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To cite this article: Karl Berggren et al 2018 Phys. Med. Biol. 63 215023

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**RECEIVED** 8 April 2018

REVISED 1 October 2018

ACCEPTED FOR PUBLICATION 11 October 2018

PUBLISHED 30 October 2018

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*In vivo* measurement of the effective atomic number of breast skin using spectral mammography

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Keywords: effective atomic number, skin, spectral imaging, mammography, x-ray attenuation

#### Abstract

PAPER

X-ray characteristics of body tissues are of crucial importance for developing and optimizing x-ray imaging techniques, in particular for dosimetry and spectral imaging applications. For breast imaging, the most important tissues are fibro-glandular, adipose and skin tissue. Some work has and is being done to better characterize these tissue types, in particular fibro-glandular and adipose tissue. In the case of breast skin, several recent studies have been published on the average skin thickness, but with regards to x-ray attenuation, the only published data, to the knowledge of the authors, is the elemental composition analysis of Hammerstein *et al* (1979 *Radiology* **130** 485–91).

This work presents an overview of breast skin thickness studies and a measurement of the effective atomic number ( $Z_{eff}$ ) of breast skin using spectral mammography.  $Z_{eff}$ , which together with the density forms the attenuation, is used to validate the work by Hammerstein *et al*, and the dependence of clinical parameters on  $Z_{eff}$  is explored. Measurements were conducted on the skin edge of spectral mammograms using clinical data from a screening population (n = 709).

The weighted average of breast skin thickness reported in studies between 1997 and 2013 was found to be  $1.56 \pm 0.28$  mm. Mean  $Z_{eff}$  was found to be 7.365 (95% CI: 7.364, 7.366) for normal breast skin and 7.441 (95% CI: 7.440, 7.442) for the nipple and areola.  $Z_{eff}$  of normal breast skin is in agreement with Hammerstein *et al*, despite the different methods and larger sample size used. A small but significant increase in  $Z_{eff}$  was found with age, but the increase is too small to be relevant for most applications.

We conclude that normal breast skin is well described by a 1.56 mm skin layer and the elemental composition presented by Hammerstein *et al* (1979 *Radiology* **130** 485–91) and recommend using these characteristics when modelling breast skin.

#### 1. Introduction

Spectral x-ray imaging, also known as energy-resolved x-ray imaging, is a technique whereby the energy dependence of the attenuation of an object is measured as part of the x-ray image. This is commonly done by acquiring multiple images using different x-ray spectra (for example by switching tube voltage) or by using an energy-resolved x-ray detector, such as a multi-bin photon-counting detector. The energy information enables material decomposition; i.e. describing the x-ray response as a combination of a set of reference materials. Without contrast agents, x-ray imaging is dominated by two interaction effects: photoelectric absorption and Compton scattering. The strength of these two interaction effects are in turn determined by two material parameters: material density and effective atomic number. Because of this, material decomposition can only be done into two materials and any additional material will be decomposed as a combination of these two.

Authors	Country	Method	Ν	$t_s (\mathrm{mm})$	$\sigma_s ({ m mm})$
Shi <i>et al</i> (2013)	USA	Breast CT	137	1.44	0.25
Sutradhar and Miller (2013)	USA	Ultrasound	23	1.55	0.25
Wong <i>et al</i> (2011)	Singapore	Ultrasound	32	1.84 <sup>a</sup>	0.33 <sup>a</sup>
Liu <i>et al</i> (2011)	USA	Ultrasound	18	2.05	0.22
Huang <i>et al</i> (2008)	USA	Breast CT	51	1.45	0.30
Ulger <i>et al</i> (2003)	Turkey	FFDM	144	1.58 <sup>a</sup>	0.30 <sup>a</sup>
Warszawski <i>et al</i> (1997)	Germany	Ultrasound	29	1.68	0.31
		Total	434	1.56	0.28

Table 1. Overview of previous studies of breast skin thickness.

<sup>a</sup> Calculated from published values.

Good knowledge regarding the thickness and attenuating properties of an object is important for x-ray system optimization and precise dosimetry. Due to the limitation of only two reference materials in normal material decomposition, it is of even higher importance for spectral imaging since any additional materials will have to be estimated using *a priori* information or complimentary non-x-ray measurements.

In the case of x-ray breast imaging, the breast can be generally categorized into three types of tissue: fibroglandular, adipose and skin tissue. The fibro-glandular tissue, mainly consisting of connective tissue, blood vessels and glandular tissue, is scattered and embedded in adipose tissue, which in turn is surrounded by the skin. Due to the naturally large variation in fibro-glandular and adipose tissue between patients, skin properties are commonly treated as known parameters in material decomposition (Johansson *et al* 2017).

Fibro-glandular and adipose tissue has been relatively well studied in terms of x-ray attenuating properties and the extent of biological variation (Dance and Sechopoulos 2016). In the case of skin, there are a number of studies regarding skin thickness, summarized in table 1, but to our knowledge the x-ray attenuation of skin can only be derived from a single study on the elemental composition of skin tissue by Hammerstein *et al* (1979). The Hammerstein study is the source for the work by the groups of Boone, Dance and Wu that is used for dosimetry and quality control standards around the world (Wu *et al* 1991, 1994, Boone 1999, Dance *et al* 2000, 2011, Dance and Sechopoulos 2016).

In the case of dosimetry in breast imaging, skin and fibro-glandular tissue are the more important constituents. Fibro-glandular tissue is the most radiosensitive part of the breast, which is why x-ray dose is normally measured as the mean glandular dose (MGD). The skin does, however, have a strong influence on the MGD because the top skin layer absorbs the majority of the low-energy x-ray photons and thus a less attenuating skin layer will cause a higher MGD (Huang *et al* 2008).

Skin naturally varies with age, from approximately the age of 40 skin thickness starts decreasing (Diridollou *et al* 2001, Ulger *et al* 2003) at a rate of about 6% per ten years, estimated from Ulger *et al* (2003). In addition, the skin becomes less elastic with age (Diridollou *et al* 2001). Skin thickness seems to be affected by radiation therapy but published research has found both decreased skin thickness (Wong *et al* 2011) as well as increased skin thickness (Warszawski *et al* 1997, Liu *et al* 2011) after radiation therapy.

In this study we investigate the effective atomic number of skin, which together with the density determines the x-ray attenuation of a material. Further, we identify the clinical determinants of the effective atomic number of skin and compare these results to other breast tissues. The investigation is partly a confirmation of the findings by Hammerstein *et al* (1979). The skin density is not measured in this work due to the lack of a complimentary thickness measurement with high enough accuracy at the breast edge.

#### 2. Methods

#### 2.1. Spectral image acquisition

Anonymized clinical data were collected with informed consent as part of the screening program at the South General Hospital, Stockholm, Sweden, and within the Karolinska mammography project for risk prediction of breast cancer (KARMA). A total of 3017 mammograms from 718 patients were acquired using a Philips MicroDose SI spectral mammography system (Philips Mammography Solutions, Kista, Sweden). Information regarding age in years and body mass index (BMI) was collected for each patient. From this data, nine patients were excluded due to implants (89 images) and 30 images were excluded due to failed breast density calculation (Johansson *et al* 2017), resulting in 709 patients and 2898 images included in the analysis. Patients were aged 40–75 years, with a median age of 50 years (357 patients aged 50 or younger and 352 patients older than 50). The age range corresponds to the age bracket that is invited to the screening program and the distribution (figure 1(a)) shows a larger number of younger women and a peak at 74–75 years. BMI was available for all but 38 patients with an average BMI of 25.2, standard deviation 4.3 and range of 17.1–47.2. Breast volume and



volumetric breast density (VBD) was calculated for each image as described by Johansson *et al* (2017). Figure 1(b) shows the compression height distribution for craniocaudal (CC) and mediolateral-oblique (MLO) projections, respectively. The MLO projections had a slightly larger median compression height (57 mm) compared to the CC projections (56 mm).

The spectral mammography system uses a slit-scanning two-bin spectral photon-counting detector, spectrally calibrated to CIRS-equivalent fibro-glandular and adipose material thickness using the method described in Johansson *et al* (2017). Images were acquired using the automatically selected tube voltage of 26, 29, 32, 35 or 38 kVp depending on the compression height. Spectral calibration was performed for each tube voltage. The high-energy threshold was selected to result in approximately equal photon counts in the low- and high-energy photon-count bins for a nominal breast at each tube voltage. All images were binned from the original pixel size of 50 × 50  $\mu$ m<sup>2</sup>–400 × 400  $\mu$ m<sup>2</sup> to reduce noise from the material decomposition. The pectoralis muscle and empty background was automatically masked by the material decomposition software.

#### 2.2. Material decomposition

For materials with low atomic number and no K edge in the imaged spectrum, it is possible to approximately describe the linear attenuation of a material ( $\mu(E)$ ) as a linear combination of two other materials with different effective atomic numbers (Alvarez and Macovski 1976). More specifically, selecting aluminum and polymethyl metacrylate (PMMA) as our reference materials, there exist unique scalar coefficients,  $a_{AI}$  and  $a_{PMMA}$ , such that for an object thickness, t,

$$t \times \mu(E) = t \times (a_{\text{Al}} \times \mu_{\text{Al}}(E) + a_{\text{PMMA}} \times \mu_{\text{PMMA}}(E)).$$
(1)

Letting  $\boldsymbol{\mu} = \begin{bmatrix} \mu_g & \mu_a \end{bmatrix}^t$  and  $\boldsymbol{\mu}_{ref} = \begin{bmatrix} \mu_{Al} & \mu_{PMMA} \end{bmatrix}^t$ , we can convert equation (1) to matrix notation,

$$T_0 \boldsymbol{\mu} = T_0 \boldsymbol{A}_{\text{CIRS}} \boldsymbol{\mu}_{ref} = T_{ref} \boldsymbol{\mu}_{ref}, \qquad (2)$$

where  $T_0$  is a vector of the measured material thicknesses in CIRS fibro-glandular (subscript *g*) and adipose tissue (subscript *a*),  $T_{ref} = \begin{bmatrix} t_{Al} & t_{PMMA} \end{bmatrix}$  is a vector of the equivalent thicknesses of the reference materials and  $A_{CIRS}$  is a 2 × 2 matrix with the conversion coefficients between the two material bases, specified in Johansson *et al* (2017).

For a region with no fibro-glandular or adipose tissue (e.g. the skin line) we can approximate the traversed skin height ( $h_s$ ) from the measured CIRS values by solving

$$\boldsymbol{T}_{0}\boldsymbol{A}_{\mathrm{CIRS}} = \boldsymbol{T}_{ref} = h_{s}\boldsymbol{A}_{s},\tag{3}$$

where  $A_s = \begin{bmatrix} a_{Al,s} & a_{PMMA,s} \end{bmatrix}$  is the attenuation coefficients for skin. Calculating the angle from the origin in Al-PMMA space ( $\theta_{Al-PMMA}$ ) for the case of pure skin we find,

$$\theta_{\text{Al-PMMA}} = \arctan(t_{\text{Al}}/t_{\text{PMMA}}) = \arctan(a_{\text{Al},s}/a_{\text{PMMA},s}). \tag{4}$$

Since the attenuation coefficients of a material is proportional to the density of the material and  $\theta_{Al-PMMA}$  depends on the fraction between the attenuation coefficients,  $\theta_{Al-PMMA}$  is independent of both height and density.

The density of the skin was not measured in this work due to the lack of an accurate-enough thickness measurement required to separate the thickness traversed by the x-rays from the density of the material. It is possible that the thickness of the breast at the skin edge could be measured using e.g. 3D surface imaging (Tyson *et al* 2009, Rodríguez-Ruiz *et al* 2016), but additional equipment or modification of the mammography system would then be necessary. Such a procedure was not within the scope of this study.







Following material decomposition, a number of steps are performed to process data before stratification and analysis, these different steps are described in figure 2.

#### 2.3. Effective atomic number of skin

The effective atomic number ( $Z_{eff}$ ) of a material has a one-to-one relationship with the angle from the origin in Al-PMMA space ( $\theta_{Al-PMMA}$ ) (Johns and Yaffe 1987), illustrated in figure 3(b). By calculating the Al-PMMA angle for various elements in the relevant atomic number range (Z = 5-9) and energy range (15 keV–40 keV) using tabulated data (Berger *et al* 2010), it is possible to fit a polynomial from  $Z_{eff}$  to  $\theta_{Al-PMMA}$ , shown in figure 4. Numerically inverting the polynomial function, we obtain a transfer function from  $\theta_{Al-PMMA}$  to  $Z_{eff}$ .

Using this transfer function, it is possible to convert images into maps of corresponding  $Z_{eff}$ . Skin has a  $Z_{eff}$  similar to fibro-glandular tissue and water (around 7.4) but since most fibro-glandular tissue is embedded in adipose tissue (with an effective atomic number around 6),  $Z_{eff}$  will be much lower for the majority of pixels imaging fibro-glandular tissue. Nevertheless, to reduce influence from fibro-glandular tissue, the central part of the breast is excluded from the analysis, described in the next section.

Because the skin is the most common material with  $Z_{eff}$  above 7, a pixel histogram over  $Z_{eff}$  exhibits a peak corresponding to the skin (see figure 5). If we fit an exponential function to the background distribution of pixels with mixed tissue and subtract it, we obtain a distribution for the skin that is close to Gaussian. The mean of the distribution and uncertainty of the mean can then be estimated by fitting a Gaussian function (using the MAT-LAB fit and confint functions) to the distribution with the mixed background tissue removed. The use of the fit and confint functions allows for any non-Gaussian behavior after background removal to be included in the error estimate.

Calculation of  $Z_{eff}$  for published attenuation values was done by calculating the corresponding Al-PMMA attenuation coefficients using the least square fitting method of (Johansson *et al* 2017).

 $Z_{eff}$  is in general not well defined and different definitions and interpretations are used in different fields. In this paper,  $Z_{eff}$  is treated as a component of the linear attenuation and more specifically as an alternative representation of  $\theta_{Al-PMMA}$ , which is used in other work to describe the linear attenuation (e.g. Johns and Yaffe (1987)). Other reference data or energy ranges may result in different  $Z_{eff}$  and the results presented are only relevant for the mammography x-ray energy range.

#### 2.4. Removal of compressed region

To avoid high-glandularity pixels inside the breast, the central part of the breast was excluded before the histogram analysis described in the previous section. The compressed region was found by first identifying the mode of the



**Figure 5.** Pixel histogram of  $Z_{eff}$  for normal skin. The distribution of  $Z_{eff}$  for skin is surrounded by a tail of mixed tissues that can be removed by fitting an exponential function to the background.

thickness distribution in CIRS-equivalent total thickness ( $t_{mode}$ ), finding the 60th percentile of the top half of the distribution ( $t_{60}$ ) and selecting all pixels within this distance of the mode, i.e. between  $t_{mode} - t_{60}$  and  $t_{mode} + t_{60}$ . A dilation and erosion operation, i.e. hole filling, was then performed on the selected pixels using a 3 pixels radius disk to obtain a continuous compressed region. The choice of the 60th percentile and a 3 pixels radius disk was determined by testing and visually inspecting the resulting identified compressed regions, ensuring that the skin border was not excluded.

#### 2.5. Nipple segmentation

A simple nipple segmentation was implemented to calculate the pixel-to-nipple distance and allow separation of the nipple and areola region from normal breast skin. For the CC view, the tip of the nipple was identified as the average position of the 20 pixels furthest away from the chest wall. For the MLO view, a similar method was used but instead the furthest distance from the chest wall at an angle of  $\pm 14^{\circ}$ , depending on the laterality, was used and the average position of the 20 pixels furthest away was calculated. The method was in general robust except for when the nipple was hidden or folded or a breast had an extreme angle for the view. These cases were, however, rare and the resulting nipple-position estimate was still within 4 cm of the real nipple position, meaning that when segmenting the nipple and areola according by pixel-to-nipple distances smaller than 44 mm, the nipple was still included in the nipple data. Additionally, since these cases were rare, any areola or nipple pixels in the wrong group will only cause minor blurring and were thus still included in the analysis.

#### 2.6. Skin height and data stratification

Using a simple half-circle model for the edge of the breast, i.e. a half-circle with an outer layer corresponding to the skin thickness and a total diameter corresponding to the compression height as shown in figure 3(a), we can



estimate the relevant skin heights calculated from equation (3). For a compression height ( $t_{comp}$ ) and skin layer thickness ( $t_s$ ), the skin height ( $h_s$ ) at the inner skin boundary is

$$h_s(t_s) = 2\sqrt{\left(\frac{t_{comp}}{2}\right)^2 - \left(\frac{t_{comp}}{2} - t_s\right)^2}.$$
(5)

Calculating the equivalent skin height from equation (3) using  $A_s$  calculated from Hammerstein *et al* (1979) we can segment the skin according to approximate skin height. At the outer edge of the breast where  $h_s$  is small there is a large risk for pile up. We therefore excluded points for which the estimated  $h_s$  is lower than  $h_s(0.1t_s)$ . Additionally, a too large  $h_s$  indicates that a point is too far into the breast, and we therefore also excluded points larger than  $h_s(t_s)$ , where  $t_s$  is the calculated mean skin thickness from table 1.

The object thickness, estimated as the equivalent skin height, has a strong impact on the spectral response of the pixel (Johansson *et al* 2017). Therefore, when investigating the skin thickness dependence on clinical parameters, the object thickness needs to be controlled for. The object thickness was controlled for by stratifying the equivalent skin height into 4 mm bins, which were large enough to allow good statistics in each strata and small enough to resolve the skin-height dependence on  $Z_{eff}$ . Clinical parameters such as age, BMI and VBD was investigated by further stratifying the pixel data according to patient information and performing the analysis presented in section 2.3 for each strata.

#### 3. Results

The impact of the nipple on  $Z_{eff}$  is shown in figure 6(a), which shows a 2D histogram of pixels, binned by  $Z_{eff}$  and pixel-to-nipple distance. The 2D histogram shows two distinct peaks depending on the pixel-to-nipple distance. The peak closest to the nipple, corresponding to the nipple and areola, shows a slightly higher  $Z_{eff}$  than the second peak, which corresponds to normal skin. Stratifying the pixel data into two groups: pixel-to-nipple distance larger or smaller than 44 mm, and excluding data outside the limits defined in section 2.6, we obtain the two distributions shown in figure 6(b). The upper limit on skin height was not used on the nipple data due to the more complex shape of the nipple. Fitting the data to find the peak centers we find the  $Z_{eff}$  for skin to be 7.365 and  $Z_{eff}$  for the nipple and areola to be 7.441, listed with 95% confidence interval errors for the mean of the distributions in table 2. Table 2 also shows  $Z_{eff}$  for published attenuation skin and fibro-glandular measurements, calculated using the transfer function of figure 4 and calculated attenuation coefficients from Johansson *et al* (2017).

Figure 7(a) shows a 2D histogram of normal skin pixels (pixel-to-nipple distance larger than 44 mm) binned by calculated skin height from equation (3) and compression height. The limits for inclusion, defined in section 2.6, are shown as dashed white lines.

Stratifying the pixel data by age, pixel-to-nipple distance and calculated skin height, the center of the distribution was measured for each stratum and plotted as a function of skin height (figure 7(b)). For normal skin,  $Z_{eff}$  has a peak around 7.38 for patients aged 50 years or younger, and 7.39 for women older than 50 years. For the nipple and areola,  $Z_{eff}$  peaks at a higher skin height with the highest  $Z_{eff}$  being approximately 7.46 for women aged 50 years or younger and 7.45 for women older than 50 years. For normal skin, there was a significant difference between the age groups (p < 0.05, comparison of confidence intervals for all stratified points). In addition to skin height and age, no additional dependence on BMI, breast volume, VBD or compression force was found,

Tissue	Source	Method	$Z_{eff}$ (95% CI)
Skin	This work	SI	7.365 (7.364,7.366)
Nipple and areola	This work	SI	7.441 (7.440,7.442)
Skin	Hammerstein et al (1979)	EC	7.36 <sup>a</sup>
Fibro-glandular	Fredenberg et al (2018)	SI	7.446 (7.390,7.502)
Fibro-glandular	Johns and Yaffe (1987)	SP	7.37 [7.34,7.38] <sup>b</sup>
Fibro-glandular	Hammerstein et al (1979)	EC	7.31 [7.12,7.47] <sup>c</sup>

**Table 2.** Measured  $Z_{eff}$  of skin and nipple compared to  $Z_{eff}$  calculated from other references and for fibro-glandular tissue. Method is indicated as elemental composition analysis (EC), spectral imaging (SI) or spectroscopy (SP).

<sup>a</sup> No error estimate available.

<sup>b</sup> Calculated from range of fitted coefficients using NIST data (Berger et al 2010).

<sup>c</sup> Calculated from range of measured elemental compositions.



**Figure 7.** (a) 2D histogram of pixels binned by skin height and compression height. Limits for inclusions from section 2.6 are shown. (b) The peaks of the histogram analysis for each  $Z_{eff}$  strata as a function of skin height, grouped by age and region. Error bars indicate 95% CI for the mean of the fitted Gaussian.

i.e. the corresponding curves to figure 7(b) when stratifying according to these parameters showed overlapping curves or had overlapping confidence intervals. BMI and breast volume are correlated to compression height and skin height but it is important to control for skin height since it affects the spectral response (Johansson *et al* 2017).

#### 4. Discussion and conclusion

The measured  $Z_{eff}$  of normal skin, 7.365 (7.364,7.366), is close to the  $Z_{eff}$  corresponding to Hammerstein *et al* (1979), 7.36, despite different methods and populations were used. This agreement confirms that even though there is a lack of skin attenuation measurements, the Hammerstein measurement is likely a good reference attenuation. The Hammerstein measurement does, however, lack an error estimate for the skin measurement and assuming a variation similar to the variation stated for fibro-glandular tissue in Hammerstein this measurement provides a substantial reduction in the error range for this component of the attenuation.

The nipple and areola seem to have a higher  $Z_{eff}$  than normal skin, however, when grouping  $Z_{eff}$  by skin height (figure 7(b)), there is a strong influence from the larger skin heights, meaning that these pixels are probably close to 100% fibro-glandular tissue concentrated close to the nipple. This explanation is further supported by the  $Z_{eff}$  for fibro-glandular tissue measured by Fredenberg *et al* (2018), which is close to the same as this peak (table 2). For the lower skin heights (around 10 mm),  $Z_{eff}$  for the nipple and areola, and skin coincides. This effect is likely due to the presence of pile-up in the detector at the lowest skin heights causing a shift in the spectral response.

For normal skin, we find a significant difference of 0.01 in  $Z_{eff}$  for women 50 years or younger in comparison to women older than 50 years. This difference is, however, too small to be relevant for most applications in dosimetry and spectral imaging. No additional dependence on BMI or VBD was found.

The spread of fibro-glandular  $Z_{eff}$  calculated from published data (table 2) overlaps with the  $Z_{eff}$  measured by us and calculated from Hammerstein *et al* (1979). Based on our results, comparing normal breast skin to that of the nipple and areola, and the higher  $Z_{eff}$  measured by Fredenberg *et al* (2018) using the same mammography system as used in this study, we would, however, conclude that fibro-glandular tissue has a slightly higher atomic number than that of normal skin. The exact reason for this is not known but a possibility is the presence of some oil and fats in the skin or intervowen with the dermis.

It should be noted that other sources than (Hammerstein *et al* 1979) exists for skin attenuation and composition, e.g. Woodard and White (1986). Nevertheless, Hammerstein *et al* (1979) is, to our knowledge, the only publication exclusively covering breast skin, and it can not be concluded that skin properties does not vary between different parts of the body. Therefore, Hammerstein *et al* (1979) appears to be the only publication relevant to this study.

In conclusion, when modeling the breast, we recommend using a skin layer thickness of 1.56 mm, together with the elemental composition calculated by Hammerstein *et al* (1979). For higher precision, age is an important factor with the primary effect being lower skin thickness and a secondary effect being a slightly increased  $Z_{eff}$ . Compared to fibro-glandular tissue, normal skin has a slightly lower  $Z_{eff}$ .

#### Acknowledgments

The clinical data used for this study were collected within the Karolinska mammography project for risk prediction of breast cancer (KARMA), initiated by co-author Prof Per Hall, Karolinska Institute, Stockholm, Sweden, and funded by Märit and Hans Rausing's Initiative Against Breast Cancer. Special thanks are extended to Dr Ann Sundbom and the staff at Södersjukhuset, Stockholm, Sweden for collecting the clinical data. Karl Berggren is funded by the Swedish Research Council.

#### **Conflict of interest**

Karl Berggren and Erik Fredenberg were employed by Philips AB at the time of the study. Matthew G Wallis has received research grants from Philips.

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