Chapter

Perspective Chapter: Additive Manufacturing in Customized Medical Device

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Abstract

The long-established application of rapid prototyping in additive manufacturing (AM) has inspired a revolution in the medical industry into a new era, in which the clinical-driven development of the customized medical device is enabled. This transformation could only be sustainable if clinical concerns could be well addressed. In this work, we propose a workflow that addresses critical clinical concerns such as translation from medical needs to product innovation, anatomical conformation and execution, and validation. This method has demonstrated outstanding advantages over the traditional manufacturing approach in terms of form, function, precision, and clinical flexibility. We further propose a protocol for the validation of biocompatibility, material, and mechanical properties. Finally, we lay out a roadmap for AM-driven customized medical device innovation based on our experiences in Hong Kong, addressing problems of certification, qualification, characterization of three dimensional (3D) printed implants according to medical demands.

Keywords: hybrid additive manufacturing, customized medical device, anatomical conformation, personalized medicine

1. Introduction

Throughout the ages, medicine, by inherent definition, has always been focused on the treatment of persons and individuals. Whilst the pursuit of scientific progress has inexorably propelled this process toward a systematic and harmonized approach to treatments [1], the advent of personalized medical solutions has begun to reintegrate the personalized and idiosyncratic element to the therapeutic action [2, 3]. This has erupted into a vast and expansive medical discipline in the current day, ranging from diagnostic testing [4] to tailored drug treatments [5], to the customized medical devices that will be focal here. The orthopedic customized medical device has become one of the more mundane and immediately practical manifestations of personalized medicine.

Tunneling on customized prosthetic implants such as those in use in dental, maxillofacial, and orthopedic disciplines, the dichotomy between the conventional manufacturing technologies and additive manufacturing (AM) become apparent; where subtractive manufacturing and its kin excel in excellent control of

repeatability, scalability, surface finishing, and product proportions, the piecewise variation seen in personalized medical solutions levels the playing field significantly, so much so that topologies unique to additive manufacturing (AM) processes such as freeform, anatomically compliant geometries and bioinductive honeycomb porous structures are allowed to shine through [6].

That being said, there are still substantial barriers between the current state of additive manufacturing and ancillary technologies, and mature, well-characterized medical applications [7]. Medical device development has and will for the foreseeable future be driven by clinical needs, and as medical device customization continues to progress, this personalized approach brings medical professionals ever closer to the engineering-based approaches used during the design and manufacture of medical devices [8]. Operating in completely disparate paradigms, efficient bridging of this chasm will be imperative going forward [9].

Based in Hong Kong, the authors have been working toward the realization of streamlined AM utilization in the manufacture of customized medical devices over the past 5 years. Experience and involvement in the formulation of customized medical devices ranging from surgical guides and instruments to long-term orthopedic implants have culminated in a relatively refined and progressively formulaic modus operandi. Putting forth a structured workflow and robust manufacturing process validation protocols, we look to initiate discussion in the space by this proof-of-concept, not in terms of technical operational detail but the constitution of the proposed system and its potency and soundness.

2. Additive manufacturing-assisted fabrication of the medical device

A typical workflow of preparing a customized medical device consists of four stages, namely, anatomic modeling, surgical planning and design, additive manufacturing, and postprocessing, as shown in **Figure 1**. This workflow has been testified and applied to fabricating 11 personalized surgical instruments in Hong Kong [10].

2.1 Anatomic modeling

Once clinical needs are identified, anatomical modeling is constructed based on the patient's anatomy. Generic processes utilized during anatomical modeling are displayed in **Figure 2**. Computed tomography (CT) DICOM data is read as 2D grayscale pixel arrays arranged in a series of planes (**Figure 2A**). Desired anatomical structures are isolated on each individual array through intensity thresholding, artifacts, noise, and distortions are minimized by using image processing tools (**Figure 2B**). Series of 2D slice pixel arrays are interpolated and converted into a three dimensional (3D) computer-aided design (CAD)-friendly format (**Figure 2C**). These models and other patient information are the basis for surgical planning and design.

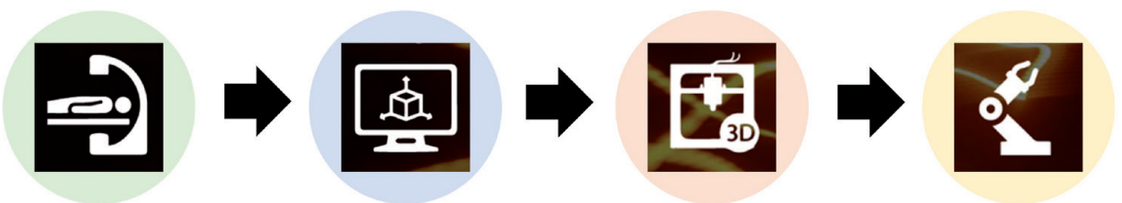

Figure 1.
A typical workflow of preparing a customized medical device. Stage 1: anatomic modeling. Stage 2: surgical planning and design. Stage 3: additive manufacturing. Stage 4: postprocessing.

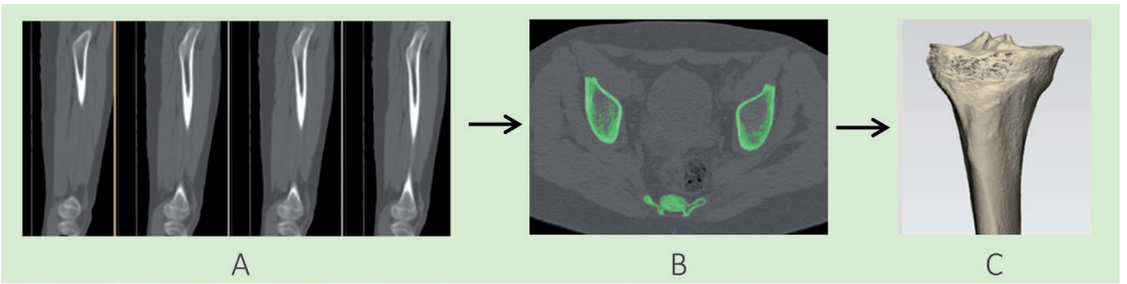

Figure 2.
Stage 1: anatomic modeling, (A) scanning, (B) segmentation, and (C) construction of 3D model. Stage 2: surgical planning and design.

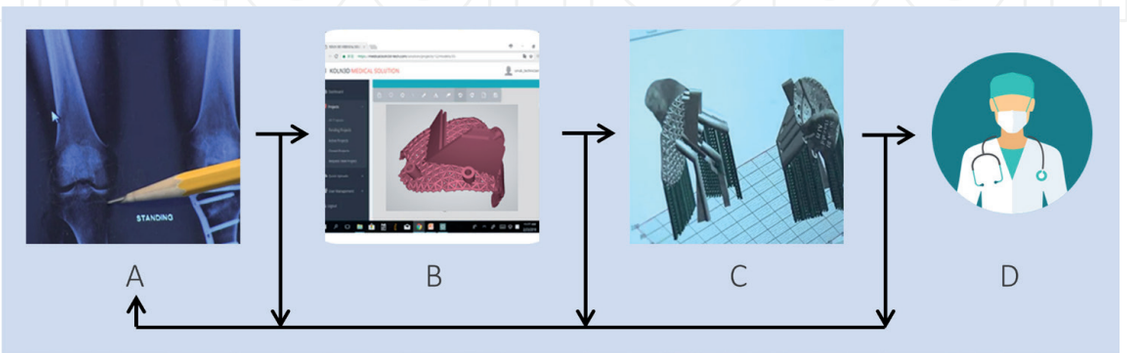

Figure 3.
Stage 2: surgical planning and design, (A) surgical planning, (B) CAD modeling, and (C) CAM modeling.

2.2 Surgical planning and design

The surgical planning and design stage include an iterative process of (**Figure 3A**) surgical planning, (**Figure 3B**) CAD modeling, and (**Figure 3C**) computer-aided manufacturing (CAM) modeling, **Figure 3**. It requires immense communication between surgeons and engineers. The success of the design strongly depends on the level of details as well as the effectiveness of the communication of inputs from both parties. An example of surgical planning and design of a patient-specific instrument is presented in **Figure 4**.

2.3 Additive manufacturing

Proceeding from design to manufacturing, one AM method commonly used for a metal medical device is direct metal laser sintering (DMLS) under the powder bed fusion category. In a typical DMLS setup (LUMEX Avance 25, Matsuura), additive manufacturing is achieved by repeated procedures of (**Figure 5A**) recoating and (**Figure 5B**) laser sintering. The hybrid AM approach incorporates an additional procedure of (**Figure 5C**) computer numerical control (CNC) machining whenever several layers are built [11]. Here, we demonstrate the DMLS method by using cobalt-chromium alloy (**Figure 5**). Spherical powder of size ranges from 25 μm to 40 μm (Koln3DCobaltChrome, Sandvik) is recoating onto the powder bed by a flat blade swiping sideways. The layer thickness is set at 0.4–0.5 mm whereas the laser power is set in the range of 100–400 W.

We examine the morphology and elemental composition of cobalt-chromium alloy before and after sintering. The morphology of cobalt-chromium alloy powder observed under field emission scanning electron microscope (FESEM) is shown in **Figure 6a**. The powder size ranges from 25 μm to 40 μm. After laser sintering,

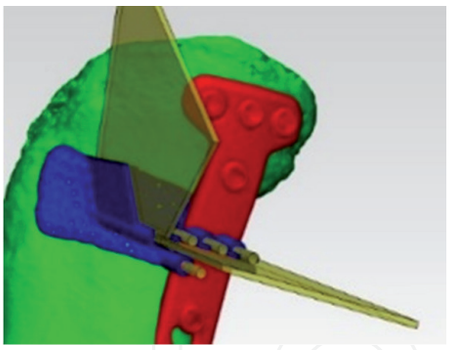

Figure 4.
Surgical planning elements highlighted: segmented patient CT data (green) is combined with surgeon input (transparent yellow) culminating in customized surgical instrument (blue) and standardized implant (red).

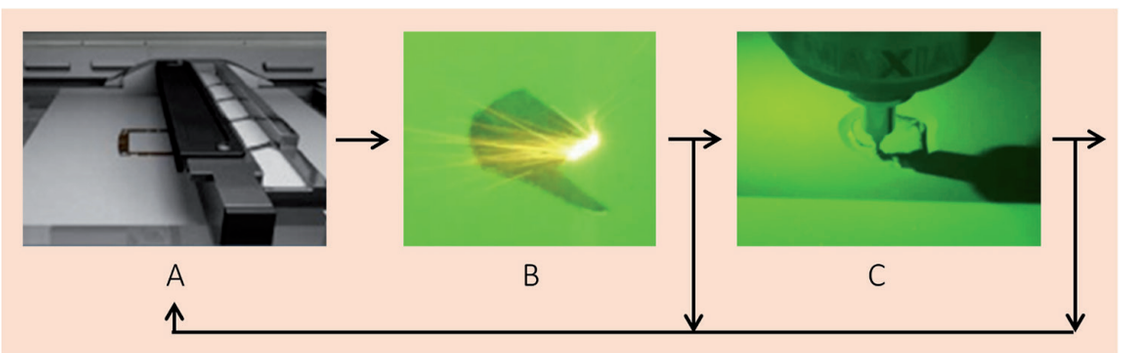

Figure 5.
Stage 3: additive manufacturing, (A) recoating, (B) laser sintering, and (C) CNC machining.

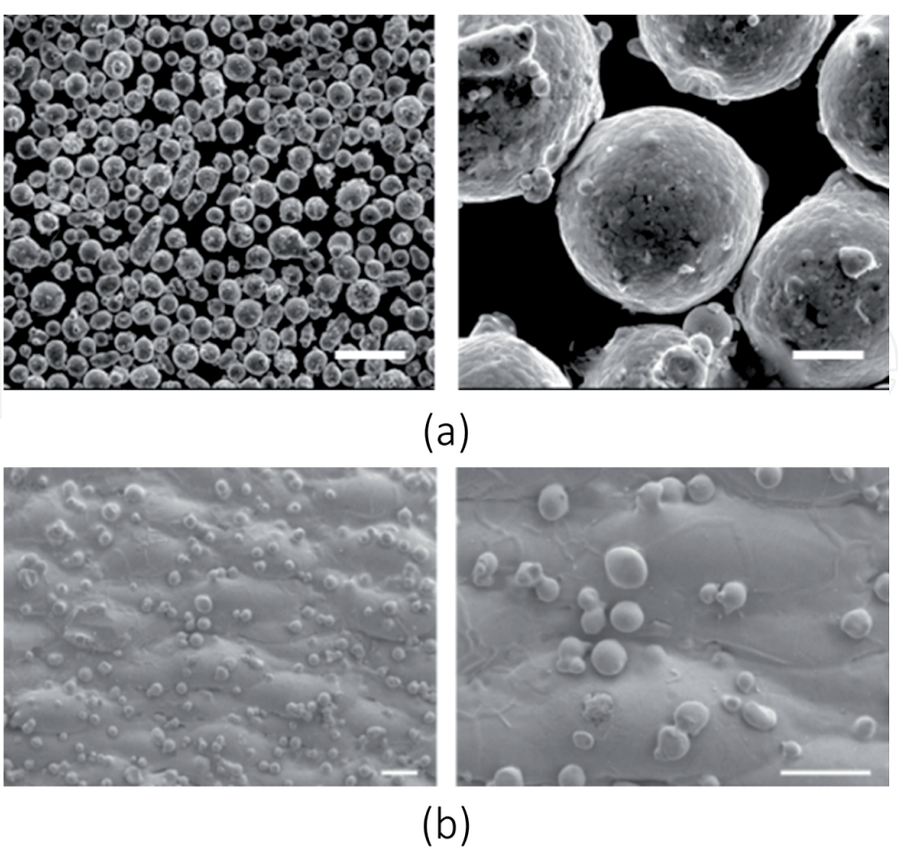

Figure 6.
FESEM images. (a) Cobalt chromium alloy powder in size range of 25–40 μm. Scale bars are 100 μm (left) and 10 μm (right). (b) Surface of a part made by sintering of cobalt-chromium alloy. Scale bars are 100 μm.

unsintered powder remains on the surface of the built part, as shown in **Figure 6b**. To improve the surface finishing of the AM product, postprocessing is required. Some AM parts undergo heat treatment to improve mechanical properties such as ductility and hardness.

Field emission scanning electron microscope/energy dispersive X-ray analysis (FESEM/EDX) was performed using an FEI Quanta 400 FEG MK2 electron microscope and an AMETEK EDAX (PV776068-ME) X-ray analyzer to investigate the composition of the samples. The back-scattered electrons (BSE) images are formed by scanning the sample with a high-energy beam of primary electrons. The primary electrons interact with the sample and generate low-energy secondary electrons and back-scattered electrons, these electrons are collected, and the surface topography of the sample can be constructed. In addition to low-energy secondary electrons, X-rays are also generated by the interaction of the primary electrons and the sample. The characteristic of X-ray emission can give qualitative elemental information of the sample. In the present case, a standardless ZAF algorithm was used for quantification.

Elemental composition measurement is performed on the powder and the sintered part. The sintered samples used in this experiment undergo heat treatment processes. Main elements, such as cobalt (Co), chromium (Cr), and molybdenum (Mo), etc., are measured by EDX. We do not observe any significant changes in the elemental composition of cobalt-chromium alloy before and after the sintering process, which are in the form of powder and sintered parts, respectively, as shown in **Figure 7**. The result shows that the discrepancy in elemental composition varies by within ±2 wt%.

2.4 Postprocessing

Completing the AM process, postprocessing is performed for (**Figure 8A**) support removal and (**Figure 8B**) polishing according to the specific clinical needs, as illustrated in **Figure 8**. The postprocessing procedures are namely product-based plate detachment, support material removal, surface machining, and surface polishing. Even though a high degree of design complexity is enabled by AM

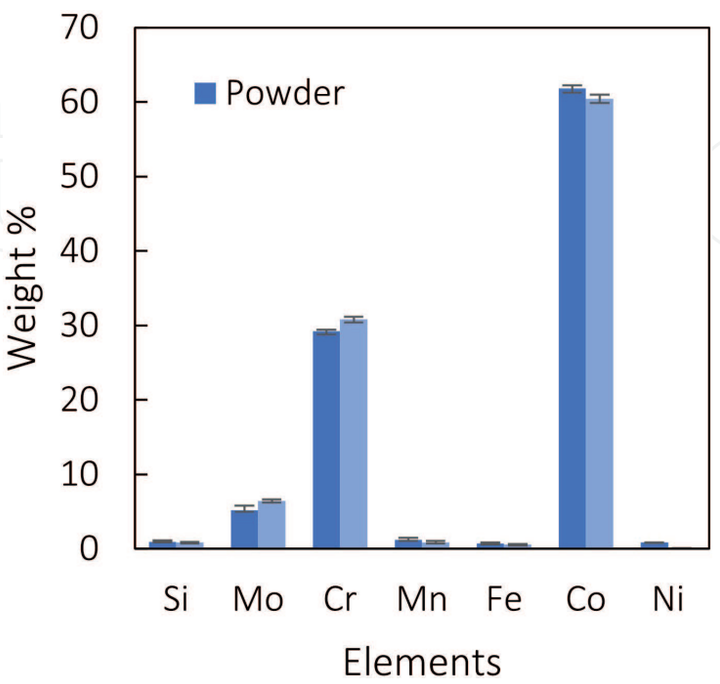

Figure 7.
Elemental composition of (a) cobalt-chromium alloy powder and (b) surface of the corresponding sintered part. Error bar is one standard deviation of five measurements.

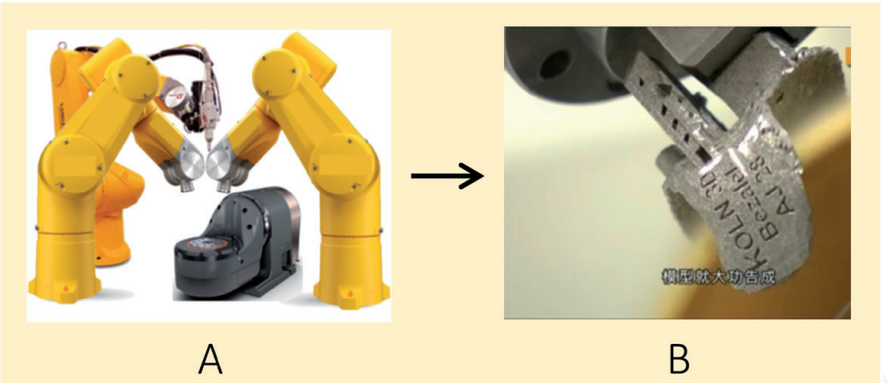

Figure 8.
Stage 4: postprocessing, (A) support removal, and (B) polishing.

technology, the low efficiency in postprocessing is a prevailing limiting factor in the entire process. To date, these postprocessing procedures are commonly conducted manually and relatively time-consuming depending on the complexity of the AM product. Recently, robotic control is introduced to automate the process and is gaining popularity in the manufacturing industry [12]. This technology is highly appealing to the medical industry for it possesses many advantages over manual operation such as higher accuracy and repeatability [13]. Full automation of robotic postprocessing systems is on its way to transforming the medical industry.

2.5 Case study

Here, we present a case study of a teenager with chondral lesions on the posterior medial quadrant of the talar dome. The treatment was performed with the aid of medial malleolar osteotomy surgical jig (**Figure 9**). Our proposed workflow for the preparation of additive manufacturing-assisted fabrication of medical devices has been adopted.

A teenager patient admitted with severe ankle pain when walking was diagnosed with abnormalities on the posterior medial quadrant of the talar dome. The suspected cause of chondral lesion is vascularization defect in subchondral talar bone. The treatment approach is laid out by (1) medial malleolus removal with the surgical jig to expose chondral lesion, (2) removal of defective chondral tissue, (3) articular surface repair, and (4) reattachment of the medial malleolus.

With patient and regulatory approval, the medical device was prepared subsequently. In the stage of anatomical modeling, a CT scan of the ankle with slice thickness 0.625 mm and slice resolution 0.5 mm was performed and the DICOM data of the talocrural joint were segmented and converted to surface mesh body. In the stage of surgical planning and device design, the chondral defect was first located. Cutting planes and fixation screw trajectories computationally were simulated and determined. Subsequently, guides for cutting planes and screw trajectories were designed, followed by patient-matched surface design according to anatomical landmarks and features coalesce to form the final design. Proceeding to the stage of additive manufacturing, the device was fabricated using a DMLS 3D printer with CoCrMo alloy (ASTM F-75 grade) powder. The process was validated with biocompatibility, mechanical, and compositional tests with critical dimensions verified. In the final stage of postprocessing, hot isostatic pressing (HIP) was performed to resolve residual stresses. After support removal, the device was ready for cleaning and packaging. The additive manufacturing-assisted fabrication of medial malleolar osteotomy surgical jig was completed.

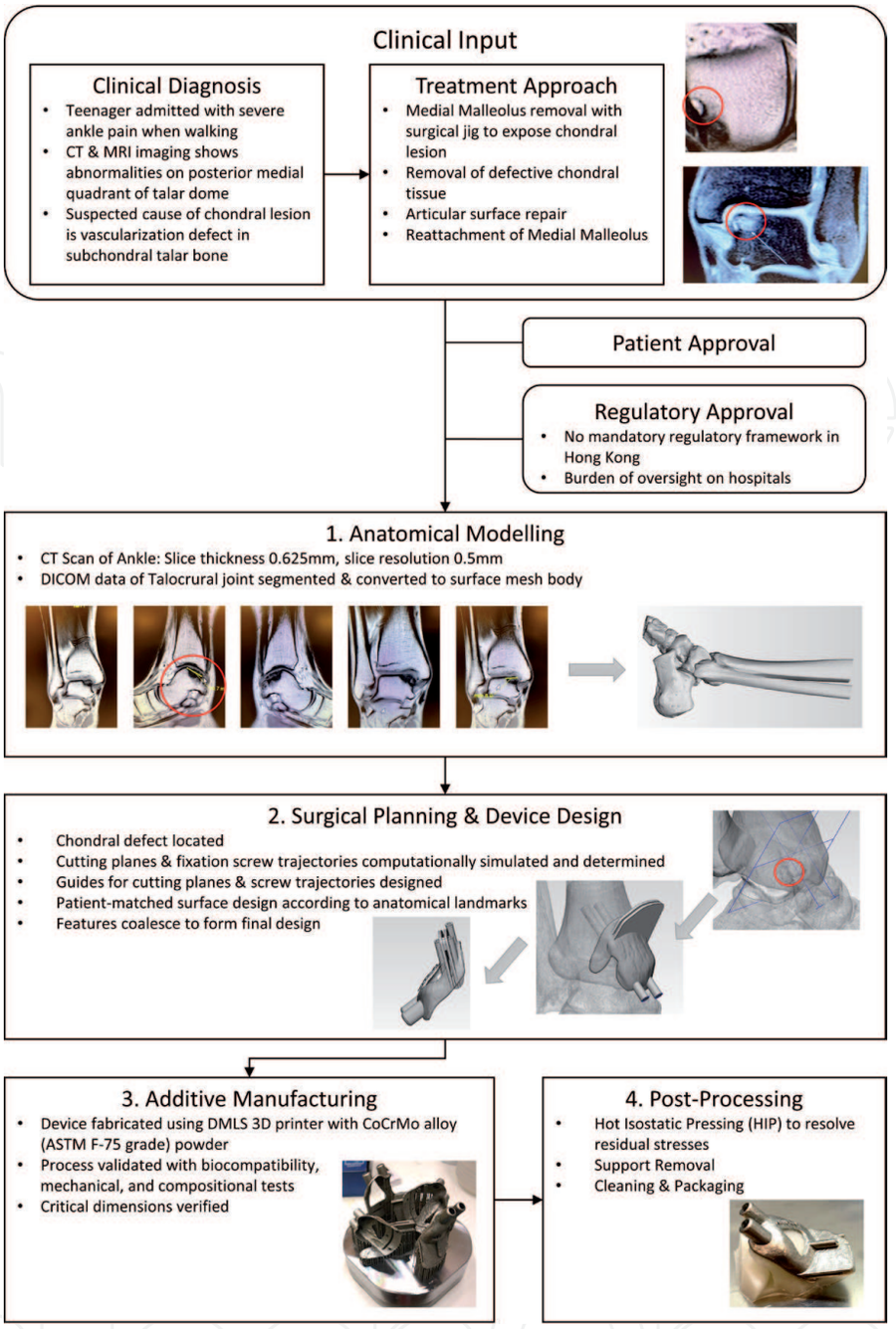

Figure 9.
Case study: medial malleolar osteotomy surgical jig.

3. Critical clinical concerns in AM technology

3.1 Error of medical AM manufacturing

AM-assisted fabrication of the medical device is not an automatic process. The clinical data including anatomy and functions of the body parts need to be analyzed and segmentation of the relevant parts on the data source is of paramount importance to the beginning of every AM process.

Upon arriving at a diagnosis, with confirmation through medical imaging, the anatomical and functional data will be transformed from DICOM data to stereolithography (STL) or CAD data formats interpretable by 3D printers. Engineers and clinicians will then corroboratively engage the design and customization effort. Given this approach, there are common pitfalls to take note of and avoid.

3.1.1 Pathologies around the joint

In the case of a tumor around the hip joint, combined use of CT scan and magnetic resonance imaging (MRI) can help to create accurate models for surgical planning by coregistration of two sets of DICOM. The bony margins can be defined on a CT scan, whereas the soft tissue component of the tumor and sites of tumor invasion, periosteal elevation, and/or edema within the bone are best defined on MRI. A single model created using the information from both modalities allows the surgeon to plan resection and reconstruction utilizing all available information.

3.1.2 Quality of bones in the very young and very old

The differences in pixel density (on CT scan) or signal intensity (on MRI) between immature bones and cartilage and between osteoporotic bones and osteophytes and diseased tissues can be subtle. This is particularly challenging when dealing with complex pelvic pathology. It would need manual input to delineate osteophytes and osteopenic areas and pathology areas. This means that the surgeon, radiologist, or engineer will have to manually identify, at least in part, the various anatomic structures so they can be printed as separate objects. Segmented images designated for printing patient-specific models for surgical planning should be carefully reviewed before the AM manufacturing process and validated after removal of the disease body part.

The above list of conditions is not exhaustive which can cause a fundamental error to the final product with AM manufacturing process. An accurate translation from medical needs to product innovation is safeguarded by the effective communication and information exchange between various parties involved, as discussed in Section 2.

The understanding of various materials for the additive manufacturing process impacts the functionality of the final product. Training, technical competence, and experience utilizing medical software and software for 3D printers determine the quality of the object architecture. Clinical concerns in AM technology fall into the following categories—translation from medical needs to product innovation, anatomical conformation and execution, and validation.

The medical implants for the replacement of defective parts of the human anatomy can be validated with various means. One way is to scan the resected body part and overlay it with the source data of AM [14]. This will provide a quantitative measurement of the accuracy of pre- and postmanufacturing data.

3.2 Geometric conformity of AM medical devices

To investigate the geometric conformity of the AM parts, five distinct metallic medical devices, namely jig 1, 2, and implant 1, 2, 3, have been made from the AM approach and 3D scanned. Turntable mode on Shining 3D Einscan Pro HD 3D scanner has been used to scan robotically milled product coated with AESUB blue scanning spray. The resultant model has then been matched and analyzed with corresponding functions in the materialize MIS 24 software suite. A clinically critical zone is defined for which the geometrical accuracy is examined. Overlaying the clinical critical surface area of the design model and the scanned model, a point-to-point spatial distance is measured for each point within the clinically critical zone. The average discrepancy and the discrepancy histogram are presented in **Table 1**. Jig 1 yields the maximum average discrepancy of 0.13 ± 0.35 mm. For a typical computed tomography (CT) scan, the spatial and axial resolutions are 0.5 mm and 0.6 mm, which set the spatial accuracy requirement of the customized medical device. The result suggests that the AM-assisted fabrication approach attains the satisfactory special accuracy required clinically.

	Jig 1	Jig 2	Implant 1	Implant 2	Implant 3
Spatial discrepancy (mm)	0.13 ± 0.35	0.02 ± 0.15	0.07 ± 0.21	−0.01 ± 0.12	0.10 ± 0.12
Graphical representation					
Discrepancy histogram					

Table 1.
Robotically machined 3D-printed products were 3D scanned and compared computationally with the base CAD model. Results of the analysis are displayed.

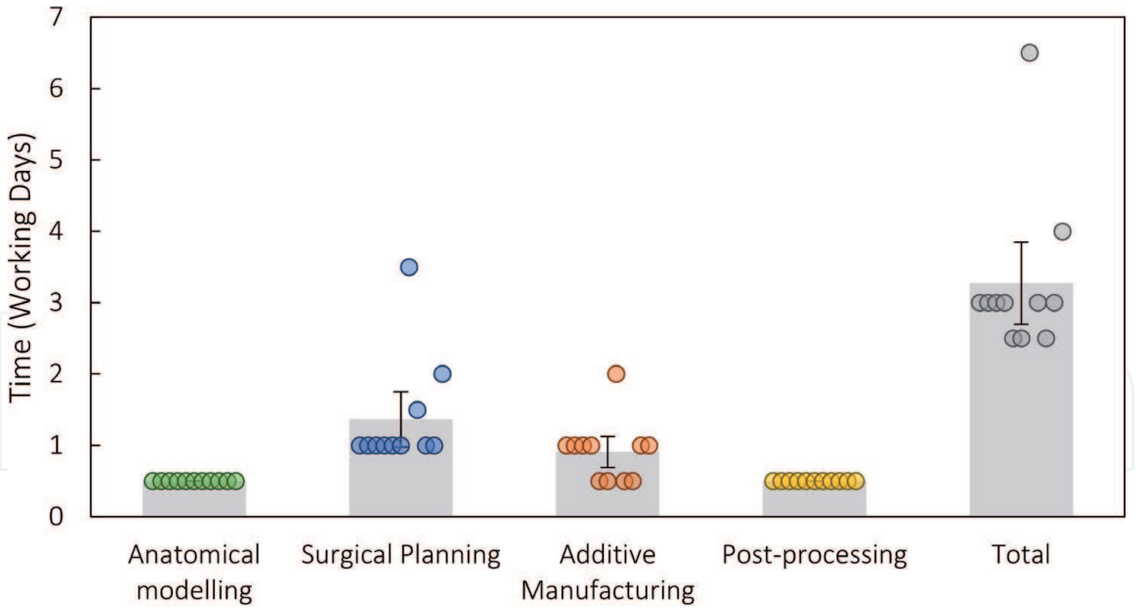

Figure 10.
Time consumed per each of the four stages. Statistics of 11 cases. Error bars indicate the standard deviation.

3.3 Time consumed in each stage of AM-assisted fabrication

Apart from spatial resolution, the time consumed in AM-assisted fabrication is investigated. About 11 patient-specific instruments undertaking the proposed four-stage workflow being made, including five for hallux valgus osteotomy, four for high tibial osteotomy, one each for proximal femur osteotomy, and calcaneal osteotomy. A statistic of the time taken per each stage is measured, as shown in **Figure 10**. Among the cases reported, the average total time taken to complete the four stages is 3.3 ± 0.6 working days. The first and last stages, that is anatomical modeling and postprocessing, are relatively routine and typically take 0.5 days to complete. Contrarily, the time is taken for surgical planning and design (Stage 2) varies. Since Stage 2 involves an iterative process requiring communication between surgeons and engineers, the time involved is not only dependent on the complexity of the design but also the effectiveness of communication between different parties. As a result, time spent on Stage 2 has been found to be the lengthiest and the most variant. The time consumed in additive manufacturing (Stage 3) is dependent on the size and resolution of the AM part. Overall, the short time frame (in the order of a few days) to fabricate metallic patient-specific instruments by AM approach has brought numerous opportunities to cater for nonemergent clinical applications, such as osteotomy as demonstrated in this work.

4. Protocol for validation

While validation is a procedurally quintessential part of a fabrication that ensures process compatibility with intended product applications, it is especially imperative when dealing with medical devices that inherently possess the risks involved with interacting directly with human physiology. To this end, regulatory bodies such as the US Food and Drug Administration (FDA), the Chinese National Medical Products Administration (NMPA), and the decentralized regulatory authorities under the European Commission have developed medical device classification systems that categorize devices in accordance with the risk, their respective intended applications bring with them. Whilst there are nuances between the

numerous classifications, medical devices are typically assessed according to their intended purpose or use, with the duration, invasiveness, reusability, sterility, and activeness being commonly scrutinized aspects that are used as indicators of the associated risk. Among medical devices, this is particularly heightened when concerning prosthetic implants that are invasive in nature and are often implicated in extremely prolonged physiological exposure during and after surgical procedures. Knowing this, validation is an exceedingly risk-dependent procedure, and as such one should always keep in mind and analyze the intended purpose or use of a product, what the associated explicit and implied product requirements are, and if and how relevant AM processes could potentially impact the conformity to these requirements.

The traditional pharmaceutical process validation structure of installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ) is generally an effective methodology when transplanted into the context of AM processes. Originating from a similarly health-related industry, this does not significantly vary when being applied to the fabrication of medical devices, though there are indeed adjustments to accommodate for the aforementioned variation in associated risk inherent to the nature of the products in question. Defining the scope and breadth of the process validation will grant it greater clarity in the considerations to be made and the extent of the validation activities to be performed. While we will continue mostly focusing on hybrid additive manufacture processes (CNC-DMLS), be mindful that the type and nature of the AM processes concerned will affect the complexity of respective validation activities.

Installation qualification (IQ) is the ascertainment, through the documentation of objective evidence acquired through predefined verification methods, that all relevant equipment and machinery, whether primary, auxiliary, or ancillary, has been installed in accordance with predetermined requirements or recommendations. In practice in terms of hybrid AM processes, this typically involves infrastructural checks on items and ancillary systems such as electrical supply, compressed air supply, inert gas supply, and chiller, information that is customarily provided by most equipment manufacturers. Equipment manufacturers will also commonly have supportive services surrounding these activities in the form of complete user documentation documents as well as site acceptance tests (SAT) to qualify the commissioning of the equipment. Calibration of all measurement devices used throughout verification processes occurring during the entire validation is also usually included as part of installation qualification. IQ validation activities for the production of medical devices do not deviate from these elements, though one small detail to take note of is that the biologically oriented verification processes taking place subsequently in OQ and PQ validations might not have calibration available as it is traditionally understood. Some examples of this include the chemical assays used to determine physiological chemical characteristics and the histological examinations for assessing biological reactions toward materials. Whilst these evaluative processes are typically performed by accredited laboratories, verifications are done in-house should always have additional device accuracy verifications performed.

Operational qualification (OQ) is the process that results in the establishment of equipment operational parameters, limits, conditions, and requirements that optimally are expected to result in products meeting and product specifications. Performance qualification (PQ) builds on the findings of OQ validation, effectively stress testing the manufacturing process under simulated worst-case scenarios to ensure product specifications are met regardless, or those potential deviations and their respective rates of occurrence are acknowledged. Both OQ and PQ typically comprise a series of tests and verifications, as well as the documentation of all pertinent methodologies, results, evidence, and conclusions. Operational conditions and

parameters, their control, veracity, and repeatability, are first verified to safeguard the authenticity of the test environment. In the case of hybrid AM processes, this can range from laser control parameters such as laser power and path overlap to sintering chamber environmental conditions such as oxygen concentration, build plate temperature, and enclosure temperature. This includes verification of metal powders used, as well as processes used to handle said metal powders and their respective control parameters. Once all highlighted aspects of operational control have been verified, operational limits and conditions can then be established and tests can be conducted on products produced by using operational parameters across this range, with acceptance criteria enacted based on product specifications. Through data collection and trend analysis, one can deduce and provide justification for the establishment of optimal operational parameters and conditions during product manufacture, and thus concludes OQ validation and moving on to PQ validation. In terms of hybrid AM processes, since there is not much variation when considering maximal system throughput and worst-case scenarios, PQ is often simply performed through periodically testing products manufactured at maximum printing load.

Nonmedical applications of hybrid AM processes will generally inspect for mechanical aspects such as strength and malleability, material properties such as product composition, grain structure, presence of impurities, as well as explicit elements of product specification such as product form and critical dimensions. While international standards concerning appraisal methodology of these quantities are well established from beyond the medical field, the uniqueness of medical devices applications often warrants their own testing methodology. For example, whilst bending strength and stiffness are well-characterized quantities in their own right, ISO 9585 and ASTM F382 both describe methodologies that are specific to bone plates.

In the case of medical devices, critical evaluative processes, standardized methodologies, and highly specific parameters for biocompatibility conformance have been outlined in the document series ISO 10993. In particular, Part 1 of ISO 10993 systematically outlines by flowchart all considerations necessitated by regulatory bodies when assessing the risk associated with a medical device, echoing factors previously mentioned surrounding intended use or purpose such as duration

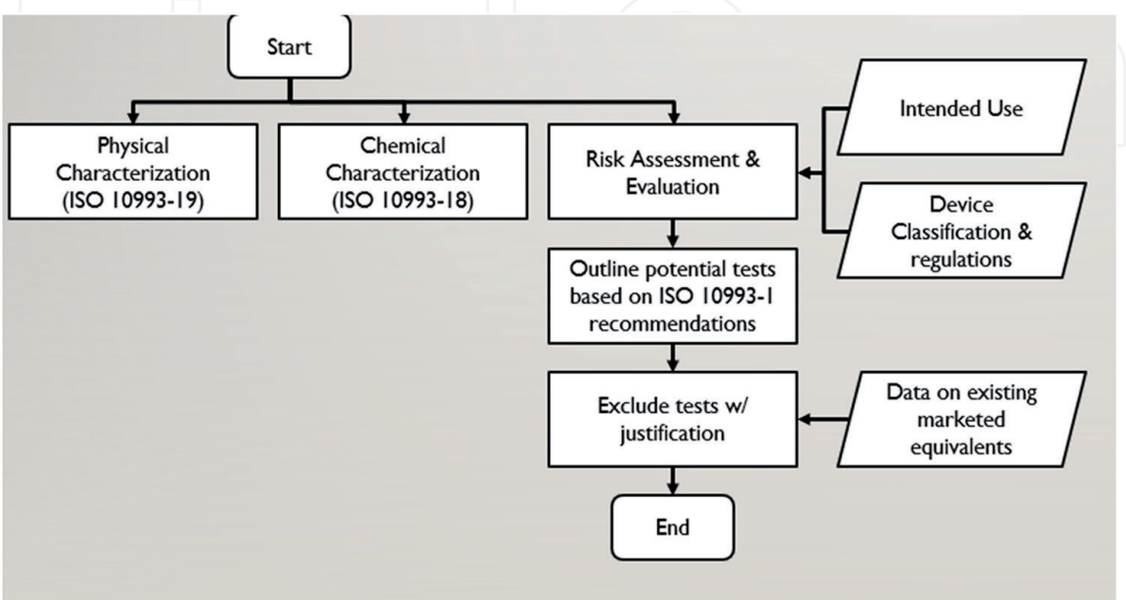

Figure 11.
Flowchart of selection of biocompatibility tests.

of use and invasiveness, but also taking into account the nature of physiological surfaces contacted as well as the characteristics of the device itself. Depending on the outcome of the evaluation, a range of endpoints of biological evaluation are recommended, indicating the types of tests required to demonstrate an affirmative biological evaluation (**Figure 11**).

Critical to the case of hybrid AM processes is the stipulation that evaluation is only necessary if there is no available preexisting biocompatibility data regarding materials involved in the manufacture of the product. Whilst customized medical devices are still somewhat of a novel therapeutic solution, functionally identical or similar products have long been in use and have been extremely well-characterized biocompatibility. The same can be said for material composition, where traditionally subtractively manufactured equivalents are well defined in terms of biocompatibility. Since hybrid AM process fabricated products are homogenous and typically established metal alloys, combined with animal guidelines detailed in ISO 10993-2, it can be expected that barring medical devices where material properties are completely novel with no biocompatibility data, most hybrid AM products will only require physical and chemical characterization, as well as cytotoxicity. *In vitro* cytotoxicity, one of the other more baseline biocompatibility evaluations required is established in Part 5 of ISO 10993, utilizing cell culture assays to gauge the viability of cell growth in the vicinity of the product, and serves as a catch-all gatekeeping evaluation that preliminarily judges feasibility of biological product applications. The procedures for chemical and physical characterization have been detailed in Parts 18 and 19 of ISO 10993, respectively, entailing extensive procedural and testing standards and references by which to carry out testing. Both put emphasis on the risk-based approach of the characterization, deriving required tests from the inherent risk of application and intended use. In the case of customized medical devices produced by hybrid AM processes, chemical characterization typically comprises of immersion and corrosion tests, detailed in Part 15 of ISO 10993, that seek to detect potentially hazardous metal ions, as well as extraction tests, found in Part 16 of ISO 10993, that identify organic compounds likely biologically disruptive in nature. The physical characterization will heavily depend on the material in use, as well as the intended use of the product, but generally, hybrid AM customized medical products will make use of scanning electron microscopes (SEMs) to identify product material and demonstrate equivalence with known materials currently in use [15].

Device type	**Biological contact**	**Length of contact**	**ISO standard for tests required**						
			ISO 10993-18	**ISO 10993-19**	**ISO 10993-5**	**ISO 10993-10**	**ISO 10993-11**	**ISO 10993-6**	**ISO 10993-3**
Implant	Tissue/bone	<24 h	×	×	×	×			
		24 h<, <30 days	×	×	×	×	o	×	o
		>30 days	×	×	×	×	o	×	o
External brace	Intact skin	<24 h	×	×	×	×			
		24 h<, <30 days	×	×	×	×			
		>30 days	×	×	×	×			

×: tests in ISO standard are recommended if no preexisting marketed equivalents exist.
o: particular tests in ISO standard are recommended if no preexisting marketed equivalents exist.

Table 2.
Biocompatibility tests required for 2 types of example medical devices.

On the flip side, if the application and/or material in use is truly novel with insufficient precedent data for biocompatibility evaluation, a wide range of costly *in vitro* and *in vivo* tests will be required to satisfy the requirements of ISO 10993. Assuming the case of orthopedic implants, in addition to previously mentioned physical, chemical, and cytotoxicity characterizations, sensitization and irritation tests (ISO 10993—Part 10), pyrogenicity and systemic, subacute, subchronic, and chronic toxicity tests (ISO 10993—Part 11), implantation tests (ISO 10993—Part 6), as well as genotoxicity and carcinogenicity testing, will be required. Fortunately, this is not a common occurrence for hybrid AM products where precedent and equivalence are the norms (**Table 2**) [15].

5. A roadmap for AM-driven customized medical device innovation in Hong Kong

As personalized medical solutions popularize across the globe, there has been a scramble from regulatory bodies in bringing patient-conforming medical devices under the scope of preexisting regulative structure. Given the uniqueness of certain anatomical features and the significant interpersonal variation that exists, by definition, these medical devices will have noticeable differences on a piece-by-piece basis. This results in increased difficulty in quality control and subsequently, regulation since these devices intrinsically are never completely identical and thus one cannot demonstrate conformance to regulatory requirements through a sample device in the present when every following iteration of the device will inherently be different, with variation often being guided by the anatomical features of patients. To this end, regulators have taken similar, risk-based approaches in incorporating these elements into their respective frameworks. The discussion will focus on the globally preeminent regulatory bodies of USFDA and the national regulatory bodies under the European Commission, as well as the locally relevant NMPA of China.

Personalized medical devices are generally split into three groups of products by regulatory bodies, based on the resemblance of their respective intended uses and manufacturing models with conventional, mass-produced medical devices that regulatory bodies devise their systems around. Here, we must part with the terminology of "Customized Medical Device" in favor of more precise language. The first group is referred to as adaptable medical devices (AMD) and are personalized medical devices that are mass manufactured as a series of compatible components and assemblies, only to be tailored to the patient's unique requirements at the point of care, by medical professionals in accordance with their medical judgment as well as device guidelines. They are essentially mass-produced products with an element of personalization in their intended use and are usually treated as such by regulatory bodies, simply following standard device classification protocols to determine regulatory requirements. In fact, the European Medical Device Regulation (EU MDR), FDA, and NMPA all do not implement additional regulatory procedures with respect to this type of device. Some AM-produced products make use of this ease of control and regulation, where the device is comprised of standardized, mass-produced parts as well as a relatively small AM-produced component that conforms to a subsection of patient anatomy that typically sees greater variation and hence requires personalization [16].

The second group is described as patient-matched medical devices (PMD) and are characterized by a largely identical manufacturing process, as well as a design envelope that encapsulates and bounds potential design features, including patient-specific features, and their potential variation. Significant portions of AM-produced medical devices will fall under this category, with products that have

slightly adaptive if not harmonized intended uses, indications, contraindications, and design envelopes, that are essentially functionally identical but are designed to cater to differing individual anatomies. The classification of PMDs is an adaptation that regulatory bodies have utilized in incorporating personalized medical devices, and by proxy AM products, into a simpler regulatory framework, where these devices are generally viewed in a similar fashion as conventional medical devices but may require additional documentation, justifications, and design controls to compensate for the increased risk brought on by potential variations in design. The NMPA, EU MDR, and FDA do not have any additional regulatory requirements with respect to "Patient-Matched Medical Devices," however, the FDA has developed and issued a guidance document titled "Technical Considerations for Additive Manufactured Medical Devices" in 2017, such that whilst there is no additional explicit requirement, there is a baseline of expectation when putting forth AM products that the FDA assumes [17].

The final category is the most original and authentic to the idea of personalized medicine, that being custom-made medical devices (CMD). This refers to devices that, at the request or prescription of a medical professional, are truly made for only one particular individual and is generally targeted toward extremely rare conditions

	CMD	**PMD**	**AMD**
Intended use	Intended for use only for a particular individual (including medical professionals), to address specific feature or condition of the said target individual	Intended for use on the specific patient, with certain features matched with said patient's anatomical data, done so according to the design envelope.	Intended for general use, with device personalized during the application, according to assembly instructions
Prescription	Mandatory	Not mandatory	Not mandatory
Design responsibility	Doctor, under manufacturer consultation	Manufacturer, under doctor consultation	Manufacturer
Production	Unique, tailored	Repeated validated process, possibly in batches	Mass produced
EU MDR regulatory requirements	Statement (Annex XIII) + conformity assessment (Annex IX/Annex XI)—Class III implantable devices only	Conformity assessment (Annex IX/Annex XI)	Conformity assessment (Annex IX/Annex XI)
US FDA regulatory requirements	Custom device exemption (FD&C act section 520(b) + requirements) + QS regulation (CFR title 21)	PMA (Class III/Class II), 510(k) approval (Class I/Class II)	PMA (Class III/Class II), 510(k) approval (Class I/Class II)
CN NMPA regulatory requirements	Notification to regulatory body for initial cases undergo standard market clearance/approval as soon as possible	Standard market clearance/approval: Pre-market notification (Class I) Pre-market registration (Class II+)	Standard market clearance/approval: Pre-market notification (Class I) Pre-market registration (Class II+)

All information is highly generalized and will deviate from product to product.

Table 3.
Personalized medical device classification and regulatory requirements.

where it is unfeasible to market the device or high specific conditions where no singular adaptive design envelope could realistically cover all facets of device. As a result of this distinctive product design and intended use, the manufacturing process is often unique in its entirety. Curiously the definition extends from devices tailored toward patients to devices catering to the medical professionals treating the patient. Owing to its inherently flexible nature, AM processes are often involved in the production of these devices, foremost being custom-made orthopedic implants. To date most regulatory bodies have implemented special exemptions and requirements to allow the use of these devices, conceding that truly customized devices will have to be evaluated and accounted for outside the general regulatory system. Annex IX [18] within the EU MDR has very clear requirements for CMDs, that a specific statement shall be prepared for all CMDs expressing key information, as well as other ancillary requirements. The EU MDR also states that Class III implantable "Custom-Made Medical Devices" shall additionally be subject to the typical conformity assessment. Meanwhile, the NMPA regulates CMDs less stringently, where "Custom-Made Medical Devices" are allowed for use after notification with key information is sent and acknowledged by regulatory authorities, with the precondition that the CMDs is to undergo standard market clearance and approval as soon as clinical data and feedback following the initial utilizations allow for the registration of the CMD (**Table 3**) [19, 20].

6. Conclusions

The demand for a customized medical device is at an all-time high. Thanks to the accuracy and variety of form and function to attain intended biomechanical function with adequate biocompatibility, AM-assisted fabrication has profound advantages in clinical flexibility. This work has demonstrated with examples a framework of AM-assisted fabrication of metallic medical devices serving intended clinical needs within a suitable time frame. The AM-assisted fabrication platform established is potentially utilizable with synthesized biomaterials and pharmaceutics [21]. Opportunities are gravitating to surgeons and researchers navigating to efficacious outcomes in clinical applications.

Acknowledgements

SYM acknowledges funding support from sponsored research RS 200263 at the University of Hong Kong.

DOI: http://dx.doi.org/10.5772/intechopen.101139

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