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Future Data Points to Implement in Adult Spinal Deformity Assessment for Artificial Intelligence Modeling Prediction: The Importance of the Biological Dimension

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ABSTRACT

Adult spinal deformity (ASD) surgery is still associated with high surgical risks. Machine learning algorithms applied to multicenter databases have been created to predict outcomes and complications, optimize patient selection, and improve overall results. However, the multiple data points currently used to create these models allow for 70% of accuracy in prediction. We need to find new variables that can capture the spectrum of probability that is escaping from our control. These proposed variables are based on patients' biological dimensions, such as frailty, sarcopenia, muscle and bone (tissue) sampling, serological assessment of cellular senescence, and circulating biomarkers that can measure epigenetics, inflammaging, and -omics. Many of these variables are proven to be modifiable and could be improved with proper nutrition, toxin avoidance, endurance exercise, and even surgery. The purpose of this manuscript is to describe the different future data points that can be implemented in ASD assessment to improve modeling prediction, allow monitoring their response to prerehabilitation programs, and improve patient counseling.

New Technology

Keywords: spinal deformities, artificial intelligence, biomarkers, frailty, sarcopenia, osteoporosis, tissue sample, metabolomics, senescence

INTRODUCTION

Adult spinal deformity (ASD) is a common cause of severe pain and disability very often linked to aging and degeneration of the spinal column.[1] Its prevalence increases with age, reaching 68% in populations older than 60 years.[2] Considering that by 2050, the population aged >60 years will nearly double,[3] ASD is increasingly being recognized as a "disease" progressively affecting a higher percentage of our adult population, and it is becoming a primary concern for health care systems.

ASD surgery when properly indicated improves patients' quality of life (QoL). However, it is plagued with high complication rates and high—direct and indirect—costs to patients and society.[4] Complications compromise surgical QoL gains and may have a significant impact on final outcomes.[5,6] Although most patients improve with surgery, there are some that do not; additionally, some patients have inherent high surgical risks or their surgeries are associated with catastrophic costs.[7] The identification of these patients will improve the delivery of care in a value-driven health care economy and allow for better-informed decision-making.[8]

Traditionally, risk assessment and patient counseling have been based on average values reported in the ASD literature: more than 40% of major complications and 28% risk of reoperation by 2 years.[4] However, these are mean values, comprised by an average of multiple values, and only a limited amount of patients follow mean values. Thus, most patients are not represented by the mean. Surgical outcomes and complications depend on a complex interplay between 3 general factors: patient characteristics, deformity/disease characteristics, and surgical characteristics. Due to the extensive heterogeneity of each of these domains, ASD is unique in that no 2 patients are alike, generalizations are hardly justified, and predictions are often flawed. At the same time, this same heterogeneity offers a unique opportunity for advanced analytics in spine surgery, covering these multiple dimensions and their complex interactions.

The development of predictive tools allowing for more personalized patient selection has been shown to be beneficial in reducing the rate of perioperative complications in different surgical fields. The International Spine Study Group and European Spine Study

Group have been at the forefront of developing predictive models for ASD patients, using their prospectively collected, multi-institutional database. Using machine learning algorithms, the first ASD-specific computerized decision support tool was created in 2019[9–11] and was recently validated in external independent prospective databases.[12] This tool allows the input of specific patient characteristics, radiographic measures, and surgical invasiveness planned for a targeted surgery. With this information, machine learning algorithms provide personalized predictions on clinical improvement and rate of potential complications in the first 2 postoperative years.

Even if the accuracy/goodness of fit of all these models can be considered very good (exceeding 70%) and are now considered the gold standard in their fields, they have some limitations. Looking at the revised models over time, it was clear that these would soon reach a saturation level that cannot be overcome by simply increasing the number of observations (patients) or observation time but rather the number of observed dimensions (variables). We have discovered that 55% of the predictive model weight for postoperative complications came from the patient's characteristics, with one-third of the variables being potentially modifiable.[4] The relevant predictive weight of frailty and aging within patient's dimensions was very high, but it has only been assessed indirectly and superficially using biological age, comorbidities, and functional scores. We have not been able yet to capture aging or frailty directly as a biological clock biomarker.

Expanding the scope of measured variables from the demographic, radiological, and surgical variables to the biological, metabolic, and physiological realm is, therefore, the missing step forward in ASD precision medicine. Thus, the purpose of this review is to describe the new biological future data points that can be implemented in ASD assessment to improve modeling prediction, allow monitoring patients' response to prerehabilitation programs, and improve patient counseling.

BIOLOGY AS THE NEXT STEP TO IMPROVE PREDICTION

In medicine, host characteristics are more determinant of "disease progression" than the disease itself. However, patient's characteristics and objective quantification of the biological, physiological, metabolic, and aging status of patients have always been the hardest dimension to grasp, and various proxies have been developed, such as the American Society of Anesthesiologists score, Charlson Index,[13] Elixhauser Comorbidity Index,[14] etc, with several limitations.

Age and comorbidities were universally associated with worse outcomes due to a diminished physiological reserve (frailty). This concept of frailty as a medical diagnosis is relatively novel and originally came about as a result of trying to explain the differences between chronological and physiological age. To help quantify and stratify host-related risk factors preoperatively, the ASD Frailty Index (ASD-FI) was developed.[15] The ASD-FI proved to be effective for preoperative risk stratification, and greater patient frailty was associated with worse outcomes, including greater risk of major complications, reoperation, and prolonged hospital stay.

However, the ASD-FI relies only on a set of comorbidities (most of them not modifiable) and responses to health questionnaires. It is still a very limited tool that does not capture all the dimensions of frailty and lacks an objective and quantifiable measure. So, even though there is a general consensus that aging and frailty have an impact on ASD prognosis and treatment-related outcomes, studies analyzing the role of basic processes of aging on ASD onset and development are scarce, and their application in spine surgery is still negligible.

Therefore, in order to feed artificial intelligence (AI) models with biological biomarkers, frailty scales, and physiological factors, the first step is identifying those that are associated with disease onset and progression and those that can have a bearing on the different outcomes. For this purpose, an alliance with experts in the fields of aging and frailty as well as biology is essential. Deep insight is needed in fields, such as circulating biomarkers, cellular senescence, genomics, proteomics, and metabolomics, to name a few. Implementing these new biological data points in ASD assessment may help in the near future to improve AI modeling and prediction.

BIOLOGICAL DIMENSIONS AND DATA POINTS

Frailty

Frailty is an aging-related multifactorial syndrome of physiological decline, which can be accelerated by stressors (infection, illness, surgery, etc). It is characterized by marked vulnerability to adverse health outcomes.[16] Frailty is the phenotypic difference between chronological age and physiological age (this difference is called age acceleration) and is influenced by genetics as well as epigenetics (DNA methylation, chromatin

remodeling, histone modification, and prolongevity transcription factors). It first stemmed from geriatric medicine and oncology and is spreading among all surgical fields. There are multiple factors impacting frailty,[17,18] such as malnutrition, obesity, sedentary lifestyle, osteoporosis, and sarcopenia. Frailty can predict a myriad of outcomes, such as disability, falls and fractures, cognitive deterioration, QoL, hospitalization, and mortality.[19,20]

From the biological point of view, frailty is triggered by a chain of cell changes that start with inflammaging (the physiological inflammation environment commonly created by aging), which has a high variability among individuals.[21] All these metabolic changes can be measured by different biomarkers (listed parenthetically).[22–24] With frailty, there is a decline in metabolism (adiponectin), mitochondrial dysfunction (mitochondrial transcription factor A and DNA degradation), oxidative stress (malondialdehyde and carbonyl), inflammation (C-reactive protein, interleukin 6, and tumor necrosis factor alpha), hormone dysregulation, and senescence. This final concept is the loss of a cell's power of division and growth and can be measured by micro-RNA (miRNA) and DNA methylation.[25,26] All of these processes create an unfavorable environment for stem cells to promote regeneration, accelerating the development of diseases such as diabetes, cardiovascular problems, tumors, or autoimmune syndromes.

The concept of frailty was first defined by phenotype criteria,[27] which describe its symptoms: unintentional weight loss ≥10%, weakness (grip strength ≤17–21 kg), low resistance and exhaustion, slowness (time to walk 4 m ≤0.65–0.76 m/s), and low physical activity (≤90 kcal/wk). The presence of 1 or more symptoms is used to conform the Fried classification, which is divided into 3 stages based on the patient's functional capacity: robust, prefrail, and frail. Frailty is not synonymous with disability; it is the state that precedes it, and it is not equal to comorbidities. However, these 3 conditions are deeply interrelated.[28] Although Fried's phenotype is the most common tool to assess frailty, other tools exist such as the Edmonton Frail Scale or the Clinical Frailty Scale.

In spine surgery, we are just starting to realize the importance of frailty in ASD surgery. As mentioned, the ASD-FI[29] was validated based on 14 comorbidities and 16 answers to patient-reported outcome measures, mainly relating to disability. Although this score proved to be predictive of outcomes, the dimensions it assesses are still limited.

Multiple clinical tests have been developed to assess frailty in the clinical setting and could be incorporated as new future data points in our databases. We highlight 3 that can be readily used in ASD patients: the short physical performance battery (SPPB), the gait speed, and the timed up-and-go test (TUG).[30]

- The SPPB[31] evaluates lower extremity functioning in older individuals. It is based on 3 clinical tests: standing balance on both feet, gait speed in a 4-m walk, and chair-stand repeated 5 times. Scores range from 0 to 12 possible points. A score ≥10 indicates robustness; 3 to 9 points indicate frailty.
- Gait speed[32] has been used as a predictor of decline in functional agility. It is measured as total distance/time. Normal walking speeds for community-dwelling older adults who are healthy generally range from 0.90 to 1.30 m/s, whereas walking speeds ≤0.60 to 0.70 m/s are strong risk factors for poor health outcomes.
- In the TUG test,[33] patients are asked to rise from a standard armchair, walk to a marker 3 m away, turn, walk back, and sit down again. Scores of ≤10 seconds indicate normal mobility, between 11 and 20 seconds mark frailty, and >20 seconds mean limited mobility and the need for external assistance.

In summary, to quantify frailty in future models, we propose to collect the 3 clinical tests together with a list of the aforementioned biomarkers shown to be related to inflammaging and senescence.

Sarcopenia

Sarcopenia is the loss of skeletal muscle mass and strength as a result of aging. Atrophy and muscle degeneration do not necessarily lead to pathology, as cell death is typically followed by cellular repair. However, when regeneration is impaired or insufficient to replace degenerated fibers, or when the rate of degeneration outmatches regeneration, contractile tissue volume is reduced over time and often results in the accumulation of adipose tissue. This muscle fatty infiltration leads to muscular inflammation and dysfunction that affect contractibility.[34]

This process is commonly associated with other aging deteriorations, such as loss of spinal cord alpha motor neurons and denervation, mitochondrial dysfunction, and oxidative stress. The final result is walking abnormalities, imbalance, and falls. All of these changes affect muscle quality and function and lead to poor QoL and increased physical disability.[35]

ASD patients have been found to have less contractile potential associated with fibrofatty replacement and muscle fiber abnormalities, such as increased sarcomere length as well as cellular and extracellular stiffness. Thus, patients have higher passive stiffness due to chronic changes that perpetuate the disease state over time. They also pose a challenge after surgery at the nonfused spine and may increase the chances for junctional failure or deformity progression.[36]

Different variables can be used and implemented to measure sarcopenia. The clinical assessment of muscle function can be performed by several tests that again could be implemented as new data variables, such as[37] muscle grip: the grip of the dominant hand is measured with a dynamometer; SPPB: especially TUG and gait speed, as lower extremity strength is what better correlates with physical function; and body mass index: kg/m^2. It remains unclear, however, the extent to which grip strength is linked to paraspinal muscle functional integrity.

Imaging can also be used to calculate muscle mass: dual-energy x-ray absorptiometry (DXA) can easily measure the appendicular lean mass index. Magnetic resonance imaging or ultrasound imaging can measure the femoral quadriceps area and volume. Additionally, lumbar magnetic resonance imaging or computed tomography can be used to assess fatty infiltration of the lumbar and psoas muscles at level L3.

Sarcopenia is intimately related to frailty as both are linked to aging, and usually both coincide in time. Both can play a role on the postoperative outcomes after adult spine surgery.[38] However, not all frail patients have sarcopenia and vice versa. Patients who have both entities are the ones who really improve with exercise and physical activity.[39] By recruiting the muscle through exercise, it is possible to activate anabolic pathways and inhibit catabolic pathways, leading to muscle fiber hypertrophy and restoration of contractile tissue volume, and resulting in improved and restored function. Proper nutrition (especially proteins and amino acids) and vitamin D supplements are also used to treat this syndrome. Prerehabilitation is essentially epigenetic modulation.

Tissue Sample

Frequently, ASD derives from local degenerative changes at the disc, bone interfaces, and muscular levels within the spine as well as surrounding connective tissue. There have been multiple in vitro studies and models about degenerative disc diseases and associated muscle changes, but how this translates into ASD is still little explored.[40] Obtaining samples could translate expression patterns of cellular function and morphology/histology into a quantifiable measure compared with risk and outcome for use by AI computing. Samples can be assessed through gross examination, cross-sectional histological analysis, cell quantification, immunohistochemistry, immunofluorescent staining, and gene expression analysis, to name a few.

Muscle Function

Impaired muscle function is central to multiple musculoskeletal conditions that impair QoL, such as ASD.[41] There are multiple causes of diminished muscle efficiency and function, ranging from simple loss of contractile protein volume to sarcomere disorganization and disruption in excitation-contraction coupling.[42] The loss of functional contractile tissue can occur due to atrophy or degeneration, in which both are different etiologies with different implications but can overlap.

Atrophy is a well-defined muscle-intrinsic process mediated by the activation of the ubiquitin-proteasome and autophagic pathways that actuate protein catabolism.[42] It is caused by decreased mechanical or neuromuscular stimulus or unmet metabolic needs. At the cellular level, atrophic muscle fibers have smaller cytoplasmic volumes but intact cellular machinery. Recently, secreted glycoprotein Dickkopf-3 (Dkk3) in muscles of young mice led to muscle atrophy. Conversely, reducing its expression in old muscles restored both muscle size and function. These findings suggest that Dkk3 may be used as a diagnostic marker and as a therapeutic target for age-related muscle atrophy.[43]

In contrast, acute muscle degeneration is a broader term encompassing a wide array of extrinsic physical and biochemical insults that lead to muscle fiber damage. If left unchecked, it eventually leads to necrosis.[44] Only recently has the distinct physiological process of muscle degeneration been linked to chronic musculoskeletal conditions.[45] In a range of degenerative models, fibers display altered characteristics, such as myophagocytosis and cellular infiltration, fiber splitting, and cytoplasmic disruptions.[46] These characteristics are also often paired with an increased presence of inflammatory markers.[47]

Similar to atrophy, acute muscle degeneration does not necessarily lead to pathology as cell death is typically followed by cellular repair mediated by satellite cells (SCs). When regeneration is impaired or insufficient, or when the rate of degeneration outmatches regeneration, contractile tissue volume is reduced over time and often results in the accumulation of adipose

tissue. This chronic degenerative disease pattern, contrary to the acute degenerative or atrophied model, cannot be reverted by resistance exercises as the underlying pathology is muscle cell death. SCs are considered to play a crucial role in muscle fiber maintenance, repairing, and remodeling.[48]

Pax7 is a transcription factor regulating the myogenic potential and function of SCs in muscle repair and regeneration. Therefore, it serves as a marker for proper SC density and function.[49] Fat accumulation in muscle is thought to arise through 2 different pathways. One direct route is via the accumulation of lipid within muscular fibers, known as intramuscular fat.[50] This is associated with insulin insensitivity, inflammation, and functional deficits in skeletal muscle and is detrimental to skeletal fiber—and muscle—function.[50] Another pathway is an accumulation of fat within skeletal muscle, known as intermuscular fat. Besides SCs, a second, more recently described, population of cells is termed fibro/adipogenic progenitors (FAPs) or mesenchymal interstitial cells. These cells are distinct from SCs and lack Pax7 expression but are Sca-1 and PDGFRα positive.[51] SCs are generally resistant to adipogenic differentiation, whereas FAPs readily differentiate into adipocytes under various conditions such as muscle injury or glucocorticoid treatment.[51] Endogenous glucocorticoid levels also increase with age, which may contribute to the deposition of intermuscular fat. Therefore, it is believed that the downregulation or dysfunction of SCs and upregulation (and adipocyte differentiation) of FAP are associated with fatty infiltration of muscles.

Bone Quality

Osteoporosis is another process related to aging and affects ASD surgery outcomes through mechanical complications. DXA scans and CT images (Hounsfield units) are currently used to assess bone quality. Advances in image analysis and informatics algorithms have produced new ways of assessing bone health through reinterpretation of the DXA scans. These now include new parameters, such as trabecular bone score, hip-axis length, hip-strength analysis, and finite element analysis, to mention just a few. These scores have proved to be more predictive of osteoporotic fracture and bone strength than a nonprocessed DXA scan. New radiological diagnostic tools have now been employed, such as the so-called radiofrequency echographic multispectrometry, which was shown to have similar predictive value as the DXA scan for fractures. However, it can also provide an estimation of bone strength (Fragility Index), which is independent of bone mineral density and has been shown to effectively predict fracture risk. High-resolution peripheral quantitative computed tomography is another alternative imaging technique that can provide both quantitative and qualitative information regarding bone health. It is, however, expensive and not readily available.

Peripheral blood markers, such as miRNA and long-noncoding RNA, are novel and promising markers and targets in the field of osteoporosis. miRNA-103a, for example, can directly inhibit gene expression correlated with osteoblast differentiation. It is overexpressed in situations such as mechanical unloading and frailty, which results in a strong inhibition of bone formation. Consequently, targeting miRNA-103a with antagomir-103a can rescue the osteoporosis caused by immobilization and mechanical unloading in animal models. These kinds of biomarkers serve as diagnostic and therapeutic targets and are still in their early age but already show a glimpse of how osteoporosis diagnosis and treatment can evolve in the future.

Ultimately, overall bone quality can also be assessed by bone biopsies grossly and by immunohistochemistry of the protein levels and spatial patterns of runt-related transcription factor 2, osteocalcin, osteoprotegerin, and the receptor activator of nuclear factor kappa-B ligand. All are relevant factors in bone remodeling and preservation. Additionally, through quantitative polymerase chain reaction, the expression levels of transcripts linked to osteoclast and osteoblast function can be quantified.

In summary, future trends would see routine access to novel radiological markers of bone health, such as trabecular bone score, finite element analysis, and high-resolution peripheral quantitative computed tomography, and even circulating biomarkers such as miRNA and long-noncoding RNA. Early and precise assessment of bone health is crucial to target the right intervention in the right patient population prior to surgery. Including such quantitative and qualitative parameters in predictive models would prove to be a step further in the direction of "precision medicine" and even serve as a monitoring tool to assess efficacy of early interventions aimed at improving bone health.

Biological Aging and the Role of -Omics

The past decade has seen significant progress in the development of biomarkers of biological age, including epigenetic clocks, telomere length, transcriptome-based, proteomic-based, and metabolomic-based age estimators.[52]

Epigenetic clocks are highly accurate age estimation tools derived by measuring the methylation pattern of specific DNA regions. Chronological age has a significant effect on the process of DNA methylation, and technological advances in DNA array technology combined with complex mathematical modeling have allowed investigators to estimate the age of source DNA from a variety of sources, including cells, tissues, and organs.[53,54] More advanced epigenetic clocks integrate laboratory values that reflect organ function and inflammatory state, including albumin, creatinine, glucose, and C-reactive protein.[55] An even more ambitious study used a longitudinal cohort followed for 2 decades to develop an epigenetic clock to calculate the pace, or rate, of aging.[56] Such epigenetic clocks have the potential to provide more quantitative data on physiologic reserve and a patient's ability to tolerate high-risk surgery.

Telomeres are DNA-protein complexes located at the ends of chromosomes that typically shorten with age. Their length is regulated by an enzyme called telomerase, and the degree of shortening is proportional to the risk of common diseases of aging and mortality.[57–59] Telomere maintenance is influenced by both genetic and environmental factors, with important implications for a number of ailments, including both diseases of aging and cancer.[57] Lifestyle modifications can alter the rate of telomere in both directions.[60,61] Even surgical intervention (ie, bariatric surgery) has been shown to increase telomere length, presumably through reversal of metabolic syndrome.[62,63] Since telomere length appears to be a dynamic marker of biological age, it has unique promise as a component of risk stratification for patients undergoing elective, high-risk surgical procedures. Furthermore, preliminary work suggests that shorter telomere length is associated with increased risk of postoperative complications in patients undergoing deformity surgery independently of biological age.[64]

A limitation of both epigenetic clocks and telomere length is that neither assesses functional gene expression like transcriptome-based aging, which has been shown to predict longevity in animal models.[65] These tools utilize complex artificial neural networks to calculate the interactions of gene transcription with multifaceted molecular pathways that provide insight into both biological age and functional phenotypes.[52] Aging and oxidative stress also have well-characterized effects on proteins, which can be analyzed through proteomic-based approaches. Since proteins are functional entities, this technique measures how aging affects cellular function, phenotype, and the pathogenesis of disease.[66] Certain age-associated proteins have also demonstrated associations with both comorbidity burden and mortality.[67] Integration of biomarkers of aging with "omics"-based approaches has the potential to provide more granular data on frailty and physiologic reserve.

Genetic analyses have become standard within basic science investigations but have not yet expanded into clinical outcomes for surgical specialties. More recently, new fields have emerged from genetics that include transcriptomics, proteomics, and now metabolomics[68]: the end of the biological chain of events.

Metabolomics refers to the study of metabolites within the human body.[69–71] These metabolites can play critical roles in physiopathological processes as they regulate cellular activity and mediate biological function (native metabolites or from tumors).[71] Endogenous metabolomics found in serum or urine are highly sensitive and can identify normal and abnormal physiological mechanisms through subtle biological changes,[71] providing a "big-picture" overview of the patient. Currently, there are approximately 18,500 quantified metabolites and counting.[72] Metabolites are detected through nuclear magnetic resonance spectroscopy, liquid chromatography-mass spectrometry, and gas chromatography-mass spectroscopy[71] as well as isotope tracing.[73] Complex bioinformatics and advanced computing algorithms are required to perform the analysis on metabolomics.[71,73]

Our current understanding of metabolomics stems from cancer biomarkers and medically treated diseases such as diabetes, osteoporosis, and rheumatoid arthritis.[69,71,74,75] However, there are few studies evaluating the metabolic profiles following bariatric surgery[76] or even assessing adverse surgical outcomes for neonates with congenital heart disease.[77] The literature regarding metabolomics and the spine is very limited looking at mechanisms for Modic changes and biomarkers for thoracic ossification of the ligamentum flavum.[78,79] However, a single study by Xiao et al found that adult idiopathic scoliosis led to significant changes in clinical indexes, bone mineral density, Cobb angles, and some plasma metabolites.[80]

The field of -omics research and technology (transcriptomics, proteomics, and metabolomics) has quickly expanded over the past few years.[68,69,71,72,81,82] It will certainly offer invaluable and much-needed insight into patients' ability to tolerate a large surgery, form a solid fusion, heal properly, and even to incur postoperative complications. The Table summarizes the new data points that have been discussed in this article.

Table. Summary of future data points to implement in adult spinal deformity assessment for artificial intelligence modeling prediction.

Category	Category and Type of Markers	Measure	Findings or Significance
Frailty	Serological markers	General etabolism	Adiponectin
		Mitochondrial dysfunction	Mitochondrial transcription factor A
			DNA degradation
		Oxidative stress	Malondialdehyde
			Carbonyl
		Systemic inflammation	C-reactive protein
			IL-6
			TNF-α
	Clinical tests	SPPB	Standing balance on both feet, gait speed in a 4-m walk, and chair-stand repeated 5 times
		Gait speed	Total distance/time
		Timed up-and-go test	Rise from a standard armchair, walk to a marker 3 m away, turn, walk back, and sit down again
Aging and senescence	Serological markers	Epigenetic clocks	Complex mathematical modeling including DNA methylation and laboratory values that reflect organ function and inflammatory state including albumin, creatinine, glucose, and C-reactive protein
		Telomere length	Telomere length is regulated by an enzyme called telomerase, and the degree of shortening is proportional to the risk of common diseases of aging and mortality.
		-Omics	Transcriptomics, proteomics, and metabolomics analysis among other. Complex bioinformatics and advanced computing algorithms are required to perform the analysis of over 10,000 different protein expressions and circulating and excreted metabolites as well as oxidative stress
Sarcopenia	Radiological	MRI/CT	Fatty acid infiltration of paravertebral and psoas muscles
		MRI/ultrasonography	Femoral quadriceps area and volume
		DXA	Appendicular lean mass index
	Clinical tests	Muscle grip	Grip of dominant hand measured with a dynamometer
		SPPB	
		Timed up-and-go test	
		Gait speed	
		Body mass index	
	Immunohistological	Glycoprotein Dickkopf 3 (Dkk3)	Marker of age-related muscle atrophy
		Pax7	Transcription factor regulating the myogenic potential and function of satellite cells in muscle repair and regeneration, marker of proper cell function
		Sca-1 and PDGFRα	Markers of fibroadipogenic progenitor cells that are readily converted into adipocytes and lead to muscle fatty infiltrates
	Gross examination	Muscle fibers	Atrophic muscle fibers have smaller cytoplasmic volumes but intact cellular machinery
			Degenerated fibers have altered characteristics such as myophagocytosis and cellular infiltration, fiber splitting, and cytoplasmic disruptions.
Bone quality	Radiological markers	CT	Hounsfield units; high-resolution peripheral quantitative CT
		DXA	Bone density; trabecular bone score; hip-axis length, hip-strength analysis, and finite element analysis
		Ultrasound	Radiofrequency echographic multispectrometry
	Serological markers	Micro-RNA and long-noncoding RNA, especially miRNA-103a	Novel markers and targets for new therapies or interventions
	Immunohistological	Expression levels of runt-related transcription factor 2, osteocalcin, osteoprotegerin, and the receptor activator of nuclear factor kappa-B ligand.	Bone remodeling and preservation

Abbreviations: CT, computed tomography; DXA, dual-energy x-ray absorptiometry; IL-6, interleukin 6; MRI, magnetic resonance imaging; SPPB, short physical performance battery; TNF-alpha, tumour necrosis factor alpha.

CONCLUSIONS

In ASD surgery, the desired goals must be achieved through decisions that take into account weighted fashion differential factors for each patient. This fits into the concept of "precision medicine," which represents the goal toward which the progress of knowledge and quality-driven care are directed.

So far, our assessment of patients has been limited to demographical variables, list of comorbidities, and some functional scores. Their integration into AI models along with deformity/radiological parameters and surgical variables has allowed us to identify complex interplays between variables and improved drastically our prediction capabilities of clinical outcomes and

complications.[83,84] Yet, these elements alone fail to explain nearly 30% of observed outcomes. As a consequence, it is evident that we still miss a big dimension that is more representative of the "inner peculiarities" of each patient.

What we call "biology" is a set of elements, some of which are purely biological entities (ie, age, frailty, sarcopenia, osteoporosis, and neurodegeneration), while others are conceptual entities that aim to summarize under a single value the multifaceted essence of each patient (ie, multimorbidity and composite biomarker scores). Frailty and sarcopenia have been shown to have a direct bearing on mortality, QoL, cognitive impairment, and disability, among others.[85] However, new biological and molecular advances have integrated serum biomarkers, tissue sample analysis, and -omics into play, which will improve greatly our capacity to individually assess patients. What we used to understand as "improper aging" is now defined at the molecular level with telomere length, complex epigenomic or "biological clocks,"[86] and biomarkers of the "pace of aging."[56] These new frontiers, mainly -omics biomarkers (ie, genomics, proteomics, and metabolomics) and tissue analysis (tissue-specific aging), will shape medical care of the future, help increase prediction ability, and improve surgical decision-making and counseling in adult deformity surgery.

There is growing evidence that biological aging can be reversed with therapeutic interventions, such as improved nutrition, avoidance of toxic stressors, endurance exercise, and even surgery.[87,88] These interventions can even be monitored in the exposed dimensions: FIs and frailty scales, muscular and tissue function, circulatory biomarkers, -omics, epigenetic clocks, and even telomeres.[89] The discovery of these biological markers in ASD and their validation with regard to disease/deformity progression and surgical outcomes is the next step forward. Integrating these into risk calculators will provide the ultimate prediction tool. This would also offer the ultimate monitoring tool as to dynamically assess fitness to surgery and even response to comprehensive rehabilitation program as a prior step to determine optimal surgical timing.

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