



The NOTIFY project - a general overview



Centro Nazionale Trapianti
Italian National Transplant Centre



WHO Collaborating Centre
on Vigilance and Surveillance for
Human Cells, Tissues and Organs

WORLD HEALTH ASSEMBLY RESOLUTION WHO 63.22

Resolution 63.22 of the World Health Assembly was adopted in 2010 and gave WHO a mandate to **facilitate Member State access to appropriate informations** on donation, processing and transplantation of tissues, cells and organs, including data about serious adverse events and reactions.

NOTIFY PROJECT



**Sharing vigilance experience and
knowledge globally
- the NOTIFY Project (WHO)**

NOTIFY PROJECT: AIMS

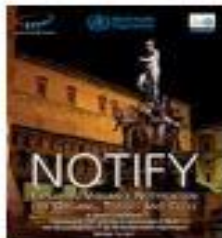
To provide professionals with relevant information helpful for determining the suitability of a potential donor.

To draft common guidelines supporting the implementation of effective vigilance and surveillance

To provide practical support to countries that are developing vigilance systems for Medical Products of Human Origin (MPHO)

NOTIFY Project: timeline

• The Bologna meeting



BRASILIA
Medical
Product of
Human
Origin

**WHO Consultation on
Vigilance and
Surveillance for Medical
Products of Human
Origin NOTIFY LIBRARY
PROJECT – First
Technical Meeting**

Barcelona, February 23-25

**NOTIFY project Second
technical meeting**

Rome, November 28-29

**Workshop with NOTIFY
experts: How to build a
vigilance system?**

1st African Society for Organ
Transplantation, 5th Egyptian
Transplantation Society
meeting

Cairo, October 18

2011

2012

2013

2014

2015

2015

2016

2018

2019

2020

**Rome Second Global
Consultation** --> first
NOTIFY Library website



**Barcelona -->
TRANSFUSION**



New NOTIFY Library
website and database

**Strategy for the NOTIFY
project as a global V&S
supporting system**

Bologna, December 1-2

**Global Vigilance
Networking for safer
transfusion,
transplantation and
assisted reproduction.**

A Joint Meeting of EU VISTART
Joint Action and the WHO
Notify Project.

**Keeping MPHO safe –
monitoring adverse
outcome and scanning
for new threats.**

A Joint ECDC and WHO NOTIFY
project meeting.

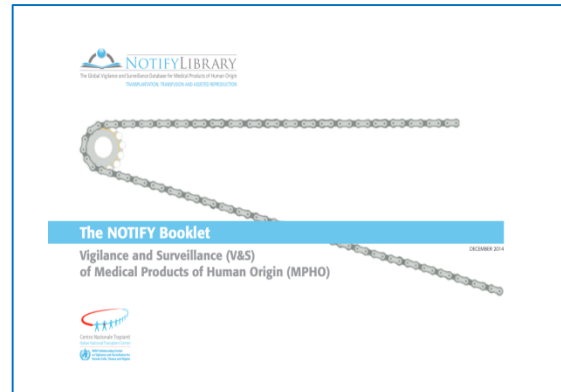
Virtual, October 1-2

Joint global initiative (WHO, CNT, SOHO V&S) to raise the profile of V&S of SOHO. Adoption of Resolution 63.22 by the World Health Assembly in 2010 “provide all Member States information about donation, processing, transplantation of tissues, cells and organs, including data about serious adverse events and reactions”.

NOTIFY PROJECT: MAIN COMPONENTS

1. NOTIFY website: <http://www.notifylibrary.org>

2. NOTIFY Booklet



3. NOTIFY Library



NOTIFY WEBSITE



The Global Vigilance and Surveillance Database for Medical Products of Human Origin
TRANSPLANTATION, TRANSFUSION AND ASSISTED REPRODUCTION



Centro Nazionale Trapianti
Italian National Transplant Centre



WHO Collaborating Centre
on Vigilance and Surveillance for
Human Cells, Tissues and Organs

THE NOTIFY PROJECT +

- History
- Who we are
- Interviews ▶
- Useful links
- Global consultation reports

SEARCH LIBRARY +

- Search tutorial
- Adverse occurrence search
- Reference search
- Bibliographic list ▶
- Add or update record
- Editorial Group Guidelines ▶
- Database content analysis

NOTIFY BOOKLET +

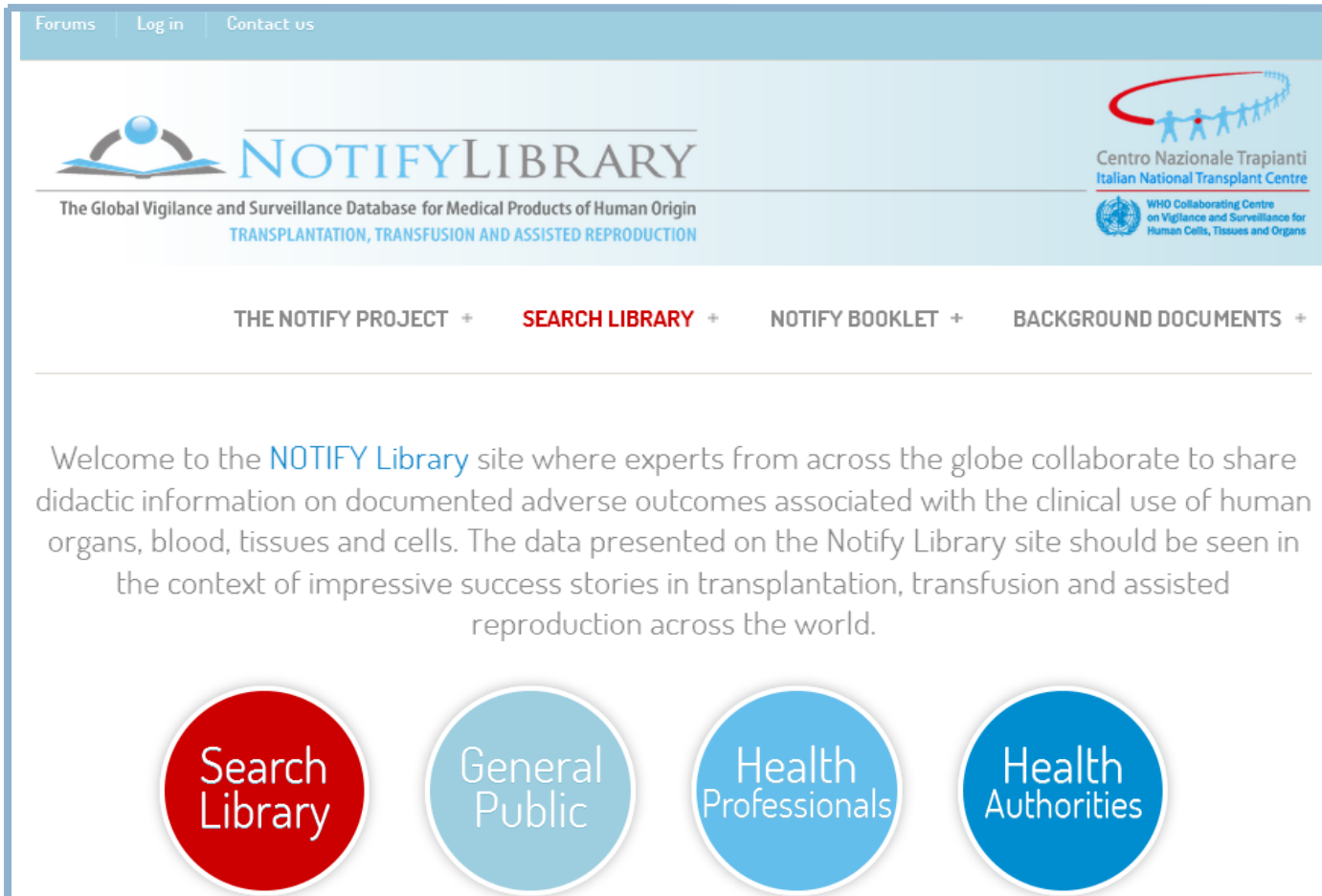
- 1 Introduction
- 2 The V&S Chain for MPHOs
- 3 History of Vigilance and Surveillance
- 4 Medical products of Human Origin (MPHO)
- 5 Towards a global governance of MPHO
- 6 The V&S system is primarily a responsibility for health authorities

BACKGROUND DOCUMENTS +

- WORLD HEALTH ORGANISATION (WHO) AND WORLD HEALTH ASSEMBLY (WHA)
- RECOMMENDATIONS ▶ FOR EPIDEMIC DISEASE OCCURRENCE
- VIGILANCE GUIDANCE DOCUMENTS
- VIGILANCE AND SURVEILLANCE REPORTS


NOTIFY WEBSITE


The website is maintained and updated on this platform and is intended as a **communication hub** for institutions and organisations worldwide collaborating in the facilitation of access to Vigilance and Surveillance information.




The screenshot shows the NOTIFYLIBRARY website interface. At the top, there is a navigation bar with links for 'Forums', 'Log in', and 'Contact us'. Below this is the main header area, which includes the NOTIFYLIBRARY logo on the left and the logos of the 'Centro Nazionale Trapianti Italian National Transplant Centre' and the 'WHO Collaborating Centre on Vigilance and Surveillance for Human Cells, Tissues and Organs' on the right. A horizontal menu bar contains the following items: 'THE NOTIFY PROJECT +', 'SEARCH LIBRARY +', 'NOTIFY BOOKLET +', and 'BACKGROUND DOCUMENTS +'. The main content area features a welcome message: 'Welcome to the NOTIFY Library site where experts from across the globe collaborate to share didactic information on documented adverse outcomes associated with the clinical use of human organs, blood, tissues and cells. The data presented on the Notify Library site should be seen in the context of impressive success stories in transplantation, transfusion and assisted reproduction across the world.' At the bottom, there are four circular buttons: 'Search Library' (red), 'General Public' (light blue), 'Health Professionals' (medium blue), and 'Health Authorities' (dark blue).

Forums | Log in | Contact us

 **NOTIFYLIBRARY**
The Global Vigilance and Surveillance Database for Medical Products of Human Origin
TRANSPLANTATION, TRANSFUSION AND ASSISTED REPRODUCTION


Centro Nazionale Trapianti
Italian National Transplant Centre

 WHO Collaborating Centre
on Vigilance and Surveillance for
Human Cells, Tissues and Organs

THE NOTIFY PROJECT + **SEARCH LIBRARY** + NOTIFY BOOKLET + BACKGROUND DOCUMENTS +

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Search Library **General Public** **Health Professionals** **Health Authorities**

NOTIFY CONSULTATION GROUP



NOTIFYLIBRARY

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THE NOTIFY PROJECT +

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Ask our experts for advice on vigilance and surveillance



Inform us of a case/reference for the Library

NOTIFY BOOKLET



- > 1 INTRODUCTION
- > 2 THE V&S CHAIN FOR MPHOS
- > 3 VIGILANCE AND SURVEILLANCE: HISTORY AND BASIC ELEMENTS
- > 4 MEDICAL PRODUCTS OF HUMAN ORIGIN (MPHO) - DONATION AND ETHICS
- > 5 TOWARDS A GLOBAL GOVERNANCE OF MPHO
- > 6 THE V&S SYSTEM IS PRIMARILY A RESPONSIBILITY FOR HEALTH AUTHORITIES
- > 7 ORGANIZATION FOR A COMPREHENSIVE - VIGILANCE & SURVEILLANCE SYSTEM
- > 8 VIGILANCE & SURVEILLANCE - RECOGNITION RELIES ON HEALTH CARE STAFF
- > 9 INVESTIGATING OCCURRENCES THAT COULD CAUSE HARM - LEARNING FROM ERRORS
- > 10 PROJECT NOTIFY

Booklet 2018

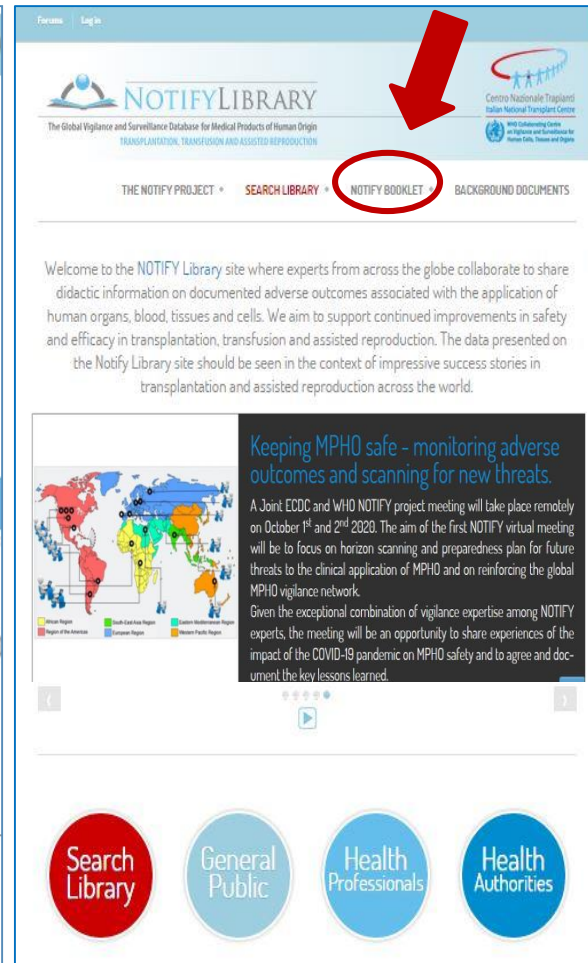


The NOTIFY Guide On Vigilance and Surveillance

Vigilance and Surveillance (V&S) of Medical Products of Human Origin (MPHO)

SECTION DISCUSSING 22nd 2017

- ▶ 1 INTRODUCTION
- 2 THE V&S CHAIN FOR MPHOS



Forum Log in

NOTIFYLIBRARY
The Global Vigilance and Surveillance Database for Medical Products of Human Origin
TRANSPLANTATION, TRANSFUSION AND ASSISTED REPRODUCTION

Centro Nazionale Trapianti
Italian National Transplant Centre
WHO Collaborating Centre
on Safety and Surveillance for
Human Cells, Tissues and Organs

THE NOTIFY PROJECT • SEARCH LIBRARY • NOTIFY BOOKLET • BACKGROUND DOCUMENTS

Welcome to the NOTIFY Library site where experts from across the globe collaborate to share didactic information on documented adverse outcomes associated with the application of human organs, blood, tissues and cells. We aim to support continued improvements in safety and efficacy in transplantation, transfusion and assisted reproduction. The data presented on the Notify Library site should be seen in the context of impressive success stories in transplantation and assisted reproduction across the world.

Keeping MPHO safe - monitoring adverse outcomes and scanning for new threats.

A Joint ECDC and WHO NOTIFY project meeting will take place remotely on October 1st and 2nd 2020. The aim of the first NOTIFY virtual meeting will be to focus on horizon scanning and preparedness plan for future threats to the clinical application of MPHO and on reinforcing the global MPHO vigilance network.

Given the exceptional combination of vigilance expertise among NOTIFY experts, the meeting will be an opportunity to share experiences of the impact of the COVID-19 pandemic on MPHO safety and to agree and document the key lessons learned.

Search Library General Public Health Professionals Health Authorities

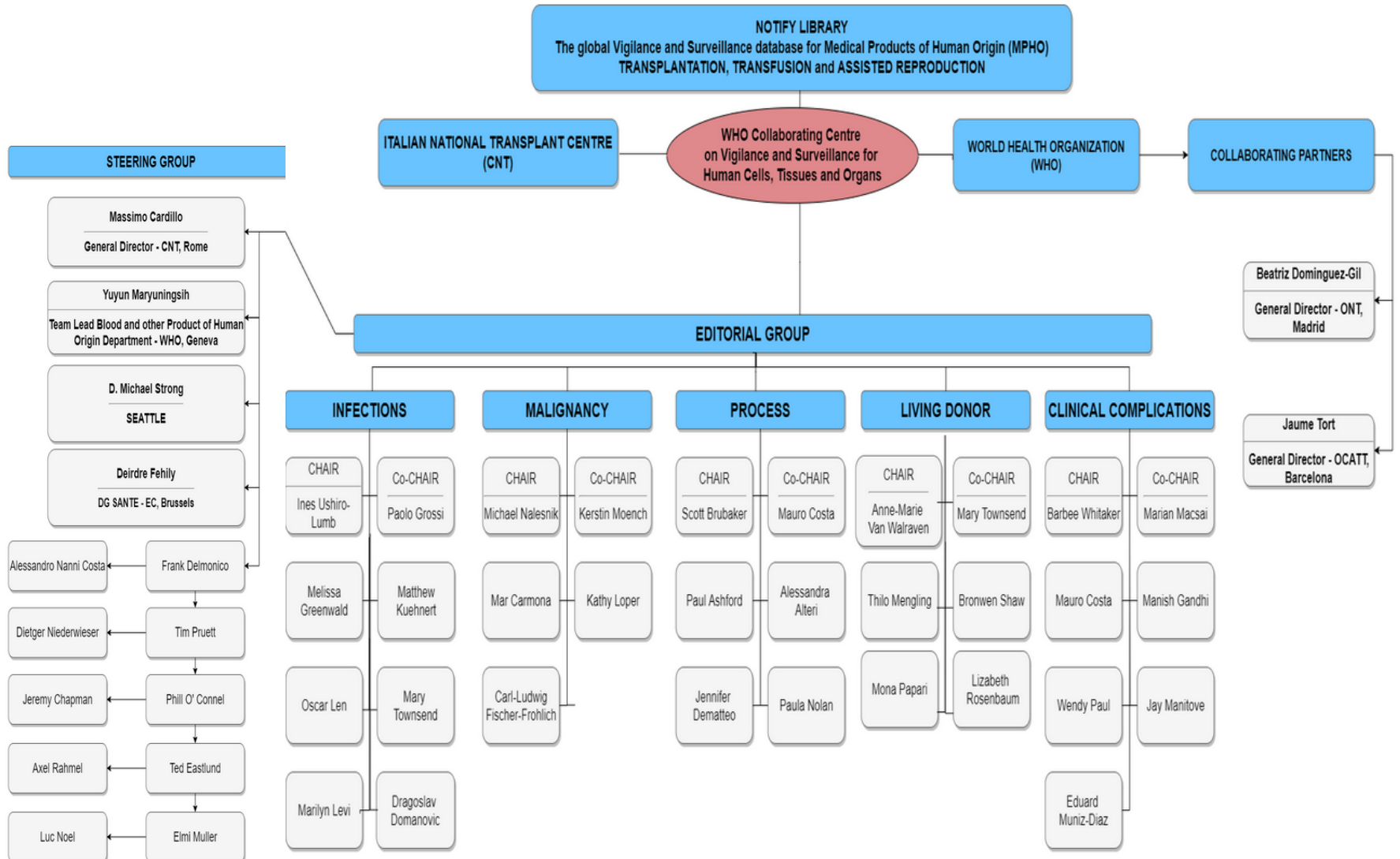
Interactive Booklet through an index

NOTIFY LIBRARY

- **publically accessible online database of didactic cases** of severe adverse reactions and events
- **from procurement and processing to clinical application** of blood, organs, tissues and cells used in transfusion, transplantation and assisted reproduction
- collected and analyzed by dedicated editorial groups of international experts, regulators and clinicians and **linked to their source reference:**
 - ✓ literature review (published articles in scientific journals and/or books)
 - ✓ case reports from regulatory or professional vigilance programs (grey literature)



WHO WE ARE



NOTIFY LIBRARY: ADVERSE OCCURRENCE DEFINITIONS

- 1. Severe Adverse Event (SAE):** any untoward occurrence, associated with the chain, from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity. *In the NOTIFY project these are referred to as cases of 'Risk of Harm'.*
- 2. Severe Adverse Reaction (SAR):** any unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity. *In the NOTIFY project these are referred to as cases of 'Harm to Donor', 'Harm to Recipient' or 'Harm to Fetus/Offspring'.*

NOTIFY LIBRARY: SEARCH PAGE

Adverse occurrence search

Adverse occurrence type

(Expand all) (Clear)

Harm to a Recipient

Harm to a Donor

Harm to a Fetus or Offspring

Risk of harm

Medical Products of Human Origin type – MPH0

(Expand all) (Clear)

Organs

Blood

Cells

Tissues

Reproductive

Derived medicinal products

Other

Keywords

(searches keywords identified by the Notify editors)

Free text

(searches the text in the database cases and includes alerting signals, imputability and keywords)

Notify Library Record ID

(searches by Notify Library Record ID, for multiple records separated by commas)

Limit results 100 per page

SEARCH

Reset

Print/Save selected items

New search

FREE
SEARCH

NOTIFY LIBRARY: SEARCH RESULTS

Search criteria:

Adverse occurrence: Risk of harm

Medical Product of Human Origin type - MPH0: Tissues >> Ocular

Feedback questionnaire

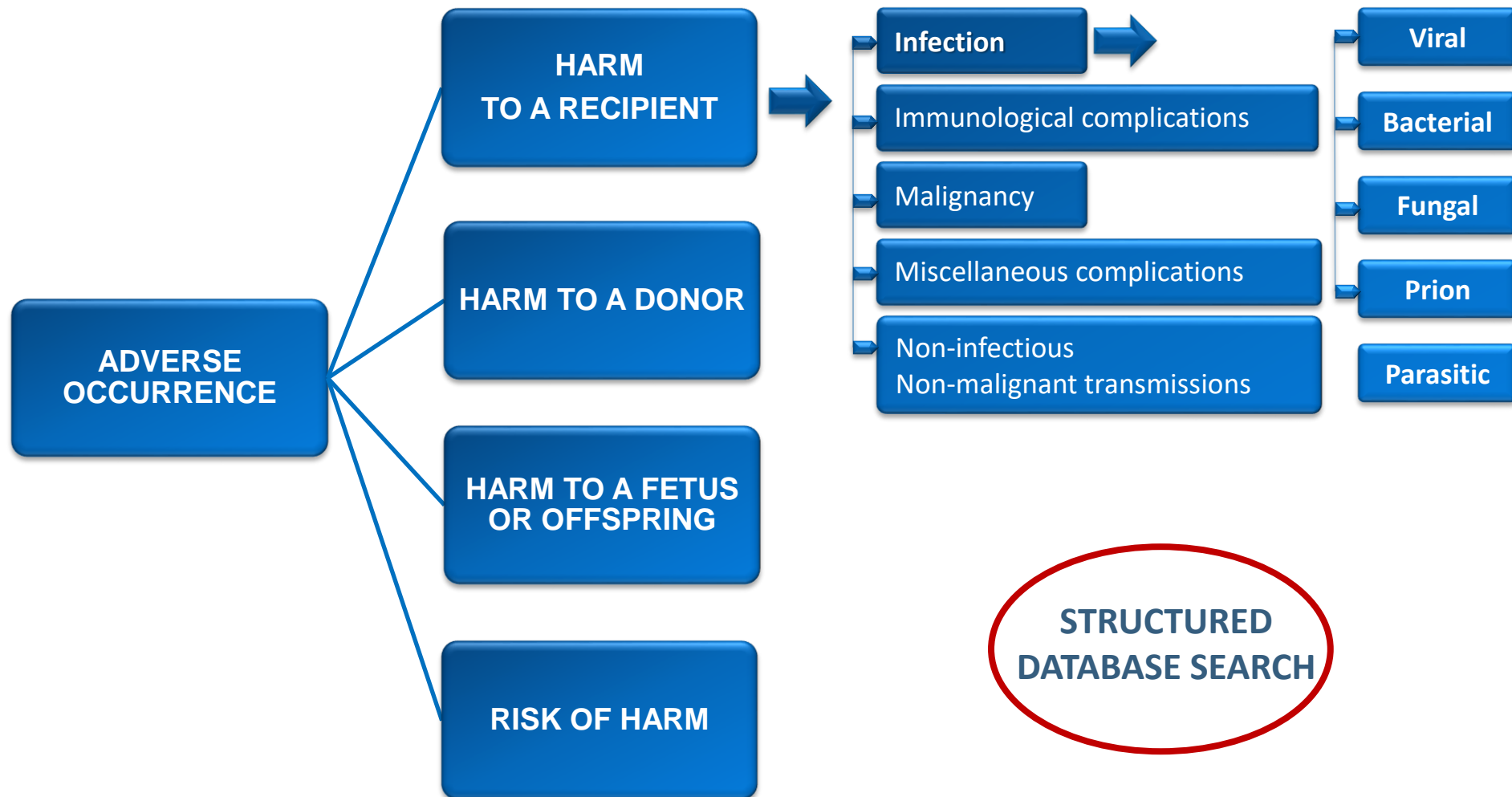
[4466] Li, J.Y.

[Donors with melanoma history: the risk to ocular tissue recipients](#)

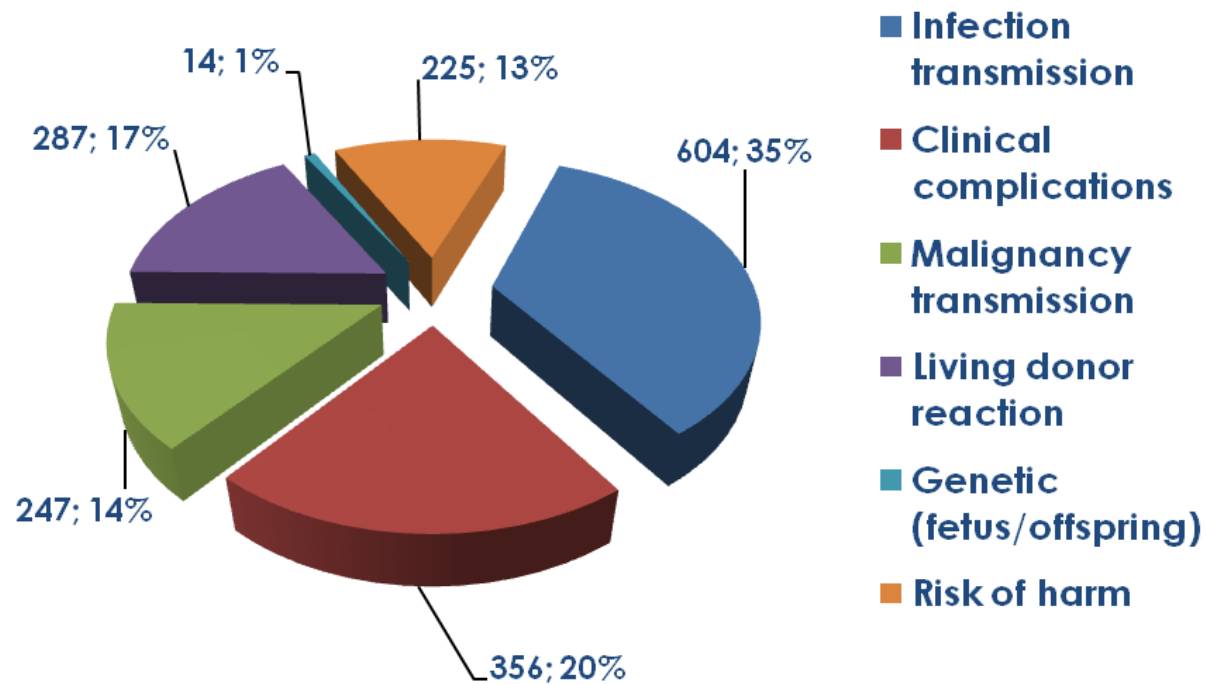
International Journal of Eye Banking 2016; 4 (1) :1-4

<input type="checkbox"/> Record ID	Adverse occurrence	
<input type="checkbox"/> 1683	<p>Adverse occurrence description: Subject review: Donors with melanoma history and risk to ocular tissue recipients</p> <p>Adverse occurrence type: Risk of harm => Other</p> <p>MPH0 type: Tissues => Ocular => Cornea</p> <p>Time to detection: 2 months</p> <p>Alerting signals, symptoms, evidence of occurrence: Recipient developed ocular melanoma within two months of surgery.</p> <p>Estimated frequency: Rare; Review article written in response to single case report of melanoma transmission following keratolimbal allograft. No existing reports in literature documenting melanoma transmission from corneal transplant. Based on the case report a moratorium on use of ocular tissue from donors with melanoma (restricted from all use) and donors with metastatic solid tumors (not to be released for use of vascular components) was issued in February 2016 to be reviewed by the Eye Bank Association of America in October 2016.</p> <p>Demonstration of Imputability or Root cause: Donor had history of malignant melanoma.</p> <p>Imputability grade:</p> <p>Expert comments for publication: Article was written as a review at the time of active discussion regarding the appropriate response to the cited case report. It is pointed out that donors with solid tumors constitute 30-40% of the ocular donor pool. In the case of melanoma, micrometastases raise concern for the possibility of transmission, but in practice this has not been seen. Possible factors contributing to the absence of known transmissions include the avascular nature of cornea and absence of immunosuppressive drugs. It is also noted that vascularized ocular components (such as keratolimbal allografts) also require immunosuppression and may have tumor transmission risks more similar to solid organ transplants. The article discusses the need to balance restoring sight and patient safety in the difficult setting of limited available evidence.</p> <p>Keywords:</p> <p>cornea transplantation cornea melanoma subject review keratolimbal metastasis exclusion criteria</p>	<p>1 reference</p>

NOTIFY LIBRARY: ADVERSE OCCURRENCE TYPE TAXONOMY (extract)

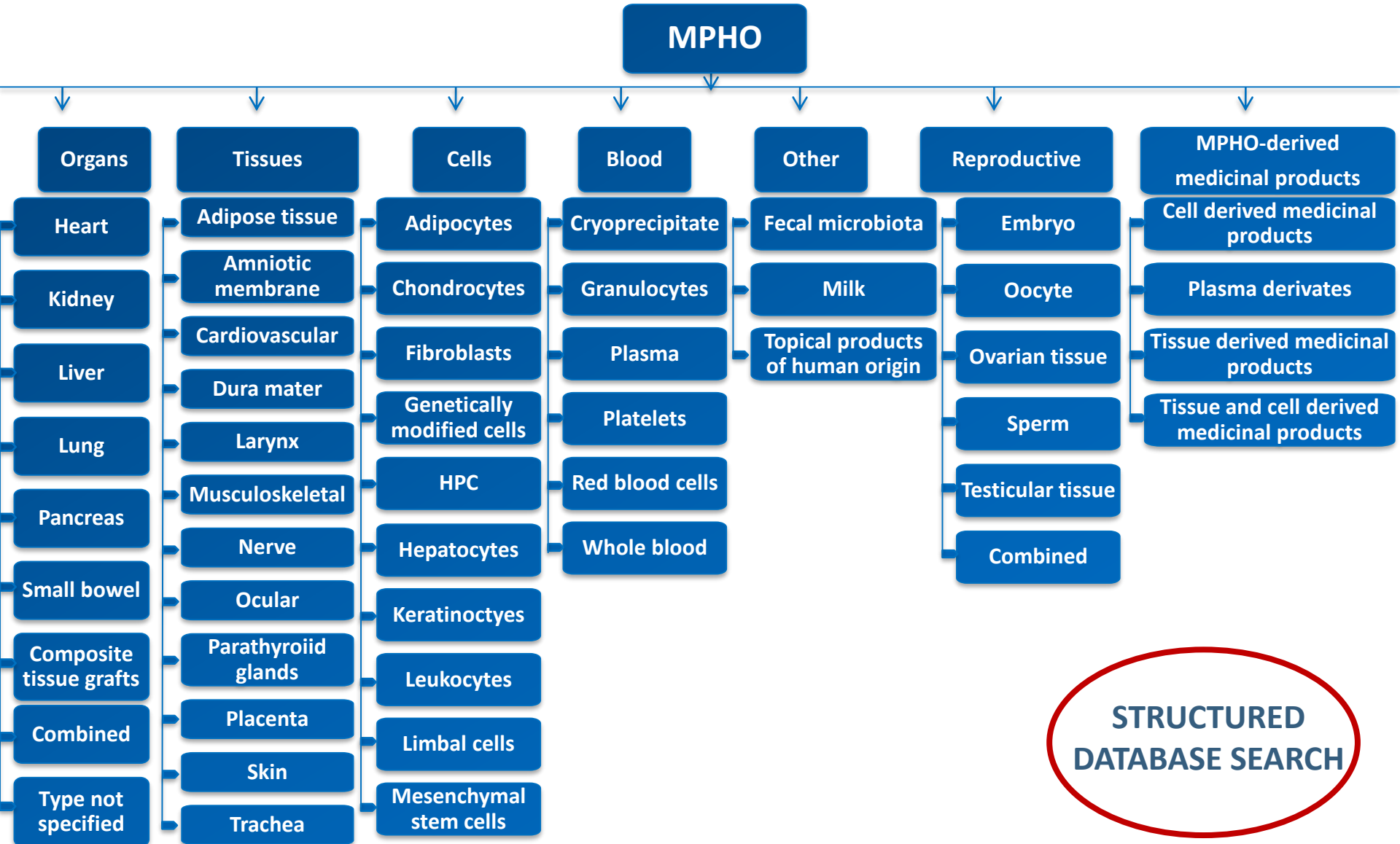


NOTIFY LIBRARY: UPLOADED RECORDS BY ADVERSE OCCURRENCE TYPE (n=1,733)

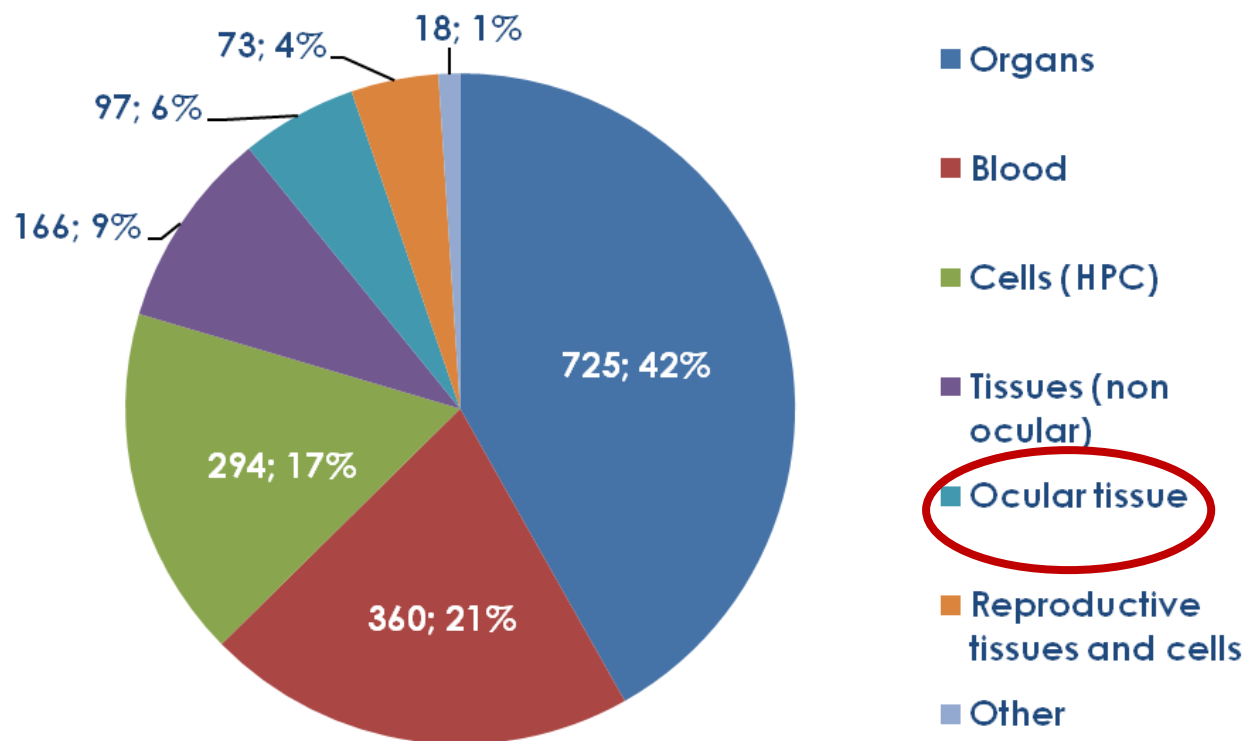


2,635 REFERENCES INDEXED

NOTIFY LIBRARY: MPHO TYPE TAXONOMY



NOTIFY LIBRARY: UPLOADED RECORDS BY MPHO TYPE (n=1,733)



2,635 REFERENCES INDEXED

Case examples from the Notify Library (1)

Record ID

☐ 1682

OCULAR TISSUE - HARM TO A RECIPIENT

Adverse occurrence

Adverse occurrence description: Subject review: Cornea transplantation from donors with cancer

Adverse occurrence type: Risk of harm => Other

MPHO type: Tissues => Ocular => Cornea

Time to detection: No cancer transmission seen. Recipients were followed for an average of 64.1 months (range 30-86 months).

Alerting signals, symptoms, evidence of occurrence: None in recipients.

Estimated frequency: In this series, 204 of 588 corneal donors (34.7%) had cancer. Of the cancer donors, 86.8% had solid cancer and 13.2% had hematological cancer. No cancer transmission was seen in 325 recipients.

Demonstration of Imputability or Root cause: Histologic study of the enucleated donor eye showed micrometastases in two cases. One donor with breast adenocarcinoma showed a single focus of malignant cells in the posterior pole, in the choroid. One donor with chronic myeloid leukemia showed leukemic infiltrates in the anterior and posterior poles, mainly in sclera and episclera with occasional foci in choroid and iris. None of the recipients developed cancer with 6.5 and 6 year follow up.

Imputability grade:

Expert comments for publication: On the basis of their review, the authors suggest that in cases of donors with cancer: 1. eyes with macroscopic tumor masses should be rejected; 2. cornea and anterior chamber should be examined by slit lamp to discard those with tumor infiltration; 3. histopathological study of the eye should be performed prior to corneal transplantation and cornea should be rejected in cases of tumor cellular infiltration. They also recommend careful recipient follow up during the first two years after transplant.

Keywords:

cornea transplantation

subject review

cancer

malignancy

histologic analysis

exclusion criteria

cornea

Case examples from the Notify Library (2)

Record ID

1065

OCULAR TISSUE - HARM TO A RECIPIENT

Adverse occurrence

Adverse occurrence description: Rabies Virus

Adverse occurrence type: Harm to a Recipient => Infection => Viral => Rabies virus

MPHO type: Tissues => Ocular => Cornea

Time to detection: 26 - 40 days

Alerting signals, symptoms, evidence of occurrence: Recipient 1: Post Op Day 26 presented with nausea and paresthesia of lips progressing to hydrophobia and death within two days. Recipient 2: Presented post op day 40 with vomiting and weakness.

Estimated frequency: N/A

Demonstration of Imputability or Root cause: Two recipients of corneas from the same donor developed rabies. Recipient 1, had diagnosis on post-mortem brain tissue using WHO-recommended laboratory techniques for FAT, RTCIT and MIT (all positive). Recipient 2, Saliva, blood and CSF using the MIT test, positive FAT on Brain, RTCIT on Brain and saliva, MIT on Serum, Monoclonal antibody test on serum. FAT fluorescence antibody test; RTCIT rapid tissue culture infection test; MIT mouse inoculation test; MNT mouse neutralization test.

Imputability grade: 3 Definite/Certain/Proven

Expert comments for publication:

Keywords:

rabies

Rabies Virus

cornea

hydrophobia

weakness

vomiting

death

CSF (cerebrospinal fluid)

FAT (fluorescent antibody test)

RTCIT (rabies tissue culture infection test)

MIT (mouse inoculation test)

Simani S, et al. Six fatal cases of classical rabies virus without biting incidents, Iran 1990-2010. J Clin Virol. 2012 Jul;54(3):251-4
Bhaumik S. Rabies after corneal transplantation: non-canine rabies and eye banking. Natl Med J India. 2012 Jul-Aug;25(4):249

Case examples from the Notify Library (3)

976

OCULAR TISSUE – RISK OF HARM

Adverse occurrence

Adverse occurrence description: 40 sclera destroyed because of blue spots

Adverse occurrence type: Risk of harm => Loss => Large quantity of unmatched MPH0

MPH0 type: Tissues => Ocular => Sclera

Time to detection: N/A

Alerting signals, symptoms, evidence of occurrence: Detected by treating physician before transplant

Estimated frequency: This problem happened before in 2008 at the same tissue establishment.

Demonstration of Imputability or Root cause: Investigation by tissue establishment: used materials, electron microscope scan, experiments with used material. Cause most likely originating from disposables. 40 sclera in stock also had blue spots and were destroyed.

Record ID

720

TRIP annual report 2010 Tissue Vigilance 2010

Adverse occurrence

Adverse occurrence description: Cornea with contact lens supplied for transplant

Adverse occurrence type: Risk of harm => Unsuitable MPH0 released for clinical use - no harm

MPH0 type: Tissues => Ocular => Cornea

Time to detection: N/A

Alerting signals, symptoms, evidence of occurrence: Evidence of a poor in situ inspection before retrieval, or inadequate recovery technique, may be discovered by the surgeon upon receiving the tissue, or at the time of surgery: an irregular or insufficient scleral rim, uveal tissue or lens residues, a contact lens still present

Estimated frequency: N/A

Demonstration of Imputability or Root cause: Self evident

Ehrenhaus, M.P, et al. Eye banking error: report of a donor cornea with a soft contact lens left in place. Cornea 2006; 25 (3) :359 - 60

Case examples from the Notify Library (4)

Guide to the Quality and Safety of TISSUES AND CELLS for Human Application



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EDQM
4th Edition
2019

The Notify Library includes some well-documented cases of adverse reactions and adverse events in transplantation of ocular tissue; for example:

- A case of donor-to-recipient transmission of the *Herpes simplex* virus (HSV) by cornea transplantation was confirmed by polymerase chain reaction-based DNA fingerprinting of donor and recipient HSV strains (Record Number 429);
- In Record Number 20, a transplant-acquired diagnosis of rabies is supported by temporal association of the recipient's illness, lack of other exposure to rabies and the retro-orbital pain of the recipient of the corneal transplant;
- In Record Number 338, a case of transmission of T-cell lymphoma is described, whereby molecular analyses were used to detect the same alleles in HLA-DQA testing of the recipient and donor of the graft;
- Record Number 720 reports a case of donor ocular tissue being examined and then shipped to the eye bank with a contact lens on the cornea, thereby highlighting the importance of *in situ* inspection before recovery;
- Record Number 1663 describes metastases from a cholangiocarcinoma in the vascularised limbal region of a corneoscleral disc. There was no evidence of transmission to the recipient of the avascular corneal graft. The authors recommended that tissue from donors with a history of malignancy should not be used for limbal allografting [14].

Further cases of adverse outcomes associated with ocular tissue can be found in the Notify Library at www.notifylibrary.org. The database is publicly accessible and can be searched by the substance type, adverse occurrence type and record number. A



THE NOTIFY PROJECT +

SEARCH LIBRARY +

NOTIFY BOOKLET +

BACKGROUND DOCUMENTS +

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WORLD HEALTH
ORGANISATION (WHO)
AND WORLD HEALTH
ASSEMBLY (WHA)

RECOMMENDATIONS
FOR EPIDEMIC
DISEASE
OCCURRENCE

SARS-CoV-2
Zika virus (ZIKAV)

VIGILANCE GUIDANCE
DOCUMENTS

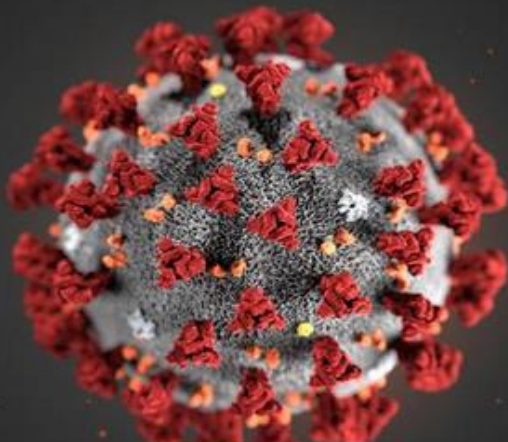
VIGILANCE AND
SURVEILLANCE
REPORTS



Ask our experts for advice on vigilance and surveillance



Inform us of a case/reference for the Library



MPHO safety recommendations related to SARS-CoV-2

A new section for [MPHO safety recommendations related to SARS-CoV-2](#) released by health authorities or professional societies is now available under Background documents. The links are being constantly updated as new information comes in. Further recommendations on COVID-19 outbreak and Rapid Risk assessment are available at the link: [ECDC Rapid Risk Assessment](#), and additional recommendation on [MPHO supply in EU/EEA](#) (latest Update April2020) [CDC Rapid Risk Assessment](#)

CONCLUSION

Notify is a joint Global initiative that **supports the sharing of published vigilance information** for teaching purposes and greater public transparency on the use of Medical Products of Human Origin.

The Notify Library is the first database that aims to **organize the current knowledge** about serious adverse events and reactions of organs, blood, tissues, cells and ART available globally **in a single, publically accessible database**.



NOTIFYLIBRARY

THANK YOU



Centro Nazionale Trapianti
Italian National Transplant Centre



WHO Collaborating Centre
on Vigilance and Surveillance for
Human Cells, Tissues and Organs