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# **Medical Device Material Performance Study**

## **Polyethylene Terephthalate (PET) Safety Profile**

*Prepared for*  
**U.S. FDA Center for Devices and Radiological Health**

*Submitted to*  
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*Date of Submission*

November 24, 2020

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## Executive Summary

### Key Points

1. Searches identified 789 citations; 62 articles were selected for inclusion.
2. The local response in the largest number of studies was inflammation, and it was associated with moderate quality of evidence. Other local responses for PET devices (including serious events such as thrombus and stroke) were associated with low or very low quality of evidence. Inflammation was reported over periods ranging from 2 days to 3 years post implantation, and other events were reported over periods ranging from 2 days to 29 years post implantation.
3. One small case series reported angiosarcoma that developed in 7 patients who received PET vascular grafts. This was a very rare event (7 cases total in the literature over a 40-year period). No other studies that met inclusion criteria investigated or reported systemic reactions to PET devices.
4. The most common complication reported within surveillance data for PET was device malfunction/fracture (76% of all PSO reports) and the vast majority of report incidents involved stents/balloons.
5. Most complications that resulted in harm had a harm score of E (13%), requiring temporary intervention, and F (5%), requiring temporary hospitalization.
6. Problem Reports and Alerts had 2 reports of transcatheter septal occluders eroding through the myocardium, which is a life-threatening complication. 1 death associated with stents and balloons was reported.
7. Evidence gaps:
  - a. Systemic response to all PET as a material and all devices.
  - b. Local response to PET in ligaments, valves, stents/balloons, atrial septal defect/left atrial appendage closure devices.
  - c. Relatively short follow-up periods ( $\leq$  years) for assessment of inflammation and related events.

### Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering 5 key questions, provided by FDA and summarized below, regarding a host's local and systemic response to polyethylene terephthalate (PET). If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

#### 1. What is the typical/expected local host response to PET?

Local responses and device events varied somewhat across different device categories and between human and animal studies (see specific responses/events under 1a. below). However, inflammation was consistently reported across almost all device categories. The majority of ECRI surveillance data was related to device malfunction or failure, particularly with stents/balloons. However, it was unclear in the data if this was related to material response due to insufficient biocompatibility or mechanical integrity and use of the device.

- a. *Can that response vary by location or type of tissue the device is implanted in or near?*
  - i. Studies of PET as a material predominantly evaluated PET sutures, and a majority of studies reported mild local inflammatory responses (including foreign body reaction). Other local responses or device events reported in fewer studies within this category included fibrosis, deep vein thrombosis, discomfort, suture migration, necrosis, and cord fracture.
  - ii. Studies of PET grafts reported inflammation and/or synovitis in a majority of studies. Events reported in fewer studies included foreign body reaction, graft failure, graft migration, occlusion, rupture, aneurysm, pseudoaneurysm, fistula formation, aortic valve dysfunction, fibrosis, bleeding, thrombosis, stenosis, endoleak, and pulmonary embolism.

- iii. Studies of PET patch/mat/mesh/substrates reported inflammation in a majority of studies. Other events reported in fewer studies include foreign body reaction, thrombosis, stroke, and device fragmentation.
- iv. Studies of PET ligaments reported inflammation in a majority of studies. Other events reported in fewer studies include swelling and effusion; graft breakage, rupture, tearing, or failure; synovitis, night pain, and capsulitis.
- v. The overall quality of evidence related to local host responses and device events was moderate to very low, with variation across different device categories.
- vi. Very little evidence was found regarding local host responses for valves, stents, and balloons.
- vii. No evidence was found regarding local host responses for atrial septal defect/left atrial appendage closure devices.

*b. Over what time course does this local host response appear?*

- i.* Follow-up time varied for different device categories and outcomes. Studies evaluated inflammation and other events following PET material exposure during periods ranging from 1 month to 3 years. Studies evaluating Dacron vascular grafts reported complications such as graft failure, occlusion, rupture, aneurysm, pseudoaneurysm, fistula formation, and aortic valve dysfunction occurring from 3 to 29 years postimplantation. Studies evaluating patch/mat/mesh/substrates reported local responses/events (e.g., inflammation, foreign body reaction, thrombosis, stroke) occurring from 2 days to 7 years postimplantation. Studies evaluating ligaments reported local responses/events (e.g., ruptures, synovitis) occurring up to 5 years postimplantation. Studies of Mitroflow valves reported thrombus, pannus formation, calcification, cusp thickening, and cusp tears within 3 to 4.5 years postimplantation.

**1. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?**

*a. What evidence exists to suggest or support this?*

No studies reported data regarding exaggerated immune responses that may lead to systemic signs or symptoms related to PET devices. However, a possible systemic manifestation is noted below.

*b. What are the likely systemic manifestations?*

One small case series reported angiosarcomas that developed in 7 patients who received PET Dacron vascular grafts. The quality of evidence is low. No other studies that met inclusion criteria investigated or reported systemic reactions to PET devices.

*c. What is the observed timeline(s) for the systemic manifestations?*

Angiosarcomas developed from 3.5 to 17 years following implantation, and they began at or near the site of the implant.

*d. Have particular cellular/molecular mechanisms been identified for such manifestations?*

No studies reported on cellular/molecular mechanisms underlying systemic manifestations.

**2. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?**

No studies addressed patient-related factors that may affect a sustained immunological/systemic response.

**3. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?**

No studies addressed material-related factors that may affect a sustained immunological/systemic response.

**4. What critical information gaps exist and what research is needed to better understand this issue?**

All gaps listed here indicate could benefit from future research.

- i. Systemic response for PET as a material and for all devices included in this review. There were very few studies on any PET devices that reported on systemic responses.
- ii. Device failure as a function of biocompatibility or mechanical integrity.
- iii. Local response to PET in ligaments, valves, stents/balloons, and atrial septal defect/left atrial appendage closure devices. There was very little (and very low to low quality) evidence for local response to these devices.
- iv. Relatively short follow-up periods ( $\leq 3$  years) for assessment of inflammation and related events.

## Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials were selected by FDA based on current priority. For 2020, the following six materials were chosen:

1. Siloxane (Si)
2. Polypropylene (PP)
3. Polyether ether ketone (PEEK)
4. Poly(lactic-co-glycolic acid) (PLGA)
5. Polyurethane (PUR)
6. Polyethylene terephthalate (PET)

The systematic review was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions:

1. What is the typical/expected local host response to the material?
  - Over what time course does this local host response appear?
  - Can that response vary by location or type of tissue the device is implanted in or near?
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
  - What evidence exists to suggest or support this?
    - In-vivo/clinical studies/reports?
    - Bench or in-vitro studies?
  - What are the likely systemic manifestations?
  - What is the observed timeline(s) for the systemic manifestations?
  - Have particular cellular/molecular mechanisms been identified for such manifestations?
3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
5. What critical information gaps/research are needed to better understand this issue?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the 6 materials listed above to include the summary of key findings from the systematic review and surveillance search and are included in this report.

## Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2010 and 2020 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
  - Strength
  - Embrittlement
  - Degradation
  - Migration
  - Delamination
  - Leaching
  
- **Host Response**
  - Local
    - Inflammation
    - Sensitization
    - Irritation
    - Scarring/fibrosis
      - *Keloid formation*
      - *Contracture*
    - Ingrowth
    - Erosion
  - Systemic
    - Cancer
    - Inflammation
    - Immune Response
    - Fatigue
    - Memory Loss
    - Rash
    - Joint Pain
    - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by the FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Resulting literature was screened by title review, then abstract review, and finally full article review. Data were extracted from the articles meeting our inclusion criteria to address the key questions for each material.

## ECRI Surveillance Search Strategy

There are 4 key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

ECRI surveillance data comprise ECRI Patient Safety Organization (PSO) event reports, accident investigations, Problem Reporting Network (PRN) reports, and alerts. The PSO, investigations, and PRN reports included in this report include mostly acute patient events. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in the clinical literature. Complications are reported directly by clinical staff, thus reports vary greatly in the level of detail provided.

## ECRI PSO

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through May 2020, unless otherwise noted.



Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

Category A (no Error)

Circumstances or events that have the capacity to cause error

Category B (Error, No Harm)

An error occurred but the error did not reach the patient (An "error of omission" does reach the patient)

Category C (Error, No Harm)

An error occurred that reached the patient but did not cause patient harm

Category D (Error, No Harm)

An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm

Category E (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention

Category F (Error, Harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization

Category G (Error, Harm)

An error occurred that may have contributed to or resulted in permanent patient harm

Category H (Error, Harm)

An error occurred that required intervention necessary to sustain life

Category I (Error, Death)

An error occurred that may have contributed to or resulted in the patient's death

Definitions

Harm – Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom

Monitoring – To observe or record relevant physiological or psychological signs

Intervention – May include change in therapy or active medical/surgical treatment

Intervention Necessary to Sustain Life – Includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation)

## Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident

simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

## Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

## Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

# Safety Profile – Polyethylene Terephthalate

Full Name: Polyethylene Terephthalate

CAS Registry Number: [25038-59-9]

## Search Overview

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response, material response) of polyethylene terephthalate (PET) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of PET. The devices in Table 1 were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data. In the latter, only those devices listed in Table 1 were included.

*Table 1: Medical devices containing PET provided by FDA to guide ECRI searches*

Regulatory Description	Pro Code	Class
Replacement heart valve	DYE	III
Suture, nonabsorbable, synthetic, polyethylene	GAT	II
Heart valve, non-allograft tissue	LWR	III
Transcatheter septal occlude	MLV	III
Aortic valve, prosthesis, percutaneously delivered	NPT	III

## Systematic Review Safety Brief

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of PET. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices document. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in Table 2. We then turn to a detailed discussion of research on PET as a material as well as research on the various device categories.

*Table 2: Summary of primary findings from our systematic review*

<b>Application</b>	<b>Local host responses and device events</b>	<b>Quality of evidence (local responses)</b>	<b>Systemic responses</b>	<b>Quality of evidence (systemic responses)</b>
PET as a material (7 human studies, 15 animal studies)	Mild inflammation, foreign body reaction, fibrosis, deep vein thrombosis, discomfort, suture migration, necrosis, cord fracture	Moderate for mild inflammation  Low for all other responses/events	Not investigated	Very low (no evidence)
Grafts (6 human studies, 7 animal studies)	Inflammation or synovitis, foreign body reaction, graft failure, graft migration, occlusion, rupture, aneurysm, pseudoaneurysm, fistula formation, aortic valve dysfunction, fibrosis, bleeding, thrombosis, stenosis, endoleak, pulmonary embolism	Moderate for inflammation or synovitis  Low for all other responses/events	Angiosarcoma	Low
Patch/Mesh/Mat/Substrates (8 human studies, 4 animal studies)	Inflammation, foreign body reaction, thrombosis, stroke, fragmentation	Moderate for inflammation  Low for all other responses/events	Not investigated	Very low (no evidence)
Ligaments (7 human studies, 4 animal studies)	Inflammation, swelling, effusion; graft breakage, rupture, tearing, or failure; synovitis, night pain, capsulitis	Low	Not investigated	Very low (no evidence)
Valves (2 human studies, 1 animal study)	Thrombus, pannus formation, calcification, cusp thickening, cusp tears, hematoma, foreign body granuloma	Very low	No systemic events related to PET valves among 6 minipigs	Very low
Stents and balloons (1 animal study)	Mild inflammation	Very low	No systemic events among 18 sheep	Very low

Application	Local host responses and device events	Quality of evidence (local responses)	Systemic responses	Quality of evidence (systemic responses)
Atrial septal defect/left atrial appendage closure devices (no studies)	No evidence	Very low	No evidence	Very low

**PET as a Material:** 7 human studies (2 randomized control trials [RCTs],<sup>2,3</sup> 6 observational studies<sup>1,2,4-7</sup>), 15 animal studies (4 RCTs,<sup>12,15,20,22</sup> 11 observational studies<sup>8-11,13,14,16-19,21</sup>). For further information, see Tables 1 and 2 in Appendix D.

*Local host responses and device events (human studies):* 6 human studies evaluated local responses and and device events related to PET sutures. 2 observational studies reported that there were no suture-related adverse events.<sup>5,6</sup> 1 RCT<sup>2</sup> and 1 large observational study<sup>2</sup> by the same authors reported that monofilament sutures were associated with lower rates of pre-term birth than braided cerclage in pregnant women (the difference was not statistically significant in the RCT, but it was in the observational study). The observational study also found a statistically significantly lower rate of nonviable births and intrauterine deaths. The second RCT<sup>3</sup> reported 2 foreign body reactions (FBRs) (leading to recurrent erythema and fluid collection) and 1 deep vein thrombosis in patients receiving PET sutures. One observational study reported discomfort from the anchor knot (3 patients) and suture migration that did not correlate with loss of function.<sup>1</sup>

Of the 2 remaining observational studies, 1 study evaluated 5 cases of Dynesys implants (which include a PET cord) explanted for pain and screw loosening.<sup>4</sup> Fraying and deformation around PET cord plus evidence of imprints were observed in 5 patients. Necrosis was observed in 4 patients. Cord fracture occurred in 1 patient. Wear debris with associated macrophage infiltration was observed in 3 patients, and extensive inflammation with macrophages and giant cells with phagocytosed and large wear debris (>10 µm) occurred in 1 patient. These events occurred from 1.9 to 5.3 years following implantation. The other study<sup>7</sup> reported a higher failure rate for PET glycol (PETG) orthodontic retainers (95%) compared to polycarbonate retainers (60%).

*Local host responses and device events (animal studies):* All 15 animal studies reported on aspects of local inflammatory responses. 7 animal studies evaluated PET sutures. All of these studies reported relatively mild inflammatory responses, although 1 RCT<sup>15</sup> comparing PET, polypropylene, polyglactine, and polydioxanone sutures with sham reported that PET sutures generated the highest inflammation, granuloma, and fibrosis scores. Another RCT<sup>12</sup> reported smaller inflammatory responses with ultrafine PET sutures compared to MERSILENE PET sutures.

Other studies of PET (prosthesis, implants, microcapsules) generally reported mild inflammatory responses, although in 1 study the response was described as chronic. 1 small study of a PET subretinal transplant reported no immune response.

*Systemic responses:* We did not identify any human or animal studies investigating systemic responses to PET as a material.

*Overall quality of evidence:* The quality of evidence for mild inflammatory responses to PET is moderate, as this was reported in all animal studies and a few human studies. Other responses/events were reported in fewer studies, so the quality of evidence is low. The quality of evidence for systemic responses is very low as no studies investigated or reported systemic responses to PET.

**Grafts:** 6 human studies (1 systematic review,<sup>24</sup> 1 retrospective controlled cohort,<sup>27</sup> and 4 cohort or case series<sup>25,26,30,31</sup>), 7 animal studies (1 RCT,<sup>33</sup> 2 comparative observational studies,<sup>34,36</sup> and 4 case series<sup>32,35,37,38</sup>). For further information, see Tables 3 and 4 in Appendix D.

*Local host responses and device events (human studies):* Of the 6 human studies reporting local host responses and device events, 5 addressed Dacron grafts:

- One systematic review<sup>24</sup> evaluated long-term complications of large diameter Dacron grafts. Long-term complications within the abdominal aorta included fistula formation (0.7% to 1.1% incidence), para-anastomotic aneurysm (3% to 15% incidence), and late rupture in 2 patients. Complications in the ascending aorta included pseudoaneurysm (in 2.09%, 3.1% and 31 cases), and aortic valve dysfunction (5.5% to 46.2%). Complications

in the arch and descending aorta included fistula formation (1 case aortopulmonary, 4 cases aortobronchial, and 2% aorto-esophageal), and late rupture in 1 patient. These complications occurred from 3 to 29 years postimplantation.

- 1 retrospective controlled cohort<sup>27</sup> examined right ventricular outflow tract reconstruction in children under 1 year with Dacron conduits (Hancock), bovine jugular vein conduits (Contegra), and homografts. Conduit exchange due to valvular stenosis occurred in 51 patients (37% with Dacron, 21% with Contegra, 41% with homograft) at 4 months to 12 years. Conduit exchange due to thrombosis occurred in 4 patients with Hancock conduits at 4 months to 6 years. Rate of freedom from at least moderate stenosis at 5 years was lowest with Hancock (years: 69.1 Hancock, 75.1 Contegra, and 85.4 homografts); rate at 10 years was lowest with Contegra (years: 49.7 Hancock, 35.8 Contegra, and 59.2 homografts).
- One retrospective cohort study<sup>26</sup> enrolled 89 patients undergoing thoracic endovascular aortic repair (TEVAR) with a branched Inoue stent graft with woven Dacron and small Dacron cuffs attached to graft edges. Complications included proximal ring migration and branch graft occlusion in 1 patient each. Type I endoleak after index TEVAR was reported in 9 patients. Endoleak caused aneurysm diameter enlargement >5 mm in 7 patients.
- The remaining 2 studies examining Dacron grafts enrolled ≤10 patients.<sup>25,30</sup> Complications included bleeding, extravasation, fibrosis, graft failure, pseudoaneurysm, stenosis, and thrombus. Graft failure occurred from 13 to 22 years postimplantation.

*Local host responses and device events (animal studies):* All 7 animal studies reported pertinent data:

- One RCT<sup>33</sup> reported inflammatory cell infiltration in all 3 PET grafts used for anterior cruciate ligament (ACL) reconstruction including those with polycaprolactone and bone morphogenic protein – 7. Authors noted that at 12 weeks, the PET group still had fibrous scar tissue at the graft–bone interface, with no osteointegration detected.
- 1 non-RCT<sup>34</sup> compared a scaffold with PET and polycaprolactone fumarate (PCLF) with semitendinosus autograft for ACL reconstruction. At 8 weeks, PCLF-PET constructs showed extensive intra-articular scaffold destruction in all specimens.
- Another non-RCT<sup>36</sup> examined abdominal aorta grafts with PET, silk fibrin (SF), and gelatin (G). At 2 weeks postimplantation, all grafts showed numerous inflammatory cells, including lymphocytes, macrophages, and foreign body giant cells (FBGCs). At 3 months, while SF/SF and PET/G grafts showed a decrease in inflammatory cells, no change was observed for PET/SF and SF/G grafts.
- 1 case series examining a heparin-loaded PET ultrafine microfiber graft reported a low inflammatory reaction that included fibroblast-like cells, macrophages, and some FBGCs at 24 weeks.<sup>32</sup>
- A second case series examined aortas wrapped with 2 test grafts (macroporous mesh and off-the-shelf woven low-porosity graft made of PET).<sup>35</sup> FBR included fibroblasts and FBGCs but no lymphocytes or granulocytes; denser cellular infiltrate and more and larger FBGCs with low-porosity PET vs. macroporous mesh.
- A third case series reported no reactions on histopathological examination of PET endoskeleton stent graft up to 6 months.<sup>37</sup>
- Finally, 1 case series reported inflammation accompanied by an FBR from a PET subcutaneous implant that included giant cells (fused macrophages) often directed to non-woven PET fibers at 30 days.<sup>38</sup>

*Systemic responses:* Angiosarcoma (and subsequent death) was reported in 3 patients undergoing vascular repair of the infrarenal aorta or right common iliac artery with Dacron grafts.<sup>31</sup> All angiosarcomas displayed extensive hemorrhage evidenced by variable stroma stenosis, and strong nuclear expression of ERG and FLI-1. The angiosarcomas were lining the original vascular lumen of the Dacron grafts. 7 case reports of angiosarcoma following Dacron graft implantation were reported in the literature between 1972 and 2015. Angiosarcomas occurred at 3.5 to 17 years postimplantation; 6 of 7 patients subsequently died from the disease. This appears to be a very rare event. We did not identify any animal studies reporting systemic responses to PET grafts.

*Overall quality of evidence:* Since inflammatory responses to PET grafts were reported in most animal studies and some human studies, the quality of evidence is moderate. For other local responses/events the quality of evidence is low. For systemic responses, angiosarcoma was reported in 3 patients with Dacron grafts and appeared to develop at the site of the graft. Therefore, the quality of evidence for systemic responses is low.

**Patch/Mesh/Mat/Substrates:** 8 human studies (4 cohort studies,<sup>39-41,43</sup> 4 case series<sup>42,44-46</sup>), 4 animal studies (3 RCTs,<sup>47,49,50</sup> 1 case series<sup>48</sup>). For further information, see Tables 5 and 6 in Appendix D.

Local host responses (human studies): Evidence for Dacron patches was reported in two cohort studies.<sup>39,40</sup> One study reported no serious adverse events with Dacron patch or imported PET patch in 48 individuals with congenital heart disease up to 6 months.<sup>39</sup> A larger study with follow-up to 7 years examined 471 patches (428 Dacron) for carotid endarterectomy.<sup>40</sup> Complications included an inflammatory reaction in 8 (1.8%) individuals, internal carotid thrombosis in 1 patient, and fluid collection around the patch in 6 (1.4%) patients. Contralateral internal carotid arterial stenosis ranged from 20% to 40% in 5 patients, 50% to 60% in 1 patient, and 99% in 2 patients.

PET mesh was examined in 5 studies.<sup>41,43-46</sup>

- 1 prospective cohort study<sup>41</sup> examining MicroNet mesh over a Nitinol stent reported new ischemic brain lesions in 6 (28%) patients; 83% occurring 48 to 72 hours postoperatively. Acute stent thrombosis and subsequent minor stroke occurred in 1 patient; clot formation remained unclear.
- 2 case series examined PET mesh interposition (with Anchois LIGASTIC) for trapeziometacarpal osteoarthritis.<sup>44,45</sup> The FBR in 1 study included the presence of giant cells in 2 (20%) cases, radiologic signs of bone erosion in 7 (70%) cases, and a severe reaction in 3 (30%) cases. Implants in 2 (20%) patients were ultimately removed at 5 and 8 years postoperatively. The FBR in the other study included persistent swelling, synovitis, and pain with presence of extensive monocytic and multinucleated FBGCs around PET. Additional complications included PET fragmentation. Authors of both studies noted they no longer use the PET implant for this indication.
- 2 studies reported no reaction with MERSILENE mesh frontalis sling for severe unilateral congenital ptosis in children under 1 year of age,<sup>46</sup> or PET/propylene mesh for isolated ascending aortic aneurysm<sup>43</sup> up to mean 13 years and 33 months, respectively.

Autologous bone marrow mononuclear cells with a PET scaffold was examined in one case series (n = 4).<sup>42</sup> Histological analysis indicated deformed fibers in the scaffold, and inflammation (infiltration with neutrophils and macrophages, fungal and bacterial contamination) up to a median 17 months follow-up.

Local host responses (animal studies): The animal studies examined mesh in 2 studies, mat in 1 study, and substrate in one study. Materials were implanted subcutaneously, in the abdomen, and in the back.

2 RCTs reported inflammation from PET mesh.<sup>49,50</sup> 1 RCT reported inflammation at 90 days from 5 PET prototype meshes.<sup>49</sup> Results indicated that the medium-weight (MW), very large pore, hexagonal mesh trended toward less inflammation than the light-weight (LW), very large square pores mesh ( $p = 0.051$ ). The MW, very large hexagonal pores, and LW, very large square pores meshes trended toward overall more favorable tissue response by composite score compared to MW, very large square pores ( $p = 0.065$  and  $p = 0.06$ , respectively).

Another RCT reported inflammatory response and FBR from mesh with PET, woven-PET, PET with chitosan (PET/C), and polypropylene (PP).<sup>50</sup> All animals showed typical non-immunogenic granulomas (foreign body granulomas mostly composed of macrophages, FBGCs, and fibroblasts) surrounding the mesh structure. Animals treated with electrospun meshes (PET, PET/C, and double layer of PET and PET/C) showed statistically significantly thicker granulomas and a higher number of FBGCs compared to PP and the woven-PET group. Woven-PET group produced the weakest inflammatory response. Long-term inflammatory response of electrospun PET indicated a decrease in inflammation at 90 days (average granuloma thickness decreased from  $959 \pm 473 \mu\text{m}$  to  $513 \pm 217 \mu\text{m}$ , number of FBGCs decreased from  $106 \pm 30$  to  $89 \pm 12$ ).

1 RCT examined local response from PET nanofiber mats at 1 and 7 days.<sup>47</sup> Substantial edema was present in all PET control samples (without silver nanoparticles [NanoAg]). Fibrous capsule with varying thickness was present in all PET samples (control and with NanoAg). Inflammatory reaction including macrophages, monocytes, lymphocytes, and neutrophils were observed between the mats and the fibrous capsule; more extensive inflammation in PET control samples vs. PET NanoAg samples. Expression of tumor necrosis factor alpha (TNF $\alpha$ ) was lower with NanoAg samples.

Finally, 1 case series examining 6 PET scaffolds (3 heterotopic, 3 orthotopic) reported an inflammatory response in heterotopic implants included a fibrous capsule, neutrophils, giant cells, macrophages, and mannose receptor expression.<sup>48</sup>

Systemic responses: We did not identify any studies reporting systemic responses to PET patch/mesh/mat/substrate.

Overall quality of evidence: Several human studies and all animal studies reported inflammation (usually mild) as a local response, so the quality of evidence for inflammation is moderate. Other local responses and device events were reported in fewer studies, so the quality of evidence for these outcomes is low. The quality of evidence for

systemic responses is very low as no studies investigated or reported systemic responses to PET patch/mesh/mat/substrate.

**Ligaments:** 7 human publications (1 systematic review,<sup>28</sup> 6 case series<sup>23, 29,51-54</sup>) and 4 animal studies (2 RCTs,<sup>55,56</sup> 1 non-randomized controlled study,<sup>58</sup> 1 case series<sup>57</sup>). For further information, see Tables 7 and 8 in Appendix D.

Local host responses and device events (human studies): 4 publications addressed the Ligament Advanced Reinforcement System (LARS).<sup>23,28,29, 51</sup>

- One systematic review<sup>28</sup> examined 675 ACL reconstructions with LARS in adults enrolled in 8 trials (75% case series). Complications up to 5 years included 16 (2.5%) ligament ruptures and 1 rupture-associated case of synovitis.
- 1 case series<sup>23</sup> reported LARS-ACL reconstruction failure in 11 adult patients; malposition in 6 (54.5%). Histological analysis indicated severe widespread villonodular synovitis to every knee joint and chronic inflammation with multiple multinucleated giant cells.
- Another case series<sup>29</sup> examining augmented hamstring tendon graft with LARS in 112 adults with ACL rupture reported no complications up to 5 years.
- The remaining LARS case series<sup>51</sup> reported 5 broken grafts among 17 patients.

Of the remaining 3 studies,<sup>52-54</sup> 2 reported rupture, tearing or failure of the graft ligament. 1 study reported a synovial reaction, 1 study reported night pain and capsulitis, and 1 study reported that no complications were observed.

Local host responses and device events (animal studies): 2 animal studies reported inflammation. 1 of those studies also reported swelling, effusion, and yellow synovial fluid. The other study also reported subtle weight bearing and partial graft rupture. The other 2 animal studies did not report any adverse effects.

Systemic responses: We did not identify any studies reporting systemic responses to PET ligaments.

Overall quality of evidence: The quality of evidence is low for all local responses/events due to the low number of studies and the low quality of the human studies. The quality of evidence for systemic responses is very low (no evidence).

**Valves:** 2 human studies (both case series<sup>59,60</sup>), and 1 animal study (observational<sup>61</sup>) reported on PET cardiac valves. For further information, see Tables 9 and 10 in Appendix D.

Local host responses and device events: 2 case series with a follow-up of 3 to 4.5 years in patients who received PET Mitroflow valves suggest thrombus and pannus formation to be a realistic concern for PET valves. Calcification, cusp thickening, and cusp tears are also frequently observed. However, these numbers have no comparison group to establish any relativity. This finding was not seen in the animal study, although 2 of 6 animals (minipigs) developed hematomas that appeared to be related to the surgical procedure rather than the implanted valve. The animal study also did not use the same device as the human study. In the animal study, the group sacrificed at 64 days showed higher foreign body granuloma scores than the groups sacrificed at 75 and 109 days.

Systemic responses: Although the single animal study reported some lung and liver inflammation in 2 animals, this was likely related to hematomas in the heart that most likely were caused by the surgical procedure rather than the PET graft. None of the other studies investigated or reported systemic responses.

Overall quality of evidence: Due to the lack of any comparison group and the observational nature of the few available studies, the quality of evidence for all outcomes is very low. Since no studies reported systemic responses related to PET grafts (including the 1 animal study that investigated systemic responses), the quality of evidence for systemic responses is very low.

**Stents and Balloons:** A single animal study (observational<sup>62</sup>) reported on PET balloons. For further information, see Table 11 in Appendix D.

Local host responses and device events: The single animal study reported 2 trials with the photodynamic bone stabilization system with PET balloon. One trial was conducted in a non-fracture model, while the other trial removed

parts of the sheeps' tibia as a fracture model. Both trials showed mild but unremarkable inflammation at the implantation site.

*Systemic responses:* The authors investigated and found no macroscopic indication of adverse systemic effects at any time point (30, 60, and 90 days).

*Overall quality of evidence:* Since the evidence base comprised only one small animal study the quality of evidence is very low. Quality of evidence for systemic response is also very low.

**Atrial septal defect/left atrial appendage closure devices:** We did not identify any human or animal studies that evaluated these devices.



## ECRI Surveillance Data

The most common complication reported within surveillance data for PET was device malfunction/fracture, accounting for approximately 76% of all PSO reports. Additional reported complications are varied and consistent with clinical literature. The vast majority of reported complications (85%) involved stents and balloons. Most complications that resulted in harm had a harm score of E (17%), requiring temporary intervention, and F (7%), requiring temporary hospitalization. Problem Reports and Alerts also reported numerous incidents of device malfunction/fracture including damaged components and components dislodging/detaching. There were 2 reports of transcatheter septal occluders eroding through the myocardium, which is a life-threatening complication. 1 death associated with stents and balloons was reported.

## Patient Safety Organization

**Search Results:** ECRI PSO identified 868 reports of incidents associated with PET materials that occurred between 1/2008 and 5/2020. 79 of these involved complications. (see Table 3). 1) Device malfunction - 30 (38.0%), T-1 Device fracture - 30 (38.0%), 3) Hematoma - 5 (6.3%), 4) Iatrogenic Injury - 4 (5.1%), and 5) Retained foreign object - 3 (3.8%). The majority of events were associated with harm scores ranging from C through E, with harm to the patient occurring in 19% of the events (Table 4). Harm scores C and D refer to errors that did not cause harm to the patient. E and F resulted in patient harm that necessitated initial or prolonged hospitalization. Complications with stents and balloons were most commonly reported.

All individual PSO event reports are redacted and included in Appendix F.

*Table 3: Complications in PET-related PSO event reports.*

<b>Complication</b>	<b>Annuloplasty Rings</b>	<b>Patch/mesh/mats/substrates</b>	<b>Stents and balloons</b>	<b>Suture</b>	<b>Total</b>
Device malfunction	2		28		30
Device fracture			27	3	30
Hematoma	1		4		5
Iatrogenic Injury		1	3		4
Retained Foreign Object			1	2	3
Serosal tear				1	1
Wrong location			1		1
Clinical Manifestations			1		1
Cardiac Arrest			1		1
Infection			1		1
Extended Fluoro time	1				1
Suture granuloma				1	1
<b>Total</b>	<b>4</b>	<b>1</b>	<b>67</b>	<b>7</b>	<b>79</b>

*\*No events identified for the following device categories: Bone Fixation, Bone Fixation Cerclage, Flexible tether to modulate spinal growth, Prosthesis, Penis, Inflatable, Reherniation Reduction Device*

Table 4: Harm score associated with PET-related event reports.

Harm Scores (NCC-MERP)		Annuloplasty Rings	Patch/mesh/mats/substrates	Stents and balloons	Suture	Total
<b>A</b>	No Error	--	--	1	--	<b>1</b>
<b>B1</b>	Error, No Harm	--	--	--	--	--
<b>B2</b>	Error, No Harm	--	--	2	1	<b>3</b>
<b>C</b>	Error, No Harm	--	--	29	2	<b>31</b>
<b>D</b>	Error, No Harm	2	--	7	--	<b>9</b>
<b>E</b>	Error, Harm	--	1	7	2	<b>10</b>
<b>F</b>	Error, Harm	--	--	4	--	<b>4</b>
<b>G</b>	Error, Harm	--	--	--	--	--
<b>H</b>	Error, Harm	--	--	--	--	--
<b>I</b>	Error, Death	--	--	1	--	<b>1</b>
<b>NULL</b>		2	--	16	2	<b>20</b>
<b>Total</b>		<b>4</b>	<b>1</b>	<b>67</b>	<b>7</b>	<b>79</b>

\*Harm score was not reported

## Accident Investigations

Search Criteria: Annuloplasty rings, watchman, amplatzer, cardioseal, sapien, mitroflow, aortic and heart valve, occuluder, hancock and valve, ATS and bileaflet, epic and valve, treo, incraft, zenith and graft, aorfix and stent, Bolton, enduring stent graft system, tx2 and graft, wallgraft, tracheobronchial endoprosthesis, composix, bioline, hemashield, gelweave, vascutek, intergard, dynesys, rescube, naja, ultraxx D nephrostomy, dacryocath, lacrimal, smi and patch, albosure cardiovascular patch, mersilene suture, ethibond suture, sovering, mitra-lift set, annular, ligapass, Nile, m-fix, penile prosthesis

Search Results: A search of the accident investigations database did not identify any cases involving PET-related devices.

Table 5: Accident investigations of patient incidents involving PET

Device Type	# Investigations	Reported Problem and Findings (number of investigations)
N/A	0	No cases involving PET-related devices

## ECRI Problem Reports

Search Criteria: AnnuloFlo, Sovering, Attune, Seguin, Attune adjustable flexible annuloplasty ring model AFR, HAART, Mitra-lift, Barricaid, LigaPASS, NAJA, NILE, Tether

**Search Results:** The search returned 6 reports submitted by ECRI members (Table 6). The reports detail device migration, myocardial perforation, and device failures leading to safety concerns detailed as patient injury, additional surgeries, and erosion of the myocardium.

All problems reports are redacted and included in Appendix F.

*Table 6: ECRI Problem Report Summary*

<b>Device Type</b>	<b># Problem Reports</b>	<b>Reported Problem and ECRI Findings</b>
Transcatheter septal occluder (MLV)	2	Device eroded through myocardium
Heart-valve, non-allograft tissue (LWR)	1	Suspect failure
Aortic valve, prosthesis, percutaneously delivered (NPT)	1	Suspect failure
Replacement heart valve (DYE)	1	Asymmetrical and leaking
Suture, nonabsorbable, synthetic, polyethylene (GAT)	1	Needle broke

## Alerts

**Search Criteria:** Specific devices and search terms are included in Appendix G.

**Search Results:** The search returned 51 manufacturer-issued alerts describing problems with labeling, damaged components during operation/deployment, tissue erosion, and implant embolization, summarized in Table 7.

*Table 7: Summary of regulatory and manufacturer alerts*

<b>Device Type</b>	<b># Alerts</b>	<b>Problems</b>
ASD/LAA Closure Devices; Occluders	11 Manufacturer-issued	<ul style="list-style-type: none"> <li>• Mislabeling</li> <li>• Excess trigger wire tension</li> <li>• Wire migration/deformity</li> <li>• Sterility compromised</li> <li>• Stent deployment complications</li> <li>• Cutting mechanism lock up</li> <li>• Component separation</li> </ul>
Valves	5 Manufacturer-issued	<ul style="list-style-type: none"> <li>• Mislabeling</li> <li>• Revised IFU due to FDA clearance</li> <li>• Damaged components</li> <li>• Sterility compromised</li> <li>• Removal procedure may require open surgery</li> </ul>
Stents/Balloons	21 Manufacturer-issued	<ul style="list-style-type: none"> <li>• Mislabeling</li> <li>• Incorrect component included</li> <li>• Wrong silicone lubricant used</li> <li>• Unanticipated erosion (life-threatening)</li> </ul>

Device Type	# Alerts	Problems
		<ul style="list-style-type: none"> <li>• Wire fracture</li> <li>• Components dislodging/detaching</li> <li>• Manufacturer discontinuations</li> <li>• Secondary sheath will not exit primary</li> <li>• Updated IFU</li> <li>• Valve cross-threading</li> <li>• Implant embolization</li> <li>• Missing CE mark</li> <li>• Fabric permeability resulting in endoleak</li> <li>• Extra surveillance required</li> <li>• Release mechanism issues</li> </ul>
Patch; Mesh; Mats; Substrates	1 Manufacturer-issued	<ul style="list-style-type: none"> <li>• Component fracture during use</li> </ul>
Grafts	9 Manufacturer-issued	<ul style="list-style-type: none"> <li>• Mislabeling</li> <li>• Updated IFU/non-indicated use</li> <li>• Intraoperative bleeding at the seam line</li> <li>• Top cap release difficulty leads to incorrect placement (requires intervention)</li> <li>• PTFE may scrape off screw</li> <li>• PET recoil ring fracture</li> <li>• Tissue erosion</li> </ul>
Ligaments	2 Manufacturer-issued	<ul style="list-style-type: none"> <li>• Deployment difficulty</li> <li>• Part out of spec leads to tip detachment</li> </ul>
Miscellaneous	2 Manufacturer-issued	<ul style="list-style-type: none"> <li>• Oversized occluders lead to hemodynamic compromise</li> <li>• Complete heart block</li> </ul>

## Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of PET. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

Overall, the literature for PET lacked data on patient-related or material-related factors that influence the likelihood and/or severity of sustained, exaggerated systemic responses. There were very few studies on any PET devices that reported on systemic responses, indicating areas of potential future research.

ECRI surveillance data largely consisted of device-related failures or malfunctions, particularly in stents and balloons, without further indication of causation. In general, material failures could be an indication of insufficient biocompatibility.

**PET as a Material:** A few animal studies identified mild inflammatory response as the most common local response to PET; however, there were no identified studies investigating systemic responses to PET as a material. This indicates a potential area of further research. In addition, the studies had relatively short follow-up periods ( $\leq 3$  years) for assessment of inflammation and related events.

**Grafts:** There is moderate quality of evidence reporting inflammatory responses with PET grafts. Other reported responses are of low quality. One study reported fibrous scar tissue at graft-bone interface for ACL reconstruction. Another study reported intra-articular scaffold destruction. Although also considered low quality of evidence, 1 study reported 7 cases of angiosarcoma as a systemic response to Dacron grafts with 6 of the 7 patients dying in the case series. However, these are considered rare events.

**Patch/Mesh/Mat/Substrates:** For these PET devices, several studies reported inflammation indicated moderate quality of evidence. All other reported responses were supported by low quality of evidence. Only 2 cohort human studies and no animal studies examined PET patches, with 1 reporting an instance of internal carotid thrombosis fluid collection in several patients and different ranges of arterial stenosis in 8 patients. 5 human studies and 2 animal RCTs examined PET meshes. The human studies reported a variety of local responses including acute stent thrombosis, new ischemic brain lesions, and FBRs. 1 animal RCT reported that woven-PET meshes produced the weakest inflammatory response. Only 1 animal RCT examined PET nanofiber mats comparing PET mats with mats including NanoAg. The mats with NanoAg elicited a weaker inflammatory response and lower expression of TNF $\alpha$ . 1 human and 1 animal case series investigated PET scaffolds. The human case series reported inflammation and deformed scaffold fibers while the animal case series reported an inflammatory response.

No studies reported systemic responses related to these PET devices resulting in very low quality of evidence. The lack of studies investigating all of these PET devices indicates a potential area of further research.

**Ligaments:** There were a total of 7 studies reporting on PET ligaments, including 6 case series and a systematic review (75% of studies reviewed were case series) and 4 animal studies. 4 of these studies examined LARS. These studies reported a low incident rate (2.5%) of ligament ruptures, and 1 case series reported severe widespread villonodular synovitis in every knee joint (11 patients). No studies reporting systemic responses to PET ligaments. This indicates a potential area of further research.

**Valves:** Only 3 observational studies (2 human, 1 animal) reported thrombus and pannus formation to be a concern with PET mitroflow valves (low quality). No studies reported systemic responses related to PET graft (1 animal study investigated systemic responses but determined they were likely not related to PET graft), resulting in very low quality of evidence. This indicates a potential area of further research.

**Stents and Balloons:** Only 1 observational animal study examining photodynamic bone stabilization system with PET balloon showed mild inflammation and there was evidence that there was no systemic response among sheep.. This indicates a potential area of further research.

**Atrial septal defect/left atrial appendage closure devices:** We did not identify any human or animal studies that evaluated these devices. This indicates a potential area of further research.

# Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

## Inclusion Criteria

1. English language publication
2. Published between January 2010 and August 2020
3. Human studies
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of PET or priority devices that include this material

## Exclusion Criteria

1. Foreign language publication
2. Published before January 2010
3. Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4. Off-topic study
5. On-topic study that does not address a key question
6. No device or material of interest
7. No relevant outcomes (adverse events or biocompatibility not reported)
8. Study is superseded by more recent or more comprehensive systematic review

## Quality of Evidence Criteria

1. **Quality of comparison** – is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2. **Quantity of data** – number of systematic reviews and individual studies providing relevant data.
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. **Magnitude of effect** – what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5. **Directness of evidence** – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)?
6. Is there evidence of a **dose response or time response** (e.g. adverse effects increase with longer exposure time)?

## Appendix B. Search Summary

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from Emtree. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called “major” headings. This “major” concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. “Exploding” in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n = 174) and their associated entry terms (lexical variants and synonyms) to the strategy using an “OR” without the searcher having to type them in. That’s one of the major advantages to searching using controlled vocabularies. We don’t rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That’s why we also include free text words in our strategies.

Set Number	Concept	Search statement
1	PET	'polyethylene terephthalate'/exp OR 'polyethylene terephthalate*' OR 'poly ethylene terephthalate*' OR 'ethylene polyterephthalate*' OR polyethyleneterephthalate* OR 'polyethylene terephthalate*' OR 'poly ethylene terephthalate*' OR 'ethylene polyterephthalate*' OR polyethyleneterephthalate*
2		(dacron* OR mylar OR amilar OR arnite OR amilon OR dallon OR diolen OR elasticum OR estrofol OR ethibond* OR fortrel OR hostaphan OR kodar OR lavsan OR melinar OR melinex OR mersilene OR mersylene OR polydek OR rynite OR sulene OR tevdek OR tergal OR terylene OR techster OR tenite OR terlenka OR trevira OR terital OR tetoron OR teron OR tricogel OR yambolen):ti,ab,kw,tn,dn
3		((pet OR pete OR petp OR petg OR pctg) NEAR/5 (polymer* OR copolymer* OR composite* OR blend? OR material* OR biomaterial* OR fiber? OR fibre* OR filament? OR film* OR bead? OR material* OR yarn* OR sheet* OR membrane* OR patch* OR tube* OR band? OR thread? OR cord? OR loop OR fixation OR fabric OR braid* OR graft? OR prosth* OR cuff* OR graft*)) AND (polyester* OR ethylene* OR polyethylene* OR terephthalate* OR terephthalate*)
4	Combine sets	#1 OR #2 OR #3



5	Limit by language and publication date	#4 AND [english]/lim AND [2010–2020]/py
6	Limit by publication type	#5 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

**Material Response**

7		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
8		'degradation'/exp OR degradation OR degrad* OR split OR splitting OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR movement OR shift* OR transfer* OR 'delamination'/exp OR delamina* OR leach* OR filtrate OR filter* OR seep* OR evaginat* OR subsidence
9		Leachable* OR extractable*
10		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat*) NEAR/3 (implant* OR pin* OR anchor* OR screw*)
11		'mechanics'/exp [see Emtree explosions section at the end of the strategy]
12		'device material'/exp/mj
13		'Biomedical and dental materials'/exp/mj
14	<b>Combine sets</b>	<b>#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13</b>

**Host Response**

15		Host NEAR/2 (reaction* OR response*)
16		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
17		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
18		Immun*:ti OR autoimmun*:ti OR hypersens*:ti
19		'inflammation'/exp OR inflamm*:ti
20		'foreign body reaction' OR granuloma*

21		('adhesion'/exp OR 'tissue adhesion'/exp OR 'biomechanics'/exp OR biocompat*)
22		'bacterium adherence'/exp OR 'biofilm'/exp OR biofilm
23		(protrude* OR protrus*)
24		Migrat* OR migration OR evaginat* OR subsidence
25	Combine sets	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26	PET AND Material Response	#6 AND #14
27	PET AND Host Response	#6 AND #25
28	Combine all	#26 OR #27

### Example Embase Explosion

Mechanics/exp

- Biomechanics
- Compliance (physical)
  - Bladder compliance
  - Blood vessel compliance
    - Artery compliance
    - Vein compliance
  - Heart muscle compliance
    - Heart left ventricle compliance
    - Heart ventricle compliance
  - Lung compliance
- Compressive strength
- Dynamics
  - Compression
  - Computational fluid dynamics
  - Decompression
    - Explosive decompression
    - Rapid decompression
    - Slow decompression
  - Gravity
    - Gravitational stress
    - Microgravity
    - Weight

- Body weight
  - Birth weight
    - High birth weight
    - Low birth weight
      - Small for date infant
      - Very low birth weight
        - Extremely low birth weight
- Body weight change
  - Body weight fluctuation
  - Body weight gain
    - Gestational weight gain
  - Body weight loss
    - Emaciation
  - Body weight control
  - Fetus weight
  - Ideal body weight
  - Lean body weight
  - Live weight gain
- Dry weight
- Fresh weight
- Molecular weight
- Organ weight
  - Brain weight
  - Ear weight
  - Heart weight
  - Liver weight
  - Lung weight
  - Placenta weight
  - Spleen weight
  - Testis weight
  - Thyroid weight
  - Uterus weight
- Seed weight
- Tablet weight
- Thrombus weight
- Weightlessness
- Hydrodynamics
  - Hypertonic solution
  - Hypotonic solution
  - Isotonic solution
  - Osmolality
    - Hyperosmolality
    - Hypoosmolality
    - Plasma osmolality
    - Serum osmolality
    - Urine osmolality
  - Osmolarity
    - Blood osmolarity
    - Hyperosmolarity
    - Hypoosmolarity
    - Plasma osmolarity
    - Serum osmolarity
    - Tear osmolarity
    - Urine osmolarity
  - Osmosis

- Electroosmotic
  - Osmotic stress
    - Hyperosmotic stress
    - Hypoosmotic stress
  - Photodynamics
    - Photoactivation
      - Photoreactivation
    - Photodegradation
    - Photoreactivity
      - Photocytotoxicity
      - Photosensitivity
      - Photosensitization
      - Phototaxis
      - Phototoxicity
    - Photostimulation
  - Proton motive force
  - Shock wave
    - High-energy shock wave
  - Stress strain relationship
  - Thermodynamics
    - Adiabaticity
    - Enthalpy
    - Entropy
- Elasticity
  - Viscoelasticity
  - Young modulus
- Force
- Friction
  - Orthodontic friction
- Hardness
- Kinetics
  - Adsorption kinetics
  - Flow kinetics
    - Electroosmotic flow
    - Flow rate
    - Gas flow
    - Laminar airflow
    - Laminar flow
    - Powder flow
      - Angle of repose
      - Hausner ration
    - Pulsatile flow
    - Shear flow
    - Thixotropy
    - Tube flow
    - Turbulent flow
    - Vortex motion
    - Water flow
  - Motion
    - Coriolis phenomenon
    - Rotation
    - Vibration
      - Hand arm vibration
      - High frequency oscillation
      - Oscillation

- Oscillatory potential
    - Whole body vibration
  - Velocity
    - Acceleration
    - Deceleration
    - Processing speed
    - Wind speed
- Mass
  - Biomass
    - Fungal biomass
    - Immobilized biomass
    - Microbial biomass
  - Body mass
  - Bone mass
  - Dry mass
  - Fat free mass
  - Fat mass
  - Heart left ventricle mass
  - Kidney mass
- Materials testing
- Mechanical stress
  - Contact stress
  - Contraction stress
  - Shear stress
  - Surface stress
  - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
  - Quantum theory
- Rigidity
- Torque
- Viscosity
  - Blood viscosity
    - Plasma viscosity
  - Gelatinization
  - Shear rate
  - Shear strength
  - Shear mass
  - Sputum viscosity

Viscoelasticity

## Appendix C: Study Flow Diagram

- I. 789 Citations Identified by Searches, of which:
  - i. 626 Citations Excluded at the Title Level – Citations excluded at this level were off-topic or not published in English.
  - ii. 163 Abstracts Reviewed, of which:
    1. 33 Citations Excluded at the Abstract Level – Citations excluded at this level were not a study design of interest, clearly did not address a key question, did not report on a device of interest, or did not report on outcome of interest
    2. 130 Full-length Articles Reviewed, of which:
      - a. 37 Citations Excluded at 1<sup>st</sup> Pass Full Article Level; Articles excluded at this level did not: address any key question, meet inclusion criteria for study design, include a device of interest or report an outcome of interest.
      - b. 82 Articles Reviewed, of which:
        - i. 20 Citations Excluded at 2<sup>nd</sup> Pass Full Article Level – Upon further review, these studies did not report an outcome of interest, did not address a key question or comparison of interest, or did not include a device or material of interest.
        - ii. 62 Included Studies

## Appendix D. Evidence Tables

Table 8: PET as a Material – Health Effects (In Vivo) Human Studies

### **Local Response/Toxicity**

Source Citation: Ribak et al. 2018<sup>1</sup>

Study Design: Case series

Device or Material: PET suture wire (ETHIBOND wire; Ethicon)

Contact Duration: Mean follow-up (months): 21.50±5.0

Dose: 2.0 mm threaded wire

Frequency/Duration: Single administration

Response: Discomfort; Migration

Patient characteristics (gender, mean age): 73% female, 60.26 years.

Number per group: 15 undergoing suspensionplasty for rhizarthrosis.

Observed adverse effects: Radiographs indicated a mean proximal migration of the first metacarpal of ~50% (preoperative mean 10.40 mm, postoperative 5.27 mm; p <0.001). Migration did not correlate with loss of function. Discomfort from anchor knot in 3 (20%) patients.

Timing of adverse effects: Discomfort early post-op.

Factors that predict response: NR

Source Citation: Kindinger et al. 2016<sup>2</sup>

Study Design: Retrospective cohort

Device or Material: PET braided sutures vs. monofilament sutures

Contact Duration: 4 to 16 weeks

Dose: NR

Frequency/Duration: NR

Response: Microbial dysbiosis; Nonviable births; PTB

Patient characteristics (gender, mean age): 100% female, 34 years.

Number per group: 671 undergoing cervical cerclage; 327 braided suture, 344 monofilament suture.

Observed adverse effects: Compared to monofilament sutures, braided cerclage was associated with statistically significantly higher rates of nonviable births (delivery <24 weeks or intrauterine deaths) (15% vs 5%; p <0.0001) and statistically significantly higher rates of PTB (28% vs. 17%; p <0.0001). Braided cerclage was also associated with a 5-fold increase in microbial dysbiosis.

Timing of adverse effects: Dysbiosis from 4 weeks to 16 weeks.

Factors that predict response: NR

Source Citation: Kindinger et al. 2016<sup>2</sup>

Study Design: RCT

Device or Material: PET braided sutures (MERSILENE) vs. monofilament suture (ETHILON)

Contact Duration: 4 to 16 weeks

Dose: 19±4.5 mm braided, 18±5.1 mm monofilament

Frequency/Duration: NR

Response: Release of inflammatory cytokines; PTB

Patient characteristics (gender, mean age): 100% female; 32.8 years monofilament, 33.9 years braided suture.

Number per group: 49 undergoing cervical cerclage (25 braided, 24 monofilament).

Observed adverse effects: PTB (<37 weeks) was higher with braided cerclage (32% vs. 25%;  $p = 0.6$ ; Fisher's exact test). With PET braided sutures, release of inflammatory cytokines (including IL-1 $\beta$ , IL-6, TNF $\alpha$ , and MMP-1) into the cervicovaginal fluid was reported.

Timing of adverse effects: Cytokine expression noted at 4 weeks post-cerclage.

Factors that predict response: NR

Source Citation: Kocaoglu et al. 2015<sup>3</sup>

Study Design: RCT

Device or Material: PET non-absorbable braided suture (ETHIBOND; Ethicon) vs. absorbable braided polyglactin suture (VICRYL; Ethicon)

Contact Duration: Mean follow-up (months): 25.3 PET, 30.5 polyglactin

Dose: NR

Frequency/Duration: Single administration

Response: DVT; Erythema; Fluid collection; Foreign body reaction; Visible mass

Patient characteristics (gender, mean age): NR, 38 years.

Number per group: 24 each. Patients undergoing Achilles tendon repair with a suture-guiding device.

Observed adverse effects: Complications with PET included DVT in 1 patient. Foreign body reaction in 2 patients included a visible mass overlying the suture at 6 months, and superficial erythema at 3 weeks post-op. Recurrent episodes of erythema continued for 2 months. At 6 months, this patient presented with fluid collection on the lateral side of the ankle. No re-ruptures were reported at 1 year.

Timing of adverse effects: DVT at 1 week post-op.

Factors that predict response: NR

Source Citation: Neukamp et al. 2014<sup>4</sup>

Study Design: Case series

Device or Material: PET cord (Sulene PET) in revised Dynesys implant

Contact Duration: Mean 2.86 years (1.9 to 5.3 years)



Dose: Wear from DYN 006 at 1.9 years (<1 µm, 1 to 10 µm, >10 µm), DYN 015 at 2.2 years (<1 µm, and 1 to 10 µm), and BRSP 011 at 5.3 years (<1 µm, 1 to 10 µm, >10 µm)

Frequency/Duration: Single administration

Response: Deformation; Extensive inflammation; Fracture; Fraying; Giant cells; Large wear particles (>10 µm); Macrophage infiltration; Necrosis; Wear debris

Patient characteristics (gender, mean age): 60% female, 48.4 years.

Number per group: 5 undergoing implant retrieval.

Observed adverse effects: Fraying, deformation around PET cord plus evidence of imprints in 5 (100%) patients. Necrosis was observed in 4 (80%) patients. Cord fracture occurred in 1 (20%) patient. Wear debris with associated macrophage infiltration in 3 patients; extensive inflammation with macrophages and giant cells with phagocytosed and large wear debris (>10 µm) in 1 patient.

Timing of adverse effects: 1.9 to 5.3 years.

Factors that predict response: NR

Source Citation: McRoberts et al. 2013<sup>5</sup>

Study Design: Case series

Device or Material: Nonabsorbable PET sutures and PET tissue anchors

Contact Duration: Mean follow-up (weeks): 18 (range 11 to 26)

Dose: NR

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): NR

Number per group: 10

Observed adverse effects: No suture-related complications were reported.

Timing of adverse effects: N/A

Factors that predict response: N/A

Source Citation: Sutipornpalangkul and Thanapipatsiri 2013<sup>6</sup>

Study Design: Case series

Device or Material: Braided nonabsorbable PET suture (Ethibond Excel; Ethicon Inc.)

Contact Duration: Mean followup (months): 18 (range 2 to 82)

Dose: Mean screw length: 40.33 mm; cable was high molecular weight

Frequency/Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): 56% male, 42 years.

Number per group: 23 undergoing posterior bone graft fixation.

Observed adverse effects: No suture-related complications were reported.

Timing of adverse effects: N/A

Factors that predict response: N/A

Source Citation: Ardeshta 2011<sup>7</sup>

Study Design: Case series

Device or Material: PETG resin matrix vs. PC resin matrix

Contact Duration: Median survival time (months): 7.6

Dose: 0.52 mm and 1.02 mm thickness

Frequency/Duration: Single administration

Response: Retainer failure

Patient characteristics (gender, mean age): Both (% NR), all ages (% NR).

Number per group: 51 undergoing placement of 76 fiber-reinforced thermoplastic (FRP)-bonded orthodontic retainers.

Observed adverse effects: Failure rate of retainers with PETG resin was 95% (22/23); 60% failure rate for PC resin. Overall failure was due to bond failure at the enamel-adhesive interface (28%), breakage of the FRP (5%), adhesive failure with debonding between the FRP and the adhesive, and cohesive separation of the FRP near the bonded surface. Mean survival time was 4.71 months for PETG retainers vs. 11.92 months for PC retainers.

Timing of adverse effects: Maximum survival was >24 months.

Factors that predict response: NR

DVT: deep vein thrombosis; IL-1 $\beta$ : interleukin-1B; IL-6: interleukin 6; mm: millimeter; MMP-1: matrix metalloproteinase-1; N/A: not applicable; NR: not reported; PC: polycarbonate; PET: poly(ethylene terephthalate) or polyester; PETG: polyethylene terephthalate glycol; PTB: preterm birth; RCT: randomized controlled trial; TNF $\alpha$ : tumor necrosis factor- $\alpha$ ;  $\mu$ m: micron

Table 9: PET as a Material – Health Effect (In Vivo) Animal Studies

### **Local Response/Toxicity**

Source Citation: Easley et al. 2020<sup>8</sup>

Study Design: Case series

Device or Material: PET SRT (OGmend Implant System; Woven Orthopedic Technologies)

Route: Right metatarsus

Dose: NR

Frequency/Duration: Single administration

Response: Fibrosis; Lymphocytes; Macrophages

Species (strain): Sheep (NR)

Gender: NR

Number per group: 6

Observed adverse effects: Histopathology results indicated SRT sleeves were embedded within reactive fibrosis and associated with a rare display of lymphocytes and macrophages. No signs of inflammation were displayed at the bone-screw-SRT interface or osteotomy site. No device degradation or migration were observed.

Timing of adverse effects: Up to 12 weeks follow-up.

Factors that predict response:

Source Citation: Koullali et al. 2020<sup>9</sup>

Study Design: Comparative

Device or Material: Cerclage with PET suture (Dacron; Alcon Surgical) vs. silk gel injection vs. saline injection

Route: Cervix

Dose: 5-0 Dacron

Frequency/Duration: Single administration

Response: Eosinophils; Expression of IL-6, CD68, CcrR, CC12, TNF $\alpha$ , IL-8; Inflammatory response; Macrophages; Neutrophils

Species (strain): Rats (Sprague Dawley, pregnant).

Gender: Female

Number per group: Day 19: histology (2 PET cerclage, 3 silk gel), RNA and protein assays (4 PET cerclage, 4 silk gel, 4 saline).

Observed adverse effects: 3 days post-injection, a mild inflammatory response (macrophages with smaller numbers of neutrophils and eosinophils) were shown with PET and silk gel. Cytokine expression levels for IL-6 (fold change  $1.8 \pm 0.22$ ;  $p < 0.05$ ), CD68 (fold change  $1.4 \pm 0.08$ ;  $p < 0.05$ ), and CcrR (fold change  $1.7 \pm 0.15$ ;  $p < 0.05$ ) were statistically significantly increased with PET vs. silk gel and saline. Expression of CC12 was statistically significantly higher with PET vs. silk gel (data not shown) and saline (fold change  $2.3 \pm 0.26$ ;  $p < 0.05$ ). Expression of TNF $\alpha$  was statistically

significantly higher with PET vs. saline (fold change  $2.1 \pm 0.37$ ;  $p < 0.05$ ). Protein level of IL-8 proinflammatory mediator was statistically significantly higher with PET vs. silk gel.

Timing of adverse effects: Cytokine expression measured 3 days post-op.

Factors that predict response: NR

Source Citation: Zhang et al. 2020<sup>10</sup>

Study Design: Comparative

Device or Material: Cerclage with PET suture (Dacron; Alcon Surgical) vs. silk hydrogel injection vs. saline injection

Route: Cervix

Dose: 5-0 Dacron

Frequency/Duration: Single administration

Response: Gene expression of IL-8, IL1 $\beta$ , CCR3, CXCR2, CCR1; Protein levels of IL-8 and IL1 $\beta$

Species (strain): Rabbits (New Zealand White, pregnant).

Gender: Female

Number per group: 4

Observed adverse effects: Increased expression of inflammation-related genes including IL-8, IL1 $\beta$ , IFN $\gamma$ , CCR3, CXCR2, and CCR1 with PET vs. saline injection; statistically significant difference for expression with IL1 $\beta$  and IL-8 ( $p < 0.05$ ). No difference in expression of TNF $\alpha$  and CCL2 between any groups. Protein-levels of IL-8 and IL1 $\beta$  were also statistically significantly increased with PET vs. saline.

Timing of adverse effects: 7 days post-op.

Factors that predict response: NR

Source Citation: Cymbaluk-Poska et al. 2019<sup>11</sup>

Study Design: Comparative

Device or Material: CPT-loaded microcapsules with PET-DLA copolymer

Route: Intraperitoneal

Dose: ~39 mg injected dose; 10 to 25  $\mu$ m microspheres

Frequency/Duration: Single administration

Response: Lymphoid infiltrate; Mild inflammation; Neutrophils; Purulent infiltrate

Species (strain): Mice (Balb C nude).

Gender: Female

Number per group: 14

Observed adverse effects: Overall only mild inflammation with PET-DLA. Inflammation in 3 specimens of parietal peritoneum included a focal purulent infiltrate, a small neutrophil cluster loosely present on the peritoneal surface, and moderately intense lymphoid infiltrate. Inflammation in 2 liver specimens included inflammation infiltrate around the gallbladder spaces; in 3 liver specimens were scattered clusters of lymphoid cells.

Timing of adverse effects: Parietal peritoneum: 6 hours for infiltrate, 12 hours for neutrophils, and lymphoid infiltrate at 7 days. Liver specimens: inflammation near gallbladder at 6 and 12 hours; lymphoid cells at 2, 3, 7, and 14 days.

Factors that predict response: NR

Source Citation: Eickhoff et al. 2019<sup>12</sup>

Study Design: RCT

Device or Material: Ultrafine PET (UFPET; Asahi Kasei Corporation) suture vs. snowflake-like shaped PVDF (ITA) vs. PET suture (MERSILENE; Ethicon) vs. PP suture (PROLENE; Ethicon)

Route: Abdomen

Dose: Diameter: UFPET: 250  $\mu$ m, PVDF: 230  $\mu$ m, MERSILENE PET 240  $\mu$ m, PROLENE PP 200  $\mu$ m

Frequency/Duration: Single administration

Response: Collagen I/III ratio; Expression of CD68 and Ki-67; Foreign body granuloma; Size of inner granuloma; Size of outer granuloma

Species (strain): Rats (Wistar).

Gender: Male

Number per group: 24

Observed adverse effects: Foreign body granuloma (FBG) evident within the UFPET suture surrounding each filament ( $\sim$ 3,000); FBG only around the MERSILENE PET suture. Size of inner granuloma (holding most of the inflammatory cells) was statistically significantly smaller with UFPET vs. MERSILENE PET (mean $\pm$ SD in  $\mu$ m: 15.0 $\pm$ 2.2 vs. 21.9 $\pm$ 5.8) at 7 days and 21 days (14.0 $\pm$ 1.7 vs. 20.4 $\pm$ 3.1). Size of inner granuloma was statistically significantly smaller with PVDF suture vs. all others at 7 days and 21 days ( $p = 0.001$ ). Size of outer granuloma was statistically significantly smaller with UFPET vs. MERSILENE PET at day 7 (61.0 $\pm$ 6.9 vs. 66.5 $\pm$ 11.0) and day 21 (59.6 $\pm$ 7.0 vs. 72.2 $\pm$ 9.4). Size of outer granuloma with PVDF was statistically significantly smaller vs. all other sutures at 21 days (272.9 $\pm$ 35.8 PVDF, 299.5 $\pm$ 38.4 PP, 349.9 $\pm$ 37.1 PET, 324.8 $\pm$ 19.2 UFPET;  $p = 0.001$ ). Expression of CD68 was similar at day 7 with UFPET (32.4), MERSILENE PET (32.4) and PVDF (31.5), but statistically significantly lower expression with PVDF vs. all other sutures at day 21 (7.2 $\pm$ 3.8 PVDF, 10.6 $\pm$ 4.1 UFPET, 18.0 $\pm$ 5.1 MERSILENE PET, 18.5 $\pm$ 5.6 PP). Expression of Ki-67 at day 7 was statistically significantly lower with UFPET vs. MERSILENE PET (14.3 $\pm$ 3.2 UFPET, 18.2 $\pm$ 3.4 MERSILENE PET;  $p = 0.001$ ); statistically significantly lower with PVDF vs. all (10.8 $\pm$ 3.4). Expression of Ki-67 at day 21 was statistically significantly lower with PVDF vs. all other sutures (13.4 $\pm$ 4.1 PVDF, 16.3 $\pm$ 5.1 UFPET, 18.3 $\pm$ 3.9 PP, 27.0 $\pm$ 9.1 Mersilene PET). Collagen I/III ratio were statistically significantly lower with UFPET vs. PP and PVDF at day 7 (4.0 $\pm$ 1.1 UFPET, 4.3 $\pm$ 1.0 PP, 4.3 $\pm$ 1.1 PVDF) and day 21 (4.0 $\pm$ 1.4 UFPET, 4.4 $\pm$ 1.2 PP, 4.3 $\pm$ 0.9 PVDF).

Timing of adverse effects: 7 and 21 days follow-up.

Factors that predict response: NR

Source Citation: Meyer et al. 2019<sup>13</sup>

Study Design: Comparative

Device or Material: PET sutures (ETHIBOND from Ethicon vs. FiberWire and FiberTape from Arthrex) vs. PDO sutures (Orthocord; DePuy Mitek)

Route: Shoulder

Dose: FiberTape: 2 mm wide

Frequency/Duration: Single administration

Response: Fibroblasts; Monocytes; Multinucleated giant cells; Neutrophils; Suture strength

Species (strain): Sheep (Swiss alpine).

Gender: Female.

Number per group: 6 per group at week 0; 11 per group weeks 6, 16, and 22.

Observed adverse effects: Higher pullout strength with FiberTape in tendon and bone vs. other sutures at all time points (FiberTape: suture-tendon: mean 0.66 N/cm week 0, 4.4 week 6, 10.1 week 16, 12.8 week 22; suture-bone: 31.8 N/cm week 22 only). Polymorphonuclear neutrophils, monocytes, and multinucleated giant cells were visible with all sutures types from 6 weeks to 22 weeks; no statistically significant difference. The maturity of surrounding connective tissue increased with all suture types, however fibroblasts with loosely well-oriented fibers were predominant in all samples (mean 1.7 FiberTape, 1.3 FiberWire, 1.6 ETHIBOND, 1 Orthocord; based on Rothamel classification). Authors noted an "unexpected circumferential space" around the PET (ETHIBOND, FiberWire) and PDO sutures (Orthocord), which frequently formed "an inner and outer capsule, separating the sutures from the surrounding tissue with a shifting layer."

Timing of adverse effects: weeks 0, 6, 16, and 22.

Factors that predict response: NR

Source Citation: Melvin et al. 2017<sup>14</sup>

Study Design: Comparative

Device or Material: FiberSecure sutures (unbraided bundle of 12 µm polyester fibers) compared with MERSILENE braided polyester suture

Route: Closure of external oblique muscle incisions

Dose: 12 µm fibers

Frequency/Duration: Single administration

Response: Inflammation; Fibrosis

Species (strain): Miniature Swine.

Gender: Female.

Number per group: 16 for each suture.

Observed adverse effects: Although the relatively open structure of FiberSecure suture allowed the inflammation to extend within the suture it was noted that the amount of inflammation was not different than the MERSILENE suture. Both types of sutures showed mild capsular fibrosis.

Timing of adverse effects: 90 days.

Factors that predict response: The increased intensity of the reaction to FiberSecure suture was described as a greater extent—but not amount—of inflammation compared to MERSILENE suture. This was attributed not to any unusual specific response to this suture, but rather to the relatively looser aggregation of filaments in FiberSecure suture, which allowed the reaction to infiltrate and spread apart individual filaments, in effect, expanding the cross-sectional area of the suture.

Source Citation: Tuken et al. 2016<sup>15</sup>

Study Design: RCT

Device or Material: Sutures: PET, polypropylene; polyglactine; and polydioxanone compared with sham

Route: Suturing cavernosal body of the penis

Dose: 5/0 sutures

Frequency/Duration: Single administration

Response: Fibrosis; Granuloma formation; Inflammation

Species (strain): Sprague-Dawley.

Gender: Male

Number per group: 6 each for 5 groups.

Observed adverse effects: PET sutures had the highest inflammation, granuloma, and fibrosis scores; statistically significantly higher than sham. Slides: inflammation score 3 in the PET group, where microabscess formation can be seen; wide granuloma formation for the PET group; fibrosis score 3 in the PET group. 3 was the highest score.

Timing of adverse effects: 3 weeks.

Factors that predict response: None noted.

Source Citation: Olmos-Zuniga et al. 2015<sup>16</sup>

Study Design: Comparative

Device or Material: PET, bovine pericardium, polytetrafluoroethylene, Teflon felt

Route: Vocal cord implants

Dose: 3 mm wide by 5 cm long

Frequency/Duration: Single administration

Response: Eosinophilic infiltration; FBGC; Fibrosis; Inflammation

Species (strain): Dog

Gender: NR.

Number per group: 3 groups of 6.

Observed adverse effects: Animals with PET vocal cord implants showed mild inflammation with presence of lymphocytes, plasma cells, FBGC, and fibrosis. Mild eosinophilic infiltration.

Timing of adverse effects: 3 months.

Factors that predict response: None noted.

Source Citation: Dinjaski et al. 2014<sup>17</sup>

Study Design: Comparative

Device or Material: PET compared with PHACOS coated PET

Route: Subcutaneously implanted disk

Dose: 2 disks (6 mm diameter)

Frequency/Duration: Single administration

Response: Minimal inflammation

Species (strain): BALB/c mice.

Gender: Male.

Number per group: NR

Observed adverse effects: Higher recruitment of inflammatory cells was found to the vicinity of the sterile poly (3-hydroxyoctanoate-co-hydroxyhexanoate) implants (76% of total cell number) compared with sterile PHACOS implants (62% of total cell number) at 14 days postimplantation.

Timing of adverse effects: 14 days

Factors that predict response: The implant coating seems to have reduced any inflammatory reaction related to PET. No PET only implant control was used in the mice experiment.

Source Citation: Liu et al. 2014<sup>18</sup>

Study Design: Comparative

Device or Material: PET and poly(L-lactide-co-ε-caprolactone) fibers

Route: Subretinal transplant

Dose: 200 to 1,000 nm fibers in 2 x 1.1 mm bullet-shaped implant

Frequency/Duration: Single administration

Response: No immune response

Species (strain): Rabbit.

Gender: Female.

Number per group: 5

Observed adverse effects: No immune cells could be distinguished around the implant on hematoxylin/eosin (paraffin) or Toluidine blue (resin) sections. The subretinal response to PET composite scaffold suggests biocompatibility.

Timing of adverse effects: 14 days.

Factors that predict response: NR

Source Citation: Muhamed et al. 2013<sup>19</sup>

Study Design: Case series

Device or Material: PET

Route: Intramuscular implant

Dose: 2 strips 10 x 6 mm

Frequency/Duration: Single administration

Response: Fibroblasts; Fibrous capsule; Foreign body reaction

Species (strain): Rabbit.

Gender: NR

Number per group: 9

Observed adverse effects: Tissue reaction was mainly constituted by the various types of inflammatory cells and fibroblasts around the implanted material with some extracellular matrix reaction. At 12 weeks



the tissue response was characterized by chronic granulomatous reaction with a well-formed fibrous capsule limiting the reaction zone around the implant.

Timing of adverse effects: FBGC reaction was minimal during week 1 and declined further by week 12.

Factors that predict response: The results suggested a phenotypic alteration of native cell types following implantation of PET fabric in rabbit skeletal muscle.

Source Citation: Melvin et al. 2011<sup>20</sup>

Study Design: Random assignment of fiber types to 1 of 4 wound incisions

Device or Material: FiberSecure sutures (unbraided bundle)

Route: 4 cross-fiber external oblique muscle incisions

Dose: Each animal received 4 sutures; 12 µm polyester fibers

Frequency/Duration: Single administration

Response: Inflammation

Species (strain): Mini-pigs.

Gender: Female

Number per group: 16 at 30 days and 8 at 180 days.

Observed adverse effects: The specimens showed plentiful fibroblasts with spindle shaped nuclei surrounded by their abundantly produced collagen (blue on trichrome staining), organized between the individual PET fibers. The fibers were surrounded by inflammatory tissue as well as proliferating granulation tissue. Histological evaluation showed an inflammatory response similar to that consistently seen at the interface of tissue, after similar time periods, with conventional implanted synthetic sutures.

Timing of adverse effects: 30 to 180 days.

Factors that predict response: None noted.

Source Citation: Selvam et al. 2011<sup>21</sup>

Study Design: Case series

Device or Material: PET

Route: Subcutaneous

Dose: 8 mm diameter disks

Frequency/Duration: Single administration

Response: Chronic inflammation

Species (strain): BALB/c mice.

Gender: Male

Number per group: NR

Observed adverse effects: Mice receiving biomaterial implants exhibited substantial increases in fluorescence signal (inflammation indicator) over time ( $p < 0.01$ ), whereas the sham control showed no time-dependent differences. These results demonstrate that reactive oxygen species dyes injected locally can detect reactive oxygen species activity associated with biomaterial-induced inflammation with no cellular toxicity. Histological analysis showed the formation of a collagenous

fibrous capsule around the implants of increasing thickness with implantation time, a hallmark of chronic inflammation to biomaterials.

Timing of adverse effects: Up to 14 days.

Factors that predict response: None noted.

Source Citation: Patrzyk et al. 2010<sup>22</sup>

Study Design: RCT

Device or Material: PET with low, medium, and high primary porosity

Route: Infrarenal aorta vascular prostheses

Dose: Length 4 cm, diameter 0.8 cm Dacron prosthesis

Frequency/Duration: Single administration

Response: Neointima thickening

Species (strain): Pigs

Gender: Females

Number per group: 5 per 3 groups.

Observed adverse effects: On day 116, the low porosity-prosthesis had a statistically significantly higher neointima thickness ( $1,500 \pm 250 \mu\text{m}$ ) compared to the high porosity-prosthesis ( $1,100 \pm 210 \mu\text{m}$ ;  $p = 0.0009$ ) and the medium porosity-prosthesis ( $1,100 \pm 220 \mu\text{m}$ ;  $p = 0.0004$ ). Neointima thickness did not differ significantly between the medium porosity and the high porosity prostheses on day 116. Only for the low porosity prosthesis was a statistically significant increase between days 28 and 116 observed ( $p < 0.0001$ ).

Timing of adverse effects: Up to 116 days.

Factors that predict response: Low porosity might interfere with capillary infiltration and inhibit tissue infiltration in the prosthesis matrix. The results of the study point to a relationship between the fibronectin formation as well as the neointima lining and the porosity of the prosthesis material, demonstrating the importance of the textile design and structure as well as the surface geometry of vascular prostheses for tissue reactions and biocompatibility.

CpT: carboplatin; FBGC: foreign body giant cell; IFN $\gamma$ : interferon gamma; IL1 $\beta$ : interleukin 1 beta; IL-6: interleukin-6; IL-8: interleukin 8; mg: milligram; NanoAg: silver nanoparticles; nm: nanometre; N/cm: newton per centimeter; NR: not reported; PDO: polydioxanone; PET: poly(ethylene terephthalate); PET-DLA: poly(ethylene terephthalate)-ethylene dilinoleate; PHACOS: poly-3-hydroxy-acetylthioalkanoate-co-3-hydroxyalkanoate; PP: polypropylene; PVDF: polyvinylidene fluoride; RCT: randomized controlled trial; SRT: screw retention technology; TNF $\alpha$ : tumor necrosis factor- $\alpha$ ;  $\mu\text{m}$ : micron; UFPET: ultrafine poly(ethylene terephthalate).

Table 10: PET Grafts – Health Effect (In Vivo) Human Studies

### **Local Response/Toxicity**

Source Citation: Spadaccio et al. 2019<sup>24</sup>

Study Design: Systematic review

Device or Material: Large-diameter Dacron vascular grafts

Contact Duration: 3 years to 30 years

Dose: NR

Frequency/Duration: NR

Response: Aortic valve dysfunction; Fistula formation; Late rupture; Para anastomotic aneurysm; Pseudoaneurysm

Patient characteristics (gender, mean age): NR

Number per group: NR

Observed adverse effects: Long-term complications with Dacron grafts in the abdominal aorta were fistula formation (0.7% to 1.1% incidence), para-anastomotic aneurysm (3% to 15% incidence), and late rupture in 2 patients. Complications in the ascending aorta included pseudoaneurysm (in 2.09%, 3.1% and 31 cases), and aortic valve dysfunction (5.5% to 46.2%). Complications in the arch and descending aorta included fistula formation (1 case aorto-pulmonary, 4 cases aorto-bronchial, and 2% aorto-esophageal), and late rupture in 1 patient.

Timing of adverse effects: Abdominal aorta: fistulization at 11 and 12 years; para-anastomotic aneurysm at 8 and 15 years; late rupture at 17 and 19 years. Ascending aorta: pseudoaneurysm at 10, 24, and 25 years; aortic valve dysfunction 7.5, 8, 13, and 15 years. Arch and descending aorta: fistulization: 3, 5, and 29 years; late rupture at 23 years.

Factors that predict response: NR

Source Citation: Aurigemma et al. 2018<sup>25</sup>

Study Design: Retrospective case series

Device or Material: Woven Dacron tube graft (Hemashield; Maquet)

Contact Duration: 13 to 22 years

Dose: 12 mm, 14 mm, 16 mm, and 22 mm

Frequency/Duration: Single administration

Response: Bleeding; Extravasation; Fibrosis; Foreign body giant cells; Graft failure; Inflammatory reaction; Pseudoaneurysm; Stenosis; Thrombus

Patient characteristics (gender, mean age): 100% males, 18 to 29 years.

Number per group: 4 with grafts in the thoracic aorta.

Observed adverse effects: Complications in Case 1 included extensive fibrosis and calcification causing fiber disorganization and inflammatory reaction with foreign body giant cells. Complications in Case 2 included stenosis, extravasation, large pseudoaneurysm, and intraluminal thrombus. In Case 3,

upsizing of Hemashield graft was aborted because of substantial bleeding. Authors noted that the graft was densely adherent to the chest wall and began to disintegrate during the dissection. In Case 4: an 8 mm pseudoaneurysm was noted at the distal aspect of a previously placed stent.

Timing of adverse effects: Failure occurred at 13, 15, 17, and 22 years postimplantation.

Factors that predict response: NR

Source Citation: Tazaki et al. 2017<sup>26</sup>

Study Design: Retrospective cohort

Device or Material: Dacron PET graft (branched Inoue stent graft (ISG); main body and branch of ISG (PTMC Institute) with woven Dacron (Dupont); small Dacron cuffs attached to graft edges to seal graft and aortic inner wall

Contact Duration: Median follow-up (days): 1,345 (IQR, 683 to 2144); follow-up to 5 years

Dose: 5 Fr and 7 Fr sheaths, 16 to 42 mm diameter for main graft, 7 to 18 mm for branched grafts

Frequency/Duration: Single administration

Response: Aneurysm enlargement; Endoleak; Migration; Occlusion

Patient characteristics (gender, mean age): 72% male, 76.8 years.

Number per group: 89 undergoing TEVAR for TAA; branches: 64 single, 18 double, 7 triple.

Observed adverse effects: Persistent Type I endoleak after index TEVAR was reported in 9 patients (8 single-branch ISG, 1 double-branched ISG). Endoleak caused aneurysm diameter enlargement >5 mm in 7 patients. Proximal ring migration and branch graft occlusion at LSCA (double-branched ISG) in 1 patient each.

Timing of adverse effects: Migration at 4 years. Endoleak occurred shortly after index TEVAR.

Factors that predict response: Smoking and COPD were major causes of death; graft not associated with long-term stroke.

Source Citation: Vitanova et al. 2014<sup>27</sup>

Study Design: Retrospective controlled cohort

Device or Material: Porcine-valved Dacron conduits (Hancock; Medtronic) vs. bovine jugular vein conduits (Contegra; Medtronic) vs. cryopreserved aortic and pulmonary homografts

Contact Duration: Median follow-up (years): 9.3 (range 8.3 to 10.3)

Dose: Mean diameter: 12.9±1.3

Frequency/Duration: Single administration

Response: Freedom from at least moderate stenosis; Conduit exchange due to valvular stenosis; Conduit exchange due to thrombosis

Patient characteristics (gender, mean age): NR, Hancock: 3.6 months, Contegra: 4.0 months, Homograft: 3.9 months.

Number per group: 48 Hancock, 35 Contegra, 62 Homograft.

Observed adverse effects: Rate of freedom from at least moderate stenosis at 5 years was lowest with Hancock (years: 69.1 Hancock, 75.1 Contegra, and 85.4 for homografts); rate at 10 years was lowest with Contegra (49.7 years Hancock, 35.8 years Contegra, and 59.2 years homografts). Conduit exchange due to valvular stenosis was reported in 51 (39%) patients [19 (37%) with

Hancock, 11 (21%) with Contegra, 21 (41%) with homograft]. Thrombosis occurred in 4 patients with Hancock and led to a conduit exchange.

Timing of adverse effects: Stenosis occurred at a median time of 4.2 years (4.3 months to 12 years). Conduit exchange due to thrombosis occurred at a median of 1.3 years, range 4 months to 6 years.

Factors that predict response: NR

Source Citation: Tang et al. 2011<sup>30</sup>

Study Design: Case series

Device or Material: Dacron graft (DuPont)

Contact Duration: Follow-up (months): 1 to 48

Dose: 24 mm (2 long segments), 28 mm (2 long segments, 1 short segment)

Frequency/Duration: Single administration

Response: Death; Pulmonary embolism

Patient characteristics (gender, mean age): 80% male, range 39 to 64 years.

Number per group: 5 patients replaced an infected aorta with Dacron grafts.

Observed adverse effects: Pulmonary embolism (PE) (and subsequent death) occurred 10 months postimplantation in 1 patient; aortic repair was intact.

Timing of adverse effects: PE at 10 months.

Factors that predict response: NR

**Systemic Response/Toxicity**

Source Citation: Agaimy et al. 2016<sup>31</sup>

Study Design: Case reports

Device or Material: Dacron vascular grafts

Contact Duration: 4.6 years and 8 years

Dose: NR

Frequency/Duration: NR

Response: Angiosarcoma; Death; Abdominal pain; ERG expression; Fatigue; FLI- expression; Hemorrhage; Stenosis; Unexplained weight loss Patient characteristics (gender, mean age):

Patient characteristics (gender, mean age): 100% males, 50, 71 and 84 years.

Number per group: 3 patients undergoing vascular repair of the infrarenal aorta (2) or right common iliac artery (1).

Observed adverse effects: Angiosarcoma and subsequent deaths in 3 patients. 1 patient died at 6 months. 1 patient died at 24 months after recurrence and lung metastases at 12 months. 1 patient died "postoperatively" with lymph nodes and vertebral metastases. Angiosarcoma symptoms included fatigue, unexplained weight loss, and abdominal pain. All angiosarcomas displayed extensive hemorrhage evidenced by variable stroma stenosis. Histology results indicated tumor tissue lining the original vascular lumen. Strong nuclear expression of ERG and FLI-1 was noted in all tumors. 7 case reports of angiosarcoma following Dacron graft implantation were reported in the literature between 1972 and 2015.

Timing of adverse effects: Angiosarcoma occurred at 4.6 years postimplantation in 1 patient and at 8 years in 2 patients. Death occurred at 6 months and 24 months in 1 patient each; timing NR in 1 patient.

Factors that predict response: NR

COPD: chronic obstructive pulmonary disorder; Fr: French; FLI-1: friend leukemia integration 1 transcription factor; IQR: interquartile range; LARS: Ligament Advanced Reinforcement System; LSCA: left subclavian artery; N/A: not applicable; NR: not reported; PET: poly(ethylene terephthalate); TAA: thoracic aortic aneurysm; TEVAR: thoracic endovascular aortic repair.

Table 11: PET Grafts – Health Effect (In Vivo) Animal Studies

### **Local Response/Toxicity**

Source Citation: Fujita et al. 2020<sup>32</sup>

Study Design: Case series

Device or Material: Heparin-loaded polyethylene terephthalate ultrafine microfiber (HL-PET) graft

Route: Carotid artery implant

Dose: 3 mm diameter, 30 mm length

Frequency/Duration: Single administration

Response: Low inflammatory reaction

Species (strain): Dogs.

Gender: Males.

Number per group: 6

Observed adverse effects: Infiltration of fibroblast-like cells, macrophages, and some FBGCs were observed in the interstices of ultrafine microfibers, showing the ongoing graft healing process.

Timing of adverse effects: 24 weeks.

Factors that predict response: Results suggest that the HL-PET graft may have potential for the clinical application as a new small caliber vascular prosthesis for infrapopliteal or coronary artery bypass use. Benefits from heparin-loaded flow surface, smooth surface of woven microfiber, and biologically high porosity fabric with ultrafine microfibers.

Source Citation: Zhang et al. 2020<sup>33</sup>

Study Design: RCT

Device or Material: 3 grafts: PET, PCL/PET, and BMP-7/PCL/PET

Route: Anterior cruciate ligament reconstruction

Dose: NR

Frequency/Duration: Single administration

Response: Inflammatory cell infiltration

Species (strain): New Zealand white rabbits.

Gender: NR

Number per group: 3 groups of 24.

Observed adverse effects: At the 6-week time point, staining showed inflammatory cell infiltration in the graft and bone interfaces in the 3 groups. At 12 weeks the PET group still had fibrous scar tissue at the graft–bone interface, and no osteointegration was detected.

Timing of adverse effects: NR

Factors that predict response: PET has appropriate strength but is disadvantaged by biological inertness and hydrophobicity, which is unfavorable for the growth of osseous tissue and blood vessels. The degradable PCL electrospun nanofiber membrane can simulate the extracellular matrix structure and has good histocompatibility, enabling it to provide a good biological microenvironment for the graft and bone tunnel.

Source Citation: Parry et al. 2018<sup>34</sup>

Study Design: Comparison study

Device or Material: PCLF/PET scaffold compared with semitendinosus autograft

Route: Anterior cruciate ligament reconstruction

Dose: 2.5 mm in diameter, 3 cm in length

Frequency/Duration: Single administration

Response: Intra-articular scaffold destruction

Species (strain): New Zealand white rabbits.

Gender: Female

Number per group: 2 groups of 6

Observed adverse effects: CLF-PET constructs showed extensive intra-articular scaffold destruction in all specimens. The portion of the scaffold in the bone tunnels remained intact. Polymer debris was evident throughout the joint and the bone tunnels appeared to increase in size. Minimal collagenous ingrowth in the bone tunnels containing PCLF-PET scaffolds with diffuse areas of polymer debris surrounded by inflammatory cells.

Timing of adverse effects: NR

Factors that predict response: PET incomplete biointegration has been linked to ligament wear and rupture.

Source Citation: Van Hoof et al. 2017<sup>35</sup>

Study Design: Case series

Device or Material: Macroporous mesh and off-the-shelf woven low-porosity graft made of PET

Route: Aortas were each wrapped by the 2 test grafts

Dose: NR

Frequency/Duration: Single administration

Response: Foreign body reaction

Species (strain): Sheep

Gender: NR

Number per group: 3

Observed adverse effects: The fabric fibers (i.e., their constituent threads) are surrounded by a cellular reaction embedded in collagen, consisting of fibroblasts, neovessels, and typical FBGCs, but no lymphocytes or granulocytes. Macroporous mesh appeared well incorporated as the cellular and fibrotic reaction permeates into the fabric, surrounding nearly all of the fabrics' loosely packed microfibrils. Low-porosity graft was associated with a denser cellular infiltrate with more and larger FBGCs than the macroporous mesh.

Timing of adverse effects: NR



Factors that predict response: Macroporous mesh is well incorporated in marked contrast to low porosity vascular graft. The macroporous mesh is fully and intimately incorporated because of its macroporous and pliant nature.

Source Citation: Fukayama et al. 2015<sup>36</sup>

Study Design: Comparison study

Device or Material: PET vascular graft compared with SF graft: SF/SF, SF/G, PET/SF, PET/G

Route: Abdominal aorta grafts

Dose: 10 mm in length, 1.5 mm inner diameter

Frequency/Duration: Single administration

Response: Inflammatory reaction

Species (strain): Rats.

Gender: NR

Number per group: 4 groups of 12.

Observed adverse effects: In the samples 2 weeks after implantation, both the hematoxylin and eosin (H&E)- and Masson trichrome (MTC)-stained images showed the presence of many inflammatory cells including lymphocytes, macrophages, and FBGCs in all types of grafts. 3 months after implantation, a decrease of inflammatory cells was observed for SF/SF and PET/G grafts, although there was no change for PET/SF and SF/G grafts. At 3 months after implantation, SF/SF and PET/G showed the presence of more collagen fibers than others. At 3 months PET/G had the lowest inflammation rating.

Timing of adverse effects: NR.

Factors that predict response: No tissues were observed inside the PET/G grafts because gelatin inhibited tissue infiltration into the graft, and the contact area was small between graft fibers and the surrounding tissue. Therefore, inflammation induced by PET/G grafts disappeared earlier because of the small contact point between graft fibers and tissue.

Source Citation: Kim et al. 2012<sup>37</sup>

Study Design: Case series

Device or Material: PET

Route: Endoskeleton stent grafts for saccular abdominal aortic aneurysms

Dose: 12 mm diameter, 60 mm length

Frequency/Duration: Single administration

Response: No reactions noted on histopathological examination

Species (strain): Dogs.

Gender: NR.

Number per group: 3 at 2 months, 5 at 6 months.

Observed adverse effects: Graft overhanging the saccular aneurysm was covered by thick or thin thrombi with no endothelial layer, and the graft over the aortic wall was completely covered by neointima with an endothelial layer.

Timing of adverse effects: 2 to 6 months.

Factors that predict response: Dacron patch can be another reason for absence of endothelialization. The patch is a good material for creating the aneurysm of intended size and shape. However, it does not allow natural expansion of an aneurysm that can be found in a true aneurysm, and it could have different hemodynamic features after endovascular grafting and prevent endothelialization over the stent graft.

Source Citation: Dimitrievska et al. 2011<sup>38</sup>

Study Design: Case series

Device or Material: PET

Route: Subcutaneous implantation

Dose: 1 cm diameter

Frequency/Duration: Single administration

Response: Inflammatory response with foreign body reaction

Species (strain): CD1 mice.

Gender: NR.

Number per group: 6 implants per sterilization condition.

Observed adverse effects: Histological sections revealed an inflammatory response in both EtO and LTP-sterilized non-woven PET implants. Inflammation was accompanied by a foreign body reaction composed of giant cells (fused macrophages) often directed to the non-woven PET fibers. The degrees of foreign body reaction varied depending on the specimens. Blinded observation revealed no difference between the non-woven PET implants sterilized by EtO or LTP after 30 days.

Timing of adverse effects: NR.

Factors that predict response: Results of the present study suggest that the most important change is the surface oxidation, i.e., benzene (C-C) groups decrease in favor of C-OH/-COOH groups, after both sterilization methods.

EtO: ethylene oxide; FBGC: foreign body giant cell; G: gelatin; LTP: low temperature plasma sterilization; NR: not reported; PCL: polycaprolactone; PCLF: polycaprolactone fumarate; PET: poly(ethylene terephthalate); RCT: randomized controlled trial; SF: silk fibroin.

Table 12: PET Patch/Mesh/Mat/Substrates – Health Effect (In Vivo) Human Studies

### **Local Response/Toxicity**

Source Citation: Deng et al. 2019<sup>39</sup>

Study Design: Controlled cohort

Device or Material: Dacron patch (Beijing Sida Medical Device) vs. imported PET patch for congenital heart disease

Contact Duration: 6 months

Dose: NR

Frequency/Duration: Single administration

Response: None

Patient characteristics (gender, mean age): 27 male, 21 female, mean 20 years.

Number per group: 26 Dacron, 22 controls.

Observed adverse effects: There was no early death (within 30 days after operation), no serious adverse events, and no early complications in the 2 groups.

Timing of adverse effects: within 6 months.

Factors that predict response: NR

Source Citation: Alawy et al. 2017<sup>40</sup>

Study Design: Controlled cohort

Device or Material: Dacron patch (28% InterVascular Hemacarotid; Datascope, 63% Ultrathin Hemacarotid; Maquet Getinge) vs. biologic patch (XenoSure; LeMaitre Vascular GmbH) for carotid endarterectomy

Contact Duration: 18 months to 7 years

Dose: NR

Frequency/Duration: Single administration

Response: Fluid collection; Inflammatory reaction; Stenosis; Thrombosis

Patient characteristics (gender, mean age): Of 8 patients showing reaction, 5 (62.5%) were female. Median age at the time of identification was 72.5 years.

Number per group: 428 Dacron, 43 XenoSure.

Observed adverse effects: 8 (1.8%) patients developed an inflammatory reaction with Dacron patch. Fluid collection around Dacron patch was noted in 6 patients. Internal carotid thrombosis in 1 patient. Contralateral ICA stenosis ranged from 20% to 40% in 5 patients, 50% to 60% in 1 patient, and 99% in 2 patients. None of the patients had elevated inflammatory markers on presentation. The total leukocyte count, CRP levels, and ESR were all within normal range for all patients.

Timing of adverse effects: 18 months to 7 years.

Factors that predict response: NR

Source Citation: Casana et al. 2017<sup>41</sup>

Study Design: Prospective cohort  
Device or Material: PET mesh (MicroNet) over a Nitinol stent  
Contact Duration: 48 hours to 30 days  
Dose: 150 to 180 µm porosity, 20 µm in thickness  
Frequency/Duration: Single administration  
Response: New ischemic brain lesions; Stent thrombosis; Stroke  
Patient characteristics (gender, mean age): 75% male, 73.8 years.  
Number per group: 2 undergoing CAS.  
Observed adverse effects: Acute stent thrombosis and subsequent minor stroke in 1 patient; clot formation remained unclear. Results of DW-MRI indicated new ischemic brain lesions observed in 5/21 (23.8%) patients perioperatively, and in 1 (20%) patient during the postoperative period.  
Timing of adverse effects: Thrombosis at 4 hours post-op. New ischemic brain lesions 48 to 72 hours post-op in 5 patients, and 30 days post-operatively in 1 patient.  
Factors that predict response: NR

Source Citation: Gilevich et al. 2017<sup>42</sup>

Study Design: Case series  
Device or Material: PET scaffold (Harvard Apparatus Regenerative Technology) with MNCs  
Contact Duration: Median follow-up (months): 17  
Dose: NR  
Frequency/Duration: NR  
Response: Bacterial contamination; Deformed fibers; Fungal contamination; Macrophage infiltration; Neutrophil infiltration  
Patient characteristics (gender, mean age): 4 patients undergoing transplantation of tracheal TEC.  
Number per group: 4 patients undergoing transplantation of tracheal TEC.  
Observed adverse effects: Histology indicated deformed fibers in the scaffold, inflammation (infiltration with neutrophils and macrophages, fungal and bacterial contamination).  
Timing of adverse effects: 3 months.  
Factors that predict response: NR

Source Citation: Pecoraro et al. 2016<sup>43</sup>

Study Design: Controlled cohort  
Device or Material: PET/PP mesh wrap for iAA  
Contact Duration: Mean 33 months  
Dose: Mean diameter 5.5 cm  
Frequency/Duration: Single administration  
Response: No reactions or deaths reported

Patient characteristics (gender, mean age): 67 years.

Number per group: 33

Observed adverse effects: No reaction to the mesh wrap.

Timing of adverse effects: NA.

Factors that predict response: NR.

Source Citation: Willekens et al. 2016<sup>44</sup>

Study Design: Retrospective case series

Device or Material: Dacron interposition (Anchois Ligastic; Orthomed SA) for trapeziometacarpal OA

Contact Duration: 2 implants removed at 5 and 8 years after surgery. 7 implants examined at 9 years.

Dose: NR

Frequency/Duration: Single administration

Response: Foreign body reaction

Patient characteristics (gender, mean age): Female, NR.

Number per group: 10

Observed adverse effects: Histological analysis confirmed the presence of a foreign body reaction with giant cells in 2 cases. 7 out of 9 hands had radiological signs of a foreign body reaction with bone erosion. A severe reaction occurred in 3 patients. The authors "no longer use the Dacron implant and recommend careful monitoring of all patients in whom this implant has been used."

Timing of adverse effects: 2 implants removed at 5 and 8 years after surgery. 7 implants examined at 9 years.

Factors that predict response: If the implant disintegrates, microparticulate debris becomes embedded into the synovium. This triggers aggressive hyperplastic synovitis. Destruction of bone and cartilage can occur because of adherence of the thickened synovium to the articulating surfaces or deposit of implant debris directly on the bone and cartilage.

Source Citation: Spaans et al. 2014<sup>45</sup>

Study Design: Case series

Device or Material: PET mesh interposition (Anchois Ligastic; Orthomed SA) for trapeziometacarpal OA

Contact Duration: Mean 14 months (range 5 to 27)

Dose: NR

Frequency/Duration: Single administration

Response: Foreign body reaction

Patient characteristics (gender, mean age): 62% female, 60 years.

Number per group: 8

Observed adverse effects: Complications included persistent swelling, synovitis, and pain with presence of extensive monocytic and multinucleated foreign body giant cells around PET. PET was also noted as fragmented. Authors noted they no longer use PET mesh for this indication.

Timing of adverse effects: Within 14 months.

Factors that predict response: not related to infection.

Source Citation: Chong et al. 2010<sup>46</sup>

Study Design: Case series

Device or Material: MERSILENE mesh (Ethicon) frontalis sling for severe unilateral congenital ptosis

Contact Duration: 13-year mean follow-up

Dose: NR

Frequency/Duration: Single administration

Response: No reaction

Patient characteristics (gender, mean age): 60% male, <1 year of age.

Number per group: 10.

Observed adverse effects: No sling extrusion, stitch granuloma, or exposure keratopathy were observed.

Timing of adverse effects: Within 13 years.

Factors that predict response: NR.

CAS: carotid artery stenting; CRP: C-reactive protein; DW-MRI: diffusion weighted magnetic resonance imaging; ESR: erythrocyte sedimentation rate; iAA: isolated ascending aortic aneurysm; ICA: internal carotid artery; MNC: mononuclear cells; NR: not reported; OA: osteoarthritis; PET: poly(ethylene terephthalate); PP: polypropylene; TEC: tissue-engineering constructs.

Table 13: PET Patch/Mesh/Mat/Substrates – Health Effect (In Vivo) Animal Studies

### **Local Response/Toxicity**

Source Citation: Grumezescu et al. 2019<sup>47</sup>

Study Design: RCT

Device or Material: PET nanofiber mats based on flow rate (mL/h): PET\_2.5 cntrl, PET\_5.0 cntrl, PET\_7.5 cntrl, and PET\_10 cntrl, PET\_2.5\_NanoAg, PET\_5\_NanoAg, PET\_7.5\_NanoAg, PET\_10\_NanoAg; vs no PET cntrl

Route: Subcutaneous

Dose: 57 to 76 µm; fiber dimension ranged from 30 to 100 100 nm, NanoAg ranged from 8 to 20 nm

Frequency/Duration: Single administration

Response: CRP levels; Edema; Fibrous capsule; Lymphocytes; Macrophage; Monocytes; Neutrophils; TNFα expression

Species (strain): Mice (CD1)

Gender: NR

Number per group: 5

Observed adverse effects: CRP blood levels were elevated for all NanoAg groups at day 1, with levels gradually decreasing up to day 7. PET\_2.5\_NanoAg had statistically significantly lower CRP levels vs. PET\_2.5 cntrl at day 1 and day 7. Substantial edema was present in all PET control samples. Fibrous capsule with varying thickness was present in all PET samples. Inflammatory reaction including macrophages, monocytes, lymphocytes, and neutrophils were observed between the mats and the fibrous capsule; more extensive inflammation in PET control samples vs. PET NanoAG samples. Giant cells were only present in PET 10 and 7.5 controls. TNFα expression was lower with NanoAg samples.

Timing of adverse effects: 1 and 7 days.

Factors that predict response: NR

Source Citation: Gilevich et al. 2018<sup>48</sup>

Study Design: Case series

Device or Material: PET scaffold

Route: Back

Dose: 10 cm<sup>2</sup> scaffold

Frequency/Duration: Single administration

Response: Fibrous capsule; Macrophages; Mannose receptor expression; Neutrophils

Species (strain): Baboon (Papio hamadryas).

Gender: Male.

Number per group: 6 (3 heterotopic, 3 orthotopic).

Observed adverse effects: Inflammatory response in heterotopic implants included a fibrous capsule, neutrophils, giant cells, macrophages, and mannose receptor expression.

Timing of adverse effects: days 20 to 30.

Factors that predict response: NR

Source Citation: Lake et al. 2015<sup>49</sup>

Study Design: RCT

Device or Material: 5 PET prototype meshes with varying mesh density, pore size, and pore shape

Route: Preperitoneal, retrorectus space in a porcine model of ventral incisional hernia repair

Dose: 8 × 10 cm meshes; LWVLS 38 g/m<sup>2</sup>, MWVLS 59 g/m<sup>2</sup>, LWMD 42 g/m<sup>2</sup>, MWMD 90 g/m<sup>2</sup>

Frequency/Duration: Single administration

Response: Inflammation

Species (strain): Pigs

Gender: NR.

Number per group: 13 pigs received 4 of the meshes using randomized assignment.

Observed adverse effects: Inflammation. The medium-weight, very large pore, hexagonal mesh trended toward less inflammation than the light-weight, very large square pores mesh ( $p = 0.051$ ). The medium-weight, very large hexagonal pores, and light-weight, very large square pores meshes trended toward overall more favorable tissue response by composite score compared to medium-weight, very large square pores ( $p = 0.065$  and  $p = 0.06$ , respectively).

Timing of adverse effects: Within 90 days.

Factors that predict response: Pore size and pore shape.

Source Citation: Veleirinho et al. 2014<sup>50</sup>

Study Design: RCT

Device or Material: Marlex30 (PP control), PET30, PET/C, DL mesh with 1 layer of PET and 1 layer of PET/C mat, woven-PET, Marlex90 (PP control), and PET90 meshes PET from Flexitex, Marlex from Intracorp

Route: Abdominal

Dose: PET diameter:  $0.71 \pm 0.28 \mu\text{m}$ ,  $3.01 \pm 0.72 \mu\text{m}$

Frequency/Duration: Single administration

Response: Inflammatory response; Foreign body reaction

Species (strain): Rat (Wistar).

Gender: Male.

Number per group: In 7 treatment groups.

Observed adverse effects: All animals showed typical non-immunogenic granulomas (foreign body granulomas mostly composed of macrophages, FBGC, and fibroblasts) surrounding the mesh structure. Animals treated with electrospun meshes (PET, PET/C, DL) showed statistically significantly thicker granulomas and a higher number of FBCGs compared to Marlex and the



woven-PET group. Woven-PET group produced the weakest inflammatory response. Long-term inflammatory response of electrospun PET indicated decrease in inflammation at 90 days (average granuloma thickness decreased from  $959\pm 473$   $\mu\text{m}$  to  $513\pm 217$   $\mu\text{m}$ , number of FBGCs decreased from  $106\pm 30$  to  $89\pm 12$ ).

Timing of adverse effects: 30 and 90 days.

Factors that predict response: Taking advantage of the anti-inflammatory and wound healing effects of chitosan, a hybrid fibrous material (PET/C) was also developed, with higher fiber diameter and pore area. Increased hydrophilic character observed for the PET/C hybrid may be advantageous for mesh integration on the parietal side. Nanostructure of the electrospun materials underlies the huge foreign body reaction found in animals implanted with electrospun meshes.

CRP: C-reactive protein; cntrl: control; DL: double-layered; FBGC: foreign body giant cell; LWMD: *light-weight*, medium pore, diamond knit pattern; LWVLS: light-weight, very large pore, square knit pattern; MWMD: *medium-weight*, medium pore, diamond knit pattern; MWVLS: medium-weight, very large pore, square knit pattern; Silver NanoAg: nanoparticles; NR: not reported; PET: polyester; PET/C: PET/chitosan; PP: polypropylene; RCT: Randomized controlled trial; TNF $\alpha$ : tumor necrosis factor alpha.

Table 14: PET Ligaments – Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Di Benedetto et al. 2020<sup>23</sup>

Study Design: Case series

Device or Material: PET graft (LARS)

Contact Duration: Mean (years): 3 (range 9 months to 5 years)

Dose: NR

Frequency/Duration: Single administration

Response: Graft failure due to rupture; Inflammation; Malposition; Multinucleated giant cells; Synovitis

Patient characteristics (gender, mean age): 91% male, 41 years.

Number per group: 11 undergoing ACL revision surgery for LARS-ACL reconstruction failure (rupture).

Observed adverse effects: 100% graft failure due to rupture. Histological analysis indicated severe widespread villonodular synovitis to every knee joint, chronic inflammation with multiple multinucleated giant cells, and poor signs of fibrovascular ingrowth of LARS. Malposition in 6 (54.5%) patients.

Timing of adverse effects: 9 months to 5 years.

Factors that predict response: NR.

Source Citation: Tiefenboeck et al. 2015<sup>51</sup>

Study Design: Case series

Device or Material: LARS (Surgical Implants and Devices, Arc-sur-Tille, France)

Contact Duration: Mean (range): 151 months (120 to 165)

Dose: Unilateral ACL reconstruction

Frequency/Duration: Single administration

Response: Superficial infection; Deep infection; Graft breakage; Unstable knee; osteoarthritis

Patient characteristics (gender, mean age): 7 males, 11 females, 29 yrs (18 to 44).

Number per group: 17

Observed adverse effects: 1 patient had superficial surgical site infection. 2 patients had deep surgical site infections. 3 patients broke the graft during sport activities. 2 suffered a broken graft due to infection. 4 patients had an unstable knee (positive Lachman testing and side-to-side difference >5mm).

Timing of adverse effects: Deep surgical site infections occurred at 19 and 25 months.

Factors that predict response: NR.

Source Citation: Stein et al. 2015<sup>52</sup>

Study Design: Case series  
Device or Material: Tendon graft augmented with MERSILENE tape (Ethicon)  
Contact Duration: Mean (range): 7 months (2 to 11)  
Dose: Dorsal or volar radioulnar ligament reconstruction  
Frequency/Duration: Single administration  
Response: No operative complications observed  
Patient characteristics (gender, mean age): 4 female, 8 male, 15 to 49 yrs.  
Number per group: 12.  
Observed adverse effects: None observed.  
Timing of adverse effects: NA.  
Factors that predict response: NA.

Source Citation: Newman et al. 2013<sup>28</sup>

Study Design: Systematic review  
Device or Material: PET graft (LARS)  
Contact Duration: Followup: 18 months to 5 years  
Dose: NR  
Frequency/Duration: NR  
Response: Rupture; Synovitis  
Patient characteristics (gender, mean age): Mostly males, 26 to 46 years.  
Number per group: 675. LARS ACL reconstructions.  
Observed adverse effects: 9 studies included (1 RCT, 2 comparative, six case series). Complications included synovitis associated with a ligament rupture in 1 patient, and 16 (2.5%) ligament ruptures.  
Timing of adverse effects: NR.  
Factors that predict response: NR.

Source Citation: Struwer et al. 2012<sup>53</sup>

Study Design: Case series  
Device or Material: Bone-patellar tendon-bone graft augmented with PET (Trevira)  
Contact Duration: 12 months (11 to 14)  
Dose: ACL reconstruction  
Frequency/Duration: Single administration  
Response: Rupture; Synovial reaction  
Patient characteristics (gender, mean age): 76 male, 50 female, 32 years (19 to 60).  
Number per group: 126.  
Observed adverse effects: 87 devices ruptured. 27 of those had synovial reactions.

Timing of adverse effects: 12 months post-op.

Factors that predict response: NR.

Source Citation: Hamido et al. 2011<sup>29</sup>

Study Design: Case series

Device or Material: ET graft (LARS artificial ligament; Surgical Implants and Devices)

Contact Duration: Follow-up: 33 to 60 months

Dose: 3.5 mm diameter

Frequency/Duration: Single administration

Response: None Reported

Patient characteristics (gender, mean age): NR, 26 years.

Number per group: 112 with ACL rupture.

Observed adverse effects: No graft rupture was observed.

Timing of adverse effects: N/A.

Factors that predict response: N/A.

Source Citation: Kany et al. 2011<sup>54</sup>

Study Design: Case series

Device or Material: SEM LAC 2T, Montrouge, France)

Contact Duration: Mean (range): 15 months (5 to 30)

Dose: Coracoclavicular ligament reconstruction

Frequency/Duration: Single administration

Response: Night pain and capsulitis; Failed or torn ligament

Patient characteristics (gender, mean age): 49 male, 5 female, 39 yrs, (16 to 69).

Number per group: 54

Observed adverse effects: Night pain and capsulitis (n = 6) resolved with medical management, failed or torn ligament (n = 2).

Timing of adverse effects: NR.

Factors that predict response: NR.

ACL: anterior cruciate ligament; NA: not applicable; NR: not reported; PET: Poly(ethylene terephthalate).

Table 15: PET Ligaments – Health Effect (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Zhang et al. 2016<sup>55</sup>

Study Design: RCT

Device or Material: LARS artificial ACL (Surgical Implants and Devices, France); LARS coated with collagen;  
LARS coated with collagen and simvastatin

Route: ACL reconstruction

Dose: 1 graft

Frequency/Duration: 4 and 8 weeks

Response: Inflammatory response

Species (strain): Rabbits (New Zealand white).

Gender: NR

Number per group: 6 animals in each group per time point (36 total). Only 1 animal per group and  
timepoint was used for histology.

Observed adverse effects: At 4 weeks, inflammatory cells infiltrated the graft-bone interface in all 3 groups.

Timing of adverse effects: 4 weeks.

Factors that predict response: NR.

Source Citation: Li et al. 2016<sup>56</sup>

Study Design: RCT

Device or Material: LARS artificial ligament

Route: Unilateral ACL reconstruction

Dose: 1 graft

Frequency/Duration: 4 to 8 weeks

Response: NR

Species (strain): Rabbits (New Zealand white).

Gender: NR

Number per group: 4 animals in each group per time point. Histology was performed on 1 animal in each  
group at each time point.

Observed adverse effects: NR

Timing of adverse effects: NA

Factors that predict response: NA

Source Citation: Yu et al. 2014<sup>57</sup>

Study Design: Case series

Device or Material: Modified LARS

Route: Unilateral ACL reconstruction

Dose: Graft segment

Frequency/Duration: 1, 3, and 6 months

Response: Swelling; Effusion; Inflammation

Species (strain): Rabbits (New Zealand white).

Gender: NR

Number per group: 4 animals at each time point (12 total).

Observed adverse effects: At 1 month, there was substantial swelling, joint effusion, and yellow synovial fluid, along with obvious inflammatory reaction in intra-articular synovial tissue. These effects were alleviated at 3 months, except inflammatory reaction continued until 6 months.

Timing of adverse effects: 1 to 6 months.

Factors that predict response: NR.

Source Citation: Vaquette et al. 2014<sup>58</sup>

Study Design: Controlled study

Device or Material: LARS (Arc sur Tille, France), LARS grafted with polystyrene sodium sulfonate

Route: Unilateral ACL reconstruction

Dose:

Frequency/Duration: 3 or 12 months

Response: Subtle weight bearing; Partial graft rupture; Moderate inflammation

Species (strain): Sheep (Prealpes).

Gender: Female.

Number per group: 23 non-grafted LARS (NGL), 6 NGL at 3 months and 5 NGL at 12 months were used for histology. 28 LARS grafted with polystyrene sodium sulfonate (PGL), 7 PGL at 3 months and 6 PGL at 12 months were used for histology.

Observed adverse effects: All but four animals showed normal weight bearing. 4 animals showed constant subtle weight bearing 12 months postoperatively. Wear resulting in partial rupture of the graft was observed in 20 animals (11 at 3 months, 9 at 12 months). Giant cells indicating moderate inflammation were observed at 3 months. The inflammatory reaction was reduced at 12 months but still present.

Timing of adverse effects: NR.

Factors that predict response: NR.

ACL: anterior cruciate ligament; NA: not applicable; NR: not reported; PET: poly(ethylene terephthalate); RCT: randomized controlled trial.

Table 16: PET Valves – Health Effect (In Vivo) Human Studies

### **Local Response/Toxicity**

Source Citation: Luk et al. 2015<sup>59</sup>

Study Design: Case series

Device or Material: Mitroflow pericardial valve (model A12)

Contact Duration: Mean 4.5 years

Dose: 1 valve per patient

Frequency/Duration: Single operation

Response: Cusp tears; Cusp thickening; Calcification; Pannus; Thrombus

Patient characteristics (gender, mean age): 15 males, 12 females; 72.2 years.

Number per group: 7 patients total.

Observed adverse effects: 18 of 27 valves had cusp tears. 26 of 27 valves showed cusp thickening. 16 of 27 valves showed calcification, all of which were implanted for more than 8 months. 21 of 27 valves demonstrated pannus deposition. 13 of 27 valves showed thrombus.

Timing of adverse effects: Mean 4.5 years, range 3 to 132 months.

Factors that predict response: NR.

Source Citation: Butany et al. 2011<sup>60</sup>

Study Design: Case series

Device or Material: Mitroflow A12 bioprostheses

Contact Duration: Mean 2.9 years

Dose: 1 valve per patient

Frequency/Duration: Single operation

Response: Cusp tears; Cusp thickening; Calcification; Pannus; Thrombus

Patient characteristics (gender, mean age): 6 males and 6 females; mean 73.0 years old.

Number per group: 12 patients total.

Observed adverse effects: 5 of 12 cases showed cusp tears. 11 of 12 valves showed cusp thickening, with all cusps beyond 6 months showing thickening. 6 of 12 valves showed calcification. 8 of 12 valves showed pannus formation, or host tissue overgrowth. Thrombus was discovered on 9 of 12 valves.

Timing of adverse effects: Mean 2.9 years, range 3 to 84 months.

Factors that predict response: NR.

NR: Not reported; PET: poly(ethylene terephthalate).

Table 17: PET Valves – Health Effect (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Ramot et al. 2016<sup>61</sup>

Study Design: Observational

Device or Material: Amend transcatheter mitral valve annuloplasty ring

Route: Aortic annulus

Dose: 1 per animal

Frequency/Duration: 64 days, 75 days, 109 days

Response: Foreign body granulomas; Hematomas

Species (strain): Minipigs (Sinclair, Ben Meir farm).

Gender: Female.

Number per group: 3 animals for 64 days, 1 animal for 75 days, and 2 animals for 109 days.

Observed adverse effects: 1 animal from 64 days and 1 animal from 109 days developed hematomas that the authors judged to be procedure-related rather than implant-related. No grossly visible thrombus or calcium deposits were observed in any animal. The 64 days group showed higher foreign body granuloma scores than the 75 and 109 days groups.

Timing of adverse effects: 64 days, 75 days, and 109 days.

Factors that predict response: NR.

NR: Not reported.



Table 18: PET Stents and Balloons – Health Effect (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Zani et al. 2016<sup>62</sup>

Study Design: Observational

Device or Material: PBSS PET Dacron balloons

Route: Non-fracture model; unilateral tibia implantations

Dose: 1 operation per animal

Frequency/Duration: 30, 60, 90 days

Response: Inflammation; Fibrosis; Cortical bone necrosis

Species (strain): Sheep (Polypay).

Gender: NR.

Number per group: 18 animals total, 6 animals per each time point at 30, 60, and 90 days.

Observed adverse effects: No macroscopic indication of adverse systemic effects were observed.

Progressive but unremarkable inflammation and fibrosis. No substantial microscopic observations observed.

Timing of adverse effects: 30, 60, and 90 days.

Factors that predict response: NR

Quality Date: NR

Source Citation: Zani et al. 2016<sup>62</sup>

Study Design: Comparative

Device or Material: PBSS PET Dacron balloons

Route: Fracture model; tibial osteotomy

Dose: 3/3 type Ia external fixator; 2/2 type Ia with PBSS

Frequency/Duration: 8, 12, 26 weeks

Response: Histiocytic inflammation

Species (strain): Sheep (Swiss Alpine).

Gender: NR

Number per group: 40 animals total. 6 animals for both groups at 8 weeks, 8 animals for both groups at 12 weeks, and a single group of 8 animals for 2/2 type Ia with PBSS at 26 weeks. 2 animals died during surgery and were excluded.

Observed adverse effects: Minimal and unremarkable histiocytic inflammation (formation and clustering of foamy macrophages) were observed at implantation site.

Timing of adverse effects: 8, 12, and 26 weeks.

Factors that predict response: NR.

Data Quality: NR

PBSS: photodynamic bone stabilization system; NR: not reported; PET: poly(ethylene terephthalate).

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## **Appendix F. Surveillance Event Reports – PSO and Accident Investigation**

*Provided with this report as separate Excel spreadsheet.*



## **Appendix G. Regulatory and Manufacturer Safety Alerts**

*The associated alerts are provided with this report as a separate PDF.*