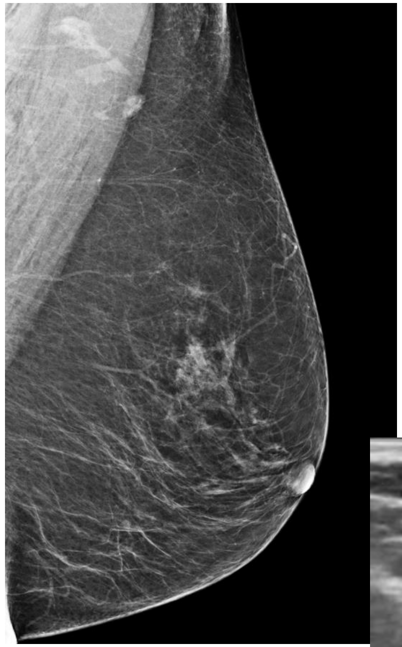
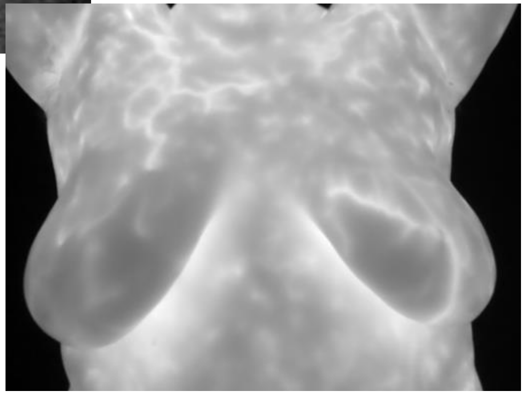
Project Interreg MACbioIDi2

"Train the trainers" meeting

Las Palmas de Gran Canaria, 1st April 2022





Breast cancer detection with mammography, ultrasound and thermography

Francisco Javier Díez

Dept. Artificial Intelligence
UNED, Madrid

Introduction: context

Breast cancer screening

- Advantage
  - Early detection
    - Higher survival rates
    - Less aggressive treatments
    - Lower costs
- Shortcomings of mammo screening
  - Ionizing radiation $\rightarrow$ risk of cancer
  - Patients' discomfort/pain $\rightarrow$ low adherence
  - False positives
    - Emotional cost
    - Unnecessary biopsies
  - False negatives, especially in dense breasts (young women)
  - Economic cost: equipment + personnel

Inclusion criteria for screening

- Usual criteria
  - Age
  - Familiar antecedents
- Other criteria
  - Breast density
  - Personal antecedents
  - Genetic tests
  - Etc.
- These criteria are used to estimate cancer risk
    - almost always implicitly; sometimes explicitly
- Some studies analyze cost-effectiveness

Screening techniques

- Usual
  - Mammography
    - sometimes with tomosynthesis and synthesized mammography
  - Ultrasound
    - especially recommended for dense breasts
    - sometimes with elastography
- Proposals
  - MRI (only for high-risk women; example: DENSE trial)
  - Microwaves (example: MammoWave project)
  - Thermography
  - Etc., etc.

Screening guidelines

- Significant differences among countries
  - and even within the USA (USPSTF, ACS, ACOG, ACR, ACP…)
- Differences
  - Starting age: 40 / 45 / 50 y.o.
  - Ending age: 69 / 74 / life expectancy < 10 years
  - Frequency: annual / biennial / every 3-4 years…
  - Techniques (in addition to mammo): ultrasound, MRI
- It would be desirable to find the **optimal pattern**
  - evidence-based
  - personalized: tailored to each woman’s features.

Example: (Schousboe et al. 2011)

- Technique: only mammo
- Cost-effectiveness analysis
- Inclusion criteria
  - age
  - familiar antecedents
  - breast density
  - previous biopsy
- Markov model

ORIGINAL RESEARCH | Annals of Internal Medicine

Personalizing Mammography by Breast Density and Other Risk Factors for Breast Cancer: Analysis of Health Benefits and Cost-Effectiveness

John T. Schousboe, MD, PhD; Karla Kerlikowske, MD, MS; Andrew Loh, BA; and Steven R. Cummings, MD

Background: Current guidelines recommend mammography every 1 or 2 years starting at age 40 or 50 years, regardless of individual risk for breast cancer.

Objective: To estimate the cost-effectiveness of mammography by age, breast density, history of breast biopsy, family history of breast cancer, and screening interval.

Design: Markov microsimulation model.

Data Sources: Surveillance, Epidemiology, and End Results program, Breast Cancer Surveillance Consortium, and the medical literature.

Target Population: U.S. women aged 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years with initial mammography at age 40 years and breast density of Breast Imaging Reporting and Data System (BI-RADS) categories 1 to 4.

Time Horizon: Lifetime.

Perspective: National health payer.

Intervention: Mammography annually, biennially, or every 3 to 4 years or no mammography.

Outcome Measures: Costs per quality-adjusted life-year (QALY) gained and number of women screened over 10 years to prevent 1 death from breast cancer.

Results of Base-Case Analysis: Biennial mammography cost less than $100 000 per QALY gained for women aged 40 to 79 years with BI-RADS category 3 or 4 breast density or aged 50 to 69 years with category 2 density; women aged 60 to 79 years with category 1 density and either a family history of breast cancer or a previous breast biopsy; and all women aged 40 to 79 years with both a family history of breast cancer and a previous breast biopsy, regardless of breast density. Biennial mammography cost less than $50 000 per QALY gained for women aged 40 to 49 years with category 3 or 4 breast density and either a previous breast biopsy or a family history of breast cancer. Annual mammography was not cost-effective for any group, regardless of age or breast density.

Results of Sensitivity Analysis: Mammography is expensive if the disutility of false-positive mammography results and the costs of detecting nonprogressive and nonlethal invasive cancer are considered.

Limitation: Results are not applicable to carriers of *BRCA1* or *BRCA2* mutations.

Conclusion: Mammography screening should be personalized on the basis of a woman's age, breast density, history of breast biopsy, family history of breast cancer, and beliefs about the potential benefit and harms of screening.

Primary Funding Source: Eli Lilly, Da Costa Family Foundation for Research in Breast Cancer Prevention of the California Pacific Medical Center, and Breast Cancer Surveillance Consortium.

Ann Intern Med. 2011;155:10-20. www.annals.org
For author affiliations, see end of text.

Another example: (Gray et al. 2017)

- Mammo + ultrasound
- Cost-effectiveness analysis
- Inclusion criteria
  - estimated risk (explicit)
  - breast density
- Model: discrete event simulation

ELSEVIER

journal homepage: www.elsevier.com/locate/jval

Evaluation of a Stratified National Breast Screening Program in the United Kingdom: An Early Model-Based Cost-Effectiveness Analysis

CrossMark

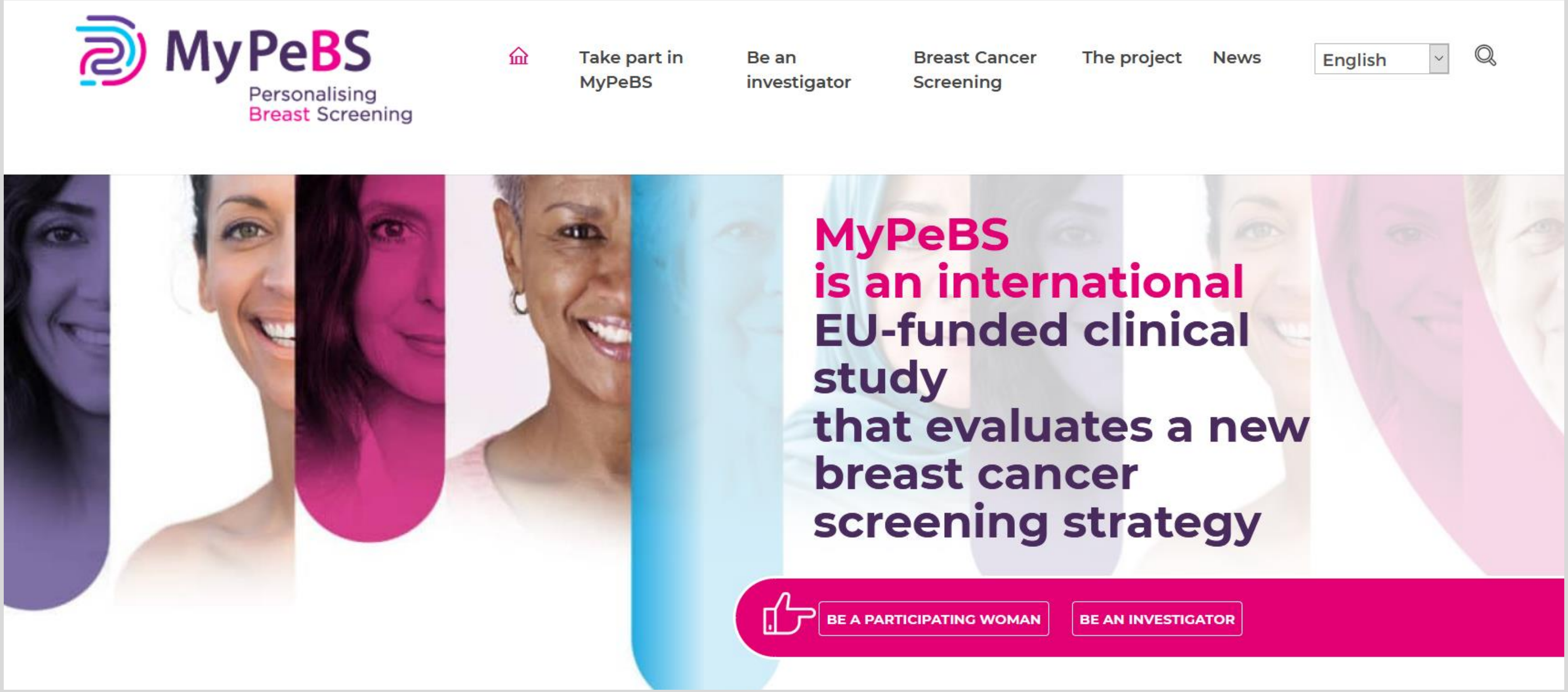
Ewan Gray, PhD[1,2], Anna Donten, MSc[1], Nico Karssemeijer, PhD[1,3], Carla van Gils, PhD[1,4], D. Gareth Evans, MD, FRCP[1,5], Sue Astley, PhD[1,6], Katherine Payne, PhD[1,]*

[1]*Manchester Centre for Health Economics, University of Manchester, Manchester, UK;* [2]*Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK;* [3]*Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands;* [4]*University Medical Centre Utrecht, Utrecht, Netherlands;* [5]*Genesis Breast Cancer Prevention Centre and Nightingale Breast Screening Centre, University Hospital of South Manchester, Manchester, UK;* [6]*Department of Imaging Science and Biomedical Engineering, University of Manchester, Manchester, UK*

ABSTRACT

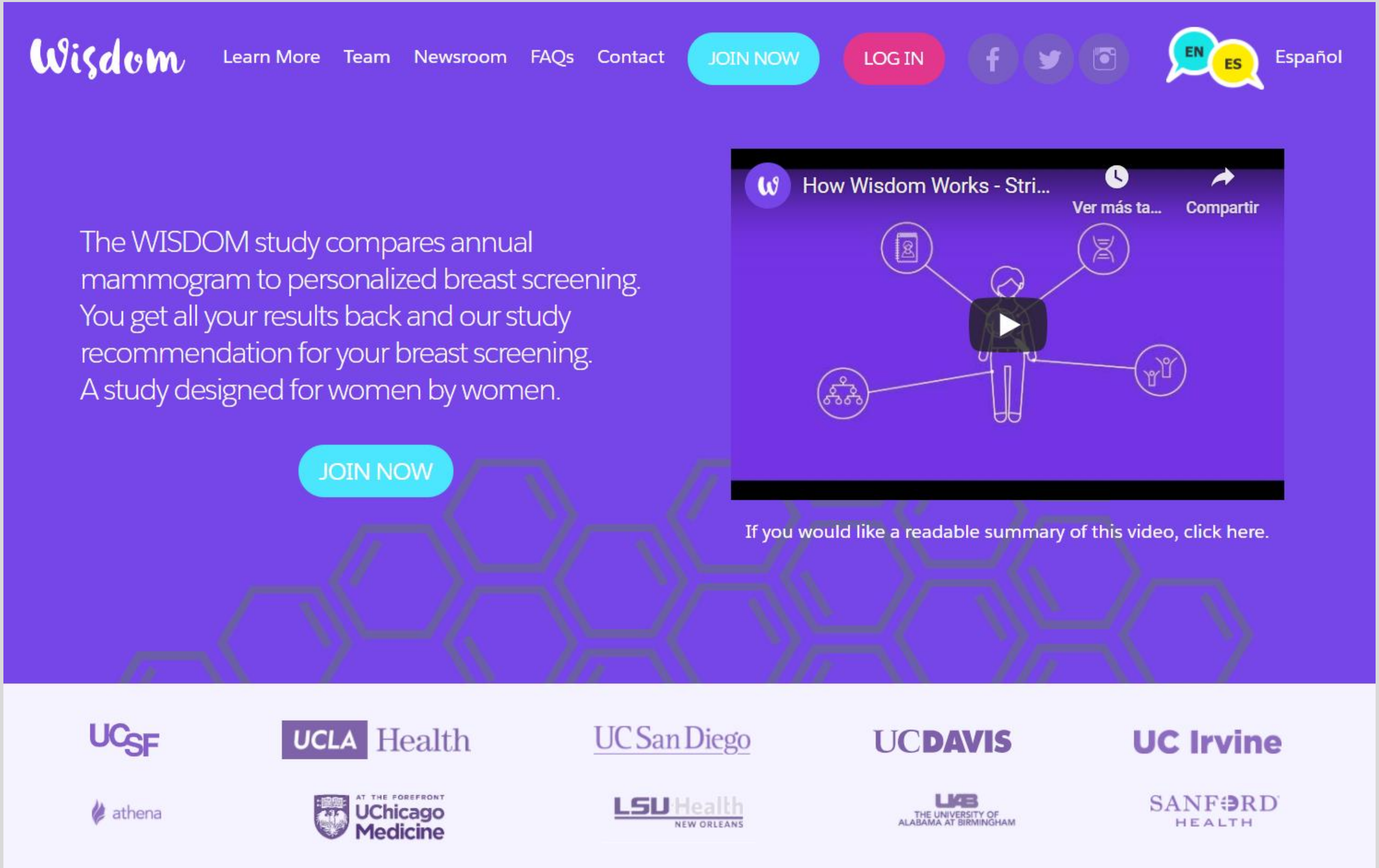
Objectives: To identify the incremental costs and consequences of stratified national breast screening programs (stratified NBSPs) and drivers of relative cost-effectiveness. **Methods:** A decision-analytic model (discrete event simulation) was conceptualized to represent four stratified NBSPs (risk 1, risk 2, masking [supplemental screening for women with higher breast density], and masking and risk 1) compared with the current UK NBSP and no screening. The model assumed a lifetime horizon, the health service perspective to identify costs (£, 2015), and measured consequences in quality-adjusted life-years (QALYs). Multiple data sources were used: systematic reviews of effectiveness and utility, published studies reporting costs, and cohort studies embedded in existing NBSPs. Model parameter uncertainty was assessed using probabilistic sensitivity analysis and one-way sensitivity analysis. **Results:** The base-case analysis, supported by probabilistic sensitivity analysis, suggested that the risk stratified NBSPs (risk 1 and risk-2) were relatively cost-effective when compared with the current UK NBSP, with incremental cost-effectiveness ratios of £16,689 per QALY and £23,924 per QALY, respectively. Stratified NBSP including masking approaches (supplemental screening for women with higher breast density) was not a cost-effective alternative, with incremental cost-effectiveness ratios of £212,947 per QALY (masking) and £75,254 per QALY (risk 1 and masking). When compared with no screening, all stratified NBSPs could be considered cost-effective. Key drivers of cost-effectiveness were discount rate, natural history model parameters, mammographic sensitivity, and biopsy rates for recalled cases. A key assumption was that the risk model used in the stratification process was perfectly calibrated to the population. **Conclusions:** This early model-based cost-effectiveness analysis provides indicative evidence for decision makers to understand the key drivers of costs and QALYs for exemplar stratified NBSP.

Keywords: breast cancer, cost-effectiveness analysis, discrete event simulation, screening.



- From 2018 to 2025. Budget: 12.5 M€, European Union
- 85,000 women, 40 to 70 y.o., from 5 countries
- Goal: optimal screening policy, depending on personal risk:

  {age, familiar antecedents} + {genetics, breast density…}



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Save this study

Tailored Screening for Breast Cancer in Premenopausal Women (TBST)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02619123

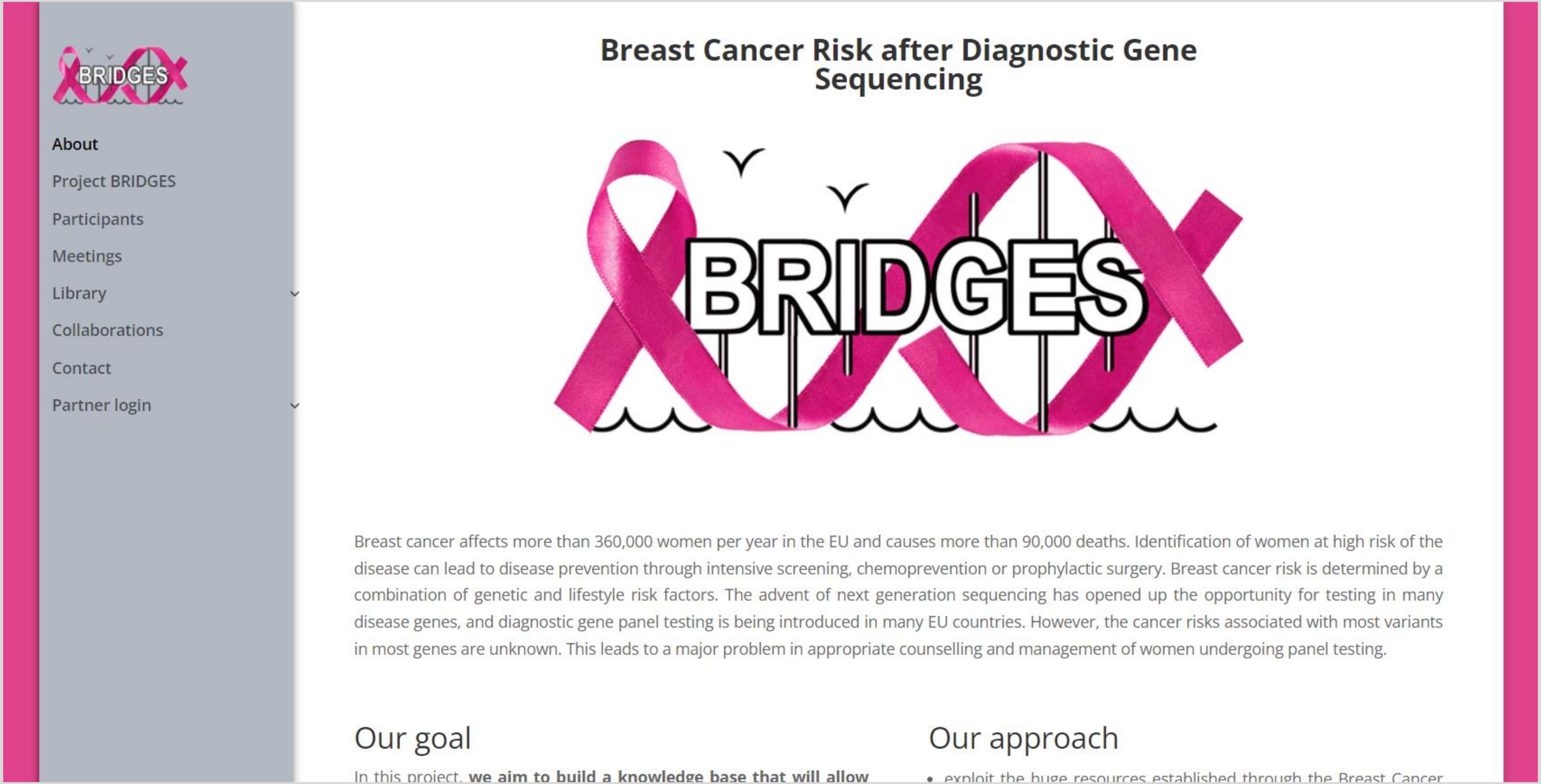
Recruitment Status : Unknown
Verified February 2017 by Cancer Prevention and Research Institute, Italy.
Recruitment status was: Recruiting
First Posted : December 2, 2015
Last Update Posted : February 10, 2017

Sponsor:
Cancer Prevention and Research Institute, Italy

Collaborator:
Ministry of Health, Italy

Information provided by (Responsible Party):
Cancer Prevention and Research Institute, Italy

Tailored Screening for Breast Cancer in Premenopausal Women (TBST)



About

Project BRIDGES

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Partner login

Breast Cancer Risk after Diagnostic Gene Sequencing

BRIDGES

Breast cancer affects more than 360,000 women per year in the EU and causes more than 90,000 deaths. Identification of women at high risk of the disease can lead to disease prevention through intensive screening, chemoprevention or prophylactic surgery. Breast cancer risk is determined by a combination of genetic and lifestyle risk factors. The advent of next generation sequencing has opened up the opportunity for testing in many disease genes, and diagnostic gene panel testing is being introduced in many EU countries. However, the cancer risks associated with most variants in most genes are unknown. This leads to a major problem in appropriate counselling and management of women undergoing panel testing.

Our goal

In this project, **we aim to build a knowledge base that will allow**

Our approach

- exploit the huge resources established through the Breast Cancer

https://bridges-research.eu

A.I. will revolutionize radiology

- This system is more accurate than 61% of radiologists
- and is still learning.

ARTICLE

Stand-Alone Artificial Intelligence for Breast Cancer Detection in Mammography: Comparison With 101 Radiologists

Alejandro Rodriguez-Ruiz, Kristina Lång, Albert Gubern-Merida, Mireille Broeders, Gisella Gennaro, Paola Clauser, Thomas H. Helbich, Margarita Chevalier, Tao Tan, Thomas Mertelmeier, Matthew G. Wallis, Ingvar Andersson, Sophia Zackrisson, Ritse M. Mann, Ioannis Sechopoulos

See the Notes section for the author's affiliations.
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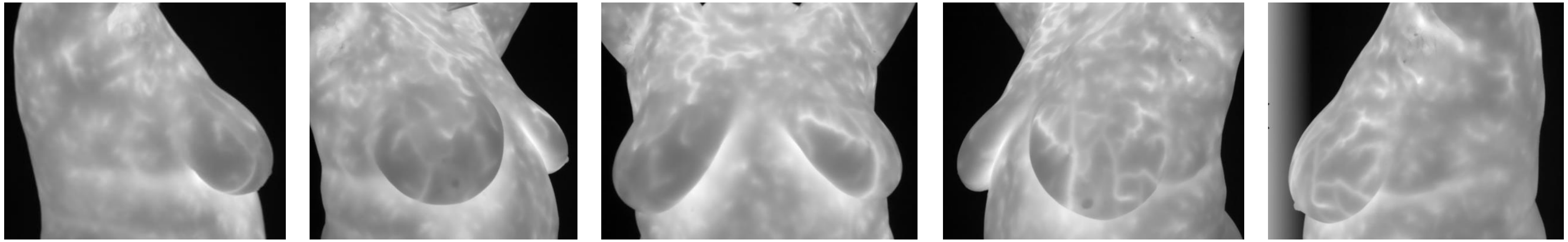
Abstract

Background: Artificial intelligence (AI) systems performing at radiologist-like levels in the evaluation of digital mammography (DM) would improve breast cancer screening accuracy and efficiency. We aimed to compare the stand-alone performance of an AI system to that of radiologists in detecting breast cancer in DM.
Methods: Nine multi-reader, multi-case study datasets previously used for different research purposes in seven countries were collected. Each dataset consisted of DM exams acquired with systems from four different vendors, multiple radiologists' assessments per exam, and ground truth verified by histopathological analysis or follow-up, yielding a total of 2652 exams (653 malignant) and interpretations by 101 radiologists (28 296 independent interpretations). An AI system analyzed these exams yielding a level of suspicion of cancer present between 1 and 10. The detection performance between the radiologists and the AI system was compared using a noninferiority null hypothesis at a margin of 0.05.
Results: The performance of the AI system was statistically noninferior to that of the average of the 101 radiologists. The AI system had a 0.840 (95% confidence interval [CI] = 0.820 to 0.860) area under the ROC curve and the average of the radiologists was 0.814 (95% CI = 0.787 to 0.841) (difference 95% CI = −0.003 to 0.055). The AI system had an AUC higher than 61.4% of the radiologists.
Conclusions: The evaluated AI system achieved a cancer detection accuracy comparable to an average breast radiologist in this retrospective setting. Although promising, the performance and impact of such a system in a screening setting needs further investigation.

Breast thermography



Breast thermography

- Advantages
  - No ionizing radiation: can be used in young and pregnant women
  - No contact with skin: painless, compatible with breast implants
  - Detects metabolic activity: more aggressive tumor → easier to detect
    - relevant for interval cancers and inflammatory cancers
  - More sensitive than mammo in dense breasts
  - Equipment is cheap and portable
  - Does not require highly-trained personnel
    - neither for image acquisition (like a photo) nor for its interpretation (A.I.)
- Problem
  - Contradictory results for several decades. Radiologists' reluctance.

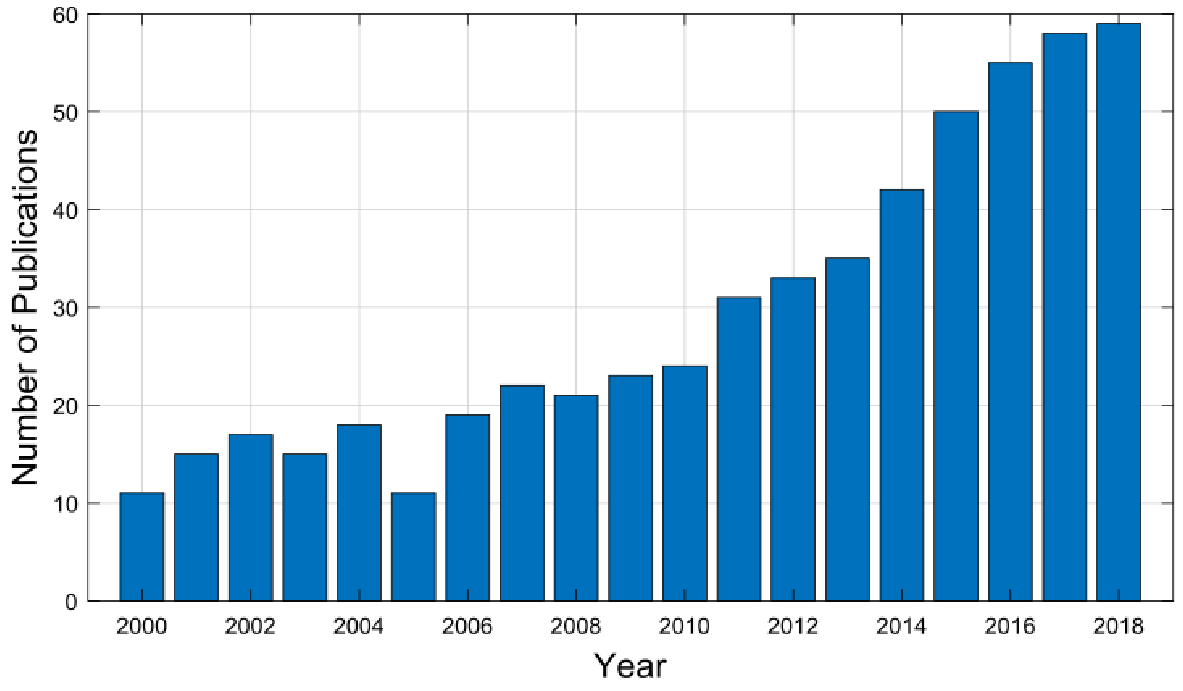
Recent progress in clinical thermography

- Modern infrared cameras; e.g., FLIR A700:
  - spatial resolution: 640 × 480
  - thermal sensitivity: 0.03 °K
  - weight: 820 g
  - price: ~12.000 €

- A.I. for image analysis
  - More reliable
    - Accurate comparison of the temperature of pixels
    - Detection of patterns that scape the naked eye
  - Reproduceable: not subjective

Recent publications about breast thermography

Source: (Gonzalez-Hernandez et al., 2019)



Effectiveness of breast thermography

- Several recent studies *suggest* that it is effective
- Two recent large rigorous studies *prove* that it is effective as an adjunct to mammography:
  - Hellgren et al. [2019]
  - Kakileti et al. [2020]

May 2019, Sweden - Israel

European Radiology (2019) 29:6227–6235
https://doi.org/10.1007/s00330-019-06248-y

BREAST

Check for updates

Does three-dimensional functional infrared imaging improve breast cancer detection based on digital mammography in women with dense breasts?

Roxanna J. Hellgren[1,2] · Ann E. Sundbom[1] · Kamila Czene[2] · David Izhaky[3] · Per Hall[2,4] · Paul W. Dickman[2]

Received: 12 February 2019 / Revised: 30 March 2019 / Accepted: 19 April 2019 / Published online: 21 May 2019

Abstract

Purpose We aimed to estimate the incremental cancer detection rate achieved by adding three-dimensional functional infrared imaging (3DIRI) to digital mammography in women with dense breasts.

Materials and methods In this prospective study conducted between December 2014 and April 2016, 1727 women (median age 56) with percentage volumetric breast density > 6% were recruited at routine screening mammography to undergo additional 3DIRI. The 3DIRI findings were classified as negative or positive. Women with a negative mammography but positive 3DIRI were referred to dynamic contrast-enhanced MRI, whereas all other women underwent routine follow-up based on the mammography finding. Diagnosis of breast cancer was verified by histopathologic examination. The number of women diagnosed with a malignancy formed the basis of our statistical analysis.

Results Mammography detected 7 cancers in 7 women. Of 1692 women with negative mammography, 222 women (13%) had a positive 3DIRI of which 219 underwent MRI. An additional 6 cancers were identified in 5 women, increasing the diagnostic yield from 7 of 1727 (0.41%) to 12 of 1727 (0.69%). The incremental cancer detection rate associated with using 3DIRI to select women for MRI was 5 of 222 (22.5 additional cancers per 1000

Conclusion The use of 3DIRI to select women for an addition
with dense breasts, but at the expense of additional false p
combined examinations. Additional studies are necessary to e

Key Points

• *Use of three-dimensional functional infrared imaging to sele*
the potential to improve breast cancer detection in women with dense breasts.

- Mammo detected 7 cancers in 7 women
- Thermo detected 6 *additional* cancers in 5 women

Oct 2020, India

BREAST CANCER

original reports

Observational Study to Evaluate the Clinical Efficacy of Thermalytix for Detecting Breast Cancer in Symptomatic and Asymptomatic Women

Siva Teja Kakileti, BTech[1]; Himanshu J. Madhu, MS[1]; Lakshmi Krishnan, MDS[1]; Geetha Manjunath, ME, PhD[1]; Sudhakar Sampangi, MBS, MD[2]; and H.V. Ramprakash, MBBS, MD, DMRD[3]

abstract

PURPOSE To evaluate the sensitivity and specificity of Thermalytix, an artificial intelligence–based computer-aided diagnostics (CADx) engine, to detect breast malignancy by comparing the CADx output with the final diagnosis derived using standard screening modalities.

METHODS This multisite observational study included 470 symptomatic and asymptomatic women who presented for a breast health checkup in two centers. Among them, 238 women had symptoms such as breast lump, nipple discharge, or breast pain, and the rest were asymptomatic. All participants underwent a Thermalytix test and one or more standard-of-care tests for breast cancer screening, as recommended by the radiologists. Results from Thermalytix and standard modalities were obtained independently in a blinded fashion for comparison. The ground truth used for analysis (normal or malignant) was the final impression of an expert clinician based on the symptoms and the available reports of standard modalities (mammography, ultrasonography, elastography, biopsy, fine-needle aspiration cytology, and so on).

RESULTS For the 470 women, Thermalytix resulted in a sensitivity of 91.02% (symptomatic, 89.85%; asymptomatic, 100%) and specificity of 82.39% (symptomatic, 69.04%; asymptomatic, 92.41%) in detection of breast malignancy. Thermalytix showed an overall area under the curve (AUC) of 0.90, with an AUC of 0.82 for symptomatic and 0.98 for asymptomatic women.

CONCLUSION High sensitivity and high AUC of Thermalytix in women of all age groups demonstrates the efficacy of the tool for breast cancer screening. Thermalytix, with its automated scoring and image annotations of potential malignancies and vascularity, can assist the clinician in better decision making and improve quality of care in an affordable and radiation-free manner. Thus, we believe Thermalytix is poise[illegible] modality for breast cancer screening.

JCO Global Oncol 6:1472-1480. © 2020 by American Society of Clinical Oncology

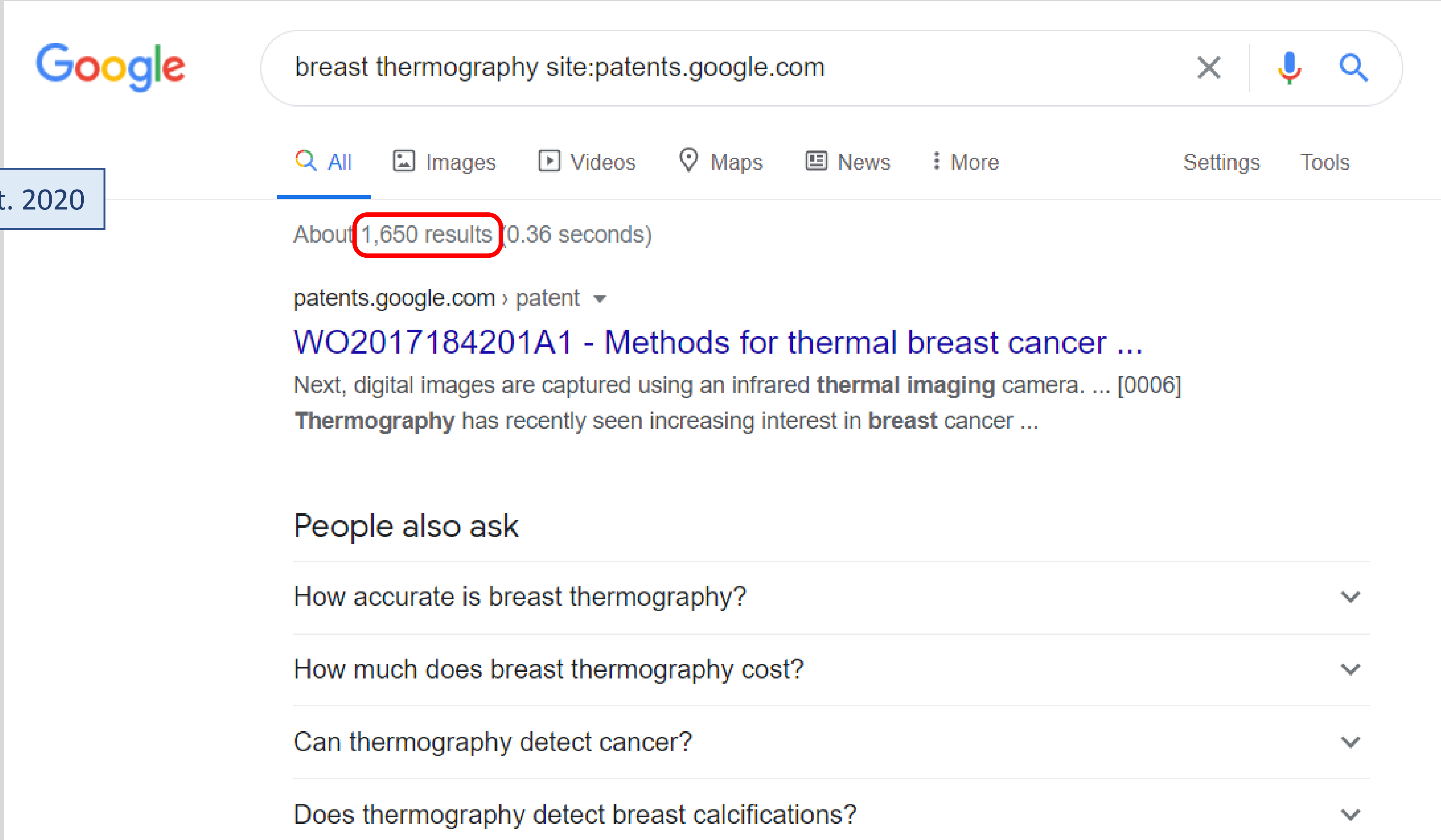
- Uses the Thermalytix software, developed by Niramai

An example of commercial interest in thermo

- Niramai is an Indian start-up, founded in 2016
- Software: Thermalytix, AI-based
  - Sensitivity: 91% (mammo: 87%)
    - In asymptomatic women, 100% (mammo: 50%) [only 4 patients]
    - In tumors < 2 cm, 71% (mammography: 68%)
  - Specificity: 68% (mammo: 94%) [some "false positives" might be true positives]
  - More accurate than mammo in dense breasts
  - Able to detect some non-palpable lesions < 4 mm
- They do screenings in rural areas and (during COVID) at home
- They have raised more then US$ 6 million from investors
- 10 patents

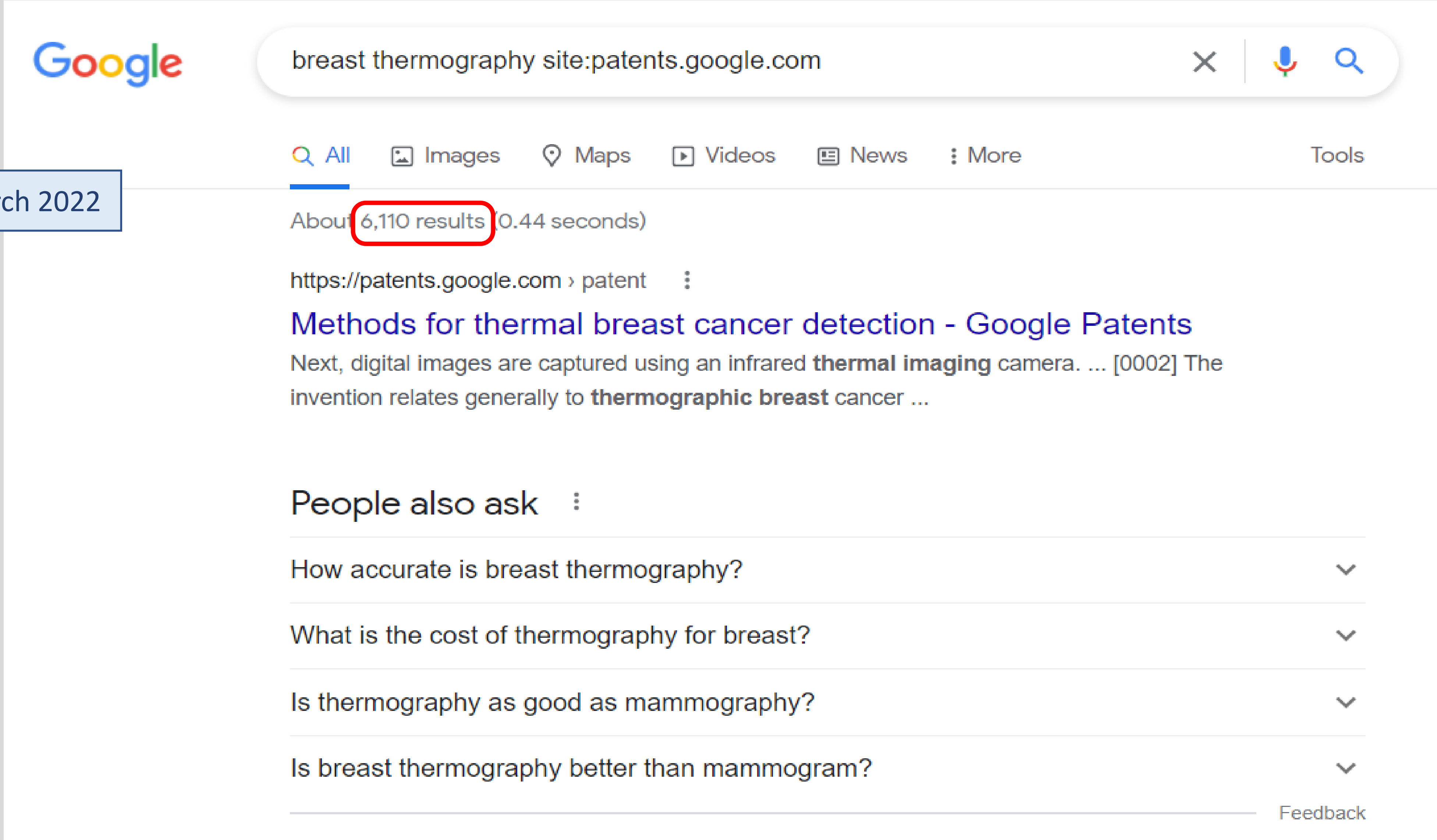
Patents about breast thermography (2020)

Sept. 2020



Patents about breast thermography (2022)

March 2022



Our project

Project data

- Title: “Cost-effective breast cancer screening with mammography, ultrasound and thermography”
- Financed by the Spanish Ministry of Science and Innovation
- From 1-6-2020 to 31-5-2023 (might be extended for 18 months)
- Participants: UNED, Univ. Francisco de Vitoria, two Hospitales
- Researchers:
  - 18 experts in A.I.
  - 4 doctors (3 radiologists)
  - 1 health economist

Goals of the project

- Computer analysis of three types of images
  - Mammo, ultrasound, thermography
  - In interaction with the radiologist
  - Generate written reports

A.I. techniques:
computer vision,
explanation of the results,
natural language generation

- Diagnostic support / Optimal screening policy (cost-effectiveness)
  - Modeling techniques
    - Markov models
    - Discrete event simulation
  - Integration of all the data
    - Several types of images
    - Personal and familiar antecedents
    - In the future: genetic tests

A.I. technique:
probabilistic graphical models

First result of our group

- Thermographies from a public dataset (Brazil)
- Neural network that combines images and clinical data
- Results:
  - sensitivity: 83%
  - specificity: 100%
  - AUC: 0.99
- In spite of the poor quality of the data

Computer Methods and Programs in Biomedicine
Available online 16 March 2021, 106045
In Press, Journal Pre-proof

Multi-input convolutional neural network for breast cancer detection using thermal images and clinical data

Raquel Sánchez-Cauce, Jorge Pérez-Martín, Manuel Luque

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https://doi.org/10.1016/j.cmpb.2021.106045 Get rights and content

Highlights

- A novel multi-input convolutional neural network is proposed to detect breast cancer.
- The model combines thermal images of different views with personal and clinical data.

Clinical study in three (very different) hospitals

- A public hospital and health center near Madrid
  - Within a programme of the regional Government of Madrid
    - systematic screening with biennial mammo, from 50 to 69 y.o.
  - Additional thermo is offered by the mammo technician
  - More than 400 thermographies done so far, ~25 per week
- A private hospital near Madrid
  - Patients usually have private insurance polices
    - opportunistic screening, with mammo + ultrasound; some patients have annual exams
    - younger women in average
  - Additional thermo is offered by a gynecologist
  - More than 50 thermographies done so far, ~8 per week
- A private hospital in Sierra Leone
  - 33 symptomatic women examined with ultrasound in Jan 2022
  - 9 cancers, confirmed by biopsy; median age: 33 y.o.
  - New visit foreseen in Jul 2022, including thermo.

Conclusions

Conclusion: usefulness of thermography

- Use in high-income countries
  - Adjuvant to mammo: more sensitive for dense breasts, safer
  - Much cheaper than MRI, no side effects due to contrast agents
  - Annual examination of high-risk women is possible
    - especially young women with familiar antecedents, and also pregnant women
  - If very sensitive, it might avoid some biopsies (in BIRADS 4A)
- Use in low-income countries
  - Mammo screening of all women is not affordable
  - Infrared cameras are cheaper and cheaper, A.I. can do the diagnosis
  - Screening can be done with thermo+ultrasound
    - reserving mammo, MRI (if available), and biopsy for suspicious cases

Collaboration: what we can offer

- Ultrasound
  - A.I. for analyzing the images (in development)
  - MACbioIDi2 project: training in ultrasound-guided biopsy
- Thermography
  - A protocol for image acquisition
  - An Excel file for collecting the clinical data, with a graphical user interface
  - A Python program for controlling the camera and getting the images
  - A.I. for analyzing the images (in development)
- Mammography
  - Future (?): A.I. for analyzing the images.

Thank you very much for your attention

Contact: fjdiez@dia.uned.es