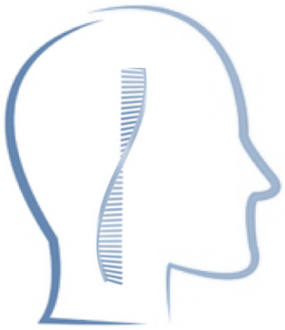
I. Cover Page

Title of proposal

Head and Neck Cancer microRNA Diagnostic Kit

Acronym of proposal

HANEMIR



List of participants

Participant number	Organisation name	Country
(Coordinator)	Genechron S.r.l.	Italy
(Clinical partner/third party)	Istituto Regina Elena (IRE)	Italy

II. Executive Summary

Head and Neck Cancer, despite being the 6th global incidence of cancer, has no cost-effective diagnosis and patient management product, that can address the immediate and growing need of enabling doctors and healing patients.

Existing solutions are based upon the patient being referred by their family doctor or oncological specialists to the oncology department of hospitals where ineffective and expensive measurements based on imaging (MRI and PET scan platforms) and direct patient examination, including tissue sampling and biological tests are performed.

The measurements are inconclusive, especially after treatment when reappearance of disease occurs in 50% of patients during 10 years, which means that the doctors are continually behind the curve, and the patients suffer.

In Europe there are over 140,000 new cases of Head and Neck cancer occurring every year (costing over €43 Bn to monitor), while by 2030 it is estimated there will be well over 1,000,000 new cases per year globally. This is not exclusively a developed country issue, with India and Central/South America being amongst the most adversely effected, and without the same healthcare infrastructure, have significantly higher mortality rates.

This volume of people cannot pass through the existing healthcare management procedure, nor can they be treated when the disease has recurred and is more aggressive than before. It is too expensive, ineffective and results in unnecessary patient suffering and healthcare over-burden.

As a result of the long standing collaboration between Genechron S.rl. and the Istituto Regina Elena, a dedicated oncology hospital (both located in Rome), we have identified a low-cost and effective solution that can be integrated easily into the existing healthcare infrastructure and marketplace that will reduce the cost burden by at least 40%, while simultaneously reducing morbidity and mortality.

We have already demonstrated that the innovation is applicable and functional. In this proposal, **HANEMIR**, we will convert this advanced stage innovation into a low-cost, high revenue-generating product, which has the additional characteristic of being able to be repositioned for a larger number of applications.

III. Content

1. Excellence

Challenge and solution

Each year, the health systems of the European Union spend at least [redacted] monitoring and managing patients with Head and Neck Squamous Cell Carcinoma (HNSCC), also known as head and neck cancer.

- HSNCC is the **6th most frequent** cause of cancer: Europe alone has [redacted] new patients per year, estimated to increase to [redacted] per year by 2020.
- Because of the high frequency of recurrence [redacted], post initial dia_nosis and during continued treatment, all patients have to be monitored monthly [redacted] years.
- Monitoring is performed monthly by expert physical and endoscopic exam [redacted] and using a medical scanner located in a hospital [redacted] every quarter, that costs on average [redacted] (equalling in total € [redacted])
- Costs for the scan include i) Radiopharmaceutical fees ii) Technical fees and iii) professional fees, excluding capital and maintenance costs

As patients have a 10 year survival of 50%, the steady state costs for health systems are 1[redacted] Bn

The major limitation is that PET or MRI scan specificity is very low for HNSCC, mainly due to post treatment effects on tissue structure, which means **that many recurrences are not identified** until an advanced stage has been reached (typically between 9 and 12 months after treatment stop) thereby costing the health system more, but all patients still have to be screened.

We have generated **a disruptive innovation** that leverages cutting edge clinical and technical insight that will:

- Decrease monitoring and health care costs by [redacted]%, which should result in a favourable health economic analysis by reimbursement bodies (the customer)
- Increase survival rates of patients (the beneficiary)

The innovation combines:

- Our existing expertise as a microRNA (miRNA) based diagnostic company,
- The clinical evidence obtained from our local clinical partner on molecular markers,
- Our latest innovation of **being able to detect these specific molecular markers in the saliva and serum of the patient**.

The final product will be a kit, that after validation, and CE marking will be able to be submitted to national reimbursement entities for approval to be sold in their markets, specifically within primary and care outpatient clinics as well as clinical diagnostic/analysis laboratories.

The kit provides the following added value:

- Patients can be more frequently monitored (at least twice a month)
- Patients can be monitored at a local doctors office or clinical analytical laboratory using existing infrastructure and staff, instead of at a hospital
- [redacted]
- [redacted]

[redacted]

Tangible benefits

Talking to oncology specialists, the test will reduce need for hospital visits by half, and medical scan imaging usage and costs by half, having the following impacts:

- [redacted]
- [redacted]

[redacted]

- Liberating the PET scan to be used for other patients with other diseases.
- Longer term benefits include a reduction in hospital and patient treatment costs

Approach

Genechron's competitive advantage in nucleic acid based molecular diagnostics is based upon its long term strategy of working very closely with its clinical collaborators and advisors who specialise in the epidemiology and aetiology of the disease to be diagnosed, who in the market are termed '***early adopters***'.

This has been applied to its three major focuses of cancer, toxicity and degenerative neuromuscular diseases. This is a critical, albeit long-term strategy that is now starting to show dividends.

As indicated in figure A and B, in the field of cancer we work hand in hand with the Istituto Regina Elena (IRE) to identify solutions that they think are critical for patient management, and then look at ways to develop and validate them throughout the total healthcare marketplace (primary, secondary and tertiary care, outsourced speciality centres).

By starting with a key stakeholders and early adopters needs, a stakeholder that in the field of cancer, is world renowned for its work in cancer aetiology, epidemiology, and experimental cancer therapies as well as being the coordination and direction centre for the Cancer Registry for the whole of Central and South America, means we only develop products that already has a clinical buy-in.

Figure A

Expression of miRNA from tissue of HNSCC patients (patient samples in blue; healthy patient baseline levels = red line)

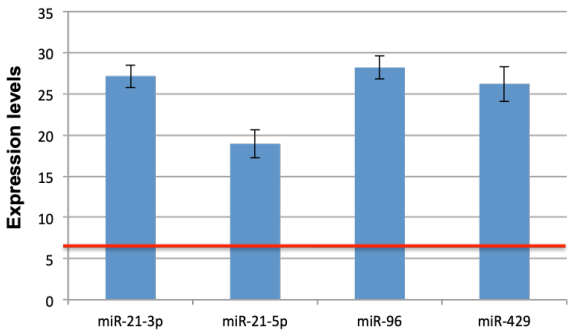
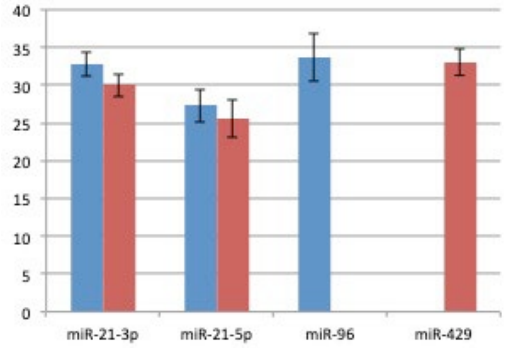


Figure B

Expression of miRNAs from liquid biopsy HNSCC patients (blue = serum, red = saliva)



**The published clinical observations of our local hospital partner has also been independently confirmed in additional studies (articles in bold represent Genechron's local partner)*

Ganci F, et al. "Expression of TP53 mutation-associated microRNAs predicts clinical outcome in head and neck squamous cell carcinoma patients". Ann Oncol. 2013 Dec;24(12):3082-8.

Ganci F, et al. "Altered peritumoral microRNA expression predicts head and neck cancer patients with a high risk of recurrence". Mod Pathol. 2017 Oct;30(10):1387-1401.)

Hsu CM, Lin PM, Wang YM, Chen ZJ, Lin SF, Yang MY. Circulating miRNA is a novel marker for head and neck squamous cell carcinoma. Tumour Biol. 2012 Dec;33(6):1933-42. doi: 10.1007/s13277-012-0454-8. Epub 2012 Jul 19.

Bo Hou, Hajime Ishinaga, Kaoru Midorikawa, Said Ahmad Shah, Satoshi Nakamura, Yusuke Hiraku, Shinji Oikawa, Mariko Murata & Kazuhiko Takeuchi (2015) Circulating microRNAs as novel prognosis biomarkers for head and neck squamous cell carcinoma, Cancer Biology & Therapy, 16:7, 1042-1046

The demand for this product has been defined by the customer, one of Europe's leading cancer hospitals and institutes, that has become frustrated with absence of affordable and helpful solutions for both themselves as professionals and the final beneficiary, the patient.

In the sector of nucleic acid based molecular diagnostics this is essential: the market history of nucleic acid diagnostics reveals that the historical approach was to identify a technology, such as an experimental marker, invest in technological development, and then try to obtain clinical validation and market penetrance. Additionally, nucleic acid based diagnostics have been pitched as a panacea for all diagnosis and a replacement for the existing diagnostic approaches.

These historical and competitor strategies are flawed for several reasons:

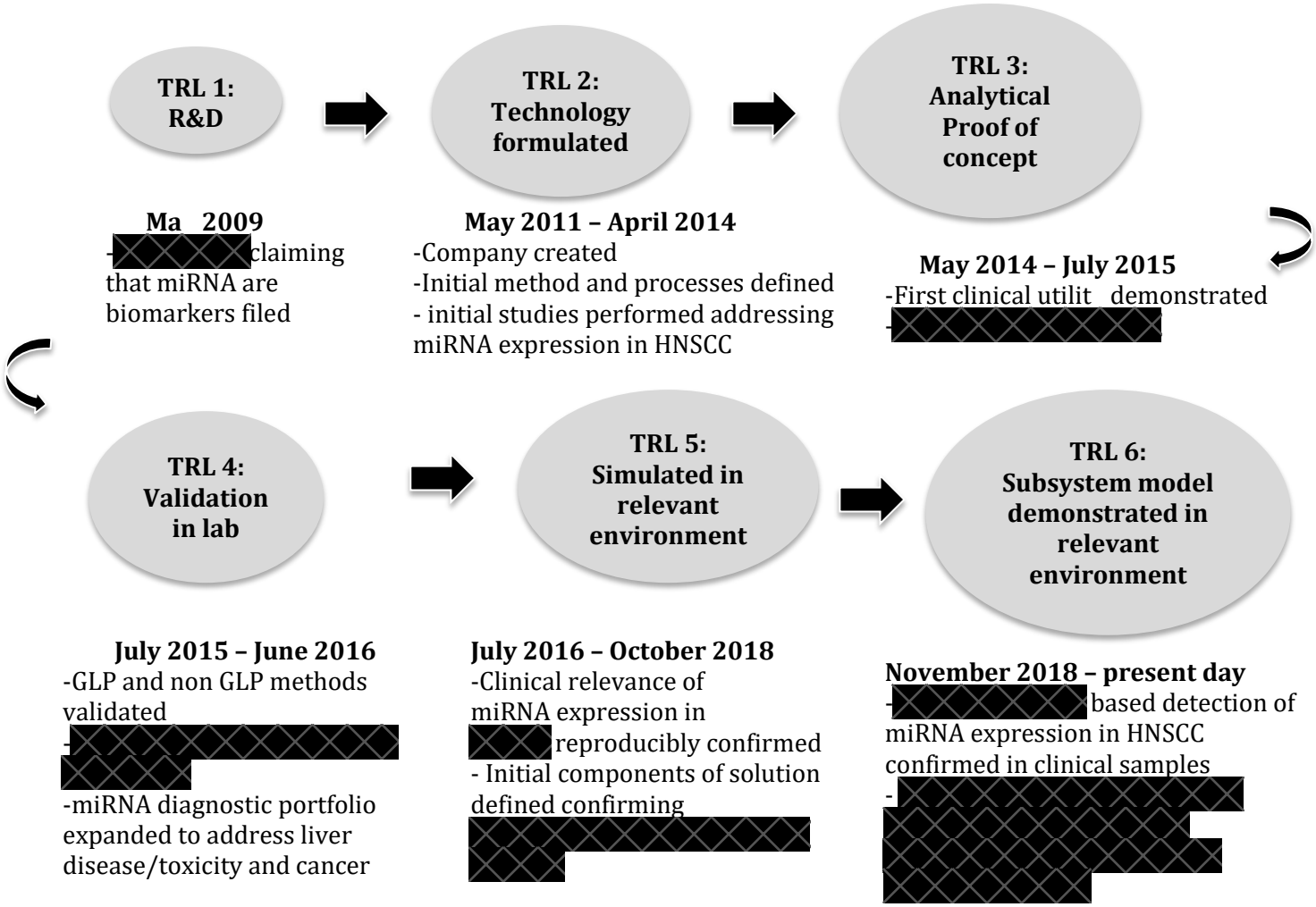
- Clinicians do not believe anyone else's data, unless it is another clinicians.
- Clinical evidence looking at complex chronic diseases reveal that nucleic acid profiles vary greatly, often requiring up to 10 different nucleic acids to be measured routinely.
- The sources of the samples to be measured are invasive so patient compliance is low
- The combined costs of these events with additional no clear clinical conclusion eliminates any cost: benefit and therefore reimbursement possibility

The outcome is that a market analysis will reveal that most nucleic acid measurement kits are sold as 'experimental use only' or to be used in 'regulated analytical laboratories as a service'.

However there have been recent market, clinical and technological changes that need to be and can be exploited that are changing the market:

- Nucleic acids in selected disease indications (oncology, acute diseases, chronic disease of large tissues) are being clinically confirmed as valid markers, and can be linked to 'personalising a therapy selection'.
- Nucleic acids are increasingly being seen as acute indicators of the early onset of chronic disease i.e. when the disease starts, indicating the patients to be prioritised.
- Nucleic acid based diagnoses are focusing more on the recurrence of a disease, rather than the emergence of disease: this is being witnessed in cardiology (for assessing the risk of a second heart attack) and oncology (using mitochondrial DNA measurements to assess if a patient treated for prostate cancer is about to relapse: presently being validated in a collaboration between Genechron and the Istituto Regina Elena).
- In the context of disease recurrence the number of nucleic acids that give an indication of the event is significantly lower, while their expression levels are significantly higher.
- Nucleic acids can now be detected in bodily fluids that are naturally excreted, and do not require blood extraction unless additional confirmatory information is needed.

Technology Readiness Level (TRL) and Genechron milestones to date



We will move the innovation through TRLs 7 to 9 and MRLs 6-9 while also performing the planning phases of product launch within 6 months of the end of the project

Actions for TRL 7: System prototype demonstration in an operational environment

The final iterations of the key components of the kit will be confirmed and refined using serum and saliva samples from at least [redacted] totally anonymised and randomly blinded patients, whose tissue miRNA levels have already been identified. This will be performed in collaboration with [redacted]. This key component information will be routinely communicated to our OEM provider to generate corresponding quality components that adhere to ISO and IVDD standards to achieving [redacted] and the start the long-term process of scale up.

Actions for TRL 8: Actual system completed and qualified through test and demonstration

Following confirmation of the final product component iteration, a final prototype kit will be generated (achieving MRL8). The [redacted] samples will tested by both ourselves and the IRE Molecular diagnostic laboratory using the prototype kits. Simultaneously we will start the IVDD registration and CE marking procedure.

Actions for TRL 9: Actual system proven through operational application

Data analysis, and if required by the Istituto Regina Elena, continued analysis of samples from patients with HNSCC will be performed to confirm the kits performance. Simultaneously our OEM provider will be informed of the components of the final kit, and informed to initiate procedure planning for scale up [redacted]. We will liaise with notified body and finalise CE-IVDD marking.

Simultaneously we will prepare HTA (Health Technology Assessment) dossiers and work with the Regional Healthcare agencies in Italy, Germany, Spain and France, who determine which products to reimburse, to start to obtain approval for sales. Approval for reimbursement in Italy by the end of the project will represent achieving TRL9.

Finalising [redacted] will mean we will be ready for product launch, and would anticipate actual product launch in the Italian market within 6 months and the 3 additional EU target markets within 12 months of the end of the project.

Commercialisation

Targeted stakeholder marketing, specific market reimbursement approval and establishment of geography dependent distribution channels will be developed. Marketin will initially focus on communicatin to the Key Opinion Leaders and Oncolo y centres, [redacted] achieved, ensuring that each pertinent sector in the healthcare marketplace is sufficiently addressed, while geography dependent reimbursement approval will be initiated once TRL9 has been achieved and IVDD registration and CE marking finalised.

HANEMIR has been assessed to be technically feasible: Genechron's prior know-how in molecular diagnostics, the Istituto Regina Elena's expertise in Oncology, and our OEM provider means there are no anticipated technical issues.

HANEMIR has been assessed to be practically and economically feasible: The planning for the project and initial data acquisition has been on-going for several years and all stakeholders are aligned and know which steps have to be performed.

HANEMIR has been assessed to be end-user feasible: The final product is based on existing molecular biology principles, and the key reagents and processes have been field tested in both public and private customer operational environments using existing infrastructure.

The expected outcome of HANEMIR:

Commercialisation of a pivotal and cutting edge product that will:

1) Result in significant company growth

Geographically following CE marking and approval, this 'stamp of quality' will enable us to submit authorisation requests in additional lucrative markets (India, where HNSCC is also very prevalent and, and the Central and S. American market where our clinical collaborator has a strong presence, and potentially N. America)

2) Lay a foundation for easy repositioning of the same innovation in multiple sectors:

The kit also has extensive opportunity to be repositioned technically. It can be easily adapted to:

- Identify other miRNA/NA molecular markers [redacted] for additional diseases
- Identify other miRNA/NA molecular markers [redacted] for additional diseases
- Work within a l[redacted] device

Key performance indicators (KPIs)

High percentage detection of false positives and false negatives: Confirmation that the product only provides accurate information to the healthcare practitioners.

Solution reliability: Confirmation that components of the kit function at 100% effectiveness every time, confirming the measurement of the HNSCC miRNAs.

IVDD and CE marking compliance: Confirmation that the product corresponds to Europe wide sales and application standards, also informing us that the product is of high enough quality to consider being submitted for registration in additional geographies.

Europe wide KOL and oncology specialist interest: Confirmation that the kit and its supporting data are positively considered as a realistic option to help healthcare practitioners.

Initial distributor interest and follow up communications: Confirmation that distributors see the value of the product, and that high value and volume sales and market channels are available at minimum cost to Genechron.

Non-European oncology KOL/specialist and distributor interest and follow up communications: Confirmation that the kit and its supporting data are positively considered as a realistic option to help healthcare practitioners in additional key lucrative markets, with matching sales channels.

New leads and opportunities: Confirmation that the product repositioning potential and therefore additional value adding component of our innovation is as broad as we think.

2. Impact

About HNSCC

At present, treatment of HNSCC typically determined in a multidisciplinary setting, with the histological subtype, sub site, staging information, patient fitness, baseline swallow and airway function guiding management decisions. Approximately one-third of patients present with early-stage disease and these patients are treated with either surgery or radiotherapy depending on the primary tumour site, with cure rates of 70–90%. The majority of patients, however, present with locally advanced stage disease. Radical treatment in this situation requires multimodality therapy with surgery, commonly followed by postoperative radiotherapy or chemo-radiotherapy, or organ preserving primary radiotherapy, with or without chemotherapy, with reduced cosmetic compromise. These treatments are intensive and associated with severe acute toxicity, such as mucositis, dermatitis and dysphagia, and long-term sequelae, for example, sensorineural hearing loss, permanent xerostomia and altered swallowing function. Despite recent advances in both surgical and radiotherapy delivery techniques, up to 50% of locally advanced tumours relapse usually within the first 2 years after treatment, with limited options for salvage surgery or re-irradiation. Several chemotherapy agents can be used for inoperable recurrences or metastatic disease, with response rates of only 10–35% and median survival of 6–12 months.

Despite apparent complete excision of primary HNSCC, there is a significant rate of local recurrence in patients with histologically negative margins. Disease progression after curative treatment is monitored by clinical evaluation combined with imaging, but their specificity is low due to post-treatment effects; indeed, tissue changes due to the radiotherapy could be misinterpreted as evidence of persistent or recurrent tumour. A more detailed molecular characterization of local recurrence and resection margin tissues is an important challenge to identify patients with high risk of recurrence, to diagnose suspected relapses and to predict response to therapy. The presence of circulating miRNAs in body fluids and blood is now well documented in HNSCC and is relevant in early detection of recurrence, in the planning of “scheduled follow-up visits” and in treatment choice in HNSCC.

The healthcare marketplace

The healthcare marketplace for patients with HNSCC is composed of 3 principal ‘patient interaction’ points:

Primary healthcare: the family doctor or general practitioner clinic. Patient is seen in an outpatient setting.

Secondary healthcare: Specialist and disease focused outpatient centres. Patient is seen at a local specialist centre.

Tertiary healthcare: Hospitals (which can be private, public or both). Patient has to go to hospital that can be local or distant.

Supporting these healthcare levels are pharmacies, mobile nurses, clinical analysis laboratories, and in some cultures dedicated private centres that provide specialist services such as medical imaging.

The latter typically only happens in private focused healthcare cultures in which a PET scan centre is located in a high density demographic and provides services to a number of hospitals because the hospitals do not want to make a capital outlay.

The patients level of healthcare insurance will determine if the costs of the scan will be covered and by how much. In the cases in which cancer has been diagnosed this can then result in increased insurance premiums for the patient).

For all forms of IVDD, decisions on ‘how’ and ‘if’ is performed is determined by two interacting bodies.

The first is a regulatory and standards level, that decides if the clinical data generated from the development of the intervention is sufficient and of good enough quality to satisfy application in a healthcare setting.

Based on Directives and policy that determines what the IVDD is, and if the relevant industry standards (ISO) have been met to satisfy environment release (this is typically an authorised notified body licensed by government to perform this work). The outcome is a CE marked IVDD or CE-IVDD.

The second are the reimbursement entities that need the green light from the previous two levels. These are either private insurance companies, or in the case of public health any of the following depending on the market geography: government bodies, hospital trusts, regional authorities, or the actual general practitioners.

Independent of private or public, in the primary and secondary healthcare setting depending on the size of the clinic, they may have a diagnostic lab on site, or outsource to a clinical analysis laboratory.

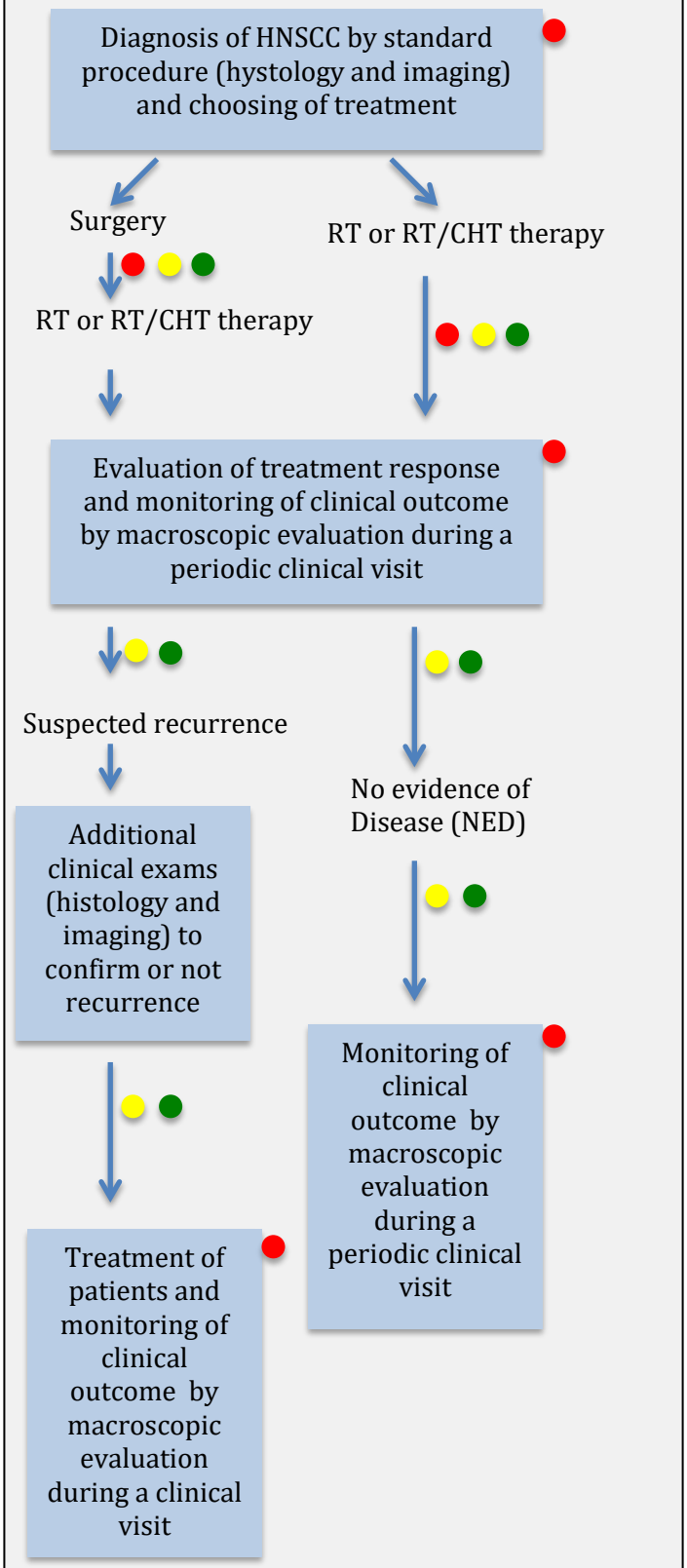
This means that if the healthcare practitioner wants it or deems it necessary the specific product is used.

In the project planning of **HANEMIR**, we have dedicated actions to address the first two levels, which form part of reaching TRL9.

On the right is the **HNSCC patient clinical management flow chart**; at present all of this happens in the tertiary care (hospital setting) which is the most expensive for healthcare and intrusive for the patient.

By applying the product in primary and secondary healthcare settings (specialist clinic and family doctor) significant bottlenecks will be removed from the process, patients will receive better and more routine management, and only the most urgent cases will be addressed in the Tertiary care setting.

HNSCC patient management flow chart



Pivot points of product and clients

In the 'HNSCC patient management flow chart' panel we indicated the 'pivot points' and the settings of healthcare the product could be used in. For each of these settings, having a significantly more accurate and easier to use solution for monitoring the patient is going to address a significant market need based on patient demographics.

The sheer volume of patients with HNSCC, that need to and should be correctly managed and the absence of solutions that enables clinicians to do this effectively and streamline the process, drives our present and future product development.

Global patient demographics

Selected countries and markets	New cases per year	Minimum total number of cases that are monitored annually	Deaths per year
Italy	[redacted]		
France	[redacted]		
Germany	[redacted]		
Spain	[redacted]		
EU27	[redacted]		
USA	[redacted]		
APAC			
-India*	[redacted]		
Central & South America**			

* [redacted]

** *Information obtained from* [redacted]

In the article assessing HNSCC in Central and South America, the authors also reported that [redacted]

(European countries chosen based o[redacted]; UK not included as target market due to lack of clarity of continued participation in EU market, that can be corrected for accordingly)

The numbers above only represent one type of cancer; increasing numbers of diseases are having molecular markers routinely identified, some of which have commercial value based on clear clinical evidence and ease of identification and confirmation (low number to be detected and clear relevance to patient pathology) which is giving rise to the published market sizes and growth rates in this field ([redacted]).

Existing and future products; market solutions, and their providers

At present, patients are diagnosed by tissue sampling (biopsy) and then by imaging (PET, MRI, CT or fibre-optic, and narrow band endoscopy. These solutions require a large scale dedicated infrastructure there are typically only found in tertiary care centres and therefore are expensive, invasive and require patient mobility. These solutions also miss a large number of early and recurring cases.

Innovation in this market segment is linked to augmenting reagents to increase sensitivity.

Innovations that have been abandoned are those that have focused on proteins and circulating tumour cells. While interesting academically, larger scale studies have revealed an absence of statistical relevance, the complexity of the solution which needs to look at multiple proteins and the associated high costs that a complex assay of this nature would entail.

The absence of significant innovation in this specific field is likely because competitors are focusing on the top 4 or 5 cancers for their diagnostic development.

There is only one dedicated HNSCC molecular product being developed:

Provider	Product	Measures	Status	Limitations
Naveris (US company)	NavDx	HPV in Blood	In development	-Does not detect all forms of recurring HNSCC -Cannot be used at early stages of diagnosis -Multiple clinical relevance not confirmed

The largest market threat is from indirect companies working in nucleic acid measurement for any clinical pathology

Entity	Potential product	Potentially Measures	Possibility
Large company e.g. Qiagen, Roche diagnostics, Illumina	Clinical miRNA test kit	miRNA in blood/saliva samples	Low, miRNA testing is performed as a lab service only No tests for saliva All existing products are experimental use only, or separate reagents sold as solutions to established diagnostic labs, who themselves have to be certified If they chose to develop and assay, it will be for the top 3 or 4 manifestations of cancer
Approved molecular diagnostic laboratories	Service providing miRNA measurements	miRNA in blood/saliva samples	No diagnostic lab has a nucleic acid saliva service focusing on oncology Key reagents are experimental use only
Molecular diagnostic kit providers	Repositioning of their tests	miRNA in blood/saliva samples	Low to mid-low: requires a dedicated high level of investment to generate the kit and clinically field prove it. Clinical grade reagents would have to be developed

Our financial predictions have incorporated in the risk that an indirect competitor may roll out a direct competing product

Genechron`s HANEMIR competitive advantage

- HNSCC is the 6th largest manifestation of cancer: competitors are focusing on the top 5
- Accurate and rapid
- Utility on-site or near-site to the actual location of the patient, generating immediate data in multiple healthcare settings
- Public and private clinical analytical laboratory infrastructure focused design
- Highly affordable: the only way for a competitor to significantly damage market predictions will be to take their margin close to zero
- Best possible to start its product life cycle, already having the 'stamp of approval' of global KOLs; competitors will need to come in with something significantly better
- High possibility to be rapidly repositioned and/or innovated for additional bodily fluids and Point-of-Care application

Commercialisation plan

i) Existing business model

Genechron's existing business model is based upon fee-for-service, in which molecular analysis is performed in certified clinical analysis laboratories in Rome. The location also has medical suites for private medical practitioners who specialise in indications for which we perform analysis. R&D is performed in our experimental labs for the development of new products, which are typically performed in collaboration with local clinical leader KOLs, or via international collaboration. R&D in the past two years has also moved towards the development of RNA/DNA based analysis kits, with one for toxicity presently in development, and another for prostate cancer in clinical validation.

Our own ***stakeholder, value and resource network*** for implementing **HANEMIR** is already established now includes, the hospitals; Istituto Regina Elena, Ospedale Bambino Gesu and La Sapienza; the OEM provider (dialabservices); Health Economics/NICE META Facilitator/reimbursement assessment (Athena Market Solutions) and our own sales and distribution consultants who focus on the Italian market.

ii) Evolution of business model following CE-marking approval

Obtaining CE marking is the critical first step for launching our product in the European market. For the Italian market we will expand our sales and distribution consultants to target high volume areas that incorporate all three healthcare marketplace sectors.

For all additional European markets we will partner with high penetrance IVD distributors.
Our potential selection of these representatives will also include evaluation of the scale, penetrance and quality of their distribution models.

Identified European distributors of In Vitro Diagnostics		
Name	**EU country focus**	**Non-EU country focus**
Eurapharma	France, Denmark, Portugal (also focus on Italy, which represents an alternative for domestic expansion)	23 different African countries, **India**
Biomedica	All 12 Eastern European countries (PL, CZ, SK, HU, RO, BG, CH, AT, SL, HR, BA, RS, ME, KO, AL, MK)	None
Axon Lab	Switzerland, Germany, Austria, Czech Republic, Croatia Slovenia, Belgium, The Netherlands Luxembourg	None

iii) Market geography launch requirements and barriers

Prior to activating the sales and distribution channels we will need to address reimbursement and registration, marketing, and penetrance issues, while for non-European markets appointment of authorised representatives or agents are a legal requirement.

All **EU27 countries** follow a similar initial process to place an IVDD on its product reimbursement list. It must be certified by a registered notified body: the nationality is not relevant, the harmonisation of standards means that CE marking obtained in one country means it can be sold in another EU country. When submitting to a national authority, all required documentation must be provided in the national language, and if the documents have been translated, a certified technical translator must perform the translation. To launch the product in each geography we will work with national specialists to facilitate the registration process and placement on the reimbursement list.

Definition of stakeholders and payers in target markets				
	Italy	**France**	**Spain**	**Germany**
National authority	NSIS	ANSM	AEMPS	BfArM/DIMDI
Reimbursement approval and payer	Regional Health authority	National body (HAS/CNEDiMTS and CEPS)	Autonomous community	Regional ASHIP
Who pays	Regional Health authority	Primary care: Patient but then reimbursed at 100% . Secondary and Tertiary care ANSM (only for cancer)	Cost sharing Between state and private insurance	Sickness funds
Primary care prescriber decision maker	Family Doctor	Family doctor	Primary care management structure	Family Doctor
Secondary care prescriber decision maker	Specialist centre	Specialist centre	Specialist centre	Specialist centre
Tertiary care prescriber decision maker	Hospital	Hospital	Hospital	Hospital
***Private stakeholders**	Private hospitals, insurance companies	Private hospitals	Insurance companies	Private hospitals, Insurance companies

**Private hospitals and private health insurers only need national authority approval, following which they perform their own HTA and have their own purchase authority.*

To be placed on the national reimbursement list each central regulatory agency performs a detailed review, including its own Health Economic and Outcomes Research, for which the Health Technology Assessment that will be performed as part of the project forms a strong support. However for most EU27 countries, in relation to actual expenditure agreement for diagnostics, the final decision to buy a product is further devolved.

By the end of **HANEMIR**, obtaining TRL9 implies also successfully obtaining the CE-IVDD mark from the notified body, and a positive evaluation at the Italian level of the national authority and initial submissions to the Regional Health Authorities.

Next stage Innovation defines our non-European expansion strategy

It is critical that to maintain competitive advantage we are always ahead of the curve with regard to our innovation and healthcare market focused solutions, and in light of the economic necessities to enter the larger and more lucrative APAC and Mercosur markets, a broader, cheaper and more mobile solution is a clear requisite; which also has the potential to be a 'Competition Killer' in Europe. Saliva is an excreted bodily fluid, as is Urine; both are easy to obtain and can be used for diagnostics, and are therefore leveraging our original data for further innovation.

At the time of the submission of this proposal, members of Genechron's Executive are presently at Bio2019 in Philadelphia in partnering meetings with the following focuses:

- ***Urine detection***: Meeting with Piemonte Agency (Urine miRNA for bladder cancer), Tech Manage Corp. (Urine miRNA for GI cancer), and Streck Inc (product stabilises nucleic acid in Urine at room temperature (37 C) for 7 days).
- ***Low tech nucleic acid detection***: Meeting with NIH/CDC who have developed rapid screening method for Zika Virus RNA from Urine and Serum using low tech isothermal methodology. We are interested in developing the same approach for our RNA targets, in both Urine and Saliva.
- ***Point of care devices***: Meeting with QuantuMDx (Q-POC system), GoDx (Low cost POC DNA/RNA extraction), Uni. Tsukuba (Room temp. PoC nucleic acid detection system)

The outcomes of these meetings and future innovative development will then drive the decisions for expansion into non-European markets, while also increase our estimated market penetrance and revenue generating potential within the EU27.

All expansion activities (legal, marketing, regulatory and manufacture) into Non-European markets will be financed exclusively from profits generated in the EU27

Expanding into the Indian market and Mercosur (Central and South American markets)

Expanding into the Indian and Mercosur markets is a more favourable non-European market, with significantly lower barriers to entry:

Advantages

- They are harmonising many of their standards with the EU standards
- For both market geographies, the importation and distribution of CE marked IVDD requires a local Authorised Agent in the specific country: the data generated to obtain the CE mark is considered of good enough quality that it can imported directly and distributed.
- Registration with the national government authority is required to launch the product onto the marketplace via a local distributor, but the processes are transparent (for India, we would likely be able to do this in partnership with Eurapharma, while the authorised agent would be CliniExperts)
- For the Latin American market, the Istituto Regina Elena is the coordinator of the cancer registry for that entire geography and therefore the clinical network can be more easily accessed, although a reliable distributor will be required for each country
- The Indian Central Drug Standard Control Organisation has implemented equivalent requirements since 2018, including an online portal for registration (http://cdsco.nic.in/writereaddata/IVD%20RC%20final%20.pdf).
- If the markets prove very lucrative local manufacturing subsidiaries could be longer term possibilities to increase product offerings, and also expand into neighbouring markets via Mutual Recognition Agreements e.g. India has agreements with several APAC and Middle East countries.

Risks

- Reimbursement is very fragmented, India does not have universal public health coverage, while the Mercosur markets are fragmented and typically hybrid private/public
- Monitoring of the Agents and distributors to ensure they are continually complying with the national regulations, and also not manipulating prices will be a necessity.
- Direct presence ***marketing and advertising is still going to be required following the same approach for the EU27 markets, including extensive interactions with clinicians***, which will require additional costs and personnel who are sensitive to each culture.

The benefits significantly outweigh the barriers for market expansion into these geographies, but we will only engage in this process if our innovations correspond to the healthcare infrastructure (high and low tech) and capacity to be reimbursed (low cost).

Expanding into North America

Expanding our product into the North American market, while lucrative by numbers presents more barriers and risks than immediate advantages.

- The manufacturer and distributor have to be located in the USA and be registered with the FDA.
- The distributor will need good relations with Managed Care Organisations of all types to ensure penetration into all 3 marketplace areas.
- Due to the likely absence of a substantially equivalent product on the market, we would be obliged to follow the Premarket approval (PMA) process, which is longer and much more rigorous than 501(k) registration.
- There are 9 bodies that influence policy on diagnostics and an additional 7 stakeholders that will need to be satisfied, of which the agreement of at least two will be required to agree to communicate the value of the product.

While the HTA we will generate as part of the project will be great value and benefit; to quote ISPOR, the professional society for Health Economics and Outcome Research, reimbursement by US payers relies *'heavily on decentralized health technology assessments when making coverage determinations. Currently value is determined through analysis of clinical and economic outcomes evidence. It is neither a uniform, nor standardized process by any means. Although there are general HTA criteria that payers adhere to, variances do exist as each payer defines their respective technology coverage processes and criteria'.* All of these represent significant barriers, therefore we would only consider the US market if the market penetration of **HANEMIR**, in the EU27 greatly exceeds our estimates.

Communication and marketing

In the instance of a positive evaluation of the proposal, in the first year we will add a webpage to the company website indicating that we have been the successful recipients of a SME grant, with the project focusing on innovative diagnostics for high impact cancers, but restrain from divulging any details or partnerships, so as to maintain our competitive advantage.

Reaching the milestone of Trl8, will result in the launch of a more elaborate and targeted communication strategy to users, accounting for the intelligence and sensibilities of the target audience. There are three stakeholder groups that need to be marketed to:

- Regulators (Government bodies)
- Purchasers (Regional agencies and Insurance companies)
- Users (KOL Market leaders who are typically GPs, and KOL Clinical leaders who typically work in hospitals)

i) Regulators *(Government bodies)*

Regulators we will start to communicate with **confidentially as soon as the project starts**. We will first liaise with the newly launched NICE Meta system. Despite being in the UK, this agency which is responsible for making reimbursement decisions for the UK NHS, is a trend setter in transparency and tool preparation for developers. For example they pioneered the use of HTAs in economic evaluation that is now adopted by the great majority of health care reimbursement bodies globally.

The NICE meta tool is 'an affordable platform developed by NICE to help product developers understand what evidence is needed to make a convincing case to payers and commissioners for their technology' see: https://meta.nice.org.uk. Genechron is already in partnership with Athena Market Solutions Ltd, that is an accredited META facilitator.

Following completion of this process, we will start to liaise directly with the target country regulatory agencies (NSIS, AEMPS, ANSM, and BfArM/DIMDI). The aim will be to inform them and keep them informed of the development of the kit and make sure we are current with all regulatory submission requirements.

ii) Purchasers *(Regional agencies and Insurance companies)*

Purchasers will start to be contacted at the **beginning of year 2**. There will be no need to contact these entities until we have completed the large-scale iteration of the kit and performed a preliminary HTA. Similar to regulators, ***Regional Agencies*** also prefer early communication and have online platforms on which you can submit product concepts or final products. For example, in Italy, AGENAS, and in Catalonia, AQuAS, the agencies that supports the regulatory bodies in performing economic evaluation likes to be informed as soon as possible when medical innovations are being developed so they can provide feedback and insight.

Private Insurance companies are more direct: for example BUPA, is a UK private health insurance company that operates in Spain, UK, India, China, Poland, Saudi Arabia, and like all such companies are constantly looking for more effective and cost reducing options of healthcare. They have a global procurement tool (https://procurement.bupa.com/web/login.html) that enables solution providers to register with them and inform them of products available. All private health insurers have such a platform, and we will register with them as soon as the product is close to completion and then inform them when regulatory approval has been obtained.

iii) Users *(KOL Market leaders who are typically family doctor's, and KOL Clinical leaders who typically work in hospitals)*

KOL product 'buy-in' is critical for generating sales. Market leader KOLs are tightly connected to the local patient and physician communities. They are typically general practitioners with large practices; Clinical leader KOLs are well-respected experts of a specific disease or therapy with a strong reputation, based on scientific publications and hospital location.

KOLs in healthcare are critical as they have the following impact:

- Convince peers to adopt innovations
- Disseminate scientific information
- Test products during development
- Provide exposure and feedback
- Build product credibility and validity
- Identify new opportunities
- Help create billing codes for reimbursement (without a billing code, the product cannot be charged)

For HNSCC, at present, 'market leader' KOLs refer patients to 'clinical leader' KOLs as these are based in hospitals where the present diagnostic platform is.

We therefore will communicate with the clinical leader KOLs, **from the beginning of year 2** to obtain their buy-in with Evidence Based Medicine (EBM) packages, organise a local 'product presentation' meeting at their hospitals and ask them to invite local oncology clinical leaders AND the local market leaders (family doctors) to the meeting.

To establish contact with and a network of clinical leader KOLs, in addition to asking the IRE to provide recommendations, we will attend the following meetings, at which we will pay for registration, a presentation booth and provide a EBM package.

- American association for cancer research-AHNS Head and Neck Cancer conference
- ICHNO: International conference on innovative approaches in head and neck cancer
- National cancer society meetings (Italy, Spain, France, Germany)
- National head and neck society meeting (Italy, Spain, France, Germany)
- International academy of oral oncology

The EBM package will contain copies of scientific publications, a flyer on the product (without proprietary technical specification) and non-confidential latest data updates providing information on efficacy and effectiveness, patient benefits, product safety, including how the product solves an unmet need and reduces healthcare costs.

Once we have established a KOL network, we will generate a dedicated **HANEMIR** Linkedin group and invite the entire network to participate. It is known that clinicians spend a lot of time on their portable devices, and this will be the best way to communicate with all of them continually and simultaneously to provide more information.

IPR and legal issues

For all our product development, we routinely perform freedom to operate studies, employing 'De Simone & Partners, our contracted IP solicitor. They have performed a global Freedom to Operate analysis related to HANEMIR, addressing competing companies, countries and classes; This was carried out by the crossing of all combinations of the 4 different miRNAs with all possible different keywords.

There are no barriers within our initial target markets nor third parties identified to prevent us from marketing and generating revenue from our product. The closest invention corresponds to a patent submitted by Australian authors, related to a method to detect miRNA for head and neck cancer (WO2018032062 (A1) link**).** Genechron will use a number of unpublished trade secrets related to nucleic acid measurement in clinical settings that provide more robust and accurate readings, and during the process of HANEMIR, in addition to patenting the kit and as many aspects of it that we can, we will also generate a series of trademarks related to our expertise (we anticipate being able to submit trademarks in classes 5, 10 and 41).

This will create an IP portfolio composed of: design rights, trademarks, copyrights (where applicable) and patents. The nature of the final kit will have individual character preventing unauthorised copying from larger competitors (which is why we choose to remain publicity silent in the first year). As part of our non-European expansion plans, given the high propensity for counterfeiting in some of our target markets, extensive IP protection will be performed prior to starting market registration, and renowned solicitors will be engaged in each geography to stringently protect our rights. For all geographies, we will continue to perform this analysis as part of the on-going process of the product development.

We will adhere to the legal requirements of the Directive 93/42/EEC (Medical Devices Directive) and IVDMDD 98/79/EC (In Vitro Diagnostic Medical Device Directive. For example the need for Genechron to have a dedicated staff for post marketing release follow up and QA/QC. Additionally, necessary, but not legally required is adherence to numerous ISO standards in which ISO 14971:2012 for risk assessment and ISO13485 are the overreaching standards (these are further detailed in the implementation section).

Financial predictions and modelling

Genechron Srl current shareholders are business an els and a public investor. [redacted]

If EU support for the project is obtained, Genechron will be able to expand from a service to a service & product company. The table below indicates the Profit and Loss (P/L) of the foreseen 5 years plan after the launch in the market of the **HANEMIR** product line.

5 year Profit and Loss forecast for HANEMIR product, after end of project

P/L	Year 1	Year 2	Year 3	Year 4	Year 5
REVENUES	9[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRODUCTION COSTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Production Personnel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Production costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GROSS MARGIN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTHER OPERATING COSTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Personnel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Marketing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Facilities & Utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EBITDA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amortization - Depreciation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EBIT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taxes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Income (Loss)	[redacted]	[redacted]	[redacted]	[redacted]	9[redacted]

[redacted]

The latter foresees an increasing profit mainly due to the growth in the revenues of the Molecular Diagnostics business line. Furthermore a new Financing Round is underway to raise between € 3million and € 5million risk capital from venture capitalist to boost the R&D pipeline, speed up the time to market of the new assays under development and to strengthen the sales network.

3. Implementation

Team

Roberta Gioia MBA (F): CEO (owner), Degree in Economics and Business. Responsible for project implementation. With over 20 years of experience in the management of projects and companies in the life science industry, her previous industry experience includes: CEO of Ylichron (4 years); cofounder of KiA Srl (start up 2010); CFO of Lay Line Genomics SpA (5 years); Manager of the TT area at SGC Sviluppo Gestione Controllo Srl Member of Eurogroup Consulting Alliance (5 years).

Jonathan Dando PhD (M): International Development/BSI trained. Responsible for international standards adherence, HTA preparation, International partnering and marketing. Has over 20 years of global industrial experience: Novartis AG (AT/CH), Systemix Inc (USA), Inserm Transfert SA (France, Director International Healthcare Projects), DWC Ltd (UK, CH, FR), Echino Ltd (UK,ES), and Genechron (IT, non-dilutable fund raising and partnering).

Valentina Spedaletti PhD (F): Senior scientist, Ph.D. in Molecular Biology, expertise in QA/QC and industrial research and clinical and GLP validation. 10 years industrial experience in Ylichron and Genechron, developing products for the diagnosis and the follow-up of degenerative diseases, nucleic acid based toxicology detection and diagnosis, including clinical study application; developed processes for GLP validation of a qPCR method for the absolute quantification of miRNA sequences in human samples.

Ramona Lupi PhD (F): Senior scientist, specialised in industrial development and validation. PhD in Oncology and Molecular Pathology and she is a specialist in Clinical Pathology. Post academia she has 5 years experience in DNA and miRNA based product development

Giorgio Tabirri (M): Laboratory Technician specialised in standardization and validation of methods in compliance with GLP regulations. 5 years industrial experience all within Genechron..

Federica Ganci PhD (F): PhD at the Oncogenomic and Epigenetic laboratory directed by Dr. Giovanni Blandino at Istituto "Regina Elena". Her expertise (see publications on page 5) is on translational projects aiming to identify key molecular determinants involved in cancer progression and their application in clinical practise. She is specialized on HNSCC tumors that she has studied for more than 10 years. In collaboration with Otolaryngology, Radiotherapy and Pathology Units of the IRE Institute, she has been the project manager for the collection and processing of biological samples including tissues and liquid biopsy from fully annotated HNSCC patients. She will be hired by Genechron as a joint project manager/ senior scientist.

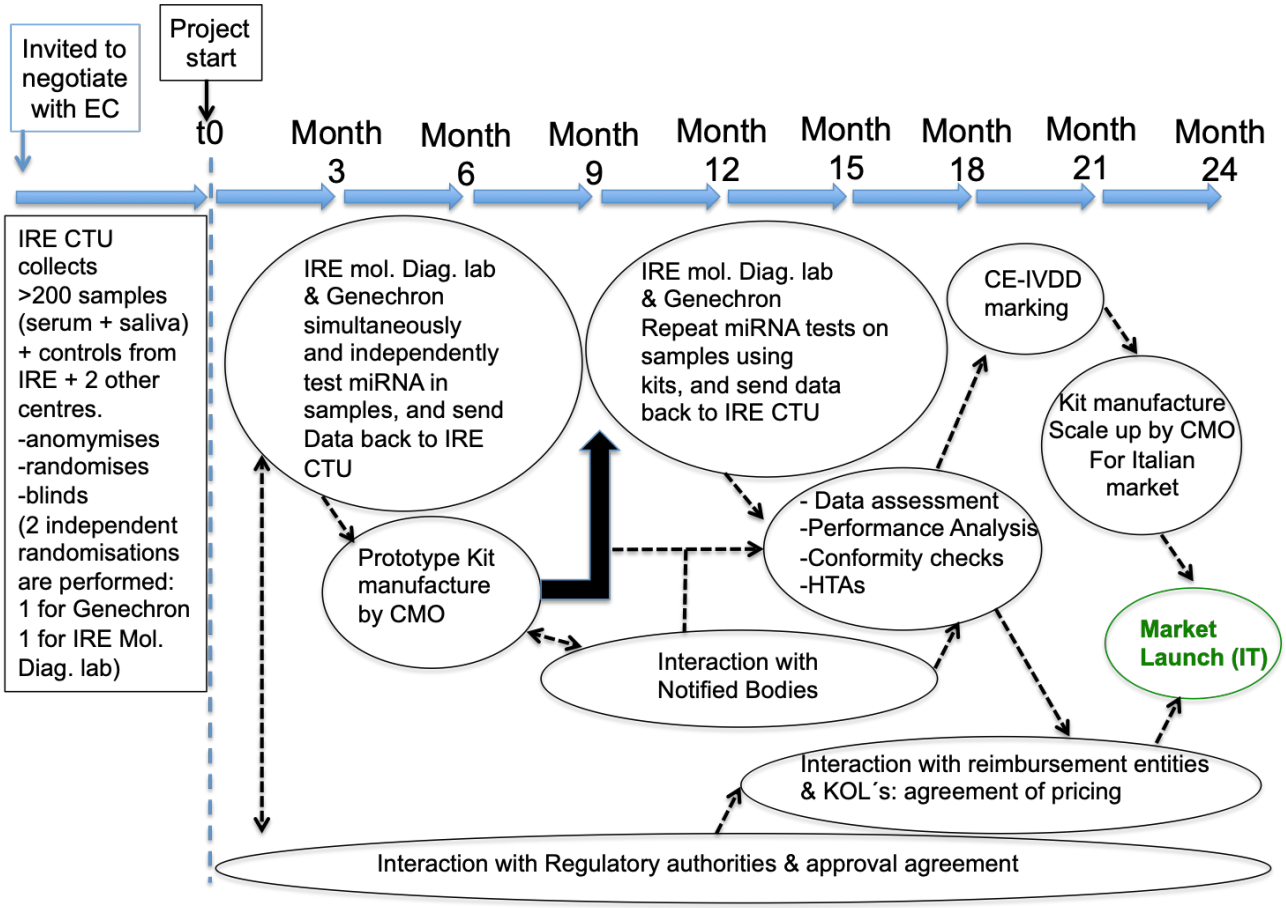
Consortium partnership complementarity

Genechron specialises in Molecular Diagnostics with a focus on NGS/Karyotyping and microRNA in cancer, toxicity and degenerative diseases; it has commercially proven services that correspond to market need and clinical applicability. Our expertise lies within a limited number of tissues, which have a large number of linked applications and market opportunities. This is reflected in our ongoing R&D strategies to develop complementary and overlapping products and services which further empower effective healthcare.

The Istituto Regina Elena, an Oncology dedicated Hospital, is a long-time collaborator of Genechron, located 1 km from the company itself; it is one of Rome's largest hospitals, globally renowned in oncology and healthcare management. They have worked with us to translate their initial observations of miRNA expression profiles in HNSCC patients into a high impact innovation, and their involvement, which we understand has to be as a third party, is necessary during the operational level validation of the kit due their access to large numbers of patient samples.

Work plan structure

Overview



The above plan and timing is divided into 6 work packages (WP)

WP1: Clinical testing of serum and saliva samples, in which Genechron and a public hospital laboratory (IRE molecular diagnostics lab) will first measure the miRNA levels using clinical laboratory testing procedures (which define the kit components), and then repeat the same test using the actual prototype kits. During the initial phases, this kit fine-tuning will be finalised so as to pass the required technical specifications onto the contract manufacturer.

WP2: Kit manufacture (pilot and initial scale up) and CE-IVDD compliance, will be performed by a Contract Manufacturing Organisation (CMO), under the supervision of Genechron personnel.

WP3: Regulatory authorities and reimbursement entity liaison will address working with the key stakeholders to ensure the product can be launched onto the market and the price.

WP4: Notified body, performance evaluation & marking, will involve direct collaboration and interaction with a government authorised notified body to ensure complete compliance with all regulations related to CE-IVDD approval and CE-IVDD marking obtention. This will also involve, HTA analysis for the preparation of the dossier for the reimbursement agencies.

WP5: Marketing, communication with KOL's and market launch, will address interactions with global KOLs and actual product launch, in which they will also be involved.

WP6: Management: Project, Innovation and Legal/IPR, will ensure that **HANEMIR** is executed to the highest quality.

Work package number	1	**Lead beneficiary**	1
Work package title	Clinical testing		
Participant number	1		
Short name of participant	Genechron		
Person months per participant:	36 months of effort (12 PM senior, 2x12 PM junior)		
Start month	1	**End**	18

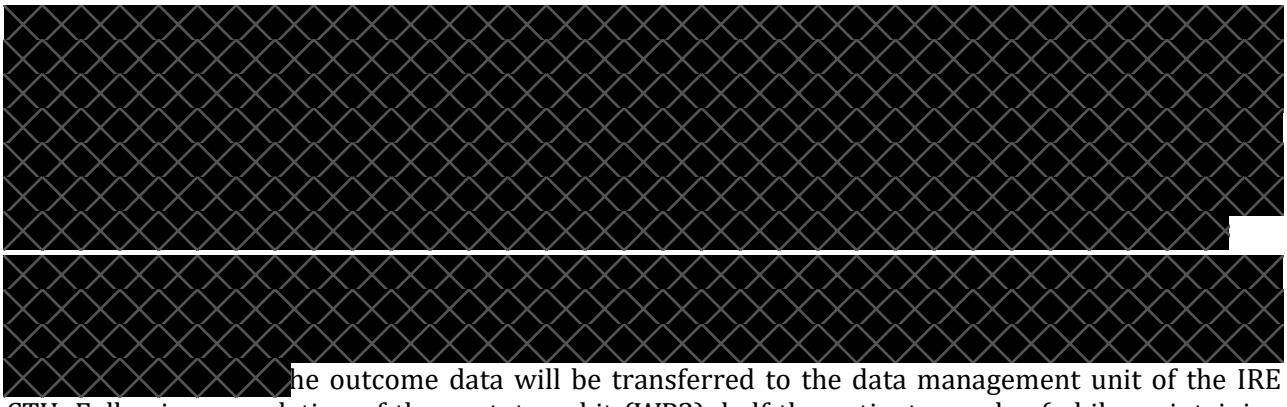
Objectives

Obtain 6 independent measurements of serum and saliva miRNA levels from >200 patients (+ controls) who are suffering from HNSCC, using procedures that can be applied in public and private settings to define the **HANEMIR** product, that will confirm the quality, integrity, reliability, reproducibility and performance of the product for the Notified Bodies.

Description of work

The government authorised notified bodies that ultimately decide whether an IVDD should be awarded the CE mark and become a CE-IVDD that can be launched into the total EU27 healthcare marketplace require that clinical validation is obtained from information from three independent locations. Under the circumstances that we are invited to negotiate with the EC, working with the IRE they will immediately activate their Global HNSCC KOL Clinical Leader network to coorindate sample collection from (Oncogenomic and Epigenetic Unit, Dr. Giovanni Blandino and Department of Otolaryngology-Head and Neck Surgery, Prof. Raul Pellini) Humanitas Hospital Milan (Department of Otolaryngology-Head and Neck Surgery, Prof. Giuseppe Spriano) and University of Chicago (Department of Otolaryngology-Head and Neck Surgery, Prof. Nishant Agrawal) to generate the collection of >200 patient samples necessary to implement our plan.

To estimate the sample size we considered the difference in terms of recurrence incidence, at 12 months from surgery, between the group of patients (group 1) characterized by high levels of miRNA expression, compared to the group characterized by none of these features (group 2). We based our estimation on these variables also because high miR-21-5p expression levels have been shown in plasma from diverse human cancers, including HNSCC, and are related to survival. Considering that a ratio 1:2 is present between groups 1 and 2, in terms of recurrence incidence, and assuming a percentage of 30% of recurrences in group 1, we will need to recruit a minimum of 138 patients (46 vs 92, respectively) for each group to observe a significant difference at 0.05% level with a statistical power of 80% (This was assessed using Fisher's Exact test).



he outcome data will be transferred to the data management unit of the IRE CTU. Following completion of the prototype kit (WP2), half the patient samples (while maintaining CTU coding) will be randomly swapped between those of Genechron and those of the IRE, and measurements repeated using the kit. The outcome data will be transferred to the data management unit of the IRE CTU.

Deliverables	***Month of delivery***
D1.1 miRNA expression profiles from HNSCC patients based on clinical lab procedures	9
D1.2 miRNA expression profiles from HNSCC patients based on kit usage	18
D1.3 fully defined technical component list for **HANEMIR** kit	3

Work package number	2	**Lead beneficiary**	1
Work package title	Kit manufacture and CE-IVDD compliance		
Participant number	1		
Short name of participant	Genechron		
Person months per participant:	12 months of effort (8 PM senior, 4 PM admin level)		
Start month	3	**End**	24

Objectives

Finalise kit manufacture based on CGMP and ISO13485 quality standards and ensure all documentation corresponds to need for CE-IVDD registration

Description of work

After the initial 3 months of the first clinical testing the precise technical components of the kit will be defined. This information, obtained from WP1 will be transferred to the Italian OEM provider.

A prototype series, of at least 40 kits (12 tests per kit), will be generated by the OEM provider. The Italian OEM provider operates under CGMP and ISO13485 quality standards, and we work with them because they adhere to the WHO guidelines, but we will continue to monitor them. (https://www.who.int/diagnostics_laboratory/procurement/170131_guidance_for_procurement_of_ivds_draft.pdf),

Specifically we will continue to monitor:

- Verifiable applicable standards and testing requirements
- Technical File or Design Dossier compilation, and file review
- Review of existing marketing materials, labeling, and user manual information to ensure compliance and consistency
- Verification of compliance with Essential Requirements
- Implementation, modification, and maintenance of a quality system (usually ISO 13485) that will meet European and other international requirements
- Risk assessment and management (ISO 14971)
- Packaging, labelling and kitting

CE-IVDD compliance, is clearly defined & requires comprehensive quality controlled documentation on:

- Design
- Manufacturer obligations
- Evidence collection

Control and confirmation of these will be followed by post-market surveillance and vigilance.

Prior to working with Notified Bodies we will ensure that this documentation is prepared, which will then be used for Italian market scale up, and then the sequential EU target markets.

In the instance that our OEM provider is unable to scale up manufacturing to ensure quality solution provision to our initially selected EU members and then total EU27 market, we will use this as the blue print to screen OEM solution providers who can (and additionally satisfy the requirements of non EU markets), which will then be contracted for production (identified solutions are: Merck Millipore (sigma Aldrich), bioline)

Deliverables	***Month of delivery***
D 2.1 Generation of a prototype kit to be used to test patient samples	9
D 2.2 Generation of a CE-IVDD kit to be used for market launch	24

Work package number	3	**Lead beneficiary**	1
Work package title	Regulatory authorities and reimbursement entity liaison		
Participant number	1		
Short name of participant	Genechron		
Person months per participant:	7 months of effort (5 PM senior, 2 PM admin level)		
Start month	1	**End**	24

Objectives

Obtain Health Ministry regulatory approval and reimbursement agreement from payers

Description of work

During the first month we will first perform an updated NICE META analysis of the HANEMIR innovation to address current requirements, and will result in the generation of a META report, which will include information on the evidence that payers, and commissioners need in order to understand the value our technology offer to patients and healthcare systems; provide information on any gaps in our current evidence base and the evidence we are planning to collect; and identify value claims that will stand scrutiny during health technology assessment (HTA. The report will be translated into Italian, French, Spanish and German.

Publication registration and reimbursement

Italy (Month 1-24)

Registration is performed directly with the Ministero della Salute http://www.salute.gov.it/portale/ministro/p4_8_0.jsp?lingua=italiano&label=servizionline&idMat=DM&idAmb=IVD&idSrv=EMO&flag=P

Reimbursement decisions pass through two bodies, a national evaluation with AGENAS, that oversees the regional expenditures (http://www.agenas.it) and then via regional bodies (the latter process is explain in detail by ISPOR at https://tools.ispor.org/htaroadmaps/Italy/Italy_MDD.asp#4

France, Germany and Spain

The same information and details of bodies, procedures and documentation can be found for:
France: https://tools.ispor.org/htaroadmaps/FranceMD.asp
Germany: https://tools.ispor.org/htaroadmaps/GermanyMD.asp)
Spain: https://tools.ispor.org/htaroadmaps/Spain.asp)

Private reimbursement

National marketing registration and approval (following CE-IVDD marking) will empower us also contact private health insurance companies and register with them as a product provider. Below we indicate a non-exhaustive list health insurers that we consider, their geographic footprint, and their procurement portal.

BUPA: Spain, UK, India, China, Poland, Saudi Arabia https://procurement.bupa.com/web/login.html
Aetna International: Global footprint. https://www1.aetna.com/about-aetna-insurance/aetna-corporate-profile/diversity/supplier-registration.html
Cigna International: Global footprint. https://www.cigna.com/suppliercommunity/supplier-registration-process

Deliverables	***Month of delivery***
D3.1 Italian Health Ministry Approval	20
D3.2 Italian Regional agencies reimbursement approval	24
D3.3 Good relations with Spanish, German and French Health Ministries	24
D3.4 Good relations with Spanish, German and French reimbursement bodies	24
D3.5 Established relations with Private Health Insurers	24

Work package number	4	**Lead beneficiary**	1
Work package title	Notified body, performance evaluation and marking		
Participant number	1		
Short name of participant	Genechron		
Person months per participant:	14 months of effort (12 PM senior, 2 PM admin level)		
Start month	9	**End**	24

Objectives

Confirm performance of HANEMIR kit
Obtain CE-IVDD mark by working with Notified bodies
Generate HTA dossier for final kit

Description of work

Notified Bodies

During the collection of the first set of data, and initial prototype kit manufacture, will make an open call for tender to some of Europe's leading notified bodies in CE-IVDD directive based conformity assessment and marking. The total requirements for obtaining CE-IVDD marking can be found at: https://www.medtecheurope.org/wp-content/uploads/2017/12/MTE_IVDR_Flowchart-Dec-2017_FINAL.pdf

We will provide the first draft documentation generated as part of WP2, and then work with the Notified Body to ensure we have all the required documents in the correct format and quality (indicated in the pdf file hyperlinked above), to enable them to perform

- Conformity assessment
- Registration

This involves an Audit on Quality Management Systems, a review the technical file and verification of the manufactured product. Typically Notified Bodies perform their own internal audits of their processes, meaning that at least two independent Certificate decision meetings are held before a final decision to issue the certificate and then plan continued assessment visits, including reviewing our post marketing monitoring and evaluation activities.

Performance evaluation and data assessment

All raw data obtained form WP1 will be transferred to the data analysis group at the Clinical Translation Unit (CTU) in the IRE. The raw data will have the sample code (that only the CTU unit will understand) and miRNA expression levels.

The data analysis group will then generate the final data file, including graphical presentations to indicate the performance of the process and kit, and the miRNA expression profiles by patient group (HNSCC vs control) and hospital location.

A Health Technology Assessment (HTA) dossier will be created once the clinical testing data has been confirmed. The structure of HTA dossiers are well established and include sections on:

- Context
- Clinical evaluation
- Economic evaluation
- Cost-effectiveness analysis
- Cost Minimisation
- Use of the product in practice
- Options for additional information

The dossier will be created and translated into the four languages of the primary target markets, and used in the Evidence Based Medicine package for the KOLs and for the product reimbursers.

Deliverables	***Month of delivery***
D4.1 Clinical performance of kit confirmed	20
D4.2 CE-IVDD mark obtained	22
D4.3 HTA dossier created and translated into four languages	22

Work package number	5	**Lead beneficiary**	1
Work package title	Marketing, communication with KOLs and market launch		
Participant number	1		
Short name of participant	Genechron		
Person months per participant:	16 months of effort (12 PM senior, 4 PM admin level)		
Start month	12	**End**	24

Objectives

- Establish 'clinical leader' and 'market leader' KOL network
- Establish private insurers network
- Generate comprehensive 'need' for our product
- Launch product

Description of work

At the start of the project we will update the Genechron website to indicate that we have been successful with regard to the SME application: it will not provide any detailed information on disease targets or approaches in the first instance. After month 12 we will update the page to reflect progress. The delay in topic communication is to prevent any competitors from innovating into our sector.

At month 12 we will create an Evidence Based Medicine package: this will include information on

- scientific knowledge (publications and latest non confidential clinical updates)
- information on efficacy and effectiveness, patient benefits, and cost effectiveness
- Non confidential product details and safety
- how the product solves an unmet need and reduces healthcare costs

We will then attend the following meetings during which we will pre-organise one-on-one meetings with the leading KOLs present:

- American association for cancer research-AHNS Head and Neck Cancer conference
- ICHNO: International conference on innovative approaches in head and neck cancer
- International academy of oral oncology
- National cancer society meetings (Italy, Spain, France, Germany)
- National head and neck society meeting (Italy, Spain, France, Germany)

The outcome will be a KOL network that will be kept informed of project progress via a dedicated linkedin **HANEMIR** network, that will be created.

Following the Oncology meetings we will perform product presentation at each KOL location, to present the benefit of the product, requesting that the clinical leader KOLs ensure the participation of the market leader KOLs (family doctors) and expand our marketing network reimbursement region by reimbursement region, throughout our primary market geographies.

We will directly market to health insurance companies, initially through their procurement procedures and then via direct presentations.

Following CE-IVDD marking, we will perform a large scale product launch in Rome, inviting all the clinical and market KOLs, and insurance companies with whom we have established a reliable network and inform them that the product is available, and as a function of the progress of WP3, indicate impact, cost effectiveness, and pricing (as a function of progress with reimbursement entities).

Deliverables	***Month of delivery***
D5,1 Genechron website updated	1
D5.2 Creation of EBM pack	20
D5.3 Establishment of private insurers, clinical leader & market leader KOL network	22
D5.4 Market launch event	24

Work package number	6	**Lead beneficiary**	1
Work package title	Management: Project, Innovation and Legal/IPR		
Participant number	1		
Short name of participant	Genechron		
Person months per participant:	13 months of effort (5x1 PM senior, 8 PM Junior)		
Start month	1	**End**	24

Objectives

Ensure **HANEMIR** achieves its objectives, correctly satisfying all stakeholder needs

Description of work

Management will be coordinated by an Executive Committee composed of Roberta Gioia (Genechron CEO), Vittorio Rosato (Genechron President), Prof. Giovanni Blandino (Director of IRE Mol. Diag. Laboratory/IRE Oncogenemoc and epigenetic unit and Genechron SAB member) Fulvio Basili (Genechron Board member and CEO of ecosafety), Jonathan Dando (Genechron Business Development), Maximillian Lebmeier (Athena Market solutions: Health Economics and Outcomes, and reimbursement specialist) and the project manager (Federica Ganci PhD).

They will meet every two months to quality control and approve:

- Monitoring, project progress and milestone achievement
- Address all stakeholder needs (including EC and additional funders reports)
- Perform risk management: internal, and external (local, national, EU27, global)
- Quality control all outputs (data, reports, publicity, funders requirements)
- Identify opportunities

Their overall role is to ensure a product that corresponds to the need in the HNSCC sector, achieves its maximum potential and is effectively launched. This will entail the definition and implementation of a legal/IPR and exploitation plan, which needs:

- Market analysis: analysis of local and global trends and feasibility analysis
- Assessment of the expected socio-economic and environmental impacts
- Identification of technical and non-technical barriers to the exploitation of project results
- Complete characterization of the exploitable results and developments
- Identification of standards, norms and regulatory aspects associated in particular within the health care manufacturing sector and infrastructure application
- IPR protection, IPR strategies and plans according to market dynamics
- Estimation of the time-to-market for any innovations

Ethics management The clinical translation unit (CTU) at the IRE has a dedicated Ethics committee coordination and clinical experimentation section to ensure that full ethical and legal procedures and requirements are adhered to prior to the commencement of the work involving human tissues. This involves both the use of human samples and in the context that the outcomes indicate that clinical performance studies are worthwhile the IRE clinical trials centers Ethics committee secretariat and the Clinical Trials unit will ensure coordination, management and compliance with the national AIFA and international ICH2 and GCP laws and regulations. For the additional selected clinical partners, we will liaise with their clinical trial units to ensure equivalent ethical management and quality control.

Deliverables	***Month of delivery***
D6.1 Management reports that quality control progress and address evolving market dynamics	12 & 24

List of work packages

WP no.	Work package title	Lead participant no. and name	Person-months	Start month	End month
1	Clinical testing	1-Genechron	36	1	18
2	Kit manufacture and CE-IVDD compliance	1-Genechron	12	3	24
3	Regulatory authorities and reimbursement entity liaison	1-Genechron	7	1	24
4	Notified body, performance evaluation & marking	1-Genechron	14	9	24
5	Marketing, communication with KOLs and market launch	1-Genechron	16	12	24
6	Management: Project, Innovation and Legal/IPR	1-Genechron	13	1	24
			98 months total		

List of key milestones

Milestone No.	Milestone name	Related work package(s)	Due date (in month)	Means of verification
1	Prototype kit manufactured	2	9	Executive review
2	Notified body selected	4	9	Executive review
3	miRNA measurements finished	1	18	Executive review
4	All components of conformity assessment finalised	4	20	Executive review
5	Market registration obtained	3	20	Executive review
6	CE marking	4	21	Executive review
7	Market Launch	5	24	Executive review

List of deliverables

Del. No.	Deliverable name	WP no.	Lead partner	Type	Dissem. level	Delivery date
D1.1	data set of miRNA expression profiles from HNSCC patients based on clinical lab procedures	1	Genechron	R	CO	9
D1.2	data set of miRNA expression profiles from HNSCC patients based on kit usage	1	Genechron	R	CO	18
D1.3	fully defined technical component list for **HANEMIR** kit	1	Genechron	R	CO	3
D2.1	Generation of a prototype kit to be used to test patient samples	2	Genechron	DEM	CO	9
D2.2	Generation of a CE-IVDD kit to be used for market launch	2	Genechron	DEM	PP	24
D3.1	Italian Health Ministry Approval	3	Genechron	R	CO	20

D3.2	Italian Regional agencies reimbursement approval	3	Genechron	R	CO	24
D3.3	Good relations with Spanish, German and French Health Ministries	3	Genechron	R	CO	24
D3.4	Good relations with Spanish, German and French reimbursement bodies	3	Genechron	R	CO	24
D3.5	Established relations with Private Health Insurers	3	Genechron	R	CO	24
D4.1	Clinical performance of kit confirmed	4	Genechron	R	CO	20
D4.2	CE-IVDD mark obtained	4	Genechron	R	CO	22
D4.3	HTA dossier created and translated into four languages	4	Genechron	R	CO	22
D5.1	Genechron website updated	5	Genechron	DEC	PP	1
D5.2	Creation of EBM pack	5	Genechron	DEC	CO	20
D5.3	Establishment of private insurers, clinical leader & market leader KOL network	5	Genechron	R	CO	22
D5.4	Market launch event	5	Genechron	DEC	PP	24
D6.1	Management reports that quality control progress and address evolving market dynamics	6	Genechron	R	CO	12 & 24

Critical risks for implementation

Description of risk & level	Related work package(s)	Proposed risk-mitigation measures
Local OEM provider unable to scale up	2, 3 , 4, 5	We have already compiled a short list of alternative OEM providers for IVD kits: most of whom are very large e.g. Merck-Millipore (former sigma Aldrich). If following prototype development the assigned OEM provider informs of this, we will immediately start to contact larger scale European based OEM providers.
Standards change (medium risk level)	2,3,4	Regulations and rules routinely change as new information is generated and standards are updated. The standards we follow are well established and globally implemented, therefore any changes that will occur (and they will), should be minor. Standards that are being updated are typically advertised on the ISO website. To address this risk, we will be liasing directly with the Notified Bodies and also reviewing all the related and pertinent standards prior to starting measurements, to ensure that our SOPs are up to standard. Standards will then be monitored for the duration of the project and any potential changes integrated into our systems.

Clinical data not sufficient for notified body performance evaluation (med/high risk level)	1,2,3,4,5	This is a natural component of performance testing; by nature there is always a med/high risk that outcomes will not be as anticipated. **This will be managed real time**. To control this, due to the geographic proximity of Genechron to IFO, we will be having Executive meetings every two months, so that there is a real time evaluation of the quality and variability of the data and statistical modelling. In the instance that risk occurs we will liaise directly with the CTU data analysis group to assess if the risk is real (i.e. as the samples are anonymised we may have inadvertently only measured control samples by a certain time point, which would imply nothing is working). This will enable us to adapt the work where necessary, and in the most extreme cases, to ensure we are moving forward adjust the budget allocation in the work packages to move more resources into the clinical measurement area to ensure obtaining healthcare valid results.

3.4 Resources to be committed

Table 3.4a: Summary of staff effort

WP	1	2	3	4	5	6	Total
Genechron	36	12	7	14	16	13	98

1 month of effort is the equivalent of 8 hours per day for 17 working days a month (average; includes national holidays and weekends)

Genechron's salary scale is divided into 3 levels: Senior (€7000/month total cost), Junior (€5000/month total cost) and administrative support (€3000/month total cost).

Table 3.4b: Cost explanation

Category	Cost (€)	Justification
Travel	61000	Attendance at 11 international congresses for marketing and KOL interaction, and visits to hospitals to present to market and clinical leader KOLs – travel, lodging, media preparation and stand/publication. Travel for meetings with regulatory authorities and reimbursement bodies.
Equipment	16000	Depreciation of key equipment
Other goods and services	611800	Intellectual property (40000), audits (5000), standards and CE marking docs (50000), notified body services for CE marking (60000), manufacturing 70 prototypes + 200 final CE marked kits(388800), publicity documents: EBM packages (8000), KOL liaison (60000)
Consumables	287000	287000 for testing in WP1 phase 1 (mol bio reagents: 90000. microRNA reagents: 91500. fluorescent probe development: 60000. Plasticware/labware: 45000.)
Total	975800	

Third party costs (IRE)

Estimated total costs are €377000: calculated as receiving 300 total human clinical samples, which cost the centres €500/sample to manage = €150000. The effort and time of the ethical boards and CTU which operate on an added-cost value calculation only as the source of funding is public, at an estimated cost of €20000. Staff costs for measuring miRNA at €144000, and the CTU data analysis team costing €63000.