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In-silico patient-specific and patient-appropriate engineering method to judiciously select an ameliorative implant design in a single-patient using finite element-n-of-1 (fe-n-of-1) empirical test analysis to reconstruct mid-sagittal osteochondrotomy of the sternum following cardiac surgery

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Abstract

Introduction: No two patients have similar normal anatomy and physiology because of genetics, physical development, and age that same type of surgery and reconstruction implant will perform equally well. Such a notion demands the need for individualization of treatment and a method to select an ameliorative implant prospectively. One such empirically testing method is the finite element-n-of-1 (fe-n-of-1), where a treatment plan is executed specifically and systematically for a single patient as part of pre-operative planning.

Objective: It is to evaluate and discuss the method of finite element analysis to carry out the fe-n-of-1 empirical test in a fact-driven manner connecting various scientific domains. It presents a preliminary protocol on how to select an ameliorative implant to mitigate sternal instability due to suboptimal standard stainless-steel cerclage wiring to reconstruct the sternum following open-heart surgery.

Methodology: The instability following the reconstruction of the sternum is a mechanical problem therefore it is appropriate to apply harmless structural engineering methods to choose a suitable implant design to fix it. This exploratory descriptive research describes finite element n-of-1 empirical testing using in-silico engineering principles applied to patient-specific and patient-appropriate mechanical loading conditions.

Conclusion: Single-patient fe-n-of-1 empirical testing is a benign engineering method based on finite element modeling and finite element analysis. It is a safe mathematical evaluation free from subjective bias to select in advance the most ameliorative implant design to opt-out of the suboptimal stainless steel cerclage wire as a 'standard of care' and improve patient-based outcome and surgeon satisfaction.

Keywords: *Sternotomy, sternal dehiscence, finite element analysis, n-of-1 trial, implant design selection, patient-specific, and patient-appropriate medicine, cardiac surgery, open heart surgery*

1.0 Background

Technically mid-sagittal osteochondrotomy of the sternum (median sternotomy) is considered a simple and excellent approach to exposing the structures of the anterior and middle mediastinum(Dalton et al., 1992). However, following reconstruction of the cut sternum with Stainless-steel cerclage wire, numerous reports suggest an unchanging incidence of deep surgical wound infections, (0.3 to 8%, mostly 1-2%) since the 1970s (Balachandran et al., 2016; Culliford et al., 1976; Filsoufi et al., 2009; Goh, 2017; Loop et al., 1990; Perrault et al., 2018), leading to life-threatening mediastinitis. The unremitting incidence has largely been shown to be due to pre-existing co-morbidities and risk factors frequently associated with cardiovascular disease increasing the probability of deep surgical wound infection (DSWI). Whereas haemostasis and attention to reconstruction technique to maintain precise alignment and rigid closure of the sternum have been the mainstay for preventing DSWI(Allen et al., 2017; Baskett et al., 1999; Nazerali et al., 2014; Raman et al., 2012). In more than 80% of the cases, simple stainless-steel cerclage wiring is the current "standard of care." If there is an intra-operative fragility fracture or a higher risk of post-operative sternal instability, then at the time of wound closure, based on clinical judgment and the surgeon's choice of a complex weave to cage the sternum is chosen (Robicsek et al., 1977; Schimmer et al., 2006; Sharma et al., 2004). In the latest study, among 237 cases of sternal dehiscence the outstanding causes were **a)** breakage of stainless-steel wire in 18%, **b)** paramedian sternotomy with multiple fractures in 26%, **c)** multiple fractures in median sternotomy in 48%, **d)** failure of Robicsek parasternal weave in 6% and **e)** 3% of the cases had mediastinum abscess(Dell'Amore et al., 2020). The mortality rate in this cohort was 9.7%. Application of an external device to support the repaired sternum fashioned in the form of a vest(Caimmi et al., 2017; Gorlitzer et al., 2013; Klement & Herrmann, 2010) post-operatively is a reasonable option.

In the classical n-of-1 trial (N=1 study, a self-controlled and self-recorded trial) a single patient is an entire trial for treating chronic disorders. It is an experimental trial in which random allocation of experimental and control (generally a placebo) drugs are given to a blinded single patient to determine optimal treatment. Each patient serves as his/her control without exclusion and inclusion criteria such as gender, age, race, etc., and most importantly allows the inclusion of co-morbidities influencing the outcome of many treatments. Individualized studies can be challenging to do but they are the most patient-specific and patient-appropriate. The present study of finite element-n-of-1 (fe-n-of-1) empirical testing of surgical implants is similar but not identical to the classical n-of-1 trial. It is a single-patient trial, but the selected surgical implants are applied to a patient-specific quantized 3D virtual finite element model (FEM) for finite element analysis (FEA) of the divided sternum in a case going for open heart surgery. All the implants are tested concurrently on either the same modeled sternum or each implant is tested on a single sternal model separately. Multiple such models can be run in parallel simultaneously on one computer or multiple computers to perform finite element analysis (FEA) to establish the effectiveness of each implant under patient-specific and patient-appropriate conditions.

Finite element analysis has a longstanding history in engineering construction and orthopaedic implant testing and development before its introduction into surgical practice. A prospective population-based partially blind randomized-controlled trial can be designed to evaluate existing and new reconstruction implants against current "standard of care" stainless-steel cerclage wire as the control. However, it does not have the benefits of patient-specific variations and patient-appropriate medical co-morbidities in a patient of cardiac surgery. On the other hand, a well-structured finite element analysis has the potential to provide purely quantitative data on structural deformation, fatigue, and failure characteristics of a bone-implant construct with an easily measurable clinical endpoint within a short period for surgical application. A surgeon is often faced with uncertainty over the best implant choice from among many different implants. To resolve the dilemma of selecting the most ameliorative implant fe-n-of-1 empirical testing is a feasible option to examine several implants. This can be done in collaboration with a clinical biomechanical engineering team to evaluate various implants simultaneously based on the principles of finite element modeling and finite element analysis. These form the objectives of the study to introduce the concept of fe-n-of-1 empirical testing for the selection of the most ameliorative implant for reconstruction of the sternum following open heart surgery.

2.0 Influence of comorbidities, risk factors, and mechanism of sternal instability

The most common co-morbidities directly related to patients with cardiovascular disease are chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), renal disease, peripheral vascular disease, and previous myocardial infarction. The associated risk factors are tobacco smoking, high body mass index (BMI), steroid use, age-related osteoporosis, fragility fracture, and irradiation. Operative risk factors are bilateral thoracic artery transfer, duration of surgery, postoperative mechanical ventilation, and hyperglycaemia in non-diabetics that can account for increased likelihood of sternal instability, delayed union, DSWI, and dehiscence(Brunet et al., 1996; Filsoufi et al., 2009; Perrault et al., 2018).

The thorax is a closed pressured vessel and even a single episode of strong cough that raises the intrathoracic pressure to 300mmHg(Casha et al., 1999; Irwin RS, 2006) could produce sufficient lateral distraction force. Such force could untwist the cerclage wires and separate the sternal verges leading to the failure of the construct permanently. Patients with obesity and large breasts despite normal bone strength can develop notching of the sternum due to high implant-bone contact stresses and sterile instability, avulsion of sutures, and dehiscence of the skin wound due to persistent lateral and high distraction force at the xiphisternum, promoting ingress of epidermal bacterial flora. In diabetes mellitus with high BMI, compromised immunity and excessive dehiscence forces lead to impaired wound healing and, superficial wound infection can advance to DSWI. A combination of superficial wound infection and sternal instability due to technical failure can prove extremely detrimental in terms of outcome; and disheartening for both patient and surgeon.

The choice of an optimal implant for re-synthesis of the sternum in the presence of modifiable and non-modifiable co-morbidities, and the attended risk factors is still undecided. Depending on the strength of the osseous tissue of the sternum high lateral traction force can easily notch or even deeply cut through the osteoporotic bone, and rapidly cause loss of bone-implant interface. The instability of the sternum following osteochondrotomy is in part an iatrogenic complication; and a manageable mechanical issue. In this regard, carte blanche application of stainless-steel cerclage wire is less than ideal for a given patient under special circumstances. The goal should be to have a thorough clinical subjective and objective evaluation of the high-risk patients pre-operatively. Still, it may be easy to miss many cases that may have a high pre-test probability of success with Stainless-steel cerclage wiring techniques that may otherwise fail when put to finite element analysis (FEA) based on patient-specific bone

geometry and material properties; and subjected to patient-appropriate pathological conditions and mechanical forces, that constitutes the [1]patient-specific and patient-appropriate medicine(Gandhi, 2022b).

3. Designation of a single-patient

The cause and effect have combined power over disease at population and individual levels. However, the cause in the case of a single patient may be a specific risk factor with or without the concurrence of a significant co-morbidity that deserves individualized attention. How individuals respond to a risk factor is variable, and this variability is believed to be due to the innate variability of the biological organization. At the population level, the cause such as smoking can be remedied based on a prospective randomized controlled trial (RCT) to prevent the deleterious effect. In these studies, the statistical variations in scores around the mean can be widely scattered and when mathematically contracted further highlight the outliers. The inference of such streamlined trials is derived based on statistics of a well-defined cohort after filtering out all the undesirable randomness in the report. The facts of interest rather than the specific mechanism of cause and effect are considered that are applied to everyone. Traditionally, RCTs were designed to validate the evidence of drug efficiency(Sackett DL, Hayes RB, 1985). Therefore, in terms of patient management, an RCT simply provides relative superiority of one treatment over the other, generally a placebo, and does not introduce a "gold standard". It does not direct the physician on how to provide optimal treatment for a single patient.

There are clinical circumstances in surgical practice where the results of RCTs cannot be easily translated to an individual patient. The general biological processes are similar in all the individuals in a cohort when judged from patient-based outcomes. However, the individual response of the body is extremely variable at molecular, cellular, and tissue level. The surgical outcome of the same technique for the same class of disease can be greatly different due to genetic, gender, geographical, and social variations, as well as the surgeon's experience and skills. In the case of reconstruction of a fracture and an osteotomy, the outcome can be extremely variable due to geometry, material properties of the bone, implant design, and physical loading conditions. Therefore, it is reasonable to carry out an intervention such as finite element modeling (FEM) and FEA in a single patient at the pre-surgical stage that applies biomechanical conditions analogous to a single patient to evaluate effects relevant to patient-specific parameters and patient-appropriate clinical circumstances.

3.1 Is fe-n-of-1 trial patient-specific and patient-appropriate medicine?

The terms patient-specific and patient-appropriate medicine (see footnote) when applied to an individual are neither synonymous nor interchangeable(Gandhi, 2019b). On the other hand, the "single-patient" is a statistical term, which refers to the classical n-of-1 trial method(Hogben & Sim, 2011) where a treatment plan is specifically developed for a single patient that is appropriate only for that person. In-silico patient-specific engineering methods of FEM and FEA mathematical evaluations appertain to a definite region and particular area of the human anatomy within an organ system. Each anatomical segment under treatment is continuously affected by the entire patient's physiology and pathology, dynamic interior milieu, and external activities. It has specific characteristics such as surface features, geometric dimensions, bone mineral density, and bone material properties that are isolated for qualitative evaluation and quantitative numerical analysis at the finite level to acquire precise data in a definite manner to develop treatment strategies. It is the clinical application of the finite element technique to design a single-patient n-of-1 trial for structural failure and fatigue analysis of bone-implant composite which has been termed as finite element n-of-1 (fe-n-of-1) empirical testing during presurgical planning.

The fe-n-of-1 trial is a judicial examination of an individual patient to test the ultimate structural strength and fatiguability of different implants and the bone, effectively forming a biomechanical bone-implant composite structure. The fe-n-of-1 test run aims to determine the ameliorative relative value of more than one implant based on patient-specific morphometry of the segmented sternum. Including its biological characteristics such as finite level bone density based on image greyscale and computed tomography numbers (Hounsfield units). It will provide objective quantitative data-driven criteria to select the best possible implant design for the tested patient. The FEM and FEA become the best available virtual platform to extract analyzed qualitative and quantitative data for informed consent and real-life surgical intervention. The whole process of gathering clinical and mechanical

[1] The word *'specific'* refers to a precise anatomical location or an entire segment of a region or organ system, e.g., head of the humerus of the skeletal system, and *'appropriate'* means that something is suitable and favourable only for a single patient under special circumstances, including patient physique and multiple influential co-morbidities. A technique can only be called *'patient-specific'* if the collected set of data to which it is applied belongs to a specific anatomical section/segment of a bone as in the case of skeleton or a specific element of an organ for biomechanical evaluation and higher numerical analysis for clinical application rather than to the entire organ system of that individual. More importantly, it is done without the inclusion of any kind of extraneous experimental or population based statistical values to constitute *'patient-appropriate medicine'*.

data for the fe-n-of-1 empirical testing is a collaborative effort of the surgical and clinical biomechanical engineering team.

For a globally successful outcome of this demanding engineering intervention, all influential factors that can quantitatively affect patient-specific biomechanical parameters and FEM and finite element analysis must be carefully taken into consideration. A limited number of RCTs comparing two or more implants to reconstruct an osteochondrotomy of the sternum(Allen et al., 2017) and available systematic reviews and meta-analyses (Pinotti et al., 2018; Veeramachaneni, 2018) have failed to make definite patient-specific and patient-appropriate recommendation. Such trials do not expound the conjoint power of the cause and effect and bring forth mechanisms to improve single-patient outcomes. Hence, the in-silico mathematical evaluation of a single-patient fe-n-of-1 trial would hold greater scientific value based on patient-specific parameters and patient-appropriate pathophysiology.

4.0 Fe-n-of-1 trial – an approach to a single-patient management

Currently, the drifting paradigm of evidence-based medicine encompasses elements of clinical experience of the physician and patient preference/s to choose from the available options for treatment supported by the evidence generated based on recent research literature after critical appraisal, with or without clinical relevance. Pierre Simon Laplace (1814) put forward the idea that essentially all knowledge was uncertain and, therefore, probabilistic. On the other hand, Francois Double felt that the treatment of an individual was more important than knowing the outcome of what happens to groups of patients. The art of medicine was defined as deductions from experience and induction from physiologic mechanisms. These were felt to be more important than the "calculus of probability"(Mayer, 2010a). This kind of paradigm falls more into the setting of patient-specific and patient-appropriate medicine ideology.

The causes of sternal instability are numerous, but ultimately dependent on the reconstruction technique. Its accretion effect starting as superficial wound infection and ingress to deeper tissue can lead to mediastinitis with a mortality rate of up to 40%(Nazerali et al., 2014; Perrault et al., 2018). Although chance concurrence of sternal instability and DSWI is a random event, however, if a cause can be remedied, then the intensity of the effect may be significantly reduced for a better outcome. An individual following a successful coronary bypass surgery may experience immense physical and psychological suffering if the sternum fails to heal in time to carry out activities of daily living efficiently. This kind of poignant situation demands the search for management strategies to match individual biological variations. Akin to classical n-of-1 trial fe-n-of-1 empirical testing is one such methodology to mitigate some of the shortcomings of the current "standard of care" to reconstruct osteochondrotomy of the sternum. It can be applied for the management of any fracture and corrective osteotomy in orthopaedic and trauma surgery during pre-operative surgical planning.

4.1 In-silico mathematical evaluation and fe-n-of-1 concept

The classical n-of-1 trial is a clinical trial done like any other investigation, but with a single patient (Guyatt et al., 1986; Hogben L, 1953). Such a case study is not random but deliberate, well-intended, non-arbitrary, specific, and systematically performed to develop and carry out a treatment plan. The n-of-1 trial is considered an effective method to identify optimal treatment in patients in whom disease management is uncertain(Scuffham et al., 2010). In surgical practice, the same principle can be used during pre-surgical planning to explore treatment options directly under single-patient circumstances, where the etiology and management of a surgical complication such as sternal instability following cardiovascular surgery are unclear. As sternal instability is a mechanical issue, the in-silico engineering finite element technique of FEM and FEA is most suitable for applying patient-specific skeletal parameters and patient-appropriate mechanical forces expected to act on reconstructed verges of the sternum. It is a quasi-controlled intervention compared to real-world surgical reconstruction of the sternum. However, by following the results of such an intervention if the sternal instability can be prevented and the osteochondrotomy heals in a timely fashion like any other cortico-cancellous bone in the skeletal system, it would establish the effectiveness of the intervention. It would help to reinforce the surgeon's experience and guide in choosing the most ameliorative implant to overcome complications directly related to instability and delayed union of the sternum.

Finite element modeling and finite element analysis evaluations are safe, non-invasive, and free of placebo-effect without incurring any harm to the prospective patient like a drug selection and dosing during a classical n-of-1 trial. At the end of a fe-n-of-1 test run, it is still up to the operating surgeon to accept or reject the results based on surgical experience. Application of the stainless-steel cerclage wire in the figure-of-zero configuration being the current "standard of care" for a large majority of patients, it can act as a control and test implant in comparison to

other options. Unlike RCTs, fe-n-of-1 empirical testing like classical n-of-1 trials can be heterogeneous in design to match single-patient requirements, reduce computational cost in time and the results of the intervention are available within a short period. Initially, even if it does not demonstrate the order of occurrence of sternal instability and DSWI, in time a drop in the current rate and reduction in infection-related morbidity and mortality will demonstrate the overall cost-effectiveness of this engineering method.

The postoperative outcome as the hypothesis testing of the effectiveness of real-life implant application would retrospectively verify and validate the robustness of the intervention and the ameliorative capability of the chosen implant for each patient (auto-verification and validation). The patient-based surgical outcome in the presence of co-morbidities and patient-specific segmental anatomy ruling in and ruling out of the patient-specific test hypothesis would provide the [2]sensitivity and specificity of the fe-n-of-1 test results. Here sensitivity is the correct identification of the implant for acceptance and specificity to reject the remainder of the implants tested simultaneously on the modeled sternum possessing patient-specific properties and patient-appropriate mechanical conditions. At this stage, it is outside the scope of the present study to discuss the sensitivity and specificity of the test further. If the patient-specific clinical factors and all relevant mechanical quantities, such as boundary conditions and loading force are correctly applied to the FEM the measured true values as the derived data (accuracy measure of fe-n-of-1) the test run to measure the effectiveness of the designed FEM would be valid (validity measure of fe-n-of-1).

In fe-n-of-1 empirical testing, there is very little opportunity for bias if all included parameters are carefully chosen and applied. Over time a sizable cohort would help build extra confidence in fe-n-of-1 empirical testing assessments as a measure of its surgical value for greater acceptance in the future. In addition, the effectiveness of the implants can be tested by simulating respiratory cycles equivalent to six weeks, approximately one million, with episodes of cough in number and intensity experienced by the patient pre-operatively measured by plethysmography. The importance of FEM and FEA evaluation lies in the fact that this virtual environment intervention can form real-world objective criteria based on single-patient subjective medical and biomechanical parameters for surgical application.

4.2 Fe-n-of-1 trial and relevance of implant hierarchy

The intervention for the fe-n-of-1 empirical testing must be designed to produce clinically relevant measurements to make identifiable differences in terms of mechanical advantage and robustness of the implants in the order of hierarchy relative to the control stainless-steel cerclage wire in the figure-of-zero configuration. To support clinical decisions *a priori* knowledge of the patient's health must relate well with the numerical values generated because of patient-specific parameters of the sternum as the integral anatomy of the thorax and patient-appropriate loading conditions. The difference between the magnitudes of the effect in each implant must be biomechanically significant and the ability to withstand an accepted safety factor of three times the physiological loads for the patient. The sternal halves must remain in contact edge-to-edge in all three planes without damage to the surface geometry of the sternal cortex at the bone-implant interface for the osteochondrotomy to heal in time.

5.0 Surgeon confidence measurement

The duration and stability of a reconstructed bone-implant system depend on the distribution of stresses and its deformation under patient-specific and patient-appropriate loading conditions. FEA evaluates both mechanical and 'biological' *events* occurring during bone healing. The multiaxial principal stresses are around a single loading site, whereas von Mises stress is a measure of stress distribution in the entire system of the bone-implant interface in all the axial planes. (The measurement units for both are in megapascals.) The confidence of the surgeon will be based on successful resistance of one or more implants and preservation of the bone under given loading conditions preventing instability, enduring contact stresses, signs of fatigue, and deformation of the entire construct.

Currently, no known surgeon confidence measurement scale can be applied to question the acceptance or rejection of an implant following the fe-n-of-1 results to check the confidence of the surgeon. The term confidence emphasizes the trust of the surgeon in the quantitative data and qualitative visual deformation of the bone-implant construct and material fatigue, maximum principal stress, and the von Mises stress maps (reactive forces) generated for review in the company of the clinical biomechanical engineer. It is the sureness of the

[2] Classically, sensitivity of a test is its ability to correctly identify individuals who have a specific disease or condition, and specificity is the ability to correctly identify individuals who do not have a specific disease or condition.

surgeon and lack of doubt about his or her abilities to implement the results. Further, the surgeon's confidence to accept or reject the FEA-derived data is based on his or her experience and skills to handle the oncoming surgery.

At the end of the fe-n-of-1 test run, there are several components of the experiment to consider. The FEA of the FEM as the *'event'*, which is outside the control of the surgeon after he/she has provided the complete patient-appropriate clinical information and the clinical biomechanical engineer has collected the patient-specific morphometric data and bone density and patient-appropriate boundary conditions and external load acting on the sternum. The *'response'* of the surgeon to the quantitative and qualitative data is dependent on the surgeon's trust in fe-n-of-1 results, experience, skills to deal with the implementation of the selected implant, and ability to improvise intraoperatively as per requirement. Yet uncontrollable intra-operative, post-operative, and bone healing *'factors'* are unknown to the surgeon. Thus, the *'outcome'* of the surgery is dependent on a multitude of surgery dynamics that are generally outside the control of a surgeon.

Outcome = Event/s + Surgeon response + Surgeon experience + Factors

Nevertheless, FEM and FEA-based fe-n-of-1 empirical testing would certainly, resolve the issue of selecting an ameliorative implant from among the available options based on patient-specific and patient-appropriate conditions. Therefore, greater confidence of the surgeon is dependent on his/her response to the fe-n-of-1 test, and experience.

Instead of a binary survey of 'yes' or 'no' for decision making a scale like the Likert scale is preferred because it shows the degree of surgeon's trust and understanding of the fe-n-of-1 empirical testing to select the most ameliorative implant and secondly to call upon her/his experience, even seek the second opinion during pre-operative planning. The surgeon's confidence can be assessed by a point score out of five by asking about the level of comfort to accept the recommended implant. The five questions such as whether the surgeon is **a)** strongly confident, **b)** somewhat confident, **c)** equivocally confident, **d)** not confident, and **e)** uncertain of the advantage of recommended implant over simple stainless steel cerclage wiring configurations. Each item in the set can be measured on a scale of 1 to 10.

An alternative implant in the hierarchy of greater biomechanical value tested during the fe-n-of-1 empirical testing made available to the surgeon must have been used in practice. Preferably, it should have a good track record in the literature with varying degrees of success before acceptance. Unless it is a customized 3D printed specialized implant design. The point scoring is intended to measure the response of the participating surgeon based on past surgical experience, concern over failure, and harm that will come to the patient as learned from extramural knowledge.

Most surgeons remain scientific in their approach to prescribing surgical treatment based on their experience and patient preferences. However, by offering an additional scientific tool in conjunction with the expertise of a clinical biomechanical engineering team, the process would culminate in an objective selection of an ameliorative implant for a single patient to improve the outcome.

The remainder of the study exploits the engineering method of FEA and the single-patient fe-n-of-1 empirical testing to mathematically evaluate the functional ability and selection of the most ameliorative implant to reconstruct osteochondrotomy of the sternum and, how the process of FEM and FEA is carried out.

6.0 In-silico mathematical evaluation: Finite element modeling and finite element analysis

6.1 Finite element tool: An engineering application to biological structures

A finite element method is an engineering tool for analyzing the mechanical and functional behaviour of physical structures(Hutton, 2003). The modeling and mathematical analysis are performed in a computer environment (in-silico) before its fabrication and instituting in the real world. The single most important objective in almost all such investigations is to understand the mechanism of failure and examine its safety to withstand three times the expected load (margin of safety factor). Biological structures as compared to engineering structures have much more complex geometries. Also, unlike homogenous and isotropic engineering materials, biological tissues have heterogeneous material properties and anisotropic behaviour. The greatest difference is that the biological structures, particularly bones are continuously turning over under changing stresses.

Under the body weight (load), the force acting on any bone segment is experienced at the same time in all three planes – sagittal, coronal, and axial, and the response of the bone tissue demonstrates distinctly different

behaviour in each plane due to its anisotropic property. Reconstruction of a fragmented skeletal segment with an internal fixation implant is a design and optimization problem when under physical loads. In this regard, depending on the skeletal segment and site of fracture or an osteotomy and the direction of the forces, the healing bone tissue can be under tension, compression, or torsion. Whereas, the normal healing of a bone fracture is a variable, slow and progressive process. Therefore, the implanted device in combination with the anatomically realigned bone fragments should be able to withstand not only physiological and pathological loads but occasionally much higher abrupt forces, until the bone has healed sufficiently to take loads of daily activities. All new implants designed for clinical application undergo rigourous experimental biomechanical examination and the collected dataset, including generic tissue material properties and loads are used to develop a finite element model to analyze the strength, stability, and safety of the constructed bone-implant system.

Like engineering structures, to acquire stress and strain values the FEM of musculoskeletal structure is represented as beams for the bones and springs for the muscles and ligaments to create a simple and ideal system. The geometry of the bone is acquired from 3D computed tomography (CT) but for FEA the tissues are generally given average homogeneous (isotropic) material properties and tested under linear forces to calculate average results. The results of such studies in a real-life individual patient are not relevant for clinical application.

6.2 Why do in-silico fe-n-of-1 mathematical evaluation?

The external surface and internal geometry of the bones are intricate, and variable compared to engineering structures of uniform materials and static geometries. The bones are dynamic living structures, and more so during the healing phase of a reconstructed fragmented osseous structure under constant multiaxial forces. Within the complex anatomical construction of the axial thoracic skeleton, the osteochondrotomy of the sternum is under extremely variable loads in all three planes, predominantly lateral distraction force, without a period of rest, unlike other fractures during the early healing phase. The acting forces can be much higher than expected with involuntary sudden episodes of cough. For a successful and safe outcome, there is a need for a fail-proof implant design for each patient based on the individual geometry of the skeleton, bone material properties, and patient-appropriate pathological and normal loading conditions. To fulfill this requirement there is a need for a method to select implant design and bone-implant configuration.

In an environment of rapidly changing demography of a patient population with cardiovascular diseases, clinical decision-making is still based on available heuristics and past surgical experience. Therefore, the current "standard of care" for the reconstruction of osteochondrotomy of the sternum with stainless-steel cerclage wire and similar configurations may turn out to be suboptimal. Under such circumstances, the selection of patient-specific and patient-appropriate implant design becomes even more important when individual biological variations and physical demands are taken into consideration. In-silico FEM and FEA evaluation can help to select and predict the performance and behaviour of implant design under patient-specific bone parameters and patient-appropriate loading conditions. It can quantify the degree of contact at the bone-implant interface, identify the deficiencies of the implant design, calculate the safety margin, and generate accurate stress and strain values to measure the behaviour of the structure (strength) and discretely evaluate the differences between the various implants selected for comparison in a single-patient based on the fe-n-of-1 method for clinical application.

6.3 Finite element modeling and analysis

Generally, the computer model is a simplified and idealized version of a more complex structure. The computer model of a structure is not examined as one whole structure but by dividing it into discrete interconnected elements, which gives it an appearance of a mesh called a mesh-model or finite element model(Hutton, 2003). These finite geometrical elements are connected through nodes having boundary lines to form 2D areal and where there are boundary surfaces they form 3D volumetric entities(Lobos et al., 2010). Each element of the mesh structure contains material information and how the applied loads are going to transform the entire structure by displacement of the elements at the nodes. The amount of stretching of the elements under loads determines the stress and strain experienced by the structure. As the finite element method is a numerical technique to solve the physical problem, the discretized FEM is governed by partial differential equations to describe the behaviour of the system under examination. To improve the solution the mesh can be refined sequentially to increase the density of elements in special regions of the structure and where the greater area of curved surfaces requires inclusion to increase the accuracy of the results(Lobos et al., 2008).

In computed tomography imaging, the voxels (volume elements) of reconstructed 3D digital images can be used as an in-situ mesh to construct FEM for FEA. The voxel-based method preserves the grid structure as the model elements are cubical and are aligned with the grid axis of the image. This helps to easily identify CT grid points

(nodes) belonging to salient model elements for FEA. The main disadvantage of the voxel-based technique is the irregular bone surfaces which create inaccuracies especially when surface stress and strain are of interest(Viceconti et al., 1998). When automatic mesh generation software is used, the mesh generation starts at the bone surface(Couteau et al., 2000). The surface anatomy is usually recreated in advance using the image segmentation technique, which removes natural surface irregularities. Thus, the CT data is not preserved, and facets of polyhedral elements are not aligned with the pre-existing CT grid anymore. 2D elements form surface membrane or shell as wire-frame and four-sided and six-sided elements, tetrahedral and hexahedral elements respectively form 3D volume solid elements. It is each element of the discretized structure to which the boundary conditions and mechanical loads are applied for stress analysis.

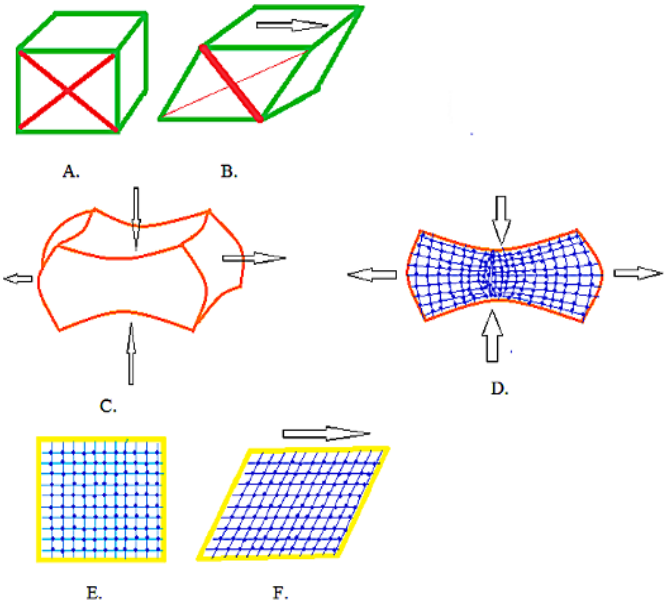

Figure 1. Illustration B shows the shear effect of load on an object A; C and D in compression and tension; E and F effect of shear load on finite element mesh with the displacement of nodes.

When the FEM is subjected to defined quantities of mechanical loads in the form of forces on the nodes, they undergo displacement (Fig 1). The whole process of FEM and FEA is much more computationally expensive for osseous structures with patient-specific irregular surfaces, cortical and internal trabecular geometry; and heterogeneous material properties due to the varying arrangement of collagen bundles and non-compressive fluid-filled interstices. It becomes even more intricate when anisotropy and patient-appropriate mechanical forces acting on the selected segment are taken into consideration

6.4 Boundary conditions and field variables

The numerical technique of the finite element method is to evaluate the behaviour of a physical structure and predict its response in terms of strength, stiffness, fatigue, and safety under realistic loading conditions. To find answers to these basic inquiries the created mathematical model is given “definite” and “specified” baseline numerical values at the level of its boundaries at which the external forces act to cause displacement of the elements constituting the structure. The given values at the boundary of a structure, before the application of external force representing the condition of a physical structure, are referred to as boundary conditions, appropriate to a patient. It is relative to these necessary boundary conditions or physical constraints that the governing differential equations are written to solve the problem, to describe the behavior of the system in one or more planes.

The application of correct patient-appropriate boundary conditions on FEM can have a great impact on the entire result of an FEA. A simple error in terms of patient-specific field-dependent variables and patient-appropriate forces acting on the FEM can cause inaccuracies. Whereas a FEM of the musculoskeletal system based on patient-specific geometry, material properties, and patient-appropriate loading conditions if correctly constrained can provide highly accurate results. The patient-specific geometry acquired from CT given excessive constraints in

the form of the higher value of material properties from experimental data would mean higher than normal stiffness of the structure and given inappropriate loading conditions in a patient would automatically produce an inaccurate response.

7.0 Patient-specific modeling

Patient-specific FEM and FEA are a reconstruction of regional anatomy of interest and functional numerical analysis in a computer environment analogous to real-world circumstances. It requires the collaboration of an expert clinical biomechanical engineer, surgeon, and computer vision scientist to solve actual surgical finite element problems for clinical applications. There are standardized musculoskeletal FEMs that can be adapted to patient-specific geometry. The material properties are based on Hounsfield units (HU) of the CT or spectrum of grey scale values and the patient-specific electromyographic values can provide forces acting on the model. However, it comes with limitations to incorporate accurate bone geometry, material properties, and the inability to transfer patient-related muscle forces and boundary conditions(Cristofolini et al., 2010; Sylvester & Kramer, 2018).

7.1 The steps to build a finite element model and methods to extract tissue material properties

The basic steps for conducting a patient-specific quantitative FEA include extraction of surface geometry of desired bones, relevant musculature, and creating volumetric mesh; assigning bone density and material properties to each element of bone, cartilage, ligament, and soft tissues; boundary constraints and load conditions to perform biomechanical analysis.

Most of the studies suggest the acquisition of 3D images from CT for musculoskeletal anatomy despite the high radiation risk. Alternatively, MRI is preferable as both hard and soft tissue structures can be included for modeling, however, being a non-radiation modality, the tissue intensities are not representative of tissue densities to calculate tissue material properties. There are significant ongoing efforts to convert 2D radiographic images from two or more planar views into 3D reconstruction(Aubert et al., 2016; Dworzak et al., 2010; Jolivet et al., 2010). Following the acquisition of a 3D image, the region of interest is segregated by employing the process called segmentation. The various segmentation methods in use are thresholding, Snakes, statistical shape modeling, level-set automatic algorithms, and the more recent ones based on deep learning convolutional neural networks(Gandhi, 2022a). Some of these may require manual intervention to improve the outlined boundaries(Kass et al., 1988; Malladi et al., 1995; Pham et al., 2000). Following segmentation and extraction of surface features each component of the model included for analysis is colour-coded to indicate tissue type and anatomy to improve visualization. The grey-level values of the segmented digital image data are used to generate labeled output voxelized images with the original grey-level scale.

There is a positive relationship between modulus of elasticity (*A measure of stiffness, which defines flexibility or relative rigidity of a material. It is a ratio of stress to corresponding strain below the proportional limit. The higher the modulus higher is the load required to stretch it.*) and bone mineral density(Currey, 1988; Nicholson et al., 1997; Rho et al., 1995). The correlation varies from bone to bone and within the same bone in an individual(Rho et al., 1995). The relationship between apparent bone density and elastic modulus is generally represented by a power law as elastic modulus = (apparent density) ^{a}. The value of 'a' varies among the reported studies (1.27 to 7.4). For cortical bone 'a' range is (4.0-7.4)(Currey, 1988), and for the trabecular bone (1.27-2.57)(Rho et al., 1995) suggests a higher modulus of elasticity for cortical bone. Mineral density range of 0.05-2.1gm/cubic mm(Rho et al., 1995) and elastic modulus range 1-30GPa(Currey, 1988). These values show variations from specimen to specimen due to differences in their anatomical sites, geometrical configuration, and testing conditions(Helgason, Perilli, et al., 2008). This demonstrates that mineral content is not the only factor that affects the elastic properties of bone, as it only explains 70% of the variation in the modulus of elasticity.

The elastic modulus and other material properties of engineering materials are well-known and spatially constant. On the other hand, the material properties of bone and soft tissues are heterogeneous and patient-specific. The behaviour of the bone tissue varies due to its material properties, and even 'a' in power laws changes with the change in direction of loads(Rho et al., 1995) due to material anisotropy(Wirtz et al., 2000). None of the empirical relationships described in the literature between apparent bone density and modulus of elasticity seems to describe material properties with certainty(Helgason, Perilli, et al., 2008; Morgan et al., 2003; Morgan & Keaveny, 2001; Nobakhti & Shefelbine, 2018). In an instance of a single-patient for fe-n-of-1 empirical testing, it is possible to extract spatial bone density by converting the HU to apparent or ash density only if the reported grey-level values and image intensity gradient are standardized for all imaging modalities. The ability to extract local bone density enables the assignment of material properties to elements of a volumetric grid created from CT/MRI data. In the case where the voxel-based mesh is used the HU of each voxel would directly provide the calculated elastic

modulus. When commercial software is used to generate variously shaped finite element mesh containing several voxels, then the HU of all the included voxels and partial or sub-voxels is averaged to account for the material properties of each element(Helgason, Taddei, et al., 2008; Taddei et al., 2007). So far there is no final consensus on the most accurate relationship between HU and bone density to extract the modulus of elasticity for clinical application. As the literature is irresolute there is a dire need for further research in this area before FEM and FEA can become a part of mainstream surgical practice.

There is relative absorption of x-rays by the tissues due to heterogeneity of tissue density. This produces a variable degree of the brightness all over an image, which is measured as grey-level values. The grey-level value of pixel intensity *(brightness)* is measured on a scale of 0 (darkest) to 255 (brightest). The decrease in pixel intensity is relative to a decrease in bone density(Oliveira et al., 2013; Tosoni et al., 2006). Therefore, the bones with higher mineral content produce higher intensity images. Alternative to the HU, it is possible to have a conversion factor to convert the distribution of image grey-level value of each voxel or average grey-level of each finite element to have an equivalent value of elastic modulus for patient-specific clinical application(Wijayathunga et al., 2008). Since the range of the grey-level scale is 0 to 255 the representative image should be able to provide the same range of values to represent the modulus of elasticity. But as the average range of grey-level values for a bone CT range between 60 and 100, it would mean grouping several grey-level values into suitable bands and finding the average modulus of elasticity values for each group of elements. Another limitation of this method is the non-standardization of the imaging modalities. The necessary image processing to improve the resolution of a medical image changes its original grey-level values to new values in the output image, thus misrepresenting the native material properties. This may be partly resolved by calibrating the image with phantoms of known density and providing the same environment during follow-up imaging to realize the true difference in the evolution of the disease process.

The correlation between mineral density and elastic modulus of bone has also been investigated with quantitative backscattered scanning electron microscopy(Casanova et al., 2017). It measures bone mineral density based on the grey-level scale and can provide information about the modulus of elasticity depending on the arrangement of the collagen and fibril organization, and water content in the tissues. Although, it is still an experimental technique but may be used retrospectively in clinical practice by taking bone samples at the surgery. The results can be applied in the future to correlate as a measure of success in-silico fe-n-of-1 testing for other patient-specific outcomes to act as a surrogate in verifying and validating selected implants for the given patient-appropriate conditions. It can also be correlated to image grey-levels for verification and validation of material properties in the future.

It is common to ignore the modeling of the muscles, ligaments, capsules of the joints, and articular cartilage in a FEM(Nishida et al., 2019) to keep the construction simple and the computational time and cost low. In practice, the intrinsic muscle forces produced during contraction are deployed at the anatomical insertion of the muscles on the bones included in the model, with its origin as the fixation point(Bitsakos et al., 2005). The assumed physical constraints including forces and pressures acting on the skeletal segment are applied as symmetrical boundary constraints for FEA. There is hardly any published literature to describe a realistic 3D computer model without assumptions to assess forces and moments acting on the sternum during normal respiratory cycle and post-operative pulmonary ventilation.

7.2 FEM and FEA of the sternum in the setting of the thoracic skeleton

Computer-aided design software such as Solidworks© or LS Dyna© can be used to reconstruct a 3D model of the thorax from the CT images, combining with the control and the test implants. The various elements of the thoracic skeleton are segmented and labeled by colour coding the sternum, costal cartilages, ribs, thoracic vertebrae; representation of the joints, ligaments, and capsules, and articular cartilages in the case of synovial joints; intercostal, sternocleidomastoid, and pectoralis major muscles, and diaphragm as they act directly on the sternum and ribs. The several implant systems including the stainless-steel cerclage wire as control and selected test implants to reconstruct the sternum are modeled following the instructions recommended by the manufacturers. Then bone and implant interface is developed accurately by positioning the implant on the divided sternum. The complete computer model is converted to a voxelized mesh model interactively or automatically by using commercial meshing software. For a patient-specific biomechanical FEA generic material properties are not recommended, and effort should be to convert the available tissue density data from the image into local modulus of elasticity values by using the best available conversion method in the literature.

Next to patient-specific material properties, the other most important factor to perform the FEA is patient-appropriate boundary conditions. This requires an understanding of how the co-morbidities would affect

the strength, stiffness, and stability of the bone-implant interface until the sternum is fully healed. It would depend on the body weight and cyclical forces acting on the sternum during normal regular respiration and episodes of cough until the healing is complete.

Once a complete FEM of the thoracic cage is available for FEA, multiple implants can be tested in parallel by setting up as many computer stations as required to provide comprehensive information for the stable fixation of the sternum. For further information on implants currently in practice see (Gandhi, 2019a). To speed up the process of computation and save cost in time for each patient advanced higher functioning graphic processing unit (GPU) can be used, which may initially come at a slightly higher investment. The results are processed using a suitable software program and presented on a visual display unit. It can be printed for critical appraisal and discussion with the concerned surgeon. Finally, the reasons to accept the results and suitability of the selected implant should be used for informed consent and adapted to patient preferences. The final decision lies in the clinical experience of the operating surgeon in conjunction with the objective numerical evaluation reported by the clinical biomechanical engineer and the expected compliance of the patient post-operatively.

The development of FEM should aim at single-patient based on the fe-n-of-1 empirical testing philosophy to match the patient-specific bone morphology and influential regional anatomy for enhanced patient-based outcome by stable fixation of the sternum. Only the most ameliorative implant design based on FEA results should be recommended to help manage the reconstruction of the sternum and provide the best solution to improve surgeon-based results.

8.0 Decision threshold and analysis

Clinical decision-making in medicine is an act of probabilities. To make these decisions, physicians rely on their acquired clinical experience(Feinstein, 1968), and extramural knowledge. As a result, subconsciously physicians often compare the present patient to previous similar cases. The fundamental objective of a clinical encounter is to assess the patient thoroughly to set goals. Based on the diagnosis and surgical principles, the reasons are formulated to develop the steps of the pre-operative plan to target index pathology and prevent the occurrence of well-recognized intraoperative and postoperative complications. The surgical principles and choice of an implant should be based not only on the index pathology but also on co-morbidities to include ancillary surgical steps to prevent short and long-term failures of the procedure. These concerns can only be reasoned and resolved by critically appraising the duration, severity, and status of co-morbidities, and associated risk factors. Even though the index pathology is the primary reason to bring the patient to the operating table!

It is equally important to rule out structural variations in the anatomy of the sternum and costal elements to mitigate biomechanical dysfunction that may introduce a suboptimal bone-implant interface. The target of in-silico fe-n-of-1 intervention during pre-operative planning is prophylaxis against mechanical failure of the bone-implant synthesis, as a result, the occurrence of serious surgical complications.

Frequently, the induction of surgical principles is a retrospective approach to personal and anecdotal experiences. Even if a treatment works in a particular patient, although poorly understood, this reinforces the behaviour of physicians to continue to do what has worked before in the hope that the same will continue to produce equally good results and will be cost-effective(Mayer, 2010b). This is the theme and the philosophy underlying evidence-based medicine to constantly encourage systematic reviews and meta-analyses. This is also true of stainless-steel cerclage wire to reconstruct the divided sternum. In-silico experiment can be considered a prospective analysis performed during pre-operative planning comparing two or more implants to deduce the likelihood of using the most ameliorative implant among the options available to the surgeon. At the end of finite element analysis, the functional end-point of each implant is a quantitative and qualitative measure for a single-patient. Each tested implant is under a homogeneous virtual environment derived from patient-specific parameters and patient-appropriate conditions.

Stainless steel cerclage wire is believed to have proven its worth in a large majority of patients undergoing osteochondrotomy of the sternum for its reconstruction. Odds are that continuing the use of this implant nothing adverse might happen in randomly selected patients. On the other hand, the probability is that it may fail in a matter of time during the healing phase of the sternum and there is a breakdown of the wound with an increased likelihood of DSWI in cases of high-risk co-morbidities. Many diagnostic and treatment interventions take place based on the concept of the Bayes theorem, which is one of the ways to predict the odds of an event happening when new factors come into play during the evolution of a disease, diagnosis, and treatment period. It becomes even more complex when there is rapid accretion of complications post-operatively.

Administering in-silico FEM and FEA intervention depends on pre-test probability based on surgeon experience to make a clinical judgment and decision to choose the best implant to match patient-specific and patient-appropriate conditions to prevent complications. Numerically, since odds and probabilities are very similar, if the stainless-steel cerclage wire is considered by the surgeon equally good or better than the other implants the odds of its being successful or failing are 1:1. It means there is one successful case for every failure. The probability is that if the stainless-steel cerclage wire in the figure-of-zero configuration is used in all cases, it will be successful in one of every two cases even before the start of the surgery.

The clinical decision-making for major surgical procedures is multifaceted, particularly where the approach to deep-seated index pathology involves the transection of a skeletal structure, which is known to take much longer to heal compared to soft tissues and demands specialist assistance. Under such circumstances it becomes paramount that the idea of the fe-n-of-1 empirical testing is considered; and pre-test probability evaluated thoroughly to acquire relevant clinical data in the form of present and past medical and surgical history, physical examination, assessment of comorbid chronic diseases, modifiable and non-modifiable risk factors to undertake diagnostic tests and refine the choice of the surgical implant. The objectives of the in-silico intervention are based on pre-test probabilities to better understand the post-test probabilities to prevent post-operative complications. So far based on existing surgical experience stainless-steel cerclage wire in figure-of-zero and other configurations are very much considered as "standard of care" in almost all the cases despite its attended adversities. However, considering the length of the successful history of the stainless-steel cerclage wire the likelihood of pre-test probability of its success is more often than failure. But there has been a dramatic change in demography and intensity of plural co-morbidities with new risk factors that may have prevented the overall reduction in the incidence of sternal instability and associated complications reported in the recent literature, despite better medical care.

In-silico FEM and FEA evaluation is one way to challenge and revise the historical success of the stainless-steel cerclage wire in comparison to more recently introduced implants for reconstruction of the divided sternum to better the current outcome. The characteristics of in-silico testing can be used to find the testing and treatment threshold to judiciously select the most ameliorative implant design. The treatment threshold is pre-test probability, where the patient in question is healthy, has one or no co-morbidity, and has no risk factor. There is likely no chance that the success of the stainless-steel cerclage wire will be jeopardized, and it can be used without in-silico testing. The low and high level of pre-test probability to perform or not the in-silico test is dependent on the ability of the surgeon to generate enough information during the clinical encounter and critically review it before making the final decision to employ a particular reconstruction implant. At the same time reflect upon the post-test probability of post-operative complications from experience.

8.1 Heuristics of decision making

Medical heuristics may be considered an application of one's intellectual ability to apply previous clinical experience and prioritize the treatment options depending on disease severity and connectedness of the data collected during a new yet similar clinical encounter. Generally, heuristic guesswork ("rule of thumb") provides reasonable patient care to solve every day common clinical scenarios to avoid serious mistakes. However, in special circumstances where multiple co-morbidities and risk factors converge, more objective measures are taken to resolve the volatile pathological milieu that requires an interdisciplinary team effort.

A smoker with COPD will heal divided sternum differently from a smoker with diabetes and one with age-related osteoporosis from one on long-term corticosteroids. The same treatment method may not apply to all smokers and patients with a history of fragility fractures without a definite history of osteoporosis. The healing of the sternum and soft tissues will be different because different loading conditions and altered immune status increase the likelihood of wound infection, which may happen due to poor glycaemic control even in a non-diabetic post-operatively.

Surgical heuristics of implant availability adds bias to the clinical decision to select an implant to fulfill political expectation because it is readily available, cost-effective, has a historical track record, and technically less demanding in the hands of even a junior colleague. The anchoring and adjustment heuristic(Mayer Dan, 2010) dictates that the reason to choose a treatment modality, say an implant, should be based on the factors which match the patient medical health to increase the probability of success and decrease the odds of its failure. The next higher level is competing heuristics where the most ameliorative implant is chosen judiciously from among several options based on in-silico mathematical evaluation by applying patient-specific biomechanical parameters and patient-appropriate mechanical forces acting on the sternum. The most common error in clinical decision-making is when the heuristics are based on a few pertinent clinical points, leading to premature closure

of implant selection. There is no common fixed clinical pattern as there is no biological homogeneity. The key to good surgical practice is to recognize the variation in the clinical spectrum that may have a variable response to an implant.

8.2 Treatment and testing thresholds

The treatment threshold is the pre-test probability at which we should initiate the treatment without first doing the test for the condition under treatment (Fig. 2). In other words, for the reconstruction of the sternum, if there are no reported adverse risk factors and co-morbidities to cause the failure of the currently accepted "standard of care," then the stainless-steel cerclage wire in figure-of-zero can be expected to sustain mechanical forces acting on it. Above this threshold, there is no need to perform in-silico testing. If the pre-test probability of failure is high, then testing would certainly produce many superior results for other advanced stainless-steel wiring configurations and recently introduced devices for its re-synthesis. However, if one of the other implants shows significantly higher mechanical values it may raise the question of denying the patient benefit of the best available implant instead of providing a present-day "standard of care" based on availability heuristics. In-silico testing does not mean that the surgeon is under duress to provide the best implant, which would mean a waste of precious resources. It is only wise and prudent of the surgeon to select only the next best stainless steel wire configuration other than figure-of-zero or a device next in the hierarchy. The surgeon may initiate the treatment confidently after discussing the pros and cons of the choice by evaluating patient preferences as well.

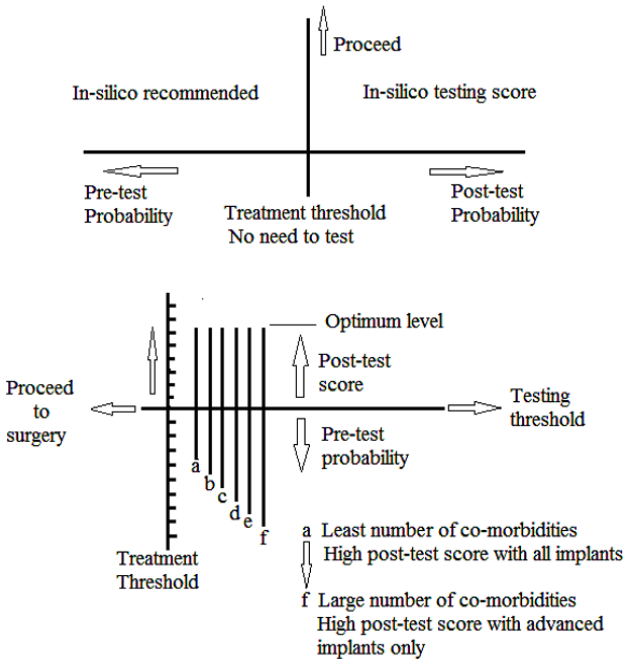

Figure 2. Pre-operative planning treatment threshold and testing threshold in cases with varying degrees of co-morbidities based on in-silico scores for the selection of an optimal implant design.

The testing threshold is pre-test-probability at which the odds of failure of the stainless-steel cerclage wire in the figure-of-zero configuration are high as judged from data collected during the clinical encounter. In other words, the testing threshold is the value at which the clinician has a sufficient subjective and objective understanding that the application of the implant considered to be the "standard of care" would fail in the early postoperative period and lead to the delayed union of the sternal verges and impair soft tissue healing to maturity due to instability. In instances where the co-morbidities are poorly controlled and the risk factors are non-modifiable the probability of sternal instability, superficial and deep wound infection, and progression to mediastinitis can be expected. Therefore, as directed by the clinical assessment it is appropriate to undertake an in-silico mathematical evaluation and select the most ameliorative implant design.

If during the clinical encounter, the pre-test probability of failure is low and the expected success of standard treatment with stainless-steel cerclage wire figure-of-zero configuration is at the threshold then one may treat based on history and clinical examination by applying clinical experience. If in doubt, it is advisable to test first to

check if it would sustain the expected loads. The surgeon does not have to ask for in-silico intervention if there is no known cause for failure of the stainless-steel cerclage wire expecting the sternum to heal fully in time. Otherwise, with pre-test probability below the treatment threshold where the likelihood of failure is high due to greater number of co-morbidities, perform in-silico FEM and FEA evaluation. It would help to select the most ameliorative implant, whether it is an alternative stainless-steel wire configuration other than figure-of-zero or an advanced design to reconstruct the anatomy of the sternum to return cardio-pulmonary function to normal.

The probability of testing threshold and selection of an ameliorative implant design is directly related to the number and severity of co-morbidities, as well as the number and duration of modifiable or non-modifiable risk factors. It does not mean that this relationship is linear. In addition, the skills of a surgeon to handle osteochondrotomy of the sternum, meticulous dissection of the anatomy, minimal collateral tissue damage, and forceful wound retraction due to shorter incision and thermal necrosis with excessive indiscriminate use of the cautery; the anatomical reduction and initial rigid stabilization of the sternal verges; all these factors account towards timely healing and minimization of untoward events postoperatively. Making surgical incisions shorter than the expected size of the pathological anatomy is against the surgical principles to reduce surgical infection and purportedly resulting in cosmetically pleasing scars are based on mistaken ideology, the evidence only being in the hands of very few select surgeons. The optimal reconstruction of the sternum includes closure of the distal end of the sternum at the xiphoid and adjacent part of the opened linea-alba or other tissues with non-absorbable suture material to oppose strong distraction forces due to conjoint insertion of false ribs(Gandhi, 2019b). Currently, there is no systematic review and meta-analysis to direct cardio-thoracic surgeons to make an optimal choice to reconstruct the sternum based on patient-specific anatomy of the thorax and patient appropriate forces acting on it. The choice of stainless-steel cerclage wire in various configurations is based on low cost and availability heuristics rather than favourable outcomes based on biomechanics and biological factors. The qualitative and quantitative FEM and FEA in-silico analysis of the bone-implant interface can provide a scientific basis to select the most ameliorative implant design.

8.3 Implant hierarchy criteria for inclusion to perform in-silico testing

The suggested hierarchy to clinically select an ameliorative implant is based on several co-morbidities and associated risk factors. The well-known applicable implants for reconstruction of the sternum are classified as circumferential, semi-circumferential, and on lay surface devices(Gandhi, 2019a) (Table 1).

Table 1. Classification of devices for the fixation of the sternum

A. Cerclage implants a. Stainless steel 316-L monofilament wire b. Stainless steel or Titanium multifilament Cable c. Stainless steel or Titanium straps or flat bands d. Ultra-high molecular weight Polyethylene and Polyethylene Ether-Ether Ketone straps e. Merselene polyester tape f. Poly-Dioxone suture g. Anchor sutures **C. On-lay surface bone plates and screws systems** a. Generic orthopaedic and trauma non-locking reconstruction, dynamic compression, and one-third semi-tubular plates and screws b. Sternum specific anatomical locking English alphabet-shaped mini-fragment plates with unicortical and bi-cortical screw system c. Trans-sternal costal-costal transverse reconstruction two-piece bridging plating system with a coupling U-pin d. Longitudinal modular non-locking sternum-specific plates with cannulated screws and multifilament cable ties	**B. Semi-circumferential clamps, clasps, and claws implants** a. Trans-sternal Staples b. Para-sternal Nickel-Titanium thermo-active metal alloy clip/clasp c. Para-sternal Titanium two-piece quick-release coupling claws d. Stainless steel 316-L two-piece coupling square-hook J-shaped plates and set screws e. Square hooks and ratchet rod f. Fishhook ties **D. Grouting Adhesive Cement** a. Glass Polyalkenoate Cement b. Calcium carbonate and castor oil-based polymer c. Tri-calcium phosphate d. Hydroxy-apatite **F. Industrial stainless steel staples across the osteotomy**

E. Re-absorbable dowels interposed between sternal halves and reinforced with cerclage wires	

The greater the number of co-morbidities and severity of plural pathologies, and risk factors more advanced the choice of implant design is generally recommended for stable fixation to mitigate instability of the sternum during the postoperative period. The implant hierarchy and preference have evolved based on design features and the timing of its entry into practice. However, the implant choice must be established based on FEA before application (Table 2). Biomechanically, the most important factors for stability are high interfragmentary shear stress, greater bone-implant contact surface area, and stiffness of the construct to match the material properties and geometry of the underlying bone. These factors are considered in conjunction with implant design to sustain patient-appropriate loads without failure until the sternal osteochondrotomy has healed sufficiently to take over the normal function.

Table 2. Suggested implant hierarchy, likely indications, and failure modes of bone-implant construction as the basis for in-silico fe-n-of-1 mathematical evaluation. (The suggestions made here are general and not based on any experimental or direct clinical experience of the author in the reconstruction of the sternum).

Implant choice hierarchy	Most likely indications	Likely qualitative adverse events
Circumferential implants: Stainless steel cerclage wire – figure-of-zero, figure-of-eight, etc.	No co-morbidities, one risk factor such as smoking, BMI <30	Signs of untwisting of the wires, notching of the bone edges, slipping of the wires at the interface with the bone, loss of reduction of the bone edges in one or more planes, interfragmentary gap formation with or without the radiology sign of bone resorption
Robicsek or a similar technique to cage the sternum	History of one or two co-morbidities such as COPD, osteoporosis, one or more risk factors such as fragility fracture, smoking, BMI <35	Signs of untwisting of the secondary cerclage wiring configuration and sliding of the wires on the underlying bone causing instability with or without loss of contact of the bone edges leading to gap development
On-lay surface implants: Plates and screws with or without the addition of cerclage wiring configurations	History of more than two co-morbidities, Diabetes mellitus, poor glycaemic control, two or more risk factors such as BMI 35-40, long-term history of smoking, large breasts, abdominal bulge, athletic activities in the early postoperative period	Signs of screw-related bone erosion and enlargement of the screw holes with loss of the bone plate/s interface, instability with the translation of sternal verges in one or more planes and gap development, fracture of the sternum during in-silico testing
Semi-circumferential implants: clamps and clasps, additional need for select cerclage wiring configurations	Two or more co-morbidities such as COPD, need for prolonged post-op ventilation, multiple risk factors, BMI more than 40, history of more than one fragility fractures	Signs of loss of contact between the verges of cut edges of the sternum in one or more planes, pull-out of the device with loss of implant-bone interface, and instability of the sternum

New reconstruction devices or hybrid fixation by using a variety of implants with reinforcement of the distal half of the sternum, designed to enhance the bone-implant contact area without additional compromise of anatomy and bone material properties and geometry during healing due to unloading of the underlying sternum	Multiple longstanding co-morbidities and risk factors that cannot be modified rapidly and early post-op return to manual work and physical activities, intra-operative segmental fracture of the sternum	Failure to maintain the stability of the fragments, integrity of bone material and geometry and loss of contact between cut edges of the sternum, and translation of the fragments in one or more planes

9.0 The implant selection and acceptance criteria

The accuracy of fe-n-of-1 empirical testing for one or more implants is purely based on quantitative technical patient data and information gathered during the clinical encounter. As there are multiple streams of quantitative and qualitative parameters to build the finite element model the resulting outcome too has multiple ramifications to select the most ameliorative implant. It cannot be accepted on coin-flip randomization nor pick the best of the lot each time. Otherwise, the accepted implant will be industry-driven rather than a recommendation based on the scientific fe-n-of-1 empirical testing. Secondly, during pre-operative planning, all the stainless steel wire configurations known to the surgeon and all the applicable implants available to the surgeon be included for fe-n-of-1 FEA. With increasing interest and availability of additive manufacturing *(3D printing)* in the case of outliers customized implant design should be encouraged.

Both quantitative data and qualitative direct visual analysis of von Mises map showing the distribution of reactive forces *(contact stress and strain)* and deformation of finite element model of bone-implant construct during the running of the fe-n-of-1 process should be included when reporting the FEA analysis. All the engineering tenets should be considered to conduct the finite element analysis properly and that the simulation reflects patient quantitative and qualitative data met at the time of clinical encounter. The rule of progressive implant failure to termination for the acceptance of an implant when five available implant designs are made available pre-emptively for consideration based on surgeon experience is shown in (Table 3).

Table 3. Empirical implant selection and acceptance criteria for fe-n-of-1 testing (The suggested criteria are hypothetical and not based on the surgical experience of the author).

Five out of five tested implants failed	Reject all implants or select one which failed last with no or minimum deformation of the bone -implant construct and support the thoracic cage with external support until the sternum is clinically healed
Four out of five tested implants failed	Accept the viable implant and consider surgeon experience and skills
Three out of five implants failed	Select one of the two which failed last based on surgeon experience and supported by literature
Two out of five implants failed	Select one of the three viable implants that failed last with minimal bone-implant deformation and have a longer surgical history of success as

	reported in literature and surgeon experience
One out of five implants failed	Select one of the four implants that failed last with minimal bone-implant construct deformation and greater endurance, based on surgeon experience, require minimal further tissue dissection, least bulky and cost-effective
None of the implants failed	Select one of the five implants with no or minimal bone deformation and signs of material fatigue, most experienced by the surgeon, and cost-effective

The FEA and FEM are performed by an in-house clinical biomechanical engineering team in collaboration with the surgical team under the care of the most responsible operating surgeon. However, it is up to the clinical biomechanical engineer in charge to decide whether all types of implants considered for the fe-n-of-1 test are run on a single bone-implant model or a set of each implant design is tested on a separate divided sternum model running multiple FEM/FEA in parallel at the same time. Each bone-implant model must simulate patient-based respiratory cycles equivalent to one million cycles for an average respiratory rate of 15 per minute with episodes of cough. Preferably, the study continues until one million cycles are completed, otherwise, the termination criterion should be either failure of the bone or implant or the whole construct. In the event, all the implants fail terribly, either an additional implant in practice is searched or endeavour to design a customized patient-specific and patient-appropriate implant.

9.1 Advocacy of a selected implant

The untoward events such as untwisting and loosening of the grip by the cerclage wire, high bone-implant interfacial contact stresses, notching, fracture propagation leading to fragmentation of the sternum, and failure of an additional suboptimal implant included in the construct lead to failure of the entire construct. It means moving to the next higher-level implant design that would be ameliorative and mitigate the adverse effects of the suboptimal tried implants. The implants adjacent to the scale of hierarchy may perform equally well. In such an instance it is only wise to use the most cost-effective, technically less demanding, and clinically most experienced implant design. The approach of in-silico fe-n-of-1 assessment of available implants in comparison to the most experienced stainless-steel cerclage wire provides the predictive value of choices during surgical planning. It is certainly more scientific than the heuristic approach in terms of patient-specific and patient-appropriate medicine in making a clinical decision than population-based observational clinical and anecdotal historical evidence, and surgeon-based past surgical experience to refine the implant choice, if in any doubt. After the in-silico evaluation, the ultimate implant choice should not be based only on the best evidence of the objective fe-n-of-1 empirical testing but also on surgeon experience to match the clinical characteristics of the patient. The method delivers rapid, qualitative, and quantitative discrete results in a single patient. It is expected that factual knowledge provided to the patient during informed consent might motivate him or her with co-morbidities and risk factors to take definite steps to make necessary lifestyle changes.

If the post-test probability of success of the standard stainless-steel wire configuration turns out to be low. Then, it means without the fe-n-of-1 test run, it would have performed poorly during real-life loading conditions. As well as in terms of bone material properties than otherwise expected from pre-test probability based on clinical encounters. Such a clinical decision is based on false reassurance falling below the treatment threshold. Thus, a pre-emptive decision based on clinical encounters and careful consideration of pre-test probability would be worthwhile to do the FEA evaluation. This kind of approach helps to prevent a compromised outcome. It encourages taking into consideration the pre-test probability after critical appraisal of all the available clinical information and choosing to proceed with FEA evaluation as a prophylactic assistive tool.

On the other hand, if the clinical encounter reveals an adverse clinical scenario and suggests a significant higher pre-test probability of failure of selecting the current "standard of care", but the post-test probability has a lower value than expected on the scale of testing threshold, it is only prudent to consider an implant higher on the hierarchy based on past surgical experience. It means the surgeon is discreet and confident in his or her choice. Both treatment and testing thresholds are dependent on the pre-test probability based on patient-appropriate medical conditions. At a low pre-test probability of success or higher adverse clinical scenarios, in-silico FEM and FEA evaluation ought to make a difference as it provides the surgeon with an objective numerical result based on subjective clinical evaluation.

10.0 Application of the Bayes theorem

Bayes' theorem is based on experiential philosophy. It provides a balanced view of suffering from adversity, where the incidence of an event depends on the expected happening of a new occurrence. It is one of the ways to predict the odds of an event happening when confronted with a new occurrence. The new information made available introduces the likelihood of ratio and the Bayes' theorem is an accepted statistical method to deal with likelihood ratios to examine probabilities objectively to optimize patient management. In medical statistics, it is related to an accepted p-value of < 0.05 for statistical significance. Odds describe the chance if something happens against the chance that it will not happen. It means the odds are that complications will not happen! Whereas probability is that if something will happen against chance it will or will not happen. It means that adverse events may or may not happen. During clinical decision making the probability is generally converted to odds – the chance that the adverse event will not happen. Accepting odds is a positive and reassuring wishful thinking of an experienced surgeon to undertake a procedure thought to be free of complications. Even in the hands of the best surgeon odds of getting the best outcome is 1:1, one surgical operation completely free of complications and one with the possibility of one or more complications. The odds can also be expressed as 1/1=1.0 and the probability of success is 1/2=0.5. So, the probability of having an outcome of a procedure completely free of complications is 50:50. Both mean one of the two procedures will be completely free of complications. They are convertible when the number of procedures is very small.

Uncertainty is the inability to determine precisely what the outcome would be for the reconstructed sternum without undertaking an in-silico mathematical evaluation of the chosen implant from among the available options. The in-silico biomechanical testing is a kind of prospective classical n-of-1 trial. Therefore, the fe-n-of-1 empirical testing is a positive action and judicious means to reduce the number of adverse events occurring post-operatively. Even a change in one clinical fact would change the results of quantitative evaluation. In practice, clinicians frequently use clinical judgment to decide the threshold values for each patient based on history and clinical examination. When the pre-test probability of success is much above the threshold as judged from the clinical picture of no significant risk factors and co-morbidities that would adversely affect the healing of the sternum then there is no logical reason to perform an in-silico biomechanical evaluation of the sternum.

11. Discussion

After a clinical encounter, physicians are frequently faced not only with the primary diagnosis but several co-morbidities and risk factors that can influence the treatment outcome. It is true in the case of patients coming for cardiovascular surgery, who suffer from age-related risks or other chronic co-morbid disorders. Some either directly alter the material properties of the bone or significantly influence the healing of surgically divided bone and soft tissues. With significant pathological changes at the tissue and molecular level, the health of a patient can be very dynamic. Despite satisfactory stabilization of the co-morbid conditions to reduce the risk of likely sudden changes in health post-operatively, one can still expect adverse events. Failure to anticipate such a pre-test probability can affect the patient outcome, which must be considered during pre-surgical planning.

Organizing and instituting a single patient classical n-of-1 clinical prospective trial of comparative therapy is an effective means of treatment in uncertain circumstances and chronic medical conditions. It has the potential for widespread acceptance and potential for therapeutic precision(Duan et al., 2013). It is not unknown that there is population selection bias and statistical averages that can result in irregular reporting on the risks and benefits of new drugs and surgical implants resulting in heterogeneous treatment effects(Allen et al., 2017; Kravitz et al., 2004; Longford, 1999). The concept of the single patient classical n-of-1 trial is not only the preserve of internal medicine for developing personalized treatment strategies. Similar principles can be applied to the practice of surgery during pre-operative planning to select an optimal implant to repair, reconstruct and replace a segment of human skeletal anatomy.

Unlike drug therapy where there is a multiple-period of crossover experiments comparing two or more treatments, in-silico FEM and FEA intervention for a single-patient fe-n-of-1 evaluation means simultaneously simulating multiple options in parallel under the same virtual environment to select the most ameliorative reconstruction implant from among the available implants in the market. The number of implants tested for comparison is limited by computational capacity and time cost. It erases the ill-defined and fallacious mindset ideology of "gold-standard" in medicine by rejecting "standard of care", one therapy for all in the real world of biological variations. It proposes an individualized solution to match patient-specific biomechanical parameters based on patient-appropriate medical conditions and mechanical forces acting on the patient-specific bone segment.

The assignment of an implant for a patient should not be a random selection process of choosing stainless-steel cerclage wire configurations, or one of the currently popularized plate and screw systems and semi-circumferential devices(Gandhi, 2019a). The application of in-silico mathematical evaluation offers a judicious means to select the most ameliorative implant design to mitigate anticipated adverse effects that may befall a patient by making less-than-ideal surgical choices. The FEA results provide objective qualitative and quantitative measurements to differentiate the mechanical advantage of an implant from among the hierarchy of tried and tested implants. During in-silico evaluation, all the patient-specific bone-implant constructs can be subjected to the same patient-appropriate condition of cyclical thoracic movements, simulating one million respiratory cycles and cough episodes experienced during the first 6 weeks following surgery. According to the structural engineering principle of a safety factor margin of three times, the expected load provides more realistic circumstances for the assessment of a structure that can also be applied to implants in-vivo.

On completion of the trial, the clinical biomechanical engineer and the surgeon meet to discuss the findings of FEA and decide on the treatment going forward. The decision must be based on a sound interpretation of the available quantitative and qualitative data resulting from the intervention comparable to findings during the clinical encounter. A careful assessment of any uncertainty is considered to avoid misinterpretation due to random noise in the data, which must be related to the pre-existing experience of the surgeon. The selected choice can also be matched to patient preference following a clear understanding of the in-silico process through well-informed consent and modified accordingly. The most ameliorative therapy selection intervention based on a single patient is primarily to produce specific clinical knowledge and over time cumulative data to modify and refine the in-silico study design. The data collected pre-operatively can be directly correlated to post-operative healing of the sternum based on imaging, surgeon satisfaction, and patient-based functional outcome.

A single-patient fe-n-of-1 intervention seems logical to provide the surgeon reasonable opportunity to strengthen clinical judgment and appreciate the potential benefits of an alternative implant choice. The presence of a clinical biomechanical engineering team in the department of surgery brings in-house opportunity to undertake in-silico testing of currently available implants, critically assess, appraise and effectively recommend a newly introduced implant for clinical application to a single-patient with greater confidence rather than acting solely on extramural knowledge. A well-informed patient appreciates personalized attention. It may improve patient compliance and doctor-patient relationship with a bilateral increase in confidence to make the procedure a success. It also helps to reduce industry-driven bias and keeps the surgeon honest in clinical decision-making independent of political expectations of the health provider in terms of availability and cost.

In-silico evaluation technique being a predictive method has its limitations in simulating the true in-vivo biomechanical environment. Currently, for a highly structured FEM and FEA mathematical evaluation to live up to its promise there are some technical difficulties in extracting true patient-specific biomechanical parameters. Primarily, it is the tissue material properties representing modulus of elasticity based on the heterogeneous nature of the cortical and trabecular bone derived from CT Hounsfield units and grey-level values as per image intensity gradient. The results can be extremely variable as the values are currently extracted from unstandardized image modalities. Secondly, there are significant variations in methods for the application of prevalent power laws or conversion factors used to translate Hounsfield units and grey-level values to bone density; and bone density to the elastic modulus. Similarly, there is also a lack of robust direct techniques to clinically collect patient-specific material properties of non-osseus musculoskeletal elements such as muscles, ligaments, and cartilage; and patient-appropriate exact quantitative loads during physiological and daily mechanical activities for FEM and FEA application to remove the ambiguities in results.

For successful FEM and FEA assessment, the computer model should be simple, such that it provides the necessary information. The finite element mesh construction is appropriately refined and has density information at specific regions of interest, particularly the bone-implant interface, and results are verified whenever possible. The surgeon should have a complete understanding of the assumptions inherent in the finite element

methodology, characteristics of applied boundary conditions at the articulations, and insertion site of the regional muscle groups on the bone/s to represent muscle activity in the model assembly.

Although initially, it is not possible to verify and validate the results of an FEA in clinical practice, however, surgeon-based experience and patient-based post-operative outcome data can be important instruments to verify and validate the results of future patients having similar skeletal geometry, material properties, and mechanical environment in the on-going practice of in-silico the prospective fe-n-of-1 testing. Still, it may never be possible to verify and validate the results before surgery in a prospective fe-n-of-1 testing. Nevertheless, it is highly unlikely that the collaborative experience of the surgeon and the clinical biomechanical engineer the results of FEA will be misleading in any way that will harm the outcome of the patient.

Risk is present in all surgical interventions even if it is a simple procedure. The idea of risk has been born out of the term probability which vaguely defines the chance occurrence of a complication. Sternal instability and its progression from infective non-union to mediastinitis, and the reported mortality among those cases is 25 to 40%. Therefore, it becomes of utmost importance that cardiovascular patients due for osteochondrotomy of the sternum are assessed not only for their index pathology but also undergo a thorough assessment of co-morbid pathologies; and risk factors that may influence the final patient-based outcome. Simply enumerating the probability of adverse events that may occur during and after the surgery at the time of informed consent and the shared decision does not absolve the operating surgeon of the professional and legal responsibilities of a failed surgical procedure. The patient-specific and patient-appropriate medicine may be regarded as a type of N=1 study method of patient management without consideration of race, gender, culture, and geography-dependent biological variations. It is a direct subjective and objective method of thorough patient-specific and patient-appropriate appraisal of an individual's health status based on basic medical sciences and understanding of clinical biomechanical engineering principles and mechanisms. Despite comprehensive examination, there will still be instances of less than one hundred percent success.

In the mind of every physician, there are three eventful thoughts, yes, no, and don't know, as the level of confidence and certainty to have complete knowledge and understanding of patient-based biological variations in each scenario. There is always the risk of a potential complication. The odds or probability of no adverse event happening is 0.5 even before the surgery begins. The other 0.5 carries a whole spectrum of complications. Surgical wound infection is common in all types of surgeries and can prove devastating and expensive. The probability of at least one adverse event such as wound infection in a single patient is 1 minus the probability. In statistical terms, p = 0 means no occurrence of an adverse event. And, if there is at least one adverse event, such as infection in a single patient scenario of osteochondrotomy of the sternum without instability to provide a strong foundation for the healing of overlying soft tissues, it is unlikely that there will be DSWI leading to devastating mediastinitis. However, if there is associated sternal instability due to ineffective less than optimal reconstruction of the sternum the cascade of failure of soft tissue healing, superficial infection, and its ingress leading to the development of mediastinitis may occur with poor outcome. 1 minus p means at least one most common adverse event can occur in a single patient of fe-n-of-1 empirical testing. Say in 1000 patients the average surgical wound infection is 5% (the reported range is 0.7 to 8%). It means there is the occurrence of 50 events in this cohort, the ratio is 50/1000 = 0.05. This makes the probability of no adverse event happening 1 – 0.05 = 0.95. Therefore, p is 0.95^n in "n" patients. So, there is a 95% chance that in a clinically well-appraised single patient there would be no adverse event related to the sternum. However, mathematically one can continue to play the game of numbers with the equation of $(1 - \text{maximum risk})^n = 0.05$ with the limit of 95% confidence interval if sternal instability and dehiscence remain unattended because of poor mechanical stabilization. The risk of at least one adverse event happening is absolute in single-patient fe-n-of-1 testing, which can be directly related to plural pathologies and risk factors deserving careful pre-operative planning for the selection of an implant. If an implant provides a better bone-implant configuration and is designed to afford stable bone-to-bone contact, less than 2mm interfragmentary gap, and low contact stresses at the bone-implant interface throughout the healing process, then it would help to prevent the occurrence of even a single adverse event related to the osteochondrotomy of the sternum.

At the time of informed consent, the patient and the family are aware of sudden death from fatal myocardial infarction, accept the temporal failure of the coronary bypass graft, and recurrence of angina. However, would repudiate morbidity and mortality from a non-cardiac complication such as mechanical failure of the sternum due to less than optimal choice of a reconstruction implant such as stainless steel cerclage wire being "standard of care". Particularly, when the problem can be mitigated by the patient-specific and patient-appropriate in-silico predictive tool of FEM and FEA mathematical evaluation to identify the most ameliorative and judicious implant.

As mentioned above, currently there are limitations to extracting exact patient-specific tissue material properties and forces acting on the sternum and entire thoracic skeleton under physiological and pathological conditions of an individual. However, there is a sufficient body of practical knowledge available to advance the program into routine surgical practice by developing a collaborative relationship with an in-house clinical biomechanical engineering team to improve individual patient care. No doubt there are ethical issues, such as distribution of funds across the patient population, cost-effectiveness, and expecting active financial contribution by the interested patients to carry out this new presurgical intervention. There may be a need for an institutional review board assessment of the in-silico evaluation and surgical application only if the selected implant is new, has recently been approved, and has only a short-term clinical track record. However, despite these limitations, after the initial investment to set up the program of clinical biomechanical engineering, once up and running the return in terms of patient outcome, the building of surgical team confidence, and cost-saving in terms of further reduction in complication rate can be considerable. At present, from experimental and clinical case studies based on available tissue material properties and assumed loading conditions at other anatomical sites, it can only be said that patient-specific and patient-appropriate empirical fe-n-of-1 testing is a feasible intervention and will appreciably reduce complications following osteochondrotomy of the sternum for mediastinal access. The fe-n-of-1 testing has the potential to radically change the way implants are selected to reconstruct the osteochondrotomy of the sternum.

12. Conclusion

The design and application of in-silico intervention can provide simulation opportunities analogous to physical patient-based surgery without performing a hurtful surgical procedure and compare more than two likely implants that may be suitable for a given patient. The same principle can be extended to in-vitro experiments on a 3D printed model of the sternum having patient-specific anatomy and material properties, subjected to patient-appropriate forces to have qualitative haptic and quantitative validation of bone-implant interface in elective cases. Once the technical parameters for application to patient-specific and patient-appropriate conditions for in-silico testing are resolved, then it would facilitate direct estimation of single-patient implant selection much more confidently and rapidly. It would enhance precision of the bone-implant interface considering varied bone surface geometry and improve individual patient outcomes by connecting the in-silico scientific method to the surgical management of patients in the future.

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References

1. Allen, K. B., Thourani, V. H., Naka, Y., Grubb, K. J., Grehan, J., Patel, N., Guy, T. S., Landolfo, K., Gerdisch, M., Bonnell, M., & Cohen, D. J. (2017). Randomized, multicenter trial comparing sternotomy closure with rigid plate fixation to wire cerclage. *Journal of Thoracic and Cardiovascular Surgery*, *153*(4), 888–896. https://doi.org/10.1016/j.jtcvs.2016.10.093
2. Aubert, B., Vergari, C., Ilharreborde, B., Courvoisier, A., & Skalli, W. (2016). 3D reconstruction of rib cage geometry from biplanar radiographs using a statistical parametric model approach. *Computer Methods in Biomechanics and Biomedical Engineering: Imaging and Visualization*, *4*(5), 281–295. https://doi.org/10.1080/21681163.2014.913990
3. Balachandran, S., Lee, A., Denehy, L., Lin, K.-Y., Royse, A., Royse, C., & El-Ansary, D. (2016). Risk Factors for Sternal Complications After Cardiac Operations: A Systematic Review. *The Annals of Thoracic Surgery*, *102*(6), 2109–2117. https://doi.org/10.1016/j.athoracsur.2016.05.047
4. Baskett, R. J. F., MacDougall, C. E., & Ross, D. B. (1999). Is mediastinitis a preventable complication? A 10-year review. *Annals of Thoracic Surgery*. https://doi.org/10.1016/S0003-4975(98)01195-3
5. Bitsakos, C., Kerner, J., Fisher, I., & Amis, A. A. (2005). The effect of muscle loading on the simulation of bone remodelling in the proximal femur. *Journal of Biomechanics*. https://doi.org/10.1016/j.jbiomech.2004.03.005
6. Brunet, F., Brusset, A., Squara, P., Philip, Y., Abry, B., Roy, A., Amrein, C., Guillemain, R., Dubois, C., De Lentdecker, P., Aberkane, L., Ouaknine, R., Tronc, F., Bruniauax, J., Duffet, J. P., Yakar, V., Lamer, C., Petrie, J., & Lucet, J. C. (1996). Risk factors for deep sternal wound infection after sternotomy: A prospective,

multicenter study. *Journal of Thoracic and Cardiovascular Surgery*. https://doi.org/10.1016/S0022-5223(96)70222-2

7. Caimmi, P., Sabbatini, M., & Kapetanakis, E. et al. (2017). A randomized trial to assess the contribution of a Novel Thorax Support Vest (Corset) in preventing mechanical complications of median sternotomy. In *Cardiol ogy Therapy* (Vol. 6, pp. 41–46).
8. Casanova, M., Balmelli, A., Carnelli, D., Courty, D., Schneider, P., & Müller, R. (2017). Nanoindentation analysis of the micromechanical anisotropy in mouse cortical bone. *Royal Society Open Science*. https://doi.org/10.1098/rsos.160971
9. Casha, A. R., Yang, L., Kay, P. H., Saleh, M., & Cooper, G. J. (1999). A biomechanical study of median sternotomy closure techniques. *European Journal of Cardio-Thoracic Surgery*, *15*(3), 365–369. https://doi.org/10.1016/S1010-7940(99)00014-7
10. Couteau, B., Payan, Y., & Lavallée, S. (2000). The mesh-matching algorithm: An automatic 3D mesh generator for finite element structures. *Journal of Biomechanics*. https://doi.org/10.1016/S0021-9290(00)00055-5
11. Cristofolini, L., Conti, G., Juszczyk, M., Cremonini, S., Sint Jan, S. Van, & Viceconti, M. (2010). Structural behaviour and strain distribution of the long bones of the human lower limbs. *Journal of Biomechanics*. https://doi.org/10.1016/j.jbiomech.2009.11.022
12. Culliford, A. T., Cunningham, J. N., Zeff, R. H., Isom, O. W., Teiko, P., & Spencer, F. C. (1976). Sternal and costochondral infections following open-heart surgery. A review of 2,594 cases. *Journal of Thoracic and Cardiovascular Surgery*.
13. Currey, J. D. (1988). The effect of porosity and mineral content on the Young's modulus of elasticity of compact bone. *Journal of Biomechanics*. https://doi.org/10.1016/0021-9290(88)90006-1
14. Dalton, M. L., Connally, S. R., & Sealy, W. C. (1992). Julian's reintroduction of Milton's operation. *The Annals of Thoracic Surgery*, *53*(3), 532–533. https://doi.org/10.1016/0003-4975(92)90293-D
15. Dell'Amore, A., Congiu, S., Campisi, A., Mazzarra, S., Zanoni, S., & Giunta, D. (2020). Sternal reconstruction after post-sternotomy dehiscence and mediastinitis. *Indian Journal of Thoracic and Cardiovascular Surgery*. https://doi.org/10.1007/s12055-019-00880-5
16. Duan, N., Kravitz, R. L., & Schmid, C. H. (2013). Single-patient (n-of-1) trials: A pragmatic clinical decision methodology for patient-centered comparative effectiveness research. *Journal of Clinical Epidemiology*. https://doi.org/10.1016/j.jclinepi.2013.04.006
17. Dworzak, J., Lamecker, H., Von Berg, J., Klinder, T., Lorenz, C., Kainmüller, D., Seim, H., Hege, H. C., & Zachow, S. (2010). 3D reconstruction of the human rib cage from 2D projection images using a statistical shape model. *International Journal of Computer Assisted Radiology and Surgery*. https://doi.org/10.1007/s11548-009-0390-2
18. Feinstein, A. R. (1968). Clinical epidemiology. I. The populational experiments of nature and of man in human illness. *Annals of Internal Medicine*, *69*(4), 807–820. https://doi.org/10.7326/0003-4819-69-4-807
19. Filsoufi, F., Castillo, J. G., Rahmanian, P. B., Broumand, S. R., Silvay, G., Carpentier, A., & Adams, D. H. (2009). Epidemiology of Deep Sternal Wound Infection in Cardiac Surgery. *Journal of Cardiothoracic and Vascular Anesthesia*. https://doi.org/10.1053/j.jvca.2009.02.007
20. Gandhi, H. S. (2019a). Rationale and options for choosing an optimal closure technique for primary midsagittal osteochondrotomy of the sternum, part 2: A theoretical and critical review of techniques and fixation devices. *Critical Reviews in Biomedical Engineering*. https://doi.org/10.1615/CritRevBiomedEng.2019026453
21. Gandhi, H. S. (2019b). Rationale and options for choosing an optimal closure technique for primary midsagittal osteochondrotomy of the sternum. Part 3: Technical decision making based on the practice of patient- appropriate medicine. *Critical Reviews in Biomedical Engineering*. https://doi.org/10.1615/CritRevBiomedEng.2019026454
22. Gandhi, H. S. (2022a). A Comprehensive Review of Computer Vision Techniques to Interest Physicians and Surgeons, Role of A Clinical Biomechanical Engineer in Pre-Operative Surgical Planning, And Preamble To HSG-Amoeba, A New Concept of Biomedical Image Modeling Technique. *International Journal of Computers and Technology*, *Vol. 22 (2022)*, 1–49. https://doi.org/10.24297/ijct.v22i.9219

23. Gandhi, H. S. (2022b). Patient-appropriate and patient-specific quantification: Application of biomedical sciences and engineering principles for the amelioration of outcomes following reconstruction of osteochondrotomy of the sternum to access the mediastinum. *International Journal Of Computers & Technology*, *22*, 86–113. https://doi.org/10.24297/ijct.v22i.9229
24. Goh, S. S. C. (2017). Post-sternotomy mediastinitis in the modern era. *Journal of Cardiac Surgery*, *32*(9), 556–566. https://doi.org/10.1111/jocs.13189
25. Gorlitzer, M., Wagner, F., Pfeiffer, S., Folkmann, S., Meinhart, J., Fischlein, T., Reichenspurner, H., & Grabenwoeger, M. (2013). Prevention of sternal wound complications after sternotomy: Results of a large prospective randomized multicentre trial. *Interactive Cardiovascular and Thoracic Surgery*, *17*(3), 515–522. https://doi.org/10.1093/icvts/ivt240
26. Guyatt, G., Sackett, D., Taylor, D. W., Ghong, J., Roberts, R., & Pugsley, S. (1986). Determining Optimal Therapy — Randomized Trials in Individual Patients. *New England Journal of Medicine*. https://doi.org/10.1056/NEJM198604033141406
27. Helgason, B., Perilli, E., Schileo, E., Taddei, F., Brynjólfsson, S., & Viceconti, M. (2008). Mathematical relationships between bone density and mechanical properties: A literature review. In *Clinical Biomechanics*. https://doi.org/10.1016/j.clinbiomech.2007.08.024
28. Helgason, B., Taddei, F., Pálsson, H., Schileo, E., Cristofolini, L., Viceconti, M., & Brynjólfsson, S. (2008). A modified method for assigning material properties to FE models of bones. *Medical Engineering and Physics*. https://doi.org/10.1016/j.medengphy.2007.05.006
29. Hogben L, Sim, M. (1953). The self-controlled and self-recorded clinical trial for low-grade morbidity. *Br J Prev Soc Med.*, *7*(4), 163–179. https://doi.org/10.1136/jech.7.4.163
30. Hogben, L., & Sim, M. (2011). The self-controlled and self-recorded clinical trial for low-grade morbidity. *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyr026
31. Hutton, D. (2003). *Fundamentals of Finite Element Analysis* (First). McGraw-Hill.
32. Irwin RS. (2006). Complications of cough: ACCP evidence-based clinical practice guidelines. *Chest*, *129*(1 Supp), 54S–58S. https://doi.org/doi: 10.1378/chest.129.1_suppl.54S
33. Jolivet, E., Sandoz, B., Laporte, S., Mitton, D., & Skalli, W. (2010). Fast 3D reconstruction of the rib cage from biplanar radiographs. *Medical and Biological Engineering and Computing*. https://doi.org/10.1007/s11517-010-0610-5
34. Kass, M., Witkin, A., & Terzopoulos, D. (1988). Snakes: Active contour models. *International Journal of Computer Vision*. https://doi.org/10.1007/BF00133570
35. Klement, A., & Herrmann, M. (2010). Supportive treatment using a compression garment vest of painful sternal instability following deep surgical wound infection: A case report. *Journal of Medical Case Reports*. https://doi.org/10.1186/1752-1947-4-266
36. Kravitz, R. L., Duan, N., & Braslow, J. (2004). Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. In *Milbank Quarterly*. https://doi.org/10.1111/j.0887-378X.2004.00327.x
37. Lobos, C., Bucki, M., Hitschfeld, N., & Payan, Y. (2008). Mixed-element mesh for an intra-operative modeling of the brain tumor extraction. *Proceedings of the 16th International Meshing Roundtable, IMR 2007*. https://doi.org/10.1007/978-3-540-75103-8_22
38. Lobos, C., Payan, Y., & Hitschfeld, N. (2010). Techniques for the generation of 3D finite element meshes of human organs. In *Informatics in Oral Medicine: Advanced Techniques in Clinical and Diagnostic Technologies*. https://doi.org/10.4018/978-1-60566-733-1.ch009
39. Longford, N. T. (1999). Selection bias and treatment heterogeneity in clinical trials. *Statistics in Medicine*. https://doi.org/10.1002/(SICI)1097-0258(19990630)18:12<1467::AID-SIM149>3.0.CO;2-H
40. Loop, F. D., Lytle, B. W., Cosgrove, D. M., Mahfood, S., McHenry, M. C., Goormastic, M., Stewart, R. W., Golding, L. A. R., & Taylor, P. C. (1990). Sternal wound complications after isolated coronary artery bypass grafting: Early and late mortality, morbidity, and cost of care. *The Annals of Thoracic Surgery*, *49*(2), 179–187. https://doi.org/10.1016/0003-4975(90)90136-T
41. Malladi, R., Sethian, J. A., & Vemuri, B. C. (1995). Shape Modeling with Front Propagation: A Level Set Approach. *IEEE Transactions on Pattern Analysis and Machine Intelligence*. https://doi.org/10.1109/34.368173

42. Mayer, D. (2010a). A brief history of medicine and statistics. In D. Mayer (Ed.), *Essential evidenced-based medicine* (Second, pp. 1–8). Cambridge University Press.
43. Mayer, D. (2010b). Randomized clinical trials. In D. Mayer (Ed.), *Essential evidence based medicine* (Second, pp. 164–178). Cambridge University Press.
44. Mayer Dan. (2010). An overview of decision making in medicine. In D. Mayer (Ed.), *Essential evidence based medicine* (Second, pp. 215–232). Cambridge University Press.
45. Morgan, E. F., Bayraktar, H. H., & Keaveny, T. M. (2003). Trabecular bone modulus-density relationships depend on anatomic site. *Journal of Biomechanics*. https://doi.org/10.1016/S0021-9290(03)00071-X
46. Morgan, E. F., & Keaveny, T. M. (2001). Dependence of yield strain of human trabecular bone on anatomic site. *Journal of Biomechanics*. https://doi.org/10.1016/S0021-9290(01)00011-2
47. Nazerali, R. S., Hinchcliff, K., & Wong, M. S. (2014). Rigid fixation for the prevention and treatment of sternal complications: A review of our experience. *Annals of Plastic Surgery*, *72*(SUPPL. 1). https://doi.org/10.1097/SAP.0000000000000155
48. Nicholson, P. H. F., Cheng, X. G., Lowet, G., Boonen, S., Davie, M. W. J., Dequeker, J., & Van Der Perre, G. (1997). Structural and material mechanical properties of human vertebral cancellous bone. *Medical Engineering and Physics*. https://doi.org/10.1016/S1350-4533(97)00030-1
49. Nishida, N., Ohgi, J., Jiang, F., Ito, S., Imajo, Y., Suzuki, H., Funaba, M., Nakashima, D., Sakai, T., & Chen, X. (2019). Finite Element Method Analysis of Compression Fractures on Whole-Spine Models Including the Rib Cage. *Computational and Mathematical Methods in Medicine*. https://doi.org/10.1155/2019/8348631
50. Nobakhti, S., & Shefelbine, S. J. (2018). On the Relation of Bone Mineral Density and the Elastic Modulus in Healthy and Pathologic Bone. In *Current Osteoporosis Reports*. https://doi.org/10.1007/s11914-018-0449-5
51. Oliveira, M. L., Pedrosa, E. F. N. C., Cruz, A. D., Haiter-Neto, F., Paula, F. J. A., & Watanabe, P. C. A. (2013). Relationship between bone mineral density and trabecular bone pattern in postmenopausal osteoporotic Brazilian women. *Clinical Oral Investigations*. https://doi.org/10.1007/s00784-012-0882-2
52. Perrault, L. P., Kirkwood, K. A., Chang, H. L., Mullen, J. C., Gulack, B. C., Argenziano, M., Gelijns, A. C., Ghanta, R. K., Whitson, B. A., Williams, D. L., Sledz-Joyce, N. M., Lima, B., Greco, G., Fumakia, N., Rose, E. A., Puskas, J. D., Blackstone, E. H., Weisel, R. D., & Bowdish, M. E. (2018). A Prospective Multi-Institutional Cohort Study of Mediastinal Infections After Cardiac Operations. *Annals of Thoracic Surgery*. https://doi.org/10.1016/j.athoracsur.2017.06.078
53. Pham, D. L., Xu, C., & Prince, J. L. (2000). A survey in current methods in medical image processing. *Annual Review of Biomedical Engineering*. https://doi.org/10.1146/annurev.bioeng.2.1.315
54. Pinotti, K. F., Cataneo, D. C., Rodrigues, O. R., & Cataneo, A. J. M. (2018). Closure of the sternum with anchoring of the steel wires: Systematic review and meta-analysis. In *Journal of Thoracic and Cardiovascular Surgery*. https://doi.org/10.1016/j.jtcvs.2018.02.033
55. Raman, J., Lehmann, S., Zehr, K., De Guzman, B. J., Aklog, L., Garrett, H. E., MacMahon, H., Hatcher, B. M., & Wong, M. S. (2012). Sternal closure with rigid plate fixation versus wire closure: A randomized controlled multicenter trial. *Annals of Thoracic Surgery*, *94*(6), 1854–1861. https://doi.org/10.1016/j.athoracsur.2012.07.085
56. Rho, J. Y., Hobatho, M. C., & Ashman, R. B. (1995). Relations of mechanical properties to density and CT numbers in human bone. *Medical Engineering and Physics*. https://doi.org/10.1016/1350-4533(95)97314-F
57. Robicsek, F., Daugherty, H. K., & Cook, J. W. (1977). The prevention and treatment of sternum separation following open-heart surgery. *The Journal of Thoracic and Cardiovascular Surgery*.
58. Sackett DL, Hayes RB, T. P. (1985). Deciding on the best therapy. In T. P. Sackett DL, Hayes RB (Ed.), *Clinical epidemiology. A basic science for clinical medicine* (First, pp. 171–197). Little, Brown and company.
59. Schimmer, C., Reents, W., & Elert, O. (2006). Primary closure of median sternotomy: A survey of all German surgical heart centers and a review of the literature concerning sternal closure technique. In *Thoracic and Cardiovascular Surgeon* (Vol. 54, Issue 6, pp. 408–413). https://doi.org/10.1055/s-2006-924193
60. Scuffham, P. A., Nikles, J., Mitchell, G. K., Yelland, M. J., Vine, N., Poulos, C. J., Pillans, P. I., Bashford, G., Del Mar, C., Schluter, P. J., & Glasziou, P. (2010). Using N-of-1 trials to improve patient management and save costs. *Journal of General Internal Medicine*. https://doi.org/10.1007/s11606-010-1352-7

61. Sharma, R., Puri, D., Panigrahi, B. P., & Virdi, I. S. (2004). A modified parasternal wire technique for prevention and treatment of sternal dehiscence. *Annals of Thoracic Surgery*, *77*(1), 210–213. https://doi.org/10.1016/S0003-4975(03)01339-0
62. Sylvester, A. D., & Kramer, P. A. (2018). Young's Modulus and Load Complexity: Modeling Their Effects on Proximal Femur Strain. *Anatomical Record*. https://doi.org/10.1002/ar.23796
63. Taddei, F., Schileo, E., Helgason, B., Cristofolini, L., & Viceconti, M. (2007). The material mapping strategy influences the accuracy of CT-based finite element models of bones: An evaluation against experimental measurements. *Medical Engineering and Physics*. https://doi.org/10.1016/j.medengphy.2006.10.014
64. Tosoni, G. M., Lurie, A. G., Cowan, A. E., & Burleson, J. A. (2006). Pixel intensity and fractal analyses: detecting osteoporosis in perimenopausal and postmenopausal women by using digital panoramic images. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology*. https://doi.org/10.1016/j.tripleo.2005.08.020
65. Veeramachaneni, N. (2018). The optimal sternal closure technique: Still elusive. In *Journal of Thoracic and Cardiovascular Surgery*. https://doi.org/10.1016/j.jtcvs.2018.03.023
66. Viceconti, M., Bellingeri, L., Cristofolini, L., & Toni, A. (1998). A comparative study on different methods of automatic mesh generation of human femurs. *Medical Engineering and Physics*. https://doi.org/10.1016/S1350-4533(97)00049-0
67. Wijayathunga, V. N., Jones, A. C., Oakland, R. J., Furtado, N. R., Hall, R. M., & Wilcox, R. K. (2008). Development of specimen-specific finite element models of human vertebrate for the analysis of vertebroplasty. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*. https://doi.org/10.1243/09544119JEIM285
68. Wirtz, D. C., Schiffers, N., Forst, R., Pandorf, T., Weichert, D., & Radermacher, K. (2000). Critical evaluation of known bone material properties to realize anisotropic FE-simulation of the proximal femur. *Journal of Biomechanics*. https://doi.org/10.1016/S0021-9290(00)00069-5