Design of the Hellenic Public Cord Blood Bank Network

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Abstract

Umbilical Cord Blood (UCB) is an alternative source of Hematopoietic Stem Cells (HSCs) used for the treatment of a wide range of diseases through transplantation. Its effectiveness together with the histocompatibility restrictions imposed by the Human Leukocyte Antigens (HLA) inheritance led to a continuous increase of the demand for UCB units. During the last fifteen years, UCB banks and bank networks were established worldwide, while the development of such a network in Greece is in its infancy and still there are several issues to be regulated. Monte Carlo simulation is employed and a simulation sampling methodology is developed to determine the relationship between the UCB units' inventory level (bank size) and the system's service level (probability that a patient finds a matching transplant/donation). Additionally, a cost-analysis regarding the UCB Bank Network development is carried out. The main result is the estimation of the required amount of UCB units that should be cryopreserved in order to ensure the desired service level. Moreover, the key design parameters are estimated, including banks location, personnel planning and the associated costs. The developed methodology provides the decision support tool for the National Healthcare System (NHS) to decide on developing or not an UCB Bank Network. Finally, taking into account the Greek NHS economic capacities, the overall cost of the project seems reasonable, while the financial contribution of the Greek government and/or sponsors is of critical importance.

Keywords: Umbilical cord blood bank, Hematopoietic stem cells transplantation, National Healthcare System management, Simulation, Cost-analysis

JEL Classification: I18

Introduction

Umbilical Cord Blood (UCB) has emerged as a widely accepted source of Hematopoietic Stem Cells (HSCs) for the treatment of a wide range of malignant and non-malignant diseases through allogeneic transplantation (Tse and Laughlin, 2005). In an allogeneic transplantation, HSCs are harvested from an individual (donor) and then they are infused into a genetically different individual (recipient) that may or may not be related to the donor, in contrast to autologous transplantation in which the person's own cells are collected, stored and then reinfused.

The prevalent practice in the field of UCB inventory management (Ballen et al., 2001; Gluckman and Rocha, 2009) (Haematopoietic Stem Cells – HSC transplantations), over the last fifteen years, employs the establishment and operation of UCB banks (Fraser et al., 1998) or bank networks at a national level (physical storage), while global donor registries, e.g. NetCord, World Marrow Donors Association (WMDA), Bone Marrow Donors Worldwide (BMDW), etc. ensure their coordination (information exchange) and their effectiveness at a global level (Gluckman, 1998; Garcia and Torrabadella, 2006; Rubinstein, 2006;). However, although in June 2009 there were more than 400,000 preserved UCB units worldwide (www.bmdw.org), the probability that a transplant candidate finds a matching allogeneic graft (Grewal, 2003) is low in several countries due to the complexity of human histocompatibility (Human Leukocyte Antigens system - HLA) and the rules regulating the inheritance of the HLA–antigens. The ease of finding an HLA-compatible donor is also a function of the ethnical and racial diversity of the donors' pool, as it is more probable to find a compatible donor among genetically similar populations (Barker, 2002). Therefore, the effective global UCB inventory for low population countries that have no (or just a few) relevant 'compatible' ethnic groups, such as Greece, is significantly lower.

The Hellenic National Transplant Organization (NTO) estimates that 30% of the Greek HSC transplant candidates are unable to find an HLA–compatible donor. Additionally, the Hellenic Society of Haematology (HSH) estimates that 50 to 60 Greek patients annually are unable to find a matching unit due to the lack of an appropriate inventory.

Furthermore, although the relevant European Union Directive on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells (Directive 2004/23/EC) has been enacted since April, 2004, Greece harmonized its legislation with this Directive only in March, 2008 (Decree-Law 26/2008), while there are still several issues to be regulated.

Considering the afore-mentioned issues and the fact that the cost of every imported UCB unit for the National Healthcare System (NHS) is about €15,000 – €20,000 (HSH estimation), it has become evident that Greece has to develop its own inventory of UCB units to satisfy the transplantation needs, with the supplementary benefit from the global UCB inventory. We believe that our methodological framework can be applicable for other countries with no national UCB bank and relatively isolated population.

In this paper, we aimed at determining the national UCB bank capacity, the key parameter for designing a UCB bank network (Prat, 1998; Donaldson et al., 2000; Rendine et al., 2000), including facilities, equipment, personnel, along with its associated costs (Sirchia et al., 1999).

Methods

System Description

A cord blood bank is a center whose central mission is to maintain a supply of cord blood for therapeutic use in transplantation.

Firstly, the mother registers with a bank prior to giving birth (informed consent). When the child is born at a maternity hospital, the blood that remains in the placenta and in the attached umbilical cord after childbirth (umbilical cord blood) is collected and transported to an UCB bank to obtain volume and cell count. Moreover, the collected UCB is submitted to several clinical tests (microbiological & virological screening, etc.). If the unit conforms to the standards established by the bank and the relevant legislation and medical protocols, a sample of the UCB is sent for HLA typing. The HLA typing process determines the HLA identity of the donated UCB unit, which plays a key-role in performing HSCs transplantations (histocompatibility). Furthermore, obtaining the HLA type is the most expensive part of the entire process, hence this is generally not done until the unit meets the bank's requirements in all other ways. Eventually, the UCB unit is stored in a cryogenic freezer (physical storage), while the associated data are stored in an appropriate data base (information storage). The HSCs of an UCB unit maintain their viability for a time period up to 15 or 20 years (typical lifetime of an UCB unit) (Berz et al., 2007). During this time period, the unit is available and accessible to anyone in need for transplantation (public bank) so that a patient has the opportunity to search and find an HLA-compatible donation.

The likelihood of finding an HLA-matching unit for an individual (transplant candidate) is limited due to the complexity of human histocombatibility. HLA are proteins that are present on the surface of our bodies' cells. Our immune system recognizes our own cells as 'self', as opposed to 'foreign', based on the HLA proteins displayed on the surface of our cells. Consequently, HLA-typing plays a key role in detecting a donor and a recipient whose cells most closely match. HLA matching is of critical importance for the performance of HSCs transplantations (where the donor's immune system in effect replaces the recipient's), since it helps prevent rejection as well as graft-versus-host disease (GVHD). The lack of an appropriate matching level may lead this new immune system to recognize the recipient's body as 'foreign' and attack various organs and tissues.

An individual's HLA type is inherited from his or her parents. The HLA type is determined by a cluster of genes on chromosome 6. An individual inherits one chromosome 6 from the mother and one from the father, thus each individual carries two copies of each of the genes in the HLA cluster. A haplotype is a set of genes that are linked closely enough to be inherited as a single set, therefore, an individual obtain one haplotype from each of his or her parents (figure 1). These haplotypes constitute an individual's genotype (pair of haplotypes).

Three genes in this cluster have been detected thus far that seem to have a crucial role in transplantation: HLA-A, HLA-B, and HLA-DR. Moreover, the existence of many different versions (alleles) of each HLA gene increases the complexity of human histocompatibility. When doctors speak of a 6-out-of-6 match, they are referring to two people matched for the same alleles at each of their two HLA-A, HLA-B, and HLA-DR genes.

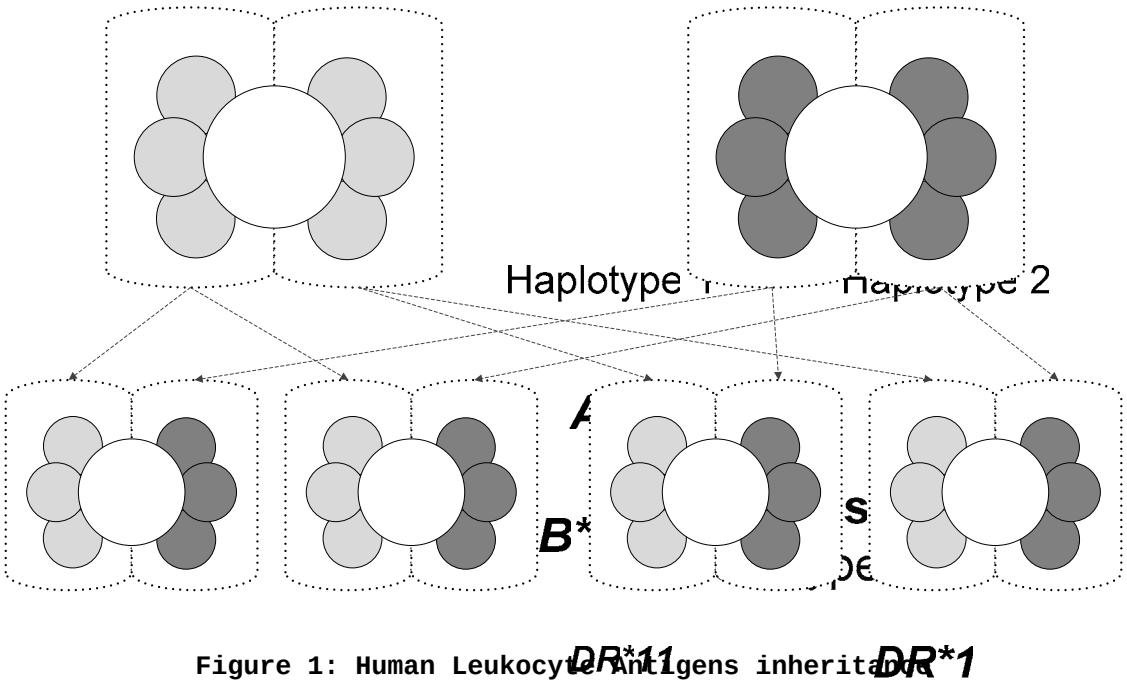

Figure 1: Human Leukocyte Antigens inheritance

Methodological Framework

Generally, the determination of a national UCB inventory level (bank size) should take into account clinical, policy, and economic parameters. Three major competitive criteria are referred in the literature (Committee on Establishing a National Cord Blood Stem Cell Bank Program, 2005) to determine this value, namely:

- the maximization of the probability that a patient in need of UCB transplantation finds a matching unit,
- the provision of equivalent and unimpeded access to the units for racial and ethnical minorities, and
- the minimization of the investment and operating costs that arise.

In this research work, we have initially focused on the first of the above criteria. The target-value for the likelihood of finding a matching unit is set to 95%, based on the desired standards proposed by Hellenic Society of Haematology.

Specifically, histocompatibility data for the Greek population were collected from all available resources. An appropriate statistical analysis followed, to capture statistical properties and develop the random genotype generator used in the simulation experiments. Then, the simulation model, after extensive validation mainly through consultation with the system's major stakeholders, was used to provide statistically sound results for a number of "what-if" analyses. The final results are obtained by executing several simulation experiments.

Furthermore, a cost analysis was also carried out in order to check the feasibility of the solution obtained through the first criterion, while benchmarking analysis and break-even point techniques were employed to determine the fundamental design parameters regarding the entire network's development project.

Statistical Analysis

The available histocompatibility data includes haplotypes and genotypes of individuals of Greek nationality obtained from two different sources.

- The first set (Dataset A) consists of the haplotypes and their frequencies (HLA-A, HLA-B, HLA-DR, all in low resolution) of 7,710 bone marrow and UCB donors of Greek nationality and was obtained through the BMDW registry. In these data, 2,397 different haplotypes appear with a range of frequencies from 1 to 485 out of 15,420.
- The second dataset (Dataset B) includes the genotypes of 410 donors of Greek nationality (source: Greek National Histocompatibility Centre) with antigens HLA-A and HLA-B in low resolution, and antigen HLA-DR in high resolution – allele level.

Both dataset were used to develop a random genotype generator producing genotypes of Greeks with HLA-A, HLA-B in low and HLA-DR in high resolution. Specifically, the generator randomly combines haplotypes in low resolution, according to their frequencies in Dataset A. The differentiation of these haplotypes at the allele level is done at a second stage based on allele frequencies of the HLA-DRB1 antigens included in Dataset B. The result of this process is a pool of potential genotypes, representative of the genetic histocompatibility information of the Greek population.

Simulation Model

Monte Carlo simulation (simulation sampling) (Hillier and Lieberman, 2005) was employed in order to estimate the required capacity of the Greek UCB bank network. Figure 2 exhibits the simulation procedure and the major steps of the developed algorithm. Firstly, a virtual bank is created by randomly choosing N genotypes (inventory level of the cryopreserved UCB units or bank size), which are considered as the donors of the system. Then, other K genotypes, which stand for the transplant candidates (patients), are formed using the generator. We recorded the percentage of K patients that find an appropriate match in the bank by comparing each of the K patient-genotypes to the N donor-genotypes (UCB units) of the bank. This process is similar to the real-life practice followed by a patient searching for a matching unit in the bank.

The total procedure (bank creation, generation of transplant candidates, histocompatibility testing, results on matching) is repeated M times (thus M replications) in order to create a sufficient sample size that reduces statistical error. Parameter K is set to 3,600 that is the number of the patients that are estimated to become in need for an HLA-compatible donor during the typical life of the bank (20 years), since the annual average number of UCB units offered is estimated to be about 180. Having carried out an appropriate number of trials, parameter M (the number of simulation replications), was selected equal to 1,000 in order to ensure narrow confidence interval thus allowing for the drawing of safe conclusions on the necessary UCB bank network capacity.

The decision variable is the inventory level N. Therefore, a wide range of N parameter values were examined to extract the probability

that a Greek patient finds an HLA-compatible UCB donor over a 20-year time horizon. The values assigned to this parameter had a range from 1,000 to 20,000 with a step increase of 500 units.

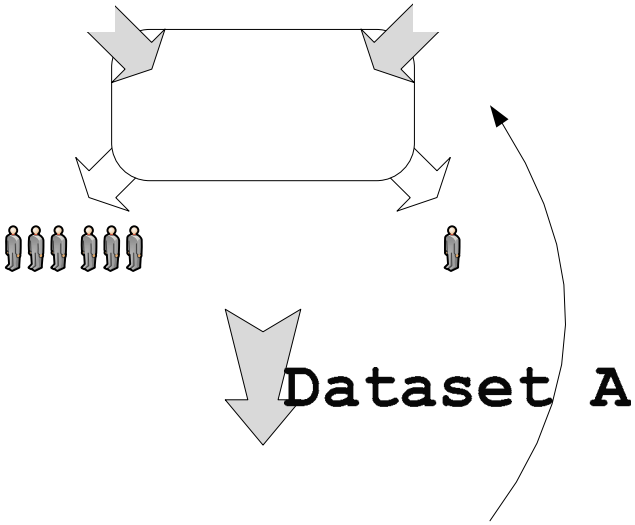

Figure 2: Simulation Process

Results

The main result of our research work is the determination of the relationship between various inventory levels and the service level of the system. The inventory level is defined as the quantity of UCB units (bank size) that the bank network should cryopreserve in order to efficiently supply the needs for cord blood transplants. The service level is defined as the probability that a transplant candidate finds a matching unit or, equivalently, the proportion of the Greek patients that find a matching unit. Additionally, the applied practices worldwide, regarding the HSCs transplantations, indicate the 4-out-of-6 HLA-match as the minimum acceptable one in order a transplantation to be carried out (Gluckman and Rocha, 2006; www.marrow.org).

The core result includes the central point estimation and the 95% confidence interval of the estimated service level versus the relevant bank size for the three histocompatibility levels of interest: 4, 5, and 6-out-of-6 HLA-match, respectively. These three curves are illustrated in figure 3. The simulation results show that 10,000 of cryopreserved UCB units (inventory level) ensure a 96.3±1.2% probability that a Greek transplant candidate finds an appropriate unit (4-out-of-6 HLA-matching). Furthermore, the likelihood for finding a 6-out-of-6 HLA-matching unit is 6.5%, and the one for finding a 5-out-of-6 HLA-matching unit is 51.8%. The HLA-match probability curves imply that there is a significant difficulty (lowest probability) in obtaining the highest level of histocompatibility (6-out-of-6 HLA-match) for a given bank size. However, we observe an increase of the service level with the bank size, although the increase rate of the service level decreases for higher inventory levels.

In the aspect of UCB network design, presuming an average discard rate of 60% for the collected units (donations) (Lasky et al., 2002), which means that 60% of the collected units are discarded, failing to conform to the applied medical standards (low CD34+ concentration, virological and microbiological testing failures, etc.), the network should collect approximately 25,000 donations in order to build up the necessary nominal inventory of 10,000 units. Furthermore, to maintain this inventory level for the Bank's long-term operation, we need to replace the UCB units reaching their end of life (500 units per year since the life of UCB units is 20 years) and the UCB units used for transplantation (180 units per year). Thus, taking into account the discard rate of 60%, the annual collection rate for the steady state operation is about 1,700 UCB units.

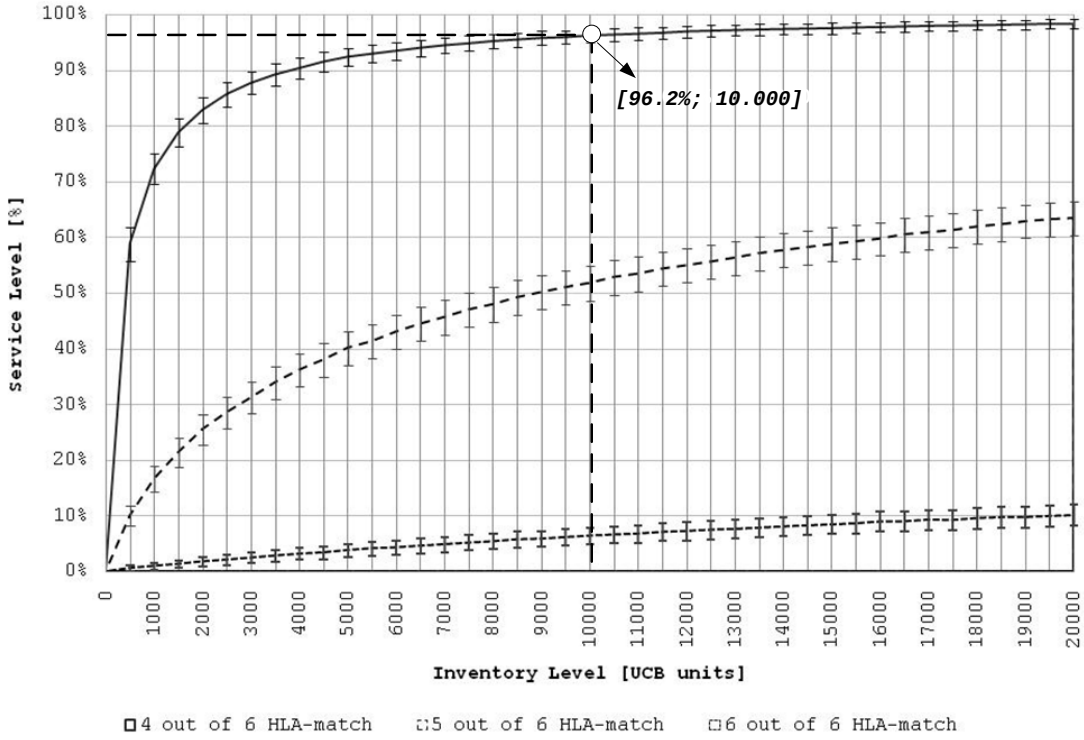

Figure 3: HLA-match probability for various inventory levels

The entire project's development plan is spread over three discrete time-periods (phases):

- The establishment/development period (phase I), with an estimated duration of approximately 1 year.
- The inventory build-up period (phase II), with an estimated duration of 8 years based on realistic average collection rates of UCB units (3,125 donations annually).
- The regular (steady-state) operation period (phase III), where the inventory remains constant (replenishment of units transferred for transplantations or units of low viability due to long term storage).

Finally, a cost-analysis was conducted for each one of the three phases of the Bank development. The relevant data and information regarding the operational procedures along with the associated costs

were obtained through international practice (e.g. The Cord Blood Transplantation Study COBLT), market research for medical equipment and materials, literature, and the experience of one of the authors. Specifically:

1 The initial investment cost is estimated to be €1.1M, allowing for buildings, equipment, accreditation, personnel training, information dissemination, etc.
2 The inventory build-up cost is the core cost element estimated to be €12.4M, including activities such as the units' collection and transportation, virological and microbiological screening, HLA-typing etc.
3 The annual steady-state operational cost is about €1.2M.

The personnel planning criteria included: (i) the requirements and standards that were set by the relevant European (Directive 2004/23/EC) and Greek legislation (Decree-Law 25/2008), (ii) the international practice (Committee on Establishing a National Cord Blood Stem Cell Bank Program, 2005), regarding the personnel requirements in order to efficiently operate an UCB Bank, and (iii) the relevant literature (Prat et al. 1998; Sirchia et al. 1999; Donaldson et al., 2000). Based on the above information, each bank should employ 11 professionals (2 administrative officers/medical doctors, 5 technicians, 3 employees, and 1 trainer) during the network's inventory-building period (when the amount of the collected units is significantly higher and thus the needs for processing them are increased), and 7 professionals (2 administrative officers/medical doctors, 3 technicians, and 2 employees) during its regular operating period.

Considering the prospect of ensuring the economic sustainability (balancing the annual operational costs) of the provided public healthcare service, with respect to the non-profit character of the overall project, a fee of about €7,000 should be received for each one of the 180 units that would be transferred annually for transplantation (break-even point). The development plan along with the major design parameters estimations are summarized in Table 1.

Table 1: Development plan

Period	**Establishment/ Development**	**Inventory building**	**Regular operation**
Duration [years]	1	8	>8
Activities	buildings,equipment, accreditation, personnel training, information dissemination,etc.	collection, transportation, virological & microbiological screening, HLA-typing, etc.	
Personnel [individuals]	11	7	7
Average Collection Rate [units/year]	-	3,125	1,700
Total Cost [M€]	1.1	12.4	1.2 annually

Conclusions and Discussion

This paper deals with the design of the Greek Public UCB Bank Network. Even though the need for the development of a National UCB Program has been recognized by all the major system's stakeholders (relevant

authorities and organizations) such as the National Transplant Organization, the Hellenic Society of Haematology, the Greek Ministry of Health and Social Solidarity, etc., the development of such a network is in its infancy, while there are still several issues to be regulated. The main goal of this research work is to contribute to the improvement of the national healthcare services by determining the required inventory of a UCB bank network.

The pivotal decision regarding the design of a UCB Bank Network is the determination of the required bank size (inventory level) for a desirable service level, under the considerable limitations that are raised by the complexity of human histocompatibility. In this paper, Monte Carlo simulation is employed and a simulation model is developed to emulate the bank's basic operational procedures. The results reveal that a 10,000 inventory level is able to assure a 96% probability that a Greek transplant candidate finds a 4-out-of-6 HLA-matching unit.

The simulation results are in agreement to those presented by Howard et al. (2008) and Querol et al. (2009) for the U.S.A. and the U.K., respectively. Under the assumption of a constant proportion among the populations of the three countries (U.S.A.:300M – U.K.:60M – Greece:11M) and the UCB inventory levels, the results are quite similar, especially for the 4-out-of-6 HLA-match level.

In the future, as more genotype data will become available, the capacity estimation might need to be updated. The evaluation of the complementary data impact on the outcomes will lead to more detailed and reliable results. Additionally, an extension of the model could be developed in order to co-evaluate racial and ethnical diversity data. Given that the existence of minorities is a characteristic of South Eastern Europe, a new UCB inventory management policy could be applied, concerning the overall region.

Another important issue is the potential increase of future demand for units with no or one HLA mismatch. The recruitment of new donors and possibly the increased representation of minorities will lead to a broader and larger pool of cryopreserved UCB units, thus, the 5/6 HLA-match likelihood should be considered more carefully (Ballen, 2005; Barker, 2007).

The network's configuration ensures an adequate communication among the collection centers, transplantation centers and banks. Each bank covers approximately 5.5M citizens, while the European and World coverage indices, regarding countries that have at least one UCB Bank, are 1 bank per 7.8M and 1 bank per 20M citizens, respectively.

The personnel profile provides a high level of performance, complying with the standards settled by the European Union Directive (Directive 2004/23/EC) and the relevant Greek legislation (Decree-Law 25/2008).

The financial contribution of the Greek government and/or sponsors is of critical importance. Moreover, the UCB banks network project is assumed to be established within existing health services, utilizing expertise already in place. That means that few critical operational procedures will be carried out by the NHS's labs and services.

The cost for adding one UCB unit to the network, estimated at €1,240, is in agreement with these referred in the literature. Moreover, the UCB banks network will be a non-profit organization, since the fee

charged for every unit transferred for transplantation – balancing the operating expenditures (€1.2M per year) – will be paid by the National Social Insurance Organizations. Furthermore, this fee is significantly lower than the one currently paid by the National Healthcare System to foreign UCB banks (€15,000 – €20,000).

Finally, taking into account the Greek NHS financial capacities, the network's development seems feasible (total cost: €13.5M).

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