

# PRoF Award abstract – Call 2016

## <Project acronym and name>

### 1. Research Outline

Acronym	AlphaReal Breast (ARBREAST)
Project name in English	AlphaReal Breast
Pitch (1 sentence)	An innovative prognostic kit for early breast cancer, based on molecular profiling of the clinical specimen predictive of Breast carcinoma prognosis, quantification recurrence probability during the period of 5 years after resection. that will be useful as an additional, affordable and valuable source of quantitative information in early breast cancer treatment decision.
Executive summary (max. 10 lines)	<p>Breast cancer is the most frequent cancer in women worldwide; according to the IARC/WHO latest estimates, 1,67 million of new breast cancer cases have been diagnosed in 2012, about 0,5 million in Europe alone, with the highest incidence (60% of all breast cancer) in women &gt;65 years old (<a href="http://globocan.iarc.fr">http://globocan.iarc.fr</a>). Due to the disease complexity is really complex to predict overall outcome. ARBREAST project <b>created an innovative prognostic kit for early breast cancer</b> that will be useful as an additional, affordable and valuable source of <b>quantitative</b> information in early breast cancer treatment decision. ARBREAST kit is based on the exploitation of a specific algorithmic analysis of the relative expression levels of <b>5 target genes</b> (Mustacchi et al., <i>Int.J.Mol.Sci</i> 2013), that allow to <b>quantify the risk of relapses in 5 years</b> after surgery.</p>

## 2. Cause and context of the research

Although early detection (through screening and increased awareness) and improvements in treatment protocol already led to a reduction in mortality rates of breast cancer in the majority of European countries since 1990, breast cancer is still the leading cause of death among women in 2012 (J. Ferlay et al., European Journal of cancer 49, 2013). Over the past 30 years, risk of relapse and death has been decreased thanks to the adjuvant treatment, usually hormonotherapy combined with chemotherapy; nevertheless, this treatment is strongly invasive and causes various side effects, such as mouth/throat sores, nausea, vomiting, diarrhoea, alopecia, cardiovascular problems, etc. For such a reason, taking a decision whether a patient might benefit from the adjuvant therapy, is highly important.

Every year, top oncology experts gather at the Europe's St.Gallen Breast Cancer Conference, in order to draw up new guidelines for breast cancer diagnosis and treatment. According to 2013 "St Gallen guidelines", use of multi-gene profiling validated devices is recommended as an effective addition to the therapeutic protocol for breast cancer. United States Insurance companies already included the multigene analysis in their routine operating protocol, while the high costs and long response time of the service are hindering the inclusion of this kind of analysis in Europe.

In this scenario, ARBREAST project plans to create an affordable kit that most molecular biology laboratories will be able to use to routinely screen all invasive breast cancers. The kit's protocol consists of RNA extraction from the formalin-fixed paraffin- embedded (FFPE) tumour samples, followed by cDNA preparation and amplification in Real Time PCR (RT-qPCR). An automated system software program will then allow for a fast, accurate and user friendly analysis of raw data. As final result, ARBREAST will provide the quantitative disease relapse risk, expressed as a confidence interval. All the steps of the protocol can be easily performed in any molecular biology laboratory equipped with a RT-qPCR thermocycler and a personal computer, along with widely available laboratory instrumentations. The assay is very fast, giving the prognosis back after just 2 working day. Just entered in the market, ARBREAST kit will allow Europe to play a leading role in global fight against breast cancer, hopefully revolutionizing breast cancer management through an efficient, low cost and accurate routine analysis.

While ARBREAST kit is entering in the market, we are willing to expand the panel of biomarkers to obtain an improved version of ARBREAST kit exploiting, through an unique protocol, 2 panel of biomarkers:

- a) A specific algorithmic analysis of the relative expression levels of **5 target genes** (already identified and validated, as published in Mustacchi et al., *Int. J. Mol. Sci* 2013, 14 , 9686-9702), that will allow to **quantify the risk of relapses in 5 years** after surgery
- b) A **5 miRNAs** panel analysis (selected from the current literature, Serpico et

al., *Cancer Treat. Rev.* 2014,40, 595-604, and under validation), that will give additional information about patient's **resistance/sensitivà to drugs**.

The extremely competitive and innovative ARBREAST procedure will **increase the effectiveness of disease management** on key European centres for the breast cancer management, and will surely promote foundation of new centres, especially in areas where today the cancer has a poorer prognosis.

### 3. Innovation results achieved

Several competitor products (see table below) especially in USA, already are on the market, showing an high market demand and allowing to consider the project a worthy investment. Alongside this, many studies regarding competitor products demonstrate the overall positive impacts on the society of such a products, too. On the other hand, the main problem in competitor products is high costs; since all of them are provided as services, response time is very long, too (typically 7-14 days). We will, therefore, put our efforts to provide a highly competitive product that could be reliable, accessible and affordable, at the same time.

The key points, that will distinguish our product from the others, are following:

- a) lower costs;
- b) shorter response time;
- c) wider information provided (beside risk of relapses in 5 years the kit will provide the information regarding drug responsiveness);
- d) quantitative prognosis;
- e) easy to use (based on user friendly software and unique protocol for both panels of biomarkers);
- f) larger target population (test covers 90% of all invasive breast cancer);
- g) minimum instrumentation required.

To date, there are several competitors that offer services characterized by multigene expression analysis; a comparison between ARBREAST kit and most relevant of them is listed in the following table.

	Oncotype DX (U.S.A)	Mammaprint (Netherlands)	Breast Cancer Index (U.S.A.)	ARBREAST	ARBREAST advantages
<b>Output</b>	Risk of recurrence	Risk of recurrence	Risk of recurrence	Risk of recurrence Drug sens./resist.	Provides more quantitative results, starting from 1 biopsy
<b>Output type</b>	Qualitative (Low-Int.-High)	Qualitative (Low-High)	Quantitative (1-10 value)	Quantitative (1-100 value)	
<b>Type of product</b>	Service	Service	Service	Kit	It is a kit, requiring standard laboratory equipment only
<b>Technology</b>	Real Time PCR	Microarray	Real Time PCR	Real Time PCR+ SW	
<b>Response time</b>	14 days	10 days	7 days	1 days	Response time is much faster
<b>Test costs</b>	3.500 €	2.675 €	3.000 €	800 €	Is greatly cheaper (3-4 times)
<b>Target</b>	50% breast carcinoma	Less than 50% breast carcinoma	Less than 40% breast carcinoma	90% breast cancer	Target population is larger (2x)
<b>Total EU Expenses /year</b>	> 630 M€	> 490 M€	> 430 M€	< 260 M€	Health system less than 1/2, considering a wider (2x) basis

#### 4. Link to the PRoF values

ARBREAST customers will be all private and public health bodies dealing with breast cancer, specifically oncologists needing a scientific support to take decisions and to define the best adjuvant therapy. This point is highly significant considering that typical adjuvant therapy is chemotherapy (CTX), well-known as strongly invasive and quite expensive, and that by use of a good prognostic tool, in many cases, it could be avoided.

In Europe alone, there are more than 4000 pathology laboratories (private, semi-public or public, linked to hospitals or clinics), all of them are potential market targets, but, in order to better evaluate ARBREAST expected impact, actual final targets of the prognostic kit have to be considered: all invasive breast cancer patients. Breast cancer is causing over 90.000 deaths and 360.000 new cases in Europe, each year, and use of ARBREAST prognostic kit will improve clinical protocol generating many socio-economic benefits.

##### **Private benefit** (for the patient):

- *Short response time*, so that treatment choice is faster.
- *Optimal CTX dosage*: the quantitative output of ARBREAST will provide oncologist with a much more accurate, complete and straightforward information, thus leading to a more precise prognosis and, consequently, to a more efficient usage of CTX adjuvant treatments. ARBREAST will greatly help in choosing right treatment approach: more or less aggressive therapy, according to patient's sensitivity/resistance to drugs and risk of relapses.
- *Increased life expectancy*: use of genomic assay increases life expectancy by at least 2,2 years (as estimated for OncotypeDx).
- *Health related quality of life* will be improved resulting in an increase of the quality adjusted life years (QALY).

##### **External benefit** (for society):

- *Lower health care costs*. Thanks to ARBREAST, the number of adjuvant CTX treatments will significantly decrease; following latest St. Gallen guidelines, our preliminary estimates indicate that use of ARBREAST kit in international protocols might decrease the number of patients treated with CTX, by about 20% (Int. J. Mol. Sci., 2013, 14, 9686 - 9702). This would result in great cost savings for cancer treatment: adjuvant CTX treatment costs about 4.500€ to 8.500€ for a complete cycle (not counting costs to treat CTX unwanted side effects) and, considering the number of patients that could avoid CTX by using our kit (approximately 18% in EU), we can roughly estimate that the cost saving of direct CXT expenses for the EU health system could be over 420 M€.
- *Increase overall productivity*. Patient that avoid CTX treatment can go back to normal life quickly.

## 5. Applicable IPR rules

At present, the Intellectual Property of ARBREAST is held by Alphagenics Biotech S.r.l. that owns patent "Gene expression profiling using 5 genes to predict prognosis in breast cancer" (number WO2014009798) that covers methods, kits and systems application in disease outcome prognosis for breast cancer. In the future we will be evaluated possible international extensions and/or other protection over other uncovered parts of the ARBREAST idea and/or other additional innovations that should be conceived. In European Union, AlphaReal Breast kit is regulated by the Directive on In Vitro Diagnostic medical devices (IVDD 98/79/EC), which became operational since December 1998; this directive establishes (in EU) the main requirements in terms of safety standards and of quality and performances needs, for all IVD procedures and methodologies. To aim the USA market, too, the product will undergo the FDA premarket submission path; according to Code of Federal Regulations (CFR), AlphaReal Breast kit is classified as Gene expression profiling test system for breast cancer prognosis (CFR- TITLE 21 Ch I, Sub Ch. H, PArt 866, Subpart. G, Sec 866.6040) and belongs to Class II. This Class requires both general and special controls for clearance that can be cleared through a 510(k) Premarket Notification, since it is clearly possible to identify a "substantially equivalent" predicate device (some competitor), already legally marketed in the USA.

## 6. Information on the partners

The R&D staff of Alphagenics, in collaboration with the Department of Oncology at the University of Bologna, has acquired, through participating to several research projects, a wide knowledge in the field of genomic alterations in tumours, specifically related to prognosis and response to chemotherapy (Temozolomide in gliomas through the analysis of methylation state of MGMT promoter). This know-how already led to development of a panel of protocols exploiting highresolution gene expression analysis, Real Time qPCR and methylation sensitive qPCR. The Alphagenics technical staff has published several papers in international journals of the field in the study of genetic alterations in several pathologies.

### Collaborations

- Institute of Oncology, University of Bologna
- I.R.C.S.S. Burlo Garofolo of Trieste
- Department of clinical sciences, general surgery, anesthesiology and intensive care medicine at the University of Trieste
- University of Genoa
- National Cancer Institute of Milan
- Department of Human Pathology, Azienda Ospedaliera Universitaria Policlinico G. Martino



of Messina

Note:

If your project is selected as laureate for the Award Symposium, a powerpoint presentation that reflects the project as suggested will be required (in advance), including a future plan how the funding will be used.

If your project is selected as the winner of the Award, you will be invited to present the results achieved thanks to the award during the Award Symposium of the next year.



## **Addendum: Contact information**

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