The Andromeda trial

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Hypothesis

Risk-based screening programmes according to different BC risk criteria (i.e. breast density, model based estimates of absolute risk, life-styles) may maximize the impact of screening in groups of women characterized by different risks.

Validated highly accurate blood molecular biomarkers associated with BC risk may represent a complementary tool to mammography in the primary screening setting-

objectives

The **first objective** **is to evaluate and compare, in a large cohort of women, the predictive value** of available criteria to define BC risk in order to identify appropriate risk-based stratifications for personalised screening. The criteria considered are:

i. general risk factors collected through a standardised risk questionnaire (SRQ) such as reproductive factors, first-degree family history, biopsy history, physical activity, body mass index and alcohol consumption). For this category the absolute risk will be evaluated using the risk prediction model of Petracci et al. that has been developed for the Italian population and validated on an independent cohort of Italian women.

ii. breast density;

iii. woman's life styles (through a detailed questionnaire on dietary habits and physical activity - LSQ).

objectives

The second main objective is to investigate whether selected circulating miRNAs previously found *associated to BC risk are significantly altered in the plasma of cancer patients compared to matched healthy controls and if they satisfy pre-specified true- and false-positive rates that are* considered minimally acceptable in the screening setting.

Sub-objectives

Andromeda will allow also achieving the following related **sub-objectives:**

- To assess the association between factors such as age, breast density, reproductive factors and family history as well as life-style and miRNA level in the cancer-free population. If such factors affect the biomarker, the threshold for screening positivity may need to be defined separately for screening subpopulations, in order to keep the false-positive rate at low level for each.
- To assess factors associated with miRNA level in cancer cases – in particular, disease characteristics such as stage, grade, and available prognostic factors. Understanding the nature of cancer that is detected with a biomarker is a key issue. A biomarker that detects cancer at an early stage is more valuable for preventive purposes than one that detects only late-stage cancers.
- To evaluate the presence of 18 currently established breast cancer risk SNPs obtained by genome-wide association studies (GWAS) that have identified common low penetrance alleles associated with breast cancer risk at multiple genetic loci (17), and test their association with circulating miRNAs, breast density and screening outcome.

- To quantify the impact of potential intervention of tailored screening on health outcomes and costs.

- To evaluate the economic and organizational feasibility of tailored intervention and to design stratified breast cancer screening strategies for future pilot programme implementation

Target Population

The study population is represented by over 35.000 women aged 45 to 67 years participating to the Proteus study, a randomized controlled trial aimed at evaluating the performance of digital breast tomosynthesis (DBT) as compared to standard digital mammography (DM).

Proteus, which has been approved by the Ethical Committee and funded separately, is now starting recruitment in the context of the regional mammographic screening programme in Piedmont (in Torino, Biella and Vercelli).

Based on previous studies carried out by us in the screening population, we have estimated that 60% (21,245) of the 35,409 women enrolled in Proteus will provide informed consent for participation in Andromeda as well.

- Along with the invitation letter for routine screening, women will receive a detailed description of both Proteus and Andromeda. Women will be asked informed consent at the time of the screening test.
- Proteus participants will then be randomized with a 1:3 ratio into two groups: the control group will follow the usual care (double reading DM) whereas the study group will be invited to undergo DBT.

- Women that refuse to participate to Proteus will be reinserted in the mammographic screening programme (usual care) and not considered in our research.
- Proteus participants will be offered participation to Andromeda. Proteus/Andromeda duration is three years and the study period will include one or two screening rounds depending on the women's age (the interval between two consecutive invitations is two years for women aged 50-67 and one year for younger women).

- Women who will agree to participate to Andromeda will get all that is proposed to the Proteus study group (breast density and the standard risk questionnaire – SRQ). In addition they will be asked to fill in a detailed questionnaire on their life style (LSQ) and to provide a blood sample, or at least one of the two.

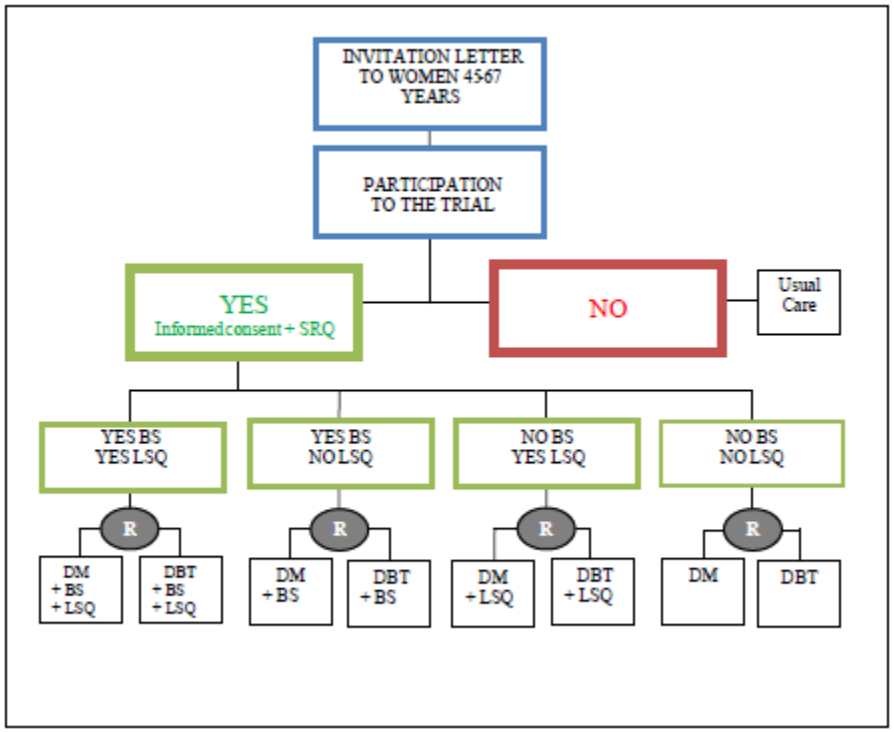

Figure 1. Flow chart of the study

SRQ= short risk questionnaire
DM= digital mammography acquisition
DBT= digital breast tomosynthesis acquisition
BS= blood sampling appointment
LSQ= life style questionnaire

- Women who will agree to participate to Andromeda will get all that is proposed to the Proteus study group with separate funding (breast density and the standard risk questionnaire - SRQ). In addition, they will be asked to fill in a detailed questionnaire on their life styles (LSQ) and to provide a blood sample, or at least one of the two