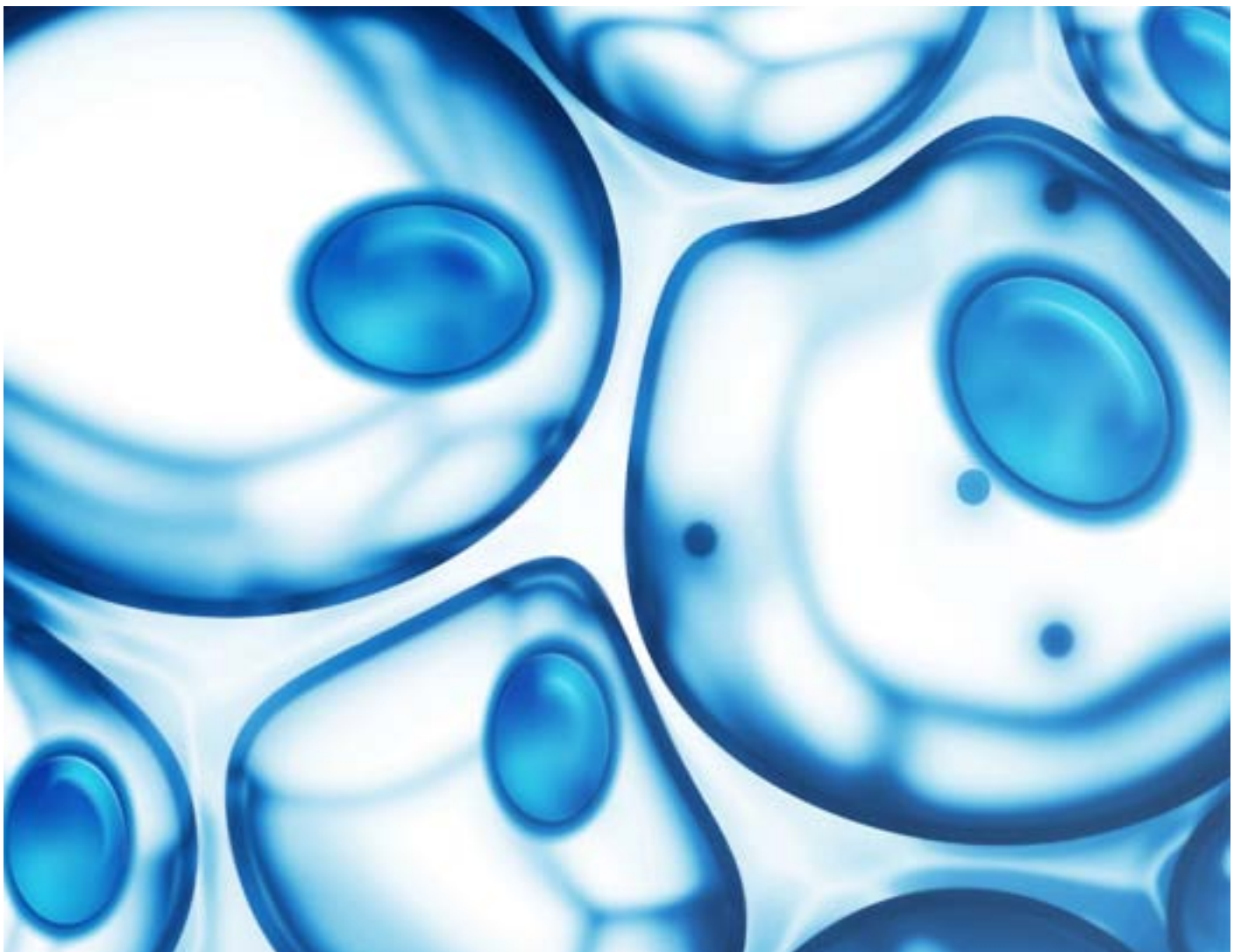


HUMAN TISSUES AND CELLS
– annual report 2011

2012



Human tissues and cells – Annual report

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1 Introduction

The Danish Tissue Act¹ from 2006 aims to ensure high and consistent quality and safety standards for the handling of human tissues and cells in Denmark. The act was fully implemented in Denmark in 2007. All tissue establishments that had applied at the appropriate time for authorisation of tissue establishment activity, pursuant to sections 4 and 5 of the Danish Tissue Act, were inspected in Q1 of 2007 by the Danish Health and Medicines Authority (previously the Danish Medicines Agency) and, in so far as they fulfilled the requirements, were granted an authorisation of their tissue establishment activity as of 7 April 2007. In the period 2007 to 2011, an additional 17 tissue establishments have been granted an authorisation from the Danish Health and Medicines Authority, and nine have stopped their on-site activities.

Practising gynaecologists performing assisted reproductive inseminations, according to the simple sperm-washing technique, must apply for authorisation to the Danish Health and Medicines Authority based on a special application procedure, pursuant to section 4 of the Danish Tissue Act. These gynaecological clinics were initially authorised based on the documents that they had submitted. Since 2008, inspections of individual gynaecology clinics were carried out on a random basis.

Procurement sites, for procuring tissues and cells and their transport to a tissue establishment, need not apply for authorisation as a tissue establishment, but must notify the Danish Health and Medicines Authority of its geographical location, the name of the responsible doctor as well as the types of tissues and cells being procured. Tissue establishments receiving tissues and cells from a procurement site are responsible for ensuring the procurement complies with the rules on donation, procurement and testing established by the Danish Health and Medicines Authority.

The provisions of the Danish Tissue Act apply only to human tissues and cells intended for therapeutic use in humans. Consequently, tissues and cells used in research are not covered by the Danish Tissue Act².

In 2011, a total of 55 tissue establishments and 32 gynaecology clinics were authorised by the Danish Health and Medicines Authority to handle human tissues and cells. Even though a tissue establishment may consist of more than one site, the number of tissue establishments is calculated based on the number of granted authorisations (*table 1*). In addition, a tissue establishment may also be authorised to perform testing, because testing is required prior to the release of human tissues and cells, cf. the Danish Tissue Act. The pie chart in *figure 1* shows the various types of human tissues and cells at end-2011.

¹ Danish act no. 273 of 1 April 2006 on requirements for quality and safety in the handling of human tissues and cells (Danish title: Lov om krav til kvalitet og sikkerhed ved håndtering af humane væv og celler nr. 273 af 01/04 2006), as amended by section 3 of act no. 534 of 17 June 2008 and section 2 of act no. 605 of 18 June 2012

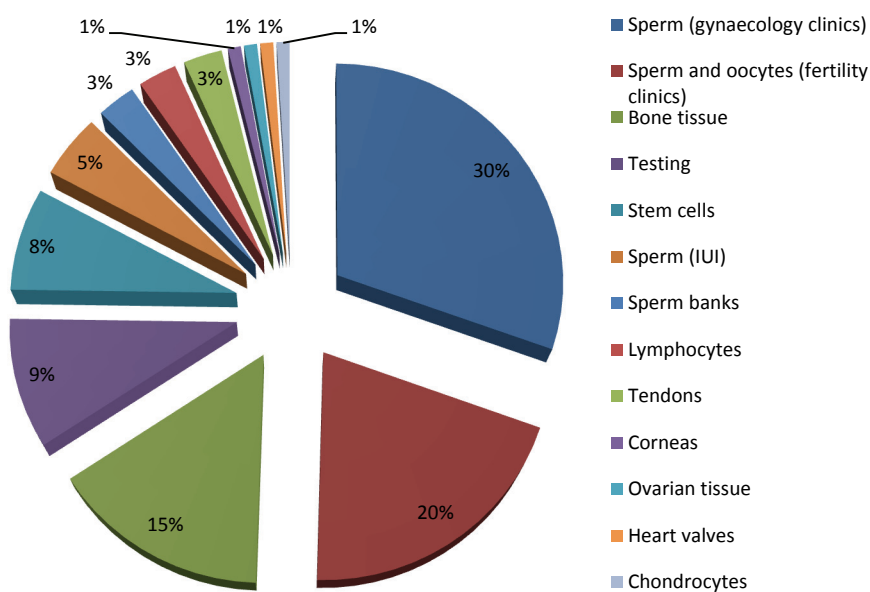
² Danish executive order no. 753 of 3 July 2006 on the quality and safety in connection with donation, procurement and testing (Danish title: Bekendtgørelse om kvalitet og sikkerhed ved donation, udtagning og testning" nr. 753 af 03/07 2006)

Table 1: Number of authorised tissue establishments and gynaecology clinics in Denmark as at 31 December 2011.

Authorised tissue establishments	2011
Reproductive cells for IVF <i>and</i> IUI	21
Reproductive cells for IUI only	6
Sperm banks	3
Bones (including 3 testing, 2 tendons, 1 IUI , and 1 bone substitute distributor)	13
Stem cells (including 4 testing, 3 bones, 2 umbilical cord, and 2 lymphocyte)	6
Stem cells from umbilical cords (<i>including 1 testing</i>)	2
Testing only	2
Chondrocytes	1
Miscellaneous (corneas, ovarian tissue, heart valves, lymphocytes)	4
Total number of authorised tissue establishments	55
Gynaecology clinics	32

Parentheses indicate if a tissue establishment is authorised to handle *several* types of tissues/cells or to perform testing. *Same organisation IVF: *in vitro* fertilisation, IUI: intrauterine insemination

Figure 1: Distribution of the various types of human tissues and cells 2011



2 Activities

A tissue establishment means a tissue bank, hospital department or other public or private unit where the activities of testing, processing, preservation, storage, distribution are undertaken or where import or export of human tissues and cells takes place. As mentioned earlier, procurement activities are not subject to authorisation.

Gynaecology clinics that exclusively wash sperm according to the swim-up technique³, can only obtain an authorisation for the processing activity, which means that their site authorisation is limited. If supplementary activities are carried out, e.g. storage activities, they must apply for a full authorisation for tissue establishment activity. Definitions of the various activities are given in *factbox 1*.

The annual report for human tissues and cells for 2011 has been prepared pursuant to section 15(2) of the Danish Tissue Act and is based on reports submitted by tissue establishments and gynaecology clinics in Denmark. The reports⁴ cover the activities having taken place in the calendar year 2011.

Since 2008, the Danish Medicines Agency has cooperated with the Danish Fertility Society (DFS). Data of reports submitted to DFS by fertility clinics, gynaecologists, and tissue establishments authorised to process sperm for IUI treatment have been used as the basis for the presentation of the relevant data in this annual report.

Factbox 1: Activities

Procurement: A process by which tissue or cells are made available.

Testing: Tests for markers of infection and other biological markers.

Processing: All operations involved in the preparation, handling, preservation and packaging of tissues/cells intended for human applications.

Preservation: The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues.

Storage: The maintaining of tissues or cells for more than 48 hours until distribution.

Distribution: Transportation and delivery of tissues/cells *in and between* Denmark and another country within the European Union (EU) and the European Economic Area (EEA).

Import/export: Transportation and delivery of tissues or cells to or from Denmark and another country within the EU and EEA (3rd country).

³ The swim-up technique is the washing of sperm cells according to a special technique. Sperm washing by means of the swim-up technique is performed in compliance with the Danish Health and Medicines Authority's 'standards for washing of sperm cells intended for partner or donor insemination' (available in Danish only).

⁴ Reports for two gynaecology clinics are missing.

3 Reproductive cells

Tissue establishments authorised to handle reproductive cells include public and private fertility clinics, gynaecology clinics as well as sperm banks (*table 2*).

Most of the tissue establishments (21) are fertility clinics performing *in vitro* fertilisation (IVF) and intrauterine insemination (IUI). Both IVF and IUI activities cover the use of sperm donations from the partner and/or a donor. Six tissue establishments exclusively handle sperm for IUI treatment.

Gynaecology clinics processing (i.e. washing) sperm cells by means of the 'swim-up' technique, intended for insemination by partner or donor, have been authorised pursuant to section 4 of the Danish Tissue Act. Sperm washing is to be performed in compliance with the Danish Health and Medicines Authority's 'standards for washing of sperm cells intended for partner or donor insemination' (available in Danish only).

The sperm banks handle and store donor sperm. The sperm is used in fertility treatment by distribution or export to the treatment facilities.

The reported data in 2011 show a general fall in the activities performed by clinics that provide fertility treatment. This fall in activity could be attributable to the introduction of user charges for fertility treatment. These charges were introduced in January 2011 and were abolished again in January 2012.

Table 2: Distribution of tissue establishments performing IVF treatment, handling sperm for IUI, or storing sperm in Denmark in 2011.

Type	Number
IVF + IUI (oocytes/embryos + sperm)	21
IUI (sperm)	6
Gynaecology clinics (<i>sperm</i>)	32
Sperm banks (<i>sperm</i>)	3

3.1 *In vitro* fertilisation (IVF) – fertility clinics

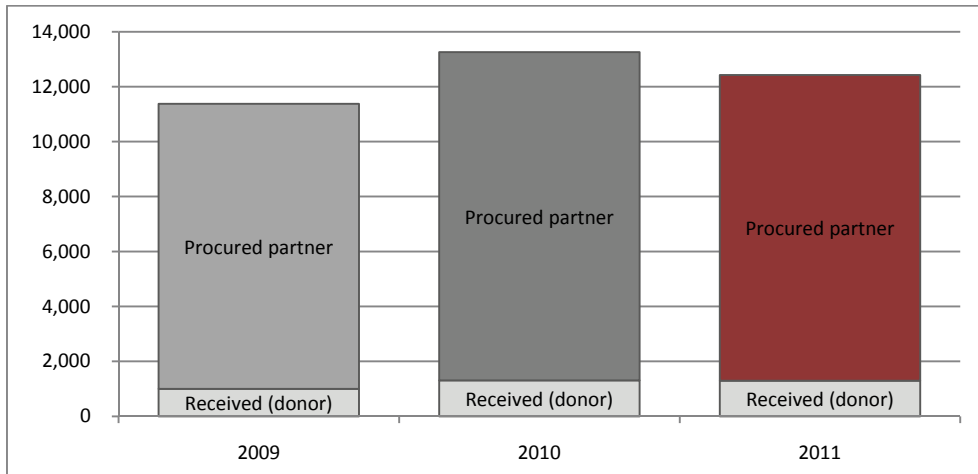
In vitro fertilisation is carried out only at fertility clinics. Like IUI, IVF treatment can take place with sperm from either the partner or a donor. A sizeable share of the sperm units processed (washed), and which are used for treatment at IVF clinics, also comprises the use of frozen sperm straws from stored units.

In IVF treatment, eggs (oocytes) are retrieved from the woman's ovaries, following which they are fertilised either via normal IVF treatment or by means of microinsemination, so-called ICSI (*Intracytoplasmic Sperm Injection*). In ICSI treatment, one single sperm cell is injected directly into the oocyte in order to fertilise it. The fertilised oocyte (the zygote) is then – after undergoing two to five days' cleavage in the laboratory – transferred as an embryo (or a blastocyst) to the woman.

Figure 2 provides an overview of the use of sperm units (samples/straws).

The total number of units procured from partner and received from donor equals the number of units processed and used in IVF treatment.

Figur 2: Activities IVF (sperm)

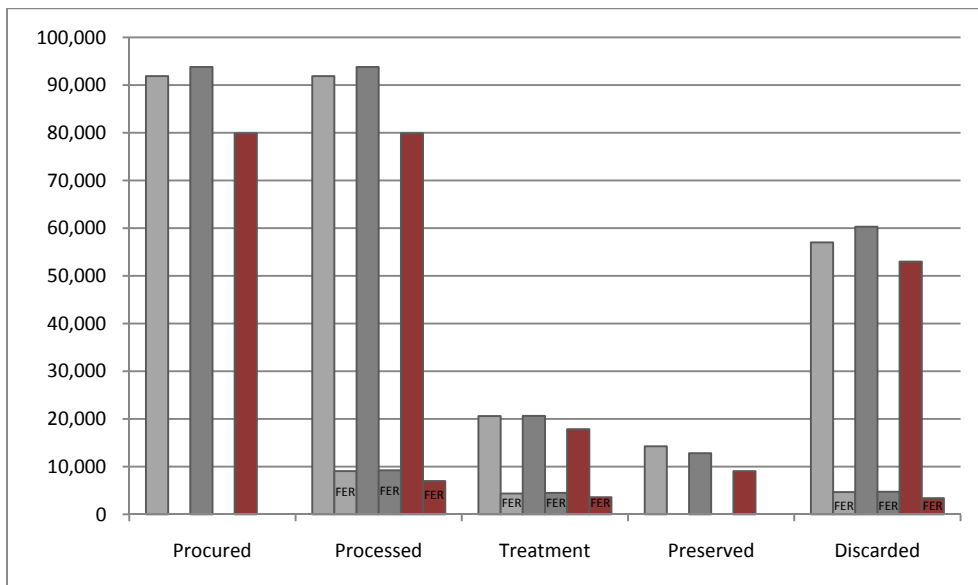


Distribution of tissue establishments performing IVF treatment, handling sperm for IUI, or storing sperm in Denmark in 2011.

Often, the treatment results in many more usable embryos than needed. These may be frozen and stored according to current Danish national legislation for up to five years. This enables so-called *frozen embryo replacement (FER)* later on in life, where the embryo originates from an earlier treatment cycle.

Figure 3 shows the number of oocytes and embryos used in IVF treatment. It also shows the share of frozen embryos (FER) processed, used or discarded. Data from 2009 and 2010 are included (*grey columns*) to facilitate comparison.

Figur 3: Activities IVF (oocytes/embryos)



Number of units of oocytes/embryos procured, processed, preserved, discarded as well as used for IVF treatment at fertility clinics in Denmark, FER: *frozen embryo replacement*. Light grey=2009, dark grey=2010, red=2011.

3.2 Intrauterine insemination (IUI) – fertility clinics and other tissue establishments for IUI

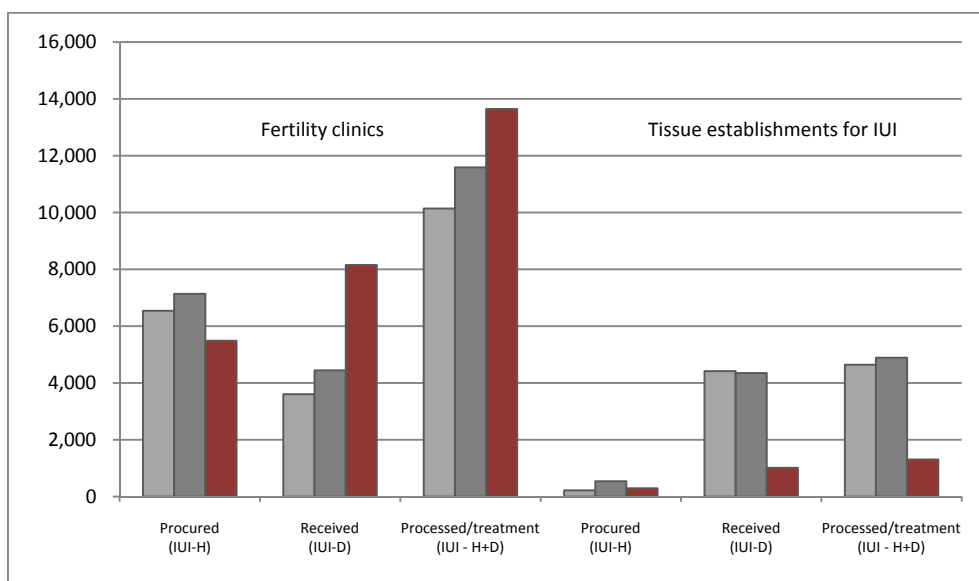
Fertility clinics as well as tissue establishments authorised to perform IUI treatment may perform insemination with partner sperm (IUI-H) or donor sperm (IUI-D).

In IUI treatment, sperm cells are washed, either by gradient centrifugation or the swim-up technique, to collect sperm of the highest quality.

The bar chart in *figure 4* shows the number of units of sperm donations or straws either procured, received or processed and used in treatments.

The chart both shows units from fertility clinics and from those tissue establishments authorised for IUI.

Figure 4: Activities IUI (sperm)



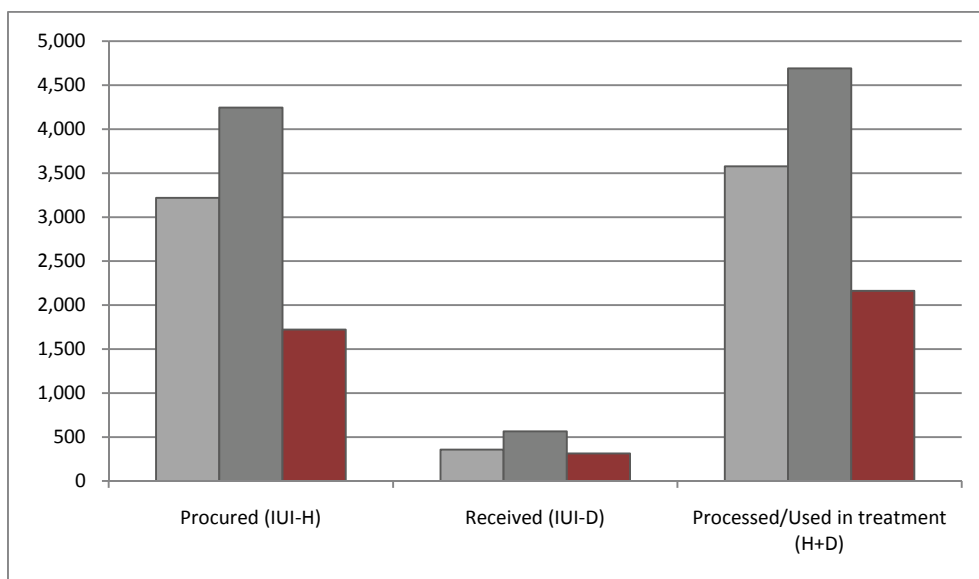
Total overview of number of sperm units (sperm donations or sperm straws) procured, received, processed and used in treatment at fertility clinics as well as tissue establishments authorised to process sperm for use in IUI treatment in Denmark. *Light grey=2009, dark grey=2010, red=2011.*

3.3 Activities at gynaecology clinics

Gynaecology clinics perform intrauterine insemination (IUI) with sperm from the partner (IUI-H) and intrauterine insemination with sperm from a donor from a sperm bank (IUI-D).

Procurement comprises the sperm donation from the partner. Processing comprises washing of sperm donations from the partner by means of the swim-up technique, as well as from a donor in the case where sperm units are not 'ready to use'. Ready to use comprises donated frozen sperm straws from a sperm bank for direct application. Units handled at gynaecology clinics appear in the bar chart in *figure 5*. Data from 2009 and 2010 are included (*grey columns*) to facilitate comparison.

Figure 5: Activities gynaecologists (IUI)

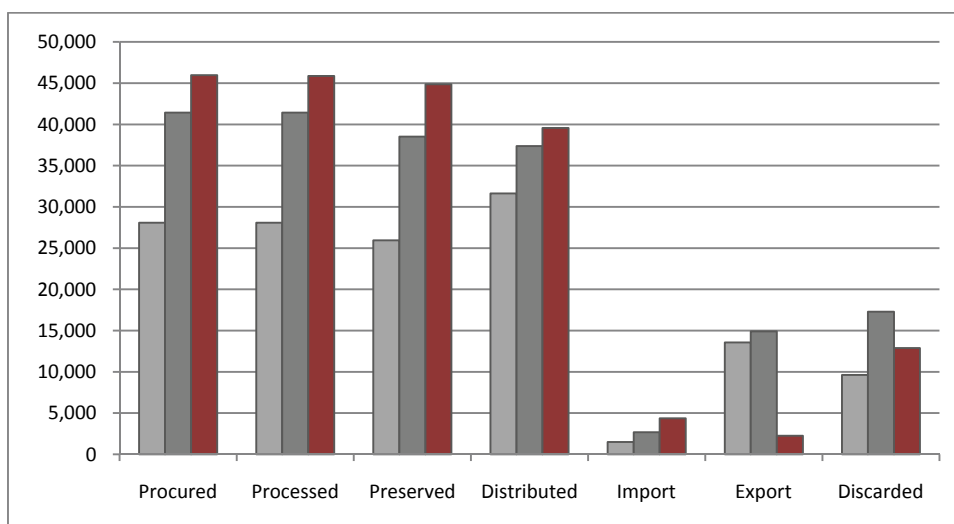


Number of units (sperm donations procured or sperm straws received) processed and used for treatment at gynaecology clinics in Denmark. *Light grey=2009, dark grey=2010, red=2011.*

3.4 Activities at sperm banks

The sperm banks procure, process, store and distribute donor sperm for use in fertility treatment. Sperm banks store sperm from patients at risk of becoming infertile due to, for example, cancer therapy. The sperm banks distribute⁵ and export⁶ to gynaecologists and fertility clinics for treatment purposes. The number of handled units (sperm donations/straws) from sperm banks appear in figure 6. Data from 2009 and 2010 are included (grey columns) to facilitate comparison.

Figure 6: Activities at sperm banks



Activities performed at sperm banks in Denmark. *Light grey=2009, dark grey=2010, red=2011.*

⁵ Within EU

⁶ Outside EU – third country

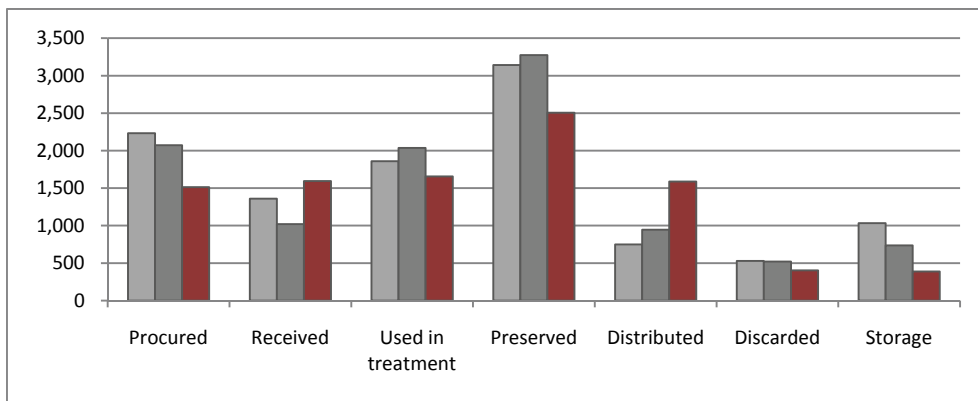
4 Other tissue establishments – non-reproductive cells

4.1 Bone tissue

Tissue establishments authorised to handle bone tissue are public hospital departments that store and redistribute bone tissues. In particular, the application of bone tissue involves the replacement of bone tissue in connection with hip and back surgery. Bone banks also receive bone tissue from other orthopaedic surgical departments which, as a result, serve as procurement sites. Processing is not included for bone tissue statements as the “preservation” practices are not classified as processing. Consequently, bone banks are typically not authorised to perform this activity.

Figure 7 provides a general view of the bone banks' activities with units of bone tissue. Stocks are stated as at 31 December 2011. Data from 2009 and 2010 are included (grey columns) to facilitate comparison.

Figure 7: Activities bone tissue



Activities at tissue establishments handling bone tissue in Denmark. *Light grey=2009, dark grey=2010, red=2011.*

4.2 Bone graft substitution

The international cooperation on tissues and cells also covers the controls with, and application of, bone substitutes for human use.

Human bone substitutes replace natural bone graft and are often based on calcium-based ceramics, growth factors, bone-forming cells or a combination thereof. Bone substitutes are used in orthopaedic surgery, both in bone loss treatment and, in a few cases, in fracture surgery.

In 2008, the regulatory status of human bone substitutes was reviewed by the European Commission and the Member States, and it was established that manufacturers, importers or distributors of human bone substitutes must submit an application to the relevant European national competent authority for authorisation of this activity.

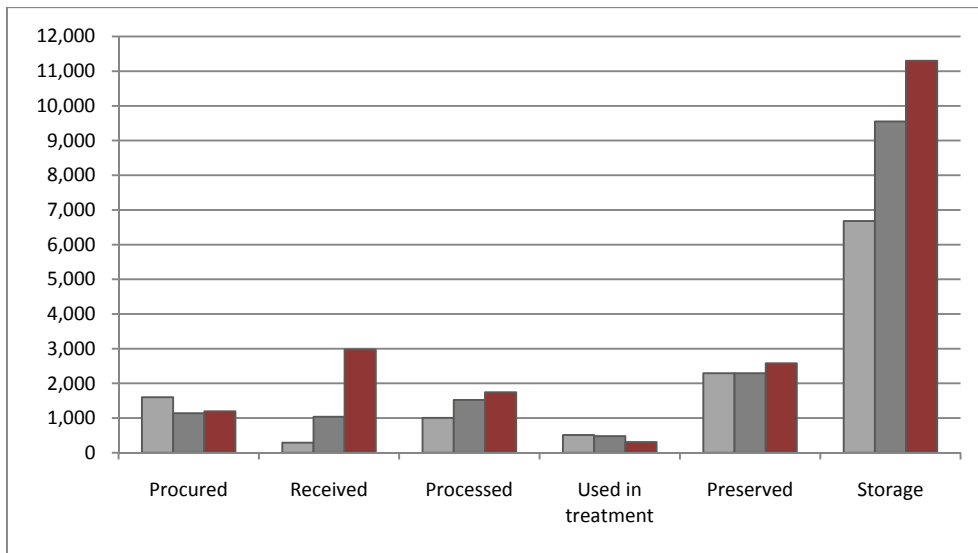
In Denmark, a distributor of human bone substitutes must therefore apply to the Danish Health and Medicines Authority for authorisation as a tissue establishment for the activities of storage and distribution, as well as importation if the product is supplied to Denmark from a third country (outside EU/EEA). Therefore, these distributors are solely responsible for ensuring that they satisfy the technical and legal requirements laid down in the Danish Tissue Act, to ensure the quality and safety of these products for the Danish and European markets.

In 2011, one distributor in Denmark was authorised by the Danish Health and Medicines Authority to handle bone substitutes.

4.3 Stem cells,

Tissue establishments authorised to handle stem cells are either public hospital units or private stem cell banks. Tissue establishments store stem cells derived from umbilical cord blood of newborns, peripheral blood stem cells or bone marrow, for allogeneic or autologous applications. Stem cell transplantations in which the stem cells are not considered an ATMP (Advanced Tissue Medicinal Product) are primarily used for the treatment of leukaemia and bone or lymphatic cancer. *Figure 8* shows the activities with stem cells in Denmark. The volume of stem cells *distributed* or *discarded* in Denmark accounts for less than 2 % of the total volume and is therefore not included. Stocks are stated as at 31 December 2011 and includes stocks of stem cells from umbilical cord blood, for autologous applications. Data from 2009 and 2010 are included (*grey columns*) to facilitate comparison.

Figure 8: Activities stem cells



Activities at tissue establishments handling stem cells in Denmark. *Light grey=2009, dark grey=2010, red=2011.*

5 Testing

Testing means the tests for markers of infection and other biological markers. Tests must be carried out on the donor's serum or plasma, as relevant. One exception is sperm donors who must also be tested negative for Chlamydia on a urine sample, and tests for Gonorrhoea which must be done via culture or PCR techniques.

Within Denmark, the national law requires all tests of human tissues and cells to be carried out at a testing centre authorised by the Danish Health and Medicines Authority. Consequently, tissue establishments that do not perform testing themselves must make contractual arrangements with an authorised testing centre.

A hospital department or other public or private unit that performs these tests, for the release of human tissues and cells, must therefore apply for authorisation as a tissue establishment.

Testing involves tests for HIV 1 and 2 (HIV), hepatitis B (HBV) and hepatitis C (HCV), and - with the exception of partner donors of reproductive cells – also tests for syphilis. Donors other than the partner of reproductive cells must furthermore be tested negative for Gonorrhoea and Chlamydia. In specific cases, tests for HTLV-1 and possibly tests for other pathogenic micro organisms may be relevant. *Factboxes 2* and *3* give an overview of the mandatory and, where relevant, the additional tests required in Denmark.

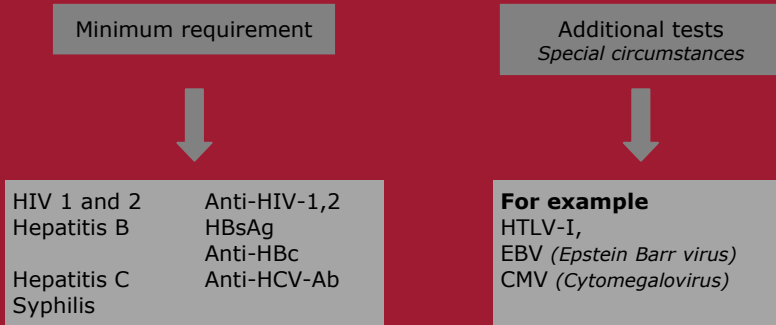
Serological testing of blood samples is the demonstration of antibody/antigen, whereas NAT testing is the detection of DNA/RNA from virus by means of the nucleic acid amplification technique. In 2011, a total of 10 tissue establishments were authorised to perform testing. *Table 3* provides an overview of the number of tissue establishments in Denmark authorised to conduct the various types of tests in 2011.

For living donors of tissues and cells for allogenic use, including sperm donors, repeat sampling and biological testing is required after an interval of 180 days. If the blood donation sample is additionally tested by the nucleic acid amplification technique (NAT) for HIV, HBV and HCV, testing of a repeat blood sample is not required. In Denmark, it is also required that blood donation samples of deceased donors be tested by the nucleic acid amplification technique (NAT) for HIV, HBV and HCV.

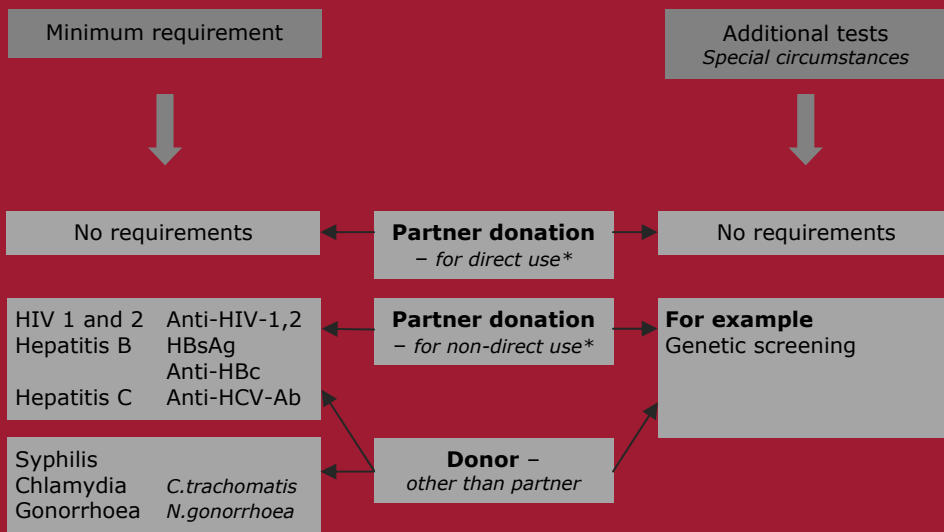
Table 3: Distribution of tissue establishments in 2011 authorised to conduct tests for different markers of infection by means of serological testing and/or the nucleic acid amplification technique (NAT).

Type of test	Serological	NAT	Syphilis	Gonorrhoea/Chlamydia
Number of tissue establishments	10	4	9	2

Factbox 2: Biological testing of donors – of cells other than reproductive cells



Factbox 3: Biological testing of donors – of reproductive cells



"Partner donation – for direct use" means that the recipient has an intimate physical relationship with the donor. This is also the case for "partner donation – for non-direct use", yet, in this case the cells either undergo subsequent processing or are stored.