Clinical 3D Printing

New horizons in medical imaging and intervention

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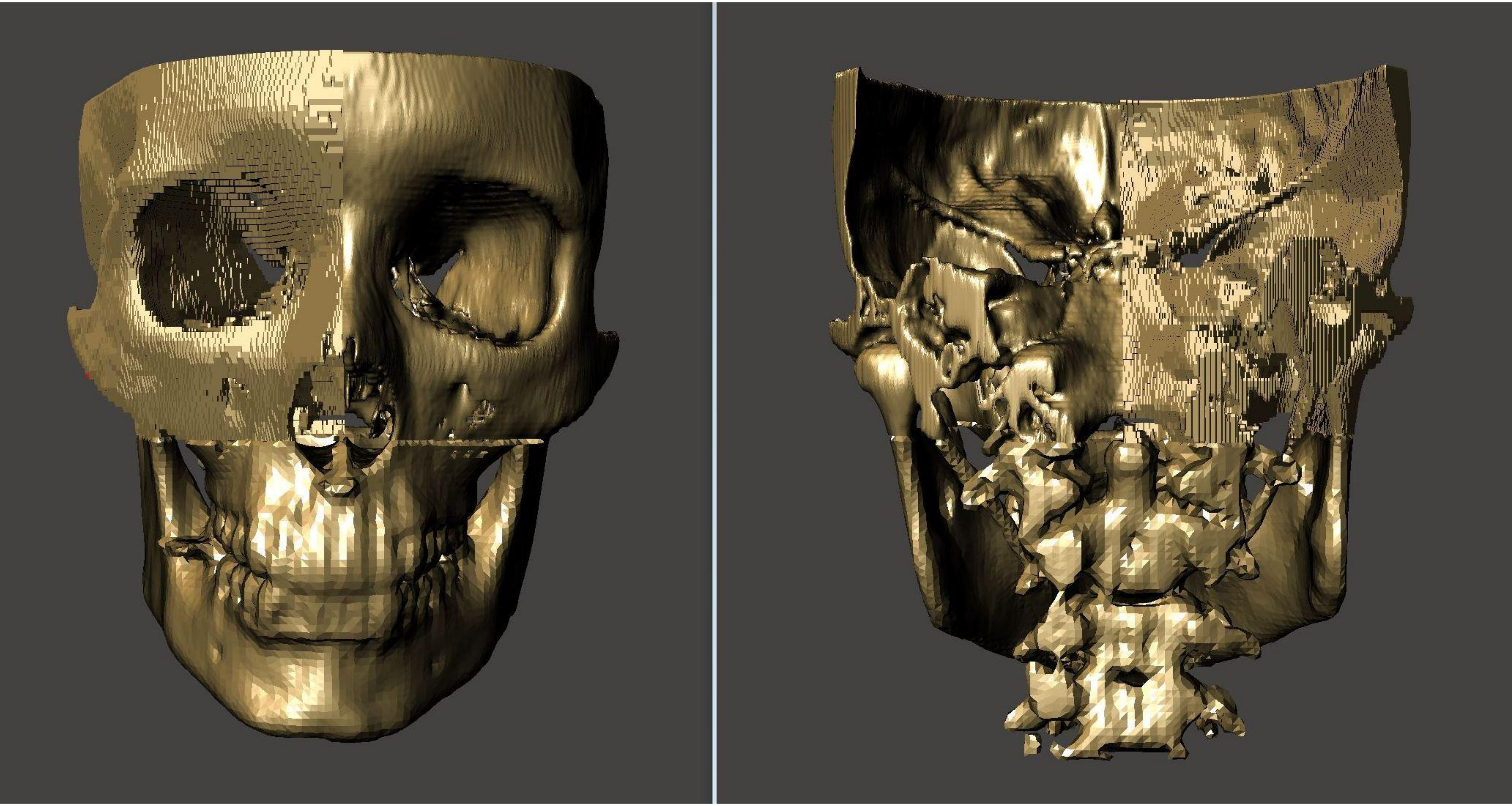
Nothing to disclose



Overview

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- Brief history 3D printing technology
  - Limited scope of most clinically relevant additive manufacturing technologies
- Relevant developments in medical imaging
  - Imaging technology
  - Image post-processing technology
- Multi-domain expertise
  - Concept of bridging expertise
- Regulatory challenges and reimbursement
  - FDA premarket clearance and exceptions
  - Intellectual property
  - Financial considerations
- Clinical applications
- Future directions

Brief History

Clinically relevant 3D printing technologies discussed:

Stereolithography (SLA)
Selective Laser Sintering (SLS)
Fused-deposition modeling (FDM)

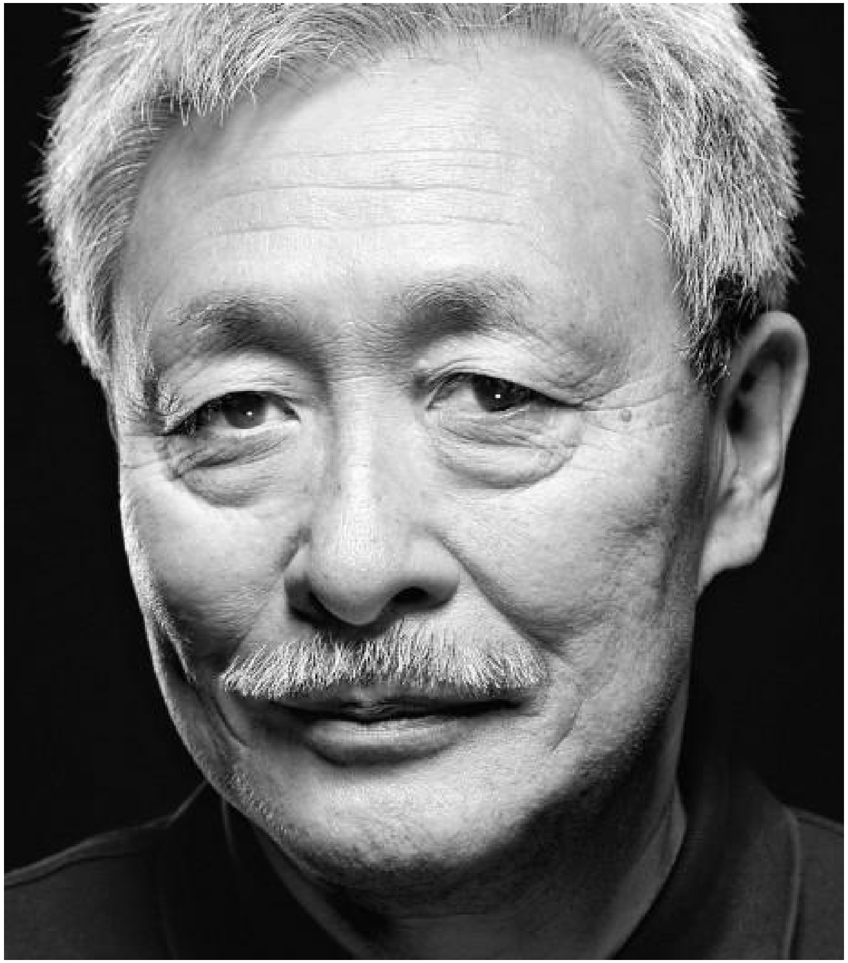
Not covered:

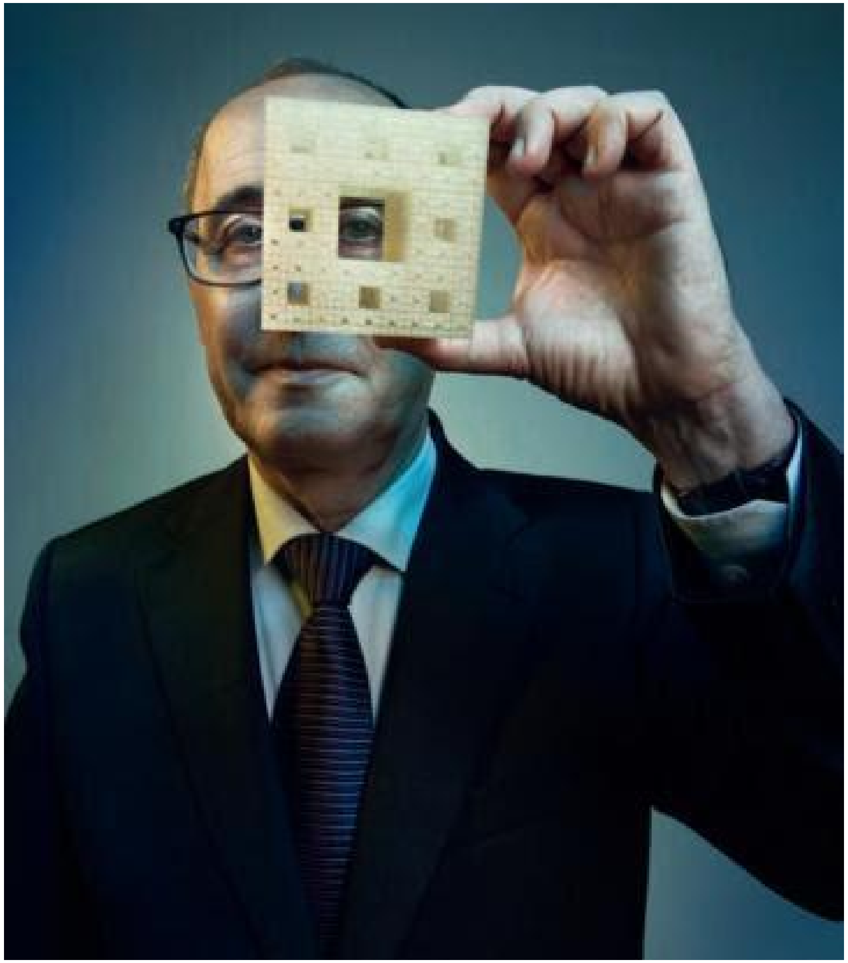
Material jetting
Binder jetting
Direct metal laser sintering
Electron beam melting
Laminated object manufacturing
Continuous liquid interface prod.
Other newer technologies

Brief History of 3D Printing

- **1970's** - Additive manufacturing in its nascency
- **1981** - Hideo Kodama of Nagoya Municipal Industrial Research Institute invents two methods to fabricate plastic models with photocurable polymers and UV exposure masks
- **1984** - Alain Le Méhauté, Olivier de Witte and Jean Claude André file patent for stereolithography (SLA) process, abandoned by French General Electric Company (now Alcatel-Alsthom and The Laser Consortium) for "lack of business perspective"
- **1984** - Chuck Hull of 3D Systems Corporation also files patent for a stereolithography process, establishes STL (STereoLithography) file format still in wide use
- **1986** - Carl Deckard and Joe Beaman of University of Texas file first commercialised patent for selective laser sintering (SLS) machine, form startup that will eventually become Desktop Manufacturing Corporation (DTM)
- **1989** - S. Scott Crump invents and patents fused deposition modeling (FDM) technology, co-founds Stratasys Ltd.

Brief History of 3D Printing





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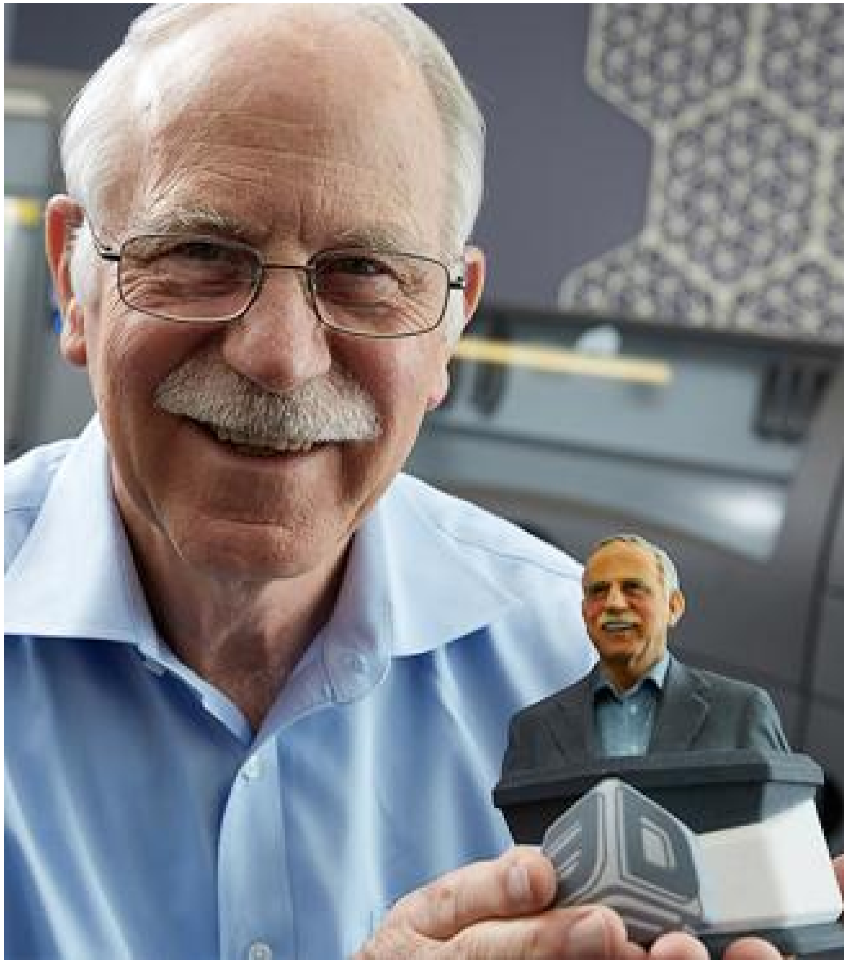

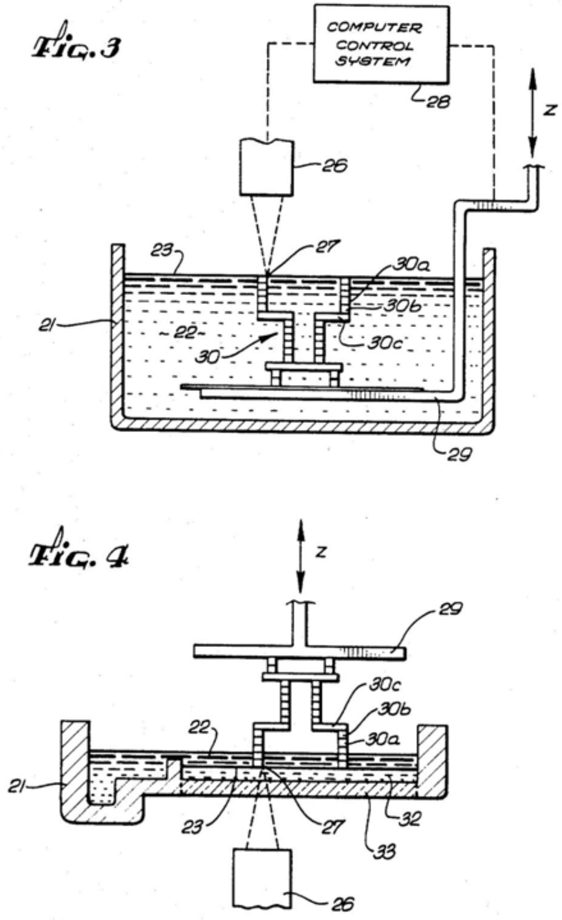

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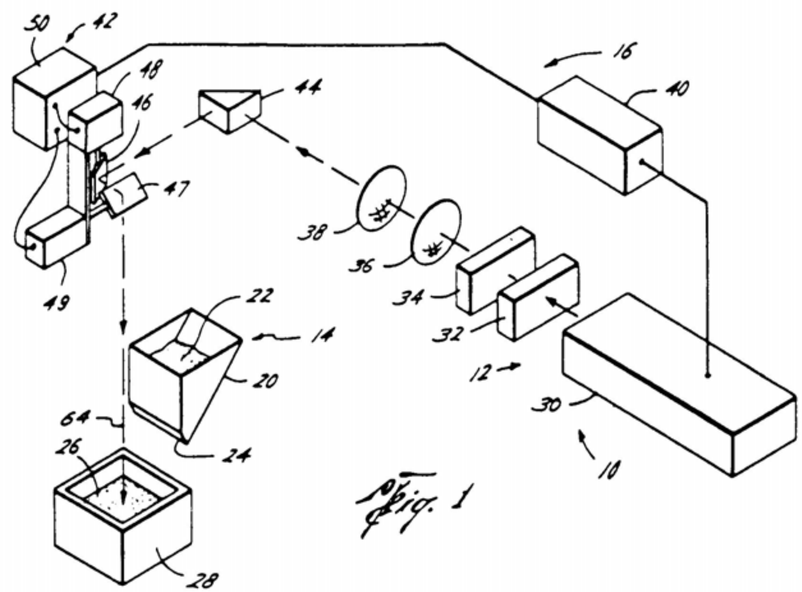

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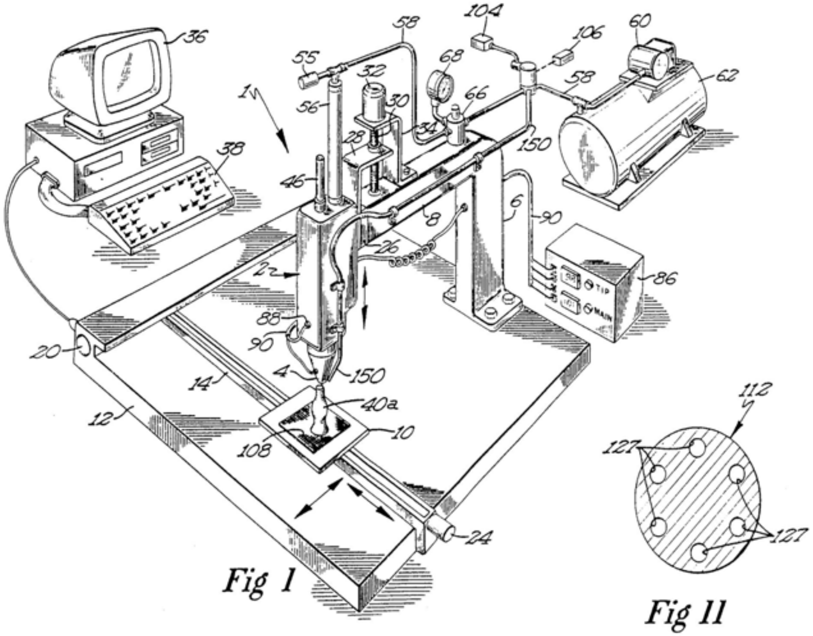

Brief History of 3D Printing

- **1990's** - 3D printing remains primarily an industrial manufacturing technology
- **2001** - 3D Systems acquires DTM and proprietary SLS technology
- **2005** - Dr. Adrian Bowyer of University of Bath (UK) begins developing affordable, open-source FDM printers under the RepRap project (REPlicating RAPid prototyper)
- **2009** - Original FDM patent assigned to Stratasys expires. Commercialized RepRap kits hit consumer market backed by active developer community
- **2012** - MIT-based Formlabs raises $2.9 million on Kickstarter to develop Form1, a desktop SLA 3D printer. 3D Systems files suit for patent infringement
- **2014** - 3D Systems vs Formlabs suit is dismissed with prejudice. Numerous SLS patents expire

Medical Imaging

Medical Imaging: Key Developments

- **1972** - Godfrey Hounsfield of EMI Lab invents computed tomography, receives Nobel Prize in 1979
- **1982** - PACS (Picture Archive and Communication System) initiative begins
  Digital storage cost is **~$650,000/GB**
- **1984** - FDA clears MRI for commercial use
- **1985** - Harvey Cline and William Lorensen of GE patent "marching cubes" algorithm for surface visualization of CT/MR data
- **1991** - Materialise releases Mimics, a popular commercial post-processing suite (currently a recurring $15,000 annual license)
  Digital storage cost is **~$3,500/GB**
- **1993** - The Visualization Toolkit (VTK) is created by Lorensen and fellow GE employees Will Schroeder and Ken Martin.

Medical Imaging: Key Developments

- **1998** - Kitware, Inc. is founded by VTK creators to maintain and contribute to further development of numerous open-source toolkits for image post-processing. 3D Slicer project begins as collaboration between BWH and MIT, with numerous federal funding sources including NIH, NCI, NSF, DOD.
  Digital storage cost is **~$63/GB**
- **2001** - Development of InVesalius begins at Brazilian Science and Technology Center to meet post-processing needs for individuals with severe facial deformities as an open-source platform
- **2005** - Marching cube's algorithm patent expires, enters public domain
- **2006** - First 256-slice CT scanner evaluated at Fujita Health University School of Medicine in Japan
  Digital storage cost is **~$0.63/GB**
- **2011** - 3D Slicer 4 is released, accumulating a decade's worth of application-specific open-source post-processing modules
  Digital storage cost stabilizes **~$0.03/GB**

Multi-domain Expertise

Multi-domain Expertise: Case Illustration

- Surgeon evaluates patient with Chiari malformation. Orders CT to evaluate bone stock and morphology. Planning for OR, thinks a physical model might help with procedural planning
- In-house route: can I request a 3D printed clinical model from my radiology department?
  - Typically, no. In the near future many departments may be able to facilitate 3D printing by providing a digital model suitable to be printed
- Outsource route: can I afford a 3D printed clinical model from a commercial vendor?
  - Inflated production costs, annual subscription and per-case consultation fees, +/- software licensing, physician time. HIPAA concern
  - Typically no input from medical imagers, limited to standard imaging protocols. Relying on engineers for anatomic accuracy, and to address DICOM issues such as artifact
- Self-help route: can I purchase my own 3D printer and make my own models?
  - Material science, image post-processing, and CAD modeling familiarity are not easily obtained without significant time and effort

Multi-domain Expertise: Key Players

- Clinical expertise:
  - Physicians
- Image acquisition expertise:
  - Radiologists, medical physicists, technologists
- Image post-processing/segmentation expertise:
  - Radiologists, technologists, R&D scientist (mathematics, computer vision, visualization)
- CAD modeling expertise:
  - Mechanical engineers (“solid modeling” CAD tools, Solidworks)
  - Graphic artists, animators, game developers (“surface modeling” CAD tools, ZBrush, Rhino3D, Blender)
- Fabrication expertise:
  - Industrial 3D printer manufacturers, commercial 3D printers, ?hobbyists

Multi-domain Expertise: The Reality

- Clinical applications of 3D printing introduce many new variables to industrial 3D modeling/printing workflows.
  - Industrial manufacturing need → CAD model → direct manufacturing
    - Engineer driven, engineering domain expertise
  - Clinical need → imaging → image post-processing → CAD modeling → fabrication → clinical use
    - Physician driven, multi-domain expertise:
      - Clinical assessment
      - Imaging anatomy and pathology
      - Advanced, non-traditional image acquisition protocols and post-processing
      - CAD modeling:
        - Unfamiliar to medical imagers
        - Unconventional for engineers and graphic artists
      - Fabrication (essentially unfamiliar to all healthcare providers)
      - Material science

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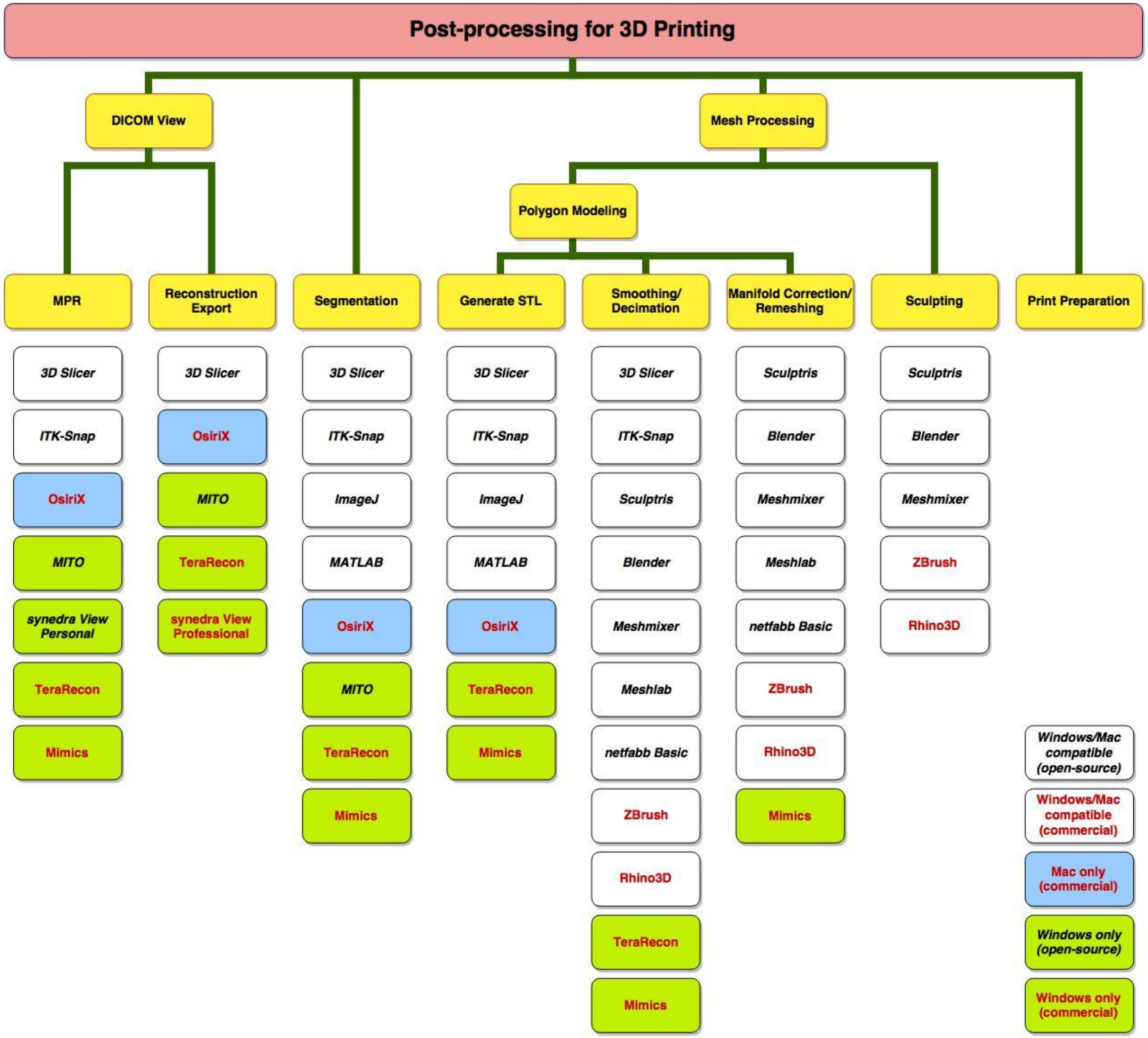
  - Bridging expertise desperately needed, shortest route is cross training existing medical imaging personnel

Multi-domain Expertise: Radiologist POV

- Logistically too complicated and prohibitively expensive to coordinate clinician, radiologist, technologist, engineer, and industrial 3D printing expertise for "routine" clinical 3D printing
- Need ***interdisciplinary teams*** of ***multidisciplinary individuals***
    - Clinicians familiar with technology and constraints
    - Modeling workflow leveraging existing medical imaging expertise
    - Fabrication arm familiar with clinical modeling needs
- **Core team** of medical imagers familiar with clinical/surgical considerations, non-traditional imaging protocols and post-processing tools, CAD modeling, and fabrication constraints
- **Extended team** of collaborating material scientists, engineers, and 3D printers familiar with clinical applications

Multi-domain Expertise: Radiologist POV

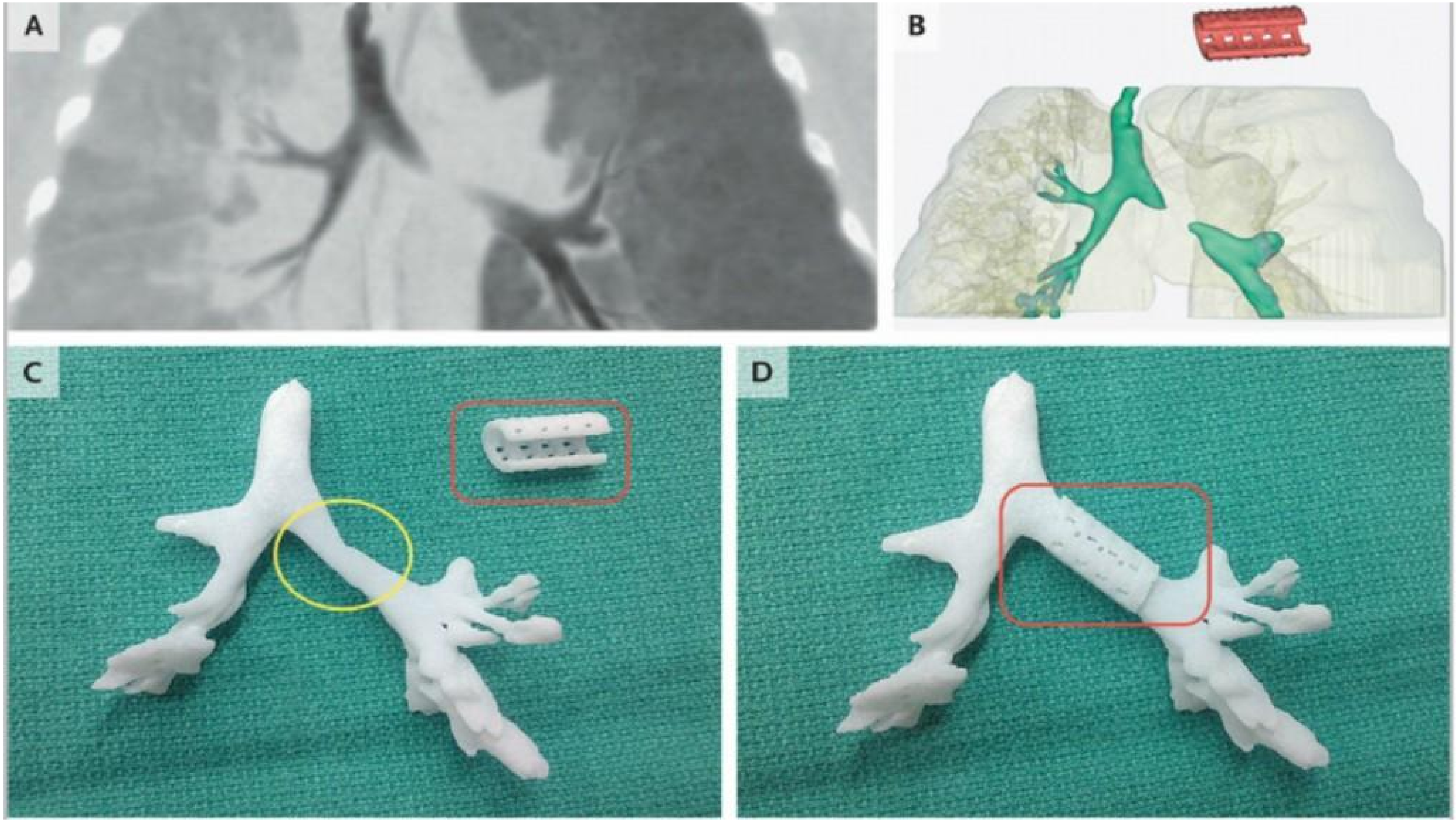


Regulation & Reimbursement

Current FDA Approval Process

- Many "traditional" manufacturers have already successfully applied for 510(k) clearance of 3D printed medical devices (almost all ortho/bone) or related technologies (e.g. post-processing software).
- Abbreviated pathways for FDA review of 3D printed devices:
  - **Emergency use**: FDA may allow physician to treat patient with unapproved device if physician concludes (i) patient has a life-threatening condition requiring immediate treatment, (ii) no generally acceptable alternative treatment exist, and (iii) because of immediate need no time to use existing FDA approval pathways.
  - **Custom device exemption**: Specific device needed is "created or modified in order to comply with the order of an individual physician...and is not generally available in the united States in finished form through labelling or advertising by the manufacturer or distributor, for commercial distribution."
  - **Compassionate use**: Requires prior FDA approval. Sponsor must submit Investigational Device Exemption supplement allowing the device to be used in a clinical study to collect safety and effectiveness data.

Current FDA Approval Process



Current FDA Approval Process

Unresolved FDA Issues

- Growth of “non-traditional” manufacturing sites such as hospitals, clinics, academic centers, which may not be under control of the 510(k)/PMA owner
    - Applicability of FDA Quality System Regulation/Good Manufacturing Practice requirements
    - Enforcement action when 3D printed devices are not manufactured under QS-compliant conditions
- Regulating services vs products. What defines a product?
- If an implanted 3D printed custom device malfunctions or fails, who is responsible? Supply chain is extensive with lots of players
- When is a 3D printed device considered an exempt “custom device?” Historically limited scope, but broad applicability to 3D printed devices
- Does a 3D model of someone’s face constitute identifiable patient data?
- Is a 3D model generated from patient data eligible for copyright protection?
- Active FDA public workshop forum engaging relevant stakeholders to establish federal guidance, but difficult to keep pace with development

Regulation & Reimbursement

- Intellectual property concerns may be overblown - a truly customized device is not immediately transferrable to a different patient with different anatomy.
- 20 year patents may be restricting development
  - Consumer 3D printing market has existed for ~5 years, characterized by extremely rapid growth beginning with expiration of patents
- The regulatory “looseness” of 510(k) clearance undermines the potential for reimbursement
  - FDA is concerned with safety and efficacy, insurers are focused on necessity and superiority over market competitors; 510(k) clearance establishes “substantial equivalence”
- Insurer requirement for FDA approval limits use of open-source software
- Active congressional lobby for 3D printing CPT codes, currently none exist
  - Track record of decreasing medical imaging reimbursement for over a decade
  - 3D reconstructions now bundled into extremity (bone) and vascular (angio) studies
  - Small opportunity to bill for 3D reconstructions applying existing CPT codes to studies without bundled 3D (non-angio, non-extremity imaging)
- Currently most clinical use-cases paid out of pocket by referring service or patients

Clinical Applications

Clinical Applications

- Education (patient/trainee)
- Training simulation
- Surgical planning / ex vivo evaluation
- Peri-/intra-operative tools*
- Implants/prosthetics*
- Bioprinting*

Clinical Applications: Cardiothoracic

Clinical Applications: Adult Cardiac

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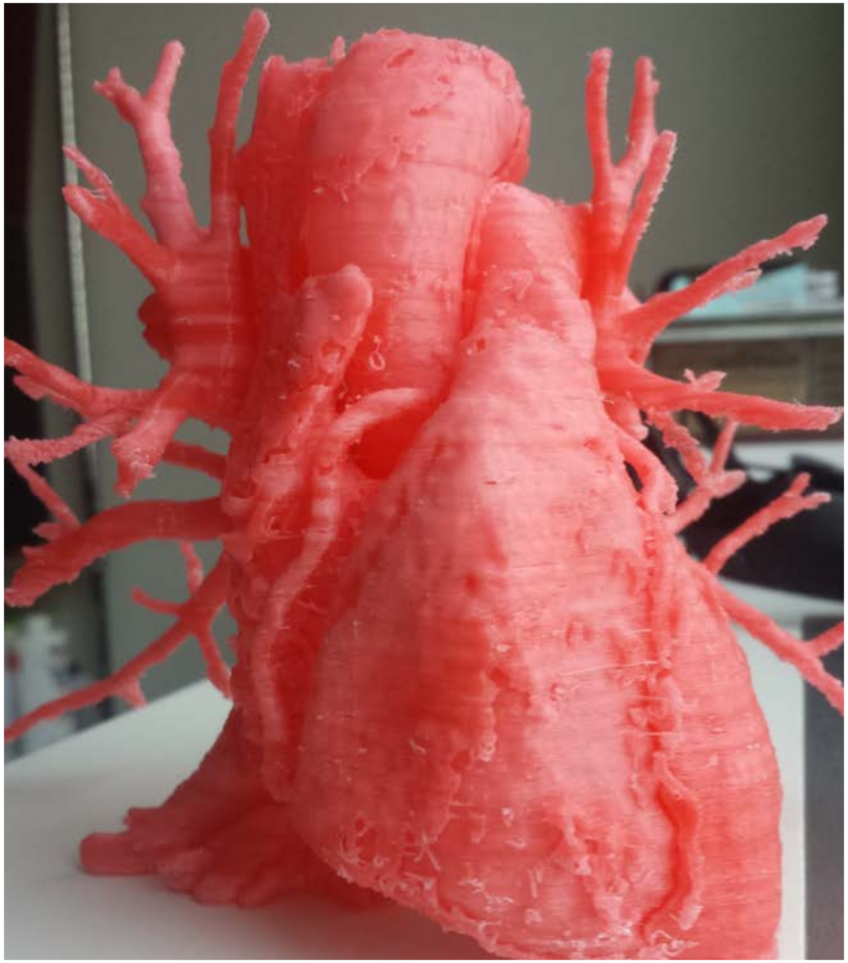

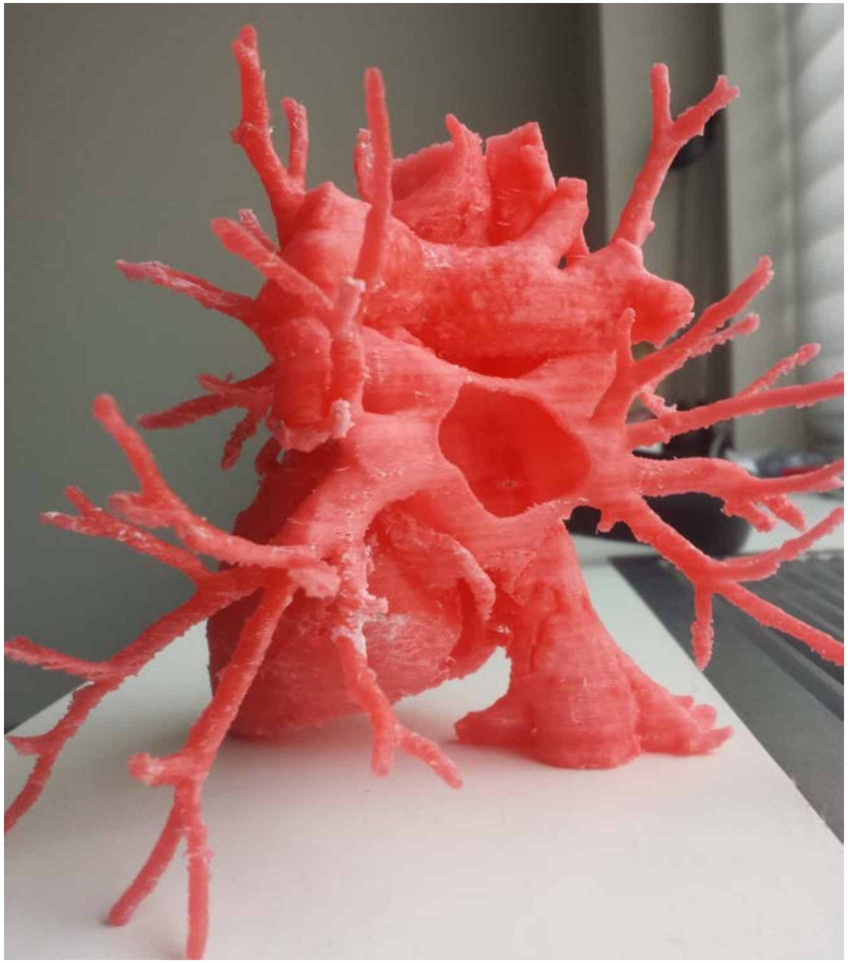

Clinical Applications: Congenital Cardiac

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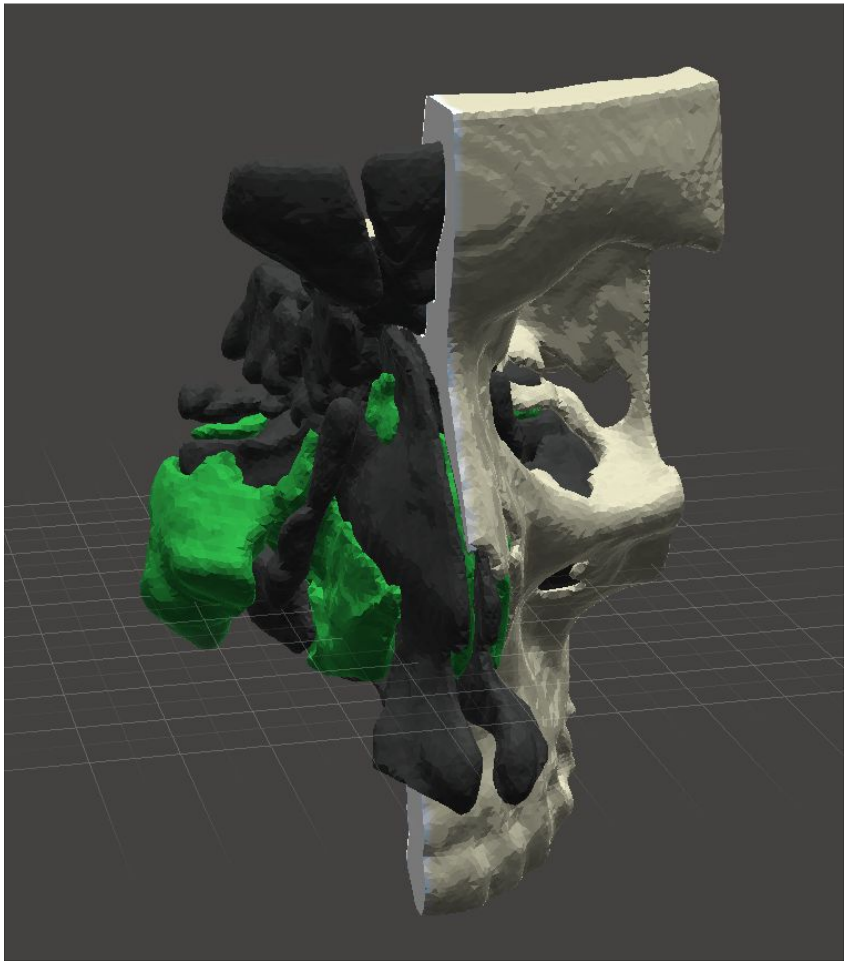
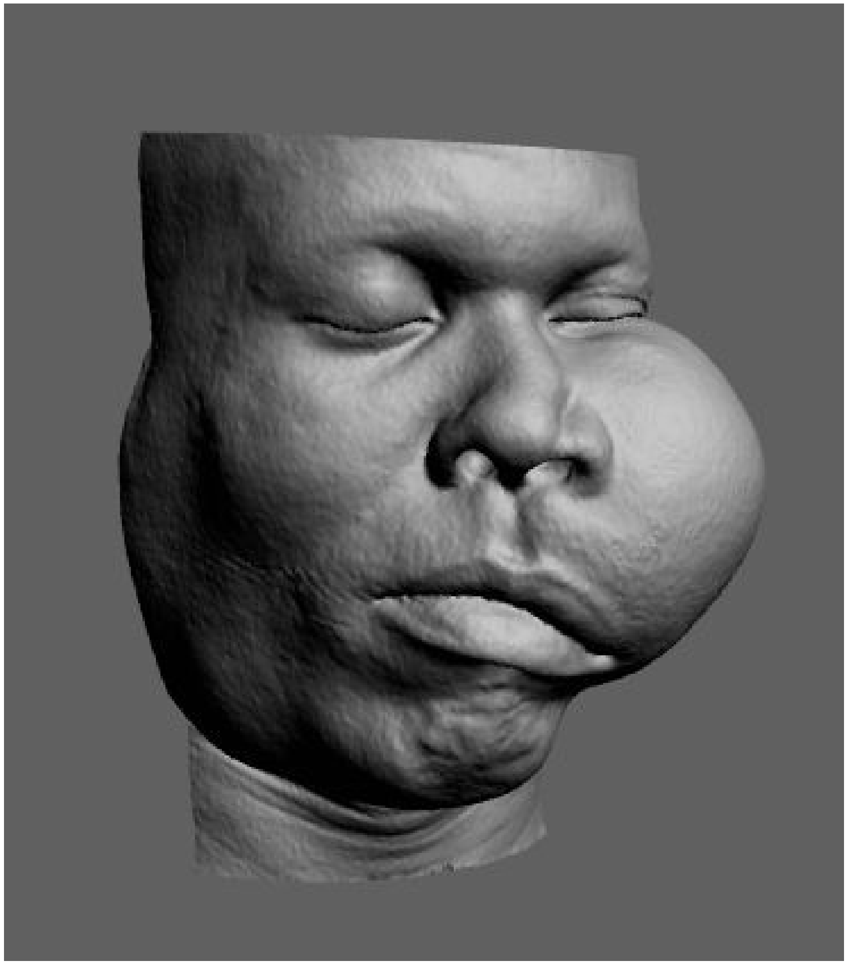
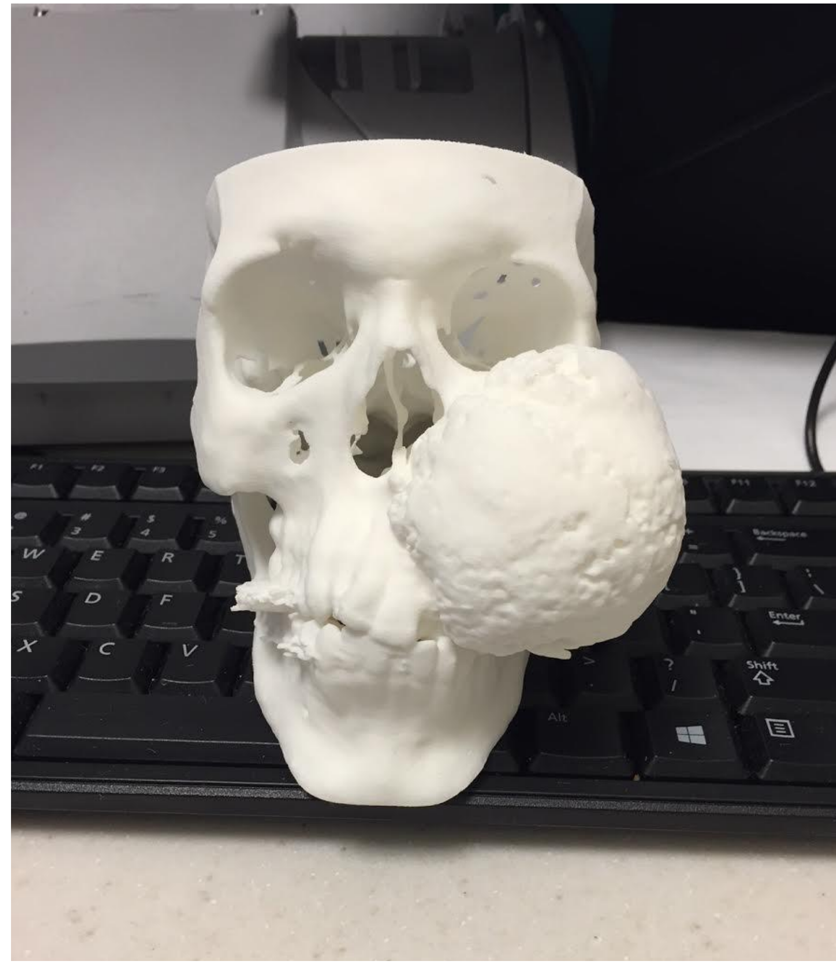
Clinical Applications: Otolaryngology

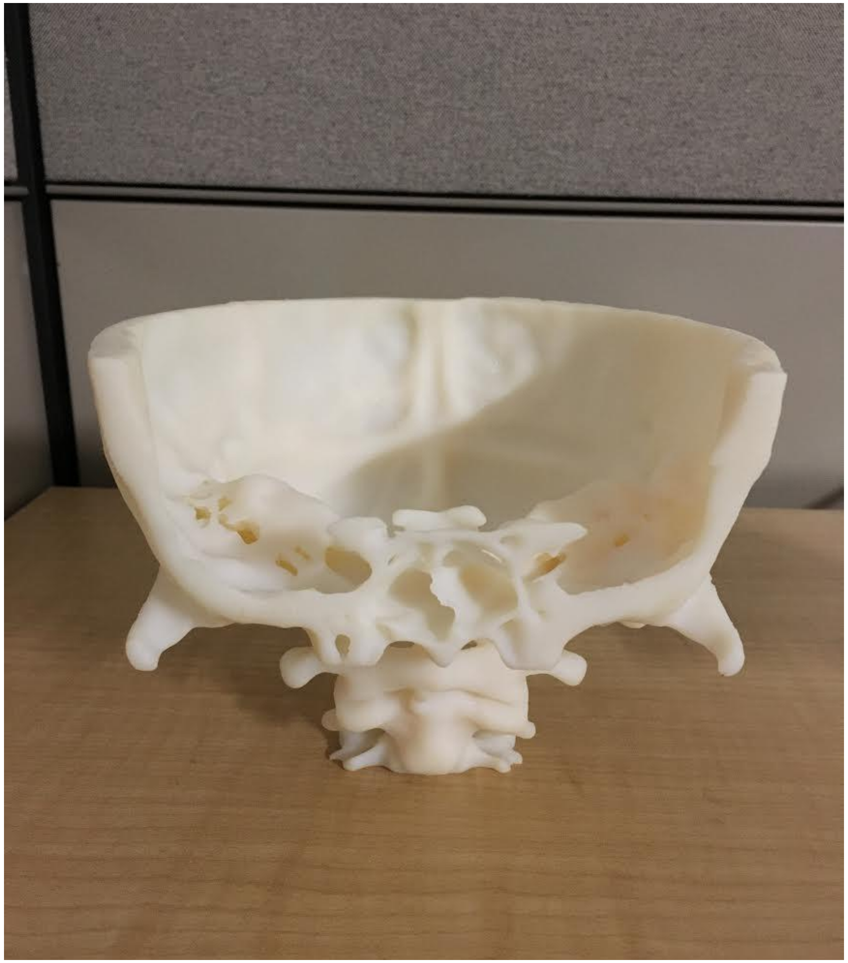


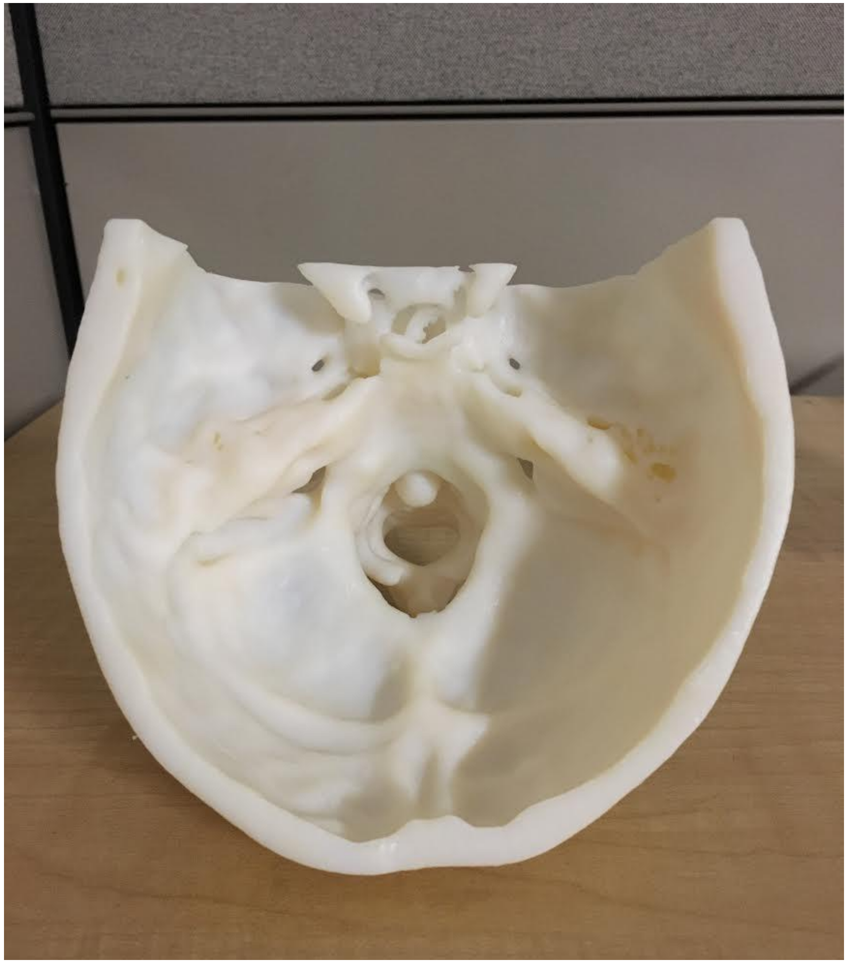
Clinical Applications: Otolaryngology





Clinical Applications: Pediatric NSG





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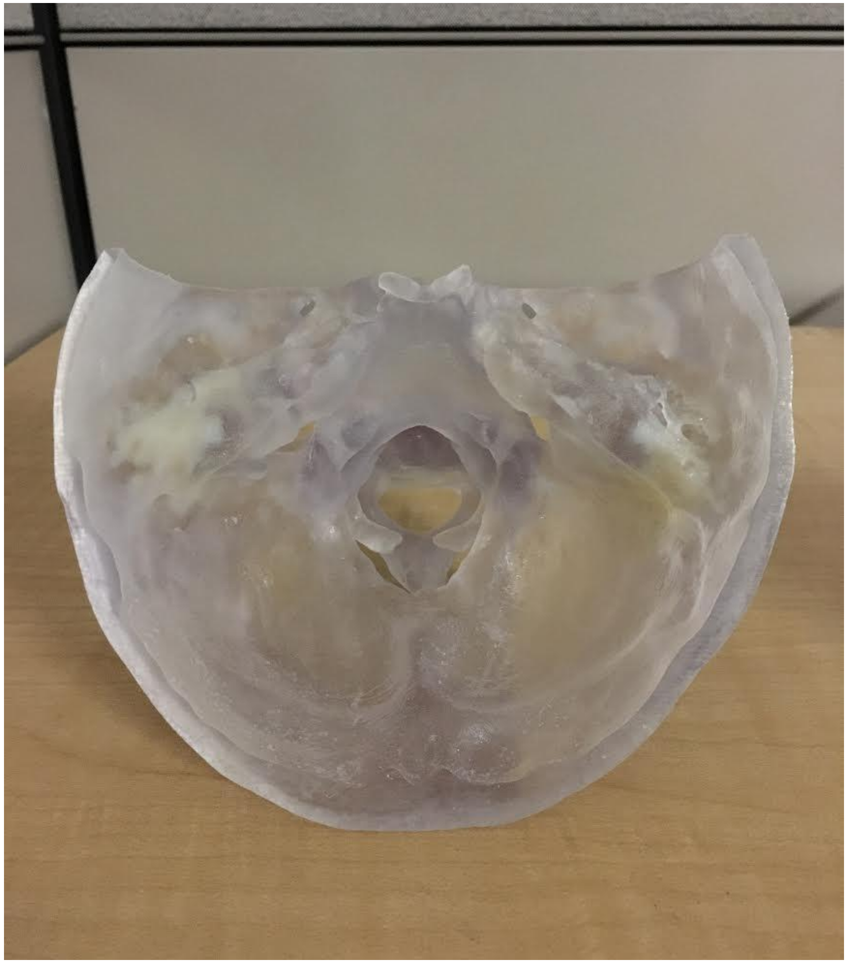

Clinical Applications: Pediatric NSG

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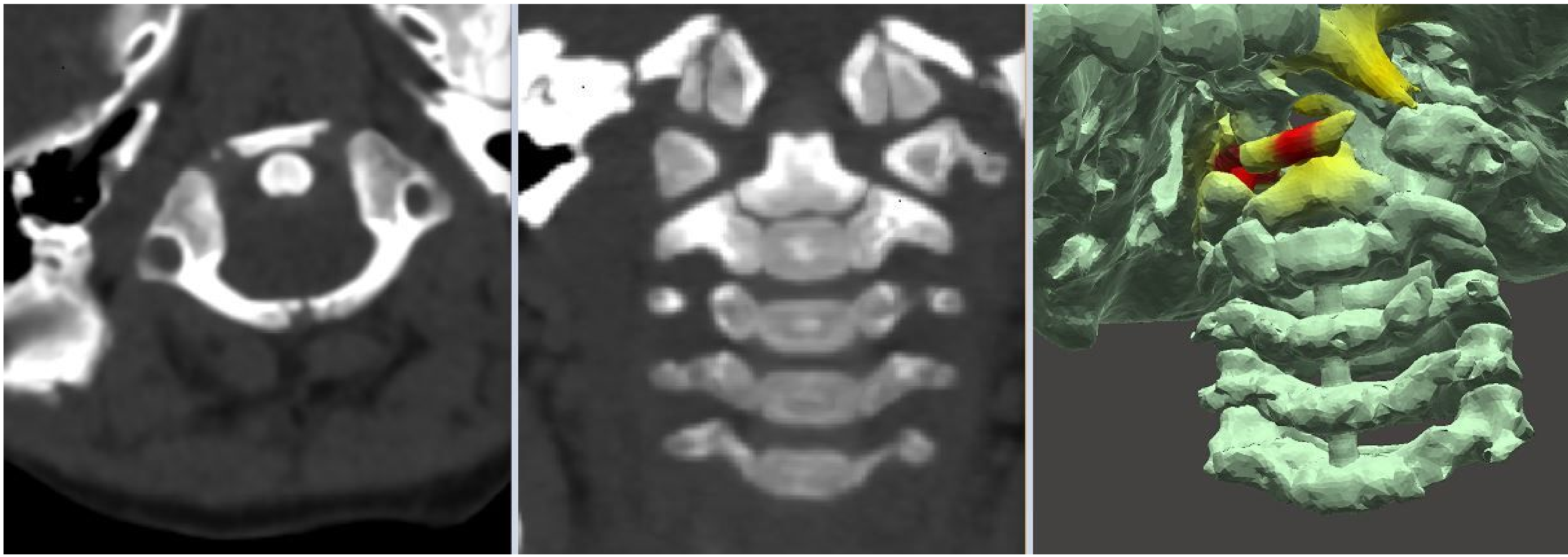
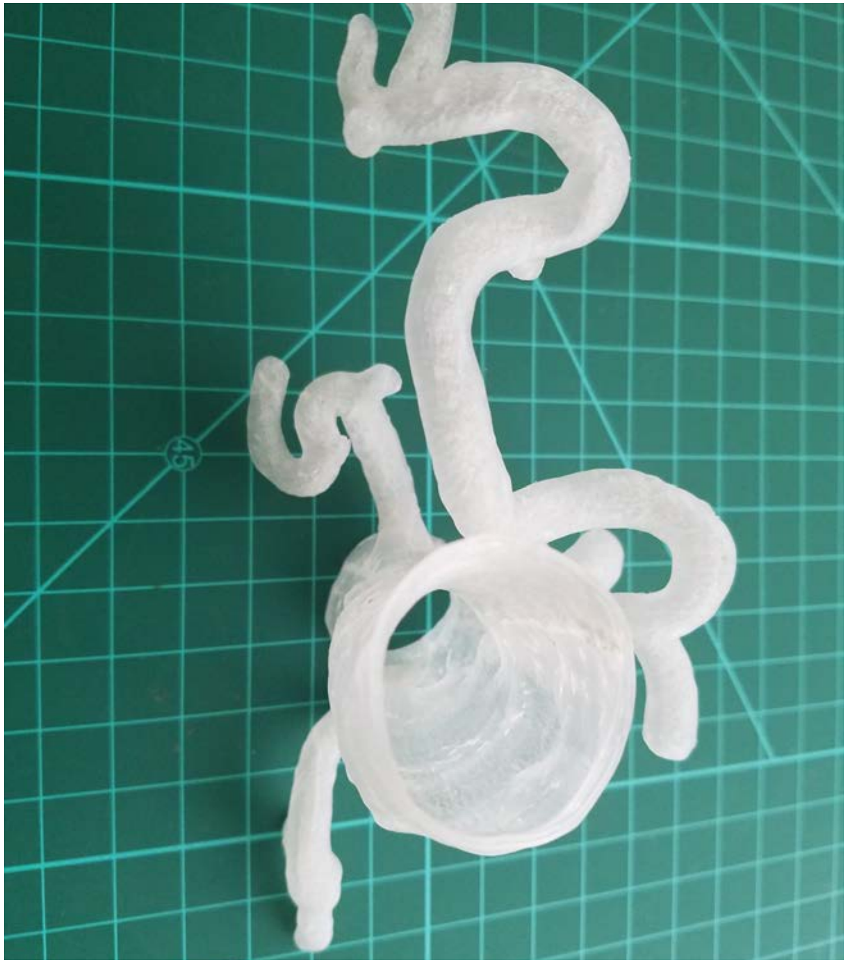


Clinical Applications: Vascular



Clinical Applications: Vascular

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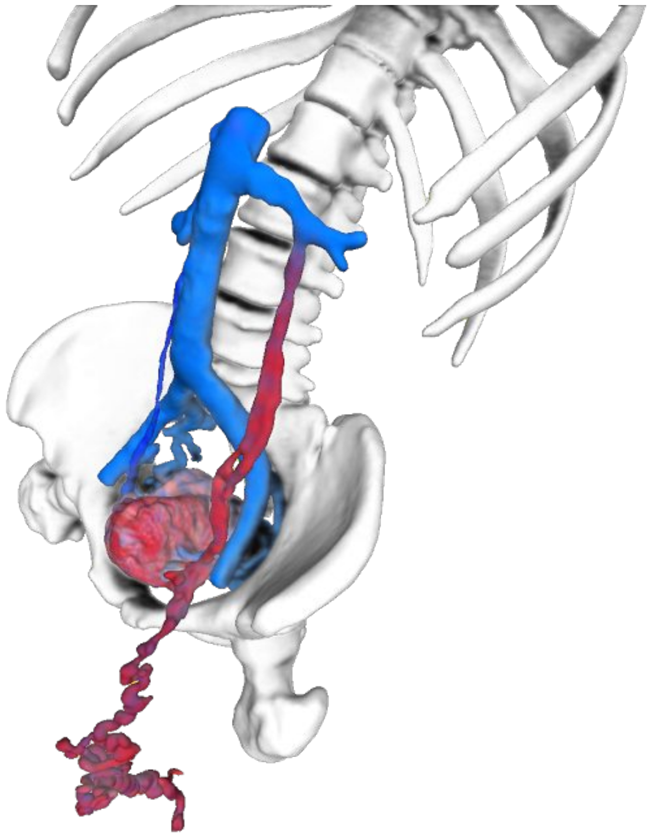

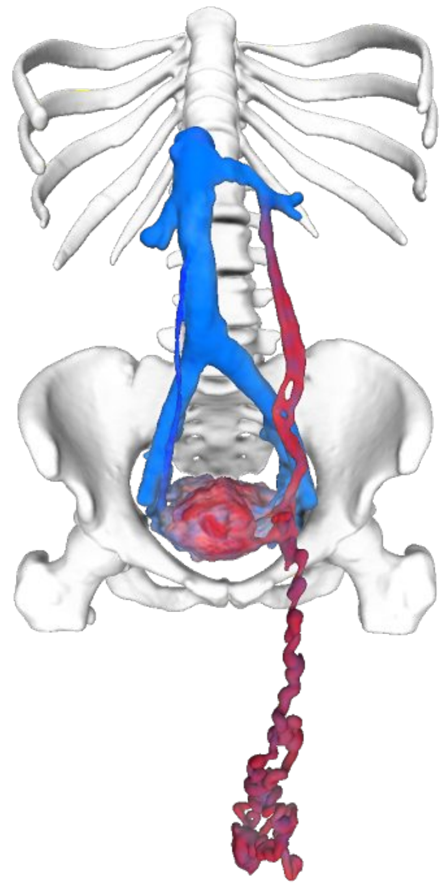

Clinical Applications: Orthopedic

Clinical Applications: Orthopedic

Clinical Applications: Orthopedic

Clinical Applications: Rehabilitation

Future Directions

Future Directions

- Despite reimbursement challenges, clinical 3D printing market is evolving and rapidly growing, projected $3bn industry by 2020.
- Open-source vs. commercial development
  - New bias towards open-source science, new incentives in an expensive commercial market with increasing federal support
  - Uncertainty in commercialization/market authorization/regulatory pathways also favor open-source development
  - 2nd wave open-source SLS 3D printers?
- Further development driven by multiple domains
  - Material science
    - Conductive/elastoresistive materials, meta-materials, “shape memory” materials
    - Novel sterilization/antiseptic methods
  - Imaging Science
    - Automated segmentation/imaging biomarkers
    - Computer vision
    - Medical photography, photogrammetry, LiDAR.
  - Tissue engineering
    - Durable scaffolds, less restrictive stem cell research
  - Changing education/training paradigms

Future Directions

- Custom cutting jig + endoprostheses as bone tumor standard of care
- On-demand custom joint replacement
- On-demand custom stent/graft
- Bioprinting:
  - Nascent science limited by structural inadequacy of current hydrogel scaffolds; holds incredible promise as an advanced synergy between clinical 3D printing and stem cell engineering
  - Soft tissue repair scaffolds/grafts
  - Direct autologous skin printing
  - Bone/cartilage defect repair (large animal trials underway in EU)
  - Micro vascularized tissue flaps
  - Genome-specific *ex vivo* disease and drug delivery models
  - Organ farming
  - Cyborg engineering?
- Outreach medicine:
  - Solar-powered 3D printing lab for on-demand surgical and clinical tools in remote settings
  - Low-cost functional prosthetics for children and adults in countries with historical legacy of unexploded ordnances (UXO) / explosive remnants of war (ERW)

Future Directions: Publications last month

State-of-the-art reconstruction of midface and facial deformities.

Chang EI, Hanasono MM.

J Surg Oncol. 2016 Jun;113(8):962-70. doi: 10.1002/jso.24150. Review.PMID:27226161

Radiology's Emerging Role in 3-D **Printing** Applications in Health Care.

Trace AP, Ortiz D, Deal A, Retrouvey M, Elzie C, Goodmurphy C, Morey J, Hawkins CM.

J Am Coll Radiol. 2016 May 26. pii: S1546-1440(16)30116-8. doi: 10.1016/j.jacr.2016.03.025. [Epub ahead of print] PMID: 27236288

3D Bioprinting for Vascularized Tissue Fabrication.

Richards D, Jia J, Yost M, Markwald R, Mei Y.

Ann Biomed Eng. 2016 May 26. [Epub ahead of print] PMID:27230253

MRI- and CT-Compatible Polymer Laryngoscope: A Step toward Image-Guided Transoral Surgery.

Paydarfar JA, Wu X, Halter RJ.

Otolaryngol Head Neck Surg. 2016 May 24. pii: 0194599816650176. [Epub ahead of print] No abstract available.PMID: 27221570

Cranioplasty Enhanced by Three-Dimensional **Printing**: Custom-Made Three-Dimensional-Printed Titanium Implants for Skull Defects.

Park EK, Lim JY, Yun IS, Kim JS, Woo SH, Kim DS, Shim KW.

J Craniofac Surg. 2016 May 17. [Epub ahead of print]. PMID: 27192643

"Three-Dimensional **Printing** in the Intestine".

Wengerter BC, Emre G, Park JY, Geibel J.

Clin Gastroenterol Hepatol. 2016 May 14. pii: S1542-3565(16)30193-8. doi: 10.1016/j.cgh.2016.05.008. [Epub ahead of print] Review. PMID: 27189913

3D Printing of Tissue Engineered Constructs for In Vitro Modeling of Disease Progression and Drug Screening.

Vanderburgh J, Sterling JA, Guelcher SA.

Ann Biomed Eng. 2016 May 11. [Epub ahead of print]. PMID:27169894

3D printing in orbital surgery: The next stage.

Malik HH, Hossain IT.

Orbit. 2016 Jun;35(3):163. doi: 10.1080/01676830.2016.1176054. Epub 2016 May 6. No abstract available. PMID: 27152987

3D Printed Modeling for Patient-Specific Mitral Valve Intervention: Repair With a Clip and a Plug.

Little SH, Vukicevic M, Avenatti E, Ramchandani M, Barker CM.

JACC Cardiovasc Interv. 2016 May 9;9(9):973-5. doi: 10.1016/j.jcin.2016.02.027. No abstract available. PMID:27151611.

Thanks for your attention!
Questions?