources. Financial support for the Centre staff members participating in these projects is provided by the Centre's research fund. Collaborations form a common fund, which covers the project's common spendings, along with the research-related expenses of the Centre (accelerator time, infrastructure, communications, and expert participation). An important task of the Centre is building an international network of research institutions and hospitals driven by their common research interests in the field of hadron therapy.

A key aspect of the SEEIIST mission is education and training of professionals in the fields of medical physics, imaging diagnostics, nuclear medicine, radiotherapy, radiobiology, radiation hygiene, and radio-oncology. The Centre will be involved in the programs for lifelong learning for specialists of universities, research institutions, and medical institutions in the member states and professionals from other fields who wish to shift to medical physics and radiotherapy or to refresh their knowledge in these areas.

5 Time schedule and status of the project

The project is divided into three main phases: a preparatory, a construction, and a running phase. The preparatory phase includes the development of the conceptual design (Conceptual Design Report – CDR), detailed technical design of the entire infrastructure, design of a new accelerator comprising three main elements (ion sources, linear accelerator, and synchrotron) and the design of the transport lines and the superconducting gantry (Technical Design Report – TDR). It also includes the preparation of the legal framework for the institute's establishment and a detailed business plan.

Currently, the project is in the preparatory phase, with the CDR practically completed. The design of various elements of the accelerator complex is under way within the HITRIplus project. The legal framework for the institute's registration and its regulations has been defined. The business plan has been developed, but due to economic, financial, and political circumstances during the last two years it should be updated next year.

The construction phase is expected to last between five and six years. It encompasses all activities related to the construction, commissioning of the equipment and its certification for patient treatment. The Center is expected to reach its full capacity for conducting scientific research and patient treatment within three years of commencing its operations.

The Running phase of the project will extend for at least 30 years, envisioning further development of the infrastructure during this period.

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Declarations

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Consent to participate Not applicable.

Consent for publication Not applicable.

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