Present and future for technologies to develop patient-specific medical devices: a systematic review approach

Abstract: The main purpose of this investigation was to systematically review the literature regarding case studies on patient-specific implants and devices, with the goal of analyzing the process of developing custom-made medical devices. A content analysis was performed to identify design processes and methodologies implemented to develop devices such as implants adapted to bone geometries. Reverse engineering, computer-aided design, simulation of assets, and rapid prototyping technologies were selected according to their interoperability in a process framework for developing new products. Finally, results from the case studies and process stages identified in the consulted research were analyzed. These results showed a relationship between the scope and complexity of the process and the stage of technology integration of the patient-specific device development. The analyzed case studies were characterized by technical, scientific, and multidisciplinary components to achieve research goals. Likewise, integration of technologies using patient-specific technologies is needed for product development that converges into designing devices, such as implants, biomodels, and cutting drilling guides.

Keywords: customized implants, virtual planning, integration of CAx technologies, technologies for patient-specific medical devices

Introduction

Currently, orthopedic research and development studies highlight investigations into the design and manufacturing of patient-specific implants (PSI), also called patient-specific devices (PSD). Such implants or devices provide an effective and precise method for the treatment of a bone fracture or several defects like oncological or congenital malformation.1–4 PSDs are designed to be adapted to bone geometry, according to the fracture type to be stabilized.5 This concept arose from advances in technology and systems integration, allowing the generation of new design methods. The inclusion of the imaging techniques used in reverse engineering (RE) for the 3D virtual reconstruction of reference models or biomodels of living tissues has been proposed.6 Those tools are sometimes called BIOCAD5 or, more traditionally, Computer-Aided Design (CAD).7

Results from this technology have been integrated into other software tools used in the design and development of PSDs.8 The PSD model is often adapted to 3D bone geometry. The mechanical behavior of the resulting devices can be evaluated by the finite element method (FEM) using Computer-Aided Engineering (CAE).9
Some design methods include a visualization phase where a physical model is manufactured by rapid prototyping (RP) for additive manufacturing (AM) or machining by computer numerical control by computer-aided manufacturing (CAM) using subtractive manufacturing (SM).\textsuperscript{10} These tools can be configured in an architecture that supports PSD design and production processes. Specific conditions are needed to design a precise implant in anatomical areas of complex geometry such as the skull, hip, or femur.\textsuperscript{11–13}

The current literature does not identify a marker to validate which technologies should be integrated, or which technologies are the most appropriate for the design and development of PSDs to provide optimal treatment for specific patients.

Based on this, it is proposed to define phases of development for technology integration. This work was conducted by consulting research involving successfully implemented PSDs with known software architectures, convergences, and divergences. A systematic review of selected case studies may help identify trends and opportunities to improve the technologies used in developing these devices.

The present article details the materials and methods used in these studies, followed by a content analysis systematic literature review identifying common features related to the design and manufacturing processes, technologies involved in each stage of development, and associated reference practices. Later in the discussion, the results of the literature review are contrasted and analyzed. Finally, the conclusion gives an account of the literature review as support for understanding the integration of technologies in the development of PSDs.

### Materials and methods

In the first stage of the study, an exploratory literature review was carried out on the development of custom medical devices. Different keywords were identified such as BIOCAD, CAD/CAE, RP, CAM, diagnosis, virtual pre-planning, implant manufacturing, and PSD design and development. Research questions were defined relating to the process, technological resources, and results in PSD development, as illustrated in Figure 1.

The second stage of this study was to carry out a systematic review of bibliometric to survey relevant technologies. The ISI Web of Science database was searched from 2006–2018, applying the same criteria of quality, inclusion, and exclusion to the selected articles. Although WOS could be set since 2001, according to Meline\textsuperscript{103} a systematic review for contemporary studies could covered prior 10 years. The bibliometric review was run in 2018. The equation used is shown in Figure 2.

This search identified 394 articles. Duplicate articles were eliminated, as were articles with fewer than 10 citations. Abstracts were then read to identify papers with case studies involving the design of customized implants, highly complex surgical intervention, technologies for patient-specific devices applied to orthopedic surgery,

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*Figure 1* Research questions for exploratory literature review.

*Abbreviation: CAx, Computer-aided Tools.*
maxillofacial surgery, orthognathic surgery, and other technologies related to the development of PSDs. From this, 70 articles were selected. Despite time-period selected, seminal papers from 1998–2005 were 10%, from 2006–2010 were 20%, from 2011–2015 were 36%, and from 2016–2018 were 34%.

In a third stage, a content analysis of the selected scientific articles was carried out to understand the processes used, the tools used, the anatomical regions treated, and the obtained results from the identified case studies of PSDs using computer-aided tools (CAx) technologies. Finally, the bibliometric results were analyzed using the Tree of Science (ToS) web tool to understand trends.

**Results**
The selected papers were categorized according to main topics: technology integration models, and trend analysis. The main findings for each topic are given below.

**Technology integration models**
The integration of technologies was not explicitly expressed when searching for PSD design case studies. Nonetheless, the 70 documents were analyzed for this content. These studies addressed complex fractures caused by trauma, oncological, or congenital pathologies. The stage in the process of PSD design and manufacture was identified for each study. Also, each stage was associated with the application of a CAx software tool: RE or BIOCAD in virtual reconstruction, CAD in virtual pre-planning and modeling, CAE in simulation, and RP in 3D printing, or machining by CAM.

Each technology integration model could also be described by combinations of stages, ie, RE + CAD + CAE + RP and/or CAM, defining the scope of the technology development of each patient-specific device. Models with higher numbers of stages involve more technologies, with models possibly having up to 5...
technology types, BIOCAD + CAD + CAE + RP + CAM. In the equation below, it is observed that the combinatorial of these 5 elements “n,” without selecting repeated elements and with a restricted order, form groups “k” from a minimum of 2 to a maximum of 5 components, with up to 26 possible combinations.

\[ \sum \frac{n!}{(n-k)! k!} = 26 \]

A total of 8 applied integration models were identified. The model with the highest number of cases was the integration of BIOCAD + CAD + RP with a frequency of 38.6%, followed by the BIOCAD + CAD + CAE + RP model with 21.4% of cases. The BIOCAD + CAD + RP + CAM model accounted for 14.3% of cases, and the BIOCAD + CAD + CAE model accounted for 11.4% of cases.

The BIOCAD + RP model accounted for 7.1%, the CAD + CAE and BIOCAD + RP models accounted for 2.9% each, and the BIOCAD + CAD + CAM model represented only 1.4% of cases. Figure 3 shows the frequencies observed for each technology integration model.

The type of medical device or process was classified, according to the technology integration model implemented in each study. PSIs were the most explored products obtained by RP and CAM in the case studies, representing 62.9%. The biomodel was the next most studied, representing 41.4%. Surgical drilling or cutting guides were developed in 21.4% of the studies. The virtual and physical pre-planning carried out in CAD represented 25.7% and 24.3% of the studies, respectively. The least explored product was the FEM mechanical simulation associated with CAE, which represented 18.6% of the cases. These results are shown in Figure 4.

Some implementation patterns were identified. As evident in the matrix of correlations in Table 1, there is a strong incidence between the biomodel and physical simulation, implant, and surgical guide, physical simulation and implant, and virtual preplanning with a surgical guide, among high values of 0.75–0.99. A moderate correlation was observed for values of 0.40–0.74, between biomodel and surgical preplanning, physical simulation and FEM analysis, virtual preplanning and implant, FEM analysis and implant, and implant with cutting guide. A low correlation was observed with values close to 0, between biomodel and FEM analysis, physical simulation and virtual preplanning, and physical simulation with cutting guide. Negative values have revealed an inverse relationship between virtual pre-planning with FEM analysis, and FEM analysis with the use of cutting guides.

The analysis by anatomical regions studied for the development of custom medical devices yielded 93 case studies reported from the 70 articles analyzed. Of the cases, 57% were related to reconstructive surgeries of the skull and face, while 43% were orthopedic surgery cases.

Papers were categorized according to the technology integration models, PSDs, and the anatomical regions studied, as shown in Table S1.

The regions with the highest number of case studies were the maxillofacial area, representing 32.3% of cases, and the skull vault, representing 17.2%. Pelvic fractures represented 12.9% and the femur represented 11.8% of the case studies. Case studies of the hands, feet, knee, and humerus were observed with less frequency. The data detailing the anatomical areas in the case studies are shown in Figure 5.
Integration of BIOCAD + CAD + CAE technologies was reported in 8 cases. In these cases, PSIs were designed and simulations were made for the treatment of maxillofacial, hip, skull, and femur fractures.

The integration of BIOCAD + CAD + CAE + RP was used in 15 cases. The authors focused on PSI design, simulating evaluation, and 3D printing. These cases included fractures in the skull, femur, maxillofacial area, and pelvis, as well as the knee, spine, hip, and the orbital area.

The integration of BIOCAD+CAD+RP was used in 27 cases. The authors described PSI and RP applications. In most cases, this integration was for fractures of the skull, maxillofacial region, and pelvis.

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Table 1 Correlation among specific medical devices. Stronger correlations were among 0.75–0.99; moderate correlations for 0.4–0.74; low correlations for values close to 0; and inverse correlations for negative values

|                      | Biomodel | Simulation using a biomodel | Virtual surgical preplanning | Simulation by finite element method | Implant | Surgical or drilling guide |
|----------------------|----------|-----------------------------|------------------------------|-------------------------------------|---------|----------------------------|
| Biomodel             | 1.00     |                             |                              |                                     |         |                            |
| Simulation using a biomodel | 0.84     | 1.00                        |                              |                                     |         |                            |
| Virtual surgical preplanning | 0.66     | 0.20                        | 1.00                         |                                     |         |                            |
| Simulation by finite element method | 0.21     | 0.57                        | -0.27                        | 1.00                                |         |                            |
| Implant              | 0.85     | 0.86                        | 0.46                         | 0.52                                | 1.00    |                            |
| Surgical or drilling guide | 0.78     | 0.34                        | 0.91                         | -0.31                               | 0.57    | 1.00                       |
The integration of BIOCAD + CAD + RP + CAM was observed in 10 cases. These works focused on 3D printing of biomodels to perform diagnostics, visualize bone defects, and define the surgical approach for cases on the skull and orbital area. In the maxillofacial cases, PSD design was required. Finally, a single implant case for the humerus was identified that used the integration model BIOCAD + CAD + CAM.

**Trend analysis**

The ToS web tool allowed citations from the scientific articles to be analyzed, classifying them as classic documents (root), structural documents (trunk), and trend documents (leaves). The trend articles obtained by ToS were analyzed using Nvivo V12 software. As shown in Figure 6, these papers predominantly use CAx software tools for product development.

The trend topics are associated with CAx technologies: data management and quality, product life-cycle management, project data management, human-machine interface, applications of technologies in industries, virtual-physical prototyping, manufacturing simulation, design education, and health applications. As shown in Figure 7, key issues were categorized and organized as a network of nodes.

This analysis provides evidence for strong interest in data integration for the development of digital products through editable files and collaborative work platforms.
connected to interfaces, and interpretation of data among geographically separated researchers. Also of interest was the realization of complex data simulations, monitoring, and control of the design and production phases in real time.\textsuperscript{71,72}

These technologies are anticipated to be used in the virtual prototyping of industrial factories, for virtual simulation of manufacturing, for training purposes, teleoperation,\textsuperscript{73,74} virtual immersion from open platforms,\textsuperscript{75} relocation of the productive chain, and industrial machinery.\textsuperscript{76}

In addition, research is being conducted into efforts to reduce computational requirements, to improve interoperability during FEM validations by multiple work teams,\textsuperscript{77} and the use of haptic interfaces during CAD/CAE activities.\textsuperscript{78}

AM is challenged to manufacture a final product, as well as to establish virtual and physical evaluation methods that enable the determination of the performance of manufactured parts.\textsuperscript{79}

Algorithms are being developed to optimize product design by reducing time and costs,\textsuperscript{80} to build decision models for knowledge management, decision making, and virtual verification in the development of complex pieces,\textsuperscript{81,82} to propose creative solutions between
interdisciplinary teams,\textsuperscript{83} and to work collaboratively with external groups that use different software during product development.\textsuperscript{72}

In the health sector, the documents indicated trends towards the use of CAx technologies for external cosmetic and functional implants of compromised body areas such as the nose\textsuperscript{84} and the ears.\textsuperscript{85}

Currently, methods for the direct manufacture of parts for orthopedic rehabilitation are being defined,\textsuperscript{86} optimizing workflows, timelines, and costs for implant development,\textsuperscript{39} craniostenosis correction,\textsuperscript{97} and mandible reconstruction.\textsuperscript{88}

Anthropometric predictive models are being developed for the estimation of cortical zones for FEM analysis,\textsuperscript{89} and for dental implants with precise drill guides.\textsuperscript{90} Strategies have been proposed to control the sources of error in RE such as imaging\textsuperscript{91} or by point cloud.\textsuperscript{92}

Collaborative work will be promoted through the development of open virtual design platforms, as stated by Castellano-Smith et al\textsuperscript{93} using the specific patient modeling method.

**Discussion**

**Advantages and disadvantages of technological integration**

From the RE + CAD + CAE + RP technologies, other types of personalized products have been generated, such as pre-operative devices adjusted to bone geometry.\textsuperscript{34,36,37,40–42,45,50,59,61,66,67,94–96} These researchers used common practices for product development such as bone reconstruction software and performing alignment and healthy bone symmetry operations on the affected area.

Design requirements were defined based on pre-planning and manufacturing devices with medical grade resin acceptable for final use. PSI models can be created to adjust the shape, geometry, and topology of the device based on the patient’s needs, following surgical requirements.\textsuperscript{39,49,55,64,70} Another advantage was the application of CAx tools in surgical pre-planning, predicting bone fixation and reducing surgical risk, manufacturing time for PSD, and time for surgery.\textsuperscript{32,44,49,54,57,66,68,71,72,77,102,107}
Implementing virtual technologies has advanced strategies such as participatory development, according to Peel et al., allowing multidisciplinary collaboration between clinical teams (dentists, surgeons, and orthopedists) and development teams (technical engineers and designers). This type of collaborative work has reduced the gap between user expectations and results and has allowed the manufacturing of complex devices.

On the other hand, some disadvantages of technology integration were also identified. Some authors claim that the integration of tools for rapid design and manufacture are economically sustainable, specifically identifying 3D printing as an accessible, accurate, and profitable resource. Other authors claim that barriers such as the high cost of 3D printing and increased manufacturing time will keep the implementation of these technologies low.

Problems were also identified related to preoperative explorations, data transfer, and segmentation, decision making for PSD fabrication, and mistakes in pre-planning that cause irreversible effects on the patient. 3D printed models are not yet suitable for some surgical procedures involving soft tissue anchors. Implementation of intraoperative navigation systems remains low due to their costs and the level of radiation exposure for both the patient and the medical team. Also, technical limitations for using specialized software cause surgeons to be dependent on external technicians.

Impact on the quality of patient care
PSD as a tool after virtual diagnosis provides greater treatment precision, while 3D printing helps both physician and patient plan and understand treatment through simulation. Biomodels and PSD are clinically justified as they reduce the complexity and improve the precision of diagnosis.

Alloplastic implants are a powerful tool for developing PSDs, especially when working with extensive or complex bone defects. The intraoperative adjustment of plates or meshes for fixation is minimized due to planning, facilitating fast and effective treatment of unilateral or bilateral defects and functional and aesthetic restoration. Surgeons and designers can also restore mechanical properties of bone and promote osseointegration, providing greater stability and minimizing patient risk due to the accelerated time for effective treatment.

Few complications have been reported during the post-operative period following neurosurgery, craniomaxillofacial surgery, orthopedic surgery, cardiothoracic surgery, and vascular surgery.

However, patients are exposed to high doses of ionizing radiation during imaging acquisition because of the use of computed tomography (CT) and cone-beam CT. These images are used to inform treatment, but the radiation may put a patient’s health at risk.

The benefits of pre-planning must be weighed against this risk, and children are particularly susceptible to the effects of radiation. Errors in setting cutting or drilling guides could also have negative functional and aesthetic effects on patients.

Benefits of technology for specialists
Patient-specific technologies (PSTs) facilitate the interpretation of CT images and reduce uncertainty in diagnosis and treatment. PSTs also improve fracture characterization and inform the surgical approach, from defining a preoperative plan to producing a final PSD.

Surgical time is reduced because the time spent on repetitive plate fixation adjustments is eliminated or decreased. The use of PSTs allows less experienced surgeons to acquire practical skills safely with less training time.

PSDs are useful in complex and difficult cases, or in cases with a high risk of complications and unfavorable sequelae for the patient. Digital and physical resources can improve data visualization during surgery, and surgical pre-planning expands the utility of intraoperative navigation devices.

Although some experienced surgeons prefer manual techniques for conventional surgical pre-planning, this can result in clinical failures or poor margin resection. In these cases, surgeons may rely more on their own technical skills than on technologies because the technologies are outside their field of expertise. Increasing the adoption of PSDs depends on specialist criteria and the availability of technology.

Regarding the quality of the product, important factors included the simplicity of piece positioning, the ease of alignment, surgical guide safety to improve cutting accuracy, and continuous and symmetrical bone restoration results.

The accuracy of position, inclination, and depth of fixation holes and osteotomies compare favorably with those achieved using conventional techniques, reducing collateral damage to nerves and adjacent organs.
The impact on cost-effectiveness for the health system

Various authors stated that certainty in the surgical procedure would reduce the cost and time of treatment, decreasing the risks of infections or adverse outcomes.\textsuperscript{2,3,4,5} Decreased surgery time would improve the quality of the intervention and make the procedure more profitable.\textsuperscript{3,7,39,41,48}

The need for specialized software and hardware to support PSD development requires additional personnel with technical skills in design and product development.\textsuperscript{37} Because these tools require high financial investment for a health care institution, their availability in hospital units is limited and they are more commonly found in laboratories and universities.\textsuperscript{39}

The consulted papers rarely analyzed the cost-benefit of these technologies. While the decreased time and cost was mentioned in most of the documents, few compared these technologies with conventional techniques. This type of information is essential to determine whether the use of these techniques can become the standard of care during treatment requiring complex surgery.\textsuperscript{37}

Reconstruction planning software and RP technologies are crucial for the design and development of PSDs such as PSIs, guides, and biomodels. Still, this software and technology is relatively expensive, laborious, and multidisciplinary, requiring investment in infrastructure, regulatory compliance, training, and planning time.\textsuperscript{39}

Marketing challenges

CAx in the surgical field can help specialists plan and perform safe, reliable, and precise surgical procedures,\textsuperscript{10,41,56} but the medical sector must diversify its value proposition through the development of new products, services, and processes.\textsuperscript{57} Enabling development units based on PSTs in remote health facilities could create new business models, decrease technological dependence,\textsuperscript{35,41} and decrease response and delivery times.\textsuperscript{37}

Adapting 3D printing for rapid response times and integrating it into standard care protocols could create a new paradigm in surgical planning,\textsuperscript{10,22,38,41} guaranteeing multidisciplinary collaboration between engineering and clinical specialties.\textsuperscript{37,39}

Universal implementation of 3D printing depends on the advancement of the technology, availability of freeware resources, and familiarity of surgeons, designers, and engineers with the technique.\textsuperscript{56} However, anticipating the demand or number of cases that could use this technique over a certain time period is a complex task.\textsuperscript{3} Despite the recognized time savings and accuracy, there is still a lack of pedagogy to enable PST as a standardized approach.\textsuperscript{39}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Requirements for design and development of specific medical devices. \textsuperscript{39}\textsuperscript{3} \textit{Abbreviations:} BIOCAD, Biological Computer Aided Design; CT, Computed tomography.}
\end{figure}
A consensus in the field of PSTs

Of the analyzed studies, 80% used imaging or RE techniques. Fewer articles were identified that used methods to obtain virtual models, measurement references, or definition of contours by 3D sketching.12,49

CAD tools were used in 50% of the consulted studies, while only 38% of these studies carried out validations through CAE simulations. The physical prototypes used for diagnosis allow proposed solutions to be visualized and were analyzed in each case study.

In the design phase, iterative verification was performed to understand deviations between surgical preplanning and the final results.2,5,10–13,18,20,21,23,24,30,33–35,39,41,44,45,48,49,51–53,55,56,58,62–64,66–70,94,95,99,100

The cases analyzed included implant prototypes developed with final materials such as titanium casting, poly-methylmethacrylate casting,46 computer numerical controlled machining of titanium alloy Ti6Al4V,13 Ti powder sintering using AM,1 and RP of polyether-ether-ketone.39

This analysis identified three basic requirements for the design, evaluation, and prototyping of customized medical devices. A conceptual map of the integration of technologies was outlined from the requirements and the possible design process and is shown in Figure 8.

Conclusion

The systematic literature review allowed us to understand the different technological integrations that researchers have adopted in the design and development of PSDs such as biomodels, surgical guides, and implants.

In 70 documents, 93 clinical case studies were identified that used interoperable technologies, including RE, CAD, evaluation by FEM simulation, CAE, and RP by AM, SM, or CAM. The analysis showed a relationship between the scope and complexity of the process, the number of stages in the process, and the integration of technologies defined during the process of new product development. The analyzed case studies used technical, scientific, and multidisciplinary strategies to achieve their proposed objectives.

Although there were 26 possible combinations of integration models, only 8 were identified in the literature. The most frequent was the BIOCAD + CAD + RP model which was used in 38.6% of cases, followed by the BIOCAD + CAD + CAE + RP model which was used in 21.4% of cases. This is evidence for the disuse of CAM tools for the manufacture of final devices, replaced in part by AM.

Although the trends indicated increased attention being paid to technologies for process management for data generated during collaborative work, different barriers remain for the incorporation of these technologies in product development related to the cost of resources. It is expected that the benefits of integrated technologies in the health sector will exceed their limitations and that these technologies will become common practice in the treatment of complex pathologies.

Abbreviations list

AM, Additive Manufacturing; BIOCAD, Biological Computer Aided Design; CAX, Computer-Aided Technologies; CAD, Computer-Aided Design; CAE, Computer-Aided Engineering; CAM, Computer-Aided Manufacturing; CT, Computed tomography; FEM, Finite Element Method; HMI, Human Machine interface; PDM, Product Data Management; PLM, Product Life-cycle Management; PSI, Patient-Specific Implant; PSD, Patient-Specific Devices; PST, Patient-Specific Technologies; RE, Reverse Engineering; RP, Rapid Prototyping; SM, Subtractive Manufacturing; ToS, Tree of Science.

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Author contributions

All authors contributed towards data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.
Disclosure
The authors report no conflicts of interest in the present work.

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## Table S1

Case studies categorized by Patient-specific Technology (PST), Patient-specific device (PSD), and anatomical zone

| Main author | Year of publication | PSD | Biomodel | Surgical or drilling guide | Surgical Preplanning | Virtual Simulation | Patient-specific implant (PSI) | Surgical or drilling guide | Surgical Preplanning | Virtual Simulation | Patient-specific implant (PSI) | Surgical or drilling guide | Surgical Preplanning | Virtual Simulation | Patient-specific implant (PSI) | Surgical or drilling guide | Surgical Preplanning | Virtual Simulation | Patient-specific implant (PSI) |
|-------------|---------------------|-----|----------|-----------------------------|---------------------|-----------------|---------------------------|-----------------------------|---------------------|-----------------|---------------------------|-----------------------------|---------------------|-----------------|---------------------------|-----------------------------|---------------------|-----------------|---------------------------|
| Senap1      | 2007                |     | CAD+CAE  | Biomechanical               |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Barone2     | 2016                |     | BIOCAD+RP |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Chul4       | 2017                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Owen5       | 2007                |     | BIOCAD+CAE |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Hu6         | 2011                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Deboisse7   | 2014                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Werner8     | 2000                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Baroc9      | 2017                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Ojeda10     | 2007                |     | BIOCAD+CAE |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Fegg11      | 2010                |     | BIOCAD+CAE |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Ammar12     | 2007                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Perestrello13| 2004               |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Mirkischke14| 2013                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Grizzi15    | 2008                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Thevenot16  | 2014                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Maudusdin17 | 2017                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Rush18      | 1998                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Heister19   | 2004                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Gibson20    | 2004                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Singh121    | 2007                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Dai22       | 2007                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| White23     | 2008                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Kuzcu24     | 2010                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Caiolo25    | 2010                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |
| Zhang26     | 2011                |     | BIOCAD   |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |                             |                     |                 |                           |

(Continued)
| PST integration | Main author | Year of publication | PSD | Simulation using a biomod | Virtual Surgical Preplanning | Simulation by finite element method (FEM) | Patient-specific implant (PSI) | Surgical or drilling guide | Number of cases — Anatomical Zone |
|-----------------|-------------|---------------------|-----|---------------------------|-----------------------------|------------------------------------------|-------------------------------|-----------------------------|-------------------------------|
|                 | Bagaria27    | 2011                |     |                           |                             |                                          |                               |                             | 1-Pelvis                     |
|                 | Mustafa28    | 2011                |     |                           |                             |                                          |                               |                             | 1-Orbital                    |
|                 | Soler29      | 2011                |     |                           |                             |                                          |                               |                             | 1-Skull                      |
|                 | Mazzoni30     | 2013                |     |                           |                             |                                          |                               |                             | 1-Maxillofacial               |
|                 | Rotaru31     | 2012                |     |                           |                             |                                          |                               |                             | 1-Skull                      |
|                 | Wang32       | 2012                |     |                           |                             |                                          |                               |                             | 1-Maxillofacial               |
|                 | Ma33         | 2012                |     |                           |                             |                                          |                               |                             | 1-Spine                      |
|                 | Du34         | 2013                |     |                           | I                           |                                          |                               |                             | 7-Maxillofacial              |
|                 | Merc35       | 2013                |     |                           | I                           |                                          | I                             |                             | 3-Knee/Femur/Pelvis          |
|                 | Mazzoni30     | 2013                |     |                           | I                           |                                          | I                             |                             | 3-Skull                      |
|                 | Starosolski36 | 2014               |     |                           | I                           |                                          | I                             |                             | 1-Maxillofacial              |
|                 | Cartraux37   | 2014                |     |                           | I                           |                                          | I                             |                             | 3-Skull                      |
|                 | Weijs38      | 2016                |     |                           | I                           |                                          | I                             |                             | 1-Maxillofacial              |
|                 | Peel39       | 2017                |     |                           | I                           |                                          | I                             |                             | 1-Pelvis                     |
|                 | Singhal40    | 2016                |     |                           | I                           |                                          | I                             |                             | 1-Knee/3-Hand-foot           |
|                 | Kalamaras41  | 2016                |     |                           | I                           |                                          | I                             |                             | 1-Hand-foot                  |
|                 | Schweizer42   | 2016                |     |                           | I                           |                                          | I                             |                             | 1-Skull                      |
|                 | Msallem43    | 2017                |     |                           | I                           |                                          | I                             |                             | 1-Spine                      |

(Continued)
### Table S1 (Continued).

| PST integration | Main author | Year of publication | Biomodel Simulation using a biomodel | Virtual Surgical Preplanning | Simulation by finite element method (FEM) | Patient-specific implant (PSI) | Surgical or drilling guide |
|------------------|-------------|---------------------|-------------------------------------|-------------------------------|------------------------------------------|-----------------------------|---------------------------|
| BIOCAD +CAD+CAE +RP | Hosni45 | 2000 | I | I | I | I | 1-Knee |
|                  | Sun46 | 2005 | | | | | I-Femur |
|                  | Harryson47 | 2008 | | | | | I-Femur |
|                  | Isaza48, 49 | 2008 | I | | | | I-Maxillofacial |
|                  | Kluess50 | 2009 | | | | | I-Pelvis |
|                  | Dhakshyani51 | 2012 | I | I | | | I-Pelvis |
|                  | Jun52 | 2010 | | | | | 1-Femur |
|                  | Parthasarathy53 | 2011 | | I | | | 1-Skull |
|                  | El Halabi54 | 2011 | | I | | | 1-Skull |
|                  | Yosibash55 | 2013 | | I | | | 1-Femur |
|                  | Iqbal56 | 2017 | I | | | | I-Pelvis |
|                  | Doerfler57 | 2017 | | I | | | 1-Orbital |
|                  | Provaggi58 | 2017 | | I | | | 1-Spine |
|                  | Malaya59 | 2016 | I | I | | | 1-Skull/1-Maxillofacial |
|                  | Borghi60 | 2017 | I | | | | 1-Skull |
| BIOCAD +CAD+RP+CAM | Rudman61 | 2011 | I | | | | 1-Orbital |
|                  | Kozakiewicz62 | 2013 | I | I | | | 1-Orbital |
|                  | Salm63 | 2012 | I | I | | | 1-Orbital |
|                  | Rohner64 | 2013 | I | | | | 1-Skull |
|                  | Kraeima65 | 2016 | | | I | | 3-Maxillofacial |
|                  | Suojanen66 | 2016 | | | I | | 1-Maxillofacial |
|                  | Probst67 | 2016 | I | I | | | 8-Maxillofacial |
|                  | Thor68 | 2016 | I | I | | | 1-Maxillofacial |
|                  | Peel69 | 2017 | | | | | 1-Skull/1-Orbital |
|                  | Maini70 | 2018 | | | | | |

**Abbreviations:** BIOCAD, Biological Computer-aided Design; CAD, Computer-aided Design; CAE, Computer-aided Engineering; CAM, Computer-aided Manufacturing; CAx, Computer-Aided Technologies; RP, Rapid Prototyping.
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