Bioprinting of freestanding vascular grafts and the regulatory considerations for additively manufactured vascular prostheses

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Abstract

Vasculature is the network of blood vessels of an organ or body part that allow for the exchange of nutrients and waste to and from every cell, thus establishing a circulatory equilibrium. Vascular health is at risk from a variety of conditions that includes disease and trauma. In some cases, medical therapy can alleviate the impacts of the condition. Intervention is needed in other instances to restore the health of abnormal vasculature. The main approaches to treat vascular conditions are endovascular procedures and open vascular reconstruction that often requires a graft to accomplish. However, current vascular prostheses have limitations that include size mismatch with the native vessel, risk of immunogenicity from allografts and xenografts, and unavailability of autografts. In this review, we discuss efforts in bioprinting, an emerging method for vascular reconstruction. This includes an overview of 3D printing processes and materials, graft characterization strategies and the regulatory aspects to consider for the commercialization of 3D bioprinted vascular prostheses.

Current strategies to address vascular disease & trauma

Vascular disease can arise directly in vasculature such as the buildup of plaque in carotid artery disease or emerge as a side effect from another health condition such as diabetes that can lead to atherosclerosis [1, 2]. Vascular trauma can result from a blunt injury that is associated with a crushed or stretched blood vessel or from a penetrating injury that is due to a punctured, torn or severed blood vessel [1]. Depending on the case, endovascular procedures or open vascular reconstruction are current viable approaches of intervention.

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Endovascular procedures

Endovascular procedures are percutaneous, minimally invasive alternatives to open surgery, thus potentially of lower morbidity and mortality risk [3]. These procedures encompass angioplasty and stenting, rely on imaging techniques and are carried out by experts using catheters and other specialized and miniature instruments [3, 4]. Application of these procedures has been reported for a variety of vascular conditions from mesenteric ischemia and iliac artery aneurysms to renal artery occlusive disease [3]. An example of taking an endovascular approach is to treat occlusive disease of the brachiocephalic arteries. The procedure can involve imaging by performing an angiogram starting from a micropuncture system to gain femoral access, then inserting a sheath and a catheter guided by ultrasound and stent deployment [3]. Because endovascular procedures are percutaneous, the approach can be perceived as low risk [3]. The intervention for a safe outcome depends on the case at hand and considerations of multiple factors such as the targeted location and the size of vasculature as well as the available resources and expertise [3, 5].

Open vascular reconstruction

Open vascular reconstruction is needed for various conditions including plaque removal, shortening or straightening of kinks and even after endovascular therapy fails [3]. Reconstruction has been performed in efforts to preserve lower extremity limbs after surgical excision of soft tissue sarcoma, to treat patients with pancreatic cancer and other tumor resections [6–8]. Different types of procedures are encompassed in reconstruction that includes endarterectomy, extra-anatomic bypass, and interposition grafting [3]. A carotid enterectomy operation, for example, can involve incision into the stenotic region of the artery, use of a shunt to temporarily re-direct blood flow to then remove plaque [3]. To seal the opening in the artery, a patch-like graft may then be used, which can be from both synthetic (e.g. Dacron) or a naturally derived source (e.g. bovine pericardium) [3]. In other instances, and depending on the severity of the vascular condition, reconstruction may require a graft. The graft source can be autologous (e.g. saphenous vein), an allograft (e.g. CryoVein® derived from cadaver saphenous vein), a xenograft (e.g. Contegra® pulmonary valve conduit derived from bovine jugular vein), a synthetic material (e.g. polytetrafluoroethylene, PTFE) or a combination (e.g. Hancock® porcine valve Dacron conduit) [3, 8–11].

A main concern for the vascular graft is the size including the diameter and length, which when mismatched with the native vessel can lead to complications [3]. In adults, the replacement of vessels with diameters less than 6 mm is problematic because the smaller synthetic conduits have poor patency rates [12, 13]. Autologous grafts are not always available or accessible, and the harvesting presents risks of donor site morbidity and complications that can be amplified in patients often suffering from disease [13]. The graft fit is also a challenge for pediatric patients given the smaller conduit sizes and expected vessel outgrowth [14, 15]. Often, the lack of patient matched grafts and emergency repairs call for the construction of improvised grafts from sheets such as bovine patches [16, 17]. A production technique that has gained traction because of the ease in customization is additive manufacturing, also referred to as three-dimensional (3D) printing. In 3D printing, a computer-aided design (CAD) model of the product guides the automated layer by layer

material build process. Thus, a change to the size of the product simply involves making digital modifications to the CAD model rather than physical changes to the production equipment. 3D printing with biological materials is an active area of research with potential to develop patient matched grafts using biodegradable materials for vascular tissue engineering. In this review, we present the underlying processes of 3D printing technology and discuss the emerging efforts toward its use for developing vascular prostheses. This work also highlights the performance and testing methods for bioprinted grafts and the United States Food and Drug Administration (FDA) guidelines to consider for prospective graft commercialization.

Brief overview of vasculature

Vascular biology

The vascular system has numerous functions in maintaining homeostasis, the most essential is the transport of oxygen and nutrients to tissues throughout the body [18]. The arteries carry blood away from the heart and branch into smaller arterioles [19]. These vessels eventually branch off into capillary beds where the interchange of blood and tissue takes place [19]. Capillaries recombine into venules and develop further into veins, which transport blood from the body back to the heart [20]. Arteries and arterioles generally have thick walls with small lumens and are round in appearance to support the high-pressure blood flow coming from the heart (Figure 1) [20]. Veins and venules are further from the blood flowing from the heart and have thin walls with large lumens which result in a flat appearance (Figure 1) [20]. This is to accommodate the lower blood pressure found further from the heart and allows for more blood to flow with less resistance [20].

Vascular histology

Blood vessels are comprised of living cells and their extracellular matrix [20]. These cells require an exchange of nutrients and produce waste [20]. Arteries and veins both share three discrete layers known as the tunica intima, tunica media, and tunica externa (also known as the adventitia) [21, 22]. The tunica intima is comprised mainly of epithelial and connective layers of tissue and is lined by the endothelium, a layer which runs continuously throughout the entire circulatory system [21, 22]. Next, the tunica media, or mid-layer of vessels, is much larger in arteries than veins (Figure 1). This mid-layer is made up of smooth muscle cells arranged in circular sheets that are supported by connective tissue composed of elastic and collagen fibers [21, 22]. These muscle sheets can be allowed to contract or relax based on signals from the nerves within the vessel allowing for vasoconstriction or vasodilation [20, 23]. The final layer, the tunica externa, is comprised of a layer of connective tissue made of collagenous and elastic fibers [20, 23]. This layer is generally the thickest in veins and in some small population of large arteries [20, 23]. The externa provides strength to keep the vessels relatively in the same spot and protects vessels from bursting [20, 23]. In larger vessels, the tunica externa's integrity and function is maintained by the "vasa vasorum", a microvascular circuit that facilitates the exchange of nutrients and waste [20].

Capturing the specific histological features of native vasculature has been a challenge in vascular graft development. An early effort with a Dacron scaffold strove to design the

vessel layers of intima, media and adventitia using endothelial cells, smooth muscle cells with a collagenous matrix, and fibroblasts, respectively [24]. Still, the burst pressure of this vessel was about ten-fold lower than the human saphenous vein [24–26]. Thereafter, a range of techniques that include cell sheet engineering, electrospinning and tubular molding have been used toward developing freestanding vascular conduits [26, 27]. Overall, the studies seldom focus on the intricacies of the histological features and rather develop simplistic tubular structures from one or two materials or cell types. For example, a key proof-of-concept study [28], focused on testing a tissue-engineered vascular grafts in a large animal model that was molded using fibrin gels and seeded with fibroblast cells. Others efforts have focused on preserving the topological features by decellularizing native vasculature [29] and even the human placenta [30]. Using bioprinting to mimic the vascular histological features is even less explored compared to other methods [31]. An attempt includes a double layered vascular tube consisting of smooth muscle and fibroblast cells that was positioned horizontally on the platform and used agarose as support for 3D printing [32]. As with other techniques, bioprinting efforts of multilayered vessel walls that used hydrogels and synthetic polymers have not been specifically designed to mimic the properties of different layers of native vessel [33–36]. In one work [37], endothelial and smooth muscle cells printed in proximity were shown to form cell-cell junctions and resulted in the formation of a structure like the lumen. Thus, accounting for the vascular histology, to design the tunica intima, tunica media, and tunica externa may be promising for the next generation of vascular prostheses. Overall, the bioengineering of vascular histological properties will require the consideration of both the composition and the fiber arrangement in each vessel layer.

Bioprinting of vascular grafts

3D bioprinting processes toward vascular graft development

The basic underlying concept of additive manufacturing is to develop a product through addition of material (liquid, solid, powder) layer by layer, but the processes to achieve this can differ [38]. The American Society for Testing and Materials (ASTM) has categorized these technologies into seven processes: material extrusion, material jetting, powder bed fusion, binder jetting, direct energy deposition, vat photopolymerization, and sheet lamination [39]. Bioprinting efforts thus far have only been based on some of these processes. In most cases, the transformation to a bioprinting process mainly involves hardware adaptation for biological materials that can range from combinations of cells, biomolecules, and biomaterials. Below we provide an overview of 3D printing process categories identified by the ASTM standard (ISO/ASTM 52900) [39, 40] and highlight examples, if any, of efforts toward bioprinting vascular grafts.

Material extrusion—Material extrusion (Figure 2A) is an "additive manufacturing process in which a material is selectively dispensed through a nozzle" [39]. The dispensed layer, which is usually a thermoplastic melt, then cools and serves as foundation to build on the next layer [41]. Fused deposition modeling (FDM) is a popular material extrusion process and these 3D printers are accessible for purchase by consumers at the household level [42]. This is because of the lowering costs of FDM printers, the components of which are often also made by FDM printers (e.g. RepRaps), using common hardware, and run on open

source software [42, 43]. Extrusion bio-printing (Table 1) has been applied for tissue engineering typically using syringe-based extruders without the heating elements of standard FDM printers that can damage biological materials [32, 44–47]. The printing solutions often contain cell-laden biopolymers or hydrogels. In one study, the extrusion bioprinting of a hydrogel was followed by a cross-linking step based on calcium ions to produce vascular structures [48]. Bioprinting based on the extrusion process is one of the most common methods used to develop 3D tissues due to a straightforward implementation and well characterized protocols [44, 46]. However, these tissues tend to lack the cell-density needed to successfully survive *in vivo* integration and have additional concerns of biocompatibility and biodegradation [44, 46]. Although less common, the extrusion bio-printing technique has also been used to create tissue without biomaterials. The scaffold-free approach enables the use of higher cell-densities, which can increase cell-cell contact and cellular signaling within a tissue and has been shown to have more accurate biomimicry [32, 49, 50]. One study incorporated spheroids into the bioink solution rather than using a free cell-suspension to make tissue strands [51]. Spheroids, or spherical conglomerations of cells typically around 300 μm–800 μm are generated from cell cultures for bioprinting [50]. A printer has even been specifically designed to pick up spheroids by vacuum suction and transfer them with high precision onto a needle array for compaction and maturation [45, 52, 53]. Although not exactly an extrusion process, reports show that three-dimensional tissues can be synthesized using this spheroid printer and the constructs can be vascularized with the use of endothelial cells [45, 52, 53]. Spheroids can also be used to express angiogenic factors through transfection of the cells [54–57]. Still, many of the biomaterial-free engineered tissues have weak mechanical properties and can be easily degraded without a structural support [45, 52–58].

Material jetting—Material jetting (Figure 2B) is an "additive manufacturing process in which droplets of build material are selectively deposited" [39]. The process is also referred to as ink-jet or drop-on-demand printing and applicable to waxy polymers and acrylic photopolymers that have a viscosity in the 20 cP to 40 cP range and can form droplets [59]. These are deposited with high spatial resolution and then transformed to solid by either evaporation or through a reaction that proceeds upon application of an energy source, for example, heat or UV light [60]. Ink-jet bio-printing (Table 1) also uses hydrogel solutions and was designed to print with a single cell resolution in controlled droplets [61, 62]. This technique has been used to horizontally print alginate tubular constructs and bifurcations [63, 64]. The method is promising for printing microstructures and has been used to create a variety of tissue constructs; however, has yet to be used to create functional vasculature. Another material jetting technique that has a drop on demand approach is laser assisted bioprinting (Table 1), which has been leveraged to deposit a cell-laden solution with micro-scale resolution [65, 66]. The benefit of this technique is the addition of computer assisted controls with the ability to create microtissues [65, 66]. These newer technologies may become applicable in the bioprinting of capillary-like structures in the future.

Powder bed fusion—Powder bed fusion (Figure 2C) is an "additive manufacturing process in which thermal energy selectively fuses regions of a powder bed" [39]. This process can be used to additively manufacture metals, ceramics, polymers and composites

parts. The energy source that joins the powder can vary with the technique. For example, the electron beam melting (EBM) process uses an electron beam while a laser beam is used for the selective laser sintering (SLS) technique [67]. Once a layer fuses, the next layer of powder is spread by a roller [68]. Powder bed fusion processes have thus far not been applied toward making vascular grafts, the extent of the technology for tissue engineering has encompassed mostly orthopedic products [69, 70]. Titanium has also been studied for making dental implants using powder bed fusion techniques [71]. The process has even been used as a technique to functionalize a biocompatible titanium alloy (Ti-6A1–4V) with copper that has potential as antimicrobial agent [72]. Other metals such as zinc have also been considered for developing biodegradable implants by SLS [73]. For orthopedic products many of which are load bearing, metal is the material of choice.

Binder jetting—Binder jetting (Figure 2D) is an "additive manufacturing process in which a liquid bonding agent is selectively deposited to join powder materials" [39]. The powder bed is lowered after printing a layer of binder and a new layer of powder is typically rolled onto the bed [74]. In contrast, the powder bed fusion process uses a thermal energy source (e.g. laser) to melt and join the powder particles [74]. The term 3D printing (3DP) was initially coined for the binder jetting process, but now synonymous for all additive manufacturing processes [74]. Binder jetting has been shown to produce parts from polymers, metals, ceramics, and composites [67, 74], yet the process has not been of focus toward 3D printing vascular prostheses. The application of binder jetting in medicine has been toward developing structures for bone implants [75, 76]. This includes the fabrication of porous bone prototypes using polyethylene that was sterilized and had promising cytotoxicity results after testing with fibroblast cells [77]. To demonstrate the production of a complex structure with binder jetting, the process was employed to develop a denture framework [78]. A metal powder was used to make the denture and overall, the sintering conditions affected the resulting density of the product [78].

Direct energy deposition—Direct energy deposition (Figure 2E) is an "additive manufacturing process in which focused thermal energy is used to fuse materials by melting as they are being deposited" [39]. The process is mainly used on metal powder [79]. The difference with the powder bed fusion process that also uses an energy source to join powder is that in directed energy deposition, the powder is not spread and rather being actively dispensed by streaming [79]. This process has not been used for bioprinting applications, but the resulting structures are of interest for orthopedic use [80]. For example, directed energy deposition has been investigated for making components with the alloy Ti-6A1–4V [81]. This titanium alloy is of interest in medical designs [82]. Additional studies that investigate the implications of directed energy deposition to produce a part directly for a medical application can determine the advantages of this technique.

Vat photopolymerization—Vat photopolymerization (Figure 2F) is an "additive manufacturing process in which liquid photopolymer in a vat is selectively cured by light-activated polymerization" [39]. Stereolithography (SLA or SL) is a well-known vat photopolymerization technique that produces parts with high accuracy and thus coveted for biomedical applications including dentistry and surgical guides [83–86]. These parts often

require post-processing [87, 88]. Although limited to photo-crosslinkable resins, material advances have expanded the application of SLA technology to photopolymer composites with ceramics [42]. In one study [89], a photocurable resin developed for the SLA technique was used to produce bifurcated structures and tubes with diameter smaller than 2 mm, which were tested for biocompatibility. Huber *et al.* [90] used SLA to 3D print porous tubular structures that were functionalized with biomolecules and resulted in the formation of an endothelial monolayer after cell seeding. The application of vat polymerization toward bioprinting vascular grafts should be accompanied by methods to assess the removal of cytotoxic substances such as uncured resin from the process [90].

Sheet lamination—Sheet lamination (Figure 2G) is an "additive manufacturing process in which sheets of material are bonded to form a part" [39]. The process is amenable to different materials from papers and plastics to metals and ceramics [91]. An example is laminated object manufacturing (LOM), which involves lamination of sheets of paper, typically within the 0.07 mm to 0.2 mm thickness range, and cut into the CAD based shape with CO_2 laser [91]. The paper can be adhesive backed, but other bonding mechanism such as thermal, clamping and ultrasonic welding have been feasible [91]. Interchanging the order of process steps that is either stacking first and then cutting or vice versa have also been possible [91]. The sheet lamination process has not been leveraged for bioprinting. However, a cell-based tissue development method is cell-sheet engineering [58]. This method uses a thermoresponsive nanofiber polymer to detach entire sheets of cells with the associated extracellular matrix from cell culture [58]. Following this step, multiple sheets may be stacked to create a tissue [58]. The prospective automation and systematization of this cell sheet approach to make tubular structures may be a step toward the application of sheet lamination for bioprinting vascular grafts.

Aside from process classifications, the ASTM standard (ISO/ASTM 52900) provides an overview of differences in material type, feedstock, distribution, and other aspects of additive manufacturing [39]. This standard together with others [92] established for additive manufacturing are resources that serve to maintain consistent terminology for product development and regulation. Emerging techniques may lead to changes in these standards. Future bioprinting techniques may involve hybrids of multiple processes or lead to the development of new methods that may not align with the underlying principles of the current ASTM processes. For example, a new printing method has recently been described that uses projected light to solidify liquid resin all at once instead of layer by layer [93]. Still, herein we strove to classify the bioprinting techniques as best as possible according to their underlying engineering principles. Other than vascular prostheses, several strategies have been used to promote vascularization in tissue constructs, which is beyond the scope of this review on vascular grafts. In brief, a main example of a 3D bioprinted tissue construct [94] involved embedding multiple materials such as a sacrificial ink to design a vascular network within a hydrogel construct. The same group [95] then used this multi-material printing strategy, including a temperature sensitive fugitive ink, to design thick vascularized tissues (> 1 cm), maintained in culture for ~6 weeks. Other reviews [27, 31, 33, 96] provide insight on various aspect of bioprinting vascular constructs and present additional perspectives on the bioprinting of vascular grafts.

Materials used for 3D bioprinting of vascular grafts

Graft materials currently on the market are derived from both synthetic and natural sources. Commercially available grafts from synthetic materials are typically knitted or woven [97]. Examples include Uni-Gaft®, GORE-TEX®, and FUSION that are made with the polymers polyethylene terephthalate (PET, Dacron®), expanded polytetrafluoroethylene (ePTFE, Teflon®), and a combination of both, respectively [97–101]. A graft derived from a natural source includes the Artegraft®, which is produced from bovine collagen [102]. Some grafts are hybrids of synthetic and natural sources, an example is AlboGraft® that combines bovine skin collagen and polyester filaments [103]. These materials may be used for 3D printing vascular grafts since the technology has been adapted for different ink types [38]. For instance, the FDM process that intakes standard rigid thermoplastic filament was modified to produce flexible structures from a heat curable silicone gel [104, 105]. Other efforts that pushed the boundaries of materials for additive manufacturing involved the 3D printing of glass [106], fiber-reinforcement [107], and even magnetic [108] inks. Vascular graft materials for 3D printing should importantly be biocompatible and non-thrombogenic and have relevant mechanical integrity and hemodynamic properties for the given application [13, 109–112]. Most research on 3D printing of vascular graft have used biodegradable inks, taking a tissue engineering approach toward regenerating vascular tissue. For example, SLA technology was used to develop a biodegradable vascular graft from poly(propylene) (PPF) with 1 mm inner diameter and 150 μm wall thickness that was maintained *in vivo* up to 6 months [113]. In another instance, a 3D printed template made by the SLA process was used to develop a patient matched tissue-engineered vascular graft (TEVG) by electrospinning biodegradable polymers [114]. The TEVG was subsequently tested in a large animal model [114]. Other printing efforts for tissue engineering vascular grafts used cell-laden inks [115], but overall 3D printed conduits from biodegradable materials or otherwise have not yet attained commercial stature.

Assessment of bioprinted vascular grafts

Developing vascular grafts is an iterative process that requires *in vitro* and subsequent *in vivo* characterization efforts. Few studies have extensively characterized bioprinted grafts as these are a new technological advancement. Many bioprinted vessels lack the appropriate mechanical properties to withstand *in vivo* hydrostatic pressures and the strain involved in surgical grafting procedures. Here we highlight the testing methods to reduce the risk of failure for vascular grafts that also apply to bioprinted grafts. The characterizations, summarized in Table 2, are grouped under the risk categories for vascular prosthesis proposed by the U.S. FDA [116] toward an outlook for clinical approval.

Thrombosis, Embolic Events, Occlusion, & Stenosis

Immunostaining, cell penetration studies, simulations, macroscopy and other visual inspection techniques represent *in vitro* methods to determine graft occlusion [51, 104]. Vascular stenosis has been linked to the proliferation of vascular smooth muscle cells (VSMCs) [117, 118]. An *in vitro* technique that Refson *et al.* [117] used to assess graft patency involved evaluating the response of VSMCs on the graft to heparin that reduces cell

proliferation [119]. Similarly, other studies have shown that immediate thrombosis, vascular rejection, and loss of vascular integrity is associated with endothelial cell activation present on the implanted grafts [56, 120, 121]. Thus, in one *in vivo* study, engineered blood vessels were intentionally grafted without being endothelialized [56, 120, 121]. Vessel thrombogenicity is characterized *in vivo* based on the implantation results, if the vessel causes coagulation or a local blood clot due to poor healing processes post-implantation [122]. Doppler signaling can reveal graft failures, which has been shown to occur in the first few days from occlusion and thrombosis formation attributed to the collagen matrix present in the vessels [56]. In another study [123] that developed pulsatile myocardial tubes, observations of the animals following implantation showed no thrombosis. This study reflects the advantage of using cells derived from the same animal species and biodegradable scaffolds [123]. In bypass surgeries, a patient's own blood vessels currently remain the best material for grafting [56, 122]

Leakage & Graft Disruption

An example of characterizations recommended by the FDA to assess the risk of leakage are tests of graft porosity and water permeability [116]. An FDA recommended graft disruption test is the suture retention strength [116]. In one study [124], an *in vitro* assay to study blood vessel permeability has been suggested by culturing endothelial cells in a three-dimensional, microfluidic, platform and measuring the flux of two fluorescent dyes. Radu *et al.* [125] developed an *in vivo* method to assess blood vessel permeability that relied on optical density measurements of an injected dye to determine the amount captured by tissue. In another study [56], histological analysis was used to determine intramural blood infiltrations of cell-based grafts transplanted intrafemorally. Leakage was not found to reduce vessel patency and relative vessel architecture was maintained after seven days [56]. Other analysis of explanted grafts [126, 127] can provide further insight on graft leakage and disruption. Efforts to develop leak-proof grafts include the incorporation of collagen within Dacron [128]. Since then, other studies have focused on strategies that involve incorporating different materials together to "seal" and prevent graft leakage [129–131]. Other studies have taken cues from the textile industry to develop techniques that include weaving, knitting or braiding that produce patterns that may be suitable to withstand leaks [132]. Thus, the inclusion of multiple materials or a finely-tuned design pattern can be promising to prevent leaks and disruptions in bioprinted grafts.

Biocompatibility, Allergic Reaction

A concern with implanting synthesized materials that do not originate from the host is immune system activation, which leads to tissue rejection and allergic reactions [122, 133–137]. Lee *et al.* [135] assessed the biocompatibility of electrospun vascular grafts from both natural and synthetic biodegradable polymers *in vitro* by looking at cell viability and mitochondrial metabolic activity. To test the biocompatibility of polyurethane based biodegradable vascular grafts *in vitro,* the grafts were seeded with fibroblast and macrophage cells to then determine the macrophage gene expression [138]. These were also compared with *in vivo* macrophage and cytokine expressions and the study also involved an analysis of the type of proliferated cells and cell infiltration [138]. Immunosuppressive drugs have been used as a strategy to prevent allergic reaction when observing the *in vivo*

performance of a graft [139]. Even with immunosuppression, endothelial cells can express the major histocompatibility complex (MHC) class II proteins [140]. The mismatch of these proteins on a vascular graft is known to lead to poor *in vivo* performance and complications [140, 141].

Aneurysm

Many aneurysms are believed to occur from inflammatory processes at locations of hemodynamic shear stress [142]. To study the effect of flow stresses on endothelial cells lining the vasculature, Kanko *et al.* [143] developed an *in vitro* intracranial aneurysm model that was subject to computational flow dynamics (CFD) analysis. The model was based on a patient-specific vasculature 3D printed in silicone, coated with fibronectin and cultured with endothelial cells [143]. Nowicki *et al.* [142] compared endothelial cell phenotype across an *in vitro* flow chamber model of a straight artery, a bifurcation and a bifurcation aneurysm. *In vivo,* magnetic resonance imaging (MRI) was used to detect abdominal aortic aneurysm based on the collagen content in a mouse model [144]. The aneurysm in this model was chemically induced, other animal models of aneurysm are made by physical techniques or use genetically predisposed animals [145]. Overall, aneurysm formations are a rare complication of certain types of grafts, including Dacron grafts used in various surgical procedures [146, 147]. Currently, bioprinted grafts have no record of aneurysms formation after *in vivo* implantation [146, 147]. This is likely because these grafts have not been tested long-term *in vivo.* In one study [113], biodegradable grafts (n = 6) printed using the SLA techniques were implanted for a six month period in mice without signs of aneurysms. Mechanical mismatch between the graft and native tissue has been identified as a cause of aneurysms [148]. In one study [149], collagen was crosslinked to increase the mechanical strength of tubes (< 1 mm diameter) made by molding and assessed as potential vascular grafts. The graft's burst pressure had improved (75 mm Hg collagen as is versus 1300 mm Hg crosslinked collagen) along with the compliance, but the values were comparable to the vein, and did not match the artery [149, 150]. Finding a biomaterial processable by 3D printing that has mechanical properties matching the targeted native vessel remains a challenge to address for progress in using bioprinting to make vascular grafts. Overall, Bozeghrane *et al.* [151] recommended standardized multicenter studies to improve the assessment of endovascular devices for aneurysm therapy.

Infection Sterility

Sterility of surgical implants is a necessity in clinical practice. An example of ensuring a modern standard of sterility is through autoclaving, which has been used to sterilize hydrogels for bioprinting vascular-like structures [152]. Jia *et al.* [153] sterilized gelatin methacryloyl (GelMA) based inks for bioprinting a vascular construct. Sterilization practices should also be applied to the additive manufacturing system to maintain bioprinted graft sterility [154]. In order to reduce the risk of bacterial infection, one study 3D printed small diameter vascular grafts with antibacterial properties by using FDA approved biodegradable inks coated with nitric oxide (NO) [155]. *In vivo,* graft infection may be observed *in situ* by using Hoechst fluorescent staining for cytoplasmic DNA [156]. Overall, limiting the use of synthetic material is known to reduce the risk of foreign body reaction and graft infection [122]

Performance

An *in vitro* assessment of vascular graft performance includes mechanical characterization, which for electrospun nanofiber scaffolds has been reported as tensile tests [135]. L'heureux *et al.* [56] designed an *in vitro* system to study the integrity of a cell-based blood vessel for tissue engineering that was circulated with phosphate-buffered saline and pressurized successively. *In vivo,* implanted femoral grafts in mongrel dogs were assessed after seven days using angiography, explantation of the grafts revealed a 50% patency rate for the six grafts [56]. The successful grafts showed no signs of degradation, tearing, or dilation and the mechanical strength was attributed to the collagenous matrix present in the adventitia [56]. In another effort [123], pulsatile myocardial tubes were transplanted in place of the abdominal aorta of athymic rats, and survived a four-week observation period. The performance evaluation included histological analysis and transmission electron microscopy, which showed the beating tubes were composed of cardiac tissues resembling the native cardiovascular tissue [123]

Commercialization of bioprinted vascular grafts

Regulation of medical products and devices in the United States and vascular grafts on the market

The U.S. FDA is an agency within the U.S. Department of Health and Human Services (HHS) that oversees more than $2.5 trillion products [157]. These are food, drugs, biologies, medical devices, electronic, cosmetics, veterinary, and tobacco products [157]. The FDA's mandate is to protect the public health by ensuring the safety and effectiveness of these products while supporting innovation [157]. To achieve this, the FDA issues regulations that are federal laws some of which are established based on the Federal Food, Drug, and Cosmetic Act (FD&C Act) that was enacted by congress [157]

The vascular grafts currently on the market are considered medical devices by the FDA [157]. Medical devices are administered by the Office of Medical Products and Tobacco [157]. The latter has different centers including the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER) and the Center for Biologies Evaluation and Research (CBER) [157]. At present, CDRH oversees the regulation of vascular grafts and classifies medical devices into three categories based on the "intended use", the "indications for use" and the risk level to the patient or user [157]. From lowest to highest risk, these categories are Class I, II and III medical devices that shape the type of application to file for receiving clearance from the FDA to market (Figure 3) [157]. In most cases, Class I and Class II devices require filing a Premarket Notification (PMN), also referred as 510(k), to notify the FDA of an intent to market [157]. A 510(k) is granted if the device can be shown to be equivalent to a device already marketed in either of the three classification categories [157]. In some cases, especially for Class I devices, a 510(k) clearance may not be needed, but an application for the device must still be filed to the FDA toward obtaining an exemption for a 510(k) clearance [157]. For Class III devices defined as "those that sustain or support human life" a 510(k) clearance may not suffice, and these require filing for a Premarket Approval (PMA) clearance [157]. To receive a PMA, the

medical device requires substantial backing of "sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s)" [157]

Vascular grafts from materials such as PET or PTFE with biological or synthetic coatings, for example intended to gain vascular access, are typically Class II medical devices with "special controls" (Figure 3) [157]. The special controls require additional measures such as complying with the FDA's "Guidance Document for Vascular Prostheses 510(k) Submissions - Guidance for Industry and FDA staff" [116, 157]. The guidance identifies potential risks and associated control measures, for example to comply with standards for endovascular prostheses such as provided by ANSI/AAMI ISO-25539–1 [157, 158]

Overall the FDA guidance applies to vascular graft prosthesis of 6 mm in diameter and larger [157]. Following the guidance may also reduce the classification level for vascular grafts that are less than 6 mm from Class III to Class II devices [157]. Still, the guidance was not developed for vascular grafts made entirely of materials derived from animals and that are intended for coronary or neurovasculature, which are likely Class III devices [157]. With progress toward the next generation of vascular grafts, other FDA centers such as CDER and CEBR may begin to have a regulatory role, for example to approve drug-eluting vascular grafts or cell-seeded ones for tissue engineering.

Technical considerations for commercializing 3D printed vascular grafts

To receive FDA clearance, a 3D printed vascular graft has to abide by the same procedure as medical devices and products regardless of the fabrication technique [157]. The type of clearance will then depend on the risk-based classification of the vascular prosthesis [157]. In December 2017, the FDA issued a "Guidance for Industry and Food and Drug Administration Staff" on the "Technical Considerations for Additively Manufactured Medical Devices" [157, 159]. Unlike its regulations, the FDA's guidance publications are not legally binding and only express the agency's perspective on a given topic [157, 159, 160]. Still, the guidance is a tool to facilitate meeting the Quality System (QS) requirements of the 3D printed graft by providing testing and characterization approaches relevant to the fabrication method [157, 159, 160]. In particular, a section of the guidance outlines Design and Manufacturing Considerations while another part focuses on Device Testing Considerations [157, 159, 160]. The Design and Manufacturing Considerations covers overall aspects and patient-matched device design, software workflow, material controls, post-processing, process validation and acceptance activities, and quality data [159]. An example of Device Testing Considerations are the provision of device description, mechanical testing, dimensional measurements, material characterization, residue removal and sterilization, and biocompatibility [159]. The FDA has held a webinar [160] and provided a review [161] in support of this guidance. Collaborations have also taken place with agencies such as the National Institute of Standards and Technology (NIST) [162]. Other resources on FDA's outlook on 3D printed medical products include an overview by Christensen and Rybicki [163]. This review covers the applications of 3D printing in medicine through categories that include anatomical models, modified anatomical models, and virtual surgical planning with surgical templates [163]

Conclusion

Vascular grafts are tools for open vasculature reconstruction procedures that are commercially available from both synthetic or natural sources. Challenges in using current vascular prostheses to treat vascular disease or trauma include i) the size mismatch between the native conduit and the graft, ii) the inability of the graft to evolve, which is needed for some patients, especially the pediatric population that can outgrow the prosthesis, iii) the poor accessibility or the lack of availability of autologous grafts, and iv) the potential of immunogenic response for xenografts and synthetic grafts. Bioprinting has emerged as a promising avenue to develop vascular grafts. As an additive manufacturing technique, bioprinting presents an automated approach to develop on demand patient-matched grafts based on medical images. These grafts can often serve for tissue engineering with the use of biodegradable materials that serve as temporary scaffolds to support the regrowth of the native tissue vessel. Advances in bioprinting have included the development of biologic inks from combinations of cells, biomaterials and biomolecules with accompanying hardware and software adaptations. Here, we provided a snapshot of current examples of efforts to bioprint vascular grafts and the testing methods developed to assess the risk of graft failure. Thus far, the FDA has not approved a 3D bioprinted vascular graft for clinical treatment. Still, we presented the current regulatory framework for vascular grafts on the market and provided the guidance to consider toward receiving approval for vascular prostheses. Along with the innovations, future efforts toward the realization of patient-matched bioprinted vascular grafts should focus on validation, reproducibility and systematization throughout the process life cycle. A framework to assess bioprinted vascular grafts that includes *in vitro,* then *in vivo* and involve long-term follow-up can support translational efforts and facilitate comparisons across studies. This framework should build on the current characterization techniques used for bioprinted vascular grafts and include assessment methods to reduce the risks associated with vascular grafts identified by the FDA (leakage, biocompatibility, aneurysm, infection, and performance). Systematization can be supported by the integration of artificial intelligence for material and process parameter selection during bioprinting and the implementation of standard testing protocols.

Acknowledgments

List of Abbreviations:

3D	Three-dimensional
CAD	computer-aided design
PTFE	polytetrafluoroethylene
FDA	United States Food and Drug Administration
ASTM	American Society for Testing and Materials

EBM	electron beam melting
SLS	selective laser sintering
SLA or SL	stereolithography
LOM	laminated object manufacturing
MEMS	microelectromechanical systems
VEGF	vascular endothelial growth factor
bFGF	basic fibroblast growth factor
PDGF	platelet-derived growth factor
PDMS	polydimethyl siloxane
PGS	poly(glycerol sebacate)
PET	polyethylene terephthalate
ePTFE	expanded polytetrafluoroethylene
FDM	fused deposition modeling
TEVG	tissue-engineered vascular graft
PPF	poly(propylene)
VSMCs	vascular smooth muscle cells
CFD	computational flow dynamics
GelMA	gelatin methacryloyl
HHS	U.S. Department of Health and Human Services
FD&C Act	Federal Food, Drug, and Cosmetic Act
CDRH	Center for Devices and Radiological Health
CDER	Center for Drug Evaluation and Research
CBER	Center for Biologics Evaluation and Research
PMN	Premarket Notification
PMA	Premarket Approval
NIST	National Institute of Standards and Technology
3DP	3D printing
MRI	magnetic resonance imaging
NO	nitric oxide

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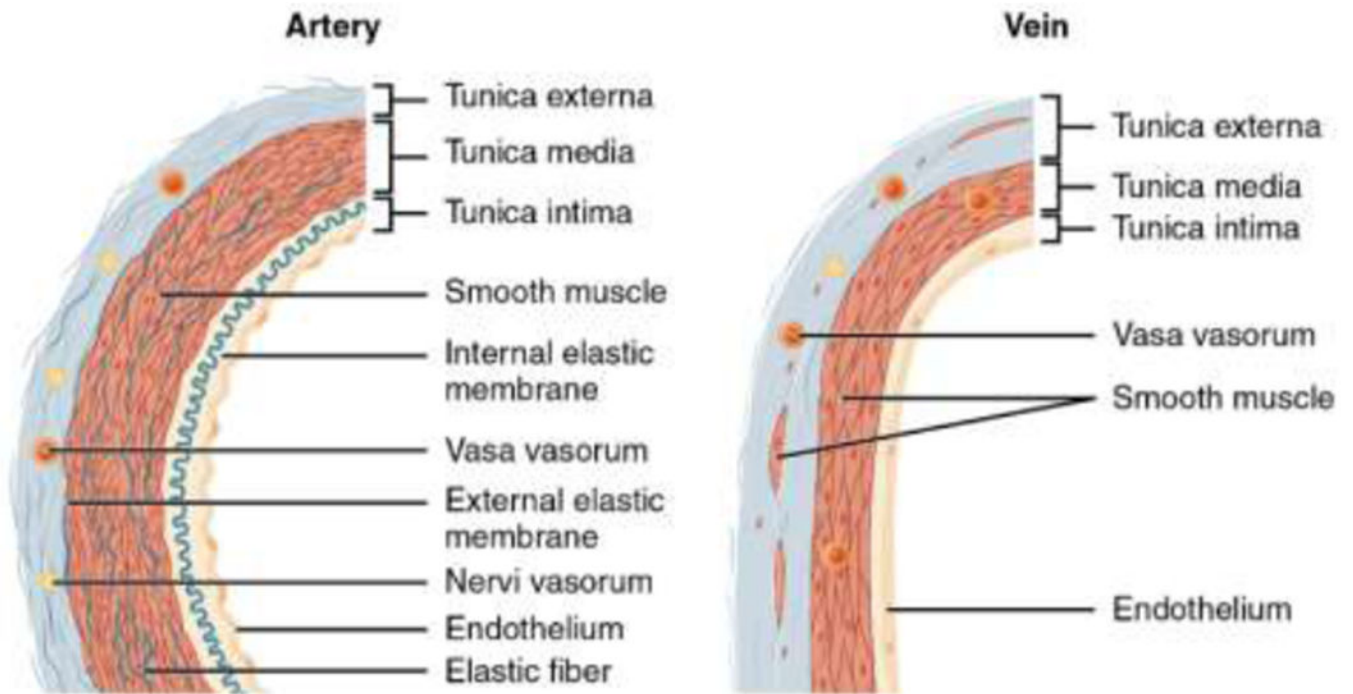
Figure 1.
Blood vessel structural features depicting the thicker wall of the artery relative to the vein because of the higher blood flow pressure in the arteries. Reproduced from [164] with permission. Download for free at http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@8.24.
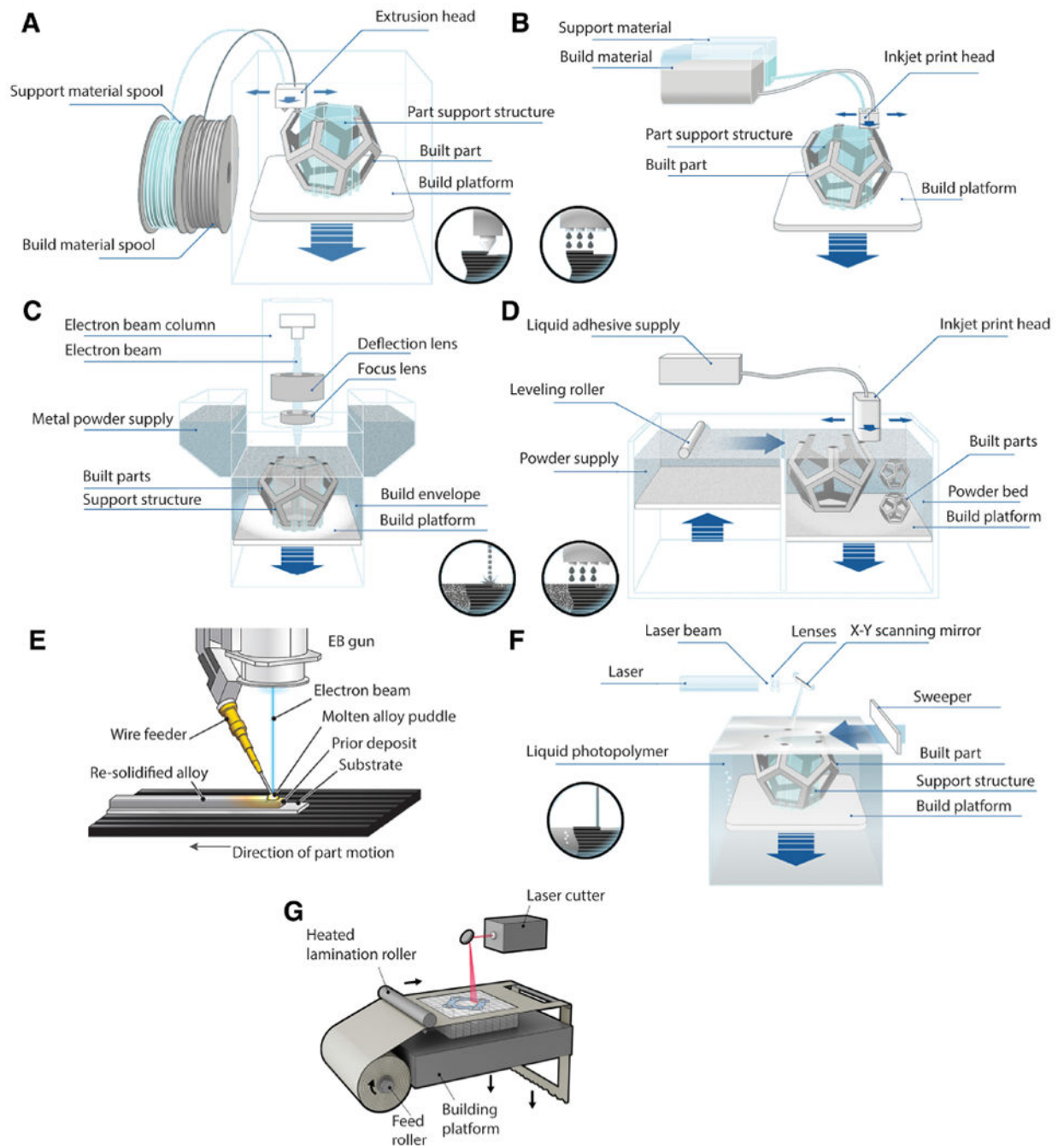
Figure 2.
3D printing process categories of the American Society for Testing and Materials (ASTM).
(A) Material extrusion. Adapted with permission from [165]. (B) Material jetting. Adapted
with permission from [165]. (C) Powder bed fusion, specifically the EBM process. Adapted
with permission from [165]. (D) Binder jetting. Adapted with permission from [165]. (E)
Directed energy deposition. Adapted with permission and photo courtesy of **Sciaky, Inc.**
[166]. (F) Vat photopolymerization, specifically the SLA process. Adapted with permission

from [165]. (G) Sheet lamination, specifically the LOM process. Adapted with permission from **Manufacturing Guide** [167].
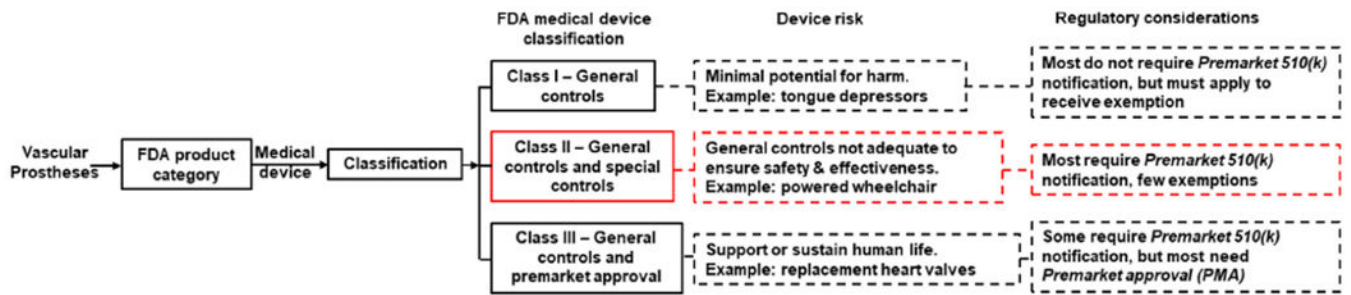
Figure 3.
FDA framework for the regulation of medical devices highlighting the regulatory pathway for vascular prostheses currently on the market. Specifically, current vascular prostheses are categorized as Class II medical devices with "special controls"and should align with the nonbinding recommendations provided by the FDA in the "Guidance Document for Vascular Prostheses 510(k) Submissions - Guidance for Industry and FDA staff' [116, 157]

Table 1.

Bioprinting methods that have been used to develop vascular grafts and vascularized constructs.

Vascular graft 3D printing strategies	3D printing ASTM process category	Material	Advantages	Disadvantages	Reference
Extrusion bioprinting	Material extrusion	Synthetic and natural biomaterials	Commonly used method with well characterized procedure. Printing resolution up to 200 µm	Bioinks have low cell densities and pressure of nozzle may be harmful to cells	32, 47, 49
Biomaterial-free extrusion bioprinting		None (cells & spheroids)	Increase cell-cell contact, cellular signaling, biomimicry, preservation of cellular fates	Poor mechanical properties	32, 50–53
Inkjet bioprinting	Material jetting	Synthetic and natural biomaterials	Single-cell printing resolution	Low cell density designs. Challenge to implement due to clogging of nozzles	47, 61, 62
Laser-assisted bioprinting	Not applicable	Synthetic and natural biomaterials	Micro-scale printing resolution & additional computer assisted controls	Less common method. Requires rapid gelation of materials after printing, thus tedious process	47, 65, 66

Table 2.

Techniques to assess vascular grafts based on FDA identified risks for vascular prostheses.

Risks for vascular prostheses identified by FDA[116]	Examples of vascular graft assessment techniques		Reference
	in vitro	*in vivo*	
Thrombosis, Embolic Events, Occlusion, & Stenosis	• Cell seeding & response to heparin •Cell penetration in graft material •Microscopy •Simulation & flow loop models	• Implantation in animal model •Diagnostic techniques •Monitoring & immunostaining	56, 116, 120, 121, 123
Leakage & Graft Disruption	• Microfluidic platform with cultured endothelial cell • Flow loop models	• Implantation in animal model • Dye injection & optical density measurement • Microscopic analysis of explanted grafts	124–127
Biocompatibility, Allergic Reaction	•Cell attachment, proliferation, penetration & viability • Gene expression of macrophages and cytokines	• Response to immunosuppressive & antibacterial drugs •Monitoring & biochemical testing •Gene expression of macrophages & cytokines	135, 137–139
Aneurysm	• Computational flow dynamic (CFD) analysis •Flow chamber model	• Animal model for aneurysm •Imaging	142–145
Infection/Sterility	• Autoclaving	• Hoechst fluorescent staining for cytoplasmic DNA	153, 154, 156
Performance	• Mechanical testing • Flow loop models	• Implantation in animal model • Imaging • Histological analysis	56, 123, 135