Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)

FINAL Opinion on the safety of breast implants in relation to anaplastic large cell lymphoma

The SCHEER adopted this Opinion by written procedure on 26 March 2021

ABSTRACT

The SCHEER was requested by the European Commission to provide a scientific opinion on the safety of breast implants in relation to anaplastic large cell lymphoma (ALCL).

Literature searches were carried out using PubMed and Find-eR. The publication period covered was from 1 September 2016 to 31 August 2019, and an additional search was performed early in 2020 covering the period from 1 September 2019 to 30 April 2020. In addition, relevant sources and literature beyond this period was considered as well. After excluding all irrelevant papers and duplicate papers, a total of 605 papers remained and were evaluated for this Scientific Opinion.

BIA-ALCL is the occurrence of ALCL adjacent to a breast implant. Diagnosis of BIA-ALCL is achieved by analysis of seroma fluid or if a mass, core needle, incisional or excisional tissue biopsy. Radical en bloc surgical resection (i.e. implant including seroma and intact capsule) with safe margins, including healthy tissue, is recommended as the standard of care treatment, with a very good prognosis. The incidence of BIA-ALCL is considered low, varies by implant type, and is mainly associated with macro-textured implants. However, estimates of incidence have significant limitations related to the frequent use of ad hoc reporting of cases compared with systematic reporting, and the use of sales data provided by manufacturers. Overall SCHEER considers that there is a moderate weight of evidence for a causal relationship between textured breast implants and ALCL, particularly in relation to implants with an intermediate to high surface roughness.

At this point it should be noted that i) there are several types of textured implants ii) surface textures of breast implants are not all manufactured in the same way, and iii) implants with diverse surface textures may also present different benefits. The magnitude of the risk per type of textured implant is difficult to establish due to the low incidence of the BIA-ALCL. Even with macro-textured implants, BIA-ALCL has a very low incidence. Therefore, risk assessments per implant type are needed. Furthermore, the risk should be weighed against the benefits. There is also a need for an unambiguous, clinically validated classification system for breast implants including more parameters than just "surface roughness". A history of textured breast implants/expanders appears to be necessary but not sufficient for the development of BIA-ALCL.

The pathogenic mechanisms of the induction of BIA - ALCL are not well understood; current hypotheses include genetic predisposition, bacterial contamination resulting in chronic inflammation, shell shedding of particulates resulting in chronic inflammation, shell surface characteristics leading to friction resulting in inflammation, and implant associated reactive compounds. The disease latency varies between a few to 20 or even more years. There are several alternatives to breast implants that involve plastic surgery techniques, either using autologous flap tissue or autologous fat transfer. However, patients' characteristics may limit the application of these techniques.

There is a need for further research to better understand the aetiology and pathogenesis of BIA-ALCL. Reporting of new BIA-ALCL cases by the relevant registries is also of major importance to obtain a better estimate of the risk of BIA-ALCL for patients with a breast implant.

Keywords: breast implants, anaplastic large cell lymphoma, cancer, BIA-ALCL

Opinion to be cited as: SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Scientific Opinion on the safety of breast implants in relation to anaplastic large cell lymphoma, 26 March 2021.

ACKNOWLEDGMENTS

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SCHEER

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PDF
ISBN
ISSN
doi

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1. MANDATE FROM THE EU COMMISSION SERVICES[1]

1.1 Background

Breast implant associated anaplastic large cell lymphoma (BIA-ALCL) is a rare sub type of non-Hodgkin's lymphoma. In 2016, World Health Organisation (WHO) defined specific diagnostic criteria for this rare disease.

BIA-ALCL is not a cancer of the breast tissue and the prognosis of the disease is generally favourable. The exact number of cases remains difficult to determine due to significant limitations in worldwide reporting. In addition, due to lack of global breast implant sales data, it is difficult to put this number into context. It has been estimated that 5 to 10 million women have received breast implants worldwide, with some estimations going as high as 35 million.[2] The U.S. Food and Drug Administration received in total 660 BIA-ALCL related medical devices reports (MDRs) until September 2018. After eliminating the duplicates, a total of 457 unique MDRs for BIA-ALCL were identified. It is acknowledged by FDA that although the MDR system is a valuable source of information it may contain incomplete, inaccurate, untimely, unverified, or biased data[3]. In January 2019, the Australian Therapeutic Goods Administration reported 78 confirmed cases of anaplastic large cell lymphoma in Australian patients[4]. In April 2019, Health Canada reported 28 confirmed Canadian cases of BIA-ALCL[5]. At EU level by March 2019, 243 cases were reported to the EU competent Authorities, out of which 211 were confirmed cases of BIA-ALCL. Of the confirmed cases, 166 were reported to be linked to textured implants at the time of diagnosis. The surface texture of the implants in the other reports remains unknown.

A number of competing theories are available to explain the causation of BIA-ALCL, such as bacterial contamination and biofilm formation leading to inflammatory and immune response; surface of the shell leading to chronic low-level inflammatory reaction; the shell shedding micro-particles that trigger an immune response; specific genetic reaction to implants; compounded chronic inflammatory reaction. As the pathogenesis of the disease has not yet been established and may be either on the implant side, e.g. low level of chronic inflammation induced by the shell, or on the surgical intervention side, e.g., bacterial contamination, or on the characteristics of the implant recipient, e.g., genetic characteristics of the patient, the best ways to address the matter is not yet identified.

Internationally, there have been some reports of BIA-ALCL associated with smooth breast implants at the time of diagnosis, however, the previous implant histories for these reports are unknown[6]. The predominance of the reports of BIA-ALCL have been reported in patients with textured implants at the time of diagnosis.

When addressing questions about the continued availability of textured implants, an important consideration is that surface textures of breast implants are not all manufactured in the same way. Some literature studies report that they appear to be

[1] Chapter 1 is presenting the mandate received by SCHEER from the European Commission, DG GROW, and has been published on the website in summer 2019
[2] https://www.ncbi.nlm.nih.gov/pubmed/29036945
[3] https://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/breastimplants/ucm239995.htm
[4] https://www.tga.gov.au/alert/breast-implants-and-anaplastic-large-cell-lymphoma
[5] http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/69052a-eng.php
[6] https://www.fda.gov/medical-devices/breast-implants/breast-implant-associated-anaplastic-large-cell-lymphoma-bia-alcl

associated with different levels of risk. Anatomically shaped implants are commonly textured in some way. Clinically, the choice between round and anatomically shaped implants is determined by anatomic aspects of the chest wall, and the patient's preferred aesthetic outcome.

The use of textured implants is preferred in most European countries to prevent the undesirable movement or rotation of the implants and are considered by some clinicians to reduce the risk of capsular contracture, which is often cited as the most common cause of revision in smooth implants. Movement or rotation is particularly undesired with anatomical implants, as this could result in an unacceptable aesthetic outcome. Additionally, there are a limited number of alternatives to the use of textured implants, and the alternatives are also associated with their own risks and contraindications. Currently there is no international consensus on a single classification system for surface texture. A harmonised classification system would need to be established in order to collate scientific evidence on the risks and benefits of each type.

The Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) advised in October 2017[7] that there was insufficient scientific information available to establish a methodologically robust risk assessment to investigate a possible association of breast implants with ALCL development. However, it was recommended that a more in-depth evaluation be conducted on the possible association of breast implants with the development of ALCL. A significant body of scientific information was published in the meantime.

The rate of diagnosis of BIA-ALCL has rising over the past years. The information to date suggests that women with breast implants may have a very low but increased risk of developing ALCL while the rarity of the disease makes it difficult to establish a definite causal relationship. Given the increase in confirmed and unconfirmed reports of BIA-ALCL, we may be confronted with an emerging health risk and SCHEER should provide an opinion on the safety of breast implants in relation to anaplastic large cell lymphoma.

When providing the opinion, given the rarity of the disease, the participation of experts and stakeholders at a global level is deemed necessary. This includes contacts with breast implant registries at national and international level whenever possible. For the global context, the Committee will make use of the SCHEER Rules of Procedure.

1.2 Terms of Reference

In the light of the above considerations, the Scientific Committee on Health Environmental and Emerging Risks (SCHEER) is requested to provide a scientific opinion on 'The safety of breast implants in relation to anaplastic large cell lymphoma'.

In particular, the SCHEER is asked:

1. To briefly describe what are the specific clinical indications and uses for various types of breast implants.
2. To briefly describe what BIA-ALCL is, what the specific diagnostic criteria are, what the state-of-the-art treatment is, and what the prognosis of the disease is. In relation to ALCL the state of the art of good clinical practices for the follow-up of women with breast implants should also be described.
3. To indicate what is the state-of-the-art knowledge in terms of incidence of BIA-ALCL.

[7] https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_007.pdf

4. To describe the state-of-the-art knowledge regarding the characterisation and classification of textures of the breast implant shells (e.g. is classification possible?).
5. To indicate whether a causal relationship between breast implants and ALCL can be established based on the evidence available to date. To discuss what may be the potential and if possible, the most plausible pathogenesis mechanisms. To evaluate the available information on incubation time, and in relation to this, discuss the importance of knowledge on previous implants history of women developing BIA-ALCL. To evaluate if preventive explantation is warranted in case reasons for concern related to breast implants or specific subcategories of breast implants are identified.
6. To describe the factors that may determine the risk of BIA-ALCL. To identify criteria regarding the characterisation of breast implants in relation to ALCL and control measures to reduce the identified risk.
7. In the context of ALCL to briefly describe alternatives to breast implants.
8. Where relevant to identify needs for further research and the best ways to collect the missing data regarding breast implants and ALCL.

The considerations should cover both reconstructive and augmentation use of breast implants.

2. CONCLUSIONS

Following the request received from the European Commission, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) performed a literature search to gather new scientific information related to a possible association between breast implants and anaplastic large cell lymphoma (ALCL), so-called Breast Implant Associated ALCL (BIA-ALCL).

The scientific information retrieved from the literature search shows there has been a continuous increase in the number of confirmed cases. This can be attributed to a variety of reasons, e.g., raised awareness of the disease leading to more frequent testing and detection, improved diagnosis due to clear diagnostic criteria, and/or a true rise in incidence. The occurrence of BIA-ALCL is uncommon, i.e., it has a very low incidence. Overall, there is a moderate[8] weight of evidence for a causal relationship between textured breast implants and BIA-ALCL.

The common factor underlying the occurrence of BIA-ALCL is the presence of a textured breast implant. This suggests that a feature of these particular devices plays a key role, directly or indirectly. A second key aspect is the T cell origin of BIA-ALCL, cells that normally detect pathogens and aid in their removal from the body. These two factors highlight potential mechanisms of disease pathogenesis. In total, there are five proposed hypotheses regarding the pathogenesis of BIA-ALCL: genetic predisposition, bacterial contamination resulting in chronic inflammation, shell shedding of particulates resulting in chronic inflammation, shell surface characteristics leading to friction resulting in chronic inflammation, and potential exposure to implant-associated reactive compounds. None of the proposed hypotheses are necessarily mutually exclusive whereby chronic inflammation, no matter what causes it, might drive lymphomagenesis by multiple pathways. In this manner, the chronically stimulated T cells would be assumed to acquire malignancy-promoting mutations. At the time of writing this report, there is insufficient

[8] Moderate weight of evidence: good evidence from a primary line of evidence but evidence from several other lines is missing (important data gaps) (see SCHEER WoE, 2018).

scientific evidence available to rule out any of these potential mechanisms of disease pathogenesis. However, based on the underlying prominence of chronic inflammation, it is highly likely that this process plays a central role in the development of BIA-ALCL.

A full implant history can be difficult to obtain in patients who have had multiple implants. However, when the breast implant surface was identified in BIA-ALCL cases, they were in almost all cases identified as textured. There has been only 1 confirmed case of BIA-ALCL in a patient with a known implant history in which only smooth implants were used. As far as the manufacturer for textured implants was known most cases were found for the Biocell implant (textured by salt loss technique), while for PU coated breast implants BIA-ALCL cases were mainly associated with Silimed implant. Incidences for other manufacturers were much lower. Based on these data SCHEER considers that there is a moderate weight of evidence for a causal relationship between textured breast implants and BIA-ALCL, particularly in relation to implants with an intermediate to high surface roughness.

At this point it should be noted that i) there are several types of textured implants ii) surface textures of breast implants are not all manufactured in the same way, and iii) implants with diverse surface textures may also present different benefits. The magnitude of the risk per type of textured implant is difficult to establish due to the low incidence of the BIA-ALCL. Even with macro-textured implants, BIA-ALCL has a very low incidence. Therefore, risk assessments per implant type are needed. Furthermore, the risk should be weighed against the benefits. There is also a need for an unambiguous, clinically validated classification system for breast implants including more parameters than just "surface roughness". A history of textured breast implants/expanders appears to be necessary but not sufficient for the development of BIA-ALCL.

Alternatives to the use of breast implants include surgical techniques using autologous tissue that can be performed by various flap techniques (whole tissue transfers) or by autologous fat transplantation. The latter may need multiple procedures before an acceptable result is obtained. However, patients' characteristics may limit the application of these techniques.

2.1 Answers to the Terms of References

The answers to the ***Terms of References*** are presented below:

1. ***To briefly describe what are the specific clinical indications and uses for various types of breast implants***

The specific clinical indications and uses of various types of breast implants are either reconstructive, primarily for the loss of breast volume or secondary to a surgical procedure, or aesthetic for the correction of breast anomalies or a volume increase and shape improvement. Clinical indications for the use of a specific type of breast implant should depend on a consultation between clinician and patient to allow informed decision making to take place with regards to the choice of an appropriate breast implant. For breast reconstruction, a shared consultation with a multidisciplinary healthcare team including a pathologist, oncologist, surgeon, breast care nurse, etc. should be held with the patient to allow informed decision making to take place with regards to the breast reconstruction procedure as well as the choice of implant. For both aesthetic and reconstructive surgery all aspects of breast implants should be evaluated and discussed with the patient, expressly covering advantages, disadvantages, follow-up procedures and risk factors.

2. ***To briefly describe what BIA-ALCL is, what the specific diagnostic criteria are, what the state-of-the-art treatment is, and what the prognosis of the disease is. In relation to ALCL the state of the art of good clinical practices for the follow-up of women with breast implants should also be described***

BIA-ALCL is the occurrence of a lymphoid malignancy adjacent to a breast implant. It often occurs within the capsule surrounding the implant and can manifest as a spectrum of presentation of one disease, from a primary fluid effusion containing tumour cells within the implant capsule, to a solid tumour mass with or without lymph node and/or organ metastasis. Diagnosis of BIA-ALCL is achieved by analysis of seroma fluid or if a mass, core needle, incisional or excisional tissue biopsy. Appropriate extensive sampling of the capsule post-capsulectomy is required when evaluating it for capsular invasion to determine disease free margins. It has been suggested that at least twelve capsule samples should be assessed for capsular invasion before BIA-ALCL is ruled out. Therapeutic implant removal with a radical *en bloc* surgical resection, including total capsulectomy and any mass or involved lymph nodes with safe oncologic margins of healthy tissue, is recommended as the state-of-the-art treatment, with a very good prognosis when the disease is promptly diagnosed at early stages.

3. ***To indicate what is the state-of-the-art knowledge in terms of incidence of BIA-ALCL***

The incidence of BIA-ALCL is considered low, varies by implant type, and is associated with textured implants. The estimation of the lifetime incidence of BIA-ALCL in women with implants has increased as presented in initial reports from 1 per million, to current highest estimates of approximately 1 per 3000 women with a breast implant in Australia and the Netherlands. However, estimates of incidence have significant limitations related to the frequent use of *ad hoc* reporting of cases compared to systematic reporting, and the difficulty of determining an accurate denominator necessitating the use of sales data provided by manufacturers. In addition, the increase in awareness of the occurrence of BIA-ALCL, and the establishment of uniform diagnostic criteria has also contributed to a rise in the rate of BIA-ALCL diagnosis.

4. ***To describe the state-of-the-art knowledge regarding the characterisation and classification of textures of the breast implant shells (e.g. is classification possible?)***

Surface textures of breast implants are not all manufactured in the same way. Breast implant surface textures are achieved by several different methods, the most commonly used are salt loss, gas diffusion, imprint stamping and polyurethane foam coating. To date, none of the proposed surface texture classifications reported have been validated in a clinical study to determine which classification best predicts the risk of BIA-ALCL.

Surface roughness can be described best by using the ISO classification of roughness being: Smooth (<10µm) Micro (10-50µm) or Macro (>50µm) based on the implant average surface roughness (ISO 14607:2018). It should be noted that ISO 14607:2018 is currently under revision as this classification, based only on surface roughness, was considered too limited as was also concluded in the TGA 2019 report.

5. ***To indicate whether a causal relationship between breast implants and ALCL can be established based on the evidence available to date. To discuss what may be the potential and, if possible, the most plausible pathogenesis mechanisms. To evaluate the available information on incubation time, and in relation to this, discuss the importance of knowledge on previous implants history of women developing BIA-ALCL. To evaluate if preventive explantation is warranted in case reasons for concern related to breast implants or specific subcategories of breast implants are identified***

A full implant history can be difficult to obtain in patients who have had multiple implants. However, when the breast implant surface was identified in BIA-ALCL cases, they were in almost all cases identified as textured. There has only been 1 confirmed case of BIA-ALCL in a patient with a known implant history in who only smooth implants were used. As far as the manufacturer for textured implants was known, most cases were found for the Biocell implant (textured by the salt loss technique), while for PU coated breast implants, BIA-ALCL cases were mainly associated with the Silimed implant. Cases for other manufacturers were much lower. Based on these data, SCHEER considers that there is a moderate weight of evidence for a causal relationship between textured breast implants and BIA-ALCL, particularly in relation to implants with an intermediate to high surface roughness.

It should be noted that i) there are several types of textured implants ii) surface textures of breast implants are not all manufactured in the same way, and iii) implants with diverse surface textures may also have different benefits for the patient. The magnitude of the risk per type of textured implant is difficult to establish due to the low incidence of BIA-ALCL. Even with macro-textured implants, BIA-ALCL has a very low incidence. Therefore, risk assessments per implant type are needed. Furthermore, the risk should be weighed against the benefits. There is also a need for an unambiguous, clinically validated classification system for breast implants including parameters beyond "surface roughness". A history of textured breast implants/expanders appears to be necessary but not sufficient for the development of BIA-ALCL. Another risk factor for BIA-ALCL may arise as a consequence of the manufacturing process for certain types of PU coating.

The weight of evidence is considered "moderate" as the pathogenic mechanisms have not been fully elucidated. Current hypotheses include genetic predisposition, bacterial contamination resulting in chronic inflammation, shell shedding of particles resulting in chronic inflammation, shell surface characteristics leading to friction resulting in inflammation, and implant associated reactive compounds. None of the proposed hypotheses are necessarily mutually exclusive whereby chronic inflammation, no matter what causes it, might drive lymphomagenesis by multiple pathways. In this manner, the chronically stimulated T cells may be prone to acquire malignancy-promoting mutations, possibly also as a consequence of exposure to mutagenic metabolites of aryl hydrocarbons.

Disease latency varies between a few and up to 20 or more years. The previous implant history of those developing BIA-ALCL is of crucial importance in relation to the role of the surface texture of the implant. Preventive explantation can be performed in cases of high risk (i.e., removal of both implants when BIA-ALCL is diagnosed unilaterally). In the case of a unilaterally diagnosed BIA-ALCL patient, a contralateral prophylactic implant removal with total capsulectomy is recommended as there have been several cases of bilateral disease reported worldwide to date. In non-symptomatic patients with textured implants or implants with unknown surface, implant removal with or without total capsulectomy for the single purpose of BIA-ALCL prophylaxis is not recommended due to the very low incidence of this disease. However, some patients may request removal of the implant and capsule, particularly patients with manufacturer-recalled implants or the reported high-risk breast implants (e.g., certain polyurethane or salt-loss macrotextured implants etc.). Any surgery should follow an informed consent discussion on the related surgical risks and that a risk of BIA-ALCL may still persist following surgery. In symptomatic patients with textured implants in place, implant removal with total capsulectomy is recommended.

6. To describe the factors that may determine the risk of BIA-ALCL. To identify criteria regarding the characterisation of breast implants in relation to ALCL and control measures to reduce the identified risk

The factor that determines the risk of BIA-ALCL is the presence of an implant with a textured or rough surface, *i.e.,* not a smooth surface. In addition, a certain type of PU implant manufacturing process might also be a risk factor for BIA-ALCL. However, it is not yet possible to determine the relative risk for BIA-ALCL and various surface characteristics. Therefore, there is a need for an unambiguous, clinically validated classification system for breast implants including parameters beyond "surface roughness". A history of textured breast implants/expanders appears to be necessary but is not sufficient for the development of BIA-ALCL. Contributing factors include, but are not limited to, a genetic predisposition to cancer and the presence of chronic inflammation, which may drive lymphomagenesis by multiple pathways.

The most important criterion that is associated with the occurrence of BIA-ALCL is the type of surface characterising the implant. The full aetiology of BIA-ALCL is not yet understood, although an appropriate control measure to reduce the identified risk, is to limit the use of macro-textured implants, notably those prepared by the salt loss technique, and those with a certain type of PU coating.

7. In the context of ALCL to briefly describe alternatives to breast implants.

There are several alternatives to breast implants that involve plastic surgery techniques, either using autologous flap tissue or autologous fat transfer. The latter may need multiple procedures before an acceptable result is obtained. However, patient characteristics may limit the application of these techniques which are rarely used outside of reconstructive surgery practice.

8. Where relevant to identify needs for further research and the best ways to collect the missing data regarding breast implants and ALCL.

There is a need to conduct further research to better understand the aetiology and pathogenesis of BIA-ALCL. Reporting of new BIA-ALCL cases by the relevant registries is also of major importance to obtain a better estimate of the risk of BIA-ALCL for people with a breast implant in place. A number of research needs are presented below:

- Breast implant registries should be established and be mandatory, and include a minimum harmonised dataset of device characteristics, which is globally uniform, in order to optimise global post-market surveillance of breast implants. This should include the UDI (Unique Device Identification) or reference/serial number to provide structured denominator data for risk calculations. Funding of these registries should be independent of industry, and it is recommended that General Data Protection Regulation should provide a means to allow data connection between data sources.
- The incidence of BIA-ALCL should be monitored with systematic data collection in registries (e.g., for breast surgery or pathology diagnosis) in preference to *ad hoc* reporting of case findings.
- A universal grading system for implant surfaces and surface characterisation should be further explored. Research should be conducted to identify surface characteristics that contribute to BIA-ALCL development. This should include research on the role of surface characteristics in relation to particle shedding, and surface characterisation related to chemical moieties for their carcinogenic potential. Implants exposed to an *in vivo* environment (i.e., explants) should especially be evaluated for surface characteristics.

- The role of the aforementioned implant qualities in inducing chronic inflammation should be investigated including the possible roles of particle shedding, bacterial contamination, and chemical moieties on the surface of breast implants.
- Further research should be conducted into the aetiology of BIA-ALCL regarding the potential contribution of genetic predisposition.

3. MINORITY OPINION

None

4. INTRODUCTION

The Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) in October 2017 advised the EC[9], that there was insufficient scientific information available to establish a methodologically robust risk assessment regarding a possible association between breast implants and anaplastic large cell lymphoma (ALCL) development. However, it was recommended that a more in-depth evaluation be conducted on the possible association of breast implants with the development of ALCL. Since 2017, a significant body of scientific information has been published which offers the possibility of a more in-depth analysis of breast implant associated anaplastic large cell lymphoma (BIA-ALCL).

All breast implant associated complications (i.e., seroma, capsular contracture, double capsule, BIA-ALCL) appear to be related not only to the materials used to manufacture the implants but also to how this interacts with the host. Every breast implant has a distinctive 3D surface architecture, which elicits a unique host response at the cellular level that needs to be further studied to establish cellular response and biocompatibility. Eventually this may be elaborated into a unique classification that takes into consideration the level of host response to the physical characteristics of the surface (Munhoz *et al.*, 2019).

This section provides up-to-date information on BIA-ALCL and breast implants, and possible alternatives for breast reconstruction/augmentation.

4.1 Use of breast implants

Clinical indications for the use of breast implants are either reconstructive or aesthetic. Reconstructive surgery comprises approximately 25% of cases with the remaining 75% conducted for aesthetic reasons, or may be evenly distributed depending on the geographical region as indicated by a survey of plastic surgeons (Heidekrueger *et al.*, 2018, Loch- Wilkinson *et al.,* 2020).

Examples of implant use for reconstructive surgery include restoration of a breast mount following mastectomy (i.e., removal of the breast), treatment for breast cancer, or to reduce breast cancer risk in women who are carriers of a *BRCA* gene mutation. Breast implants may also be employed to correct breast anomalies, such as women with asymmetrically developed breasts (anisomastia, Poland syndrome, tuberous breast), or completely undeveloped breasts (amastia). Finally, breast reconstruction with implants can also be performed following accidental or iatrogenic trauma sustained during paediatric surgery or radiotherapy, or for male to female gender reassignment surgery. A

[9] https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_007.pdf

recent patient survey showed that after breast cancer therapy, quality of life was higher for women having undergone breast reconstruction compared to mastectomy without reconstruction (Kouwenberg *et al.* 2020).

Aesthetic indications include patients who wish to change their native body image, by increasing the breast volume and adjusting its shape.

Some trends are apparent in the literature for the use of one or another type of breast implant. However, the clinical indications for the use of a specific type of breast implant should depend on a consultation between clinician and patient to allow informed decision making to take place with regards to the choice of an appropriate breast implant. For breast reconstruction, a shared consultation with a multidisciplinary healthcare team including a pathologist, oncologist, surgeon, breast care nurse, etc. should be held with the patient to allow informed decision making to take place with regards to the breast reconstruction procedure as well as the choice of implant. For both aesthetic and reconstructive surgery, all aspects of breast implants should be evaluated and discussed with the patient, expressly covering advantages, disadvantages, follow-up procedures and risk factors.

In summary, breast implants are used for:

- Primary Reconstruction, i.e., the replacement of breast volume lost after accidental or iatrogenic trauma, mastectomy for breast cancer, and developmental anatomic anomalies such as amastia, tuberous breast and Poland syndrome.
- Secondary reconstruction following a previous surgical procedure after breast cancer or preventive surgery in women with a BRCA mutation.
- Correction of aesthetic variants such as hypomastia and anisomastia.
- Aesthetic use for increasing breast volume and improving its shape.

4.2 Types of breast implants

Breast implants have a limited number of characteristics that can be used for their categorisation. The most frequently used categories for breast implants include those that differentiate them by:

- Fill
- Shell Surface
- Three-dimensional Shape

Fill

Breast implants can be filled with various materials with the most frequently used being silicone gels. These gels are designed to have differing levels of cohesiveness resulting in varying levels of viscosity and hence firmness. The second most commonly used filling material is a saline solution, although silicone accounts for the vast majority of fillings used in implants available on the European and USA markets. Besides silicone and saline, less commonly used filling materials sometimes include methylcellulose, polyvinylpyrrolidone (PVP), the now discarded soybean oil, or a combination of various filling materials (Handel *et al.* 1993, Scuderi *et al.* 2005, Brunner and Gröner 2006, Williams *et al.* 2009).

Tissue expanders are temporary implants. They are empty shells that are filled after their placement in the breast area. The most commonly used filling material is saline that is injected through the skin into the device. As the volume increases, it expands and stretches the skin, and when fully expanded creates a "pocket" into which, after removal of the expander, the final breast implant or autologous tissue is placed.

Shell Surface
The shell surface, or outer layer of the implant otherwise known as the envelope, contains the filling material. Processes employed to produce these surfaces are proprietary information. However, at present all shells are made of silicone and are fabricated by adding a number of different layers (3-5) on top of each other in order to increase their strength. The shell can rupture over time and there are reports of shells being permeable to silicones as well as to biomolecules from the surrounding tissues (Van Diest *et al.*, 1998; Beretta *et al.*, 2013; Kappel *et al.*, 2016; Tortolano *et al.*, 2017). The most outer layer represents the surface in contact with patient tissues and can be smooth or rough with different degrees of roughness ranging from macro (with deep texturing), micro (with shallow texturing) to smooth (with minimal texturing). In addition, the silicone shell surface may also be coated with polyurethane. The total surface area in contact with the patient is also affected to a certain extent by the volume of the implant and by the number of implants a patient has had in their lifetime (Magnussen *et al.*, 2019). Textured surfaces and coatings were developed in an attempt to reduce implant-related complications such as rotation and capsular contraction.

Surface texture of objects can be characterised by the following features that may affect interactions between the implant and host cells (Gadelmawla *et al.* 2002, ISO 14607:2018):

a) pore size or diameter (µm);
b) peak maximum height (µm);
c) peak mean height (µm);
d) kurtosis (sharpness of the profile), measured by the number and height of peaks (µm);
e) skewness (profile symmetry), measured by the number and depth of valleys and peaks (µm);
f) density (profile topography), measured by the average distance between morphological features (µm);
g) roughness (µm).

Some of the above features are not applicable to all types of texture.

Three-dimensional (3-D) shape
Breast implants can either be round or anatomical in the latter case being teardrop shaped. Round implants have a lenticular shape, with a symmetrical curved anterior side (dome) and a flat round posterior base, with no apparent differences in the shape between the top and bottom of the implant. In contrast, anatomical breast implants have a teardrop shape with the upper half being "flatter", with little projection and the lower half having an enhanced projection. They have an asymmetric curved anterior side and a flat, more often round or elliptic posterior base. These implants require a highly cohesive gel filling to maintain their anatomical shape and in order to prevent their rotation, they need to 'stick' to their surrounding tissue, which is generally achieved by roughening their surface (texturing).

4.3 Alternatives to breast implants

Alternatives exist for both the aesthetic and reconstructive use of breast implants. The goal of breast reconstruction is to restore the breast's volume and shape. Typically, reconstruction is performed after a mastectomy, following breast conserving therapy or quadrantectomy/lumpectomy following breast cancer (Santanelli *et al.* 2009).

There are three popular techniques for breast reconstruction:

- implant-based,
- autologous tissues,

- a combination of implants and autologous tissues.

The choice of technique is decided in a shared decision-making process between clinicians and patients taking into consideration several aspects, including preoperative clinical conditions:

- the type of breast defect (size and location);
- the general condition of the patient;
- the characteristics of the contralateral breast;
- the necessity for radiotherapy;
- the availability of donor autologous tissues.

a) Alternatives to breast implants following breast conserving surgery: plastic surgery techniques

Breast conserving surgery for the treatment of breast cancer shows a higher level of patient satisfaction than breast mastectomy alone (Kouwenberg *et al.* 2020). Therefore, several techniques have been developed to increase the use of breast conserving surgery over mastectomy. For small resections, the breast mount remains relatively undisturbed. However, as the size of the resected tissue increases, the shape of the breast and the position of the nipple are disturbed and outcomes of surgery are, in general, less pleasing. For larger resections, adding so-called tissue remodelling plastic surgery techniques can prevent major deformities. Defects can be reconstructed using a breast reduction mammaplasty technique that restores the shape of the breast and the position of the nipple. This results in a smaller breast with immediate reconstruction and often excellent aesthetic results. However, it should be noted that the need for radiotherapy in any type of surgery may hamper tissue healing/regeneration.

Besides using breast size reduction techniques, the addition of new tissue to the breast can be carried out in cases where the resected tissues are greater in size. The defect is filled by adding tissue from the surrounding area, for example, tissue flaps vascularized by the rib vasculature or lateral intercostal artery perforator flaps. Certain patient characteristics (e.g., a slim body with a low Body Mass Index) can limit the use of such techniques.

b) Alternatives to breast implants following mastectomy: autologous tissues

In cases of mastectomy, the whole breast needs to be restored. Women desiring breast reconstruction can be operated on at the same time as the procedure for the mastectomy, or reconstructive surgery can be delayed, first allowing time for healing of the mastectomy wound.

For autologous reconstruction, tissue flaps or Autologous Fat Transfer (AFT) can be used. Tissue flaps survive due to perfusion provided by the existing vasculature. They can be "*pedicled"*, if the tissue remains attached to the vasculature of the body, or "*free"* when disconnected from the vasculature but later reconnected to blood vessels in the breast area by means of a microvascular anastomosis, to guarantee flap perfusion and tissue viability. For free flaps, tissue can be transferred from areas far away from the breast, while pedicled flaps can only be transferred from sites nearby. Tissue flap selection is based on donor site availability and the surgeon's experience. It should be noted that for complex surgeries for autologous reconstruction involving the various flap transfer techniques, specific training, expertise and experience is required as is usually present in specialised hospitals.

c) Autologous fat transfer (AFT)

Autologous fat transfer (AFT) can be used for total breast reconstruction mainly in patients with a small to medium-sized breast (Colemann and Saboeiro 2007). It can also be used as a complementary procedure during plastic surgery techniques to offer aesthetic refinements, or in flaps to increase their volume and hence, the final breast volume. AFT involves aspiration of fat tissue from available donor areas, and its reinjection into the recipient site through micro incisions using cannulas. The harvested fat is injected into the recipient area in tiny droplets. To survive, these droplets must be surrounded by live tissues in order to form connections with the local vascular framework. Usually, to form a proper connection, the amount of fat needed to restore the required breast volume cannot be transferred in a single procedure, instead requiring more surgical procedures. Hence the volume of fat that can be transferred depends not only on donor site availability, but also on the capacity of the recipient site to accommodate it, thus generating a need for more surgical procedures to produce a breast of the same volume as could easily be obtained with a flap. The advantage of AFT over flap surgery is that it produces fewer scars although, like all surgical procedures there is a risk of complications (Kontoes and Gounnaris 2017, Kang and Luan 2018).

d) Alternatives in aesthetic cases

Breast implants are used in aesthetic procedures for the correction of developmental anomalies of the breast such as amastia, hypoplasia, breast asymmetry, tuberous breast and when breast volume augmentation is desired. AFT, as in breast reconstruction, is an autologous alternative to breast implants, offering comparable results. However, the predictability of outcomes with autologous fat transfer may be uncertain, especially in cases in which radiotherapy was applied. Also, patients have to undergo several operative sessions for aesthetic purposes. Moreover, repetitive fat graft sessions might not be possible in some patients because of a lack of availability of the required fat volume (e.g. a slim body with a low Body Mass Index).

Fat transfer can be combined with a non-surgical external expansion by sustained tension (generated by a low negative pressure) on the natural breast tissue to cause the cells to proliferate (Oranges *et al.*, 2018).

4.4 Breast Implant Associated - Anaplastic Large Cell Lymphoma

Concerns of a possible association between breast implants and ALCL first arose in the mid-1990s (Duvic *et al.*, 1995; Keech and Creech, 1997) and have now become a serious issue with respect to the use of breast implants. It was suggested that BIA-ALCL be defined as a distinct clinico-pathological entity by Thomson *et al.*, (2010). In 2016, the World Health Organization (WHO) classified a number of lymphomas as provisional entities to distinguish these from other lymphomas, including BIA-ALCL which was associated with an excellent outcome when non-invasive disease stages are treated by surgical resection (Swerdlow *et al.*, 2016).

4.4.1. Anaplastic Large Cell Lymphoma (ALCL)

Non-Hodgkin lymphoma is a cancer of the immune system that consists of over 70 separate diseases (Swerdlow *et al.*, 2016, 2017). According to the International Agency for Research on Cancer - IARC (indicated in the 2012 GLOBOCAN database), the age-standardized annual incidence of non-Hodgkin lymphomas in Europe is estimated to be

8.8 cases for males and 5.9 cases for females per 100,000 individuals (Ferlay *et al.* 2015), with rates varying from 0.8 to 11.2 cases per 100,000[10] .

Anaplastic Large Cell Lymphoma (ALCL, ICD-10: C84.6/7) is a very rare class of non-Hodgkin lymphoma and one of the classes of T-cell lymphoma, which by itself comprises approximately 10-15% of the non-Hodgkin lymphomas (Swerdlow *et al.*, 2017, Prantl *et al.*, 2020). ALCL is further divided into sub-entities based on whether the tumours aberrantly express a protein called Anaplastic Lymphoma Kinase (ALK); systemic forms of ALCL can be ALK+ or ALK-. ALCL is also differentially diagnosed based on its primary location in the body whereby cutaneous and breast implant associated ALCL are in the skin or breast adjacent to implants, respectively, and are (almost) always ALK- (Swerdlow *et al.*, 2017). Overall, ALCL comprises about 1% of all non-Hodgkin lymphomas and approximately 16% of all T-cell lymphomas (Swerdlow *et al.*, 2016). It should be noted that ALCL occurring in breast tissue in the absence of an implant is very rare (Thomas *et al.*, 2017; De Boer *et al.*, 2018), although from 1975-1977 to 2011-2013 an increase in primary lymphoma involving the breast was noted, with ALCL diagnosed as a primary lymphoma of the breast having an incidence of just 0.037 per 1,000,000 women in the period 2000-2013 (Thomas *et al.*, 2017). Only 12 ALK- and CD30+ ALCL cases were observed in a survey of a tumour registry with 170,405 malignancies. None of these ALCL cases was located in the breast and none of the patients had a history of breast implants (Prantl *et al.*, 2020). The time span of tumour diagnosis in this survey was from 2002 to 2018. Most primary breast lymphomas are of a B cell origin and malignancies with a T cell phenotype account for less than 6% of cases (Jeanneret-Sozzi *et al.* 2008, Fleury *et al.*2017).

4.4.2. Breast Implant Associated – Anaplastic Large Cell Lymphoma (BIA-ALCL)

Disease characteristics
BIA-ALCL is the uncommon occurrence of ALCL adjacent to a breast implant. Generally, BIA-ALCL follows an indolent clinical course and has an excellent prognosis when diagnosed and treated promptly (Campanale *et al.* 2020). It most often occurs within the capsule surrounding the implant and can manifest as a spectrum of presentation of one disease, from a primary fluid effusion containing tumour cells, to a solid tumour mass with or without lymph node and/or organ metastasis (Clemens *et al.*, 2016). Swelling is caused by a local fluid effusion, called a seroma. "*Late seromas*" are those occurring greater than one year after implantation. This occurs after a median interval of 10 years (ranging from a few to >20 years, and in exceptional cases prior to 1 year) following implant insertion (Miranda *et al.*, 2014). In most cases the capsule looks entirely normal except for the seroma, which often contains free floating debris that is best appreciated by ultrasound (Adrada *et al.*, 2014). Localised capsule thickening or mass formation may or may not be associated with the seroma.

Diagnosis
Unexplained swelling of the breast, delayed seroma, or a capsular mass requires further investigation. Mammograms have relatively poor specificity for BIA-ALCL (Adrada *et al.* 2014). Breast scanning techniques that can be used for BIA-ALCL diagnosis include computed tomography (CT), positron emission tomography (PET), PET-CT combined and magnetic resonance imaging (MRI). Ultrasound has similar or even better sensitivity and specificity when compared to computed tomography (CT) and magnetic resonance

[10] http://globocan.iarc.fr/old/summary_table_site-html.asp?selection=19260&title=Non-Hodgkin+lymphoma&sex=0&type=0&window=1&europe=4&sort=4&submit=%C2%A0Execute%C2%A0

imaging (MRI) in the evaluation of fluid collections, masses and regional lymphadenopathy (Adrada *et al.*, 2014). Diagnosis of BIA-ALCL is achieved by analysis of seroma fluid, or if a mass is present core needle, incisional or excisional tissue biopsy (Clemens *et al.*, 2019). BIA-ALCL diagnosis based on the seroma aspirate may be difficult. After ruling out other causes of delayed seroma (e.g., infection, trauma to the chest wall), the aspirate (suggested minimum of 10 to 50 mL) should be sent for cytopathology and analysis should include immunocytochemistry and, if possible, flow cytometry and molecular analyses such as for T-cell receptor gene rearrangements (Jaffe *et al.*, 2020). Following "en bloc" capsulectomy, the capsule tissue should be sampled to evaluate it for the presence of capsular invasion by tumour cells. It has been recommended that at least twelve samples are taken (Lyapichev *et al.*, 2019).

While a small amount of fluid (10-15 mL) can be common around most breast implants, a considerable symptomatic fluid accumulation, for example sufficient to cause a visible difference in breast size should also be investigated by cytological evaluation for the presence of BIA-ALCL (Chacko and Lloyd, 2018).

When a solid mass is present, it is important to conduct histopathology of the biopsy material (Jaffe *et al.*, 2020). In these cases, diagnosis is largely made based on the patterns of growth and morphology of the cells together with appropriate immunohistochemistry. It is important to note that while CD30 expression is characteristic of BIA-ALCL, it is not specific to this malignancy as it is expressed in various other lymphoma classes, non-malignant lymphoid cells, and even non-lymphoid cells and malignancies. Rare or scant CD30 positive lymphocytes with otherwise normal morphology do not raise concerns for BIA-ALCL although the reason for their presence and the implications of this are uncertain (Clemens *et al.*, 2019). Under these circumstances, a diagnosis can be challenging, and other supporting diagnostic tools are being explored, such as genetic or immune-based assays (Di Napoli *et al.*, 2020, Kadin, 2020, Los-de Vries *et al.,* 2020). It should be noted that neither this, nor other supportive assays are currently used in diagnostic practice.

BIA-ALCL is considered to be related to the use of the implant and its aetiology might be patient, surgery, or implant-related. Therefore, the disease has an impact on the safety of breast implants used for aesthetic and reconstructive purposes. More insight into BIA-ALCL is required as this is important for regulatory agencies, manufacturers and most importantly for patients receiving the devices.

Recommendations for diagnosis

As can be seen in ***Table 1***, the majority of countries in Europe have produced recommendations for early diagnosis and have established mandatory reporting of cases of BIA-ALCL, but do not have specific recommendations for the use of implants with a certain type of surface (i.e., textured implants) (Cardoso *et al.*, 2019).

Table 1 – EU and UK recommendations for the diagnosis and reporting of cases of BIA-ALCL

Recommendations towards BIA-ALCL and attitudes towards textured implants as adapted from Cardoso *et al.*, (2019)					
Country	Regulatory Board	Report mandatory	Recommendation towards all textured implants	Ministry of Health Recommendations	Recommendations for early diagnosis
AT	Osterreichisches Register für Medizinprodukte	NO	NO	NO	YES
BE	Federal Agency for Medicines and Health Products	YES	NO	YES	YES
BG	Bulgarian Drug Agency	YES	NO	YES	YES
DK	Danish Medicines Agency	YES	YES	YES	YES
IS	Lyfjastofnun Islands	YES	YES	YES	YES
IE	Health Products Regulatory Authority	NO	NO	NO	YES
IT	Ministry of Health	YES	NO	YES	YES
FI	Social and Health Ministry	YES	NO	NO	YES
FR	Agence nationale de securite dumedicament et des produits de sante	YES	YES	YES	YES
DE	Bundesinstitut für Arzneimittel und Medizinprodukte	YES	NO	NO	NO
GR	National Medicines Agency	NO	NO	YES	YES
LV	State Agency of Medicines	YES	NO	NO	YES
PL	The Office for Medicinal Products, Medical Devices and Biocidal Products	YES	NO	YES	YES
PT	INFARMED	YES	NO	NO	YES
ES	Agencia Espanola de Medicamentos y Productos Sanitarios	YES	NO	NO	YES
SE	Lakemedelsverket	YES	NO	NO	YES
CH	Swiss Medics	YES	NO	YES	YES
UK	Medicines and health care products regulatory authority	YES	NO	YES	YES
NL	Health and Youth Care Inspectorate	YES	YES	YES	YES

Relationship to breast implants

A number of reviews based on epidemiological and experimental studies on the subject of BIA-ALCL have been published, stating a positive association with breast implants, but low in effect size (Berlin *et al.*, 2018, Clemens *et al.*, 2017, Calobrace *et al.*, 2018, Collet *et al.*, 2019, Ezekwudo *et al.*, 2017, Fleury *et al.* 2017, Kaartinen *et al.*, 2017, Kricheldorff *et al.* 2018, Laurent *et al.* 2018, Leberfinger *et al.*, 2017, Miranda *et al.*, 2019, Quesada *et al.*, 2019, Rastogi *et al.* 2018, Ramos-Gallardo *et al.*, 2017 Shahriari et al, 2017). In addition, case series have been reported for Australia and New Zealand (Loch-Wilkinson *et al.*, 2017), Europe (Cardoso et al, 2019), the Netherlands (De Boer *et al.*, 2018), the UK (Johnson *et al.*, 2017), the USA (Doren *et al.* 2017, McCarthy *et al.* 2019) and worldwide (Srinivasa *et al.*, 2017). The rate of diagnosis of BIA-ALCL has risen considerably over the past few years.

4.5 Treatment and prognosis of Breast Implant Associated - Anaplastic Large Cell Lymphoma

A standardised guideline for the diagnosis and treatment of BIA-ALCL proposed by the National Comprehensive Cancer Network (NCCN, Plymouth Meeting, PA, USA, https://www.nccn.org/) based on the consensus opinion of lymphoma oncologists, plastic surgeons, radiation oncologists and surgical oncologists has been published (Clemens *et al.* 2017, 2019). Besides the NCCN guidelines, those written on behalf of the UK MHRA plastics, reconstructive and aesthetic surgery expert advisory group (PRASEAG) have also been published suggesting similar mechanisms for the diagnosis of BIA-ALCL, and recommending that multi-disciplinary teams are engaged early in the diagnostic and treatment process to manage these patients at specialised centres (Turton *et al.*, 2020). Austrian guidelines have also been published reflecting the NCCN guidelines but are only available in German (Flores *et al.*, 2020).

Based on the epidemiology, it was suggested that the uncommon occurrence of BIA-ALCL might be a consequence of spontaneous regression/resolution of the disease (Fleming *et al.*, 2018, 2020, 2020). To date, true cases of spontaneous regression/resolution of BIA-ALCL have not been reported. Of note, cases described by Fleming *et al.*, as spontaneously regressing were treated, and only reduced numbers of BIA-ALCL cell numbers were observed rather than a complete absence. In general, BIA-ALCL has a favourable prognosis (Clemens *et al.* 2016, 2018). Capsule-confined BIA-ALCL most commonly follows an indolent course following adequate surgical treatment, without the need for adjuvant therapy (chemotherapy and/or radiotherapy). However, the recognition and timely diagnosis of BIA-ALCL is critical to prevent progression to more advanced disease that requires additional adjuvant systemic chemotherapy (Collins *et al.* 2019, Campanale *et al.* 2020).

For all patients with BIA-ALCL, complete surgical resection is recommended for improved overall long-term survival and disease-free progression. Surgical resection includes removal of the implant, radical capsulectomy and any disease mass with negative margins of healthy tissue. An incomplete resection or inadequate local surgical control may subject the patient to adjunctive treatments (i.e., chemotherapy or radiation therapy), whereas complete resection provides definitive therapy and cure in the majority of cases (Clemens *et al.*, 2019). For patients with bilateral implants, NCCN guidelines recommend removal of the contralateral uninvolved implant and capsule to avoid the risk of contralateral disease, which presents in up to 2 to 4% of patients (Clemens *et al.*, 2017, 2019).

Because an implant capsule can drain to multiple regional lymph node basins, even when most of the breast drains to the axillary lymph nodes, there appears to be no role for sentinel lymph node biopsy. Rather, excisional biopsies should be performed for axillary (and any other) lymph nodes found to be enlarged on clinical examination or following imaging studies. Approximately 60% of enlarged axillary nodes are pathologically involved; fine needle aspiration is to be avoided, as it can yield false-negative results (Ferrufino-Schmidt *et al.*, 2019).

For patients with proven disseminated disease or patients in which surgical therapy alone fails, oncologists may consider a systemic chemotherapy regimen (e.g., CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone with or without etoposide). Alternatively, NCCN guidelines recommend oncologists consider targeted immunotherapy with brentuximab vedotin (an anti-CD30 antibody-drug conjugate) as a primary treatment or in combination with CHOP. In European countries, treatment according to national guidelines of first line and second line treatment for disseminated T-cell lymphomas are recommended. The role of radiation therapy in the treatment of BIA-

ALCL is unclear. Radiation therapy has been used in more locoregionally advanced cases for un-resectable chest wall invasion. After surgery for BIA-ALCL, immediate or delayed breast reconstruction or further augmentation has been reported using implants or autologous tissue (Lamaris *et al.*, 2019). The patient needs to be fully informed regarding current uncertainty about the safety of various types of breast implants with regards to BIA-ALCL and capsule formation.

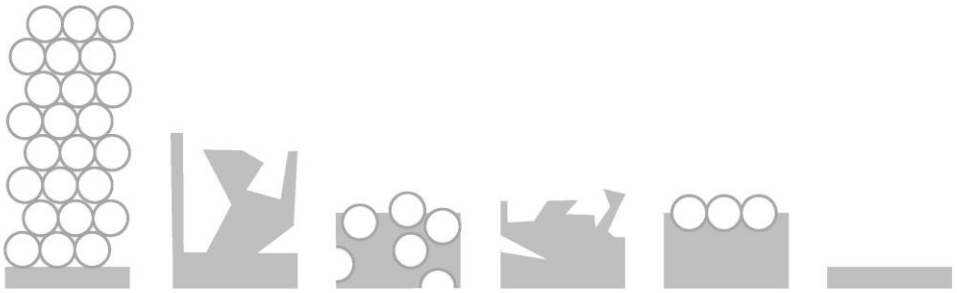
In a retrospective analysis of 87 patients with BIA-ALCL followed for a median of 30 months, the estimated median overall survival was 13 years with three- and five-year survival rates of 93% and 89%, respectively (Clemens *et al.*, 2016). The event-free survival (EFS) rate at one year was higher in those undergoing complete surgical excision (96%) when compared with those treated with more limited surgery (40%), radiation therapy (82%), or chemotherapy (76%). Surgery should be performed with strict oncologic technique, including the use of specimen orientation sutures, placement of surgical clips within the tumour bed, and the use of new instruments for removal of the contralateral implant (Tevis *et al.*, 2019).

4.6 Breast implant surface textures

Breast implant surface textures can be achieved with several different techniques (Figure 1). The most commonly used methods are:

a) the salt-loss technique: refers to the application of sodium chloride to uncured silicone with different methods (dipping, spraying, sprinkling), and it can be performed both closed (extra layer of silicone is applied over the salt and abraded after curing to remove the salt) or open (the salt is washed away after curing).
b) gas diffusion (volatilisation/vulcanisation): refers to the application of ammonium carbonate to the uncured silicone surface, leaving grain-shaped openings when it thermally decomposes during curing. This can also be done at a subsurface level when the ammonium carbonate is embedded in the silicone and the gasses (ammonia and carbon dioxide) to which it decomposes, bubble through the uncured silicone during thermal curing.
c) imprint stamping: refers to the negative stamping of a structure onto uncured silicone. It can be done with polyurethane foam that is pressed onto the uncured silicone and removed before curing, or with a mandrel being sandblasted and the texture transferred to the silicone during curing (the shell is turned inside out). Imprint stamping with the process of turning the shell inside out can also produce low surface area and low roughness surfaces, including nano-surfaces with minimal surface area and roughness (Figure 1).
d) polyurethane foam coating: refers to the application of an extra layer of foam coating to the implant.

For the breast implants with a polyurethane (PU) coated surface, it was suggested that this cannot be considered a macro-textured implant, even though according to Figure 1 these PU coated implants do have a high surface area and high surface roughness (Hamdi 2019). For the PU coated Silimed implants, the highest surface roughness and surface area was observed when various brands of breast implants were compared with each other (Jones *et al.* 2018). Also, according to the ISO 14607 classification, PU coated breast implants should be considered macro-textured.



Manufacturing Process	Polyurethane foam	Salt loss	Vulcanisation	Salt loss	Imprinting	Smooth/Nano
Surface Area	High	Intermediate	Intermediate	Low	Low	Minimal
Roughness	High	Intermediate	Low	Low	Low	Minimal

Figure 1. Implant surface texturing as it relates to the manufacturing method, surface area and surface roughness (based on Jones *et al.*, 2018).

A number of different systems have been proposed to classify implant surfaces:

- *ISO 14607:2018* is the most widely accepted and divides breast implants into Smooth (<10μm), Micro (10-50μm) or Macro (>50μm) textured surfaces based on the implant's average surface roughness. Average roughness is determined as a height parameter by integration of peaks and valleys around a lineal surface.

- *Atlan et al.,* (2018) used an X-ray CT to determine the actual surface area of 10mm diameter discs, four from the anterior and four from the posterior implant shell as a proxy of texture, and divided breast implants into Smooth (80-100mm^2), Micro (100-200mm^2), Macro (200-300mm^2) and +Macro (>300mm^2) surfaces.

- *Jones et al.,* (2018) measured the surface area and roughness of implants using scanning electron microscopy (SEM) and subjected the shells to an *in vitro* bacterial attachment assay with four bacterial pathogens studying their growth in relationship to the surface area and roughness. According to roughness (and propensity for bacterial growth), they classified implant surfaces into: Minimal (<25μm), Low (25-75μm), Intermediate (75-150μm) and High (>150μm) textured surfaces.

- *Barr et al.,* (2017) used SEM and laser confocal microscopy (LCM) and classified implant surfaces based on roughness (peaks and valleys) into Nano (<5μm), Meso (<15μm), Micro (10-75μm), and Macro (>75μm), further dividing Macro and Micro categories into porous and non-porous.

A recent TGA report has evaluated breast implants on the Australian market (TGA 2019). The TGA concluded that the ISO method did not adequately describe the complexities of surface textures resulting from the myriad of texturing techniques manufacturers employ. Additionally, the TGA employed micro-Computed Tomography to extend the categories for surface characterization and was able to group breast implants according to surface characteristics. These groupings include polyurethane-coated, closed salt-loss, open salt-loss, imprinting, subsurface gas diffusion, surface gas diffusion and smooth. It was concluded that the current classification systems require refinement and further examination to develop practical and clinical applications.

To date, none of the proposed surface texture classifications mentioned above have been validated in a clinical study to determine which classification best predicts the risk of BIA-ALCL.

Conclusions
In conclusion, several different classifications for implant surfaces are available. However, none of these is fully satisfactory, as they don't reflect the inflammatory mechanisms inducing adverse effects due to breast implants. To date the most credited and accepted classification by government authorities and manufacturers around the world is the ISO classification (*ISO 14607:2018)*, and it is recommended that this is adhered to because it is the product/outcome of a wide consensus among the scientific and technical communities that deal with breast implants. The ISO 14607:2018 is currently under revision as this classification, based on surface roughness only, was considered too limited, as was also concluded in the TGA 2019 report.

5. METHODOLOGY

Information regarding the availability of scientific data concerning a possible association between breast implants and ALCL was obtained by two literature searches, one dealing with the period 2016 – 2019 and one for the period 2019 – 2020.

5.1 Literature searches

A literature search was conducted to retrieve scientific literature available on ALCL. The major search terms, i.e., *breast implants and ALCL*, were used in combination with the selected additional terms listed below in *Table 3*. Searches were carried out using PubMed and Find-eR (a tool for searching multiple library resources in one interface which includes the European Commission Library collections, plus millions of online full-text journal articles and eBooks). The publication period covered was from September 1st, 2016 to August 31st 2019, and an additional search was performed early in 2020 covering the period from September 1st 2019 to April 30th 2020. The search terms were applied to the 'title', 'abstract' and 'key word' fields. Reference lists of review papers were also retrieved and used in order to find papers that were not found through the search procedure.

The terms used for the literature search were as followed:
- Breast AND implant OR implants OR implantation AND lymphoma
- Breast AND lymphoma AND implant
- Breast AND lymphoma AND prostheses
- Breast AND lymphoma AND endoprostheses
- Breast AND anaplastic large cell lymphoma AND implant
- Breast AND anaplastic large cell lymphoma AND PIP silicone breast implants
- Breast AND ALCL AND implant
- Breast AND BIA-ALCL AND implant
- Breast AND textured implant
- Breast AND smooth implant

The types of documents retrieved were:
- Case reports
- Original research
- Letters to the Editor
- Discussions / Commentaries
- Reviews and meta-analyses

- Book chapters
- Government funded publications.

The literature search using PubMed resulted in 1234 entries, and that using FINDER-eR in an additional 64 new entries. Thus, 1298 entries were retrieved in both search periods (including duplicates). In ***Table 2,*** the key words used and number of entries obtained from the literature search during the entire search period are presented (search results include duplicates).

The literature review was conducted by WG SCHEER members who first evaluated the papers independently and then discussed them as a group before reaching their conclusions. In addition, relevant sources and literature beyond the period of the most recent literature search were considered as well.

Table 2 - Results from literature search

Key words used in the literature search	No of entries PubMed	No of entries FINDER-eR
Breast AND implant OR implants OR implantation AND lymphoma	391	17
Breast AND lymphoma AND implant	194	8
Breast AND lymphoma AND prostheses	17	3
Breast AND lymphoma AND endoprostheses	26	0
Breast AND anaplastic large cell lymphoma AND implant	179	11
Breast AND anaplastic large cell lymphoma AND PIP silicone breast implants	3	4
Breast AND ALCL AND implant	203	10
Breast AND BIA-ALCL AND implant	134	2
Breast AND textured implant	61	3
Breast AND smooth implant	26	6

After excluding all irrelevant papers and duplicate papers, a total of 605 papers remained from the literature search and were evaluated in this Scientific Opinion (see *References* and *Annex 1*). The papers retrieved were case reports and case series, original research, reviews, commentaries and letters to the Editor. The original research papers referred to epidemiologic (observational) studies, either case-control or longitudinal studies.

5.2 Methodology applied to the evaluation of scientific information

The methodology applied to the scientific evaluation of the collected information followed standard procedures for grading scientific evidence, and the WoE guidelines (SCHEER, 2018). The recovered literature was evaluated according to the SCHEER WoE procedure (see *Annex 1*).

6. ASSESSMENT

6.1 Epidemiology of BIA-ALCL

The BIA-ALCL literature needs to be carefully considered and interpreted, especially when looking at risk estimations. Accuracy of the true number of exposed individuals (i.e., denominator data) is of major importance. There is a significant lack of knowledge of the actual total number of women with a breast implant, as it is rather difficult to obtain reliable data on the number of women with breast implants in the population, for which sometimes, sales data can give an indication (Campanale *et al.* 2018, De Boer *et al.* 2018). Conservative estimates suggest that ≥35 million women worldwide have breast implants, with approximately 1.5 million breast implants inserted in 2016 alone and an

increase to more than 1.8 million breast implants in 2018, making itthe number one surgical procedure in the world (International Society of Aesthetic Plastic Surgery global survey – 2016 and 2018). Even more challenging is obtaining knowledge concerning the subtypes of implants. Attention should also be given to the reporting of confirmed BIA-ALCL cases (i.e., numerator data); potential under-reporting leads to inaccurate estimation of the true prevalence and incidence rates. Finally, special attention should also be placed on industry involvement; including whether the authors of these papers have declared conflicts of interest, and if so, whether they are reported in full.

Europe

One of the first systematic works in the area was presented by De Jong *et al.* in 2008 and was based on a case-control study using a population-based nationwide pathology database. The investigators matched 11 cases of ALCL in the breast, of which 5 cases had breast implants, with 35 other cases with lymphomas in the breast, of which only one patient had a breast implant. They found that the Odds Ratio (OR) for ALCL in the breast associated with breast implants was 18.2 (95% CI 2.1-156.8), i.e., women with implants were 18 times more likely to develop ALCL in the breast than patients without breast implants, supporting an association between breast implants and ALCL. Based on estimated sales data from 1999, De Jong *et al.*, estimated that the incidence of ALCL in the breast varies between 0.1 and 0.3 per 100,000 women with prostheses per year in the Netherlands (i.e., 5 new cases in 1.7 to 5.1 million person-years) (De Jong *et al.*, 2008).

Contrary to this, Vase *et al.* (2013) examined lymphoma occurrence in a nationwide cohort of 19,885 Danish women who underwent breast implant surgery between 1973 and 2010; during the almost 4 decades of follow-up using national cancer registries, the investigators observed 31 cases of lymphoma but no cases of ALCL were identified. This study did not support an association between ALCL and breast implants.

More recently, De Boer *et al.*, (2018) performed a case-control study using the population-based nationwide Dutch pathology registry as a follow-up to the study of De Jong *et al.*, in 2008. They identified 43 women with ALCL in the breast of whom 32 had ipsilateral breast implants and compared them to 146 women with other primary breast lymphomas (control group) of whom 1 had breast implants. Thus, the odds for women with breast implants developing ALCL was 421.8 times higher than women without breast implants (OR 421.8, 95% CI 52.6-3385.0), indicating that implants strongly increase the risk of ALCL in the breast. The estimated prevalence of breast implants in women aged 20-70 years was 3.3%, derived from the age-specific prevalence of breast implants in Dutch women, estimated from an examination of 3000 chest X-rays and time trends from implant sales. The absolute cumulative risk of BIA-ALCL in women with an implant was 29 per million at 50 years, and 82 per million at 70 years. The number needed to harm i.e., the number of women with implants needed to cause 1 BIA-ALCL case before the age of 75 years, was reported as being 6920 (De Boer *et al.*, 2018). Of the 28 patients with ALCL in the breast and a known implant type, 23 (82%) had a macrotextured surface implant in place at diagnosis, whereas 45% of implants sold in the Netherlands were macrotextured, and no cases with smooth or polyurethane covered implants were observed. The lack of reliable denominator data concerning textured implants used, precluded risk calculations based on implant type or manufacturer in this study.

For Italy, the Italian Ministry of Health coordinated and centralized the collection of information on 46 cases of BIA-ALCL (Campanale *et al.*, 2020). Confirmed cases must be notified to the Ministry of Health. The mean time to onset of symptoms was 6.4 ± 3.8 years (range 1 to 22 years) with a time to diagnosis of 7.2 ± 3.7 years (range 2-22 years). Most of the patients (91%) presented with a late seroma. The incidence for Italy has been reported as 2.8 per 100,000 patients receiving breast implants in 2015, 2.1 per 100,000 in 2016, 3.2 per 100,000 in 2017 and 3.5 per 100,000 in 2018, although the

population at risk (women bearing implants) was estimated but not disclosed in this study. The disease was easily recognised with a favourable prognosis also when diagnosed at advanced stages if complete surgical excision was performed. As reported, 38 patients are free of disease, four are under follow-up, two had a recurrence 1 year later, and one patient died as result of an unrelated disease. The mean number of implants sold in Italy is approximately 51094 per year of which 95% have a textured surface. According to the International Organization for Standardization standard 14607:2018,17 at the onset of first symptoms, the implant surface was macrotextured in 38 cases, microtextured in three cases, polyurethane in four cases, and unknown in one case. The history of previous implants was confirmed in 29 patients (63%) which showed that the devices involved at the time of the onset of symptoms were different from those implanted at the time of diagnosis in 18 cases (62 percent) (Campanale *et al.* 2020).

Other countries

Brody *et al.,* (2015) identified 173 cases of BIA-ALCL throughout the world through published reports and cases identified from authors and colleagues. This review characterised the widely variable clinical course of BIA-ALCL. They describe BIA-ALCL as "extremely rare", although they did not provide a calculation of risk. This work identified that when implant history was known, the patient had received at least one textured surface device, and no cases were identified in patients who had only smooth devices. It should be noted that it is extremely important to evaluate the history of implants in BIA-ALCL patients in order to identify a possible relationship with implant brand and/or implant characteristics at the onset of disease (Campanale *et al.* 2020).

Doren *et al.* (2017), retrospectively evaluated the US incidence and lifetime prevalence of BIA-ALCL in women with textured implants from 1996 to 2015. The incidence and prevalence were estimated based on pathologically confirmed cases in the literature combined with a single institution's database review of US-based ALCL cases, and textured breast implant sales from either publicly available information or that provided by implant manufacturers. This study found 100 pathologically confirmed ALCL cases associated with breast implants, with a mean interval from implant placement to diagnosis of 10.7±4.6 years. Assuming that BIA-ALCL "*occurs only in textured breast implants*", the authors calculated an incidence rate of 203 cases per 100 million person-years or an overall lifetime risk of 33 cases per 1,000,000 people with textured breast implants. This rate was 67.6 times higher than that of primary ALCL of the breast in the general population (i.e., 3 per 100 million per year; $p < 0.001$). Within this study, the rate of BIA-ACL for Allergan Biocell implants manufactured by the salt loss texturing technique (see ***Figure 1***), was approximately six times that of Mentor Siltex implants manufactured using the negative imprinting technique (1 in 6600 versus 1 in 53,300, respectively) (Doren *et al.*, 2017).

Allergan Inc. reported a prospective series of 17,656 women receiving 31,985 Biocell textured implants from the US Continued Access/Continued Access Reconstruction/Revision Expansion (CA/CARE) clinical trial (McGuire *et al.*, 2017). All subjects were scheduled to undergo regular monitoring for capsular contracture, malposition and late seroma for 10 years after implantation. In a 2017 report, the mean follow-up after implantation was 4.1 years for the augmentation group, 3.7 years for revision-augmentation, 2.9 years for reconstruction and 3.5 years for revision-reconstruction, and four cases of BIA-ALCL had been reported. In 2019, the study's outcomes were updated to 8 cases of BIA-ALCL and calculated an overall risk for Allergan Biocell implants of 1 in 2207 (95% CI 1/1120, 1/5112) (Clemens and McGuire, 2019).

Cordeiro *et al.*, (2020) reported on a prospective cohort of 3546 women from a single surgeon's experience at a tertiary cancer centre in the US between 1992 and 2017. Women were followed from the time of tissue expander insertion to diagnosis of BIA-ALCL or the last follow-up. The median follow-up in the study was 8.1 years (range 3

months to 30.9 years) and 77.3% of patients had been seen in the previous three years. Ten patients were diagnosed with BIA-ALCL in this cohort leading to an estimated 26-year cumulative incidence of 1 in 355 patients with an Allergan Biocell implant and a patient-specific incidence rate of 0.311 cases per 1,000 person-years (95% CI: 0.018-0.503) (Cordeiro *et al.*, 2020). This study was extended to include 9373 patients over the period 1991-2017, of which eleven women developed BIA-ALCL, all with a history of textured implants. The 26-year incidence of BIA-ALCL was reported as 1 in 559 (1.79 per 1000, 0.18%) patients and 1 in 871 (1.15 per 1000, 0.11%) textured implants (0.11%) (Nelson *et al.*, 2020).

Reports from Australia and New Zealand described a total of 104 cases of BIA-ALCL that were identified between 2007 and 2019. In 2020, and based on manufacturer specific rates, the risk of BIA-ALCL was calculated as 1 per 2596 for Silimed Polyurethane, 1 per 3194 for Allergan Biocell, 1 per 6024 for Nagor, and 1 per 36730 for Mentor Siltex breast implants (Loch-Wilkinson *et al.*, 2020).

In an analysis of BIA-ALCL cases throughout the world, a substantial variation in reported incidences was evident, with the lowest rates being reported in the Eurozone, as well as China and Brazil, and the highest being reported in Australia and New Zealand. Reasons for this variation are not clearly understood. Moreover, the incidence of BIA-ALCL was reported to be rarer in people of Asian, African and Native American descent (Brody *et al.*, 2015).

6.2. Epidemiology of BIA-ALCL based on data from Competent Authorities and Scientific Communities

Competent Authorities
At the EU level, the EU Taskforce on Breast Implant Associated-ALCL[11] composed of EU competent authorities received 398 BIA-ALCL reports (probable cases; some of these were unconfirmed cases due to the lack of actual testing). Out of these reports, 345 (86.7%) were confirmed cases of BIA-ALCL that met the NCCN classification (Plymouth Meeting, PA, USA, https://www.nccn.org/) (***Table 3a***).

Table 3a – Confirmed cases of BIA-ALCL from EU member states and the UK (July 2020).

	BIA-ALCL Cases	**Filler[a]**		**Surface[b]**	
EU Member State		*Silicone*	*Saline*	*Textured*	*Smooth*
CH	1	1	0	1	0
FR	71	60	3	60	0
*BE**	9	7	0	7	0
DK	4	4	0	4	0
IT	59	58	1	56	0
DE	19	18	0	16	0
NL	49	39	0	41	0
SE	5	5	0	4	0
FI	5	5	0	1	0
AT	3	3	0	2	0
PT	2	1	0	1	0
ES	41	20	0	27	0
IE	1	1	0	1	0
UK	76	66	0	58	0
TOTAL	345	288	4	279	0

[11] The EU Taskforce was established to enable Member States to pool data and share information on BIA-ALCL.

- Total number of cases in Belgium n=13 as of July 2020.

The mean age of BIA-ALCL patients was 54.1 years (SD 12.1; range 27 to 84 years). The median duration from implantation to diagnosis was 9 years (25%, 75% quartile, 6 to 13 years). Of the confirmed cases with available information concerning the implant's surface (i.e., 295), 279 (94.5%) were reported to be linked to textured implants at the time of diagnosis; of these 72 were linked to macro-textured implants, 11 were linked to micro-textured implants (as reported), and 12 were linked to polyurethane implants. The vast majority of implant filler of the reported cases was silicone, i.e., 288 cases, and there was a balanced distribution between aesthetic (55%) and reconstructive (45%) surgeries.

In 2019, the Dutch Health and Youth Care Inspectorate reported a total of 52 known cases of BIA-ALCL in women in the Netherlands (IGJ, 2019).

The FDA released[12] an updated report on BIA-ALCL incidence on August 20, 2020 and conveyed that they had received reports of "*733 unique cases of BIA-ALCL and 36 patient deaths globally*" as of January 2020. The number of US cases in this series was 384. The manufacturer was known for 686 cases, and of these, companies represented included Allergan Aesthetics Abbvie Corporation (90.4%), Mentor Corporation (7.3%), Sientra Corporation (1.5%), or other manufacturers (0.9%). Of the 733 total unique cases of BIA-ALCL reported, 496 patients were reported to have textured implants and 209 cases did not specify the implant surface. The FDA noted that 28 cases had presented with a smooth implant at the time of BIA-ALCL diagnosis. Of those cases, eight had a history of at least one textured implant, nine had a history of prior implants with unknown texture, one had a history of one smooth implant and no known textured implants, and 10 had an unknown prior history of implants. The FDA also explained that many MDR reports do not contain any information, or contain incomplete information, on the prior implant history of the patient, so this information may change over time.[13]

In July 2020, the Therapeutic Goods Administration (TGA) of Australia received 107 reports of confirmed BIA-ALCL cases including four patient deaths[14]. Most cases involved implants with either a polyurethane coating (n=22, 20.5%) or a textured surface (n=63, 58.8%), while for 22 patients, the surface structure was unknown.

In April 2019, Health Canada reported 28 confirmed cases of BIA-ALCL[15] which was updated in December 2019, to 106 case reports of BIA-ALCL[16] including both confirmed and suspected cases, the latter of which are under further investigation. Of those, 52 were reported after April 2019, double the number of confirmed cases received before that date.

Regarding the rest of the world, the distribution of BIA-ALCL cases is presented in ***Table 3b*** (Collett *et al.*, 2019).

[12] https://www.fda.gov/news-events/press-announcements/fda-updates-analysis-medical-device-reports-breast-implant-illness-and-breast-implant-associated
[13] https://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/breastimplants/ucm239995.htm
[14] https://www.tga.gov.au/alert/breast-implants-and-anaplastic-large-cell-lymphoma
[15] http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/69052a-eng.php
[16] https://www.cbc.ca/news/health/breast-implants-rare-1.5422457

Table 3b - Cases of BIA-ALCL from the rest of the world.

Country (November 2018)	**BIA-ALCL Cases**
Argentina	6
Brazil	3
Canada	28
Chile	2
China	0
Colombia	6
Egypt	1
Japan	0
Mexico	4
New Zealand	13
Russia	2
Singapore	0
South Africa	1
South Korea	1
Thailand	1
Country (July and August 2020)	
Australia (July 2020)	107
USA (August 2020)	384
Total	559

No information on filler, surface nor surgical indication was available at the time of writing this report.

In July 2019, the US FDA released a safety communication accompanied by the issuing of a Class I device recall for Allergan Biocell Inc., textured surface implants and tissue expanders out of concern for a disproportionately higher rate of BIA-ALCL cases reported with these devices. The FDA classifies recalls by a numerical designation (I, II, or III) indicating the relative degree of the health hazard, with class-I being the most serious, signifying "*a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death*". The recall was for implants in stock not yet used in patients. Removal of Biocell implants is not recommended in view of the very low risk for BIA-ALCL.

Scientific Societies

In addition to the Competent Authorities, scientific societies of plastic surgeons have also been collecting data on BIA-ALCL. Cases of BIA-ALCL and related deaths, are actively collected according to NCCN guidelines (Clemens *et al.*, 2019), by the European Association of Plastic Surgeons (EURAPS) Committee on Device Safety and Development (DSDC), through National Plastic Surgery Societies, Health Authorities and Disease Specific Registries (***Table 4***).

According to the number of cases collected from the EURAPS-DSDC, the prevalence in Europe was calculated as 1 BIA-ALCL per 13,745 patients with implants. European countries, where specific measures have been implemented to tackle BIA-ALCL have reported 91% of all cases (i.e., 382 out of 420), with an overall BIA-ALCL prevalence of 1:9,121 patients with implants.

The Netherlands reported a prevalence of 1:2,969, close to that observed in Australia which was 1:2,976. Both countries have a breast implant registry in which patients are registered by default, with the choice to opt out (Santanelli di Pompeo *et al.*, 2020).

Table 4 - BIA-ALCL cases reported to the Scientific Societies of the indicated countries according to the European Association of Plastic Surgeons (EURAPS) (July 2020).

Country	BIA-ALCL cases	Deaths
*UK^*	68	1
FR	86	4
NL	65	2
IT	59	1
ES	40	1
BE	13	0
FI	13	0
SE	11	2
*DK^*	9	0
AT	6	1
NW	6	0
CH	6	1
DE	27	0
PL	7	0
RO	1	0
SI	0	0
HR	1	0
GR	1	0
PT	1	0
**TR*	4	0
**IL*	9	0
Total	433	13

*^Update as of May 2020; *non-EU member state.*

Conclusions

Based on the aforementioned reports from epidemiologic studies (De Jong *et al.*, 2008, Doren *et al.*, 2017, De Boer *et al.*, 2018, Cordeiro *et al.*, 2020, Loch-Wilkinson *et al.*, 2020), the lifetime incidence of BIA-ALCL varies from 1.65 cases per 100,000 women with implants to 35 cases per 100,000 women with implants (for comparison reasons, the incidence of breast cancer in the world in 2018 was estimated to be 2,088.8 cases per 100,000 women aged 0-74 years, and the incidence of non-Hodgkin lymphoma in women was 224.9 cases per 100.000 women (Ferlay *et al.*, 2019); while in Europe, the incidence of breast cancer was estimated 1,195.2 cases per 100,000 women (Heer *et al.*, 2020). The relative risk (odds) of those with breast implants developing BIA-ALCL varies from 18.2 to 421.8; of note, a few earlier studies, prior to 2017, have reported zero cases of BIA-ALCL, suggesting no association. There may be some discrepancies in the prevalence of BIA-ALCL between data obtained from epidemiologic studies and Competent Authorities or Scientific Communities due to information bias (i.e., delays in collecting all relevant information from studies and other sources).

Thus, the available data obtained from epidemiological studies, Competent Authorities and Scientific Societies, suggest that people with breast implants have a low absolute, but high relative risk of developing BIA-ALCL. Moreover, there is substantial variation in the prevalence and incidence of BIA-ALCL reported around the world, which may be attributed to the inherent diagnostic and underreporting bias due to a lack of professional awareness. The increase in incidence noted in more recent reports might be partially attributed to the increase in professional awareness and the establishment of uniform diagnostic criteria. However, estimates of risk have significant limitations related to the frequent use of *ad hoc* reporting of cases compared with systematic reporting, and the use of sales data provided by manufacturers. There is also variation in the incidence of BIA-ALCL among manufacturer-specific surface textures. There is no universally agreed, classification system for surface texture. Implants that are ISO (ISO 14607:2018)

classified as macrotextured have been associated with a greater incidence of BIA-ALCL compared to microtextured implants. A full implant history can be difficult to obtain in patients who have had multiple implants. However, when the breast implant surface was identified in BIA-ALCL cases, they were in almost all cases identified as textured. There has been only 1 confirmed case of BIA-ALCL in a patient with a known implant history in which only smooth implants were used. As far as the manufacturer for textured implants was known, most cases were found for the Biocell implant (texture manufactured by the salt loss technique), while for PU coated breast implants BIA-ALCL cases were mainly associated with Silimed implants. Cases for other manufacturers were much lower. Although it cannot be considered to induce a textured surface on an implant, PU coating does result in an increase in surface area and roughness. The highest surface roughness and surface area was observed for PU coated Silimed implants, when various brands of breast implants were compared with each other (Jones *et al.* 2018).

6.3 Epidemiology of BIA-ALCL based on reports obtained from registries

As was underlined in the previous SCHEER advice regarding BIA-ALCL, to account and correct biases in risk estimation regarding BIA-ALCL, registries of recipients with breast implants should be established to provide accurate information. Registries are the most powerful resource with regards to post-market surveillance, tracking and epidemiological profiling. This need has already been suggested by several investigators (Evans *et al.*, 2011; Cooter *et al.*, 2015; Brown *et al.*, 2016).

Since 2015, a number of national breast implant registries have been established which record the details of any individual who has breast implant surgery for any reason (Hopper *et al.* 2018). These clinical quality registries evaluate breast implant performance and when mature, can provide clinicians, health service managers, patients and other stakeholders with ongoing, risk adjusted, benchmarked feedback on clinical practice and patient outcomes to facilitate audit and support quality improvement (Begum *et al.*, 2019). They can also assist in contacting patients in the event of a product recall or other safety concern. Patient opt out consent and mandatory surgeon participation result in high uptake of registries. Funding independent of industry is optimal.

Registries have been established in Australia (Hopper *et al.* 2017), the Netherlands (Spronk *et al.*, 2019), Sweden (BRIMP 2018), US, UK, France and Germany. The current situation of breast implant registries worldwide is presented in Bargon *et al.* 2020. These registries work together through the International Collaboration of Breast Registry Activities (ICOBRA) (Cooter et al, 2015). Members of ICOBRA include the national plastic surgery societies of Australia, Austria, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, South Africa, Spain, the United Kingdom and the United States. ICOBRA breast implant registries collect an internationally agreed and comparable minimum data set, made up of standardised and epidemiologically sound data that reflect global best practice (Spronk *et al.*, 2020)[17]. ICOBRA registries are working towards combining over 170,000 currently registered breast implants to perform multi-national post-market surveillance. The current environment with General Data Protection Regulation (GDPR) increases the complexity of this task.

Cases of BIA-ALCL are reported in an *ad hoc* way, although case capture must be confirmed with systematic collection of cases through e.g., pathology services or cancer registries. In the Netherlands, 100% of cases were reported to the Dutch Breast Implant Registry in its first year of registering patients (2016) and 70% in its second year, as validated by the national pathology service. A further ten patients were reported to the

[17] https://plasticsurgeryfoundation.org.au/

registry with suspected BIA-ALCL for which subsequent pathology confirmed that they did not have the disease (Becherer *et al.*, 2019). As the registries mature, the ICOBRA dataset will be available for new cases of BIA-ALCL and will form the basis of a cohort study to identify patient, device and surgical factors associated with BIA-ALCL. Importantly, these registries will be able to provide more accurate denominator data for incidence calculations. Data linkage will also extend the utility of this dataset (Hopper et al, 2018).

There are also a number of disease-specific registries that capture cases of BIA-ALCL. In France there is the national network of experts 'LYMPHOPATH', which is a government-supported network that aims to review lymphoma diagnoses or suspected lymphoma diagnoses; since 2010, 43,830 lymphomas have been registered in this database (Laurent *et al.*, 2016). Ruffenach *et al.* (2019) evaluated 36 cases in the LYMPHOPATH registry and reported that all 36 patients with BIA-ALCL had either a macro-textured implant manufactured with the Biocell salt loss technique or a history of a macro-textured implant. In the Netherlands, the Dutch BIA-ALCL Consortium, consisting of a multidisciplinary group of scientists, is investigating ALCL occurrences in women with breast implants using the national pathology registry[18]. In France and Belgium, the Lymphoma Study Association (LYSA) established a registry to collect patient clinical data including reasons for breast implantation (breast augmentation, reconstruction), implant manufacturer, treatments and outcome. In Italy, the Ministry of Health has created a specific registry of BIA-ALCL patients (Campanale *et al.*, 2018, 2020). In the USA, a collaborative project has been established with the American Society of Plastic Surgeons and the Plastic Surgery Foundation, in order to collect data through the Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Aetiology and Epidemiology (PROFILE) registry.

According to LYSA, 58 patients with BIA-ALCL were studied among the 88 (67 in France and 21 in Belgium) cases identified from 2009 to 2019. The median age at diagnosis was 58 years (range 29-82). For 29 of the 58 patients (50%) the first implant followed a mastectomy for breast cancer. Four patients (6.9%) had bilateral BIA-ALCL and 54 patients had unilateral BIA-ALCL (50% left side and 50% right side), 25 patients were implanted once (43.1%), 24 twice (41.4%) and 9 patients (15.5%) 3 times or more. The median delay between first implant and BIA-ALCL diagnosis was 11.9 years (range 4.1-37), and the median delay from the last implant to diagnosis was 6.5 years (range 0.2-25.4). The two clinical presentations i.e., seroma (n = 43, 74.1%) and breast tumour mass with or without seroma (n = 12, 20.7%) correlated most often with the two distinct histological subtypes (*in situ* /mixed (n=41) or infiltrative (n=17). Three patients were diagnosed without any mass or seroma. The majority of patients were stage I-II (77.6%), and 13 (22.4%) were stage IV. Considering available information regarding the type of implants, almost all patients had at least one silicone-filled (n=51) and at least one textured implant (n=49) with 40 of these having the Biocell texture. No patient had previously received smooth implants. Implant removal with total capsulectomy was performed for 49 patients and 17 underwent chemotherapy. After a median follow-up of 21 months, 52 patients were alive and free of recurrent disease and one was lost to follow up. Five patients have died, either from lymphoma progression alone (n=2) or associated with concomitant active breast cancer (n=2) and one due to another disease (Le Bras *et al.*, 2019).

The PROFILE registry, which is a prospective registry and tissue repository for BIA-ALCL has collected data from 2012 to 2018, identifying a total of 186 distinct cases of BIA-ALCL in the United States (McCarthy *et al.* 2019). Of these 186 distinct cases of BIA-ALCL there were 3 deaths; complete case report forms have been received for

[18] https://www.nvpc.nl/uploads/stand/170118DOC-PL-BIA-ALCL_achtergrondinforrmatie_en_FAQ_BIA-ALCL162.pdf

approximately half of the cases. The median time from implantation of any device to BIA-ALCL diagnosis was 11.0 years (2 to 44 years; n = 89). The vast majority of cases had local symptoms (96%) and 9% had concurrent systemic symptoms. The most common local symptom was a periprosthetic fluid collection as seen in 86% of patients. All patients had a history of a textured device; there were no patients who had a smooth-only device history.

Conclusions
Breast implant registries are growing in importance for monitoring the safety and performance of breast implants as their capture rates increase, the dataset matures, and their international connectivity increases. Breast implant registries of BIA-ALCL cases aid in further monitoring and characterizing BIA-ALCL. Alternatively, in the absence of a breast implant registry, cases of BIA-ALCL can be included in a dedicated disease-specific (e.g., cancer) registry.

6.4. Mediating and/or moderating factors associated with the risk of BIA-ALCL

The aetiology and pathogenesis of BIA-ALCL has not been elucidated although some theories have been proposed (Fitzal *et al.* 2019, Rastogi *et al.* 2019). The common characteristic is the presence of a textured breast implant suggesting an aspect of these particular devices is causative whether that be direct or indirect. Another clear factor is that the tumour cells are of a T cell origin, a key component of the immune system which again points towards potential mechanisms of disease pathogenesis. The key role of T cells is to detect pathogens and aid in their removal from the body although there are sub-sets of T cells that play different roles in this process. Considering these two factors, a number of hypotheses have been presented in the scientific literature as described below.

Genetic alterations
A very minor group of recipients of textured implants develop BIA-ALCL. So far, it is unknown whether accumulation of genetic defects might be involved in the development of BIA-ALCL. To date, few studies have been conducted whereby matched germline and tumour DNA has been assessed for potential driving oncogenic events or susceptibility loci. This has been hampered by the lack of tumour samples available of sufficient quality or with matched germline DNA. However, in one study whereby 2 patient tumours with matched germline material were assessed, for 1 patient, a mutation in JAK3 was reported in the germline that might indicate genetic predisposition (Blombery *et al.*, 2016). There have also been a small number of cases reported in those with Li Fraumeni Syndrome, a cancer predisposition whereby patients carry mutations in *TP53* (Pastorello *et al.*, 2019, Adlard *et al.*, 2019). In addition, certain Human Leukocyte Antigen (HLA) alleles are more predominant in patients with BIA-ALCL, particularly HLA A*26 although whether this plays a role remains to be determined (Tevis *et al.*, 2019). Considering that many women who elect to have breast reconstructive surgery with breast implants are women at risk of developing breast cancer, it would not be surprising that a higher incidence of BIA-ALCL would occur in women who are genetically predisposed to breast cancer through the inheritance of mutations in the *BRCA1/2* genes. Indeed, a Dutch study has shown that the absolute risk of developing BIA-ALCL is 1:1551 for women who carry mutations in *BRCA1/2* compared to 1:7577 for non-carriers (De Boer *et al.*, 2020). In all, these studies have been conducted with limited numbers of patients and require expansion with far larger cohorts before conclusions can be made.

Other studies have focussed on the genetics of the tumour material itself and the genetic changes within those malignancies that may be involved in its pathogenesis. A central role for activation of the JAK/STAT pathway, particularly STAT3 has been suggested by

these data as it has for systemic ALCL, ALK-(Crescenzo *et al.*, 2015, Di Napoli *et al.*, 2018, Oishi *et al.*, 2018, Blombery *et al.*, 2016, 2018, Laurent *et al.*, 2020). In one study in which a limited panel of genes was assessed, 10/11 patients presented with mutations in genes attributed to activation of JAK/STAT signalling (Blombery *et al.*, 2018) and in a second study in which whole exome sequencing was conducted, 59% of 22 evaluable cases showed activating mutations in JAK/STAT pathway genes (Laurent *et al.*, 2020). This latter study also showed mutations in epigenetic modifiers and proteins of the PI 3-Kinase pathway (Laurent *et al.*, 2020). Recently, the important role of chromosomal copy number alterations over mutations was highlighted in the "in situ" phase with class-specific loss of chromosome 20q13.13 in 66% of BIA-ALCL cases which may be of diagnostic significance (Los–de Vries *et al.*, 2020). In addition, rare cases have been reported with mutations in or losses of genomic regions encoding *TP53* that were not found in the germline of the patients (Laurent *et al.*, 2020). In all, activation of JAK/STAT signalling is consistent with chronic inflammation mediated by cytokines as an oncogenic driver of BIA-ALCL.

Bacterial contamination and chronic inflammation

Every surgical procedure carries with it the inherent risk of contamination despite being conducted under sterile conditions. Surgery-associated contamination is for the most part controlled by antibiotic treatment and infection risks resolves over time in immunocompetent patients. Bacteria might also be introduced long after surgery e.g., by local migration from milk ducts or hematogenous spread from other infectious foci in the body. Some studies have indicated that the aetiology of BIA-ALCL may involve infection and the development of biofilms. Infections may cause inflammation surrounding a breast implant and cause increased rates of capsular contracture (Nava *et al.*, 2017). It might be that an increased inflammatory response to the presence of bacteria can cause seroma to form and further cause immunological responses leading to the development of BIA-ALCL (Ramos-Gallardo *et al.,* 2016, Clemens *et al.*, 2016).

It has been proposed that chronic bacterial sub-clinical infection may provide the stimulus to implant associated T cells to develop lymphoproliferations, in time transforming into malignancies. This chronic stimulus may be provided in an antigen-specific manner through the T cell receptor (TCR) or cytokine dependent activity (Malcolm *et al.*, 2016). Higher bacterial loads have been found on macro-textured implants. However, data regarding the identity of the causative bacterial species are controversial and remain to be elucidated. Initial studies detected *Ralstonia sp*. at higher levels at sites of BIA-ALCL-involved tumours compared to the contralateral breast although these data have since been disputed (Hu *et al.*, 2016, Walker *at al*., 2019). In particular, later studies have shown that there is no difference in the bacterial species composition nor bacterial load in the breast tissue of women with or without BIA-ALCL, neither in the contralateral breast or in comparison to normal controls.

Regardless of its direct mechanism, chronic stimulation of T cells either via the TCR, or driven by a cytokine-rich microenvironment likely plays an important role in BIA-ALCL. This is clearly underpinned by studies showing that a specific cytokine profile is associated with BIA-ALCL effusions (IL-10, IL-13, Eotaxin and IL-10/IL-6 ratio detected using a multiplexed immuno-based assay) and distinguishes BIA-ALCL from all types of benign late seromas with high specificity and sensitivity (Di Napoli *et al.*, 2020, Kadin, 2020). Chronic T- cell activation might facilitate the rapid proliferation of T cells, facilitating the acquisition of mutations in genes that favour the hallmarks of cancer and cellular transformation (Hu *et al.*, 2016, Walker *et al.*, 2019, James *et al.*, 2019). Indeed, the presence of activating JAK/STAT pathway mutations in many BIA-ALCL as detailed above, and the higher incidence of these mutations in tumour mass-type versus *in situ* seroma BIA-ALCL (80% vs 42%) is suggestive of a malignancy that is initiated by cytokine-induced JAK/STAT pathway activity. The tumour cells may become independent of the driving cytokines as JAK/STAT pathway mutations are clonally selected (Laurent *et al.*, 2020).

Shell shedding microparticles resulting in chronic inflammation
Shedding of particulate matter from textured implant surfaces can be precipitated by moderate adhesion (Webb *et al.,* 2017). Particles, presumably shed from implants, have been detected in multiple cases of BIA-ALCL associated with a textured implant and encapsulated within macrophages. Whether these are involved in the pathogenesis of BIA-ALCL remains to be demonstrated. Particulates shed from orthopaedic implants and the associated inflammatory response has been shown although their effects on the body are debatable and only a small number of orthopaedic implants have been associated with lymphoma in comparison to the rate of incidence in those with textured surface breast implants (Hallab *et al.*, 2019). These inflammatory reactions involve the formation of granulomas with a high number of macrophages with and without multinucleated giant cells (Hallab *et al.*, 2019). In addition, cells were present indicative of delayed type hypersensitivity (DTH) otherwise known as Type IV hypersensitivity which has also been reported in the context of BIA-ALCL (Kadin *et al.* 2018, Kadin *et al.* 2019). Differential diagnosis of BIA-ALCL and silicone-induced granuloma of breast implant capsule (SIGBIC) has been problematic in some cases (Fleury *et al.*, 2017). Activated macrophages produce cytokines that induce the chronic proliferation of Th1 cells which could be a mechanism towards the development of BIA-ALCL (Turner *et al.*, 2020).

Shell surface characteristics resulting in chronic inflammation
As described above, implant shells fall into one of two main categories: smooth and textured. The shell surface is in intimate/direct contact with the body tissue inducing, as is common for biomaterials, a foreign body reaction which may result in a chronic inflammatory reaction (Atlan *et al.*, 2018, Vassey *et al.*, 2020, Sheikh *et al.*, 2015, Wozniak *et al.*, 2004). This reaction can differ from implant to implant depending on the production methodology (salt loss, gas diffusion, imprint stamping, polyurethane foam coating) and final 3D aspects of the surface, which can be characterized by several parameters such as surface area, roughness, kurtosis, topography, skewness and tribology (Barr *et al.*, 2017, James *et al.*, 2019, Fleury *et al.*, 2017, Kadin *et al.*, 2018, Valencia-Lazcano *et al.*, 2013).

Friction is defined as the resistance to motion, measured as static friction (the force that must be overcome to start the object moving), or dynamic friction (the force needed to keep a surface in motion at a constant velocity) both expressed as the friction coefficient (FC) (Mendonça-Munhoz *et al.*, 2017, Dowson 2012). It has been shown that mechanical shear stress, i.e., friction on the periprosthetic tissue of the capsule, may induce different levels of inflammation with delamination within 80µm above the peaks of the macrotextured surfaces (Pitenis and Sawyer, 2020). The repetitive trauma and friction between breast tissue and the implant's surface have been associated with double capsule formation and synovial metaplasia, both signs of trauma and therefore chronic inflammation (Giot *et al.*, 2015). This continuous and unresolved inflammatory phenomenon may lead to chronic T cell stimulation and eventually lymphomagenesis through acquired malignancy-promoting mutations. It can therefore be assumed that a higher FC will result in more microtrauma with subsequent inflammatory reactions, consequently carrying a higher risk of neoplastic transformation.

Implant-associated reactive compounds
BIA-ALCL cells have been demonstrated to express the Aryl Hydrocarbon Receptor (AHR), a ligand activated transcription factor that binds chemicals of the aryl hydrocarbon (AH) family (Turner, 2019). On activation, it induces transcription of genes via binding to xenobiotic response elements (XRE) in their promoters including cytochrome P450 enzymes such as CYP1A1, CTP1A2 and CYP1B1 which can result in the production of toxic metabolites. Most notably, benzo[a]pyrene is converted to the carcinogen benzo[*a*]pyrene-7,8-diol-9,10-epoxide which induces DNA mutations. When expressed in T cells in particular, engagement of the AHR can mediate cellular differentiation between immunosuppressive regulatory T cells (Treg) to pro-inflammatory Th17 cells through up-regulation of expression of distinct cytokines dependent on the

substrate to which the cells are exposed. The presence of the AHR is supportive of a Treg/Th17 origin for BIA-ALCL, although Th1 and Th2 ancestry has also been proposed (Turner *et al.*, 2020). Whether the presence of the AHR is reflective of the cell of origin and/or disease pathogenesis remains to be determined as does the chemical composition of textured surface breast implants, particularly those that have been present in the body for protracted periods. Once the ligand for the AHR in the context of BIA-ALCL has been determined, its functional consequences to the cells in which it is expressed can be better elucidated (Kadin *et al.*, 2016, Kadin *et al.*, 2018, Turner S, 2020).

Conclusions
None of the proposed hypotheses are necessarily mutually exclusive. A combination of a textured breast implant, bacterial contamination, and genetic predisposition has been suggested to be necessary for BIA-ALCL to occur (Groth and Graf 2019). However, the presence of chronic inflammation, no matter what causes it, might drive lymphomagenesis by multiple pathways. In this manner, the chronically stimulated T cells would be assumed to acquire malignancy-promoting mutations. Alternatively/additively, gene mutations might also be a consequence of exposure to aryl hydrocarbons whereby toxic metabolites induce transversions in the genetic code of cells in the vicinity of the implant.

6.5 The safety of breast implants in relation to BIA-ALCL

Breast implants carry a *reasonable assurance* of safety and efficacy in that they perform as they were intended, as indicated by the long term follow-up evaluated by Calobrace *et al.* (Calobrace *et al.*, 2018). For the majority of patients, implants result in high levels of patient satisfaction (Ng *et al.*, 2019, Kouwenberg *et al.*, 2020). However, and based on epidemiological and other data from Competent Authorities, the lifetime incidence of BIA-ALCL has increased dramatically from initial reports of 1 per million to current highest estimates of approximately 1 per 3000 women with a breast implant in Australia and the Netherlands. The incidence is largely dependent on the "population" examined (region, implant type and characteristics) and increased awareness of this disease (Collett *et al.*, 2019). Breast implants have inherent risks, including both common and rare events. Patient and physician awareness of these risks ensure that an adverse event can be addressed in a timely manner. Breast implants are not lifetime devices, and women can expect that they will need to be replaced in time. Breast implant packaging includes box insert labelling, detailed safety information and directions for use. Prior to implantation, surgeons should seek reasonable and adequate informed consent by providing educational materials and ensuring that patients are aware of the benefits and risks of different types of implants, including the low absolute but high relative risk of BIA-ALCL associated with textured implants.

6.6 Future directions/research

There is an imminent need for an in-depth understanding of the pathophysiology and the role of patient genetics and/or the microbiome as well as features of the implant devices themselves in the development of BIA-ALCL. Moreover, reporting by the relevant registries of new BIA-ALCL cases is of major importance in order to produce a clear picture of the epidemiology of this disease with regards to the types of breast implants implicated in BIA-ALCL, the level of related and attributed risk, and the effectiveness of treatment procedures.

As BIA-ALCL is an uncommon malignancy, finding answers needs further research as presented above in section 2.1 "Answers to the Terms of References". Being an uncommon disease, developing and maintaining networks with cross-country communication are important. Also, current registries should collaborate and strengthen

their networks as well as aim to inform. This should be encouraged and actively supported by providing funding and infrastructural support.

There is a need to further evaluate the role of the implant surface on the induction of BIA-ALCL. For a proper characterization and classification of the implants surface more in depth knowledge of the surface is needed beyond average surface roughness.

7. CONSIDERATION OF THE RESPONSES RECEIVED DURING THE PUBLIC CONSULTATION

A public consultation on this Opinion was opened on the website of the Scientific Committees from 23 October to 7 December 2020.

Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

37 persons and organisations participated in the public consultation, providing input to different parts of the Opinion, resulting in 160 contributions.

All comments were answered in a separate table. Comments included issues regarding the causal relationship of BIA-ALCL and macro-textured implants, the lack of distinction between various types of textured implant surfaces, the choice of breast implant, the characterisation of breast implant surface, and the literature search and selection. In many cases, the Opinion was adapted based on these comments and a selection of the additional literature suggested in the comments.

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Annex

List of additional references retrieved through the literature search.

Microsoft Excel Worksheet